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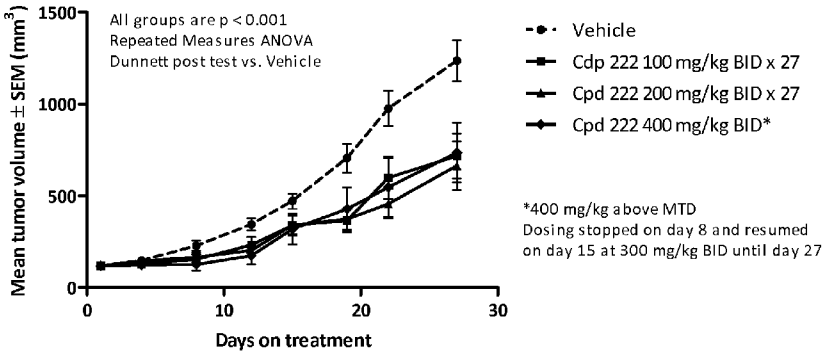

Figure 4

(57) Abstract: The present invention relates to substituted benzene compounds. The present invention also relates to pharmaceutical compositions containing these compounds and methods of treating cancer by administering these compounds and pharmaceutical compositions to subjects in need thereof. The present invention also relates to the use of such compounds for research or other non-therapeutic purposes.

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SUBSTITUTED BENZENE COMPOUNDS

RELATED APPLICATIONS

[001] This application claims priority to, and the benefit of, U.S. provisional application Nos. 61/474,825, filed April 13, 2011, and 61/505,676 filed July 08, 2011, the entire contents of each are incorporated herein by reference in their entireties.

INCORPORATION-BY-REFERENCE OF SEQUENCE LISTING

[002] The contents of the text file named "41478508001WOST25.txt," which was created on March 28, 2012 and is 2 KB in size, are hereby incorporated by reference in their entireties.

BACKGROUND OF THE INVENTION

[003] In eukaryotic cells DNA is packaged with histones to form chromatin. Changes in the ordered structure of chromatin can lead to alterations in transcription of associated genes. Control of changes in chromatin structure (and hence of transcription) is mediated by covalent modifications to histones, most notably of their N-terminal tails. These modifications are often referred to as epigenetic because they can lead to heritable changes in gene expression, but do not affect the sequence of the DNA itself. Covalent modifications (for example, methylation, acetylation, phosphorylation, and ubiquitination) of the side chains of amino acids are enzymatically mediated. The selective addition of methyl groups to specific amino acid sites on histones is controlled by the action of a unique family of enzymes known as histone methyltransferases (HMTs).

[004] The orchestrated collection of biochemical systems behind transcriptional regulation must be tightly controlled in order for cell growth and differentiation to proceed optimally. Disease states result when these controls are disrupted by aberrant expression and/or activity of the enzymes responsible for DNA and histone modification. In human cancers, for example, there is a growing body of evidence to suggest that dysregulated epigenetic enzyme activity contributes to the uncontrolled cell proliferation associated with cancer as well as other cancer-relevant phenotypes such as enhanced cell migration and invasion. Beyond cancer, there is growing evidence for a role of epigenetic enzymes in a number of other human diseases, including metabolic diseases (such as diabetes), inflammatory diseases (such as Crohn's

disease), neurodegenerative diseases (such as Alzheimer's disease) and cardiovascular diseases. Therefore, selectively modulating the aberrant action of epigenetic enzymes may hold promise for the treatment of a range of diseases.

[005] Polycomb group (PcG) and trithorax group (trxG) proteins are known to be part of the cellular memory system. See, e.g., Francis et al. (2001) *Nat Rev Mol Cell Biol* 2:409-21 and Simon et al. (2002) *Curr Opin Genet Dev* 12:210-8. In general, PcG proteins are transcriptional repressors that maintain the "off state," and trxG proteins are transcriptional activators that maintain the "on state." Because members of PcG and trxG proteins contain intrinsic histone methyltransferase (HMTase) activity, PcG and trxG proteins may participate in cellular memory through methylation of core histones. See, e.g., Beisel et al. (2002) *Nature* 419:857-62; Cao et al. (2002) *Science* 298:1039-43; Czermin et al. (2002) *Cell* 111:185-96; Kuzmichev et al. (2002) *Genes Dev* 16:2893-905; Milne et al. (2002) *Mol Cell* 10:1107-17; Muller et al. (2002) *Cell* 111:197-208; and Nakamura et al. (2002) *Mol Cell* 10:1119-28.

[006] Biochemical and genetic studies have provided evidence that *Drosophila* PcG proteins function in at least two distinct protein complexes, the Polycomb repressive complex 1 (PRC1) and the ESC-E(Z) complex (also known as Polycomb repressive complex 2 (PRC2)). Otte et al. (2003) *Curr Opin Genet Dev* 13:448-54. Studies in *Drosophila* have demonstrated that the ESC-E(Z)/EED-EZH2 (i.e., PRC2) complexes have intrinsic histone methyltransferase activity. Although the compositions of the complexes isolated by different groups are slightly different, they generally contain EED, EZH2, SUZ12, and RbAp48 or *Drosophila* homologs thereof. However, a reconstituted complex comprising only EED, EZH2, and SUZ12 retains histone methyltransferase activity for lysine 27 of histone H3. US Patent 7,563,589.

[007] Of the various proteins making up PRC2 complexes, EZH2 (Enhancer of Zeste Homolog 2) is the catalytic subunit. The catalytic site of EZH2 in turn is present within a SET domain, a highly conserved sequence motif (named after Su(var)3–9, Enhancer of Zeste, Trithorax) that is found in several chromatin-associated proteins, including members of both the Trithorax group and Polycomb group. SET domain is characteristic of all known histone lysine methyltransferases except the H3-K79 methyltransferase DOT1.

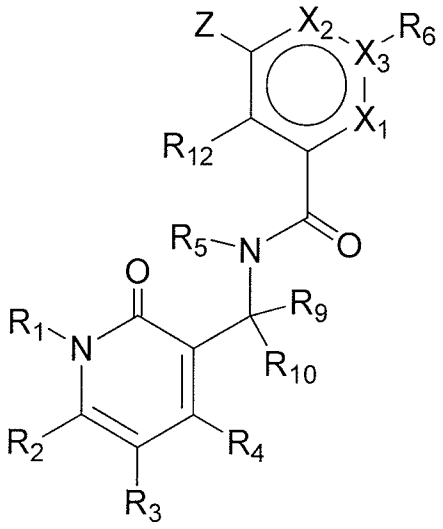
[008] In addition to Hox gene silencing, PRC2-mediated histone H3-K27 methylation has been shown to participate in X-inactivation. Plath et al. (2003) *Science* 300:131-5; Silva et al. (2003) *Dev Cell* 4:481-95. Recruitment of the PRC2 complex to Xi and subsequent

trimethylation on histone H3-K27 occurs during the initiation stage of X-inactivation and is dependent on Xist RNA. Furthermore, EZH2 and its associated histone H3-K27 methyltransferase activity were found to mark differentially the pluripotent epiblast cells and the differentiated trophectoderm, and consistent with a role of EZH2 in maintaining the epigenetic modification patterns of pluripotent epiblast cells, Cre-mediated deletion of EZH2 results in loss of histone H3-K27 methylation in the cells. Erhardt et al. (2003) *Development* 130:4235-48). Further, studies in prostate and breast cancer cell lines and tissues have revealed a strong correlation between the levels of EZH2 and SUZ12 and the invasiveness of these cancers, indicating that dysfunction of the PRC2 complex may contribute to cancer. Bracken et al. (2003) *EMBO J* 22:5323-35; Kirmizis et al. (2003) *Mol Cancer Ther* 2:113-21; Kleer et al. (2003) *Proc Natl Acad Sci USA* 100:11606-11; Varambally et al. (2002) *Nature* 419:624-9.

[009] Recently, somatic mutations of tyrosine 641 (Y641C, Y641F, Y641N, Y641S and Y641H; sometimes also referred to as Y646C, Y646F, Y646N, Y646S and Y646H, respectively) of EZH2 were reported to be associated with follicular lymphoma (FL) and the germinal center B cell-like (GCB) subtype of diffuse large B-cell lymphoma (DLBCL). Morin et al. (2010) *Nat Genet* 42:181-5. In all cases, occurrence of the mutant EZH2 gene was found to be heterozygous, and expression of both wild-type and mutant alleles was detected in the mutant samples profiled by transcriptome sequencing. It was also demonstrated that all of the mutant forms of EZH2 could be incorporated into the multi-protein PRC2 complex, but that the resulting complexes lacked the ability to catalyze methylation of the H3-K27 equivalent residue of a peptidic substrate. Hence, it was concluded that the disease-associated changes at Tyr641 of EZH2 resulted in loss of function with respect to EZH2-catalyzed H3-K27 methylation.

SUMMARY OF THE INVENTION

[010] In one aspect, the present invention features a substituted benzene compound of Formula (I) below or a pharmaceutically acceptable salt or ester thereof.



(I).

In this formula:

X_1 is N or CR_{11};

X_2 is N or CR_{13};

X_3 is N or C, and when X_3 is N, R_6 is absent;

Z is NR_7R_8, OR_7, $S(O)_aR_7$, or $CR_7R_8R_{14}$, in which a is 0, 1, or 2;

each of R_1, R_5, R_9, and R_{10}, independently, is H or C_1-C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl;

each of R_2, R_3, and R_4, independently, is $-Q_1$-T_1, in which Q_1 is a bond or C_1-C_3 alkyl linker optionally substituted with halo, cyano, hydroxyl or C_1-C_6 alkoxy, and T_1 is H, halo, hydroxyl, COOH, cyano, azido, or R_{S1}, in which R_{S1} is C_1-C_3 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxyl, C(O)O-C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl, and R_{S1} is optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, oxo, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl;

R_6 is H, halo, cyano, azido, OR_a, $-NR_aR_b$, $-C(O)R_a$, $-C(O)OR_a$, $-C(O)NR_aR_b$, $-NR_bC(O)R_a$, $-S(O)_bR_a$, $-S(O)_bNR_aR_b$, or R_{S2}, in which R_{S2} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, or 4 to 12-membered heterocycloalkyl; b is 0, 1, or 2; each of R_a and R_b, independently is H or R_{S3}, and R_{S3} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl; or R_a and R_b, together with the N atom to which they are attached, form a 4 to 12-membered heterocycloalkyl ring having 0 or 1 additional heteroatom; and each of R_{S2}, R_{S3}, and the 4 to 12-membered heterocycloalkyl ring formed by R_a and R_b, is optionally substituted with one or more $-Q_2$-T_2, wherein Q_2 is a bond or C_1-C_3 alkyl linker each optionally substituted with halo, cyano, hydroxyl or C_1-C_6 alkoxy, and T_2 is H, halo, cyano, $-OR_c$, $-NR_cR_d$, $-C(O)R_c$, $-C(O)OR_c$, $-C(O)NR_cR_d$, $-NR_dC(O)R_c$, $-NR_dC(O)OR_c$, $-S(O)_2R_c$, $-S(O)_2NR_cR_d$, or R_{S4}, in which each of R_c and R_d, independently is H or R_{S5}, each of R_{S4} and R_{S5}, independently, is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl, or R_c and R_d, together with the N atom to which they are attached, form a 4 to 12-membered heterocycloalkyl ring having 0 or 1 additional heteroatom, and each of R_{S4}, R_{S5}, and the 4 to 12-membered heterocycloalkyl ring formed by R_c and R_d, is optionally substituted with one or more $-Q_3$-T_3, wherein Q_3 is a bond or C_1-C_3 alkyl linker each optionally substituted with halo, cyano, hydroxyl or C_1-C_6 alkoxy, and T_3 is selected from the group consisting of halo, cyano, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, 5- or 6-membered heteroaryl, OR_e, $COOR_e$, $-S(O)_2R_e$, $-NR_eR_f$, and $-C(O)NR_eR_f$, each of R_e and R_f independently being H or C_1-C_6 alkyl, or $-Q_3$-T_3 is oxo; or $-Q_2$-T_2 is oxo;

R_7 is $-Q_4$-T_4, in which Q_4 is a bond, C_1-C_4 alkyl linker, or C_2-C_4 alkenyl linker, each linker optionally substituted with halo, cyano, hydroxyl or C_1-C_6 alkoxy, and T_4 is H, halo, cyano, NR_gR_h, $-OR_g$, $-C(O)R_g$, $-C(O)OR_g$, $-C(O)NR_gR_h$, $-C(O)NR_gOR_h$, $-NR_gC(O)R_h$, $-S(O)_2R_g$, or R_{S6}, in which each of R_g and R_h, independently is H or R_{S7}, each of R_{S6} and R_{S7}, independently is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 14-membered heterocycloalkyl, or 5- or 6-membered heteroaryl, and each of R_{S6} and R_{S7} is optionally substituted with one or more $-Q_5$-T_5, wherein Q_5 is a bond, C(O), $C(O)NR_k$, $NR_kC(O)$, $S(O)_2$, or C_1-C_3 alkyl linker, R_k being

H or C_1-C_6 alkyl, and T_5 is H, halo, C_1-C_6 alkyl, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, 5- or 6-membered heteroaryl, or $S(O)_qR_q$ in which q is 0, 1, or 2 and R_q is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl, and T_5 is optionally substituted with one or more substituents selected from the group consisting of halo, C_1-C_6 alkyl, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl except when T_5 is H, halo, hydroxyl, or cyano; or $-Q_5$-T_5 is oxo;

each of R_8, R_{11}, R_{12}, and R_{13}, independently, is H, halo, hydroxyl, COOH, cyano, R_{S8}, OR_{S8}, or $COOR_{S8}$, in which R_{S8} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, 4 to 12-membered heterocycloalkyl, amino, mono-C_1-C_6 alkylamino, or di-C_1-C_6 alkylamino, and R_{S8} is optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, and di-C_1-C_6 alkylamino; or R_7 and R_8, together with the N atom to which they are attached, form a 4 to 12-membered heterocycloalkyl ring having 0 to 2 additional heteroatoms, or R_7 and R_8, together with the C atom to which they are attached, form C_3-C_8 cycloalkyl or a 4 to 12-membered heterocycloalkyl ring having 1 to 3 heteroatoms, and each of the 4 to 12-membered heterocycloalkyl ring or C_3-C_8 cycloalkyl formed by R_7 and R_8 is optionally substituted with one or more $-Q_6$-T_6, wherein Q_6 is a bond, C(O), $C(O)NR_m$, $NR_mC(O)$, $S(O)_2$, or C_1-C_3 alkyl linker, R_m being H or C_1-C_6 alkyl, and T_6 is H, halo, C_1-C_6 alkyl, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, 5- or 6-membered heteroaryl, or $S(O)_pR_p$ in which p is 0, 1, or 2 and R_p is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl, and T_6 is optionally substituted with one or more substituents selected from the group consisting of halo, C_1-C_6 alkyl, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4

to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl except when T_6 is H, halo, hydroxyl, or cyano; or $-Q_6-T_6$ is oxo; and

R_{14} is absent, H, or C_1-C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl;

provided that the compound is not

N-(5-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)furan-2-carboxamide,

N,N'-(5-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-1,3-phenylene)diacetamide,

N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-pivalamidobenzamide,

3-(3,4-dihydro-2H-benzo[b][1,4]dioxepine-7-sulfonamido)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)benzamide,

N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3,5-dimethoxybenzamide,

N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3,4,5-trimethoxybenzamide,

3-allyl-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-4,5-dimethoxybenzamide,

4-(2-amino-2-oxoethoxy)-3-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-methoxybenzamide,

3-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-4-hydroxy-5-methoxybenzamide, or

3-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-methoxy-4-propoxybenzamide.

[011] In another aspect, the present invention features a substituted benzene compound of Formula (I) above or a pharmaceutically acceptable salt or ester thereof, in which

X_1 is N or CR_{11};

X_2 is N or CR_{13};

X_3 is N or C, and when X_3 is N, R_6 is absent;

Z is NR_7R_8, OR_7, $S(O)_aR_7$, or $CR_7R_8R_{14}$, in which a is 0, 1, or 2;

each of R_1, R_5, R_9, and R_{10}, independently, is H or C_1-C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl;

each of R_2, R_3, and R_4, independently, is $-Q_1$-T_1, in which Q_1 is a bond or C_1-C_3 alkyl linker optionally substituted with halo, cyano, hydroxyl or C_1-C_6 alkoxy, and T_1 is H, halo, hydroxyl, COOH, cyano, azido, or R_{S1}, in which R_{S1} is C_1-C_3 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxyl, C(O)O-C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl, and R_{S1} is optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, oxo, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl;

R_6 is H, halo, cyano, azido, $-NR_aR_b$, $-C(O)R_a$, $-C(O)OR_a$, $-C(O)NR_aR_b$, $-NR_bC(O)R_a$, $-S(O)_bR_a$, $-S(O)_bNR_aR_b$, or R_{S2}, in which R_{S2} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, or 4 to 12-membered heterocycloalkyl, b is 0, 1, or 2, each of R_a and R_b, independently is H or R_{S3}, and R_{S3} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl; or R_a and R_b, together with the N atom to which they are attached, form a 4 to 12-membered heterocycloalkyl ring having 0 or 1 additional heteroatom; and each of R_{S2}, R_{S3}, and the 4 to 12-membered heterocycloalkyl ring formed by R_a and R_b, is optionally substituted with one or more $-Q_2$-T_2, wherein Q_2 is a bond or C_1-C_3 alkyl linker each optionally substituted with halo, cyano, hydroxyl or C_1-C_6 alkoxy, and T_2 is H, halo, cyano, $-OR_c$, $-NR_cR_d$, $-C(O)R_c$, $-C(O)OR_c$, $-C(O)NR_cR_d$, $-NR_dC(O)R_c$, $-NR_dC(O)OR_c$, $-S(O)_2R_c$, $-S(O)_2NR_cR_d$, or R_{S4}, in which each of R_c and R_d, independently is H or R_{S5}, each of R_{S4} and R_{S5}, independently, is C_1-C_6 alkyl, C_3-C_8

cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl, or R_c and R_d, together with the N atom to which they are attached, form a 4 to 12-membered heterocycloalkyl ring having 0 or 1 additional heteroatom, and each of R_{S4}, R_{S5}, and the 4 to 12-membered heterocycloalkyl ring formed by R_c and R_d, is optionally substituted with one or more $-Q_3$-T_3, wherein Q_3 is a bond or C_1-C_3 alkyl linker each optionally substituted with halo, cyano, hydroxyl or C_1-C_6 alkoxy, and T_3 is selected from the group consisting of halo, cyano, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, 5- or 6-membered heteroaryl, OR_e, $COOR_e$, $-S(O)_2R_e$, $-NR_eR_f$, and $-C(O)NR_eR_f$, each of R_e and R_f independently being H or C_1-C_6 alkyl, or $-Q_3$-T_3 is oxo; or$-Q_2$-T_2 is oxo;

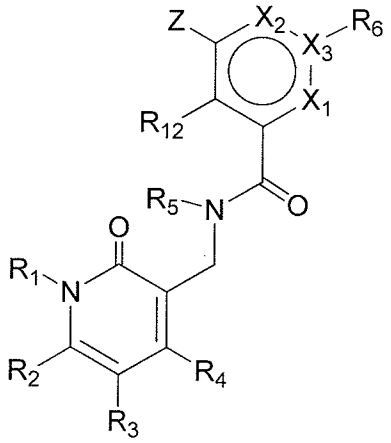
R_7 is $-Q_4$-T_4, in which Q_4 is a bond, C_1-C_4 alkyl linker, or C_2-C_4 alkenyl linker, each linker optionally substituted with halo, cyano, hydroxyl or C_1-C_6 alkoxy, and T_4 is H, halo, cyano, NR_gR_h, $-OR_g$, $-C(O)R_g$, $-C(O)OR_g$, $-C(O)NR_gR_h$, $-C(O)NR_gOR_h$, $-NR_gC(O)R_h$, $-S(O)_2R_g$, or R_{S6}, in which each of R_g and R_h, independently is H or R_{S7}, each of R_{S6} and R_{S7}, independently is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 14-membered heterocycloalkyl, or 5- or 6-membered heteroaryl, and each of R_{S6} and R_{S7} is optionally substituted with one or more $-Q_5$-T_5, wherein Q_5 is a bond, C(O), $C(O)NR_k$, $NR_kC(O)$, $S(O)_2$, or C_1-C_3 alkyl linker, R_k being H or C_1-C_6 alkyl, and T_5 is H, halo, C_1-C_6 alkyl, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, 5- or 6-membered heteroaryl, or $S(O)_qR_q$ in which q is 0, 1, or 2 and R_q is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl, and T_5 is optionally substituted with one or more substituents selected from the group consisting of halo, C_1-C_6 alkyl, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl except when T_5 is H, halo, hydroxyl, or cyano; or $-Q_5$-T_5 is oxo; provided that (i) R_7 is not $C(O)R_g$ or $-S(O)_2R_g$ when Z is NR_7R_8; (ii) R_7 is not C_1-C_6 alkyl when Z is OR_7, and (iii) R_7 is not H;

each of R_8, R_{11}, R_{12}, and R_{13}, independently, is H, halo, hydroxyl, COOH, cyano, R_{S8}, OR_{S8}, or $COOR_{S8}$, in which R_{S8} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6

alkynyl, C_3-C_8 cycloalkyl, 4 to 12-membered heterocycloalkyl, amino, mono-C_1-C_6 alkylamino, or di-C_1-C_6 alkylamino, and R_{S8} is optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, and di-C_1-C_6 alkylamino; or R_7 and R_8, together with the N atom to which they are attached, form a 4 to 12-membered heterocycloalkyl ring having 0 to 2 additional heteroatoms, or R_7 and R_8, together with the C atom to which they are attached, form C_3-C_8 cycloalkyl or a 4 to 12-membered heterocycloalkyl ring having 1 to 3 heteroatoms, and each of the 4 to 12-membered heterocycloalkyl rings or C_3-C_8 cycloalkyl formed by R_7 and R_8 is optionally substituted with one or more $-Q_6$-T_6, wherein Q_6 is a bond, C(O), C(O)NR_m, NR_mC(O), $S(O)_2$, or C_1-C_3 alkyl linker, R_m being H or C_1-C_6 alkyl, and T_6 is H, halo, C_1-C_6 alkyl, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, 5- or 6-membered heteroaryl, or $S(O)_pR_p$ in which p is 0, 1, or 2 and R_p is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl, and T_6 is optionally substituted with one or more substituents selected from the group consisting of halo, C_1-C_6 alkyl, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl except when T_6 is H, halo, hydroxyl, or cyano; or $-Q_6$-T_6 is oxo; and

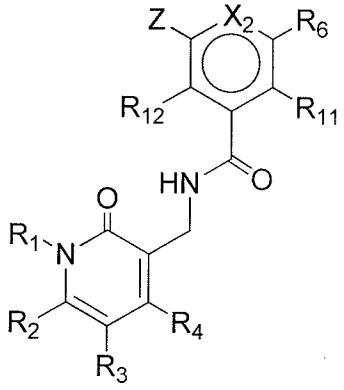
R_{14} is absent, H, or C_1-C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl.

[012] One subset of the compounds of Formula (I) includes those of Formula (Ia):

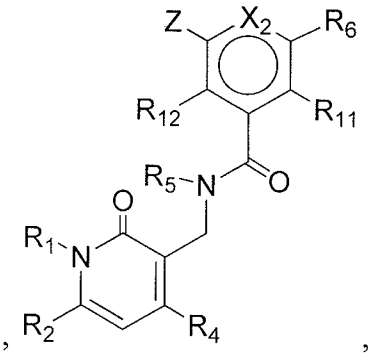


(Ia).

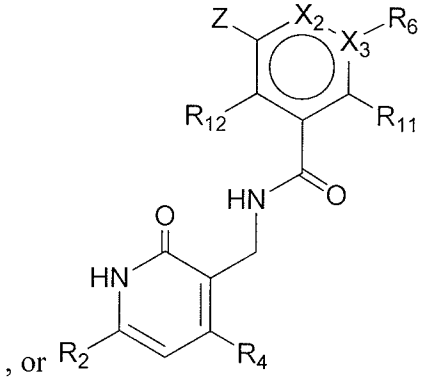
[013] Another subset of the compounds of Formula (I) includes those of Formula (Ib), (Ic), or (Id):



(Ib)

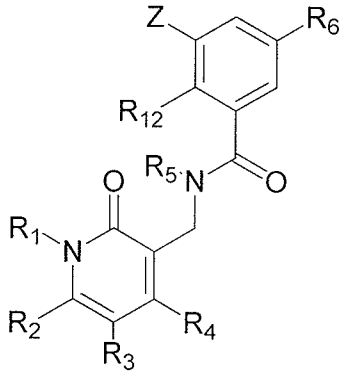


(Ic)

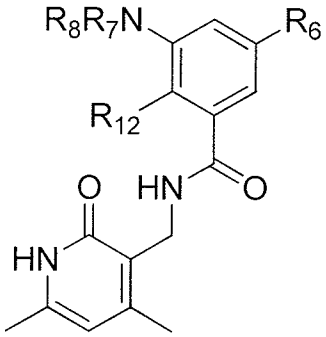


(Id)

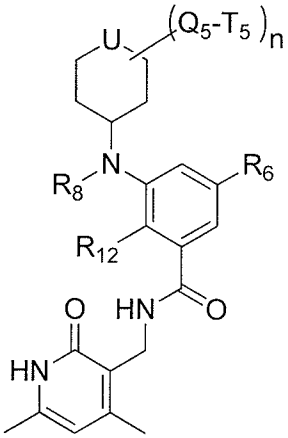
[014] Still another subset of the compounds of Formula (I) includes those of Formula (Ie), (II) or (IIA):



(Ie)



(II)



(IIA)

[015] The compounds of Formulae (I), (Ia), (Ib), (Ic), (Id), (Ie), (II), and (IIA) can include one or more of the following features:

[016] X_1 is CR_{11} and X_2 is CR_{13}.

[017] X_1 is CR_{11} and X_2 is N.

[018] X_1 is N and X_2 is CR_{13}.

[019] X_1 is N and X_2 is N.

[020] Z is NR_7R_8.

[021] Z is $CR_7R_8R_{14}$.

[022] Z is OR_7.

[023] Z is $S(O)_aR_7$, in which a is 0, 1, or 2.

[024] Z is SR_7.

[025] R_6 is halo, C_1-C_3 alkyl, C_2-C_6 alkenyl, C_3-C_6 cycloalkyl, C(O)H, or -$C(O)R_a$, in which R_a is C_1-C_6 alkyl or 4 to 12-membered (e.g., 4 to 7-membered) heterocycloalkyl.

[026] R_6 is 4 to 12-membered (e.g., 4 to 7-membered) heterocycloalkyl optionally substituted with one or more $-Q_2$-T_2, in which $-Q_2$-T_2 is oxo or Q_2 is a bond and T_2 is C_1-C_6 alkyl, -OR_c, -NR_cR_d, -$C(O)R_c$, -$C(O)OR_c$, -$S(O)_2R_c$, or 4 to 12-membered (e.g., 4 to 7-membered) heterocycloalkyl optionally substituted with one or more $-Q_3$-T_3.

[027] $-Q_2$-T_2 is not H.

[028] Q_3 is a bond or C_1-C_3 alkyl linker and T_3 is selected from the group consisting of C_1-C_3 alkyl, OR_e, -$S(O)_2R_e$, or -NR_eR_f.

[029] R_6 is piperidinyl, 2,2,6,6-tetramethyl-piperidinyl, 1,2,3,6-tetrahydropyridinyl, 2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridinyl, piperazinyl, morpholinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, or pyrrolidinyl.

[030] R_6 is F, Br, or Cl.

[031] R_7 is not H.

[032] R_7 is C_1-C_6 alkyl, C_3-C_8 cycloalkyl or 4 to 14-membered (e.g., 4 to 7-membered) heterocycloalkyl, each optionally substituted with one or more $-Q_5$-T_5.

[033] R_7 is piperidinyl, tetrahydropyran, tetrahydrothiopyran, oxetanyl, azetidinyl, pyrrolidinyl, 1,4-dioxaspiro[4.5]decanyl, 1-oxaspiro[4.5]decanyl, 3'H-spiro[cyclohexane-1,1'-isobenzofuran]-3'-one-4-yl, 7'H-spiro[cyclohexane-1,5'-furo[3,4-b]pyridin]-7'-one-4-yl, 3'H-

spiro[cyclohexane-1,1'-furo[3,4-c]pyridin]-3'-one-4-yl, 1-azaspiro[4.5]decan-2-one-8-yl, cyclobutyl, cyclopentyl, or cyclohexyl, each optionally substituted with one or more $-Q_5-T_5$.

[034] T_5 is H, halo, C_1-C_6 alkyl, C_1-C_6 alkoxyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, or 4 to 12-membered (e.g., 4 to 7-membered) heterocycloalkyl.

[035] Q_5 is a bond and T_5 is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, or 4 to 12-membered (e.g., 4 to 7-membered) heterocycloalkyl.

[036] Q_5 is a bond and T_5 is H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, 4 to 12-membered heterocycloalkyl, 5- or 6-membered heteroaryl, amino, mono-C_1-C_6 alkylamino, or di-C_1-C_6 alkylamino, T_5 being optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, C_1-C_6 alkoxyl, or C_3-C_8 cycloalkyl.

[037] Q_5 is CO, $S(O)_2$, or NHC(O); and T_5 is C_1-C_6 alkyl, C_1-C_6 alkoxyl, C_3-C_8 cycloalkyl, or 4 to 12-membered (e.g., 4 to 7-membered) heterocycloalkyl.

[038] Q_5 is C_1-C_3 alkyl linker and T_5 is H or C_6-C_{10} aryl.

[039] Q_5 is C_1-C_3 alkyl linker and T_5 is C_3-C_8 cycloalkyl, 4 to 12-membered (e.g., 4 to 7-membered) heterocycloalkyl, or $S(O)_qR_q$.

[040] R_{11} is H.

[041] R_7 is cyclopentyl or cyclohexyl, each optionally substituted with one $-Q_5-T_5$.

[042] Q_5 is NHC(O) and T_5 is C_1-C_6 alkyl or C_1-C_6 alkoxy.

[043] R_7 is isopropyl.

[044] Each of R_2 and R_4, independently is C_1-C_3 alkyl optionally substituted withC_1-C_6 alkoxyl.

[045] Each of R_2 and R_4 is methyl.

[046] R_1 is H.

[047] R_{12} is H, methyl, ethyl, ethenyl, or halo.

[048] R_{12} is methyl.

[049] R_{12} is ethyl.

[050] R_{12} is ethenyl.

[051] R_8 is H, methyl, or ethyl.

[052] R_8 is methyl.

[053] R_8 is ethyl.

[054] R_8 is ethenyl or propenyl.

[055] R_8 is 4 to 12-membered (e.g., 4 to 7-membered) heterocycloalkyl, such as piperidinyl or tetrahydropyranyl.

[056] Z is NR_7R_8 or $CR_7R_8R_{14}$ wherein R_7 and R_8, together with the atom to which they are attached, form a ring selected from the group consisting of piperidinyl, morpholinyl, piperazinyl, azetidinyl, pyrrolidinyl, 2-oxa-5-azabicyclo[2.2.1]heptan-5-yl, 1,4-dioxa-8-azaspiro[4.5]decanyl, and cyclohexenyl, each optionally substituted with one $-Q_6$-T_6.

[057] R_{13} is H or methyl.

[058] R_{13} is H.

[059] R_3 is H.

[060] Z is NR_7R_8, OR_7, or $S(O)_aR_7$; R_1 is H or C_1-C_6 alkyl optionally substituted with one or more substituents selected from hydroxyl, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, and C_6-C_{10} aryl; each of R_2 and R_4 independently, is $-Q_1$-T_1 , in which Q_1 is a bond or C_1-C_3 alkyl linker optionally substituted with one or more substituents selected from halo and hydroxyl, and T_1 is H, halo, or azido; R_3 is H or halo; R_5 is H or C_1-C_6 alkyl; R_6 is H, halo, cyano, azido, OR_a, $-NR_aR_b$, $-C(O)NR_aR_b$, $-S(O)_bR_a$, or R_{S2}; wherein R_{S2} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or 4 to 12-membered heterocycloalkyl, and wherein each of R_a and R_b, independently is H, C_1-C_6 alkyl, or 4 to 12-membered heterocycloalkyl,; or R_a and R_b, together with the N atom to which they are attached, form a 4 to 12-membered heterocycloalkyl ring having 0 or 1 additional heteroatom; and each of R_a, R_{S2} and the 4 to 12-membered heterocycloalkyl ring formed by R_a and R_b, is optionally substituted with one or more $-Q_2$-T_2; wherein Q_2 is a bond or C_1-C_3 alkyl linker, and T_2 is H, halo, $-OR_c$, $-NR_cR_d$, $-C(O)OR_c$, or C_1-C_6 alkyl, in which each of R_c and R_d, independently is H or C_1-C_6 alkyl, or R_c and R_d, together with the N atom to which they are attached, form a 4 to 12-membered heterocycloalkyl ring having 0 or 1 additional heteroatom and optionally substituted with C_1-C_6 alkyl; R_7 is $-Q_4$-T_4, in which Q_4 is a bond or C_1-C_4 alkyl linker and T_4 is H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, C(O)-C_{1-6} alkyl, C(O)-C_{3-6} cycloalkyl, or 4 to 14-membered heterocycloalkyl, each optionally substituted with one or more $-Q_5$-T_5; R_8 is H, C_1-C_6 alkyl optionally substituted with halo, hydroxyl or C_1-C_6 alkoxyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, or 4 to 7-membered heterocycloalkyl; or R_7 and R_8, together with the N atom to which they are attached, form a 4 to 12-membered heterocycloalkyl ring having 0 to 2 additional heteroatoms, and the 4 to 12-membered heterocycloalkyl ring formed by R_7 and R_8 is optionally substituted with one or

more $-Q_6$-T_6; and R_{12} is halo, C_1-C_6 alkoxyl, or C_1-C_6 alkyl optionally substituted with halo or C_2-C_6 alkenyl.

[061] R_1 is H or C_1-C_6 alkyl optionally substituted one or more times with a substituent selected from hydroxyl, C_1-C_6 alkoxyl and C_6-C_{10} aryl; R_7 is $-Q_4$-T_4, in which Q_4 is a bond or a C_1-C_4 alkyl linker, and T_4 is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, C(O)- C_1-C_6 alkyl, C(O)- C_3-C_6 cycloalkyl, dihydropyranyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperidinyl, pyrrolidinyl, azetidinyl and oxetanyl, each optionally substituted with one or more substituents independently selected from oxo and $-Q_5$-T_5; R_8 is H or C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl or C_3-C_8 cycloalkyl; and R_{12} is halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl or C_1-C_6 alkoxyl.

[062] Z is NR_7R_8 or SR_7; R_6 is H, halo, cyano, OR_a, $-C(O)NR_aR_b$, $-S(O)_2R_a$, or R_{S2}; wherein R_{S2} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or 4 to 12-membered heterocycloalkyl, and wherein each of R_a and R_b, independently is H or C_1-C_6 alkyl; or R_a and R_b, together with the N atom to which they are attached, form a 4 to 12-membered heterocycloalkyl ring having 0 or 1 additional heteroatom; and each of R_{S2} and the 4 to 12-membered heterocycloalkyl ring formed by R_a and R_b, is optionally substituted with one or more $-Q_2$-T_2; wherein Q_2 is a bond or C_1-C_3 alkyl linker, and T_2 is H, halo, $-OR_c$, $-NR_cR_d$, $-C(O)OC_1$-C_6 alkyl, or C_1-C_6 alkyl, in which each of R_c and R_d, independently is H or C_1-C_6 alkyl, or R_c and R_d, together with the N atom to which they are attached, form a 4 to 12-membered heterocycloalkyl ring having 0 or 1 additional heteroatom and 0 or 1 C_1-C_6 alkyl substituents; R_7 is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, dihydropyranyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperidinyl, pyrrolidinyl, azetidinyl and oxetanyl, each optionally substituted with one or more substituents independently selected from oxo and $-Q_5$-T_5; and R_{12} is halo or C_1-C_6 alkyl.

[063] R_2, R_4 and R_{12} are each independently C_1-C_6 alkyl and R_5 is H.

[064] R_7 is cyclohexyl, dihydropyranyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperidinyl, pyrrolidinyl, azetidinyl oxetanyl, 1,4-dioxaspiro[4.5]decan-8-yl, 1-oxaspiro[4.5]decan-8-yl, 3'H-spiro[cyclohexane-1,1'-isobenzofuran]-4-yl, 7'H-spiro[cyclohexane-1,5'-furo[3,4-b]pyridin]-4-yl, 3'H-spiro[cyclohexane-1,1'-furo[3,4-c]pyridin]-4-yl, or 1-azaspiro[4.5]decan-8-yl, each substituted with one or more $-Q_5$-T_5.

[065] Z is selected from the group consisting of piperidinyl, morpholinyl, piperazinyl, azetidinyl, pyrrolidinyl, 2-oxa-5-azabicyclo[2.2.1]heptan-5-yl, 1,4-dioxa-8-azaspiro[4.5]decan-8-yl, and cyclohexenyl, each optionally substituted with one $-Q_6$-T_6.

[066] R_6 is halo and Z is $S(O)_aR_7$, in which a is 0, 1, or 2 and R_7 is C_1-C_6 alkyl, C_3-C_8 cycloalkyl or 4 to 7-membered heterocycloalkyl and R_7 is optionally substituted with one or more $-Q_5$-T_5.

[067] R_6 is halo and Z is OR_7, in which R_7 is 4 to 7-membered heterocycloalkyl optionally substituted with one or more $-Q_5$-T_5.

[068] R_6 is $-S(O)_bR_a$ or azido, in which b is 0, 1, or 2 and R_a is C_1-C_6 alkyl or C_3-C_8 cycloalkyl; and Z is NR_7R_8, in which R_7 is C_3-C_8 cycloalkyl or 4 to 14-membered heterocycloalkyl, each optionally substituted with one or more $-Q_5$-T_5; and R_8 is H or C_1-C_6 alkyl.

[069] R_6 is halo and Z is NR_7R_8 or $CR_7R_8R_{14}$ wherein R_7 and R_8, together with the atom to which they are attached, form a 4 to 11-membered heterocycloalkyl ring having 1 to 3 heteroatoms or C_3-C_8 cycloalkyl, each optionally substituted with one or more $-Q_6$-T_6.

[070] U is O, S, N-Q_5-T_5, or CH-Q_5-T_5.

[071] n is 0, 1, or 2.

[072] R_{12} is Cl, Br, or methyl.

[073] One or more $-Q_5$-T_5 are oxo.

[074] U is CH-Q_5-T_5 and n is 0

[075] One or more $-Q_6$-T_6 are oxo.

[076] Q_6 is a bond or C(O) and T_6 is C_1-C_6 alkyl or C_1-C_6 alkoxy.

[077] The present invention also provides pharmaceutical compositions comprising one or more pharmaceutically acceptable carriers and one or more compounds selected from those of any of the Formulae described herein, and N-(5-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)furan-2-carboxamide, N,N'-(5-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-1,3-phenylene)diacetamide, N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-pivalamidobenzamide, 3-(3,4-dihydro-2H-benzo[b][1,4]dioxepine-7-sulfonamido)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)benzamide, N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3,5-dimethoxybenzamide, N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3,4,5-trimethoxybenzamide, 3-allyl-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-4,5-dimethoxybenzamide, 4-(2-amino-2-oxoethoxy)-3-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-methoxybenzamide, 3-chloro-N-((4,6-dimethyl-2-oxo-1,2-

dihydropyridin-3-yl)methyl)-4-hydroxy-5-methoxybenzamide, and 3-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-methoxy-4-propoxybenzamide.

[078] Another aspect of this invention is a method of treating or preventing cancer. The method includes administering to a subject in need thereof a therapeutically effective amount of one or more compounds selected from those of any of the Formulae described herein, and N-(5-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)furan-2-carboxamide, N,N'-(5-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-1,3-phenylene)diacetamide, N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-pivalamidobenzamide, 3-(3,4-dihydro-2H-benzo[b][1,4]dioxepine-7-sulfonamido)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)benzamide, N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3,5-dimethoxybenzamide, N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3,4,5-trimethoxybenzamide, 3-allyl-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-4,5-dimethoxybenzamide, 4-(2-amino-2-oxoethoxy)-3-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-methoxybenzamide, 3-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-4-hydroxy-5-methoxybenzamide, and 3-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-methoxy-4-propoxybenzamide.

[079] Unless otherwise stated, any description of a method of treatment includes uses of the compounds to provide such treatment or prophylaxis as is described in the specification, as well as uses of the compounds to prepare a medicament to treat or prevent such condition. The treatment includes treatment of human or non-human animals including rodents and other disease models.

[080] For example, the method comprises the step of administering to a subject having a cancer with aberrant H3-K27 methylation an effective amount of one or more compounds of Formulae described herein, wherein the compound(s) inhibits histone methyltransferase activity of EZH2, thereby treating the cancer. Examples of aberrant H3-K27 methylation may include a global increase in and/or altered distribution of H3-K27 di or tri-methylation within the cancer cell chromatin.

[081] For example, the cancer is selected from the group consisting of cancers that overexpress EZH2 or other PRC2 subunits, contain loss-of-function mutations in H3-K27 demethylases such as UTX, or overexpress accessory proteins such as PHF19/PCL3 capable of

increasing and or mislocalizing EZH2 activity (see references in Sneeringer *et al. Proc Natl Acad Sci USA* 107(49):20980-5, 2010).

[082] For example, the method comprises the step of administering to a subject having a cancer overexpressing EZH2 a therapeutically effective amount of one or more compounds of Formulae described herein, wherein the compound(s) inhibits histone methyltransferase activity of EZH2, thereby treating the cancer.

[083] For example, the method comprises the step of administering to a subject having a cancer with a loss-of-function mutation in the H3-K27 demethylase UTX a therapeutically effective amount of one or more compounds of Formulae described herein, wherein the compound(s) inhibits histone methyltransferase activity of EZH2, thereby treating the cancer

[084] For example, the method comprises the step of administering to a subject having a cancer overexpressing an accessory component(s) of the PRC2, such as PHF19/PCL3, a therapeutically effective amount of one or more compounds of Formulae described herein, wherein the compound(s) inhibits histone methyltransferase activity of EZH2, thereby treating the cancer

[085] In still another aspect, this invention relates to a method of modulating the activity of the wild-type EZH2, the catalytic subunit of the PRC2 complex which catalyzes the mono- through tri-methylation of lysine 27 on histone H3 (H3-K27). For example, the present invention relates to a method of inhibiting the activity of EZH2 in a cell. This method can be conducted either *in vitro* or *in vivo*.

[086] In yet another aspect, this invention features to a method of inhibiting in a subject conversion of H3-K27 to trimethylated H3-K27. The method comprises administering to a subject a therapeutically effective amount of one or more of the compound of Formulae described herein to inhibit histone methyltransferase activity of EZH2, thereby inhibiting conversion of H3-K27 to trimethylated H3-K27 in the subject.

[087] For example, the method comprises the step of administering to a subject having a cancer expressing a Y641 mutant of EZH2 a therapeutically effective amount of one or more compounds of Formulae described herein, wherein the compound(s) inhibits histone methyltransferase activity of EZH2, thereby treating the cancer.

[088] For example, the cancer is selected from the group consisting of follicular lymphoma and diffuse large B-cell lymphoma (DLBCL) of germinal center B cell-like (GCB) subtype.

For example, the cancer is lymphoma, leukemia or melanoma. Preferably, the lymphoma is non-Hodgkin lymphoma, follicular lymphoma or diffuse large B-cell lymphoma. Alternatively, the leukemia is chronic myelogenous leukemia (CML), acute myeloid leukemia, acute lymphocytic leukemia or mixed lineage leukemia.

[089] The precancerous condition is myelodysplastic syndromes (MDS, formerly known as preleukemia).

[090] For example, the cancer is a hematological cancer.

[091] For example, the method comprises the step of administering to a subject having a cancer expressing a Y641 mutant of EZH2 a therapeutically effective amount of one or more compounds of Formulae described herein, wherein the compound(s) selectively inhibits histone methyltransferase activity of the Y641 mutant of EZH2, thereby treating the cancer.

[092] For example, the method further comprises the steps of performing an assay to detect a Y641 mutant of EZH2 in a sample comprising cancer cells from a subject having a cancer.

[093] In still another aspect, this invention relates to a method of modulating the activity of the wild-type and mutant histone methyltransferase EZH2, the catalytic subunit of the PRC2 complex which catalyzes the mono- through tri-methylation of lysine 27 on histone H3 (H3-K27). For example, the present invention relates to a method of inhibiting the activity of certain mutant forms of EZH2 in a cell. The mutant forms of EZH2 include a substitution of another amino acid residue for tyrosine 641 (Y641, also Tyr641) of wild-type EZH2. The method includes contacting the cell with an effective amount of one or more of the compound of any Formula described herein. This method can be conducted either *in vitro* or *in vivo*.

[094] In yet another aspect, this invention features to a method of inhibiting in a subject conversion of H3-K27 to trimethylated H3-K27. The method comprises administering to a subject expressing a Y641 mutant of EZH2 a therapeutically effective amount of one or more of the compound of any Formula described herein to inhibit histone methyltransferase activity of EZH2, thereby inhibiting conversion of H3-K27 to trimethylated H3-K27 in the subject. For example, the histone methyltransferase activity inhibited is that of the Y641 mutant of EZH2. For example, the compound of this invention selectively inhibits histone methyltransferase activity of the Y641 mutant of EZH2. For example, the Y641 mutant of EZH2 is selected from the group consisting of Y641C, Y641F, Y641H, Y641N, and Y641S.

[095] The method of inhibiting in a subject conversion of H3-K27 to trimethylated H3-K27 may also comprise performing an assay to detect a Y641 mutant of EZH2 in a sample from a subject before administering to the subject expressing a Y641 mutant of EZH2 a therapeutically effective amount of one or more of the compound of any Formula described herein. For example, performing the assay to detect the Y641 mutant of EZH2 includes whole-genome resequencing or target region resequencing that detects a nucleic acid encoding the Y641 mutant of EZH2. For example, performing the assay to detect the Y641 mutant of EZH2 includes contacting the sample with an antibody that binds specifically to a polypeptide or fragment thereof characteristic of the Y641 mutant of EZH2. For example, performing the assay to detect the Y641 mutant of EZH2 includes contacting the sample under highly stringent conditions with a nucleic acid probe that hybridizes to a nucleic acid encoding a polypeptide or fragment thereof characteristic of the Y641 mutant of EZH2.

[096] Further, the invention also relates to a method of identifying an inhibitor of a Y641 mutant of EZH2. The method comprises the steps of combining an isolated Y641 mutant of EZH2 with a histone substrate, a methyl group donor, and a test compound, wherein the histone substrate comprises a form of H3-K27 selected from the group consisting of unmethylated H3-K27, monomethylated H3-K27, dimethylated H3-K27, and any combination thereof; and performing an assay to detect methylation of H3-K27 (e.g., formation of trimethylated H3-K27) in the histone substrate, thereby identifying the test compound as an inhibitor of the Y641 mutant of EZH2 when methylation of H3-K27 (e.g., formation of trimethylated H3-K27) in the presence of the test compound is less than methylation of H3-K27 (e.g., formation of trimethylated H3-K27) in the absence of the test compound.

[097] In one embodiment, performing the assay to detect methylation of H3-K27 in the histone substrate comprises measuring incorporation of labeled methyl groups.

[098] In one embodiment, the labeled methyl groups are isotopically labeled methyl groups.

[099] In one embodiment, performing the assay to detect methylation of H3-K27 in the histone substrate comprises contacting the histone substrate with an antibody that binds specifically to trimethylated H3-K27.

[0100] Also within the scope of the invention is a method of identifying a selective inhibitor of a Y641 mutant of EZH2. The method comprises the steps of combining an isolated Y641 mutant of EZH2 with a histone substrate, a methyl group donor, and a test compound, wherein

the histone substrate comprises a form of H3-K27 selected from the group consisting of monomethylated H3-K27, dimethylated H3-K27, and a combination of monomethylated H3-K27 and dimethylated H3-K27, thereby forming a test mixture; combining an isolated wild-type EZH2 with a histone substrate, a methyl group donor, and a test compound, wherein the histone substrate comprises a form of H3-K27 selected from the group consisting of monomethylated H3-K27, dimethylated H3-K27, and a combination of monomethylated H3-K27 and dimethylated H3-K27, thereby forming a control mixture; performing an assay to detect trimethylation of the histone substrate in each of the test mixture and the control mixture; calculating the ratio of (a) trimethylation with the Y641 mutant of EZH2 and the test compound (M+) to (b) trimethylation with the Y641 mutant of EZH2 without the test compound (M-); calculating the ratio of (c) trimethylation with wild-type EZH2 and the test compound (WT+) to (d) trimethylation with wild-type EZH2 without the test compound (WT-); comparing the ratio (a)/(b) with the ratio (c)/(d); and identifying the test compound as a selective inhibitor of the Y641 mutant of EZH2 when the ratio (a)/(b) is less than the ratio (c)/(d).

[0101] The present invention further provides a method of identifying a subject as a candidate for treatment with one or more compounds of the invention. The method comprises the steps of performing an assay to detect a Y641 mutant of EZH2 in a sample from a subject; and identifying a subject expressing a Y641 mutant of EZH2 as a candidate for treatment with one or more compounds of the invention, wherein the compound(s) inhibits histone methyltransferase activity of EZH2.

[0102] Still another aspect of the invention is a method of inhibiting conversion of H3-K27 to trimethylated H3-K27. The method comprises the step of contacting a Y641 mutant of EZH2 with a histone substrate comprising H3-K27 and an effective amount of a compound of the present invention, wherein the compound inhibits histone methyltransferase activity of EZH2, thereby inhibiting conversion of H3-K27 to trimethylated H3-K27.

[0103] Further, the compounds or methods described herein can be used for research (e.g., studying epigenetic enzymes) and other non-therapeutic purposes.

[0104] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. In the specification, the singular forms also include the plural unless the context clearly dictates otherwise. Although methods and materials similar or equivalent to those

described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, patents and other references mentioned herein are incorporated by reference. The references cited herein are not admitted to be prior art to the claimed invention. In the case of conflict, the present specification, including definitions, will control. In addition, the materials, methods and examples are illustrative only and are not intended to be limiting.

[0105] Other features and advantages of the invention will be apparent from the following detailed description and claims.

BRIEF DESCRIPTIONS OF FIGURES

[0106] Figure 1 (A) is an idealized plot of cell count (i.e., cell number) as a function of time showing exponential proliferation during log-phase cell growth.

[0107] Figure 1(B) is an idealized plot of ln(cell count) as a function of time for the data from panel (A).

[0108] Figure 2 is a graph showing biphasic cell growth curves in the presence of an antiproliferative compound for which there is a delay before the impact of the compound on cell growth is realized. The compound begins to affect cell growth at the time point labeled "start of impact." The solid circles represent idealized data for the vehicle (or solvent) control sample that is not treated with compound. The other symbols represent biphasic growth curves for cells treated with different concentrations of compound (i.e., drug).

[0109] Figure 3 is a replot of k_p as a function of compound concentration for (A) a cytostatic and (B) a cytotoxic compound, illustrating the graphic determination of the LCC for a cytotoxic agent. Note that for a cytostatic compound (panel A), the value of k_p can never drop below zero.

[0110] Figure 4 is a diagram showing tumor growth of WSU-DLCL2 xenograft bearing mice treated with Compound 222 over 27 days.

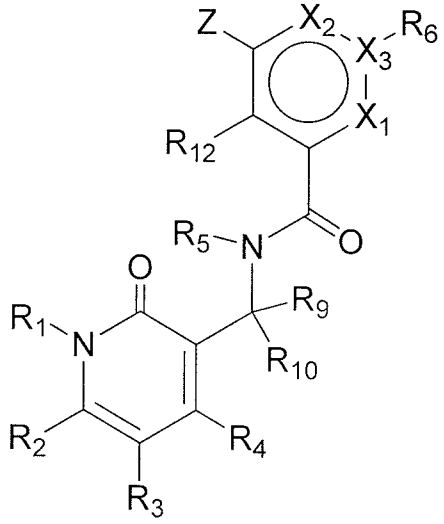
[0111] Figure 5 is a diagram showing lobal H3K27me3 methylation in WSU-DLCL2 tumors from mice treated with Compound 222 or vehicle for 27 days.

DETAILED DESCRIPTION OF THE INVENTION

[0112] The present invention provides novel substituted benzene compounds, synthetic methods for making the compounds, pharmaceutical compositions containing them and various uses of the compounds.

1. Substituted Benzene Compounds

[0113] The present invention provides the compounds of Formula (I):



(I).

In this formula:

X_1 is N or CR_{11};

X_2 is N or CR_{13};

X_3 is N or C, and when X_3 is N, R_6 is absent;

Z is NR_7R_8, OR_7, $S(O)_aR_7$, or $CR_7R_8R_{14}$, in which a is 0, 1, or 2;

each of R_1, R_5, R_9, and R_{10}, independently, is H or C_1-C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl;

each of R_2, R_3, and R_4, independently, is $-Q_1$-T_1, in which Q_1 is a bond or C_1-C_3 alkyl linker optionally substituted with halo, cyano, hydroxyl or C_1-C_6 alkoxy, and T_1 is H, halo, hydroxyl, COOH, cyano, azido, or R_{S1}, in which R_{S1} is C_1-C_3 alkyl, C_2-C_6

alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxyl, C(O)O-C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl, and R_{S1} is optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, oxo, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl;

R_6 is H, halo, cyano, azido, OR_a, $-NR_aR_b$, $-C(O)R_a$, $-C(O)OR_a$, $-C(O)NR_aR_b$, $-NR_bC(O)R_a$, $-S(O)_bR_a$, $-S(O)_bNR_aR_b$, or R_{S2}, in which R_{S2} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, or 4 to 12-membered heterocycloalkyl; b is 0, 1, or 2, each of R_a and R_b, independently is H or R_{S3}, and R_{S3} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl; or R_a and R_b, together with the N atom to which they are attached, form a 4 to 12-membered heterocycloalkyl ring having 0 or 1 additional heteroatom; and each of R_{S2}, R_{S3}, and the 4 to 12-membered heterocycloalkyl ring formed by R_a and R_b, is optionally substituted with one or more $-Q_2$-T_2, wherein Q_2 is a bond or C_1-C_3 alkyl linker each optionally substituted with halo, cyano, hydroxyl or C_1-C_6 alkoxy, and T_2 is H, halo, cyano, $-OR_c$, $-NR_cR_d$, $-C(O)R_c$, $-C(O)OR_c$, $-C(O)NR_cR_d$, $-NR_dC(O)R_c$, $-NR_dC(O)OR_c$, $-S(O)_2R_c$, $-S(O)_2NR_cR_d$, or R_{S4}, in which each of R_c and R_d, independently is H or R_{S5}, each of R_{S4} and R_{S5}, independently, is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl, or R_c and R_d, together with the N atom to which they are attached, form a 4 to 12-membered heterocycloalkyl ring having 0 or 1 additional heteroatom, and each of R_{S4}, R_{S5}, and the 4 to 12-membered heterocycloalkyl ring formed by R_c and R_d, is optionally substituted with one or more $-Q_3$-T_3, wherein Q_3 is a bond or C_1-C_3 alkyl linker each optionally substituted with halo, cyano, hydroxyl or C_1-C_6 alkoxy, and T_3 is selected from the group consisting of halo, cyano, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, 5- or 6-membered heteroaryl, OR_e, $COOR_e$, $-S(O)_2R_e$, $-NR_eR_f$, and $-C(O)NR_eR_f$, each of R_e and R_f independently being H or C_1-C_6 alkyl, or $-Q_3$-T_3 is oxo; or $-Q_2$-T_2 is oxo;

R_7 is $-Q_4$-T_4, in which Q_4 is a bond, C_1-C_4 alkyl linker, or C_2-C_4 alkenyl linker, each linker optionally substituted with halo, cyano, hydroxyl or C_1-C_6 alkoxy, and T_4 is H, halo, cyano, NR_gR_h, $-OR_g$, $-C(O)R_g$, $-C(O)OR_g$, $-C(O)NR_gR_h$, $-C(O)NR_gOR_h$, $-NR_gC(O)R_h$, $-S(O)_2R_g$, or R_{S6}, in which each of R_g and R_h, independently is H or R_{S7}, each of R_{S6} and R_{S7}, independently is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl, and each of R_{S6} and R_{S7} is optionally substituted with one or more $-Q_5$-T_5, wherein Q_5 is a bond, C(O), $C(O)NR_k$, $NR_kC(O)$, $S(O)_2$, or C_1-C_3 alkyl linker, R_k being H or C_1-C_6 alkyl, and T_5 is H, halo, C_1-C_6 alkyl, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, 5- or 6-membered heteroaryl, or $S(O)_qR_q$ in which q is 0, 1, or 2 and R_q is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl, and T_5 is optionally substituted with one or more substituents selected from the group consisting of halo, C_1-C_6 alkyl, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl except when T_5 is H, halo, hydroxyl, or cyano; or $-Q_5$-T_5 is oxo;

each of R_8, R_{11}, R_{12}, and R_{13}, independently, is H, halo, hydroxyl, COOH, cyano, R_{S8}, OR_{S8}, or $COOR_{S8}$, in which R_{S8} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, 4 to 12-membered heterocycloalkyl, amino, mono-C_1-C_6 alkylamino, or di-C_1-C_6 alkylamino, and R_{S8} is optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, and di-C_1-C_6 alkylamino; or R_7 and R_8, together with the N atom to which they are attached, form a 4 to 12-membered heterocycloalkyl ring having 0 to 2 additional heteroatoms, or R_7 and R_8, together with the C atom to which they are attached, form C_3-C_8 cycloalkyl or a 4 to 12-membered heterocycloalkyl ring having 1 to 3 heteroatoms, and each of the 4 to 12-membered heterocycloalkyl rings or C_3-C_8 cycloalkyl formed by R_7 and R_8 is optionally substituted with one or more $-Q_6$-T_6, wherein Q_6 is a bond, C(O), $C(O)NR_m$, $NR_mC(O)$, $S(O)_2$, or C_1-C_3 alkyl linker, R_m being H or C_1-C_6 alkyl, and T_6 is H, halo, C_1-C_6 alkyl,

hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, 5- or 6-membered heteroaryl, or $S(O)_pR_p$ in which p is 0, 1, or 2 and R_p is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl, and T_6 is optionally substituted with one or more substituents selected from the group consisting of halo, C_1-C_6 alkyl, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl except when T_6 is H, halo, hydroxyl, or cyano; or $-Q_6$-T_6 is oxo; and

R_{14} is absent, H, or C_1-C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl;

provided that the compound is not

N-(5-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)furan-2-carboxamide,

N,N'-(5-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-1,3-phenylene)diacetamide,

N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-pivalamidobenzamide,

3-(3,4-dihydro-2H-benzo[b][1,4]dioxepine-7-sulfonamido)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)benzamide,

N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3,5-dimethoxybenzamide,

N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3,4,5-trimethoxybenzamide,

3-allyl-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-4,5-dimethoxybenzamide,

4-(2-amino-2-oxoethoxy)-3-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-methoxybenzamide,

3-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-4-hydroxy-5-methoxybenzamide, or

3-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-methoxy-4-propoxybenzamide.

[0114] For example, X_1 is CR_{11} and X_2 is CR_{13}.

[0115] For example, X_1 is CR_{11} and X_2 is N.

[0116] For example, X_1 is N and X_2 is CR_{13}.

[0117] For example, X_1 is N and X_2 is N.

[0118] For example, X_3 is C.

[0119] For example, X_3 is N and R_6 is absent.

[0120] For example, Z is NR_7R_8.

[0121] For example, Z is $CR_7R_8R_{14}$.

[0122] For example, Z is OR_7.

[0123] For example, Z is $S(O)_aR_7$, in which a is 0, 1, or 2.

[0124] For example, Z is SR_7.

[0125] For example, R_6 is H.

[0126] For example, R_6 is halo (*e.g.*, fluorine, chlorine, bromine, and iodine).

[0127] For example, R_6 is C_1-C_3 alkyl optionally substituted with one or more $-Q_2$-T_2.

[0128] For example, R_6 is CF_3.

[0129] For example, R_6 is C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_3-C_6 cycloalkyl each optionally substituted with one or more $-Q_2$-T_2.

[0130] For example, R_6 is ethenyl.

[0131] For example, R_6 is ethynyl.

[0132] For example, R_6 is ethynyl substituted with one or more $-Q_2$-T_2, in which Q_2 is a bond or C_1-C_3 alkyl linker and T_2 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or 4 to 7-membered heterocycloalkyl (e.g., azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, tetrahydro-2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, and morpholinyl, and the like) optionally substituted with one or more $-Q_3$-T_3.

[0133] For example, R_6 is azido.

[0134] For example, R_6 is cyano.

[0135] For example, R_6 is C(O)H.

[0136] For example, R_6 is OR_a or $-C(O)R_a$.

[0137] For example, R_a is C_1-C_6 alkyl or 4 to 7-membered heterocycloalkyl (e.g., azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, tetrahydro-2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, and morpholinyl, and the like), which is optionally substituted with one or more $-Q_2$-T_2.

[0138] For example, R_6 is 4 to 7-membered heterocycloalkyl (e.g., azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, tetrahydro-2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, and morpholinyl, and the like) optionally substituted with one or more $-Q_2$-T_2.

[0139] For example, R_6 is piperidinyl, 2,2,6,6-tetramethyl-piperidinyl, 1,2,3,6-tetrahydropyridinyl, 2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridinyl, piperazinyl, morpholinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, or pyrrolidinyl, each of which is optionally substituted with one or more $-Q_2$-T_2.

[0140] For example, R_6 is 4 to 7-membered heterocycloalkyl optionally substituted with one or more $-Q_2$-T_2, and $-Q_2$-T_2 is oxo or Q_2 is a bond and T_2 is $-OR_c$, $-NR_cR_d$, $-C(O)R_c$, $-C(O)OR_c$, $-S(O)_2R_c$, C_1-C_6 alkyl, or 4 to 7-membered heterocycloalkyl, each of which is optionally substituted with one or more $-Q_3$-T_3 when R_c or R_d is not H.

[0141] For example, R_6 is $-NR_aR_b$, $-C(O)R_a$, $-C(O)OR_a$, $-C(O)NR_aR_b$, $-NR_bC(O)R_a$, $-SR_a$, $-S(O)_2R_a$, or $-S(O)_2NR_aR_b$.

[0142] For example, each of R_a and R_b, independently is H, C_1-C_6 alkyl or C_3-C_8 cycloalkyl optionally substituted with one or more $-Q_2$-T_2.

[0143] For example, one of R_a and R_b is H.

[0144] For example, R_a and R_b, together with the N atom to which they are attached, form a 4 to 7-membered heterocycloalkyl ring having 0 or 1 additional heteroatoms to the N atom (e.g., azetidinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, and morpholinyl, and the like) and the ring is optionally substituted with one or more $-Q_2$-T_2.

[0145] For example, $-Q_2$-T_2 is not H.

[0146] For example, $-Q_2$-T_2 is oxo.

[0147] For example, Q_2 is a bond.

[0148] For example, Q_2 is an unsubstituted C_1-C_3 alkyl linker.

[0149] For example, T_2 is C_1-C_6 alkyl or C_6-C_{10} aryl, each optionally substituted with one or more $-Q_3$-T_3.

[0150] For example, T_2 is an unsubstituted substituted straight chain C_1-C_6 or branched C_3-C_6 alkyl, including but not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl and n-hexyl.

[0151] For example, T_2 is phenyl.

[0152] For example, T_2 is halo (*e.g.*, fluorine, chlorine, bromine, and iodine).

[0153] For example, T_2 is 4 to 7-membered heterocycloalkyl (e.g., azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, tetrahydro-2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, and morpholinyl, and the like) optionally substituted with one or more $-Q_3$-T_3.

[0154] For example, T_2 is $-OR_c$, $-NR_cR_d$, $-C(O)R_c$, $-C(O)OR_c$, or $-S(O)_2R_c$.

[0155] For example, R_c is C_1-C_6 alkyl or 4 to 7-membered heterocycloalkyl (e.g., azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, tetrahydro-2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 2-oxa-6-

azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, and morpholinyl, and the like), which is optionally substituted with one or more $-Q_3$-T_3.

[0156] For example, each of R_c and R_d, independently is H or C_1-C_6 alkyl optionally substituted with one or more $-Q_3$-T_3.

[0157] For example, R_c is H.

[0158] For example, R_d is H.

[0159] For example, R_c and R_d, together with the N atom to which they are attached, form a 4 to 7-membered heterocycloalkyl ring having 0 or 1 additional heteroatoms to the N atom (e.g., azetidinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, and morpholinyl, and the like) and the ring is optionally substituted with one or more $-Q_3$-T_3.

[0160] For example, Q_2 is a bond and T_2 is $-OR_c$, $-NR_cR_d$, $-C(O)R_c$, $-C(O)OR_c$, $-S(O)_2R_c$, C_1-C_6 alkyl, or 4 to 7-membered heterocycloalkyl, each of which is optionally substituted with one or more $-Q_3$-T_3 when R_c or R_d is not H.

[0161] For example,$-Q_3$-T_3 is oxo.

[0162] For example, T_2 is 4 to 7-membered heterocycloalkyl or C_3-C_8 cycloalkyl and one or more $-Q_3$-T_3 are oxo.

[0163] For example, Q_3 is a bond or unsubstituted or substituted C_1-C_3 alkyl linker.

[0164] For example, T_3 is H, halo, 4 to 7-membered heterocycloalkyl, C_1-C_3 alkyl, OR_e, $COOR_e$,$-S(O)_2R_e$,$-NR_eR_f$, or $-C(O)NR_eR_f$.

[0165] For example, one of R_d and R_e is H.

[0166] For example, Q_3 is a bond or C_1-C_3 alkyl linker and T_3 is selected from the group consisting of C_1-C_3 alkyl, halo, OR_e, $-S(O)_2R_e$, $-NR_eR_f$, and$-C(O)NR_eR_f$.

[0167] For example, Q_3 is a bond or C_1-C_3 alkyl linker and T_3 is selected from the group consisting of C_1-C_3 alkyl, OR_e, $-S(O)_2R_e$, or $-NR_eR_f$.

[0168] For example, R_e is H.

[0169] For example, R_f is H.

[0170] For example, R_7 is not H.

[0171] For example, R_7 is $-C(O)R_g$.

[0172] For example, R_7 is -C(O)R_g, in which R_g is C_3-C_8 cycloalkyl, or 4 to 7-membered heterocycloalkyl, C_3-C_8 cycloalkyl.

[0173] For example, R_7 is C_6-C_{10} aryl substituted with one or more $-Q_5$-T_5.

[0174] For example, R_7 is phenyl optionally substituted with one or more $-Q_5$-T_5.

[0175] For example, R_7 is C_1-C_6 alkyl optionally substituted with one or more $-Q_5$-T_5.

[0176] For example, R_7 is C_3-C_8 cycloalkyl optionally substituted with one or more $-Q_5$-T_5.

[0177] For example, R_7 is 4 to 7-membered heterocycloalkyl (e.g., azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, tetrahydro-2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, and morpholinyl, and the like) optionally substituted with one or more $-Q_5$-T_5.

[0178] For example, R_7 is 8 to 14-membered heterocycloalkyl such as 1,4-dioxaspiro[4.5]decanyl (e.g., 1,4-dioxaspiro[4.5]decan-8-yl), 1,4-dioxa-8-azaspiro[4.5]decanyl (e.g., 1,4-dioxa-8-azaspiro[4.5]decan-8-yl), 1-oxaspiro[4.5]decanyl (e.g., 1-oxaspiro[4.5]decan-8-yl or 1-oxaspiro[4.5]decan-2-one-8-yl), 1-azaspiro[4.5]decanyl (e.g., 1-azaspiro[4.5]decan-8-yl or 1-azaspiro[4.5]decan-2-one-8-yl), 3'H-spiro[cyclohexane-1,1'-isobenzofuran]-yl (e.g., 3'H-spiro[cyclohexane-1,1'-isobenzofuran]-4-yl or 3'H-spiro[cyclohexane-1,1'-isobenzofuran]-3'-one-4-yl), 7'H-spiro[cyclohexane-1,5'-furo[3,4-b]pyridin]-yl (e.g., 7'H-spiro[cyclohexane-1,5'-furo[3,4-b]pyridin]-4-yl or 7'H-spiro[cyclohexane-1,5'-furo[3,4-b]pyridin]-7'-one-4-yl), or 3'H-spiro[cyclohexane-1,1'-furo[3,4-c]pyridin]-yl (e.g., 3'H-spiro[cyclohexane-1,1'-furo[3,4-c]pyridin]-4-yl or 3'H-spiro[cyclohexane-1,1'-furo[3,4-c]pyridin]-3'-one-4-yl), each optionally substituted with one or more $-Q_5$-T_5.

[0179] For example, R_7 is 5 to 6-membered heterocycloalkyl optionally substituted with one or more $-Q_5$-T_5.

[0180] For example, R_7 is isopropyl.

[0181] For example, R_7 is pyrrolidinyl, piperidinyl, tetrahydropyran, cyclopentyl, or cyclohexyl, cycloheptyl, each optionally substituted with one $-Q_5$-T_5.

[0182] For example, R_7 is cyclopentyl or cyclohexyl, each optionally substituted with one –Q_5-T_5.

[0183] For example, Q_5 is NHC(O) and T_5 is C_1-C_6 alkyl or C_1-C_6 alkoxy.

[0184] For example, –Q_5-T_5 is oxo.

[0185] For example, T_4 is 4 to 7-membered heterocycloalkyl or C_3-C_8 cycloalkyl or C_6-C_{10} aryl, and one or more –Q_5-T_5 are oxo.

[0186] For example, R_7 is 1-oxide-tetrahydro-2H-thiopyranyl or 1,1-dioxide-tetrahydro-2H-thiopyranyl.

[0187] For example, R_7 is cyclohexanonyl, e.g., cyclohexanon-4-yl.

[0188] For example, T_5 is H, halo, C_1-C_6 alkyl, C_1-C_6 alkoxyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, or 4 to 7-membered heterocycloalkyl.

[0189] For example, Q_5 is a bond and T_5 is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, or 4 to 7-membered heterocycloalkyl.

[0190] For example, Q_5 is a bond and T_5 is 5- or 6-membered heteroaryl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, T_5 being optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, C_1-C_6 alkoxyl, or C_3-C_8 cycloalkyl.

[0191] For example, Q_5 is CO, $S(O)_2$, or NHC(O); and T_5 is C_1-C_6 alkyl, C_1-C_6 alkoxyl, C_3-C_8 cycloalkyl, or 4 to 7-membered heterocycloalkyl.

[0192] For example, T_5 is C_1-C_6 alkyl or C_1-C_6 alkoxyl, each optionally substituted with halo, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, or C_3-C_8 cycloalkyl.

[0193] For example, Q_5 is C_1-C_3 alkyl linker and T_5 is H or C_6-C_{10} aryl.

[0194] For example, Q_5 is C_1-C_3 alkyl linker and T_5 is C_3-C_8 cycloalkyl, 4 to 7-membered heterocycloalkyl, or $S(O)_qR_q$.

[0195] For example, R_6 is halo (*e.g.*, fluorine, chlorine, bromine, and iodine) and Z is $S(O)_aR_7$, in which a is 0, 1, or 2 and R_7 is C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, butyl, or t-butyl), C_3-C_8 cycloalkyl (e.g., cyclopentyl, cyclohexyl, or cycloheptyl) or 4 to 14-membered heterocycloalkyl (e.g., azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, tetrahydro-2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-

diazabicyclo[2.2.1]heptanyl, morpholinyl, 1,4-dioxaspiro[4.5]decanyl, 1,4-dioxa-8-azaspiro[4.5]decanyl, 1-oxaspiro[4.5]decanyl, 1-azaspiro[4.5]decanyl, 3'H-spiro[cyclohexane-1,1'-isobenzofuran]-yl, 7'H-spiro[cyclohexane-1,5'-furo[3,4-b]pyridin]-yl, or 3'H-spiro[cyclohexane-1,1'-furo[3,4-c]pyridin]-yl, and the like) and R_7 is optionally substituted with one or more $-Q_5$-T_5.

[0196] For example, R_6 is halo (*e.g.*, fluorine, chlorine, bromine, and iodine) and Z is OR_7 in which R_7 is 4 to 14-membered heterocycloalkyl (e.g., azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, tetrahydro-2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, morpholinyl, 1,4-dioxaspiro[4.5]decanyl, 1,4-dioxa-8-azaspiro[4.5]decanyl, 1-oxaspiro[4.5]decanyl, 1-azaspiro[4.5]decanyl, 3'H-spiro[cyclohexane-1,1'-isobenzofuran]-yl, 7'H-spiro[cyclohexane-1,5'-furo[3,4-b]pyridin]-yl, or 3'H-spiro[cyclohexane-1,1'-furo[3,4-c]pyridin]-yl, and the like) and R_7 is optionally substituted with one or more $-Q_5$-T_5.

[0197] For example, R_{11} is H.

[0198] For example, each of R_2 and R_4, independently, is H or C_1-C_6 alkyl optionally substituted with amino, azido, halo, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, or C_6-C_{10} aryl.

[0199] For example, each of R_2 and R_4, independently is C_1-C_3 alkyl optionally substituted withC_1-C_6 alkoxyl.

[0200] For example, each of R_2 and R_4 is methyl.

[0201] For example, R_1 is H.

[0202] For example, R_1 is C_1-C_6 alkyl optionally substituted with azido, halo, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, or C_6-C_{10} aryl.

[0203] For example, R_{12} is H, methyl, ethyl, ethenyl, or halo.

[0204] For example, R_{12} is methyl.

[0205] For example, R_{12} is ethyl or propenyl.

[0206] For example, R_{12} is methoxyl.

[0207] For example, R_{12} is ethenyl.

[0208] For example, R_8 is H, methyl, ethyl, or ethenyl.

[0209] For example, R_8 is methyl.

[0210] For example, R_8 is ethyl.

[0211] For example, R_8 is propyl.

[0212] For example, R_8 is ethenyl or propenyl.

[0213] For example, R_8 is C_1-C_6 alkyl substituted with one or more substituents selected from the group consisting of halo (e.g., F, Cl, or Br), hydroxyl, or C_1-C_6 alkoxyl.

[0214] For example, R_8 is 4 to 7-membered optionally substituted heterocycloalkyl (e.g., azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, tetrahydro-2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, and morpholinyl, and the like).

[0215] For example, R_8 is piperidinyl.

[0216] For example, R_8 is 4 to 7-membered optionally substituted heterocycloalkyl and R_7 is $-Q_4$-T_4, in which Q_4 is a bond or C_1-C_4 alkyl linker and T_4 is H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl or 4 to 7-membered heterocycloalkyl.

[0217] For example, Z is NR_7R_8 or $CR_7R_8R_{14}$ wherein R_7 and R_8, together with the atom to which they are attached, form a 4 to 11-membered heterocycloalkyl ring having 1 to 3 heteroatoms (e.g., azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, tetrahydro-2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, morpholinyl, 1,4-dioxa-8-azaspiro[4.5]decanyl, and the like) or C_3-C_8 cycloalkyl, each optionally substituted with one or more $-Q_6$-T_6.

[0218] For example, the ring formed by R_7 and R_8 is selected from the group consisting of azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, 1,4-dioxa-8-azaspiro[4.5]decanyl, and cyclohexenyl, each optionally substituted with one $-Q_6$-T_6.

[0219] For example, Z is 1,4-dioxa-8-azaspiro[4.5]decan-8-yl, pyrrolidine-2,5-dione-1-yl, or piperidine-2,6-dione-1-yl.

[0220] For example, one or more $-Q_6$-T_6 is oxo.

[0221] For example, T_6 is H, halo, C_1-C_6 alkyl, C_1-C_6 alkoxyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, or 4 to 7-membered heterocycloalkyl.

[0222] For example, Q_6 is a bond and T_6 is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, or 4 to 7-membered heterocycloalkyl.

[0223] For example, Q_6 is CO, $S(O)_2$, or NHC(O); and T_6 is C_1-C_6 alkyl, C_1-C_6 alkoxyl, C_3-C_8 cycloalkyl, or 4 to 7-membered heterocycloalkyl.

[0224] For example, T_6 is C_1-C_6 alkyl or C_1-C_6 alkoxyl, each optionally substituted with halo, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, or C_3-C_8 cycloalkyl.

[0225] For example, Q_6 is C_1-C_3 alkyl linker and T_6 is H or C_6-C_{10} aryl.

[0226] For example, Q_6 is C_1-C_3 alkyl linker and T_6 is C_3-C_8 cycloalkyl, 4 to 7-membered heterocycloalkyl, or $S(O)_pR_p$.

[0227] For example, each of R_p and R_q, independently, is C_1-C_6 alkyl.

[0228] For example, R_6 is $-S(O)_bR_a$ or azido, in which b is 0, 1, or 2 and R_a is C_1-C_6 alkyl or C_3-C_8 cycloalkyl; and Z is NR_7R_8, in which R_7 is C_3-C_8 cycloalkyl (e.g., cyclopentyl, cyclohexyl, or cycloheptyl) or 4 to 14-membered heterocycloalkyl (e.g., azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, tetrahydro-2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, morpholinyl, 1,4-dioxaspiro[4.5]decanyl, 1,4-dioxa-8-azaspiro[4.5]decanyl, 1-oxaspiro[4.5]decanyl, 1-azaspiro[4.5]decanyl, 3'H-spiro[cyclohexane-1,1'-isobenzofuran]-yl, 7'H-spiro[cyclohexane-1,5'-furo[3,4-b]pyridin]-yl, or 3'H-spiro[cyclohexane-1,1'-furo[3,4-c]pyridin]-yl, and the like), each optionally substituted with one or more $-Q_5$-T_5; and R_8 is H or C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, butyl, or t-butyl).

[0229] For example, R_6 is halo (*e.g.*, fluorine, chlorine, bromine, and iodine) and Z is NR_7R_8 or $CR_7R_8R_{14}$ wherein R_7 and R_8, together with the atom to which they are attached, form a 4 to 11-membered heterocycloalkyl ring having 1 to 3 heteroatoms (e.g., azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl,

3,6-dihydro-2H-pyranyl, tetrahydro-2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, morpholinyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, 1,4-dioxa-8-azaspiro[4.5]decanyl, 1,4-dioxa-8-azaspiro[4.5]decan-8-yl, pyrrolidine-2,5-dione-1-yl, piperidine-2,6-dione-1-yl, and the like) or C_3-C_8 cycloalkyl, each optionally substituted with one or more $-Q_6$-T_6.

[0230] For example, R_{13} is H or methyl.

[0231] For example, R_{13} is H.

[0232] For example, R_3 is H.

[0233] For example, each of R_5, R_9, and R_{10} is H.

[0234] In another aspect, the present invention features a substituted benzene compound of Formula (I) above or a pharmaceutically acceptable salt or ester thereof, in which

X_1 is N or CR_{11};

X_2 is N or CR_{13};

X_3 is N or C, and when X_3 is N, R_6 is absent;

Z is NR_7R_8, OR_7, $S(O)_aR_7$, or $CR_7R_8R_{14}$, in which a is 0, 1, or 2;

each of R_1, R_5, R_9, and R_{10}, independently, is H or C_1-C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl;

each of R_2, R_3, and R_4, independently, is $-Q_1$-T_1, in which Q_1 is a bond or C_1-C_3 alkyl linker optionally substituted with halo, cyano, hydroxyl or C_1-C_6 alkoxy, and T_1 is H, halo, hydroxyl, COOH, cyano, azido, or R_{S1}, in which R_{S1} is C_1-C_3 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxyl, C(O)O-C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl, and R_{S1} is optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, oxo, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl;

R_6 is H, halo, cyano, azido, OR_a, $-NR_aR_b$, $-C(O)R_a$, $-C(O)OR_a$, $-C(O)NR_aR_b$, $-NR_bC(O)R_a$, $-S(O)_bR_a$, $-S(O)_bNR_aR_b$, or R_{S2}, in which R_{S2} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, or 4 to 12-membered heterocycloalkyl; b is 0, 1, or 2, each of R_a and R_b, independently is H or R_{S3}, and R_{S3} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl; or R_a and R_b, together with the N atom to which they are attached, form a 4 to 12-membered heterocycloalkyl ring having 0 or 1 additional heteroatom; and each of R_{S2}, R_{S3}, and the 4 to 12-membered heterocycloalkyl ring formed by R_a and R_b, is optionally substituted with one or more $-Q_2$-T_2, wherein Q_2 is a bond or C_1-C_3 alkyl linker each optionally substituted with halo, cyano, hydroxyl or C_1-C_6 alkoxy, and T_2 is H, halo, cyano, $-OR_c$, $-NR_cR_d$, $-C(O)R_c$, $-C(O)OR_c$, $-C(O)NR_cR_d$, $-NR_dC(O)R_c$, $-NR_dC(O)OR_c$, $-S(O)_2R_c$, $-S(O)_2NR_cR_d$, or R_{S4}, in which each of R_c and R_d, independently is H or R_{S5}, each of R_{S4} and R_{S5}, independently, is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl, or R_c and R_d, together with the N atom to which they are attached, form a 4 to 12-membered heterocycloalkyl ring having 0 or 1 additional heteroatom, and each of R_{S4}, R_{S5}, and the 4 to 12-membered heterocycloalkyl ring formed by R_c and R_d, is optionally substituted with one or more $-Q_3$-T_3, wherein Q_3 is a bond or C_1-C_3 alkyl linker each optionally substituted with halo, cyano, hydroxyl or C_1-C_6 alkoxy, and T_3 is selected from the group consisting of halo, cyano, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, 5- or 6-membered heteroaryl, OR_e, $COOR_e$, $-S(O)_2R_e$, $-NR_eR_f$, and $-C(O)NR_eR_f$, each of R_e and R_f independently being H or C_1-C_6 alkyl, or $-Q_3$-T_3 is oxo; or $-Q_2$-T_2 is oxo;

R_7 is $-Q_4$-T_4, in which Q_4 is a bond, C_1-C_4 alkyl linker, or C_2-C_4 alkenyl linker, each linker optionally substituted with halo, cyano, hydroxyl or C_1-C_6 alkoxy, and T_4 is H, halo, cyano, NR_gR_h, $-OR_g$, $-C(O)R_g$, $-C(O)OR_g$, $-C(O)NR_gR_h$, $-C(O)NR_gOR_h$, $-NR_gC(O)R_h$, $-S(O)_2R_g$, or R_{S6}, in which each of R_g and R_h, independently is H or R_{S7}, each of R_{S6} and R_{S7}, independently is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl, and each of R_{S6} and R_{S7} is optionally substituted with one or more $-Q_5$-T_5, wherein Q_5 is a bond, C(O), $C(O)NR_k$, $NR_kC(O)$, $S(O)_2$, or C_1-C_3 alkyl linker, R_k being

H or C_1-C_6 alkyl, and T_5 is H, halo, C_1-C_6 alkyl, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, 5- or 6-membered heteroaryl, or $S(O)_qR_q$ in which q is 0, 1, or 2 and R_q is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl, and T_5 is optionally substituted with one or more substituents selected from the group consisting of halo, C_1-C_6 alkyl, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl except when T_5 is H, halo, hydroxyl, or cyano; or $-Q_5$-T_5 is oxo; provided that (i) R_7 is not $C(O)R_g$ or $-S(O)_2R_g$ when Z is NR_7R_8; (ii) R_7 is not C_1-C_6 alkyl when Z is OR_7, and (iii) R_7 is not H;

each of R_8, R_{11}, R_{12}, and R_{13}, independently, is H, halo, hydroxyl, COOH, cyano, R_{S8}, OR_{S8}, or $COOR_{S8}$, in which R_{S8} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, 4 to 12-membered heterocycloalkyl, amino, mono-C_1-C_6 alkylamino, or di-C_1-C_6 alkylamino, and R_{S8} is optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, and di-C_1-C_6 alkylamino; or R_7 and R_8, together with the N atom to which they are attached, form a 4 to 12-membered heterocycloalkyl ring having 0 to 2 additional heteroatoms, or R_7 and R_8, together with the C atom to which they are attached, form C_3-C_8 cycloalkyl or a 4 to 12-membered heterocycloalkyl ring having 1 to 3 heteroatoms, and each of the 4 to 12-membered heterocycloalkyl rings or C_3-C_8 cycloalkyl formed by R_7 and R_8 is optionally substituted with one or more $-Q_6$-T_6, wherein Q_6 is a bond, C(O), $C(O)NR_m$, $NR_mC(O)$, $S(O)_2$, or C_1-C_3 alkyl linker, R_m being H or C_1-C_6 alkyl, and T_6 is H, halo, C_1-C_6 alkyl, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, 5- or 6-membered heteroaryl, or $S(O)_pR_p$ in which p is 0, 1, or 2 and R_p is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl, and T_6 is optionally substituted with one or more substituents selected from the group consisting of halo, C_1-C_6 alkyl, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4

to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl except when T_6 is H, halo, hydroxyl, or cyano; or $-Q_6$-T_6 is oxo; and

R_{14} is absent, H, or C_1-C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl.

[0235] For example, X_1 is CR_{11} and X_2 is CR_{13}.

[0236] For example, X_1 is CR_{11} and X_2 is N.

[0237] For example, X_1 is N and X_2 is CR_{13}.

[0238] For example, X_1 is N and X_2 is N.

[0239] For example, X_3 is C.

[0240] For example, X_3 is N and R_6 is absent.

[0241] For example, Z is NR_7R_8.

[0242] For example, Z is $CR_7R_8R_{14}$.

[0243] For example, Z is OR_7.

[0244] For example, Z is $S(O)_aR_7$, in which a is 0, 1, or 2.

[0245] For example, Z is SR_7.

[0246] For example, R_6 is H.

[0247] For example, R_6 is halo (*e.g.*, fluorine, chlorine, bromine, and iodine).

[0248] For example, R_6 is C_1-C_3 alkyl optionally substituted with one or more $-Q_2$-T_2.

[0249] For example, R_6 is CF_3.

[0250] For example, R_6 is C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_3-C_6 cycloalkyl each optionally substituted with one or more $-Q_2$-T_2.

[0251] For example, R_6 is ethenyl.

[0252] For example, R_6 is ethynyl.

[0253] For example, R_6 is ethynyl substituted with one or more $-Q_2$-T_2, in which Q_2 is a bond or C_1-C_3 alkyl linker and T_2 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or 4 to 7-membered heterocycloalkyl (e.g., azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, tetrahydro-

2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, and morpholinyl, and the like) optionally substituted with one or more $-Q_3$-T_3.

[0254] For example, R_6 is azido.

[0255] For example, R_6 is cyano.

[0256] For example, R_6 is C(O)H.

[0257] For example, R_6 is -C(O)R_a.

[0258] For example, R_a is C_1-C_6 alkyl or 4 to 7-membered heterocycloalkyl (e.g., azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, tetrahydro-2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, and morpholinyl, and the like), which is optionally substituted with one or more $-Q_2$-T_2.

[0259] For example, R_6 is 4 to 7-membered heterocycloalkyl (e.g., azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, tetrahydro-2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, and morpholinyl, and the like) optionally substituted with one or more $-Q_2$-T_2.

[0260] For example, R_6 is piperidinyl, 2,2,6,6-tetramethyl-piperidinyl, 1,2,3,6-tetrahydropyridinyl, 2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridinyl, piperazinyl, morpholinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, or pyrrolidinyl, each of which is optionally substituted with one or more $-Q_2$-T_2.

[0261] For example, R_6 is 4 to 7-membered heterocycloalkyl optionally substituted with one or more $-Q_2$-T_2, and $-Q_2$-T_2 is oxo or Q_2 is a bond and T_2 is -OR_c, -NR_cR_d, -C(O)R_c, -C(O)OR_c, -$S(O)_2R_c$, C_1-C_6 alkyl, or 4 to 7-membered heterocycloalkyl, each of which is optionally substituted with one or more $-Q_3$-T_3 when R_c or R_d is not H.

[0262] For example, R_6 is -NR_aR_b, -C(O)R_a, -C(O)OR_a, -C(O)NR_aR_b, -$NR_bC(O)R_a$, -SR_a, -$S(O)_2R_a$, or -$S(O)_2NR_aR_b$.

[0263] For example, each of R_a and R_b, independently is H, C_1-C_6 alkyl or C_3-C_8 cycloalkyl optionally substituted with one or more $-Q_2$-T_2.

[0264] For example, one of R_a and R_b is H.

[0265] For example, R_a and R_b, together with the N atom to which they are attached, form a 4 to 7-membered heterocycloalkyl ring having 0 or 1 additional heteroatoms to the N atom (e.g., azetidinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, and morpholinyl, and the like) and the ring is optionally substituted with one or more $-Q_2$-T_2.

[0266] For example, $-Q_2$-T_2 is not H.

[0267] For example, $-Q_2$-T_2 is oxo.

[0268] For example, Q_2 is a bond.

[0269] For example, Q_2 is an unsubstituted C_1-C_3 alkyl linker.

[0270] For example, T_2 is C_1-C_6 alkyl or C_6-C_{10} aryl, each optionally substituted with one or more $-Q_3$-T_3.

[0271] For example, T_2 is an unsubstituted substituted straight chain C_1-C_6 or branched C_3-C_6 alkyl, including but not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl and n-hexyl.

[0272] For example, T_2 is phenyl.

[0273] For example, T_2 is halo (*e.g.*, fluorine, chlorine, bromine, and iodine).

[0274] For example, T_2 is 4 to 7-membered heterocycloalkyl (e.g., azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, tetrahydro-2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, and morpholinyl, and the like) optionally substituted with one or more $-Q_3$-T_3.

[0275] For example, T_2 is $-OR_c$, $-NR_cR_d$, $-C(O)R_c$, $-C(O)OR_c$, or $-S(O)_2R_c$.

[0276] For example, R_c is C_1-C_6 alkyl or 4 to 7-membered heterocycloalkyl (e.g., azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl,

triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, tetrahydro-2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, and morpholinyl, and the like), which is optionally substituted with one or more $-Q_3$-T_3.

[0277] For example, each of R_c and R_d, independently is H or C_1-C_6 alkyl optionally substituted with one or more $-Q_3$-T_3.

[0278] For example, R_c is H.

[0279] For example, R_d is H.

[0280] For example, R_c and R_d, together with the N atom to which they are attached, form a 4 to 7-membered heterocycloalkyl ring having 0 or 1 additional heteroatoms to the N atom (e.g., azetidinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, and morpholinyl, and the like) and the ring is optionally substituted with one or more $-Q_3$-T_3.

[0281] For example, Q_2 is a bond and T_2 is $-OR_c$, $-NR_cR_d$, $-C(O)R_c$, $-C(O)OR_c$, $-S(O)_2R_c$, C_1-C_6 alkyl, or 4 to 7-membered heterocycloalkyl, each of which is optionally substituted with one or more $-Q_3$-T_3 when R_c or R_d is not H.

[0282] For example,$-Q_3$-T_3 is oxo.

[0283] For example, T_2 is 4 to 7-membered heterocycloalkyl or C_3-C_8 cycloalkyl and one or more $-Q_3$-T_3 are oxo.

[0284] For example, Q_3 is a bond or unsubstituted or substituted C_1-C_3 alkyl linker.

[0285] For example, T_3 is H, halo, 4 to 7-membered heterocycloalkyl, C_1-C_3 alkyl, OR_e, $COOR_e$,$-S(O)_2R_e$,$-NR_eR_f$, or $-C(O)NR_eR_f$.

[0286] For example, one of R_d and R_e is H.

[0287] For example, Q_3 is a bond or C_1-C_3 alkyl linker and T_3 is selected from the group consisting of C_1-C_3 alkyl, halo, OR_e, $-S(O)_2R_e$, $-NR_eR_f$, and-$C(O)NR_eR_f$.

[0288] For example, Q_3 is a bond or C_1-C_3 alkyl linker and T_3 is selected from the group consisting of C_1-C_3 alkyl, OR_e, $-S(O)_2R_e$, or $-NR_eR_f$.

[0289] For example, R_e is H.

[0290] For example, R_f is H.

[0291] For example, R_7 is not H.

[0292] For example, R_7 is -C(O)R_g.

[0293] For example, R_7 is -C(O)R_g, in which R_g is C_3-C_8 cycloalkyl, or 4 to 7-membered heterocycloalkyl, C_3-C_8 cycloalkyl.

[0294] For example, R_7 is C_6-C_{10} aryl substituted with one or more $-Q_5$-T_5.

[0295] For example, R_7 is phenyl optionally substituted with one or more $-Q_5$-T_5.

[0296] For example, R_7 is C_1-C_6 alkyl optionally substituted with one or more $-Q_5$-T_5.

[0297] For example, R_7 is C_3-C_8 cycloalkyl optionally substituted with one or more $-Q_5$-T_5.

[0298] For example, R_7 is 4 to 7-membered heterocycloalkyl (e.g., azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, tetrahydro-2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, and morpholinyl, and the like) optionally substituted with one or more $-Q_5$-T_5.

[0299] For example, R_7 is 8 to 14-membered heterocycloalkyl such as 1,4-dioxaspiro[4.5]decanyl (e.g., 1,4-dioxaspiro[4.5]decan-8-yl), 1,4-dioxa-8-azaspiro[4.5]decanyl (e.g., 1,4-dioxa-8-azaspiro[4.5]decan-8-yl), 1-oxaspiro[4.5]decanyl (e.g., 1-oxaspiro[4.5]decan-8-yl or 1-oxaspiro[4.5]decan-2-one-8-yl), 1-azaspiro[4.5]decanyl (e.g., 1-azaspiro[4.5]decan-8-yl or 1-azaspiro[4.5]decan-2-one-8-yl), 3'H-spiro[cyclohexane-1,1'-isobenzofuran]-yl (e.g., 3'H-spiro[cyclohexane-1,1'-isobenzofuran]-4-yl or 3'H-spiro[cyclohexane-1,1'-isobenzofuran]-3'-one-4-yl), 7'H-spiro[cyclohexane-1,5'-furo[3,4-b]pyridin]-yl (e.g., 7'H-spiro[cyclohexane-1,5'-furo[3,4-b]pyridin]-4-yl or 7'H-spiro[cyclohexane-1,5'-furo[3,4-b]pyridin]-7'-one-4-yl), or 3'H-spiro[cyclohexane-1,1'-furo[3,4-c]pyridin]-yl (e.g., 3'H-spiro[cyclohexane-1,1'-furo[3,4-c]pyridin]-4-yl or 3'H-spiro[cyclohexane-1,1'-furo[3,4-c]pyridin]-3'-one-4-yl), each optionally substituted with one or more $-Q_5$-T_5.

[0300] For example, R_7 is 5 to 6-membered heterocycloalkyl optionally substituted with one or more $-Q_5$-T_5.

[0301] For example, R_7 is isopropyl.

[0302] For example, R_7 is pyrrolidinyl, piperidinyl, tetrahydropyran, cyclopentyl, or cyclohexyl, cycloheptyl, each optionally substituted with one $-Q_5$-T_5.

[0303] For example, R_7 is cyclopentyl or cyclohexyl, each optionally substituted with one $-Q_5$-T_5.

[0304] For example, Q_5 is NHC(O) and T_5 is C_1-C_6 alkyl or C_1-C_6 alkoxy.

[0305] For example, $-Q_5$-T_5 is oxo.

[0306] For example, T_4 is 4 to 7-membered heterocycloalkyl or C_3-C_8 cycloalkyl or C_6-C_{10} aryl, and one or more $-Q_5$-T_5 are oxo.

[0307] For example, R_7 is 1-oxide-tetrahydro-2H-thiopyranyl or 1,1-dioxide-tetrahydro-2H-thiopyranyl.

[0308] For example, R_7 is cyclohexanonyl, e.g., cyclohexanon-4-yl.

[0309] For example, T_5 is H, halo, C_1-C_6 alkyl, C_1-C_6 alkoxyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, or 4 to 7-membered heterocycloalkyl.

[0310] For example, Q_5 is a bond and T_5 is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, or 4 to 7-membered heterocycloalkyl.

[0311] For example, Q_5 is a bond and T_5 is 5- or 6-membered heteroaryl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, T_5 being optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, C_1-C_6 alkoxyl, or C_3-C_8 cycloalkyl.

[0312] For example, Q_5 is CO, $S(O)_2$, or NHC(O); and T_5 is C_1-C_6 alkyl, C_1-C_6 alkoxyl, C_3-C_8 cycloalkyl, or 4 to 7-membered heterocycloalkyl.

[0313] For example, T_5 is C_1-C_6 alkyl or C_1-C_6 alkoxyl, each optionally substituted with halo, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, or C_3-C_8 cycloalkyl.

[0314] For example, Q_5 is C_1-C_3 alkyl linker and T_5 is H or C_6-C_{10} aryl.

[0315] For example, Q_5 is C_1-C_3 alkyl linker and T_5 is C_3-C_8 cycloalkyl, 4 to 7-membered heterocycloalkyl, or $S(O)_qR_q$.

[0316] For example, R_6 is halo (*e.g.*, fluorine, chlorine, bromine, and iodine) and Z is $S(O)_aR_7$, in which a is 0, 1, or 2 and R_7 is C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, butyl, or t-butyl), C_3-C_8 cycloalkyl (e.g., cyclopentyl, cyclohexyl, or cycloheptyl) or 4 to 14-membered heterocycloalkyl (e.g., azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-

tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, tetrahydro-2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, morpholinyl, 1,4-dioxaspiro[4.5]decanyl, 1,4-dioxa-8-azaspiro[4.5]decanyl, 1-oxaspiro[4.5]decanyl, 1-azaspiro[4.5]decanyl, 3'H-spiro[cyclohexane-1,1'-isobenzofuran]-yl, 7'H-spiro[cyclohexane-1,5'-furo[3,4-b]pyridin]-yl, or 3'H-spiro[cyclohexane-1,1'-furo[3,4-c]pyridin]-yl, and the like) and R_7 is optionally substituted with one or more $-Q_5$-T_5.

[0317] For example, R_6 is halo (*e.g.*, fluorine, chlorine, bromine, and iodine) and Z is OR_7 in which R_7 is 4 to 14-membered heterocycloalkyl (e.g., azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, tetrahydro-2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, morpholinyl, 1,4-dioxaspiro[4.5]decanyl, 1,4-dioxa-8-azaspiro[4.5]decanyl, 1-oxaspiro[4.5]decanyl, 1-azaspiro[4.5]decanyl, 3'H-spiro[cyclohexane-1,1'-isobenzofuran]-yl, 7'H-spiro[cyclohexane-1,5'-furo[3,4-b]pyridin]-yl, or 3'H-spiro[cyclohexane-1,1'-furo[3,4-c]pyridin]-yl, and the like) and R_7 is optionally substituted with one or more $-Q_5$-T_5.

[0318] For example, R_{11} is H.

[0319] For example, each of R_2 and R_4, independently, is H or C_1-C_6 alkyl optionally substituted with amino, azido, halo, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, or C_6-C_{10} aryl.

[0320] For example, each of R_2 and R_4, independently is C_1-C_3 alkyl optionally substituted withC_1-C_6 alkoxyl.

[0321] For example, each of R_2 and R_4 is methyl.

[0322] For example, R_1 is H.

[0323] For example, R_1 is C_1-C_6 alkyl optionally substituted with azido, halo, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, or C_6-C_{10} aryl.

[0324] For example, R_{12} is H, methyl, ethyl, ethenyl, or halo.

[0325] For example, R_{12} is methyl.

[0326] For example, R_{12} is ethyl or propenyl.

[0327] For example, R_{12} is methoxyl.

[0328] For example, R_{12} is ethenyl.

[0329] For example, R_8 is H, methyl, ethyl, or ethenyl.

[0330] For example, R_8 is methyl.

[0331] For example, R_8 is ethyl.

[0332] For example, R_8 is propyl.

[0333] For example, R_8 is ethenyl or propenyl.

[0334] For example, R_8 is C_1-C_6 alkyl substituted with one or more substituents selected from the group consisting of halo (e.g., F, Cl, or Br), hydroxyl, or C_1-C_6 alkoxyl.

[0335] For example, R_8 is 4 to 7-membered optionally substituted heterocycloalkyl (e.g., azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, tetrahydro-2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, and morpholinyl, and the like).

[0336] For example, R_8 is piperidinyl.

[0337] For example, R_8 is 4 to 7-membered optionally substituted heterocycloalkyl and R_7 is $-Q_4$-T_4, in which Q_4 is a bond or C_1-C_4 alkyl linker and T_4 is H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl or 4 to 7-membered heterocycloalkyl.

[0338] For example, Z is NR_7R_8 or $CR_7R_8R_{14}$ wherein R_7 and R_8, together with the atom to which they are attached, form a 4 to 11-membered heterocycloalkyl ring having 1 to 3 heteroatoms (e.g., azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, tetrahydro-2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, morpholinyl, 1,4-dioxa-8-azaspiro[4.5]decanyl, and the like) or C_3-C_8 cycloalkyl, each optionally substituted with one or more $-Q_6$-T_6.

[0339] For example, the ring formed by R_7 and R_8 is selected from the group consisting of azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, 1,4-dioxa-8-azaspiro[4.5]decanyl, and cyclohexenyl, each optionally substituted with one $-Q_6$-T_6.

[0340] For example, Z is 1,4-dioxa-8-azaspiro[4.5]decan-8-yl, pyrrolidine-2,5-dione-1-yl, or piperidine-2,6-dione-1-yl.

[0341] For example, one or more $-Q_6-T_6$ is oxo.

[0342] For example, T_6 is H, halo, C_1-C_6 alkyl, C_1-C_6 alkoxyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, or 4 to 7-membered heterocycloalkyl.

[0343] For example, Q_6 is a bond and T_6 is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, or 4 to 7-membered heterocycloalkyl.

[0344] For example, Q_6 is CO, $S(O)_2$, or NHC(O); and T_6 is C_1-C_6 alkyl, C_1-C_6 alkoxyl, C_3-C_8 cycloalkyl, or 4 to 7-membered heterocycloalkyl.

[0345] For example, T_6 is C_1-C_6 alkyl or C_1-C_6 alkoxyl, each optionally substituted with halo, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, or C_3-C_8 cycloalkyl.

[0346] For example, Q_6 is C_1-C_3 alkyl linker and T_6 is H or C_6-C_{10} aryl.

[0347] For example, Q_6 is C_1-C_3 alkyl linker and T_6 is C_3-C_8 cycloalkyl, 4 to 7-membered heterocycloalkyl, or $S(O)_pR_p$.

[0348] For example, each of R_p and R_q, independently, is C_1-C_6 alkyl.

[0349] For example, R_6 is $-S(O)_bR_a$ or azido, in which b is 0, 1, or 2 and R_a is C_1-C_6 alkyl or C_3-C_8 cycloalkyl; and Z is NR_7R_8, in which R_7 is C_3-C_8 cycloalkyl (e.g., cyclopentyl, cyclohexyl, or cycloheptyl) or 4 to 14-membered heterocycloalkyl (e.g., azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, tetrahydro-2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, morpholinyl, 1,4-dioxaspiro[4.5]decanyl, 1,4-dioxa-8-azaspiro[4.5]decanyl, 1-oxaspiro[4.5]decanyl, 1-azaspiro[4.5]decanyl, 3'H-spiro[cyclohexane-1,1'-isobenzofuran]-yl, 7'H-spiro[cyclohexane-1,5'-furo[3,4-b]pyridin]-yl, or 3'H-spiro[cyclohexane-1,1'-furo[3,4-c]pyridin]-yl, and the like), each optionally substituted with one or more $-Q_5-T_5$; and R_8 is H or C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, butyl, or t-butyl).

[0350] For example, R_6 is halo (*e.g.*, fluorine, chlorine, bromine, and iodine) and Z is NR_7R_8 or $CR_7R_8R_{14}$ wherein R_7 and R_8, together with the atom to which they are attached, form a 4 to 11-membered heterocycloalkyl ring having 1 to 3 heteroatoms (e.g., azetidinyl, oxetanyl,

thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, tetrahydro-2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, morpholinyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, 1,4-dioxa-8-azaspiro[4.5]decanyl, 1,4-dioxa-8-azaspiro[4.5]decan-8-yl, pyrrolidine-2,5-dione-1-yl, piperidine-2,6-dione-1-yl, and the like) or C_3-C_8 cycloalkyl, each optionally substituted with one or more $-Q_6$-T_6.

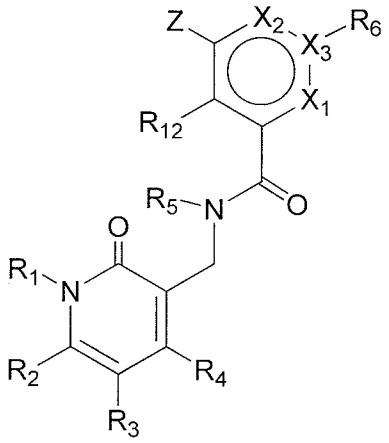
[0351] For example, R_{13} is H or methyl.

[0352] For example, R_{13} is H.

[0353] For example, R_3 is H.

[0354] For example, each of R_5, R_9, and R_{10} is H.

[0355] The present invention provides the compounds of Formula (Ia)



(Ia),

or a pharmaceutically acceptable salt or ester thereof, wherein:

X_1 is N or CR_{11};

X_2 is N or CR_{13};

X_3 is N or C, and when X_3 is N, R_6 is absent;

Z is NR_7R_8, OR_7, $S(O)_aR_7$, or $CR_7R_8R_{14}$, in which a is 0, 1, or 2;

each of R_1 and R_5, independently, is H or C_1-C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl;

each of R_2, R_3, and R_4, independently, is $-Q_1$-T_1, in which Q_1 is a bond or C_1-C_3 alkyl linker optionally substituted with halo, cyano, hydroxyl or C_1-C_6 alkoxy, and T_1 is H, halo, hydroxyl, COOH, cyano, azido, or R_{S1}, in which R_{S1} is C_1-C_3 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxyl, C(O)O-C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl, and R_{S1} is optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, oxo, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl;

R_6 is H, halo, cyano, azido, OR_a, $-NR_aR_b$, $-C(O)R_a$, $-C(O)OR_a$, $-C(O)NR_aR_b$, $-NR_bC(O)R_a$, $-S(O)_bR_a$, $-S(O)_bNR_aR_b$, or R_{S2}, in which R_{S2} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, or 4 to 12-membered heterocycloalkyl, b is 0, 1, or 2, each of R_a and R_b, independently is H or R_{S3}, and R_{S3} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl; or R_a and R_b, together with the N atom to which they are attached, form a 4 to 12-membered heterocycloalkyl ring having 0 or 1 additional heteroatom; and each of R_{S2}, R_{S3}, and the 4 to 12-membered heterocycloalkyl ring formed by R_a and R_b, is optionally substituted with one or more $-Q_2$-T_2, wherein Q_2 is a bond or C_1-C_3 alkyl linker each optionally substituted with halo, cyano, hydroxyl or C_1-C_6 alkoxy, and T_2 is H, halo, cyano, $-OR_c$, $-NR_cR_d$, $-C(O)R_c$, $-C(O)OR_c$, $-C(O)NR_cR_d$, $-NR_dC(O)R_c$, $-NR_dC(O)OR_c$, $-S(O)_2R_c$, $-S(O)_2NR_cR_d$, or R_{S4}, in which each of R_c and R_d, independently is H or R_{S5}, each of R_{S4} and R_{S5}, independently, is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl, or R_c and R_d, together with the N atom to which they are attached, form a 4 to 12-membered heterocycloalkyl ring having 0 or 1 additional heteroatom, and each of R_{S4}, R_{S5}, and the 4 to 12-membered heterocycloalkyl ring formed by R_c and R_d, is optionally substituted with one or more $-Q_3$-T_3, wherein Q_3 is a bond or C_1-C_3 alkyl linker each optionally substituted with halo, cyano, hydroxyl or C_1-C_6 alkoxy, and T_3 is selected from the group consisting of halo, cyano, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, 5- or 6-membered

heteroaryl, OR_e, $COOR_e$, $-S(O)_2R_e$, $-NR_eR_f$, and $-C(O)NR_eR_f$, each of R_e and R_f independently being H or C_1-C_6 alkyl, or $-Q_3$-T_3 is oxo; or$-Q_2$-T_2 is oxo; or

R_6 is H, halo, cyano, azido, $-NR_aR_b$, $-C(O)R_a$, $-C(O)OR_a$, $-C(O)NR_aR_b$, $-NR_bC(O)R_a$, $-S(O)_bR_a$, $-S(O)_bNR_aR_b$, or R_{S2}, in which R_{S2} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, or 4 to 12-membered heterocycloalkyl, b is 0, 1, or 2, each of R_a and R_b, independently is H or R_{S3}, and R_{S3} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl; or R_a and R_b, together with the N atom to which they are attached, form a 4 to 12-membered heterocycloalkyl ring having 0 or 1 additional heteroatom; and each of R_{S2}, R_{S3}, and the 4 to 12-membered heterocycloalkyl ring formed by R_a and R_b, is optionally substituted with one or more $-Q_2$-T_2, wherein Q_2 is a bond or C_1-C_3 alkyl linker each optionally substituted with halo, cyano, hydroxyl or C_1-C_6 alkoxy, and T_2 is H, halo, cyano, $-OR_c$, $-NR_cR_d$, $-C(O)R_c$, $-C(O)OR_c$, $-C(O)NR_cR_d$, $-NR_dC(O)R_c$, $-NR_dC(O)OR_c$, $-S(O)_2R_c$, $-S(O)_2NR_cR_d$, or R_{S4}, in which each of R_c and R_d, independently is H or R_{S5}, each of R_{S4} and R_{S5}, independently, is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl, or R_c and R_d, together with the N atom to which they are attached, form a 4 to 12-membered heterocycloalkyl ring having 0 or 1 additional heteroatom, and each of R_{S4}, R_{S5}, and the 4 to 12-membered heterocycloalkyl ring formed by R_c and R_d, is optionally substituted with one or more $-Q_3$-T_3, wherein Q_3 is a bond or C_1-C_3 alkyl linker each optionally substituted with halo, cyano, hydroxyl or C_1-C_6 alkoxy, and T_3 is selected from the group consisting of halo, cyano, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, 5- or 6-membered heteroaryl, OR_e, $COOR_e$, $-S(O)_2R_e$, $-NR_eR_f$, and $-C(O)NR_eR_f$, each of R_e and R_f independently being H or C_1-C_6 alkyl, or $-Q_3$-T_3 is oxo; or$-Q_2$-T_2 is oxo;

R_7 is $-Q_4$-T_4, in which Q_4 is a bond, C_1-C_4 alkyl linker, or C_2-C_4 alkenyl linker, each linker optionally substituted with halo, cyano, hydroxyl or C_1-C_6 alkoxy, and T_4 is H, halo, cyano, NR_gR_h, $-OR_g$, $-C(O)R_g$, $-C(O)OR_g$, $-C(O)NR_gR_h$, $-C(O)NR_gOR_h$, $-NR_gC(O)R_h$, $-S(O)_2R_g$, or R_{S6}, in which each of R_g and R_h, independently is H or R_{S7}, each of R_{S6} and R_{S7}, independently is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 14-membered heterocycloalkyl, or 5- or 6-membered

heteroaryl, and each of R_{S6} and R_{S7} is optionally substituted with one or more $-Q_5-T_5$, wherein Q_5 is a bond, C(O), $C(O)NR_k$, $NR_kC(O)$, $S(O)_2$, or C_1-C_3 alkyl linker, R_k being H or C_1-C_6 alkyl, and T_5 is H, halo, C_1-C_6 alkyl, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, 5- or 6-membered heteroaryl, or $S(O)_qR_q$ in which q is 0, 1, or 2 and R_q is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl, and T_5 is optionally substituted with one or more substituents selected from the group consisting of halo, C_1-C_6 alkyl, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl except when T_5 is H, halo, hydroxyl, or cyano; or $-Q_5-T_5$ is oxo; or

R_7 is $-Q_4-T_4$, in which Q_4 is a bond, C_1-C_4 alkyl linker, or C_2-C_4 alkenyl linker, each linker optionally substituted with halo, cyano, hydroxyl or C_1-C_6 alkoxy, and T_4 is H, halo, cyano, NR_gR_h, $-OR_g$, $-C(O)R_g$, $-C(O)OR_g$, $-C(O)NR_gR_h$, $-C(O)NR_gOR_h$, $-NR_gC(O)R_h$, $-S(O)_2R_g$, or R_{S6}, in which each of R_g and R_h, independently is H or R_{S7}, each of R_{S6} and R_{S7}, independently is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl, and each of R_{S6} and R_{S7} is optionally substituted with one or more $-Q_5-T_5$, wherein Q_5 is a bond, C(O), $C(O)NR_k$, $NR_kC(O)$, $S(O)_2$, or C_1-C_3 alkyl linker, R_k being H or C_1-C_6 alkyl, and T_5 is H, halo, C_1-C_6 alkyl, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, 5- or 6-membered heteroaryl, or $S(O)_qR_q$ in which q is 0, 1, or 2 and R_q is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl, and T_5 is optionally substituted with one or more substituents selected from the group consisting of halo, C_1-C_6 alkyl, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl except when T_5 is H, halo, hydroxyl, or cyano; or $-Q_5-T_5$ is oxo; provided that (i) R_7 is not $C(O)R_g$ or $-S(O)_2R_g$ when Z is NR_7R_8; (ii) R_7 is not C_1-C_6 alkyl when Z is OR_7, and (iii) R_7 is not H;

each of R_8, R_{11}, R_{12}, and R_{13}, independently, is H, halo, hydroxyl, COOH, cyano, R_{S8}, OR_{S8}, or $COOR_{S8}$, in which R_{S8} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, 4 to 12-membered heterocycloalkyl, amino, mono-C_1-C_6 alkylamino, or di-C_1-C_6 alkylamino, and R_{S8} is optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, and di-C_1-C_6 alkylamino; or R_7 and R_8, together with the N atom to which they are attached, form a 4 to 12-membered heterocycloalkyl ring having 0 to 2 additional heteroatoms, or R_7 and R_8, together with the C atom to which they are attached, form C_3-C_8 cycloalkyl or a 4 to 12-membered heterocycloalkyl ring having 1 to 3 heteroatoms, and each of the 4 to 12-membered heterocycloalkyl rings or C_3-C_8 cycloalkyl formed by R_7 and R_8 is optionally substituted with one or more $-Q_6$-T_6, wherein Q_6 is a bond, C(O), $C(O)NR_m$, $NR_mC(O)$, $S(O)_2$, or C_1-C_3 alkyl linker, R_m being H or C_1-C_6 alkyl, and T_6 is H, halo, C_1-C_6 alkyl, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, 5- or 6-membered heteroaryl, or $S(O)_pR_p$ in which p is 0, 1, or 2 and R_p is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl, and T_6 is optionally substituted with one or more substituents selected from the group consisting of halo, C_1-C_6 alkyl, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl except when T_6 is H, halo, hydroxyl, or cyano; or $-Q_6$-T_6 is oxo; and

R_{14} is absent, H, or C_1-C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl;

provided that the compound is not

N-(5-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)furan-2-carboxamide,

N,N'-(5-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-1,3-phenylene)diacetamide,

N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-pivalamidobenzamide,

3-(3,4-dihydro-2H-benzo[b][1,4]dioxepine-7-sulfonamido)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)benzamide,

N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3,5-dimethoxybenzamide,

N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3,4,5-trimethoxybenzamide,

3-allyl-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-4,5-dimethoxybenzamide,

4-(2-amino-2-oxoethoxy)-3-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-methoxybenzamide,

3-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-4-hydroxy-5-methoxybenzamide, or

3-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-methoxy-4-propoxybenzamide.

[0356] For example, X_1 is CR_{11} and X_2 is CR_{13}.

[0357] For example, X_1 is CR_{11} and X_2 is N.

[0358] For example, X_1 is N and X_2 is CR_{13}.

[0359] For example, X_1 is N and X_2 is N.

[0360] For example, X_3 is C.

[0361] For example, X_3 is N and R_6 is absent.

[0362] For example, Z is NR_7R_8.

[0363] For example, Z is $CR_7R_8R_{14}$.

[0364] For example, Z is OR_7.

[0365] For example, Z is $S(O)_aR_7$, in which a is 0, 1, or 2.

[0366] For example, Z is SR_7.

[0367] For example, R_6 is H.

[0368] For example, R_6 is halo (*e.g.*, fluorine, chlorine, bromine, and iodine).

[0369] For example, R_6 is C_1-C_3 alkyl optionally substituted with one or more $-Q_2$-T_2.

[0370] For example, R_6 is CF_3.

[0371] For example, R_6 is C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_3-C_6 cycloalkyl each optionally substituted with one or more $-Q_2$-T_2.

[0372] For example, R_6 is ethenyl.

[0373] For example, R_6 is ethynyl.

[0374] For example, R_6 is ethynyl substituted with one or more $-Q_2$-T_2, in which Q_2 is a bond or C_1-C_3 alkyl linker and T_2 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or 4 to 7-membered heterocycloalkyl (e.g., azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, tetrahydro-2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, and morpholinyl, and the like) optionally substituted with one or more $-Q_3$-T_3.

[0375] For example, R_6 is azido.

[0376] For example, R_6 is cyano.

[0377] For example, R_6 is C(O)H.

[0378] For example, R_6 is OR_a or -C(O)R_a.

[0379] For example, R_a is C_1-C_6 alkyl or 4 to 7-membered heterocycloalkyl (e.g., azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, tetrahydro-2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, and morpholinyl, and the like), which is optionally substituted with one or more $-Q_2$-T_2.

[0380] For example, R_6 is 4 to 7-membered heterocycloalkyl (e.g., azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, tetrahydro-2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2,6-

diazaspiro[3.3]heptanyl, and morpholinyl, and the like) optionally substituted with one or more $-Q_2-T_2$.

[0381] For example, R_6 is piperidinyl, 2,2,6,6-tetramethyl-piperidinyl, 1,2,3,6-tetrahydropyridinyl, 2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridinyl, piperazinyl, morpholinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, or pyrrolidinyl, each of which is optionally substituted with one or more $-Q_2-T_2$.

[0382] For example, R_6 is 4 to 7-membered heterocycloalkyl optionally substituted with one or more $-Q_2-T_2$, and $-Q_2-T_2$ is oxo or Q_2 is a bond and T_2 is $-OR_c$, $-NR_cR_d$, $-C(O)R_c$, $-C(O)OR_c$, $-S(O)_2R_c$, C_1-C_6 alkyl, or 4 to 7-membered heterocycloalkyl, each of which is optionally substituted with one or more $-Q_3-T_3$ when R_c or R_d is not H.

[0383] For example, R_6 is $-NR_aR_b$, $-C(O)R_a$, $-C(O)OR_a$, $-C(O)NR_aR_b$, $-NR_bC(O)R_a$, $-SR_a$, $-S(O)_2R_a$, or $-S(O)_2NR_aR_b$.

[0384] For example, each of R_a and R_b, independently is H, C_1-C_6 alkyl or C_3-C_8 cycloalkyl optionally substituted with one or more $-Q_2-T_2$.

[0385] For example, one of R_a and R_b is H.

[0386] For example, R_a and R_b, together with the N atom to which they are attached, form a 4 to 7-membered heterocycloalkyl ring having 0 or 1 additional heteroatoms to the N atom (e.g., azetidinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, and morpholinyl, and the like) and the ring is optionally substituted with one or more $-Q_2-T_2$.

[0387] For example, $-Q_2-T_2$ is not H.

[0388] For example, $-Q_2-T_2$ is oxo.

[0389] For example, Q_2 is a bond.

[0390] For example, Q_2 is an unsubstituted C_1-C_3 alkyl linker.

[0391] For example, T_2 is C_1-C_6 alkyl or C_6-C_{10} aryl, each optionally substituted with one or more $-Q_3-T_3$.

[0392] For example, T_2 is an unsubstituted substituted straight chain C_1-C_6 or branched C_3-C_6 alkyl, including but not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl and n-hexyl.

[0393] For example, T_2 is phenyl.

[0394] For example, T_2 is halo (*e.g.*, fluorine, chlorine, bromine, and iodine).

[0395] For example, T_2 is 4 to 7-membered heterocycloalkyl (e.g., azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, tetrahydro-2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, and morpholinyl, and the like) optionally substituted with one or more $-Q_3$-T_3.

[0396] For example, T_2 is $-OR_c$, $-NR_cR_d$, $-C(O)R_c$, $-C(O)OR_c$, or $-S(O)_2R_c$.

[0397] For example, R_c is C_1-C_6 alkyl or 4 to 7-membered heterocycloalkyl (e.g., azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, tetrahydro-2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, and morpholinyl, and the like), which is optionally substituted with one or more $-Q_3$-T_3.

[0398] For example, each of R_c and R_d, independently is H or C_1-C_6 alkyl optionally substituted with one or more $-Q_3$-T_3.

[0399] For example, R_c is H.

[0400] For example, R_d is H.

[0401] For example, R_c and R_d, together with the N atom to which they are attached, form a 4 to 7-membered heterocycloalkyl ring having 0 or 1 additional heteroatoms to the N atom (e.g., azetidinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, and morpholinyl, and the like) and the ring is optionally substituted with one or more $-Q_3$-T_3.

[0402] For example, Q_2 is a bond and T_2 is $-OR_c$, $-NR_cR_d$, $-C(O)R_c$, $-C(O)OR_c$, $-S(O)_2R_c$, C_1-C_6 alkyl, or 4 to 7-membered heterocycloalkyl, each of which is optionally substituted with one or more $-Q_3$-T_3 when R_c or R_d is not H.

[0403] For example,–Q_3-T_3 is oxo.

[0404] For example, T_2 is 4 to 7-membered heterocycloalkyl or C_3-C_8 cycloalkyl and one or more –Q_3-T_3 are oxo.

[0405] For example, Q_3 is a bond or unsubstituted or substituted C_1-C_3 alkyl linker.

[0406] For example, T_3 is H, halo, 4 to 7-membered heterocycloalkyl, C_1-C_3 alkyl, OR_e, $COOR_e$,-$S(O)_2R_e$,–NR_eR_f, or -$C(O)NR_eR_f$.

[0407] For example, one of R_d and R_e is H.

[0408] For example, Q_3 is a bond or C_1-C_3 alkyl linker and T_3 is selected from the group consisting of C_1-C_3 alkyl, halo, OR_e, -$S(O)_2R_e$, -NR_eR_f, and-$C(O)NR_eR_f$.

[0409] For example, Q_3 is a bond or C_1-C_3 alkyl linker and T_3 is selected from the group consisting of C_1-C_3 alkyl, OR_e, -$S(O)_2R_e$, or -NR_eR_f.

[0410] For example, R_e is H.

[0411] For example, R_f is H.

[0412] For example, R_7 is not H.

[0413] For example, R_7 is -$C(O)R_g$.

[0414] For example, R_7 is -$C(O)R_g$, in which R_g is C_3-C_8 cycloalkyl, or 4 to 7-membered heterocycloalkyl, C_3-C_8 cycloalkyl.

[0415] For example, R_7 is C_6-C_{10} aryl substituted with one or more –Q_5-T_5.

[0416] For example, R_7 is phenyl optionally substituted with one or more –Q_5-T_5.

[0417] For example, R_7 is C_1-C_6 alkyl optionally substituted with one or more –Q_5-T_5.

[0418] For example, R_7 is C_3-C_8 cycloalkyl optionally substituted with one or more –Q_5-T_5.

[0419] For example, R_7 is 4 to 7-membered heterocycloalkyl (e.g., azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, tetrahydro-2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, and morpholinyl, and the like) optionally substituted with one or more –Q_5-T_5.

[0420] For example, R_7 is 8 to 14-membered heterocycloalkyl such as 1,4-dioxaspiro[4.5]decanyl (e.g., 1,4-dioxaspiro[4.5]decan-8-yl), 1,4-dioxa-8-azaspiro[4.5]decanyl

(e.g., 1,4-dioxa-8-azaspiro[4.5]decan-8-yl), 1-oxaspiro[4.5]decanyl (e.g., 1-oxaspiro[4.5]decan-8-yl or 1-oxaspiro[4.5]decan-2-one-8-yl), 1-azaspiro[4.5]decanyl (e.g., 1-azaspiro[4.5]decan-8-yl or 1-azaspiro[4.5]decan-2-one-8-yl), 3'H-spiro[cyclohexane-1,1'-isobenzofuran]-yl (e.g., 3'H-spiro[cyclohexane-1,1'-isobenzofuran]-4-yl or 3'H-spiro[cyclohexane-1,1'-isobenzofuran]-3'-one-4-yl), 7'H-spiro[cyclohexane-1,5'-furo[3,4-b]pyridin]-yl (e.g., 7'H-spiro[cyclohexane-1,5'-furo[3,4-b]pyridin]-4-yl or 7'H-spiro[cyclohexane-1,5'-furo[3,4-b]pyridin]-7'-one-4-yl), or 3'H-spiro[cyclohexane-1,1'-furo[3,4-c]pyridin]-yl (e.g., 3'H-spiro[cyclohexane-1,1'-furo[3,4-c]pyridin]-4-yl or 3'H-spiro[cyclohexane-1,1'-furo[3,4-c]pyridin]-3'-one-4-yl), each optionally substituted with one or more $-Q_5$-T_5.

[0421] For example, R_7 is 5 to 6-membered heterocycloalkyl optionally substituted with one or more $-Q_5$-T_5.

[0422] For example, R_7 is isopropyl.

[0423] For example, R_7 is pyrrolidinyl, piperidinyl, tetrahydropyran, cyclopentyl, or cyclohexyl, cycloheptyl, each optionally substituted with one $-Q_5$-T_5.

[0424] For example, R_7 is cyclopentyl or cyclohexyl, each optionally substituted with one $-Q_5$-T_5.

[0425] For example, Q_5 is NHC(O) and T_5 is C_1-C_6 alkyl or C_1-C_6 alkoxy.

[0426] For example, $-Q_5$-T_5 is oxo.

[0427] For example, T_4 is 4 to 7-membered heterocycloalkyl or C_3-C_8 cycloalkyl or C_6-C_{10} aryl, and one or more $-Q_5$-T_5 are oxo.

[0428] For example, R_7 is 1-oxide-tetrahydro-2H-thiopyranyl or 1,1-dioxide-tetrahydro-2H-thiopyranyl.

[0429] For example, R_7 is cyclohexanonyl, e.g., cyclohexanon-4-yl.

[0430] For example, T_5 is H, halo, C_1-C_6 alkyl, C_1-C_6 alkoxyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, or 4 to 7-membered heterocycloalkyl.

[0431] For example, Q_5 is a bond and T_5 is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, or 4 to 7-membered heterocycloalkyl.

[0432] For example, Q_5 is a bond and T_5 is 5- or 6-membered heteroaryl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, T_5 being optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, C_1-C_6 alkoxyl, or C_3-C_8 cycloalkyl.

[0433] For example, Q_5 is CO, $S(O)_2$, or NHC(O); and T_5 is C_1-C_6 alkyl, C_1-C_6 alkoxyl, C_3-C_8 cycloalkyl, or 4 to 7-membered heterocycloalkyl.

[0434] For example, T_5 is C_1-C_6 alkyl or C_1-C_6 alkoxyl, each optionally substituted with halo, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, or C_3-C_8 cycloalkyl.

[0435] For example, Q_5 is C_1-C_3 alkyl linker and T_5 is H or C_6-C_{10} aryl.

[0436] For example, Q_5 is C_1-C_3 alkyl linker and T_5 is C_3-C_8 cycloalkyl, 4 to 7-membered heterocycloalkyl, or $S(O)_qR_q$.

[0437] For example, R_6 is halo (*e.g.*, fluorine, chlorine, bromine, and iodine) and Z is $S(O)_aR_7$, in which a is 0, 1, or 2 and R_7 is C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, butyl, or t-butyl), C_3-C_8 cycloalkyl (e.g., cyclopentyl, cyclohexyl, or cycloheptyl) or 4 to 14-membered heterocycloalkyl (e.g., azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, tetrahydro-2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, morpholinyl, 1,4-dioxaspiro[4.5]decanyl, 1,4-dioxa-8-azaspiro[4.5]decanyl, 1-oxaspiro[4.5]decanyl, 1-azaspiro[4.5]decanyl, 3'H-spiro[cyclohexane-1,1'-isobenzofuran]-yl, 7'H-spiro[cyclohexane-1,5'-furo[3,4-b]pyridin]-yl, or 3'H-spiro[cyclohexane-1,1'-furo[3,4-c]pyridin]-yl, and the like) and R_7 is optionally substituted with one or more $-Q_5$-T_5.

[0438] For example, R_6 is halo (*e.g.*, fluorine, chlorine, bromine, and iodine) and Z is OR_7 in which R_7 is 4 to 14-membered heterocycloalkyl (e.g., azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, tetrahydro-2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, morpholinyl, 1,4-dioxaspiro[4.5]decanyl, 1,4-dioxa-8-azaspiro[4.5]decanyl, 1-oxaspiro[4.5]decanyl, 1-azaspiro[4.5]decanyl, 3'H-spiro[cyclohexane-1,1'-isobenzofuran]-yl, 7'H-spiro[cyclohexane-1,5'-furo[3,4-b]pyridin]-yl, or 3'H-spiro[cyclohexane-1,1'-furo[3,4-c]pyridin]-yl, and the like) and R_7 is optionally substituted with one or more $-Q_5$-T_5.

[0439] For example, R_{11} is H.

[0440] For example, each of R_2 and R_4, independently, is H or C_1-C_6 alkyl optionally substituted with amino, azido, halo, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, or C_6-C_{10} aryl.

[0441] For example, each of R_2 and R_4, independently is C_1-C_3 alkyl optionally substituted withC_1-C_6 alkoxyl.

[0442] For example, each of R_2 and R_4 is methyl.

[0443] For example, R_1 is H.

[0444] For example, R_1 is C_1-C_6 alkyl optionally substituted with azido, halo, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, or C_6-C_{10} aryl.

[0445] For example, R_{12} is H, methyl, ethyl, ethenyl, or halo.

[0446] For example, R_{12} is methyl.

[0447] For example, R_{12} is ethyl or propenyl.

[0448] For example, R_{12} is methoxyl.

[0449] For example, R_{12} is ethenyl.

[0450] For example, R_8 is H, methyl, ethyl, or ethenyl.

[0451] For example, R_8 is methyl.

[0452] For example, R_8 is ethyl.

[0453] For example, R_8 is propyl.

[0454] For example, R_8 is ethenyl or propenyl.

[0455] For example, R_8 is C_1-C_6 alkyl substituted with one or more substituents selected from the group consisting of halo (e.g., F, Cl, or Br), hydroxyl, or C_1-C_6 alkoxyl.

[0456] For example, R_8 is 4 to 7-membered optionally substituted heterocycloalkyl (e.g., azetidinyl, oxctanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, tetrahydro-2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, and morpholinyl, and the like).

[0457] For example, R_8 is piperidinyl.

[0458] For example, R_8 is 4 to 7-membered optionally substituted heterocycloalkyl and R_7 is $-Q_4$-T_4, in which Q_4 is a bond or C_1-C_4 alkyl linker and T_4 is H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl or 4 to 7-membered heterocycloalkyl.

[0459] For example, Z is NR_7R_8 or $CR_7R_8R_{14}$ wherein R_7 and R_8, together with the atom to which they are attached, form a 4 to 11-membered heterocycloalkyl ring having 1 to 3 heteroatoms (e.g., azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, tetrahydro-2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, morpholinyl, 1,4-dioxa-8-azaspiro[4.5]decanyl, and the like) or C_3-C_8 cycloalkyl, each optionally substituted with one or more $-Q_6$-T_6.

[0460] For example, the ring formed by R_7 and R_8 is selected from the group consisting of azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, 1,4-dioxa-8-azaspiro[4.5]decanyl, and cyclohexenyl, each optionally substituted with one $-Q_6$-T_6.

[0461] For example, Z is 1,4-dioxa-8-azaspiro[4.5]decan-8-yl, pyrrolidine-2,5-dione-1-yl, or piperidine-2,6-dione-1-yl.

[0462] For example, one or more $-Q_6$-T_6 is oxo.

[0463] For example, T_6 is H, halo, C_1-C_6 alkyl, C_1-C_6 alkoxyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, or 4 to 7-membered heterocycloalkyl.

[0464] For example, Q_6 is a bond and T_6 is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, or 4 to 7-membered heterocycloalkyl.

[0465] For example, Q_6 is CO, $S(O)_2$, or NHC(O); and T_6 is C_1-C_6 alkyl, C_1-C_6 alkoxyl, C_3-C_8 cycloalkyl, or 4 to 7-membered heterocycloalkyl.

[0466] For example, T_6 is C_1-C_6 alkyl or C_1-C_6 alkoxyl, each optionally substituted with halo, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, or C_3-C_8 cycloalkyl.

[0467] For example, Q_6 is C_1-C_3 alkyl linker and T_6 is H or C_6-C_{10} aryl.

[0468] For example, Q_6 is C_1-C_3 alkyl linker and T_6 is C_3-C_8 cycloalkyl, 4 to 7-membered heterocycloalkyl, or $S(O)_pR_p$.

[0469] For example, each of R_p and R_q, independently, is C_1-C_6 alkyl.

[0470] For example, R_6 is $-S(O)_bR_a$ or azido, in which b is 0, 1, or 2 and R_a is C_1-C_6 alkyl or C_3-C_8 cycloalkyl; and Z is NR_7R_8, in which R_7 is C_3-C_8 cycloalkyl (e.g., cyclopentyl, cyclohexyl, or cycloheptyl) or 4 to 14-membered heterocycloalkyl (e.g., azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, tetrahydro-2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, morpholinyl, 1,4-dioxaspiro[4.5]decanyl, 1,4-dioxa-8-azaspiro[4.5]decanyl, 1-oxaspiro[4.5]decanyl, 1-azaspiro[4.5]decanyl, 3'H-spiro[cyclohexane-1,1'-isobenzofuran]-yl, 7'H-spiro[cyclohexane-1,5'-furo[3,4-b]pyridin]-yl, or 3'H-spiro[cyclohexane-1,1'-furo[3,4-c]pyridin]-yl, and the like), each optionally substituted with one or more $-Q_5$-T_5; and R_8 is H or C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, butyl, or t-butyl).

[0471] For example, R_6 is halo (*e.g.*, fluorine, chlorine, bromine, and iodine) and Z is NR_7R_8 or $CR_7R_8R_{14}$ wherein R_7 and R_8, together with the atom to which they are attached, form a 4 to 11-membered heterocycloalkyl ring having 1 to 3 heteroatoms (e.g., azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, tetrahydro-2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, morpholinyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, 1,4-dioxa-8-azaspiro[4.5]decanyl, 1,4-dioxa-8-azaspiro[4.5]decan-8-yl, pyrrolidine-2,5-dione-1-yl, piperidine-2,6-dione-1-yl, and the like) or C_3-C_8 cycloalkyl, each optionally substituted with one or more $-Q_6$-T_6.

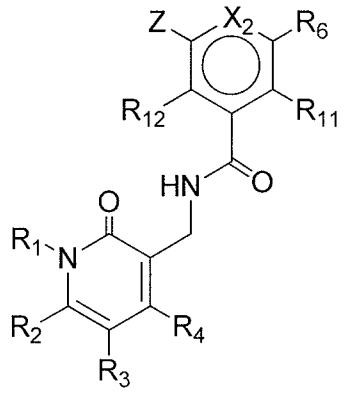
[0472] For example, R_{13} is H or methyl.

[0473] For example, R_{13} is H.

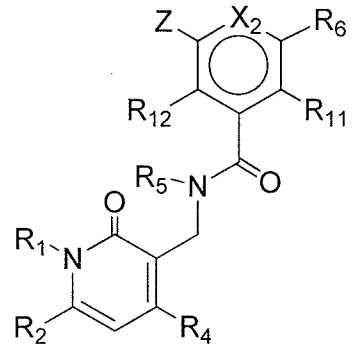
[0474] For example, R_3 is H.

[0475] For example, each of R_5, R_9, and R_{10} is H.

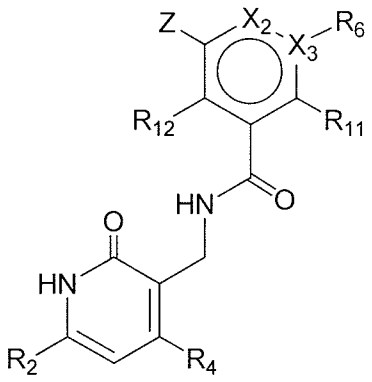
[0476] Another subset of the compounds of Formula (I) includes those of Formula (Ib), (Ic), or (Id):



(Ib)

, 

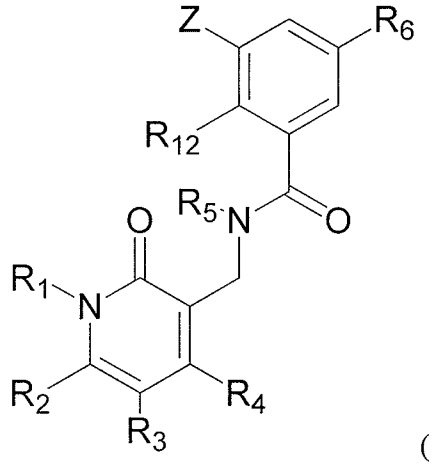
(Ic)

, or 

(Id)

or a pharmaceutically acceptable salt or ester thereof, wherein Z, X_2, X_3, R_1, R_2, R_3, R_4, R_5, R_6, R_{11}, and R_{12} are as defined herein for Formula (I).

[0477] Yet another subset of the compounds of Formula (I) is those of Formula (Ie):



(Ie),

wherein

Z is NR_7R_8, OR_7, or $S(O)_aR_7$;

R_1 is H or C_1-C_6 alkyl optionally substituted with one or more substituents selected from hydroxyl, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, and C_6-C_{10} aryl;

each of R_2 and R_4 independently, is $-Q_1$-T_1 , in which Q_1 is a bond or C_1-C_3 alkyl linker optionally substituted with one or more substituents selected from halo and hydroxyl, and T_1 is H, halo, or azido;

R_3 is H or halo;

R_5 is H or C_1-C_6 alkyl;

R_6 is H, halo, cyano, azido, OR_a, $-NR_aR_b$, $-C(O)NR_aR_b$, $-S(O)_bR_a$, or R_{S2}; wherein R_{S2} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or 4 to 12-membered heterocycloalkyl, and wherein each of R_a and R_b, independently is H, C_1-C_6 alkyl, or 4 to 12-membered heterocycloalkyl,; or R_a and R_b, together with the N atom to which they are attached, form a 4 to 12-membered heterocycloalkyl ring having 0 or 1 additional heteroatom; and each of R_a, R_{S2} and the 4 to 12-membered heterocycloalkyl ring formed by R_a and R_b, is optionally substituted with one or more $-Q_2$-T_2; wherein Q_2 is a bond or C_1-C_3 alkyl linker, and T_2 is H, halo, $-OR_c$, $-NR_cR_d$, $-C(O)OR_c$, or C_1-C_6 alkyl, in which each of R_c and R_d, independently is H or C_1-C_6 alkyl, or R_c and R_d, together with the N atom to which they are attached, form a 4 to 12-membered heterocycloalkyl ring having 0 or 1 additional heteroatom and optionally substituted with C_1-C_6 alkyl;

R_7 is $-Q_4$-T_4, in which Q_4 is a bond or C_1-C_4 alkyl linker and T_4 is H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, C(O)-C_{1-6} alkyl, C(O)-C_{3-6} cycloalkyl, or 4 to 14-membered heterocycloalkyl, each optionally substituted with one or more $-Q_5$-T_5;

R_8 is H, C_1-C_6 alkyl optionally substituted with halo, hydroxyl or C_1-C_6 alkoxyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, or 4 to 7-membered heterocycloalkyl; or R_7 and R_8, together with the N atom to which they are attached, form a 4 to 12-membered heterocycloalkyl ring having 0 to 2 additional heteroatoms, and the 4 to 12-membered heterocycloalkyl ring formed by R_7 and R_8 is optionally substituted with one or more $-Q_6$-T_6; and

R_{12} is halo, C_1-C_6 alkoxyl, or C_1-C_6 alkyl optionally substituted with halo or C_2-C_6 alkenyl.

[0478] In addition to the above-described features of the compounds of this invention where applicable, the compounds of Formula (Ie) can include one or more of the following features:

[0479] For example, R_1 is H or C_1-C_6 alkyl optionally substituted one or more times with a substituent selected from hydroxyl, C_1-C_6 alkoxyl and C_6-C_{10} aryl; R_7 is $-Q_4$-T_4, in which Q_4 is a bond or a C_1-C_4 alkyl linker, and T_4 is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, C(O)- C_1-C_6 alkyl, C(O)- C_3-C_6 cycloalkyl, dihydropyranyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperidinyl, pyrrolidinyl, azetidinyl and oxetanyl, each optionally substituted with one or more substituents independently selected from oxo and $-Q_5$-T_5; R_8 is H or C_1-C_6 alkyl, C_1-C_6

haloalkyl, C_2-C_6 alkenyl or C_3-C_8 cycloalkyl; and R_{12} is halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl or C_1-C_6 alkoxyl.

[0480] For example, Z is NR_7R_8 or SR_7; R_6 is H, halo, cyano, OR_a, $-C(O)NR_aR_b$, $-S(O)_2R_a$, or R_{S2}; wherein R_{S2} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or 4 to 12-membered heterocycloalkyl, and wherein each of R_a and R_b, independently is H or C_1-C_6 alkyl; or R_a and R_b, together with the N atom to which they are attached, form a 4 to 12-membered heterocycloalkyl ring having 0 or 1 additional heteroatom; and each of R_{S2} and the 4 to 12-membered heterocycloalkyl ring formed by R_a and R_b, is optionally substituted with one or more $-Q_2$-T_2; wherein Q_2 is a bond or C_1-C_3 alkyl linker, and T_2 is H, halo, $-OR_c$, $-NR_cR_d$, $-C(O)OC_1$-C_6 alkyl, or C_1-C_6 alkyl, in which each of R_c and R_d, independently is H or C_1-C_6 alkyl, or R_c and R_d, together with the N atom to which they are attached, form a 4 to 12-membered heterocycloalkyl ring having 0 or 1 additional heteroatom and 0 or 1 C_1-C_6 alkyl substituents; R_7 is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, dihydropyranyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperidinyl, pyrrolidinyl, azetidinyl and oxetanyl, each optionally substituted with one or more substituents independently selected from oxo and $-Q_5$-T_5; and R_{12} is halo or C_1-C_6 alkyl.

[0481] For example, R_2, R_4 and R_{12} are each independently C_1-C_6 alkyl and R_5 is H.

[0482] For example, R_7 is cyclohexyl, dihydropyranyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperidinyl, pyrrolidinyl, azetidinyl oxetanyl, 1,4-dioxaspiro[4.5]decan-8-yl, 1-oxaspiro[4.5]decan-8-yl, 3'H-spiro[cyclohexane-1,1'-isobenzofuran]-4-yl, 7'H-spiro[cyclohexane-1,5'-furo[3,4-b]pyridin]-4-yl, 3'H-spiro[cyclohexane-1,1'-furo[3,4-c]pyridin]-4-yl, or 1-azaspiro[4.5]decan-8-yl, each substituted with one or more $-Q_5$-T_5.

[0483] For example, Z is selected from the group consisting of piperidinyl, morpholinyl, piperazinyl, azetidinyl, pyrrolidinyl, 2-oxa-5-azabicyclo[2.2.1]heptan-5-yl, 1,4-dioxa-8-azaspiro[4.5]decan-8-yl, and cyclohexenyl, each optionally substituted with one $-Q_6$-T_6.

[0484] For example, R_6 is halo (*e.g.*, fluorine, chlorine, bromine, and iodine) and Z is $S(O)_aR_7$, in which a is 0, 1, or 2 and R_7 is C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, butyl, or t-butyl), C_3-C_8 cycloalkyl (e.g., cyclopentyl, cyclohexyl, or cycloheptyl) or 4 to 14-membered heterocycloalkyl (e.g., azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, tetrahydro-

2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, morpholinyl, 1,4-dioxaspiro[4.5]decanyl, 1,4-dioxa-8-azaspiro[4.5]decanyl, 1-oxaspiro[4.5]decanyl, 1-azaspiro[4.5]decanyl, 3'H-spiro[cyclohexane-1,1'-isobenzofuran]-yl, 7'H-spiro[cyclohexane-1,5'-furo[3,4-b]pyridin]-yl, or 3'H-spiro[cyclohexane-1,1'-furo[3,4-c]pyridin]-yl, and the like) and R_7 is optionally substituted with one or more $-Q_5$-T_5.

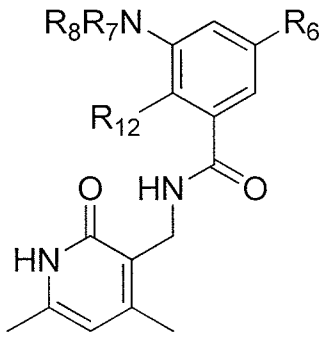
[0485] For example, R_6 is halo (*e.g.*, fluorine, chlorine, bromine, and iodine) and Z is OR_7 in which R_7 is 4 to 14-membered heterocycloalkyl (e.g., azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, tetrahydro-2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, morpholinyl, 1,4-dioxaspiro[4.5]decanyl, 1,4-dioxa-8-azaspiro[4.5]decanyl, 1-oxaspiro[4.5]decanyl, 1-azaspiro[4.5]decanyl, 3'H-spiro[cyclohexane-1,1'-isobenzofuran]-yl, 7'H-spiro[cyclohexane-1,5'-furo[3,4-b]pyridin]-yl, or 3'H-spiro[cyclohexane-1,1'-furo[3,4-c]pyridin]-yl, and the like) and R_7 is optionally substituted with one or more $-Q_5$-T_5.

[0486] For example, R_6 is $-S(O)_bR_a$ or azido, in which b is 0, 1, or 2 and R_a is C_1-C_6 alkyl or C_3-C_8 cycloalkyl; and Z is NR_7R_8, in which R_7 is C_3-C_8 cycloalkyl (e.g., cyclopentyl, cyclohexyl, or cycloheptyl) or 4 to 14-membered heterocycloalkyl (e.g., azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, tetrahydro-2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, morpholinyl, 1,4-dioxaspiro[4.5]decanyl, 1,4-dioxa-8-azaspiro[4.5]decanyl, 1-oxaspiro[4.5]decanyl, 1-azaspiro[4.5]decanyl, 3'H-spiro[cyclohexane-1,1'-isobenzofuran]-yl, 7'H-spiro[cyclohexane-1,5'-furo[3,4-b]pyridin]-yl, or 3'H-spiro[cyclohexane-1,1'-furo[3,4-c]pyridin]-yl, and the like), each optionally substituted with one or more $-Q_5$-T_5; and R_8 is H or C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, butyl, or t-butyl).

[0487] For example, R_6 is halo (*e.g.*, fluorine, chlorine, bromine, and iodine) and Z is NR_7R_8 or $CR_7R_8R_{14}$ wherein R_7 and R_8, together with the atom to which they are attached, form a 4 to 11-membered heterocycloalkyl ring having 1 to 3 heteroatoms (e.g., azetidinyl, oxetanyl,

thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, tetrahydro-2H-thiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, morpholinyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, 1,4-dioxa-8-azaspiro[4.5]decanyl, 1,4-dioxa-8-azaspiro[4.5]decan-8-yl, pyrrolidine-2,5-dione-1-yl, piperidine-2,6-dione-1-yl, and the like) or C_3-C_8 cycloalkyl, each optionally substituted with one or more $-Q_6$-T_6.

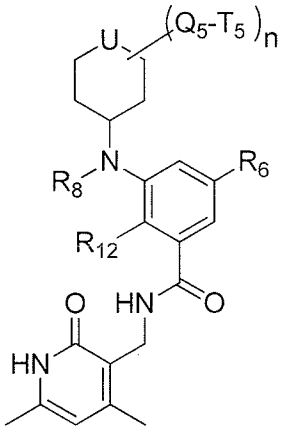
[0488] Another subset of the compounds of Formula (I) includes those of Formula (II):



(II),

or a pharmaceutically acceptable salts or esters thereof, wherein R_6, R_7, R_8, and R_{12} are defined herein.

[0489] Yet another subset of the compounds of Formula (I) includes those of Formula (IIA):



(IIA),

or a pharmaceutically acceptable salts or esters thereof, wherein n is 0, 1, or 2; U is O, S, N-Q_5-T_5, or CH-Q_5-T_5; R_{12} is Cl, Br, or methyl; and R_6, R_7, R_8, Q_5, and T_5 are defined herein.

[0490] In addition to the above-described features of the compounds of this invention where applicable, the compounds of Formula (II) or (IIA) can include one or more of the following features:

[0491] For example, Q_5 is a bond and T_5 is H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, 4 to 12-membered heterocycloalkyl, 5- or 6-membered heteroaryl, amino, mono-C_1-C_6 alkylamino, or di-C_1-C_6 alkylamino, T_5 being optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, C_1-C_6 alkoxyl, or C_3-C_8 cycloalkyl.

[0492] For example, Q_5 is CO, $S(O)_2$, or NHC(O); and T_5 is C_1-C_6 alkyl, C_1-C_6 alkoxyl, C_3-C_8 cycloalkyl, or 4 to 12-membered heterocycloalkyl.

[0493] For example, Q_5 is C_1-C_3 alkyl linker and T_5 is H or C_6-C_{10} aryl.

[0494] For example, Q_5 is C_1-C_3 alkyl linker and T_5 is C_3-C_8 cycloalkyl, 4 to 12-membered heterocycloalkyl, or $S(O)_qR_q$.

[0495] For example, Q_5 is NHC(O) and T_5 is C_1-C_6 alkyl or C_1-C_6 alkoxy.

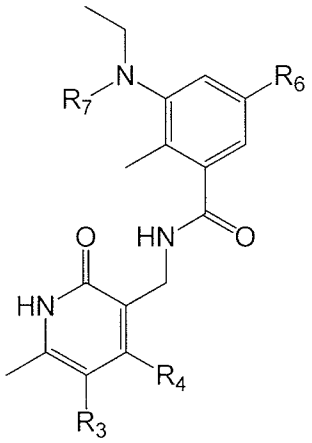
[0496] For example, one or more $-Q_5$-T_5 are oxo.

[0497] For example, U is CH-Q_5-T_5 and n is 0

[0498] For example, one or more $-Q_6$-T_6 are oxo.

[0499] For example, Q_6 is a bond or C(O) and T_6 is C_1-C_6 alkyl or C_1-C_6 alkoxy.

[0500] Still another subset of the compounds of Formula (I) includes those of Formula (III):



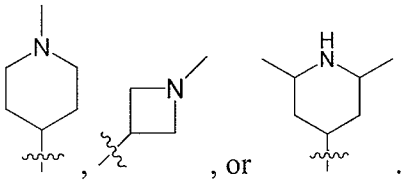
(III),

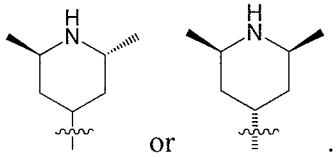
or a pharmaceutically acceptable salts or esters thereof, wherein R_7 is a 4 or 6-membered heterocycloalkyl having one nitrogen atom in the ring and is substituted with one or two methyl groups or one i-propyl group; R^3 is H or F; R_4 is methyl, ethyl, n-propyl, isopropyl, or CF_3, and R_6 is CF_3, Cl, or F, provided that when R_4 is methyl, (1) R_6 is CF_3, or (2) R_3 is F, or (3) R_6 is CF_3 and R_3 is F, or (4) R_6 is F or Cl and R_7 is a 6-membered heterocycloalkyl having only one nitrogen and is substituted with two methyl groups.

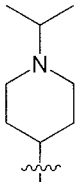
[0501] In addition to the above-described features of the compounds of this invention where applicable, the compounds of Formula (III) can include one or more of the following features:

[0502] For example, R_7 is a 4 or 6-membered heterocycloalkyl having one and only one heteroatom in the ring and the heteroatom is nitrogen.

[0503] For example, R_7 is not further substituted besides the one or two methyl groups or the one i-propyl group.

[0504] For example, R_7 is  .

[0505] For example, R_7 is  .

[0506] For example, R_7 is 

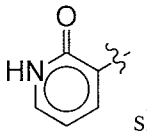
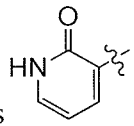
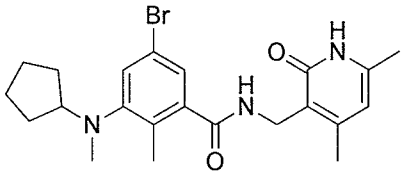
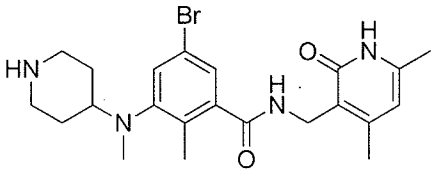
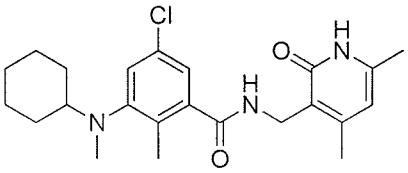
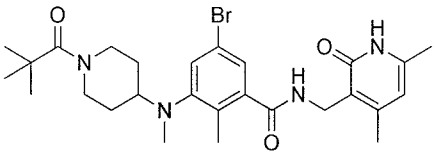
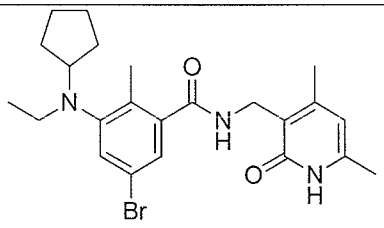
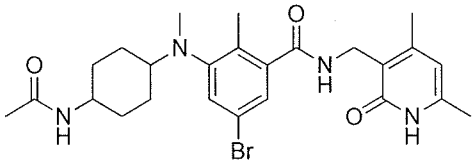
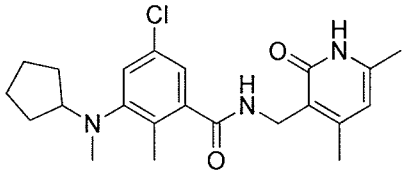
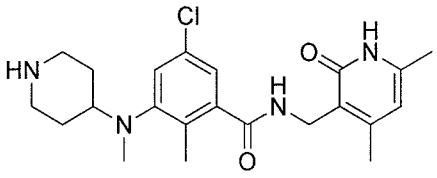
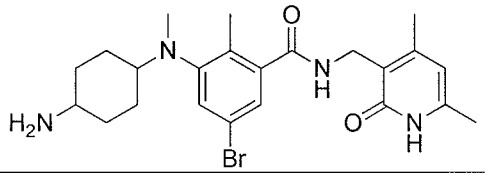
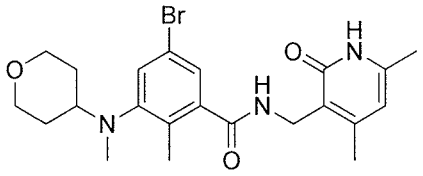
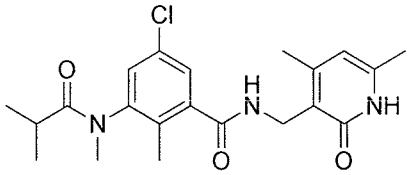
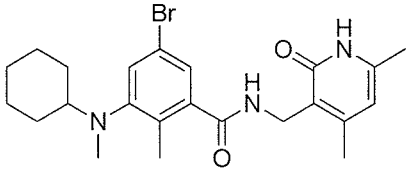
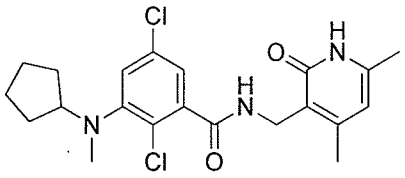
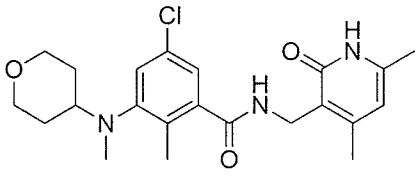
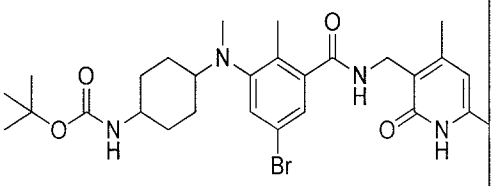
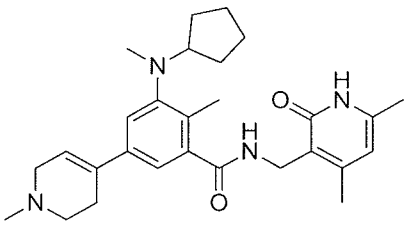
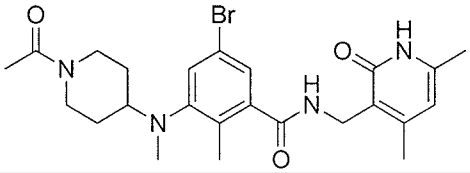
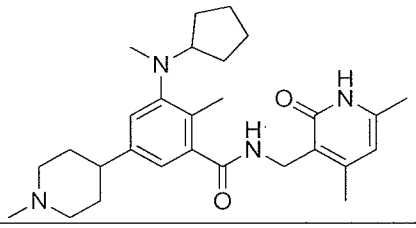
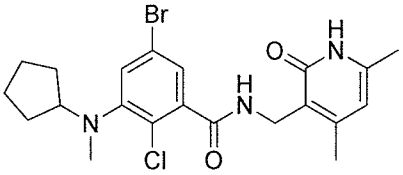
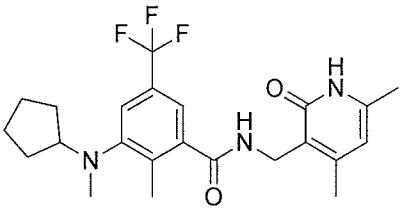
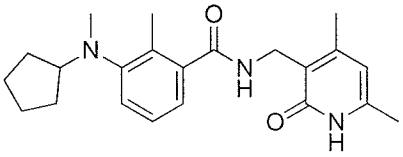
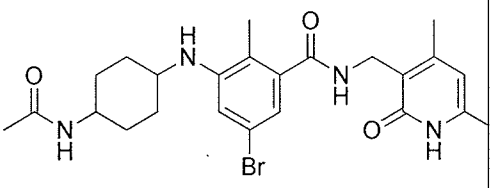
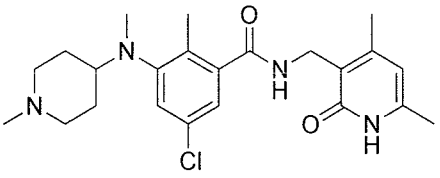
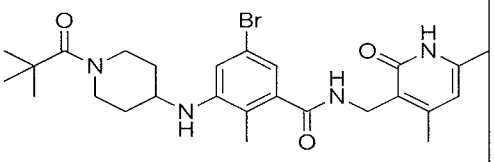
[0507] Representative compounds of the present invention include compounds listed in Table 1. In the table below, each occurrence of  should be construed as  .

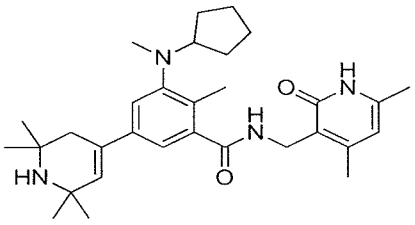
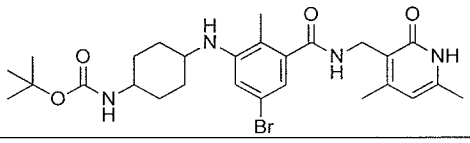
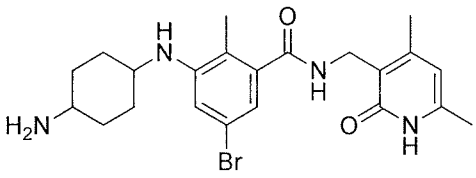
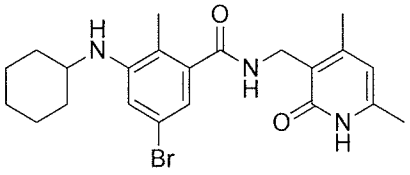
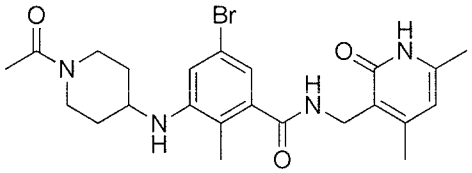
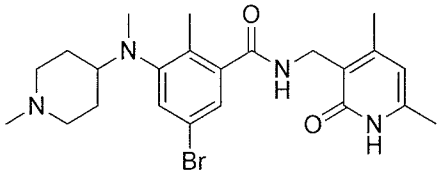
Table 1

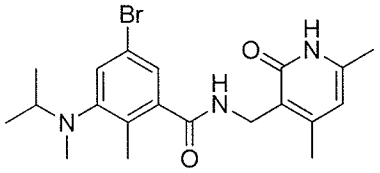
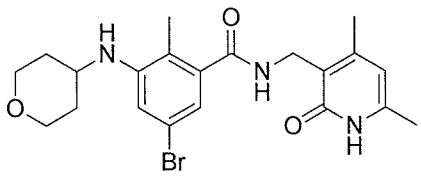
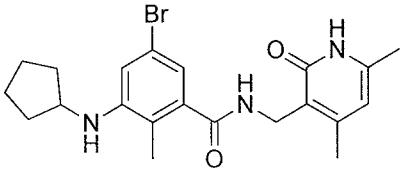
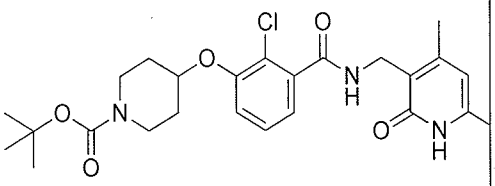
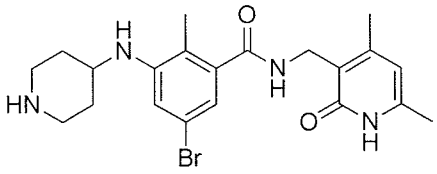
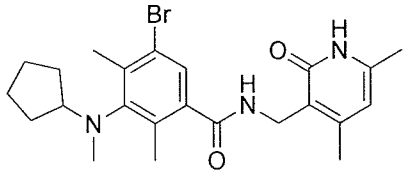
Compound Number	Structure	Name	MS†
1		5-bromo-3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	446.2
2		5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(methyl(piperidin-4-yl)amino)benzamide	462.2
3		5-chloro-3-(cyclohexyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	416.4
4		5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(methyl(1-pivaloylpiperidin-4-yl)amino)benzamide	545.2
5		5-bromo-3-(cyclopentyl(ethyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	460.1
6		3-((4-acetamidocyclohexyl)(methyl)amino)-5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	516.9

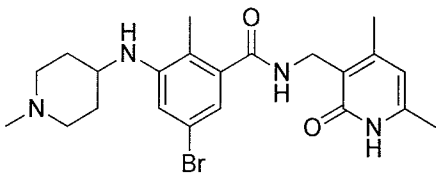
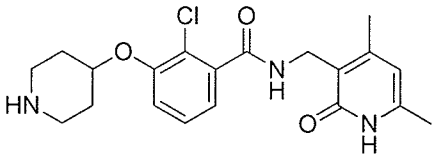
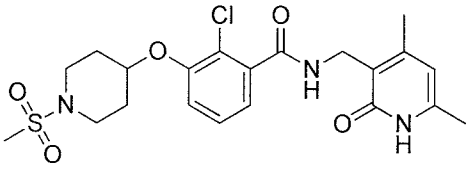
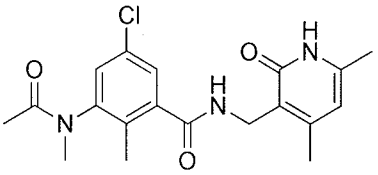
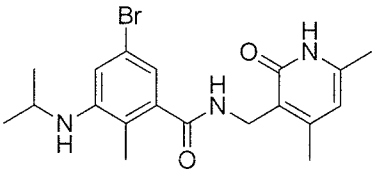
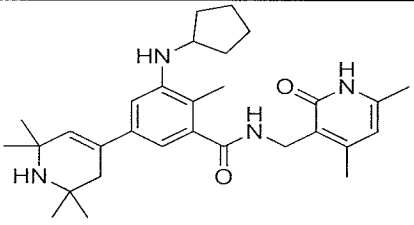
Compound Number	Structure	Name	MS†
7		5-chloro-3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	402.2
8		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(methyl(piperidin-4-yl)amino)benzamide	417.3
9		3-((4-aminocyclohexyl)(methyl)amino)-5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	475.1
10		5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(methyl(tetrahydro-2H-pyran-4-yl)amino)benzamide	462.2
11		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(N-methylisobutyramido)benzamide	404.2
12		5-bromo-3-(cyclohexyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	460.1

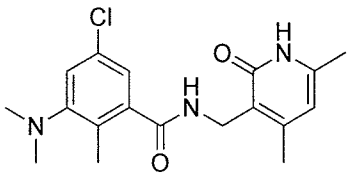
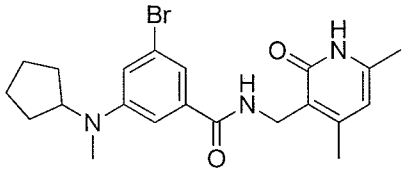
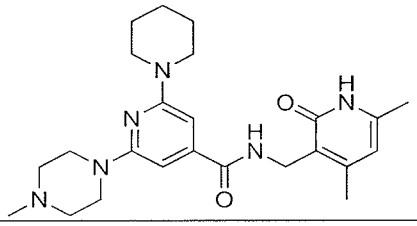
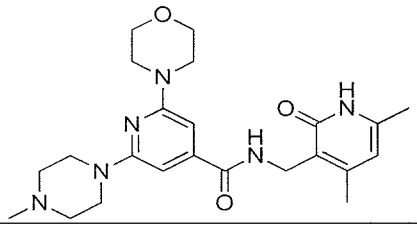
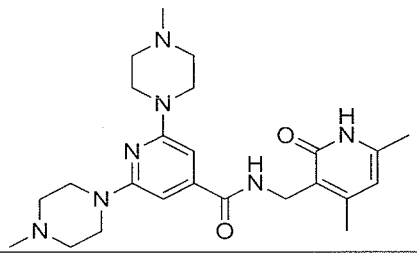
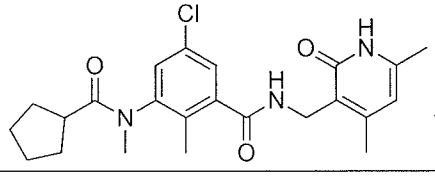
Compound Number	Structure	Name	MS†
13		2,5-dichloro-3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)benzamide	422.1
14		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(methyl(tetrahydro-2H-pyran-4-yl)amino)benzamide	418.3
15		tert-butyl (4-((5-bromo-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(methyl)amino)cyclohexyl)carbamate	575.8
16		3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-5-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)benzamide	463.4
17		3-((1-acetylpiperidin-4-yl)(methyl)amino)-5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	503.2
18		3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-5-(1-methylpiperidin-4-yl)benzamide	465.4

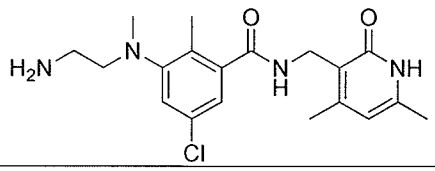
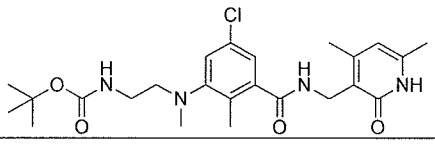
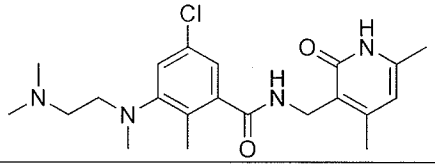
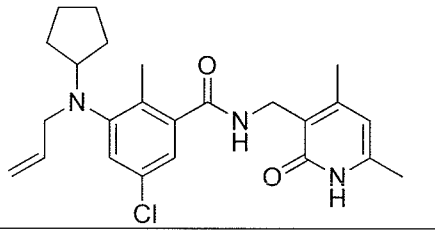
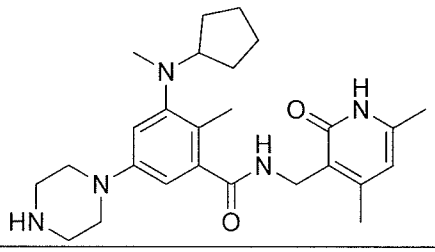
Compound Number	Structure	Name	MS†
19		5-bromo-2-chloro-3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)benzamide	466.1
20		3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-5-(trifluoromethyl)benzamide	436.2
21		3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-5-(trifluoromethyl)benzamide	368.2
22		3-((4-acetamidocyclohexyl)amino)-5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	503.1
23		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(methyl(1-methylpiperidin-4-yl)amino)benzamide	431.3
24		5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-((1-pivaloylpiperidin-4-yl)amino)benzamide	531.1

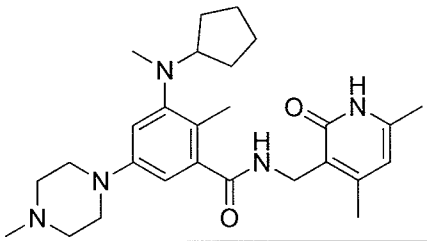
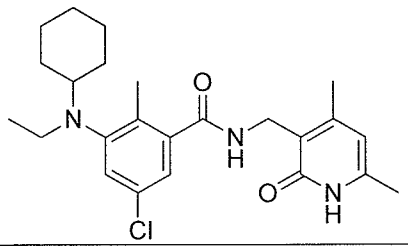
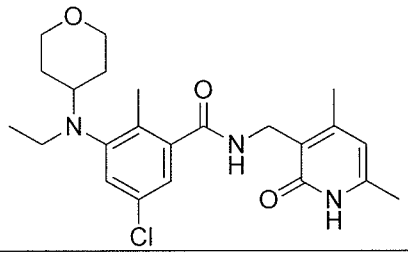
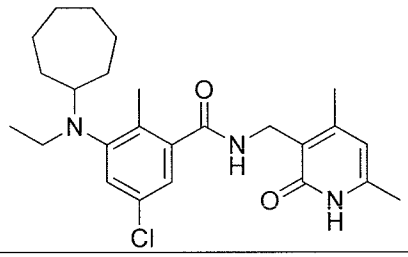
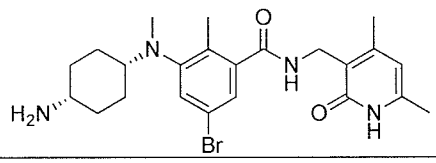
Compound Number	Structure	Name	MS†
25		3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-5-(2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridin-4-yl)benzamide	505.4
26		tert-butyl (4-((5-bromo-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)amino)cyclohexyl)carbamate	562.2
27		3-((4-aminocyclohexyl)amino)-5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	461.1
28		5-bromo-3-(cyclohexylamino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	446.2
29		3-((1-acetylpiperidin-4-yl)amino)-5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	489.2
30		5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(methyl(1-methylpiperidin-4-yl)amino)benzamide	475.02

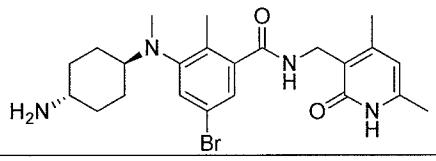
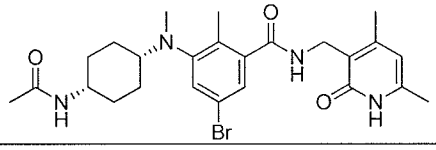
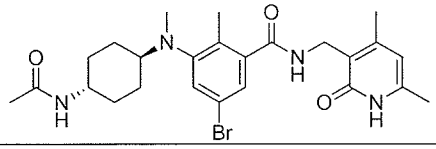
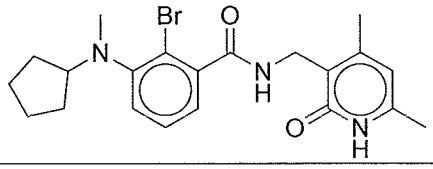
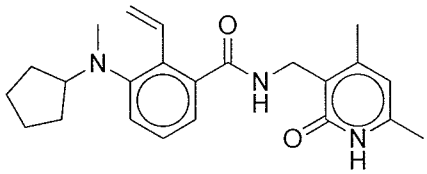
Compound Number	Structure	Name	MS†
31		5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(isopropyl(methyl)amino)-2-methylbenzamide	420.2
32		5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-((tetrahydro-2H-pyran-4-yl)amino)benzamide	447.9
33		5-bromo-3-(cyclopentylamino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	432.1
34		tert-butyl 4-(2-chloro-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)phenoxy)piperidine-1-carboxylate	490.3
35		5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(piperidin-4-ylamino)benzamide	447.1
36		5-bromo-3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,4-dimethylbenzamide	460.1

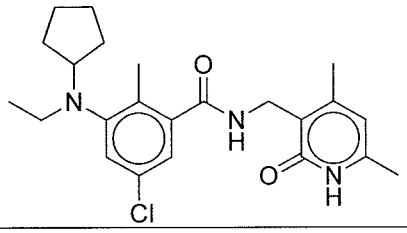
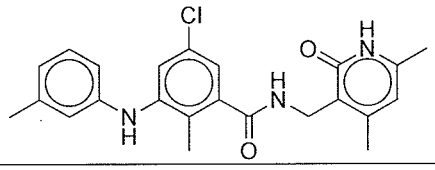
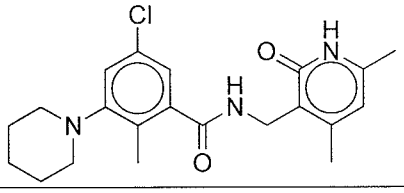
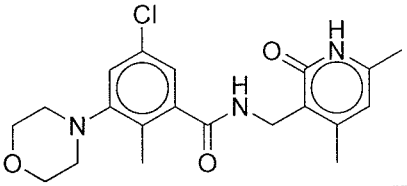
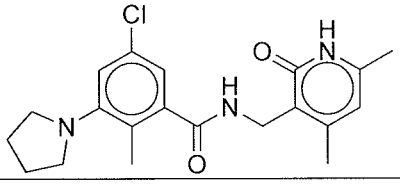
Compound Number	Structure	Name	MS†
37		5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-((1-methylpiperidin-4-yl)amino)benzamide	460.96
38		2-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(piperidin-4-yloxy)benzamide	390.1
39		2-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-((1-(methylsulfonyl)piperidin-4-yl)oxy)benzamide	468.1
40		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(N-methylacetamido)benzamide	376.2
41		5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(isopropylamino)-2-methylbenzamide	406.1
42		3-(cyclopentylamino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-5-(2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridin-4-yl)benzamide	491.2

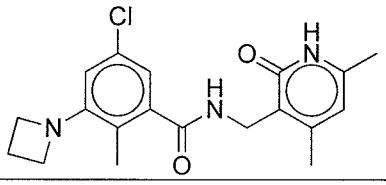
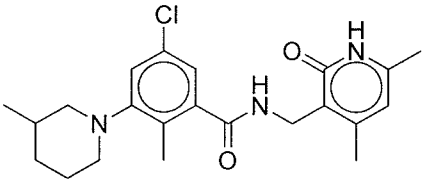
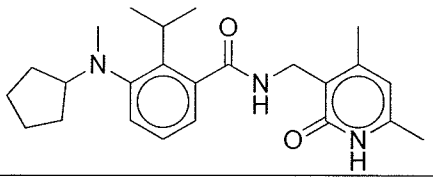
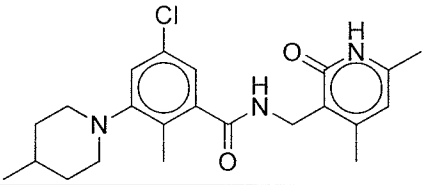
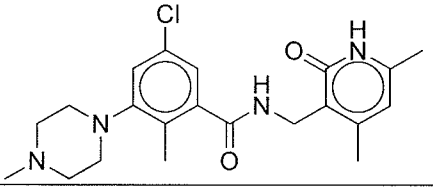
Compound Number	Structure	Name	MS†
43		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(dimethylamino)-2-methylbenzamide	348.2
44		3-bromo-5-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)benzamide	432
45		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-(4-methylpiperazin-1-yl)-6-(piperidin-1-yl)isonicotinamide	438.3
46		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-(4-methylpiperazin-1-yl)-6-morpholinoisonicotinamide	441.2
47		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,6-bis(4-methylpiperazin-1-yl)isonicotinamide	454.2
48		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,6-bis(4-methylpiperazin-1-yl)isonicotinamide	430.2

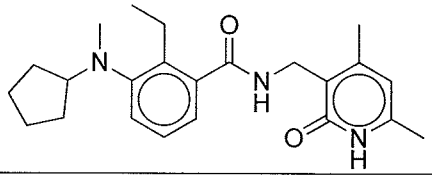
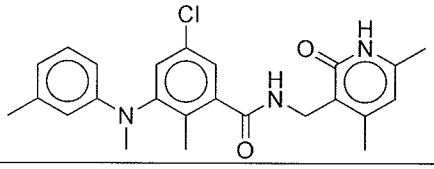
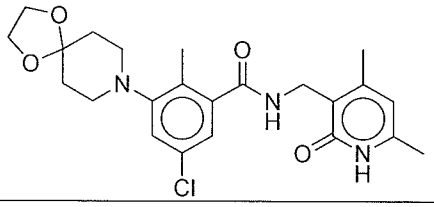
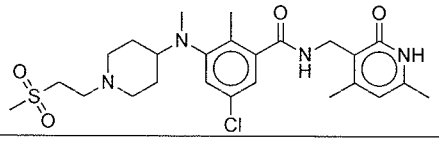
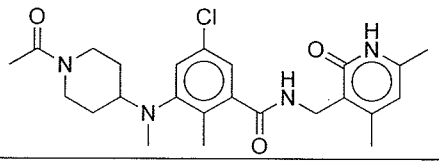
Compound Number	Structure	Name	MS†
49		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(N-methylcyclopentanecarboxamido)benzamide	377.2
50		tert-butyl (2-((5-chloro-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(methyl)amino)ethyl)carbamate	477.3
51		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-((2-(dimethylamino)ethyl)(methyl)amino)-2-methylbenzamide	405.3
52		3-(allyl(cyclopentyl)amino)-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	428.3
53		3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-5-(piperazin-1-yl)benzamide	452.4

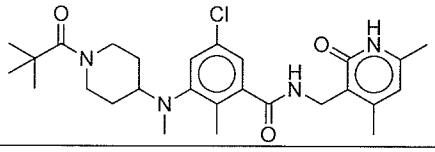
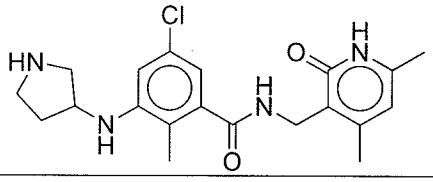
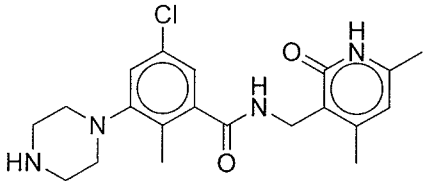
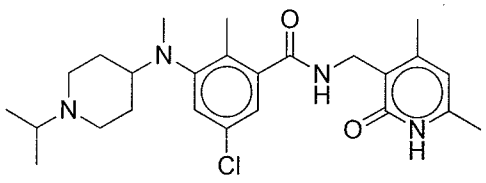
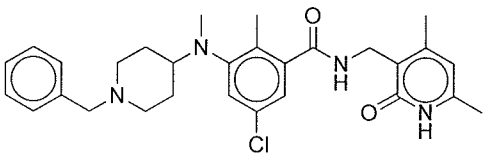
Compound Number	Structure	Name	MS†
54		3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-5-(4-methylpiperazin-1-yl)benzamide	466.4
55		5-chloro-3-(cyclohexyl(ethyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	430.2
56		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-2-methylbenzamide	432.3
57		5-chloro-3-(cycloheptyl(ethyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	444.3
58		3-(((1s,4s)-4-aminocyclohexyl)(methyl)amino)-5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	475.2

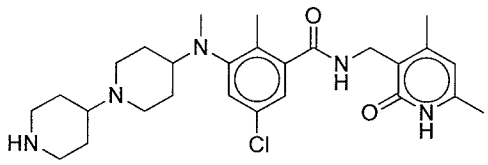
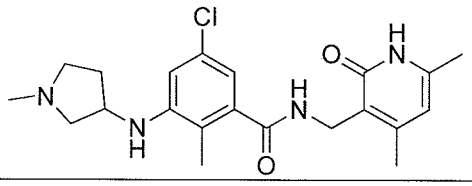
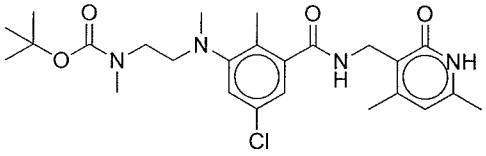
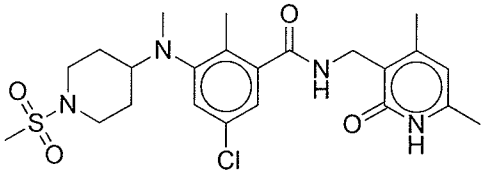
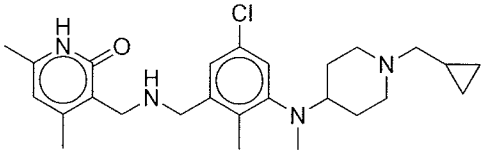
Compound Number	Structure	Name	MS†
59		3-(((1r,4r)-4-aminocyclohexyl)(methyl)amino)-5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	475.2
60		3-(((1s,4s)-4-acetamidocyclohexyl)(methyl)amino)-5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	517.3
61		3-(((1r,4r)-4-acetamidocyclohexyl)(methyl)amino)-5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	517.3
62		2-bromo-3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)benzamide	432.1
63		3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-vinylbenzamide	380.3

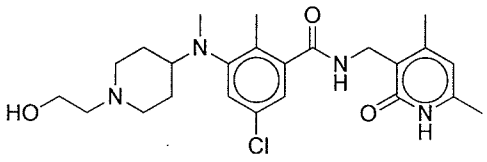
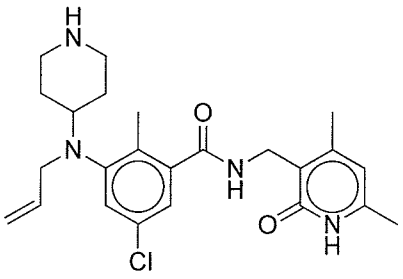
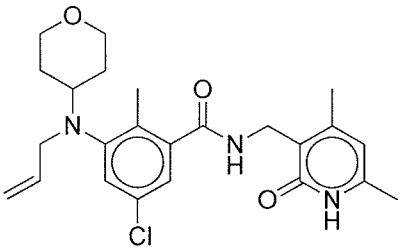
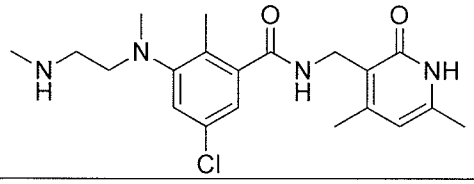
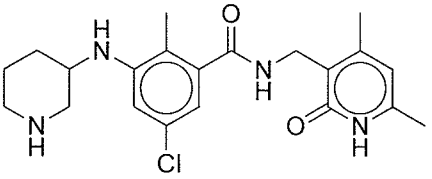
Compound Number	Structure	Name	MS†
64		5-chloro-3-(cyclopentyl(ethyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	416.3
65		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(m-tolylamino)benzamide	410.3
66		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(piperidin-1-yl)benzamide	388.2
67		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-morpholinobenzamide	390.2
68		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(pyrrolidin-1-yl)benzamide	374.2

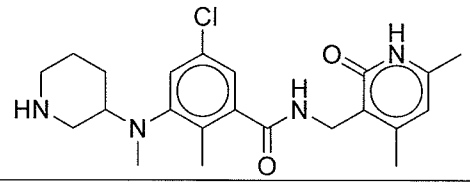
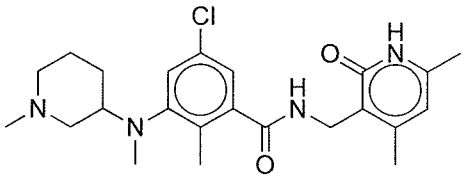
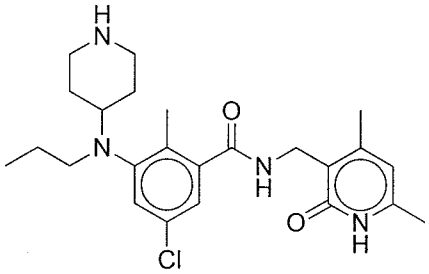
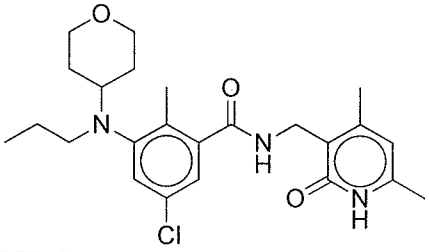
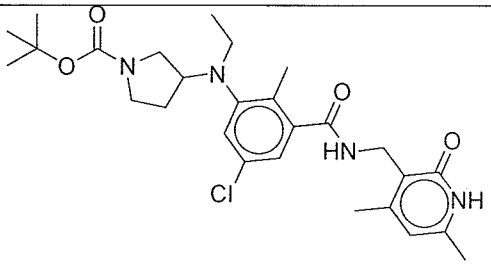
Compound Number	Structure	Name	MS†
69		3-(azetidin-1-yl)-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	360.2
70		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(3-methylpiperidin-1-yl)benzamide	402.3
71		3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-isopropylbenzamide	396.25
72		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(4-methylpiperidin-1-yl)benzamide	402.2
73		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(4-methylpiperazin-1-yl)benzamide	403.2

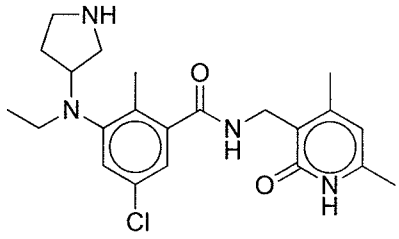
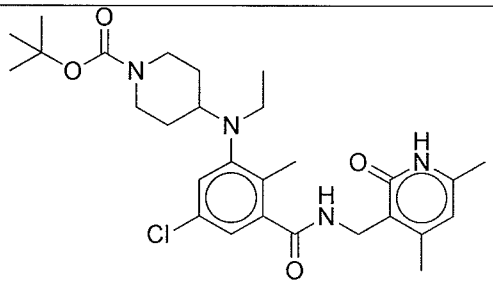
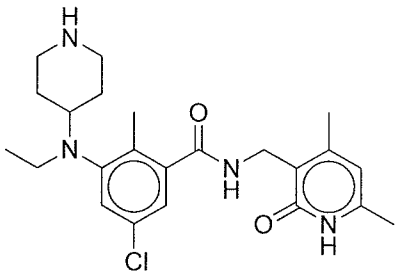
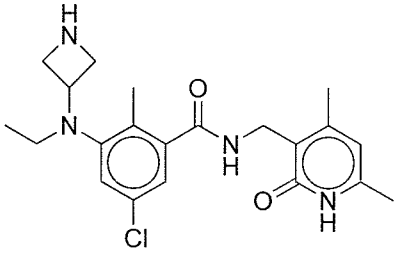
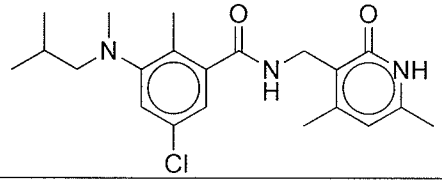
Compound Number	Structure	Name	MS†
74		3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-ethylbenzamide	382.3
75		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(methyl(m-tolyl)amino)benzamide	424.2
76		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)benzamide	446.2
77		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(methyl(1-(2-(methylsulfonyl)ethyl)piperidin-4-yl)amino)benzamide	523.2
78		3-((1-acetylpiperidin-4-yl)(methyl)amino)-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	459.3

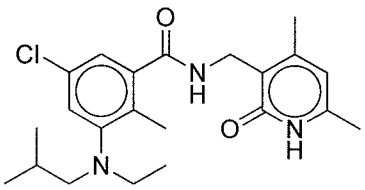
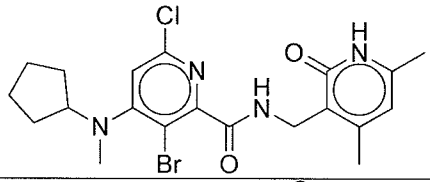
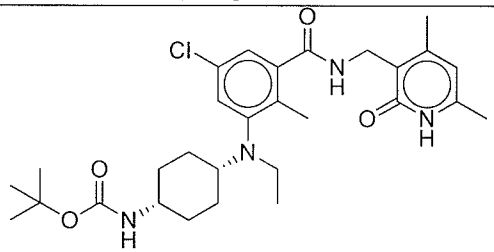
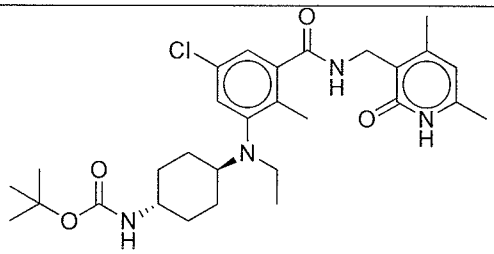
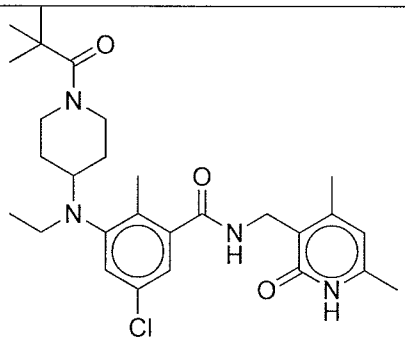
Compound Number	Structure	Name	MS†
79		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(methyl(1-pivaloylpiperidin-4-yl)amino)benzamide	501.2
80		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(pyrrolidin-3-ylamino)benzamide	389.2
81		[[Duplicate with #19]]	
82		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(piperazin-1-yl)benzamide	389.1
83		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-((1-isopropylpiperidin-4-yl)(methyl)amino)-2-methylbenzamide	459.3
84		3-((1-benzylpiperidin-4-yl)(methyl)amino)-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	507.2

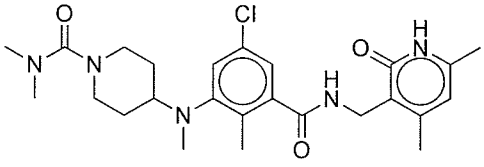
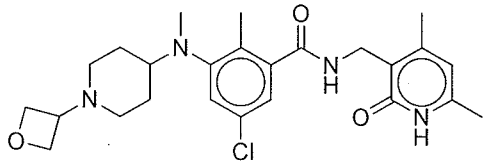
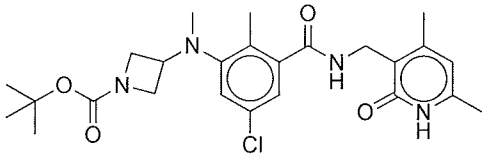
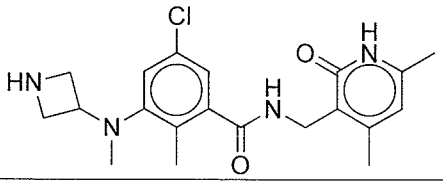
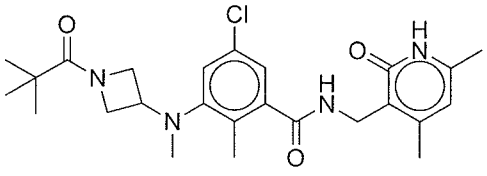
Compound Number	Structure	Name	MS†
85		3-([1,4'-bipiperidin]-4-yl(methyl)amino)-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	500.2
86		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-((1-methylpyrrolidin-3-yl)amino)benzamide	403.1
87		tert-butyl (2-((5-chloro-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(methyl)amino)ethyl)(methyl)carbamate	391.2
88		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(methyl(1-(methylsulfonyl)piperidin-4-yl)amino)benzamide	494.9
89		5-chloro-3-((1-(cyclopropylmethyl)piperidin-4-yl)(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	471.2

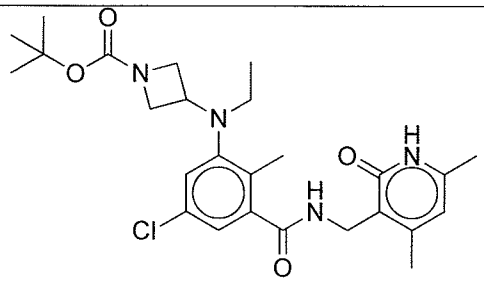
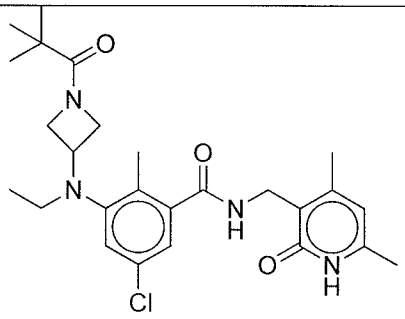
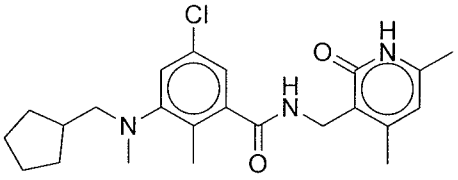
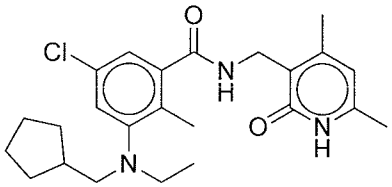
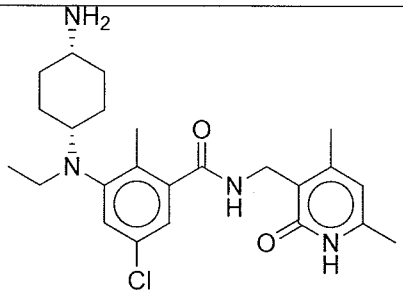
Compound Number	Structure	Name	MS†
90		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-((1-(2-hydroxyethyl)piperidin-4-yl)(methyl)amino)-2-methylbenzamide	461.2
91		3-(allyl(piperidin-4-yl)amino)-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	443.3
92		3-(allyl(tetrahydro-2H-pyran-4-yl)amino)-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	444.3
93		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(methyl(2-(methylamino)ethyl)amino)benzamide	391.2
94		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(piperidin-3-ylamino)benzamide	403.3

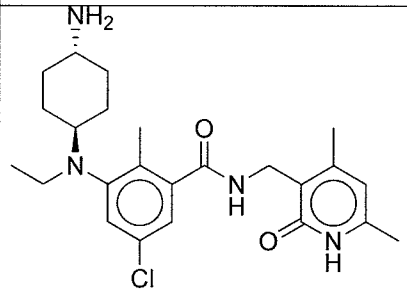
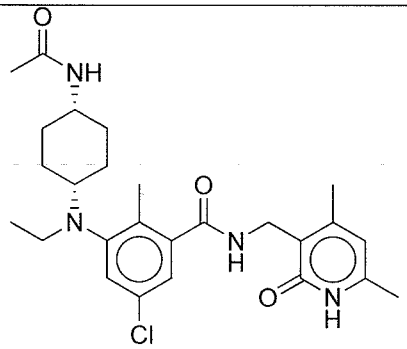
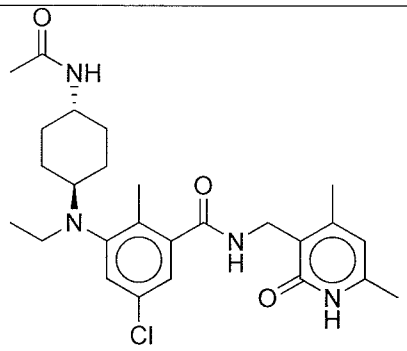
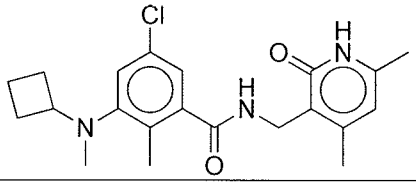
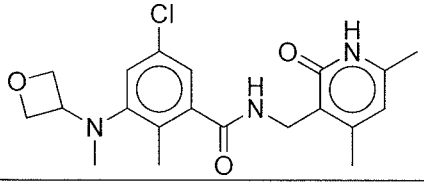
Compound Number	Structure	Name	MS†
95		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(methyl(piperidin-3-yl)amino)benzamide	417.3
96		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(methyl(1-methylpiperidin-3-yl)amino)benzamide	431.2
97		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(piperidin-4-yl(propyl)amino)benzamide	445.3
98		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(propyl(tetrahydro-2H-pyran-4-yl)amino)benzamide	445.3
99		tert-butyl 3-((5-chloro-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(ethyl)amino)pyrrolidine-1-carboxylate	517.4

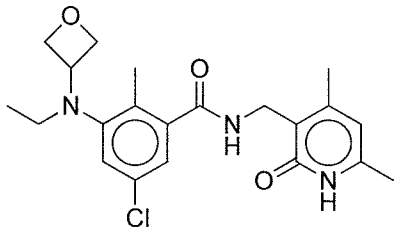
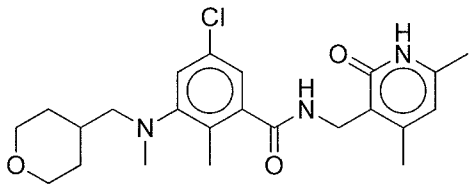
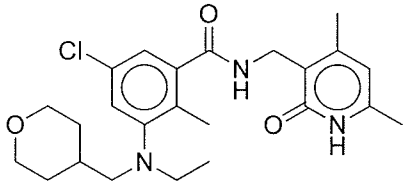
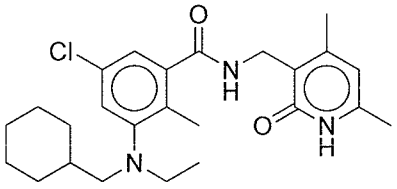
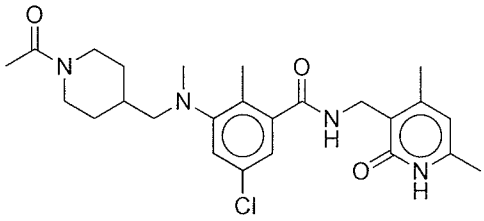
Compound Number	Structure	Name	MS†
100		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(pyrrolidin-3-yl)amino)-2-methylbenzamide	417.3
101		tert-butyl 4-((5-chloro-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(ethyl)amino)piperidine-1-carboxylate	531.4
102		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(piperidin-4-yl)amino)-2-methylbenzamide	431.2
103		3-(azetidin-3-yl(ethyl)amino)-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	403.2
104		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(isobutyl(methyl)amino)-2-methylbenzamide	390.3

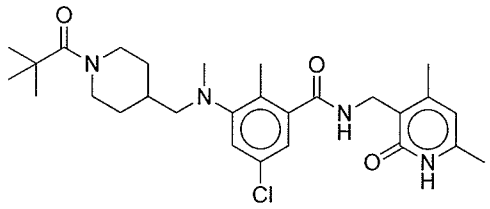
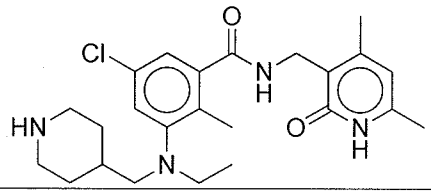
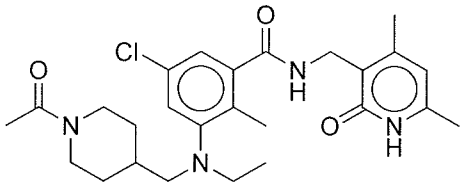
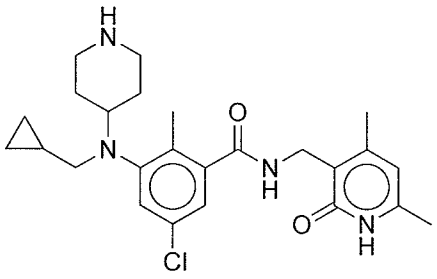
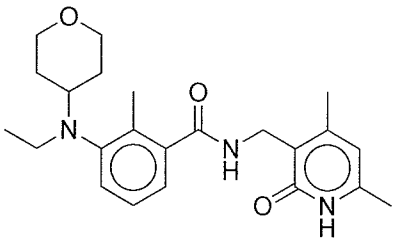
Compound Number	Structure	Name	MS†
105		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(isobutyl)amino)-2-methylbenzamide	404.3
106		3-bromo-6-chloro-4-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)picolinamide	469.2
107		tert-butyl ((1s,4s)-4-((5-chloro-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(ethyl)amino)cyclohexyl)carbamate	545.4
108		tert-butyl ((1r,4r)-4-((5-chloro-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(ethyl)amino)cyclohexyl)carbamate	545.3
109		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(1-pivaloylpiperidin-4-yl)amino)-2-methylbenzamide	515.4

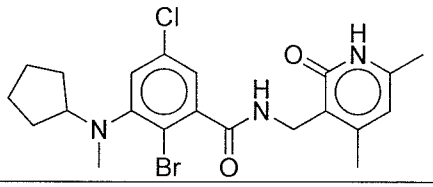
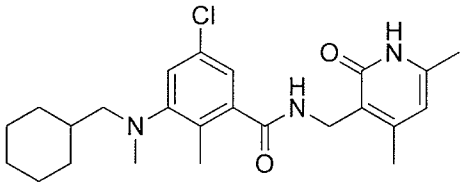
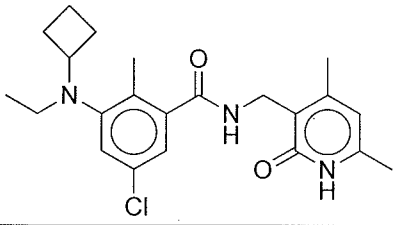
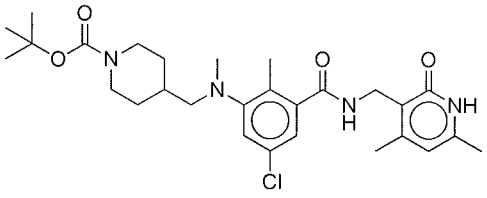
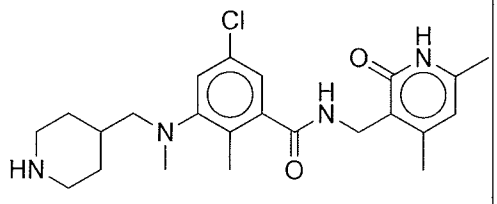
Compound Number	Structure	Name	MS†
110		4-((5-chloro-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(methyl)amino)-N,N-dimethylpiperidine-1-carboxamide	488.2
111		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(methyl(1-(oxetan-3-yl)piperidin-4-yl)amino)benzamide	473.3
112		tert-butyl 3-((5-chloro-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(methyl)amino)azetidine-1-carboxylate	489.3
113		3-(azetidin-3-yl(methyl)amino)-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	389.3
114		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(methyl(1-pivaloylazetidin-3-yl)amino)benzamide	473.2

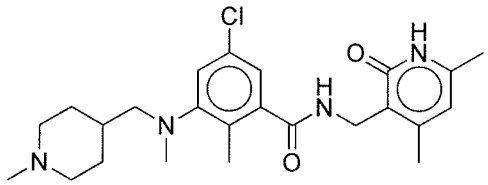
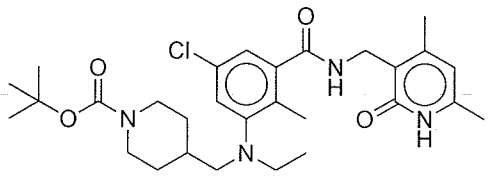
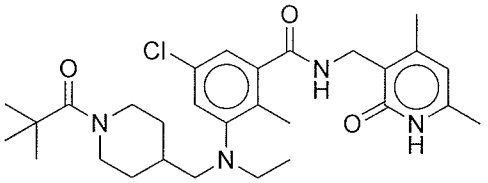
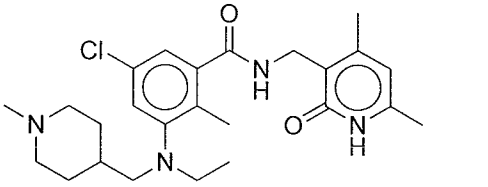
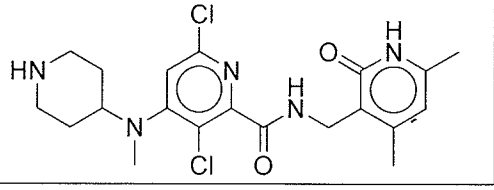
Compound Number	Structure	Name	MS†
115		tert-butyl 3-((5-chloro-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(ethyl)amino)azetidine-1-carboxylate	503.3
116		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(1-pivaloylazetidin-3-yl)amino)-2-methylbenzamide	487.2
117		5-chloro-3-((cyclopentylmethyl)(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	416.2
118		5-chloro-3-((cyclopentylmethyl)(ethyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	430.2
119		3-(((1s,4s)-4-aminocyclohexyl)(ethyl)amino)-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	445.3

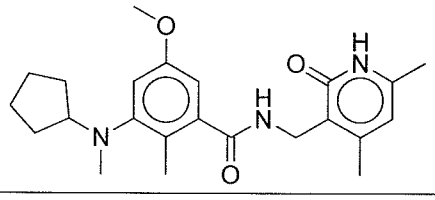
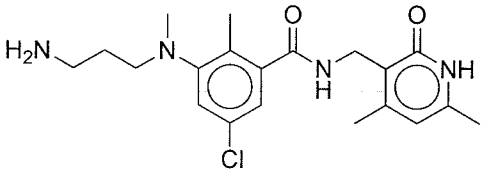
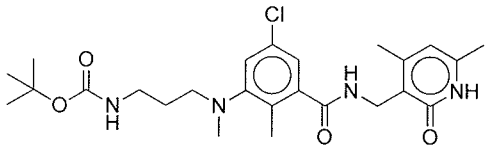
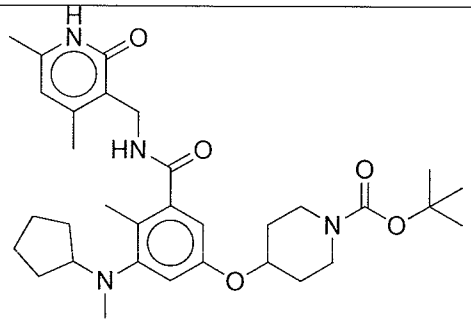
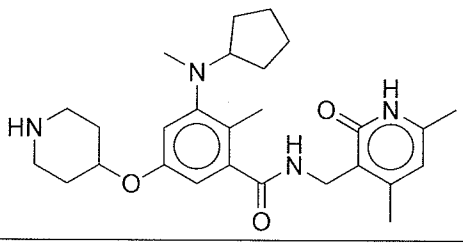
Compound Number	Structure	Name	MS†
120		3-(((1r,4r)-4-aminocyclohexyl)(ethyl)amino)-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	445.2
121		3-(((1s,4s)-4-acetamidocyclohexyl)(ethyl)amino)-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	487.3
122		3-(((1r,4r)-4-acetamidocyclohexyl)(ethyl)amino)-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	487.3
123		5-chloro-3-(cyclobutyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	388.1
124		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(methyl(oxetan-3-yl)amino)benzamide	390.2

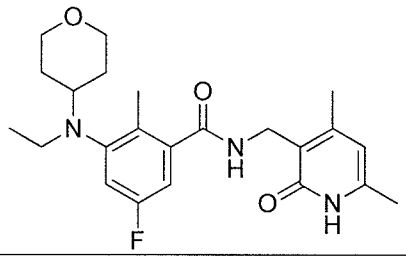
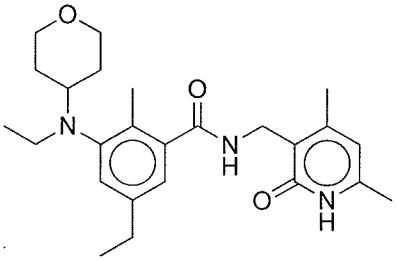
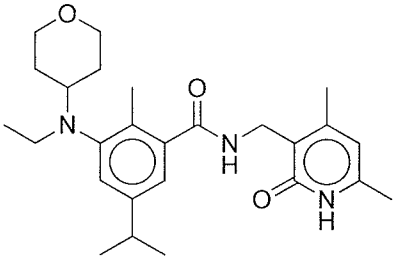
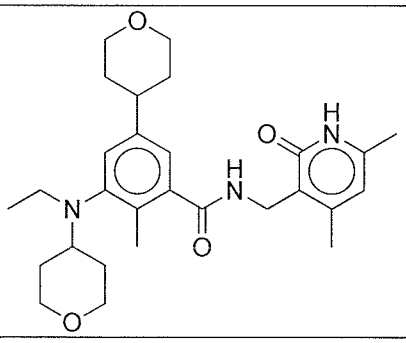
Compound Number	Structure	Name	MS†
125		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(oxetan-3-yl)amino)-2-methylbenzamide	404.2
126		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(methyl((tetrahydro-2H-pyran-4-yl)methyl)amino)benzamide	432.3
127		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((tetrahydro-2H-pyran-4-yl)methyl)amino)-2-methylbenzamide	446.2
128		5-chloro-3-((cyclohexylmethyl)(ethyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	444.3
129		3-(((1-acetylpiperidin-4-yl)methyl)(methyl)amino)-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	473.3

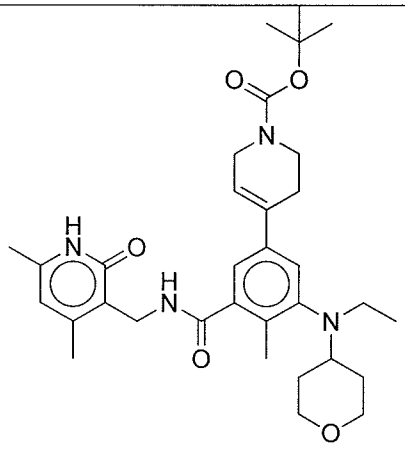
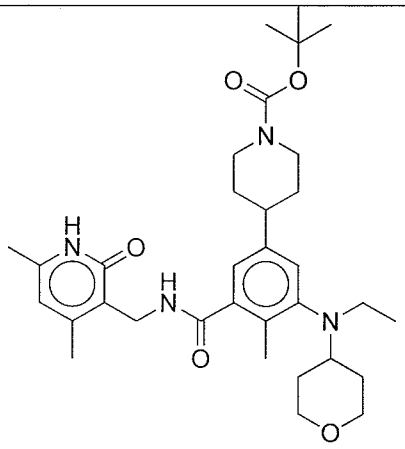
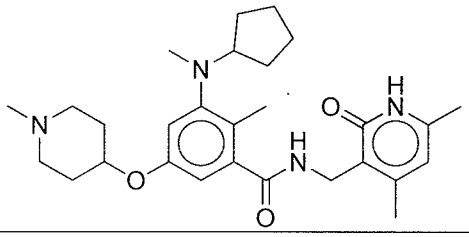
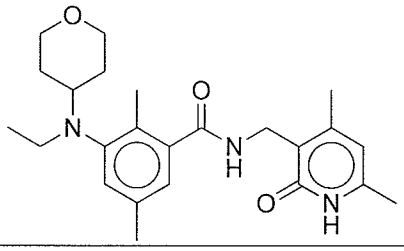
Compound Number	Structure	Name	MS†
130		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(methyl((1-pivaloylpiperidin-4-yl)methyl)amino)benzamide	515.3
131		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(piperidin-4-ylmethyl)amino)-2-methylbenzamide	445.2
132		3-(((1-acetylpiperidin-4-yl)methyl)(ethyl)amino)-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	487.3
133		5-chloro-3-((cyclopropylmethyl)(piperidin-4-yl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	457.2
134		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-2-methylbenzamide	398.3

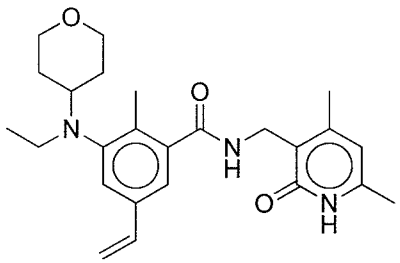
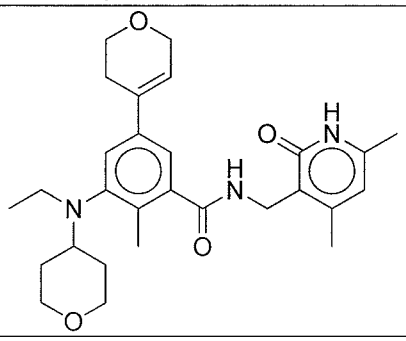
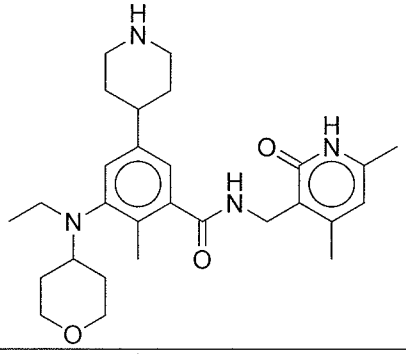
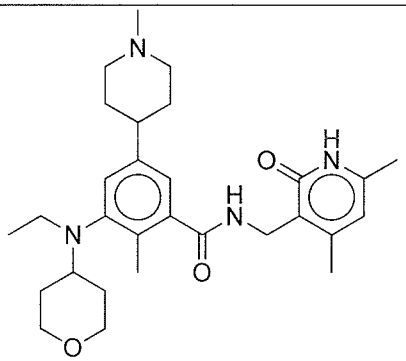
Compound Number	Structure	Name	MS†
135		2-bromo-5-chloro-3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)benzamide	466.1
136		5-chloro-3-((cyclohexylmethyl)(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	430.2
137		5-chloro-3-(cyclobutyl(ethyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	402.2
138		tert-butyl 4-(((5-chloro-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(methyl)amino)methyl)piperidine-1-carboxylate	531.3
139		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(methyl(piperidin-4-ylmethyl)amino)benzamide	431.2

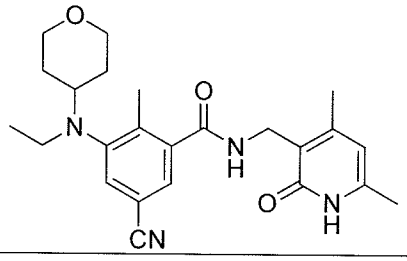
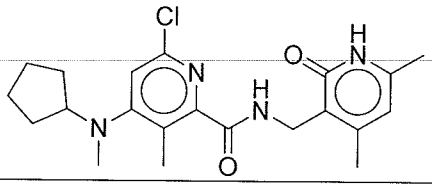
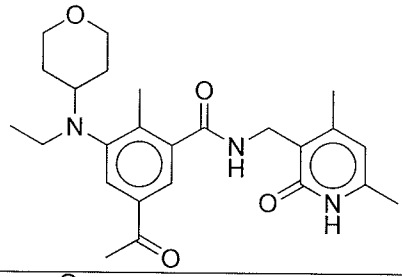
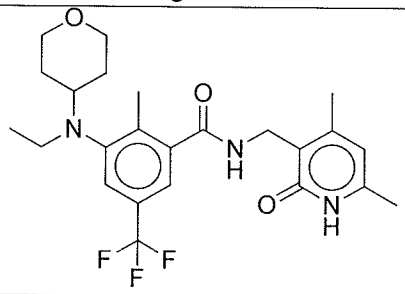
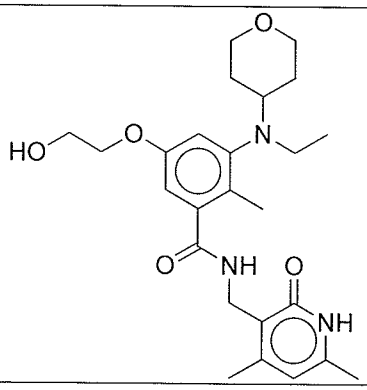
Compound Number	Structure	Name	MS†
140		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(methyl((1-methylpiperidin-4-yl)methyl)amino)benzamide	445.2
141		tert-butyl 4-(((5-chloro-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(ethyl)amino)methyl)piperidine-1-carboxylate	545.3
142		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((1-pivaloylpiperidin-4-yl)methyl)amino)-2-methylbenzamide	530.4
143		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((1-methylpiperidin-4-yl)methyl)amino)-2-methylbenzamide	459.3
144		3,6-dichloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-4-(methyl(piperidin-4-yl)amino)picolinamide	439.8

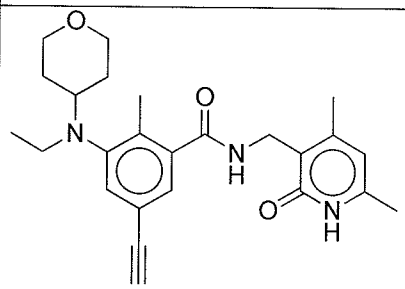
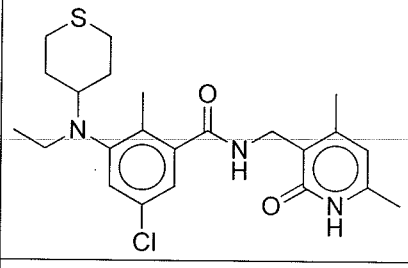
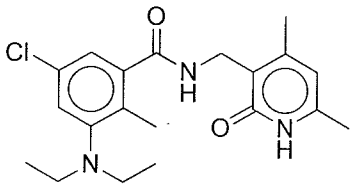
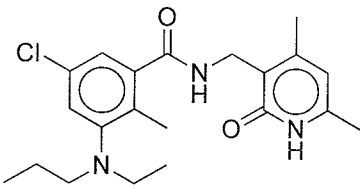
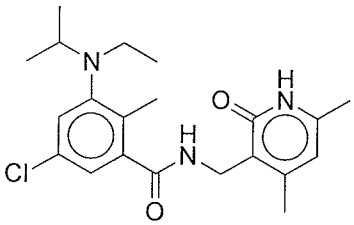
Compound Number	Structure	Name	MS†
145		3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-methoxy-2-methylbenzamide	398.1
146		3-((3-aminopropyl)(methyl)amino)-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	391.1
147		tert-butyl (3-((5-chloro-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(methyl)amino)propyl)carbamate	491.1
148		tert-butyl 4-(3-(cyclopentyl(methyl)amino)-5-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-4-methylphenoxy)piperidine-1-carboxylate	567.3
149		3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-5-(piperidin-4-yloxy)benzamide	467.2

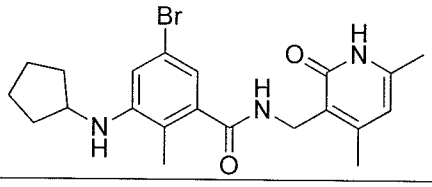
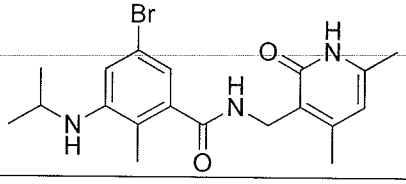
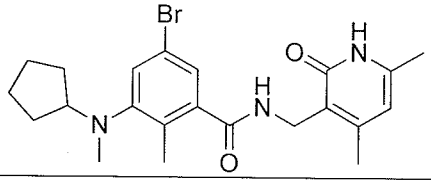
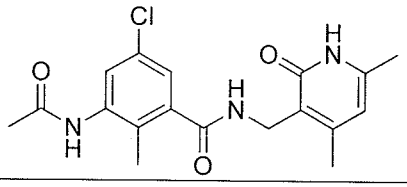
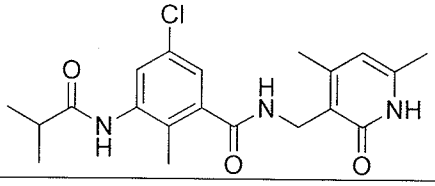
Compound Number	Structure	Name	MS†
150		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-5-fluoro-2-methylbenzamide	416.1
151		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-ethyl-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-2-methylbenzamide	446.2
152		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-5-isopropyl-2-methylbenzamide	440.2
153		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-2-methyl-5-(tetrahydro-2H-pyran-4-yl)benzamide	482.2

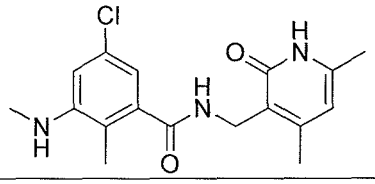
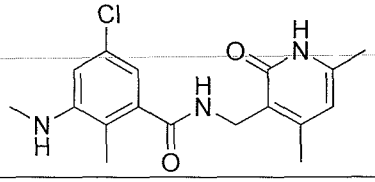
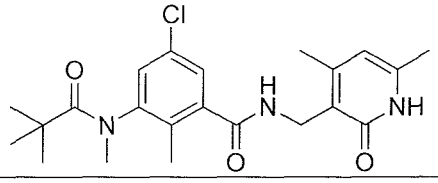
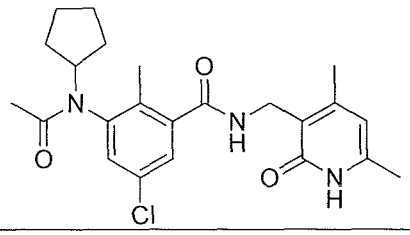
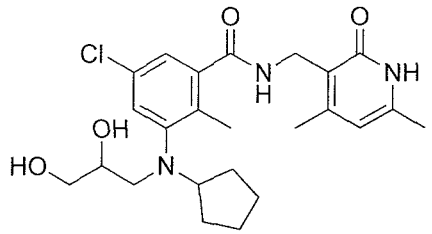
Compound Number	Structure	Name	MS†
154		tert-butyl 4-(3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-5-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-4-methylphenyl)-5,6-dihydropyridine-1(2H)-carboxylate	579.3
155		tert-butyl 4-(3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-5-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-4-methylphenyl)piperidine-1-carboxylate	581.2
156		3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-5-((1-methylpiperidin-4-yl)oxy)benzamide	481.3
157		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-2,5-dimethylbenzamide	412.2

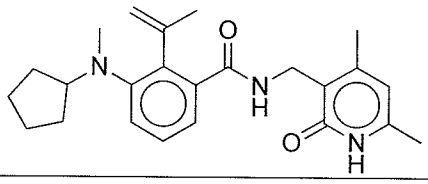
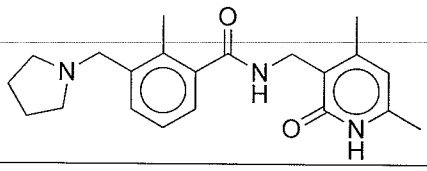
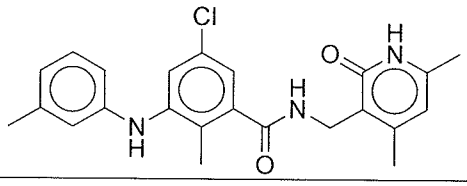
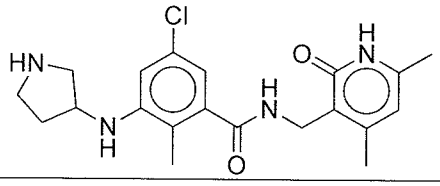
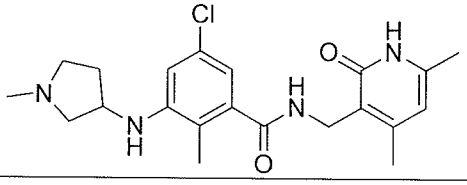
Compound Number	Structure	Name	MS†
158		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-2-methyl-5-vinylbenzamide	424.1
159		5-(3,6-dihydro-2H-pyran-4-yl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-2-methylbenzamide	480.3
160		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-2-methyl-5-(piperidin-4-yl)benzamide	481.3
161		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-2-methyl-5-(1-methylpiperidin-4-yl)benzamide	495.3

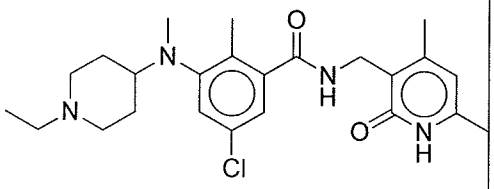
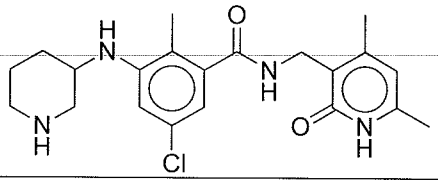
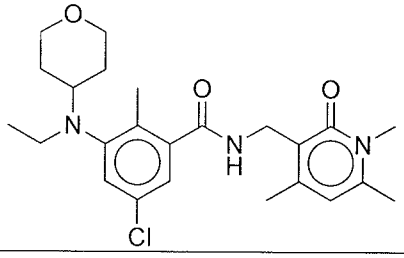
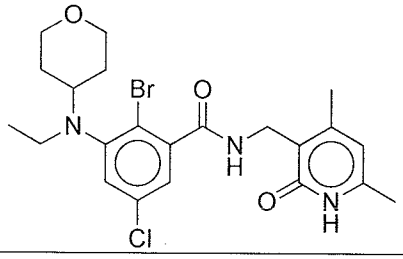
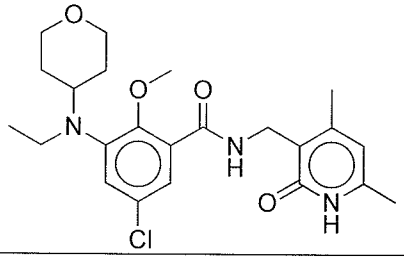
Compound Number	Structure	Name	MS†
162		5-cyano-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-2-methylbenzamide	423.2
163		6-chloro-4-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-methylpicolinamide	403.2
164		5-acetyl-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-2-methylbenzamide	440.2
165		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-2-methyl-5-(trifluoromethyl)benzamide	466.2
166		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-5-(2-hydroxyethoxy)-2-methylbenzamide	458. 2

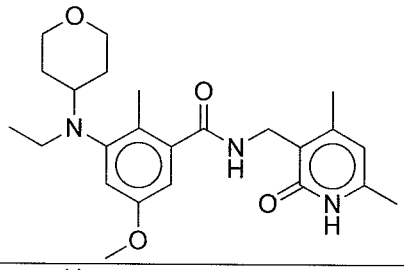
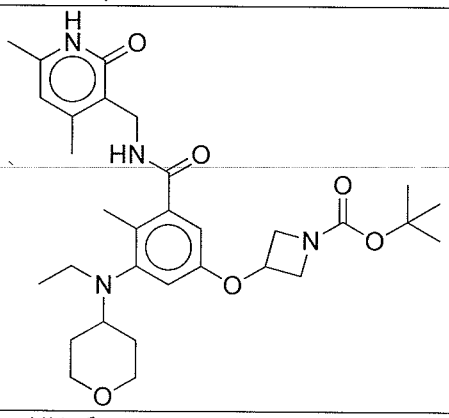
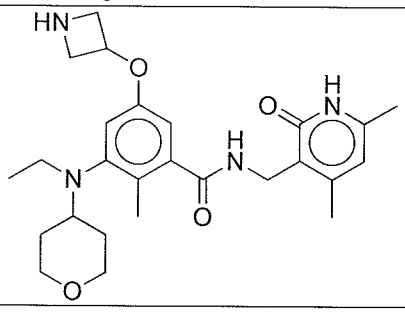
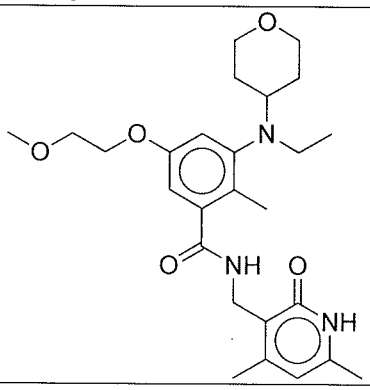
Compound Number	Structure	Name	MS†
167		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-5-ethynyl-2-methylbenzamide	422.3
168		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-thiopyran-4-yl)amino)-2-methylbenzamide	448.1
169		5-chloro-3-(diethylamino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	376
170		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(propyl)amino)-2-methylbenzamide	390.2
171		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(isopropyl)amino)-2-methylbenzamide	390.1

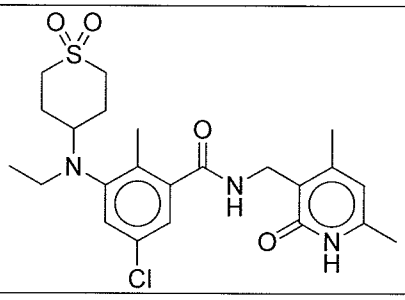
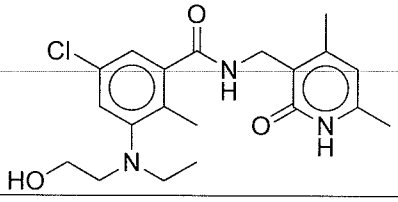
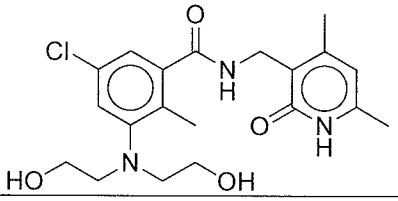
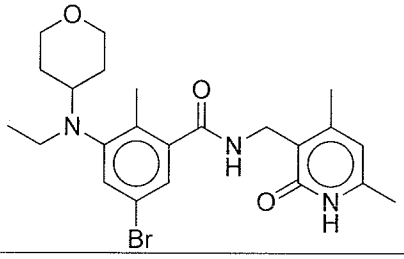
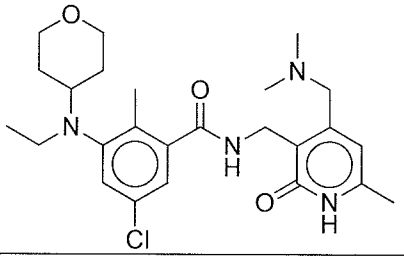
Compound Number	Structure	Name	MS†
172		5-bromo-3-(cyclopentylamino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	432.1
173		5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(isopropylamino)-2-methylbenzamide	406.1
174		5-bromo-3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	446.2
175		3-acetamido-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	362.1
176		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-isobutyramido-2-methylbenzamide	390.1

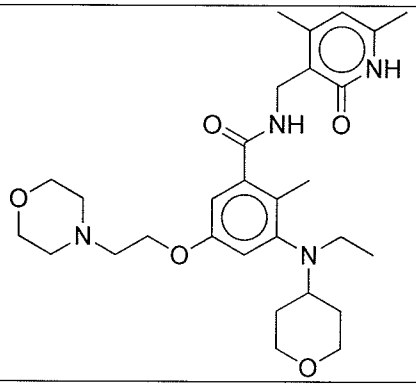
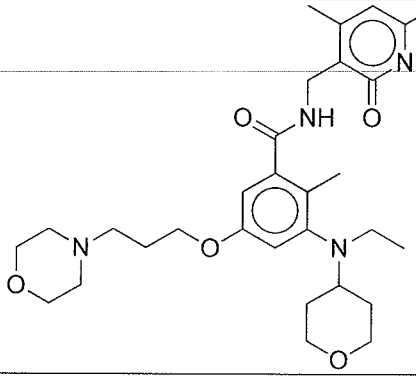
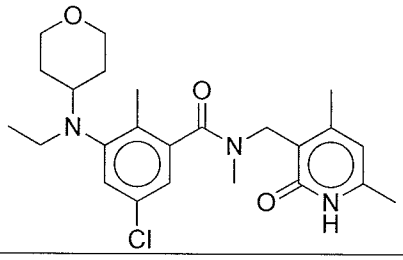
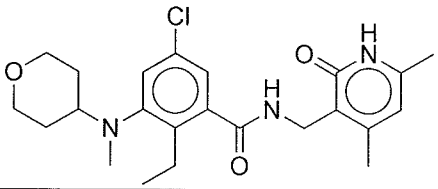
Compound Number	Structure	Name	MS†
177		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(methylamino)benzamide	334.2
178		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(methylamino)benzamide	334.2
179		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(N-methylpivalamido)benzamide	418.2
180		5-chloro-3-(N-cyclopentylacetamido)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	430.3
181		5-chloro-3-(cyclopentyl(2,3-dihydroxypropyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	462.2

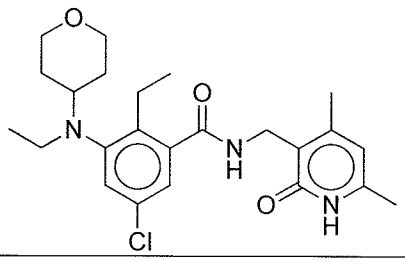
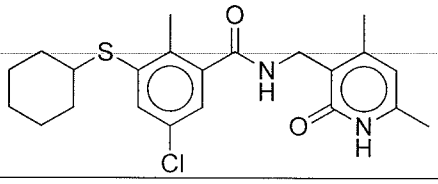
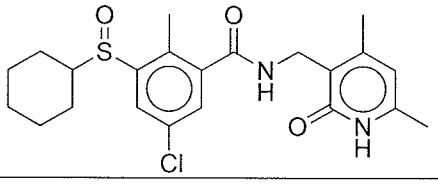
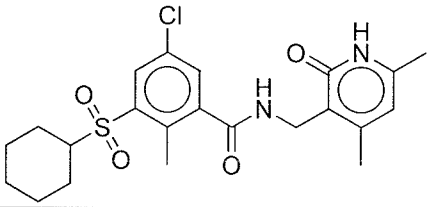
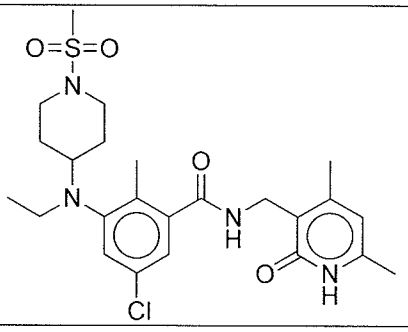
Compound Number	Structure	Name	MS†
182		3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-(prop-1-en-2-yl)benzamide	394.3
183		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(pyrrolidin-1-ylmethyl)benzamide	354.3
184		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(m-tolylamino)benzamide	410.3
185		[[Duplicate with #184]]	
186		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(pyrrolidin-3-ylamino)benzamide	389.2
187		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-((1-methylpyrrolidin-3-yl)amino)benzamide	403.1

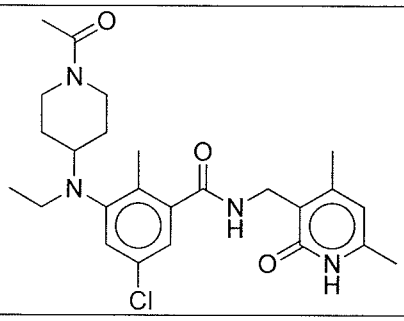
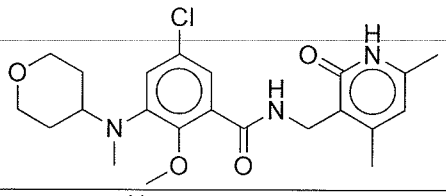
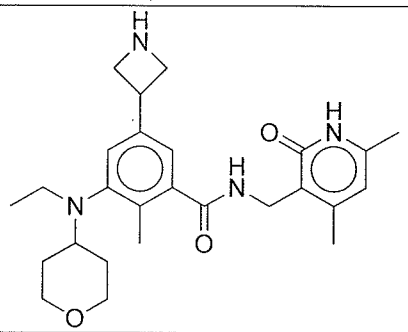
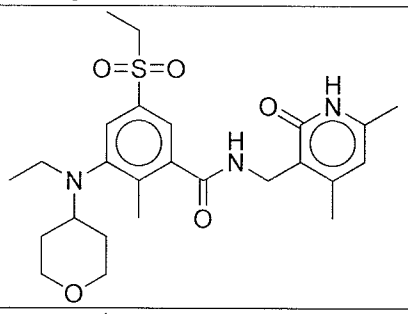
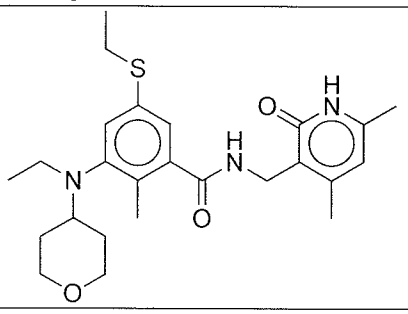
Compound Number	Structure	Name	MS†
188		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-((1-ethylpiperidin-4-yl)(methyl)amino)-2-methylbenzamide	445.4
189		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(piperidin-3-ylamino)benzamide	403.3
190		5-chloro-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-2-methyl-N-((1,4,6-trimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)benzamide	446.3
191		2-bromo-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)benzamide	498
192		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-2-methoxybenzamide	449.5

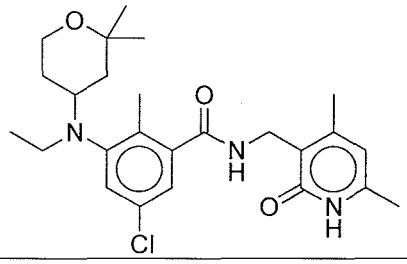
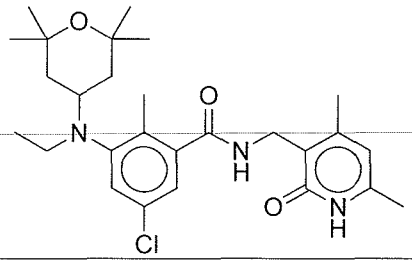
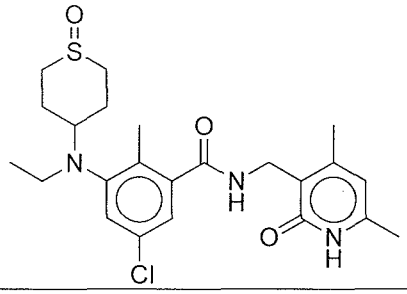
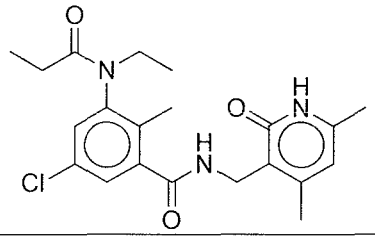
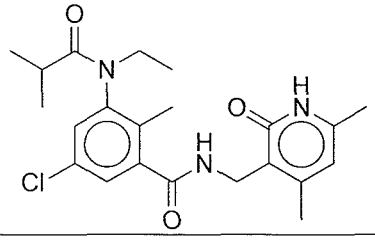
Compound Number	Structure	Name	MS†
193		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-5-methoxy-2-methylbenzamide	428.2
194		tert-butyl 3-(3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-5-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-4-methylphenoxy)azetidine-1-carboxylate	569.3
195		5-(azetidin-3-yloxy)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-2-methylbenzamide	469.3
196		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-5-(2-methoxyethoxy)-2-methylbenzamide	472.2

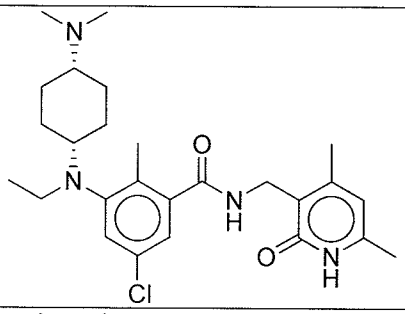
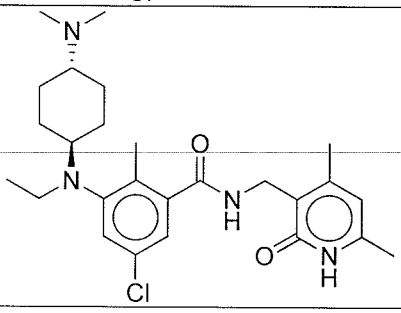
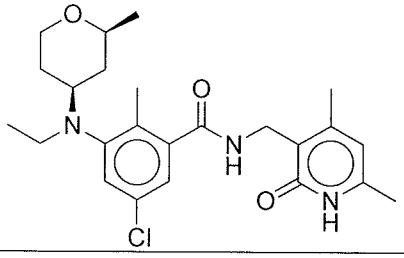
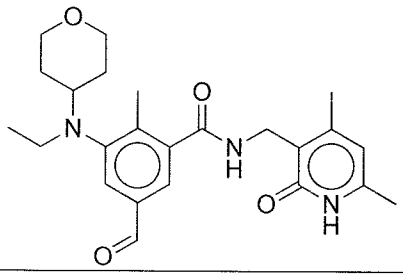
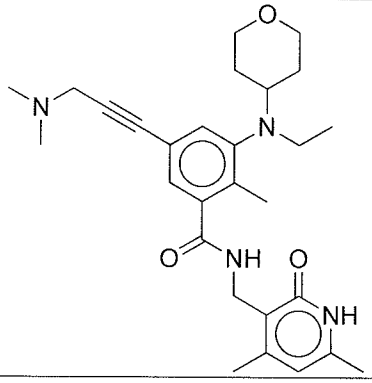
Compound Number	Structure	Name	MS†
197		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)-2-methylbenzamide	480.1
198		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(2-hydroxyethyl)amino)-2-methylbenzamide	392.1
199		3-(bis(2-hydroxyethyl)amino)-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	408.1
200		5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-2-methylbenzamide	476.1
201		5-chloro-N-((4-((dimethylamino)methyl)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-2-methylbenzamide	475.2

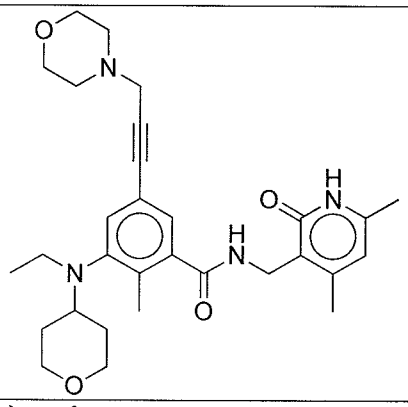
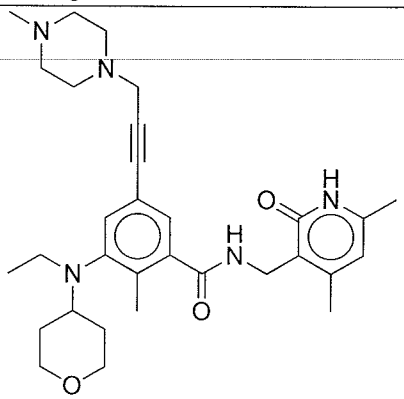
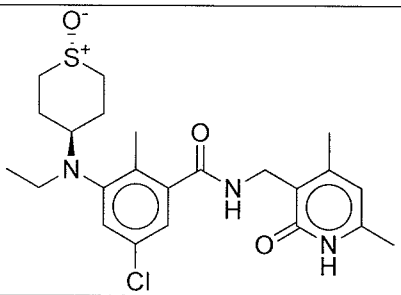
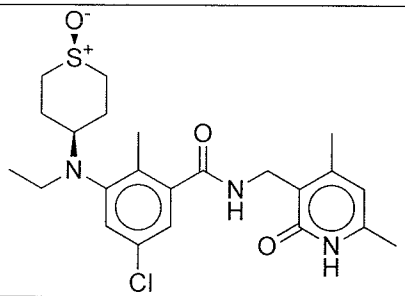
Compound Number	Structure	Name	MS†
202		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-2-methyl-5-(2-morpholinoethoxy)benzamide	527.4
203		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-2-methyl-5-(3-morpholinopropoxy)benzamide	541.4
204		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-N,2-dimethylbenzamide	446.1
205		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-ethyl-3-(methyl(tetrahydro-2H-pyran-4-yl)amino)benzamide	432.1

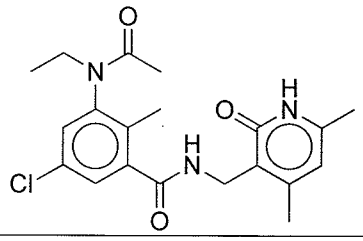
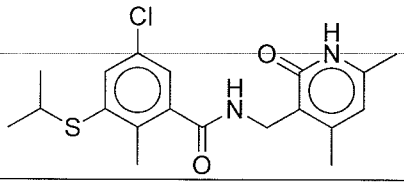
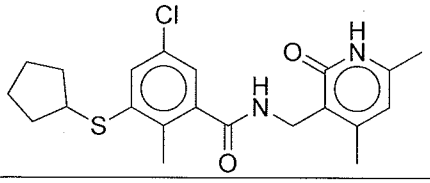
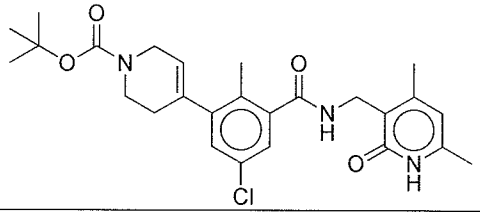
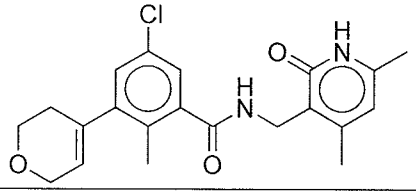
Compound Number	Structure	Name	MS†
206		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-ethyl-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)benzamide	446.1
207		5-chloro-3-(cyclohexylthio)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	419.2
208		5-chloro-3-(cyclohexylsulfinyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	435.1
209		5-chloro-3-(cyclohexylsulfonyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	451.1
210		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(1-(methylsulfonyl)piperidin-4-yl)amino)-2-methylbenzamide	509.2

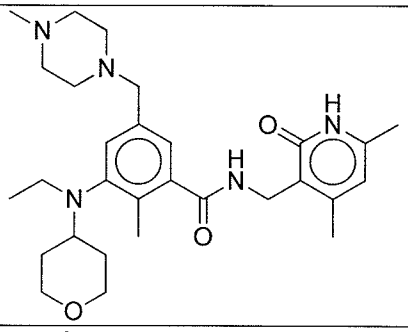
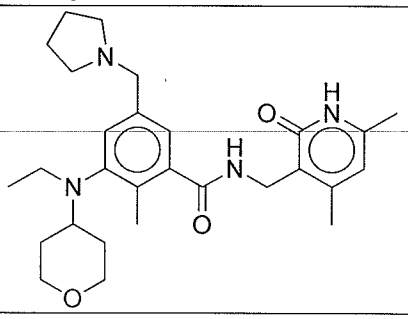
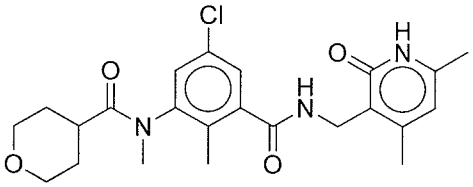
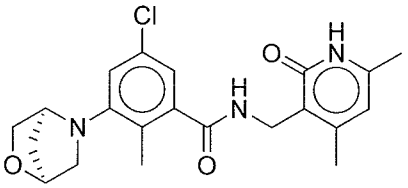
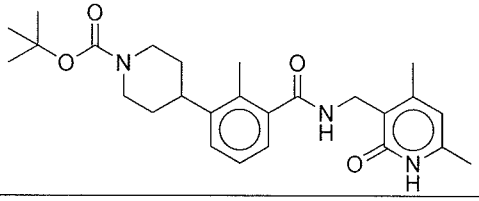
Compound Number	Structure	Name	MS†
211		3-((1-acetylpiperidin-4-yl)(ethyl)amino)-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	495.1
212		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methoxy-3-(methyl(tetrahydro-2H-pyran-4-yl)amino)benzamide	434.1
213		5-(azetidin-3-yl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-2-methylbenzamide	453.2
214		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-5-(ethylsulfonyl)-2-methylbenzamide	490.3
215		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-5-(ethylthio)-2-methylbenzamide	458.2

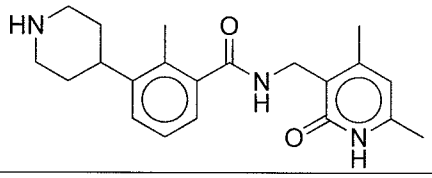
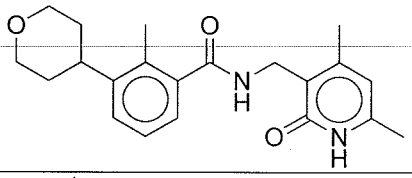
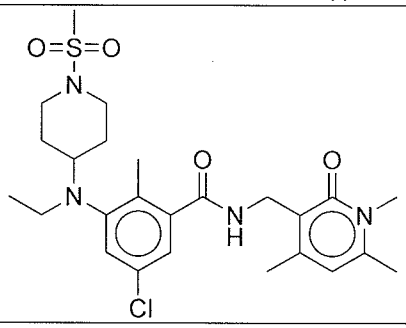
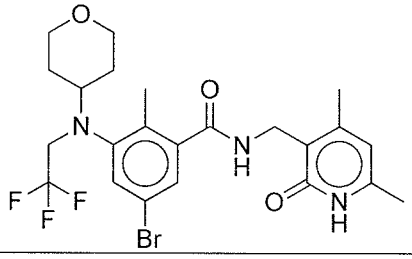
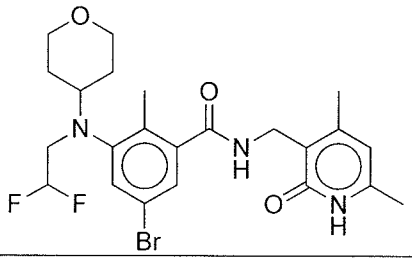
Compound Number	Structure	Name	MS†
216		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-((2,2-dimethyltetrahydro-2H-pyran-4-yl)(ethyl)amino)-2-methylbenzamide	460.3
217		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(2,2,6,6-tetramethyltetrahydro-2H-pyran-4-yl)amino)-2-methylbenzamide	488.5
218		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(1-oxidotetrahydro-2H-thiopyran-4-yl)amino)-2-methylbenzamide	464.1
219		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(N-ethylpropionamido)-2-methylbenzamide	404.2
220		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(N-ethylisobutyramido)-2-methylbenzamide	418.2

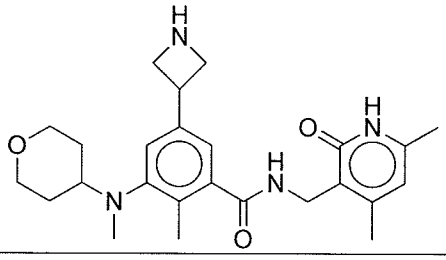
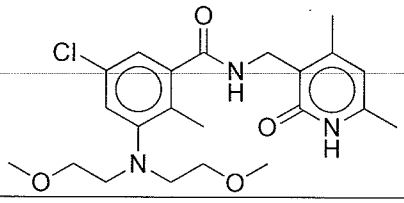
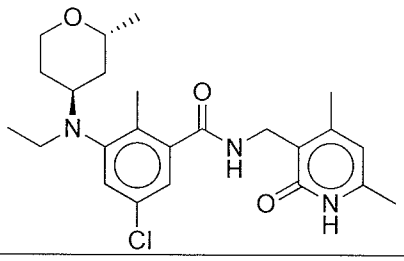
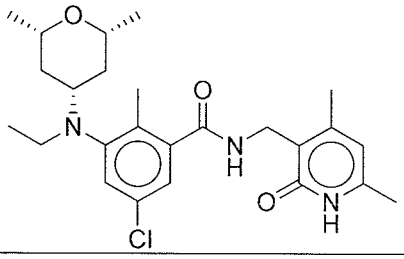
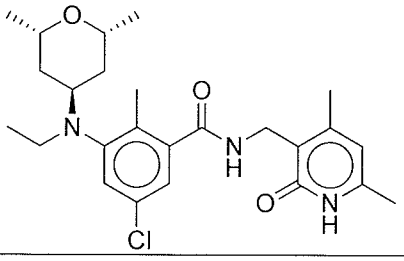
Compound Number	Structure	Name	MS†
221		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1s,4s)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methylbenzamide	473.3
222		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methylbenzamide	473.4
223		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((2S,4S)-2-methyltetrahydro-2H-pyran-4-yl)amino)-2-methylbenzamide	446.2
224		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-5-formyl-2-methylbenzamide	426.2
225		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(3-(dimethylamino)prop-1-yn-1-yl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-2-methylbenzamide	479.2

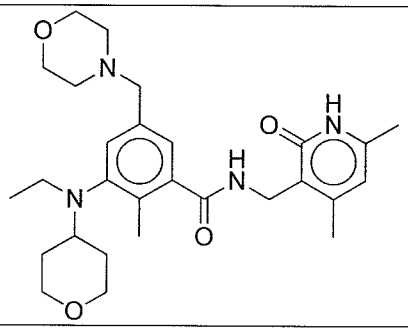
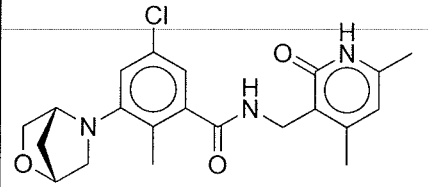
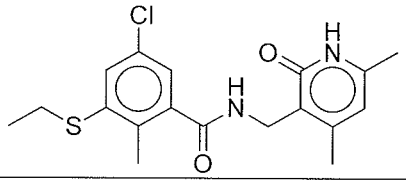
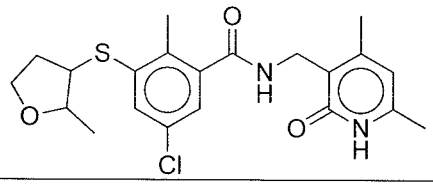
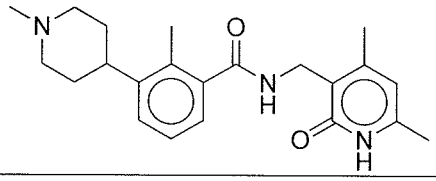
Compound Number	Structure	Name	MS†
226		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-2-methyl-5-(3-morpholinoprop-1-yn-1-yl)benzamide	521.3
227		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-2-methyl-5-(3-(4-methylpiperazin-1-yl)prop-1-yn-1-yl)benzamide	534.4
228		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((1r,4r)-1-oxidotetrahydro-2H-thiopyran-4-yl)amino)-2-methylbenzamide	464.1
229		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((1s,4s)-1-oxidotetrahydro-2H-thiopyran-4-yl)amino)-2-methylbenzamide	464.2

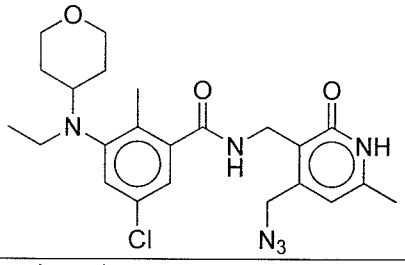
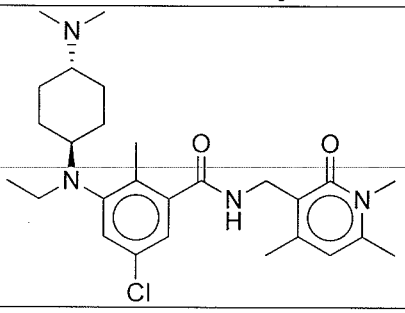
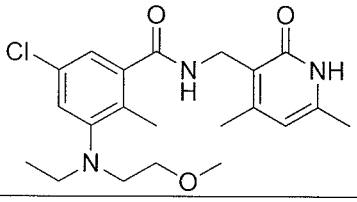
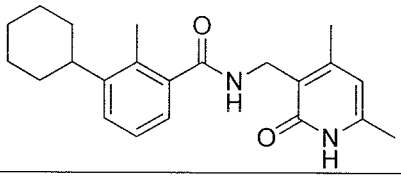
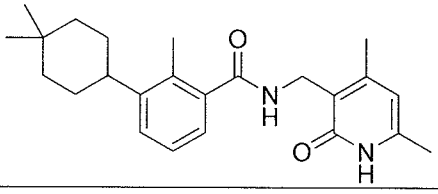
Compound Number	Structure	Name	MS†
230		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(N-ethylacetamido)-2-methylbenzamide	390.2
231		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(isopropylthio)-2-methylbenzamide	379.1
232		5-chloro-3-(cyclopentylthio)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	405.1
233		tert-butyl 4-(5-chloro-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)-5,6-dihydropyridine-1(2H)-carboxylate	486.2
234		5-chloro-3-(3,6-dihydro-2H-pyran-4-yl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	387.1

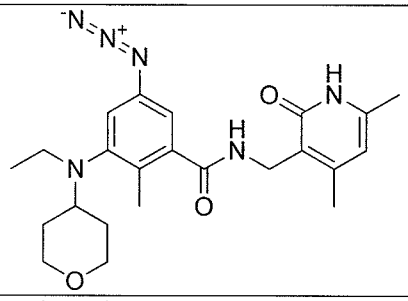
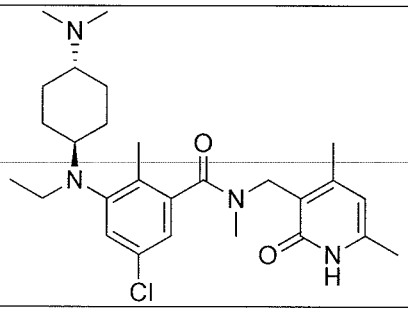
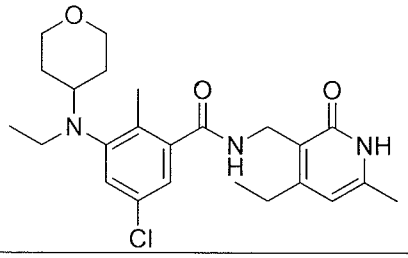
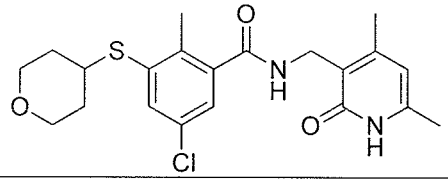
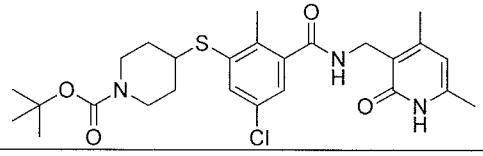
Compound Number	Structure	Name	MS†
235		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-2-methyl-5-((4-methylpiperazin-1-yl)methyl)benzamide	510.4
236		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-2-methyl-5-(pyrrolidin-1-ylmethyl)benzamide	481.3
237		N-(5-chloro-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)-N-methyltetrahydro-2H-pyran-4-carboxamide	446.1
238		3-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	402.1
239		tert-butyl 4-(3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)piperidine-1-carboxylate	454.2

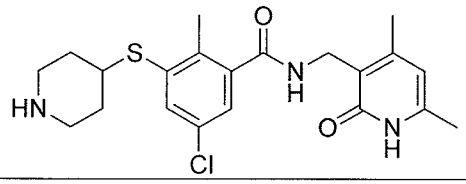
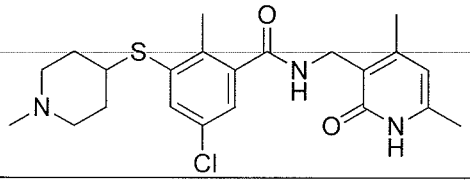
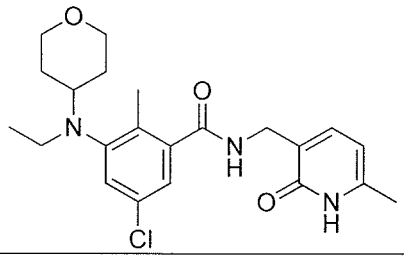
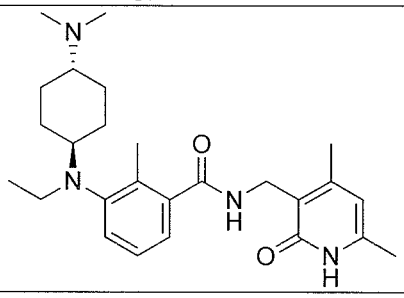
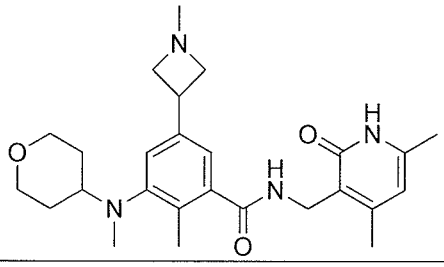
Compound Number	Structure	Name	MS†
240		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(piperidin-4-yl)benzamide	354.2
241		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(tetrahydro-2H-pyran-4-yl)benzamide	355.2
242		5-chloro-3-(ethyl(1-(methylsulfonyl)piperidin-4-yl)amino)-2-methyl-N-((1,4,6-trimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)benzamide	522.2
243		5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-((tetrahydro-2H-pyran-4-yl)(2,2,2-trifluoroethyl)amino)benzamide	531
244		5-bromo-3-((2,2-difluoroethyl)(tetrahydro-2H-pyran-4-yl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	513

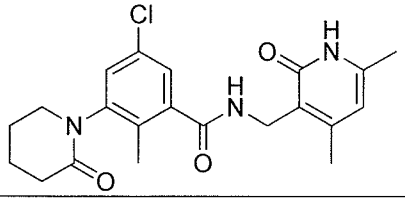
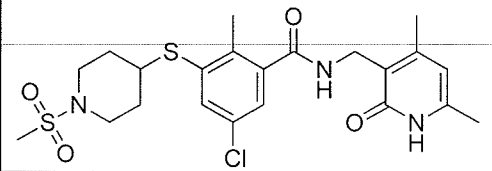
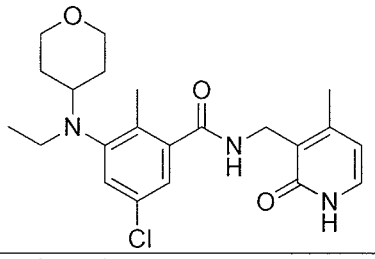
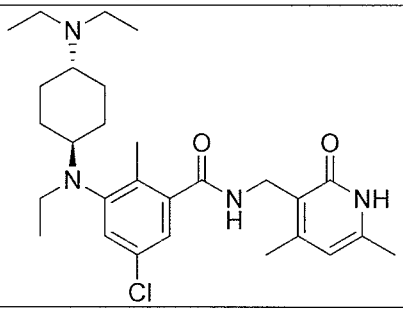
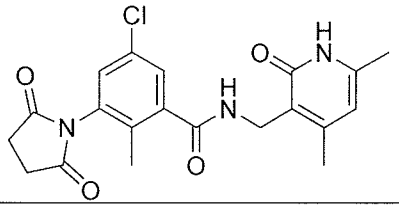
Compound Number	Structure	Name	MS†
245		5-(azetidin-3-yl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(methyl(tetrahydro-2H-pyran-4-yl)amino)benzamide	439.3
246		3-(bis(2-methoxyethyl)amino)-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	436.2
247		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((2R,4S)-2-methyltetrahydro-2H-pyran-4-yl)amino)-2-methylbenzamide	446.2
248		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((2R,4r,6S)-2,6-dimethyltetrahydro-2H-pyran-4-yl)(ethyl)amino)-2-methylbenzamide	460.3
249		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((2R,4s,6S)-2,6-dimethyltetrahydro-2H-pyran-4-yl)(ethyl)amino)-2-methylbenzamide	460.3

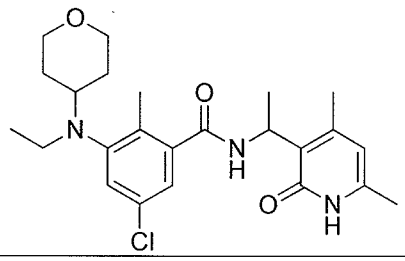
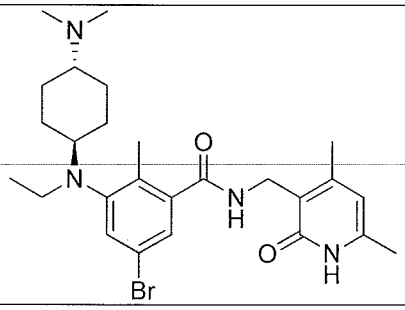
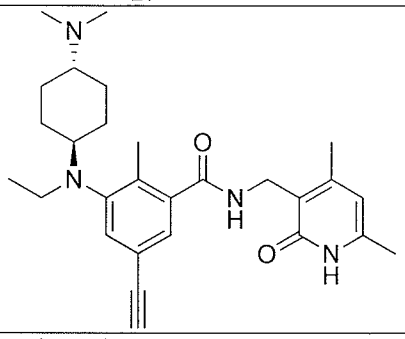
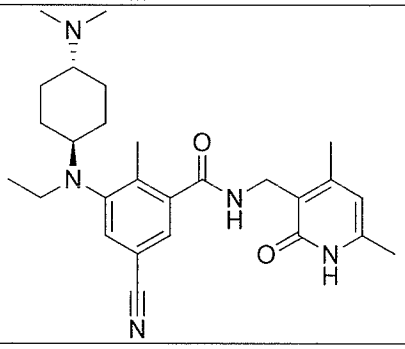
Compound Number	Structure	Name	MS†
250		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-2-methyl-5-(morpholinomethyl)benzamide	497.3
251		3-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	402.2
252		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethylthio)-2-methylbenzamide	365.2
253		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-((2-methyltetrahydrofuran-3-yl)thio)benzamide	421.1
254		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(1-methylpiperidin-4-yl)benzamide	368.3

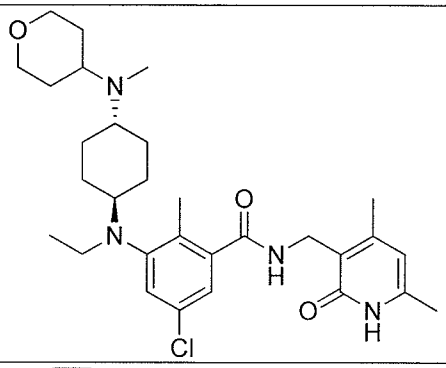
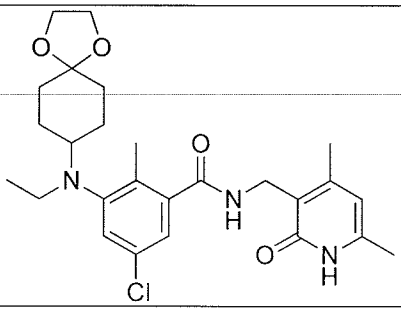
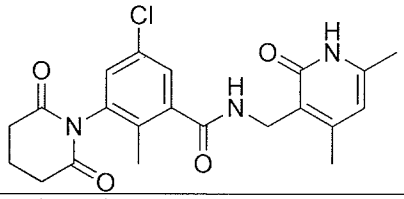
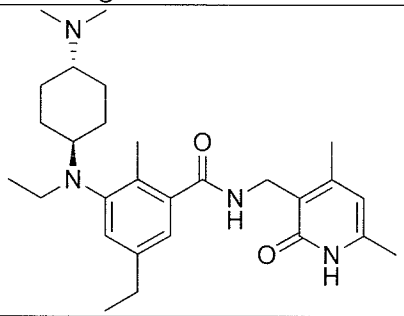
Compound Number	Structure	Name	MS†
255		N-((4-(azidomethyl)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-chloro-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-2-methylbenzamide	473.2
256		5-chloro-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methyl-N-((1,4,6-trimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)benzamide	487.4
257		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(2-methoxyethyl)amino)-2-methylbenzamide	406.2
258		3-cyclohexyl-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	353.2
259		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(4,4-dimethylcyclohexyl)-2-methylbenzamide	381.3

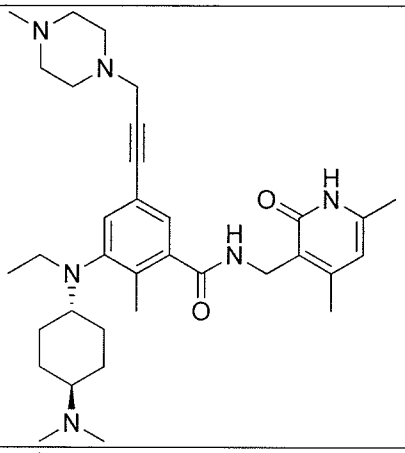
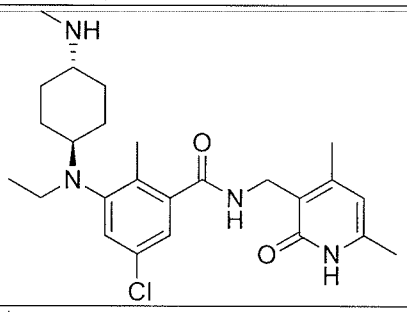
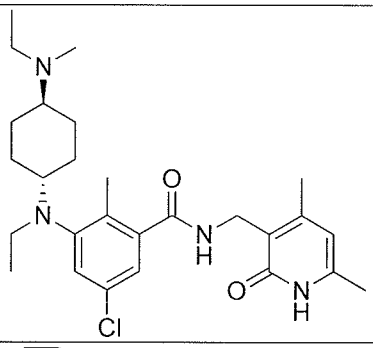
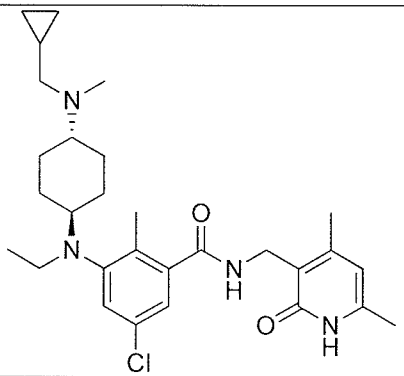
Compound Number	Structure	Name	MS†
260		5-azido-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-2-methylbenzamide	439.3
261		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-N,2-dimethylbenzamide	487.2
262		5-chloro-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-N-((4-ethyl-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	446.1
263		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-((tetrahydro-2H-pyran-4-yl)thio)benzamide	421
264		tert-butyl 4-((5-chloro-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)thio)piperidine-1-carboxylate	542.2

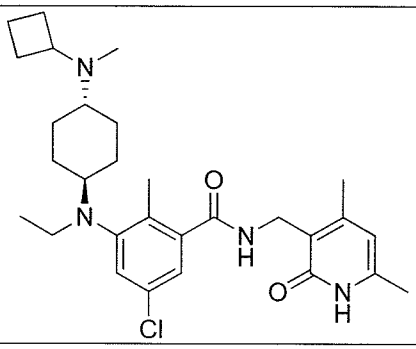
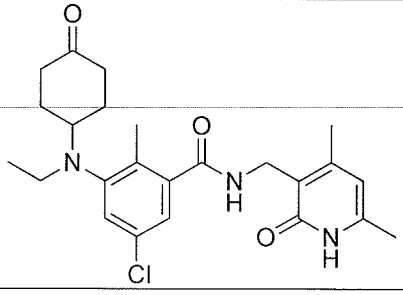
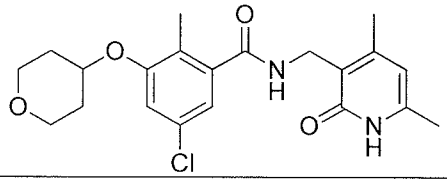
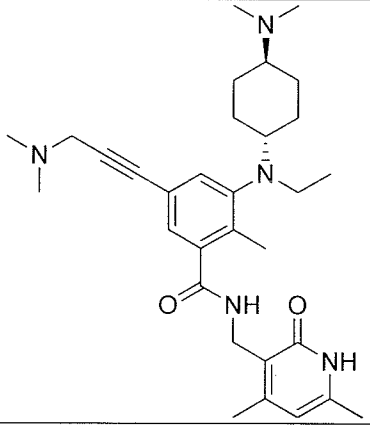
Compound Number	Structure	Name	MS†
265		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(piperidin-4-ylthio)benzamide	420.1
266		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-((1-methylpiperidin-4-yl)thio)benzamide	434.1
267		5-chloro-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-2-methyl-N-((6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)benzamide	418.1
268		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methylbenzamide	439.3
269		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(methyl(tetrahydro-2H-pyran-4-yl)amino)-5-(1-methylazetidin-3-yl)benzamide	453.2

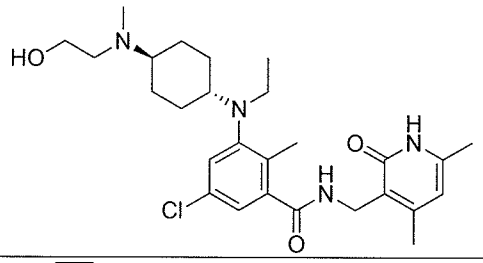
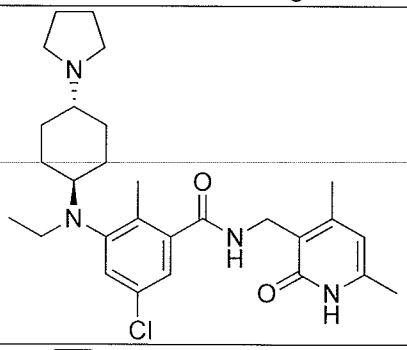
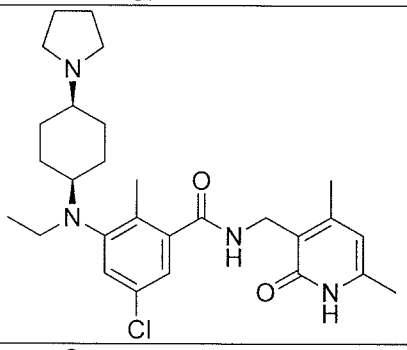
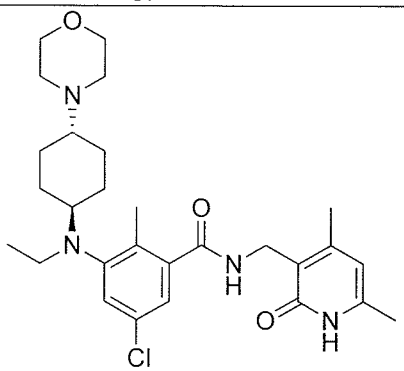
Compound Number	Structure	Name	MS†
270		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(2-oxopiperidin-1-yl)benzamide	402.1
271		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-((1-(methylsulfonyl)piperidin-4-yl)thio)benzamide	498
272		5-chloro-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-2-methyl-N-((4-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)benzamide	418.2
273		5-chloro-3-(((1r,4r)-4-(diethylamino)cyclohexyl)(ethyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	501.5
274		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(2,5-dioxopyrrolidin-1-yl)-2-methylbenzamide	402.3

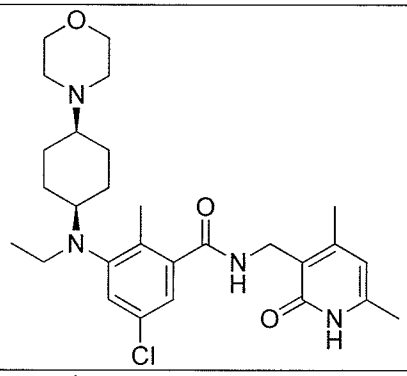
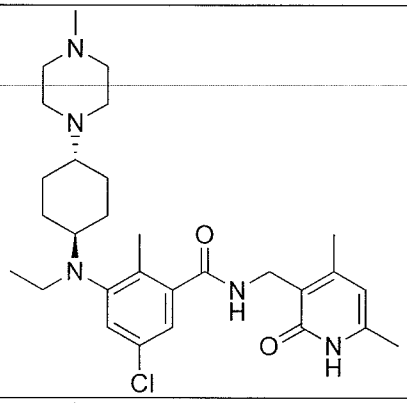
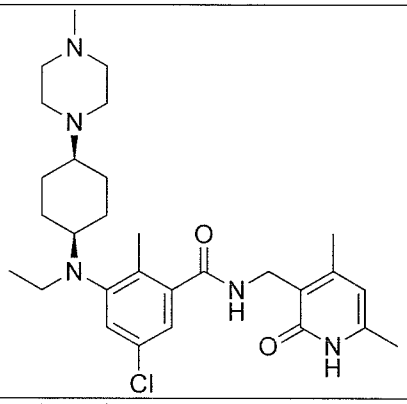
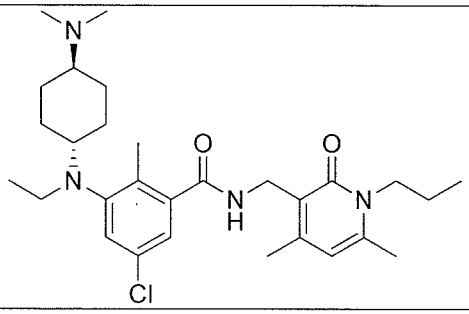
Compound Number	Structure	Name	MS†
275		5-chloro-N-(1-(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)ethyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-2-methylbenzamide	446.2
276		5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methylbenzamide	519.3
277		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-5-ethynyl-2-methylbenzamide	463.5
278		5-cyano-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methylbenzamide	464.3

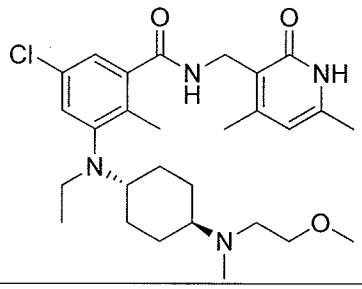
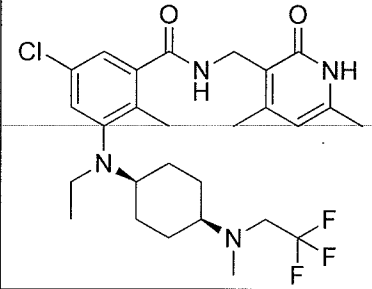
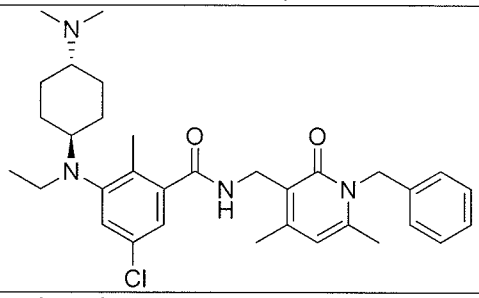
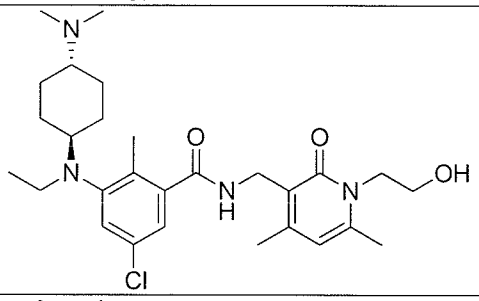
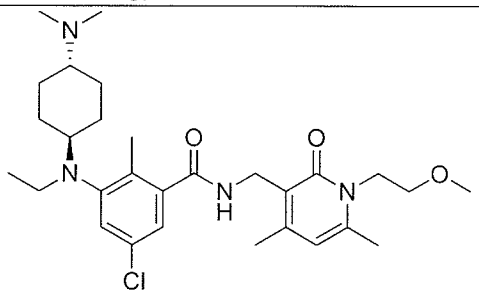
Compound Number	Structure	Name	MS†
279		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((1r,4r)-4-(methyl(tetrahydro-2H-pyran-4-yl)amino)cyclohexyl)amino)-2-methylbenzamide	543.7
280		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(1,4-dioxaspiro[4.5]decan-8-yl)amino)-2-methylbenzamide	488.3
281		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(2,6-dioxopiperidin-1-yl)-2-methylbenzamide	416.1
282		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-5-ethyl-2-methylbenzamide	467.4

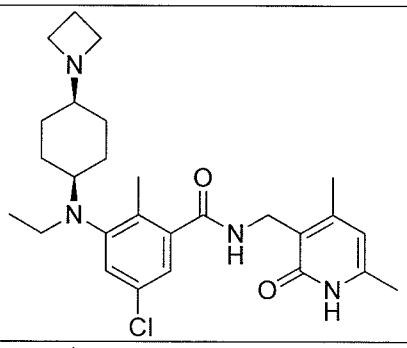
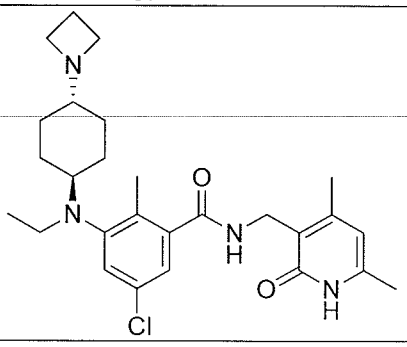
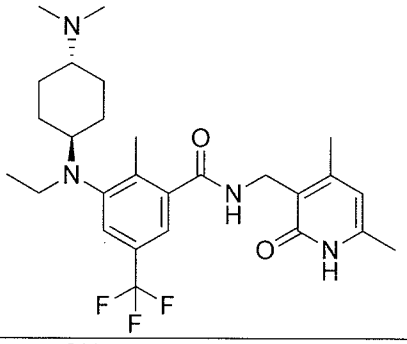
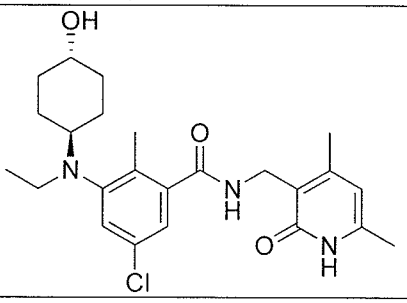
Compound Number	Structure	Name	MS†
283		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methyl-5-(3-(4-methylpiperazin-1-yl)prop-1-yn-1-yl)benzamide	575.5
284		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((1r,4r)-4-(methylamino)cyclohexyl)amino)-2-methylbenzamide	459.4
285		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((1r,4r)-4-(ethyl(methyl)amino)cyclohexyl)amino)-2-methylbenzamide	487.4
286		5-chloro-3-(((1r,4r)-4-((cyclopropylmethyl)(methyl)amino)cyclohexyl)(ethyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	513.4

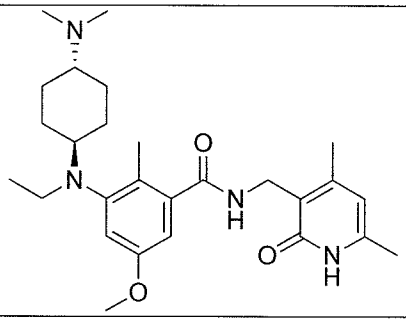
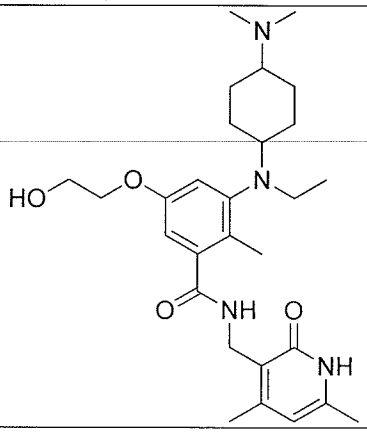
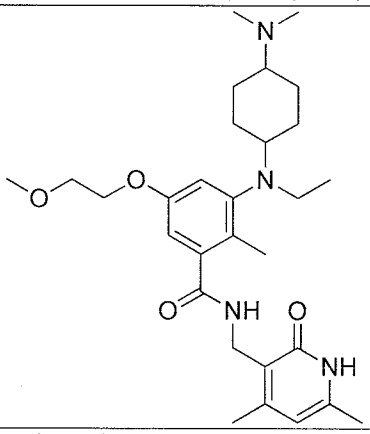
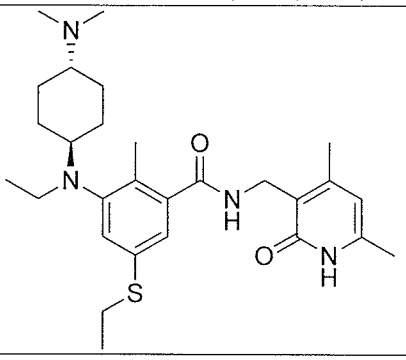
Compound Number	Structure	Name	MS†
287		5-chloro-3-(((1r,4r)-4-(cyclobutyl(methyl)amino)cyclohexyl)(ethyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	513.3
288		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(4-oxocyclohexyl)amino)-2-methylbenzamide	444.3
289		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-((tetrahydro-2H-pyran-4-yl)oxy)benzamide	405.2
290		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-5-(3-(dimethylamino)prop-1-yn-1-yl)-2-methylbenzamide	520.6

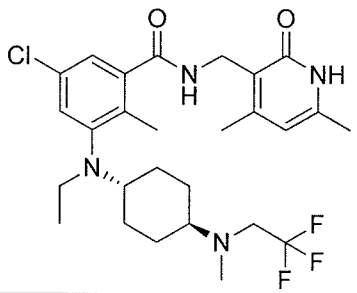
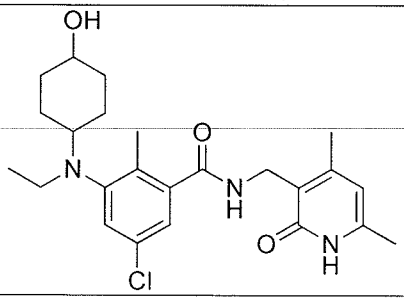
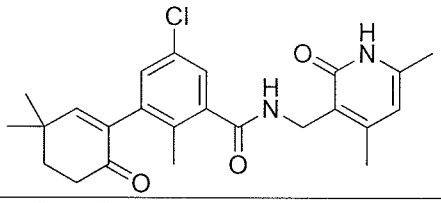
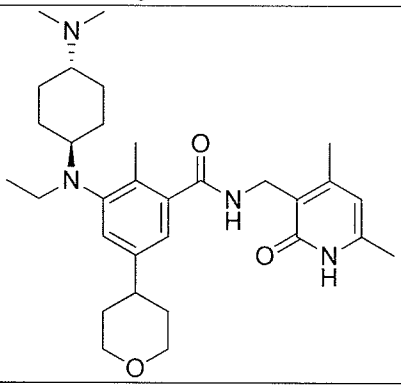
Compound Number	Structure	Name	MS†
291		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((1r,4r)-4-((2-hydroxyethyl)(methyl)amino)cyclohexyl)amino)-2-methylbenzamide	503.3
292		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((1r,4r)-4-(pyrrolidin-1-yl)cyclohexyl)amino)-2-methylbenzamide	499.3
293		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((1s,4s)-4-(pyrrolidin-1-yl)cyclohexyl)amino)-2-methylbenzamide	499.3
294		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((1r,4r)-4-morpholinocyclohexyl)amino)-2-methylbenzamide	515.3

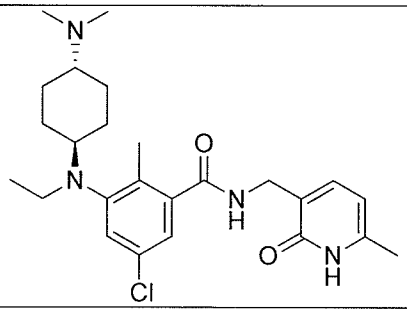
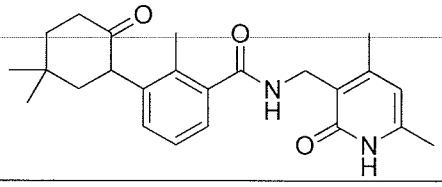
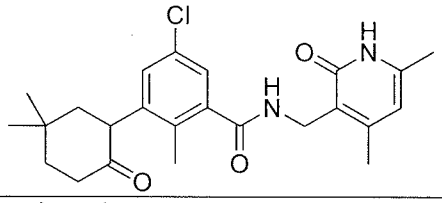
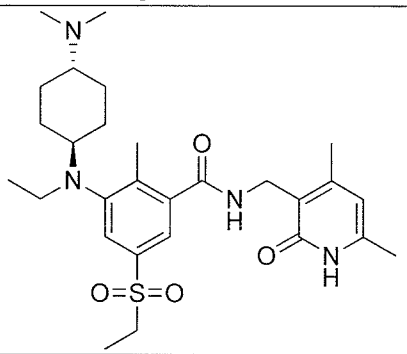
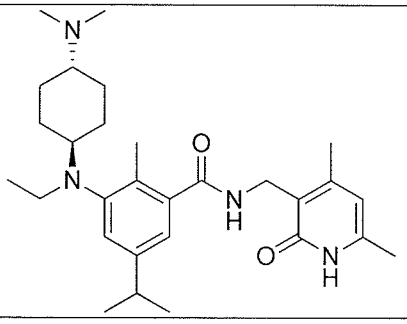
Compound Number	Structure	Name	MS†
295		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((1s,4s)-4-morpholinocyclohexyl)amino)-2-methylbenzamide	515.3
296		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((1r,4r)-4-(4-methylpiperazin-1-yl)cyclohexyl)amino)-2-methylbenzamide	528.4
297		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((1s,4s)-4-(4-methylpiperazin-1-yl)cyclohexyl)amino)-2-methylbenzamide	528.3
298		5-chloro-N-((4,6-dimethyl-2-oxo-1-propyl-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methylbenzamide	515.3

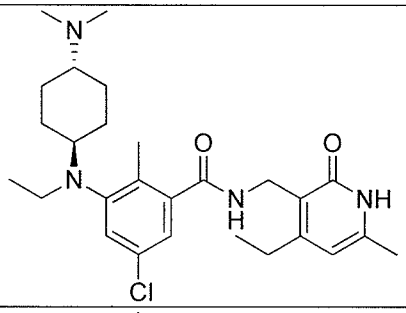
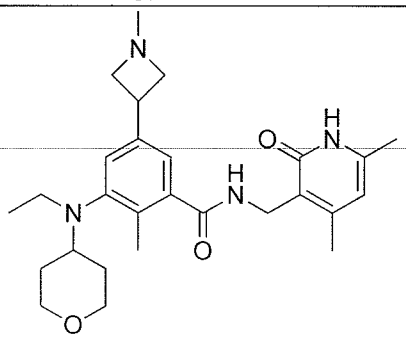
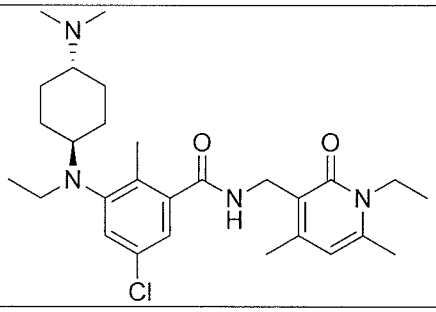
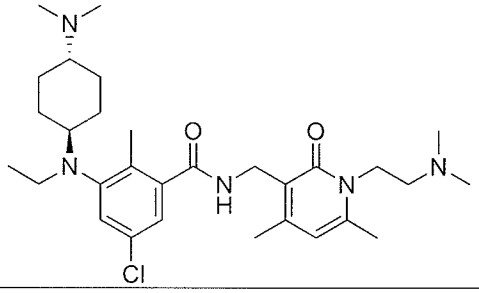
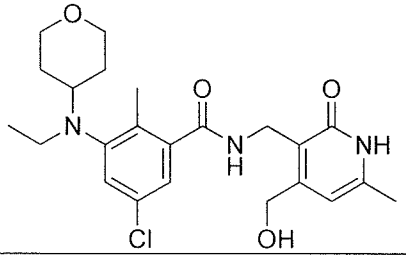
Compound Number	Structure	Name	MS†
299		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((1r,4r)-4-((2-methoxyethyl)(methyl)amino)cyclohexyl)amino)-2-methylbenzamide	517.4
300		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((1s,4s)-4-(methyl(2,2,2-trifluoroethyl)amino)cyclohexyl)amino)-2-methylbenzamide	541.4
301		N-((1-benzyl-4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-chloro-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methylbenzamide	563.4
302		5-chloro-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-N-((1-(2-hydroxyethyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	517.4
303		5-chloro-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-N-((1-(2-methoxyethyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	531.4

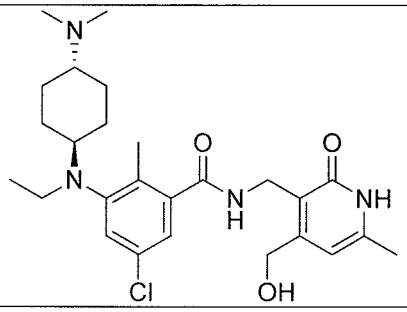
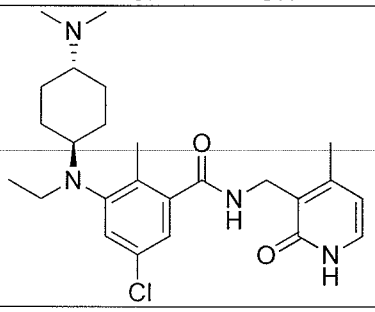
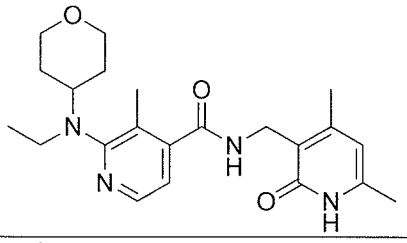
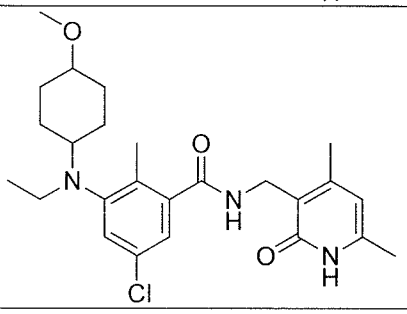
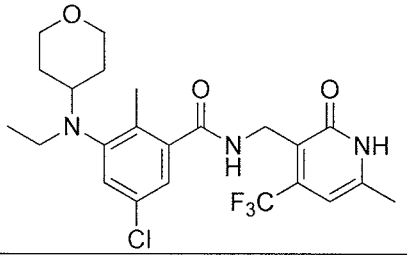
Compound Number	Structure	Name	MS†
304		3-(((1s,4s)-4-(azetidin-1-yl)cyclohexyl)(ethyl)amino)-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	485.2
305		3-(((1r,4r)-4-(azetidin-1-yl)cyclohexyl)(ethyl)amino)-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	485.2
306		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methyl-5-(trifluoromethyl)benzamide	507.5
307		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((1r,4r)-4-hydroxycyclohexyl)amino)-2-methylbenzamide	446.3

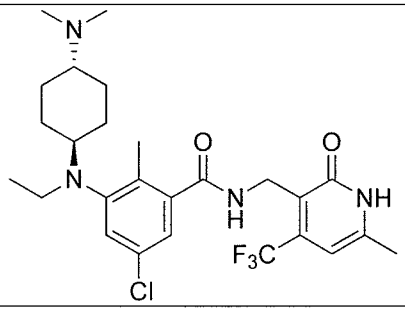
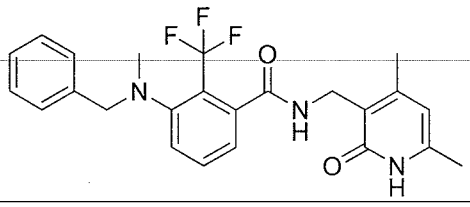
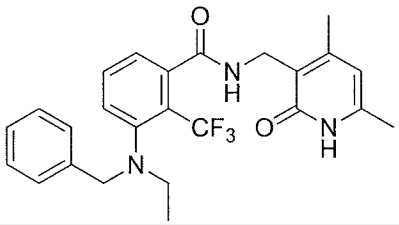
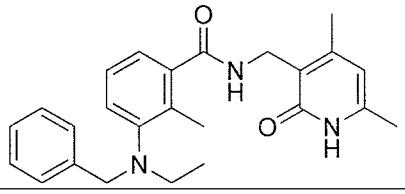
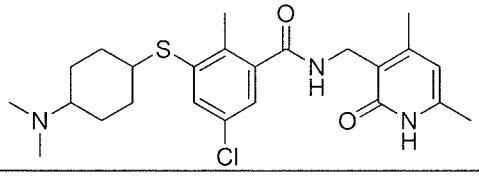
Compound Number	Structure	Name	MS†
308		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-5-methoxy-2-methylbenzamide	469.8
309		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-((4-(dimethylamino)cyclohexyl)(ethyl)amino)-5-(2-hydroxyethoxy)-2-methylbenzamide	499.6
310		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-((4-(dimethylamino)cyclohexyl)(ethyl)amino)-5-(2-methoxyethoxy)-2-methylbenzamide	513.6
311		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-5-(ethylthio)-2-methylbenzamide	499.6

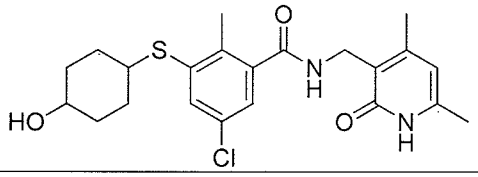
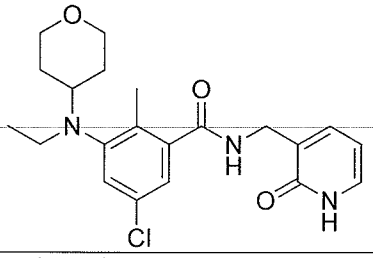
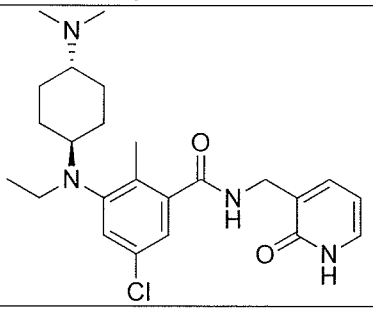
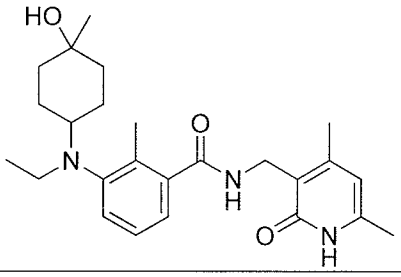
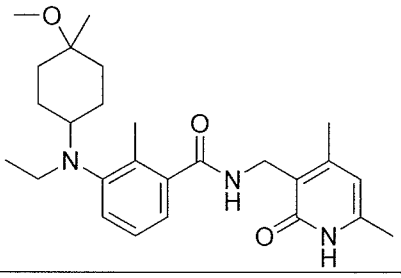
Compound Number	Structure	Name	MS†
312		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((1r,4r)-4-(methyl(2,2,2-trifluoroethyl)amino)cyclohexyl)amino)-2-methylbenzamide	541.5
313		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(4-hydroxycyclohexyl)amino)-2-methylbenzamide	446.3
314		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,5',5'-trimethyl-2'-oxo-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-3-carboxamide	427.4
315		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methyl-5-(tetrahydro-2H-pyran-4-yl)benzamide	523.6

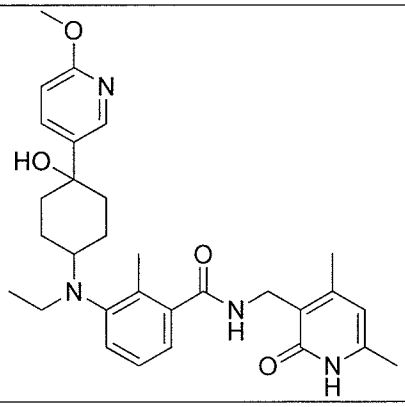
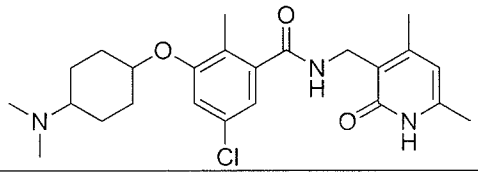
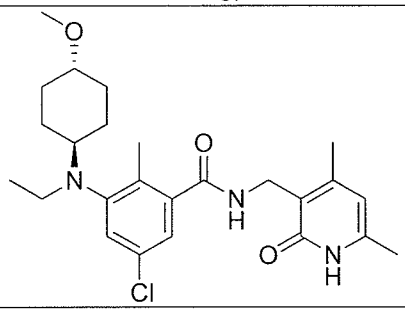
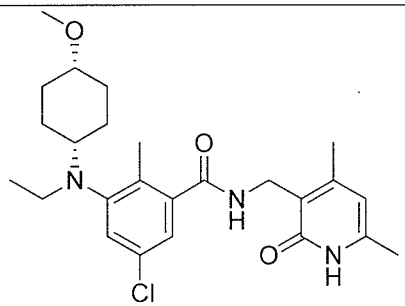
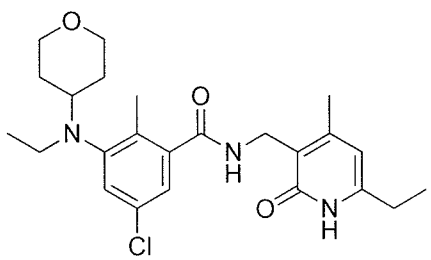
Compound Number	Structure	Name	MS†
316		5-chloro-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methyl-N-((6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)benzamide	459.5
317		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(5,5-dimethyl-2-oxocyclohexyl)-2-methylbenzamide	395.4
318		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(5,5-dimethyl-2-oxocyclohexyl)-2-methylbenzamide	429.4
319		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-5-(ethylsulfonyl)-2-methylbenzamide	531.6
320		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-5-isopropyl-2-methylbenzamide	481.4

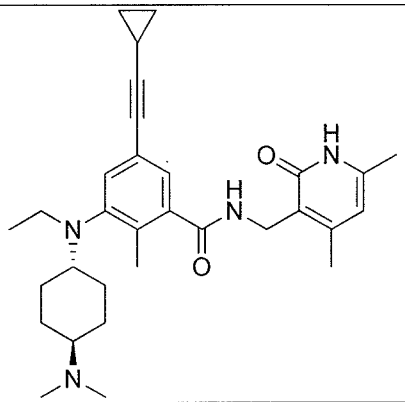
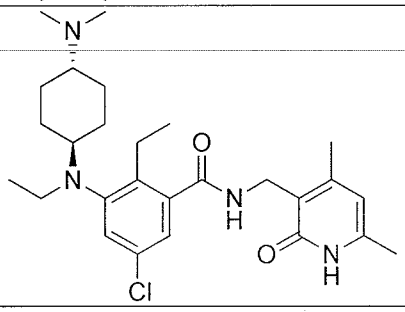
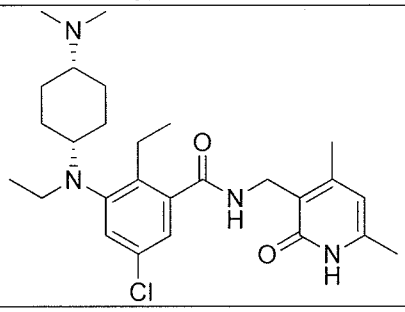
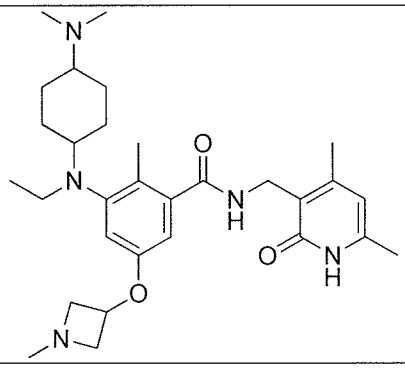
Compound Number	Structure	Name	MS†
321		5-chloro-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-N-((4-ethyl-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	487.5
322		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-2-methyl-5-(1-methylazetidin-3-yl)benzamide	467.3
323		5-chloro-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-N-((1-ethyl-4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	501.5
324		5-chloro-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-N-((1-(2-(dimethylamino)ethyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	544.6
325		5-chloro-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-N-((4-(hydroxymethyl)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	448.4

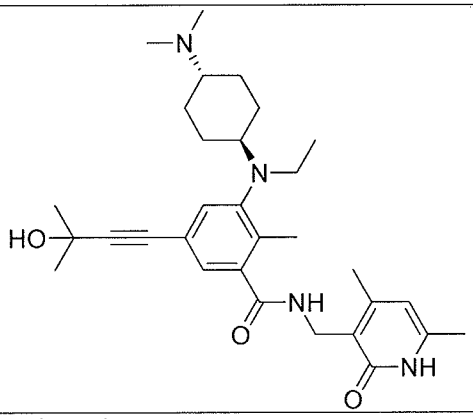
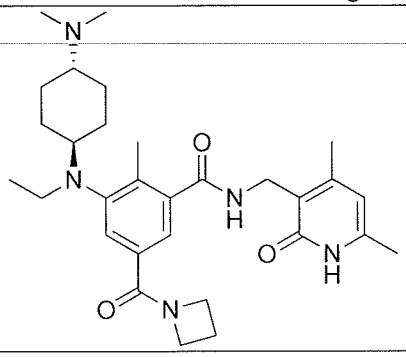
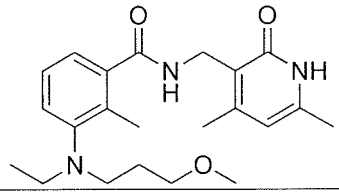
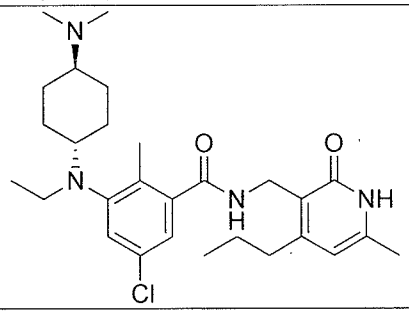
Compound Number	Structure	Name	MS†
326		5-chloro-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-N-((4-(hydroxymethyl)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	489.5
327		5-chloro-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methyl-N-((4-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)benzamide	459.4
328		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-methylisonicotinamide	399.1
329		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(4-methoxycyclohexyl)amino)-2-methylbenzamide	460.4
330		5-chloro-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-2-methyl-N-((6-methyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)methyl)benzamide	486.4

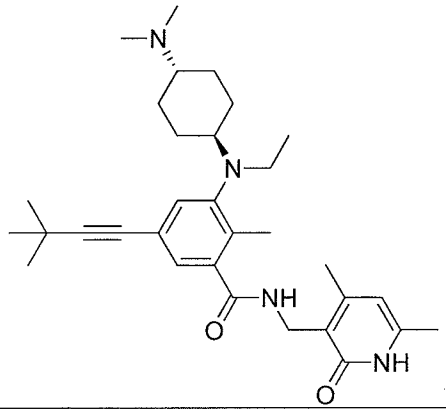
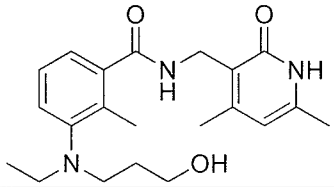
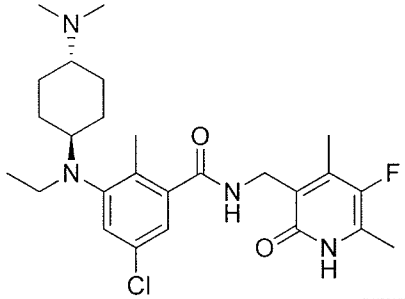
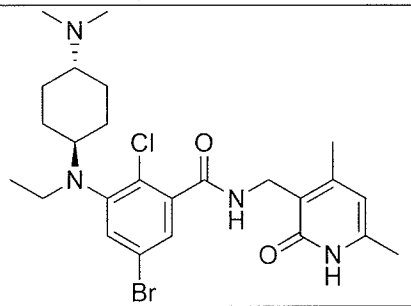
Compound Number	Structure	Name	MS†
331		5-chloro-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methyl-N-((6-methyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)methyl)benzamide	527.5
332		3-(benzyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-(trifluoromethyl)benzamide	444.2
333		3-(benzyl(ethyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-(trifluoromethyl)benzamide	458.3
334		3-(benzyl(ethyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	404.3
335		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-((4-(dimethylamino)cyclohexyl)thio)-2-methylbenzamide	462.4

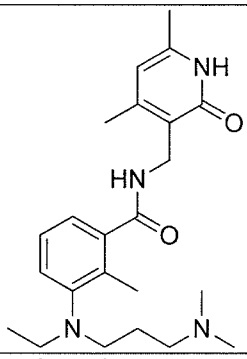
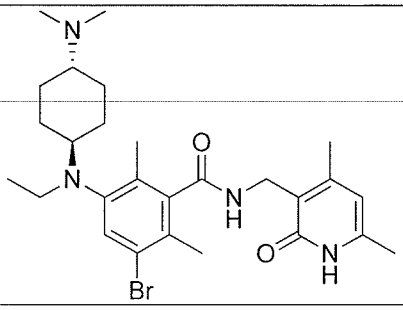
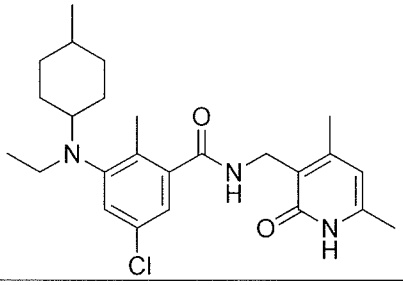
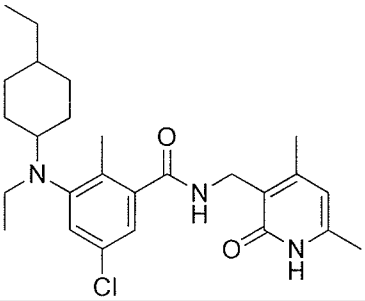
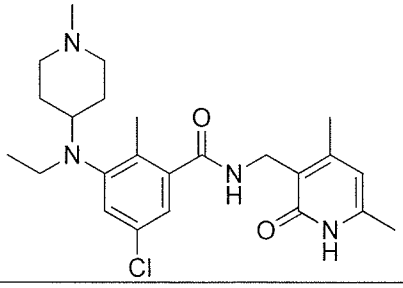
Compound Number	Structure	Name	MS†
336		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-((4-hydroxycyclohexyl)thio)-2-methylbenzamide	435.3
337		5-chloro-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-2-methyl-N-((2-oxo-1,2-dihydropyridin-3-yl)methyl)benzamide	404.3
338		5-chloro-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methyl-N-((2-oxo-1,2-dihydropyridin-3-yl)methyl)benzamide	445.5
339		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(4-hydroxy-4-methylcyclohexyl)amino)-2-methylbenzamide	426.5
340		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(4-methoxy-4-methylcyclohexyl)amino)-2-methylbenzamide	440.45

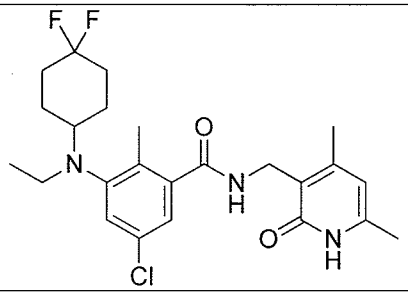
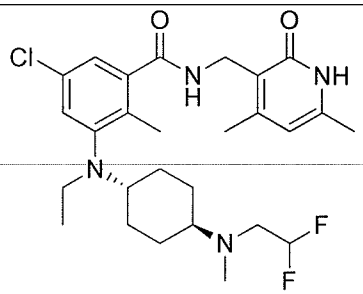
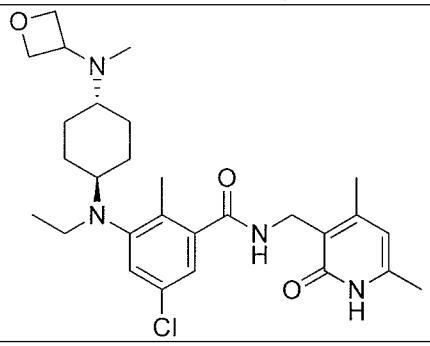
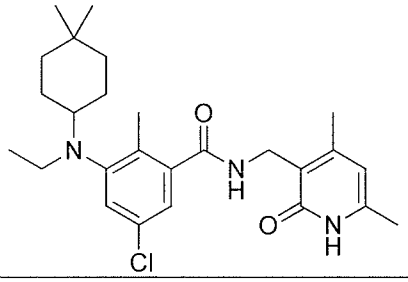
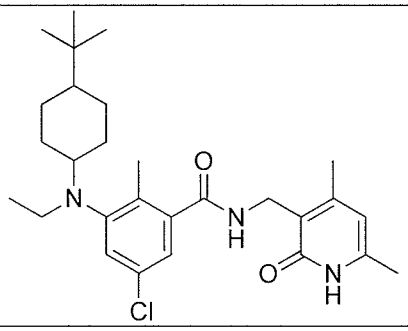
Compound Number	Structure	Name	MS†
341		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(4-hydroxy-4-(6-methoxypyridin-3-yl)cyclohexyl)amino)-2-methylbenzamide	519.3
342		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-((4-(dimethylamino)cyclohexyl)oxy)-2-methylbenzamide	446.3
343		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((1r,4r)-4-methoxycyclohexyl)amino)-2-methylbenzamide	460.4
344		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((1s,4s)-4-methoxycyclohexyl)amino)-2-methylbenzamide	460.3
345		5-chloro-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-N-((6-ethyl-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	446.3

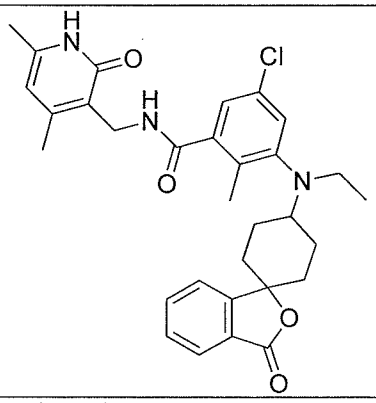
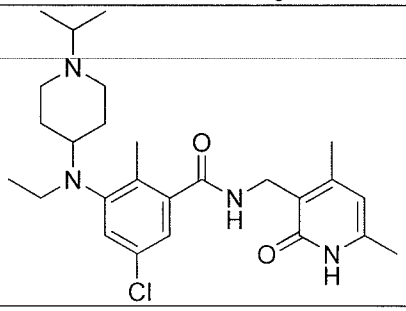
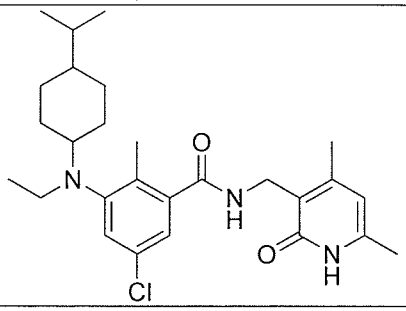
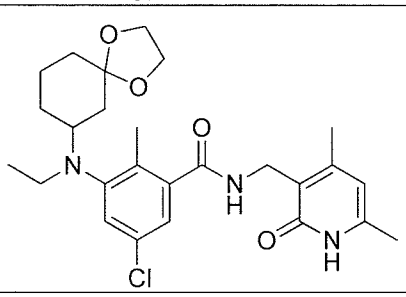
Compound Number	Structure	Name	MS†
346		5-(cyclopropylethynyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methylbenzamide	503.5
347		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r, 4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-ethylbenzamide	487.2
348		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1s,4s)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-ethylbenzamide	487.2
349		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-((4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methyl-5-((1-methylazetidin-3-yl)oxy)benzamide	524.6

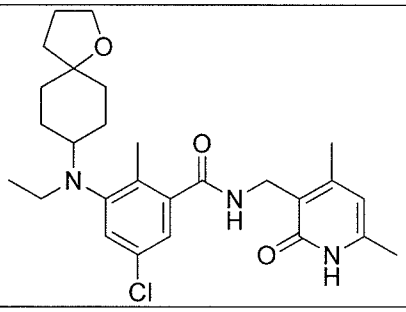
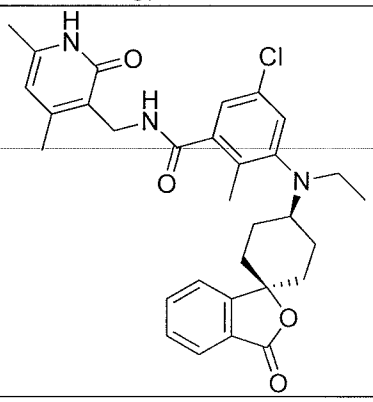
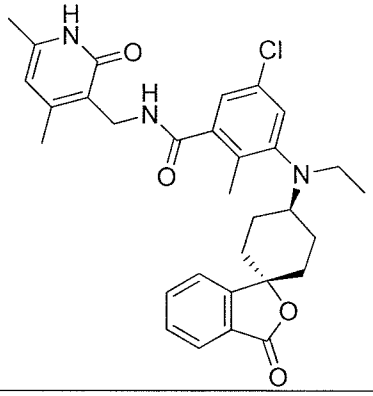
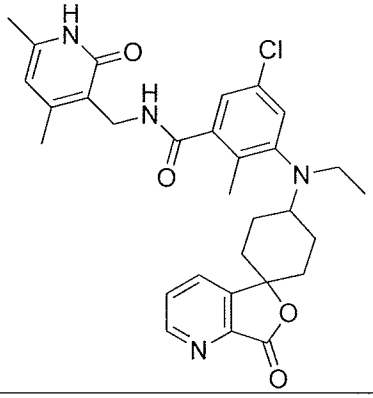
Compound Number	Structure	Name	MS†
350		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-5-(3-hydroxy-3-methylbut-1-yn-1-yl)-2-methylbenzamide	521.5
351		5-(azetidine-1-carbonyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methylbenzamide	522.8
352		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(3-methoxypropyl)amino)-2-methylbenzamide	386.4
353		5-chloro-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methyl-N-((6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)benzamide	501.5

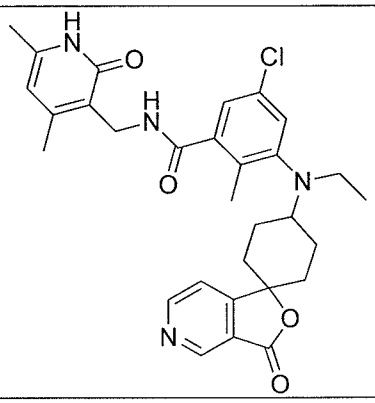
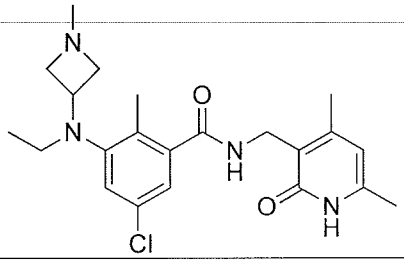
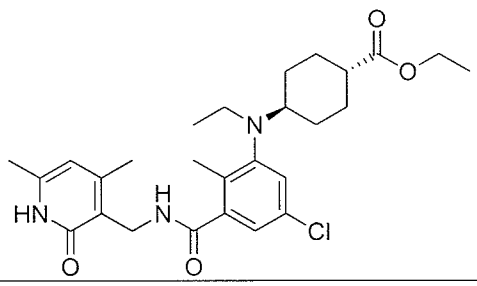
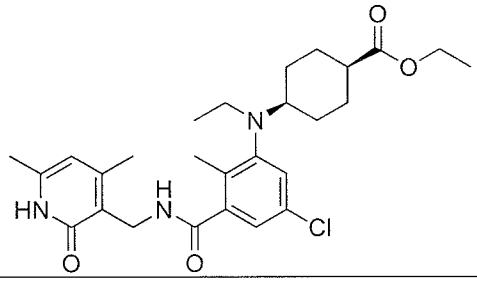
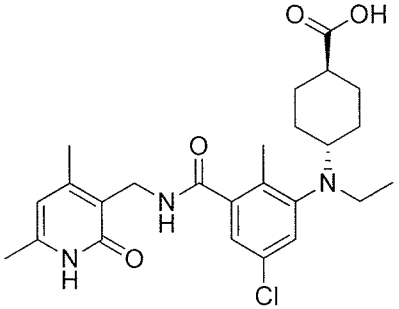
Compound Number	Structure	Name	MS†
354		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-5-(3,3-dimethylbut-1-yn-1-yl)-2-methylbenzamide	519.6
355		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(3-hydroxypropyl)amino)-2-methylbenzamide	372.3
356		5-chloro-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-N-((5-fluoro-4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	491.1
357		5-bromo-2-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)benzamide	539.25

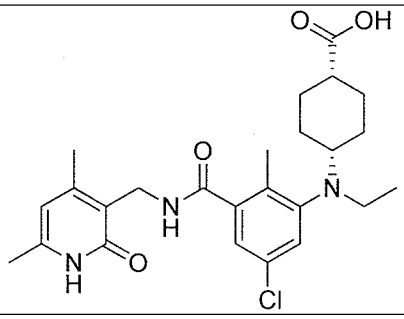
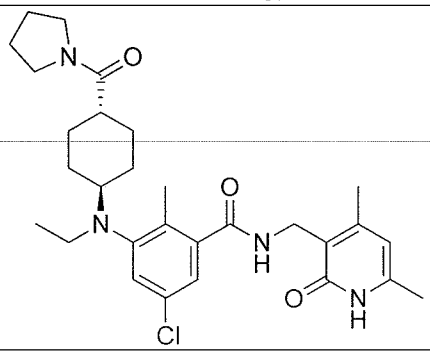
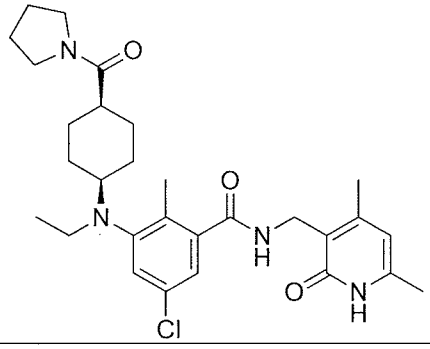
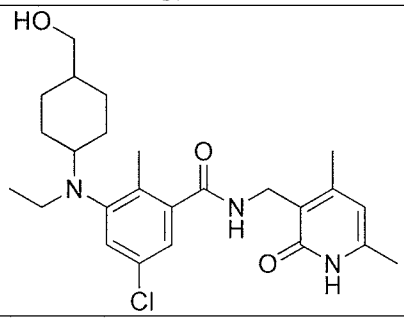
Compound Number	Structure	Name	MS†
358		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-((3-(dimethylamino)propyl)(ethyl)amino)-2-methylbenzamide	399.4
359		3-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2,6-dimethylbenzamide	531.4
360		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(4-methylcyclohexyl)amino)-2-methylbenzamide	444.4
361		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(4-ethylcyclohexyl)amino)-2-methylbenzamide	458.4
362		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(1-methylpiperidin-4-yl)amino)-2-methylbenzamide	445.4

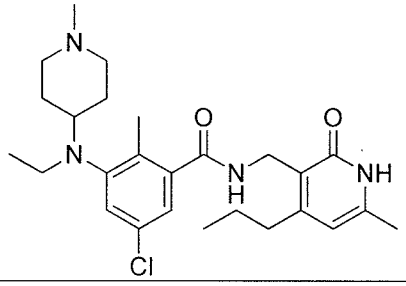
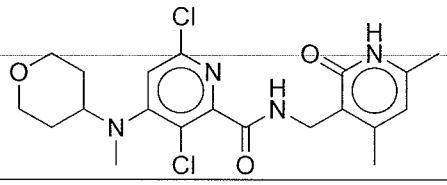
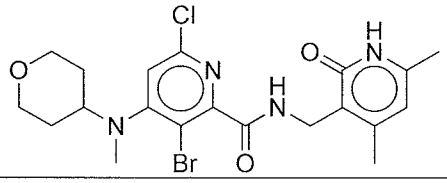
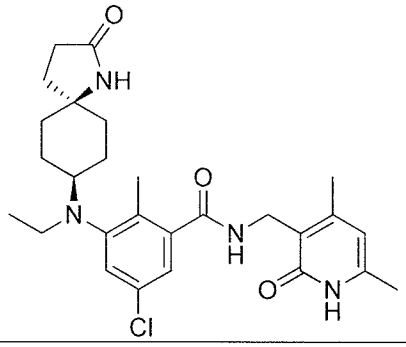
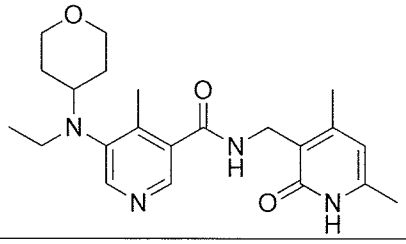
Compound Number	Structure	Name	MS†
363		5-chloro-3-((4,4-difluorocyclohexyl)(ethyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	466.2
364		5-chloro-3-(((1r,4r)-4-((2,2-difluoroethyl)(methyl)amino)cyclohexyl)(ethyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	523.5
365		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((1r,4r)-4-(methyl(oxetan-3-yl)amino)cyclohexyl)amino)-2-methylbenzamide	515.4
366		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-((4,4-dimethylcyclohexyl)(ethyl)amino)-2-methylbenzamide	458.4
367		3-((4-(tert-butyl)cyclohexyl)(ethyl)amino)-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	486.5

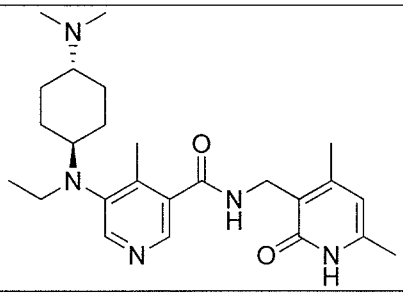
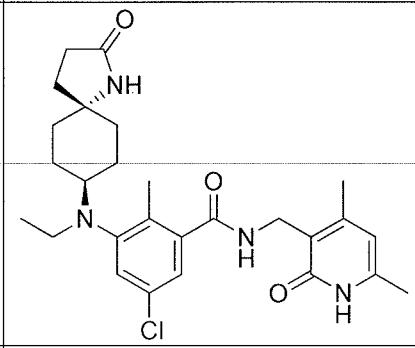
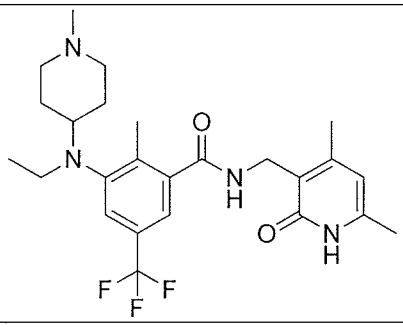
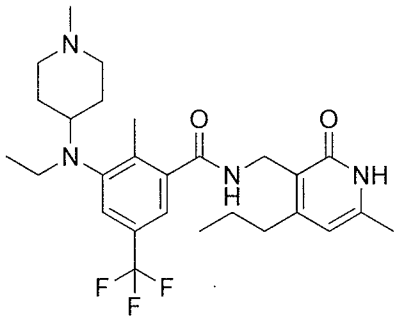
Compound Number	Structure	Name	MS†
368		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(3'-oxo-3'H-spiro[cyclohexane-1,1'-isobenzofuran]-4-yl)amino)-2-methylbenzamide	548.5
369		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(1-isopropylpiperidin-4-yl)amino)-2-methylbenzamide	473.5
370		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(4-isopropylcyclohexyl)amino)-2-methylbenzamide	472.3
371		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(1,4-dioxaspiro[4.5]decan-7-yl)amino)-2-methylbenzamide	488.4

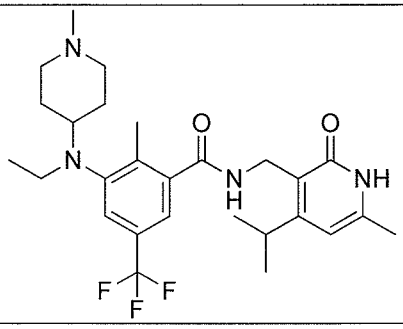
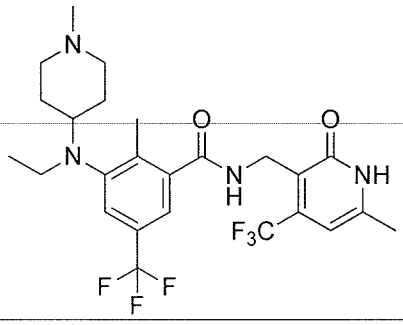
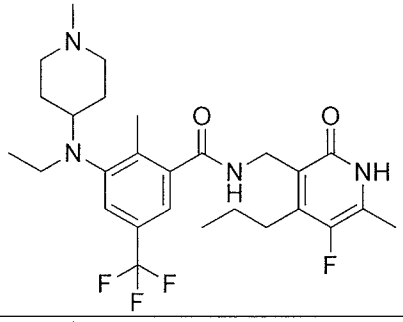
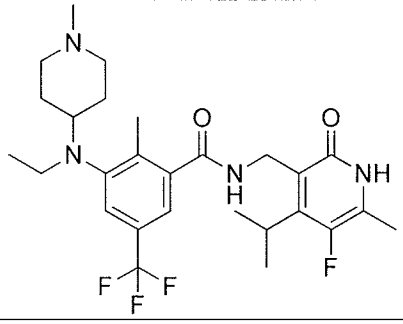
Compound Number	Structure	Name	MS†
372		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(1-oxaspiro[4.5]decan-8-yl)amino)-2-methylbenzamide	486.35
373		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((1s,4s)-3'-oxo-3'H-spiro[cyclohexane-1,1'-isobenzofuran]-4-yl)amino)-2-methylbenzamide	548.4
374		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((1r,4r)-3'-oxo-3'H-spiro[cyclohexane-1,1'-isobenzofuran]-4-yl)amino)-2-methylbenzamide	548.4
375		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(7'-oxo-7'H-spiro[cyclohexane-1,5'-furo[3,4-b]pyridin]-4-yl)amino)-2-methylbenzamide	549.3

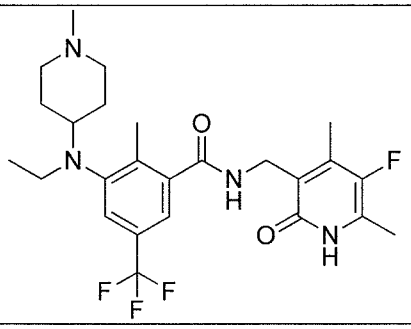
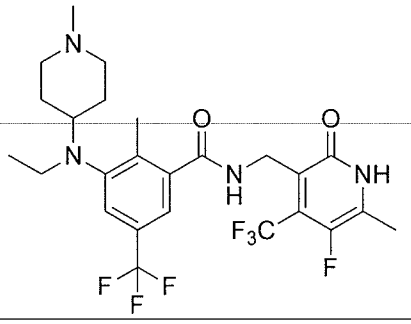
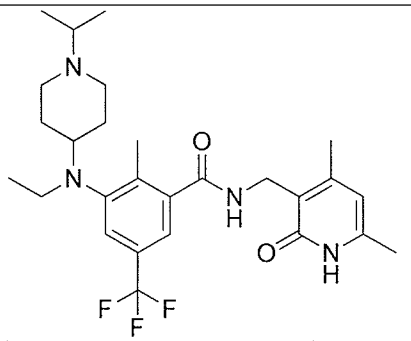
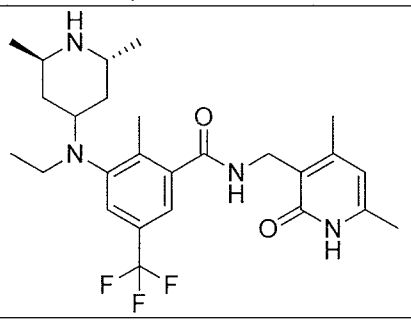
Compound Number	Structure	Name	MS†
376		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(3'-oxo-3'H-spiro[cyclohexane-1,1'-furo[3,4-c]pyridin]-4-yl)amino)-2-methylbenzamide	549.5
377		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(1-methylazetidin-3-yl)amino)-2-methylbenzamide	417.3
378		(1r,4r)-ethyl 4-((5-chloro-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(ethyl)amino)cyclohexanecarboxylate	502.5
379		(1s,4s)-ethyl 4-((5-chloro-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(ethyl)amino)cyclohexanecarboxylate	502.4
380		(1r,4r)-4-((5-chloro-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(ethyl)amino)cyclohexanecarboxylic acid	474.3

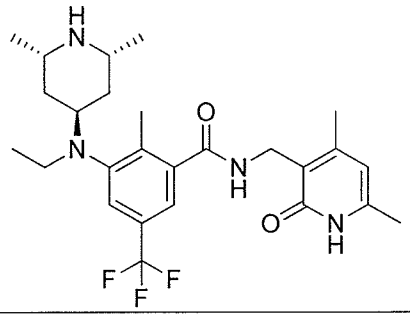
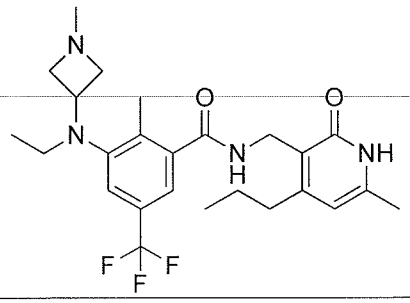
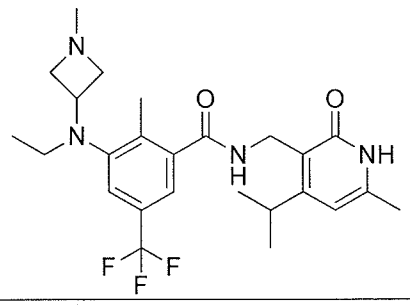
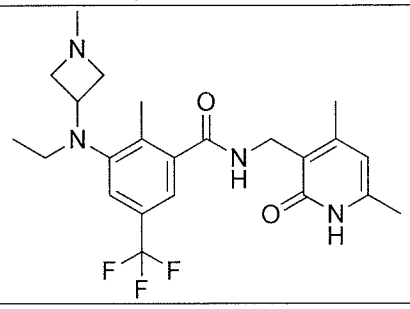
Compound Number	Structure	Name	MS†
381		(1s,4s)-4-((5-chloro-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(ethyl)amino)cyclohexanecarboxylic acid	474.4
382		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((1r,4r)-4-(pyrrolidine-1-carbonyl)cyclohexyl)amino)-2-methylbenzamide	527.5
383		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((1s,4s)-4-(pyrrolidine-1-carbonyl)cyclohexyl)amino)-2-methylbenzamide	527.4
384		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(4-(hydroxymethyl)cyclohexyl)amino)-2-methylbenzamide	460.2

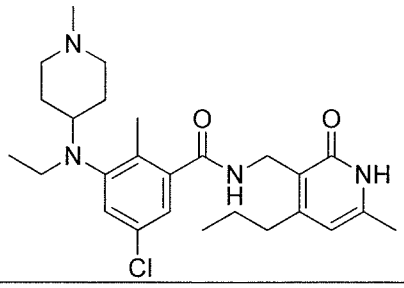
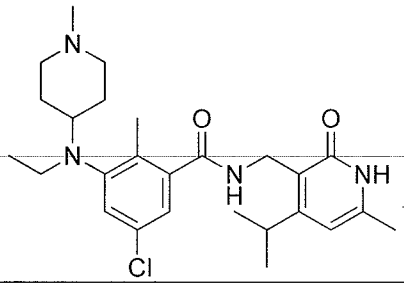
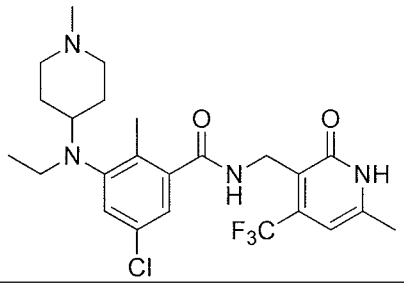
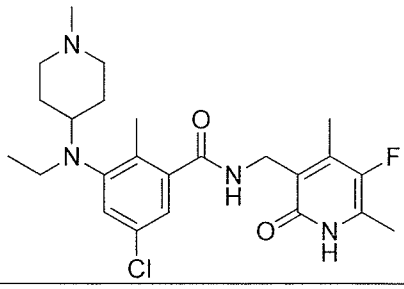
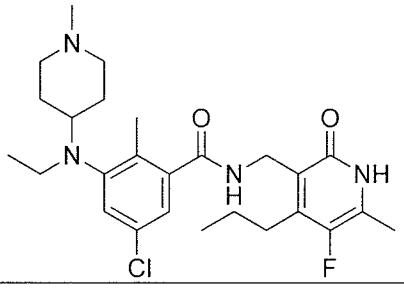
Compound Number	Structure	Name	MS†
385		5-chloro-3-(ethyl(1-methylpiperidin-4-yl)amino)-2-methyl-N-((6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)benzamide	473.4
386		3,6-dichloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-4-(methyl(tetrahydro-2H-pyran-4-yl)amino)picolinamide	440.8
387		3-bromo-6-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-4-(methyl(tetrahydro-2H-pyran-4-yl)amino)picolinamide	485
388		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((5s,8s)-2-oxo-1-azaspiro[4.5]decan-8-yl)amino)-2-methylbenzamide	499.35
389		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-4-methylnicotinamide	399.5

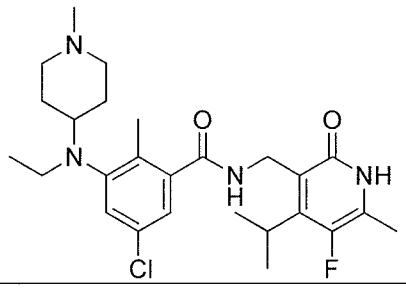
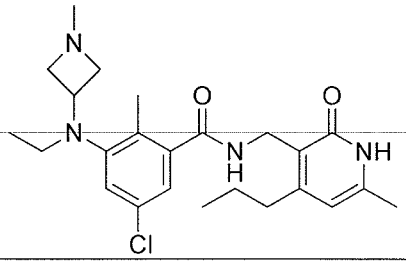
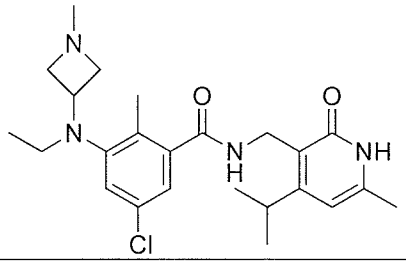
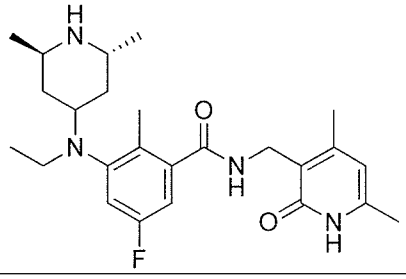
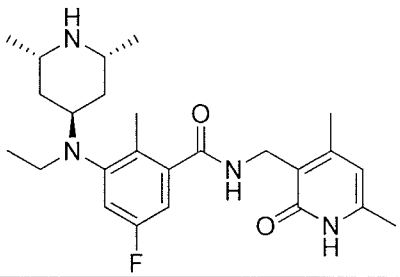
Compound Number	Structure	Name	MS†
390		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-4-methylnicotinamide	440.5
391		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((5r,8r)-2-oxo-1-azaspiro[4.5]decan-8-yl)amino)-2-methylbenzamide	499.4
392		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(1-methylpiperidin-4-yl)amino)-2-methyl-5-(trifluoromethyl)benzamide	501.3
393		3-(ethyl(1-methylpiperidin-4-yl)amino)-2-methyl-N-((6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)-5-(trifluoromethyl)benzamide	505.2

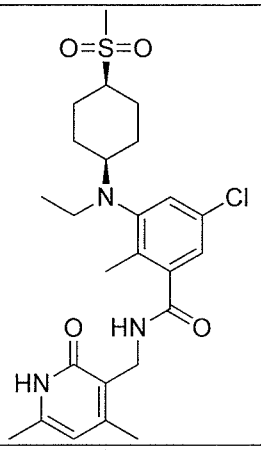
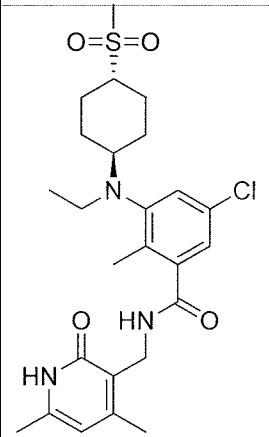
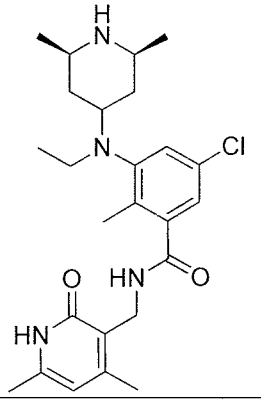
Compound Number	Structure	Name	MS†
394		3-(ethyl(1-methylpiperidin-4-yl)amino)-N-((4-isopropyl-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-5-(trifluoromethyl)benzamide	529.2
395		3-(ethyl(1-methylpiperidin-4-yl)amino)-2-methyl-N-((6-methyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)methyl)-5-(trifluoromethyl)benzamide	555.2
396		3-(ethyl(1-methylpiperidin-4-yl)amino)-N-((5-fluoro-6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)-2-methyl-5-(trifluoromethyl)benzamide	525.6
397		3-(ethyl(1-methylpiperidin-4-yl)amino)-N-((5-fluoro-4-isopropyl-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-5-(trifluoromethyl)benzamide	525.6

Compound Number	Structure	Name	MS†
398		3-(ethyl(1-methylpiperidin-4-yl)amino)-N-((5-fluoro-4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-5-(trifluoromethyl)benzamide	497.5
399		3-(ethyl(1-methylpiperidin-4-yl)amino)-N-((5-fluoro-6-methyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)methyl)-2-methyl-5-(trifluoromethyl)benzamide	551.5
400		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(1-isopropylpiperidin-4-yl)amino)-2-methyl-5-(trifluoromethyl)benzamide	507.2
401		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((2R,6R)-2,6-dimethylpiperidin-4-yl)(ethyl)amino)-2-methyl-5-(trifluoromethyl)benzamide	493.1

Compound Number	Structure	Name	MS†
402		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((2S,4s,6R)-2,6-dimethylpiperidin-4-yl)(ethyl)amino)-2-methyl-5-(trifluoromethyl)benzamide	493.2
403		3-(ethyl(1-methylazetidin-3-yl)amino)-2-methyl-N-((6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)-5-(trifluoromethyl)benzamide	480.5
404		3-(ethyl(1-methylazetidin-3-yl)amino)-N-((4-isopropyl-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-5-(trifluoromethyl)benzamide	479.5
405		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(1-methylazetidin-3-yl)amino)-2-methyl-5-(trifluoromethyl)benzamide	451.5

Compound Number	Structure	Name	MS†
406		5-chloro-3-(ethyl(1-methylpiperidin-4-yl)amino)-2-methyl-N-((6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)benzamide	473.1
407		5-chloro-3-(ethyl(1-methylpiperidin-4-yl)amino)-N-((4-isopropyl-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	495.2
408		5-chloro-3-(ethyl(1-methylpiperidin-4-yl)amino)-2-methyl-N-((6-methyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)methyl)benzamide	499.1
409		5-chloro-3-(ethyl(1-methylpiperidin-4-yl)amino)-N-((5-fluoro-4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	463.5
410		5-chloro-3-(ethyl(1-methylpiperidin-4-yl)amino)-N-((5-fluoro-6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	491.5

Compound Number	Structure	Name	MS†
411		5-chloro-3-(ethyl(1-methylpiperidin-4-yl)amino)-N-((5-fluoro-4-isopropyl-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	491.5
412		5-chloro-3-(ethyl(1-methylazetidin-3-yl)amino)-2-methyl-N-((6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)benzamide	445.5
413		5-chloro-3-(ethyl(1-methylazetidin-3-yl)amino)-N-((4-isopropyl-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide	445.6
414		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((2R,6R)-2,6-dimethylpiperidin-4-yl)(ethyl)amino)-5-fluoro-2-methylbenzamide	443.1
415		N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((2S,4s,6R)-2,6-dimethylpiperidin-4-yl)(ethyl)amino)-5-fluoro-2-methylbenzamide	443.2

Compound Number	Structure	Name	MS†
416		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((1s,4s)-4-(methylsulfonyl)cyclohexyl)amino)-2-methylbenzamide	508.1
417		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((1r,4r)-4-(methylsulfonyl)cyclohexyl)amino)-2-methylbenzamide	508
418		5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((2S,6R)-2,6-dimethylpiperidin-4-yl)(ethyl)amino)-2-methylbenzamide	

*The cis/trans stereochemical assignments of Compounds 58/59, 60/61, 107/108, and 416/417 are arbitrarily assigned.

† MS- Mass spectrometry of sample. This can be recorded in positive or negative ion modes and potential ions include M, M+1, M+23 (M+Na) and M-1.

[0508] As used herein, "alkyl", "C_1, C_2, C_3, C_4, C_5 or C_6 alkyl" or "C_1-C_6 alkyl" is intended to include C_1, C_2, C_3, C_4, C_5 or C_6 straight chain (linear) saturated aliphatic hydrocarbon groups

and C_3, C_4, C_5 or C_6 branched saturated aliphatic hydrocarbon groups. For example, C_1-C_6 alkyl is intended to include C_1, C_2, C_3, C_4, C_5 and C_6 alkyl groups. Examples of alkyl include, moieties having from one to six carbon atoms, such as, but not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl or n-hexyl.

[0509] In certain embodiments, a straight chain or branched alkyl has six or fewer carbon atoms (*e.g.*, C_1-C_6 for straight chain, C_3-C_6 for branched chain), and in another embodiment, a straight chain or branched alkyl has four or fewer carbon atoms.

[0510] As used herein, the term "cycloalkyl" refers to a saturated or unsaturated nonaromatic hydrocarbon mono-or multi-ring (e.g., fused, bridged, or spiro rings) system having 3 to 30 carbon atoms (e.g., C_3-C_{10}). Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, and adamantyl. The term "heterocycloalkyl" refers to a saturated or unsaturated nonaromatic 3-8 membered monocyclic, 7-12 membered bicyclic (fused, bridged, or spiro rings), or 11-14 membered tricyclic ring system (fused, bridged, or spiro rings) having one or more heteroatoms (such as O, N, S, or Se), unless specified otherwise. Examples of heterocycloalkyl groups include, but are not limited to, piperidinyl, piperazinyl, pyrrolidinyl, dioxanyl, tetrahydrofuranyl, isoindolinyl, indolinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, oxiranyl, azetidinyl, oxetanyl, thietanyl, 1,2,3,6-tetrahydropyridinyl, tetrahydropyranyl, dihydropyranyl, pyranyl, morpholinyl, tetrahydrothiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, 1,4-dioxa-8-azaspiro[4.5]decanyl, 1,4-dioxaspiro[4.5]decanyl, 1-oxaspiro[4.5]decanyl, 1-azaspiro[4.5]decanyl, 3'H-spiro[cyclohexane-1,1'-isobenzofuran]-yl, 7'H-spiro[cyclohexane-1,5'-furo[3,4-b]pyridin]-yl, 3'H-spiro[cyclohexane-1,1'-furo[3,4-c]pyridin]-yl, and the like.

[0511] The term "optionally substituted alkyl" refers to unsubstituted alkyl or alkyl having designated substituents replacing one or more hydrogen atoms on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate,

phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[0512] An "arylalkyl" or an "aralkyl" moiety is an alkyl substituted with an aryl (*e.g.*, phenylmethyl (benzyl)). An "alkylaryl" moiety is an aryl substituted with an alkyl (*e.g.*, methylphenyl).

[0513] As used herein, "alkyl linker" is intended to include C_1, C_2, C_3, C_4, C_5 or C_6 straight chain (linear) saturated divalent aliphatic hydrocarbon groups and C_3, C_4, C_5 or C_6 branched saturated aliphatic hydrocarbon groups. For example, C_1-C_6 alkyl linker is intended to include C_1, C_2, C_3, C_4, C_5 and C_6 alkyl linker groups. Examples of alkyl linker include, moieties having from one to six carbon atoms, such as, but not limited to, methyl (-CH_2-), ethyl (-CH_2CH_2-), n-propyl (-$CH_2CH_2CH_2$-), i-propyl (-$CHCH_3CH_2$-), n-butyl (-$CH_2CH_2CH_2CH_2$-), s-butyl (-$CHCH_3CH_2CH_2$-), i-butyl (-$C(CH_3)_2CH_2$-), n-pentyl (-$CH_2CH_2CH_2CH_2CH_2$-), s-pentyl (-$CHCH_3CH_2CH_2CH_2$-) or n-hexyl (-$CH_2CH_2CH_2CH_2CH_2CH_2$-).

[0514] "Alkenyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double bond. For example, the term "alkenyl" includes straight chain alkenyl groups (*e.g.*, ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl), and branched alkenyl groups. In certain embodiments, a straight chain or branched alkenyl group has six or fewer carbon atoms in its backbone (*e.g.*, C_2-C_6 for straight chain, C_3-C_6 for branched chain). The term "C_2-C_6" includes alkenyl groups containing two to six carbon atoms. The term "C_3-C_6" includes alkenyl groups containing three to six carbon atoms.

[0515] The term "optionally substituted alkenyl" refers to unsubstituted alkenyl or alkenyl having designated substituents replacing one or more hydrogen atoms on one or more hydrocarbon backbone carbon atoms. Such substituents can include, for example, alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino

and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[0516] "Alkynyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but which contain at least one triple bond. For example, "alkynyl" includes straight chain alkynyl groups (*e.g.*, ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl), and branched alkynyl groups. In certain embodiments, a straight chain or branched alkynyl group has six or fewer carbon atoms in its backbone (*e.g.*, C_2-C_6 for straight chain, C_3-C_6 for branched chain). The term "C_2-C_6" includes alkynyl groups containing two to six carbon atoms. The term "C_3-C_6" includes alkynyl groups containing three to six carbon atoms.

[0517] The term "optionally substituted alkynyl" refers to unsubstituted alkynyl or alkynyl having designated substituents replacing one or more hydrogen atoms on one or more hydrocarbon backbone carbon atoms. Such substituents can include, for example, alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[0518] Other optionally substituted moieties (such as optionally substituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl) include both the unsubstituted moieties and the moieties having one or more of the designated substituents. For example, substituted heterocycloalkyl includes those substituted with one or more alkyl groups, such as 2,2,6,6-tetramethyl-piperidinyl and 2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridinyl.

[0519] "Aryl" includes groups with aromaticity, including "conjugated," or multicyclic systems with at least one aromatic ring and do not contain any heteroatom in the ring structure. Examples include phenyl, benzyl, 1,2,3,4-tetrahydronaphthalenyl, etc.

[0520] "Heteroaryl" groups are aryl groups, as defined above, except having from one to four heteroatoms in the ring structure, and may also be referred to as "aryl heterocycles" or "heteroaromatics." As used herein, the term "heteroaryl" is intended to include a stable 5-, 6-, or 7-membered monocyclic or 7-, 8-, 9-, 10-, 11- or 12-membered bicyclic aromatic heterocyclic ring which consists of carbon atoms and one or more heteroatoms, *e.g.*, 1 or 1-2 or 1-3 or 1-4 or 1-5 or 1-6 heteroatoms, or *e.g.*,1, 2, 3, 4, 5, or 6 heteroatoms, independently selected from the group consisting of nitrogen, oxygen and sulfur. The nitrogen atom may be substituted or unsubstituted (*i.e.*, N or NR wherein R is H or other substituents, as defined). The nitrogen and sulfur heteroatoms may optionally be oxidized (*i.e.*, N→O and $S(O)_p$, where p = 1 or 2). It is to be noted that total number of S and O atoms in the aromatic heterocycle is not more than 1.

[0521] Examples of heteroaryl groups include pyrrole, furan, thiophene, thiazole, isothiazole, imidazole, triazole, tetrazole, pyrazole, oxazole, isoxazole, pyridine, pyrazine, pyridazine, pyrimidine, and the like.

[0522] Furthermore, the terms "aryl" and "heteroaryl" include multicyclic aryl and heteroaryl groups, *e.g.*, tricyclic, bicyclic, *e.g.*, naphthalene, benzoxazole, benzodioxazole, benzothiazole, benzoimidazole, benzothiophene, methylenedioxyphenyl, quinoline, isoquinoline, naphthrydine, indole, benzofuran, purine, benzofuran, deazapurine, indolizine.

[0523] In the case of multicyclic aromatic rings, only one of the rings needs to be aromatic (*e.g.*, 2,3-dihydroindole), although all of the rings may be aromatic (*e.g.*, quinoline). The second ring can also be fused or bridged.

[0524] The cycloalkyl, heterocycloalkyl, aryl, or heteroaryl ring can be substituted at one or more ring positions (e.g., the ring-forming carbon or heteroatom such as N) with such substituents as described above, for example, alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkoxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkylaminocarbonyl, aralkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido,

nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. Aryl and heteroaryl groups can also be fused or bridged with alicyclic or heterocyclic rings, which are not aromatic so as to form a multicyclic system (*e.g.*, tetralin, methylenedioxyphenyl).

[0525] As used herein, "carbocycle" or "carbocyclic ring" is intended to include any stable monocyclic, bicyclic or tricyclic ring having the specified number of carbons, any of which may be saturated, unsaturated, or aromatic. Carbocycle includes cycloalkyl and aryl. For example, a C_3-C_{14} carbocycle is intended to include a monocyclic, bicyclic or tricyclic ring having 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 carbon atoms. Examples of carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cycloheptenyl, cycloheptyl, cycloheptenyl, adamantyl, cyclooctyl, cyclooctenyl, cyclooctadienyl, fluorenyl, phenyl, naphthyl, indanyl, adamantyl and tetrahydronaphthyl. Bridged rings are also included in the definition of carbocycle, including, for example, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, and [4.4.0] bicyclodecane and [2.2.2] bicyclooctane. A bridged ring occurs when one or more carbon atoms link two non-adjacent carbon atoms. In one embodiment, bridge rings are one or two carbon atoms. It is noted that a bridge always converts a monocyclic ring into a tricyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge. Fused (*e.g.*, naphthyl, tetrahydronaphthyl) and spiro rings are also included.

[0526] As used herein, "heterocycle" or "heterocyclic group" includes any ring structure (saturated, unsaturated, or aromatic) which contains at least one ring heteroatom (*e.g.*, N, O or S). Heterocycle includes heterocycloalkyl and heteroaryl. Examples of heterocycles include, but are not limited to, morpholine, pyrrolidine, tetrahydrothiophene, piperidine, piperazine, oxetane, pyran, tetrahydropyran, azetidine, and tetrahydrofuran.

[0527] Examples of heterocyclic groups include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzoxazolinyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4a*H*-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1*H*-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl,

isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazol5(4H)-one, oxazolidinyl, oxazolyl, oxindolyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl.

[0528] The term "substituted," as used herein, means that any one or more hydrogen atoms on the designated atom is replaced with a selection from the indicated groups, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is oxo or keto (*i.e.*, =O), then 2 hydrogen atoms on the atom are replaced. Keto substituents are not present on aromatic moieties. Ring double bonds, as used herein, are double bonds that are formed between two adjacent ring atoms (*e.g.*, C=C, C=N or N=N). "Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

[0529] When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom in the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such formula. Combinations of substituents and/or variables are permissible, but only if such combinations result in stable compounds.

[0530] When any variable (*e.g.*, R_1) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R_1 moieties, then

the group may optionally be substituted with up to two R_1 moieties and R_1 at each occurrence is selected independently from the definition of R_1. Also, combinations of substituents and/or variables are permissible, but only if such combinations result in stable compounds.

[0531] The term "hydroxy" or "hydroxyl" includes groups with an -OH or -O^-.

[0532] As used herein, "halo" or "halogen" refers to fluoro, chloro, bromo and iodo. The term "perhalogenated" generally refers to a moiety wherein all hydrogen atoms are replaced by halogen atoms. The term "haloalkyl" or "haloalkoxyl" refers to an alkyl or alkoxyl substituted with one or more halogen atoms.

[0533] The term "carbonyl" includes compounds and moieties which contain a carbon connected with a double bond to an oxygen atom. Examples of moieties containing a carbonyl include, but are not limited to, aldehydes, ketones, carboxylic acids, amides, esters, anhydrides, etc.

[0534] The term "carboxyl" refers to –COOH or its C_1-C_6 alkyl ester.

[0535] "Acyl" includes moieties that contain the acyl radical (R-C(O)-) or a carbonyl group. "Substituted acyl" includes acyl groups where one or more of the hydrogen atoms are replaced by, for example, alkyl groups, alkynyl groups, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[0536] "Aroyl" includes moieties with an aryl or heteroaromatic moiety bound to a carbonyl group. Examples of aroyl groups include phenylcarboxy, naphthyl carboxy, etc.

[0537] "Alkoxyalkyl," "alkylaminoalkyl," and "thioalkoxyalkyl" include alkyl groups, as described above, wherein oxygen, nitrogen, or sulfur atoms replace one or more hydrocarbon backbone carbon atoms.

[0538] The term "alkoxy" or "alkoxyl" includes substituted and unsubstituted alkyl, alkenyl and alkynyl groups covalently linked to an oxygen atom. Examples of alkoxy groups or

alkoxyl radicals include, but are not limited to, methoxy, ethoxy, isopropyloxy, propoxy, butoxy and pentoxy groups. Examples of substituted alkoxy groups include halogenated alkoxy groups. The alkoxy groups can be substituted with groups such as alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moieties. Examples of halogen substituted alkoxy groups include, but are not limited to, fluoromethoxy, difluoromethoxy, trifluoromethoxy, chloromethoxy, dichloromethoxy and trichloromethoxy.

[0539] The term "ether" or "alkoxy" includes compounds or moieties which contain an oxygen bonded to two carbon atoms or heteroatoms. For example, the term includes "alkoxyalkyl," which refers to an alkyl, alkenyl, or alkynyl group covalently bonded to an oxygen atom which is covalently bonded to an alkyl group.

[0540] The term "ester" includes compounds or moieties which contain a carbon or a heteroatom bound to an oxygen atom which is bonded to the carbon of a carbonyl group. The term "ester" includes alkoxycarboxy groups such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, pentoxycarbonyl, etc.

[0541] The term "thioalkyl" includes compounds or moieties which contain an alkyl group connected with a sulfur atom. The thioalkyl groups can be substituted with groups such as alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, carboxyacid, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates,

alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moieties.

[0542] The term "thiocarbonyl" or "thiocarboxy" includes compounds and moieties which contain a carbon connected with a double bond to a sulfur atom.

[0543] The term "thioether" includes moieties which contain a sulfur atom bonded to two carbon atoms or heteroatoms. Examples of thioethers include, but are not limited to alkthioalkyls, alkthioalkenyls, and alkthioalkynyls. The term "alkthioalkyls" include moieties with an alkyl, alkenyl, or alkynyl group bonded to a sulfur atom which is bonded to an alkyl group. Similarly, the term "alkthioalkenyls" refers to moieties wherein an alkyl, alkenyl or alkynyl group is bonded to a sulfur atom which is covalently bonded to an alkenyl group; and alkthioalkynyls" refers to moieties wherein an alkyl, alkenyl or alkynyl group is bonded to a sulfur atom which is covalently bonded to an alkynyl group.

[0544] As used herein, "amine" or "amino" refers to unsubstituted or substituted $-NH_2$. "Alkylamino" includes groups of compounds wherein nitrogen of $-NH_2$ is bound to at least one alkyl group. Examples of alkylamino groups include benzylamino, methylamino, ethylamino, phenethylamino, etc. "Dialkylamino" includes groups wherein the nitrogen of $-NH_2$ is bound to at least two additional alkyl groups. Examples of dialkylamino groups include, but are not limited to, dimethylamino and diethylamino. "Arylamino" and "diarylamino" include groups wherein the nitrogen is bound to at least one or two aryl groups, respectively. "Aminoaryl" and "aminoaryloxy" refer to aryl and aryloxy substituted with amino. "Alkylarylamino," "alkylaminoaryl" or "arylaminoalkyl" refers to an amino group which is bound to at least one alkyl group and at least one aryl group. "Alkaminoalkyl" refers to an alkyl, alkenyl, or alkynyl group bound to a nitrogen atom which is also bound to an alkyl group. "Acylamino" includes groups wherein nitrogen is bound to an acyl group. Examples of acylamino include, but are not limited to, alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido groups.

[0545] The term "amide" or "aminocarboxy" includes compounds or moieties that contain a nitrogen atom that is bound to the carbon of a carbonyl or a thiocarbonyl group. The term includes "alkaminocarboxy" groups that include alkyl, alkenyl or alkynyl groups bound to an amino group which is bound to the carbon of a carbonyl or thiocarbonyl group. It also includes "arylaminocarboxy" groups that include aryl or heteroaryl moieties bound to an amino group that is bound to the carbon of a carbonyl or thiocarbonyl group. The terms

"alkylaminocarboxy", "alkenylaminocarboxy", "alkynylaminocarboxy" and "arylaminocarboxy" include moieties wherein alkyl, alkenyl, alkynyl and aryl moieties, respectively, are bound to a nitrogen atom which is in turn bound to the carbon of a carbonyl group. Amides can be substituted with substituents such as straight chain alkyl, branched alkyl, cycloalkyl, aryl, heteroaryl or heterocycle. Substituents on amide groups may be further substituted.

[0546] Compounds of the present invention that contain nitrogens can be converted to N-oxides by treatment with an oxidizing agent (*e.g.*, 3-chloroperoxybenzoic acid (*m*CPBA) and/or hydrogen peroxides) to afford other compounds of the present invention. Thus, all shown and claimed nitrogen-containing compounds are considered, when allowed by valency and structure, to include both the compound as shown and its N-oxide derivative (which can be designated as $N \rightarrow O$ or $N^{+}\text{-}O^{-}$). Furthermore, in other instances, the nitrogens in the compounds of the present invention can be converted to N-hydroxy or N-alkoxy compounds. For example, N-hydroxy compounds can be prepared by oxidation of the parent amine by an oxidizing agent such as *m*-CPBA. All shown and claimed nitrogen-containing compounds are also considered, when allowed by valency and structure, to cover both the compound as shown and its N-hydroxy (*i.e.*, N-OH) and N-alkoxy (*i.e.*, N-OR, wherein R is substituted or unsubstituted C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, 3-14-membered carbocycle or 3-14-membered heterocycle) derivatives.

[0547] In the present specification, the structural formula of the compound represents a certain isomer for convenience in some cases, but the present invention includes all isomers, such as geometrical isomers, optical isomers based on an asymmetrical carbon, stereoisomers, tautomers, and the like, it being understood that not all isomers may have the same level of activity. In addition, a crystal polymorphism may be present for the compounds represented by the formula. It is noted that any crystal form, crystal form mixture, or anhydride or hydrate thereof is included in the scope of the present invention. Furthermore, so-called metabolite which is produced by degradation of the present compound *in vivo* is included in the scope of the present invention.

[0548] "Isomerism" means compounds that have identical molecular formulae but differ in the sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers."

Stereoisomers that are not mirror images of one another are termed "diastereoisomers," and stereoisomers that are non-superimposable mirror images of each other are termed "enantiomers" or sometimes optical isomers. A mixture containing equal amounts of individual enantiomeric forms of opposite chirality is termed a "racemic mixture."

[0549] A carbon atom bonded to four nonidentical substituents is termed a "chiral center."

[0550] "Chiral isomer" means a compound with at least one chiral center. Compounds with more than one chiral center may exist either as an individual diastereomer or as a mixture of diastereomers, termed "diastereomeric mixture." When one chiral center is present, a stereoisomer may be characterized by the absolute configuration (R or S) of that chiral center. Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center. The substituents attached to the chiral center under consideration are ranked in accordance with the *Sequence Rule* of Cahn, Ingold and Prelog. (Cahn *et al.*, *Angew. Chem. Inter. Edit.* 1966, 5, 385; errata 511; Cahn *et al.*, *Angew. Chem.* 1966, 78, 413; Cahn and Ingold, *J. Chem. Soc.* 1951 (London), 612; Cahn *et al.*, *Experientia* 1956, 12, 81; Cahn, *J. Chem. Educ.* 1964, 41, 116).

[0551] "Geometric isomer" means the diastereomers that owe their existence to hindered rotation about double bonds or a cycloalkyl linker (e.g., 1,3-cylcobutyl). These configurations are differentiated in their names by the prefixes cis and trans, or Z and E, which indicate that the groups are on the same or opposite side of the double bond in the molecule according to the Cahn-Ingold-Prelog rules.

[0552] It is to be understood that the compounds of the present invention may be depicted as different chiral isomers or geometric isomers. It should also be understood that when compounds have chiral isomeric or geometric isomeric forms, all isomeric forms are intended to be included in the scope of the present invention, and the naming of the compounds does not exclude any isomeric forms, it being understood that not all isomers may have the same level of activity.

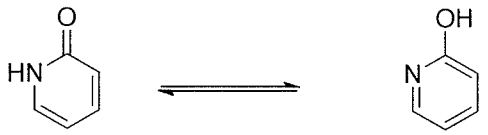
[0553] Furthermore, the structures and other compounds discussed in this invention include all atropic isomers thereof, it being understood that not all atropic isomers may have the same level of activity. "Atropic isomers" are a type of stereoisomer in which the atoms of two isomers are arranged differently in space. Atropic isomers owe their existence to a restricted rotation caused by hindrance of rotation of large groups about a central bond. Such atropic

isomers typically exist as a mixture, however as a result of recent advances in chromatography techniques, it has been possible to separate mixtures of two atropic isomers in select cases.

[0554] "Tautomer" is one of two or more structural isomers that exist in equilibrium and is readily converted from one isomeric form to another. This conversion results in the formal migration of a hydrogen atom accompanied by a switch of adjacent conjugated double bonds. Tautomers exist as a mixture of a tautomeric set in solution. In solutions where tautomerization is possible, a chemical equilibrium of the tautomers will be reached. The exact ratio of the tautomers depends on several factors, including temperature, solvent and pH. The concept of tautomers that are interconvertable by tautomerizations is called tautomerism.

[0555] Of the various types of tautomerism that are possible, two are commonly observed. In keto-enol tautomerism a simultaneous shift of electrons and a hydrogen atom occurs. Ring-chain tautomerism arises as a result of the aldehyde group (-CHO) in a sugar chain molecule reacting with one of the hydroxy groups (-OH) in the same molecule to give it a cyclic (ring-shaped) form as exhibited by glucose.

[0556] Common tautomeric pairs are: ketone-enol, amide-nitrile, lactam-lactim, amide-imidic acid tautomerism in heterocyclic rings (*e.g.*, in nucleobases such as guanine, thymine and cytosine), imine-enamine and enamine-enamine. An example of keto-enol equilibria is between pyridin-2(1H)-ones and the corresponding pyridin-2-ols, as shown below.



pyridin-2(1*H*)-one pyridin-2-ol

[0557] It is to be understood that the compounds of the present invention may be depicted as different tautomers. It should also be understood that when compounds have tautomeric forms, all tautomeric forms are intended to be included in the scope of the present invention, and the naming of the compounds does not exclude any tautomer form. It will be understood that certain tautomers may have a higher level of activity than others.

[0558] The term "crystal polymorphs", "polymorphs" or "crystal forms" means crystal structures in which a compound (or a salt or solvate thereof) can crystallize in different crystal packing arrangements, all of which have the same elemental composition. Different crystal

forms usually have different X-ray diffraction patterns, infrared spectral, melting points, density hardness, crystal shape, optical and electrical properties, stability and solubility. Recrystallization solvent, rate of crystallization, storage temperature, and other factors may cause one crystal form to dominate. Crystal polymorphs of the compounds can be prepared by crystallization under different conditions.

[0559] The compounds of any Formula described herein include the compounds themselves, as well as their salts, their solvates, and their prodrugs, if applicable. A salt, for example, can be formed between an anion and a positively charged group (e.g., amino) on a substituted benzene compound. Suitable anions include chloride, bromide, iodide, sulfate, bisulfate, sulfamate, nitrate, phosphate, citrate, methanesulfonate, trifluoroacetate, glutamate, glucuronate, glutarate, malate, maleate, succinate, fumarate, tartrate, tosylate, salicylate, lactate, naphthalenesulfonate, and acetate (e.g., trifluoroacetate). The term "pharmaceutically acceptable anion" refers to an anion suitable for forming a pharmaceutically acceptable salt. Likewise, a salt can also be formed between a cation and a negatively charged group (e.g., carboxylate) on a substituted benzene compound. Suitable cations include sodium ion, potassium ion, magnesium ion, calcium ion, and an ammonium cation such as tetramethylammonium ion. The substituted benzene compounds also include those salts containing quaternary nitrogen atoms.

[0560] Examples of prodrugs include esters and other pharmaceutically acceptable derivatives, which, upon administration to a subject, are capable of providing active substituted benzene compounds.

[0561] Additionally, the compounds of the present invention, for example, the salts of the compounds, can exist in either hydrated or unhydrated (the anhydrous) form or as solvates with other solvent molecules. Nonlimiting examples of hydrates include monohydrates, dihydrates, etc. Nonlimiting examples of solvates include ethanol solvates, acetone solvates, etc.

[0562] "Solvate" means solvent addition forms that contain either stoichiometric or non stoichiometric amounts of solvent. Some compounds have a tendency to trap a fixed molar ratio of solvent molecules in the crystalline solid state, thus forming a solvate. If the solvent is water the solvate formed is a hydrate; and if the solvent is alcohol, the solvate formed is an alcoholate. Hydrates are formed by the combination of one or more molecules of water with one molecule of the substance in which the water retains its molecular state as H_2O.

[0563] As used herein, the term "analog" refers to a chemical compound that is structurally similar to another but differs slightly in composition (as in the replacement of one atom by an atom of a different element or in the presence of a particular functional group, or the replacement of one functional group by another functional group). Thus, an analog is a compound that is similar or comparable in function and appearance, but not in structure or origin to the reference compound.

[0564] As defined herein, the term "derivative" refers to compounds that have a common core structure, and are substituted with various groups as described herein. For example, all of the compounds represented by Formula (I) are substituted benzene compounds, and have Formula (I) as a common core.

[0565] The term "bioisostere" refers to a compound resulting from the exchange of an atom or of a group of atoms with another, broadly similar, atom or group of atoms. The objective of a bioisosteric replacement is to create a new compound with similar biological properties to the parent compound. The bioisosteric replacement may be physicochemically or topologically based. Examples of carboxylic acid bioisosteres include, but are not limited to, acyl sulfonimides, tetrazoles, sulfonates and phosphonates. See, *e.g.*, Patani and LaVoie, *Chem. Rev.* 96, 3147-3176, 1996.

[0566] The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium, and isotopes of carbon include C-13 and C-14.

2. Synthesis of Substituted Benzene Compounds

[0567] The present invention provides methods for the synthesis of the compounds of any of the Formulae described herein. The present invention also provides detailed methods for the synthesis of various disclosed compounds of the present invention according to the following schemes as shown in the Examples.

[0568] Throughout the description, where compositions are described as having, including, or comprising specific components, it is contemplated that compositions also consist essentially of, or consist of, the recited components. Similarly, where methods or processes are described as having, including, or comprising specific process steps, the processes also consist essentially

of, or consist of, the recited processing steps. Further, it should be understood that the order of steps or order for performing certain actions is immaterial so long as the invention remains operable. Moreover, two or more steps or actions can be conducted simultaneously.

[0569] The synthetic processes of the invention can tolerate a wide variety of functional groups, therefore various substituted starting materials can be used. The processes generally provide the desired final compound at or near the end of the overall process, although it may be desirable in certain instances to further convert the compound to a pharmaceutically acceptable salt, ester, or prodrug thereof.

[0570] Compounds of the present invention can be prepared in a variety of ways using commercially available starting materials, compounds known in the literature, or from readily prepared intermediates, by employing standard synthetic methods and procedures either known to those skilled in the art, or which will be apparent to the skilled artisan in light of the teachings herein. Standard synthetic methods and procedures for the preparation of organic molecules and functional group transformations and manipulations can be obtained from the relevant scientific literature or from standard textbooks in the field. Although not limited to any one or several sources, classic texts such as Smith, M. B., March, J., *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 5th edition, John Wiley & Sons: New York, 2001; Greene, T.W., Wuts, P.G. M., *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons: New York, 1999; R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995), incorporated by reference herein, are useful and recognized reference textbooks of organic synthesis known to those in the art. The following descriptions of synthetic methods are designed to illustrate, but not to limit, general procedures for the preparation of compounds of the present invention.

[0571] Compounds of the present invention can be conveniently prepared by a variety of methods familiar to those skilled in the art. The compounds of this invention with any of the Formulae described herein may be prepared according to the procedures illustrated in Schemes 1-10 below, from commercially available starting materials or starting materials which can be prepared using literature procedures. The Z and R groups (such as R_1, R_2, R_3, R_4, R_6, R_7, R_8,

and R_{12}) in Schemes 1-10 are as defined in any Formula described herein, unless otherwise specified.

[0572] One of ordinary skill in the art will note that, during the reaction sequences and synthetic schemes described herein, the order of certain steps may be changed, such as the introduction and removal of protecting groups.

[0573] One of ordinary skill in the art will recognize that certain groups may require protection from the reaction conditions via the use of protecting groups. Protecting groups may also be used to differentiate similar functional groups in molecules. A list of protecting groups and how to introduce and remove these groups can be found in Greene, T.W., Wuts, P.G. M., *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons: New York, 1999.

[0574] Preferred protecting groups include, but are not limited to:

[0575] For a hydroxyl moiety: TBS, benzyl, THP, Ac

[0576] For carboxylic acids: benzyl ester, methyl ester, ethyl ester, allyl ester

[0577] For amines: Cbz, BOC, DMB

[0578] For diols: Ac (x2) TBS (x2), or when taken together acetonides

[0579] For thiols: Ac

[0580] For benzimidazoles: SEM, benzyl, PMB, DMB

[0581] For aldehydes: di-alkyl acetals such as dimethoxy acetal or diethyl acetyl.

[0582] In the reaction schemes described herein, multiple stereoisomers may be produced. When no particular stereoisomer is indicated, it is understood to mean all possible stereoisomers that could be produced from the reaction. A person of ordinary skill in the art will recognize that the reactions can be optimized to give one isomer preferentially, or new schemes may be devised to produce a single isomer. If mixtures are produced, techniques such as preparative thin layer chromatography, preparative HPLC, preparative chiral HPLC, or preparative SFC may be used to separate the isomers.

[0583] The following abbreviations are used throughout the specification and are defined below:

[0584]	AA	ammonium acetate
[0585]	ACN	acetonitrile
[0586]	Ac	acetyl
[0587]	AcOH	acetic acid

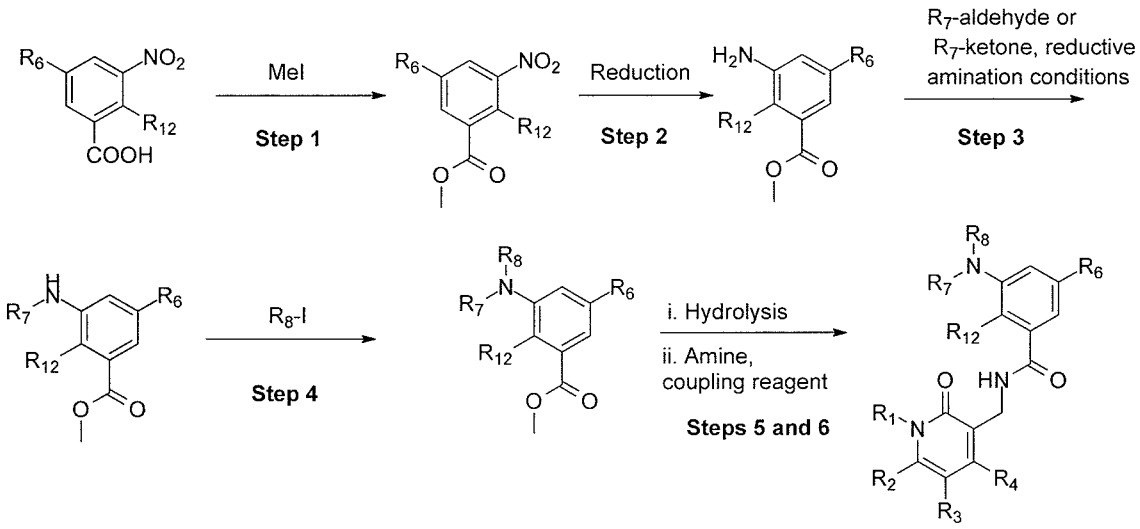
[0588]	atm	atmosphere
[0589]	aq.	Aqueous
[0590]	BID or b.i.d.	bis in die (twice a day)
[0591]	tBuOK	potassium t-butoxide
[0592]	Bn	benzyl
[0593]	BOC	tert-butoxy carbonyl
[0594]	BOP	(benzotriazol-1-yloxy)tris(dimethylamino)-phosphoniumhexafluorophosphate
[0595]	Cbz	benzyloxy carbonyl
[0596]	$CDCl_3$	deuterated chloroform
[0597]	CH_2Cl_2	dichloromethane
[0598]	COMU	(1-Cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethyl-amino-morpholino-carbenium hexafluorophosphate
[0599]	d	days
[0600]	DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
[0601]	DCE	1,2 dichloroethane
[0602]	DCM	dichloromethane
[0603]	DEAD	Diethyl azodicarboxylate
[0604]	DIAD	Diisopropyl azodicarboxylate
[0605]	DiBAL-H	diisobutyl aluminium hydride
[0606]	DIPEA	N,N-diisopropylethylamine (Hunig's base)
[0607]	DMA	Dimethylacetamide
[0608]	DMAP	N, N dimethyl-4-aminopyridine
[0609]	DMB	2,4 dimethoxy benzyl
[0610]	DMF	N,N-Dimethylformamide
[0611]	DMSO	Dimethyl sulfoxide
[0612]	DPPA	Diphenylphosphonic azide
[0613]	EA or EtOAc	Ethyl acetate
[0614]	EDC or EDCI	N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide
[0615]	Et_2O	diethyl ether
[0616]	ELS	Evaporative Light Scattering

[0617]	ESI-	Electrospray negative mode
[0618]	ESI+	Electrospray positive mode
[0619]	Et_3N or TEA	triethylamine
[0620]	EtOH	ethanol
[0621]	FA	formic acid
[0622]	FC or FCC	Flash chromatogrpahy
[0623]	h	hours
[0624]	H_2O	water
[0625]	HATU	O-(7-Azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate
[0626]	HOAT	1-Hydroxy-7-azabenzotriazole
[0627]	HOBt	1-Hydroxybenzotriazole
[0628]	HO-Su	N-Hydroxysuccinimide
[0629]	HCl	hydrogen chloride or hydrochloric acid
[0630]	HPLC	High performance liquid chromatography
[0631]	K_2CO_3	potassium carbonate
[0632]	KHMDs	Potassium hexamethyldisilazide
[0633]	LC/MS or LC-MS	Liquid chromatography mass spectrum
[0634]	LDA	Lithium diisopropylamide
[0635]	LiHMDs	Lithium hexamethyldisilazide
[0636]	LG	leaving group
[0637]	M	Molar
[0638]	m/z	mass/charge ratio
[0639]	m-CPBA	meta-chloroperbenzoic acid
[0640]	MeCN	Acetonitrile
[0641]	MeOD	d4-methanol
[0642]	MeI	Methyl iodide
[0643]	MS3Å	3Å molecular sieves
[0644]	$MgSO_4$	Magnesium Sulfate
[0645]	min	minutes
[0646]	Ms	Mesyl

[0647]	MsCl	Mesyl chloride
[0648]	MsO	Mesylate
[0649]	MS	Mass Spectrum
[0650]	MWI	microwave irradiation
[0651]	Na_2CO_3	sodium carbonate
[0652]	Na_2SO_4	sodium sulfate
[0653]	$NaHCO_3$	sodium bicarbonate
[0654]	NaHMDs	Sodium hexamethyldisilazide
[0655]	NaOH	sodium hydroxide
[0656]	$NaHCO_3$	sodium bicarbonate
[0657]	Na_2SO_4	sodium sulfate
[0658]	NIS	N-iodosuccinimide
[0659]	NMR	Nuclear Magnetic Resonance
[0660]	o/n or O/N	overnight
[0661]	Pd/C	Palladium on carbon
[0662]	Pd(dppf)Cl_2.DCM	[1,1'-Bis(diphenylphosphino)ferrocene] dichloropalladium(II),complex with dichloromethane
[0663]	PPAA	1-Propanephosphonic acid cyclic anhydride
[0664]	$Pd(OH)_2$	Palladium dihydroxide
[0665]	PE	Petroleum Ether
[0666]	PG	protecting group
[0667]	PMB	para methoxybenzyl
[0668]	ppm	parts per million
[0669]	p.o.	per os (oral adinsitration)
[0670]	prep HPLC	preparative High Performance Liquid Chromatography
[0671]	prep TLC	preparative thin layer chromatography
[0672]	p-TsOH	para-toluenesulfonic acid
[0673]	PyBOP	(Benzotriazol-1-yloxy)tripyrrolidinophosphonium Hexafluorophosphate
[0674]	QD or q.d.	quaque die (once a day)
[0675]	RBF	round bottom flask

[0676]	RP-HPLC	Reverse phase High Perfomance liquid chromatography
[0677]	Rt or RT	Room temperature
[0678]	SEM	(Trimethylsilyl)ethoxymethyl
[0679]	SEMCl	(Trimethylsilyl)ethoxymethyl chloride
[0680]	SFC	Super critical chromatography
[0681]	SGC	silica gel chromatography
[0682]	STAB	Sodium triacetoxy borohydride
[0683]	TBAF	tetra-n-butylammonium fluoride
[0684]	TBME	*tert*-Butyl methyl ether
[0685]	TEA	Triethylamine
[0686]	TFA	trifluoroacetic acid
[0687]	TfO	triflate
[0688]	THF	tetrahydrofuran
[0689]	THP	tetrahydropyran
[0690]	TID or t.i.d	ter in die (three times a day)
[0691]	TLC	thin layer chromatography
[0692]	TMSCl	Trimethylsilyl chloride
[0693]	Ts	tosyl
[0694]	TsOH	tosic acid
[0695]	UV	ultraviolet

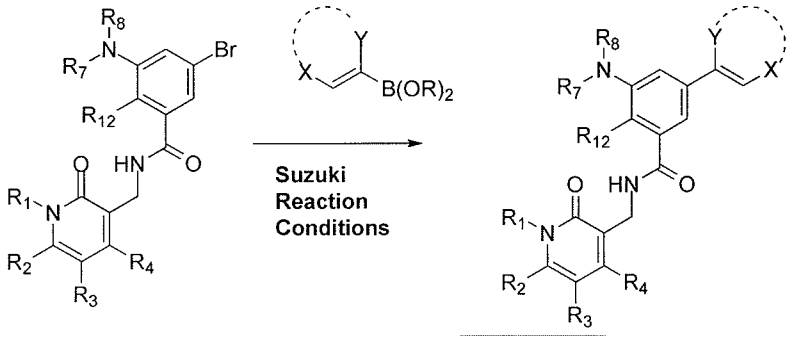
Scheme 1



[0696] Scheme 1 shows the synthesis of benzene analogs wherein Z = -N(R_7)(R_8) following a general route that utilizes well-established chemistry. Substituted nitrobenzoic acids, many of which are commercially available or can be prepared by nitrations of the appropriate substituted benzoic acids or other chemistry known to one skilled in the art, can be converted to their methyl esters by treatment with methyliodide in a polar solvent such as DMF in the presence of an appropriate base such as sodium carbonate at an appropriate temperature such as 60 °C (Step 1). The nitro group can be reduced to an amine using an appropriate reducing agent such as iron in the presence of an acid such as ammonium chloride in a protic solvent such as ethanol at an appropriate temperature such as 80 °C (Step 2). Introduction of the R_7 can be done using a reductive amination with an appropriate R_7-ketone or R_7-aldehyde in the presence of an appropriate reducing agent such as sodium cyanoborohydride and catalytic acid such as acetic acid in an appropriate solvent such as methanol. A variety of R_8 groups can be introduced by alkylation using R_8-LG, where LG is a leaving group such as iodine, in the presence of a mild base such as cesium carbonate in an appropriate polar solvent such as acetonitrile at an appropriate temperature such as 80 °C (Step 4). Alternatively, R_8 groups can be introduced by reductive amination with R_8-ketone or R_8-aldehyde in the presence of an appropriate reducing agent such as sodium cyanoborohydride and catalytic acid such as acetic acid in an appropriate solvent such as methanol. The ester moiety can be converted to an amide using a standard two step protocol. The ester can be hydrolyzed to the corresponding acid using a suitable base such as sodium hydroxide in a polar solvent such as ethanol (Step 5). The acid would then be subjecting to a standard amide coupling reaction whereupon the appropriate

amine would be added along with a suitable amide coupling reagent such as PYBOP in a suitable solvent such as DMSO to give the desired amide (Step 6).

Scheme 2



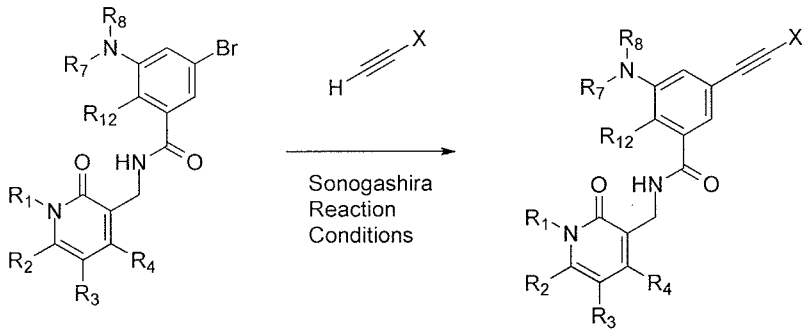
[0697] Depending upon the nature of the R_6 substituent, further chemical modification could be employed to convert the R_6 substituent into an alternative R_6 substituent. A representative sampling of such modifications could include hydrogenation, protecting group removal followed by additional amide coupling reactions, palladium catalyzed coupling reactions, reductive amination reactions or alkylation reactions. For example, if R_6 is a bromide, alternative R_6 substituents could then be introduced using standard transition metal-based protocols that rely upon a leaving group such as a bromide as a connection point.

[0698] In one such protocol as depicted in Scheme 2 non-aromatic R_6 substituents attached via a carbon-carbon bond may be introduced by Suzuki reaction of a compound where R_6 = Br with an appropriate unsaturated non-aromatic boronic ester derivative (e.g. an olefinic boronic ester derivative such as vinyl 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane) in the presence of a mild base and a palladium catalyst in a polar solvent such as dioxane/water, at elevated temperature to give the desired new R_6 substituent. Depending upon the nature of the R_6 substituent, further chemical modification could be employed to convert the unsaturated R_6 substituent into an alternative R_6 substituent. A representative sampling of such modifications could include hydrogenation, protecting group removal followed by additional amide coupling reactions, palladium catalyzed coupling reactions, reductive amination reactions or alkylation reactions. For example, in cases where an unsaturated non-aromatic R_6 group is introduced, further modification by hydrogenation can give the corresponding saturated R_6 group (e.g. conversion of a vinyl group to an ethyl group). In cases of where R_6 groups introduced have

protected amine functionality further modifications include deprotection to give amines which may in subsequent steps be further modified for example by amide formation or reductive amination reactions.

[0699] In another protocol as depicted in Scheme 3, non-aromatic R_6 substituents attached via a carbon-carbon bond may be introduced by Sonogashira reaction of a compound where R_6 = Br optionally followed by further modification of the introduced alkynyl group. In the Sonogashira reaction, a compound where R_6 = Br is coupled with a terminal alkyne derivative in the presence of a mild base, a copper catalyst and a palladium catalyst in an organic solvent such as toluene at elevated temperature. This results in the replacement of the Br group with an alkynyl group. The resulting compound wherein the R_6 substituent is an alkynyl group may be subject to subsequent suitable modifications to give an alternative R_6 substituent. A representative sampling of such modifications could include hydrogenation, protecting group removal followed by additional amide coupling reactions, reductive amination reactions or alkylation reactions.

Scheme 3

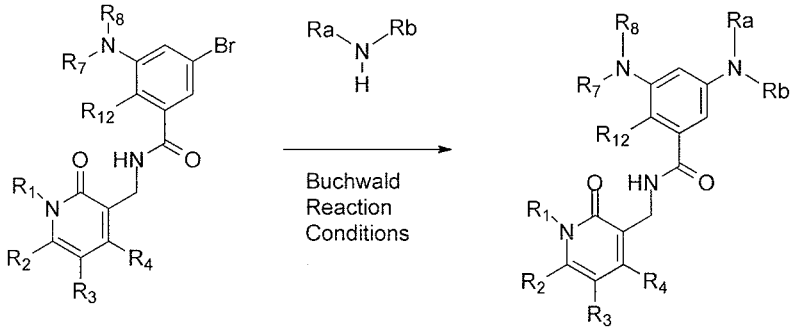


[0700] In another protocol non-aromatic R_6 substituents attached via a carbon-carbon bond may be prepared by other substitution reactions of the bromine atom compounds where R_6 = Br, optionally followed by further modification of the introduced R_6 group. Examples of such substitution reactions include coupling reactions with zinc reagents such as cyanation and Negishi reactions. In the case of cyanation reaction, compounds where R_6 = Br may be reacted with zinc cyanide under standard palladium catalyst mediated reaction conditions to give compounds where R_6 = CN. The cyano group in such compounds may be subject to further modification to give other R_6 groups. Such cyano modifications include i. reduction to an

amine which may be subsequently converted to an amide by acylation or alkylation, ii. reduction to an aldehyde which may be subjected to reductive amination reaction to give corresponding derivatives. In Negishi reactions alkylzinc reagents which may be prepared from alkyl iodides (e.g. *N*-Boc-3-iodoazetidine) are coupled to compounds where R_6 = Br using palladium or nickel catalysts. In the resulting products the introduced R_6 group may be converted to an alternative group by further modifications of the R_6 group in subsequent steps such as deprotection, amide formation or alkylation.

[0701] Compounds with R_6 substituents which are amines attached via a nitrogen-carbon bond may be introduced by Buchwald coupling reaction of compounds where R_6 = Br followed by optional modification of the R_6 group as depicted in Scheme 4. In the Buchwald reaction compounds where R_6 = Br are treated with a primary or secondary amine (e.g. tert-butyl piperazine-1-carboxylate) in the presence of a palladium catalyst (e.g. Pd(dba)2/BINAP) and a base (e.g. cesium carbonate) in an organic solvent (e.g. toluene) at elevated temperature. The Buchwald coupling product may be subjected to subsequent suitable modifications to give an alternative R_6 substituent. Such modifications are exemplified by protecting group removal, amide coupling reactions, reductive amination reactions or alkylation reactions.

Scheme 4

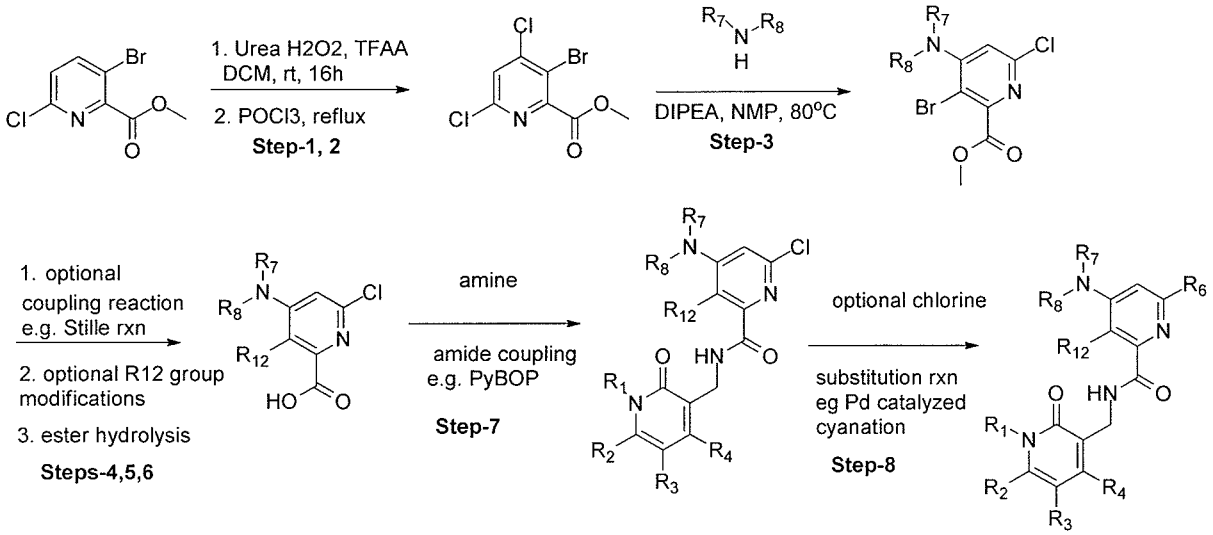


[0702] Compounds with R_6 substituents which are alkylthio groups attached via a sulfur-carbon bond may be prepared by coupling reaction of compounds where R_6 = Br with thiols in the presence of a palladium catalyst and a weak base (e.g.DIPEA) in an organic solvent at elevated temperature. The coupling product sulfides may be subject to subsequent suitable modifications to give an alternative R_6 substituent. Such modifications include sulfur oxidation reactions to give sulfoxides and sulfones, protecting group removal, amide coupling reactions, reductive amination reactions or alkylation reactions.

[0703] In a modification of the general synthesis in Scheme 1, depending upon the nature of the R_7 substituent, further chemical modification subsequent to Step 6 of Scheme 1 could be employed to convert the R_7 substituent into an alternative R_7 substituent. For example a protected amino group contained within R_7 may be subjected to deprotection reaction (e.g. Boc group cleavage) to give free amino groups. Such free amino groups may be subjected to reductive amination reactions or alkylation reactions to give substituted amines.

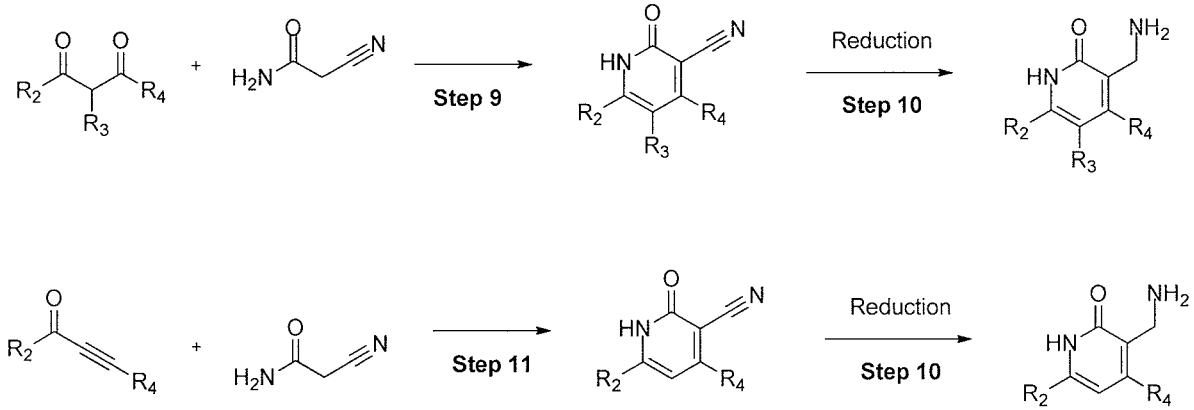
[0704] Scheme 5 shows the general synthesis of picolinamide compounds. Starting from methyl 3-bromo-6-chloropicolinate oxidation to the N-oxide followed by chlorination with phosphorus oxychloride gives methyl 3-bromo-4,6-dichloropicolinate. The 4-chloro group can be selectively substituted with diverse mono and dialkyl amines which may also contain functional or protected functional groups that may be unmasked at a later stage. The 3-bromo group may be retained or may be optionally converted into an alternative R_{12} group by suitable substitution reaction and further functional group modifications. Such reactions include coupling reactions mediated with palladium catalysts. For example the 3-bromo group may be converted to an R_{12} = methyl group by Stille reaction with tetramethyltin. Ester hydrolysis followed by amide coupling with appropriate 3-(aminomethyl)-pyridin-2-ones yields picolinamide compounds wherein R_6 is a chloro group. The chloro group may optionally be converted to alternative R_6 groups by suitable substitution reactions either in a final step or alternatively prior to ester hydrolysis Step 6. Examples of such substitution reactions include cyanation and amination reactions either directly or mediated with palladium catalysts. Analogous compounds wherein R_{12} is chloro may be prepared in analogous fashion from methyl 3,4, 6-trichloropyridine-2-carboxylate.

Scheme 5



[0705] General syntheses of 3-(aminomethyl)-pyridin-2(1H)-ones intermediates for the amide coupling reaction from Scheme 1 are depicted in Scheme 6. In one method, a diketone can be condensed with 2-cyanoacetamide in the presence of an appropriate reagent such as piperidine acetate in a polar solvent such as ethanol to provide a cyanopyridone (Step 9). In another method, when R_3 is H, an appropriately substituted alkynyl ketone can be condensed with 2-cyanoacetamide in the presence of an appropriate reagent such as piperidine acetate in a polar solvent such as ethanol to provide a cyanopyridone (Step 11). The cyano group can be reduced under appropriate conditions such as hydrogenation in the presence of catalytic Raney nickel in a polar solvent such as ammonium in methanol to provide the amine (Step 10).

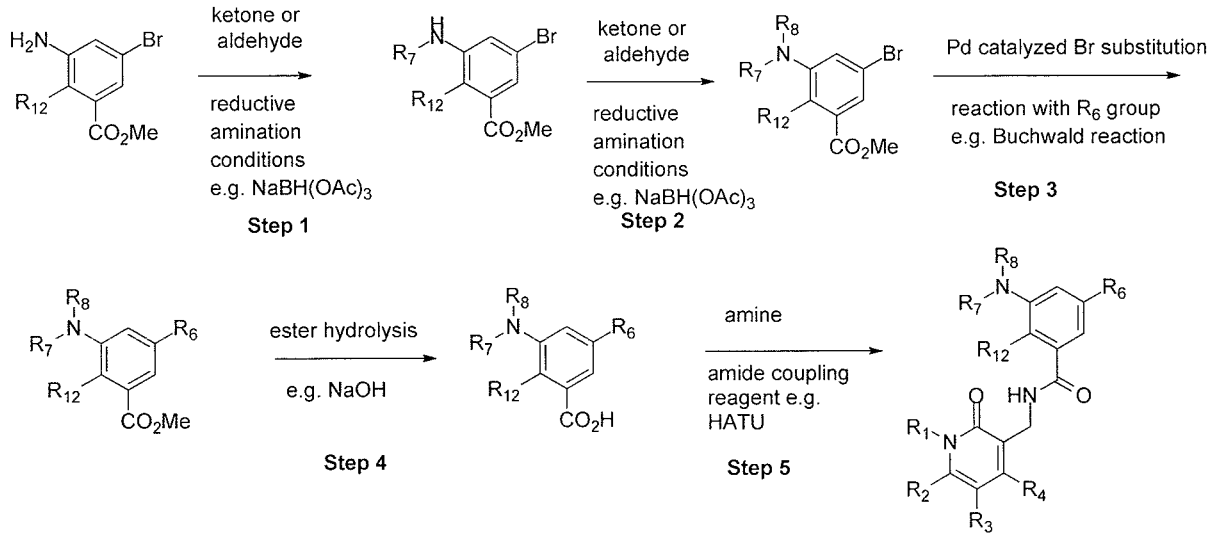
Scheme 6



[0706] Additionally, depending upon the nature of the R_2, R_3, or R_4 group, further chemical modification can be employed to convert each of them independently into an alternative substituent. A representative sampling of such modifications can include hydrogenation, protecting group removal followed by additional amide coupling reactions, palladium catalyzed coupling reactions, reductive amination reactions, and alkylation reactions.

[0707] Scheme 7 depicts a variant of the general synthesis route of Scheme 1 based on 2-substituted (substituent is an R_{12} group) methyl 3-amino-5-bromo-benzoate starting materials. These starting materials can in turn be prepared from 2-substituted 3-nitro-benzoic acids which are commercially available or can be prepared by nitration of 2-substituted benzoic acids. Thus, bromination of 2-substituted 3-nitro-benzoic acids with a suitable reagent such as 1,3-dibromo-5,5-dimethyl-2,4-imidazolidinedione yields the appropriate 2-substituted 3-nitro-5-bromo-benzoic acids. A variety of esterification and then nitro group reduction methods can then be sequentially implemented to prepare the 2-substituted methyl 3-amino-5-bromo-benzoate starting materials from the 2-substituted 3-nitro-5-bromo-benzoic acids.

Scheme 7

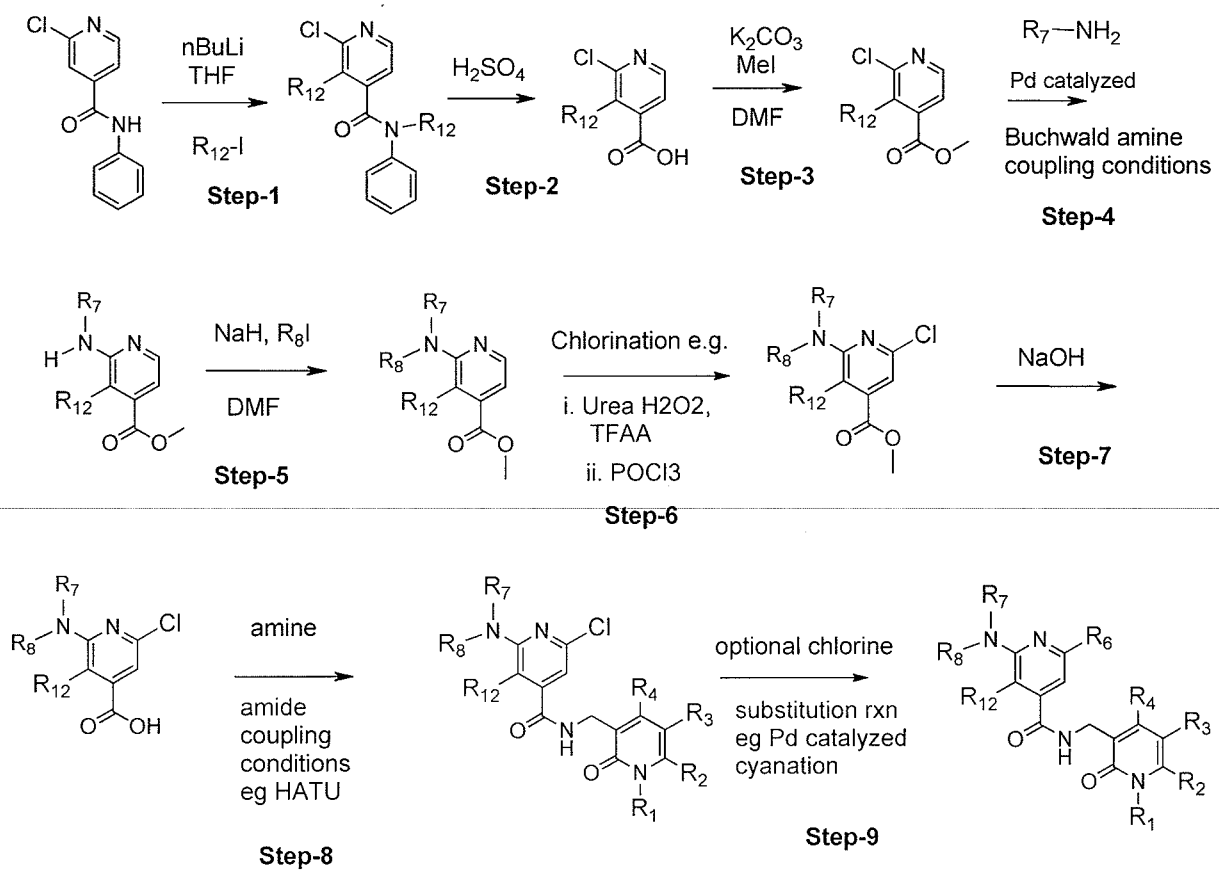


[0708] As depicted in Scheme 7 the R_7 group can be introduced from 2-substituted methyl 3-amino-5-bromo-benzoates in Step 1 using a reductive amination with an appropriate R_7-ketone or R_7-aldehyde in the presence of an appropriate reducing agent such as sodium cyanoborohydride and catalytic acid such as acetic acid in an appropriate solvent such as

methanol. Similarly, R_8 groups can be introduced in Step 2 by reductive amination with R_8-ketone or R_8-aldehyde in the presence of an appropriate reducing agent such as sodium cyanoborohydride and catalytic acid such as acetic acid in an appropriate solvent such as methanol. Alternatively, a variety of R_8 groups can be introduced by alkylation using R_8-LG, where LG is a leaving group such as iodine, in the presence of a mild base such as cesium carbonate in an appropriate polar solvent such as acetonitrile at an appropriate temperature such as 80 °C. In Step 3, R_6 groups other than bromine can be introduced via palladium catalyzed coupling reactions. Examples of such R_6 groups and methods have been described above. For example amines may be introduced by Buchwald reactions and unsaturated groups may be introduced by Suzuki or Sonogashiri reactions. The R_6 substituent may be subject to subsequent suitable modifications to give an alternative R_6 substituent. A representative sampling of such modifications could include hydrogenation (e.g. to saturate unsaturated groups), protecting group removal followed by additional amide coupling reactions, reductive amination reactions or alkylation reactions. In Step 4 the ester moiety can be hydrolyzed to the corresponding acid using a suitable base such as sodium hydroxide in a polar solvent such as ethanol. In Step 5, the acid can be subjected to a standard amide coupling reaction whereupon the appropriate 3-(aminomethyl)-pyridin-2-one would be added along with a suitable amide coupling reagent such as PYBOP in a suitable solvent such as DMSO to give the desired amide. Depending upon the nature of the R_7 substituent, further chemical modification subsequent to Step 5 of Scheme 4 could be employed to convert the R_7 substituent into an alternative R_7 substituent. For example a protected amino group contained within R_7 may be subjected to deprotection reaction (e.g. Boc group cleavage) to give free amino groups. Such free amino groups may be subjected to reductive amination reactions or alkylation reactions to give substituted amines.

[0709] Scheme 8 below depicts the general synthesis of 2-monoalkylamino and 2-dialkylamino-3,6-disubstituted-isonicotinamides wherein the 3-substituent corresponds to R_{12} and the 6-substituent corresponds to R_6. In Step 1 the 3-substituent may be introduced by the method described by Epsztain J. et al. *Tetrahedron*, **1991**, v. 47, 1697-16708, by metalation of 2-chloro-isonicotinanilide with n-butyllithium followed by trapping with an alkyliodide such as methyliodide or aldehyde or other electrophilic group.

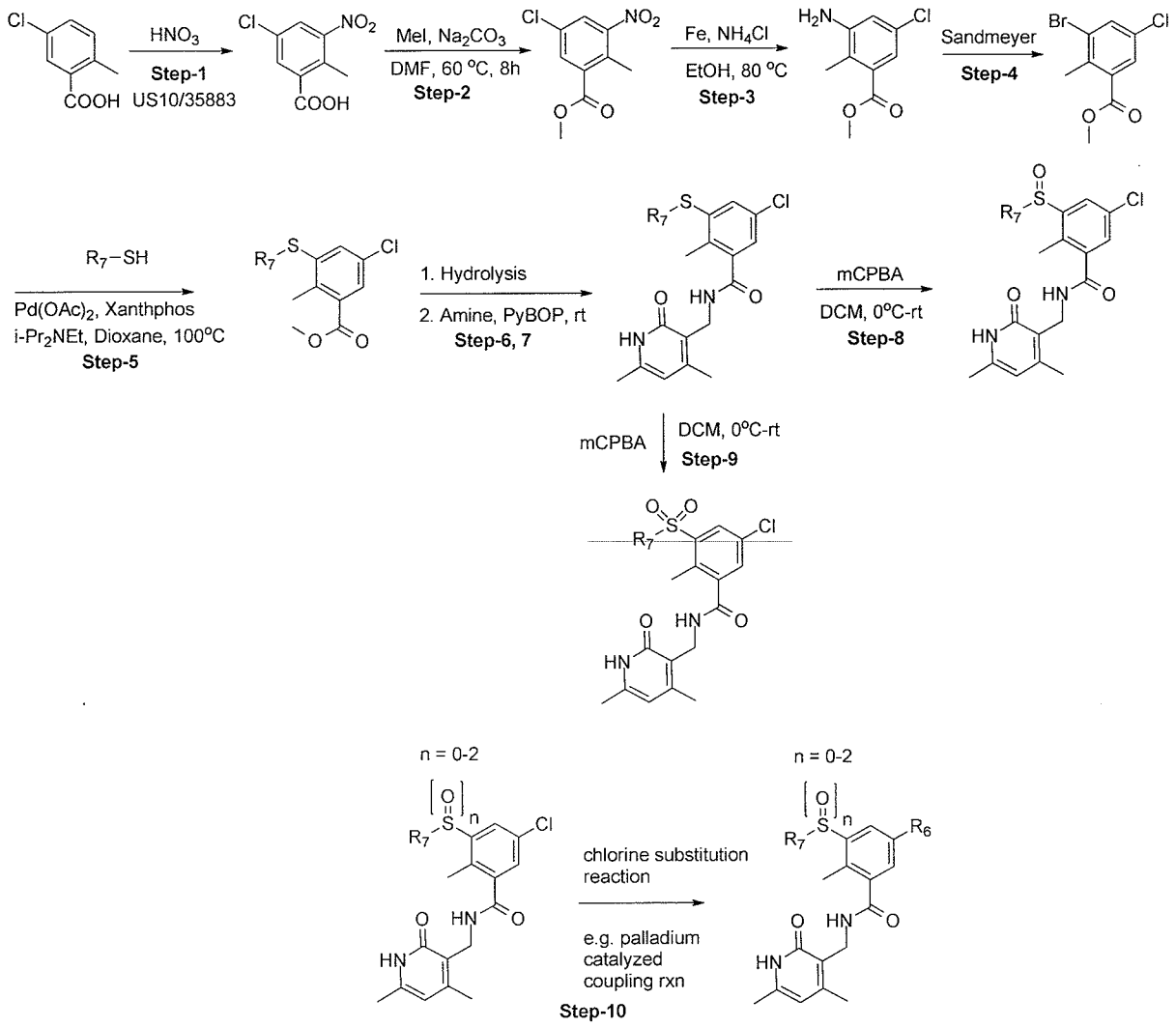
Scheme 8



[0710] In cases where the trapping reagent yields a substituent with a functional group this group may be masked or converted into another functional group compatible with the subsequent chemical steps. In Step 2 anilide amide hydrolysis under standard acidic conditions may be conducted followed by methyl ester synthesis under standard conditions for example as shown with methyl iodide and base gives corresponding methyl 2-chloro-3-substituted isonicotinates. In Step 4 an alkylamino group can be introduced by Buchwald coupling reaction of an R_7NH_2 monoalkylamine with the methyl 2-chloro-3-substituted isonicotinates. This reaction is well precedented for diverse 2-chloropyridine systems in the chemical literature. In an optional Step 5 for dialkylamino compounds R_8 groups can be introduced by reductive amination with R_8-ketone or R_8-aldehyde in the presence of an appropriate reducing agent such as sodium cyanoborohydride and catalytic acid such as acetic acid in an appropriate solvent such as methanol. Alternatively, a variety of R_8 groups can be introduced by alkylation using R_8-LG, where LG is a leaving group such as iodine, in the presence of a mild base such

as cesium carbonate in an appropriate polar solvent such as acetonitrile at an appropriate temperature such as 80 °C. In Step 6, oxidation to the N-oxide followed by chlorination with phosphorus oxychloride gives methyl 6-chloro-2-mono or dialkylamino-3-substituted isonicotinates. In Step 7 the ester moiety can be hydrolyzed to the corresponding acid using a suitable base such as sodium hydroxide in a polar solvent such as ethanol. In Step 8, the acid can be subjected to a standard amide coupling reaction whereupon the appropriate substituted 3-(aminomethyl)-pyridin-2-one would be added along with a suitable amide coupling reagent such as PYBOP in a suitable solvent such as DMSO to give the desired amide. In Step 9, the chloro group may optionally be converted to alternative R_6 groups by suitable substitution reactions either in a final step or alternatively prior to ester hydrolysis Step 6. Examples of such substitution reactions include cyanation and amination reactions either directly or mediated with palladium catalysts. The R_6 substituent may be subject to subsequent suitable modifications to give an alternative R_6 substituent. A representative sampling of such modifications could include hydrogenation (e.g. to saturate unsaturated groups), protecting group removal followed by additional amide coupling reactions, reductive amination reactions or alkylation reactions. Depending upon the nature of the R_7 substituent, further chemical modification steps may be employed to convert the R_7 substituent into an alternative R_7 substituent. For example a protected amino group contained within R_7 may be subjected to deprotection reaction (e.g. Boc group cleavage) to give free amino groups. Such free amino groups may be subjected to reductive amination reactions or alkylation reactions to give substituted amines.

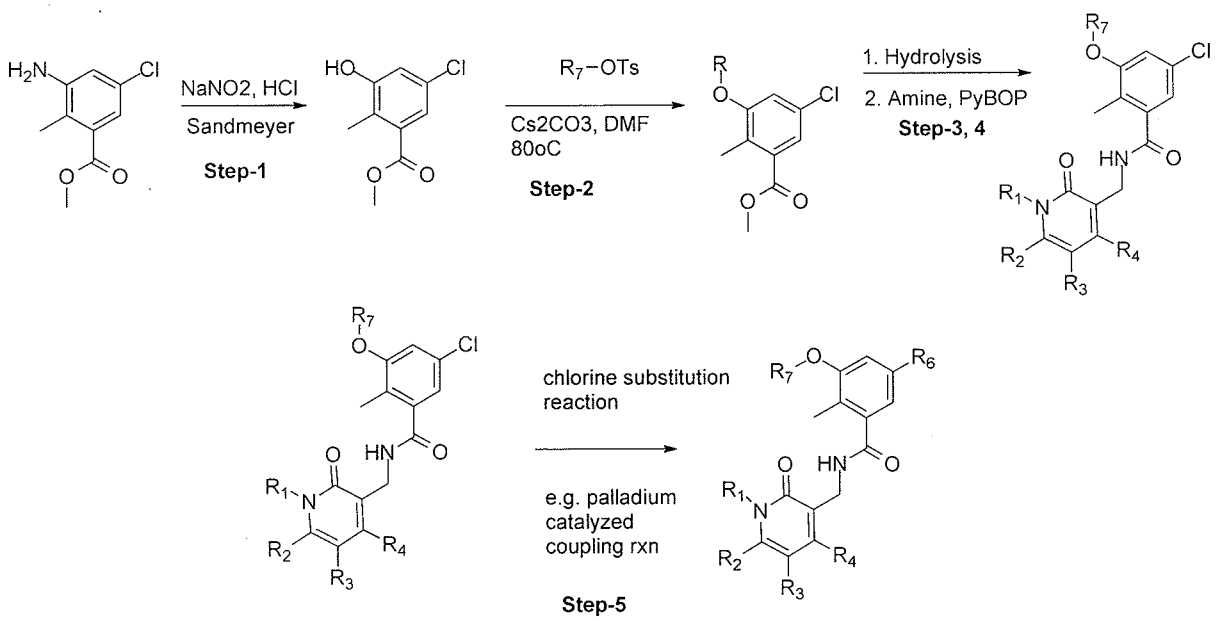
Scheme 9



[0711] Scheme 9 depicts a synthesis of benzene analogs wherein Z is a sulfide, sulfoxide or sulfone group following a general route that utilizes well-established chemistry. Starting with a substituted benzoic acid such as 5-chloro-2-methylbenzoic acid, nitration using standard conditions such as treatment with conc. H_2SO_4 and conc. HNO_3 can provide the nitro analog. Esterification of the acid can be achieved using an alkylating agent such as methyl iodide in the presence of a base such as sodium carbonate in a polar solvent such as DMF. The nitro group can be reduced using conditions such iron and ammonium chloride in a protic solvent such as ethanol with heating to a temperature such as 80 °C. The resulting aniline can be converted to a bromide using a Sandmeyer reaction such treatment with $CuBr_2$ and t-butyl nitrite in a solvent such as acetonitrile. A palladium catalyzed coupling of a thiol with the bromide can be achieved using a palladium source such as $Pd(OAc)_2$ with a ligand such as Xanthphos in the

presence of a base such as N,N-diisopropyl ethylamine in a solvent such as 1,4-dioxane optionally heating to a temperature such as 100 °C. The ester can be hydrolyzed with an aqueous base such as NaOH in water. The resulting acid can be coupled to the appropriate substituted 3-(aminomethyl)-pyridin-2-one (e.g. 3-(amino methyl)-4, 6-dimethylpyridin-2(1H)-one as depicted in Scheme 9) using standard amino acid coupling conditions such as PyBOP in DMSO. The resulting thioether may be oxidized to the corresponding sulfoxide or sulfone by using the appropriate equivalents of an oxidant such as m-CPBA in a solvent such as DCM. The R_6 chloro group may be replaced with an alternative R_6 group in an additional Step 10 or after Step 5 or prior to amide coupling. Examples of alternative R_6 groups include substituents that can be incorporated by using palladium couplings such as a Buchwald reaction to give amine groups (e.g. morpholino). The R_6 substituent may be subject to subsequent suitable modifications to give an alternative R_6 substituent. A representative sampling of such modifications includes protecting group removal followed by additional amide coupling reactions, reductive amination reactions or alkylation reactions.

Scheme 10



[0712] Scheme 10 depicts a synthesis of modified benzene analogs wherein Z is an ether group following a general route that utilizes well-established chemistry. Starting with a substituted aniline such as methyl 3-amino-5-chloro-2-methylbenzoate, the aniline can be

converted to a phenol using a Sandmeyer reaction such as treatment with aqueous $NaNO_2$ solution in a aqueous acid such as 50% H_2SO_4. The phenol can be alkylated using an alkylating agent such as tetrahydro-2H-pyran-4-yl 4-methylbenzenesulfonate in the presence of an appropriate base such as cesium carbonate in as polar solvent such as DMF optionally heating to a temperature such as 80 °C. The ester can be hydrolyzed with an aqueous base such as NaOH in water. The resulting acid can be coupled to the appropriate substituted 3-(aminomethyl)-pyridin-2-one using standard amino acid coupling conditions such as PyBOP in DMSO. The R_6 chloro group may be replaced with an alternative R_6 group in an additional after Step 5 or prior to amide coupling. Examples of alternative R_6 groups include substituents that can be incorporated by using palladium couplings such as a Buchwald reaction to give amine groups (e.g. morpholino). The R_6 substituent may be subject to subsequent suitable modifications to give an alternative R_6 substituent. A representative sampling of such modifications includes protecting group removal followed by additional amide coupling reactions, reductive amination reactions or alkylation.

[0713] A person of ordinary skill in the art will recognize that in the above schemes the order of many of the steps are interchangeable.

3. Methods of Treatment

[0714] Compounds of the present invention inhibit the histone methyltransferase activity of EZH2 or a mutant thereof and, accordingly, the present invention also provides methods for treating conditions and diseases the course of which can be influenced by modulating the methylation status of histones or other proteins, wherein said methylation status is mediated at least in part by the activity of EZH2. In one aspect of the invention, certain compounds disclosed herein are candidates for treating, or preventing certain conditions and diseases. Modulation of the methylation status of histones can in turn influence the level of expression of target genes activated by methylation, and/or target genes suppressed by methylation. The method includes administering to a subject in need of such treatment, a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph, solvate, or stereoisomeror thereof.

[0715] The disorder in which EZH2-mediated protein methylation plays a part can be cancer or a precancerous condition. The present invention further provides the use of a compound of the

present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof in the treatment of cancer or pre-cancer the course of which can be influenced by modulating EZH2-mediated protein methylation, or, for the preparation of a medicament useful for the treatment of such cancer or pre-cancer. Exemplary cancers that may be treated include lymphomas, including non-Hodgkin lymphoma, follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL); melanoma; and leukemia, including CML. Exemplary precancerous condition includes myelodysplastic syndrome (MDS; formerly known as preleukemia).

[0716] The present invention also provides methods of protecting against a disorder in which EZH2-mediated protein methylation plays a part in a subject in need thereof by administering a therapeutically effective amount of compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, to a subject in need of such treatment. The disorder can be cancer, e.g., cancer in which EZH2-mediated protein methylation plays a role. The present invention also provides the use of compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph, solvate, or stereoisomeror thereof, for the preparation of a medicament useful for the prevention of a cell proliferative disorder associated, at least in part, with EZH2-mediated protein methylation.

[0717] The compounds of this invention can or may be used to modulate protein (e.g., histone) methylation, e.g., to modulate histone methyltransferase or histone demethylase enzyme activity. At least some of the compounds of the invention can be used *in vivo* or *in vitro* for modulating protein methylation. Histone methylation has been reported to be involved in aberrant expression of certain genes in cancers, and in silencing of neuronal genes in non-neuronal cells. At least some compounds described herein are suitable candidates for treating these diseases, i.e., to decrease methylation or restore methylation to roughly its level in counterpart normal cells.

[0718] Compounds that are methylation modulators can or may be used for modulating cell proliferation. For example, in some cases excessive proliferation may be reduced with agents that decrease methylation, whereas insufficient proliferation may be stimulated with agents that increase methylation. Accordingly, diseases that may be treated by the compounds of the

invention could include hyperproliferative diseases, such as benign cell growth and malignant cell growth.

[0719] As used herein, a "subject in need thereof" is a subject having a disorder in which EZH2-mediated protein methylation plays a part, or a subject having an increased risk of developing such disorder relative to the population at large. A subject in need thereof can have a precancerous condition. Preferably, a subject in need thereof has cancer. A "subject" includes a mammal. The mammal can be *e.g.*, a human or appropriate non-human mammal, such as primate, mouse, rat, dog, cat, cow, horse, goat, camel, sheep or a pig. The subject can also be a bird or fowl. In one embodiment, the mammal is a human.

[0720] As used herein, the term "cell proliferative disorder" refers to conditions in which unregulated or abnormal growth, or both, of cells can lead to the development of an unwanted condition or disease, which may or may not be cancerous. Exemplary cell proliferative disorders that may be treated with the compounds of the invention encompass a variety of conditions wherein cell division is deregulated. Exemplary cell proliferative disorder include, but are not limited to, neoplasms, benign tumors, malignant tumors, pre-cancerous conditions, *in situ* tumors, encapsulated tumors, metastatic tumors, liquid tumors, solid tumors, immunological tumors, hematological tumors, cancers, carcinomas, leukemias, lymphomas, sarcomas, and rapidly dividing cells. The term "rapidly dividing cell" as used herein is defined as any cell that divides at a rate that exceeds or is greater than what is expected or observed among neighboring or juxtaposed cells within the same tissue. A cell proliferative disorder includes a precancer or a precancerous condition. A cell proliferative disorder includes cancer. The methods and uses provided herein can be or may be used to treat or alleviate a symptom of cancer or to identify suitable candidates for such purposes. The term "cancer" includes solid tumors, as well as, hematologic tumors and/or malignancies. A "precancer cell" or "precancerous cell" is a cell manifesting a cell proliferative disorder that is a precancer or a precancerous condition. A "cancer cell" or "cancerous cell" is a cell manifesting a cell proliferative disorder that is a cancer. Any reproducible means of measurement may be used to identify cancer cells or precancerous cells. Cancer cells or precancerous cells can be identified by histological typing or grading of a tissue sample (*e.g.*, a biopsy sample). Cancer cells or precancerous cells can be identified through the use of appropriate molecular markers.

[0721] Exemplary non-cancerous conditions or disorders that may be treated using one or more compounds of the present invention include, but are not limited to, rheumatoid arthritis; inflammation; autoimmune disease; lymphoproliferative conditions; acromegaly; rheumatoid spondylitis; osteoarthritis; gout, other arthritic conditions; sepsis; septic shock; endotoxic shock; gram-negative sepsis; toxic shock syndrome; asthma; adult respiratory distress syndrome; chronic obstructive pulmonary disease; chronic pulmonary inflammation; inflammatory bowel disease; Crohn's disease; psoriasis; eczema; ulcerative colitis; pancreatic fibrosis; hepatic fibrosis; acute and chronic renal disease; irritable bowel syndrome; pyresis; restenosis; cerebral malaria; stroke and ischemic injury; neural trauma; Alzheimer's disease; Huntington's disease; Parkinson's disease; acute and chronic pain; allergic rhinitis; allergic conjunctivitis; chronic heart failure; acute coronary syndrome; cachexia; malaria; leprosy; leishmaniasis; Lyme disease; Reiter's syndrome; acute synovitis; muscle degeneration, bursitis; tendonitis; tenosynovitis; herniated, ruptures, or prolapsed intervertebral disk syndrome; osteopetrosis; thrombosis; restenosis; silicosis; pulmonary sarcosis; bone resorption diseases, such as osteoporosis; graft-versus-host reaction; Multiple Sclerosis; lupus; fibromyalgia; AIDS and other viral diseases such as Herpes Zoster, Herpes Simplex I or II, influenza virus and cytomegalovirus; and diabetes mellitus.

[0722] Exemplary cancers that may be treated using one or more compounds of the present invention include, but are not limited to, adrenocortical carcinoma, AIDS-related cancers, AIDS-related lymphoma, anal cancer, anorectal cancer, cancer of the anal canal, appendix cancer, childhood cerebellar astrocytoma, childhood cerebral astrocytoma, basal cell carcinoma, skin cancer (non-melanoma), biliary cancer, extrahepatic bile duct cancer, intrahepatic bile duct cancer, bladder cancer, urinary bladder cancer, bone and joint cancer, osteosarcoma and malignant fibrous histiocytoma, brain cancer, brain tumor, brain stem glioma, cerebellar astrocytoma, cerebral astrocytoma/malignant glioma, ependymoma, medulloblastoma, supratentorial primitive neuroectodeimal tumors, visual pathway and hypothalamic glioma, breast cancer, bronchial adenomas/carcinoids, carcinoid tumor, gastrointestinal, nervous system cancer, nervous system lymphoma, central nervous system cancer, central nervous system lymphoma, cervical cancer, childhood cancers, chronic lymphocytic leukemia, chronic myelogenous leukemia, chronic myeloproliferative disorders, colon cancer, colorectal cancer, cutaneous T-cell lymphoma, lymphoid neoplasm, mycosis fungoides, Seziary Syndrome, endometrial cancer, esophageal

cancer, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, eye cancer, intraocular melanoma, retinoblastoma, gallbladder cancer, gastric (stomach) cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor (GIST), germ cell tumor, ovarian germ cell tumor, gestational trophoblastic tumor glioma, head and neck cancer, hepatocellular (liver) cancer, Hodgkin lymphoma, hypopharyngeal cancer, intraocular melanoma, ocular cancer, islet cell tumors (endocrine pancreas), Kaposi Sarcoma, kidney cancer, renal cancer, kidney cancer, laryngeal cancer, acute lymphoblastic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, hairy cell leukemia, lip and oral cavity cancer, liver cancer, lung cancer, non-small cell lung cancer, small cell lung cancer, AIDS-related lymphoma, non-Hodgkin lymphoma, primary central nervous system lymphoma, Waldenstram macroglobulinemia, medulloblastoma, melanoma, intraocular (eye) melanoma, merkel cell carcinoma, mesothelioma malignant, mesothelioma, metastatic squamous neck cancer, mouth cancer, cancer of the tongue, multiple endocrine neoplasia syndrome, mycosis fungoides, myelodysplastic syndromes, myelodysplastic/ myeloproliferative diseases, chronic myelogenous leukemia, acute myeloid leukemia, multiple myeloma, chronic myeloproliferative disorders, nasopharyngeal cancer, neuroblastoma, oral cancer, oral cavity cancer, oropharyngeal cancer, ovarian cancer, ovarian epithelial cancer, ovarian low malignant potential tumor, pancreatic cancer, islet cell pancreatic cancer, paranasal sinus and nasal cavity cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pheochromocytoma, pineoblastoma and supratentorial primitive neuroectodermal tumors, pituitary tumor, plasma cell neoplasm/multiple myeloma, pleuropulmonary blastoma, prostate cancer, rectal cancer, renal pelvis and ureter, transitional cell cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, ewing family of sarcoma tumors, Kaposi Sarcoma, soft tissue sarcoma, uterine cancer, uterine sarcoma, skin cancer (non-melanoma), skin cancer (melanoma), merkel cell skin carcinoma, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma, stomach (gastric) cancer, supratentorial primitive neuroectodermal tumors, testicular cancer, throat cancer, thymoma, thymoma and thymic carcinoma, thyroid cancer, transitional cell cancer of the renal pelvis and ureter and other urinary organs, gestational trophoblastic tumor, urethral cancer, endometrial uterine cancer, uterine sarcoma, uterine corpus cancer, vaginal cancer, vulvar cancer, and Wilm's Tumor.

[0723] A "cell proliferative disorder of the hematologic system" is a cell proliferative disorder involving cells of the hematologic system. A cell proliferative disorder of the hematologic system can include lymphoma, leukemia, myeloid neoplasms, mast cell neoplasms, myelodysplasia, benign monoclonal gammopathy, lymphomatoid granulomatosis, lymphomatoid papulosis, polycythemia vera, chronic myelocytic leukemia, agnogenic myeloid metaplasia, and essential thrombocythemia. A cell proliferative disorder of the hematologic system can include hyperplasia, dysplasia, and metaplasia of cells of the hematologic system. In one aspect, compositions of the present invention may be used to treat a cancer selected from the group consisting of a hematologic cancer of the present invention or a hematologic cell proliferative disorder of the present invention, or used to identify suitable candidates for such purposes. A hematologic cancer of the present invention can include multiple myeloma, lymphoma (including Hodgkin's lymphoma, non-Hodgkin's lymphoma, childhood lymphomas, and lymphomas of lymphocytic and cutaneous origin), leukemia (including childhood leukemia, hairy-cell leukemia, acute lymphocytic leukemia, acute myelocytic leukemia, chronic lymphocytic leukemia, chronic myelocytic leukemia, chronic myelogenous leukemia, and mast cell leukemia), myeloid neoplasms and mast cell neoplasms.

[0724] A "cell proliferative disorder of the lung" is a cell proliferative disorder involving cells of the lung. Cell proliferative disorders of the lung can include all forms of cell proliferative disorders affecting lung cells. Cell proliferative disorders of the lung can include lung cancer, a precancer or precancerous condition of the lung, benign growths or lesions of the lung, and malignant growths or lesions of the lung, and metastatic lesions in tissue and organs in the body other than the lung. In one aspect, compositions of the present invention may be used to treat lung cancer or cell proliferative disorders of the lung, or used to identify suitable candidates for such purposes. Lung cancer can include malignant lung neoplasms, carcinoma *in situ*, typical carcinoid tumors, and atypical carcinoid tumors. Lung cancer can include small cell lung cancer ("SCLC"), non-small cell lung cancer ("NSCLC"), squamous cell carcinoma, adenocarcinoma, small cell carcinoma, large cell carcinoma, adenosquamous cell carcinoma, and mesothelioma. Lung cancer can include "scar carcinoma," bronchioalveolar carcinoma, giant cell carcinoma, spindle cell carcinoma, and large cell neuroendocrine carcinoma. Lung cancer can include lung neoplasms having histologic and ultrastructual heterogeneity (*e.g.*, mixed cell types).

[0725] Cell proliferative disorders of the lung can include all forms of cell proliferative disorders affecting lung cells. Cell proliferative disorders of the lung can include lung cancer, precancerous conditions of the lung. Cell proliferative disorders of the lung can include hyperplasia, metaplasia, and dysplasia of the lung. Cell proliferative disorders of the lung can include asbestos-induced hyperplasia, squamous metaplasia, and benign reactive mesothelial metaplasia. Cell proliferative disorders of the lung can include replacement of columnar epithelium with stratified squamous epithelium, and mucosal dysplasia. Individuals exposed to inhaled injurious environmental agents such as cigarette smoke and asbestos may be at increased risk for developing cell proliferative disorders of the lung. Prior lung diseases that may predispose individuals to development of cell proliferative disorders of the lung can include chronic interstitial lung disease, necrotizing pulmonary disease, scleroderma, rheumatoid disease, sarcoidosis, interstitial pneumonitis, tuberculosis, repeated pneumonias, idiopathic pulmonary fibrosis, granulomata, asbestosis, fibrosing alveolitis, and Hodgkin's disease.

[0726] A "cell proliferative disorder of the colon" is a cell proliferative disorder involving cells of the colon. In one aspect, compositions of the present invention may be used to treat colon cancer or cell proliferative disorders of the colon, or used to identify suitable candidates for such purposes. Colon cancer can include all forms of cancer of the colon. Colon cancer can include sporadic and hereditary colon cancers. Colon cancer can include malignant colon neoplasms, carcinoma *in situ*, typical carcinoid tumors, and atypical carcinoid tumors. Colon cancer can include adenocarcinoma, squamous cell carcinoma, and adenosquamous cell carcinoma. Colon cancer can be associated with a hereditary syndrome selected from the group consisting of hereditary nonpolyposis colorectal cancer, familial adenomatous polyposis, Gardner's syndrome, Peutz-Jeghers syndrome, Turcot's syndrome and juvenile polyposis. Colon cancer can be caused by a hereditary syndrome selected from the group consisting of hereditary nonpolyposis colorectal cancer, familial adenomatous polyposis, Gardner's syndrome, Peutz-Jeghers syndrome, Turcot's syndrome and juvenile polyposis.

[0727] Cell proliferative disorders of the colon can include all forms of cell proliferative disorders affecting colon cells. Cell proliferative disorders of the colon can include colon cancer, precancerous conditions of the colon, adenomatous polyps of the colon and metachronous lesions of the colon. A cell proliferative disorder of the colon can include

adenoma. Cell proliferative disorders of the colon can be characterized by hyperplasia, metaplasia, and dysplasia of the colon. Prior colon diseases that may predispose individuals to development of cell proliferative disorders of the colon can include prior colon cancer. Current disease that may predispose individuals to development of cell proliferative disorders of the colon can include Crohn's disease and ulcerative colitis. A cell proliferative disorder of the colon can be associated with a mutation in a gene selected from the group consisting of p53, *ras*, *FAP* and *DCC*. An individual can have an elevated risk of developing a cell proliferative disorder of the colon due to the presence of a mutation in a gene selected from the group consisting of p53, *ras*, *FAP* and *DCC*.

[0728] A "cell proliferative disorder of the pancreas" is a cell proliferative disorder involving cells of the pancreas. Cell proliferative disorders of the pancreas can include all forms of cell proliferative disorders affecting pancreatic cells. Cell proliferative disorders of the pancreas can include pancreas cancer, a precancer or precancerous condition of the pancreas, hyperplasia of the pancreas, and dysaplasia of the pancreas, benign growths or lesions of the pancreas, and malignant growths or lesions of the pancreas, and metastatic lesions in tissue and organs in the body other than the pancreas. Pancreatic cancer includes all forms of cancer of the pancreas. Pancreatic cancer can include ductal adenocarcinoma, adenosquamous carcinoma, pleomorphic giant cell carcinoma, mucinous adenocarcinoma, osteoclast-like giant cell carcinoma, mucinous cystadenocarcinoma, acinar carcinoma, unclassified large cell carcinoma, small cell carcinoma, pancreatoblastoma, papillary neoplasm, mucinous cystadenoma, papillary cystic neoplasm, and serous cystadenoma. Pancreatic cancer can also include pancreatic neoplasms having histologic and ultrastructual heterogeneity (*e.g.*, mixed cell types).

[0729] A "cell proliferative disorder of the prostate" is a cell proliferative disorder involving cells of the prostate. Cell proliferative disorders of the prostate can include all forms of cell proliferative disorders affecting prostate cells. Cell proliferative disorders of the prostate can include prostate cancer, a precancer or precancerous condition of the prostate, benign growths or lesions of the prostate, and malignant growths or lesions of the prostate, and metastatic lesions in tissue and organs in the body other than the prostate. Cell proliferative disorders of the prostate can include hyperplasia, metaplasia, and dysplasia of the prostate.

[0730] A "cell proliferative disorder of the skin" is a cell proliferative disorder involving cells of the skin. Cell proliferative disorders of the skin can include all forms of cell proliferative

disorders affecting skin cells. Cell proliferative disorders of the skin can include a precancer or precancerous condition of the skin, benign growths or lesions of the skin, melanoma, malignant melanoma and other malignant growths or lesions of the skin, and metastatic lesions in tissue and organs in the body other than the skin. Cell proliferative disorders of the skin can include hyperplasia, metaplasia, and dysplasia of the skin.

[0731] A "cell proliferative disorder of the ovary" is a cell proliferative disorder involving cells of the ovary. Cell proliferative disorders of the ovary can include all forms of cell proliferative disorders affecting cells of the ovary. Cell proliferative disorders of the ovary can include a precancer or precancerous condition of the ovary, benign growths or lesions of the ovary, ovarian cancer, malignant growths or lesions of the ovary, and metastatic lesions in tissue and organs in the body other than the ovary. Cell proliferative disorders of the skin can include hyperplasia, metaplasia, and dysplasia of cells of the ovary.

[0732] A "cell proliferative disorder of the breast" is a cell proliferative disorder involving cells of the breast. Cell proliferative disorders of the breast can include all forms of cell proliferative disorders affecting breast cells. Cell proliferative disorders of the breast can include breast cancer, a precancer or precancerous condition of the breast, benign growths or lesions of the breast, and malignant growths or lesions of the breast, and metastatic lesions in tissue and organs in the body other than the breast. Cell proliferative disorders of the breast can include hyperplasia, metaplasia, and dysplasia of the breast.

[0733] A cell proliferative disorder of the breast can be a precancerous condition of the breast. Compositions of the present invention may be used to treat a precancerous condition of the breast. A precancerous condition of the breast can include atypical hyperplasia of the breast, ductal carcinoma *in situ* (DCIS), intraductal carcinoma, lobular carcinoma *in situ* (LCIS), lobular neoplasia, and stage 0 or grade 0 growth or lesion of the breast (*e.g.*, stage 0 or grade 0 breast cancer, or carcinoma *in situ*). A precancerous condition of the breast can be staged according to the TNM classification scheme as accepted by the American Joint Committee on Cancer (AJCC), where the primary tumor (T) has been assigned a stage of T0 or Tis; and where the regional lymph nodes (N) have been assigned a stage of N0; and where distant metastasis (M) has been assigned a stage of M0.

[0734] The cell proliferative disorder of the breast can be breast cancer. In one aspect, compositions of the present invention may be used to treat breast cancer, or used to identify

suitable candidates for such purposes. Breast cancer may include all forms of cancer of the breast. Breast cancer includes all forms of cancer of the breast. Breast cancer can include primary epithelial breast cancers. Breast cancer can include cancers in which the breast is involved by other tumors such as lymphoma, sarcoma or melanoma. Breast cancer can include carcinoma of the breast, ductal carcinoma of the breast, lobular carcinoma of the breast, undifferentiated carcinoma of the breast, cystosarcoma phyllodes of the breast, angiosarcoma of the breast, and primary lymphoma of the breast. Breast cancer can include Stage I, II, IIIA, IIIB, IIIC and IV breast cancer. Ductal carcinoma of the breast can include invasive carcinoma, invasive carcinoma *in situ* with predominant intraductal component, inflammatory breast cancer, and a ductal carcinoma of the breast with a histologic type selected from the group consisting of comedo, mucinous (colloid), medullary, medullary with lymphcytic infiltrate, papillary, scirrhous, and tubular. Lobular carcinoma of the breast can include invasive lobular carcinoma with predominant *in situ* component, invasive lobular carcinoma, and infiltrating lobular carcinoma. Breast cancer can include Paget's disease, Paget's disease with intraductal carcinoma, and Paget's disease with invasive ductal carcinoma. Breast cancer can include breast neoplasms having histologic and ultrastructual heterogeneity (*e.g.*, mixed cell types).

[0735] A compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph, or solvate thereof, may be used to treat breast cancer, or used to identify suitable candidates for such purposes. A breast cancer that is to be treated can include familial breast cancer. A breast cancer that is to be treated can include sporadic breast cancer. A breast cancer that is to be treated can arise in a male subject. A breast cancer that is to be treated can arise in a female subject. A breast cancer that is to be treated can arise in a premenopausal female subject or a postmenopausal female subject. A breast cancer that is to be treated can arise in a subject equal to or older than 30 years old, or a subject younger than 30 years old. A breast cancer that is to be treated has arisen in a subject equal to or older than 50 years old, or a subject younger than 50 years old. A breast cancer that is to be treated can arise in a subject equal to or older than 70 years old, or a subject younger than 70 years old.

[0736] A breast cancer that is to be treated can be typed to identify a familial or spontaneous mutation in BRCA1, BRCA2, or p53. A breast cancer that is to be treated can be typed as having a HER2/neu gene amplification, as overexpressing HER2/neu, or as having a low,

intermediate or high level of HER2/neu expression. A breast cancer that is to be treated can be typed for a marker selected from the group consisting of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor-2, Ki-67, CA15-3, CA 27-29, and c-Met. A breast cancer that is to be treated can be typed as ER-unknown, ER-rich or ER-poor. A breast cancer that is to be treated can be typed as ER-negative or ER-positive. ER-typing of a breast cancer may be performed by any reproducible means. ER-typing of a breast cancer may be performed as set forth in Onkologie 27: 175-179 (2004). A breast cancer that is to be treated can be typed as PR-unknown, PR-rich, or PR-poor. A breast cancer that is to be treated can be typed as PR-negative or PR-positive. A breast cancer that is to be treated can be typed as receptor positive or receptor negative. A breast cancer that is to be treated can be typed as being associated with elevated blood levels of CA 15-3, or CA 27-29, or both.

[0737] A breast cancer that is to be treated can include a localized tumor of the breast. A breast cancer that is to be treated can include a tumor of the breast that is associated with a negative sentinel lymph node (SLN) biopsy. A breast cancer that is to be treated can include a tumor of the breast that is associated with a positive sentinel lymph node (SLN) biopsy. A breast cancer that is to be treated can include a tumor of the breast that is associated with one or more positive axillary lymph nodes, where the axillary lymph nodes have been staged by any applicable method. A breast cancer that is to be treated can include a tumor of the breast that has been typed as having nodal negative status (*e.g.*, node-negative) or nodal positive status (*e.g.*, node-positive). A breast cancer that is to be treated can include a tumor of the breast that has metastasized to other locations in the body. A breast cancer that is to be treated can be classified as having metastasized to a location selected from the group consisting of bone, lung, liver, or brain. A breast cancer that is to be treated can be classified according to a characteristic selected from the group consisting of metastatic, localized, regional, local-regional, locally advanced, distant, multicentric, bilateral, ipsilateral, contralateral, newly diagnosed, recurrent, and inoperable.

[0738] A compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, may be used to treat or prevent a cell proliferative disorder of the breast, or to treat or prevent breast cancer, in a subject having an increased risk of developing breast cancer relative to the population at large, or used to identify suitable candidates for such purposes. A subject with an increased risk of developing breast cancer

relative to the population at large is a female subject with a family history or personal history of breast cancer. A subject with an increased risk of developing breast cancer relative to the population at large is a female subject having a germ-line or spontaneous mutation in BRCA1 or BRCA2, or both. A subject with an increased risk of developing breast cancer relative to the population at large is a female subject with a family history of breast cancer and a germ-line or spontaneous mutation in BRCA1 or BRCA2, or both. A subject with an increased risk of developing breast cancer relative to the population at large is a female who is greater than 30 years old, greater than 40 years old, greater than 50 years old, greater than 60 years old, greater than 70 years old, greater than 80 years old, or greater than 90 years old. A subject with an increased risk of developing breast cancer relative to the population at large is a subject with atypical hyperplasia of the breast, ductal carcinoma *in situ* (DCIS), intraductal carcinoma, lobular carcinoma *in situ* (LCIS), lobular neoplasia, or a stage 0 growth or lesion of the breast (*e.g.*, stage 0 or grade 0 breast cancer, or carcinoma *in situ*).

[0739] A breast cancer that is to be treated can histologically graded according to the Scarff-Bloom-Richardson system, wherein a breast tumor has been assigned a mitosis count score of 1, 2, or 3; a nuclear pleiomorphism score of 1, 2, or 3; a tubule formation score of 1, 2, or 3; and a total Scarff-Bloom-Richardson score of between 3 and 9. A breast cancer that is to be treated can be assigned a tumor grade according to the International Consensus Panel on the Treatment of Breast Cancer selected from the group consisting of grade 1, grade 1-2, grade 2, grade 2-3, or grade 3.

[0740] A cancer that is to be treated can be staged according to the American Joint Committee on Cancer (AJCC) TNM classification system, where the tumor (T) has been assigned a stage of TX, T1, T1mic, T1a, T1b, T1c, T2, T3, T4, T4a, T4b, T4c, or T4d; and where the regional lymph nodes (N) have been assigned a stage of NX, N0, N1, N2, N2a, N2b, N3, N3a, N3b, or N3c; and where distant metastasis (M) can be assigned a stage of MX, M0, or M1. A cancer that is to be treated can be staged according to an American Joint Committee on Cancer (AJCC) classification as Stage I, Stage IIA, Stage IIB, Stage IIIA, Stage IIIB, Stage IIIC, or Stage IV. A cancer that is to be treated can be assigned a grade according to an AJCC classification as Grade GX (*e.g.*, grade cannot be assessed), Grade 1, Grade 2, Grade 3 or Grade 4. A cancer that is to be treated can be staged according to an AJCC pathologic

classification (pN) of pNX, pN0, PN0 (I-), PN0 (I+), PN0 (mol-), PN0 (mol+), PN1, PN1(mi), PN1a, PN1b, PN1c, pN2, pN2a, pN2b, pN3, pN3a, pN3b, or pN3c.

[0741] A cancer that is to be treated can include a tumor that has been determined to be less than or equal to about 2 centimeters in diameter. A cancer that is to be treated can include a tumor that has been determined to be from about 2 to about 5 centimeters in diameter. A cancer that is to be treated can include a tumor that has been determined to be greater than or equal to about 3 centimeters in diameter. A cancer that is to be treated can include a tumor that has been determined to be greater than 5 centimeters in diameter. A cancer that is to be treated can be classified by microscopic appearance as well differentiated, moderately differentiated, poorly differentiated, or undifferentiated. A cancer that is to be treated can be classified by microscopic appearance with respect to mitosis count (*e.g.*, amount of cell division) or nuclear pleiomorphism (*e.g.*, change in cells). A cancer that is to be treated can be classified by microscopic appearance as being associated with areas of necrosis (*e.g.*, areas of dying or degenerating cells). A cancer that is to be treated can be classified as having an abnormal karyotype, having an abnormal number of chromosomes, or having one or more chromosomes that are abnormal in appearance. A cancer that is to be treated can be classified as being aneuploid, triploid, tetraploid, or as having an altered ploidy. A cancer that is to be treated can be classified as having a chromosomal translocation, or a deletion or duplication of an entire chromosome, or a region of deletion, duplication or amplification of a portion of a chromosome.

[0742] A cancer that is to be treated can be evaluated by DNA cytometry, flow cytometry, or image cytometry. A cancer that is to be treated can be typed as having 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% of cells in the synthesis stage of cell division (*e.g.*, in S phase of cell division). A cancer that is to be treated can be typed as having a low S-phase fraction or a high S-phase fraction.

[0743] As used herein, a "normal cell" is a cell that cannot be classified as part of a "cell proliferative disorder". A normal cell lacks unregulated or abnormal growth, or both, that can lead to the development of an unwanted condition or disease. Preferably, a normal cell possesses normally functioning cell cycle checkpoint control mechanisms.

[0744] As used herein, "contacting a cell" refers to a condition in which a compound or other composition of matter is in direct contact with a cell, or is close enough to induce a desired biological effect in a cell.

[0745] As used herein, "candidate compound" refers to a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, that has been or will be tested in one or more *in vitro* or *in vivo* biological assays, in order to determine if that compound is likely to elicit a desired biological or medical response in a cell, tissue, system, animal or human that is being sought by a researcher or clinician. A candidate compound is a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof. The biological or medical response can be the treatment of cancer. The biological or medical response can be treatment or prevention of a cell proliferative disorder. The biological response or effect can also include a change in cell proliferation or growth that occurs *in vitro* or in an animal model, as well as other biological changes that are observable *in vitro*. *In vitro* or *in vivo* biological assays can include, but are not limited to, enzymatic activity assays, electrophoretic mobility shift assays, reporter gene assays, *in vitro* cell viability assays, and the assays described herein.

[0746] As used herein, "monotherapy" refers to the administration of a single active or therapeutic compound to a subject in need thereof. Preferably, monotherapy will involve administration of a therapeutically effective amount of an active compound. For example, cancer monotherapy with one of the compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, analog or derivative thereof, to a subject in need of treatment of cancer. Monotherapy may be contrasted with combination therapy, in which a combination of multiple active compounds is administered, preferably with each component of the combination present in a therapeutically effective amount. Monotherapy with a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, may be more effective than combination therapy in inducing a desired biological effect.

[0747] As used herein, "treating" or "treat" describes the management and care of a patient for the purpose of combating a disease, condition, or disorder and includes the administration of a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, to alleviate the symptoms or complications of a disease,

condition or disorder, or to eliminate the disease, condition or disorder. The term "treat" can also include treatment of a cell *in vitro* or an animal model.

[0748] A compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, can or may also be used to prevent a relevant disease, condition or disorder, or used to identify suitable candidates for such purposes. As used herein, "preventing" or "prevent" describes reducing or eliminating the onset of the symptoms or complications of such disease, condition or disorder.

[0749] As used herein, the term "alleviate" is meant to describe a process by which the severity of a sign or symptom of a disorder is decreased. Importantly, a sign or symptom can be alleviated without being eliminated. The administration of pharmaceutical compositions of the invention can or may lead to the elimination of a sign or symptom, however, elimination is not required. Effective dosages should be expected to decrease the severity of a sign or symptom. For instance, a sign or symptom of a disorder such as cancer, which can occur in multiple locations, is alleviated if the severity of the cancer is decreased within at least one of multiple locations.

[0750] As used herein, the term "severity" is meant to describe the potential of cancer to transform from a precancerous, or benign, state into a malignant state. Alternatively, or in addition, severity is meant to describe a cancer stage, for example, according to the TNM system (accepted by the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC)) or by other art-recognized methods. Cancer stage refers to the extent or severity of the cancer, based on factors such as the location of the primary tumor, tumor size, number of tumors, and lymph node involvement (spread of cancer into lymph nodes). Alternatively, or in addition, severity is meant to describe the tumor grade by art-recognized methods (see, National Cancer Institute, www.cancer.gov). Tumor grade is a system used to classify cancer cells in terms of how abnormal they look under a microscope and how quickly the tumor is likely to grow and spread. Many factors are considered when determining tumor grade, including the structure and growth pattern of the cells. The specific factors used to determine tumor grade vary with each type of cancer. Severity also describes a histologic grade, also called differentiation, which refers to how much the tumor cells resemble normal cells of the same tissue type (see, National Cancer Institute, www.cancer.gov). Furthermore, severity describes a nuclear grade, which refers to the size and shape of the nucleus in tumor

cells and the percentage of tumor cells that are dividing (see, National Cancer Institute, www.cancer.gov).

[0751] Severity can also describe the degree to which a tumor has secreted growth factors, degraded the extracellular matrix, become vascularized, lost adhesion to juxtaposed tissues, or metastasized. Moreover, severity can describe the number of locations to which a primary tumor has metastasized. Finally, severity can include the difficulty of treating tumors of varying types and locations. For example, inoperable tumors, those cancers which have greater access to multiple body systems (hematological and immunological tumors), and those which are the most resistant to traditional treatments are considered most severe. In these situations, prolonging the life expectancy of the subject and/or reducing pain, decreasing the proportion of cancerous cells or restricting cells to one system, and improving cancer stage/tumor grade/histological grade/nuclear grade are considered alleviating a sign or symptom of the cancer.

[0752] As used herein the term "symptom" is defined as an indication of disease, illness, injury, or that something is not right in the body. Symptoms are felt or noticed by the individual experiencing the symptom, but may not easily be noticed by others. Others are defined as non-health-care professionals.

[0753] As used herein the term "sign" is also defined as an indication that something is not right in the body. But signs are defined as things that can be seen by a doctor, nurse, or other health care professional.

[0754] Cancer is a group of diseases that may cause almost any sign or symptom. The signs and symptoms will depend on where the cancer is, the size of the cancer, and how much it affects the nearby organs or structures. If a cancer spreads (metastasizes), then symptoms may appear in different parts of the body.

[0755] As a cancer grows, it begins to push on nearby organs, blood vessels, and nerves. This pressure creates some of the signs and symptoms of cancer. If the cancer is in a critical area, such as certain parts of the brain, even the smallest tumor can cause early symptoms.

[0756] But sometimes cancers start in places where it does not cause any symptoms until the cancer has grown quite large. Pancreas cancers, for example, do not usually grow large enough to be felt from the outside of the body. Some pancreatic cancers do not cause symptoms until they begin to grow around nearby nerves (this causes a backache). Others grow around the bile duct, which blocks the flow of bile and leads to a yellowing of the skin known as jaundice. By

the time a pancreatic cancer causes these signs or symptoms, it has usually reached an advanced stage.

[0757] A cancer may also cause symptoms such as fever, fatigue, or weight loss. This may be because cancer cells use up much of the body's energy supply or release substances that change the body's metabolism. Or the cancer may cause the immune system to react in ways that produce these symptoms.

[0758] Sometimes, cancer cells release substances into the bloodstream that cause symptoms not usually thought to result from cancers. For example, some cancers of the pancreas can release substances which cause blood clots to develop in veins of the legs. Some lung cancers make hormone-like substances that affect blood calcium levels, affecting nerves and muscles and causing weakness and dizziness.

[0759] Cancer presents several general signs or symptoms that occur when a variety of subtypes of cancer cells are present. Most people with cancer will lose weight at some time with their disease. An unexplained (unintentional) weight loss of 10 pounds or more may be the first sign of cancer, particularly cancers of the pancreas, stomach, esophagus, or lung.

[0760] Fever is very common with cancer, but is more often seen in advanced disease. Almost all patients with cancer will have fever at some time, especially if the cancer or its treatment affects the immune system and makes it harder for the body to fight infection. Less often, fever may be an early sign of cancer, such as with leukemia or lymphoma.

[0761] Fatigue may be an important symptom as cancer progresses. It may happen early, though, in cancers such as with leukemia, or if the cancer is causing an ongoing loss of blood, as in some colon or stomach cancers.

[0762] Pain may be an early symptom with some cancers such as bone cancers or testicular cancer. But most often pain is a symptom of advanced disease.

[0763] Along with cancers of the skin (see next section), some internal cancers can cause skin signs that can be seen. These changes include the skin looking darker (hyperpigmentation), yellow (jaundice), or red (erythema); itching; or excessive hair growth.

[0764] Alternatively, or in addition, cancer subtypes present specific signs or symptoms. Changes in bowel habits or bladder function could indicate cancer. Long-term constipation, diarrhea, or a change in the size of the stool may be a sign of colon cancer. Pain with urination,

blood in the urine, or a change in bladder function (such as more frequent or less frequent urination) could be related to bladder or prostate cancer.

[0765] Changes in skin condition or appearance of a new skin condition could indicate cancer. Skin cancers may bleed and look like sores that do not heal. A long-lasting sore in the mouth could be an oral cancer, especially in patients who smoke, chew tobacco, or frequently drink alcohol. Sores on the penis or vagina may either be signs of infection or an early cancer.

[0766] Unusual bleeding or discharge could indicate cancer. Unusual bleeding can happen in either early or advanced cancer. Blood in the sputum (phlegm) may be a sign of lung cancer. Blood in the stool (or a dark or black stool) could be a sign of colon or rectal cancer. Cancer of the cervix or the endometrium (lining of the uterus) can cause vaginal bleeding. Blood in the urine may be a sign of bladder or kidney cancer. A bloody discharge from the nipple may be a sign of breast cancer.

[0767] A thickening or lump in the breast or in other parts of the body could indicate the presence of a cancer. Many cancers can be felt through the skin, mostly in the breast, testicle, lymph nodes (glands), and the soft tissues of the body. A lump or thickening may be an early or late sign of cancer. Any lump or thickening could be indicative of cancer, especially if the formation is new or has grown in size.

[0768] Indigestion or trouble swallowing could indicate cancer. While these symptoms commonly have other causes, indigestion or swallowing problems may be a sign of cancer of the esophagus, stomach, or pharynx (throat).

[0769] Recent changes in a wart or mole could be indicative of cancer. Any wart, mole, or freckle that changes in color, size, or shape, or loses its definite borders indicates the potential development of cancer. For example, the skin lesion may be a melanoma.

[0770] A persistent cough or hoarseness could be indicative of cancer. A cough that does not go away may be a sign of lung cancer. Hoarseness can be a sign of cancer of the larynx (voice box) or thyroid.

[0771] While the signs and symptoms listed above are the more common ones seen with cancer, there are many others that are less common and are not listed here.

[0772] Treating cancer may result in or can result in a reduction in size of a tumor. A reduction in size of a tumor may also be referred to as "tumor regression". Preferably, after treatment, tumor size would be reduced by 5% or greater relative to its size prior to treatment; more

preferably, tumor size is reduced by 10% or greater; more preferably, reduced by 20% or greater; more preferably, reduced by 30% or greater; more preferably, reduced by 40% or greater; even more preferably, reduced by 50% or greater; and most preferably, reduced by greater than 75% or greater. Size of a tumor may be measured by any reproducible means of measurement. The size of a tumor may be measured as a diameter of the tumor.

[0773] Treating cancer may result in or can result in a reduction in tumor volume. Preferably, after treatment, tumor volume would be reduced by 5% or greater relative to its size prior to treatment; more preferably, tumor volume is reduced by 10% or greater; more preferably, reduced by 20% or greater; more preferably, reduced by 30% or greater; more preferably, reduced by 40% or greater; even more preferably, reduced by 50% or greater; and most preferably, reduced by greater than 75% or greater. Tumor volume may be measured by any reproducible means of measurement.

[0774] Treating cancer may result in or can result in a decrease in number of tumors. Preferably, after treatment, tumor number would be reduced by 5% or greater relative to number prior to treatment; more preferably, tumor number is reduced by 10% or greater; more preferably, reduced by 20% or greater; more preferably, reduced by 30% or greater; more preferably, reduced by 40% or greater; even more preferably, reduced by 50% or greater; and most preferably, reduced by greater than 75%. Number of tumors may be measured by any reproducible means of measurement. The number of tumors may be measured by counting tumors visible to the naked eye or at a specified magnification. Preferably, the specified magnification is 2x, 3x, 4x, 5x, 10x, or 50x.

[0775] Treating cancer may result in or can result in a decrease in number of metastatic lesions in other tissues or organs distant from the primary tumor site. Preferably, after treatment, the number of metastatic lesions would be reduced by 5% or greater relative to number prior to treatment; more preferably, the number of metastatic lesions is reduced by 10% or greater; more preferably, reduced by 20% or greater; more preferably, reduced by 30% or greater; more preferably, reduced by 40% or greater; even more preferably, reduced by 50% or greater; and most preferably, reduced by greater than 75%. The number of metastatic lesions may be measured by any reproducible means of measurement. The number of metastatic lesions may be measured by counting metastatic lesions visible to the naked eye or at a specified magnification. Preferably, the specified magnification is 2x, 3x, 4x, 5x, 10x, or 50x.

[0776] Treating cancer may result in or can result in an increase in average survival time of a population of treated subjects in comparison to a population receiving carrier alone. Preferably, the average survival time would be increased by more than 30 days; more preferably, by more than 60 days; more preferably, by more than 90 days; and most preferably, by more than 120 days. An increase in average survival time of a population may be measured by any reproducible means. An increase in average survival time of a population may be measured, for example, by calculating for a population the average length of survival following initiation of treatment with an active compound. An increase in average survival time of a population may also be measured, for example, by calculating for a population the average length of survival following completion of a first round of treatment with an active compound.

[0777] Treating cancer may result in or can result in an increase in average survival time of a population of treated subjects in comparison to a population of untreated subjects. Preferably, the average survival time would be increased by more than 30 days; more preferably, by more than 60 days; more preferably, by more than 90 days; and most preferably, by more than 120 days. An increase in average survival time of a population may be measured by any reproducible means. An increase in average survival time of a population may be measured, for example, by calculating for a population the average length of survival following initiation of treatment with an active compound. An increase in average survival time of a population may also be measured, for example, by calculating for a population the average length of survival following completion of a first round of treatment with an active compound.

[0778] Treating cancer may result in or can result in increase in average survival time of a population of treated subjects in comparison to a population receiving monotherapy with a drug that is not a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, analog or derivative thereof. Preferably, the average survival time would be increased by more than 30 days; more preferably, by more than 60 days; more preferably, by more than 90 days; and most preferably, by more than 120 days. An increase in average survival time of a population may be measured by any reproducible means. An increase in average survival time of a population may be measured, for example, by calculating for a population the average length of survival following initiation of treatment with an active compound. An increase in average survival time of a population may also be measured, for

example, by calculating for a population the average length of survival following completion of a first round of treatment with an active compound.

[0779] Treating cancer may result in or can result in a decrease in the mortality rate of a population of treated subjects in comparison to a population receiving carrier alone. Treating cancer may result in or can result in a decrease in the mortality rate of a population of treated subjects in comparison to an untreated population. Treating cancer may result in or can result in a decrease in the mortality rate of a population of treated subjects in comparison to a population receiving monotherapy with a drug that is not a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, analog or derivative thereof. Preferably, the mortality rate would be decreased by more than 2%; more preferably, by more than 5%; more preferably, by more than 10%; and most preferably, by more than 25%. A decrease in the mortality rate of a population of treated subjects may be measured by any reproducible means. A decrease in the mortality rate of a population may be measured, for example, by calculating for a population the average number of disease-related deaths per unit time following initiation of treatment with an active compound. A decrease in the mortality rate of a population may also be measured, for example, by calculating for a population the average number of disease-related deaths per unit time following completion of a first round of treatment with an active compound.

[0780] Treating cancer may result in or can result in a decrease in tumor growth rate. Preferably, after treatment, tumor growth rate would be reduced by at least 5% relative to number prior to treatment; more preferably, tumor growth rate would be reduced by at least 10%; more preferably, reduced by at least 20%; more preferably, reduced by at least 30%; more preferably, reduced by at least 40%; more preferably, reduced by at least 50%; even more preferably, reduced by at least 50%; and most preferably, reduced by at least 75%. Tumor growth rate may be measured by any reproducible means of measurement. Tumor growth rate can be measured according to a change in tumor diameter per unit time.

[0781] Treating cancer may result in or can result in a decrease in tumor regrowth. Preferably, after treatment, tumor regrowth would be less than 5%; more preferably, tumor regrowth would be less than 10%; more preferably, less than 20%; more preferably, less than 30%; more preferably, less than 40%; more preferably, less than 50%; even more preferably, less than 50%; and most preferably, less than 75%. Tumor regrowth may be measured by any

reproducible means of measurement. Tumor regrowth is measured, for example, by measuring an increase in the diameter of a tumor after a prior tumor shrinkage that followed treatment. A decrease in tumor regrowth is indicated by failure of tumors to reoccur after treatment has stopped.

[0782] Treating or preventing a cell proliferative disorder may result in or can result in a reduction in the rate of cellular proliferation. Preferably, after treatment, the rate of cellular proliferation would be reduced by at least 5%; more preferably, by at least 10%; more preferably, by at least 20%; more preferably, by at least 30%; more preferably, by at least 40%; more preferably, by at least 50%; even more preferably, by at least 50%; and most preferably, by at least 75%. The rate of cellular proliferation may be measured by any reproducible means of measurement. The rate of cellular proliferation is measured, for example, by measuring the number of dividing cells in a tissue sample per unit time.

[0783] Treating or preventing a cell proliferative disorder may result in or can result in a reduction in the proportion of proliferating cells. Preferably, after treatment, the proportion of proliferating cells would be reduced by at least 5%; more preferably, by at least 10%; more preferably, by at least 20%; more preferably, by at least 30%; more preferably, by at least 40%; more preferably, by at least 50%; even more preferably, by at least 50%; and most preferably, by at least 75%. The proportion of proliferating cells may be measured by any reproducible means of measurement. Preferably, the proportion of proliferating cells is measured, for example, by quantifying the number of dividing cells relative to the number of nondividing cells in a tissue sample. The proportion of proliferating cells can be equivalent to the mitotic index.

[0784] Treating or preventing a cell proliferative disorder may result in or can result in a decrease in size of an area or zone of cellular proliferation. Preferably, after treatment, size of an area or zone of cellular proliferation would be reduced by at least 5% relative to its size prior to treatment; more preferably, reduced by at least 10%; more preferably, reduced by at least 20%; more preferably, reduced by at least 30%; more preferably, reduced by at least 40%; more preferably, reduced by at least 50%; even more preferably, reduced by at least 50%; and most preferably, reduced by at least 75%. Size of an area or zone of cellular proliferation may be measured by any reproducible means of measurement. The size of an area or zone of

cellular proliferation may be measured as a diameter or width of an area or zone of cellular proliferation.

[0785] Treating or preventing a cell proliferative disorder may result in or can result in a decrease in the number or proportion of cells having an abnormal appearance or morphology. Preferably, after treatment, the number of cells having an abnormal morphology would be reduced by at least 5% relative to its size prior to treatment; more preferably, reduced by at least 10%; more preferably, reduced by at least 20%; more preferably, reduced by at least 30%; more preferably, reduced by at least 40%; more preferably, reduced by at least 50%; even more preferably, reduced by at least 50%; and most preferably, reduced by at least 75%. An abnormal cellular appearance or morphology may be measured by any reproducible means of measurement. An abnormal cellular morphology can be measured by microscopy, *e.g.*, using an inverted tissue culture microscope. An abnormal cellular morphology can take the form of nuclear pleiomorphism.

[0786] As used herein, the term "selectively" means tending to occur at a higher frequency in one population than in another population. The compared populations can be cell populations. Acompound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, may or can act selectively on a cancer or precancerous cell but not on a normal cell. Acompound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, may or can act selectively to modulate one molecular target (*e.g.*, a target protein methyltransferase) but does not significantly modulate another molecular target (*e.g.*, a non-target protein methyltransferase). The invention also provides a method for selectively inhibiting the activity of an enzyme, such as a protein methyltransferase. Preferably, an event occurs selectively in population A relative to population B if it occurs greater than two times more frequently in population A as compared to population B. An event occurs selectively if it occurs greater than five times more frequently in population A. An event occurs selectively if it occurs greater than ten times more frequently in population A; more preferably, greater than fifty times; even more preferably, greater than 100 times; and most preferably, greater than 1000 times more frequently in population A as compared to population B. For example, cell death would be said to occur selectively in cancer cells if it occurred greater than twice as frequently in cancer cells as compared to normal cells.

[0787] A compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, may or can modulate the activity of a molecular target (*e.g.*, a target protein methyltransferase). Modulating refers to stimulating or inhibiting an activity of a molecular target. Preferably, a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, modulates the activity of a molecular target if it stimulates or inhibits the activity of the molecular target by at least 2-fold relative to the activity of the molecular target under the same conditions but lacking only the presence of said compound. More preferably, a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, modulates the activity of a molecular target if it stimulates or inhibits the activity of the molecular target by at least 5-fold, at least 10-fold, at least 20-fold, at least 50-fold, at least 100-fold relative to the activity of the molecular target under the same conditions but lacking only the presence of said compound. The activity of a molecular target may be measured by any reproducible means. The activity of a molecular target may be measured *in vitro* or *in vivo*. For example, the activity of a molecular target may be measured *in vitro* by an enzymatic activity assay or a DNA binding assay, or the activity of a molecular target may be measured *in vivo* by assaying for expression of a reporter gene.

[0788] A compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, does not significantly modulate the activity of a molecular target if the addition of the compound does not stimulate or inhibit the activity of the molecular target by greater than 10% relative to the activity of the molecular target under the same conditions but lacking only the presence of said compound.

[0789] As used herein, the term "isozyme selective" means preferential inhibition or stimulation of a first isoform of an enzyme in comparison to a second isoform of an enzyme (*e.g.*, preferential inhibition or stimulation of a protein methyltransferase isozyme alpha in comparison to a protein methyltransferase isozyme beta). Preferably, a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, demonstrates a minimum of a fourfold differential, preferably a tenfold differential, more preferably a fifty fold differential, in the dosage required to achieve a biological effect. Preferably, a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, demonstrates this

differential across the range of inhibition, and the differential is exemplified at the IC_{50}, *i.e.*, a 50% inhibition, for a molecular target of interest.

[0790] Administering a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, to a cell or a subject in need thereof may result in or can result in modulation (*i.e.*, stimulation or inhibition) of an activity of a protein methyltransferase of interest.

[0791] The present invention provides methods to assess biological activity of a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof or methods of identifying a test compound as an inhibitor of a Y641 mutant of EZH2. In one embodiment the method includes combining an isolated Y641 mutant of EZH2 with a histone substrate, a methyl group donor (such as *S*-adenosylmethionine (SAM)), and a test compound, wherein the histone substrate comprises a form of H3-K27 selected from the group consisting of unmethylated H3-K27, monomethylated H3-K27, dimethylated H3-K27, and any combination thereof; and performing an assay to detect methylation of H3-K27 in the histone substrate, thereby identifying the test compound as an inhibitor of the Y641 mutant of EZH2 when methylation of H3-K27 in the presence of the test compound is less than methylation of H3-K27 in the absence of the test compound. The assay to detect methylation of H3-K27 can be selected to measure the rate of methylation, the extent of methylation, or both the rate and extent of methylation.

[0792] The Y641 mutant of EZH2 is isolated as a PRC2 complex or functional equivalent thereof. As used herein, the term "isolated" means substantially separated from other components with which the complex may be found as it occurs in nature. A compound can be isolated without necessarily being purified. In one embodiment the mutant of EZH2 is isolated as a complex of a Y641 mutant of EZH2 together with EED and SUZ12. In another embodiment the mutant of EZH2 is isolated as a complex of a Y641 mutant of EZH2 together with EED, SUZ12, and RbAp48. Under appropriate conditions, a PRC2 complex or functional equivalent thereof exhibits histone methyltransferase activity for H3-K27. In one embodiment the complex is composed of recombinantly expressed component polypeptides, e.g., EZH2, EED, SUZ12, with or without RbAp48.

[0793] The isolated Y641 mutant of EZH2 is combined with a histone substrate. A histone substrate includes any suitable source of histone polypeptides or fragments thereof that can

serve as substrate for EZH2. In one embodiment the histone substrate includes histones isolated from a subject. The histones can be isolated from cells of a subject using any suitable method; such methods are well known to persons skilled in the art and need not be further specified here. See, for example, Fang et al. (2004) *Methods Enzymol* 377:213-26. In accordance with the Examples below, in one embodiment the histone substrate is provided as nucleosomes. In accordance with the Examples below, in one embodiment the histone substrate is provided as avian (chicken) erythrocyte nucleosomes.

[0794] Histone substrate so provided may include an admixture of states of histone modification, including various states of H3-K27 methylation as judged by Western blotting with H3-K27 methylation state-specific antibodies. In one embodiment the histone substrate may be provided as purified full-length histone H3. Such purified full-length histone H3 may be provided as a homogeneous preparation in respect of states of H3-K27 methylation, or as an admixture of various states of H3-K27 methylation. Homogeneous preparations of isolated histone H3 in respect of states of H3-K27 methylation may be prepared in part by passage over an immunoaffinity column loaded with suitable H3-K27 methylation state-specific antibodies or by immunoprecipitation using magnetic beads coated with suitable H3-K27 methylation state-specific antibodies. Alternatively or in addition, the methylation state of H3-K27 can be characterized as part of performing the assay. For example, the starting material histone substrate might be characterized as containing 50 percent unmethylated H3-K27, 40 percent monomethylated H3-K27, 10 percent dimethylated H3-K27, and 0 percent trimethylated H3-K27.

[0795] In one embodiment the histone substrate includes a peptide library or a suitable peptide comprising one or more amino acid sequences related to histone H3, including, in particular, a sequence that encompasses H3-K27. For example, in one embodiment, the histone substrate is a peptide fragment that corresponds to amino acid residues 21-44 of histone H3. The peptide library or peptide can be prepared by peptide synthesis according to techniques well known in the art and optionally modified so as to incorporate any desired degree of methylation of lysine corresponding to H3-K27. As described in the Examples below, such peptides can also be modified to incorporate a label, such as biotin, useful in performing downstream assays. In one embodiment the label is appended to the amino (N)-terminus of the peptide(s). In one embodiment the label is appended to the carboxy (C)-terminus of the peptide(s).

[0796] Detection of methylation of H3-K27 can be accomplished using any suitable method. In one embodiment, the source of donor methyl groups includes methyl groups that are labeled with a detectable label. The detectable label in one embodiment is an isotopic label, e.g., tritium. Other types of labels may include, for example, fluorescent labels.

[0797] Detection of formation of trimethylated H3-K27 can be accomplished using any suitable method. For example, detection of formation of trimethylated H3-K27 can be accomplished using an assay to detect incorporation of labeled methyl groups, such as described above, optionally combined with a chromatographic or other method to separate labeled products by size, e.g., polyacrylamide gel electrophoresis (PAGE), capillary electrophoresis (CE), or high pressure liquid chromatography (HPLC). Alternatively or in addition, detection of formation of trimethylated H3-K27 can be accomplished using antibodies that are specific for trimethylated H3-K27.

[0798] Detection of conversion of monomethylated H3-K27 to dimethylated H3-K27 can be accomplished using any suitable method. In one embodiment the conversion is measured using antibodies specific for monomethylated H3-K27 and dimethylated H3-K27. For example, starting amounts or concentrations of monomethylated H3-K27 and dimethylated H3-K27 may be determined using appropriate antibodies specific for monomethylated H3-K27 and dimethylated H3-K27. Following the combination of enzyme, substrate, methyl group donor, and test compound, resulting amounts or concentrations of monomethylated H3-K27 and dimethylated H3-K27 may then be determined using appropriate antibodies specific for monomethylated H3-K27 and dimethylated H3-K27. The beginning and resulting amounts or concentrations of monomethylated H3-K27 and dimethylated H3-K27 can then be compared. Alternatively or in addition, beginning and resulting amounts or concentrations of monomethylated H3-K27 and dimethylated H3-K27 can then be compared to corresponding amounts of concentrations from a negative control. A negative control reaction, in which no test agent is included in the assay, can be run in parallel or as a historical control. Results of such control reaction can optionally be subtracted from corresponding results of the experimental reaction prior to or in conjunction with making the comparison mentioned above.

[0799] Because the dimethylated form of H3-K27 may be further methylated in the same assay, a reduction in the amount or concentration of monomethylated H3-K27 may not appear to correspond directly to an increase in dimethylated H3-K27. In this instance, it may be

presumed, however, that a reduction in the amount or concentration of monomethylated H3-K27 is, by itself, reflective of conversion of monomethylated H3-K27 to dimethylated H3-K27.

[0800] Detection of conversion of dimethylated H3-K27 to trimethylated H3-K27 can be accomplished using any suitable method. In one embodiment the conversion is measured using antibodies specific for dimethylated H3-K27 and trimethylated H3-K27. For example, starting amounts or concentrations of dimethylated H3-K27 and trimethylated H3-K27 may be determined using appropriate antibodies specific for dimethylated H3-K27 and trimethylated H3-K27. Following the combination of enzyme, substrate, and test compound, resulting amounts or concentrations of dimethylated H3-K27 and trimethylated H3-K27 may then be determined using appropriate antibodies specific for dimethylated H3-K27 and trimethylated H3-K27. The beginning and resulting amounts or concentrations of dimethylated H3-K27 and trimethylated H3-K27can then be compared. Alternatively or in addition, beginning and resulting amounts or concentrations of dimethylated H3-K27 and trimethylated H3-K27 can then be compared to corresponding amounts of concentrations from a negative control. A negative control reaction, in which no test agent is included in the assay, can be run in parallel or as a historical control. Results of such control reaction can optionally be subtracted from corresponding results of the experimental reaction prior to or in conjunction with making the comparison mentioned above.

[0801] A test agent is identified as an inhibitor of the Y641 mutant of EZH2 when methylation of H3-K27 with the test compound is less than methylation of H3-K27 without the test compound. In one embodiment, a test agent is identified as an inhibitor of the Y641 mutant of EZH2 when formation of trimethylated H3-K27 in the presence of the test compound is less than formation of trimethylated H3-K27 in the absence of the test compound.

[0802] The present invention also provides a method for identifying a selective inhibitor of a Y641 mutant of EZH2. In one embodiment the method includes combining an isolated Y641 mutant of EZH2 with a histone substrate, a methyl group donor (e.g., SAM), and a test compound, wherein the histone substrate comprises a form of H3-K27 selected from the group consisting of monomethylated H3-K27, dimethylated H3-K27, and a combination of monomethylated H3-K27 and dimethylated H3-K27, thereby forming a test mixture; combining an isolated wild-type EZH2 with a histone substrate, a methyl group donor (e.g., SAM), and a test compound, wherein the histone substrate comprises a form of H3-K27

selected from the group consisting of monomethylated H3-K27, dimethylated H3-K27, and a combination of monomethylated H3-K27 and dimethylated H3-K27, thereby forming a control mixture; performing an assay to detect trimethylation of the histone substrate in each of the test mixture and the control mixture; calculating the ratio of (a) trimethylation with the Y641 mutant of EZH2 and the test compound (M+) to (b) trimethylation with the Y641 mutant of EZH2 without the test compound (M-); calculating the ratio of (c) trimethylation with wild-type EZH2 and the test compound (WT+) to (d) trimethylation with wild-type EZH2 without the test compound (WT-); comparing the ratio (a)/(b) with the ratio (c)/(d); and identifying the test compound as a selective inhibitor of the Y641 mutant of EZH2 when the ratio (a)/(b) is less than the ratio (c)/(d). In one embodiment the method further includes taking into account a negative control without test compound for either or both of the test mixture and the control mixture.

[0803] In some assays, immunological reagents, *e.g.*, antibodies and antigens, are employed. Fluorescence can be utilized in the measurement of enzymatic activity in some assays. As used herein, "fluorescence" refers to a process through which a molecule emits a photon as a result of absorbing an incoming photon of higher energy by the same molecule. Specific methods for assessing the biological activity of the disclosed compounds are described in the examples.

[0804] Administering a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, to a cell or a subject in need thereof may or can result in modulation (*i.e.*, stimulation or inhibition) of an activity of an intracellular target (*e.g.*, substrate). Several intracellular targets may or can be modulated with the compounds of the present invention, including, but not limited to, protein methyltrasferase.

[0805] Activating refers to placing a composition of matter (*e.g.*, protein or nucleic acid) in a state suitable for carrying out a desired biological function. A composition of matter capable of being activated also has an unactivated state. An activated composition of matter may have an inhibitory or stimulatory biological function, or both.

[0806] Elevation refers to an increase in a desired biological activity of a composition of matter (*e.g.*, a protein or a nucleic acid). Elevation may occur through an increase in concentration of a composition of matter.

[0807] As used herein, "a cell cycle checkpoint pathway" refers to a biochemical pathway that is involved in modulation of a cell cycle checkpoint. A cell cycle checkpoint pathway may have

stimulatory or inhibitory effects, or both, on one or more functions comprising a cell cycle checkpoint. A cell cycle checkpoint pathway is comprised of at least two compositions of matter, preferably proteins, both of which contribute to modulation of a cell cycle checkpoint. A cell cycle checkpoint pathway may be activated through an activation of one or more members of the cell cycle checkpoint pathway. Preferably, a cell cycle checkpoint pathway is a biochemical signaling pathway.

[0808] As used herein, "cell cycle checkpoint regulator" refers to a composition of matter that can function, at least in part, in modulation of a cell cycle checkpoint. A cell cycle checkpoint regulator may have stimulatory or inhibitory effects, or both, on one or more functions comprising a cell cycle checkpoint. A cell cycle checkpoint regulator can be a protein or not a protein.

[0809] Treating cancer or a cell proliferative disorder may result in or can result in cell death, and preferably, cell death would result in a decrease of at least 10% in number of cells in a population. More preferably, cell death means a decrease of at least 20%; more preferably, a decrease of at least 30%; more preferably, a decrease of at least 40%; more preferably, a decrease of at least 50%; most preferably, a decrease of at least 75%. Number of cells in a population may be measured by any reproducible means. A number of cells in a population can be measured by fluorescence activated cell sorting (FACS), immunofluorescence microscopy and light microscopy. Methods of measuring cell death are as shown in Li *et al.*, *Proc Natl Acad Sci U S A.* 100(5): 2674-8, 2003. In an aspect, cell death occurs by apoptosis.

[0810] Preferably, an effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, would not be significantly cytotoxic to normal cells. A therapeutically effective amount of a compound is not significantly cytotoxic to normal cells if administration of the compound in a therapeutically effective amount does not induce cell death in greater than 10% of normal cells. A therapeutically effective amount of a compound does not significantly affect the viability of normal cells if administration of the compound in a therapeutically effective amount does not induce cell death in greater than 10% of normal cells. In an aspect, cell death occurs by apoptosis.

[0811] Contacting a cell with a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, may or can induce or

activate cell death selectively in cancer cells. Administering to a subject in need thereof a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, may or can induce or activate cell death selectively in cancer cells. Contacting a cell with a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, may or can induce cell death selectively in one or more cells affected by a cell proliferative disorder. Preferably, administering to a subject in need thereof a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, would induce cell death selectively in one or more cells affected by a cell proliferative disorder.

[0812] One aspect of the present invention relates to a method of treating or preventing cancer (e.g., the course of which can be influenced by modulating EZH2-mediated protein methylation) by administering a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, to a subject in need thereof, where administration of the compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, results in one or more of the following: prevention of cancer cell proliferation by accumulation of cells in one or more phases of the cell cycle (e.g. G1, G1/S, G2/M), or induction of cell senescence, or promotion of tumor cell differentiation; promotion of cell death in cancer cells via cytotoxicity, necrosis or apoptosis, without a significant amount of cell death in normal cells, antitumor activity in animals with a therapeutic index of at least 2. As used herein, "therapeutic index" is the maximum tolerated dose divided by the efficacious dose. The present invention also relates to a method used to identify suitable candidates for treating or preventing cancer.

[0813] One skilled in the art may refer to general reference texts for detailed descriptions of known techniques discussed herein or equivalent techniques. These texts include Ausubel *et al., Current Protocols in Molecular Biology*, John Wiley and Sons, Inc. (2005); Sambrook *et al., Molecular Cloning, A Laboratory Manual* (3rd edition), Cold Spring Harbor Press, Cold Spring Harbor, New York (2000); Coligan *et al., Current Protocols in Immunology*, John Wiley & Sons, N.Y.; Enna *et al., Current Protocols in Pharmacology*, John Wiley & Sons, N.Y.; Fingl *et al., The Pharmacological Basis of Therapeutics* (1975), *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, PA, 18th edition (1990). These texts can, of course, also be referred to in making or using an aspect of the invention.

[0814] As used herein, "combination therapy" or "co-therapy" includes the administration of a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, and at least a second agent as part of a specific treatment regimen intended to provide the beneficial effect from the co-action of these therapeutic agents. The beneficial effect of the combination may include, but is not limited to, pharmacokinetic or pharmacodynamic co-action resulting from the combination of therapeutic agents. Administration of these therapeutic agents in combination typically is carried out over a defined time period (usually minutes, hours, days or weeks depending upon the combination selected). "Combination therapy" may be, but generally is not, intended to encompass the administration of two or more of these therapeutic agents as part of separate monotherapy regimens that incidentally and arbitrarily result in the combinations of the present invention.

[0815] "Combination therapy" is intended to embrace administration of these therapeutic agents in a sequential manner, wherein each therapeutic agent is administered at a different time, as well as administration of these therapeutic agents, or at least two of the therapeutic agents, in a substantially simultaneous manner. Substantially simultaneous administration can be accomplished, for example, by administering to the subject a single capsule having a fixed ratio of each therapeutic agent or in multiple, single capsules for each of the therapeutic agents. Sequential or substantially simultaneous administration of each therapeutic agent can be effected by any appropriate route including, but not limited to, oral routes, intravenous routes, intramuscular routes, and direct absorption through mucous membrane tissues. The therapeutic agents can be administered by the same route or by different routes. For example, a first therapeutic agent of the combination selected may be administered by intravenous injection while the other therapeutic agents of the combination may be administered orally. Alternatively, for example, all therapeutic agents may be administered orally or all therapeutic agents may be administered by intravenous injection. The sequence in which the therapeutic agents are administered is not narrowly critical.

[0816] "Combination therapy" also embraces the administration of the therapeutic agents as described above in further combination with other biologically active ingredients and non-drug therapies (*e.g.*, surgery or radiation treatment). Where the combination therapy further comprises a non-drug treatment, the non-drug treatment may be conducted at any suitable time so long as a beneficial effect from the co-action of the combination of the therapeutic agents

and non-drug treatment is achieved. For example, in appropriate cases, the beneficial effect is still achieved when the non-drug treatment is temporally removed from the administration of the therapeutic agents, perhaps by days or even weeks.

[0817] A compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, analog or derivative thereof, may be administered in combination with a second chemotherapeutic agent. The second chemotherapeutic agent (also referred to as an anti-neoplastic agent or anti-proliferative agent) can be an alkylating agent; an antibiotic; an anti-metabolite; a detoxifying agent; an interferon; a polyclonal or monoclonal antibody; an EGFR inhibitor; a HER2 inhibitor; a histone deacetylase inhibitor; a hormone; a mitotic inhibitor; an MTOR inhibitor; a multi-kinase inhibitor; a serine/threonine kinase inhibitor; a tyrosine kinase inhibitors; a VEGF/VEGFR inhibitor; a taxane or taxane derivative, an aromatase inhibitor, an anthracycline, a microtubule targeting drug, a topoisomerase poison drug, an inhibitor of a molecular target or enzyme (e.g., a kinase or a protein methyltransferase), a cytidine analogue drug or any chemotherapeutic, anti-neoplastic or anti-proliferative agent listed in www.cancer.org/docroot/cdg/cdg_0.asp.

[0818] Exemplary alkylating agents include, but are not limited to, cyclophosphamide (Cytoxan; Neosar); chlorambucil (Leukeran); melphalan (Alkeran); carmustine (BiCNU); busulfan (Busulfex); lomustine (CeeNU); dacarbazine (DTIC-Dome); oxaliplatin (Eloxatin); carmustine (Gliadel); ifosfamide (Ifex); mechlorethamine (Mustargen); busulfan (Myleran); carboplatin (Paraplatin); cisplatin (CDDP; Platinol); temozolomide (Temodar); thiotepa (Thioplex); bendamustine (Treanda); or streptozocin (Zanosar).

[0819] Exemplary antibiotics include, but are not limited to, doxorubicin (Adriamycin); doxorubicin liposomal (Doxil); mitoxantrone (Novantrone); bleomycin (Blenoxane); daunorubicin (Cerubidine); daunorubicin liposomal (DaunoXome); dactinomycin (Cosmegen); epirubicin (Ellence); idarubicin (Idamycin); plicamycin (Mithracin); mitomycin (Mutamycin); pentostatin (Nipent); or valrubicin (Valstar).

[0820] Exemplary anti-metabolites include, but are not limited to, fluorouracil (Adrucil); capecitabine (Xeloda); hydroxyurea (Hydrea); mercaptopurine (Purinethol); pemetrexed (Alimta); fludarabine (Fludara); nelarabine (Arranon); cladribine (Cladribine Novaplus); clofarabine (Clolar); cytarabine (Cytosar-U); decitabine (Dacogen); cytarabine liposomal (DepoCyt); hydroxyurea (Droxia); pralatrexate (Folotyn); floxuridine (FUDR); gemcitabine

(Gemzar); cladribine (Leustatin); fludarabine (Oforta); methotrexate (MTX; Rheumatrex); methotrexate (Trexall); thioguanine (Tabloid); TS-1 or cytarabine (Tarabine PFS).

[0821] Exemplary detoxifying agents include, but are not limited to, amifostine (Ethyol) or mesna (Mesnex).

[0822] Exemplary interferons include, but are not limited to, interferon alfa-2b (Intron A) or interferon alfa-2a (Roferon-A).

[0823] Exemplary polyclonal or monoclonal antibodies include, but are not limited to, trastuzumab (Herceptin); ofatumumab (Arzerra); bevacizumab (Avastin); rituximab (Rituxan); cetuximab (Erbitux); panitumumab (Vectibix); tositumomab/iodine131 tositumomab (Bexxar); alemtuzumab (Campath); ibritumomab (Zevalin; In-111; Y-90 Zevalin); gemtuzumab (Mylotarg); eculizumab (Soliris) ordenosumab.

[0824] Exemplary EGFR inhibitors include, but are not limited to, gefitinib (Iressa); lapatinib (Tykerb); cetuximab (Erbitux); erlotinib (Tarceva); panitumumab (Vectibix); PKI-166; canertinib (CI-1033); matuzumab (Emd7200) or EKB-569.

[0825] Exemplary HER2 inhibitors include, but are not limited to, trastuzumab (Herceptin); lapatinib (Tykerb) or AC-480.

[0826] Histone Deacetylase Inhibitors include, but are not limited to, vorinostat (Zolinza).

[0827] Exemplary hormones include, but are not limited to, tamoxifen (Soltamox; Nolvadex); raloxifene (Evista); megestrol (Megace); leuprolide (Lupron; Lupron Depot; Eligard; Viadur) ; fulvestrant (Faslodex); letrozole (Femara); triptorelin (Trelstar LA; Trelstar Depot) ; exemestane (Aromasin) ; goserelin (Zoladex) ; bicalutamide (Casodex); anastrozole (Arimidex); fluoxymesterone (Androxy; Halotestin); medroxyprogesterone (Provera; Depo-Provera); estramustine (Emcyt); flutamide (Eulexin); toremifene (Fareston); degarelix (Firmagon); nilutamide (Nilandron); abarelix (Plenaxis); or testolactone (Teslac).

[0828] Exemplary mitotic inhibitors include, but are not limited to, paclitaxel (Taxol; Onxol; Abraxane); docetaxel (Taxotere); vincristine (Oncovin; Vincasar PFS); vinblastine (Velban); etoposide (Toposar; Etopophos; VePesid); teniposide (Vumon); ixabepilone (Ixempra); nocodazole; epothilone; vinorelbine (Navelbine); camptothecin (CPT); irinotecan (Camptosar); topotecan (Hycamtin); amsacrine or lamellarin D (LAM-D).

[0829] Exemplary MTOR inhibitors include, but are not limited to, everolimus (Afinitor) or temsirolimus (Torisel); rapamune, ridaforolimus; or AP23573.

[0830] Exemplary multi-kinase inhibitors include, but are not limited to, sorafenib (Nexavar); sunitinib (Sutent); BIBW 2992; E7080; Zd6474; PKC-412; motesanib; or AP24534.

[0831] Exemplary serine/threonine kinase inhibitors include, but are not limited to, ruboxistaurin; eril/easudil hydrochloride; flavopiridol; seliciclib (CYC202; Roscovitrine); SNS-032 (BMS-387032); Pkc412; bryostatin; KAI-9803;SF1126; VX-680; Azd1152; Arry-142886 (AZD-6244); SCIO-469; GW681323; CC-401; CEP-1347 or PD 332991.

[0832] Exemplary tyrosine kinase inhibitors include, but are not limited to, erlotinib (Tarceva); gefitinib (Iressa); imatinib (Gleevec); sorafenib (Nexavar); sunitinib (Sutent); trastuzumab (Herceptin); bevacizumab (Avastin); rituximab (Rituxan); lapatinib (Tykerb); cetuximab (Erbitux); panitumumab (Vectibix); everolimus (Afinitor); alemtuzumab (Campath); gemtuzumab (Mylotarg); temsirolimus (Torisel); pazopanib (Votrient); dasatinib (Sprycel); nilotinib (Tasigna); vatalanib (Ptk787; ZK222584); CEP-701; SU5614; MLN518; XL999; VX-322; Azd0530; BMS-354825; SKI-606 CP-690; AG-490; WHI-P154; WHI-P131; AC-220; or AMG888.

[0833] Exemplary VEGF/VEGFR inhibitors include, but are not limited to, bevacizumab (Avastin); sorafenib (Nexavar); sunitinib (Sutent); ranibizumab; pegaptanib; or vandetinib.

[0834] Exemplary microtubule targeting drugs include, but are not limited to, paclitaxel, docetaxel, vincristin, vinblastin, nocodazole, epothilones and navelbine.

[0835] Exemplary topoisomerase poison drugs include, but are not limited to, teniposide, etoposide, adriamycin, camptothecin, daunorubicin, dactinomycin, mitoxantrone, amsacrine, epirubicin and idarubicin.

[0836] Exemplary taxanes or taxane derivatives include, but are not limited to, paclitaxel and docetaxol.

[0837] Exemplary general chemotherapeutic, anti-neoplastic, anti-proliferative agents include, but are not limited to, altretamine (Hexalen); isotretinoin (Accutane; Amnesteem; Claravis; Sotret); tretinoin (Vesanoid); azacitidine (Vidaza); bortezomib (Velcade) asparaginase (Elspar); levamisole (Ergamisol); mitotane (Lysodren); procarbazine (Matulane); pegaspargase (Oncaspar); denileukin diftitox (Ontak); porfimer (Photofrin); aldesleukin (Proleukin); lenalidomide (Revlimid); bexarotene (Targretin); thalidomide (Thalomid); temsirolimus (Torisel); arsenic trioxide (Trisenox); verteporfin (Visudyne); mimosine (Leucenol); (1M tegafur - 0.4 M 5-chloro-2,4-dihydroxypyrimidine - 1 M potassium oxonate) or lovastatin.

[0838] In another aspect, the second chemotherapeutic agent can be a cytokine such as G-CSF (granulocyte colony stimulating factor). In another aspect, a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, analog or derivative thereof, may be administered in combination with radiation therapy. Radiation therapy can also be administered in combination with a compound of the present invention and another chemotherapeutic agent described herein as part of a multiple agent therapy. In yet another aspect, a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, analog or derivative thereof, may be administered in combination with standard chemotherapy combinations such as, but not restricted to, CMF (cyclophosphamide, methotrexate and 5-fluorouracil), CAF (cyclophosphamide, adriamycin and 5-fluorouracil), AC (adriamycin and cyclophosphamide), FEC (5-fluorouracil, epirubicin, and cyclophosphamide), ACT or ATC (adriamycin, cyclophosphamide, and paclitaxel), rituximab, Xeloda (capecitabine), Cisplatin (CDDP), Carboplatin, TS-1 (tegafur, gimestat and otastat potassium at a molar ratio of 1:0.4:1), Camptothecin-11 (CPT-11, Irinotecan or Camptosar™), CHOP (cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone or prednisolone), R-CHOP (rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone or prednisolone), or CMFP (cyclophosphamide, methotrexate, 5-fluorouracil and prednisone).

[0839] In preferred embodiments, a compound of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, may be administered with an inhibitor of an enzyme, such as a receptor or non-receptor kinase. Receptor and non-receptor kinases are, for example, tyrosine kinases or serine/threonine kinases. Kinase inhibitors described herein are small molecules, polynucleic acids, polypeptides, or antibodies.

[0840] Exemplary kinase inhibitors include, but are not limited to, Bevacizumab (targets VEGF), BIBW 2992 (targets EGFR and Erb2), Cetuximab/Erbitux (targets Erb1), Imatinib/Gleevic (targets Bcr-Abl), Trastuzumab (targets Erb2), Gefitinib/Iressa (targets EGFR), Ranibizumab (targets VEGF), Pegaptanib (targets VEGF), Erlotinib/Tarceva (targets Erb1), Nilotinib (targets Bcr-Abl), Lapatinib (targets Erb1 and Erb2/Her2), GW-572016/lapatinib ditosylate (targets HER2/Erb2), Panitumumab/Vectibix (targets EGFR), Vandetinib (targets RET/VEGFR), E7080 (multiple targets including RET and VEGFR), Herceptin (targets HER2/Erb2), PKI-166 (targets EGFR), Canertinib/CI-1033 (targets EGFR), Sunitinib/SU-11464/Sutent (targets EGFR and FLT3), Matuzumab/Emd7200 (targets EGFR),

EKB-569 (targets EGFR), Zd6474 (targets EGFR and VEGFR), PKC-412 (targets VEGR and FLT3), Vatalanib/Ptk787/ZK222584 (targets VEGR), CEP-701 (targets FLT3), SU5614 (targets FLT3), MLN518 (targets FLT3), XL999 (targets FLT3), VX-322 (targets FLT3), Azd0530 (targets SRC), BMS-354825 (targets SRC), SKI-606 (targets SRC), CP-690 (targets JAK), AG-490 (targets JAK), WHI-P154 (targets JAK), WHI-P131 (targets JAK), sorafenib/Nexavar (targets RAF kinase, VEGFR-1, VEGFR-2, VEGFR-3, PDGFR- ß, KIT, FLT-3, and RET), Dasatinib/Sprycel (BCR/ABL and Src), AC-220 (targets Flt3), AC-480 (targets all HER proteins, "panHER"), Motesanib diphosphate (targets VEGF1-3, PDGFR, and c-kit), Denosumab (targets RANKL, inhibits SRC), AMG888 (targets HER3), and AP24534 (multiple targets including Flt3).

[0841] Exemplary serine/threonine kinase inhibitors include, but are not limited to, Rapamune (targets mTOR/FRAP1), Deforolimus (targets mTOR), Certican/Everolimus (targets mTOR/FRAP1), AP23573 (targets mTOR/FRAP1), Eril/Fasudil hydrochloride (targets RHO), Flavopiridol (targets CDK), Seliciclib/CYC202/Roscovitrine (targets CDK), SNS-032/BMS-387032 (targets CDK), Ruboxistaurin (targets PKC), Pkc412 (targets PKC), Bryostatin (targets PKC), KAI-9803 (targets PKC), SF1126 (targets PI3K), VX-680 (targets Aurora kinase), Azd1152 (targets Aurora kinase), Arry-142886/AZD-6244 (targets MAP/MEK), SCIO-469 (targets MAP/MEK), GW681323 (targets MAP/MEK), CC-401 (targets JNK), CEP-1347 (targets JNK), and PD 332991 (targets CDK).

[0842] The disorder in which EZH2-mediated protein methylation plays a part can be a neurological disease. The compounds of this invention may thus also be used for treating or studying neurologic diseases such as epilepsy, schizophrenia, bipolar disorder or other psychological and/or psychiatric disorders, neuropathies, skeletal muscle atrophy, and neurodegenerative diseases, e.g., a neurodegenerative disease. Exemplary neurodegenerative diseases include: Alzheimer's, Amyotrophic Lateral Sclerosis (ALS), and Parkinson's disease. Another class of neurodegenerative diseases includes diseases caused at least in part by aggregation of poly-glutamine. Diseases of this class include: Huntington's Diseases, Spinalbulbar Muscular Atrophy (SBMA or Kennedy's Disease) Dentatorubropallidoluysian Atrophy (DRPLA), Spinocerebellar Ataxia 1 (SCA1), Spinocerebellar Ataxia 2 (SCA2), Machado-Joseph Disease (MJD; SCA3), Spinocerebellar Ataxia 6 (SCA6), Spinocerebellar Ataxia 7 (SCA7), and Spinocerebellar Ataxia 12 (SCA12).

[0843] Any other disease in which epigenetic methylation, which is mediated by EZH2, plays a role may be treatable or preventable using compounds and methods described herein, or such diseases and potential treatments thereof may be studied with the compounds described herein.

4. Pharmaceutical Compositions

[0844] The present invention also provides pharmaceutical compositions comprising a compound of any of the Formulae described herein in combination with at least one pharmaceutically acceptable excipient or carrier.

[0845] A "pharmaceutical composition" is a formulation containing the compounds of the present invention in a form suitable for administration to a subject. In one embodiment, the pharmaceutical composition is in bulk or in unit dosage form. The unit dosage form is any of a variety of forms, including, for example, a capsule, an IV bag, a tablet, a single pump on an aerosol inhaler or a vial. The quantity of active ingredient (*e.g.*, a formulation of the disclosed compound or salt, hydrate, solvate or isomer thereof) in a unit dose of composition is an effective amount and is varied according to the particular treatment involved. One skilled in the art will appreciate that it is sometimes necessary to make routine variations to the dosage depending on the age and condition of the patient. The dosage will also depend on the route of administration. A variety of routes are contemplated, including oral, pulmonary, rectal, parenteral, transdermal, subcutaneous, intravenous, intramuscular, intraperitoneal, inhalational, buccal, sublingual, intrapleural, intrathecal, intranasal, and the like. Dosage forms for the topical or transdermal administration of a compound of this invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. In one embodiment, the active compound is mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that are required.

[0846] As used herein, the phrase "pharmaceutically acceptable" refers to those compounds, anions, cations, materials, compositions, carriers, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0847] "Pharmaceutically acceptable excipient" means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither

biologically nor otherwise undesirable, and includes excipient that is acceptable for veterinary use as well as human pharmaceutical use. A "pharmaceutically acceptable excipient" as used in the specification and claims includes both one and more than one such excipient.

[0848] A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral (*e.g.*, inhalation), transdermal (topical), and transmucosal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates, and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[0849] A compound or pharmaceutical composition of the invention can be administered to a subject in many of the well-known methods currently used for chemotherapeutic treatment. For example, for treatment of cancers, a compound of the invention may be injected directly into tumors, injected into the blood stream or body cavities or taken orally or applied through the skin with patches. The dose chosen should be sufficient to constitute effective treatment but not so high as to cause unacceptable side effects. The state of the disease condition (*e.g.*, cancer, precancer, and the like) and the health of the patient should preferably be closely monitored during and for a reasonable period after treatment.

[0850] The term "therapeutically effective amount", as used herein, refers to an amount of a pharmaceutical agent to treat, ameliorate, or prevent an identified disease or condition, or to exhibit a detectable therapeutic or inhibitory effect. The effect can be detected by any assay method known in the art. The precise effective amount for a subject will depend upon the subject's body weight, size, and health; the nature and extent of the condition; and the therapeutic or combination of therapeutics selected for administration. Therapeutically effective amounts for a given situation can be determined by routine experimentation that is within the skill and judgment of the clinician. In a preferred aspect, the disease or condition to

be treated is cancer. In another aspect, the disease or condition to be treated is a cell proliferative disorder.

[0851] For any compound, the therapeutically effective amount can be estimated initially either in cell culture assays, *e.g.*, of neoplastic cells, or in animal models, usually rats, mice, rabbits, dogs, or pigs. The animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans. Therapeutic/prophylactic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, ED_{50} (the dose therapeutically effective in 50% of the population) and LD_{50} (the dose lethal to 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index, and it can be expressed as the ratio, LD_{50}/ED_{50}. Pharmaceutical compositions that exhibit large therapeutic indices are preferred. The dosage may vary within this range depending upon the dosage form employed, sensitivity of the patient, and the route of administration.

[0852] Dosage and administration are adjusted to provide sufficient levels of the active agent(s) or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, general health of the subject, age, weight, and gender of the subject, diet, time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy. Long-acting pharmaceutical compositions may be administered every 3 to 4 days, every week, or once every two weeks depending on half-life and clearance rate of the particular formulation.

[0853] The pharmaceutical compositions containing active compounds of the present invention may be manufactured in a manner that is generally known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes. Pharmaceutical compositions may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers comprising excipients and/or auxiliaries that facilitate processing of the active compounds into preparations that can be used pharmaceutically. Of course, the appropriate formulation is dependent upon the route of administration chosen.

[0854] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous

preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringeability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol and sorbitol, and sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[0855] Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0856] Oral compositions generally include an inert diluent or an edible pharmaceutically acceptable carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the

composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[0857] For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser, which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer.

[0858] Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

[0859] The active compounds can be prepared with pharmaceutically acceptable carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811.

[0860] It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired

therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved.

[0861] In therapeutic applications, the dosages of the pharmaceutical compositions used in accordance with the invention vary depending on the agent, the age, weight, and clinical condition of the recipient patient, and the experience and judgment of the clinician or practitioner administering the therapy, among other factors affecting the selected dosage. Generally, the dose should be sufficient to result in slowing, and preferably regressing, the growth of the tumors and also preferably causing complete regression of the cancer. Dosages can range from about 0.01 mg/kg per day to about 5000 mg/kg per day. In preferred aspects, dosages can range from about 1 mg/kg per day to about 1000 mg/kg per day. In an aspect, the dose will be in the range of about 0.1 mg/day to about 50 g/day; about 0.1 mg/day to about 25 g/day; about 0.1 mg/day to about 10 g/day; about 0.1 mg to about 3 g/day; or about 0.1 mg to about 1 g/day, in single, divided, or continuous doses (which dose may be adjusted for the patient's weight in kg, body surface area in m^2, and age in years). An effective amount of a pharmaceutical agent is that which provides an objectively identifiable improvement as noted by the clinician or other qualified observer. For example, regression of a tumor in a patient may be measured with reference to the diameter of a tumor. Decrease in the diameter of a tumor indicates regression. Regression is also indicated by failure of tumors to reoccur after treatment has stopped. As used herein, the term "dosage effective manner" refers to amount of an active compound to produce the desired biological effect in a subject or cell.

[0862] The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

[0863] The compounds of the present invention are capable of further forming salts. All of these forms are also contemplated within the scope of the claimed invention.

[0864] As used herein, "pharmaceutically acceptable salts" refer to derivatives of the compounds of the present invention wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines, alkali or organic salts of acidic residues such as carboxylic acids, and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent

compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include, but are not limited to, those derived from inorganic and organic acids selected from 2-acetoxybenzoic, 2-hydroxyethane sulfonic, acetic, ascorbic, benzene sulfonic, benzoic, bicarbonic, carbonic, citric, edetic, ethane disulfonic, 1,2-ethane sulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, glycollyarsanilic, hexylresorcinic, hydrabamic, hydrobromic, hydrochloric, hydroiodic, hydroxymaleic, hydroxynaphthoic, isethionic, lactic, lactobionic, lauryl sulfonic, maleic, malic, mandelic, methane sulfonic, napsylic, nitric, oxalic, pamoic, pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicyclic, stearic, subacetic, succinic, sulfamic, sulfanilic, sulfuric, tannic, tartaric, toluene sulfonic, and the commonly occurring amine acids, *e.g.*, glycine, alanine, phenylalanine, arginine, etc.

[0865] Other examples of pharmaceutically acceptable salts include hexanoic acid, cyclopentane propionic acid, pyruvic acid, malonic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo-[2.2.2]-oct-2-ene-1-carboxylic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, muconic acid, and the like. The present invention also encompasses salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like. In the salt form, it is understood that the ratio of the compound to the cation or anion of the salt can be 1:1, or any ration other than 1:1, e.g., 3:1, 2:1, 1:2, or 1:3.

[0866] It should be understood that all references to pharmaceutically acceptable salts include solvent addition forms (solvates) or crystal forms (polymorphs) as defined herein, of the same salt.

[0867] The compounds of the present invention can also be prepared as esters, for example, pharmaceutically acceptable esters. For example, a carboxylic acid function group in a compound can be converted to its corresponding ester, *e.g.*, a methyl, ethyl or other ester. Also, an alcohol group in a compound can be converted to its corresponding ester, *e.g.*, acetate, propionate or other ester.

[0868] The compounds of the present invention can also be prepared as prodrugs, for example, pharmaceutically acceptable prodrugs. The terms "pro-drug" and "prodrug" are used interchangeably herein and refer to any compound which releases an active parent drug *in vivo*. Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (*e.g.*, solubility, bioavailability, manufacturing, etc.), the compounds of the present invention can be delivered in prodrug form. Thus, the present invention is intended to cover prodrugs of the presently claimed compounds, methods of delivering the same and compositions containing the same. "Prodrugs" are intended to include any covalently bonded carriers that release an active parent drug of the present invention *in vivo* when such prodrug is administered to a subject. Prodrugs in the present invention are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds of the present invention wherein a hydroxy, amino, sulfhydryl, carboxy or carbonyl group is bonded to any group that may be cleaved *in vivo* to form a free hydroxyl, free amino, free sulfhydryl, free carboxy or free carbonyl group, respectively.

[0869] Examples of prodrugs include, but are not limited to, esters (*e.g.*, acetate, dialkylaminoacetates, formates, phosphates, sulfates and benzoate derivatives) and carbamates (*e.g.*, N,N-dimethylaminocarbonyl) of hydroxy functional groups, esters (*e.g.*, ethyl esters, morpholinoethanol esters) of carboxyl functional groups, N-acyl derivatives (*e.g.*, N-acetyl) N-Mannich bases, Schiff bases and enaminones of amino functional groups, oximes, acetals, ketals and enol esters of ketone and aldehyde functional groups in compounds of the invention, and the like, See Bundegaard, H., *Design of Prodrugs*, p1-92, Elesevier, New York-Oxford (1985).

[0870] The compounds, or pharmaceutically acceptable salts, esters or prodrugs thereof, are administered orally, nasally, transdermally, pulmonary, inhalationally, buccally, sublingually, intraperintoneally, subcutaneously, intramuscularly, intravenously, rectally, intrapleurally, intrathecally and parenterally. In one embodiment, the compound is administered orally. One skilled in the art will recognize the advantages of certain routes of administration.

[0871] The dosage regimen utilizing the compounds is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic

function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the condition.

[0872] Techniques for formulation and administration of the disclosed compounds of the invention can be found in *Remington: the Science and Practice of Pharmacy*, 19th edition, Mack Publishing Co., Easton, PA (1995). In an embodiment, the compounds described herein, and the pharmaceutically acceptable salts thereof, are used in pharmaceutical preparations in combination with a pharmaceutically acceptable carrier or diluent. Suitable pharmaceutically acceptable carriers include inert solid fillers or diluents and sterile aqueous or organic solutions. The compounds will be present in such pharmaceutical compositions in amounts sufficient to provide the desired dosage amount in the range described herein.

[0873] All percentages and ratios used herein, unless otherwise indicated, are by weight. Other features and advantages of the present invention are apparent from the different examples. The provided examples illustrate different components and methodology useful in practicing the present invention. The examples do not limit the claimed invention. Based on the present disclosure the skilled artisan can identify and employ other components and methodology useful for practicing the present invention.

[0874] In the synthetic schemes described herein, compounds may be drawn with one particular configuration for simplicity. Such particular configurations are not to be construed as limiting the invention to one or another isomer, tautomer, regioisomer or stereoisomer, nor does it exclude mixtures of isomers, tautomers, regioisomers or stereoisomers; however, it will be understood that a given isomer, tautomer, regioisomer or stereoisomer may have a higher level of activity than another isomer, tautomer, regioisomer or stereoisomer.

[0875] Compounds designed, selected and/or optimized by methods described above, once produced, can be characterized using a variety of assays known to those skilled in the art to determine whether the compounds have biological activity. For example, the molecules can be characterized by conventional assays, including but not limited to those assays described below, to determine whether they have a predicted activity, binding activity and/or binding specificity.

[0876] Furthermore, high-throughput screening can be used to speed up analysis using such assays. As a result, it can be possible to rapidly screen the molecules described herein for

activity, using techniques known in the art. General methodologies for performing high-throughput screening are described, for example, in Devlin (1998) High Throughput Screening, Marcel Dekker; and U.S. Patent No. 5,763,263. High-throughput assays can use one or more different assay techniques including, but not limited to, those described below.

[0877] All publications and patent documents cited herein are incorporated herein by reference as if each such publication or document was specifically and individually indicated to be incorporated herein by reference. Citation of publications and patent documents is not intended as an admission that any is pertinent prior art, nor does it constitute any admission as to the contents or date of the same. The invention having now been described by way of written description, those of skill in the art will recognize that the invention can be practiced in a variety of embodiments and that the foregoing description and examples below are for purposes of illustration and not limitation of the claims that follow.

5. Examples

[0878] General experimental

NMR

[0879] ^{1}H-NMR spectra were taken using $CDCl_3$ unless otherwise stated and were recorded at 400 or 500 MHz using a Varian or Oxford instruments magnet (500 MHz) instruments. Multiplicities indicated are s=singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sxt = sextet, m = multiplet, dd =doublet of doublets, dt = doublet of triplets; br indicates a broad signal.

LCMS and HPLC

[0880] Shimadzu LC-Q, Shimadzu LCMS-2010EV or Waters Acquity Ultra Performance LC. HPLC: Products were analyzed by Shimadzu SPD-20A with 150 x 4.5mm YMC ODS-M80 column or 150 x 4.6mm YMC-Pack Pro C18 column at 1.0ml/min.

[0881] Mobile phase was MeCN:H2O=3:2 (containing 0.3% SDS and 0.05% H_3PO_4),

[0882] 0.05% TFA in water, 0.05% TFA in acetonitrile (gradient Initial 20 %, then 0.05%TFA/MeCN to conc. to 95 % in 3 min. holds for 0.5 min. at 3.51 to 4.50 min then 0.05%TFA/MeCN conc. 20 %).

[0883] Alternatively the LCMS, 2 different methods were used; the one we use the most is the high pH (METCR1600) and the other one for more standard compounds (METCR1416).

[0884] 0.1% Formic acid in water – Mobile phase "A" 0.1% Formic acid in acetonitrile – Mobile phase "B" utilizing Waters Atlantis dC18, 2.1 mm x 100 mm, 3µm column, with a flow rate = 0.6 ml/min Column temperature = 40°C; Time (mins) %B 0.00 min 5% B. 5.0 mins 100% B, 5.4 mins 100% B and .42 mins 5%B

[0885] 3.5 minute method refers to Atlantis dC18, 2.1 mm x 50 mm, 3µm column, flow rate of 1ml/min at 40C. Mobile phase A Formic acid (aq.) 0.1% mobile phase B formic acid (MeCN) 0.1%, injection 3 µL, gradient 0 mins (5% organic), 2.5 min (100 % organic), 2.7 mins (100 % organic), 2.71 min (5% organic), 3.5 min (5% organic)

[0886] 7.0 minute method refers to Atlantis dC18, 2.1 mm x 100 mm, 3µm column, flow rate of 0.6ml/min at 40C. Mobile phase A Formic acid (aq.) 0.1% mobile phase B formic acid (MeCN) 0.1%, injection 3 µL, gradient 0 mins (5% organic), 5 min (100 % organic), 5.4 mins (100 % organic), 5.42 min (5% organic), 7 min (5% organic)

[0887] Both the 3. 5 and 7 minute methods were performed on a MS18 Shimadzu LCMS-2010EV or a MS19 Shimadzu LCMS-2010EV system utilizing LC-20AB pumps and SPD-M20A PDA detectors.

[0888] Products were purified by HPLC/MS using Waters AutoPurification System with 3100 Mass Detector.

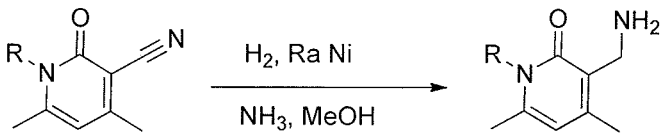
[0889] HPLC analyses may also be performed on a Shimdazu LC-2010 CHT using an YMC ODS-A, C18, (150x4.6 x5 µm) column at ambient temperature with a flow Rate of 1.4 ml/min. An injection volume of 10 µl is utilized and detection occurs via UV/PDA. Mobile Phase A is 0.05 % TFA in water and Mobile Phase B is 0.05 % TFA in acetonitrile with a gradient program of Initial 5 % B to 95 % B in 8min, hold for 1.5 min, at 9.51 to 12 min B. conc. 0.5 %. The diluent is the mobile phase

Other

[0890] Automated flash column chromatography was performed on a Biotage Isolera version 4. 10g SNAP cartridge running at 12 ml/min or a 25g SNAP cartridge running at 25 ml/min and detecting at 254 nm and 280 nm.

[0891] Select Nitrile reductions may be performed on a ThalesNano H-Cube® according to the conditions described in the experimental procedure.

General procedure for the synthesis of the pyridone amines



R= e.g. -CH_2Ph, -CH_2CH_2OH, CH_2CH_2OMe

[0892] To a solution of the cyano compound (1 eq.) in MeOH, a catalytic amount of Raney Nickel and ammonia solution were added. The mixture was stirred at RT under hydrogen (balloon pressure) for 1 hr. On completion of the reaction, the mixture was filtered through a celite bed washing with MeOH. The filtrate was concentrated under reduced pressure to afford the desired amine. This procedure is applicable to a wide variety of R groups described within the examples. In general the cyano pyridines care available from commercial vendors or can be synthesized via methods known to those of ordinary skill in the art.

Syntheses of starting materials or intermediates

[0893] **3-(Aminomethyl)-6-methyl-4-propyl-1,2-dihydropyridin-2-one HCl salt**

[0894] To a stirred solution of *t*-BuOK (20.0 g, 179 mmol) and cyanoacetamide (16.5 g, 196 mmol) in DMSO (300 mL) was added (3E)-3-hepten-2-one (20.0 g, 178 mmol). The reaction mixture was stirred at 23°C for 30 minutes and then additional *t*-BuOK (60.0 g, 712 mmol) was added to the reaction mixture. The reaction mixture was placed under oxygen atmosphere and stirred for 16 h. The reaction mixture was then purged with argon and was cooled to 0 °C. The mixture was diluted with aq. HCl and the resulting precipitate was collected. The solid was washed with water and dried to give 6-methyl-2-oxo-4-propyl-1,2-dihydropyridine-3-carbonitrile (15.0 g, 47% yield).

[0895] To a stirred solution of 6-methyl-2-oxo-4-propyl-1,2-dihydropyridine-3-carbonitrile (15.0 g, 85.1 mmol) in methanol (600 mL) and concentrated HCl (15 mL) was added $Pd(OH)_2$ (15.0 g). The mixture was stirred for 48 hours under H_2 atmosphere. The reaction mixture was filtered and filtrate was concentrated *in vacuo*. Ethanol was added to the residue, the resulting precipitate was collected and dried to give the titled compound as a white solid (13.0 g, 60% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δppm; 11.86 (br. s., 1H), 6.00 (s, 1H), 3.78 (q, J = 5.5 Hz,

2H), 3.61 (br. s., 2H), 2.46 (m, 2H), 2.17 (s, 3H), 1.50 (sxt, J = 7.4 Hz, 2H), 0.91 (t, J=7.4 Hz, 3H).

[0896] **6-Methyl-2-oxo-4-(propan-2-yl)-1,2-dihydropyridine-3-carbonitrile**

[0897] To a solution of 2-cyanoacetamide (35.1 g, 417 mmol) and *t*-BuOK (42.5 g, 379 mmol) in DMSO (631 ml) was added 5-methyl-3-hexen-2-one (50.0 ml, 379 mmol) under N_2 atmosphere. The mixture was stirred at 23°C for 30 min and then additional *t*-BuOK (127 g, 1137 mmol) was added. The N_2 gas was displaced by O_2 gas and the mixture was stirred for 45 h at 23°C under oxygen. The mixture was cooled to 0°C, diluted with H_2O (200 ml) and HCl (5N, 227 ml, slowly added). The mixture was stirred for 15 min at 0°C and the solid was filtered with Buchner funnel. The solid was washed with H_2O (1500 ml) and dried with hot-air (55°C, 16h) to give 6-methyl-2-oxo-4-(propan-2-yl)-1,2-dihydropyridine-3-carbonitrile (26.6 g, 40% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.14 ppm (s, 1H), 3.25-3.29 (m, 1H), 2.45 (s, 3H), 1.26 (d, J = 6.8Hz, 6H); LC-MS: m/z 177.1 [M+1], 198.9 [M+23].

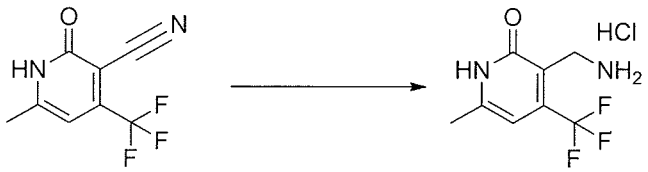
[0898] **3-(Aminomethyl)-6-methyl-4-(propan-2-yl)-1,2-dihydropyridin-2-one HCl salt**

[0899] To a solution of 6-methyl-2-oxo-4-(propan-2-yl)-1,2-dihydropyridine-3-carbonitrile (5.00 g, 28.4 mmol) and in MeOH (400 ml) and HCl (8.8 ml, 12 M) was added 10% $Pd(OH)_2$ (5.17 g, 3.68 mmol) under N_2 atmosphere. The N_2 gas was displaced by H_2 gas and the mixture was stirred for 24 h at 23°C under hydrogen. The H_2 gas was displaced by N_2 gas and the mixture was filtered through celite, washed with MeOH and concentrated. The residue was triturated with EtOH-TBME, the solid was collected with Buchner funnel and dried in vacuo to give the titled compound (6.15 g, 100%). ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 11.9 (br-s, 1H), 8.03 (br-s, 2H), 6.12 (s, 1H), 3.82-3.84 (m, 2H), 3.08-3.12 (m, 1H), 2.19 (s, 3H), 1.12 (d, J = 6.8Hz, 6H).

[0900] **6-Methyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile**

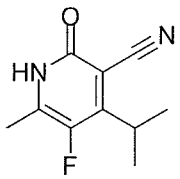
[0901] To a solution of 2-cyanoacetamide (14.0 g, 166 mmol) and trifluoroacetylacetone (20.0 ml, 166 mmol) in H_2O (332 ml) was added K_2CO_3 (6.60 g, 47.9 mmol). The mixture was stirred at 23°C for 15 h. The precipitated solid was filtered with Buchner funnel, washed with ice cold H_2O, and dried with hot air (60 °C, 16 h) to give the titled compound (17.6 g, 52%). ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 2.38 (s, 3H), 6.66 (s, 1H).

[0902] **3-(Aminomethyl)-6-methyl-4-(trifluoromethyl)-1,2-dihydropyridin-2-one hydrochloride HCl salt**



[0903] To a solution of 6-methyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile (400 mg, 1.98 mmol) in MeOH (19.8 ml) and HCl (436 ul, 12M) was added 10% $Pd(OH)_2$ (361 mg, 0.257 mmol) under N_2 atmosphere. The N_2 gas was displaced by H_2 gas and the mixture was stirred for 18 h at 23°C under hydrogen. The H_2 gas was displaced by N_2 gas. The mixture was filtered through Celite, washed with MeOH and concentrated. The residue was triturated with MeOH-Et_2O, collected with Buchner funnel, and dried *in vacuo* to give the titled compound (433 mg, 100%). ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 2.31 (s, 3H), 3.88 (s, 2H), 6.43 (s, 1H).

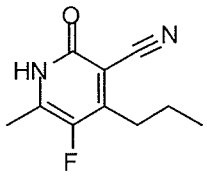
[0904] **5-Fluoro-4-isopropyl-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile**



[0905] To a stirred solution of 6-methyl-2-oxo-4-(propan-2-yl)-1,2-dihydropyridine-3-carbonitrile (225 mg, 1.277 mmol) in MeCN (6 mL) was added Selectfluor (620 mg, 1.75 mmol). The reaction mixture was stirred at 50 °C for 3 h. After cooling to 23°C, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography (50% to 100% EtOAc-heptane to obtain the titled compound (90 mg, 36%). ^{1}H NMR (400 MHz,

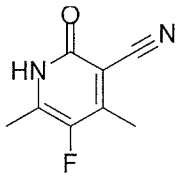
$CDCl_3$) δ ppm 3.39 (m, 1 H), 2.44 (d, J = 3.1 Hz, 3 H), 1.41 (dd, J = 7.0, 3.1 Hz, 6 H); LCMS E-S (M+H) = 195.2.

[0906] **5-Fluoro-6-methyl-2-oxo-4-propyl-1,2-dihydropyridine-3-carbonitrile**



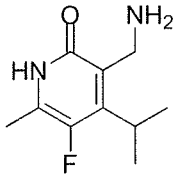
[0907] The title compound was prepared in the same manner as described for 5-Fluoro-4-isopropyl-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (20% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.80 (dt, J = 7.9, 1.9 Hz 2 H), 2.31 (d, J = 2.1 Hz, 3 H), 1.73 (tq, J = 7.4, 7.4 Hz, 2 H), 1.06 (t, J = 7.3 Hz, 3 H); LCMS E-S (M+H) = 195.2.

[0908] **5-Fluoro-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile**



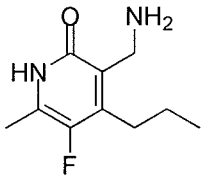
[0909] The title compound was prepared in the same manner as described for 5-Fluoro-4-isopropyl-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (15% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.46 (d, J = 3.1 Hz, 3 H), 2.44 (d, J = 7.4, 3.1 Hz, 3 H); LCMS E-S (M+H) = 167.2.

[0910] **3-(Aminomethyl)-5-fluoro-4-isopropyl-6-methylpyridin-2(1H)-one**



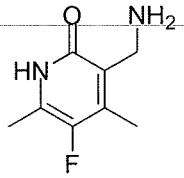
[0911] 5-Fluoro-4-isopropyl-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (100 mg, 0.515 mmol) in 100 mL flask was dissolved in a mixture of MeOH (6 mL) and 2 mL NH_{3aq} (2 mL, 25%). Reduction was conducted using H-Cube with Raney-Ni as a catalyst at room temperature for 3-4 h. On completion of reaction (monitored by TLC), reaction was concentrated under reduced pressure to afford titled compound as a grey solid (90 mg, 90 %). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 4.04 (s, 2 H), 3.22 (m, 1 H), 2.24 (d, J = 3.4 Hz, 3 H), 1.32 (dd, J = 7.0, 1.8 Hz, 6 H); LCMS E-S (M+H) = 199.2.

[0912] **3-(Aminomethyl)-5-fluoro-6-methyl-4-propylpyridin-2(1H)-one**



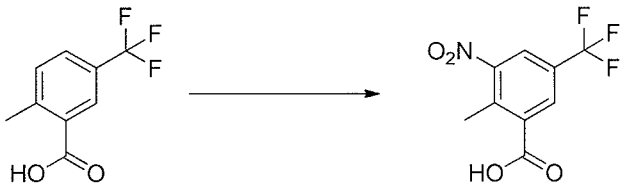
[0913] The titled compound was prepared in the same manner as described for 3-(aminomethyl)-5-fluoro-4-isopropyl-6-methylpyridin-2(1H)-one (92% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.76 (s, 2 H), 2.61 (dt, J = 7.2, 1.8 Hz 2 H), 2.31 (d, J = 2.8 Hz, 3 H), 1.57 (tq, J = 7.6, 7.6 Hz, 2 H), 1.00 (t, J = 7.3 Hz, 3 H); LCMS E-S (M+H) = 199.2.

[0914] **3-(Aminomethyl)-5-fluoro-4,6-dimethylpyridin-2(1H)-one**



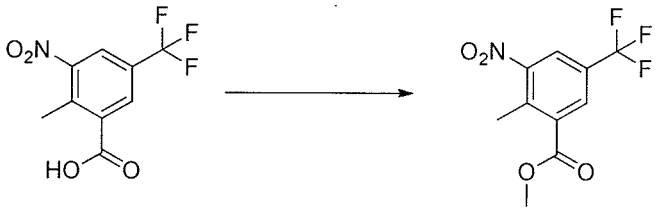
[0915] The title compound was prepared in the same manner as described for 3-(Aminomethyl)-5-fluoro-4-isopropyl-6-methylpyridin-2(1H)-one (92% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.79 (s, 2 H), 2.29 (d, J = 3.3 Hz, 3 H), 2.24 (d, J = 2.1 Hz, 3 H); LCMS E-S (M+H) = 171.2.

[0916] **2-Methyl-3-nitro-5-(trifluoromethyl)benzoic acid**



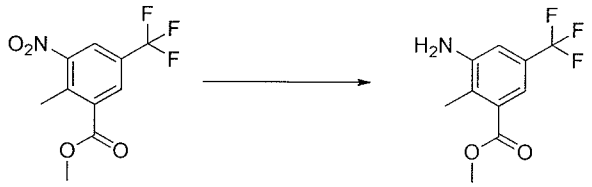
[0917] To a stirred solution of 2-methyl-5-(trifluoromethyl)benzoic acid (2.00 g, 9.80 mmol) in H_2SO_4 (20 mL, 12 N) was added HNO_3 (2 mL, 12N) at 0 ^{0}C. After stirring for 3 hours, water was added and resulting precipitate was collected. The solid was washed with water and dried to give the titled compound as a white solid (1.90 g, 76% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δppm; 8.43 (s, 1H), 8.15 (s, 1H), 2.77 (s, 3H); MS (ES) [M-H] 247.8.

[0918] **Methyl 2-methyl-3-nitro-5-(trifluoromethyl)benzoate**



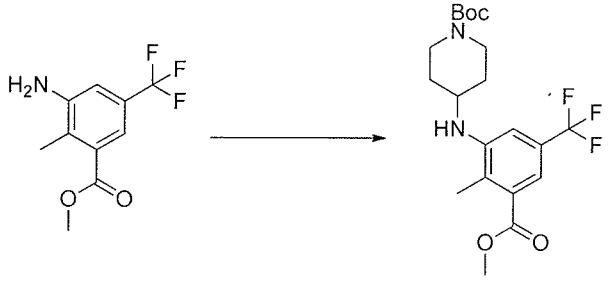
[0919] To a solution of 2-methyl-3-nitro-5-(trifluoromethyl)benzoic acid (21.0 g, 84.3 mmol) in DMF (200 mL) was added potassium carbonate (35.0 g, 253 mmol) and methyl iodide (24.0 g, 169 mmol). The mixture was stirred at 60 ^{0}C and after stirring for 6 h the reaction mixture was cooled to 23°C and was filtered. The filtrate was concentrated *in vacuo* and the residue was dissolved in EtOAc and water. The aqueous phase was extracted with EtOAc (2 x 250 mL and the combined organic layers were concentrated in vacuo. The residue was purified by column chromatography (SiO_2 heptane-EtOAc =4/1) to give the titled compound (20.0 g, 90% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm); 8.27 (s, 1H), 8.11 (s, 1H), 3.99 (s, 3H), 2.71 (s, 3H); MS (ES) [M-H] 261.9.

[0920] **Methyl 3-amino-2-methyl-5-(trifluoromethyl)benzoate**



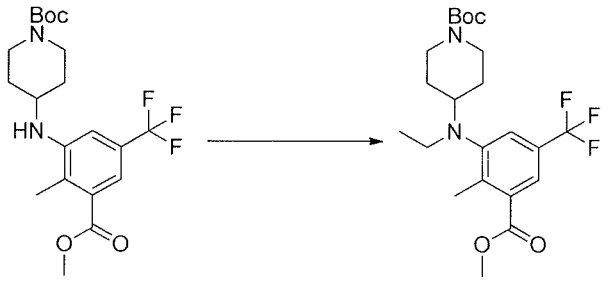
[0921] To a stirred solution of methyl 2-methyl-3-nitro-5-(trifluoromethyl)benzoate (20.0 g, 76.0 mmol) in MeOH (400 ml) was added $Pd(OH)_2$ (2.00 g). The reaction mixture was stirred for 3 hours under hydrogen atmosphere. After purging with nitrogen, the mixture was filtered and the filtrate was concentrated *in vacuo* to give the titled compound as an orange solid (10.2 g, 58% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δppm; 7.47 (brs, 1H), 7.01 (d, J = 2.0 Hz, 1H), 3.92 (m, 2H), 3.91 (s, 3H), 2.39 (s, 3H).

[0922] ***tert*-Butyl-4-{[3-(methoxycarbonyl)-2-methyl-5-(trifluoromethyl)phenyl]amino}piperidine-1-carboxylate**



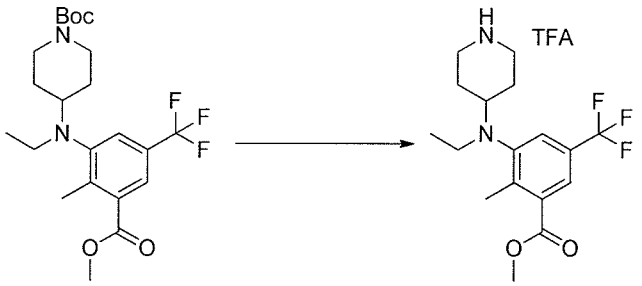
[0923] To a stirred solution of methyl 3-amino-2-methyl-5-(trifluoromethyl)benzoate (6.00 g, 25.7mmol) in CH_2Cl_2 (120 mL) and AcOH (6 mL) was added *N*-Boc piperidinone (6.70 g, 33.4 mmol) and sodium triacetoxyborohydride (13.6 g, 64.3 mmol). The reaction mixture was stirred at 23°C for 20 hours. Then saturated $NaHCO_3$ was added and the mixture was separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layer were concentrated *in vacuo*. The residue was purified by silica gel column chromatography (SiO_2 heptane/EtOAc = 4/1) to give the titled compound (10.6 g, 98% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δppm; 7.37 (s, 1H), 6.88 (s, 1H), 4.05 (m, 2H), 3.90 (s, 3H), 3.01 (m, 3H), 2.32 (s, 3H), 1.71 (m, 2H), 1.48-1.61 (m, 2H), 1.45 (s, 9H); MS (ES) [M-H] 415.1.

[0924] ***tert*-Butyl-4-{ethyl[3-(methoxycarbonyl)-2-methyl-5-(trifluoromethyl)phenyl]amino}piperidine-1-carboxylate**



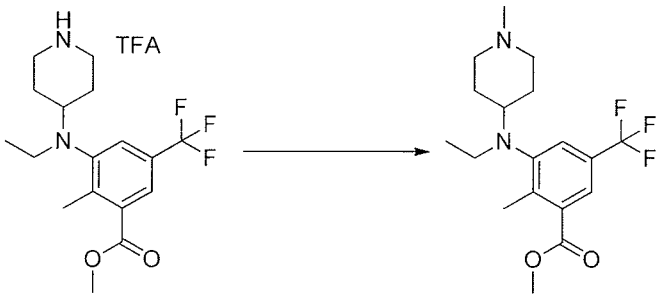
[0925] To a stirred solution of tert-butyl 4-{[3-(methoxycarbonyl)-2-methyl- 5-(trifluoromethyl)phenyl]amino}piperidine-1-carboxylate (10.6 g, 25.4 mmol) in CH_2Cl_2 (200 mL) and AcOH (10 mL) was added acetaldehyde (2.80 g, 63.5 mmol) and sodium triacetoxyborohydride (13.4 g, 63.5 mmol). The reaction mixture was stirred at 23°C for 24 hours. Then saturated $NaHCO_3$ was added and the mixture was separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layer was concentrated in vacuo. The residue was purified by silica gel column chromatography (SiO_2 Heptane/EtOAc = 5/1) to give the titled compound as oil (4.50 g, 40% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δppm; 7.82 (br.s., 1H), 7.45 (d, J = 1.6 Hz, 1H), 3.96-4.18 (m, 2H), 3.92 (s, 3H), 3.08 (q, J = 7.0 Hz, 2H), 2.89 (tt, J = 11.0, 3.7 Hz, 1H), 2.69 (m, 2H), 2.55 (s, 3H), 1.73 (m, 2H), 1.49-1.56 (m, 2H), 1.45 (s, 9H), 0.86 (t, J = 7.0 Hz, 3H); MS (ES) [M+Na] 467.0.

[0926] **Methyl 3-[ethyl(piperidin-4-yl)amino]-2-methyl-5-(trifluoromethyl)benzoate TFA salt**



[0927] To a stirred solution of tert-butyl 4-{ethyl[3-(methoxycarbonyl)-2-methyl- 5-(trifluoromethyl)phenyl]amino}piperidine-1-carboxylate (4.50 g, 10.1 mmol) in CH_2Cl_2 (50 mL) was added TFA (5 mL). The reaction mixture was stirred at rt for 18 hours. Then reaction mixture was concentrated in vacuo to give the titled compound as a crude product (7.70 g).

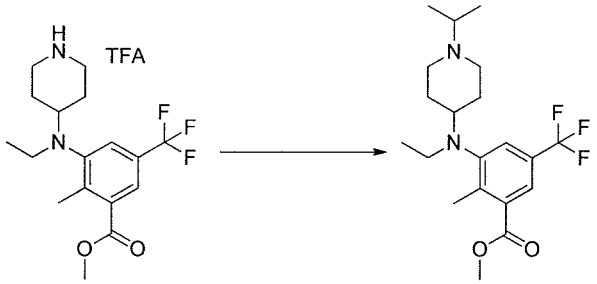
[0928] **Methyl 3-[ethyl(1-methylpiperidin-4-yl)amino]-2-methyl-5-(trifluoromethyl)benzoate**



[0929] To a stirred solution of methyl 3-[ethyl(piperidin-4-yl)amino]-2-methyl-5-(trifluoromethyl)benzoate TFA salt (crude material, 5.30 g, 12.0 mmol) in CH_2Cl_2 (150 mL) and AcOH (10 mL) was added formaldehyde (15 mL, 44% aqueous solution) and sodium triacetoxyborohydride (6.40 g, 30.0 mmol). The reaction mixture was stirred at 23°C for 2.5 days. Then saturated $NaHCO_3$ was added and the mixture was separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layers were concentrated *in vacuo*. The residue was purified by silica gel column chromatography ($NH\text{-}SiO_2$ heptane/EtOAc=2/1) to give the titled compound as oil (1.20cg, 28% yield). ^{1}H-NMR (400cMHz, $CDCl_3$) δppm; 7.81 (br.s., 1H), 7.45 (d, J = 2.0 Hz, 1H), 3.92 (s, 3H), 3.10 (q, J = 7.0 Hz, 2H), 2.83 (m, 2H), 2.66-2.77 (m, 1H), 2.54 (s, 3H), 2.24 (s, 3H), 1.84-1.94 (m, 2H), 1.63-1.78 (m, 4H), 0.86 (t, J = 7.0 Hz, 3H); MS (ES) [M+H] 359.1.

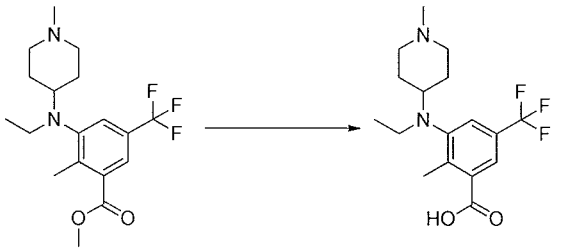
[0930]

[0931] **Methyl 3-{ethyl[1-(propan-2-yl)piperidin-4-yl]amino}-2-methyl-5-(trifluoromethyl)benzoate**



[0932] To a stirred solution of methyl 3-[ethyl(piperidin-4-yl)amino]-2-methyl-5-(trifluoromethyl)benzoate TFA salt (crude material, 1.30 g, 3.36 mmol) in CH_2Cl_2 (20 mL) and AcOH (5 mL) was added acetone (590 mg, 10.1 mmol) and sodium triacetoxyborohydride (1.80 g, 8.40 mmol). The reaction mixture was stirred at 23°C for 6 days and then saturated $NaHCO_3$ was added and the mixture was separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic layer was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (NH-SiO_2 heptane/ethylacetate=5/1) to give the titled compound as oil (220 mg, 17% yield). ^{1}HNMR (400 MHz, $CDCl_3$) δppm; 7.79 (br.s., 1H), 7.44 (d, J = 1.6 Hz, 1H), 3.91 (s, 3H), 3.10 (q, J = 7.0 Hz, 2H), 2.86 (m, 2H), 2.61-2.75 (m, 2H), 2.53 (s, 3H), 2.06 (m, 2H), 1.70-1.80 (m, 2H), 1.58-1.69 (m, 2H), 1.00 (s x 2, 6H), 0.84 (t, J = 7.0 Hz, 3H); MS (ES) [M+H] 387.2.

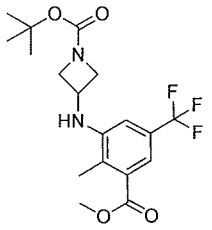
[0933] **3-[Ethyl(1-methylpiperidin-4-yl)amino]-2-methyl-5-(trifluoromethyl)benzoic acid**



[0934] To a stirred solution of methyl 3-[ethyl(1-methylpiperidin-4-yl)amino]-2-methyl-5-(trifluoromethyl)benzoate (700 mg, 1.95 mmol) in methanol (15 mL) was added aq. NaOH (5M, 590 ul, 2.93 mmol). The reaction mixture was stirred at 50°C for 3 hours. After cooling to 23°C, HCl (2 M) was added to the mixture. The mixture was acidified to pH = 5 and was concentrated *in vacuo* to give the titled compound as crude products (1.26 g).

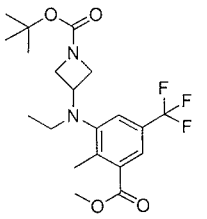
[0935] Following the same preparation method for 3-[ethyl(1-methylpiperidin-4-yl)amino]-2-methyl-5-(trifluoromethyl)benzoic acid, the following titled compounds were prepared from methyl 3-amino-2-methyl-5-(trifluoromethyl)benzoate and tert-butyl 3-oxoazetidine-1-carboxylate.

[0936] **t-butyl 3-((3-(methoxycarbonyl)-2-methyl-5-(trifluoromethyl)phenyl)amino)azetidine -1-carboxylate**



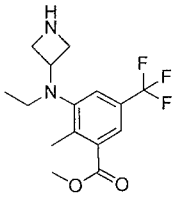
[0937] ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.49 (s, 1H), 6.60 (s, 1H), 4.39 (dd, J = 7.2 Hz, 8.8 Hz, 2H), 4.26 (m, 1H), 4.19 (br, d, J = 5.6 Hz, 1H), 3.93 (s, 3H), 3.78 (m, 2H), 2.41 (s, 3H), 1.47 (s, 9H).

[0938] **tert-butyl 3-(ethyl(3-(methoxycarbonyl)-2-methyl-5-(trifluoromethyl)phenyl)amino)azetidine-1-carboxylate**



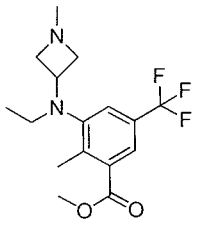
[0939] ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.86 (s, 1H), 7.20 (s, 1H), 4.15 (m, 1H), 3.99 (dd, J = 8.4 Hz, J = 8.4 Hz, 2H), 3.94 (s, 3H), 3.65 (br, 2H), 3.00 (q, J = 7.2 Hz, 2H), 2.60 (s, 3H), 1.43 (s, 9H), 0.90 (t, J = 6.8 Hz, 3H); MS (ES) (M+1) 417.41.

[0940] **Methyl 3-(azetidin-3-yl(ethyl)amino)-2-methyl-5-(trifluoromethyl)benzoate**



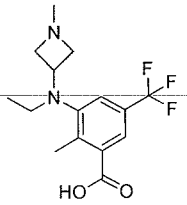
[0941] ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.89 (s, 1H), 7.20 (s, 1H), 4.39 (m, 1H), 3.94 (s, 3H), 3.87 (m, 2H), 3.68 (br, 2H), 2.99 (q, J = 6.8 Hz, 2H), 2.64 (s, 3H), 0.92 (t, J = 6.8 Hz, 3H); MS (ES) (M+1) 317.32.

[0942] **Methyl 3-(ethyl(1-methylazetidin-3-yl)amino)-2-methyl-5-(trifluoromethyl)benzoate**



[0943] ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.83 (s, 1H), 7.24 (s, 1H), 4.03 (m, 1H), 3.94 (s, 3H), 3.60 (br, dd, J = 7.2, 7.2 Hz, 2H), 2.94 (q, J = 7.6 Hz, 2H), 2.72 (br, t, J = 6.8 Hz, 2H), 2.59 (s, 3H), 2.33 (s, 3H), 0.90 (t, J = 7.2 Hz, 3H); MS (ES) (M+1) 331.09.

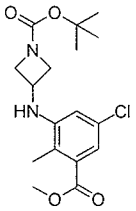
[0944] **3-(ethyl(1-methylazetidin-3-yl)amino)-2-methyl-5-(trifluoromethyl)benzoic acid**



[0945] ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.83 (s, 1H), 7.37 (s, 1H), 4.44 (br, 1H), 3.86 (br, 2H), 3.33 (s, 2H), 3.04 (q, J = 6.8 Hz, 2H), 3.03 (s, 3H), 2.64 (s, 3H), 0.90 (t, J = 7.2 Hz, 3H); MS (ES) (M+1) 317.32.

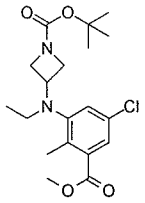
[0946]

[0947] **tert-butyl 3-((5-Chloro-3-(methoxycarbonyl)-2-methylphenyl)amino)azetidine -1-carboxylate**



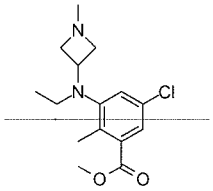
[0948] ^{1}H-NMR (500 MHz, CD_3OD) δ ppm 7.05 (d, J = 2.0 Hz, 1H), 6.48 (d, J = 2.0 Hz, 1H), 4.31 (dd, J = 7.2, 7.8 Hz, 2H), 4.26-4.21 (m, 1H), 3.87 (s, 3H), 3.82 (dd, J = 4.4, 8.3 Hz, 2 H), 2.29 (s, 3H), 1.45 (s, 9H).

[0949] **tert-butyl 3-((5-Chloro-3-(methoxycarbonyl)-2-methylphenyl)(ethyl)amino)azetidine-1-carboxylate**



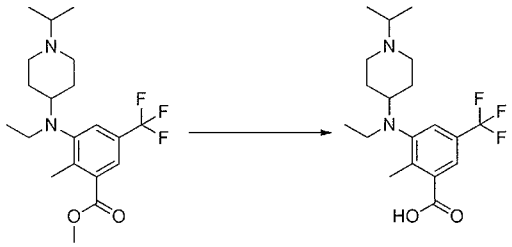
[0950] ^{1}H-NMR (500 MHz, CD_3OD) δ ppm 7.57 (d, J = 2.0 Hz, 1H), 7.18 (d, J = 2.0 Hz, 1H), 4.19-4,14 (m, 1H), 3.98 (dd, J = 8.0, 7.5 Hz, 2H), 3.89(s, 3H), 3.62-3.56 (br, 2H), 2.98 (q, J = 6.7 Hz, 2H), 2.49 (s, 3H), 1.42(s, 9 H), 0.88 (t, J = 7.2 Hz, 3H).

[0951] **Methyl 5-chloro-3-(ethyl(1-methylazetidin-3-yl)amino)-2-methylbenzoate**



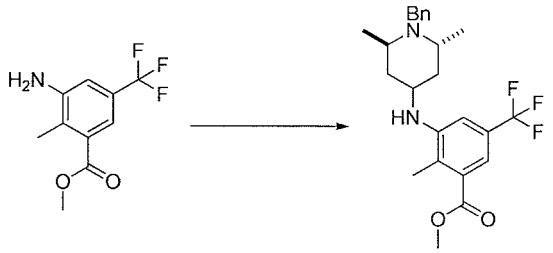
[0952] ^{1}H-NMR (500 MHz, CD_3OD) δ ppm 7.53 (d, J = 2.0 Hz, 1H), 7.17 (d, J = 2.0 Hz, 1H), 4.01 (m, 1H), 3.89 (s, 3H), 3.57 (dd, J = 6.5, 8.0 Hz, 2H), 2.93 (q, J = 7.5 Hz, 2H), 2.83 (bt, J = 7.0 Hz, 2H), 2.49 (s, 3H), 2.33 (s, 3H), 0.90 (t, J = 7.0 Hz, 3H); LCMS (M+H)=297.30 .

[0953] **3-{Ethyl[1-(propan-2-yl)piperidin-4-yl]amino}-2-methyl-5-(trifluoromethyl)benzoic acid**



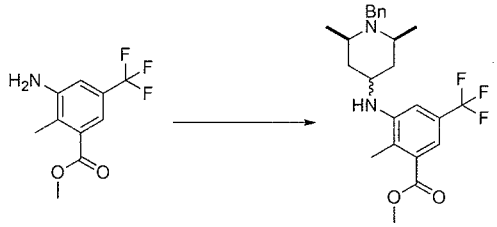
[0954] To a stirred solution of methyl 3-{ethyl[1-(propan-2-yl)piperidin-4-yl]amino}-2-methyl- 5-(trifluoromethyl)benzoate (220 mg, 0.569 mmol) in methanol (4 mL) was added aq. NaOH (5M, 170 ul, 0.854 mmol). The reaction mixture was stirred at 50°C for 2 hours. After cooling to 23°C HCl (2 M) was added to the mixture. The mixture was acidified to pH = 5 and was concentrated in vacuo to give the titled compound as crude products (510 mg).

[0955] **Methyl 3-{[(2R*,6R*)-1-benzyl-2,6-dimethylpiperidin-4-yl]amino}-2-methyl-5-(trifluoromethyl)benzoate**



[0956] To a stirred solution of methyl 3-amino-2-methyl-5-(trifluoromethyl)benzoate (400 mg, 1.72 mmol) in THF (15 mL) and TFA (491 uL) was added (2R, 6S)-1-benzyl-2,6-dimethylpiperidin-4-one (410 mg, 1.89 mmol) at 0°C. The mixture was stirred at 60°C for 1 hour under nitrogen atmosphere. Then the mixture was cooled to 0°C in an ice bath, sodium triacetoxyborohydride (765 mg, 3.43 mmol) was added. The reaction mixture was stirred at 23°C for 2 hours. Then aq. $NaHCO_3$ was added at 0°C until pH8-9, and the content was extracted with ethylacetate. The organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (NH-SiO_2; heptane/ethylacetate=3/1) to give the titled compound as a colorless oil. (278 mg, 37% yield). ^{1}H-NMR (400M Hz, $CDCl_3$) δppm; 7.21-7.40 (m, 6H), 6.90 (s, 1H), 3.95 (d, J = 14.0 Hz, 1H), 3.90 (s, 3H), 3.60-3.73 (m, 2H), 3.46 (d, J = 14.0 Hz, 1H), 3.08-3.12 (m, 1H), 2.98-3.03 (m, 1H), 2.30 (s, 3H), 2.02-2.08 (m, 1H), 1.83-1.88 (m, 1H), 1.52-1.60 (m, 1H), 1.17-1.26 (m, 1H), 1.11 (d, J = 6.8 Hz, 3H), 1.13 (d, J = 6.4 Hz, 3H).

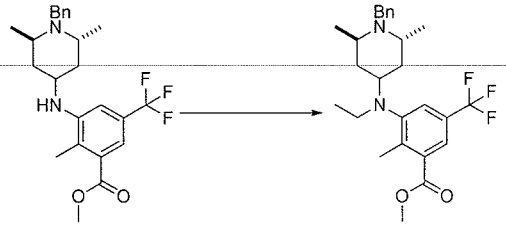
[0957] **Methyl 3-{[(2R*,6S*)-1-benzyl-2,6-dimethylpiperidin-4-yl]amino}-2-methyl-5-(trifluoromethyl)benzoate (diastereomeric mixture)**



[0958] To a stirred mixture of MS3A (1.0 g), methyl 3-amino-2-methyl-5-(trifluoromethyl) benzoate (350 mg, 1.50 mmol) and (2R, 6S)-1-benzyl-2,6-dimethylpiperidin-4-one (359 mg, 1.65 mmol) in chloroform (10 mL) was added acetic acid (500 uL) at 0°C and stirred at r.t. for 7 hours. To the reaction mixture was added sodium triacetoxyborohydride (670 mg, 3.00 mmol) at 0°C. The reaction mixture was stirred at 23°C for 1.5 hours. Then the reaction mixture was quenched with aq. $NaHCO_3$ until pH8-9. The MS 3Å was removed by Celite filtration and the content was extracted with ethylacetate, dried over $MgSO_4$, filtered and the filtrate was

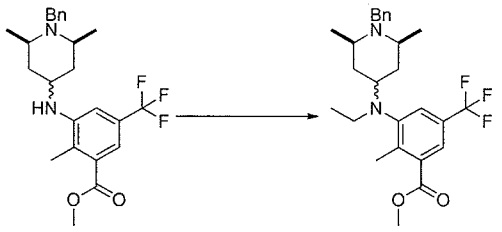
concentrated *in vacuo*. The residue was purified by silica gel column chromatography (heptane/ethylacetate=5/1 to 3/1). Target fractions were collected and concentrated in vacuo. The residue was purified by silica gel column chromatography (NH-SiO_2; heptane/ethylacetate=5/1) to give the titled compound as a light yellow oil (223 mg, 62% yield.). For major isomer; ^{1}H-NMR (400 MHz, $CDCl_3$) δppm; 7.40-7.21 (m, 6H), 6.85 (s, 1H), 4.00-3.95 (m, 1H), 3.91(s, 3H), 3.88 (d, 2H), 3.84-3.76 (m, 1H), 2.83-2.73 (m, 2H), 2.25 (s, 3H), 1.83-1.69 (m, 4H), 1.13 (d, J = 6.4Hz, 6H).

[0959] **Methyl 3-{[(2R*,6R*)-1-benzyl-2,6-dimethylpiperidin-4-yl](ethyl)amino}-2-methyl-5-(trifluoromethyl)benzoate**



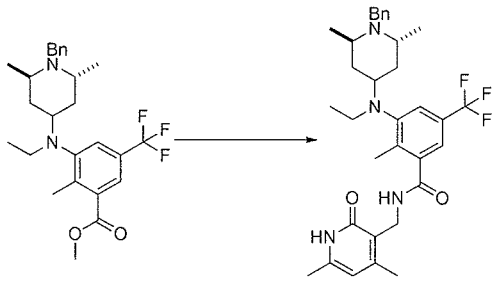
[0960] To a stirred solution of methyl 3-{[(2R, 6R)-1-benzyl-2,6- dimethylpiperidin-4-yl]amino}-2-methyl-5-(trifluoromethyl)benzoate (278 mg, 0.640 mmol) in CH_2Cl_2 (5 mL) and AcOH (500 uL) was added acetaldehyde (359 mg, 6.40 mmol) and sodium triacetoxyborohydride (428 mg, 1.92 mmol) at 0 °C. The reaction mixture was stirred at 23°C for 7 hours. Then the reaction mixture was quenched with aq. $NaHCO_3$ until pH8-9. The content was extracted with ethylacetate, dried over $MgSO_4$ and filtered. The filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (NH-SiO_2; heptane/ethylacetate=5/1) to give the titled compound as a light yellow oil (236 mg, 80% yield.). ^{1}H-NMR (400 MHz, $CDCl_3$) δppm; 7.79 (s, 1H), 7.43 (s, 1H), 7.21-7.36 (m, 5H), 3.92 (s, 3H), 3.87 (d, J = 14.0 Hz, 1H), 3.38 (d, J = 14.0 Hz, 1H), 3.04-3.15 (m, 4H), 2.73-2.80 (m, 1H), 2.53 (s, 3H), 1.76-1.82 (m, 1H), 1.51-1.63 (m, 2H), 1.34-1.42 (m, 1H), 1.06 (d, J = 6.0 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H), 0.86 (t, J = 6.8 Hz, 3H).

[0961] **Methyl 3-{[(2R*,6S*)-1-benzyl-2,6-dimethylpiperidin-4-yl](ethyl)amino}-2-methyl-5-(trifluoromethyl)benzoate(diastereomeric mixture)**



[0962] To a stirred solution of methyl 3-{[(2R, 6S)-1-benzyl-2,6-dimethylpiperidin-4-yl] amino}-2-methyl-5-(trifluoromethyl)benzoate (223 mg, 0.513 mmol) in chloroform (4 mL) and acetic acid (500 uL) was added acetaldehyde(1.0ml) and stirred for 30 min at 0°C. Then sodium triacetoxyborohydride (343 mg, 1.54 mmol) was added to the reaction mixture at 0°C. The reaction mixture was stirred at 23°C for 4 hours. Then the reaction mixture was quenched with aq. $NaHCO_3$ until pH8-9. The content was extracted with ethylacetate. The organic layer was washed with brine. The organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (heptane/ethylacetate=4/1 to 1/2) to give the titled compound as a colorless oil. (105.5 mg, 44% yield). MS (ES) [M+H] 463.3.

[0963] **3-{[(2R*,4S*,6R*)-1-Benzyl-2,6-dimethylpiperidin-4-yl](ethyl)amino}-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-2-methyl-5-(trifluoromethyl)benzamide**

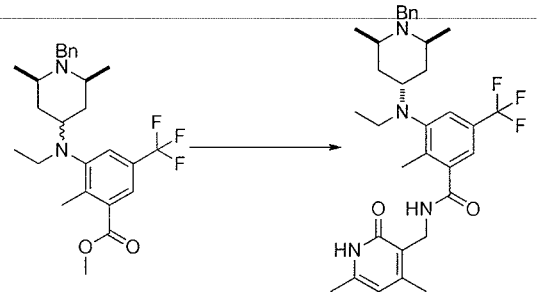


[0964] To a stirred solution of methyl 3-{[(2R, 6R)-1-benzyl-2,6-dimethylpiperidin-4-yl] (ethyl)amino}-2-methyl-5-(trifluoromethyl)benzoate (236 mg, 0.510 mmol) in ethanol (5 mL) was added aq. NaOH (5 M, 269 ul, 1.02 mmol). The reaction mixture was stirred at 80°C for 2 hours. After cooling to rt, the reaction mixture was concentrated in vacuo and dried under reduced pressure to give crude carboxylic acid sodium salt.

[0965] To a stirred solution of crude carboxylic acid sodium salt and 3-(aminomethyl)-4,6-dimethyl-1,2-dihydropyridin-2-one HCl salt (125 mg, 0.664 mmol) in DMSO (5 mL) was added PyBOP (398 mg, 0.766 mmol) and Hunig's base (445 ul, 2.55 mmol). The reaction mixture was stirred at 23°C for 19 hours. The reaction mixture was quenched with water and

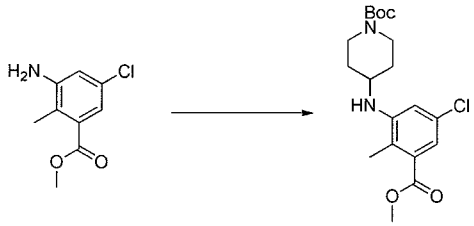
extracted with ethylacetate. The organic layer was washed with water (twice) and brine. The organic layer was dried over $MgSO_4$ and filtered. The combined organic layer was concentrated in vacuo. The residue was purified by silica gel column chromatography (NH-SiO_2; ethylacetate/MeOH=50/1-8/1) to give the titled compound as a white amorphous (267 mg, 90% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δppm; 7.14-7.36 (m, 8H), 5.94 (s, 1H), 4.53-4.56 (m, 2H), 3.85 (d, J = 14.0 Hz, 1H), 3.58 (d, J = 14.0 Hz, 1H), 3.02-3.14 (m, 4H), 2.72-2.80 (m, 1H), 2.40 (s, 3H), 2.32 (s, 3H), 2.21 (s, 3H), 1.32-1.82 (m, 4H), 1.05 (d, J = 6.4 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.84 (t, J = 6.8 Hz, 3H).

[0966] **3-{[(2R*,4R*,6S*)-1-Benzyl-2,6-dimethylpiperidin-4-yl](ethyl)amino}-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-2-methyl-5-(trifluoromethyl)benzamide**



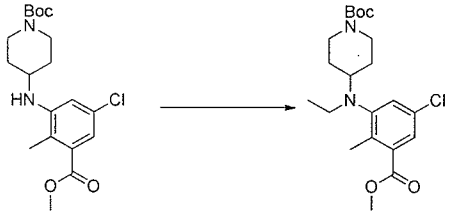
[0967] To a stirred solution of methyl 3-{[(2R, 6S)-1-benzyl-2,6-dimethylpiperidin -4-yl](ethyl)amino}-2-methyl-5-(trifluoromethyl)benzoate (106 mg, 0.228 mmol) in ethanol (2.0 mL) was added aq. NaOH (5 M, 91.2 ul, 0.456 mmol). The reaction mixture was stirred at 80 ^{0}C for 1.5 hours. After cooling to rt, solvent was removed in vacuo and dried under reduced pressure. To a stirred solution of this residue and 3-(aminomethyl)-4,6-dimethyl-1,2-dihydropyridin-2-one HCl salt (55.9 mg, 0.297 mmol) in DMSO (2 mL) was added Hunig's base (199 ul, 1.14 mmol) and PyBOP (178 mg, 0.342 mmol). The reaction mixture was stirred at rt for 4 hours. The reaction mixture was quenched with water. The content was extracted with ethylacetate. The organic layer was washed with water twice and brine. The organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (NH SiO_2, ethylacetate/MeOH=50/1 to 40/1) to give the titled compound as a colorless oil (35.6 mg, 27% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δppm; 7.34-7.08 (m, 7H), 5.96 (s, 1H), 4.54 (d, J = 6.0Hz, 2H), 3.81 (s, 2H), 3.53 (m, 1H), 2.99-2.91 (m, 2H), 2.81 (m, 2H), 2.41 (s, 3H), 2.24 (s, 3H), 2.20 (s, 3H), 1.82-1.47 (m, 4H), 1.00 (d, J = 6.4Hz, 6H), 0.81(t, J = 6.8Hz, 3H); MS(ES) [M+H] 583.0.

[0968] ***tert*-Butyl 4-{[5-chloro-3-(methoxycarbonyl)-2-methylphenyl]amino}piperidine-1-carboxylate**



[0969] To a stirred solution of methyl 3-amino-5-chloro-2-methylbenzoate (1.40 g, 7.04 mmol) in CH_2Cl_2 (30 mL) and AcOH (2.50 g, 42.2 mmol) was added *N*-Boc piperidinone (1.96 g, 9.85 mmol) and sodium triacetoxyborohydride (4.40 g, 21.1 mmol). The reaction mixture was stirred at 23°C for 18 hours and then saturated $NaHCO_3$ was added and the mixture was separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers were concentrated *in vacuo*. The residue was purified by silica gel column chromatography (SiO_2 heptane/ethylacetate=10/1 to 1/1) to give the titled compound as oil (2.40 g, 89% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δppm; 7.09 (s, 1H), 6.69 (s, 1H), 4.05(m, 2H), 3.88 (s, 3H), 3.63 (m, 1H), 3.42 (m, 1H), 2.97 (m, 2H), 2.23 (s, 3H), 2.05 (m, 2H), 1.45 (s, 9H), 1.27 (m, 2H).

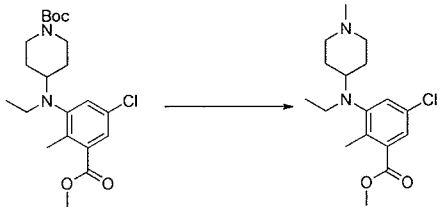
[0970] ***tert*-Butyl 4-{[5-chloro-3-(methoxycarbonyl)-2-methylphenyl](ethyl)amino}piperidine- 1-carboxylate**



[0971] To a stirred solution of tert-butyl 4-{[5-chloro-3-(methoxycarbonyl)-2-methylphenyl] amino}piperidine-1-carboxylate (2.40 g, 6.28 mmol) in dichloromethane (50 mL) and acetic acid (1.8 mL) was added acetaldehyde (830 ul, 12.6 mmol) and sodium triacetoxyborohydride (4.00 g, 18.8 mmol). The reaction mixture was stirred at rt for 18 hours. Then aq. $NaHCO_3$ was added and the mixture was separated. The aqueous layer was extracted with dichloromethane. The combined organic layer was concentrated in vacuo. The residue was purified by silica gel column chromatography (SiO_2 heptane/ethylacetate=10/1) to give the titled compound as oil (2.40 g, 89% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δppm; 7.56 (s, 1H), 7.21 (d, J = 1.6 Hz, 1H),

4.04(m, 2H), 3.89 (s, 3H), 3.02 (q, J = 7.0 Hz, 2H), 2.88 (m, 1H), 2.68 (m, 2H), 2.44 (s, 3H), 1.71 (m, 2H), 1.48-1.61 (m, 2H), 1.45 (s, 9H), 0.83-0.89 (t, J = 7.0 Hz, 3H); MS(ES) [M+Na] 433.0.

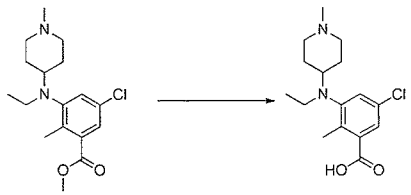
[0972] **Methyl 5-chloro-3-[ethyl(1-methylpiperidin-4-yl)amino]-2-methylbenzoate**



[0973] To a stirred solution of tert-butyl 4-{ethyl[3-(methoxycarbonyl)-2-methyl -5-chlorophenyl]amino}piperidine-1-carboxylate (2.20 g, 5.35 mmol) in dichloromethane (20 mL) was added TFA (4 mL). The reaction mixture was stirred at rt for 2 hours. Then reaction mixture was concentrated in vacuo to give TFA salt as a crude product.

[0974] To a stirred solution of TFA salt in THF (20 mL) and acetic acid (305 ul) was added formaldehyde (3 mL, 44% aqueous solution) and sodium triacetoxyborohydride (3.40 g, 16.1 mmol) at 0 ^{0}C. The reaction mixture was stirred at 23°C for 19 hours and then saturated $NaHCO_3$ was added and the mixture was separated. The aqueous layer was extracted with EtOAc (50 mL) and the combined organic layer was washed with brine, dried over Na_2SO_4 and filtered and the filtrate concentrated *in vacuo*. The residue was purified by silica gel column chromatography (NH-SiO_2 heptane/ethylacetate=1/1) to give title compound as oil (1.54 g, 89% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δppm; 7.54 (d, J = 2 .4 Hz, 1H), 7.21 (d, J=2.4 Hz, 1H), 3.89 (s, 3H), 3.07 (q, J = 6.8 Hz, 2H), 2.81-2.85 (m, 2H), 2.66-2.70 (m, 1H), 2.44 (s, 3H), 2.24 (s, 3H), 1.86-1.93 (m, 2H), 1.65-1.75 (m, 4H), 0.86 (t, J = 6.8 Hz, 3H).

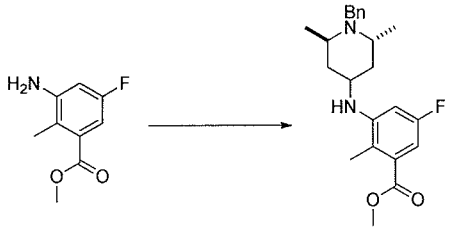
[0975] **5-Chloro-3-[ethyl(1-methylpiperidin-4-yl)amino]-2-methylbenzoic acid**



[0976] To a stirred solution of methyl 5-chloro-3-[ethyl(1-methylpiperidin-4-yl) amino]-2-methylbenzoate (1.06 g, 3.26 mmol) in methanol (10 mL) was added aq. NaOH (5 M, 780 ul, 3.92 mmol). The reaction mixture was stirred at 50 ^{0}C for 18 hours. After cooling to 23°C, HCl

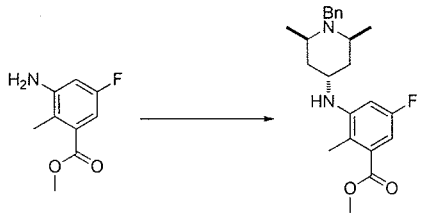
(2 M, 2 mL)) was added to the mixture and the mixture was acidified to pH = 5 and was concentrated *in vacuo* to give the titled compound as crude products (1.80 g).

[0977] **Methyl 3-{[(2R,6R)-1-benzyl-2,6-dimethylpiperidin-4-yl]amino}-5-fluoro-2-methylbenzoate**



[0978] To a stirred solution of methyl 3-amino-5-fluoro-2-methylbenzoate (520 mg, 2.84 mmol) in THF (20 mL) and TFA (813 uL) was added (2R,6S)-1-benzyl-2,6-dimethylpiperidin-4-one (679 mg, 3.12 mmol) at 0 ^{0}C. The mixture was stirred at 60 ^{0}C for 1 hour under nitrogen atmosphere. Then the mixture was cooled to 0 ^{0}C in an ice bath, sodium triacetoxyborohydride (1.27 g, 5.68 mmol) was added. The reaction mixture was stirred at rt for 2 hours. Then aq. $NaHCO_3$ was added at 0 ^{0}C until pH8-9, and the content was extracted with ethylacetate. The organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (NH-SiO_2; heptane/ethylacetate=5/1) to give titled compound as a colorless oil (331 mg, 30% yield.). ^{1}H-NMR (400 MHz, $CDCl_3$) δppm; 7.35-7.39 (m, 2H), 7.27-7.30 (m, 2H), 7.21-7.26 (m, 1H), 6.76 (dd, *J*=2.4, 9.2 Hz, 1H), 6.45 (dd, *J*=2.4, 11.2 Hz, 1H), 3.94 (d, *J*=14.4 Hz, 1H), 3.87 (s, 3H), 3.58-3.65 (m, 2H), 3.46 (d, *J*=14.4 Hz, 1H), 3.06-3.12 (m, 1H), 2.94-3.01 (m, 1H), 2.21 (s, 3H), 2.02-2.07 (m, 1H), 1.82-1.89 (m, 1H), 1.15-1.22 (m, 1H), 1.12 (d, *J*=6.0 Hz, 3H), 1.09 (d, *J*=7.2 Hz, 3H).

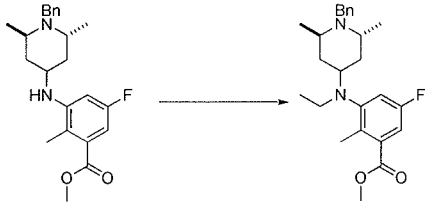
[0979] **Methyl 3-{[(2R,4R,6S)-1-benzyl-2,6-dimethylpiperidin-4-yl]amino}-5-fluoro-2-methylbenzoate**



[0980] To a stirred solution of methyl 3-amino-5-fluoro-2-methylbenzoate (171 mg, 0.931 mmol) in chloroform (6 mL) and AcOH (266 uL) was added (2R,6S)-1-benzyl- 2,6-dimethylpiperidin-4-one (212 mg, 0.980 mmol) and MS3A (500 mg) at 0 ^{0}C. The mixture was

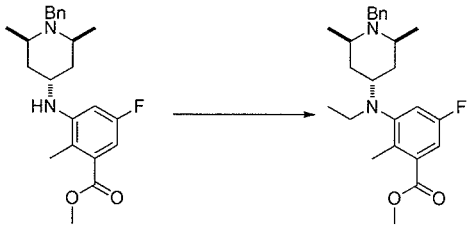
stirred at rt for 2 hour under nitrogen atmosphere. Then the mixture was cooled to 0 ^{0}C in an ice bath and sodium triacetoxyborohydride (415 mg, 1.86 mmol) was added. The reaction mixture was stirred at rt for 5 hours. Then aq. $NaHCO_3$ was added at 0 ^{0}C until pH8-9, and the content was extracted with ethylacetate. The organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (1. SiO_2; heptane/ethylacetate=5/1 to 3/1, 2. NH-SiO_2; heptane/ethylacetate=5/1, 3. NH-SiO_2; heptane/ethylacetate=10/1 to 6/1) to give the titled compound as a colorless oil (85.0 mg, 24% yield.). ^{1}H-NMR (400 MHz, $CDCl_3$) δppm; 7.38-7.20 (m, 5H), 6.77 (dd, J = 2.4, 9.2 Hz, 1H), 6.40 (dd, J = 2.4, 11.6 Hz, 1H), 3.95-3.90 (m, 1H), 3.88 (s, 3H), 3.87 (s, 2H), 2.84-2.74 (m, 2H), 2.16 (s, 3H), 1.81-1.66 (m, 4H), 1.11 (d, J=6.0 Hz, 6H).

[0981] **Methyl 3-{[(2R,6R)-1-benzyl-2,6-dimethylpiperidin-4-yl](ethyl)amino}-5-fluoro-2-methylbenzoate**



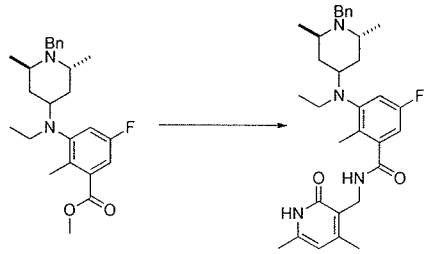
[0982] To a stirred solution of methyl 3-{[(2R,6R)-1-benzyl-2,6-dimethylpiperidin-4-yl] amino}-5-fluoro-2-methylbenzoate (269 mg, 0.701 mmol) in dichloromethane (5 mL) and acetic acid (500 uL) was added acetaldehyde (124 mg, 2.80 mmol) and sodium triacetoxyborohydride (469 mg, 2.10 mmol) at 0 ^{0}C. The reaction mixture was stirred at rt for 12 hours. Then the reaction mixture was quenched with aq. $NaHCO_3$ until pH8-9. The content was extracted with ethylacetate. The organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (NH-SiO_2; heptane/ethylacetate=5/1) to give the titled compound as a light yellow oil (277 mg, 96% yield). ^{1}HNMR (400 MHz, $CDCl_3$) δppm; 7.19-7.36 (m, 6H), 6.97 (dd, J = 2.4, 10.4 Hz, 1H), 3.89 (s, 3H), 3.86 (d, J = 10.4 Hz, 1H), 3.39 (d, J = 10.4 Hz, 1H), 3.02-3.10 (m, 4H), 2.74-2.80 (m, 1H), 2.43 (s, 3H), 1.74-1.82 (m, 1H), 1.51-1.63 (m, 2H), 1.32-1.40 (m, 1H), 1.05 (d, J = 6.4 Hz, 3H), 0.93 (d, J = 7.2 Hz, 3H), 0.86 (t, J = 6.8 Hz, 3H); MS (ES) [M+H] 413.0.

[0983] **Methyl 3-{[(2R,4R,6S)-1-benzyl-2,6-dimethylpiperidin-4-yl](ethyl)amino}-5-fluoro-2-methylbenzoate**



[0984] To a stirred solution of methyl 3-{[(2R,4R,6S)-1-benzyl- 2,6-dimethylpiperidin-4-yl]amino}-5-fluoro-2-methylbenzoate (84.9 mg, 0.221 mmol) and acetaldehyde (124 mg, 2.21 mmol) in chloroform (2 mL), was added acetic acid (200 uL) at 0°C and stirred at 23°C for 1 hour. To the reaction mixture was added sodium triacetoxyborohydride (148 mg, 0.662 mmol) at 0°C. The reaction mixture was stirred at RT for 3.5 hours. To the reaction mixture were added MS 3Å (200 mg) and acetaldehyde (500 ul) at 0°C and stirred at r.t. for 25 minutes. To the reaction mixture was added sodium triacetoxyborohydride (148 mg, 0.662 mmol) at 0°C and stirred at rt for 12 hours. Then the reaction mixture was then quenched with saturated $NaHCO_3$ until pH = 8-9. The content was extracted with EtOAc. The organic layer was washed with brine. The organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (NH-SiO2; heptane/ethylacetate=5/1) to give title compound as a colorless oil (48.5 mg, 53% yield). ^{1}HNMR (400 MHz, $CDCl_3$) δppm; 7.36-7.19 (m, 6H), 6.96 (dd, J = 2.8, 9.6Hz, 1H), 3.90 (s, 3H), 3.82 (s, 2H), 3.44 (m, 1H), 2.98-2.91 (m, 2H), 2.88-2.87 (m, 2H), 2.31 (s, 3H), 1.82-1.70 (m, 2H), 1.57-1.4 7(m, 2H), 0.99 (d, J = 6.4Hz, 6H), 0.83 (t, J = 6.8Hz, 3H).

[0985] **3-{[(2R,6R)-1-Benzyl-2,6-dimethylpiperidin-4-yl](ethyl)amino}-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-5-fluoro-2-methylbenzamide**

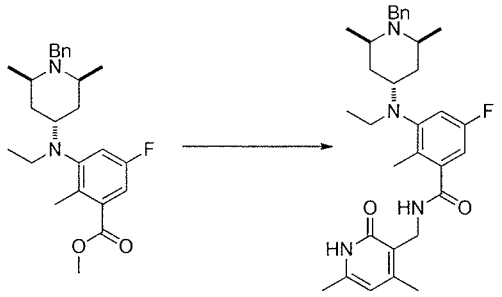


[0986] To a stirred solution of methyl 3-{[(2R,6R)-1-benzyl-2,6-dimethylpiperidin-4-yl](ethyl)amino}-5-fluoro-2-methylbenzoate (277 mg, 0.672 mmol) in ethanol (5 mL) was added aq. NaOH (5 M, 269 ul, 1.35 mmol). The reaction mixture was stirred at 80 ^{0}C for 2 hours.

After cooling to rt, the reaction mixture was concentrated in vacuo and dried under reduced pressure to give crude carboxylic acid sodium salt.

[0987] To a stirred solution of crude carboxylic acid sodium salt and 3-(aminomethyl)-4,6-dimethyl-1,2-dihydropyridin-2-one HCl salt (165 mg, 0.874 mmol) in DMSO (5 mL) was added PyBOP (525 mg, 1.01 mmol) and Hunig's base (586 ul, 3.36 mmol). The reaction mixture was stirred at 23°C for 5 hours. The reaction mixture was quenched with water and extracted with ethylacetate. The organic layer was washed with water (2 x 10 mL) and brine (1 x 10 mL). The organic layer was dried over $MgSO_4$ and filtered and the filtrate concentrated *in vacuo*. The residue was purified by silica gel column chromatography (NH-SiO_2; ethylacetate only to ethylacetate/MeOH=50/1-8/1) to give titled compound as a white solid (378 mg, quantitative yield). ^{1}HNMR (400 MHz, $CDCl_3$) δppm; 7.20-7.38 (m, 5H), 7.02-7.10 (m, 1H), 6.80-6.84 (m, 1H), 6.73-6.78 (m, 1H), 5.93 (s, 1H), 4.51 (d, J = 6.0 Hz, 2H), 3.85 (d, J = 10.0 Hz, 1H), 3.38 (d, J = 10.0 Hz, 1H), 3.01-3.05 (m, 4H), 2.67-2.81 (m, 1H), 2.40 (s, 3H), 2.23 (s, 3H), 2.23 (s, 3H), 1.52-1.83 (m, 3H), 1.32-1.39 (m, 1H), 1.05 (d, J = 6.4 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H), 0.84 (t, J = 6.8 Hz, 3H).

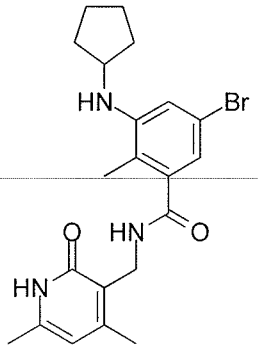
[0988] **3-{[(2R,4R,6S)-1-Benzyl-2,6-dimethylpiperidin-4-yl](ethyl)amino}-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-5-fluoro-2-methylbenzamide**



[0989] To a stirred solution of methyl 3-{[(2R,4R,6S)-1-benzyl-2,6-dimethylpiperidin-4-yl](ethyl)amino}-5-fluoro-2-methylbenzoate (48.5 mg, 0.118 mmol) in ethanol (1.5 mL) was added aq. NaOH (5 M, 47.0 ul, 0.235 mmol). The reaction mixture was stirred at 80 ^{0}C for 1.5 hours. After cooling to rt, solvent was removed in vacuo and dried under reduced pressure. To a stirred solution of this residue and 3-(aminomethyl)-4,6-dimethyl -1,2-dihydropyridin-2-one HCl salt (28.8 mg, 0.153 mmol) in DMSO (1 mL) was added PyBOP (91.8 mg, 0.176 mmol) and Hunig's base (102 ul, 0.588 mmol). The reaction mixture was stirred at 23°C for 13.5 hours. The reaction mixture was quenched with water, and the mixture was extracted with

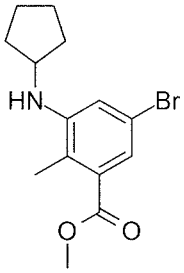
ethylacetate. The organic layer was washed with water (2 x 10 mL) and brine (1 x 10 mL). The organic layer was dried over $MgSO_4$, filtered and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (NH SiO_2, ethylacetate/MeOH=50/1 to 8/1) to give title compound as a white solid (50.1 mg, 79% yield). MS(ES) [M+H] 533.3.

[0990] **Example 1:** Synthesis of Compound 1: 5-bromo-3-(cyclopentylamino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide



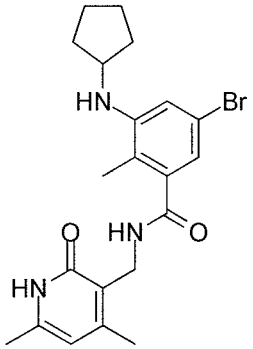
Compound 1

[0991] Step 1: Synthesis of methyl 5-bromo-3-(cyclopentyl(methyl)amino)-2-methylbenzoate



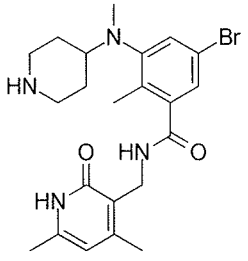
[0992] To a stirred solution of methyl 5-bromo-3-(cyclopentylamino)-2-methylbenzoate (0.5 g, 1.75 mmol) in acetonitrile (10 mL), Cs_2CO_3 (1.02 g, 2.63 mmol) and methyl iodide (1.45 g, 3.5 mmol) were added to it. The resulting reaction mixture was stirred at 80°C for 4 h. Upon completion, the solvent was removed under reduced pressure and residue dissolved in water and extracted with ethyl acetate. Crude material obtained was purified by column chromatography over silica gel affording the desired compound product without further purification (0.39 g).

[0993] Step 2: Synthesis of 5-bromo-3-(cyclopentylamino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide



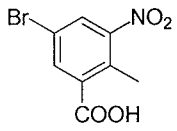
[0994] To a stirred solution of methyl 5-bromo-3-(cyclopentyl(methyl)amino)-2-methylbenzoate (1 equiv.) in ethanol (5 mL), aqueous NaOH solution (1 equiv.) was added and reaction stirred at 60°C for 4 h. On completion, ethanol was removed under reduced pressure and residue acidified with 1N HCl to pH 6. The aqueous phase was extracted with 10% MeOH/DCM. Combined organic layers were dried over sodium sulfate and solvent removed under reduced pressure affording pure acid (yield 50-60%). To a solution of this acid (1 equiv.) in DMSO (1.5 mL), PyBOP (1.5 equiv.) was added and reaction stirred at room temperature for 15 min. Then 3-(aminomethyl)-4,6-dimethylpyridin-2(1H)-one (2 equiv.) was added and reaction stirred overnight. On completion, water was added and the resulting solid precipitate filtered and washed with water. Then this solid was stirred with acetonitrile for 10 min and filtered again to obtain pure target molecule (yield 50-60%). LCMS: 446.15 $(M + 1)^+$; HPLC: 94.48% (@ 254 nm) (R_t;5.257); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.47 (s, 1H), 8.20 (t, 1H, J=4.8 Hz), 7.25 (s, 1H), 7.04 (s, 1H), 5.85 (s, 1H), 4.23 (d, 2H, J=4.8 Hz), 3.37-3.45 (m, 1H), 2.49 (3H merged in solvent peak), 2.17 (s, 3H), 2.13 (s, 3H), 2.10 (s, 3H), 1.53-1.67 (m, 4H), 1.38-1.50 (m, 4H).

[0995] **Example 2:** Synthesis of Compound 2: 5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(methyl(piperidine-4-yl)amino)benzamide



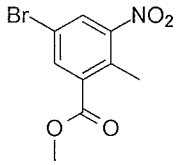
Compound 2

[0996] Step 1: 5-bromo-2-methyl-3-nitrobenzoic acid



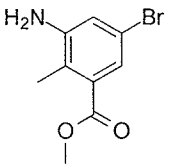
[0997] To stirred solution of 2-methyl-3-nitrobenzoic acid (50 g, 276.2 mmol) in conc. H_2SO_4 (200 mL), 1,3-dibromo-5,5-dimethyl-2,4-imidazolidinedione (43.4 g, 151.8 mmol) was added portion wise at room temperature and reaction mass was stirred at room temperature for 5 h. On completion, reaction mass was poured on ice cold water, solid precipitated was filtered, resulting residue was washed with water and dried under vacuum giving the desired compound (71.7 g, 99.9%) which was used for further reaction.

[0998] Step 2: methyl 5-bromo-2-methyl-3-nitrobenzene



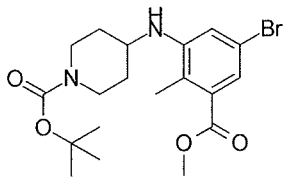
[0999] To a stirred solution of 5-bromo-2-methyl-3-nitrobenzoic acid (287 g, 1103 mmol) in DMF (150 mL), sodium carbonate (468 g, 4415 mmol) and methyl iodide (626.63 g, 4415 mmol) were added. Resulting reaction mass was heated at 60 °C for 8 h. On completion, solid precipitated was filtered, residue washed with diethyl ether (5 times). Combined organic layers were dried, concentrated under reduced pressure giving the desired compound (302 g, 99%) which was used for further reaction.

[01000] Step 3: methyl 3-amino-5-bromo-2-methylbenzoate



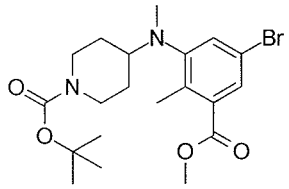
[01001] To a stirred solution of methyl 5-bromo-2-methyl-3-nitrobenzene (150 g, 544 mmol) in ethanol (750 mL), ammonium chloride (150 g, 2777 mmol) dissolved in water (750 mL) and iron powder (93.3 g, 1636 mmol) were added under stirring. Resulting reaction mass was heated at 80 °C for 7 h. On completion, reaction mass was filtered through celite giving washing of water and ethyl acetate, filtrate was extracted with ethyl acetate. The combined organic layers were dried, concentrated under reduced pressure giving the desired compound.

[01002] Step 4: tert-butyl 4-((5-bromo-3-(methoxycarbonyl)amino)piperidine-1-carboxylate



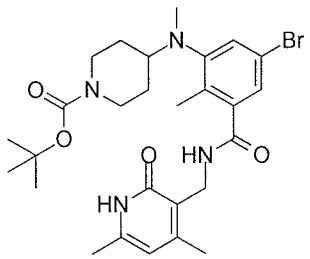
[01003] To a stirred solution of above crude methyl 3-amino-5-bromo-2-methylbenzoate (5 g, 20.57 mmol) and tert-butyl 4-oxopiperidine-1-carboxylate (8.2 g, 41.15 mmol) in methanol (50 mL), acetic acid (1.2 g, 20.57 mmol) was added and reaction stirred at room temperature for 3 h. Then sodium cyanoborohydride (1.55 g, 24.6 mmol) was added at 0 °C and reaction stirred overnight at room temperature. On completion, solvent was removed under reduced pressure and crude material was purified by column chromatography to afford compound **5** (5 g, 57%).

[01004] Step 5: tert-butyl 4-((5-bromo-3-(methoxycarbonyl)-2-methylphenyl (methyl)amino)piperidine-1-carboxylate



[01005] To a stirred solution of tert-butyl 4-((5-bromo-3-(methoxycarbonyl)amino)piperidine-1-carboxylate (3 g, 7.06 mmol) in acetonitrile (25 mL), cesium carbonate (4.57 g, 14.11 mmol) and methyl iodide (5 g, 35.2 mmol) were added; resulting reaction mass was heated at 80 °C for 7 h. On completion, reaction mass was cooled to room temperature and filtered, residue was washed with ethyl acetate and filtrate was concentrated and then purified by column chromatography to afford the desired compound (2.5 g, 81%).

[01006] Step 6: tert-butyl 4-((5-bromo-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(methyl)amino)piperidin-1-carboxylate

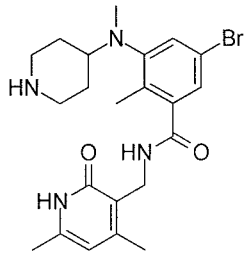


[01007] Aqueous NaOH (0.37 g, 9.38 mmol) was added to a solution of tert-butyl 4-((5-bromo-3-(methoxycarbonyl)-2-methylphenyl (methyl)amino)piperidine-1-carboxylate (2 g, 4.69 mmol) in MeOH (20 mL) and stirred at 60 °C for 1 h. After completion of the reaction,

ethanol was removed under reduced pressure and acidified using dilute HCl up to pH 6 and pH 4 was adjusted using citric acid. Extraction was carried out using ethyl acetate. Combined organic layers were dried concentrated giving respective acid (1.7 g, 90%).

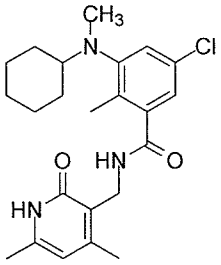
[01008] The acid (1.7 g, 4.22 mmol) was then dissolved in DMSO (10 mL) and 3-(amino methyl)-4,6-dimethylpyridin-2(1H)-one (1.42 g, 9.38 mmol) was added to it. The reaction mixture was stirred at room temperature for 15 min before PYBOP (3.66 g, 7.04 mmol) was added to it and stirring was continued for overnight. After completion, reaction mass was poured into ice to obtain solid, this was filtered and washed with acetonitrile followed by purification with column chromatography to afford the desired compound (1.3 g, 50%).

[01009] Step 7: 5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(methyl(piperidine-4-yl)amino)benzamide



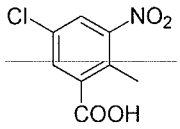
[01010] A stirred solution of tert-butyl 4-((5-bromo-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(methyl)amino)piperidin-1-carboxylate (1.3 g, 2.39 mmol) in DCM (10 mL) was cooled to 0°C and TFA (2 mL) was added to it. Reaction mass was stirred at room temperature for 1 h. On completion, reaction was concentrated to dryness. Residue was basified with aqueous sodium bicarbonate till pH 8 and aqueous layer extracted with 20% MeOH/DCM. Combined organic layers were dried over sodium sulfate and concentrated to afford the desired compound (0.9 g, 85%). LCMS: 461.15 $(M + 1)^+$; HPLC: 98.52% (@ 254 nm) (R_t;4.673; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 μ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 μL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.22 (t, 1H), 7.19 (s, 1H), 7.01 (s, 1H), 5.85 (s, 1H), 4.23 (d, 2H, J=4 Hz), 2.91 (d, 2H, J=11.6 Hz), 2.78 (bs, 1H), 2.55 (s, 3H), 2.32-2.35 (m, 2H), 2.18 (s, 3H), 2.10 (s, 6H), 1.44-1.50 (m, 4H).

[01011] **Example 3:** Synthesis of Compound 3: 5-chloro-3-(cyclohexyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide



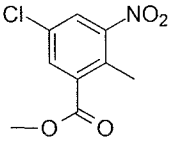
Compound 3

[01012] Step 1: 5-chloro-2-methyl-3-nitrobenzoic acid



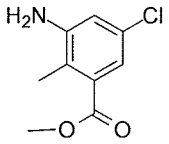
[01013] 5-Chloro-2-methylbenzoic acid (4 g, 23.39 mmol) was added to cooled conc. H_2SO_4 (27 mL) at -10 °C lot wise. After 10 minutes nitrating mixture {prepared as mixing Conc. HNO3 (3.3 g, 52.68 mmol) with conc.H_2SO_4 (4.4 mL)} was added drop wise at -10 °C. Resulting reaction mass was stirred at -10 °C for 30 minutes. On completion, reaction mixture was poured on ice cold water, solid precipitated was filtered, washed with water and dried under vacuum giving desired compound (4.95 g, 99%).

[01014] Step 2: methyl 5-chloro-2-methyl-3-nitrobenzoate



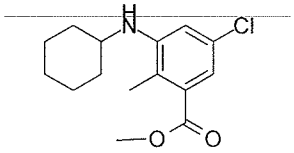
[01015] To stirred solution of 5-chloro-2-methyl-3-nitrobenzoic acid (6.75 g, 31.25 mmol) in DMF (33 mL), sodium carbonate (13.23 g, 125.18 mmol) and methyl iodide (17.77 g, 125.2 mmol) were added. Resulting reaction mass was heated at 60 °C for 4 h. On completion, water was added to the reaction mass and extraction was carried out using DCM. Combined organic layers were dried, concentrated under reduced pressure and purified by column chromatography over silica (60-120 mesh size) giving desired compound (6 g, 83%).

[01016] Step 3: methyl 3-amino-5-chloro-2-methyl benzoate



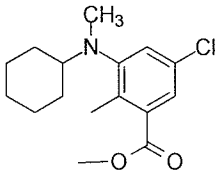
[01017] To stirred solution of methyl 5-chloro-2-methyl-3-nitrobenzoate (6 g, 26.13 mmol) in ethanol (60 mL), ammonium chloride (6 g, 112.1 mmol) dissolved in water (60 mL) and iron powder (11.88 g, 208.4 mmol) were added under stirring. Resulting reaction mass was heated at 80 °C for 1 h. On completion, water was added to reaction mass and reaction mixture was filtered through celite, filtrate was extracted with ethyl acetate. Combined organic layers were washed with water, dried, concentrated under reduced pressure giving desired compound.

[01018] Step 4: methyl 5-chloro-3-(cyclohexylamino)-2-methylbenzoate



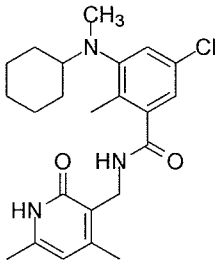
[01019] To a stirred solution of methyl 3-amino-5-chloro-2-methyl benzoate (1 g, 5.025 mmol) and cyclohexanone (0.739 g, 7.75 mmol) in methanol (10 mL), acetic acid (0.301 g, 5.02 mmol) was added and reaction stirred at room temperature for 3 h. Then sodium cyanoborohydride (390 mg, 0.00621 mmol) was added and reaction stirred overnight. On completion, solvent was removed under reduced pressure and crude material was purified by column chromatography to afford the desired compound (1.4 g, contaminated with cyclohexanone).

[01020] Step 5: methyl 5-chloro-3-(cyclohexyl(methyl)amino)-2-methylbenzoate (6):



[01021] To a stirred solution of methyl 5-chloro-3-(cyclohexylamino)-2-methylbenzoate (1.4 g, 0.0049 mole) in acetonitrile (10 mL), cesium carbonate (3.2 g, 0.0099 mole) and methyl iodide (3.5 g, 0.0024 mole) were added; resulting reaction mass was heated at 80 °C for 13 h. On completion, reaction mass was cooled to room temperature and filtered, residue was washed with ethyl acetate and filtrate was concentrated and then purified by column chromatography to afford desired compound (800 mg, 55%).

[01022] Step 6: 5-chloro-3-(cyclohexyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide

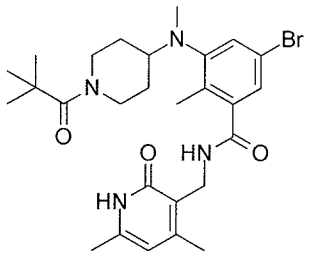


[01023] Aqueous NaOH (0.16 g, 4.06 mmol) was added to a solution of compound **6** (0.8 g, 2.71 mmol) in EtOH (5 mL) and stirred at 60 °C for 1 h. After completion of the reaction, ethanol was removed under reduced pressure and acidified using dilute HCl up to pH 6 and pH 4 was adjusted using citric acid. Extraction was carried out using ethyl acetate. Combined organic layers were dried concentrated giving respective acid (0.7 g, 91%).

[01024] The acid (0.7 g, 2.49 mmol) was then dissolved in DMSO (2 mL) and 3-(amino methyl)-4,6-dimethylpyridin-2(1H)-one (0.752 g, 4.98 mmol) was added to it. The reaction mixture was stirred at room temperature for 15 min before PYBOP (1.9 g, 3.73 mmol) was added to it and stirring was continued for overnight. After completion of the reaction, reaction mass was poured into ice to obtain solid, this was filtered and washed with acetonitrile followed column purification to provide the title compound (0.250 g, 25 %).

[01025] LCMS: 416.35 $(M + 1)^+$; HPLC: 99.01% (@ 254 nm) (R_t;5.408; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 µ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 µL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.46 (s, 1H), 8.20 (t, 1H, J=4.8 Hz), 7.05 (d, 1H, J=2 Hz), 6.88 (d, 1H, J=2 Hz), 5.85 (s, 1H), 4.24 (d, 2H, J=4.8 Hz), 2.70 (m, 1H), 2.56 (s, 3H), 2.18 (s, 3H), 2.12 (s, 3H), 2.10 (s, 3H), 1.75-1.35 (m, 7H), 1.25-1.05 (m, 3H).

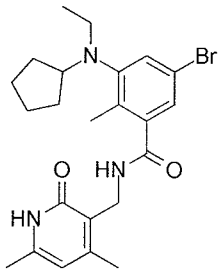
[01026] **Example 4:** Synthesis of Compound 4: 5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(methyl(1-pivaloylpiperidin-4-yl)amino)benzamide



Compound 4

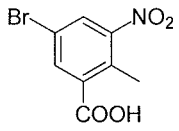
[01027] To a stirred solution of 5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(methyl(piperidine-4-yl)amino)benzamide (0.05 g, 0.112 mmol) in DMF (2 mL), EDCI.HCl (0.064 g, 0.336 mmol), HOBt (0.03 g, 0.22 mmol), triethyl amine (0.03 g, 0.336 mmol) and pivalic acid (0.023 g, 0.224 mmol) were added at room temperature and stirred at same temperature for 18 h. On completion, water was added and extracted with 10% MeOH/DCM. Combined organic layers were dried, concentrated giving crude material; which then purified by column chromatography to afford the desired compound (0.03g, 56%). LCMS: 545.20 $(M + 1)^+$; HPLC: 98.60% (@ 254 nm) (R_t;6.355; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 μ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 μL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.46 (s, 1H), 8.20 (t, 1H, J=4.4 Hz), 7.25 (d, 1H, J=2.8 Hz), 7.05 (d, 1H, J=1.2 Hz), 5.85 (s, 1H), 4.23-4.25 (m, 4H), 3.00 (m, 1H), 2.76 (t, 2H, J=12.4 Hz), 2.54 (s, 3H), 2.18 (s, 3H), 2.14 (s, 3H), 2.10 (s, 3H), 1.62-1.65 (m, 2H), 1.42-1.48 (m, 2H), 1.18 (s, 9H).

[01028] **Example 5:** Synthesis of Compound 5: 5-bromo-3-(cyclopentyl(ethyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide



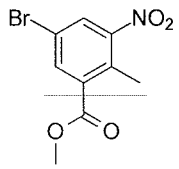
Compound 5

[01029] Step 1: 5-bromo-2-methyl-3-nitrobenzoic acid



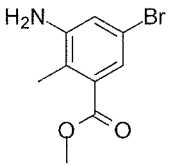
[01030] To a mixture of 2-methyl-3-nitrobenzoic acid (15 g, 82.80 mmol) in conc. H_2SO_4 (60 mL), 1,3-dibromo-5,5-dimethyl 2,4-imidazolidinedione (13.07 g, 45.71 mmol) was added and reaction mixture was stirred at room temperature for 5 h. Then reaction mixture was slowly poured in to 400 mL of ice cold water. Solid that precipitated out was filtered, washed and dried under vacuum the desired compound (21 g, 98.22%).

[01031] Step 2: methyl 3-bromo-5-nitrobenzoate (3):



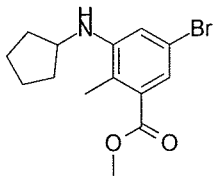
[01032] To a stirred solution of 5-bromo-2-methyl-3-nitrobenzoic acid (16 g, 61.54 mmol) in DMF (160 mL), iodomethane (35.72 g, 248 mmol) and sodium carbonate (26.28 g, 248 mmol) were added. Resulting reaction mass was stirred at 60° C for 8 h. On completion, reaction mass was filtered and inorganic solid residue washed with ethyl acetate. Combined filtrates were concentrated under vacuum till dryness. The residue was re-dissolved in ethyl acetate and washed with 5% sodium bicarbonate solution (700 mL) followed by 5M HCl solution (300 mL). Organic layer was finally washed with brine, dried over sodium sulfate and concentrated to afford desired compound (16 g, 95%).

[01033] Step 3: ethyl 3-amino-5-bromobenzoate



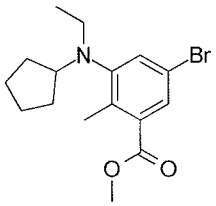
[01034] To a stirred solution of methyl 3-bromo-5-nitrobenzoate (17 g, 62.04 mmol) in ethanol (85 mL), was added NH_4Cl solution (17 g in 85 mL water, 317.8 mmol) followed by Fe powder (27.82 g, 498.12 mmol). Resulting reaction mass was stirred at 90° C for 1 h. On completion, reaction mass was filtered and filtrate concentrated till dryness to get solid which was dissolved in sat. sodium bicarbonate solution. Aqueous layer was extracted with ethyl acetate (3X50 mL). Combined organic layers were dried over sodium sulfate and concentrated to afford the desired compound (15 g, 99.14%).

[01035] Step 4: methyl 3-bromo-5-(cyclopentylamino)benzoate



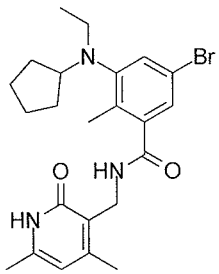
[01036] To a stirred solution of ethyl 3-amino-5-bromobenzoate (2 g, 8.73 mmol) and cyclopentanone (2.2 g, 26.1 mmol) in methanol (20 mL), acetic acid (1.04 g, 17.4 mmol) was added and reaction stirred at room temperature for 3 h. Then sodium cyanoborohydride (1.37 g, 21.83 mmol) was added and reaction stirred overnight. On completion, solvent was removed under reduced pressure and crude material was purified by column chromatography to afford desired compound (1.6 g, 61%).

[01037] Step 5: methyl 5-bromo-3-(cyclopentyl(ethyl)amino)-2-methylbenzoate



[01038] To a stirred solution of methyl 3-bromo-5-(cyclopentylamino)benzoate (0.3 g, 0.96 mmol) in DMF (5 mL), cesium carbonate (0.628 g, 1.92 mmol) and ethyl iodide (0.748 g, 4.8 mmol) were added; resulting reaction mass was heated at 80 °C for 24h. On completion, reaction mass was cooled to room temperature and filtered, residue was washed with ethyl acetate and filtrate was concentrated and then purified by column chromatography to afford desired compound (0.150 g, 46 %).

[01039] Step 6: 5-bromo-3-(cyclopentyl(ethyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide

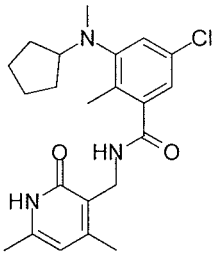


[01040] Aqueous NaOH (0.03 g, 0.75 mmol) was added to a solution of methyl 5-bromo-3-(cyclopentyl(ethyl)amino)-2-methylbenzoate (0.170 g, 0.75 mmol) in EtOH (10 mL) and

stirred at 60 °C for 1 h. After completion of the reaction, ethanol was removed under reduced pressure and acidified using dilute HCl up to pH 6. Extraction was carried out using ethyl acetate. Combined organic layers were dried concentrated giving respective acid (0.15 g, 92.59 %).

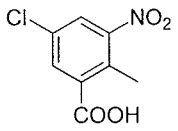
[01041] The acid (0.15 g, 0.461 mmol) was then dissolved in DMSO (5 mL) and 3-(amino methyl)-4,6-dimethylpyridin-2(1H)-one (0.14 g, 0.923 mmol) was added to it. The reaction mixture was stirred at room temperature for 15 min before PYBOP (0.35 g, 0.692 mmol) was added to it and stirring was continued for overnight. After completion of the reaction, reaction mass was poured into ice to obtain solid, this was filtered and washed with acetonitrile followed by HPLC purification to provide the title compound (0.050 g, 24%) as the TFA salt.: LCMS: 460.10 $(M + 1)^+$; HPLC: 99.22% (@ 254 nm) (R_t;5.115; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 μ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 μL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.47 (s, 1H), 8.24 (s, 1H), 7.32 (s, 1H), 7.09 (s, 1H), 5.86 (s, 1H), 4.24 (d, 2H, J=4.8 Hz), 3.47-3.48 (m, 1H), 2.96 (m, 2H), 2.18 (s, 3H), 2.15 (s, 3H), 2.10 (s, 3H), 1.33-1.63 (m, 8H), 0.78 (t, 3H, J=6.4 Hz).

[01042] **Example 6:** Synthesis of Compound 7: 5-chloro-3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide



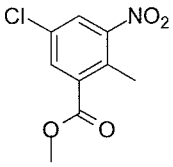
Compound 7

[01043] Step 1: Synthesis of 5-chloro-2-methyl-3-nitrobenzoic acid



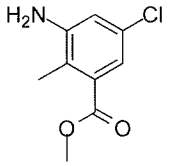
[01044] 5-chloro-2-methylbenzoic acid (4 g, 23.4 mmol) was added to cooled conc. H_2SO_4 (27 mL) at -10 °C in small portions and stirred for 10 minutes. Nitrating mixture {prepared by mixing Conc. HNO3 (3.3 g, 52.68 mmol) with conc.H_2SO_4 (4.4 mL)} was added drop wise at -10 °C. The resulting mixture was stirred at -10 °C for 30 minutes. On completion, the reaction mixture was poured into ice cold water, the solid was collected by filtration, washed with water and dried under vacuum to give 5-chloro-2-methyl-3-nitrobenzoic acid (4.95 g, 99%).

[01045] Step 2: Synthesis of methyl 5-chloro-2-methyl-3-nitrobenzoate



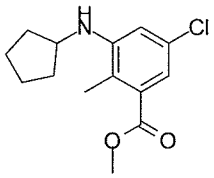
[01046] To a stirred solution of 5-chloro-2-methyl-3-nitrobenzoic acid, prepared analogously to above, (6.75 g, 31.3 mmol) in DMF (33 mL) was added sodium carbonate (13.2 g, 125 mmol) and methyl iodide (17.8 g, 125 mmol). The resulting mixture was heated at 60 °C for 4 h. On completion, water was added to the mixture and extraction was carried out using DCM. Combined organic layers were dried, concentrated under reduced pressure and purified by column chromatography over silica to give methyl 5-chloro-2-methyl-3-nitrobenzoate (6 g, 83.6%).

[01047] Step 3: Synthesis of methyl 3-amino-5-chloro-2-methyl benzoate



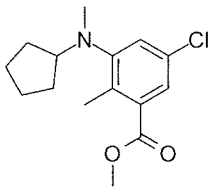
[01048] To a stirred solution of methyl 5-chloro-2-methyl-3-nitrobenzoate (6 g, 26.1 mmol) in ethanol (60 mL), was added ammonium chloride (6 g, 112 mmol) dissolved in water (60 mL) and iron powder (11.9 g, 208 mmol). The resulting mixture was heated at 80 °C for 1 h. On completion, water was added to mixture and reaction mixture was filtered through celite, and the filtrate was extracted with ethyl acetate. Combined organic layers were washed with water, dried, and concentrated under reduced pressure to give methyl 3-amino-5-chloro-2-methyl benzoate.

[01049] Step 4: Synthesis of methyl 5-chloro-3-(cyclopentylamino)-2-methylbenzoate



[01050] To a stirred solution of methyl 3-amino-5-chloro-2-methyl benzoate (1 g, 5.0 mmol) and cyclopentanone (2.1 g, 25.0 mmol) in methanol (10 mL) was added acetic acid (0.6 g, 5.0 mmol), and the mixture was stirred at room temperature for 3 h. Then sodium cyanoborohydride (0.78 g, 12.5 mmol) was added and the reaction stirred overnight. On completion, solvent was removed under reduced pressure and crude material was purified by column silica chromatography to afford methyl 5-chloro-3-(cyclopentylamino)-2-methylbenzoate (1.2 g, 89%).

[01051] Step 5: Synthesis of methyl 5-chloro-3-(cyclopentyl(methyl)amino)-2-methylbenzoate



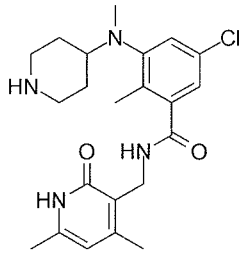
[01052] To a stirred solution of methyl 5-chloro-3-(cyclopentylamino)-2-methylbenzoate (0.5 g, 1.86 mmol) in acetonitrile (5 mL) was added cesium carbonate (1.22 g, 3.7 mmol) and methyl iodide (1.32 g, 9.33 mmol). The resulting mixture was heated at 80 °C for 12 h. On completion, the mixture was cooled to room temperature and filtered, the residue was washed with ethyl acetate and the filtrate was concentrated and then purified by column chromatography to afford methyl 5-chloro-3-(cyclopentyl(methyl)amino)-2-methylbenzoate (0.5 g, 95%).

[01053] Step 6: Synthesis of 5-chloro-3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide

[01054] Aqueous NaOH (0.106 g, 2.66 mmol) was added to a solution of methyl 5-chloro-3-(cyclopentyl(methyl)amino)-2-methylbenzoate (0.5 g, 1.77 mmol) in MeOH (5 mL) and stirred at 60 °C for 1 h. After completion of the reaction, methanol was removed under reduced pressure and acidified using dilute HCl up to pH 6 and pH 4 was adjusted using citric acid. Extraction was carried out using ethyl acetate. Combined organic layers were dried concentrated giving respective acid (0.4 g, 84%).

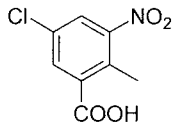
[01055] The acid (0.1 g, 0.37 mmol) was then dissolved in DMSO (0.5 mL) and 3-(amino methyl)-4,6-dimethylpyridin-2(1H)-one (0.114 g, 0.74 mmol) was added to it. The reaction mixture was stirred at room temperature for 15 min before PYBOP (0.29 g, 0.56 mmol) was added to it and stirring was continued for overnight. After completion of the reaction, mixture was poured into ice to obtain a solid, this was filtered and washed with acetonitrile followed column purification to provide 5-chloro-3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide (100 mg, 66%). LCMS: 402.15 $(M+1)^+$; HPLC: 96.46% (@ 254 nm) (R_t;5.289; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 µ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 µL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.45 (s, 1H), 8.19 (t, 1H, J=4.8 Hz), 7.13 (d, 1H, J=2 Hz), 6.91 (d, 1H, J=2 Hz), 5.85 (s, 1H), 4.23 (d, 2H, J=5.2 Hz), 3.41-3.45 (m, 1H), 2.50 (3H merged in solvent peak), 2.18 (s, 3H), 2.15 (s, 3H), 2.10 (s, 3H), 1.38-1.67 (m, 8H).

[01056] **Example 7:** Synthesis of Compound 8: 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(methyl(piperidin-4-yl)amino)benzamide



Compound 8

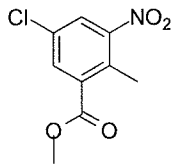
[01057] Step 1: 5-chloro-2-methyl-3-nitrobenzoic acid



[01058] 5-Chloro-2-methylbenzoic acid (4 g, 23.39 mmol) was added to cooled conc. H_2SO_4 (27 mL) at -10 °C lot wise. After 10 minutes nitrating mixture {prepared as mixing Conc. HNO3 (3.3 g, 52.68 mmol) with conc.H_2SO_4 (4.4 mL)} was added drop wise at -10 °C. Resulting reaction mass was stirred at -10 °C for 30 minutes. On completion, reaction mixture

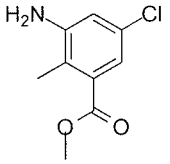
was poured on ice cold water, solid precipitated was filtered, washed with water and dried under vacuum giving desired compound (4.95 g, 99%).

[01059] Step 2: methyl 5-chloro-2-methyl-3-nitrobenzoate



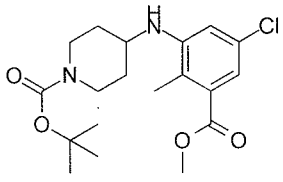
[01060] To stirred solution of 5-chloro-2-methyl-3-nitrobenzoic acid (6.75 g, 31.25 mmol) in DMF (33 mL), sodium carbonate (13.23 g, 125.18 mmol) and methyl iodide (17.77 g, 125.2 mmol) were added. Resulting reaction mass was heated at 60 °C for 4 h. On completion, water was added to the reaction mass and extraction was carried out using DCM. Combined organic layers were dried, concentrated under reduced pressure and purified by column chromatography over silica (60-120 mesh size) giving desired compound (6 g, 84%).

[01061] Step 3: methyl 3-amino-5-chloro-2-methyl benzoate



[01062] To stirred solution of methyl 5-chloro-2-methyl-3-nitrobenzoate (6 g, 26.13 mmol) in ethanol (60 mL), ammonium chloride (6 g, 112.1 mmol) dissolved in water (60 mL) and iron powder (11.88 g, 208.4 mmol) were added under stirring. Resulting reaction mass was heated at 80 °C for 1 h. On completion, water was added to reaction mass and reaction mixture was filtered through celite, filtrate was extracted with ethyl acetate. Combined organic layers were washed with water, dried, concentrated under reduced pressure giving the desired compound.

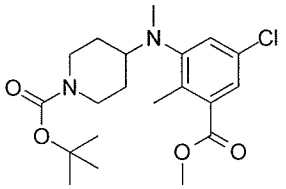
[01063] Step 4: tert-butyl 4-((5-chloro-3-(methoxycarbonyl)-2-methylphenyl)amino) piperidine-1-carboxylate



[01064] To a stirred solution of methyl 3-amino-5-chloro-2-methyl benzoate (6 g, 30.15 mmol) and tert-butyl 4-oxopiperidine-1-carboxylate (29 g, 150 mmol) in methanol (10 mL), acetic acid (1.8 g, 30.1 mmol) was added and reaction stirred at room temperature for 3 h. Then

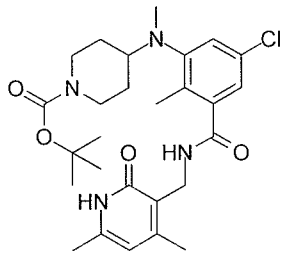
sodium cyanoborohydride (4.7 g, 75.3 mmol) was added and reaction stirred overnight. On completion, solvent was removed under reduced pressure and crude material was purified by column chromatography to afford the desired compound (4 g, 30%).

[01065] Step 5: tert-butyl 4-((5-chloro-3-(methoxycarbonyl)-2-methylphenyl) (methyl)amino)piperidine-1-carboxylate



[01066] To a stirred solution of tert-butyl 4-((5-chloro-3-(methoxycarbonyl)-2-methylphenyl)amino) piperidine-1-carboxylate (4 g, 9.09 mmol) in acetonitrile (50 mL), cesium carbonate (5.9 g, 18.09 mmol) and methyl iodide (6.95 g, 48.94 mmol) were added; resulting reaction mass was heated at 80 °C for 12 h. On completion, reaction mass was cooled to room temperature and filtered, residue was washed with ethyl acetate and filtrate was concentrated and then purified by column chromatography to afford the desired compound (2.2 g, 53%).

[01067] Step 6: tert-butyl 4-((5-chloro-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(methyl)amino)piperidine-1-carboxylate

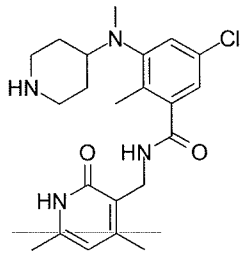


[01068] Aqueous NaOH (0.75 g, 1.86 mmol) was added to a solution of tert-butyl 4-((5-chloro-3-(methoxycarbonyl)-2-methylphenyl) (methyl)amino)piperidine-1-carboxylate (0.5 g, 1.26 mmol) in MeOH (5 mL) and stirred at 60 °C for 1 h. After completion of the reaction, ethanol was removed under reduced pressure and acidified using dilute HCl up to pH 6 and pH 4 was adjusted using citric acid. Extraction was carried out using ethyl acetate. Combined organic layers were dried concentrated giving respective acid (0.4 g, 84%).

[01069] The acid (0.4 g, 1.04 mmol) was then dissolved in DMSO (1 mL) and 3-(amino methyl)-4, 6-dimethylpyridin-2(1H)-one (0.316 g, 2.09 mmol) was added to it. The reaction

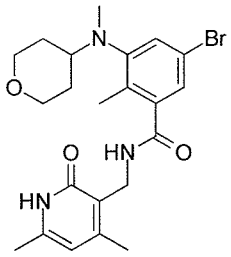
mixture was stirred at room temperature for 15 min before PYBOP (0.816 g, 1.56 mmol) was added to it and stirring was continued for overnight. After completion of the reaction, reaction mass was poured into ice to obtain solid, this was filtered and washed with acetonitrile followed column purification to provide the desired compound (0.225 g, 41 %).

[01070] Step 7: 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(methyl(piperidin-4-yl)amino)benzamide



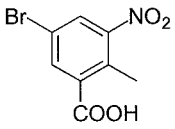
[01071] A stirred solution of tert-butyl 4-((5-chloro-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(methyl)amino)piperidine-1-carboxylate (0.2 g, 0.632 mmol) in DCM (5 mL) was cooled to 0°C and TFA (0.15 mL) was added to it. Reaction mass was stirred at room temperature for 1 h. On completion, reaction was concentrated to dryness. Residue was purified by solvent washings to afford the desired compound (0.14 g, 53 %) as its TFA salt. LCMS: 417.25 $(M + 1)^+$; HPLC: 96.16% (@ 254 nm) (R_t;4.677; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 µ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 µL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.47 (s, 1H), 8.49 (bs, 1H), 8.20 (t, 1H), 8.18 (bs, 1H), 7.19 (s, 1H), 6.96 (s, 1H), 5.86 (s, 1H), 4.25 (d, 2H, J=4.4 Hz), 3.25 (d, 2H, J=12 Hz), 3.08 (m, 1H), 2.88 (bs, 2H), 2.56 (s, 3H), 2.18 (s, 3H), 2.17 (s, 3H), 2.10 (s, 3H), 1.76 (bs, 4H).

[01072] **Example 8:** Synthesis of Compound 10: 5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(methyl(tetrahydro-2H-pyran-4-yl)amino)benzamide:



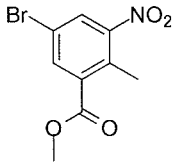
Compound 10

[01073] Step 1: Synthesis of 5-bromo-2-methyl-3-nitrobenzoic acid



[01074] To stirred solution of 2-methyl-3-nitrobenzoic acid (50 g, 276 mmol) in conc. H_2SO_4 (200 mL), 1,3-dibromo-5,5-dimethyl-2,4-imidazolidinedione (43.4 g, 152 mmol) was added portion wise at room temperature, and stirring was continued at room temperature for 5 h. On completion, the mixture was poured into ice cold water, the resulting solid was filtered, washed with water and dried under vacuum to give 5-bromo-2-methyl-3-nitrobenzoic acid (71.7 g, 99.9%).

[01075] Step 2: Synthesis of methyl 5-bromo-2-methyl-3-nitrobenzene

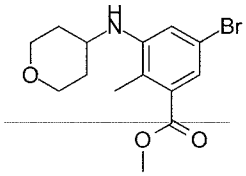


[01076] To stirred solution of 5-bromo-2-methyl-3-nitrobenzoic acid, prepared analogously to above, (287 g, 1103 mmol) in DMF (150 mL), sodium carbonate (468 g, 4415 mmol) and methyl iodide (626.6 g, 4415 mmol) were added. Resulting mixture was heated at 60 °C for 8 h. On completion, solid was remove by filtration, and the residue washed with diethyl ether (5 times). The combined organic layers were dried, concentrated under reduced pressure to give methyl 5-bromo-2-methyl-3-nitrobenzene (302 g, 99%).

[01077] Step 3: Synthesis of methyl 3-amino-5-bromo-2-methylbenzoate

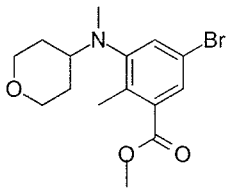
[01078] To a stirred solution of 5-bromo-2-methyl-3-nitrobenzene (150 g, 544 mmol) in ethanol (750 mL) was added a solution of ammonium chloride (150 g, 2777 mmol) in water (750 mL) and iron powder (93.3 g, 1636 mmol). The resulting mixture was heated at 80 °C for 7 h. On completion, mixture was filtered through celite; the celite was washed with water and ethyl acetate and the filtrate was extracted with ethyl acetate. Combined organic layers were dried, concentrated under reduced pressure to give methyl 3-amino-5-bromo-2-methylbenzoate.

[01079] Step 4: Synthesis of methyl 5-bromo-2-methyl-3-((tetrahydro-2H-pyran-4-yl)amino)benzoate



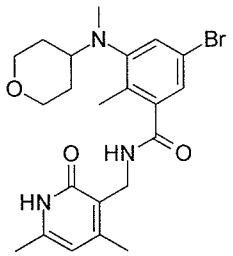
[01080] To a stirred solution of methyl 3-amino-5-bromo-2-methylbenzoate (2 g, 8.23 mmol) and dihydro-2H-pyran-4(3)-one (1.06 g, 10.6 mmol) in methanol (20 mL), acetic acid (0.5 g, 8.23 mmol) was added and the reaction stirred at room temperature for 3 h. Then sodium cyanoborohydride (0.622 g, 9.87 mmol) was added at 0 °C and reaction stirred overnight at room temperature. On completion, the solvent was removed under reduced pressure and the crude material was purified by column chromatography to afford methyl 5-bromo-2-methyl-3-((tetrahydro-2H-pyran-4-yl)amino)benzoate (1.6 g, 61%).

[01081] Step 5: Synthesis of methyl 5-bromo-2-methyl-3-(methyl(tetrahydro-2H-pyran-4-yl)amino)benzoate



[01082] To a stirred solution of methyl 5-bromo-2-methyl-3-((tetrahydro-2H-pyran-4-yl)amino)benzoate (0.4 g, 1.26 mmol) in acetonitrile (15 mL), cesium carbonate (0.79 g, 2.44 mmol) and methyl iodide (0.86 g, 6.11 mmol) were added; resulting mixture was heated at 80 °C for 7 h. On completion, the mixture was cooled to room temperature and filtered, the residue was washed with ethyl acetate and the filtrate was concentrated and then purified by column chromatography to afford Synthesis of methyl 5-bromo-2-methyl-3-(methyl(tetrahydro-2H-pyran-4-yl)amino)benzoate (0.33 g, 80%).

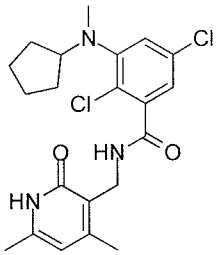
[01083] Step 6: Synthesis of 5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(methyl(tetrahydro-2H-pyran-4-yl)amino)benzamide



[01084] Aqueous NaOH (0.19 g, 4.89 mmol) was added to a solution of compound **6** (0.8 g, 2.4 mmol) in MeOH (20 mL) and stirred at 60 °C for 1 h. After completion of the reaction, ethanol was removed under reduced pressure and acidified using dilute HCl up to pH 6 and pH 4 was adjusted using citric acid. Extraction was carried out using ethyl acetate. Combined organic layers were dried concentrated giving respective acid (0.70 g, 92%).

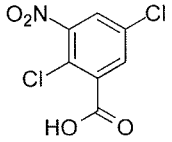
[01085] The acid (0.7 g, 2.24 mmol) was then dissolved in DMSO (3 mL) and 3-(amino methyl)-4,6-dimethylpyridin-2(1H)-one (0.74 g, 4.89 mmol) was added to it. The reaction mixture was stirred at room temperature for 15 min before PYBOP (1.9 g, 3.6 mmol) was added to it and stirring was continued for overnight. After completion, mixture was poured into ice to obtain a solid. The solid was filtered and washed with acetonitrile followed by purification with column chromatography to afford 5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(methyl(tetrahydro-2H-pyran-4-yl)amino)benzamide (0.53g, 54%). LCMS: 462.23 $(M + 1)^+$; HPLC: 98.57% (@ 254 nm) (R_t;5.276; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 µ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 µL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.46 (s, 1H), 8.20 (t, 1H, J=4.8 Hz), 7.24 (d, 1H, J=2 Hz), 7.04 (d, 1H, J=2 Hz), 5.85 (s, 1H), 4.24 (d, 2H, J=4.8 Hz), 3.84 (d, 2H, J=10.8 Hz), 3.22-3.28 (m, 2H), 2.96 (m, 1H), 2.56 (s, 3H), 2.18 (s, 3H), 2.13 (s, 3H), 2.10 (s, 3H), 1.52-1.61 (m, 4H).

[01086] **Example 9:** Synthesis of Compound 13: 2, 5-dichloro-3-(cyclopentyl (methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl) benzamide



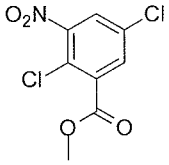
Compound 13

[01087] Step1: Synthesis of 2,5-dichloro-3-nitrobenzoic acid:



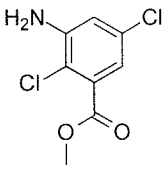
[01088] 2,5-dichlorobenzoic acid (5 g, 26.2 mmol) was added to cooled conc. H_2SO_4 (50 mL) at -10 °C in small portions. After 10 minutes nitrating mixture {prepared by mixing Conc. HNO_3 (2.5 mL) with conc.H_2SO_4 (10 mL)} was added drop wise at -10 °C. The resulting reaction mixture was stirred at -10 °C for 2 h. On completion, the reaction mixture was poured into ice cold water and a solid precipitated. The solid was collected by filtration, washed with water and dried under vacuum to give 2,5-dichloro-3-nitrobenzoic acid (3.4 g, 65%).

[01089] Step 2: Synthesis of methyl 2,5-dichloro-3-nitrobenzoate:



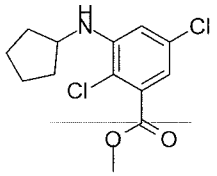
[01090] To stirred solution of 2,5-dichloro-3-nitrobenzoic acid (3.2 g, 13.67 mmol) in DMF (30 mL) was added sodium carbonate (4.3 g, 40.56 mmol) and methyl iodide (9.7 g, 68.30 mmol). The reaction mixture was heated at 60 °C for 18 h. On completion, water was added to the reaction mixture, and the product was extracted using DCM. The combined organic layers were dried and concentrated under reduced pressure to give methyl 2,5-dichloro-3-nitrobenzoate (3 g, 90%).

[01091] Step 3: Synthesis of methyl 3-amino-2,5-dichlorobenzoate:



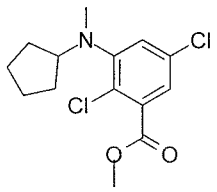
[01092] To stirred solution of methyl 2,5-dichloro-3-nitrobenzoate (3.3 g, 13.1 mmol) in ethanol (20 mL) was added ammonium chloride (3.5 g, 64.81 mmol) dissolved in water (20 mL) and iron powder (7 g, 82.35 mmol). The reaction mixture was heated at 80 °C for 3 h. On completion, water was added to the reaction mixture and the solids removed by filtration through celite. The filtrate was extracted with ethyl acetate. The combined organic layers were washed with water, dried, and concentrated under reduced pressure to give methyl 3-amino-2,5-dichlorobenzoate (2.5 g, 66 %).

[01093] Step 4: Synthesis of methyl 2, 5-dichloro-3-(cyclopentylamino) benzoate:



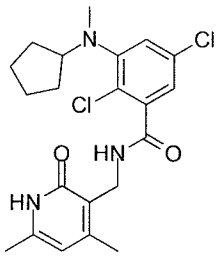
[01094] To a stirred solution of methyl 3-amino-2,5-dichlorobenzoate (2.5 g, 11.5 mmol) and cyclopentanone (4.8 g, 57.1 mmol) in methanol (5 mL) was added acetic acid (0.6 g, 11.3 mmol) and stirring was continued at room temperature for 3 h. Then sodium cyanoborohydride (1.4 g, 22.2 mmol) was added and the reaction stirred overnight. On completion, the solvent was removed under reduced pressure and the product was purified by column chromatography to afford methyl 2, 5-dichloro-3-(cyclopentylamino) benzoate (0.275 g, 8%).

[01095] Step 5: Synthesis of methyl 2, 5-dichloro-3-(cyclopentyl (methyl) amino) benzoate:



[01096] To a stirred solution of methyl 2, 5-dichloro-3-(cyclopentylamino) benzoate (0.275 g, 0.958 mmol) in acetonitrile (5 mL) was added cesium carbonate (0.622 g, 1.9 mmol) and methyl iodide (0.689 g, 4.78 mmol). The reaction mixture was heated at 80 °C for 18 h. On completion, the reaction was cooled to room temperature and filtered. The residue was washed with ethyl acetate and the filtrate was concentrated to afford methyl 2, 5-dichloro-3-(cyclopentyl (methyl) amino) benzoate (0.27 g, 93%).

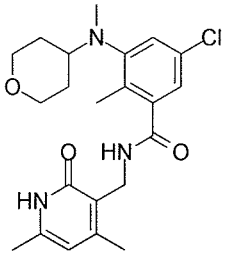
[01097] Step6: Synthesis of 2, 5-dichloro-3-(cyclopentyl (methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl) benzamide



[01098] Aqueous NaOH (0.50 g, 1.24 mmol) was added to a solution of methyl 2, 5-dichloro-3-(cyclopentyl (methyl) amino) benzoate (0.25 g, 0.83 mmol) in MeOH (5 mL) and stirred at 60 °C for 1 h. After completion of the reaction, methanol was removed under reduced pressure and acidified using dilute HCl up to pH 6 and to pH 4 using citric acid. The product was extracted using ethyl acetate. The combined organic layers were dried and concentrated to give the desired acid (0.21 g, 88%).

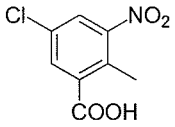
[01099] The acid (0.21 g, 0.755 mmol) was then dissolved in DMSO (3 mL) and 3-(amino methyl)-4,6-dimethylpyridin-2(1H)-one (0.3 g, 1.97 mmol) was added to it. The reaction mixture was stirred at room temperature for 15 min before PYBOP (0.757 g, 1.45 mmol) was added to it and stirring was continued for overnight. After completion of the reaction, reaction mixture was poured into ice to obtain a solid. The solid was filtered and washed with acetonitrile. The compound was further purified by prep. HPLC to afford 2, 5-dichloro-3-(cyclopentyl (methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl) benzamide (0.1 g, 36 %) as TFA salt. LCMS: 422.10 $(M + 1)^+$; HPLC: 97.58% (@ 254 nm) (R_t;6.973; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 μ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 μL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.46 (s, 1H), 8.35 (t, 1H), 7.23 (s, 1H), 6.98 (s, 1H), 5.85 (s, 1H), 4.24 (d, 2H, J=4.4 Hz), 3.66 (m, 1H), 2.59 (s, 3H), 2.18 (s, 3H), 2.10 (s, 3H), 1.70 (bs, 2H), 1.61 (bs, 2H), 1.48 (bs, 4H).

[01100] **Example 10:** Synthesis of Compound 14: 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(methyl(tetrahydro-2H-pyran-4-yl)amino)benzamide



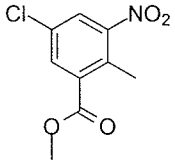
Compound 14

[01101] Step 1: 5-chloro-2-methyl-3-nitrobenzoic acid



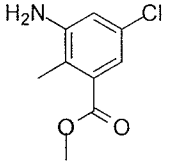
[01102] 2-Methyl-3-nitrobenzoic acid (4 g, 23.39 mmol) was added to cooled conc. H_2SO_4 (27 mL) at -10 °C lot wise. After 10 minutes nitrating mixture {prepared as mixing Conc. HNO3 (3.3 g, 52.68 mmol) with conc.H_2SO_4 (4.4 mL)} was added drop wise at -10 °C. Resulting reaction mass was stirred at -10 °C for 30 minutes. On completion, reaction mixture was poured on ice cold water, solid precipitated was filtered, washed with water and dried under vacuum giving desired compound (4.95 g, 99%).

[01103] Step 2: methyl 5-chloro-2-methyl-3-nitrobenzoate



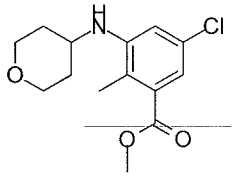
[01104] To a stirred solution of 5-chloro-2-methyl-3-nitrobenzoic acid (6.75 g, 31.25 mmol) in DMF (33 mL), sodium carbonate (13.23 g, 125.18 mmol) and methyl iodide (17.77 g, 125.2 mmol) were added. Resulting reaction mass was heated at 60 °C for 4 h. On completion, water was added to the reaction mass and extraction was carried out using DCM. Combined organic layers were dried, concentrated under reduced pressure and purified by column chromatography over silica (60-120 mesh size) giving desired compound (6 g, 84%).

[01105] Step 3: methyl 3-amino-5-chloro-2-methyl benzoate



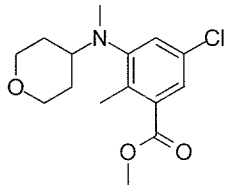
[01106] To stirred solution of methyl 5-chloro-2-methyl-3-nitrobenzoate (6 g, 26.13 mmol) in ethanol (60 mL), ammonium chloride (6 g, 112.1 mmol) dissolved in water (60 mL) and iron powder (11.88 g, 208.4 mmol) were added under stirring. Resulting reaction mass was heated at 80 °C for 1 h. On completion, water was added to reaction mass and reaction mixture was filtered through celite, filtrate was extracted with ethyl acetate. Combined organic layers were washed with water, dried, concentrated under reduced pressure giving desired compound which was used as is.

[01107] Step 4: methyl 5-chloro-2-methyl-3-((tetrahydro-2H-pyran-4-yl)amino) benzoate



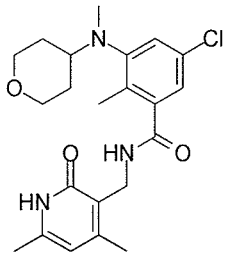
[01108] To a stirred solution of methyl 3-amino-5-chloro-2-methyl benzoate (1 g, 5.025 mmol) and dihydro-2H-pyran-4(3H)-one (753 mg, 7.537 mmol) in methanol (10 mL), acetic acid (301 mg, 5.025 mmol) was added and reaction stirred at room temperature for 3 h. Then sodium cyanoborohydride (373 mg, 6.03 mmol) was added and reaction stirred overnight. On completion, solvent was removed under reduced pressure and crude material was purified by column chromatography to afford the desired compound (700 mg, 49%).

[01109] Step 5: methyl 5-chloro-2-methyl-3-(methyl(tetrahydro-2H-pyran-4-yl)amino) benzoate



[01110] To a stirred solution of methyl 5-chloro-2-methyl-3-((tetrahydro-2H-pyran-4-yl)amino) benzoate (700 mg, 2.473 mmol) in acetonitrile (10 mL), cesium carbonate (1.61 g, 4.946 mmol) and methyl iodide (1.82 g, 0.8 ml, 12.36 mmol) were added; resulting reaction mass was heated at 80 °C for 13 h. On completion, reaction mass was cooled to room temperature and filtered, residue was washed with ethyl acetate and filtrate was concentrated and then purified by column chromatography to afford desired compound (480 mg, 65%).

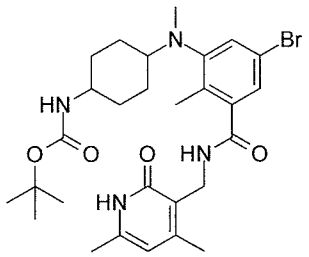
[01111] Step 6: 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(methyl(tetrahydro-2H-pyran-4-yl)amino)benzamide



[01112] Aqueous NaOH (96 mg, 2.424 mmol) was added to a solution of methyl 5-chloro-2-methyl-3-(methyl(tetrahydro-2H-pyran-4-yl)amino) benzoate (0.48 g, 1.616 mmol) in EtOH (2 mL) and stirred at 60 °C for 1 h. After completion of the reaction, ethanol was removed under reduced pressure and acidified using dilute HCl up to pH 6 and pH 4 was adjusted using citric acid. Extraction was carried out using ethyl acetate. Combined organic layers were dried concentrated giving respective acid (0.4 g, 87%).

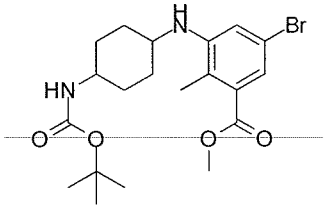
[01113] The acid (0.4 g, 1.41 mmol) was then dissolved in DMSO (1 mL) and 3-(amino methyl)-4,6-dimethylpyridin-2(1H)-one (0.429 g, 2.82 mmol) was added to it. The reaction mixture was stirred at room temperature for 15 min before PYBOP (1.10 g, 2.12 mmol) was added to it and stirring was continued for overnight. After completion of the reaction, reaction mass was poured into ice to obtain solid, this was filtered and washed with acetonitrile followed column purification to provide the title compound (0.17 g, 29 %): LCMS: 418.25 (M + 1)$^+$; HPLC: 97.72% (@ 254 nm) (R_t;5.022; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 μ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 μL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.48 (s, 1H), 8.21 (t, 1H, J=4.4 Hz), 7.13 (s, 1H), 6.92 (s, 1H), 5.85 (s, 1H), 4.24 (d, 2H, J=4.4 Hz), 3.84 (d, 2H, J=10.8 Hz), 3.25 (t, 2H, J=11.2 Hz), 2.96 (m, 1H), 2.56 (s, 3H), 2.18 (s, 3H), 2.15 (s, 3H), 2.10 (s, 3H), 1.65-1.52 (m, 4H).

[01114] **Example 11:** Synthesis of Compound 15: tert-butyl (4-((5-bromo-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(methyl)amino)cyclohexyl)carbamate



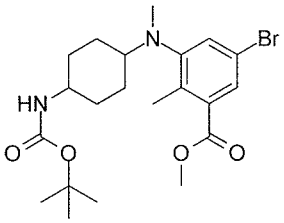
Compound 15

[01115] Step 1: Synthesis of methyl 5-bromo-3-((4-((tert-butoxycarbonyl)amino) cyclohexyl) amino)-2-methylbenzoate



[01116] To a stirred solution of methyl 3-amino-5-bromo-2-methylbenzoate (5 g, 20.6 mmol) and tert-butyl (4-oxocyclohexyl)carbamate (5.6 g, 26.7 mmol) in methanol (50 mL) was added acetic acid (1.2 g, 20.6 mmol) and the mixture was stirred at room temperature for 3 h. Then sodium cyanoborohydride (1.6 g, 26.7 mmol) was added and the reaction stirred overnight. On completion, the solvent was removed under reduced pressure and the product purified by column chromatography to afford compound methyl 5-bromo-3-((4-((tert-butoxycarbonyl)amino) cyclohexyl) amino)-2-methylbenzoate (3 g, 33.3%).

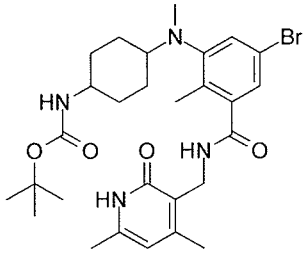
[01117] Step 2: Synthesis of methyl 5-bromo-3-((4-((tert-butoxycarbonyl) amino) cyclohexyl) (methyl) amino)- 2-methylbenzoate



[01118] To a stirred solution of methyl 5-bromo-3-((4-((tert-butoxycarbonyl)amino) cyclohexyl) amino)-2-methylbenzoate (1.5 g, 4.6 mmol) in acetonitrile (15 mL) was added cesium carbonate (2.63 g, 8.1 mmol) and methyl iodide (2.86 g, 20.32 mmol). The mixture was heated at 80 °C for 7 h. On completion, the reaction was cooled to room temperature, filtered, and the residue was washed with ethyl acetate. The filtrate was concentrated to afford

methyl 5-bromo-3-((4-((tert-butoxycarbonyl) amino) cyclohexyl) (methyl) amino)- 2-methylbenzoate (1.5 g).

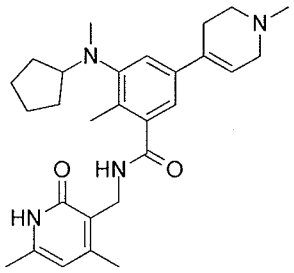
[01119] Step 3: Synthesis of tert-butyl (4-((5-bromo-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(methyl)amino)cyclohexyl)carbamate



[01120] Aqueous NaOH (0.26 g, 6.62 mmol) was added to a solution of methyl 5-bromo-3-((4-((tert-butoxycarbonyl) amino) cyclohexyl) (methyl) amino)- 2-methylbenzoate (1.5 g, 3.3 mmol) in MeOH (20 mL) and stirred at 60 °C for 1 h. After completion of the reaction, methanol was removed under reduced pressure and the mixture was acidified using dilute HCl up to pH 6 and to pH 4 using citric acid. The product was extracted with ethyl acetate. Combined organic layers were dried and concentrated to give the desired acid (1.33 g, 92%).

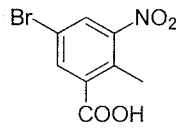
[01121] The acid (1.3 g, 2.96 mmol) was then dissolved in DMSO (10 mL) and 3-(amino methyl)-4,6-dimethylpyridin-2(1H)-one (0.34 g, 2.2 mmol) was added to it. The reaction mixture was stirred at room temperature for 15 min before PYBOP (0.88 g, 1.7 mmol) was added to it and stirring was continued for overnight. After completion of the reaction, the mixture was poured onto ice to obtain solid. The solid was filtered and washed with acetonitrile followed by purification with column chromatography to afford tert-butyl (4-((5-bromo-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(methyl)amino)cyclohexyl)carbamate. (0.5g, 26%). LCMS: 575.80 $(M + 1)^+$; HPLC: 99.99% (@ 254 nm) (R_t;6.094,7.065 [mixture of diastereomers]; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 µ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 µL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.45 (s, 1H), 8.20 (d, 1H, J=3.6 Hz), 7.21 (s, 1H), 7.18 (s, 1H), 7.01 (s, 1H), 6.66 (d, 1H, J=7.2 Hz), 5.85 (s, 1H), 4.23 (d, 2H, J=3.2 Hz), 3.44 (bs, 1H), 3.15 (bs, 1H), 2.55-2.66 (m, 3H), 2.18 (s, 3H), 2.10 (s, 6H), 1.76-1.79 (m, 2H), 1.51-1.63 (m, 3H), 1.36-1.38 (m, 11H), 1.07-1.16 (m, 1H).

[01122] **Example 12:** Synthesis of Compound 16: 3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-5-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)benzamide



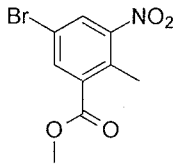
Compound 16

[01123] Step 1: 5-bromo-2-methyl-3-nitrobenzoic acid



[01124] To stirred solution of 2-methyl-3-nitrobenzoic acid (50 g, 276.2 mmol) in conc. H_2SO_4 (200 mL), 1,3-dibromo-5,5-dimethyl-2,4-imidazolidinedione (43.4 g, 151.8 mmol) was added portion wise at room temperature and reaction mass was stirred at room temperature for 5 h. On completion, reaction mass was poured on ice cold water, solid precipitated was filtered, resulting residue was washed with water and dried under vacuum giving the desired compound (71.7 g, 100%)

[01125] Step 2: methyl 5-bromo-2-methyl-3-nitrobenzene

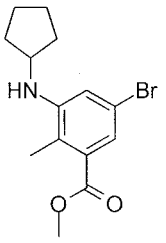


[01126] To stirred solution of 5-bromo-2-methyl-3-nitrobenzoic acid (287 g, 1103 mmol) in DMF (150 mL), sodium carbonate (468 g, 4415 mmol) and methyl iodide (626.63 g, 4415 mmol) were added. Resulting reaction mass was heated at 60 °C for 8 h. On completion, solid precipitated was filtered, residue washed with diethyl ether (5 times). Combined organic layers were dried, concentrated under reduced pressure giving the desired crude compound (302 g, 99%) which was used without further purification.

[01127] Step 3: methyl 3-amino-5-bromo-2-methylbenzoate

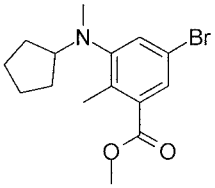
[01128] To a stirred solution of methyl 5-bromo-2-methyl-3-nitrobenzene (150 g, 544 mmol) in ethanol (750 mL), ammonium chloride (150 g, 2777 mmol) dissolved in water (750 mL) and iron powder (93.3 g, 1636 mmol) were added under stirring. Resulting reaction mass was heated at 80 °C for 7 h. On completion, reaction mass was filtered through celite giving washing of water and ethyl acetate, filtrate was extracted with ethyl acetate. Combined organic layers were dried, concentrated under reduced pressure giving the desired compound which was used further as is.

[01129] Step 4: methyl 5-bromo-3-(cyclopentylamino)-2-methylbenzoate



[01130] To a stirred solution of methyl 3-amino-5-bromo-2-methylbenzoate (0.3 g, 1.33 mmol) and cyclopentanone (0.56 g, 6.6 mmol) in methanol (3 mL), acetic acid (0.159 g, 2.6 mmol) was added and reaction stirred at room temperature for 3 h. Then sodium cyanoborohydride (0.208 g, 3.3 mmol) was added and reaction stirred overnight. On completion, solvent was removed under reduced pressure and crude material was used as is in the next step.

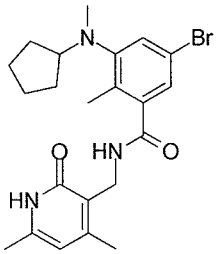
[01131] Step 5: Synthesis of methyl 5-bromo-3-(cyclopentyl(methyl)amino)-2-methylbenzoate



[01132] A solution of methyl 5-bromo-3-(cyclopentylamino)-2-methylbenzoate (1 g, 3.22 mmol) , Cs_2CO_3 (2.10 g,, 6.45 mmol) and methyl iodide (2.3 g, 16.12 mmol) in acetonitrile (15 mL) was heated at 80 °C for 14 h. After complete consumption of starting material reaction

mixture was filtered. The filtrate was concentrated and the obtained residue was purified by column chromatography to provide the desired compound (0.9 g, 86%).

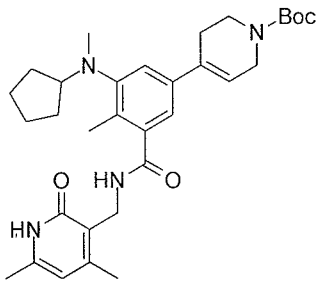
[01133] Step 6: 5-bromo-3-(cyclopentylamino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide



[01134] Aqueous NaOH (0.166 g, 4.15 mmol) was added to a solution of methyl 5-bromo-3-(cyclopentyl(methyl)amino)-2-methylbenzoate (0.9 g, 2.76 mmol) in EtOH (9 mL) and water (2.2 mL) and stirred at 60 °C for 1 h. After completion of the reaction, ethanol was removed under reduced pressure and acidified using dilute HCl up to pH 6 and pH 4 was adjusted using citric acid. Extraction was carried out using ethyl acetate. Combined organic layers were dried concentrated giving respective acid (0.85 g, 98%).

[01135] The acid (0.85 g, 2.73 mmol) was then dissolved in DMSO (10 mL) and 3-(amino methyl)-4,6-dimethylpyridin-2(1H)-one (0.83 g, 5.46 mmol) was added to it. The reaction mixture was stirred at room temperature for 15 min before PYBOP (2.13 g, 4.09 mmol) was added to it and stirring was continued for overnight. After completion of the reaction, reaction mass was poured into ice to obtain solid, this was filtered and washed with acetonitrile followed by ether to provide the desired compound (0.450 g, 37%).

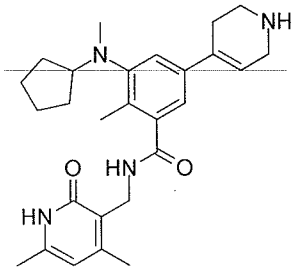
[01136] Step 7: tert-butyl 4-(3-(cyclopentyl(methyl)amino)-5-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-4-methylphenyl)-5,6-dihydropyridine-1(2H)-carboxylate



[01137] To a degassed solution of 5-bromo-3-(cyclopentylamino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide (1.0 g, 2.24 mmol) and boronic acid

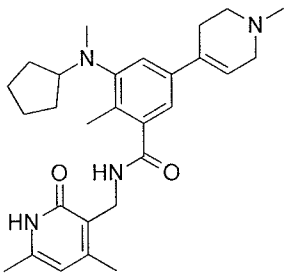
(0.833 g, 2.69 mmol) in dioxane (20 mL) was added $Pd(PPh_3)_4$ (0.260 g, 0.224 mmol, 0. 1eq) and the solution was again purged with argon for 20 min. To the reaction mixture Aq Na_2CO_3 (0.857, 8.08 mmol) solution in 1 mL water was added and reaction mixture was again purged with argon for 20 min. The reaction was heated at 100 °C for 90 min. The reaction mixture was then cooled to room temperature and poured in to cold water and extracted with dichloromethane. Crude compound purified by column chromatography to provide the desired compound (0.900 g, 64%).

[01138] Step 8: 3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-5-(1,2,3,6-tetrahydropyridin-4-yl)benzamide



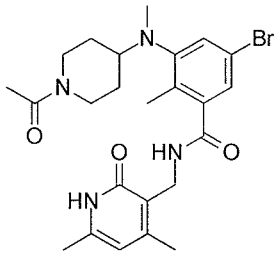
[01139] To a stirred solution of tert-butyl 4-(3-(cyclopentyl(methyl)amino)-5-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-4-methylphenyl)-5,6-dihydropyridine-1(2H)-carboxylate (0.800 g, 1.45 mmol) in DCM was added TFA (3 mL) and the reaction mixture was stirred at RT for 2h. On completion, reaction was concentrated to dryness. Residue was basified with aqueous sodium bicarbonate till pH 8 and aqueous layer extracted with 20% MeOH/DCM. Combined organic layers were dried over sodium sulfate and concentrated to afford crude material which was purified by preparative HPLC to afford the desired compound (0.620 g, 95%).

[01140] Step 9: 3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-5-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)benzamide



[01141] 3-(Cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-5-(1,2,3,6-tetrahydropyridin-4-yl)benzamide (0.100 g, 0.223 mmol) was dissolved in methanol (5 mL) and cooled to 0 ° C, formalin (0.067 g, 0.19 mL, 2.23 mmol) was added. Resulting reaction mass was stirred at same temperature for 30 minutes. Sodium cyanoborohydride (0.041 g, 0.66 mmol) was added to above reaction mass and stirred at room temperature for 4 h. After completion, solvent were removed under reduced pressure and water was added to the residue, extraction was carried out using DCM. Combined organic layers were dried, concentrated and purified by column chromatography to provide the desired compound (0.065 g, 63%): LCMS: 463.40 $(M + 1)^+$; HPLC: 98.79% (@ 254 nm) (R_t;3.911; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 µ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 µL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.43 (s, 1H), 8.04 (t, 1H, J=4.8 Hz), 7.17 (s, 1H), 6.95 (s, 1H), 6.07 (s, 1H), 5.85 (s, 1H), 4.25 (d, 2H, J=4.8 Hz), 3.45 (m, 1H), 2.98 (bs, 2H), 2.53 (m, 2H), 2.42 (bs, 2H), 2.26 (s, 3H), 2.18 (s, 3H), 2.17 (s, 3H), 2.10 (s, 3H), 1.67 (m, 2H), 1.59 (m, 2H), 1.49 (m, 2H), 1.40 (m, 2H).

[01142] **Example 13:** Synthesis of Compound 17: 3-((1-acetylpiperidin-4-yl)(methyl)amino)-5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide

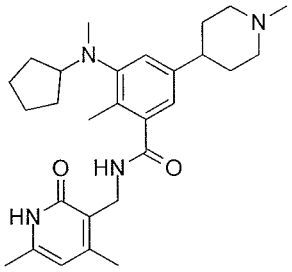


Compound 17

[01143] The 5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(methyl(piperidine-4-yl)amino)benzamide (0.2 g, 0.447 mmol) dissolved in DMSO (2 mL) and acetic acid (0.054 g, 0.896 mmol) were added to it. The reaction mixture was stirred at room temperature for 15 min before PYBOP (0.342 g, 0.672 mmol) was added to it and stirring was continued for overnight. After completion, reaction mass was poured into ice, and extracted using 10% MeOH/DCM. Combined organic layers were dried, concentrated to provide crude

material, which then purified with column chromatography using silica (100-200 mesh size) to afford the desired compound (0.15g, 17%). LCMS: 503.20 $(M + 1)^+$; HPLC: 96.06% (@ 254 nm) (R_t;5.143; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 μ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 μL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.48 (s, 1H), 8.21 (t, 1H, J=4.8 Hz), 7.23 (d, 1H, J=1.6 Hz), 7.04 (d, 1H, J=1.6 Hz), 5.85 (s, 1H), 4.32 (d, 1H, J=12.4 Hz), 4.23 (d, 2H, J=4.8 Hz), 3.77 (d, 1H, J=13.2 Hz), 2.98 (t, 2H, J=11.2 Hz), 2.54 (s, 3H), 2.18 (s, 3H), 2.13 (s, 3H), 2.10 (s, 3H), 1.97 (s, 3H), 1.53-1.60 (m, 4H), 1.38-1.41 (m, 1H).

[01144] **Example 14:** Synthesis of Compound 18: 3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-5-(1-methylpiperidin-4-yl)benzamide

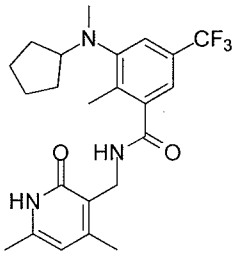


Compound 18

[01145] To a solution of 3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-5-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)benzamide (0.045 g, 0.097 mmol) in ethanol added 10% Pd/C and the reaction was stirred under H_2 at bladder pressure. After complete consumption of the starting material reaction mixture was filtered through celite. The filtrate was concentrated and triturated in acetonitrile and filtered to provide the desired compound (0.030 g, 66%): LCMS: 465.40 $(M + 1)^+$; HPLC: 95.39% (@ 254 nm) (R_t;3.884; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 μ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 μL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.44 (s, 1H), 7.98 (t, 1H), 7.00 (s, 1H), 6.77 (s, 1H), 5.85 (s, 1H), 4.25 (d, 2H, J=4.4 Hz), 3.42 (m, 1H), 2.84 (d, 2H, J=11.2 Hz), 2.47 (s, 3H), 2.37

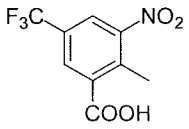
(m, 1H), 2.18 (s, 6H), 2.15 (s, 3H), 2.10 (s, 3H), 1.93 (t, 2H, J=10.8 Hz), 1.70-1.55 (m, 8H), 1.48 (m, 2H), 1.38 (m, 2H).

[01146] **Example 15:** Synthesis of Compound 20: 3-(cyclopentyl (methyl)amino) -N- ((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl) methyl)-2-methyl-5- (trifluoromethyl) benzamide



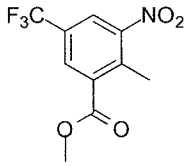
Compound 20

[01147] Step 1: Synthesis of 2-methyl-3-nitro-5-(trifluoromethyl) benzoic acid



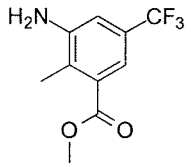
[01148] 2-methyl-5-(trifluoromethyl) benzoic acid (4 g, 19.6 mmol) was added to cooled conc. H_2SO_4 (27 mL) at -10 °C in small portions. After 10 minutes nitrating mixture {prepared by mixing conc. HNO_3 (2.77 g, 44.44 mmol) with conc.H_2SO_4 (3.6 mL)} was added drop wise at -10 °C. The resulting solution was stirred at -10 °C for 30 minutes. On completion, the reaction mixture was poured into ice cold water. The solid was filtered, washed with water and dried under vacuum to give 2-methyl-3-nitro-5-(trifluoromethyl) benzoic acid (4.95 g, 99%).

[01149] Step 2: Synthesis of methyl 2-methyl-3-nitro-5-(trifluoromethyl) benzoate



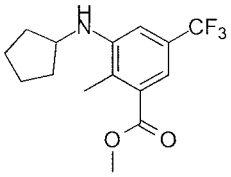
[01150] To stirred solution of 2-methyl-3-nitro-5-(trifluoromethyl) benzoic acid (1 g, 4.01 mmol) in DMF (3 mL) was added sodium carbonate (0.63 g, 6.02 mmol) and methyl iodide (1.14 g, 8.03 mmol). The resulting mixture was heated at 60 °C for 4 h. On completion, water was added to the reaction, and the product extracted using DCM. Combined organic layers were dried, concentrated under reduced pressure and purified by column chromatography over silica to give methyl 2-methyl-3-nitro-5-(trifluoromethyl) benzoate (1 g, 95.2%).

[01151] Step 3: Synthesis of methyl 3-amino-2-methyl-5-(trifluoromethyl) benzoate



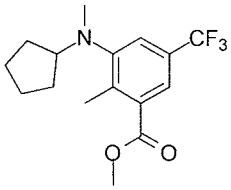
[01152] To a stirred solution of methyl 2-methyl-3-nitro-5-(trifluoromethyl) benzoate (5.6 g, 20.97 mmol) in ethanol (40 mL) was added ammonium chloride (5.6 g, 104.6 mmol) dissolved in water (30 mL) and iron powder (4.67 g, 85.16 mmol). The resulting mixture was heated at 80 °C for 1 h. On completion, water was added to the reaction then the mixture was filtered through celite. The filtrate was extracted with ethyl acetate. The combined organic layers were dried then concentrated under reduced pressure to give methyl 3-amino-2-methyl-5-(trifluoromethyl) benzoate.

[01153] Step 4: Synthesis of methyl 3-(cyclopentylamino)-2-methyl-5-(trifluoromethyl)benzoate



[01154] To a stirred solution of methyl 3-amino-2-methyl-5-(trifluoromethyl) benzoate (2.5 g, 10.7 mmol) and cyclopentanone (4.5 g, 53.49 mmol) in methanol (25 mL) was added acetic acid (1.98 g, 21.44 mmol). After 3h, sodium cyanoborohydride (1.68 g, 24.3 mmol) was added and the reaction stirred overnight. On completion, the solvent was removed under reduced pressure and crude material was purified by column chromatography to afford methyl 3-(cyclopentylamino)-2-methyl-5-(trifluoromethyl)benzoate (1.8 g, 55.9%).

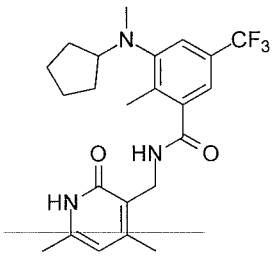
[01155] Step 5: Synthesis of methyl 3-(cyclopentyl (methyl) amino)-2-methyl-5-(trifluoromethyl) benzoate



[01156] To a stirred solution of methyl 3-(cyclopentylamino)-2-methyl-5-(trifluoromethyl)benzoate (1.6 g, 5.38 mmol) in acetonitrile (25 mL) was added cesium

carbonate (3.5 g, 10.7 mmol) and methyl iodide (3.8 g, 26.8 mmol). The mixture was heated at 80 °C for 8 h. On completion, the reaction was cooled to room temperature and filtered. The residue was washed with ethyl acetate and the filtrate was concentrated to give methyl 3-(cyclopentyl (methyl) amino)-2-methyl-5-(trifluoromethyl) benzoate.

[01157] Step 6: Synthesis of 3-(cyclopentyl (methyl)amino) -N- ((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl) methyl)-2-methyl-5- (trifluoromethyl) benzamide

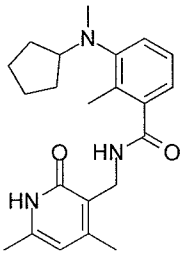


[01158] Aqueous NaOH (0.762 g, 15.4 mmol) was added to a solution of methyl 3-(cyclopentyl (methyl) amino)-2-methyl-5-(trifluoromethyl) benzoate (2 g, 6.34 mmol) in MeOH (20 mL) and the mixture was stirred at 60 °C for 1 h. After completion of the reaction, methanol was removed under reduced pressure and the residue acidified using dilute HCl up to pH 6 and to pH 4 using citric acid. The product was extracted using ethyl acetate. The combined organic layers were dried and concentrated to give the desired acid (1.5 g, 78%).

[01159] The acid (0.5 g, 1.69 mmol) was then dissolved in DMSO (3 mL) and 3-(amino methyl)-4,6-dimethylpyridin-2(1H)-one (0.505 g, 3.32 mmol) was added to it. The reaction mixture was stirred at room temperature for 15 min before PYBOP (1.29 g, 2.49 mmol) was added and stirring was continued overnight. After completion of the reaction, the mixture was poured onto ice to obtain a solid. The solid was filtered and washed with acetonitrile followed by ether to provide compound 3-(cyclopentyl (methyl)amino) -N- ((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl) methyl)-2-methyl-5- (trifluoromethyl) benzamide (100 mg, 14%).

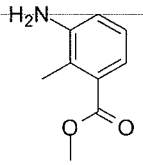
Analytical Data: LCMS: 436.20 $(M + 1)^+$; HPLC: 89.22% (@ 254 nm) (R_t;6.094; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 μ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 μL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.47 (s, 1H), 8.30 (t, 1H), 7.37 (s, 1H), 7.18 (s, 1H), 5.86 (s, 1H), 4.26 (d, 2H, J=4.4 Hz), 3.51 (m, 1H), 2.53 (s, 3H), 2.25 (s, 3H), 2.19 (s, 3H), 2.10 (s, 3H), 1.41-1.69 (m, 8H).

[01160] **Example 16:** Synthesis of Compound 21: 3-(cyclopentyl (methyl) amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide



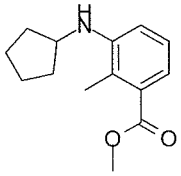
Compound 21

[01161] Step 1: Synthesis of methyl 3-amino-2-methylbenzoate



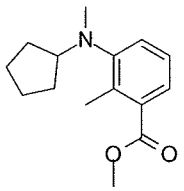
[01162] To stirred solution of methyl 3-amino-2-methylbenzoic acid (5 g, 33.1 mmol) in methanol (50 mL), was added conc. H_2SO_4 (5 mL) at 0 ° C and the mixture was heated at 70 °C for 22 h. On completion, methanol was removed under reduced pressure, and then sat. sodium bicarbonate solution was added and the product extracted with 10 %MeOH/DCM. Combined organic layers were dried, concentrated to yield methyl 3-amino-2-methylbenzoate (5 g, 91%).

[01163] Step 2: Synthesis of methyl 3-(cyclopentylamino)-2-methylbenzoate



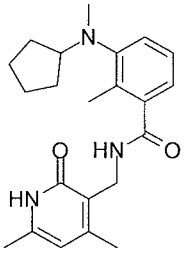
[01164] To a stirred solution of methyl 3-amino-2-methylbenzoate (2 g, 12.1 mmol) and cyclopentanone (5 g, 60.6 mmol) in methanol (20 mL) was added acetic acid (0.72 g, 12.12 mmol) and the reaction stirred at room temperature for 3 h. Sodium cyanoborohydride (1.13 g, 18.2 mmol) was added and the reaction stirred overnight. On completion, the solvent was removed under reduced pressure and the product was purified by column chromatography to afford methyl 3-(cyclopentylamino)-2-methylbenzoate (2.2 g, 78%).

[01165] Step 3: Synthesis of methyl 3-(cyclopentyl (methyl) amino)-2-methylbenzoate



[01166] To a stirred solution of methyl 3-(cyclopentylamino)-2-methylbenzoate (2.2 g, 9.44 mmol) in acetonitrile (20 mL) was added cesium carbonate (6.13 g, 18.8 mmol) and methyl iodide (6.7 g, 47.2 mmol). The resulting mixture was heated at 80 °C for 12 h. On completion, the mixture was cooled to room temperature and filtered, washing with ethyl acetate. The filtrate was concentrated and then purified by column chromatography to afford methyl 3-(cyclopentyl (methyl) amino)-2-methylbenzoate (2 g, 85%).

[01167] Step 4: Synthesis of 3-(cyclopentyl (methyl) amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide

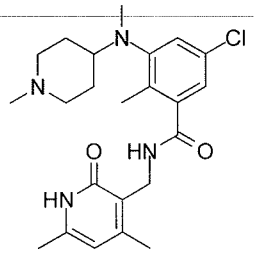


[01168] Aqueous NaOH (0.48 g, 12.14 mmol) was added to a solution of methyl 3-(cyclopentyl (methyl) amino)-2-methylbenzoate (2 g, 8.09 mmol) in MeOH (20 mL) and stirred at 60 °C for 1 h. After completion of the reaction, methanol was removed under reduced pressure and acidified using dilute HCl up to pH 6 and pH 4 was adjusted using citric acid. Extraction was carried out using ethyl acetate. Combined organic layers were dried and concentrated to give the desired acid (1.3 g, 69%).

[01169] The acid (0.3 g, 1.28 mmol) was then dissolved in DMSO (5 mL) and 3-(amino methyl)-4,6-dimethylpyridin-2(1H)-one (0.39 g, 2.5 mmol) was added to it. The reaction mixture was stirred at room temperature for 15 min before PYBOP (0.99 g, 1.92 mmol) was added to it and stirring was continued for overnight. After completion of the reaction, mixture was poured into ice to obtain solid, this was filtered and washed with acetonitrile followed column purification to provide 3-(cyclopentyl (methyl) amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide (0.020 g, 4%).

[01170] **Analytical Data:** LCMS: 368.15 $(M + 1)^+$; HPLC: 99.49% (@ 254 nm) (R_t;4.186; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 µ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 µL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.43 (s, 1H), 8.00 (t, 1H, J=4 Hz), 7.09-7.16 (m, 2H), 6.90 (d, 1H, J=6.8 Hz), 5.84 (s, 1H), 4.25 (d, 2H, J=5.2 Hz), 3.41 (t, 1H, J=6.8 Hz), 2.47 (s, 3H), 2.18 (d, 6H, J=4.4 Hz), 2.10 (s, 3H), 1.58-1.67(m, 4H),1.37-1.52 (m, 4H).

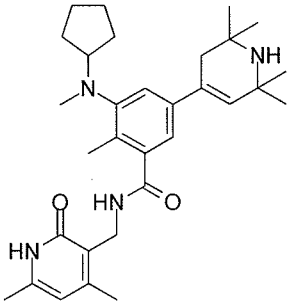
[01171] **Example 17:** Synthesis of Compound 23: 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(methyl(1-methylpiperidin-4-yl)amino)benzamide



Compound 23

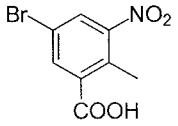
[01172] 5-Chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(methyl(piperidin-4-yl)amino)benzamide (0.08 g, 0.192 mmol) was dissolved in methanol (5 mL) and cooled to 0 ° C, formalin (0.028 g, 0.965 mmol) was added. Resulting reaction mass was stirred at same temperature for 30 minutes. Sodium cyanoborohydride (0.023 g, 0.38 mmol) was added to above reaction mass and stirred at room temperature for 4 h. After completion, solvent were removed under reduced pressure and water was added to the residue, extraction was carried out using DCM. Combined organic layers were dried, concentrated and purified by column chromatography giving the desired compound (0.02 g, 24 %): LCMS: 431.25 $(M + 1)^+$; HPLC: 98.80% (@ 254 nm) (R_t;4.757; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 µ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 µL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.46 (s, 1H), 8.20 (t, 1H), 7.15 (d, 1H, J=1.2 Hz), 6.94 (d, 1H, J=2 Hz), 5.85 (s, 1H), 4.25 (d, 2H, J=4.8 Hz), 3.05 (bs, 2H), 2.88 (bs, 1H), 2.55 (s, 3H), 2.44 (bs, 2H), 2.18 (s, 3H), 2.14 (s, 3H), 2.10 (s, 3H), 1.68 (bs, 4H).

[01173] **Example 18:** Synthesis of Compound 25: 3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-5-(2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridin-4-yl)benzamide



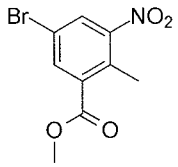
Compound 25

[01174] Step 1: 5-bromo-2-methyl-3-nitrobenzoic acid



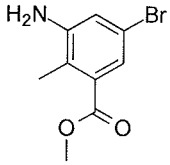
[01175] To stirred solution of 2-methyl-3-nitrobenzoic acid (50 g, 276.2 mmol) in conc. H_2SO_4 (200 mL), 1,3-dibromo-5,5-dimethyl-2,4-imidazolidinedione (43.4 g, 151.8 mmol) was added portion wise at room temperature and reaction mass was stirred at room temperature for 5 h. On completion, reaction mass was poured on ice cold water, solid precipitated was filtered, resulting residue was washed with water and dried under vacuum to give the desired compound (71.7 g, 100%).

[01176] Synthesis of methyl 5-bromo-2-methyl-3-nitrobenzene



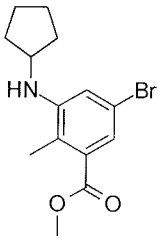
[01177] To a stirred solution of 5-bromo-2-methyl-3-nitrobenzoic acid (287 g, 1103 mmol) in DMF (150 mL), sodium carbonate (468 g, 4415 mmol) and methyl iodide (626.63 g, 4415 mmol) were added. Resulting reaction mass was heated at 60 °C for 8 h. On completion, solid precipitated was filtered, residue washed with diethyl ether (5 times). Combined organic layers were dried, concentrated under reduced pressure giving the desired crude compound (302 g, 99%).

[01178] Step 2: methyl 3-amino-5-bromo-2-methylbenzoate



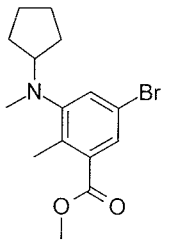
[01179] To stirred solution of methyl 5-bromo-2-methyl-3-nitrobenzene (150 g, 544 mmol) in ethanol (750 mL), ammonium chloride (150 g, 2777 mmol) dissolved in water (750 mL) and iron powder (93.3 g, 1636 mmol) were added under stirring. Resulting reaction mass was heated at 80 °C for 7 h. On completion, reaction mass was filtered through celite giving washing of water and ethyl acetate, filtrate was extracted with ethyl acetate. Combined organic layers were dried, concentrated under reduced pressure giving the desired compound.

[01180] Step 3: methyl 5-bromo-3-(cyclopentylamino)-2-methylbenzoate



[01181] To a stirred solution of methyl 3-amino-5-bromo-2-methylbenzoate (0.3 g, 1.33 mmol) and cyclopentanone (0.56 g, 6.6 mmol) in methanol (3 mL), acetic acid (0.159 g, 2.6 mmol) was added and reaction stirred at room temperature for 3 h. Then sodium cyanoborohydride (0.208 g, 3.3 mmol) was added and reaction stirred overnight. On completion, solvent was removed under reduced pressure to give the desired compound.

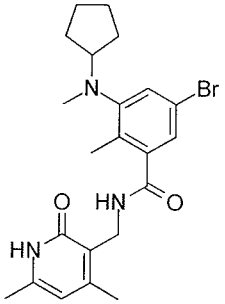
[01182] Step 4: methyl 5-bromo-3-(cyclopentyl(methyl)amino)-2-methylbenzoate



[01183] To a stirred solution of the crude methyl 5-bromo-3-(cyclopentylamino)-2-methylbenzoate (0.7 g, 2.25 mmol) in acetonitrile (15 mL), cesium carbonate (1.47 g, 4.50 mmol) and methyl iodide (1.6 g, 11.26 mmol) were added; resulting reaction mass was heated at 80 °C for 7 h. On completion, reaction mass was cooled to room temperature and filtered,

residue was washed with ethyl acetate and filtrate was concentrated and then purified by column chromatography to afford the desired compound (0.6 g, 82%).

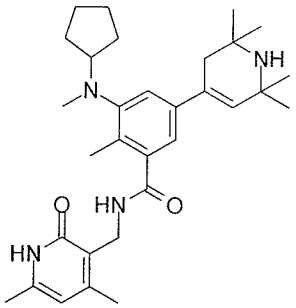
[01184] Step 5: 5-bromo-3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide



[01185] Aqueous NaOH (0.11 g, 2.75 mmol) was added to a solution of methyl 5-bromo-3-(cyclopentyl(methyl)amino)-2-methylbenzoate (0.6 g, 1.8 mmol) in MeOH (1.5 mL) and stirred at 60 °C for 1 h. After completion of the reaction, ethanol was removed under reduced pressure and acidified using dilute HCl up to pH 6 and pH 4 was adjusted using citric acid. Extraction was carried out using ethyl acetate. The combined organic layers were dried and concentrated to give the respective acid (0.5 g, 87%).

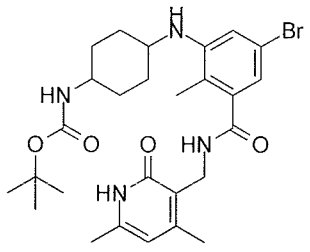
[01186] The acid (0.5 g, 1.60 mmol) was then dissolved in DMSO (3 mL) and 3-(amino methyl)-4,6-dimethylpyridin-2(1H)-one (0.49 g, 3.22 mmol) was added to it. The reaction mixture was stirred at room temperature for 15 min before PYBOP (1.25 g, 2.41 mmol) was added to it and stirring was continued for overnight. After completion of the reaction, reaction mass was poured into ice to obtain solid, this was filtered and washed with acetonitrile followed by ether to provide the desired compound (0.315 g, 44%).

[01187] Step 6: 3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-5-(2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridin-4-yl)benzamide



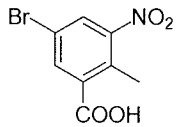
[01188] A solution of 5-bromo-3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide (1 equiv.), (2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridin-4-yl)boronic acid (1.2 equiv.) and Pd $(PPh_3)_4$ (0.1 equiv.) in 1,4-dioxane (4 mL) was purged with argon for 10 min. Then, 2 M Na_2CO_3 solution (3.6 equiv.) was added to it and argon was purged again for 10 min. The reaction mixture was stirred at 100 °C for 2 h. After completion of the reaction, water was added to it and extraction was carried out using DCM. The combined organic layers were washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude material which was purified preparative HPLC to give the desired compound as its TFA salt (0.045, 23%). LCMS: 505.39 $(M + 1)^+$; HPLC: 99.95% (@ 254 nm) (R_t;4.091; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 µ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 µL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (MeOD, 400 MHz) δ 7.70 (s, 1H), 7.46 (s, 1H), 6.21 (s, 1H), 6.13 (s, 1H), 4.48 (s, 2H), 4.23 (bs, 1H), 3.14 (s, 3H), 2.69 (s, 2H), 2.42 (s, 3H), 2.39 (s, 3H), 2.24 (s, 3H), 1.92 (, 2H), 1.81 (m, 2H), 1.67 (m, 4H), 1.60 (s, 6H), 1.53 (s, 6H).

[01189] **Example 19:** Synthesis of Compound 26: tert-butyl (4-((5-bromo-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)amino)cyclohexyl)carbamate



Compound 26

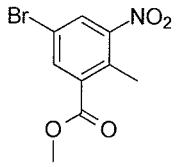
[01190] Step 1: 5-bromo-2-methyl-3-nitrobenzoic acid



[01191] To a mixture of 2-methyl-3-nitrobenzoic acid (15 g, 82.80 mmol) in conc. H_2SO_4 (60 mL), 1,3-dibromo-5,5-dimethyl-2,4-imidazolidinedione (13.07 g, 45.71 mmol) was added and reaction mixture was stirred at room temperature for 5 h. After completion of reaction, reaction

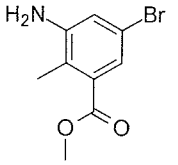
mixture was slowly poured onto ice cold water (400 mL). The precipitate was collected by filtration to give the desired compound (21 g, 98.22%).

[01192] Step 2: methyl 5-bromo-2-methyl-3-nitrobenzoate



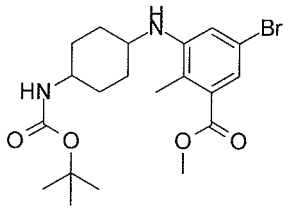
[01193] To a stirred solution of 5-bromo-2-methyl-3-nitrobenzoic acid (16 g, 61.54 mmol) in DMF (160 mL), iodomethane (35.72 g, 248 mmol) and sodium carbonate (26.28 g, 248 mmol) were added. Resulting reaction mass was stirred at 60 °C for 8 h. On completion, reaction mass was filtered and inorganic solid residue washed with ethyl acetate. Combined filtrate was concentrated under vacuum till dryness. The residue was re-dissolved in ethyl acetate and washed with 5% sodium bicarbonate solution (700 mL) followed by 5M HCl solution (300 mL). Organic layer was finally washed with brine, dried over sodium sulfate, filtered and concentrated to afford the desired compound (16 g, 94.50%).

[01194] Step 3: methyl 3-amino-5-bromo-2-methylbenzoate



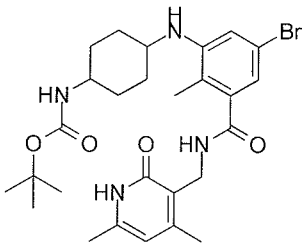
[01195] To a stirred solution of methyl 5-bromo-2-methyl-3-nitrobenzoate (17 g, 62.04 mmol) in ethanol (85 mL), was added NH_4Cl solution (17 g in 85 mL water, 317.8 mmol) followed by Fe powder (27.82 g, 498.11 mmol). Resulting reaction mass was stirred at 90 °C for 1 h. On completion, reaction mass was filtered and filtrate was concentrated till dryness to get solid which was dissolved in saturated sodium bicarbonate solution. The aqueous layer was extracted with ethyl acetate. Combined organic layers were dried over sodium sulfate and concentrated to afford the desired compound 4 (15 g, 99%).

[01196] Step 4: methyl 5-bromo-3-((4-((tert-butoxycarbonyl) amino)cyclohexyl)amino)-2-methylbenzoate



[01197] To a stirred solution of methyl 3-amino-5-bromo-2-methylbenzoate (5 g, 20.57 mmol) and tert-butyl (4-oxocyclohexyl)carbamate (5.67 g, 26.74 mmol) in methanol (50 mL), acetic acid (1.2 g, 20.57 mmol) was added and reaction stirred at room temperature for 4 h. Then sodium cyanoborohydride (1.68 g, 26.74 mmol) was added and reaction stirred 18 h. On completion, solvent was removed under reduced pressure; water was added and extracted with DCM. Combined organic were dried, concentrated and purified by column chromatography using silica (100-200 mesh size) to afford the desired compound (3 g, 33%).

[01198] Step 5: tert-butyl (4-((5-bromo-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)amino)cyclohexyl)carbamate

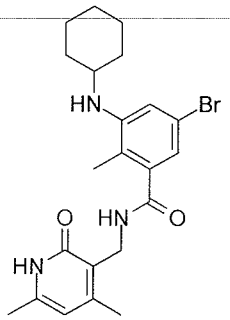


[01199] Aqueous NaOH (0.247 g, 6.83 mmol) was added to a solution of methyl 5-bromo-3-((4-((tert-butoxycarbonyl) amino)cyclohexyl)amino)-2-methylbenzoate (1.5 g, 3.41 mmol) in MeOH (20 mL) and stirred at 60 °C for 1 h. After completion of the reaction, ethanol was removed under reduced pressure and acidified using dilute HCl up to pH 6 and pH 4 was adjusted using citric acid. Extraction was carried out using DCM. Combined organic layers were dried concentrated giving respective acid (1.28 g, 89%).

[01200] The acid (1.28 g, 3.01 mmol) was then dissolved in DMSO (10 mL) and 3-(amino methyl)-4,6-dimethylpyridin-2(1H)-one (1.03 g, 6.83 mmol) was added to it. The reaction mixture was stirred at room temperature for 15 min before PYBOP (2.6 g, 5.12 mmol) was added to it and stirring was continued for overnight. After completion of the reaction, reaction mass was poured into ice and extracted with 5% MeOH/DCM. The combined organic layers were dried and concentrated to obtain a crude solid, which was purified by column chromatography to afford the desired compound (0.75g, 45%). LCMS: 561.15 $(M + 1)^+$;

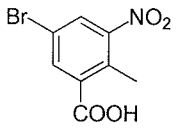
HPLC: 99.99% (@ 254 nm) (R_t;6.876,7.080 [mixture of diastereomers]; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 μ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 μL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.44 (s, 1H), 8.07 (t, 1H, J=4.8 Hz), 6.77 (d, 1H, J=7.6 Hz), 6.66 (s, 1H), 6.51-6.54 (m, 1H), 5.84 (s, 1H), 4.71 (d, 1H, J=7.6 Hz), 4.21-4.22 (m, 2H), 3.44 (bs, 1H), 3.19 (bs, 1H), 2.16 (s, 3H), 2.10 (s, 3H), 1.93-2.03 (m, 5H), 1.78 (s, 1H), 1.56-1.72 (m, 3H), 1.37 (s, 9H), 1.26-1.31 (m, 2H).

[01201] **Example 20:** Synthesis of Compound 28: 5-bromo-3-(cyclohexylamino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide



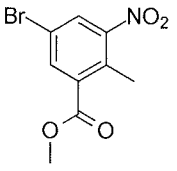
Compound 28

[01202] Step 1: 5-bromo-2-methyl-3-nitrobenzoic acid



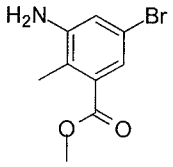
[01203] To stirred solution of 2-methyl-3-nitrobenzoic acid (50 g, 276.2 mmol) in conc. H_2SO_4 (200 mL), 1,3-dibromo-5,5-dimethyl-2,4-imidazolidinedione (43.4 g, 151.8 mmol) was added portion wise at room temperature and reaction mass was stirred at room temperature for 5 h. On completion, reaction mass was poured on ice cold water, solid precipitated was filtered, resulting residue was washed with water and dried under vacuum giving the desired compound (71.7 g, 100%).

[01204] Step 2: methyl 5-bromo-2-methyl-3-nitrobenzene



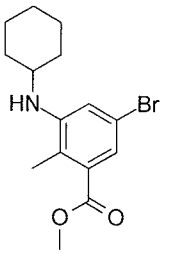
[01205] To stirred solution of 5-bromo-2-methyl-3-nitrobenzoic acid (287 g, 1103 mmol) in DMF (150 mL), sodium carbonate (468 g, 4415 mmol) and methyl iodide (626.63 g, 4415 mmol) were added. Resulting reaction mass was heated at 60 °C for 8 h. On completion, solid precipitated was filtered, residue washed with diethyl ether (5 times). Combined organic layers were dried, concentrated under reduced pressure giving the desired compound (302 g, 99%).

[01206] Step 3: methyl 3-amino-5-bromo-2-methylbenzoate



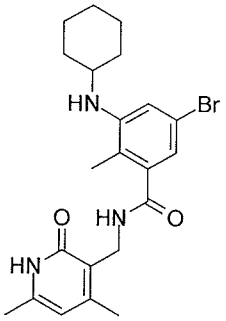
[01207] To a stirred solution of methyl 5-bromo-2-methyl-3-nitrobenzene (150 g, 544 mmol) in ethanol (750 mL), ammonium chloride (150 g, 2777 mmol) dissolved in water (750 mL) and iron powder (93.3 g, 1636 mmol) were added under stirring. Resulting reaction mass was heated at 80 °C for 7 h. On completion, reaction mass was filtered through celite giving washing of water and ethyl acetate, filtrate was extracted with ethyl acetate. Combined organic layers were dried, concentrated under reduced pressure to give the desired compound which was used directly in the next step.

[01208] Step 4: methyl 5-bromo-3-(cyclohexylamino)-2-methylbenzoate



[01209] To a stirred solution of methyl 3-amino-5-bromo-2-methylbenzoate (0.3 g, 1.33 mmol) and cyclohexanone (0.64 g, 6.6 mmol) in methanol (3 mL), acetic acid (0.159 g, 2.6 mmol) was added and reaction stirred at room temperature for 3 h. Then sodium cyanoborohydride (0.208 g, 3.3 mmol) was added and reaction stirred overnight. On completion, solvent was removed under reduced pressure and was used directly in the next step.

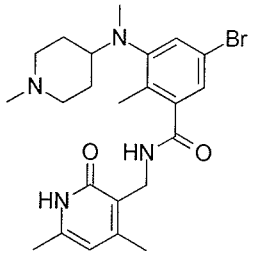
[01210] Step 5: 5-bromo-3-(cyclohexylamino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide



[01211] Aqueous NaOH (0.049 g, 1.23 mmol) was added to a solution of methyl 5-bromo-3-(cyclohexylamino)-2-methylbenzoate (0.2 g, 0.61 mmol) in MeOH (5 mL) and stirred at 60 °C for 1 h. After completion of the reaction, ethanol was removed under reduced pressure and acidified using dilute HCl up to pH 6 and pH 4 was adjusted using citric acid. Extraction was carried out using ethyl acetate. Combined organic layers were dried concentrated giving respective acid (0.17 g, 89%).

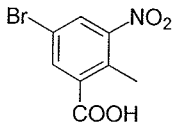
[01212] The acid (0.17 g, 0.54 mmol) was then dissolved in DMSO (3 mL) and 3-(amino methyl)-4,6-dimethylpyridin-2(1H)-one (0.099 g, 0.65 mmol) was added to it. The reaction mixture was stirred at room temperature for 15 min before PYBOP (0.42 g, 0.817 mmol) was added to it and stirring was continued for overnight. After completion of the reaction, reaction mass was poured into ice to obtain solid, this was purified by preparative HPLC to provide the desired compound as its TFA salt (0.042g, 15%). LCMS: 446.16 $(M + 1)^+$; HPLC: 99.85% (@ 254 nm) (R_t;6.918; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 μ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 μL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.45 (s,1H), 8.08 (s, 1H), 6.66 (s, 1H), 6.51 (d, 1H, J=0.8 Hz), 5.84 (s, 1H), 4.70(s, 1H), 4.21 (d, 2H, J=4.4 Hz), 3.24 (s, 1H), 2.16 (s, 3H), 2.10 (s, 3H), 1.94 (s, 3H), 1.88 (d, 2H, J=10 Hz), 1.69-1.72 (m, 3H), 1.22-1.36 (m, 5H).

[01213] **Example 21:** Synthesis of Compound 30: 5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(methyl(1-methylpiperidin-4-yl)amino)benzamide



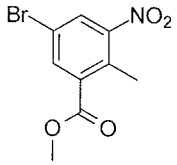
Compound 30

[01214] Step 1: 5-bromo-2-methyl-3-nitrobenzoic acid



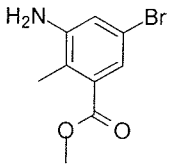
[01215] To stirred solution of 2-methyl-3-nitrobenzoic acid (50 g, 276.2 mmol) in conc. H_2SO_4 (200 mL), 1,3-dibromo-5,5-dimethyl-2,4-imidazolidinedione (43.4 g, 151.8 mmol) was added portion wise at room temperature and reaction mass was stirred at room temperature for 5 h. On completion, reaction mass was poured on ice cold water, solid precipitated was filtered, resulting residue was washed with water and dried under vacuum giving the desired compound (71.7 g, 99.9%) which was used for further reaction.

[01216] Step 2: methyl 5-bromo-2-methyl-3-nitrobenzene



[01217] To stirred solution of 5-bromo-2-methyl-3-nitrobenzoic acid (287 g, 1103 mmol) in DMF (150 mL), sodium carbonate (468 g, 4415 mmol) and methyl iodide (626.63 g, 4415 mmol) were added. Resulting reaction mass was heated at 60 °C for 8 h. On completion, solid precipitated was filtered, residue washed with diethyl ether (5 times). Combined organic layers were dried, concentrated under reduced pressure giving the desired compound (302 g, 99).

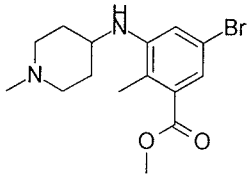
[01218] Step 3: methyl 3-amino-5-bromo-2-methylbenzoate



[01219] To a stirred solution of methyl 5-bromo-2-methyl-3-nitrobenzene (150 g, 544 mmol) in ethanol (750 mL), ammonium chloride (150 g, 2777 mmol) dissolved in water (750 mL) and

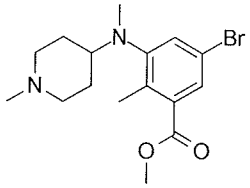
iron powder (93.3 g, 1636 mmol) were added under stirring. Resulting reaction mass was heated at 80 °C for 7 h. On completion, reaction mass was filtered through celite giving washing of water and ethyl acetate, filtrate was extracted with ethyl acetate. The combined organic layers were dried, concentrated under reduced pressure giving the desired compound.

[01220] Step 4: methyl 5-bromo-2-methyl-3-((1-methylpiperidin-4-yl)amino)benzoate



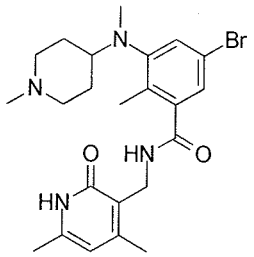
[01221] To a stirred solution of methyl 3-amino-5-bromo-2-methylbenzoate (2 g, 8.23 mmol) and 1-methylpiperidin-4-one (1.86 g, 16.46 mmol) in methanol (20 mL), acetic acid (0.5 g, 8.23 mmol) was added and reaction stirred at room temperature for 3 h. Then sodium cyanoborohydride (0.622 g, 9.87 mmol) was added and reaction stirred overnight. On completion, solvent was removed under reduced pressure and crude material was purified by column chromatography to afford the desired compound (0.9 g, 33%).

[01222] Step 5: methyl 5-bromo-2-methyl-3-(methyl(1-methylpiperidin-4-yl)amino)benzoate



[01223] To a stirred solution of methyl 5-bromo-2-methyl-3-((1-methylpiperidin-4-yl)amino)benzoate (0.6 g, 1.76 mmol) in acetonitrile (15 mL), cesium carbonate (1.14 g, 3.52 mmol) and methyl iodide (1.2 g, 8.8 mmol) were added; resulting reaction mass was heated at 80 °C for 7 h. On completion, reaction mass was cooled to room temperature and filtered, residue was washed with ethyl acetate and filtrate was concentrated and then purified by column chromatography to afford the desired compound (0.5 g, 80%).

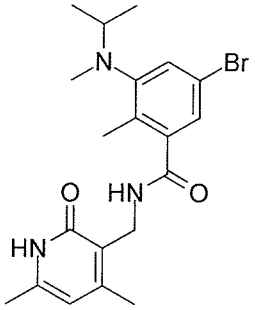
[01224] Step 6: 5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(methyl(1-methylpiperidin-4-yl)amino)benzamide



[01225] Aqueous NaOH (0.11 g, 2.75 mmol) was added to a solution of methyl 5-bromo-2-methyl-3-(methyl(1-methylpiperidin-4-yl)amino)benzoate (0.5 g, 1.4 mmol) in MeOH (20 mL) and stirred at 60 °C for 1 h. After completion of the reaction, ethanol was removed under reduced pressure and acidified using dilute HCl up to pH 6 and pH 4 was adjusted using citric acid. Extraction was carried out using ethyl acetate. Combined organic layers were dried concentrated giving respective acid (0.42 g, 90%).

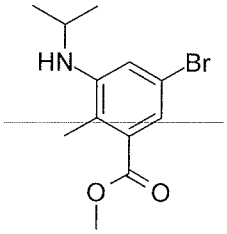
[01226] The acid (0.5 g, 0.974 mmol) was then dissolved in DMSO (3 mL) and 3-(amino methyl)-4,6-dimethylpyridin-2(1H)-one (0.45 g, 2.8 mmol) was added to it. The reaction mixture was stirred at room temperature for 15 min before PYBOP (1.1 g, 2.1 mmol) was added to it and stirring was continued for overnight. After completion of the reaction, reaction mass was poured into ice to obtain solid, this was filtered and washed with acetonitrile followed by purification with column chromatography to afford the desired compound (0.2g, 30%). LCMS: 475.02 $(M + 1)^+$; HPLC: 94.25% (@ 254 nm) (R_t;4.570; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 μ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 μL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.45 (s, 1H), 8.13 (t, 1H, J=4.8 Hz), 6.78 (d, 1H, J=0.8 Hz), 6.60 (d, 1H, J=1.6 Hz), 5.85 (s, 1H), 4.94 (d, 1H, J=8.8 Hz), 4.22 (d, 2H, J=4.8 Hz), 3.62-3.64 (m, 1H), 3.37-3.46 (m, 3H), 3.11 (s, 3H), 3.09 (s, 3H), 2.17 (s, 3H), 2.10 (s, 3H), 1.99-2.09 (m, 2H), 1.98 (s, 3H), 1.86-1.93 (m, 2H).

[01227] **Example 22:** Synthesis of Compound 31: 5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(isopropyl(methyl)amino)-2-methylbenzamide



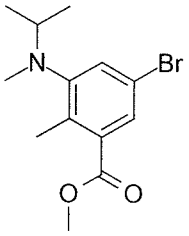
Compound 31

[01228] Step 1: Synthesis of methyl 5-bromo-3-(isopropylamino)-2-methylbenzoate



[01229] To a stirred solution of methyl 3-amino-5-bromo-2-methylbenzoate (1 equiv.) in methanol (5 mL), acetone (5 equiv.) and acetic acid (2 equiv.) were added and reaction mixture stirred at room temperature for 2 h. Then $NaBH_3CN$ (3 equiv.) was added at 0°C. The resulting reaction mixture was stirred further for 16 h at room temperature. On completion, solvent was evaporated and water added to the residue and the extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated to afford crude product which was used in next step without further purification (yield 80-90%).

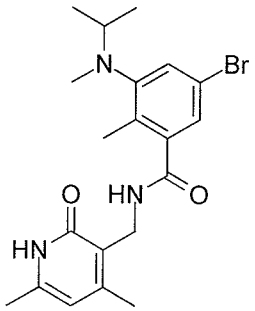
[01230] Step 2: Synthesis of methyl 5-bromo-3-(isopropyl(methyl)amino)-2-methylbenzoate



[01231] To a stirred solution of methyl 5-bromo-3-(isopropylamino)-2-methylbenzoate (0.5 g, 1.75 mmol) in acetonitrile (10 mL), Cs_2CO_3 (1.02 g, 2.63 mmol) and methyl iodide (1.45 g, 3.5 mmol) were added to it. The resulting reaction mixture was stirred at 80°C for 4 h. Upon completion, the solvent was removed under reduced pressure and residue dissolved in water and extracted with ethyl acetate. Crude material obtained was purified by column

chromatography over silica gel affording the desired compound product without further purification (0.39 g)

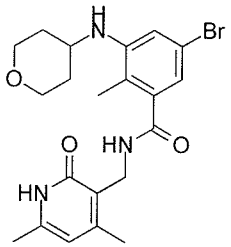
[01232] Step 3: 5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(isopropyl(methyl)amino)-2-methylbenzamide



[01233] To a stirred solution of methyl 5-bromo-3-(isopropyl(methyl)amino)-2-methylbenzoate (1 equiv.) in ethanol (5 mL), aqueous NaOH solution (1 equiv.) was added and reaction stirred at 60°C for 4 h. On completion, ethanol was removed under reduced pressure and residue acidified with 1N HCl to pH 6. The aqueous phase was extracted with 10% MeOH/DCM. Combined organic layers were dried over sodium sulfate and solvent removed under reduced pressure affording pure acid (yield 50-60%). To a solution of this acid (1 equiv.) in DMSO (1.5 mL), PyBOP (1.5 equiv.) was added and reaction stirred at room temperature for 15 min. Then 3-(aminomethyl)-4,6-dimethylpyridin-2(1H)-one (2 equiv.) was added and reaction stirred overnight. On completion, water was added and the resulting solid precipitate filtered and washed with water. Then this solid was stirred with acetonitrile for 10 min and filtered again to obtain pure target molecule (yield 50-60%).

[01234] LCMS: 420.15 $(M + 1)^+$; HPLC: 93.04% (@ 254 nm) (R_t;4.791); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.47 (s, 1H), 8.19 (t, 1H, J=4.8 Hz), 7.14 (d, 1H, J=1.6 Hz), 7.00 (d, 1H, J=1.2 Hz), 5.85 (s, 1H), 4.23 (d, 2H, J=4.4 Hz), 3.16-3.20 (m, 1H), 2.52 (s, 3H), 2.17 (s, 3H), 2.10 (s, 6H), 1.01 (d, 6H, J=6.4 Hz).

[01235] **Example 23:** Synthesis of Compound 32: 5-bromo-N-((4,6-dihydro-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-((tetrahydro-2H-pyran-4-yl)amino)benzoate

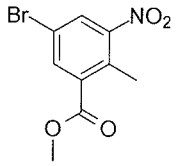


Compound 32

[01236] Step 1: 5-bromo-2-methyl-3-nitrobenzoic acid

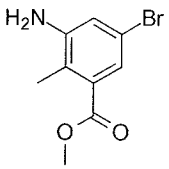
[01237] To a mixture of 2-methyl-3-nitrobenzoic acid (15 g, 82.80 mmol) in conc. H_2SO_4 (60 mL), 1,3-dibromo-5,5-dimethyl-2,4-imidazolidinedione (13.07 g, 45.71 mmol) was added and reaction mixture was stirred at room temperature for 5 h. After completion of reaction, reaction mixture was slowly poured onto ice cold water (400 mL). Solid that precipitated out was filtered and dried under vacuum to obtain the desired compound (21 g, 98%).

[01238] Step 2: methyl 5-bromo-2-methyl-3-nitrobenzoate



[01239] To a stirred solution of 5-bromo-2-methyl-3-nitrobenzoic acid (16 g, 61.54 mmol) in DMF (160 mL), iodomethane (35.72 g, 248 mmol) and sodium carbonate (26.28 g, 248 mmol) were added. Resulting reaction mass was stirred at 60 °C for 8 h. On completion, reaction mass was filtered and inorganic solid residue washed with ethyl acetate. Combined filtrate was concentrated under vacuum till dryness. The residue was re-dissolved in ethyl acetate and washed with 5% sodium bicarbonate solution (700 mL) followed by 5M HCl solution (300 mL). Organic layer was finally washed with brine, dried over sodium sulfate and concentrated to afford the desired compound (16 g, 95%).

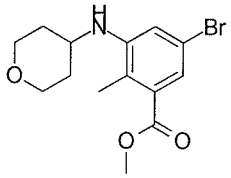
[01240] Step 3: methyl 3-amino-5-bromo-2-methylbenzoate



[01241] To a stirred solution of methyl 5-bromo-2-methyl-3-nitrobenzoate (17 g, 62.04 mmol) in ethanol (85 mL), was added NH_4Cl solution (17 g in 85 mL water, 317.8 mmol) followed by

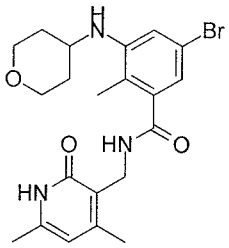
Fe powder (27.82 g, 498.11 mmol). Resulting reaction mass was stirred at 90 °C for 1 h. On completion, reaction mass was filtered and filtrate was concentrated till dryness to get solid which was dissolved in saturated sodium bicarbonate solution. Aqueous layer was extracted with ethyl acetate. Combined organic layers were dried over sodium sulfate and concentrated to afford the desired compound (15 g, 99%).

[01242] Step 4: methyl 5-bromo-2-methyl-3-((tetrahydro-2H-pyran-4-yl)amino)benzoate



[01243] To a stirred solution of methyl 3-amino-5-bromo-2-methylbenzoate (2 g, 8.23 mmol) and tetra hydro pyran-4-one (1.06 g, 10.66 mmol) in methanol (20 mL), acetic acid (0.5 g, 8.23 mmol) was added and reaction stirred at room temperature for 18 h. Then sodium cyanoborohydride (0.62 g, 9.83 mmol) was added and reaction stirred 3 h. On completion, solvent was removed under reduced pressure; water was added and extracted with DCM. Combined organic were dried, concentrated and purified by column chromatography using silica (100-200 mesh size) to afford the desired compound (1.6 g, 62%).

[01244] Step 5: 5-bromo-N-((4,6-dihydro-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-((tetrahydro-2H-pyran-4-yl)amino)benzoate

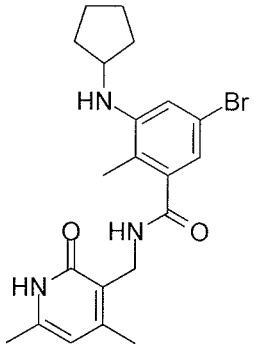


[01245] Aqueous NaOH (0.146 g, 3.66 mmol) was added to a solution of methyl 5-bromo-2-methyl-3-((tetrahydro-2H-pyran-4-yl)amino)benzoate (0.6 g, 1.88 mmol) in MeOH (8 mL) and stirred at 60 °C for 1 h. After completion of the reaction, ethanol was removed under reduced pressure and acidified using dilute HCl up to pH 6 and pH 4 was adjusted using citric acid. Extraction was carried out using DCM. Combined organic layers were dried concentrated giving respective acid (0.515 g, 90%).

[01246] The acid (0.515 g, 1.67 mmol) was then dissolved in DMSO (3 mL) and 3-(amino methyl)-4,6-dimethylpyridin-2(1H)-one (0.50 g, 3.3 mmol) was added to it. The reaction

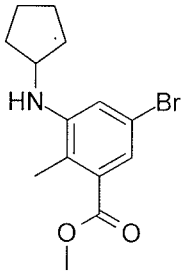
mixture was stirred at room temperature for 15 min before PYBOP (1 g, 1.98 mmol) was added to it and stirring was continued for overnight. After completion of the reaction, reaction mass was poured into ice and extracted with 5% MeOH/DCM. Combined organic layers were dried and concentrated to obtain crude solid, this was purified by column chromatography to afford the desired compound (0.30g, 37%). LCMS: 447.84 $(M + 1)^+$; HPLC: 99.78% (@ 254 nm) (R_t;5.753; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 µ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 µL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.45 (s, 1H), 8.09 (t, 1H, J=4.8 Hz), 6.76 (s, 1H), 6.53 (d, 1H, J=1.6 Hz), 5.84 (s, 1H), 4.82 (d, 1H, J=8 Hz), 4.42 (d, 2H, J=4.8 Hz), 3.85 (d, 2H, J=11.2 Hz), 3.37-3.53 (m, 3H), 2.16 (s, 3H), 2.10 (s, 3H), 1.95 (s, 3H), 1.81 (d, 2H, J=12.8 Hz), 1.44-1.54 (m, 2H).

[01247] **Example 24:** Synthesis of Compound 33: 5-bromo-3-(cyclopentylamino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide



Compound 33

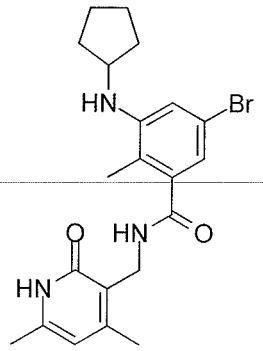
[01248] Step 1: Synthesis of methyl 5-bromo-3-(cyclopentylamino)-2-methylbenzoate



[01249] To a stirred solution of methyl 3-amino-5-bromo-2-methylbenzoate (1 equiv.) in methanol (5 mL), cyclopentanone (5 equiv.) and acetic acid (2 equiv.) were added and reaction

mixture stirred at room temperature for 2 h. Then $NaBH_3CN$ (3 equiv.) was added at 0°C. The resulting reaction mixture was stirred further for 16 h at room temperature. On completion, solvent was evaporated and water added to the residue and the extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated to afford crude product which was used in next step without further purification (yield 80-90%).

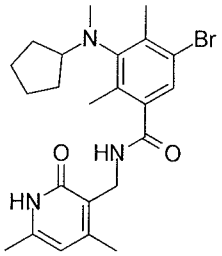
[01250] Step 2: Synthesis of 5-bromo-3-(cyclopentylamino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide



[01251] To a stirred solution of methyl 5-bromo-3-(cyclopentylamino)-2-methylbenzoate (1 equiv.) in ethanol (5 mL), aqueous NaOH solution (1 equiv.) was added and reaction stirred at 60°C for 4 h. On completion, ethanol was removed under reduced pressure and residue acidified with 1N HCl to pH 6. Aqueous phase was extracted with 10% MeOH/DCM. Combined organic layers were dried over sodium sulfate and solvent removed under reduced pressure affording pure acid (yield 50-60%). To a solution of this acid (1 equiv.) in DMSO (1.5 mL), PyBOP (1.5 equiv.) was added and reaction stirred at room temperature for 15 min. Then 3-(aminomethyl)-4,6-dimethylpyridin-2(1H)-one (2 equiv.) was added and reaction stirred overnight. On completion, water was added and the solid precipitate filtered and washed with water. This solid was then stirred with acetonitrile for 10 min and filtered again to obtain the pure target molecule (50-60% yield).

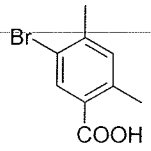
[01252] LCMS: 432.10 $(M + 1)^+$; HPLC: 97.15% (@ 254 nm) (R_t;6.834); ^1H NMR (DMSO-d_6, 400 MHz) δ 11.45 (s, 1H), 8.09 (t, 1H, J=4.4&5.2 Hz), 6.65 (d, 1H, J=1.6 Hz), 6.54 (d, 1H, J=1.6 Hz), 5.84 (s, 1H), 4.85 (d, 1H, J=6 Hz), 4.22 (d, 2H, J=5.2 Hz), 3.73 (m, 1H), 2.16 (s, 3H), 2.10 (s, 3H), 1.95 (s, 3H), 1.91 (m 2H), 1.70-1.62 (m, 2H), 1.60-1.45 (m, 4H).

[01253] **Example 25:** Synthesis of Compound 36: 5-bromo-3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,4-dimethylbenzamide



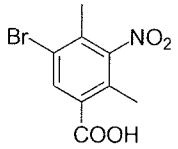
Compound 36

[01254] Step 1: 5-bromo-2,4-dimethylbenzoic acid



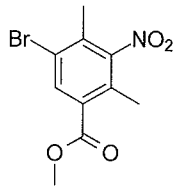
[01255] To the stirred solution of NaOH (60 g) in water (1152 ml) was added bromine (36 ml) dropwise at 0 °C and stirred the reaction mixture for 45 min. at same temperature. 2,4-dimethylbenzoic acid (12 g, 79.9 mmol) was added in above reaction mixture at 0 °C portion wise and stirred the reaction at room temperature for 3h. After completion of reaction of reaction (TLC) reaction mixture was acidified using conc. HCl, solid was filtered through Buchner funnel and wash with water and dried to afford the desired compound (12 g, 65 %) which was used without further purification.

[01256] Step 2: 5-bromo-2,4-dimethyl-3-nitrobenzoic acid



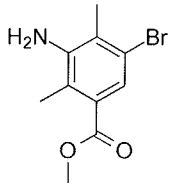
[01257] 5-Bromo-2,4-dimethylbenzoic acid (12 g, 52.17 mmol) was added to cooled conc. H_2SO_4 (48 mL) at -10 °C lot wise. After 10 minutes nitrating mixture {prepared as mixing Conc. HNO_3 (6 mL,) with conc.H_2SO_4 (24 mL)} was added drop wise at -10 °C. Resulting reaction mass was stirred at -10 °C for 30 minutes. On completion, reaction mixture was poured on ice cold water, solid precipitated was filtered, washed with water and dried under vacuum giving desired compound (13 g, 91%).

[01258] Step 3: methyl 3-bromo-5-nitrobenzoate



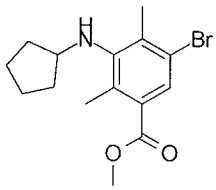
[01259] To stirred solution of 5-bromo-2,4-dimethyl-3-nitrobenzoic acid (13 g, 47.44 mmol) in DMF (120 mL), sodium carbonate (15 g, 142.2 mmol) and methyl iodide (4.4 ml, 71.16 mmol) were added. Resulting reaction mass was heated at 60 °C for 8 h. On completion, water was added to the reaction mass and extraction was carried out using ethyl acetate. Combined organic layers were washed with sat. bicarbonate solution and 5 N HCl, dried over sodium sulphate, concentrated under reduced pressure giving desired compound (12.9 g, 86 %).

[01260] Step 4: methyl 3-amino-5-bromo-2,4-dimethylbenzoate



[01261] To stirred solution of methyl 3-bromo-5-nitrobenzoate (12.9 g, 44.79 mmol) in ethanol (65 mL), ammonium chloride (13 g, 223.95 mmol) dissolved in water (65 mL) and iron powder (20 g, 358.33 mmol) were added under stirring. Resulting reaction mass was heated at 80 °C for 1 h. On completion, reaction mixture was filtered through celite bed, celite bed was washed with ethanol, filtrate was extracted with ethyl acetate. Combined organic layers were washed with water, dried, concentrated under reduced pressure giving desired compound (11.0 g, 95%).

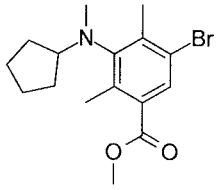
[01262] Step 5: methyl 5-bromo-3-(cyclopentylamino)-2,4-dimethylbenzoate



[01263] To a stirred solution of methyl 3-amino-5-bromo-2,4-dimethylbenzoate (1.4 g, 5.42 mmol) and cyclopentanone (2.4 mL, 27.13 mmol) in methanol (20 mL), acetic acid (0.650 g, 10.84 mmol) was added and reaction stirred at room temperature for 3 h. Then sodium cyanoborohydride (0.85 g, 13.56 mmol) was added and reaction was stirred for overnight. On completion, solvent was removed water was added and compound was extracted with ethyl

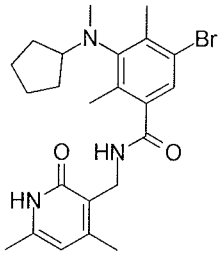
acetate. Combined organic layer was collected, dried over Na_2SO_4 and concentrate under reduced pressure and crude material was purified by column chromatography to afford the desired compound (1.2 g, 68 %).

[01264] Step 6:methyl 5-bromo-3-(cyclopentyl(methyl)amino)-2,4-dimethylbenzoate



[01265] To a stirred solution of methyl 5-bromo-3-(cyclopentylamino)-2,4-dimethylbenzoate (0.3 g, 1.07 mmol) in DMF (5 mL), cesium carbonate (0.697g, 2.14 mmol) and ethyl iodide (0.3 mL, 5.38mmol) were added; resulting reaction mass was heated at 80 °C for 12h. On completion, reaction mass was cooled to room temperature and filtered, residue was washed with ethyl acetate and filtrate was concentrated and then purified by column chromatography to afford desired compound (0.3 g, 82%).

[01266] Step 7: 5-bromo-3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,4-dimethylbenzamide

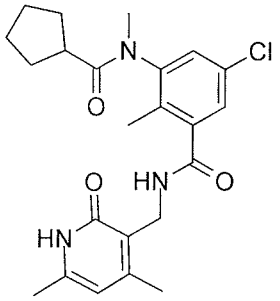


[01267] Aqueous NaOH (0.022 g, 0.553 mmol) was added to a solution of methyl 5-bromo-3-(cyclopentyl(methyl)amino)-2,4-dimethylbenzoate (0.125 g, 0.368 mmol) in EtOH (10 mL) and H_2O (1 mL) and stirred at 60 °C for 1 h. After completion of the reaction, ethanol was removed under reduced pressure and acidified using dilute HCl up to pH 6. Extraction was carried out using ethyl acetate. Combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure to give respective acid (0.1 g, 84.03%).

[01268] The acid (0.1 g, 0.308 mmol) was then dissolved in DMSO (3 mL) and 3-(amino methyl)-4,6-dimethylpyridin-2(1H)-one (0.07 g, 0.462 mmol) was added to it. The reaction mixture was stirred at room temperature for 15 min before PYBOP (0.320 g, 0.616 mmol) was added to it and stirring was continued for overnight. After completion of the reaction, reaction

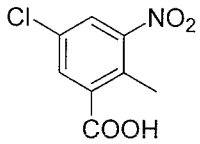
mass was poured into ice to obtain solid, this was filtered and washed with acetonitrile followed by HPLC purification to provide the title compound (0.018 g, 12.7 %) as its TFA salt : LCMS: 460.10 $(M + 1)^+$; HPLC: 98.10% (@ 254 nm) (R_t;8.291; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 μ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 μL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.46 (s, 1H), 8.18 (t, 1H, J=4.4 Hz), 7.20 (s, 1H), 5.85 (s, 1H), 4.26 (d, 2 H, J=4.8 Hz), 3.51-3.52 (m, 1H), 2.64 (s, 3H), 2.30 (s, 3H), 2.17 (s, 3H), 2.14 (s, 3H), 2.10 (s, 3H), 1.48-1.59 (m, 6H), 1.31-1.32 (m, 2H).

[01269] **Example 26:** Synthesis of Compound 48: 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(N-methylcyclopentanecarboxamido)benzamide



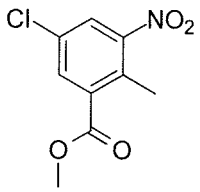
Compound 48

[01270] Step 1: Synthesis of 5-chloro-2-methyl-3-nitrobenzoic acid



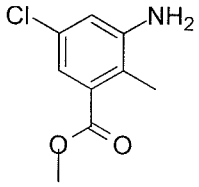
[01271] To a stirred ice cold (-10 to -15 °C) conc. H_2SO_4 (136 mL) was added 5-chloro-2-methylbenzoic acid (20 g, 0.117 mmol) in portions. The nitrating mixture [Conc. H_2SO_4 (22 mL) and HNO_3 (11.05 mL] was added dropwise at -10 to -15 °C and resulting mixture was allowed stir for 30 min. The obtained precipitate was filtered and dried. The solid was the dissolved in ethyl acetate and dried (Na_2SO_4) and concentrated to provide desired product (23.6 g, 93%) as a white solid.

[01272] Step 2: Synthesis of methyl 5-chloro-2-methyl-3-nitrobenzoate



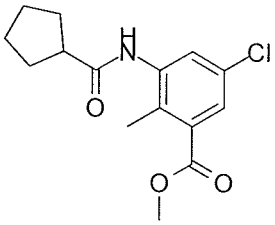
[01273] To a solution of 5-chloro-2-methyl-3-nitrobenzoic acid (23.5 g, 0.109 mmol) in DMF (120 mL) was added sodium carbonate (46.21, 0.436 mmol) and methyl iodide (27.2 mL, 0.43 mmol) at room temperature. The reaction mixture was heated at 60 °C for 3 h. After complete consumption of starting material the reaction mixture was filtered and the residue washed with ethyl acetate. The filtrate was concentrated under reduced pressure and the crude product purified by column chromatography to provide the desired compound (16 g, 64%) as thick oil which solidified on standing.

[01274] Step 3: Synthesis of methyl 3-amino-5-chloro-2-methylbenzoate



[01275] To stirred solution of methyl 5-chloro-2-methyl-3-nitrobenzoate (16 g, 69 mmol) in ethanol (160 mL), ammonium chloride (16 g, 53.4 mmol) dissolved in water (160 mL) and iron powder (31.2 g, 55.85 mmol) were added under stirring. The resulting reaction mixture was heated at 80 °C for 1 h. On completion, water was added to and the reaction mixture filtered through celite. The filtrate was extracted with ethyl acetate and the combined organic layers washed with water, dried and concentrated under reduced pressure giving desired compound (12.10 g, 86%) without further purification.

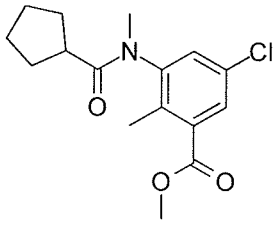
[01276] Step 4: Synthesis of methyl 5-chloro-3-(cyclopentanecarboxamido)-2-methylbenzoate



[01277] To a stirred solution of methyl 3-amino-5-chloro-2-methylbenzoate (0.4 g, 2.0 mmol) in pyridine (2 mL), cyclopentyl chloride (0.39 mL, 3.00 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature for 2h. After complete consumption of the starting

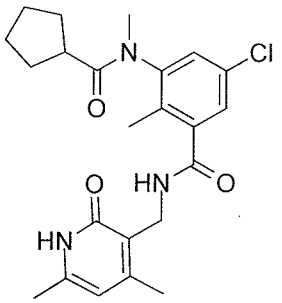
material the reaction was quenched with ice water. The resulting precipitate was filtered of to provide desired product (0.5 g, 84%).

[01278] Step 5: Synthesis of methyl 5-chloro-2-methyl-3-(N-methylcyclopentanecarboxamido)benzoate



[01279] To a stirred solution of methyl 5-chloro-3-(cyclopentanecarboxamido)-2-methylbenzoate (0.3 g, 1.01 mmol) in DMF, sodium hydride (0.060 g, 0.0015 mmol) was added at 0 °C and reaction mixture was allowed to stir for 15 min. Methyl iodide (0.32 mL, 0.50 mmol) was added and reaction mixture and was stirred at room temperature. After complete consumption of starting material, the reaction was quenched with addition of water and extracted with ethyl acetate. The combined organic layer was the washed with brine, dried (Na_2SO_4) and concentrated. The crude compound was used for the next step.

[01280] Step 6: Synthesis of 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(N-methylcyclopentanecarboxamido)benzamide



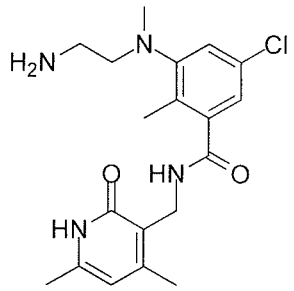
[01281] Aq. NaOH (0.077 g, 1.94 mmol) was added to a solution of methyl 5-chloro-2-methyl-3-(N-methylcyclopentanecarboxamido)benzoate (0.4 g, 1.2 mmol) in 4:1 EtOH: Water (15 mL) and stirred at 65 °C for 1 h. After completion of the reaction, ethanol was removed under reduced pressure and acidified with 1N HCl. The reaction mixture was extracted with ethyl acetate. Combined organic layers were washed with brine, dried and concentrated to provide respective acid (0.35 g, 91%).

[01282] The acid (0.3 g, 0.10 mmol) was then dissolved in DMSO (3 mL) and 3-(amino methyl)-4,6-dimethylpyridin-2(1H)-one (0.309 g, 0.20 mmol) was added to it. The reaction

mixture was stirred at room temperature for 15 min before PYBOP (0.826 g, 0.155 mmol) was added to it and stirring was continued overnight. After completion the reaction mixture was poured into ice to obtain a solid which was filtered and washed with acetonitrile. Final purification was performed using prep. HPLC purification to the desired product as the TFA salt (0.120 g, 27 %).

[01283] LCMS: 430.20 $(M + 1)^+$; HPLC: 99.79% (@ 254 nm) (R_t;6.086); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.55 (bs, 1H), 8.43 (t, 1H), 7.46 (s, 1H), 7.29 (s, 1H), 5.87 (s, 1H), 4.25 (s, 2H), 3.01 (s, 3H), 2.35 (m, 1H), 2.19 (s, 3H), 2.10 (s, 3H), 2.06 (s, 3H), 1.70-1.45 (m, 6H), 1.35 (m, 2H).

[01284] **Example 27:** Synthesis of Compound 49: 3-((2-aminoethyl)(methyl)amino)-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide



Compound 49

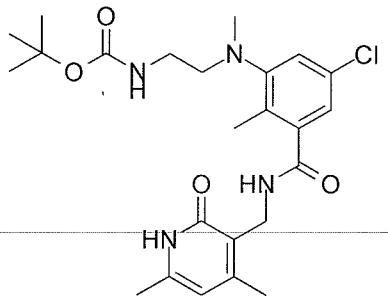
[01285] A stirred solution of tert-butyl (2-((5-chloro-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(methyl)amino)ethyl)carbamate (0.2 g, 4.2 mmol) in DCM (5 mL) was cooled to 0°C and TFA (1 mL) was added to it. The reaction mixture was stirred at room temperature for 1 h. On completion, the reaction was concentrated to dryness. Half of the material was purified by solvent washings giving pure 3-((2-aminoethyl)(methyl)amino)-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide as the TFA salt (0.060 g, 76 %).

[01286] LCMS: 377.15 $(M + 1)^+$; HPLC: 97.57% (@ 254 nm) (R_t;4.611); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.47 (s, 1H), 8.21 (t, 1H), 7.69 (bs, 3H), 7.16 (s, 1H), 6.97 (s, 1H), 5.86 (s, 1H), 4.25 (d, 2H, J=4.4 Hz), 3.07 (t, 2H), 2.96 (m, 2H), 2.59 (s, 3H), 2.18 (s, 6H), 2.10 (s, 3H).

[01287] Remaining material was basified with aqueous sodium bicarbonate till pH 8 and aqueous layer extracted with 20% MeOH/DCM. Combined organic layers were dried over

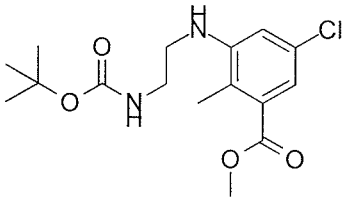
sodium sulfate and concentrated to afford desired compound as free base which used for further reaction (0.075g).

[01288] **Example 28:** Synthesis of Compound 50: tert-butyl (2-((5-chloro-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(methyl)amino)ethyl)carbamate



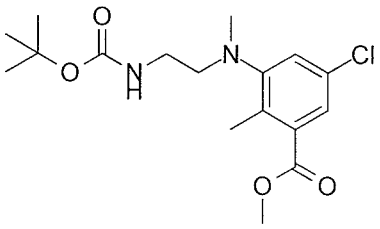
Compound 50

[01289] Step 1: Synthesis of methyl 3-((2-((tert-butoxycarbonyl)amino)ethyl)amino)-5-chloro-2-methylbenzoate



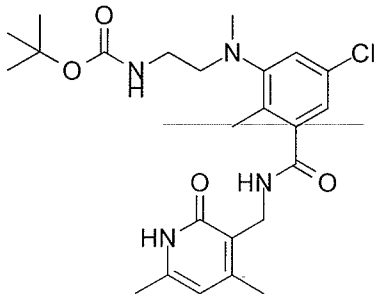
[01290] To a stirred solution of methyl 3-amino-5-chloro-2-methylbenzoate (1 g, 4.6 mmol) and tert-butyl (2-oxoethyl)carbamate (1.4 g, 8.8 mmol) in methanol (10 mL), acetic acid (0.027 g, 4.6 mmol) was added and reaction stirred at room temperature for 3 h. Then sodium cyanoborohydride (0.352 g, 4.68 mmol) was added and reaction stirred overnight. On completion, solvent was removed under reduced pressure and crude material was purified by column chromatography to afford the desired product (0.62 g, 38 %).

[01291] Step 2: Synthesis of methyl 3-((2-((tert-butoxycarbonyl)amino)ethyl)(methyl)amino)-5-chloro-2-methylbenzoate



[01292] To a stirred solution of methyl 3-((2-((tert-butoxycarbonyl)amino)ethyl)amino)-5-chloro-2-methylbenzoate (0.5 g, 1.46 mmol) in acetonitrile (10 mL), cesium carbonate (0.95 g, 2.92 mmol) and methyl iodide (1 g, 7.3 mmol) were added and the resulting reaction mixture heated at 80 °C for 12 h. On completion, the reaction mixture was cooled to room temperature and filtered, the residue washed with ethyl acetate and the filtrate concentrated before purification by column chromatography to afford desired product (0.325 g, 62 %).

[01293] Step 3: Synthesis of tert-butyl (2-((5-chloro-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(methyl)amino)ethyl)carbamate



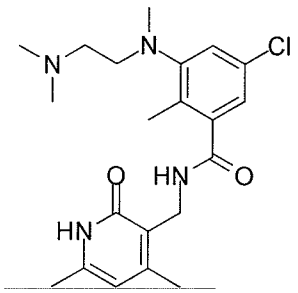
[01294] Aqueous NaOH (0.071 g, 1.79 mmol) was added to a solution of methyl 3-((2-((tert-butoxycarbonyl)amino)ethyl)(methyl)amino)-5-chloro-2-methylbenzoate (0.425 g, 1.19 mmol) in MeOH (5 mL) and stirred at 60 °C for 1 h. After completion of the reaction, ethanol was removed under reduced pressure and acidified using dilute HCl up to pH 6 and pH 4 and adjusted using citric acid. Extraction was carried out using ethyl acetate and the combined organic layers dried and concentrated giving respective acid (0.34 g, 84%).

[01295] The acid (0.34 g, 0.99 mmol) was then dissolved in DMSO (1.5 mL) and 3-(amino methyl)-4,6-dimethylpyridin-2(1H)-one (0.300 g, 1.98 mmol) was added to it. The reaction mixture was stirred at room temperature for 15 min before PYBOP (0.77 g, 1.48 mmol) was added to it and stirring was continued for overnight. After completion of the reaction, the reaction mixture was poured into ice to obtain solid, this was filtered and washed with acetonitrile followed column purification to provide tert-butyl (2-((5-chloro-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(methyl)amino)ethyl)carbamate (0.27 g, 58%).

[01296] LCMS: 477.25 $(M + 1)^+$; HPLC: 97.92% (@ 254 nm) (R_t;6.229); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.46 (s, 1H), 8.17 (t, 1H), 7.07 (s, 1H), 6.88 (s, 1H), 6.78 (bs, 1H), 5.85 (s,

1H), 4.24 (d, 2H, J=4.4 Hz), 3.07 (t, 2H), 2.84 (t, 2H), 2.62 (s, 3H), 2.17 (s, 3H), 2.13 (s, 3H), 2.10 (s, 3H), 1.35 (s, 9H).

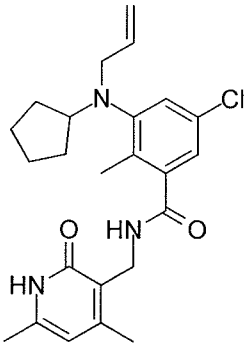
[01297] **Example 29:** Synthesis of Compound 51: 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-((2-(dimethylamino)ethyl)(methyl)amino)-2-methylbenzamide



Compound 51

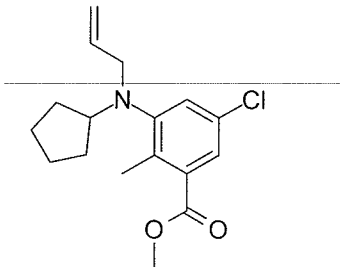
[01298] 3-((2-Aminoethyl)(methyl)amino)-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide (0.075 g, 0.199 mmol) was dissolved in methanol (5 mL) and cooled to 0° C, formaldehyde (0.056 g, 1.86 mmol) was added. The resulting reaction mixture was stirred at the same temperature for 30 minutes then sodium cyanoborohydride (0.023 g, 0.366 mmol) was added to above reaction mixture and stirred at room temperature for 4 h. After completion, solvent was removed under reduced pressure and water added before extraction with DCM. The combined organic layers were dried, concentrated and purified by column chromatography to provide 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-((2-(dimethylamino)ethyl)(methyl)amino)-2-methylbenzamide (0.040 g, 50%). LCMS: 405.25 $(M + 1)^+$; HPLC: 89.93% (@ 254 nm) (R_t;4.634); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.47 (s, 1H), 8.21 (s, 1H), 7.08 (s, 1H), 5.85 (s, 1H), 4.24 (bs, 2H), 2.91 (t, 2H), 2.63 (s, 3H), 2.33-2.35 (m, 2H), 2.11-2.18 (m, 15H).

[01299] **Example 30:** Synthesis of Compound 52: 3-(allyl(cyclopentyl)amino)-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide



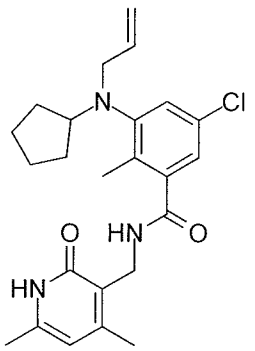
Compound 52

[01300] Step 1: Synthesis of methyl 3-(allyl(cyclopentyl)amino)-5-chloro-2-methylbenzoate



[01301] Methyl 5-chloro-3-(cyclopentylamino)-2-methylbenzoate (1.2 g, 4.46 mmol) was dissolved in DMF (12 mL) and cooled to 0°C. NaH (0.21 g, 8.92 mmol) was added after 10 minutes and allyl bromide (1.07 g, 8.9 mmol) was added. The reaction mixture was stirred at room temperature for 4 h and then heated at 80 0°C for 18 h. The reaction was quenched with ice water and extracted with ethyl acetate. Combined organic layers were dried, concentrated giving crude methyl 3-(allyl(cyclopentyl)amino)-5-chloro-2-methylbenzoate (0.4 g, 29.4 %).

[01302] Step 2: Synthesis of 3-(allyl (cyclopentyl) amino)-5-chloro-N-((4, 6-dimethyl-2-oxo-1, 2-dihydropyridin-3-yl) methyl)-2-methylbenzamide



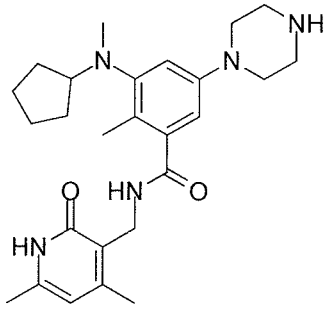
[01303] Aqueous NaOH (0.078 g, 1.95 mmol) was added to a solution of methyl 3-(allyl(cyclopentyl)amino)-5-chloro-2-methylbenzoate (0.4 g, 1.30 mmol) in MeOH (5 mL) and

stirred at 60 °C for 1 h. After completion of the reaction, ethanol was removed under reduced pressure and acidified using dilute HCl up to pH 6 and pH 4 was adjusted using citric acid. Extraction was carried out using ethyl acetate and the combined organic layers concentrated giving respective acid (0.37 g, 97.6%).

[01304] The acid (0.25 g, 0.85 mmol) was then dissolved in DMSO (3 mL) and 3-(amino methyl)-4,6-dimethylpyridin-2(1H)-one (0.259 g, 1.74 mmol) was added to it. The reaction mixture was stirred at room temperature for 15 min before PYBOP (0.66 g, 1.27 mmol) was added to it and stirring was continued for overnight. After completion of the reaction, reaction mixture was poured into ice to obtain a solid, which was filtered and washed with acetonitrile followed column purification to provide the desired 3-(allyl (cyclopentyl) amino)-5-chloro-N-((4, 6-dimethyl-2-oxo-1, 2-dihydropyridin-3-yl) methyl)-2-methylbenzamide (0.175 g, 48%).

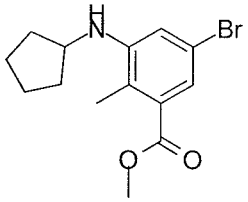
[01305] LCMS: 428.30 $(M + 1)^+$; HPLC: 96.37% (@ 254 nm) (R_t;6.357); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.47 (s, 1H), 8.21 (t, 1H), 7.16 (s, 1H), 6.92 (s, 1H), 5.85 (s, 1H), 5.63-5.69 (m, 1H), 4.98 (m, 2H), 4.23 (d, 2H, J=4 Hz), 3.54 (d, 2H, J=5.6 Hz), 3.46-3.50 (m, 1H), 2.18 (s, 3H), 2.16 (s, 3H), 2.10 (s, 3H), 1.67 (m, 2H), 1.59 (m, 2H), 1.47 (m, 2H), 1.36 (m, 2H).

[01306] **Example 31:** Synthesis of Compound 53: 3-(cyclopentyl (methyl) amino)-N-((4, 6-dimethyl-2-oxo-1, 2-dihydropyridin-3-yl) methyl)-2-methyl-5-(piperazin-1-yl) benzamide



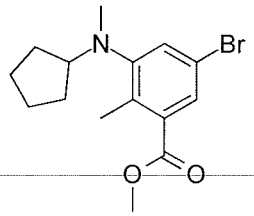
Compound 53

[01307] Step 1: Synthesis of methyl 5-bromo-3-(cyclopentylamino)-2-methylbenzoate



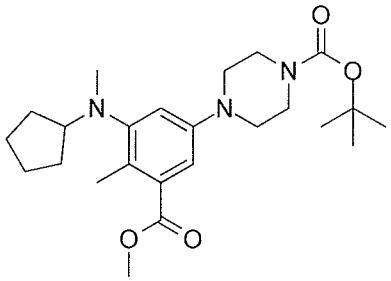
[01308] To a stirred solution of methyl 3-amino-5-bromo-2-methylbenzoate (3 g, 13.3 mmol) and cyclopentanone (5.6 g, 66 mmol) in methanol (30 mL), acetic acid (1.59 g, 26.6 mmol) was added and reaction stirred at room temperature for 3 h. Then sodium cyanoborohydride (2.08 g, 29.4 mmol) was added and reaction stirred overnight. On completion, solvent was removed under reduced pressure and crude material was used without further purification.

[01309] Step 2: Synthesis of methyl 5-bromo-3-(cyclopentyl (methyl) amino)-2-methylbenzoate



[01310] To a stirred solution of methyl 5-bromo-3-(cyclopentylamino)-2-methylbenzoate (1.6 g, 5.38 mmol) in acetonitrile (20 mL), cesium carbonate (3.5 g, 10.73 mmol) and methyl iodide (3.87 g, 27.25 mmol) were added and the resulting reaction mixture heated at 80 °C for 12 h. On completion, the reaction mixture was cooled to room temperature and filtered. The residue was washed with ethyl acetate and filtrate concentrated and purified by column chromatography to afford desired compound (1.6 g, 95 %).

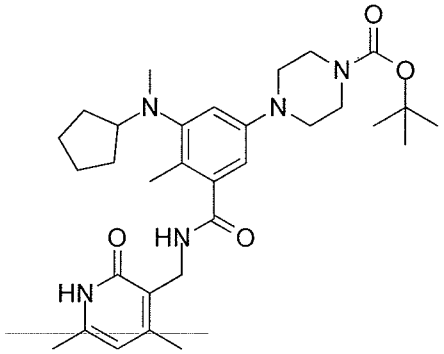
[01311] Step 3: Synthesis of tert-butyl 4-(3-(cyclopentyl (methyl) amino)-5-(methoxycarbonyl)-4-methylphenyl)piperazine-1-carboxylate



[01312] A solution of methyl 5-bromo-3-(cyclopentyl (methyl) amino)-2-methylbenzoate (1 g, 3.07 mmol), tert-butyl piperazine-1-carboxylate (0.85 g, 4.61 mmol) and Cs_2CO_3 (0.5 g, 1.53 mmol) in toluene (25 mL) was purged with argon for 10 min. Then, $Pd_2(dba)_3$ (0.31 g, 0.307 mmol) and BINAP (0.038 g, 0.061 mmol) was added to it and argon purged again for 10 min. The reaction mixture was stirred at 100 °C for 8 h. After completion, water was added to it and extracted with ethyl acetate. The combined organic layers were washed with water, dried over

anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude material which was purified by column chromatography to afford the title compound (0.44 g, 33.3 %).

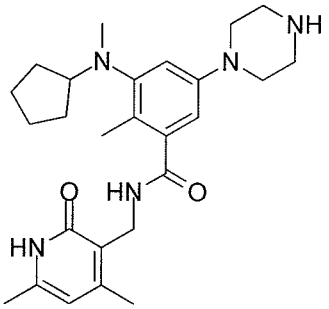
[01313] Step 4: Synthesis tert-butyl 4-(3-(cyclopentyl (methyl) amino)-5-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-4-methylphenyl)piperazine-1-carboxylate



[01314] Aqueous NaOH (0.061 g, 1.53 mmol) was added to a solution of tert-butyl 4-(3-(cyclopentyl (methyl) amino)-5-(methoxycarbonyl)-4-methylphenyl)piperazine-1-carboxylate (0.44 g, 1.02 mmol) in MeOH (10 mL) and stirred at 60 °C for 1 h. After completion of the reaction, ethanol was removed under reduced pressure and acidified using dilute HCl up to pH 6 and pH 4 was adjusted using citric acid. Extraction was carried out using ethyl acetate. Combined organic layers were dried concentrated giving respective acid (0.3 g, 70%).

[01315] The acid (0.3 g, 0.71 mmol) was then dissolved in DMSO (3 mL) and 3-(amino methyl)-4,6-dimethylpyridin-2(1H)-one (0.215 g, 1.43 mmol) was added to it. The reaction mixture was stirred at room temperature for 15 min before PYBOP (0.56 g, 1.07 mmol) was added to it and stirring was continued for overnight. After completion of the reaction, reaction mixture was poured into ice to obtain solid, which was filtered and washed with acetonitrile followed by ether to provide tert-butyl 4-(3-(cyclopentyl (methyl) amino)-5-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-4-methylphenyl)piperazine-1-carboxylate (0.30 g, 75.7%).

[01316] Step 5: Synthesis of 3-(cyclopentyl (methyl) amino)-N-((4, 6-dimethyl-2-oxo-1, 2-dihydropyridin-3-yl) methyl)-2-methyl-5-(piperazin-1-yl) benzamide

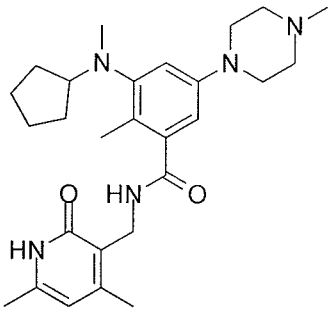


[01317] A stirred solution of tert-butyl 4-(3-(cyclopentyl (methyl) amino)-5-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-4-methylphenyl)piperazine-1-carboxylate (0.30, 0.54 mmol) in DCM (10 mL) was cooled to 0°C and TFA (3 mL) was added to it. The reaction mixture was stirred at room temperature for 1 h. Upon completion, the mixture was concentrated to dryness. Half crude was purified by solvent washing giving the title compound as TFA salt (0.01 g, 8.33 %).

[01318] LCMS: 452.39 $(M + 1)^+$; HPLC: 83.92% (@ 254 nm) (R_t;3.825); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.45 (s, 1H), 8.71 (s, 2H), 7.98 (s, 1H), 6.79 (s, 1H), 6.55 (s, 1H), 5.85 (s, 1H), 4.24 (d, 2H, J=3.2 Hz), 3.46 (1H in solvent peak), 3.22-3.26 (m, 8H), 2.50 (3H in solvent peak), 2.18 (s, 3H), 2.10 (s, 6H), 1.41-1.67 (m, 8H).

[01319] Half of the crude was basified with aqueous sodium bicarbonate till pH 8 and aqueous layer extracted with 20% MeOH/DCM. Combined organic layers were dried over sodium sulfate and concentrated to afford the title compound as free base.

[01320] **Example 32:** Synthesis of Compound 54: 3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-5-(4-methylpiperazin-1-yl)benzamide

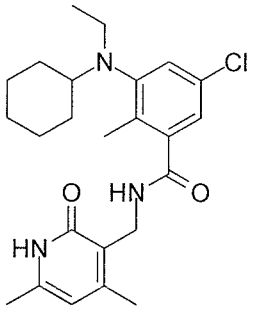


Compound 54

[01321] 3-(Cyclopentyl (methyl) amino)-N-((4, 6-dimethyl-2-oxo-1, 2-dihydropyridin-3-yl) methyl)-2-methyl-5-(piperazin-1-yl) benzamide (free base) (0.100 g, 0.223 mmol) was dissolved in methanol (5 mL) and cooled to 0 ° C before formalin (0.033 g, 1.1 mL, 2.23 mmol) was added. The resulting reaction mixture was stirred at same temperature for 30 minutes. Sodium cyanoborohydride (0.013 g, 0.22 mmol) was added to above reaction mixture and stirred at room temperature for 4 h. After completion, solvent was removed under reduced pressure and water added to the residue, with extraction carried out using DCM. The combined organic layers were dried, concentrated and purified by column chromatography to provide desired 3-(cyclopentyl (methyl) amino)-N-((4, 6-dimethyl-2-oxo-1, 2-dihydropyridin-3-yl) methyl)-2-methyl-5-(4-methylpiperazin-1-yl) benzamide (0.037 g, 36%).

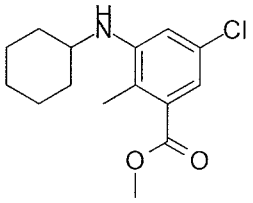
[01322] LCMS: 466.40 $(M+1)^+$; HPLC: 99.18% (@ 254 nm) (R_t;3.871); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.45 (s, 1H), 7.94 (t, 1H), 6.71 (s, 1H), 6.48 (s, 1H), 5.85 (s, 1H), 4.24 (d, 2H, J=3.2 Hz), 3.39-3.43 (m, 1H), 3.07 (bs, 4H), 2.46 (s, 3H), 2.31 (s, 3H), 2.18 (s, 3H), 2.10 (s, 3H), 2.08 (s, 3H), 1.66 (m, 2H), 1.59 (m, 2H), 1.39-1.48 (m, 4H).

[01323] **Example 33:** Synthesis of Compound 55: 5-chloro-3-(cyclohexyl(ethyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide



Compound 55

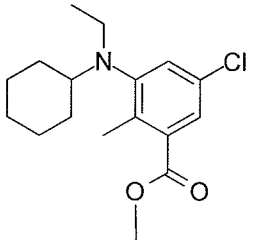
[01324] Step 1: Synthesis of methyl 5-chloro-3-(cyclohexylamino)-2-methylbenzoate



[01325] To a stirred solution of methyl 3-amino-5-chloro-2-methylbenzoate (1 g, 5.02 mmol) and cyclohexanone (2.45 g, 25 mmol) in methanol (10 mL), acetic acid (0.3 g, 5.02 mmol) was

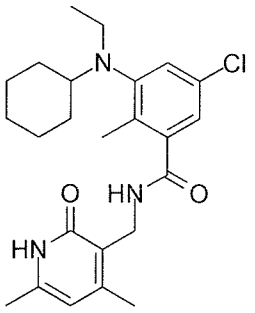
added and reaction stirred at room temperature for 3 h. Then sodium cyanoborohydride (0.63 g, 10.05 mmol) was added and reaction stirred overnight. On completion, solvent was removed under reduced pressure and crude material was purified by column chromatography to afford methyl 5-chloro-3-(cyclohexylamino)-2-methylbenzoate (1.2 g, 89.92 %).

[01326] Step 2: Synthesis of methyl 5-chloro-3-(cyclohexyl (ethyl) amino)-2-methylbenzoate



[01327] To a stirred solution of methyl 5-chloro-3-(cyclohexylamino)-2-methylbenzoate (1.2 g, 4.3 mmol) in dry DMF (15 mL), cesium carbonate (2.78 g, 8.5 mmol) and ethyl iodide (3.35 g, 21.47 mmol) were added. The resulting reaction mixture was heated at 80 °C for 18 h. On completion, the reaction mixture was cooled to room temperature and filtered, and the residue washed with ethyl acetate. The filtrate was concentrated and purified by column chromatography to afford methyl 5-chloro-3-(cyclohexyl (ethyl) amino)-2-methylbenzoate (0.25 g, 22.7 %).

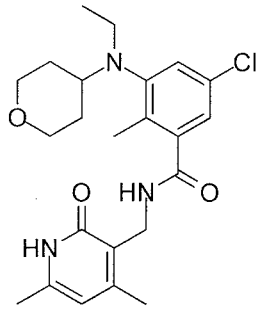
[01328] Step 3: Synthesis of 5-chloro-3-(cyclohexyl (ethyl) amino)-N-((4, 6-dimethyl-2-oxo-1, 2-dihydropyridin-3-yl) methyl)-2-methylbenzamide



[01329] Aqueous NaOH (0.065 g, 1.61 mmol) was added to a solution of methyl 5-chloro-3-(cyclohexyl (ethyl) amino)-2-methylbenzoate (0.25 g, 0.809 mmol) in EtOH (5 mL) and stirred at 60 °C for 1 h. After completion of the reaction, ethanol was removed under reduced pressure and acidified using dilute HCl up to pH 6 and pH 4 was adjusted using citric acid. Extraction was carried out using ethyl acetate. Combined organic layers were dried concentrated giving respective acid (0.22 g, 92 %).

[01330] The acid (0.22 g, 0.745 mmol) was then dissolved in DMSO (2 mL) and 3-(amino methyl)-4,6-dimethylpyridin-2(1H)-one (0.246 g, 1.49 mmol) was added to it. The reaction mixture was stirred at room temperature for 15 min before PYBOP (0.58 g, 1.11 mmol) was added to it and stirring was continued for overnight. After completion of the reaction, the mixture was poured into ice to obtain a solid which was filtered and washed with acetonitrile. Final purification by column purification gave 5-chloro-3-(cyclohexyl (ethyl) amino)-N-((4, 6-dimethyl-2-oxo-1, 2-dihydropyridin-3-yl) methyl)-2-methylbenzamide (0.200 g, 46.6%). LCMS: 430.20 $(M + 1)^+$; HPLC: 92.49% (@ 254 nm) (R_t;5.264); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.45 (s, 1H), 8.21 (t, 1H), 7.12 (s, 1H), 6.91 (s, 1H), 5.85 (s, 1H), 4.23 (d, 2H, J=4.4 Hz), 3.01-3.03 (m, 2H), 2.64-2.66 (m, 1H), 2.18 (s, 3H), 2.13 (s, 3H), 2.10 (s, 3H), 1.68 (m, 4H), 1.51-1.53 (m, 1H), 1.07-1.34 (m, 5H), 0.78 (t, 3H, J=6.8 Hz).

[01331] **Example 34:** Synthesis of Compound 56: 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-2-methylbenzamide

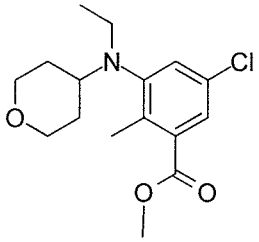


Compound 56

[01332] Step 1: Synthesis of methyl 5-chloro-2-methyl-3-((tetrahydro-2H-pyran-4-yl)amino) benzoate

[01333] To a stirred solution of methyl 3-amino-5-chloro-2-methylbenzoate (1 g, 5.02 mmol) and tetrahydropyran-4-one (2.5 g, 25 mmol) in methanol (10 mL), acetic acid (0.3 g, 5.02 mmol) was added and reaction stirred at room temperature for 3 h. Then sodium cyanoborohydride (0.63 g, 10.05 mmol) was added and reaction stirred overnight. On completion, solvent was removed under reduced pressure and crude material was purified by column chromatography to afford methyl 5-chloro-2-methyl-3-((tetrahydro-2H-pyran-4-yl)amino)benzoate (0.5 g, 35.5 %).

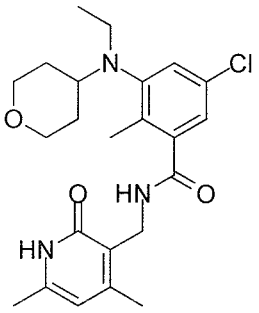
[01334] Step 2: Synthesis of methyl 5-chloro-3-(ethyl (tetrahydro-2H-pyran-4-yl) amino)-2-methylbenzoate



[01335] To a stirred solution of methyl 5-chloro-2-methyl-3-((tetrahydro-2H-pyran-4-yl)amino)benzoate (0.5 g, 1.76 mmol) in dry CAN (15 mL), cesium carbonate (1.2 g, 3.68 mmol) and ethyl iodide (2.7 g, 17.3 mmol) were added and the resulting reaction mixture was heated at 80 °C for 18 h. On completion, the mixture was cooled to room temperature and filtered with the residue washed with ethyl acetate. The filtrate was concentrated and then purified by column chromatography to afford desired methyl 5-chloro-3-(ethyl (tetrahydro-2H-pyran-4-yl) amino)-2-methylbenzoate (0.180 g, 34 %).

[01336]

[01337] Step 3: Synthesis of 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-2-methylbenzamide

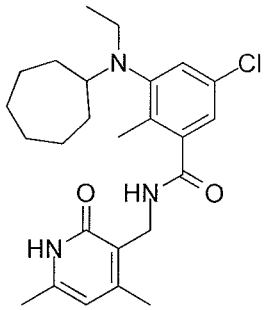


[01338] Aqueous NaOH (0.05 g, 1.22 mmol) was added to a solution of methyl 5-chloro-3-(ethyl (tetrahydro-2H-pyran-4-yl) amino)-2-methylbenzoate (0.18 g, 0.608 mmol) in EtOH (5 mL) and stirred at 60 °C for 1 h. After completion of the reaction, ethanol was removed under reduced pressure and acidified using dilute HCl up to pH 6 and pH 4 and adjusted using citric acid. Extraction was carried out using ethyl acetate and the combined organic layers were dried and concentrated giving respective acid (0.15 g, 87 %).

[01339] The acid (0.15 g, 0.530 mmol) was then dissolved in DMSO (1 mL) and 3-(amino methyl)-4,6-dimethylpyridin-2(1H)-one (0.160 g, 1.06 mmol) was added to it. The reaction

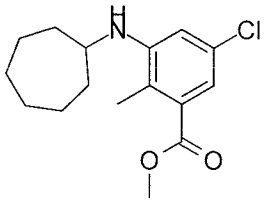
mixture was stirred at room temperature for 15 min before PYBOP (0.413 g, 0.79 mmol) was added to it and stirring was continued for overnight. After completion of the reaction, reaction mixture was poured into ice and extraction was carried out using 10%MeOH/DCM. Combined organic layers were dried, concentrated and purified by silica gel column to afford 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-2-methylbenzamide (0.100 g, 43.88%). LCMS: 432.25 $(M + 1)^+$; HPLC: 90.46% (@ 254 nm) (R_t;4.833); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.46 (s, 1H), 8.22 (t, 1H), 7.19 (s, 1H), 6.96 (s, 1H), 5.85 (s, 1H), 4.23 (d, 2H, J=4 Hz), 3.81 (d, 2H, J=10 Hz), 3.20-3.21 (m, 2H), 2.94-3.02 (m, 3H), 2.18 (s, 3H), 2.15 (s, 3H), 2.10 (s, 3H), 1.48-1.61 (m, 4H), 0.78 (t, 3H, J=6.4 Hz).

[01340] **Example 35:** Synthesis of Compound 57: 5-chloro-3-(cycloheptyl(ethyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide



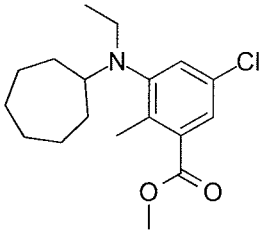
Compound 57

[01341] Step 1: Synthesis of methyl 5-chloro-3-(cycloheptylamino)-2-methylbenzoate



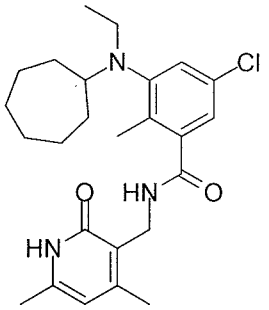
[01342] To a stirred solution of methyl 3-amino-5-chloro-2-methylbenzoate (1 g, 5.02 mmol) and cycloheptanone (2.81 g, 25 mmol) in methanol (10 mL), acetic acid (0.3 g, 5.02 mmol) was added and reaction stirred at room temperature for 3 h. Then sodium cyanoborohydride (0.65 g, 10.05 mmol) was added and reaction stirred overnight. On completion, solvent was removed under reduced pressure and crude material was purified by column chromatography to afford 5-chloro-3-(cycloheptylamino)-2-methylbenzoate (0.8 g, 56.2 %).

[01343] Step 2: Synthesis of methyl 5-chloro-3-(cycloheptyl (ethyl) amino)-2-methylbenzoate



[01344] To a stirred solution of 5-chloro-3-(cycloheptylamino)-2-methylbenzoate (0.8 g, 2.70 mmol) in dry DMF (10 mL), cesium carbonate (1.76 g, 5.4 mmol) and ethyl iodide (2.11 g, 13.5 mmol) were added and the resulting reaction mixture heated at 80 °C for 18 h. On completion, the mixture was cooled to room temperature and filtered, the residue washed with ethyl acetate and the filtrate concentrated before purification by column chromatography to afford the desired methyl 5-chloro-3-(cycloheptyl (ethyl) amino)-2-methylbenzoate (0.220 g, 25 %).

[01345] Step 3: Synthesis of 5-chloro-3-(cycloheptyl (ethyl) amino)-N-((4, 6-dimethyl-2-oxo-1, 2-dihydropyridin-3-yl) methyl)-2-methylbenzamide

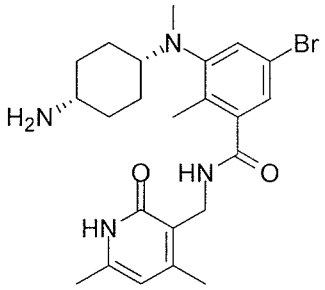


[01346] Aqueous NaOH (0.04g, 1.02 mmol) was added to a solution of methyl 5-chloro-3-(cycloheptyl (ethyl) amino)-2-methylbenzoate (0.22 g, 0.68 mmol) in EtOH (5 mL) and stirred at 60 °C for 1 h. After completion of the reaction, ethanol was removed under reduced pressure and acidified using dilute HCl up to pH 6 and pH 4 and adjusted using citric acid. Extraction was carried out using ethyl acetate. With the combined organic layers dried and concentrated giving the respective acid (0.18 g, 85 %).

[01347] The acid (0.18 g, 0.585 mmol) was then dissolved in DMSO (1.5 mL) and 3-(amino methyl)-4,6-dimethylpyridin-2(1H)-one (0.177 g, 1.16 mmol) was added to it. The reaction mixture was stirred at room temperature for 15 min before PYBOP (0.45 g, 0.87 mmol) was added to it and stirring was continued for overnight. After completion of the reaction, the

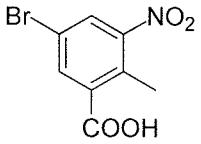
reaction mixture was poured into ice to obtain solid, which was filtered and washed with acetonitrile before column purification to 5-chloro-3-(cycloheptyl (ethyl) amino)-N-((4, 6-dimethyl-2-oxo-1, 2-dihydropyridin-3-yl) methyl)-2-methylbenzamide (0.100 g, 38.7%). LCMS: 444.25 $(M + 1)^+$; HPLC: 89.74% (@ 254 nm) (R_t;5.933); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.46 (s, 1H), 8.21 (t, 1H), 7.07 (s, 1H), 6.88 (s, 1H), 5.85 (s, 1H), 4.23 (d, 2H, J=4 Hz), 3.02-3.03 (m, 2H), 2.77 (bs, 1H), 2.18 (s, 3H), 2.13 (s, 3H), 2.10 (s, 3H), 1.76 (m, 2H), 1.59-1.62 (m, 4H), 1.46 (m, 4H), 1.28 (m, 2H), 0.78 (t, 3H, J=6 Hz).

[01348] **Example 36:** Synthesis of Compound 58: *Cis*-3-((4-aminocyclohexyl)(methyl)amino)-5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide



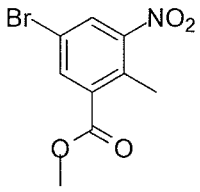
Compound 58

[01349] Step1: Synthesis of 5-bromo-2-methyl-3-nitrobenzoic acid



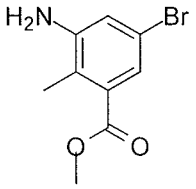
[01350] To stirred solution of 2-methyl-3-nitrobenzoic acid (50 g, 276.2 mmol) in conc. H_2SO_4 (200 mL), 1,3-dibromo-5,5-dimethyl-2,4-imidazolidinedione (43.4 g, 151.8 mmol) was added portion wise at room temperature and reaction mass was stirred at room temperature for 5 h. On completion, reaction mixture was poured onto ice cold water, solid precipitated was filtered, resulting residue was washed with water and dried under vacuum giving desired compound (71.7 g, 100%) which was used as is in subsequent steps.

[01351] Step2: Synthesis of methyl 5-bromo-2-methyl-3-nitrobenzene



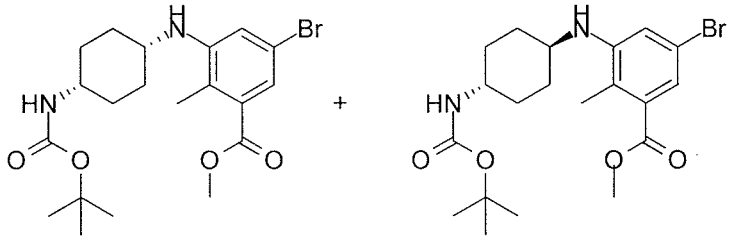
[01352] To stirred solution of 5-bromo-2-methyl-3-nitrobenzoic acid (287 g, 1103 mmol) in DMF (150 mL), sodium carbonate (468 g, 4415 mmol) and methyl iodide (626.63 g, 4415 mmol) were added. The resulting reaction mixture was heated at 60 °C for 8 h. On completion, a solid precipitated was filtered, residue washed with diethyl ether (5 times). The combined organic layers were dried, concentrated under reduced pressure giving desired compound (302 g, 99%) which was used as is in subsequent steps.

[01353] Step3: Synthesis of methyl 3-amino-5-bromo-2-methylbenzoate



[01354] To a stirred solution of methyl 5-bromo-2-methyl-3-nitrobenzene (150 g, 544 mmol) in ethanol (750 mL), ammonium chloride (150 g, 2777 mmol) dissolved in water (750 mL) and iron powder (93.3 g, 1636 mmol) were added under stirring. The resulting reaction mixture was heated at 80 °C for 7 h. On completion, reaction mass was filtered through celite; giving washings of water and ethyl acetate to the residue, filtrate was extracted with ethyl acetate. Combined organic layers were dried, concentrated under reduced pressure giving desired compound which was used in subsequent steps without further purification.

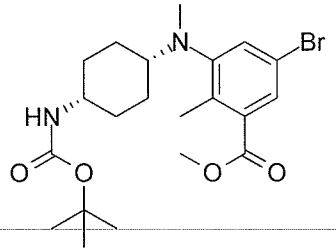
[01355] Step 4: Synthesis of cis and trans methyl 5-bromo-3-((4-((tert-butoxycarbonyl)amino) cyclohexyl) amino)-2-methylbenzoate



[01356] To a stirred solution of methyl 3-amino-5-bromo-2-methylbenzoate (5 g, 20.57 mmol) and tert-butyl (4-oxocyclohexyl)carbamate (5.6 g, 26.7 mmol) in methanol (50 mL), acetic acid (1.2 g, 20.57 mmol) was added and reaction stirred at room temperature for 8 h. Then sodium

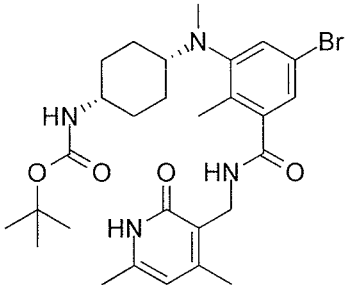
cyanoborohydride (1.6 g, 26.74 mmol) was added at 0oC and reaction stirred overnight. On completion, solvent was removed under reduced pressure and crude material was purified by column chromatography twice eluting with ethyl acetate: hexane to afford (4g , 44%) of less polar cis isomer and (3g, 33%) of the pure more polar trans isomer.

[01357] Step 5: Synthesis of *Cis*-methyl 5-bromo-3-((4-((tert-butoxycarbonyl) amino) cyclohexyl) (methyl) amino)- 2-methylbenzoate



[01358] To a stirred solution of mixture of cis isomer of methyl 5-bromo-3-((4-((tert-butoxycarbonyl)amino) cyclohexyl) amino)-2-methylbenzoate (4 g, 9.09 mmol) in acetonitrile (50 mL) was added cesium carbonate (5.9 g, 18.18 mmol) and methyl iodide (6.45 g, 45.45 mmol). The resulting reaction mixture was heated at 80 °C for 7 h. On completion, the reaction mixture was cooled to room temperature and filtered, the residue was washed with ethyl acetate and filtrate was concentrated to afford desired crude compound which then purified by column chromatography giving desired compound (1.4 g, 34%).

[01359] Step6: Synthesis of *Cis*-tert-butyl (4-((5-bromo-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(methyl)amino)cyclohexyl)carbamate

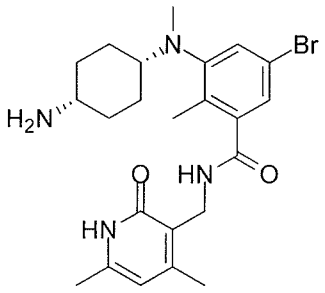


[01360] Aqueous NaOH (0.23 g, 5.72 mmol) was added to a solution of *cis*-methyl 5-bromo-3-((4-((tert-butoxycarbonyl) amino) cyclohexyl) (methyl) amino)- 2-methylbenzoate (1.3 g, 2.86 mmol) in MeOH (20 mL) and stirred at 60 °C for 1 h. After completion of the reaction, ethanol was removed under reduced pressure and acidified using dilute HCl up to pH 6 and pH

4 was adjusted using citric acid. Extraction was carried out using ethyl acetate. Combined organic layers were dried concentrated giving respective acid (1.13 g, 90.1%).

[01361] The acid (1.13 g, 2.57 mmol) was then dissolved in DMSO (10 mL) and 3-(amino methyl)-4,6-dimethylpyridin-2(1H)-one (0.87 g, 5.72 mmol) was added to it. The reaction mixture was stirred at room temperature for 15 min before PYBOP (2.23 g, 4.28 mmol) was added to it and stirring was continued for overnight. After completion of the reaction, reaction mass was poured into ice to obtain solid, this was filtered and washed with acetonitrile followed by purification with column chromatography to afford the desired compound (0.8 g, 49%).

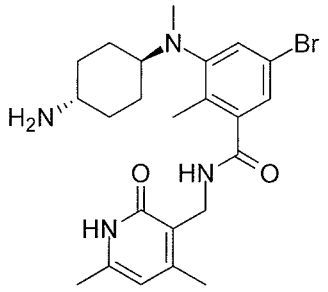
[01362] Step7: Synthesis of *Cis*-3-((4-aminocyclohexyl)(methyl)amino)-5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide



[01363] A stirred solution of *cis*-tert-butyl (4-((5-bromo-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl) (methyl)amino)cyclohexyl)carbamate (0.8 g, 1.39 mmol) in DCM (25 mL) was cooled to 0°C and TFA (5 mL) was added to it. The reaction mixture was stirred at room temperature for 1 h. Upon completion, reaction was concentrated to dryness. Residue was basified with aqueous sodium bicarbonate till pH 8 and aqueous layer extracted with 20% MeOH/DCM. The combined organic layers were dried over sodium sulfate, filtered and concentrated to afford the desired compound (600 mg, 91% yield). LCMS: 475.15 $(M + 1)^+$; HPLC% 95.88(@ 254 nm) (R_t;4.832; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 µ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 µL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.22 (t, 1H), 7.20 (s, 1H), 7.01 (s, 1H), 5.85 (s, 1H), 4.23 (d, 2H, J=3.6 Hz), 2.82-2.86 (m, 2H), 2.53 (s, 3H), 2.18 (s, 3H), 2.13 (s, 3H), 2.10 (s, 3H), 1.82-1.84 (m, 2H), 1.34-1.44 (m, 6H).

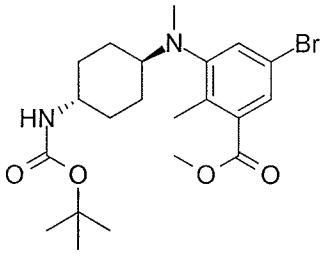
[01364] 100mg of *cis*-3-((4-aminocyclohexyl)(methyl)amino)-5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide (free base) was then dissolved in methanolic HCl (5 mL) and stirred at room temperature for 1 h. On completion of salt formation solvent was removed under reduced pressure and resulting solid was purified by washing with diethyl ether to afford the corresponding HCl salt. **Analytical Data of HCl salt:** LCMS: 475.20(M + 1)$^+$; HPLC% 96.09(@ 254 nm) (R_t;4.818; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 μ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 μL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.51 (s, 1H), 8.28 (t, 1H), 8.08 (s, 3H), 7.31 (s, 1H), 7.08 (s, 1H), 5.90 (s, 1H), 4.24 (d, 2H, J=4.4 Hz), 3.05-3.13 (m, 2H), 2.54 (s, 3H), 2.19 (s, 6H), 2.12 (s, 3H), 1.83 (m, 2H), 1.66 (m, 2H), 1.59-1.60 (m, 2H), 1.46 (m, 2H).

[01365] **Example 37:** Synthesis of Compounds 59: *Trans*-3-((4-aminocyclohexyl)(methyl)amino)-5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide



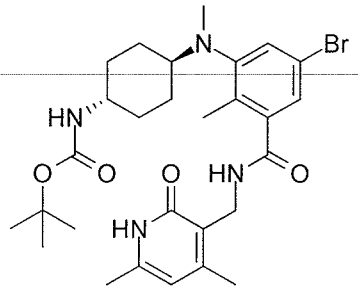
Compound 59

[01366] Step 1: Synthesis of *Trans*-methyl 5-bromo-3-((4-((tert-butoxycarbonyl) amino) cyclohexyl) (methyl) amino)- 2-methylbenzoate



[01367] To a stirred solution of *trans*-methyl 5-bromo-3-((4-((tert-butoxycarbonyl)amino)cyclohexyl)amino)-2-methylbenzoate (3 g, 6.81 mmol) in acetonitrile (40 mL), cesium carbonate (4.4 g, 13.62 mmol) and methyl iodide (4.83 g, 34.05 mmol) were added; the resulting reaction mixture was heated at 80 °C for 7 h. Upon completion, the reaction mixture was cooled to room temperature and filtered, the residue was washed with ethyl acetate and filtrate was concentrated to afford desired crude compound which then purified by column chromatography giving the desired compound (1.3 g, 43%).

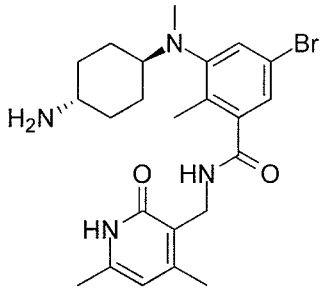
[01368] Step2: Synthesis of *Trans*-tert-butyl (4-((5-bromo-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(methyl)amino) cyclohexyl)carbamate



[01369] Aqueous NaOH (0.23 g, 5.72 mmol) was added to a solution of *trans*-methyl 5-bromo-3-((4-((tert-butoxycarbonyl) amino) cyclohexyl) (methyl) amino)- 2-methylbenzoate (1.3 g, 2.86 mmol) in MeOH (20 mL) and was stirred at 60 °C for 1 h. After completion of the reaction, ethanol was removed under reduced pressure and the residue was acidified using dilute HCl up to pH 6 and to pH 4 using citric acid. The mixture was extracted was with ethyl acetate. The combined organic layers were dried, filtered and concentrated to give the respective acid (1 g, 83%).

[01370] The acid (1 g, 2.27 mmol) was then dissolved in DMSO (5 mL) and 3-(amino methyl)-4,6-dimethylpyridin-2(1H)-one (0.65 g, 4.54 mmol) was added to it. The reaction mixture was stirred at room temperature for 15 min before PYBOP (1.7 g, 3.4 mmol) was added to it and stirring was continued for overnight. After completion of the reaction, reaction mass was poured into ice to obtain solid, this was filtered and washed with acetonitrile followed by purification with column chromatography to afford the desired compound (0.7 g, 54%).

[01371] Step 3: Synthesis of *Trans*-3-((4-aminocyclohexyl)(methyl)amino)-5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide

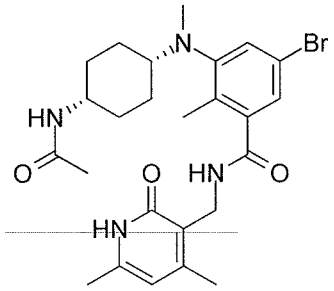


[01372] A stirred solution of *trans*-tert-butyl (4-((5-bromo-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(methyl)amino) cyclohexyl)carbamate (0.7 g, 1.21 mmol) in DCM (8 mL) was cooled to 0°C and TFA (2.5 mL) was added to it. Reaction mass was stirred at room temperature for 1 h. On completion, reaction was concentrated to dryness. Residue was basified with aqueous sodium bicarbonate till pH 8 and aqueous layer extracted with 20% MeOH/DCM. The combined organic layers were dried over sodium sulfate, filtered and concentrated to afford crude material which was then purified by solvent washings giving desired compound (0.5 g, 86 %). LCMS: 475.20 $(M + 1)^+$; HPLC% 92.35(@ 254 nm) (R_t;4.416; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 µ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 µL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.21 (t, 1H), 7.18 (s, 1H), 7.01 (s, 1H), 5.85 (s, 1H), 4.23 (d, 2H), 2.63-2.66 (m, 2H), 2.55 (s, 3H), 2.17 (s, 3H), 2.10 (s, 6H), 1.79-1.82 (m, 2H), 1.60 (m, 2H), 1.46-1.49 (m, 2H), 1.06-1.09 (m, 2H).

[01373] 100mg of *trans*-3-((4-aminocyclohexyl)(methyl)amino)-5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide (free base) was then dissolved in methanolic HCl (5 mL) and stirred at room temperature for 1 h. On completion of salt formation, the solvent was removed under reduced pressure and resulting solid was purified by washing with diethyl ether to afford the corresponding HCl salt. **Analytical data of HCl salt:** LCMS: 475.20$(M + 1)^+$; HPLC% 91.40(@ 254 nm) (R_t;4.408; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 µ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 µL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.51 (s, 1H), 8.28 (t, 1H), 8.06 (s, 3H), 7.31 (s, 1H), 7.08 (s, 1H), 5.89 (s, 1H), 4.24 (d, 2H, J=4.4

Hz), 2.92 (bs, 1H), 2.62-2.91 (m, 4H), 2.19 (s, 3H), 2.13 (s, 3H), 2.11 (s, 3H), 1.97 (d, 2H, J=10.8 Hz), 1.70 (m, 2H), 1.53-1.56 (m, 2H), 1.31-1.34 (m, 2H).

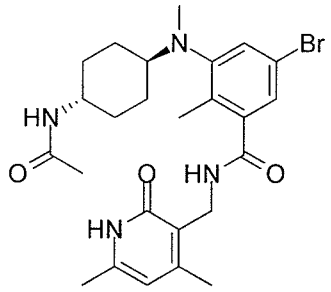
[01374] **Example 38:** Synthesis of Compound 60: *Cis*-3-((4-acetamidocyclohexyl)(methyl)amino)-5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide



Compound 60

[01375] To a stirred solution of compound *cis*-3-((4-aminocyclohexyl)(methyl)amino)-5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide (free base) (0.225, 0.474mmol) in DMF (3 mL), EDCI.HCl (0.138 g, 0.718 mmol), HOBt (0.064 g, 0.47 mmol), triethyl amine (0.1 g, 0.99 mmol) and acetic acid (0.057 g, 0.949 mmol) were added at room temperature and stirred at same temperature for 18 h. On completion, water was added and extracted with 10% MeOH/DCM. Combined organic layers were dried, concentrated giving crude material; which then purified by column chromatography to afford the desired compound (0.17 g, 72%). LCMS: 517.25$(M + 1)^+$; HPLC% 95.83(@ 254 nm) (R_t;4.894; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 µ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 µL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.46 (s, 1H), 8.22 (t, 1H), 7.76 (d, 1H, J=7.2 Hz), 7.23 (s, 1H), 7.03 (s, 1H), 5.85 (s, 1H), 4.23 (d, 2H, J=3.6 Hz), 3.71 (bs, 1H), 2.89 (m, 1H), 2.53 (s, 3H), 2.18 (s, 3H), 2.16 (s, 3H), 2.10 (s, 3H), 1.81 (s, 3H), 1.74-1.76 (m, 2H), 1.53 (m, 2H), 1.39 (m, 4H).

[01376] **Example 39:** Synthesis of Compounds 61: *Trans*-3-((4-acetamidocyclohexyl)(methyl)amino)-5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide

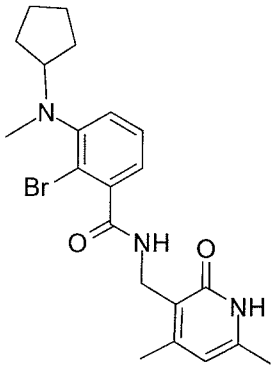


Compound 61

[01377] To a stirred solution of *trans*-3-((4-aminocyclohexyl)(methyl)amino)-5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide (0.225, 0.474mmol) in DMF (3 mL), EDCI.HCl (0.138 g, 0.718 mmol), HOBt (0.064 g, 0.47 mmol), triethyl amine (0.1 g, 0.99 mmol) and acetic acid (0.057 g, 0.949 mmol) were added at room temperature and stirred at same temperature for 18 h. On completion, water was added and extracted with 10% MeOH/DCM. Combined organic layers were dried, concentrated giving crude material; which then purified by column chromatography to afford desired compound (0.13 g, 53%).

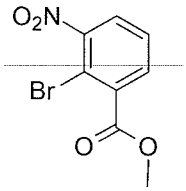
[01378] LCMS: 517.20 $(M + 1)^+$; HPLC% 93.92(@ 254 nm) (R_t;4.713; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 µ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 µL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.45 (s, 1H), 8.20 (t, 1H), 7.65 (d, 1H, J=7.6 Hz), 7.18 (s, 1H), 7.01 (s, 1H), 5.85 (s, 1H), 4.23 (d, 2H, J=3.6 Hz), 3.42-3.44 (m, 1H), 2.68-2.71 (m, 1H), 2.56 (s, 3H), 2.18 (s, 3H), 2.10 (s, 6H), 1.77-1.80 (m, 2H), 1.74 (s, 3H), 1.62-1.65 (m, 2H), 1.46-1.54 (m, 2H), 1.07-1.23 (m, 2H).

[01379] **Example 40:** Synthesis of Compound 62: 2-bromo-3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)benzamide



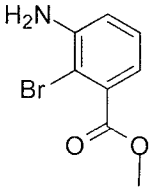
Compound 62

[01380] Step 1: methyl 2-bromo-3-nitrobenzoate



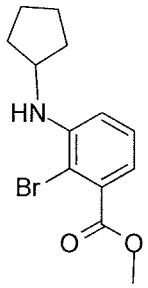
[01381] To a stirred solution of 2-bromo-3-nitrobenzoate (3 g, 12.19 mmol) in DMF (33 mL), sodium carbonate (5.16 g, 48.67 mmol) and methyl iodide (6.92 g, 48.67 mmol) were added. Resulting reaction mixture was heated at 60 °C for 4 h. On completion, water was added to the mixture and extraction carried out using DCM. The combined organic layers were dried and concentrated under reduced pressure to obtain crude methyl 2-bromo-3-nitrobenzoate (4 g, crude).

[01382] Step 2: Synthesis of methyl 3-amino-2-bromobenzoate



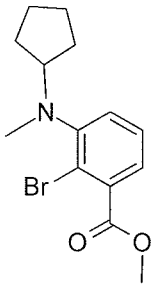
[01383] To a stirred solution of methyl 2-bromo-3-nitrobenzoate (4 g, 15.38 mmol) in ethanol (20 mL), ammonium chloride (4 g, 74.07 mmol) dissolved in water (20 mL) and iron powder (6.88 g, 123 mmol) were added under stirring. Resulting reaction mixture was heated at 80 °C for 1 h. On completion, water was added to the mixture and filtered through celite. The filtrate was extracted with ethyl acetate and the combined organic layers washed with water and sodium bicarbonate solution, dried and concentrated under reduced pressure giving the desired methyl 3-amino-2-bromobenzoate (3 g, 85 %) which was used without further purification.

[01384] Step 3: Synthesis of methyl 2-bromo-3-(cyclopentylamino) benzoate



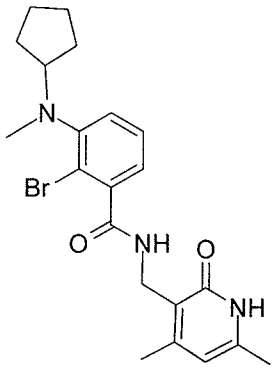
[01385] To a stirred solution of methyl 3-amino-2-bromobenzoate (3 g, 13.0 mmol) and cyclopentanone (5.4 g, 64.28 mmol) in methanol (20 mL), acetic acid (1.56 g, 26 mmol) was added and reaction stirred at room temperature for 3 h. Then sodium cyanoborohydride (2 g, 31.7 mmol) was added and reaction stirred overnight. On completion, solvent was removed under reduced pressure and crude material purified by column chromatography to afford methyl 2-bromo-3-(cyclopentylamino) benzoate (1.4 g, 36 %).

[01386] Step 4: Synthesis of methyl 2-bromo-3-(cyclopentyl (methyl) amino) benzoate



[01387] To a stirred solution of methyl 2-bromo-3-(cyclopentylamino) benzoate (1.4 g, 4.69 mmol) in acetonitrile (10 mL), cesium carbonate (3 g, 9.2 mmol) and methyl iodide (3.38 g, 23.3 mmol) were added and the resulting reaction mixture heated at 80 °C for 12 h. On completion, the mixture was cooled to room temperature and filtered and the residue was washed with ethyl acetate. The filtrate was concentrated and purified by column chromatography to afford methyl 2-bromo-3-(cyclopentyl (methyl) amino) benzoate (1.1 g, 75 %).

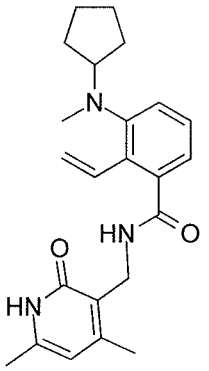
[01388] Step 5: Synthesis of 2-bromo-3-(cyclopentyl (methyl) amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)benzamide



[01389] Aqueous NaOH (0.064 g, 1.6 mmol) was added to a solution of methyl 2-bromo-3-(cyclopentyl (methyl) amino) benzoate (0.25 g, 0.801 mmol) in MeOH (5 mL) and stirred at 60 °C for 1 h. After completion of the reaction, ethanol was removed under reduced pressure and acidified using dilute HCl up to pH 6 and pH 4 was adjusted using citric acid. Extraction was carried out using ethyl acetate. Combined organic layers were dried concentrated giving respective acid (0.2 g, 84%).

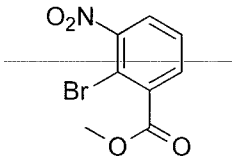
[01390] The acid (0.2 g, 0.67 mmol) was then dissolved in DMSO (1.5 mL) and 3-(amino methyl)-4,6-dimethylpyridin-2(1H)-one (0.204 g, 1.34 mmol) was added to it. The reaction mixture was stirred at room temperature for 15 min before PYBOP (0.516 g, 1.00 mmol) was added to it and stirring was continued for overnight. After completion of the reaction, the mixture was poured into ice to obtain a solid, which was filtered and washed with acetonitrile. Final purification by preparative HPLC provided 2-bromo-3-(cyclopentyl (methyl) amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)benzamide as the TFA salt (0.02 g, 6.89%). LCMS: 432.10 $(M + 1)^+$; HPLC% 96.05(@ 254 nm) (R_t;4.908); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.47 (s, 1H), 8.21 (t, 1H), 7.26-7.29 (m, 2H), 6.94 (d, 1H, J=8 Hz), 5.86 (s, 1H), 4.25 (d, 2H), 3.59 (m, 1H), 2.56 (s, 3H), 2.19 (s, 3H), 2.10 (s, 3H), 1.61-1.67 (m, 4H), 1.46 (bs, 4H).

[01391] **Example 41:** Synthesis of Compound 63: 3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-vinylbenzamide



Compound 63

[01392] Step 1: Synthesis of methyl 2-bromo-3-nitrobenzoate

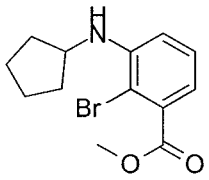


[01393] To a stirred solution of 2-bromo-3-nitrobenzoic acid (3 g, 12.19 mmol) in DMF (30 mL), sodium carbonate (5.16 g, 48.6 mmol) and methyl iodide (6.92 g, 48.7 mmol) were added. Resulting reaction mixture was heated at 60 °C for 8 h. On completion, solid precipitated was filtered, residue washed with ethyl acetate (5 times). Combined organic layers were dried, concentrated under reduced pressure giving desired crude 2-bromo-3-nitrobenzoate (4 g, 99%) which was used without further purification.

[01394] Step 2: Synthesis of methyl 3-amino-2-bromobenzoate

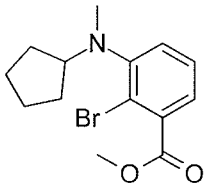
[01395] To stirred solution of above crude 2-bromo-3-nitrobenzoate (4 g, 15.38 mmol) in ethanol (20 mL), ammonium chloride (4 g, 74.0 mmol) dissolved in water (20 mL) and iron powder (6.87 g, 123 mmol) were added under stirring. The resulting reaction mixture was heated at 80 °C for 7 h. On completion, the reaction mixture was filtered through celite, washing with water and ethyl acetate and the filtrate extracted with ethyl acetate. The combined organic layers were dried and concentrated under reduced pressure giving the desired crude product (3 g).

[01396] Step 3: Synthesis of methyl 2 -bromo-3-(cyclopentylamino) benzoate



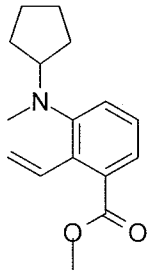
[01397] To a stirred solution of methyl 3-amino-2-bromobenzoate (3 g, 13.01 mmol) and cyclopentanone (5.6 g, 66 mmol) in methanol (30 mL), acetic acid (1.59 g, 26.6 mmol) was added and the reaction stirred at room temperature for 3 h. Then sodium cyanoborohydride (2.08 g, 29.4 mmol) was added and the mixture stirred overnight. On completion, solvent was removed under reduced pressure and crude material was purified by column chromatography to afford methyl 2-bromo-3-(cyclopentylamino) benzoate (1.4 g, 36%).

[01398] Step 4: Synthesis of methyl 2-bromo-3-(cyclopentyl (methyl) amino) benzoate



[01399] To a stirred solution of methyl 2-bromo-3-(cyclopentylamino) benzoate (1.4 g, 4.69 mmol) in acetonitrile (20 mL), cesium carbonate (3.0 g, 9.2 mmol) and methyl iodide (3.38 g, 23.4 mmol) were added and the resulting reaction mixture heated at 80 °C for 12 h. On completion, the mixture was cooled to room temperature and filtered and the residue washed with ethyl acetate. The filtrate was concentrated and then purified by column chromatography to afford desired methyl 2-bromo-3-(cyclopentyl (methyl) amino) benzoate (1.1 g, 75 %).

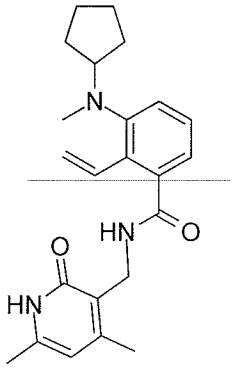
[01400] Step 5: Synthesis of methyl 3-(cyclopentyl(methyl)amino)-2-vinylbenzoate



[01401] To a stirred solution of methyl 2-bromo-3-(cyclopentyl (methyl) amino) benzoate (1 equiv.) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (1.2 equiv.) in dioxane/water mixture (5 mL+1 mL), Na_2CO_3 (3.6 equiv.) was added and solution purged with argon for 15 min. Then, $Pd(PPh_3)_4$ (0.1 equiv.) was added and argon purged for 10 min. and the reaction

mixture heated at 100°C for 2 h. On completion, the reaction mixture was diluted with water and extracted with 10% MeOH/DCM. The combined organic layers were dried over Na_2SO_4 and solvent removed under reduced pressure to afford crude material which was purified by column chromatography over silica gel to afford the desired methyl 3-(cyclopentyl(methyl)amino)-2-vinylbenzoate.

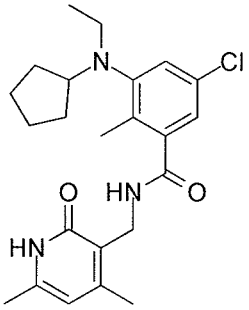
[01402] Step 6: Synthesis of 3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-vinylbenzamide



[01403] To a stirred solution of methyl 3-(cyclopentyl(methyl)amino)-2-vinylbenzoate (1 equiv.) in ethanol (10 mL), aqueous NaOH solution (1.5 equiv. in 10 mL water) was added and reaction stirred at 60°C for 4 h. On completion, ethanol was removed under reduced pressure and residue acidified with 1N HCl to pH 6. The precipitate was filtered, washed with water and dried to obtain pure corresponding acid.

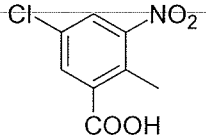
[01404] To a solution of this respective acid (1 equiv.) in DMSO (10 mL), PyBOP (1.5 equiv.) was added and reaction stirred at rt for 15 min. Then 3-(amino methyl)-4,6-dimethylpyridin-2(1H)-one (2 equiv.) was added and reaction stirred overnight. On completion, water was added and the resulting solid filtered and washed with water. This solid was stirred with acetonitrile for 10 min and filtered again to obtain 3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-vinylbenzamide which was purified by preparative HPLC yielding the TFA salt (0.045 g, 10.39 %). LCMS: 380.25 $(M + 1)^+$; HPLC% 98.00(@ 254 nm) (R_t;4.323); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.51 (s, 1H), 8.01 (s, 1H), 7.25 (bs, 2H), 6.81-6.88 (m, 2H), 5.85 (s, 1H), 5.49 (d, 1H, J=18 Hz), 5.40 (bs, 1H), 4.34 (3H merged in solvent peak), 4.19 (d, 3H, J=4.8 Hz), 2.17 (s, 3H), 2.10 (s, 3H), 1.61 (m, 4H), 1.47 (bs, 4H).

[01405] **Example 42:** Synthesis of Compound 64: 5-chloro-3-(cyclopentyl(ethyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide



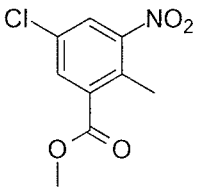
Compound 64

[01406] Step 1: Synthesis of 5-chloro-2-methyl-3-nitrobenzoic acid



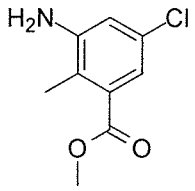
[01407] 5-Chloro-2-methylbenzoic acid (4 g, 23.39 mmol) was added to cooled conc. H_2SO_4 (27 mL) at -10 °C lot wise. After 10 minutes nitrating mixture [Prepared by mixing Conc. HNO3 (3.3 g, 52.68 mmol) with conc.H_2SO_4 (4.4 mL)] was added drop wise at -10 °C. Resulting reaction mixture was stirred at -10 °C for 30 minutes. On completion, the mixture was poured on ice cold water and the resulting solid precipitated was filtered, washed with water and dried under vacuum giving the desired chloro-2-methyl-3-nitrobenzoic acid (4.95 g, 99%).

[01408] Step 2: Synthesis of methyl 5-chloro-2-methyl-3-nitrobenzoate



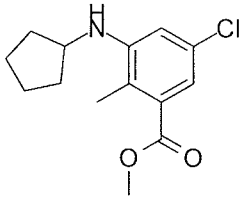
[01409] To a stirred solution of chloro-2-methyl-3-nitrobenzoic acid (6.75 g, 31.25 mmol) in DMF (33 mL), sodium carbonate (13.23 g, 125.18 mmol) and methyl iodide (17.77 g, 125.2 mmol) were added. The resulting reaction mixture was heated at 60 °C for 4 h. On completion, water was added and extracted out using DCM. Combined organic layers were dried, concentrated under reduced pressure and purified by column chromatography over silica (60-120 mesh size) giving methyl 5-chloro-2-methyl-3-nitrobenzoate (6 g, 83.65%).

[01410] Step 3: Synthesis of methyl 3-amino-5-chloro-2-methyl benzoate



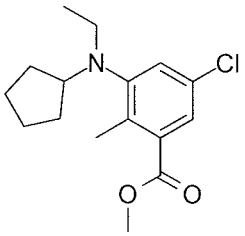
[01411] To a stirred solution of methyl 5-chloro-2-methyl-3-nitrobenzoate (6 g, 26.13 mmol) in ethanol (60 mL), ammonium chloride (6 g, 112.1 mmol) dissolved in water (60 mL) and iron powder (11.88 g, 208.4 mmol) were added under stirring. The resulting reaction mixture was heated at 80 °C for 1 h. On completion, water was added to reaction and the mixture was filtered through celite. The filtrate was extracted with ethyl acetate and the combined organic layers were washed with water, dried, concentrated under reduced pressure giving methyl 3-amino-5-chloro-2-methyl benzoate which was used without further purification.

[01412] Step 4: Synthesis of methyl 5-chloro-3-(cyclopentylamino)-2-methylbenzoate



[01413] To a stirred solution of methyl 3-amino-5-chloro-2-methyl benzoate (1 g, 5.02 mmol) and cyclopentanone (2.1 g, 25 mmol) in methanol (10 mL), acetic acid (0.3 g, 5.02 mmol) was added and reaction stirred at room temperature for 3 h. Then sodium cyanoborohydride (0.37 g, 5.90 mmol) was added and reaction stirred overnight. On completion, solvent was removed under reduced pressure and crude material was purified by column chromatography to afford methyl 5-chloro-3-(cyclopentylamino)-2-methylbenzoate (0.62 g, 46.2 %).

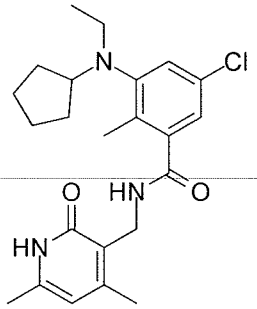
[01414] Step 5: Synthesis of methyl 5-chloro-3-(cyclopentyl (ethyl) amino)-2-methylbenzoate



[01415] To a stirred solution of methyl 5-chloro-3-(cyclopentylamino)-2-methylbenzoate (0.62 g, 2.32 mmol) in dry DMF (10 mL), cesium carbonate (3.78 g, 11.6 mmol) and ethyl iodide (5.43 g, 34.8 mmol) were added and the resulting reaction mass was heated at 80 °C for

18 h. On completion, reaction mixture was cooled to room temperature and filtered. The residue was washed with ethyl acetate and filtrate concentrated and purified by column chromatography to afford desired methyl 5-chloro-3-(cyclopentyl (ethyl) amino)-2-methylbenzoate (0.101 g,
15 %).

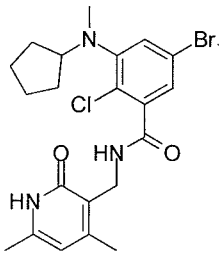
[01416] Step 6: Synthesis of 5-chloro-3-(cyclopentyl (ethyl) amino)-N-((4, 6-dimethyl-2-oxo-1, 2-dihydropyridin-3-yl) methyl)-2-methylbenzamide



[01417] Aqueous NaOH (0.1g, 2.5 mmol) was added to a solution of methyl 5-chloro-3-(cyclopentyl (ethyl) amino)-2-methylbenzoate (0.5 g, 1.69 mmol) in EtOH (10 mL) and stirred at 60 °C for 1 h. After completion of the reaction, ethanol was removed under reduced pressure and acidified using dilute HCl up to pH 6 and pH 4 was adjusted using citric acid. Extraction was carried out using ethyl acetate and the combined organic layers were dried concentrated giving respective acid (0.41 g, 86 %).

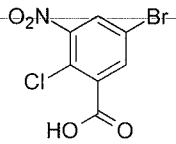
[01418] The acid (0.10 g, 0.355 mmol) was then dissolved in DMSO (1.5 mL) and 3-(amino methyl)-4,6-dimethylpyridin-2(1H)-one (0.104 g, 0.77 mmol) was added to it. The reaction mixture was stirred at room temperature for 15 min before PYBOP (0.277 g, 0.533 mmol) was added to it and stirring was continued for overnight. After completion of the reaction, the mixture was poured into ice and the resulting solid filtered and washed with acetonitrile followed by additional solvent washings to yield 5-chloro-3-(cyclopentyl (ethyl) amino)-N-((4, 6-dimethyl-2-oxo-1, 2-dihydropyridin-3-yl) methyl)-2-methylbenzamide (0.107 g, 72%). LCMS: 416.25 $(M + 1)^+$; HPLC% 91.83(@ 254 nm) (R_t;5.021); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.45 (s, 1H), 8.21 (t, 1H), 7.19 (s, 1H), 6.95 (s, 1H), 5.85 (s, 1H), 4.23 (d, 2H, J=4 Hz), 3.45 (t, 1H), 2.94-2.96 (m, 2H), 2.18 (s, 3H), 2.15 (s, 3H), 2.10 (s, 3H), 1.58-1.64 (m, 4H), 1.47 (m, 2H), 1.32 (m, 2H), 0.77 (t, 3H, J=6.8 Hz).

[01419] **Example 43:** Synthesis of Compound 19: 5-bromo-2-chloro-3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)benzamide



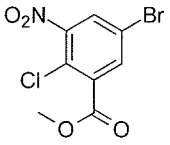
Compound 19

[01420] Step 1: Synthesis of 5-bromo-2-chloro-3-nitrobenzoic acid:



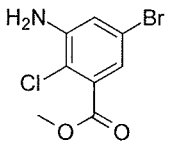
[01421] 5-bromo-2-chlorobenzoic acid: (5 g, 27.3 mmol) was added to cooled conc. H_2SO_4 (20 mL) at -10 °C in small portions. After 10 minutes nitrating mixture {prepared by mixing conc. HNO_3 (2.5 mL) with conc. H_2SO_4 (10 mL)} was added drop wise at -10 °C. The reaction mixture was stirred at -10 °C for 30 minutes. On completion, the reaction mixture was poured into ice cold water and the solid collected by filtration. The solid was washed with water and dried under vacuum to give 5-bromo-2-chloro-3-nitrobenzoic acid: (3.6 g, 60.5 %).

[01422] Step 2: Synthesis of methyl 5-bromo-2-chloro-3-nitrobenzoate:



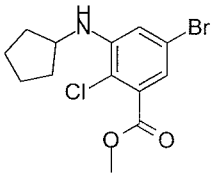
[01423] To stirred solution of –bromo-2-chloro-3-nitrobenzoic acid (3.6 g, 12.9 mmol) in DMF (40 mL) was added sodium carbonate (4.1 g, 38.6 mmol) and methyl iodide (4 mL, 64.3 mmol). The reaction mixture was heated at 60 °C for 8 h. On completion, water was added to the reaction mixture and the product was extracted with ethyl acetate. The combined organic layers were washed with sat. bicarbonate solution and 5 N HCl. The organics were dried and concentrated under reduced pressure to afford methyl 5-bromo-2-chloro-3-nitrobenzoate (3.4 g, 89.9 %).

[01424] Step 3: Synthesis of methyl 3-amino-5-bromo-2-chlorobenzoate:



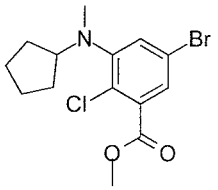
[01425] To stirred solution of methyl 5-bromo-2-chloro-3-nitrobenzoate (3.4 g, 11.6 mmol) in ethanol (19 mL) was added ammonium chloride (3.4 g, 57.8 mmol) dissolved in water (30 mL) and iron powder (5.16 g, 92.5 mmol). The reaction mixture was heated at 80 °C for 1 h. On completion, the reaction mixture was filtered through celite washing with ethanol and ethylacetate. The filtrate was extracted with ethyl acetate and the combined organic layers were washed with water, dried and concentrated under reduced pressure to give methyl 3-amino-5-bromo-2-chlorobenzoate (2.8 g, 92.1 %).

[01426] Step 4: Synthesis of methyl 5-bromo-2-chloro-3-(cyclopentylamino)benzoate:



[01427] To a stirred solution of methyl 3-amino-5-bromo-2-chlorobenzoate (2.8 g, 10.6 mmol) and cyclopentanone (4.47 g, 53.2 mmol) in methanol (20 mL) was added acetic acid (1.3 mL, 21.2 mmol) and the reaction stirred at room temperature for 3 h. Then sodium cyanoborohydride (1.7 g, 26.6 mmol) was added and the reaction stirred overnight. On completion, the solvent was removed under reduced pressure and the product was purified by column chromatography to afford methyl 5-bromo-2-chloro-3-(cyclopentylamino)benzoate (0.5 g, 14.2 %).

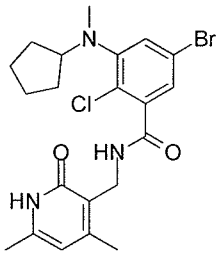
[01428] Step 5: Synthesis of methyl 5-bromo-2-chloro-3-(cyclopentyl(methyl)amino)benzoate:



[01429] To a stirred solution of methyl 5-bromo-2-chloro-3-(cyclopentylamino)benzoate (0.550 g, 1.65 mmol) in acetonitrile (20 mL) was added cesium carbonate (1.08 g, 3.31 mmol) and methyl iodide (1.17 g, 8.25 mmol). The reaction mixture was heated at 80 °C for 12 h. On completion, the reaction mixture was cooled to room temperature and filtered. The residue

was washed with ethyl acetate and the filtrate was concentrated and purified by column chromatography to afford methyl 5-bromo-2-chloro-3-(cyclopentyl(methyl)amino)benzoate (0.350 g, 61%).

[01430] Step 6: Synthesis of 5-bromo-2-chloro-3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)benzamide



[01431] Aqueous NaOH (0.06 g, 1.52 mmol) was added to a solution of methyl 5-bromo-2-chloro-3-(cyclopentyl(methyl)amino)benzoate (0.350 g, 1.01 mmol) in EtOH (4 mL) and water (1 mL) and stirred at 60 °C for 1 h. After completion of the reaction, ethanol was removed under reduced pressure and acidified using dilute HCl up to pH 6 and to pH 4 with citric acid. The product was extracted with ethyl acetate. The combined organic layers were dried and concentrated to give the desired acid (0.266 g, 79.4 %).

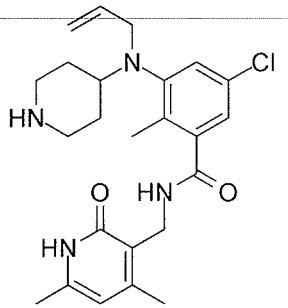
[01432] The acid (0.265 g, 0.80 mmol) was then dissolved in DMSO (3 mL) and 3-(amino methyl)-4,6-dimethylpyridin-2(1H)-one (0.243 g, 1.60 mmol) was added to it. The reaction mixture was stirred at room temperature for 15 min before PYBOP (0.624 g, 1.20 mmol) was added and stirring was continued overnight. After completion of the reaction, the reaction mixture was poured into ice to obtain a solid. The solid was filtered and washed with acetonitrile followed by purification by column chromatography and prep. HPLC to give 5-bromo-2-chloro-3-(cyclopentyl(methyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)benzamide (0.012 g, 3.22 %).

[01433] **Analytical Data:** LCMS: 466.05 $(M + 1)^+$; HPLC: 99.28% (@ 254 nm) (R_t;6.917; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 μ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 μL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (CD3OD, 400 MHz) δ 7.42 (d, 1H, J=2 Hz), 7.24 (d, 1H, J=1.6 Hz), 6.16 (s, 1H), 4.66 (s, 2H), 3.71 (m, 1H), 2.70 (s, 3H), 2.37 (s, 3H), 2.25 (s, 3H), 1.79 (m, 2H), 1.70 (m, 2H), 1.56 (m, 4H).

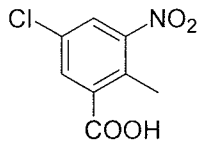
[01434] **Example 44:** Syntheses of Compounds 91, 92, 97, 98, 102, 104, 105, 117-123, 126, 127, 137, 144, 157, 191, 192, 205-209, 212, 213, 222, 243-245, 268, 269, 273, 276-279, 282-287, 290, 301, 302, 306, 308-311, 313, 315, 319-322, 328, 332-336, 339, 340, 344, 347-349, 356, 386, 387, 389, 390, and 392-417

[01435] Compounds 91, 92, 97, 98, 102, 104, 105, 117-123, 126, 127, 137, 144, 157, 191, 192, 205-209, 212, 213, 222, 243-245, 268, 269, 273, 276-279, 282-287, 290, 301, 302, 306, 308-311, 313, 315, 319-322, 328, 332-336, 339, 340, 344, 347-349, 356, 386, 387, 389, 390, and 392-417 were synthesized as described below.

[01436] **Compound 91: 3-(allyl (piperidin-4-yl) amino)-5-chloro-N-((4, 6-dimethyl-2-oxo-1, 2-dihydropyridin-3-yl) methyl)-2-methylbenzamide**

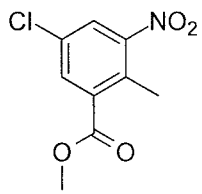


[01437] Step 1: Synthesis of 5-chloro-2-methyl-3-nitrobenzoic acid



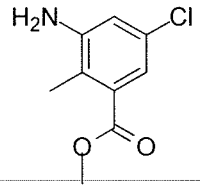
[01438] 5-Chloro-2-methylbenzoic acid (4.0 g, 23 mmol) was added portionwise to cooled conc. H_2SO_4 (27 mL) at -10 °C. After 10 minutes the nitrating mixture {consisting of concentrated HNO3 (3.3 g, 52 mmol) and concentrated H_2SO_4 (4.4 mL)} was added dropwise at -10 °C. The mixture was stirred at -10 °C for 30 minutes and poured on ice cold water. The solid precipitate was filtered, washed with water and dried under vacuum to give the title compound (4.95 g, 99%).

[01439] Step 2: Synthesis of methyl 5-chloro-2-methyl-3-nitrobenzoate



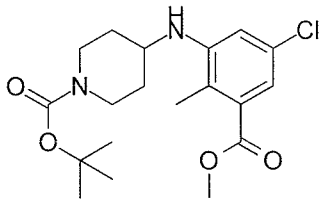
[01440] To a stirred solution of 5-chloro-2-methyl-3-nitrobenzoic acid (6.75 g, 31.3 mmol) in DMF (33 mL), were added sodium carbonate (13.23 g, 125 mmol) and methyl iodide (17.77 g, 125 mmol). The mixture was heated at 60 °C for 4 h. On completion, water was added to the reaction mass and extraction was carried out using DCM. The combined organic layers were dried, concentrated under reduced pressure, and purified by column chromatography over silica gel (to afford the title compound (6.0 g, 83%).

[01441] Step 3: Synthesis of methyl 3-amino-5-chloro-2-methyl benzoate



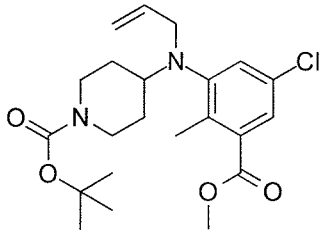
[01442] To a stirred solution of methyl 5-chloro-2-methyl-3-nitrobenzoate (6.0 g, 26 mmol) in ethanol (60 mL) were added ammonium chloride (6.0 g, 110 mmol) dissolved in water (60 mL) and iron powder (11.9 g, 208 mmol) under stirring. The mixture was heated at 80 °C for 1 h. On completion, water was added and the reaction mixture was filtered through celite. The filtrate was extracted with ethyl acetate. The combined organic layers were washed with water, dried, concentrated under reduced pressure to afford the title compound which was used without further purification.

[01443] Step 4: Synthesis of tert-butyl 4-((5-chloro-3-(methoxycarbonyl)-2-methylphenyl) amino) piperidine-1-carboxylate



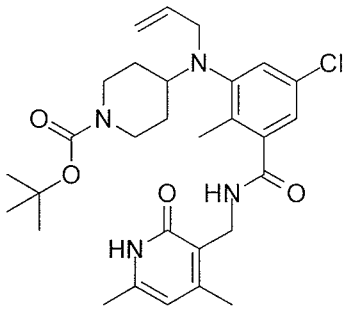
[01444] To a stirred solution of methyl 3-amino-5-chloro-2-methyl benzoate (5.0 g, 25 mmol) and tert-butyl 4-oxopiperidine-1-carboxylate (25.3 g, 127 mmol) in methanol (50 mL), acetic acid (1.5 g, 25 mmol) was added and the reaction stirred at room temperature for 8 h. Then sodium cyanoborohydride (1.89 g, 30.1 mmol) was added at 0°C and the reaction stirred overnight at room temperature. On completion, the solvent was removed under reduced pressure and the crude material was purified by column chromatography to afford the title compound (5.0 g, 52 %).

[01445] Step 5: Synthesis of tert-butyl 4-(allyl(5-chloro-3-(methoxycarbonyl)-2-methylphenyl) amino)piperidine-1-carboxylate



[01446] To a stirred solution of tert-butyl 4-((5-chloro-3-(methoxycarbonyl)-2-methylphenyl) amino) piperidine-1-carboxylate (0.70 g, 1.82 mmol) in DMF (7 mL), was added NaH (0.052 g, 2.19 mmol) at 0°C. After stirring for 20 minutes, 3-bromoprop-1-ene (0.44 g, 3.64 mmol) was added and the mixture was heated at 80°C for 15 h. On completion, the reaction mass was quenched with ice cold water and extraction was carried out using DCM. The combined organic layers were dried, concentrated under reduced pressure and the residue was purified by column chromatography to afford the title compound (0.3 g, 39 %).

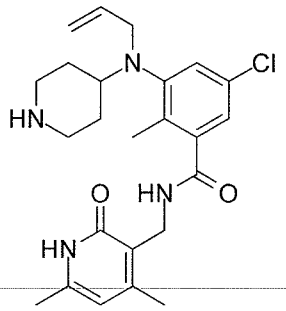
[01447] Step 6: Synthesis of tert-butyl 4-(allyl (5-chloro-3-(((4, 6-dimethyl-2-oxo-1, 2-dihydropyridin-3-yl) methyl) carbamoyl)-2-methylphenyl) amino) piperidine-1-carboxylate



[01448] Aqueous NaOH (0.113 g, 2.83 mmol) was added to a solution of tert-butyl 4-(allyl(5-chloro-3-(methoxycarbonyl)-2-methylphenyl) amino)piperidine-1-carboxylate (0.60 g, 1.41 mmol) in ethanol (15 mL). After stirring at 60 °C for 1 h ethanol was removed under reduced pressure and the mixture acidified using dilute HCl up to pH 6 and pH 4 was adjusted using citric acid. Extraction was carried out using DCM. The combined organic layers were dried and concentrated giving respective acid (0.5 g, 86%).The above acid (0.5 g, 1.22 mmol) was then dissolved in DMSO (5 mL) and 3-(amino methyl)-4, 6-dimethylpyridin-2(1H)-one (0.37 g, 2.44 mmol) was added to it. The reaction mixture was stirred at room temperature for 15 min before PYBOP (0.95 g, 1.83 mmol) was added to it and stirring was continued overnight. The

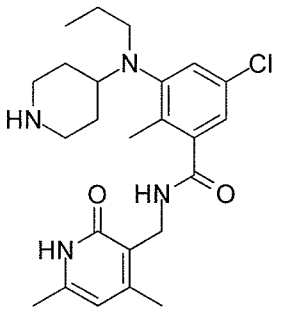
mixture was poured into ice and extracted with 10 % MeOH/DCM. The combined organic layers were dried, concentrated, and purified by column chromatography to afford the title compound (0.2 g, 30%).

[01449] Step 7: Synthesis of 3-(allyl (piperidin-4-yl) amino)-5-chloro-N-((4, 6-dimethyl-2-oxo-1, 2-dihydropyridin-3-yl) methyl)-2-methylbenzamide



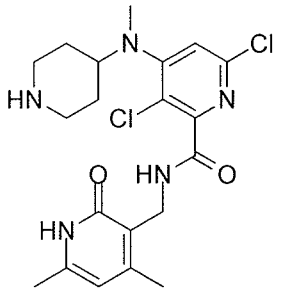
[01450] A stirred solution of compound tert-butyl 4-(allyl (5-chloro-3-(((4, 6-dimethyl-2-oxo-1, 2-dihydropyridin-3-yl) methyl) carbamoyl)-2-methylphenyl) amino) piperidine-1-carboxylate (0.2 g, 0.36 mmol) in DCM (5 mL) was cooled to 0°C and TFA (0.5 mL) was added. The mixture was stirred at room temperature for 18 h. and concentrated to dryness. The residue was washed with diethyl ether and then purified by preparative HPLC to afford the title compound as TFA salt (0.06 g, 37%).LCMS: 443.25 $(M + 1)^+$; HPLC: 97.14% (@ 254 nm) (R_t;5.074; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 μ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 μL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.46 (s, 1H), 8.38 (bs, 1H), 8.21 (t, 1H), 8.05 (d, 1H), 7.21 (d, 1H, J=4.4 Hz), 6.97 (d, 1H, J=1.6 Hz), 5.86 (s, 1H), 5.56-5.64 (m, 1H), 4.97-5.09 (m, 2H), 4.24 (d, 2H, J=4.4 Hz), 3.62 (d, 2H, J=5.2 Hz), 3.23 (m, 2H), 3.10-3.16 (m, 1H), 2.85-2.88 (m, 2H), 2.19 (s, 3H), 2.18 (s, 3H), 2.10 (s, 3H), 1.83-1.86 (m, 2H), 1.68-1.73 (m, 2H).

[01451] **Compound 97: 5-chloro-N-((4, 6-dimethyl-2-oxo-1, 2-dihydropyridin-3-yl) methyl)-2-methyl-3-(piperidin-4-yl (propyl) amino) benzamide**

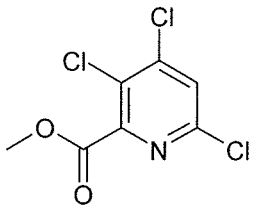


[01452] To a stirred solution of 3-(allyl (piperidin-4-yl) amino)-5-chloro-N-((4, 6-dimethyl-2-oxo-1, 2-dihydropyridin-3-yl) methyl)-2-methylbenzamide (0.04 g, 0.09 mmol) in MeOH (3 mL) was added 10% Pd/C (0.01 g) and reaction stirred at room temperature under hydrogen (balloon pressure) for 2 h. The mixture was filtered through celite and the filtrate was concentrated under reduced pressure to obtain a crude solid which was purified by preparative HPLC to afford the title compound as TFA salt (0.012 g, 40%). LCMS: 445.25 $(M + 1)^+$; HPLC: 95.52% (@ 254 nm) (R_t;5.102; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 µ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 µL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.46 (s, 1H), 8.39 (bs, 1H), 8.22 (t,1H), 8.03 (bs, 1H), 7.25 (s, 1H), 6.98 (s, 1H), 5.86 (s, 1H), 4.24 (d, 2H, J=4.8 Hz), 3.24-3.27 (m, 2H), 3.00 (m, 1H), 2.92 (m, 2H), 2.83-2.86 (m, 2H), 2.18 (s, 3H), 2.17 (s, 3H), 2.10 (s, 3H), 1.79-1.82 (m, 2H), 1.67-1.71 (m, 2H), 1.18-1.23 (m, 2H), 0.75 (t, 3H, J=8 Hz).

[01453] **Compound 144: 3,6-dichloro-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-4-[methyl(piperidin-4-yl)amino]pyridine-2-carboxamide**

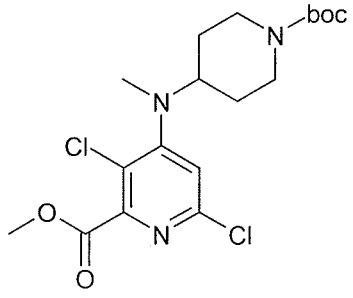


[01454] Step 1: Synthesis of methyl 3,4,6-trichloropyridine-2-carboxylate



[01455] To a stirred solution of methyl 3,6-dichloropyridine-2-carboxylate (0.96 g, 4.66 mmol) in TFA (5ml) was added hydrogen peroxide (30% w/w aqueous solution, 435µl, 2.5 mmol) and the reaction mixture was heated at 60°C for 20h. The reaction mixture was then cooled and slowly poured onto saturated K_2CO_3 solution (100ml), followed by extraction of the aqueous layer with EtOAc (2x200ml), washing of the combined organic phases with brine (2x50ml), drying (Na_2SO_4) and evaporation. The desired 3,6-dichloro-2-(methoxycarbonyl)pyridin-1-ium-1-olate was used crude in the next stage of the synthesis without any further purification. To the crude 3,6-dichloro-2-(methoxycarbonyl)pyridin-1-ium-1-olate (~70% purity, 2.40 g, 7.7 mmol) was added $POCl_3$ (3.5 ml, 38 mmol) and the solution was heated to 100°C for 4h. After cooling the $POCl_3$ was removed *in vacuo* to give a white solid which was chromatographed over silica gel eluting with 0% to 10% of EtOAc in heptane to afford the title compound as colourless needles (340 mg, 30% over two steps). LC-MS 100%, 2.20 min (3.5 minute LC-MS method), m/z= 239.8/241.7, ^{1}H NMR (500 MHz, Chloroform-d) δ 7.51 (1H, s), 3.92(3H, s).

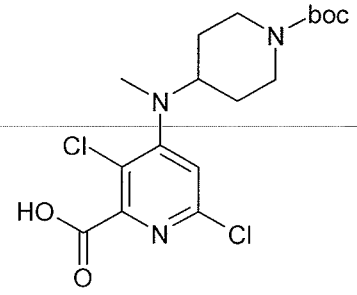
[01456] Step 2: Synthesis of methyl 4-({1-[(tert-butoxy)carbonyl]piperidin-4-yl}(methyl)amino)-3,6-dichloropyridine-2-carboxylate



[01457] To a stirred solution of methyl 3,4,6-trichloropyridine-2-carboxylate (310 mg, 1.29 mmol) in DMF (5ml) was added TEA (359µl, 2.58 mmol) followed by tert-butyl 4-(methylamino)piperidine-1-carboxylate (276mg, 1.29 mmol) and the reaction mixture was heated at 100°C for 4h. The reaction mixture was then cooled to room temperature and poured onto water (50ml), followed by extraction of the product into TBME (3x50ml), washing of the

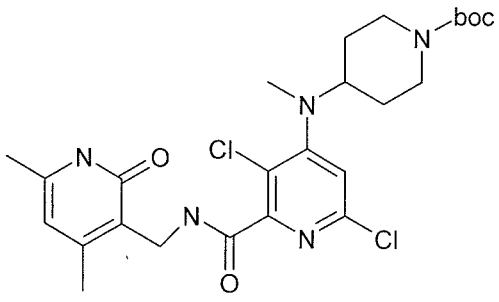
combined organics with brine (50ml), drying with Na_2SO_4 and evaporation. The crude product was then purified over a 10g silica Isolute column eluting with a gradient of 0% to 50% EtOAc in heptane to afford the title compound as a white solid (95 mg, 18%). LC-MS 95%, 2.29min (3.5 minute LC-MS method), m/z= 418.1/419.8, ^{1}H NMR (500 MHz, Chloroform-d) δ 6.87 (s, 1 H) 4.12 - 4.34 (m, 2 H) 3.99 (s, 3 H) 3.69 - 3.80 (m, 1 H) 2.79 (s, 3 H) 2.64 - 2.77 (m, 2 H) 1.75 (br. s., 4 H) 1.48 (s, 9 H).

[01458] Step 3: Synthesis of 4-({1-[(tert-butoxy)carbonyl]piperidin-4-yl}(methyl)amino)-3,6-dichloropyridine-2-carboxylic acid



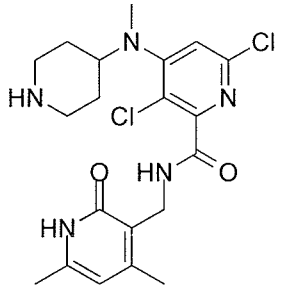
[01459] To a stirred solution of methyl 4-({1-[(tert-butoxy)carbonyl]piperidin-4-yl}(methyl)amino)-3,6-dichloropyridine-2-carboxylate (95 mg, 0.23 mmol) in THF (5ml) was added 2M aqueous NaOH (2.3ml, 4.54mmol) and the reaction mixture was left to stir at room temperature for 16h after which time the THF was evaporated *in vacuo*. The aqueous phase was then treated with an aqueous 10% citric acid solution to pH 5-6 and then extracted with EtOAc (3x50ml), the combined organic phases were then dried with Na_2SO_4 and evaporated to give the title compound as a white powder (77 mg, 84%). LC-MS 100%, 2.02 min (3.5 minute LC-MS method), m/z= 403.9/405.6, ^{1}H NMR (500 MHz, Methanol-*d*4) δ 7.09 (s, 1 H) 4.14 - 4.22 (m, 2 H) 3.80 - 3.89 (m, 1 H) 2.84 (s, 5 H) 1.74 - 1.81 (m, 4 H) 1.46 (s, 9 H).

[01460] Step 4: Synthesis of tert-butyl 4-[(3,6-dichloro-2-{[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]carbamoyl} pyridin-4-yl)(methyl)amino]piperidine-1-carboxylate



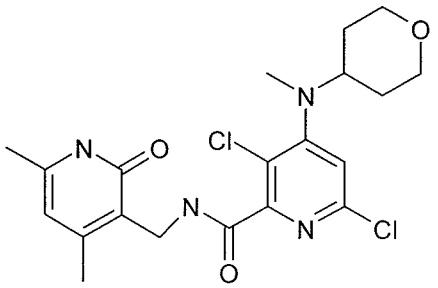
[01461] To a stirred solution of 4-({1-[(tert-butoxy)carbonyl]piperidin-4-yl}(methyl)amino)-3,6-dichloropyridine-2-carboxylic acid (75 mg, 0.19 mmol) in DMF (2ml) cooled to 0°C h was added DIPEA (48 µl, 0.28 mmol) followed by PyBOP (116 mg, 0.22 mmol) and 3-(aminomethyl)-4,6-dimethyl-1,2-dihydropyridin-2-one (89% purity, 35 mg, 0.2 mmol). The reaction mixture was then stirred at room temperature for 16h after which the reaction was poured onto water (30ml) and extracted with EtOAc (3x50ml) after which the combined organics were washed with brine (50ml) and dried (Na_2SO_4) and evaporated. The crude product was purified using a 5g silica Isolute column eluting with a gradient of 0% to 100% EtOAc in heptane to afford the title compound as a white solid which contained ~45% w/w tripyrrolidinophosphene oxide by NMR – this compound was used in the next stage of the synthesis without any further purification. LC-MS 93%, 1.97 min (3.5 minute LC-MS method), m/z= 538.0/539.45/542.05, ^{1}H NMR (500 MHz, Chloroform-d) δ 10.03 (br. s, 1H), 8.13 – 7.97 (m, 1H), 6.79 (s, 1H), 5.87 (s, 1H), 4.50 (d, J = 6.1 Hz, 2H), 4.16 (br. m, 2H), 3.78 – 3.62 (m, 1H), 2.72 (s, 3H), 2.65 (br. m, 2H), 2.35 (s, 3H), 2.22 (s, 3H), 1.73 – 1.63 (m, 4H), 1.44 (s, 9H).

[01462] Step 5: Synthesis of 3,6-dichloro-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-4-[methyl(piperidin-4-yl)amino]pyridine-2-carboxamide hydrochloride



[01463] Tert-butyl4-[(3,6-dichloro-2-{[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]carbamoyl}pyridin-4-yl) (methyl)amino]piperidine-1-carboxylate (310mg, 1.29mmol) was dissolved in 4M HCl in dioxane solution (3ml) and stirred at room temperature for 16h after which the solvent was evaporated and the compound purified by preparative HPLC to afford the title compound as a beige powder (13mg, 14%). LC-MS 100%, 2.41min (7 minute LC-MS method), m/z= 438.1/439.8, ^{1}H NMR (500 MHz, Methanol-*d*4) δ 7.12 (s, 1H), 6.11 (s, 1H), 4.46 (s, 2H), 4.01 – 3.81 (m, 1H), 3.45 (d, J = 12.9 Hz, 2H), 3.12 – 2.97 (m, 2H), 2.82 (s, 3H), 2.35 (s, 3H), 2.22 (s, 3H), 2.13 –1.93 (m, 4H).

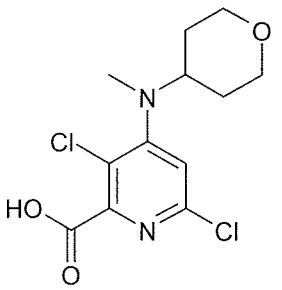
[01464] **Compound 386: 3,6-dichloro-n-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-4-[methyl (oxan-4-yl)amino]pyridine-2-carboxamide**



[01465] Step 1: Synthesis of methyl 3,6-dichloro-4-[methyl(oxan-4-yl)amino]pyridine-2-carboxylate

[01466] To a stirred solution of methyl 3,4,6-trichloropyridine-2-carboxylate (600 mg, 2.50 mmol) in DMF (12ml) was added TEA (696 µl, 4.99 mmol) followed by *N*-methyloxan-4-amine (287 mg, 2.50 mmol)and the reaction mixture was heated at 100°C for 20h. The reaction mixture was then cooled to room temperature and poured onto water (100ml), followed by extraction of the product into EtOAc (3x100ml), washing of the combined organics with brine (50ml), drying with Na_2SO_4 and evaporation. The crude product was then purified over a 10g silica Isolute column eluting with a gradient of 0% to 60% EtOAc in heptane to afford the title compound as a white solid (114 mg, 14%). LC-MS 100%, 1.91 min (3.5 minute LC-MS method), m/z= 319.3/320.9, ^{1}H NMR (500 MHz, Chloroform-d) δ 6.87 (s, 1H), 4.15 – 4.00 (m, 2H), 3.98 (s, 3H), 3.93 – 3.71 (m, 1H), 3.54 – 3.24 (m, 2H), 2.82 (s, 3H), 1.94 (dd, J = 12.1, 4.7 Hz, 2H), 1.70 (d, J = 10.2 Hz, 2H). (br. s., 4 H) 1.48 (s, 9 H)

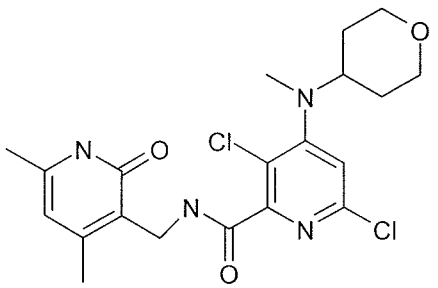
[01467] Step 2: Synthesis of 3,6-dichloro-4-[methyl(oxan-4-yl)amino]pyridine-2- carboxylic acid



[01468] To a stirred solution of methyl 3,6-dichloro-4-[methyl(oxan-4-yl)amino]pyridine-2-

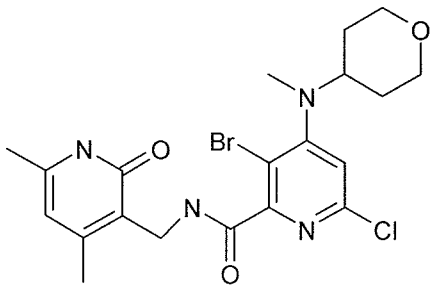
carboxylate (114 mg, 0.36 mmol) in THF (5ml) was added 2M aqueous NaOH (0.89 ml, 1.79 mmol) and the reaction mixture was left to stir at room temperature for 20h after which time the THF was evaporated *in vacuo*. The aqueous phase was then treated with an aqueous 10% citric acid solution to pH 5-6 and then extracted with EtOAc (3x50ml) followed by a solution of 1:1 IPA/$CHCl_3$ (2 x 50ml), the combined organic phases were then washed with brine (50ml) dried with Na_2SO_4 and evaporated to give the title compound as a white solid (85 mg, 78%). LC-MS 100%, 1.47 min (3.5 minute LC-MS method), m/z= 305.5/306.9, ^{1}H NMR (500 MHz, Methanol-*d*4) δ 7.10 (s, 1H), 4.03 (dd, J = 11.5, 4.4 Hz, 2H), 3.99 – 3.86 (m, 1H), 3.47 (t, J = 11.0 Hz, 2H), 2.90 (s, 3H), 2.05 – 1.90 (m, 2H), 1.74 (d, J = 12.4 Hz, 2H).

[01469] Step 3: Synthesis of 3,6-dichloro-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-4-[methyl (oxan-4- yl)amino]pyridine-2-carboxamide

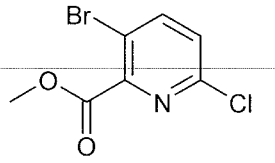


[01470] To a stirred solution of 3,6-dichloro-4-[methyl(oxan-4-yl)amino]pyridine-2-carboxylic acid (85 mg, 0.28 mmol) in DMF (2ml) was added DIPEA (73 µl, 0.42 mmol) and HATU (127mg, 0.33 mmol). The reaction was stirred at room temperature for 5 min after which time 3-(aminomethyl)-4,6-dimethyl-1,2-dihydropyridin-2-one (89%, 52 mg, 0.31 mmol) was added and the reaction was stirred at room temperature for 16h. The reaction mixture was then poured onto 50ml of water and the aqueous phase was extracted with EtOAc (3x50ml), washed with brine (50ml) dried (Na_2SO_4) and evaporated to give an oil. The product was then purified using a 5g silica Isolute column eluting with 0% to 5% MeOH in DCM and evaporated to give a glassy solid which was triturated with diethyl ether and filtered to afford the title compound as a white powder (50 mg, 41%). LC-MS 95%, , m/z=439.0/440.8, ^{1}H NMR (500 MHz, Chloroform-d) δ 11.33 (br. s, 1H), 8.20 (br. s, 1H), 6.79 (s, 1H), 5.93 (s, 1H), 4.51 (s, 2H), 4.02 (dd, J = 11.4, 3.8 Hz, 2H), 3.92 – 3.72 (m, 1H), 3.39 (t, J = 11.3 Hz, 2H), 2.78 (s, 3H), 2.38 (s, 3H), 2.27 (s, 3H), 1.89 (tt, J = 12.0, 6.2 Hz, 2H), 1.83 – 1.52 (m, 2H).

[01471] **Compound 387: 3-bromo-6-chloro-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-4-[methyl(oxan-4-yl)amino]pyridine-2-carboxamide**

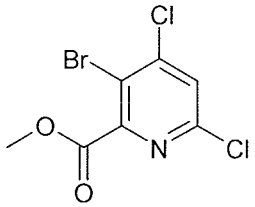


[01472] Step 1: Synthesis of methyl 3-bromo-6-chloropyridine-2-carboxylate



[01473] To a stirred solution of 3-bromo-6-chloropyridine-2-carboxylic acid (2.00 g, 8.46 mmol) in MeOH (40ml) was added H_2SO_4 (189 µl, 3.55 mmol) and the solution was heated to reflux for 16h. The reaction was cooled and the MeOH removed under reduced pressure, the resulting solid was dissolved in EtOAc (100ml) and washed with saturated $NaHCO_3$ solution (2x50ml) followed by brine (50ml), dried (Na_2SO_4) and evaporated under reduced pressure to afford the title compound as an off-white solid (1.97 g, 93%) which was used without any further purification. LC-MS 98%, m/z=249.8/251.7/253.7

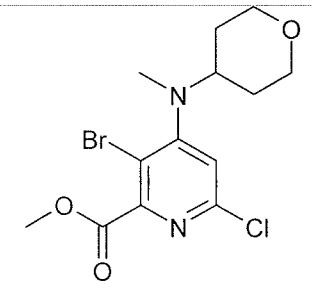
[01474] Step 2: Synthesis of methyl 3-bromo-4,6-dichloropyridine-2-carboxylate



[01475] To a stirred solution of methyl 3-bromo-6-chloropyridine-2-carboxylate (1.92 g, 7.67 mmol) in TFA (18ml) was added hydrogen peroxide (30% w/w aqueous solution, 5.22 ml, 53.7 mmol) and the reaction mixture was heated at 60°C for 21h. The reaction mixture was then cooled and slowly poured onto saturated K_2CO_3 solution (100ml), followed by extraction of the aqueous layer with EtOAc (3x100ml), washing of the combined organic phases with brine (2x50ml), drying (Na_2SO_4) and evaporation. The desired 3-bromo-6-chloro-2-

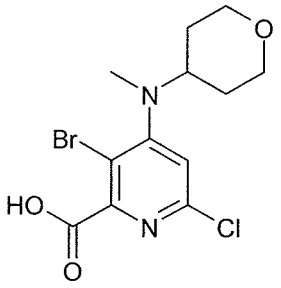
(methoxycarbonyl)pyridin-1-ium-1-olate (2.61g, ~75% purity) was used crude in the next stage of the synthesis without any further purification. To the crude 3-bromo-6-chloro-2-(methoxycarbonyl)pyridin-1-ium-1- olate (~75% purity, 2.61 g, 7.35 mmol) was added $POCl_3$ (3.42 ml, 36.7 mmol) and the solution was heated to 100°C for 4h. After cooling the $POCl_3$ was remove *in vacuo* to give a white solid which was columned over silica eluting with 0% to 10% of EtOAc in heptane to afford the title compound as a pale yellow powder (1.07 g, 49% over two steps). LC-MS 99%, 2.02 min (3.5 minute LC-MS method), m/z= 283.7/285.7/287.7, ^{1}H NMR (500 MHz, Chloroform-d) δ ppm 7.56 (s, 1 H) 4.00 (s, 3 H).

[01476] Step 3: Synthesis of methyl 3-bromo-6-chloro-4-[methyl(oxan-4- yl)amino]pyridine-2-carboxylate



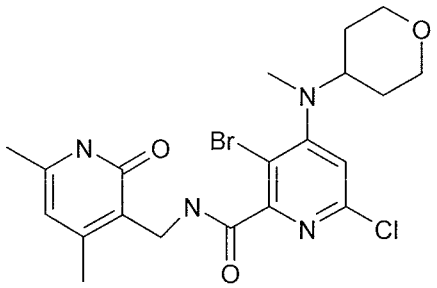
[01477] To a stirred solution of methyl 3-bromo-4,6-dichloropyridine-2-carboxylate (600 mg, 2.1 mmol) in DMF (5ml) was added TEA (587 µl, 4.21 mmol) followed by *N*-methyloxan-4-amine (240 mg, 2.1 mmol) and the reaction mixture was heated at 80°C for 20h. The reaction mixture was then cooled to room temperature and poured onto water (100ml), followed by extraction of the product into EtOAc (3x100ml), washing of the combined organics with brine (50ml), drying with Na_2SO_4 and evaporation. The crude product was then purified over a 10g silica Isolute column eluting with a gradient of 0% to 100% EtOAc in heptane to afford the title compound as a white solid (110 mg, 14%). LC-MS 100%, 1.94 min (3.5 minute LC-MS method), m/z= 362.8/365.2/346.8, ^{1}H NMR (250 MHz, Chloroform-d) δ 6.87 (s, 1H), 4.17 – 3.99 (m, 2H), 3.98 (s, 3H), 3.93 – 3.70 (m, 1H), 3.41 (t, J = 10.9 Hz, 2H), 2.81 (s, 3H), 1.93 (dd, J = 11.9, 4.6 Hz, 2H), 1.71 (d, J = 10.3Hz, 2H).

[01478] Step 4: Synthesis of 3-bromo-6-chloro-4-[methyl(oxan-4- yl)amino]pyridine-2-carboxylic acid



[01479] To a stirred solution of methyl 3-bromo-6-chloro-4-[methyl(oxan-4-yl)amino]pyridine-2-carboxylate (102 mg, 0.28 mmol) in THF (2ml) was added 2M aqueous NaOH (0.70 ml, 1.40 mmol) and the reaction mixture was left to stir at room temperature for 18h after which time the THF was evaporated *in vacuo*. The aqueous phase was then treated with an aqueous 10% citric acid solution to pH 5-6 and then extracted with EtOAc (3x50ml) followed by a solution of 1:1 IPA/$CHCl_3$ (2x50ml), the combined organic phases were then washed with brine (50ml) dried with Na_2SO_4 and evaporated to give the title compound as a white solid (72 mg, 73%). LC-MS 100%, 1.49 min (3.5 minute LC-MS method), m/z= 349.0/351.0/352.9, ^{1}H NMR (500 MHz, Methanol-*d*4) δ 7.07 (s, 1H), 4.02 (dd, J = 11.3, 4.3 Hz, 2H), 3.96 – 3.87 (m, 1H), 3.46 (t, J = 11.0 Hz, 2H), 2.85 (s, 3H), 1.96 (dd, J = 12.3, 4.3 Hz, 2H), 1.77 (s, 2H).

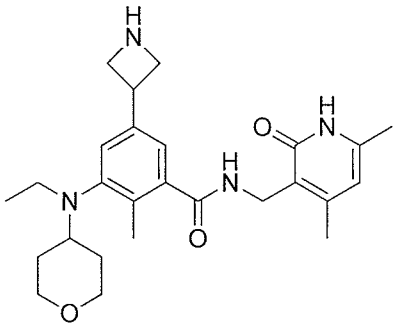
[01480] Step 5: Synthesis of 3-bromo-6-chloro-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-4-[methyl(oxan-4-yl)amino]pyridine-2-carboxamide



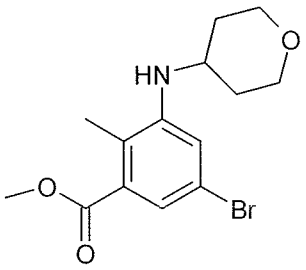
[01481] To a stirred solution of 3-bromo-6-chloro-4-[methyl(oxan-4- yl)amino]pyridine-2-carboxylic acid (73 mg, 0.21 mmol) in DMF (2ml) were added DIPEA (56 µl, 0.31 mmol) and HATU (95 mg, 0.25 mmol) at 0°C. The reaction was stirred at 0°C for 5 min after which time 3-(aminomethyl)-4,6-dimethyl-1,2-dihydropyridin-2-one (89%, 52 mg, 0.31 mmol) was added and the reaction was stirred at room temperature for 16h. The reaction mixture was then poured onto 50ml of water, the aqueous phase was extracted with EtOAc (3x50ml), washed

with brine (50ml) dried (Na_2SO_4) and evaporated to give an oil. The product was then purified using a 5g silica Isolute column eluting with 0% to 4% MeOH in DCM and evaporated to give a glassy solid which was triturated with diethyl ether and filtered and dried in a vacuum oven at 40°C for 24h to afford the title compound as a white powder (50mg, 41%). LC-MS 99%, m/z=483.1/485.0/486.9, ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.94 (br. s, 1H), 8.14 – 7.98 (m, 1H), 6.83 (s, 1H), 5.92 (s, 1H), 4.55 (d, J = 6.1 Hz, 2H), 4.15 – 3.94 (m, 2H), 3.93 – 3.70 (m, 1H), 3.40 (t, J = 11.0 Hz, 2H), 2.78 (s, 3H), 2.39 (s, 3H), 2.28 (s, 3H), 1.99 – 1.82 (m, 2H), 1.79 – 1.64 (m, 2H).

[01482] **Compound 213: 5-(azetidin-3-yl)-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3-[ethyl(oxan-4- yl)amino]-2-methylbenzamide**



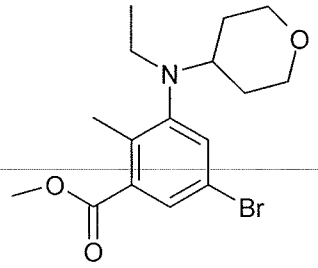
[01483] Step 1: Synthesis of methyl 5-bromo-2-methyl-3-[(oxan-4-yl)amino]benzoate



[01484] To a stirred solution of methyl 3-amino-2-methy-5-bromobenzoate (4.06 g, 16.6 mmol) in DCE (60ml) under a nitrogen atmosphere was added oxan-4-one (3.07 ml, 33.3 mmol) followed by acetic acid (5.71 ml, 99.8 mmol) and the reaction was left to stir for 5 min before the addition of sodium triacetoxyborohydride (10.6 g, 49.9 mmol). The reaction was stirred for 3h at room temperature whereupon distilled water (50ml) was added and the solution was neutralised with solid NaHCO3. The phases were separated and then the aqueous phase was washed with EtOAc (2x100ml), the combined organics were then dried using Na2SO4,

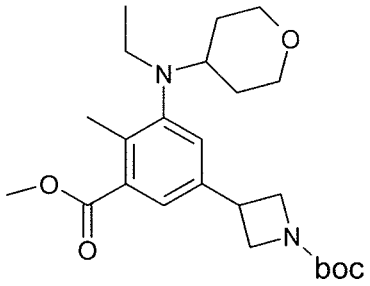
filtered and evaporated. The residue was purified by FCC using silica and eluting with a 10% to 40% EtOAc in heptane gradient to afford the title compound as an off-white solid (3.88 g, 71%). LC-MS 100%, 2.10min (3.5 minute LC-MS method), m/z=327.9/329.8, ^{1}H NMR (500 MHz, Chloroform-d) δ 7.23 (d, J = 1.9 Hz, 1H), 6.84 (d, J = 1.7 Hz, 1H), 4.02 (dt, J = 11.7, 3.5 Hz, 2H), 3.87 (s, 3H), 3.65 (d, J = 7.2 Hz, 1H), 3.59 – 3.45 (m, 3H), 2.23 (s, 3H), 2.05 (d, J = 13.8 Hz, 2H), 1.51 (ddd, J = 24.1, 10.8, 4.2 Hz, 2H).

[01485] Step 2: Synthesis of methyl 5-bromo-3-[ethyl(oxan-4-yl)amino]-2-methylbenzoate



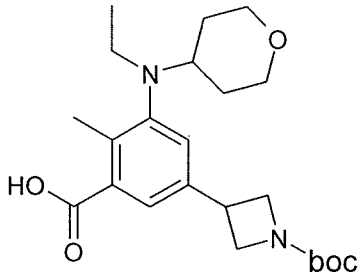
[01486] To a stirred solution of methyl 5-bromo-2-methyl-3-[(oxan-4-yl)amino]benzoate (2.0 g, 6.1 mmol) in DCE (10ml) under a nitrogen atmosphere was added acetaldehyde (1.0 ml, 18 mmol)followed by acetic acid (2.1 ml, 37 mmol) and the reaction was left to stir for 5 min before the addition of sodium triacetoxyborohydride (6.6 g, 31 mmol). The reaction was stirred for 16h at room temperature after which time additional acetaldehyde (1.0ml, 22mmol) and sodium triacetoxyborohydride (3.0 g, 14mmol) were added and the reaction was stirred for a further 6h whereupon distilled water (100ml) was added and the phases were separated. The aqueous phase was washed with EtOAc (3x100ml), the combined organics were then dried using Na_2SO_4, filtered and evaporated to afford the title compound as a colourless oil (2.10 g, 93%) which was suitable for use without any further purification. LC-MS 96%, 2.38min (3.5 minute LC-MS method), m/z=356.1/357.9, ^{1}H NMR (500 MHz, Chloroform-d) δ 7.70 (d, J = 2.0 Hz, 1H), 7.36 (d, J = 2.0 Hz, 1H), 3.95 (d, J = 11.3 Hz, 2H), 3.88 (d, J = 9.1 Hz, 3H), 3.32 (td, J = 11.5, 2.5 Hz, 2H), 3.04 (q, J = 7.1 Hz, 2H), 2.98 – 2.87 (m, 1H), 2.44 (s, 3H), 1.77 – 1.55 (m, 4H), 0.86 (t, J = 7.1 Hz, 3H).

[01487] Step 3: Synthesis of tert-butyl 3-{3-[ethyl(oxan-4-yl)amino]-5-(methoxycarbonyl)-4-methylphenyl} azetidine-1-carboxylate



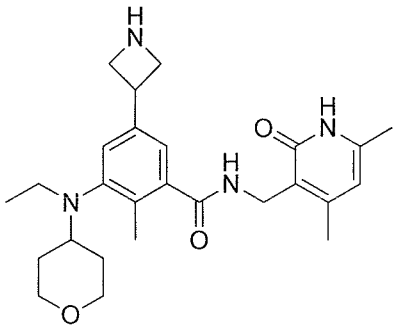
[01488] To a dry flask was added zinc dust (40 mg, 0.61 mmol) followed by anhydrous DMA (2ml) and the vessel was flushed with nitrogen whilst stirring vigorously and heating to 65°C. TMS-Cl (9 µl, 0.07 mmol) and 1,2-dibromoethane (6 µl, 0.07 mmol) were added and the reaction was stirred at 65°C for 30mins, followed by the dropwise addition of *N*-Boc-3-iodoazetidine (133 mg, 0.47 mmol) as a solution in anhydrous DMA (1ml). The reaction was then cooled to room temperature and methyl 5-bromo-3-[ethyl(oxan-4-yl)amino]-2-methylbenzoate (100 mg, 0.28 mmol) was added as a solution in anhydrous DMA (2ml). The resulting solution was degassed with nitrogen for 5 mins after which $Pd(dppf)Cl_2$.DCM (7 mg, 0.01 mmol) and copper (I) iodide (3 mg, 0.02 mmol) were added as solids. The reaction was heated to 80°C for 16h and then cooled to room temperature followed by the addition of saturated NH_4Cl solution (50ml). The aqueous phase was extracted with EtOAc (3x100ml), and then the combined organic phases were washed with brine (2x50ml), dried with Na_2SO_4, filtered and evaporated. The residue was purified over a 5g Isolute column using 10-30% EtOAc in heptane as the eluent to afford the title compound as a colourless oil (77 mg, 62%). LC-MS 98%, 2.19min (3.5 minute LC-MS method), m/z=433.2, ^{1}H NMR (500 MHz, CDCl3) δ 7.49 (d, J = 1.6 Hz, 1H), 7.16 (d, J = 1.6 Hz, 1H), 4.31 (t, J = 8.7 Hz, 2H), 3.94 (dd, J = 14.4, 5.5 Hz, 4H), 3.89 (s, 3H), 3.77 – 3.64 (m, 1H), 3.31 (td, J =11.4, 2.7 Hz, 2H), 3.06 (q, J = 7.0 Hz, 2H), 2.99 – 2.87 (m, 1H), 2.46 (s, 3H), 1.65 (ddd, J = 11.1, 8.6, 6.0 Hz, 4H), 1.46 (s, 9H), 0.85 (dd, J = 13.1, 6.1 Hz, 3H).

[01489] Step 4: Synthesis of 5-{1-[(tert-butoxy)carbonyl]azetidin-3-yl}-3-[ethyl(oxan-4-yl)amino]-2-methylbenzoic acid



[01490] To a stirred solution of tert-butyl 3-{3-[ethyl(oxan-4-yl)amino]-5-(methoxycarbonyl)-4-methylphenyl}azetidine-1-carboxylate (78 mg, 0.18 mmol) in THF (2ml) and MeOH (0.1ml) was added 2M NaOH solution (0.9 ml, 1.8mmol) and the reaction was stirred at room temperature for 16h followed by heating at 50°C for 22h. The reaction was cooled to room temperature and the solvent removed *in vacuo* after which the aqueous solution was adjusted to pH5 using 1M HCl. The product was extracted into DCM (2x50ml), dried with Na_2SO_4 and filtered to afford the title compound as a colourless oil (54 mg, 72%). LC-MS 100%, 1.70min (3.5 minute LC-MS method), m/z=419.2, 1H NMR (500 MHz, MeOD) δ 7.77 (s, 1H), 7.55 (s, 1H), 4.36 (t, J = 8.2 Hz, 2H), 3.90 (d, J = 27.0 Hz, 5H), 3.71 (t, J = 6.5 Hz, 1H), 3.36 (t, J = 11.3 Hz, 3H), 2.55 (s, 3H), 1.92 – 1.81 (m, 1H), 1.64 (d, J = 55.8 Hz, 3H), 1.49 – 1.42 (m, 10H), 0.93 (s, 3H).

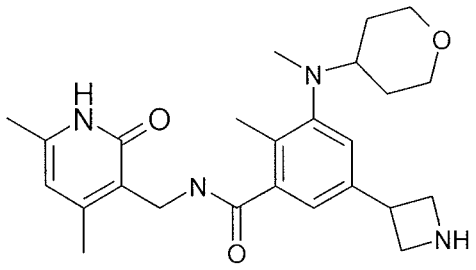
[01491] Step 5: Synthesis of 5-(azetidin-3-yl)-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3-[ethyl(oxan-4- yl)amino]-2-methylbenzamide



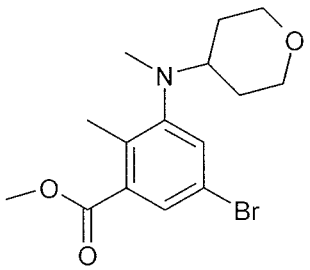
[01492] To a stirred solution of 5-{1-[(tert-butoxy)carbonyl]azetidin-3-yl}-3-[ethyl(oxan-4-yl)amino]-2-methylbenzoic acid (54 mg, 0.13 mmol) in DMF (2ml) and the reaction was cooled using an ice bath followed by the addition of DIPEA (45 µl, 0.26 mmol) and HATU (59 mg, 0.15 mmol)). The reaction was stirred at 0°C for 5 min after which time 3-(aminomethyl)-4,6-dimethyl-1,2-dihydropyridin-2-one (89%, 24 mg, 0.14 mmol) was added and the reaction was warmed room temperature for 16h. The reaction mixture was then poured onto 50ml of

water and the aqueous phase was extracted with EtOAc (3x50ml), washed with brine (50ml) dried (Na_2SO_4), filtered and evaporated to give an oil. The product was then purified using a 5g silica Isolute column eluting with 0% to 2.5% MeOH in DCM and evaporated to afford tert-butyl 3-(3-{[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]carbamoyl}-5-[ethyl(oxan-4-yl)amino]-4-methylphenyl)azetidine-1-carboxylate as a colourless oil (29mg). LC-MS 90%, m/z=553.3. This material was dissolved in 4M HCl in dioxane solution (3ml) and stirred at room temperature for 90min after which the solvent was evaporated to dryness and the compound purified by preparative HPLC to afford the title compound as a white solid (11mg, 8% over 2 steps). LC-MS 97%, 2.17min (7 minute LC-MS method), m/z= 453.2, 1H NMR (500 MHz, MeOD) δ 7.26 (s, 1H), 7.18 (s, 1H), 6.14 (s, 1H), 4.48 (s, 2H), 4.39 (s, 2H), 4.22 (s, 3H), 3.93 (d, J = 10.5 Hz, 2H), 3.40 – 3.33 (m, 2H), 3.29 – 2.90 (m, 3H), 2.40 (s, 3H), 2.31 (s, 3H), 2.26 (s, 3H), 1.68 (d, J = 26.3 Hz, 4H), 0.87 (s, 3H).

[01493] **Compound 245: 5-(azetidin-3-yl)-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-2-methyl-3-[methyl(oxan-4-yl)amino]benzamide**



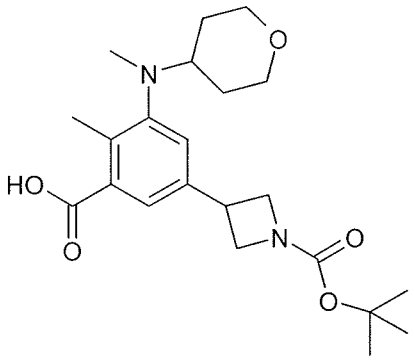
[01494] Step 1: Synthesis of methyl 5-bromo-2-methyl-3-[methyl(oxan-4- yl)amino]benzoate



[01495] To a stirred solution of methyl 5-bromo-2-methyl-3-[(oxan-4-yl)amino]benzoate (1.20 g, 3.66 mmol) in DCE (10ml) under a nitrogen atmosphere was added paraformaldehyde (659 mg, 21.9 mmol) followed by acetic acid (1.26 ml, 21.9 mmol) and the reaction was left to stir for 5 min before the addition of sodium triacetoxyborohydride (4.65 g, 21.9 mmol). The

reaction was stirred for 16h at room temperature after which time additional paraformaldehyde (325 mg, 10.8 mmol) and sodium triacetoxyborohydride (2.40 g, 11.3 mmol) was added and the reaction was stirred for a further 18h whereupon distilled water (30ml) was added and solid $NaHCO_3$ was added until the aqueous phase was pH7 and the phases were separated, the aqueous phase was washed with EtOAc (3x50ml), the combined organics were then washed with brine (50ml), dried using Na_2SO_4, filtered and evaporated. The crude residue was purified using FCC over silica eluting with 0-10% EtOAc in heptane to afford the title compound as a colourless oil (728 mg, 52%). LC-MS 87%, m/z= 341.9/343.9, 1H NMR (500 MHz, Chloroform-d) δ 7.60 (d, J = 2.0 Hz, 1H), 7.25 (d, J = 1.9 Hz, 1H), 3.92 (d, J = 11.1 Hz, 2H), 3.82 (s, 3H), 3.27 (td, J = 11.5, 2.0 Hz, 2H), 2.94 – 2.79 (m, 1H), 2.57 (s, 3H), 2.36 (s, 3H), 1.74 – 1.52 (m, 4H).

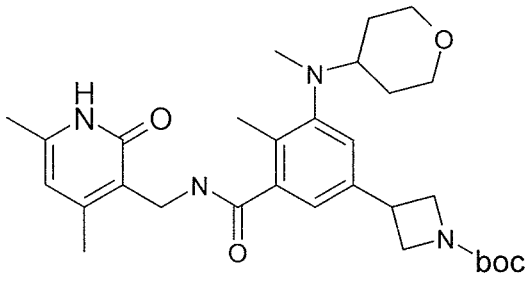
[01496] Step 2: Synthesis of 5-{1-[(tert-butoxy)carbonyl]azetidin-3-yl}-2-methyl-3-[methyl(oxan-4-yl)amino] benzoic acid



[01497] To a dry flask was added zinc dust (436 mg, 6.67 mmol) and the flask was heated using a heat gun for a few minutes. Then anhydrous DMA (20ml) was added under nitrogen whilst stirring vigorously and heating to 65°C. TMS-Cl (102 µl, 0.8 mmol) and 1,2-dibromoethane (70 µl, 0.8 mmol) were added and the reaction was stirred at 65 °C for 30 min followed by the dropwise addition of *N*-Boc-3-iodoazetidine (1.46 g, 5.16 mmol) as a solution in anhydrous DMA (15ml). The reaction was then cooled to room temperature and methyl 5-bromo-2-methyl-3-[methyl(oxan-4-yl)amino]benzoate (1.06 g, 3.09 mmol) was added as a solution in anhydrous DMA (15ml). The resulting solution was degassed with nitrogen for 10 mins after which $Pd(dppf)Cl_2$.DCM (76 mg, 0.09 mmol) and copper (I) iodide (35 mg, 0.19 mmol) were added as solids. The reaction was heated to 80 °C for 90 min and then cooled to room temperature followed by the addition of distilled water (100ml) and saturated NH_4Cl

solution (10ml). The aqueous phase was extracted with TBME (3x50ml), and then the combined organic phases were dried with Na_2SO_4, filtered and evaporated. The residue was purified over a 25g Isolute column using 0%-40% EtOAc in heptane as the eluent to afford the title compound as a pale brown oil (507 mg). LC-MS 97%, m/z=420.0. To a stirred solution of tert-butyl 3-[3-(methoxycarbonyl)-4-methyl-5-[methyl(oxan-4-yl)amino]phenyl]azetidine-1-carboxylate (85 mg, 0.2 mmol) in THF (2ml) and MeOH (0.1 ml) was added 2M NaOH solution (1.02 ml, 2.03mmol) and the reaction was stirred at 50°C for 16h after which time 4M NaOH solution (0.5ml, 2,0mmol) was added and the reaction was heated for a further 24h. The reaction was cooled to room temperature and the solvent removed *in vacuo* after which the aqueous solution was adjusted to pH3 using 1M HCl. The product was extracted into DCM (2x50ml), washed with brine (20ml), dried with Na_2SO_4 and filtered to afford the title compound as an off-white solid (47mg, 21% over two steps). LC-MS 95%, m/z=405.1, 1H NMR (500 MHz, Chloroform-d) δ 7.66 (t, J = 7.0 Hz, 1H), 7.19 (d, J = 1.3 Hz, 1H), 4.34 (t, J = 8.7 Hz, 2H), 3.98 (dd, J = 16.6, 10.2 Hz, 4H), 3.79 – 3.69 (m, 2H), 3.35 (dd, J = 11.5, 10.0 Hz,2H), 2.97 (td, J = 10.8, 5.3 Hz, 1H), 2.67 (s, 3H), 2.55 (d, J = 6.6 Hz, 3H), 1.74 (ddd, J = 15.5, 12.1, 4.3 Hz, 2H), 1.66 (d, J = 11.1 Hz, 2H), 1.48 (s, 9H).

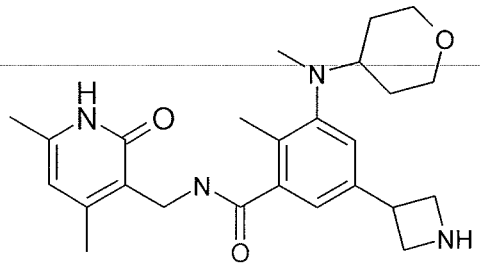
[01498] Step 3: Synthesis of tert-butyl 3-(3-{[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]carbamoyl}-4-methyl-5-[methyl(oxan-4-yl)amino]phenyl)azetidine-1-carboxylate



[01499] To a stirred solution of 5-{1-[(tert-butoxy)carbonyl]azetidin-3-yl}-2-methyl-3-[methyl(oxan-4-yl)amino]benzoic acid (47 mg, 0.12 mmol) in DMF (2ml) were added DIPEA (40 µl, 0.23 mmol) and HATU (53 mg, 0.14 mmol) at 0°C. The reaction was stirred at 0°C for 5 min after which time 3-(aminomethyl)-4,6-dimethyl-1,2-dihydropyridin-2-one (89%, 22 mg, 0.13 mmol) was added and the reaction was warmed room temperature for 16h. The reaction mixture was then poured onto distilled water (50ml) and the aqueous phase was extracted with DCM (3x50ml), washed with brine (50ml) dried (Na_2SO_4), filtered and evaporated to give an

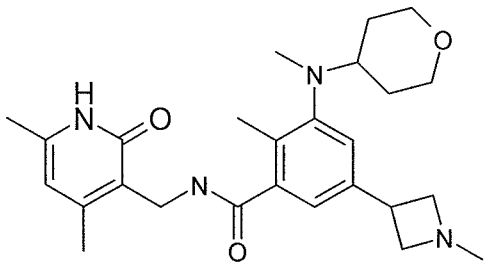
oil. The product was then purified using a 5g silica Isolute column eluting with 0% to 5% MeOH in DCM and evaporated to afford the title compound as a colourless oil (44 mg, 67%). LC-MS 96%, m/z=539.4, ^{1}H NMR (500 MHz, Chloroform-d) δ 11.68 (s, 1H), 6.95 (t, J = 5.8 Hz, 1H), 6.92 (d, J = 4.2 Hz, 2H), 5.88 (s, 1H), 4.47 (d, J = 5.8 Hz, 2H), 4.20 (t, J = 8.7 Hz, 2H), 3.90 (d, J = 11.2 Hz, 2H), 3.86 – 3.73 (m, 2H), 3.62 –3.50 (m, 1H), 3.26 (t, J = 10.8 Hz, 2H), 2.89 (ddd, J = 14.6, 10.8, 3.7 Hz, 1H), 2.55 (s, 3H), 2.33 (s, 3H), 2.20 (s, 3H), 2.14 (s, 3H), 1.75 – 1.47 (m, 4H), 1.39 (d, J = 5.7 Hz, 9H).

[01500] Step 4: Synthesis of 5-(azetidin-3-yl)-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-2-methyl-3-[methyl(oxan-4-yl)amino]benzamide

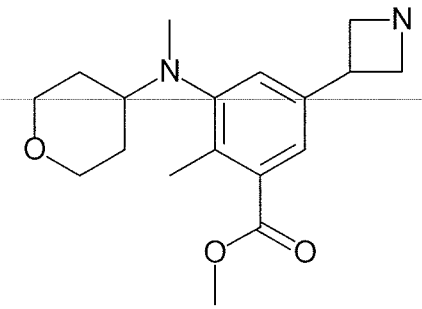


[01501] To a stirred solution of tert-butyl 3-(3-{[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]carbamoyl}-4-methyl-5-[methyl(oxan-4-yl)amino]phenyl)azetidine-1-carboxylate (29mg, 1.29mmol) in DCM (4ml) was added TFA (1ml) and the solution was stirred at room temperature for 90min after which the solvent was evaporated and saturated aqueous $NaHCO_3$ was added until pH7-8. The aqueous phase was extracted with a 1:1 mixture IPA:$CHCl_3$ (2x50ml), and the combined organic phases washed with brine (30ml, dried with Na_2SO_4, filtered and evaporated. The residue was purified by preparative HPLC to afford the title compound as a white solid (15 mg, 42%). LC-MS 100%, m/z= 439.3, 1H NMR (500 MHz, MeOD) δ 7.19 (d, J = 1.4 Hz, 1H), 7.10 (d, J = 1.5 Hz, 1H), 6.12 (s, 1H), 4.46 (s, 2H), 4.41 – 4.27 (m, 2H), 4.26 – 4.13 (m, 3H), 3.93 (d, J = 11.4 Hz, 2H), 3.36 (td, J =11.3, 3.3 Hz, 2H), 3.06 (dq, J = 14.6, 5.0 Hz, 1H), 2.65 (s, 3H), 2.39 (s, 3H), 2.26 (s, 3H), 2.24 (s, 3H), 1.75 – 1.60 (m, 4H).

[01502] **Compound 269: N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-2-methyl-3-[methyl(oxan -4-yl)amino]-5-(1-methylazetidin-3-yl)benzamide**

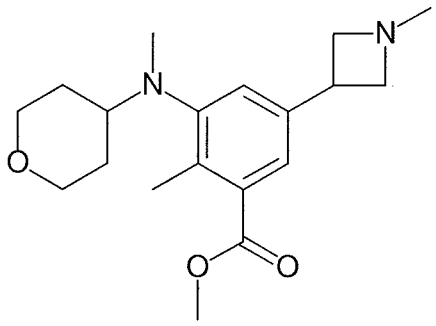


[01503] Step 1: Synthesis of methyl 5-(azetidin-3-yl)-2-methyl-3-[methyl(oxan-4-yl)amino]benzoate



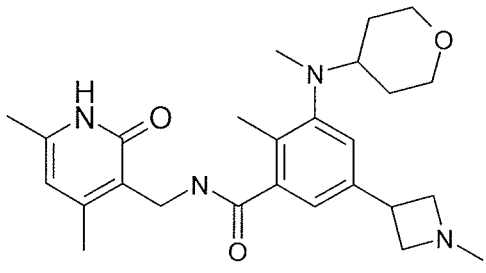
[01504] To a stirred solution of tert-butyl 3-[3-(methoxycarbonyl)-4-methyl-5-[methyl(oxan-4-yl)amino]phenyl]azetidine-1-carboxylate (400 mg, 0.96 mmol) in DCM (4ml) was added TFA (1ml) and the solution was stirred at room temperature for 45min after which the solvent was evaporated to dryness and saturated aqueous $NaHCO_3$ was added until pH7-8. The aqueous phase was extracted with DCM (3x30ml), washed with brine (30ml), dried with $MgSO_4$, filtered and evaporated to afford the title compound as an orange oil (370 mg, 95%). LC-MS 96%, m/z= 319.1, ^{1}H NMR (500 MHz, Chloroform-d) δ 7.49 (d, J = 1.4 Hz, 1H), 7.20 (d, J = 1.3 Hz, 1H), 4.32 – 4.10 (m, 5H), 3.98 (d, J = 11.0 Hz, 2H), 3.90 (d, J = 8.4 Hz, 3H), 3.34 (t, J = 10.8 Hz, 2H), 2.99 (ddd, J = 14.7, 10.9, 3.8 Hz, 1H), 2.65 (d, J = 8.3 Hz, 3H), 2.51 – 2.41 (m, 3H), 1.73 (ddd, J = 15.7, 12.1, 4.3 Hz, 2H), 1.64 (d, J = 11.2 Hz, 2H).

[01505] Step 2: Synthesis of methyl 2-methyl-3-[methyl(oxan-4-yl)amino]-5-(1-methylazetidin-3-yl)benzoate



[01506] To a stirred solution of methyl 5-(azetidin-3-yl)-2-methyl-3-[methyl(oxan-4-yl)amino]benzoate (320 mg, 1.01 mmol) in DCE (10ml) under a nitrogen atmosphere was added paraformaldehyde (151 mg, 5.03 mmol) followed by acetic acid (0.115 ml, 2.01 mmol) and the reaction was left to stir for 5 min before the addition of sodium triacetoxyborohydride (852 mg, 4.02 mmol). The reaction was stirred for 16h at room temperature after which time additional paraformaldehyde (21 mg) and sodium triacetoxyborohydride (98 mg) was added and the reaction was stirred for a further 4h whereupon distilled water (20ml) was added and solid $NaHCO_3$ was added until the aqueous phase was pH7. The phases were separated, the aqueous phase was washed with DCM (3x20ml), the combined organic phases were then washed with brine (50ml), dried using $MgSO_4$, filtered and evaporated to afford the title compound as an oil (296 mg, 89%). LC-MS 100%, m/z= 333.1, 1H NMR (500 MHz, Chloroform-d) δ 7.42 (d, J = 1.4 Hz, 1H), 7.09 (s, 1H), 3.96 (d, J = 11.2 Hz, 2H), 3.92 – 3.82 (m, 5H), 3.74 (d, J = 7.2 Hz, 1H), 3.30 (dt, J = 22.2, 15.0 Hz, 4H), 3.00 – 2.89(m, 1H), 2.62 (s, 3H), 2.49 – 2.39 (m, 6H), 1.75 – 1.59 (m, 4H).

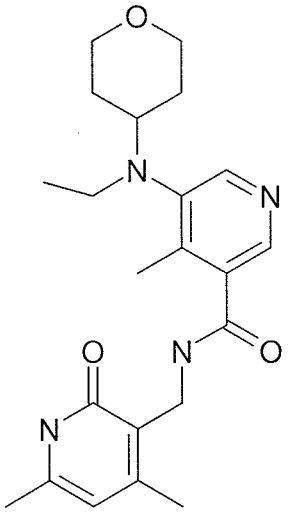
[01507] Step 3: Synthesis of N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-2-methyl-3-[methyl(oxan -4-yl)amino]-5-(1-methylazetidin-3-yl)benzamide



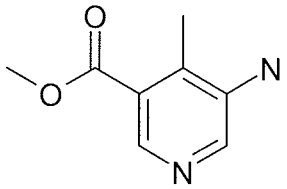
[01508] To a stirred solution of methyl 2-methyl-3-[methyl(oxan-4-yl)amino]-5-(1-methylazetidin-3-yl)benzoate (296 mg, 0.89 mmol) in THF (10ml) and MeOH (1ml) was added 2M NaOH solution (4.5 ml, 8.9 mmol) and the reaction was stirred at 50°C for 16h after which

time 4M NaOH solution (1ml, 4.5mmol) was added and the reaction was heated for a further 24h. The reaction was cooled to room temperature and the product was neutralised with 1M HCl and evaporated to dryness followed by azeotrope with toluene to remove residual water. The crude acid was taken through to the next stage without any purification. The crude residue of 2-methyl-3-[methyl(oxan-4-yl)amino]-5-(1-methylazetidin-3-yl)benzoic acid was suspended in DMF (10ml) and the solution was cooled using an ice bath followed by the addition of DIPEA (433 µl, 2.49 mmol) and HATU (567 mg, 1.49 mmol). The reaction was stirred at 0°C for 5 min after which time 3-(aminomethyl)-4,6-dimethyl-1,2-dihydropyridin-2-one (89%, 221 mg, 1.29 mmol) was added and the reaction was warmed room temperature for 16h. The reaction mixture was then poured onto distilled water (50ml) and the aqueous phase was extracted with DCM (3x50ml), washed with brine (50ml) dried (Na_2SO_4), filtered and evaporated to give an oil. The product was then purified using preparative HPLC method (and evaporated to dryness followed by trituration with ether and filtration to afford the title compound as an off-white solid (51 mg, 10%). LC-MS 91%, m/z=453.2, 1H NMR (500 MHz, MeOD) δ 7.14 (d, J = 1.7 Hz, 1H), 7.09 (d, J = 1.7 Hz, 1H), 6.12 (s, 1H), 4.46 (s, 2H), 4.41 (t, J = 9.2 Hz, 2H), 4.22 (t, J = 9.3 Hz, 2H), 4.14 (dd, J = 17.4, 8.5 Hz, 1H), 3.98 – 3.89 (m, 2H), 3.36 (td, J = 11.3, 3.4 Hz, 2H), 3.06 (ddd, J = 14.6, 9.8, 4.9 Hz, 1H), 2.97 (s, 3H), 2.64 (s, 3H), 2.39 (s, 3H), 2.26 (s, 3H), 2.24 (s, 3H), 1.73 – 1.62 (m, 4H).

[01509] **Compound 389: N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-5-[ethyl(oxan-4-yl) amino]-4- methylpyridine-3-carboxamide**

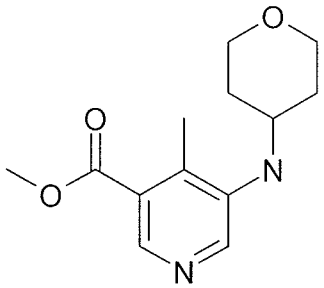


[01510] Step 1: Synthesis of methyl 5-amino-4-methylpyridine-3-carboxylate



[01511] To a stirred solution of 5-amino-4-methylpyridine-3-carboxylic acid (0.94 g, 6.18 mmol) in MeOH (20mlat 0°C was added thionyl chloride drop-wise. The solution was then heated to 50°C for 3.5h, a further 10ml of MeOH was added and the reaction heated at 50°C for 5h followed by stirring at room temperature for 64h. The solvent was then evaporated under reduced pressure and saturated $NaHCO_3$ solution was added until pH7-8. The product was extracted into EtOAc (2x50ml) and the combined organics were washed with brine (50ml) dried using Na_2SO_4, filtered and evaporated to afford the title compound as an off-white powder (824 mg, 80%) which was suitable for use in the next stage without any purification. LC-MS m/z=167.0, 1H NMR (500 MHz, Chloroform-d) δ 8.52 (d, J = 34.2 Hz, 1H), 8.16 (s, 1H), 3.95 (d, J = 4.8 Hz, 3H), 3.78 (s, 2H), 2.42 (s, 3H).

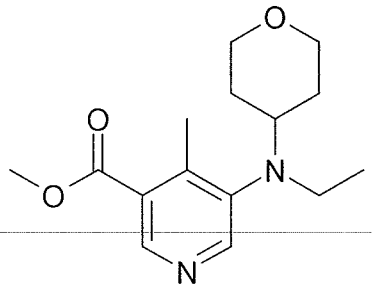
[01512] Step 2: Synthesis of methyl 4-methyl-5-[(oxan-4-yl)amino]pyridine-3-carboxylate



[01513] To a stirred solution of methyl 5-amino-4-methylpyridine-3-carboxylate (805 mg, 4.84 mmol) in DCE (20ml) under a nitrogen atmosphere was added oxan-4-one (537 µl, 5.80 mmol) followed by trifluoroacetic acid (742 µl, 9.69 mmol) and the reaction was left to stir for 5 min before the addition of sodium triacetoxyborohydride (1.54 g, 7.27 mmol). The reaction was stirred for 16h at room temperature after which time more oxan-4-one (100 µl) and sodium triacetoxyborohydride (300mg) were added and the reaction stirred for a further 6h. Distilled water (20ml) was added and solid $NaHCO_3$ was added until pH8. The phases were separated and then the aqueous phase was washed with EtOAc (2x50ml), the combined organics were washed with brine (50ml), dried using Na_2SO_4, filtered and evaporated to afford the title

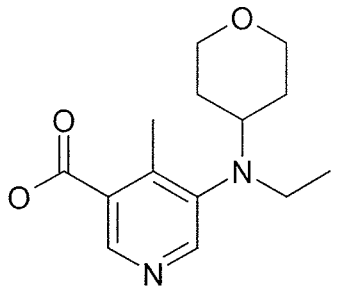
compound as a pale yellow solid (1.11g, 88%) which was used in the next stage without any further purification. LC-MS 96%, m/z=251.0, 1H NMR (500 MHz, Chloroform-d) δ 8.40 (s, 1H), 8.10 (s, 1H), 4.03 (dt, J = 11.9, 3.5 Hz, 2H), 3.92 (s, 3H), 3.68 – 3.58 (m, 1H), 3.54 (tt, J = 8.1, 4.1 Hz, 3H), 2.35 (s, 3H), 2.12 – 2.05 (m, 2H), 1.53 (ddd, J = 23.8, 11.0,4.3 Hz, 2H).

[01514] Step 3: Synthesis of methyl 5-[ethyl(oxan-4-yl)amino]-4-methylpyridine-3-carboxylate



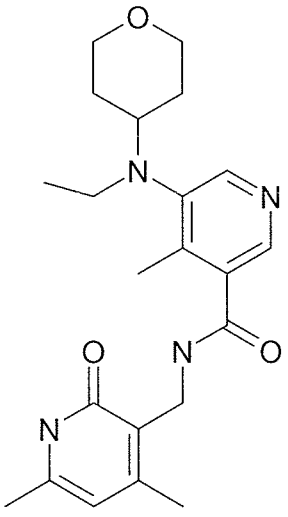
[01515] To a stirred solution of methyl 4-methyl-5-[(oxan-4-yl)amino]pyridine-3-carboxylate (600 mg, 2.40 mmol) in DCE (20ml) under a nitrogen atmosphere was added acetaldehyde (1.07 ml, 19.2 mmol) followed by trifluoroacetic acid (367 µl, 4.79 mmol) and the reaction was left to stir for 5 min before the addition of sodium triacetoxyborohydride (3.05 g, 14.4 mmol). The reaction was stirred for 16h at room temperature after which time more acetaldehyde (500 µl) and sodium triacetoxyborohydride (1.0g) were added and the reaction stirred for a further 16h. Distilled water (20ml) was added and solid $NaHCO_3$ was added until pH8. The phases were separated and then the aqueous phase was washed with DCM (2x50ml), the combined organics were washed with brine (50ml), dried using Na_2SO_4, filtered and evaporated. The residue was purified using a 25g Isolute silica column using a gradient of 0% to 50% EtOAc in heptane to afford the title compound as a pale yellow oil (418 mg, 60%). LC-MS 96%, m/z=279.1, 1H NMR (500 MHz, Chloroform-d) δ 8.76 (s, 1H), 8.44 (s, 1H), 3.97 (d, J = 11.0 Hz, 2H), 3.93 (s, 3H), 3.33 (td, J = 11.6, 2.1 Hz, 2H), 3.13 (q, J = 7.1 Hz, 2H), 3.04 (tt, J = 10.9, 4.0 Hz, 1H), 2.54 (s, 3H), 1.76 – 1.59 (m, 4H), 0.89 (t, J = 7.1 Hz, 3H).

[01516] Step 4: Synthesis of 5-[ethyl(oxan-4-yl)amino]-4-methylpyridine-3- carboxylic acid



[01517] To a stirred solution of methyl 5-[ethyl(oxan-4-yl)amino]-4-methylpyridine-3-carboxylate (415 mg, 1.49 mmol) in THF (7 ml) and MeOH (3 ml) was added 4M NaOH solution (932 µl, 3.73 mmol).The reaction was stirred at room temperature for 4.5h after which the solution was neutralised via the addition of 1M HCl and the solvent was removed under reduced pressure, followed by the addition of saturated brine (10ml). The aqueous phase was extracted with 1:1 IPA:$CHCl_3$ (3X50ml), the combined organics washed with brine (30ml), dried using Na_2SO_4, filtered and evaporated to afford the title compound as an off-white solid (305 mg, 77%) which was suitable for use in the next stage without any further purification. LC-MS 99%, m/z=265.1, 1H NMR (500 MHz, DMSO-d6) δ 8.57 (s, 1H), 8.46 (s, 1H), 3.82 (d, J = 11.6 Hz, 2H), 3.25 (t, J = 10.9 Hz, 2H), 3.16 – 2.99 (m, 3H), 2.45 (s, 3H), 1.64 (d, J = 11.0 Hz, 2H), 1.48 (dt, J =11.9, 5.7 Hz, 2H), 0.81 (t, J = 7.0 Hz, 3H).

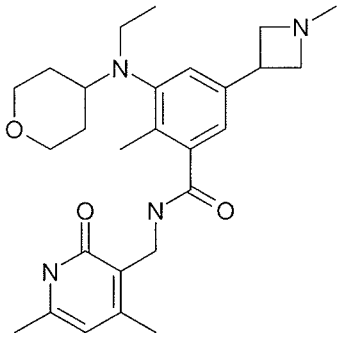
[01518] Step 5: Synthesis of N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-5-[ethyl(oxan-4-yl) amino]-4- methylpyridine-3-carboxamide



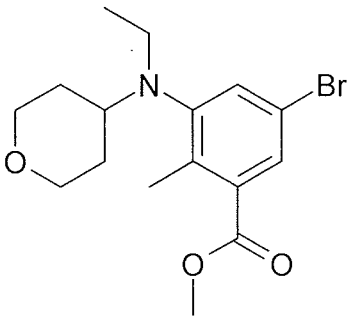
[01519] To a stirred solution of 5-[ethyl(oxan-4-yl)amino]-4-methylpyridine-3-carboxylic acid (300 mg, 1.13 mmol) in DMF (10ml) was added DIPEA (395 µl, 2.27 mmol) and HATU (518

mg, 1.36 mmol). The reaction was stirred at room temperature for 5 min after which time 3-(aminomethyl)-4,6-dimethyl-1,2-dihydropyridin-2-one (89%, 214 mg, 1.25 mmol) was added and the reaction was stirred at room temperature for 18h. The reaction mixture was then poured onto 500ml of water and the product was extracted into EtOAc (3x200ml), the combined organic phase was washed with brine (2x100ml), dried (Na_2SO_4) and evaporated. The crude product was then purified using preparative-HPLC and the resulting solid was triturated with diethyl ether and isolated by filtration to afford the title compound as an off white solid (115 mg, 25%). LC-MS 100%, m/z=399.2, ^{1}H NMR (500 MHz, Acetone) δ 10.97 (s, 1H), 8.32 (s, 1H), 8.22 (s, 1H), 7.73 (s, 1H), 5.92 (s, 1H), 4.41 (d, J = 5.3 Hz, 2H), 3.85 (dd, J = 11.3, 3.0 Hz, 2H), 3.28 (td, J = 11.7, 1.9 Hz, 2H), 3.15 (q, J = 7.1 Hz, 2H),3.09 (ddd, J = 11.1, 7.2, 3.9 Hz, 1H), 2.32 (d, J = 1.5 Hz, 6H), 2.23 (s, 3H), 1.69 (dd, J = 12.6, 1.7 Hz, 2H), 1.55 (ddd, J = 24.3, 12.2, 4.4 Hz, 2H), 0.85 (t, J = 7.1 Hz, 3H).

[01520] **Compound 322: N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3-[ethyl(oxan-4-yl) amino]-2-methyl-5-(1-methylazetidin-3-yl)benzamide**



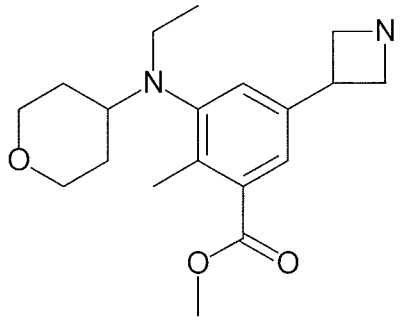
[01521] Step 1: Synthesis of methyl 5-bromo-3-[ethyl(oxan-4-yl)amino]-2- methylbenzoate



[01522] To a stirred solution of methyl 5-bromo-3-[ethyl(oxan-4-yl)amino]-2-methylbenzoate (622 mg, 1.90 mmol) in DCE (10 ml) under a nitrogen atmosphere was added acetaldehyde

(318 µl, 5.69 mmol) followed by acetic acid (650 µl, 11.4mmol) and the reaction was left to stir for 5 min before the addition of sodium triacetoxyborohydride (2.00 g, 9.48 mmol). The reaction was stirred for 16h at room temperature after which time additional acetaldehyde (300 µl) and sodium triacetoxyborohydride (1.2 g) were added. The reaction was stirred for a further 6h whereupon distilled water (100ml) was added and solid $NaHCO_3$ was added until the aqueous phase was pH7.The phases were separated, the aqueous phase was washed with DCM (2x50ml), the combined organic phases were then washed with brine (100ml), dried using Na_2SO_4, filtered and evaporated. The crude residue was purified using FCC over silica eluting with 0-5% EtOAc in heptane to afford the title compound as a pale yellow oil (47 0mg, 70%). LC-MS 100m/z= 356.0/357.9. 1H NMR (500 MHz, Chloroform-d) δ 7.64 (d, J = 2.0 Hz, 1H), 7.29 (d, J = 2.0 Hz, 1H), 3.89 (d, J = 11.3 Hz, 2H), 3.83 (s, 3H), 3.26 (td, J = 11.5, 2.6 Hz, 2H), 2.98 (q, J = 7.1 Hz, 2H), 2.86 (dd, J = 9.7, 5.2 Hz, 1H), 2.38 (s, 3H), 1.67 – 1.52 (m, 4H), 0.80 (t, J = 7.1 Hz, 3H).

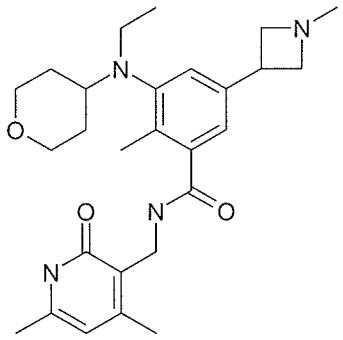
[01523] Step 2: Synthesis of methyl 5-(azetidin-3-yl)-3-[ethyl(oxan-4-yl)amino]-2-methylbenzoate



[01524] To a dry flask was added zinc dust (186 mg, 2.85 mmol) and the flask was heated using a heat gun for a few minutes. Then anhydrous DMA (15ml) was added under nitrogen whilst stirring vigorously and heating to 65°C. TMSCl (44 µl, 0.34 mmol) and 1,2-dibromoethane (30µl, 0.34 mmol) were added and the reaction was stirred at 65°C for 30mins followed by the dropwise addition of N-Boc-3-iodoazetidine (624 mg, 2.20 mmol) as a solution in anhydrous DMA (5ml). The reaction was then cooled to room temperature methyl 5-bromo-3-[ethyl(oxan-4-yl)amino]-2-methylbenzoate (470 mg, 1.32 mmol) was added as a solution in anhydrous DMA (10ml). The resulting solution was degassed with nitrogen for 10 mins after which $Pd(dppf)Cl_2$.DCM (32 mg, 0.04 mmol) and copper (I) iodide (15mg, 0.08 mmol) were

added as solids. The reaction was heated to 80°C for 60min and then cooled to room temperature followed by the addition of distilled water (50ml) and saturated NH_4Cl solution (10ml). The aqueous phase was extracted with EtOAc (3x50ml) and then the combined organics were washed with brine (20ml), dried with Na_2SO_4, filtered and evaporated to dryness followed by heptane azeotrope to remove any residual DMA. The residue was purified over a 10g Isolute column using 0%-25% EtOAc in heptane as the eluent to afford the title compound as a pale brown oil (565 mg). LC-MS 100%, 2.12min (3.5 minute LC-MS method), m/z=433.2. To this oil was added DCM (4 ml) followed by TFA (1 ml) and the solution was stirred at room temperature for 2 h after which the solvent was evaporated and saturated aqueous $NaHCO_3$ was added until pH7-8. The aqueous phase was extracted with DCM (3 x 30ml), washed with brine (30 ml), dried with MgSO4, filtered and evaporated to afford the title compound as a yellow oil (440 mg). LC-MS 100%, m/z= 333.1.

[01525] Step 3: Synthesis of N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3-[ethyl(oxan-4-yl) amino]-2-methyl-5-(1-methylazetidin-3-yl)benzamide

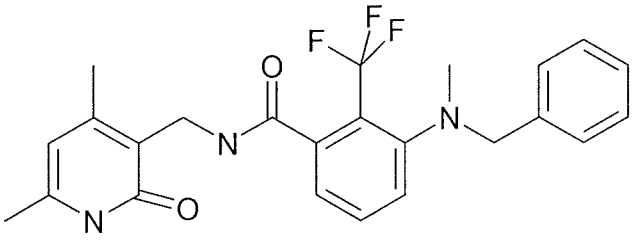


[01526] To a stirred solution of methyl 5-(azetidin-3-yl)-3-[ethyl(oxan-4-yl)amino]-2-methylbenzoate (440 mg, 1.32 mmol) in DCE (10ml) under a nitrogen atmosphere was added paraformaldehyde (278 mg, 9.27 mmol) followed by acetic acid (0.15 ml, 2.65 mmol) and the reaction was left to stir for 5 min before the addition of sodium triacetoxyborohydride (1.40 g, 6.62 mmol). The reaction was stirred for 16h at room temperature after which time distilled water (20ml) was added and solid $NaHCO_3$ was added until the aqueous phase was pH8 and the phases were separated, the aqueous phase was washed with DCM (3x30ml), the combined organics were then washed with brine (50ml), dried using Na_2SO_4, filtered and evaporated. The residue was purified by chromatography over a 10g Isolute (elution with 0% to 5% MeOH in DCM) and evaporated followed by purification over alumina (elution with 0% to 1% MeOH in

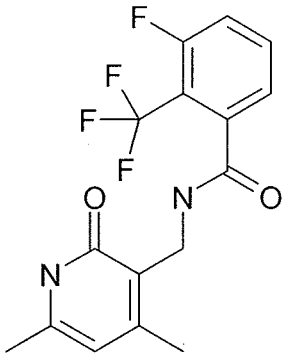
DCM) to afford the title compound as a yellow oil which was used directly in the next stage of the synthesis. LC-MS 77%, 1m/z= 347.1.

[01527] Methyl 3-[ethyl(oxan-4-yl)amino]-2-methyl-5-(1-methylazetidin-3-yl)benzoate (103 mg, 0.30 mmol) was dissolved in THF (20ml) and MeOH (5ml) and 2M NaOH (1.49 ml, 2.97 mmol) was added. The reaction was stirred at 50°C for 16h, cooled, acidified to pH4 using 6M HCl and the solvent evaporated under reduced pressure, and the residue dried in a vacuum oven at 40°C for 5h to afford the crude acid. To the acid in DMF (1 0ml) were added HATU (170 mg, 0.45 mmol) and DIPEA (130µl, 0.74 mmol). The mixture was stirred at room temperature for 5 min and then 3-(aminomethyl)-4,6-dimethyl-1,2-dihydropyridin-2-one (89%, 66mg, 0.39 mmol) was added. The reaction was stirred for 16h after which additional HATU (80mg) and 3-(aminomethyl)-4,6-dimethyl-1,2-dihydropyridin-2-one (30mg) and the mixture stirred for a further 5h. The reaction mixture was poured onto distilled after (50ml), extracted with EtOAc (3x50ml), washed with brine (2x20ml), dried with Na_2SO_4, filtered and evaporated. The crude residue was purified using preparative HPLC and evaporated to afford the title compound as an off-white solid (28 mg, 5% over three steps). LC-MS 95%, m/z=467.3, 1H NMR (500 MHz, Acetone-d_6) δ 10.73 (s, 1H), 7.61 (s, 1H), 7.30 (s, 1H), 7.26 (s, 1H), 5.97 (s, 1H), 4.74 (t, J = 9.9 Hz, 2H), 4.60 (t, J = 9.6 Hz, 2H), 4.38 (q, J = 6.2 Hz, 3H), 3.83 (d, J = 11.6 Hz, 2H), 3.27 (s, 3H),3.23 (t, J = 11.6 Hz, 2H), 3.10 (dd, J = 14.1, 7.0 Hz, 2H), 3.04 – 2.97 (m, 1H), 2.34 (s, 3H), 2.31 (s, 3H), 2.25 (s, 3H), 1.67 (d, J = 11.1 Hz, 2H), 1.56 (td, J = 11.8, 4.1 Hz, 2H), 0.83 (t, J = 7.0 Hz, 3H).

[01528] **Compound 332: 3-[benzyl(methyl)amino]-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl) methyl]-2-(trifluoromethyl)benzamide**

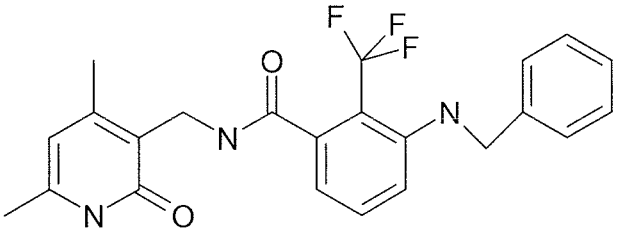


[01529] Step 1: Synthesis of N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3-fluoro-2-(trifluoromethyl)benzamide



[01530] To a stirred solution of 3-fluoro-2-(trifluoromethyl)benzoic acid (1.00 g, 4.81 mmol) in DMF (25ml) cooled in an ice bath was added HATU (2.19 g, 5.77 mmol) and DIPEA (1.67 ml, 9.61 mmol). The reaction was stirred at 0°C for 5 min after which time 3-(aminomethyl)-4,6-dimethyl-1,2-dihydropyridin-2-one (89%, 904 mg, 5.29mmol) was added and the reaction was warmed room temperature for 4h. The reaction mixture was then poured onto distilled water (300ml) and stirred for 1h after which time the precipitate was collected via vacuum filtration using microfibre paper. The resulting solid was triturated using diethyl ether and filtered to afford the title compound as a pale brown solid (1.19 g, 72%). LC-MS 100%, m/z=343.0, 1H NMR (500 MHz, DMSO) δ 11.48 (s, 1H), 8.54 (t, J = 4.8 Hz, 1H), 7.71 (dd, J = 13.3, 8.0 Hz, 1H), 7.56 – 7.45 (m, 1H), 7.20 (d, J = 7.6 Hz, 1H), 5.86 (s, 1H), 4.25 (d, J = 4.9 Hz, 2H), 2.18 (s, 3H), 2.11 (s, 3H).

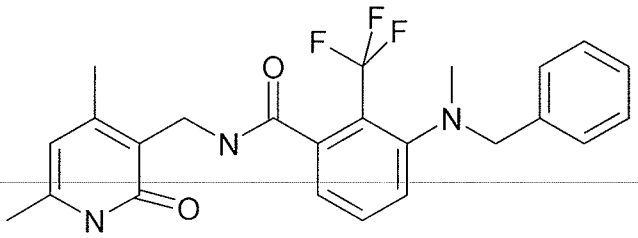
[01531] Step 2: Synthesis of 3-(benzylamino)-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-2- (trifluoromethyl)benzamide



[01532] A suspension of N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3-fluoro-2-(trifluoro methyl)benzamide (0.80 g, 2.34 mmol) in benzylamine (2.6 ml, 23.4 mmol) was heated in a microwave reactor at 210°C for 4h. After cooling distilled water (20 ml) was added to the slurry and 2M HCl was added until the suspension was at pH5. and the mixture was extracted using EtOAc (3x50ml). The combined organics were washed with pH5 HCl solution (2x50ml), brine (30ml), dried using Na_2SO_4 filtered and evaporated. The resultant oil was

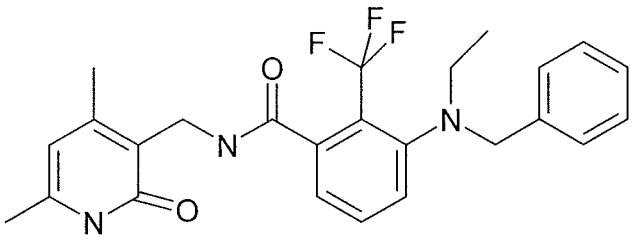
purified using a 50g Isolute silica column eluting with a gradient of 0% to 5% MeOH in DCM to afford the title compound as an off-white solid (313 mg, 29%). LC-MS 94%, m/z=430.2, 1H NMR (500 MHz, Acetone-d6) δ 7.41 – 7.16 (m, 8H), 6.69 (d, J = 8.5 Hz, 1H), 6.50 (d, J = 7.4 Hz, 1H), 5.87 (s, 1H), 5.84 (s, 1H), 4.53 (d, J = 5.7 Hz, 2H), 4.35 (d, J = 5.6 Hz, 2H), 2.28, (d, J = 4.0 Hz, 3H), 2.21 (s, 3H).

[01533] Step 3: Synthesis of 3-[benzyl(methyl)amino]-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-2-(trifluoromethyl)benzamide



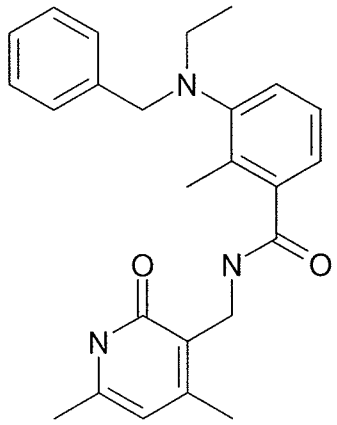
[01534] To a solution of 3-(benzylamino)-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-2-(trifluoromethyl)benzamide (100 mg, 0.23 mmol) in DCE (5 ml) was added acetic acid (27 µl, 0.47 mmol) followed by paraformaldehyde (7 mg, 0.23 mmol) after which the reaction was stirred at room temperature for 10min. Then sodium triacetoxyborohydride (74 mg, 0.35 mmol) was added in one portion and the reaction was stirred at room temperature for 16h. Further treatment with acetaldehyde (35 mg), sodium triacetoxyborohydride (250 mg) and AcOH (100ml) was performed. After a further 24h further acetaldehyde (445 mg) and sodium triacetoxyborohydride (250 mg) were added and the reaction was stirred for a further 3h. Water (20 ml) was then added to the reaction mixture and the aqueous phase was neutralised by the portionwise addition of $NaHCO_3$. The aqueous phase was extracted with DCM (2x50ml), then the combined organic phases were washed with brine, dried (Na_2SO_4) and evaporated. The product was purified using FCC over a 5g Isolute, eluting with 0-5% MeOH in DCM to afford the title compound as an off-white powder (24 mg, 22%). LC-MS 95%, 4.12min (7 minute LC-MS method), m/z=444.2, 1H NMR (500 MHz, Chloroform-d) δ 11.10 (br. s, 1H), 7.44 (t, J = 7.8 Hz, 1H), 7.38 – 7.29 (m, 5H), 7.27 – 7.23 (m, 1H), 7.12 (d, J = 7.4 Hz, 1H), 7.04 (t, J = 5.6 Hz, 1H), 5.92 (s, 1H), 4.52 (d, J = 5.9 Hz, 2H), 4.09 (s, 2H), 2.60 (s, 3H), 2.38 (s, 3H), 2.19 (s, 3H).

[01535] **Compound 333: 3-[benzyl(ethyl)amino]-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl) methyl]-2-(trifluoromethyl)benzamide**

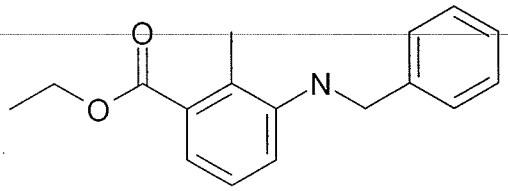


[01536] To a solution of 3-(benzylamino)-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-2-(trifluoromethyl)benzamide (198 mg, 0.46 mmol) in DCE (5 ml) was added acetic acid (80 µl, 1.38 mmol) followed by acetaldehyde (129 µl, 2.31 mmol) after which the reaction was stirred at room temperature for 10min. Then sodium triacetoxyborohydride (490 mg, 2.31 mmol) was added in one portion and the reaction was stirred at room temperature for 16h. Further 4x130uL treatments with acetaldehyde and 4x0.5g sodium triacetoxyborohydride were performed over 3 days to completed the reaction. Water (100ml) was then added to the reaction mixture and the aqueous phase was neutralized by the portionwise addition of $NaHCO_3$. The aqueous phase was extracted with DCM (2 x 50ml), then the combined organic phases washed with brine, dried (Na_2SO_4) and evaporated. The product was purified using FCC over a 5g Isolute, eluting with 0-5% MeOH in DCM followed by purification via RP-HPLC to give the title compound as an off-white powder (76 mg, 34%). LC-MS 100%, m/z=458.3, 1H NMR (500 MHz, Chloroform-d) δ 11.70 (s, 1H), 7.42 (t, J = 7.8 Hz, 1H), 7.36 – 7.27 (m, 5H), 7.24 (d, J = 7.1 Hz, 1H), 7.12 (d, J = 7.4 Hz, 1H), 7.03 (d, J = 5.4 Hz, 1H), 5.90 (s, 1H), 4.50 (d, J = 5.7 Hz, 2H), 4.05 (s, 2H), 2.96 (q, J = 7.1 Hz, 2H), 2.36 (s, 3H), 2.15 (s, 3H), 0.89 (t, J = 7.1 Hz, 3H).

[01537] **Compound 334: 3-[benzyl(ethyl)amino]-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-2-methylbenzamide**

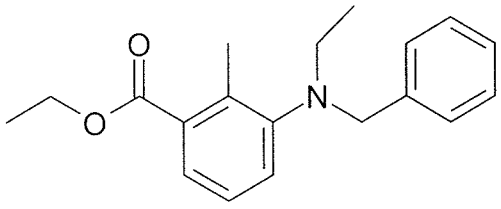


[01538] Step 1: Synthesis of ethyl 3-(benzylamino)-2-methylbenzoate



[01539] To a stirred solution of ethyl 3-amino-2-methylbenzoate (1.00 g, 5.58 mmol) in DCE (20 ml) was added benzaldehyde (569 µl, 5.58 mmol) followed by acetic acid (0.64 ml, 11.2 mmol). The reaction was stirred at room temperature for 1h and then sodium triacetoxyborohydride (1.77 g, 8.37 mmol) was added and the reaction stirred for 2h. Distilled water (20ml) was added and solid $NaHCO_3$ was added until the aqueous phase was pH7 and the phases were separated. The aqueous phase was washed with DCM (2 x5 0ml), the combined organics were then washed with brine (50ml), dried using Na_2SO_4, filtered and evaporated to afford the title compound as a yellow oil (1.52 g, 96%) which was used in the next stage without any further purification. LC-MS 95%, m/z=270.0, 1H NMR (500 MHz, Chloroform-d) δ 7.42 – 7.32 (m, 4H), 7.32 – 7.28 (m, 1H), 7.17 – 7.06 (m, 2H), 6.73 (dd, J = 7.8, 1.1 Hz, 1H), 4.40 (s, 2H), 4.36 (q, J = 14.3, 5.3 Hz, 2H), 4.08 (br. s, 1H), 2.35, (s, 3H), 1.39 (t, 3H).

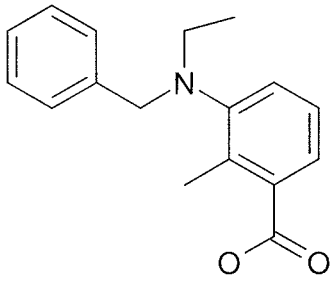
[01540] Step 2: Synthesis of ethyl 3-[benzyl(ethyl)amino]-2-methylbenzoate



[01541] To a stirred solution of ethyl 3-(benzylamino)-2-methylbenzoate (396 mg, 1.47 mmol)

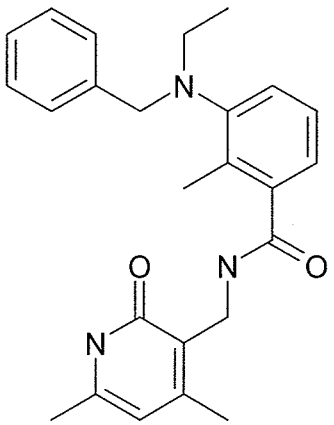
in DCE (10 ml) was added acetaldehyde (164 µl, 2.94 mmol) followed by acetic acid (0.17 ml, 2.94 mmol) The reaction was stirred at room temperature for 10min and then sodium triacetoxyborohydride (0.62 g, 2.94 mmol) was added and the reaction stirred for 16h. Distilled water (30ml) was added and solid $NaHCO_3$ was then added until the aqueous phase was pH7, the phases were separated, the aqueous phase was washed with DCM (2x50ml), the combined organics were then washed with brine (50 ml), dried using Na_2SO_4, filtered and evaporated. The resultant residue was then purified using a 25g silica Isolute column eluting using a gradient of 0% to 5% EtOAc in heptane to afford the title compound as a colourless oil (372 mg, 81%). LC-MS 94%, m/z= 298.1, 1H NMR (500 MHz, Chloroform-d) δ 7.48 (dd, J = 7.5, 1.3 Hz, 1H), 7.29 – 7.08 (m, 8H), 4.32 (q, J = 7.1 Hz, 2H), 4.05 (s, 2H), 2.92 (q, J = 7.1 Hz, 2H), 2.56 (s, 3H), 1.35 (t, J = 7.1 Hz, 3H), 0.92 (t, J = 7.1 Hz, 3H).

[01542] Step 3: Synthesis of 3-[benzyl(ethyl)amino]-2-methylbenzoic acid



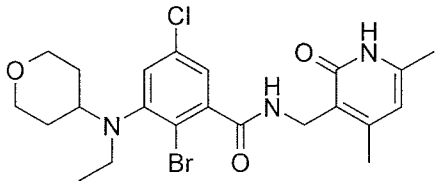
[01543] To a stirred solution of ethyl 3-[benzyl(ethyl)amino]-2-methylbenzoate (370 mg, 1.24 mmol) in THF (20 ml) and MeOH (5 ml) was added 2M NaOH (3.11 ml, 6.22 mmol) and the reaction was stirred at 50°C for 16h. The reaction was cooled to room temperature and the solvent removed *in vacuo* after which the aqueous solution was adjusted to pH1 using 1M HCl. The product was extracted into DCM (3 x 50ml), washed with brine (2 0ml), dried with Na_2SO_4 concentrated and filtered to afford the title compound as an orange oil (296 mg, 80%) which was used in the next stage without any further purification. LC-MS 91%, m/z=270.0, 1H NMR (500 MHz, Chloroform-d) δ 7.73 (d, J = 7.5 Hz, 1H), 7.34 – 7.30 (m, 4H), 7.23 (dt, J = 15.4, 6.9 Hz, 3H), 4.12 (d, J = 13.5 Hz, 2H), 3.04 – 2.94 (m, 2H), 2.69 (s, 3H), 0.99 (t, J =7.0 Hz, 3H).

[01544] Step 4: Synthesis of 3-[benzyl(ethyl)amino]-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-2-methylbenzamide

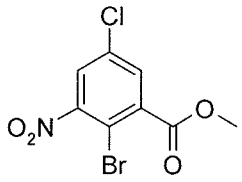


[01545] To a stirred solution of (3-[benzyl(ethyl)amino]-2-methylbenzoic acid (91% purity, 296 mg, 1.0 mmol) in DMF (10 ml) was added DIPEA (440 µl, 2.5 mmol) and HATU (570 mg, 1.5 mmol). The reaction was stirred at room temperature for 5 min after which time 3-(aminomethyl)-4,6-dimethyl-1,2-dihydropyridin-2-one (89%, 222 mg, 1.3 mmol) was added and the reaction was stirred at room temperature for 16h. The reaction mixture was then poured onto 150ml of water and stirred for 20 min. , The product was filtered, air dried under vacuum and then purified using RP-HPLC. The resulting solid was triturated with diethyl ether and isolated by filtration to afford the title compound as an off white solid (86 mg, 21%). LC-MS 99%, m/z=404.3, ^{1}H NMR (500 MHz, Chloroform-d) δ 12.04 (s, 1H), 7.33 – 7.23 (m, 4H), 7.21 (t, J = 6.8 Hz, 1H), 7.14 – 7.05 (m, 3H), 7.05 – 6.99 (m, 1H), 5.92 (s, 1H), 4.53 (d, J = 5.9 Hz, 2H), 4.06 (s,2H), 2.92 (q, J = 6.9 Hz, 2H), 2.41 (s, 3H), 2.39 (s, 3H), 2.16 (s, 3H), 0.92 (t, J = 7.0 Hz, 3H).

[01546] **Compound 191: 2-bromo-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)benzamide**

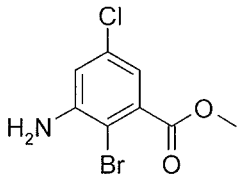


[01547] Step 1: Synthesis of methyl 2-bromo-5-chloro-3-nitrobenzoate



[01548] A solution of methyl 2-bromo-5-chlorobenzoate (10 g, 40 mmol) in concentrated H_2SO_4 (48 ml, 910 mmol) was cooled to -5°C in an acetone/ice bath in air. A mixture of concentrated nitric acid (3.35 ml, 52 mmol) and concentrated H_2SO_4 (3.4 ml, 64 mmol) was added dropwise to the reaction mixture at 0°C over 30 minutes. The yellow reaction mixture was stirred at 0 °C for 1.5 hours before being poured onto ice. EtOAc (150 ml) was added and the phases were separated. The organic phase was washed with deionized water (3 x 50 ml) followed by brine (50 ml). The organic phase was dried over MgSO4, filtered and concentrated under reduced pressure to give 12.0 g (60%) of the title compound material as a pale yellow oil which solidified upon standing. This material contained 40% of the 6-nitro isomer. This material was used without further purification. LC-MS 91%, m/z= no ionisation, ^{1}H NMR (500 MHz, Chloroform-d) δ 7.86 (1 H, d, *J*=2.52 Hz), 7.77 (1 H, d, *J*=2.52 Hz), 3.99 (3 H, s).

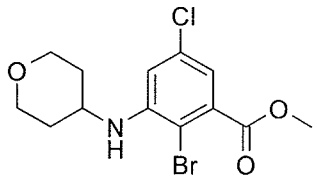
[01549] Step 2: Synthesis of methyl 3-amino-2-bromo-5-chlorobenzoate



[01550] To a solution of methyl 2-bromo-5-chloro-3-nitrobenzoate (4.0 g, 14 mmol) in methanol (130 ml) at room temperature was added ammonium chloride (7.13 g, 136 mmol) followed by deionized water (65 ml). The mixture was heated to 70°C in air before the addition of iron (4.55 g, 81.5 mmol). The reaction was stirred at 70°C for 3 hours, allowed to cool to room temperature and filtered through Kieselgel. The filter pad was washed with MeOH (65 ml) and the filtrate concentrated under reduced pressure. The residue was dissolved in saturated $NaHCO_3$ (50 ml) and EtOAc (100 ml). The phases were separated and the organic phase was washed with saturated $NaHCO_3$(aq) (3 x 50 ml) before being dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by FCC (50g silica, Isolute cartridge, gradient of eluents; 95:5 Heptane:EtOAc to 7:3 Heptane:EtOAc) to give 1.92 g (48%) of the title compound as a colourless oil. LC-MS 92%, m/z=268.8/265.8/267.6, ^{1}H NMR (500 MHz, Chloroform-d) δ 7.08 (1 H, d, *J*=2.36 Hz), 6.86 (1 H, d, *J*=2.36 Hz), 4.34 - 4.49 (2

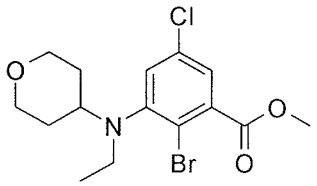
H, m), 3.93 (3 H, s).

[01551] Step 3: Synthesis of methyl 2-bromo-5-chloro-3-(oxan-4-ylamino)benzoate



[01552] To a solution of methyl 3-amino-2-bromo-5-chlorobenzoate (1.0 g, 3.8 mmol) in 1,2-dichloroethane (15 ml) at room temperature under nitrogen was added oxan-4-one (0.7 ml, 7.6 mmol) followed by acetic acid (1.3 ml, 23 mmol). This solution was stirred for 5 minutes before the addition of sodium triacetoxyborohydride (2.4 g, 11 mmol) at room temperature. After 21h, additional oxan-4-one (0.7 ml, 7.6 mmol) was added to the reaction mixture, with stirring for 10 minutes before adding sodium triacetoxyborohydride (2.4 g, 11 mmol). After stirring for 20h, deionized water (30 ml) was added and the mixture was neutralised with solid $NaHCO_3$. The phases were separated and the aqueous layer was extracted with EtOAc (2 x 30 ml). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by FCC (25g silica, Isolute cartridge, gradient of eluents; 9:1 Heptane:EtOAc to 8:2 Heptane:EtOAc) to give 903 mg (68%) of the title compound as a white solid. LC-MS 92%, 2.11min (3 minute LC-MS method), m/z=348.2/350.2/351.9, ^{1}H NMR (500 MHz, Chloroform-d) δ 6.94 - 7.07 (1 H, m), 6.70 (1 H, d, *J*=2.36 Hz), 4.72 (1 H, d, *J*=7.57 Hz), 3.96 - 4.15 (2 H, m), 3.87 - 3.96 (3 H, m), 3.40 - 3.67 (3 H, m), 2.05 (2 H, d, *J*=13.08 Hz), 1.49 - 1.69 (2 H, m).

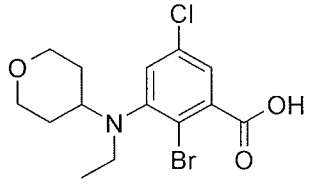
[01553] Step 4: Synthesis of methyl 2-bromo-5-chloro-3-[ethyl(oxan-4-yl)amino]benzoate



[01554] To a solution of methyl 2-bromo-5-chloro-3-(oxan-4-ylamino)benzoate (300 mg, 0.86 mmol) in 1,2-dichloroethane (3 ml) at room temperature under nitrogen was added acetaldehyde (96 µl, 1.7 mmol) followed by acetic acid (0.3 ml, 5.16 mmol). This solution was stirred for 5 minutes before the addition of sodium triacetoxyborohydride (0.55 g, 2.6 mmol) at room temperature with reaction monitoring by LCMS. After 22h, further acetaldehyde (96 µl,

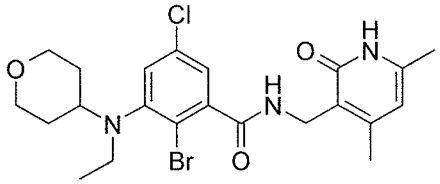
1.7 mmol) was added to the reaction mixture and this was stirred for 10 minutes before the addition of sodium triacetoxyborohydride (0.55 g, 2.6 mmol). After 3 days, the reaction mixture was diluted with 1,2-dichloroethane (5 ml). Acetaldehyde (962µl, 17.2 mmol) was added to the reaction mixture and this was stirred for 10 minutes before the addition of sodium triacetoxyborohydride (1.82 g, 8.6 mmol). After 15h, further acetaldehyde (960 µl, 17.2 mmol) was added to the reaction mixture and this was stirred for 10 minutes before the addition of sodium triacetoxyborohydride (1.82 g, 8.6 mmol). The reaction mixture was then stirred at room temperature for a further 22 hours before deionized water (25 ml) was added and the mixture was neutralised with solid $NaHCO_3$. EtOAc (25 ml) was added and the phases were separated. The aqueous layer was then extracted with EtOAc (2 x 25 ml) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by FCC (10g silica, Isolute cartridge, gradient of eluents; 99:1 Heptane:EtOAc to 8:2 Heptane:EtOAc) to give 122 mg (38%) of the title compound as a colourless oil. LC-MS 85%, m/z=376.3/378.2/379.9, ^{1}H NMR (500 MHz, Chloroform-d) δ 7.31 (d, J = 2.5 Hz, 1H), 7.18 (d, J = 2.4 Hz, 1H), 3.98 (dd, J = 8.7, 5.5 Hz, 2H), 3.94 (s, 3H), 3.35 (td, J = 11.6, 5.5 Hz, 2H), 3.19 (t, J = 7.1 Hz, 1H), 3.12 (q, J = 7.1 Hz, 2H), 1.75 (td, J = 10.1, 8.8, 3.9 Hz, 4H), 0.92 (t, J = 7.1 Hz, 3H).

[01555] Step 5: Synthesis of 2-bromo-5-chloro-3-[ethyl(oxan-4-yl)amino]benzoic acid



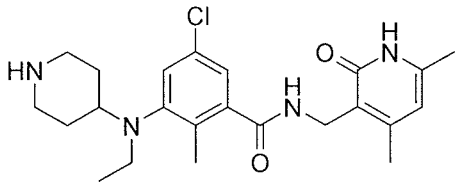
[01556] To a solution of methyl 2-bromo-5-chloro-3-[ethyl(oxan-4-yl)amino]benzoate (122 mg, 0.32 mmol) in tetrahydrofuran (3 ml) was added 4M NaOH (3.2 ml). The reaction mixture was stirred at 50 °C for 20 hours. The reaction mixture was acidified to pH 2-3 with 6M HCl and extracted with DCM (3 x 100 ml). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give 109 mg (93%, 83% corrected yields) of 2-bromo-5-chloro-3-[ethyl(oxan-4-yl)amino]benzoic acid as a pale yellow foam. LC-MS 89%, m/z=361.9/364.2/365.8, ^{1}H NMR (500 MHz, Chloroform-d) δ 7.50 (d, J = 2.4 Hz, 1H), 7.23 (d, J = 2.4 Hz, 1H), 4.00 (d, J = 11.5 Hz, 2H), 3.49 – 3.27 (m, 2H), 3.21 (t, J = 7.4 Hz, 1H), 3.14 (q, J = 7.0 Hz, 2H), 1.78 (dd, J = 7.4, 3.4 Hz, 4H), 0.93 (t, J = 7.0 Hz, 3H).

[01557] Step 6: Synthesis of 2-bromo-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)benzamide

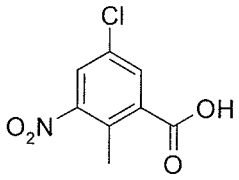


[01558] To a solution of 2-bromo-5-chloro-3-[ethyl(oxan-4-yl)amino]benzoic acid (109 mg, 0.3 mmol) in DMF (3 ml) at room temperature under nitrogen was added PyBOP (187 mg, 0.36 mmol) followed by N-ethyl-N-(propan-2-yl)propan-2-amine (78 µl, 0.45 mmol) and 3-(aminomethyl)-4,6-dimethyl-1,2-dihydropyridin-2-one (89%, 56 mg, 0.33 mmol). After stirring for 1 hour at room EtOAc (30ml) was added to the reaction mixture and this was then washed with deionized water (2 x 10 ml) followed by saturated $NaHCO_3$(aq) (2 x 10 ml). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified twice by FCC (5g silica, Isolute cartridge, gradient of eluents; 100% DCM to 98:2 DCM:MeOH). The sample was dried in a vacuum oven for 18 hours to give 103 mg (65%) of the title compound as a pale yellow solid. LC-MS 94%, m/z=496.0/498.0/500.0, ^{1}H NMR (500 MHz, Chloroform-d) δ 11.00 (s, 1H), 7.20 – 7.10 (m, 1H), 7.10 – 7.05 (m, 2H), 5.94 (s, 1H), 4.54 (d, J = 5.9 Hz, 2H), 3.96 (d, J = 11.4 Hz, 2H), 3.42 – 3.26 (m, 2H), 3.28 – 3.12 (m, 1H), 3.09 (q, J = 7.0 Hz, 2H), 2.39 (s, 3H), 2.23 (s, 3H), 1.72 (td, J = 8.5, 3.8 Hz, 4H), 0.90 (t, J = 7.0 Hz, 3H).

[01559] **Compound 102: 5-chloro-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3-[ethyl(piperidin-4-yl)amino]-2-methylbenzamide**

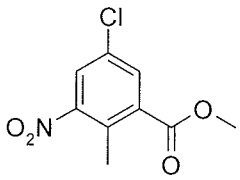


[01560] Step 1: Synthesis of 5-chloro-2-methyl-3-nitrobenzoic acid



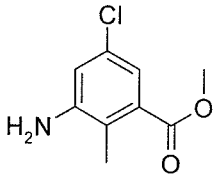
[01561] A solution of 5-chloro-2-methylbenzoic acid (9.9 g, 58 mmol) in concentrated H_2SO_4 (70 ml, 1310 mmol) was cooled to -5°C in an acetone/ice bath.. A mixture of concentrated nitric acid (4.9 ml, 75 mmol) and concentrated H_2SO_4 (5.0 ml, 94 mmol) was added dropwise to the reaction mixture at -5°C over 30 minutes. The reaction mixture was stirred at -5 °C for 2 hours before being poured onto ice (150g) and the precipitate collected by filtration. The precipitate was dissolved in EtOAc (100 ml) and washed with brine (100 ml) before being dried over $MgSO_4$, filtered and concentrated under reduced pressure to give 11.9 g of the title compound as an off-white solid. This material was used without further purification. LC-MS 57%, m/z=214.0/216.0, ^{1}H NMR (500 MHz, Chloroform-d) δ 10.37 (1 H, br. s.), 8.19 (1 H, d, *J*=2.21 Hz), 7.91 (1 H, d, *J*=2.21 Hz), 2.67 (2 H, s).

[01562] Step 2: Synthesis of methyl 5-chloro-2-methyl-3-nitrobenzoate



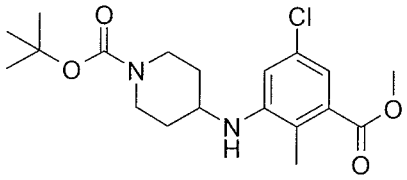
[01563] To a solution of 5-chloro-2-methyl-3-nitrobenzoic acid (1.17 g, 5.43 mmol) in DMF (11 ml) at room temperature and nitrogen was added Na_2CO_3 (862 mg, 8.14 mmol) followed by iodomethane (0.51 ml, 8.14 mmol). The reaction mixture was stirred at room temperature for 19 hours before being diluted with deionized water (30 ml) and extracted with EtOAc (3 x 30 ml). The combined organic phases were washed with saturated $NaHCO_3$(aq) (30 ml), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by FCC (10g silica, Isolute cartridge, gradient of eluents; 99:1 Heptane:EtOAc to 95:5 Heptane:EtOAc) to give 900 of the title compound as a pale yellow oil. LC-MS 89%, m/z=no ionisation, ^{1}H NMR (500 MHz, Chloroform-d) δ 8.00 (1 H, d, *J*=2.21 Hz), 7.86 (1 H, d, *J*=2.21 Hz), 3.96 (3 H, s), 2.60 (3 H, s).

[01564] Step 3: Synthesis of methyl 3-amino-5-chloro-2-methylbenzoate



[01565] To a solution of methyl 5-chloro-2-methyl-3-nitrobenzoate (9.19 g, 40 mmol) in methanol (200 ml) at room temperature was added ammonium chloride (21 g, 400 mmol) followed by deionized water (100 ml). The mixture was heated to 70 °C before the addition of iron (13.4 g, 240 mmol). The reaction turned to a dark colour over the 2.5 hours it was stirred at 70 °C. This mixture was allowed to cool to room temperature and was filtered through Kieselgel. The filter pad was washed with MeOH (100 ml) and the filtrate concentrated under reduced pressure. The residue was dissolved in deionized water (100 ml) and EtOAc (100 ml). The phases were separated and the aqueous phase was extracted with EtOAc (2 x 100 ml). The combined organic extracts were washed with brine (100 ml), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give 7.6g of the title compound as a viscous orange oil that solidified upon standing. This material was used without further purification. LC-MS 63%, m/z=200.3/202.0, ^{1}H NMR (500 MHz, Chloroform-d) δ 7.20 (1 H, d, *J*=2.21 Hz), 6.80 (1 H, d, *J*=2.05 Hz), 3.89 (3 H, s), 3.74 - 3.87 (2 H, m), 2.30 (3 H, s).

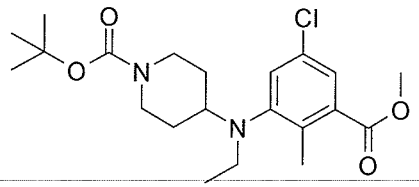
[01566] Step 4: Synthesis of tert-butyl 4-{[5-chloro-3-(methoxycarbonyl)-2-methylphenyl]amino}piperidine-1-carboxylate



[01567] To a solution of methyl 3-amino-5-chloro-2-methylbenzoate (100 mg, 0.50 mmol) in 1,2-dichloroethane (2.5 ml) at room temperature and under nitrogen was added tert-butyl 4-oxopiperidine-1-carboxylate (200 mg, 1.0 mmol) followed by acetic acid (0.17 ml, 3.0 mmol). This solution was stirred for 5 minutes before the addition of sodium triacetoxyborohydride (0.32 g, 1.5 mmol) at room temperature. The resulting mixture was stirred for 20 hours under nitrogen. Deionized water (5 ml) was added and the mixture was neutralised with solid $NaHCO_3$. The phases were separated and the aqueous layer was extracted with EtOAc (2 x 5 ml). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by FCC (10g silica, Isolute cartridge, gradient of

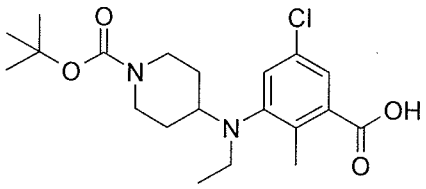
eluents; 99:1 Heptane:EtOAc to 7:3 Heptane:EtOAc) to give 131 mg (68%) of the title compound as a white solid. LC-MS 98%, m/z=405.4/406.9 (M+Na), ^{1}H NMR (500 MHz, Chloroform-d) δ ppm 7.10 (1 H, d, *J*=2.05 Hz), 6.70 (1 H, d, *J*=1.89 Hz), 3.98 - 4.16 (2 H, m), 3.88 (3 H, s), 3.58 - 3.72 (1 H, m), 3.37 - 3.52 (1 H, m), 2.97 (2 H, br. t, *J*=11.50, 11.50 Hz), 2.24 (3 H, s), 2.06 (2 H, br. d, *J*=10.60 Hz), 1.44 - 1.51 (9 H, m), 1.32 - 1.44 (2 H, m).

[01568] Step 5: Synthesis of tert-butyl 4-{[5-chloro-3-(methoxycarbonyl)-2-methylphenyl](ethyl)amino}piperidine-1-carboxylate



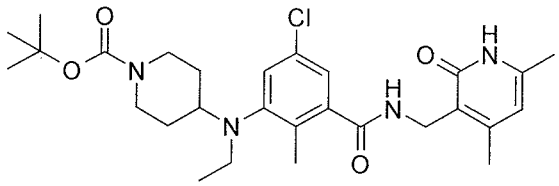
[01569] To a solution of tert-butyl 4-{[5-chloro-3-(methoxycarbonyl)-2-methylphenyl]amino}piperidine-1-carboxylate (125 mg, 0.33 mmol) in 1,2-dichloroethane (1.6 ml) at room temperature under nitrogen was added acetaldehyde (37 µl, 0.65 mmol) followed by acetic acid (0.11 ml, 1.96 mmol). This solution was stirred for 5 minutes before adding sodium triacetoxyborohydride (0.21 g, 0.98 mmol) at room temperature. The reaction was monitored by LCMS and after 4.5h a further acetaldehyde (73 µl, 1.31 mmol) and sodium triacetoxyborohydride (0.28 g, 1.31 mmol) were added to the reaction mixture. The mixture was stirred for a further 18 hours after which deionized water (10 ml) was added and the mixture was neutralised with solid $NaHCO_3$. The phases were separated and the aqueous layer was extracted with EtOAc (2 x 10 ml). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by FCC (10g silica, Isolute cartridge, gradient of eluents; 99:1 Heptane:EtOAc to 8:2 Heptane:EtOAc) to give 131 mg (98%) of the title compound as a thick colourless oil. LC-MS 98%, m/z=433.5/435.1 (M+Na), ^{1}H NMR (500 MHz, Chloroform-d) δ ppm 7.57 (1 H, d, *J*=2.21 Hz), 7.22 (1 H, d, *J*=2.05 Hz), 3.97 - 4.14 (2 H, m), 3.90 (3 H, s), 3.04 (2 H, q, *J*=6.99 Hz), 2.81 - 2.91 (1 H, m), 2.70 (2 H, br. t, *J*=11.50, 11.50 Hz), 2.45 (3 H, s), 1.69 - 1.80 (2 H, m), 1.47 - 1.56 (2 H, m), 1.46 (9 H, s), 0.87 (3 H, t, *J*=7.09 Hz).

[01570] Step 6: Synthesis of 3-({1-[(tert-butoxy)carbonyl]piperidin-4-yl}(ethyl)amino)-5-chloro-2-methylbenzoic acid



[01571] To a solution of tert-butyl 4-{[5-chloro-3-(methoxycarbonyl)-2-methylphenyl](ethyl)amino}piperidine-1-carboxylate (131 mg, 0.32 mmol) in tetrahydrofuran (2 ml) was added LiOH (8.4 mg, 0.35 mmol) in deionized water (2 ml). The reaction mixture was stirred in air at room temperature for 24 hours. 1M NaOH (3.19 ml) was added to the reaction mixture and this was stirred for a further 24 hours. The reaction mixture was then warmed to 40 °C for 25h. The reaction mixture was acidified to pH 2-3 with 1M HCl and extracted with EtOAc (3 x 20 ml). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give 122 mg of the title compound as a thick orange oil. LC-MS 76%, m/z=397.5/399.4, ^{1}H NMR (500 MHz, Chloroform-d) δ ppm 7.74 (1 H, s), 7.20 - 7.35 (2 H, m), 3.92 - 4.11 (2 H, m), 2.97 - 3.13 (2 H, m), 2.81 - 2.95 (1 H, m), 2.62 - 2.79 (2 H, m), 2.53 (3 H, s), 1.75 (2 H, br. s.), 1.48 - 1.61 (2 H, m), 1.46 (9 H, s), 0.89 (3 H, t, J=6.86 Hz).

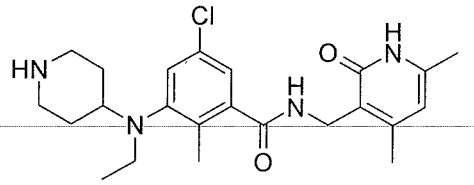
[01572] Step 7: Synthesis of tert-butyl 4-[(5-chloro-3-{[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]carbamoyl}-2-methylphenyl)(ethyl)amino]piperidine-1-carboxylate



[01573] To a solution of 3-({1-[(tert-butoxy)carbonyl]piperidin-4-yl}(ethyl)amino)-5-chloro-2-methylbenzoic acid (60 mg, 0.15 mmol) in DMF (2 ml) at room temperature under nitrogen was added PyBOP (94 mg, 0.18 mmol) followed by N-ethyl-N-(propan-2-yl)propan-2-amine (40 µl, 0.23 mmol) and 3-(aminomethyl)-4,6-dimethyl-1,2-dihydropyridin-2-one (89%, 28 mg, 0.17 mmol). After stirring for 1 hour at room temperature EtOAc (30 ml) was added to the reaction mixture and this was then washed with deionized water (5 ml) followed by saturated $NaHCO_3$(aq) (3 x 5 ml). The organic phase was dried over MgSO4, filtered and concentrated under reduced pressure. The residue was purified by FCC (2g silica, Isolute cartridge, gradient

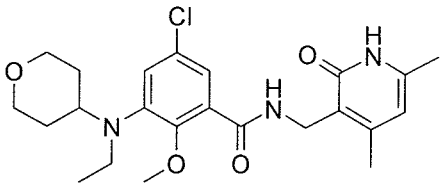
of eluents; 100% EtOAc to 96:4 EtOAc:MeOH) to give 71 mg (88%) of the title compound as a pale yellow solid. LC-MS 97%, m/z=531.1/533.1, ^{1}H NMR (250 MHz, Chloroform-d) δ ppm 11.17 (1 H, br. s.), 7.11 - 7.18 (1 H, m), 7.06 (2 H, dd, *J*=7.46, 2.28 Hz), 5.96 (1 H, s), 4.53 (2 H, d, *J*=5.94 Hz), 3.93 - 4.14 (2 H, m), 2.97 - 3.08 (2 H, m), 2.78 - 2.88 (1 H, m), 2.68 (2 H, t, *J*=11.57 Hz), 2.39 (3 H, s), 2.26 (3 H, s), 2.24 (3 H, s), 1.71 (2 H, d, *J*=11.27 Hz), 1.52 (2 H, br. s.), 1.45 (9 H, s), 0.86 (3 H, t, *J*=6.93 Hz).

[01574] Step 8: Synthesis of 5-chloro-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3-[ethyl(piperidin-4-yl)amino]-2-methylbenzamide

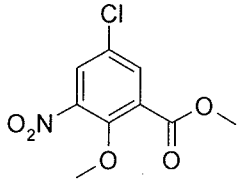


[01575] To a solution of tert-butyl 4-[(5-chloro-3-{[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]carbamoyl}-2-methylphenyl)(ethyl)amino]piperidine-1-carboxylate (140 mg, 0.26 mmol) in 1,4-dioxane (5 ml) at room temperature was added HCl (4M in dioxane) (1.32 ml). A gum formed after stirring for a short time which then dissolved upon the addition of deionized water (2 ml). The reaction was stirred for 21 h before being concentrated under reduced pressure to give a thick oil. DCM (3 ml) was added and a solid formed. This mixture was concentrated to give 105mg of a yellow solid which was stirred in DCM (10 ml) for 1 hour before being filtered and dried under high vacuum in a vacuum oven for 24 hours. The sample was then dissolved in deionized water (0.2 ml) and lyophilized to give 86 mg (70%) of the title compound as a beige solid. LC-MS 100%, m/z=431.2/433.2, ^{1}H NMR (500 MHz, Chloroform-d) δ ppm 7.44 (bs, 1H), 7.26 (bs, 1H), 6.69 (bs, 1H), 4.55 (s, 2H), 3.53 – 3.34 (m, 3H), 3.28 – 3.08 (m, 2H), 3.01 (t, *J* = 11.8 Hz, 2H), 2.51 (s, 3H), 2.43 (s, 3H), 2.33 (s, 3H), 2.16 – 1.96 (m, 2H), 1.91 – 1.76 (m, 2H), 0.92 (t, *J* = 6.9 Hz, 3H).

[01576] **Compound 192: 5-chloro-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3-[ethyl(oxan-4-yl)amino]-2-methoxybenzamide**

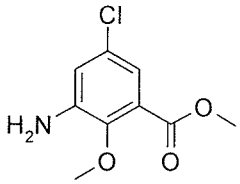


[01577] ***Step 1: Synthesis of methyl 5-chloro-2-methoxy-3-nitrobenzoate***



[01578] To concentrated H_2SO_4 (90 mL) was added portionwise 5-chloro-2-methylbenzoic acid (13.2 g, 77.6 mmol) at 0°C. Then a mixture of conc. HNO_3 (10.5 g, 1740 mmol) in conc. H_2SO_4 (15 mL) was added dropwise at 0°C over a period of about 1.5 hr. After the addition, the mixture was stirred at this temperature for 2 hr. The mixture was poured into ice water with vigorous stirring and the precipitate was collected by filtration. The precipitate was dissolved in EtOAc, washed with brine, dried over anhydrous Na_2SO_4, and concentrated to give a crude title compound (13.2 g), which was used in the next step without further purification. LC-MS 95%, m/z=245.9/247.9, ^{1}H NMR (500 MHz, Chloroform-d) δ ppm 8.01 (1 H, d, *J*=2.68 Hz), 7.91 (1 H, d, *J*=2.68 Hz), 4.01 (3 H, s), 3.97 - 3.99 (3 H, s).

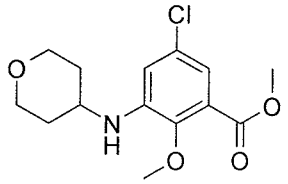
[01579] Step 2: Synthesis of methyl 3-amino-5-chloro-2-methoxybenzoate



[01580] To a solution of methyl 5-chloro-2-methoxy-3-nitrobenzoate (1.21 g, 4.93 mmol) in methanol (50 ml) at room temperature was added ammonium chloride (2.59 g, 49.2 mmol) followed by deionized water (25 ml). The mixture was heated to 70°C before the addition of iron (1.65 g, 29.6 mmol). The reaction turned to a dark color over the 2 hours it was stirred at 70°C. This mixture was allowed to cool to room temperature and was filtered through Kieselgel. The filter pad was washed with MeOH (50 ml) and the filtrate concentrated under reduced pressure. The residue was dissolved in deionized water (25 ml) and EtOAc (25 ml). The phases were separated and the aqueous phase was extracted with EtOAc (2 x 25 ml). The combined organic extracts were washed with brine (25 ml), dried over $MgSO_4$, filtered and

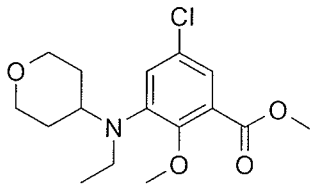
concentrated under reduced pressure to give 892 mg (67%) of the title compound as a viscous brown oil. This material was used without further purification. LC-MS 89%, 1.75min (3 minute LC-MS method), m/z=216.3/218.0, ^{1}H NMR (500 MHz, Chloroform-d) δ ppm 7.16 (1 H, d, *J*=2.52 Hz), 6.87 (1 H, d, *J*=2.52 Hz), 4.03 (2 H, br. s.), 3.89 - 3.94 (3 H, m), 3.84 (3 H, s).

[01581] Step 3: Synthesis of methyl 5-chloro-2-methoxy-3-[(oxan-4-yl)amino]benzoate



[01582] To a solution of methyl 3-amino-5-chloro-2-methoxybenzoate (440 mg, 2 mmol) in 1,2-dichloroethane (8 ml) at room temperature under nitrogen was added oxan-4-one (0.38 ml, 4.0 mmol) followed by acetic acid (0.7 ml, 12 mmol). This solution was stirred for 5 minutes before the addition of sodium triacetoxyborohydride (1.3 g, 6.1 mmol) at room temperature. After stirring for 23 hours deionized water (16 ml) was added and the mixture was neutralized with solid $NaHCO_3$. The phases were separated and the aqueous layer was extracted with EtOAc (2 x 16 ml). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by FCC (10g silica, Isolute cartridge, gradient of eluents; 9:1 Heptane:EtOAc to 7:3 Heptane:EtOAc) to give 439 mg (72%) of the title compound as a white solid. LC-MS 97%, m/z=300.3/302.0, ^{1}H NMR (500 MHz, Chloroform-d) δ ppm 7.06 (1 H, d, *J*=2.52 Hz), 6.73 (1 H, d, *J*=2.52 Hz), 4.38 - 4.45 (1 H, m), 4.02 (2 H, dt, *J*=11.78, 3.49 Hz), 3.91 (3 H, s), 3.81 (3 H, s), 3.54 (2 H, td, *J*=11.47, 2.13 Hz), 3.40 - 3.50 (1 H, m), 2.03 (2 H, br. d, *J*=13.70 Hz), 1.48 - 1.55 (2 H, m).

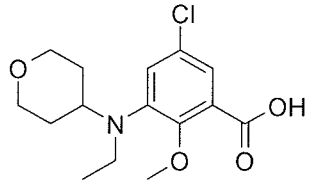
[01583] Step 4: Synthesis of methyl 5-chloro-3-[ethyl(oxan-4-yl)amino]-2-methoxybenzoate



[01584] To a solution of methyl 5-chloro-2-methoxy-3-[(oxan-4-yl)amino]benzoate (220 mg, 0.73 mmol) in 1,2-dichloroethane (2 ml) at room temperature under nitrogen was added acetaldehyde (82 µl, 1.47 mmol) followed by acetic acid (0.25 ml, 4.4 mmol). This solution was stirred for 5 minutes before the addition of sodium triacetoxyborohydride (0.47 g, 2.2

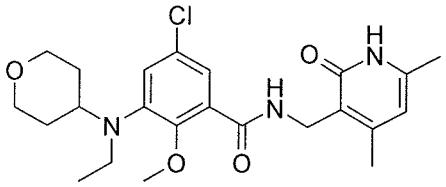
mmol) at room temperature. After stirring for 16 hours acetaldehyde (82 µl, 1.47 mmol) was added to the reaction mixture and stirred for 5 minutes before the addition of sodium triacetoxyborohydride (0.47 g, 2.2 mmol). After stirring for 24 hours, a further acetaldehyde (82 µl, 1.47 mmol) was added to the reaction mixture and stirred for 5 minutes before the addition of sodium triacetoxyborohydride (0.47 g, 2.2 mmol). The reaction was stirred for 24h after which deionized water (10 ml) was added and the mixture was neutralized with solid $NaHCO_3$. The phases were separated and the aqueous layer was extracted with EtOAc (2 x 10 ml). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by FCC (10g silica, Isolute cartridge, gradient of eluents; 95:5 Heptane:EtOAc to 7:3 Heptane:EtOAc) to give 127 mg (53%) of the title compound as a yellow oil. LC-MS 93%, m/z=328.4/330.0, ^{1}H NMR (500 MHz, Chloroform-d) δ ppm 7.35 (d, J = 2.6 Hz, 1H), 7.09 (d, J = 2.6 Hz, 1H), 3.98 (dd, J = 11.3, 4.2 Hz, 2H), 3.91 (s, 3H), 3.85 (s, 3H), 3.48 (tt, J = 11.6, 4.0 Hz, 1H), 3.36 (td, J = 11.8, 1.9 Hz, 2H), 3.15 (q, J = 7.0 Hz, 2H), 1.78 (qd, J = 12.2, 4.6 Hz, 2H), 1.72 – 1.59 (m, 2H), 0.99 (t, J = 7.0 Hz, 3H).

[01585] Step 5: Synthesis of 5-chloro-3-[ethyl(oxan-4-yl)amino]-2-methoxybenzoic acid



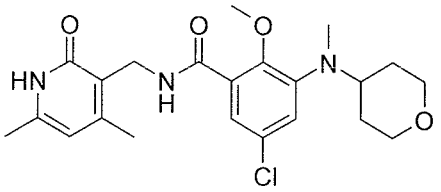
[01586] To a solution of methyl 5-chloro-3-[ethyl(oxan-4-yl)amino]-2-methoxybenzoate (127 mg, 0.39 mmol) in THF (4 ml) was added 4M NaOH (3.87 ml) . The reaction mixture was stirred at 50 °C for 24 hours. The reaction mixture was acidified to pH 2-3 with 6M HCl and extracted with DCM (5 x 15 ml). The combined organic extracts were dried over MgSO4, filtered and concentrated under reduced pressure to give 111 mg (91%) of the title compound as a yellow oil. LC-MS 80%, 1.25min (3 minute LC-MS method), m/z=314.4/315.9, ^{1}H NMR (500 MHz, Chloroform-d) δ ppm 10.02 – 9.55 (m, 1H), 8.01 – 7.47 (m, 1H), 7.36 – 6.96 (m, 1H), 4.15 – 3.86 (m, 5H), 3.76 (t, J = 6.6 Hz, 2H), 3.55 – 3.12 (m, 3H), 1.95 – 1.59 (m, 4H), 1.15 – 0.88 (m, 3H).

[01587] Step 6: Synthesis of 5-chloro-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3-[ethyl(oxan-4-yl)amino]-2-methoxybenzamide

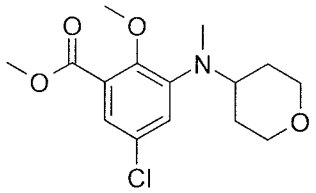


[01588] To a solution of 5-chloro-3-[ethyl(oxan-4-yl)amino]-2-methoxybenzoic acid (111 mg, 0.35 mmol) in DMF (3 ml) at room temperature under nitrogen was added PyBOP (220 mg, 0.42 mmol) followed by N-ethyl-N-(propan-2-yl)propan-2-amine (92 µl, 0.53 mmol) and 3-(aminomethyl)-4,6-dimethyl-1,2-dihydropyridin-2-one (89%, 66 mg, 0.39 mmol). After stirring for 1.5 hours at room temperature no starting material was observed by LCMS. Deionized water (20 ml) was added to the reaction mixture and the resultant precipitate was collected by filtration. The solid was washed with deionized water (3 x 5 ml) before being air dried. The solid was further purified by FCC (5g silica, Isolute cartridge, gradient of eluents; 100% DCM to 97:3 DCM:MeOH). The sample was dried in a vacuum oven for 18 hours to give 105 mg (64%) the title compound as an off-white solid. LC-MS 98%, m/z=449.5/452.1, ^{1}H NMR (500 MHz, Chloroform-d) δ ppm 11.47 (s, 1H), 8.79 (t, J = 5.8 Hz, 1H), 7.73 (d, J = 2.6 Hz, 1H), 7.05 (d, J = 2.6 Hz, 1H), 5.92 (s, 1H), 4.55 (d, J = 6.0 Hz, 2H), 3.98 (dd, J = 11.3, 3.8 Hz, 2H), 3.78 (s, 3H), 3.35 (t, J = 11.6 Hz, 3H), 3.12 (q, J = 7.0 Hz, 2H), 2.42 (s, 3H), 2.28 (s, 3H), 1.92 – 1.61 (m, 4H), 0.94 (t, J = 7.0 Hz, 3H).

[01589] **Compound 212: 5-chloro-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-2-methoxy-3-[methyl(oxan-4-yl)amino]benzamide**

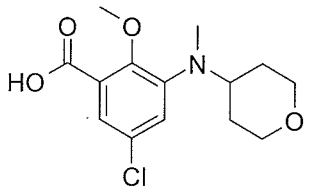


[01590] Step 1: Synthesis of methyl 5-chloro-2-methoxy-3-[methyl(oxan-4-yl)amino]benzoate



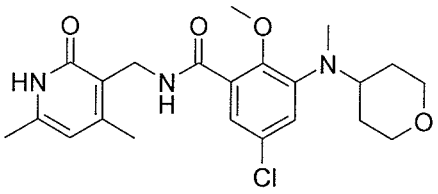
[01591] To a solution of methyl 5-chloro-2-methoxy-3-[(oxan-4-yl)amino]benzoate (500 mg, 1.67 mmol) in 1,2-dichloroethane (16 ml) at room temperature under nitrogen was added paraformaldehyde (300 mg, 10 mmol) followed by acetic acid (0.57 ml, 10 mmol). This mixture was stirred for 5 minutes before the addition of sodium triacetoxyborohydride (2.12 g, 10 mmol). After stirring for 64 hours deionized water (30 ml) was added and the mixture was neutralized with solid $NaHCO_3$ and the phases were separated. The aqueous layer was extracted with EtOAc (3 x 15 ml) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by FCC (10g silica, Isolute cartridge, gradient of eluents; 9:1 Heptane:EtOAc to 7:3 Heptane:EtOAc) to give 431 mg (82%) of the title compound as a colorless oil. LC-MS 98%, m/z=314.0/316.0, ^{1}H NMR (500 MHz, Chloroform-d) δ ppm 7.30 (d, J = 2.5 Hz, 1H), 7.04 (d, J = 2.5 Hz, 1H), 4.00 (dd, J = 11.3, 4.3 Hz, 2H), 3.90 (s, 3H), 3.82 (s, 3H), 3.70 (ddt, J = 11.7, 7.7, 3.8 Hz, 1H), 3.39 (t, J = 11.1 Hz, 2H), 2.71 (s, 3H), 1.84 (qd, J = 12.3, 4.6 Hz, 2H), 1.66 – 1.55 (m, 2H).

[01592] Step 2: Synthesis of 5-chloro-2-methoxy-3-[methyl(oxan-4-yl)amino]benzoic acid



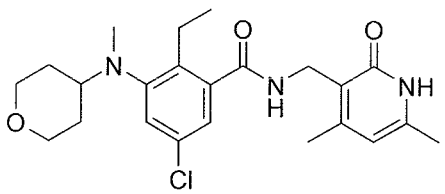
[01593] To a solution of methyl 5-chloro-2-methoxy-3-[methyl(oxan-4-yl)amino]benzoate (413 mg, 1.32 mmol) in THF (13 ml) and MeOH (2 ml) was added 4M NaOH (13.16 ml) . The reaction mixture was stirred at 50°C for 16 hours. The reaction mixture was acidified to pH 2-3 with 6M HCl and extracted with DCM (5 x 10 ml). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give 385 mg (98%) of the title compound as a thick yellow oil. LC-MS 94%, m/z=300.0/302.0, ^{1}H NMR (500 MHz, Chloroform-d) δ ppm 7.74 (d, J = 2.0 Hz, 1H), 7.30 – 7.12 (m, 1H), 4.11 – 4.02 (m, 2H), 4.01 (s, 3H), 3.54 (t, J = 11.6 Hz, 1H), 3.40 (t, J = 11.3 Hz, 2H), 2.76 (s, 3H), 1.97 – 1.78 (m, 2H), 1.63 (d, J = 11.8 Hz, 2H).

[01594] Step 3: Synthesis of 5-chloro-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-2-methoxy-3-[methyl(oxan-4-yl)amino]benzamide

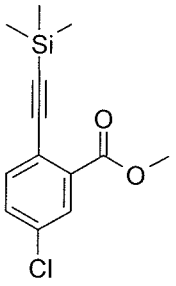


[01595] To a solution of 5-chloro-2-methoxy-3-[methyl(oxan-4-yl)amino]benzoic acid (200 mg, 0.67 mmol) in DMF (2 ml) at room temperature under nitrogen was added HBTU (304 mg, 0.80 mmol) followed by N-ethyl-N-(propan-2-yl)propan-2-amine (174 µl, 1.0 mmol) and 3-(aminomethyl)-4,6-dimethyl-1,2-dihydropyridin-2-one (89%, 125 mg, 0.73 mmol). After stirring for 2 hours at room temperature EtOAc (30ml) was added to the reaction mixture and this was then washed with deionized water (5 ml) followed by saturated $NaHCO_3$(aq) (3 x 5 ml). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by FCC (10g silica, Isolute cartridge, gradient of eluents; 100% DCM to 96:4 DCM:MeOH) to give 182 mg (63%) of the title compound as an off-white solid. LC-MS 98%, m/z=434.1/436.1, ^{1}H NMR (500 MHz, Chloroform-d) δ ppm 12.52 (br s, 1H), 8.76 (t, *J* = 5.8 Hz, 1H), 7.69 (d, *J* = 2.6 Hz, 1H), 7.01 (d, *J* = 2.6 Hz, 1H), 5.94 (s, 1H), 4.56 (d, *J* = 6.0 Hz, 2H), 3.99 (dd, *J* = 11.2, 3.9 Hz, 2H), 3.72 (s, 3H), 3.49 (tt, *J* = 11.5, 3.7 Hz, 1H), 3.36 (t, *J* = 11.2 Hz, 2H), 2.67 (s, 3H), 2.42 (s, 3H), 2.31 (s, 3H), 1.93 – 1.73 (m, 2H), 1.64 – 1.52 (m, 2H).

[01596] **Compound 205: 5-chloro-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-2-ethyl-3-[methyl(oxan-4-yl)amino]benzamide**

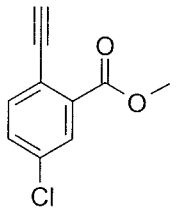


[01597] Step 1: Synthesis of methyl 5-chloro-2-[2-(trimethylsilyl)ethynyl]benzoate



[01598] To a solution of methyl 2-bromo-5-chlorobenzoate (14.8 g, 59 mmol) in TEA (124 ml, 890 mmol) was added copper(I) iodide (338 mg, 1.78 mmol) and triphenylphosphine (778 mg, 2.97 mmol) at room temperature under nitrogen. This mixture had nitrogen bubbled through it for 10 minutes before the addition of ethynyl(trimethyl)silane (12.45 ml, 89 mmol) and $Pd(OAc)_2$ (266 mg, 1.19 mmol). The reaction mixture was stirred at 50 °C for 20 hours before being concentrated under reduced pressure. The residue was dissolved in deionized water (50 ml) and EtOAc (50 ml) and filtered through celite. The filter cake was washed with EtOAc (50 ml) before the phases were separated and the aqueous layer was extracted with EtOAc (2 x 50 ml). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by FCC (10g silica, Isolute cartridge, gradient of eluents; 99:1 Heptane:EtOAc to 85:15 Heptane:EtOAc) to give 16.2 g (102.4%) of the title compound as an orange oil that solidified upon standing and contained residual heptane. LC-MS 91%, m/z=267.4/268.9, ^{1}H NMR (500 MHz, Chloroform-d) δ ppm 7.89 (d, J = 2.2 Hz, 1H), 7.51 (d, J = 8.3 Hz, 1H), 7.41 (dd, J = 8.3, 2.3 Hz, 1H), 3.92 (s, 3H), 0.27 (s, 9H).

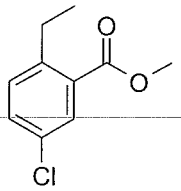
[01599] Step 2: Synthesis of methyl 5-chloro-2-ethynylbenzoate



[01600] To a solution of methyl 5-chloro-2-[2-(trimethylsilyl)ethynyl]benzoate (10 g, 37.5 mmol) in MeOH (150 ml) was added K_2CO_3 (10.4 g, 75 mmol) at room temperature. The reaction mixture was stirred for 1 hour before being concentrated under reduced pressure. The residue was dissolved in deionized water (50 ml) and EtOAc (50 ml). The phases were separated and the aqueous layer was extracted with EtOAc (2 x 50 ml). The combined organic

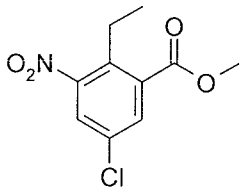
extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by FCC (50g silica, Isolute cartridge, gradient of eluents; 95:5 Heptane:EtOAc to 9:1 Heptane:EtOAc) to give 5.75 g (55%) of the title compound as an orange oil that solidified upon standing. This material contained 30% of ethyl ester and was suitable for use without any further purification. LC-MS 38%, m/z=195.0/196.9, ^{1}H NMR (500 MHz, Chloroform-d) δ ppm 7.93 (d, J = 2.2 Hz, 1H), 7.55 (d, J = 8.3 Hz, 1H), 7.45 (dd, J = 8.3, 2.3 Hz, 1H), 3.94 (s, 3H), 3.43 (s, 1H).

[01601] Step 3: Synthesis of methyl 5-chloro-2-ethylbenzoate



[01602] To a solution of methyl 5-chloro-2-ethynylbenzoate (5.34 g, 27 mmol) in ethyl acetate (135 ml) was added Pd/C (10%) (50% water, 2.92 g, 1.37 mmol). The reaction mixture was stirred under a hydrogen atmosphere at room temperature for 3 hours. The mixture was filtered through Celite. The filter cake washed with EtOAc (50 ml) and the filtrate was concentrated under reduced pressure to give 5.12 g (94%) of the title compound as a brown oil which was suitable for use without any further purification. LC-MS 56%, m/z=198.9/200.9, ^{1}H NMR (500 MHz, Chloroform-d) δ ppm 7.84 (d, J = 2.3 Hz, 1H), 7.39 (dd, J = 8.3, 2.3 Hz, 1H), 7.21 (d, J = 8.3 Hz, 1H), 3.90 (s, 3H), 2.94 (q, J = 7.5 Hz, 2H), 1.21 (t, J = 7.5 Hz, 3H).

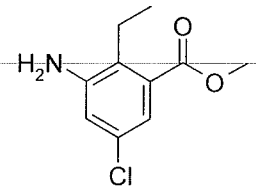
[01603] Step 4: Synthesis of methyl 5-chloro-2-ethyl-3-nitrobenzoate



[01604] A solution of methyl 5-chloro-2-ethylbenzoate (5.12 g, 25.8 mmol) in concentrated H_2SO_4 (31 ml, 587 mmol) was cooled to -5 °C in an acetone/ice bath. A mixture of concentrated nitric acid (2.15 ml, 33.5 mmol) and concentrated H_2SO_4 (2.0 ml, 37.5 mmol) was added dropwise to the reaction mixture at -5°C over 15 minutes. The pale yellow reaction mixture was stirred at -5 °C for 1 hour before being poured onto ice (500ml) and this was extracted with EtOAc (3 x 100 ml). The combined organic phases were washed with deionized

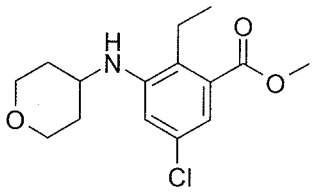
water (100 ml) and then brine (100ml). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. LCMS and NMR showed ~30% hydrolysis of the ester. The crude material was dissolved in methanol (30 ml) and cooled to 0°C under nitrogen where $SOCl_2$ (2.25 ml, 30.93 mmol) was added slowly. The reaction mixture was then heated to reflux for 6 hours before being concentrated under reduced pressure to give 6.18 g (98%) of the title compound containing material as an orange oil which was a 1:1 mixture of 3-nitro:6-nitro isomers along with some ethyl ester. The material was suitable for use in the next step without any further purification.

[01605] Step 5:Synthesis of methyl 3-amino-5-chloro-2-ethylbenzoate



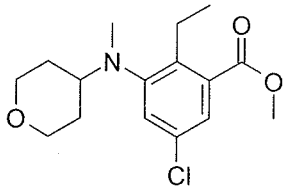
[01606] To a solution of methyl 5-chloro-2-ethyl-3-nitrobenzoate (6.18 g, 25.4 mmol) in methanol (250 ml) at room temperature was added ammonium chloride (13.3 g, 253 mmol) followed by deionized water (125 ml). The mixture was heated to 70°C before the addition of iron (8.50 g, 152 mmol). The reaction turned to a dark color over the 2.5 hours it was stirred at 70°C. This mixture was allowed to cool to room temperature and was filtered through Kieselgel. The filter pad was washed with MeOH (250 ml) and the filtrate concentrated under reduced pressure. The residue was dissolved in saturated $NaHCO_3$(aq) (50 ml) and EtOAc (150 ml). The phases were separated and the organic phase was washed with saturated $NaHCO_3$(aq) (2 x 50 ml) before being dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by FCC (50g silica, Isolute cartridge, gradient of eluents; 95:5 Heptane:EtOAc to 75:25 Heptane:EtOAc) to give 2.42 g of crude methyl 3-amino-5-chloro-2-ethylbenzoate as a yellow oil. The material was taken through the next step without further purification. LC-MS 31%, m/z=295.0, ^{1}H NMR (500 MHz, Chloroform-d) δ ppm 7.17 (d, J = 2.1 Hz, 1H), 6.79 (d, J = 2.1 Hz, 1H), 3.87 (s, 3H), 3.86 – 3.81 (m, 2H), 2.74 (q, J = 7.5 Hz, 2H), 1.20 (t, J = 7.5 Hz, 3H).

[01607] Step 6: Synthesis of methyl 5-chloro-2-ethyl-3-[(oxan-4-yl)amino]benzoate



[01608] To a solution of methyl 3-amino-5-chloro-2-ethylbenzoate (1.5 g, 7.02 mmol) in 1,2-dichloroethane (28 ml) at room temperature under nitrogen was added oxan-4-one (1.3 ml, 14. mmol) followed by acetic acid (2.41 ml, 42 mmol). This solution was stirred for 5 minutes before the addition of sodium triacetoxyborohydride (4.46 g, 21 mmol) at room temperature. After stirring for 20 hours, deionized water (28 ml) was added and the mixture was neutralized with solid $NaHCO_3$. The phases were separated and the aqueous layer was extracted with EtOAc (2 x 28 ml). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by FCC (50g silica, Isolute cartridge, gradient of eluents; 95:5 Heptane:EtOAc to 8:2 Heptane:EtOAc) to give 1.76 g of crude methyl 5-chloro-2-ethyl-3-[(oxan-4-yl)amino]benzoate as a white solid. The material was taken through the next step without further purification. LC-MS 60%, m/z=298.0/300.0, ^{1}H NMR (500 MHz, Chloroform-d) δ ppm 7.07 (d, J = 2.0 Hz, 1H), 6.71 (d, J = 1.9 Hz, 1H), 4.01 (dt, J = 11.8, 3.4 Hz, 2H), 3.87 (s, 3H), 3.82 – 3.76 (m, 1H), 3.64 – 3.47 (m, 3H), 2.79 – 2.63 (m, 2H), 2.06 (d, J = 13.2 Hz, 2H), 1.55 – 1.46 (m, 2H), 1.18 (t, J = 7.5 Hz, 3H).

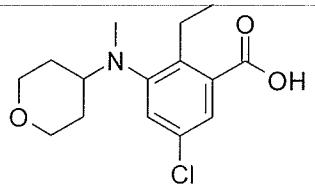
[01609] Step 7: Synthesis of methyl 5-chloro-2-ethyl-3-[methyl(oxan-4-yl)amino]benzoate



[01610] To a solution of methyl 5-chloro-2-ethyl-3-[(oxan-4-yl)amino]benzoate (350 mg, 1.18 mmol) in 1,2-dichloroethane (10 ml) at room temperature under nitrogen was added paraformaldehyde (212 mg, 7.05 mmol) followed by acetic acid (0.4 ml, 7.05 mmol). This mixture was stirred for 5 minutes before the addition of sodium triacetoxyborohydride (1.49 g, 7.05 mmol). After stirring for 23 hours, further paraformaldehyde (212 mg, 7.05 mmol) was added to the reaction mixture and this was stirred for 10 minutes before the addition of sodium triacetoxyborohydride (1.49 g, 7.05 mmol). After stirring for 3 hours, deionized water (15 ml) was added and the mixture was neutralized with solid $NaHCO_3$ and the phases were separated.

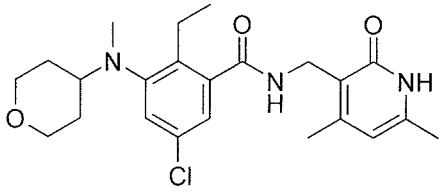
The aqueous layer was extracted with EtOAc (2 x 15 ml) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by FCC (10g silica, Isolute cartridge, gradient of eluents; 99:1 Heptane:EtOAc to 85:15 Heptane:EtOAc) to give 334 mg of the title compound as a colorless oil. The product contains ~22% ethyl ester. The material was taken through the next step without further purification. LC-MS 56%, m/z=312.0/314.0, ^{1}H NMR (500 MHz, Chloroform-d) δ ppm 7.52 (d, J = 2.2 Hz, 1H), 7.24 (d, J = 2.2 Hz, 1H), 4.01 – 3.93 (m, 2H), 3.89 (s, 3H), 3.34 (td, J = 11.7, 2.3 Hz, 2H), 3.06 – 2.96 (m, 2H), 2.94 – 2.85 (m, 1H), 2.61 (s, 3H), 1.76 – 1.59 (m, 4H), 1.10 (t, J = 7.4 Hz, 3H).

[01611] Step 8: Synthesis of 5-chloro-2-ethyl-3-[methyl(oxan-4-yl)amino]benzoic acid



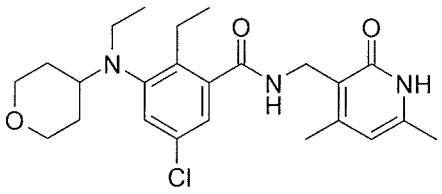
[01612] To a solution of methyl 5-chloro-2-ethyl-3-[methyl(oxan-4-yl)amino]benzoate (334 mg, 1.07 mmol) in THF (11 ml) was added 4M NaOH (10.7 ml). The reaction mixture was stirred at 50 °C for 27 hours. MeOH (5 ml) was added to the reaction mixture and this was stirred for a further 21 hours at 50°C. The reaction mixture was acidified to pH 2-3 with 6M HCl and extracted with DCM (5 x 10 ml). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give 311 mg of the title compound as an orange oil that solidified upon standing. The material was taken through the next step without further purification. LC-MS 79%, 2.01min (3 minute LC-MS method), m/z=298.0/300.0, ^{1}H NMR (500 MHz, Chloroform-d) δ ppm 7.72 (d, J = 2.1 Hz, 1H), 7.37 – 7.27 (m, 1H), 4.00 (brd, J = 11.1 Hz, 2H), 3.36 (td, J = 11.6, 2.0 Hz, 2H), 3.11 (q, J = 7.4 Hz, 2H), 2.94 (t, J = 10.6 Hz, 1H), 2.64 (s, 3H), 1.78 – 1.56 (m, 4H), 1.15 (t, J = 7.4 Hz, 3H).

[01613] Step 9: Synthesis of 5-chloro-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-2-ethyl-3-[methyl(oxan-4-yl)amino]benzamide

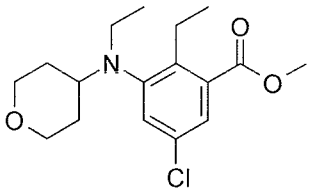


[01614] To a solution of 5-chloro-2-ethyl-3-[methyl(oxan-4-yl)amino]benzoic acid (100 mg, 0.34 mmol) in DMF (2 ml) at room temperature under nitrogen was added HBTU (153 mg, 0.4 mmol) followed by N-ethyl-N-(propan-2-yl)propan-2-amine (88 µl, 0.5 mmol) and 3-(aminomethyl)-4,6-dimethyl-1,2-dihydropyridin-2-one (89%, 63 mg, 0.37 mmol). After stirring for 3 hours at room temperature EtOAc (30ml) was added to the reaction mixture and this was then washed with deionized water (5 ml) followed by saturated $NaHCO_3$(aq) (3 x 5 ml). The organic phase was dried over MgSO4, filtered and concentrated under reduced pressure. The residue was purified by FCC (5g silica, Isolute cartridge, gradient of eluents; 100% DCM to 96:4 DCM:MeOH) to give 94 mg (65%) of the title compound as an off-white solid. LC-MS 95%, m/z=432.1/434.1, ^{1}H NMR (500 MHz, Chloroform-d) δ ppm 11.34 (s, 1H), 7.14 – 7.08 (m, 2H), 7.03 (d, *J* = 2.0 Hz, 1H), 5.95 (s, 1H), 4.52 (d, *J* = 5.8 Hz, 2H), 3.96 (d, *J* = 11.2 Hz, 2H), 3.33 (td, *J* = 11.4, 2.3 Hz, 2H), 2.96 – 2.85 (m, 1H), 2.79 (q, *J* = 7.4 Hz, 2H), 2.58 (s, 3H), 2.39 (s, 3H), 2.23 (s, 3H), 1.73 – 1.62 (m, 4H), 1.05 (t, *J* = 7.4 Hz, 3H).

[01615] **Compound 206: 5-chloro-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-2-ethyl-3-[ethyl(oxan-4-yl)amino]benzamide**



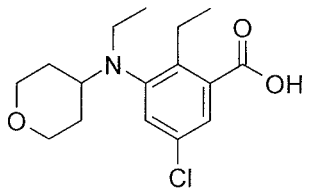
[01616] Step 1: Synthesis of methyl 5-chloro-2-ethyl-3-[ethyl(oxan-4-yl)amino]benzoate



[01617] To a solution of methyl 5-chloro-2-ethyl-3-[(oxan-4-yl)amino]benzoate (350 mg, 1.18 mmol) in 1,2-dichloroethane (10 ml) at room temperature under nitrogen was added acetaldehyde (0.66 ml, 11.8 mmol) followed by acetic acid (0.4 ml, 7.05 mmol). This solution was stirred for 5 minutes before the addition of sodium triacetoxyborohydride (2.49 g, 11.8 mmol) at room temperature. After stirring for 23 hours acetaldehyde (0.66 ml, 11.8 mmol) was added to the dark reaction mixture and this was stirred for 10 minutes before the addition of

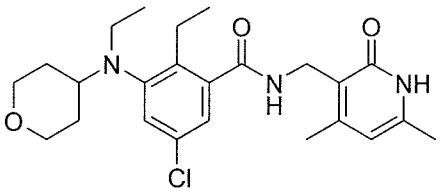
sodium triacetoxyborohydride (2.49 g, 11.8 mmol). After stirring for 3 hours deionized water (15 ml) was added and the mixture was neutralized with solid $NaHCO_3$. The phases were separated and the aqueous layer was extracted with EtOAc (2 x 15 ml). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by FCC (10g silica, Isolute cartridge, gradient of eluents; 99:1 Heptane:EtOAc to 85:15 Heptane:EtOAc) to give 317 mg of the title compound as a colorless oil. The product contains ~25% ether ester. The material was taken through the next step without further purification. LC-MS 55%, 2m/z=326.0/328.0, ^{1}H NMR (500 MHz, Chloroform-d) δ ppm 7.52 (d, J = 2.2 Hz, 1H), 7.23 (d, J = 2.2 Hz, 1H), 3.97 (d, J = 11.1 Hz, 2H), 3.90 (s, 3H), 3.32 (td, J = 11.6, 2.5 Hz, 2H), 3.04 (q, J = 7.1 Hz, 4H), 2.93 (ddd, J = 15.1, 10.8, 4.3 Hz, 1H), 1.76 – 1.62 (m, 4H), 1.08 (t, J = 7.4 Hz, 3H), 0.88 (t, J = 7.1 Hz, 3H).

[01618] Step 2: Synthesis of 5-chloro-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-2-ethyl-3-[ethyl(oxan-4-yl)amino]benzamide



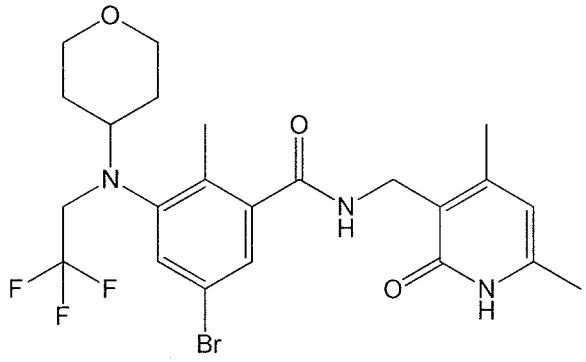
[01619] To a solution of methyl 5-chloro-2-ethyl-3-[ethyl(oxan-4-yl)amino]benzoate (317 mg, 0.97 mmol) in THF (10 ml) was added 4M NaOH (9.73 ml). The reaction mixture was stirred at 50°C for 27 hours. MeOH (5 ml) was added to the reaction mixture and this was stirred for a further 21 hours at 50°C. The reaction mixture was acidified to pH 2-3 with 6M HCl and extracted with DCM (5 x 10 ml). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give 289 mg of the title compound as an orange oil that solidified upon standing. The material was taken through the next step without further purification. LC-MS 79%, m/z=311.95/313.95, ^{1}H NMR (500 MHz, Chloroform-d) δ ppm 7.73 (d, J = 1.7 Hz, 1H), 7.29 (d, J = 1.8 Hz, 1H), 3.99 (d, J = 11.0 Hz, 2H), 3.38 – 3.29 (m, 2H), 3.20 – 3.03 (m, 4H), 3.02 – 2.91 (m, 1H), 1.78 – 1.61 (m, 4H), 1.13 (t, J = 7.4 Hz, 3H), 0.91 (t, J = 7.0 Hz, 3H).

[01620] Step 3: Synthesis of 5-chloro-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-2-ethyl-3-[ethyl(oxan-4-yl)amino]benzamide

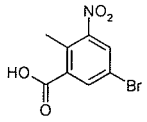


[01621] To a solution of 5-chloro-2-ethyl-3-[ethyl(oxan-4-yl)amino]benzoic acid (100 mg, 0.32 mmol) in DMF (2 ml) at room temperature under nitrogen was added HBTU (146 mg, 0.38 mmol) followed by N-ethyl-N-(propan-2-yl)propan-2-amine (84 µl, 0.48 mmol) and 3-(aminomethyl)-4,6-dimethyl-1,2-dihydropyridin-2-one (89%, 60.3 mg, 0.35 mmol). After stirring for 3 hours at room EtOAc (30ml) was added to the reaction mixture and this was then washed with deionized water (5 ml) followed by saturated $NaHCO_3$(aq) (3 x 5 ml). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by FCC (5g silica, Isolute cartridge, gradient of eluents; 100% EtOAc to 97:3 EtOAc:MeOH) to give 90 mg (63%) of the title compound as a white solid. LC-MS 97%, m/z=446.1/448.2, ^{1}H NMR (500 MHz, Chloroform-d) δ ppm 11.93 (s, 1H), 7.14 (t, J = 5.7 Hz, 1H), 7.10 (d, J = 2.0 Hz, 1H), 7.04 (d, J = 2.0 Hz, 1H), 5.95 (s, 1H), 4.52 (d, J = 5.8 Hz, 2H), 3.95 (d, J = 11.2 Hz, 2H), 3.30 (td, J = 11.3, 3.6 Hz, 2H), 3.01 (q, J = 7.0 Hz, 2H), 2.93 (ddd, J = 15.3, 10.0, 5.3 Hz, 1H), 2.83 (q, J = 7.4 Hz, 2H), 2.38 (s, 3H), 2.22 (s, 3H), 1.71 – 1.63 (m, 4H), 1.02 (t, J = 7.5 Hz, 3H), 0.86 (t, J = 7.0 Hz, 3H).

[01622] **Compound 243: 5-bromo-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-2-methyl-3-[(oxan-4-yl)(2,2,2-trifluoroethyl)amino]benzamide**

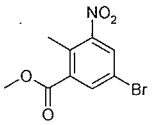


[01623] Step 1: Synthesis of 5-bromo-2-methyl-3-nitrobenzoic acid



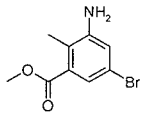
[01624] A solution of 5-bromo-2-methylbenzoic acid (5.0 g, 23 mmol) in concentrated H_2SO_4 (27 ml, 512 mmol) was cooled to 5 °C in an acetone/ice bath. A mixture of concentrated nitric acid (1.9 ml, 30 mmol) and concentrated H_2SO_4 (2.8 ml, 52 mmol) was added dropwise to the reaction mixture at -5 t0 °C over 15 minutes. The yellow reaction mixture was stirred at -5 °C for 2 hours during which time a yellow precipitate formed. The reaction mixture was poured onto ice (150 g) and the precipitate was then collected by filtration. The precipitate was air dried to give the title compound (5.5 g, 52%) as a pale yellow solid. ; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.29 (s, 1 H) 8.13 (d, J=1.58 Hz, 1 H) 2.43 (s, 3 H).

[01625] Step 2: Synthesis of methyl 5-bromo-2-methyl-3-nitrobenzoate



[01626] To a solution of 5-bromo-2-methyl-3-nitrobenzoic acid (5.5 g, 21 mmol) in DMF (42 ml) under nitrogen, was added Na_2CO_3 (3.4 g, 32 mmol) followed by iodomethane (2.0 ml, 32 mmol). The reaction mixture was stirred at room temperature for 2 hours. The mixture was diluted with deionized water (150 ml) and extracted with EtOAc (4 x 50 ml). The combined organic phases were washed with saturated $NaHCO_3$ (aq) (2 x 50 ml), dried over $MgSO_4$, filtered and concentrated in-vacuo to give the title compound (6.3 g, 61%) as a yellow oil. ^{1}H NMR (500 MHz, Chloroform-d) δ ppm 7.38 (d, J=2.05 Hz, 1 H) 7.23 (d, J=2.05 Hz, 1 H) 3.20 (s, 3 H) 1.82 (s, 3 H).

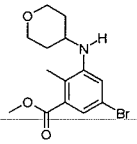
[01627] Step 3: Synthesis of methyl 3-amino-5-bromo-2-methylbenzoate



[01628] To a solution of methyl 5-bromo-2-methyl-3-nitrobenzoate (6.3 g, 21 mmol) in methanol (150 ml) was added ammonium chloride (11.0 g, 210 mmol) followed by deionized water (75 ml). The mixture was heated to 70 °C before the addition of iron (7.0 g, 125 mmol). The reaction mixture was stirred at 70 °C for 2 hours, before being allowed to cool to room temperature and filtered through Kieselgel. The filter pad was washed with MeOH (150 ml)

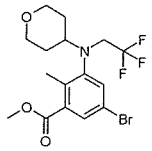
and the filtrate concentrated in-vacuo. The residue was dissolved in saturated $NaHCO_3$ (aq) (50 ml) and EtOAc (150 ml). The phases were separated and the organic phase was washed with saturated $NaHCO_3$ (aq) (3 x 50 ml), dried over $MgSO_4$, filtered and concentrated in-vacuo. The residue was purified by flash column chromatography (50g silica Isolute cartridge, 5-20% EtOAc:Heptanes) to give the title compound (3.0 g, 51%) as a thick pale yellow oil. LC-MS 87%, , m/z = 243.9, 244.9, 245.9, 246.9; ^{1}H NMR (500 MHz, Chloroform-d) δ ppm 7.34 (d, J=1.89 Hz, 1 H) 6.95 (d, J=1.89 Hz, 1 H) 3.88 (s, 3 H) 3.80 (br. s., 2 H) 2.29 (s, 3 H).

[01629] Step 4: Synthesis of methyl 5-bromo-2-methyl-3-[(oxan-4-yl)amino]benzoate



[01630] To a solution of methyl 3-amino-5-bromo-2-methylbenzoate (3.0 g, 12 mmol) in 1,2-dichloroethane (48 ml) under nitrogen, was added oxan-4-one (2.3 ml, 25 mmol) followed by acetic acid (4.2 ml, 74 mmol). The reaction mixture was stirred for 5 minutes before the addition of sodium triacetoxyborohydride (7.8 g, 37 mmol). After stirring for 64 hours, deionized water (100 ml) was added and the mixture was neutralized with solid $NaHCO_3$. The phases were separated and the aqueous layer was extracted with EtOAc (4 x 50 ml). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated in-vacuo. The residue was purified by flash column chromatography (50g silica, Isolute cartridge, 10–30% EtOAc:Heptanes) to give the title compound (3.5 g 85%) as a white solid. LC-MS 99.8m/z= 327.9, 328.9, 329.9, 330.9; ^{1}H NMR (500 MHz, Chloroform-d) δ ppm 7.24 (d, J=1.73 Hz, 1 H) 6.85 (d, J=1.58 Hz, 1 H) 4.03 (dt, J=11.82, 3.31 Hz, 2 H) 3.88 (s, 3 H) 3.66 (br.s., 1 H) 3.56 (td, J=11.55, 1.97 Hz, 2 H) 3.47 - 3.55 (m, 1 H) 2.24 (s, 3 H) 2.06 (d, J=13.56 Hz, 2 H) 1.47 - 1.60 (m, 2 H).

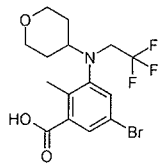
[01631] Step 5: Synthesis of methyl 5-bromo-2-methyl-3-[(oxan-4-yl)(2,2,2-trifluoroethyl)amino]benzoate



[01632] To a solution of methyl 5-bromo-2-methyl-3-[(oxan-4-yl)amino]benzoate (500 mg, 1.5 mmol) and TFA (15 ml), was added $NaBH_4$ (1.0 g, 26 mmol) portionwise over 5 minutes.

The reaction mixture was stirred at room temperature for 2 hours and then heated to 50 °C for 3 hours and treated with a further aliquot of $NaBH_4$ (300 mg) over 25 minutes. The reaction mixture was then heated to 60 °C for 2 hours and left to stir at room temperature for 17 hours. The reaction mixture was treated with TFA (5 ml) and $NaBH_4$ (200 mg) and heated back up to 60 °C for 3.5 hours. A further aliquot of $NaBH_4$ (200 mg) was added over 15 minutes, along with TFA (5 ml) and heating continued for a further 3 hours, before being left to stand at room temperature overnight. The reaction mixture was poured over ice (75 ml) and stirred until the ice had melted. The reaction mixture was then basified by the addition of 6M NaOH (aq) (40 ml) and re-adjusted to pH 7 using 1M HCl (aq) (40 ml). The resulting white suspension was collected by filtration, the solid washed with water (20 ml) and dried in-vacuo at 40 °C for 3 hours to give the title compound (577 mg, 91%) as a white solid. LC-MS 98%,), m/z = 409.90, 410.9, 411.90, 412.9; ^{1}H NMR (500 MHz, Chloroform-d) δ ppm 7.80 (d, J=1.73 Hz, 1 H) 7.41 (d, J=1.73 Hz, 1 H) 4.01 (dd, J=11.51, 4.10 Hz, 2 H) 3.91 (s, 3 H) 3.64 (d,J=5.20 Hz, 2 H) 3.32 (t, J=11.82 Hz, 2 H) 2.99 (tt, J=11.43, 3.63 Hz, 1 H) 2.48 (s, 3 H) 1.80 (dd, J=12.53, 1.50 Hz, 2 H) 1.54 - 1.62 (m, 2 H).

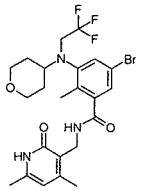
[01633] Step 6: Synthesis of 5-bromo-2-methyl-3-[(oxan-4-yl)(2,2,2-trifluoroethyl)amino]benzoic acid



[01634] To a stirred solution of methyl 5-bromo-2-methyl-3-[(oxan-4-yl)(2,2,2-trifluoroethyl)amino]benzoate (572 mg, 1.4 mmol) in a mixture of THF (14 ml) and MeOH (2.1 ml), was added 4M NaOH (aq) (13.9 ml). The reaction mixture was stirred at 50 °C for 5.5 hours and then stirred at room temperature for 17 hours. The THF was removed by concentrating in-vacuo and the aqueous residue was acidified to pH 4 with 6M HCl (9.5 ml). The resulting suspension was allowed to stand at room temperature for 20 minutes before collecting the solid by filtration. The solid cake was washed with water (20 ml) and dried under high vacuum for 2 hours to give the title compound (507 mg, 90%) as a white solid. LC-MS 98%, m/z = 395.9, 396.9, 397.9, 398.9; ^{1}H NMR (500 MHz, Chloroform-d) δ ppm 7.97 (d, J=1.73 Hz, 1 H) 7.48 (d, J=1.73 Hz, 1 H) 4.02 (dd, J=11.35, 3.94 Hz, 2 H) 3.65 (br. s, 2 H) 3.33

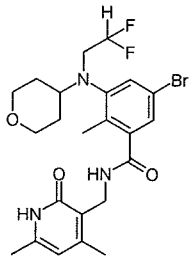
(t, J=11.59 Hz, 2 H) 3.00 (tt, J=11.49, 3.80 Hz, 1 H) 2.55 (s, 3 H) 1.82 (d, J=11.98 Hz, 2 H) 1.55 - 1.69 (m, 2 H). OH not visible.

[01635] Step 7: Synthesis of 5-bromo-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-2-methyl-3-[(oxan-4-yl)(2,2,2-trifluoroethyl)amino]benzamide

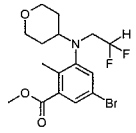


[01636] A stirred solution of methyl 5-bromo-2-methyl-3-[(oxan-4-yl)(2,2,2-trifluoroethyl)amino]benzoate (250 mg, 0.63 mmol) in dry DMF (3.0 ml) at 0 °C under nitrogen, was treated with HATU (288 mg, 0.76 mmol) and DIPEA (220 µl, 1.3 mmol) dropwise. The resulting solution was stirred for 5 minutes and then treated with 3-(aminomethyl)-4,6-dimethyl-1,2-dihydropyridin-2-one (89%, 119 mg, 0.69 mmol). The resulting suspension was stirred at 0 °C for 20 minutes and then stirred at room temperature for 16.5 hours. The reaction mixture was treated with 3-(aminomethyl)-4,6-dimethyl-1,2-dihydropyridin-2-one (30 mg). Stirring was continued for 23 hours and the reaction mixture was then partitioned between water (30 ml) and CH_2Cl_2 (20 ml). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 ml). The combined organics were washed with a saturated solution of $NaHCO_3$) (50 ml), water (60 ml), brine (2 x 40 ml), dried over $MgSO_4$, filtered and concentrated in-vacuo. The crude residue was purified by flash column chromatography (10g SNAP cartridge, Isolera, 0-10% MeOH/CH_2Cl_2) and triturated from ether (10 ml) with sonication. The resulting precipitate was collected by filtration and dried in-vacuo to give the title compound (249 mg, 74%) as a white solid. LC-MS 100%, m/z = 530.0, 531.0, 532.0, 533.0; ^{1}H NMR (500 MHz, Acetone) δ 10.67 (s, 1H), 7.55 (d, J = 1.8 Hz, 2H), 7.27 (d, J = 1.9 Hz, 1H), 5.90 (s, 1H), 4.40 (d, J = 5.5 Hz, 2H), 3.90 (dd, J = 11.2, 4.6 Hz, 4H), 3.28 (t, J = 11.6 Hz,2H), 3.07 – 2.97 (m, 1H), 2.32 (s, 3H), 2.29 (s, 3H), 2.24 (s, 3H), 1.76 (dd, J = 12.3, 1.6 Hz, 2H), 1.61 (qd, J = 12.0, 4.5 Hz, 2H).

[01637] **Compound 244: 5-bromo-3-[(2,2-difluoroethyl)(oxan-4-yl)amino]-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-2-methylbenzamide**

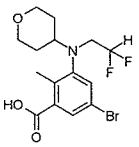


[01638] Step 1: Synthesis of methyl 5-bromo-3-[(2,2-difluoroethyl)(oxan-4-yl)amino]-2-methylbenzoate



[01639] A stirred solution of methyl 5-bromo-2-methyl-3-[(oxan-4-yl)amino]benzoate (500 mg, 1.5 mmol) in difluoroacetic acid (15 ml), was treated with sodium tetrahydroborate (1000 mg, 26 mmol) portionwise over 12 minutes. The reaction mixture was warmed to 50 °C and stirred for 4 hours. The reaction mixture was allowed to reach room temperature and then poured over ice (130 ml) and left for 5 minutes. The mixture was basified by the addition of 6M NaOH (aq) (35 ml) and the pH adjusted to 7 using 1M HCl (aq) (20 ml). The resulting suspension was allowed to stand until the solution was clear and the resulting solid collected by filtration and dried in-vacuo at 40 °C to give the title compound (572 mg, 96%) as a white solid. LC-MS 100%, m/z = 391.9, 392.9, 393.9, 394.9; ^{1}H NMR (500 MHz, Chloroform-d) δ ppm 7.79 (d, J=1.89 Hz, 1 H) 7.44 (d, J=1.89 Hz, 1 H) 5.44 - 5.71 (m, 1 H) 4.00 (dd, J=11.51, 4.10 Hz, 2 H) 3.91 (s, 3 H) 3.41 (td, J=13.99, 4.18 Hz, 2 H) 3.32 (t, J=11.27 Hz, 2 H) 2.97 (tt, J=11.37, 3.84 Hz, 1 H) 2.47 (s, 3 H) 1.72 - 1.81 (m, 2 H) 1.59 - 1.67 (m, 2 H).

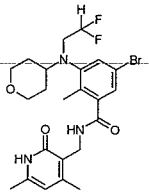
[01640] Step 2: Synthesis of 5-bromo-3-[(2,2-difluoroethyl)(oxan-4-yl)amino]-2-methylbenzoic acid



[01641] To a stirred solution of methyl 5-bromo-3-[(2,2-difluoroethyl)(oxan-4-yl)amino]-2-methylbenzoate (571 mg, 1.5 mmol) in a mixture of THF (14.6 ml) and MeOH (2.2 ml), was added 4M NaOH (14.6 ml). The reaction mixture was stirred at 50 °C for 7 hours. The heat was switched off and the reaction mixture was stirred at room temperature for 16.5 hours. THF

was removed in-vacuo and the aqueous residue was acidified to pH 4 by the addition of 6M HCl (aq) (10 ml) with ice cooling. The resulting solid was collected by filtration, washed with water (20 ml), and dried in-vacuo to give the title compound (526 mg, 96%) as a light beige solid. LC-MS 100%, m/z = 377.9, 378.9, 379.9, 380.9; ^{1}H NMR (500 MHz, Chloroform-d) δ ppm 7.91 (d, J=1.58 Hz, 1 H) 7.49 (d, J=1.58 Hz, 1 H) 5.43 - 5.75 (m, 1 H) 4.01 (dd, J=11.43, 3.55 Hz, 2 H) 3.42 (td, J=13.95, 3.78 Hz, 2 H) 3.32 (t, J=11.35 Hz, 2 H) 2.98 (tt, J=11.37, 3.53 Hz, 1 H) 2.52 (s, 3 H) 1.77 (d, J=10.88 Hz, 2 H) 1.56 - 1.69 (m, 2 H). OH not visible.

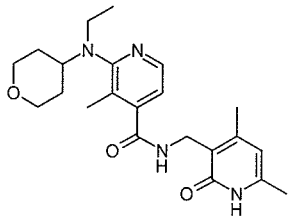
[01642] Step 3: Synthesis of 5-bromo-3-[(2,2-difluoroethyl)(oxan-4-yl)amino]-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-2-methylbenzamide



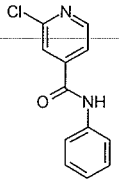
[01643] A stirred solution of 5-bromo-3-[(2,2-difluoroethyl)(oxan-4-yl)amino]-2-methylbenzoic acid (250 mg, 0.66 mmol) in dry DMF (3.0 ml) at 0 °C under nitrogen, was treated with HATU (327 mg, 0.86 mmol) and DIPEA (230 µl, 1.3 mmol) dropwise. The resulting solution was stirred for 5 minutes and then treated with 3-(aminomethyl)-4,6-dimethyl-1,2-dihydropyridin-2-one (89%, 136 mg, 0.79 mmol). The resulting suspension was stirred at 0 °C for 20 minutes and then stirred at room temperature overnight. After 18 hours, 3-(aminomethyl)-4,6-dimethyl-1,2-dihydropyridin-2-one (25 mg) was added and stirring continued for a further 25 hours. The reaction mixture was diluted with water (30 ml) and CH_2Cl_2 (30 ml). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 15 ml). The combined organic phases were washed with a saturated solution of $NaHCO_3$ (aq) (45 ml), water (2 x 50 ml), brine (2 x 50 ml), dried ($MgSO_4$), filtered and concentrated in-vacuo. The residue was purified by column chromatography (10g SNAP cartridge, Isolera, 0-3% MeOH:CH_2Cl_2) and then triturated with ether. The resulting solid was collected by filtration and dried in-vacuo at 40 °C to give the title compound (259 mg, 77%) as an off white solid. LC-MS 100%, m/z = 512.0, 513.0, 514.0, 515.0; ^{1}H NMR (500 MHz, Acetone) δ 10.71 (s, 1H), 7.57 – 7.49 (m, 2H), 7.25 (d, J = 1.9 Hz, 1H), 5.91 (s, 1H), 5.76 (tt, J = 56.2, 4.3 Hz, 1H), 4.40 (d, J = 5.5 Hz, 2H), 3.88 (dd, J = 11.3, 4.2 Hz, 2H), 3.52 (td, J = 14.6, 4.2 Hz, 2H), 3.33 – 3.23 (m, 2H), 3.02 (tt, J = 11.6, 3.9 Hz, 1H), 2.32 (s, 3H), 2.28 (s, 3H), 2.24 (s, 3H), 1.73

(dd, J = 12.4, 1.9 Hz, 2H), 1.59 (qd, J = 12.2, 4.5 Hz, 2H).

[01644] **Compound 328: N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-2-[ethyl(oxan-4-yl)amino]-3-methylpyridine-4-carboxamide**



[01645] Step 1: Synthesis of 2-chloro-N-phenylpyridine-4-carboxamide

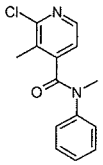


[01646] To a stirred suspension of 2-chloroisonicotinic acid (5.0 g, 0.03 mol) in dry toluene (100 ml) and 4 drops of DMF, was added dropwise thionyl chloride (7.4 ml, 0.10 mol) under nitrogen. The reaction mixture was stirred at 60 °C for 2.5 hours and the temperature was gradually increased to 100 °C over 1.5 hours and held at this temperature for 2 hours. The reaction mixture was stirred at room temperature for 65 hours, before being treated with another equivalent of thionyl chloride (2.3 ml) and heated to 95 °C for 40 minutes. The reaction was allowed to cool to room temperature and was then concentrated to dryness in-vacuo and azeotroped with dry toluene (2 x 10 ml) to give a yellow mobile oil which was used directly in the next step without further purification.

[01647] To a stirred solution of aniline (2.9 ml, 0.03 mol) and N-ethyl-N-(propan-2-yl)propan-2-amine (13.6 ml, 83 mmol) in dry THF (50 ml) was added the acid chloride prepared above dropwise. The reaction mixture was stirred under nitrogen for 19 hours. The reaction mixture was then quenched by the addition of a saturated solution of sodium hydrogen carbonate (aq) (100 ml) and stirred for 35 minutes. The layers were separated and the aqueous phase extracted with ethyl acetate (3 x 55 ml). The combined organic extracts were washed with water (3 x 66 ml), brine (80 ml), dried ($MgSO_4$), filtered and concentrated in-vacuo. The residue was suspended in diethyl ether (100 ml), briefly sonicated and the product collected by filtration. It was dried under high vacuum for 3 hours at room temperature, then left under vacuum

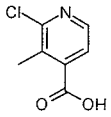
overnight to give the title compound (6.1 g, 83%) as a white solid. LC-MS 100%, m/z = 233.0, 234.9; ^{1}H NMR (500 MHz, Chloroform-d) δ ppm 8.58 (d, J=5.04 Hz, 1 H) 7.81 (br. s., 1 H) 7.77 (s, 1 H) 7.63 (d, J=7.41 Hz, 3 H) 7.42 (t, J=7.96 Hz, 2 H) 7.19 - 7.26 (m, 1 H).

[01648] Step 2: Synthesis of 2-chloro-N,3-dimethyl-N-phenylpyridine-4-carboxamide



[01649] To a stirred solution of 2-chloro-N-phenylpyridine-4-carboxamide (2.0 g, 8.6 mmol) in dry THF (40 ml) at -78°C under nitrogen, was added dropwise 1.6M butyllithium in n-hexanes (11.8 ml, 18.9 mmol) over 24 minutes. The reaction mixture was stirred at -78°C for 50 minutes and then treated with iodomethane (1.8 ml, 28 mmol) dropwise over 8 minutes. The reaction mixture was stirred at -78°C for 1 hour and then left to slowly reach room temperature and stirred for 20 hours. The reaction mixture was quenched with water (20 ml), and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 20 ml). The combined organic phases were washed with brine (60 ml), dried ($MgSO_4$), filtered, concentrated in-vacuo and to give the title compound (2.2 g, 93%) as a thick brown oil. LC-MS 95%, m/z = 261.0, 263.0; ^{1}H NMR (500 MHz, Chloroform-d) δ ppm 8.03 (d, J=4.89 Hz, 1 H) 7.23 (d, J=7.88 Hz, 2 H) 7.16 - 7.21 (m, 1 H) 7.02 (d, J=7.25 Hz, 2 H) 6.89 (d, J=4.89 Hz, 1 H) 3.51 (s, 3 H) 2.34 (s, 3 H).

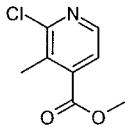
[01650] Step 3: Synthesis of 2-chloro-3-methylpyridine-4-carboxylic acid



[01651] 2-chloro-N,3-dimethyl-N-phenylpyridine-4-carboxamide (2.2 g, 8.5 mmol) was treated with a mixture of concentrated H_2SO_4 (23.2 ml) and water (16.8 ml) and then heated to 130 °C for 46 hours. After which time, the reaction mixture was allowed to reach room temperature and poured onto ice (200 ml) and stirred until the ice had melted. The mixture was made alkaline (pH 8) by the addition of solid Na_2CO_3 (50.3 g) portionwise. The suspension was filtered and the filtrate acidified to pH 3 by the addition of 6M HCl (aq) (~1.5 ml). The resulting solid was collected by filtration, washed with water (20 ml) and dried in-vacuo at 40 °C for 10 hours to give the title compound (779 mg, 54%) as a pink solid. LC-MS 100%, m/z

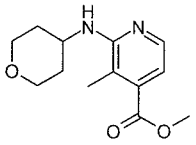
= 171.9, 173.9; ^{1}H NMR (500 MHz, MeOD) δ ppm 8.30 (d, J=4.89 Hz, 1 H) 7.64 (d, J=5.04 Hz, 1 H) 2.58 (s, 3 H).

[01652] Step 4: Synthesis of methyl 2-chloro-3-methylpyridine-4-carboxylate



[01653] To a stirred solution of 2-chloro-3-methylpyridine-4-carboxylic acid (780 mg, 4.5 mmol) in anhydrous DMF (5.0 ml), was added potassium carbonate (1.25 g, 9.1 mmol), followed by methyl iodide (0.42 ml, 6.8 mmol) dropwise. A further 4 ml of DMF was added and the reaction mixture was stirred at room temperature under nitrogen for 18.5 hours. The solvent was removed in-vacuo and the residue was then partitioned between CH_2Cl_2 (20 ml) and water (20 ml). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 15 ml). The combined organic layers were washed with water (2 x 30 ml), brine (40 ml), dried ($MgSO_4$), filtered and concentrated in-vacuo. The residue was purified by column chromatography (10g SNAP cartridge, Isolera, 0-6% ethyl acetate:heptanes) to give the title compound (591 mg, 59%) as a colourless oil. LC-MS 84%, m/z = 185.9, 187.9; ^{1}H NMR (500 MHz, Chloroform-d) δ ppm 8.33 (d, J=5.04 Hz, 1 H) 7.54 (d, J=5.04 Hz, 1 H) 3.95 (s, 3 H) 2.60 (s, 3 H).

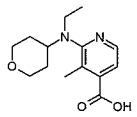
[01654] Step 5: Synthesis of methyl 3-methyl-2-[(oxan-4-yl)amino]pyridine-4-carboxylate



[01655] . A nitrogen purged suspension of $Pd(OAc)_2$ (77 mg, 0.34 mmol) and 1,1'-binaphthalene-2,2'-diylbis(diphenylphosphane) (430 mg, 0.69 mmol) in 1,4-dioxane (11 ml) was heated at 40 °C for 1 hour. Oxan-4-amine (237 µl, 2.3 mmol), a solution of methyl 2-chloro-3-methylpyridine-4-carboxylate (213 mg, 1.2 mmol) in degassed dioxane (2 ml) and Cs_2CO_3 (562 mg, 1.7 mmol) were then added and the red suspension was heated at 100 °C for 6 hours. After cooling to room temperature, the mixture was diluted with CH_2Cl_2 (30 ml) and water (20 ml). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 15 ml). The combined organic phases were washed with brine (25 ml), dried ($MgSO_4$), filtered and concentrated in-vacuo. The crude residue was purified by column chromatography

(25g SNAP cartridge, Isolera, 0-28% ethyl acetate:heptanes) followed by prep-HPLC (MeCN/Water) to give the title compound (112 mg, 39%) as a white crystalline solid. LC-MS 100%, m/z = 251.0; ^{1}H NMR (500 MHz, MeOD) δ ppm 7.91 (d, J=5.20 Hz, 1 H) 6.77 (d, J=5.36 Hz, 1 H) 4.07 - 4.17 (m, 1 H) 3.98 (dd, J=12.06, 1.81 Hz, 2 H) 3.88 (s, 3 H) 3.55 (td, J=11.78, 1.66 Hz, 2 H) 2.22 (s, 3 H) 1.97 (dd, J=12.69, 1.97 Hz, 2 H) 1.62 (qd, J=12.03, 4.41 Hz, 2 H). NH not observed.

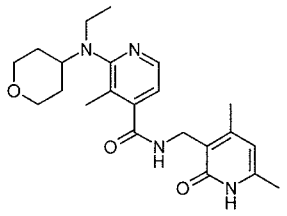
[01656] Step 6: Synthesis of 2-[ethyl(oxan-4-yl)amino]-3-methylpyridine-4-carboxylic acid



[01657] A solution of methyl 3-methyl-2-[(oxan-4-yl)amino]pyridine-4-carboxylate (67 mg, 0.27 mmol) in dry DMF (1.0 ml), was added to a stirred suspension of sodium hydride (60% dispersion in mineral oil, 16 mg, 0.4 mmol) in DMF (0.3 ml) at 0 °C under nitrogen. The reaction mixture was allowed to warm to room temperature and stirred for 30 minutes. The reaction was then treated with iodoethane (16 µl, 0.20 mmol) and stirred for 30 minutes, and then treated again with iodoethane (16 µl, 0.20 mmol) and stirred for a further 30 minutes. The reaction mixture was added to a suspension of sodium hydride (16 mg, 0.4 mmol) in DMF (0.3 ml) at 0°C. Once addition was complete, the reaction mixture was allowed to reach room temperature and stirred for 1 hour before treating with iodoethane (2 x 16 µl, 0.40 mmol). The reaction mixture was stirred for a further 30 minutes. Sodium hydride (16 mg, 0.4 mmol) was added to the reaction mixture and the mixture stirred for 45 minutes before treating with iodoethane (2 x 16 µl, 0.40 mmol) and stirred for 15 minutes before adding under nitrogen to a solution of 4M HCl / dioxane (5.0 ml) with cooling.

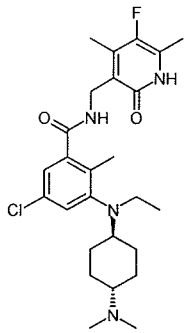
[01658] The reaction mixture was then concentrated in-vacuo at 40 °C was treated with 1M NaOH (aq) (5 ml) and basified by the addition of 10 NaOH pellets to pH 12 with cooling. The pH was adjusted back to pH 10 by the addition of 6M HCl. The resulting solution was stirred at room temperature for 18 hours. The reaction mixture was then acidified to pH 5 by the addition of 1M HCl (80 drops). The resulting solution was extracted with $CHCl_3$ / IPA (1:1) (6 x 10 ml). The combined extracts were concentrated in-vacuo to give the crude title compound (207 mg) as a yellow oil. LC-MS 100%, m/z = 265.1. This material was used directly in the coupling reaction as described below.

[01659] Step 7: Synthesis of N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-2-[ethyl(oxan-4-yl)amino]-3-methylpyridine-4-carboxamide

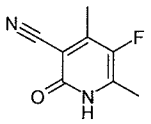


[01660] A stirred solution of 2-[ethyl(oxan-4-yl)amino]-3-methylpyridine-4-carboxylic acid (20 mg, 0.08 mmol) in dry DMF (1.0 ml) at 0 °C under nitrogen, was treated with HATU (37 mg, 0.1 mmol) and DIPEA (26 µl, 0.15 mmol) dropwise. The resulting solution was stirred for 10 minutes and then treated with 3-(aminomethyl)-4,6-dimethyl-1,2-dihydropyridin-2-one (89%, 15 mg, 0.09 mmol). The resulting suspension was stirred at 0 °C for 20 minutes and then stirred at room temperature for 18.5 hours. The reaction mixture was cooled to 0 °C and retreated with HATU (120 mg, 0.31 mmol) and DIPEA (84 µl, 0.48 mmol). After stirring for 10 minutes, 3-(aminomethyl)-4,6-dimethyl-1,2-dihydropyridin-2-one (89%, 49 mg, 0.29 mmol) was added. The reaction mixture was stirred for 1 hour at 0 °C and was then lifted out of the ice bath stirred at room temperature for 48 hours. The reaction mixture was diluted with water (20 ml) and CH_2Cl_2 (20 ml). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 15 ml). The combined organic phases were washed with water (2 x 25 ml), brine (2 x 25 ml), dried ($MgSO_4$), filtered and concentrated in-vacuo. The crude residue was purified by column chromatography (10 g SNAP cartridge, Isolera, 0-40% MeOH:CH_2Cl_2 and 0-25% MeOH (containing 10% NH_4OH):CH_2Cl_2) to give 6.7 mg (22% Yield) of the title compound as an off white solid. LC-MS 100%, , m/z = 399.1; ^{1}H NMR (250 MHz, DMSO) δ 11.49 (s, 1H), 8.32 (t, J = 4.9 Hz, 1H), 8.14 (d, J = 4.9 Hz, 1H), 6.84 (d, J = 4.9 Hz, 1H), 5.86 (s, 1H), 4.26 (d, J = 4.7 Hz, 2H), 3.84 (dd, J = 10.3, 3.5 Hz,2H), 3.21 (dt, J = 13.6, 4.6 Hz, 5H), 2.19 (s, 3H), 2.15 (s, 3H), 2.11 (s, 3H), 1.62 (dt, J = 21.1, 6.6 Hz, 4H), 0.80 (t, J = 6.9 Hz, 3H).

[01661] **Compound 356: 5-chloro-3-{ethyl[(1r,4r)-4-(dimethylamino)cyclohexyl]amino}-N-[(5-fluoro-4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-2-methylbenzamide**

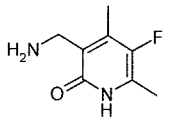


[01662] Step 1: Synthesis of 5-fluoro-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile



[01663] To a stirred solution of 2-cyanoacetamide (689 mg, 8.2 mmol) in anhydrous EtOH (7.0 ml) at 75 °C, was added 3-fluoropentane-2,4-dione (880 mg, 7.5 mmol), followed by piperidine (96 µl, 0.97 mmol). The reaction mixture was stirred at this temperature for 3 hours and the reaction mixture left to reach room temperature before being stored in the refrigerator for 4 days. The beige solid was collected by filtration and rinsed with cold EtOH (4 x 0.4 ml) until the filtrate ran clear. The resulting beige solid was dried in-vacuo at 40 °C for 5 hours to give the title compound (733 mg, 58%) as a beige solid. LC-MS 97%, m/z = 166.9, ^{1}H NMR (500 MHz, Chloroform-d) δ ppm 13.67 (br. s., 1 H) 2.46 (d, J=2.05 Hz, 3 H) 2.45 (d, J=2.84 Hz, 3 H).

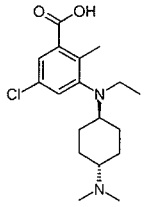
[01664] Step 2: Synthesis of 3-(aminomethyl)-5-fluoro-4,6-dimethyl-1,2-dihydropyridin-2-one



[01665] A solution of 0.05M 5-fluoro-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (731 mg, 4.4 mmol) in 1.75M NH_3/MeOH (87 ml) was passed through the H-Cube flow hydrogenator at 80 °C and 50 bar at a flow rate of 1 ml/min. The resulting solution was concentrated in-vacuo. The resulting solid was split into 2 batches and 350 mg of the crude product was purified by column chromatography (25g SNAP cartridge, Isolera, 0-25% MeOH (containing 10% NH_4OH):CH_2Cl_2) to give the title compound (307 mg, 20%) as an off white solid and a 1:1 mixture of product:starting material. LC-MS (ELS) 100%, m/z = 170.9, ^{1}H

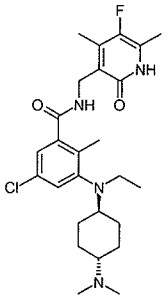
NMR (500 MHz, Chloroform-d) δ ppm 3.79 (s, 2 H) 2.31 (d, J=2.84 Hz, 3 H) 2.25 (d, J=2.05 Hz, 3 H).

[01666] Step 3: Synthesis of 5-chloro-3-{ethyl[(1r,4r)-4-(dimethylamino)cyclohexyl]amino}-2-methylbenzoic acid



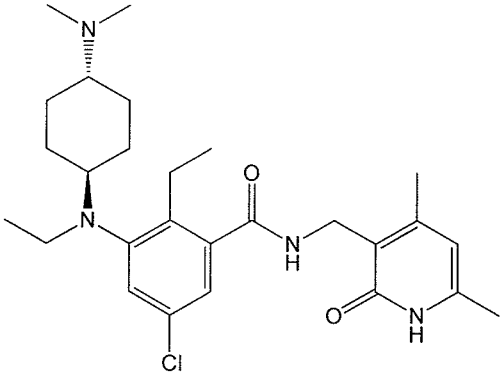
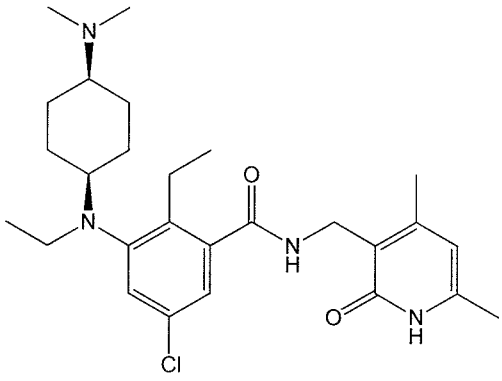
[01667] To a stirred solution of methyl 5-chloro-3-{ethyl[(1r,4r)-4-(dimethylamino)cyclohexyl]amino}-2-methylbenzoate (1.0 g, 2.8 mmol) in THF (21 ml), was added a solution of 4M NaOH (aq) (21.3 ml, 85.0 mmol), followed by MeOH (8.0 ml). The resulting solution was stirred at 50 °C for 16.5 hours and cooled to room temperature. The organic solvents were removed in-vacuo and the remaining aqueous phase was treated with a solution of 6M HCl (aq) (14 ml) to adjust the pH to 7 and then 0.1 M HCl (aq) (24 ml) to adjust the pH to 4. The mixture was extracted with ethyl acetate (3 x 35 ml). The aqueous extract was further extracted with a mixture of $CHCl_3$:IPA (1:1) (3 x 30 ml). The combined $CHCl_3$:IPA extracts were dried ($MgSO_4$), filtered and concentrated in-vacuo and then thoroughly dried on the high vac line. The resulting solid was azeotroped with toluene (3 x 20 ml). CH_2Cl_2 (10 ml) was then added to the sample, concentrated in-vacuo and further dried on the high vac line for several hours. This gave the title compound (831 mg, 88%) as a white solid. LC-MS 92m/z = 339.0, 341.0; ^{1}H NMR (500 MHz, Chloroform-d) δ ppm 12.21 (s, 1 H) 7.69 (d, J=2.05 Hz, 1 H) 7.22 - 7.26 (m, 1 H) 2.99 - 3.11 (m, 3 H) 2.69 - 2.79 (m, 7 H) 2.47 (s, 3 H) 2.28 (d, J=11.98 Hz, 2 H) 2.05 (d, J=13.08 Hz, 2 H) 1.35 - 1.65 (m, 4 H) 0.88 (t, J=7.01 Hz, 3 H).

[01668] Step 4: Synthesis of 5-chloro-3-{ethyl[(1r,4r)-4-(dimethylamino)cyclohexyl]amino}-N-[(5-fluoro-4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-2-methylbenzamide

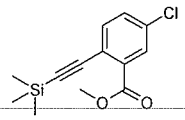


[01669] To a stirred solution of 5-chloro-3-{ethyl[(1r,4r)-4-(dimethylamino)cyclohexyl]amino}-2-methylbenzoic acid (100 mg, 0.27 mmol) in anhydrous DMF (2.0 ml) at 0 °C under a f nitrogen, was treated with HATU (121 mg, 0.32 mmol) and DIPEA (93 µl, 0.53 mmol) dropwise. The resulting solution was stirred for 10 minutes and then treated with 3-(aminomethyl)-5-fluoro-4,6-dimethyl-1,2-dihydropyridin-2-one (50%, 99 mg, 0.29 mmol). The resulting suspension was stirred at 0 °C for 1 hour and then stirred for 17 hours at room temperature. The reaction mixture was partitioned between water (15 ml) and CH_2Cl_2 (20 ml). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 15 ml). The combined organics were washed with a saturated solution of $NaHCO_3$ (aq) (30 ml), water (2 x 25 ml), brine (20 ml), dried ($MgSO_4$), filtered and concentrated in-vacuo. The crude residue was purified by flash column chromatography (10g SNAP cartridge, Isolera, 0-29% MeOH:CH_2Cl_2) to give the title compound (68 mg, 52%) as a beige solid. LC-MS 99%, m/z = 491.1, 493.1; ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.17 (d, J = 1.9 Hz, 1H), 7.02 (d, J = 2.0 Hz, 1H), 4.59 (s, 1H), 4.44 (s, 2H), 3.06 (q, J = 7.0 Hz, 2H), 2.69 (tt, J = 12.1, 3.2 Hz, 1H), 2.41 – 2.29 (m, 10H), 2.24(d, J = 2.8 Hz, 3H), 2.20 (s, 3H), 1.91 (dd, J = 27.7, 12.2 Hz, 4H), 1.44 (q, J = 12.3, 11.1 Hz, 2H), 1.30 – 1.20 (m, 2H), 0.83 (t, J = 7.0 Hz, 3H). One proton assumed to be coincident with a solvent peak.

[01670] **Compound 347: 5-chloro-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-2-ethyl-3-{ethyl[(1r,4r)-4-(dimethylamino)cyclohexyl]amino}benzamide and Compound 348: 5-chloro-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-2-ethyl-3-{ethyl[(1s,4s)-4-(dimethylamino)cyclohexyl]amino}benzamide**

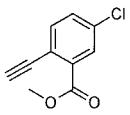

and


[01671] Step 1: Synthesis of methyl 5-chloro-2-[2-(trimethylsilyl)ethynyl]benzoate



[01672] To a stirred solution of methyl 2-bromo-5-chlorobenzoate (14.8 g, 59 mmol) in triethylamine (124 ml, 890 mmol) was added copper iodide (339 mg, 1.8 mmol) and triphenylphosphine (778 mg, 3.0 mmol) at room temperature, under nitrogen. This mixture was purged with nitrogen before the addition of ethynyl(trimethyl)silane (12.5 ml, 89 mmol) and $Pd(OAc)_2$ (266 mg, 1.2 mmol). The reaction mixture was stirred at 50 °C for 20 hours and concentrated in-vacuo. The residue was dissolved in deionized water (50 ml) and EtOAc (50 ml) and filtered through Celite. The filter cake was washed with EtOAc (50 ml) before the phases were separated and the aqueous layer was extracted with EtOAc (2 x 50 ml). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (10g Silica Isolute cartridge, 1 - 15% EtOAc:Heptanes) to give the title compound (16.2 g, 93%) as an orange solid. LC-MS 91%, m/z = 267.4, 268.9; ^{1}H NMR (500 MHz, Chloroform-d) δ ppm 7.90 (d, J=2.21 Hz, 1 H) 7.52 (d, J=8.35 Hz, 1 H) 7.42 (dd, J=8.28, 2.29 Hz, 1 H) 3.93 (s, 3 H) 0.28 (s, 9H).

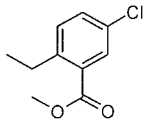
[01673] Step 2: Synthesis of methyl 5-chloro-2-ethynylbenzoate



[01674] A suspension of potassium carbonate (5.0 g, 36 mmol) in methanol (20 ml) was stirred under nitrogen whilst adding a solution of methyl 5-chloro-2-[2-(trimethylsilyl)ethynyl]benzoate (4.8 g, 18.0 mmol) in methanol (50 ml). The resulting mixture was stirred at 20 °C for 2 hours. The reaction mixture was filtered, and the solid washed with

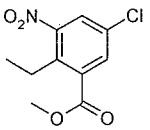
methanol. The filtrate was concentrated in-vacuo and then re-dissolved in methanol (50 ml) and carefully treated with acetyl chloride (4.0 ml). The reaction mixture was stirred overnight and concentrated in-vacuo. TBME (50 ml) was added to the residue and the resulting suspension filtered. The filtrate was washed with a saturated solution of $NaHCO_3$ (40 ml).The layers were separated and the aqueous phase was extracted with TBME (3 x 40 ml). The combined organics were dried over $MgSO_4$, filtered and concentrated in-vacuo. The crude residue was purified by flash column chromatography (50g Isolute cartridge, 0-10% TBME:Heptanes) to give the title compound (1.2 g, 33%) as a white solid. LC-MS 93%, m/z = 194.9, 196.9; ^{1}H NMR (500 MHz, Chloroform-d) δ ppm 7.94 (s, 1 H), 7.56 (d, J = 8.4 Hz, 1 H), 7.46 (d, J = 8.4 Hz, 1 H), 3.95 (s, 3 H), 3.44 (s, 1 H).

[01675] Step 3: Synthesis of methyl 5-chloro-2-ethylbenzoate



[01676] To a solution of methyl 5-chloro-2-ethynylbenzoate (1.13 g, 5.8 mmol) in TBME (50 ml) was added Pd/C (10%) (50% water, 0.61 g, 0.29 mmol). The reaction mixture was stirred under a hydrogen atmosphere for 130 minutes. The mixture was filtered through Celite and the filter cake was washed with TBME. The filtrate was concentrated in-vacuo to give the title compound (1.08 g, 74%) as a pale brown oil. LC-MS 79%, m/z = 198.9 / 200.9; ^{1}H NMR (500 MHz, Chloroform-d) δ ppm 7.85 (s, 1 H) 7.40 (d, J=8.20 Hz, 1 H) 7.22 (d, J=8.20 Hz, 1 H) 3.91 (s, 3 H) 2.95 (q, J=7.46 Hz, 2 H) 1.22 (t, J=7.49 Hz, 3 H).

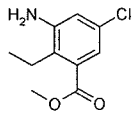
[01677] Step 4: Synthesis of methyl 5-chloro-2-ethyl-3-nitrobenzoate



[01678] A solution of methyl 5-chloro-2-ethylbenzoate (1.08 g, 5.4 mmol) in concentrated sulphuric acid (7.0 ml) was cooled to -5 °C in an acetone/ice bath. A mixture of 70% nitric acid (0.45 ml, 7.1 mmol) and concentrated sulphuric acid (0.5 ml) was added dropwise to the reaction mixture at -5 °C over 15 minutes. The resulting pale yellow reaction mixture was stirred at -5 °C for 1 hour before being poured onto ice (100ml) and extracted with CH_2Cl_2 (3 x 20 ml). The combined organic phases were washed with deionized water (20 ml), brine (20 ml), dried over Na_2SO_4, filtered and concentrated in-vacuo. The resulting oil was added to a

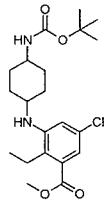
solution containing methanol (25 ml) and thionyl chloride (0.75 ml) at 0 °C. Following addition, the mixture was heated under gentle reflux for 6 hours, before cooling to room temperature and concentrating in-vacuo to give the title compound (1.2 g) as an orange oil which was used without further purification in the next step.

[01679] Step 5: Synthesis of methyl 3-amino-5-chloro-2-ethylbenzoate



[01680] To a solution of methyl 5-chloro-2-ethyl-3-nitrobenzoate (1.2 g, 5.0 mmol) in methanol (50 ml) and deionised water (25 ml), was added ammonium chloride (2.6 g, 50 mmol). The mixture was heated to 70 °C before the addition of iron (1.7 g, 30 mmol). The reaction mixture was stirred at 70 °C for 3.5 hours, hot filtered through Celite and the filter pad was washed with MeOH (20 ml). The filtrate was concentrated in-vacuo and the aqueous residue was dissolved in a saturated solution of $NaHCO_3$(aq) (50 ml) and EtOAc (100 ml). The phases were separated and the organic phase was washed with saturated $NaHCO_3$(aq) (2 x 65 ml), brine (30 ml), dried over $MgSO_4$, filtered and concentrated in-vacuo. The residue was purified by column chromatography (25g SNAP cartridge, Isolera, 0-11% ethyl acetate/heptanes) to give the title compound (372 mg, 33%) as a yellow oil. LC-MS 94%, m/z = 213.9, 215.9; ^{1}H NMR (500 MHz, Chloroform-d) d ppm 7.18 (d, J=2.21 Hz, 1 H) 6.80 (d, J=2.05 Hz, 1 H) 3.88 (s, 3 H) 3.85 (d, J=2.52 Hz, 2 H) 2.75 (q, J=7.57Hz, 2 H) 1.21 (t, J=7.49 Hz, 3 H).

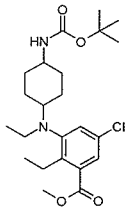
[01681] Step 6: Synthesis of methyl 3-[(4-{[(tert-butoxy)carbonyl]amino}cyclohexyl)amino]-5-chloro-2-ethylbenzoate



[01682] To a stirred solution of methyl 3-amino-5-chloro-2-ethylbenzoate (365 mg, 1.7 mmol) in 1,2-dichloroethane (20 ml) under nitrogen, was added tert-butyl (4-oxocyclohexyl)carbamate (364 mg, 1.7 mmol) followed by acetic acid (587 µl, 10.3 mmol). The solution was stirred for 10 minutes before the portionwise addition of sodium triacetoxyborohydride (1.09 g, 5.1 mmol) over 1 hour. The resulting solution was stirred at room temperature for 17 hours, before

treating with tert-butyl (4-oxocyclohexyl)carbamate (364 mg, 1.7 mmol). The reaction mixture was stirred for 30 minutes and then treated with sodium triacetoxyborohydride(1.09 g, 5.1 mmol) over 2.5 hours. The reaction mixture was stirred at room temperature for a further 26 hours before addition of deionized water (40 ml). The mixture was neutralised with solid $NaHCO_3$ (2.95 g) and was extracted with ethyl acetate (3 x 50 ml). The combined organic extracts were washed with brine (35 ml), dried ($MgSO_4$), filtered and concentrated in-vacuo. The crude residue was purified by column chromatography (25g SNAP cartridge, Isolera, 0-18% EtOAc / Heptanes) to give as an oil the title compound (623 mg, 85%) as a mixture of cis/trans isomers. LC-MS 46.1%, 2.61 min (3.5 minute LC-MS method), m/z = 411.1, 413.1 and 50.2%, 2.66 min (3.5 minute LC-MS method), m/z = 411.1, 413.1; ^{1}H NMR (500 MHz, Chloroform-d) d ppm 7.05 (dd, J=7.09, 2.05 Hz, 1 H) 6.68 (t, J=2.36 Hz, 1 H) 4.36 - 4.63 (m, 1 H) 3.88 (d, J=3.31 Hz, 3 H) 3.62 - 3.78 (m, 1 H) 3.49 (br. s., 1 H) 3.23 (br. s., 1 H) 2.63 - 2.76 (m, 2 H) 2.07 - 2.18 (m, 2 H) 1.77 - 1.89 (m, 2 H) 1.69 (br. s., 1 H) 1.46 (s, 9 H) 1.27 (m, 3 H) 1.13 - 1.24 (m, 3 H).

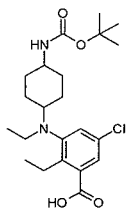
[01683] Step 7: Synthesis of methyl 3-[(4-{[(tert-butoxy)carbonyl]amino}cyclohexyl)(ethyl)amino]-5-chloro-2-ethylbenzoate



[01684] To a stirred solution of methyl 3-[(4-{[(tert-butoxy)carbonyl]amino}cyclohexyl)amino]-5-chloro-2-ethylbenzoate (200 mg, 0.49 mmol) in dry 1,2-dichloroethane (5.0 ml), was added acetaldehyde (54 µl, 1.0 mmol), followed by acetic acid (167 µl, 2.9 mmol). The reaction mixture was stirred for 50 minutes, sodium triacetoxyborohydride (309 mg, 1.5 mmol) was added over 2 hours and the reaction was stirred for 20 hours. The reaction mixture was treated with acetaldehyde (54 µl, 1.0 mmol) stirred for 1 hour and sodium triacetoxyborohydride(309 mg, 1.5 mmol) was added portionwise over 2 hours. The reaction mixture was stirred for a further 22 hours and then treated with acetaldehyde (136 µl, 2.4 mmol) and stirred for 1 hour, followed by sodium triacetoxyborohydride (516 mg, 2.4 mmol) over 1.5 hours and stirred for 22 hours. The reaction mixture was treated with acetaldehyde (109 µl, 2.0 mmol) and stirred for 1.5 hours

before sodium triacetoxyborohydride (413 mg, 2.0 mmol) was added over 2 hours, along with dichloroethane (5.0 ml) to aid stirring. The reaction mixture was stirred for 19 hours before the addition of acetaldehyde (82 µl, 1.5 mmol), stirred for 1.5 hours, followed by sodium triacetoxyborohydride (309 mg, 1.5 mmol) over 45 minutes. The reaction mixture was stirred for a further 70 hours before being diluted with water (20 ml) and the pH was adjusted to 8 by the gradual addition of solid $NaHCO_3$ (2.53 g). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 ml). The combined organic phases were washed with brine (60 ml), dried ($MgSO_4$), filtered and concentrated in-vacuo. The crude residue was purified by flash column chromatography (10g SNAP cartridge, Isolera, 0-30% EtOAc/Heptanes) to give the title compound (163 mg, 73%) as a yellow oil and a mixture of cis/trans isomers. LC-MS 100%, 5.83 min (7 minute LC-MS method), m/z = 439.2, 441.2; ^{1}H NMR (500 MHz, Chloroform-d) δ ppm 7.45 - 7.55 (m, 1 H) 7.22 (dd, J=4.33, 2.13 Hz, 1 H) 4.25 - 4.67 (m, 1 H) 3.90 (d, J=2.21 Hz, 3 H) 3.29 -3.76 (m, 1 H) 2.95 - 3.11 (m, 4 H) 2.58 - 2.96 (m, 1 H) 1.62 - 2.03 (m, 4 H) 1.38 - 1.53 (m, 11 H) 1.01 - 1.14 (m, 4 H) 0.81 - 0.94 (m, 4 H).

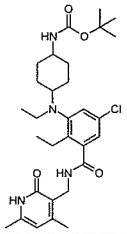
[01685] Step 8: Synthesis of 3-[(4-{[(tert-butoxy)carbonyl]amino}cyclohexyl)(ethyl)amino]-5-chloro-2-ethylbenzoic acid



[01686] To a stirred solution of methyl 3-[(4-{[(tert-butoxy)carbonyl]amino}cyclohexyl)(ethyl)amino]-5-chloro-2-ethylbenzoate (156 mg, 0.36 mmol) in THF (4.0 ml) and MeOH (0.29 ml), was added a solution of 4M NaOH (aq) (2.7 ml, 10.7 mmol). The resulting solution was stirred at 50 °C for 17 hours. The reaction mixture was treated with 4M NaOH (aq) (0.5 ml, 2.0 mmol) and stirring was continued at 50 °C for 32 hours. The heat was removed and the reaction mixture was left to stir at room temperature for 65 hours. The reaction mixture was treated with 4M NaOH (aq) (1.0 ml, 4.0 mmol) and heated back up to 50 °C for 24 hours. The organic solvents were removed in-vacuo and the aqueous phase was treated with a solution of 0.5M citric acid (20 ml) to adjust the pH to 4/5 . The product was extracted with ethyl acetate (3 x 25 ml). The combined organic phases were

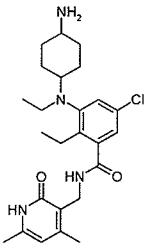
washed with brine (30 ml), dried ($MgSO_4$), filtered and concentrated in-vacuo and then further dried on the high vac line for 4 hours to give the title compound (142 mg, 92%) as a white solid and a mixture of cis/trans isomers. LC-MS 98%, 5.49 min (7 minute LC-MS method), m/z = 425.1, 427.1. ^{1}H NMR shows a mixture of cis/trans isomers.

[01687] Step 9: Synthesis of tert-butyl N-{4-[(5-chloro-3-{[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]carbamoyl}-2-ethylphenyl)(ethyl)amino]cyclohexyl}carbamate



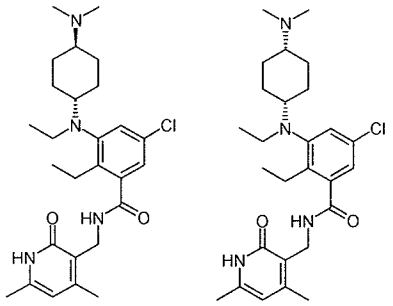
[01688] A stirred solution of 3-[(4-{[(tert-butoxy)carbonyl]amino}cyclohexyl)(ethyl)amino]-5-chloro-2-ethylbenzoic acid (139 mg, 0.33 mmol) in anhydrous DMF (2.0 ml) at 0 °C under nitrogen, was treated with HATU (149 mg, 0.39 mmol) and DIPEA (114 µl, 0.65 mmol). The resulting solution was stirred for 10 minutes and then treated with 3-(aminomethyl)-4,6-dimethyl-1,2-dihydropyridin-2-one (89%, 61 mg, 0.36 mmol). The resulting suspension was stirred at 0 °C for 1 hour and then stirred at room temperature for 98.5 hours. The reaction mixture was treated with HATU (37 mg, 0.1 mmol), stirred for 1 hour and then 3-(aminomethyl)-4,6-dimethyl-1,2-dihydropyridin-2-one (89%, 11 mg, 0.07 mmol). The reaction mixture was stirred at room temperature for a further 23 hours and then partitioned between water (20 ml) and CH_2Cl_2 (20 ml). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 ml). The combined organics were washed with a saturated solution of $NaHCO_3$ (aq) (40 ml), water (20 ml), brine (2 x 20 ml), dried ($MgSO_4$), filtered and concentrated in-vacuo. The crude residue was purified by flash column chromatography (10g SNAP cartridge, Isolera, 0-13% MeOH/CH_2Cl_2) and triturated from ether /heptane (2.0 ml) with sonication and the liquor decanted. The remaining solid was dried under high vacuum to give the title compound (101 mg, 52%) as a beige solid. LC-MS 93%, 4.54 min (7 minute LC-MS method), m/z = 559.2, 561.2. ^{1}H NMR shows a mixture of cis/trans isomers.

[01689] Step 10: Synthesis of 3-[(4-aminocyclohexyl)(ethyl)amino]-5-chloro-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-2-ethylbenzamide



[01690] To a stirred solution of tert-butyl N-{4-[(5-chloro-3-{[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]carbamoyl}-2-ethylphenyl)(ethyl)amino]cyclohexyl}carbamate (100 mg, 0.18 mmol) in CH_2Cl_2 (4.0 ml) at 0 °C, was added trifluoroacetic acid (1.0 ml). The reaction mixture was stirred at 0 °C for 40 minutes and then stirred for 2 hours at room temperature. The reaction mixture was concentrated in-vacuo and the residue was basified with a saturated solution of $NaHCO_3$ (aq) (10 ml) until the pH was 8. The aqueous residue was extracted with 20% MeOH/CH_2Cl_2 (4 x 15 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in-vacuo to give the title compound (108 mg, 113%) as a yellow solid. LC-MS 48%, 2.88 min (7 minute LC-MS method), m/z = 459.1 and 39%, 2.96 min (7 minute LC-MS method), m/z = 459.1. ^{1}H NMR shows a mixture of cis/trans isomers.

[01691] Step 11: Synthesis of 5-chloro-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-2-ethyl-3-{ethyl[(1r,4r)-4-(dimethylamino)cyclohexyl]amino}benzamide and 5-chloro-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-2-ethyl-3-{ethyl[(1s,4s)-4-(dimethylamino)cyclohexyl]amino}benzamide.



[01692] A stirred solution of 3-[(4-aminocyclohexyl)(ethyl)amino]-5-chloro-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-2-ethylbenzamide (80 mg, 0.18 mmol) in 1,2-dichloroethane (3.0 ml), was treated with acetic acid (60 µl, 1.0 mmol) and paraformaldehyde (31 mg, 1.0 mmol). The reaction mixture was stirred for 35 minutes under nitrogen before the addition of sodium triacetoxyborohydride (222 mg, 1.0 mmol). The reaction mixture was stirred for 16.5 hours before paraformaldehyde (16 mg, 0.52 mmol) was added and stirring was

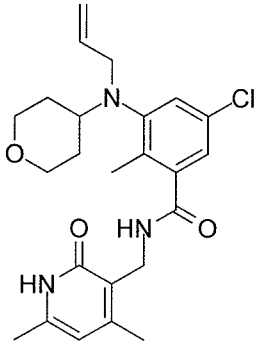
continued for 1 hour prior to the addition of sodium triacetoxyborohydride (111 mg, 0.52 mmol). The reaction mixture was stirred for a further 6 hours and then treated with paraformaldehyde (10 mg, 0.35 mmol), stirred for 10 minutes before the addition of sodium triacetoxyborohydride (74 mg, 0.35 mmol) and 1,2-dichloroethane (1.0 ml) and stirred for a further 89 hours. The reaction mixture was diluted with water (20 ml) and basified to pH 8 by the addition of solid $NaHCO_3$ (1.45 g). CH_2Cl_2 (20 ml) was added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 ml). The combined organic phases were washed with brine (30 ml), dried ($MgSO_4$), filtered and concentrated in-vacuo. The crude residue was purified by preparative-HPLC (MeCN / water + 0.2% ammonium hydroxide) to give pure trans isomer title compound 347: 5-chloro-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-2-ethyl-3-{ethyl[(1r,4r)-4-(dimethylamino)cyclohexyl]amino}benzamide (22 mg, 26%) as a white solid and pure cis isomer title compound 348: 5-chloro-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-2-ethyl-3-{ethyl[(1s,4s)-4-(dimethylamino)cyclohexyl]amino}benzamide-(18 mg, 21%) as a white solid.

[01693] 5-chloro-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-2-ethyl-3-{ethyl[(1r,4r)-4-(dimethylamino)cyclohexyl]amino}benzamide

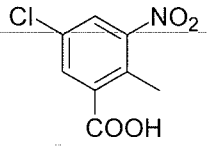
[01694] LC-MS 100%, 3.07 min (7 minute LC-MS method), m/z = 487.2, 489.2; ^{1}H NMR (500 MHz, Chloroform-d) δ 11.09 (s, 1H), 7.11 – 7.04 (m, 2H), 7.00 (d, J = 2.1 Hz, 1H), 5.94 (s, 1H), 4.51 (d, J = 5.9 Hz, 2H), 3.00 (q, J = 7.0 Hz, 2H), 2.79 (q, J = 7.4 Hz, 2H), 2.65 (t, J = 11.5 Hz, 1H), 2.38 (s, 3H), 2.24 (s, 6H), 2.22 (s, 3H), 2.14 (t, J = 11.4 Hz, 1H), 1.87 (d, J = 10.3 Hz, 4H), 1.37 (q, J = 12.1 Hz, 2H), 1.17 (q, J = 11.5 Hz, 2H), 1.02 (t, J = 7.4 Hz, 3H), 0.85 (t, J = 7.0 Hz, 3H).

[01695] 5-chloro-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-2-ethyl-3-{ethyl[(1s,4s)-4-(dimethylamino)cyclohexyl]amino}benzamide LC-MS 100%, 3.13 min (7 minute LC-MS method), m/z = 487.2, 489.2;^{1}H NMR (500 MHz, chloroform-d) δ 10.72 (s, 1H), 7.09 (d, J = 2.0 Hz, 2H), 7.01 (d, J = 2.1 Hz, 1H), 5.93 (s, 1H), 4.51 (d, J = 5.9 Hz, 2H), 3.01 (q, J = 6.7 Hz, 3H), 2.89 (q, J = 7.4 Hz, 2H), 2.39 (s, 3H), 2.23 (s, 9H), 2.06 (s, 1H), 1.87 – 1.72 (m, 4H), 1.43 (td, J = 8.3, 3.8 Hz, 2H), 1.33 (dd, J = 12.6, 9.2 Hz, 2H), 1.01 (t, J = 7.5 Hz, 3H), 0.84 (t, J = 7.0 Hz, 3H).

[01696] **Compound 92: 3-(allyl (tetrahydro-2H-pyran-4-yl) amino)-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide**

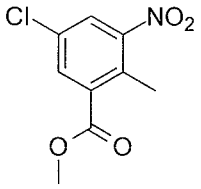


[01697] Step 1: Synthesis of 5-chloro-2-methyl-3-nitrobenzoic acid



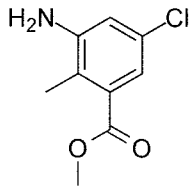
[01698] 5-chloro-2-methylbenzoic acid (4.0 g, 23 mmol) was added portionwise to cooled conc. H_2SO_4 (27 mL) at -10 °C. After 10 minutes a nitrating mixture {prepared by mixing conc. HNO3 (3.3 g, 52.68 mmol) with conc. H_2SO_4 (4.4 mL)} was added dropwise at -10 °C. The resulting reaction mass was stirred at -10 °C for 30 minutes. On completion, the reaction mixture was poured on ice cold water, the solid precipitate was filtered, washed with water and dried under vacuum giving the title compound (4.95 g, 99%).

[01699] Step 2: Synthesis of methyl 5-chloro-2-methyl-3-nitrobenzoate



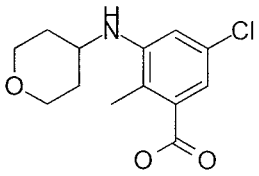
[01700] To a stirred solution of 5-chloro-2-methyl-3-nitrobenzoic acid (6.75 g, 31.3 mmol) in DMF (33 mL), sodium carbonate (13.2 g, 125 mmol) and methyl iodide (17.8 g, 125 mmol) were added. The mixture was heated at 60 °C for 4 h. On completion, water was added to the reaction mass and extraction was carried out using DCM. The combined organic layers were dried, concentrated under reduced pressure and purified by column chromatography over silica gel giving the title compound (6.0 g, 83%).

[01701] Step 3: Synthesis of methyl 3-amino-5-chloro-2-methyl benzoate



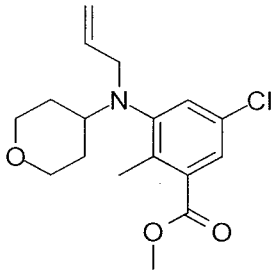
[01702] To stirred solution of methyl 5-chloro-2-methyl-3-nitrobenzoate (6.0 g, 26 mmol) in ethanol (60 mL), ammonium chloride (6.0 g, 110 mmol) dissolved in water (60 mL) and iron powder (11.9 g, 208 mmol) were added under stirring. The resulting reaction mass was heated at 80 °C for 1 h. On completion, water was added to reaction mass and reaction mixture was filtered through celite, the filtrate was extracted with ethyl acetate. The combined organic layers were washed with water, dried, and concentrated under reduced pressure giving the title compound which was used as is.

[01703] Step 4: Synthesis of methyl 5-chloro-2-methyl-3-((tetrahydro-2H-pyran-4-yl) amino) benzoate



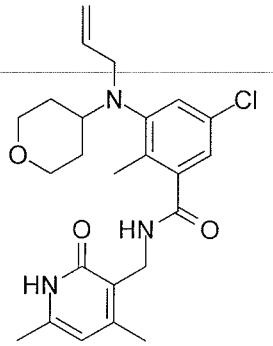
[01704] To a stirred solution of methyl 3-amino-5-chloro-2-methyl benzoate (5.0 g, 19 mmol) and dihydro-2H-pyran-4(3H)-one (2.86 g, 28.6 mmol) in methanol (50 mL), acetic acid (2.3 g, 38 mmol) was added and reaction stirred at room temperature for 8 h. Then sodium cyanoborohydride (3.0 g, 48 mmol) was added at 0°C and reaction stirred overnight at room temperature. On completion, the solvent was removed under reduced pressure and crude material was purified by column chromatography to afford the title compound (3.0 g, 42 %).

[01705] Step 5: Synthesis of methyl 3-(allyl (tetrahydro-2H-pyran-4-yl) amino)-5-chloro-2-methylbenzoate



[01706] To a stirred solution of methyl 5-chloro-2-methyl-3-((tetrahydro-2H-pyran-4-yl) amino) benzoate (1.0 g, 3.3 mmol) in DMF (10 mL), NaH (0.25 g, 10 mmol) was added at 0°C and the mixture stirred for 20 minutes. 3-bromoprop-1-ene (1.7 g, 14.13 mmol) was added and the mixture was heated at 80°C for 15 h. On completion, the reaction was quenched with ice cold water and extraction was carried out using DCM. The combined organic layers were dried, concentrated and resulting crude was purified by column chromatography giving the title compound (0.50 g, 44 %).

[01707] Step 6: Synthesis of 3-(allyl (tetrahydro-2H-pyran-4-yl) amino)-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide

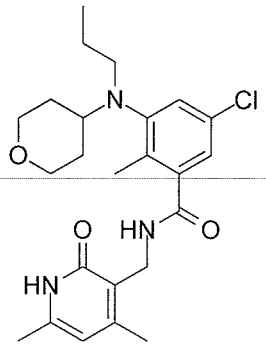


[01708] Aqueous NaOH (0.092 g, 2.32 mmol) was added to a solution of methyl 3-(allyl (tetrahydro-2H-pyran-4-yl) amino)-5-chloro-2-methylbenzoate (0.50 g, 1.54 mmol) in ethanol (15 mL) and the mixture stirred at 60 °C for 1 h. After completion of the reaction, ethanol was removed under reduced pressure and acidified using dilute HCl up to pH 6 and pH 4 was adjusted using citric acid. Extraction was carried out using DCM. The combined organic layers were dried and concentrated giving respective acid (0.47 g, 98%).

[01709] The above acid (0.47 g, 1.52 mmol) was then dissolved in DMSO (5 mL) and 3-(amino methyl)-4, 6-dimethylpyridin-2(1H)-one (0.462 g, 3.04 mmol) was added.. The reaction mixture was stirred at room temperature for 15 min before PYBOP (1.18 g, 2.28 mmol) was added to it and stirring was continued overnight. After completion of the reaction, reaction mass was poured into ice to obtain a solid which was filtered and dried to afford the title compound (0.40 g, 59%). LCMS: 444.25 $(M + 1)^+$; HPLC: 96.85% (@ 254 nm) (R_t;6.310; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 µ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 µL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR

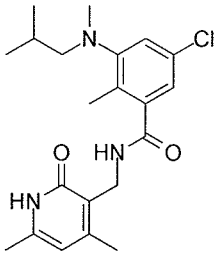
(DMSO-d_6, 400 MHz) δ 11.47 (s, 1H), 8.22 (t, 1H), 7.16 (s, 1H), 6.93 (s, 1H), 5.85 (s, 1H), 5.56-5.62 (m, 1H), 5.02-5.07 (m, 1H), 4.94-4.96 (m, 1H), 4.23 (d, 2H, J=3.6 Hz), 3.83 (d, 2H, J=9.6 Hz), 3.64 (d, 2H, J=4 Hz), 3.23 (t, 2H, J=10 Hz), 2.97 (m, 1H), 2.18 (s, 3H), 2.17 (s, 3H), 2.10 (s, 3H), 1.54-1.60 (m, 4H).

[01710] **Compound 98: 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-(propyl(tetrahydro-2H-pyran-4-yl)amino)benzamide**

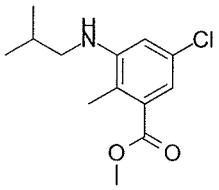


[01711] To a stirred solution of 3-(allyl (tetrahydro-2H-pyran-4-yl) amino)-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide (0.10 g) in MeOH (10 mL) was added 10% Pd/C (0.03 g) and the reaction stirred at room temperature under hydrogen (balloon pressure) for 2 h. On completion, the reaction mixture was filtered through celite and the filtrate was concentrated under reduced pressure to obtain crude solid which was purified by column chromatography to afford the title compound (0.02 g, 20%). LCMS: 445.25 $(M + 1)^+$; HPLC: 90.40% (@ 254 nm) (R_t;5.609; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 μ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 μL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.47 (s, 1H), 8.23 (t, 1H), 7.19 (s,1H), 6.93 (d, 1H, J=1.6 Hz), 5.88 (s, 1H), 4.24 (d, 2H, J=4.4 Hz), 3.83 (d, 2H, J=10.4 Hz), 3.22-3.25 (m, 2H), 2.94 (t, 2H, J=7.2 Hz), 2.88-2.90 (m, 1H), 2.18 (s, 3H), 2.15 (s, 3H), 2.10 (s, 3H), 1.56 (m, 4H), 1.14-1.23 (m, 2H), 0.75 (t, 3H, J=8 Hz).

[01712] **Compound 104: 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(isobutyl(methyl)amino)-2-methylbenzamide**

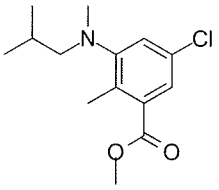


[01713] Step 1: Synthesis of methyl 5-chloro-3-(isobutyl amino)-2-methylbenzoate



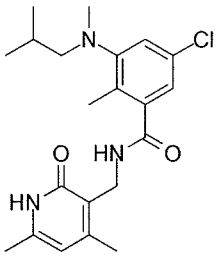
[01714] To a stirred solution of methyl 3-amino-5-chloro-2-methyl benzoate (5.0 g, 25 mmol) and isobutyraldehyde (4.5 g, 62 mmol) in methanol (50 mL), acetic acid (3.0 g, 50 mmol) was added and reaction stirred at room temperature for 2 h. Then sodium cyanoborohydride (3.94 g, 62 mmol) was added at 0°C and reaction stirred overnight at room temperature. On completion, the solvent was removed under reduced pressure and the crude material was purified by column chromatography to afford the title compound (6.0 g, 94 %).

[01715] Step2: Synthesis of methyl 5-chloro-3-(isobutyl (methyl) amino)-2-methylbenzoate



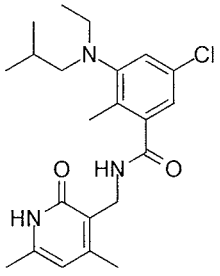
[01716] To a stirred solution of methyl 5-chloro-3-(isobutyl amino)-2-methylbenzoate (1.0 g, 3.9 mmol) in dry acetonitrile (10 mL), cesium carbonate (2.55 g, 7.8 mmol) and methyl iodide (5.55 g, 39 mmol) were added. The mixture was heated at 80 °C for 12 h. On completion, the mixture was cooled to room temperature and filtered. The residue was washed with ethyl acetate and the filtrate was concentrated to the title compound (1.0 g, 95 %).

[01717] Step 3: Synthesis of 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(isobutyl(methyl)amino)-2-methylbenzamide

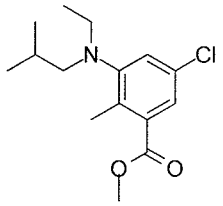


[01718] Aqueous NaOH (0.22g, 5.5 mmol) was added to a solution of methyl 5-chloro-3-(isobutyl (methyl) amino)-2-methylbenzoate (1.0 g, 3.7 mmol) in EtOH (5 mL) and the mixture stirred at 60 °C for 1 h. After completion of the reaction, ethanol was removed under reduced pressure. The residue was acidified using dilute HCl up to pH 6 and pH 4 was adjusted using citric acid. Extraction was carried out using ethyl acetate. The combined organic layers were dried and concentrated giving the respective acid (0.900 g, 95 %).The acid (0.30 g, 1.17 mmol) was then dissolved in DMSO (1.5 mL) and 3-(amino methyl)-4, 6-dimethylpyridin-2(1H)-one (0.357 g, 2.34 mmol) was added. The reaction mixture was stirred at room temperature for 15 min before PYBOP (0.915 g, 1.76 mmol) was added to it and stirring was continued overnight. After completion of the reaction, the reaction mass was poured into ice to obtain a solid, this was filtered and purified by column chromatography to afford the title compound (0.245 g, 53%). LCMS: 390.25 $(M + 1)^+$; HPLC: 97.59% (@ 254 nm) (R_t;6.063; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 µ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 µL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.47 (s, 1H), 8.20 (t, 1H), 7.07 (s, 1H), 6.90 (s, 1H), 5.85 (s, 1H), 4.23 (d, 2H, J=4.4 Hz), 2.63 (d, 2H, J=7.2 Hz), 2.54 (s, 3H), 2.18 (s, 3H), 2.16 (s, 3H), 2.10 (s, 3H), 1.75-1.78 (m, 1H), 0.85 (d, 6H, J=6 Hz).

[01719] **Compound 105: 5-chloro-N-((4, 6-dimethyl-2-oxo-1, 2-dihydropyridin-3-yl) methyl)-3-(ethyl (isobutyl) amino)-2-methylbenzamide**

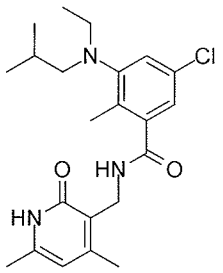


[01720] Step 1: Synthesis of methyl 5-chloro-3-(ethyl (isobutyl) amino)-2-methylbenzoate



[01721] To a stirred solution of methyl 5-chloro-3-(isobutyl amino)-2-methylbenzoate (1.0 g, 3.9 mmol) in dry DMF (10 mL), cesium carbonate (2.55 g, 7.82 mmol) and ethyl iodide (6.09 g, 39.1 mmol) were added. The resulting reaction mass was heated at 80 °C for 12 h. On completion, the reaction mass was cooled to room temperature and filtered. The residue was washed with ethyl acetate and the filtrate was concentrated to give crude material which then used for next step as is (1.0 g, 91 %).

[01722] Step 2: Synthesis of 5-chloro-N-((4, 6-dimethyl-2-oxo-1, 2-dihydropyridin-3-yl) methyl)-3-(ethyl (isobutyl) amino)-2-methylbenzamide

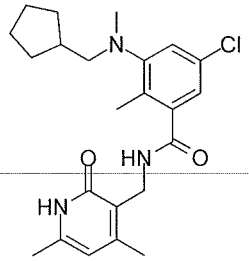


[01723] Aqueous NaOH (0.212g, 5.28 mmol) was added to a solution of compound 7 (1.0 g, 3.50 mmol) in EtOH (5 mL) and stirred at 60 °C for 1 h. After completion of the reaction, ethanol was removed under reduced pressure and acidified using dilute HCl up to pH 6 and pH 4 was adjusted using citric acid. Extraction was carried out using ethyl acetate. The combined organic layers were dried concentrated giving the respective acid (0.900 g).

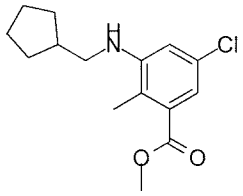
[01724] The acid (0.90 g, 3.33 mmol) was then dissolved in DMSO (4.5 mL) and 3-(amino methyl)-4, 6-dimethylpyridin-2(1H)-one (1.01 g, 6.67 mmol) was added to it. The reaction mixture was stirred at room temperature for 15 min before PYBOP (2.60 g, 4.9 mmol) was added and stirring was continued for overnight. The mixture was poured into ice to give a solid, this was filtered and purified by acetonitrile and diethyl ether washings to afford the title compound (1.0 g, 75%). LCMS: 404.25 $(M + 1)^+$; HPLC: 90.28% (@ 254 nm) (R_t;6.063; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 µ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 µL, Col. Temp.: 30 °C; Flow rate: 1.4

mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.45 (s, 1H), 8.19 (t, 1H), 7.10 (s, 1H), 6.90 (s, 1H), 5.85 (s, 1H), 4.24 (d, 2H, J=4.8 Hz), 2.86 (q, 2H, J=7.2 Hz), 2.73 (d, 2H, J=7.6 Hz), 2.18 (s, 3H), 2.16 (s, 3H), 2.10 (s, 3H), 1.57-1.61 (m, 1H), 0.91 (t, 3H, J=6.8 Hz), 0.82 (d, 6H, J=6.4 Hz).

[01725] **Compound 117: 5-chloro-3-((cyclopentylmethyl) (methyl) amino)-N-((4, 6-dimethyl-2-oxo-1, 2-dihydropyridin-3-yl) methyl)-2-methylbenzamide**

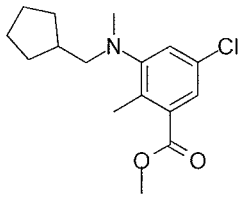


[01726] Step 1: Synthesis of methyl 5-chloro-3-((cyclopentylmethyl) amino)-2-methylbenzoate



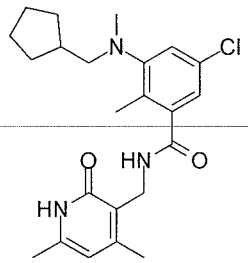
[01727] To a stirred solution of methyl 3-amino-5-chloro-2-methyl benzoate (3.0 g, 15 mmol) and cyclopentanecarbaldehyde (2.2 g, 22 mmol) in methanol (30 mL), acetic acid (1.8 g, 30 mmol) was added and reaction stirred at room temperature for 8 h. Then sodium cyanoborohydride (2.4 g, 37 mmol) was added at 0°C and the reaction stirred overnight at room temperature. On completion, the solvent was removed under reduced pressure and the crude material was purified by column chromatography to afford the title compound (4.2 g, 99%).

[01728] Step 2: Synthesis of methyl 5-chloro-3-((cyclopentylmethyl) (methyl) amino)-2-methylbenzoate



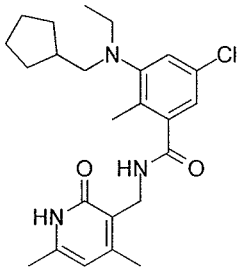
[01729] To a stirred solution of methyl 5-chloro-3-((cyclopentylmethyl) amino)-2-methylbenzoate (1.0 g, 3.5 mmol) in acetonitrile (10 mL), cesium carbonate (2.3 g, 7.1 mmol) and methyl iodide (5.0 g, 35 mmol) were added. The mixture was heated at 80 °C for 12 h. cooled to room temperature and filtered. The residue was washed with ethyl acetate and the filtrate was concentrated and then purified by column chromatography to afford the title compound (1.0 g, 95%).

[01730] Step 3: Synthesis of 5-chloro-3-((cyclopentylmethyl) (methyl) amino)-N-((4, 6-dimethyl-2-oxo-1, 2-dihydropyridin-3-yl) methyl)-2-methylbenzamide

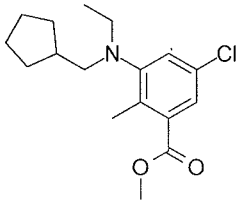


[01731] Aqueous NaOH (0.206 g, 15.1 mmol) was added to a solution of methyl 5-chloro-3-((cyclopentylmethyl) (methyl) amino)-2-methylbenzoate (1.0 g, 3.38 mmol) in ethanol (10 mL) and the mixture stirred at 60 °C for 1 h. The ethanol was removed under reduced pressure and the residue acidified using dilute HCl up to pH 6 and pH 4 was adjusted using citric acid. Extraction was carried out using DCM. The combined organic layers were dried and concentrated giving the respective acid (0.9 g)The above acid (0.3 g, 1.06 mmol) was then dissolved in DMSO (1.5 mL) and 3-(amino methyl)-4, 6-dimethylpyridin-2(1H)-one (0.324 g, 2.12 mmol) was added. The reaction mixture was stirred at room temperature for 15 min before PYBOP (0.831 g, 1.57 mmol) was added and stirring was continued overnight. The mixture was poured into ice to obtain a solid, this was filtered and washed with acetonitrile to provide the title compound (0.25 g, 56%). LCMS: 416.15 $(M + 1)^+$; HPLC: 92.58% (@ 254 nm) (R_t;6.169; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 μ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 μL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.45 (s, 1H), 8.19 (t, 1H), 7.08 (s, 1H), 6.89 (s, 1H), 5.85 (s, 1H), 4.23 (d, 2H, J=4.4 Hz), 2.77 (d, 2H, J=7.2 Hz), 2.57 (s, 3H), 2.18 (s, 3H), 2.15 (s, 3H), 2.10 (s, 3H), 2.04-2.06 (m, 1H), 1.63-1.65 (m, 2H), 1.49-1.52 (m, 2H), 1.45-1.46 (m, 2H), 1.15-1.18 (m, 2H).

[01732] **Compound118: 5-chloro-3-((cyclopentylmethyl) (ethyl) amino)-N-((4, 6-dimethyl-2-oxo-1, 2-dihydropyridin-3-yl) methyl)-2-methylbenzamide**

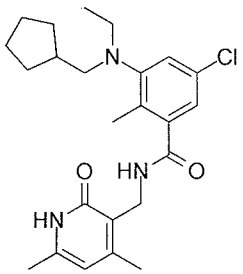


[01733] Step 1: Synthesis of methyl 5-chloro-3-((cyclopentylmethyl) (ethyl) amino)-2-methylbenzoate



[01734] To a stirred solution of methyl 5-chloro-3-((cyclopentylmethyl) amino)-2-methylbenzoate (1.0 g, 3.54 mmol) in DMF (10 mL), cesium carbonate (2.31 g, 7.09 mmol) and ethyl iodide (5.53 g, 35.4 mmol) were added. The resulting reaction mass was heated at 80 °C for 12 h. The mixture was cooled to room temperature and filtered. The residue was washed with ethyl acetate and the filtrate was concentrated to a residue which was purified by column chromatography to afford the title compound (1.0 g, 91 %).

[01735] Step 2: Synthesis of 5-chloro-3-((cyclopentylmethyl) (ethyl) amino)-N-((4, 6-dimethyl-2-oxo-1, 2-dihydropyridin-3-yl) methyl)-2-methylbenzamide

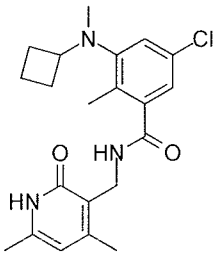


[01736] Aqueous NaOH (0.193 g, 15.1 mmol) was added to a solution of methyl 5-chloro-3-((cyclopentylmethyl) (ethyl) amino)-2-methylbenzoate (1.0 g, 3.22 mmol) in ethanol (10 mL) and the mixture stirred at 60 °C for 1 h. After completion of the reaction, ethanol was removed

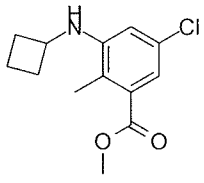
under reduced pressure and the residue acidified using dilute HCl up to pH 6 and pH 4 was adjusted using citric acid. Extraction was carried out using DCM. The combined organic layers were dried concentrated giving respective acid (0.9 g).

[01737] The above acid (0.3 g, 1.01 mmol) was then dissolved in DMSO (1.5 mL) and 3-(amino methyl)-4, 6-dimethylpyridin-2(1H)-one (0.308 g, 2.12 mmol) was added. The reaction mixture was stirred at room temperature for 15 min before PYBOP (0.791 g, 1.52 mmol) was added and stirring was continued overnight. After completion of the reaction, the reaction mass was poured into ice to obtain a solid, this was filtered and washed with acetonitrile to provide the title compound (0.25 g, 57%). LCMS: 430.2 $(M + 1)^+$; HPLC: 91.54% (@ 210 nm) (R_t;9.378; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 µ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 µL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.46 (s, 1H), 8.20 (t, 1H), 7.12 (s, 1H), 6.91 (s, 1H), 5.85 (s, 1H), 4.23 (d, 2H, J=3.6 Hz), 2.83-2.89 (m, 4H), 2.18 (s, 3H), 2.14 (s, 3H), 2.10 (s, 3H), 1.85-1.89 (m, 1H), 1.51-1.58 (m, 4H), 1.41-1.46 (m, 2H), 1.14-1.15 (m 2H), 0.91 (t, 3H, J=8 Hz).

[01738] **Compound 123: 5-chloro-3-(cyclobutyl (methyl) amino)-N-((4, 6-dimethyl-2-oxo-1, 2-dihydropyridin-3-yl) methyl)-2-methylbenzamide**



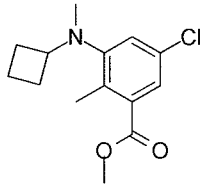
[01739] Step 1: Synthesis of methyl 5-chloro-3-(cyclobutylamino)-2-methylbenzoate



[01740] To a stirred solution of methyl 3-amino-5-chloro-2-methylbenzoate (2.0 g, 10 mmol) and cyclobutanone (1.4 g, 20 mmol) in dichloroethane (20 mL), acetic acid (3.6 g, 60 mmol) was added and reaction stirred at room temperature for10 minutes. Then sodium

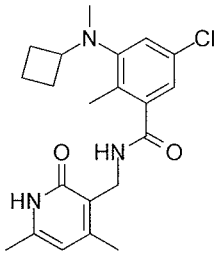
triacetoxyborohydride (6.3 g, 30 mmol) was added at 0°C and the reaction stirred for 3 h at room temperature. On completion, the solvent was removed under reduced pressure and the crude material was purified by column chromatography to afford the title compound (1.4 g, 56 %).

[01741] Step 2: Synthesis of methyl 5-chloro-3-(cyclobutyl (methyl) amino)-2-methylbenzoate



[01742] To a stirred solution of methyl 5-chloro-3-(cyclobutylamino)-2-methylbenzoate (0.7 g, 2.8 mmol) in acetonitrile (10 mL), cesium carbonate (2.2 g, 6.8 mmol) and methyl iodide (3.9 g, 28 mmol) were added. The resulting reaction mass was heated at 80 °C for 8 h. On completion, the reaction mass was cooled to room temperature and filtered. The residue was washed with ethyl acetate and the filtrate was concentrated to give the title compound (0.62 g, 84 %).

[01743] Step 3: Synthesis of 5-chloro-3-(cyclobutyl (methyl) amino)-N-((4, 6-dimethyl-2-oxo-1, 2-dihydropyridin-3-yl) methyl)-2-methylbenzamide

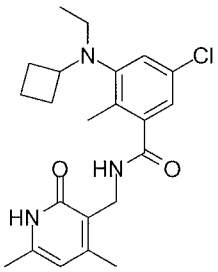


[01744] Aqueous NaOH (0.134 g, 3.34 mmol) was added to a solution of methyl 5-chloro-3-(cyclobutyl (methyl) amino)-2-methylbenzoate (0.60 g, 2.23 mmol) in ethanol (10 mL) and the mixture stirred at 60 °C for 1 h. After completion of the reaction, ethanol was removed under reduced pressure and acidified using dilute HCl up to pH 6 and pH 4 was adjusted using citric acid. Extraction was carried out using DCM. The combined organic layers were dried concentrated giving respective acid (0.5 g).

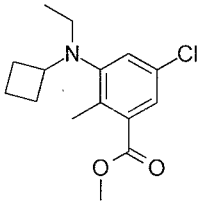
[01745] The above acid (0.25 g, 0.98 mmol) was then dissolved in DMSO (5 mL) and 3-(amino methyl)-4, 6-dimethylpyridin-2(1H)-one (0.22 g, 1.41 mmol) was added. The reaction mixture was stirred at room temperature for 15 min before PYBOP (0.767 g, 1.47 mmol) was

added and stirring was continued overnight. After completion of the reaction, the reaction mass was poured into ice and extraction was carried out using 10 % MeOH/DCM. The combined organic layers were dried over sodium sulphate and concentrated under reduced pressure to obtain crude material which was then purified by column chromatography giving the title compound (0.36 g, 95 %). LCMS:388.09 $(M + 1)^+$; HPLC: 96.62% (@ 254 nm) (R_t;5.461; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 µ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 µL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.44 (s, 1H), 8.18 (t, 1H), 6.90 (d, 2H, J=7.2 Hz), 5.85 (s, 1H), 4.24 (d, 2H, J=4.4 Hz), 3.65 (m, 1H), 2.45 (s, 3H), 2.18 (s,3H), 2.15 (s, 3H), 2.10 (s, 3H), 2.03 (bs, 2H), 1.76-1.81 (m, 2H), 1.61-1.62 (m, 2H).

[01746] **Compound 137: 5-chloro-3-(cyclobutyl (ethyl) amino)-N-((4, 6-dimethyl-2-oxo-1, 2-dihydropyridin-3-yl) methyl)-2-methylbenzamide**

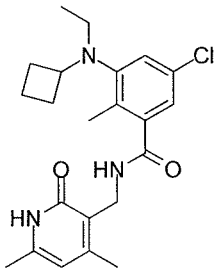


[01747] Step1: Synthesis of methyl 5-chloro-3-(cyclobutyl (ethyl) amino)-2-methylbenzoate



[01748] To a stirred solution of methyl 5-chloro-3-(cyclobutylamino)-2-methylbenzoate (0.70 g, 2.73 mmol) and acetaldehyde (0.36 g, 8.20 mmol) in dichloroethane (15 mL), acetic acid (0.98 g, 16.4 mmol) was added and the reaction stirred at room temperature for10 minutes. Then sodium triacetoxyborohydride (1.7 g, 8.2 mmol) was added at 0°C and the reaction stirred for 3 h at room temperature. On completion, the solvent was removed under reduced pressure to give title compound (0.71 g, 91 %).

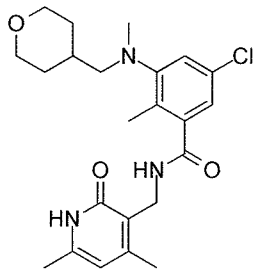
[01749] Step 2: Synthesis of 5-chloro-3-(cyclobutyl (ethyl) amino)-N-((4, 6-dimethyl-2-oxo-1, 2-dihydropyridin-3-yl) methyl)-2-methylbenzamide



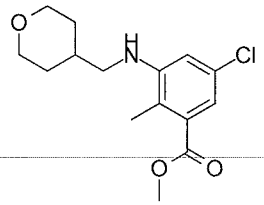
[01750] Aqueous NaOH (0.149 g, 3.7 mmol) was added to a solution of methyl 5-chloro-3-(cyclobutyl (ethyl) amino)-2-methylbenzoate (0.70 g, 2.48 mmol) in ethanol (10 mL) and the mixture stirred at 60 °C for 1 h. After completion of the reaction, ethanol was removed under reduced pressure and the residue acidified using dilute HCl up to pH 6 and pH 4 was adjusted using citric acid. Extraction was carried out using DCM. The combined organic layers were dried and concentrated giving respective acid (0.6 g,).

[01751] The above acid (0.6 g, 2.2mmol) was then dissolved in DMSO (5 mL) and 3-(amino methyl)-4, 6-dimethylpyridin-2(1H)-one (0.67 g, 4.44 mmol) was added. The reaction mixture was stirred at room temperature for 15 min before PYBOP (1.7 g, 3.33 mmol) was added and stirring was continued overnight. After completion of the reaction, the reaction mass was poured into ice; extraction was carried out using 10 % MeOH/DCM. The combined organic layers were dried over sodium sulphate and concentrated under reduced pressure to obtain crude material which was then purified by solvent washings giving the title compound (0.45 g, 50%). LCMS:402.20 $(M + 1)^+$; HPLC: 98.73% (@ 254 nm) (R_t;4.096; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 µ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 µL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.47 (s, 1H), 8.22 (t, 1H, J=4.4 Hz), 6.97 (s, 1H), 6.92 (s, 1H), 5.85 (s, 1H), 4.23 (d, 2H, J=4.4 Hz), 3.75-3.79 (m, 1H), 2.87-2.93 (m,2H), 2.18 (s, 3H), 2.15 (s, 3H), 2.10 (s, 3H), 1.99 (m, 2H), 1.58-1.69 (m, 4H), 0.77 (t, 3H, J=6.8 Hz).

[01752] **Compound 126: 5-chloro-N-((4, 6-dimethyl-2-oxo-1, 2-dihydropyridin-3-yl) methyl)-2-methyl-3-(methyl ((tetrahydro-2H-pyran-4-yl) methyl) amino) benzamide**

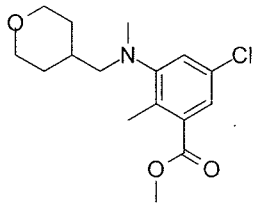


[01753] Step 1: Synthesis of methyl 5-chloro-2-methyl-3-(((tetrahydro-2H-pyran-4-yl) methyl) amino) benzoate



[01754] To a stirred solution of methyl 3-amino-5-chloro-2-methyl benzoate (2.0 g, 10 mmol) and tetrahydro-2H-pyran-4-carbaldehyde (1.71 g, 15 mmol) in methanol (20 mL), acetic acid (1.2 g, 20 mmol) was added and the reaction stirred at room temperature for 8 h. Then sodium cyanoborohydride (2.11 g, 25.1mmol) was added at 0°C and the reaction stirred overnight at room temperature. On completion, the solvent was removed under reduced pressure and the crude material was purified by column chromatography to afford the title compound (1.8 g, 60 %).

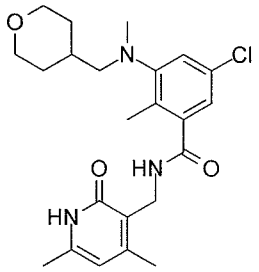
[01755] Step 2: Synthesis of methyl 5-chloro-2-methyl-3-(methyl ((tetrahydro-2H-pyran-4-yl) methyl) amino) benzoate



[01756] To a stirred solution of methyl 5-chloro-2-methyl-3-(((tetrahydro-2H-pyran-4-yl) methyl) amino) benzoate (0.80 g, 2.71 mmol) in acetonitrile (20 mL), cesium carbonate (1.75 g, 5.42 mmol) and methyl iodide (1.93 g, 13.6 mmol) were added. The resulting reaction mass was heated at 80 °C for 8 h. On completion, the mixture was cooled to room temperature and filtered. The residue was washed with ethyl acetate and the filtrate was concentrated to give

crude material which was purified by column chromatography to give the title compound(0.70 g, 84 %).

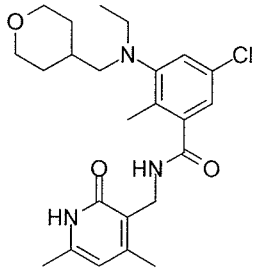
[01757] Step 3: Synthesis of 5-chloro-N-((4, 6-dimethyl-2-oxo-1, 2-dihydropyridin-3-yl) methyl)-2-methyl-3-(methyl ((tetrahydro-2H-pyran-4-yl) methyl) amino) benzamide



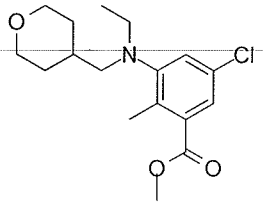
[01758] Aqueous NaOH (0.18 g, 4.5 mmol) was added to a solution of methyl 5-chloro-2-methyl-3-(methyl ((tetrahydro-2H-pyran-4-yl) methyl) amino) benzoate (0.70 g, 2.25 mmol) in ethanol (10 mL) and the mixture stirred at 60 °C for 1 h. The ethanol was removed under reduced pressure and the residue acidified using dilute HCl up to pH 6 and pH 4 was adjusted using citric acid. Extraction was carried out using DCM. The combined organic layers were dried and concentrated giving the respective acid (0.2 g).

[01759] The above acid (0.2 g, 0.68 mmol) was then dissolved in DMSO (0.5 mL) and 3-(amino methyl)-4, 6-dimethylpyridin-2(1H)-one (0.206 g, 1.35 mmol) was added. The reaction mixture was stirred at room temperature for 15 min before PYBOP (0.528 g, 1.01 mmol) was added t and stirring was continued overnight. The mixture was poured into ice and extraction was carried out using 10 % MeOH/DCM. The combined organic layers were dried over sodium sulphate and concentrated under reduced pressure to obtain crude material which was purified by column chromatography giving the title compound (0.2 g, 69 %). LCMS: 432.25 $(M + 1)^+$; HPLC: 99.95% (@ 254 nm) (R_t;5.750; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 µ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 µL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.45 (s, 1H), 8.19 (t, 1H), 7.10 (d, 1H, J=1.6 Hz), 6.90 (d, 1H, J=2 Hz), 5.85 (s, 1H), 4.23 (d, 2H, J=4.8 Hz), 3.80 (d, 2H, J=8.4 Hz), 3.21-3.27 (m, 2H), 2.73 (d, 2H, J=7.2 Hz), 2.55 (s, 3H), 2.18 (s, 3H), 2.15 (s, 3H), 2.10 (s, 3H), 1.74-1.75 (m, 1H), 1.58-1.61 (m, 2H), 1.07-1.16 (m, 2H).

[01760] **Compound 127: 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((tetrahydro-2H-pyran-4-yl)methyl)amino)-2-methylbenzamide**

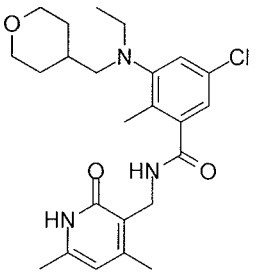


[01761] Step 1: Synthesis of methyl 5-chloro-3-(ethyl ((tetrahydro-2H-pyran-4-yl) methyl) amino)-2-methylbenzoate



[01762] To a stirred solution of methyl 5-chloro-2-methyl-3-(((tetrahydro-2H-pyran-4-yl) methyl) amino) benzoate (0.40 g, 1.35 mmol) and acetaldehyde (0.120 g, 2.71 mmol) in dichloroethane (5 mL), acetic acid (0.48 g, 8.1 mmol) was added and the reaction stirred at room temperature for 10 minutes. Then sodium triacetoxyborohydride (0.663 g, 4.05 mmol) was added at 0°C and the reaction stirred for 3 h at room temperature. On completion, the solvent was removed under reduced pressure and the crude material purified by column chromatography to the title compound (0.38 g, 86%).

[01763] Step 2: Synthesis of 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((tetrahydro-2H-pyran-4-yl)methyl)amino)-2-methylbenzamide

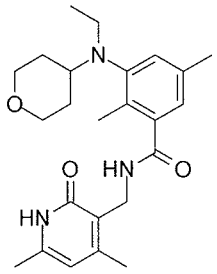


[01764] Aqueous NaOH (0.099 g, 2.46 mmol) was added to a solution of methyl 5-chloro-3-(ethyl ((tetrahydro-2H-pyran-4-yl) methyl) amino)-2-methylbenzoate (0.38 g, 1.2 mmol) in ethanol (20 mL) and the mixture stirred at 60 °C for 1 h. After completion of the reaction,

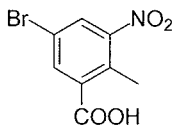
ethanol was removed under reduced pressure and the residue acidified using dilute HCl up to pH 6 and pH 4 was adjusted using citric acid. Extraction was carried out using DCM. The combined organic layers were dried concentrated giving the respective acid (0.2 g).

[01765] The above acid (0.2 g, 0.64 mmol) was then dissolved in DMSO (2 mL) and 3-(amino methyl)-4, 6-dimethylpyridin-2(1H)-one (0.196 g, 1.29 mmol) was added. The reaction mixture was stirred at room temperature for 15 min before PYBOP (0.504 g, 0.97 mmol) was added and stirring was continued overnight. The mixture was poured into ice and extraction was carried out using 10 % MeOH/DCM. The combined organic layers were dried over sodium sulphate and concentrated under reduced pressure to obtain crude material which was purified by column chromatography to afford the title compound (0.15 g, 52 %). LCMS: 446.20 (M + 1)$^+$; HPLC: 99.89% (@ 254 nm) (R_t;5.381; Method: Column: YMC ODS-A 150 mm x 4.6 mm x 5 µ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 µL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.47 (s, 1H), 8.21 (t, 1H), 7.14 (s, 1H), 6.91 (s, 1H), 5.85 (s, 1H), 4.23 (d, 2H, J=4.4 Hz), 3.78 (d, 2H, J=8.8 Hz), 3.18 (t, 2H, J=11.6 Hz), 2.82-2.89 (m, 4H), 2.18 (s, 3H), 2.13 (s, 3H), 2.10 (s, 3H), 1.54-1.57 (m, 3H), 1.09-1.15 (m, 2H), 0.91 (t, 3H, J=6.8 Hz).

[01766] **Compound 157: N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-2,5-dimethylbenzamide**



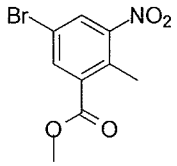
[01767] Step 1: Synthesis of 5-bromo-2-methyl-3-nitrobenzoic acid



[01768] To stirred solution of 2-methyl-3-nitrobenzoic acid (50 g, 276 mmol) in conc. H_2SO_4 (200 mL), 1,3-dibromo-5,5-dimethyl-2,4-imidazolidinedione (43.4 g, 152 mmol) was added portionwise at room temperature. The mixture was stirred at room temperature for 5 h. and

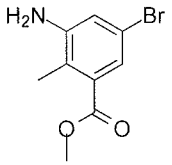
poured on ice cold water. The precipitate was filtered, washed with water and dried under vacuum giving the title compound (71 g, 99%).

[01769] Step 2: Synthesis of methyl 5-bromo-2-methyl-3-nitrobenzene



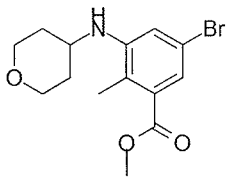
[01770] To a stirred solution of 5-bromo-2-methyl-3-nitrobenzoic acid (287 g, 1100 mmol) in DMF (150 mL), were added sodium carbonate (468 g, 4415 mmol) and methyl iodide (627 g, 4415 mmol). The mixture was heated at 60 °C for 8 h. The precipitate was filtered and washed with diethyl ether (5 times). The combined organic layers were dried, concentrated under reduced pressure giving the title compound (302 g, 99%) which was used directly without further purification.

[01771] Step 3: Synthesis of methyl 3-amino-5-bromo-2-methylbenzoate



[01772] To a stirred solution of methyl 5-bromo-2-methyl-3-nitrobenzene (150 g, 544 mmol) in ethanol (750 mL), ammonium chloride (150 g, 2777 mmol) dissolved in water (750 mL) and iron powder (93.3 g, 1636 mmol) were added under stirring. The mixture was heated at 80 °C for 7 h. and filtered through celite. ; The solids were washed with water and ethyl acetate and the combined filtrates were extracted with ethyl acetate. The combined organic layers were dried and concentrated under reduced pressure to give the title compound (175 g) which was used without further purification.

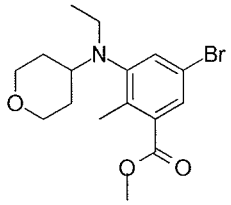
[01773] Step 4: Synthesis of methyl 5-bromo-2-methyl-3-((tetrahydro-2H-pyran-4-yl) amino) benzoate



[01774] To a stirred solution of methyl 3-amino-5-bromo-2-methylbenzoate (15 g, 61 mmol) and dihydro-2H-pyran-4(3H)-one (9.2 g, 92 mmol) in dichloroethane (300 mL), acetic acid (22

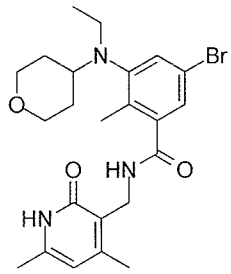
g, 368.4 mmol) was added and the reaction stirred at room temperature for 2 h. Then sodium triacetoxyborohydride (39 g, 184 mmol) was added at 0 °C and the reaction stirred overnight at room temperature. The solvent was removed under reduced pressure and the crude material was purified by column chromatography to afford the title compound (14 g, 69%).

[01775] Step 5: Synthesis of methyl 5-bromo-3-(ethyl (tetrahydro-2H-pyran-4-yl) amino)-2-methylbenzoate



[01776] To a stirred solution of methyl 5-bromo-2-methyl-3-((tetrahydro-2H-pyran-4-yl) amino) benzoate (14 g, 43 mmol) and acetaldehyde (3.75 g, 85 mmol) in dichloroethane (150 mL), was added acetic acid (15.4 g, 256 mmol) and the reaction stirred at room temperature for 20 minutes. Then sodium triacetoxyborohydride (27.0 g, 128 mmol) was added at 0 °C and the reaction stirred at room temperature for 2 h. The solvent was removed under reduced pressure and water added to the residue. Extraction was carried out using DCM and the combined organic layers were dried over sodium sulphate and concentrated under reduced pressure to give crude material was purified by column chromatography to afford the title compound (14 g, 93%).

[01777] Step 6: Synthesis of 5-bromo-N-((4, 6-dimethyl-2-oxo-1, 2-dihydropyridin-3-yl) methyl)-3-(ethyl (tetrahydro-2H-pyran-4-yl) amino)-2-methylbenzamide

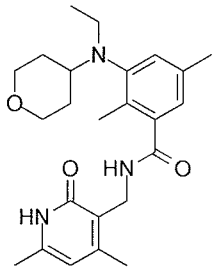


[01778] Aqueous NaOH (2.36 g, 59 mmol) was added to a solution of methyl 5-bromo-3-(ethyl (tetrahydro-2H-pyran-4-yl) amino)-2-methylbenzoate (14 g, 39 mmol) in ethanol (100 mL) and the mixture stirred at 60 °C for 1 h. The ethanol was removed under reduced pressure and the residue acidified using dilute HCl up to pH 6 and pH 4 was adjusted using citric acid.

Extraction was carried out using ethyl acetate. The combined organic layers were dried and concentrated giving the respective acid (13.9 g).

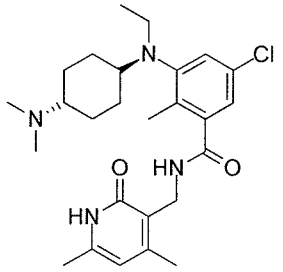
[01779] The above acid (10 g, 29 mmol) was then dissolved in DMSO (25 mL) and 3-(amino methyl)-4, 6-dimethylpyridin-2(1H)-one (8.8 g, 58 mmol) and triethyl amine (5.6 g, 58 mmol) was added. The reaction mixture was stirred at room temperature for 15 min before PYBOP (22 g, 43.8 mmol) was added and stirring was continued overnight. The mixture was poured into ice and extracted with 10 % MeOH/DCM. The combined organic layers were dried and concentrated to obtain crude material which was purified by solvent washings to afford the title compound (14 g, 74 %).

[01780] Step 7: Synthesis of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-2,5-dimethylbenzamide

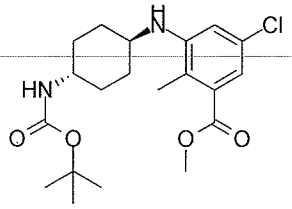


[01781] To stirred solution of 5-bromo-N-((4, 6-dimethyl-2-oxo-1, 2-dihydropyridin-3-yl) methyl)-3-(ethyl (tetrahydro-2H-pyran-4-yl) amino)-2-methylbenzamide (0.30 g, 0.63 mmol) in DMF (2 mL), was added dichlorobis (triphenylphosphine) palladium (II) (0.028 g, 0.034 mmol) followed by tetramethyl tin (0.124 g, 0.69 mmol). The mixture was heated at 160 °C for 30 minutes in a microwave reactor. The reaction mass was quenched with water and extraction was carried out using 10 %MeOH/DCM. The combined organic layers were dried and concentrated giving crude material. Purification by column chromatography and then by preparative HPLC gave the title compound as the corresponding TFA salt (0.15 g, 57.7 %). LCMS: 412.15 $(M + 1)^+$; HPLC: 94.29% (@ 254 nm) (R_t;4.245; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 μ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 μL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (CD3OD, 400 MHz) δ 7.54 (s, 1H), 7.33 (s, 1H), 6.13 (s, 1H), 4.47 (s, 2H), 3.95-3.98 (m, 4H), 3.74 (bs, 2H), 3.37 (m, 1H), 2.42 (s, 3H), 2.38 (s, 3H), 2.37 (s, 3H), 2.24 (s, 3H), 1.61-1.91 (bs, 4H), 1.01 (t, 3H, J=3.2 Hz).

[01782] **Compound 222: 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1s,4s)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methylbenzamide**

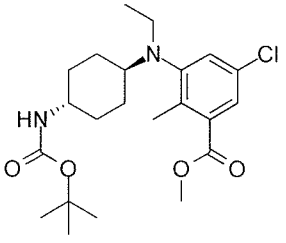


[01783] Step 1: Synthesis of methyl 3-(((1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl)amino)-5-chloro-2-methylbenzoate



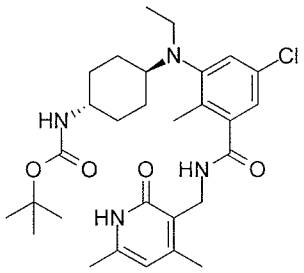
[01784] To a stirred solution of methyl 3-amino-5-chloro-2-methyl benzoate (5.0 g, 25 mmol) and tert-butyl (4-oxocyclohexyl)carbamate (6.95 g, 32.6 mmol) in 25 ml of dichloroethane, was added acetic acid (9.0 mL, 450.75 mmol) at room temperature. The reaction mixture was cooled and sodium triacetoxyborohydride (22.8 g, 108 mmol) was added and the mixture stirred at room temperature overnight. The mixture was neutralized with sat. $NaHCO_3$ and extracted with DCM. The combined organic phases were dried over Na_2SO_4, concentrated under reduced pressure and the product isomers separated by silica gel (100-200) column chromatography to give the less polar as *cis*-isomer, methyl 3-(((1s,4s)-4-((tert-butoxycarbonyl)amino)cyclohexyl)amino)-5-chloro-2-methylbenzoate (5.2 g, 52%) and the more polar title compound *trans*-isomer, methyl 3-(((1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl)amino)-5-chloro-2-methylbenzoate (3.5 g, 35%).

[01785] Step 2 : Synthesis of methyl 3-(((1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl)(ethyl) amino)-5-chloro-2-methylbenzoate



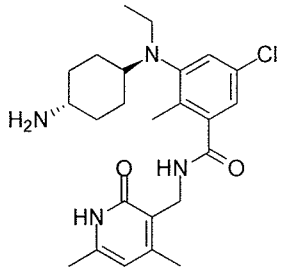
[01786] To a stirred solution of methyl 3-(((1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl)amino)-5-chloro-2-methylbenzoate (3.0 g, 7.6 mmol) and acetaldehyde (0.66 g, 15 mmol) in 15 ml of dichloroethane, was added acetic acid (2.72 mL, 45.45 mmol) and the mixture stirred at room temperature for 20 minutes. The reaction mixture was cooled to 0 °C and sodium triacetoxyborohydride (4.81 g, 22.72 mmol) was added and the mixture stirred at room temperature overnight. The reaction mixture was neutralized with sat. $NaHCO_3$ extracted with DCM. The combined organic phases were dried over Na_2SO_4, concentrated under reduced pressure and the crude material purified by silica gel (100-200) column chromatography to yield the title compound (3.5 g, 96%).

[01787] Step 3: Synthesis of tert-butyl((1r,rs)-4-((5-chloro-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(ethyl)amino)cyclohexyl) carbamate



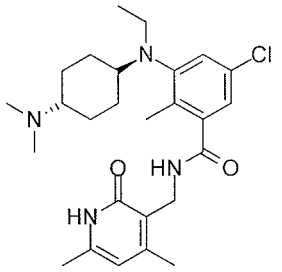
[01788] A mixture of methyl 3-(((1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl)(ethyl) amino)-5-chloro-2-methylbenzoate (3.5 g, 8.2 mmol) and NaOH (0.49 g, 12 mmol) in 20 ml of ethanol:water (4:1) was heated at 70 °C for 2 h. The reaction mixture was cooled to 0 °C and acidified to pH 6 by using 1N HCl. The mixture was concentrated and the residue partitioned between water and ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford 3.2 g of crude acid. A mixture of the crude acid (3.2 g, 7.8 mmol), 3-(aminomethyl)-4,6-dimethylpyridin-2(1H)-one (2.36 mg, 15.5 mmol) and PyBOP (6.07 mg, 11.7 mmol) was stirred in 15 ml of DMSO at room temperature overnight. The reaction mixture was diluted with water and extracted with 10% MeOH in DCM. The organic layer was dried over Na_2SO_4, concentrated under reduced pressure and the residue purified by silica gel (100-200) column chromatography to give the title compound (3.0 g, 71%).

[01789] Step 4: Synthesis of 3-(((1r,4r)-4-aminocyclohexyl)(ethyl)amino)-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide



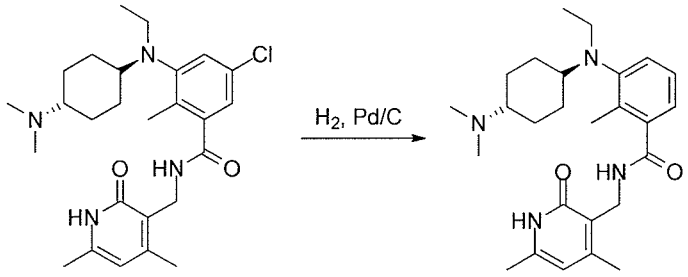
[01790] To a cooled solution of tert-butyl((1r,4r)-4-((5-chloro-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(ethyl)amino)cyclohexyl) carbamate (400 mg, 0.73 mmol) in 5 ml of DCM, 2 ml of TFA was added and the reaction mixture stirred at room temperature for 2 h. The reaction mixture was concentrated to dryness under reduced pressure. The crude product was dissolved in 10% MeOH in DCM and washed with sat $NaHCO_3$, water and brine. The organic phase was dried over Na_2SO_4, concentrated under reduced pressure to afford the title compound (320 mg, 98%).

[01791] Step 5: Synthesis of 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methylbenzamide



[01792] To a stirred solution of 3-(((1r,4r)-4-aminocyclohexyl)(ethyl)amino)-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide (300 mg, 0.67 mmol) and formaldehyde (0.5 ml of 38% solution, 6.75 mmol) in 3 ml of methanol, sodium triacetoxyborohydride (83.0 mg, 1.35 mmol) was added at 0 °C and the mixture stirred at room temperature for 3 h. The reaction mixture was concentrated to dryness and partitioned between water and 10% MeOH in DCM. The organic layer was dried over Na_2SO_4, concentrated under reduced pressure and the crude material was purified over basic alumina to yield the title compound (120 mg, 32%).

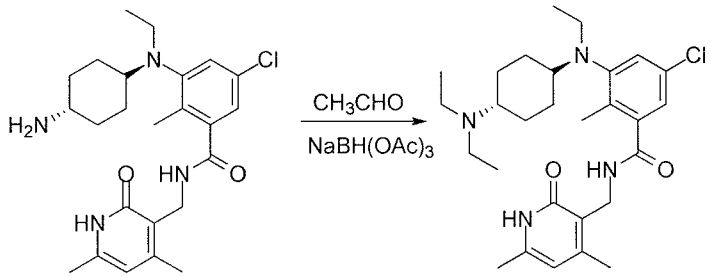
[01793] **Compound 268: N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methylbenzamide**



[01794] To a solution of 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methylbenzamide (80 mg, 0.16 mmol) in 5 mL of methanol, was added a catalytic amount of 10% palladium on carbon. The mixture was stirred under hydrogen atmosphere at balloon pressure for 13 h. The reaction mixture was filtered through a bed of celite, concentrated under reduced pressure to a viscous oil which on ether washing afforded the title compound (40 mg, 54%) as an off-white solid.

[01795] LCMS: 439.25 $(M + 1)^+$; HPLC: 88.61% (@ 254 nm) (R_t4.084; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 μ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 μL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.46 (bs, 1H), 8.03 (t, 1H), 7.15-7.13 m, 2H), 6.94 (d, 1H), 4.26 (d, 2H, J=4.4Hz), 3.02(d, 2H, J= 6.8 Hz), 2.61 (s, 6H),2.18 (s 6H), 2.10 (s, 3H), 1.97-1.83 (m, 4H),1.39 (m, 4H), 0.8 (t, 3H, J=6.8 Hz), (3H merged in solvent peak).

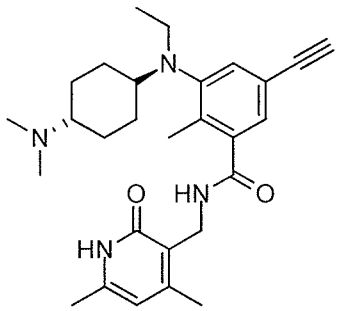
[01796] **Compound 273: 5-chloro-3-(((1s,4s)-4-(diethylamino)cyclohexyl)(ethyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide**



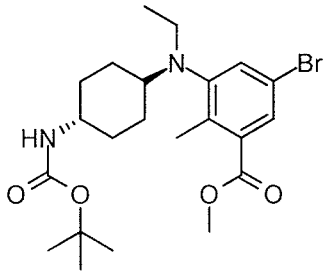
[01797] To a stirred solution of 3-(((1r,4r)-4-aminocyclohexyl)(ethyl)amino)-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide (150 mg, 0.33 mmol) and acetaldehyde (0.15 ml, 2.70 mmol) in 5 ml of dichloroethane, acetic acid (0.14 mL, 2.36 mmol) was added and the mixture stirred at room temperature for 20 minutes. The

reaction mixture was cooled to 0 °C and sodium triacetoxyborohydride (286 mg, 1.35 mmol) was added and the mixture stirred at room temperature overnight. The reaction mixture was neutralized with sat. $NaHCO_3$ and extracted with DCM, dried over Na_2SO_4 and concentrated under reduced pressure to a residue. Purification by prep. HPLC gave the title compound (100 mg, 59%). LCMS: 501.50 $(M + 1)^+$; HPLC: 93.90% (@ 210-370 nm) (R_t;4.543; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 μ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 μL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^1H NMR (DMSO-d_6, 400 MHz) δ 11.45 (bs, 1H), 8.21 (t, 1H), 7.13 (s, 1H), 6.92 (s, 1H), 5.85 (s, 1H), 4.25 (d, 2H, J = 3.6 Hz), 3.03-3.01 (m, 2H), 2.67-2.61 (m, 2H), 2.42-2.33 (m, 4H), 2.19 (s, 3H), 2.14 (s, 3H), 2.11 (s, 3H), 1.73 (m, 4H), 1.39-1.19 (m, 4H), 0.92 (m, 6H), 0.78 (t, 3H).

[01798] **Compound 277: N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-5-ethynyl-2-methylbenzamide**



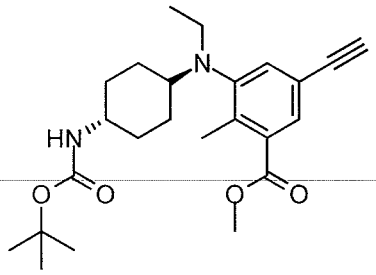
[01799] Step 1: Synthesis of methyl 5-bromo-3-(((1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl) (ethyl)amino)-2-methylbenzoate.



[01800] To a stirred solution of methyl 5-bromo-3-(((1r,4r)-4-((tert-butoxycarbonyl)amino) cyclohexyl)amino)-2-methylbenzoate 6.0 g, 13.0 mmol) and acetaldehyde (1.5 ml, 27.0 mmol) in dichloroethane (60 mL), was added acetic acid (5.4 ml, 82 mmol) and the mixture was stirred at room temperature for 20 minutes. Sodium triacetoxyborohydride (8.6 g, 41 mmol)

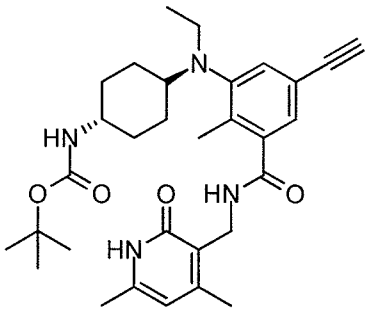
was added at 0 °C and the mixture stirred at room temperature for 2 h. The reaction mixture was neutralized with sat. $NaHCO_3$ and was extracted with DCM. The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel (100-200) column chromatography to afford the title compound (5.0 g, 79%).

[01801] Steps 2 and 3: Synthesis of methyl 3-(((1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl) (ethyl) amino)-5-ethynyl-2-methylbenzoate.



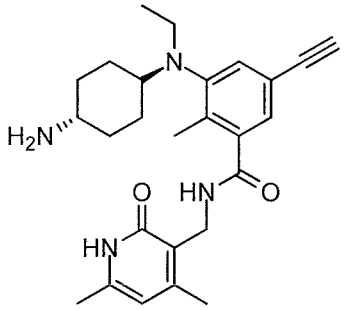
[01802] A solution of methyl 5-bromo-3-(((1r,4r)-4-((tert-butoxycarbonyl)amino) cyclohexyl)(ethyl)amino)-2-methylbenzoate (1.5 g, 3.20 mmol), trimethylsilyl acetylene (0.52 ml, 3.84 mmol), copper iodide (12 mg, 0.06 mmol) and N,N-diisopropyl amine (1.0 ml, 8.38 mmol) in 20 ml of toluene was purged with argon. Dichloro-bis(triphenyl phosphine) palladium (II) (44 mg, 0.06 mmol) was added the reaction mixture heated at 80 °C for 16 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and washed with water. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to obtain 1.8 g of crude silyl protected compound. This was dissolved in 15 ml of THF and *tetra*-butylammonium fluoride (7.5 ml of 1M solution in THF, 7.40 mmol) was added at room temperature. The mixture stirred for 2h,diluted with ethyl acetate and washed with water. The organic layer was dried over Na_2SO_4, concentrated under reduced pressure, and the residue purified by silica gel (100-200) column chromatography to give the title compound (800 mg, 52%).

[01803] Steps 4 and 5: Synthesis of tert-butyl ((1r,4r)-4-((3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-5-ethynyl-2-methylphenyl)(ethyl)amino)cyclohexyl) carbamate.



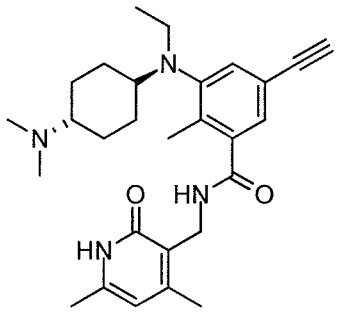
[01804] A mixture of methyl 3-(((1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl) (ethyl) amino)-5-ethynyl-2-methylbenzoate (800 mg, 1.92 mmol) and NaOH (115 mg, 2.89 mmol) in 12 ml of ethanol:water (3:1) was heated at 70 °C for 2 h. The reaction mixture was concentrated to dryness and the residue was partitioned between water and DCM. The organic layer was dried over $Na_2SO_4$and concentrated under reduced pressure to afford 700 mg of the crude acid. The crude acid (700 mg, 1.75 mmol), 3-(aminomethyl)-4,6-dimethylpyridin-2(1H)-one (532 mg, 3.5 mmol) and PyBOP (1.36 g, 2.6 mmol) were stirred in 7 ml of DMSO at room temperature overnight. The reaction mixture was diluted with water, and the precipitated product was filtered and purified by silica gel column chromatography to give the title compound (750 mg, 80%).

[01805] Step 6: Synthesis of 3-(((1r,4r)-4-aminocyclohexyl)(ethyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-ethynyl-2-methylbenzamide.



[01806] To a cooled solution of tert-butyl ((1r,4r)-4-((3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-5-ethynyl-2-methylphenyl)(ethyl)amino)cyclohexyl)carbamate (750 mg, 1.40 mmol) in 10 ml of DCM, was added 3 ml of TFA The mixture was stirred at rt for 2 h and was concentrated to dryness under reduced pressure. The residue was dissolved in 10% MeOH in DCM and washed with sat $NaHCO_3$, water and brine. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to give the crude title compound (600 mg, 98%).

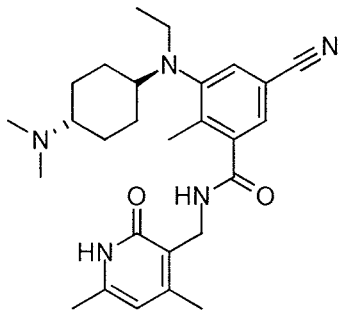
[01807] Step 7: Synthesis of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-5-ethynyl-2-methylbenzamide.



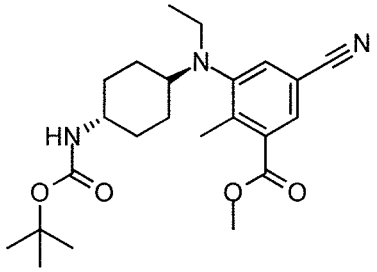
[01808] To a stirred solution of crude 3-(((1r,4r)-4-aminocyclohexyl)(ethyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-ethynyl-2-methylbenzamide (600 mg, 1.38 mmol) and formaldehyde (0.4 ml of 38% solution, 6.75 mmol) in 10 ml of dichloroethane was added sodium triacetoxyborohydride (731 mg, 3.45 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 3 h and partitioned between water and 10% MeOH in DCM The organic layer was separated, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified over basic alumina to give the title compound (450 mg, 70%).

[01809] Analytical Data for N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-5-ethynyl-2-methylbenzamide -TFA salt : LCMS: 463.65 $(M + 1)^+$; HPLC: 92.65% (@ 254 nm) (R_t;4.748; Method: Column: YMC ODS-A 150 mm x 4.6 mm x 5 μ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 μL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.46 (bs, 1H), 9.43(bs, 1H), 8.23 (t, 1H), 7.36 (s, 1H), 7.12 (s, 1H), 5.87 (s, 1H), 4.26 (d, 2H, J=4.0Hz), 3.17-3.03(m, 4H),2.69-2.68 (m, 6H), 2.50 (1H merged in solvent peak), 2.21 (s, 3H), 2.19 (s, 3H), 2.11 (s, 3H), 1.96-1.84 (m, 4H), 1.43 (m, 4H), 0.79 (t, 3H).

[01810] **Compound 278: 5-cyano-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methylbenzamide**

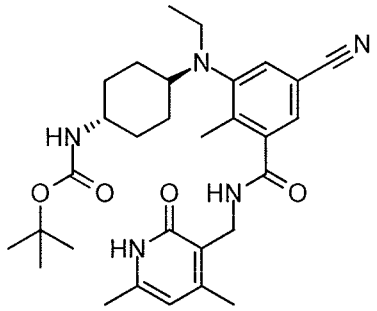


[01811] Step 1: Synthesis of methyl 3-(((1s,4s)-4-((tert-butoxycarbonyl)amino)cyclohexyl)(ethyl) amino)-5-cyano-2-methylbenzoate.



[01812] A solution of compound methyl 5-bromo-3-(((1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl) (ethyl)amino)-2-methylbenzoate (1.0 gm, 2.13 mmol) and $Zn(CN)_2$ (370 mg, 3.19 mmol) in 6 ml of DMF was degassed with argon for 20 min followed by addition of $Pd(PPh_3)_4$ (240 mg, 0.21 mmol). The mixture was heated at 100 °C overnight, diluted with water and was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, concentrated and the residue purified by silica gel column chromatography to give the title compound (280 mg, 82%).

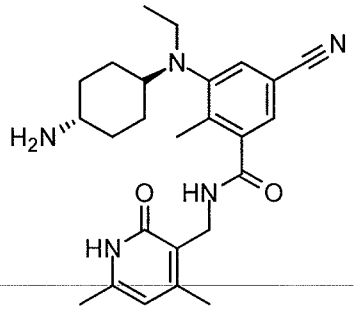
[01813] Steps 2 and 3: Synthesis of *tert*-butyl ((1r,4r)-4-((5-cyano-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(ethyl)amino)cyclohexyl) carbamate.



[01814] A mixture of methyl 3-(((1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl) (ethyl)amino)-5-cyano-2-methylbenzoate (735 mg, 1.78 mmol) and NaOH (85 mg, 2.13 mmol) in 12 ml of ethanol:water (3:1) was heated at 70 °C for 2 h. The mixture was concentrated to dryness and the crude product was partitioned between water and DCM. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford 380 mg of crude acid. A mixture of the crude acid (380 mg, 0.94 mmol), 3-(aminomethyl)-4,6-dimethylpyridin-2(1H)-one (287 mg, 1.89 mmol) and PyBOP (737 mg, 1.41 mmol) in 4 ml of DMSO was stirred at room temperature overnight. The reaction mixture was diluted with water and was extracted

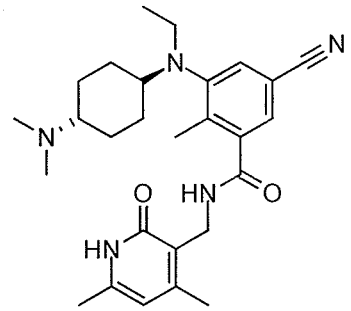
with 10% MeOH in DCM. The combined organic phases were dried over Na2SO4, concentrated under reduced pressure and the residue purified by silica column chromatography to afford the title compound (350 mg, 75%).

[01815] Step 4: Synthesis of 3-(((1r,4r)-4-aminocyclohexyl)(ethyl)amino)-5-cyano-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide.



[01816] To a cooled solution of compound tert-butyl ((1r,4r)-4-((5-cyano-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(ethyl)amino)cyclohexyl)carbamate (350 mg, 0.80 mmol) in 5 ml of DCM, was added 1 ml of TFA. The mixture was stirred at rt for 2 h. and concentrated to dryness under reduced pressure. The residue was dissolved in 10% MeOH in DCM and washed with sat $NaHCO_3$, water and brine. The organic phase was dried over Na_2SO_4, and concentrated under reduced pressure to obtain 284 mg of the crude title compound.

[01817] Step 5: Synthesis of 5-cyano-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methylbenzamide.

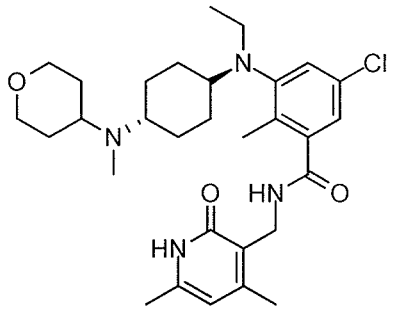


[01818] To a stirred solution of crude 3-(((1r,4r)-4-aminocyclohexyl)(ethyl)amino)-5-cyano-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide (325 mg, 0.74 mmol) and formaldehyde (0.3 ml of 38% solution, 3.72 mmol) in 10 ml of methanol, sodium cyanoborohydride (100 mg, 1.49 mmol) was added at 0 °C. The mixture was stirred at room temperature for 4 h and partitioned between water and 10% MeOH in DCM. The organic layer

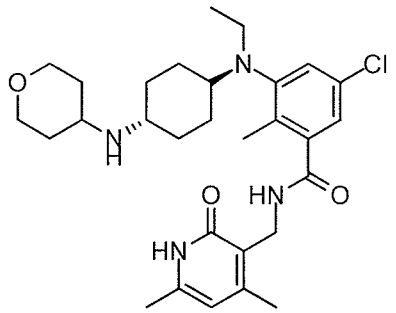
was dried over Na_2SO_4, concentrated under reduced pressure and the residue was purified by basic alumina column purification to give the title compound (75 mg, 22%).

[01819] Analytical Data of 5-cyano-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1s,4s)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methylbenzamide: LCMS: 464.30 $(M + 1)^+$; HPLC: 87.24% (@ 254 nm) (R_t;4.540; Method: Column: YMC ODS-A 150 mm x 4.6 mm x 5 μ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 μL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.47 (bs, 1H), 8.31 (t, 1H), 7.61 (s, 1H), 7.35 (s, 1H), 5.87 (s, 1H), 4.26 (d, 2H, J=4.4 Hz), 3.07-3.05(m, 3H), 2.73-2.63 (m, 7H), 2.25 (s, 3H), 2.20 (s, 3H), 2.11 (s, 3H), 1.96-1.82 (m, 4H), 1.41-1.37 (m, 4H), 0.78 (t, 3H).

[01820] **Compound 279: 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((1r,4r)-4-(methyl(tetrahydro-2H-pyran-4-yl)amino)cyclohexyl)amino)-2-methylbenzamide**



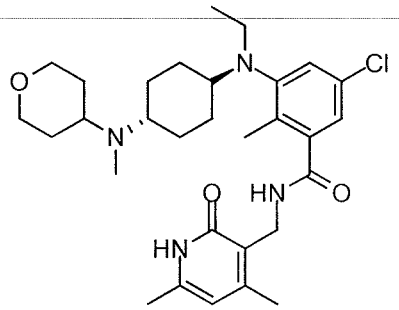
[01821] Step 1: Synthesis of 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((1r,4r)-4-(methyl(tetrahydro-2H-pyran-4-yl)amino)cyclohexyl)amino)-2-methylbenzamide.



[01822] To a stirred solution of 3-(((1r,4r)-4-aminocyclohexyl)(ethyl)amino)-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide (300 mg, 0.67

mmol) and dihydro-2H-pyran-4(3H)-one (99 mg, 1.01 mmol) in 5 ml of dichloroethane, was added acetic acid (0.24 mL, 4.05 mmol) and the mixture stirred at room temperature for 20 minutes. The mixture was cooled to 0 °C and sodium triacetoxyborohydride (429 mg, 2.02 mmol) was added and the reaction stirred at room temperature overnight. The reaction mixture was neutralized with sat. $NaHCO_3$ and extracted with DCM. The combined organic phases were dried over Na_2SO_4, concentrated under reduced pressure and the residue purified by silica gel column chromatography to give the title compound (175 mg, 57%).

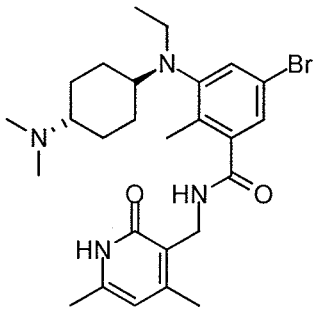
[01823] Step 2: Synthesis of 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((1r,4r)-4-(methyl(tetrahydro-2H-pyran-4-yl)amino)cyclohexyl)amino)-2-methylbenzamide.



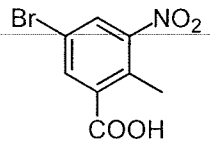
[01824] To a stirred solution of 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((1r,4r)-4-((tetrahydro-2H-pyran-4-yl)amino)cyclohexyl)amino)-2-methylbenzamide (175 mg, 0.33 mmol) and formalin (99 mg, 3.31 mmol) in 2 ml of methanol was added sodium cyanoborohydride (41 mg, 0.66 mmol) at 0 °C. The mixture was stirred at room temperature overnight , neutralized with sat. $NaHCO_3$ and extracted with DCM. The combined organic phases were dried over Na_2SO_4, concentrated under reduced pressure and the residue purified by preparative HPLC to afford the title compound (70 mg, 39%).

[01825] LCMS: 543.65 $(M + 1)^+$; HPLC: 98.19% (@ 210-370 nm) (R_t;4.515; Method: Column: YMC ODS-A 150 mm x 4.6 mm x 5 μ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 μL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.45 (bs, 1H), 8.21 (t, 1H), 7.13 (s, 1H), 6.92 (s, 1H), 5.85 (s, 1H), 4.25 (d, 2H, J = 4 Hz), 3.84-3.82 (m, 2H), 3.26-3.23 (m, 3H), 3.03-3.01 (m, 2H), 2.67-2.53 (m, 2H), 2.19 (s, 3H), 2.14 (s, 3H), 2.11 (s, 6H), 1.75-1.57 (m, 6H), 1.41-1.24 (m, 6H), 0.78 (t, 3H).

[01826] **Compound 276: Synthesis of compound 5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methylbenzamide**

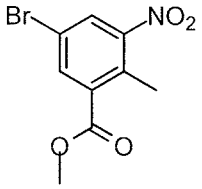


[01827] Step 1: Synthesis of 5-bromo-2-methyl-3-nitrobenzoic acid



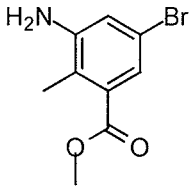
[01828] To stirred solution of compound 2-methyl-3-nitrobenzoic acid (50.0 g, 276 mmol) in conc. H_2SO_4 (200 mL), 1,3-dibromo-5,5-dimethyl-2,4-imidazolidinedione (43.4 g, 152 mmol) was added portionwise at room temperature and stirring was continued for 5 h. On completion, the reaction mass was poured on ice cold water, the solid precipitate was filtered, washed with water and dried under vacuum giving the crude title compound (71.7 g, 99.9%) which was used without further purification..

[01829] Step 2: Synthesis of methyl 5-bromo-2-methyl-3-nitrobenzoate.



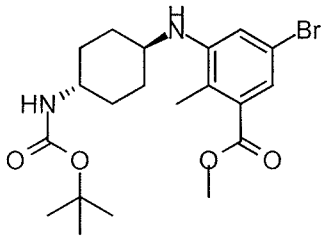
[01830] To a stirred solution of crude 5-bromo-2-methyl-3-nitrobenzoic acid (287 g, 1103 mmol) in DMF (150 mL), sodium carbonate (468 g, 4415 mmol) and methyl iodide (626 g, 4415 mmol) were added. The mixture was heated at 60 °C for 8 h, cooled to room temperature. The solid precipitate was filtered and washed with diethyl ether (5 times). The combined organic layers were dried and concentrated under reduced pressure to give the title compound (302 g, 99%) which was used directly.

[01831] Step 3: Synthesis of methyl 3-amino-5-bromo-2-methylbenzoate.



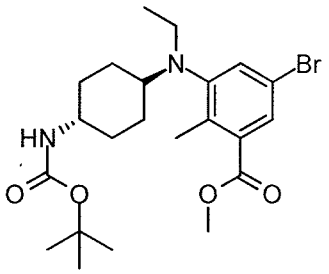
[01832] To a stirred solution of above crude compound methyl 5-bromo-2-methyl-3-nitrobenzoate (150 g, 0.54 mol) in ethanol (750 mL), ammonium chloride (150 g, 2.78 mol) dissolved in 750 ml of water was added followed by iron powder (93.3 g, 1.64 mol) with vigorous stirring. The mixture was heated at 80 °C for 7 hand filtered through celite. The filter pad was washed with water and ethyl acetate and the filtrates were extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give the title compound (175g crude).

[01833] Step 4: Synthesis of methyl 5-bromo-3-(((1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl) amino)-2-methylbenzoate.



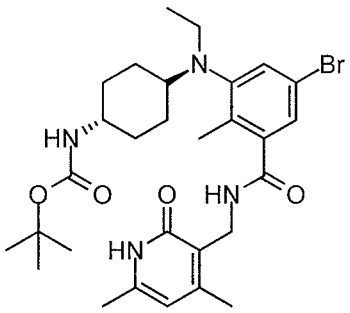
[01834] To a stirred solution of crude compound methyl 3-amino-5-bromo-2-methylbenzoate (15 g, 62 mmol) and tert-butyl (4-oxocyclohexyl)carbamate (17 g, 8 mmol) in dichloroethane (200 mL), was added acetic acid (23 ml, 368 mmol) and the reaction stirred at room temperature for 10 min. Sodium triacetoxyborohydride (40 g, 185mmol) was added at 0 °C and the mixture stirred at room temperature for overnight. The reaction mixture was neutralized with sat. $NaHCO_3$ and extracted with DCM. The combined organic phases were dried over Na_2SO_4, and concentrated under reduced pressure. Separation by column chromatography of the crude isomeric mixture gave desired the title compound (6.0 g, 22%).

[01835] Step 5: Synthesis of methyl 5-bromo-3-(((1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl) (ethyl)amino)-2-methylbenzoate.



[01836] To a stirred solution of compound methyl 5-bromo-3-(((1r,4r)-4-((tert-butoxycarbonyl) amino)cyclohexyl) amino)-2-methylbenzoate (6.0 g, 13.0 mmol) and acetaldehyde (1.5 ml, 27.0 mmol) in dichloroethane (60 mL)was added acetic acid (5.4 ml, 82 mmol) and the mixture was stirred at room temperature for 20 minutes. Sodium triacetoxyborohydride (8.6 g, 40.9 mmol) was added at 0 °C and the mixture stirred at room temperature for 2 h. The reaction mixture was neutralized with sat. $NaHCO_3$ and extracted with DCM. The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography to afford the title compound (5.0 g, 79%).

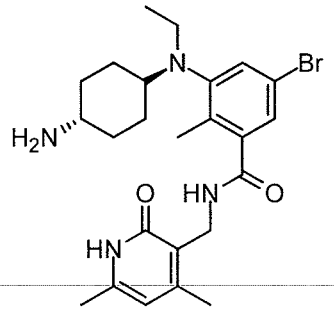
[01837] Steps 6 and 7: Synthesis of tert-butyl ((1r,4r)-4-((5-bromo-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(ethyl)amino) cyclohexyl)carbamate.



[01838] A mixture of methyl 5-bromo-3-(((1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl) (ethyl)amino)-2-methylbenzoate (1.00 g, 2.13 mmol) and NaOH (102 mg, 2.56 mmol) in 6 ml of ethanol:water (2:1) was heated at 70 °C for 2 h. The reaction mixture was concentrated to dryness and the residue was partitioned between water and DCM. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford 1.0 g of crude acid. The crude acid (1.0 g, 2.20 mmol), 3-(aminomethyl)-4,6-dimethylpyridin-2(1H)-one (669 mg, 4.40 mmol), PyBOP (1.71 g, 3.30 mmol) and 1 ml of triethyl amine were stirred in 2 ml of DMSO at room temperature overnight. The reaction mixture was diluted with water and extracted with

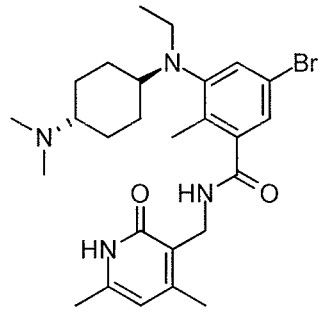
DCM. The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure and the residue purified by silica gel column chromatography to give the title compound (1.0 g, 83%).

[01839] Step 8: Synthesis of 3-(((1r,4r)-4-aminocyclohexyl)(ethyl)amino)-5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide.



[01840] To a cooled solution of compound tert-butyl ((1r,4r)-4-((5-bromo-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(ethyl)amino) cyclohexyl)carbamate (1.0 g, 1.60 mmol) in 10 ml of DCM, was added 2 ml of TFA. The reaction mixture was stirred at rt for 2 h, and concentrated to dryness under reduced pressure. The residue was dissolved in 10% MeOH in DCM and washed with sat $NaHCO_3$, water and brine. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to give the crude title compound (650 mg, 81%).

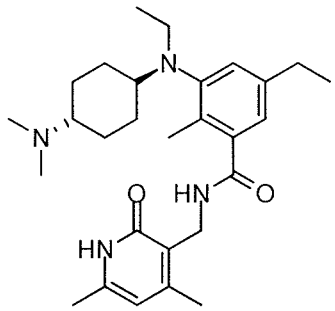
[01841] Step 9: Synthesis of 5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methylbenzamide.



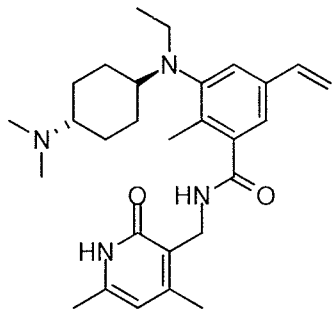
[01842] To a stirred solution of crude 3-(((1r,4r)-4-aminocyclohexyl)(ethyl)amino)-5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide (650 mg, 1.32 mmol) and formaldehyde (0.5 ml of 38% solution, 13.3 mmol) in 10 ml of methanol, was added sodium cyanoborohydride (82 mg, 1.32 mmol at 0 °C and the mixture stirred at room temperature overnight. The reaction mixture was partitioned between water and 10% MeOH in

DCM. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by basic alumina column purification to give the title compound (450 mg, 65%). Analytical data of 5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methylbenzamide: LCMS: 519.30 $(M+1)^+$; HPLC: 98.35% (@ 254nm) (R_t; 4.392); Method: Column: YMC ODS-A 150 mm x 4.6 mm x 5 μ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 μL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.46 (bs, 1H), 9.39 (bs, 1H), 8.23 (t, 1H), 7.30 (s, 1H), 7.09 (s, 1H), 5.86 (s, 1H), 4.25 (d, 2H, J=4.0 Hz),3.03-3.01 (m, 3H), 2.69-2.69 (m, 6H), 2.50 (1H merged in solvent peak), 2.18 (s, 3H), 2.14 (s, 3H), 2.11 (s, 3H), 1.94-1.84 (m, 4H), 1.42 (m, 4H), 0.79 (t, 3H, J=6.8 Hz).

[01843] **Compound 282: N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-5-ethyl-2-methylbenzamide**



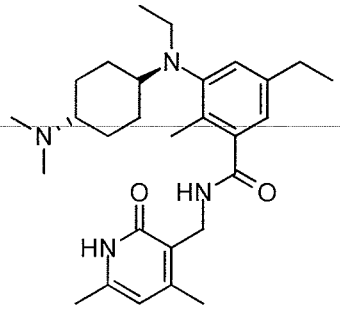
[01844] Step 1: Synthesis of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methyl-5-vinylbenzamide.



[01845] A mixture of 5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methylbenzamide (200 mg, 0.38 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (71 mg, 0.46 mmol) and sodium

carbonate (147 mg, 1.39 mmol) in 10 ml of dioxane was degassed with argon for 20 min, $Pd(PPh_3)_4$ (44 mg, 0.04 mmol) was added and the mixture heated at 100 °C overnight. The reaction was cooled to room temperature and diluted with water. The mixture was extracted with 10% MeOH in DCM, the combined organic phases dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography to obtain the title compound (150 mg, 83 %).

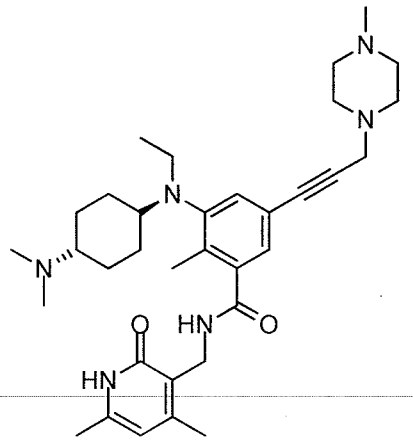
[01846] Step 2: Synthesis of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-5-ethyl-2-methylbenzamide.



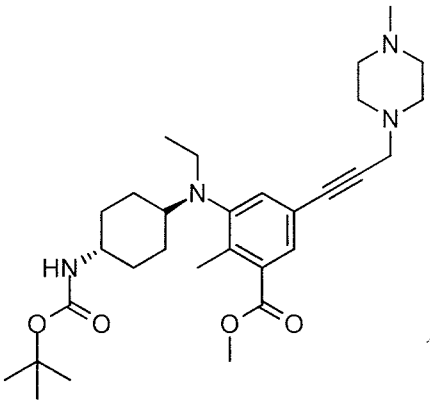
[01847] To a solution of compound N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methyl-5-vinylbenzamide (150 mg, 0.32 mmol) in 5 mL of methanol, was added a catalytic amount of 10% palladium on carbon The mixture was stirred under hydrogen atmosphere at balloon pressure for 12 h, filtered through celite, and concentrated under reduced pressure. The residue was purified by prep. HPLC to give the title compound as a TFA salt (65 mg, 43%).

[01848] LCMS: 467.35 $(M+1)^+$; HPLC: 93.41% (@ 254 nm) (R_t;10.946; Method: Column: YMC ODS-A 150 mm x 4.6 mm x 5 μ; Mobile Phase: A; 10m M ammonium formate in water + 0.1% NH_3, B; Acetonitrile + 5% solvent A + 0.1% NH_3; Inj. Vol: 10 μL, Col. Temp.: 30 °C; Flow rate: 1.0 mL/min.; Gradient: 15% B to 95% B in 6.0 min, Hold till 8.0 min, 15% B at 8.5 min hold up to 15 min); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.47 (bs, 1H), 9.45 (s, 1H), 8.38 (s, 1H), 8.03 (s, 2H), 7.26-6.84 (m, 2H), 5.87 (s, 1H), 4.26 (d, J = 4.0 Hz, 2H), 3.17-2.89 (m, 3H), 2.70, 2.68 (2s, 6H), 2.19, 2.11 (3s, 9H), 1.96-1.87 (m, 4H), 1.42 (m, 4H), 1.15 (t, J = 7.2 Hz, 3H), 0.80 (s, 3H).

[01849] **Compound 283: N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methyl-5-(3-(4-methylpiperazin-1-yl)prop-1-yn-1-yl)benzamide**

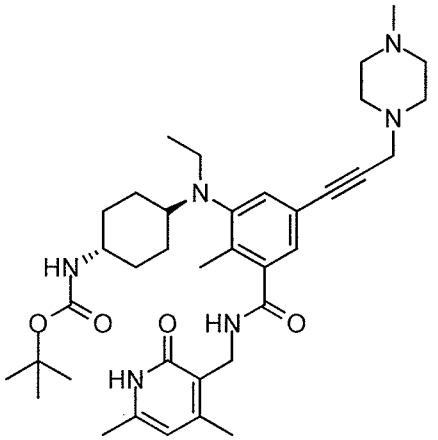


[01850] Step 1 Synthesis of methyl 3-(((1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl)(ethyl) amino)-2-methyl-5-(3-(4-methylpiperazin-1-yl)prop-1-yn-1-yl)benzoate.



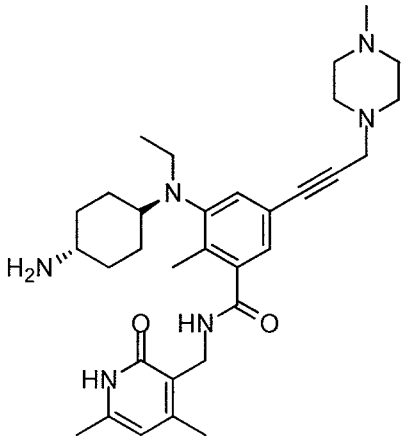
[01851] A solution of methyl 5-(3-bromoprop-1-yn-1-yl)-3-(((1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl)(ethyl)amino)-2-methylbenzoate (500 mg, 1.0 mmol) and 1-methylpiperazine (0.49 ml, 4.9 mmol) in 5 ml of DMF was stirred at room temperature overnight. The reaction mixture was diluted with water and extracted with DCM. The combined organic phases were dried over Na_2SO_4, and concentrated under vacuum to give the title compound (550 mg).

[01852] Steps 2 and 3: Synthesis of tert-butyl ((1r,4r)-4-((3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methyl-5-(3-(4-methylpiperazin-1-yl)prop-1-yn-1-yl)phenyl) (ethyl)amino)cyclohexyl)carbamate.



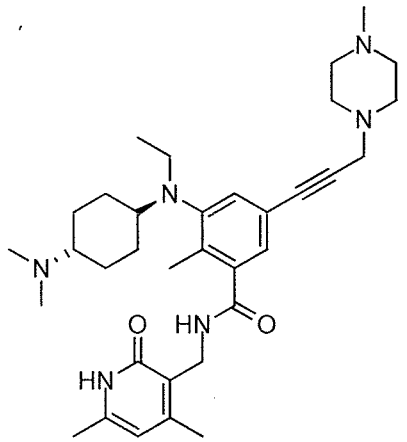
[01853] A mixture of compound methyl 3-(((1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl)(ethyl) amino)-2-methyl-5-(3-(4-methylpiperazin-1-yl)prop-1-yn-1-yl)benzoate (550 mg, 1.0 mmol) and NaOH (83 mg, 2.1 mmol) in 8 ml of ethanol:water (3:1) was heated at 70 °C for 2 h. The reaction mixture was concentrated to dryness and the residue was partitioned between water and DCM. The organic layer was dried over Na_2SO_4, concentrated under reduced pressure to afford 470 mg of acid. The crude acid (470 mg, 0.92 mmol), 3-(aminomethyl)-4,6-dimethylpyridin-2(1H)-one (279 mg, 1.83 mmol), PyBOP (716 mg, 1.37 mmol) and triethyl amine (0.38 ml, 2.75 mmol) mixture were stirred in 5 ml of DMSO at room temperature overnight. The reaction mixture was diluted with water and the compound was extracted into 10% MeOH in DCM. The organic layer was dried over Na_2SO_4, concentrated under reduced pressure and the residue purified by silica gel column chromatography to give the title compound (350 mg, 50%).

[01854] Step 4: Synthesis of 3-(((1r,4r)-4-aminocyclohexyl)(ethyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-5-(3-(4-methylpiperazin-1-yl)prop-1-yn-1-yl)benzamide.



[01855] To a cooled solution of tert-butyl ((1r,4r)-4-((3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methyl-5-(3-(4-methylpiperazin-1-yl)prop-1-yn-1-yl)phenyl)(ethyl)amino)cyclohexyl)carbamate (350 mg, 0.54 mmol) in 5 ml of DCM, were added 2 ml of TFA . The reaction mixture was stirred at rt for 2 h, concentrated to dryness under reduced pressure. The residue was dissolved in 10% MeOH in DCM and washed with sat $NaHCO_3$, water and brine. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to obtain the crude title compound (250 mg, 84%).

[01856] Step 5: Synthesis of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methyl-5-(3-(4-methylpiperazin-1-yl)prop-1-yn-1-yl)benzamide.

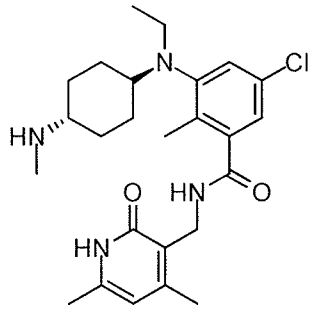


[01857] To a stirred solution of crude 3-(((1r,4r)-4-aminocyclohexyl)(ethyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-5-(3-(4-methylpiperazin-1-yl)prop-1-yn-1-yl)benzamide (250 mg, 0.45 mmol) and formaldehyde (0.35 ml of 38% solution, 4.56 mmol) in 3 ml of methanol was added sodium cyanoborohydride (85 mg, 1.37 mmol) at 0 °C.

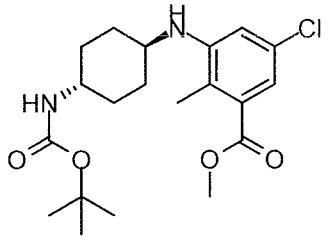
The mixture was stirred at room temperature for 4 hand partitioned between water and 10% MeOH in DCM. The organic layer was separated, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by prep. HPLC to afford the title compound as a TFA salt (40 mg, 15%).

[01858] LCMS: 575.45 $(M+1)^+$; HPLC: 99.30% (@ 254 nm) (R_t;3.849; Method: Column: YMC ODS-A 150 mm x 4.6 mm x 5 μ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 μL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (D_2O, 400 MHz) δ 7.75 (s, 1H), 7.60 (s, 1H), 6.28 (s, 1H), 4.45 (d, J = 4.0Hz, 2H), 3.80-3.63 (m, 5H), 3.40-3.21 (m, 9H), 2.92 (s, 3H), 2.79 (2s, 6H), 2.35 (m, 3H), 2.32 (s, 3H), 2.26 (s, 3H), 2.19-2.05 (m, 4H), 1.65-1.57 (m, 4H), 0.97 (t, J = 7.2 Hz, 3H).

[01859] **Compound 284: 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((1r,4r)-4-(methylamino)cyclohexyl)amino)-2-methylbenzamide**



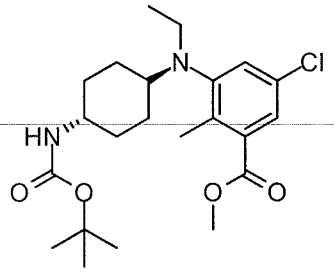
[01860] Step 1: Synthesis of methyl 3-(((1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl)amino)-5-chloro-2-methylbenzoate.



[01861] To a stirred solution of compound methyl 3-amino-5-chloro-2-methylbenzoate (5.0 g, 25 mmol) and tert-butyl (4-oxocyclohexyl)carbamate (6.95 g, 32.7 mmol) in 25 ml of dichloroethane was added acetic acid (9.0 mL, 450 mmol) and the mixture stirred at room temperature for 10 min. The mixture was cooled and sodium triacetoxyborohydride (22.8 g, 108 mmol) was added and the mixture stirred at room temperature overnight. The mixture was

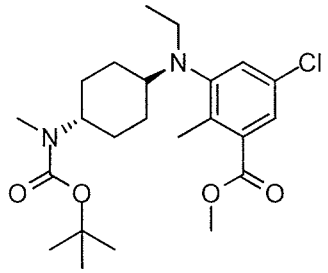
neutralized with sat. $NaHCO_3$ and was extracted with DCM. The combined organic phases were dried over Na_2SO_4, concentrated under reduced pressure and the residue was purified by silica gel column chromatography to give (3.5 g , 35%) of the more polar *trans*-isomer title compound 3-(((1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl)amino)-5-chloro-2-methylbenzoate, along with (5.2 g, 52%) of the less polar *cis*-isomer 3-(((1s,4s)-4-((tert-butoxycarbonyl)amino)cyclohexyl)amino)-5-chloro-2-methylbenzoate.

[01862] Step 2: Synthesis of methyl 3-(((1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl)(ethyl) amino)-5-chloro-2-methylbenzoate.



[01863] To a stirred solution of methyl 3-(((1r,4r)-4-((tert-butoxycarbonyl)amino) cyclohexyl)amino)-5-chloro-2-methylbenzoate (3.0 g, 7.6 mmol) and acetaldehyde (0.66 g, 15 mmol) in 15 ml of dichloroethane, was added acetic acid (2.7 mL, 45 mmol) and the mixture was stirred at room temperature for 20 minutes. The mixture was cooled to 0 °C, sodium triacetoxyborohydride (4.8 g, 22 mmol) was added and the mixture stirred at room temperature overnight. The mixture was neutralized with sat. $NaHCO_3$ and was extracted with DCM. The combined organic phases were dried over Na_2SO_4, concentrated under reduced pressure and the residue purified by silica gel column chromatography to give the title compound (3.5 g, 96%).

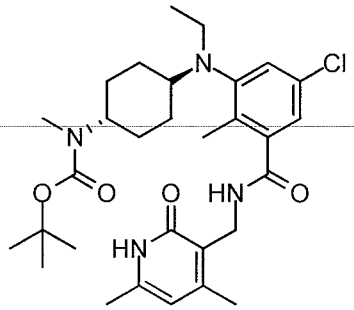
[01864] Step 3: Synthesis of methyl 3-(((1r,4r)-4-((tert-butoxycarbonyl)(methyl)amino)cyclohexyl) (ethyl)amino)-5-chloro-2-methylbenzoate.



[01865] To a cooled solution of methyl 3-(((1r,4r)-4-((tert-butoxycarbonyl)amino) cyclohexyl)(ethyl)amino)-5-chloro-2-methylbenzoate (1.1 g, 3.3 mmol) in 12 ml of THF, was

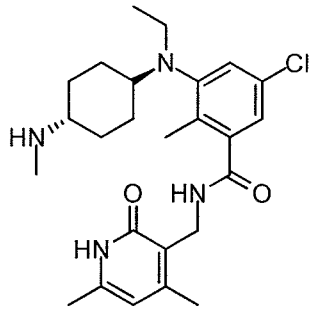
added sodium hydride (410 mg, 10 mmol) followed by methyl iodide (2.1 ml, 34 mmol), The mixture was stirred at room temperature overnight, quenched by slow addition of ice water and acidified with citric acid solution. Extraction with 10% MeOH in DCM followed by drying and concentration of the combined organic phases under reduced pressure gave the title compound (1.0 g, 88%).

[01866] Steps 4 and 5: Synthesis of tert-butyl ((1r,4r)-4-((5-chloro-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(ethyl)amino)cyclohexyl)(methyl) carbamate.



[01867] A mixture of methyl 3-(((1r,4r)-4-((tert-butoxycarbonyl)(methyl)amino) cyclohexyl)(ethyl)amino)-5-chloro-2-methylbenzoate (1.0 g, 2.4 mmol) and NaOH (140 mg, 3.5 mmol) in 10 ml of ethanol:water (4:1) was heated at 70 °C for 2 h. The reaction mixture was concentrated to dryness and the residue was partitioned between water and DCM. The organic layer was dried over Na_2SO_4, and concentrated under reduced pressure to afford 1.0 g of crude acid. A mixture of the crude acid (1.0 g, 2.4 mmol), 3-(aminomethyl)-4,6-dimethylpyridin-2(1H)-one (716 mg, 4.71 mmol), PyBOP (1.83 g, 3.53 mmol) and 2 ml of triethyl amine was stirred in 5 ml of DMSO at room temperature overnight. The mixture was diluted with water and extracted with 10% MeOH in DCM. The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure and the residue purified by silica gel column chromatography to give the title compound (700 mg, 53%).

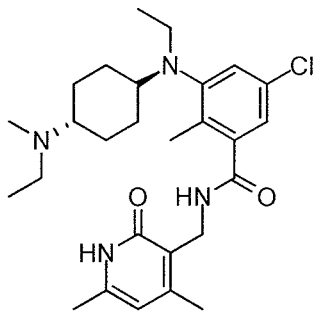
[01868] Step 6: Synthesis of 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((1r,4r)-4-(methylamino)cyclohexyl)amino)-2-methylbenzamide.



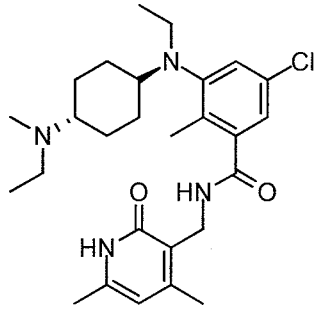
[01869] To a cooled solution of tert-butyl ((1s,4s)-4-((5-chloro-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(ethyl)amino)cyclohexyl)(methyl) carbamate (700 mg, 1.25 mmol) in 20 ml of DCM, were added 3 ml of TFA . The reaction mixture was stirred at room temperature for 2 h, and concentrated to dryness under reduced pressure. The residue was dissolved in 10% MeOH in DCM and washed with sat $NaHCO_3$, water and brine. The organic phase was dried over Na_2SO_4, concentrated under reduced pressure and the residue purified by preparative HPLC to obtain the title compound as its TFA salt (500 mg, 87%).

[01870] LCMS: 459.35 $(M+1)^+$; HPLC: 97.63% (@ 254 nm) (R_t;4.565; Method: Column: YMC ODS-A 150 mm x 4.6 mm x 5 μ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 μL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-D_6, 400 MHz) δ 11.46 (bs, 1H), 8.32 (s, 2H), 8.22 (m, 1H), 7.20 (s, 1H), 7.00 (s, 1H), 5.86 (s, 1H), 4.25 (d, J = 4.0 Hz, 2H), 3.74 (m, 3H), 3.03-3.01 (m, 3H), 2.67 (m, 1H), 2.19 (s, 3H), 2.14 (s, 3H), 2.11 (s, 3H), 1.33 (m, 2H), 1.82-1.80 (m, 2H), 1.42-1.23 (m, 2H+2H), 0.78 (t, J = 7.2 Hz, 3H).

[01871] **Compound 285: 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((1r,4r)-4-(ethyl(methyl)amino)cyclohexyl)amino)-2-methylbenzamide**

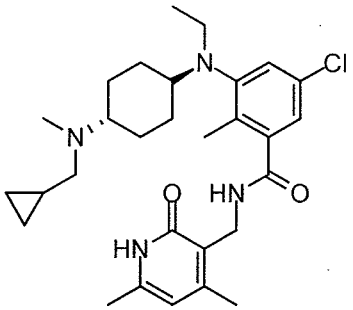


[01872] Step 1: Synthesis of 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((1r,4r)-4-(ethyl(methyl)amino)cyclohexyl)amino)-2-methylbenzamide.

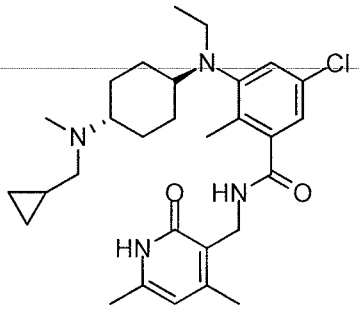


[01873] To a stirred solution of compound 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((1r,4r)-4-(methylamino)cyclohexyl)amino)-2-methylbenzamide (200 mg, 0.43 mmol) and acetaldehyde (0.03 ml, 0.43 mmol) in 5 ml of dichloroethane, was added acetic acid (0.15 mL, 2.62 mmol) and the mixture stirred at room temperature for 20 minutes. The mixture was cooled to 0 °C and sodium triacetoxyborohydride (0.28 g, 1.31 mmol) was added and the mixture stirred at room temperature overnight. The reaction mixture was neutralized with sat. $NaHCO_3$ and was extracted with DCM. The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure, and the residue purified by prep. HPLC to give the title compound as a TFA salt (80 mg, 37%). LCMS: 487.35 $(M+1)^+$; HPLC: 99.87% (@ 254 nm) (R_t;4.711; Method: Column: YMC ODS-A 150 mm x 4.6 mm x 5 μ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 μL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-D_6, 400 MHz) δ 11.47 (bs, 1H), 9.15 (s, 1H), 8.22 (s, 1H), 7.19 (s, 1H), 6.97 (s, 1H), 5.86 (s, 1H), 4.24 (d, J = 4.0 Hz, 2H), 3.16-3.01 (m, 5H), 2.64-2.63 (m, 4H), 2.19 (s, 3H), 2.15 (s, 3H), 2.10 (s, 3H), 1.91-1.83 (m, 4H), 1.47 (m, 4H), 1.19 (m, 3H), 0.79 (t, J = 7.2 Hz, 3H).

[01874] **Compound 286: 5-chloro-3-(((1r,4r)-4-((cyclopropylmethyl)(methyl)amino)cyclohexyl) (ethyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide**



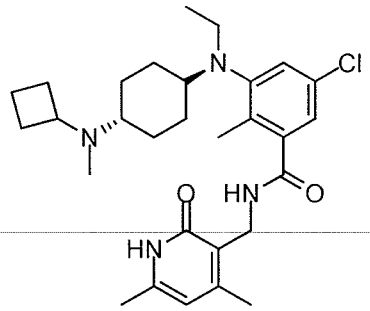
[01875] Step 1: Synthesis of 5-chloro-3-(((1r,r)-4-((cyclopropylmethyl)(methyl)amino)cyclohexyl) (ethyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide.



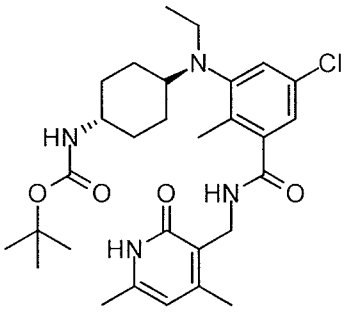
[01876] To a stirred solution of d 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((1r,4r)-4-(methylamino)cyclohexyl)amino)-2-methylbenzamide (200 mg, 0.43 mmol) and cyclopropanecarbaldehyde (0.03 gm, 0.43 mmol) in 5 ml of dichloroethane, was added acetic acid (0.15 mL, 2.62 mmol) and the mixture stirred at room temperature for 20 minutes. The mixture was cooled to 0 °C and sodium triacetoxyborohydride (0.277 g, 1.31 mmol) was added and the mixture stirred at room temperature overnight. The mixture was neutralized with sat. $NaHCO_3$ and was extracted with DCM. The combined organic phases were dried over Na_2SO_4, concentrated under reduced pressure, and the residue purified by prep. HPLC to give the title compound as a TFA salt (100 mg, 44%). LCMS: 513.40 $(M+1)^+$; HPLC: 94.81% (@ 254 nm) (R_t;4.924; Method: Column: YMC ODS-A 150 mm x 4.6 mm x 5 μ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 μL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^1H NMR (DMSO-D_6, 400 MHz) δ 11.47 (bs, 1H), 9.09 (s, 1H), 8.21 (s, 1H), 7.18 (s, 1H), 6.97 (s, 1H), 5.86 (s, 1H), 4.25 (d, J = 4.0 Hz, 2H), 3.24 (m, 1H), 3.03-3.01 (m, 3H), 2.89-2.87 (m, 1H), 2.71-2.70 (m, 4H), 2.18 (s, 3H), 2.15 (s, 3H), 2.10 (s, 3H), 1.93-

1.83 (m, 4H), 1.46-1.44 (m, 4H), 1.05 (m, 1H), 0.79 (t, J = 7.2 Hz, 3H), 0.63 (m, 2H),0.38-0.31 (m, 2H).

[01877] **Compound 287: Synthesis of compound 5-chloro-3-(((1r,4r)-4-(cyclobutyl(methyl)amino)cyclohexyl)(ethyl) amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide**



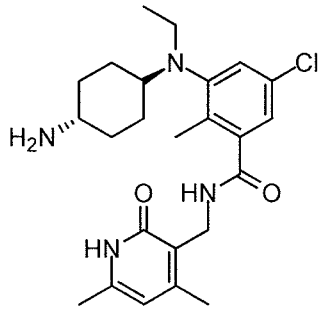
[01878] Steps 1 and 2: Synthesis of tert-butyl((1r,4r)-4-((5-chloro-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(ethyl)amino)cyclohexyl) carbamate.



[01879] A mixture of compound methyl 3-(((1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl) (ethyl)amino)-5-chloro-2-methylbenzoate (3.5 g, 8.2 mmol) and NaOH (0.5 g, 12 mmol) in 20 ml of ethanol:water (4:1) was heated at 70 °C for 2 h. The reaction mixture was cooled to 0 °C and acidified to pH 6 by using 1N HCl and concentrated. The residue was partitioned between water and ethyl acetate, the organic layer was dried over $Na_2SO_4$and concentrated under reduced pressure to afford 3.2 g of crude acid. The crude acid (3.2 g, 7.8 mmol), 3-(aminomethyl)-4,6-dimethylpyridin-2(1H)-one (2.36 mg, 15.6 mmol) and PyBOP (6.1 mg, 11 mmol) were stirred in 15 ml of DMSO at room temperature overnight. The reaction mixture was diluted with water and extracted with 10% MeOH in DCM. The

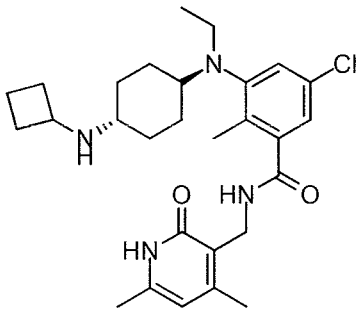
combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure and the residue purified by silica gel column chromatography to give the title compound (3.0 g, 71%).

[01880] Step 3: Synthesis of 3-(((1r,4r)-4-aminocyclohexyl)(ethyl)amino)-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide.



[01881] To a cooled solution of tert-butyl((1s,4s)-4-((5-chloro-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(ethyl)amino)cyclohexyl) carbamate (400 mg, 0.73 mmol) in 5 ml of DCM, were added 2 ml of TFA. The reaction mixture was stirred at room temperature for 2 h and concentrated to dryness under reduced pressure. The residue was dissolved in 10% MeOH in DCM and washed with sat $NaHCO_3$, water and brine. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to give the title compound (320 mg, 98%).

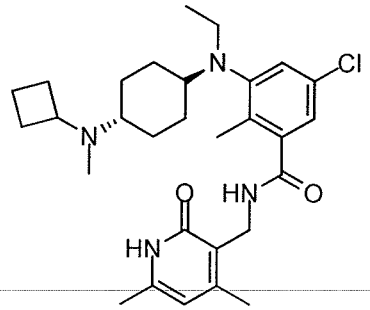
[01882] Step 4: Synthesis of 5-chloro-3-(((1r,4r)-4-(cyclobutylamino)cyclohexyl)(ethyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide.



[01883] To a stirred solution of 3-(((1r,4r)-4-aminocyclohexyl)(ethyl)amino)-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide (300 mg, 0.67 mmol) and cyclobutanone (141 mg, 2.02 mmol) in 20 ml of methanol, was added sodium cyanoborohydride (127 mg, 2.02 mmol) at 0 °C. The mixture was stirred at rt overnight, neutralized with sat. $NaHCO_3$ and extracted with DCM. The combined organic phases were

dried over Na_2SO_4 and concentrated under reduced pressure to obtain crude title compound (260 mg, 77%).

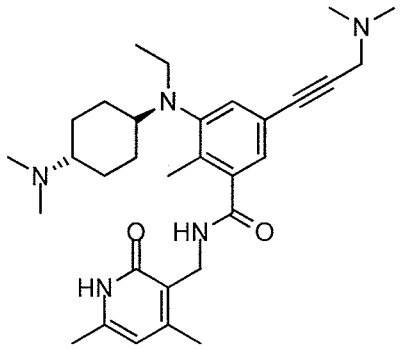
[01884] Step 5: Synthesis of 5-chloro-3-(((1r,4r)-4-(cyclobutyl(methyl)amino)cyclohexyl)(ethyl) amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide.



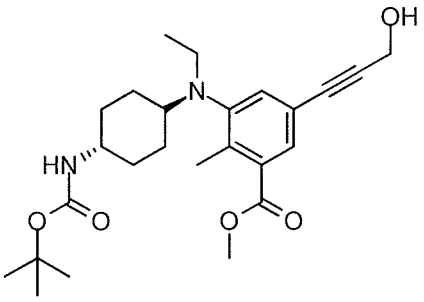
[01885] To a stirred solution of 5-chloro-3-(((1r,4r)-4-(cyclobutylamino)cyclohexyl)(ethyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide (230 mg, 0.46 mmol) and formalin (138 mg, 4.61 mmol) in10 ml of methanol, was added sodium cyanoborohydride (43 mg, 0.69 mmol) at 0 °C. The mixture was stirred at rt for overnight neutralized with sat. $NaHCO_3$ and extracted with DCM. The combined organic phases were dried over Na_2SO_4, concentrated under reduced pressure and the residue purified by silica gel column chromatography to give the title compound (150 mg, 63%).

[01886] Analytical Data of 5-chloro-3-(((1r,4r)-4-(cyclobutyl(methyl)amino)cyclohexyl)(ethyl) amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide -TFA salt : LCMS: 513.25 $(M+1)^+$; HPLC: 96.89% (@ 254 nm) (R_t;4.886; Method: Column: YMC ODS-A 150 mm x 4.6 mm x 5 µ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 µL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^1H NMR (DMSO-D_6, 400 MHz) δ 11.45 (bs, 1H), 9.40 (s, 1H), 8.21 (s, 1H), 7.18 (s, 1H), 6.97 (s, 1H), 5.86 (s, 1H), 4.25 (d, J = 4.0 Hz, 2H), 3.77-3.75 (m, 1H), 3.12-3.02 (m, 3H), 2.69 (m, 1H), 2.50 (4H merged in solvent peak), 2.18, 2.15, 2.11 (3s, 6H+3H+3H), 1.83-1.44 (m, 10H), 0.78 (t, 3H).

[01887] **Compound 290: N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-5-(3-(dimethylamino)prop-1-yn-1-yl)-2-methylbenzamide**

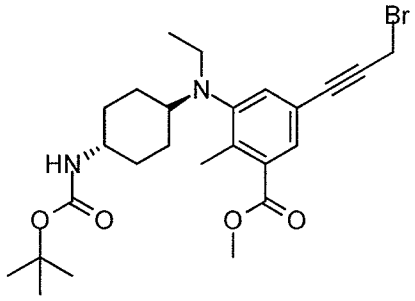


[01888] Steps 1 and 2: Synthesis of methyl 3-(((1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl) (ethyl)amino)-5-(3-hydroxyprop-1-yn-1-yl)-2-methylbenzoate:



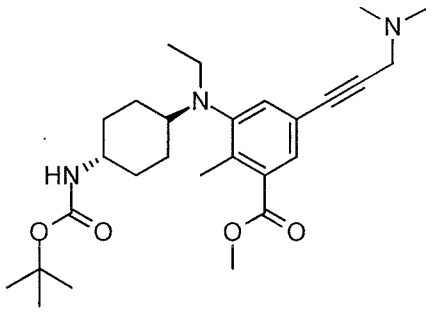
[01889] A solution of methyl 5-bromo-3-(((1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl) (ethyl)amino)-2-methylbenzoate (1.5 g, 3.2 mmol), *tert*-butyldimethyl(prop-2-yn-1-yloxy)silane (1.6 g, 9.6 mmol), copper iodide (183 mg, 0.96 mmol) and triethyl amine (1.30 ml, 9.60 mmol) in 10 ml of DMF was purged with argon gas for 20 min. Tetrakis-(triphenylphosphine)palladium (369 mg, 0.32 mmol) was added to the reaction mixture and the mixture heated at 100 °C for 5 h and cooled to room temperature. The mixture was diluted with ethyl acetate, washed with water, and the organic layer was dried over $Na_2SO_4$and concentrated under reduced pressure to obtain crude 1.9 g of the silyl protected intermediate product. The product was dissolved in 15 ml of THF and *tetra*-butyl ammonium fluoride (6.81 ml of 1M solution in THF, 6.81 mmol) was added at room temperature and the mixture stirred for 2h. The reaction mixture was diluted with ethyl acetate and washed with water. The organic layer was dried over Na_2SO_4, concentrated under reduced pressure, and the residue purified by silica gel column chromatography to give the title compound (950 mg, 630%).

[01890] Step 3: Synthesis of methyl 5-(3-bromoprop-1-yn-1-yl)-3-(((1r,4r)-4-((tert-butoxycarbonyl) amino)cyclohexyl)(ethyl)amino)-2-methylbenzoate.



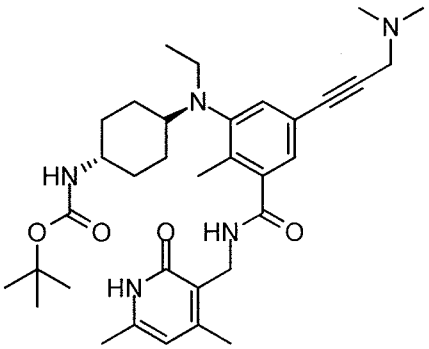
[01891] To a solution of methyl 3-(((1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl) (ethyl)amino)-5-(3-hydroxyprop-1-yn-1-yl)-2-methylbenzoate (950 mg, 2.14 mmol) in 13 ml of DCM, triphenylphosphine (840 mg, 3.21 mmol) and carbon tetrabromide (1.06 gm, 3.21 mmol) were added at room temperature. The mixture was stirred for 3 h, diluted with DCM and washed with water. The organic layer was dried over Na_2SO_4, concentrated under reduce pressure and the residue column purified over silica gel to give the title compound (900 mg, 82%).

[01892] Step 4: Synthesis of methyl 3-(((1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl)(ethyl) amino)-5-(3-(dimethylamino)prop-1-yn-1-yl)-2-methylbenzoate.



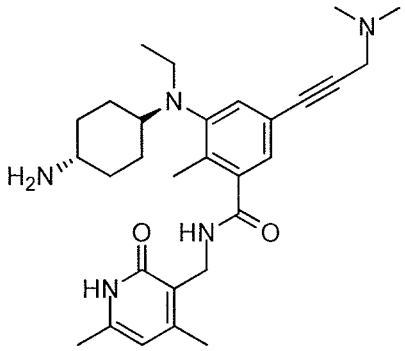
[01893] A solution of methyl 5-(3-bromoprop-1-yn-1-yl)-3-(((1r,4r)-4-((tert-butoxycarbonyl) amino)cyclohexyl)(ethyl)amino)-2-methylbenzoate (500 mg, 0.98 mmol) and a 2M solution in THF of *N,N*-dimethylamine (2.5 ml, 4.9 mmol) in 5 ml of DMF was stirred at room temperature overnight. The mixture was concentrated under reduced pressure, diluted with water and extracted with DCM. The combined organic phases were dried over Na_2SO_4 and concentrated under vacuum to afford the title compound (450 mg, 96%).

[01894] Steps 5 and 6: Synthesis of tert-butyl ((1r,4r)-4-((3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-5-(3-(dimethylamino)prop-1-yn-1-yl)-2-methylphenyl)(ethyl) amino)cyclohexyl)carbamate.



[01895] A mixture of methyl 3-(((1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl)(ethyl) amino)-5-(3-(dimethylamino)prop-1-yn-1-yl)-2-methylbenzoate (450 mg, 0.95 mmol) and NaOH (57 mg, 1.40 mmol) in 10 ml of ethanol:water (4:1) was heated at 70 °C for 2 h. The reaction mixture was concentrated to dryness and the residue partitioned between water and DCM. The organic layer was dried over Na_2SO_4cand concentrated under reduced pressure to afford 430 mg of acid. The crude acid (430 mg, 0.94 mmol), 3-(aminomethyl)-4,6-dimethylpyridin-2(1H)-one (280 mg, 1.88 mmol), PyBOP (733 mg, 1.40 mmol) and triethyl amine (0.1 ml, 0.94 mmol) were stirred in 7 ml of DMSO at rt overnight. The reaction mixture was diluted with water, the precipitated compound was filtered and dried under vacuum to obtain the crude title compound (450 mg, 81%).

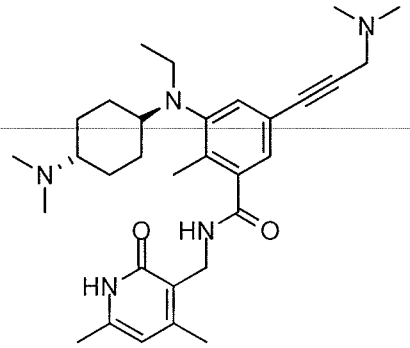
[01896] Step 7: Synthesis of 3-(((1r,4r)-4-aminocyclohexyl)(ethyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(3-(dimethylamino)prop-1-yn-1-yl)-2-methylbenzamide.



[01897] To a cooled solution of methyl 3-(((1r,4r)-4-((tert-butoxycarbonyl)amino) cyclohexyl)(ethyl)amino)-5-(3-(dimethylamino)prop-1-yn-1-yl)-2-methylbenzoate (450 mg,

0.76 mmol) in 6 ml of DCM, was added 1 ml of TFA. The reaction mixture was stirred at rt for 2 h, and concentrated to dryness under reduced pressure. The residue was dissolved in 10% MeOH in DCM and washed with sat $NaHCO_3$, water and brine. The organic phase was dried over Na_2SO_4, concentrated under reduced pressure to obtain the crude title compound (350 mg, 93%).

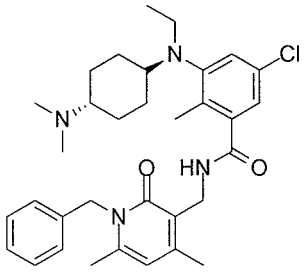
[01898] Step 8: Synthesis of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-5-(3-(dimethylamino)prop-1-yn-1-yl)-2-methylbenzamide.



[01899] To a stirred solution of crude compound 3-(((1r,4r)-4-aminocyclohexyl)(ethyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(3-(dimethylamino)prop-1-yn-1-yl)-2-methylbenzamide (350 mg, 0.71 mmol) and formaldehyde (0.56 ml of 38% solution, 7.10 mmol) in 8 ml of methanol, was added sodium cyanoborohydride (132 mg, 2.10 mmol) at 0 °C. The mixture was stirred at room temperature for 4 h, and partitioned between water and 10% MeOH in DCM. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by basic alumina column chromatography to afford the title compound (120 mg, 32%).

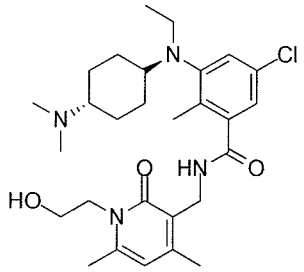
[01900] LCMS: 520.6 $(M + 1)^+$; HPLC: 92.27% (@ 254nm) (R_t;3.886; Method: Column: YMC ODS-A 150 mm x 4.6 mm x 5 µ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 µL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.45 (bs, 1H), 8.18 (t, 1H), 7.15 (s, 1H), 6.96 (s, 1H), 5.86 (s, 1H), 4.25 (d, 2H), 3.02-3.00 (m, 2H), 2.50 (13 protons merged in solvent peak), 2.33 (s, 3H), 2.23 (s, 3H), 2.18 (s, 3H), 2.11 (s, 3H), 1.82 (m, 4H), 1.39-1.28 (m, 4H), 0.77 (t, 3H).

[01901] **Compound 301: N-((1-benzyl-4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-chloro-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methylbenzamide**

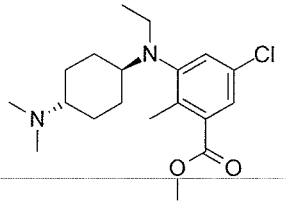


[01902] 5-Chloro-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methylbenzoic acid (1 eq) was dissolved in DMSO and 3-(aminomethyl)-1-(2-hydroxyethyl)-4,6-dimethylpyridin-2(1H)-one (2 eq) and triethylamine (1 eq) was added to it. The reaction mixture was stirred at room temperature for 15 min, PYBOP (1.5 eq) was added and stirring was continued overnight. The reaction mixture was poured into ice and extracted with 10 % MeOH/DCM. The combined organic layers were dried and concentrated to obtain crude product which was purified by prep. HPLC to afford the title compound (0.011g, 16 %) as the TFA salt. LCMS: 563.40 $(M + 1)^+$; HPLC: 90.27% (@ 210 nm-370 nm) (R_t;6.122; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 μ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 μL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (MeOD, 400 MHz) δ ,7.31-7.26(m, 2H), 7.24-7.04 (m, 5H), 6.23 (s, 1H), 5.40 (d, 2H), 4.50(s, 2H), 3.34 (1 Protons merged in solvent peak), 3.11-3.08 (m, 2H+1H), 2.81(s, 3H+3H), 2.42 (s, 3H), 2.29 (s, 3H), 2.21 (s, 3H), 2.08-1.99 (m, 2H+2H), 1.52-1.49 (m, 4H), 0.86 (t, 3H J=7.2Hz).

[01903] **Compound 302: 5-chloro-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-N-((1-(2-hydroxyethyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide**



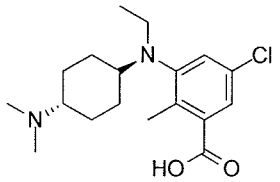
[01904] Step 1: Synthesis of methyl 5-chloro-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methylbenzoate



[01905] To a stirred solution of ethyl 3-(((1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl)(ethyl)amino)-5-chloro-2-methylbenzoate (3.4 g, 8.0 mmol) in DCM (35 mL) was added TFA (10 mL) . The mixture was stirred at room temperature for 1 hour, the solvent was removed under reduced pressure and saturated $NaHCO_3$ solution was added. Extraction was carried out using 10%MeOH/DCM and the combined organic layers were washed with water and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure gave methyl 3-(((1r,4r)-4-aminocyclohexyl)(ethyl)amino)-5-chloro-2-methylbenzoate (2.5 g, 96%).

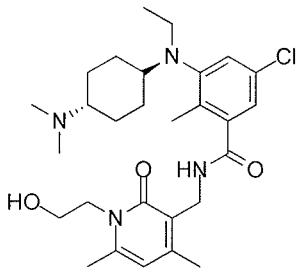
[01906] The above compound (2.4 g, 7.4 mmol) was dissolved in methanol (25 mL) and the mixture cooled to 0 °C. Formalin (2.21 g, 73.95 mmol) was added and the resulting reaction mixture was stirred at same temperature for 20 minutes. Sodium cyanoborohydride (0.92 g, 14.8 mmol) was added and the mixture stirred at room temperature for 1 hour. The solvent was removed under reduced pressure, water added to the residue, and extraction was carried out using 10 % MeOH/DCM. The combined organic layers were dried and concentrated under reduced pressure giving the title compound (2.3 g, 88) which was used further without further purification.

[01907] Step 2: Synthesis of 5-chloro-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methylbenzoic acid



[01908] Aqueous NaOH (0.73g, 18.35 mmol) was added to a solution of ethyl 5-chloro-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methylbenzoate (2.3 g, 9.1 mmol) in ethanol (25mL) and the mixture stirred at 60 °C for 1 hour. The ethanol was removed under reduced pressure and the residue acidified using dilute HCl up to pH 6 and adjusted to pH 4 using citric acid. Extraction was carried out using ethyl acetate. The combined organic layers were dried and concentrated giving the title compound (2.0 g, 92%).

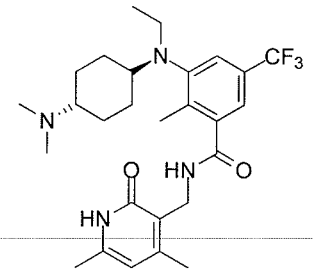
[01909] Step 3: Synthesis of 5-chloro-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-N-((1-(2-hydroxyethyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide



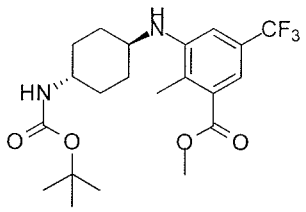
[01910] 5-Chloro-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methylbenzoic acid (1 eq) was dissolved in DMSO and 3-(aminomethyl)-1-(2-hydroxyethyl)-4,6-dimethylpyridin-2(1H)-one (2 eq) and triethylamine (1 eq) was added. The reaction mixture was stirred at room temperature for 15 min, PYBOP (1.5 eq) was added and stirring was continued overnight. After completion, the reaction mixture was poured into ice and extracted with 10 % MeOH/DCM. The combined organic layers were dried and concentrated to obtain a crude product which was purified by prep. HPLC to afford the title compound (0.07g, 20%) as the TFA salt. LCMS: 517.35 $(M + 1)^+$; HPLC: 91.15% (@ 254 nm) (R_t;5.134; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 μ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 μL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-D_2O Exchange, 400 MHz) δ 7.17 (s, 1H), 6.94 (s, 1H), 6.01 (s, 1H), 4.26 (m, 2H), 3.99 (s, 2H),

3.01-2.99 (m, 3H), 2.67(s, 3H+3H), 2.35 (1 Protons merged in solvent peak), 2.33 (m, 2H+2H), 2.19 (s, 3H), 2.12 (s, 3H), 1.94-1.81 (m, 5H) 1.40 (m, 4H), 0.77 (t, 3H).

[01911] **Compound 306: N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methyl-5-(trifluoromethyl)benzamide**

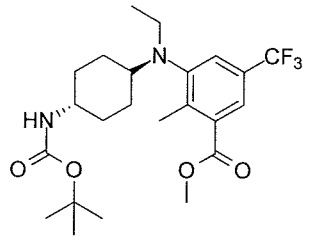


[01912] Step 1: Synthesis of methyl 3-(((1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl)amino)-2-methyl-5-(trifluoromethyl)benzoate



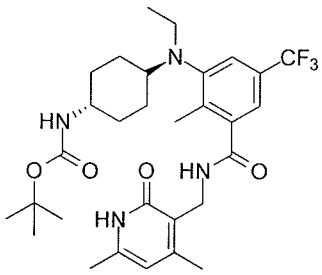
[01913] Acetic acid (3.28g, 54.8 mmol) was added to a stirred solution of methyl 3-amino-2-methyl-5-(trifluoromethyl)benzoate (2.0 g, 9.1 mmol) and tert-butyl (4-oxocyclohexyl)carbamate (2.52 g, 11.87 mmol) in dichloroethane (20 mL) and the reaction mixture was stirred at room temperature for 10 minutes. Then sodium triacetoxyborohydride (5.80 g, 27.4 mmol) was added at 0°C and the reaction mixture was stirred overnight at room temperature. On completion the reaction was quenched with aqueous sodium bicarbonate. The organic phase was separated and the aqueous phase extracted with dichloromethane. The combined organic layers were washed with water, dried, and concentrated under reduced pressure. The crude material was purified by column chromatography to afford the title compound (2.8 g, 82%).

[01914] Step 2: Synthesis of methyl 3-(((1r,4r)-4-((tert-butoxycarbonyl)amino)-cyclohexyl)(ethyl)amino)-2-methyl-5-(trifluoromethyl)benzoate



[01915] Acetic acid (0.85 g, 14.2 mmol) was added to a stirred solution of methyl 3-(((1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl)amino)-2-methyl-5-(trifluoromethyl)benzoate (0.9g, 2.40 mmol) and acetaldehyde (0.21 g, 4.80 mmol) in dichloroethane (10 mL) and the reaction mixture stirred at room temperature for 20 minutes. Then sodium triacetoxyborohydride (1.53 g, 7.21 mmol) was added at 0°C and the reaction mixture stirred overnight at room temperature. The reaction was quenched with aqueous sodium bicarbonate, the organic phase separated and the aqueous phase extracted with dichloromethane. The combined organic layers were washed with water, dried, concentrated under reduced pressure, and the crude material was purified by column chromatography to afford the title compound (0.8 g, 83%).

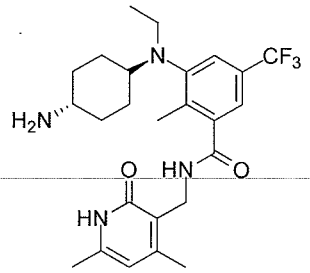
[01916] Step 3: Synthesis of tert-butyl ((1r,4r)-4-((3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methyl-5-(trifluoromethyl)phenyl)(ethyl)amino)cyclohexyl)carbamate



[01917] Aqueous sodium hydroxide (0.12 g, 2.97 mmol) was added to a solution of compound methyl 3-(((1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl)(ethyl)amino)-2-methyl-5-(trifluoromethyl)benzoate (0.80 g, 1.98 mmol) in ethanol (8 mL) and the mixture was stirred at 60 °C for 1 hour. After completion of the reaction, ethanol was removed under reduced pressure and the residue acidified using dilute HCl up to pH 6 and then adjusted to pH 4 using citric acid. Extraction was carried out using 10%MeOH/DCM. The combined organic layers were dried and concentrated giving the respective acid (0.7 g,)The acid (0.7 g, 1.8 mmol) was then dissolved in DMSO (10 mL) and 3-(amino methyl)-4, 6-dimethylpyridin-2(1H)-one (0.54 g, 3.59 mmol) was added. The reaction mixture was stirred at room temperature for 15 min,

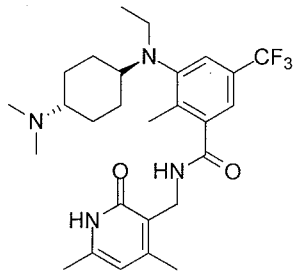
PYBOP (1.40 g, 2.69 mmol) was added and stirring was continued overnight. After completion of the reaction, the reaction mixture was poured into ice and extracted with 10% MeOH/DCM. The combined organic layers were dried, concentrated to obtain crude product which was then purified by washing with acetonitrile to afford the title compound (0.7 g, 74 %).

[01918] Step 4: Synthesis of 3-(((1r,4r)-4-aminocyclohexyl)(ethyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-5-(trifluoromethyl)benzamide



[01919] To a solution of tert-butyl ((1r,4r)-4-((3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methyl-5-(trifluoromethyl)phenyl)(ethyl)amino)cyclohexyl)carbamate (0.7 g, 1.3 mmol) in DCM (10 mL) was added TFA (3 mL) and the reaction mixture stirred at room temperature for 1 h. After completion of reaction, the solvent was removed under reduced pressure and saturated $NaHCO_3$ solution was added. Extraction was carried out using 10% MeOH/DCM; the combined organic layers were washed with water and brine; dried over anhydrous Na_2SO_4; filtered and concentrated under reduced pressure to give the title compound (0.56g, 98%) which was used directly in the next step.

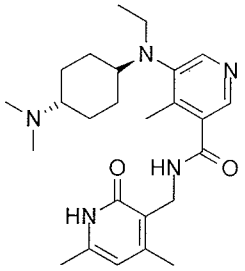
[01920] Step 5: Synthesis of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methyl-5-(trifluoromethyl)benzamide



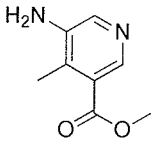
[01921] To a solution of 3-(((1r,4r)-4-aminocyclohexyl)(ethyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-5-(trifluoromethyl)benzamide (0.5 g, 1.2 mmol) in DCM (5 mL) at 0 ^{0}C was added formalin (0.124 g, 4.13 mmol). The reaction mixture was

stirred at 0 ^{0}C for 20 minutes. Sodium triacetoxyborohydride (0.63 g, 2.95 mmol) was added and the reaction mixture was stirred at room temperature for 1 h. After completion, water was added and extraction was carried out using 10 % MeOH/DCM. The combined organic layers were dried and concentrated under reduced pressure. The crude solid obtained was washed with acetonitrile and ether to afford the title compound (0.4 g, 67%). LCMS: 507.45 $(M + 1)^+$; HPLC: 96.81% (@ 210-370 nm) (R_t;4.857; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 µ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 µL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-*d6*, 400 MHz) δ 11.46 (bs, 1H), 8.34 (s, 1H), 7.38 (s, 1H), 7.20 (s, 1H), 5.86 (s, 1H), 4.27 (d, 2H), 3.08 (m, 2H), 2.67 (m, 1H), 2.40 (s, 6H), 2.24 (s, 3H), 2.19 (s, 3H), 2.10 (s, 3H), 1.85 (m, 2H), 1.80 (m, 2H), 1.42 (m, 2H), 1.25 (m, 2H), 0.78 (t, 3H).

[01922] **Compound 390: N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-4-methylnicotinamide**

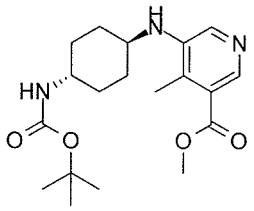


[01923] Step 1:Synthesis of methyl 5-amino-4-methylnicotinate



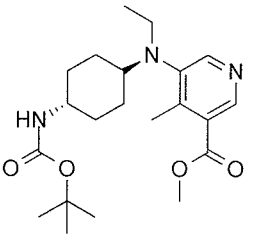
[01924] To a stirred solution of 5-amino-4-methylnicotinic acid (5.0 g, 32 mmol) in methanol (75 mL), was added conc. H_2SO_4 (5 mL) slowly at room temperature. The mixture was stirred at 70 ^{0}C for 12h. On completion, the solvent was removed under reduced pressure and the residue was neutralized with saturated $NaHCO_3$ solution. Extraction was carried out using EtOAc; the combined organic layers were washed with water, brine and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the title compound (4.1 g, 75 %) which used without further purification.

[01925] Step 2: Synthesis of methyl 5-(((1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl)amino)-4-methylnicotinate



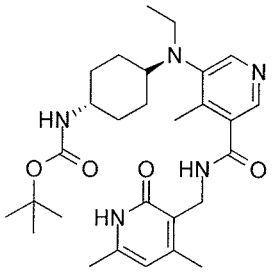
[01926] To a stirred solution of methyl 5-amino-4-methylnicotinate (1.20 g, 7.22 mmol) and tert-butyl (4-oxocyclohexyl)carbamate (2.30 g, 10.8 mmol) in dichloroethane (20 mL), was added acetic acid (2.59 g, 43 mmol) and the mixture stirred at room temperature for 10 minutes. Then sodium triacetoxyborohydride (4.59 g, 21.56 mmol) was added at 0°C and the reaction stirred overnight at room temperature. On completion, the reaction was quenched with aqueous sodium bicarbonate, the organic phase separated and the aqueous phase extracted with dichloromethane. The combined organic layers were dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography to afford the title compound (0.65 g, 25%).

[01927] Step 3: Synthesis of methyl 5-(((1r,4r)-4-((tert-butoxycarbonyl)-amino)-cyclohexyl)-(ethyl)-amino)-4-methylnicotinate



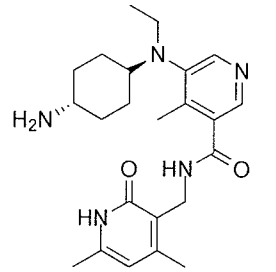
[01928] To a stirred solution of methyl 5-(((1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl)amino)-4-methylnicotinate (0.65 g, 1.79 mmol) and acetaldehyde (0.39 g, 8.95 mmol) in dichloroethane (20 mL) was added acetic acid (0.64 g, 10.7 mmol) and the mixture stirred at room temperature for 10 minutes. Then sodium triacetoxyborohydride (1.13 g, 5.33 mmol) was added at 0°C and the reaction stirred overnight at room temperature. On completion, the reaction was quenched with aqueous sodium bicarbonate, the organic phase separated and the aqueous phase extracted with dichloromethane. The combined organic layers were dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford the title compound (0.55 g, 79%).

[01929] Step 4: Synthesis of tert-butyl ((1r,4r)-4-((5-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-4-methylpyridin-3-yl)(ethyl)amino)cyclohexyl)carbamate



[01930] Aqueous NaOH (0.11 g, 2.81 mmol) was added to a solution of methyl 5-(((1r,4r)-4-((tert-butoxycarbonyl)-amino)-cyclohexyl)-(ethyl)-amino)-4-methylnicotinate (0.55 g, 1.40 mmol) in ethanol (7 mL) and the mixture stirred at 60 °C for 1 h. After completion of the reaction, ethanol was removed under reduced pressure and the mixture acidified using dilute HCl up to pH 6 and pH 4 was adjusted using citric acid. Extraction was carried out using ethyl acetate. The combined organic layers were dried concentrated giving respective acid (0.5 g). The above acid (0.5 g, 1.3 mmol) was then dissolved in DMSO (5 mL) and 3-(amino methyl)-4, 6-dimethylpyridin-2(1H)-one (0.48 g, 2.65mmol) was added. The reaction mixture was stirred at room temperature for 15 min, PYBOP (1.02 g, 1.58 mmol) was added and stirring was continued overnight. After completion of the reaction, the mixture was poured into ice and extracted with 10 %MeOH/DCM. The combined organic layers were dried and concentrated to a residue which was purified by silica gel chromatography to afford the title compound (0.5 g, 74 %).

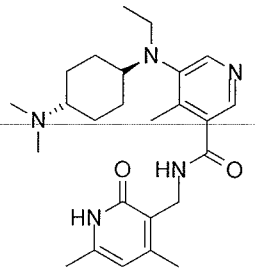
[01931] Step 5: Synthesis of 5-(((1r,r)-4-aminocyclohexyl)(ethyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-4-methylnicotinamide



[01932] To a stirred solution of tert-butyl ((1r,4r)-4-((5-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-4-methylpyridin-3-

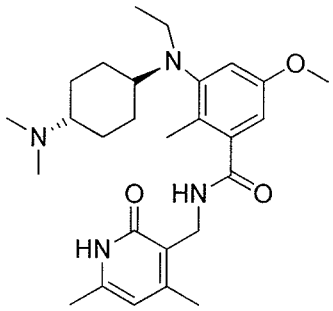
yl)(ethyl)amino)cyclohexyl)carbamate (0.5 g, 0.97 mmol) in DCM (10 mL) was added TFA (2 mL). The mixture was stirred at rt for 1 the solvent was removed under reduced pressure. Saturated $NaHCO_3$ solution was added to The residue and extraction was carried out using 10%MeOH/DCM. The combined organic layers were washed with water and brine; dried over anhydrous Na_2SO_4; filtered and concentrated under reduced pressure to give the title compound (0.35 g, 88%).

[01933] Step 6: Synthesis of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-4-methylnicotinamide

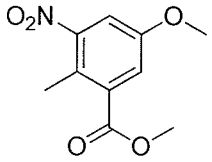


[01934] 5-(((1r,4r)-4-aminocyclohexyl)(ethyl)amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-4-methylnicotinamide (0.35g, 0.85 mmol) was dissolved in DCM (5 mL) and formalin (0.089 g, 2.96 mmol) was added at 0 °C. The mixture was stirred for 20 minutes, sodium triacetoxyborohydride (0.45 g, 2.12 mmol) was added and the mixture stirred at room temperature for 1 h. After completion, the mixture was diluted with water and extraction was carried out using 10 % MeOH/DCM. The combined organic layers were dried and concentrated under reduced pressure. The solid obtained was further purified by washings with acetonitrile and ether to afford the title compound (0.3 g, 80%). LCMS: 440.45 $(M + 1)^+$; HPLC: 73.44% & 21.34% (@ 210-370 nm) (R_t;3.769 & 3.965); **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 μ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 μL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-*d6*, 400 MHz) δ 11.45 (bs, 1H), 8.34 (s, 1H), 8.29 (s, 1H), 8.07 (s, 1H), 5.86 (s, 1H), 4.27 (d, 2H), 3.18 (m, 1H), 3.01 (m, 2H), 2.22 (s, 3H), 2.19 (s, 3H), 2.12 (s, 6H), 2.10 (s, 3H), 1.74 (m, 2H), 1.64 (m, 2H), 1.40-1.20 (m, 4H), 0.81 (t, 3H).

[01935] **Compound 308: N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-5-methoxy-2-methylbenzamide**

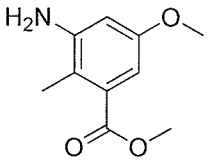


[01936] Step 1: Synthesis of methyl 5-methoxy-2-methyl-3-nitrobenzoate



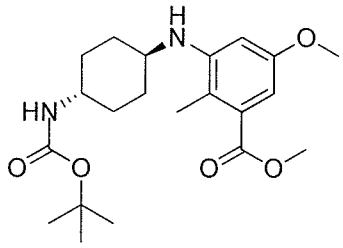
[01937] To a stirred solution of 5-hydroxy-2-methyl-3-nitrobenzoic acid (1.50 g, 7.61 mmol) in DMF (15 mL) was added sodium carbonate (3.23 g, 30.5 mmol) and methyl iodide (1.88 mL, 30.5 mmol). The resulting reaction mixture was heated at 60 °C for 8h. On completion, the reaction mixture was diluted with water and extraction was carried out using ethyl acetate. The combined organic layers were dried and concentrated under reduced pressure to give the crude title compound (1.7 g) which was used directly in the next step.

[01938] Step 2: Synthesis of methyl 3-amino-5-methoxy-2-methylbenzoate



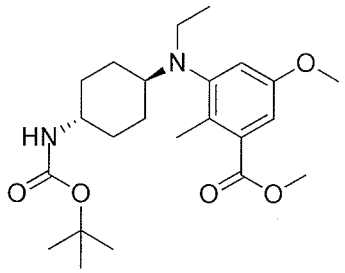
[01939] To a stirred solution of methyl 5-methoxy-2-methyl-3-nitrobenzoate (1.7 g, 7.6 mmol) in ethanol (20 mL) was added ammonium chloride (1.7 g, 32 mmol) dissolved in water (20 mL) and iron powder (3.38 g, 60.44 mmol). The mixture was heated at 80 °C for 3h, filtered and the residue washed well with hot ethanol. The filtrate was concentrated and the residue was basified with aqueous sodium bicarbonate. The aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with water, dried, and concentrated under reduced pressure to give the crude title compound (1.2 g) which was used directly in the next step.

[01940] Step 3: Synthesis methyl 3-(((1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl)amino)-5-methoxy-2-methylbenzoate



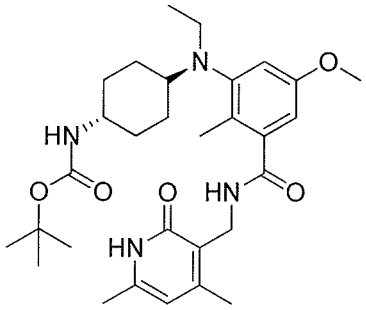
[01941] To a stirred solution of methyl 3-amino-5-methoxy-2-methylbenzoate (1.2 g, 6.15 mmol) and tert-butyl (4-oxocyclohexyl)carbamate (1.70 g, 7.99 mmol) in dichloroethane (20 mL) was added acetic acid (2.21 g, 36.8 mmol). The reaction was stirred at room temperature for 20 minutes. Sodium triacetoxyborohydride (3.91 g, 18.4 mmol) was added at 0 °C and the reaction mixture was stirred at room temperature overnight. On completion, the reaction was quenched with aqueous sodium bicarbonate, the organic phase separated and the aqueous phase extracted with dichloromethane. The combined organic layers were washed with water, dried, and concentrated under reduced pressure. The crude material obtained was purified by column chromatography to afford the title compound (0.35 g, 14%).

[01942] Step 4: Synthesis of methyl 3-(((1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl)-(ethyl)amino)-5-methoxy-2-methylbenzoate



[01943] To a stirred solution of 3-(((1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl)amino)-5-methoxy-2-methylbenzoate (0.35 g, 0.89 mmol) and acetaldehyde (0.2 g, 4.46 mmol) in dichloroethane (5 mL) was added acetic acid (0.32 g, 5.35 mmol) and the reaction mixture stirred at room temperature for 20 minutes. Then sodium triacetoxyborohydride (0.57 g, 2.67 mmol) was added at 0 °C and the reaction mixture was stirred at room temperature for 2 h. On completion, the reaction was quenched with aqueous sodium bicarbonate, the organic phase separated and the aqueous phase extracted with dichloromethane. The combined organic layers were washed with water, dried, and concentrated under reduced pressure. The crude material was purified by column chromatography to afford the title compound (0.3 g, 80%).

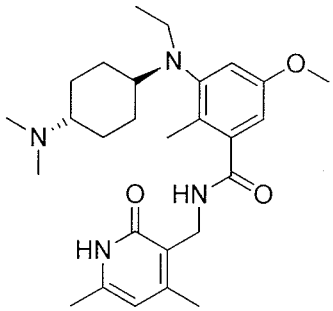
[01944] Step 5: Synthesis of tert-butyl ((1r,4r)-4-((3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-5-methoxy-2-methylphenyl)(ethyl)amino)cyclohexyl)carbamate



[01945] Aqueous NaOH (0.06 g, 1.42 mmol) was added to a solution of methyl 3-(((1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl)-(ethyl)amino)-5-methoxy-2-methylbenzoate (0.3 g, 0.71 mmol) in ethanol (4 mL) and the mixture stirred at 60 °C for 1 h. After completion of the reaction, ethanol was removed under reduced pressure and the residue acidified using dilute HCl up to pH 6 and pH 4 was adjusted using citric acid. Extraction was carried out using ethyl acetate. The combined organic layers were dried concentrated to give the crude acid (0.25g).

[01946] The acid (0.25 g, 0.62 mmol) was dissolved in DMSO (3 mL) and 3-(amino methyl)-4, 6-dimethylpyridin-2(1H)-one (0.19 g, 1.23 mmol) was added. The reaction mixture was stirred at room temperature for 15 min, PYBOP (0.48 g, 0.92 mmol) was added and the mixture was stirred overnight. The reaction was quenched by pouring into ice, and the mixture was extracted with 10%MeOH/DCM. The combined organic layers were washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude material which was purified by column chromatography to give the title compound (0.2 g, 60 %).

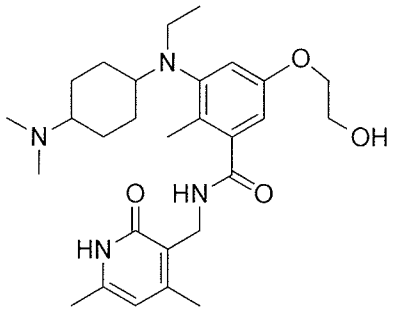
[01947] Step 6: Synthesis of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-5-methoxy-2-methylbenzamide



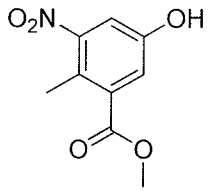
[01948] To a solution of tert-butyl ((1r,4r)-4-((3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-5-methoxy-2-methylphenyl)(ethyl)amino)cyclohexyl)carbamate (0.2g, 0.37 mmol) in DCM (4 mL) was added TFA (2 mL) and the reaction mixture was stirred at rt for 1 h. After completion of reaction the solvent was removed under reduced pressure and saturated $NaHCO_3$ solution was added. Extraction was carried out using 10% MeOH/DCM; the combined organic layers were washed with water and brine; dried over anhydrous Na_2SO_4; filtered and concentrated under reduced pressure to give Boc- deprotected compound (0.15g,).

[01949] The Boc deprotected compound (0.15g, 0.34 mmol) was dissolved in DCM (2 mL) and formalin (0.035 g, 1.19 mmol) was added to it at 0 ^{0}C. The resulting reaction mixture was stirred at 0 ^{0}C for 10 minutes. Sodium triacetoxyborohydride (0.18 g, 0.85 mmol) was the added and the mixture stirred at room temperature carried for 1 h. After reaction completion, water was added and extraction was carried out using 10% MeOH/DCM. The combined organic layers were dried and concentrated under reduced pressure to afford crude material which was purified by prep. HPLC to give the title compound as a TFA salt (0.02g, 12%). LCMS: 469.80 $(M + 1)^+$; HPLC: 96.80% (@ 210-370 nm) (R_t;3.802); **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 μ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 μL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-*d6*, 400 MHz) δ 11.46 (s, 1H), 9.42 (s, 1H), 8.06 (s, 1H), 6.75 (s, 1H), 6.58 (s, 1H), 5.86 (s, 1H), 4.26 (d, 2H, J=4 Hz), 3.72 (s, 3H), 3.09 (m, 3H), 2.69 (s, 3H), 2.68 (s, 3H), 2.19 (s, 3H), 2.10 (s, 6H), 1.95 (m, 2H), 1.87 (m, 2H), 1.41 (m, 4H), 0.801 (t, 3H).

[01950] **Compound 309: N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-((4-(dimethylamino)cyclohexyl)(ethyl)amino)-5-(2-hydroxyethoxy)-2-methylbenzamide**

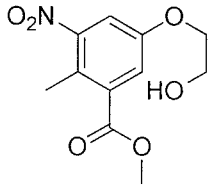


[01951] Step 1: synthesis of methyl 5-hydroxy-2-methyl-3-nitrobenzoate



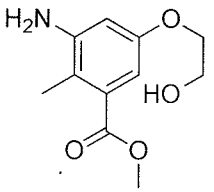
[01952] To a stirred solution of 5-hydroxy-2-methyl-3-nitrobenzoic acid (3.50 g, 17.8 mmol) in methanol (40 mL) was added thionyl chloride (3.9 mL, 53 mmol) at 0 °C. The reaction mixture was heated at reflux for 3 h. On completion, the solvent was removed under reduced pressure. Aqueous sodium bicarbonate was added, followed by extraction with ethyl acetate. The combined organic layers were washed with water, dried and concentrated under reduced pressure. The crude material was purified by column chromatography to afford the title compound (3.0 g, 80%).

[01953] Step 2: synthesis of methyl 5-(2-hydroxyethoxy)-2-methyl-3-nitrobenzoate



[01954] To a stirred solution of methyl 5-hydroxy-2-methyl-3-nitrobenzoate (1.5 g, 7.1 mmol) in ACN (15 mL), were added cesium carbonate (4.6 g, 14 mmol) and 2-bromoethanol (2.5 mL, 35 mmol). The resulting reaction mixture was heated at 80 °C overnight. On completion, the reaction mixture was diluted with water and extraction was carried out using ethyl acetate. The combined organic layers were washed with water, dried and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography to afford the title compound (1.35 g, 74%).

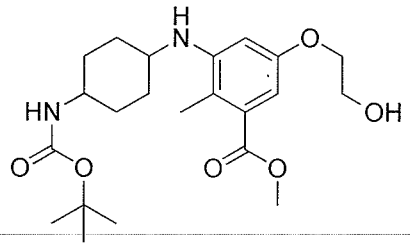
[01955] Step 3: synthesis of methyl 3-amino-5-(2-hydroxyethoxy)-2-methylbenzoate



[01956] To a stirred solution of methyl 5-(2-hydroxyethoxy)-2-methyl-3-nitrobenzoate (1.5 g, 5.88 mmol) in ethanol (20 mL), were added ammonium chloride (1.5 g, 28 mmol) dissolved in water (20 mL) and iron powder (1.3 g, 23 mmol). The resulting reaction mixture was heated at 80 °C for 3h. On completion, the reaction mixture was filtered and the residue washed well

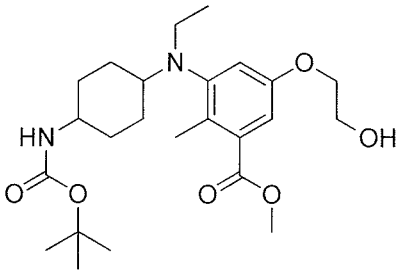
with hot ethanol. The filtrate was concentrated and the residue was basified by aqueous sodium bicarbonate. The aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with water, dried, and concentrated under reduced pressure giving the crude title compound (1.3 g) which was used directly.

[01957] Step 4: synthesis of methyl 3-((4-((tert-butoxycarbonyl)amino)cyclohexyl)amino)-5-(2-hydroxyethoxy)-2-methylbenzoate



[01958] To a stirred solution of methyl 3-amino-5-(2-hydroxyethoxy)-2-methylbenzoate (1.3 g, 5.77 mmol) and tert-butyl (4-oxocyclohexyl)carbamate (1.6 g, 7.5 mmol) in dichloroethane (20 mL) was added acetic acid (2.07 g, 34.66 mmol) and the reaction mixture stirred at room temperature for 20 minutes. Then sodium triacetoxyborohydride (3.7 g, 17 mmol) was added at 0 °C and the reaction mixture was stirred at room temperature overnight. On completion, the reaction was quenched with aqueous sodium bicarbonate, the organic phase separated and the aqueous phase extracted with dichloromethane. The combined organic layers were washed with water, dried, and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography to afford the title compound (2.0 g, 82%) as a mixture of cis/trans-isomers which was carried forward as a mixture through to the final compound 309 which was also isolate as a mixture of cis/trans-isomers.

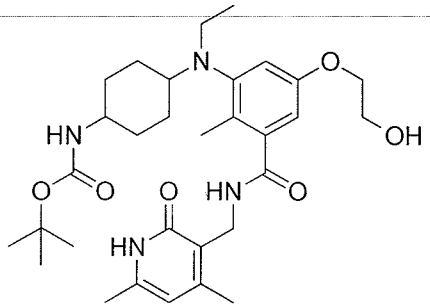
[01959] Step 5: synthesis of methyl 3-((4-((tert-butoxycarbonyl)amino)cyclohexyl)-(ethyl)amino)-5-(2-hydroxyethoxy)-2-methylbenzoate



[01960] To a stirred solution of methyl 3-((4-((tert-butoxycarbonyl)amino)cyclohexyl)amino)-5-(2-hydroxyethoxy)-2-methylbenzoate (2.0 g, 4.7 mmol) and acetaldehyde (0.63 g, 14.2

mmol) in dichloroethane (20 mL) was added acetic acid (1.7 g, 28 mmol) and the reaction mixture stirred at room temperature for 20 minutes. Then sodium triacetoxyborohydride (3.0 g, 14.2 mmol) was added at 0 °C and reaction was stirred at room temperature for 2 h. On completion, the reaction was quenched with aqueous sodium bicarbonate, the organic phase was separated and the aqueous phase extracted with dichloromethane. The combined organic layers were washed with water, dried, concentrated under reduced pressure; Crude material was purified by column chromatography to afford the title compound (1.9 g, 89%).

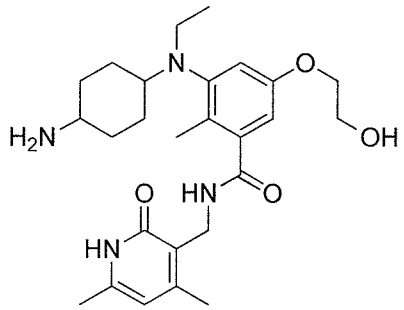
[01961] Step 6: synthesis of tert-butyl (4-((3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-5-(2-hydroxyethoxy)-2-methylphenyl)-(ethyl)-amino)cyclohexyl)carbamate



[01962] Aqueous NaOH (0.25 g, 6.33 mmol) was added to a solution of methyl 3-((4-((tert-butoxycarbonyl)amino)cyclohexyl)-(ethyl)amino)-5-(2-hydroxyethoxy)-2-methylbenzoate (1.9 g, 4.2 mmol) in ethanol (20 mL) and the mixture stirred at 60 °C for 1 h. After completion of the reaction, ethanol was removed under reduced pressure and acidified using dilute HCl up to pH 6 and pH 4 was adjusted using citric acid. Extraction was carried out using ethyl acetate. The combined organic layers were dried and concentrated giving the corresponding crude acid (1.8 g).

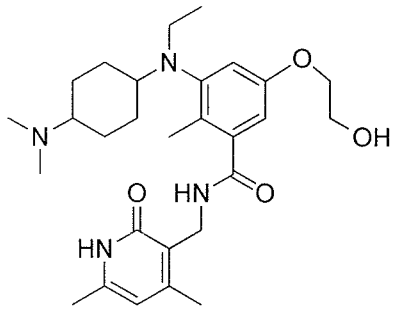
[01963] The acid (1.8 g, 4.1 mmol) was then dissolved in DMSO (15 mL) and 3-(amino methyl)-4, 6-dimethylpyridin-2(1H)-one (1.25 g, 8.25 mmol) was added. The reaction mixture was stirred at room temperature for 15 min, PYBOP (3.22 g, 6.19 mmol) was added and stirring was continued overnight. After completion of the reaction, the reaction mixture was poured into ice and extracted with 10% MeOH/DCM. The combined organic layers were washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude material which was purified by column chromatography to give the title compound (1.4 g, 59%).

[01964] Step 7: synthesis of 3-((4-aminocyclohexyl)-(ethyl)-amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(2-hydroxyethoxy)-2-methylbenzamide



[01965] To a solution of tert-butyl (4-((3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-5-(2-hydroxyethoxy)-2-methylphenyl)-(ethyl)-amino)cyclohexyl)carbamate (0.80 g, 1.40 mmol) in DCM (5 mL) was added TFA (2 mL) and the reaction mixture was stirred at rt for 1 h. After completion of reaction, the solvent was removed under reduced pressure and saturated $NaHCO_3$ solution was added. Extraction was carried out using 10% MeOH/DCM; the combined organic layers were washed with water and brine; dried over anhydrous Na_2SO_4; filtered and concentrated under reduced pressure to give the title compound (0.5g, 76%).

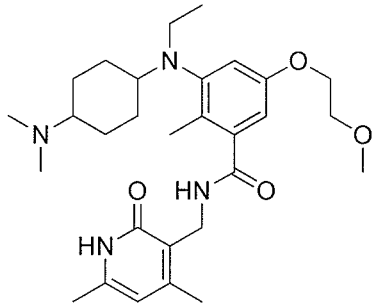
[01966] Step 8: synthesis of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-((4-(dimethylamino)cyclohexyl)(ethyl)amino)-5-(2-hydroxyethoxy)-2-methylbenzamide



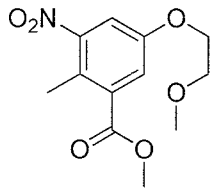
[01967] To a solution of 3-((4-aminocyclohexyl)-(ethyl)-amino)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(2-hydroxyethoxy)-2-methylbenzamide (0.30 g, 0.63 mmol) in DCM (3 mL) was added formalin (0.07 g, 2.23 mmol) at 0 ^{0}C. The resulting reaction mixture was stirred at 0 ^{0}C for 20 minutes. Sodium triacetoxyborohydride (0.34 g, 1.59 mmol) was added and the reaction mixture stirred at room temperature for 1 h. After completion, solvent was removed under reduced pressure and water was added to the residue and extraction was carried out using 10 % MeOH/DCM. The combined organic layers were dried and concentrated

under reduced pressure. The solid obtained was further purified by washings with acetonitrile and ether to afford the title compound N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-((4-(dimethylamino)cyclohexyl)(ethyl)amino)-5-(2-hydroxyethoxy)-2-methylbenzamide as a mixture of cis/trans-isomers (0.25 g, 78%). LCMS: 499.55 $(M + 1)^+$; HPLC: 51.61 & 47.78% (@ 210-370 nm) (R_t;3.539 & 3.751); **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 µ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 µL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-*d6*, 400 MHz) δ 11.45 (bs, 1H), 8.04 (s, 1H), 6.68 (s, 1H), 6.51 (s, 1H), 5.85 (s, 1H), 4.25 (d, 2H), 3.92 (t, 2H), 3.67 (t, 2H), 2.97 (m, 2H), 2.18 (s, 3H), 2.16 (s, 3H), 2.12 (s, 3H), 2.10 (s, 3H), 2.08 (s, 3H), 1.89 (s, 3H), 1.76 (m, 3H), 1.65 (bs, 1H), 1.33 (m, 3H), 1.10 (m, 1H), 0.788 (bs, 3H).

[01968] **Compound 310: N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-((4-(dimethylamino)cyclohexyl)-(ethyl)-amino)-5-(2-methoxyethoxy)-2-methylbenzamide**



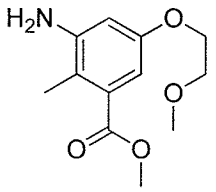
[01969] Step 1: synthesis of methyl 5-(2-methoxyethoxy)-2-methyl-3-nitrobenzoate



[01970] To stirred solution of methyl 5-hydroxy-2-methyl-3-nitrobenzoate (1.50 g, 7.61 mmol) in ACN (15 mL) was added cesium carbonate (4.96 g, 15.2 mmol) and 1-bromo-2-methoxyethane (1.57 g, 11.4 mmol). The resulting reaction mixture was heated at 80 °C overnight. On completion, the reaction mixture was diluted with water and extraction was carried out using ethyl acetate. The combined organic layers were washed with water, dried,

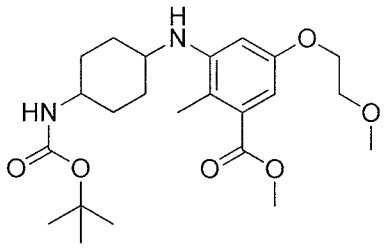
and concentrated under reduced pressure. The crude material was purified by column chromatography to afford the title compound (1.3 g, 68).

[01971] Step 2: synthesis of methyl 3-amino-5-(2-methoxyethoxy)-2-methylbenzoate



[01972] To stirred solution of methyl 5-(2-methoxyethoxy)-2-methyl-3-nitrobenzoate (1.35 g, 4.83 mmol) in ethanol (20 mL) were added ammonium chloride (1.35 g, 25.0 mmol) dissolved in water (20 mL) and iron powder (1.07 g, 19.3mmol). The resulting reaction mixture was heated at 80 °C for 3h. On completion, the reaction mixture was filtered and the residue washed well with hot ethanol. The filtrate was concentrated and the residue was basified by aqueous sodium bicarbonate. The aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with water, dried, concentrated under reduced pressure to give the crude title compound (1.23 g) which was used directly in the next step.

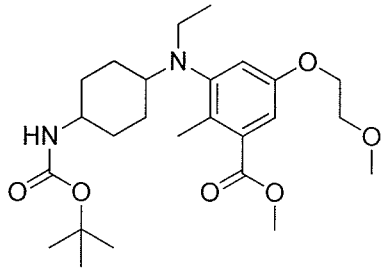
[01973] Step 3: synthesis of methyl 3-((4-((tert-butoxycarbonyl)amino)cyclohexyl)amino)-5-(2-methoxyethoxy)-2-methylbenzoate



[01974] To a stirred solution of methyl 3-amino-5-(2-methoxyethoxy)-2-methylbenzoate (1.23 g, 5.14 mmol) and tert-butyl (4-oxocyclohexyl)carbamate (1.42 g, 6.69 mmol) in dichloroethane (15 mL) was added acetic acid (1.8 g, 31 mmol) and the reaction mixture stirred at room temperature for 20 minutes. Then sodium triacetoxyborohydride (3.2 g, 15 mmol) was added at 0 °C and the reaction was stirred at room temperature overnight. On completion, the reaction was quenched with aqueous sodium bicarbonate, the organic phase separated and the aqueous phase extracted with dichloromethane. The combined organic layers were washed with water, dried and concentrated under reduced pressure. The crude material was purified by column chromatography to afford methyl the title compound (1.6 g, 72%) as a mixture of

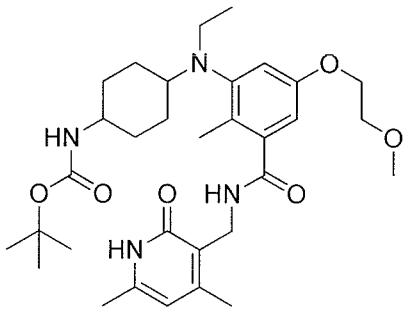
cis/trans-isomers which was carried forward through to the final compound as a cis/trans-isomer mixture .

[01975] Step 4: synthesis of methyl 3-((4-((tert-butoxycarbonyl)amino)cyclohexyl)-(ethyl)-amino)-5-(2-methoxyethoxy)-2-methylbenzoate



[01976] To a stirred solution of methyl 3-((4-((tert-butoxycarbonyl)amino)cyclohexyl)amino)-5-(2-methoxyethoxy)-2-methylbenzoate (1.60 g, 3.67 mmol) and acetaldehyde (0.48 g, 10.9 mmol) in dichloroethane (20 mL) was added acetic acid (1.3 g, 22 mmol) and the reaction mixture stirred at room temperature for 20 minutes. Then sodium triacetoxyborohydride (2.33 g, 11.0 mmol) was added at 0 °C and the reaction was stirred at room temperature for 2 h. The reaction was quenched with aqueous sodium bicarbonate, the organic phase separated and the aqueous phase extracted with dichloromethane. The combined organic layers were washed with water, dried, concentrated under reduced pressure, the crude material was purified by column chromatography to afford the title compound (1.6 g, 94%).

[01977] Step 5: synthesis of tert-butyl (4-((3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-5-(2-methoxyethoxy)-2-methylphenyl)-(ethyl)-amino)-cyclohexyl)carbamate

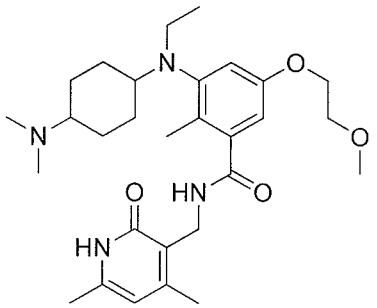


[01978] Aqueous NaOH (0.2 g, 5.3 mmol) was added to a solution of methyl 3-((4-((tert-butoxycarbonyl)amino)cyclohexyl)-(ethyl)-amino)-5-(2-methoxyethoxy)-2-methylbenzoate (1.6 g, 3.5 mmol) in ethanol (20 mL) and stirred at 60 °C for 1 h. After completion of the reaction, ethanol was removed under reduced pressure and acidified using dilute HCl up to pH

6 and pH 4 was adjusted using citric acid. Extraction was carried out using ethyl acetate. The combined organic layers were concentrated to give the corresponding crude acid (1.4 g).

[01979] The acid (1.4 g, 3.1 mmol) was then dissolved in DMSO (15 mL) and 3-(amino methyl)-4, 6-dimethylpyridin-2(1H)-one (0.95 g, 6.2 mmol) was added. The reaction mixture was stirred at room temperature for 15 min, PYBOP (2.4 g, 4.6 mmol) was added and stirring was continued overnight. The reaction mixture was poured into ice and extracted with 10%MeOH/DCM. The combined organic layers were washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude material which was purified by column chromatography to afford the title compound (1.9 g, 95 %).

[01980] Step 5: synthesis of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-((4-(dimethylamino)cyclohexyl)-(ethyl)-amino)-5-(2-methoxyethoxy)-2-methylbenzamide

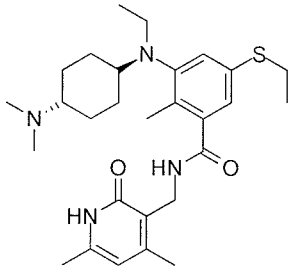


[01981] To a solution of methyl 3-((4-((tert-butoxycarbonyl)amino)cyclohexyl)-(ethyl)-amino)-5-(2-methoxyethoxy)-2-methylbenzoate (1.2 g, 2.67 mmol) in DCM (10 mL) was added TFA (2 mL) and the reaction mixture stirred at rt for 1 h. After completion of reaction, the solvent was removed under reduced pressure and saturated $NaHCO_3$ solution was added to the residue. Extraction was carried out using 10% MeOH/DCM; the combined organic layers were washed with water and brine; dried over anhydrous Na_2SO_4; filtered and concentrated under reduced pressure to give the Boc deprotected-compound (0.78g,).

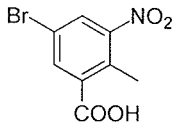
[01982] The Boc deprotected compound (0.30 g, 0.62 mmol) was dissolved in DCM (3 mL) and formalin (0.07 g, 2.33 mmol) was added at 0 ^{0}C. The resulting reaction mixture was stirred at 0 ^{0}C for 20 minutes. Sodium triacetoxyborohydride (0.33 g, 1.56 mmol) was added and the reaction mixture was stirred at room temperature for 1 h. After completion, the solvent was removed under reduced pressure and water was added to the residue, extraction was carried out using 10% MeOH/DCM. The combined organic layers were dried and concentrated under reduced pressure to afford crude material which was purified by prep. HPLC to give the title

compound N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-((4-(dimethylamino)cyclohexyl)-(ethyl)-amino)-5-(2-methoxyethoxy)-2-methylbenzamide as a mixture of cis/trans-isomers (0.02g, 6.3 %). LCMS: 513.60 $(M + 1)^+$; HPLC: 44.48% & 50.77% (@ 210-370 nm) (R_t;3.879 & 4.316); **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 μ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 μL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-*d6*, 400 MHz) δ 11.45 (s, 1H), 8.04 (s, 1H), 6.68 (s, 1H), 6.52 (s, 1H), 5.85 (s, 1H), 4.25 (d, 2H, J=4.4 Hz), 4.03 (bs, 2H), 3.61 (bs, 2H), 3.28 (s, 3H), 3.10 (m, 1H), 2.95 (m, 2H), 2.18 (s, 6H), 2.12 (s, 3H), 2.10 (s, 3H), 2.08 (s, 3H), 1.77 (m, 2H), 1.65 (bs, 2H), 1.33 (m, 3H), 1.15 (m, 1H), 0.78 (t, 3H, J=4 Hz).

[01983] **Compound 311: N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)-(ethyl)-amino)-5-(ethylthio)-2-methylbenzamide**

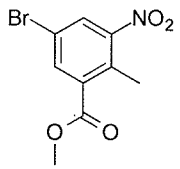


[01984] Step 1: synthesis of 5-bromo-2-methyl-3-nitrobenzoic acid



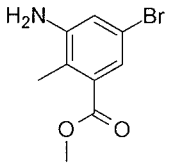
[01985] To stirred solution of 2-methyl-3-nitrobenzoic acid (50.0 g, 276 mmol) in conc. H_2SO_4 (200 mL) was added 1,3-dibromo-5,5-dimethyl-2,4-imidazolidinedione (43.4 g, 151.8 mmol) portion-wise at room temperature and the reaction mixture was stirred at room temperature for 5 h. On completion, the reaction mixture was poured on ice cold water, the resulting precipitate was filtered, washed with water, and dried under vacuum giving desired crude title compound (71.7 g, 99.9%) which was used directly in the next step.

[01986] Step 2: synthesis of methyl 5-bromo-2-methyl-3-nitrobenzoate



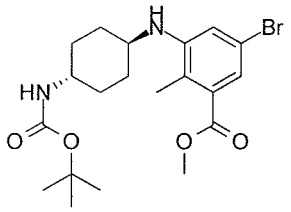
[01987] To stirred solution of 5-bromo-2-methyl-3-nitrobenzoic acid (285 g, 1104 mmol) in DMF (2.8L) was added sodium carbonate (468 g, 4415 mmol) followed by addition of methyl iodide (626 g, 4415 mmol) at room temperature. The resulting reaction mixture was heated at 60 °C for 8 h. After completion , the reaction mixture was filtered and washed with ethyl acetate. The combined filtrates were washed with water and the aqueous phase was back extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford the title compound as an off-white solid (290g, 97% yield). The isolated compound was taken directly into the next step.

[01988] Step 3: synthesis of methyl 3-amino-5-bromo-2-methylbenzoate



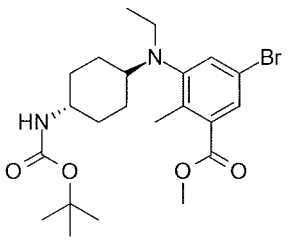
[01989] To stirred solution of methyl 5-bromo-2-methyl-3-nitrobenzoate (290 g, 1060mmol) in ethanol (1.5L) was added aqueous ammonium chloride (283 g, 5290 mmol dissolved in 1.5L water). The resulting mixture was stirred and heated at 80°C followed by addition of iron powder (472 g, 8450 mmol) in portions at 80°C. The resulting reaction mixture was heated at 80 °C for 12 h. After completion , the reaction mixture was hot filtered over celite and the celite bed was washed with methanol (5L) followed by washing with 30% MeOH in DCM (5L). The combined filtrate was concentrated in-vacuo, the residue obtained was diluted with aqueous bicarbonate and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford the title compound as brown solid (220 g, 89% yield).

[01990] Step 4: synthesis of methyl 5-bromo-3-(((1*R*,4*R*)-4-((tert-butoxycarbonyl)-amino)-cyclohexyl)amino)-2-methylbenzoate



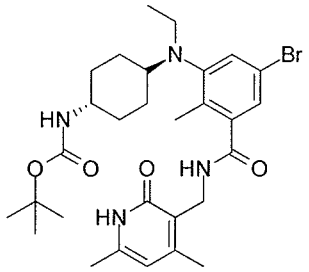
[01991] To a stirred solution of methyl 3-amino-5-bromo-2-methylbenzoate (15.0 g, 617 mmol) and tert-butyl (4-oxocyclohexyl)carbamate (17.1 g, 80.2 mmol) in dichloroethane (150 mL) was added acetic acid (22.2g, 370 mmol) and the reaction mixture stirred at room temperature for 10 minutes. Then sodium triacetoxyborohydride (39.3 g, 185 mmol) was added at 0°C and the reaction stirred overnight at room temperature. On completion, the reaction was quenched with aqueous sodium bicarbonate, the organic phase separated and the aqueous phase extracted with dichloromethane. The combined organic layers were washed with water, dried, and concentrated under reduced pressure. The crude material was purified by column chromatography to afford the title compound methyl 5-bromo-3-(((1r,4r)-4-((tert-butoxycarbonyl)-amino)-cyclohexyl)amino)-2-methylbenzoate (10.5 g, 39%).

[01992] Step 5: synthesis of methyl 5-bromo-3-(((1r,4r)-4-((tert-butoxycarbonyl)-amino)-cyclohexyl)-(ethyl)-amino)-2-methylbenzoate



[01993] To a stirred solution of 5-bromo-3-(((1r,4r)-4-((tert-butoxycarbonyl)-amino)-cyclohexyl)amino)-2-methylbenzoate (10.0 g, 22.7 mmol) and acetaldehyde (2.99 g, 68 mmol) in dichloroethane (100 mL) was added acetic acid (8.18 g, 136 mmol) and the reaction mixture was stirred at room temperature for 20 minutes. Then sodium triacetoxyborohydride (14.5 g, 68.1 mmol) was added at 0°C and the reaction stirred overnight at room temperature. On completion, the reaction was quenched with aqueous sodium bicarbonate, the organic phase separated and the aqueous phase extracted with dichloromethane. The combined organic layers were washed with water, dried, concentrated under reduced pressure, crude material was purified by column chromatography to afford the title compound (9.0 g, 84%).

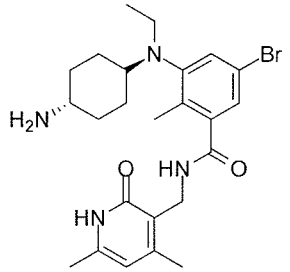
[01994] Step 6: synthesis of tert-butyl ((1r,4r)-4-((5-bromo-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)-(ethyl)-amino)-cyclohexyl)carbamate



[01995] Aqueous NaOH (1.15 g, 28.8 mmol) was added to a solution of methyl 5-bromo-3-(((1r,4r)-4-((tert-butoxycarbonyl)-amino)-cyclohexyl)-(ethyl)-amino)-2-methylbenzoate (9.0 g, 19 mmol) in ethanol (100 mL) and the mixture stirred at 60 °C for 1 h. After completion of the reaction, ethanol was removed under reduced pressure and the residue was acidified using dilute HCl up to pH 6 and adjusted to pH 4 with citric acid. Extraction was carried out using 10% MeOH/DCM. The combined organic layers were dried and concentrated to give the crude acid (8.6 g,).

[01996] The acid (8.6 g, 19 mmol) was then dissolved in DMSO (10 mL) and 3-(amino methyl)-4, 6-dimethylpyridin-2(1H)-one (5.74 g, 37.8 mmol) was added. The reaction mixture was stirred at room temperature for 15 min, PYBOP (14.7 g, 2845mmol) was added and stirring was continued overnight. The reaction mixture was poured into ice and extracted with 10 % MeOH/DCM. The combined organic layers were dried, concentrated to obtain crude material which was purified by washing with acetonitrile to afford the title compound (10.2 g, 92 %).

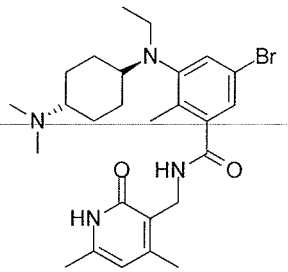
[01997] Step 7: synthesis of 3-(((1r,4r)-4-aminocyclohexyl)-(ethyl)-amino)-5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide



[01998] To a solution of tert-butyl ((1r,4r)-4-((5-bromo-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)-(ethyl)-amino)-cyclohexyl)carbamate

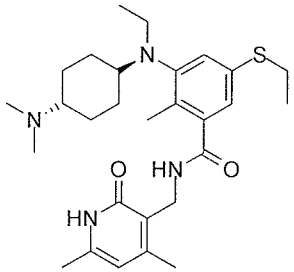
(3.0 g, 5.10 mmol) in DCM (20 mL) was added TFA (5 mL) and the reaction mixture was stirred at rt for 1 h. After completion of reaction, the solvent was removed under reduced pressure and saturated $NaHCO_3$ solution was added to the residue. Extraction was carried out using 10% MeOH/DCM; the combined organic layers were washed with water and brine; dried over anhydrous Na_2SO_4; filtered and concentrated under reduced pressure to give the title compound (2.2 g, 88%) which was used directly in the next step.

[01999] Step 8: synthesis of 5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)-(ethyl)-amino)-2-methylbenzamide



[02000] To a solution of 3-(((1r,4r)-4-aminocyclohexyl)-(ethyl)-amino)-5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide (2.20 g, 4.50 mmol) in DCM (25 mL) was added formalin (0.49 g, 16.3 mmol) at 0 ^{0}C. The resulting reaction mixture was stirred at 0 ^{0}C for 20 minutes. Sodium triacetoxyborohydride (2.39 g, 11.2 mmol) was added and the reaction mixture was stirred at room temperature for 1 h. After completion, water was added and extraction was carried out using 10 % MeOH/DCM. The combined organic layers were dried and concentrated under reduced pressure to give the title compound (2.3 g, 98%) which was used directly in the next step.

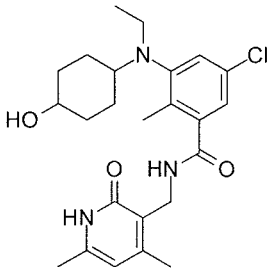
[02001] Step 9: synthesis of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)-(ethyl)-amino)-5-(ethylthio)-2-methylbenzamide



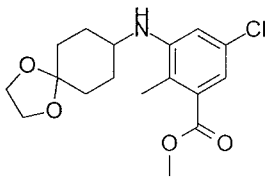
[02002] To a stirred solution of 5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)-(ethyl)-amino)-2-methylbenzamide (0.40

g, 0.77 mmol) in dioxane was added ethanethiol (0.048 g, 0.77 mmol) and DIPEA (2.70 mL, 1.55 mmol) and the reaction mixture then purged with argon for 10 min. Then, Pd $(OAc)_2$ (0.009 g, 0.038 mmol) and Xantphos (0.045 g, 0.077 mmol) were added and the reaction mixture was stirred at 100 °C overnight. After completion of the reaction, water was added and extraction was carried out using ethyl acetate. The combined organic layers were washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude material which was purified by column chromatography to give the title compound (0.17 g, 44%). LCMS: 499.55 $(M + 1)^+$; HPLC: 99.30% (at 210-370 nm) (R_t;4.264); **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 μ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 μL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-*d6*, 400 MHz) δ 11.46 (bs, 1H), 9.37 (s, 1H), 8.14 (s, 1H), 7.08 (s, 1H), 6.89 (s, 1H), 5.86 (s, 1H), 4.25 (d, 2H, J=4 Hz), 3.15-2.90 (m, 6H), 2.69 (s, 3H), 2.68 (s, 3H), 2.18 (s, 3H), 2.14 (s, 3H), 2.10 (s, 3H), 1.94 (m, 2H), 1.85 (m, 2H), 1.41 (m, 4H), 1.20 (t, 3H, J=7.2), 0.78 (t, 3H, J=6 Hz).

[02003] **Compound 313: 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(4-hydroxycyclohexyl)-amino)-2-methylbenzamide**



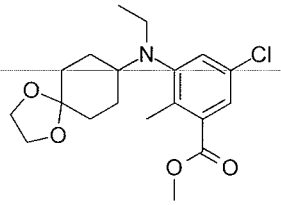
[02004] Step 1: synthesis of methyl 3-(1,4-dioxaspiro[4.5]decan-8-ylamino)-5-chloro-2-methylbenzoate



[02005] To a stirred solution of methyl 3-amino-5-chloro-2-methylbenzoate (5.0 g, 25 mmol) and 1,4-dioxaspiro[4.5]decan-8-one (5.86 g, 37.8 mmol) in dichloroethane (50 mL) was added

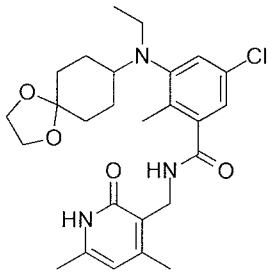
acetic acid (9.0 g, 150 mmol) and the reaction mixture stirred at room temperature for 10 minutes. Then sodium triacetoxyborohydride (15.9 g, 752 mmol) was added at 0°C and the reaction stirred overnight at room temperature. On completion, the reaction was quenched with aqueous sodium bicarbonate, the organic phase separated and the aqueous phase extracted with dichloromethane. The combined organic layers were dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography to afford the title compound (6.6 g, 76%).

[02006] Step 2: synthesis of methyl 5-chloro-3-(ethyl(1,4-dioxaspiro[4.5]decan-8-yl)amino)-2-methylbenzoate



[02007] To a stirred solution of methyl 3-(1,4-dioxaspiro[4.5]decan-8-ylamino)-5-chloro-2-methylbenzoate (6.6 g, 19 mmol) and acetaldehyde (2.56 g, 58.4 mmol) in dichloroethane (70 mL) was added acetic acid (7.0 g, 120 mmol) and the reaction mixture stirred at room temperature for 10 minutes. Then sodium triacetoxyborohydride (12 g, 57 mmol) was added at 0°C and the reaction stirred overnight at room temperature. On completion, the reaction was quenched with aqueous sodium bicarbonate, the organic phase separated and the aqueous phase extracted with dichloromethane. The combined organic layers were dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford the title compound (4.0 g, 56%).

[02008] Step 3: synthesis of 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(1,4-dioxaspiro[4.5]decan-8-yl)amino)-2-methylbenzamide

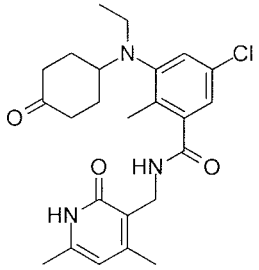


[02009] Aqueous NaOH (1.5 g, 38 mmol) was added to a solution of methyl 5-chloro-3-(ethyl(1,4-dioxaspiro[4.5]decan-8-yl)amino)-2-methylbenzoate (6.9 g, 19 mmol) in ethanol (70

mL) and the mixture stirred at 60 °C for 1 h. After completion of the reaction, ethanol was removed under reduced pressure and acidified using dilute HCl up to pH 6 and adjusted to pH 4 with citric acid. Extraction was carried out using ethyl acetate. The combined organic layers were dried concentrated to give the crude acid (6.5 g).

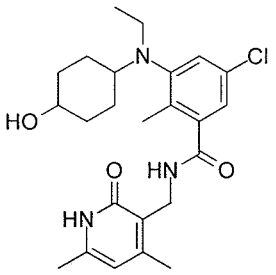
[02010] The crude acid (6.5 g, 18 mmol) was dissolved in DMSO (50 mL) and 3-(amino methyl)-4, 6-dimethylpyridin-2(1H)-one (5.6 g, 37 mmol) was added. The reaction mixture was stirred at room temperature for 15 min, PYBOP (14.3 g, 27.5 mmol) was added and stirring was continued overnight. The reaction mixture was poured into ice and extracted with 10 % MeOH/DCM. The combined organic layers were washed with water, dried, concentrated under reduced pressure to give the title compound (5.9 g 66%) which was used directly in the next step.

[02011] Step 4: synthesis of 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(4-oxocyclohexyl)amino)-2-methylbenzamide



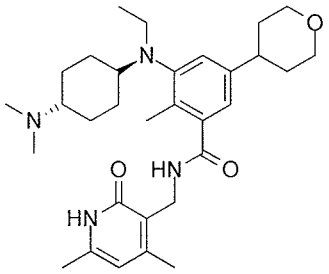
[02012] To a stirred solution of 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(1,4-dioxaspiro[4.5]decan-8-yl)amino)-2-methylbenzamide (2.0 g, 4.1 mmol) in acetone: water (14 mL+6 mL) was added PTSA (3.1 g, 16 mmol). The resulting reaction mixture was stirred at 70 °C overnight. On completion, the solvent was removed under reduced pressure and the residue was basified with aqueous sodium bicarbonate. The aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with water, dried, concentrated under reduced pressure to give the title compound (1.5 g, 83%) which was used directly in the next step.

[02013] Step 5: synthesis of 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(4-hydroxycyclohexyl)-amino)-2-methylbenzamide

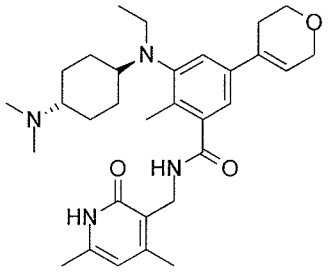


[02014] To a stirred solution of 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(4-oxocyclohexyl)amino)-2-methylbenzamide (0.30 g, 0.68 mmol) in MeOH was added $NaBH_4$ (0.038 g, 1.01 mmol) slowly at 0 ^{0}C. The resulting reaction mixture was stirred at 0 ^{0}C for 2 h. On completion, the reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with water, dried, concentrated under reduced pressure and the crude material obtained was purified by acetonitrile and ether washings to afford the title compound as a mixture of isomers (175mg, 58%). LCMS: 446.35 $(M + 1)^+$; HPLC: 74.32% & 24.18% (@ 210-370 nm) (R_t;5.157 & 5.276); **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 µ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 µL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-*d6*, 400 MHz) δ 11.49 (s, 1H), 8.25 (s, 1H), 7.17 (s, 1H), 6.96 (s, 1H), 5.86 (s, 1H), 4.25 (d, 2H, J=4 Hz), 3.33 (m, 1H), 3.04 (m, 2H), 2.19 (s, 3H), 2.14 (s, 3H), 2.10 (s, 3H), 1.78 (m, 2H), 1.66 (m, 2H), 1.38 (m, 3H), 1.10 (m, 2H), 0.78 (t, 3H).

[02015] **Compound 315: N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methyl-5-(tetrahydro-2H-pyran-4-yl)benzamide**

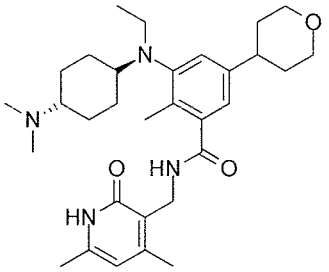


[02016] Step 1: Synthesis of 5-(3,6-dihydro-2H-pyran-4-yl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methylbenzamide



[02017] To a stirred solution of 5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methylbenzamide (0.30 g, 0.58 mmol) and 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.18 g, 0.88 mmol) in dioxane-water mixture was added Na_2CO_3 (0.22 g, 2.07 mmol) . The solution was purged with argon for 15 min, Pd $(PPh_3)_4$ (0.067 g, 0.05 mmol) was added and the solution was purged again with argon for 10 min. The reaction mixture was heated at 100°C for 3 hours. On completion, the reaction mixture was diluted with water and extracted with 10% MeOH/DCM. The combined organic layers were dried over Na_2SO_4 and the solvent removed under reduced pressure to afford the title compound (0.30 g, 98 %).

[02018] Step 2: Synthesis of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methyl-5-(tetrahydro-2H-pyran-4-yl)benzamide

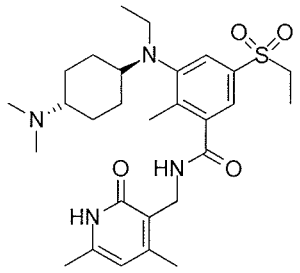


[02019] To a stirred solution of 5-(3,6-dihydro-2H-pyran-4-yl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methylbenzamide (0.3 g, 0.576 mmol) in methanol, was added a catalytic amount of 10% Pd/C. The reaction mixture was stirred at room temperature under hydrogen balloon pressure for 1hour. On completion, the reaction mixture was filtered through a celite bed, the celite washed

with methanol and the filtrate concentrated under reduced pressure, to yield a crude compound which was purified by prep. HPLC to afford the target compound N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1s,4s)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methyl-5-(tetrahydro-2H-pyran-4-yl)benzamide as the TFA salt (0.08 g, 26%).

[02020] LCMS: 523.60 $(M + 1)^+$; HPLC: 48.41+51.05% (@ 210nm-370 nm) (R_t; 3.93& 3.99); **Method**: Column: YMC ODS-A 150 mm x 4.6 mm x 5 µ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 µL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6,, 400 MHz) δ 11.47 (bs, 1H), 8.39 (t, 1H), 8.08 (s, 1H), 7.07(s,1H), 6.86 (s, 1H), 5.87 (s, 1H), 4.26 (d, 2H, J=2.8Hz), 3.94-3.92 (m, 2H), 3.41 (m, 2H), 3.09-2.89 (m, 3H), 2.69 (s, 3H+3H), 2.19 (s, 3H+3H), 2.11 (s,3H), 1.99-1.86 (m,5H), 1.64 (m,4H), 1.42(m,3H), 1.25(m,2H), 0.79 (t, 3H).

[02021] **Compound 319: N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-5-(ethylsulfonyl)-2-methylbenzamide**

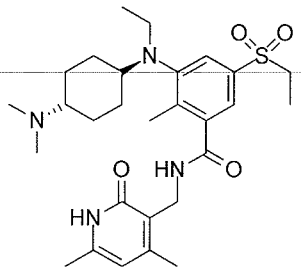


[02022] Step 1: Synthesis of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-5-(ethylthio)-2-methylbenzamide

[02023] To a stirred solution of 5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methylbenzamide (0.4 g, 0.77 mmol.) in dioxane was added ethanethiol (0.048 g, 0.77 mmol) and DIPEA (2.7 mL, 1.55 mmol) . The solution was purged with argon for 10 min, Pd $(OAc)_2$ (0.009 g, 0.038 mmol) and Xantphos (0.045 g, 0.077 mmol) were added to it and argon was purged again for 10 min. The reaction mixture was stirred at 100 °C for overnight, water was and extraction was carried out using ethyl acetate. The combined organic layers were washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude material which was purified by column chromatography to afford compound the title compound (0.17 g,

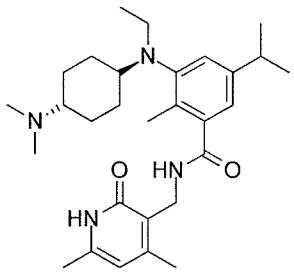
44%).LCMS: 499.55 $(M + 1)^+$; HPLC: 99.30% (@ 210-370 nm) (R_t;4.264); **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 μ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 μL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-*d6*, 400 MHz) δ 11.46 (bs, 1H), 9.37 (s, 1H), 8.14 (s, 1H), 7.08 (s, 1H), 6.89 (s, 1H), 5.86 (s, 1H), 4.25 (d, 2H, J=4 Hz), 3.15-2.90 (m, 6H), 2.69 (s, 3H), 2.68 (s, 3H), 2.18 (s, 3H), 2.14 (s, 3H), 2.10 (s, 3H), 1.94 (m, 2H), 1.85 (m, 2H), 1.41 (m, 4H), 1.20 (t, 3H, J=7.2), 0.78 (t, 3H, J=6 Hz).

[02024] Step 2: Synthesis of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-5-(ethylsulfonyl)-2-methylbenzamide

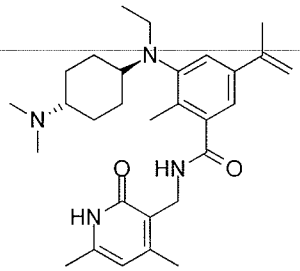


[02025] To a stirred solution of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-5-(ethylthio)-2-methylbenzamide (0.085 g, 0.17 mmol.) in methanol was added oxone (0.105g, 0.34 mmol) at room temperature. The reaction mixture was stirred at room temperature for 4h,water was added and extraction was carried out using 10% MeOH/DCM. The combined organic layers were washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude material which was purified by prep. HPLC to afford the title compound as the TFA salt (0.07g, 77%). LCMS: 531.60 $(M + 1)^+$; HPLC: 89.24% (@ 210nm-370 nm) (R_t;4.082; Method: Column: YMC ODS-A 150 mm x 4.6 mm x 5 μ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 μL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); **^{1}H NMR** (DMSO-d_6,, 400 MHz) δ 11.47 (s, 1H), 9.36 (s, 1H), 8.36 (s, 1H), 7.53 (s, 1H), 7.38 (s, 1H), 7.22 (m, 1H), 7.09 (s, 1H), 6.96 (s, 1H), 5.87 (s, 1H), 4.29-4.28 (d, 2H, J= 4.8Hz), 3.0-3.20 (m, 4H), 2.60-2.80 (m, 8H), 2.27 (s, 9H), 2.20 (s, 3H), 2.11 (s, 3H), 1.90-2.0 (m, 2H), 1.80-1.90 (m, 2H), 1.40-1.50(m, 4H), 1.05-1.15 (t, 3H, J=7.6Hz), 0.75-0.85 (t, 3H, J=6.8Hz).

[02026] **Compound 320: N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-5-isopropyl-2-methylbenzamide**

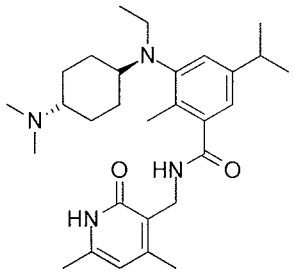


[02027] Step 1: Synthesis of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methyl-5-(prop-1-en-2-yl)benzamide



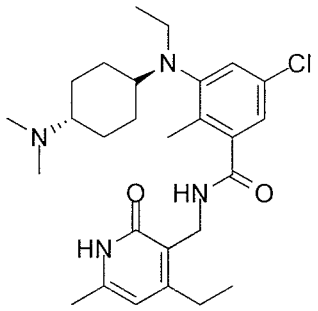
[02028] To a stirred solution of 5-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methylbenzamide (0.30 g, 0.58 mmol) and 4, 4, 5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (0.147 g, 0.875 mmol) in dioxane/water mixture was added Na_2CO_3 (0.22 g, 2.07 mmol) and the solution purged with argon for 15 min. Then Pd $(PPh_3)_4$ (0.067 g, 0.058 mmol) was added and argon was purged again for 10 min. The reaction mixture was heated at 100°C for 2 hours diluted with water and extracted with 10% MeOH/DCM. The combined organic layers were dried over Na_2SO_4 and the solvent removed under reduced pressure to afford crude material which was purified by column chromatography over silica gel to afford the title compound (0.20 g, 71 %).

[02029] Step 2: N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-5-isopropyl-2-methylbenzamide

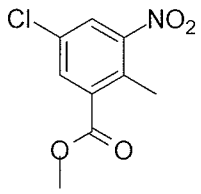


[02030] To a stirred solution of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methyl-5-(prop-1-en-2-yl)benzamide (0.20 g, 0.41 mmol) in methanol was added a catalytic amount of 10% Pd/C. The reaction mixture was stirred at room temperature under hydrogen pressure (balloon pressure) for 2h. The mixture was filtered through a celite bed, washed with methanol and the filtrate was concentrated under reduced pressure. The resulting crude compound was purified by prep. HPLC to afford the title compound as the TFA salt (0.07 g, 35%). LCMS: 481.40 $(M + 1)^+$; HPLC: 97.01% (@ 210 nm-370 nm) (R_t;3.996; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 μ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 μL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.46 (bs, 1H), 9.37 (bs, 1H), 8.00 (s, 1H), 7.01 (s, 1H), 6.83 (s, 1H), 5.86 (s, 1H), 4.26-4.25 (d, 2H, J= 4.0Hz), 3.0-3.25 (m, 3H), 2.70-2.8 (m, 1H), 2.60-2.75 (m, 6H), 2.19 (s, 3H), 2.15 (s, 3H), 2.10 (s, 3H), 1.90-2.0 (m, 2H), 1.80-1.90 (m, 2H), 1.35-1.50(m, 4H), 1.16-1.20 (d, 6H, J= 6.8Hz), 0.75-0.85 (t, 3H).

[02031] **Compound 321: 5-chloro-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)-(ethyl)-amino)-N-((4-ethyl-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide**



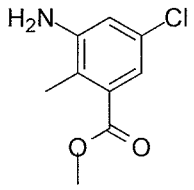
[02032] Step 1: synthesis of methyl 5-chloro-2-methyl-3-nitrobenzoate



[02033] To stirred solution of 5-chloro-2-methyl-3-nitrobenzoic acid (126 g, 0.59 mol) in DMF (1.0 L) was added sodium carbonate (249 g, 2.34 mol) and methyl iodide (145 mL, 2.34 mol). The reaction mixture was heated at 60 °C for 4 h. On completion, the reaction mixture

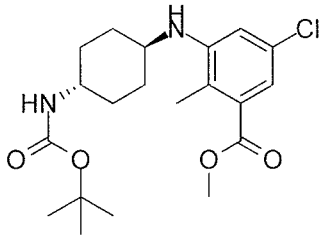
was filtered and the residue washed with DCM. The aqueous phase was separated and extracted with DCM. The combined organic layers were dried, concentrated under reduced pressure and purified by column chromatography over silica eluting with ethyl acetate: hexane to afford the title compound (85 g, 63%).^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.25 (d, 1H), 8.05 (s, 1H), 3.9 (s, 1H), 2.4 (s, 1H).

[02034] Step 2: synthesis of methyl 3-amino-5-chloro-2-methyl benzoate



[02035] To stirred solution of methyl 5-chloro-2-methyl-3-nitrobenzoate (85 g, 0.37 mol) in ethanol (425 mL) were added ammonium chloride (85 g, 112 mmol) dissolved in water (425 mL) and iron powder (169 g, 2.96 mol) with stirring. The resulting reaction mixture was heated at 80 °C for 16 h filtered and the residue washed well with hot ethanol. The filtrate was concentrated and the residue was basified with aqueous sodium bicarbonate. The aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with water, dried, concentrated under reduced pressure to give the crude title compound (70 g) which was used directly. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 6.8 (s, 2H), 5.45 (s, 2H), 3.75 (s, 3H), 2.15 (s, 3H)

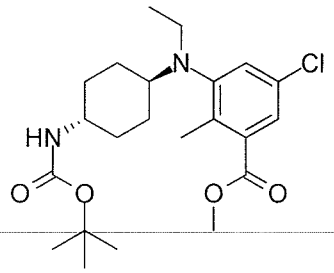
[02036] Step 3: synthesis of methyl 3-(((1r, 4r)-4-((tert-butoxy-carbonyl)amino)cyclohexyl)amino)-5-chloro-2-methylbenzoate



[02037] To a stirred solution of methyl 3-amino-5-chloro-2-methyl benzoate (12 g, 60 mmol) and tert-butyl (4-oxocyclohexyl)carbamate (15.4g, 72 mmol) in dichloroethane (120 mL) was added acetic acid (21 g, 360 mmol) and the reaction mixture was stirred at room temperature for 10 minutes. Then sodium triacetoxyborohydride (38.2g, 180 mmol) was added and the reaction stirred for 2 h at room temperature. On completion, water was added to the reaction mixture and extraction was carried out using DCM. The combined organic layers were washed

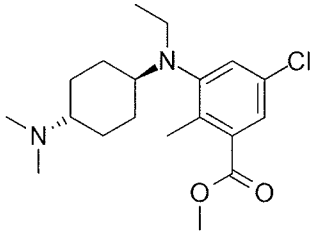
with bicarbonate solution, dried over sodium sulphate and concentrated under reduced pressure to give crude material which was then column purified to give *trans*-isomer title compound methyl 3-(((1r, 4rs)-4-((tert-butoxycarbonyl)amino)cyclohexyl)amino)-5-chloro-2-methylbenzoate (8.0 g, 33 %).

[02038] Step 4: synthesis of methyl 3-(((1r, 4r)-4-((tert-butoxycarbonyl)amino)-cyclohexyl)-(ethyl)amino)-5-chloro-2-methylbenzoate



[02039] To a stirred solution of methyl 3-(((1r, 4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl)amino)-5-chloro-2-methylbenzoate (11.4 g, 28.8 mmol) and acetaldehyde (2.5 g, 56 mmol) in dichloroethane (120 mL) was added acetic acid (10.7 g, 169 mmol) and the reaction mixture was stirred at room temperature for 10 minutes. Then sodium triacetoxyborohydride (17.95 g, 84.6 mmol) was added and reaction stirred for 2 h at room temperature. On completion, water was added to the reaction mixture and extraction was carried out using DCM. Combined organic layers were washed with bicarbonate solution, dried over sodium sulphate and concentrated under reduced pressure to give crude material which was then column purified to give the title compound (9.8 g, 80 %).

[02040] Step 5: synthesis of methyl 5-chloro-3-(((1r, 4r)-4-(dimethylamino)-cyclohexyl)-(ethyl)amino)-2-methylbenzoate

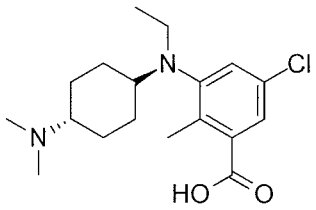


[02041] To a stirred solution of methyl 3-(((1r, 4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl)amino)-5-chloro-2-methylbenzoate (9.8 g, 23 mmol) in DCM (50 mL) at 0 °C was added TFA (10 mL) and the reaction mixture was stirred for 2 h at room temperature. After completion, the reaction was concentrated to dryness. The residue was

then basified with aqueous sat. bicarbonate solution (100 mL) to pH 8 and the aqueous layer extracted with 20% methanol in DCM (100 mL x 4). The combined organic layers were dried over Na_2SO_4 and the solvent removed under reduced pressure to afford crude amine (7.4 g) which was used as such for next reaction.

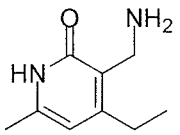
[02042] To a stirred solution of the amine (7.4 g, 23 mmol) in DCM (70 mL) at 0 °C, was added 37-41 % aq. formalin solution (2.4 g, 81 mmol) and the reaction mixture stirred at room temperature for 10 min. $NaBH(OAc)_3$ (12.1 g, 57 mmol) was then added and the reaction stirred for 2 h. On completion, the reaction mixture was quenched with water. MeOH (8 mL) was added and the layers were separated. Extraction was performed with 10% MeOH in DCM and the combined organic phases were dried and concentrated. The residue was column purified over basic alumina to afford the title compound (8.0 g, 99%).

[02043] Step 6: synthesis of 5-chloro-3-(((1r, 4r)-4-(dimethylamino)cyclohexyl)-(ethyl)-amino)-2-methyl-benzoic acid



[02044] Aqueous NaOH (1.8g, 45 mmol in 7 mL H_2O) was added to a solution of compound methyl 3-(((1r, 4r)-4-((tert-butoxycarbonyl)amino)-cyclohexyl)-(ethyl)amino)-5-chloro-2-methylbenzoate (8.0 g, 23 mmol) in ethanol (70 mL) and stirred at 60 °C for 1 h. After completion of the reaction, ethanol was removed under reduced pressure and the residue acidified using dilute HCl up to pH 6 and adjusted to pH 4 with citric acid. Extraction was carried out using 10% MeOH in DCM. The combined organic layers were dried over Na_2SO_4 and concentrated to afford the title compound (7.6 g, 99%).

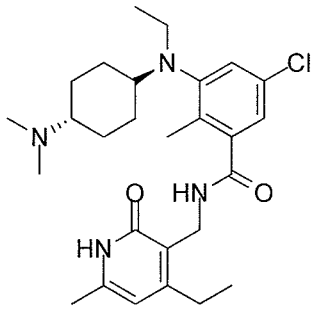
[02045] Step 7: synthesis of 3-(aminomethyl)-4-ethyl-6-methylpyridin-2(1H)-one



[02046] To a solution of 4-ethyl-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (1 eq) in methanol and aq. ammonia solution (9:1)was added a catalytic amount of Raney Nickel. The reaction mixture was stirred at room temperature under hydrogen pressure (balloon pressure)

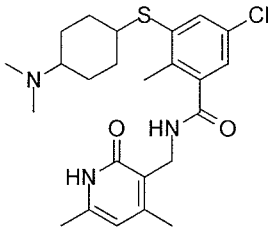
for 2-5 h. On completion of reaction, it was filtered through a celite bed and the filtrate was concentrated under reduced pressure to afford the title compound.

[02047] Step 8: synthesis of 5-chloro-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)-(ethyl)-amino)-N-((4-ethyl-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide

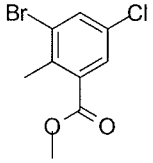


[02048] The above acid, 5-chloro-3-(((trans)-4-(dimethylamino)cyclohexyl)-(ethyl)-amino)-2-methyl-benzoic acid, (1 eq) was dissolved in DMSO and 3-(aminomethyl)-4-ethyl-6-methylpyridin-2(1H)-one (2 eq.) was added. The reaction mixture was stirred at room temperature for 15 min, PYBOP (1.5 eq.) and triethylamine (1 eq.) were added. The reaction mixture was stirred overnight. The reaction mixture was then poured into ice, and extracted with 10% MeOH/DCM. The combined organic layers were dried, and concentrated to obtain which was purified by column chromatography followed by prep. HPLC to afford the title compound as a TFA salt (0.1 g, 70%). LCMS: 487.45 $(M + 1)^+$; HPLC: 96.17% (@ 254 nm) (R_t;6.026; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 μ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 μL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.46 (bs, 1H), 9.33 (s, 1H), 8.22 (s, 1H), 7.19 (s, 1H), 6.97 (s, 1H), 5.88 (s, 1H), 4.20-4.25 (d, 2H), 3.0-3.15 (m, 1H+2H), 2.60-2.75 (m, 1H+3H+3H), 2.35-2.45 (m, 2H), 2.20 (s, 3H), 2.15 (s, 3H), 1.90-2.0 (m, 2H), 1.80-1.90 (m, 2H), 1.35-1.50 (m, 4H), 1.10-1.20 (t, 3H, J=7.2 Hz), 0.75-0.85 (t, 3H).

[02049] **Compound 335: 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-((4-(dimethylamino)cyclohexyl)thio)-2-methylbenzamide**

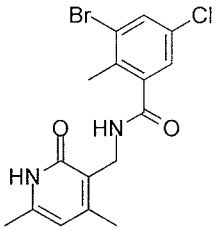


[02050] Step 1: Synthesis of methyl 3-bromo-5-chloro-2-methylbenzoate



[02051] To stirred solution of $CuBr_2$ (12.3 g, 55.3 mmol) in acetonitrile (150 mL), tert-butyl nitrite (7.77 g, 75.4 mmol) was added at 0 ^{0}C and then methyl 3-amino-5-chloro-2-methylbenzoate (10.0 g, 50.3 mmol) dissolved in acetonitrile was added to it. The resulting reaction mixture was stirred at 0 ^{0}C for 2 hours and then at room temperature for 18h. On completion, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were dried, concentrated under reduced pressure and purified by silica gel column chromatography giving the title compound (6.6 g, 50%).

[02052] Step 2: Synthesis of 3-bromo-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)-methyl)-2-methylbenzamide

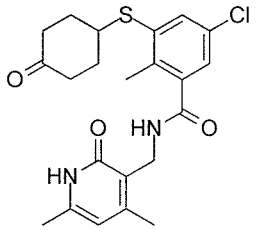


[02053] Aqueous NaOH (0.45g, 11.4 mmol) was added to a solution of methyl 3-bromo-5-chloro-2-methylbenzoate (2.0 g, 7.6 mmol) in EtOH (20 mL) and the mixture stirred at 60 °C for 1 hour. After completion of the reaction, ethanol was removed under reduced pressure and the residue acidified using dilute HCl up to pH 8 and then with citric acid till pH 6. The aqueous phase was extracted with 10% methanol in DCM. The combined organic layers were dried and concentrated to give respective crude acid intermediate (1.5 g).

[02054] The acid (1.5 g, 6.2 mmol) was dissolved in DMSO (15 mL) and 3-(amino methyl)-4, 6-dimethylpyridin-2(1H)-one (1.67 g, 12.43 mmol) and triethylamine (0.61 g, 6.01 mmol) was added. The reaction mixture was stirred at room temperature for 15 min, PyBop (4.81 g, 9.26

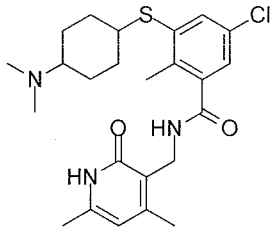
mmol) was added and stirring was continued overnight at room temperature. After completion, the reaction mixture was poured into ice water. The suspended solid was collected by filtration, washed well with water and dried. The solid obtained was further purified by washings with acetonitrile to afford the title compound (2.18 g, 92 %).

[02055] Step 3: Synthesis of 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-((4-oxocyclohexyl)thio)benzamide



[02056] A solution of 3-bromo-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)-methyl)-2-methylbenzamide (0.35g, 0.91 mmol.), 4-mercaptocyclohexanone (0.142 g, 1.09 mmol) and DIPEA (0.235 g, 1.82 mmol) in dioxane was purged with argon for 10 min. Then, $Pd(OAc)_2$ (0.01 g, 0.044 mmol) and Xantphos (0.052 g, 0.089 mmol) were added and argon was purged again for 10 min. The reaction mixture was stirred at 100 °C overnight. After completion of the reaction, water was added and extraction was carried out using ethyl acetate. The combined organic layers were washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude material which was purified by column chromatography to afford the title compound (0.50 g, 88%).

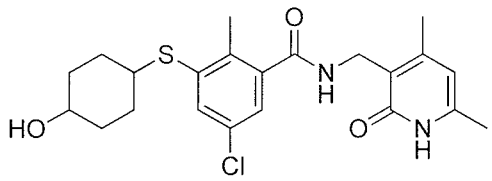
[02057] Step 4: Synthesis of 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-((4-(dimethylamino)cyclohexyl)thio)-2-methylbenzamide



[02058] To a stirred solution of 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-3-((4-oxocyclohexyl)thio)benzamide (0.45 g, 1.03 mmol) and dimethylamine (0.14 g, 3.11 mmol) in dichloroethane (5 mL) was added acetic acid (0.37g, 6.16 mmol) and the mixture stirred at room temperature for 20 minutes. Then sodium triacetoxyborohydride (0.66 g, 3.11 mmol) was added at 0°C and the mixture stirred overnight

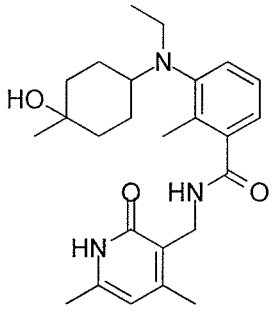
at room temperature. On completion of the reaction, the solvent was removed under reduced pressure. Water was added to the residue and extraction was performed using 5%MeOH/DCM. The combined organic layers were dried and concentrated to afford crude material which was purified by column chromatography to afford the title compound (0.016 g, 3.3 %). **Analytical Data:** LCMS: 462.35 $(M + 1)^+$; HPLC: 89.00% (@ 210-370 nm) (R_t;4.949; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 µ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 µL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.44 (s, 1H), 7.16 (s, 1H), 6.10 (s, 1H), 4.44 (s, 2H), 3.63 (m, 1H), 3.13 (m, 1H), 2.38 (s, 3H), 2.36 (s, 3H), 2.35 (s, 3H), 2.31 (s, 3H), 2.24 (s, 3H), 1.75-2.08 (m, 8H).

[02059] **Compound 336**: **5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-((4-hydroxycyclohexyl)thio)-2-methylbenzamide**

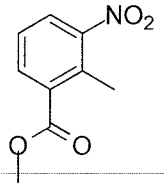


[02060] This compound was also isolated as an additional product from the purification of compound 335 (0.235 g, 50%) **Analytical Data of:** LCMS: 435.30 $(M + 1)^+$; HPLC: 99.37% (@ 210-370 nm) (R_t;5.900; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 µ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 µL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.46 (bs, 1H), 8.31 (t, 1H), 7.72-7.68 (m, 1H), 7.41 (s, 1H), 7.07 (s, 1H), 5.85 (s, 1H), 4.58 (d, 1H, J=4 Hz), 4.24 (d, 2H, J=4 Hz), 4.13 (m, 1H), 3.43 (m, 1H), 2.20 (s, 3H), 2.18 (s, 3H), 2.10 (s, 3H), 1.95-1.80 (m, 1H), 1.75-1.55 (m, 1H), 1.40-1.20 (m, 4H), 0.87 (m, 2H).

[02061] **Compound 339: N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(4-hydroxy-4-methylcyclohexyl)amino)-2-methylbenzamide**

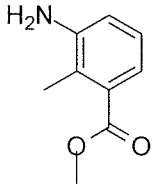


[02062] Step 1: synthesis of methyl 2-methyl-3-nitrobenzoate



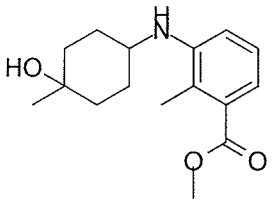
[02063] To a solution of 2-methyl-3-nitrobenzoic acid (10.0 g, 55.0 mmol) in 120 ml of methanol, was added conc. H_2SO_4 (15 ml) at room temperature and the mixture stirred at 60 °C overnight. The mixture was concentrated under reduced pressure, the crude material was neutralized with sat. $NaHCO_3$, and extracted with ethyl acetate. The organic phase was dried over Na_2SO_4, and concentrated under reduced pressure to afford the title compound(10 g).

[02064] Step 2: synthesis of methyl 3-amino-2-methylbenzoate



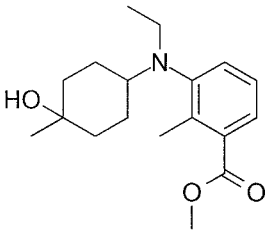
[02065] To a stirred solution of methyl 2-methyl-3-nitrobenzoate (10.0 g, 56.4 mmol) in 60 ml of ethanol were added ammonium chloride (18.0 g, 338 mmol) dissolved in 60 mL of water and iron powder (18.8 g, 338.2 mmol). The resulting reaction mixture was heated at 80 °C for 3 h. Water was added to the reaction mixture and then it was filtered through celite. The filtrate was extracted with ethyl acetate. The combined organic layers were washed with water, dried over Na_2SO_4, concentrated under reduced pressure to give the title compound (7.0 g, 83%).

[02066] Step 3: synthesis of methyl 3-((4-hydroxy-4-methylcyclohexyl)amino)-2-methylbenzoate



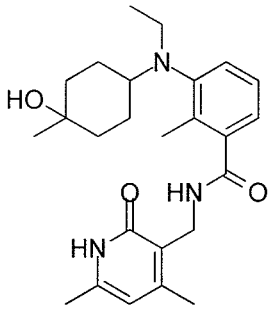
[02067] To a stirred solution of methyl 3-amino-2-methylbenzoate (1.5 g, 9.1 mmol) and 4-hydroxy-4-methylcyclohexanone (1.51 ml, 11.8 mmol) in 10 ml of dichloroethane was added acetic acid (3.2 mL, 55 mmol) and the reaction mixture stirred at room temperature for 20 minutes. The reaction mixture was cooled to 0 °C and sodium triacetoxyborohydride (5.78 g, 27.3 mmol) was added and the mixture stirred at room temperature overnight. The reaction mixture was neutralized with sat. $NaHCO_3$, extracted with DCM, dried over Na_2SO_4, concentrated under reduced pressure, and purified by silica gel column chromatography to afford the title compound which was carried forward as a mixture of cis and trans isomers (1.4 g, 56%).

[02068] Step 4: synthesis of methyl 3-(ethyl(4-hydroxy-4-methylcyclohexyl)amino)-2-methylbenzoate



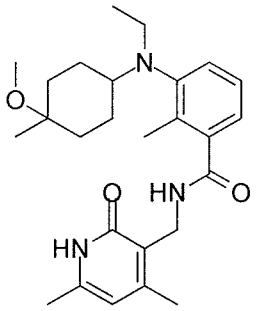
[02069] To a stirred solution of methyl 3-((4-hydroxy-4-methylcyclohexyl)amino)-2-methylbenzoate (1.4 g, 5.05 mmol) and acetaldehyde (0.7 ml, 13 mmol) in 20 ml of dichloroethane was added acetic acid (1.7 mL, 30 mmol) and the reaction mixture was stirred at room temperature for 20 minutes. The reaction mixture was cooled to 0 °C and sodium triacetoxyborohydride (3.2 g, 15 mmol) was added and the mixture was stirred at room temperature for overnight. The reaction mixture was neutralized with sat. $NaHCO_3$ and extracted with DCM. The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure, and the residue purified by silica gel column chromatography to afford the title compound (1.42 g, 94%).

[02070] Step 5: synthesis of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(4-hydroxy-4-methylcyclohexyl)amino)-2-methylbenzamide

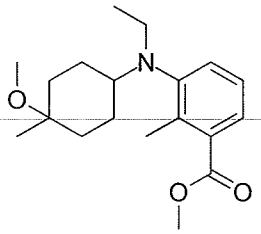


[02071] A mixture of methyl 3-(ethyl(4-hydroxy-4-methylcyclohexyl)amino)-2-methylbenzoate (300 mg, 0.98 mmol) and NaOH (58 mg, 1.47 mmol) in 5 ml of ethanol and water (3:2) was heated at 70 °C for 2 h. The reaction mixture was concentrated to dryness and the residue was partitioned between water and ethyl acetate. The organic layer was dried over $Na_2SO_4$and concentrated under reduced pressure to afford 270 mg of the crude acid. The crude acid (270 g, 0.92 mmol), 3-(aminomethyl)-4,6-dimethylpyridin-2(1H)-one (282 mg, 1.85 mmol), PyBOP (717 mg, 1.38 mmol) and triethylamine (0.12 ml, 0.92 mmol) were stirred in 3 ml of DMSO at room temperature overnight. The reaction mixture was diluted with water and extracted with 10% MeOH in DCM. The combined organic phases were dried over Na_2SO_4, concentrated and the residue purified by silica gel column chromatography to give the title compound N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(4-hydroxy-4-methylcyclohexyl)amino)-2-methylbenzamide as a mixture of isomers (120 mg, 30%). LCMS: 426.45 $(M + 1)^+$; HPLC: 62.09 & 33.24% (@ 210-370 nm) (R_t;3.982 & 4.164; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 µ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 µL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6 ,400 MHz) δ 11.44 (s, 1H), 8.04 (m, 1H), 7.12 (s, 2H), 6.91 (m, 1H), 5.85 (s, 1H), 4.25 (d, 2H, J=4 Hz), 4.15 (m, 1H), 3.00 (m, 2H), 2.84 (m, 1H), 2.18 (s, 6H), 2.10 (s, 3H), 1.75-1.60 (m, 2H), 1.55-1.35 (m, 4H), 1.35-1.15 (m, 4H), 1.08 & 1.03 (s, 3H), 0.87 & 0.77 (t, 3H).

[02072] **Compound 340**: **N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(4-methoxy-4-methylcyclohexyl)amino)-2-methylbenzamide**

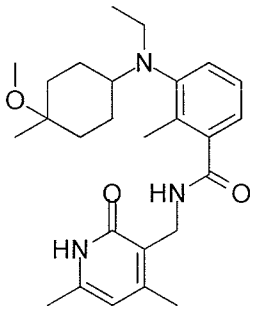


[02073] Step 1: synthesis of methyl 3-(ethyl(4-methoxy-4-methylcyclohexyl)amino)-2-methylbenzoate



[02074] To a cooled solution of methyl 3-(ethyl(4-hydroxy-4-methylcyclohexyl)amino)-2-methylbenzoate (300 mg, 0.98 mmol) in THF (5 ml), was added sodium hydride (235 mg, 5.89 mmol) portion-wise followed by methyl iodide (0.61 ml, 9.8 mmol).The mixture was stirred at room temperature for 1 h, cooled to 0 °C quenched with ice cold water and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give 300 mg of the crude title compound.

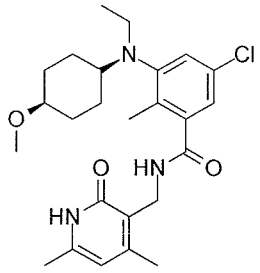
[02075] Step 2: Synthesis of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(4-methoxy-4-methylcyclohexyl)amino)-2-methylbenzamide



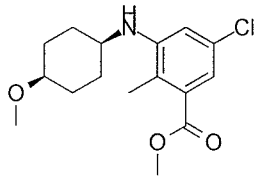
[02076] A mixture of 3-(ethyl(4-methoxy-4-methylcyclohexyl)amino)-2-methylbenzoate (300 mg, 0.94 mmol) and NaOH (56 mg, 1.41 mmol) in 5 ml of ethanol and water (4:1) was heated at 70 °C for 2 h. The reaction mixture was concentrated to dryness and the crude material was partitioned between water and ethyl acetate. The organic layer was dried over Na_2SO_4, and

concentrated under reduced pressure to afford 280 mg of the crude acid. A mixture of the crude acid (280 mg, 0.91 mmol), 3-(aminomethyl)-4,6-dimethylpyridin-2(1H)-one (279 mg, 1.83 mmol), PyBOP (716 mg, 1.37 mmol) and triethylamine (0.12 ml, 0.91 mmol) in DMSO (3 ml) was stirred at room temperature overnight. The reaction mixture was diluted with water, extracted with 10% MeOH in DCM, dried over Na_2SO_4, and concentrated to a residue which was purified by silica gel column chromatography to afford the title compound N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(4-methoxy-4-methylcyclohexyl)amino)-2-methylbenzamide as a mixture of isomers (70 mg, 17%). LCMS: 440.45 $(M + 1)^+$; HPLC: 45.77 & 48.47% (@ 210-370 nm) (R_t;4.297 & 4.430; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 μ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 μL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6 ,400 MHz) δ 11.45 (s, 1H), 8.03 (bs, 1H), 7.15 (bs, 2H), 6.91 (s, 1H), 5.85 (s, 1H), 4.25 (d, 2H, J=2.8 Hz), 3.10-2.90 (m, 7H), 2.19 (s, 6H), 2.10 (s, 3H), 1.72-1.10 (m, 8H), 1.08 & 0.99 (s, 3H), 0.77 (t, 3H).

[02077] **Compound 344: 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((1s,4s)-4-methoxycyclohexyl)amino)-2-methylbenzamide**



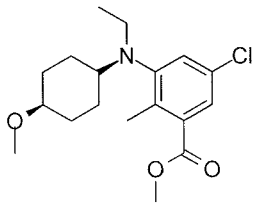
[02078] Step 1: Synthesis of methyl 5-chloro-3-(((1s,4s)-4-methoxycyclohexyl)amino)-2-methylbenzoate



[02079] To a stirred solution of methyl 3-amino-5-chloro-2-methylbenzoate (1.0 g, 5.0 mmol) and 4-methoxycyclohexanone (1.28 g, 10.0 mmol) in dichloroethane (10 mL) was added acetic

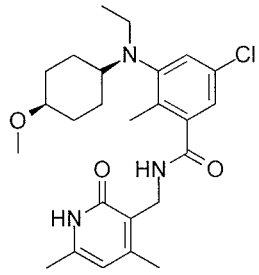
acid (1.8 g, 30 mmol) and the mixture stirred at room temperature for 10 minutes. Then sodium triacetoxyborohydride (3.2 g, 15 mmol) was added at 0°C and the reaction stirred overnight at room temperature. On completion, the reaction was quenched with aqueous sodium bicarbonate, the organic phase separated and the aqueous phase extracted with dichloromethane. The combined organic layers were dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material obtained was purified by silica gel column chromatography and the cis-isomer title compound was isolated as the less polar product isomer (0.60 g, 38%). The trans isomer can also be carried forward to produce the corresponding trans final product, compound 343.

[02080] Step 2: Synthesis of methyl 5-chloro-3-(ethyl((1s,4s)-4-methoxycyclohexyl)amino)-2-methylbenzoate



[02081] To a stirred solution of methyl 5-chloro-3-(((1s,4s)-4-methoxycyclohexyl)amino)-2-methylbenzoate (0.60 g, 1.92 mmol) and acetaldehyde (0.25 g, 5.78 mmol) in dichloroethane (10 mL), was added acetic acid (0.69g, 11.6 mmol) and the mixture stirred at room temperature for 10 minutes. Then sodium triacetoxyborohydride (1.22 g, 5.78 mmol) was added at 0°C and the reaction stirred overnight at room temperature. On completion, the reaction was quenched with aqueous sodium bicarbonate, the organic phase separated and the aqueous phase extracted with dichloromethane. The combined organic layers were dried over anhydrous sodium sulphate and concentrated under reduced pressure and the crude product purified by silica gel column chromatography to afford the title compound (0.60 g, 92%).

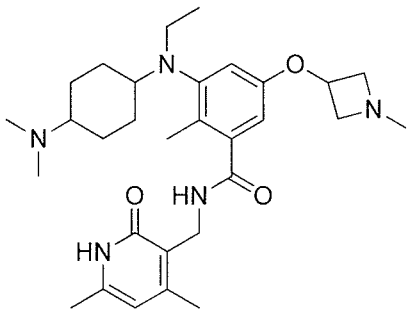
[02082] Step 3: Synthesis of 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((1s,4s)-4-methoxycyclohexyl)amino)-2-methylbenzamide



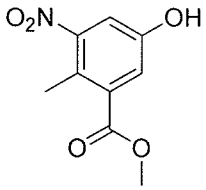
[02083] Aqueous NaOH (0.07 g, 1.76 mmol) was added to a solution of methyl 5-chloro-3-(ethyl((1r,4r)-4-methoxycyclohexyl)amino)-2-methylbenzoate (0.4 g, 1.17 mmol) in ethanol (5 mL) and the mixture was stirred at 60 °C for 1 h. After completion of the reaction, ethanol was removed under reduced pressure and acidified using dilute HCl up to pH 6 and adjusted using to pH 4 citric acid. Extraction was carried out using ethyl acetate and the combined organic layers were dried concentrated giving the respective crude acid (0.35 g).

[02084] The above crude acid (0.35g, 1.1 mmol) was dissolved in DMSO (4 mL) and 3-(amino methyl)-4, 6-dimethylpyridin-2(1H)-one (0.33g, 2.14 mmol) was added.. The reaction mixture was stirred at room temperature for 15 min, PYBOP (0.84 g, 1.61 mmol) was added and stirring was continued overnight. After completion of the reaction, the mixture was poured into ice and extracted with 10 % MeOH/DCM. The combined organic layers were dried over anhydrous sodium sulphate and concentrated under reduced pressure to yield a crude product which was purified by silica gel column chromatography to afford the title compound (0.55 g, 79%). LCMS: 460.30 $(M + 1)^+$; HPLC: 97.37% (@ 210-370 nm) (R_t;5.026; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 µ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 µL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.44 (bs, 1H), 8.21 (t, 1H), 7.13 (s, 1H), 6.93 (s, 1H), 5.85 (s, 1H), 4.25 (d, 2H, J=3.2 Hz), 3.27 (m, 1H), 3.18 (s, 3H), 2.99 (q, 2H), 2.79 (m, 1H), 2.18 (s, 3H), 2.14 (s, 3H), 2.10 (s, 3H), 1.77 (m, 2H), 1.60 (m, 2H), 1.45 (m, 2H), 1.33 (m, 2H), 0.78 (t, 3H, J=6 Hz).

[02085] **Compound 349: N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-((4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methyl-5-((1-methylazetidin-3-yl)oxy)benzamide**

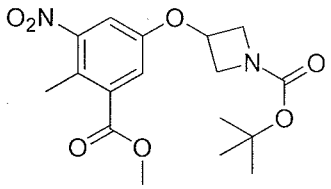


[02086] Step 1: Synthesis of methyl 5-hydroxy-2-methyl-3-nitrobenzoate



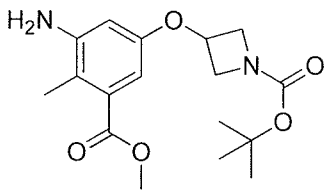
[02087] To a stirred solution of 5-hydroxy-2-methyl-3-nitrobenzoic acid (3.50 g, 17.8 mmol) in methanol (40 mL), was added thionyl chloride (3.9 mL, 53 mmol) at 0 °C. The mixture was heated under reflux for 3 hours and concentrated under reduced pressure. Aqueous sodium bicarbonate was added to the residue which was extracted with ethyl acetate. The combined organic layers were washed with water, dried and concentrated under reduced pressure. The crude material was purified by column chromatography to afford the title compound (3.0 g, 80%).

[02088] Step 2: Synthesis of tert-butyl 3-(3-(methoxycarbonyl)-4-methyl-5-nitrophenoxy)azetidine-1-carboxylate



[02089] To stirred solution of 5-hydroxy-2-methyl-3-nitrobenzoate (1.5 g, 7.1 mmol) in ACN (15 mL)were added cesium carbonate (4.64 g, 14.2 mmol) and tert-butyl 3-iodoazetidine-1-carboxylate (3.0 g, 11 mmol). The resulting mixture was heated at 80 °C overnight. On completion, the reaction mixture was diluted with water and extraction was carried out using ethyl acetate. The combined organic layers were washed with water, dried and concentrated under reduced pressure. The crude material was purified by column chromatography to afford the title compound (1.2 g, 46%).

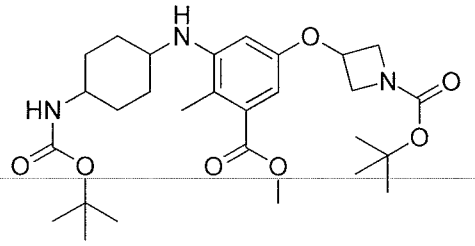
[02090] Step 3: Synthesis of tert-butyl 3-(3-amino-5-(methoxycarbonyl)-4-methylphenoxy)azetidine-1-carboxylate



[02091] To stirred solution of tert-butyl 3-(3-(methoxycarbonyl)-4-methyl-5-nitrophenoxy)azetidine-1-carboxylate (1.0 g, 2.7 mmol) in methanol (10 mL) was added a

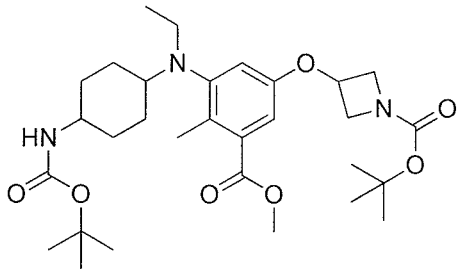
catalytic amount of 10% Pd/C.. The mixture was stirred at room temperature under a hydrogen atmosphere (balloon pressure) for 3 hours. On completion, the reaction mixture was filtered through a celite bed which was further washed with methanol. The combined filtrates were concentrated under reduced pressure to afford the title compound (0.90 g, 98%).

[02092] Step 4: Synthesis of tert-butyl 3-(3-((4-((tert-butoxycarbonyl)amino)cyclohexyl)amino)-5-(methoxycarbonyl)-4-methylphenoxy)azetidine-1-carboxylate



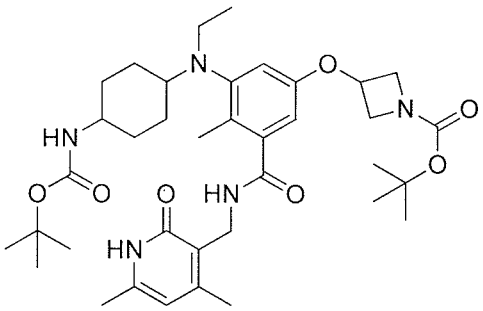
[02093] To a stirred solution of tert-butyl 3-(3-amino-5-(methoxycarbonyl)-4-methylphenoxy)azetidine-1-carboxylate (0.90 g, 2.67 mmol) and tert-butyl (4-oxocyclohexyl)carbamate (0.741 g, 3.47 mmol) in dichloroethane (10 mL) was added acetic acid (0.96 g, 16.1 mmol) and the mixture stirred at room temperature for 20 minutes. Then sodium triacetoxyborohydride (1.7 g, 8.0 mmol) was added at 0 °C and the reaction stirred at room temperature for 2 h. On completion, the reaction was quenched with aqueous sodium bicarbonate, the organic phase separated and the aqueous phase extracted with dichloromethane. The combined organic layers were washed with water, dried, concentrated under reduced pressure and the crude material purified by column chromatography to afford the title compound (0.9 g, 63%) as a mixture of cis/trans isomers.

[02094] Step 5: Synthesis of tert-butyl 3-(3-((4-((tert-butoxycarbonyl)amino)cyclohexyl)(ethyl)amino)-5-(methoxycarbonyl)-4-methylphenoxy)azetidine-1-carboxylate



[02095] To a stirred solution of tert-butyl 3-(3-((4-((tert-butoxycarbonyl)amino)cyclohexyl)amino)-5-(methoxycarbonyl)-4-methylphenoxy)azetidine-1-carboxylate (0.90 g, 1.69 mmol) and acetaldehyde (0.22 g, 5.06 mmol) in dichloroethane (10 mL), was added acetic acid (0.61 g, 10 mmol) and the reaction stirred at room temperature for 20 minutes. Then sodium triacetoxyborohydride (1.07 g, 5.05 mmol) was added at 0 °C and the reaction was stirred at room temperature for 2 h. On completion, the reaction was quenched with aqueous sodium bicarbonate, the organic phase separated and the aqueous phase extracted with dichloromethane. The combined organic layers were washed with water, dried, concentrated under reduced pressure giving the title compound which was used without further purification (0.85g).

[02096] Step 6: Synthesis of tert-butyl 3-(3-((4-((tert-butoxycarbonyl)amino)cyclohexyl)(ethyl)amino)-5-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-4-methylphenoxy)azetidine-1-carboxylate

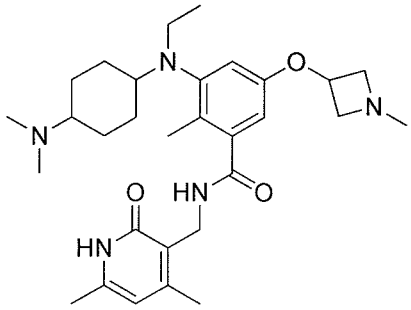


[02097] Aqueous NaOH (0.12 g, 3.03 mmol) was added to a solution of tert-butyl 3-(3-((4-((tert-butoxycarbonyl)amino)cyclohexyl)(ethyl)amino)-5-(methoxycarbonyl)-4-methylphenoxy)azetidine-1-carboxylate(0.85 g, 1.52 mmol) in ethanol (10 mL) and the mixture stirred at 60 °C for 1 h. After completion of the reaction, ethanol was removed under reduced pressure and acidified using dilute HCl up to pH 6 and adjusted using citric acid to pH 4. Extraction was carried out using ethyl acetate. The combined organic layers were dried and concentrated giving the respective acid (0.75 g).

[02098] The above acid (0.75 g, 1.37 mmol) was then dissolved in DMSO (7 mL) and 3-(amino methyl)-4, 6-dimethylpyridin-2(1H)-one (0.42 g, 2.74 mmol) was added to it. The reaction mixture was stirred at room temperature for 15 min, PYBOP (1.06 g, 2.05 mmol) was added to it and stirring was continued overnight. After completion, the reaction mixture was poured into ice, extracted with 10% MeOH/DCM. The combined organic layers were washed

with water, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the title compound (0.80 g, 85 %).

[02099] Step 7: Synthesis of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-((4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methyl-5-((1-methylazetidin-3-yl)oxy)benzamide



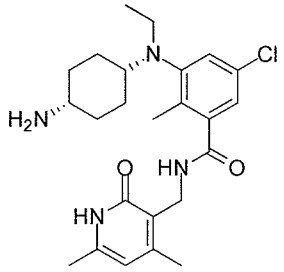
[02100] To a cooled stirred solution of tert-butyl 3-(3-((4-((tert-butoxycarbonyl)amino)cyclohexyl)(ethyl)amino)-5-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-4-methylphenoxy)azetidine-1-carboxylate (0.80 g, 1.17 mmol) in DCM (10 mL) was added TFA (2 mL). The mixture was stirred at rt for 1 h, concentrated under reduced pressure and saturated $NaHCO_3$ solution was added to the residue. Extraction was carried out using 10%MeOH/DCM and the combined organic layers were washed with water and brine and dried over anhydrous Na_2SO_4.The solvent was removed under reduced pressure to give the Boc deprotected intermediate compound (0.5 g).

[02101] The above intermediate (0.5 g, 1.0 mmol) was dissolved in MeOH (3 mL) and formalin (0.16 g, 5.33 mmol) was added at 0 ^{0}C. The mixture was stirred at same temperature for 20 minutes. Sodium triacetoxyborohydride (0.55 g, 2.59 mmol) was added and the mixture stirred at room temperature for 1 h. After completion, the solvent was removed under reduced pressure and water added to the residue. Extraction was carried out using 10 % MeOH/DCM. The combined organic layers were dried and concentrated under reduced pressure to afford crude material which was purified by column chromatography to afford the title compound (0.03 g, 5.5 %).

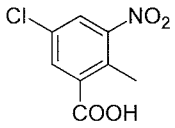
[02102] LCMS: 524.55 $(M + 1)^+$; HPLC: 37.93+61.46% (@ 210-370 nm) (R_t;3.462 and 3.810; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 µ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 µL, Col. Temp.: 30 ^{o}C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.45 (bs, 1H), 8.05 (bs, 1H), 6.56 (s, 1H), 6.36 (s, 1H), 5.85 (s, 1H),

4.69 (bs, 1H), 4.24 (bs, 2H), 3.67 (m, 2H), 3.08-2.92 (m, 4H), 2.33-2.11 (m, 20H), 1.73-1.65 (m, 4H), 1.35-1.29 (m, 4H), 0.77 (t, 3H).

[02103] **Compound 119: 3-(((1*s*,4*s*)-4-aminocyclohexyl)(ethyl)amino)-5-chloro-*N*-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide**

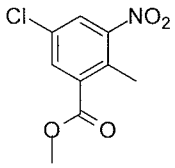


[02104] Step 1: synthesis of 5-chloro-2-methyl-3-nitrobenzoic acid



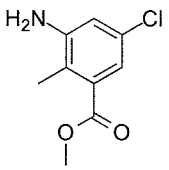
[02105] To a stirred solution of 5-chloro-2-methylbenzoic acid (4.0 g, 24 mmol) in concentrated H_2SO_4 (27 mL) at -10 °C was added a nitrating solution comprised of concentrated HNO_3 (3.3 g, 53 mmol) dissolved in concentrated H_2SO_4 (4.4 mL). The resulting mixture was stirred at -10 °C for 3 h and poured onto ice water. The resulting precipitate was filtered, washed with water and dried under vacuum to give the title compound (4.95 g, 99%).

[02106] Step 2: synthesis of methyl 5-chloro-2-methyl-3-nitrobenzoate



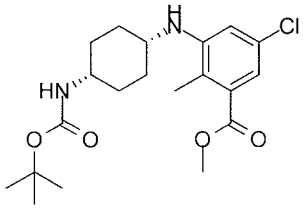
[02107] To a stirred solution of 5-chloro-2-methyl-3-nitrobenzoic acid (6.75 g, 31.3 mmol) in DMF (33 mL), were added sodium carbonate (13.2 g, 125 mmol) and methyl iodide (17.8 g, 125 mmol). The mixture was heated at 60 °C for 4 h. Water was added to the reaction mixture followed by extraction with dichloromethane. The combined organic extracts were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel to afford the title compound (6.0 g, 84%).

[02108] Step 3: synthesis of methyl 3-amino-5-chloro-2-methyl benzoate



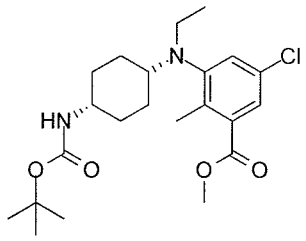
[02109] To stirred solution of methyl 5-chloro-2-methyl-3-nitrobenzoate (6.0 g, 26 mmol) in ethanol (60 mL), were added a solution of ammonium chloride (6.0 g, 112 mmol) in water (60 mL) and iron powder (11.9 g, 208 mmol). The mixture was heated at 80 °C for 1 h. Water was added and the resulting mixture was filtered through celite followed by extraction with ethyl acetate. The combined organic layers were washed with water, dried over sodium sulfate and concentrated under reduced pressure to afford the crude title compound (5.0 g).

[02110] Step 4: synthesis of methyl 3-(((1*s*,4*s*)-4-((*tert*-butoxycarbonyl)amino)cyclohexyl) amino)-5-chloro-2-methylbenzoate



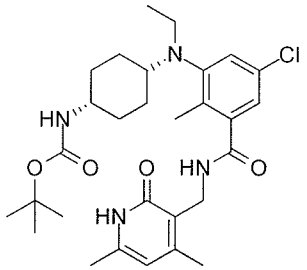
[02111] To a stirred solution of 3-amino-5-chloro-2-methyl benzoate (5.0 g, 25 mmol) and *tert*-butyl (4-oxocyclohexyl)carbamate (6.95 g, 32.7 mmol) in dichloroethane (25 mL), was added acetic acid (9.0 g, 150 mmol) at room temperature. Sodium triacetoxyborohydride (15.97 g, 75.4 mmol) was added and reaction stirred 1 h at room temperature. The solvent was removed under reduced pressure and the crude material was purified by column chromatography over silica gel to afford to afford 5.2 g (52%) of the first eluting title compound *cis*-isomer product methyl 3-(((1*s*,4*s*)-4-((*tert*-butoxycarbonyl)amino)cyclohexyl) amino)-5-chloro-2-methylbenzoate and 3.5 g (35%) the more polar isomer *trans*-isomer product methyl 3-(((1*r*,4*r*)-4-((*tert*-butoxycarbonyl)amino)cyclohexyl)amino)-5-chloro-2-methylbenzoate.

[02112] Step 5: synthesis of methyl 3-(((1*s*,4*s*)-4-((*tert*-butoxycarbonyl)amino)cyclohexyl) (ethyl)amino)-5-chloro-2-methylbenzoate



[02113] To a stirred solution of 3-(((1*s*,4*s*)-4-((*tert*-butoxycarbonyl)amino)cyclohexyl) amino)-5-chloro-2-methylbenzoate (5.20 g, 13.1 mmol) and acetaldehyde (1.15 g, 26.3 mmol) in dichloroethane (15 mL), was added acetic acid (4.72 g, 78.8 mmol) at room temperature. Sodium triacetoxyborohydride (8.35 g, 39.4 mmol) was added and the mixture was stirred for 1 h. Water was added the mixture was extracted with dichloromethane. The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel to afford the title compound (5.3 g, 99 %).

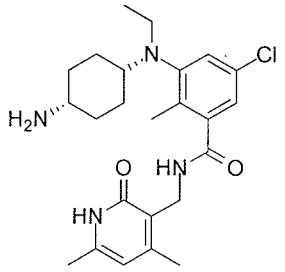
[02114] Step 6: synthesis of *tert*-butyl ((1*s*, 4*s*)-4-((5-chloro-3-(((4,6-dimethyl-2-oxo-1, 2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(ethyl)amino)cyclohexyl) carbamate



[02115] To a stirred solution of 3-(((1*s*,4*s*)-4-((*tert*-butoxycarbonyl)amino)-cyclohexyl)(ethyl)amino)-5-chloro-2-methylbenzoate (5.20 g, 12.2 mmol) in ethanol (15 mL) was added an aqueous solution of NaOH (0.73 g, 18.4 mmol). The mixture was stirred at 60 °C for 1 h, concentrated under reduced pressure and then acidified to pH 4 by addition of dilute HCl followed by citric acid. The resulting mixture was extracted with ethyl acetate and the combined extracts were dried and concentrated under reduced pressure to afford the corresponding crude acid (4.4 g). To a stirred solution of the acid (4.4 g, 10.7 mmol), 3-(aminomethyl)-4, 6-dimethylpyridin-2(1H)-one (3.25 g, 21.4 mmol) and triethylamine (1.08 g, 10.70 mmol) in DMSO (15 mL) was added PYBOP (8.34 g, 16.05 mmol) at 0° C. After stirring overnight at room temperature, the mixture was poured onto ice and extracted with 10 % MeOH/CH_2Cl_2. The combined organic layers were dried over sodium sulfate and concentrated

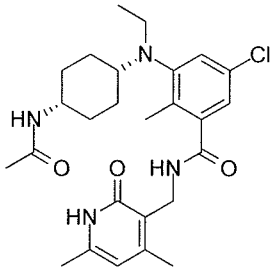
under reduced pressure to obtain crude material which was purified by column chromatography over silica gel to afford the title compound (4.20 g, 72 %). LCMS: 548.40 $(M + 1)^+$; HPLC: 98.62% (@ 254 nm) (R_t;5.736; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 µ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 µL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.45 (s, 1H), 8.20 (t, 1H), 7.13 (s, 1H), 6.91 (m, 2H), 5.85 (s, 1H), 4.22 (d, 2H), 3.47 (bs, 1H), 3.00-3.02 (m, 3H), 2.18 (s, 3H), 2.16 (s, 3H), 2.10 (s, 3H), 1.71 (m, 2H), 1.53 (m, 2H), 1.39 (m, 4H), 1.37 (s, 9H), 0.78 (t, 3H, J=6.8 Hz).

[02116] Step 7: synthesis of 3-(((1*s*,4*s*)-4-aminocyclohexyl)(ethyl)amino)-5-chloro-N-((4,6-dimethyl-2-oxo-1, 2-dihydropyridin-3-yl)methyl)-2-methylbenzamide



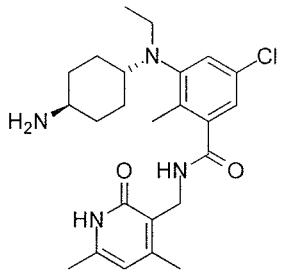
[02117] To a stirred solution of *tert*-butyl ((1*s*, 4*s*)-4-((5-chloro-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(ethyl)amino)cyclohexyl) carbamate (0.60 g, 1.10 mmol) in CH_2Cl_2 (10 mL) was added trifluoroacetic acid (2 mL) at 0°C. The mixture was stirred at room temperature for 2 h and concentrated to dryness. The residue was dissolved in aqueous sodium bicarbonate followed by extraction with 20% MeOH/CH_2Cl_2. The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to afford a residue which was triturated to afford the title compound (0.5 g, 100 %). LCMS:445.30 $(M + 1)^+$; HPLC: 99.3 % (@ 254 nm) (R_t;4.524; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 µ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 µL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.21 (t, 1H), 7.13 (s, 1H), 6.91 (d, 1H, J=1.6 Hz), 5.85 (s, 1H), 4.24 (d, 2H, J=4.8 Hz), 2.99-3.04 (m, 2H), 2.82-2.85 (m, 2H), 2.18 (s, 3H), 2.15 (s, 3H), 2.10 (s, 3H), 1.75-1.77 (m, 2H), 1.36-1.39 (m, 6H), 0.79 (t, 3H, J=6.8 Hz).

[02118] **Compound 121: 3-(((1*s*,4*s*)-4-acetamidocyclohexyl)(ethyl)amino)-5-chloro-N-((4,6-dimethyl-2-oxo-1, 2-dihydropyridin-3-yl) methyl)-2-methylbenzamide**

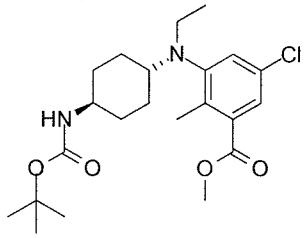


[02119] To a stirred solution of 3-(((1*s*,4*s*)-4-aminocyclohexyl)(ethyl)amino)-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide (0.30g, 0.68 mmol) and EDCI.HCl (0.194 g, 1.01 mmol) in DMF (5 mL) were added HOBt (0.091 g, 0.675 mmol) and acetic acid (0.081 g, 1.35 mmol) at room temperature. After stirring for 18 h water was added and the mixture was extracted with 10% $MeOH/CH_2Cl_2$. The combined organic layers were dried over sodium sulfate and concentrated to a residue which was purified by column chromatography over silica gel to afford the title compound (0.10 g, 30 %). LCMS:487.30 $(M + 1)^+$; HPLC: 91.72% (@ 254 nm) (R_t;4.585; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 µ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 µL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^1H NMR (DMSO-d_6, 400 MHz) δ 8.22 (t, 1H), 7.75 (d, 1H, J=7.2 Hz), 7.15 (s, 1H), 6.93 (s, 1H), 5.85 (s, 1H), 4.24 (d, 2H, J=4.4 Hz), 3.69 (bs, 1H), 3.01-3.03 (m, 2H), 2.94 (m,1H), 2.18 (s, 6H), 2.10 (s, 3H), 1.80 (s, 3H), 1.69-1.71 (m, 2H), 1.37-1.51 (m, 6H), 0.79 (t, 3H, J=6.8. Hz).

[02120] **Compound 120: 3-(((1*r*,4*r*)-4-aminocyclohexyl)(ethyl)amino)-5-chloro-*N*-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide**

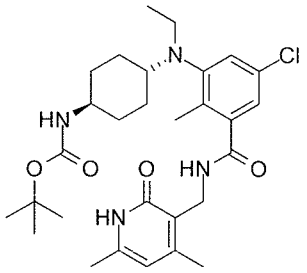


[02121] Step 1: synthesis of methyl 3-(((1*r*,4*r*)-4-((*tert*-butoxycarbonyl)amino)cyclohexyl) (ethyl)amino)-5-chloro-2-methylbenzoate



[02122] To a stirred solution of methyl 3-(((1*r*,4*r*)-4-((*tert*-butoxycarbonyl)amino)cyclohexyl) amino)-5-chloro-2-methylbenzoate (3.5 g, 8.8 mmol) prepared as described above and acetaldehyde (0.77 g, 17.7 mmol) in dichloroethane (15 mL), was added acetic acid (3.17 g, 53 mmol) at room temperature. After stirring for 10 minutes, sodium triacetoxyborohydride (5.61 g, 26.5 mmol) was added and the reaction was stirred for 1 h at room temperature. Water was added and the mixture was extracted with dichloromethane. The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to give crude material which was purified by column chromatography over silica gel to afford the title compound (3.5 g, 93 %).

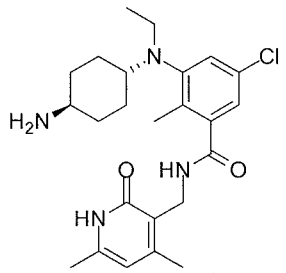
[02123] Step 2: synthesis of *tert*-butyl ((1*r*, 4*r*)-4-((5-chloro-3-(((4,6-dimethyl-2-oxo-1, 2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(ethyl)amino)cyclohexyl) carbamate



[02124] To a stirred solution of 3-(((1*r*,4*r*)-4-((*tert*-butoxycarbonyl)amino)cyclohexyl) (ethyl)amino)-5-chloro-2-methylbenzoate (3.50 g, 8.23 mmol) in ethanol (15 mL) was added an aqueous solution of NaOH (0.49g, 12.4 mmol). The mixture was stirred at 60 °C for 1 h, concentrated under reduced pressure and acidified to pH 4 by addition of dilute HCl followed by citric acid solution. The resulting mixture was extracted with ethyl acetate, and the combined organic layers were dried under reduced pressure to give the corresponding crude acid (3.2 g). To a stirred solution of the acid (3.2 g, 7.8 mmol), 3-(aminomethyl)-4, 6-dimethylpyridin-2(1H)-one (2.36 g, 15.6 mmol) and triethylamine (0.79 g, 7.8 mmol) in DMSO

(15 mL) was added PYBOP (6.07 g, 11.7 mmol) at 0° C. After stirring overnight at room temperature, the mixture was poured onto ice and extracted with 10 % MeOH/ CH_2Cl_2. The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to obtain crude material which was purified by column chromatography over silica gel to afford the title compound (3.0 g, 70 %). **Analytical Data:** LCMS: 545.25 $(M + 1)^+$; HPLC: 99.92% (@ 254 nm) (R_t;5.677; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 µ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 µL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.46 (s, 1H), 8.23 (t, 1H), 7.14 (s, 1H), 6.92 (s, 1H), 6.65 (d, 1H, J=7.2 Hz), 5.85 (s, 1H), 4.23 (d, 2H, J=4 Hz), 3.14 (bs, 1H), 3.00-3.02 (m, 2H), 2.18 (s, 3H), 2.11 (s, 3H), 2.10 (s, 3H), 1.67-1.76 (m, 4H), 1.40 (m, 2H), 1.35 (m, 9H), 1.04-1.13 (m, 2H), 0.77 (t, 3H, J=6 Hz).

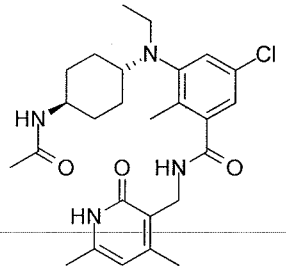
[02125] Step 3: synthesis of 3-(((1*r*,4*r*)-4-aminocyclohexyl)(ethyl)amino)-5-chloro-N-((4,6-dimethyl-2-oxo-1, 2-dihydropyridin-3-yl)methyl)-2-methylbenzamide



[02126] To a stirred solution of *tert*-butyl ((1*r*, 4*r*)-4-((5-chloro-3-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)(ethyl)amino)cyclohexyl) carbamate (0.6 g, 1.10 mmol) in dichloromethane (2 mL) was added TFA (2 mL) at 0°C. The mixture was stirred at room temperature for 2 h and concentrated to dryness. The residue was dissolved in aqueous sodium bicarbonate and extracted with 20% MeOH/ CH_2Cl_2. The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to afford crude product which was purified by column chromatography over silica get to afford the title compound (0.40 g, 81 %). LCMS:445.18 $(M + 1)^+$; HPLC: 98.13% (@ 254 nm) (R_t;4.096; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 µ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 µL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.22 (t, 1H), 7.13 (s, 1H), 6.92 (s, 1H), 5.85 (s, 1H), 4.23 (d, 2H, J=4

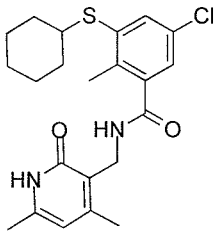
Hz), 3.00-3.01 (m, 2H), 2.59 (m,1H), 2.18 (s, 3H), 2.12 (s, 3H), 2.10 (s, 3H), 1.73-1.76 (m, 2H), 1.65-1.68 (m, 2H), 1.36-1.39 (m, 2H), 0.97-1.00 (m, 2H), 0.77 (t, 3H, J=6 Hz). [1H merged in solvent peak].

[02127] **Compound 122: 3-(((1*r*,4*r*)-4-acetamidocyclohexyl)(ethyl)amino)-5-chloro-N-((4,6-dimethyl-2-oxo-1, 2-dihydropyridin-3-yl) methyl)-2-methylbenzamide**



[02128] To a stirred solution of 3-(((1*r*,4*r*)-4-aminocyclohexyl)(ethyl)amino)-5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide (0.30 g, 0.68 mmol) and EDCI.HCl (0.19 g, 1.0 mmol) in DMF (5 mL) were added HOBt (0.09 g, 0.68 mmol) and acetic acid (0.081 g, 1.35 mmol) at room temperature. After stirring for 18 h, water was added and the mixture was extracted with 10% MeOH/DCM. The combined organic layers were dried and concentrated giving crude material which was then purified by column chromatography over silica get to afford the title compound (0.10 g, 30 %). LCMS:487.25 $(M + 1)^+$; HPLC: 92.95% (@ 254 nm) (R_t;4.445; **Method:** Column: YMC ODS-A 150 mm x 4.6 mm x 5 µ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 µL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ11.45 (s, 1H), 8.21 (t, 1H), 7.64 (d, 1H, J=7.6 Hz), 7.14 (s, 1H), 6.92 (s, 1H), 5.85 (s, 1H), 4.24 (d, 2H, J=4.8 Hz), 3.41-3.43 (m, 1H), 3.01-3.03 (m, 2H), 2.61 (m,1H), 2.18 (s, 3H), 2.13 (s, 3H), 2.10 (s, 3H), 1.74 (t, 7H, J=18 Hz), 1.40-1.43 (m, 2H), 1.07-1.12 (m, 2H), 0.77 (t, 3H, J=6.8 Hz).

[02129] **Compound 207: 5-chloro-3-(cyclohexylthio)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide**



[02130] Step 1: Synthesis of methyl 3-bromo-5-chloro-2-methylbenzoate

[02131] To a stirred solution of $CuBr_2$ (12.3 g, 55.3 mmol) in acetonitrile (100 mL), t-butyl nitrite (7.79g, 75.4 mmol) was added at 0 °C. To this solution, methyl 3-amino-5-chloro-2-methylbenzoate (10 g, 50.3 mmol) in acetonitrile (50 mL) was added and stirred at 0 °C for 2 h and at rt for overnight. On completion, water added and the product extracted with ethyl acetate. The organic layer was washed with aq. NH_4Cl solution and dried over sodium sulphate, then concentrated under reduced pressure. Silica gel column purification afforded the title compound (6.6 g, 50%).

[02132] Step 2: Synthesis of methyl 5-chloro-3-(cyclohexylthio)-2-methylbenzoate

[02133] To a stirred solution of methyl 3-bromo-5-chloro-2-methylbenzoate (1.0 g, 3.79 mmol) in 1,4-dioxane was added N,N-diisopropyl ethylamine (0.98 g, 7.59 mmol). The reaction mixture was purged with argon for 20 min. then $Pd(OAc)_2$ (0.042 g, 0.189 mmol), Xanthphos (0.22 g, 0.38 mmol) and cyclohexylthiol (0.44 g, 3.79 mmol) was added to it sequentially and again purged with argon for 10 min. The reaction mixture was then refluxed for 16 h. On completion, water was added, and the product extracted with ethyl acetate. The organic layer was dried over sodium sulphate and the product was purified by silica gel column to afford the title compound (1.0 g, 83%)

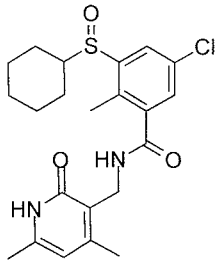
[02134] Step 3: Synthesis of 5-chloro-3-(cyclohexylthio)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide

[02135] Aqueous NaOH (0.2 g in 2.5 mL H_2O, 5.02 mmol) was added to a solution of methyl 5-chloro-3-(cyclohexylthio)-2-methylbenzoate (1.0 g, 3.35 mmol) in ethanol (10 mL) and the solution stirred at 60 °C for 1 h. After completion of the reaction, ethanol was removed under reduced pressure and the aqueous layer was acidified using dilute HCl to pH 6 and then citric acid to pH 4. The product was extracted was using 10% methanol in DCM. The combined organic layers were dried and concentrated to give the respective acid (0.91g, 95%).

[02136] The above acid (0.91g, 3.2 mmol) was then dissolved in DMSO (2 mL) and 3-(amino methyl)-4, 6-dimethylpyridin-2(1H)-one (0.974g, 6.41 mmol) and triethyl amine (0.65g, 3.2 mmol) was added to it. The reaction mixture was stirred at room temperature for 15 min before PyBOP (2.5g, 4.8 mmol) was added to it and stirring was continued for overnight. After completion of the reaction, the solution was poured into ice and the product was extracted with 10% MeOH in DCM. The combined organic layers were dried, concentrated to obtain crude product. Purification by solvent washings afforded the title compound (1.3 g, 93 %).

[02137] Analytical Data: LCMS: 419.2 $(M + 1)^+$; HPLC: 98.38% (@ 254 nm) (R_t;7.989; Method: Column: YMC ODS-A 150 mm x 4.6 mm x 5 µ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 µL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.47 (bs, 1H), 8.32 (t, 1H), 7.40 (s, 1H), 7.07 (s, 1H), 5.85 (s, 1H), 4.24-4.25 (d, 1H, J = 4Hz), 2.21 (s, 3H), 2.18 (s, 3H), 2.11 (s, 3H), 1.88-1.91 (m, 2H), 1.56-1.69 (m, 3H), 1.25-1.38 (m, 5H), 2 protons merged in solvent peak.

[02138] **Compound 208: 5-chloro-3-(cyclohexylsulfinyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydro-pyridin-3-yl)methyl)-2-methylbenzamide**

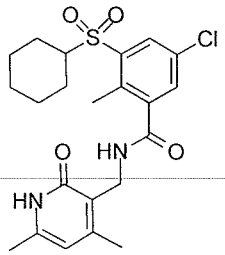


[02139] To a stirred solution of 5-chloro-3-(cyclohexylthio)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide (0.2g, 0.48 mmol) in DCM (7 mL) at 0 °C, m-CPBA (0.098g, 0.57 mmol) was added and stirred at 0 °C for 2 h. Reaction was monitored by TLC. After completion, the reaction mixture was diluted with DCM and washed with aqs. $NaHCO_3$. The product was purified by solvent washings to afford the title compound (0.17g, 82.3%).

[02140] Analytical Data: LCMS: 435.1 $(M + 1)^+$; HPLC: 92.68% (@ 220 nm) (R_t;5.996; Method: Column: YMC ODS-A 150 mm x 4.6 mm x 5 µ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 µL, Col. Temp.: 30 °C; Flow rate: 1.4

mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (CDCl3, 400 MHz) δ 11.44 (bs, 1H), 7.82 (s, 1H), 7.45 (t, 1H), 7.39 (s, 1H), 5.97 (s, 1H), 4.52 (bs, 2H), 2.53-2.59 (m, 1H), 2.38 (s, 3H), 2.34 (s, 3H), 2.23 (s, 3H), 1.85-1.93 (m, 3H), 1.65 (m, 2H), 1.20-1.29 (m, 3H).

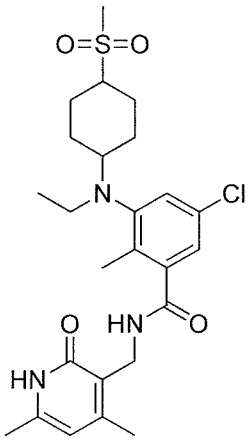
[02141] **Compound 209: 5-chloro-3-(cyclohexylsulfonyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydro-pyridin-3-yl)methyl)-2-methylbenzamide**



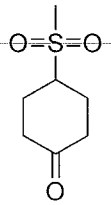
[02142] To a stirred solution of 5-chloro-3-(cyclohexylthio)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide (0.1g, 0.238 mmol) in DCM (4 mL) at 0 °C, m-CPBA (0.082g, 0.48 mmol) was added and stirred at rt for 2 h. Reaction was monitored by TLC. After completion reaction mixture was diluted with DCM and washed with aqs. $NaHCO_3$. The product was purified by prep. HPLC to afford the title compound (0.075g, 23%).

[02143] Analytical Data: LCMS: 451.1 $(M + 1)^+$; HPLC: 83.44% (@ 254 nm) (R_t;6.547; Method: Column: YMC ODS-A 150 mm x 4.6 mm x 5 μ; Mobile Phase: A; 0.05% TFA in water/ B; 0.05% TFA in acetonitrile; Inj. Vol: 10 μL, Col. Temp.: 30 °C; Flow rate: 1.4 mL/min.; Gradient: 5% B to 95% B in 8 min, Hold for 1.5 min, 9.51-12 min 5% B); ^{1}H NMR (CDCl3, 400 MHz) δ 11.44 (bs, 1H), 7.98 (s, 1H), 7.50 (s, 1H), 7.45 (t, 1H), 5.97 (s, 1H), 4.51 (d, 2H, J = 4Hz), 2.94-3.00 (m, 1H), 2.62 (s, 3H), 2.38 (s, 3 H), 2.21 (s, 3H), 1.88-1.95 (m, 4H), 1.70 (m, 1H), 1.52-1.55 (m, 2H), 1.21 (m, 3H).

[02144] **Compound 416: 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((1s,4s)-4-(methylsulfonyl)cyclohexyl)amino)-2-methylbenzamide**

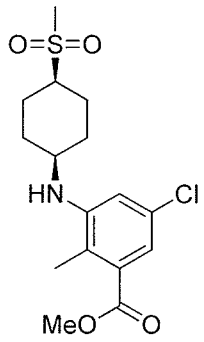


[02145] Step 1: Synthesis of 4-methanesulfonylcyclohexan-1-one



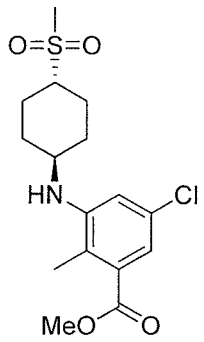
[02146] A solution containing (buta-1,3-dien-2-yloxy)(trimethyl)silane (12.5 ml, 70.7 mmol) in toluene (50 ml), was treated with (methylsulfonyl)ethene (4.1 ml, 47.1 mmol) and heated under reflux for 76 hours. After which time, the reaction mixture was cooled to room temperature and concentrated in-vacuo to give a yellow oil. The oil was dissolved in CH_2Cl_2 (120 ml) and filtered through Celite®. The filtrate was concentrated in-vacuo and the resulting residue was then dissolved in MeOH (8 ml) with cooling (ice/water). It was then treated with TFA (2.0 ml). The reaction mixture was stirred at 0 °C for a further 10 minutes and then at room temperature for 25 hours. The reaction mixture was concentrated in-vacuo and the residue was purified by flash column chromatography (0-10% MeOH/CH_2Cl_2) 100g SNAP cartridge on the Biotage Isolera to give the title compound 1.2g (14%) as a thick yellow oil. LC-MS 94%, 0.39 min (3.5 minute LC-MS method), m/z = 177.0 (ELS visible only). ^{1}H NMR (500 MHz, CHLOROFORM-d) δ ppm 3.24 - 3.32 (m, 1 H) 2.94 (s, 3 H) 2.62 - 2.70 (m, 2 H) 2.50 - 2.56 (m, 2 H) 2.38 - 2.45 (m, 2 H) 2.07 - 2.18 (m, 2 H).

[02147] Step 2: Synthesis of methyl 5-chloro-2-methyl-3-(((1s,4s)-4-(methylsulfonyl)cyclohexyl)amino)benzoate



[02148] To a stirred solution of 4-methanesulfonylcyclohexan-1-one (94%, 0.56 g, 3.0 mmol) in 1,2-dichloroethane (10 ml) under a balloon of nitrogen, was added methyl 3-amino-5-chloro-2-methylbenzoate (0.60 g, 3.0 mmol), followed by acetic acid (1.0 ml, 18.0 mmol). The solution was stirred for 50 minutes before the portionwise addition of sodium triacetoxyborohydride (1.9 g, 9.0 mmol) over 4 hours. The resulting suspension was stirred overnight before the addition of 4-methanesulfonylcyclohexan-1-one (0.28 g, 1.5 mmol) in 1,2-dichloroethane (1.5 ml) and sodium triacetoxyborohydride (0.96 g, 4.5 mmol) over 2.5 hours. The reaction mixture was stirred for a further 67 hours before the addition of deionized water (40 ml) to the reaction mixture and neutralisation (pH 8) by the gradual addition of solid $NaHCO_3$ (4.8 g). The mixture was extracted with CH_2Cl_2 (3 x 25 ml). The combined organic extracts were washed with brine (40 ml), dried over $MgSO_4$, filtered and concentrated in-vacuo. The residue was pre-absorbed onto silica and purified by flash column chromatography (0-55% ethyl acetate / heptanes) 100g SNAP cartridge on the Biotage Isolera to give the title compound (131 mg, 12%). LC-MS 96%, 2.09 min (3.5 minute LC-MS method), m/z = 359.85, 360.85, 361.90, 362.85; ^{1}H NMR (500 MHz, CHLOROFORM-d) δ ppm 7.12 (br. s., 1 H) 6.68 (br. s., 1 H) 3.89 (s, 3 H) 3.82 (br. s., 1 H) 3.71 (br. s., 1 H) 2.93 - 3.02 (m, 1 H) 2.89 (s, 3 H) 2.29 (s, 3 H) 2.03 - 2.18 (m, 4 H) 1.91 - 2.02 (m, 2 H) 1.71 - 1.83 (m, 2 H).

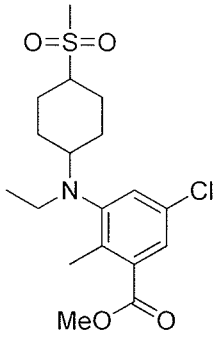
[02149] The other isomer methyl 5-chloro-2-methyl-3-(((1r,4r)-4-(methylsulfonyl)cyclohexyl)amino)benzoate was also isolated



[02150] (92 mg, 8%), LC-MS 96%, 2.06 min (3.5 minute LC-MS method), m/z = 359.85, 360.90, 361.90, 362.85; ^{1}H NMR (500 MHz, CHLOROFORM-d) δ ppm 7.11 (br. s, 1 H) 6.68 (br. s., 1 H) 3.89 (s, 3 H) 3.62 (br. s., 1 H) 3.27 - 3.36 (m, 1 H) 2.84 - 2.95 (m, 4 H) 2.32 - 2.42 (m, 4 H) 2.24 (br. s., 3 H) 1.72 - 1.85 (m, 2 H) 1.27 - 1.35 (m, 2 H).

[02151] The assignment of cis and trans from further NMR experiments could not be made and assignment is arbitrary.

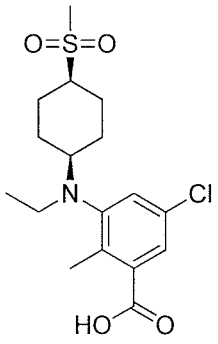
[02152] Step 3: Synthesis of methyl 5-chloro-3-(ethyl((1s,4s)-4-(methylsulfonyl)cyclohexyl)amino)-2-methylbenzoate



[02153] To a stirred solution of methyl 5-chloro-2-methyl-3-(((1s,4s)-4-(methylsulfonyl)cyclohexyl)amino)benzoate (246 mg, 0.68 mmol) in dry 1,2-dichloroethane (6.0 ml), was added acetaldehyde (115 µl, 2.1 mmol), followed by acetic acid (235 µl, 4.1 mmol). The reaction was stirred for 35 minutes before sodium triacetoxyborohydride (435 mg, 2.1 mmol) was added in portions over 50 minutes and the reaction was stirred overnight and then treated with acetaldehyde (115 µl, 2.1 mmol). The reaction mixture was stirred for 1 hour before addition of sodium triacetoxyborohydride (435 mg, 2.1 mmol) in portions over 1 hour and the reaction mixture stirred overnight. Acetaldehyde (229 µl, 4.1 mmol) was added and the reaction stirred for 2.5 hours, followed by the addition of sodium triacetoxyborohydride (869 mg, 4.1 mmol) in portions over 1.5 hours and stirring was continued overnight. Acetaldehyde

(229 µl, 4.1 mmol) was added along with 1,2-dichloroethane (4.0 ml) to aid solution and the reaction stirred for 4 hours. Sodium triacetoxyborohydride (869 mg, 4.1 mmol) was added in portions over 2 hours and stirring was continued over the weekend. Acetaldehyde (229 µl, 4.1 mmol) was added and the reaction stirred for 1.5 hours, followed by the addition of sodium triacetoxyborohydride (869 mg, 4.1 mmol) in equal portions over 1 hour, along with 1,2-dichloroethane (5.0 ml) and stirring was continued overnight. Acetaldehyde (382 µl, 6.8 mmol) was added and the reaction stirred for 2.5 hours, followed by the addition of sodium triacetoxyborohydride (1.4 g, 6.8 mmol) in equal portions over 4 hours, along with 1,2-dichloroethane (10 ml) and stirring was continued overnight. The reaction mixture was diluted with water (40 ml) and neutralised (to pH 8) by the gradual addition of solid $NaHCO_3$ (5.79 g). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 ml). The combined organic phases were washed with brine (20 ml), dried ($MgSO_4$), filtered and concentrated in-vacuo. The crude residue was pre-absorbed onto silica and purified by column chromatography (0-50% EtOAc/Heptanes) 10g SNAP cartridge on the Biotage Isolera to give the title compound (140 mg, 51%) as a colourless glassy solid. LC-MS 97%, 2.29 min (3 minute LC-MS method), m/z = 387.95, 388.95, 389.90, 390.95. ^{1}H NMR (500 MHz, CHLOROFORM-d) δ ppm 7.59 (d, J=1.89 Hz, 1 H) 7.21 (d, J=1.89 Hz, 1 H) 3.91 (s, 3 H) 3.45 (br. s., 1 H) 3.01 (m, 2 H) 2.86 - 2.95 (m, 1 H) 2.82 (s, 3 H) 2.52 (s, 3 H) 2.08 (br. s., 2 H) 1.94 (br. s., 2 H) 1.86 (br. s., 2 H) 1.46 - 1.54 (m, 2 H) 0.89 (t, J=7.01 Hz, 3 H).

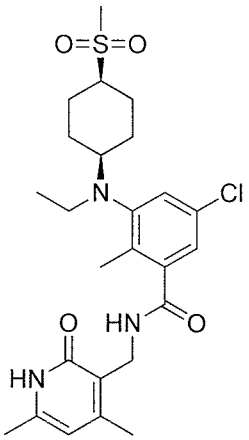
[02154] Step 4: Synthesis of 5-chloro-3-(ethyl((1s,4s)-4-(methylsulfonyl)cyclohexyl)amino)-2-methylbenzoic acid



[02155] To a stirred solution of methyl 5-chloro-3-(ethyl((1s,4s)-4-(methylsulfonyl)cyclohexyl)amino)-2-methylbenzoate (140 mg, 0.36 mmol) in THF (5.0 ml) and MeOH (0.3 ml), was added a solution of 4M NaOH (2.7 ml). The resulting solution was

stirred at 50 °C for 21 hours and then treated with 4M NaOH (0.9 ml, 3.6 mmol) and heating was continued for a further 4 hours. After which time, the reaction mixture was left to reach room temperature and then concentrated in-vacuo. The resulting aqueous residue was extracted with CH_2Cl_2 (20 ml) and ether (20 ml). The pH of the aqueous phase was then adjusted to 3-4 by the addition of 1M HCl (aq) (13 ml) and extracted with ethyl acetate (3 x 25 ml). The combined ethyl acetate extracts were dried over $MgSO_4$, filtered and concentrated in-vacuo to give the title compound (122 mg, 80% yield) as a light yellow solid. LC-MS 89%, 4.03 min (7 minute LC-MS method), m/z = 373.95, 374.90, 375.95, 377.00. ^{1}H NMR (500 MHz, CHLOROFORM-d) δ ppm 7.77 (d, J=1.89 Hz, 1 H) 3.47 (br. s., 1 H) 3.03 (br. s., 2 H) 2.88 - 2.97 (m, 1 H) 2.84 (s, 3 H) 2.60 (s, 3H) 2.12 (br. s, 2 H) 1.96 (br. s, 2 H) 1.88 (br. s., 2 H) 1.55 (br. s., 2 H) 0.91 (t, J=7.01 Hz, 3 H). 1 x ArH assumed to be under the $CDCl_3$ peak and the CO_2H peak also not visible.

[02156] Step 5: Synthesis of 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((1s,4s)-4-(methylsulfonyl)cyclohexyl)amino)-2-methylbenzamide

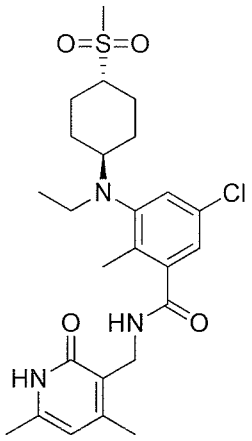


[02157] A stirred solution of 5-chloro-3-(ethyl((1s,4s)-4-(methylsulfonyl)cyclohexyl)amino)-2-methylbenzoic acid (90%, 122 mg, 0.29 mmol) in anhydrous DMF (2.0 ml) at 0 °C under a balloon of N_2, was treated with HATU (134 mg, 0.35 mmol) and DIPEA (102 µl, 0.59 mmol) dropwise. The resulting solution was stirred for 10 minutes and then treated with 3-(aminomethyl)-4,6-dimethyl-1,2-dihydropyridin-2-one (89%, 60 mg, 0.35 mmol). The resulting suspension was stirred at 0 °C for 15 minutes and then stirred at room temperature over the weekend. The reaction mixture was partitioned between water (10 ml) and CH_2Cl_2 (10 ml). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 15

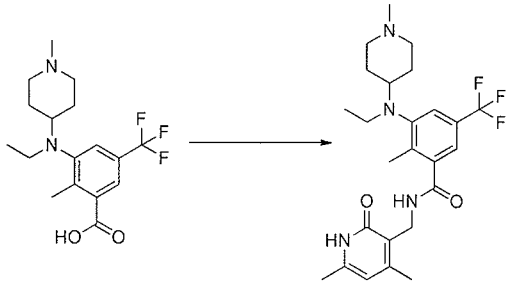
ml). The combined organics were washed with a saturated solution of $NaHCO_3$ (aq) (10 ml), water (40 ml), brine (2 x 25 ml), dried ($MgSO_4$), filtered and concentrated in-vacuo. The residue was purified by flash column chromatography (0-9% MeOH/CH_2Cl_2) 10g SNAP cartridge on the Biotage Isolera to give the title compound (120 mg, 76% yield) as an off-white solid. LC-MS: 95%, 3.71 min (7 minute LC-MS method), m/z = 508.10, 509.10, 510.10, 511.10. ^{1}H NMR (500 MHz, Chloroform-d) δ 10.84 (s, 1H), 7.07 (s, 2H), 7.00 (m, 1H), 6.10 (s, 1H), 4.53 (d, J = 5.8 Hz, 2H), 3.45 (s, 1H), 3.07 – 2.95 (m, 2H), 2.93 – 2.85 (m, 1H), 2.81 (s, 3H), 2.45 (s, 3H), 2.31 (s, 3H), 2.29 (s, 3H), 2.14 – 2.01 (m, 2H), 1.97-1.89 (m, 2H), 1.87-1.80 (m, 2H), 1.50 (br s, 2H), 0.88 (t, J = 5.9 Hz, 3H).

[02158] **Compound 417: 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl((1r,4r)-4-(methylsulfonyl)cyclohexyl)amino)-2-methylbenzamide**

[02159] This compound was prepared in an analogous manner to that of compound 416 using the other isomer obtained in step 2

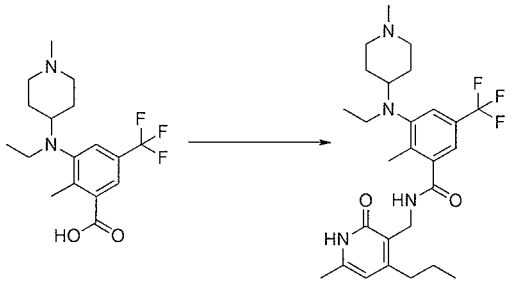


[02160] **Compound 392**: ***N*-[(4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3-[ethyl(1-methylpiperidin-4-yl)amino]-2-methyl-5-(trifluoromethyl)benzamide**



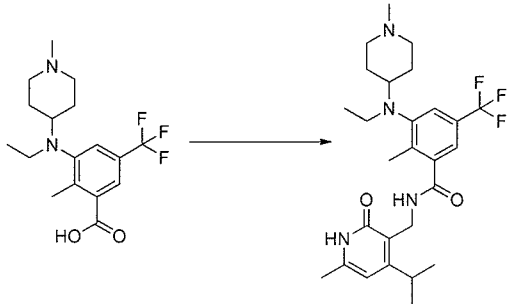
[02161] To a stirred solution of 3-[ethyl(1-methylpiperidin-4-yl)amino]-2-methyl- 5-(trifluoromethyl)benzoic acid (crude material, 580 mg, 1.68 mmol) and 3-(aminomethyl)-4,6-dimethyl-1,2-dihydropyridin-2-one HCl salt (477 mg, 2.53 mmol) in DMSO (6 mL) was added PyBOP (1.57 g, 3.02 mmol) and hunig base (650 mg, 5.04 mmol). The reaction mixture was stirred at 23°C for 20 hours. The reaction mixture was quenched with water and resulting precipitate was collected. The solid was purified by silica gel column chromatography (NH-SiO_2 ethylacetate/MeOH=25/1) to give the titled compound as a white amorphous (386 mg, 48% yield). ^{1}HNMR (400 MHz, $CDCl_3$) δppm; 7.31 (s, 1H), 7.27 (s, 1H), 7.18 (t, J = 5.7 Hz, 1H), 5.95 (s, 1H), 4.55 (d, J = 5.9 Hz, 2H), 3.17 (dq, J = 6.4, 3.3 Hz, 2H), 3.08 (q, J = 7.0 Hz, 2H), 2.81 (m, 2H), 2.70 (m, 1H), 2.40 (s, 3H), 2.33 (s, 3H), 2.23 (s, 3H), 2.21 (s, 3H), 1.78-1.93 (m, 2H), 1.70 (m, 2H), 0.84 (t, J = 7.0 Hz, 3H); MS(ES) [M+H] 479.2, [M+Na] 501.3; HPLC 96.8% purity.

[02162] **Compound 393: 3-[Ethyl(1-methylpiperidin-4-yl)amino]-2-methyl-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]-5-(trifluoromethyl)benzamide**



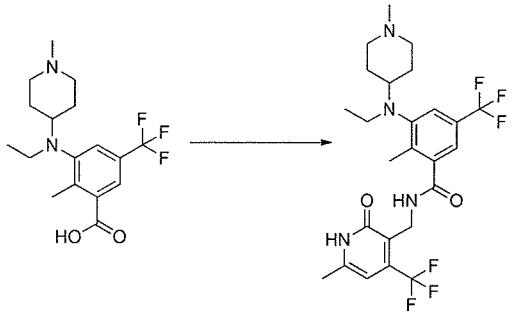
[02163] To a stirred solution of 3-[ethyl(1-methylpiperidin-4-yl)amino]-2-methyl- 5-(trifluoromethyl)benzoic acid (crude material, 680 mg, 1.97 mmol) and 3-(aminomethyl)-6-methyl-4-propyl-1,2-dihydropyridin-2-one HCl salt (642 mg, 2.96 mmol) in DMSO (7 mL) was added PyBOP (1.85 g, 3.55 mmol) and hunig base (764 mg, 5.91 mmol). The reaction mixture was stirred at 23°C for 20 hours. The reaction mixture was quenched with water and resulting precipitate was collected. The solid was purified by silica gel column chromatography (NH-SiO_2 ethylacetate/MeOH=20/1) to give the titled compound as a white solid (224 mg, 22% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δppm; 7.31 (s, 1H), 7.26 (s, 1H), 7.16 (m, 1H), 5.94 (s, 1H), 4.55 (d, J = 5.9 Hz, 2H), 3.08 (q, J = 7.0 Hz, 2H), 2.82 (m, 2H), 2.66-2.73 (m, 3H), 2.33 (s, 3H), 2.24 (s x 2, 6H), 1.79-1.98 (m, 2H), 1.67-1.75 (m, 4H), 1.59-1.66 (m, 2H), 1.02 (t, J = 7.2 Hz, 3H), 0.84 (t, J = 7.0 Hz, 3H); MS (ES) [M-H] 505.2; HPLC 98.1% purity.

[02164] **Compound 394: 3-[Ethyl(1-methylpiperidin-4-yl)amino]-2-methyl-N-{[6-methyl-2-oxo-4-(propan-2-yl)-1,2-dihydropyridin-3-yl]methyl}-5-(trifluoromethyl)benzamide**



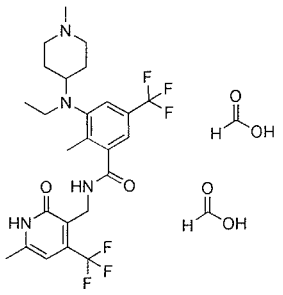
[02165] To a stirred solution of 3-[ethyl(1-methylpiperidin-4-yl)amino]-2-methyl- 5-(trifluoromethyl)benzoic acid (crude material, ~0.313 mmol) and 3-(aminomethyl) -6-methyl-4-(propan-2-yl)-1,2-dihydropyridin-2-one HCl salt (88.0 mg, 0.407 mmol) in DMSO (2.4 mL) was added PyBOP (244 mg, 0.470 mmol) and hunig base (164 ul, 0.939 mmol). The reaction mixture was stirred at rt for 16 hours. The reaction mixture was quenched with water and diluted with ethylacetate. The aqueous layer was extracted with dichloromethane. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography (NH-SiO_2 ethylacetate/MeOH=20/1+5% triethylamine). The crude compound was dissolved with DMSO, diluted with water. The precipitated solid was collected and triturated with ethylacetate/TBME/hexane to give the titled compound as a white solid (80.0 mg, 51% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δppm; 7.31 (s, 1H), 7.26 (s, 1H), 7.03-7.10 (m, 1H), 6.04 (s, 1H), 4.59 (d, *J*=6.0 Hz, 2H), 3.49-3.55 (m, 1H), 3.09 (q, *J* = 6.8 Hz, 2H), 2.81-2.84 (m, 2H), 2.70-2.78 (m, 1H), 2.32 (s, 3H), 2.26 (s, 3H), 2.24 (s, 3H), 1.86-1.89 (m, 2H), 1.68-1.71 (m, 4H), 1.22 (d, *J* = 6.4 Hz, 6H), 0.84 (t, *J* = 6.8 Hz, 3H); MS (ES) [M+H] 507.2, [M+Na] 529.2 ; HPLC 97.7% purity.

[02166] **Compound 395: 3-[Ethyl(1-methylpiperidin-4-yl)amino]-2-methyl-N-{[6-methyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl]methyl}-5-(trifluoromethyl)benzamide**



[02167] To a stirred solution of 3-[ethyl(1-methylpiperidin-4-yl)amino]-2-methyl -5-(trifluoromethyl)benzoic acid (crude material, ~0.313 mmol) and 3-(aminomethyl) -6-methyl-4-(trifluoromethyl)-1,2-dihydropyridin-2-one hydrochloride HCl salt (100 mg, 0.91 mmol) in DMSO (2.4 mL) was added PyBOP (248 mg, 1.05 mmol) and hunig base (166 ul, 2.10 mmol). The reaction mixture was stirred at rt for 16 hours. The reaction mixture was quenched with water and resulting precipitate was collected. The solid was triturated from ethylacetate/hexane. The resulting solid was purified by silica gel column chromatography (NH-SiO_2 ethylacetate/MeOH=10/1+10% triethylamine). The crude compound was triturated from ethylacetate/hexane, and dried to give the titled compound as a white solid (75.0 mg, 44% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δppm; 7.32 (s, 1H), 7.26 (s, 1H), 6.86-6.89 (m, 1H), 6.34 (s, 1H), 4.73 (d, J = 6.4 Hz, 2H), 3.08 (q, J = 7.2 Hz, 2H), 2.80-2.85 (m, 2H), 2.70-2.78 (m, 1H), 2.37 (s, 3H), 2.35 (s, 3H), 2.24 (s, 3H), 1.85-1.89 (m, 2H), 1.69-1.72 (m, 4H), 0.84 (t, J = 7.2 Hz, 3H); MS (ES) [M+H] 533.1, [M+Na] 555.2 ; HPLC 95.8% purity.

[02168] **Compound 395**: **3-(ethyl(1-methylpiperidin-4-yl)amino)-2-methyl-N-((6-methyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)methyl)-5-(trifluoromethyl)benzamide diformate**

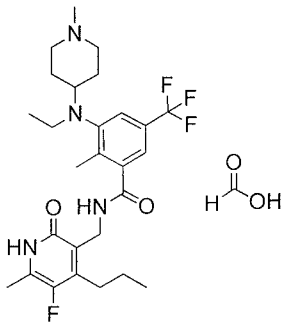


[02169] ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.39 (s, 2H), 7.48 (s, 1H), 7.36 (s, 1H), 6.36 (s, 1H), 4.52 (s, 2H), 3.38 (br, 2H), 3.18 (br, m, 1H), 3.11 (q, J = 7.2 Hz, 2H), 2.96 (br, m, 2H),

2.77 (s, 3H), 2.35 (s, 3H), 2.31 (s, 3H), 1.97 (br, d, J = 12.0 Hz, 2H), 1.83 (br, m, 2H), 0.84 (t, J = 7.2 Hz, 3H); MS (ES) (M+H)=533.53.

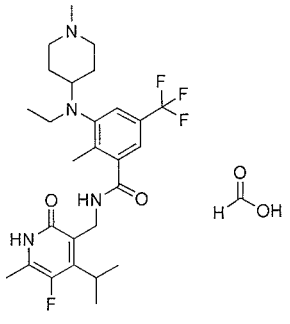
[02170] Following the same preparation method above of 3-[Ethyl(1-methylpiperidin-4-yl)amino] -2-methyl-N-{[6-methyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl]methyl}-5-(trifluoromethyl)benzamide, the following analogs have been prepared using the corresponding carboxylic acid and amine, and purified by reverse phase HPLC (ACN-H_2O containing 0.1 % formic acid).

[02171] **Compound 396: 3-(ethyl(1-methylpiperidin-4-yl)amino)-N-((5-fluoro-6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)-2-methyl-5-(trifluoromethyl)benzamide formate**



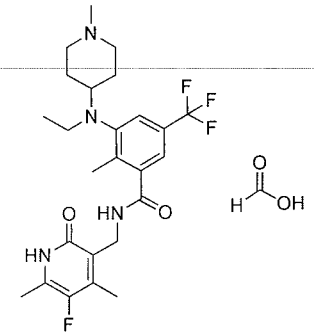
[02172] ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.31 (s, 1H), 7.49 (s, 1H), 7.34 (s, 1H), 4.45 (s, 2H), 3.39 (br, 2H), 3.17 (br, 1H), 3.10 (q, J = 7.2 Hz, 2H), 2.97 (br, m, 2H), 2.77 (s, 3H), 2.74 (br, m, 2H), 2.33 (s, 3H), 2.22 (d, J = 2.8 Hz, 3H), 1.97 (br, m, 2H), 1.85 (br, m, 2H), 1.60 (m, 2H), 1.02 (t, J = 7.2Hz, 3H), 0.84 (t, J = 6.8 Hz, 3H); MS (ES) (M+H)=525.58.

[02173] **Compound 397: 3-(ethyl(1-methylpiperidin-4-yl)amino)-N-((5-fluoro-4-isopropyl-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-5-(trifluoromethyl)benzamide formate**



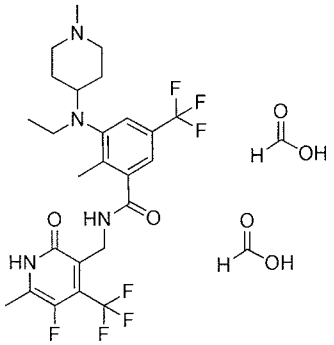
[02174] LCMS ES+ (M+1)=525.58. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.31 (s, 1H), 7.50 (s, 1H), 7.34 (s, 1H), 4.49 (s, 2H), 3.48 (m, 1H), 3.39 (br, 2H), 3.18 (br, m, 1H), 3.09 (q, J=6.8 Hz, 2H), 2.97 (br, m, 2H), 2.78 (s, 3H), 2.34 (s, 3H), 2.21 (d, J = 3.2 Hz, 3H), 1.96 (br, d, J = 12.0 Hz, 2H), 1.86 (br, m, 2H), 1.32 (dd, J = 1.6 Hz, J = 7.2 Hz, 6H), 0.84 (t, J = 6.8 Hz, 3H); MS (ES) (M+H)=525.58.

[02175] **Compound 398: 3-(ethyl(1-methylpiperidin-4-yl)amino)-N-((5-fluoro-4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-5-(trifluoromethyl)benzamide formate**



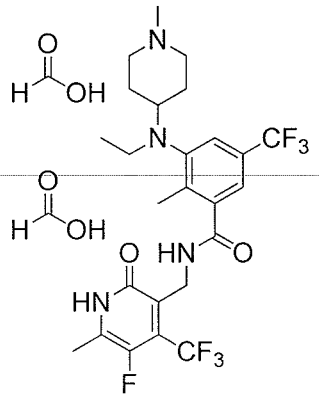
[02176] ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.29 (s, 1H), 7.49 (s, 1H), 7.35 (s, 1H), 4.45 (s, 2H), 3.39 (br, 2H), 3.19 (br, 1H), 3.09 (q, J = 7.2 Hz, 2H), 2.97 (br, m, 2H), 2.77 (s, 3H), 2.34 (d, J = 2.4 Hz, 3H), 2.33 (s, 3H), 2.22 (d, J = 3.2 Hz, 3H), 1.97 (br, m, 2H), 1.86 (br, m, 2H), 0.84 (t, J = 6.8 Hz, 3H); MS (ES) (M+H)=497.51.

[02177] **Compound 399: 3-(ethyl(1-methylpiperidin-4-yl)amino)-N-((5-fluoro-6-methyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)methyl)-2-methyl-5-(trifluoromethyl)benzamide diformate**



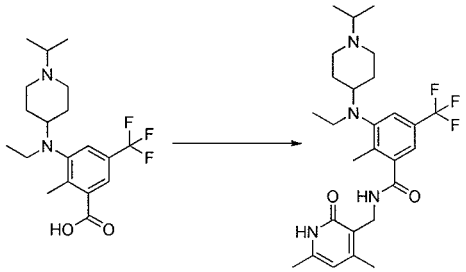
[02178] ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.32 (s, 2H), 7.50 (s, 1H), 7.34 (s, 1H), 4.59 (s, 2H), 3.40 (br, 2H), 3.18 (br, m, 2H), 3.09 (q, J = 6.8, 2H), 2.96 (br, m, 2H), 2.78 (s, 3H), 2.35 (s, 3H), 2.29 (d, J = 3.2 Hz, 3H), 1.98 (br, d, J = 13.2 Hz, 2H), 1.86 (m, 1H), 1.80 (br, m, 2H), 0.84 (t, J = 6.8 Hz, 3H); MS (ES) (M+H)=551.53.

[02179] **Compound 399: 3-(ethyl(1-methylpiperidin-4-yl)amino)-N-((5-fluoro-6-methyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)methyl)-2-methyl-5-(trifluoromethyl)benzamide diformate**



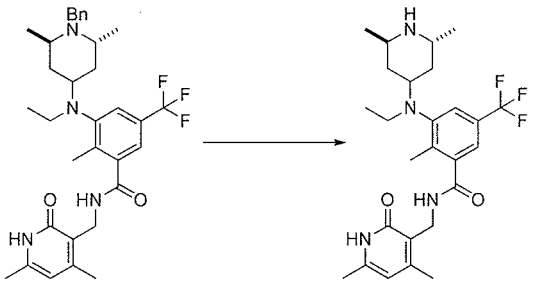
[02180] 6-Methyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile was fluorinated as described for 5-fluoro-4-isopropyl-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile. The product was isolated as a 3:1 mixture of 6-methyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile (starting material) and 5-fluoro-6-methyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile. For 5-fluoro-6-methyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile, LCMS E-S (M+H) = 221.2. This mixture of nitriles was subjected to the reduction conditions as described above for 3-(Aminomethyl)-5-fluoro-4-isopropyl-6-methylpyridin-2(1H)-one. For fluorinated compound LCMS (ES) (M+H) showed 225.2 and for non-fluorinated analog LCMS (ES) (M+H) showed 207.2. Subsequent coupling reaction was performed with the crude mixture of amines without further purifications. For 3-(ethyl(1-methylpiperidin-4-yl)amino)-N-((5-fluoro-6-methyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)methyl)-2-methyl-5-(trifluoromethyl)benzamide diformate; ^{1}HNMR (400 MHz, CD_3OD) δ ppm 8.32 (s, 2H), 7.50 (s, 1H), 7.34 (s, 1H), 4.59 (s, 2H), 3.40 (br, 2H), 3.18 (br, m, 1H), 3.09 (q, J = 6.8, 2H), 2.96 (br, m, 2H), 2.78 (s, 3H), 2.35 (s, 3H), 2.29 (d, J = 3.2 Hz, 3H), 1.98 (br, d, J = 13.2 Hz, 2H), 1.80 (br, m, 2H), 0.84 (t, J = 6.8 Hz, 3H); MS (ES) (M+H) 551.5.

[02181] **Compound 400**: ***N*-[(4,6-Eimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3-{ethyl[1-(propan-2-yl)piperidin-4-yl]amino}-2-methyl-5-(trifluoromethyl)benzamide**



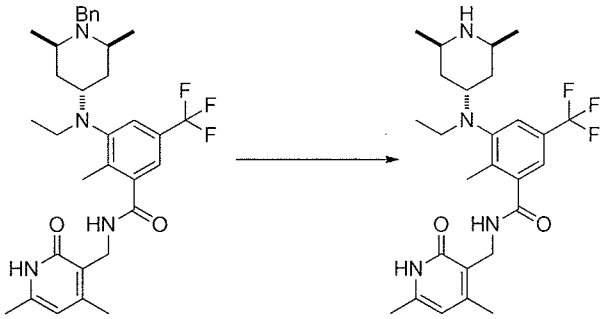
[02182] To a stirred solution of 3-{ethyl[1-(propan-2-yl)piperidin-4-yl]amino} -2-methyl-5-(trifluoromethyl)benzoic acid (crude material, 510 mg, 0.569 mmol) and 3-(aminomethyl)-4,6-dimethyl-1,2-dihydropyridin-2-one HCl salt (161 mg, 0.854 mmol) in DMSO (2 mL) was added PyBOP (534 mg, 1.02 mmol) and hunig base (220 mg, 1.71 mmol). The reaction mixture was stirred at 23°C for 20 hours. The reaction mixture was quenched with water and resulting precipitate was collected. The solid was purified by silica gel column chromatography (NH-SiO_2 ethylacetate/MeOH=20/1) to give the titled compound as a white solid (129 mg, 44% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δppm; 7.30 (s, 1H), 7.26 (s, 1H), 7.22 (t, J = 5.9 Hz, 1H), 5.95 (s, 1H), 4.54 (d, J = 5.9 Hz, 2H), 3.16 (m, 2H), 3.08 (q, J = 7.0 Hz, 2H), 2.85 (m, 2H), 2.62-2.74 (m, 1H), 2.38 (s, 3H), 2.33 (s, 3H), 2.19 (s, 3H), 2.00-2.09 (m, 1H), 1.81 (m, 2H), 1.58-1.76 (m, 2H), 0.99 (s x 2, 6H), 0.83 (t, J = 7.0 Hz, 3H); MS (ES) [M+H] 507.2, [M+Na] 529.3; HPLC 97.2% purity.

[02183] **Compound 401**: ***N*-[(4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3-{[(2R*,6R*)-2,6-dimethylpiperidin-4-yl](ethyl)amino}-2-methyl-5-(trifluoromethyl)benzamide**



[02184] To a stirred solution of 3-{[(2R, 6R)-1-benzyl-2,6-dimethylpiperidin-4-yl](ethyl)amino}-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-2-methyl-5-(trifluoromethyl)benzamide (267 mg, 0.459 mmol) in MeOH (5 mL) was added Pd/C (250 mg). The reaction mixture was stirred at et for 2 hour under hydrogen atmosphere. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (1. NAM-300H silica gel produced by Nagara Science Co., Ltd., ethylacetate/MeOH=4/1 to ethylacetate/MeOH/triethylamine=1/1/0.01, 2. NH-SiO_2, heptane/ethylacetate=30/1 to 8/1) to give the titled compound as a white solid (127 mg, 56% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δppm; 7.30 (s, 1H), 7.26 (s, 1H), 7.14 (t, J = 6.1 Hz, 1H), 5.94 (s, 1H), 4.54 (dd, J = 5.9, 1.6 Hz, 2H), 3.41-3.49 (m, 1H), 3.01-3.13 (m, 3H), 2.85-2.92 (m, 1H), 2.40 (s, 3H), 2.32 (s, 3H), 2.22 (s, 3H), 1.63-1.80 (m, 4H), 1.13 (d, J = 7.0 Hz, 3H), 1.02 (d, J = 6.2 Hz, 3H), 0.83 (t, J = 7.0 Hz, 3H);LC-MS: m/z [M+H] 493.1, [M+Na] 515.3; HPLC; 97.2% purity.

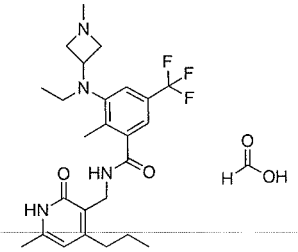
[02185] **Compound 402**: ***N*-[(4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3-{[(2R*,4R*,6S*)-2,6-dimethylpiperidin-4-yl](ethyl)amino}-2-methyl-5-(trifluoromethyl)benzamide**



[02186] To a stirred solution of 3-{[(2R, 4R, 6S)-1-benzyl-2,6- dimethylpiperidin-4-yl](ethyl)amino}-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-2-methyl-5-(trifluoromethyl)benzamide (35.6 mg, 0.0611 mmol) in MeOH (3.0 ml) was added Pd/C (120 mg). The reaction mixture was stirred for 30 minutes under hydrogen atmosphere. After purging with nitrogen, the mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by preparative TLC (TLC silica gel 60F254, MERCK, MeOH/ Et_3N=100/1) twice to give title compound as a white solid (4.4 mg, 15% yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ ppm; 7.33(s, 1H), 7.30 (s, 1H), 7.18 (m, 1H), 5.96 (s, 1H), 4.54 (d, J = 6.0Hz,

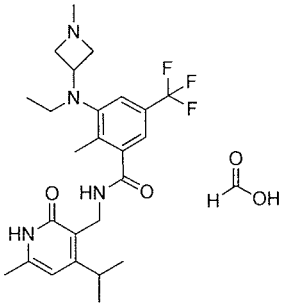
2H), 3.73 (m, 1H), 3.26-2.69 (m, 4H), 2.40 (s, 3H), 2.38 (s, 3H), 2.23 (s, 3H), 1.90-1.10 (m, 4H), 1.10-0.86 (m, 6H), 0.83 (t, J = 7.2Hz, 3H). (-2H); LC-MS: m/z [M+H] 493.2, [M+Na] 515.3; HPLC; 88.8% purity.

[02187] **Compound 403: 3-(ethyl(1-methylazetidin-3-yl)amino)-2-methyl-N-((6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)-5-(trifluoromethyl)benzamide formate**



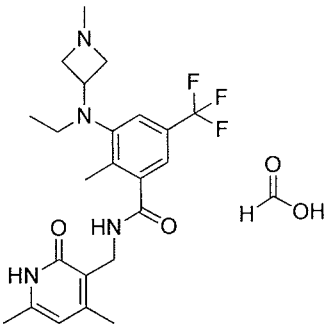
[02188] ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.33 (s, 1H), 7.37 (s, 1H), 7.26 (s, 1H), 6.11 (s, 1H), 4.46 (s, 2H), 4.42 (br, m, 1H), 4.21 (br, 2H), 3.82 (br, 2H), 3.00 (q, J = 6.8 Hz, 2H), 2.88 (s, 3H), 2.65 (m, 2H), 2.40 (s, 3H), 2.22 (s, 3H), 1.61 (m, 2H), 0.99 (t, J = 7.2 Hz, 3H), 0.86 (t, J = 6.8 Hz, 3H); MS (ES) (M+1) 480.53.

[02189] **Compound 404: 3-(ethyl(1-methylazetidin-3-yl)amino)-N-((4-isopropyl-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-5-(trifluoromethyl)benzamide formate**



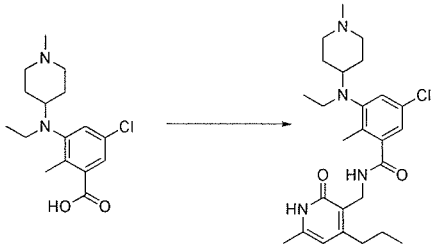
[02190] ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.31 (s, 1H), 7.37 (s, 1H), 7.27 (s, 1H), 6.21 (s, 1H), 4.50 (s, 2H), 4.41 (br, 1H0, 4.21 (br, 2H), 3.81 (br, 2H), 3.38 (m, 1H), 3.00 (q, J = 6.8 Hz, 2H), 2.87 (s, 3H), 2.40 (s, 3H), 2.24 (s, 3H), 1.20 (d, J = 6.4 Hz, 6H), 0.86 (t, J = 6.8 Hz, 3H); MS (ES) (M+1) 479.54.

[02191] **Compound 405: N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(ethyl(1-methylazetidin-3-yl)amino)-2-methyl-5-(trifluoromethyl)benzamide formate**



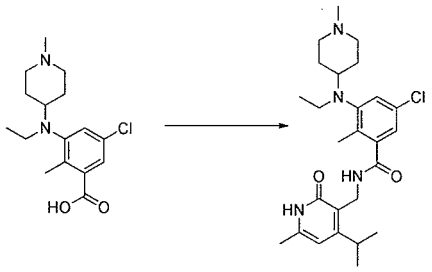
[02192] ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.32 (s, 1H), 7.39 (s, 1H), 7.26 (s, 1H), 6.08 (s, 1H), 4.44 (s, 2H), 4.41 (br, m, 1H), 4.21 (br, 2H), 3.82 (br, 2H), 3.00 (q, J = 6.8 Hz, 2H), 2.88 (s, 3H), 2.39 (s, 3H), 2.34 (d, J = 1.2 Hz, 3H), 2.21 (s, 3H), 0.86 (t, J = 6.8 Hz, 3H); MS (ES) (M+1) 451.49.

[02193] **Compound 406: 5-Chloro-3-[ethyl(1-methylpiperidin-4-yl)amino]-2-methyl-N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]benzamide**



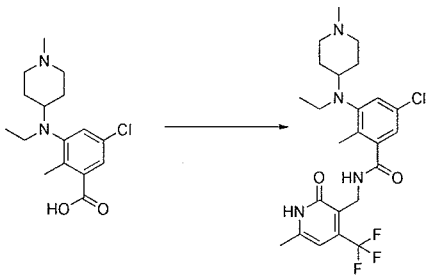
[02194] To a stirred solution of 5-chloro-3-[ethyl(1-methylpiperidin-4-yl) amino]-2-methylbenzoic acid(crude material, 1.80 g, 3.26 mmol) and 3-(aminomethyl)-6-methyl-4-propyl -1,2-dihydropyridin-2-one HCl salt (916 mg, 4.24 mmol) in DMSO (10 mL) was added PyBOP (3.10 g, 5.87 mmol) and hunig base (1.20 g, 9.78 mmol). The reaction mixture was stirred at 23°C for 16 hours. The reaction mixture was quenched with water and resulting precipitate was collected. The solid was purified by silica gel column chromatography (NH-SiO_2 Ethylacetate/MeOH=10/1) to give the titled compound as a white solid (264 mg, 17% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δppm; 7.20 (t, J = 5.9 Hz, 1H), 7.06 (d, J = 2.0 Hz, 1H), 7.02 (d, J = 2.0 Hz, 1H), 5.96 (s, 1H), 4.54 (d, J = 5.9 Hz, 2H), 3.02 (q, J = 7.0 Hz, 2H), 2.81 (m, 2H), 2.64-2.71 (m, 3H), 2.21-2.27 (s x 3, 9H), 1.84-1.94 (m, 2H), 1.55-1.65 (m, 6H), 1.00 (t, J = 7.4 Hz, 3H), 0.84 (t, J=7.0 Hz, 3H); MS (ES) [M+H] 473.1, [M+Na] 495.3; HPLC 94.7% purity.

[02195] **Compound 407: 5-Chloro-3-[ethyl(1-methylpiperidin-4-yl)amino]-2-methyl-N-{[6-methyl-2-oxo-4-(propan-2-yl)-1,2-dihydropyridin-3-yl]methyl}benzamide**



[02196] To a stirred solution of 5-chloro-3-[ethyl(1-methylpiperidin-4-yl)amino]-2-methylbenzoic acid (crude material, ~0.7 mmol) and 3-(aminomethyl)-6-methyl-4-(propan-2-yl) -1,2-dihydropyridin-2-one hydrochloride HCl salt (200 mg, 0.91 mmol) in DMSO (5.3 mL) was added PyBOP (550 mg, 1.05 mmol) and hunig base (366 ul, 2.10 mmol). The reaction mixture was stirred at 23°C for 7 hours. The reaction mixture was quenched with water and resulting precipitate was collected. The solid was purified by silica gel column chromatography (NH-SiO_2 Ethylacetate/MeOH=10/1+10% triethylamine). The crude compound was triturated from ethylacetate/hexane, and dried to give the titled compound as a white solid (166 mg, 50% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δppm; 7.06 (d, J = 2.4 Hz, 1H), 7.01-7.05 (m, 1H), 7.00 (d, J = 2.4 Hz, 1H), 6.04 (s, 1H), 4.57 (d, J = 6.0 Hz, 2H), 3.49-3.57 (m, 1H), 3.02 (q, J = 6.8 Hz, 2H), 2.80-2.84 (m, 2H), 2.61-2.69 (m, 1H), 2.29 (s, 3H), 2.23 (s, 3H), 2.23 (s, 3H), 1.86-1.90 (m, 2H), 1.66-1.70 (m, 4H), 1.21 (d, J = 6.8 Hz, 6H), 0.84 (t, J = 6.8 Hz, 3H); MS (ES) [M+Na] 495.2 ; HPLC 95.7% purity.

[02197] **Compound 408: 5-Chloro-3-[ethyl(1-methylpiperidin-4-yl)amino]-2-methyl-N-{[6-methyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl]methyl}benzamide**

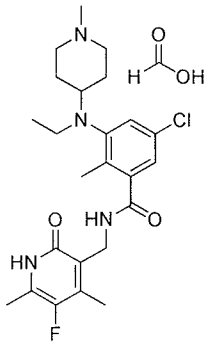


[02198] To a stirred solution of 5-chloro-3-[ethyl(1-methylpiperidin-4-yl)amino]-2-methylbenzoic acid (crude material, ~0.7 mmol) and 3-(aminomethyl)-6-methyl-4-

(trifluoromethyl)- 1,2-dihydropyridin-2-one hydrochloride HCl salt (200 mg, 0.91 mmol) in DMSO (5.3 mL) was added PyBOP (550 mg, 1.05 mmol) and hunig base (366 ul, 2.10 mmol). The reaction mixture was stirred at 23°C for 7 hours. The reaction mixture was quenched with water and diluted with ethylacetate. The aqueous layer was extracted with dichloromethane. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography (SiO_2 Ethylacetate/MeOH=10/1+5% triethylamine). The crude compound was triturated with ethylacetate/hexane, and dried to give the titled compound as a white solid (145 mg, 42% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δppm; 7.08 (d, *J*=2.4Hz, 1H), 7.03 (d, *J* = 2.4Hz, 1H), 6.81-6.85 (m, 1H), 6.35 (s, 1H), 4.71 (d, *J* = 5.2 Hz, 2H), 3.03 (q, *J* = 6.8 Hz, 2H), 2.81-2.85 (m, 2H), 2.68-2.72 (m, 1H), 2.39 (s, 3H), 2.27 (s, 3H), 2.24 (s, 3H), 1.88-1.94 (m, 2H), 1.67-1.72 (m, 4H), 0.85 (t, *J*=6.8 Hz, 3H); MS (ES) [M+H] 499.1, [M+Na] 521.1 ; HPLC 96.0% purity.

[02199] Following the same preparation method described above for 5-chloro-3-[ethyl(1-methylpiperidin-4-yl)amino]-2-methyl-N-{[6-methyl-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl]methyl}benzamide, the following analogs were prepared using the corresponding pyridone fragments described earlier, and purified by reverse HPLC/MS (ACN-H_2O, containing 0.1% formic acid).

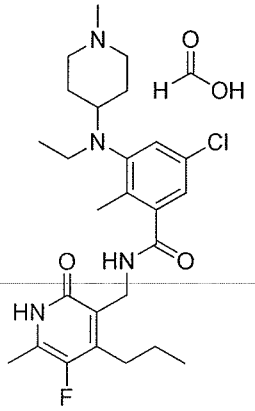
[02200] **Compound 409: 5-chloro-3-(ethyl(1-methylpiperidin-4-yl)amino)-N-((5-fluoro-4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide formate**



[02201] ^{1}H-NMR (500 MHz, CD_3OD) δ ppm 8.45-8.25 (br, 1H), 7.30 (d, J = 2.0 Hz, 1H), 7.13 (d, *J* = 2.0 Hz, 1H), 4.47 (s, 2H), 3.50-3.38 (br, 2H), 3.25-3.15 (br, 1H), 3.08 (q, *J* = 7.0 Hz, 2H), 3.06-2.98 (br, 2H), 2.83 (s, 3H), 2.38 (d, *J* = 2.0 Hz, 3H), 2.27 (s, 3H), 2.26 (d, *J* = 2.0 Hz,

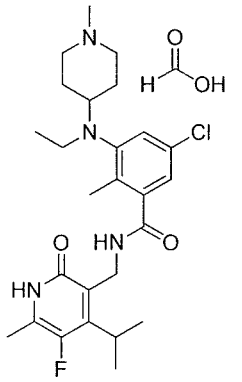
3H), 2.03 (bd, J = 14.75 Hz, 2H), 1.90-1.77 (br, 2H), 0.89 (t, J = 7.0 Hz, 3H); MS (ES) (M+H) 463.50.

[02202] **Compound 410: 5-chloro-3-(ethyl(1-methylpiperidin-4-yl)amino)-N-((5-fluoro-6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide formate**



[02203] ^{1}H-NMR (500 MHz, CD_3OD) δ ppm 8.43-8.26 (br, 1H), 7.30 (d, J = 2.0 Hz, 1H), 7.12 (d, J = 2.0 Hz, 1H), 4.47 (s, 2H), 3.47-3.39 (br, 2H), 3.23-3.15 (br, 1H), 3.08 (q, J = 7.0 Hz, 2H), 3.05-2.96 (br, 2H), 2.82 (s, 3H), 2.79 (bd, J = 8.2 Hz, 2H), 2.28-2.26 (br, 6H), 2.06-1.99 (br, 2H), 1.93-1.82 (br, 2H), 1.68-1.59 (m, 2H), 1.06 (t, J = 7.5 Hz, 3H), 0.89 (t, J = 7.0 Hz, 3H); MS (ES) (M+H) 491.52.

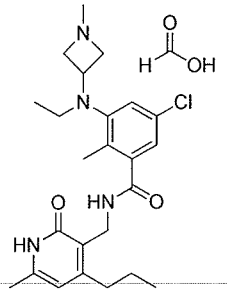
[02204] **Compound 411: 5-chloro-3-(ethyl(1-methylpiperidin-4-yl)amino)-N-((5-fluoro-4-isopropyl-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide formate**



[02205] ^{1}H-NMR (500 MHz, CD_3OD) δ ppm 8.48-8.34 (br, 1H), 7.35 (d, J =2 .0 Hz, 1H), 7.16 (d, J = 2.0 Hz, 1H), 4.57 (s, 2H), 3.61-3.53 (m, 1H), 3.52-3.44 (br, 2H), 3.30-3.20 (br, 1H), 3.13 (q, J = 7.0 Hz, 2H), 3.10-3.01 (br, 2H), 2.87 (s, 3H), 2.33 (s, 3H), 2.31 (d, J = 2.8 Hz,

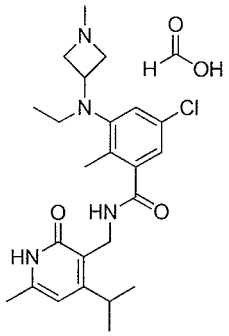
3H), 2.10-2.04 (br, 2H), 1.98-1.87 (br, 2H), 1.41 (d, J = 6.5 Hz, 6H), 0.93 (t, J = 7.0 Hz, 3H); MS (ES) (M+H) 491.51.

[02206] **Compound 412: 5-chloro-3-(ethyl(1-methylazetidin-3-yl)amino)-2-methyl-N-((6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)benzamide formate**



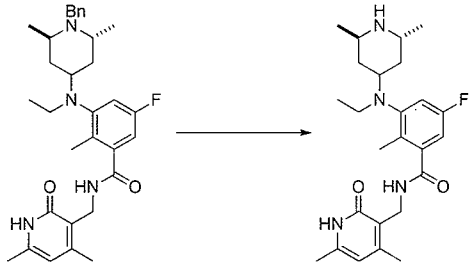
[02207] Methyl 5-chloro-3-(ethyl(1-methylazetidin-3-yl)amino)-2-methylbenzoate was hydrolyzed to 5-chloro-3-(ethyl(1-methylazetidin-3-yl)amino)-2-methylbenzoic acid following the same preparation method for 3-{Ethyl[1-(propan-2-yl)piperidin-4-yl]amino} -2-methyl-5-(trifluoromethyl)benzoic acid from its corresponding carboxylate. The crude 5-chloro-3-(ethyl(1-methylazetidin-3-yl)amino)-2-methylbenzoic acid was then coupled with 3-(Aminomethyl)-6-methyl-4-propyl-1,2-dihydropyridin-2-one HCl salt prepared earlier following the preparation method described for *N*-[(4,6-Dimethyl-2-oxo- 1,2-dihydropyridin-3-yl)methyl]-3-[ethyl(1-methylpiperidin-4-yl)amino]-2-methyl-5-(trifluoromethyl)benzamide. After purification by reverse phase HPLC/MS (CAN-H_2O containing 0.1 % formic acid), the titled compound was obtained. ^{1}H-NMR (500 MHz, CD_3OD) δ ppm 8.58-8.24 (br, 1H), 7.15 (d, J = 2.0 Hz, 1H), 7.08 (d, J = 2.0 Hz, 1H), 6.14 (s, 1H), 4.48 (s, 2H), 4.41-4.34 (m, 1H), 4.25 (br, 2H), 3.85 (br, 2H), 3.00 (q, J = 7.0 Hz, 2H), 2.92 (s, 3H), 2.72-2.66 (m, 2H), 2.34 (s, 3H), 2.26 (s, 3H), 1.70-1.61 (m, 2H), 1.04 (t, J = 7.2 Hz, 3H), 0.91 (t, J = 7.0 Hz, 3H); MS (ES) (M+H) 445.48.

[02208] **Compound 413: 5-chloro-3-(ethyl(1-methylazetidin-3-yl)amino)-N-((4-isopropyl-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methylbenzamide formate**



[02209] The same way for the previous compound 5-chloro-3-(ethyl(1-methylazetidin-3-yl)amino) -2-methyl-N-((6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)benzamide formate prepared, the titled compound prepared using 5-chloro-3-(ethyl(1-methylazetidin-3-yl)amino)-2-methylbenzoic acid and 3-(Aminomethyl)-6-methyl-4-(propan-2-yl)-1,2-dihydropyridin-2-one HCl salt. After purification by reverse phase HPLC/MS (CAN-H_2O containing 0.1 % formic acid), the titled compound was obtained. ^{1}H-NMR (500 MHz, CD_3OD) δ ppm 8.43-8.25(br, 1H), 7.15 (d, J = 2.0 Hz, 1H), 7.08 (d, J = 2.0 Hz, 1H), 6.25 (s, 1H), 4.52 (s, 2H), 4.40-4.34 (m, 1H), 4.29-4.21 (br, 2H), 3.90-3.79 (br, 2H), 3.48-3.40 (m, 1H), 3.00 (q, J = 7.0 Hz, 2H), 2.92 (s, 3H), 2.34 (s, 3H), 2.28 (s, 3H), 1.24 (d, J = 7.0 Hz, 6H), 0.90 (t, J = 7.0 Hz, 3H). MS (ES) (M+H) 445.47.

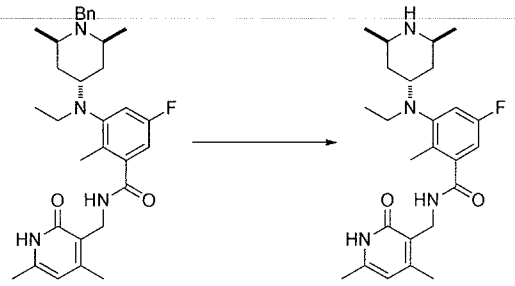
[02210] **Compound 414: *N*-[(4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3-{[(2R,6R)-2,6-dimethylpiperidin-4-yl](ethyl)amino}-5-fluoro-2-methylbenzamide**



[02211] To a stirred solution of 3-{[(2R,6R)-1-benzyl-2,6-dimethylpiperidin-4-yl](ethyl)amino}-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-5-fluoro-2-methylbenzamide (378 mg, 0.709 mmol) in MeOH (7 mL) was added Pd/C (150 mg). The reaction mixture was stirred at 23°C for 1 hour under hydrogen atmosphere. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (1. NAM-300H silica gel produced by Nagara Science Co.,

Ltd., ethylacetate/MeOH=4/1 to ethylacetate/MeOH/triethylamine=1/1/0.01, 2. NH-SiO_2, heptane/ethylacetate=30/1 to 8/1) to give title compound as a white solid (235 mg, 75% yield). ^{1}HNMR (400 MHz, $CDCl_3$) δppm; 7.08 (t, *J*=6.2 Hz, 1H), 6.82 (dd, *J*=10.7, 2.5 Hz, 1H), 6.75 (dd, *J*=8.2, 2.7 Hz, 1H), 5.93 (s, 1H), 4.51 (d, *J*=6.2 Hz, 2H), 3.40-3.48 (m, 1H), 2.95-3.09 (m, 3H), 2.83-2.92 (m, 1H), 2.39 (s, 3H), 2.22 (s x 2, 6H), 1.63-1.78 (m, 4H), 1.13 (d, *J* = 7.0 Hz, 3H), 1.02 (d, *J* = 6.2 Hz, 3H), 0.84 (t, *J* = 7.0 Hz, 3H); MS (ES) [M+H] 443.1, [M+Na] 465.2; HPLC; 99.3% purity.

[02212] **Compound 415**: ***N*-[(4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3-{[(2R,4R,6S)-2,6-dimethylpiperidin-4-yl](ethyl)amino}-5-fluoro-2-methylbenzamide**



[02213] To a stirred solution of 3-{[(2R,4R,6S)-1-benzyl-2,6-dimethylpiperidin-4-yl](ethyl)amino}-N-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-5-fluoro-2-methylbenzamide (50.1 mg, 0.0860 mmol) in MeOH (2 ml) was added Pd/C (100 mg). The reaction mixture was stirred for 3 hours under hydrogen atmosphere at 23°C. After purging with nitrogen, the mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (NAM-300H silica gel produced by Nagara Science Co., Ltd., ethylacetate/MeOH=4/1 to ethylacetate/MeOH/triethylamine=1/1/0.01). The target fractions were collected and concentrated in vacuo. The residue was purified by silica gel column chromatography (NH-SiO_2, ethylacetate/MeOH=30/1 to 20/1 to 8/1). The target fractions were collected and concentrated in vacuo. The residue was purified with preparative TLC (TLC silica gel $60F_{254}$, MERCK, MeOH/Et_3N=100/1) to give the titled compound as a white solid (17.2 mg, 45% yield). ^{1}HNMR (400 MHz, $CDCl_3$) δppm; 7.10 (m, 1H), 6.81 (m, 2H), 5.91 (s, 1H), 4.52 (d, *J* = 6.0Hz, 2H), 3.61 (m, 1H), 3.23-2.73 (m, 4H), 2.40 (s, 3H), 2.28 (s, 3H), 2.24 (s, 3H), 1.64-1.05 (m, 4H), 1.05-0.86 (m, 6H), 0.82 (t, *J* = 7.2Hz, 3H). (-2H); LC-MS: m/z [M+H] 443.2, [M+Na] 465.3; HPLC; 97.4% purity.

[02214] **Example 45**: Syntheses of Compounds 6, 9, 11-12, 19, 22, 24, 27, 29, 34-35, 37-47, 65-90, 93-96, 99-101, 103, 106-116, 124, 125, 128-136, 138-143, 145-156, 158-190, 193-204, 210, 211, 214-221, 223-242, 244-267, 270-272, 274, 275, 280, 281, 288, 289, 291-300, 303-305, 307, 312, 314, 316-318, 323-327, 329-331, 337, 338, 341-343, 345, 346, 350-355, 357-385, 388, 391, and 418

[02215] Compounds 6, 9, 11-12, 19, 22, 24, 27, 29, 34-35, 37-47, 65-90, 93-96, 99-101, 103, 106-116, 124, 125, 128-136, 138-143, 145-156, 158-190, 193-204, 210, 211, 214-221, 223-242, 244-267, 270-272, 274, 275, 280, 281, 288, 289, 291-300, 303-305, 307, 312, 314, 316-318, 323-327, 329-331, 337, 338, 341-343, 345, 346, 350-355, 357-385, 388, 391, and 418 were synthesized by methods similar to those described for Examples 1-44 or by reaction schemes depicted in the general schemes.

[02216] **Example 46:** Bioassay protocol and General Methods

Protocol for Wild-Type and Mutant PRC2 Enzyme Assays

[02217] **General Materials.** *S*-adenosylmethionine (SAM), *S*-adenosylhomocyteine (SAH), bicine, KCl, Tween20, dimethylsulfoxide (DMSO) and bovine skin gelatin (BSG) were purchased from Sigma-Aldrich at the highest level of purity possible. Dithiothreitol (DTT) was purchased from EMD. ^{3}H-SAM was purchased from American Radiolabeled Chemicals with a specific activity of 80 Ci/mmol. 384-well streptavidin Flashplates were purchased from PerkinElmer.

[02218] **Substrates.** Peptides representative of human histone H3 residues 21 – 44 containing either an unmodified lysine 27 (H3K27me0) or dimethylated lysine 27 (H3K27me2) were synthesized with a C-terminal G(K-biotin) linker-affinity tag motif and a C-terminal amide cap by 21st Century Biochemicals. The peptides were high-performance liquid chromatography (HPLC) purified to greater than 95% purity and confirmed by liquid chromatography mass spectrometry (LC-MS). The sequences are listed below.

H3K27me0: ATKAARKSAPATGGVKKPHRYRPGGK(biotin)-amide (SEQ ID NO: 1)

H3K27me2: ATKAARK(me2)SAPATGGVKKPHRYRPGGK(biotin)-amide (SEQ ID NO: 2)

[02219] Chicken erythrocyte oligonucleosomes were purified from chicken blood according to established procedures.

[02220] **Recombinant PRC2 Enzymes.** Human PRC2 enzymes were purified as 4-component enzyme complexes co-expressed in *Spodoptera frugiperda* (sf9) cells using a baculovirus expression system. The subunits expressed were wild-type EZH2 (NM_004456) or EZH2 Y641F, N, H, S or C mutants generated from the wild-type EZH2 construct, EED (NM_003797), Suz12 (NM_015355) and RbAp48 (NM_005610). The EED subunit contained an N-terminal FLAG tag that was used to purify the entire 4-component complex from sf9 cell lysates. The purity of the complexes met or exceeded 95% as determined by SDS-PAGE and Agilent Bioanalyzer analysis. Concentrations of enzyme stock concentrations (generally 0.3 – 1.0 mg/mL) was determined using a Bradford assay against a bovine serum albumin (BSA) standard.

[02221] **General Procedure for PRC2 Enzyme Assays on Peptide Substrates.** The assays were all performed in a buffer consisting of 20 mM bicine (pH = 7.6), 0.5 mM DTT, 0.005% BSG and 0.002% Tween20, prepared on the day of use. Compounds in 100% DMSO (1 μL) were spotted into polypropylene 384-well V-bottom plates (Greiner) using a Platemate 2 X 3 outfitted with a 384-channel pipet head (Thermo). DMSO (1 μL) was added to columns 11, 12, 23, 24, rows A – H for the maximum signal control, and SAH, a known product and inhibitor of PRC2 (1 μL) was added to columns 11,12, 23, 24, rows I – P for the minimum signal control. A cocktail (40 μL) containing the wild-type PRC2 enzyme and H3K27me0 peptide or any of the Y641 mutant enzymes and H3K27me2 peptide was added by Multidrop Combi (Thermo). The compounds were allowed to incubate with PRC2 for 30 min at 25 °C, then a cocktail (10 μL) containing a mixture of non-radioactive and ^{3}H-SAM was added to initiate the reaction (final volume = 51 μL). In all cases, the final concentrations were as follows: wild-type or mutant PRC2 enzyme was 4 nM, SAH in the minimum signal control wells was 1 mM and the DMSO concentration was 1%. The final concentrations of the rest of the components are indicated in Table 2, below. The assays were stopped by the addition of non-radioactive SAM (10 μL) to a final concentration of 600 μM, which dilutes the ^{3}H-SAM to a level where its incorporation into the peptide substrate is no longer detectable. 50 μL of the reaction in the 384-well polypropylene plate was then transferred to a 384-well Flashplate and the biotinylated peptides were allowed to bind to the streptavidin surface for at least 1h before being washed

three times with 0.1% Tween20 in a Biotek ELx405 plate washer. The plates were then read in a PerkinElmer TopCount platereader to measure the quantity of ^{3}H-labeled peptide bound to the Flashplate surface, measured as disintegrations per minute (dpm) or alternatively, referred to as counts per minute (cpm).

Table 2: Final concentrations of components for each assay variation based upon EZH2 identity (wild-type or Y641 mutant EZH2)

PRC2 Enzyme (denoted by EZH2 identity)	Peptide (nM)	Non-radioactive SAM (nM)	^{3}H-SAM (nM)
Wild-type	185	1800	150
Y641F	200	850	150
Y641N	200	850	150
Y641H	200	1750	250
Y641S	200	1300	200
Y641C	200	3750	250

[02222] **General Procedure for Wild-Type PRC2 Enzyme Assay on Oligonucleosome Substrate.** The assays was performed in a buffer consisting of 20 mM bicine (pH = 7.6), 0.5 mM DTT, 0.005% BSG, 100 mM KCl and 0.002% Tween20, prepared on the day of use. Compounds in 100% DMSO (1 μL) were spotted into polypropylene 384-well V-bottom plates (Greiner) using a Platemate 2 X 3 outfitted with a 384-channel pipet head (Thermo). DMSO (1 μL) was added to columns 11, 12, 23, 24, rows A – H for the maximum signal control, and SAH, a known product and inhibitor of PRC2 (1 μL) was added to columns 11,12, 23, 24, rows I – P for the minimum signal control. A cocktail (40 μL) containing the wild-type PRC2 enzyme and chicken erythrocyte oligonucleosome was added by Multidrop Combi (Thermo). The compounds were allowed to incubate with PRC2 for 30 min at 25 °C, then a cocktail (10 μL) containing a mixture of non-radioactive and ^{3}H-SAM was added to initiate the reaction (final volume = 51 μL). The final concentrations were as follows: wild-type PRC2 enzyme was 4 nM, non-radioactive SAM was 430 nM, ^{3}H-SAM was 120 nM, chicken erythrocyte oligonucleosome was 120 nM, SAH in the minimum signal control wells was 1 mM and the DMSO concentration was 1%. The assay was stopped by the addition of non-radioactive SAM (10 μL) to a final concentration of 600 μM, which dilutes the ^{3}H-SAM to a level where its incorporation into the chicken erythrocyte oligonucleosome substrate is no longer detectable. 50 μL of the reaction in the 384-well polypropylene plate was then transferred to a 384-well

Flashplate and the chicken erythrocyte nucleosomes were immobilized to the surface of the plate, which was then washed three times with 0.1% Tween20 in a Biotek ELx405 plate washer. The plates were then read in a PerkinElmer TopCount platereader to measure the quantity of ^{3}H-labeled chicken erythrocyte oligonucleosome bound to the Flashplate surface, measured as disintegrations per minute (dpm) or alternatively, referred to as counts per minute (cpm).

[02223] **% Inhibition Calculation**

$$\% \text{ inh} = 100 - \left(\frac{dpm_{cmpd} - dpm_{min}}{dpm_{max} - dpm_{min}} \right) \times 100$$

[02224] Where dpm = disintegrations per minute, cmpd = signal in assay well, and min and max are the respective minimum and maximum signal controls.

[02225] **Four-parameter IC_{50} fit**

$$Y = \text{Bottom} + \frac{(\text{Top} - \text{Bottom})}{1 + \left(\frac{X}{IC_{50}}\right)^{\text{Hill Coefficeint}}}$$

[02226] Where top and bottom are the normally allowed to float, but may be fixed at 100 or 0 respectively in a 3-parameter fit. The Hill Coefficient normally allowed to float but may also be fixed at 1 in a 3-parameter fit. Y is the % inhibition and X is the compound concentration.

[02227] IC_{50} values for the PRC2 enzyme assays on peptide substrates (e.g., EZH2 wild type andY641F) are presented in Table 3 below.

[02228] **WSU-DLCL2 Methylation Assay**

[02229] WSU-DLCL2 suspension cells were purchased from DSMZ (German Collection of Microorganisms and Cell Cultures, Braunschweig, Germany). RPMI/Glutamax Medium, Penicillin-Streptomycin, Heat Inactivated Fetal Bovine Serum, and D-PBS were purchased from Life Technologies, Grand Island, NY, USA. Extraction Buffer and Neutralization Buffer(5X) were purchased from Active Motif, Carlsbad, CA, USA. Rabbit anti-Histone H3 antibody was purchased from Abcam, Cambridge, MA, USA. Rabbit anti-H3K27me3 and HRP-conjugated anti-rabbit-IgG were purchased from Cell Signaling Technology, Danvers, MA, USA. TMB "Super Sensitive" substrate was sourced from BioFX Laboratories, Owings

Mills, MD, USA. IgG-free Bovine Serum Albumin was purchased from Jackson ImmunoResearch, West Grove, PA, USA. PBS with Tween (10X PBST) was purchased from KPL, Gaithersburg, MD, USA. Sulfuric Acid was purchased from Ricca Chemical, Arlington, TX, USA. Immulon ELISA plates were purchased from Thermo, Rochester, NY, USA. V-bottom cell culture plates were purchased from Corning Inc., Corning, NY, USA.V-bottom polypropylene plates were purchased from Greiner Bio-One, Monroe, NC, USA.

[02230] WSU-DLCL2 suspension cells were maintained in growth medium (RPMI 1640 supplemented with 10% v/v heat inactivated fetal bovine serum and 100 units/mL penicillin-streptomycin) and cultured at 37 °C under 5% CO_2. Under assay conditions, cells were incubated in Assay Medium (RPMI 1640 supplemented with 20% v/v heat inactivated fetal bovine serum and 100 units/mL penicillin-streptomycin) at 37 °C under 5% CO_2 on a plate shaker.

[02231] WSU-DLCL2 cells were seeded in assay medium at a concentration of 50,000 cells per mL to a 96-well V-bottom cell culture plate with 200 µL per well. Compound (1µL) from 96 well source plates was added directly to V-bottom cell plate. Plates were incubated on a titer-plate shaker at 37°C, 5% CO2 for 96 hours. After four days of incubation, plates were spun at 241 x g for five minutes and medium was aspirated gently from each well of cell plate without disturbing cell pellet. Pellet was resuspended in 200 µL DPBS and plates were spun again at 241 x g for five minutes. The supernatant was aspirated and cold (4°C) Extraction buffer (100 µL) was added per well. Plates were incubated at 4°C on orbital shaker for two hours. Plates were spun at 3427 x g x 10 minutes. Supernatant (80 µL per well) was transferred to its respective well in 96 well V-bottom polypropylene plate. Neutralization Buffer 5X (20 µL per well) was added to V-bottom polypropylene plate containing supernatant. V-bottom polypropylene plates containing crude histone preparation (CHP) were incubated on orbital shaker x five minutes. Crude Histone Preparations were added (2µL per well) to each respective well into duplicate 96 well ELISA plates containing 100 µL Coating Buffer (1X PBS + BSA 0.05% w/v). Plates were sealed and incubated overnight at 4°C. The following day, plates were washed three times with 300 µL per well 1X PBST. Wells were blocked for two hours with 300 µL per well ELISA Diluent ((PBS (1X) BSA (2% w/v) and Tween20 (0.05% v/v)). Plates were washed three times with 1X PBST. For the Histone H3 detection plate, 100 µL per well were added of anti-Histone-H3 antibody (Abcam, ab1791) diluted 1:10,000 in

ELISA Diluent. For H3K27 trimethylation detection plate, 100 µL per well were added of anti-H3K27me3 diluted 1:2000 in ELISA diluent. Plates were incubated for 90 minutes at room temperature. Plates were washed three times with 300 µL 1X PBST per well. For Histone H3 detection, 100 µL of HRP-conjugated anti-rabbit IgG antibody diluted to 1:6000 in ELISA diluent was added per well. For H3K27me3 detection, 100 µL of HRP conjugated anti-rabbit IgG antibody diluted to 1:4000 in ELISA diluent was added per well. Plates were incubated at room temperature for 90 minutes. Plates were washed four times with 1X PBST 300 µL per well. TMB substrate100 µL was added per well. Histone H3 plates were incubated for five minutes at room temperature. H3K27me3 plates were incubated for 10 minutes at room temperature. The reaction was stopped with sulfuric acid 1N (100 µL per well). Absorbance for each plate was read at 450 nm.

[02232] First, the ratio for each well was determined by: $\left(\frac{H3K27me3\ OD450\ value}{Histone\ H3\ OD450\ value}\right)$

[02233] Each plate included eight control wells of DMSO only treatment (Minimum Inhibition) as well as eight control wells for maximum inhibition (Background wells).

[02234] The average of the ratio values for each control type was calculated and used to determine the percent inhibition for each test well in the plate. Test compound was serially diluted three-fold in DMSO for a total of ten test concentrations, beginning at 25 µM. Percent inhibition was determined and IC_{50} curves were generated using duplicate wells per concentration of compound. IC_{50} values for this assay are presented in Table 3 below.

[02235] Percent Inhibition = 100-

$$\left(\left(\frac{(\text{Individual Test Sample Ratio})-(\text{Background Avg Ratio})}{(\text{Minimum Inhibition Ratio})-(\text{Background Average Ratio})}\right)*100\right)$$

[02236] **Cell proliferation analysis**

[02237] WSU-DLCL2 suspension cells were purchased from DSMZ (German Collection of Microorganisms and Cell Cultures, Braunschweig, Germany). RPMI/Glutamax Medium, Penicillin-Streptomycin, Heat Inactivated Fetal Bovine Serum were purchased from Life Technologies, Grand Island, NY, USA. V-bottom polypropylene 384-well plates were purchased from Greiner Bio-One, Monroe, NC, USA. Cell culture 384-well white opaque plates were purchased from Perkin Elmer, Waltham, MA, USA. Cell-Titer Glo® was purchased from Promega Corporation, Madison, WI, USA. SpectraMax M5 plate reader was purchased from Molecular Devices LLC, Sunnyvale, CA, USA.

[02238] WSU-DLCL2 suspension cells were maintained in growth medium (RPMI 1640 supplemented with 10% v/v heat inactivated fetal bovine serum and cultured at 37 °C under 5% CO_2. Under assay conditions, cells were incubated in Assay Medium (RPMI 1640 supplemented with 20% v/v heat inactivated fetal bovine serum and 100 units/mL penicillin-streptomycin) at 37 °C under 5% CO_2.

[02239] For the assessment of the effect of compounds on the proliferation of the WSU-DLCL2 cell line, exponentially growing cells were plated in 384-well white opaque plates at a density of 1250 cell/ml in a final volume of 50 µl of assay medium. A compound source plate was prepared by performing triplicate nine-point 3-fold serial dilutions in DMSO, beginning at 10 mM (final top concentration of compound in the assay was 20 µM and the DMSO was 0.2%). A 100 nL aliquot from the compound stock plate was added to its respective well in the cell plate. The 100% inhibition control consisted of cells treated with 200 nM final concentration of staurosporine and the 0% inhibition control consisted of DMSO treated cells. After addition of compounds, assay plates were incubated for 6 days at 37°C, 5% CO_2, relative humidity > 90% for 6 days. Cell viability was measured by quantization of ATP present in the cell cultures, adding 35 µl of Cell Titer Glo® reagent to the cell plates. Luminescence was read in the SpectraMax M5. The concentration inhibiting cell viability by 50% was determined using a 4-parametric fit of the normalized dose response curves. IC_{50} values for this assay are also presented in Table 3 below.

Table 3

Cpd #	WT EZH2 IC_{50} (µM)	Mutant Y641F IC_{50} (µM)	H3K27Me3 ELISA IC_{50} (µM)	WSU proliferation IC_{50} (µM)
1	0.0199			3.09728
2	0.02348			0.62109
3	0.04011			
4	0.02231			0.54412
5	0.02389			2.19558
6	0.02703			0.50577
7	0.03317			
8	0.03622	0.02506		
9	0.03501			
10	0.03978			
11	0.04682			

Cpd #	WT EZH2 IC_{50} (μM)	Mutant Y641F IC_{50} (μM)	H3K27Me3 ELISA IC_{50} (μM)	WSU proliferation IC_{50} (μM)
12	0.05026			
13	0.06396			
14	0.04353			
15	0.07173			
16	0.10471			
17	0.08438			
18	0.1603			
19	0.10845			
20	0.16251			
21	0.17104			
22	0.20549			
23	0.17755			
24	0.22919			
25	0.23			
26	0.29374			
27	0.48381			
28	0.54889			
29	0.62173			
30	0.62615			
31	0.6324			
32	0.63441			
33	0.65963			
35	0.82442			
36	0.91712			
37	1.00379			
38	1.0545			
39	1.07137			
40	1.09168			
41	1.13408			
42	2.59043			
43	2.67651			
44	4.32369			
45	25.22746			
46	26.53597			
47	39.133			
48	0.24998			
49	3.59887			
50	0.30813			
51	0.37599			

Cpd #	WT EZH2 IC_{50} (μM)	Mutant Y641F IC_{50} (μM)	H3K27Me3 ELISA IC_{50} (μM)	WSU proliferation IC_{50} (μM)
52	0.04814			
53	0.41267			
54	0.50073			
55	0.01626			3.91279
56	0.01519			0.21216
57	0.02987			7.72974
58	0.05639			
59	0.03149			
60	0.05852			
61	0.01585			0.33187
62	0.09429			
63	0.05709			
64	0.02472			2.06774
65	1.07044			
66	1.71172			
67	3.61905			
68	1.3267			
69	4.71695			
70	0.90608			
71	1.21512			
72	1.01436			
73	4.14125			
74	0.07113			
75	0.3843			
76	1.24461			
77	0.14901			
78	0.14362			
79	0.02465	0.02116		
80	1.64878			
82	4.20192			
83	0.18011	0.09576		
84	0.11391	0.10243		
85	0.10754	0.07626		
86	2.57252			
87	0.09019	0.10057		
88	0.03758	0.02817		
89	0.07342	0.08298		
90	0.0998	0.1002		
91	0.02271	0.0176		2.5696

Cpd #	WT EZH2 IC_{50} (μM)	Mutant Y641F IC_{50} (μM)	H3K27Me3 ELISA IC_{50} (μM)	WSU proliferation IC_{50} (μM)
92	0.01655	0.02341		1.23721
93	1.18036	1.08352		
94	3.80992	5.5015		
95	0.35125	0.33255		
96	0.38143	0.40305		
97	0.02024	0.0292		2.4644
98	0.0174	0.03732		1.75896
99	0.01481	0.01028		3.86397
100	0.03203	0.01966		
101	0.00711	0.00717		1.07296
102	0.01545	0.00727		0.61272
103	0.072	0.06724		
104	0.03077	0.0318		9.05638
105	0.01728	0.01229		6.47052
106	0.2446	0.19119		
107	0.05396	0.10057		
108	0.02003	0.0175		4.42418
109	0.01112	0.01094		0.44691
110	0.04792	0.06226		
111	0.05328	0.02875		
112	0.0587	0.02666		
113	0.18895	0.17503		
114	0.1051	0.11091		
115	0.06117	0.05267		
116	0.06276	0.0452		
117	0.02807	0.02213		
118	0.01759	0.01615		8.60536
119	0.00951	0.00748		1.40617
120	0.00911	0.01085		0.36889
121	0.01385	0.0133		0.5035
122	0.01511	0.01932		0.18096
123	0.09153	0.06041		
124	0.16779	0.11113		
125	0.04721	0.0315		
126	0.04784	0.03472		
127	0.01691	0.01923		1.50101
128	0.04911	0.0438		
129	0.11098	0.08998		
130	0.01722	0.01508		2.3697

Cpd #	WT EZH2 IC_{50} (μM)	Mutant Y641F IC_{50} (μM)	H3K27Me3 ELISA IC_{50} (μM)	WSU proliferation IC_{50} (μM)
131	0.02287	0.00778		1.65122
132	0.06337	0.0717		
133	0.04829	0.03059		
134	0.02562	0.02189		1.08958
135	0.04667	0.02555		4.14394
136	0.11517	0.0957		
137	0.01602	0.00604		3.29434
138	0.03495	0.04493		> 20.0 uM
139	0.0204	0.01392		1.79898
140	1.66626	0.91482		
141	0.06632	0.18147		
142	0.02672	0.02005		3.72097
143	0.13711	0.05828		
144	2.294	1.3667		
145	0.10444	0.07112		
146	0.32313	0.28854		
147	0.14779	0.25593		
148	0.10411	0.0887		
149	0.04469	0.03168		
150	0.02894	0.02965		0.57037
151	0.01594	0.0157		0.52874
152	0.02585	0.02197		1.40549
153	0.08502	0.09128		
154	0.013	0.01062		1.16887
155	0.02133	0.02385		0.46034
156	0.0588	0.01936		
157	0.00315	0.02001		0.71676
158	0.00901	0.00955		0.65779
159	0.02579	0.02495		0.58237
160	0.01766	0.02255		6.6023
161	0.01969	0.01299		1.59243
162	0.01532	0.01819		1.18391
163	0.46447	0.26959		
164	0.0546	0.06284		
165	0.02452	0.01895		0.84174
166	0.01495	0.01835		0.69533
167	0.0131	0.00987		0.10896
168	0.00808	0.00611		0.82333
169	0.09611	0.1054		

Cpd #	WT EZH2 IC_{50} (μM)	Mutant Y641F IC_{50} (μM)	H3K27Me3 ELISA IC_{50} (μM)	WSU proliferation IC_{50} (μM)
170	0.01635	0.01145		4.16823
171	0.07652	0.0652		
172	0.65963			
173	1.13408			
174	0.0199			3.09728
175	15.49647			
176	35.36685			
177	4.13196			
178	4.13196			
179	2.875			
180	2.31858			
181	1.18357			
182	0.13256			
183	7.67584			
184	1.07044			
186	1.64878			
187	2.57252			
188	0.15624	0.16162		
189	3.80992	5.5015		
190	0.2839	0.21448		
191	0.0109	0.00548		0.43262
192	0.13004	0.09414		
193	0.0822	0.05193		
194	0.01771	0.00919		0.41697
195	0.01654	0.01113		1.45306
196	0.01817	0.01479		0.35933
197	0.01822	0.00537		1.05176
198	0.20387	0.13976		
199	1.38563	0.99179		
200	0.00624	0.00596		0.2826
201	1.33026	1.11031		
202	0.04811	0.03758		3.12395
203	0.02138	0.0142		0.47667
204	0.22175	0.21976		
205	0.0077	0.00479	0.82074	
206	0.01284	0.01106		0.63322
207	0.10198	0.11905		> 20.0 uM
208	1.31405	1.19521		
209	1.487	1.18544		

Cpd #	WT EZH2 IC_{50} (μM)	Mutant Y641F IC_{50} (μM)	H3K27Me3 ELISA IC_{50} (μM)	WSU proliferation IC_{50} (μM)
210				1.26697
211	0.00679	0.0147		0.54832
212	1.05201	0.98451		
213	0.05325	0.0438		14.71083
214	0.07475	0.06722		2.45231
215	0.01551	0.02167		0.80033
216	0.02489	0.04884		1.54705
217	0.18259	0.34753		
218	0.02083	0.02903		1.27027
219	0.1748	0.16449		
220	0.0205	0.04357		1.04201
221	0.0191	0.01616		1.11978
222	0.00078	0.00225	0.18533	0.13712
223	0.0136	0.02689		1.54605
224	0.03257	0.03334		1.76879
225	0.00695	0.01342		0.20778
226	0.03426	0.06624		0.23132
227	0.00365	0.00622		0.21515
228	0.0144	0.02015		1.27869
229	0.02235	0.02847		1.54848
230	0.34423	0.25475		
231	0.29712	0.15945		> 20.0 uM
232	0.15485	0.0881		8.04526
233	1.42344	0.5799		
234	1.97267	1.62693		
235	0.0632	0.05138		3.79895
236	0.61213	0.83099		14.62129
237	2.18156	1.47293		
238	1.40428	0.80506		
239	4.95504	4.77826		
240	6.94031	6.8594		
241	6.57787			
242	0.1998	0.12679		8.4057
243	0.06318			6.47336
244	0.03749			3.06427
245	0.33295			
246				
247	0.01787	0.02136		3.19941
248	0.03458	0.0601		4.57081

Cpd #	WT EZH2 IC_{50} (μM)	Mutant Y641F IC_{50} (μM)	H3K27Me3 ELISA IC_{50} (μM)	WSU proliferation IC_{50} (μM)
249				11.45613
250	0.15959	0.20744		4.58295
251				13.11386
252				> 20.0 uM
253	0.45669	0.28936		14.42495
254				
255	0.01095	0.009		1.63338
256	0.00648	0.00738		1.69149
257	0.02224	0.07406		4.49758
258	1.90754			
259	0.58066	0.60207		> 20.0 uM
260	0.01282	0.01164		1.08525
261	0.01426	0.02069		0.9055
262	0.00961	0.00523		1.89119
263	0.03631	0.02181		4.89099
264	0.04094	0.04072		8.72536
265	0.02507	0.01843		5.09483
266	0.19847	0.08014		8.72547
267	0.16128			> 20.0 uM
268	0.00131	0.0024		0.38531
269	0.09984	0.11108		14.2318
270	9.47417	> 10.0 uM		
271	0.05109	0.02565		5.32683
272	0.11472	0.06925		
273	0.00328	0.00537		0.28489
274	7.76353	> 10.0 uM		> 20.0 uM
275	0.90643	3.32337		> 20.0 uM
276	0.00152	0.00407		0.18228
277	0.0023	0.00264		2.47797
278	0.00493	0.01117		0.61255
279	0.01143	0.01999		0.78715
280	0.00139	0.00556		0.43228
281	> 10.0 uM	> 10.0 uM		
282	0.00492	0.00985		0.21356
283	0.00316	0.0177		0.27638
284	0.008	0.0119		0.26282
285	0.00211	0.00506		0.21307

Cpd #	WT EZH2 IC_{50} (μM)	Mutant Y641F IC_{50} (μM)	H3K27Me3 ELISA IC_{50} (μM)	WSU proliferation IC_{50} (μM)
286	0.00122	0.00272		0.46721
287	0.00882	0.01141		1.35674
288	0.00694	0.00732		0.53484
289	0.14621	0.09339		
290	0.00743			0.53732
291	0.00951			0.71974
292	0.01046			1.21021
293	0.01737	0.01158		1.29406
294	0.02412			2.16178
295	0.01161	0.01056		2.51445
296	0.00655	0.01825		4.33357
297	0.03337	0.02251		11.2951
298	0.0371	0.04303		6.54579
299	0.00324	0.00307		0.25937
300	0.02277	0.01709		4.94656
301	0.00497	0.00507		
302	0.01217	0.01607		1.97477
303	0.03293	0.04119		3.89541
304	0.01722	0.0126		2.14418
305	0.00254	0.00785		0.28787
306	0.00942	0.00922		0.17284
307	0.0402	0.10188		3.85437
308	0.00997	0.01169		0.16744
309	0.00817			
310	0.00596			0.60994
311	0.00323			0.16549
312	0.01507			
313	0.00818			
314	2.90826	4.7092		
315	0.00973	0.00922		
316		0.01202		1.40268
317	1.37527	1.96382		
318	1.06978	0.91775		9.7596
319	0.0108	0.01137		2.95728
320	0.01694	0.01579		0.17566
321	0.00783	0.01144		
322	0.03101	0.02239		3.59961
323	0.05148	0.03445		4.15894
324	0.40349	0.15525		16.80211

Cpd #	WT EZH2 IC_{50} (μM)	Mutant Y641F IC_{50} (μM)	H3K27Me3 ELISA IC_{50} (μM)	WSU proliferation IC_{50} (μM)
325	0.13585	0.21534		13.3829
326	0.0206	0.0095		1.43256
327	0.23134	0.09407		3.11887
328	0.84894			> 20.0 uM
329	0.00755	0.00371		0.88119
330	0.03576	0.0368		1.20313
331	0.03891	0.01805		0.19105
332	0.27993	0.45426		> 20.0 uM
333	0.30257	0.54098		> 20.0 uM
334	0.05384	0.11977		
335	0.01004	0.0027		0.97124
336	0.03144	0.02075		
337	4.32339	3.56167		> 20.0 uM
338	0.49234	0.19347		> 20.0 uM
339	0.00858	0.00734		0.97312
340	0.01056	0.00412		1.59354
341	0.00592	0.00552		2.28944
342	0.03972	0.01592		1.9859
343	0.01081	0.00912		0.63289
344	0.00623	0.00396		1.30672
345	0.02228	0.01819		1.2346
346	0.00428	0.00245		0.12639
347	0.00654	0.00328		0.13526
348	0.00566	0.00363		0.32865
349	0.00872	0.00153		
350	0.01244	0.00357		0.38084
351	0.00911	0.00138		4.85151
352	0.13195			5.54765
353	0.00792	0.00463		0.14599
354	0.01312	0.01039	0.14232	0.15832
355	0.08966	0.06081		
356	0.03629	0.00721		
357	0.00437	0.00456	0.14928	
358	0.17315	0.06636		
359	0.00729	0.00554		
360	0.00883	0.00841		
361	0.00661	0.00423		
362	0.01388	0.00491		
363	0.00394	0.00206		

Cpd #	WT EZH2 IC_{50} (μM)	Mutant Y641F IC_{50} (μM)	H3K27Me3 ELISA IC_{50} (μM)	WSU proliferation IC_{50} (μM)
364	0.00943	0.00687		
365	0.00609	0.00665	0.23299	
366	0.03483	0.02934	> 25.0 uM	
367	0.33336	0.16784	> 25.0 uM	
368	0.02799	0.03855	> 25.0 uM	
369	0.07146	0.02755	3.7881	
370	0.02998	0.01113		
371	0.01181	0.00537		
372	0.00801	0.0081	0.3659	
373	0.00694	0.00369		
374	0.00319	0.00831		
375	0.01661	0.04182		
376	0.01641	0.01977		
377	0.07647	0.02552		
378	0.00296	0.0031	> 25.0 uM	
379	0.00516	0.00322	> 25.0 uM	
380	0.02778	0.04196	> 25.0 uM	
381	0.05627	0.05243	> 25.0 uM	
382	0.00341	0.02167	4.16185	
383	0.03974	0.04428	> 25.0 uM	
384	0.00206	0.00156	1.53716	
385	0.06573	0.03511	> 25.0 uM	
386	2.42146	1.15144		
387	0.74351	0.39771		
388	0.00728	0.00396	2.29835	
389	0.01564	0.0177		
390	0.01251	0.01037		1.32773
391	0.04809	0.06404	> 25.0 uM	
392	0.048	0.039		
393	0.12932	0.10995		
394	0.29421	0.23058		
395	0.30434	0.17359		
396	4.42445	6.6822		
397	3.37221	2.39173		
398	2.61756	2.00394		
399	> 10.0 uM	8.31018		
400	0.025	0.018		
401	0.01466	0.01426		
402	> 10.0 uM	8.0921		
403	0.53602	0.58786		

Cpd #	WT EZH2 IC_{50} (μM)	Mutant Y641F IC_{50} (μM)	H3K27Me3 ELISA IC_{50} (μM)	WSU proliferation IC_{50} (μM)
404	2.27552	1.40203		
405	0.172	0.107		
406	0.017	0.053		
407	0.0861	0.04069		
408	0.1656	0.0936		
409	0.45616	0.3404		
410	2.28273	2.85881		
411	1.19988	1.40119		
412	0.22183	0.21475		
413	0.76484	0.64167		
414	0.00692	0.0084		
415	1.5555	0.89979		
416	0.016	0.015		

[02240] **Example 47:** Derivation of the Lowest Cytotoxic Concentration (LCC)

[02241] It is well established that cellular proliferation proceeds through cell division that results in a doubling of the number of cells after division, relative to the number of cells prior to division. Under a fixed set of environmental conditions (e.g., pH, ionic strength, temperature, cell density, medium content of proteins and growth factors, and the like) cells will proliferate by consecutive doubling (i.e., division) according to the following equation, provided that sufficient nutrients and other required factors are available.

[02242] $$N_t = N_0 \times 2^{\frac{t}{t_D}} \quad \text{(A.1)}$$

where N_t is the cell number at a time point (t) after initiation of the observation period, N_0 is the cell number at the initiation of the observation period, t is the time after initiation of the observation period and t_D is the time interval required for cell doubling, also referred to as the doubling time. Equation A.1 can be converted into the more convenient form of an exponential equation in base e, taking advantage of the equality, 0.693 = ln(2).

[02243] $$N_t = N_0 e^{\frac{0.693t}{t_D}} \quad \text{(A.2)}$$

[02244] The rate constant for cell proliferation (k_p) is inversely related to the doubling time as follows.

[02245] $$k_p = \frac{0.693}{t_D} \quad \text{(A.3)}$$

[02246] Combining equation A.2 and A.3 yields,

[02247] $$N_t = N_0 e^{k_p t} \quad \text{(A.4)}$$

[02248] Thus, according to equation A.4 cell number is expected to increase exponentially with time (Figure 1 A) during the early period of cell growth referred to as log-phase growth. Exponential equations like equation A.4 can be linearized by taking the natural logarithm of each side.

[02249] $$\ln(N_t) = \ln(N_0) + k_p t \quad \text{(A.5)}$$

[02250] Thus a plot of $\ln(N_t)$ as a function of time is expected to yield an ascending straight line with slope equal to k_p and y-intercept equal to $\ln(N_0)$, as illustrated in Figure 1 B.

[02251] Changes in environmental conditions can result in a change in the rate of cellular proliferation that is quantifiable as changes in the proliferation rate constant k_p. Among conditions that may result in a change in proliferation rate is the introduction to the system of an antiproliferative compound at the initiation of the observation period (i.e., at $t = 0$). When an antiproliferative compound has an immediate impact on cell proliferation, one expects that plots of $\ln(N_t)$ as a function of time will continue to be linear at all compound concentrations, with diminishing values of k_p at increasing concentrations of compound.

[02252] Depending on the mechanistic basis of antiproliferative action, some compounds may not immediately effect a change in proliferation rate. Instead, there may be a period of latency before the impact of the compound is realized. In such cases a plot of $\ln(N_t)$ as a function of time will appear biphasic, and a time point at which the impact of the compound begins can be identified as the breakpoint between phases (Figure 2). Regardless of whether a compound's impact on proliferation is immediate or begins after a latency period, the rate constant for proliferation at each compound concentration is best defined by the slope of the $\ln(N_t)$ vs. time curve from the time point at which compound impact begins to the end of the observation period of the experiment.

[02253] A compound applied to growing cells may affect the observed proliferation in one of two general ways: by inhibiting further cell division (cytostasis) or by cell killing

(cytotoxicity). If a compound is cytostatic, increasing concentration of compound will reduce the value of k_p until there is no further cell division. At this point, the rate of cell growth, and therefore the value of k_p, will be zero. If, on the other hand, the compound is cytotoxic, then the value of k_p will be composed of two rate constants: a rate constant for continued cell growth in the presence of the compound (k_g) and a rate constant for cell killing by the compound (k_d). The overall rate constant for proliferation at a fixed concentration of compound will thus be the difference between the absolute values of these opposing rate constants.

[02254] $$k_p = |k_g| - |k_d| \qquad \text{(A.6)}$$

[02255] At compound concentrations for which the rate of cell growth exceeds that of cell killing, the value of k_p will have a positive value (i.e., $k_p > 0$). At compound concentrations for which the rate of cell growth is less than that for cell killing, the value of k_p will have a negative value (i.e., $k_p < 0$) and the cell number will decrease with time, indicative of robust cytotoxicity. When k_g exactly matches k_d then the overall proliferation rate constant, k_p, will have a value of zero. We can thus define the lowest cytotoxic concentration (LCC) as that concentration of compound that results in a value of k_p equal to zero, because any concentration greater than this will result in clearly observable cytotoxicity. *Nota bene*: at concentrations below the LCC there is likely to be cell killing occurring, but at a rate that is less than that of residual cell proliferation. The treatment here is not intended to define the biological details of compound action. Rather, the goal here is to merely define a practical parameter with which to objectively quantify the concentration of compound at which the rate of cell killing exceeds new cell growth. Indeed, the LCC represents a breakpoint or critical concentration above which frank cytotoxicity is observed, rather than a cytotoxic concentration per se. In this regard, the LCC can be viewed similar to other physical breakpoint metrics, such as the critical micelle concentration (CMC) used to define the concentration of lipid, detergent or other surfactant species above which all molecules incorporate into micellar structures.

[02256] Traditionally, the impact of antiproliferative compounds on cell growth has been most commonly quantified by the IC_{50} value, which is defined as that concentration of compound that reduces the rate of cell proliferation to one half that observed in the absence of compound (i.e., for the vehicle or solvent control sample; Figure 2). The IC_{50}, however, does

not allow the investigator to differentiate between cytostatic and cytotoxic compounds. The LCC, in contrast, readily allows one to make such a differentiation and to further quantify the concentration at which the transition to robust cytotoxic behavior occurs.

[02257] If one limits the observation time window to between the start of impact (as defined above and in Figure 2) and the end of the experiment, then the data will generally fit well to a linear equation when plotted as $\ln(N_t)$ as a function of time (*vide supra*). From fits of this type, the value of k_p can be determined at each concentration of compound tested. A replot of the value of k_p as a function of compound concentration ([I]) will have the form of a descending isotherm, with a maximum value at [I] = 0 of k_{max} (defined by the vehicle or solvent control sample) and a minimum value at infinite compound concentration of k_{min} (Figure 3).

[02258] $$k_p = \frac{\left(k_{\max} - k_{\min}\right)}{1 + \frac{[I]}{I_{mid}}} + k_{\min} \qquad \text{(A.7)}$$

where I_{mid} is the concentration of compound yielding a value of k_p that is midway between the values of k_{max} and k_{min} (note that the value of I_{mid} is not the same as the IC_{50}, except in the case of a complete and purely cytostatic compound). Thus, fitting the replot data to equation A.7 provides estimates of k_{max}, k_{min} and I_{mid}. If a compound is cytostatic (as defined here), the value of k_{min} cannot be less than zero. For cytotoxic compounds, k_{min} will be less than zero and the absolute value of k_{min} will relate directly to the effectiveness of the compound in killing cells.

[02259] The fitted values derived from equation A.7 can also be used to determine the value of the LCC. By definition, when [I] = LCC, $k_p = 0$. Thus, under these conditions equation A.7 becomes.

[02260] $$0 = \frac{\left(k_{\max} - k_{\min}\right)}{1 + \frac{LCC}{I_{mid}}} + k_{\min} \qquad \text{(A.8)}$$

[02261] Algebraic rearrangement of equation A.8 yields an equation for the LCC.

[02262] $$LCC = I_{mid}\left[\left(\frac{k_{\max} - k_{\min}}{-k_{\min}}\right) - 1\right] \qquad \text{(A.9)}$$

[02263] This analysis is simple to implement with nonlinear curve fitting software and may be applied during cellular assays of compound activity throughout the drug discovery and development process. In this manner, the LCC may provide a valuable metric for the assessment of compound SAR (structure-activity relationship).

[02264] Table 4 below provides LCC and IC_{50} data for certain compounds of the invention on WSU-DLCL2 cells.

Table 4

Cpd#	WSU-DLCL2 11-day LCC (μM)	WSU-DLCL2 11-day IC50 (μM)
8	0.207	0.076
56	0.442	0.0097
88	1.27	0.035
101	2.59	0.25
120	0.343	0.006
121	0.0597	0.0094
222	0.0268	0.0043
261	0.556	0.051
277	0.037	0.0024
354	0.043	0.013
357	0.026	0.0095

[02265] **Example 48:** *In vivo* Assay

Mice

[02266] Female Fox Chase SCID® Mice (CB17/Icr-*Prkdcscid*/IcrIcoCrl, Charles River Laboratories) or athymic nude mice (Crl:NU(Ncr)-*Foxn1nu*, Charles River Laboratories) were 8 weeks old and had a body-weight (BW) range of 16.0–21.1 g on D1 of the study. The animals were fed *ad libitum* water (reverse osmosis 1 ppm Cl) and NIH 31 Modified and Irradiated Lab Diet® consisting of 18.0% crude protein, 5.0% crude fat, and 5.0% crude fiber. The mice were housed on irradiated Enrich-o'cobs™ bedding in static microisolators on a 12-hour light cycle at 20–22 °C (68–72 °F) and 40–60% humidity. All procedures comply with the recommendations of the *Guide for Care and Use of Laboratory Animals* with respect to restraint, husbandry, surgical procedures, feed and fluid regulation, and veterinary care.

Tumor Cell Culture

[02267] Human lymphoma cell lines line were obtained from different sources (ATCC, DSMZ) and maintained at Piedmont as suspension cultures in RPMI-1640 medium containing 100 units/mL penicillin G sodium salt, 100 g/mL streptomycin, and 25 g/mL gentamicin. The medium was supplemented with 10% fetal bovine serum and 2 mM glutamine. The cells were cultured in tissue culture flasks in a humidified incubator at 37 °C, in an atmosphere of 5% CO2 and 95% air.

***In Vivo* Tumor Implantation**

[02268] Human lymphoma cell lines were harvested during mid-log phase growth, and re-suspended in PBS with 50% Matrigel™ (BD Biosciences). Each mouse received 1 x 10^7 cells (0.2 mL cell suspension) subcutaneously in the right flank. Tumors were calipered in two dimensions to monitor growth as the mean volume approached the desired 80–120 mm^3 range. Tumor size, in mm^3, was calculated from:

$$Tumor\ volume = \frac{w^2 \times l}{2}$$

where w = width and l = length, in mm, of the tumor. Tumor weight can be estimated with the assumption that 1 mg is equivalent to 1 mm3 of tumor volume. After 10-30 days (depending on the cell line used) mice with 108–126 mm^3 tumors were sorted into eight groups with mean tumor volumes of 117–119 mm3.

Test Articles

[02269] Test compounds were stored at room temperature and protected from light. On each treatment day, a fresh compound formulations were prepared by suspending the powders in 0.5% sodium carboxymethylcellulose (NaCMC) and 0.1% Tween® 80 in deionized water. The EM10 vehicle, 0.5% NaCMC and 0.1% Tween® 80 in deionized water, Was used to treat the control groups at the same schedules. Formulations were stored away from light at 4 °C prior to administration.

Treatment Plan

[02270] Mice were treated at compound doses ranging from 1 – 1000 mg/kg and at TID (3 times a day every 8 h), BID (twice a day every 12 h) or QD (once a day) schedules for various

amount of days by oral gavage or injections via the intravenous, intraperitoneal or subcutaneous routes. Each dose was delivered in a volume of 0.2 mL/20 g mouse (10 mL/kg), and adjusted for the last recorded weight of individual animals. The maximal treatment length was 28 days.

Median Tumor Volume (MTV) and Tumor Growth Inhibition (TGI) Analysis

[02271] Treatment efficacy was determined on the last treatment day. MTV(n), the median tumor volume for the number of animals, n, evaluable on the last day, was determined for each group. Percent tumor growth inhibition (%TGI) can be defined several ways. First, the difference between the MTV(n) of the designated control group and the MTV(n) of the drug-treated group is expressed as a percentage of the MTV(n) of the control group:

$$\%TGI = \left(\frac{MTV(n)_{control} - MTV(n)_{treated}}{MTV(n)_{control}}\right) \times 100$$

[02272] Another way of calculating %TGI is taking the change of the tumor size from day 1 to day n into account with n being the last treatment day.

$$\%TGI = \left(\frac{\Delta MTV_{control} - \Delta MTV_{treated}}{\Delta MTV_{control}}\right) \times 100$$

$$\Delta MTV_{control} = MTV(n)_{control} - MTV(1)_{control}$$

$$\Delta MTV_{treated} = MTV(n)_{treated} - MTV(1)_{treated}$$

Tumor growth delay analysis

[02273] Alternatively, mice were kept alive after the last treatment day for tumor growth delay analysis. Tumors were callipered twice-weekly and each test animal was euthanized when its neoplasm reached the endpoint volume of 2000 mm^3 or on the pre-specified last day of the study, whichever came first. The time-to-endpoint (TTE) for each mouse was calculated from the following equation:

$$TTE\ (days) = \frac{log_{10}(endpoint\ volume, mm^3) - b}{m}$$

where b is the intercept and m is the slope of the line obtained by linear regression of a log-transformed tumor growth data set. The data sets were composed of the first observation that exceeded the study endpoint volume and the three consecutive observations that immediately preceded the attainment of the endpoint volume. Animals that did not reach the volume endpoint were assigned a TTE value equal to the last day of the study (prespecified). Any animal classified as a treatment-related (TR) death was to be assigned a TTE value equal to the day of death. Any animal classified as a nontreatment- related (NTR) death was excluded from TTE calculations and all further analyses.

[02274] Treatment outcome was determined from tumor growth delay (TGD), defined as the increase in the median TTE in a treatment group compared to the control group:

$$TGD = T - C$$

expressed in days, or as a percentage of the median TTE of the control group:

$$\%TGD = \frac{T - C}{C} \times 100$$

where:

T = median TTE for a treatment group

C = median TTE for the control group

Toxicity

[02275] Animals were weighed daily on Days 1–5, and then twice weekly until the completion of the study. The mice were examined frequently for overt signs of any adverse, treatment related side effects, which were documented. Acceptable toxicity for the maximum tolerated dose (MTD) was defined as a group mean BW loss of less than 20% during the test, and not more than 10% mortality due to TR deaths. A death was to be classified as TR if it was attributable to treatment side effects as evidenced by clinical signs and/or necropsy, or due to unknown causes during the dosing period. A death was to be classified as NTR if there was evidence that the death was unrelated to treatment side effects. NTR deaths during the dosing interval would typically be categorized as NTRa (due to an accident or human error) or NTRm (due to necropsy-confirmed tumor dissemination by invasion and/or metastasis). Orally treated animals that die from unknown causes during the dosing period may be classified as NTRu

when group performance does not support a TR classification and necropsy, to rule out a dosing error, is not feasible.

Sampling

[02276] On several days during the study mice were sampled in a pre-specified fashion. Sampling included non-terminal bleeds (0.25 mL) from the mandibular vein without anesthesia and full volume blood collection via terminal cardiac puncture under CO_2 anesthesia. Blood samples were processed for plasma, with K2-EDTA as anti-coagulant. The plasma samples were frozen at –80 °C and stored prior to bioanalysis of compound levels.

[02277] Tumors were harvested from specified mice under RNAse free conditions and bisected. A 2 mm thick slice from one half of each tumor was formalin-fixed for 24 h and transferred to 70% ethanol. The fixed tumor tissues were paraffin embedded. The remaining tumor tissue from each animal was snap frozen in liquid N_2 and pulverized with a mortar and pestle.

[02278] Specified mice were sampled for the surrogate tissues including spleen, skin, bone marrow, and whiskers. Each tissue was isolated and fixed and/or snap frozen.

Statistical and Graphical Analyses

[02279] All statistical and graphical analyses were performed with Prism 3.03 (GraphPad) for

[02280] Windows. Several analyses methods were applied. Median D29 tumor volumes were compared with the Kruskal-Wallis test, and a post hoc Dunn's multiple comparison test. These tests were performed three times.

[02281] The two-tailed statistical analyses were conducted at $P = 0.05$. Prism reports results as non-significant (ns) at $P > 0.05$, significant (symbolized by "*") at $0.01 < P < 0.05$, very significant ("**") at $0.001 < P < 0.01$ and extremely significant ("***") at $P < 0.001$.

[02282] To test statistical significance between the control and treated groups over the whole treatment time course, either a repeated measures ANOVA test followed by Dunnets multiple comparison post test or a 2 way ANOVA test was employed.

[02283] For graphical representations s "box and whiskers" diagram was constructed to show the distribution of individual tumor volumes for each group. The box represents the 25th to

75th percentile of observations, the horizontal line corresponds to the median value, and the "whiskers" indicate the maximum and minimum values. Median or mean (± SEM) tumor volumes were graphed on a semilog or linear plot as functions of time. Group mean BW changes during the study were plotted as percent change, ± SEM, from D1.

[02284] A scatter plot was constructed to show TTE values, by group. The TTE plot includes NTR deaths, which are excluded from all other graphical analyses. When an animal exited the study because of tumor size, the final tumor volume recorded for the animal was included with the data used to calculate the median volume at subsequent time points. The percentage of animals in each group remaining in the study versus time was presented in a Kaplan-Meier survival plot.

Histone Extraction

[02285] For isolation of histones, 60-90 mg tumor tissue was homogenized in 1.5 ml nuclear extraction buffer (10 mM Tris-HCl, 10 mM MgCl2, 25 mM KCl, 1% Triton X-100, 8.6% Sucrose, plus a Roche protease inhibitor tablet 1836145) and incubated on ice for 5 minutes. Nuclei were collected by centrifugation at 600 g for 5 minutes at 4° C and washed once in PBS. Supernatant was removed and histones extracted for one hour, with vortexing every 15 minutes, with 0.4 N cold sulfuric acid. Extracts were clarified by centrifugation at 10000 g for 10 minutes at 4°C and transferred to a fresh microcentrifuge tube containing 10x volume of ice cold acetone. Histones were precipitated at -20° C for 2 hours-overnight, pelleted by centrifugation at 10000 g for 10 minutes and resuspended in water.

Western Blot Analysis

[02286] Protein concentrations for acid extracted histones were determined by BCA assay (Pierce). 400-800 ng of each lysate was fractionated on 10-20% Tris-Glycine gel (Biorad), transferred using iBlot (7 minutes on program 3, using Nitrocellulose transfer stacks), and probed with the following antibodies in Odyssey blocking buffer: rabbit anti-H3K27me3 (CST 9733; 1:20000 dilution) and mouse anti-Total H3 (CST 3638; 1:20000 dilution). Following primary Ab incubation, membranes were probed with IRDye 800CW Donkey-anti-mouse IgG (LiCOR #926-32212) and Alexa Fluor 680 goat-anti-rabbit IgG (Invitrogen #A-21076) secondary Ab and imaged using the LiCOR Odyssey system.

ELISA

[02287] Histones were prepared in equivalent concentrations in coating buffer (PBS+0.05%BSA) yielding 0.5 ng/ul of sample, and 100 ul of sample or standard was added in duplicate to 2 96-well ELISA plates (Thermo Labsystems, Immulon 4HBX #3885). The plates were sealed and incubated overnight at 4°C. The following day, plates were washed 3x with 300 ul/well PBST (PBS+0.05% Tween 20; 10X PBST, KPL #51-14-02) on a Bio Tek plate washer. Plates were blocked with 300 ul/well of diluent (PBS+2%BSA+0.05% Tween 20), incubated at RT for 2 hours, and washed 3x with PBST. All antibodies were diluted in diluent. 100 ul/well of anti-H3K27me3 (CST #9733, 50% glycerol stock 1:1,000) or anti-total H3 (Abcam ab1791, 50% glycerol 1:10,000) was added to each plate. Plates were incubated for 90 min at RT and washed 3x with PBST. 100 ul/well of anti-Rb-IgG-HRP (Cell Signaling Technology, 7074) was added 1:2,000 to the H3K27Me3 plate and 1:6,000 to the H3 plate and incubated for 90 min at RT. Plates were washed 4X with PBST. For detection, 100 ul/well of TMB substrate (BioFx Laboratories, #TMBS) was added and plates incubated in the dark at RT for 5 min. Reaction was stopped with 100 ul/well 1N H_2SO_4. Absorbance at 450 nm was read on SpectaMax M5 Microplate reader.

[02288] The *in vivo* results for Compound 222 were shown in Figures 4 and 5. Figure 4 shows tumor growth of WSU-DLCL2 xenograft bearing mice treated with Compound 222 over 27 days. Tumor growth inhibition was observed at all 3 doses 100 mg/kg (b.i.d., 27 days), 200 mg/kg (b.i.d., 27 days) and 400 mg/kg (400mg/kg b.i.d. 7 days, 0 mg/kg for 7 days and 300 mg/kg b.i.d., 13 days days). Figure 5 shows global H3K27me3 methylation in WSU-DLCL2 tumors from mice treated with compound 222 or vehicle for 27 days. This figure shows a reduction in the H3K27Me3 mark for each of the dose groups.

INCORPORATION BY REFERENCE

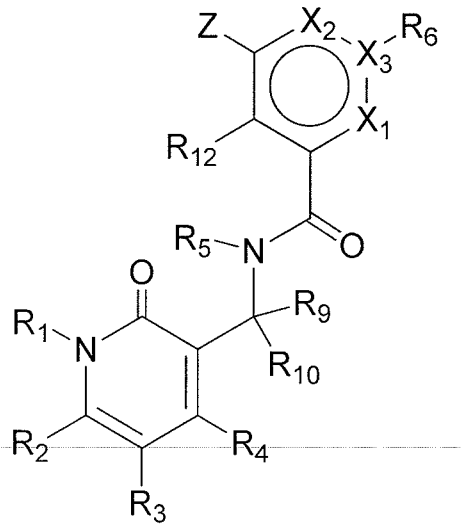
[02289] The entire disclosure of each of the patent documents and scientific articles referred to herein is incorporated by reference for all purposes.

EQUIVALENTS

[02290] The invention can be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting on the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

What is claimed is:

1. A compound of Formula (I) or a pharmaceutically acceptable salt thereof:



(I),

wherein

X_1 is N or CR_{11};

X_2 is N or CR_{13};

X_3 is N or C, and when X_3 is N, R_6 is absent;

Z is NR_7R_8, OR_7, $S(O)_aR_7$, or $CR_7R_8R_{14}$, in which a is 0, 1, or 2;

each of R_1, R_5, R_9, and R_{10}, independently, is H or C_1-C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl;

each of R_2, R_3, and R_4, independently, is $-Q_1$-T_1, in which Q_1 is a bond or C_1-C_3 alkyl linker optionally substituted with halo, cyano, hydroxyl or C_1-C_6 alkoxy, and T_1 is H, halo, hydroxyl, COOH, cyano, azido, or R_{S1}, in which R_{S1} is C_1-C_3 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxyl, C(O)O-C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl, and R_{S1} is optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, oxo, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl,

amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl;

R_6 is H, halo, cyano, azido, OR_a, $-NR_aR_b$, $-C(O)R_a$, $-C(O)OR_a$, $-C(O)NR_aR_b$, $-NR_bC(O)R_a$, $-S(O)_bR_a$, $-S(O)_bNR_aR_b$, or R_{S2}, in which R_{S2} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, or 4 to 12-membered heterocycloalkyl, b is 0, 1, or 2, each of R_a and R_b, independently is H or R_{S3}, and R_{S3} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl; or R_a and R_b, together with the N atom to which they are attached, form a 4 to 12-membered heterocycloalkyl ring having 0 or 1 additional heteroatom; and each of R_{S2}, R_{S3}, and the 4 to 12-membered heterocycloalkyl ring formed by R_a and R_b, is optionally substituted with one or more $-Q_2$-T_2, wherein Q_2 is a bond or C_1-C_3 alkyl linker each optionally substituted with halo, cyano, hydroxyl or C_1-C_6 alkoxy, and T_2 is H, halo, cyano, $-OR_c$, $-NR_cR_d$, $-C(O)R_c$, $-C(O)OR_c$, $-C(O)NR_cR_d$, $-NR_dC(O)R_c$, $-NR_dC(O)OR_c$, $-S(O)_2R_c$, $-S(O)_2NR_cR_d$, or R_{S4}, in which each of R_c and R_d, independently is H or R_{S5}, each of R_{S4} and R_{S5}, independently, is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl, or R_c and R_d, together with the N atom to which they are attached, form a 4 to 12-membered heterocycloalkyl ring having 0 or 1 additional heteroatom, and each of R_{S4}, R_{S5}, and the 4 to 12-membered heterocycloalkyl ring formed by R_c and R_d, is optionally substituted with one or more $-Q_3$-T_3, wherein Q_3 is a bond or C_1-C_3 alkyl linker each optionally substituted with halo, cyano, hydroxyl or C_1-C_6 alkoxy, and T_3 is selected from the group consisting of halo, cyano, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, 5- or 6-membered heteroaryl, OR_e, $COOR_e$, $-S(O)_2R_e$, $-NR_eR_f$, and $-C(O)NR_eR_f$, each of R_e and R_f independently being H or C_1-C_6 alkyl, or $-Q_3$-T_3 is oxo; or $-Q_2$-T_2 is oxo;

R_7 is $-Q_4$-T_4, in which Q_4 is a bond, C_1-C_4 alkyl linker, or C_2-C_4 alkenyl linker, each linker optionally substituted with halo, cyano, hydroxyl or C_1-C_6 alkoxy, and T_4 is H, halo, cyano, NR_gR_h, $-OR_g$, $-C(O)R_g$, $-C(O)OR_g$, $-C(O)NR_gR_h$, $-C(O)NR_gOR_h$, $-NR_gC(O)R_h$, $-S(O)_2R_g$, or R_{S6}, in which each of R_g and R_h, independently is H or R_{S7}, each of R_{S6} and R_{S7}, independently is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 14-membered heterocycloalkyl, or 5- or 6-membered heteroaryl, and each of R_{S6} and R_{S7} is optionally substituted with one or more $-Q_5$-T_5, wherein Q_5 is a bond, C(O), $C(O)NR_k$, $NR_kC(O)$, $S(O)_2$, or C_1-C_3 alkyl linker, R_k being H or C_1-C_6 alkyl, and T_5 is H, halo, C_1-C_6

alkyl, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, 5- or 6-membered heteroaryl, or $S(O)_qR_q$ in which q is 0, 1, or 2 and R_q is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl, and T_5 is optionally substituted with one or more substituents selected from the group consisting of halo, C_1-C_6 alkyl, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl except when T_5 is H, halo, hydroxyl, or cyano; or $-Q_5$-T_5 is oxo;

each of R_8, R_{11}, R_{12}, and R_{13}, independently, is H, halo, hydroxyl, COOH, cyano, R_{S8}, OR_{S8}, or $COOR_{S8}$, in which R_{S8} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, 4 to 12-membered heterocycloalkyl, amino, mono-C_1-C_6 alkylamino, or di-C_1-C_6 alkylamino, and R_{S8} is optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, and di-C_1-C_6 alkylamino; or R_7 and R_8, together with the N atom to which they are attached, form a 4 to 12-membered heterocycloalkyl ring having 0 to 2 additional heteroatoms, or R_7 and R_8, together with the C atom to which they are attached, form C_3-C_8 cycloalkyl or a 4 to 12-membered heterocycloalkyl ring having 1 to 3 heteroatoms, and each of the 4 to 12-membered heterocycloalkyl rings or C_3-C_8 cycloalkyl formed by R_7 and R_8 is optionally substituted with one or more $-Q_6$-T_6, wherein Q_6 is a bond, C(O), $C(O)NR_m$, $NR_mC(O)$, $S(O)_2$, or C_1-C_3 alkyl linker, R_m being H or C_1-C_6 alkyl, and T_6 is H, halo, C_1-C_6 alkyl, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, 5- or 6-membered heteroaryl, or $S(O)_pR_p$ in which p is 0, 1, or 2 and R_p is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl, and T_6 is optionally substituted with one or more substituents selected from the group consisting of halo, C_1-C_6 alkyl, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl except when T_6 is H, halo, hydroxyl, or cyano; or $-Q_6$-T_6 is oxo; and

R_{14} is absent, H, or C_1-C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl;

provided that the compound is not

N-(5-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)furan-2-carboxamide,

N,N'-(5-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-1,3-phenylene)diacetamide,

N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-pivalamidobenzamide,

3-(3,4-dihydro-2H-benzo[b][1,4]dioxepine-7-sulfonamido)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)benzamide,

N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3,5-dimethoxybenzamide,

N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3,4,5-trimethoxybenzamide,

3-allyl-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-4,5-dimethoxybenzamide,

4-(2-amino-2-oxoethoxy)-3-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-methoxybenzamide,

3-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-4-hydroxy-5-methoxybenzamide, or

3-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-methoxy-4-propoxybenzamide.

2. The compound of claim 1,

wherein

X_1 is N or CR_{11};

X_2 is N or CR_{13};

X_3 is N or C, and when X_3 is N, R_6 is absent;

Z is NR_7R_8, OR_7, $S(O)_aR_7$, or $CR_7R_8R_{14}$, in which a is 0, 1, or 2;

each of R_1, R_5, R_9, and R_{10}, independently, is H or C_1-C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, COOH,

C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl;

each of R_2, R_3, and R_4, independently, is $-Q_1$-T_1, in which Q_1 is a bond or C_1-C_3 alkyl linker optionally substituted with halo, cyano, hydroxyl or C_1-C_6 alkoxy, and T_1 is H, halo, hydroxyl, COOH, cyano, azido, or R_{S1}, in which R_{S1} is C_1-C_3 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxyl, C(O)O-C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl, and R_{S1} is optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, oxo, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl;

R_6 is H, halo, cyano, azido, $-NR_aR_b$, $-C(O)R_a$, $-C(O)OR_a$, $-C(O)NR_aR_b$, $-NR_bC(O)R_a$, $-S(O)_bR_a$, $-S(O)_bNR_aR_b$, or R_{S2}, in which R_{S2} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, or 4 to 12-membered heterocycloalkyl, b is 0, 1, or 2, each of R_a and R_b, independently is H or R_{S3}, and R_{S3} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl; or R_a and R_b, together with the N atom to which they are attached, form a 4 to 12-membered heterocycloalkyl ring having 0 or 1 additional heteroatom; and each of R_{S2}, R_{S3}, and the 4 to 12-membered heterocycloalkyl ring formed by R_a and R_b, is optionally substituted with one or more $-Q_2$-T_2, wherein Q_2 is a bond or C_1-C_3 alkyl linker each optionally substituted with halo, cyano, hydroxyl or C_1-C_6 alkoxy, and T_2 is H, halo, cyano, $-OR_c$, $-NR_cR_d$, $-C(O)R_c$, $-C(O)OR_c$, $-C(O)NR_cR_d$, $-NR_dC(O)R_c$, $-NR_dC(O)OR_c$, $-S(O)_2R_c$, $-S(O)_2NR_cR_d$, or R_{S4}, in which each of R_c and R_d, independently is H or R_{S5}, each of R_{S4} and R_{S5}, independently, is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl, or R_c and R_d, together with the N atom to which they are attached, form a 4 to 12-membered heterocycloalkyl ring having 0 or 1 additional heteroatom, and each of R_{S4}, R_{S5}, and the 4 to 12-membered heterocycloalkyl ring formed by R_c and R_d, is optionally substituted with one or more $-Q_3$-T_3, wherein Q_3 is a bond or C_1-C_3 alkyl linker each optionally substituted with halo, cyano, hydroxyl or C_1-C_6 alkoxy, and T_3 is selected from the group consisting of halo, cyano, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, 5- or 6-

membered heteroaryl, OR_e, $COOR_e$, $-S(O)_2R_e$, $-NR_eR_f$, and $-C(O)NR_eR_f$, each of R_e and R_f independently being H or C_1-C_6 alkyl, or $-Q_3$-T_3 is oxo; or $-Q_2$-T_2 is oxo;

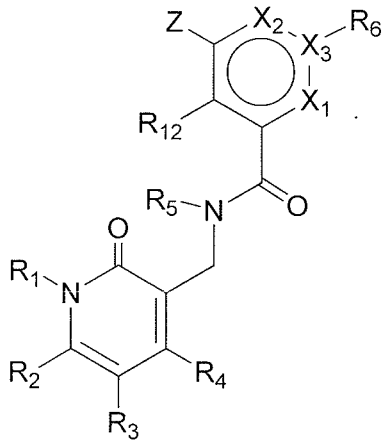
R_7 is $-Q_4$-T_4, in which Q_4 is a bond, C_1-C_4 alkyl linker, or C_2-C_4 alkenyl linker, each linker optionally substituted with halo, cyano, hydroxyl or C_1-C_6 alkoxy, and T_4 is H, halo, cyano, NR_gR_h, $-OR_g$, $-C(O)R_g$, $-C(O)OR_g$, $-C(O)NR_gR_h$, $-C(O)NR_gOR_h$, $-NR_gC(O)R_h$, $-S(O)_2R_g$, or R_{S6}, in which each of R_g and R_h, independently is H or R_{S7}, each of R_{S6} and R_{S7}, independently is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 14-membered heterocycloalkyl, or 5- or 6-membered heteroaryl, and each of R_{S6} and R_{S7} is optionally substituted with one or more $-Q_5$-T_5, wherein Q_5 is a bond, C(O), $C(O)NR_k$, $NR_kC(O)$, $S(O)_2$, or C_1-C_3 alkyl linker, R_k being H or C_1-C_6 alkyl, and T_5 is H, halo, C_1-C_6 alkyl, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, 5- or 6-membered heteroaryl, or $S(O)_qR_q$ in which q is 0, 1, or 2 and R_q is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl, and T_5 is optionally substituted with one or more substituents selected from the group consisting of halo, C_1-C_6 alkyl, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl except when T_5 is H, halo, hydroxyl, or cyano; or $-Q_5$-T_5 is oxo; provided that (i) R_7 is not $C(O)R_g$ or $-S(O)_2R_g$ when Z is NR_7R_8; (ii) R_7 is not C_1-C_6 alkyl when Z is OR_7, and (iii) R_7 is not H;

each of R_8, R_{11}, R_{12}, and R_{13}, independently, is H, halo, hydroxyl, COOH, cyano, R_{S8}, OR_{S8}, or $COOR_{S8}$, in which R_{S8} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, 4 to 12-membered heterocycloalkyl, amino, mono-C_1-C_6 alkylamino, or di-C_1-C_6 alkylamino, and R_{S8} is optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, and di-C_1-C_6 alkylamino; or R_7 and R_8, together with the N atom to which they are attached, form a 4 to 12-membered heterocycloalkyl ring having 0 to 2 additional heteroatoms, or R_7 and R_8, together with the C atom to which they are attached, form C_3-C_8 cycloalkyl or a 4 to 12-membered heterocycloalkyl ring having 1 to 3 heteroatoms, and each of the 4 to 12-membered heterocycloalkyl rings or C_3-C_8 cycloalkyl formed by R_7 and R_8 is optionally substituted with one or more $-Q_6$-T_6, wherein Q_6 is a bond, C(O), $C(O)NR_m$,

$NR_mC(O)$, $S(O)_2$, or C_1-C_3 alkyl linker, R_m being H or C_1-C_6 alkyl, and T_6 is H, halo, C_1-C_6 alkyl, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, 5- or 6-membered heteroaryl, or $S(O)_pR_p$ in which p is 0, 1, or 2 and R_p is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl, and T_6 is optionally substituted with one or more substituents selected from the group consisting of halo, C_1-C_6 alkyl, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl except when T_6 is H, halo, hydroxyl, or cyano; or $-Q_6$-T_6 is oxo; and

R_{14} is absent, H, or C_1-C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, COOH, C(O)O-C_1-C_6 alkyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl.

3. The compound of any of claims 1 and 2, wherein the compound is of Formula (Ia):



(Ia).

4. The compound of any of claims 1-3, wherein X_1 is CR_{11} and X_2 is CR_{13}.

5. The compound of any of claims 1-3, wherein X_1 is CR_{11} and X_2 is N.

6. The compound of any of claims 1-3, wherein X_1 is N and X_2 is CR_{13}.

7. The compound of any of claims 1-3, wherein X_1 is N and X_2 is N.

8. The compound of any of claims 1-7, wherein Z is NR_7R_8.

9. The compound of any of claims 1-7, wherein Z is $CR_7R_8R_{14}$.

10. The compound of any of claims 1-7, wherein Z is OR_7.

11. The compound of any of claims 1-7, wherein Z is $S(O)_aR_7$.

12. The compound of any of claims 1-11, wherein R_6 is halo, C_1-C_3 alkyl, C_2-C_6 alkenyl, C_3-C_6 cycloalkyl, C(O)H, or -C(O)R_a, in which R_a is C_1-C_6 alkyl or 4 to 12-membered heterocycloalkyl.

13. The compound of claim any of claims 1-11, wherein R_6 is 4 to 12-membered heterocycloalkyl optionally substituted with one or more $-Q_2$-T_2, in which $-Q_2$-T_2 is oxo or Q_2 is a bond and T_2 is C_1-C_6 alkyl, -OR_c, -NR_cR_d, -C(O)R_c, -C(O)OR_c, -$S(O)_2R_c$, or 4 to 12-membered heterocycloalkyl optionally substituted with one or more $-Q_3$-T_3.

14. The compound of any of claims 1-13, wherein Q_3 is a bond or C_1-C_3 alkyl linker and T_3 is selected from the group consisting of C_1-C_3 alkyl, OR_e, -$S(O)_2R_e$, or -NR_eR_f.

15. The compound of claim any of claims 1-11 and 13-14, wherein R_6 is piperidinyl, 2,2,6,6-tetramethyl-piperidinyl, 1,2,3,6-tetrahydropyridinyl, 2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridinyl, piperazinyl, morpholinyl, tetrahydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl, or pyrrolidinyl.

16. The compound of claims 1-11, wherein R_6 is F, Br, or Cl.

17. The compound of any of claims 1-16, wherein R_7 is C_1-C_6 alkyl, C_3-C_8 cycloalkyl or 4 to 14-membered heterocycloalkyl, each optionally substituted with one or more $-Q_5$-T_5.

18. The compound of any of claims 1-17, wherein R_7 is piperidinyl, tetrahydropyran, tetrahydrothiopyran, oxetanyl, azetidinyl, pyrrolidinyl, 1,4-dioxaspiro[4.5]decanyl, 1-oxaspiro[4.5]decanyl, 3'H-spiro[cyclohexane-1,1'-isobenzofuran]-3'-one-4-yl, 7'H-spiro[cyclohexane-1,5'-furo[3,4-b]pyridin]-7'-one-4-yl, 3'H-spiro[cyclohexane-1,1'-furo[3,4-c]pyridin]-3'-one-4-yl, 1-azaspiro[4.5]decan-2-one-8-yl, cyclobutyl, cyclopentyl, or cyclohexyl, each optionally substituted with one $-Q_5$-T_5.

19. The compound of any of claims 1-18, wherein T_5 is H, halo, C_1-C_6 alkyl, C_1-C_6 alkoxyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, or 4 to 12-membered heterocycloalkyl.

20. The compound of any of claims 1-18, wherein Q_5 is a bond and T_5 is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, or 4 to 12-membered heterocycloalkyl.

21. The compound of any of claims 1-18, wherein Q_5 is CO, $S(O)_2$, or NHC(O); and T_5 is C_1-C_6 alkyl, C_1-C_6 alkoxyl, C_3-C_8 cycloalkyl, or 4 to 12-membered heterocycloalkyl.

22. The compound of any of claims 1-18, wherein Q_5 is C_1-C_3 alkyl linker and T_5 is H or C_6-C_{10} aryl.

23. The compound of any of claims 1-18, wherein Q_5 is C_1-C_3 alkyl linker and T_5 is C_3-C_8 cycloalkyl, 4 to 12-membered heterocycloalkyl, or $S(O)_qR_q$.

24. The compound of any of claims 1-23, wherein R_{11} is H.

25. The compound of any of claims 1-17 and 24, wherein R_7 is tetrahydrothiopyran, cyclopentyl or cyclohexyl, each optionally substituted with one or more $-Q_5$-T_5.

26. The compound of any of claims 1-17 and 24-25, wherein Q_5 is NHC(O) and T_5 is C_1-C_6 alkyl or C_1-C_6 alkoxy.

27. The compound of any of claims 1-17 and 24-25, wherein one or more $-Q_5$-T_5 are oxo.

28. The compound of any of claims 1-17 and 24, wherein R_7 is isopropyl.

29. The compound of any of claims 1-28, wherein each of R_2 and R_4, independently is C_1-C_3 alkyl optionally substituted withC_1-C_6 alkoxyl.

30. The compound of any of claims 1-29, wherein each of R_2 and R_4 is methyl.

31. The compound of any of claims 1-30, wherein R_1 is H.

32. The compound of any of claims 1-31, wherein R_{12} is H, methyl, ethyl, ethenyl, or halo.

33. The compound of any of claims 1-32, wherein R_{12} is methyl.

34. The compound of any of claims 1-32, wherein R_{12} is ethyl.

35. The compound of any of claims 1-32, wherein R_{12} is ethenyl.

36. The compound of any of claims 1-35, wherein R_8 is H, methyl, or ethyl.

37. The compound of any of claims 1-36, wherein R_8 is methyl.

38. The compound of any of claims 1-36, wherein R_8 is ethyl.

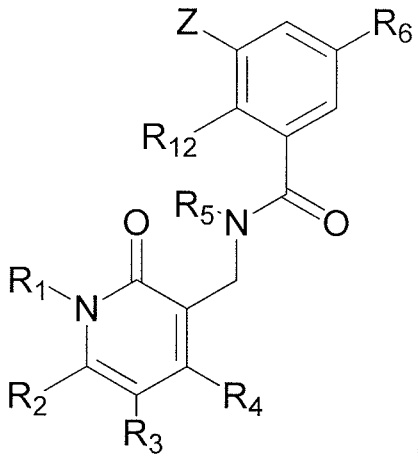
39. The compound of any of claims 1-9, 12-16, 24, and 29-35, wherein Z is NR_7R_8 or $CR_7R_8R_{14}$ wherein R_7 and R_8, together with the atom to which they are attached, form a ring selected from the group consisting of piperidinyl, morpholinyl, piperazinyl, azetidinyl, pyrrolidinyl, 2-oxa-5-azabicyclo[2.2.1]heptan-5-yl, 1,4-dioxa-8-azaspiro[4.5]decanyl, and cyclohexenyl, each optionally substituted with one $-Q_6$-T_6.

40. The compound of any of claims 1-39, wherein R_{13} is H or methyl.

41. The compound of any of claims 1-39, wherein R_{13} is H.

42. The compound of any of claims 1-40, wherein R_3 is H.

43. The compound of any of claim 1 or 2, wherein the compound is of Formula (Ie):



(Ie),

wherein

Z is NR_7R_8, OR_7, or $S(O)_aR_7$;

R_1 is H or C_1-C_6 alkyl optionally substituted with one or more substituents selected from hydroxyl, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, and C_6-C_{10} aryl;

each of R_2 and R_4 independently, is $-Q_1$-T_1 , in which Q_1 is a bond or C_1-C_3 alkyl linker optionally substituted with one or more substituents selected from halo and hydroxyl, and T_1 is H, halo, or azido;

R_3 is H or halo;

R_5 is H or C_1-C_6 alkyl;

R_6 is H, halo, cyano, azido, OR_a, $-NR_aR_b$, $-C(O)NR_aR_b$, $-S(O)_bR_a$, or R_{S2}; wherein R_{S2} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or 4 to 12-membered heterocycloalkyl, and wherein each of R_a and R_b, independently is H, C_1-C_6 alkyl, or 4 to 12-membered heterocycloalkyl,; or R_a and R_b, together with the N atom to which they are attached, form a 4 to 12-membered heterocycloalkyl ring having 0 or 1 additional heteroatom; and each of R_a, R_{S2} and the 4 to 12-membered heterocycloalkyl ring formed by R_a and R_b, is optionally substituted with one or more $-Q_2$-T_2; wherein Q_2 is a bond or C_1-C_3 alkyl linker, and T_2 is H, halo, $-OR_c$, $-NR_cR_d$, $-C(O)OR_c$, or C_1-C_6 alkyl, in which each of R_c and R_d, independently is H or C_1-C_6 alkyl, or R_c and R_d, together with the N atom to which they are attached, form a 4 to 12-membered heterocycloalkyl ring having 0 or 1 additional heteroatom and optionally substituted with C_1-C_6 alkyl;

R_7 is $-Q_4$-T_4, in which Q_4 is a bond or C_1-C_4 alkyl linker and T_4 is H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, C(O)-$C_{1\text{-}6}$ alkyl, C(O)-$C_{3\text{-}6}$ cycloalkyl, or 4 to 14-membered heterocycloalkyl, each optionally substituted with one or more $-Q_5$-T_5;

R_8 is H, C_1-C_6 alkyl optionally substituted with halo, hydroxyl or C_1-C_6 alkoxyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, or 4 to 7-membered heterocycloalkyl; or R_7 and R_8, together with the N atom to which they are attached, form a 4 to 12-membered heterocycloalkyl ring having 0 to 2 additional heteroatoms, and the 4 to 12-membered heterocycloalkyl ring formed by R_7 and R_8 is optionally substituted with one or more $-Q_6$-T_6; and

R_{12} is halo, C_1-C_6 alkoxyl, or C_1-C_6 alkyl optionally substituted with halo or C_2-C_6 alkenyl.

44. The compound of any of claims 1-3 and 43, wherein

R_1 is H or C_1-C_6 alkyl optionally substituted one or more times with a substituent selected from hydroxyl, C_1-C_6 alkoxyl and C_6-C_{10} aryl;

R_7 is $-Q_4$-T_4, in which Q_4 is a bond or a C_1-C_4 alkyl linker, and T_4 is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, C(O)- C_1-C_6 alkyl, C(O)- C_3-C_6 cycloalkyl, dihydropyranyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperidinyl, pyrrolidinyl, azetidinyl and oxetanyl, each optionally substituted with one or more substituents independently selected from oxo and $-Q_5$-T_5;

R_8 is H or C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl or C_3-C_8 cycloalkyl; and

R_{12} is halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl or C_1-C_6 alkoxyl.

45. The compound of any of claims 1-3, 43, and 44, wherein

Z is NR_7R_8 or SR_7;

R_6 is H, halo, cyano, OR_a, $-C(O)NR_aR_b$, $-S(O)_2R_a$, or R_{S2}; wherein R_{S2} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or 4 to 12-membered heterocycloalkyl, and wherein each of R_a and R_b, independently is H or C_1-C_6 alkyl; or R_a and R_b, together with the N atom to which they are attached, form a 4 to 12-membered heterocycloalkyl ring having 0 or 1 additional heteroatom; and each of R_{S2} and the 4 to 12-membered heterocycloalkyl ring formed by R_a and R_b, is optionally substituted with one or more $-Q_2$-T_2; wherein Q_2 is a bond or C_1-C_3 alkyl linker, and T_2 is H, halo, $-OR_c$, $-NR_cR_d$, $-C(O)OC_1$-C_6 alkyl, or C_1-C_6 alkyl, in which each of R_c and R_d, independently is H or C_1-C_6 alkyl, or R_c and R_d, together with the N atom to which they are attached, form a 4 to 12-membered heterocycloalkyl ring having 0 or 1 additional heteroatom and 0 or 1 C_1-C_6 alkyl substituents;

R_7 is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, dihydropyranyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperidinyl, pyrrolidinyl, azetidinyl and oxetanyl, each optionally substituted with one or more substituents independently selected from oxo and $-Q_5$-T_5; and

R_{12} is halo or C_1-C_6 alkyl.

46. The compound of any of claims 1-3, and 43-45, wherein R_2, R_4 and R_{12} are each independently C_1-C_6 alkyl and R_5 is H.

47. The compound of any of claims 1-3 and 43, wherein R_7 is cyclohexyl, dihydropyranyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperidinyl, pyrrolidinyl, azetidinyl oxetanyl, 1,4-dioxaspiro[4.5]decan-8-yl, 1-oxaspiro[4.5]decan-8-yl, 3'H-spiro[cyclohexane-1,1'-isobenzofuran]-4-yl, 7'H-spiro[cyclohexane-1,5'-furo[3,4-b]pyridin]-4-yl, 3'H-spiro[cyclohexane-1,1'-furo[3,4-c]pyridin]-4-yl, or 1-azaspiro[4.5]decan-8-yl, each substituted with one or more $-Q_5$-T_5.

48. The compound of any of claims 1-3 and 43-47, wherein Z is selected from the group consisting of piperidinyl, morpholinyl, piperazinyl, azetidinyl, pyrrolidinyl, 2-oxa-5-azabicyclo[2.2.1]heptan-5-yl, 1,4-dioxa-8-azaspiro[4.5]decan-8-yl, and cyclohexenyl, each optionally substituted with one $-Q_6$-T_6.

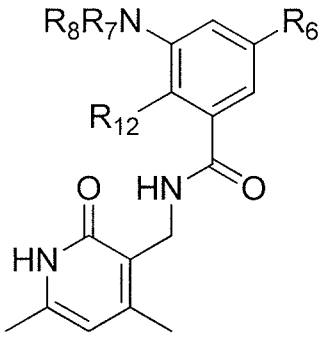
49. The compound of any of claims 1-3 and 43-48, wherein R_6 is halo and Z is $S(O)_aR_7$, in which a is 0, 1, or 2 and R_7 is C_1-C_6 alkyl, C_3-C_8 cycloalkyl or 4 to 7-membered heterocycloalkyl and R_7 is optionally substituted with one or more $-Q_5$-T_5.

50. The compound of any of claims 1-3 and 43-48, wherein R_6 is halo and Z is OR_7, in which R_7 is 4 to 7-membered heterocycloalkyl optionally substituted with one or more $-Q_5$-T_5.

51. The compound of any of claims 1-3 and 43-48, wherein R_6 is $-S(O)_bR_a$ or azido, in which b is 0, 1, or 2 and R_a is C_1-C_6 alkyl or C_3-C_8 cycloalkyl; and Z is NR_7R_8, in which R_7 is C_3-C_8 cycloalkyl or 4 to 14-membered heterocycloalkyl, each optionally substituted with one or more $-Q_5$-T_5; and R_8 is H or C_1-C_6 alkyl.

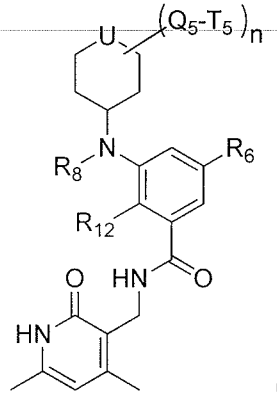
52. The compound of any of claims 1-3 and 43-48, wherein R_6 is halo and Z is NR_7R_8 or $CR_7R_8R_{14}$ wherein R_7 and R_8, together with the atom to which they are attached, form a 4 to 11-membered heterocycloalkyl ring having 1 to 3 heteroatoms or C_3-C_8 cycloalkyl, each optionally substituted with one or more $-Q_6$-T_6.

53. The compound of any of claims 1-3 and 43-47, wherein the compound is of Formula (II):



(II).

54. The compound of any of claims 1-3, 43-47, and 53, wherein the compound is of Formula (IIA):



(IIA),

wherein n is 0, 1, or 2; U is O, S, N-Q_5-T_5, or CH-Q_5-T_5; and R_{12} is Cl, Br, or methyl.

55. The compound of any of claims 43-54, wherein Q_5 is a bond and T_5 is H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, 4 to 12-membered heterocycloalkyl, 5- or 6-membered heteroaryl, amino, mono-C_1-C_6 alkylamino, or di-C_1-C_6 alkylamino, T_5 being optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, C_1-C_6 alkoxyl, or C_3-C_8 cycloalkyl.

56. The compound of any of claims 43-54, wherein Q_5 is CO, $S(O)_2$, or NHC(O); and T_5 is C_1-C_6 alkyl, C_1-C_6 alkoxyl, C_3-C_8 cycloalkyl, or 4 to 12-membered heterocycloalkyl.

57. The compound of any of claims 43-54, wherein Q_5 is C_1-C_3 alkyl linker and T_5 is H or C_6-C_{10} aryl.

58. The compound of any of claims 43-54, wherein Q_5 is C_1-C_3 alkyl linker and T_5 is C_3-C_8 cycloalkyl, 4 to 12-membered heterocycloalkyl, or $S(O)_qR_q$.

59. The compound of any of claims 43-54, wherein Q_5 is NHC(O) and T_5 is C_1-C_6 alkyl or C_1-C_6 alkoxy.

60. The compound of any of claims 43-54, wherein one or more $-Q_5$-T_5 are oxo.

61. The compound of claim 54, wherein U is CH-Q_5-T_5 and n is 0

62. The compound of any of claims 1-61, wherein one or more $-Q_6$-T_6 are oxo.

63. The compound of any of claims 1-61, wherein Q_6 is a bond or C(O) and T_6 is C_1-C_6 alkyl or C_1-C_6 alkoxy.

64. The compound of claim 1, wherein the compound is selected from those in Table 1.

65. The compound of claim 1 being 5-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-(((1r,4r)-4-(dimethylamino)cyclohexyl)(ethyl)amino)-2-methylbenzamide or a pharmaceutically acceptable salt thereof.

66. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any of claims 1-65, N-(5-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)furan-2-carboxamide, N,N'-(5-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-1,3-phenylene)diacetamide, N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-pivalamidobenzamide, 3-(3,4-dihydro-2H-benzo[b][1,4]dioxepine-7-sulfonamido)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)benzamide, N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3,5-dimethoxybenzamide, N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3,4,5-trimethoxybenzamide, 3-allyl-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-4,5-

dimethoxybenzamide, 4-(2-amino-2-oxoethoxy)-3-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-methoxybenzamide, 3-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-4-hydroxy-5-methoxybenzamide, or 3-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-methoxy-4-propoxybenzamide, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

67. A method of treating cancer comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any of claims 1-65, N-(5-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-2-methylphenyl)furan-2-carboxamide, N,N'-(5-(((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-1,3-phenylene)diacetamide, N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-pivalamidobenzamide, 3-(3,4-dihydro-2H-benzo[b][1,4]dioxepine-7-sulfonamido)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)benzamide, N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3,5-dimethoxybenzamide, N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3,4,5-trimethoxybenzamide, 3-allyl-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-4,5-dimethoxybenzamide, 4-(2-amino-2-oxoethoxy)-3-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-methoxybenzamide, 3-chloro-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-4-hydroxy-5-methoxybenzamide, or 3-bromo-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-methoxy-4-propoxybenzamide, or a pharmaceutically acceptable salt thereof.

68. A compound of any of claims 1-65 for use in the treatment or prevention of cancer.

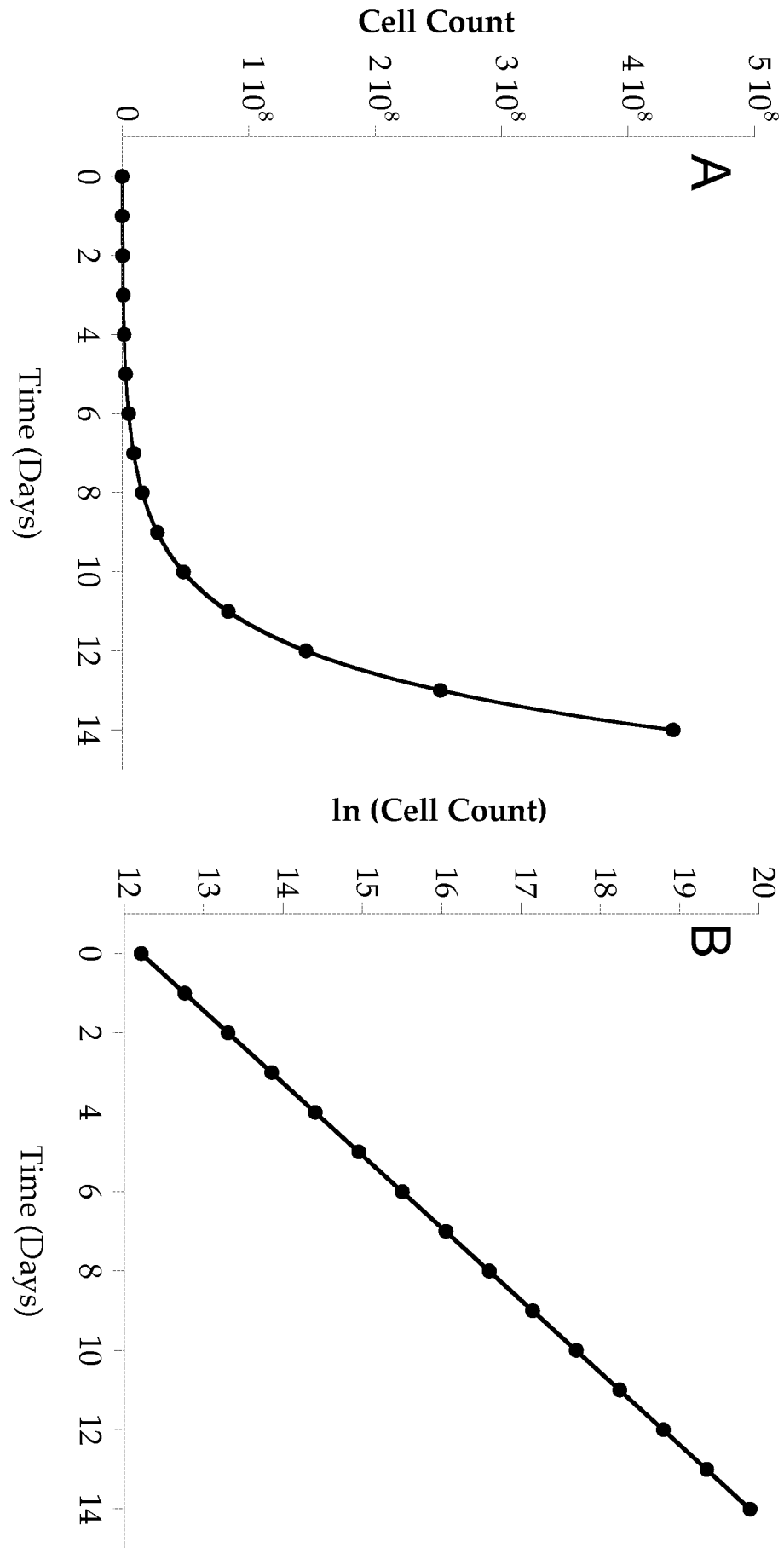

A
Cell Count
0
1 10^8
2 10^8
3 10^8
4 10^8
5 10^8
0 2 4 6 8 10 12 14
Time (Days)
B
ln (Cell Count)
12 13 14 15 16 17 18 19 20
0 2 4 6 8 10 12 14
Time (Days)

Figure 1

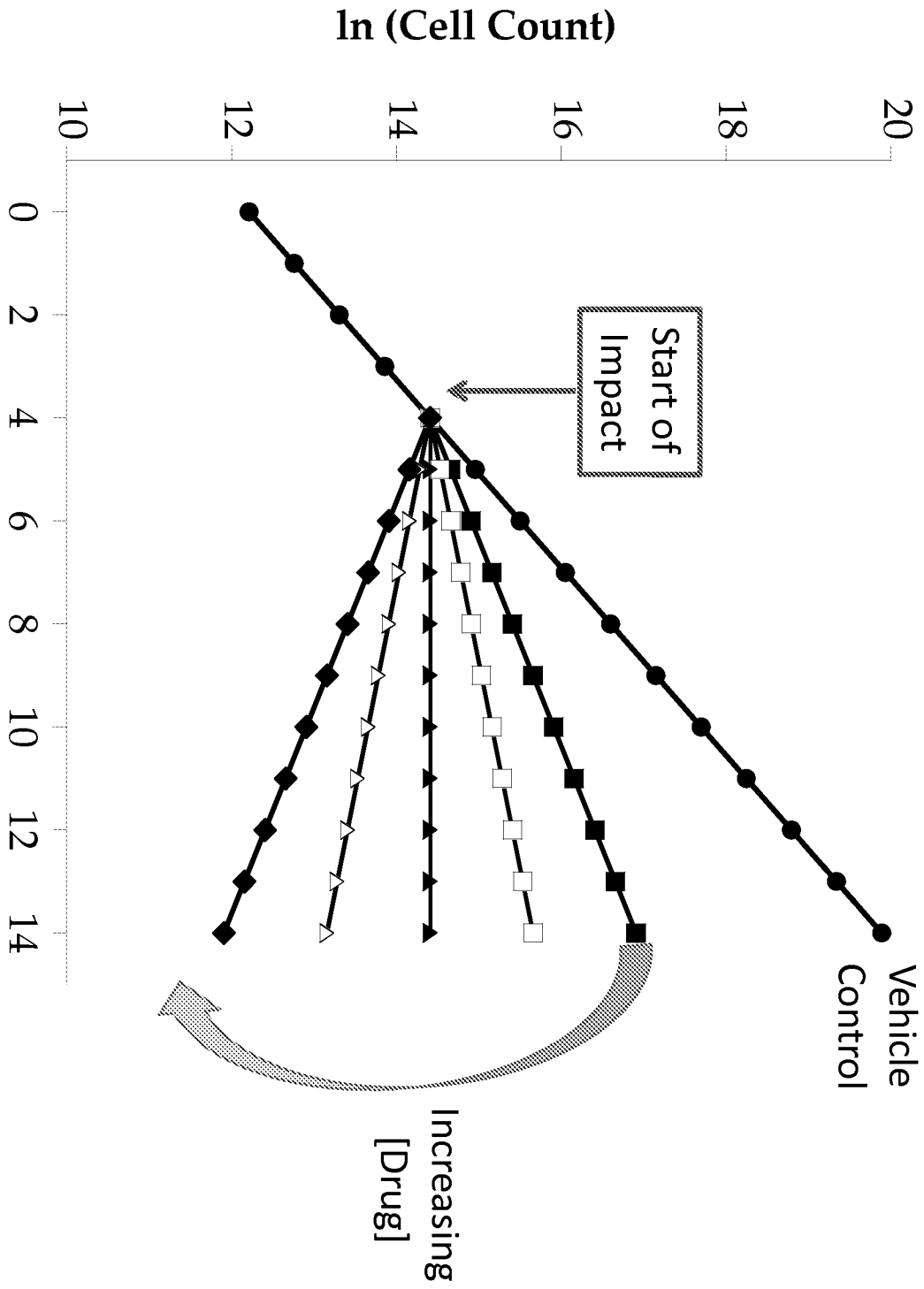

ln (Cell Count)
10
12
14
16
18
20
0
2
4
6
8
10
12
14
Time (Days)
Start of Impact
Vehicle Control
Increasing [Drug]

Figure 2

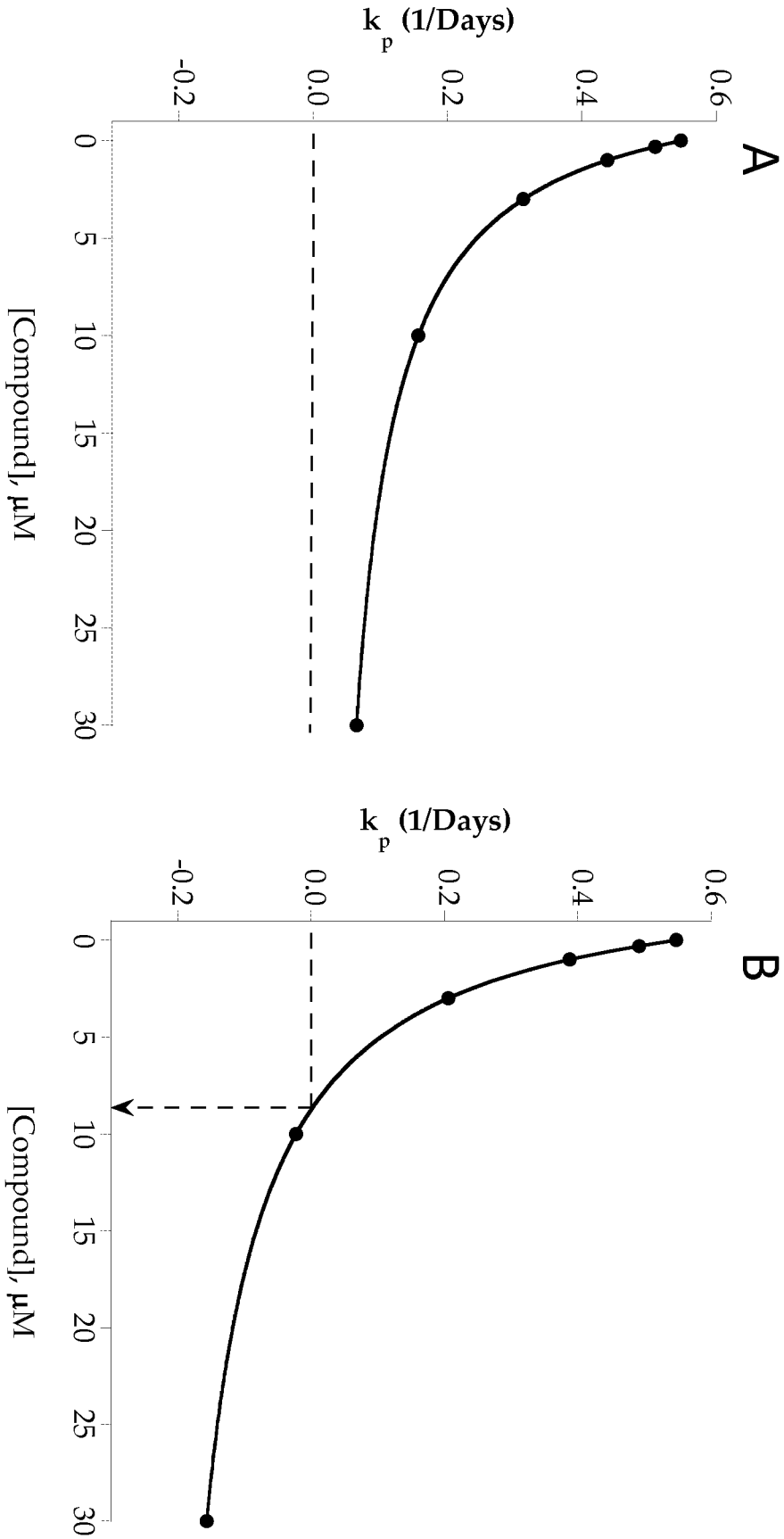

A
k_p (1/Days)
-0.2
0.0
0.2
0.4
0.6
0
5
10
15
20
25
30
[Compound], μM
B
k_p (1/Days)
-0.2
0.0
0.2
0.4
0.6
0
5
10
15
20
25
30
[Compound], μM

Figure 3

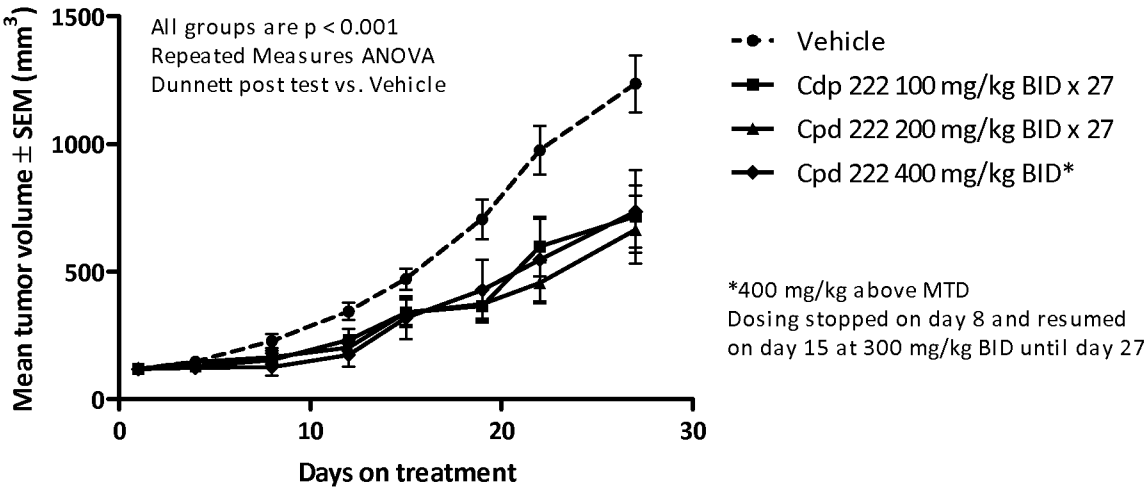


Figure 4

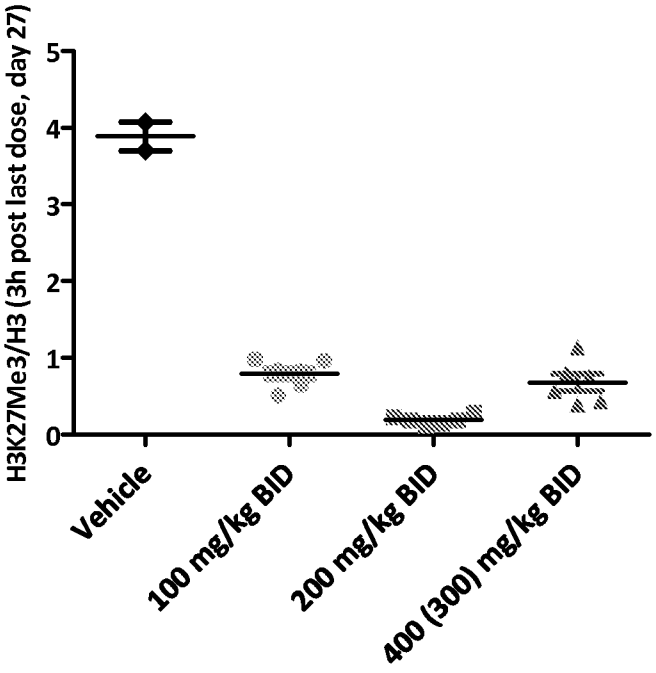


Figure 5

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/033662

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D213/64 C07D401/12 C07D401/14 C07D407/12 C07D409/12
C07D413/12 C07D413/14 C07D491/10 C07D491/113 A61K31/4427
A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 12 April 2011 (2011-04-12), XP002678594, retrieved from STN CAS Registry Numbers: 1278854-92-4, 1278854-91-3 -----	1-52, 55-60, 62,63
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 10 April 2011 (2011-04-10), XP002678595, retrieved from STN CAS Registry Numbers: 1278089-60-3, 1277914-52-9, 1277529-83-5 ----- -/--	1-52, 55-60, 62,63

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 June 2012	13/07/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Bissmire, Stewart

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 11 March 2009 (2009-03-11), XP002678596, retrieved from STN CAS Registry Numbers: 1118856-92-0, 1118847-80-5, 1118847-59-8, 1118826-65-5, 1118826-02-0, 1118825-96-9, 1118825-75-4, 1118825-72-1, 1118825-69-6 -----	1-52, 55-60, 62,63
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 25 February 2009 (2009-02-25), XP002678597, retrieved from STN CAS Registry Numbers: 1111568-29-6, 1111508-57-6, 1111473-93-8 -----	1-52, 55-60, 62,63
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 4 July 2007 (2007-07-04), XP002678598, retrieved from STN CAS Registry Numbers: 941139-86-2, 941091-93-6 -----	1-52, 55-60, 62,63
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 28 February 2007 (2007-02-28), XP002678599, retrieved from STN CAS Registry Numbers: 923774-47-4, 923730-10-3, 923690-12-4 -----	1-52, 55-60, 62,63
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 26 February 2007 (2007-02-26), XP002678600, retrieved from STN CAS Registry Numbers: 923162-97-4, 923152-74-3, 923111-85-7 -----	1-52, 55-60, 62,63
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 8 February 2007 (2007-02-08), XP002678601, retrieved from STN CAS Registry Numbers: 919939-47-2, 919873-05-5 -----	1-52, 55-60, 62,63
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/033662

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2007/136592 A2 (AMPHORA DISCOVERY CORP [US]; DICKSON JOHN K [US]; CHEN KE [US]; HODGE) 29 November 2007 (2007-11-29) the whole document	1-68
A	EP 1 357 111 A1 (SHIONOGI & CO [JP]) 29 October 2003 (2003-10-29) the whole document	1-68
A	US 2010/035912 A1 (DEBNATH ASIM KUMAR [US] ET AL) 11 February 2010 (2010-02-11) the whole document	1-68
A	WO 2008/113006 A1 (XENON PHARMACEUTICALS INC [CA]; CHAKKA NAGASREE [CA]; FRASER ROBERT [C) 18 September 2008 (2008-09-18) the whole document	1-68

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2012/033662

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007136592 A2	29-11-2007	CA 2652634 A1	29-11-2007
		EP 2040711 A2	01-04-2009
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		WO 2007136592 A2	29-11-2007
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		DK 1357111 T3	02-11-2009
		EP 1357111 A1	29-10-2003
		ES 2330719 T3	15-12-2009
		JP 4137636 B2	20-08-2008
		JP 2008169217 A	24-07-2008
		KR 20060033816 A	19-04-2006
		PT 1357111 E	20-10-2009
		TW I287004 B	21-09-2007
		US 2004082619 A1	29-04-2004
		US 2006052411 A1	09-03-2006
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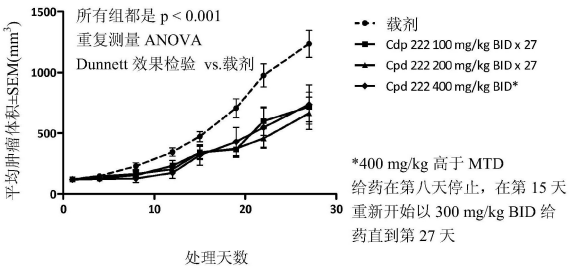
(54)发明名称

取代苯化合物

(57)摘要

本发明涉及取代苯化合物。本发明也涉及包含这些化合物的药物组合物和通过向有需要的受试者给药以包含这些化合物的药物组合物治疗癌症的方法。本发明也涉及这样的化合物用于研究或其它非治疗目的的用途。



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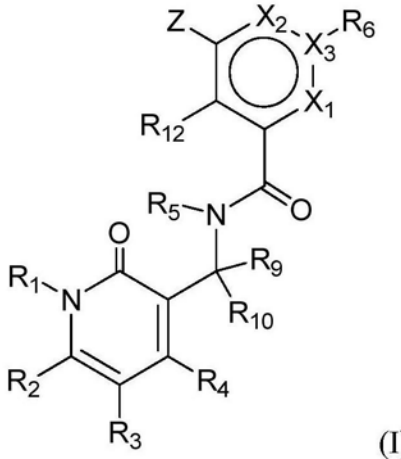
1. 式 (I) 化合物或其药学上可接受的盐：



(I)，

其中

X_1 是 N 或 CR_{11}；

X_2 是 N 或 CR_{13}；

X_3 是 N 或 C，且当 X_3 是 N 时，R_6 不存在；

Z 是 NR_7R_8、OR_7、$S(O)_aR_7$ 或 $CR_7R_8R_{14}$，其中 a 为 0、1 或 2；

R_1、R_5、R_9 和 R_{10} 各自独立为 H 或任选地被选自下列组的一个或多个取代基取代的 C_1-C_6 烷基：卤素、羟基、羧基、$C(O)O$-C_1-C_6 烷基、氰基、C_1-C_6 烷氧基、氨基、单 -C_1-C_6 烷基氨基、双 -C_1-C_6 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基和五或六元杂芳基；

R_2、R_3 和 R_4 各自独立为 $-Q_1$-T_1，其中 Q_1 为键或是任选地被选自下列组的取代基取代的 C_1-C_3 烷基连接体：卤素、氰基、羟基或 C_1-C_6 烷氧基，T_1 选自氢、卤素、羟基、羧基、氰基、叠氮基或 R_{S1}，其中 R_{S1} 选自 C_1-C_3 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_1-C_6 烷氧基、$C(O)O$-C_1-C_6 烷基、C_3-C_8 环烷基、C_6-C_{10} 芳基、氨基、单 -C_1-C_6 烷基氨基、双 -C_1-C_6 烷基氨基、4-12 元杂环烷基或者五或六元杂芳基，且 R_{S1} 任选地被一个或多个选自下列组的取代基取代：卤素、羟基、氧代、羧基、$C(O)O$-C_1-C_6 烷基、氰基、C_1-C_6 烷氧基、氨基、单 -C_1-C_6 烷基氨基、双 -C_1-C_6 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基和五或六元杂环芳基；

R_6 选自氢、卤素、氰基、叠氮基、OR_a、$-NR_aR_b$、$-C(O)R_a$、$-C(O)OR_a$、$-C(O)NR_aR_b$、$-NR_bC(O)R_a$、$-S(O)_bR_a$、$-S(O)_bNR_aR_b$ 或 R_{S2}，其中 R_{S2} 选自 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_3-C_8 环烷基或 4-12 元杂环烷基；b 是 0、1 或 2；R_a 和 R_b 各自独立为氢或 R_{S3}，其中 R_{S3} 选自 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基或者五元或六元杂环芳基；或 R_a 和 R_b 连同它们所连接的氮原子一起形成含 0 或 1 个额外杂原子的 4-12 元杂环烷基环；R_{S2}、R_{S3} 以及由 R_a 和 R_b 形成的 4-12 元杂环烷基环任选地被一个或多个 $-Q_2$-T_2 取代，其中 Q_2 为键或是任选地被下列取代基取代的 C_1-C_3 烷基连接体：卤素、氰基、羟基或 C_1-C_6 烷氧基；T_2 选自氢、卤素、氰基、$-OR_c$、$-NR_cR_d$、$-C(O)R_c$、$-C(O)OR_c$、$-C(O)NR_cR_d$、$-NR_dC(O)R_c$、$-NR_dC(O)OR_c$、$-S(O)_2R_c$、$-S(O)_2NR_cR_d$ 或 R_{S4}，其中 R_c 和 R_d 各自独立选自 H 或 R_{S5}，其中 R_{S4} 和 R_{S5} 各自独立选自 C_1-C_6 烷基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基或者五元或六元杂芳基，或 R_c 和 R_d 连同它们所连接的氮原子一起形成含 0 或 1 个额外杂原子的 4-12 元杂环烷基环，R_{S4}、R_{S5} 以及由 R_c 和 R_d 形成的 4-12 元杂环烷基环任选地被一个或多个 $-Q_3$-T_3 取代，其中 Q_3 是键或是任选地被下列取代基取代的 C_1-C_3 烷基连接体：卤素、氰基、羟基或 C_1-C_6 烷氧基，

T_3 选自卤素、氰基、C_1-C_6 烷基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基、五元或六元杂芳基、OR_e、$COOR_e$、$-S(O)_2R_e$、$-NR_eR_f$ 和 $-C(O)NR_eR_f$，R_e 和 R_f 各自独立地选自氢或 C_1-C_6 烷基，或 $-Q_3$-T_3 为氧代；或 $-Q_2$-T_2 为氧代；

R_7 是 $-Q_4$-T_4，其中 Q_4 为键、C_1-C_4 烷基连接体或 C_2-C_4 烯基连接体，每个连接体任选地被下列取代基取代：卤素、氰基、羟基或 C_1-C_6 烷氧基，T_4 选自氢、卤素、氰基、NR_gR_h、$-OR_g$、$-C(O)R_g$、$-C(O)OR_g$、$-C(O)NR_gR_h$、$-C(O)NR_gOR_h$、$-NR_gC(O)R_h$、$-S(O)_2R_g$ 或 R_{S6}，其中 R_g 和 R_h 各自独立地选自氢或 R_{S7}，R_{S6} 和 R_{S7} 各自独立地选自 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-14 元杂环烷基或者五或六元杂芳基，R_{S6} 和 R_{S7} 可任选地被一个或多个 $-Q_5$-T_5 取代，其中 Q_5 是键、羰基、$C(O)NR_k$、$NR_kC(O)$、硫酰基或 C_1-C_3 烷基连接体，R_k 是氢或 C_1-C_6 烷基，T_5 选自氢、卤素、C_1-C_6 烷基、羟基、氰基、C_1-C_6 烷氧基、氨基、单 -C_1-C_6 烷基氨基、双 -C_1-C_6 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基、五或六元杂芳基或 $S(O)_qR_q$，其中 q 为 0、1 或 2，R_q 选自 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基或者五或六元杂芳基，T_5 任选地被选自下列组的一个或多个取代基取代：卤素、C_1-C_6 烷基、羟基、氰基、C_1-C_6 烷氧基、氨基、单 -C_1-C_6 烷基氨基、双 -C_1-C_6 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基和五或六元杂芳基，当 T_5 是氢、卤素、羟基或氰基时除外；或 $-Q_5$-T_5 是氧代；

R_8、R_{11}、R_{12} 和 R_{13} 均各自独立选自氢、卤素、羟基、羧基、氰基、R_{S8}、OR_{S8} 或 $COOR_{S8}$，其中 R_{S8} 选自 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_3-C_8 环烷基、4-12 元杂环烷基、氨基、单 -C_1-C_6 烷基氨基或双 -C_1-C_6 烷基氨基，R_{S8} 任选地被选自下列组的一或多个取代基取代：卤素、羟基、羧基、$C(O)O$-C_1-C_6 烷基、氰基、C_1-C_6 烷氧基、氨基、单 -C_1-C_6 烷基氨基和双 -C_1-C_6 烷基氨基；或 R_7 和 R_8 连同它们所连接的氮原子一起形成含 0-2 个额外杂原子的 4-12 杂环烷基环，或 R_7 和 R_8 连同它们所连接的碳原子一起形成 C_3-C_8 环烷基或含 1-3 个杂原子的 4-12 元杂环烷基环，所述的由 R_7 和 R_8 形成的 4-12 元杂环烷基环或 C_3-C_8 环烷基任选地被一个或多个 $-Q_6$-T_6 取代，其中 Q_6 是键、羰基、$C(O)NR_m$、$NR_mC(O)$、硫酰基或 C_1-C_3 烷基连接体，R_m 为氢或 C_1-C_6 烷基，T_6 选自氢、卤素、C_1-C_6 烷基、羟基、氰基、C_1-C_6 烷氧基、氨基、单 -C_1-C_6 烷基氨基、双 -C_1-C_6 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基、五或六元杂芳基或 $S(O)_pR_p$，其中 p 是 0、1 或 2，R_p 选自 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基或者五或六元杂芳基，T_6 任选地被选自下列组的一个或多个取代基取代：卤素、C_1-C_6 烷基、羟基、氰基、C_1-C_6 烷氧基、氨基、单 -C_1-C_6 烷基氨基、双 -C_1-C_6 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基、五或六元杂芳基，当 T_6 为氢、卤素、羟基或氰基时除外；或 $-Q_6$-T_6 为氧代；以及

R_{14} 不存在或为氢或任选地被选自下列组的一个或多个取代基取代的 C_1-C_6 烷基：卤素、羟基、羧基、$C(O)O$-C_1-C_6 烷基、氰基、C_1-C_6 烷氧基、氨基、单 -C_1-C_6 烷基氨基、双 -C_1-C_6 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基和五或六元杂芳基；

条件是，所述化合物不包括

N-(5-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）氨基甲酰）-2- 甲基苯基）呋喃 -2- 甲酰胺、

N,N'-(5-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）氨基甲酰）-1,3- 亚苯基）二乙酰胺、

N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-特戊酰基氨基苯甲酰胺、

3-(3,4-二羟基-2H-苯并[b][1,4]二氧杂环庚烯-7-磺酰胺基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)苯甲酰胺、

N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3,5-二甲氧基苯甲酰胺、

N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3,4,5-三甲氧基苯甲酰胺、

3-烯丙基-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-4,5-二甲氧基苯甲酰胺、

4-(2-氨基-2-氧代乙氧基)-3-氯-N-((4,6-二甲基-2-氧代-1,2-二羟基吡啶-3-基)甲基)-5-甲氧基苯甲酰胺、

3-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-4-羟基-5-甲氧基苯甲酰胺,或

3-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-5-甲氧基-4-丙氧基苯甲酰胺。

2. 权利要求1的化合物,其中

X_1 是N或 CR_{11} ;

X_2 是N或 CR_{13} ;

X_3 是N或C,且当 X_3 是N时, R_6 不存在 ;

Z是 NR_7R_8、OR_7、$S(O)_aR_7$ 或 $CR_7R_8R_{14}$,其中a为0、1或2 ;

R_1、R_5、R_9 和 R_{10} 各自独立为氢或是任选地被选自下列组的一个或多个取代基取代的 C_1-C_6 烷基 :卤素、羟基、羧基、$C(O)O$-C_1-C_6 烷基、氰基、C_1-C_6 烷氧基、氨基、单-C_1-C_6 烷基氨基、双-C_1-C_6 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12元杂环烷基和五或六元杂芳基 ;

R_2、R_3 和 R_4 各自独立为 -Q_1-T_1,其中 Q_1 为键或是任选地被下列取代基取代的 C_1-C_3 烷基连接体 :卤素、氰基、羟基或 C_1-C_6 烷氧基,T_1 选自氢、卤素、羟基、羧基、氰基、叠氮基或 R_{S1},其中 R_{S1} 选自 C_1-C_3 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_1-C_6 烷氧基、$C(O)O$-C_1-C_6 烷基、C_3-C_8 环烷基、C_6-C_{10} 芳基、氨基、单-C_1-C_6 烷基氨基、双-C_1-C_6 烷基氨基、4-12元杂环烷基或者五或六元杂芳基,且 R_{S1} 任选地被一个或多个选自下列组的取代基取代 :卤素、羟基、氧代、羧基、$C(O)O$-C_1-C_6 烷基、氰基、C_1-C_6 烷氧基、氨基、单-C_1-C_6 烷基氨基、双-C_1-C_6 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12元杂环烷基和五或六元杂环芳基 ;

R_6 选自氢、卤素、氰基、叠氮基、$-NR_aR_b$、$-C(O)R_a$、$-C(O)OR_a$、$-C(O)NR_aR_b$、$-NR_bC(O)R_a$、$-S(O)_bR_a$、$-S(O)_bNR_aR_b$ 或 R_{S2},其中 R_{S2} 选自 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_3-C_8 环烷基或4-12元杂环烷基,其中b是0、1或2, R_a 和 R_b 各自独立为氢或 R_{S3},且 R_{S3} 选自 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12元杂环烷基或五元或六元杂环芳基 ;或 R_a 和 R_b 连同它们所连接的氮原子一起形成含0或1个额外杂原子的4-12元杂环烷基环 ;R_{S2}、R_{S3} 以及由 R_a 和 R_b 形成的4-12元杂环烷基环任选地被一个或多个 -Q_2-T_2 取代,其中 Q_2 为键或是任选地被下列取代基取代的 C_1-C_3 烷基连接体 :卤素、氰基、羟基或 C_1-C_6 烷氧基,T_2 选自氢、卤素、氰基、$-OR_c$、$-NR_cR_d$、$-C(O)R_c$、$-C(O)OR_c$、$-C(O)NR_cR_d$、$-NR_dC(O)R_c$、$-NR_dC(O)OR_c$、$-S(O)_2R_c$、$-S(O)_2NR_cR_d$ 或 R_{S4},其中 R_c 和 R_d 各自独立选自H或 R_{S5}, R_{S4} 和 R_{S5} 各自独立地选自 C_1-C_6 烷基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12元杂环烷基或者五元或六元杂芳基,或 R_c 和 R_d 连同它们所连接的氮原子一起形成含0或1个额外杂原子的4-12元杂环烷基环,R_{S4}、R_{S5}

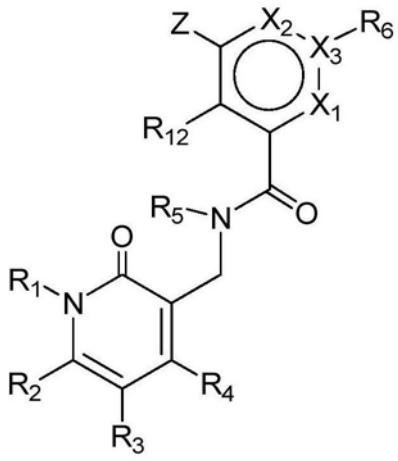
以及由 R_c 和 R_d 形成的 4-12 元杂环烷基环任选地被一个或多个 $-Q_3-T_3$ 取代，其中 Q_3 是键或是任选地被下列取代基取代的 C_1-C_3 烷基连接体：卤素、氰基、羟基或 C_1-C_6 烷氧基，T_3 选自下列组：卤素、氰基、C_1-C_6 烷基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基、五元或六元杂芳基、OR_e、$COOR_e$、$-S(O)_2R_e$、$-NR_eR_f$ 和 $-C(O)NR_eR_f$，R_e 和 R_f 各自独立地选自氢或 C_1-C_6 烷基，或 $-Q_3-T_3$ 为氧代；或 $-Q_2-T_2$ 为氧代；

R_7 是 $-Q_4-T_4$，其中 Q_4 为键、C_1-C_4 烷基连接体或 C_2-C_4 烯基连接体，每个连接体任选地被下列取代基取代：卤素、氰基、羟基或 C_1-C_6 烷氧基，T_4 选自氢、卤素、氰基、NR_gR_h、$-OR_g$、$-C(O)R_g$、$-C(O)OR_g$、$-C(O)NR_gR_h$、$-C(O)NR_gOR_h$、$-NR_gC(O)R_h$、$-S(O)_2R_g$ 或 R_{S6}，其中 R_g 和 R_h 各自独立地选自氢或 R_{S7}，R_{S6} 和 R_{S7} 各自独立地选自 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-14 元杂环烷基或者五或六元杂芳基，R_{S6} 和 R_{S7} 各自任选地被一个或多个 $-Q_5-T_5$ 取代，其中 Q_5 选自键、羰基、$C(O)NR_k$、$NR_kC(O)$、硫酰基或 C_1-C_3 烷基连接体，R_k 是氢或 C_1-C_6 烷基，T_5 选自氢、卤素、C_1-C_6 烷基、羟基、氰基、C_1-C_6 烷氧基、氨基、单 $-C_1-C_6$ 烷基氨基、双 $-C_1-C_6$ 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基、五或六元杂芳基或 $S(O)_qR_q$，其中 q 为 0、1 或 2，R_q 选自 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基或者五或六元杂芳基，T_5 任选地被选自下列组的一个或多个取代基取代：卤素、C_1-C_6 烷基、羟基、氰基、C_1-C_6 烷氧基、氨基、单 $-C_1-C_6$ 烷基氨基、双 $-C_1-C_6$ 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基和五或六元杂芳基，T_5 是氢、卤素、羟基或氰基的情况除外；或 $-Q_5-T_5$ 是氧代；条件是 (i) 当 Z 是 NR_7R_8 时 R_7 不是 $C(O)R_g$ 或 $-S(O)_2R_g$；(ii) 当 Z 是 OR_7 时 R_7 不是 C_1-C_6 烷基，以及 (iii) R_7 不是氢；

R_8、R_{11}、R_{12} 和 R_{13} 各自独立选自氢、卤素、羟基、羧基、氰基、R_{S8}、OR_{S8} 或 $COOR_{S8}$，其中 R_{S8} 选自 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_3-C_8 环烷基、4-12 元杂环烷基、氨基、单 $-C_1-C_6$ 烷基氨基或双 $-C_1-C_6$ 烷基氨基，且 R_{S8} 任选地被选自下列组的一或多个取代基取代：卤素、羟基、羧基、$C(O)O-C_1-C_6$ 烷基、氰基、C_1-C_6 烷氧基、氨基、单 $-C_1-C_6$ 烷基氨基和双 $-C_1-C_6$ 烷基氨基；或 R_7 和 R_8 连同它们所连接的氮原子一起形成含 0-2 个额外杂原子的 4-12 杂环烷基环，或 R_7 和 R_8 连同它们所连接的碳原子一起形成 C_3-C_8 环烷基或含 1-3 个杂原子的 4-12 元杂环烷基环，所述的由 R_7 和 R_8 形成的 4-12 元杂环烷基环或 C_3-C_8 环烷基各自任选地被一个或多个 $-Q_6-T_6$ 取代，其中 Q_6 选自键、羰基、$C(O)NR_m$、$NR_mC(O)$、硫酰基或 C_1-C_3 烷基连接体，R_m 为氢或 C_1-C_6 烷基，且 T_6 选自氢、卤素、C_1-C_6 烷基、羟基、氰基、C_1-C_6 烷氧基、氨基、单 $-C_1-C_6$ 烷基氨基、双 $-C_1-C_6$ 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基、五或六元杂芳基或 $S(O)_pR_p$，其中 p 是 0、1 或 2，R_p 选自 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基或者五或六元杂芳基，并且 T_6 任选地被选自下列组的一个或多个取代基取代：卤素、C_1-C_6 烷基、羟基、氰基、C_1-C_6 烷氧基、氨基、单 $-C_1-C_6$ 烷基氨基、双 $-C_1-C_6$ 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基、五或六元杂芳基，T_6 为氢、卤素、羟基或氰基的情况除外；或 $-Q_6-T_6$ 为氧代；以及

R_{14} 不存在或选自氢或任选地被选自下列组的一个或多个取代基取代的 C_1-C_6 烷基：卤素、羟基、羧基、$C(O)O-C_1-C_6$ 烷基、氰基、C_1-C_6 烷氧基、氨基、单 $-C_1-C_6$ 烷基氨基、双 $-C_1-C_6$ 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基和五或六元杂芳基。

3. 权利要求 1 或 2 的化合物，其中所述化合物的结构式为 (Ia)：



(Ia)。

4. 权利要求 1-3 中任意一项的化合物，其中 X_1 是 CR_{11} 且 X_2 是 CR_{13}。

5. 权利要求 1-3 中任意一项的化合物，其中 X_1 是 CR_{11} 且 X_2 是 N。

6. 权利要求 1-3 中任意一项的化合物，其中 X_1 是 N 且 X_2 是 CR_{13}。

7. 权利要求 1-3 中任意一项的化合物，其中 X_1 是 N 且 X_2 是 N。

8. 权利要求 1-7 中任意一项的化合物，其中 Z 是 NR_7R_8。

9. 权利要求 1-7 中任意一项的化合物，其中 Z 是 $CR_7R_8R_{14}$。

10. 权利要求 1-7 中任意一项的化合物，其中 Z 是 OR_7。

11. 权利要求 1-7 中任意一项的化合物，其中 Z 是 $S(O)_aR_7$。

12. 权利要求 1-11 中任意一项的化合物，其中 R_6 选自卤素、C_1-C_3 烷基、C_2-C_6 烯基、C_3-C_6 环烷基、醛基或 $-C(O)R_a$，其中 R_a 是 C_1-C_6 烷基或 4-12 元杂环烷基。

13. 权利要求 1-11 中任意一项的化合物，其中 R_6 是任选地被一个或多个 $-Q_2$-T_2 取代的 4-12 元杂环烷基，其中 $-Q_2$-T_2 是氧代或 Q_2 是键，并且 T_2 选自 C_1-C_6 烷基、$-OR_c$、$-NR_cR_d$、$-C(O)R_c$、$-C(O)OR_c$、$-S(O)_2R_c$，或任选地被一个或多个 $-Q_3$-T_3 取代的 4-12 元杂环烷基。

14. 权利要求 1-13 中任意一项的化合物，其中 Q_3 是键或 C_1-C_3 烷基连接体，并且 T_3 选自 C_1-C_3 烷基、OR_e、$-S(O)_2R_e$ 或 $-NR_eR_f$。

15. 权利要求 1-11 和 13-14 中任意一项的化合物，其中 R_6 选自哌啶基、2,2,6,6- 四甲基哌啶基、1,2,3,6- 四氢哌啶基、2,2,6,6- 四甲基 -1,2,3,6- 四氢哌啶基、哌嗪基、吗啉基、四氢 -2H- 吡喃基、3,6- 二氢 -2H- 吡喃基或吡咯烷基。

16. 权利要求 1-11 中任意一项的化合物，其中 R_6 选自氟、溴或氯。

17. 权利要求 1-16 中任意一项的化合物，其中 R_7 是 C_1-C_6 烷基、C_3-C_8 环烷基或 4-14 元杂环烷基，每个任选地被一个或多个 $-Q_5$-T_5 取代。

18. 权利要求 1-17 中任意一项的化合物，其中 R_7 选自哌啶基、四氢吡喃基、硫代环己烷基、氧杂环丁烷基、氮杂环丁烷基、吡咯烷基、1,4- 二氧杂螺 [4.5] 癸烷基、1- 氧杂螺 [4.5] 癸烷基、3'H- 螺 [环己烷 -1,1'- 异苯并呋喃]-3'- 酮 -4- 基、7'H- 螺 [环己烷 -1,5'- 呋喃 [3,4-b] 吡啶]-7' 酮 -4- 基、3'H- 螺 [环己烷 -1,1'- 呋喃 [3,4-c] 吡啶]-3'- 酮 -4- 基、1- 氮杂螺 [4.5] 癸烷 -2- 酮 -8- 基、环丁基、环戊基或环己基，每一个 R_7 任选地被一个 $-Q_5$-T_5 取代。

19. 权利要求 1-18 中任意一项的化合物，其中 T_5 选自氢、卤素、C_1-C_6 烷基、C_1-C_6 烷氧基、C_3-C_8 环烷基、C_6-C_{10} 芳基或 4-12 元杂环烷基。

20. 权利要求 1-18 中任意一项的化合物，其中 Q_5 是键，且 T_5 选自 C_1-C_6 烷基、C_3-C_8 环烷基或 4-12 元杂环烷基。

21. 权利要求 1-18 中任意一项的化合物，其中 Q_5 选自羰基、硫酰基或 NHC(O)，且 T_5 选自 C_1-C_6 烷基、C_1-C_6 烷氧基、C_3-C_8 环烷基或 4-12 元杂环烷基。

22. 权利要求 1-18 中任意一项的化合物，其中 Q_5 是 C_1-C_3 烷基连接体，且 T_5 是氢或 C_6-C_{10} 芳基。

23. 权利要求 1-18 中任意一项的化合物，其中 Q_5 是 C_1-C_3 烷基连接体，且 T_5 是 C_3-C_8 环烷基、4-12 元杂环烷基或 $S(O)_qR_q$。

24. 权利要求 1-23 中任意一项的化合物，其中 R_{11} 是氢。

25. 权利要求 1-17 和 24 中任意一项的化合物，其中 R_7 是四氢噻喃基、环戊基或环己基，每一个任选被一个或多个 $-Q_5$-T_5 取代。

26. 权利要求 1-17 和 24-25 中任意一项的化合物，其中 Q_5 是 NHC(O) 并且 T_5 是 C_1-C_6 烷基或 C_1-C_6 烷氧基。

27. 权利要求 1-17 和 24-25 中任意一项的化合物，其中一个或多个 $-Q_5$-T_5 是氧代。

28. 权利要求 1-17 和 24 中任意一项的化合物，其中 R_7 是异丙基。

29. 权利要求 1-28 中任意一项的化合物，其中 R_2 和 R_4 各自独立为任选被 C_1-C_6 烷氧基取代的 C_1-C_3 烷基。

30. 权利要求 1-29 中任意一项的化合物，其中 R_2 和 R_4 各自是甲基。

31. 权利要求 1-30 中任意一项的化合物，其中 R_1 是氢。

32. 权利要求 1-31 中任意一项的化合物，其中 R_{12} 是氢、甲基、乙基、乙烯基或卤素。

33. 权利要求 1-32 中任意一项的化合物，其中 R_{12} 是甲基。

34. 权利要求 1-32 中任意一项的化合物，其中 R_{12} 是乙基。

35. 权利要求 1-32 中任意一项的化合物，其中 R_{12} 是乙烯基。

36. 权利要求 1-35 中任意一项的化合物，其中 R_8 是氢、甲基或乙基。

37. 权利要求 1-36 中任意一项的化合物，其中 R_8 是甲基。

38. 权利要求 1-36 中任意一项的化合物，其中 R_8 是乙基。

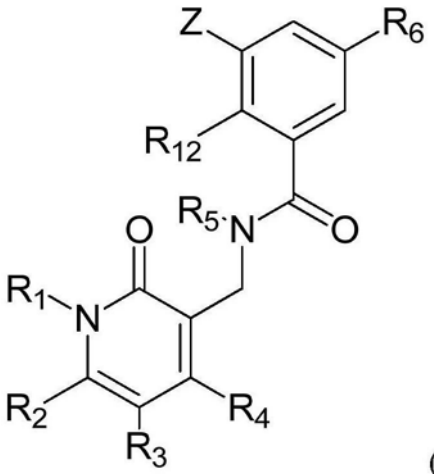
39. 权利要求 1-9、12-16、24 和 29-35 中任意一项的化合物，其中 Z 是 NR_7R_8 或 $CR_7R_8R_{14}$，其中 R_7 和 R_8 连同它们所连接的原子形成选自下列组的环：哌啶基、吗啉基、哌嗪基、氮杂环丁烷基、吡咯烷基、2-氧代-5-氮杂双环[2.2.1]庚烷-5-基、1,4-二氧杂-8-氮杂螺[4.5]癸烷基和环己烯基，每一个 Z 任选被一个 $-Q_6$-T_6 取代。

40. 权利要求 1-39 中任意一项的化合物，其中 R_{13} 是氢或甲基。

41. 权利要求 1-39 中任意一项的化合物，其中 R_{13} 是氢。

42. 权利要求 1-40 中任意一项的化合物，其中 R_3 是氢。

43. 权利要求 1 或 2 的化合物，其中所述化合物的结构式为式 (Ie)：



(Ie),

其中

Z 是 NR_7R_8、OR_7 或 $S(O)_aR_7$;

R_1 是氢或任选被一个或多个选自下列组的取代基取代的 C_1-C_6 烷基 :羟基、C_1-C_6 烷氧基、氨基、单 -C_1-C_6 烷基氨基、双 -C_1-C_6 烷基氨基和 C_6-C_{10} 芳基 ;

R_2 和 R_4 各自独立地为 -Q_1-T_1,其中 Q_1 是键或任选被一个或多个选自卤素和羟基的取代基取代的 C_1-C_3 烷基连接体,并且 T_1 选自氢、卤素或叠氮基 ;

R_3 是氢或卤素 ;

R_5 是氢或 C_1-C_6 烷基 ;

R_6 是氢、卤素、氰基、叠氮基、OR_a、$-NR_aR_b$、$-C(O)NR_aR_b$、$-S(O)_bR_a$ 或 R_{S2} ;其中 R_{S2} 是 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基或 4-12 元杂环烷基,其中 R_a 和 R_b 各自独立选自氢、C_1-C_6 烷基或 4-12 杂环烷基 ;或 R_a 和 R_b 连同它们所连接的氮原子形成含 0 或 1 个额外的杂原子的 4-12 元杂环烷基环 ;R_a、R_{S2} 和所述由 R_a 和 R_b 形成的 4-12 元杂环烷基环各自任选地被一个或多个 -Q_2-T_2 取代,其中 Q_2 是键或 C_1-C_3 烷基连接体,T_2 选自氢、卤素、$-OR_c$、$-NR_cR_d$、$-C(O)OR_c$ 或 C_1-C_6 烷基,其中 R_c 和 R_d 各自独立为氢或 C_1-C_6 烷基,或 R_c 和 R_d 连同它们所连接的氮原子形成含 0 或 1 个额外杂原子的、任选地被 C_1-C_6 烷基取代的 4-12 元杂环烷基环 ;

R_7 是 -Q_4-T_4,其中 Q_4 是键或 C_1-C_4 烷基连接体,T_4 选自氢、C_1-C_6 烷基、C_3-C_8 环烷基、C_6-C_{10} 芳基、$C(O)$-C_{1-6} 烷基、$C(O)$-C_{3-6} 环烷基或 4-14 元杂环烷基,每一个 T_4 任选地被一个或多个 -Q_5-T_5 取代 ;

R_8 是氢、任选地被卤素或羟基或 C_1-C_6 烷氧基取代的 C_1-C_6 烷基、C_2-C_6 烯基、C_3-C_8 环烷基或 4-7 元杂环烷基 ;或 R_7 和 R_8 连同它们所连接的氮原子形成含 0-2 个额外的杂原子的 4-12 元杂环烷基环,且所述由 R_7 和 R_8 形成的 4-12 元杂环烷基环任选地被一个或多个 -Q_6-T_6 取代 ;以及

R_{12} 是卤素、C_1-C_6 烷氧基或任选地被卤素或 C_2-C_6 烯基取代的 C_1-C_6 烷基。

44. 权利要求 1-3 和 43 中任意一项的化合物,其中

R_1 是氢或任选地被选自羟基、C_1-C_6 烷氧基和 C_6-C_{10} 芳基的取代基所取代一次或多次的 C_1-C_6 烷基 ;

R_7 是 -Q_4-T_4,其中 Q_4 是键或 C_1-C_4 烷基连接体,T_4 选自 C_1-C_6 烷基、C_3-C_8 环烷基、C_6-C_{10} 芳基、$C(O)$-C_1-C_6 烷基、$C(O)$-C_3-C_6 环烷基、二氢吡喃基、四氢吡喃基、四氢噻喃基、哌啶基、吡咯烷基、氮杂环丁烷基和氧杂环丁烷基,每一个 T_4 各自独立地被一个或多个下列取代基

取代 :氧代和 $-Q_5-T_5$;

R_8 是氢或 C_1-C_6 烷基、C_1-C_6 卤代烷基、C_2-C_6 烯基或 C_3-C_8 环烷基 ;以及

R_{12} 选自卤素、C_1-C_6 烷基、C_1-C_6 卤代烷基或 C_1-C_6 烷氧基。

45. 权利要求 1-3、43 和 44 中任意一项的化合物,其中

Z 是 NR_7R_8 或 SR_7 ;

R_6 选自氢、卤素、氰基、OR_a、$-C(O)NR_aR_b$、$-S(O)_2R_a$ 或 R_{S2} ;其中 R_{S2} 是 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基或 4-12 元杂环烷基,且其中 R_a 和 R_b 各自独立为氢或 C_1-C_6 烷基 ;或 R_a 和 R_b 连同它们所连接的氮原子形成含 0 或 1 个额外的杂原子的 4-12 元杂环烷基环 ;R_{S2} 和所述的由 R_a 和 R_b 形成的 4-12 元杂环烷基环各自任选地被一个或多个 $-Q_2-T_2$ 取代 ;其中 Q_2 是键或 C_1-C_3 烷基连接体,T_2 选自氢、卤素、$-OR_c$、$-NR_cR_d$、$-C(O)OC_1-C_6$ 烷基或 C_1-C_6 烷基,其中 R_c 和 R_d 各自独立为氢或 C_1-C_6 烷基,或 R_c 和 R_d 连同它们所连接的氮原子形成含 0 或 1 个额外的杂原子和含 0 或 1 个 C_1-C_6 烷基取代基的 4-12 元杂环烷基环 ;

R_7 选自 C_1-C_6 烷基、C_3-C_8 环烷基、二氢吡喃基、四氢吡喃基、四氢噻喃基、哌啶基、吡咯烷基、氮杂环丁烷基和氧杂环丁烷基,每一个任选地被一个或多个独立地选自氧代和 $-Q_5-T_5$ 的取代基取代 ;以及

R_{12} 是卤素或 C_1-C_6 烷基。

46. 权利要求 1-3 和 43-45 中任意一项的化合物,其中 R_2、R_4 和 R_{12} 各自独立为 C_1-C_6 烷基,且 R_5 是氢。

47. 权利要求 1-3 和 43 中任意一项的化合物,其中 R_7 是环己基、二氢吡喃基、四氢吡喃基、四氢噻喃基、哌啶基、吡咯烷基、氮杂环丁烷基、氧杂环丁烷基、1,4- 二氧杂螺 [4.5] 癸烷 -8- 基、1- 氧杂螺 [4.5] 癸烷 -8- 基、3'H- 螺 [环己烷 -1,1'- 异苯并呋喃]-4- 基、7'H- 螺 [环己烷 -1,5'- 呋喃 [3,4-b] 吡啶]-4- 基、3'H- 螺 [环己烷 -1,1'- 呋喃 [3,4-c] 吡啶]-4- 基或 1- 氮杂螺 [4.5] 癸烷 -8- 基,每一个 R_7 任选地被一个或多个 $-Q_5-T_5$ 取代。

48. 权利要求 1-3 和 43-47 中任意一项的化合物,其中 Z 选自哌啶基、吗啉基、哌嗪基、氮杂环丁烷基、吡咯烷基、2- 氧杂 -5- 氮杂二环 [2.2.1] 庚烷 -5- 基,1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸烷 -8- 基和环己烯基,每一个 Z 任选地被一个 $-Q_6-T_6$ 取代。

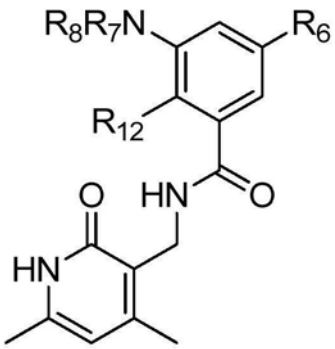
49. 权利要求 1-3 和 43-48 中任意一项的化合物,其中 R_6 是卤素且 Z 是 $S(O)_aR_7$,其中 a 是 0、1 或 2,R_7 是 C_1-C_6 烷基、C_3-C_8 环烷基或 4-7 元杂环烷基,并且 R_7 任选地被一个或多个 $-Q_5-T_5$ 取代。

50. 权利要求 1-3 和 43-48 中任意一项的化合物,其中 R_6 是卤素且 Z 是 OR_7,其中 R_7 是任选地被一个或多个 $-Q_5-T_5$ 取代 4-7 元的杂环烷基。

51. 权利要求 1-3 和 43-48 中任意一项的化合物,其中 R_6 是 $-S(O)_bR_a$ 或叠氮基,其中 b 是 0、1 或 2,R_a 是 C_1-C_6 烷基或 C_3-C_8 环烷基 ;Z 是 NR_7R_8,其中 R_7 是 C_3-C_8 环烷基或 4-14 元杂环烷基,每一个 R_7 任选地被一个或多个 $-Q_5-T_5$ 取代 ;R_8 是氢或 C_1-C_6 烷基。

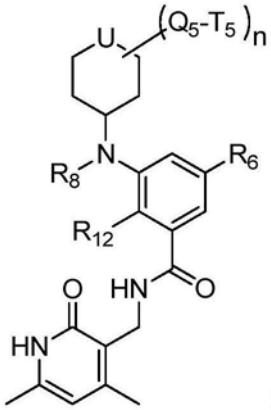
52. 权利要求 1-3 和 43-48 中任意一项的化合物,其中 R_6 是卤素且 Z 是 NR_7R_8 或 $CR_7R_8R_{14}$,其中 R_7 和 R_8 连同它们所连接的原子一起形成含 1-3 个杂原子的 4-11 元杂环烷基环或 C_3-C_8 环烷基,每一个任选地被一个或多个 $-Q_6-T_6$ 取代。

53. 权利要求 1-3 和 43-47 中任意一项的化合物,其中所述化合物的结构式为式 (II):



(II)。

54. 权利要求 1-3、43-47 和 53 中任意一项的化合物，其中所述化合物的结构式为式 (IIA)：



(IIA)

其中 n 是 0、1 或 2；U 是 O、S、N-Q_5-T_5 或 CH-Q_5-T_5；以及 R_{12} 是氯、溴或甲基。

55. 权利要求 43-54 中任意一项的化合物，其中 Q_5 是键，且 T_5 选自氢、C_1-C_6 烷基、C_3-C_8 环烷基、4-12 元杂环烷基、五或六元杂芳基、氨基、单 -C_1-C_6 烷基氨基或双 -C_1-C_6 烷基氨基，T_5 任选被一个或多个选自下列组的取代基取代：卤素、羟基、C_1-C_6 烷氧基或 C_3-C_8 环烷基。

56. 权利要求 43-54 中任意一项的化合物，其中 Q_5 选自羰基、硫酰基或 NHC(O)，且 T_5 选自 C_1-C_6 烷基、C_1-C_6 烷氧基、C_3-C_8 环烷基或 4-12 元杂环烷基。

57. 权利要求 43-54 中任意一项的化合物，其中 Q_5 是 C_1-C_3 烷基连接体，且 T_5 是氢或 C_6-C_{10} 芳基。

58. 权利要求 43-54 中任意一项的化合物，其中 Q_5 是 C_1-C_3 烷基连接体，且 T_5 是 C_3-C_8 环烷基、4-12 元杂环烷基或 $S(O)_qR_q$。

59. 权利要求 43-54 中任意一项的化合物，其中 Q_5 是 NHC(O) 并且 T_5 是 C_1-C_6 烷基或 C_1-C_6 烷氧基。

60. 权利要求 43-54 中任意一项的化合物，其中一个或多个 -Q_5-T_5 是氧代。

61. 权利要求 54 的化合物，其中 U 是 CH-Q_5-T_5 且 n 是 0。

62. 权利要求 1-61 中任意一项的化合物，其中一个或多个 -Q_6-T_6 是氧代。

63. 权利要求 1-61 中任意一项的化合物，其中 Q_6 是键或羰基，T_6 是 C_1-C_6 烷基或 C_1-C_6 烷氧基。

64. 权利要求 1 的化合物，其中所述化合物选自表 1。

65. 权利要求 1 中的化合物，为 5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-3-(((1r,4r)-4-（二甲基氨基）环己基）（乙基）氨基）-2- 甲基苯甲酰

胺或其药学上可接受的盐。

66. 一种药物组合物，包含治疗有效量的权利要求 1-65 中任意一项的化合物、N-(5-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）氨基甲酰基)-2- 甲基苯基）呋喃 -2- 甲酰胺、N,N'-(5-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）氨基甲酰基)-1,3- 亚苯基）二乙酰基、N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基)-3- 特戊酰基苯甲酰胺、3-(3,4- 二氢 -2H- 苯并 [b][1,4] 二氧杂环庚烯 -7- 磺酰胺基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）苯甲酰胺、N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基)-3,5- 二甲氧基苯甲酰胺、N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基)-3,4,5- 三甲氧基苯甲酰胺、3- 烯丙基 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基)-4,5- 二甲氧基苯甲酰胺、4-(2- 氨基 2- 氧代乙氧基)-3- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基)-5- 甲氧基苯甲酰胺、3- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基)-4- 羟基 -5- 甲氧基苯甲酰胺或 3- 溴 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基)-5- 甲氧基 -4- 丙氧基苯甲酰胺，或其药学上可接受的盐和药学上可接受的载体。

67. 一种治疗癌症的方法，包括向需要的受试者给药以治疗有效量的权利要求 1-65 中任意一项的化合物、N-(5-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）氨基甲酰)-2- 甲基苯基）呋喃 -2- 甲酰胺、N,N'-(5-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）氨基甲酰)-1,3- 亚苯基）二乙酰胺、N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基)-3- 特戊酰基苯甲酰胺、3-(3,4- 二氢 -2H- 苯并 [b][1,4] 二氧杂环庚烯 -7- 磺酰胺基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）苯甲酰胺、N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基)-3,5- 二甲氧基苯甲酰胺、N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基)-3,4,5- 三甲氧基苯甲酰胺、3- 烯丙基 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基)-4,5- 二甲氧基苯甲酰胺、4-(2- 氨基 -2- 氧代乙氧基)-3- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基)-5- 甲氧基苯甲酰胺、3- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基)-4- 羟基 -5- 甲氧基苯甲酰胺或 3- 溴 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基)-5 甲氧基 -4- 丙氧基苯甲酰胺或其药学上可接受的盐。

68. 权利要求 1-65 中任意一项的化合物在治疗或预防癌症方面的用途。

取代苯化合物

[0001] 相关申请

[0002] 本申请要求 2011 年 4 月 13 日提交的美国临时申请 61/474825 和 2011 年 7 月 8 日提交的美国临时申请 61/505676 的优先权，其全部内容通过引用结合到本文中。

[0003] 引用序列表

[0004] 创建于 2012 年 3 月 28 日、大小为 2KB 的文件“41478508001wost25.txt”的全部内容通过引用结合到本文中。

背景技术

[0005] 在真核细胞中，DNA 被组蛋白包裹形成染色质。染色质有序结构的变化会引起相关基因转录的改变。染色质结构变化（并因此转录）的控制通过对组蛋白的共价修饰来调节，最显著的是对其 N- 端尾部的修饰。这些修饰通常认为是表观的，因为它们会导致基因表达的遗传变化，但不影响 DNA 本身的序列。对氨基酸侧链的共价修饰（例如甲基化、乙酰化、磷酸化和泛素化）是由酶介导的。向组蛋白上的特定氨基酸位点选择性加入甲基基团被一类独特的酶、即被称为组蛋白甲基化转移酶（HMT）的作用所控制。

[0006] 对转录调控背后的生化系统的精心策划的收集必须进行严格控制，以便优化地进行细胞生长和分化。当这些控制被负责 DNA 和组蛋白修饰的酶的异常表达和 / 或活性破坏时，就产生了疾病。例如在人类癌症中，有越来越多的证据表明，异常表达的表观遗传酶活性有助于与癌症关联的不受控制的细胞增殖以及其他癌症相关的表型，如增强的细胞迁移和入侵。除癌症之外，有越来越多的证据表明表观遗传酶在一些其他的人类疾病中起到作用，包括新陈代谢疾病（如糖尿病）、炎性疾病（如克罗恩病）、神经退行性疾病（如阿尔茨海默氏病）和心血管疾病。因此，选择性地调节表观遗传酶的异常行为可为一系列疾病的治疗带来希望。

[0007] 已知 Polycomb 家族 (PcG) 和 trithorax 家族 (trxG) 蛋白质是细胞记忆系统的一部分（参阅如 Francis et al.(2001)Nat Rev Mol Cell Biol2:409-21 和 Simon et al.(2002)Curr Opin Genet Dev12:210-8）。通常情况下，PcG 蛋白质是维持“关闭状态”的转录抑制因子，而 trxG 蛋白质是维持“开启状态”的转录活化因子。由于 PcG 蛋白质和 trxG 蛋白质的家族成员中包含内在组蛋白甲基化转移酶 (HMTase) 活性，因此 PcG 蛋白质和 trxG 蛋白质可以通过核心组蛋白的甲基化而参与细胞记忆（参阅如 Beisel et al.(2002) Nature419:857-62 ;Cao et al.(2002)Science298:1039-43 ;Czermin et al.(2002) Cell111:185-96 ;Kuzmichev et al.(2002)Genes Dev16:2893-905 ;Milne et al.(2002) Mol Cell10:1107-17 ;Muller et al.(2002)Cell111:197-208 和 Nakamura et al.(2002) Mol Cell10:1119-28.）。

[0008] 生化和遗传学研究已经提供证据表明，果蝇 PcG 蛋白质以至少两种不同的蛋白质复合物来起作用，即 Polycomb 抑制复合物 1(PRC1) 和 ESC-E(Z) 复合物（也被称为 Polycomb 抑制复合物 2(PRC2)）。可参阅 Otte et al.(2003)Curr Opin Genet Dev13:448-54。对果蝇的研究已经证明了 ESC-E(Z)/EED-EZH2（即 PRC2）复合物具有内在组蛋白甲基转移酶活

性。尽管被不同基团分离的复合物的组成都略有不同，但它们通常都包含 EED、EZH2、SUZ12 和 RbAp48 或其果蝇同源染色体。而在美国专利 7563589 中公开了一个仅包含 EED、EZH2 和 SUZ12 的再造复合物为组蛋白 H3 的赖氨酸 27 保留组蛋白甲基化转移酶活性。

[0009] 在组成 PRC2 复合物的各种蛋白质中，EZH2(Enhancer of Zeste Homolog2) 是催化亚基。EZH2 的催化位点又出现在 SET 结构域内，其为发现于少数染色质相关的蛋白中的高度保守的序列基元(以 Su(var)3-9 来命名，Enhancer of Zeste,Trithorax)，包括 Trithorax 家族和 Polycomb 家族的成员。除了组蛋白 H3-K79 甲基转移酶 DOT1，其它所有已知的组蛋白赖氨酸甲基转移酶都含有 SET 结构域。

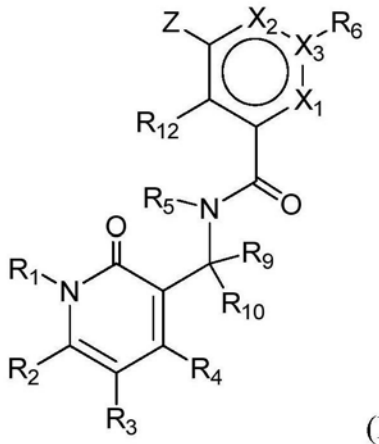
[0010] 除了同源盒基因(Hox)沉默外，PRC2 介导的组蛋白 H3-K27 甲基化已经表明参与了 X 染色体灭活(Plath et al.(2003)Science300:131-5 ;Silva et al.(2003)Dev Cell4:481-95)。向 Xi 上募集 PRC2 复合物以及随后在组蛋白 H3-K27 上的三甲基化发生在 X 染色体灭活的起始阶段，且依赖于 Xist RNA。此外，发现 EZH2 和其相关的组蛋白 H3-K27 甲基化转移酶活性区别地标记多能性的上胚层细胞和分化的滋养外胚层，并与 EZH2 在保持多能性上胚层细胞的表观遗传修饰模式中的作用相一致，EZH2 的 Cre 重组酶介导的删除导致细胞中组蛋白 H3-K27 甲基化的损失(Erhardt et al.(2003)Development130:4235-48)。另外，对前列腺癌和乳腺癌的细胞系和组织的研究显示了 EZH2 和 SUZ12 的水平与这些癌症的侵入力之间存在密切的联系，表明 PRC2 复合物的功能紊乱可能会导致癌症(Bracken et al.(2003)EMBO J22:5323-35;Kirmizis et al.(2003)Mol Cancer Ther2:113-21;Kleer et al.(2003)Proc Natl Acad Sci USA100:11606-11;Varambally et al.(2002) Nature419:624-9)。

[0011] 最近有报道称，EZH2 的酪氨酸 641 (Y641C，Y641F，Y641N，Y641S 和 Y641H ；有时也称为 Y646C，Y646F，Y646N，Y646S 和 Y646H) 的体细胞突变与滤泡性淋巴瘤 (FL) 和弥漫性大 B 细胞淋巴瘤 (DLBCL) 的生发中心 B 细胞样 (GCB) 的亚型有关(Morin et al.(2010)Nat Genet42:181-5)。在任何情况下，发现突变的 EZH2 基因的出现都是杂合的，在突变样品中通过转录组测序显示检测到野生型和突变体等位基因的表达。还证明的是，EZH2 基因的所有突变类型都可以结合到多蛋白 PRC2 复合物中，但是所生成的复合物不能催化缩氨酸底物的 H3-K27 等效残基的甲基化作用。因此，得出的结论是，EZH2 的 Tyr641 处的与疾病相关的变化导致了关于 EZH2 催化的 H3-K27 甲基化的功能缺失。

发明内容

[0012] 一方面，本发明提供了如下所示的式 (I) 的取代苯化合物或其药学上可接受的盐或酯。

[0013]



(I)

[0014] 在该式中：

[0015] X_1 是 N 或 CR_{11}；

[0016] X_2 是 N 或 CR_{13}；

[0017] X_3 是 N 或 C，且当 X_3 是 N 时，R_6 不存在；

[0018] Z 是 NR_7R_8、OR_7、$S(O)_aR_7$ 或 $CR_7R_8R_{14}$，其中 a 为 0、1 或 2；

[0019] R_1、R_5、R_9 和 R_{10} 各自独立为 H 或任选地被选自下列组的一个或多个取代基取代的 C_1-C_6 烷基：卤素、羟基、羧基、C(O)O-C_1-C_6 烷基、氰基、C_1-C_6 烷氧基、氨基、单 -C_1-C_6 烷基氨基、双 -C_1-C_6 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基和五或六元杂芳基；

[0020] R_2、R_3 和 R_4 各自独立为 -Q_1-T_1，其中 Q_1 为键或是任选地被一个或多个选自下列组的取代基取代的 C_1-C_3 烷基连接体：卤素、氰基、羟基或 C_1-C_6 烷氧基，T_1 选自氢、卤素、羟基、羧基、氰基、叠氮基或 R_{S1}，其中 R_{S1} 选自 C_1-C_3 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_1-C_6 烷氧基、C(O)O-C_1-C_6 烷基、C_3-C_8 环烷基、C_6-C_{10} 芳基、氨基、单 -C_1-C_6 烷基氨基、双 -C_1-C_6 烷基氨基、4-12 元杂环烷基和五或六元杂芳基，且 R_{S1} 任选地被一个或多个选自下列组的取代基取代：卤素、羟基、氧代、羧基、C(O)O-C_1-C_6 烷基、氰基、C_1-C_6 烷氧基、氨基、单 -C_1-C_6 烷基氨基、双 -C_1-C_6 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基和五或六元杂环芳基；

[0021] R_6 选自氢、卤素、氰基、叠氮基、OR_a、$-NR_aR_b$、$-C(O)R_a$、$-C(O)OR_a$、$-C(O)NR_aR_b$、$-NR_bC(O)R_a$、$-S(O)_bR_a$、$-S(O)_bNR_aR_b$ 或 R_{S2}，其中 R_{S2} 选自 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_3-C_8 环烷基或 4-12 元杂环烷基；b 是 0、1 或 2；R_a 和 R_b 各自独立为氢或 R_{S3}，其中 R_{S3} 选自 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基或者五元或六元杂环芳基；或 R_a 和 R_b，连同它们所连接的氮原子一起形成含 0 或 1 个额外杂原子的 4-12 元杂环烷基环；R_{S2}、R_{S3} 以及由 R_a 和 R_b 形成的 4-12 元杂环烷基环任选地被一个或多个 -Q_2-T_2 取代，其中 Q_2 为键或是任选地被下列取代基取代的 C_1-C_3 烷基连接体：卤素、氰基、羟基或 C_1-C_6 烷氧基；T_2 选自氢、卤素、氰基、$-OR_c$、$-NR_cR_d$、$-C(O)R_c$、$-C(O)OR_c$、$-C(O)NR_cR_d$、$-NR_dC(O)R_c$、$-NR_dC(O)OR_c$、$-S(O)_2R_c$、$-S(O)_2NR_cR_d$ 或 R_{S4}，其中 R_c 和 R_d 各自独立选自 H 或 R_{S5}，其中 R_{S4} 和 R_{S5} 各自独立选自 C_1-C_6 烷基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基或者五元或六元杂芳基，或 R_c 和 R_d 连同它们所连接的氮原子一起形成含 0 或 1 个额外杂原子的 4-12 元杂环烷基环，R_{S4}、R_{S5} 以及由 R_c 和 R_d 形成的 4-12 元杂环烷基环任选地被一个或多个 -Q_3-T_3 取代，其中 Q_3 是键或是任选地被下列取代基取代的 C_1-C_3 烷基连接体：卤素、氰基、羟基或 C_1-C_6 烷氧基，T_3 选自卤素、氰基、C_1-C_6 烷基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基、五元或六元杂芳基、

OR_e、$COOR_e$、$-S(O)_2R_e$、$-NR_eR_f$ 和 $-C(O)NR_eR_f$，R_e 和 R_f 各自独立选自氢或 C_1-C_6 烷基，或 $-Q_3-T_3$ 为氧代；或 $-Q_2-T_2$ 为氧代；

[0022] R_7 是 $-Q_4-T_4$，其中 Q_4 为键、C_1-C_4 烷基连接体或 C_2-C_4 烯基连接体，每个连接体任选地被下列取代基取代：卤素、氰基、羟基或 C_1-C_6 烷氧基，T_4 选自氢、卤素、氰基、NR_gR_h、$-OR_g$、$-C(O)R_g$、$-C(O)OR_g$、$-C(O)NR_gR_h$、$-C(O)NR_gOR_h$、$-NR_gC(O)R_h$、$-S(O)_2R_g$ 或 R_{S6}，其中 R_g 和 R_h 各自独立地选自氢或 R_{S7}，R_{S6} 和 R_{S7} 各自独立地选自 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-14 元杂环烷基或者五或六元杂芳基，R_{S6} 和 R_{S7} 可任选地被一个或多个 $-Q_5-T_5$ 取代，其中 Q_5 是键、羰基、$C(O)NR_k$、$NR_kC(O)$、硫酰基或 C_1-C_3 烷基连接体，R_k 是氢或 C_1-C_6 烷基，T_5 选自氢、卤素、C_1-C_6 烷基、羟基、氰基、C_1-C_6 烷氧基、氨基、单 $-C_1$-C_6 烷基氨基、双 $-C_1$-C_6 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基、五或六元杂芳基或 $S(O)_qR_q$，其中 q 为 0、1 或 2，R_q 选自 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基或者五或六元杂芳基，T_5 任选地被选自下列组的一个或多个取代基取代：卤素、C_1-C_6 烷基、羟基、氰基、C_1-C_6 烷氧基、氨基、单 $-C_1$-C_6 烷基氨基、双 $-C_1$-C_6 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基和五或六元杂芳基，当 T_5 是氢、卤素、羟基或氰基时除外；或 $-Q_5-T_5$ 是氧代；

[0023] R_8、R_{11}、R_{12} 和 R_{13} 均各自独立选自氢、卤素、羟基、羧基、氰基、R_{S8}、OR_{S8} 或 $COOR_{S8}$，其中 R_{S8} 选自 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_3-C_8 环烷基、4-12 元杂环烷基、氨基、单 $-C_1$-C_6 烷基氨基或双 $-C_1$-C_6 烷基氨基，R_{S8} 任选地被选自下列组的一或多个取代基取代：卤素、羟基、羧基、$C(O)O$-C_1-C_6 烷基、氰基、C_1-C_6 烷氧基、氨基、单 $-C_1$-C_6 烷基氨基和双 $-C_1$-C_6 烷基氨基；或 R_7 和 R_8 连同它们所连接的接的氮原子一起形成含 0-2 个额外杂原子的 4-12 杂环烷基环，或 R_7 和 R_8 连同它们所连接的碳原子一起形成 C_3-C_8 环烷基或含 1-3 个杂原子的 4-12 元杂环烷基环，所述的由 R_7 和 R_8 形成的 4-12 元杂环烷基环或 C_3-C_8 环烷基任选地被一个或多个 $-Q_6-T_6$ 取代，其中 Q_6 是键、羰基、$C(O)NR_m$、$NR_mC(O)$、硫酰基或 C_1-C_3 烷基连接体，R_m 为氢或 C_1-C_6 烷基，T_6 选自氢、卤素、C_1-C_6 烷基、羟基、氰基、C_1-C_6 烷氧基、氨基、单 $-C_1$-C_6 烷基氨基、双 $-C_1$-C_6 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基、五或六元杂芳基或 $S(O)_pR_p$，其中 p 是 0、1 或 2，R_p 选自 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基、五或六元杂芳基，T_6 任选地被选自下列组的一个或多个取代基取代：卤素、C_1-C_6 烷基、羟基、氰基、C_1-C_6 烷氧基、氨基、单 $-C_1$-C_6 烷基氨基、双 $-C_1$-C_6 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基、五或六元杂芳基，当 T_6 为氢、卤素、羟基或氰基时除外；或 $-Q_6-T_6$ 为氧代；以及

[0024] R_{14} 不存在或为氢或任选地被选自下列组的一个或多个取代基取代的 C_1-C_6 烷基：卤素、羟基、羧基、$C(O)O$-C_1-C_6 烷基、氰基、C_1-C_6 烷氧基、氨基、单 $-C_1$-C_6 烷基氨基、双 $-C_1$-C_6 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基和五或六元杂芳基；

[0025] 条件是，所述化合物不包括

[0026] N-(5-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）氨基甲酰）-2- 甲基苯基）呋喃 -2- 甲酰胺、

[0027] N,N'-(5-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）氨基甲酰）-1,3- 亚苯基）二乙酰胺、

[0028] N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-3- 特戊酰基氨基苯甲

酰胺、

[0029] 3-(3,4- 二羟基 -2H- 苯并 [b][1,4] 二氧杂环庚烯 -7- 磺酰胺基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基) 苯甲酰胺、

[0030] N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-3,5- 二甲氧基苯甲酰胺、

[0031] N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-3,4,5- 三甲氧基苯甲酰胺、

[0032] 3- 烯丙基 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-4,5- 二甲氧基苯甲酰胺、

[0033] 4-(2- 氨基 -2- 氧代乙氧基)-3- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二羟基吡啶 -3- 基) 甲基)-5- 甲氧基苯甲酰胺、

[0034] 3- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-4- 羟基 -5- 甲氧基苯甲酰胺,或

[0035] 3- 溴 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-5- 甲氧基 -4- 丙氧基苯甲酰胺。

[0036] 另一方面,本发明涉及如上文所述式 (I) 的取代苯化合物或其药学上可接受的盐或酯,其中

[0037] X_1 是 N 或 CR_{11} ;

[0038] X_2 是 N 或 CR_{13} ;

[0039] X_3 是 N 或 C,且当 X_3 是 N 时,R_6 不存在 ;

[0040] Z 是 NR_7R_8、OR_7、$S(O)_aR_7$ 或 $CR_7R_8R_{14}$,其中 a 为 0、1 或 2 ;

[0041] R_1、R_5、R_9 和 R_{10} 各自独立为 H 或任选地被选自下列组的一个或多个取代基取代的 C_1-C_6 烷基 :卤素、羟基、羧基、C(O)O-C_1-C_6 烷基、氰基、C_1-C_6 烷氧基、氨基、单 -C_1-C_6 烷基氨基、双 -C_1-C_6 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基和五或六元杂芳基 ;

[0042] R_2、R_3 和 R_4 各自独立为 -Q_1-T_1,其中 Q_1 为键或是任选地被下列取代基取代的 C_1-C_3 烷基连接体 :卤素、氰基、羟基或 C_1-C_6 烷氧基,T_1 选自氢、卤素、羟基、羧基、氰基、叠氮基或 R_{S1},其中 R_{S1} 选自 C_1-C_3 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_1-C_6 烷氧基、C(O)O-C_1-C_6 烷基、C_3-C_8 环烷基、C_6-C_{10} 芳基、氨基、单 -C_1-C_6 烷基氨基、双 -C_1-C_6 烷基氨基、4-12 元杂环烷基和五或六元杂芳基,且 R_{S1} 任选地被一个或多个选自下列组的取代基取代 :卤素、羟基、氧代、羧基、C(O)O-C_1-C_6 烷基、氰基、C_1-C_6 烷氧基、氨基、单 -C_1-C_6 烷基氨基、双 -C_1-C_6 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基和五或六元杂环芳基 ;

[0043] R_6 选自氢、卤素、氰基、叠氮基、-NR_aR_b、-C(O)R_a、-C(O)OR_a、-C(O)NR_aR_b、-$NR_bC(O)R_a$、-$S(O)_bR_a$、-$S(O)_bNR_aR_b$ 或 R_{S2},其中 R_{S2} 选自 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_3-C_8 环烷基或 4-12 元杂环烷基,其中 b 是 0、1 或 2,R_a 和 R_b 各自独立为氢或 R_{S3},且 R_{S3} 选自 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基或者五元或六元杂环芳基 ;或 R_a 和 R_b 连同它们所连接的氮原子一起形成含 0 或 1 个额外杂原子的 4-12 元杂环烷基环 ;R_{S2}、R_{S3} 以及由 R_a 和 R_b 形成的 4-12 元杂环烷基环任选地被一个或多个 -Q_2-T_2 取代,其中 Q_2 为键或是任选地被下列取代基取代的 C_1-C_3 烷基连接体 :卤素、氰基、羟基或 C_1-C_6 烷氧基,T_2 选自氢、卤素、氰基、-OR_c、-NR_cR_d、-C(O)R_c、-C(O)OR_c、-C(O)NR_cR_d、-$NR_dC(O)$

R_c、$-NR_dC(O)OR_c$、$-S(O)_2R_c$、$-S(O)_2NR_cR_d$ 或 R_{S4}，其中 R_c 和 R_d 各自独立选自 H 或 R_{S5}，R_{S4} 和 R_{S5} 各自独立选自 C_1-C_6 烷基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基或者五元或六元杂芳基，或 R_c 和 R_d 连同它们所连接的氮原子一起形成含 0 或 1 个额外杂原子的 4-12 元杂环烷基环，R_{S4}、R_{S5} 以及由 R_c 和 R_d 形成的 4-12 元杂环烷基环任选地被一个或多个 $-Q_3$-T_3 取代，其中 Q_3 是键或是任选地被下列取代基取代的 C_1-C_3 烷基连接体：卤素、氰基、羟基或 C_1-C_6 烷氧基，T_3 选自下列组：卤素、氰基、C_1-C_6 烷基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基、五元或六元杂芳基、OR_e、$COOR_e$、$-S(O)_2R_e$、$-NR_eR_f$ 和 $-C(O)NR_eR_f$，R_e 和 R_f 各自独立地选自氢或 C_1-C_6 烷基，或 $-Q_3$-T_3 为氧代；或 $-Q_2$-T_2 为氧代；

[0044] R_7 是 $-Q_4$-T_4，其中 Q_4 为键、C_1-C_4 烷基连接体或 C_2-C_4 烯基连接体，每个连接体任选地被下列取代基取代：卤素、氰基、羟基或 C_1-C_6 烷氧基，T_4 选自氢、卤素、氰基、NR_gR_h、$-OR_g$、$-C(O)R_g$、$-C(O)OR_g$、$-C(O)NR_gR_h$、$-C(O)NR_gOR_h$、$-NR_gC(O)R_h$、$-S(O)_2R_g$ 或 R_{S6}，其中 R_g 和 R_h 各自独立地选自氢或 R_{S7}，R_{S6} 和 R_{S7} 各自独立地选自 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-14 元杂环烷基或者五或六元杂芳基，R_{S6} 和 R_{S7} 各自任选地被一个或多个 $-Q_5$-T_5 取代，其中 Q_5 选自键、羰基、$C(O)NR_k$、$NR_kC(O)$、硫酰基或 C_1-C_3 烷基连接体，R_k 是氢或 C_1-C_6 烷基，T_5 选自氢、卤素、C_1-C_6 烷基、羟基、氰基、C_1-C_6 烷氧基、氨基、单 $-C_1$-C_6 烷基氨基、双 $-C_1$-C_6 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基、五或六元杂芳基或 $S(O)_qR_q$，其中 q 为 0、1 或 2，R_q 选自 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基或者五或六元杂芳基，T_5 任选地被选自下列组的一个或多个取代基取代：卤素、C_1-C_6 烷基、羟基、氰基、C_1-C_6 烷氧基、氨基、单 $-C_1$-C_6 烷基氨基、双 $-C_1$-C_6 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基和五或六元杂芳基，T_5 是氢、卤素、羟基或氰基的情况除外；或 $-Q_5$-T_5 是氧代；条件是 (i) 当 Z 是 NR_7R_8 时 R_7 不是 $C(O)R_g$ 或 $-S(O)_2R_g$；(ii) 当 Z 是 OR_7 时 R_7 不是 C_1-C_6 烷基，以及 (iii) R_7 不是氢；

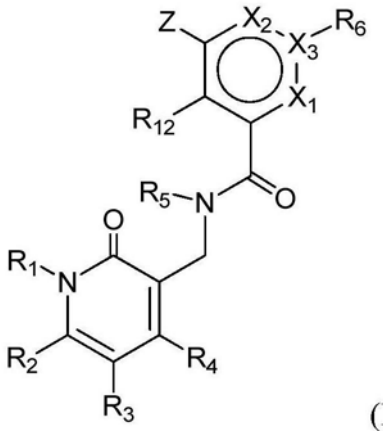
[0045] R_8、R_{11}、R_{12} 和 R_{13} 各自独立选自氢、卤素、羟基、羧基、氰基、R_{S8}、OR_{S8} 或 $COOR_{S8}$，其中 R_{S8} 选自 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_3-C_8 环烷基、4-12 元杂环烷基、氨基、单 $-C_1$-C_6 烷基氨基或双 $-C_1$-C_6 烷基氨基，且 R_{S8} 任选地被选自下列组的一或多个取代基取代：卤素、羟基、羧基、$C(O)O$-C_1-C_6 烷基、氰基、C_1-C_6 烷氧基、氨基、单 $-C_1$-C_6 烷基氨基和双 $-C_1$-C_6 烷基氨基；或 R_7 和 R_8 连同它们所连接的氮原子一起形成含 0-2 个额外杂原子的 4-12 杂环烷基环，或 R_7 和 R_8 连同它们所连接的碳原子一起形成 C_3-C_8 环烷基或含 1-3 个杂原子的 4-12 元杂环烷基环，所述的由 R_7 和 R_8 形成的 4-12 元杂环烷基环或 C_3-C_8 环烷基各自任选地被一个或多个 $-Q_6$-T_6 取代，其中 Q_6 选自键、羰基、$C(O)NR_m$、$NR_mC(O)$、硫酰基或 C_1-C_3 烷基连接体，R_m 为氢或 C_1-C_6 烷基，且 T_6 选自氢、卤素、C_1-C_6 烷基、羟基、氰基、C_1-C_6 烷氧基、氨基、单 $-C_1$-C_6 烷基氨基、双 $-C_1$-C_6 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基、五或六元杂芳基或 $S(O)_pR_p$，其中 p 是 0、1 或 2，R_p 选自 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基或者五或六元杂芳基，并且 T_6 任选地被选自下列组的一个或多个取代基取代：卤素、C_1-C_6 烷基、羟基、氰基、C_1-C_6 烷氧基、氨基、单 $-C_1$-C_6 烷基氨基、双 $-C_1$-C_6 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基、五或六元杂芳基，T_6 为氢、卤素、羟基或氰基的情况除外；或 $-Q_6$-T_6 为氧代；以及

[0046] R_{14} 不存在或选自氢或任选地被选自下列组的一个或多个取代基取代的 C_1-C_6 烷基：卤素、羟基、羧基、$C(O)O$-C_1-C_6 烷基、氰基、C_1-C_6 烷氧基、氨基、单 $-C_1$-C_6 烷基氨基、

双 -C_1-C_6 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基和五或六元杂芳基。

[0047] 式 (I) 的化合物的一个子集包括式 (Ia) 的化合物。

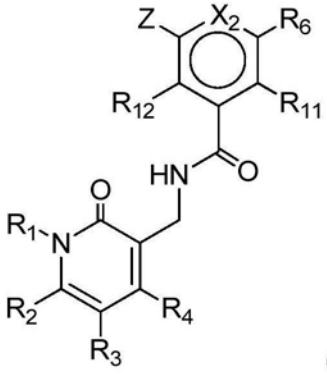
[0048]



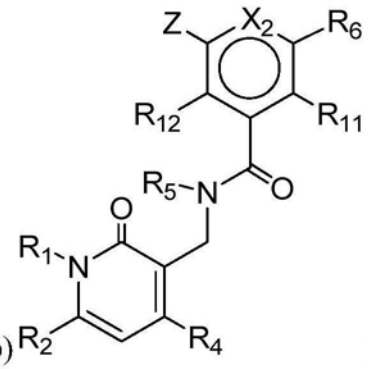
(Ia)

[0049] 式 (I) 的化合物的另一个子集包括式 (Ib)、(Ic) 或 (Id) 的化合物。

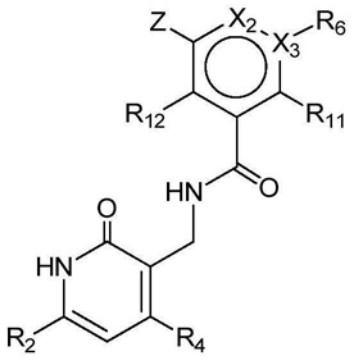
[0050]



(Ib)



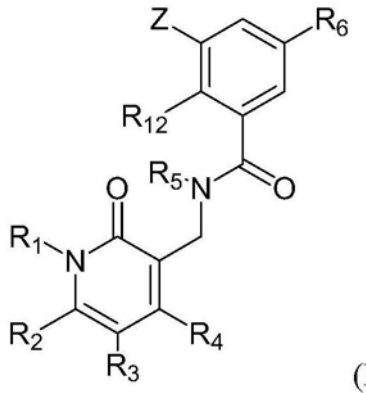
(Ic)



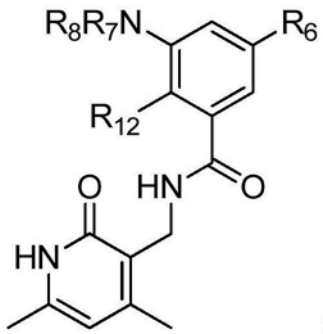
(Id)

[0051] 式 (I) 的化合物的其它子集还包括式 (Ie)、(II) 或 (IIA) 的化合物。

[0052]

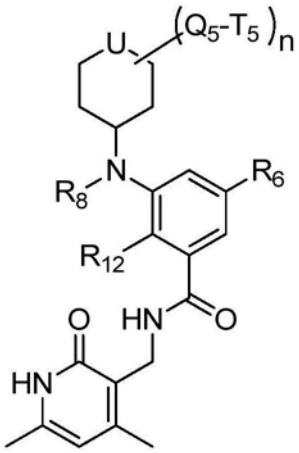


(Ie)



(II)

[0053]



(IIA)

[0054] 式 (I)、(Ia)、(Ib)、(Ic)、(Id)、(Ie)、(II) 和 (IIA) 的化合物可包含一个或多个下列特征：

[0055] X_1 是 CR_{11} 且 X_2 是 CR_{13}。

[0056] X_1 是 CR_{11} 且 X_2 是 N。

[0057] X_1 是 N 且 X_2 是 CR_{13}。

[0058] X_1 是 N 且 X_2 是 N。

[0059] Z 是 NR_7R_8。

[0060] Z 是 $CR_7R_8R_{14}$。

[0061] Z 是 OR_7。

[0062] Z 是 $S(O)_aR_7$，其中 a 是 0、1 或 2。

[0063] Z 是 SR_7。

[0064] R_6 选自卤素、C_1-C_3 烷基、C_2-C_6 烯基、C_3-C_6 环烷基、醛基或 $-C(O)R_a$，其中 R_a 是 C_1-C_6 烷基或 4-12 元(例如 4-7 元)杂环烷基。

[0065] R_6 是任选地被一个或多个 $-Q_2$-T_2 取代的 4-12 元(例如 4-7 元)杂环烷基，其中 $-Q_2$-T_2 是氧代或 Q_2 是键，并且 T_2 选自 C_1-C_6 烷基、$-OR_c$、$-NR_cR_d$、$-C(O)R_c$、$-C(O)OR_c$、$-S(O)_2R_c$ 或任选地被一个或多个 $-Q_3$-T_3 取代的 4-12 元(例如 4-7 元)杂环烷基。

[0066] $-Q_2$-T_2 不是氢。

[0067] Q_3 是键或 C_1-C_3 烷基连接体，并且 T_3 选自 C_1-C_3 烷基、OR_e、$-S(O)_2R_e$ 或 $-NR_eR_f$。

[0068] R_6 选自哌啶基、2,2,6,6- 四甲基哌啶基、1,2,3,6- 四氢哌啶基、2,2,6,6- 四甲基 -1,2,3,6- 四氢哌啶基、哌嗪基、吗啉基、四氢 -2H- 吡喃基、3,6- 二氢 -2H- 吡喃基或吡咯烷基。

[0069] R_6 选自氟、溴或氯。

[0070] R_7 不是氢。

[0071] R_7 是 C_1-C_6 烷基、C_3-C_8 环烷基或 4-14 元(例如 4-7 元)杂环烷基,每个任选地被一个或多个 $-Q_5$-T_5 取代。

[0072] R_7 选自哌啶基、四氢吡喃基、硫代环己烷基、氧杂环丁烷基、氮杂环丁烷基、吡咯烷基、1,4- 二氧杂螺 [4.5] 癸烷基、1- 氧杂螺 [4.5] 癸烷基、3'H- 螺 [环己烷 -1,1'- 异苯并呋喃]-3'- 酮 -4- 基、7'H- 螺 [环己烷 -1,5'- 呋喃 [3,4-b] 吡啶]-7' 酮 -4- 基、3'H- 螺 [环己烷 -1,1'- 呋喃 [3,4-c] 吡啶]-3'- 酮 -4- 基、1- 氮杂螺 [4.5] 癸烷 -2- 酮 -8- 基、环丁基、环戊基或环己基,每一个 R_7 任选地被一个或多个 $-Q_5$-T_5 取代。

[0073] T_5 选自氢、卤素、C_1-C_6 烷基、C_1-C_6 烷氧基、C_3-C_8 环烷基、C_6-C_{10} 芳基或 4-12 元(例如 4-7 元)杂环烷基。

[0074] Q_5 是键,且 T_5 选自 C_1-C_6 烷基、C_3-C_8 环烷基或 4-12 元(例如 4-7 元)杂环烷基。

[0075] Q_5 是键,且 T_5 选自氢、C_1-C_6 烷基、C_3-C_8 环烷基、4-12 元杂环烷基、五或六元杂芳基、氨基、单 -C_1-C_6 烷基氨基或双 -C_1-C_6 烷基氨基,T_5 任选被一个或多个选自下列组的取代基取代 :卤素、羟基、C_1-C_6 烷氧基或 C_3-C_8 环烷基。

[0076] Q_5 选自羰基、硫酰基或 NHC(O),且 T_5 选自 C_1-C_6 烷基、C_1-C_6 烷氧基、C_3-C_8 环烷基或 4-12 元(例如 4-7 元)杂环烷基。

[0077] Q_5 是 C_1-C_3 烷基连接体,且 T_5 是氢或 C_6-C_{10} 芳基。

[0078] Q_5 是 C_1-C_3 烷基连接体,且 T_5 是 C_3-C_8 环烷基,4-12 元(例如 4-7 元)杂环烷基或 $S(O)_qR_q$。

[0079] R_{11} 是氢。

[0080] R_7 是环戊基或环己基,每一个任选被一个 $-Q_5$-T_5 取代。

[0081] Q_5 是 NHC(O) 并且 T_5 是 C_1-C_6 烷基或 C_1-C_6 烷氧基。

[0082] R_7 是异丙基。

[0083] R_2 和 R_4 是各自独立为任选被 C_1-C_6 烷氧基取代的 C_1-C_3 烷基。

[0084] R_2 和 R_4 各自是甲基。

[0085] R_1 是氢。

[0086] R_{12} 是氢、甲基、乙基、乙烯基或卤素。

[0087] R_{12} 是甲基。

[0088] R_{12} 是乙基。

[0089] R_{12} 是乙烯基。

[0090] R_8 是氢、甲基或乙基。

[0091] R_8 是甲基。

[0092] R_8 是乙基。

[0093] R_8 是乙烯基或丙烯基。

[0094] R_8 是 4-12 元(例如 4-7 元)杂环烷基,如哌啶基或四氢吡喃基。

[0095] Z 是 NR_7R_8 或 $CR_7R_8R_{14}$，其中 R_7 和 R_8 连同它们所连接的原子形成选自下列组的环：哌啶基、吗啉基、哌嗪基、氮杂环丁烷基、吡咯烷基、2- 氧代 -5- 氮杂双环 [2.2.1] 庚烷 -5- 基、1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸烷基和环己烯基，每一个 Z 任选被一个 $-Q_6-T_6$ 取代。

[0096] R_{13} 是氢或甲基。

[0097] R_{13} 是氢。

[0098] R_3 是氢。

[0099] Z 是 NR_7R_8、OR_7 或 $S(O)_aR_7$；R_1 是氢或任选被一个或多个选自下列组的取代基取代的 C_1-C_6 烷基：羟基、C_1-C_6 烷氧基、氨基、单 -C_1-C_6 烷基氨基、双 -C_1-C_6 烷基氨基和 C_6-C_{10} 芳基；R_2 和 R_4 各自独立地为 $-Q_1-T_1$，其中 Q_1 是键或任选被一个或多个选自卤素和羟基取代的 C_1-C_3 烷基连接体，并且 T_1 选自氢、卤素或叠氮基；R_3 是氢或卤素；R_5 是氢或 C_1-C_6 烷基；R_6 是氢、卤素、氰基、叠氮基、OR_a、$-NR_aR_b$、$-C(O)NR_aR_b$、$-S(O)_bR_a$ 或 R_{S2}；其中 R_{S2} 是 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基或 4-12 元杂环烷基，其中 R_a 和 R_b 各自独立选自氢、C_1-C_6 烷基或 4-12 杂环烷基；或 R_a 和 R_b 连同它们所连接的氮原子形成含 0 或 1 个额外的杂原子的 4-12 元杂环烷基环；R_a、R_{S2} 和所述由 R_a 和 R_b 形成的 4-12 元杂环烷基环各自任选地被一个或多个 $-Q_2-T_2$ 取代，其中 Q_2 是键或 C_1-C_3 烷基连接体，T_2 选自氢、卤素、$-OR_c$、$-NR_cR_d$、$-C(O)OR_c$ 或 C_1-C_6 烷基，其中 R_c 和 R_d 各自独立为氢或 C_1-C_6 烷基，或 R_c 和 R_d 连同它们所连接的氮原子形成含 0 或 1 个额外的杂原子的、任选地被 C_1-C_6 烷基取代的 4-12 元杂环烷基环；R_7 是 $-Q_4-T_4$，其中 Q_4 是键或 C_1-C_4 烷基连接体，T_4 选自氢、C_1-C_6 烷基、C_3-C_8 环烷基、C_6-C_{10} 芳基、$C(O)-C_{1-6}$ 烷基、$C(O)-C_{3-6}$ 环烷基或 4-14 元杂环烷基，每一个 T_4 任选地被一个或多个 $-Q_5-T_5$ 取代；R_8 是氢、任选地被卤素或羟基或 C_1-C_6 烷氧基取代的 C_1-C_6 烷基、C_2-C_6 烯基、C_3-C_8 环烷基或 4-7 元杂环烷基；或 R_7 和 R_8 连同它们所连接的氮原子形成含 0-2 个额外的杂原子的 4-12 元杂环烷基环，且所述由 R_7 和 R_8 形成的 4-12 元杂环烷基环任选地被一个或多个 $-Q_6-T_6$ 取代；R_{12} 是卤素、C_1-C_6 烷氧基或任选地被卤素或 C_2-C_6 烯基取代的 C_1-C_6 烷基。

[0100] R_1 是氢或任选地被选自羟基、C_1-C_6 烷氧基和 C_6-C_{10} 芳基的取代基所取代一次或多次的 C_1-C_6 烷基；R_7 是 $-Q_4-T_4$，其中 Q_4 是键或 C_1-C_4 烷基连接体，T_4 选自 C_1-C_6 烷基、C_3-C_8 环烷基、C_6-C_{10} 芳基、$C(O)-C_1-C_6$ 烷基、$C(O)-C_3-C_6$ 环烷基、二氢吡喃基、四氢吡喃基、四氢噻喃基、哌啶基、吡咯烷基、氮杂环丁烷基和氧杂环丁烷基，每一个 T_4 各自独立地被一个或多个下列取代基取代：氧代和 $-Q_5-T_5$；R_8 是氢或 C_1-C_6 烷基、C_1-C_6 卤代烷基、C_2-C_6 烯基或 C_3-C_8 环烷基；R_{12} 选自卤素、C_1-C_6 烷基、C_1-C_6 卤代烷基或 C_1-C_6 烷氧基。

[0101] Z 是 NR_7R_8 或 SR_7；R_6 选自氢、卤素、氰基、OR_a、$-C(O)NR_aR_b$、$-S(O)_2R_a$ 或 R_{S2}；其中 R_{S2} 是 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基或 4-12 元杂环烷基，且其中 R_a 和 R_b 各自独立为氢或 C_1-C_6 烷基；或 R_a 和 R_b 连同它们所连接的氮原子形成含 0 或 1 个额外的杂原子的 4-12 元杂环烷基环；R_{S2} 和所述的由 R_a 和 R_b 形成的 4-12 元杂环烷基环各自任选地被 1 个或多个 $-Q_2-T_2$ 取代；其中 Q_2 是键或 C_1-C_3 烷基连接体，T_2 选自氢、卤素、$-OR_c$、$-NR_cR_d$、$-C(O)OC_1-C_6$ 烷基或 C_1-C_6 烷基，其中 R_c 和 R_d 各自独立为氢或 C_1-C_6 烷基，或 R_c 和 R_d 连同它们所连接的氮原子形成含 0 或 1 个额外的杂原子和含 0 或 1 个 C_1-C_6 烷基取代基的 4-12 元杂环烷基环；R_7 选自 C_1-C_6 烷基、C_3-C_8 环烷基、二氢吡喃基、四氢吡喃基、四氢噻喃基、哌啶基、吡咯烷基、氮杂环丁烷基和氧杂环丁烷基，每一个任选地被一个或多个独立地选自氧代和 $-Q_5-T_5$ 的取代基取代；R_{12} 是卤素或 C_1-C_6 烷基。

[0102] R_2、R_4 和 R_{12} 各自独立为 C_1-C_6 烷基，且 R_5 是氢。

[0103] R_7 选自环己基、二氢吡喃基、四氢吡喃基、四氢噻喃基、哌啶基、吡咯烷基、氮杂环丁烷基、氧杂环丁烷基、1,4- 二氧杂螺 [4.5] 癸烷 -8- 基、1- 氧杂螺 [4.5] 癸烷 -8- 基、3'H- 螺 [环己烷 -1,1'- 异苯并呋喃]-4- 基、7'H- 螺 [环己烷 -1,5'- 呋喃 [3,4-b] 吡啶]-4- 基、3'H- 螺 [环己烷 -1,1'- 呋喃 [3,4-c] 吡啶]-4- 基或 1- 氮杂螺 [4.5] 癸烷 -8- 基，每一个 R_7 任选地被一个或多个 $-Q_5$-T_5 取代。

[0104] Z 选自哌啶基、吗啉基、哌嗪基、氮杂环丁烷基、吡咯烷基、2- 氧杂 -5- 氮杂二环 [2.2.1] 庚烷 -5- 基，1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸烷 -8- 基和环己烯基，每一个 Z 任选地被一个 $-Q_6$-T_6 取代。

[0105] R_6 是卤素时，Z 是 $S(O)_aR_7$，其中 a 是 0、1 或 2，R_7 是 C_1-C_6 烷基、C_3-C_8 环烷基或 4-7 元杂环烷基，并且 R_7 任选地被一个或多个 $-Q_5$-T_5 取代。

[0106] R_6 是卤素时，Z 是 OR_7，其中 R_7 是任选地被一个或多个 $-Q_5$-T_5 取代 4-7 元的杂环烷基。

[0107] R_6 是 $-S(O)_bR_a$ 或叠氮基，其中 b 是 0、1 或 2，R_a 是 C_1-C_6 烷基或 C_3-C_8 环烷基；Z 是 NR_7R_8，其中 R_7 是 C_3-C_8 环烷基或 4-14 元杂环烷基，每一个 R_7 任选地被一个或多个 $-Q_5$-T_5 取代；R_8 是氢或 C_1-C_6 烷基。

[0108] R_6 是卤素时，Z 是 NR_7R_8 或 $CR_7R_8R_{14}$，其中 R_7 和 R_8 连同它们所连接的原子一起形成含 1-3 个杂原子的 4-11 元杂环烷基环或 C_3-C_8 环烷基，每一个任选地被一个或多个 $-Q_6$-T_6 取代。

[0109] U 是氧、硫、$N-Q_5$-T_5 或 $CH-Q_5$-T_5。

[0110] n 是 0、1 或 2。

[0111] R_{12} 是氯、溴或甲基。

[0112] 一个或多个 $-Q_5$-T_5 是氧代。

[0113] U 是 $CH-Q_5$-T_5 且 n 是 0。

[0114] 一个或多个 $-Q_6$-T_6 是氧代。

[0115] Q_6 是键或羰基，T_6 是 C_1-C_6 烷基或 C_1-C_6 烷氧基。

[0116] 本发明还提供了药物组合物，所述药物组合物包含一种或多种药学上可接受的载体和一种或多种选自本文描述的任意一种结构式的化合物，以及 N-(5-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基) 氨基甲酰)-2- 甲基苯基) 呋喃 -2- 甲酰胺、N,N'-(5-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基) 氨基甲酰)-1,3- 亚苯基) 二乙酰胺、N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-3- 特戊酰氨基苯甲酰胺、3-(3,4- 二氢 -2H- 苯并 [b][1,4] 二氧杂环庚烯 -7- 磺酰胺基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基) 苯甲酰胺、N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-3,5- 二甲氧基苯甲酰胺、N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-3,4,5 三甲氧基苯甲酰胺、3- 烯丙基 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-4,5- 二甲氧基苯甲酰胺、4-(2- 氨基 -2- 氧代乙氧基)-3- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-5- 甲氧基苯甲酰胺、3- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-4- 羟基 -5- 甲氧基苯甲酰胺和 3- 溴 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-5- 甲氧基 -4- 丙

氧基苯甲酰胺。

[0117] 本发明另一方面提供一种治疗或预防癌症的方法。该方法包括向需要治疗的受试者给予治疗有效量的一种或多种选自本文所描述的任意结构式的化合物，以及N-(5-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰)-2-甲基苯基)呋喃-2-甲酰胺、N,N'-(5-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰)-1,3-亚苯基)二乙酰胺、N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-特戊酰氨基苯甲酰胺、3-(3,4-二氢-2H-苯并[b][1,4]二氧杂环庚烯-7-磺酰胺基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基))苯甲酰胺、N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基))-3,5-二甲氧基苯甲酰胺、N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基))-3,4,5-三甲氧基苯甲酰胺、3-烯丙基-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基))-4,5-二甲氧基苯甲酰胺、4-(2-氨基-2-氧代乙氧基)-3-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-5-甲氧基苯甲酰胺，3-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-4-羟基-5-甲氧基苯甲酰胺和3-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-5-甲氧基-4-丙氧基苯甲酰胺。

[0118] 除非另有说明，有关治疗方法的任何描述包括化合物在用于提供如说明书中所描述的这种治疗或预防方法的用途，以及化合物在制备用于治疗或预防这样的疾病的药物中的用途。所述治疗包括治疗人类或非人类的动物，包括啮齿动物和其他疾病模型。

[0119] 例如，本方法包括向患有异常的H3-K27甲基化的癌症受试者给予治疗有效剂量的一个或多个本文所描述的结构式的化合物的步骤，其中该化合物抑制EZH2的组蛋白甲基转移酶活性，从而治疗癌症。异常的H3-K27甲基化的例子可包括在癌细胞染色质内的H3-K27二甲基化或三甲基化的全面增长和/或改变的分布。

[0120] 例如，所述癌症选自下列组的癌症：其过表达EZH2或其它PRC2亚基，包含H3-K27脱甲基酶例如UTX中的失去功能的突变，或过表达能够增加和/或去本土化EZH2活性的附属蛋白，如PHF19/PCL3（参阅Sneeringer et al.Proc Natl Acad Sci USA107(49):20980-5,2010）。

[0121] 例如，本方法包括向患有EZH2过表达的癌症受试者给予治疗有效剂量的一种或多种本文所描述的结构式的化合物的步骤，其中该化合物抑制EZH2的组蛋白甲基化酶活性，从而治疗癌症。

[0122] 例如，本方法包括向患有带有H3-K27脱甲基酶UTX失去功能的突变的癌症受试者给予治疗有效剂量的一种或多种本文所描述的结构式的化合物的步骤，其中该化合物抑制EZH2的组蛋白甲基化酶活性，从而治疗癌症。

[0123] 例如，本方法包括向过表达PRC2的附属组成(如PHF19/PCL3)的癌症受试者给予治疗有效剂量的一种或多种本文所描述的结构式的化合物的步骤，其中该化合物抑制EZH2的组蛋白甲基化转移酶活性，从而治疗癌症。

[0124] 在又一方面中，本发明涉及调节野生型EZH2的活性的方法，所述野生型EZH2是PRC2复合物中的可催化组蛋白H3上的赖氨酸27(H3-K27)的单基化至三甲基化的催化亚基。例如，本发明涉及在细胞内抑制EZH2活性的方法。该方法可在体内或体外进行。

[0125] 在又一个方面，本发明涉及一种抑制受试者中H3-K27向三甲基化H3-K27转化的

方法。本方法包括向受试者给予治疗有效剂量的一种或多种本文所描述的结构式的化合物，以抑制 EZH2 的组蛋白甲基化转移酶活性，从而抑制受试者体内的 H3-K27 向三甲基化 H3-K27 的转化。

[0126] 例如，本方法包括向表达 EZH2 的 Y641 突变体的癌症受试者给予治疗有效剂量的一种或多种本文所描述的结构式的化合物的步骤，其中该化合物抑制 EZH2 的组蛋白甲基化转移酶活性，从而治疗癌症。

[0127] 例如，所述癌症选自滤泡性淋巴癌和生发中心 B 细胞样 (GCB) 亚型的弥漫性大 B 细胞淋巴瘤 (DLBCL)。例如，该癌症是淋巴瘤、白血病或黑色素瘤。优选地，淋巴瘤是非霍奇金淋巴瘤、滤泡性淋巴瘤或弥漫性大 B 细胞淋巴瘤。或者，白血病是慢性髓性白血病 (CML)、急性髓性白血病、急性淋巴细胞白血病或混合谱系白血病。

[0128] 癌前疾病是骨髓增生异常综合症(MDS，原名叫白血病前期)。

[0129] 例如，癌症是一种血液癌症。

[0130] 例如，本方法包括向表达 EZH2 的 Y641 突变体的癌症受试者给予治疗有效剂量的一种或多种本文所描述的结构式的化合物的步骤，其中该化合物选择地抑制 EZH2 的 Y641 突变体的组蛋白甲基化转移酶活性，从而治疗癌症。

[0131] 例如，该方法进一步包括进行用来检测来自于癌症受试者的含有癌细胞的样品中的 EZH2 的 Y641 突变体的试验的步骤。

[0132] 在又一方面，本发明涉及调节野生型和突变型组蛋白甲基化转移酶 EZH2 的活性的方法，所述野生型 EZH2 是可催化组蛋白 H3 上的赖氨酸 27(H3-K27) 的单甲基化至三甲基化的 PRC2 复合物的催化亚基。例如，本发明涉及抑制细胞内 EZH2 的某些突变体形式的活性的方法。所述 EZH2 的突变体形式包括另一个氨基酸残基对野生型 EZH2 的酪氨酸 641 (Y641，也称 Tyr641)的替换。该方法包括使细胞与有效剂量的一种或多种本文描述的任何一个结构式化合物接触。所述方法可以在体内或体外进行。

[0133] 本发明的又一方面涉及抑制受试者体内的 H3-K27 向三甲基化 H3-K27 转化的方法。所述方法包括向表达 EZH2 的 Y641 突变体的受试者给予治疗有效剂量一种或多种本文描述的任何一个式的化合物，以抑制 EZH2 的组蛋白甲基化转移酶的活性，从而抑制受试者体内的 H3-K27 向三甲基化的 H3-K27 的转化。例如，被抑制的组蛋白甲基化转移酶活性是 EZH2 的 Y641 突变体的活性。例如，本发明化合物选择性地抑制 EZH2 的 Y641 突变体的组蛋白甲基化转移酶活性。例如，所述 EZH2 的 Y641 突变体选自下列组 :Y641C、Y641F、Y641H、Y641N 和 Y641S。

[0134] 抑制受试者体内的 H3-K27 向三甲基化 H3-K27 转化的方法同样可以包括在向表达 EZH2 的 Y641 突变体的受试者给予治疗有效剂量的一种或多种本文描述的任何一种式的化合物之前，对来自受试者的样本进行用来检测 EZH2 的 Y641 突变体的测试。例如，进行测试来检测 EZH2 的 Y641 突变体包括检测编码 EZH2 的 Y641 突变体的核酸的全基因组测序或目标区域测序。例如，进行测试来检测 EZH2 的 Y641 突变体包括使样品与一种特异结合具有 EZH2 的 Y641 突变体的特征的多肽或其片段的抗体接触。例如，进行测试来检测 EZH2 的 Y641 突变体包括使样品在非常严格的条件下与核酸探针接触，该核酸探针与编码具有 EZH2 的 Y641 突变体特征的多肽或其片段的核酸杂合。

[0135] 进一步地，本发明还涉及一种识别 EZH2 的 Y641 突变体的抑制剂的方法。该方法

包括步骤：使EZH2的一个孤立的Y641突变体与组蛋白底物、甲基基团供体和测试化合物结合，其中所述组蛋白底物包括选自下列组的H3-K27形式：未甲基化的H3-K27、单甲基化的H3-K27、二甲基化的H3-K27和它们的任意组合；以及进行用来检测组蛋白底物中的H3-K27的甲基化（例如三甲基化的H3-K27的形成）的测试，从而当在测试化合物存在下的H3-K27的甲基化（例如三甲基化的H3-K27的形成）少于在测试化合物不存在时的H3-K27的甲基化（例如三甲基化的H3-K27的形成）时，识别该测试化合物作为EZH2的Y641突变体的抑制剂。

[0136] 在一个实施例中，进行用来检测组蛋白底物中的H3-K27的甲基化的测试包括测量标记的甲基基团的结合。

[0137] 在一个实施例中，标记的甲基基团是同位素标记的甲基基团。

[0138] 在一个实施例中，进行用来检测组蛋白底物中的H3-K27的甲基化的测试包括使组蛋白底物与特异性结合在三甲基化的H3-K27上的抗体接触。

[0139] 识别EZH2的Y641突变体的选择性抑制剂的方法同样在本发明范围内。本方法包括步骤：使EZH2的孤立的Y641突变体同组蛋白底物、甲基基团供体和测试化合物结合，其中所述组蛋白底物包括选自下列组的H3-K27形式：单甲基化的H3-K27、双甲基化的H3-K27以及单甲基化的H3-K27和双甲基化的H3-K27的组合，从而形成测试混合物；使孤立的野生型EZH2同组蛋白底物、甲基基团供体和测试化合物结合，其中所述组蛋白底物包括选自下列组的H3-K27形式：单甲基化的H3-K27、双甲基化的H3-K27以及单甲基化的H3-K27和双甲基化的H3-K27的组合，从而形成对照混合物；进行用来检测每个测试混合物和对照混合物中组蛋白底物的三甲基化的测试；计算(a)用EZH2的Y641突变体和测试化合物的三甲基化(M+)与(b)用EZH2的Y641突变体而没有测试化合物的三甲基化(M-)的比值；计算(c)用野生型EZH2和测试化合物的三甲基化(WT+)与用(d)野生型EZH2而没有测试化合物的三甲基化(WT-)的比值；对比比值(a)/(b)与比值(c)/(d)；当比值(a)/(b)小于比值(c)/(d)时，识别该测试化合物作为EZH2的Y641突变体的选择性抑制剂。

[0140] 本发明进一步提供了识别作为可用一种或多种本发明化合物来治疗的候选者的受试者的方法。所述方法包括步骤：进行用来检测来自于受试者的样本中的EZH2的Y641突变体的测试；以及识别作为可用一种或多种本发明的化合物来治疗的表达EZH2的Y641突变体的候选者的受试者，其中该化合物抑制EZH2的组蛋白甲基化转移酶活性。

[0141] 本发明又一方面涉及一种抑制H3-K27向三甲基化H3-K27转化的方法。所述方法包括使EZH2的Y641突变体与蛋白底物接触的步骤，所述组蛋白底物包含H3-K27和有效剂量的本发明的化合物，其中所述化合物抑制EZH2的组蛋白甲基化转移酶活性，从而抑制H3-K27向三甲基化H3-K27的转化。

[0142] 进一步地，本文所述化合物或方法可用于研究（例如研究表观遗传酶）和其他非治疗的用途。

[0143] 除非另外特别说明，否则本文所述的所有的技术和科学术语均指本发明所属领域普通技术人员所通常理解的含义。在说明书中，除非上下文清楚地规定，否则单数形式也包括复数。虽然本文所述方法和材料的类似或等同替代物也可以应用在本发明的实践或检测中，但是下文只描述适宜的方法和材料。本文提到的所有的出版物、专利申请、专利和其它参考文献均通过引用而并入本文中。本文所引用的文献并不认为是本发明的现有技术。如

有冲突，以本说明书包括定义为准。此外，本文所述材料、方法和实施例仅意图说明本发明而非限制本发明。

[0144] 通过下面的详细描述和权利要求，本发明的其它特征和优点将变得显而易见。

附图说明

[0145] 图 1（A）是细胞计数（即细胞数量）作为时间的函数的理想图，其显示了细胞对数生长期期间的指数增殖。

[0146] 图 1（B）是对于图（A）中数据的 ln（细胞计数）作为时间的函数的理想图。

[0147] 图 2 是显示了在抗恶性细胞增生化合物存在下的两相细胞生长曲线的图，对于抗恶性细胞增生化合物在其对细胞生长的作用实现之前有延迟。该化合物在标记为“作用开始”的时间点开始影响细胞生长。实心圆表示对于没有用化合物处理的载剂（或溶剂）对照样品的理想化数据。其他符号表示对于以不同浓度的化合物（即药物）处理的细胞的两相生长曲线。

[0148] 图 3 是对于（A）细胞抑制化合物和（B）细胞毒性化合物的 k_p 作为化合物浓度的函数的重制图，显示了对细胞毒剂的 LCC 的绘图测定。注意：对细胞抑制化合物（图 A），k_p 值永远不能降到低于零。

[0149] 图 4 是显示了以化合物 222 处理了超过 27 天的 WSU-DLCL2 异种移植小鼠的肿瘤生长的图示。

[0150] 图 5 是显示了来源于以化合物 222 或载剂处理了 27 天的小鼠的 WSU-DLCL2 肿瘤中的局部 H3K27me3 甲基化的图示。

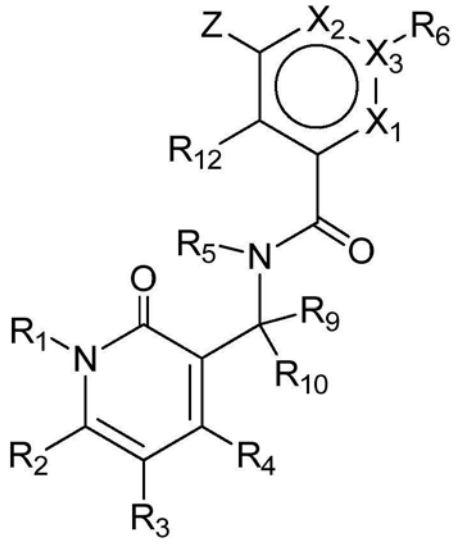
具体实施方式

[0151] 本发明提供了新颖的取代苯化合物、制备该化合物的合成方法、包含它们的药物组合物以及该化合物的各种用途。

[0152] 1. 取代苯化合物

[0153] 本发明提供式（I）的化合物：

[0154]



(I)

[0155] 在该式中：

[0156] X_1 是 N 或 CR_{11}；

[0157] X_2 是 N 或 CR_{13}；

[0158] X_3 是 N 或 C，且当 X_3 是 N 时，R_6 不存在；

[0159] Z 是 NR_7R_8、OR_7、$S(O)_aR_7$ 或 $CR_7R_8R_{14}$，其中 a 为 0、1 或 2；

[0160] R_1、R_5、R_9 和 R_{10} 各自独立为 H 或任选地被选自下列组的一个或多个取代基取代的 C_1-C_6 烷基：卤素、羟基、羧基、$C(O)O$-C_1-C_6 烷基、氰基、C_1-C_6 烷氧基、氨基、单 -C_1-C_6 烷基氨基、双 -C_1-C_6 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基和五或六元杂芳基；

[0161] R_2、R_3 和 R_4 各自独立为 -Q_1-T_1，其中 Q_1 为键或是任选地被一个或多个选自下列组的取代基取代的 C_1-C_3 烷基连接体：卤素、氰基、羟基或 C_1-C_6 烷氧基，T_1 选自氢、卤素、羟基、羧基、氰基、叠氮基或 R_{S1}，其中 R_{S1} 选自 C_1-C_3 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_1-C_6 烷氧基、$C(O)O$-C_1-C_6 烷基、C_3-C_8 环烷基、C_6-C_{10} 芳基、氨基、单 -C_1-C_6 烷基氨基、双 -C_1-C_6 烷基氨基、4-12 元杂环烷基和五或六元杂芳基，且 R_{S1} 任选地被一个或多个选自下列组的取代基取代：卤素、羟基、氧代、羧基、$C(O)O$-C_1-C_6 烷基、氰基、C_1-C_6 烷氧基、氨基、单 -C_1-C_6 烷基氨基、双 -C_1-C_6 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基和五或六元杂环芳基；

[0162] R_6 选自氢、卤素、氰基、叠氮基、OR_a、$-NR_aR_b$、$-C(O)R_a$、$-C(O)OR_a$、$-C(O)NR_aR_b$、$-NR_bC(O)R_a$、$-S(O)_bR_a$、$-S(O)_bNR_aR_b$ 或 R_{S2}，其中 R_{S2} 选自 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_3-C_8 环烷基或 4-12 元杂环烷基；b 是 0、1 或 2；R_a 和 R_b 各自独立为氢或 R_{S3}，其中 R_{S3} 选自 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基或者五元或六元杂环芳基；或 R_a 和 R_b，连同它们所连接的氮原子一起形成含 0 或 1 个额外杂原子的 4-12 元杂环烷基环；R_{S2}、R_{S3} 以及由 R_a 和 R_b 形成的 4-12 元杂环烷基环任选地被一个或多个 -Q_2-T_2 取代，其中 Q_2 为键或是任选地被下列取代基取代的 C_1-C_3 烷基连接体：卤素、氰基、羟基或 C_1-C_6 烷氧基；T_2 选自氢、卤素、氰基、$-OR_c$、$-NR_cR_d$、$-C(O)R_c$、$-C(O)OR_c$、$-C(O)NR_cR_d$、$-NR_dC(O)R_c$、$-NR_dC(O)OR_c$、$-S(O)_2R_c$、$-S(O)_2NR_cR_d$ 或 R_{S4}，其中 R_c 和 R_d 各自独立选自 H 或 R_{S5}，其中 R_{S4} 和 R_{S5} 各自独立选自 C_1-C_6 烷基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基或者五元或六元杂芳基，或 R_c 和 R_d 连同它们所连接的氮原子一起形成含 0 或 1 个额外杂原子的 4-12 元杂环烷基环，R_{S4}、

R_{S5} 以及由 R_c 和 R_d 形成的 4-12 元杂环烷基环任选地被一个或多个 $-Q_3-T_3$ 取代，其中 Q_3 是键或是任选地被下列取代基取代的 C_1-C_3 烷基连接体：卤素、氰基、羟基或 C_1-C_6 烷氧基，T_3 选自卤素、氰基、C_1-C_6 烷基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基、五元或六元杂芳基、OR_e、$COOR_e$、$-S(O)_2R_e$、$-NR_eR_f$ 和 $-C(O)NR_eR_f$，R_e 和 R_f 各自独立选自氢或 C_1-C_6 烷基，或 $-Q_3-T_3$ 为氧代；或 $-Q_2-T_2$ 为氧代；

[0163] R_7 是 $-Q_4-T_4$，其中 Q_4 为键、C_1-C_4 烷基连接体或 C_2-C_4 烯基连接体，每个连接体任选地被下列取代基取代：卤素、氰基、羟基或 C_1-C_6 烷氧基，T_4 选自氢、卤素、氰基、NR_gR_h、$-OR_g$、$-C(O)R_g$、$-C(O)OR_g$、$-C(O)NR_gR_h$、$-C(O)NR_gOR_h$、$-NR_gC(O)R_h$、$-S(O)_2R_g$ 或 R_{S6}，其中 R_g 和 R_h 各自独立地选自氢或 R_{S7}，R_{S6} 和 R_{S7} 各自独立地选自 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-14 元杂环烷基或者五或六元杂芳基，R_{S6} 和 R_{S7} 可任选地被一个或多个 $-Q_5-T_5$ 取代，其中 Q_5 是键、羰基、$C(O)NR_k$、$NR_kC(O)$、硫酰基或 C_1-C_3 烷基连接体，R_k 是氢或 C_1-C_6 烷基，T_5 选自氢、卤素、C_1-C_6 烷基、羟基、氰基、C_1-C_6 烷氧基、氨基、单 $-C_1-C_6$ 烷基氨基、双 $-C_1-C_6$ 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基、五或六元杂芳基或 $S(O)_qR_q$，其中 q 为 0、1 或 2，R_q 选自 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基或者五或六元杂芳基，T_5 任选地被选自下列组的一个或多个取代基取代：卤素、C_1-C_6 烷基、羟基、氰基、C_1-C_6 烷氧基、氨基、单 $-C_1-C_6$ 烷基氨基、双 $-C_1-C_6$ 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基和五或六元杂芳基，当 T_5 是氢、卤素、羟基或氰基时除外；或 $-Q_5-T_5$ 是氧代；

[0164] R_8、R_{11}、R_{12} 和 R_{13} 均各自独立选自氢、卤素、羟基、羧基、氰基、R_{S8}、OR_{S8} 或 $COOR_{S8}$，其中 R_{S8} 选自 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_3-C_8 环烷基、4-12 元杂环烷基、氨基、单 $-C_1-C_6$ 烷基氨基或双 $-C_1-C_6$ 烷基氨基，R_{S8} 任选地被选自下列组的一或多个取代基取代：卤素、羟基、羧基、$C(O)O-C_1-C_6$ 烷基、氰基、C_1-C_6 烷氧基、氨基、单 $-C_1-C_6$ 烷基氨基和双 $-C_1-C_6$ 烷基氨基；或 R_7 和 R_8 连同它们所连接的接的氮原子一起形成含 0-2 个额外杂原子的 4-12 杂环烷基环，或 R_7 和 R_8 连同它们所连接的碳原子一起形成 C_3-C_8 环烷基或含 1-3 个杂原子的 4-12 元杂环烷基环，所述的由 R_7 和 R_8 形成的 4-12 元杂环烷基环或 C_3-C_8 环烷基任选地被一个或多个 $-Q_6-T_6$ 取代，其中 Q_6 是键、羰基、$C(O)NR_m$、$NR_mC(O)$、硫酰基或 C_1-C_3 烷基连接体，R_m 为氢或 C_1-C_6 烷基，T_6 选自氢、卤素、C_1-C_6 烷基、羟基、氰基、C_1-C_6 烷氧基、氨基、单 $-C_1-C_6$ 烷基氨基、双 $-C_1-C_6$ 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基、五或六元杂芳基或 $S(O)_pR_p$，其中 p 是 0、1 或 2，R_p 选自 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基、五或六元杂芳基，T_6 任选地被选自下列组的一个或多个取代基取代：卤素、C_1-C_6 烷基、羟基、氰基、C_1-C_6 烷氧基、氨基、单 $-C_1-C_6$ 烷基氨基、双 $-C_1-C_6$ 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基、五或六元杂芳基，当 T_6 为氢、卤素、羟基或氰基时除外；或 $-Q_6-T_6$ 为氧代；以及

[0165] R_{14} 不存在或为氢或任选地被选自下列组的一个或多个取代基取代的 C_1-C_6 烷基：卤素、羟基、羧基、$C(O)O-C_1-C_6$ 烷基、氰基、C_1-C_6 烷氧基、氨基、单 $-C_1-C_6$ 烷基氨基、双 $-C_1-C_6$ 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基和五或六元杂芳基；

[0166] 条件是，所述化合物不是

[0167] N-(5-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰)-2-甲基苯基)呋喃-2-甲酰胺、N,N'-(5-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)

氨基甲酰)-1,3-亚苯基)二乙酰胺、N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-特戊酰基氨基苯甲酰胺、3-(3,4-二羟基-2H-苯并[b][1,4]二氧杂环庚烯-7-磺酰胺基)-N-((4,6-二甲基-2-氧代-1,2-二羟基吡啶-3-基)甲基)苯甲酰胺、N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3,5-二甲氧基苯甲酰胺、N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3,4,5-三甲氧基苯甲酰胺、3-烯丙基-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-4,5-二甲氧基苯甲酰胺、4-(2-氨基-2-氧代乙氧基)-3-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-5-甲氧基苯甲酰胺、3-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-4-羟基-5-甲氧基苯甲酰胺或3-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-5-甲氧基-4-丙氧基苯甲酰胺。

[0168] 例如，X_1 是 CR_{11} 且 X_2 是 CR_{13}。

[0169] 例如，X_1 是 CR_{11} 且 X_2 是 N。

[0170] 例如，X_1 是 N 且 X_2 是 CR_{13}。

[0171] 例如，X_1 是 N 且 X_2 是 N。

[0172] 例如，X_3 是碳。

[0173] 例如，X_3 是 N，R_6 不存在。

[0174] 例如，Z 是 NR_7R_8。

[0175] 例如，Z 是 $CR_7R_8R_{14}$。

[0176] 例如，Z 是 OR_7。

[0177] 例如，Z 是 $S(O)_aR_7$，其中 a 是 0、1 或 2。

[0178] 例如，Z 是 SR_7。

[0179] 例如，R_6 是氢。

[0180] 例如，R_6 是卤素(如氟、氯、溴、碘)。

[0181] 例如，R_6 是任选被一个或多个 $-Q_2-T_2$ 取代的 C_1-C_3 烷基。

[0182] 例如，R_6 是三氟甲基。

[0183] 例如，R_6 是 C_2-C_6 烯基、C_2-C_6 炔基或 C_3-C_6 环烷基，每一个任选被一个或多个 $-Q_2-T_2$ 取代。

[0184] 例如，R_6 是乙烯基。

[0185] 例如，R_6 是乙炔基。

[0186] 例如，R_6 是被一个或多个 $-Q_2-T_2$ 取代的乙炔基，其中 Q_2 是键或 C_1-C_3 烷基连接体，且 T_2 是 C_1-C_6 烷基、C_3-C_6 环烷基或任选被一个或多个 $-Q_3-T_3$ 取代的 4-7 元杂环烷基(例如氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、四氢呋喃基、哌啶基、1,2,3,6-四氢吡啶基、哌嗪基、四氢-2H-吡喃基、3,6-二氢-2H-吡喃基、四氢-2H-噻喃基、1,4-二氮杂环庚烷基、1,4-氧杂氮杂环庚烷基、2-氧杂-5-氮杂双环[2.2.1]庚烷基、2,5-二氮杂双环[2.2.1]庚烷基和吗啉基等)。

[0187] 例如，R_6 是叠氮基。

[0188] 例如，R_6 是氰基。

[0189] 例如，R_6 是醛基。

[0190] 例如，R_6 是 OR_a 或 $-C(O)R_a$。

[0191] 例如，R_a 是 C_1-C_6 烷基或 4-7 元杂环烷基(例如氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、四氢呋喃基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、四氢 -2H- 吡喃基、3,6- 二氢 -2H- 吡喃基、四氢 -2H- 噻喃基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基、2- 氧杂 -6- 氮杂螺 [3.3] 庚烷基、2,6- 二氮杂螺 [3.3] 庚烷基和吗啉基等)，所述 R_a 任选地被一个或多个 $-Q_2$-T_2 取代。

[0192] 例如，R_6 是任选被一个或多个 $-Q_2$-T_2 取代的 4-7 元杂环烷基(如，氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、四氢呋喃基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、四氢 -2H- 吡喃基、3,6- 二氢 -2H- 吡喃基、四氢 -2H- 噻喃基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基、2- 氧杂 -6- 氮杂螺 [3.3] 庚烷基、2,6- 二氮杂螺 [3.3] 庚烷基和吗啉基等)。

[0193] 例如，R_6 是哌啶基、2,2,6,6- 四甲基哌啶基、1,2,3,6- 四羟基哌啶基、2,2,6,6- 四甲基 -1,2,3,6- 四羟基哌啶基、哌嗪基、吗啉基、四氢 -2H- 吡喃基、3,6- 二氢 -2H- 吡喃基或吡咯烷基，其中每一个任选被一个或多个 $-Q_2$-T_2 取代。

[0194] 例如，R_6 是任选被一个或多个 $-Q_2$-T_2 取代的 4-7 元杂环烷基，并且 $-Q_2$-T_2 是氧代或 Q_2 是键且 T_2 是 $-OR_c$、$-NR_cR_d$、$-C(O)R_c$、$-C(O)OR_c$、$-S(O)_2R_c$、C_1-C_6 烷基或 4-7 元杂环烷基，当 R_c 或 R_d 不是氢时，每一个任选被一个或多个 $-Q_3$-T_3 取代。

[0195] 例 如，R_6 是 $-NR_aR_b$、$-C(O)R_a$、$-C(O)OR_a$、$-C(O)NR_aR_b$、$-NR_bC(O)R_a$、$-SR_a$、$-S(O)_2R_a$ 或 $-S(O)_2NR_aR_b$。

[0196] 例如，R_a 和 R_b 各自独立为氢、C_1-C_6 烷基或任选被一个或多个 $-Q_2$-T_2 取代的 C_3-C_8 环烷基。

[0197] 例如，R_a 和 R_b 其中之一为氢。

[0198] 例如，R_a 和 R_b 连同它们所连接的氮原子一起形成含 0 或 1 个除氮以外的额外杂原子的 4-7 元杂环烷基环(例如氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、四氢呋喃基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基、2- 氧杂 -6- 氮杂螺 [3.3] 庚烷基、2,6- 二氮杂螺 [3.3] 庚烷基和吗啉基等)，并且所述环任选被一个或多个 $-Q_2$-T_2 取代。

[0199] 例如，$-Q_2$-T_2 不是氢。

[0200] 例如，$-Q_2$-T_2 是氧代。

[0201] 例如，Q_2 是键。

[0202] 例如，Q_2 是未取代的 C_1-C_3 烷基连接体。

[0203] 例如，T_2 是 C_1-C_6 烷基或 C_6-C_{10} 芳基，每一个任选被一个或多个 $-Q_3$-T_3 取代。

[0204] 例如，T_2 是未被取代或被取代的直链 C_1-C_6 或支链 C_3-C_6 烷基，包括但不限于甲基、乙基、正丙基、异丙基、正丁基、仲丁基、叔丁基、正戊基、仲戊基和正己基。

[0205] 例如，T_2 是苯基。

[0206] 例如，T_2 是卤素(如氟、氯、溴、碘)。

[0207] 例如，T_2 是任选被一个或多个 $-Q_3$-T_3 取代的 4-7 元杂环烷基(如，氮杂环丁烷

基、氧杂环丁烷基、硫杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、四氢呋喃基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、四氢 -2H- 吡喃基、3,6- 二氢 -2H- 吡喃基、四氢 -2H- 噻喃基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基、2- 氧杂 -6- 氮杂螺 [3.3] 庚烷基、2,6- 二氮杂螺 [3.3] 庚烷基和吗啉基等)。

[0208] 例如，T_2 是 $-OR_c$、$-NR_cR_d$、$-C(O)R_c$、$-C(O)OR_c$ 或 $-S(O)_2R_c$。

[0209] 例如，R_c 是 C_1-C_6 烷基或 4-7 元杂环烷基(例如氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、四氢呋喃基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、四氢 -2H- 吡喃基、3,6- 二氢 -2H- 吡喃基、四氢 -2H- 噻喃基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基、2- 氧杂 -6- 氮杂螺 [3.3] 庚烷基、2,6- 二氮杂螺 [3.3] 庚烷基和吗啉基等)，任选地被一个或多个 $-Q_3$-T_3 取代的。

[0210] 例如，R_c 和 R_d 各自独立为氢或任选被一个或多个 $-Q_3$-T_3 取代的 C_1-C_6 烷基。

[0211] 例如，R_c 是氢。

[0212] 例如，R_d 是氢。

[0213] 例如，R_c 和 R_d 连同它们所连接的氮原子一起形成含 0 或 1 个除氮以外的额外杂原子的 4-7 元杂环烷基环(例如氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、四氢呋喃基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基、2- 氧杂 -6- 氮杂螺 [3.3] 庚烷基、2,6- 二氮杂螺 [3.3] 庚烷基和吗啉基等)，并且所述环任选被一个或多个 $-Q_3$-T_3 取代。

[0214] 例如，Q_2 是键并且 T_2 是 $-OR_c$、$-NR_cR_d$、$-C(O)R_c$、$-C(O)OR_c$、$-S(O)_2R_c$、C_1-C_6 烷基或 4-7 元杂环烷基，当 R_c 或 R_d 不为氢时，每一个任选被一个或多个 $-Q_3$-T_3 取代。

[0215] 例如，$-Q_3$-T_3 是氧代。

[0216] 例如，T_2 是 4-7 元杂环烷基或 C_3-C_8 环烷基，并且一个或多个 $-Q_3$-T_3 是氧代。

[0217] 例如，Q_3 是键或未被取代或被取代的 C_1-C_3 烷基连接体。

[0218] 例如，T_3 选自氢、卤素、4-7 元杂环烷基、C_1-C_3 烷基、OR_e、$COOR_e$、$-S(O)_2R_e$、$-NR_eR_f$ 或 $-C(O)NR_eR_f$。

[0219] 例如，R_d 和 R_e 其中之一为氢。

[0220] 例如，Q_3 是键或 C_1-C_3 烷基连接体，T_3 选自 C_1-C_3 烷基、卤素、OR_e、$-S(O)_2R_e$、$-NR_eR_f$ 和 $-C(O)NR_eR_f$。

[0221] 例如，Q_3 是键或 C_1-C_3 烷基连接体，T_3 选自 C_1-C_3 烷基、OR_e、$-S(O)_2R_e$ 或 $-NR_eR_f$。

[0222] 例如，R_e 是氢。

[0223] 例如，R_f 是氢。

[0224] 例如，R_7 不是氢。

[0225] 例如，R_7 是 $-C(O)R_g$。

[0226] 例如，R_7 是 $-C(O)R_g$，其中 R_g 是 C_3-C_8 环烷基或 4-7 元杂环烷基、C_3-C_8 环烷基。

[0227] 例如，R_7 是被一个或多个 $-Q_5$-T_5 取代的 C_6-C_{10} 芳基。

[0228] 例如，R_7 是任选被一个或多个 $-Q_5$-T_5 取代的苯基。

[0229] 例如，R_7 是任选被一个或多个 $-Q_5-T_5$ 取代的 C_1-C_6 烷基。

[0230] 例如，R_7 是任选被一个或多个 $-Q_5-T_5$ 取代的 C_3-C_8 环烷基。

[0231] 例如，R_7 是任选被一个或多个 $-Q_5-T_5$ 取代的 4-7 元杂环烷基(例如氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、四氢呋喃基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、四氢 -2H- 吡喃基、3,6- 二氢 -2H- 吡喃基、四氢 -2H- 噻喃基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基、2- 氧杂 -6- 氮杂螺 [3.3] 庚烷基、2,6- 二氮杂螺 [3.3] 庚烷基和吗啉基等)。

[0232] 例如，R_7 是 8-14 元杂环烷基，比如 1,4- 二氧杂螺 [4.5] 癸烷基(例如 1,4- 二氧杂螺 [4.5] 癸烷 -8- 基)、1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸烷基(例如 1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸烷 -8- 基)、1- 氧杂螺 [4.5] 癸烷基(例如 1- 氧杂螺 [4.5] 癸烷 -8- 基或 1- 氧杂螺 [4.5] 癸烷 -2- 酮 -8- 基)、1- 氮杂螺 [4.5] 癸烷基(例如 1- 氮杂螺 [4.5] 癸烷 -8- 基或 1- 氮杂螺 [4.5] 癸烷 -2- 酮 -8- 基)、3'H- 螺 [环己烷 -1,1'- 异苯并呋喃]- 基(例如 3'H- 螺 [环己烷 -1,1'- 异苯并呋喃]-4- 基或 3'H- 螺 [环己烷 -1,1'- 异苯并呋喃]-3'- 酮 -4- 基)、7'H- 螺 [环己烷 -1,5'- 呋喃并 [3,4-b] 吡啶]- 基(例如 7'H- 螺 [环己烷 -1,5'- 呋喃并 [3,4-b] 吡啶]-4- 基或 7'H- 螺 [环己烷 -1,5'- 呋喃并 [3,4-b] 吡啶]-7'- 酮 -4- 基)或 3'H- 螺 [环己烷 -1,1'- 呋喃并 [3,4-c] 吡啶]- 基(例如 3'H- 螺 [环己烷 -1,1'- 呋喃并 [3,4-c] 吡啶]-4- 基或 3'H- 螺 [环己烷 -1,1'- 呋喃并 [3,4-c] 吡啶]-3'- 酮 -4- 基)，每一个任选被一个或多个 $-Q_5-T_5$ 取代。

[0233] 例如，R_7 是任选被一个或多个 $-Q_5-T_5$. 取代的五或六元杂环烷基。

[0234] 例如，R_7 是异丙基。

[0235] 例如，R_7 是吡咯烷基、哌啶基、四氢吡喃基、环戊基或环己基、环庚基，每一个任选被一个 $-Q_5-T_5$ 取代。

[0236] 例如，R_7 是环戊基或环己基，每一个任选被一个 $-Q_5-T_5$ 取代。

[0237] 例如，Q_5 是 NHC(O)，T_5 是 C_1-C_6 烷基或 C_1-C_6 烷氧基。

[0238] 例如，$-Q_5-T_5$ 是氧代。

[0239] 例如，T_4 是 4-7 元杂环烷基或 C_3-C_8 环烷基或 C_6-C_{10} 芳基，并且一个或多个 $-Q_5-T_5$ 是氧代。

[0240] 例如，R_7 是 1- 氧化 - 四氢 -2H- 噻喃基或 1,1- 二氧化 - 四氢 -2H- 噻喃基。

[0241] 例如，R_7 是环己酮基，例如环己酮 -4- 基。

[0242] 例如，T_5 是氢、卤素、C_1-C_6 烷基、C_1-C_6 烷氧基、C_3-C_8 环烷基、C_6-C_{10} 芳基或 4-7 元杂环烷基。

[0243] 例如，Q_5 是键，T_5 是 C_1-C_6 烷基、C_3-C_8 环烷基或 4-7 元杂环烷基。

[0244] 例如，Q_5 是键，T_5 是五或六元杂芳基、氨基、单 -C_1-C_6 烷基氨基、双 -C_1-C_6 烷基氨基，T_5 任选被一个或多个选自下列组的取代基取代：卤素、羟基、C_1-C_6 烷氧基或 C_3-C_8 环烷基。

[0245] 例如，Q_5 是羰基、硫酰基或 NHC(O)；且 T_5 是 C_1-C_6 烷基、C_1-C_6 烷氧基、C_3-C_8 环烷基或 4-7 元杂环烷基。

[0246] 例如，T_5 是 C_1-C_6 烷基或 C_1-C_6 烷氧基，并任选被卤素、羟基、氰基、C_1-C_6 烷氧基、氨基、单 -C_1-C_6 烷基氨基、双 -C_1-C_6 烷基氨基或 C_3-C_8 环烷基取代。

[0247] 例如，Q_5 是 C_1-C_3 烷基连接体，且 T_5 是氢或 C_6-C_{10} 芳基。

[0248] 例如，Q_5 是 C_1-C_3 烷基连接体，且 T_5 是 C_3-C_8 环烷基、4-7 元杂环烷基或 $S(O)_qR_q$。

[0249] 例如，R_6 是卤素（例如氟、氯、溴、碘）并且 Z 是 $S(O)_aR_7$，其中 a 是 0、1 或 2，R_7 选自 C_1-C_6 烷基（例如甲基、乙基、正丙基、异丙基、丁基或叔丁基）、C_3-C_8 环烷基（例如环戊基、环己基或环庚基）或 4-14 元杂环烷基（例如氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、四氢呋喃基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、四氢 -2H- 吡喃基、3,6- 二氢 -2H- 吡喃、四氢 -2H- 噻喃基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基、吗啉基、1,4- 二氧杂螺 [4.5] 癸烷基、1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸烷基、1- 氧杂螺 [4.5] 癸烷基、1- 氮杂螺 [4.5] 癸烷基、3'H- 螺 [环己烷 -1,1'- 异苯并呋喃]- 基、7'H- 螺 [环己烷 -1,5'- 呋喃并 [3,4-b] 吡啶]- 基或 3'H- 螺 [环己烷 -1,1'- 呋喃并 [3,4-c] 吡啶]- 基等），并且 R_7 任选地被一个或多个 $-Q_5$-T_5 取代。

[0250] 例如，R_6 是卤素（例如氟、氯、溴、碘），并且 Z 是 OR_7，其中 R_7 是 4-14 元杂环烷基（例如氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、四氢呋喃基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、四氢 -2H- 吡喃基、3,6- 二氢 -2H- 吡喃、四氢 -2H- 噻喃基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基、吗啉基、1,4- 二氧杂螺 [4.5] 癸烷基、1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸烷基、1- 氧杂螺 [4.5] 癸烷基、1- 氮杂螺 [4.5] 癸烷基、3'H- 螺 [环己烷 -1,1'- 异苯并呋喃]- 基、7'H- 螺 [环己烷 -1,5'- 呋喃并 [3,4-b] 吡啶]- 基或 3'H- 螺 [环己烷 -1,1'- 呋喃并 [3,4-c] 吡啶]- 基等），并且 R_7 任选地被一个或多个 $-Q_5$-T_5 取代。

[0251] 例如，R_{11} 是氢。

[0252] 例如，R_2 和 R_4 各自独立为氢或任选被氨基、叠氮基、卤素、单 -C_1-C_6 烷基氨基、双 -C_1-C_6 烷基氨基或 C_6-C_{10} 芳基取代的 C_1-C_6 烷基。

[0253] 例如，R_2 和 R_4 各自独立为任选被 C_1-C_6 烷氧基取代的 C_1-C_3 烷基。

[0254] 例如，R_2 和 R_4 各自为甲基。

[0255] 例如，R_1 是氢。

[0256] 例如，R_1 是任选被叠氮基、卤素、氨基、单 -C_1-C_6 烷基氨基、双 -C_1-C_6 烷基氨基或 C_6-C_{10} 芳基取代的 C_1-C_6 烷基。

[0257] 例如，R_{12} 是氢、甲基、乙基、乙烯基或卤素。

[0258] 例如，R_{12} 是甲基。

[0259] 例如，R_{12} 是乙基或丙烯基。

[0260] 例如，R_{12} 是甲氧基。

[0261] 例如，R_{12} 是乙烯基。

[0262] 例如，R_8 是氢、甲基、乙基或乙烯基。

[0263] 例如，R_8 是甲基。

[0264] 例如，R_8 是乙基。

[0265] 例如，R_8 是丙基。

[0266] 例如，R_8 是乙烯基或丙烯基。

[0267] 例如，R_8 是被一个或多个下列组的取代基取代的 C_1-C_6 烷基：卤素（例如氟、氯、溴、碘）、羟基或 C_1-C_6 烷氧基。

[0268] 例如，R_8 是 4-7 元任选被取代的杂环烷基（例如氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、四氢呋喃基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、四氢 -2H- 吡喃基、3,6- 二氢 -2H- 吡喃、四氢 -2H- 噻喃基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基、2- 氧杂 -6- 氮杂螺 [3.3] 庚烷基、2,6- 二氮杂螺 [3.3] 庚烷基和吗啉基等）。

[0269] 例如，R_8 是哌啶基。

[0270] 例如，R_8 是 4-7 元任选被取代的杂环烷基，且 R_7 是 $-Q_4$-T_4，其中 Q_4 是键或 C_1-C_4 烷基连接体，T_4 是氢、C_1-C_6 烷基、C_3-C_8 环烷基或 4-7 元杂环烷基。

[0271] 例如，Z 是 NR_7R_8 或 $CR_7R_8R_{14}$，其中 R_7 和 R_8 连同它们所连接的原子一起形成含 1-3 个杂原子的 4-11 元杂环烷基环（例如氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、四氢呋喃基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、四氢 -2H- 吡喃基、3,6- 二氢 -2H- 吡喃、四氢 -2H- 噻喃基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基、2- 氧杂 -6- 氮杂螺 [3.3] 庚烷基、2,6- 二氮杂螺 [3.3] 庚烷基和吗啉基、1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸烷基等）或 C_3-C_8 环烷基，每一个任选被一个或多个 $-Q_6$-T_6 取代。

[0272] 例如，所述由 R_7 和 R_8 形成的环选自下列组：氮杂环庚烷基、吡唑烷基、哌嗪基、吗啉基、哌嗪基、1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸烷基和环己烯基，每一个任选被一个 $-Q_6$-T_6 取代。

[0273] 例如，Z 是 1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸烷基 -8- 基、吡咯烷 -2,5- 二酮 -1- 基或哌啶 -2,6- 二酮 -1- 基。

[0274] 例如，一个或多个 $-Q_6$-T_6 是氧代。

[0275] 例如，T_6 是氢、卤素、C_1-C_6 烷基、C_1-C_6 烷氧基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-7 元杂环烷基。

[0276] 例如，Q_6 是键，T_6 是 C_1-C_6 烷基，C_3-C_8 环烷基或 4-7 元杂环烷基。

[0277] 例如，Q_6 是羰基、硫酰基或 NHC(O)；并且 T_6 选自 C_1-C_6 烷基、C_1-C_6 烷氧基、C_3-C_8 环烷基或 4-7 元杂环烷基。

[0278] 例如，T_6 是 C_1-C_6 烷基或 C_1-C_6 烷氧基，每一个任选被卤素、羟基、氰基、C_1-C_6 烷氧基、氨基、单 -C_1-C_6 烷基氨基、双 -C_1-C_6 烷基氨基或 C_3-C_8 环烷基取代。

[0279] 例如，Q_6 是 C_1-C_3 烷基连接体且 T_6 是氢或 C_6-C_{10} 芳基。

[0280] 例如，Q_6 是 C_1-C_3 烷基连接体且 T_6 是 C_3-C_8 环烷基、4-7 元杂环烷基或 $S(O)_pR_p$。

[0281] 例如，R_p 和 R_q 各自独立为 C_1-C_6 烷基。

[0282] 例如，R_6 是 $-S(O)_bR_a$ 或叠氮基，其中 b 是 0、1 或 2，并且 R_a 是 C_1-C_6 烷基或 C_3-C_8 环烷基；且 Z 是 NR_7R_8，其中 R_7 是 C_3-C_8 环烷基（例如环戊基，环己基或环庚基）或 4-14 元杂环烷基（例如氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、四氢呋喃基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、四

氢 -2H- 吡喃基、3,6- 二氢 -2H- 吡喃、四氢 -2H- 噻喃基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基、吗啉基、1,4- 二氧杂螺 [4.5] 癸烷基、1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸烷基、1- 氧杂螺 [4.5] 癸烷基、1- 氮杂螺 [4.5] 癸烷基、3'H- 螺 [环己烷 -1,1'- 异苯并呋喃]- 基、7'H- 螺 [环己烷 -1,5'- 呋喃并 [3,4-b] 吡啶]- 基或 3'H- 螺 [环己烷 -1,1'- 呋喃并 [3,4-c] 吡啶]- 基等),每一个任选地被一个或多个 $-Q_5-T_5$ 取代 ;并且 R_8 是氢或 C_1-C_6 烷基(例如甲基、乙基、正丙基、异丙基、正丁基或叔丁基)。

[0283] 例如,R_6 是卤素(例如氟、氯、溴和碘),并且 Z 是 NR_7R_8 或 $CR_7R_8R_{14}$,其中 R_7 和 R_8 连同它们所连接的原子一起形成含 1-3 个杂原子的 4-11 杂环烷基环(例如氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、四氢呋喃基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、四氢 -2H- 吡喃基、3,6- 二氢 -2H- 吡喃、四氢 -2H- 噻喃基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基、吗啉基、2- 氧杂 -6- 氮杂螺 [3.3] 庚烷基、2,6- 二氮杂螺 [3.3] 庚烷基、1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸烷基、1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸烷 -8- 基、吡唑啉 -2,5- 二酮 -1- 基,哌啶 -2,6- 二酮 -1- 基等)或 C_3-C_8 环烷基,每一个任选被一个或多个 $-Q_6-T_6$ 取代。

[0284] 例如,R_{13} 是氢或甲基。

[0285] 例如,R_{13} 是氢。

[0286] 例如,R_3 是氢。

[0287] 例如,R_5、R_9 和 R_{10} 均为氢。

[0288] 另一方面,本发明的特征是提供上述式 (I) 的取代苯化合物或其药学上可接受的盐或酯,其中

[0289] X_1 是 N 或 CR_{11} ;

[0290] X_2 是 N 或 CR_{13} ;

[0291] X_3 是 N 或 C,且当 X_3 是 N 时,R_6 不存在。

[0292] Z 是 NR_7R_8、OR_7、$S(O)_aR_7$ 或 $CR_7R_8R_{14}$,其中 a 是 0、1 或 2;

[0293] R_1、R_5、R_9 和 R_{10} 各自独立为 H 或任选被一个或多个选自下组的取代基取代的 C_1-C_6 烷基 :卤素、羟基、羧基、$C(O)O$-C_1-C_6 烷基、氰基、C_1-C_6 烷氧基、氨基、单 -C_1-C_6 烷基氨基、双 -C_1-C_6 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基和五或六元杂芳基 ;

[0294] R_2、R_3 和 R_4 各自独立为 $-Q_1-T_1$,其中 Q_1 为键或任选被选自卤素、氰基、羟基或 C_1-C_6 烷氧基的取代基取代的 C_1-C_3 烷基连接体,T_1 选自氢、卤素、羟基、羧基、氰基、叠氮基或 R_{S1},其中 R_{S1} 选自 C_1-C_3 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_1-C_6 烷氧基、$C(O)O$-C_1-C_6 烷基、C_3-C_8 环烷基、C_6-C_{10} 芳基、氨基、单 -C_1-C_6 烷基氨基、双 -C_1-C_6 烷基氨基、4-12 元杂环烷基或者五或六元杂芳基,且 R_{S1} 任选地被一个或多个选自下列组的取代基取代 :卤素、羟基、氧代、羧基、$C(O)O$-C_1-C_6 烷基、氰基、C_1-C_6 烷氧基、氨基、单 -C_1-C_6 烷基氨基、双 -C_1-C_6 烷基氨基、C_6-C_{10} 芳基、4-12 元杂环烷基和五或六元杂环芳基 ;

[0295] R_6 选自氢、卤素、氰基、叠氮基、OR_a、$-NR_aR_b$、$-C(O)R_a$、$-C(O)OR_a$、$-C(O)NR_aR_b$、$-NR_bC(O)R_a$、$-S(O)_bR_a$、$-S(O)_bNR_aR_b$ 或 R_{S2},其中 R_{S2} 选自 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_3-C_8 环烷基或 4-12 元杂环烷基 ;b 是 0、1 或 2,R_a 和 R_b 各自独立为氢或 R_{S3},其中 R_{S3} 选自 C_1-C_6 烷基,

C_2-C_6 烯基，C_2-C_6 炔基，C_3-C_8 环烷基，C_6-C_{10} 芳基，4-12 元杂环烷基或者五元或六元杂环芳基；或 R_a 和 R_b 连同它们所连接的氮原子一起形成含 0 或 1 个额外杂原子的 4-12 元杂环烷环；每一个 R_{S2}、R_{S3} 以及所述 R_a 和 R_b 形成的 4-12 元杂环烷环任选地被一个或多个 $-Q_2-T_2$ 取代，其中 Q_2 为键或是任选地被下列取代基取代的 C_1-C_3 烷基连接体：卤素、氰基、羟基或 C_1-C_6 烷氧基，T_2 选自氢、卤素、氰基、$-OR_c$、$-NR_cR_d$、$-C(O)R_c$、$-C(O)OR_c$、$-C(O)NR_cR_d$、$-NR_dC(O)R_c$、$-NR_dC(O)OR_c$、$-S(O)_2R_c$、$-S(O)_2NR_cR_d$ 或 R_{S4}，其中 R_c 和 R_d 各自独立选自氢或 R_{S5}，其中 R_{S4} 和 R_{S5}，各自独立选自 C_1-C_6 烷基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基或者五元或六元杂芳基，或 R_c 和 R_d 连同它们所连接的氮原子一起形成含 0 或 1 个额外杂原子的 4-12 元杂环烷环，R_{S4}、R_{S5} 以及由 R_c 和 R_d 形成的 4-12 元杂环烷基环任选地被一个或多个 $-Q_3-T_3$ 取代，其中 Q_3 是键或是任选地被下列取代基取代的 C_1-C_3 烷基连接体：卤素、氰基、羟基或 C_1-C_6 烷氧基，T_3 选自卤素、氰基、C_1-C_6 烷基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基、五元或六元杂芳基、OR_e、$COOR_e$、$-S(O)_2R_e$、$-NR_eR_f$ 和 $-C(O)NR_eR_f$，R_e 和 R_f 各自独立地选自氢或 C_1-C_6 烷基，或 $-Q_3-T_3$ 为氧代；或 $-Q_2-T_2$ 为氧代；

[0296] R_7 是 $-Q_4-T_4$，其中 Q_4 为键、C_1-C_4 烷基连接体或 C_2-C_4 烯基连接体，每个连接体任选地被下列取代基取代：卤素、氰基、羟基或 C_1-C_6 烷氧基，T_4 选自氢、卤素、氰基、NR_gR_h、$-OR_g$、$-C(O)R_g$、$-C(O)OR_g$、$-C(O)NR_gR_h$、$-C(O)NR_gOR_h$、$-NR_gC(O)R_h$、$-S(O)_2R_g$ 或 R_{S6}，其中 R_g 和 R_h 各自独立地选自氢或 R_{S7}，R_{S6} 和 R_{S7} 各自独立地选自 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基或者五或六元杂芳基，R_{S6} 和 R_{S7} 可任选被一个或多个 $-Q_5-T_5$ 取代，其中 Q_5 是键、羰基、$C(O)NR_k$、$NR_kC(O)$、硫酰基或 C_1-C_3 烷基连接体，R_k 是氢或 C_1-C_6 烷基，T_5 选自氢、卤素、C_1-C_6 烷基、羟基、氰基、C_1-C_6 烷氧基、氨基、单 $-C_1$-C_6 烷基氨基、双 $-C_1$-C_6 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基、五或六元杂芳基或 $S(O)_qR_q$，其中 $_q$ 为 0、1 或 2，R_q 选自 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基或者五或六元杂芳基，T_5 任选地被选自下列组的一个或多个取代基取代：卤素、C_1-C_6 烷基、羟基、氰基、C_1-C_6 烷氧基、氨基、单 $-C_1$-C_6 烷基氨基、双 $-C_1$-C_6 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基和五或六元杂芳基，当 T_5 是氢、卤素、羟基或氰基时除外；或 $-Q_5-T_5$ 是氧代；假设 (i) 当 Z 是 NR_7R_8 时，R_7 不是 $C(O)R_g$ 或 $-S(O)_2R_g$；(ii) 当 Z 是 OR_7 时，R_7 不是 C_1-C_6 烷基以及 (iii) R_7 不是氢；

[0297] R_8、R_{11}、R_{12} 和 R_{13} 各自独立选自氢、卤素、羟基、羧基、氰基、R_{S8}、OR_{S8} 或 $COOR_{S8}$，其中 R_{S8} 选自 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_3-C_8 环烷基、4-12 元杂环烷基、氨基、单 $-C_1$-C_6 烷基氨基或双 $-C_1$-C_6 烷基氨基，且 R_{S8} 任选被选自下列组的一或多个取代基取代：卤素、羟基、羧基、$C(O)O$-C_1-C_6 烷基、氰基、C_1-C_6 烷氧基、氨基、单 $-C_1$-C_6 烷基氨基和双 $-C_1$-C_6 烷基氨基；或 R_7 和 R_8 连同它们所连接的氮原子一起形成含 0-2 个额外杂原子的 4-12 杂环烷基环，或 R_7 和 R_8 同它们所连接的碳原子一起形成 C_3-C_8 环烷基或一个含 1-3 个额外杂原子的 4-12 元杂环烷基环，每一个所述的 R_7 和 R_8 形成的 4-12 元杂环烷基环或 C_3-C_8 环烷基任选被一个或多个 $-Q_6-T_6$ 取代，其中 Q_6 是键、羰基、$C(O)NR_m$、$NR_mC(O)$、硫酰基或 C_1-C_3 烷基连接体，R_m 为氢或 C_1-C_6 烷基，T_6 选自氢、卤素、C_1-C_6 烷基、羟基、氰基、C_1-C_6 烷氧基、氨基、单 $-C_1$-C_6 烷基氨基、双 $-C_1$-C_6 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基、五或六元杂芳基或 $S(O)_pR_p$，其中 p 是 0、1 或 2，且 R_p 选自 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基、五或六元杂芳基，并且 T_6 任选地被选自下列组的一个或多个

取代基取代：卤素、C_1-C_6 烷基、羟基、氰基、C_1-C_6 烷氧基、氨基、单 -C_1-C_6 烷基氨基、双 -C_1-C_6 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基和五或六元杂芳基，T_6 是氢、卤素、羟基或氰基时情况除外；或 -Q_6-T_6 为氧代；并且

[0298] R_{14} 选自不存在、氢或任选地被选自下列组的一个或多个取代基取代的 C_1-C_6 烷基：卤素、羟基、羧基、C(O)O-C_1-C_6 烷基、氰基、C_1-C_6 烷氧基、氨基、单 -C_1-C_6 烷基氨基、双 -C_1-C_6 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基和五或六元杂芳基。

[0299] 例如，X_1 是 CR_{11} 且 X_2 是 CR_{13}。

[0300] 例如，X_1 是 CR_{11} 且 X_2 是 N。

[0301] 例如，X_1 是 N 且 X_2 是 CR_{13}。

[0302] 例如，X_1 是 N 且 X_2 是 N。

[0303] 例如，X_3 是碳。

[0304] 例如，X_3 是 N 且 R_6 不存在。

[0305] 例如，Z 是 NR_7R_8。

[0306] 例如，Z 是 $CR_7R_8R_{14}$。

[0307] 例如，Z 是 OR_7。

[0308] 例如，Z 是 $S(O)_aR_7$，其中 a 是 0、1 或 2。

[0309] 例如，Z 是 SR_7。

[0310] 例如，R_6 是氢。

[0311] 例如，R_6 是卤素(如氟、氯、溴、碘)。

[0312] 例如，R_6 是任选被一个或多个 -Q_2-T_2 取代的 C_1-C_3 烷基。

[0313] 例如，R_6 是三氟甲基。

[0314] 例如，R_6 是 C_2-C_6 烯基、C_2-C_6 炔基或 C_3-C_6 环烷基，每一个任选被一个或多个 -Q_2-T_2 取代。

[0315] 例如，R_6 是乙烯基。

[0316] 例如，R_6 是乙炔基。

[0317] 例如，R_6 是被一个或多个 -Q_2-T_2 取代的乙炔基，其中 Q_2 是键或 C_1-C_3 烷基连接体，且 T_2 是 C_1-C_6 烷基、C_3-C_6 环烷基或 4-7 元杂环烷基(如，氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、四氢呋喃基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、四氢 -2H- 吡喃基、3,6- 二氢 -2H- 吡喃基、四氢 -2H- 噻喃基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基和吗啉基等) 其任选地被一个或多个 -Q_3-T_3 取代。

[0318] 例如，R_6 是叠氮基。

[0319] 例如，R_6 是氰基。

[0320] 例如，R_6 是醛基。

[0321] 例如，R_6 是 -C(O)R_a。

[0322] 例如，R_a 是 C_1-C_6 烷基或 4-7 元杂环烷基 (例如氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、四氢呋喃基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、四氢 -2H- 吡喃基、3,6- 二氢 -2H- 吡喃基、

四氢 -2H- 噻喃基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基、2- 氧杂 -6- 氮杂螺 [3.3] 庚烷基、2,6- 二氮杂螺 [3.3] 庚烷基和吗啉基等),其任选被一个或多个 $-Q_2-T_2$ 取代。

[0323] 例如，R_6 是任选被一个或多个 $-Q_2-T_2$ 取代的 4-7 元杂环烷基(例如氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、四氢呋喃基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、四氢 -2H- 吡喃基、3,6- 二氢 -2H- 吡喃基、四氢 -2H- 噻喃基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基、2- 氧杂 -6- 氮杂螺 [3.3] 庚烷基、2,6- 二氮杂螺 [3.3] 庚烷基和吗啉基等)。

[0324] 例如，R_6 是哌啶基、2,2,6,6- 四甲基哌啶基、1,2,3,6- 四氢吡啶基、2,2,6,6- 四甲基 -1,2,3,6- 四氢吡啶基、哌嗪基、吗啉基、四氢 -2H- 吡喃基、3,6- 二氢 -2H- 吡喃基或吡咯烷基，其中每一个任选被一个或多个 $-Q_2-T_2$ 取代。

[0325] 例如，R_6 是任选被一个或多个 $-Q_2-T_2$ 取代的 4-7 元杂环烷基，并且 $-Q_2-T_2$ 是氧代或 Q_2 是键，且 T_2 是 $-OR_c$、$-NR_cR_d$、$-C(O)R_c$、$-C(O)OR_c$、$-S(O)_2R_c$、C_1-C_6 烷基或 4-7 元杂环烷基，当 R_c 或 R_d 不是氢时，其中每一个任选被一个或多个 $-Q_3-T_3$ 取代。

[0326] 例 如，R_6 是 $-NR_aR_b$、$-C(O)R_a$、$-C(O)OR_a$、$-C(O)NR_aR_b$、$-NR_bC(O)R_a$、$-SR_a$、$-S(O)_2R_a$ 或 $-S(O)_2NR_aR_b$。

[0327] 例如，R_a 和 R_b 各自独立为氢、C_1-C_6 烷基或任选被一个或多个 $-Q_2-T_2$ 取代的 C_3-C_8 环烷基。

[0328] 例如，R_a 和 R_b 其中之一为氢。

[0329] 例如，R_a 和 R_b 连同它们所连接的氮原子一起形成含 0 或 1 个除氮原子以外的额外杂原子的 4-7 元杂环烷基环(例如氮杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基、2- 氧杂 -6- 氮杂螺 [3.3] 庚烷基、2,6- 二氮杂螺 [3.3] 庚烷基和吗啉基等)，并且所述环任选被一个或多个 $-Q_2-T_2$ 取代。

[0330] 例如，$-Q_2-T_2$ 不是氢。

[0331] 例如，$-Q_2-T_2$ 是氧代。

[0332] 例如，Q_2 是键。

[0333] 例如，Q_2 是未取代的 C_1-C_3 烷基连接体。

[0334] 例如，T_2 是 C_1-C_6 烷基或 C_6-C_{10} 芳基，每一个任选被一个或多个 $-Q_3-T_3$ 取代。

[0335] 例如，T_2 是未被取代或被取代的直链 C_1-C_6 或支链 C_3-C_6 烷基，包括但不限于甲基、乙基、正丙基、异丙基、正丁基、仲丁基、叔丁基、正戊基、仲戊基和正己基。

[0336] 例如，T_2 是苯基。

[0337] 例如，T_2 是卤素(如氟、氯、溴、碘)。

[0338] 例如，T_2 是任选被一个或多个 $-Q_3-T_3$ 取代的 4-7 元杂环烷基(如 , 氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、四氢呋喃基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、四氢 -2H- 吡喃基、3,6- 二氢 -2H- 吡喃基、四氢 -2H- 噻喃基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧

杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基、2- 氧杂 -6- 氮杂螺 [3.3] 庚烷基、2,6- 二氮杂螺 [3.3] 庚烷基和吗啉基等)。

[0339] 例如，T_2 是 $-OR_c$、$-NR_cR_d$、$-C(O)R_c$、$-C(O)OR_c$ 或 $-S(O)_2R_c$。

[0340] 例如，R_c 是任选被一个或多个 $-Q_3-T_3$ 取代的 4-7 元杂环烷基(例如氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、四氢呋喃基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、四氢 -2H- 吡喃基、3,6- 二氢 -2H- 吡喃基、四氢 -2H- 噻喃基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基、2- 氧杂 -6- 氮杂螺 [3.3] 庚烷基、2,6- 二氮杂螺 [3.3] 庚烷基和吗啉基等)。

[0341] 例如，R_c 和 R_d 各自独立为氢或任选被一个或多个 $-Q_3-T_3$ 取代的 C_1-C_6 烷基。

[0342] 例如，R_c 是氢。

[0343] 例如，R_d 是氢。

[0344] 例如，R_c 和 R_d 连同它们所连接的氮原子一起形成含 0 或 1 个除氮以外的额外杂原子的 4-7 元杂环烷基环(例如氮杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、四氢呋喃基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基、2- 氧杂 -6- 氮杂螺 [3.3] 庚烷基、2,6- 二氮杂螺 [3.3] 庚烷基和吗啉基等)，并且所述环任选被一个或多个 $-Q_3-T_3$ 取代。

[0345] 例如，Q_2 是键，并且 T_2 是 $-OR_c$、$-NR_cR_d$、$-C(O)R_c$、$-C(O)OR_c$、$-S(O)_2R_c$、C_1-C_6 烷基或 4-7 元杂环烷基，当 R_c 或 R_d 不为氢时其中每一个任选被一个或多个 $-Q_3-T_3$ 取代。

[0346] 例如，$-Q_3-T_3$ 是氧代。

[0347] 例如，T_2 是 4-7 元杂环烷基或 C_3-C_8 环烷基，并且一个或多个 $-Q_3-T_3$ 是氧代。

[0348] 例如，Q_3 是键或未被取代或被取代的 C_1-C_3 烷基连接体。

[0349] 例如，T_3 是氢、卤素、4-7 元杂环烷基、C_1-C_3 烷基、OR_e、$COOR_e$、$-S(O)_2R_e$、$-NR_eR_f$ 或 $-C(O)NR_eR_f$。

[0350] 例如，R_d 和 R_e 其中之一为氢。

[0351] 例如，Q_3 是键或 C_1-C_3 烷基连接体，T_3 选自 C_1-C_3 烷基、卤素、OR_e、$-S(O)_2R_e$、$-NR_eR_f$、和 $-C(O)NR_eR_f$。

[0352] 例如，Q_3 是键或 C_1-C_3 烷基连接体，T_3 选自 C_1-C_3 烷基、OR_e、$-S(O)_2R_e$ 或 $-NR_eR_f$。

[0353] 例如，R_e 是氢。

[0354] 例如，R_f 是氢。

[0355] 例如，R_7 不是氢。

[0356] 例如，R_7 是 $-C(O)R_g$。

[0357] 例如，R_7 是 $-C(O)R_g$，其中 R_g 是 C_3-C_8 环烷基或 4-7 元杂环烷基、C_3-C_8 环烷基。

[0358] 例如，R_7 是被一个或多个 $-Q_5-T_5$ 取代的 C_6-C_{10} 芳基。

[0359] 例如，R_7 是任选被一个或多个 $-Q_5-T_5$ 取代的苯基。

[0360] 例如，R_7 是任选被一个或多个 $-Q_5-T_5$ 取代的 C_1-C_6 烷基。

[0361] 例如，R_7 是任选被一个或多个 $-Q_5-T_5$ 取代的 C_3-C_8 环烷基。

[0362] 例如，R_7 是任选被一个或多个 $-Q_5-T_5$ 取代的 4-7 元杂环烷基(例如氮杂环丁烷

基、氧杂环丁烷基、硫杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、四氢呋喃基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、四氢 -2H- 吡喃基、3,6- 二氢 -2H- 吡喃基、四氢 -2H- 噻喃基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基、2- 氧杂 -6- 氮杂螺 [3.3] 庚烷基、2,6- 二氮杂螺 [3.3] 庚烷基和吗啉基等)。

[0363] 例如,R_7 是 8-14 元杂环烷基,比如 1,4- 二氧杂螺 [4.5] 癸烷基(例如 1,4- 二氧杂螺 [4.5] 癸烷 -8- 基)、1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸烷基(例如 1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸烷 -8- 基)、1- 氧杂螺 [4.5] 癸烷基(例如 1- 氧杂螺 [4.5] 癸烷 -8- 基或 1- 氧杂螺 [4.5] 癸烷 -2- 酮 -8- 基)、1- 氮杂螺 [4.5] 癸烷基(例如 1- 氮杂螺 [4.5] 癸烷 -8- 基或 1- 氮杂螺 [4.5] 癸烷 -2- 酮 -8- 基)、3'H- 螺 [环己烷 -1,1'- 异苯并呋喃]- 基(例如 3'H- 螺 [环己烷 -1,1'- 异苯并呋喃]-4- 基或 3'H- 螺 [环己烷 -1,1'- 异苯并呋喃]-3'- 酮 -4- 基)、7'H- 螺 [环己烷 -1,5'- 呋喃并 [3,4-b] 吡啶]- 基(例如 7'H- 螺 [环己烷 -1,5'- 呋喃并 [3,4-b] 吡啶]-4- 基或 7'H- 螺 [环己烷 -1,5'- 呋喃并 [3,4-b] 吡啶]-7'- 酮 -4- 基)或 3'H- 螺 [环己烷 -1,1'- 呋喃并 [3,4-c] 吡啶]- 基(例如 3'H- 螺 [环己烷 -1,1'- 呋喃并 [3,4-c] 吡啶]-4- 基或 3'H- 螺 [环己烷 -1,1'- 呋喃并 [3,4-c] 吡啶]-3'- 酮 -4- 基),每一个任选被一个或多个 $-Q_5-T_5$ 取代。

[0364] 例如,R_7 是任选被一个或多个 $-Q_5-T_5$. 取代的五或六元杂环烷基。

[0365] 例如,R_7 是异丙基。

[0366] 例如,R_7 是吡咯烷基、哌啶基、四氢吡喃基、环戊基或环己基、环庚基,每一个任选被一个 $-Q_5-T_5$ 取代。

[0367] 例如,R_7 是环戊基或环己基,每一个任选被一个 $-Q_5-T_5$ 取代。

[0368] 例如,Q_5 是 NHC(O),T_5 是 C_1-C_6 烷基或 C_1-C_6 烷氧基。

[0369] 例如,$-Q_5-T_5$ 是氧代。

[0370] 例如,T_4 是 4-7 元杂环烷基或 C_3-C_8 环烷基或 C_6-C_{10} 芳基并且一个或多个 $-Q_5-T_5$ 是氧代。

[0371] 例如,R_7 是 1- 氧化 - 四氢 -2H- 噻喃基或 1,1- 二氧化 - 四氢 -2H- 噻喃基。

[0372] 例如,R_7 是环己酮基,例如环己酮 -4- 基。

[0373] 例如,T_5 是氢、卤素、C_1-C_6 烷基、C_1-C_6 烷氧基、C_3-C_8 环烷基、C_6-C_{10} 芳基或 4-7 元杂环烷基。

[0374] 例如,Q_5 是键,T_5 是 C_1-C_6 烷基、C_3-C_8 环烷基或 4-7 元杂环烷基。

[0375] 例如,Q_5 是键,T_5 是五或六元杂芳基、氨基、单 -C_1-C_6 烷基氨基、双 -C_1-C_6 烷基氨基,T_5 任选被一个或多个选自下列组的取代基取代 :卤素、羟基、C_1-C_6 烷氧基或 C_3-C_8 环烷基。

[0376] 例如,Q_5 是羰基、硫酰基或 NHC(O) ;且 T_5 是 C_1-C_6 烷基、C_1-C_6 烷氧基、C_3-C_8 环烷基或 4-7 元杂环烷基。

[0377] 例如,T_5 是 C_1-C_6 烷基或 C_1-C_6 烷氧基,每一个任选被卤素、羟基、氰基、C_1-C_6 烷氧基、氨基、单 -C_1-C_6 烷基氨基、双 -C_1-C_6 烷基氨基或 C_3-C_8 环烷基取代。

[0378] 例如,Q_5 是 C_1-C_3 烷基连接体,且 T_5 是氢或 C_6-C_{10} 芳基。

[0379] 例如,Q_5 是 C_1-C_3 烷基连接体,且 T_5 是 C_3-C_8 环烷基,4-7 元杂环烷基或 $S(O)_qR_q$。

[0380] 例如,R_6 是卤素(例如氟、氯、溴、碘) 并且 Z 是 $S(O)_aR_7$,其中 a 是 0,1 或 2,R_7 选

自 C_1-C_6 烷基(例如甲基、乙基、正丙基、异丙基、丁基或叔丁基)，C_3-C_8 环烷基(例如环戊基、环己基或环庚基)或 4-14 元杂环烷基(例如氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、四氢呋喃基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、四氢 -2H- 吡喃基、3,6- 二氢 -2H- 吡喃基、四氢 -2H- 噻喃基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基、吗啉基、1,4- 二氧杂螺 [4.5] 癸烷基、1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸烷基、1- 氧杂螺 [4.5] 癸烷基、1- 氮杂螺 [4.5] 癸烷基、3'H- 螺 [环己烷 -1,1'- 异苯并呋喃]- 基、7'H- 螺 [环己烷 -1,5'- 呋喃并 [3,4-b] 吡啶]- 基或 3'H- 螺 [环己烷 -1,1'- 呋喃并 [3,4-c] 吡啶]- 基等)，并且 R_7 任选地被一个或多个 $-Q_5$-T_5 取代。

[0381] 例如，R_6 是卤素(例如氟、氯、溴、碘)，并且 Z 是 OR_7，其中 R_7 是 4-14 元杂环烷基(例如氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、四氢呋喃基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、四氢 -2H- 吡喃基、3,6- 二氢 -2H- 吡喃基、四氢 -2H- 噻喃基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基、吗啉基、1,4- 二氧杂螺 [4.5] 癸烷基、1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸烷基、1- 氧杂螺 [4.5] 癸烷基、1- 氮杂螺 [4.5] 癸烷基、3'H- 螺 [环己烷 -1,1'- 异苯并呋喃]- 基、7'H- 螺 [环己烷 -1,5'- 呋喃并 [3,4-b] 吡啶]- 基或 3'H- 螺 [环己烷 -1,1'- 呋喃并 [3,4-c] 吡啶]- 基等)，并且 R_7 任选地被一个或多个 $-Q_5$-T_5 取代。

[0382] 例如，R_{11} 是氢。

[0383] 例如，R_2 和 R_4 各自独立为氢或任选被氨基、叠氮基、卤素、单 -C_1-C_6 烷基氨基、双 -C_1-C_6 烷基氨基或 C_6-C_{10} 芳基取代的 C_1-C_6 烷基。

[0384] 例如，R_2 和 R_4 各自独立为任选被 C_1-C_6 烷氧基取代的 C_1-C_3 烷基。

[0385] 例如，R_2 和 R_4 均为甲基。

[0386] 例如，R_1 是氢。

[0387] 例如，R_1 是氢或任选被叠氮基、卤素、氨基、单 -C_1-C_6 烷基氨基、双 -C_1-C_6 烷基氨基或 C_6-C_{10} 芳基取代的 C_1-C_6 烷基。

[0388] 例如，R_{12} 是氢、甲基、乙基、乙烯基或卤素。

[0389] 例如，R_{12} 是乙基或丙烯基。

[0390] 例如，R_{12} 是甲氧基。

[0391] 例如，R_{12} 是乙烯基。

[0392] 例如，R_8 是氢、甲基、乙基或乙烯基。

[0393] 例如，R_8 是甲基。

[0394] 例如，R_8 是乙基。

[0395] 例如，R_8 是丙基。

[0396] 例如，R_8 是乙烯基或丙烯基。

[0397] 例如，R_8 是任选被一个或多个下列组的取代基取代的 C_1-C_6 烷基：卤素(例如氟、氯、溴、碘)、羟基或 C_1-C_6 烷氧基。

[0398] 例如，R_8 是 4-7 元任选被取代的杂环烷基(例如氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、四氢呋

喃基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、四氢 -2H- 吡喃基、3,6- 二氢 -2H- 吡喃基、四氢 -2H- 噻喃基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基、2- 氧杂 -6- 氮杂螺 [3.3] 庚烷基、2,6- 二氮杂螺 [3.3] 庚烷基和吗啉基等)。

[0399] 例如，R_8 是哌啶基。

[0400] 例如，R_8 是 4-7 元任选被取代的杂环烷基，且 R_7 是 $-Q_4-T_4$，其中 Q_4 是键或 C_1-C_4 烷基连接体，T_4 是氢、C_1-C_6 烷基、C_3-C_8 环烷基或 4-7 元杂环烷基。

[0401] 例如，Z 是 NR_7R_8 或 $CR_7R_8R_{14}$，其中 R_7 和 R_8 连同它们所连接的原子一起形成含 1-3 个杂原子的 4-11 杂环烷基环(例如氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、四氢呋喃基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、四氢 -2H- 吡喃基、3,6- 二氢 -2H- 吡喃基、四氢 -2H- 噻喃基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基、2- 氧杂 -6- 氮杂螺 [3.3] 庚烷基、2,6- 二氮杂螺 [3.3] 庚烷基、吗啉基、1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸烷基等)或 C_3-C_8 环烷基，每一个任选被一个或多个 $-Q_6-T_6$ 取代。

[0402] 例如，所述由 R_7 和 R_8 形成的环选自下列组：氮杂环丁烷基、吡咯烷基、哌啶基、吗啉基、哌嗪基、1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸烷基和环己烯基，每一个任选被一个 $-Q_6-T_6$ 取代。

[0403] 例如，Z 是 1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸烷基 -8- 基、吡咯烷 -2,5- 二酮 -1- 基或哌啶 -2,6- 二酮 -1- 基。

[0404] 例如，一个或多个 $-Q_6-T_6$ 是氧代。

[0405] 例如，T_6 是氢、卤素、C_1-C_6 烷基、C_1-C_6 烷氧基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-7 元杂环烷基。

[0406] 例如，Q_6 是键，T_6 是 C_1-C_6 烷基，C_3-C_8 环烷基或 4-7 元杂环烷基。

[0407] 例如，Q_6 是羰基、硫酰基或 NHC(O)，并且 T_6 选自 C_1-C_6 烷基、C_1-C_6 烷氧基、C_3-C_8 环烷基或 4-7 元杂环烷基。

[0408] 例如，T_6 是 C_1-C_6 烷基或 C_1-C_6 烷氧基，每一个任选被卤素、羟基、氰基、C_1-C_6 烷氧基、氨基、单 -C_1-C_6 烷基氨基、双 -C_1-C_6 烷基氨基或 C_3-C_8 环烷基取代。

[0409] 例如，Q_6 是 C_1-C_3 烷基连接体且 T_6 是氢或 C_6-C_{10} 芳基。

[0410] 例如，Q_6 是 C_1-C_3 烷基连接体且 T_6 是 C_3-C_8 环烷基、4-7 元杂环烷基或 $S(O)_pR_p$。

[0411] 例如，R_p 和 R_q 各自独立为 C_1-C_6 烷基。

[0412] 例如，R_6 是 $-S(O)_bR_a$ 或叠氮基，其中 b 是 0、1 或 2，并且 R_a 是 C_1-C_6 烷基或 C_3-C_8 环烷基；且 Z 是 NR_7R_8，其中 R_7 是 C_3-C_8 环烷基(例如环戊基、环己基或环庚基)或 4-14 元杂环烷基(例如氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、四氢呋喃基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、四氢 -2H- 吡喃基、3,6- 二氢 -2H- 吡喃基、四氢 -2H- 噻喃基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基、吗啉基、1,4- 二氧杂螺 [4.5] 癸烷基、1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸烷基、1- 氧杂螺 [4.5] 癸烷基、1- 氮杂螺 [4.5] 癸烷基、3'H- 螺 [环己烷 -1,1'- 异苯并呋喃]- 基、7'H- 螺 [环己

烷-1,5'-呋喃并[3,4-b]吡啶]-基或3'H-螺[环己烷-1,1'-呋喃并[3,4-c]吡啶]-基等),每一个任选地被一个或多个 $-Q_5-T_5$ 取代;并且 R_8 是氢或 C_1-C_6 烷基(例如甲基、乙基、正丙基、异丙基、丁基或叔丁基)。

[0413] 例如,R_6 是卤素(例如氟、氯、溴和碘),并且 Z 是 NR_7R_8 或 $CR_7R_8R_{14}$,其中 R_7 和 R_8 连同它们所连接的原子一起形成含 1-3 个杂原子的 4-11 杂环烷基环(例如氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、四氢呋喃基、哌啶基、1,2,3,6-四氢吡啶基、哌嗪基、四氢-2H-吡喃基、3,6-二氢-2H-吡喃基、四氢-2H-噻喃基、1,4-二氮杂环庚烷基、1,4-氧杂氮杂环庚烷基、2-氧杂-5-氮杂双环[2.2.1]庚烷基、2,5-二氮杂双环[2.2.1]庚烷基、吗啉基、2-氧杂-6-氮杂螺[3.3]庚烷基、2,6-二氮杂螺[3.3]庚烷基、1,4-二氧杂-8-氮杂螺[4.5]癸烷基、1,4-二氧杂-8-氮杂螺[4.5]癸烷-8-基、吡咯烷-2,5-二酮-1-基,哌啶-2,6-二酮-1-基等)或 C_3-C_8 环烷基,每一个任选被一个或多个 $-Q_6-T_6$ 取代。

[0414] 例如,R_{13} 是氢或甲基。

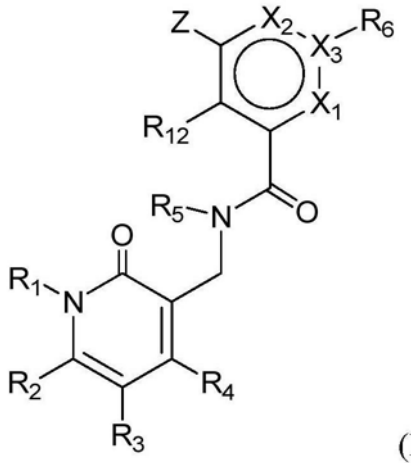
[0415] 例如,R_{13} 是氢。

[0416] 例如,R_3 是氢。

[0417] 例如,R_5、R_9 和 R_{10} 均为氢。

[0418] 本发明提供式(Ia)的化合物:

[0419]



(Ia),

[0420] 或其药学上可接受的盐或酯,其中

[0421] X_1 是 N 或 CR_{11};

[0422] X_2 是 N 或 CR_{13};

[0423] X_3 是 N 或 C,且当 X_3 是 N 时,R_6 不存在;

[0424] Z 是 NR_7R_8、OR_7、$S(O)_aR_7$ 或 $CR_7R_8R_{14}$,其中 a 是 0、1 或 2;

[0425] R_1 和 R_5 各自独立为 H 或任选被一个或多个选自下列组的取代基取代的 C_1-C_6 烷基:卤素、羟基、羧基、$C(O)O-C_1-C_6$ 烷基、氰基、C_1-C_6 烷氧基、氨基、单-C_1-C_6 烷基氨基、双-C_1-C_6 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基和五或六元杂芳基;

[0426] R_2、R_3 和 R_4 各自独立为 $-Q_1-T_1$,其中 Q_1 为键或任选被一个或多个选自卤素、氰基、羟基或 C_1-C_6 烷氧基的取代基取代的 C_1-C_3 烷基连接体,T_1 选自氢、卤素、羟基、羧基、氰基、叠氮基或 R_{S1},其中 R_{S1} 选自 C_1-C_3 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_1-C_6 烷氧基、$C(O)O-C_1-C_6$ 烷

基、C_3-C_8 环烷基、C_6-C_{10} 芳基、氨基、单 -C_1-C_6 烷基氨基、双 -C_1-C_6 烷基氨基、4-12 元杂环烷基和五或六元杂芳基，且 R_{S1} 任选地被一个或多个选自下列组的取代基取代：卤素、羟基、氧代、羧基、C(O)O-C_1-C_6 烷基、氰基、C_1-C_6 烷氧基、氨基、单 -C_1-C_6 烷基氨基、双 -C_1-C_6 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基和五或六元杂环芳基；

[0427] R_6 选自氢、卤素、氰基、叠氮基、OR_a、$-NR_aR_b$、$-C(O)R_a$、$-C(O)OR_a$、$-C(O)NR_aR_b$、$-NR_bC(O)R_a$、$-S(O)_bR_a$、$-S(O)_bNR_aR_b$ 或 R_{S2}，其中 R_{S2} 选自 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_3-C_8 环烷基或 4-12 元杂环烷基，b 是 0、1 或 2，R_a 和 R_b 各自独立为氢或 R_{S3}，其中 R_{S3} 选自 C_1-C_6 烷基，C_2-C_6 烯基，C_2-C_6 炔基，C_3-C_8 环烷基，C_6-C_{10} 芳基，4-12 元杂环烷基或者五元或六元杂环芳基；或 R_a 和 R_b 连同它们所连接的氮原子一起形成含 0 或 1 个额外杂原子的 4-12 元杂环烷环；每一个 R_{S2}、R_{S3} 以及所述由 R_a 和 R_b 形成的 4-12 元杂环烷环任选地被一个或多个 -Q_2-T_2 取代，其中 Q_2 为键或是任选被下列取代基取代的 C_1-C_3 烷基连接体：卤素、氰基、羟基或 C_1-C_6 烷氧基，T_2 选自氢、卤素、氰基、$-OR_c$、$-NR_cR_d$、$-C(O)R_c$、$-C(O)OR_c$、$-C(O)NR_cR_d$、$-NR_dC(O)R_c$、$-NR_dC(O)OR_c$、$-S(O)_2R_c$、$-S(O)_2NR_cR_d$ 或 R_{S4}，其中 R_c 和 R_d 各自独立为氢或 R_{S5}，其中 R_{S4} 和 R_{S5} 各自独立地选自 C_1-C_6 烷基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基或者五元或六元杂芳基，或 R_c 和 R_d 连同它们所连接的氮原子一起形成含 0 或 1 个额外杂原子的 4-12 元杂环烷环，每一个 R_{S4}、R_{S5} 以及所述由 R_c 和 R_d 形成的 4-12 元杂环烷基环任选地被一个或多个 -Q_3-T_3 取代，其中 Q_3 是键或是任选被选自卤素、氰基、羟基或 C_1-C_6 烷氧基的取代基取代的 C_1-C_3 烷基连接体，T_3 选自下列组的取代基：卤素、氰基、C_1-C_6 烷基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基、五元或六元杂芳基、OR_e、$COOR_e$、$-S(O)_2R_e$、$-NR_eR_f$ 和 $-C(O)NR_eR_f$，每一个 R_e 和 R_f 各自独立为氢或 C_1-C_6 烷基，或 -Q_3-T_3 为氧代；或 -Q_2-T_2 为氧代；或者

[0428] R_6 选自氢、卤素、氰基、叠氮基、$-NR_aR_b$、$-C(O)R_a$、$-C(O)OR_a$、$-C(O)NR_aR_b$、$-NR_bC(O)R_a$、$-S(O)_bR_a$、$-S(O)_bNR_aR_b$ 或 R_{S2}，其中 R_{S2} 选自 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_3-C_8 环烷基或 4-12 元杂环烷基，b 是 0、1 或 2，R_a 和 R_b 各自独立为氢或 R_{S3}，其中 R_{S3} 选自 C_1-C_6 烷基，C_2-C_6 烯基，C_2-C_6 炔基，C_3-C_8 环烷基，C_6-C_{10} 芳基，4-12 元杂环烷基或者五元或六元杂环芳基；或 R_a 和 R_b 连同它们所连接的氮原子一起形成含 0 或 1 个额外杂原子的 4-12 元杂环烷环；每一个 R_{S2}、R_{S3} 以及所述由 R_a 和 R_b 形成的 4-12 元杂环烷环任选地被一个或多个 -Q_2-T_2 取代，其中 Q_2 为键或是任选被下列取代基取代的 C_1-C_3 烷基连接体：卤素、氰基、羟基或 C_1-C_6 烷氧基，T_2 选自氢、卤素、氰基、$-OR_c$、$-NR_cR_d$、$-C(O)R_c$、$-C(O)OR_c$、$-C(O)NR_cR_d$、$-NR_dC(O)R_c$、$-NR_dC(O)OR_c$、$-S(O)_2R_c$、$-S(O)_2NR_cR_d$ 或 R_{S4}，其中 R_c 和 R_d 各自独立为氢或 R_{S5}，其中 R_{S4} 和 R_{S5} 各自独立地选自 C_1-C_6 烷基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基或者五元或六元杂芳基，或 R_c 和 R_d 连同它们所连接的氮原子一起形成含 0 或 1 个额外杂原子的 4-12 元杂环烷环，每一个 R_{S4}、R_{S5} 以及所述由 R_c 和 R_d 形成的 4-12 元杂环烷基环任选地被一个或多个 -Q_3-T_3 取代，其中 Q_3 是键或是任选被选自卤素、氰基、羟基或 C_1-C_6 烷氧基的取代基取代的 C_1-C_3 烷基连接体，T_3 选自下列组的取代基：卤素、氰基、C_1-C_6 烷基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基、五元或六元杂芳基、OR_e、$COOR_e$、$-S(O)_2R_e$、$-NR_eR_f$ 和 $-C(O)NR_eR_f$，每一个 R_e 和 R_f 各自独立为氢或 C_1-C_6 烷基，或 -Q_3-T_3 为氧代；或 -Q_2-T_2 为氧代；

[0429] R_7 是 -Q_4-T_4，其中 Q_4 为键、C_1-C_4 烷基连接体或 C_2-C_4 烯基连接体，每个连接体任选被下列取代基取代：卤素、氰基、羟基或 C_1-C_6 烷氧基，T_4 选自氢、卤素、氰基、NR_gR_h、$-OR_g$、$-C(O)R_g$、$-C(O)OR_g$、$-C(O)NR_gR_h$、$-C(O)NR_gOR_h$、$-NR_gC(O)R_h$、$-S(O)_2R_g$ 或 R_{S6}，其中 R_g

和 R_h 各自独立地选自氢或 R_{S7}，R_{S6} 和 R_{S7} 各自独立地选自 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-14 元杂环烷基或者五或六元杂芳基，R_{S6} 和 R_{S7} 各自任选被一个或多个 $-Q_5$-T_5 取代，其中 Q_5 是键、羰基、$C(O)NR_k$、$NR_kC(O)$、硫酰基或 C_1-C_3 烷基连接体，R_k 是氢或 C_1-C_6 烷基，T_5 选自氢、卤素、C_1-C_6 烷基、羟基、氰基、C_1-C_6 烷氧基、氨基、单 $-C_1$-C_6 烷基氨基、双 $-C_1$-C_6 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基、五或六元杂芳基或 $S(O)_qR_q$，其中 $_q$ 为 0、1 或 2 且 R_q 选自 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基或者五或六元杂芳基，T_5 任选被选自下列组的一个或多个取代基取代：卤素、C_1-C_6 烷基、羟基、氰基、C_1-C_6 烷氧基、氨基、单 $-C_1$-C_6 烷基氨基、双 $-C_1$-C_6 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基和五或六元杂芳基，T_5 是氢、卤素、羟基或氰基时的情况除外；或 $-Q_5$-T_5 是氧代；或

[0430] R_7 是 $-Q_4$-T_4，其中 Q_4 为键、C_1-C_4 烷基连接体或 C_2-C_4 烯基连接体，每个连接体任选被下列取代基取代：卤素、氰基、羟基或 C_1-C_6 烷氧基，T_4 选自氢、卤素、氰基、NR_gR_h、$-OR_g$、$-C(O)R_g$、$-C(O)OR_g$、$-C(O)NR_gR_h$、$-C(O)NR_gOR_h$、$-NR_gC(O)R_h$、$-S(O)_2R_g$ 或 R_{S6}，其中 R_g 和 R_h 各自独立地选自氢或 R_{S7}，R_{S6} 和 R_{S7} 各自独立地选自 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基或者五或六元杂芳基，R_{S6} 和 R_{S7} 各自任选被一个或多个 $-Q_5$-T_5 取代，其中 Q_5 是键、羰基、$C(O)NR_k$、$NR_kC(O)$、硫酰基或 C_1-C_3 烷基连接体，R_k 是氢或 C_1-C_6 烷基，T_5 选自氢、卤素、C_1-C_6 烷基、羟基、氰基、C_1-C_6 烷氧基、氨基、单 $-C_1$-C_6 烷基氨基、双 $-C_1$-C_6 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基、五或六元杂芳基或 $S(O)_qR_q$，其中 $_q$ 为 0、1 或 2 且 R_q 选自 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基或者五或六元杂芳基，T_5 任选被选自下列组的一个或多个取代基取代：卤素、C_1-C_6 烷基、羟基、氰基、C_1-C_6 烷氧基、氨基、单 $-C_1$-C_6 烷基氨基、双 $-C_1$-C_6 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基和五或六元杂芳基，T_5 是氢、卤素、羟基或氰基时情况除外；或 $-Q_5$-T_5 是氧代；条件是 (i) 当 Z 是 NR_7R_8 时，R_7 不是 $C(O)R_g$ 或 $-S(O)2R_g$；(ii) 当 Z 是 OR_7 时，R_7 不是 C_1-C_6 烷基，以及 (iii) R_7 不是氢；

[0431] R_8、R_{11}、R_{12} 和 R_{13} 各自独立地选自氢、卤素、羟基、羧基、氰基、R_{S8}、OR_{S8} 或 $COOR_{S8}$，其中 R_{S8} 选自 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_3-C_8 环烷基、4-12 元杂环烷基、氨基、单 $-C_1$-C_6 烷基氨基或双 $-C_1$-C_6 烷基氨基，且 R_{S8} 任选被选自下列组的一个或多个取代基取代：卤素、羟基、羧基、$C(O)O$-C_1-C_6 烷基、氰基、C_1-C_6 烷氧基、氨基、单 $-C_1$-C_6 烷基氨基和双 $-C_1$-C_6 烷基氨基；或 R_7 和 R_8 连同它们所连接的氮原子一起构成一个含 0-2 个额外杂原子的 4-12 元杂环烷基环，或 R_7 和 R_8 连同它们所连接的碳原子一起构成一个 C_3-C_8 环烷基或一个含 1-3 个杂原子的 4-12 元杂环烷基环，每一个所述的由 R_7 和 R_8 形成的 4-12 元杂环烷基环或 C_3-C_8 环烷基任选被一个或多个 $-Q_6$-T_6 取代，其中 Q_6 是键、羰基、$C(O)NR_m$、$NR_mC(O)$、硫酰基或 C_1-C_3 烷基连接体，R_m 为氢或 C_1-C_6 烷基，T_6 选自氢、卤素、C_1-C_6 烷基、羟基、氰基、C_1-C_6 烷氧基、氨基、单 $-C_1$-C_6 烷基氨基、双 $-C_1$-C_6 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基、五或六元杂芳基或 $S(O)_pR_p$，其中 p 是 0、1 或 2，且 R_p 选自 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基、五或六元杂芳基，并且 T_6 任选地被选自下列组的一个或多个取代基取代：卤素、C_1-C_6 烷基、羟基、氰基、C_1-C_6 烷氧基、氨基、单 $-C_1$-C_6 烷基氨基、双 $-C_1$-C_6 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基和五或六元杂芳基，T_6 是氢、卤素、羟基或氰基时的情况除外；或 $-Q_6$-T_6 为氧代；并且

[0432] R_{14} 不存在或为氢或任选地被选自下列组的一个或多个取代基取代的 C_1-C_6 烷基：卤素、羟基、羧基、C(O)O-C_1-C_6 烷基、氰基、C_1-C_6 烷氧基、氨基、单 -C_1-C_6 烷基氨基、双 -C_1-C_6 烷基氨基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-12 元杂环烷基和五或六元杂芳基；

[0433] 条件是，所述化合物不是

[0434] N-(5-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）氨基甲酰）-2- 甲基苯基）呋喃 -2- 甲酰胺、N,N'-(5-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）氨基甲酰）-1,3- 亚苯基）二乙酰胺、N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-3- 特戊酰基氨基苯甲酰胺、3-(3,4- 二羟基 -2H- 苯并 [b][1,4] 二氧杂环庚烯 -7- 磺酰胺基）-N-((4,6- 二甲基 -2- 氧代 -1,2- 二羟基吡啶 -3- 基）甲基）苯甲酰胺、N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-3,5- 二甲氧基苯甲酰胺、N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-3,4,5- 三甲氧基苯甲酰胺、3- 烯丙基 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-4,5- 二甲氧基苯甲酰胺、4-(2- 氨基 -2- 氧代乙氧基）-3- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-5- 甲氧基苯甲酰胺、3- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-4- 羟基 -5- 甲氧基苯甲酰胺或 3- 溴 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-5- 甲氧基 -4- 丙氧基苯甲酰胺。

[0435] 例如，X_1 是 CR_{11} 且 X_2 是 CR_{13}。

[0436] 例如，X_1 是 CR_{11} 且 X_2 是氮。

[0437] 例如，X_1 是 N 且 X_2 是 CR_{13}。

[0438] 例如，X_1 是 N 且 X_2 是 N。

[0439] 例如，X_3 是 C。

[0440] 例如，X_3 是 N 且 R_6 不存在。

[0441] 例如，Z 是 NR_7R_8。

[0442] 例如，Z 是 $CR_7R_8R_{14}$。

[0443] 例如，Z 是 OR_7。

[0444] 例如，Z 是 $S(O)_aR_7$，其中 a 是 0、1 或 2。

[0445] 例如，Z 是 SR_7。

[0446] 例如，R_6 是氢。

[0447] 例如，R_6 是卤素（如氟、氯、溴、碘）。

[0448] 例如，R_6 是任选被一个或多个 -Q_2-T_2 取代的 C_1-C_3 烷基。

[0449] 例如，R_6 是三氟甲基。

[0450] 例如，R_6 是 C_2-C_6 烯基、C_2-C_6 炔基或 C_3-C_6 环烷基，每一个任选被一个或多个 -Q_2-T_2 取代。

[0451] 例如，R_6 是乙烯基。

[0452] 例如，R_6 是乙炔基。

[0453] 例如，R_6 是被一个或多个 -Q_2-T_2 取代的乙炔基，其中 Q_2 是键或 C_1-C_3 烷基连接体，且 T_2 是 C_1-C_6 烷基、C_3-C_6 环烷基或任选被一个或多个 -Q_3-T_3 取代的 4-7 元杂环烷基（如，氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、四氢呋喃基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、四氢 -2H- 吡喃基、

3,6- 二氢 -2H- 吡喃基、四氢 -2H- 噻喃基噻喃基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基和吗啉基等)。

[0454] 例如，R_6 是叠氮基。

[0455] 例如，R_6 是氰基。

[0456] 例如，R_6 是醛基。

[0457] 例如，R_6 是 OR_a 或 $-C(O)R_a$。

[0458] 例如，R_a 是 C_1-C_6 烷基或 4-7 元杂环烷基(如，氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、四氢呋喃基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、四氢 -2H- 吡喃基、3,6- 二氢 -2H- 吡喃基、四氢 -2H- 噻喃基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基、2- 氧杂 -6- 氮杂螺 [3.3] 庚烷基、2,6- 二氮杂螺 [3.3] 庚烷基和吗啉基等)，其任选被一个或多个 $-Q_2$-T_2 取代。

[0459] 例如，R_6 是任选被一个或多个 $-Q_2$-T_2 取代的 4-7 元杂环烷基(如，氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、四氢呋喃基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、四氢 -2H- 吡喃基、3,6- 二氢 -2H- 吡喃基、四氢 -2H- 噻喃基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基、2- 氧杂 -6- 氮杂螺 [3.3] 庚烷基、2,6- 二氮杂螺 [3.3] 庚烷基和吗啉基等)。

[0460] 例如，R_6 是哌啶基、2,2,6,6- 四甲基哌啶基、1,2,3,6- 四氢吡啶基、2,2,6,6- 四甲基 -1,2,3,6- 四氢吡啶基、哌嗪基、吗啉基、四氢 -2H- 吡喃基、3,6- 二氢 -2H- 吡喃基或吡咯烷基，其中每一个任选被一个或多个 $-Q_2$-T_2 取代。

[0461] 例如，R_6 是任选被一个或多个 $-Q_2$-T_2 取代的 4-7 元杂环烷基，并且 $-Q_2$-T_2 是氧代或 Q_2 是键，且 T_2 是 $-OR_c$、$-NR_cR_d$、$-C(O)R_c$、$-C(O)OR_c$、$-S(O)_2R_c$、C_1-C_6 烷基或 4-7 元杂环烷基，当 R_c 或 R_d 不是氢时，每一个任选被一个或多个 $-Q_3$-T_3 取代。

[0462] 例 如，R_6 是 $-NR_aR_b$、$-C(O)R_a$、$-C(O)OR_a$、$-C(O)NR_aR_b$、$-NR_bC(O)R_a$、$-SR_a$、$-S(O)_2R_a$ 或 $-S(O)_2NR_aR_b$。

[0463] 例如，R_a 和 R_b 各自独立为氢、C_1-C_6 烷基或任选被一个或多个 $-Q_2$-T_2 取代的 C_3-C_8 环烷基。

[0464] 例如，R_a 和 R_b 其中之一为氢。

[0465] 例如，R_a 和 R_b 连同它们所连接的氮原子一起形成含 0 或 1 个除氮以外额外杂原子的 4-7 元杂环烷基环(如，氮杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基、2- 氧杂 -6- 氮杂螺 [3.3] 庚烷基、2,6- 二氮杂螺 [3.3] 庚烷基和吗啉基等)，并且所述环任选被一个或多个 $-Q_2$-T_2 取代。

[0466] 例如，$-Q_2$-T_2 不是 H。

[0467] 例如，$-Q_2$-T_2 是氧代。

[0468] 例如，Q_2 是键。

[0469] 例如，Q_2 是未取代的 C_1-C_3 烷基连接体。

[0470] 例如，T_2 是 C_1-C_6 烷基或 C_6-C_{10} 芳基，每一个任选被一个或多个 -Q_3-T_3 取代。

[0471] 例如，T_2 是未被取代或被取代的直链 C_1-C_6 烷基或支链 C_3-C_6 烷基，包括但不限于甲基、乙基、正丙基、异丙基、正丁基、仲丁基、叔丁基、正戊基、仲戊基和正己基。

[0472] 例如，T_2 是苯基。

[0473] 例如，T_2 是卤素(如氟、氯、溴、碘)。

[0474] 例如，T_2 是任选被一个或多个 -Q_3-T_3 取代的 4-7 元杂环烷基(如，氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、四氢呋喃基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、四氢 -2H- 吡喃基、3,6- 二氢 -2H- 吡喃基、四氢 -2H- 噻喃基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基、2- 氧杂 -6- 氮杂螺 [3.3] 庚烷基、2,6- 二氮杂螺 [3.3] 庚烷基和吗啉基等)。

[0475] 例如，T_2 是 -OR_c、-NR_cR_d、-$C(O)R_c$、-$C(O)OR_c$ 或 -$S(O)_2R_c$。

[0476] 例如，R_c 是任选被一个或多个 -Q_3-T_3 取代的 C_1-C_6 烷基或 4-7 元杂环烷基(如，氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、四氢呋喃基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、四氢 -2H- 吡喃基、3,6- 二氢 -2H- 吡喃基、四氢 -2H- 噻喃基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基、2- 氧杂 -6- 氮杂螺 [3.3] 庚烷基、2,6- 二氮杂螺 [3.3] 庚烷基和吗啉基等)。

[0477] 例如，R_c 和 R_d 各自独立为氢或任选被一个或多个 -Q_3-T_3 取代的 C_1-C_6 烷基。

[0478] 例如，R_c 是 H。

[0479] 例如，R_d 是 H。

[0480] 例如，R_c 和 R_d 连同它们所连接的氮原子一起形成含 0 或 1 个除氮原子以外的额外杂原子的 4-7 元杂环烷基环(如，氮杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基、2- 氧杂 -6- 氮杂螺 [3.3] 庚烷基、2,6- 二氮杂螺 [3.3] 庚烷基和吗啉基等)，并且所述环任选被一个或多个 -Q_3-T_3 取代。

[0481] 例如，Q_2 是键，并且 T_2 是 -OR_c、-NR_cR_d、-$C(O)R_c$、-$C(O)OR_c$、-$S(O)_2R_c$、C_1-C_6 烷基或 4-7 元杂环烷基，当 R_c 或 R_d 不为氢时，其中每一个任选被一个或多个 -Q_3-T_3 取代。

[0482] 例如，-Q_3-T_3 是氧代。

[0483] 例如，T_2 是 4-7 元杂环烷基或 C_3-C_8 环烷基，并且一个或多个 -Q_3-T_3 是氧代。

[0484] 例如，Q_3 是键或未被取代或被取代的 C_1-C_3 烷基连接体。

[0485] 例如，T_3 是氢、卤素、4-7 元杂环烷基、C_1-C_3 烷基、OR_e、$COOR_e$、-$S(O)_2R_e$、-NR_eR_f 或 -$C(O)NR_eR_f$。

[0486] 例如，R_d 和 R_e 其中之一为氢。

[0487] 例如，Q_3 是键或 C_1-C_3 烷基连接体，T_3 选自 C_1-C_3 烷基、卤素、OR_e、-$S(O)_2R_e$、-NR_eR_f 和 -$C(O)NR_eR_f$。

[0488] 例如，Q_3 是键或 C_1-C_3 烷基连接体，T_3 选自 C_1-C_3 烷基、OR_e、-$S(O)_2R_e$ 或 -NR_eR_f。

[0489] 例如，R_e 是氢。

[0490] 例如，R_f 是氢。

[0491] 例如，R_7 不是氢。

[0492] 例如，R_7 是 $-C(O)R_g$。

[0493] 例如，R_7 是 $-C(O)R_g$，其中 R_g 是 C_3-C_8 环烷基或 4-7 元杂环烷基、C_3-C_8 环烷基。

[0494] 例如，R_7 是被一个或多个 $-Q_5$-T_5 取代的 C_6-C_{10} 芳基。

[0495] 例如，R_7 是任选被一个或多个 $-Q_5$-T_5 取代的苯基。

[0496] 例如，R_7 是任选被一个或多个 $-Q_5$-T_5 取代的 C_1-C_6 烷基。

[0497] 例如，R_7 是任选被一个或多个 $-Q_5$-T_5 取代的 C_3-C_8 环烷基。

[0498] 例如，R_7 是任选被一个或多个 $-Q_5$-T_5 取代的 4-7 元杂环烷基(如，氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、四氢呋喃基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、四氢 -2H- 吡喃基、3,6- 二氢 -2H- 吡喃基、四氢 -2H- 噻喃基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基、2- 氧杂 -6- 氮杂螺 [3.3] 庚烷基、2,6- 二氮杂螺 [3.3] 庚烷基和吗啉基等)。

[0499] 例如，R_7 是 8-14 元杂环烷基，比如 1,4- 二氧杂螺 [4.5] 癸烷基(如，1,4- 二氧杂螺 [4.5] 癸烷 -8- 基)、1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸烷基(如，1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸烷 -8- 基)、1- 氧杂螺 [4.5] 癸烷基(如，1- 氧杂螺 [4.5] 癸烷 -8- 基或 1- 氧杂螺 [4.5] 癸烷 -2- 酮 -8- 基)、1- 氮杂螺 [4.5] 癸烷基(如，1- 氮杂螺 [4.5] 癸烷 -8- 基或 1- 氮杂螺 [4.5] 癸烷 -2- 酮 -8- 基)、3'H- 螺 [环己烷 -1,1'- 异苯并呋喃]- 基(如，3'H- 螺 [环己烷 -1,1'- 异苯并呋喃]-4- 基或 3'H- 螺 [环己烷 -1,1'- 异苯并呋喃]-3'- 酮 -4- 基)、7'H- 螺 [环己烷 -1,5'- 呋喃并 [3,4-b] 吡啶]- 基(如，7'H- 螺 [环己烷 -1,5'- 呋喃并 [3,4-b] 吡啶]-4- 基或 7'H- 螺 [环己烷 -1,5'- 呋喃并 [3,4-b] 吡啶]-7'- 酮 -4- 基)或 3'H- 螺 [环己烷 -1,1'- 呋喃并 [3,4-c] 吡啶]- 基(如，3'H- 螺 [环己烷 -1,1'- 呋喃并 [3,4-c] 吡啶]-4- 基或 3'H- 螺 [环己烷 -1,1'- 呋喃并 [3,4-c] 吡啶]-3'- 酮 -4- 基)，每一个任选被一个或多个 $-Q_5$-T_5 取代。

[0500] 例如，R_7 是任选被一个或多个 $-Q_5$-T_5. 取代的五或六元杂环烷基。

[0501] 例如，R_7 是异丙基。

[0502] 例如，R_7 是吡咯烷基、哌啶基、四氢吡喃基、环戊基或环己基、环庚基，每一个任选被一个 $-Q_5$-T_5 取代。

[0503] 例如，R_7 是环戊基或环己基，每一个任选被一个 $-Q_5$-T_5 取代。

[0504] 例如，Q_5 是 NHC(O)，T_5 是 C_1-C_6 烷基或 C_1-C_6 烷氧基。

[0505] 例如，$-Q_5$-T_5 是氧代。

[0506] 例如，T_4 是 4-7 元杂环烷基或 C_3-C_8 环烷基或 C_6-C_{10} 芳基，并且一个或多个 $-Q_5$-T_5 是氧代。

[0507] 例如，R_7 是 1- 氧化 - 四氢 -2H- 噻喃基或 1,1- 二氧化 - 四氢 -2H- 噻喃基。

[0508] 例如，R_7 是环己酮基，例如环己酮 -4- 基。

[0509] 例如，T_5 是氢、卤素、C_1-C_6 烷基、C_1-C_6 烷氧基、C_3-C_8 环烷基、C_6-C_{10} 芳基或 4-7 元杂环烷基。

[0510] 例如，Q_5 是键，T_5 是 C_1-C_6 烷基、C_3-C_8 环烷基或 4-7 元杂环烷基。

[0511] 例如，Q_5 是键，T_5 是五或六元杂芳基、氨基、单 -C_1-C_6 烷基氨基、双 -C_1-C_6 烷基氨基，T_5 任选被一个或多个选自下列组的取代基取代：卤素、羟基、C_1-C_6 烷氧基或 C_3-C_8 环烷基。

[0512] 例如，Q_5 是羰基、硫酰基或 NHC(O)；且 T_5 是 C_1-C_6 烷基、C_1-C_6 烷氧基、C_3-C_8 环烷基或 4-7 元杂环烷基。

[0513] 例如，T_5 是 C_1-C_6 烷基或 C_1-C_6 烷氧基，每一个任选被卤素、羟基、氰基、C_1-C_6 烷氧基、氨基、单 -C_1-C_6 烷基氨基、双 -C_1-C_6 烷基氨基或 C_3-C_8 环烷基取代。

[0514] 例如，Q_5 是 C_1-C_3 烷基连接体，且 T_5 是氢或 C_6-C_{10} 芳基。

[0515] 例如，Q_5 是 C_1-C_3 烷基连接体，且 T_5 是 C_3-C_8 环烷基，4-7 元杂环烷基或 $S(O)_qR_q$。

[0516] 例如，R_6 是卤素(如，氟、氯、溴、碘)，并且 Z 是 $S(O)_aR_7$，其中 a 是 0，1 或 2，R_7 选自 C_1-C_6 烷基(如，甲基、乙基、正丙基、异丙基、丁基或叔丁基)，C_3-C_8 环烷基(如，环戊基、环己基或环庚基)或 4-14 元杂环烷基(如，氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、四氢呋喃基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、四氢 -2H- 吡喃基、3,6- 二氢 -2H- 吡喃基、四氢 -2H- 噻喃基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基、吗啉基、1,4- 二氧杂螺 [4.5] 癸烷基、1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸烷基、1- 氧杂螺 [4.5] 癸烷基、1- 氮杂螺 [4.5] 癸烷基、3'H- 螺 [环己烷 -1,1'- 异苯并呋喃]- 基、7'H- 螺 [环己烷 -1,5'- 呋喃并 [3,4-b] 吡啶]- 基或 3'H- 螺 [环己烷 -1,1'- 呋喃并 [3,4-c] 吡啶]- 基等)，并且 R_7 任选地被一个或多个 -Q_5-T_5 取代。

[0517] 例如，R_6 是卤素(如，氟、氯、溴、碘)，并且 Z 是 OR_7，其中 R_7 是 4-14 元杂环烷基(如，氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、四氢呋喃基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、四氢 -2H- 吡喃基、3,6- 二氢 -2H- 吡喃基、四氢 -2H- 噻喃基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基、吗啉基、1,4- 二氧杂螺 [4.5] 癸烷基、1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸烷基、1- 氧杂螺 [4.5] 癸烷基、1- 氮杂螺 [4.5] 癸烷基、3'H- 螺 [环己烷 -1,1'- 异苯并呋喃]- 基、7'H- 螺 [环己烷 -1,5'- 呋喃并 [3,4-b] 吡啶]- 基或 3'H- 螺 [环己烷 -1,1'- 呋喃并 [3,4-c] 吡啶]- 基等)，并且 R_7 任选地被一个或多个 -Q_5-T_5 取代。

[0518] 例如，R_{11} 是氢。

[0519] 例如，R_2 和 R_4 各自独立为氢，或任选被氨基、叠氮基、卤素、单 -C_1-C_6 烷基氨基、双 -C_1-C_6 烷基氨基或 C_6-C_{10} 芳基取代的 C_1-C_6 烷基。

[0520] 例如，R_2 和 R_4 各自独立为任选被 C_1-C_6 烷氧基取代的 C_1-C_3 烷基。

[0521] 例如，R_2 和 R_4 均为甲基。

[0522] 例如，R_1 是氢。

[0523] 例如，R_1 是任选被叠氮基、卤素、氨基、单 -C_1-C_6 烷基氨基、双 -C_1-C_6 烷基氨基或 C_6-C_{10} 芳基取代的 C_1-C_6 烷基。

[0524] 例如，R_{12} 是氢、甲基、乙基、乙烯基或卤素。

[0525] 例如，R_{12} 是甲基。

[0526] 例如，R_{12} 是乙基或丙烯基。

[0527] 例如，R_{12} 是甲氧基。

[0528] 例如，R_{12} 是乙烯基。

[0529] 例如，R_8 是氢、甲基、乙基或乙烯基。

[0530] 例如，R_8 是甲基。

[0531] 例如，R_8 是乙基。

[0532] 例如，R_8 是丙基。

[0533] 例如，R_8 是乙烯基或丙烯基。

[0534] 例如，R_8 是任选被一个或多个下列组的取代基取代的 C_1-C_6 烷基：卤素(如，氟、氯、溴)、羟基或 C_1-C_6 烷氧基。

[0535] 例如，R_8 是 4-7 元任选被取代的杂环烷基(如，氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、四氢呋喃基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、四氢 -2H- 吡喃基、3,6- 二氢 -2H- 吡喃基、四氢 -2H- 噻喃基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基、2- 氧杂 -6- 氮杂螺 [3.3] 庚烷基、2,6- 二氮杂螺 [3.3] 庚烷基和吗啉基等)。

[0536] 例如，R_8 是哌啶基。

[0537] 例如，R_8 是 4-7 元任选被取代的杂环烷基，且 R_7 是 $-Q_4$-T_4，其中 Q_4 是键或 C_1-C_4 烷基连接体，T_4 是氢、C_1-C_6 烷基、C_3-C_8 环烷基或 4-7 元杂环烷基。

[0538] 例如，Z 是 NR_7R_8 或 $CR_7R_8R_{14}$，其中 R_7 和 R_8 连同它们所连接的的原子一起形成含 1-3 个杂原子的 4-11 杂环烷基环(如，氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、四氢呋喃基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、四氢 -2H- 吡喃基、3,6- 二氢 -2H- 吡喃基、四氢 -2H- 噻喃基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基、2- 氧杂 -6- 氮杂螺 [3.3] 庚烷基、2,6- 二氮杂螺 [3.3] 庚烷基和吗啉基、1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸烷基等)或 C_3-C_8 环烷基，每一个任选被一个或多个 $-Q_6$-T_6 取代。

[0539] 例如，所述由 R_7 和 R_8 形成的环选自下列组：氮杂环丁烷基、吡咯烷基、哌啶基、吗啉基、哌嗪基、1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸烷基和环己烯基，每一个任选被一个 $-Q_6$-T_6 取代。

[0540] 例如，Z 是 1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸烷基 -8- 基，吡咯烷 -2,5- 二酮 -1- 基或哌啶 -2,6- 二酮 -1- 基。

[0541] 例如，一个或多个 $-Q_6$-T_6 是氧代。

[0542] 例如，T_6 是氢、卤素、C_1-C_6 烷基、C_1-C_6 烷氧基、C_3-C_8 环烷基、C_6-C_{10} 芳基、4-7 元杂环烷基。

[0543] 例如，Q_6 是键，T_6 是 C_1-C_6 烷基、C_3-C_8 环烷基或 4-7 元杂环烷基。

[0544] 例如，Q_6 是羰基、硫酰基或 NHC(O)；并且 T_6 选自 C_1-C_6 烷基、C_1-C_6 烷氧基、C_3-C_8 环烷基或 4-7 元杂环烷基。

[0545] 例如，T_6 是 C_1-C_6 烷基或 C_1-C_6 烷氧基，每一个任选被卤素、羟基、氰基、C_1-C_6 烷氧基、氨基、单 -C_1-C_6 烷基氨基、双 -C_1-C_6 烷基氨基或 C_3-C_8 环烷基取代。

[0546] 例如，Q_6 是 C_1-C_3 烷基连接体且 T_6 是氢或 C_6-C_{10} 芳基。

[0547] 例如，Q_6 是 C_1-C_3 烷基连接体且 T_6 是 C_3-C_8 环烷基、4-7 元杂环烷基或 $S(O)_pR_p$。

[0548] 例如，R_p 和 R_q 各自独立为 C_1-C_6 烷基。

[0549] 例如，R_6 是 $-S(O)_bR_a$ 或叠氮基，其中 b 是 0、1 或 2，并且 R_a 是 C_1-C_6 烷基或 C_3-C_8 环烷基；且 Z 是 NR_7R_8，其中 R_7 是 C_3-C_8 环烷基(如，环戊基、环己基或环庚基)或 4-14 元杂环烷基(如，氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、四氢呋喃基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、四氢 -2H- 吡喃基、3,6- 二氢 -2H- 吡喃基、四氢 -2H- 噻喃基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基、吗啉基、1,4- 二氧杂螺 [4.5] 癸烷基、1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸烷基、1- 氧杂螺 [4.5] 癸烷基、1- 氮杂螺 [4.5] 癸烷基、3'H- 螺 [环己烷 -1,1'- 异苯并呋喃]- 基、7'H- 螺 [环己烷 -1,5'- 呋喃并 [3,4-b] 吡啶]- 基或 3'H- 螺 [环己烷 -1,1'- 呋喃并 [3,4-c] 吡啶]- 基等)，每一个任选地被一个或多个 $-Q_5$-T_5 取代；并且 R_8 是氢或 C_1-C_6 烷基(如，甲基、乙基、正丙基、异丙基、丁基或叔丁基)。

[0550] 例如，R_6 是卤素(如，氟、氯、溴和碘)，并且 Z 是 NR_7R_8 或 $CR_7R_8R_{14}$，其中 R_7 和 R_8 连同它们所连接的的原子一起形成含 1-3 个杂原子的 4-11 杂环烷基环(如，氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、四氢呋喃基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、四氢 -2H- 吡喃基、3,6- 二氢 -2H- 吡喃、四氢 -2H- 噻喃基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基、吗啉基、2- 氧杂 -6- 氮杂螺 [3.3] 庚烷基、2,6- 二氮杂螺 [3.3] 庚烷基、1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸烷基、1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸烷 -8- 基、吡咯烷 -2,5- 二酮 -1- 基，哌啶 -2,6- 二酮 -1- 基等)或 C_3-C_8 环烷基，每一个任选被一个或多个 $-Q_6$-T_6 取代。

[0551] 例如，R_{13} 是氢或甲基。

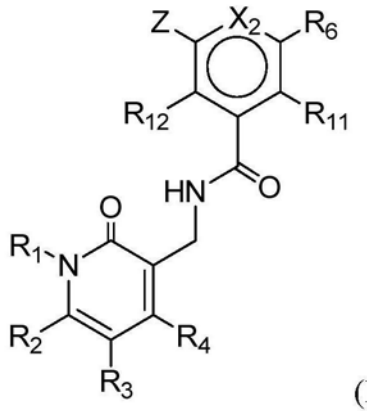
[0552] 例如，R_{13} 是氢。

[0553] 例如，R_3 是氢。

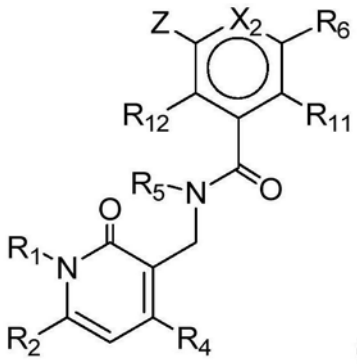
[0554] 例如，R_5、R_9 和 R_{10} 均为氢。

[0555] 式 (I) 的化合物的其它子集包括式 (Ib)、(Ic) 或 (Id) 的化合物或其药学上可接受的盐或酯，其中 Z、X_2、X_3、R_1、R_2、R_3、R_4、R_5、R_6、R_{11} 和 R_{12} 如本文对式 (I) 所定义的一样。

[0556]

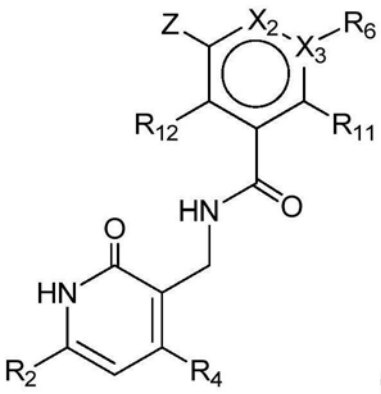


(Ib)



(Ic)

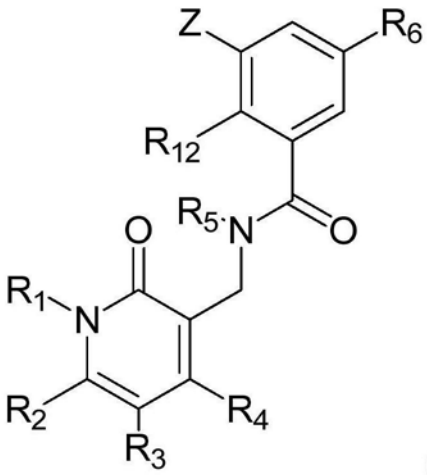
[0557]



(Id)

[0558] 式 (I) 的化合物的另一个子集是式 (Ie) 的化合物 :

[0559]



(Ie),

[0560] 其中

[0561] Z 是 NR_7R_8、OR_7 或 $S(O)_aR_7$;

[0562] R_1 为氢或任选被一个或多个选自下列组的取代基取代的 C_1-C_6 烷基 :羟基、C_1-C_6 烷氧基、氨基、单 -C_1-C_6 烷基氨基、双 -C_1-C_6 烷基氨基和 C_6-C_{10} 芳基 ;

[0563] R_2 和 R_4 各自独立为 -Q_1-T_1,其中 Q_1 为键或任选被一个或多个卤素和羟基的取代基取代的 C_1-C_3 烷基连接体,T_1 选自氢、卤素或叠氮基 ;

[0564] R_3 是氢或卤素 ;

[0565] R_5 是氢或 C_1-C_6 烷基 ;

[0566] R_6 是氢、卤素、氰基、叠氮基、OR_a、$-NR_aR_b$、$-C(O)NR_aR_b$、$-S(O)_bR_a$ 或 R_{S2} ;其中 R_{S2} 是 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基或 4-12 元杂环烷基,且其中 R_a 和 R_b 各自独立选自氢、C_1-C_6 烷基或 4-12 元杂环烷基 ;或 R_a 和 R_b 连同它们所连接的氮原子形成含 0 或 1 个额外杂原子的 4-12 元杂环烷基环 ;R_a、R_{S2} 和所述由 R_a 和 R_b 形成的 4-12 元杂环烷基环各自任选地被一个或多个 -Q_2-T_2 取代,其中 Q_2 是键或 C_1-C_3 烷基连接体,T_2 选自氢、卤素、$-OR_c$、$-NR_cR_d$、$-C(O)OR_c$ 或 C_1-C_6 烷基,其中 R_c 和 R_d 各自独立为氢或 C_1-C_6 烷基,或 R_c 和 R_d 连同它们所连接的氮原子一起形成含 0 或 1 个额外杂原子的、任选被 C_1-C_6 烷基取代的 4-12 元杂环烷基环 ;

[0567] R_7 是 -Q_4-T_4,其中 Q_4 是键或 C_1-C_4 烷基连接体,T_4 选自氢、C_1-C_6 烷基、C_3-C_8 环烷基、C_6-C_{10} 芳基、C(O)-C_{1-6} 烷基、C(O)-C_{3-6} 环烷基或 4-14 元杂环烷基,每一个 T_4 任选地被一

个或多个 $-Q_5-T_5$ 取代；

[0568] R_8 是氢、任选地被卤素或羟基或 C_1-C_6 烷氧基取代的 C_1-C_6 烷基、C_2-C_6 烯基、C_3-C_8 环烷基或 4-7 元杂环烷基；或 R_7 和 R_8 连同它们所连接的氮原子形成含 0-2 个额外的杂原子的 4-12 元杂环烷基环，且所述由 R_7 和 R_8 形成的 4-12 元杂环烷基环任选地被一个或多个 $-Q_6-T_6$ 取代；以及

[0569] R_{12} 是卤素、C_1-C_6 烷氧基或任选地被卤素或 C_2-C_6 烯基取代的 C_1-C_6 烷基。

[0570] 除了本发明化合物的以上所述的特征(如适用)之外，式 (Ie) 的化合物还可以包括一个或多个以下特征：

[0571] 例如，R_1 是氢或任选被选自羟基、C_1-C_6 烷氧基和 C_6-C_{10} 芳基的取代基所取代一次或多次的 C_1-C_6 烷基；R_7 是 $-Q_4-T_4$，其中 Q_4 是键或 C_1-C_4 烷基连接体，T_4 选自 C_1-C_6 烷基、C_3-C_8 环烷基、C_6-C_{10} 芳基、$C(O)-C_1-C_6$ 烷基、$C(O)-C_3-C_6$ 环烷基、二氢吡喃基、四氢吡喃基、四氢噻喃基、哌啶基、吡咯烷基、氮杂环丁烷基和氧杂环丁烷基，每一个 T_4 各自独立地被一个或多个下列取代基取代：氧代和 $-Q_5-T_5$；R_8 是氢或 C_1-C_6 烷基、C_1-C_6 卤代烷基、C_2-C_6 烯基或 C_3-C_8 环烷基；以及 R_{12} 选自卤素、C_1-C_6 烷基、C_1-C_6 卤代烷基或 C_1-C_6 烷氧基。

[0572] 例如，Z 是 NR_7R_8 或 SR_7；

[0573] R_6 选自氢、卤素、氰基、OR_a、$-C(O)NR_aR_b$、$-S(O)_2R_a$ 或 R_{S2}；其中 R_{S2} 是 C_1-C_6 烷基、C_2-C_6 烯基、C_2-C_6 炔基或 4-12 元杂环烷基，且其中 R_a 和 R_b 各自独立为氢或 C_1-C_6 烷基；或 R_a 和 R_b 连同它们所连接的氮原子形成含 0 或 1 个额外的杂原子的 4-12 元杂环烷基环；R_{S2} 和所述的由 R_a 和 R_b 形成的 4-12 元杂环烷基环各自任选地被一个或多个 $-Q_2-T_2$ 取代；其中 Q_2 是键或 C_1-C_3 烷基连接体，T_2 选自氢、卤素、$-OR_c$、$-NR_cR_d$、$-C(O)OC_1-C_6$ 烷基或 C_1-C_6 烷基，其中 R_c 和 R_d 各自独立为氢或 C_1-C_6 烷基，或 R_c 和 R_d 连同它们所连接的氮原子形成含 0 或 1 个额外的杂原子和含 0 或 1 个 C_1-C_6 烷基取代基的 4-12 元杂环烷基环；

[0574] R_7 选自 C_1-C_6 烷基、C_3-C_8 环烷基、二氢吡喃基、四氢吡喃基、四氢噻喃基、哌啶基、吡咯烷基、氮杂环丁烷基和氧杂环丁烷基，每一个任选地被一个或多个独立地选自氧代和 $-Q_5-T_5$ 的取代基取代；以及 R_{12} 是卤素或 C_1-C_6 烷基。

[0575] 例如，R_2、R_4 和 R_{12} 各自独立为 C_1-C_6 烷基，且 R_5 为氢。

[0576] 例如，R_7 是环己基、二氢吡喃基、四氢吡喃基、四氢噻喃基、哌啶基、吡咯烷基、氮杂环丁烷基、氧杂环丁烷基、1,4- 二氧杂螺 [4.5] 癸烷 -8- 基、1- 氧杂螺 [4.5] 癸烷 -8- 基、3'H- 螺 [环己烷 -1,1'- 异苯并呋喃]-4- 基、7'H- 螺 [环己烷 -1,5'- 呋喃 [3,4-b] 吡啶]-4- 基、3'H- 螺 [环己烷 -1,1'- 呋喃 [3,4-c] 吡啶]-4- 基或 1- 氮杂螺 [4.5] 癸烷 -8- 基，每一个 R_7 任选地被一个或多个 $-Q_5-T_5$ 取代。

[0577] 例如，Z 选自哌啶基、吗啉基、哌嗪基、氮杂环丁烷基、吡咯烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷 -5- 基、1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸烷 -8- 基和环己烯基，每一个 Z 任选地被一个或多个 $-Q_5-T_5$ 取代。

[0578] 例如，R_6 是卤素(如，氟、氯、溴、碘)且 Z 是 $S(O)_aR_7$，其中 a 是 0、1 或 2，R_7 选自 C_1-C_6 烷基(如，甲基、乙基、正丙基、异丙基、丁基或叔丁基)、C_3-C_8 环烷基(如，环戊基、环己基或环庚基)或 4-14 元杂环烷基(如，氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、四氢呋喃基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、四氢 -2H- 吡喃基、3,6- 二氢 -2H- 吡喃、四氢 -2H- 噻喃基、1,4- 二氮杂环

庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基、吗啉基、1,4- 二氧杂螺 [4.5] 癸烷基、1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸烷基、1- 氧杂螺 [4.5] 癸烷基、1- 氮杂螺 [4.5] 癸烷基、3'H- 螺 [环己烷 -1,1'- 异苯并呋喃]- 基、7'H- 螺 [环己烷 -1,5'- 呋喃并 [3,4-b] 吡啶]- 基或 3'H- 螺 [环己烷 -1,1'- 呋喃并 [3,4-c] 吡啶]- 基等),并且 R_7 任选地被一个或多个 $-Q_5-T_5$ 取代。

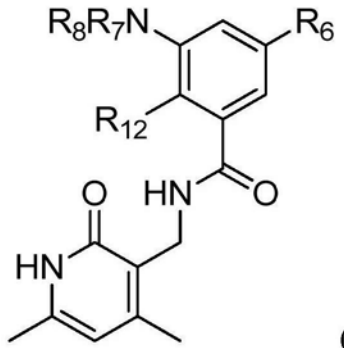
[0579] 例如,R_6 是卤素(如,氟、氯、溴、碘)且 Z 是 OR_7,其中 R_7 是 4-14 元杂环烷基 (如,氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、四氢呋喃基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、四氢 -2H- 吡喃基、3,6- 二氢 -2H- 吡喃、四氢 -2H- 噻喃基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基、吗啉基、1,4- 二氧杂螺 [4.5] 癸烷基、1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸烷基、1- 氧杂螺 [4.5] 癸烷基、1- 氮杂螺 [4.5] 癸烷基、3'H- 螺 [环己烷 -1,1'- 异苯并呋喃]- 基、7'H- 螺 [环己烷 -1,5'- 呋喃并 [3,4-b] 吡啶]- 基或 3'H- 螺 [环己烷 -1,1'- 呋喃并 [3,4-c] 吡啶]- 基等),并且 R_7 任选地被一个或多个 $-Q_5-T_5$ 取代。

[0580] 例如,R_6 是 $-S(O)_bR_a$ 或叠氮基,其中 b 是 0、1 或 2,并且 R_a 是 C_1-C_6 烷基或 C_3-C_8 环烷基 ;且 Z 是 NR_7R_8,其中 R_7 是 C_3-C_8 环烷基(如,环戊基、环己基或环庚基) 或 4-14 元杂环烷基(如,氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、四氢呋喃基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、四氢 -2H- 吡喃基、3,6- 二氢 -2H- 吡喃基、四氢 -2H- 噻喃基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基、吗啉基、1,4- 二氧杂螺 [4.5] 癸烷基、1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸烷基、1- 氧杂螺 [4.5] 癸烷基、1- 氮杂螺 [4.5] 癸烷基、3'H- 螺 [环己烷 -1,1'- 异苯并呋喃]- 基、7'H- 螺 [环己烷 -1,5'- 呋喃并 [3,4-b] 吡啶]- 基或 3'H- 螺 [环己烷 -1,1'- 呋喃并 [3,4-c] 吡啶]- 基等),每一个任选地被一个或多个 $-Q_5-T_5$ 取代 ;并且 R_8 是氢或 C_1-C_6 烷基(如,甲基、乙基、正丙基、异丙基、丁基或叔丁基)。

[0581] 例如,R_6 是卤素(如,氟、氯、溴和碘) 且 Z 是 NR_7R_8 或 $CR_7R_8R_{14}$,其中 R_7 和 R_8 连同它们所连接的原子一起形成含 1-3 个杂原子的 4-11 杂环烷基环 (如,氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、吡咯烷基、咪唑烷基、吡唑烷基、恶唑烷基、异恶唑烷基、三唑烷基、四氢呋喃基、哌啶基、1,2,3,6- 四氢吡啶基、哌嗪基、四氢 -2H- 吡喃基、3,6- 二氢 -2H- 吡喃基、四氢 -2H- 噻喃基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基、吗啉基、2- 氧杂 -6- 氮杂螺 [3.3] 庚烷基、2,6- 二氮杂螺 [3.3] 庚烷基、1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸烷基、1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸烷 -8- 基、吡咯烷 -2,5- 二酮 -1- 基,哌啶 -2,6- 二酮 -1- 基等) 或 C_3-C_8 环烷基,每一个任选被一个或多个 $-Q_6-T_6$ 取代。

[0582] 式 (I) 的化合物的另一个子集是式 (II) 的化合物或其药学上可接受的盐或酯,其中 R_6、R_7、R_8 和 R_{12} 如本文所定义。

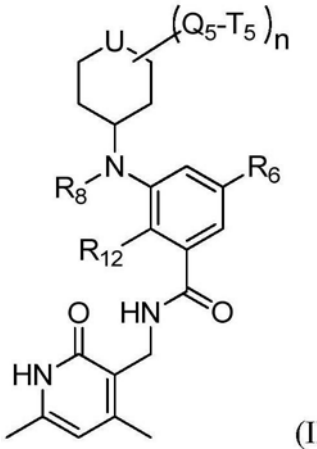
[0583]



(II)

[0584] 式 (I) 的化合物的还有一个子集是式 (IIA) 的化合物或其药学上可接受的盐或酯，

[0585]



(IIA)

[0586] 其中 n 是 0、1 或 2；U 是氧、硫、$N-Q_5-T_5$ 或 $CH-Q_5-T_5$；R_{12} 是氯、溴或甲基；且 R_6、R_7、R_8、Q_5 和 T_5 如本文所定义。

[0587] 除了本发明的化合物的以上所述的特征(如适用)之外，式 (II) 或 (IIA) 化合物还可以包括一个或多个以下特征：

[0588] 例如，Q_5 是键，且 T_5 选自氢、C_1-C_6 烷基、C_3-C_8 环烷基、4-12 元杂环烷基、五或六元杂芳基、氨基、单 $-C_1-C_6$ 烷基氨基或双 $-C_1-C_6$ 烷基氨基，T_5 任选被一个或多个选自下列组的取代基取代：卤素、羟基、C_1-C_6 烷氧基、或 C_3-C_8 环烷基。

[0589] 例如，Q_5 是羰基、硫酰基或 NHC(O)；且 T_5 是 C_1-C_6 烷基、C_1-C_6 烷氧基、C_3-C_8 环烷基或 4-12 元杂环烷基。

[0590] 例如，Q_5 是 C_1-C_3 烷基连接体，且 T_5 是氢或 C_6-C_{10} 芳基。

[0591] 例如，Q_5 是 C_1-C_3 烷基连接体，且 T_5 是 C_3-C_8 环烷基、4-12 元杂环烷基或 $S(O)_qR_q$。

[0592] 例如，Q_5 是 NHC(O)，T_5 是 C_1-C_6 烷基或 C_1-C_6 烷氧基。

[0593] 例如，一个或多个 $-Q_5-T_5$ 是氧代。

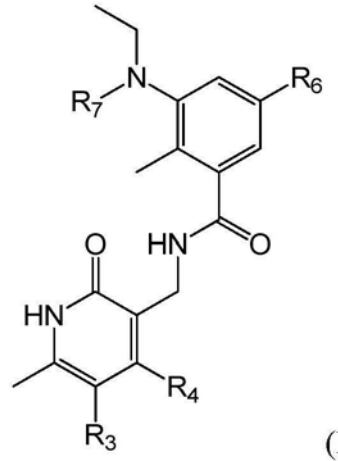
[0594] 例如，U 是 $CH-Q_5-T_5$ 且 n 是 0。

[0595] 例如，一个或多个 $-Q_6-T_6$ 是氧代。

[0596] 例如，Q_6 是键或羰基，且 T_6 是 C_1-C_6 烷基或 C_1-C_6 烷氧基。

[0597] 式 (I) 的化合物还有一个子集是式 (III) 的化合物或其药学上可接受的盐或酯，

[0598]



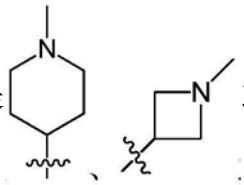
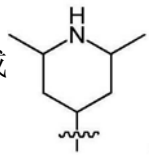
(III)

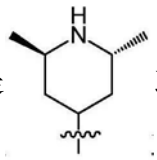
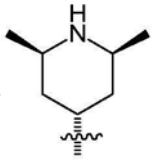
[0599] 其中，R_7 是一个环内含一个氮原子的 4-6 元杂环烷基且被一个或两个甲基或一个异丙基取代；R_3 是氢或氟；R_4 是甲基、乙基、正丙基、异丙基或三氟甲基，R_6 是三氟甲基、氯或氟，假设当 R_4 是甲基时，(1) R_6 是三氟甲基，或(2) R_3 是氟，或(3) R_6 是三氟甲基且 R_3 是氟，或(4) R_6 是氟或氯，且 R_7 是只含一个氮原子且被两个甲基取代的六元杂环烷基。

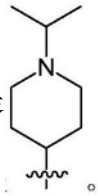
[0600] 除了本发明的化合物的以上所述的特征(如适用)之外，式 (III) 的化合物还可以包括一个或多个以下特征：

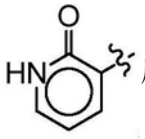
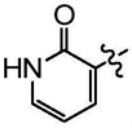
[0601] 例如，R_7 是在环中有且只有一个杂原子并且该杂原子为氮原子的 4-6 元杂环烷基。

[0602] 例如，除一个或两个甲基或一个异丙基之外，R_7 不再被其他取代基进一步取代。

[0603] 例如，R_7 是  或  。

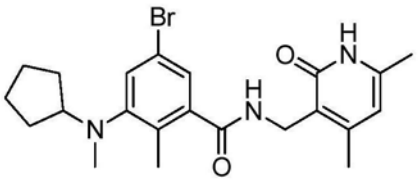
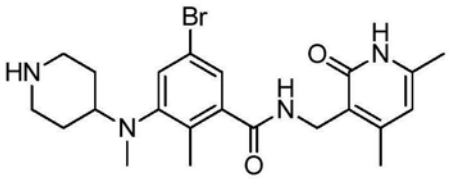
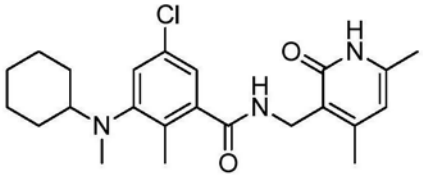
[0604] 例如，R_7 是  或  。

[0605] 例如，R_7 是  。

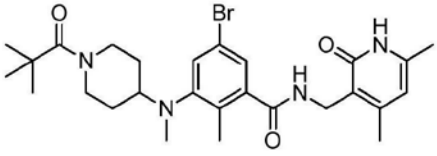
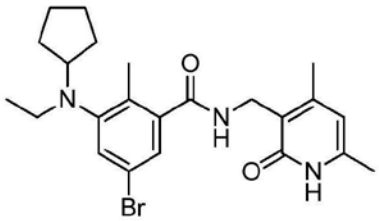
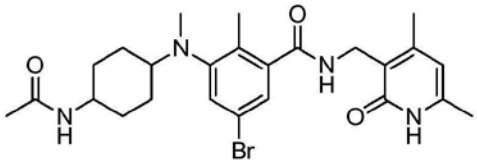
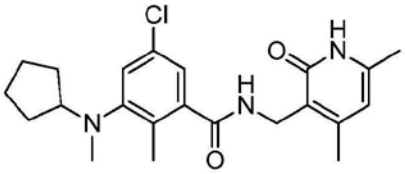
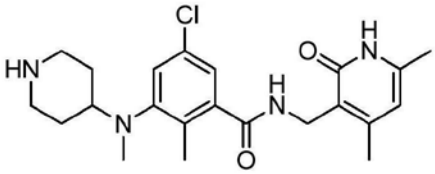
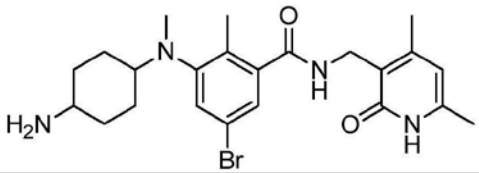
[0606] 本发明的代表性化合物列在表 1 中。在下表中，每次出现的  应理解为  。

[0607] 表 1

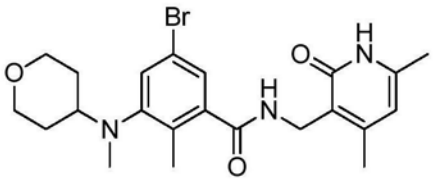
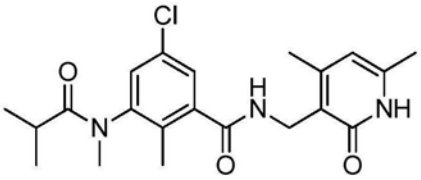
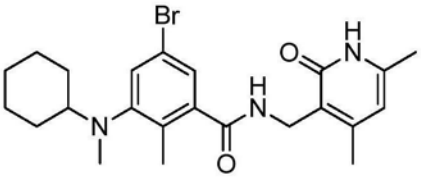
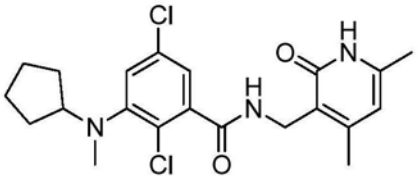
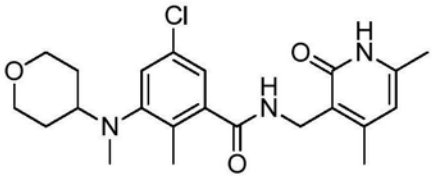
[0608]

化合物编号	结构	名称	分子量†
1		5-溴-3-(环戊基(甲基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	446.2
2		5-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(甲基(哌啶-4-基)氨基)苯甲酰胺	462.2
3		5-氯-3-(环己基(甲基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	416.4

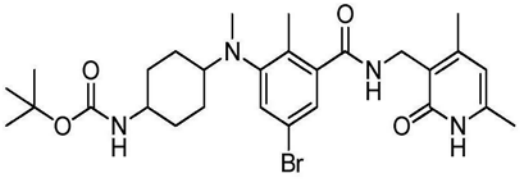
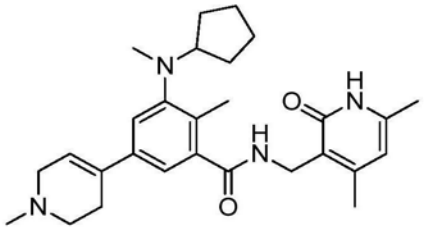
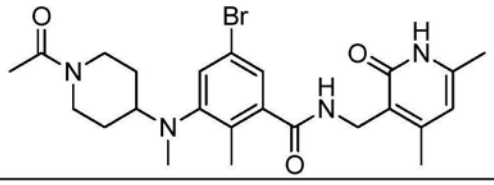
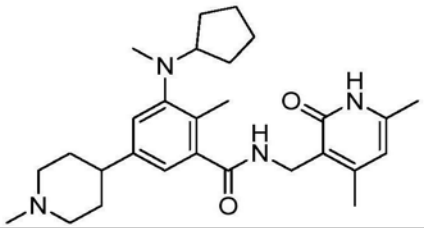
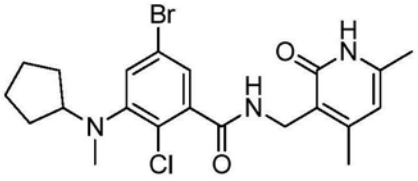
[0609]

化合物编号	结构	名称	分子量†
4		5-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(甲基(1-特戊酰基哌啶-4-基)氨基)苯甲酰胺	545.2
5		5-溴-3-(环戊基(乙基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	460.1
6		3-((4-乙酰氨基环己基)(甲基)氨基)-5-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	516.9
7		5-氯-3-(环戊基(甲基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	402.2
8		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(甲基(哌啶-4-基)氨基)苯甲酰胺	417.3
9		3-((4-氨基环己基)(甲基)氨基)-5-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡	475.1

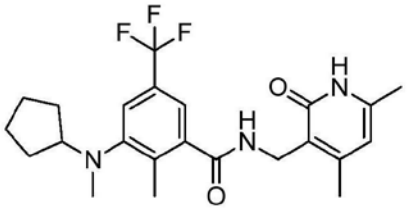
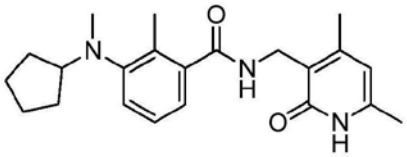
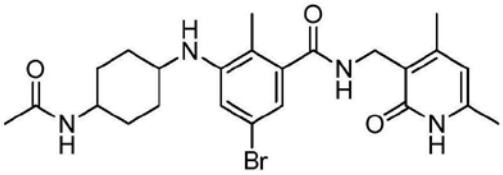
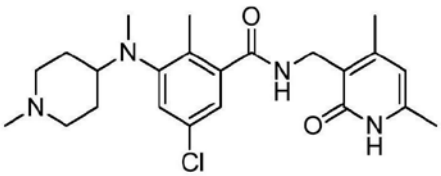
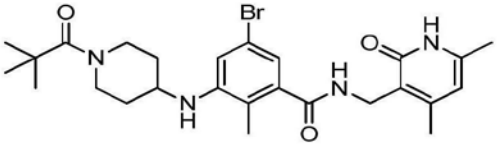
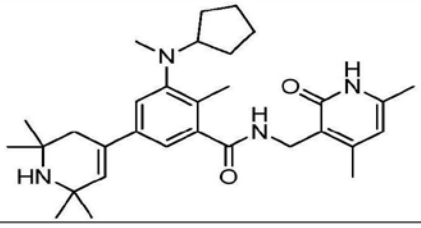
[0610]

化合物编号	结构	名称	分子量†
		啶-3-基)甲基)-2-甲基苯甲酰胺	
10		5-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(甲基(四氢-2H-吡喃-4-基)氨基)苯甲酰胺	462.2
11		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(N-甲基异丁酰胺基)苯甲酰胺	404.2
12		5-溴-3-(环己基(甲基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	460.1
13		2,5-二氯-3-(环戊基(甲基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)苯甲酰胺	422.1
14		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(甲基(四氢-2H-吡喃-4-基)氨基)苯甲酰胺	418.3

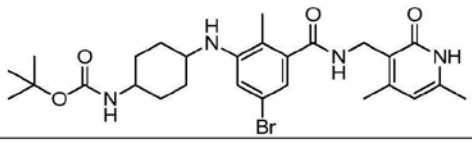
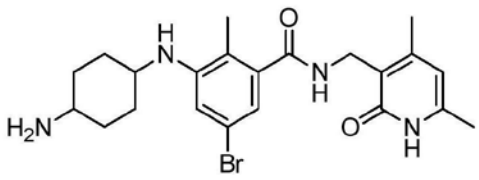
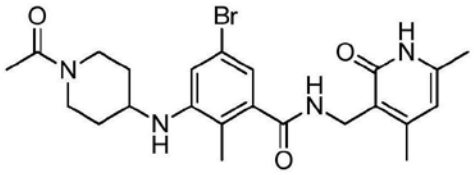
[0611]

化合物编号	结构	名称	分子量†
15		(4-((5- 溴 -3-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰基)-2-甲基苯基)(甲基)氨基)环己基)氨基甲酸叔丁酯	575.8
16		3-(环戊基(甲基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基 -5-(1- 甲 基 -1,2,3,6- 四氢吡啶-4-基)苯甲酰胺	463.4
17		3-((1- 乙酰哌啶 -4-基)(甲基)氨基)-5-溴 -N-((4,6- 二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	503.2
18		3-(环戊基(甲基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基 -5-(1- 甲基哌啶-4-基)苯甲酰胺	465.4
19		5- 溴 -2- 氯 -3-(环戊基 (甲 基) 氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)苯甲酰胺	466.1

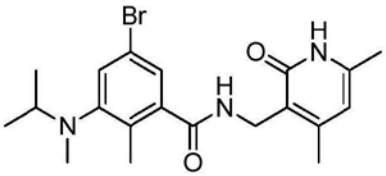
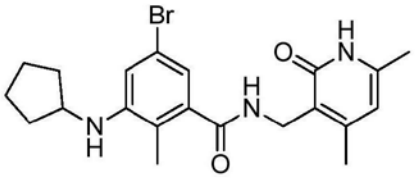
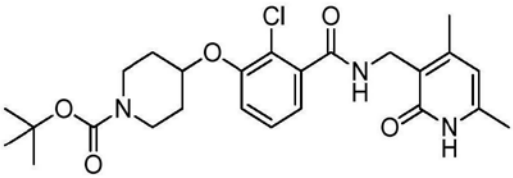
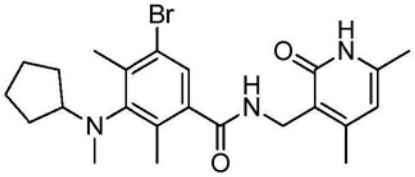
[0612]

化合物编号	结构	名称	分子量†
20		3-(环戊基(甲基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-5-(三氟甲基)苯甲酰胺	436.2
21		3-(环戊基(甲基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-5-(三氟甲基)苯甲酰胺	368.2
22		3-((4-乙酰氨基环己基)氨基)-5-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	503.1
23		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(甲基(1-甲基哌啶-4-基)氨基)苯甲酰胺	431.3
24		5-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-((1-特戊酰基哌啶-4-基)氨基)苯甲酰胺	531.1
25		3-(环戊基(甲基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲	505.4

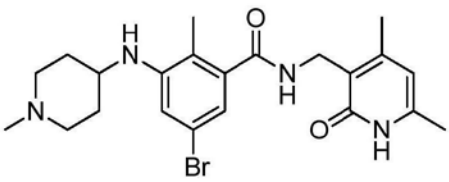
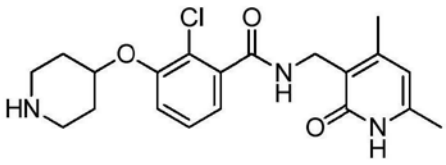
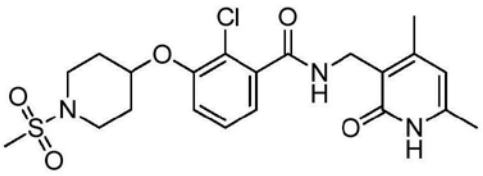
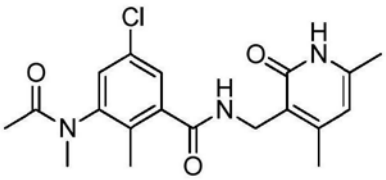
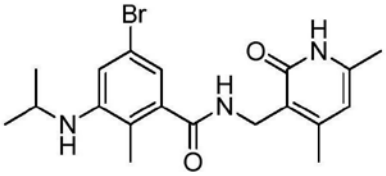
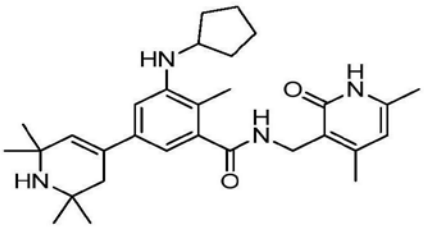
[0613]

化合物编号	结构	名称	分子量†
		基-5-(2,2,6,6-四甲基-1,2,3,6-四氢吡啶-4-基)苯甲酰胺	
26		(4-((5-溴-3-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰基)-2-甲基苯基)氨基)环己基)氨基甲酸叔丁酯	562.2
27		3-((4-氨基环己基)氨基)-5-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	461.1
28		5-溴-3-(环己基氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	446.2
29		3-((1-乙酰哌啶-4-基)氨基)-5-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	489.2
30		5-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(甲基(1-甲基哌啶-4-基)氨基)苯甲酰胺	475.02

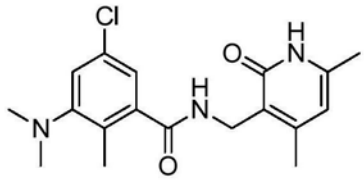
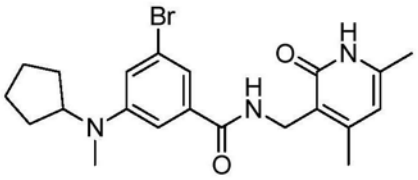
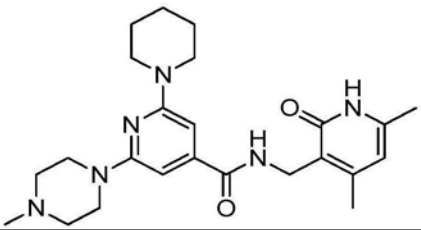
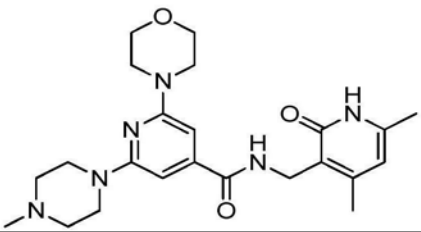
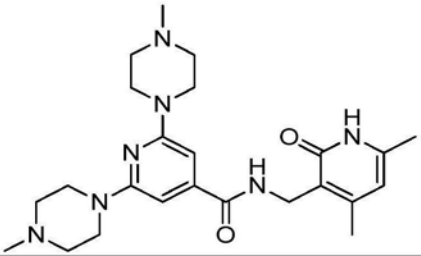
[0614]

化合物编号	结构	名称	分子量†
31		5-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(异丙基(甲基)氨基)-2-甲基苯甲酰胺	420.2
32		5-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-((四氢-2H-吡喃-4-基)氨基)苯甲酰胺	447.9
33		5-溴-3-(环戊基氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	432.1
34		4-(2-氯-3-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰基)苯氧基)哌啶-1-羧酸叔丁酯	490.3
35		5-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(哌啶-4-基氨基)苯甲酰胺	447.1
36		5-溴-3-(环戊基(甲基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2,4-甲基苯甲酰胺	460.1

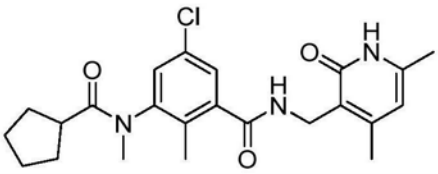
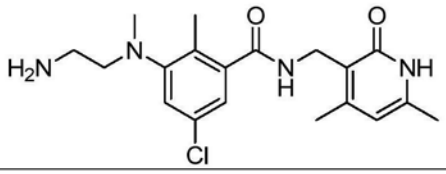
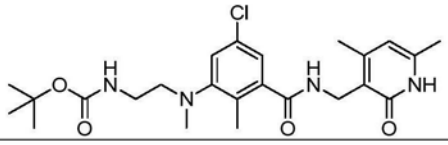
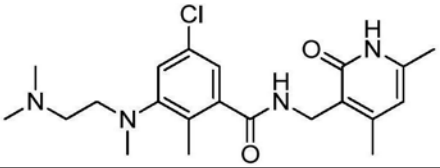
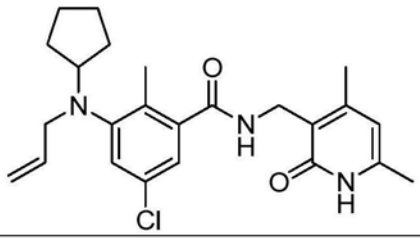
[0615]

化合物编号	结构	名称	分子量†
37		5-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-((1-甲基哌啶-4-基)氨基)苯甲酰胺	460.96
38		2-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(哌啶-4-基氧基)苯甲酰胺	390.1
39		2-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-((1-(甲基磺酰基)哌啶-4-基)氧基)苯甲酰胺	468.1
40		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(N-甲基乙酰氨基)苯甲酰胺	376.2
41		5-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(异丙基氨基)-2-甲基苯甲酰胺	406.1
42		3-(环戊基氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-5-(2,2,6,6-四甲基-1,2,3,6-四氢吡	491.2

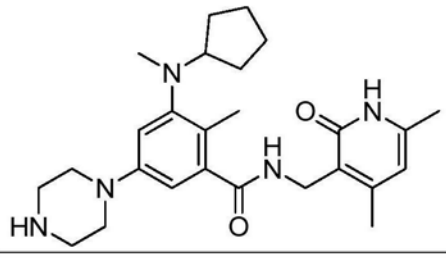
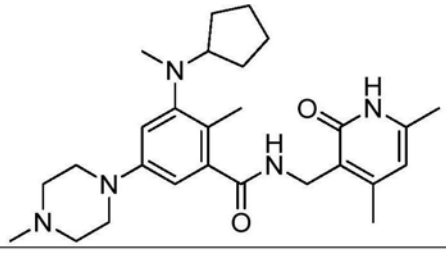
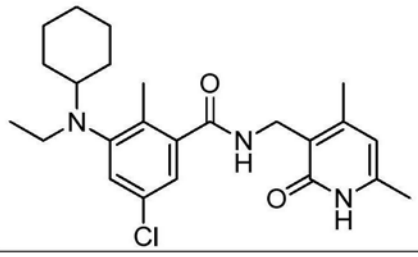
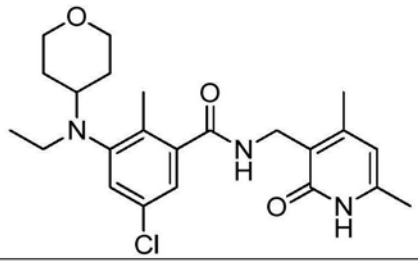
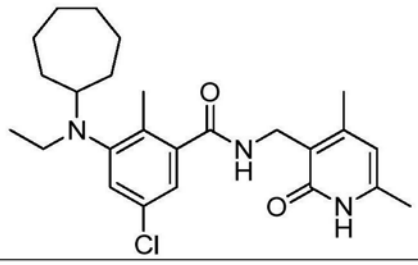
[0616]

化合物编号	结构	名称	分子量†
		啶-4-基)苯甲酰胺	
43		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(甲基氨基)-2-甲基苯甲酰胺	348.2
44		3-溴-5-(环戊基(甲基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)苯甲酰胺	432
45		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-(4-甲基哌嗪-1-基)-6-(哌啶-1-基)异烟酰胺	438.3
46		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-(4-甲基哌嗪-1-基)-6-吗啉基异烟酰胺	441.2
47		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2,6-二(4-甲基哌嗪-1-基)异烟酰胺	454.2

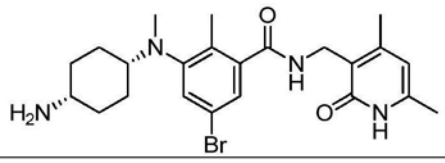
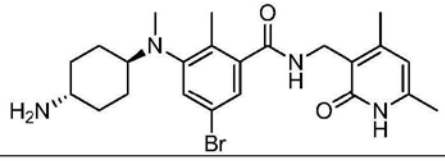
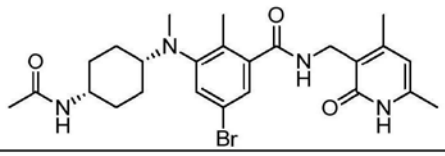
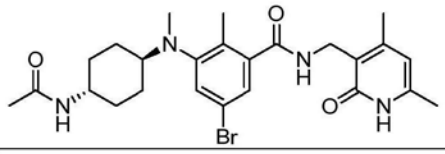
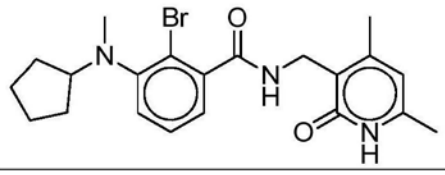
[0617]

化合物编号	结构	名称	分子量†
48		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2,6-二(4-甲基哌嗪-1-基)异烟酰胺	430.2
49		3-((2-氨基乙基)(甲基)氨基)-5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	377.2
50		(2-((5-氯-3-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰基)-2-甲基苯基)(甲基)氨基)乙基)氨基甲酸叔丁酯	477.3
51		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-((2-(甲基氨基)乙基)(甲基)氨基)-2-甲基苯甲酰胺	405.3
52		3-(烯丙基(环戊基)氨基)-5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	428.3

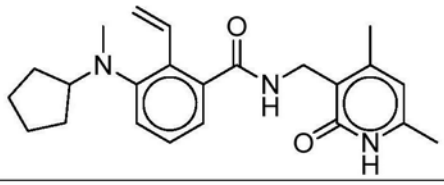
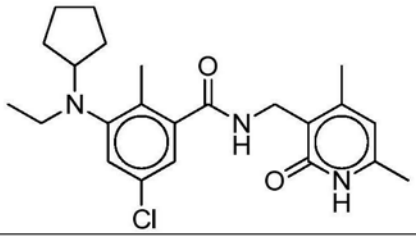
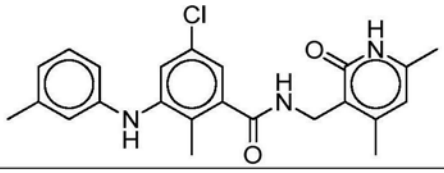
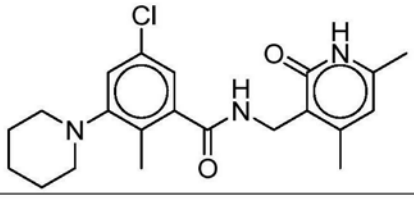
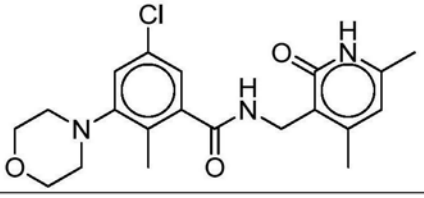
[0618]

化合物编号	结构	名称	分子量†
53		3-(环戊基(甲基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-5-(哌嗪-1-基)苯甲酰胺	452.4
54		3-(环戊基(甲基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-5-(4-甲基哌嗪-1-基)苯甲酰胺	466.4
55		5-氯-3-(环己基(乙基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	430.2
56		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(四氢-2H-吡喃-4-基)氨基)-2-甲基苯甲酰胺	432.3
57		5-氯-3-(环庚基(乙基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	444.3

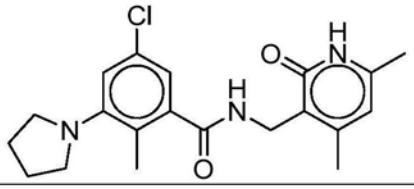
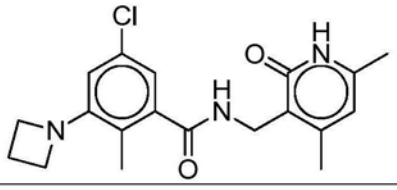
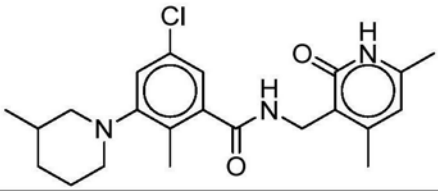
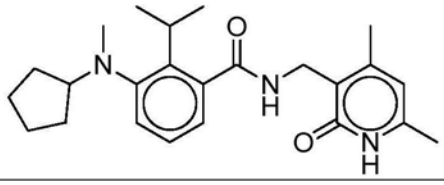
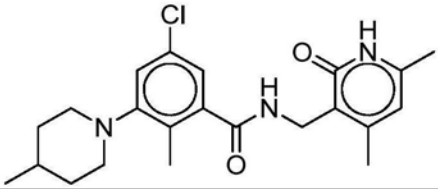
[0619]

化合物编号	结构	名称	分子量†
58		3-(((1s,4s)-4-氨基环己基)(甲基)氨基)-5-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	475.2
59		3-(((1r,4r)-4-氨基环己基)(甲基)氨基)-5-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	475.2
60		3-(((1s,4s)-4-乙酰氨基环己基)(甲基)氨基)-5-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	517.3
61		3-(((1r,4r)-4-乙酰氨基环己基)(甲基)氨基)-5-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	517.3
62		2-溴-3-(环戊基(甲基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)苯甲酰胺	432.1

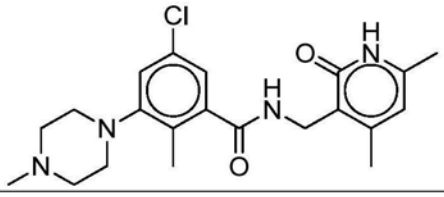
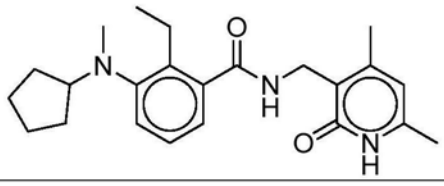
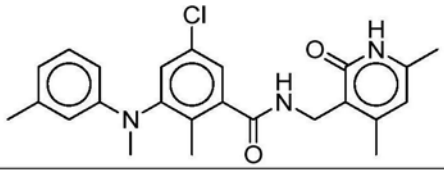
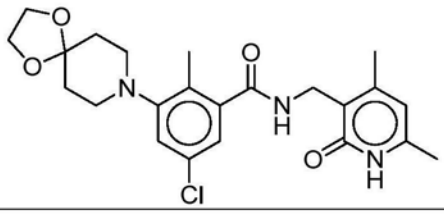
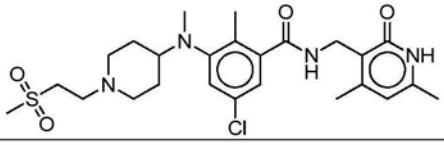
[0620]

化合物编号	结构	名称	分子量†
63		3-(环戊基(甲基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-乙烯基苯甲酰胺	380.3
64		5-氯-3-(环戊基(乙基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	416.3
65		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(间-苯甲基氨基)苯甲酰胺	410.3
66		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(哌啶-1-基)苯甲酰胺	388.2
67		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-吗啉基苯甲酰胺	390.2

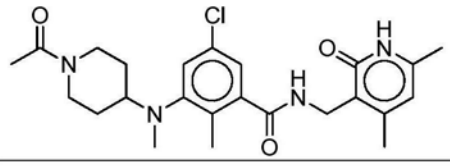
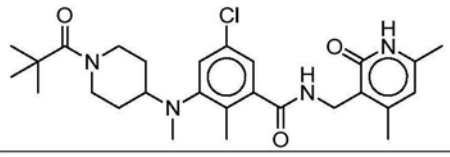
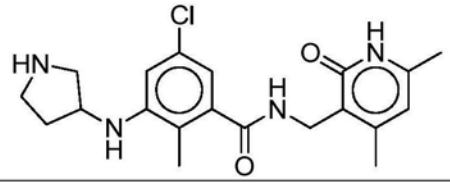
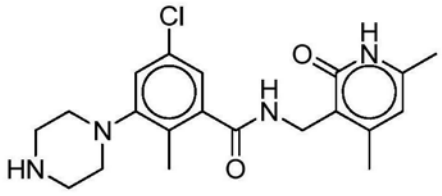
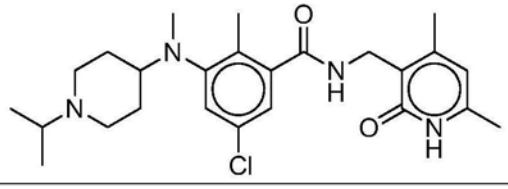
[0621]

化合物编号	结构	名称	分子量†
68		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(吡咯烷-1-基)苯甲酰胺	374.2
69		3-(氮杂环丁烷-1-基)-5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	360.2
70		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(3-甲基哌啶-1-基)苯甲酰胺	402.3
71		3-(环戊基(甲基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-异丙基苯甲酰胺	396.25
72		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(4-甲基哌啶-1-基)苯甲酰胺	402.2

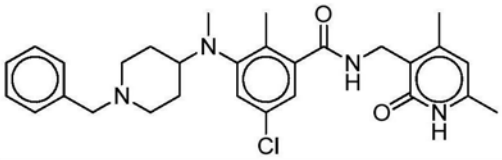
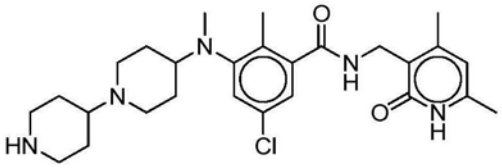
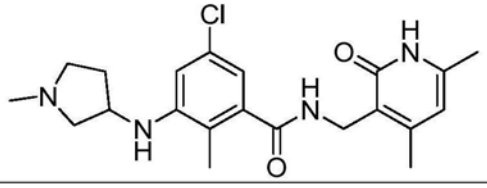
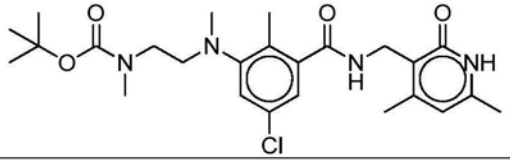
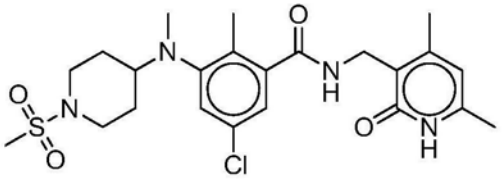
[0622]

化合物编号	结构	名称	分子量†
73		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(4-甲基哌嗪-1-基)苯甲酰胺	403.2
74		3-(环戊基(甲基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-乙基苯甲酰胺	382.3
75		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(甲基(间-苯甲基)氨基)苯甲酰胺	424.2
76		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(1,4-二氧杂-8-氮杂螺[4.5]癸烷-8-基)苯甲酰胺	446.2
77		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(甲基(1-(2-(甲基磺酰基)乙基)哌啶-4-基)氨基)苯甲酰胺	523.2

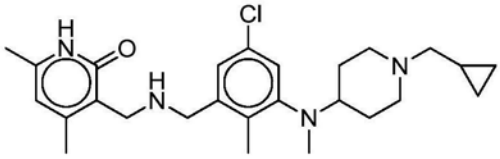
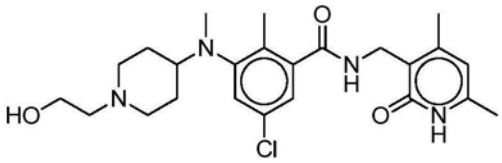
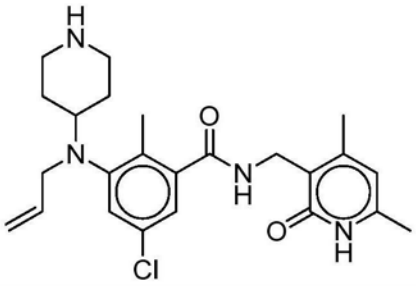
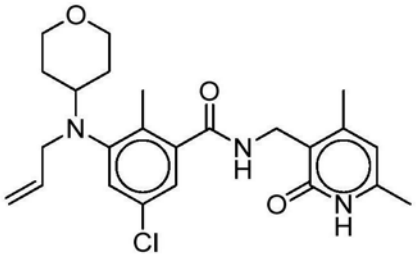
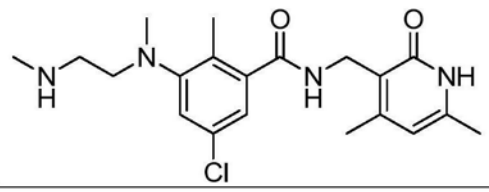
[0623]

化合物编号	结构	名称	分子量†
78		3-((1-乙酰哌啶-4-基)(甲基)氨基)-5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	459.3
79		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(甲基(1-特戊酰基哌啶-4-基)氨基)苯甲酰胺	501.2
80		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(吡咯烷-3-基氨基)苯甲酰胺	389.2
81		[[复制#19]]	
82		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(哌嗪-1-基)苯甲酰胺	389.1
83		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-((1-异丙基哌啶-4-基)(甲基)氨基)-2-甲基苯甲酰胺	459.3

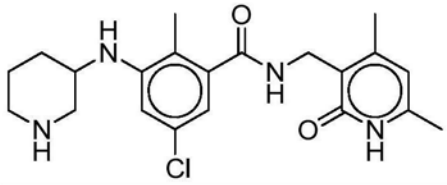
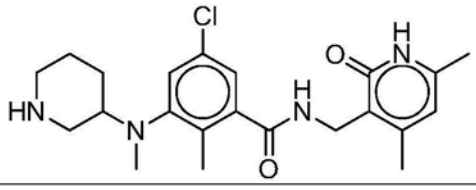
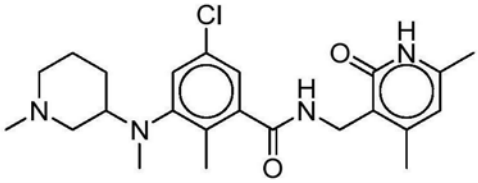
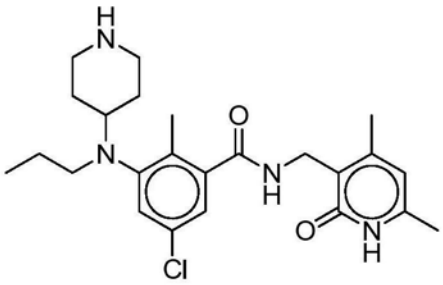
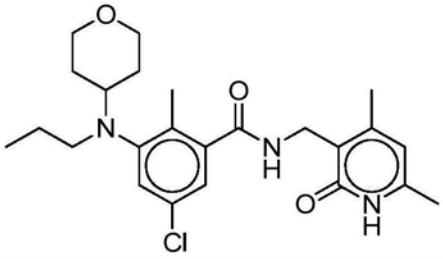
[0624]

化合物编号	结构	名称	分子量†
84		3-((1-苄基哌啶-4-基)(甲基)氨基)-5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	507.2
85		3-([1,4'-二哌啶]-4-基(甲基)氨基)-5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	500.2
86		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-((1-甲基吡咯烷-3-基)氨基)苯甲酰胺	403.1
87		(2-((5-氯-3-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰基)-2-甲基苯基)(甲基)氨基)乙基)(甲基)氨基甲酸叔丁酯	391.2
88		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(甲基(1-(甲基磺酰基)哌啶-4-基)氨基)苯甲酰胺	494.9

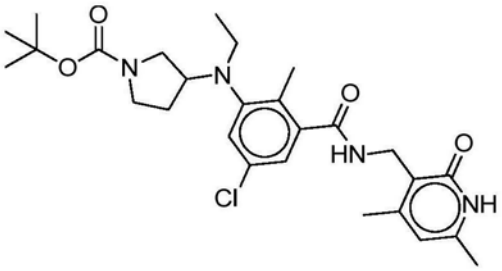
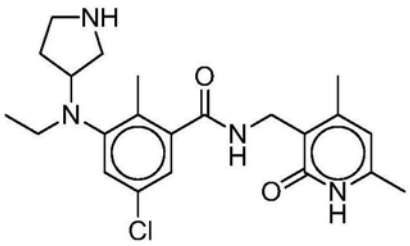
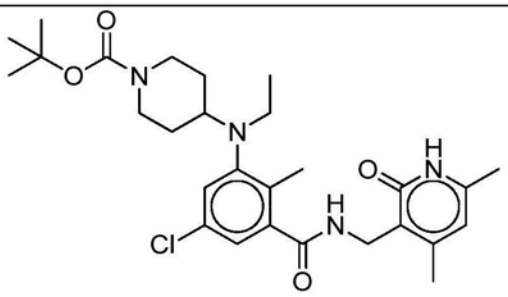
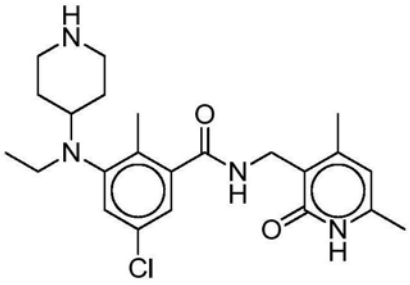
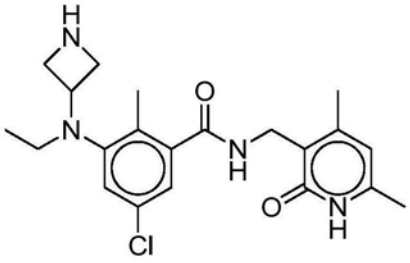
[0625]

化合物编号	结构	名称	分子量†
89		5-氯-3-((1-(环丙甲基)哌啶-4-基)(甲基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	471.2
90		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-((1-(2-羟乙基)哌啶-4-基)(甲基)氨基)-2-甲基苯甲酰胺	461.2
91		3-(烯丙基(哌啶-4-基)氨基)-5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	443.3
92		3-(烯丙基(四氢-2H-吡喃-4-基)氨基)-5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	444.3
93		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(甲基(2-(甲基氨基)乙基)氨基)苯甲酰胺	391.2

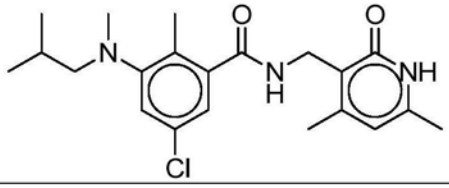
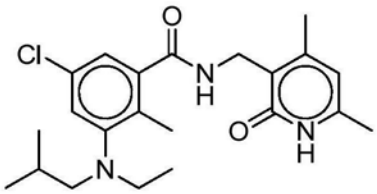
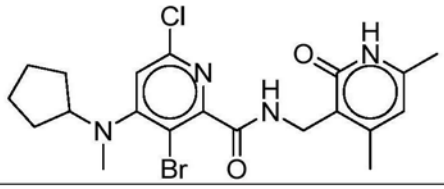
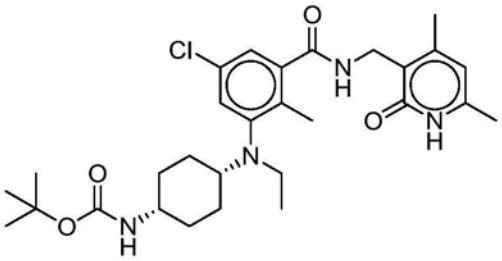
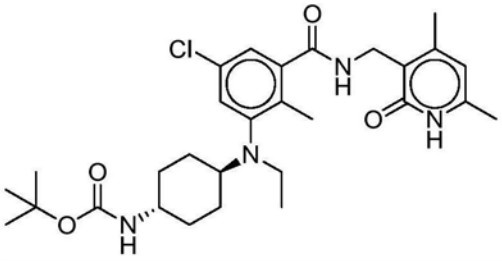
[0626]

化合物编号	结构	名称	分子量†
94		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(哌啶-3-基氨基)苯甲酰胺	403.3
95		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(甲基(哌啶-3-基)氨基)苯甲酰胺	417.3
96		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(甲基(1-甲基哌啶-3-基)氨基)苯甲酰胺	431.2
97		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(哌啶-4-基(丙基)氨基)苯甲酰胺	445.3
98		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(丙基(四氢-2H-吡喃-4-基)氨基)苯甲酰胺	445.3

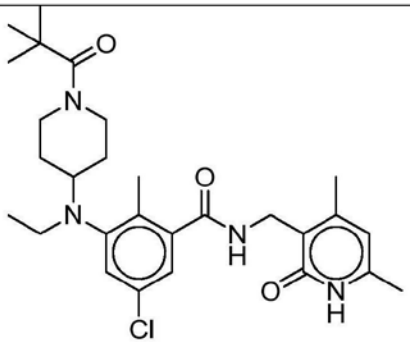
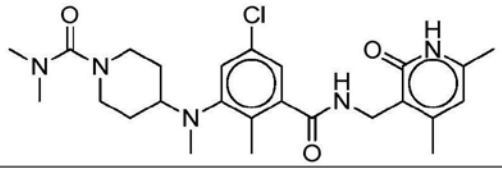
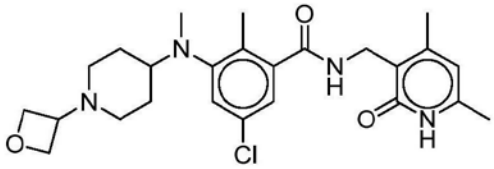
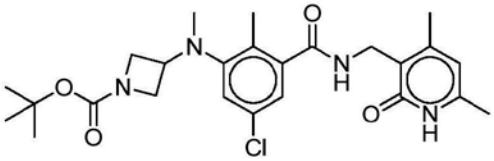
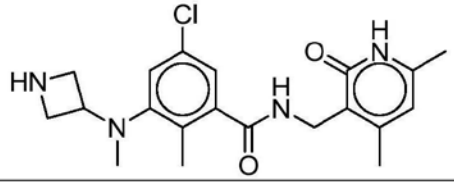
[0627]

化合物编号	结构	名称	分子量†
99		3-((5-氯-3-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰基)-2-甲基苯基)(乙基)氨基)吡咯烷-1-羧酸叔丁酯	517.4
100		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(吡咯烷-3-基)氨基)-2-甲基苯甲酰胺	417.3
101		4-((5-氯-3-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰基)-2-甲基苯基)(乙基)氨基)哌啶-1-羧酸叔丁酯	531.4
102		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(哌啶-4-基)氨基)-2-甲基苯甲酰胺	431.2
103		3-(氮杂环丁烷-3-基(乙基)氨基)-5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	403.2

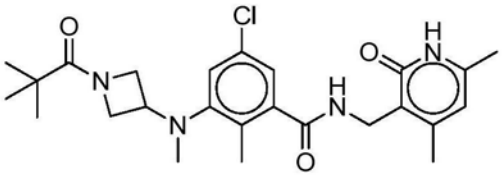
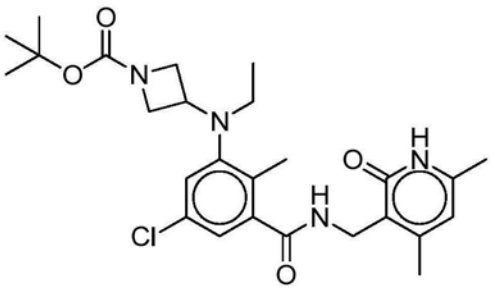
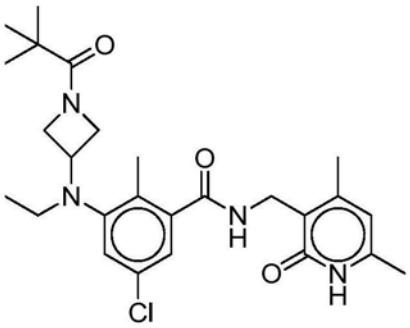
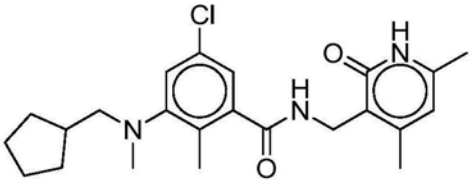
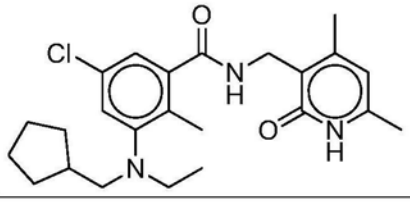
[0628]

化合物编号	结构	名称	分子量†
104		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(异丁基(甲基)氨基)-2-甲基苯甲酰胺	390.3
105		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(异丁基)氨基)-2-甲基苯甲酰胺	404.3
106		3-溴-6-氯-4-(环戊基(甲基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)吡啶酰胺	469.2
107		((1s,4s)-4-((5-氯-3-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰基)-2-甲基苯基)(乙基)氨基)环己基)氨基甲酸叔丁酯	545.4
108		((1r,4r)-4-((5-氯-3-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰基)-2-甲基苯基)(乙基)氨基)环己基)氨基甲酸叔丁酯	545.3

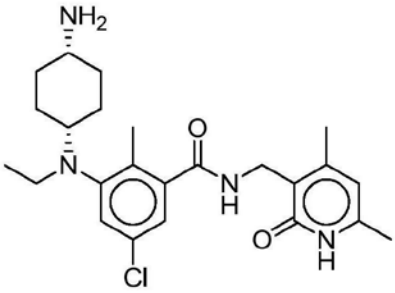
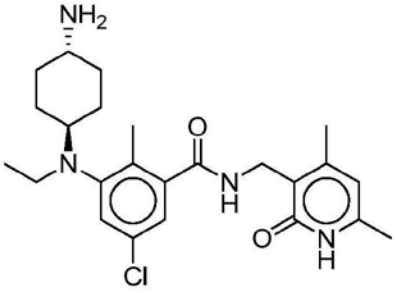
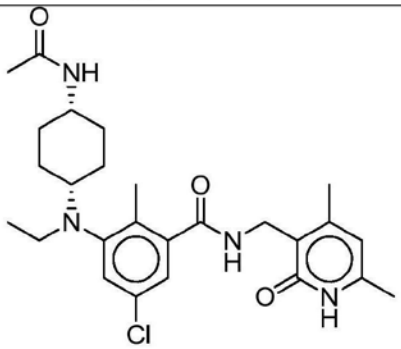
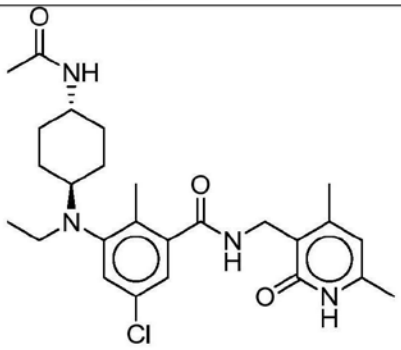
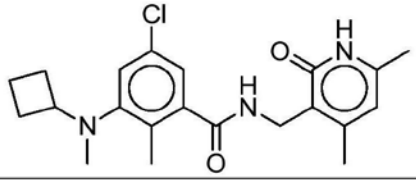
[0629]

化合物编号	结构	名称	分子量†
109		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(1-特戊酰基哌啶-4-基)氨基)-2-甲基苯甲酰胺	515.4
110		4-((5-氯-3-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰基)-2-甲基苯基)(甲基)氨基)-N,N-二甲基哌啶-1-甲酰胺	488.2
111		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(甲基(1-(氧杂环丁烷-3-基)哌啶-4-基)氨基)苯甲酰胺	473.3
112		3-((5-氯-3-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰基)-2-甲基苯基)(甲基)氨基)氮杂环丁烷-1-羧酸叔丁酯	489.3
113		3-(氮杂环丁烷-3-基(甲基)氨基)-5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	389.3

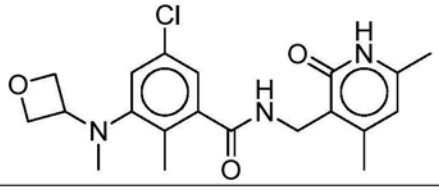
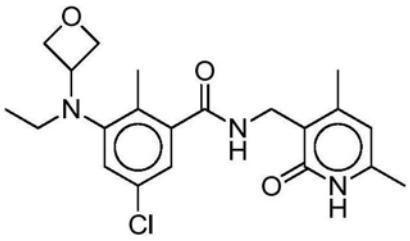
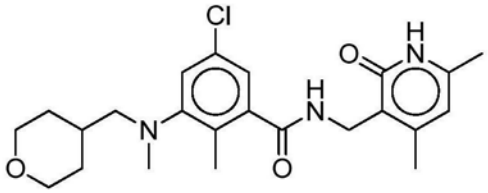
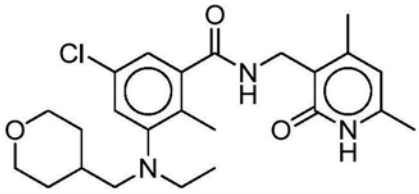
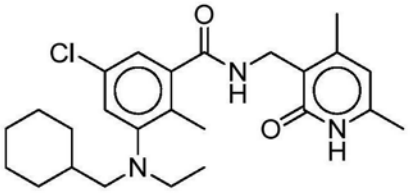
[0630]

化合物编号	结构	名称	分子量†
114		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(甲基(1-特戊酰基氮杂环丁烷-3-基)氨基)苯甲酰胺	473.2
115		3-((5-氯-3-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰基)-2-甲基苯基)(乙基)氨基)氮杂环丁烷-1-羧酸叔丁酯	503.3
116		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(1-特戊酰基氮杂环丁烷-3-基)氨基)-2-甲基苯甲酰胺	487.2
117		5-氯-3-((环戊基甲基)(甲基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	416.2
118		5-氯-3-((环戊基甲基)(乙基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	430.2

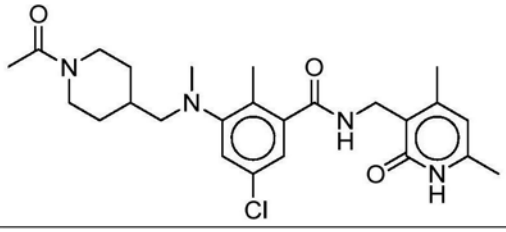
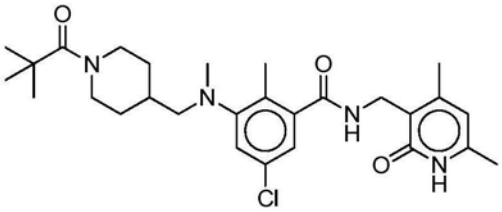
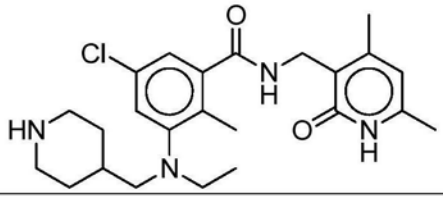
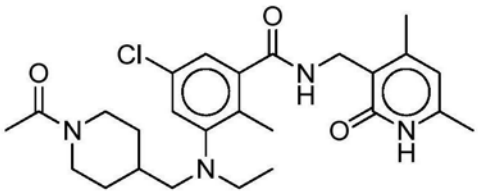
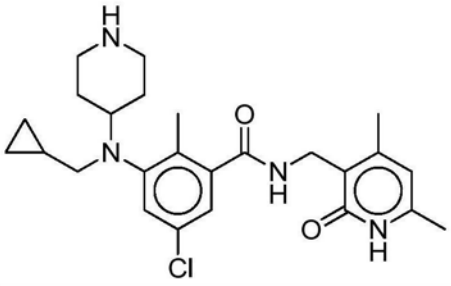
[0631]

化合物编号	结构	名称	分子量†
119		3-(((1s,4s)-4-氨基环己基)(乙基)氨基)-5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	445.3
120		3-(((1r,4r)-4-氨基环己基)(乙基)氨基)-5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	445.2
121		3-(((1s,4s)-4-乙酰氨基环己基)(乙基)氨基)-5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	487.3
122		3-(((1r,4r)-4-乙酰氨基环己基)(乙基)氨基)-5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	487.3
123		5-氯-3-(环丁基(甲基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	388.1

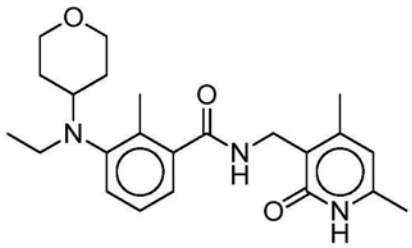
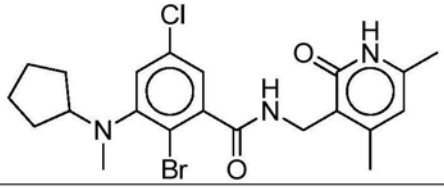
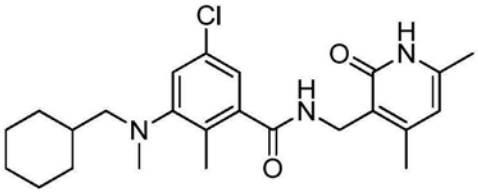
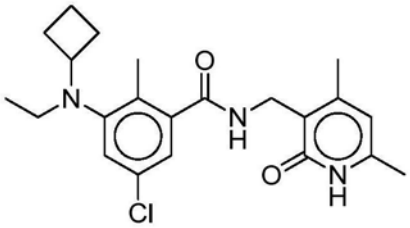
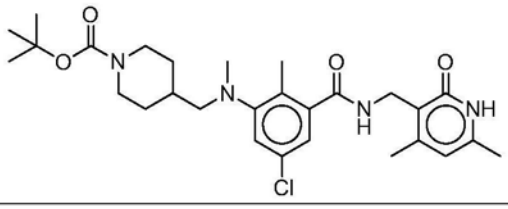
[0632]

化合物编号	结构	名称	分子量†
124		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(甲基(氧杂环丁烷-3-基)氨基)苯甲酰胺	390.2
125		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(氧杂环丁烷-3-基)氨基)-2-甲基苯甲酰胺	404.2
126		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(甲基((四氢-2H-吡喃-4-基)甲基)氨基)苯甲酰胺	432.3
127		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基((四氢-2H-吡喃-4-基)甲基)氨基)-2-甲基苯甲酰胺	446.2
128		5-氯-3-((环己基甲基)(乙基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	444.3

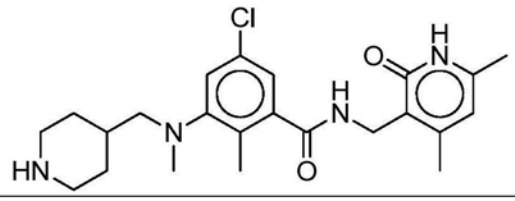
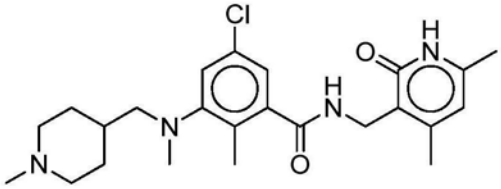
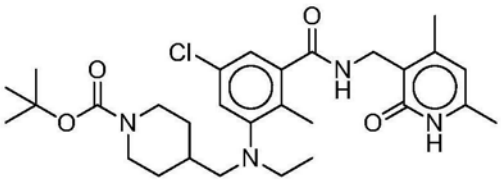
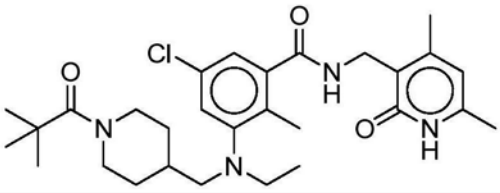
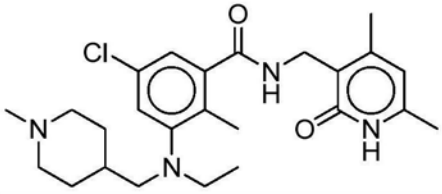
[0633]

化合物编号	结构	名称	分子量†
129		3-(((1-乙酰哌啶-4-基)甲基)(甲基)氨基)-5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	473.3
130		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(甲基((1-特戊酰基哌啶-4-基)甲基)氨基)苯甲酰胺	515.3
131		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(哌啶-4-基甲基)氨基)-2-甲基苯甲酰胺	445.2
132		3-(((1-乙酰哌啶-4-基)甲基)(乙基)氨基)-5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	487.3
133		5-氯-3-((环丙甲基)(哌啶-4-基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	457.2

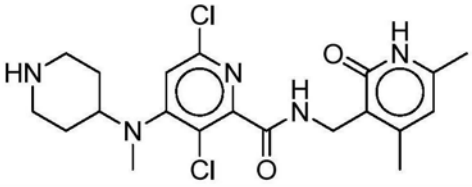
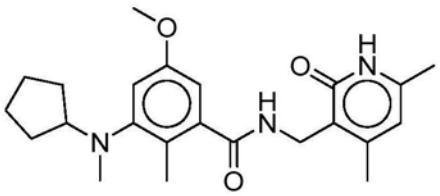
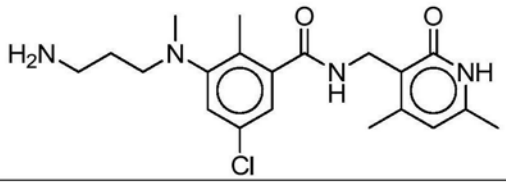
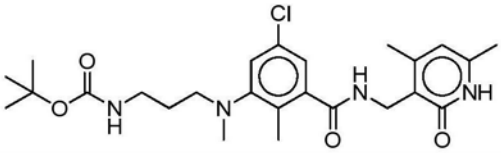
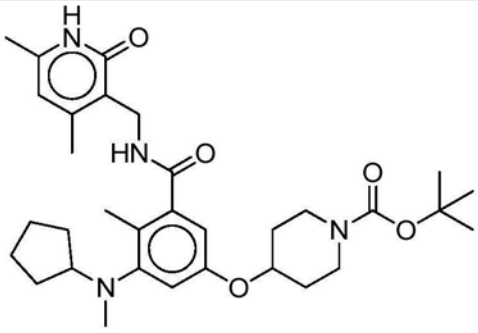
[0634]

化合物编号	结构	名称	分子量†
134		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(四氢-2H-吡喃-4-基)氨基)-2-甲基苯甲酰胺	398.3
135		2-溴-5-氯-3-(环戊基(甲基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)苯甲酰胺	466.1
136		5-氯-3-((环己基甲基)(甲基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	430.2
137		5-氯-3-(环丁基(乙基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	402.2
138		4-(((5-氯-3-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰基)-2-甲基苯基)(甲基)氨基)甲基)哌啶-1-羧酸叔丁酯	531.3

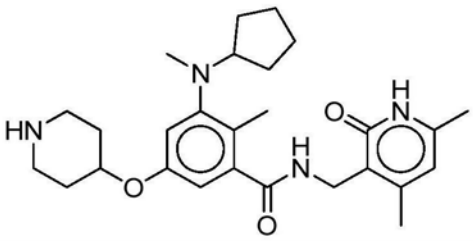
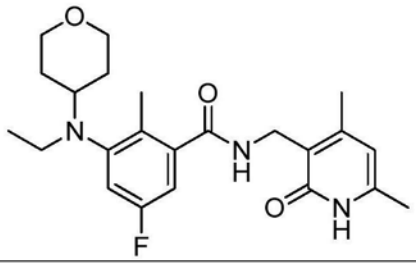
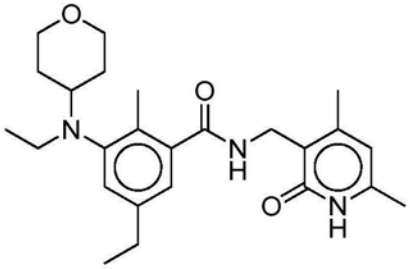
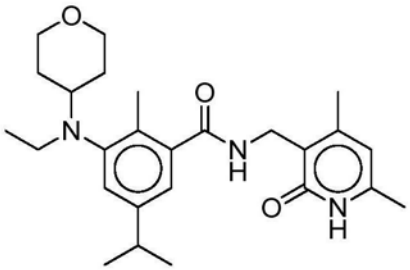
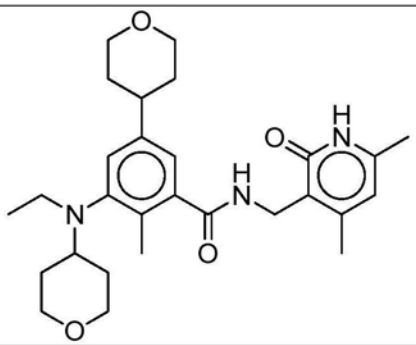
[0635]

化合物编号	结构	名称	分子量†
139		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(甲基(哌啶-4-基甲基)氨基)苯甲酰胺	431.2
140		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(甲基((1-甲基哌啶-4-基)甲基)氨基)苯甲酰胺	445.2
141		4-(((5-氯-3-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰基)-2-甲基苯基)(乙基)氨基)甲基)哌啶-1-羧酸叔丁酯	545.3
142		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基((1-特戊酰基哌啶-4-基)甲基)氨基)-2-甲基苯甲酰胺	530.4
143		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基((1-甲基哌啶-4-基)甲基)氨基)-2-甲基苯甲酰胺	459.3

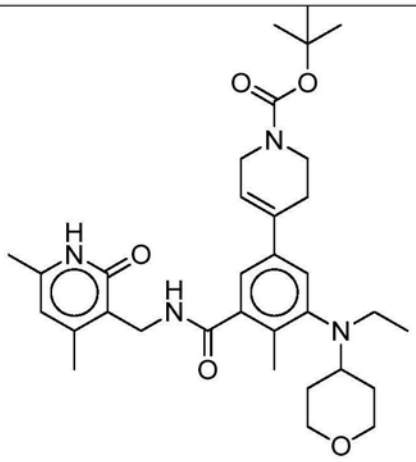
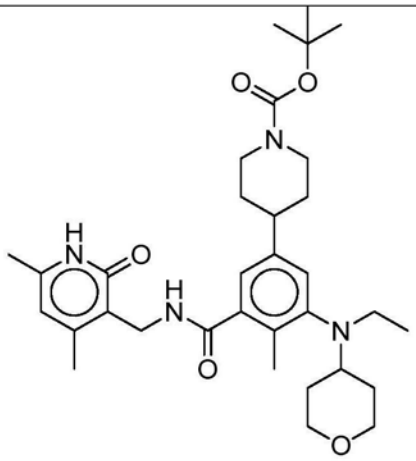
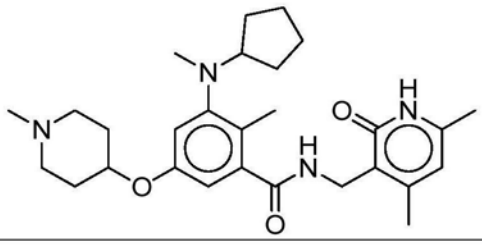
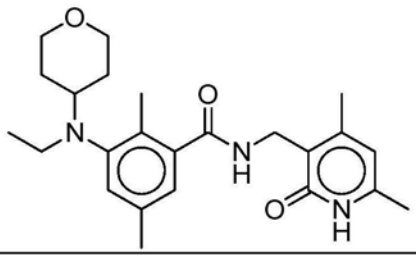
[0636]

化合物编号	结构	名称	分子量†
144		3,6-二氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-4-(甲基(哌啶-4-基)氨基)吡啶酰胺	439.8
145		3-(环戊基(甲基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-5-甲氧基-2-甲基苯甲酰胺	398.1
146		3-((3-氨基丙基)(甲基)氨基)-5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	391.1
147		(3-((5-氯-3-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰基)-2-甲基苯基)(甲基)氨基)丙基)氨基甲酸叔丁酯	491.1
148		4-(3-(环戊基(甲基)氨基)-5-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰基)-4-甲基苯氧基)哌啶-1-羧酸叔丁酯	567.3

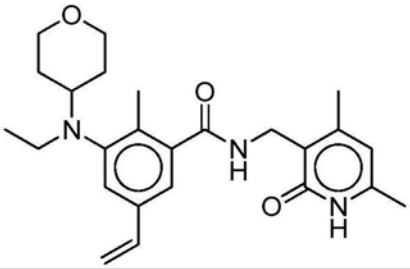
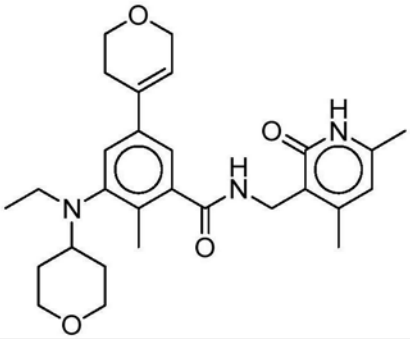
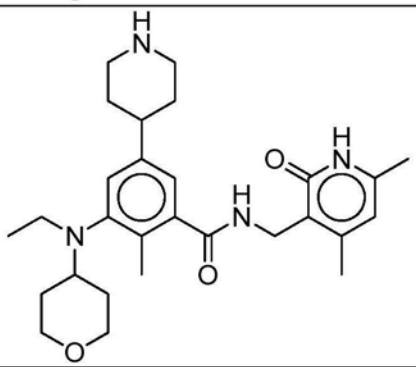
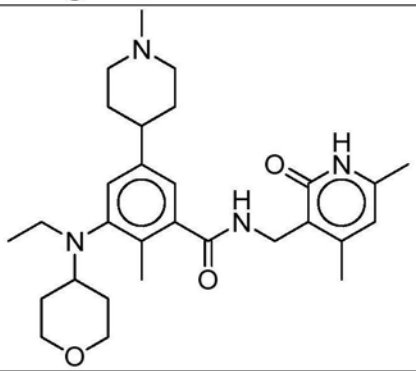
[0637]

化合物编号	结构	名称	分子量†
149		3-(环戊基(甲基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-5-(哌啶-4-基氧)苯甲酰胺	467.2
150		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(四氢-2H-吡喃-4-基)氨基)-5-氟-2-甲基苯甲酰胺	416.1
151		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-5-乙基-3-(乙基(四氢-2H-吡喃-4-基)氨基)-2-甲基苯甲酰胺	446.2
152		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(四氢-2H-吡喃-4-基)氨基)-5-异丙基-2-甲基苯甲酰胺	440.2
153		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(四氢-2H-吡喃-4-基)氨基)-2-甲基-5-(四氢-2H-吡喃-4-基)苯甲酰胺	482.2

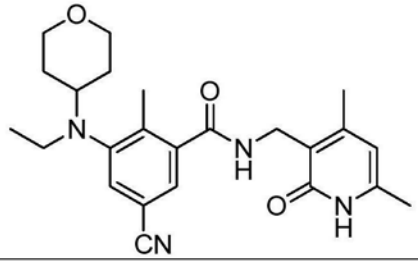
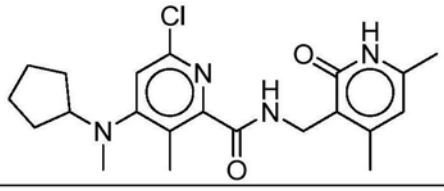
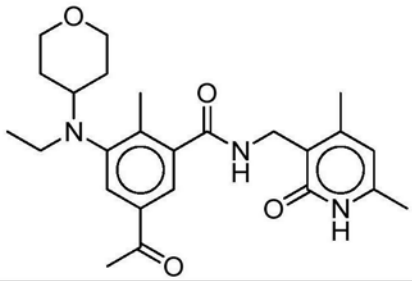
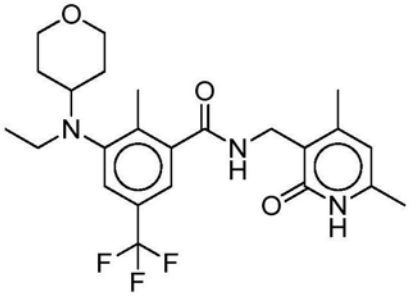
[0638]

化合物编号	结构	名称	分子量†
154		4-(3-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰基)-5-(乙基(四氢-2H-吡喃-4-基)氨基)-4-甲基苯基)-5,6-二氢吡啶-1(2H)-羧酸叔丁酯	579.3
155		4-(3-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰基)-5-(乙基(四氢-2H-吡喃-4-基)氨基)-4-甲基苯基)哌啶-1-羧酸叔丁酯	581.2
156		3-(环戊基(甲基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-5-((1-甲基哌啶-4-基)氧基)苯甲酰胺	481.3
157		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(四氢-2H-吡喃-4-基)氨基)-2,5-二甲基苯甲酰胺	412.2

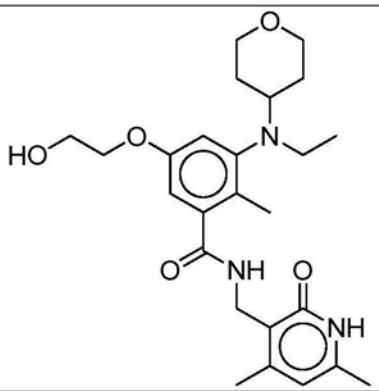
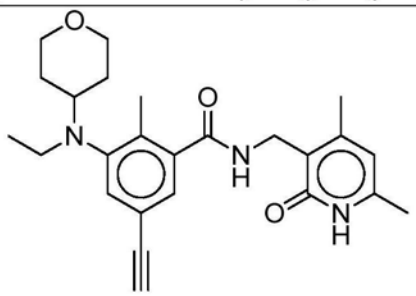
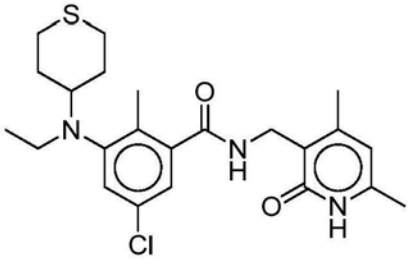
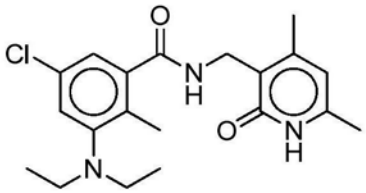
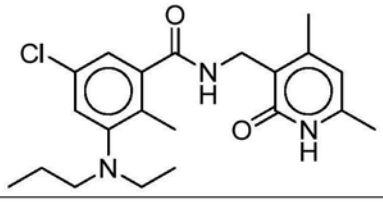
[0639]

化合物编号	结构	名称	分子量†
158		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(四氢-2H-吡喃-4-基)氨基)-2-甲基-5-乙烯基苯甲酰胺	424.1
159		5-(3,6-二氢-2H-吡喃-4-基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(四氢-2H-吡喃-4-基)氨基)-2-甲基苯甲酰胺	480.3
160		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(四氢-2H-吡喃-4-基)氨基)-2-甲基-5-(哌啶-4-基)苯甲酰胺	481.3
161		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(四氢-2H-吡喃-4-基)氨基)-2-甲基-5-(1-甲基哌啶-4-基)苯甲酰胺	495.3

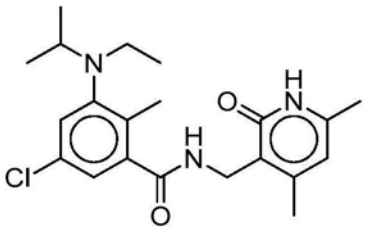
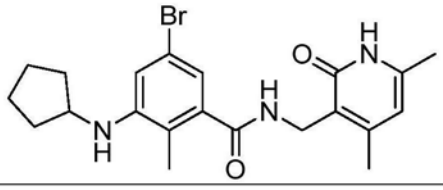
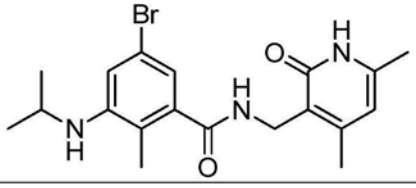
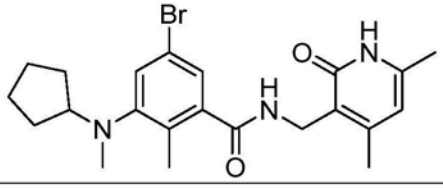
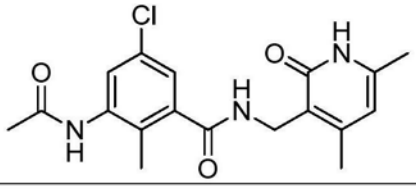
[0640]

化合物编号	结构	名称	分子量†
162		5-氰基-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(四氢-2H-吡喃-4-基)氨基)-2-甲基苯甲酰胺	423.2
163		6-氯-4-(环戊基(甲基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-甲基吡啶酰胺	403.2
164		5-乙酰-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(四氢-2H-吡喃-4-基)氨基)-2-甲基苯甲酰胺	440.2
165		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(四氢-2H-吡喃-4-基)氨基)-2-甲基-5-(三氟甲基)苯甲酰胺	466.2

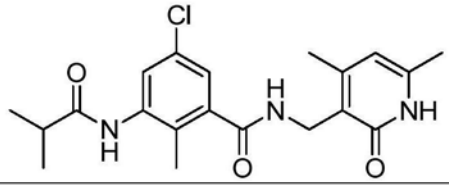
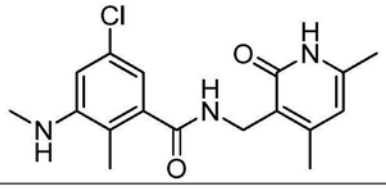
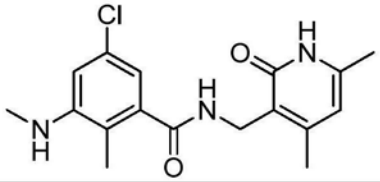
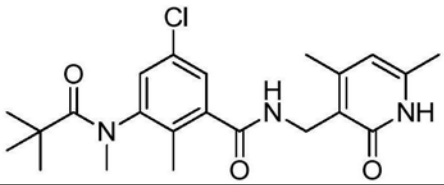
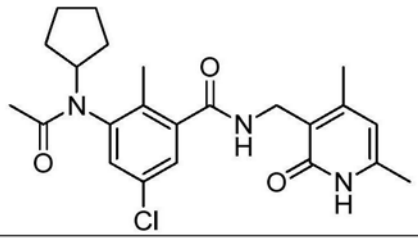
[0641]

化合物编号	结构	名称	分子量†
166		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(四氢-2H-吡喃-4-基)氨基)-5-(2-羟基乙氧)-2-甲基苯甲酰胺	458.2
167		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(四氢-2H-吡喃-4-基)氨基)-5-乙炔基-2-甲基苯甲酰胺	422.3
168		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(四氢-2H-噻喃-4-基)氨基)-2-甲基苯甲酰胺	448.1
169		5-氯-3-(二乙基氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	376
170		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(丙基)氨基)-2-甲基苯甲酰胺	390.2

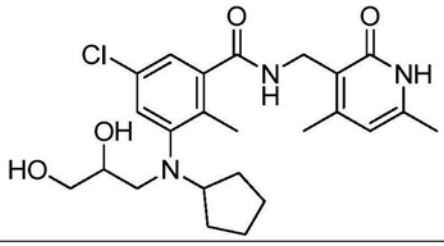
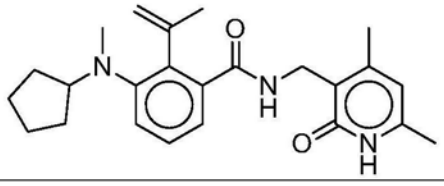
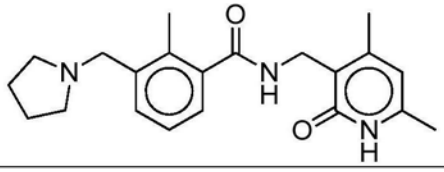
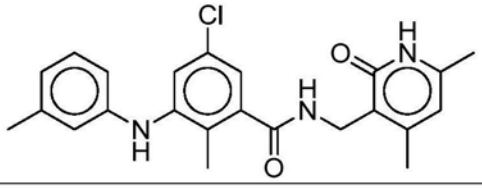
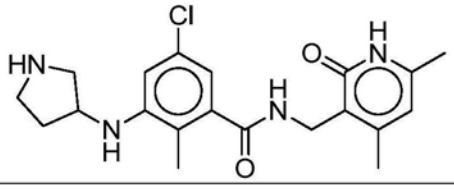
[0642]

化合物编号	结构	名称	分子量†
171		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(异丙基)氨基)-2-甲基苯甲酰胺	390.1
172		5-溴-3-(环戊基氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	432.1
173		5-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(异丙基氨基)-2-甲基苯甲酰胺	406.1
174		5-溴-3-(环戊基(甲基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	446.2
175		3-乙酰氨基-5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	362.1

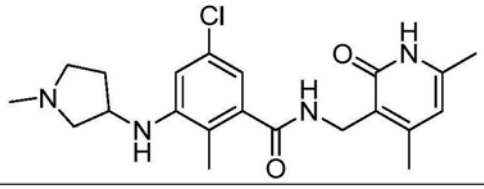
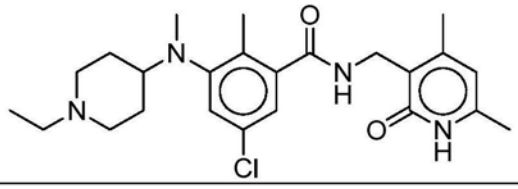
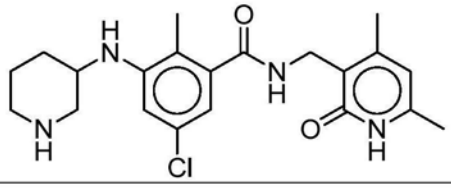
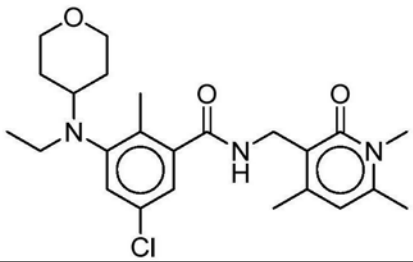
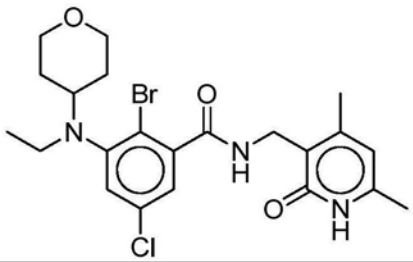
[0643]

化合物编号	结构	名称	分子量†
176		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡-3-基)甲基)-3-异丁酰胺基-2-甲基苯甲酰胺	390.1
177		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(甲基氨基)苯甲酰胺	334.2
178		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(甲基氨基)苯甲酰胺	334.2
179		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(N-甲基特戊酰基氨基)苯甲酰胺	418.2
180		5-氯-3-(N-环戊基乙酰氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	430.3

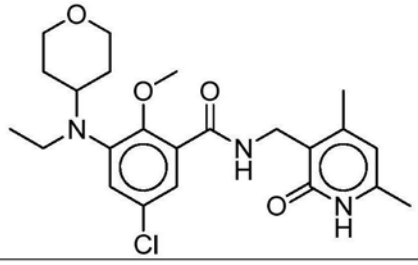
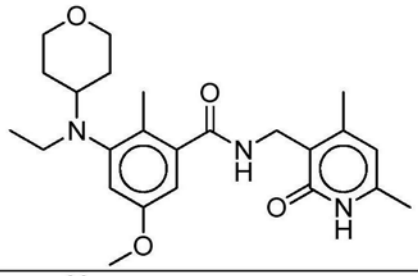
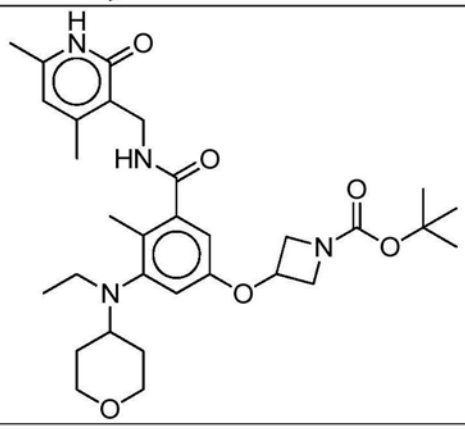
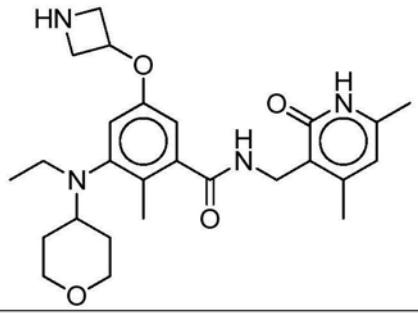
[0644]

化合物编号	结构	名称	分子量†
181		5-氯-3-(环戊基(2,3-二羟基丙基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	462.2
182		3-(环戊基(甲基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-(丙-1-烯-2-基)苯甲酰胺	394.3
183		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(吡咯烷-1-基甲基)苯甲酰胺	354.3
184		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(间-苯甲基氨基)苯甲酰胺	410.3
185		[[复制 1184#184]]	
186		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(吡咯烷-3-基氨基)苯甲酰胺	389.2

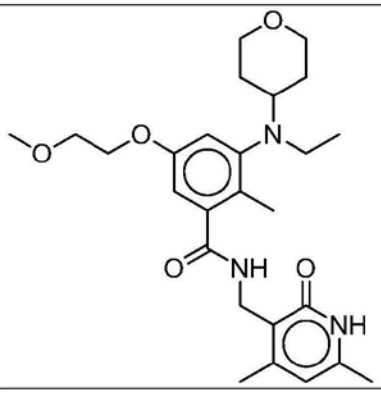
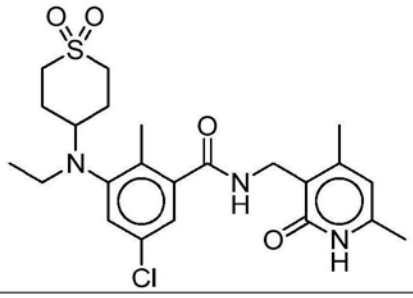
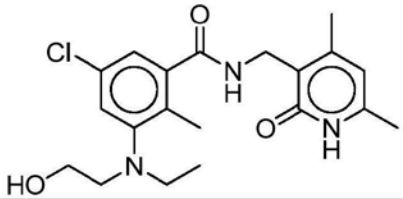
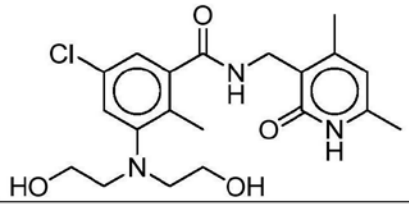
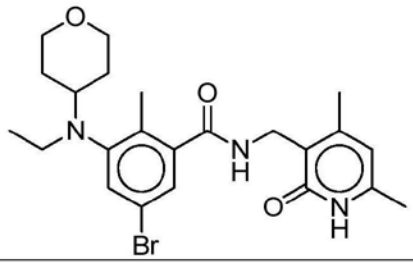
[0645]

化合物编号	结构	名称	分子量†
187		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-((1-甲基吡咯烷-3-基)氨基)苯甲酰胺	403.1
188		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-((1-乙基哌啶-4-基)(甲基)氨基)-2-甲基苯甲酰胺	445.4
189		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(哌啶-3-基氨基)苯甲酰胺	403.3
190		5-氯-3-(乙基(四氢-2H-吡喃-4-基)氨基)-2-甲基-N-((1,4,6-三甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)苯甲酰胺	446.3
191		2-溴-5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(四氢-2H-吡喃-4-基)氨基)苯甲酰胺	498

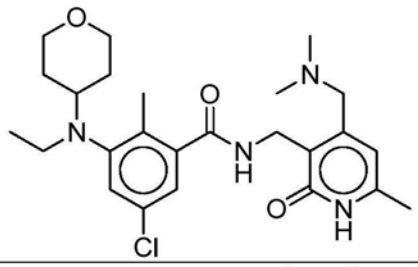
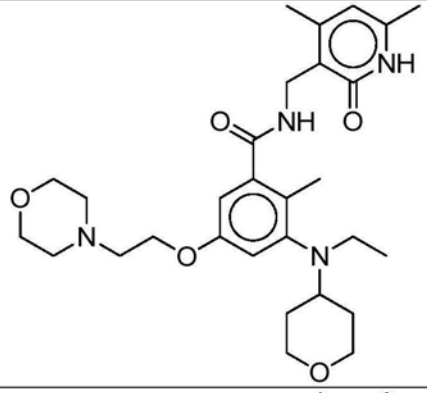
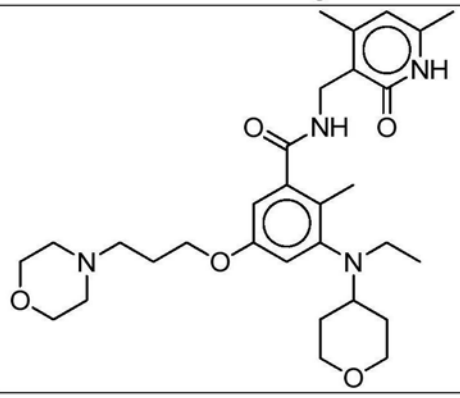
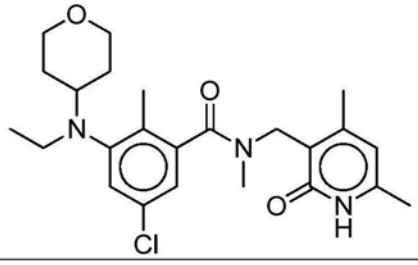
[0646]

化合物编号	结构	名称	分子量†
192		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(四氢-2H-吡喃-4-基)氨基)-2-甲氧基苯甲酰胺	449.5
193		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(四氢-2H-吡喃-4-基)氨基)-5-甲氧基-2-甲基苯甲酰胺	428.2
194		3-(3-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰基)-5-(乙基(四氢-2H-吡喃-4-基)氨基)-4-甲基苯氧基)氮杂环丁烷-1-羧酸叔丁酯	569.3
195		5-(氮杂环丁烷-3-基氧基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(四氢-2H-吡喃-4-基)氨基)-2-甲基苯甲酰胺	469.3

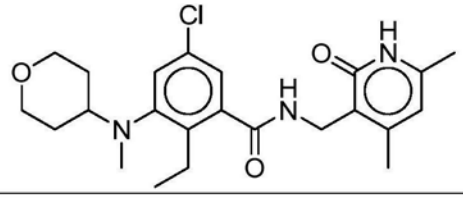
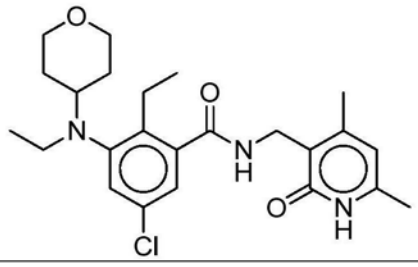
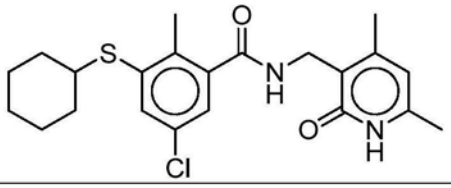
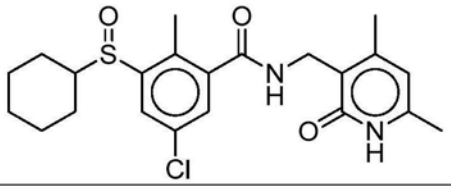
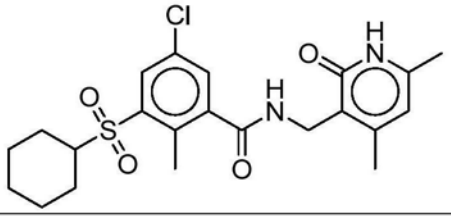
[0647]

化合物编号	结构	名称	分子量†
196		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(四氢-2H-吡喃-4-基)氨基)-5-(2-甲氧基乙氧基)-2-甲基苯甲酰胺	472.2
197		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-((1,1-二氧化四氢-2H-噻喃-4-基)(乙基)氨基)-2-甲基苯甲酰胺	480.1
198		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(2-羟乙基)氨基)-2-甲基苯甲酰胺	392.1
199		3-(双(2-羟乙基)氨基)-5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	408.1
200		5-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(四氢-2H-吡喃-4-基)氨基)-2-甲基苯甲酰胺	476.1

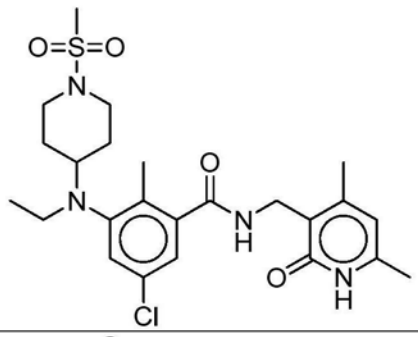
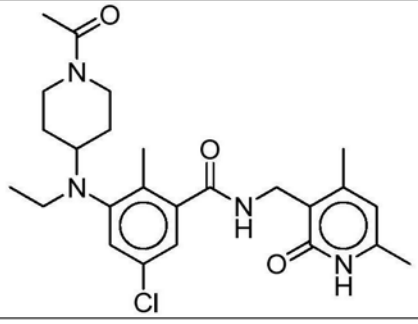
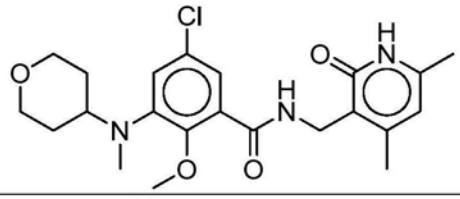
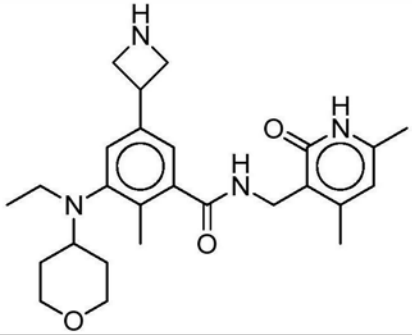
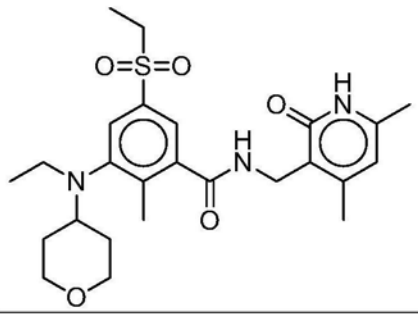
[0648]

化合物编号	结构	名称	分子量†
201		5-氯-N-((4-((二甲基氨基)甲基)-6-甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(四氢-2H-吡喃-4-基)氨基)-2-甲基苯甲酰胺	475.2
202		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(四氢-2H-吡喃-4-基)氨基)-2-甲基-5-(2-吗啉基乙氧基)苯甲酰胺	527.4
203		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(四氢-2H-吡喃-4-基)氨基)-2-甲基-5-(3-吗啉基丙氧基)苯甲酰胺	541.4
204		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(四氢-2H-吡喃-4-基)氨基)-N,2-二甲基苯甲酰胺	446.1

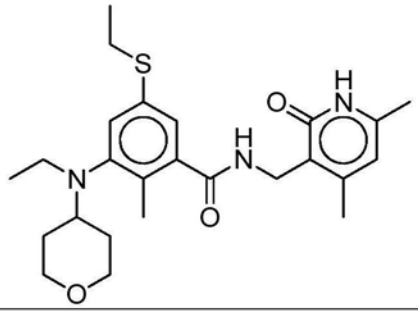
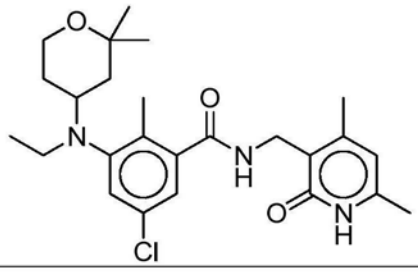
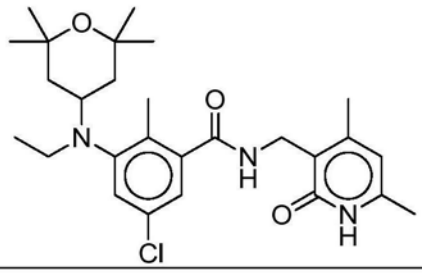
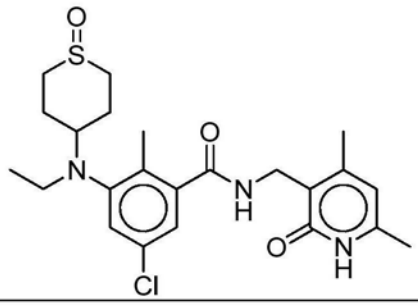
[0649]

化合物编号	结构	名称	分子量†
205		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-乙基-3-(甲基(四氢-2H-吡喃-4-基)氨基)苯甲酰胺	432.1
206		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-乙基-3-(乙基(四氢-2H-吡喃-4-基)氨基)苯甲酰胺	446.1
207		5-氯-3-(环己基硫代)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	419.2
208		5-氯-3-(环己基亚磺酰基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	435.1
209		5-氯-3-(环己基磺酰基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	451.1

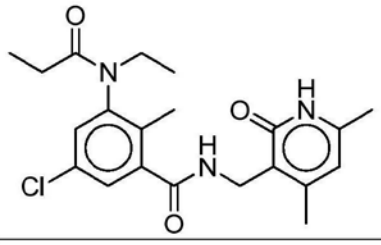
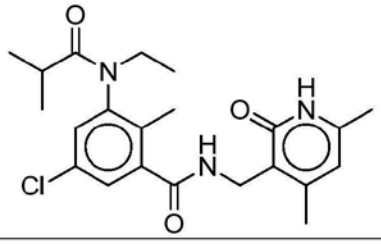
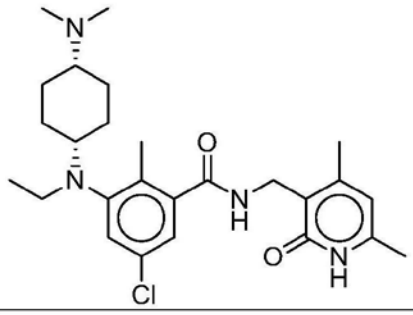
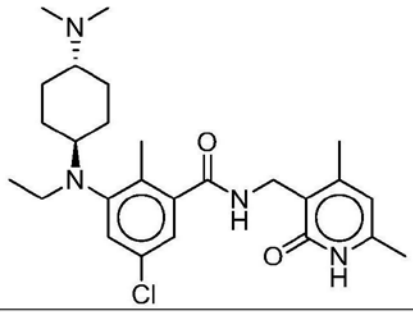
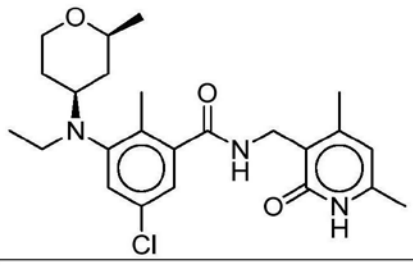
[0650]

化合物编号	结构	名称	分子量†
210		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(1-(甲基磺酰基)哌啶-4-基)氨基)-2-甲基苯甲酰胺	509.2
211		3-((1-乙酰哌啶-4-基)(乙基)氨基)-5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	495.1
212		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲氧基-3-(甲基(四氢-2H-吡喃-4-基)氨基)苯甲酰胺	434.1
213		5-(氮杂环丁烷-3-基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(四氢-2H-吡喃-4-基)氨基)-2-甲基苯甲酰胺	453.2
214		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(四氢-2H-吡喃-4-基)氨基)-5-(乙基磺酰基)-2-甲基苯甲酰胺	490.3

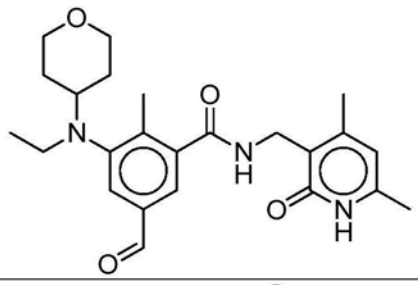
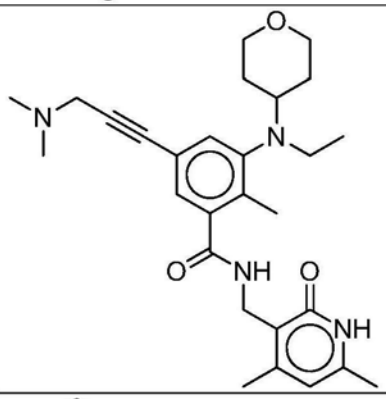
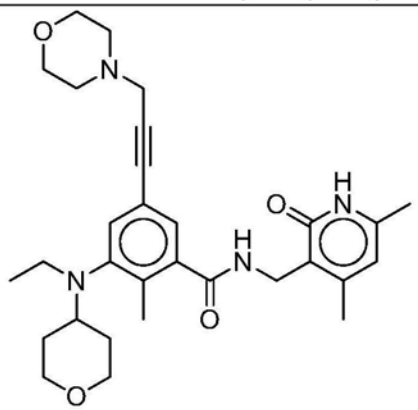
[0651]

化合物编号	结构	名称	分子量†
215		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(四氢-2H-吡喃-4-基)氨基)-5-(乙基硫代)-2-甲基苯甲酰胺	458.2
216		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-((2,2-二甲基四氢-2H-吡喃-4-基)(乙基)氨基)-2-甲基苯甲酰胺	460.3
217		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(2,2,6,6-四甲基四氢-2H-吡喃-4-基)氨基)-2-甲基苯甲酰胺	488.5
218		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(1-氧化四氢-2H-噻喃-4-基)氨基)-2-甲基苯甲酰胺	464.1

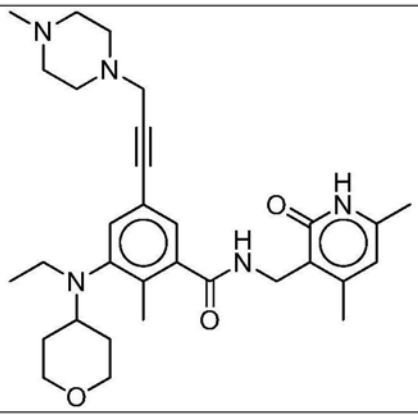
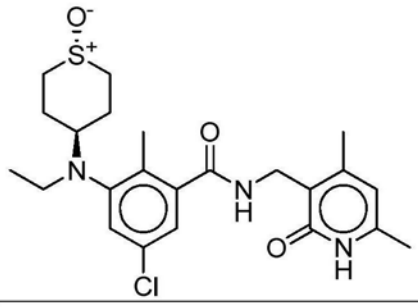
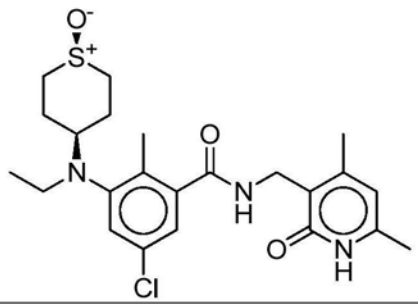
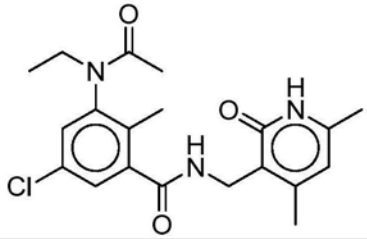
[0652]

化合物编号	结构	名称	分子量†
219		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(N-乙基丙酰胺基)-2-甲基苯甲酰胺	404.2
220		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(N-乙基异丁酰胺基)-2-甲基苯甲酰胺	418.2
221		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((1s,4s)-4-(二甲基氨基)环己基)(乙基)氨基)-2-甲基苯甲酰胺	473.3
222		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-2-甲基苯甲酰胺	473.4
223		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基((2S,4S)-2-甲基四氢-2H-吡喃-4-基)氨基)-2-甲基苯甲	446.2

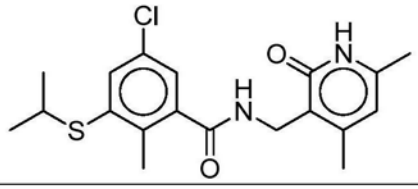
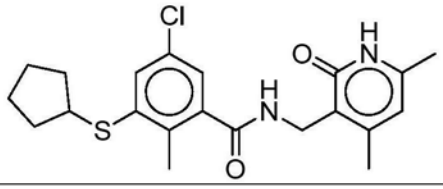
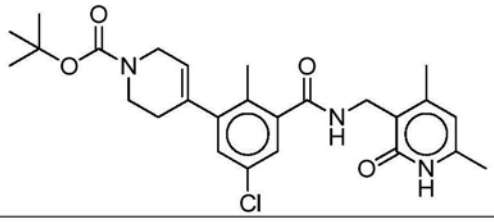
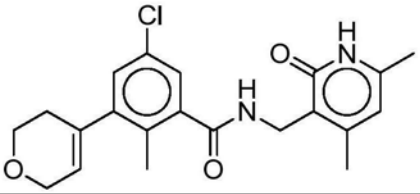
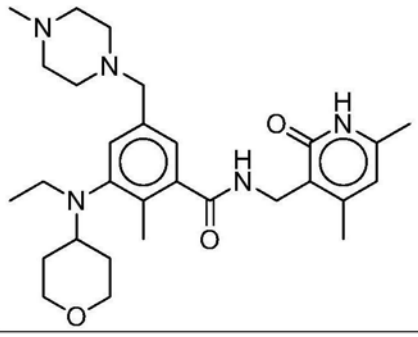
[0653]

化合物编号	结构	名称	分子量†
		酰胺	
224		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(四氢-2H-吡喃-4-基)氨基)-5-甲酰基-2-甲基苯甲酰胺	426.2
225		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-5-(3-(二甲基氨基)丙-1-炔-1-基)-3-(乙基(四氢-2H-吡喃-4-基)氨基)-2-甲基苯甲酰胺	479.2
226		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(四氢-2H-吡喃-4-基)氨基)-2-甲基-5-(3-吗啉基丙-1-炔-1-基)苯甲酰胺	521.3

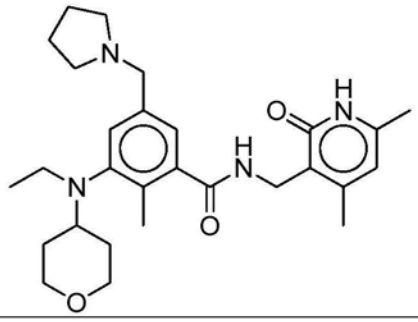
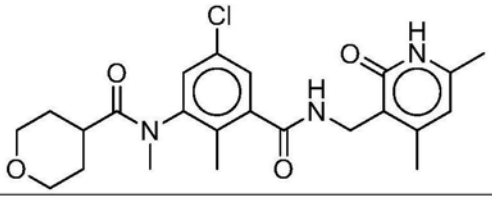
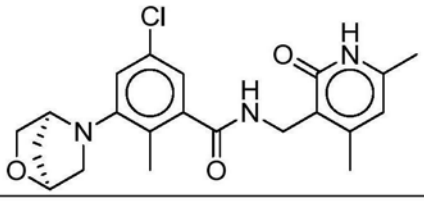
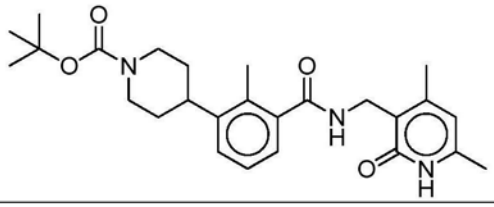
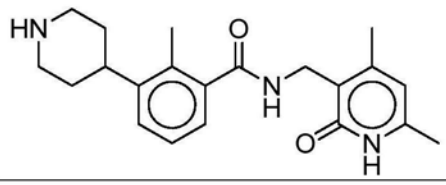
[0654]

化合物编号	结构	名称	分子量†
227		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(四氢-2H-吡喃-4-基)氨基)-2-甲基-5-(3-(4-甲基哌嗪-1-基)丙-1-炔-1-基)苯甲酰胺	534.4
228		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基((1r,4r)-1-氧化四氢-2H-噻喃-4-基)氨基)-2-甲基苯甲酰胺	464.1
229		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基((1s,4s)-1-氧化四氢-2H-噻喃-4-基)氨基)-2-甲基苯甲酰胺	464.2
230		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(N-乙基乙酰胺基)-2-甲基苯甲酰胺	390.2

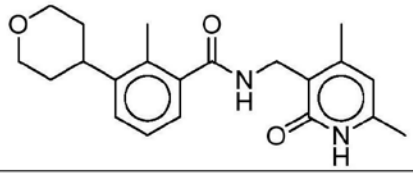
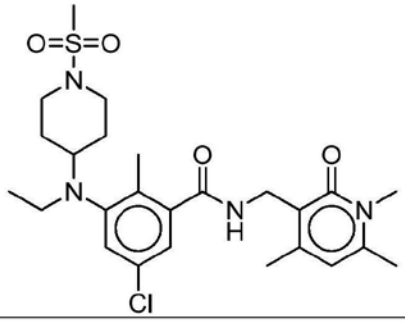
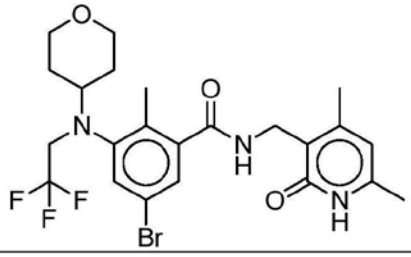
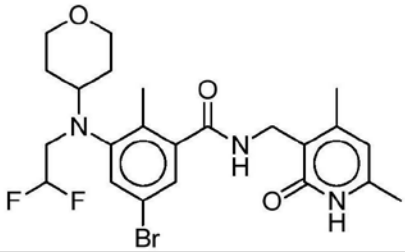
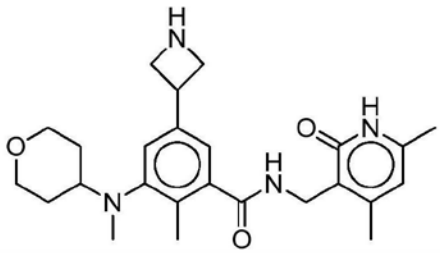
[0655]

化合物编号	结构	名称	分子量†
231		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(异丙基硫代)-2-甲基苯甲酰胺	379.1
232		5-氯-3-(环戊基硫代)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	405.1
233		4-(5-氯-3-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰基)-2-甲基苯基)-5,6-二氢吡啶-1(2H)-羧酸叔丁酯	486.2
234		5-氯-3-(3,6-二氢-2H-吡喃-4-基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	387.1
235		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(四氢-2H-吡喃-4-基)氨基)-2-甲基-5-((4-甲基哌嗪-1-基)甲基)苯甲酰胺	510.4

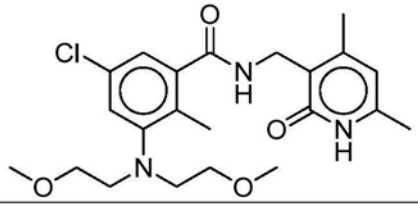
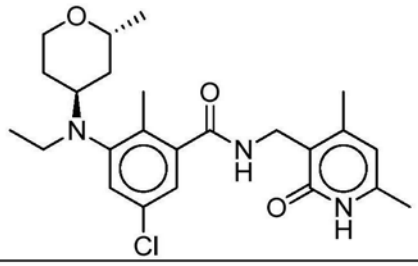
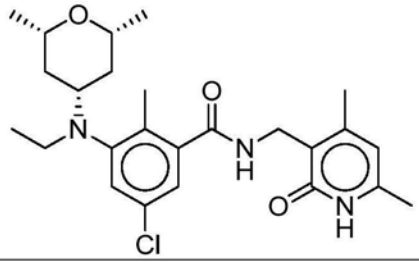
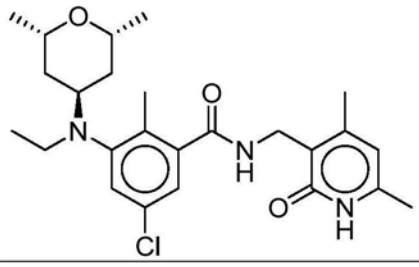
[0656]

化合物编号	结构	名称	分子量†
236		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(四氢-2H-吡喃-4-基)氨基)-2-甲基-5-(吡咯烷-1-基甲基)苯甲酰胺	481.3
237		N-(5-氯-3-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰基)-2-甲基苯基)-N-甲基四氢-2H-吡喃-4-甲酰胺	446.1
238		3-((1S,4S)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	402.1
239		4-(3-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰基)-2-甲基苯基)哌啶-1-羧酸叔丁酯	454.2
240		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(哌啶-4-基)苯甲酰胺	354.2

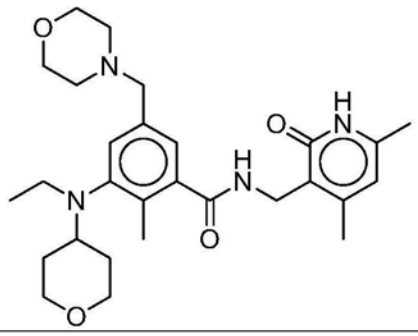
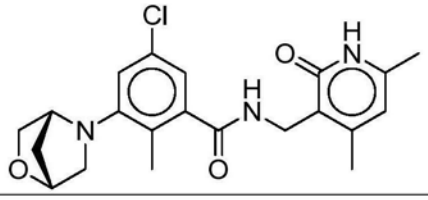
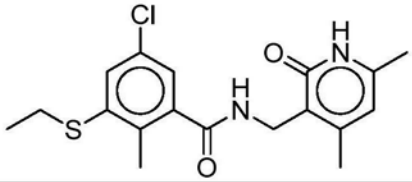
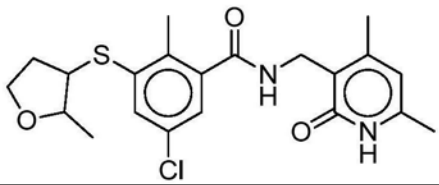
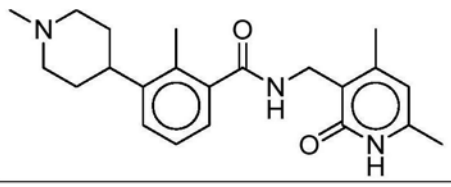
[0657]

化合物编号	结构	名称	分子量†
241		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(四氢-2H-吡喃-4-基)苯甲酰胺	355.2
242		5-氯-3-(乙基(1-(甲基磺酰基)哌啶-4-基)氨基)-2-甲基-N-((1,4,6-三甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)苯甲酰胺	522.2
243		5-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-((四氢-2H-吡喃-4-基)(2,2,2-三氟乙基)氨基)苯甲酰胺	531
244		5-溴-3-((2,2-二氟乙基)(四氢-2H-吡喃-4-基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	513
245		5-(氮杂环丁烷-3-基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(甲基(四氢-2H-吡喃-4-基)氨基)苯甲酰胺	439.3

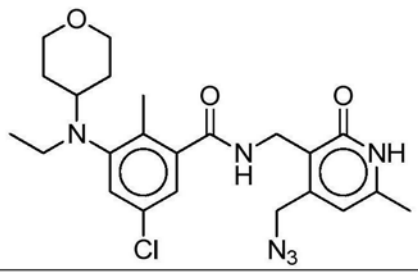
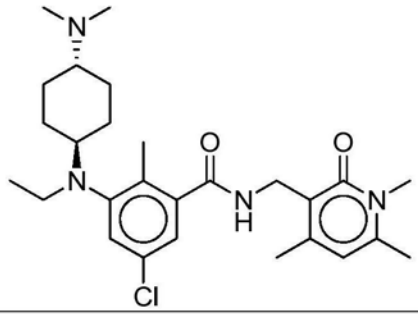
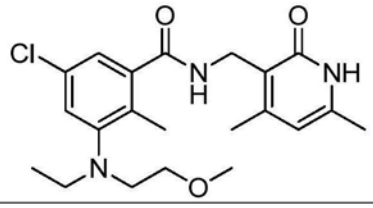
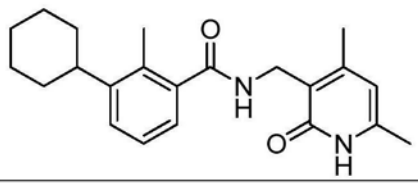
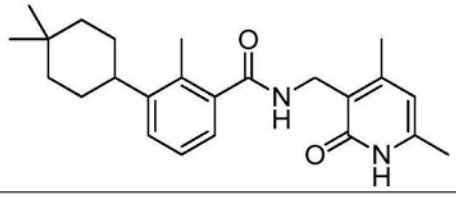
[0658]

化合物编号	结构	名称	分子量†
246		3-(双(2-甲氧基乙基)氨基)-5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	436.2
247		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-((乙基((2R,4S)-2-甲基四氢-2H-吡喃-4-基)氨基)-2-甲基苯甲酰胺	446.2
248		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((2R,4r,6S)-2,6-二甲基四氢-2H-吡喃-4-基)(乙基)氨基)-2-甲基苯甲酰胺	460.3
249		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((2R,4s,6S)-2,6-二甲基四氢-2H-吡喃-4-基)(乙基)氨基)-2-甲基苯甲酰胺	460.3

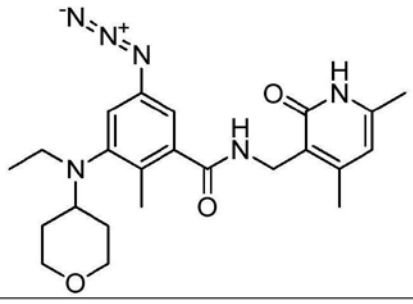
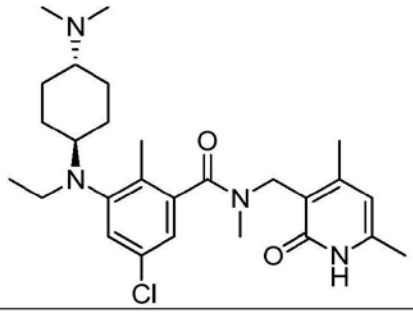
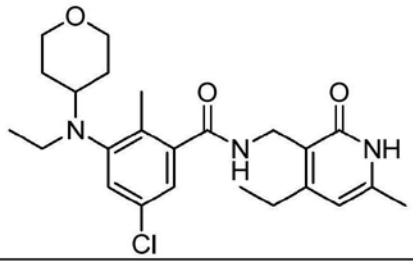
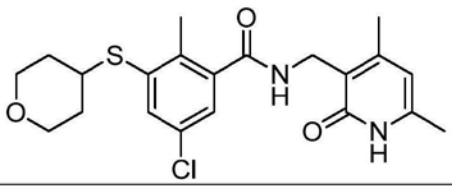
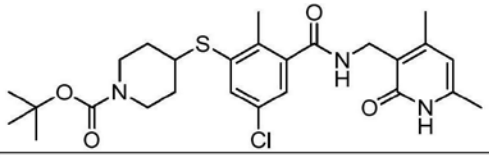
[0659]

化合物编号	结构	名称	分子量†
250		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(四氢-2H-吡喃-4-基)氨基)-2-甲基-5-(吗啉基甲基)苯甲酰胺	497.3
251		3-((1R,4R)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	402.2
252		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基硫代)-2-甲基苯甲酰胺	365.2
253		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-((2-甲基四氢呋喃-3-基)硫代)苯甲酰胺	421.1
254		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(1-甲基哌啶-4-基)苯甲酰胺	368.3

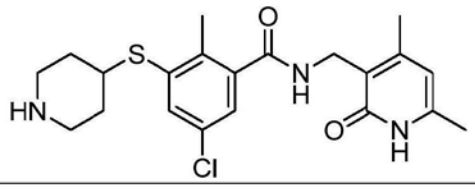
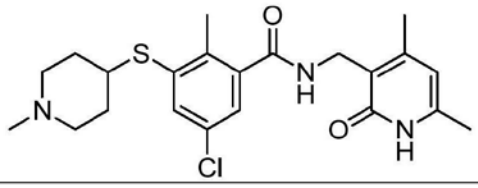
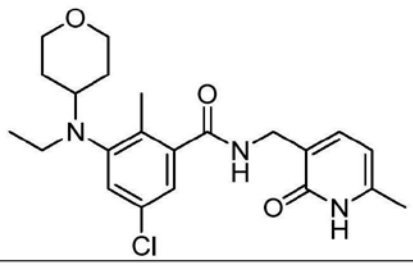
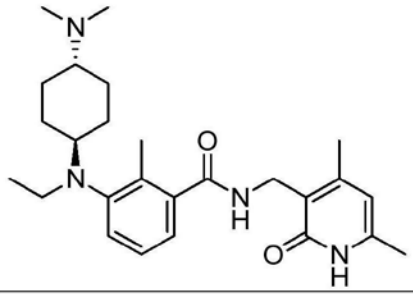
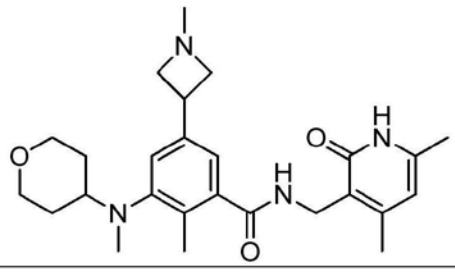
[0660]

化合物编号	结构	名称	分子量†
255		N-((4-(叠氮甲基)-6-甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-5-氯-3-(乙基(四氢-2H-吡喃-4-基)氨基)-2-甲基苯甲酰胺	473.2
256		5-氯-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-2-甲基-N-((1,4,6-三甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)苯甲酰胺	487.4
257		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(2-甲氧乙基)氨基)-2-甲基苯甲酰胺	406.2
258		3-环己基-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	353.2
259		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(4,4-二甲基环己基)-2-甲基苯甲酰胺	381.3

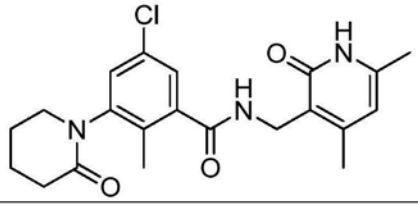
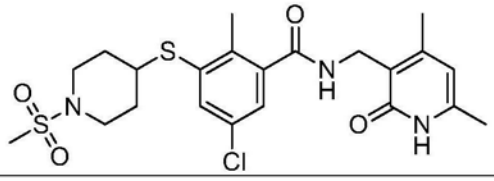
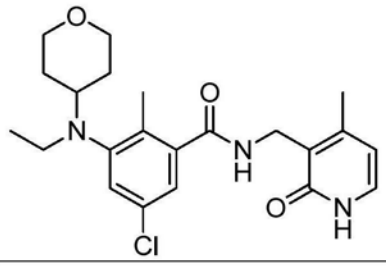
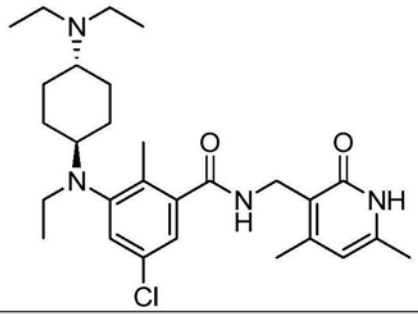
[0661]

化合物编号	结构	名称	分子量†
260		5-叠氮基-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(四氢-2H-吡喃-4-基)氨基)-2-甲基苯甲酰胺	439.3
261		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-N,2-二甲基苯甲酰胺	487.2
262		5-氯-3-(乙基(四氢-2H-吡喃-4-基)氨基)-N-((4-乙基-6-甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	446.1
263		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-((四氢-2H-吡喃-4-基)硫代)苯甲酰胺	421
264		4-((5-氯-3-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰基)-2-甲基苯基)硫代)哌啶-1-羧酸叔丁酯	542.2

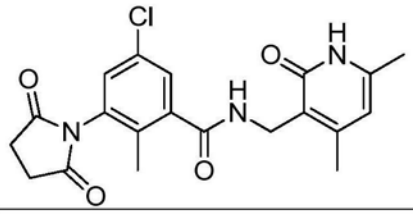
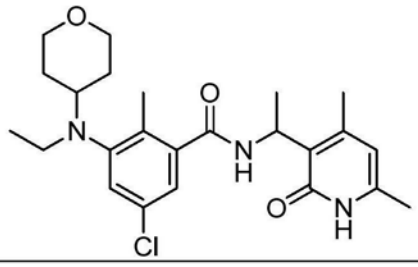
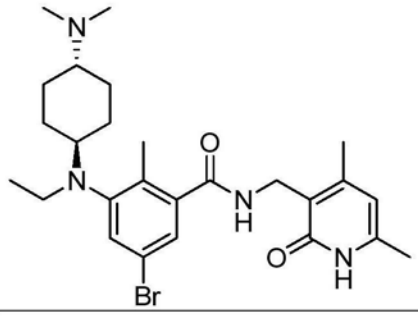
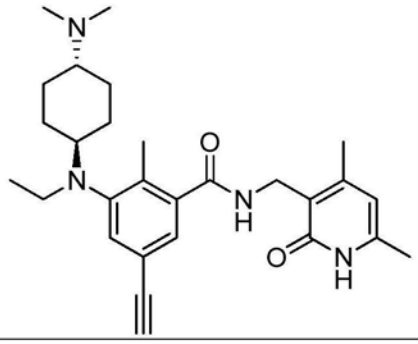
[0662]

化合物编号	结构	名称	分子量†
265		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(哌啶-4-基硫代)苯甲酰胺	420.1
266		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-((1-甲基哌啶-4-基)硫代)苯甲酰胺	434.1
267		5-氯-3-(乙基(四氢-2H-吡喃-4-基)氨基)-2-甲基-N-((6-甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)苯甲酰胺	418.1
268		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-2-甲基苯甲酰胺	439.3
269		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(甲基(四氢-2H-吡喃-4-基)氨基)-5-(1-甲基氮杂环丁烷-3-基)苯甲	453.2

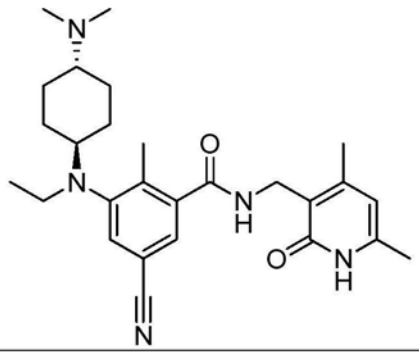
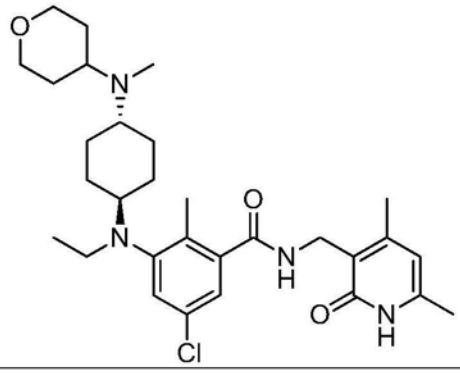
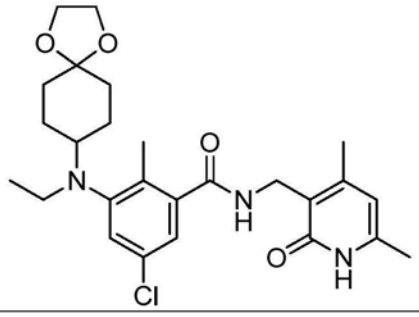
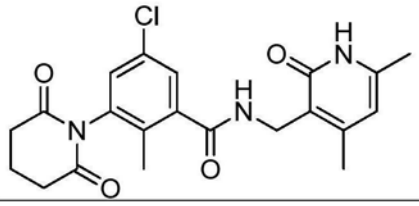
[0663]

化合物编号	结构	名称	分子量†
		酰胺	
270		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(2-氧代哌啶-1-基)苯甲酰胺	402.1
271		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-((1-(甲基磺酰基)哌啶-4-基)硫代)苯甲酰胺	498
272		5-氯-3-(乙基(四氢-2H-吡喃-4-基)氨基)-2-甲基-N-((4-甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)苯甲酰胺	418.2
273		5-氯-3-(((1r,4r)-4-(二乙基氨基)环己基)(乙基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	501.5

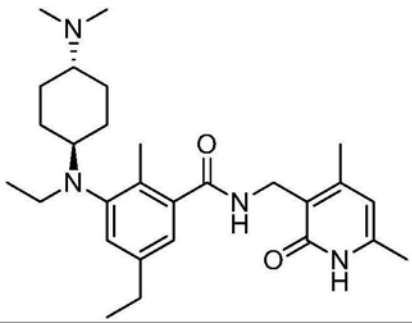
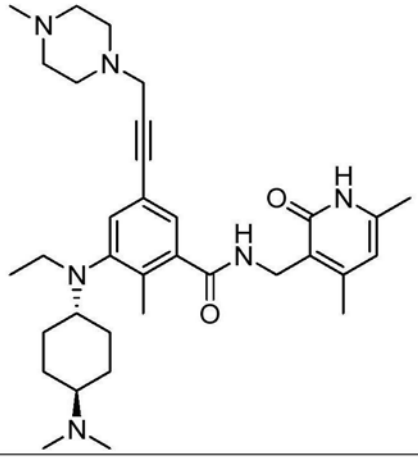
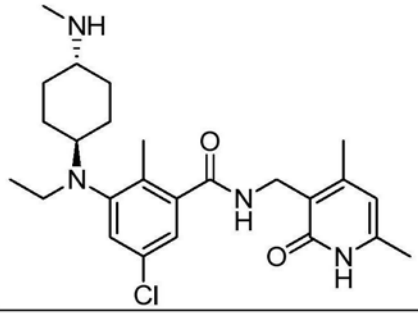
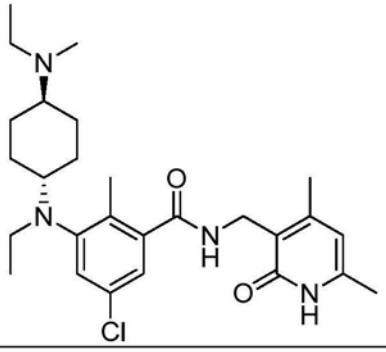
[0664]

化合物编号	结构	名称	分子量†
274		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(2,5-二氧代吡咯烷-1-基)-2-甲基苯甲酰胺	402.3
275		5-氯-N-(1-(4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)乙基)-3-(乙基(四氢-2H-吡喃-4-基)氨基)-2-甲基苯甲酰胺	446.2
276		5-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-2-甲基苯甲酰胺	519.3
277		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-5-乙炔基-2-甲基苯甲酰胺	463.5

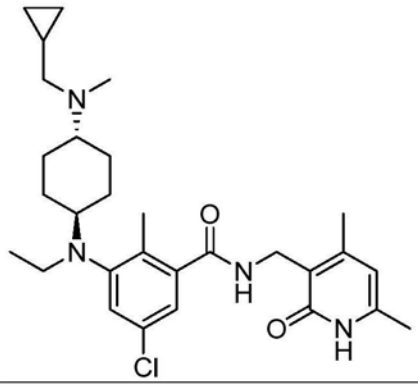
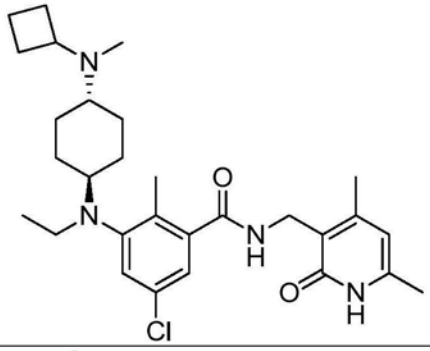
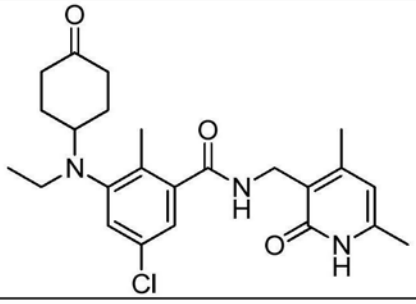
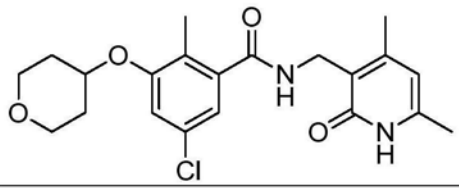
[0665]

化合物编号	结构	名称	分子量†
278		5-氰基-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-2-甲基苯甲酰胺	464.3
279		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基((1r,4r)-4-(甲基(四氢-2H-吡喃-4-基)氨基)环己基)氨基)-2-甲基苯甲酰胺	543.7
280		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(1,4-二氧杂螺[4.5]癸烷-8-基)氨基)-2-甲基苯甲酰胺	488.3
281		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(2,6-二氧代哌啶-1-基)-2-甲基苯甲酰胺	416.1

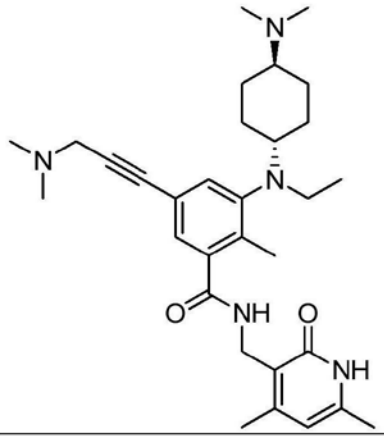
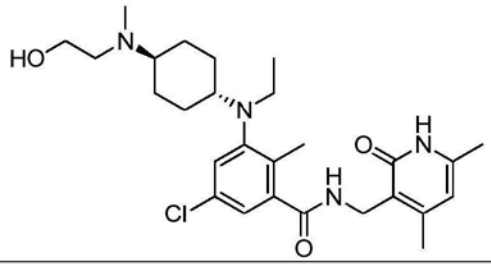
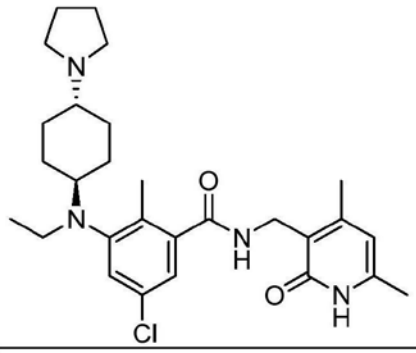
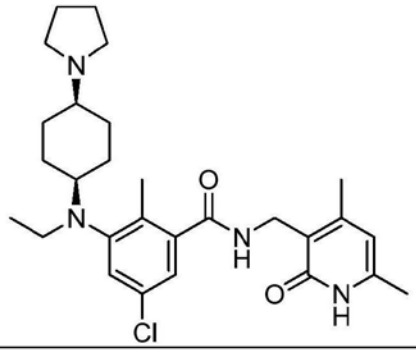
[0666]

化合物编号	结构	名称	分子量†
282		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-5-乙基-2-甲基苯甲酰胺	467.4
283		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-2-甲基-5-(3-(4-甲基哌嗪-1-基)丙-1-炔-1-基)苯甲酰胺	575.5
284		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基((1r,4r)-4-(甲基氨基)环己基)氨基)-2-甲基苯甲酰胺	459.4
285		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基((1r,4r)-4-(乙基(甲基)氨基)环己基)氨基)-2-甲基苯甲酰胺	487.4

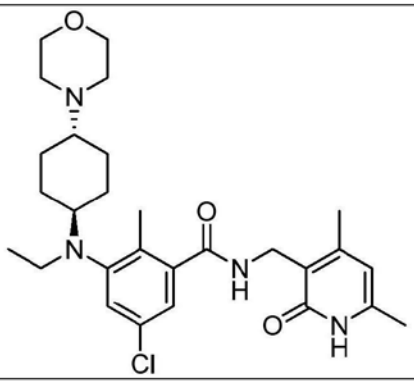
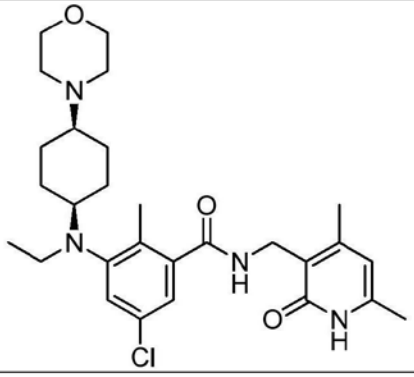
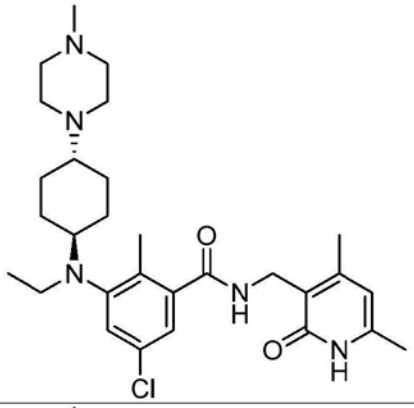
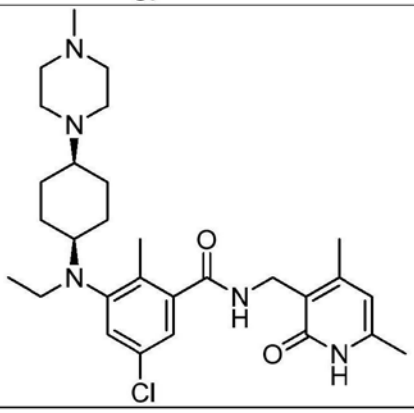
[0667]

化合物编号	结构	名称	分子量 †
286		5-氯-3-(((1r,4r)-4-((环丙甲基)(甲基)氨基)环己基)(乙基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	513.4
287		5-氯-3-(((1r,4r)-4-(环丁基(甲基)氨基)环己基)(乙基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	513.3
288		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(4-氧代环己基)氨基)-2-甲基苯甲酰胺	444.3
289		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-((四氢-2H-吡喃-4-基)氧基)苯甲酰胺	405.2

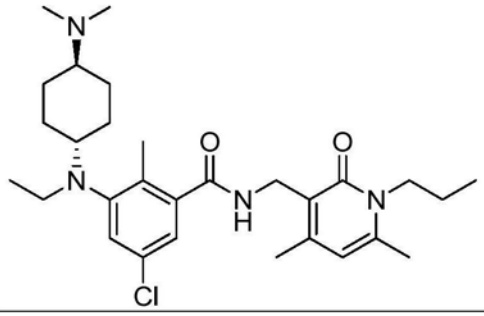
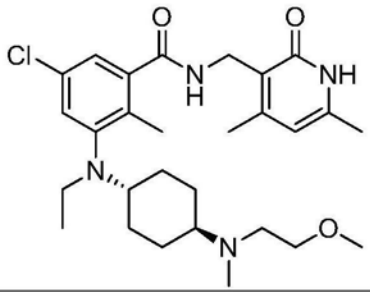
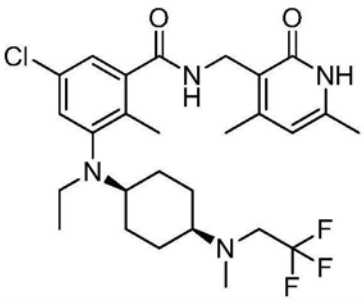
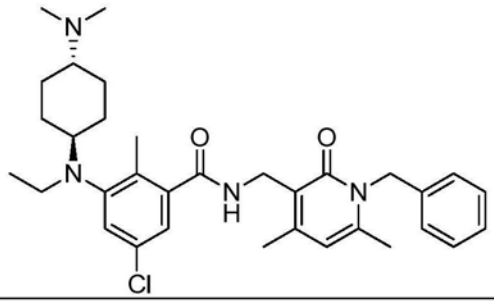
[0668]

化合物编号	结构	名称	分子量†
290		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-5-(3-(二甲基氨基)丙-1-炔-1-基)-2-甲基苯甲酰胺	520.6
291		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基((1r,4r)-4-((2-羟乙基)(甲基)氨基)环己基)氨基)-2-甲基苯甲酰胺	503.3
292		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基((1r,4r)-4-(吡咯烷-1-基)环己基)氨基)-2-甲基苯甲酰胺	499.3
293		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基((1s,4s)-4-(吡咯烷-1-基)环己基)氨基)-2-甲基苯甲酰胺	499.3

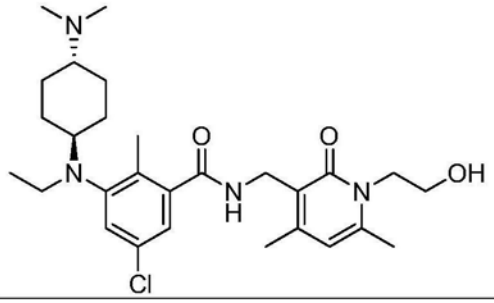
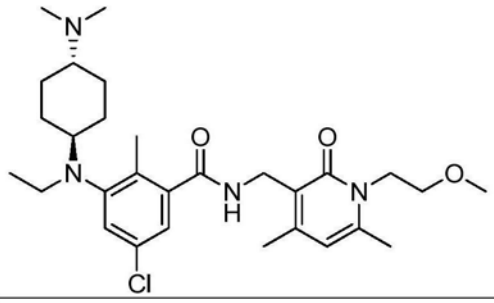
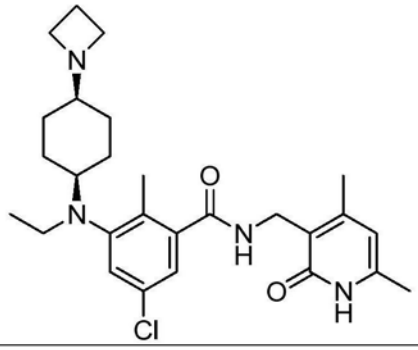
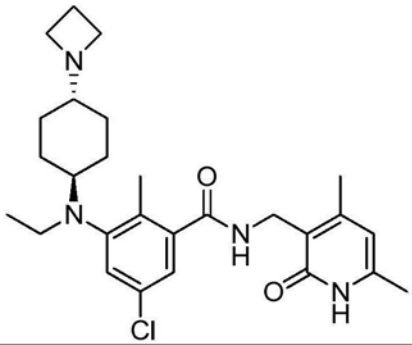
[0669]

化合物编号	结构	名称	分子量†
294		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-((乙基((1r,4r)-4-吗啉基环己基)氨基)-2-甲基苯甲酰胺	515.3
295		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-((乙基((1s,4s)-4-吗啉基环己基)氨基)-2-甲基苯甲酰胺	515.3
296		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-((乙基((1r,4r)-4-(4-甲基哌嗪-1-基)环己基)氨基)-2-甲基苯甲酰胺	528.4
297		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-((乙基((1s,4s)-4-(4-甲基哌嗪-1-基)环己基)氨基)-2-甲基苯甲酰胺	528.3

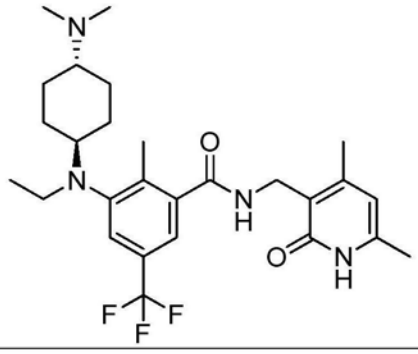
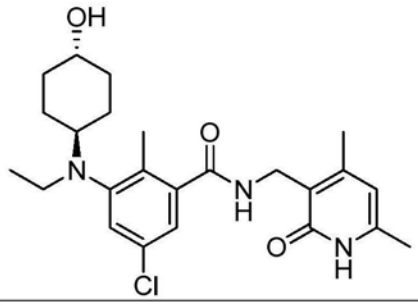
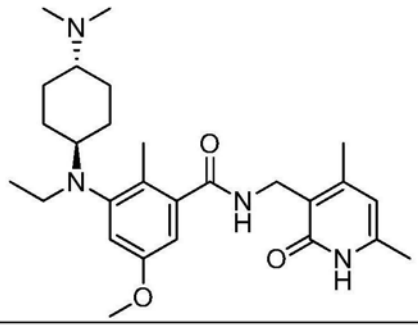
[0670]

化合物编号	结构	名称	分子量†
298		5-氯-N-((4,6-二甲基-2-氧代-1-丙基-1,2-二氢吡啶-3-基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-2-甲基苯甲酰胺	515.3
299		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基((1r,4r)-4-((2-甲氧乙基)(甲基)氨基)环己基)氨基)-2-甲基苯甲酰胺	517.4
300		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基((1s,4s)-4-(甲基(2,2,2-三氟乙基)氨基)环己基)氨基)-2-甲基苯甲酰胺	541.4
301		N-((1-苄基-4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-5-氯-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-2-甲基苯甲酰胺	563.4

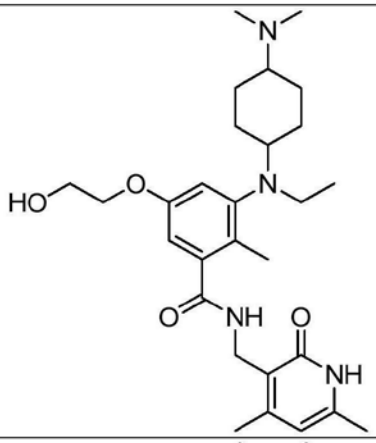
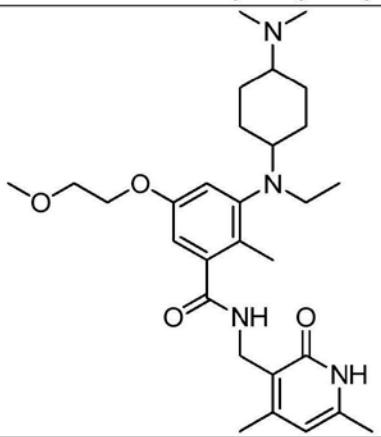
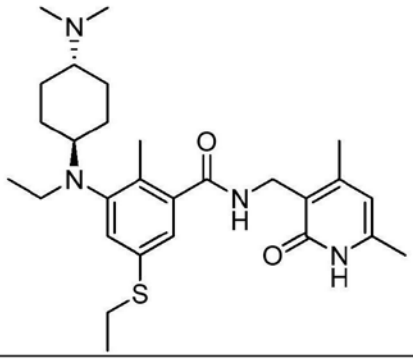
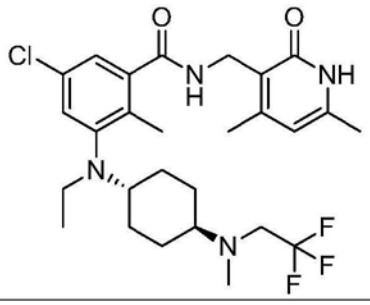
[0671]

化合物编号	结构	名称	分子量†
302		5-氯-3-(((1r,4r)-4-(甲基氨基)环己基)(乙基)氨基)-N-((1-(2-羟乙基)-4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	517.4
303		5-氯-3-(((1r,4r)-4-(甲基氨基)环己基)(乙基)氨基)-N-((1-(2-甲氧乙基)-4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	531.4
304		3-(((1s,4s)-4-(氮杂环丁烷-1-基)环己基)(乙基)氨基)-5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	485.2
305		3-(((1r,4r)-4-(氮杂环丁烷-1-基)环己基)(乙基)氨基)-5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	485.2

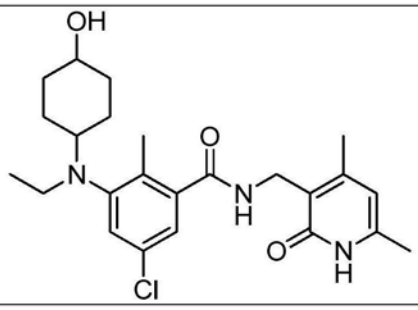
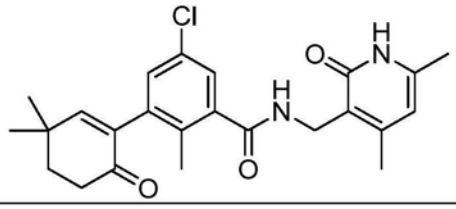
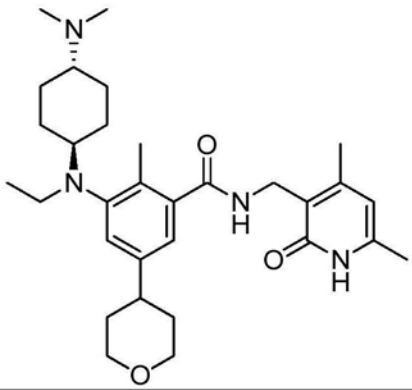
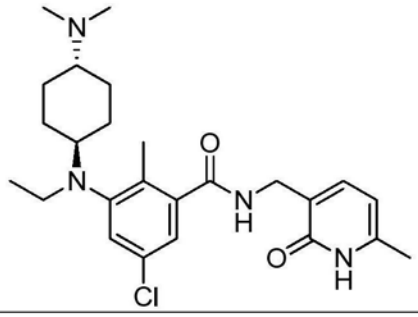
[0672]

化合物编号	结构	名称	分子量†
306		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((1r,4r)-4-(甲基氨基)环己基)(乙基)氨基)-2-甲基-5-(三氟甲基)苯甲酰胺	507.5
307		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基((1r,4r)-4-羟基环己基)氨基)-2-甲基苯甲酰胺	446.3
308		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-5-甲氧基-2-甲基苯甲酰胺	469.8

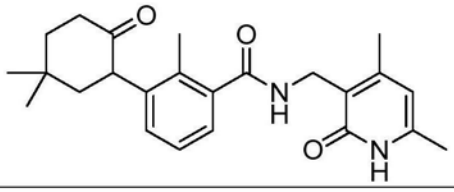
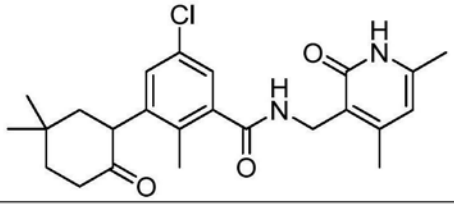
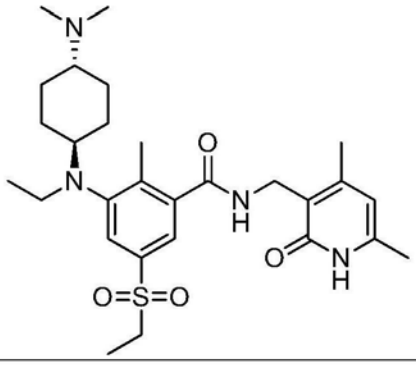
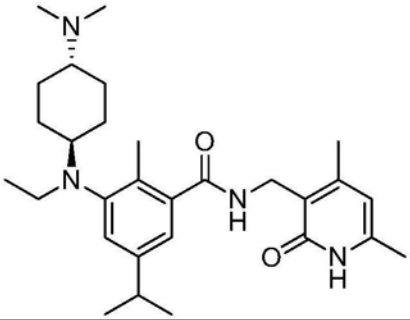
[0673]

化合物编号	结构	名称	分子量†
309		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-((4-(二甲基氨基)环己基)(乙基)氨基)-5-(2-羟基乙氧基)-2-甲基苯甲酰胺	499.6
310		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-((4-(二甲基氨基)环己基)(乙基)氨基)-5-(2-甲氧乙氧基)-2-甲基苯甲酰胺	513.6
311		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-5-(乙基硫代)-2-甲基苯甲酰胺	499.6
312		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基((1r,4r)-4-(甲基(2,2,2-三氟乙基)氨基)环己基)氨基)-2-甲基苯甲酰胺	541.5

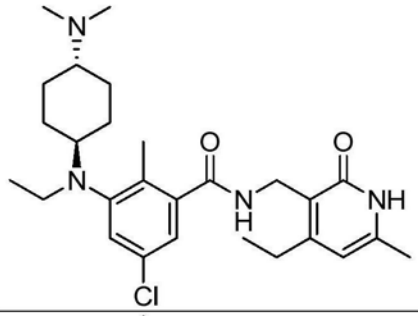
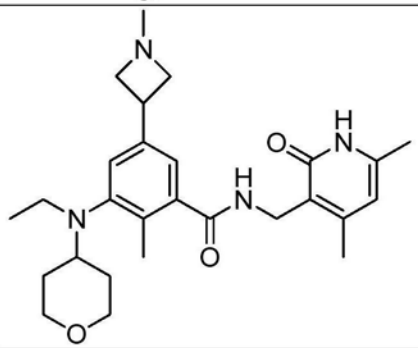
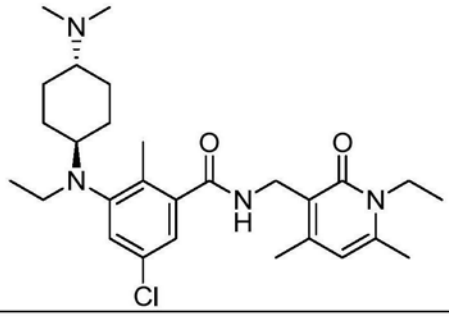
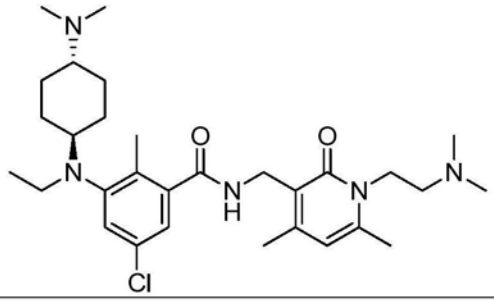
[0674]

化合物编号	结构	名称	分子量†
313		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(4-羟基环己基)氨基)-2-甲基苯甲酰胺	446.3
314		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2,5',5'-三甲基-2'-氧代-2',3',4',5'-四氢-[1,1'-联苯]-3-甲酰胺	427.4
315		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-2-甲基-5-(四氢-2H-吡喃-4-基)苯甲酰胺	523.6
316		5-氯-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-2-甲基-N-((6-甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)苯甲酰胺	459.5

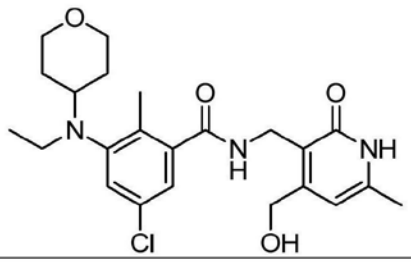
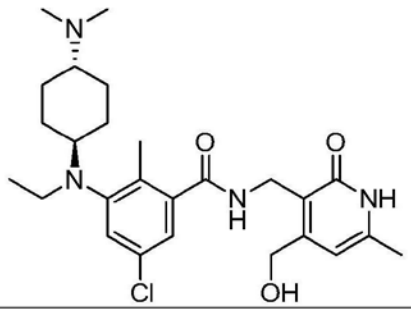
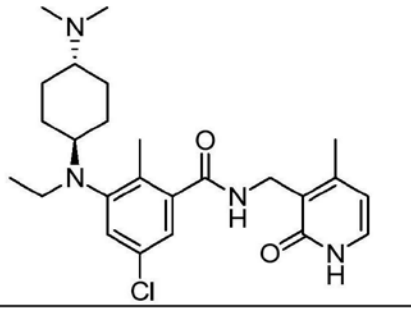
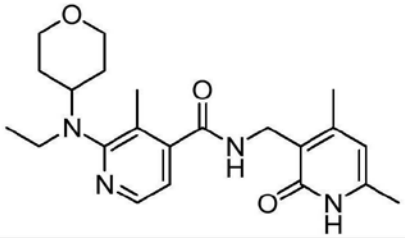
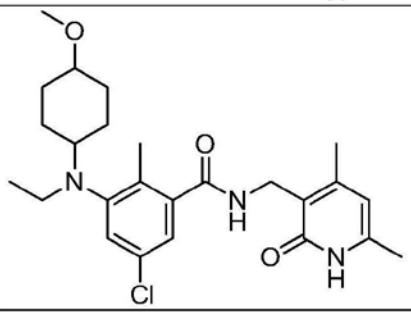
[0675]

化合物编号	结构	名称	分子量†
317		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(5,5-二甲基-2-氧代环己基)-2-甲基苯甲酰胺	395.4
318		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(5,5-二甲基-2-氧代环己基)-2-甲基苯甲酰胺	429.4
319		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-5-(乙基磺酰基)-2-甲基苯甲酰胺	531.6
320		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-5-异丙基-2-甲基苯甲酰胺	481.4

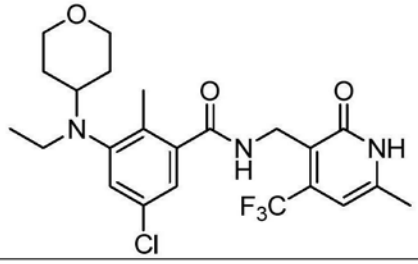
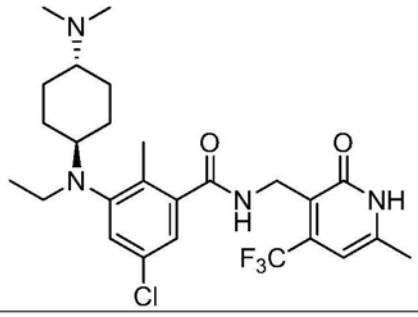
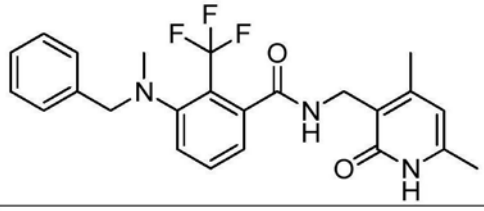
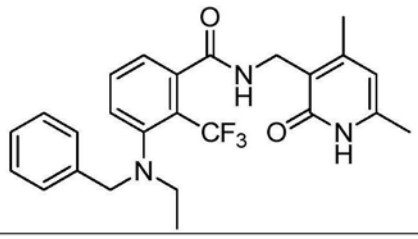
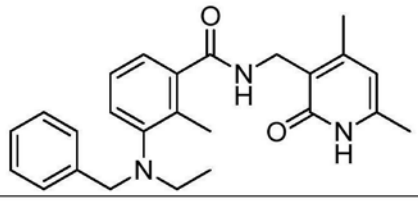
[0676]

化合物编号	结构	名称	分子量†
321		5-氯-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-N-((4-乙基-6-甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	487.5
322		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(四氢-2H-吡喃-4-基)氨基)-2-甲基-5-(1-甲基氮杂环丁烷-3-基)苯甲酰胺	467.3
323		5-氯-3-(((1r,4r)-4-(甲基氨基)环己基)(乙基)氨基)-N-((1-乙基-4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	501.5
324		5-氯-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-N-((1-(2-(二甲基氨基)乙基)-4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	544.6

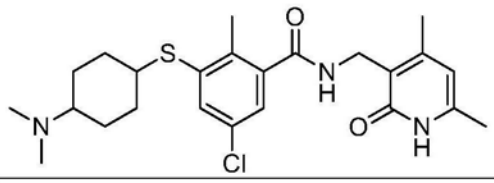
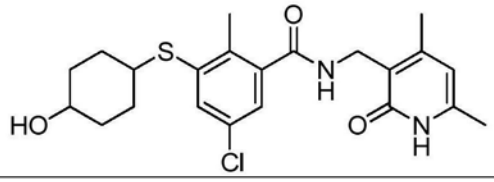
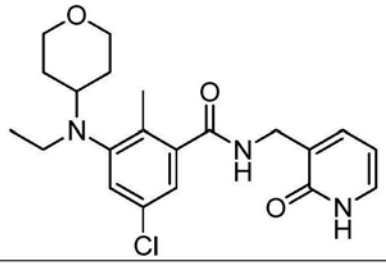
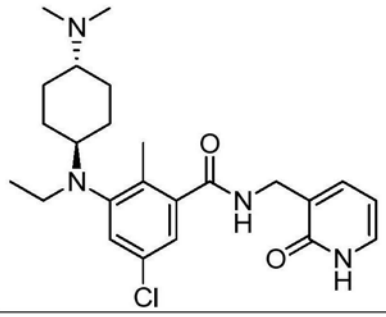
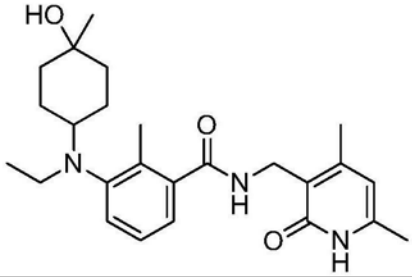
[0677]

化合物编号	结构	名称	分子量†
325		5-氯-3-(乙基(四氢-2H-吡喃-4-基)氨基)-N-((4-(羟基甲基)-6-甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	448.4
326		5-氯-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-N-((4-(羟甲基)-6-甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	489.5
327		5-氯-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-2-甲基-N-((4-甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)苯甲酰胺	459.4
328		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-(乙基(四氢-2H-吡喃-4-基)氨基)-3-甲基异烟酰胺	399.1
329		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(4-甲氧基环己基)氨基)-2-甲基苯甲酰胺	460.4

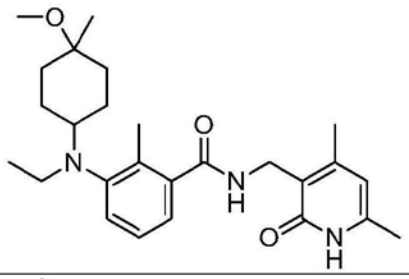
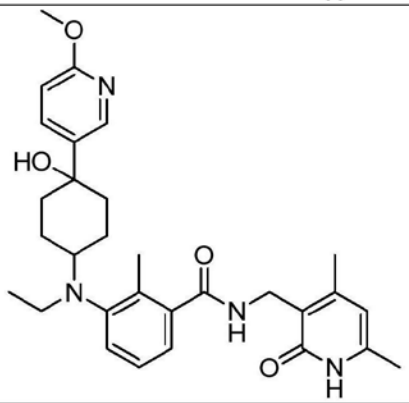
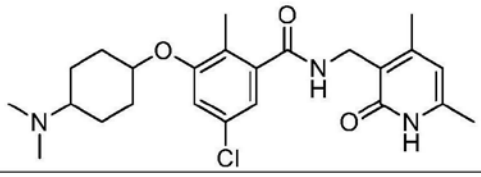
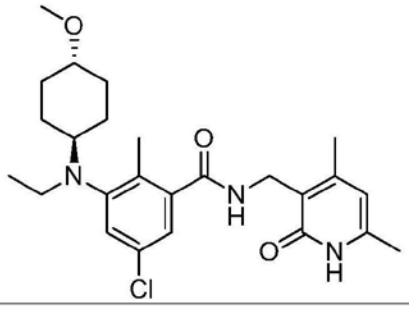
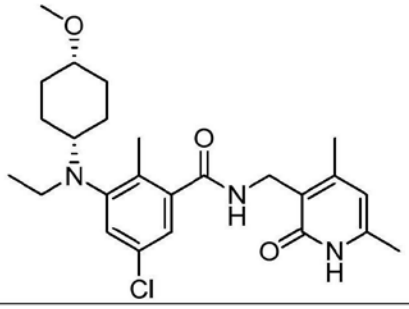
[0678]

化合物编号	结构	名称	分子量†
330		5-氯-3-(乙基(四氢-2H-吡喃-4-基)氨基)-2-甲基-N-((6-甲基-2-氧代-4-(三氟甲基)-1,2-二氢吡啶-3-基)甲基)苯甲酰胺	486.4
331		5-氯-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-2-甲基-N-((6-甲基-2-氧代-4-(三氟甲基)-1,2-二氢吡啶-3-基)甲基)苯甲酰胺	527.5
332		3-(苄基(甲基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-(三氟甲基)苯甲酰胺	444.2
333		3-(苄基(乙基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-(三氟甲基)苯甲酰胺	458.3
334		3-(苄基(乙基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	404.3

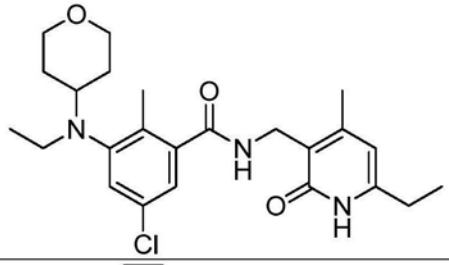
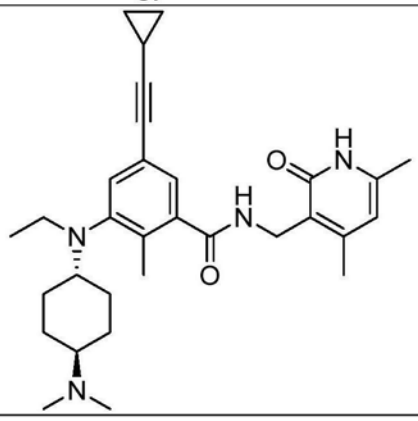
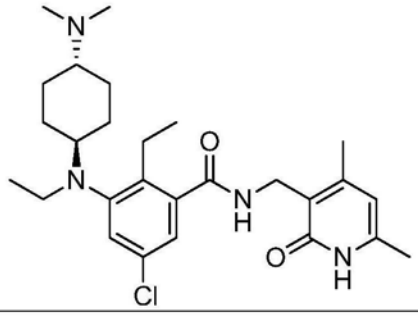
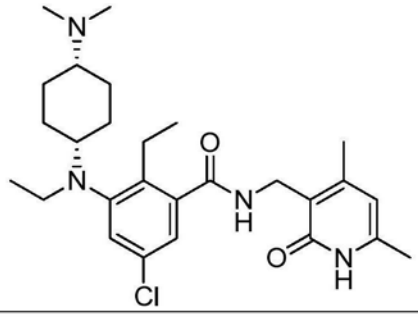
[0679]

化合物编号	结构	名称	分子量†
335		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-((4-(二甲基氨基)环己基)硫代)-2-甲基苯甲酰胺	462.4
336		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-((4-羟基环己基)硫代)-2-甲基苯甲酰胺	435.3
337		5-氯-3-(乙基(四氢-2H-吡喃-4-基)氨基)-2-甲基-N-((2-氧代-1,2-二氢吡啶-3-基)甲基)苯甲酰胺	404.3
338		5-氯-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-2-甲基-N-((2-氧代-1,2-二氢吡啶-3-基)甲基)苯甲酰胺	445.5
339		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(4-羟基-4-甲基环己基)氨基)-2-甲基苯甲酰胺	426.5

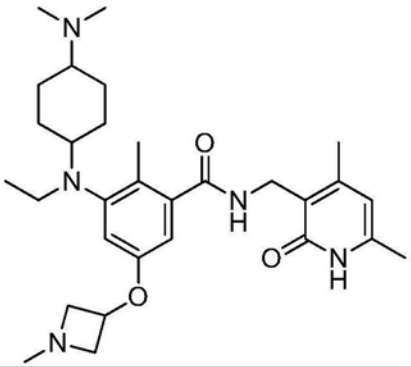
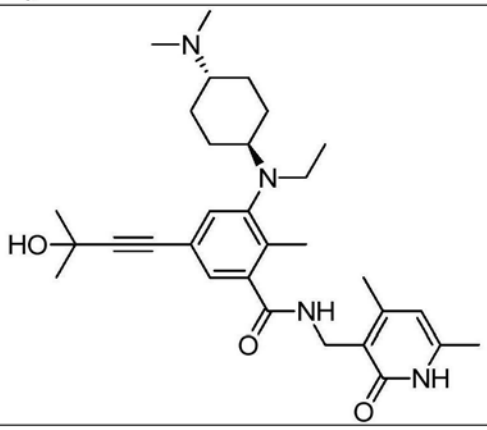
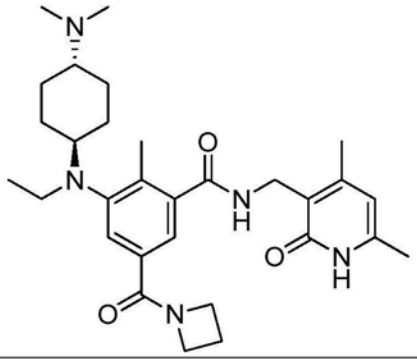
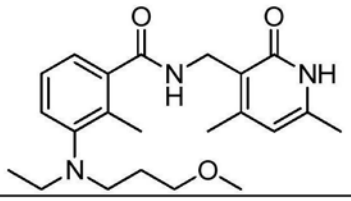
[0680]

化合物编号	结构	名称	分子量†
340		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(4-甲氧基-4-甲基环己基)氨基)-2-甲基苯甲酰胺	440.45
341		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(4-羟基-4-(6-甲氧基吡啶-3-基)环己基)氨基)-2-甲基苯甲酰胺	519.3
342		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-((4-(二甲基氨基)环己基)氧基)-2-甲基苯甲酰胺	446.3
343		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基((1r,4r)-4-甲氧基环己基)氨基)-2-甲基苯甲酰胺	460.4
344		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基((1s,4s)-4-甲氧基环己基)氨基)-2-甲基苯甲酰胺	460.3

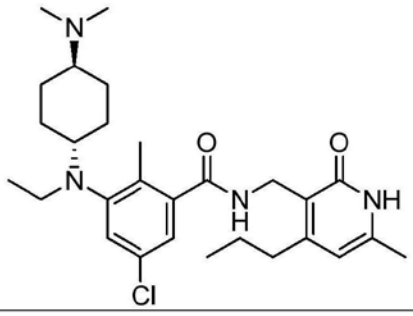
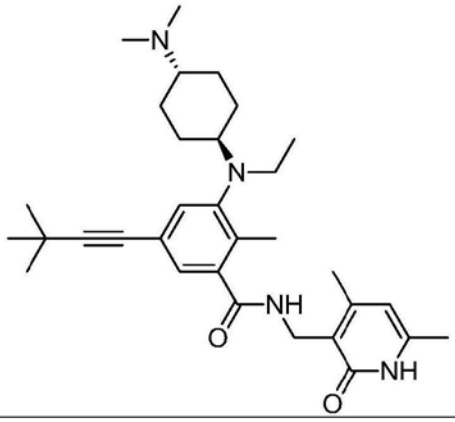
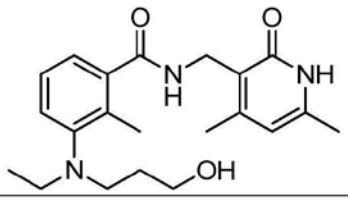
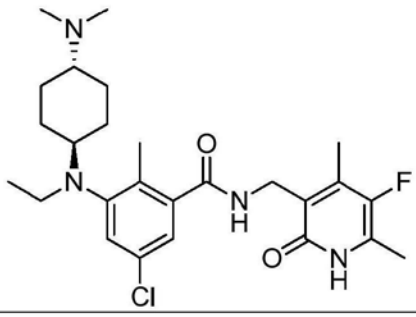
[0681]

化合物编号	结构	名称	分子量†
345		5-氯-3-(乙基(四氢-2H-吡喃-4-基)氨基)-N-((6-乙基-4-甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	446.3
346		5-(环丙乙炔基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-2-甲基苯甲酰胺	503.5
347		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((1r, 4r)-4-(二甲基氨基)环己基)(乙基)氨基)-2-乙基苯甲酰胺	487.2
348		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((1s,4s)-4-(二甲基氨基)环己基)(乙基)氨基)-2-乙基苯甲酰胺	487.2

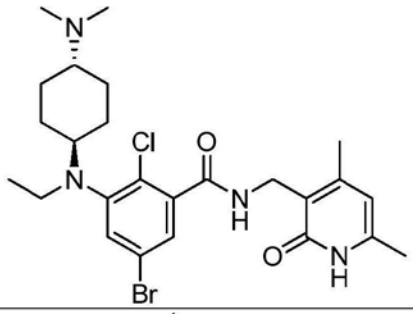
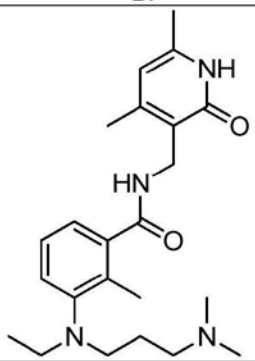
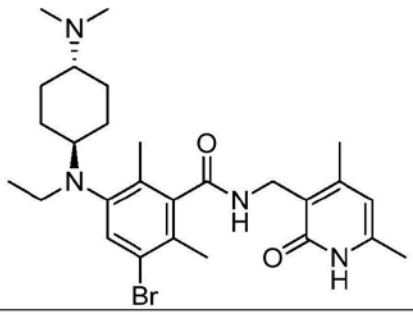
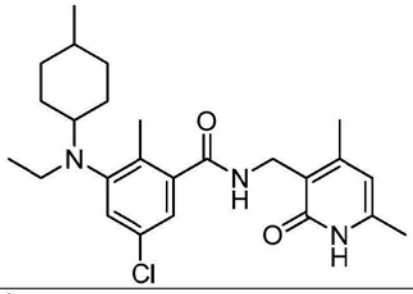
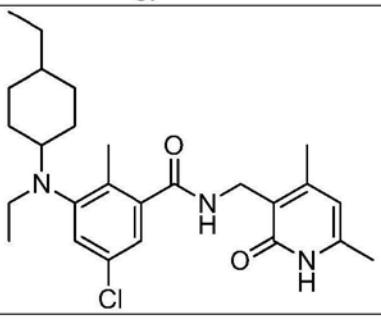
[0682]

化合物编号	结构	名称	分子量†
349		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-((4-(二甲基氨基)环己基)(乙基)氨基)-2-甲基-5-((1-甲基氮杂环丁烷-3-基)氧基)苯甲酰胺	524.6
350		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-5-(3-羟基-3-甲基丁-1-炔-1-基)-2-甲基苯甲酰胺	521.5
351		5-(氮杂环丁烷-1-碳酰基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-2-甲基苯甲酰胺	522.8
352		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(3-甲氧基丙基)氨基)-2-甲基苯甲酰胺	386.4

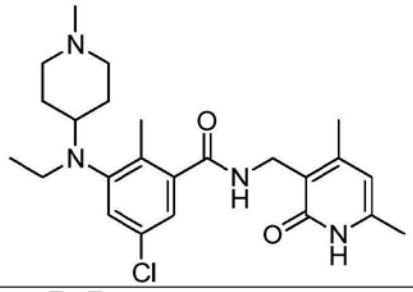
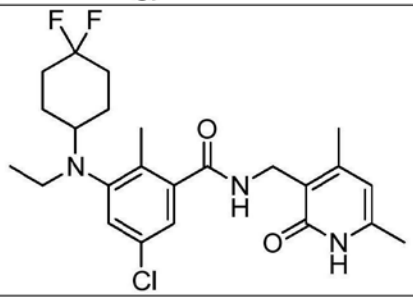
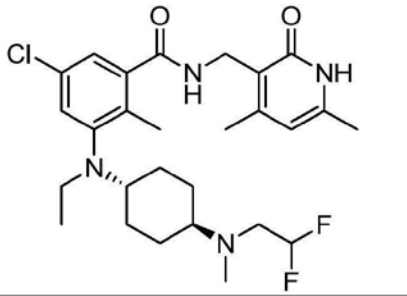
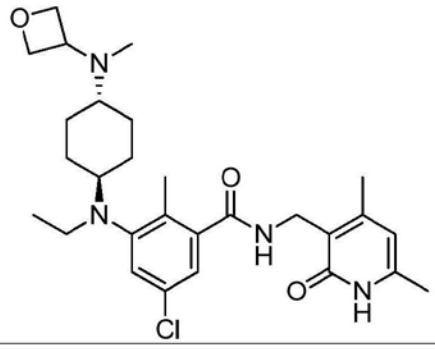
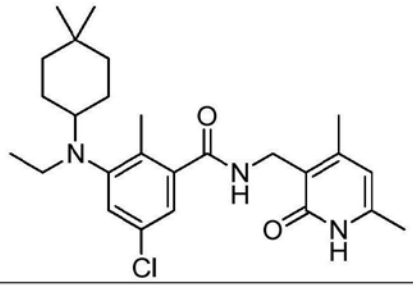
[0683]

化合物编号	结构	名称	分子量†
353		5-氯-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-2-甲基-N-((6-甲基-2-氧代-4-丙基-1,2-二氢吡啶-3-基)甲基)苯甲酰胺	501.5
354		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-5-(3,3-二甲基丁-1-炔-1-基)-2-甲基苯甲酰胺	519.6
355		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(3-羟基丙基)氨基)-2-甲基苯甲酰胺	372.3
356		5-氯-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-N-((5-氟-4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	491.1

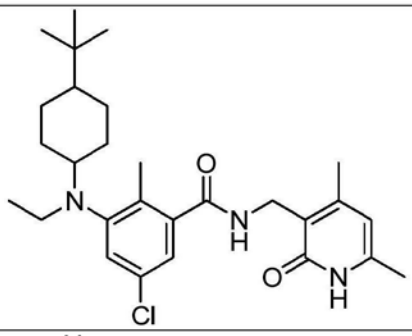
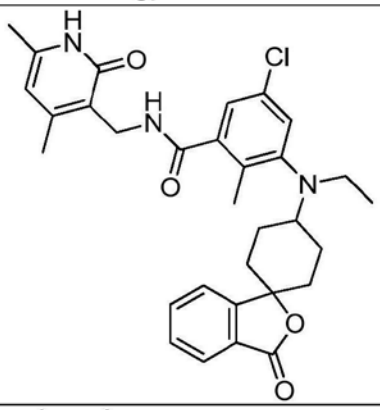
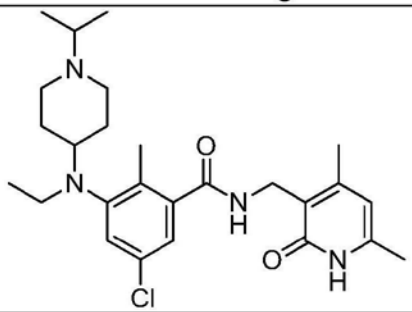
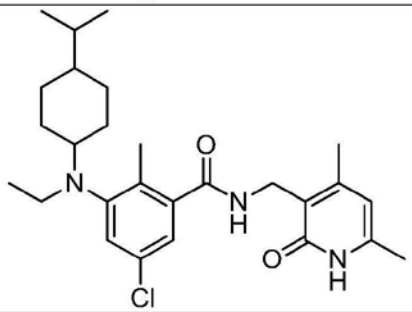
[0684]

化合物编号	结构	名称	分子量†
357		5-溴-2-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)苯甲酰胺	539.25
358		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-((3-(二甲基氨基)丙基)(乙基)氨基)-2-甲基苯甲酰胺	399.4
359		3-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-5-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-2,6-甲基苯甲酰胺	531.4
360		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(4-甲基环己基)氨基)-2-甲基苯甲酰胺	444.4
361		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(4-乙基环己基)氨基)-2-甲基苯甲酰胺	458.4

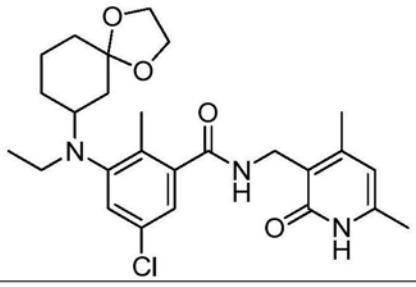
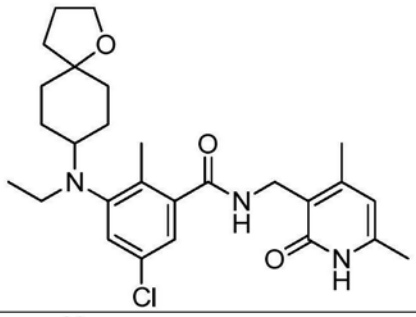
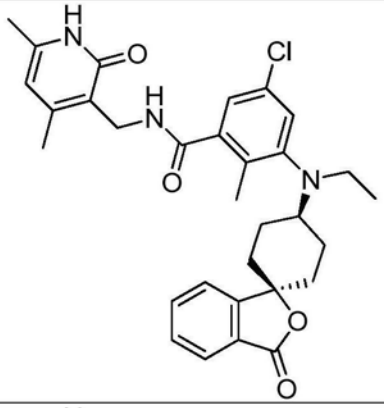
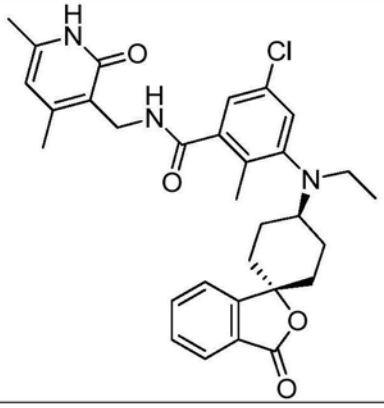
[0685]

化合物编号	结构	名称	分子量†
362		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(1-甲基哌啶-4-基)氨基)-2-甲基苯甲酰胺	445.4
363		5-氯-3-((4,4-氟环己基)(乙基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	466.2
364		5-氯-3-(((1r,4r)-4-((2,2-二氟乙基)(甲基)氨基)环己基)(乙基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	523.5
365		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基((1r,4r)-4-(甲基(氧杂环丁烷-3-基)氨基)环己基)氨基)-2-甲基苯甲酰胺	515.4
366		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-((4,4-二甲基环己基)(乙基)氨基)-2-甲基苯甲酰	458.4

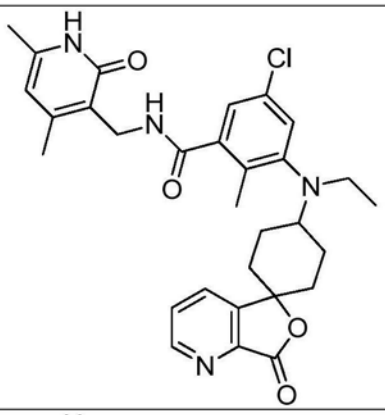
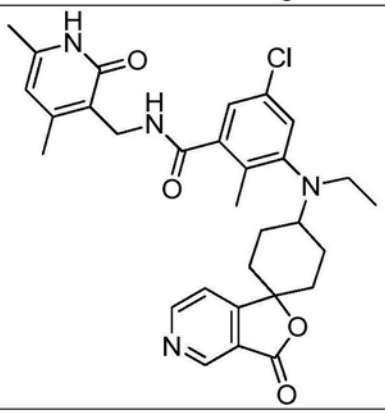
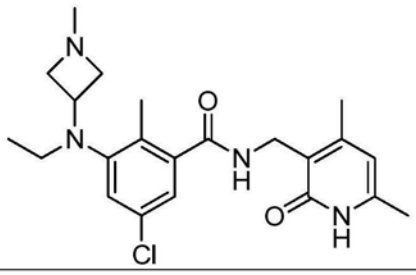
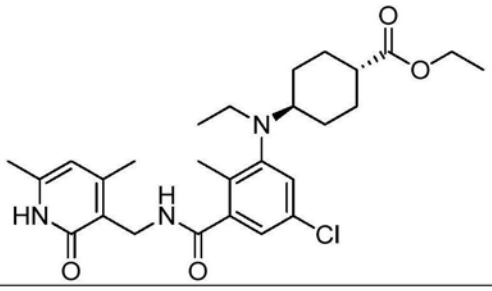
[0686]

化合物编号	结构	名称	分子量†
		胺	
367		3-((4-(叔丁基)环己基)(乙基)氨基)-5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	486.5
368		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(3'-氧代-3'H-螺[环己烷-1,1'-异苯并呋喃]-4-基)氨基)-2-甲基苯甲酰胺	548.5
369		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(1-异丙基哌啶-4-基)氨基)-2-甲基苯甲酰胺	473.5
370		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(4-异丙基环己基)氨基)-2-甲基苯甲酰胺	472.3

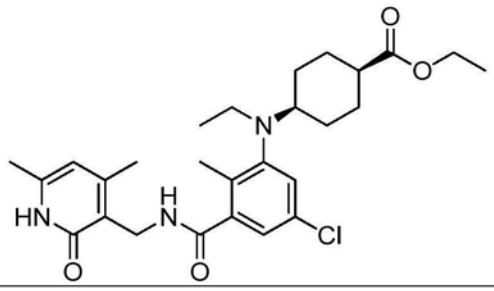
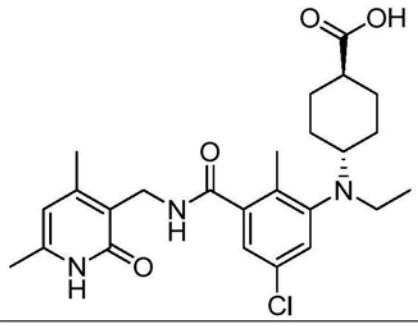
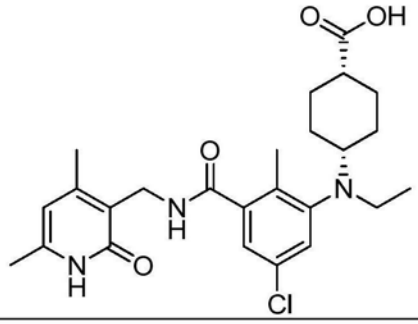
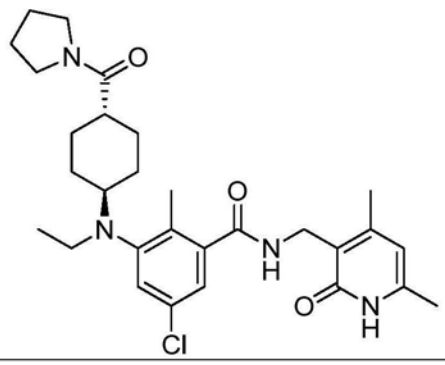
[0687]

化合物编号	结构	名称	分子量†
371		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(1,4-二氧杂螺[4.5]癸烷-7-基)氨基)-2-甲基苯甲酰胺	488.4
372		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(1-氧杂螺[4.5]癸烷-8-基)氨基)-2-甲基苯甲酰胺	486.35
373		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基((1s,4s)-3'-氧代-3'H-螺[环己烷-1,1'-异苯并呋喃]-4-基)氨基)-2-甲基苯甲酰胺	548.4
374		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基((1r,4r)-3'-氧代-3'H-螺[环己烷-1,1'-异苯并呋喃]-4-基)氨基)-2-甲基苯甲酰胺	548.4

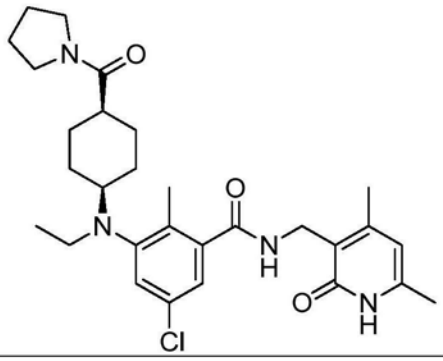
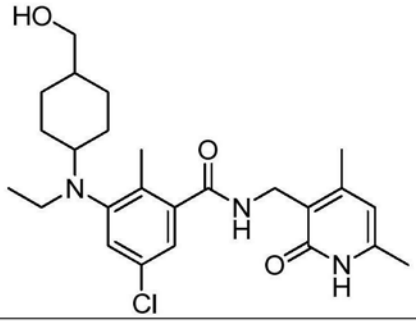
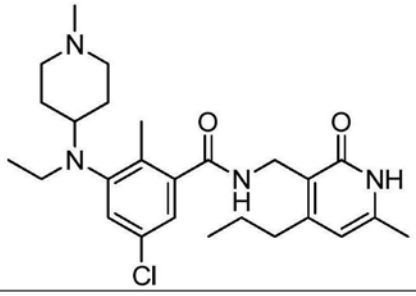
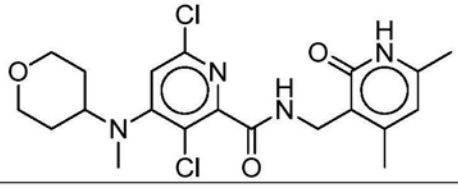
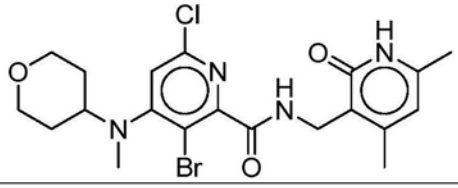
[0688]

化合物编号	结构	名称	分子量†
375		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(7'-氧代-7'H-螺[环己烷-1,5'-呋喃并[3,4-b]吡啶]-4-基)氨基)-2-甲基苯甲酰胺	549.3
376		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(3'-氧代-3'H-螺[环己烷-1,1'-呋喃并[3,4-c]吡啶]-4-基)氨基)-2-甲基苯甲酰胺	549.5
377		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(1-甲基氮杂环丁烷-3-基)氨基)-2-甲基苯甲酰胺	417.3
378		(1r,4r)-4-((5-氯-3-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰基)-2-甲基苯基)(乙基)氨基)环己烷羧酸乙酯	502.5

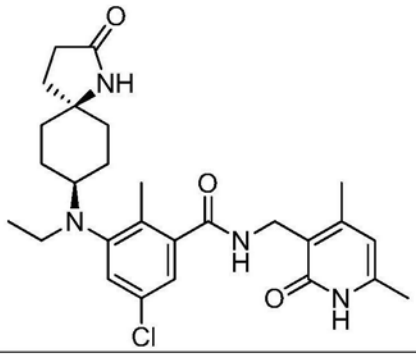
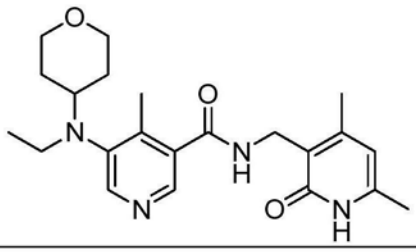
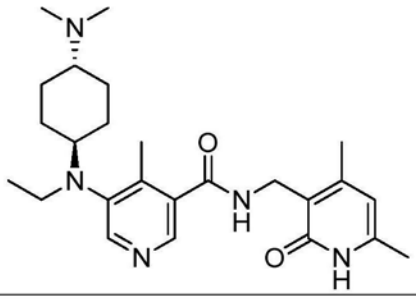
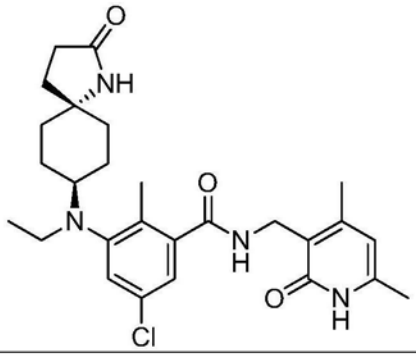
[0689]

化合物编号	结构	名称	分子量†
379		(1s,4s)-4-((5-氯-3-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰基)-2-甲基苯基)(乙基)氨基)环己烷羧酸乙酯	502.4
380		(1r,4r)-4-((5-氯-3-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰基)-2-甲基苯基)(乙基)氨基)环己羧酸	474.3
381		(1s,4s)-4-((5-氯-3-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰基)-2-甲基苯基)(乙基)氨基)环己羧酸	474.4
382		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基((1r,4r)-4-(吡咯烷-1-碳酰基)环己基)氨基)-2-甲基苯甲酰胺	527.5

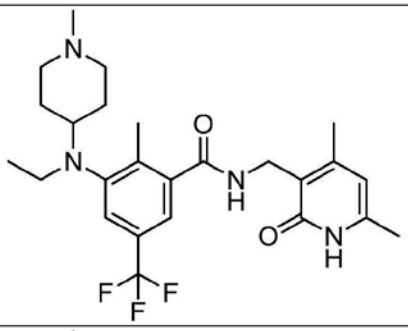
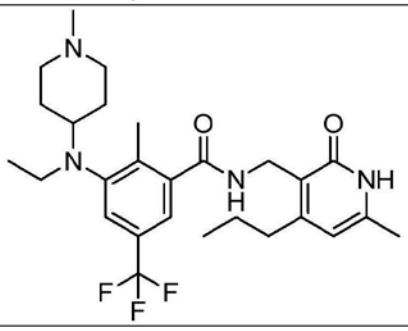
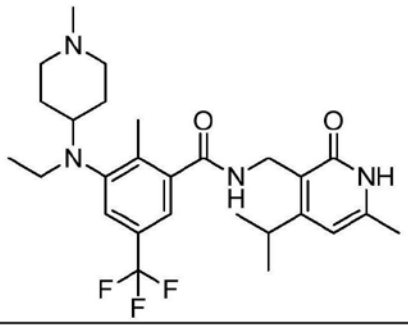
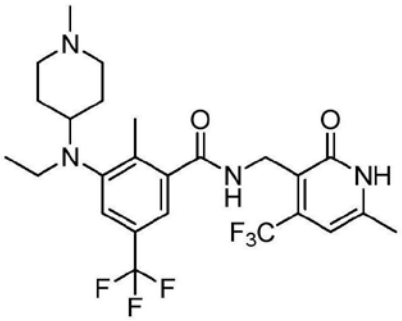
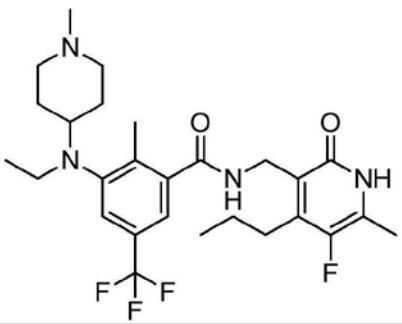
[0690]

化合物编号	结构	名称	分子量 †
383		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基((1s,4s)-4-(吡咯烷-1-碳酰基)环己基)氨基)-2-甲基苯甲酰胺	527.4
384		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(4-(羟基甲基)环己基)氨基)-2-甲基苯甲酰胺	460.2
385		5-氯-3-(乙基(1-甲基哌啶-4-基)氨基)-2-甲基-N-((6-甲基-2-氧代-4-丙基-1,2-二氢吡啶-3-基)甲基)苯甲酰胺	473.4
386		3,6-二氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-4-(甲基(四氢-2H-吡喃-4-基)氨基)吡啶酰胺	440.8
387		3-溴-6-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-4-(甲基(四氢-2H-吡喃-4-基)氨基)吡啶酰胺	485

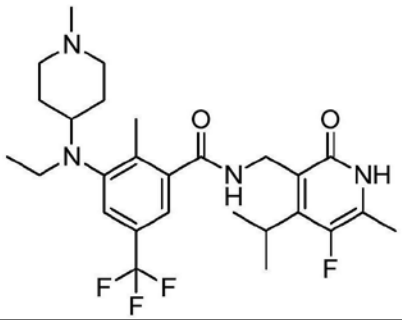
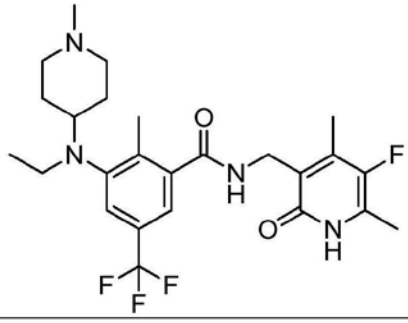
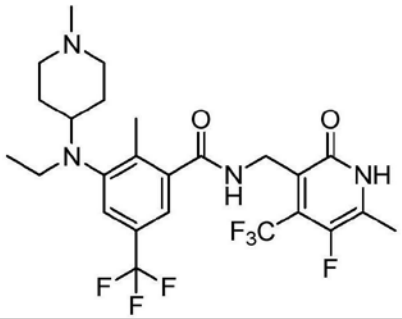
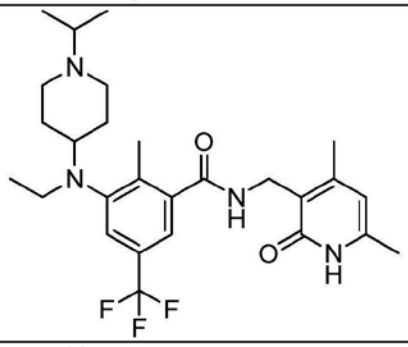
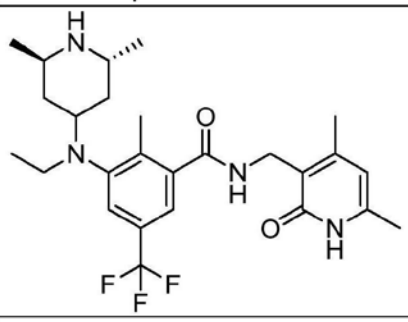
[0691]

化合物编号	结构	名称	分子量†
388		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基((5s,8s)-2-氧代-1-氮杂螺[4.5]癸烷-8-基)氨基)-2-甲基苯甲酰胺	499.35
389		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-5-(乙基(四氢-2H-吡喃-4-基)氨基)-4-甲基烟酰胺	399.5
390		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-5-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-4-甲基烟酰胺	440.5
391		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基((5r,8r)-2-氧代-1-氮杂螺[4.5]癸烷-8-基)氨基)-2-甲基苯甲酰胺	499.4

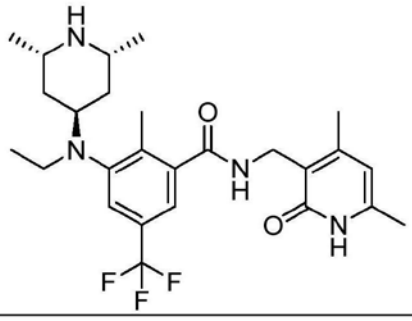
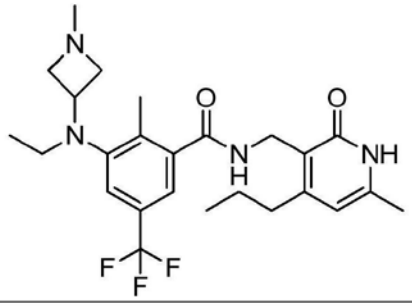
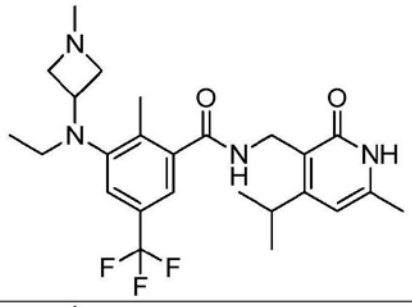
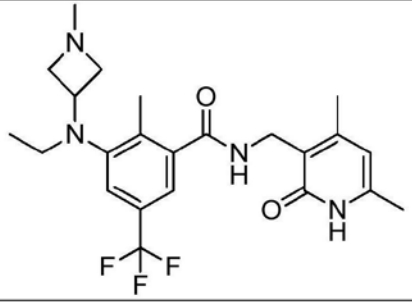
[0692]

化合物编号	结构	名称	分子量†
392		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(1-甲基哌啶-4-基)氨基)-2-甲基-5-(三氟甲基)苯甲酰胺	501.3
393		3-(乙基(1-甲基哌啶-4-基)氨基)-2-甲基-N-((6-甲基-2-氧代-4-丙基-1,2-二氢吡啶-3-基)甲基)-5-(三氟甲基)苯甲酰胺	505.2
394		3-(乙基(1-甲基哌啶-4-基)氨基)-N-((4-异丙基-6-甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-5-(三氟甲基)苯甲酰胺	529.2
395		3-(乙基(1-甲基哌啶-4-基)氨基)-2-甲基-N-((6-甲基-2-氧代-4-(三氟甲基)-1,2-二氢吡啶-3-基)甲基)-5-(三氟甲基)苯甲酰胺	555.2
396		3-(乙基(1-甲基哌啶-4-基)氨基)-N-((5-氟代-6-甲基-2-氧代-4-丙基-1,2-二氢吡啶-3-基)甲基)-2-甲基-5-(三氟甲基)苯甲酰胺	525.6

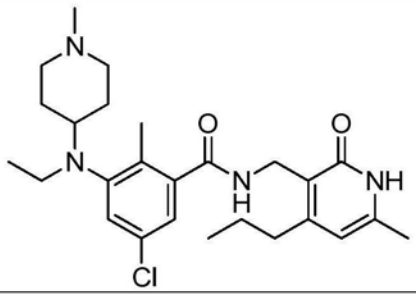
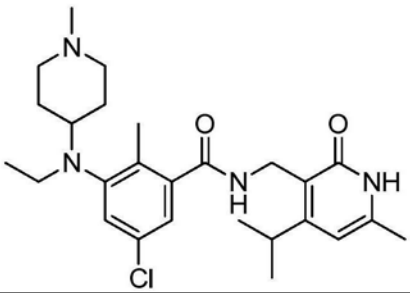
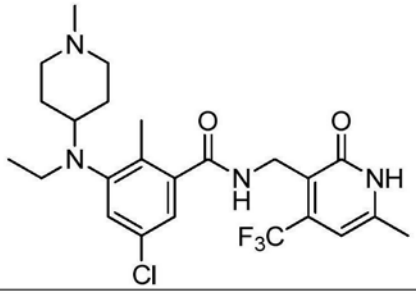
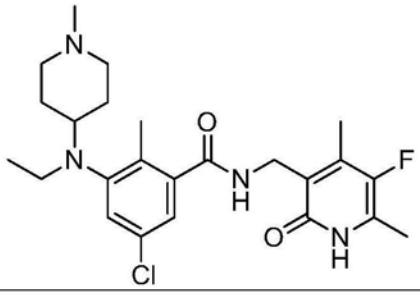
[0693]

化合物编号	结构	名称	分子量†
397		3-(乙基(1-甲基哌啶-4-基)氨基)-N-((5-氟代-4-异丙基-6-甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-5-(三氟甲基)苯甲酰胺	525.6
398		3-(乙基(1-甲基哌啶-4-基)氨基)-N-((5-氟代-4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-5-(三氟甲基)苯甲酰胺	497.5
399		3-(乙基(1-甲基哌啶-4-基)氨基)-N-((5-氟代-6-甲基-2-氧代-4-(三氟甲基)-1,2-二氢吡啶-3-基)甲基)-2-甲基-5-(三氟甲基)苯甲酰胺	551.5
400		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(1-异丙基哌啶-4-基)氨基)-2-甲基-5-(三氟甲基)苯甲酰胺	507.2
401		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((2R,6R)-2,6-二甲基哌啶-4-基)(乙基)氨基)-2-	493.1

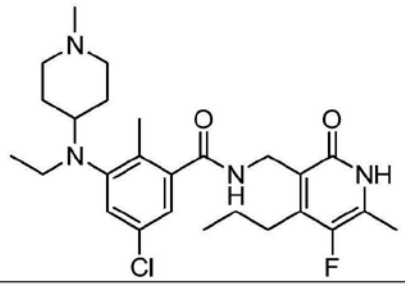
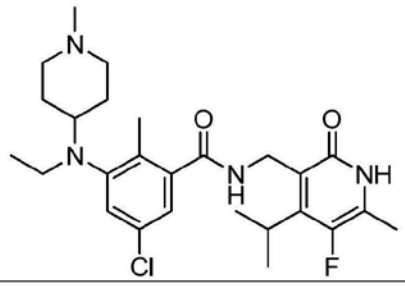
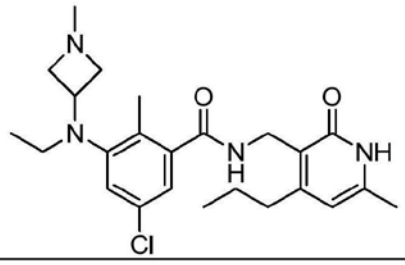
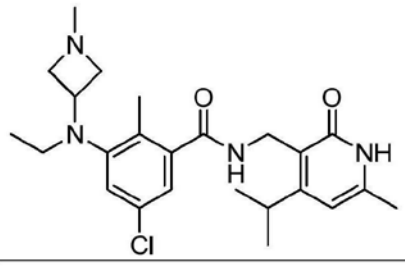
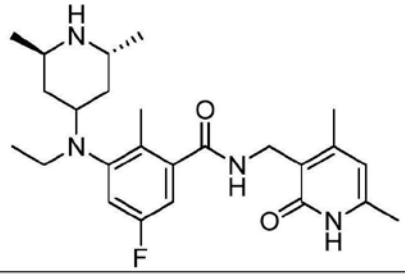
[0694]

化合物编号	结构	名称	分子量 †
		甲基-5-(三氟甲基)苯甲酰胺	
402		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((2S,4s,6R)-2,6-二甲基哌啶-4-基)(乙基)氨基)-2-甲基-5-(三氟甲基)苯甲酰胺	493.2
403		3-(乙基(1-甲基氮杂环丁烷-3-基)氨基)-2-甲基-N-((6-甲基-2-氧代-4-丙基-1,2-二氢吡啶-3-基)甲基)-5-(三氟甲基)苯甲酰胺	480.5
404		3-(乙基(1-甲基氮杂环丁烷-3-基)氨基)-N-((4-异丙基-6-甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-5-(三氟甲基)苯甲酰胺	479.5
405		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(1-甲基氮杂环丁烷-3-基)氨基)-2-甲基-5-(三氟甲基)苯甲	451.5

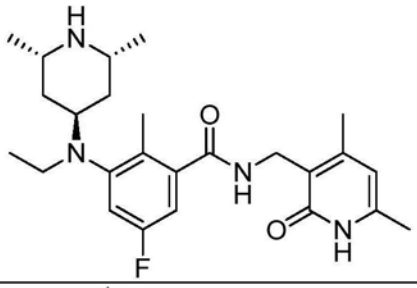
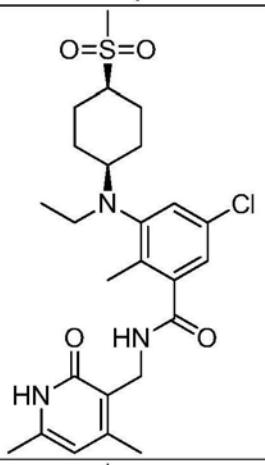
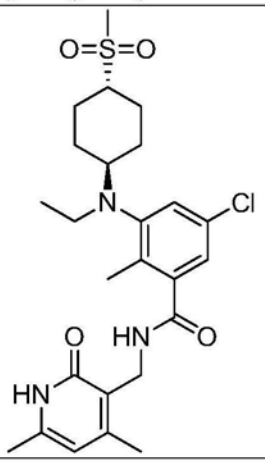
[0695]

化合物编号	结构	名称	分子量†
		酰胺	
406		5-氯-3-(乙基(1-甲基哌啶-4-基)氨基)-2-甲基-N-((6-甲基-2-氧代-4-丙基-1,2-二氢吡啶-3-基)甲基)苯甲酰胺	473.1
407		5-氯-3-(乙基(1-甲基哌啶-4-基)氨基)-N-((4-异丙基-6-甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	495.2
408		5-氯-3-(乙基(1-甲基哌啶-4-基)氨基)-2-甲基-N-((6-甲基-2-氧代-4-(三氟甲基)-1,2-二氢吡啶-3-基)甲基)苯甲酰胺	499.1
409		5-氯-3-(乙基(1-甲基哌啶-4-基)氨基)-N-((5-氟代-4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	463.5

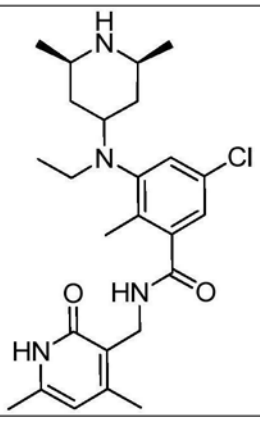
[0696]

化合物编号	结构	名称	分子量†
410		5-氯-3-(乙基(1-甲基哌啶-4-基)氨基)-N-((5-氟代-6-甲基-2-氧代-4-丙基-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	491.5
411		5-氯-3-(乙基(1-甲基哌啶-4-基)氨基)-N-((5-氟代-4-异丙基-6-甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	491.5
412		5-氯-3-(乙基(1-甲基氮杂环丁-3-基)氨基)-2-甲基-N-((6-甲基-2-氧代-4-丙基-1,2-二氢吡啶-3-基)甲基)苯甲酰胺	445.5
413		5-氯-3-(乙基(1-甲基氮杂环丁-3-基)氨基)-N-((4-异丙基-6-甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺	445.6
414		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((2R,6R)-2,6-二甲基哌啶-4-基)(乙基)氨基)-5-氟-2-甲基苯	443.1

[0697]

化合物编号	结构	名称	分子量†
		甲酰胺	
415		N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((2S,4s,6R)-2,6-二甲基哌啶-4-基)(乙基)氨基)-5-氟-2-甲基苯甲酰胺	443.2
416		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基((1s,4s)-4-(甲基磺酰基)环己基)氨基)-2-甲基苯甲酰胺	508.1
417		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基((1r,4r)-4-(甲基磺酰基)环己基)氨基)-2-甲基苯甲酰胺	508

[0698]

化合物编号	结构	名称	分子量 †
418		5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((2S,6R)-2,6-二甲基哌啶-4-基)(乙基)氨基)-2-甲基苯甲酰胺	

[0699] *化合物 58/59,60/61,107/108 和 416/417 的顺反立体化学任意分配。

[0700] †MS- 样品的质谱。其可以以正或负离子的模式以及包括 M,M+1,M+23,(M+Na) 和 M-1 的潜在离子来记录。

[0701] 本文所使用的“烷基”、“C_1、C_2、C_3、C_4、C_5 或 C_6 烷基”或“C_1-C_6 烷基”旨在包括 C_1、C_2、C_3、C_4、C_5 或 C_6 直链(线性)的饱和脂肪族烃基和 C_3、C_4、C_5 或 C_6 支链的饱和脂肪族烃基。例如,C_1-C_6 烷基旨在包括 C_1、C_2、C_3、C_4、C_5 或 C_6 烷基基团。烷基的例子包括主链具有 1-6 个碳原子的部分,例如,但不限于甲基、乙基、正丙基、异丙基、正丁基、仲丁基、叔丁基、正戊基、仲戊基或正己基。

[0702] 在某些实施例中,直链或支链的烷基具有 6 个或更少碳原子(例如,直链的 C_1-C_6 或支链的 C_3-C_6),在另一个实施例中,直链或支链的烷基具有 4 个或更少碳原子。

[0703] 本文所使用的“环烷基”是指具有 3-30 个碳原子(例如,C_3-C_{10})的饱和或不饱和的非芳族烃单环或多环(如稠环、桥环或螺环)) 体系。环烷基的例子包括但不限于环丙基、环丁基、环戊基、环己基、环庚基、环辛基、环戊烯基、环己烯基、环庚烯基和金刚烷基。除非另有明确说明,否则术语“杂环烷基”是指饱和或不饱和非芳族 3-8 元单环、7-12 元双环(稠环、桥环或螺环)或具有一个或多个杂原子(如氧原子、氮原子、硫原子或硒原子)的 11-14 元三环(稠环、桥环或螺环)体系。杂环烷基团的例子包括但不限于哌啶基、哌嗪基、吡咯烷基、二氧六环基、四氢呋喃基、异二氢吲哚基、二氢吲哚基、咪唑烷基、吡唑烷基,恶唑烷基、异恶唑烷基、三唑烷基、四氢呋喃基、环氧乙烷基、氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、1,2,3,6- 四氢吡啶基、四氢吡喃基、二氢吡喃基、吡喃基、吗啉基、四氢噻喃基、1,4- 二氮杂环庚烷基、1,4- 氧杂氮杂环庚烷基、2- 氧杂 -5- 氮杂双环 [2.2.1] 庚烷基、2,5- 二氮杂双环 [2.2.1] 庚烷基、2- 氧杂 -6- 氮杂螺 [3.3] 庚烷基、2,6- 二氮杂螺 [3.3] 庚烷基、1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸烷基、1,4- 二氧杂螺 [4.5] 癸烷基、1- 氧杂螺 [4.5] 癸烷基、1- 氮杂螺 [4.5] 癸烷基、3’H- 螺 [环己烷 -1,1’- 异苯并呋喃]- 基、7’H- 螺 [环己烷 -1,5’- 呋喃并 [3,4-b] 吡啶]- 基,3’H- 螺 [环己烷 -1,1’- 呋喃并 [3,4-c] 吡啶]- 基等。

[0704] 术语“任选取代的烷基”是指未取代的烷基或烃主链上一个或多个碳原子上的一个或多个氢原子被指定的取代基取代的烷基。所述取代基可以包括例如烷基、烯基、炔基、卤素、羟基、烷基羰氧基、芳基羰氧基、烷氧基羰氧基、芳氧基羰氧基、羧酸酯、烷基羰基、芳基羰基、烷氧基羰基、氨基羰基、烷基氨基羰基、二烷基氨基羰基、烷硫基羰基、烷氧基、磷

酸酯、膦酸根合 (phosphonato)、次膦酸根合 (phosphinato)、氨基(包括烷基氨基、二烷基氨基、芳基氨基、二芳基氨基和烷基芳基氨基)、酰氨基(包括烷基羰基氨基、芳基羰基氨基、氨基甲酰基和脲基)、脒基、亚氨基、巯基、烷硫基、芳硫基、硫代羧酸酯、硫酸酯、烷基亚磺酰基、磺酸基、氨磺酰基、磺酰氨基、硝基、三氟甲基、氰基、叠氮基、杂环基、烷基芳基,或芳族或杂芳族片段。

[0705] “芳基烷基”或“芳烷基”片段是指芳基取代的烷基(例如,苯基甲基(苄基))。“烷基芳基”片段是指烷基取代的芳基(例如,甲基苯基)。

[0706] 本文所述“烷基连接体”旨在包括 C_1、C_2、C_3、C_4、C_5 或 C_6 直链(线型的)饱和的二价脂肪族烃基团和 C_3、C_4、C_5 或 C_6 支链的饱和的脂肪族烃基团。例如,C_1-C_6 烷基连接体包括 C_1、C_2、C_3、C_4、C_5 或 C_6 烷基连接体。烷基连接体的例子包括,具有一至六个碳原子的部分,例如但不限于甲基 ($-CH_2-$)、乙基 ($-CH_2CH_2-$)、正丙基 ($-CH_2CH_2CH_2-$)、异丙基 ($-CHCH_3CH_2-$)、正丁基 ($-CH_2CH_2CH_2CH_2-$)、仲丁基 ($-CHCH_3CH_2CH_2-$)、异丁基 ($-C(CH_3)_2CH_2-$)、正戊基 ($-CH_2CH_2CH_2CH_2CH_2-$)、仲戊基 ($-CHCH_3CH_2CH_2CH_2-$) 或正己基 ($-CH_2CH_2CH_2CH_2CH_2CH_2-$)。

[0707] “烯基”包括不饱和脂肪族基团,其长度和可能的取代方面类似于上述烷基,但是其包含至少一个双键。例如,术语“烯基”包括直链的烯基基团(例如,乙烯基、丙烯基、丁烯基、戊烯基、己烯基、庚烯基、辛烯基、壬烯基、癸烯基)和支链的烯基。在某些实施例中,直链或支链的烯基基团在其主链上具有 6 个或更少的碳原子数(例如,直链的 C_2-C_6、支链的 C_3-C_6)。术语“C_2-C_6”包括含有 2-6 个碳原子的烯基基团。术语“C_3-C_6”包括具有 3-6 个碳原子的烯基基团。

[0708] 术语“任选取代的烯基”是指未取代的烯基或在一个或多个烃主链碳原子上的一个或多个氢原子被指定的取代基取代的烯基。所述取代基可以包括例如烷基,烯基、炔基、卤素、羟基、烷基羰氧基、芳基羰氧基、烷氧基羰氧基、芳氧基羰氧基、羧酸酯、烷基羰基、芳基羰基、烷氧基羰基、氨基羰基、烷基氨基羰基、二烷基氨基羰基、烷硫基羰基、烷氧基、磷酸酯、膦酸根合、次膦酸根合、氨基(包括烷基氨基、二烷基氨基、芳基氨基、二芳基氨基和烷基芳基氨基)、酰氨基(包括烷基羰基氨基、芳基羰基氨基、氨基甲酰基和脲基)、脒基、亚氨基、巯基、烷硫基、芳硫基、硫代羧酸酯、硫酸酯、烷基亚磺酰基、磺酸基、氨磺酰基、磺酰氨基、硝基、三氟甲基、氰基、杂环基、烷基芳基,或芳族或杂芳族片段。

[0709] “炔基”包括不饱和脂肪族基团,其长度和可能的取代方面类似于上述烷基,但是其至少包含一个三键。例如,“炔基”包括直链的炔基基团(例如,乙炔基、丙炔基、丁炔基、戊炔基、己炔基、庚炔基、辛炔基、壬炔基、癸炔基)和支链炔基。在某些实施例中,直链或支链的炔基基团在其主链上具有 6 个或更少的碳原子数(例如,直链的 C_2-C_6,支链的 C_3-C_6)。术语“C_2-C_6”包括含有 2-6 个碳原子的炔基基团。术语“C_3-C_6”包括含有 3-6 个碳原子的炔基基团。

[0710] 术语“任选取代的炔基”是指未取代的炔基或一个或多个烃主链碳原子上的一个或多个氢原子被指定的取代基取代的炔基。所述取代基可以包括例如烷基、烯基、炔基、卤素、羟基、烷基羰氧基、芳基羰氧基、烷氧基羰氧基、芳氧基羰氧基、羧酸酯、烷基羰基、芳基羰基、烷氧基羰基、氨基羰基、烷基氨基羰基、二烷基氨基羰基、烷硫基羰基、烷氧基、磷酸酯、膦酸根合、次膦酸根合、氨基(包括烷基氨基、二烷基氨基、芳基氨基、二芳基氨基和烷基芳基氨基)、酰氨基(包括烷基羰基氨基、芳基羰基氨基、氨基甲酰基和脲基)、脒基、亚氨基、

巯基、烷硫基、芳硫基、硫代羧酸酯、硫酸酯、烷基亚磺酰基，磺酸基、氨磺酰基、磺酰氨基、硝基、三氟甲基、氰基、叠氮基、杂环基、烷基芳基，或芳族或杂芳族片段。

[0711] 其他任选取代部分(例如任选取代的环烷基、杂环烷基、芳基或杂芳基)包括未被取代的部分和具有一个或多个指定取代基的部分。例如，取代的杂环烷基包括被一个或多个烷基取代的杂环烷基，如 2,2,6,6- 四甲基 - 哌啶基和 2,2,6,6- 四甲基 -1,2,3,6- 四氢吡啶基。

[0712] “芳基”包括具有芳香性的基团，包括“共轭的”或多环体系，所述多环体系含有至少一个芳香环且在其环形结构中不含任何杂原子。其实例包括苯基、苄基、1,2,3,4- 四氢萘基等。

[0713] “杂芳基”是指如上所定义的芳基，只是在环结构中具有 1-4 个杂原子，其还可以被称为“芳杂环”或“杂芳族化合物”。如本文所使用的，术语“杂芳基”是指包括稳定的 5、6 或 7 元单环或 7、8、9、10、11 或 12 元由碳原子和一个或多个杂原子构成的双环芳族杂环，例如 1 或 1-2 或 1-3 或 1-4 或 1-5 或 1-6 个杂原子，或者例如 1、2、3、4、5 或 6 个杂原子，所述杂原子独立地选自氮、氧和硫。氮原子可以被取代或不被取代(即，N 或 NR，其中 R 是氢或是如本文定义的其它取代基)。氮和硫杂原子可任选被氧化(即，N → O 和 $S(O)_p$，其中 p=1 或 2)。但是应当注意的是，芳族杂环中硫和氧原子的总数不超过 1。

[0714] 杂芳基基团的例子包括吡咯、呋喃、噻吩、噻唑、异噻唑、咪唑、三唑、四唑、吡唑、恶唑、异恶唑、吡啶、吡嗪、哒嗪、嘧啶等。

[0715] 此外，术语“芳基”和“杂芳基”包括多环芳基和杂芳基基团，例如，三环、双环，例如，萘、苯并恶唑、苯并二恶唑、苯并噻唑、苯并咪唑、苯并噻吩、亚甲二氧基苯基、喹啉、异喹啉、萘啶基、吲哚、苯并呋喃、嘌呤、苯并呋喃、脱氮嘌呤、吲哚嗪。

[0716] 在多环芳族环中，尽管所有的环都可以是芳族的(例如，喹啉)，但是只有一个环必须是芳族的(例如，2,3- 二氢吲哚)。第二环可以是稠合的或桥连的。

[0717] 环烷基、杂环烷基、芳基或杂芳基环可以在一个或多个环位置(例如，成环碳原子或杂原子，如氮原子)被取代基取代，所述取代基如上文所述，例如烷基、烯基、炔基、卤素、羟基、烷氧基、烷基羰氧基、芳基羰氧基、烷氧基羰氧基、芳氧基羰氧基、羧酸酯、烷基羰基、烷基氨基羰基、芳基烷基氨基羰基、烯基氨基碳酰基、烷基羰基、芳基羰基、芳基烷基、烯基羰基、烷氧基羰基、氨基羰基、烷硫基羰基、磷酸酯、膦酸根合、次膦酸根合、氨基(包括烷基氨基、二烷基氨基、芳基氨基、二芳基氨基和烷基芳基氨基)、酰氨基(包括烷基羰基氨基、芳基羰基氨基、氨基甲酰基和脲基)、脒基、亚氨基、巯基、烷硫基、芳硫基、硫代羧酸酯、硫酸酯、烷基亚磺酰基、磺酸基、氨磺酰基、磺酰氨基、硝基、三氟甲基、氰基、叠氮基、杂环基、烷基芳基，或芳族或杂芳族片段。芳基和杂芳基基团也可以与非芳族的脂环族环或杂环稠合或桥连，以形成一个多环体系(例如，四氢化萘，亚甲基二氧基苯基)。

[0718] 本文所使用的“碳环”或“碳环基环”是指包括任何稳定的具有特定数目碳原子的单环、双环或三环，其中任何一个都可以是饱和的、不饱和的或芳族的。碳环包括环烷基和芳基。例如，C_3-C_{14} 碳环是指包括具有 3、4、5、6、7、8、9、10、11、12、13 或 14 个碳原子的单环、双环或三环。碳环的例子包括，但不限于环丙基、环丁基、环丁烯基、环戊基、环戊烯基、环己基、环庚烯基、环庚基、环庚烯基、金刚烷基、环辛基、环辛烯基、环辛二烯基、苏基、苯基、萘基、二氢化茚基、金刚烷基和四氢萘基。桥环同样包括在碳环的定义中，包括例如 [3.3.0]

二环辛烷、[4.3.0] 二环壬烷、[4.4.0] 二环癸烷和 [2.2.2] 二环辛烷。一个或多个碳原子连接两个不相邻的碳原子时会形成桥环。在一个实施例中，桥环是 1 个或 2 个碳原子。应当注意的是，一个桥总是将单环转换为三环。当环被桥接时，列举用于该环的取代基也可以存在于桥上。稠环（例如，萘基、四氢萘基）和螺环也包括在内。

[0719] 本文所使用的“杂环”或“杂环基”包括包含至少一个环杂原子（例如，氮原子、氧原子或硫原子）的任何环结构（饱和的、不饱和的或芳族的）。杂环包括杂环烷基和杂芳基。杂环的例子包括，但不限于吗啉、吡咯烷、四氢噻吩、哌啶、哌嗪、氧杂环丁烷、吡喃、四氢吡喃、氮杂环丁烷和四氢呋喃。

[0720] 杂环基团的实例包括，但不限于吖啶基、吖辛因基、苯并咪唑基、苯并呋喃基、苯并硫代呋喃基（benzothiofuranyl）、苯并噻吩基、苯并恶唑基、苯并恶唑啉基、苯并噻唑基、苯并三唑基、苯并四唑基、苯并异恶唑基、苯并异噻唑基、苯并咪唑啉基、咔唑基、4aH- 咔唑基、咔啉基、苯并二氢吡喃基、苯并吡喃基、噌啉基、十氢喹啉基、2H,6H-1,5,2- 二噻嗪基、二氢呋喃并 [2,3-b] 四氢呋喃基、呋喃基、呋咱基（furazanyl）、咪唑烷基、咪唑啉基、咪唑基，1H- 吲唑基、假吲哚基（indolenyl）、二氢吲哚基、中氮茚基（indolizinyl）、吲哚基、3H- 吲哚基、靛红基（isatinoyl）、异苯并呋喃基、异苯并二氢吡喃基（isochromanyl）、异吲唑基、异二氢吲哚基、异吲哚基、异喹啉基、异噻唑基、异恶唑基、亚甲二氧基苯基、吗啉基、萘啶基（naphthyridinyl）、八氢异喹啉基、恶二唑基（oxadiazolyl）、1,2,3- 恶二唑基、1,2,4- 恶二唑基、1,2,5- 恶二唑基、1,3,4- 恶二唑基、1,2,4- 恶二唑 5(4H)- 酮、恶唑烷基、恶唑基、羟吲哚基（oxindolyl）、嘧啶基、菲啶基、菲咯啉基（phenanthrolinyl）、吩嗪基、吩噻嗪基、酚黄素基（phenoxathinyl）、吩恶嗪基、酞嗪基、哌嗪基、哌啶基、哌啶酮基、4- 哌啶酮基、胡椒基、蝶啶基、嘌呤基、吡喃基、吡嗪基、吡唑烷基、吡唑啉基、吡唑基、哒嗪基、吡啶并恶唑、吡啶并咪唑、吡啶并噻唑、吡啶基（pyridinyl）、吡啶基（pyridyl）、嘧啶基、吡咯烷基、吡咯啉基、2H- 吡咯基、吡咯基、喹唑啉基、喹啉基、4H- 喹嗪基、喹喔啉基、奎宁环基、四氢呋喃基、四氢异喹啉基、四氢喹啉基、四唑基、6H-1,2,5- 噻二嗪基、1,2,3- 噻二唑基、1,2,4- 噻二唑基、1,2,5- 噻二唑基、1,3,4- 噻二唑基、噻蒽基、噻唑基、噻吩基、噻吩并噻唑基、噻吩并恶唑基、噻吩并咪唑基、苯硫基、三嗪基、1,2,3- 三唑基、1,2,4- 三唑基、1,2,5- 三唑基、1,3,4- 三唑基和呫吨基。

[0721] 本文所使用的术语“取代的”是指指定原子上的任何一个或多个氢原子被选自指定组的取代基取代，条件是所述指定原子不超过正常价态，并且取代的结果是产生稳定的化合物。当取代基是氧代或酮基（即，=O）时，那么原子上的 2 个氢原子被取代。酮取代基在芳香环上不存在。本文所使用的环双键是在两个相邻的环原子（例如，C=C，C=N 或 N=N）之间形成的双键。“稳定的化合物”和“稳定的结构”是指能够足够强健地从反应混合物中分离至有效的纯度并配制成有效的治疗剂的化合物。

[0722] 当取代基所连的化学键与连接环中的两个原子的一个键交叉时，则这样的取代基可以同环上的任何原子键连。当列出的取代基没有表明其原子通过哪一个原子键将该取代基连到给定通式的化合物的其余部分时，则该取代基可以通过该结构式中的任何原子键连。取代基和 / 或变量的组合是允许的，条件是这种组合能够产生稳定的化合物。

[0723] 当任何变量（例如，R_1）在化合物的任何成分或结构式中出现一次以上时，其在每一种情况下出现的定义是各自独立的。因此，例如如果一个基团显示了被 0-2 个 R_1 取代，则

该基团可以任选被多达两个 R_1 取代，并且 R_1 在每一种情况下独立地选自 R_1 的定义。此外，取代基和 / 或变量的组合是允许的，条件是这种组合能够产生稳定的化合物。

[0724] 术语“含羟基的”或“羟基”包括含 -OH 或 $-O^-$ 的基团。

[0725] 本文所使用的“卤”或“卤素”是指氟、氯、溴和碘。术语“全卤代的”通常指所有的氢原子都被卤原子取代的片段。术语“卤代烷基”或“卤代烷氧基”指的是一个或多个卤素原子取代的烷基或烷氧基。

[0726] 术语“羰基”包括含有通过双键与氧原子连接的碳原子的化合物和片段。含有羰基的片段的例子包括但不限于醛、酮、羧酸、酰胺、酯、酸酐等。

[0727] 术语“羧基”是指 -COOH 或其 C_1-C_6 烷基酯。

[0728] “酰基”包括含有酰基 (R-C(O)-) 或羰基的片段。“取代的酰基”包括其中一个或多个氢原子被例如下列取代基取代的酰基，所述取代基包括烷基、炔基、卤素、羟基、烷基羰氧基、芳基羰氧基、烷氧基羰氧基、芳氧基羰氧基、羧酸酯、烷基羰基、芳基羰基、烷氧基羰基、氨基羰基、烷基氨基羰基、二烷基氨基羰基、烷硫基羰基、烷氧基、磷酸酯、膦酸根合、次膦酸根合、氨基(包括烷基氨基、二烷基氨基、芳基氨基、二芳基氨基和烷基芳基氨基)、酰氨基(包括烷基羰基氨基、芳基羰基氨基、氨基甲酰基和脲基)、脒基、亚氨基、巯基、烷硫基、芳硫基、芳硫代羧酸酯、硫酸酯、烷基亚磺酰基、磺酸基、氨磺酰基、磺酰氨基、硝基、三氟甲基、氰基、叠氮基、杂环基、烷基芳基或芳族或杂芳族基团。

[0729] “芳酰基”包括含有键连到羰基基团上的芳基或杂芳基的片段。芳酰基的例子包括苯基羧基、萘羧基等。

[0730] “烷氧基烷基”、“烷基氨基烷基”和“硫代烷氧基烷基”包括如上所述的烷基基团，其中氧原子、氮原子或硫原子取代一个或多个烃主链上的碳原子。

[0731] 术语“烷氧”或“烷氧基”包括与氧原子共价键连的取代和未取代的烷基、烯基和炔基基团。烷氧基团或烷氧基的例子包括，但不限于甲氧基、乙氧基、异丙氧基、丙氧基、丁氧基和戊氧基。取代烷氧基团的例子包括卤代烷氧基。烷氧基团可以被下列取代基取代，如烯基、炔基、卤素、羟基、烷基羰氧基、芳基羰氧基、烷氧基羰氧基、芳氧基羰氧基、羧酸酯、烷基羰基、芳基羰基、烷氧基羰基、氨基羰基、烷基氨基羰基、二烷基氨基羰基、烷硫基羰基、烷氧基、磷酸酯、膦酸根合、次膦酸根合、氨基(包括烷基氨基、二烷基氨基、芳基氨基、二芳基氨基和烷基芳基氨基)，酰氨基(包括烷基羰基氨基、芳基羰基氨基、氨基甲酰基和脲基)、脒基、亚氨基、巯基、烷硫基、芳硫基、硫代羧酸酯、硫酸酯、烷基亚磺酰基、磺酸基、氨磺酰基、磺酰氨基、硝基甲基、三氟甲基、氰基、叠氮基、杂环基、烷基芳基或芳族或杂芳族基团。卤素取代的烷氧基团的例子包括，但不限于一氟甲氧基、二氟甲氧基、三氟甲氧基、一氯甲氧基、二氯甲氧基、三氯甲氧基。

[0732] 术语“醚”或“烷氧”包括含有键连到两个碳原子或杂原子上的氧的化合物或片段。例如，该术语包括“烷氧基烷基”，是指共价键连到与烷基基团共价键连的氧原子上的烷基、烯基或炔基基团。

[0733] 术语“酯”包括含有键连到与羰基上的碳键连的氧原子上的碳原子或杂原子的化合物或片段。术语“酯”包括烷氧羰基基团，如甲氧羰基、乙氧羰基、丙氧羰基、丁氧羰基、戊氧羰基等。

[0734] 术语“硫代烷基”包括包含与硫原子键连的烷基基团的化合物或片段。所述硫代

烷基可以被下列取代基取代，如烷基、烯基、炔基、卤素、羟基、烷基羰氧基、芳基羰氧基、烷氧基羰氧基、芳氧基羰氧基、羧酸酯、羧酸、烷基羰基、芳基羰基、烷氧基羰基、氨基羰基、烷基氨基羰基、二烷基氨基羰基、烷硫基羰基、烷氧基、氨基(包括烷基氨基、二烷基氨基、芳基氨基、二芳基氨基和烷基芳基氨基)、酰氨基(包括烷基羰基氨基、芳基羰基氨基、氨基甲酰基和脲基)、脒基、亚氨基、巯基、烷硫基、芳硫基、硫代羧酸酯、硫酸酯、烷基亚磺酰基、磺酸基、氨磺酰基、磺酰氨基、硝基、三氟甲基、氰基、叠氮基、杂环基、烷基芳基或芳族或杂芳族片段。

[0735] 术语“硫代羰基”或“硫代羧基”包括包含通过双键与硫原子键连的碳原子的化合物和片段。

[0736] 术语“硫醚”包括含有与两个碳原子或杂原子键连的硫原子的片段。硫醚的例子包括，但不限于烷硫烷基、烷硫烯基、烷硫炔基。术语“烷硫烷基”包括具有与和烷基基团键连的硫原子键连的烷基、烯基或炔基的片段。类似地，术语“硫代烯基”指其中烷基、烯基或炔基与共价键连至烯基基团的硫原子键连的片段；“硫代炔基”指其中烷基、烯基或炔基与共价键连至炔基基团的硫原子键连的片段。

[0737] 本文所使用的“胺”或“氨基”是指未取代的或取代的 $-NH_2$。“烷基氨基”包括其中 $-NH_2$ 的氮原子同至少一个烷基基团键连的化合物的基团。烷基氨基的例子包括苄基氨基、甲氨基、乙氨基、苯乙基氨基等。“二烷基氨基”包括其中 $-NH_2$ 的氮原子同至少两个额外的烷基基团键连的基团。二烷基氨基的例子包括，但不限于二甲基氨基和二乙基氨基。“芳氨基”和“二芳氨基”包括其中氮原子同至少一个或两个芳基分别键连的基团。“氨基芳基”和“氨基芳氧基”指氨基取代的芳基、芳氧基。“烷基芳基氨基”、“烷基氨基芳基”或“芳基氨基烷基”是指同至少一个烷基基团和至少一个芳基基团键连的氨基。“烷基氨基烷基”是指同氮原子键连的烷基、烯基或炔基基团，所述氮原子还与烷基键连。“酰氨基”包括其中氮原子与酰基基团键连的基团。酰氨基的例子包括，但不限于烷基羰基氨基、芳基羰基氨基、氨基甲酰基和脲基。

[0738] 术语“酰胺基”或“氨基羧基”包括包含与羰基或硫代羰基基团的碳键连的氮原子的化合物或基团。该术语包括“烷氨基羧基”基团，所述烷氨基羧基包括与羰基或硫代羰基的碳键连的氨基键连的烷基、烯基或炔基基团的基团。该术语还包括“芳基氨基羧基”基团，所述芳基氨基羧基包括与和羰基或硫代羰基的碳键连的氨基键连的芳基或杂芳基片段的片段。术语“烷基氨基羧基”、“烯基氨基羧基”、“炔基氨基羧基”和“芳基氨基羧基”包括其中烷基、烯基、炔基和芳基分别与又和羰基的碳键连的氮原子键连的片段。酰胺可以被取代基如直链烷基、支链烷基、环烷基、芳基、杂芳基或杂环取代。酰胺基团上的取代基可被进一步取代。

[0739] 本发明中含氮原子的化合物可以通过用氧化剂(例如，间氯过氧苯甲酸 (mCPBA) 和 / 或过氧化氢)处理而转化成 N- 氧化物，以得到本发明中的其它化合物。因此，所有本文所示的和所要求保护的含氮化合物在价态和结构允许的情况下都应考虑为包括本文所示的化合物和其 N- 氧化物衍生物(它可以指定为 $N \rightarrow O$ 或 N^+-O^-)。此外，在其他情况下，本发明化合物中的氮原子可以被转换为 N- 羟基或 N- 烷氧基化合物。例如，N- 羟基化合物可以通过氧化剂氧化母体胺来制备，所述氧化剂例如为间氯过氧苯甲酸。因此，所有本文所示的和所要求保护的含氮化合物在价态和结构允许的情况下都应考虑为包括本文所示的化合

物和其 N- 羟基衍生物（即 N-OH）和 N- 烷氧基衍生物(即，N-OR，其中 R 是取代或未取代的 C_1-C_6 烷基，C_1-C_6 烯基，C_1-C_6 炔基，3-14 元碳环或 3-14 元杂环)。

[0740] 在本说明书中，在某些情况下为了方便，化合物的结构式表示某一个异构体，但本发明包括所有的异构体，如几何异构体、基于不对称碳的光学异构体、立体异构体、互变异构体等，应当理解，不是所有的同分异构体都可以具有相同水平的活性。此外，结构式表示的化合物可能存在同质多晶现象。值得注意的是，化合物的任何晶体形式、晶体形式的混合物或无水物或水合物都包括在本发明的范围内。此外，通过本发明化合物在体内的降解产生的所谓的代谢产物也包括在本发明的范围内。

[0741] “异构现象”是指化合物具有相同的分子式，但原子的键连顺序或原子空间排列不同。原子空间排列不同的异构体称为“立体异构体”。彼此间为非镜像关系的立体异构体称为“非对映异构体”，彼此为非重叠镜像关系的立体异构体称为“对映体”或有时称为光学异构体。含有等量的相反手性的单个对映体的混合物称为“外消旋混合物”。

[0742] 与四个不同的取代基键连的碳原子称为“手性中心”。

[0743] “手性异构体”是指具有至少一个手性中心的化合物。具有一个以上手性中心的化合物可以作为一个单独的非对映异构体或作为非对映异构体的混合物存在，所述混合物被称为“非对映体混合物”。当存在一个手性中心时，立体异构体可以通过手性中心的绝对构型 (R 或 S) 进行表征。绝对构型是指与手性中心连接的取代基在空间的排列。所考虑的与手性中心连接的取代基的位次排列顺序符合 Cahn-Ingold-Prelog 顺序规则 (Cahn et al.,Angew.Chem.Inter.Edit.1966,5,385;errata511;Cahn et al.,Angew.Chem.1966,78,413;Cahn and Ingold,J.Chem.Soc.1951(London),612;Cahn et al.,Experientia1956,12,81;Cahn,J.Chem.Educ.1964,41,116)。

[0744] “几何异构体”是指阻碍双键或环烷基连接体（例如，1,3- 环丁基）旋转而存在的非对映体异构体。根据 Cahn-Ingold-Prelog 顺序规则，这些构型在名称上的区别在于前缀顺 - 和反 -，或 Z 和 E，这表示基团是在分子中的双键的同侧或异侧。

[0745] 应当理解，本发明的化合物可以描述为不同的手性异构体或几何异构体。还应当理解的是，当化合物具有手性异构体或几何异构体的形式时，所有的异构体形式都应包括在本发明的范围内，并且该化合物的命名不排除任何化学异构体形式，当然，不是所有的异构体都可能具有相同水平的活性。

[0746] 此外，在本发明中所讨论的结构和其他化合物包括其所有的阿托异构体，容易理解，并不是所有的阿托异构体都可能具有相同水平的活性。“阿托异构体”是立体异构体的一种类型，其中两种异构体的原子的空间排列不同。阿托异构体的存在归功于由阻碍大基团围绕中心键旋转而引起的受限制的旋转。这样的阿托异构体一般以混合物形式存在，然而作为色谱技术的最新进展的结果，已经能够在选定的情形下对两个阿托异构体的混合物进行分离。

[0747] “互变异构体”是两种或多种结构异构体中的一个，所述结构异构体以均衡的状态存在，并且易于从一种异构形式转换到另一种异构形式。这种转换的结果导致氢原子的形式迁移，并伴随着相邻共轭双键的转换。互变异构体作为溶液中的互变异构体组的混合物而存在。在可能发生互变异构化的溶液中，互变异构体的化学平衡是能够达到的。互变异构体的确切比例取决于几个因素，包括温度、溶剂和 pH 值。互变异构体可以通过互变异构

化进行相互转化的概念称为互变现象。

[0748] 在各类可能的互变异构中，通常可以观察到两种类型。在酮－烯醇互变异构现象中会发生电子和氢原子的同时迁移。环－链互变异构现象的发生是糖链分子中的醛基(-CHO)与同一分子中的一个羟基(-OH)反应而使其具有如葡萄糖所展示的环(环状)形式的结果。

[0749] 常见的互变异构体对是：酮－烯醇、酰胺－腈、内酰胺－内酰亚胺、杂环中的酰胺－亚胺酸的互变异构现象(例如在诸如鸟嘌呤、胸腺嘧啶和胞嘧啶的核酸碱基中)、亚胺－烯胺和烯胺－烯胺。酮－烯醇平衡的一个例子是吡啶-2(1H)-酮和相应的吡啶-2-醇之间，如下图所示：

[0750]

吡啶-2(1H)-酮 吡啶-2-醇

[0751] 应当理解的是，本发明的化合物可以描述为不同的互变异构体。还应当理解的是，当化合物具有互变异构形式时，所有的互变异构体形式都应包括在本发明的范围内，并且该化合物的命名不排除任何互变异构体形式。应理解，某些互变异构体可能比其他互变异构体具有更高水平的活性。

[0752] 术语“晶体多晶型”、“多晶型”或“晶体形式”是指其中化合物(或它的盐或溶剂化物)可以以不同的晶体堆积排列形式结晶的晶体结构，所有的晶体结构都具有相同的元素组成。不同晶型通常具有不同的X-射线衍射图、红外光谱、熔点、密度、硬度、晶体形状、光学和电学性质、稳定性和溶解性。重结晶溶剂、结晶速率、储存温度以及其他因素可能会导致一种晶体形式占主导地位。化合物的晶体多晶型物可通过在不同的条件下的结晶化来制得。

[0753] 本文描述的任何结构式的化合物包括化合物本身及其盐、溶剂化物和前体药物(如果适用)。例如，阴离子和取代苯化合物上带正电荷的基团(例如，氨基)之间可以形成盐。适合的阴离子包括氯离子、溴离子、碘离子、硫酸根离子、硫酸氢根离子、氨基磺酸根离子、硝酸根离子、磷酸根离子、柠檬酸根离子、甲磺酸根离子、三氟乙酸根离子、谷氨酸根离子、葡糖醛酸根离子、戊二酸根离子、苹果酸根离子、马来酸根离子、琥珀酸根离子、富马酸根离子、酒石酸根离子、甲苯磺酸根离子、水杨酸根离子、乳酸根离子、萘磺酸根离子和乙酸根离子(例如，三氟乙酸根离子)。术语“药学上可接受的阴离子”是指适于形成药学上可接受的盐的阴离子。同样地，阳离子与取代苯化合物上带负电荷的基团(例如，羧酸酯基)之间也可以形成盐。适合的阳离子包括钠离子、钾离子、镁离子、钙离子和铵离子，如四甲基铵离子。取代苯化合物还包括那些含有季氮原子的盐。

[0754] 前体药物的例子包括酯和其他药学上可接受的衍生物，其在向受试者给药后能够提供有活性的取代苯化合物。

[0755] 另外，本发明的化合物，例如该化合物的盐，可以以水合或未水合的(无水物)的形式或结合其它溶剂分子作为溶剂化物存在。水合物的非限制性实例包括一水合物、二水合物等。溶剂化物的非限制性实例包括乙醇溶剂化物、丙酮溶剂化物等。

[0756] “溶剂化物”是指含有化学计量或非化学计量的量的溶剂的溶剂加成形式。一些化合物倾向于在晶体固体状态中捕获固定摩尔比的溶剂分子，从而形成溶剂化物。如果溶剂是水，所形成的溶剂化物是水合物；如果溶剂是醇，所形成的溶剂化物是醇化物。一个或多个水分子与一分子的物质的结合形成水合物，其中水保持其分子状态 H_2O。

[0757] 本文所使用的术语“类似物”指在结构上类似于另一个但组成略有不同(如用不同元素的原子替换一个原子或在存在特定的官能团的情况下，或用一个官能团替换另一个官能团)的化合物。因此，类似物是在功能和形态方面而不是在结构或来源方面与参照化合物类似或相当的化合物。

[0758] 本文所定义的术语“衍生物”是指有共同的母核结构并被本文所述的各种基团取代的化合物。例如，由式(I)表示的所有化合物都是取代苯化合物，并且具有式(I)作为共同的母核。

[0759] 术语“生物电子等排体”是指原子或原子团与大致相似的另一原子或原子团交换所产生的化合物。生物电子等排替换的目的是创造出具有与母体化合物相似的生物学特性的新化合物。生物电子等排替换可以基于物理化学或拓扑学。羧酸生物电子等排体的例子包括，但不限于酰基磺酰亚胺、四唑类、磺酸酯和膦酸酯。参阅如Patani and LaVoie,Chem. Rev.96,3147-3176,1996。

[0760] 另外，本发明旨在包括在本发明化合物中所出现的原子的所有同位素。同位素包括原子序数相同，但质量数不同的原子。作为一般的例子(但不限于此)，氢的同位素包括氚和氘，碳的同位素包括 C-13 与 C-14。

[0761] 2. 取代苯化合物的合成

[0762] 本发明提供本文所描述的任意结构式的化合物的合成方法。本发明还提供了本发明公开的多种化合物的、根据实施例中所示的反应方案的详细的合成方法。

[0763] 在整个描述中，其中组合物被描述为具有、包括或包含特定的成分时，可以预计所述组合物也基本由或由所述成分组成。同样地，当方法或过程被描述为具有、包括或包含特定的处理步骤时，所述过程或方法也基本上由或由所述处理步骤组成。此外，应当理解的是，只要本发明仍然是可实施的，那么执行某些操作的步骤或顺序不是十分重要的。此外，两个或以上的步骤或操作可以同时进行。

[0764] 本发明的合成方法可以容许很多种官能团，因此可以使用多种取代的起始原料。该方法通常在整个过程的结尾或接近结尾时提供所需的最终化合物，然而在某些情况下可能期望将该化合物进一步转换成其药学上可接受的盐、酯或前体药物。

[0765] 本发明的化合物可以以使用市售的起始原料、文献中已知的化合物或来自易制备的中间体，通过采用本领域技术人员已知的或者根据本文的技术启示对本领域技术人员变得显而易见的标准合成方法和步骤的多种方式来制备。制备有机分子以及官能团转换和操作的标准合成方法及步骤可以从相关的科技文献或该领域的标准教科书中得到。虽然并不限于任何一个或几个来源，作为参考引入本文的经典文本，如 Smith,M.B.,March,J.,March’s Advanced Organic Chemistry:Reactions,Mechanisms,and Structure,5th edition,John Wiley & Sons:New York,2001;Greene,T.W.,Wuts,P.G.M.,Protective Groups in Organic Synthesis,3rd edition,John Wiley & Sons:New York,1999;R.Larock,Comprehensive Organic Transformations,VCH

Publishers(1989);L.Fieser and M.Fieser,Fieser and Fieser's Reagents for Organic Synthesis,John Wiley and Sons(1994);以及L.Paquette,ed.,Encyclopedia of Reagents for Organic Synthesis,John Wiley and Sons(1995)是有用的,并且是本领域技术人员公知的有机合成的公认的参考教科书,它们通过引用结合于本文中。以下有关合成方法的描述旨在说明而不是限制用于制备本发明化合物的一般步骤。

[0766] 本发明的化合物可以很方便地通过本领域技术人员熟悉的各种方法来制备。具有本文所描述的任何一个结构式的本发明的化合物可以根据以下反应方案1-10所示的步骤,从市售的起始原料或可以用文献步骤制备的起始原料来制备。除非另有明确说明,否则在反应方案1-10中Z和R基团(例如R_1、R_2、R_3、R_4、R_6、R_7、R_8和R_{12})为如本文所描述的任何结构式中的定义。

[0767] 本领域的技术人员将会注意到,在本文所描述的反应顺序和合成反应方案中,某些步骤的顺序可以改变,如保护基的引入和去除。

[0768] 本领域的技术人员将认识到,某些基团在反应条件下可能需要用保护基来保护。保护基也可用来区分分子中相似的官能团。保护基名单以及如何引入和去除这些基团的方法可以参阅Greene,T.W.,Wuts,P.G.M.,Protective Groups in Organic Synthesis,3rd edition,John Wiley & Sons:New York,1999。

[0769] 优选的保护基包括,但不限于:

[0770] 对于羟基部分:TBS、苄基、四氢吡喃基,乙酰基;

[0771] 对于羧酸:苄基酯、甲酯、乙酯、烯丙基酯;

[0772] 对于胺:Cbz、BOC、DMB;

[0773] 对于二醇:乙酰基(2个)TBS(2个),或者(两个羟基)一起形成缩丙酮;

[0774] 对于硫醇:乙酰基;

[0775] 对于苯并咪唑类:SEM、苄基、PMB、DMB;

[0776] 对于醛:二烷基缩醛类,如二甲氧基乙缩醛或二乙基乙酰基。

[0777] 在本文中所描述的反应反应方案中可以产生多个立体异构体。当没有指明任何特定的立体异构体时,可以理解为是指可以从反应中产生的所有可能的立体异构体。本领域的技术人员将认识到,可以将该反应进行优化以优先得到一种异构体,或者可以设计出新的反应方案以产生单一的异构体。如果产生的是混合物,也可以使用如制备型薄层色谱、制备型HPLC、制备手性HPLC或制备型SFC技术来分离异构体。

[0778] 在整个说明书中使用了下列缩写词,其定义如下:

[0779]

AA	醋酸铵
ACN	乙腈
Ac	乙酰基
AcOH	醋酸
atm	大气压
aq.	水的
BID 或 b.i.d.	每日两次（一天两次）
tBuOK	叔丁醇钾
Bn	苄基
BOC	叔丁氧羰基
BOP	苯并三氮唑-1-基氧基三（二甲基氨基）磷鎓六氟磷酸盐
Cbz	苄氧羰基
$CDCl_3$	氘代氯仿
CH_2Cl_2	二氯甲烷
COMU	(1-氰基-2-乙氧基-2-氧代亚乙基氨基氧基)二甲基氨基-吗啉代-碳鎓六氟磷酸盐
d	天
DBU	1,8-二氮杂二环[5.4.0]十一碳-7-烯
DCE	1,2-二氯乙烷
DCM	二氯甲烷
DEAD	偶氮二甲酸二乙酯
DIAD	偶氮二甲酸二异丙酯
DiBAL-H	二异丁基氢化铝
DIPEA	N,N-二异丙基乙基胺（Hunig 碱）
DMA	二甲基乙酰胺
DMAP	N, N-二甲基-4-氨基吡啶
DMB	2,4–二甲氧基苄基

[0780]

DMF	N,N-二甲基甲酰胺
DMSO	二甲基亚砜
DPPA	叠氮磷酸二苯酯
EA 或 EtOAc	乙酸乙酯
EDC 或 EDCI	N-(3-二甲基氨基丙基)-N′-乙基碳化二酰胺
Et_2O	乙醚
ELS	蒸发光散射检测器
ESI-	电喷雾负离子模式
ESI+	电喷雾正离子模式
Et_3N or TEA	三乙胺
EtOH	乙醇
FA	甲酸
FC 或 FCC	快速色谱
h	小时
H_2O	水
HATU	O-(7-偶氮苯并三氮唑)-N,N,N',N'-四甲基脲六氟磷酸酯
HOAT	1-羟基-7-偶氮苯并三氮唑
HOBt	1-羟基苯并三氮唑
HO-Su	N-羟基丁二酰亚胺
HCl	氯化氢或盐酸
HPLC	高效液相色谱
K_2CO_3	碳酸钾
KHMDs	六甲基二硅基氨基钾
LC/MS 或 LC-MS	液相色谱和质谱联用
LDA	二异丙基氨基锂
LiHMDs	六甲基二硅基氨基锂
LG	离去基团
M	摩尔

[0781]

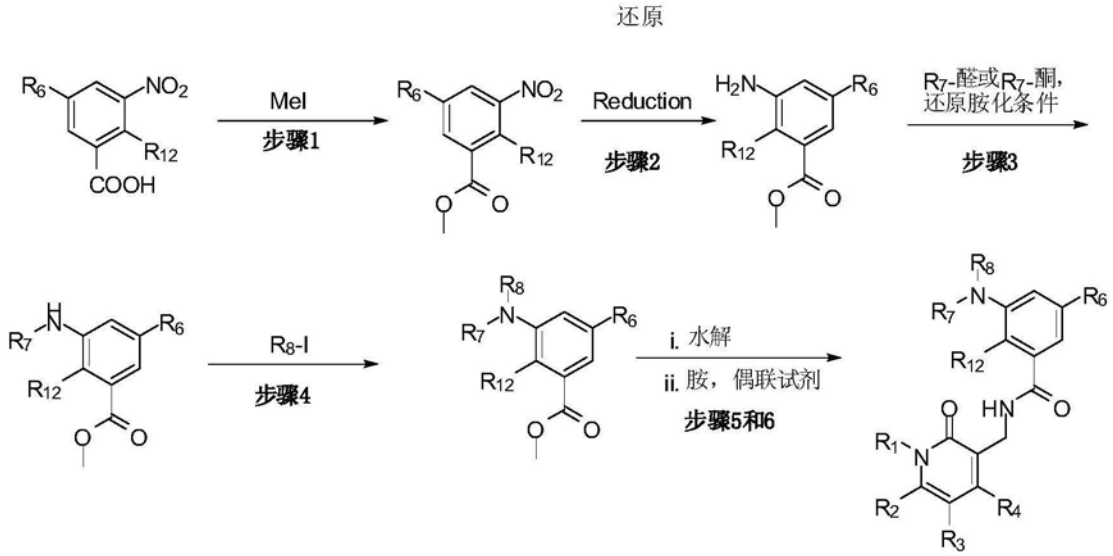
m/z	质荷比
m-CPBA	间氯过氧苯甲酸
MeCN	乙腈
MeOD	氘代甲醇
MeI	碘甲烷
MS3Å	3Å 分子筛
$MgSO_4$	硫酸镁
min	分钟
Ms	甲磺酰基
MsCl	甲磺酰氯
MsO	甲磺酸酯
MS	质谱
MWI	微波照射
Na_2CO_3	碳酸钠
Na_2SO_4	硫酸钠
$NaHCO_3$	碳酸氢钠
NaHMDs	六甲基二硅基氨基钠
NaOH	氢氧化钠
$NaHCO_3$	碳酸氢钠
Na_2SO_4	硫酸钠
NIS	N-碘代丁二酰亚胺
NMR	核磁共振
o/n or O/N	过夜
Pd/C	钯碳
$Pd(dppf)Cl_2.DCM$	[1,1'-双(二苯基膦)二茂铁]二氯化钯（II）与二氯甲烷的络合物
PPAA	1-丙烷磷酸环酐
$Pd(OH)_2$	氢氧化钯
PE	石油醚
PG	保护基团

[0782]

PMB	对甲氧基苄基
ppm	百万分之几
p.o.	经口服（口服给药）
prep HPLC	制备型高效液相色谱
prep TLC	制备型薄层色谱法
p-TsOH	对甲苯磺酸
PyBOP	（苯并三唑-1-基氧基）三吡咯烷基磷鎓六氟磷酸盐
QD 或 q.d.	每日一次(一天一次)
RBF	圆底烧瓶
RP-HPLC	反相高效液相色谱
Rt 或 RT	室温
SEM	(三甲基硅基)乙氧甲基
SEMCl	(三甲基硅基)乙氧基甲基氯
SFC	超临界色谱
SGC	硅胶层析
STAB	三乙酰氧基硼氢化钠
TBAF	四正丁基氟化铵
TBME	叔丁甲醚
TEA	三乙胺
TFA	三氟乙酸
TfO	三氟甲磺酸酯
THF	四氢呋喃
THP	四氢吡喃
TID 或 t.i.d	每日三次（一天三次)
TLC	薄层色谱
TMSCl	三甲基硅基氯
Ts	甲苯磺酰基
TsOH	甲苯磺酸
UV	紫外光

[0783] 反应方案 1

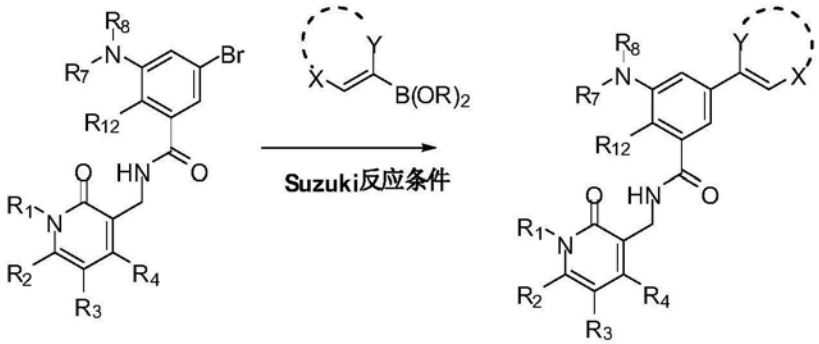
[0784]



[0785] 反应方案 1 显示了根据利用成熟化学设计的一般反应路线来合成苯类似物，其中 Z=-N(R_7)(R_8)。将取代硝基苯甲酸（其中有许多可以商购获得，或者可以通过硝化适当的取代苯甲酸或其他本领域技术人员已知的化学方法制备）在适当的温度（如 60℃）下，在适当的碱（如碳酸钠）存在下，在极性溶剂（如二甲基甲酰胺）中用碘甲烷处理，可以将其转化为它们的甲酯（步骤 1）。通过使用适当的还原剂（如铁），在酸（如氯化铵）的存在下，在适当的温度（如 80℃），在质子溶剂（如乙醇）中，硝基可以被还原为氨基（步骤 2）。在适当的溶剂（如甲醇）中，在适当的还原剂（如氰基硼氢化钠）和催化的酸（如乙酸）的存在下，可以通过对合适的 R_7- 酮或 R_7- 醛还原胺化来引入 R_7。各种 R_8 基团可以通过在适当的温度（如 80℃）下，在适当的极性溶剂（如乙腈）中，在温和碱（如碳酸铯）存在下，使用 R_8-LG 烷基化反应来引入，其中 LG 是离去基团（如碘）（步骤 4）。备选的是，R_8 基团还可以通过在适当的溶剂（如甲醇）中，在适当的还原剂（如氰基硼氢化钠）和催化的酸（如乙酸）存在下对相应的 R_8- 酮或 R_8- 醛的还原胺化来引入。酯基可以通过标准两步法转换为酰胺。所述酯在极性溶剂（如乙醇）中通过使用合适的碱（如氢氧化钠）可以水解成相应的酸（步骤 5）。将所述酸再进行标准酰胺偶联反应，于是将合适的胺随同在合适的溶剂（如 DMSO）中的合适的酰胺偶联试剂（如 PYBOP）一起加入，产生所需的酰胺（步骤 6）。

[0786] 反应方案 2

[0787]



[0788] 根据 R_6 取代基的性质，可以采用进一步的化学修饰将 R_6 取代基转换成另一种 R_6 取代基。所述修饰的代表性的例子可以包括氢化、保护基团去除之后再进行附加的酰胺偶联反应、钯催化偶联反应、还原胺化反应或烷基化反应。例如，如果 R_6 是溴，可以之后通过标

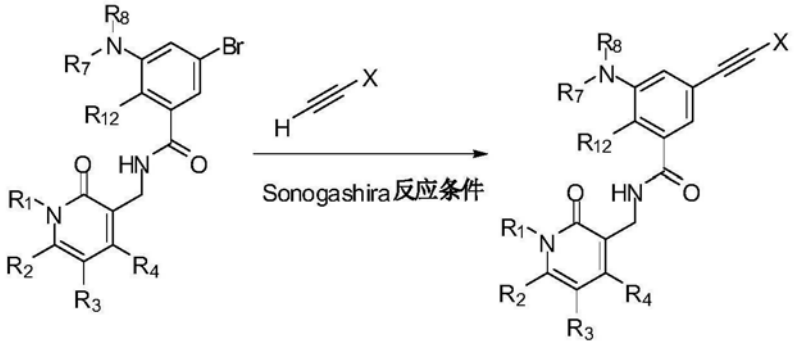
准过渡金属基方法引入另一种 R_6 取代基，该方法依赖于一个离去基团(如溴)作为连接点。

[0789] 在反应方案 2 所描述的一个这样的方法中，通过碳 - 碳键连接的非芳族 R_6 取代基可以通过化合物(其中 R_6 为 Br) 的 Suzuki 反应引入，其中所述化合物同合适的不饱和非芳族硼酸酯衍生物(例如烯烃类的硼酸酯衍生物，如乙烯 4,4,5,5- 四甲基 -2- 乙烯基 -1,3,2- 二氧杂环戊硼烷)在温和碱和钯催化剂存在下，在极性溶剂(如二氧六环 / 水)中在加热条件下发生 Suzuki 反应得到所需的新的 R_6 取代基。根据不同 R_6 取代基的性质，可以采用进一步的化学修饰将不饱和的 R_6 取代基转化为另一种 R_6 取代基。所述化学修饰的代表性的例子可以包括加氢、保护基团除去之后再进行附加的酰胺偶联反应、钯催化偶联反应、还原胺化反应或烷基化反应。例如，在不饱和非芳族 R_6 基被引入的情况中，通过氢化对 R_6 基的进一步修饰可以得到相应的饱和 R_6 基团(例如，将乙烯基转化为乙基)。在其中所引入的 R_6 基团已经保护氨基功能的情况下，进一步的修饰包括脱保护以得到胺，所得到的胺可在随后的步骤中通过如形成酰胺或还原胺化反应进行进一步修饰。

[0790] 在反应方案 3 所描述的另一个方法中，通过碳 - 碳键连接的非芳族 R_6 取代基可通过化合物(其中 R_6 为 Br)的 Sonogashira 反应来引入，并任选地之后对所引入的炔基进行进一步修饰。在 Sonogashira 反应中，在温和碱、铜催化剂和钯催化剂存在下，在有机溶剂(如甲苯)中加热条件下，化合物(其中 R_6 为 Br)与末端炔烃衍生物偶联。反应的结果是溴基被炔基取代。可对所得的其中溴取代基为炔基的化合物进行后续的合适的修饰，以生成另一种 R_6 取代基。所述化学修饰的代表性的例子可以包括加氢、保护基团除去之后再进行附加的酰胺偶联反应、钯催化偶联反应、还原胺化反应或烷基化反应。

[0791] 反应方案 3

[0792]



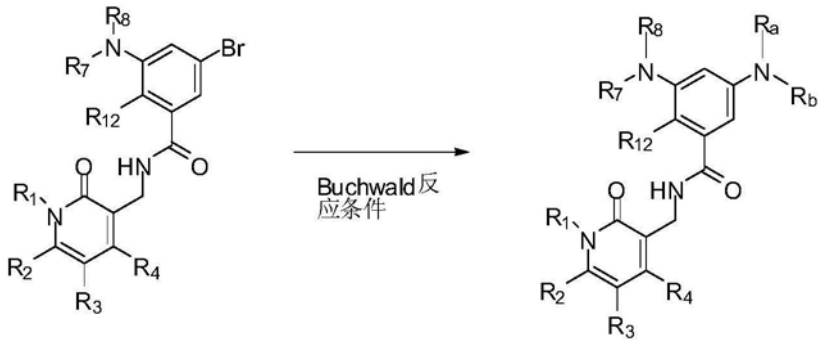
[0793] 另一种方法中，通过碳 - 碳键连接的非芳族 R_6 取代基可通过溴原子化合物(其中 R_6 为 Br) 的其它取代反应来制备，并任选地之后对所引入的 R_6 取代基进行进一步修饰。所述取代反应的例子包括使用锌试剂的偶联反应，如氰化反应和 Negishi 反应。在氰化反应中，化合物(其中 R_6 为 Br) 可同氰化锌在标准的钯催化剂催化的反应条件下得到化合物(其中 R_6=CN)。这种化合物中的氰基可以被进一步修饰为其他的 R_6 基团。这样的氰基修饰包括：i 还原为胺，所述胺随后可通过酰基化或烷基化转化为酰胺，ii 还原为醛，所述醛可经还原胺化反应得到相应的衍生物。在 Negishi 反应中，可用烷基碘(如 N- 叔丁氧羰基 -3- 碘代氮杂环丁烷)制备的烷基锌试剂在钯或镍催化剂存在下同化合物(其中 R_6 为 Br)进行偶联。在所得的产物中，所引入的 R_6 基团可以在后续步骤中通过 R_6 基团的进一步修饰(例如脱保护、形成酰胺或烷基化) 转换成另一种基团。

[0794] 具有 R_6 取代基的化合物(其中 R_6 取代基为通过氮 - 碳键与其连接的氨基) 可以通

过化合物(其中 R_6 为 Br)的 Buchwald 偶联反应来引入,随后 R_6 取代基可任选进行修饰,如反应方案 4 所述。在 Buchwald 反应中,化合物(其中 R_6 为 Br)在钯催化剂(例如 Pd(dba)2/BINAP)和碱(例如碳酸铯)的存在下,在有机溶剂(如甲苯)中在加热条件下,用伯胺或仲胺(如哌嗪 -1- 甲酸叔丁酯)处理。Buchwald 偶联产物可进行后续的适当修饰,以产生另一种 R_6 取代基。所述修饰的例子包括保护基团的去除、酰胺偶联反应、还原胺化反应或烷基化反应。

[0795] 反应方案 4

[0796]



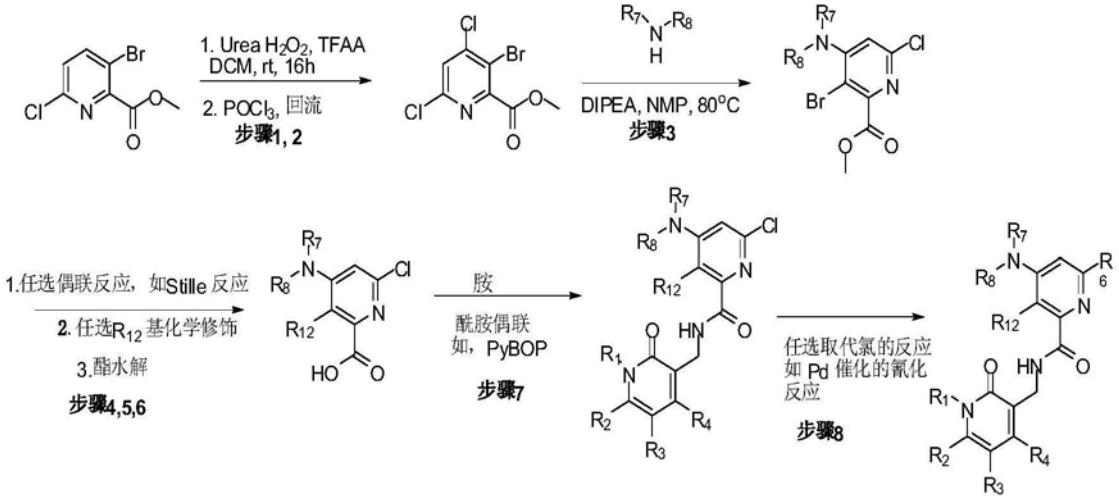
[0797] 具有 R_6 取代基的化合物(其中 R_6 取代基为通过硫 - 碳键与其连接的烷硫基)可通过化合物(其中 R_6 为 Br)与硫醇在钯催化剂和弱碱(如 DIPEA)存在下,在溶剂中加热条件下的偶联反应制备得到。所述偶联产物硫化物可进行后续的适当修饰,以得到另外的 R_6 取代基。所述修饰的例子包括硫的氧化反应得到亚砜和砜、保护基的去除、酰胺偶联反应、还原胺化反应或烷基化反应。

[0798] 在反应方案 1 的一般合成方法的修饰中,根据 R_7 取代基的性质,反应方案 1 中步骤 6 之后的进一步化学修饰可以用于将 R_7 取代基转换成另一种 R_7 取代基。例如,R_7 中包含的被保护的氨基基团可以进行脱保护反应(例如,Boc 基团裂解)以得到游离的氨基基团。可以对所得的游离的氨基基团进行还原胺化反应或烷基化反应,以得到取代的胺。

[0799] 反应方案 5 显示了吡啶酰胺化合物的一般合成方法。开始先将 3- 溴 -6- 氯吡啶甲酸甲酯氧化为 N- 氧化物,然后用三氯氧磷氯化所得 N- 氧化物,得到 3- 溴 -4,6- 二氯吡啶甲酸甲酯。所述 4- 氯基团可以选择性地被不同的单和二烷基胺取代,所述单和二烷基胺取代还可以包含功能的或被保护的官能团,所述被保护的官能团可在后期脱掉保护基。所述 3- 溴基团可被保留或任选通过合适的取代反应和进一步的官能团修饰而转换成另一种 R_{12} 的基团。所述反应包括钯催化剂催化的偶联反应。例如,3- 溴基团可通过 Stille 反应用四甲基锡转换为 R_{12}= 甲基的基团。酯水解后通过酰胺与适当的 3-(氨基甲基)- 吡啶 -2- 酮的偶联生成吡啶酰胺化合物(其中 R_6 是氯基团)。氯基团可任选被在最后一步或者步骤 6 酯水解之前的合适的取代反应转换为另一个 R_6 基团。所述取代反应的例子包括直接的或钯催化剂催化的氰化反应和氨化反应。类似化合物(其中 R_{12} 是氯)可以以类似方式从 3,4,6- 三氯吡啶 -2- 羧酸甲酯制备。

[0800] 反应方案 5

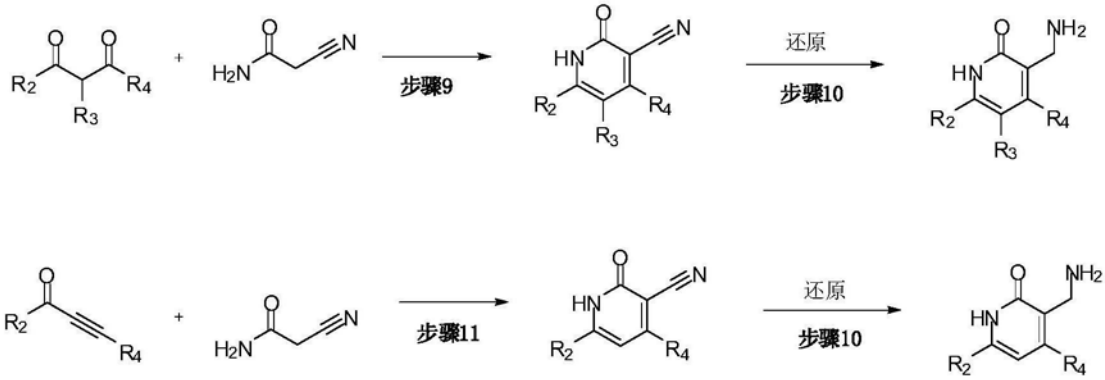
[0801]



[0802] 用于反应方案 1 中的酰胺偶联反应的 3-(氨基甲基)- 吡啶 -2(1H)- 酮中间体的一般合成方法如反应方案 6 所示。在一种方法中，二酮在适当的试剂(如哌啶乙酸酯) 存在下，在极性溶剂中(如乙醇) 与 2- 氰基乙酰胺缩合，生成氰基吡啶酮(步骤 9)。在另一种方法中，当 R_3 是氢时，合适的取代炔基酮在适当的试剂(如哌啶乙酸酯)存在下，在极性溶剂中(如乙醇) 与 2- 氰基乙酰胺缩合，生成氰基吡啶酮(步骤 11)。氰基可以在适当条件下被还原，例如，在催化剂雷尼镍存在下，在极性溶剂中(如铵在甲醇中) 被氢化还原生成胺(步骤 10)。

[0803] 反应方案 6

[0804]

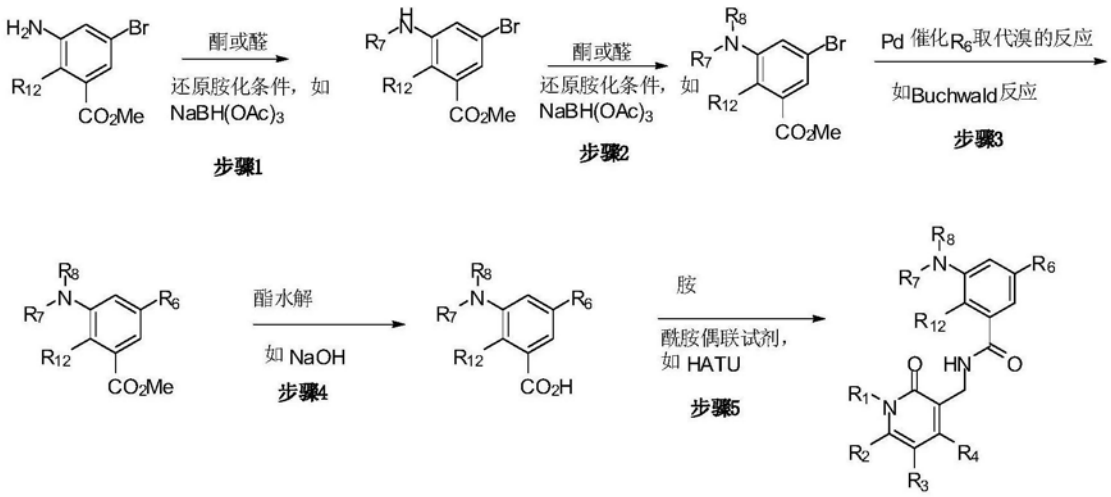


[0805] 另外，根据 R_2、R_3 或 R_4 基团的性质，可采用进一步的化学修饰将它们各自独立地转换为另外的取代基。所述化学修饰的代表性例子可以包括加氢、除去保护基后进行额外的酰胺偶联反应、钯催化偶联反应、还原胺化反应、烷基化反应。

[0806] 反应方案 7 提供了基于 2- 取代的(取代基为 R_{12} 基) 3- 氨基 -5- 溴 - 苯甲酸甲酯为起始原料的反应方案 1 的一般合成反应方案的另一个版本。这些起始原料又可以由市售获得或通过 2- 取代苯甲酸的硝化制备得到的 2- 取代的 3- 硝基 - 苯甲酸来制备。因此，用合适的试剂如 1,3- 二溴 -5,5- 二甲基 -2,4- 咪唑烷二酮来溴化 2- 取代的 -3- 硝基 - 苯甲酸，产生适当的 2- 取代的 3- 硝基 -5- 溴 - 苯甲酸。然后依次进行各种酯化反应和之后的硝基还原反应，以从 2- 取代的 3- 硝基 -5- 溴 - 苯甲酸制备 2- 取代的 -3- 氨基 -5- 溴 - 苯甲酸甲酯起始原料。

[0807] 反应方案 7

[0808]

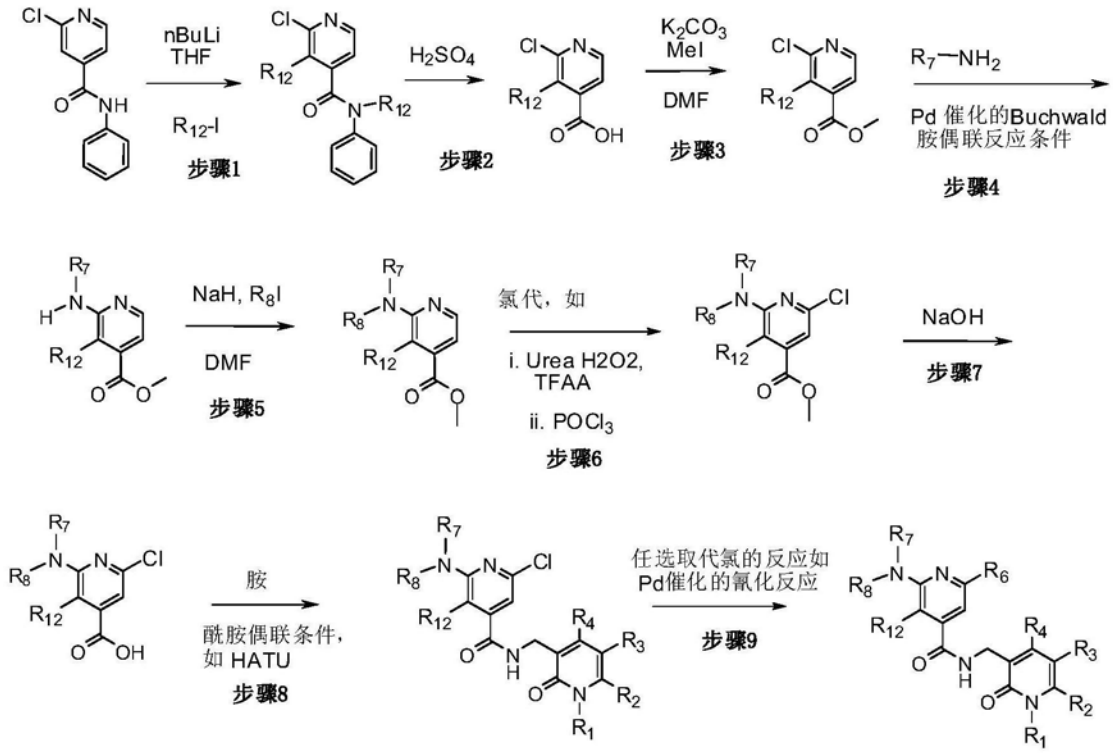


[0809] 如反应方案 7 所示，在步骤 1 中，R_7 基团可以通过用合适的 R_7- 酮或 R_7- 醛，在适当的还原剂（如氰基硼氢化钠）和催化的酸（如乙酸）的存在下，在合适的溶剂（如甲醇）中的还原胺化反应从 2- 取代 -3- 氨基 -5- 溴苯甲酸甲酯中引入。同样地，R_8 基团可以通过用合适的 R_8- 酮或 R_8- 醛，在适当的还原剂（如氰基硼氢化钠）和催化的酸（如乙酸）的存在下，在合适的溶剂（如甲醇）中的还原胺化反应而在步骤 2 中引入。或者，各种 R_8 基团可以通过使用 R_8-LG，在温和碱（如碳酸铯）的存在下，在适当的极性溶剂中（如乙腈），在适当的温度下（如 80℃）的烷基化反应来引入，其中 LG 是离去基团（如碘）。在步骤 3 中，通过钯催化的偶联反应可以引入除溴以外的 R_6 基团。所述 R_6 基团和方法的例子在上文中已描述。例如胺可以通过 Buchwald 反应引入，不饱和基团可以通过 Suzuki 或 Sonogashiri 反应引入。R_6 取代基可以进行随后的适当的修饰，以得到另一种 R_6 取代基。所述修饰的代表性例子可以包括加氢（如使不饱和基团饱和）、除去保护基后进行额外的酰胺偶联反应、钯催化偶联反应、还原胺化反应或烷基化反应。在步骤 4 中，酯基可在极性溶剂（如乙醇）中用适当的碱（如氢氧化钠）水解成相应的酸。在步骤 5 中，可以对所述酸进行标准的酰胺偶联反应，于是适当的 3-（氨基甲基）- 吡啶 -2- 酮在合适的溶剂（如 DMSO）中随同合适的酰胺偶合试剂（例如 PYBOP）一起被加入，得到所需的酰胺。根据 R_7 取代基的性质，反应方案 4 中的步骤 5 之后的进一步化学修饰可以用于将 R_7 取代基转换成另一种 R_7 取代基。例如，R_7 中包含的被保护的氨基可以通过脱保护反应（例如，Boc 基团裂解）得到游离的氨基基团。可以对所得的游离的氨基基团进行还原胺化反应或烷基化反应，以得到取代的胺。

[0810] 以下的反应方案 8 显示了 2- 单烷氨基和 2- 双烷氨基 -3,6- 二取代 - 异烟酰胺的一般合成方法，其中 3- 取代基对应于 R_{12}，而 6- 取代基对应于 R_6。在步骤 1 中，3- 取代基可以通过 Epsztain J.et al.Tetrahedron,1991,v.47,1697-16708 中所描述的方法引入，所述方法将 2- 氯异烟酰苯胺用正丁基锂金属化，然后再用烷基碘（如甲基碘）或醛或其他亲电子基团将其捕获。

[0811] 反应方案 8

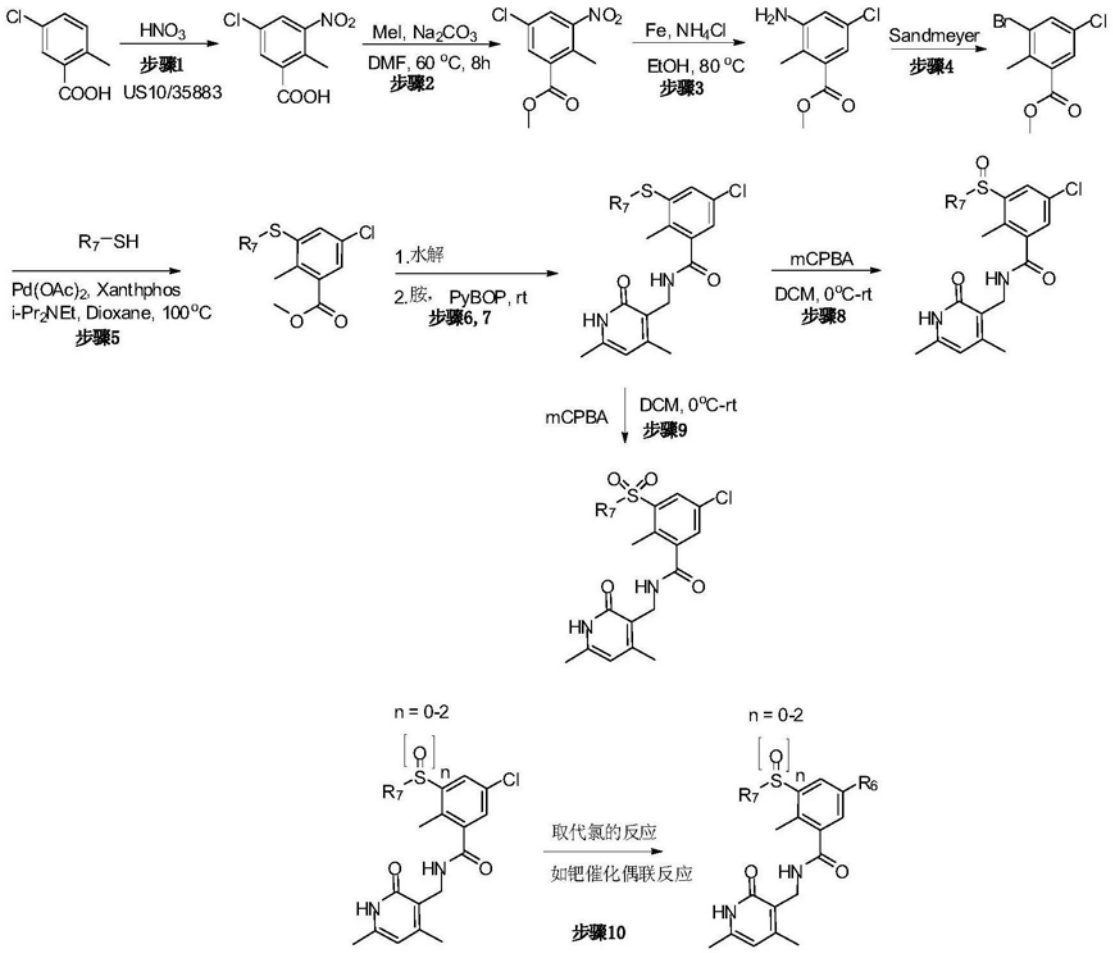
[0812]



[0813] 上述捕集试剂产生带有官能团的取代基时，所述官能团可以被屏蔽或转换为与后续化学步骤相兼容的另一个官能团。在步骤 2 中，酰苯胺在标准的酸性条件下水解，然后在标准条件下合成甲酯，例如所示的在碘甲烷和碱存在条件下生成了相应的 2- 氯 -3- 取代异烟酸甲酯。在步骤 4 中，通过 R_7NH2 单烷基胺与 2- 氯 -3- 取代的异烟酸甲酯的 Buchwald 偶联反应可以引入烷基氨基基团。不同的 2- 氯吡啶体系中的该反应在化学文献中已有先例。在针对二烷基氨基化合物的一个可选步骤 5 中，R_8 基团可以通过用 R_8- 酮或 R_8- 醛，在适当的还原剂（如氰基硼氢化钠）和催化的酸（如乙酸）的存在下，在合适的溶剂（如甲醇）中的还原胺化反应来引入。或者，各种 R_8 基团可以通过使用 R_8-LG，在温和碱（如碳酸铯）的存在下，在适当的极性溶剂中（如乙腈），在适当的温度下（如 80℃）的烷基化反应引入，其中 LG 是离去基团（如碘）。在步骤 6 中，氧化成 N- 氧化物然后用三氯氧磷氯化，可以得到 6- 氯 -2- 单或二烷基氨基 -3- 取代的异烟酸甲酯。在步骤 7 中，酯基可在极性溶剂中（如乙醇）用适当的碱（如氢氧化钠）水解成相应的酸。在步骤 8 中，可以对所述酸进行标准的酰胺偶联反应，于是将适当的取代的 3-（氨基甲基）- 吡啶 -2- 酮随同在合适的溶剂中（如 DMSO）的合适的酰胺偶合试剂 (PYBOP) 一起加入，反应得到所需的酰胺。在步骤 9 中，氯基团可任选被在最后一步或者步骤 6 酯水解之前的合适的取代反应转换为另一个 R_6 基团。所述取代反应的例子包括直接的或钯催化剂催化的氰化反应和氨化反应。可对 R_6 取代基进行后续的适当的修饰，以生成另一种 R_6 取代基。所述修饰的代表性例子可以包括加氢（如使不饱和基团饱和）、除去保护基后进行额外的酰胺偶联反应、还原胺化反应或烷基化反应。根据不同的 R_7 取代基的性质，可采用进一步的修饰将 R_7 取代基转换成另一种的 R_7 取代基。例如，R_7 中包含的被保护的氨基可以通过脱保护（例如，Boc 基团裂解）得到游离的氨基基团。所得的游离的氨基基团可以进行还原胺化反应或烷基化反应，以得到取代的胺。

[0814] 反应方案 9

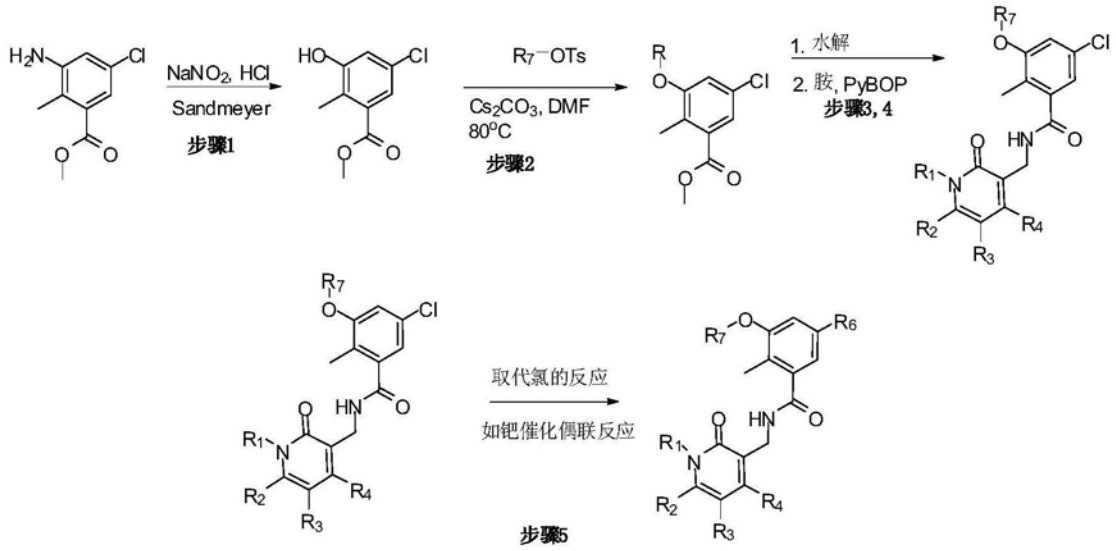
[0815]



[0816] 反应方案 9 描绘了根据利用成熟的化学设计的一般反应路线合成苯类似物的方法，其中 Z 为硫、亚砜或砜基团。起始于取代的苯甲酸(如 5- 氯 -2- 甲基苯甲酸)，使用标准条件硝化，如用浓硫酸和浓硝酸处理，可以得到硝基类似物。所得到的酸可与烷基化剂(如甲基碘)在碱(如碳酸钠)的存在下，在极性溶剂中(如 DMF)进行酯化反应。通过使用例如铁和氯化铵，在质子溶剂(如乙醇)中，加热至例如 80℃的条件下，可以将硝基还原为氨基。得到的苯胺可用 $CuBr_2$ 和亚硝酸叔丁基酯在溶剂(如乙腈)中处理而进行 Sandmeyer 反应转换成溴代物。使用钯源(例如醋酸钯)与配体(如 Xanthphos)，在碱(如 N,N- 二异丙基乙胺)存在下，在 1,4- 二氧六环中，任选加热至例如 100℃的温度下，可以实现硫醇与溴代物的钯催化偶联。使用水溶碱(如 NaOH 水溶液)可以将所述酯水解。使用标准的氨基和酸偶联的条件(如在 DMSO 中的 PyBOP)，可以将由此产生的酸于适当的取代的 3-(氨基甲基)- 吡啶 -2- 酮(如反应方案 9 中所描述的 3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮) 进行偶联。通过使用在溶剂(如二氯甲烷)中的适当当量的氧化剂(如 m-CPBA)，可以将得到的硫醚氧化为相应的亚砜或砜。R_6 氯基团可在一个额外的步骤 10 中或在步骤 5 之后或在酰胺偶联之前被替换为另一种 R_6 基团。可替换的 R_6 基团的例子包括可以通过使用钯偶联如 Buchwald 反应而并入以得到胺基团(如吗啉基) 的取代基。R_6 取代基可随后进行适当的修饰，以生成另一种 R_6 取代基。所述修饰的代表性例子包括除去保护基后进行额外的酰胺偶联反应、还原胺化反应或烷基化反应。

[0817] 反应方案 10

[0818]



[0819] 反应方案 10 描述了根据利用成熟的化学的一般反应路线合成改性的苯类似物的方法，其中 Z 为醚基。起始于取代的苯胺(如 3- 氨基 -5- 氯 -2- 甲基苯甲酸甲酯)，用 Sandmeyer 反应条件，如用含水酸(如 50％硫酸水溶液)中的 $NaNO_2$ 水溶液处理，可以将该苯胺转化成酚。使用烷基化剂(如 4- 甲基苯磺酸四氢 -2H- 吡喃 -4- 基酯)在适当的碱（如碳酸铯）的存在下，在极性溶剂（如 DMF）中，并任选加热至例如 80℃的温度，可将所得苯酚化合物进行烷基化。用水溶碱(如 NaOH 水溶液）可以将所述酯水解。使用标准的氨基和酸偶联的条件(如在 DMSO 中的 PyBOP)，可以将由此产生的酸与适当的取代的 3-(氨基甲基)- 吡啶 -2- 酮进行偶联。R_6 氯基团在步骤 5 之后或之前的额外的酰胺偶联反应中被替换为另一种 R_6 基团。可替换的 R_6 基团的例子包括可以通过使用钯偶联如 Buchwald 反应而并入，以得到胺基团(如吗啉基）的取代基。R_6 取代基可随后进行适当的修饰以生成另一种 R_6 取代基。所述修饰的代表性例子可以包括除去保护基后进行额外的酰胺偶联反应、还原胺化反应或烷基化反应。

[0820] 本领域技术人员将认识到，在上述的反应方案中，其中许多步骤的顺序是可以互换的。

[0821] 3. 治疗方法

[0822] 本发明的化合物可抑制 EZH2 或其突变体的组蛋白甲基转移酶活性，因此，本发明还提供了治疗症状和疾病的方法，所述方法可以通过调节组蛋白或其他蛋白质的甲基化状态来影响治疗过程，其中所述甲基化状态至少部分被 EZH2 的活性所介导。在本发明的一个方面，本文所公开的某些化合物是用于治疗或预防某些症状和疾病的候选药物。组蛋白甲基化状态的调节又可以影响被甲基化激活的靶基因和 / 或被甲基化抑制的靶基因的表达水平。所述方法包括向需要这种治疗的受试者给予治疗有效剂量的本发明的化合物或其药学上可接受的盐、前体药物、代谢物、多晶型物、溶剂化物或立体异构体。

[0823] EZH2 介导的蛋白质甲基化参与的疾病可以是癌症或癌前状态。本发明进一步提供了本发明的化合物或其药学上可接受的盐、前体药物、代谢物、多晶型物或溶剂化物在治疗癌症或癌前期中的用途，其中可以通过调节组蛋白或其他蛋白质的甲基化状态来影响治疗过程，或在用于治疗这类癌症或癌前期的有用的药物的制备中的用途。可治疗的示例性癌症包括淋巴瘤，包括非霍奇金淋巴瘤、滤泡性淋巴瘤（FL）和弥漫性大 B 细胞淋巴瘤

(DLBCL);黑色素瘤;白血病,包括慢性粒细胞白血病(CML)。示例性的癌前病症包括骨髓增生异常综合征(MDS,以前称为白血病前期)。

[0824] 本发明还提供了免受 EZH2 介导的蛋白质甲基化参与的疾病的方法,其中向需要治疗的受试者给予治疗有效量的本发明的化合物或其药学上可接受的盐、前药、代谢物、多晶型物或溶剂化物。所述疾病可以是癌症,如其中 EZH2 介导的蛋白质甲基化起作用的癌症。本发明还提供了本发明化合物或其药学上可接受的盐、前体药物、代谢物、多晶型物、溶剂化物或立体异构体的用于制备预防细胞增殖性障碍的有用药物的用途,所述细胞增殖性障碍至少部分地与 EZH2 介导的蛋白质甲基化相关。

[0825] 本发明化合物可以或可能用来调节蛋白(如组蛋白)的甲基化,例如调节组蛋白甲基转移酶或组蛋白去甲基化酶的活性。至少部分本发明化合物可用于在体内或体外调节蛋白的甲基化。已有报道称,组蛋白甲基化参与癌症中的某些基因的异常表达和非神经元细胞中的神经元基因的基因沉默。至少部分本文所述的化合物是适合治疗这些疾病的候选药物,即将甲基化降低或恢复到对应正常细胞的大致水平。

[0826] 作为甲基化调节器的化合物可以或可能用于调节细胞增殖。例如,在某些情况下,使用减少甲基化的药物可减少细胞的过度增殖,而使用增加甲基化的药物可能会激发不足的细胞增殖。因此,可被本发明的化合物治疗的疾病可包括过度增殖性疾病,如良性细胞生长和恶性细胞生长。

[0827] 本文使用的“需要治疗的受试者”是指患 EZH2 介导的蛋白甲基化参与的疾病的受试者,或相对于大多数人具有患此疾病的高风险的受试者。需要治疗的受试者可以有一个癌前状态。优选地,需要治疗的受试者有癌症。所述“受试者”包括哺乳动物。所述哺乳动物可以是如人类或适当的非人类的哺乳动物,如灵长类动物、小鼠、大鼠、狗、猫、牛、马、山羊、骆驼、羊或猪。所述受试者也可以是鸟或家禽。在一个实施例中,所述哺乳动物是人。

[0828] 本文使用的术语“细胞增殖性障碍”指的是细胞的不受控制的或异常的生长,或两者兼而有之的状况,所述状况会导致可能是或可能不是癌性的有害的症状或疾病。可使用本发明的化合物来治疗的示例性的细胞增殖性障碍包括各种细胞分裂不受控制的状况。示例性的细胞增殖性障碍包括,但不限于肿瘤、良性肿瘤、恶性肿瘤、癌前状态、原位肿瘤、包膜肿瘤、转移瘤、液体瘤、实体瘤、免疫性肿瘤、血液肿瘤、癌症、癌、白血病、淋巴瘤、肉瘤和迅速分裂的细胞。本文中使用的术语“迅速分裂的细胞”被定义为分裂速率超过或大于同一组织中相邻的或并列的细胞的所期望的或观察到的分裂速率的任何细胞。细胞增殖性障碍包括初癌或癌前状态。细胞增殖性障碍包括癌症。本文提供的方法和用途可以或可能用于治疗或缓解癌症的症状,或用于识别用于上述目的的合适的候选人。术语“癌症”包括实体瘤以及血液肿瘤和/或恶性肿瘤。“初癌细胞”或“癌前细胞”是一种表现出作为初癌或癌前状态的细胞增殖障碍的细胞。“癌症细胞”或“癌细胞”是表现出作为癌症的增殖性障碍的细胞。可以使用任何可再现的测量手段识别癌细胞或癌前期细胞。通过组织样本(如活检样本)的组织学分类或分级可以识别癌细胞或癌前期细胞。通过使用合适的分子标记物可以识别癌细胞或癌前期细胞。

[0829] 可使用一个或多个本发明的化合物来治疗的示例性非癌性状况或病症包括,但不限于类风湿关节炎、炎症、自身免疫性疾病、淋巴组织增生、肢端肥大症、类风湿性脊椎炎、骨关节炎、痛风及其他关节炎、败血症、败血性休克、内毒素休克、革兰氏阴性败血症、中毒

性休克综合征、哮喘、成人呼吸窘迫综合征、慢性阻塞性肺病、慢性肺部炎症、炎症性肠道疾病、克罗恩病、牛皮癣、湿疹、溃疡性结肠炎、胰腺纤维化、肝纤维化、急性和慢性肾脏疾病、肠易激综合征、麻痹性痴呆(pyresis)、再狭窄、脑型疟疾、中风和缺血性损伤、神经损伤、阿尔茨海默氏病、亨廷顿氏病、帕金森氏病、急性和慢性疼痛、过敏性鼻炎、过敏性结膜炎、慢性心脏衰竭、急性冠脉综合征、恶病质、疟疾、麻风病、利什曼病、莱姆病、赖特综合征、急性滑膜炎、肌肉退化、滑囊炎、肌腱炎、腱鞘炎、突出或破裂或脱出的椎间盘盘综合征、血栓症、再狭窄、矽肺、肺肉瘤病、骨吸收性疾病(如骨质疏松症)、移植物抗宿主反应、多发性硬化症、红斑狼疮、纤维肌痛症、艾滋病和其它病毒性疾病(如带状疱疹、单纯疱疹病毒 I 或 II、流感病毒和巨细胞病毒)、糖尿病。

[0830] 可使用一个或多个本发明的化合物来治疗的示例性癌症包括,但不限于肾上腺皮质癌、AIDS 相关的癌症、AIDS 相关的淋巴瘤、肛门癌、肛门直肠癌、肛管癌、阑尾癌、儿童小脑星形细胞瘤、儿童大脑星形细胞瘤、基底细胞癌、皮肤癌(非黑色素瘤)、胆道癌、肝外胆管癌、肝内胆管癌、泌尿膀胱癌、骨和关节恶性肿瘤、骨肉瘤恶性纤维组织细胞瘤、脑癌、脑肿瘤、脑干胶质瘤、小脑星形细胞瘤、大脑星形细胞瘤 / 恶性神经胶质瘤、室管膜瘤、髓母细胞瘤、幕上原始神经外胚层肿瘤、视觉通路和下丘脑胶质瘤、乳腺癌、支气管腺瘤 / 类癌瘤、类癌肿瘤、胃肠道癌症,神经系统癌症、神经系统淋巴瘤、中枢神经系统癌症、中枢神经系统淋巴瘤、子宫颈癌、儿童期癌症、慢性淋巴细胞白血病、慢性骨髓性白血病、慢性骨髓及外骨髓增殖性疾病、结肠癌、大肠癌、皮肤 T 细胞淋巴瘤、淋巴肿瘤、蕈样真菌病、塞泽里综合症、子宫内膜癌、食道癌、颅外生殖细胞瘤、性腺外生殖细胞肿瘤、肝外胆管癌、眼肿瘤、眼内黑色素瘤、视网膜母细胞瘤、胆囊癌、胃(胃部)癌、胃肠道类癌瘤、胃肠道间质瘤(GIST)、生殖细胞肿瘤、卵巢生殖细胞肿瘤、妊娠滋养细胞肿瘤神经胶质瘤、头颈部癌、肝细胞(肝脏)癌、霍奇金淋巴瘤、下咽癌、眼内黑色素瘤、眼癌、胰岛细胞瘤(内分泌胰脏)、卡波氏肉瘤、肾癌(kidney cancer)、肾癌(renal cancer)、喉癌、急性淋巴细胞白血病、急性髓细胞性白血病、慢性淋巴细胞白血病、慢性骨髓性白血病、毛细胞白血病、唇癌、口腔癌、肝癌、肺癌、非小细胞肺癌、小细胞肺癌、艾滋病相关的淋巴瘤、非霍奇金淋巴瘤、原发性中枢神经系统淋巴瘤、Waldenstram 巨球蛋白血症、髓母细胞瘤、黑色素瘤、眼内(眼睛)黑色素瘤、默克尔细胞癌、恶性间皮瘤、间皮瘤、转移性鳞状颈部癌、口腔癌、舌癌、多发性内分泌腺瘤综合征、蕈样真菌病、骨髓增生异常综合征、骨髓增生异常 / 骨髓及外骨髓增殖性疾病、慢性骨髓性白血病、急性髓细胞性白血病、多发性骨髓瘤、慢性骨髓及外骨髓增殖性疾病,鼻咽癌、神经母细胞瘤、口腔癌(oral cancer)、口腔癌(oral cavity cancer)、口咽癌、卵巢癌、卵巢上皮癌、卵巢低恶性潜在的肿瘤、胰腺癌、胰岛细胞胰腺癌、鼻窦和鼻腔癌、甲状旁腺癌、阴茎癌、咽癌、嗜铬细胞瘤、松果体母细胞瘤和幕上原始神经外胚层肿瘤、垂体瘤、浆细胞肿瘤 / 多发性骨髓瘤、胸膜肺胚细胞瘤、前列腺癌、直肠癌、肾盂和输尿管移行细胞癌、视网膜母细胞瘤、横纹肌肉瘤、唾液腺肿瘤、尤文氏肉瘤家族、卡波济氏肉瘤、软组织肉瘤、子宫癌、子宫肉瘤、皮肤癌(非黑色素瘤)、皮肤癌(黑色素瘤)、默克尔细胞皮肤癌、小肠肿瘤、软组织肉瘤、鳞状细胞癌、胃(胃部的)癌、幕上原始神经外胚层肿瘤、睾丸癌、咽喉癌、胸腺瘤、胸腺瘤和胸腺癌、甲状腺癌、肾盂和输尿管等泌尿器官移行细胞癌、妊娠滋养层细胞肿瘤、尿道癌、子宫内膜癌、子宫肉瘤、子宫体癌、阴道癌、外阴癌、肾母细胞瘤。

[0831] “血液系统的细胞增殖障碍”是一种涉及血液系统细胞的细胞增殖障碍。血液系

统的细胞增殖障碍包括淋巴瘤、白血病、髓系肿瘤、肥大细胞瘤、骨髓增生异常、良性单克隆丙种球蛋白病、淋巴瘤样肉芽肿、淋巴瘤样丘疹病、红细胞增多症、慢性粒细胞白血病、病因不明的髓样化生、原发性血小板增多症。血液系统细胞增殖障碍包括血液系统细胞的增生、异型增生和化生。一方面，本发明的组合物可用于治疗癌症，所述癌症包括本发明所述血液癌症或血液细胞增殖性障碍，或用于识别用于上述目的的合适的候选人。本发明所述血液癌症包括多发性骨髓瘤、淋巴瘤（包括霍奇金淋巴瘤、非霍奇金淋巴瘤、儿童淋巴瘤、淋巴细胞和皮肤原发的淋巴瘤），白血病（包括儿童白血病、多毛细胞白血病、急性淋巴细胞白血病、急性髓细胞白血病、慢性淋巴细胞白血病、慢性粒细胞性白血病、慢性粒细胞性白血病、肥大细胞性白血病），髓系肿瘤和肥大细胞肿瘤。

[0832] “肺细胞增殖性障碍”是一种涉及肺细胞的细胞增殖性疾病。肺细胞增殖性障碍可以包括影响肺细胞的所有形式的细胞增殖性疾病。肺细胞增殖性障碍可包括肺癌、肺部初癌或癌前状态、肺部良性肿瘤或病变、肺部恶性肿瘤或病变，以及肺部以外的身体的其它组织和器官中的转移病灶。一方面，本发明的组合物可用于治疗肺癌或肺细胞增殖性障碍，或用于识别用于上述目的合适的候选者。肺癌可以包括恶性肺肿瘤、原位癌、典型类癌瘤和非典型类癌瘤。肺癌可以包括小细胞肺癌 (SCLC)、非小细胞肺癌 (NSCLC)、鳞状细胞癌、腺癌、小细胞癌、大细胞癌、腺细胞癌、间皮瘤。肺癌可以包括“疤痕癌”、细支气管肺泡癌、巨细胞癌、梭形细胞癌、大细胞神经内分泌癌。肺癌可以包括具有组织学和超微结构异质性（例如，混合细胞型）的肺部肿瘤。

[0833] 肺细胞增殖性障碍可以包括影响肺细胞的所有形式的细胞增殖性障碍。肺细胞增生性障碍包括肺癌、肺癌前状态。肺细胞增殖性障碍可以包括肺的增生、化生、异型增生。肺细胞增生性障碍可以包括石棉诱导的增生、鳞状上皮化生、良性反应性间皮化生。肺细胞增殖性障碍可以包括复层鳞状上皮替换柱状上皮、粘膜异型增生。暴露于吸入性有害环境物质（如香烟烟雾和石棉）的个体会增加患肺细胞增生性障碍的风险。会使个体更易患肺细胞增殖性障碍的在先的肺部疾病包括坏死性肺疾病、硬皮病、类风湿疾病、结节病、间质性肺炎、肺结核、反复性肺炎、特发性肺纤维化、肉芽肿、石棉沉着病、纤维化性肺泡炎、霍奇金病。

[0834] “结肠细胞增殖性障碍”是一种涉及结肠细胞的细胞增殖性疾病。一方面，本发明的组合物可用于治疗结肠癌或结肠细胞增殖性障碍，或用于识别用于这样的目的合适的候选人。结肠癌可以包括各种形式的结肠癌。结肠癌可以包括偶发性和遗传性结肠癌。结肠癌可以包括恶性结肠肿瘤、原位癌、典型类癌肿瘤和不典型类癌肿瘤。结肠癌可以包括腺癌、鳞状细胞癌、腺细胞癌。结肠癌可以与遗传性综合征相关，所述遗传性综合征包括遗传性非息肉病性结肠直肠癌、家族性腺瘤性息肉病、加德纳氏综合征、黑斑息肉综合征、Turcot 综合征（又名“胶质瘤息肉病综合征”）、幼年性息肉病。结肠癌可由遗传性综合征引起，所述遗传性综合征包括遗传性非息肉病性结肠直肠癌、家族性腺瘤性息肉病、加德纳氏综合征、黑斑息肉综合征、Turcot 综合征、幼年性息肉病。

[0835] 结肠细胞增殖性障碍可以包括影响结肠细胞的所有形式的细胞增殖性障碍。结肠细胞增殖性障碍可以包括结肠癌、结肠癌前状态、结肠腺瘤性息肉病、结肠异时性病变。结肠细胞增殖性障碍可以包括腺瘤。结肠细胞增殖性障碍可以用结肠细胞的增生、化生和异型增生表征。可使个体更易患结肠细胞增生性障碍的在先所患的结肠疾病可以包括在先的

结肠癌。会使个体更易患结肠细胞增生性的当前疾病障碍可以包括克罗恩病和溃疡性结肠炎。结肠细胞增殖性障碍与基因突变相关，所述基因突变包括 p53、ras、FAP 和 DCC 的基因突变。由于存在选自包括 p53、ras、FAP 和 DCC 的基因突变，个体患结肠细胞增殖性障碍的风险升高。

[0836] “胰腺细胞增殖性障碍”是一种涉及胰腺细胞的细胞增殖性障碍。胰腺细胞增殖性障碍可以包括影响胰腺细胞的所有形式的细胞增殖性障碍。胰腺细胞增殖性障碍包括胰腺癌、胰腺癌初癌或癌前状态、胰腺增生、胰腺的异型增生、胰腺良性肿瘤或病变、胰腺恶性肿瘤或病变，以及在胰腺以外的身体的其它组织和器官中的转移病灶。胰腺癌包括所有形式的胰腺癌。胰腺癌可以包括导管腺癌、腺鳞癌、多形性巨细胞癌、粘液腺癌、破骨细胞样巨细胞癌、粘液性囊腺癌、腺泡细胞癌、未分类的大细胞癌、小细胞癌、胰母细胞瘤、乳头状肿瘤、粘液性囊腺瘤、乳头状囊性肿瘤、浆液性囊腺瘤。胰腺癌还包括具有组织学和超微结构的异质性(例如，混合细胞型)的胰腺肿瘤。

[0837] “前列腺细胞增殖性障碍”是一种涉及前列腺细胞的细胞增殖性障碍。前列腺的细胞增殖性障碍可以包括影响前列腺细胞的所有形式的细胞增殖性障碍。前列腺细胞增殖性障碍包括前列腺初癌或癌前状态、前列腺良性肿瘤或病变、前列腺恶性肿瘤或病变，以及在前列腺以外的身体的其它组织和器官中的转移病灶。前列腺细胞增殖性障碍可以包括前列腺的增生、化生和异型增生。

[0838] “皮肤细胞增殖性障碍”是一种涉及皮肤细胞的细胞增殖性障碍。皮肤细胞增殖性障碍可以包括影响皮肤细胞的所有形式的细胞增殖性障碍。皮肤细胞增殖性障碍可以包括皮肤初癌或癌前状态、皮肤良性肿瘤或病变、黑色素瘤、皮肤的恶性黑色素瘤或其他恶性肿瘤或病变，以及在皮肤以外的身体的其它组织和器官中的转移病灶。皮肤细胞增殖性障碍可以包括皮肤的增生、化生和异型增生。

[0839] “卵巢细胞增殖性障碍”是一种涉及卵巢细胞的细胞增殖性障碍。卵巢细胞增殖性障碍可以包括影响卵巢细胞的所有形式的细胞增殖性障碍。卵巢细胞增殖性障碍可以包括卵巢初癌或癌前状态、卵巢良性肿瘤或病变、卵巢癌、卵巢恶性肿瘤或病变，以及在卵巢以外的身体的其它组织和器官中的转移病灶。卵巢细胞增殖性障碍可以包括卵巢的增生、化生和异型增生。

[0840] “乳房细胞增殖性障碍”是一种涉及乳房细胞的细胞增殖性障碍。乳房细胞增殖性障碍可以包括影响乳腺细胞的所有形式的细胞增殖性障碍。乳房细胞增殖性障碍可以包括乳腺癌、乳腺初癌或癌前状态、乳房良性肿瘤或病变、乳腺恶性增生或病变，以及在乳房以外的身体的其它组织和器官中的转移病灶。乳腺细胞增殖性障碍可以包括乳腺的增生、化生和异型增生。

[0841] 乳房细胞增殖性障碍可以是乳房的一种癌前状态。本发明的组合物可用于治疗的乳房的癌前状态。乳房的癌前状态可以包括非典型乳腺增生、导管原位癌(DCIS)、导管内癌、小叶原位癌(LCIS)、小叶瘤、乳房的 0 阶段或 0 级增长或病变(例如 0 阶段或 0 级别乳腺癌，或原位癌)。乳房的癌前状态可根据被美国癌症联合委员会(AJCC)认可的 TNM 分期表来分期，其中原发肿瘤(T)被指定为 T0 或 Tis 期；区域淋巴结(N)被指定为 N0 期；以及远处转移(M)被指定为 M0 期。

[0842] 乳房细胞增殖性障碍可以是乳腺癌。一方面，本发明的组合物可用于治疗乳腺癌，

或用于识别用于这样的目的的合适的候选人。乳腺癌可包括各种形式的乳腺癌。乳腺癌包括各种形式的乳房癌症。乳腺癌可以包括原发性乳腺上皮癌。乳腺癌可以包括其中乳房被其他肿瘤如淋巴瘤、肉瘤或黑色素牵涉的乳房癌。乳腺癌可以包括乳房的癌、乳房导管癌、乳房小叶癌，乳房未分化癌、乳腺叶状囊肉瘤、乳房血管肉瘤和原发性乳腺淋巴瘤癌。乳腺癌可以包括 I 期、II 期、IIIA 期、IIIB 期、IIIC 期和 IV 期乳腺癌。乳房导管癌可以包括侵入性癌、带有主要的导管内成分的原位侵入性导管癌、炎性乳腺癌，以及具有选自粉刺、粘液(胶体)、骨髓、淋巴细胞浸润骨髓、乳头状、硬癌、管状的组织学类型的乳房导管癌。乳房小叶癌包括带有主要的原位成分的侵入性小叶癌、侵入性小叶癌和浸润性小叶癌。乳腺癌可以包括派杰氏病(Paget’s disease)、导管内癌合并派杰氏病和侵入性导管癌合并派杰氏病。乳腺癌可以包括具有组织学和超微结构的异质性(例如，混合细胞型)的乳腺肿瘤。

[0843] 本发明中的化合物或其药学上可接受的盐、前体药物、代谢物、多晶型物或溶剂化物可用于治疗乳腺癌，或用于识别用于这样的目的的候选人。要治疗的乳腺癌可以包括家族性乳腺癌。要治疗的乳腺癌可以包括散发性乳腺癌。要治疗的乳腺癌可能会出现于男性受试者。要治疗的乳腺癌可能会出现于女性受试者。要治疗的乳腺癌可能会出现于绝经前的女性受试者或绝经后的女性受试者。要治疗的乳腺癌可能出现于年龄等于或大于 30 岁的受试者，或小于 30 岁的受试者。要治疗的乳腺癌可能出现于年龄等于或大于 50 岁的受试者，或小于 50 岁的受试者。要治疗的乳腺癌可能出现于年龄等于或大于 70 岁的受试者，或小于 70 岁的受试者。

[0844] 可将要治疗的乳腺癌分类，以识别 BRCA1，BRCA2 或 p53 的家族性突变或自发性突变。可将要治疗的乳腺癌分类为具有 HER2/neu 基因扩增的、HER2/neu 过度表达的或具有低、中、高水平的 HER2/neu 表达的。可将要治疗的乳腺癌根据选自雌激素受体(ER)，孕酮受体(PR)，人表皮生长因子受体 -2、Ki-67、CA15-3、CA27-29 和 c-Met 的标记物来分类。可将要治疗的乳腺癌分类为未知 ER 的、富含 ER 的或缺乏 ER 的乳腺癌。可将要治疗的乳腺癌分类为 ER 阴性或 ER 阳性的乳腺癌。乳腺癌的 ER 分类可以通过任何具有重复性的方法来施行。乳腺癌的 ER 分类可以按 Onkologie27:175-179(2004) 中的规定来施行。可将要治疗的乳腺癌分类为未知 PR 的、富含 PR 的或缺乏 PR 的乳腺癌。可将要治疗的乳腺癌分型为 PR 阴性或 PR 阳性的乳腺癌。可将要治疗的乳腺癌分型为受体阳性或受体阴性的乳腺癌。可将要治疗的乳腺癌根据 CA15-3 或 CA27-29 或两者的升高的血液水平来分类。

[0845] 要治疗的乳腺癌可以包括乳房的局部肿瘤。要治疗的乳腺癌可包括与阴性的前哨淋巴结 (SLN) 活检相关的乳房肿瘤。要治疗的乳腺癌可包括与阳性的前哨淋巴结 (SLN) 活检相关的乳房肿瘤。要治疗的乳腺癌可包括与一个或多个阳性的腋淋巴结相关的乳房肿瘤，其中腋窝淋巴结已经被采用任何适用的方法来分期。要治疗的乳腺癌可以包括已被分类为有淋巴结阴性的状态(例如，淋巴结阴性)或淋巴结阳性的状态(例如，淋巴结阳性)的乳房肿瘤。要治疗的乳腺癌可以包括已转移到身体其他位置的乳房肿瘤。要治疗的乳腺癌可以包括已转移到选自骨、肺、肝或脑的位置的乳房肿瘤。可将要治疗的乳腺癌根据选自转移的、局部的、区域的、局部区域的、局部晚期的、远处的、多中心的、双侧的、同侧的、对侧的、初诊的、复发的、不宜动手术的特性的进行分类。

[0846] 本发明的化合物或其药学上可接受的盐、前体药物、代谢物、多晶型物或溶剂化物可施用于相对于大多数人有上升的患乳腺癌风险的受试者，以治疗或预防乳房细胞增殖性

障碍，或治疗或预防乳腺癌，或者用来识别用于这样的目的的适合的候选人。相对于大多数人有上升的患乳腺癌风险的受试者是有乳腺癌家族史或个人史的女性受试者。相对于大多数人有上升的患乳腺癌风险的受试者有BRCA1或BRCA2或两者兼而有之的生殖细胞系或自发性突变的女性受试者。相对于大多数人有上升的患乳腺癌风险的受试者有乳腺癌的家族史和BRCA1或BRCA2或两者兼而有之的生殖细胞系或自发性突变的女性受试者。相对于大多数人有上升的患乳腺癌风险的受试者是大于30岁、大于40岁、大于50岁、大于60岁、大于70岁、大于80岁或大于90岁的女性受试者。相对于大多数人有上升的患乳腺癌风险的受试者是患有非典型乳腺增生、原位导管癌(DCIS)、导管内癌、小叶型原位癌(LCIS)、小叶瘤或乳房的0阶段生长或病变(例如，0阶段或0级乳腺癌或原位癌)。

[0847] 要治疗的乳腺癌可以根据Scarff-Bloom-Richardson分级系统进行组织学分级，其中乳腺肿瘤已经被指定为有丝分裂分数为1、2或3；核多型性分数为1、2或3；小管形成分数为1、2或3；以及Scarff-Bloom-Richardson总分为3和9之间。要治疗的乳腺癌可以根据乳腺癌治疗国际共识专家组指定肿瘤级别，所述级别选自1级、1-2级、2级、2-3级或3级。

[0848] 要治疗的癌症可以根据美国癌症联合委员会(AJCC)TNM分期系统进行分期，肿瘤(T)已被指定为TX、T1、T1mic、T1a、T1b、T1c、T2、T3、T4、T4a、T4b、T4c或T4d期；区域淋巴结(N)已被指定为NX、N0、N1、N2、N2a、N2b、N3、N3a、N3b或N3c期；远处转移(M)可以被指定为MX、M0或M1期。要治疗的癌症可以根据美国癌症联合委员会(AJCC)分期为I期、IIA期、IIB期、IIIA期、IIIB期、IIIC期或IV期。要治疗的癌症可以根据AJCC分级分为GX级(例如，等级无法进行评估)、1级、2级、3级或4级。要治疗的癌症可以根据AJCC病理分类(PN)进行分期，其中包括PNX、PN0、PN0(I-)、PN0(1+)、PN0(mol-)、PN0(mol+)、PN1、PN1(mi)、PN1a、PN1b、PN1c、PN2、pN2a、pN2b、PN3、pN3a、pN3b或pN3c。

[0849] 要治疗的癌症可以包括已经被确定为小于或等于约2厘米直径的肿瘤。待治疗的癌症可以包括已被确定为约2至约5厘米直径的肿瘤。待治疗的癌症可以包括已经被确定为大于或等于大约3厘米直径的肿瘤。待治疗的癌症可以包括已被确定为大于5厘米直径的肿瘤。待治疗的癌症可以根据微观形貌分类为良好分化的、中等分化的、不良分化的或未分化的。待治疗的癌症可以以被处理可以根据有丝分裂计数(例如，细胞分裂量)或细胞核的多型性(例如，细胞的改变)来分类。待治疗的癌症可以根据微观形貌分类为与坏死面积(例如，正在死亡或退化的细胞的面积)相关。待治疗的癌症可以分类为具有异常核型、具有异常的染色体数目或具有一个或多个外观异常的染色体。待治疗的癌症可分类为非整倍体、三倍体、四倍体或具有改变的倍性。待治疗的癌症可以分类为具有染色体易位，或整个染色体的缺失或重复，或一部分染色体删除、复制或扩增的区域。待治疗的癌症可以通过DNA细胞分析术、流式细胞分析术、图像细胞分析术来评价。待治疗的癌症可以分类为在细胞分裂的合成期(例如在细胞分裂的S期)具有10%，20%，30%，40%，50%，60%，70%，80%，或90%的细胞。待治疗的癌症可以分类成具有低的S期细胞比率或高的S期细胞比率。

[0850] 如本文所述的“正常细胞”是不能被归类为“细胞增殖性障碍”的一部分的细胞。正常细胞缺乏可能会导致不必要的病症或疾病的发展的不受管制的生长或不正常的生长，或缺乏此两者。优选地，正常细胞具有正常运行的细胞周期检查点控制机制。

[0851] 如本文所述的“接触细胞”是指其中物质的化合物或其它组合物与细胞直接接触

或者足够近以诱导所期望的细胞中的生物效应的状态。

[0852] 本文所使用的“候选化合物”是指本发明的化合物或其药学上可接受的盐、前体药物、代谢物、多晶型物或溶剂化物，所述本发明的化合物或其药学上可接受的盐、前体药物、代谢物、多晶型物或溶剂化物已经或将被在一个或多个体外或体内生物测试中进行检测，以确定该化合物是否在细胞、组织、系统、动物或人类中可能引起研究者或临床医生所寻求的所需的生物学或医学反应。候选化合物是指本发明中的化合物或其药学上可接受的盐、前体药物、代谢物、多晶型物或溶剂化物。所述生物学或医学反应可以是癌症的治疗。所述生物学或医学反应可以是细胞增殖性障碍的治疗或预防。生物学反应或效果还可以包括发生在体外或在动物模型中的细胞增殖或生长的变化，以及在体外可观察到的其他生物学变化。体外或体内生物测试可以包括但不限于酶的活性测试、电泳迁移率变动分析测试、报告基因测试、体外细胞存活率测试和本文所描述的测试。

[0853] 本文所使用的“单药治疗”是指向需要的受试者给予单一的活性的或治疗的化合物的给药。优选地，单药治疗包括治疗上有效剂量的活性化合物给药。例如，用本发明中的一种化合物或其药学上可接受的盐、前体药物、代谢物、类似物或衍生物对需要治疗癌症的受试者进行癌症单药治疗。单药治疗可与联合治疗相比，所述联合治疗为多个活性化合物的组合联合给药，优选在组合中每个成分均以治疗有效剂量存在。应用本发明中的化合物或其药学上可接受的盐、前体药物、代谢物、多晶型物或溶剂化物进行的单药治疗在诱导所需的生物效应方面可能比联合治疗更为有效。

[0854] 本文所使用的“治疗中”或“治疗”描述了为对抗疾病、病症或紊乱的目的对患者的管理和护理，并包括向其给药本发明的化合物或其药学上可接受盐、前体药物、代谢物、多晶型物或溶剂化物，以减轻疾病、病症或紊乱的症状或并发症，或消除疾病、病症或紊乱。术语“治疗”还可以包括体外的细胞或动物模型的治疗。

[0855] 本发明中的化合物或其药学上可接受的盐、前体药物、代谢物、多晶型物或溶剂化物，也可以或可能用于预防有关的疾病、病症或紊乱，或用于识别用于这样的目的的合适的候选人。本文使用的“预防中”或“预防”描述了减少或消除这样的疾病、病症或紊乱的症状或并发症的发作。

[0856] 本文所使用的术语“缓解”是为了描述一个过程，经过该过程一种疾病的体征或症状的严重程度降低。重要的是，所述体征或症状可缓解而没有消除。本发明的药物组合物的给药可以或可能导致疾病的症状或体征的消除，然而，消除不是必需的。有效剂量应该被期望能减轻症状或体征的严重程度。例如，诸如癌症的疾病，它可以发生在多个位置，如果在多个位置中的至少一个位置中的癌症的严重程度减轻了，那么它的体征或症状就缓解了。

[0857] 本文所使用的术语“严重程度”是为了描述癌症从癌前或良性状态转化成恶性状态的潜力。作为另选或附加，严重程度用于描述癌症的阶段，例如，根据 TNM 分期系统(被国际抗癌联盟(UICC)和美国癌症联合委员会(AJCC)所接受)或其他本领域认可的方法。癌症的阶段是指癌症的基于各种因素的范围或严重程度，所述因素例如为原发肿瘤的位置、肿瘤大小、肿瘤数目、淋巴结转移(进入淋巴结的癌症的扩散)。作为另选或附加，严重程度是通过本领域公认的方法来描述肿瘤的分级(见美国国家癌症研究所，www.cancer.gov)。肿瘤分级是用来依据显微镜下看到的癌细胞的异常程度以及该肿瘤可能的生长和扩散的快速程度来为癌细胞分类的体系。确定肿瘤级别时会考虑许多因素，包括细胞的结构和增长

方式。用于确定肿瘤级别的具体因素随癌症类型的不同而不同。严重程度还描述了组织学分级，也称为分化，这是指相同的组织类型中有多少类似于正常细胞的肿瘤细胞（见美国国家癌症研究所，www.cancer.gov）。此外，严重程度描述了细胞核级别，所述细胞核级别是指肿瘤细胞中的细胞核的大小和形状，以及正在分裂的肿瘤细胞的百分比（参见，美国国家癌症研究所，www.cancer.gov）。

[0858] 严重程度还可以描述肿瘤已经分泌生长因子、降解细胞外基质、变为血管化、失去与并列组织的附着力或转移的程度。此外，严重程度可以形容原发肿瘤已经转移到的位置的数量。最后，严重程度可以包括不同类型和位置的肿瘤的治疗的难度。例如，不能手术的肿瘤、有更多通道进入到全身多个系统的那些肿瘤（血液学和免疫学肿瘤）和那些最能抵抗传统治疗方法的肿瘤被认为是最严重的。在这些情况下，延长受试者的寿命和／或减轻疼痛、减少癌变细胞的比例或将细胞限制在一个系统内，以及改善癌症分期／肿瘤分级／组织学分级／细胞核级别被认为是缓解癌症的症状或体征。

[0859] 本文所使用的术语“症状”被定义为疾病、病、受伤或身体某部分不正常的表现。症状能被经历所述症状的人感觉或注意到，但可能不容易被其他人注意到。其他人被定义为非卫生保健专业人员。

[0860] 本文所使用的术语“体征”也被定义为身体某部分不正常的表现。但体征可以由医生、护士或其他卫生保健人员发现。

[0861] 癌症是可能会导致几乎任何体征或症状的一组疾病。症状和体征将取决于癌症的位置、癌症的大小以及其影响附近器官或组织的程度。如果癌细胞扩散（转移），那么症状可能会出现在身体的不同部位。

[0862] 随着癌症的生长，其开始压迫附近的器官、血管和神经。这种压力导致癌症的一些症状和体征。如果癌症是在一个关键的区域，如脑的某些部位，即使是最小的肿瘤也能导致早期症状。

[0863] 但有时癌症起始于除非癌症已经变得相当大，否则不会引起任何症状的地方。例如，胰腺的癌症通常不会生长到大得足以从身体的外部感觉到。有些胰腺癌不引起症状，直到它们开始在附近的神经周围生长（这会导致背痛）。其他的在胆管周围生长，这会阻止胆汁的流动，因此导致皮肤泛黄，称为黄疸。到胰腺癌导致这些体征或症状的时候，通常已经到了晚期。

[0864] 癌症也可能会造成如发烧、疲劳或体重减轻的症状。这可能是因为癌症细胞利用了身体的能量供应或释放了改变人体新陈代谢的物质。或者，癌症可能会导致免疫系统以产生这些症状的方式反应。

[0865] 有时，癌症细胞释放物质到血液中，引起通常不被认为是癌症导致的症状。例如，一些胰腺癌可以释放引起血液凝块在腿部静脉发展的物质。有些肺癌会产生影响血钙水平的激素样物质，从而影响神经和肌肉并导致虚弱和头晕。

[0866] 癌症存在几个当癌症细胞的各种亚型存在时会产生的症状或体征。大多数癌症患者会在某一段时间伴随着疾病而体重减轻。不明原因的（非故意的）减重 10 磅或更多可能是癌症的第一个体征，特别是胰腺癌、胃癌、食道癌或肺癌。

[0867] 发烧常常伴随着癌症，但更经常出现在疾病晚期。几乎所有的癌症患者会在某一段时间内会发烧，特别是如果癌症或其治疗影响免疫系统，从而使得身体更难以对抗感染。

在很少的情况下，发烧可能是癌症的早期体征，如白血病或淋巴瘤。

[0868] 随着癌症的进展，疲劳成为一个重要的症状。然而在诸如白血病的癌症中，或者如果癌症正引起一个持续的失血、如在某些结肠或胃癌中，那么它可能发生于癌症早期。

[0869] 疼痛可能是某些癌症如骨肿瘤或睾丸癌的早期症状。但最常见的是，疼痛是癌症晚期的一种症状。

[0870] 伴随皮肤癌（见下一节），一些内部的癌症可引起可见的皮肤体征。这些变化包括皮肤看起来较暗（色素沉着）、黄色（黄疸）或红色（红斑）、瘙痒或过度毛发生长。

[0871] 作为另选或附加，肿瘤亚型存在特定的体征或症状。排便习惯或膀胱功能的变化可能表明癌症。长期便秘、腹泻或大便的大小的变化可能是结肠癌的一个体征。排尿疼痛、尿中带血或膀胱功能的变化（如更加频繁或更加不频繁的排尿），可能与膀胱或前列腺癌有关。

[0872] 皮肤状况的变化或新的皮肤状况的出现可能预示癌症。皮肤癌可能会流血，看起来像不愈合的疮。持久的的嘴疮可能是口腔癌，尤其是在吸烟、咀嚼烟草或经常喝酒的患者中。阴茎或阴道上的溃疡可能是感染或早期癌症的体征。

[0873] 不寻常的出血或排泄可能预示癌症。不寻常的出血可以发生在癌症早期或晚期。唾液（痰）带血可能是肺癌的一个体征。便血（或暗或黑便）可能是结肠癌或直肠癌的一个体征。子宫颈或子宫内膜（子宫的内层）的癌症可以引起阴道出血。尿中带血可能是膀胱或肾脏癌的体征。来自乳头的血性溢液可能是乳腺癌的一个标志。

[0874] 乳房或其他身体部位增厚或有肿块可能表明癌症的存在。许多癌症可以通过主要是在乳房、睾丸、淋巴结（腺）、身体的软组织处的皮肤察觉。肿块或增厚可能是癌症的早期或晚期体征。任何肿块或增厚可以是癌症的征兆，特别是新形成的或已经长到一定的大小。

[0875] 消化不良或吞咽困难可能预示癌症。尽管这些症状通常有其他原因，但是消化不良或吞咽困难问题可能是食道癌、胃癌、或咽（喉）癌的体征。

[0876] 疣或痣的近期变化可能预示癌症。任何疣、痣或雀斑的颜色、大小或形状的变化或失去其明确的边界表明癌症的潜在发展。例如，皮肤的病变可能是黑色素瘤。

[0877] 持续咳嗽或声音嘶哑可能预示癌症。咳嗽不消失可能是肺癌的一个标志。声音嘶哑可能是喉部（喉头）或甲状腺癌的一个体征。

[0878] 虽然上面列出的症状和体征在癌症中比较常见，但是还有许多其它不常见的症状和体征这里没有列出。

[0879] 所述癌症治疗可能或可以导致肿瘤尺寸变小。肿瘤尺寸变小也可以被称为“肿瘤衰退”。优选地，在治疗后，相对于治疗前肿瘤尺寸将减小 5% 或以上；更优选地，肿瘤尺寸减小 10% 或以上；更优选地，减小 20% 或以上；更优选地，减小 30% 或以上；更优选的是，减小 40% 或以上；更优选的是，减小 50% 或以上；最优选的，减小大于 75% 或以上。肿瘤的大小可通过任何可再现的测量手段测量。肿瘤的尺寸可通过其直径测量。

[0880] 癌症治疗可能或可以导致肿瘤体积减小。优选地，在治疗后，相对于治疗之前肿瘤体积将减少 5% 或更大；更优选的是，肿瘤体积减小 10% 或以上；更优选地，减少 20% 或以上；更优选地，减少 30% 或以上；更优选的是，减少 40% 或以上；更优选的是，减少 50% 或以上；最优选的，大于 75% 或更大的减少。肿瘤的体积可通过任何可再现的测量手段测量。

[0881] 癌症治疗可能或可以导致肿瘤数目减少。优选的是经过治疗，相对于治疗之前肿

瘤数目将减少 5% 或更多 ;更优选地是肿瘤数目减少 10% 或更多 ;更优选地,减少 20% 或更多 ;更优选地,减少 30% 或更多 ;更优选地,减少 40% 或更多 ;更优选的是,减少 50% 或更多 ;最优选的是,减少大于 75%。肿瘤数目可通过任何可再现的测量手段测量。肿瘤的数量可以通过对肉眼可见的或特定的放大倍率下的肿瘤进行计数来测量。优选地,所述特定的放大倍率为 2 倍、3 倍、4 倍、5 倍、10 倍或 50 倍。

[0882] 癌症治疗可能或可以导致在远离原发肿瘤部位的其他组织或器官的转移灶的数量减少。优选的是,经过治疗,相对于治疗之前转移灶的数目将减少 5% 或更多 ;更优选地,转移灶的数量减少了 10% 或更多 ;更优选地,减少了 20% 或更多 ;更优选的是,减少了 30% 或更多 ;更优选的是,减少了 40% 或更多 ;更优选的是,减少了 50% 或更多 ;最优选的是,减少大于 75%。转移灶的数目可通过任何可再现的测量手段测量。转移灶的数目可通过对肉眼可见的或特定的放大倍率下的转移灶进行计数来测量。优选地,所述指定的放大倍率为 2 倍、3 倍、4 倍、5 倍、10 倍或 50 倍。

[0883] 癌症治疗可能或可以导致接受治疗的受试者群体同仅接受载体的群体相比,平均生存期增加。优选地,平均生存期将增加超过 30 天 ;更优选超过 60 天 ;更优选超过 90 天 ;最优选超过 120 天。群体的平均生存期的增加可由任何可再现的测量手段测量。群体的平均生存期的增加可例如通过计算用活性化合物开始治疗后的群体的平均存活时间来测量。群体的平均生存期的增加也可例如通过计算采用活性化合物进行第一轮治疗结束后的群体的平均存活时间来测量。

[0884] 癌症治疗可能或可以导致接受治疗的受试者群体同未接受治疗的受试者群体相比,平均生存期增加。优选地,平均生存期将增加超过 30 天 ;更优选超过 60 天 ;更优选超过 90 天 ;最优选超过 120 天。群体的平均生存期的增加可由任何可再现的测量手段测量。群体的平均生存期的增加可例如通过计算群体用活性化合物开始治疗后的平均存活时间来测量。群体的平均生存期的增加也可例如通过计算群体采用活性化合物进行第一轮治疗结束后的平均存活时间来测量。

[0885] 癌症治疗可能或可以导致接受治疗的受试者群体同采用非本发明的化合物或其药学上可接受的盐、前体药物、代谢物、类似物或衍生物的药物进行单药治疗的受试者群体相比,平均生存期增加。优选地,平均生存期将增加将超过 30 天 ;更优选地,增加将超过 60 天 ;更优选地,增加将超过 90 天 ;最优选地,增加将超过 120 天。群体的平均生存期的增加可由任何可再现的测量手段测量。群体的平均生存期的增加可例如通过计算群体用活性化合物开始治疗后的平均存活时间来测量。群体的平均生存期的增加也可例如通过计算群体采用活性化合物进行第一轮治疗结束后的平均存活时间来测量。

[0886] 癌症治疗可能或可以导致接受治疗的受试者群体同仅接收载体的受试者群体相比,死亡率降低。癌症治疗可能或可以导致治疗的受试者群体受试者同未接受治疗的受试者群体相比,死亡率降低。癌症治疗可能或可以导致接受治疗的受试者群体同采用非本发明的化合物或其药学上可接受的盐、前体药物、代谢物、类似物或衍生物的药物进行单药治疗的受试者群体相比,死亡率降低。优选地,死亡率减少将超过 2% ;更优选地,减少将超过 5% ;更优选地,减少将超过 10% ;最优选地,减少将超过 25%。接受所述治疗的受试者群体死亡率的减少可由任何可再现的测量手段测量。群体死亡率的减少可例如通过计算用活性化合物开始治疗后每单位时间与疾病相关的平均死亡人数来测量。群体死亡率的减少也可以

例如通过计算用活性化合物完成第一轮治疗后每单位时间与疾病相关的平均死亡人数来测量。

[0887] 癌症治疗可能或可以导致肿瘤的生长速度降低。优选地，在治疗后，相对于治疗之前肿瘤的生长速度将降低至少 5% ；更优选地，肿瘤的生长速度将降低至少 10% ；更优选地，将降低至少 20% ；更优选地，降低至少 30% ；更优选地，将降低至少 40% ；更优选地，将降低至少 50% ；更优选地，将降低至少 50% ；更优选地，将降低至少 75%。测量肿瘤的生长速率可由任何可再现的测量手段测量。根据每单位时间肿瘤直径的变化，可以测量肿瘤的生长速度。

[0888] 癌症治疗可能或可以导致肿瘤再生减少。优选地，在治疗后，肿瘤再生将少于 5% ；更优选地，肿瘤再生将少于 10% ；更优选地，肿瘤再生将少于 20% ；更优选地，肿瘤再生将少于 30% ；更优选地，肿瘤再生将少于 40% ；更优选地，肿瘤再生将少于 50% ；甚至更优选地，肿瘤再生将少于 50% ；最优选地，肿瘤再生将少于 75%。肿瘤生长可由任何可再现的测量手段测量。肿瘤再生可以通过例如测量经过治疗后先前肿瘤收缩后的肿瘤直径的增加来测量。肿瘤治疗结束后肿瘤复发失败表明肿瘤再生的减少。

[0889] 对细胞增殖性障碍的治疗或预防可能或可以导致细胞增殖率降低。优选地，在治疗后，细胞增殖率将降低至少 5% ；更优选地，将降低至少 10% ；更优选地，将降低至少 20% ；更优选地，将降低至少 30% ；更优选地，将降低至少 40% ；更优选地，将降低至少 50% ；甚至更优选地，将降低至少 50% ；最优选地，将降低至少 75%。细胞增殖率可由任何可再现的测量手段测量。细胞增殖率可通过例如测量每单位时间组织样本中分裂的细胞数量来测量。

[0890] 对细胞增殖性障碍的治疗或预防可能或可以导致增殖细胞比例减少。优选地，在治疗后，增殖细胞比例将减少至少 5% ；更优选地，将减少至少 10% ；更优选地，将减少至少 20% ；更优选地，将减少至少 30% ；更优选地，将减少至少 40% ；更优选地，将减少至少 50% ；甚至更优选地，将减少至少 50% ；最优选地，将减少至少 75%。增殖细胞比例可由任何可再现的测量手段测量。优选地，增殖细胞比例通过例如量化组织样本中分裂细胞数目与非分裂细胞的数量相对量来测量。增殖细胞比例可以等同于有丝分裂指数。

[0891] 对细胞增殖性障碍的治疗或预防可能或可以导致细胞增殖区域尺寸减小。优选地，在治疗后，相对于治疗之前细胞增殖区域的尺寸将减小至少 5% ；更优选地，将减小至少 10% ；更优选地，将减小至少 20% ；更优选地，将减小至少 30% ；更优选地，将减小至少 40% ；更优选地，将减小至少 50% ；甚至更优选地，将减小至少 50% ；更优选地，将减小至少 75%。细胞增殖区域的尺寸可由任何可再现的测量手段测量。细胞增殖区域的尺寸可以以细胞增殖区域的直径或宽度来测量。

[0892] 对细胞增殖性障碍的治疗或预防可能或可以导致具有异常外观或形态的细胞数目或比例减少。优选地，在治疗后，相对于治疗之前具有异常形态的细胞数量将减少至少 5% ；更优选地，将被减少至少 10% ；更优选地，将减少至少 20% ；更优选地，将减少至少 30% ；更优选地，将减少至少 40% ；更优选地，将减少至少 50% ；甚至更优选的是，将减少至少 50% ；以及最优选地，将减少至少 75%。细胞的异常外观或形态可由任何可再现的测量手段测量。异常的细胞形态可以通过例如使用倒置的组织培养显微镜来显微镜测量。细胞形态异常可以表现为核多型性的形式。

[0893] 本文所使用的术语“选择性地”是指在一个群体中比在另一个群体中倾向于发生的频率更高。比较的群体可以是细胞群。本发明化合物或其药学上可接受的盐、前体药物、

代谢物、多晶型物或溶剂化物可能或可以选择性地作用于癌症或癌症前期的细胞，但不包括正常细胞。本发明化合物或其药学上可接受的盐、前体药物、代谢物、多晶型物或溶剂化物可能或可以选择性地作用来调节一个分子靶标(例如，靶蛋白甲基转移酶)，但不显著调节另一种分子靶标(例如，非靶蛋白甲基转移酶)。本发明还提供了一种选择性地抑制酶(如蛋白甲基转移酶)活性的方法。优选地，如果事件发生于群体 A 的频率大于发生于群体 B 的 2 倍，那么相对于群体 B，事件选择性地发生于群体 A。如果相对于群体 B 五倍以上更频繁地发生于群体 A，那么事件是选择性地发生。如果相对于群体 B 十倍以上更频繁地发生于群体 A，那么事件是选择性地发生；更优选地，五十倍以上；甚至更优选地，一百倍以上；最优选地，相对于群体 B 一千倍以上更频繁地发生于群体 A。例如，如果与正常细胞相比细胞凋亡两倍以上更频繁地发生于肿瘤细胞，那么可以说细胞凋亡选择性地发生在癌细胞中。

[0894] 本发明化合物或其药学上可接受的盐、前体药物、代谢物、多晶型物或溶剂化物可能或可以调节分子靶标(例如，靶蛋白甲基转移酶)的活性。调节是指刺激或抑制分子靶标的活性。优选地，如果刺激或抑制了相对于只是缺少所述化合物存在的相同条件下的分子靶标的活性的至少两倍的分子靶标的活性，那么本发明化合物或其药学上可接受的盐、前体药物、代谢物、多晶型物或溶剂化物调节了分子靶标的活性。更优选地，如果刺激或抑制了相对于缺少所述化合物存在的相同条件下的分子靶标的活性的至少 5 倍、至少 10 倍、至少 20 倍、至少 50 倍、至少 100 倍的分子靶标的活性，那么本发明化合物或其药学上可接受的盐、前体药物、代谢物、多晶型物或溶剂化物调节了分子靶点的活性。分子靶标的活性可由任何可再现的测量手段测量。分子靶标的活性可在体外或体内测定。例如，分子靶标的活性可以通过酶活性测定方法或 DNA 结合分析法在体外测定，或者分子靶标的活性可通过测定报告基因的表达在体内测定。

[0895] 如果所述化合物的加入没有刺激或抑制相对于只是缺少所述化合物存在的相同条件下的分子靶标活性的 10％以上的分子靶标活性，那么本发明的化合物或其药学上可接受的盐、前体药物、代谢物、多晶型物或溶剂化物没有显著调节分子靶标的活性。

[0896] 本文所使用的术语“同工酶选择性的”是指相比同一种酶的第二种异构体优先抑制或刺激所述酶的第一种异构体(例如，相比蛋白甲基转移酶的 β－异构体优先抑制或刺激其 α－异构体)。优选地，本发明化合物或其药学上可接受的盐、前体药物、代谢物、多晶型物或溶剂化物表明所需剂量上最小值为四倍差，优选十倍的差，更优选为五十倍差来实现生物效应。优选地，本发明化合物或其药学上可接受的盐、前体药物、代谢物、多晶型物或溶剂化物表明了整个抑制范围的这种差别，并且所述差别体现在对于感兴趣的分子靶标的 IC_{50} 值，即 50％抑制。

[0897] 对细胞或有需要的受试者给药本发明化合物或其药学上可接受的盐、前体药物、代谢物、多晶型物或溶剂化物可能或可以导致所感兴趣的蛋白甲基转移酶的活性的调节(即，刺激或抑制)。

[0898] 本发明提供评价本发明化合物或其药学上可接受的盐、前体药物，代谢物、多晶型物或溶剂化物的生物活性的方法，或识别作为 EZH2 的 Y641 突变体的抑制剂的测试化合物的方法。在一个实施例中，所述方法包括使孤立的 EZH2 基因 Y641 突变体同组蛋白底物、甲基供体(如 S- 腺苷甲硫氨酸(SAM))和测试化合物结合，其中所述组蛋白底物包括选自非甲基化、单甲基化的 H3-K27、二甲基化的 H3-K27 和它们的任意组合的 H3-K27 形式；进行试验

以检测组蛋白底物中的 H3-K27 的甲基化，从而当在测试化合物存在下的 H3-K27 的甲基化少于在其不存在下的 H3-K27 的甲基化时识别测试化合物作为 EZH2 基因 Y641 突变体的抑制剂。可以选择用于检测 H3-K27 的甲基化的试验来测量甲基化的速率、甲基化的程度或甲基化的速率和程度。

[0899] EZH2 基因 Y641 突变体以 PRC2 复合物或其功能等同物形式被分离。本文所使用的术语“分离”是指基本上与其它成分分离，带有所述其他成分的复合物由于存在于自然界中而被发现。化合物可以被分离而不必被纯化。在一个实施例中，EZH2 基因突变体作为 EZH2 基因 Y641 突变体同 EED 和 SUZ12 的复合物被分离。在另一个实施例中，EZH2 基因突变体作为 EZH2 基因 Y641 突变体同 EED、SUZ12 和 RbAp48 的复合物被分离。在适当的条件下，PRC2 复合物或其功能等同物具有组蛋白 H3-K27 的甲基转移酶活性。在一个实施例中，该复合物由重组表达成分多肽组成，例如，EZH2、EED、SUZ12，含或不含 RBAP48。

[0900] 分离的 EZH2 基因 Y641 突变体与组蛋白底物相结合。组蛋白底物包括任何合适来源的可以作为 EZH2 底物的组蛋白多肽或其片段。在一个实施例中，组蛋白底物包括从受试者分离的组蛋白。可以使用任何合适的方法从受试者的细胞分离该组蛋白；所述方法为本领域普通技术人员所公知，不需要在此进一步指定(参阅如 Fang et al.(2004)Methods Enzymol377:213-26)。根据下面的实施例，在一个实施例中，组蛋白底物为核小体。根据下面的实施例，在一个实施例中，组蛋白底物为禽鸟类(鸡)红细胞的核小体。

[0901] 所提供的组蛋白底物可能包括组蛋白修饰状态的掺合物，包括通过用 H3-K27 甲基化特异性抗体的免疫印迹法来判断的 H3-K27 甲基化的各种状态。在一个实施例中，所提供的组蛋白底物是纯化的全长组蛋白 H3。这种纯化的全长组蛋白 H3 可提供为 H3-K27 的甲基化状态的均匀的制剂，或提供为 H3-K27 的甲基化的各种状态的混合物。涉及 H3-K27 甲基化状态的孤立的组蛋白 H3 的均匀制剂可以部分地通过经过装有适合的 H3-K27 甲基化状态的特异性抗体的免疫亲和性柱来制备，或者通过使用包覆有适合的 H3-K27 甲基化状态的特异性抗体的磁珠的免疫沉淀反应来制备。作为另选或附加，可以 H3-K27 的甲基化状态可以表征为施行该试验的一部分。例如，起始原料组蛋白底物可能被表征为含有 50%％未甲基化的 H3-K27、40% 单甲基化的 H3-K27、10% 二甲基化的 H3-K27 和 0% 三甲基化的 H3-K27。

[0902] 在一个实施例中，组蛋白底物包括肽库或含有一个或多个同组蛋白 H3 相关的氨基酸序列的合适的肽，特别是包括包含 H3-K27 的序列。例如，在一个实施例中，组蛋白底物是肽片段，该片段对应组蛋白 H3 的氨基酸残基 21-44。肽库或肽可以通过根据本领域公知的技术的肽合成法来制备，并且任选被修饰以掺入任何所需的与 H3-K27 对应的赖氨酸的甲基化程度。如下面的实施例中所描述的，这些肽也可以被修饰以掺入适用于执行下游检测的标记物(如生物素)。在一个实施例中，该标记物被附加到肽的氨基 (N) 末端。在一个实施例中，该标记物被附加到肽的羧基 (C) 末端。

[0903] 可以通过使用任何合适的方法来检测 H3-K27 的甲基化。在一个实施例中，甲基供体源包括用可检测的标记物标记的甲基基团。在一个实施例中，可检测的标记物为同位素标记物，例如氚。其他类型的标签可以包括例如荧光标记物。

[0904] 可以通过使用任何合适的方法检测三甲基化 H3-K27 的形成。例如，对三甲基化 H3-K27 的形成的检测可以通过使用用来检测掺入的标记的甲基基团的测试方法来完成，诸如上述，任选与色谱或其他方法结合来按大小分离标记产品，例如聚丙烯酰胺凝胶电泳

(PAGE)、毛细管电泳 (CE) 或高压液相色谱 (HPLC)。作为另选或附加，可以通过使用对三甲基化 H3-K27 具有特异性的抗体来检测三甲基化 H3-K27 的形成。

[0905] 可以通过使用任何合适的方法来检测单甲基化的 H3-K27 向二甲基化的 H3-K27 的转化。在一个实施例中，使用单甲基化 H3-K27 和二甲基化的 H3-K27 的特异性抗体来测定所述转化。例如，通过使用合适的单甲基化 H3-K27 和二甲基化 H3-K27 的特异性抗体可以确定单甲基化 H3-K27 和二甲基化 H3-K27 的起始量或浓度。结合酶、底物、甲基供体和测试化合物之后，通过使用合适的单甲基化 H3-K27 和二甲基化 H3-K27 的特异性抗体可以确定由此产生的单甲基化 H3-K27 和二甲基化 H3-K27 的量或浓度。然后可以对起始的和由此产生的单甲基化 H3-K27 和二甲基化 H3-K27 的量或浓度进行比较。作为另选或附加，起始的以及由此产生的单甲基化 H3-K27 和二甲基化 H3-K27 的量或浓度可以同作为阴性对照的相应的浓度量相比较。阴性对照反应中没有测试剂检测，可以平行地运行或作为历史对照。这种对照反应的结果可以任选从相应的之前的反应结果中减去或与上述所做的对比结合。

[0906] 因为在相同的测试中二甲基化形式的 H3-K27 可以进一步甲基化，所以单甲基化 H3-K27 的量或浓度的降低可能不会出现直接对应于二甲基化 H3-K27 的增加。然而在这种情况下，单甲基化 H3-K27 的量或浓度的减少本身可能会被认为反映了单甲基化 H3-K27 向二甲基化 H3-K27 的转化。

[0907] 可以通过使用任何合适的方法来检测二甲基化的 H3-K27 向三甲基化的 H3-K27 的转化。在一个实施例中，使用二甲基化 H3-K27 和三甲基化的 H3-K27 的特异性抗体来测定所述转化。例如，通过使用合适的二甲基化 H3-K27 和三甲基化 H3-K27 的特异性抗体可以确定二甲基化 H3-K27 和三甲基化 H3-K27 的起始量或浓度。结合酶、底物、测试化合物之后，通过使用合适的二甲基化 H3-K27 和三甲基化 H3-K27 的特异性抗体可以确定由此产生的二甲基化 H3-K27 和三甲基化 H3-K27 的量或浓度。然后可以对起始的和由此产生的二甲基化 H3-K27 和三甲基化 H3-K27 的量或浓度进行比较。作为另选或附加，起始的以及由此产生的二甲基化 H3-K27 和三甲基化 H3-K27 的量或浓度可以同来自阴性对照的相应的浓度量相比较。阴性对照反应中没有测试剂检测，可以平行运行或作为历史对照。这种对照反应的结果可以任选从相应的之前的反应结果中减去或与上述所做对比结合。

[0908] 如果测试化合物存在时的 H3-K27 甲基化少于测试化合物不存在时的 H3-K27 甲基化，则测试剂被鉴定为 EZH2 基因 Y641 突变体的抑制剂。在一个实施例中，当在测试化合物存在下生成的三甲基化 H3-K27 少于在测试化合物不存在时生成的三甲基化 H3-K27 时，测试剂被鉴定为 EZH2 基因 Y641 突变体的抑制剂。

[0909] 本发明还提供了一种识别 EZH2 基因 Y641 突变体的选择性抑制剂的方法。在一个实施方案中，所述方法包括使孤立的 EZH2 基因 Y641 突变体同组蛋白底物、甲基供体(如 SAM）和测试化合物结合，其中所述组蛋白底物包括选自单甲基化 H3-K27、二甲基化 H3-K27 和单甲基化 H3-K27 与二甲基化 H3-K27 的组合的 H3-K27 形式，从而形成测试混合物；使孤立的野生型 EZH2 同组蛋白底物、甲基供体(如 SAM）和测试化合物结合，其中所述组蛋白底物包括选自下列形式的 H3-K27：单甲基化 H3-K27、双甲基化 H3-K27 以及单甲基化 H3-K27 和双甲基化 H3-K27 的组合，从而形成对照混合物；进行测试以检测在每种测试混合物和对照混合物中的组蛋白底物的三甲基化；计算 (a) 用 EZH2 的 Y641 突变体和测试化合物的三甲基化 (M+) 与 (b) 用 EZH2 的 Y641 突变体而没有测试化合物的三甲基化 (M-) 的比值；计

算 (c) 用野生型 EZH2 和测试化合物的三甲基化 (WT+) 与用 (d) 野生型 EZH2 而没有测试化合物的三甲基化 (WT-) 的比值；对比比值 (a)/(b) 与 (c)/(d)；当比值 (a)/(b) 小于 (c)/(d) 时，识别测试化合物作为 EZH2 的 Y641 突变体的选择性抑制剂。在一个实施例中，该方法进一步包括针对测试混合物和对照混合物两者或两者之一的情况考虑不含测试化合物的阴性对照。

[0910] 在一些实验中使用免疫试剂，如抗体和抗原。在某些试验中荧光反应可以用来测量酶的活性。本文使用的“荧光反应”是指由于分子吸收了能量较高的入射光子而导致所述分子再发射光子的过程。用于评估本发明所公开化合物生物活性的具体方法在实施例中描述。

[0911] 向细胞或需要治疗的受试者给药以本发明化合物或其药学上可接受的盐、前体药物、代谢物、多晶型物或溶剂化物，可能或可以导致对细胞内靶标（例如，底物）活性的调节（即，刺激或抑制）。可以用本发明的化合物调节的几种细胞内靶标包括，但不限于蛋白甲基转移酶。

[0912] 激活是指使物质组合物（例如，蛋白质或核酸）处于适合实现所需的生物功能的状态。能够被激活的物质组合物也有未激活的状态。激活的物质组合物可能具有抑制或刺激的生物功能，或两者兼而有之。

[0913] 提高是指物质组合物（例如，蛋白质或核酸）的期望的生物活性的增加。通过增加物质组合物的浓度可能会发生这种提高。

[0914] 本文使用的“细胞周期检查点途径”是指细胞周期检查点调节机制中涉及的生化途径。细胞周期检查点途径可以具有对包括细胞周期检查点的一个或多个功能有刺激或抑制的效果，或两者兼而有之。细胞周期检查点途径由至少两种物质组合物组成，优选的是蛋白质，所述的两种物质都有助于细胞周期检查点的调节机制。通过激活细胞周期检查点途径的一个或多个组成成员，可将细胞周期检查点途径激活。优选地，细胞周期检查点途径是生化信号通路。

[0915] 本文使用的“细胞周期检查点调节剂”是指可以至少部分作用于细胞周期检查点调节机制的物质组合物。一个细胞周期检查点调节剂可以对包括细胞周期检查点的一个或多个功能有刺激或抑制的效果，或两者兼而有之。细胞周期检查点调节剂可以是蛋白质或不是蛋白质。

[0916] 对癌症或细胞增殖性障碍的治疗可能或可以导致或者可能导致细胞死亡，优选地，细胞死亡会导致细胞群中至少 10% 的细胞数减少。更优选地，细胞死亡意味着减少至少 20%；更优选地，减少至少 30%；更优选地，减少至少 40%；更优选地，减少了至少 50%；最优选地，减少至少 75%。细胞群中的细胞数目可由任何可再现的测量手段测量。在细胞群中的细胞数目可以通过荧光激活细胞分类（FACS）、免疫荧光显微镜和光学显微镜测量。测量细胞死亡的方法如 Li et al.,Proc Natl Acad Sci U S A.100(5):2674-8,2003 所示。在一个方面中，细胞死亡以凋亡形式发生。

[0917] 优选地，有效量的本发明化合物或其药学上可接受的盐、前体药物、代谢物、多晶型物或溶剂化物对正常细胞没有显著的细胞毒性。如果给药以治疗有效量的化合物在正常细胞中诱导细胞死亡不超过 10%，则治疗有效量的所述化合物对正常细胞没有显著的细胞毒性。如果给药以治疗有效量的化合物在正常细胞中诱导细胞死亡不超过 10%，则治疗有效

量的所述化合物对正常细胞的生存力没有显著影响。在一个方面中，细胞死亡以凋亡形式发生。

[0918] 细胞与本发明化合物或其药学上可接受的盐、前体药物、代谢物、多晶型物或溶剂化物相接触可能或可以选择性地诱导或激活癌细胞中的细胞死亡。向需要治疗的受试者给药以本发明化合物或其药学上可接受的盐、前体药物、代谢物、多晶型物或溶剂化物，可能或可以选择性地诱导或激活癌细胞中的细胞死亡。细胞与本发明化合物或其药学上可接受的盐、前体药物、代谢物、多晶型物或溶剂化物相接触可能或可以选择性地诱导一个或多个受细胞增殖性疾病影响的细胞的细胞死亡。优选地，向需要治疗的受试者给药以本发明化合物或其药学上可接受的盐、前体药物、代谢物、多晶型物或溶剂化物可选择性地诱导一个或多个受细胞增殖性疾病影响的细胞的细胞死亡。

[0919] 本发明的一个方面涉及一种通过向需要的受试者给药以本发明化合物或其药学上可接受的盐、前体药物、代谢物、多晶型物或溶剂化物来治疗或预防癌症(例如可以通过调节 EZH2 介导的蛋白甲基化影响这一过程)的方法。所述给药以本发明化合物或其药学上可接受的盐、前体药物、代谢物、多晶型物或溶剂化物会导致一个或多个下列结果 :通过在细胞周期中的一个或多个阶段(例如，G1、G1/S、G2/M)的细胞积累、细胞衰老的诱导或肿瘤细胞分化的促进来预防癌细胞增殖 ;通过细胞毒性作用促进癌细胞中的细胞死亡、坏死或凋亡，而不造成显著的正常细胞中的细胞死亡，在动物中的抗肿瘤活性的治疗指数至少为 2。如本文所使用的，“治疗指数”是最大耐受剂量除以有效剂量。本发明还涉及用于识别治疗或预防癌症的合适的候选人的方法。

[0920] 对于本文讨论的公知技术或等效技术的详细描述，本领域的普通技术人员可以参考通用参考文本。所述参考文本包括 Ausubel et al.,Current Protocols in Molecular Biology,John Wiley and Sons,Inc.(2005);Sambrook et al.,Molecular Cloning,A Laboratory Manual(3rd edition),Cold Spring Harbor Press,Cold Spring Harbor,New York(2000);Coligan et al.,Current Protocols in Immunology,John Wiley & Sons,N.Y.;Enna et al.,Current Protocols in Pharmacology,John Wiley & Sons,N.Y.;Fingl et al.,The Pharmacological Basis of Therapeutics(1975),Remington's Pharmaceutical Sciences,Mack Publishing Co.,Easton,PA,18th edition(1990)。当然，这些文本在制造或应用本发明的一个方面时可被提及。

[0921] 如本文所使用的，“联合治疗”或“共同治疗”包括用本发明的化合物或其药学上可接受的盐、前体药物、代谢物、多晶型物或溶剂化物，以及至少一种第二剂进行给药，所述第二剂是特定的治疗方案的一部分，所述治疗方案的目的是提供这些治疗剂共同作用所产生的有益效果。所述有益效果包括，但不限于由治疗剂的联合所产生的药代动力学或药效的共同作用。这些治疗剂的联合给药一般是通过确定的周期（通常为分钟、小时、天或者星期，这取决于所选择的组合）进行的。“联合治疗”可以，但通常不试图包括下述的给药方式，即将两种或更多种这些治疗剂作为单独的单药治疗方案的一部分进行给药而偶然地并且随意地产生了本发明的联合作用。

[0922] “联合治疗”试图既包括以顺序方式给药以这些治疗剂，也就是说其中各治疗剂的给药是在不同时间进行的，也包括以基本上同时的方式给药以这些治疗剂或者所述治疗剂中的至少两种。基本上同时的给药可以例如通过向受试者给药以具有固定比例的各治疗剂

的单一胶囊或者通过给药以多种各治疗剂的单独胶囊而实现。各治疗剂的顺序或者基本上同时的给药可能会受到任何适当途径的影响，所述途径包括但不限于口服途径、静脉途径、肌内注射途径和通过粘膜组织的直接吸收。治疗剂可以通过相同或不同的途径给药。例如，联合治疗所选择的第一治疗剂可以通过静脉注射进行给药，而联合治疗的另一个治疗剂可以进行口服给药。可选地，例如，所有的治疗剂均可以通过口服进行给药或通过静脉注射进行给药。治疗剂的给药顺序并不是十分关键。

[0923] “联合治疗”还包括将上述治疗剂的给药进一步与其它生物活性成分和非药物疗法(如手术或放射治疗)结合。在联合治疗还包括非药物治疗的情况中，所述非药物治疗可以在任何合适的时期进行，只要能够获得来自治疗剂和非药物治疗联合共同作用的有益效果。例如，在一个恰当的例子中，当给予了治疗剂而暂时地停止了非药物治疗，也许是几天或者甚至是几周时，仍然能够获得有益的效果。

[0924] 本发明化合物或其药学上可接受的盐、前体药物、代谢物、类似物或衍生物可以同第二化疗药物联合给药。第二化疗药物(也称为抗肿瘤剂或抗增殖剂)可以是烷基化剂、抗生素、抗代谢药、解毒剂、干扰素、多克隆或单克隆抗体、EGFR 抑制剂、HER2 抑制剂、组蛋白去乙酰化酶抑制剂、激素、有丝分裂抑制剂、MTOR 抑制剂、多激酶抑制剂、丝氨酸 / 苏氨酸激酶抑制剂、酪氨酸激酶抑制剂、VEGF/VEGFR 抑制剂、紫杉类或紫杉烷类衍生物、芳香酶抑制剂、葸环类药物、微管靶向药物、拓扑异构酶毒物药物、分子靶向或酶(如激酶或蛋白甲基转移酶)的抑制剂、胞苷类似物药物或在 www.cancer.org/docroot/cdg/cdg_0.asp 所列的任何化疗剂、抗肿瘤或抗增殖剂。

[0925] 示例性的烷基化剂包括，但不限于环磷酰胺(Cytoxan ;Neosar)、丁酸氮芥(Leukeran)、美法仑(Alkeran)、卡莫司汀(BiCNU)、白消安(Busulfex)、洛莫司汀(CeeNU)、氮烯咪胺(DTIC-Dome)、奥沙利铂(Eloxatin)、卡莫司汀(Gliadel)、异环磷酰胺(Ifex)、氮芥(Mustargen)、白消安(Myleran)、卡铂(Paraplatin)、顺铂(CDDP ;Platinol)、替莫唑胺(Temodar)、噻替哌(Thioplex)、苯达莫司汀(Treanda)或链脲佐菌素 (Zanosar)。

[0926] 示例性抗生素包括，但不限于多柔比星(阿霉素)、多柔比星脂质体(Doxil)、米托蒽醌(诺肖林)、博莱霉素(Blenoxane)、柔红霉素(Cerubidine)、柔红霉素脂质体(DaunoXome)、放线菌素 D (Cosmegen)、表柔比星(Ellence)、伊达比星(Idamycin)、普卡霉素(Mithracin)、丝裂霉素(Mutamycin)、喷司他丁(Nipent)或戊柔比星(VALSTAR)。

[0927] 示例性的抗代谢物包括，但不限于氟尿嘧啶(Adrucil)、卡培他滨(Xeloda)、羟基脲(Hydrea)、巯基嘌呤(Purinethol)、培美曲塞(Alimta)、氟达拉滨(Fludara)、奈拉滨(Arranon)、克拉屈滨(Cladribine Novaplus)、氯法拉滨(Clolar)、阿糖胞苷(Cytosar-U)、地西他滨(Dacogen)、阿糖胞苷脂质体(DepoCyt)、羟基脲(Droxia)、普拉曲沙(Folotyn)、氟尿苷(FUDR)、吉西他滨(Gemzar)、克拉屈滨 (Leustatin)、氟达拉滨(Oforta)、氨甲喋呤(MTX ;Rheumatrex)、氨甲喋呤(Trexall)、硫鸟嘌呤(Tabloid)、TS-1 或阿糖胞苷(Tarabine PFS)。

[0928] 示例性的解毒剂包括，但不限于氨磷汀(Ethyol)或美司钠(Mesnex)。

[0929] 示例性的干扰素包括，但不限于干扰素 α-2b (Intron A)或干扰素 α-2a (Roferon-A)。

[0930] 示例性的多克隆或单克隆抗体包括，但不限于曲妥珠单抗(Herceptin)、木单抗

(Arzerra)、贝伐单抗(Avastin)、利妥昔单抗(Rituxan)、西妥昔单抗(Erbitux)、帕尼单抗(Vectibix)、托西莫单抗 / 碘 131 托西莫单抗(Bexxar)、阿仑单抗(Campath)、替伊莫单抗(Zevalin、In-111、Y-90Zevalin)、吉妥单抗(Mylotarg)、依库丽单抗(Soliris)或德尼单抗。

[0931] 示例性的 EGFR 抑制剂包括,但不限于吉非替尼 (Iressa)、拉帕替尼 (Tykerb)、西妥昔单抗 (Erbitux)、埃罗替尼 (Tarceva)、帕尼单抗 (Vectibix)、PKI-166、卡拉替尼 (CI-1033)、马妥珠单抗 (Emd7200) 或 EKB-569。

[0932] 示例性的 HER2 抑制剂包括,但不限于曲妥珠单抗 (Herceptin)、拉帕替尼 (Tykerb) 或 AC-480。

[0933] 组蛋白去乙酰化酶抑制剂包括,但不限于伏立诺他 (Zolinza)。

[0934] 示例性的激素包括,但不限于他莫昔芬 (Soltamox、Nolvadex)、雷洛昔芬 (Evista)、甲地孕酮 (Megace)、亮丙瑞林 (Lupron、Lupron Depot、Eligard、Viadur)、氟维司群 (Faslodex)、来曲唑 (Femara)、曲普瑞林 (Trelstar LA、Trelstar Depot)、依西美坦 (Aromasin)、戈舍瑞林 (Zoladex)、比卡鲁胺 (Casodex)、阿那曲唑 (Arimidex)、氟甲睾酮 (Androxy、Halotestin)、甲羟孕酮 (Provera、Depo-Provera)、雌氮芥 (Emcyt)、氟他米特 (Eulexin)、托瑞米芬 (Fareston)、地加瑞克 (Firmagon)、尼鲁米特 (Nilandron)、阿巴瑞克 (Plenaxis) 或睾内酯 (Teslac)。

[0935] 示例性的有丝分裂抑制剂包括,但不限于紫杉醇 (Taxol、Onxol、Abraxane)、多西他赛 (Taxotere)、长春新碱 (Oncovin、Vincasar PFS)、长春花碱 (Velban)、依托泊苷 (Toposar、Etopophos、VePesid)、替尼泊苷 (Vumon)、伊沙匹隆 (Ixempra)、噻氨酯哒唑、埃博霉素、长春瑞滨 (Navelbine)、喜树碱 (CPT)、伊立替康 (Camptosar)、托泊替康 (Hycamtin)、安吖啶或片螺素 D(LAM-D)。

[0936] 示例性的 MTOR 抑制剂包括,但不限于依维莫司 (Afinitor) 或西罗莫司脂化物 (Torisel)、西罗莫司、药雷帕霉素或 AP23573。

[0937] 示例性的多激酶抑制剂包括,但不限于索拉菲尼 (Nexavar)、舒尼替尼 (Sutent)、BIBW2992、E7080、Zd6474、PKC-412、莫特塞尼或 AP24534。

[0938] 示例性的丝氨酸 / 苏氨酸激酶抑制剂包括,但不限于鲁伯斯塔、依立卢 / 盐酸法舒地尔、夫拉平度、Seliciclib(CYC202、Roscovitrine)、SNS-032(BMS-387032)、Pkc412、苔藓抑素、KAI-9803、SF1126、VX-680、Azd1152、Arry-142886(AZD-6244)、SCIO-469、GW681323、CC-401、CEP-1347 或 PD332991。

[0939] 示例性的酪氨酸激酶抑制剂包括,但不限于厄洛替尼(特罗凯)、吉非替尼(易瑞沙)、伊马替尼(格列卫)、索拉非尼(多吉美)、舒尼替尼(索坦)、曲妥珠单抗(赫赛汀)、贝伐单抗(阿瓦斯丁)、利妥昔单抗(Rituxan)、拉帕替尼(Tykerb)、西妥昔单抗(爱必妥)、帕尼单抗(维克替比)、依维莫司(癌伏妥)、阿仑单抗(坎帕斯)、吉妥单抗(米罗他)、西罗莫司脂化物(特癌适)、帕唑帕尼 (Votrient)、达沙替尼(Sprycel)、利妥昔单抗(Rituxan)、尼洛替尼(Tasigna)、瓦他拉尼(Ptk787、ZK222584)、CEP-701、SU5614、MLN518、XL999、VX-322、Azd0530、BMS-354825、SKI-606CP-690、AG-490、WHI-P154、WHI-P131、AC-220 或 AMG888。

[0940] 示例性的 VEGF/VEGFR 抑制剂包括,但不限于贝伐单抗(阿瓦斯丁)、索拉非尼(多吉美)、舒尼替尼(索坦)、兰尼单抗、哌加他尼钠或凡德替尼。

[0941] 示例性的微管靶向药物包括，但不限于紫杉醇、多西紫杉醇、长春新碱、长春碱、诺考达唑、埃坡霉素和长春瑞滨。

[0942] 示例性的拓扑异构酶毒物药物包括，但不限于替尼泊甙、依托泊苷、亚德里亚霉素、喜树碱、柔红霉素、更生霉素、米托蒽醌、安吖啶、表柔比星和伊达比星。

[0943] 示例性的紫杉烷类或紫杉烷衍生物包括，但不限于紫杉醇和多西紫杉醇。

[0944] 示例性的一般化疗药物、抗肿瘤剂、抗增殖剂包括，但不限于六甲蜜胺(Hexalen)、异维甲酸(Accutane、Amnesteem、Claravis、Sotret)、维甲酸(Vesanoid)、阿扎胞苷(Vidaza)、硼替佐米(万珂)、天冬酰胺酶(Elspar)、左旋咪唑(Ergamisol)、米托坦(Lysodren)、丙卡巴肼(Matulane)、培门冬酶(Oncaspar)、地尼白介素(Ontak)、卟吩姆钠(Photofrin)、阿地白介素(Proleukin)、来那度胺(Revlimid)、贝沙罗汀(Ergamisol、Targretin)、沙利度胺(Thalomid)、西罗莫司脂化物(特癌适)、三氧化二砷(Trisenox)、维替泊芬(Visudyne)、含羞草碱(Leucenol)(1M 替加氟 -0.4M 的 5- 氯 -2,4- 二羟基嘧啶 -1M 的氧嗪酸钾) 或洛伐他汀。

[0945] 在另一个方面中，第二化疗剂可以是细胞因子如 G-CSF (粒细胞集落刺激因子)。在另一个方面，本发明化合物或其药学上可接受的盐、前体药物、代谢物、类似物或衍生物都可以与放射疗法组合给药。放射治疗也可与本发明化合物和本文描述的作为多剂治疗的一部分的另一种化疗剂联合给药。在又一个方面中，本发明化合物或其药学上可接受的盐、前体药物、代谢物、类似物或衍生物可与标准联合化疗组合相结合给药，所述标准联合化疗组合例如为(但并不限于) CMF (环磷酰胺，甲氨喋呤和 5- 氟尿嘧啶)、CAF (环磷酰胺、阿霉素、5- 氟尿嘧啶)、AC (阿霉素和环磷酰胺)、FEC (5- 氟尿嘧啶、表柔比星和环磷酰胺)、ACT 或 ATC (阿霉素、环磷酰胺和紫杉醇)、利妥昔单抗、希罗达(卡培他滨)、顺铂(CDDP)、卡铂、TS-1 (替加氟、吉莫斯特和 otastat 钾的摩尔比为 1:0.4:1)、喜树 =11 (CPT-11、伊立替康或 Camptosar™)、CHOP (环磷酰胺、羟基柔红霉素、长春新碱和强的松或强的松龙)、R-CHOP (利妥昔单抗、环磷酰胺、羟基柔红霉素、长春新碱、强的松或强的松龙) 或 CMFP (环磷酰胺、氨甲喋呤、5- 氟尿嘧啶和强的松)。

[0946] 在优选的实施方案中，本发明化合物或其药学上可接受的盐、前体药物、代谢物、多晶型物或溶剂化物可以和酶的抑制剂(如受体或非受体激酶)一起给药。所述受体和非受体激酶例如是酪氨酸激酶和丝氨酸 / 苏氨酸激酶。所述激酶抑制剂是小分子、聚核酸、多肽或抗体。

[0947] 示例性的激酶抑制剂包括，但不限于贝伐珠单抗(靶向 VEGF)、BIBW2992 (靶向 EGFR 和 Erb2)、西妥昔单抗 / 爱必妥(靶向 Erb1)、伊马替尼 / 格列卫(靶向 Bcr-Abl)、曲妥珠单抗(靶向 Erb2)、吉非替尼 / 易瑞沙(靶向 EGFR)、兰尼单抗(靶向 VEGF)、哌加他尼钠(靶向 VEGF)、厄洛替尼 / 特罗凯(靶向 Erb1)、尼洛替尼(靶向 Bcr-Abl)、拉帕替尼(靶向 Erb1、Erb2/Her2)、GW-572016/ 二甲苯磺酸拉帕替尼(靶向 HER2/Erb2)、帕尼单抗 / 维克替比(靶向 EGFR)、凡德替尼(靶向 RET/VEGFR)、E7080 (多个靶标，包括 RET 和 VEGFR)、赫赛汀(靶向 HER2/Erb2)、PKI-166 (靶向 EGFR)、卡奈替尼 /CI-1033 (靶向 EGFR)、舒尼替尼 /SU-11464/ 索坦(靶向 EGFR 和 FLT3)、吗妥珠单抗 /Emd7200 (靶向 EGFR)、EKB-569 (靶向 EGFR)、Zd6474 (靶向 EGFR 和 VEGFR、PKC-412 (靶向 VEGR 和 FLT3)、瓦他拉尼 /Ptk787/ZK222584 (靶向 VEGR)、CEP-701 (靶向 FLT3)、SU5614 (靶向 FLT3)、MLN518 (靶向 FLT3)、XL999 (靶向 FLT3)、

VX-322（靶向 FLT3）、Azd0530（靶向 SRC）、BMS-354825（靶向 SRC）、SKI-606（靶向 SRC）、CP-690（靶向 JAK）、AG-490（靶向 JAK）、WHI-P154（靶向 JAK）、WHI-P131（靶向 JAK）、索拉非尼 / 多吉美（靶向 RAF 激酶、VEGFR-1、VEGFR-2、VEGFR-3、PDGFR-β、KIT、FLT-3 和 RET）、达沙替尼 /Sprycel（靶向 BCR/ABL 和 SRC）、AC-220（靶向 Flt3）、AC-480（靶向所有的 HER 蛋白质，“panHER”）、二磷酸莫特塞尼（靶向 VEGF1-3、PDGFR 和 c-kit）、狄诺塞麦（靶向 RANKL，抑制 SRC）、AMG888（靶向 HER3）、AP24534（多个靶标，包括 Flt3）。

[0948] 示例性的丝氨酸 / 苏氨酸激酶抑制剂包括，但不限于西罗莫司（靶向 mTOR/FRAP1）、雷帕霉素（靶向 mTOR）、Certican/ 依维莫司（靶向 mTOR/FRAP1）、AP23573（靶向 mTOR/FRAP1）、依立卢 / 盐酸法舒地尔（靶向 RHO）、夫拉平度（靶向 CDK）、Seliciclib/CYC202/Roscovitrine（靶向 CDK）、SNS-032/BMS-387032（靶向 CDK）、鲁伯斯塔（靶向 PKC）、Pkc412（靶向 PKC）、苔藓抑素（靶向 PKC）、KAI-9803（靶向 PKC）、SF1126（PI3K 的靶向）、VX-680（针对极光激酶）、Azd1152（靶向极光激酶）、Arry-142886/AZD-6244（靶向 MAP/MEK）、SCIO-469（靶向 MAP/MEK）、GW681323（靶向 MAP/MEK）、CC-401（靶向 JNK）、CEP-1347（靶向 JNK）、PD332991（靶向 CDK）。

[0949] EZH2 介导的蛋白甲基化参与的障碍是一种神经系统疾病。因此，本发明的化合物也可用于神经系统疾病的治疗或研究，如癫痫症、精神分裂症、双相情感障碍或其他心理和 / 或精神疾病、神经病、骨骼肌萎缩、神经退行性疾病（如神经变性疾病）。神经退行性疾病的例子包括：阿尔茨海默氏症、肌萎缩性脊髓侧索硬化症（ALS）和帕金森氏病。另一类的神经变性疾病包括至少部分地由聚集的聚谷氨酰胺引起的疾病。这类疾病包括：亨廷顿氏病、脊髓延髓肌肉萎缩（SBMA 或肯尼迪疾病）、齿状核红核苍白球路易体萎缩（DRPLA）、脊髓小脑性共济失调 1（SCA1）、脊髓小脑性共济失调 2（SCA2）、马查多 - 约瑟夫病（MJD、SCA3）、脊髓小脑性共济失调 6（SCA6）、脊髓小脑性共济失调 7（SCA7）、脊髓小脑性共济失调 12（SCA12）。

[0950] 其中 EZH2 基因介导的表观遗传甲基化起到了重要作用的任何其他疾病可以用本文所述的化合物和方法治疗或预防，或者可以用本文所述化合物研究这些疾病和其潜在的治疗方法。

[0951] 4. 药物组合物

[0952] 本发明还提供了药物组合物，所述组合物包括本文所述的任何结构式的化合物和至少一种药学上可接受的赋形剂或载体的组合。

[0953] “药物组合物”是以适于给药予受试者的形式含有本发明化合物的制剂。在一个实施方案中，药物组合物是散装的或单位剂型。所述单位剂型是多种形式中的任意一种，所述多种形式包括例如胶囊、IV 包、片、气雾剂吸入器上的单泵，或者瓶。单位剂量组合物中的活性成分（例如，所公开化合物或其盐、水合物、溶剂化物或异构体的制剂）的量是有效量，并且所述量是根据所涉及的具体治疗而改变。本领域技术人员会理解，有时必须根据患者的年龄和病况对剂量进行常规的改变。剂量还取决于给药途径。能够想到许多途径，包括口服、肺、直肠、肠胃外、透皮、皮下、静脉内、肌内、腹膜内、吸入、颊、舌下、胸膜内、囊内和鼻内等等。本发明化合物的局部或透皮给药剂型包括粉末、喷雾、膏剂、糊剂、乳膏剂、洗液、凝胶、溶液、贴剂和吸入剂。在一个实施方案中，将活性化合物在无菌条件下与药学上可接受的载体以及任何所需要的防腐剂、缓冲剂或者推进剂进行混合。

[0954] 本文使用的术语“药学上可接受的”是指那些化合物、阴离子、阳离子、材料、组合

物、载体和 / 或剂型在可靠的医学判断的范围之内适合用于接触人类和动物的组织，而没有过多的毒性、放射性、过敏性反应或其它问题或并发症，与合理的利益 / 风险比相称。

[0955] “药学上可接受的赋形剂”是指在制备药物组合物中有用的赋形剂，所述药物组合物通常是安全、无毒并且不具有生物学上或其他不良的特性，所述赋形剂包括在兽药和人类药物应用中可接受的赋形剂。在本说明书和权利要求书中所用的“药学上可接受的赋形剂”包括一个和多个此类赋形剂。

[0956] 本发明的药物组合物根据其拟定的给药途径配制。给药途径的例子包括肠胃外给药，例如静脉内、皮内、皮下、口服（例如，吸入）、透皮（局部）和粘膜给药。用于肠胃外、真皮内、皮下应用的溶液或悬浮液可以包括下列组分：无菌稀释剂，例如注射用水、生理盐水溶液、固定油，聚乙二醇、甘油、丙二醇或其它合成溶剂；抗菌剂，例如苄基醇或对羟苯甲酸甲酯；抗氧化剂，例如抗坏血酸或亚硫酸氢钠；螯合剂，例如乙二胺四乙酸；缓冲剂，例如乙酸盐、柠檬酸盐或磷酸盐以及渗透压调节剂，例如氯化钠或葡萄糖。pH 值可以用酸或碱（如盐酸或氢氧化钠）调节。肠道外制剂可封装在安瓿、玻璃或塑料制成的一次性注射器或多剂量小瓶中。

[0957] 本发明的化合物或药物组合物可以用于通过目前许多公知的用于化疗治疗的方法向受试者给药。例如，用于治疗癌症，本发明的化合物可被直接注射到肿瘤内、注射到血液或体腔中或口服或使用贴剂通过皮肤来应用。所选择的剂量应该是足以构成有效治疗，但也不能过高而导致不可接受的副作用。治疗期间和治疗后一段合理时间内最好应密切监测病人的疾病状态（如癌症、癌前期等）和健康状态。

[0958] 本文使用的术语“治疗有效量”是指用于治疗、减轻或预防可识别的疾病或病症或表现出可检测的治疗或抑制效果的药剂的量。所述效果可通过本领域中已知的任何测定方法检测。对于受试者的精确的有效量将取决于受试者的体重、身高和健康状况；病症的性质和程度；选择给药的治疗方法或共同疗法。给定的情况下的治疗有效量可以通过技术人员的常规实验和临床医师的判断确定。在一个优选的方面，待治疗的疾病或病症是癌症。在另一个方面，待治疗的疾病或病症是一种细胞增殖性障碍。

[0959] 任何化合物的治疗有效量可以在例如肿瘤细胞的细胞培养实验中或在动物模型（通常为大鼠、小鼠、兔、狗、猪）中初步估算。动物模型也可以用来确定合适的浓度范围和给药途径。然后，这些信息可以用来确定对人类给药的有用剂量和途径。治疗 / 预防的疗效和毒性可以通过细胞培养或实验动物中的标准药学步骤确定，例如，ED_{50}（在 50％的群体中的治疗有效剂量）和 LD_{50}（50％的群体中的致死剂量）来确定。毒性和治疗效果之间的剂量比是治疗指数，其可以表示为 LD_{50}/ED_{50} 的比率。表现出大的治疗指数的药物组合物是首选。根据所采用的剂型、患者的敏感性和给药途径，剂量可在此范围内变化。

[0960] 调整剂量和给药方式以提供足够的活性剂水平或维持所需的效果。需要考虑的因素包括疾病状态的严重程度、患者的综合健康状况、年龄、体重和受试者的性别、饮食、给药时间和频率、药物组合、反应灵敏度和对治疗的耐受 / 响应。长效药物组合物可以每 3 到 4 天、每星期或每两周给药一次，这取决于特定药物的半衰期和清除率。

[0961] 含有本发明的活性化合物的药物组合物通常可按现有技术公知的方式制备，例如，通过常规的混合、溶解、制粒、制糖衣丸、磨细、乳化、封装、包埋或冻干来制备。药物组合物可以以使用一种或多种生理学可接受的载体的常规方式来进行制备，所述载体包含便于

将所述活性化合物加工成可药用的制剂的赋形剂和 / 或助剂。当然，适合的制剂取决于所选择的给药途径。

[0962] 适于注射用的药物组合物包括无菌水溶液（水溶性的）或用于临时配制无菌注射溶液或分散体的分散体和无菌粉末。对于静脉内给药，合适的载体包括生理盐水、抑菌水、聚氧乙烯蓖麻油（巴斯夫，帕西帕尼，新泽西）或磷酸盐缓冲盐水（PBS）。在所有情况下，所述药物组合物必须是无菌的并且应该是存在易注射性能的可流动程度。所述药物组合物在制造和贮存条件下必须是稳定的，并且必须防止微生物（如细菌和真菌）的污染作用。载体可以是溶剂或分散介质，例如包括水、乙醇、多元醇（例如，甘油、丙二醇、液体聚乙二醇等）或其合适的混合物。适当流动性可例如通过使用诸如卵磷脂的涂层，通过在分散体的情况下维持所需颗粒大小以及通过使用表面活性剂来保持。对微生物作用的预防可以通过各种抗菌剂和抗真菌剂，例如对羟基苯甲酸酯类、氯丁醇、苯酚、抗坏血酸、硫柳汞等来实现。在许多情况下，组合物中优选包括等渗剂，例如糖、多元醇（如甘露醇、山梨糖醇）和氯化钠。可以通过在组合物中包括可延迟吸收的试剂（例如，单硬脂酸铝和明胶）来延长可注射组合物的吸收。

[0963] 可通过在合适的溶剂中加入需要量的活性化合物以及根据需要加入上述列举的成分中的一种或其组合，随后过滤灭菌来制备无菌注射液。一般情况下，通过将活性化合物加入到无菌载体中制备分散剂，所述无菌载体包含基本的分散介质和所需的选自上述所列举成分的成分。用于制备无菌注射溶液的无菌粉末的制备方法是真空干燥和冷冻干燥，所述方法得到的是含活性成分和来自于其先前无菌过滤的溶液中的任何额外所需成分的粉末。

[0964] 口服组合物一般包括惰性稀释剂或可食用的药学上可接受的载体。它们可以被封装在明胶胶囊中或压成片剂。为口服治疗给药，活性化合物可加入赋形剂中，并以片剂、锭剂或胶囊形式使用。还可以使用液态载体制备用作漱口药的口服组合物，其中在液态载体中的化合物口用嗽口，然后吐出或吞咽。可包含药学上相容的结合剂和 / 或佐剂材料作为所述组合物的一部分。片剂，丸剂，胶囊，锭剂等可以包含任何以下成分或类似性质的化合物 :结合剂（如微晶纤维素，西黄蓍胶或明胶）、赋形剂（如淀粉或乳糖）、崩解剂（如藻酸、Primogel 或玉米淀粉）、润滑剂（如硬脂酸镁或 Sterotes）、助流剂（如胶态二氧化硅）、甜味剂（如蔗糖或糖精）或调味剂（如薄荷、水杨酸甲酯或橙味剂）。

[0965] 对于用吸入法给药，化合物通过来自于加压容器或分配器中的气溶胶喷雾剂的形式来传递，其中包含适宜的推进剂，例如气体（如二氧化碳）或雾化剂。

[0966] 也可以通过粘膜或透皮手段进行全身给药。对于经粘膜或透皮给药，在制剂中使用适于用来渗入屏障的渗透剂。这样的渗透剂通常是本领域已知的，并例如对于粘膜给药，包括清洁剂、胆盐和夫西地酸衍生物。粘膜给药可以通过使用喷鼻剂或栓剂实现。对于透皮给药，将活性化合物配制成在本领域中通常已知的软膏、油膏、凝胶或霜剂。

[0967] 活性化合物可以与药学上可接受的载体一起制备，所述载体将保护化合物避免其在体内快速消除，例如控释制剂，包括植入物和微胶囊化的运输系统。可以使用可生物降解的、生物可相容的聚合物，如乙烯乙酸乙烯酯、聚酐、聚乙醇酸、胶原、聚原酸酯和聚乳酸。对于本领域技术人员来说，制备这些制剂的方法是公知的。所用材料也可以通过商购从阿尔扎公司和 Nova Pharmaceuticals 公司获得。脂质体悬浮液（包括靶向感染细胞对病毒抗原

单克隆抗体的脂质体）也可以用作药学上可接受的载体。这些都可以根据本领域技术人员已知的方法制备，例如专利号为 4522811 的美国专利中公开的方法。

[0968] 配制为了便于给药和剂量均匀的单位剂量形式的口服或肠胃外的组合物尤其有利。本文所用的单位剂量形式指适合作为接受治疗的患者的单一剂量的物理分散单位，每一单位含有经计算的与所需药物载体联合能产生所需治疗效果的预定量的活性化合物。本发明的单位剂型的规格取决并直接依赖于活性化合物的独特特征及所要达到的特定的治疗效果。

[0969] 在治疗上的应用中，根据本发明使用的药物组合物的剂量根据药剂、年龄、体重和接受治疗的病人的临床状况、实施该治疗的临床医生或从业人员的经验和判断而不同，还有其他因素会影响选定的剂量。通常，所述剂量应足以导致肿瘤的生长的减慢，优选消退，并优选导致癌症的完全消退。剂量范围可以从每天每千克体重约 0.01 毫克到每天每千克体重约 5000 毫克。在优选的方面中，剂量范围可以从每天每千克体重约 1 毫克到每天每千克体重约 1000 毫克。在一个方面，本发明的剂量将在约 0.1 毫克 / 天到约 50 克 / 天、约 0.1 毫克 / 天至约 25 克 / 天、约 0.1 毫克 / 天至约 10 克 / 天、约 0.1 毫克 / 天至约 3 克 / 天、约 0.1 毫克 / 天至约 1 克 / 天的范围内，以单一的、分开的或连续的剂量（剂量根据病人的体重（千克）、身体表面面积（平方米）和年龄调整）方式给药。药剂的有效量是指提供了被临床医生或其他有资格的观察者注意到的客观的可辨认的改善。例如，在患者体内的肿瘤消退可以参考肿瘤直径来测量。一个肿瘤的直径减小表示消退。消退也表明了治疗停止后肿瘤复发的失败。本文所使用的术语“剂量有效方式”是指活性化合物在患者或细胞中产生所需的生物效应的量。

[0970] 药物组合物可以同给药说明书一起包含在容器、包装或分配器中。

[0971] 本发明的化合物能够进一步形成盐。所有这些形式均考虑在所述要求保护的发明范围内。

[0972] 本文使用的“药学上可接受的盐”是指本发明化合物的衍生物，其中母体化合物通过制造其酸或碱的盐而被修饰。药学上可接受的盐的例子包括，但不限于碱性残基（如胺）的无机酸盐或有机酸盐、酸性残基（如羧酸）的碱金属盐或有机盐，等等。所述药学上可接受的盐包括例如由无毒的无机酸或有机酸形成的常规的无毒性的盐或母体化合物形成的季铵盐。例如，所述常规的无毒性的盐包括，但不限于那些衍生自无机酸或有机酸的盐，所述无机酸或有机酸选自 2- 乙酰氧基苯甲酸、2- 羟基乙磺酸、乙酸、抗坏血酸、苯磺酸、苯甲酸、碳酸氢根、碳酸、柠檬酸、依地酸、乙烷二磺酸、1,2- 乙烷磺酸、富马酸、葡庚糖酸、葡糖酸、谷氨酸、乙醇酸、乙醇酰对氨苯基砷酸（glycollyarsanilic）、己基间苯二酚酸（hexylresorcinic）、海巴明（hydrabamic）、氢溴酸、盐酸、氢碘酸、羟基马来酸、羟基萘甲酸、羟乙磺酸、乳酸、乳糖酸、月桂基磺酸、马来酸、苹果酸、扁桃酸、甲磺酸、萘磺酸（napsylic）、硝酸、草酸、双羟萘酸、泛酸、苯乙酸、磷酸、多聚半乳糖醛酸、丙酸、水杨酸、硬脂酸、碱式乙酸（subacetic）、琥珀酸、氨基磺酸、磺胺酸、硫酸、单宁酸、酒石酸、甲苯磺酸，以及常用的氨基酸，例如甘氨酸、丙氨酸、苯丙氨酸、精氨酸等。

[0973] 药学上可接受的盐的其他例子包括己酸、环戊烷丙酸、丙酮酸、丙二酸、3-(4- 羟基苯甲酰基）苯甲酸、肉桂酸、4- 氯苯磺酸、2- 萘磺酸、4- 甲苯磺酸、樟脑磺酸、4- 甲基双环 -[2.2.2]- 辛 -2- 烯 -1- 羧酸、3- 苯基丙酸、三甲基乙酸、叔丁基乙酸、粘康酸等。本发

明还包括当母体化合物中存在的酸性质子被金属离子(例如碱金属离子、碱土金属离子或铝离子)取代时形成的盐;或当母体化合物与有机碱配合时形成的盐,所述有机碱例如为乙醇胺、二乙醇胺、三乙醇胺、氨丁三醇、N- 甲基葡糖胺等。在盐的形式中,可以理解的是化合物对该盐的阳离子或阴离子的比例可为 1 :1,或 1 :1 以外的任意的比例,例如,3 :1、2 :1、1 :2 或 1 :3。

[0974] 应当理解的是,所有引用的药学上可接受的盐包括相同的盐的如本文所定义的溶剂加成形式(溶剂化物)或晶体形式(多晶型物)。

[0975] 本发明的化合物也可以以酯的形式来制备,例如药学上可接受的酯。例如,化合物的羧酸官能团可以被转换成其相应的酯,例如甲酯、乙酯或其它酯。此外,化合物中的醇羟基可以被转换成其相应的酯,例如乙酸酯、丙酸酯或其它酯。

[0976] 本发明的化合物也可以以前药的形式来制备,例如药学上可接受的前体药物。术语“前体药物”和“前药”本文中可互换使用,是指在体内释放活性母体药物的任何化合物。由于已知前药可以提高药品的许多可取的品质(例如,溶解度、生物利用度、制造等),所以本发明的化合物可以前药的形式来输送。因此,本发明意在覆盖本发明要求保护的化合物的前药、其输送方法以及包含它们的组合物。“前药”意在包括任何共价键合的载体,当所述前药给药于受试者时所述载体在体内释放本发明中的活性母体药物。本发明中的前药通过对化合物中存在的官能团进行修饰的方式来制备,所述修饰在常规操作中或在体内裂解为母体化合物。前药包括本发明的化合物,其中,羟基、氨基、巯基、羧基或羰基键连到可在体内裂解分别形成游离羟基、游离氨基、游离巯基、游离羧基或游离羰基的任何基团。

[0977] 前药的例子包括,但不限于本发明化合物中的羟基官能团的酯(例如,乙酸酯、二烷基氨基乙酸酯、甲酸酯、磷酸酯、硫酸酯和苯甲酸酯衍生物)和氨基甲酸酯类(例如,N,N- 二甲基氨基羰基),羧基官能团的酯(如乙酯、吗啉乙醇酯),N- 酰基衍生物(例如,N- 乙酰基),氨基官能团的 N- 曼尼希碱、席夫碱和烯胺酮,酮和醛官能团的肟类、缩醛、缩酮和烯醇酯等等(参阅 Bundegaard,H.,Design of Prodrugs,p1-92,Elesevier,New York-Oxford(1985))。

[0978] 所述化合物或其药学上可接受的盐、酯或前药经口服、鼻内、经皮、肺、吸入、颊、舌下、腹膜内、皮下、肌肉、静脉、直肠、胸腔内、鞘内和肠道外给药。在一个实施方案中,所述化合物经口服给药。本领域技术人员将认识到某些给药途径的优点。

[0979] 利用所述化合物的给药方案根据多种因素选择,包括患者的品种、物种、年龄、体重、性别和病情;需治疗的疾病的严重程度;给药途径;病人的肾肝功能,以及使用的具体化合物或其盐。本领域普通技术的医生或兽医可以很容易地确定和规定所需药物的有效量来防止、对抗或阻止病情的发展。

[0980] 本发明公开的化合物的制剂和给药技术可以参阅 Remington:the Science and Practice of Pharmacy,19th edition,Mack Publishing Co.,Easton,PA(1995)。在一个实施方案中,本文所描述的化合物和其药学上可接受的盐与其药学上可接受的载体或稀释剂结合用于制备药物。合适的药学上可接受的载体包括惰性固体填充剂或稀释剂、无菌水溶液或有机溶液。所述化合物将以足以提供本文描述范围内的所需剂量存在于所述药物组合物中。

[0981] 除非另有说明,否则本文所使用的百分比和比率均以重量计。本发明的其它特征

和优点在不同的实施例中变得显而易见。所提供的实施例说明可用于实施本发明的不同的组分和方法。这些实施例并不限制所要求保护的发明。基于本发明的公开内容，本领域技术人员可以识别和采用可用于实施本发明的其他组分和方法。

[0982] 本文描述的合成反应方案中，为简单起见化合物可以用一个特定的构型来绘制。所述特定的构型不被解释为将本发明限制为一种或另一种异构体、互变异构体、结构异构体或立体异构体的，其也不排除异构体、互变异构体、结构异构体或立体异构体的混合物，但是，应理解，一个给定的异构体、互变异构体、结构异构体或立体异构体比另一种异构体、互变异构体、结构异构体或立体异构体可能具有较高的活性水平。

[0983] 通过上述方法进行设计、选择和 / 或优化的化合物，一旦产生，其特征可以采用本领域技术人员已知的多种试验来表征，以确定该化合物是否具有生物活性。例如，分子可以通过常规的试验来表征，以确定它们是否具有预测的活性、结合活性和 / 或结合特异性，所述试验包括，但不限于下文描述的试验。

[0984] 此外，高通量筛选可以用于加快使用所述检测的分析。因此，通过使用在本领域中已知的技术迅速地筛选本文所描述的分子的活性成为可能。高通量筛选的一般方法的描述可参阅例如 Devlin(1998)High Throughput Screening, Marcel Dekker 和专利号为 5763263 的美国专利。高通量检测方法可以使用一个或多个不同的检测技术，包括但不限于下文描述的那些技术。

[0985] 本文所引用的所有出版物和专利文件通过引用结合到本文中，每一个出版物和专利文件是专门地、单独地被引入本文作为参考。对出版物和专利文件的引用并非承认其是本发明任何有关的现有技术，也非承认其与本发明的内容或日期相同。本发明已经通过书面描述的方式进行描述，本技术领域的技术人员将认识到，本发明可以在各种实施方案中实行，前面的描述和下面的实施例是为了说明而不是限制后面的权利要求。

[0986] 实施例

[0987] 通用实验

[0988] NMR

[0989] 除非另有声明，否则使用 $CDCl_3$ 来取得 ^{1}H-NMR（核磁共振）波谱，并用瓦里安（Varian）或牛津仪器（Oxford instruments）磁体（500MHz）仪器在 400 或 500MHz 下记载。所指的多重性是 s 为单峰，d 为双重峰，t 为三重峰，q 为四重峰，quint 为五重峰，sxt 为六重峰，m 为多重峰，dd 为双二重峰，dt 为双三重峰 ；br 表示宽单峰信号。

[0990] LCMS 和 HPLC

[0991] 岛津（Shimadzu）LC-Q、岛津 LCMS-2010EV 或 Waters Acquity 超高效液相色谱。HPCL ：通过岛津 SPD-20A，用 150×4.5mm YMC ODS-M80 柱或 150×4.6mm YMC-Pack Pro C18 柱，以 1.0ml/min 分析产品。

[0992] 流动相是 MeCN ：H_2O=3 ：2（包含 0.3%SDS 和 0.05%H_3PO_4）。

[0993] 0.05%TFA 的水溶液，0.05%TFA 的乙腈溶液（初始梯度为 20%，然后在三分钟内 0.05%TFA/MeCN 达到浓度为 95%，保持 0.5 分钟，在 3.51 到 4.50 分钟然后 0.05%TFA/MeCN 浓度为 20%）。

[0994] 可选地，液相色谱质谱联用法（LCMS）使用了两种不同方法 ：最常用的一种是高 pH 法（METCR1600），另一种用于更加标准的化合物（METCR1416）。

[0995] 0.1% 甲酸水溶液 - 流动相“A”0.1% 甲酸乙腈溶液 - 流动相“B”利用了 Waters Atlantis dC18,2.1mm×100mm,3μm 柱,流速 =0.6ml/min,柱温 =40℃ ;时间(分钟)%B0.00 分钟 5%B。5.0 分钟 100%B,5.4 分钟 100%B 和 0.42 分钟 5%B。

[0996] 3.5 分钟方法是指 Atlantis dC18,2.1mm×50mm,3μm 柱,在 40℃下流速为 1ml/min。流动相 A0.1% 甲酸(aq),流动相 B0.1% 甲酸(MeCN),进样 3μL,梯度 0 分钟(5% 有机的),2.5 分钟(100% 有机的),2.7 分钟(100% 有机的),2.71 分钟(5% 有机的),3.5 分钟(5% 有机的)。

[0997] 7.0 分钟方法是指 Atlantis dC18,2.1mm×100mm,3μm 柱,在 40℃下流速为 0.6ml/min。流动相 A0.1% 甲酸(aq),流动相 B0.1% 甲酸(MeCN),进样 3μL,梯度 0 分钟(5% 有机的),5 分钟(100% 有机的),5.4 分钟(100% 有机的),5.42 分钟(5% 有机的),7 分钟(5% 有机的)。

[0998] 3.5 分钟方法和 7 分钟方法都在 MS18 岛津 LCMS-2010EV 或 MS19 岛津 LCMS-2010EV 系统上实行,它们利用 LC-20AB 泵和 SPD-M20A PDA 检测器。

[0999] 使用带有 3100 质量检测器的 Waters 自动纯化系统通过 HPLC/MS 来纯化产物。

[1000] 还可在岛津 LC-2010CHT 上进行 HPLC 分析,其在室温下使用 YMC ODS-A,C18,(150×4.6×5μm)柱,流速为 1.4ml/min。使用 10μl 的进样量,通过 UV/PDA 来检测。流动相 A 是 0.05%TFA 的水溶液,流动相 B 是 0.05%TFA 的乙腈溶液,初始梯度程序为 8 分钟内 5%B-95%B,保持 1.5 分钟,在 9.51-12 分钟 B 浓度为 0.5%。稀释液是流动相。

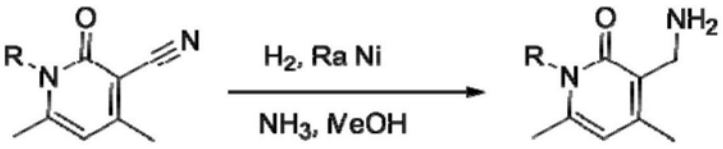
[1001] 其他

[1002] 在 Biotage Isolera(第四代)上施行自动快速柱层析。10g SNAP 柱,流速为 12ml/min,或 25g SNAP 柱,流速为 25ml/min,在 254nm 和 280nm 检测。

[1003] 根据在实验步骤中描述的条件可在 ThalesNano H-Cube® 上施行选择腈还原反应。

[1004] 用于吡啶酮胺合成的一般步骤

[1005]



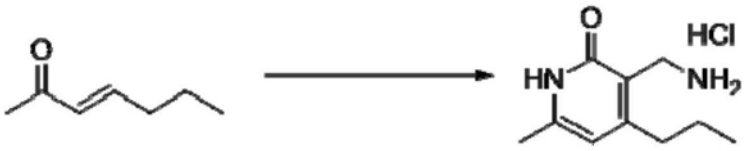
R= e.g. -CH_2Ph, -CH_2CH_2OH, CH_2CH_2OMe

[1006] 向氰基化合物(1eq.)的 MeOH 溶液中加入催化量的雷尼镍(Raney Nickel)和氨溶液。混合物在室温和氢气(气球压力)下搅拌 1 小时。反应完成时,通过硅藻土床过滤混合物,用 MeOH 洗涤。滤液在减压下浓缩,以得到所要的胺。此步骤可用于在实施例中描述的多种 R 基团。通常,氰基吡啶可从市场上的供应商处购得,或者可通过本领域一般技术人员所知的方法合成。

[1007] 起始原料或中间体的合成

[1008] 3- 氨甲基 -6- 甲基 -4- 丙基 -1,2- 二氢吡啶 -2- 酮 HCl 盐

[1009]

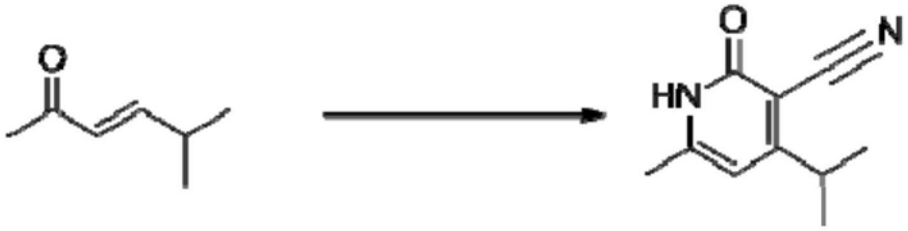


[1010] 向 t-BuOK（20.0g，179mmol）和氰基乙酰胺（16.5g，196mmol）的 DMSO（300mL）搅拌溶液中加入 (3E)-3- 庚烯 -2- 酮（20.0g，178mmol）。反应混合物在 23℃下搅拌 30 分钟，然后向反应混合物中加入额外的 t-BuOK（60.0g，712mmol）。反应混合物放置在氧气气氛下，搅拌 16 小时。然后用氩气净化反应混合物，冷却至 0℃。混合物用 HCl 水溶液稀释，收集产生的沉淀物。用水洗涤固体并干燥，以得到 6- 甲基 -2- 氧代 -4- 丙基 -1,2- 二氢吡啶 -3- 甲腈（15.0g，产率为 47%）。

[1011] 向 6- 甲基 -2- 氧代 -4- 丙基 -1,2- 二氢吡啶 -3- 甲腈（15.0g，85.1mmol）的甲醇（600ml）和浓盐酸（15ml）搅拌溶液中加入 $Pd(OH)_2$（15.0g）。混合物在 H_2 气氛下搅拌 48 小时。过滤反应混合物，在真空中浓缩滤液。向残余物中加入乙醇，收集沉淀物并干燥，以得到标题化合物（13.0g，产率为 60%），其为白色固体。^{1}H-NMR(400MHz,$CDCl_3$) δ ppm;11.86(br.s.,1H),6.00(s,1H),3.78(q,J=5.5Hz,2H),3.61(br.s.,2H),2.46(m,2H),2.17(s,3H),1.50(sxt,J=7.4Hz,2H),0.91(t,J=7.4Hz,3H)。

[1012] 6- 甲基 -2- 氧代 -4-（丙烷 -2- 基）-1,2- 二氢吡啶 -3- 甲腈

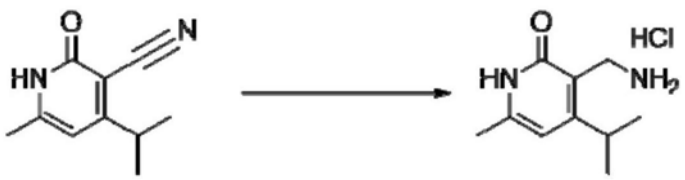
[1013]



[1014] 在 N_2 气氛下，向 2- 氰基乙酰胺（35.1g，417mmol）和 t-BuOK（42.5g，379mmol）的 DMSO（631ml）溶液中加入 5- 甲基 -3- 己烯 -2- 酮（50.0ml，379mmol）。在 23℃下搅拌混合物 30 分钟，然后加入额外的 t-BuOK（127g，1137mmol）。用 O_2 气体置换 N_2 气体，在 23℃和氧气下搅拌混合物 45 小时。将混合物冷却至 0℃，用 H_2O（200ml）和 HCl（5N，227ml，缓慢加入）稀释。在 0℃下搅拌混合物 15 分钟，用布氏漏斗过滤固体。固体用 H_2O（1500ml）洗涤，用热风（55℃，16h）干燥，以得到 6- 甲基 -2- 氧代 -4-（丙烷 -2- 基）-1,2- 二氢吡啶 -3- 甲腈（26.6g，产率为 40%）。^{1}H NMR(400MHz,$CDCl_3$)：δ 6.14ppm(s,1H),3.25-3.29(m,1H),2.45(s,3H),1.26(d,J=6.8Hz,6H);LC-MS:m/z177.1[M+1],198.9[M+23]。

[1015] 3-（氨甲基）-6- 甲基 -4-（丙烷 -2- 基）-1,2- 二氢吡啶 -2- 酮 HCl 盐

[1016]



[1017] 在 N_2 气氛下，向 6- 甲基 -2- 氧代 -4-（丙烷 -2- 基）-1,2- 二氢吡啶 -3- 甲腈（5.00g，28.4mmol）的 MeOH（400ml）和 HCl（8.8ml，12M）溶液中加入 10%$Pd(OH)_2$（5.17g，3.68mmol）。用 H_2 气体置换 N_2 气体，在 23℃和氢气下搅拌混合物 24 小时。用 N_2 气体置换 H_2 气

体，将混合物通过硅藻土过滤，用 MeOH 洗涤并浓缩。将残余物和 EtOH-TBME 一起磨碎，用布氏漏斗收集固体并真空干燥，以得到标题化合物（6.15g，100%）。^{1}H-NMR（400MHz，DMSO-d_6）：δ ppm11.9(br-s,1H),8.03(br-s,2H),6.12(s,1H),3.82-3.84(m,2H),3.08-3.12(m,1H),2.19(s,3H),1.12(d,J=6.8Hz,6H)。

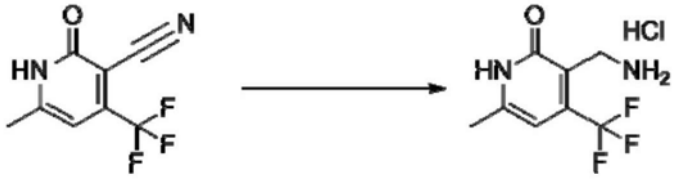
[1018] 6- 甲基 -2- 氧代 -4-（三氟甲基）-1,2- 二氢吡啶 -3- 甲腈

[1019]

[1020] 向 2- 氰基乙酰胺（14.0g，166mmol）和三氟乙酰丙酮（20.0ml，166mmol）的 H_2O（332ml）溶液中加入 K_2CO_3（6.60g，47.9mmol）。在 23℃搅拌混合物 15 小时。用布氏漏斗过滤沉淀的固体，用冰冷 H_2O 洗涤，用热风（60℃，16h）干燥，以得到标题化合物（17.6g，52%）。H NMR(400MHz,DMSO-d_6)：δ ppm2.38(s,3H),6.66(s,1H)。

[1021] 3-（氨甲基）-6- 甲基 -4-（三氟甲基）-1,2- 二氢吡啶 -2- 酮 HCl 盐

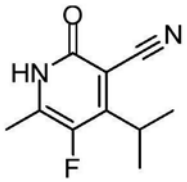
[1022]



[1023] 在 N_2 气氛下，向 6- 甲基 -2- 氧代 -4-（三氟甲基）-1,2- 二氢吡啶 -3- 甲腈（400mg，1.98mmol）的 MeOH（19.8ml）和 HCl（436μl，12M）溶液中加入 10%Pd(OH)$_2$（361g，0.257mmol）。用 H_2 气体置换 N_2 气体，在 23℃和氢气条件下搅拌混合物 18 小时。用 N_2 气体置换 H_2 气体。用硅藻土过滤混合物，用 MeOH 洗涤并浓缩。将残余物在 MeOH-Et_2O 中磨碎，用布氏漏斗收集，在真空中干燥，以得到标题化合物（433mg，100%）。^{1}H NMR(400MHz,DMSO-d_6)：δ ppm2.31(s,3H),3.88(s,2H),6.43(s,1H)。

[1024] 5- 氟 -4- 异丙基 -6- 甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 甲腈

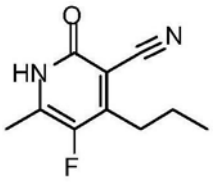
[1025]



[1026] 向 6- 甲基 -2- 氧代 -4-（丙烷 -2- 基）-1,2- 二氢吡啶 -3- 甲腈（225mg，1.277mmol）的 MeCN（6ml）搅拌溶液中加入 Selectfluor 氟试剂（620mg，1.75mmol）。反应混合物在 50℃搅拌 3 小时。冷却至 23℃后，将反应混合物在真空中浓缩。用柱层析（50% 到 100%EtOAc- 庚烷）纯化残余物，以得到标题化合物（90mg，36%）。^{1}H NMR(400MHz,$CDCl_3$) δ ppm3.39(m,1H),2.44(d,J=3.1Hz,3H),1.41(dd,J=7.0,3.1Hz,6H);LCMS E-S(M+H)=195.2。

[1027] 5- 氟 -6- 甲基 -2- 氧代 -4- 丙基 -1,2- 二氢吡啶 -3- 甲腈

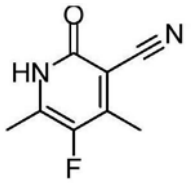
[1028]



[1029] 用与为 5- 氟 -4- 异丙基 -6- 甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 甲腈(20% 产率)描述的相同的方式来制备标题化合物。^{1}H NMR(400MHz,$CDCl_3$) δ ppm2.80(dt,J=7.9,1.9Hz2H),2.31(d,J=2.1Hz,3H),1.73(tq,J=7.4,7.4Hz,2H),1.06(t,J=7.3Hz,3H);LCMS E-S(M+H)=195.2。

[1030] 5- 氟 -4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 甲腈

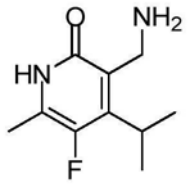
[1031]



[1032] 用与为 5- 氟 -4- 异丙基 -6- 甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 甲腈(15% 产率)描述的相同的方式来制备标题化合物。^{1}H NMR(400MHz,$CDCl_3$) δ ppm2.46(d,J=3.1Hz,3H),2.44(d,J=7.4,3.1Hz,3H);LCMS E-S(M+H)=167.2。

[1033] 3-(氨甲基)-5- 氟 -4- 异丙基 -6- 甲基吡啶 -2(1H)- 酮

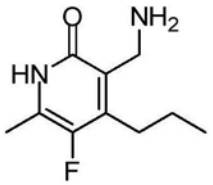
[1034]



[1035] 将 100mL 烧瓶中的 5- 氟 -4- 异丙基 -6- 甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 甲腈(100mg,0.515mmol)溶解于 MeOH (6mL)和 2mL 氨水(2mL,25%)的混合物中。在室温下使用 H-Cube 以 Raney-Ni 作为催化剂实施还原反应 3-4 小时。反应结束时(通过 TLC 监控),在减压条件下浓缩反应物,以得到作为灰色固体的标题化合物(90mg,90%)。1H NMR(400MHz,CD_3OD) δ ppm4.04(s,2H),3.22 (m,1H),2.24(d,J=3.4Hz,3H),1.32 (dd,J=7.0,1.8Hz,6H);LCMS E-S(M+H)=199.2。

[1036] 3-(氨甲基)-5- 氟 -6- 甲基 -4- 丙基吡啶 -2(1H)- 酮

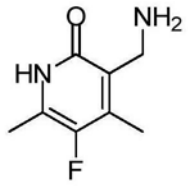
[1037]



[1038] 用与为 3-(氨甲基)-5- 氟 -4- 异丙基 -6- 甲基吡啶 -2(1H)- 酮(92% 产率)描述的相同的方式来制备标题化合物。1H NMR(400MHz,$CDCl_3$) δ ppm3.76(s,2H),2.61(dt,J=7.2,1.8Hz,2H),2.31 (d,J=2.8Hz,3H),1.57 (tq,J=7.6,7.6Hz,2H),1.00 (t,J=7.3Hz,3H);LCMS E-S(M+H)=199.2。

[1039] 3-(氨甲基)-5-氟-4,6-二甲基吡啶-2(1H)-酮

[1040]



[1041] 用与对3-(氨甲基)-5-氟-4-异丙基-6-甲基吡啶-2(1H)-酮(92%产率)描述的相同的方式来制备标题化合物。1H NMR(400MHz,$CDCl_3$) δ ppm3.79(s,2H),2.29(d,J=3.3Hz,3H),2.24 (d,J=2.1Hz,3H);LCMS E-S(M+H)=171.2。

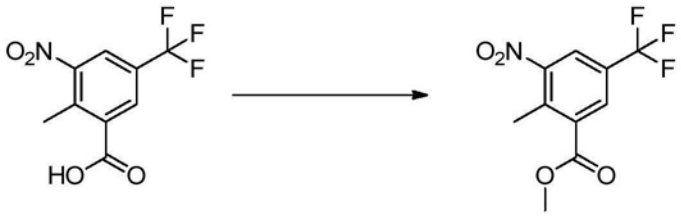
[1042] 2-甲基-3-硝基-5-(三氟甲基)苯甲酸

[1043]

[1044] 在0℃下,向2-甲基-5-(三氟甲基)苯甲酸(2.00g,9.80mmol)的H_2SO_4 (20mL,12N)搅拌溶液中加入HNO_3(2mL,12N)。搅拌3小时后,加入水,收集得到的沉淀。用水洗涤固体并干燥,以得到作为白色固体的标题化合物(1.90g,76%产率)。^{1}H NMR(400MHz,$CDCl_3$) δ ppm;8.43(s,1H),8.15(s,1H),2.77 (s,3H);MS (ES)[M-H]247.8。

[1045] 2-甲基-3-硝基-5-(三氟甲基)苯甲酸甲酯

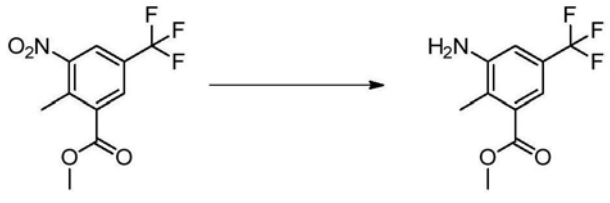
[1046]



[1047] 向2-甲基-3-硝基-5-(三氟甲基)甲苯酸(21.0g,84.3mmol)的DMF (200mL)溶液中加入碳酸钾(35.0g,253mmol)和碘甲烷(24.0g,169mmol)。在60℃下搅拌化合物,搅拌6小时后将混合物冷却至23℃并过滤。在真空中浓缩滤液,将残余物溶解在EtOAc和水中。用EtOAc (2×250mL)萃取水相,并在真空中浓缩合并的有机层。通过柱层析(SiO_2庚烷-EtOAc=4/1)纯化残余物,以得到标题化合物(20.0g,90%产率)。1H NMR(400MHz,$CDCl_3$) δ (ppm);8.27(s,1H),8.11 (s,1H),3.99 (s,3H),2.71 (s,3H);MS (ES)[M-H]261.9。

[1048] 3-氨基-2-甲基-5-(三氟甲基)苯甲酸甲酯

[1049]

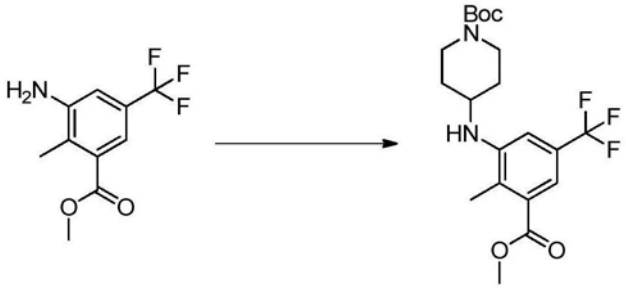


[1050] 向2-甲基-3-硝基-5-(三氟甲基)苯甲酸甲酯(20.0g,76.0mmol)的MeOH

(400ml)搅拌溶液中加入 $Pd(OH)_2$(2.00g)。反应混合物在氢气气氛下搅拌 3 小时。用氮气净化后,过滤混合物,在真空中浓缩滤液,以得到作为橙色固体的标题化合物(10.2g,58%产率)。1H-NMR(400MHz,$CDCl_3$) δ ppm ;7.47(brs,1H),7.01 (d,J=2.0Hz,1H),3.92 (m,2H),3.91 (s,3H),2.39 (s,3H)。

[1051] 4-{[3-(甲氧基羰基)-2- 甲基 -5-(三氟甲基)苯基]氨基}哌啶 -1- 羧酸叔丁酯

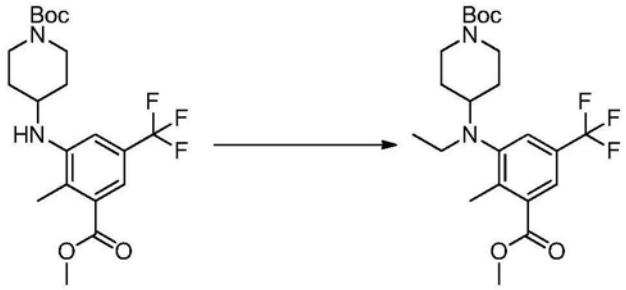
[1052]



[1053] 对 CH_2Cl_2 (120mL)和 AcOH (6mL)中的 3- 氨基 -2- 甲基 -5-(三氟甲基)苯甲酸甲酯(6.00g,25.7mmol)的搅拌溶液中加入 N-Boc 哌啶酮(6.70g,33.4mmol)和三乙酰氧基硼氢化钠(13.6g,64.3mmol)。在 23℃下搅拌反应混合物 20 小时。加入饱和 $NaHCO_3$,分离混合物。用 CH_2Cl_2 (3×50mL)萃取水层,在真空中浓缩合并的有机层。用硅胶柱层析(SiO_2 庚烷 /EtOAc=4/1)纯化残余物,以得到标题化合物(10.6g,98% 产率)。^{1}H-NMR(400MHz,$CDCl_3$) δ ppm;7.37(s,1H),6.88 (s,1H),4.05 (m,2H),3.90 (s,3H),3.01 (m,3H),2.32 (s,3H),1.71 (m,2H),1.48-1.61 (m,2H),1.45 (s,9H);MS (ES)[M-H]415.1。

[1054] 4-{乙基[3-(甲氧基羰基)-2- 甲基 -5-(三氟甲基)苯基]氨基}哌啶 -1- 羧酸叔丁酯

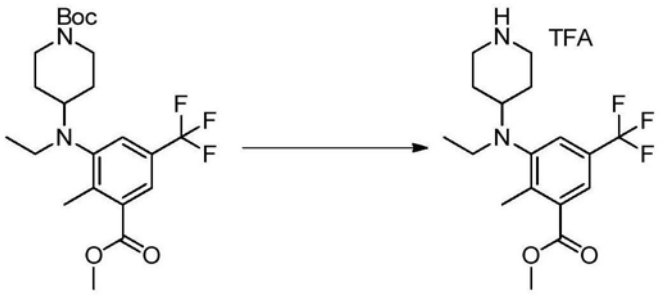
[1055]



[1056] 向 4-{[3-(甲氧基羰基)-2- 甲基 -5-(三氟甲基)苯基]氨基}哌啶 -1- 羧酸叔丁酯(10.6g,25.4mmol) 的 CH_2Cl_2 (200mL)和 AcOH (10mL)搅拌溶液中加入乙醛(2.80g,63.5mmol)和三乙酰氧基硼氢化钠(13.4g,63.5mmol)。在 23℃下搅拌反应混合物 24 小时。然后加入饱和 $NaHCO_3$,分离混合物。用 CH_2Cl_2 (3×50mL)萃取水层,在真空中浓缩合并的有机层。用硅胶柱层析(SiO_2 庚烷 /EtOAc=5/1)纯化残余物,以得到油状的标题化合物(4.50g,40% 产率)。^{1}H-NMR(400MHz,$CDCl_3$) δ ppm;7.82(br.s.,1H),7.45 (d,J=1.6Hz,1H),3.96-4.18 (m,2H),3.92 (s,3H),3.08 (q,J=7.0Hz,2H),2.89 (tt,J=11.0,3.7Hz,1H),2.69 (m,2H),2.55 (s,3H),1.73 (m,2H),1.49-1.56 (m,2H),1.45 (s,9H),0.86 (t, J=7.0Hz,3H);MS (ES)[M+Na]467.0。

[1057] 3-[乙基(哌啶 -4- 基)氨基]-2- 甲基 -5-(三氟甲基)苯甲酸甲酯 TFA 盐

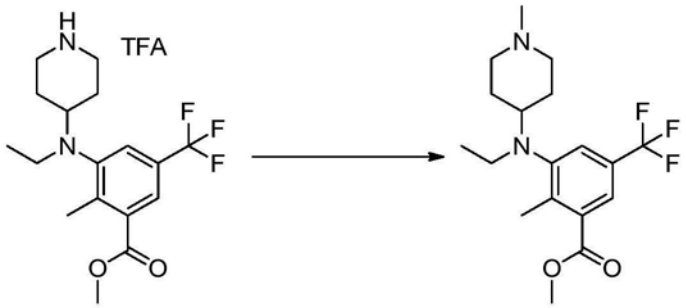
[1058]



[1059] 向 4-{ 乙基 [3-(甲氧基羰基)-2- 甲基 -5-(三氟甲基) 苯基] 氨基 } 哌啶 -1- 羧酸叔丁酯(4.50g,10.1mmol) 的 CH_2Cl_2 (50mL) 搅拌溶液中加入 TFA (5mL)。在室温下搅拌反应混合物 18 小时。然后在真空中浓缩反应混合物,以得到作为粗产物的标题化合物 (7.70g)。

[1060] 3-[乙基 (1- 甲基哌啶 -4- 基) 氨基]-2- 甲基 -5-(三氟甲基) 苯甲酸甲酯

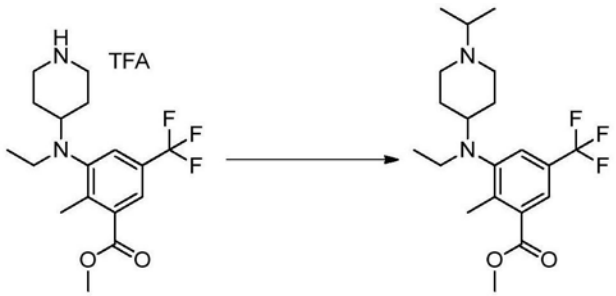
[1061]



[1062] 向 3-[乙基 (哌啶 -4- 基) 氨基]-2- 甲基 -5-(三氟甲基) 苯甲酸甲酯 TFA 盐 (粗原料,5.30g,12.0mmol) 的 CH_2Cl_2 (150mL) 和 AcOH (10mL) 搅拌溶液中加入甲醛 (15mL,44% 水溶液)和三乙酰氧基硼氢化钠 (6.40g,30.0mmol)。在 23℃下搅拌反应混合物 2.5 天。然后加入饱和 $NaHCO_3$,分离混合物。用 CH_2Cl_2 (3×50mL) 萃取水层,在真空中浓缩合并的有机层。用硅胶柱层析 (NH-SiO_2 庚烷 /EtOAc=2/1) 纯化残余物,以得到油状的标题化合物 (1.20g,28% 产率)。^{1}H-NMR(400MHz,$CDCl_3$) δ ppm;7.81(br.s.,1H),7.45 (d,J=2.0Hz,1H),3.92 (s,3H),3.10 (q, J=7.0Hz,2H),2.83 (m,2H),2.66-2.77 (m,1H),2.54 (s,3H),2.24 (s,3H),1.84-1.94 (m,2H),1.63-1.78 (m,4H),0.86 (t,J=7.0Hz,3H);MS (ES)[M+H]359.1。

[1063] 3-{ 乙基 [1-(丙烷 -2- 基) 哌啶 -4- 基] 氨基 }-2- 甲基 -5-(三氟甲基) 苯甲酸甲酯

[1064]

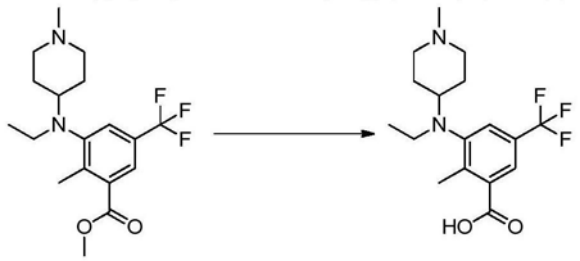


[1065] 向 3-[乙基 (哌啶 -4- 基) 氨基]-2- 甲基 -5-(三氟甲基) 苯甲酸甲酯 TFA 盐 (粗原料,1.30g,3.36mmol) 的 CH_2Cl_2 (20mL) 和 AcOH (5mL) 搅拌溶液中加入丙酮 (590mg,

10.1mmol）和三乙酰氧基硼氢化钠（1.80g，8.40mmol）。在 23℃下搅拌反应混合物 6 天，然后加入饱和 $NaHCO_3$，分离混合物。用 CH_2Cl_2（3×30mL）萃取水层，在真空中浓缩合并的有机层。用硅胶柱层析（NH-SiO_2 庚烷 / 乙酸乙酯 =5/1）纯化残余物，以得到油状的标题化合物（220mg，17% 产率）。^{1}H-NMR（400MHz，$CDCl_3$）δ ppm；7.79（br. s.，1H），7.44（d，J=1.6Hz，1H），3.91（s，3H），3.10（q，J=7.0Hz，2H），2.86（m，2H），2.61-2.75（m，2H），2.53（s，3H），2.06（m，2H），1.70-1.80（m，2H），1.58-1.69（m，2H），1.00（s×2，6H），0.84（t，J=7.0Hz，3H）；MS（ES）[M+H]387.2。

[1066] 3-[乙基 (1- 甲基哌啶 -4- 基) 氨基]-2- 甲基 -5-(三氟甲基) 苯甲酸

[1067]

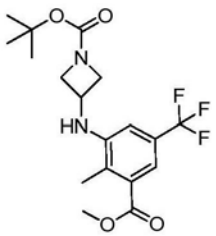


[1068] 向 3-[乙基 (1- 甲基哌啶 -4- 基) 氨基]-2- 甲基 -5-(三氟甲基) 苯甲酸甲酯（700mg，1.95mmol）的甲醇（15mL）搅拌溶液中加入 NaOH 水溶液（5M，590μl，2.93mmol）。在 50℃下搅拌反应混合物 3 小时。冷却至 23℃后，向混合物中加入 HCl（2M）。将混合物酸化到 pH 值为 5，并在真空中浓缩，以得到作为粗产物的标题化合物（1.26g）。

[1069] 遵循与制备 3-[乙基 (1- 甲基哌啶 -4- 基) 氨基]-2- 甲基 -5-(三氟甲基) 苯甲酸同样的方法，由 3- 氨基 -2- 甲基 -5-(三氟甲基) 苯甲酸甲酯和 3- 氧杂氮杂环丁烷 -1- 羧酸叔丁酯制备了下列标题化合物。

[1070] 3((3-(甲酯基)-2- 甲基 -5-(三氟甲基) 苯基) 氨基) 氮杂环丁烷 -1- 羧酸叔丁酯

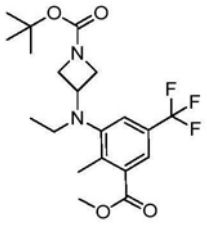
[1071]



[1072] 1H NMR（400MHz，CDCl3）δ ppm7.49（s，1H），6.60（s，1H），4.39（dd，J=7.2Hz，8.8Hz，2H），4.26（m，1H），4.19（br，d，J=5.6Hz，1H），3.93（s，3H），3.78（m，2H），2.41（s，3H），1.47（s，9H）。

[1073] 3-(乙基 (3-(甲氧基羰基)-2- 甲基 -5-(三氟甲基) 苯基) 氨基) 氮杂环丁烷 -1- 羧酸叔丁酯

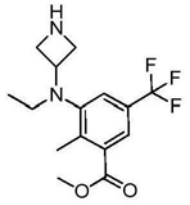
[1074]



[1075] ^{1}H NMR(400MHz,$CDCl_3$) δ ppm7.86(s,1H),7.20（s,1H),4.15（m,1H),3.99（dd,J=8.4Hz,J=8.4Hz,2H),3.94（s,3H),3.65（br,2H),3.00（q,J=7.2Hz,2H),2.60（s,3H),1.43（s,9H),0.90（t,J=6.8Hz,3H);MS（ES）(M+1)417.41。

[1076] 3-(氮杂环丁烷-3-基(乙基)氨基)-2-甲基-5-(三氟甲基)苯甲酸甲酯

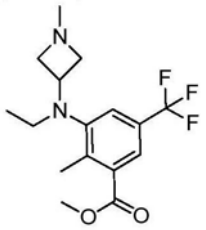
[1077]



[1078] ^{1}H NMR(400MHz,$CDCl_3$) δ ppm7.89(s,1H),7.20(s,1H),4.39(m,1H),3.94(s,3H),3.87（m,2H),3.68（br,2H),2.99（q,J=6.8Hz,2H),2.64（s,3H),0.92（t,J=6.8Hz,3H);MS（ES）(M+1)317.32。

[1079] 3-(乙基(1-甲基氮杂环丁烷-3-基)氨基)-2-甲基-5-(三氟甲基)苯甲酸甲酯

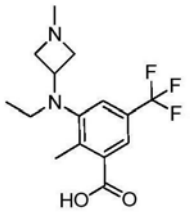
[1080]



[1081] ^{1}H NMR(400MHz,$CDCl_3$) δ ppm7.83(s,1H),7.24(s,1H),4.03(m,1H),3.94(s,3H),3.60（br,dd,J=7.2,7.2Hz,2H),2.94（q,J=7.6Hz,2H),2.72（br,t,J=6.8Hz,2H),2.59（s,3H),2.33（s,3H),0.90（t,J=7.2Hz,3H);MS（ES）(M+1)331.09。

[1082] 3-(乙基(1-甲基氮杂环丁烷-3-基)氨基)-2-甲基-5-(三氟甲基)苯甲酸

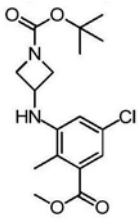
[1083]



[1084] ^{1}H NMR(400MHz,CD_3OD) δ ppm7.83(s,1H),7.37（s,1H),4.44（br,1H),3.86（br,2H),3.33（s,2H),3.04（q,J=6.8Hz,2H),3.03（s,3H),2.64（s,3H),0.90（t,J=7.2Hz,3H);MS（ES）(M+1)317.32。

[1085] 3-((5-氯-3-(甲氧基羰基)-2-甲基苯基)氨基)氮杂环丁烷-1-羧酸叔丁酯

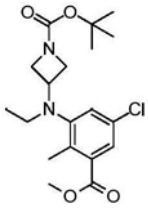
[1086]



[1087] ^{1}H-NMR(500MHz,CD_3OD) δ ppm7.05 (d, J=2.0Hz,1H),6.48 (d, J=2.0Hz,1H),4.31 (dd,J=7.2,7.8Hz,2H),4.26-4.21 (m,1H),3.87 (s,3H),3.82 (dd,J=4.4,8.3Hz,2H),2.29 (s,3H),1.45 (s,9H)。

[1088] 3-((5- 氯 -3-(甲氧基羰基)-2- 甲基苯基)(乙基) 氨基) 氮杂环丁烷 -1- 羧酸叔丁酯

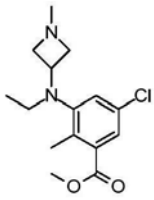
[1089]



[1090] ^{1}H-NMR(500MHz,CD_3OD) δ ppm7.57 (d, J=2.0Hz,1H),7.18 (d, J=2.0Hz,1H), 4.19-4.14 (m,1H),3.98 (dd, J=8.0,7.5Hz,2H),3.89 (s,3H),3.62-3.56 (br,2H),2.98 (q, J=6.7Hz,2H),2.49 (s,3H),1.42 (s,9H),0.88 (t, J=7.2Hz,3H)。

[1091] 5- 氯 -3-(乙基 (1- 甲基氮杂环丁烷 -3- 基) 氨基)-2- 甲基苯甲酸甲酯

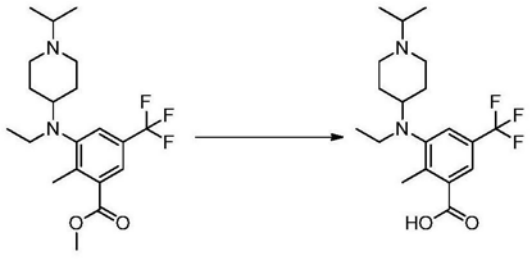
[1092]



[1093] ^{1}H-NMR(500MHz,CD_3OD) δ ppm7.53(d,J=2.0Hz,1H),7.17(d,J=2.0Hz,1H),4.01(m, 1H),3.89 (s,3H),3.57 (dd,J=6.5,8.0Hz,2H),2.93 (q,J=7.5Hz,2H),2.83 (bt,J=7.0Hz, 2H),2.49 (s,3H),2.33 (s,3H),0.90 (t, J=7.0Hz,3H);LCMS(M+H)=297.30。

[1094] 3-{ 乙基 [1-(丙烷 -2- 基) 哌啶 -4- 基] 氨基 }-2- 甲基 -5-(三氟甲基) 苯甲酸

[1095]

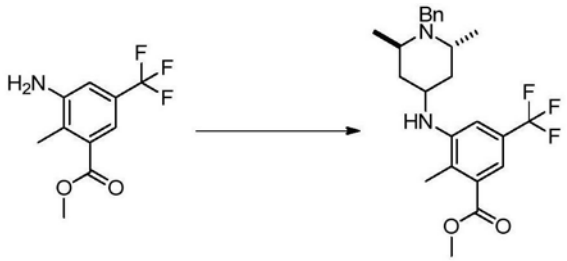


[1096] 向 3-{ 乙基 [1-(丙烷 -2- 基) 哌啶 -4- 基] 氨基 }-2- 甲基 -5-(三氟甲基) 苯甲酸甲酯(220mg,0.569mmol) 的甲醇(4mL) 搅拌溶液中加入 NaOH 水溶液(5M,170μl, 0.854mmol)。在 50℃下搅拌反应混合物 2 小时。冷却至 23℃后,往混合物中加入 HCl(2M)。

将混合物酸化到 pH 值为 5，在真空中浓缩，以得到作为粗产物的标题化合物（510mg）。

[1097] 3-{[(2R*,6R*)-1- 苯甲基 -2,6- 二甲基哌啶 -4- 基] 氨基 }-2- 甲基 -5-（三氟甲基）苯甲酸甲酯

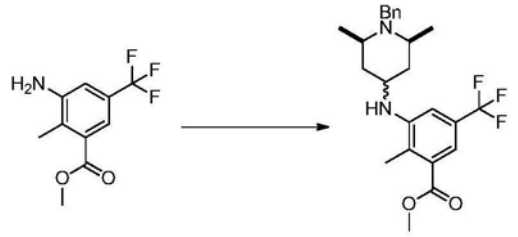
[1098]



[1099] 在 0℃下，向 3- 氨基 -2- 甲基 -5-（三氟甲基）苯甲酸甲酯（400mg，1.72mmol）的 THF（15mL）和 TFA（491μL）搅拌溶液中加入 (2R,6S)-1- 苯甲基 -2,6- 二甲基哌啶 -4- 酮（410mg，1.89mmol）。在 60℃和氮气气氛下搅拌混合物 1 小时。然后将混合物在冰浴中冷却至 0℃，加入三乙酰氧基硼氢化钠（765mg，3.43mmol）。在 23℃下搅拌反应混合物 2 小时。然后在 0℃下加入 $NaHCO_3$ 水溶液，直到 pH 值为 8-9，用乙酸乙酯萃取内容物。用 $MgSO_4$ 干燥有机层并过滤。在真空下将滤液浓缩。用硅胶柱层析（NH-SiO_2 庚烷 / 乙酸乙酯 =3/1）纯化残余物，以得到无色油状的标题化合物（278mg，37% 产率）。^{1}H-NMR（400MHz，$CDCl_3$）δ ppm；7.21-7.40（m，6H），6.90（s，1H），3.95（d，J=14.0Hz，1H），3.90（s，3H），3.60-3.73（m，2H），3.46（d，J=14.0Hz，1H），3.08-3.12（m，1H），2.98-3.03（m，1H），2.30（s，3H），2.02-2.08（m，1H），1.83-1.88（m，1H），1.52-1.60（m，1H），1.17-1.26（m，1H），1.11（d，J=6.8Hz，3H），1.13（d，J=6.4Hz，3H）。

[1100] 3-{[(2R*,6S*)-1- 苯甲基 -2,6- 二甲基哌啶 -4- 基] 氨基 }-2- 甲基 -5-（三氟甲基）苯甲酸甲酯（非对映异构体混合物）

[1101]

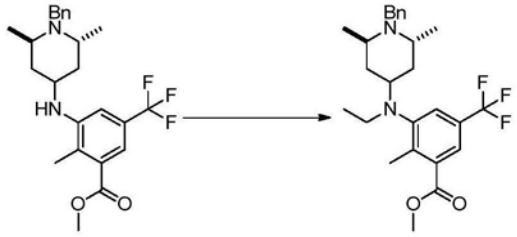


[1102] 在 0℃下，向 MS3A（1.0g）、3- 氨基 -2- 甲基 -5-（三氟甲基）苯甲酸甲酯（350mg，1.50mmol）和 (2R,6S)-1- 苯甲基 -2,6- 二甲基哌啶 -4- 酮（359mg，1.65mmol）的混合物的氯仿（10mL）搅拌溶液中加入醋酸（500μL），在室温下搅拌 7 小时。在 0℃下，向反应混合物中加入三乙酰氧基硼氢化钠（670mg，3.00mmol）。在 23℃下搅拌反应混合物 1.5 小时。然后用 $NaHCO_3$ 水溶液淬灭反应混合物，直到 pH 值为 8-9。通过硅藻土过滤除去 MS 3Å，用乙酸乙酯萃取内容物，用 $MgSO_4$ 干燥并过滤，在真空中浓缩滤液。用硅胶柱层析（庚烷 / 乙酸乙酯 =5/1 到 3/1）纯化残余物。收集目标部分并在真空中浓缩。通过硅胶柱层析（NH-SiO_2；庚烷 / 乙酸乙酯 =5/1）纯化残余物，以得到浅黄色油状的标题化合物（223mg，62% 产率）。^{1}H-NMR（400MHz，$CDCl_3$）δ ppm；7.40-7.21（m，6H），6.85（s，1H），4.00-3.95（m，1H），3.91（s，3H），3.88（d，2H），3.84-3.76（m，1H），2.83-2.73（m，2H），2.25（s，3H），1.83-1.69（m，4H），

1.13（d，J=6.4Hz，6H）。

[1103] 3-{[(2R*，6R*)-1- 苯甲基 -2，6- 二甲基哌啶 -4- 基]（乙基）氨基 }-2- 甲基 -5-（三氟甲基）苯甲酸甲酯

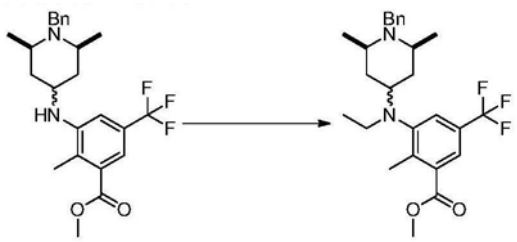
[1104]



[1105] 在 0℃下，向 3-{[(2R，6R)-1- 苯甲基 -2，6- 二甲基哌啶 -4- 基] 氨基 }-2- 甲基 -5-（三氟甲基）苯甲酸甲酯（278mg，0.640mmol）的 CH_2Cl_2（5mL）和 AcOH（500μL）搅拌溶液中加入乙醛（359mg，6.40mmol）和三乙酰氧基硼氢化钠（428mg，1.92mmol）。在 23℃下搅拌反应混合物 7 小时。然后用 $NaHCO_3$ 水溶液淬灭反应混合物，直到 pH 值为 8-9。用乙酸乙酯萃取内容物，用 $MgSO_4$ 干燥并过滤。在真空中浓缩滤液。用硅胶柱层析（NH-SiO_2；庚烷 / 乙酸乙酯 =5/1）纯化残余物，以得到浅黄色油状的标题化合物（236mg，80% 产率）。^{1}H-NMR(400MHz，$CDCl_3$) δ ppm；7.79（s，1H），7.43（s，1H），7.21-7.36（m，5H），3.92（s，3H），3.87（d，J=14.0Hz，1H），3.38（d，J=14.0Hz，1H），3.04-3.15（m，4H），2.73-2.80（m，1H），2.53（s，3H），1.76-1.82（m，1H），1.51-1.63（m，2H），1.34-1.42（m，1H），1.06（d，J=6.0Hz，3H），0.93（d，J=6.8Hz，3H），0.86（t，J=6.8Hz，3H）。

[1106] 3-{[(2R*，6S*)-1- 苯甲基 -2，6- 二甲基哌啶 -4- 基]（乙基）氨基 }-2- 甲基 -5-（三氟甲基）苯甲酸甲酯（非对映异构体混合物）

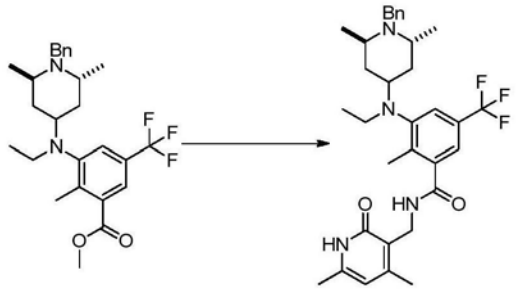
[1107]



[1108] 在 0℃下，向 3-{[(2R，6S)-1- 苯甲基 -2，6- 二甲基哌啶 -4- 基] 氨基 }-2- 甲基 -5-（三氟甲基）苯甲酸甲酯（223mg，0.513mmol）的氯仿（4mL）和醋酸（500μL）搅拌溶液中加入乙醛（1.0ml），并搅拌 30 分钟。然后在 0℃下向反应混合物中加入三乙酰氧基硼氢化钠（343mg，1.54mmol）。在 23℃下搅拌反应混合物 4 小时。然后用 $NaHCO_3$ 水溶液淬灭反应混合物，直到 pH8-9。用乙酸乙酯萃取内容物。用盐水洗涤有机层。用 $MgSO_4$ 干燥有机层并过滤。在真空中浓缩滤液。通过硅胶柱层析（庚烷 / 乙酸乙酯 =4/1 到 1/2）纯化残余物，以得到无色油状的标题化合物（105.5mg，44% 产率）。MS（ES）[M+H]463.3。

[1109] 3-{[(2R*，4S*，6R*)-1- 苯甲基 -2，6- 二甲基哌啶 -4- 基]（乙基）氨基 }-N-[(4，6- 二甲基 -2- 氧代 -1，2- 二氢吡啶 -3- 基）甲基]-2- 甲基 -5-（三氟甲基）苯甲酰胺

[1110]

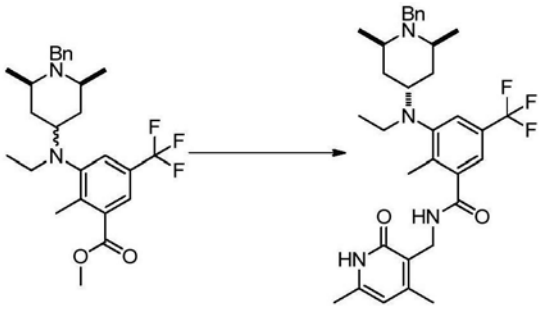


[1111] 向 3-{[(2R,6R)-1- 苯甲基 -2,6- 二甲基哌啶 -4- 基](乙基) 氨基 }-2- 甲基 -5-(三氟甲基) 苯甲酸甲酯(236mg,0.510mmol)的乙醇(5mL)搅拌溶液中加入 NaOH 水溶液(5M,269μl,1.02mmol)。在 80℃下搅拌反应混合物 2 小时。冷却至室温后,在真空中浓缩反应混合物,并在减压条件下干燥,以得到粗制羧酸钠盐。

[1112] 向粗制羧酸钠盐和 3-(氨甲基)-4,6- 二甲基 -1,2- 二氢吡啶 -2- 酮 HCl 盐(125mg,0.664mmol)的 DMSO (5mL)搅拌溶液中加入 PyBOP (398mg,0.766mmol)和 Hunig 碱(445μl,2.55mmol)。在 23℃下搅拌反应混合物 19 小时。用水淬灭反应混合物,并用乙酸乙酯萃取。用水(两次)和盐水洗涤有机层。用 $MgSO_4$ 干燥有机层并过滤。在真空中浓缩合并的有机层。通过硅胶柱层析(NH-SiO_2 ;乙酸乙酯 /MeOH=50/1 到 8/1)纯化残余物,以得到白色无定形状的标题化合物(267mg,90% 产率)。^{1}H-NMR(400MHz,$CDCl_3$) δ ppm ;7.14-7.36 (m,8H),5.94 (s,1H),4.53-4.56 (m,2H),3.85 (d,J=14.0Hz,1H),3.58 (d,J=14.0Hz,1H),3.02-3.14 (m,4H),2.72-2.80 (m,1H),2.40 (s,3H),2.32 (s,3H),2.21 (s,3H),1.32-1.82 (m,4H),1.05 (d,J=6.4Hz,3H),0.92 (d,J=6.8Hz,3H),0.84 (t,J=6.8Hz,3H)。

[1113] 3-{[(2R*,4R*,6S*)-1- 苯甲基 -2,6- 二甲基哌啶 -4- 基](乙基) 氨基 }-N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基]-2- 甲基 -5-(三氟甲基) 苯甲酰胺

[1114]

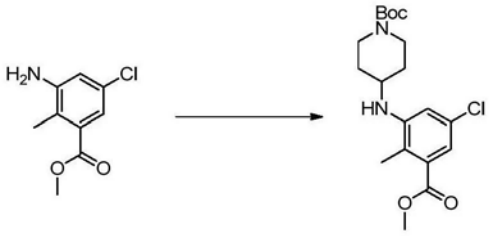


[1115] 向 3-{[(2R,6R)-1- 苯甲基 -2,6- 二甲基哌啶 -4- 基](乙基) 氨基 }-2- 甲基 -5-(三氟甲基) 苯甲酸甲酯(106mg,0.228mmol)的乙醇(2.0mL)搅拌溶液中加入 NaOH 水溶液(5M,91.2μl,0.456mmol)。在 80℃下搅拌反应混合物 1.5 小时。冷却至室温后,在真空中去除溶剂,并在减压条件下干燥。向此残余物和 3-(氨甲基)-4,6- 二甲基 -1,2- 二氢吡啶 -2- 酮 HCl 盐(55.9mg,0.297mmol)的 DMSO (2mL)搅拌溶液中加入 Hunig 碱(199μl,1.14mmol)和 PyBOP (178mg,0.342mmol)。室温下搅拌反应混合物 4 小时。用水淬灭反应混合物。用乙酸乙酯萃取内容物。用水(两次)和盐水洗涤有机层。用 $MgSO_4$ 干燥有机层并过滤。在真空中浓缩滤液。通过硅胶柱层析(NH-SiO_2,乙酸乙酯 /MeOH=50/1 到 40/1)纯化残余物,以得到无色油状的标题化合物(35.6mg,27% 产率)。^{1}H-NMR(400MHz,$CDCl_3$)

δ ppm ;7.34-7.08 (m,7H),5.96 (s,1H),4.54 (d,J=6.0Hz,2H),3.81 (s,2H),3.53 (m,1H),2.99-2.91 (m,2H),2.81 (m,2H),2.41 (s,3H),2.24 (s,3H),2.20 (s,3H),1.82-1.47 (m,4H),1.00 (d,J=6.4Hz,6H),0.81 (t,J=6.8Hz,3H);MS (ES)[M+H]583.0。

[1116] 4-{[5- 氯 -3-(甲氧基羰基)-2- 甲苯基] 氨基 } 哌啶 -1- 羧酸叔丁酯

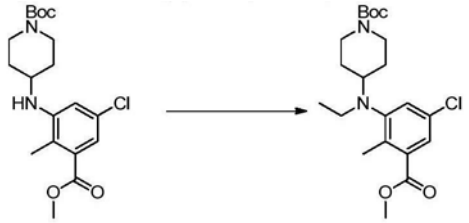
[1117]



[1118] 向 3- 氨基 -5- 氯 -2- 甲基苯甲酸甲酯(1.40g,7.04mmol)的 CH_2Cl_2(30mL)和 AcOH(2.50g,42.2mmol) 搅拌溶液中加入 N-Boc 哌啶酮(1.96g,9.85mmol) 和三乙酰氧基硼氢化钠(4.40g,21.1mmol)。在 23℃下搅拌反应混合物 18 小时,然后加入饱和的 $NaHCO_3$,分离混合物。用 CH_2Cl_2 (3×20mL) 萃取水层,在真空中浓缩合并的有机层。用硅胶柱层析(SiO_2 庚烷 / 乙酸乙酯 =10/1 到 1/1) 纯化残余物,以得到油状的标题化合物(2.4g,89% 产率)。^{1}H-NMR(400MHz,$CDCl_3$) δ ppm;7.09 (s,1H),6.69 (s,1H),4.05 (m,2H),3.88 (s,3H),3.63 (m,1H),3.42 (m,1H),2.97 (m,2H),2.23 (s,3H),2.05 (m,2H),1.45 (s,9H),1.27 (m,2H)。

[1119] 4-{[5- 氯 -3-(甲氧基羰基)-2- 甲苯基](乙基) 氨基 } 哌啶 -1- 羧酸叔丁酯

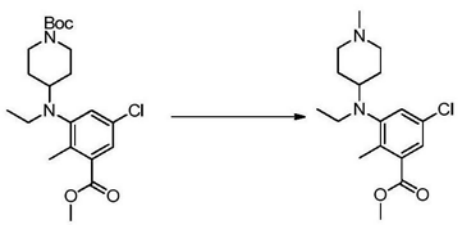
[1120]



[1121] 向 4-{[5- 氯 -3-(甲氧基羰基)-2- 甲苯基] 氨基 } 哌啶 -1- 羧酸叔丁酯(2.40g,6.28mmol) 的二氯甲烷(50mL) 和醋酸(1.8mL) 搅拌溶液中加入乙醛(830μl,12.6mmol) 和三乙酰氧基硼氢化钠(4.00g,18.8mmol)。室温下搅拌反应混合物 18 小时。然后加入 $NaHCO_3$ 水溶液,分离混合物。用二氯甲烷萃取水层。在真空中浓缩合并的有机层。用硅胶柱层析(SiO_2 庚烷 / 乙酸乙酯 =10/1) 纯化残余物,以得到油状的标题化合物(2.40g,89% 产率)。^{1}H-NMR(400MHz,$CDCl_3$) δ ppm;7.56 (s,1H),7.21 (d,J=1.6Hz,1H),4.04 (m,2H),3.89 (s,3H),3.02(q,J=7.0Hz,2H),2.88(m,1H),2.68(m,2H),2.44(s,3H),1.71(m,2H),1.48-1.61(m,2H),1.45 (s,9H),0.83-0.89 (t,J=7.0Hz,3H);MS (ES)[M+Na]433.0。

[1122] 5- 氯 -3-[乙基 (1- 甲基哌啶 -4- 基) 氨基]-2- 甲基苯甲酸甲酯

[1123]

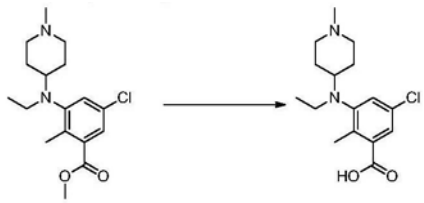


[1124] 向 4-{ 乙基 [3-(甲氧基羰基)-2- 甲苯 -5- 氯代苯基] 氨基 } 哌啶 -1- 羧酸叔丁酯(2.20g,5.35mmol)的二氯甲烷(20mL)搅拌溶液中加入 TFA (4mL)。室温下搅拌反应混合物 2 小时。然后在真空中浓缩反应混合物,以得到作为粗产物的 TFA 盐。

[1125] 在 0℃下,向 TFA 盐的 THF (20mL)和醋酸(305μl)搅拌溶液中加入甲醛(3mL,44%水溶液)和三乙酰氧基硼氢化钠(3.40g,16.1mmol)。在 23℃下搅拌反应混合物 19 小时,然后加入饱和的 $NaHCO_3$,分离混合物。用 EtOAc (50mL)萃取水层,用盐水洗涤合并的有机层,用 Na_2SO_4 干燥并过滤,在真空中浓缩滤液。用硅胶柱层析(NH-SiO_2,庚烷 / 乙酸乙酯 =1/1)纯化残余物,以得到油状的标题化合物(1.54g,89% 产率)。^{1}H-NMR(400MHz,$CDCl_3$) δ ppm ;7.54 (d, J=2.4Hz,1H),7.21 (d, J=2.4Hz,1H),3.89 (s,3H),3.07 (q, J=6.8Hz,2H),2.81-2.85 (m,2H),2.66-2.70 (m,1H),2.44 (s,3H),2.24 (s,3H),1.86-1.93 (m,2H),1.65-1.75 (m,4H),0.86 (t, J=6.8Hz,3H)。

[1126] 5- 氯 -3-[乙基 (1- 甲基哌啶 -4- 基) 氨基]-2- 甲基苯甲酸

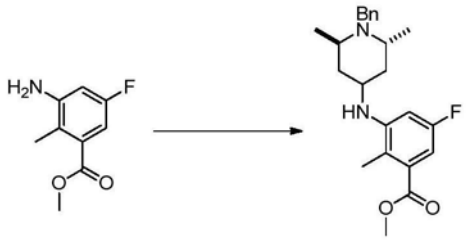
[1127]



[1128] 向 5- 氯 -3-[乙基 (1- 甲基哌啶 -4- 基) 氨基]-2- 甲基苯甲酸甲酯(1.06g,3.26mmol)的甲醇(10mL)搅拌溶液中加入 NaOH 水溶液(5M,780μl,3.92mmol)。在 50℃下搅拌反应混合物 18 小时,冷却至 23℃后,向混合物中加入 HCl (2M,2mL),混合物被酸化至 pH 值为 5,并在真空中浓缩,以得到作为粗产物(1.80g)的标题化合物。

[1129] 3-{[(2R,6R)-1- 苯甲基 -2,6- 二甲基哌啶 -4- 基] 氨基 }-5- 氟代 -2- 甲基苯甲酸甲酯

[1130]

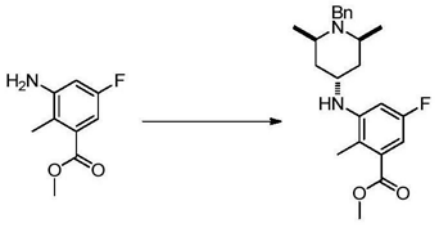


[1131] 在 0℃下,向 3- 氨基 -5- 氟代 -2- 甲基苯甲酸甲酯(520mg,2.84mmol)的 THF(20mL)和 TFA (813μl) 搅拌溶液中加入 (2R,6S)-1- 苯甲基 -2,6- 二甲基哌啶 -4- 酮(679mg,3.12mmol)。在 60℃、氮气气氛下搅拌混合物 1 小时。然后将混合物在冰浴中冷却至 0℃,加入三乙酰氧基硼氢化钠(1.27g,5.68mmol)。室温下搅拌反应混合物 2 小时。然后在 0℃加入 $NaHCO_3$ 水溶液,直到 pH 值为 8-9,用乙酸乙酯萃取内容物。用 $MgSO_4$ 干燥有机层并过滤。在真空中浓缩滤液。用硅胶柱层析(NH-SiO_2,庚烷 / 乙酸乙酯 =5/1) 纯化残余物,以得到无色油状的标题化合物(331mg,30% 产率)。^{1}H-NMR(400MHz,$CDCl_3$) δ ppm ;7.35-7.39 (m,2H),7.27-7.30 (m,2H),7.21-7.26 (m,1H),6.76 (dd, J=2.4,9.2Hz,1H),6.45 (dd, J=2.4,11.2Hz,1H),3.94 (d, J=14.4Hz,1H),3.87 (s,3H),3.58-3.65 (m,2H),3.46 (d,

J=14.4Hz,1H),3.06-3.12（m,1H),2.94-3.01（m,1H),2.21（s,3H),2.02-2.07（m,1H),1.82-1.89（m,1H),1.15-1.22（m,1H),1.12（d,J=6.0Hz,3H),1.09（d,J=7.2Hz,3H)。

[1132] 3-{[(2R,4R,6R)-1-苯甲基-2,6-二甲基哌啶-4-基]氨基}-5-氟代-2-甲基苯甲酸甲酯

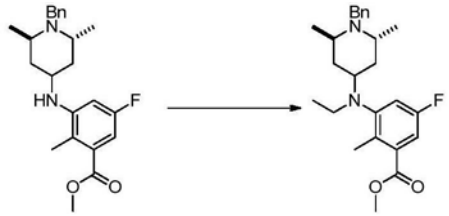
[1133]



[1134] 在0℃下,向3-氨基-5-氟代-2-甲基苯甲酸甲酯(171mg,0.931mmol)的氯仿(6mL)和AcOH（266μl)搅拌溶液中加入(2R,6S)-1-苯甲基-2,6-二甲基哌啶-4-酮(212mg,0.980mmol)和MS3A（500mg)。在室温、氮气气氛下搅拌混合物2小时。然后将混合物在冰浴中冷却至0℃,加入三乙酰氧基硼氢化钠(415mg,1.86mmol)。室温下搅拌反应混合物5小时。然后在0℃加入$NaHCO_3$水溶液,直到pH值为8-9,用乙酸乙酯萃取内容物。用$MgSO_4$干燥有机层并过滤。在真空中浓缩滤液。用硅胶柱层析(1.SiO_2,庚烷/乙酸乙酯=5/1到3/1,2.NH-SiO_2,庚烷/乙酸乙酯=5/1,3.NH-SiO_2,庚烷/乙酸乙酯=10/1到6/1)纯化残余物,以得到无色油状的标题化合物(85.0mg,24%产率)。^{1}H-NMR(400MHz,$CDCl_3$)δppm;7.38-7.20（m,5H),6.77（dd,J=2.4,9.2Hz,1H),6.40（dd,J=2.4,11.6Hz,1H),3.95-3.90(m,1H),3.88（s,3H),3.87（s,2H),2.84-2.74（m,2H),2.16（s,3H),1.81-1.66（m,4H),1.11（d,J=6.0Hz,6H)。

[1135] 3-{[(2R,6R)-1-苯甲基-2,6-二甲基哌啶-4-基](乙基)氨基}-5-氟代-2-甲基苯甲酸甲酯

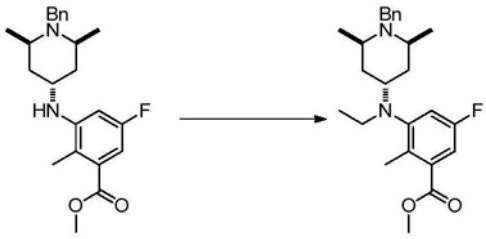
[1136]



[1137] 在0℃下,向3-{[(2R,6R)-1-苯甲基-2,6-二甲基哌啶-4-基]氨基}-5-氟代-2-甲基苯甲酸甲酯(269mg,0.701mmol)的二氯甲烷(5mL)和醋酸(500μl)搅拌溶液中加入乙醛(124mg,2.80mmol)和三乙酰氧基硼氢化钠(469mg,2.10mmol)。在室温下搅拌反应混合物12小时。然后反应混合物用$NaHCO_3$水溶液淬灭至pH8-9。用乙酸乙酯萃取内容物。用$MgSO_4$干燥有机层并过滤。在真空中浓缩滤液。用硅胶柱层析(NH-SiO_2,庚烷/乙酸乙酯=5/1)纯化残余物,以得到浅黄色油状的标题化合物(277mg,96%产率)。^{1}H-NMR(400MHz,$CDCl_3$)δppm;7.19-7.36（m,6H),6.97（dd,J=2.4,10.4Hz,1H),3.89（s,3H),3.86（d,J=10.4Hz,1H),3.39（d,J=10.4Hz,1H),3.02-3.10（m,4H),2.74-2.80（m,1H),2.43（s,3H),1.74-1.82（m,1H),1.51-1.63（m,2H),1.32-1.40（m,1H),1.05（d,J=6.4Hz,3H),0.93（d,J=7.2Hz,3H),0.86（t,J=6.8Hz,3H);MS（ES)[M+H]413.0。

[1138] 3-{[(2R,4R,6S)-1- 苯甲基 -2,6- 二甲基哌啶 -4- 基](乙基) 氨基 }-5- 氟代 -2- 甲基苯甲酸甲酯

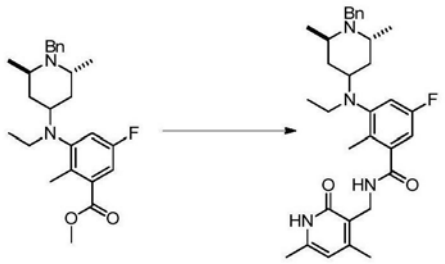
[1139]



[1140] 在 0℃下,向 3-{[(2R,4R,6S)-1- 苯甲基 -2,6- 二甲基哌啶 -4- 基] 氨基 }-5- 氟代 -2- 甲基苯甲酸甲酯(84.9mg,0.221mmol)和乙醛(124mg,2.21mmol)的氯仿(2mL)搅拌溶液中加入醋酸(200μl),并在 23℃下搅拌 1 小时。在 0℃下往反应混合物中加入三乙酰氧基硼氢化钠(148mg,0.662mmol)。在室温下搅拌反应混合物 3.5 小时。在 0℃下往反应混合物中加入MS 3Å(200mg)和乙醛(500μl),在室温下搅拌 25 分钟。在 0℃下向反应混合物中加入三乙酰氧基硼氢化钠(148mg,0.662mmol),并在室温下搅拌 12 小时。然后反应混合物用饱和 $NaHCO_3$ 淬灭至 pH 值为 8-9。用 EtOAc 萃取内容物。用盐水洗涤有机层。用 $MgSO_4$ 干燥有机层并过滤。在真空中浓缩滤液。用硅胶柱层析(NH-SiO_2,庚烷 / 乙酸乙酯 =5/1)纯化残余物,以得到无色油状的标题化合物(48.5mg,53% 产率)。^{1}H-NMR(400MHz,$CDCl_3$) δ ppm ;7.36-7.19 (m,6H),6.96 (dd,J=2.8,9.6Hz,1H),3.90 (s,3H),3.82 (s,2H),3.44 (m,1H),2.98-2.91 (m,2H),2.88-2.87 (m,2H),2.31 (s,3H),1.82-1.70 (m,2H),1.57-1.47 (m,2H),0.99 (d,J=6.4Hz,6H),0.83 (t,J=6.8Hz,3H)。

[1141] 3-{[(2R,6R)-1- 苯甲基 -2,6- 二甲基哌啶 -4- 基](乙基) 氨基 }-N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基]-5- 氟代 -2- 甲基苯甲酰胺

[1142]



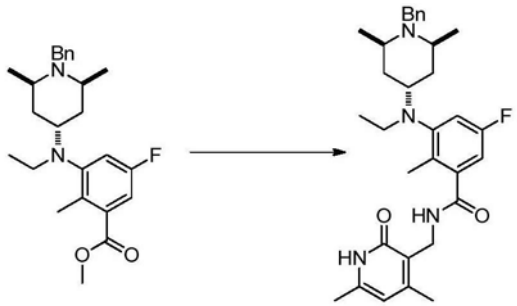
[1143] 向 3-{[(2R,6R)-1- 苯甲基 -2,6- 二甲基哌啶 -4- 基](乙基) 氨基 }-5- 氟代 -2- 甲基苯甲酸甲酯(277mg,0.672mmol)的乙醇(5mL)搅拌溶液中加入 NaOH 水溶液(5M,269μl,1.35mmol)。在 80℃下搅拌反应混合物 2 小时。冷却至室温后,将反应混合物在真空中浓缩并在减压下干燥,以得到粗制羧酸钠盐。

[1144] 向粗制羧酸钠盐和 3-(氨甲基)-4,6- 二甲基 -1,2- 二氢吡啶 -2- 酮 HCl 盐(165mg,0.874mmol)的 DMSO (5mL)搅拌溶液中加入 PyBOP (525mg,1.01mmol)和 Hunig 碱(586μl,3.36mmol)。在 23℃下搅拌反应混合物 5 小时。用水淬灭反应混合物,并用乙酸乙酯萃取。用水(2×10mL)和盐水(1×10mL)洗涤有机层。用 $MgSO_4$ 干燥有机层并过滤,在真空中浓缩滤液。用硅胶柱层析(NH-SiO_2,乙酸乙酯至乙酸乙酯 /MeOH=50/1 到 8/1)纯化残余物,以得到作为白色固体的标题化合物(378mg,定量产率)。^{1}H-NMR(400MHz,$CDCl_3$)

δ ppm ;7.20-7.38 (m,5H),7.02-7.10 (m,1H),6.80-6.84 (m,1H),6.73-6.78 (m,1H),5.93 (s,1H),4.51 (d,J=6.0Hz,2H),3.85 (d,J=10.0Hz,1H),3.38 (d,J=10.0Hz,1H),3.01-3.05 (m,4H),2.67-2.81 (m,1H),2.40 (s,3H),2.23 (s,3H),1.52-1.83 (m,3H),1.32-1.39 (m,1H),1.05 (d,J=6.4Hz,3H),0.93 (d,J=6.8Hz,3H),0.84 (t,J=6.8Hz,3H)。

[1145] 3-{[(2R,4R,6S)-1- 苯甲基 -2,6- 二甲基哌啶 -4- 基](乙基) 氨基 }-N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基]-5- 氟代 -2- 甲基苯甲酰胺

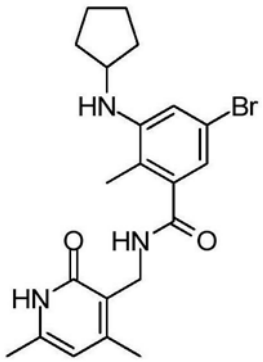
[1146]



[1147] 向 3-{[(2R,4R,6S)-1- 苯甲基 -2,6- 二甲基哌啶 -4- 基](乙基) 氨基 }-5- 氟代 -2- 甲基苯甲酸甲酯 (48.5mg,0.118mmol) 的乙醇 (1.5mL) 搅拌溶液中加入 NaOH 水溶液 (5M,47.0μl,0.235mmol)。在 80℃下搅拌反应混合物 1.5 小时。冷却至室温后,在真空中去除溶剂,并在减压条件下干燥。往 DMSO (1mL) 中的该残余物和 3-(氨甲基)-4,6- 二甲基 -1,2- 二氢吡啶 -2- 酮 HCl 盐 (28.8mg,0.153mmol) 的搅拌溶液中加入 PyBOP (91.8mg,0.176mmol) 和 Hunig 碱 (102μl,0.588mmol)。在 23℃下搅拌反应混合物 13.5 小时。用水淬灭反应混合物,并用乙酸乙酯萃取混合物。用水 (2×10mL) 和盐水 (1×10mL) 洗涤有机层。用 $MgSO_4$ 干燥有机层并过滤,在真空中浓缩滤液。用硅胶柱层析 (NH-SiO_2,乙酸乙酯 /MeOH=50/1 到 8/1) 纯化残余物,以得到作为白色固体的标题化合物 (50.1mg,79% 产率)。MS(ES)[M+H]533.3。

[1148] 实施例 1 :合成化合物 1 :5- 溴 -3-(环戊基氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基苯甲酰胺

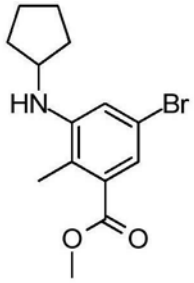
[1149]



化合物 1

[1150] 步骤 1 :5- 溴 -3-(环戊基 (甲基) 氨基)-2- 甲基苯甲酸甲酯的合成

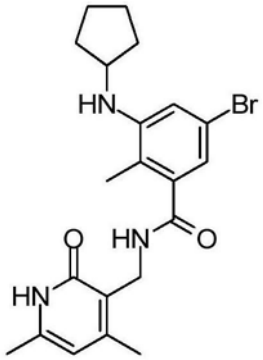
[1151]



[1152] 向 5- 溴 -3-(环戊基氨基)-2- 甲基苯甲酸甲酯(0.5g,1.75mmol) 的乙腈(10mL) 搅拌溶液中加入 CS_2CO_3 (1.02g,2.63mmol) 和碘甲烷(1.45g,3.5mmol)。在 80℃下搅拌所得的反应混合物 4 小时。完成时,在减压下除去溶剂,将残余物溶解于水中,并用乙酸乙酯萃取。通过硅胶柱层析纯化所得的原料粗品,以得到所需的化合物产品(0.39g),无需进一步纯化。

[1153] 步骤 2 :合成 5- 溴 -3-(环戊基氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基苯甲酰胺

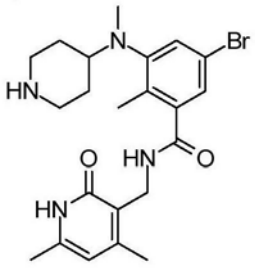
[1154]



[1155] 向 5- 溴 -3-(环戊基 (甲基) 氨基)-2- 甲基苯甲酸甲酯(1 当量)的乙醇(5mL)搅拌溶液中加入 NaOH 水溶液(1 当量),在 60℃下搅拌反应 4 小时。完成时,在减压下除去乙醇,用 1N HCl 酸化残余物至 pH 值为 6。用 10%MeOH/DCM 萃取水相。用硫酸钠干燥合并的有机层,在减压下除去溶剂,得到纯酸(产率 50-60%)。向该酸(1 当量) 的 DMSO (1.5mL) 溶液中加入 PyBOP(1.5 当量),室温下搅拌反应物 15 分钟。然后加入 3-(氨甲基)-4,6- 二甲基吡啶 -2(1H)- 酮(2 当量),搅拌反应物过夜。完成时,加入水,过滤得到的固体沉淀并用水洗涤。然后用乙腈搅拌该固体 10 分钟,重新过滤以得到纯净的目标分子(产率 50-60%)。LCMS :446.15 (M+1)$^+$;HPLC :94.48% (@254nm) (R_t ;5.257);^{1}H NMR(DMSO-d_6,400MHz) δ 11.47 (s,1H),8.20 (t,1H,J=4.8Hz),7.25 (s,1H),7.04 (s,1H),5.85 (s,1H),4.23 (d,2H,J=4.8Hz),3.37-3.45 (m,1H),2.49 (3H 合并于溶剂峰),2.17 (s,3H),2.13 (s,3H),2.10 (s,3H),1.53-1.67 (m,4H),1.38-1.50 (m,4H)。

[1156] 实施例 2 :合成化合物 2 :5- 溴 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基 -3-(甲基 (哌啶 -4- 基) 氨基) 苯甲酰胺

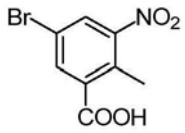
[1157]



化合物 2

[1158] 步骤 1 :5- 溴 -2- 甲基 -3- 硝基苯甲酸

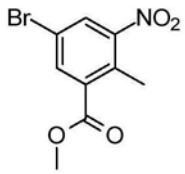
[1159]



[1160] 在室温下,向 2- 甲基 -3- 硝基苯甲酸(50g,276.2mmol)的浓 H_2SO_4 (200mL)搅拌溶液中分批加入 1,3- 二溴 -5,5- 二甲基 -2,4- 咪唑烷二酮(43.4g,151.8mmol),在室温下搅拌反应物料 5 小时。完成时,将反应物料倒入冰冷水中,过滤沉淀的固体,用水洗涤得到的残余物,并在真空下干燥,以得到用于进一步反应的所需的化合物(71.7g,99.9%)。

[1161] 步骤 2 :5- 溴 -2- 甲基 -3- 硝基甲苯

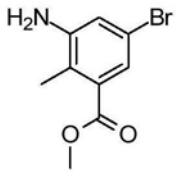
[1162]



[1163] 向 5- 溴 -2- 甲基 -3- 硝基苯甲酸(287g,1103mmol)的 DMF (150mL)搅拌溶液中加入碳酸钠(468g,4415mmol)和碘甲烷(626.63g,4415mmol)。得到的反应物料在 60℃下加热 8 小时。完成时,过滤沉淀的固体,用乙醚洗涤残余物(5 次)。将合并的有机层干燥,在减压下浓缩,以得到用于进一步反应的所需的化合物(302g,99%)。

[1164] 步骤 3 :3- 氨基 -5- 溴 -2- 甲基苯甲酸甲酯

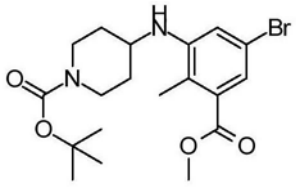
[1165]



[1166] 在搅拌下,向 5- 溴 -2- 甲基 -3- 硝基甲苯(150g,544mmol)的乙醇(750mL)搅拌溶液中加入铁粉(93.3g,1636mmol)和溶解于水(750mL)中的氯化铵(150g,2777mmol)。得到的反应物料在 80℃下加热 7 小时。完成时,通过硅藻土过滤反应物料,同时用水和乙酸乙酯洗涤,滤液用乙酸乙酯萃取。将合并的有机层干燥,在减压下浓缩,得到所需的化合物。

[1167] 步骤 4 :4-((5- 溴 -3-(甲氧基羰基) 氨基) 哌啶 -1- 羧酸叔丁酯

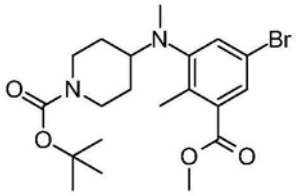
[1168]



[1169] 向上述粗制 3- 氨基 -5- 溴 -2- 甲基苯甲酸甲酯(5g,20.57mmol)和 4- 氧代哌啶 -1- 羧酸叔丁酯(8.2g,41.15mmol)的甲醇(50mL)搅拌溶液中加入醋酸(1.2g,20.57mmol),在室温下搅拌反应 3 小时。然后在 0℃下加入氰基硼氢化钠(1.55g,24.6mmol),室温下搅拌反应过夜。完成时,在减压下去除溶剂,并用柱层析纯化粗原料,以得到化合物 5 (5g,57%)。

[1170] 步骤 5 :4-((5- 溴 -3-(甲氧基羰基)-2- 甲基苯基 (甲基) 氨基) 哌啶 -1- 羧酸叔丁酯

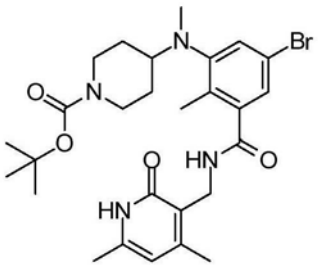
[1171]



[1172] 向 4-((5- 溴 -3-(甲氧基羰基) 氨基) 哌啶 -1- 羧酸叔丁酯(3g,7.06mmol)的乙腈(25mL)搅拌溶液中加入碳酸铯(4.57g,14.11mmol)和碘甲烷(5g,35.2mmol);得到的反应物料在 80℃下加热 7 小时。完成时,将反应物料冷却至室温并过滤,用乙酸乙酯洗涤残余物,浓缩滤液,然后通过柱层析纯化,以得到所需的化合物(2.5g,81%)。

[1173] 步骤 6 :4-((5- 溴 -3-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基) 氨基甲酰基)-2- 甲基苯基)(甲基) 氨基) 哌啶 -1- 羧酸叔丁酯

[1174]

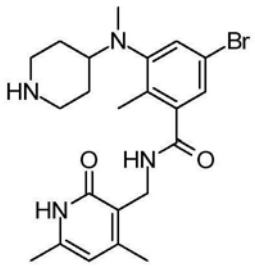


[1175] 向 4-((5- 溴 -3-(甲氧基羰基)-2- 甲基苯基 (甲基) 氨基) 哌啶 -1- 羧酸叔丁酯(2g,4.69mmol)的 MeOH (20mL)溶液中加入 NaOH (0.37g,9.38mmol)水溶液,在 60℃下搅拌 1 小时。反应完成后,减压除去乙醇,用稀 HCl 酸化直到 pH 值为 6,并用柠檬酸调至 pH 值为 4。使用乙酸乙酯实施萃取。将合并的有机层干燥浓缩,产生单独的酸(1.7g,90%)。

[1176] 然后将此酸(1.7g,4.22mmol)溶解到 DMSO (10mL)中,并向其中加入 3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮(1.42g,9.38mmol)。室温下搅拌反应混合物 15 分钟,然后加入 PYBOP (3.66g,7.04mmol),继续搅拌过夜。完成后,将反应物料倒入冰中以得到固体,将其过滤并用乙腈洗涤,然后通过柱层析纯化,以得到所需的化合物(1.3g,50%)。

[1177] 步骤 7 :5- 溴 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基 -3-(甲基 (哌啶 -4- 基) 氨基) 苯甲酰胺

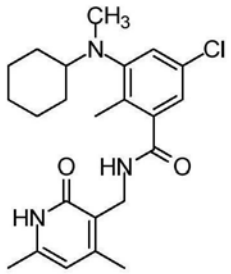
[1178]



[1179] 向 4-((5- 溴 -3-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基) 氨基甲酰基)-2- 甲基苯基)(甲基) 氨基) 哌啶 -1- 羧酸叔丁酯(1.3g,2.39mmol)的 DCM(10mL) 搅拌溶液冷却至 0℃,并向其加入 TFA(2mL)。反应物料在室温下搅拌 1 小时。完成时,将反应浓缩至干燥。用碳酸氢钠水溶液将残余物碱化至 pH 值为 8,然后用 20%MeOH/DCM 萃取水层。将合并的有机层用硫酸钠干燥并浓缩,以得到所需的化合物(0.9g,85%)。LCMS:461.15(M+1)$^+$;HPLC:98.52%(@254nm)(R_t;4.673; 方法 : 柱 :YMC ODS-A150mm x4.6mm x5μ; 流动相 :A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液 ; 进样量 :10μL, 柱温 :30℃ ; 流速 :1.4mL/min.; 梯度 :8 分钟内 5%B 至 95%B, 保持 1.5min,9.51-12min5%B);^{1}HNMR(DMSO-d_6,400MHz) δ 8.22(t,1H),7.19(s,1H),7.01(s,1H),5.85(s,1H),4.23(d,2H,J=4Hz),2.91(d,2H,J=11.6Hz),2.78(bs,1H),2.55(s,3H),2.32-2.35(m,2H),2.18(s,3H),2.10(s,6H),1.44-1.50(m,4H)。

[1180] 实施例 3 :合成化合物 3 :5- 氯 -3-(环己基 (甲基) 氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基苯甲酰胺

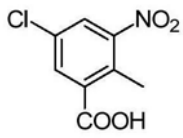
[1181]



化合物 3

[1182] 步骤 1 :5- 氯 -2- 甲基 -3- 硝基苯甲酸

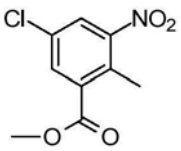
[1183]



[1184] 在 -10℃下,向冷却的浓 H_2SO_4(27mL) 中逐份地加入 5- 氯 -2- 甲基苯甲酸(4g,23.39mmol)。10 分钟后,在 -10℃下逐滴加入硝化混合物 { 将浓 HNO_3(3.3g,52.68mmol) 和浓 H_2SO_4(4.4mL)混合来制备 }。在 -10℃下搅拌得到的反应物料 30 分钟。完成时,将反应混合物倒入冰冷水中,过滤沉淀的固体,用水洗涤并在真空下干燥,以得到所需的化合物(4.95g,99%)。

[1185] 步骤 2 :5- 氯 -2- 甲基 -3- 硝基苯甲酸甲酯

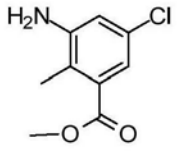
[1186]



[1187] 向 5- 氯 -2- 甲基 -3- 硝基苯甲酸(6.75g,31.25mmol)的 DMF (33mL)搅拌溶液中加入碳酸钠(13.23g,125.18mmol)和碘甲烷(17.77g,125.2mmol)。将得到的反应物在 60℃下加热 4 小时。完成时,向反应物中加入水,用 DCM 进行萃取。将合并的有机层干燥,在减压下浓缩并通过硅胶(60-120 目)柱层析来纯化,得到所需的化合物(6g,83%)。

[1188] 步骤 3 :3- 氨基 -5- 氯 -2- 甲基苯甲酸甲酯

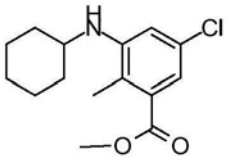
[1189]



[1190] 向 5- 氯 -2- 甲基 -3- 硝基苯甲酸甲酯(6g,26.13mmol)的乙醇(60mL)搅拌溶液中边搅拌边加入铁粉(11.88g,208.4mmol)和溶解于水(60mL)中的氯化铵(6g,112.1mmol)。将得到的反应物在 80℃下加热 1 小时。完成时,向反应物料中加入水,将反应混合物通过硅藻土过滤,用乙酸乙酯萃取滤液。用水洗涤合并的有机层并干燥,在减压下浓缩,得到所需的化合物。

[1191] 步骤 4 :5- 氯 -3-(环己基氨基)-2- 甲基苯甲酸甲酯

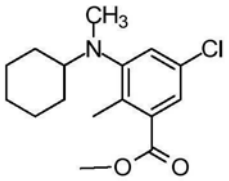
[1192]



[1193] 向 3- 氨基 -5- 氯 -2- 甲基苯甲酸甲酯(1g,5.025mmol)和环己酮(0.739g,7.75mmol)的甲醇(10mL)搅拌溶液中加入乙酸(0.301g,5.02mmol),在室温下搅拌反应 3 小时。加入氰基硼氢化钠(390mg,0.00621mmol),搅拌反应过夜。完成时,减压去除溶剂,并通过柱层析纯化原料粗品,以得到所需的化合物(1.4g,被环己酮污染)。

[1194] 步骤 5 :5- 氯 -3-(环己基 (甲基) 氨基)-2- 甲基苯甲酸甲酯(6):

[1195]

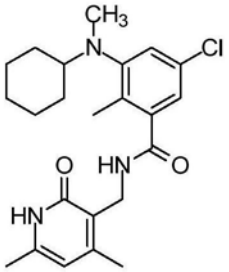


[1196] 向 5- 氯 -3-(环己基氨基)-2- 甲基苯甲酸甲酯(1.4g,0.0049 摩尔)的乙腈(10mL)搅拌溶液中加入碳酸铯(3.2g,0.0099 摩尔)和碘甲烷(3.5g,0.0024 摩尔);在 80℃下加热得到的反应物 13 小时。完成时,将反应物冷却至室温并过滤,用乙酸乙酯洗涤残余物,浓缩滤液,然后通过柱层析纯化,以得到所需的化合物(800mg,55%)。

[1197] 步骤 6 :5- 氯 -3-(环己基 (甲基) 氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢

吡啶 -3- 基) 甲基)-2- 甲基苯甲酰胺

[1198]



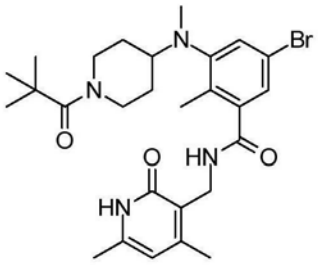
[1199] 向化合物 6 (0.8g,2.71mmol)的 EtOH (5mL)溶液中加入 NaOH (0.16g,4.06mmol) 水溶液,在 60℃下搅拌 1 小时。反应完成后,在减压条件下除去乙醇,用稀 HCl 酸化至 pH 值为 6,并用柠檬酸调节至 pH 值为 4。用乙酸乙酯进行萃取。干燥、浓缩合并的有机层,得到单独的酸(0.7g,91%)。

[1200] 然后将该酸(0.7g,2.49mmol)溶解到 DMSO (2mL)中,并向其中加入 3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮(0.752g,4.98mmol)。室温下搅拌反应混合物 15 分钟,然后向其中加入 PYBOP (1.9g,3.73mmol),继续搅拌过夜。反应完成后,将反应物倒入冰中以得到固体,将其过滤,用乙腈洗涤,然后柱纯化,以提供标题化合物(0.250g,25%)。

[1201] LCMS:416.35(M+1)$^+$;HPLC:99.01%(@254nm)(R_t;5.408; 方 法 : 柱 :YMC ODS-A150mm x4.6mm x5μ; 流动相 :A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液 ; 进样量 :10μL, 柱温 :30℃ ; 流速 :1.4mL/min.; 梯度 :8 分钟内 5%B 至 95%B, 保持 1.5 分钟,9.51-12min5%B);^{1}H NMR(DMSO-d_6,400MHz) δ 11.46(s,1H),8.20(t,1H,J=4.8Hz),7.05(d,1H,J=2Hz),6.88(d,1H,J=2Hz),5.85(s,1H),4.24(d,2H,J=4.8Hz),2.70(m,1H),2.56(s,3H),2.18(s,3H),2.12(s,3H),2.10(s,3H),1.75-1.35(m,7H),1.25-1.05(m,3H)。

[1202] 实施例 4 :合成化合物 4 :5- 溴 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)-2- 甲基 -3-(甲基 (1- 特戊酰哌啶 -4- 基) 氨基) 苯甲酰胺

[1203]



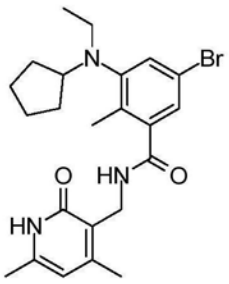
化合物 4

[1204] 在室温下,向 5- 溴 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基 -3-(甲基 (哌啶 -4- 基) 氨基) 苯甲酰胺(0.05g,0.112mmol)的 DMF (2mL) 搅拌溶液中加入 EDCI.HCl (0.064g,0.336mmol)、HOBt (0.03g,0.22mmol)、三乙胺(0.03g,0.336mmol) 和特戊酸(0.023g,0.224mmol),并在相同温度下搅拌 18 小时。完成时,加入水,并用 10%MeOH/DCM 萃取。干燥、浓缩合并的有机层,得到原料粗品 ;然后将其通过柱层析纯化,以得到所需的化合物(0.03g,56%)。LCMS:545.20(M+1)$^+$;HPLC:98.60%(@254nm)(R_t;6.355; 方法 : 柱 :YMC ODS-A150mm x4.6mm x5μ; 流动相 :A;0.05%TFA 的水溶液 /

B;0.05%TFA 的乙腈溶液；进样量 :10μL, 柱温 :30℃；流速 :1.4mL/min.；梯度 :8 分钟内 5%B 至 95%B, 保持 1.5 分钟，9.51-12min5%B);^{1}H NMR(DMSO-d_6,400MHz) δ 11.46(s,1H),8.20(t,1H,J=4.4Hz),7.25(d,1H,J=2.8Hz),7.05(d,1H,J=1.2Hz),5.85(s,1H),4.23-4.25(m,4H),3.00(m,1H),2.76(t,2H,J=12.4Hz),2.54(s,3H),2.18(s,3H),2.14(s,3H),2.10(s,3H),1.62-1.65(m,2H),1.42-1.48(m,2H),1.18(s,9H)。

[1205] 实施例 5 :合成化合物 5 :5- 溴 -3-（环戊基（乙基）氨基）-N-((4,6- 二甲基 -2- 氧代 -1,2,- 二氢吡啶 -3- 基）甲基）-2- 甲基苯甲酰胺

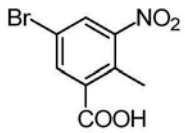
[1206]



化合物 5

[1207] 步骤 1 :5- 溴 -2- 甲基 -3- 硝基苯甲酸

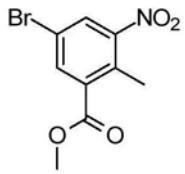
[1208]



[1209] 向 2- 甲基 -3- 硝基苯甲酸（15g,82.80mmol）的浓 H_2SO_4（60mL）混合物中加入 1,3- 二溴 -5,5- 二甲基 -2,4- 咪唑烷二酮（13.07g,45.71mmol),在室温下搅拌反应混合物 5 小时。然后将反应混合物缓慢倒入 400mL 冰冷水中。过滤沉淀出的固体,洗涤,并在真空下干燥所需的化合物（21g,98.22%)。

[1210] 步骤 2 :3- 溴 -5- 硝基苯甲酸甲酯

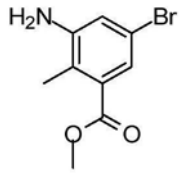
[1211]



[1212] 向 5- 溴 -2- 甲基 -3- 硝基苯甲酸（16g,61.54mmol）的 DMF（160mL）搅拌溶液中加入碘甲烷（35.72g,248mmol）和碳酸钠（26.28g,248mmol)。在 60℃下搅拌反应物料 8 小时。完成时,过滤反应物料,用乙酸乙酯洗涤无机固体残余物。在真空下浓缩合并的滤液直至干燥。将残余物重新溶解于乙酸乙酯中,并用 5% 碳酸氢钠溶液（700mL）洗涤,然后用 5M HCl 溶液（300mL）洗涤。有机层最后用盐水洗涤,用硫酸钠干燥并浓缩,以得到所需的化合物（16g,95%)。

[1213] 步骤 3 :3- 氨基 -5- 溴苯甲酸乙酯

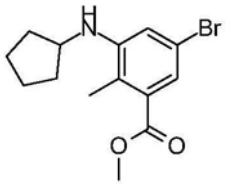
[1214]



[1215] 向 3- 溴 -5- 硝基苯甲酸甲酯(17g,62.04mmol)的乙醇(85mL)搅拌溶液中加入 NH_4Cl 溶液(17g 在 85mL 水中,317.8mmol),然后加入铁粉(27.82g,498.12mmol)。在 90℃下搅拌得到的反应物料 1 小时。完成时,过滤反应物料,并浓缩滤液直至干燥以得到固体,将其溶解于饱和碳酸氢钠溶液。用乙酸乙酯(3×50mL)萃取水层。用硫酸钠干燥合并的有机层并浓缩,以得到所需的化合物(15g,99.14%)。

[1216] 步骤 4 :3- 溴 -5-(环戊基氨基) 苯甲酸甲酯

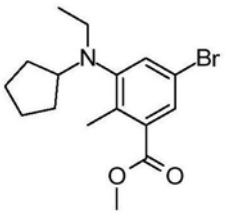
[1217]



[1218] 向 3- 氨基 -5- 溴苯甲酸乙酯(2g,8.73mmol)和环戊酮(2.2g,26.1mmol)的甲醇(20mL)搅拌溶液中加入醋酸(1.04g,17.4mmol),在室温下搅拌反应 3 小时。然后加入氰基硼氢化钠(1.37g,21.83mmol),搅拌反应过夜。完成时,在减压条件下去除溶剂,并通过柱层析纯化原料粗品,以得到所需的化合物(1.6g,61%)。

[1219] 步骤 5 :5- 溴 -3-(环戊基 (乙基) 氨基)-2- 甲基苯甲酸甲酯

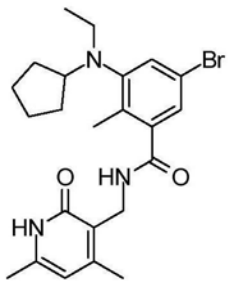
[1220]



[1221] 向 3- 溴 -5-(环戊基氨基) 苯甲酸甲酯(0.3g,0.96mmol)的 DMF (5mL)搅拌溶液中加入碳酸铯(0.628g,1.92mmol)和碘乙烷(0.748g,4.8mmol);在 80℃下加热得到的反应物料 24 小时。完成时,将反应物冷却至室温并过滤,用乙酸乙酯洗涤残余物,浓缩滤液,然后通过柱层析纯化,以得到所需的化合物(0.150g,46%)。

[1222] 步骤 6 :5- 溴 -3-(环戊基 (乙基) 氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基苯甲酰胺

[1223]

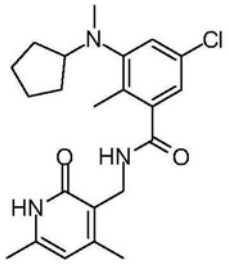


[1224] 向 5- 溴 -3-(环戊基 (乙基) 氨基)-2- 甲基苯甲酸甲酯 (0.170g,0.75mmol) 的 EtOH (10mL) 溶液中加入 NaOH (0.03g,0.75mmol) 水溶液,并在 60℃下搅拌 1 小时。反应完成后,在减压条件下去除乙醇,使用稀 HCl 酸化至 pH 值为 6。用乙酸乙酯进行萃取。干燥、浓缩合并的有机层,得到单独的酸 (0.15g,92.59%)。

[1225] 然后将该酸 (0.15g,0.461mmol) 溶解在 DMSO (5mL) 中,并向其中加入 3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮 (0.14g,0.923mmol)。室温下搅拌反应混合物 15 分钟,然后向其中加入 PYBOP (0.35g,0.692mmol),继续搅拌过夜。反应完成后,将反应物料倒入冰中以得到固体,将其过滤并用乙腈洗涤,然后通过 HPLC 纯化,以提供作为 TFA 盐的标题化合物 (0.050g,24%)。LCMS:460.10(M+1)$^+$;HPLC:99.22%(@254nm)(Rt;5.115; 方法 : 柱 :YMC ODS-A150mm x4.6mm x5μ; 流动相 :A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液 ; 进样量 :10μL, 柱温 :30℃ ; 流速 :1.4mL/min.; 梯度 :8 分钟内 5%B 至 95%B, 保持 1.5min,9.51-12min5%B);^{1}H NMR(DMSO-d_6,400MHz) δ 11.47(s,1H),8.24(s,1H),7.32(s,1H),7.09(s,1H),5.86(s,1H),4.24(d,2H,J=4.8Hz),3.47-3.48(m,1H),2.96(m,2H),2.18(s,3H),2.15(s,3H),2.10(s,3H),1.33-1.63(m,8H),0.78(t,3H,J=6.4Hz)。

[1226] 实施例 6 : 合成化合物 7 :5- 氯 -3-(环戊基 (甲基) 氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基苯甲酰胺

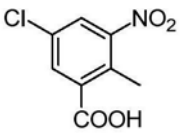
[1227]



化合物 7

[1228] 步骤 1 :5- 氯 -2- 甲基 -3- 硝基苯甲酸的合成

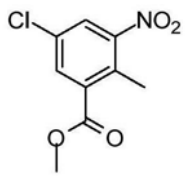
[1229]



[1230] 在 -10℃下,分批将 5- 氯 -2- 甲基苯甲酸 (4g,23.4mmol) 加入冷却的浓 H_2SO_4 (27mL) 中,并搅拌 10 分钟。在 -10℃下逐滴加入硝化混合物 { 将浓 HNO_3 (3.3g,52.68mmol) 和浓 H_2SO_4 (4.4mL) 混合来制备 }。在 -10℃下搅拌得到的混合物 30 分钟。完成时,将反应混合物倒入冰冷水中,通过过滤收集固体,用水洗涤并在真空条件下干燥,以得到 5- 氯 -2- 甲基 -3- 硝基苯甲酸 (4.95g,99%)。

[1231] 步骤 2 :5- 氯 -2- 甲基 -3- 硝基苯甲酸甲酯的合成

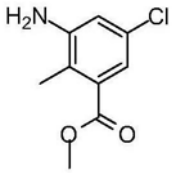
[1232]



[1233] 向用类似上述的方法制备的 5- 氯 -2- 甲基 -3- 硝基苯甲酸(6.75g,31.3mmol)的 DMF (33mL)搅拌溶液中加入碳酸钠(13.2g,125mmol)和碘甲烷(17.8g,125mmol)。在 60℃下加热得到的化合物 4 小时。完成时,往混合物中加入水,使用 DCM 进行萃取。干燥合并的有机层,在减压条件下浓缩,并通过硅胶柱层析纯化,以得到 5- 氯 -2- 甲基 -3- 硝基苯甲酸甲酯(6g,83.6%)。

[1234] 步骤 3 :3- 氨基 -5- 氯 -2- 甲基苯甲酸甲酯的合成

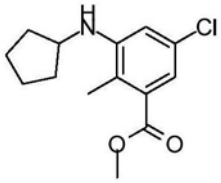
[1235]



[1236] 向 5- 氯 -2- 甲基 -3- 硝基苯甲酸甲酯(6g,26.1mmol)的乙醇(60mL)搅拌溶液中加入铁粉(11.9g,208mmol)和溶解于水(60mL)中的氯化铵(6g,112mmol)。在 80℃下加热得到的混合物 1 小时。完成时,向混合物中加入水,通过硅藻土过滤反应混合物,并用乙酸乙酯萃取滤液。用水洗涤合并的有机层,干燥,并在减压条件下浓缩,以得到 3- 氨基 -5- 氯 -2- 甲基苯甲酸甲酯。

[1237] 步骤 4 :5- 氯 -3-(环戊基氨基)-2- 甲基苯甲酸甲酯的合成

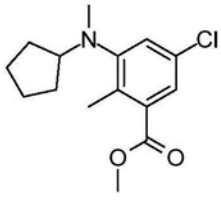
[1238]



[1239] 向 3- 氨基 -5- 氯 -2- 甲基 - 苯甲酸甲酯(1g,5.0mmol)和环戊酮(2.1g,25.0mmol)的甲醇(10mL)搅拌溶液中加入醋酸(0.6g,5.0mmol),在室温下搅拌混合物 3 小时。然后加入氰基硼氢化钠(0.78g,12.5mmol),反应搅拌过夜。完成时,在减压条件下去除溶剂,通过硅胶柱层析纯化粗原料,以得 5- 氯 -3-(环戊基氨基)-2- 甲基苯甲酸甲酯(1.2g,89%)。

[1240] 步骤 5 :5- 氯 -3-(环戊基 (甲基) 氨基)-2- 甲基苯甲酸甲酯的合成

[1241]



[1242] 向 5- 氯 -3-(环戊基氨基)-2- 甲基苯甲酸甲酯(0.5g,1.86mmol)的乙腈(5mL)搅拌溶液中加入碳酸铯(1.22g,3.7mmol)和碘甲烷(1.32g,9.33mmol)。在 80℃下加热得到的混合物 12 小时。完成时,将混合物冷却至室温并过滤,用乙酸乙酯洗涤残余物,浓缩滤液,

然后通过柱层析纯化，以得到 5- 氯 -3-（环戊基（甲基）氨基）-2- 甲基苯甲酸甲酯（0.5g，95%）。

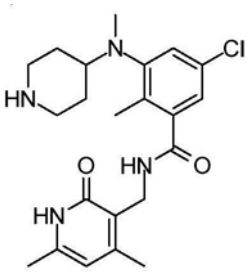
[1243] 步骤 6：5- 氯 -3-（环戊基（甲基）氨基）-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-2- 甲基苯甲酰胺的合成

[1244] 向 5- 氯 -3-（环戊基（甲基）氨基）-2- 甲基苯甲酸甲酯（0.5g，1.77mmol）的 MeOH（5mL）溶液中加入 NaOH（0.106g，2.66mmol）水溶液，在 60℃下搅拌 1 小时。反应完成后，在减压条件下去除甲醇，用稀 HCl 酸化至 pH 值为 6，并用柠檬酸调节至 pH 值为 4。用乙酸乙酯实行萃取。干燥、浓缩合并的有机层得到单独的酸（0.4g，84%）。

[1245] 然后将该酸溶解在 DMSO（0.5mL）中，并向其中加入 3-（氨基甲基）-4,6- 二甲基吡啶 -2(1H)- 酮（0.114g，0.74mmol）。在室温下搅拌反应混合物 15 分钟，然后向其中加入 PYBOP（0.29g，0.56mmol），继续搅拌过夜。反应完成后，将混合物倒入冰中以得到固体，将其过滤，用乙腈洗涤，然后柱纯化，以提供 5- 氯 -3-（环戊基（甲基）氨基）-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-2- 甲基苯甲酰胺（100mg，66%）。LCMS:402.15(M+1)$^+$;HPLC:96.46%(@254nm)(R_t;5.289; 方法：柱：YMC ODS-A150mm x4.6mm x5μ；流动相：A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液；进样量：10μL，柱温：30℃；流速：1.4mL/min.；梯度：8 分钟内 5%B 至 95%B，保持 1.5 分钟，9.51-12min5%B);^{1}H NMR(DMSO-d_6,400MHz) δ 11.45(s,1H),8.19(t,1H,J=4.8Hz),7.13(d,1H,J=2Hz),6.91(d,1H,J=2Hz),5.85(s,1H),4.23(d,2H,J=5.2Hz),3.41-3.45(m,1H),2.50(3H 合并于溶剂峰),2.18(s,3H),2.15(s,3H),2.10(s,3H),1.38-1.67(m,8H)。

[1246] 实施例 7：合成化合物 8：5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-2- 甲基 -3-（甲基（哌啶 -4- 基）氨基）苯甲酰胺

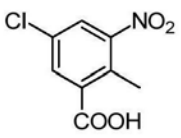
[1247]



化合物 8

[1248] 步骤 1：5- 氯 -2- 甲基 -3- 硝基苯甲酸

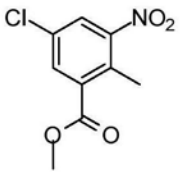
[1249]



[1250] 在 -10℃下逐份地向冷却的浓 H_2SO_4（27mL）中加入 5- 氯 -2- 甲基苯甲酸（4g，23.39mmol）。10 分钟后，在 -10℃下逐滴加入硝化混合物｛将浓 HNO_3（3.3g，52.68mmol）和浓 H_2SO_4（4.4mL）混合来制备｝。在 -10℃下搅拌得到的反应物 30 分钟。完成时，将反应混合物倒入冰冷水中，过滤沉淀的固体，用水洗涤，在真空中干燥，以得到所需的化合物（4.95g，99%）。

[1251] 步骤 2 :5- 氯 -2- 甲基 -3- 硝基苯甲酸甲酯

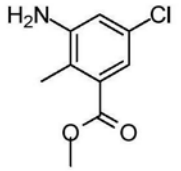
[1252]



[1253] 向 5- 氯 -2- 甲基 -3- 硝基苯甲酸(6.75g,31.25mmol)的 DMF (33mL)搅拌溶液中加入碳酸钠(13.23g,125.18mmol)和碘甲烷(17.77g,125.2mmol)。在 60℃下加热得到的反应物料 4 小时。完成时,向反应物料中加入水,并用 DCM 实行萃取。干燥合并的有机层,在减压条件下浓缩,并通过硅胶柱层析(60-120 目)纯化,以得到所需的化合物(6g,84%)。

[1254] 步骤 3 :3- 氨基 -5- 氯 -2- 甲基苯甲酸甲酯

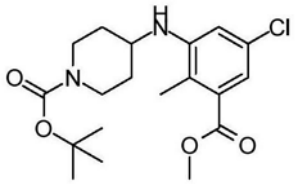
[1255]



[1256] 向 5- 氯 -2- 甲基 -3- 硝基苯甲酸甲酯(6g,26.13mmol)的乙醇(60mL)搅拌溶液中边搅拌边加入铁粉(11.88g,208.4mmol)和溶解于水(60mL)的氯化铵(6g,112.1mmol)。在 80℃下加热得到的反应物料 1 小时。完成时,往反应物料中加入水,反应混合物通过硅藻土过滤,用乙酸乙酯萃取滤液。用水洗涤合并的有机层,干燥,在减压条件下浓缩,得到所需的化合物。

[1257] 步骤 4 :4-((5- 氯 -3-(甲氧基羰基)-2- 甲基苯基) 氨基) 哌啶 -1- 羧酸叔丁酯

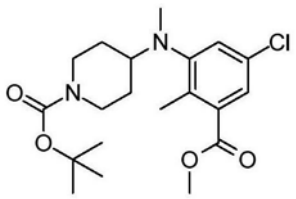
[1258]



[1259] 向 3- 氨基 -5- 氯 -2- 甲基苯甲酸甲酯(6g,30.15mmol) 和 4- 氧代哌啶 -1- 羧酸叔丁酯(29g,150mmol) 的甲醇(10mL) 搅拌溶液中加入醋酸(1.8g,30.1mmol),在室温下搅拌反应 3 小时。然后加入氰基硼氢化钠(4.7g,75.3mmol),搅拌反应过夜。完成时,在减压条件下去除溶剂,通过柱层析纯化原料粗品,以得到所需的化合物(4g,30%)。

[1260] 步骤 5 :4-((5- 氯 -3-(甲氧基羰基)-2- 甲基苯基)(甲基) 氨基) 哌啶 -1- 羧酸叔丁酯

[1261]

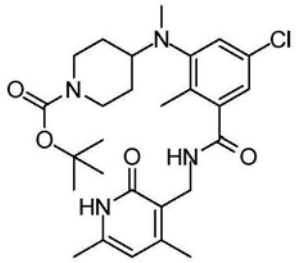


[1262] 向 4-((5- 氯 -3-(甲氧基羰基)-2- 甲基苯基) 氨基) 哌啶 -1- 羧酸叔丁酯(4g,

9.09mmol）的乙腈（50mL）搅拌溶液中加入碳酸铯（5.9g,18.09mmol）和碘甲烷（6.95g,48.94mmol）;在 80℃下加热得到的反应物料 12 小时。完成时,将反应物料冷却至室温并过滤,用乙酸乙酯洗涤残余物,浓缩滤液,然后通过柱层析纯化,以得到所需的化合物（2.2g,53%）。

[1263] 步骤 6 :4-((5- 氯 -3-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）氨基甲酰基)-2- 甲基苯基)(甲基) 氨基) 哌啶 -1- 羧酸叔丁酯

[1264]

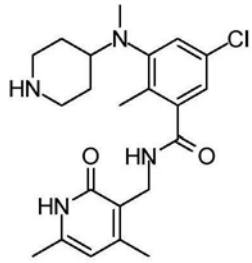


[1265] 向 4-((5- 氯 -3-(甲氧基羰基)-2- 甲基苯基)(甲基) 氨基) 哌啶 -1- 羧酸叔丁酯（0.5g,1.26mmol）的 MeOH （5mL）溶液中加入 NaOH （0.75g,1.86mmol）水溶液,并在 60℃下搅拌 1 小时。反应完成后,在减压条件下去除乙醇,用稀 HCl 酸化至 pH 值为 6,并用柠檬酸调节至 pH 值为 4。用乙酸乙酯实行萃取。干燥、浓缩合并的有机层以得到单独的酸（0.4g,84%）。

[1266] 然后将该酸（0.4g,1.04mmol）溶解于 DMSO （1mL）中,并向其中加入 3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮（0.316g,2.09mmol）。在室温下搅拌反应混合物 15 分钟,然后向其中加入 PYBOP （0.816g,1.56mmol),继续搅拌过夜。反应完成后,将反应物料倒入冰中以得到固体,将其过滤,用乙腈洗涤,然后柱纯化,以提供所需的化合物（0.225g,41%）。

[1267] 步骤 7 :5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基 -3-(甲基 (哌啶 -4- 基) 氨基) 苯甲酰胺

[1268]

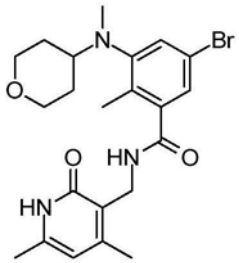


[1269] 将 4-((5- 氯 -3-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基) 氨基甲酰基)-2- 甲基苯基)(甲基) 氨基) 哌啶 -1- 羧酸叔丁酯（0.2g,0.632mmol）的 DCM（5mL）溶液冷却至 0℃,并向其中加入 TFA （0.15mL)。室温下搅拌反应物 1 小时。完成时,浓缩反应至干燥。通过溶剂洗涤纯化残余物,以得到作为其 TFA 盐的所需的化合物（0.14g,53%）。LCMS:417.25(M+1)$^+$;HPLC:96.16%(@254nm)(R_t;4.677; 方法 : 柱 :YMC ODS-A150mm x4.6mm x5μ ; 流动相 :A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液 ; 进样量 :10μL, 柱温 :30℃ ; 流速 :1.4mL/min.; 梯度 :8 分钟内 5%B 至 95%B, 保持 1.5 分钟 ,9.51-12min5%B);^{1}HNMR(DMSO-d6,400MHz) δ 11.47(s,1H),8.49(bs,1H),8.20(t,1H),8.18(bs,1H),7.19(s

,1H),6.96(s,1H),5.86(s,1H),4.25(d,2H,J=4.4Hz),3.25(d,2H,J=12Hz),3.08(m,1H),2.88(bs,2H),2.56(s,3H),2.18(s,3H),2.17(s,3H),2.10(s,3H),1.76(bs,4H)。

[1270] 实施例8:合成化合物10:5-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(甲基(四氢-2H-吡喃-4-基)氨基)苯甲酰胺

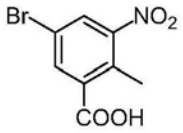
[1271]



化合物10

[1272] 步骤1:5-溴-2-甲基-3-硝基苯甲酸的合成

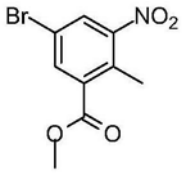
[1273]



[1274] 在室温下,向2-甲基-3-硝基苯甲酸(50g,276mmol)的浓H_2SO_4(200mL)搅拌溶液中逐份加入1,3-二溴-5,5-二甲基-2,4-咪唑烷二酮(43.4g,152mmol),在室温下继续搅拌5小时。完成时,将混合物倒入冰冷水中,过滤得到的固体,用水洗涤,在真空条件下干燥,以得到5-溴-2-甲基-3-硝基苯甲酸(71.7g,99.9%)。

[1275] 步骤2:5-溴-2-甲基-3-硝基苯甲酸甲酯的合成

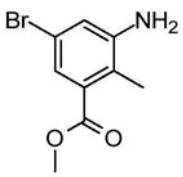
[1276]



[1277] 向用类似上述的方法制备的5-溴-2-甲基-3-硝基苯甲酸(287g,1103mmol)的DMF(150mL)搅拌溶液中加入碳酸钠(468g,4415mmol)和碘甲烷(626.6g,4415mmol)。在60℃下加热得到的化合物8小时。完成时,通过过滤去除固体,用乙醚洗涤残余物(5次)。干燥合并的有机层,在减压条件下浓缩,以得到5-溴-2-甲基-3-硝基苯甲酸甲酯(302g,99%)。

[1278] 步骤3:3-氨基-5-溴-2-甲基苯甲酸甲酯的合成

[1279]

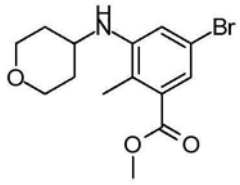


[1280] 向5-溴-2-甲基-3-硝基苯(150g,544mmol)的乙醇(750mL)搅拌溶液中加入铁

粉(93.3g,1636mmol)和在水(750mL)中的氯化铵(150g,2777mmol)溶液。在80℃下加热得到的混合物7小时。完成时,通过硅藻土过滤混合物;用水和乙酸乙酯洗涤硅藻土,用乙酸乙酯萃取滤液。干燥、在减压条件下浓缩合并的有机层,以得到3-氨基-5-溴-2-甲基苯甲酸甲酯。

[1281] 步骤4:5-溴-2-甲基-3-((四氢-2H-吡喃-4-基)氨基)苯甲酸甲酯的合成

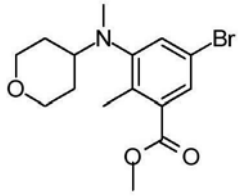
[1282]



[1283] 向3-氨基-5-溴-2-甲基苯甲酸甲酯(2g,8.23mmol)和二氢-2H-吡喃-4(3)-酮(1.06g,10.6mmol)的甲醇(20mL)搅拌溶液中加入醋酸(0.5g,8.23mmol),在室温下搅拌反应3小时。然后在0℃下加入氰基硼氢化钠(0.622g,9.87mmol),室温下搅拌反应过夜。完成时,在减压条件下去除溶剂,并通过柱层析纯化原料粗品,以得到5-溴-2-甲基-3-((四氢-2H-吡喃-4-基)氨基)苯甲酸甲酯(1.6g,61%)。

[1284] 步骤5:5-溴-2-甲基-3-(甲基(四氢-2H-吡喃-4-基)氨基)苯甲酸甲酯

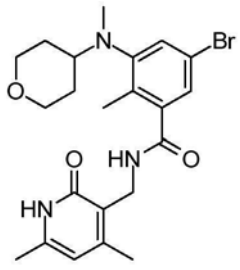
[1285]



[1286] 向5-溴-2-甲基-3-((四氢-2H-吡喃-4-基)氨基)苯甲酸甲酯(0.4g,1.26mmol)的乙腈(15mL)搅拌溶液中加入碳酸铯(0.79g,2.44mmol)和碘甲烷(0.86g,6.11mmol);在80℃下加热得到的混合物7小时。完成时,将混合物冷却至室温并过滤,用乙酸乙酯洗涤残余物,浓缩滤液,然后通过柱层析纯化,以得到5-溴-2-甲基-3-(甲基(四氢-2H-吡喃-4-基)氨基)苯甲酸甲酯(0.33g,80%)。

[1287] 步骤6:5-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(甲基(四氢-2H-吡喃-4-基)氨基)苯甲酰胺的合成

[1288]

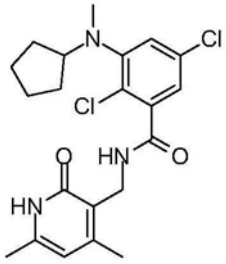


[1289] 向化合物6(0.8g,2.4mmol)的MeOH(20mL)溶液中加入NaOH(0.19g,4.89mmol)水溶液,在60℃下搅拌1小时。反应完成后,在减压条件下去除乙醇,用稀HCl酸化至pH值为6,并用柠檬酸调节至pH值为4。用乙酸乙酯进行萃取。干燥、浓缩合并的有机层以得到单独的酸(0.70g,92%)。

[1290] 然后将该酸(0.7g,2.24mmol)溶解于DMSO(3mL)中,并向其中加入3-(氨基甲基)-4,6-二甲基吡啶-2(1H)-酮(0.74g,4.89mmol)。在室温下搅拌反应混合物15分钟,然后向其中加入PYBOP(1.9g,3.6mmol),继续搅拌过夜。完成后,将混合物倒入冰中以得到固体。过滤固体,用乙腈洗涤,然后通过柱层析纯化,以得到5-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(甲基(四氢-2H-吡喃-4-基)氨基)苯甲酰胺(0.53g,54%)。LCMS:462.23(M+1)$^+$;HPLC:98.57%(@254nm)(R_t;5.276;方法:柱:YMC ODS-A150mm x4.6mm x5μ;流动相:A;0.05%TFA的水溶液/B;0.05%TFA的乙腈溶液;进样量:10μL,柱温:30℃;流速:1.4mL/min.;梯度:8分钟内5%B至95%,保持1.5分钟,9.51-12min5%B);^{1}H NMR(DMSO-d_6,400MHz)δ11.46(s,1H),8.20(t,1H,J=4.8Hz),7.24(d,1H,J=2Hz),7.04(d,1H,J=2Hz),5.85(s,1H),4.24(d,2H,J=4.8Hz),3.84(d,2H,J=10.8Hz),3.22-3.28(m,2H),2.96(m,1H),2.56(s,3H),2.18(s,3H),2.13(s,3H),2.10(s,3H),1.52-1.61(m,4H)。

[1291] 实施例9:合成化合物13:2,5-二氯-3-(环戊基(甲基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)苯甲酰胺

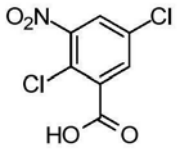
[1292]



化合物13

[1293] 步骤1:2,5-二氯-3-硝基苯甲酸的合成:

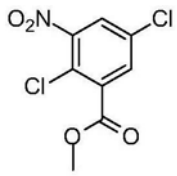
[1294]



[1295] 在-10℃下,向冷却的浓H_2SO_4(50mL)中分批加入2,5-二氯苯甲酸(5g,26.2mmol)。10分钟后,在-10℃下逐滴加入硝化混合物{将浓HNO_3(2.5mL)和浓H_2SO_4(10mL)混合来制备}。在-10℃下搅拌得到的反应混合物2小时。完成时,将反应混合物倒入冰冷水中,固体沉淀出来。通过过滤收集该固体,用水洗涤,并在真空下干燥,以得到2,5-二氯-3-硝基苯甲酸(3.4g,65%)。

[1296] 步骤2:2,5-二氯-3-硝基苯甲酸甲酯的合成:

[1297]

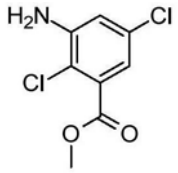


[1298] 向2,5-二氯-3-硝基苯甲酸(3.2g,13.67mmol)的DMF(30mL)搅拌溶液中加入碳

酸钠(4.3g,40.56mmol)和碘甲烷(9.7g,68.30mmol)。在 60℃下加热反应混合物 18 小时。完成时,向反应混合物中加入水,用 DCM 萃取产物。在减压条件下干燥、浓缩合并的有机层以得到 2,5- 二氯 -3- 硝基苯甲酸甲酯(3g,90%)。

[1299] 步骤 3 :3- 氨基 -2,5- 二氯苯甲酸甲酯的合成 :

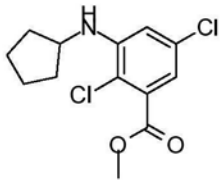
[1300]



[1301] 向 2,5- 二氯 -3- 硝基苯甲酸甲酯(3.3g,13.1mmol)的乙醇(20mL)搅拌溶液中加入铁粉(7g,82.35mmol)和溶解于水(20mL)中的氯化铵(3.5g,64.81mmol)。在 80℃下加热反应混合物 3 小时。完成时,向反应混合物加入水,通过硅藻土过滤来去除固体。用乙酸乙酯萃取滤液。用水洗涤合并的有机层,干燥,在减压条件下浓缩,以得到 3- 氨基 -2,5- 二氯苯甲酸甲酯(2.5g,66%)。

[1302] 步骤 4 :2,5- 二氯 -3-(环戊基氨基) 苯甲酸甲酯的合成 :

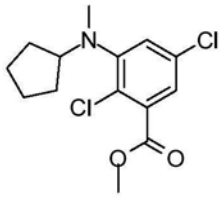
[1303]



[1304] 向 3- 氨基 -2,5- 二氯苯甲酸甲酯(2,5g,11.5mmol)和环戊酮(4.8g,57.1mmol)的甲醇(5mL)搅拌溶液中加入醋酸(0.6g,11.3mmol),在室温下继续搅拌 3 小时。然后加入氰基硼氢化钠(1.4g,22.2mmol),搅拌反应过夜。完成时,在减压条件下去除溶剂,通过柱层析纯化产物,以得到 2,5- 二氯 -3-(环戊基氨基) 苯甲酸甲酯(0.275g,8%)。

[1305] 步骤 5 :2,5- 二氯 -3-(环戊基 (甲基) 氨基) 苯甲酸甲酯的合成 :

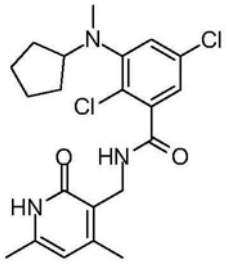
[1306]



[1307] 向 2,5- 二氯 -3-(环戊基氨基) 苯甲酸甲酯(0.275g,0.958mmol)的乙腈(5mL)搅拌溶液中加入碳酸铯(0.622g,1.9mmol)和碘甲烷(0.689g,4.78mmol)。在 80℃下加热反应混合物 18 小时。完成时,将反应冷却至室温并过滤。用乙酸乙酯洗涤残余物,并浓缩滤液,以得到 2,5- 二氯 -3-(环戊基 (甲基) 氨基) 苯甲酸甲酯(0.27g,93%)。

[1308] 步骤 6 :2,5- 二氯 -3-(环戊基 (甲基) 氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基) 苯甲酰胺的合成

[1309]

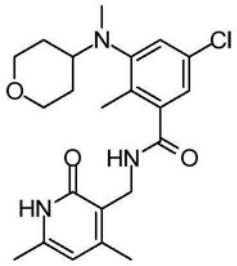


[1310] 向 2,5- 二氯 -3-(环戊基 (甲基) 氨基) 苯甲酸甲酯(0.25g,0.83mmol)的 MeOH (5mL)溶液中加入 NaOH (0.50g,1.24mmol)水溶液,在 60℃下搅拌 1 小时。反应完成后,在减压条件下去除甲醇,用稀 HCl 酸化至 pH 值为 6,并用柠檬酸酸化至 pH 值为 4。用乙酸乙酯萃取产物。干燥并浓缩合并的有机层,以得到所需的酸(0.21g,88%)。

[1311] 然后将该酸(0.21g,0.755mmol)溶解在 DMSO (3mL)中,并向其中加入 3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮(0.3g,1.97mmol)。在室温下搅拌反应混合物 15 分钟,然后向其中加入 PYBOP (0.757g,1.45mmol),继续搅拌过夜。反应完成后,将反应混合物倒入冰中以得到固体。过滤固体,用乙腈洗涤。通过制备型 HPLC 将化合物进一步纯化,以得到作为 TFA 盐的 2,5- 二氯 -3-(环戊基 (甲基) 氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基) 苯甲酰胺(0.1g,36%)。LCMS:422.10(M+1)$^+$;HPLC:97.58%(@254nm)(R_t;6.973; 方法 : 柱 :YMC ODS-A150mm x4.6mm x5μ ; 流动相 :A;0.05%TFA 的水溶液 / B;0.05%TFA 的乙腈溶液 ; 进样量 :10μL, 柱温 :30℃ ; 流速 :1.4mL/min. ; 梯度 :8 分钟内 5%B 至 95%B, 保持 1.5 分钟 ,9.51-12min5%B);^{1}H NMR(DMSO-d_6,400MHz) δ 11.46(s,1H),8.35(t,1H),7.23(s,1H),6.98(s,1H),5.85(s,1H),4.24(d,2H,J=4.4Hz),3.66(m,1H),2.59(s,3H),2.18(s,3H),2.10(s,3H),1.70(bs,2H),1.61(bs,2H),1.48(bs,4H)。

[1312] 实施例 10 : 合成化合物 14 :5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基 -3-(甲基 (四氢 -2H- 吡喃 -4- 基) 氨基) 苯甲酰胺

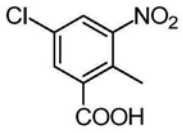
[1313]



[1314] 化合物 14

[1315] 步骤 1 :5- 氯 -2- 甲基 -3- 硝基苯甲酸

[1316]

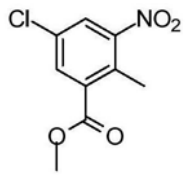


[1317] 在 -10℃下逐份地向冷却的浓 H_2SO_4 (27mL) 中加入 2- 甲基 -3- 硝基苯甲酸(4g,23.39mmol)。10 分钟后,在 -10℃下逐滴加入硝化混合物 { 将浓 HNO_3 (3.3g,52.68mmol) 和浓 H_2SO_4 (4.4mL) 混合来制备 }。在 -10℃下搅拌得到的反应物料 30 分钟。完成时,将

反应混合物倒入冰冷水中，过滤沉淀的固体，用水洗涤并在真空下干燥，得到所需的化合物（4.95g，99%）。

[1318] 步骤 2 ：5- 氯 -2- 甲基 -3- 硝基苯甲酸甲酯

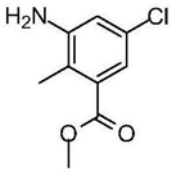
[1319]



[1320] 向 5- 氯 -2- 甲基 -3- 硝基苯甲酸（6.75g，31.25mmol）的 DMF （33mL）搅拌溶液中加入碳酸钠（13.23g，125.18mmol）和碘甲烷（17.77g，125.2mmol）。在 60℃下加热得到的反应物料 4 小时。完成时，向反应物料中加入水，并用 DCM 实行萃取。干燥、在减压条件下浓缩合并的有机层，通过硅胶柱层析（60-120 目）纯化，以得到所需的化合物（6g，84%）。

[1321] 步骤 3 ：3- 氨基 -5- 氯 -2- 甲基苯甲酸甲酯

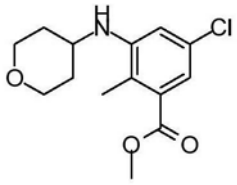
[1322]



[1323] 向 5- 氯 -2- 甲基 -3- 硝基苯甲酸甲酯（6g，26.13mmol）的乙醇（60mL）搅拌溶液中边搅拌边加入铁粉（11.88g，208.4mmol）和溶解于水（60mL）中的氯化铵（6g，112.1mmol）。在 80℃下加热得到的反应物料 1 小时。完成时，向反应物料中加入水，通过硅藻土过滤反应混合物，用乙酸乙酯萃取滤液。用水洗涤合并的有机层，干燥，在减压条件下浓缩，以得到照现状使用的所需的化合物。

[1324] 步骤 4 ：5- 氯 -2- 甲基 -3-（（四氢 -2H- 吡喃 -4- 基）氨基）苯甲酸甲酯

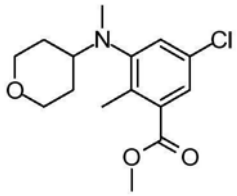
[1325]



[1326] 向 3- 氨基 -5- 氯 -2- 甲基苯甲酸甲酯（1g，5.025mmol）和二氢 -2H- 吡喃 -4(3H)- 酮（753mg，7.537mmol）的甲醇（10mL）搅拌溶液中加入醋酸（301mg，5.025mmol），在室温下搅拌反应 3 小时。然后加入氰基硼氢化钠（373mg，6.03mmol），搅拌反应过夜。完成时，在减压条件下去除溶剂，并通过柱层析纯化原料粗品，以得到所需的化合物（700mg，49%）。

[1327] 步骤 5 ：5- 氯 -2- 甲基 -3-（甲基（四氢 -2H- 吡喃 -4- 基）氨基）苯甲酸甲酯

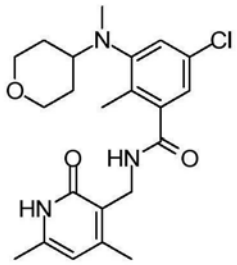
[1328]



[1329] 向 5- 氯 -2- 甲基 -3-((四氢 -2H- 吡喃 -4- 基)氨基)苯甲酸甲酯(700mg,2.473mmol)的乙腈(10mL)搅拌溶液中加入碳酸铯(1.61g,4.946mmol)和碘甲烷(1.82g,0.8ml,12.36mmol);在 80℃下加热得到的反应物 13 小时。完成时,将反应物料冷却至室温并过滤,用乙酸乙酯洗涤残余物,浓缩滤液,然后通过柱层析纯化,以得到所需的化合物(480mg,65%)。

[1330] 步骤 6:5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)-2- 甲基 -3-(甲基(四氢 -2H- 吡喃 -4- 基)氨基)苯甲酰胺

[1331]

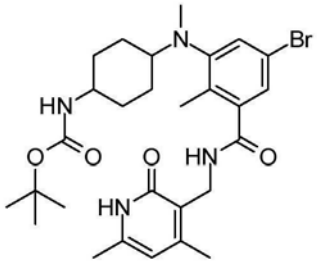


[1332] 向 5- 氯 -2- 甲基 -3-(甲基(四氢 -2H- 吡喃 -4- 基)氨基)苯甲酸甲酯(0.48g,1.616mmol)的 EtOH (2mL)溶液中加入 NaOH (96mg,2.424mmol)水溶液,在 60℃下搅拌 1 小时。反应完成后,在减压条件下去除乙醇,用稀 HCl 酸化至 pH 值为 6,并用柠檬酸调节至 pH 值为 4。用乙酸乙酯实行萃取。干燥、浓缩合并的有机层以得到单独的酸(0.4g,87%)。

[1333] 然后将该酸(0.4g,1.41mmol)溶解于 DMSO (1mL)中,并向其中加入 3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮(0.429g,2.82mmol)。室温下搅拌反应混合物 15 分钟,然后向其中加入 PYBOP (1.10g,2.12mmol),继续搅拌过夜。反应完成后,将反应物料倒入冰中以得到固体,将其过滤,用乙腈洗涤,然后柱纯化,以提供标题化合物(0.17g,29%):LCMS:418.25(M+1)$^+$;HPLC:97.72%(@254nm)(R_t;5.022;方法:柱:YMC ODS-A150mm x4.6mm x5μ;流动相:A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液;进样量:10μL, 柱温:30℃;流速:1.4mL/min.;梯度:8 分钟内 5%B 至 95%B, 保持 1.5 分钟,9.51-12min5%B);^{1}H NMR(DMSO-d_6,400MHz) δ 11.48(s,1H),8.21(t,1H,J=4.4Hz),7.13(s,1H),6.92(s,1H),5.85(s,1H),4.24(d,2H,J=4.4Hz),3.84(d,2H,J=10.8Hz),3.25(t,2H,J=11.2Hz),2.96(m,1H),2.56(s,3H),2.18(s,3H),2.15(s,3H),2.10(s,3H),1.65-1.52(m,4H)。

[1334] 实施例 11:合成化合物 15:(4-((5- 溴 -3-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)氨基甲酰基)-2- 甲基苯基)(甲基)氨基)环己基)氨基甲酸叔丁酯

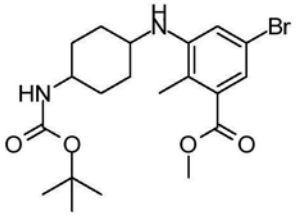
[1335]



化合物 15

[1336] 步骤 1 :5- 溴 -3-((4-((叔丁氧羰基) 氨基) 环己基) 氨基)-2- 甲基苯甲酸甲酯的合成

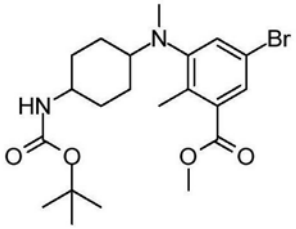
[1337]



[1338] 向 3- 氨基 -5- 溴 -2- 甲基苯甲酸甲酯(5g,20.6mmol)和 (4- 氧代环己基) 氨基甲酸叔丁酯(5.6g,26.7mmol)的甲醇(50mL)搅拌溶液中加入醋酸(1.2g,20.6mmol),室温下搅拌混合物 3 小时。然后加入氰基硼氢化钠(1.6g,26.7mmol),搅拌反应过夜。完成时,在减压条件下去除溶剂,并通过柱层析纯化产物,以得到化合物 5- 溴 -3-((4-((叔丁氧羰基) 氨基) 环己基) 氨基)-2- 甲基苯甲酸甲酯(3g,33.3%)。

[1339] 步骤 2 :5- 溴 -3-((4-((叔丁氧羰基) 氨基) 环己基)(甲基) 氨基)-2- 甲基苯甲酸甲酯的合成

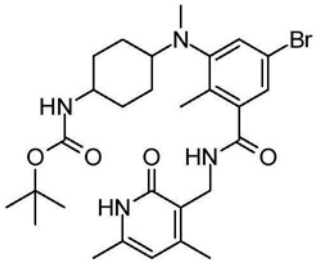
[1340]



[1341] 向 5- 溴 -3-((4-((叔丁氧羰基) 氨基) 环己基) 氨基)-2- 甲基苯甲酸甲酯(1.5g,4.6mmol)的乙腈(15mL)搅拌溶液中加入碳酸铯(2.63g,8.1mmol)和碘甲烷(2.86g,20.32mmol)。在 80℃下加热混合物 7 小时。完成时,将反应冷却至室温,过滤,用乙酸乙酯洗涤残余物。浓缩滤液以得到 5- 溴 -3-((4-((叔丁氧羰基) 氨基) 环己基)(甲基) 氨基)-2- 甲基苯甲酸甲酯(1.5g)。

[1342] 步骤 3 :(4-((5- 溴 -3-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基) 氨基甲酰基)-2- 甲基苯基)(甲基) 氨基) 环己基) 氨基甲酸叔丁酯的合成

[1343]

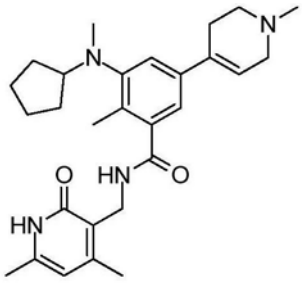


[1344] 向 5- 溴 -3-((4-((叔丁氧羰基)氨基)环己基)(甲基)氨基)-2- 甲基苯甲酸甲酯(1.5g,3.3mmol)的 MeOH (20mL)溶液中加入 NaOH (0.26g,6.62mmol)水溶液,在 60℃下搅拌 1 小时。反应完成后,在减压条件下去除甲醇,用稀 HCl 酸化混合物至 pH 值为 6,并用柠檬酸酸化至 pH 值为 4。用乙酸乙酯萃取产物。干燥、浓缩合并的有机层以得到所需的酸(1.33g,92%)。

[1345] 然后将该酸(1.3g,2.96mmol)溶解在 DMSO (10mL)中,并向其中加入 3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮(0.34g,2.2mmol)。在室温下搅拌反应混合物 15 分钟,然后向其中加入 PYBOP (0.88g,1.7mmol),继续搅拌过夜。反应完成后,将混合物倒入冰中以得到固体。过滤固体,用乙腈洗涤,然后通过柱层析纯化,以得到 (4-((5- 溴 -3-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)氨基甲酰基)-2- 甲基苯基)(甲基)氨基)环己基)氨基甲酸叔丁酯(0.5g,26%)。LCMS:575.80(M+1)$^+$;HPLC:99.99%(@254nm)(R_t;6.094,7.065[非对映异构体的混合物]; 方法 : 柱 :YMC ODS-A150mm x4.6mm x5μ; 流动相 :A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液 ; 进样量 :10μL, 柱温 :30℃ ; 流速 :1.4mL/min.; 梯度 :8 分钟内 5%B 至 95%B, 保持 1.5 分钟,9.51-12min5%B);^{1}H NMR(DMSO-d_6,400MHz) δ 11.45(s,1H),8.20(d,1H,J=3.6Hz),7.21(s,1H),7.18(s,1H),7.01(s,1H),6.66(d,1H,J=7.2Hz),5.85(s,1H),4.23(d,2H,J=3.2Hz),3.44(bs,1H),3.15(bs,1H),2.55-2.66(m,3H),2.18(s,3H),2.10(s,6H),1.76-1.79(m,2H),1.51-1.63(m,3H),1.36-1.38(m,11H),1.07-1.16(m,1H)。

[1346] 实施例 12 :合成化合物 16 :3-(环戊基(甲基)氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)-2- 甲基 -5-(1- 甲基 -1,2,3,6- 四氢吡啶 -4- 基)苯甲酰胺

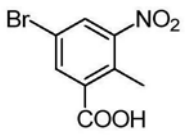
[1347]



化合物 16

[1348] 步骤 1 :5- 溴 -2- 甲基 -3- 硝基苯甲酸

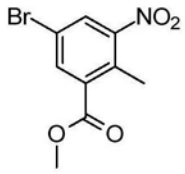
[1349]



[1350] 在室温下，向 2- 甲基 -3- 硝基苯甲酸（50g，276.2mmol）的浓 H_2SO_4（200mL）搅拌溶液中逐份加入 1,3- 二溴 -5,5- 二甲基 -2,4- 咪唑烷二酮（43.4g，151.8mmol），在室温下搅拌反应物料 5 小时。完成时，将反应物料倒入冰冷水中，过滤沉淀的固体，用水洗涤得到的残余物，并在真空下干燥，得到所需的化合物（71.7g，100%）。

[1351] 步骤 2 ：5- 溴 -2- 甲基 -3- 硝基苯甲酸甲酯

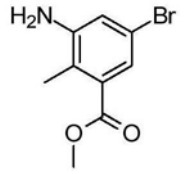
[1352]



[1353] 向 5- 溴 -2- 甲基 -3- 硝基苯甲酸（287g，1103mmol）的 DMF（150mL）搅拌溶液中加入碳酸钠（468g，4415mmol）和碘甲烷（626.63g，4415mmol）。在 60℃下加热得到的反应物料 8 小时。完成时，过滤沉淀的固体，用乙醚洗涤残余物（5 次）。干燥、在减压条件下浓缩合并的有机层，得到所需的粗制化合物（302g，99%），其不需要进一步纯化就使用。

[1354] 步骤 3 ：3- 氨基 -5- 溴 -2- 甲基苯甲酸甲酯

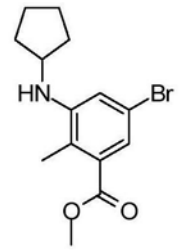
[1355]



[1356] 向 5- 溴 -2- 甲基 -3- 硝基甲苯（150g，544mmol）的乙醇（750mL）搅拌溶液中边搅拌边加入铁粉（93.3g，1636mmol）和溶解于水（750mL）中的氯化铵（150g，2777mmol）。在 80℃下加热得到的反应物 7 小时。完成时，通过硅藻土过滤反应物料，同时用水和乙酸乙酯洗涤，用乙酸乙酯萃取滤液。干燥、在减压条件下浓缩合并的有机层，得到照现状进一步使用的所需的化合物。

[1357] 步骤 4 ：5- 溴 -3-（环戊基氨基）-2- 甲基苯甲酸甲酯

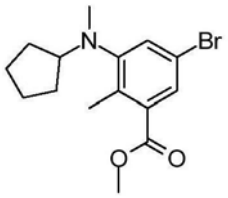
[1358]



[1359] 向 3- 氨基 -5- 溴 -2- 甲基苯甲酸甲酯（0.3g，1.33mmol）和环戊酮（0.56g，6.6mmol）的甲醇（3mL）搅拌溶液中加入醋酸（0.159g，2.6mmol），在室温下搅拌反应 3 小时。然后加入氰基硼氢化钠（0.208g，3.3mmol），搅拌反应过夜。完成时，在减压条件下去除溶剂，原料粗品照现状使用于下一步中。

[1360] 步骤 5 :5- 溴 -3-(环戊基 (甲基) 氨基)-2- 甲基苯甲酸甲酯的合成

[1361]



[1362] 将 5- 溴 -3-(环戊基氨基)-2- 甲基苯甲酸甲酯(1g,3.22mmol)、Cs_2CO_3 (2.10g,6.45mmol)和碘甲烷(2.3g,16.12mmol)的乙腈(15mL)溶液在 80℃下加热 14 小时。起始原料完全耗尽后,过滤反应混合物。浓缩滤液,并通过柱层析纯化得到的残余物,以提供所需的化合物(0.9g,86%)。

[1363] 步骤 6 :5- 溴 -3-(环戊基氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基苯甲酰胺

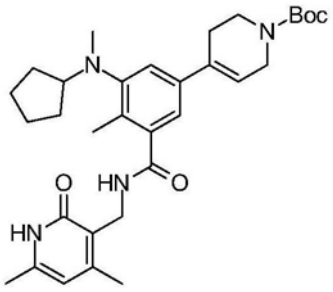
[1364]

[1365] 向 5- 溴 -3-(环戊基 (甲基) 氨基)-2- 甲基苯甲酸甲酯(0.9g,2.76mmol)的 EtOH(9mL)和水(2.2mL)溶液中加入 NaOH 水溶液(0.166g,4.15mmol),在 60℃下搅拌 1 小时。反应完成后,在减压条件下去除乙醇,用稀 HCl 酸化至 pH 值为 6,并用柠檬酸调节至 pH 值为 4。用乙酸乙酯实行萃取。干燥、浓缩合并的有机层来得到单独的酸(0.85g,98%)。

[1366] 然后将该酸(0.85g,2.73mmol)溶解于 DMSO (10mL)中,并向其中加入 3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮(0.83g,5.46mmol)。室温下搅拌反应混合物 15 分钟,然后向其中加入 PYBOP(2.13g,4.09mmol),继续搅拌过夜。反应完成后,将反应物料倒入冰中以得到固体,将其过滤,先用乙腈再用乙醚洗涤,以得到所需的化合物(0.450g,37%)。

[1367] 步骤 7 :4-(3-(环戊基 (甲基) 氨基)-5-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基) 氨基甲酰基)-4- 甲基苯基)-5,6- 二氢吡啶 -1(2H)- 羧酸叔丁酯

[1368]

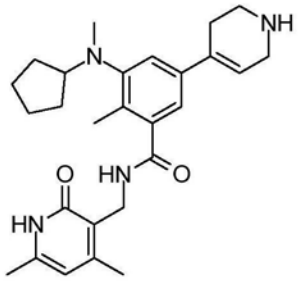


[1369] 向 5- 溴 -3-(环戊基氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基苯甲酰胺(1.0g,2.24mmol)和硼酸(0.833g,2.69mmol)的二氧六环(20mL)脱气溶液中加入 $Pd(PPh_3)_4$ (0.260g,0.224mmol,0.1eq),再用氩气净化溶液 20 分钟。向反

应混合物中加入在 1mL 水中的 Na_2CO_3（0.857，8.08mmol）水溶液，再用氩气净化反应混合物 20 分钟。反应在 100℃下加热 90 分钟。然后将反应混合物冷却至室温，然后倒入冷水中，用二氯甲烷萃取。通过柱层析纯化粗制化合物以提供所需的化合物（0.900g，64%）。

[1370] 步骤 8：3-（环戊基（甲基）氨基）-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-2- 甲基 -5-(1,2,3,6- 四氢吡啶 -4- 基）苯甲酰胺

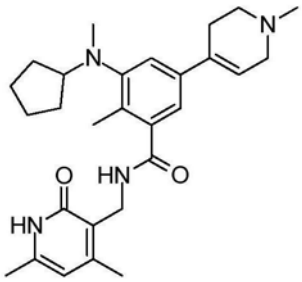
[1371]



[1372] 向 4-(3-（环戊基（甲基）氨基）-5-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）氨基甲酰基）-4- 甲基苯基）-5,6- 二氢吡啶 -1(2H)- 羧酸叔丁酯（0.800g，1.45mmol）的 DCM 搅拌溶液中加入 TFA（3mL），在室温下搅拌反应混合物 2 小时。完成时，将反应浓缩至干燥。用碳酸氢钠水溶液碱化残余物至 pH 值为 8，用 20%MeOH/DCM 萃取水层。用硫酸钠干燥合并的有机层并浓缩以得到原料粗品，将该原料粗品通过制备型 HPLC 纯化，以得到所需的化合物（0.620g，95%）。

[1373] 步骤 9：3-（环戊基（甲基）氨基）-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-2- 甲基 -5-(1- 甲基 -1,2,3,6- 四氢吡啶 -4- 基）苯甲酰胺

[1374]

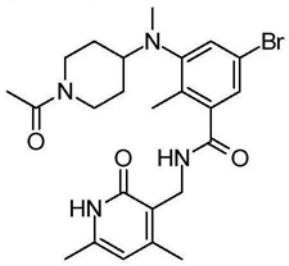


[1375] 将 3-（环戊基（甲基）氨基）-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-2- 甲基 -5-(1,2,3,6- 四氢吡啶 -4- 基）苯甲酰胺（0.100g，0.223mmol）溶解于甲醇（5mL）中，冷却至 0℃，加入福尔马林（0.067g，0.19mL，2.23mmol）。在同样温度下搅拌得到的反应物 30 分钟。把氰基硼氢化钠（0.041g，0.66mmol）加入到上述反应物料中，在室温下搅拌 4 小时。完成后，在减压条件下去除溶剂，并向残余物中加入水，用 DCM 实行萃取。干燥、浓缩合并的有机层，并通过柱层析纯化，以得到所需的化合物（0.065g，63%）：LCMS:463.40(M+1)$^+$;HPLC:98.79%(@254nm)(R_t;3.911; 方法：柱：YMC ODS-A150mm x4.6mm x5μ；流动相：A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液；进样量：10μL, 柱温：30℃；流速：1.4mL/min.；梯度：8 分钟内 5%B 至 95%B, 保持 1.5 分钟，9.51-12min5%B);^{1}H NMR(DMSO-d_6, 400MHz) δ 11.43(s,1H), 8.04(t,1H,J=4.8Hz), 7.17(s,1H), 6.95(s,1H), 6.07(s,1H), 5.85(s,1H), 4.25(d,2H,J=4.8Hz), 3.45(m,1H), 2.98(bs,2H), 2.53(m,2H), 2.42(bs,2H), 2.26(s,3H), 2.18(s,3H), 2.17(s,3H), 2.10(s,3H), 1.67(m,2H), 1.59(m,2H), 1.49

(m,2H),1.40(m,2H)。

[1376] 实施例13:合成化合物17:3-((1-乙酰基哌啶-4-基)(甲基)氨基)-5-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺

[1377]

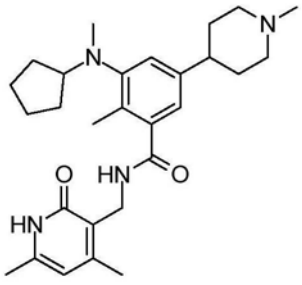


化合物17

[1378] 将5-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(甲基(哌啶-4-基)氨基)苯甲酰胺(0.2g,0.447mmol)溶解于DMSO(2mL)中,向其中加入醋酸(0.054g,0.896mmol)。室温下搅拌反应混合物15分钟,然后向其中加入PYBOP(0.342g,0.672mmol),继续搅拌过夜。结束后,将反应物料倒入冰中,并用10%MeOH/DCM进行萃取。干燥、浓缩合并的有机层以得到原料粗品,然后将其通过硅胶柱层析(100-200目)纯化,以得到所需的化合物(0.15g,17%)。LCMS:503.20(M+1)$^+$;HPLC:96.06%(@254nm)(R_t;5.143;方法:柱:YMC ODS-A150mm x4.6mm x5μ;流动相:A;0.05%TFA的水溶液/B;0.05%TFA的乙腈溶液;进样量:10μL,柱温:30℃;流速:1.4mL/min.;梯度:8分钟内5%B至95%B,保持1.5分钟,9.51-12min5%B);^{1}H NMR(DMSO-d_6,400MHz)δ11.48(s,1H),8.21(t,1H,J=4.8Hz),7.23(d,1H,J=1.6Hz),7.04(d,1H,J=1.6Hz),5.85(s,1H),4.32(d,1H,J=12.4Hz),4.23(d,2H,J=4.8Hz),3.77(d,1H,J=13.2Hz),2.98(t,2H,J=11.2Hz),2.54(s,3H),2.18(s,3H),2.13(s,3H),2.10(s,3H),1.97(s,3H),1.53-1.60(m,4H),1.38-1.41(m,1H)。

[1379] 实施例14:合成化合物18:3-(环戊基(甲基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-5-(1-甲基哌啶-4-基)苯甲酰胺

[1380]



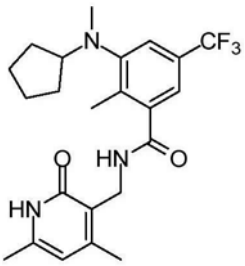
化合物18

[1381] 向3-(环戊基(甲基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-5-(1-甲基-1,2,3,6-四氢吡啶-4-基)苯甲酰胺(0.045g,0.097mmol)的乙醇溶液中加入10%Pd/C,在膨胀压力的H_2下搅拌反应。起始原料完全耗尽后,通过硅藻土过滤反应混合物。浓缩滤液,在乙腈中磨碎并过滤,以提供所需的化合物(0.030g,66%):LCMS:465.40(M+1)$^+$;HPLC:95.39%(@254nm)(Rt;3.884;方法:柱:YMC ODS-A150mm x4.6mm x5μ;

流动相 :A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液 ; 进样量 :10μL, 柱温 :30℃ ; 流速 :1.4mL/min.; 梯度 :8 分钟内 5%B 至 95%B, 保持 1.5 分钟 ,9.51-12min5%B);^{1}H NMR(DMSO-d_6,400MHz) δ 11.44(s,1H),7.98(t,1H),7.00(s,1H),6.77(s,1H),5.85(s,1H),4.25(d,2H,J=4.4Hz),3.42(m,1H),2.84(d,2H,J=11.2Hz),2.47(s,3H),2.37(m,1H),2.18(s,6H),2.15(s,3H),2.10(s,3H),1.93(t,2H,J=10.8Hz),1.70-1.55(m,8H),1.48(m,2H),1.38(m,2H)。

[1382] 实施例 15 :合成化合物 20 :3-(环戊基 (甲基) 氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基 -5-(三氟甲基) 苯甲酰胺

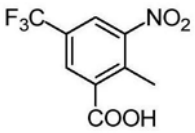
[1383]



化合物 20

[1384] 步骤 1 :2- 甲基 -3- 硝基 -5-(三氟甲基) 苯甲酸的合成

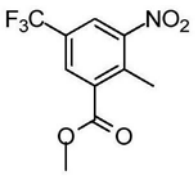
[1385]



[1386] 在 -10℃下,向冷却的浓 H_2SO_4(27mL)中逐份加入 2- 甲基 -5-(三氟甲基) 苯甲酸 (4g,19.6mmol)。10 分钟后,在 -10℃下逐滴加入硝化混合物 { 将浓 HNO_3(2.77g,44.44mmol) 和浓 H_2SO_4 (3.6mL)混合来制备 }。在 -10℃下搅拌得到的溶液 30 分钟。完成时,将反应混合物倒入冰冷水中。过滤固体,用水洗涤并在真空下干燥,以得到 2- 甲基 -3- 硝基 -5-(三氟甲基) 苯甲酸 (4.95g,99%)。

[1387] 步骤 2 :2- 甲基 -3- 硝基 -5-(三氟甲基) 苯甲酸甲酯的合成

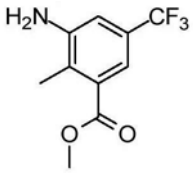
[1388]



[1389] 向 2- 甲基 -3- 硝基 -5-(三氟甲基) 苯甲酸 (1g,4.01mmol) 的 DMF (3mL) 搅拌溶液中加入碳酸钠 (0.63g,6.02mmol) 和碘甲烷 (1.14g,8.03mmol)。在 60℃下加热得到的混合物 4 小时。完成时,向反应中加入水,用 DCM 萃取产物。干燥、在减压条件下浓缩合并的有机层,并通过硅胶柱层析纯化,以得到 2- 甲基 -3- 硝基 -5-(三氟甲基) 苯甲酸甲酯 (1g, 95.2%)。

[1390] 步骤 3 :3- 氨基 -2- 甲基 -5-(三氟甲基) 苯甲酸甲酯的合成

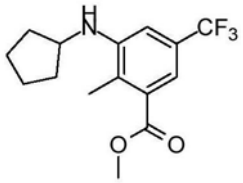
[1391]



[1392] 向 2- 甲基 -3- 硝基 -5-(三氟甲基) 苯甲酸甲酯(5.6g,20.97mmol) 的乙醇(40mL) 搅拌溶液中加入铁粉(4.67g,85.16mmol) 和溶解于水(30mL) 中的氯化铵(5.6g,104.6mmol)。在 80℃下加热得到的混合物 1 小时。完成时,向反应中加入水,通过硅藻土过滤混合物。用乙酸乙酯萃取滤液。然后干燥,在减压条件下浓缩合并的有机层,以得到 3- 氨基 -2- 甲基 -5-(三氟甲基) 苯甲酸甲酯。

[1393] 步骤 4 :3-(环戊基氨基)-2- 甲基 -5-(三氟甲基) 苯甲酸甲酯的合成

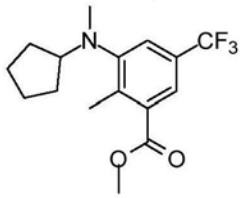
[1394]



[1395] 向 3- 氨基 -2- 甲基 -5-(三氟甲基) 苯甲酸甲酯(2.5g,10.7mmol) 和环戊酮(4.5g,53.49mmol)的甲醇(25mL)搅拌溶液中加入醋酸(1.98g,21.44mmol)。3 小时后,加入氰基硼氢化钠(1.68g,24.3mmol),搅拌反应过夜。完成时,在减压条件下去除溶剂,通过柱层析纯化原料粗品,以得到 3-(环戊基氨基)-2- 甲基 -5-(三氟甲基) 苯甲酸甲酯(1.8g,55.9%)。

[1396] 步骤 5 :3-(环戊基 (甲基) 氨基)-2- 甲基 -5-(三氟甲基) 苯甲酸甲酯的合成

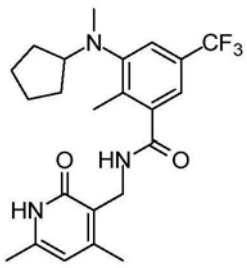
[1397]



[1398] 向 3-(环戊基氨基)-2- 甲基 -5-(三氟甲基) 苯甲酸甲酯(1.6g,5.38mmol)的乙腈(25mL) 搅拌溶液中加入碳酸铯(3.5g,10.7mmol) 和碘甲烷(3.8g,26.8mmol)。在 80℃下加热混合物 8 小时。完成时,将反应冷却至室温并过滤。用乙酸乙酯洗涤残余物,浓缩滤液,以得到 3-(环戊基 (甲基) 氨基)-2- 甲基 -5-(三氟甲基) 苯甲酸甲酯。

[1399] 步骤 6 :3-(环戊基 (甲基) 氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基 -5-(三氟甲基) 苯甲酰胺的合成

[1400]

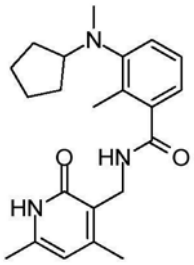


[1401] 向 3-(环戊基(甲基)氨基)-2- 甲基 -5-(三氟甲基)苯甲酸甲酯(2g,6.34mmol)的 MeOH(20mL)溶液中加入 NaOH(0.762g,15.4mmol)水溶液,60℃下搅拌混合物 1 小时。反应完成后,在减压条件下去除甲醇,用稀 HCl 酸化残余物至 pH 值为 6,并用柠檬酸酸化至 pH 值为 4。用乙酸乙酯萃取产物。干燥并浓缩合并的有机层以得到所需的酸(1.5g,78%)。

[1402] 然后将该酸(0.5g,1.69mmol)溶解于 DMSO(3mL)中,并向其中加入 3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮(0.505g,3.32mmol)。室温下搅拌反应混合物 15 分钟,然后加入 PYBOP(1.29g,2.49mmol),继续搅拌过夜。反应完成后,将混合物倒入冰中以得到固体。过滤固体,并先用乙腈再用乙醚洗涤,以提供化合物 3-(环戊基(甲基)氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)-2- 甲基 -5-(三氟甲基)苯甲酰胺(100mg,14%)。分析数据 :LCMS:436.20(M+1)$^+$;HPLC:89.22%(@254nm)(R_t;6.094; 方法 : 柱 :YMC ODS-A150mm x4.6mm x5μ ; 流动相 :A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液 ; 进样量 :10μL, 柱温 :30℃ ; 流速 :1.4mL/min.; 梯度 :8 分钟内 5%B 至 95%B, 保持 1.5 分钟,9.51-12min5%B);^{1}H NMR(DMSO-d_6,400MHz) δ 11.47(s,1H),8.30(t,1H),7.37(s,1H),7.18(s,1H),5.86(s,1H),4.26(d,2H,J=4.4Hz),3.51(m,1H),2.53(s,3H),2.25(s,3H),2.19(s,3H),2.10(s,3H),1.41-1.69(m,8H)。

[1403] 实施例 16 :化合物 21 的合成 :3-(环戊基(甲基)氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)-2- 甲基苯甲酰胺

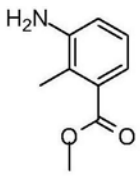
[1404]



化合物 21

[1405] 步骤 1 :3- 氨基 -2- 甲基苯甲酸甲酯的合成

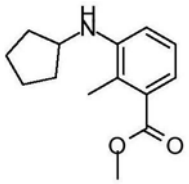
[1406]



[1407] 在 0℃下,向 3- 氨基 -2- 甲基苯甲酸(5g,33.1mmol)的甲醇(50mL)搅拌溶液中加入浓 H_2SO_4(5mL),并在 70℃下加热该混合物 22 小时。完成时,在减压条件下去除甲醇,然后加入饱和碳酸氢钠溶液,用 10%MeOH/DCM 萃取产物。干燥、浓缩合并的有机层以生产 3- 氨基 -2- 甲基苯甲酸甲酯(5g,91%)。

[1408] 步骤 2 :3-(环戊基氨基)-2- 甲基苯甲酸甲酯的合成

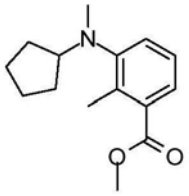
[1409]



[1410] 向 3- 氨基 -2- 甲基苯甲酸甲酯(2g,12.1mmol)和环戊酮(5g,60.6mmol)的甲醇(20mL)搅拌溶液中加入醋酸(0.72g,12.12mmol),室温下搅拌反应 3 小时。加入氰基硼氢化钠(1.13g,18.2mmol),反应搅拌过夜。完成时,减压条件下去除溶剂,通过柱层析纯化产物以得到 3-(环戊基氨基)-2- 甲基苯甲酸甲酯(2.2g,78%)。

[1411] 步骤 3 :3-(环戊基(甲基)氨基)-2- 甲基苯甲酸甲酯的合成

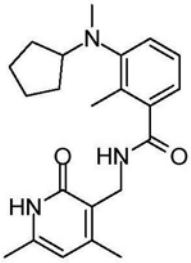
[1412]



[1413] 向 3-(环戊基氨基)-2- 甲基苯甲酸甲酯(2.2g,9.44mmol)的乙腈(20mL)搅拌溶液中加入碳酸铯(6.13g,18.8mmol)和碘甲烷(6.7g,47.2mmol)。在 80℃下加热得到的混合物 12 小时。完成时,将混合物冷却至室温并过滤,用乙酸乙酯洗涤。浓缩滤液,然后通过柱层析纯化以得到 3-(环戊基(甲基)氨基)-2- 甲基苯甲酸甲酯(2g,85%)。

[1414] 步骤 4 :3-(环戊基(甲基)氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)-2- 甲基苯甲酰胺的合成

[1415]



[1416] 向 3-(环戊基(甲基)氨基)-2- 甲基苯甲酸甲酯(2g,8.09mmol)的 MeOH(20mL)溶液中加入 NaOH(0.48g,12.14mmol)水溶液,在 60℃下搅拌 1 小时。反应完成后,在减压条件下去除甲醇,用稀 HCl 酸化至 pH 值为 6,并用柠檬酸调节至 pH 值为 4。用乙酸乙酯实行萃取。干燥、浓缩合并的有机层以得到想要的酸(1.3g,69%)。

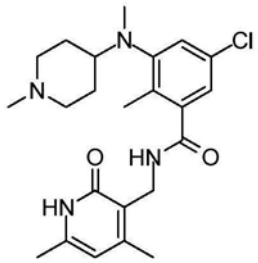
[1417] 然后将该酸(0.3g,1.28mmol)溶解于 DMSO(5mL)中,并向其中加入 3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮(0.39g,2.5mmol)。室温下搅拌反应混合物 15 分钟,然后向其中加入 PYBOP(0.99g,1.92mmol),继续搅拌过夜。反应完成后,将混合物倒入冰中以得到固体,将其过滤,用乙腈洗涤,然后柱纯化,以提供 3-(环戊基(甲基)氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)-2- 甲基苯甲酰胺(0.020g,4%)。

[1418] 分析数据 :LCMS:368.15(M+1)$^+$;HPLC:99.49%(@254nm)(R_t;4.186; 方法 : 柱 :YMC ODS-A150mm x4.6mm x5μ ; 流动相 :A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液 ; 进样量 :10μL, 柱温 :30℃ ; 流速 :1.4mL/min.; 梯度 :8 分钟内 5%B 至 95%B, 保持 1.5 分

钟，9.51-12min5%B)；^{1}H NMR(DMSO-d_6，400MHz) δ 11.43(s,1H)，8.00(t,1H,J=4Hz)，7.09-7.16(m,2H)，6.90(d,1H,J=6.8Hz)，5.84(s,1H)，4.25(d,2H,J=5.2Hz)，3.41(t,1H,J=6.8Hz)，2.47(s,3H)，2.18(d,6H,J=4.4Hz)，2.10(s,3H)，1.58-1.67(m,4H)，1.37-1.52(m,4H)。

[1419] 实施例 17：化合物 23 的合成：5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基)-2- 甲基 -3-（甲基 (1- 甲基哌啶 -4- 基）氨基）苯甲酰胺

[1420]

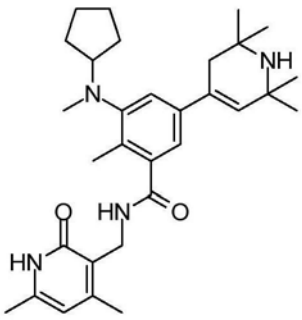


化合物 23

[1421] 将 5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基)-2- 甲基 -3-（甲基（哌啶 -4- 基）氨基）苯甲酰胺（0.08g，0.192mmol)溶解于甲醇（5mL)中，并冷却至 0℃，加入福尔马林（0.028g，0.965mmol)。同样温度下搅拌得到的反应物料 30 分钟。向上述反应物中加入氰基硼氢化钠（0.023g，0.38mmol)，室温下搅拌 4 小时。完成后，减压条件下去除溶剂，向残余物中加入水，用 DCM 实行萃取。干燥、浓缩合并的有机层，并通过柱层析纯化来得到所需的化合物（0.02g，24%)：LCMS:431.25(M+1)$^+$;HPLC:98.80%(@254nm)(R_t;4.757;方法：柱：YMC ODS-A150mm x4.6mm x5μ；流动相：A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液；进样量：10μL，柱温：30℃；流速：1.4mL/min.；梯度：8 分钟内 5%B 至 95%B，保持 1.5 分钟，9.51-12min5%B)；^{1}H NMR(DMSO-d_6，400MHz) δ 11.46(s,1H)，8.20(t,1H)，7.15(d,1H,J=1.2Hz)，6.94(d,1H,J=2Hz)，5.85(s,1H)，4.25(d,2H,J=4.8Hz)，3.05(bs,2H)，2.88(bs,1H)，2.55(s,3H)，2.44(bs,2H)，2.18(s,3H)，2.14(s,3H)，2.10(s,3H)，1.68(bs,4H)。

[1422] 实施例 18：合成化合物 25：3-（环戊基（甲基）氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基)-2- 甲基 -5-(2,2,6,6- 四甲基 -1,2,3,6- 四氢吡啶 -4- 基）苯甲酰胺

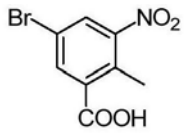
[1423]



化合物 25

[1424] 步骤 1：5- 溴 -2- 甲基 -3- 硝基苯甲酸

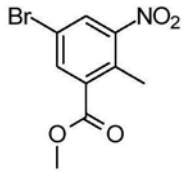
[1425]



[1426] 在室温下，向 2- 甲基 -3- 硝基苯甲酸（50g，276.2mmol）的浓 H_2SO_4（200mL）搅拌溶液中逐份加入 1,3- 二溴 -5,5- 二甲基 -2,4- 咪唑烷二酮（43.4g，151.8mmol），室温下搅拌反应物 5 小时。完成时，反应物倒入冰冷水中，过滤沉淀的固体，用水洗涤得到的残余物，真空下干燥，以得到所需的化合物（71.7g，100%）。

[1427] 5- 溴 -2- 甲基 -3- 硝基甲基苯的合成

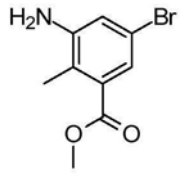
[1428]



[1429] 向 5- 溴 -2- 甲基 -3- 硝基苯甲酸（287g，1103mmol）的 DMF（150mL）搅拌溶液中加入碳酸钠（468g，4415mmol）和碘甲烷（626.63g，4415mmol）。在 60℃下加热得到的反应物 8 小时。完成时，将沉淀的固体过滤，用乙醚洗涤残余物（5 次）。干燥、在减压条件下浓缩合并的有机层，得到所需的粗制化合物（302g，99%）。

[1430] 步骤 2 ：3- 氨基 -5- 溴 -2- 甲基苯甲酸甲酯

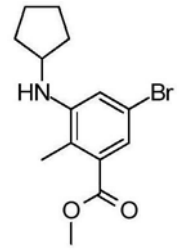
[1431]



[1432] 向 5- 溴 -2- 甲基 -3- 硝基甲苯（150g，544mmol）的乙醇（750mL）搅拌溶液中边搅拌边加入铁粉（93.3g，1636mmol）和溶解于水（750mL）的氯化铵（150g，2777mmol）。在 80℃下加热得到的反应物料 7 小时。完成时，通过硅藻土过滤反应物料，同时用水和乙酸乙酯洗涤，用乙酸乙酯萃取滤液。干燥、在减压条件下浓缩合并的有机层，得到所需的化合物。

[1433] 步骤 3 ：5- 溴 -3-（环戊基氨基）-2- 甲基苯甲酸甲酯

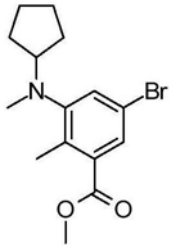
[1434]



[1435] 向 3- 氨基 -5- 溴 -2- 甲基苯甲酸甲酯（0.3g，1.33mmol）和环戊酮（0.56g，6.6mmol）的甲醇（3mL）搅拌溶液中加入醋酸（0.159g，2.6mmol），室温下搅拌反应 3 小时。然后加入氰基硼氢化钠（0.208g，3.3mmol），搅拌反应过夜。完成时，在减压条件下去除溶剂以得到所需的化合物。

[1436] 步骤 4 ：5- 溴 -3-（环戊基（甲基）氨基）-2- 甲基苯甲酸甲酯

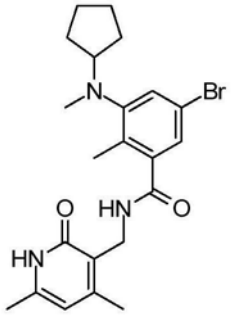
[1437]



[1438] 向 5- 溴 -3-(环戊基氨基)-2- 甲基苯甲酸甲酯(0.7g,2.25mmol) 的乙腈(15mL) 搅拌溶液中加入碳酸铯(1.47g,4.50mmol) 和碘甲烷(1.6g,11.26mmol);在 80℃下加热得到的反应物料 7 小时。完成时,将反应物料冷却至室温并过滤,用乙酸乙酯洗涤残余物,浓缩滤液,然后通过柱层析纯化,以得到所需的化合物(0.6g,82%)。

[1439] 步骤 5 :5- 溴 -3-(环戊基 (甲基) 氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基苯甲酰胺

[1440]

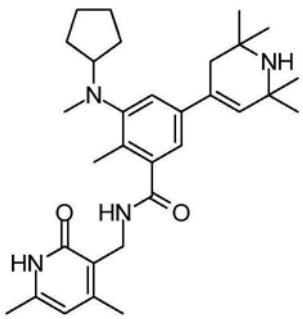


[1441] 向 5- 溴 -3-(环戊基 (甲基) 氨基)-2- 甲基苯甲酸甲酯的 MeOH (1.5mL)溶液中加入 NaOH (0.11g,2.75mmol) 水溶液,在 60℃下搅拌 1 小时。反应完成后,在减压条件下去除乙醇,用稀 HCl 酸化至 pH 值为 6,并用柠檬酸调节至 pH 值为 4。用乙酸乙酯实行萃取。干燥、浓缩合并的有机层以得到单独的酸(0.5g,87%)。

[1442] 然后将该酸(0.5g,1.60mmol) 溶解于 DMSO (3mL) 中,并向其中加入 3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮(0.49g,3.22mmol)。室温下搅拌反应混合物 15 分钟,然后向其中加入 PYBOP(1.25g,2.41mmol),继续搅拌过夜。反应完成后,将反应物倒入冰中以得到固体,将其过滤,并先用乙腈再用乙醚洗涤,以提供所需的化合物(0.315g,44%)。

[1443] 步骤 6 :3-(环戊基 (甲基) 氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基 -5-(2,2,6,6- 四甲基 -1,2,3,6- 四氢吡啶 -4- 基) 苯甲酰胺

[1444]

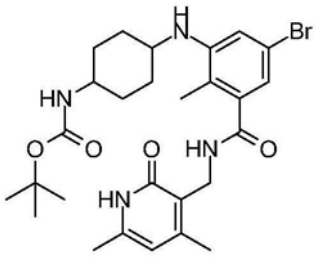


[1445] 用氩气净化 5- 溴 -3-(环戊基 (甲基) 氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二

氢吡啶 -3- 基) 甲基)-2- 甲基苯甲酰胺(1 当量)、(2,2,6,6- 四甲基 -1,2,3,6- 四氢吡啶 -4- 基) 硼酸(1.2 当量)和 $Pd(PPh_3)_4$ (0.1 当量)的 1,4- 二氧六环(4mL)溶液 10 分钟。然后,向其中加入 2M Na_2CO_3 溶液(3.6 当量),再用氩气净化 10 分钟。在 100℃下搅拌反应混合物 2 小时。反应完成后,向其中加入水,用 DCM 实行萃取。用水洗涤合并的有机层,用无水 Na_2SO_4 干燥,并过滤、在减压条件下浓缩,以得到原料粗品,其用制备型 HPLC 纯化,以得到作为其 TFA 盐的所需的化合物(0.045,23%)。LCMS:505.39$(M+1)^+$;HPLC:99.95%(@254 nm)(R_t;4.091; 方法 : 柱 :YMC ODS-A150mm x4.6mm x5μ ; 流动相 :A;0.05%TFA 的水溶液 / B;0.05%TFA 的乙腈溶液 ; 进样量 :10μL, 柱温 :30℃ ; 流速 :1.4mL/min. ; 梯度 :8 分钟内 5%B 至 95%B, 保持 1.5 分钟 ,9.51-12min5%B);^{1}H NMR(MeOD,400MHz) δ 7.70(s,1H),7.46(s,1H),6.21(s,1H),6.13(s,1H),4.48(s,2H),4.23(bs,1H),3.14(s,3H),2.69(s,2H),2.42(s,3H),2.39(s,3H),2.24(s,3H),1.92(,2H),1.81(m,2H),1.67(m,4H),1.60(s,6H),1.53(s,6H)。

[1446] 实施例 19 :合成化合物 26 :(4-((5- 溴 -3-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基) 氨基甲酰)-2- 甲基苯基) 氨基) 环己基) 氨基甲酸叔丁酯

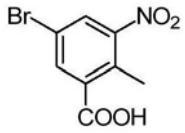
[1447]



化合物 26

[1448] 步骤 1 :5- 溴 -2- 甲基 -3- 硝基苯甲酸

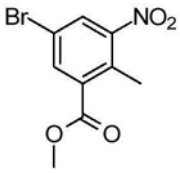
[1449]



[1450] 向 2- 甲基 -3- 硝基苯甲酸(15g,82.80mmol) 的浓 H_2SO_4 (60mL) 混合物中加入 1,3- 二溴 -5,5- 二甲基 -2,4- 咪唑烷二酮(13.07g,45.71mmol),室温下搅拌反应混合物 5 小时。反应完成后,将反应混合物缓慢倒入冰冷水(400mL) 中。通过过滤收集沉淀物以得到所需的化合物(21g,98.22%)。

[1451] 步骤 2 :5- 溴 -2- 甲基 -3- 硝基苯甲酸甲酯

[1452]

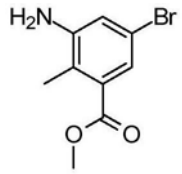


[1453] 向 5- 溴 -2- 甲基 -3- 硝基苯甲酸(16g,61.54mmol) 的 DMF (160mL) 搅拌溶液中加入碘甲烷(35.72g,248mmol) 和碳酸钠(26.28g,248mmol)。在 60℃下搅拌得到的反应物

料 8 小时。完成时，将反应物料过滤，用乙酸乙酯洗涤无机固体残余物。在真空下浓缩合并的滤液直至干燥。在乙酸乙酯中重新溶解残余物，并用 5% 碳酸氢钠溶液（700mL）洗涤，然后用 5M HCl 溶液（300mL）洗涤。最后用盐水洗涤有机层，用硫酸钠干燥，过滤并浓缩，以得到所需的化合物（16g，94.50%）。

[1454] 步骤 3 ：3- 氨基 -5- 溴 -2- 甲基苯甲酸甲酯

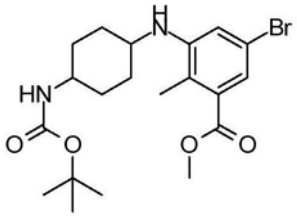
[1455]



[1456] 向 5- 溴 -2- 甲基 -3- 硝基苯甲酸甲酯（17g，62.04mmol）的乙醇（85mL）搅拌溶液中加入 NH_4Cl 溶液（85mL 水中 17g，317.8mmol），然后加入铁粉（27.82g，498.11mmol）。在 90℃下搅拌得到的反应物料 1 小时。完成时，过滤反应物，浓缩滤液直至干燥以得到固体，将该固体溶解至饱和的碳酸氢钠溶液中。用乙酸乙酯萃取水层。用硫酸钠干燥并浓缩合并的有机层，以得到所需的化合物 4 （15g，99%）。

[1457] 步骤 4 ：5- 溴 -3-((4-((（叔丁氧羰基）氨基）环己基）氨基）-2- 甲基苯甲酸甲酯

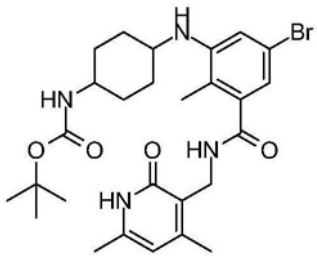
[1458]



[1459] 向 3- 氨基 -5- 溴 -2- 甲基苯甲酸甲酯（5g，20.57mmol）和（4- 氧代环己基）氨基甲酸叔丁酯（5.67g，26.74mmol）的甲醇（50mL）搅拌溶液中加入醋酸（1.2g，20.57mmol），室温下搅拌反应 4 小时。然后加入氰基硼氢化钠（1.68g，26.74mmol），搅拌反应 18 小时。完成时，在减压条件下去除溶剂 ；加入水，用 DCM 萃取。干燥、浓缩合并的有机层，并通过硅胶柱层析纯化（100-200 目）以得到所需的化合物（3g，33%）。

[1460] 步骤 5 ：(4-((5- 溴 -3-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）氨基甲酰）-2- 甲基苯基）氨基）环己基）氨基甲酸叔丁酯

[1461]

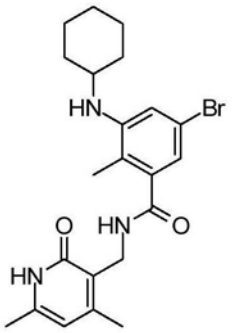


[1462] 向 5- 溴 -3-((4-((（叔丁氧羰基）氨基）环己基）氨基）-2- 甲基苯甲酸甲酯（1.5g，3.41mmol）的 MeOH （20mL）溶液中加入 NaOH （0.247g，6.83mmol）水溶液，60℃下搅拌 1 小时。反应完成后，在减压条件下去除乙醇，用稀 HCl 酸化至 pH 值为 6，并用柠檬酸调节至 pH 值为 4。用 DCM 实行萃取。干燥、浓缩合并的有机层来得到单独的酸（1.28g，89%）。

[1463] 然后将该酸(1.28g,3.01mmol)溶解于 DMSO (10mL)中,并向其中加入 3-(氨基甲基)-4,6-二甲基吡啶-2(1H)-酮(1.03g,6.83mmol)。室温下搅拌反应混合物 15 分钟,然后向其中加入 PYBOP(2.6g,5.12mmol),继续搅拌过夜。反应完成后,将反应物料倒入冰中,用 5%MeOH/DCM 萃取。干燥、浓缩合并的有机层以得到粗制固体,其通过柱层析纯化以得到所需的化合物(0.75g,45%)。LCMS:561.15(M+1)$^+$;HPLC:99.99%(@254nm)(R_t;6.876,7.080[非对映异构体的混合物];方法:柱:YMC ODS-A150mm x4.6mm x5μ;流动相:A;0.05%TFA 的水溶液/B;0.05%TFA 的乙腈溶液;进样量:10μL,柱温:30℃;流速:1.4mL/min.;梯度:8 分钟内 5%B 至 95%B,保持 1.5 分钟,9.51-12min5%B);^{1}HNMR(DMSO-d_6,400MHz) δ 11.44(s,1H),8.07(t,1H,J=4.8Hz),6.77(d,1H,J=7.6Hz),6.66(s,1H),6.51-6.54(m,1H),5.84(s,1H),4.71(d,1H,J=7.6Hz),4.21-4.22(m,2H),3.44(bs,1H),3.19(bs,1H),2.16(s,3H),2.10(s,3H),1.93-2.03(m,5H),1.78(s,1H),1.56-1.72(m,3H),1.37(s,9H),1.26-1.31(m,2H)。

[1464] 实施例 20:合成化合物 28:5-溴-3-(环己基氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺

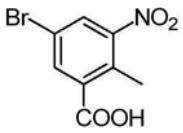
[1465]



化合物 28

[1466] 步骤 1:5-溴-2-甲基-3-硝基苯甲酸

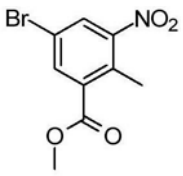
[1467]



[1468] 在室温下,向 2-甲基-3-硝基苯甲酸(50g,276.2mmol)的浓 H_2SO_4 (200mL)搅拌溶液中逐份加入 1,3-二溴-5,5-二甲基-2,4-咪唑烷二酮(43.4g,151.8mmol),室温下搅拌反应物 5 小时。完成时,将反应物料倒入冰冷水中,过滤沉淀的固体,用水洗涤得到的残余物并在真空下干燥,以得到所需的化合物(71.7g,100%)。

[1469] 步骤 2:5-溴-2-甲基-3-硝基甲基苯甲酸甲酯

[1470]

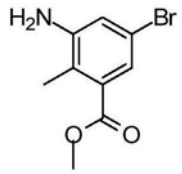


[1471] 向 5-溴-2-甲基-3-硝基苯甲酸(287g,1103mmol)的 DMF (150mL)搅拌溶液中加入碳酸钠(468g,4415mmol)和碘甲烷(626.63g,4415mmol)。在 60℃下加热得到的反应物

料 8 小时。完成时，过滤沉淀的固体，用乙醚洗涤残余物（5 次）。干燥、在减压条件下浓缩合并的有机层，以得到所需的化合物（302g，99%）。

[1472] 步骤 3 ：3- 氨基 -5- 溴 -2- 甲基苯甲酸甲酯

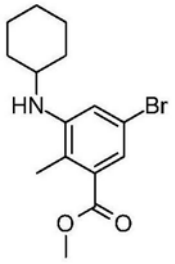
[1473]



[1474] 向 5- 溴 -2- 甲基 -3- 硝基甲基苯（150g，544mmol）的乙醇（750mL）搅拌溶液中边搅拌边加入铁粉（93.3g，1636mmol）和溶解于水（750mL）中的氯化铵（150g，2777mmol）。在 80℃下加热得到的反应物料 7 小时。完成时，通过硅藻土过滤反应物，同时用水和乙酸乙酯洗涤，用乙酸乙酯萃取滤液。干燥、在减压条件下浓缩合并的有机层以得到所需的化合物，其直接用于下一步中。

[1475] 步骤 4 ：5- 溴 -3-（环己基氨基）-2- 甲基苯甲酸甲酯

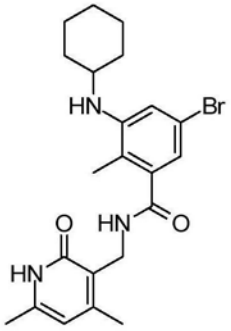
[1476]



[1477] 向 3- 氨基 -5- 溴 -2- 甲基苯甲酸甲酯（0.3g，1.33mmol）和环己酮（0.64g，6.6mmol）的甲醇（3mL）搅拌溶液中加入醋酸（0.159g，2.6mmol），室温下搅拌反应 3 小时。然后加入氰基硼氢化钠（0.208g，3.3mmol），反应搅拌过夜。完成时，在减压条件下去除溶剂，并直接用于下一步中。

[1478] 步骤 5 ：5- 溴 -3-（环己基氨基）-N-（（4，6- 二甲基 -2- 氧代 -1，2- 二氢吡啶 -3- 基）甲基）-2- 甲基苯甲酰胺

[1479]

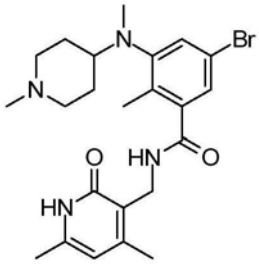


[1480] 向 5- 溴 -3-（环己基氨基）-2- 甲基苯甲酸甲酯（0.2g，0.61mmol）的 MeOH （5mL）溶液中加入 NaOH （0.049g，1.23mmol）水溶液，在 60℃下搅拌 1 小时。反应完成后，在减压条件下去除乙醇，用稀 HCl 酸化至 pH 值为 6，并用柠檬酸调节至 pH 值为 4。用乙酸乙酯实行萃取。干燥、浓缩合并的有机层来得到单独的酸（0.17g，89%）。

[1481] 然后将该酸(0.17g,0.54mmol)溶解于DMSO(3mL)中,并向其中加入3-(氨基甲基)-4,6-二甲基吡啶-2(1H)-酮(0.099g,0.65mmol)。室温下搅拌反应混合物15分钟,然后向其中加入PYBOP(0.42g,0.817mmol),继续搅拌过夜。反应完成后,反应物倒入冰中以得到固体,通过制备型HPLC将其纯化以提供作为其TFA盐的所需的化合物(0.042g,15%)。LCMS:446.16$(M+1)^+$;HPLC:99.85%(@254nm)(R_t;6.918;方法:柱:YMC ODS-A150mm x4.6mm x5μ;流动相:A;0.05%TFA的水溶液/B;0.05%TFA的乙腈溶液;进样量:10μL,柱温:30℃;流速:1.4mL/min.;梯度:8分钟内5%B至95%B,保持1.5分钟,9.51-12min5%B);^{1}H NMR(DMSO-d_6,400MHz)δ11.45(s,1H),8.08(s,1H),6.66(s,1H),6.51(d,1H,J=0.8Hz),5.84(s,1H),4.70(s,1H),4.21(d,2H,J=4.4Hz),3.24(s,1H),2.16(s,3H),2.10(s,3H),1.94(s,3H),1.88(d,2H,J=10Hz),1.69-1.72(m,3H),1.22-1.36(m,5H)。

[1482] 实施例21:合成化合物30:5-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(甲基(1-甲基哌啶-4-基)氨基)苯甲酰胺

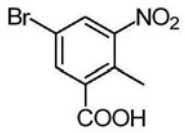
[1483]



[1484] 化合物30

[1485] 步骤1:5-溴-2-甲基-3-硝基苯甲酸

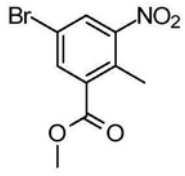
[1486]



[1487] 室温下,向搅拌后的2-甲基-3-硝基苯甲酸(50g,276.2mmol)的浓硫酸(200mL)溶液中分批加入1,3-二溴-5,5-二甲基-2,4-咪唑二烷酮(43.4g,151.8mmol),将反应混合物在室温下搅拌5小时。反应结束后,反应混合物加入到冰水中,将析出的固体过滤,用水洗涤所得残余物,真空干燥后得到需要的化合物(71.7g,99.9%),所得化合物可用于下一步反应。

[1488] 步骤2:5-溴-2-甲基-3-硝基苯甲酸甲酯

[1489]

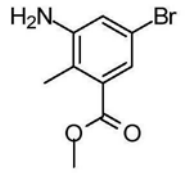


[1490] 室温下,向搅拌后的5-溴-2-甲基-3-硝基苯甲酸(287g,1103mmol)的DMF(150mL)溶液中加入碳酸钠(468g,4415mmol)和碘甲烷(626.63g,4415mmol)。所得反应混合物在60℃下加热8小时。反应结束后,过滤固体沉淀物,残余物用乙醚洗涤(5次)。对合

并的有机层进行干燥和减压浓缩，得到所需的化合物（302g，99%）。

[1491] 步骤 3 ：3- 氨基 -5- 溴 -2- 甲基苯甲酸甲酯

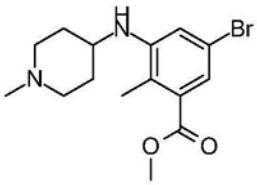
[1492]



[1493] 向搅拌后的 5- 溴 -2- 甲基 -3- 硝基苯甲酸甲酯（150g，544mmol）的乙醇（750mL）溶液中在搅拌下加入溶于水（750mL）中的氯化铵（150g，2777mmol）和铁粉（93.3g，1636mmol）。所得反应混合物在 80℃下加热 7 小时。反应结束后，反应混合物通过硅藻土过滤，并用水和乙酸乙酯洗涤，滤液用乙酸乙酯萃取。对合并的有机相层进行干燥和减压浓缩，得到所需化合物。

[1494] 步骤 4 ：5- 溴 -2- 甲基 -3-（(1- 甲基哌啶 -4- 基）氨基）苯甲酸甲酯

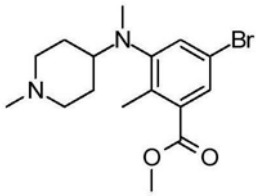
[1495]



[1496] 室温下，向搅拌后的 3- 氨基 -5- 溴 -2- 甲基苯甲酸甲酯（2g，8.23mmol）和 1- 甲基哌啶 -4- 酮（1.86g，16.46mmol）的甲醇（20mL）溶液中加入醋酸（0.5g，8.23mmol），并在室温下搅拌 3 小时。然后加入氰基硼氢化钠（0.622g，9.87mmol）并搅拌反应过夜。反应结束后，减压除去溶剂，粗品经柱层析纯化后得到所需化合物（0.9g，33%）。

[1497] 步骤 5 ：5- 溴 -2- 甲基 -3-（甲基 (1- 甲基哌啶 -4- 基）氨基）苯甲酸甲酯

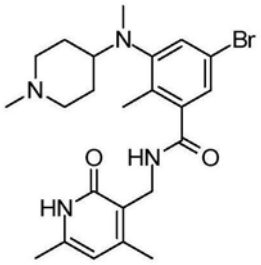
[1498]



[1499] 向搅拌后的 5- 溴 -2- 甲基 -3-（(1- 甲基哌啶 -4- 基）氨基）苯甲酸甲酯（0.6g，1.76mmol）的乙腈（15mL）溶液中加入碳酸铯（1.14g，3.52mmol）和碘甲烷（1.2g，8.8mmol）；所得反应混合物在 80℃下加热 7 小时。反应结束后，反应混合物冷却到室温并过滤，残余物用乙酸乙酯洗涤，滤液浓缩后经柱层析纯化而得到所需化合物（0.5g，80%）。

[1500] 步骤 6 ：5- 溴 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-2- 甲基 -3-（甲基 (1- 甲基哌啶 -4- 基）氨基）苯甲酰胺

[1501]

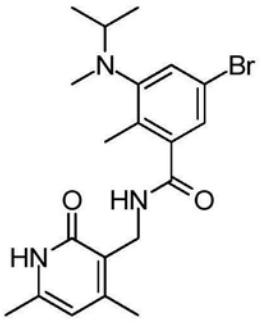


[1502] 向 5- 溴 -2- 甲基 -3-(甲基 (1- 甲基哌啶 -4- 基) 氨基) 苯甲酸甲酯(0.5g,1.4mmol) 的甲醇(20mL) 溶液中加入 NaOH (0.11g,2.75mmol) 水溶液,60℃下搅拌 1 小时。反应结束后,减压除去乙醇,用稀盐酸将 pH 值调至 6,再用柠檬酸将 pH 值调至 4。残余物用乙酸乙酯萃取。对合并的有机层进行干燥和浓缩,得到单独的酸(0.42g,90%)。

[1503] 将所得到的酸(0.5g,0.974mmol)溶于 DMSO(3mL),并加入 3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮(0.45g,2.8mmol)。反应混合物室温下搅拌 15 分钟后加入 PYBOP(1.1g,2.1mmol),然后继续搅拌过夜。反应结束后,反应混合物加到冰中得到固体,将固体过滤,用乙腈洗涤,之后进行柱层析纯化以得到所需化合物(0.2g,30%)。LCMS:475.02(M+1)+;HPLC:94.25%(@254nm)(R_t;4.570; 方法 : 色谱柱 :YMC ODS-A150mm x4.6mm x5μ; 流动相 A;0.05%TFA 的水溶液 / 流动相 B;0.05%TFA 的乙腈溶液 ; 进样量 :10μL, 柱温 :30℃, 流速 :1.4mL/min; 梯度 :0-8min.5%B-95%B, 保持 1.5min,9.51-12min.5%B);^{1}H NMR(DMSO-d_6,400MHz) δ 11.45(s,1H),8.13(t,1H,J=4.8Hz),6.78(d,1H,J=0.8Hz),6.60(d,1H,J=1.6Hz),5.85(s,1H),4.94(d,1H,J=8.8Hz),4.22(d,2H,J=4.8Hz),3.62-3.64(m,1H),3.37-3.46(m,3H),3.11(s,3H),3.09(s,3H),2.17(s,3H),2.10(s,3H),1.99-2.09(m,2H),1.98(s,3H),1.86-1.93(m,2H)。

[1504] 实施例 22 : 合成化合物 31 :5- 溴 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-3-(异丙基 (甲基) 氨基)-2- 甲基苯甲酰胺

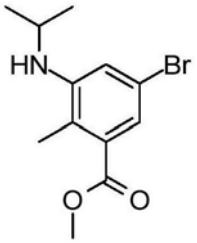
[1505]



化合物 31

[1506] 步骤 1 : 合成 5- 溴 -3-(异丙基氨基)-2- 甲基苯甲酸甲酯

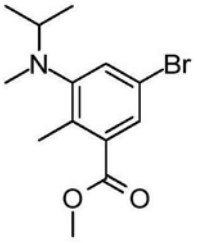
[1507]



[1508] 向搅拌后的 3- 氨基 -5- 溴 -2- 甲基苯甲酸甲酯(1equiv.) 的甲醇(5mL)溶液中加入丙酮(5equiv.)和醋酸(2equiv),反应混合物在室温下搅拌 2 小时。在 0℃加入 $NaBH_3CN$ (3equiv.)。所得反应混合物继续在室温下搅拌 16 小时。反应结束后,将溶剂蒸发,向残余物中加入水,并用乙酸乙酯萃取。合并的有机相用无水硫酸钠干燥,浓缩,得到的粗品(产率 80-90%),其无需进一步纯化而可直接用于下一步反应。

[1509] 步骤 2 :合成 5- 溴 -3-(异丙基 (甲基) 氨基)-2- 甲基苯甲酸甲酯

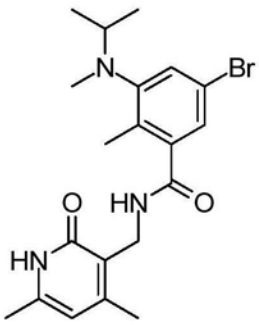
[1510]



[1511] 向搅拌后的 5- 溴 -3-(异丙基氨基)-2- 甲基苯甲酸甲酯(0.5g,1.75mmol) 的乙腈(10mL)溶液中加入 Cs_2CO_3(1.02g,2.63mmol)和碘甲烷(1.45g,3.5mmol)。将所得反应混合物在 80℃搅拌 4 小时。反应结束后,减压除去溶剂,将残余残余物溶于水,并用乙酸乙酯萃取。所得粗品经硅胶柱层析纯化后得到所需的化合物(0.39g),无需进一步纯化。

[1512] 步骤 3 :5- 溴 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-3-(异丙基 (甲基) 氨基)-2- 甲基苯甲酰胺

[1513]

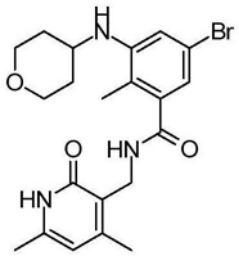


[1514] 向搅拌后的 5- 溴 -3-(异丙基 (甲基) 氨基)-2- 甲基苯甲酸甲酯(1equiv.) 的乙醇(5mL) 溶液中加入 NaOH (1equiv.) 水溶液,并在 60℃加热 4 小时。反应结束后,减压除去乙醇,残余物用 1N 盐酸酸化至 pH 值为 6。水相用 10%MeOH/DCM 萃取,用无水硫酸钠干燥合并后的有机相,减压除去溶剂得到纯净的酸(产率为 50-60%)。向所得酸(1equiv.) 的 DMSO (1.5mL) 溶液中加入 PYBOP (1.5equiv.),在室温下搅拌 15 分钟后,加入 3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮(2equiv.),反应搅拌过夜。反应结束后,加入水,将所得固体沉淀过滤,用水洗涤。然后所得固体在乙腈中搅拌 10 分钟后,再一次过滤,以得到纯净

的所需分子(产率为 50-60%)。LCMS:420.15(M+1)+;HPLC:93.04%(@254nm)(Rt;4.791);^{1}H NMR(DMSO-d_6,400MHz) δ 11.47(s,1H),8.19(t,1H,J=4.8Hz),7.14(d,1H,J=1.6Hz),7.00(d,1H,J=1.2Hz),5.85(s,1H),4.23(d,2H,J=4.4Hz),3.16-3.20(m,1H),2.52(s,3H),2.17(s,3H),2.10(s,6H),1.01(d,6H,J=6.4Hz)。

[1515] 实施例 23 :合成化合物 32 :5- 溴 -N-((4,6- 二氢 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)-2- 甲基 -3-((四氢 -2H- 吡喃 -4- 基) 氨基) 苯甲酸酯

[1516]



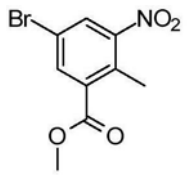
化合物 32

[1517] 步骤 1 :5- 溴 -2- 甲基 -3- 硝基苯甲酸

[1518] 向 2- 甲基 -3- 硝基苯甲酸(15g,82.80mmol)的浓硫酸(60mL)溶液中加入 1,3- 二溴 -5,5- 二甲基 -2,4- 咪唑二烷酮(13.07g,45.71mmol),反应混合物在室温下搅拌 5 小时。反应结束后,将反应混合物慢慢加到冰冷水中(400mL)。将析出的固体过滤,在真空中干燥,以得到所需化合物(21g,98%)。

[1519] 步骤 2 :5- 溴 -2- 甲基 -3- 硝基苯甲酸甲酯

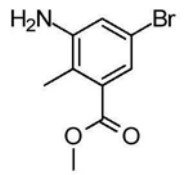
[1520]



[1521] 向搅拌后的 5- 溴 -2- 甲基 -3- 硝基苯甲酸(16g,61.54mmol)的 DMF (160mL)溶液中加入碘甲烷(35.72g,248mmol)和碳酸钠(26.28g,248mmol)。所得反应物料在 60℃搅拌 8 小时。将反应物料过滤,用乙酸乙酯洗涤无机固体残余物。将合并的滤液在减压下浓缩直至干燥。将残余物溶于乙酸乙酯,依次用 5% 碳酸氢钠水溶液(700mL),5M 盐酸溶液(300mL)洗涤。有机相最后用盐水洗涤,用无水硫酸钠干燥,并浓缩,得到所需化合物(16g,95%)。

[1522] 步骤 3 :3- 氨基 -5- 溴 -2- 甲基苯甲酸甲酯

[1523]

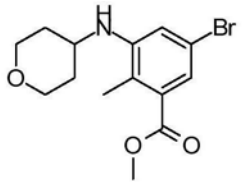


[1524] 向搅拌后的 5- 溴 -2- 甲基 -3- 硝基苯甲酸甲酯(17g,62.04mmol)的乙醇(85mL)溶液中加入溶解于水(85mL)中的 NH_4Cl (17g,317.8mmol)后,再加入铁粉(27.82g,498.11mmol)。将所得的反应物料在 90℃搅拌 1 小时。反应结束后,将反应物料过滤,将滤

液浓缩至干燥以获得固体，然后将该固体溶解于饱和碳酸氢钠水溶液。用乙酸乙酯萃取水层，用无水硫酸钠干燥并浓缩合并的有机相，得到所需化合物（15g，99%）。

[1525] 步骤 4：5- 溴 -2- 甲基 -3-（（四氢 -2H- 吡喃 -4- 基）氨基）苯甲酸甲酯

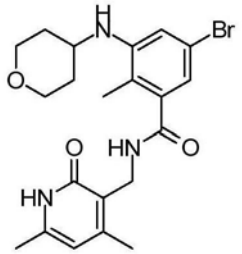
[1526]



[1527] 向搅拌后的 3- 氨基 -5- 溴 -2- 甲基苯甲酸甲酯（2g，8.23mmol）和四氢吡喃 -4- 酮（1.06g，10.66mmol）的甲醇（20mL）溶液中，加入醋酸（0.5g，8.23mmol），并在室温下搅拌反应 18 小时。然后加入氰基硼氢化钠（0.62g，9.83mmol），并搅拌反应 3 小时。反应结束后，减压除去溶剂，加入水，并用二氯甲烷萃取，干燥，浓缩合并的有机相，并用硅胶柱层析（100-200 目）纯化，以得到所需化合物（1.6g，62%）。

[1528] 步骤 5：5- 溴 -N-（(4,6- 二氢 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-2- 甲基 -3-（（四氢 -2H- 吡喃 -4- 基）氨基）苯甲酸甲酯

[1529]

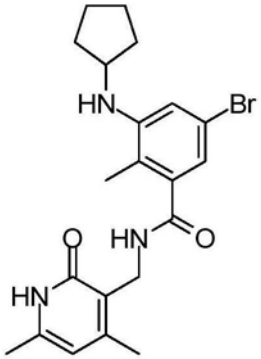


[1530] 将氢氧化钠（0.146g，3.66mmol）水溶液加入到 5- 溴 -2- 甲基 -3-（（四氢 -2H- 吡喃 -4- 基）氨基）苯甲酸甲酯（0.6g，1.88mmol）的甲醇（8mL）溶液中，并在 60℃搅拌 1 小时。反应结束后，减压除去甲醇，并用稀盐酸酸化至 pH 值为 6，再用柠檬酸酸化至 pH 值为 4。用二氯甲烷萃取，干燥浓缩合并的有机相，得到单独的酸（0.515g，90%）。

[1531] 然后将所得酸（0.515g，1.67mmol）溶解到 DMSO（3mL）中，并加入 3-（氨基甲基）-4,6- 二甲基吡啶 -2(1H)- 酮（0.50g，3.3mmol）。反应混合物在室温下搅拌 15 分钟后加入 PYBOP（1g，1.98mmol），继续搅拌过夜。反应结束后，将反应物料倒入冰中，并用 5%MeOH/DCM 萃取。干燥，浓缩合并的有机相，并通过柱层析纯化，以得到所需化合物（0.30g，37%）。LCMS:447.84(M+1)+;HPLC:99.78%(@254nm)(Rt;5.753; 方法：色谱柱：YMC ODS-A150mm x4.6mm x5μ；流动相 A:0.05%TFA 的水溶液 / 流动相 B:0.05%TFA 的乙腈溶液；进样量：10μL，柱温：30℃；流速：1.4mL/min.；梯度：0-8min.5%B-95%B，保持 1.5min，9.51-12min.5%B)；^{1}H NMR(DMSO-d_6，400MHz) δ 11.45(s,1H),8.09(t,1H,J=4.8Hz),6.76(s,1H),6.53(d,1H,J=1.6Hz),5.84(s,1H),4.82(d,1H,J=8Hz),4.42(d,2H,J=4.8Hz),3.85(d,2H,J=11.2Hz),3.37-3.53(m,3H),2.16(s,3H),2.10(s,3H),1.95(s,3H),1.81(d,2H,J=12.8Hz),1.44-1.54(m,2H)。

[1532] 实施例 24：合成化合物 33：5- 溴 -3-（环戊基氨基）-N-（(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-2- 甲基苯甲酰胺

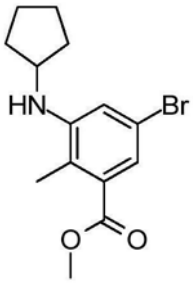
[1533]



化合物 33

[1534] 步骤 1 :合成 5- 溴 -3-(环戊基氨基)-2- 甲基苯甲酸甲酯

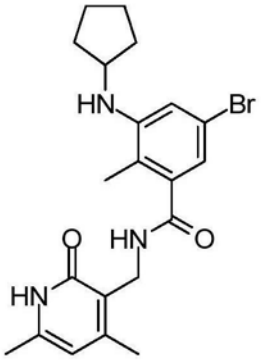
[1535]



[1536] 向搅拌后的 3- 氨基 -5- 溴 -2- 甲基苯甲酸甲酯(1equiv.) 的甲醇(5mL)溶液中加入环戊酮(5equiv.) 和醋酸(2equiv.),反应混合物在室温下搅拌 2 小时。然后在 0℃加入 $NaBH_3CN$ (3equiv.)。得到的反应混合物继续在室温下搅拌 16 小时。反应结束后,蒸掉溶剂,并向残留物中加入水,然后乙酸乙酯用萃取。用无水硫酸钠干燥并浓缩合并的有机相,以得到粗产品(产率 80-90%),其无需进一步纯化而直接用于下一步反应。

[1537] 步骤 2 :合成 5- 溴 -3-(环戊基氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基苯甲酰胺

[1538]

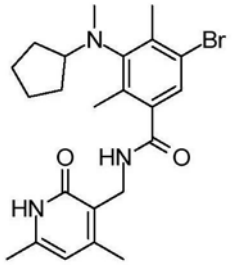


[1539] 向搅拌后的 5- 溴 -3-(环戊基氨基)-2- 甲基苯甲酸甲酯(1equiv.) 的乙醇(5mL) 溶液中加入 NaOH (1equiv.) 水溶液,在 60℃搅拌反应 4 小时。结束时,减压除去乙醇,残留物用 1N 盐酸酸化至 pH 值为 6。用 10%MeOH/DCM 萃取水相。无水硫酸钠干燥合并的有机相,减压除去溶剂,得到纯净的酸(产率 50-60%)。向所得酸(1equiv.) 的 DMSO (1.5mL) 溶液中加入 PYBOP(1.5equiv.),并在室温下搅拌 15 分钟。然后加入 3-(氨基甲基)-4,6- 二

甲基吡啶 -2(1H)- 酮(2equiv.),并搅拌反应过夜。结束时,加入水,将产生的沉淀物过滤并用水洗涤。然后将固体在乙腈中搅拌 10 分钟后再次过滤,以得到纯净的目标分子(产率 50-60%)。LCMS:432.10(M+1)$^+$;HPLC:97.15%(@254nm)(R_t;6.834);^{1}H NMR(DMSO-d_6,400MHz) δ 11.45(s,1H),8.09(t,1H,J=4.4&5.2Hz),6.65(d,1H,J=1.6Hz),6.54(d,1H,J=1.6Hz),5.84(s,1H),4.85(d,1H,J=6Hz),4.22(d,2H,J=5.2Hz),3.73(m,1H),2.16(s,3H),2.10(s,3H),1.95(s,3H),1.91(m2H),1.70-1.62(m,2H),1.60-1.45(m,4H)。

[1540] 实施例 25 :合成化合物 36 :5- 溴 -3-(环戊基 (甲基) 氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2,4- 二甲基苯甲酰胺

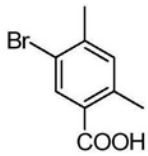
[1541]



化合物 36

[1542] 步骤 1 :5- 溴 -2,4- 二甲基苯甲酸

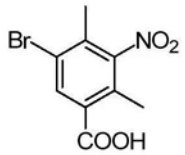
[1543]



[1544] 在 0℃下,向搅拌后的氢氧化钠(60g) 的水(1152mL)溶液中逐滴滴加溴素 (36mL),反应混合物在同一温度下搅拌 45 分钟。在 0℃下,将 2,4- 二甲基苯甲酸(12g,79.9mmol) 分批加入到上述反应混合物中,并在室温下搅拌反应 3 小时。反应结束后 (TLC),反应混合物用浓盐酸酸化,固体通过布氏漏斗过滤,用水洗涤,干燥,得到所需化合物(12g,65%),其无需进一步纯化即可使用。

[1545] 步骤 2 :5- 溴 -2,4- 二甲基 -3- 硝基苯甲酸

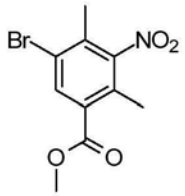
[1546]



[1547] 在 -10℃下,将 5- 溴 -2,4- 二甲基苯甲酸(12g,52.17mmol) 分批加入冷却的浓硫酸(48mL) 中。10 分钟后,在 -10℃下逐滴滴加硝化混合物 { 混合浓硝酸(6mL) 与浓硫酸 (24mL)来制备 }。在 -10℃下搅拌反应物料 30 分钟。结束时,将反应混合物倒入冰水中,过滤固体沉淀物,用水洗涤,在真空中干燥,得到所需化合物(13g,91%)。

[1548] 步骤 3 :3- 溴 -5- 硝基苯甲酸甲酯

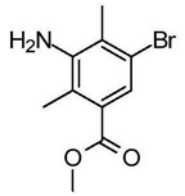
[1549]



[1550] 向搅拌后的 5- 溴 -2,4- 二甲基 -3- 硝基苯甲酸(13g,47.44mmol)的 DMF (120mL)溶液中加入碳酸钠(15g,142.2mmol)和碘甲烷(4.4ml,71.16mmol)。反应物料在 60℃加热 8 小时。结束时,向反应物料中加水,用乙酸乙酯萃取。合并的有机相用饱和碳酸氢钠和 5N 盐酸洗涤,用硫酸钠干燥,减压浓缩,得到所需化合物(12.9g,86%)。

[1551] 步骤 4 :3- 氨基 -5- 溴 -2,4- 二甲基苯甲酸甲酯

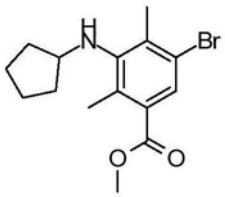
[1552]



[1553] 在搅拌下,向搅拌后的 3- 溴 -5- 硝基苯甲酸甲酯(12.9g,44.79mmol)的乙醇(65mL)溶液中加入溶解于水(65mL)中的氯化铵(13g,223.95mmol)溶液和铁粉(20g,358.33mmol)。产生的反应物料在 80℃加热 1 小时。结束时,将反应混合物通过硅藻土床层过滤,用乙醇洗涤硅藻土床层,滤液用乙酸乙酯萃取。合并的有机相用水洗涤,干燥,减压浓缩后得到所需化合物(11.0g,95%)。

[1554] 步骤 5 :5- 溴 -3-(环戊基氨基)-2,4- 二甲基苯甲酸甲酯

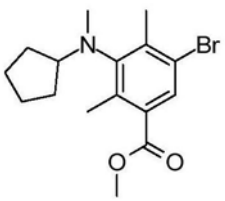
[1555]



[1556] 向搅拌后的 3- 氨基 -5- 溴 -2,4- 二甲基苯甲酸甲酯(1.4g,5.42mmol)和环戊酮(2.4ml,27.13mmol)的甲醇(20mL)溶液中加入醋酸(0.650g,10.84mmol),反应在室温下搅拌 3 小时。然后加入氰基硼氢化钠(0.85g,13.56mmol),搅拌反应过夜。结束时,除去溶剂,残余物加入水,并用乙酸乙酯萃取化合物。收集合并的有机相,用 Na_2SO_4 干燥,减压浓缩,并经柱层析纯化粗原料,得到所需化合物(1.2g,68%)。

[1557] 步骤 6 :5- 溴 -3-(环戊基 (甲基) 氨基)-2,4- 二甲基苯甲酸甲酯

[1558]

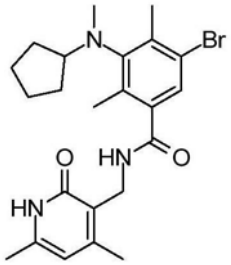


[1559] 向搅拌后的 5- 溴 -3-(环戊基氨基)-2,4- 二甲基苯甲酸甲酯(0.3g,1.07mmol)的 DMF (5mL)溶液中加入碳酸铯(0.697g,2.14mmol)和碘乙烷(0.3ml,5.38mmol);反应物

料在 80℃加热 12 小时。结束时，将反应物料冷却至室温，过滤，用乙酸乙酯洗涤残余物，将滤液浓缩后经柱层析纯化，以得到所需化合物（0.3g，82%）。

[1560] 步骤 7：5- 溴 -3-（环戊基（甲基）氨基）-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-2,4- 二甲基苯甲酰胺

[1561]

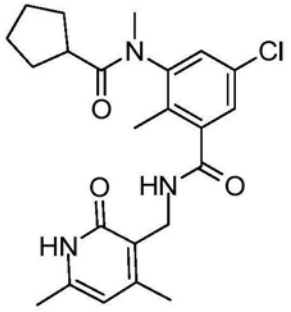


[1562] 将 NaOH（0.022g，0.553mmol）水溶液加入到 5- 溴 -3-（环戊基（甲基）氨基）-2,4- 二甲基苯甲酸甲酯（0.125g，0.368mmol）的 EtOH（10mL）/H_2O（1mL）溶液中，在 60℃搅拌 1 小时。反应结束后，减压除去乙醇，并用稀盐酸酸化至 pH 值为 6。用乙酸乙酯萃取。将合并的有机相用 Na_2SO_4 干燥，减压浓缩，以得到单独的酸（0.1g，84.03%）。

[1563] 然后将所得酸（0.1g，0.308mmol）溶解在 DMSO（3mL）中，并向其中加入 3-（氨基甲基）-4,6- 二甲基吡啶 -2(1H)- 酮（0.07g，0.462mmol）。反应混合物在室温下搅拌 15 分钟后加入 PYBOP（0.320g，0.616mmol），继续搅拌过夜。反应结束后，将反应物料加入到冰中以产生的固体，过滤该固体，并用乙腈洗涤，然后经 HPLC 纯化得到标题化合物（0.018g，12.7%）的三氟乙酸盐。LCMS:460.10(M+1)$^+$;HPLC:98.10%(@254nm)(Rt;8.291; 方法：色谱柱：YMC ODS-A150mm x4.6mm x5μ；流动相 A:0.05%TFA 的水溶液 / 流动相 B:0.05%TFA 的乙腈溶液；进样量：10μL，柱温：30℃；流速：1.4mL/min; 梯度：0-8min5%B-95%B，保持 1.5min,9.51-12min5%B);^{1}H NMR(DMSO-d_6,400MHz) δ 11.46(s,1H),8.18(t,1H,J=4.4Hz),7.20(s,1H),5.85(s,1H),4.26(d,2H,J=4.8Hz),3.51-3.52(m,1H),2.64(s,3H),2.30(s,3H),2.17(s,3H),2.14(s,3H),2.10(s,3H),1.48-1.59(m,6H),1.31-1.32(m,2H)。

[1564] 实施例 26：合成化合物 48：5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-2- 甲基 -3-(N- 甲基环戊甲酰氨基）苯甲酰胺

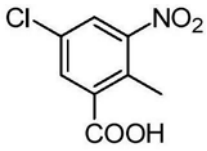
[1565]



化合物 48

[1566] 步骤 1：合成 5- 氯 -2- 甲基 -3- 硝基苯甲酸

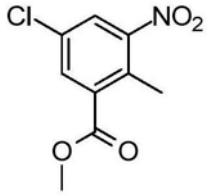
[1567]



[1568] 搅拌下，将 5- 氯 -2- 甲基苯甲酸（20g，0.117mmol）分批加入搅拌后的冰冷的（-10℃至 -15℃）的浓硫酸（136mL）中。在 -10℃至 -15℃下逐滴滴入硝化混合物［浓硫酸（22mL）和浓硝酸（11.05mL）］，所得反应混合物允许搅拌 30 分钟。将所得沉淀过滤，干燥。将固体溶解于乙酸乙酯中，干燥（Na_2SO_4），浓缩，以得到所需白色固体产物（23.6g，93%）。

[1569] 步骤 2 ：合成 5- 氯 -2- 甲基 -3- 硝基苯甲酸甲酯

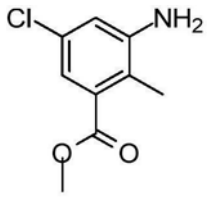
[1570]



[1571] 在室温下，向 5- 氯 -2- 甲基 -3- 硝基苯甲酸（23.5g，0.109mmol）的 DMF （120mL）溶液中加入碳酸钠（46.21，0.436mmol）和碘甲烷（27.2ml，0.43mmol）。反应混合物在 60℃加热 3 小时。起始原料完全耗尽后，将反应混合物过滤，用乙酸乙酯洗涤残余物。减压浓缩滤液，用柱层析纯化粗产品，得到所需化合物（16g，64%），该化合物为稠油状，静置时固化。

[1572] 步骤 3 ：合成 3- 氨基 -5- 氯 -2- 甲基苯甲酸甲酯

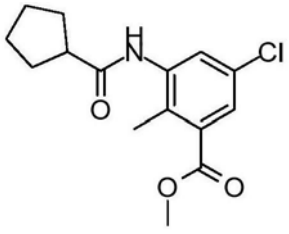
[1573]



[1574] 在搅拌下，向搅拌后的 5- 氯 -2- 甲基 -3- 硝基苯甲酸甲酯（16g，69mmol）的乙醇（160mL）溶液中加入溶解于水（160mL）中的氯化铵（16g，53.4mmol）溶液和铁粉（31.2g，55.85mmol）。将反应混合物在 80℃加热 1 小时。结束时，加入水，并通过硅藻土过滤反应混合物。滤液用乙酸乙酯萃取，合并的有机相用水洗涤，干燥，减压浓缩，得到所需化合物（12.10g，86%），无需进一步纯化。

[1575] 步骤 4 ：合成 5- 氯 -3-（环戊甲酰氨基）-2- 甲基苯甲酸甲酯

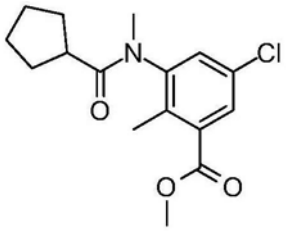
[1576]



[1577] 在 0℃下，向搅拌后的 3- 氨基 -5- 氯 -2- 甲基苯甲酸甲酯（0.4g，2.0mmol）的吡啶（2mL）溶液中加入环戊基甲酰氯（0.39ml，3.00mmol）。反应混合物在室温下搅拌 2 小时。起使原料完全消耗后，用冰水淬灭反应。将产生的沉淀物过滤，得到所需产品（0.5g，84%）。

[1578] 步骤 5 :合成 5- 氯 -2- 甲基 -3-(N- 甲基环戊甲酰氨基) 苯甲酸甲酯

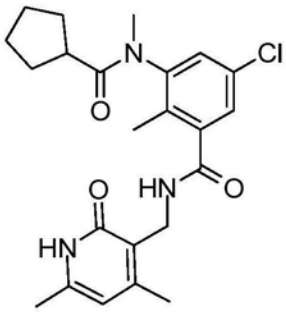
[1579]



[1580] 在 0℃下,向搅拌后的 5- 氯 -3-(环戊烷甲酰氨基)-2- 甲基苯甲酸甲酯(0.3g,1.01mmol)的 DMF 溶液中加入氢化钠(0.060g,0.0015mmol),反应混合物允许搅拌 15 分钟。然后加入碘甲烷(0.32ml,0.50mmol),所得反应混合物在室温下搅拌。起始原料完全消耗后,加水淬灭反应,用乙酸乙酯萃取。合并的有机相用盐水洗涤,干燥(Na_2SO_4),浓缩。所得粗化合物用于下一步反应。

[1581] 步骤 6 :合成 5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基 -3-(N- 甲基环戊甲酰氨基) 苯甲酰胺

[1582]



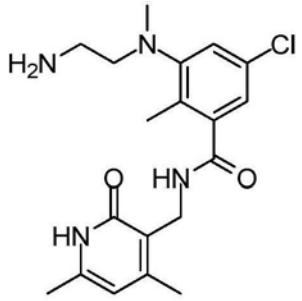
[1583] 将 NaOH(0.077g,1.94mmol)水溶液加入到 5- 氯 -2- 甲基 -3-(N- 甲基环戊甲酰氨基) 苯甲酸甲酯(0.4g,1.2mmol) 的乙醇 / 水(4:1,15mL) 溶液中,在 65℃搅拌 1 小时。反应结束后,减压除去乙醇,然后用 1N 盐酸酸化。反应混合物用乙酸乙酯萃取。用盐水洗涤合并的有机相,干燥,浓缩,得到单独的酸(0.35g,91%)。

[1584] 然后将所得酸(0.3g,0.10mmol)溶解在 DMSO (3mL)中,并向其中加入 3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮(0.309g,0.20mmol)。将反应混合物在室温下搅拌 15 分钟后,加入 PYBOP (0.826g,0.155mmol),继续搅拌过夜。反应结束后,将反应混合物加入到冰中以产生固体,将该固体过滤并用乙腈洗涤。用制备 HPLC 施行最后的纯化,得到所需产品的三氟乙酸盐(0.120g,27%)。

[1585] LCMS:430.20(M+1)$^+$;HPLC:99.79%(@254nm)(R_t;6.086);^{1}H NMR(DMSO-d_6,400MHz) δ 11.55(bs,1H),8.43(t,1H),7.46(s,1H),7.29(s,1H),5.87(s,1H),4.25(s,2H),3.01(s,3H),2.35(m,1H),2.19(s,3H),2.10(s,3H),2.06(s,3H),1.70-1.45(m,6H),1.35(m,2H)。

[1586] 实施例 27 :合成化合物 49 :3-((2- 氨基乙基)(甲基) 氨基)-5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基苯甲酰胺

[1587]



化合物 49

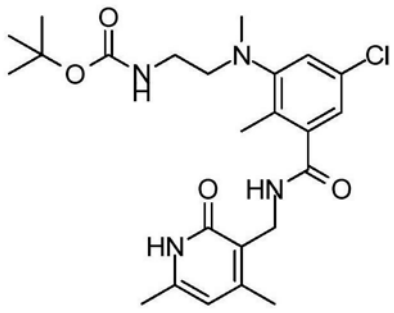
[1588] 将 (2-((5- 氯 -3-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基) 氨基甲酰基)-2- 甲基苯基)(甲基) 氨基) 乙基) 氨基甲酸叔丁酯 (0.2g,4.2mmol) 的二氯甲烷 (5mL) 溶液冷却至 0℃,然后向其中加入 TFA (1mL)。反应混合物在室温下搅拌 1 小时。结束时,将反应浓缩至干燥。其中一半的原料经溶剂洗涤纯化得到纯净的 3-((2- 氨基乙基)(甲基) 氨基)-5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基苯甲酰胺的三氟乙酸盐 (0.060g,76%)。

[1589] LCMS:377.15(M+1)$^{+}$;HPLC:97.57%(@254nm)(R_t;4.611);^{1}H NMR(DMSO-d_6,400MHz) δ 11.47(s,1H),8.21(t,1H),7.69(bs,3H),7.16(s,1H),6.97(s,1H),5.86(s,1H),4.25(d,2H,J=4.4Hz),3.07(t,2H),2.96(m,2H),2.59(s,3H),2.18(s,6H),2.10(s,3H)。

[1590] 剩下的原料用碳酸氢钠水溶液碱化至 pH 值为 8,水相用 20%MeOH/DCM 萃取。合并的有机相用硫酸钠干燥,浓缩,得到作为游离碱的所需化合物 (0.075g),其用于下一步反应。

[1591] 实施例 28 :合成化合物 50 :(2-((5- 氯 -3-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基) 氨基甲酰)-2- 甲基苯基)(甲基) 氨基) 乙基) 氨基甲酸叔丁酯

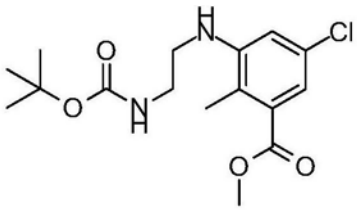
[1592]



化合物 50

[1593] 步骤 1 :合成 3-((2-((叔丁氧羰基) 氨基) 乙基) 氨基)-5- 氯 -2- 甲基苯甲酸甲酯

[1594]

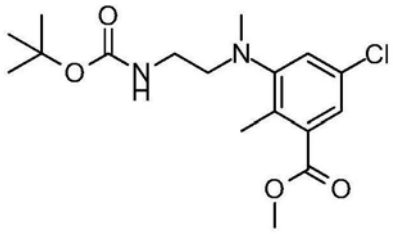


[1595] 向搅拌后的 3- 氨基 -5- 氯 -2- 甲基苯甲酸甲酯 (1g,4.6mmol) 和 (2- 氧代乙基) 氨基甲酸叔丁酯 (1.4g,8.8mmol) 的甲醇 (10mL) 溶液中加入醋酸 (0.027g,4.6mmol),并在

室温下搅拌反应 3 小时。然后加入氰基硼氢化钠(0.352g,4.68mmol)并搅拌过夜。反应结束时,减压除去溶剂,粗原料经柱层析纯化后得到所需产品(0.62g,38%)。

[1596] 步骤 2 :合成 3-((2-((叔丁氧羰基)氨基)乙基)(甲基)氨基)-5- 氯 -2- 甲基苯甲酸甲酯

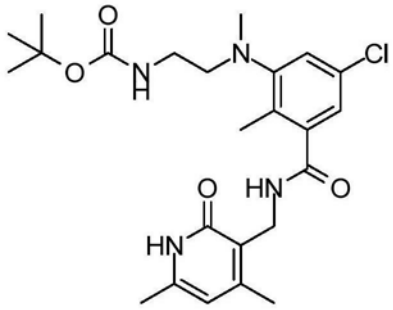
[1597]



[1598] 向搅拌后的 3-((2-((叔丁氧羰基)氨基)乙基)氨基)-5- 氯 -2- 甲基苯甲酸甲酯(0.5g,1.46mmol)的乙腈(10mL)溶液中加入碳酸铯(0.95g,2.92mmol)和碘甲烷(1g,7.3mmol),反应混合物在 80℃加热 12 小时。反应结束后,将反应混合物冷却至室温,然后过滤,用乙酸乙酯洗涤残余物,浓缩滤液,然后经柱层析纯化,得到得到所需产品(0.325g,62%)。

[1599] 步骤 3 :合成 (2-((5- 氯 -3-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)氨基甲酰基)-2- 甲基苯基)(甲基)氨基)乙基)氨基甲酸叔丁酯

[1600]



[1601] 将 NaOH (0.071g,1.79mmol)水溶液加入到 3-((2-((叔丁氧羰基)氨基)乙基)(甲基)氨基)-5- 氯 -2- 甲基苯甲酸甲酯(0.425g,1.19mmol)的甲醇(5mL)溶液中,并在 60℃搅拌 1 小时。反应结束后,减压除去甲醇,残余物用稀盐酸酸化至 pH 值为 6,再用柠檬酸酸化至 pH 值为 4。用乙酸乙酯萃取,干燥并浓缩合并的有机相,得到单独的酸(0.34g,84%)。

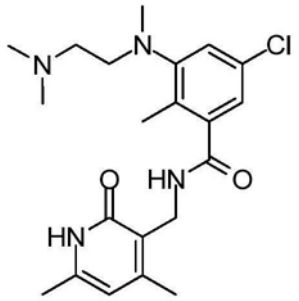
[1602] 将所得酸(0.34g,0.99mmol)溶解于 DMSO (1.5mL)中,并向其中加入 3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮(0.300g,1.98mmol)。所得反应混合物在室温下搅拌 15 分钟后加入 PYBOP(0.77g,1.48mmol),并继续搅拌过夜。反应结束后,将反应混合物倒入冰中以产生固体,将固体过滤并用乙腈洗涤,然后柱层析纯化,得到 (2-((5- 氯 -3-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)氨基甲酰基)-2- 甲基苯基)(甲基)氨基)乙基)氨基甲酸叔丁酯(0.27g,58%)。

[1603] LCMS:477.25(M+1)$^+$;HPLC:97.92%(@254nm)(R_t;6.229);^{1}H NMR(DMSO-d_6,400MHz) δ 11.46(s,1H),8.17(t,1H),7.07(s,1H),6.88(s,1H),6.78(bs,1H),5.85(s,1H),4.24(d,2H,J=4.4Hz),3.07(t,2H),2.84(t,2H),2.62(s,3H),2.17(s,3H),2.13(s,3H),2.

10(s,3H),1.35(s,9H)。

[1604] 实施例 29：合成化合物 51：5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基)-3-((2-(二甲基氨基）乙基)(甲基）氨基)-2- 甲基苯甲酰胺

[1605]

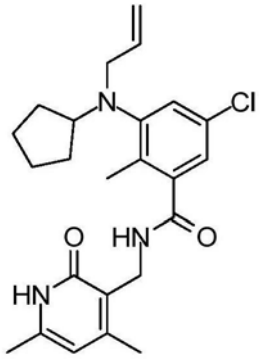


化合物 51

[1606] 将 3-((2- 氨基乙基)(甲基）氨基)-5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基)-2- 甲基苯甲酰胺(0.075g,0.199mmol）溶解于甲醇(5mL）并冷却至 0℃，加入甲醛(0.056g,1.86mmol)。反应混合物在相同温度下搅拌 30 分钟，然后加入氰基硼氢化钠(0.023g,0.366mmol)，并在室温下搅拌 4 小时。反应结束后，减压除去溶剂，加水，并用二氯甲烷萃取。干燥，浓缩合并的有机相，并柱层析纯化，得到 5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基)-3-((2-(二甲基氨基）乙基)(甲基）氨基)-2- 甲基苯甲酰胺(0.040g,50%)。LCMS:405.25(M+1)$^+$;HPLC:89.93%(@254nm)(R_t;4.634);^{1}H NMR(DMSO-d_6,400MHz) δ 11.47(s,1H),8.21(s,1H),7.08(s,1H),5.85(s,1H),4.24(bs,2H),2.91(t,2H),2.63(s,3H),2.33-2.35(m,2H),2.11-2.18(m,15H)。

[1607] 实施例 30：合成化合物 52：3-(烯丙基（环戊基）氨基)-5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基)-2- 甲基苯甲酰胺

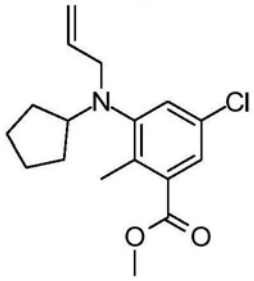
[1608]



化合物 52

[1609] 步骤 1：合成 3-(烯丙基（环戊基）氨基)-5- 氯 -2- 甲基苯甲酸甲酯

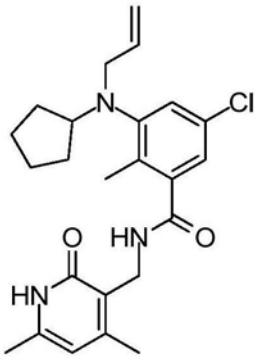
[1610]



[1611] 将 5- 氯 -3-(环戊基氨基)-2- 甲基苯甲酸甲酯(1.2g,4.46mmol) 溶于 DMF (12mL)中,并冷却至 0℃。10 分钟后加入 NaH (0.21g,8.92mmol),并加入烯丙基溴(1.07g,8.9mmol)。反应混合物在室温下搅拌 4 小时,然后在 80℃加热 18 小时。用冰水淬灭反应,用乙酸乙酯萃取。干燥,浓缩合并的有机相,得到 3-(烯丙基 (环戊基) 氨基)-5- 氯 -2- 甲基苯甲酸甲酯粗品(0.4g,29.4%)。

[1612] 步骤 2 :3-(烯丙基 (环戊基) 氨基)-5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基苯甲酰胺的合成

[1613]



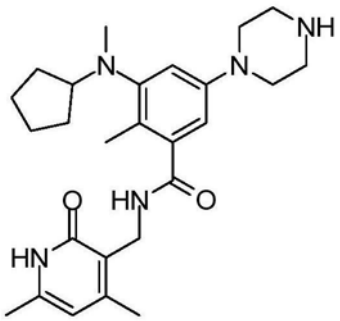
[1614] 将氢氧化钠(0.078g,1.95mmol) 水溶液加入到 3-(烯丙基 (环戊基) 氨基)-5- 氯 -2- 甲基苯甲酸甲酯(0.4g,1.30mmol) 的甲醇(5mL) 溶液中,并在 60℃下搅拌 1 小时。反应结束后,减压除去甲醇,用稀盐酸酸化至 pH 值为 6,再用柠檬酸将 pH 值调至 4。用乙酸乙酯萃取,浓缩合并有机相,得到单独的酸(0.37g,97.6%)。

[1615] 将所得酸(0.25g,0.85mmol) 溶解到 DMSO (3mL) 中,并向其中加入 3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮(0.259g,1.74mmol)。反应混合物在室温下搅拌 15 分钟后加入 PYBOP (0.66g,1.27mmol),继续搅拌过夜。反应结束后,将反应混合物倒入冰中以获得固体,将该固体过滤并用乙腈洗涤,然后经柱层析纯化,得到所需的 3-(烯丙基 (环戊基) 氨基)-5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基苯甲酰胺(0.175g,48%)。

[1616] LCMS:428.30(M+1)$^+$;HPLC:96.37%(@254nm)(R_t;6.357);^{1}H NMR(DMSO-d_6,400MHz) δ 11.47(s,1H),8.21(t,1H),7.16(s,1H),6.92(s,1H),5.85(s,1H),5.63-5.69(m,1H),4.98(m,2H),4.23(d,2H,J=4Hz),3.54(d,2H,J=5.6Hz),3.46-3.50(m,1H),2.18(s,3H),2.16(s,3H),2.10(s,3H),1.67(m,2H),1.59(m,2H),1.47(m,2H),1.36(m,2H)。

[1617] 实施例 31 :合成化合物 53 :3-(环戊基 (甲基) 氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基 -5-(哌嗪 -1- 基) 苯甲酰胺

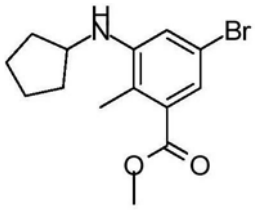
[1618]



化合物 53

[1619] 步骤 1 :合成 5- 溴 -3-(环戊基氨基)-2- 甲基苯甲酸甲酯

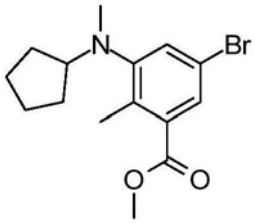
[1620]



[1621] 向搅拌后的 3- 氨基 -5 溴 -2- 甲基苯甲酸甲酯(3g,13.3mmol)和环戊酮(5.6g,66mmol)的甲醇(30mL)溶液中加入醋酸(1.59g,26.6mmol),在室温下搅拌反应 3 小时。然后加入氰基硼氢化钠(2.08g,29.4mmol),搅拌反应过夜。结束时,减压除去溶剂,粗品无需进一步纯化即可使用。

[1622] 步骤 2 :合成 5- 溴 -3-(环戊基 (甲基) 氨基)-2- 甲基苯甲酸甲酯

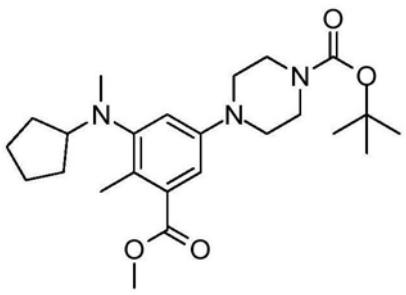
[1623]



[1624] 向搅拌后的 5- 溴 -3-(环戊基氨基)-2- 甲基苯甲酸甲酯(1.6g,5.38mmol)的乙腈(20mL)溶液中加入碳酸铯(3.5g,10.73mmol)和碘甲烷(3.87g,27.25mmol),产生的反应混合物 80℃加热 12 小时。结束时,将反应混合物冷却至室温,过滤。残余物用乙酸乙酯洗涤,滤液浓缩后柱层析纯化,得到所需化合物(1.6g,95%)。

[1625] 步骤 3 :合成 4-(3-(环戊基 (甲基) 氨基)-5-(甲氧基羰基)-4- 甲基苯基) 哌嗪 -1- 羧酸叔丁酯

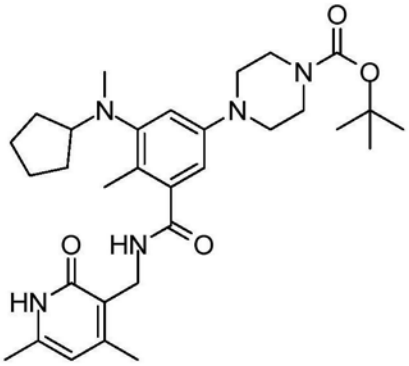
[1626]



[1627] 向 5- 溴 -3-(环戊基 (甲基) 氨基)-2- 甲基苯甲酸甲酯(1g,3.07mmol)、哌嗪 -1- 羧酸叔丁酯(0.85g,4.61mmol)和 Cs_2CO_3(0.5g,1.53mmol)的甲苯(25mL)溶液通入氩气 10 分钟。然后,向其中加入 $Pd_2(dba)_3$(0.31g,0.307mmol)和 BINAP(0.038g,0.061mmol),继续通入氩气 10 分钟。反应混合物在 100℃搅拌 8 小时。结束后,加入水,用乙酸乙酯萃取。合并的有机相用水洗涤,用无水 Na_2SO_4 干燥,过滤,减压浓缩,以得到粗品,该粗品经柱层析纯化得到标题化合物(0.44g,33.3%)。

[1628] 步骤 4 :合成 4-(3-(环戊基 (甲基) 氨基)-5-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基) 氨基甲酰基)-4- 甲基苯基) 哌嗪 -1- 羧酸叔丁酯

[1629]

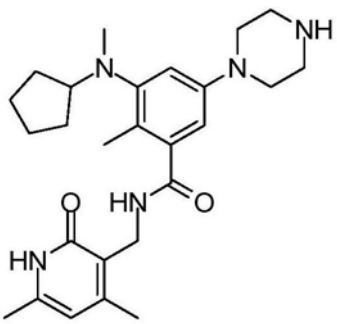


[1630] 将 NaOH (0.061g,1.53mmol)水溶液加入到 4-(3-(环戊基 (甲基) 氨基)-5-(甲氧基羰基)-4- 甲基苯基) 哌嗪 -1- 羧酸叔丁酯(0.44g,1.02mmol)的 MeOH (10mL)溶液中,在 60℃搅拌 1 小时。反应结束后,减压除去甲醇,用稀盐酸酸化至 pH 值为 6,再用柠檬酸酸化至 pH 值为 4。用乙酸乙酯进行萃取。干燥,浓缩合并的有机相,得到单独的酸(0.3g,70%)。

[1631] 然后将所得酸(0.3g,0.71mmol) 溶解到 DMSO (3mL) 中,并向其中加入 3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮(0.215g,1.43mmol)。反应混合物在室温下搅拌 15 分钟后加入 PYBOP (0.56g,1.07mmol),继续搅拌过夜。反应结束后,将反应混合物加入到冰中以产生固体,将该固体过滤,依次用乙腈和乙醚洗涤后得到 4-(3-(环戊基 (甲基) 氨基)-5-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基) 氨基甲酰)-4- 甲基苯基) 哌嗪 -1- 羧酸叔丁酯(0.30g,75.7%)。

[1632] 步骤 5 :合成 3-(环戊基 (甲基) 氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基 -5-(哌嗪 -1- 基) 苯甲酰胺

[1633]



[1634] 将搅拌后的 4-(3-(环戊基 (甲基) 氨基)-5-(((4,6- 二甲基 -2- 氧代 -1,2- 二

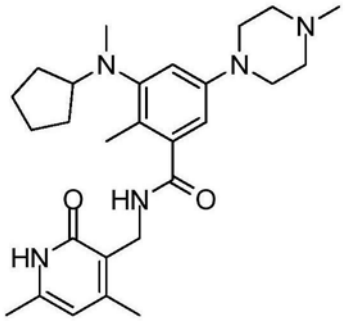
氢吡啶 -3- 基) 甲基) 氨基甲酰基)-4- 甲基苯基) 哌嗪 -1- 羧酸叔丁酯 (0.30,0.54mmol) 的 DCM (10mL) 溶液冷却至 0℃,并向其中加入 TFA (3mL)。反应混合物在室温下搅拌 1 小时。反应结束后,将混合物浓缩至干燥。所得粗产品的一半通过溶剂洗涤纯化得到标题化合物的三氟乙酸盐 (0.01g,8.33%)。

[1635] LCMS:452.39(M+1)$^+$;HPLC:83.92%(@254nm)(R_t;3.825);^{1}H NMR(DMSO-d_6,400MHz) δ 11.45(s,1H),8.71(s,2H),7.98(s,1H),6.79(s,1H),6.55(s,1H),5.85(s,1H),4.24(d,2H,J=3.2Hz),3.46(1H 在溶剂峰中),3.22-3.26(m,8H),2.50(3H 并入溶剂峰中),2.18(s,3H),2.10(s,6H),1.41-1.67(m,8H)。

[1636] 另外一半粗产品用碳酸氢钠水溶液碱化至 pH 值为 8,再用 20%MeOH/DCM 萃取水层。用硫酸钠干燥合并的有机相,然后浓缩,得到作为游离碱的标题化合物。

[1637] 实施例 32 :合成化合物 54 :3-(环戊基 (甲基) 氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基 -5-(4- 甲基哌嗪 -1- 基) 苯甲酰胺

[1638]



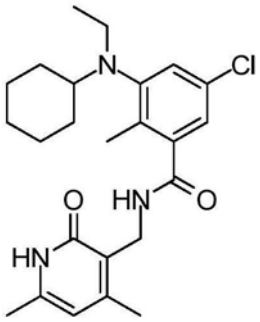
化合物 54

[1639] 将 3-(环戊基 (甲基) 氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基 -5-(哌嗪 -1- 基) 苯甲酰胺 (游离碱)(0.100g,0.223mmol) 溶于甲醇 (5mL) 并冷却至 0℃,然后加入福尔马林 (0.033g,1.1ml,2.23mmol)。反应混合物在相同温度下搅拌 30 分钟。将氰基硼氢化钠 (0.013g,0.22mmol) 加入到上述反应混合物中,并在室温下搅拌 4 小时。结束后,减压除去溶剂,向残余物中加水,用二氯甲烷萃取。将合并的有机相干燥,浓缩,柱层析纯化,得到所需的 3-(环戊基 (甲基) 氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基 -5-(4- 甲基哌嗪 -1- 基) 苯甲酰胺 (0.037g,36%)。

[1640] LCMS:466.40(M+1)$^+$;HPLC:99.18%(@254nm)(R_t;3.871);^{1}H NMR(DMSO-d_6,400MHz) δ 11.45(s,1H),7.94(t,1H),6.71(s,1H),6.48(s,1H),5.85(s,1H),4.24(d,2H,J=3.2Hz),3.39-3.43(m,1H),3.07(bs,4H),2.46(s,3H),2.31(s,3H),2.18(s,3H),2.10(s,3H),2.08(s,3H),1.66(m,2H),1.59(m,2H),1.39-1.48(m,4H)。

[1641] 实施例 33 :合成化合物 55 :5- 氯 -3-(环己基 (乙基) 氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基苯甲酰胺

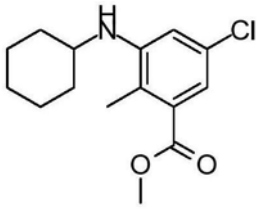
[1642]



化合物 55

[1643] 步骤 1 :合成 5- 氯 -3-(环己基氨基)-2- 甲基苯甲酸甲酯

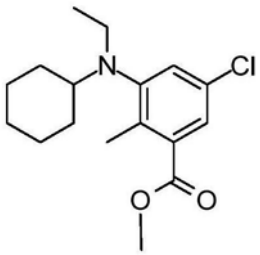
[1644]



[1645] 向搅拌后的 3- 氨基 -5- 氯 -2- 甲基苯甲酸甲酯(1g,5.02mmol)和环己酮(2.45g,25mmol)的甲醇(10mL)溶液中加入醋酸(0.3g,5.02mmol),室温下搅拌反应 3 小时。然后加入氰基硼氢化钠(0.63g,10.05mmol)并搅拌反应过夜。结束时,减压除去溶剂,粗品经柱层析纯化得到 5- 氯 -3-(环己基氨基)-2- 甲基苯甲酸甲酯(1.2g,89.92%)。

[1646] 步骤 2 :合成 5- 氯 -3-(环己基 (乙基) 氨基)-2- 甲基苯甲酸甲酯

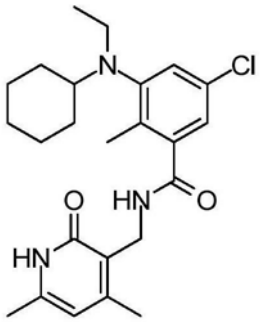
[1647]



[1648] 向搅拌后的 5- 氯 -3-(环己基氨基)-2- 甲基苯甲酸甲酯(1.2g,4.3mmol)的无水 DMF (15mL) 溶液中加入碳酸铯(2.78g,8.5mmol) 和碘乙烷(3.35g,21.47mmol)。产生的反应混合物在 80℃反应 18 小时。结束时,将反应混合物冷却至室温并过滤,用乙酸乙酯洗涤残余物。将滤液浓缩,柱层析纯化得到 5- 氯 -3-(环己基 (乙基) 氨基)-2- 甲基苯甲酸甲酯(0.25g,22.7%)。

[1649] 步骤 3 :合成 5- 氯 -3-(环己基 (乙基) 氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基苯甲酰胺

[1650]

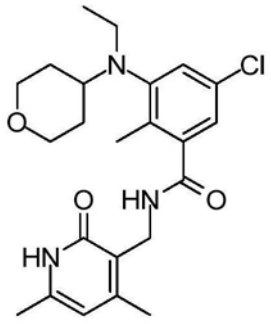


[1651] 将 NaOH(0.065g,1.61mmol)水溶液加入到 5- 氯 -3-(环己基 (乙基) 氨基)-2- 甲基苯甲酸甲酯(0.25g,0.809mmol)的乙醇(5mL)溶液中,并在 60℃搅拌 1 小时。反应结束后,减压除去乙醇,用稀盐酸酸化至 pH 值为 6,再用柠檬酸酸化至 pH 值为 4。用乙酸乙酯实施萃取。干燥,浓缩合并的有机相,得到单独的酸(0.22g,92%)。

[1652] 然后将所得酸(0.22g,0.745mmol)溶解到 DMSO(2mL)中,并向其中加入 3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮(0.246g,1.49mmol)。反应混合物在室温下搅拌 15 分钟后加入 PYBOP(0.58g,1.11mmol),继续搅拌过夜。反应结束后,将混合物加入到冰中以产生固体,将该固体过滤并用乙腈洗涤。经柱层析进行最终的纯化,得到 5- 氯 -3-(环己基 (乙基) 氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基苯甲酰胺(0.200g,46.6%)。LCMS:430.20(M+1)$^+$;HPLC:92.49%(@254nm)(R_t;5.264);^{1}H NMR(DMSO-d_6,400MHz) δ 11.45(s,1H),8.21(t,1H),7.12(s,1H),6.91(s,1H),5.85(s,1H),4.23(d,2H,J=4.4Hz),3.01-3.03(m,2H),2.64-2.66(m,1H),2.18(s,3H),2.13(s,3H),2.10(s,3H),1.68(m,4H),1.51-1.53(m,1H),1.07-1.34(m,5H),0.78(t,3H,J=6.8Hz)。

[1653] 实施例 34 : 合成化合物 56 :5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-3-(乙基 (四氢 -2H- 吡喃 -4- 基) 氨基)-2- 甲基苯甲酰胺

[1654]



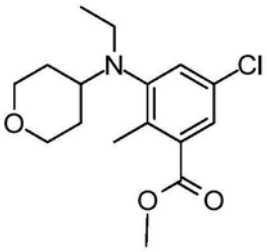
化合物 56

[1655] 步骤 1 : 合成 5- 氯 -2- 甲基 -3-((四氢 -2H- 吡喃 -4- 基) 氨基) 苯甲酸甲酯

[1656] 向搅拌后的 3- 氨基 -5- 氯 -2- 甲基苯甲酸甲酯(1g,5.02mmol)和四氢吡喃 -4- 酮(2.5g,25mmol)的甲醇(10mL)溶液中加入醋酸(0.3g,5.02mmol),在室温下搅拌反应 3 小时。然后加入氰基硼氢化钠(0.63g,10.05mmol),搅拌反应过夜。结束时,减压除去溶剂,粗品经柱层析纯化得到 5- 氯 -2- 甲基 -3-((四氢 -2H- 吡喃 -4- 基) 氨基) 苯甲酸甲酯(0.5g,35.5%)。

[1657] 步骤 2 : 合成 5- 氯 -3-(乙基 (四氢 -2H- 吡喃 -4- 基) 氨基)-2- 甲基苯甲酸甲酯

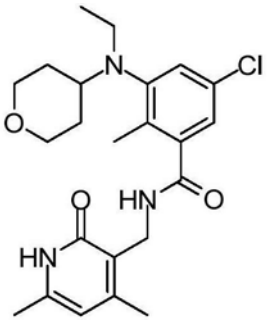
[1658]



[1659] 向搅拌后的 5- 氯 -2- 甲基 -3-((四氢 -2H- 吡喃 -4- 基)氨基)苯甲酸甲酯(0.5g,1.76mmol)的无水 CAN(15mL)溶液中加入碳酸铯(1.2g,3.68mmol)和碘乙烷(2.7g,17.3mmol),产生的反应混合物在 80℃搅拌反应 18 小时。结束时,将混合物冷却至室温,过滤,用乙酸乙酯洗涤残余物。将滤液浓缩并经柱层析纯化得到所需的 5- 氯 -3-(乙基(四氢 -2H- 吡喃 -4- 基)氨基)-2- 甲基苯甲酸甲酯(0.180g,34%)。

[1660] 步骤 3:合成 5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)-3-(乙基(四氢 -2H- 吡喃 -4- 基)氨基)-2- 甲基苯甲酰胺

[1661]

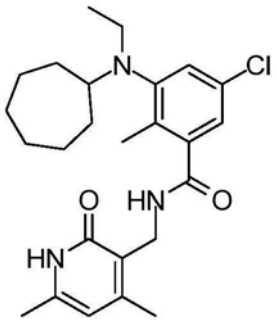


[1662] 将 NaOH(0.05g,1.22mmol)水溶液加入到 5- 氯 -3-(乙基(四氢 -2H- 吡喃 -4- 基)氨基)-2- 甲基苯甲酸甲酯(0.18g,0.608mmol)的 EtOH (5mL)溶液中,在 60℃搅拌 1 小时。反应结束后,减压除去乙醇,用稀盐酸酸化至 pH 值为 6,再用柠檬酸酸化至 pH 值为 4。用乙酸乙酯进行萃取。干燥并浓缩合并的有机相后得到单独的酸(0.15g,87%)。

[1663] 将所得酸(0.15g,0.530mmol)溶解到 DMSO (1mL)中,并向其中加入 3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮(0.160g,1.06mmol)。将反应混合物在室温下搅拌 15 分钟后加入 PYBOP (0.413g,0.79mmol),继续搅拌过夜。反应结束后,将反应混合物加入到冰中,用 10%MeOH/DCM 进行萃取。干燥,浓缩合并有机相,并经硅胶柱层析纯化得到 5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)-3-(乙基(四氢 -2H- 吡喃 -4- 基)氨基)-2- 甲基苯甲酰胺(0.100g,43.88%)。LCMS:432.25(M+1)$^+$;HPLC:90.46%(@254nm)(R_t;4.833);^{1}H NMR(DMSO-d_6,400MHz) δ 11.46(s,1H),8.22(t,1H),7.19(s,1H),6.96(s,1H),5.85(s,1H),4.23(d,2H,J=4Hz),3.81(d,2H,J=10Hz),3.20-3.21(m,2H),2.94-3.02(m,3H),2.18(s,3H),2.15(s,3H),2.10(s,3H),1.48-1.61(m,4H),0.78(t,3H,J=6.4Hz)。

[1664] 实施例 35:合成化合物 57:5- 氯 -3-(环庚基(乙基)氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)-2- 甲基苯甲酰胺

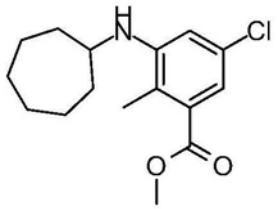
[1665]



化合物 57

[1666] 步骤 1 :合成 5- 氯 -3-(环庚基氨基)-2- 甲基苯甲酸甲酯

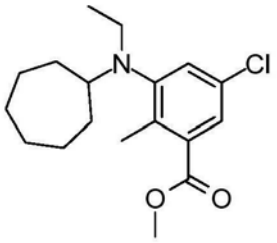
[1667]



[1668] 向搅拌后的 3- 氨基 -5- 氯 -2- 甲基苯甲酸甲酯(1g,5.02mmol)和环庚酮(2.81g,25mmol)的甲醇(10mL)溶液中加入醋酸(0.3g,5.02mmol),在室温下搅拌反应 3 小时。然后加入氰基硼氢化钠(0.65g,10.05mmol),搅拌过夜。结束时,减压除去溶剂,粗品经柱层析纯化得到 5- 氯 -3-(环庚基氨基)-2- 甲基苯甲酸甲酯(0.8g,56.2%)。

[1669] 步骤 2 :合成 5- 氯 -3-(环庚基 (乙基) 氨基)-2- 甲基苯甲酸甲酯

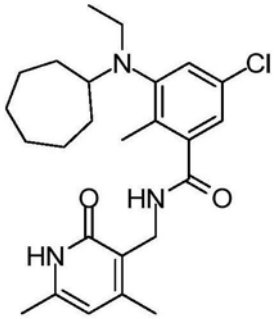
[1670]



[1671] 向搅拌后的 5- 氯 -3-(环庚基氨基)-2- 甲基苯甲酸甲酯(0.8g,2.70mmol)的无水 DMF (10mL) 溶液中加入碳酸铯(1.76g,5.4mmol) 和碘乙烷(2.11g,13.5mmol),产生的反应混合物在 80℃加热 18 小时。结束时,将混合物冷却至室温,过滤,用乙酸乙酯洗涤残余物,滤液浓缩后经柱层析纯化得到所需的 5- 氯 -3-(环庚基 (乙基) 氨基)-2- 甲基苯甲酸甲酯(0.220g,25%)。

[1672] 步骤 3 :合成 5- 氯 -3-(环庚基 (乙基) 氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基苯甲酰胺

[1673]

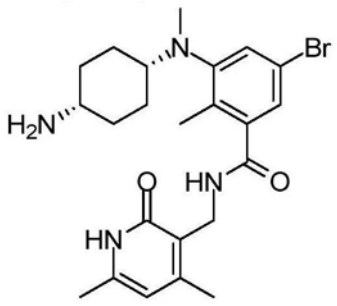


[1674] 将 NaOH(0.04g,1.02mmol)水溶液加入到 5- 氯 -3-(环庚基 (乙基) 氨基)-2- 甲基苯甲酸甲酯(0.22g,0.68mmol)的 EtOH (5mL)溶液中,在 60℃搅拌 1 小时。反应结束后,减压除去乙醇,用稀盐酸酸化至 pH 值为 6,再用柠檬酸酸化至 pH 值为 4。用乙酸乙酯进行萃取。合并的有机相经干燥,浓缩得到单独的酸(0.18g,85%)。

[1675] 然后将所得酸(0.18g,0.585mmol)溶解到 DMSO (1.5mL)中,并向其中加入 3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮(0.177g,1.16mmol)。将反应混合物在室温下搅拌 15 分钟后向其中加入 PYBOP (0.45g,0.87mmol),继续搅拌过夜。反应结束后,将反应混合物加入到冰中以获得固体,将该固体过滤并用乙腈洗涤,经柱层析纯化得到 5- 氯 -3-(环庚基 (乙基) 氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基苯甲酰胺(0.100g,38.7%)。LCMS:444.25(M+1)+;HPLC:89.74%(@254nm)(Rt;5.933);^{1}H NMR(DMSO-d_6,400MHz) δ 11.46(s,1H),8.21(t,1H),7.07(s,1H),6.88(s,1H),5.85(s,1H),4.23(d,2H,J=4Hz),3.02-3.03(m,2H),2.77(bs,1H),2.18(s,3H),2.13(s,3H),2.10(s,3H),1.76(m,2H),1.59-1.62(m,4H),1.46(m,4H),1.28(m,2H),0.78(t,3H,J=6Hz)。

[1676] 实施例 36 : 合成化合物 58 : 顺式 3-((4- 氨基环己基)(甲基) 氨基)-5- 溴 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基苯甲酰胺

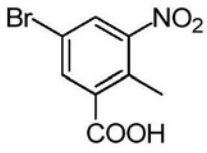
[1677]



化合物 58

[1678] 步骤 1 :合成 5- 溴 -2- 甲基 -3- 硝基苯甲酸

[1679]

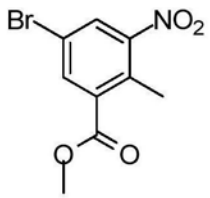


[1680] 在室温下,向搅拌后的 2- 甲基 -3- 硝基苯甲酸(50g,276.2mmol) 的浓硫酸(200mL)溶液中分批加入 1,3- 二溴 -5,5- 二甲基 -2,4- 咪唑烷二酮(43.4g,151.8mmol),反应物料在室温下搅拌 5 小时。结束时,将反应混合物加入到冰水中,将析出的固体过滤,

残余物用水洗涤，并在真空下干燥，得到用于后续步骤的所需化合物（71.7g，100%）。

[1681] 步骤 2：合成 5- 溴 -2- 甲基 -3- 硝基苯甲酸甲酯

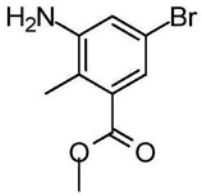
[1682]



[1683] 向搅拌后的 5- 溴 -2- 甲基 -3- 硝基苯甲酸（287g，1103mmol）的 DMF（150mL）溶液中加入碳酸钠（468g，4415mmol）和碘甲烷（626.63g，4415mmol）。反应混合物在 60℃加热 8 小时。结束时，将析出的固体过滤，用乙醚洗涤（5 次）残余物。合并的有机相经干燥，减压浓缩得到用于后续步骤的所需化合物（302g，99%）。

[1684] 步骤 3：合成 3- 氨基 -5- 溴 -2- 甲基苯甲酸甲酯

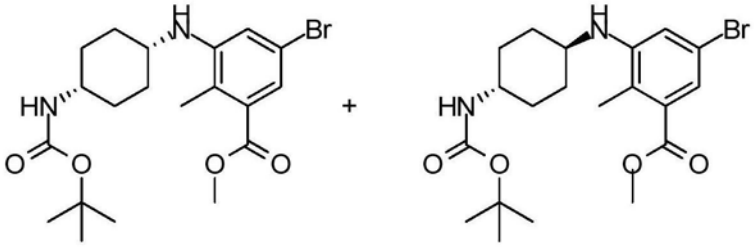
[1685]



[1686] 向搅拌后的 5- 溴 -2- 甲基 -3- 硝基苯甲酸甲酯（150g，544mmol）的乙醇（750mL）溶液中加入溶解于水（750mL）中的氯化铵（150g，2777mmol）和铁粉（93.3g，1636mmol）。将产生的反应混合物在 80℃加热 7 小时。结束时，将反应物料通过硅藻土过滤，同时用水和乙酸乙酯洗涤，用乙酸乙酯萃取滤液。干燥，减压浓缩合并的有机相，得到所需化合物，其无需进一步纯化便可以直接用于后续步骤。

[1687] 步骤 4：合成顺式和反式 5- 溴 -3-((4-((叔丁氧羰基）氨基）环己基）氨基）-2- 甲基苯甲酸甲酯

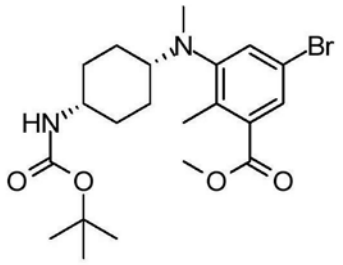
[1688]



[1689] 向搅拌后的 3- 氨基 -5- 溴 -2- 甲基苯甲酸甲酯（5g，20.57mmol）和（4- 氧代环己基）氨基甲酸叔丁酯（5.6g，26.7mmol）的甲醇（50mL）溶液中加入醋酸（1.2g，20.57mmol），在室温下搅拌反应 8 小时。然后在 0℃加入氰基硼氢化钠（1.6g，26.74mmol）并搅拌过夜。结束时，减压除去溶剂，粗品经两次柱层析纯化（洗脱剂：乙酸乙酯 / 己烷）得到极性较小的顺式异构体（4g，44%）和纯净的极性较大的反式异构体（3g，33%）。

[1690] 步骤 5：合成顺式 5- 溴 -3-((4-((叔丁氧羰基）氨基）环己基）（甲基）氨基）-2- 甲基苯甲酸甲酯

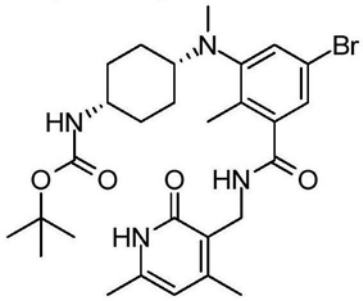
[1691]



[1692] 向搅拌后的 5- 溴 -3-((4-((叔丁氧羰基) 氨基) 环己基) 氨基)-2- 甲基苯甲酸甲酯(4g,9.09mmol)的顺式异构体混合物的乙腈(50mL)溶液中加入碳酸铯(5.9g,18.18mmol)和碘甲烷(6.45g,45.45mmol)。产生的反应混合物在 80℃加热 7 小时。结束时,将反应混合物冷却至室温后过滤,残余物用乙酸乙酯洗涤,滤液经浓缩后得到粗化合物,然后将该粗化合物经柱层析纯化,得到所需化合物(1.4g,34%)。

[1693] 步骤 6 :合成顺式 (4-((5- 溴 -3-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基) 氨基甲酰)-2- 甲基苯基)(甲基) 氨基) 环己基) 氨基甲酸叔丁酯

[1694]

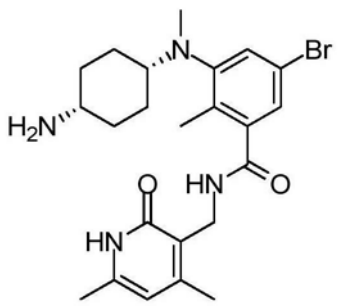


[1695] 将 NaOH (0.23g,5.72mmol) 水溶液加入到顺式 5- 溴 -3-((4-((叔丁氧羰基) 氨基) 环己基)(甲基) 氨基)-2- 甲基苯甲酸甲酯(1.3g,2.86mmol)的 MeOH (20mL)溶液中,然后在 60℃搅拌 1 小时。反应结束后,减压除去甲醇,用稀盐酸酸化至 pH 值为 6,再用柠檬酸酸化至 pH 值为 4。用乙酸乙酯进行萃取。合并有机相经干燥,浓缩得到单独的酸(1.13g,90.1%)。

[1696] 将所得酸(1.13g,2.57mmol) 溶解到 DMSO (10mL) 中,并向其中加入 3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮(0.87g,5.72mmol)。反应混合物在室温下搅拌 15 分钟后加入 PYBOP(2.23g,4.28mmol),继续搅拌过夜。反应结束后,将反应物料加入到冰中以产生固体,将该固体过滤,用乙腈洗涤后经柱层析纯化得到所需化合物(0.8g,49%)。

[1697] 步骤 7 :合成顺式 3-((4- 氨基环己基)(甲基) 氨基)-5- 溴 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基苯甲酰胺

[1698]



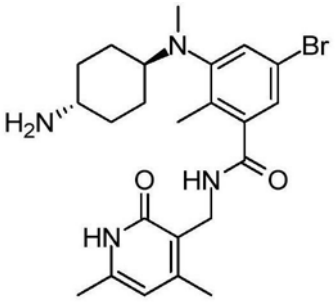
[1699] 将搅拌后的顺式(4-((5-溴-3-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰)-2-甲基苯基)(甲基)氨基)环己基)氨基甲酸叔丁酯(0.8g,1.39mmol)的DCM(25mL)溶液冷却至0℃,然后向其中加入TFA(5mL)。反应混合物在室温下搅拌1小时。反应结束后,将混合物浓缩至干燥。残余物用碳酸氢钠水溶液碱化至pH值为8,水层用20%MeOH/DCM萃取。合并的有机相用硫酸钠干燥,过滤,浓缩得到所需化合物(600mg,产率91%)。LCMS:475.15(M+1)+;HPLC%95.88(@254nm)(Rt;4.832;方法:色谱柱:YMC ODS-A150mm x4.6mm x5μ;流动相A:0.05%TFA水溶液/流动相B:0.05%TFA的乙腈溶液;进样量:10μL;柱温:30℃;流速:1.4mL/min.;梯度:0-8min5%B-95%B,保持1.5min,9.51-12min5%B);^{1}H NMR(DMSO-d_6,400MHz)δ8.22(t,1H),7.20(s,1H),7.01(s,1H),5.85(s,1H),4.23(d,2H,J=3.6Hz),2.82-2.86(m,2H),2.53(s,3H),2.18(s,3H),2.13(s,3H),2.10(s,3H),1.82-1.84(m,2H),1.34-1.44(m,6H)。

[1700] 将100mg的顺式3-((4-氨基环己基)(甲基)氨基)-5-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺(游离碱)溶解于氯化氢的甲醇溶液(5mL)中,并在室温下搅拌1小时。成盐结束时,减压除去溶剂,所得到的固体用乙醚洗涤纯化得到相应的盐酸盐。

[1701] 盐酸盐的分析数据:LCMS:475.20(M+1)+;HPLC%96.09(@254nm)(Rt;4.818;方法:色谱柱:YMC ODS-A150mm x4.6mm x5μ;流动相A:0.05%TFA的水溶液/流动相B:0.05%TFA的乙腈溶液;进样量:10μL;柱温:30℃;流速:1.4mL/min.;梯度:0-8min5%B-95%B,保持1.5min,9.51-12min5%B);^{1}H NMR(DMSO-d_6,400MHz)δ11.51(s,1H),8.28(t,1H),8.08(s,3H),7.31(s,1H),7.08(s,1H),5.90(s,1H),4.24(d,2H,J=4.4Hz),3.05-3.13(m,2H),2.54(s,3H),2.19(s,6H),2.12(s,3H),1.83(m,2H),1.66(m,2H),1.59-1.60(m,2H),1.46(m,2H)。

[1702] 实施例37:合成化合物59:反式3-((4-氨基环己基)(甲基)氨基)-5-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺

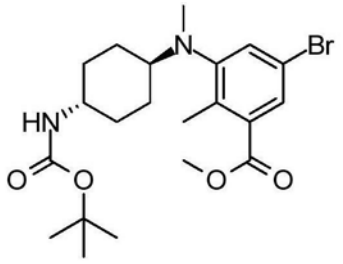
[1703]



化合物59

[1704] 步骤1:合成反式5-溴-3-((4-((叔丁氧羰基)氨基)环己基)(甲基)氨基)-2-甲基苯甲酸甲酯

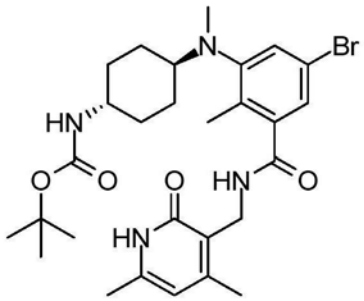
[1705]



[1706] 向搅拌后的反式 5- 溴 -3-((4-((叔丁氧羰基) 氨基) 环己基) 氨基)-2- 甲基苯甲酸甲酯(3g,6.81mmol)的乙腈(40mL)溶液中加入碳酸铯(4.4g,13.62mmol)和碘甲烷(4.83g,34.05mmol),产生的反应混合物在 80℃加热 7 小时。结束时,将反应混合物冷却至室温,过滤,残余物用乙酸乙酯洗涤,滤液经浓缩后得到粗化合物,然后该粗化合物经柱层析纯化得到所需化合物(1.3g,43%)。

[1707] 步骤 2 :合成反式 (4-((5- 溴 -3-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基) 氨基甲酰基)-2- 甲基苯基)(甲基) 氨基) 环己基) 氨基甲酸叔丁酯

[1708]

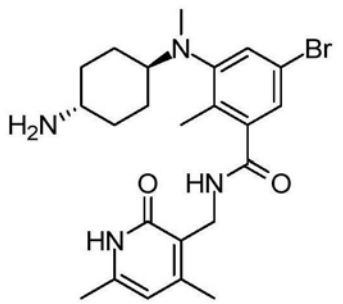


[1709] 将 NaOH (0.23g,5.72mmol) 水溶液加入到反式 5- 溴 -3-((4-((叔丁氧羰基) 氨基) 环己基)(甲基) 氨基)-2- 甲基苯甲酸甲酯(1.3g,2.86mmol)的 MeOH (20mL)溶液中,并在 60℃搅拌 1 小时。反应结束后,减压除去乙醇,用稀盐酸酸化至 pH 值为 6,再用柠檬酸酸化至 pH 值为 4。混合物用乙酸乙酯进行萃取。合并的有机相经干燥,过滤,浓缩得到单独的酸(1g,83%)。

[1710] 将所得酸(1g,2.27mmol)溶解到 DMSO (5mL)中,并向其中加入 3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮(0.65g,4.54mmol)。反应混合物在室温下搅拌 15 分钟后加入 PYBOP(1.7g,3.4mmol),继续搅拌过夜。反应结束后,将反应物料加入到冰中以获得固体,将该固体过滤并用乙腈洗涤,然后经柱层析纯化得到所需化合物(0.7g,54%)。

[1711] 步骤 3 :合成反式 3-((4- 氨基环己基)(甲基) 氨基)-5- 溴 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基苯甲酰胺

[1712]

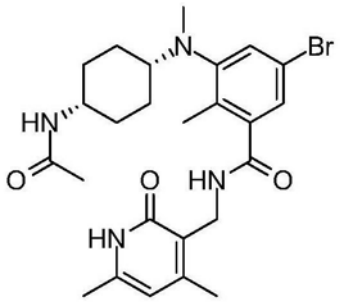


[1713] 将搅拌后的反式(4-((5-溴-3-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰基)-2-甲基苯基)(甲基)氨基)环己基)氨基甲酸叔丁酯(0.7g,1.21mmol)的DCM(8mL)溶液冷却至0℃,然后加入TFA(2.5mL)。反应物料在室温下搅拌1小时。结束时,将反应浓缩至干燥。残余物用碳酸氢钠水溶液碱化至pH值为8,水层用20%MeOH/DCM萃取。合并的有机相用硫酸钠干燥,过滤,浓缩得到粗品,然后该粗品通过用溶剂洗涤来进一步纯化得到所需化合物(0.5g,86%)。LCMS:475.20(M+1)+;HPLC%92.35(@254nm)(Rt;4.416;方法:色谱柱:YMC ODS-A150mm x4.6mm x5μ;流动相A:0.05%TFA的水溶液/流动相B:0.05%TFA的乙腈溶液;进样量:10μL;柱温:30℃;流速:1.4mL/min.;梯度:0-8min5%B-95%B,保持1.5min,9.51-12min5%B);^{1}H NMR(DMSO-d_6,400MHz)δ8.21(t,1H),7.18(s,1H),7.01(s,1H),5.85(s,1H),4.23(d,2H),2.63-2.66(m,2H),2.55(s,3H),2.17(s,3H),2.10(s,6H),1.79-1.82(m,2H),1.60(m,2H),1.46-1.49(m,2H),1.06-1.09(m,2H)。

[1714] 将100mg的反式3-((4-氨基环己基)(甲基)氨基)-5-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺(游离碱)溶于氯化氢的甲醇(5mL)溶液中,在室温下搅拌1小时。成盐结束时,减压除去溶剂,所得到的固体用乙醚洗涤纯化得到相应的盐酸盐。盐酸盐的分析数据:LCMS:475.20(M+1)$^+$;HPLC%91.40(@254nm)(R_t;4.408;方法:色谱柱:YMC ODS-A150mm x4.6mm x5μ;流动相A:0.05%TFA的水溶液/流动相B:0.05%TFA的乙腈溶液;进样量:10μL,柱温:30℃;流速:1.4mL/min.;梯度:0-8min5%B-95%B,保持1.5min,9.51-12min5%B);^{1}H NMR(DMSO-d_6,400MHz)δ11.51(s,1H),8.28(t,1H),8.06(s,3H),7.31(s,1H),7.08(s,1H),5.89(s,1H),4.24(d,2H,J=4.4Hz),2.92(bs,1H),2.62-2.91(m,4H),2.19(s,3H),2.13(s,3H),2.11(s,3H),1.97(d,2H,J=10.8Hz),1.70(m,2H),1.53-1.56(m,2H),1.31-1.34(m,2H)。

[1715] 实施例38:合成化合物60:顺式3-((4-乙酰氨基环己基)(甲基)氨基)-5-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺

[1716]



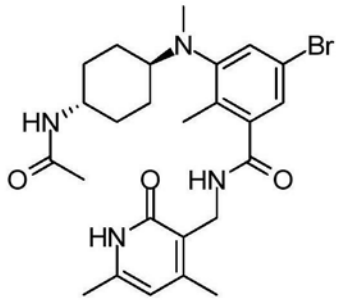
化合物60

[1717] 在室温下,向搅拌后的顺式3-((4-氨基环己基)(甲基)氨基)-5-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺(游离碱)(0.225,0.474mmol)的DMF(3mL)溶液中加入EDCI.HCl(0.138g,0.718mmol)、HOBt(0.064g,0.47mmol)、三乙胺(0.1g,0.99mmol)和醋酸(0.057g,0.949mmol),并在相同温度下搅拌18小时。结束时,加水,用10%MeOH/DCM萃取。合并有机相经干燥,浓缩后得到粗品,然后该粗品经柱层析纯化得到所需化合物(0.17g,72%)。LCMS:517.25(M+1)$^+$;HPLC%95.83(@254nm)(R_t;4.894;方法:柱子:YMC ODS-A150mm x4.6mm x5μ;流动相A:0.05%TFA的水溶液/流动相B:0.05%TFA

的乙腈溶液；进样量：10μL，柱温：30℃；流速：1.4mL/min.；梯度：0-8min5%B-95%B，保持1.5min，9.51-12min5%B)；^{1}H NMR(DMSO-d_6，400MHz) δ11.46(s,1H)，8.22(t,1H)，7.76(d,1H,J=7.2Hz)，7.23(s,1H)，7.03(s,1H)，5.85(s,1H)，4.23(d,2H,J=3.6Hz)，3.71(bs,1H)，2.89(m,1H)，2.53(s,3H)，2.18(s,3H)，2.16(s,3H)，2.10(s,3H)，1.81(s,3H)，1.74-1.76(m,2H)，1.53(m,2H)，1.39(m,4H)。

[1718] 实施例39：合成化合物61：反式3-((4-乙酰氨基环己基)(甲基)氨基)-5-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺

[1719]



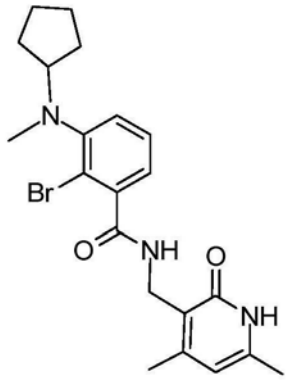
化合物61

[1720] 在室温下，向搅拌后的反式3-((4-氨基环己基)(甲基)氨基)-5-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺(0.225,0.474mmol)的DMF(3mL)溶液中加入EDCI.HCl(0.138g,0.718mmol)、HOBt(0.064g,0.47mmol)、三乙胺(0.1g,0.99mmol)和醋酸(0.057g,0.949mmol)，并在相同温度下搅拌18小时。结束时，加水，用10%MeOH/DCM萃取。合并有机相经干燥，浓缩后得到粗品；然后该粗品经柱层析纯化得到所需化合物(0.13g,53%)。

[1721] LCMS:517.20(M+1)$^+$;HPLC%93.92(@254nm)(Rt;4.713;方法：色谱柱：YMC ODS-A150mm x4.6mm x5μ；流动相A:0.05%TFA的水溶液/流动相B:0.05%TFA的乙腈溶液；进样量：10μL，柱温：30℃；流速：1.4mL/min.；梯度：0-8min5%B-95%B，保持1.5min,9.51-12min5%B)；^{1}H NMR(DMSO-d_6，400MHz) δ11.45(s,1H)，8.20(t,1H)，7.65(d,1H,J=7.6Hz)，7.18(s,1H)，7.01(s,1H)，5.85(s,1H)，4.23(d,2H,J=3.6Hz)，3.42-3.44(m,1H)，2.68-2.71(m,1H)，2.56(s,3H)，2.18(s,3H)，2.10(s,6H)，1.77-1.80(m,2H)，1.74(s,3H)，1.62-1.65(m,2H)，1.46-1.54(m,2H)，1.07-1.23(m,2H)。

[1722] 实施例40：合成化合物62：2-溴-3-(环戊基(甲基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)苯甲酰胺

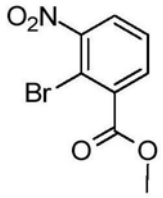
[1723]



化合物 62

[1724] 步骤 1 :2- 溴 -3- 硝基苯甲酸甲酯

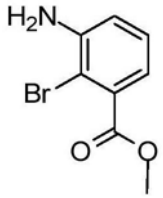
[1725]



[1726] 向搅拌后的 2- 溴 -3- 硝基苯甲酸甲酯(3g,12.19mmol)的 DMF (33mL)溶液中加入碳酸钠(5.16g,48.67mmol)和碘甲烷(6.92g,48.67mmol)。产生的所得反应混合物 60℃加热 4 小时。结束时,向混合物加水,用 DCM 进行萃取。合并的有机相经干燥,减压浓缩得到 2- 溴 -3- 硝基苯甲酸甲酯(4g,粗品)。

[1727] 步骤 2 :合成 3- 氨基 -2- 溴苯甲酸甲酯

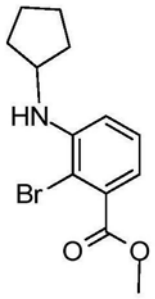
[1728]



[1729] 在搅拌下,向搅拌后的 2- 溴 -3- 硝基苯甲酸甲酯(4g,15.38mmol)的乙醇(20mL)溶液中加入溶解于水(20mL)中的氯化铵(4g,74.07mmol)和铁粉(6.88g,123mmol)。所得反应混合物 80℃加热 1 小时。结束时,向混合物加水,通过硅藻土过滤。滤液用乙酸乙酯萃取,合并的有机相用水和碳酸氢钠溶液洗涤,干燥,减压浓缩,得到所需的 3- 氨基 -2- 溴苯甲酸甲酯(3g,85%),其使用时无需进一步纯化。

[1730] 步骤 3 :合成 2- 溴 -3-(环戊基氨基) 苯甲酸甲酯

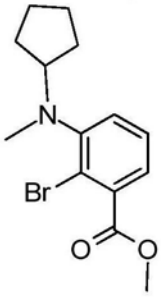
[1731]



[1732] 向搅拌后的3-氨基-2-溴苯甲酸甲酯(3g,13.0mmol)和环戊酮(5.4g,64.28mmol)的甲醇(20mL)溶液中加入醋酸(1.56g,26mmol),在室温下搅拌反应3小时。然后加入氰基硼氢化钠(2g,31.7mmol),搅拌反应过夜。结束时,减压除去溶剂,粗品经柱层析纯化得到2-溴-3-(环戊基氨基)苯甲酸甲酯(1.4g,36%)。

[1733] 步骤4:合成2-溴-3-(环戊基(甲基)氨基)苯甲酸甲酯

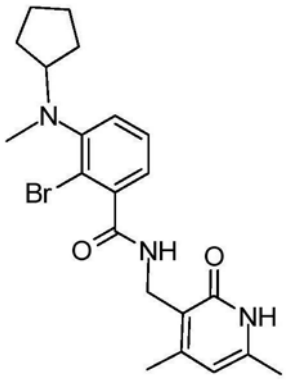
[1734]



[1735] 向搅拌后的2-溴-3-(环戊基氨基)苯甲酸甲酯(1.4g,4.69mmol)的乙腈(10mL)溶液中加入碳酸铯(3g,9.2mmol)和碘甲烷(3.38g,23.3mmol),产生的反应混合物在80℃加热12小时。结束时,将混合物冷却至室温后过滤,残余物用乙酸乙酯洗涤。将滤液浓缩后经柱层析纯化得到2-溴-3-(环戊基(甲基)氨基)苯甲酸甲酯(1.1g,75%)。

[1736] 步骤5:合成2-溴-3-(环戊基(甲基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)苯甲酰胺

[1737]



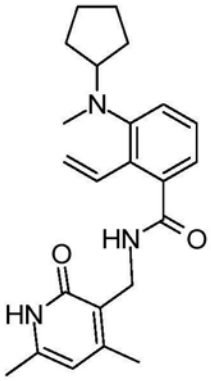
[1738] 将NaOH(0.064g,1.6mmol)水溶液加入到2-溴-3-(环戊基(甲基)氨基)苯甲酸甲酯(0.25g,0.801mmol)的MeOH(5mL)溶液中,在60℃搅拌1小时。反应结束后,减压除去甲醇,用稀盐酸酸化至pH值为6,再用柠檬酸酸化至pH值为4。用乙酸乙酯萃取。合并有机相经干燥,浓缩得到单独的酸(0.2g,84%)。

[1739] 将所得酸(0.2g,0.67mmol)溶解到DMSO(1.5mL)中,并向其中加入3-(氨基甲

基)-4,6- 二甲基吡啶 -2(1H)- 酮(0.204g,1.34mmol)。反应混合物在室温下搅拌 15 分钟后加入 PYBOP (0.516g,1.00mmol),继续搅拌过夜。反应结束后,将混合物加入到冰中以产生的固体,将该固体过滤,用乙腈洗涤。通过制备 HPLC 进行最终的纯化,得到 2- 溴 -3-(环戊基 (甲基) 氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基) 苯甲酰胺的三氟乙酸盐(0.02g,6.89%)。LCMS:432.10(M+1)+;HPLC%96.05(@254nm)(Rt;4.908);^{1}H NMR(DMSO-d_6,400MHz) δ 11.47(s,1H),8.21(t,1H),7.26-7.29(m,2H),6.94(d,1H,J=8Hz),5.86(s,1H),4.25(d,2H),3.59(m,1H),2.56(s,3H),2.19(s,3H),2.10(s,3H),1.61-1.67(m,4H),1.46(bs,4H)。

[1740] 实施例 41 :合成化合物 63 :3-(环戊基 (甲基) 氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 乙烯基苯甲酰胺

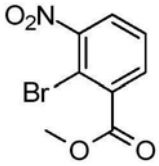
[1741]



化合物 63

[1742] 步骤 1 :合成 2- 溴 -3- 硝基苯甲酸甲酯

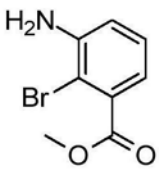
[1743]



[1744] 向搅拌后的 2- 溴 -3- 硝基苯甲酸(3g,12.19mmol) 的 DMF (30mL) 溶液中加入碳酸钠(5.16g,48.6mmol) 和碘甲烷(6.92g,48.7mmol)。将产生的反应混合物在 60℃加热 8 小时。结束时,将析出的固体过滤,残余物用乙酸乙酯洗涤(5 次)。合并有机相经干燥,减压浓缩得到所需粗品 2- 溴 -3- 硝基苯甲酸甲酯(4g,99%),其无需进一步纯化而使用

[1745] 步骤 2 :合成 3- 氨基 -2- 溴苯甲酸甲酯

[1746]

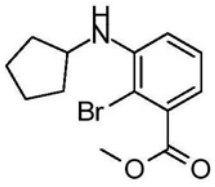


[1747] 在搅拌下,向搅拌后的上述粗品 2- 溴 -3- 硝基苯甲酸甲酯(4g,15.38mmol)的乙醇(20mL) 溶液中加入溶解在水(20mL) 中的氯化铵(4g,74.0mmol) 和铁粉(6.87g,123mmol)。将产生的反应混合物在 80℃加热 7 小时。结束时,反应混合物通过硅藻土过滤,同时用水

和乙酸乙酯洗涤，滤液用乙酸乙酯萃取。合并的有机相经干燥，减压浓缩得到所需粗产品（3g）。

[1748] 步骤 3 ：合成 2- 溴 -3-（环戊基氨基）苯甲酸甲酯

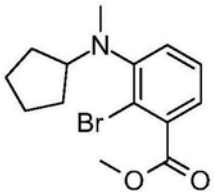
[1749]



[1750] 向搅拌后的 3- 氨基 -2- 溴苯甲酸甲酯（3g，13.01mmol）和环戊酮（5.6g，66mmol）的甲醇（30mL）溶液中加入醋酸（1.59g，26.6mmol），在室温下搅拌反应 3 小时。然后加入氰基硼氢化钠（2.08g，29.4mmol），混合物搅拌过夜。结束时，减压除去溶剂，粗品经柱层析纯化得到 2- 溴 -3-（环戊基氨基）苯甲酸甲酯（1.4g，36%）。

[1751] 步骤 4 ：合成 2- 溴 -3-（环戊基（甲基）氨基）苯甲酸甲酯

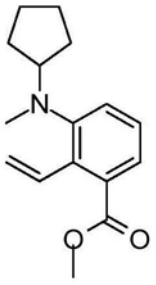
[1752]



[1753] 向搅拌后的 2- 溴 -3-（环戊基氨基）苯甲酸甲酯（1.4g，4.69mmol）的乙腈（20mL）溶液中加入碳酸铯（3.0g，9.2mmol）和碘甲烷（3.38g，23.4mmol），产生的反应混合物在 80℃加热 12 小时。结束时，将混合物冷却至室温后过滤，残余物用乙酸乙酯洗涤。将滤液浓缩，然后经柱层析纯化得到所需的 2- 溴 -3-（环戊基（甲基）氨基）苯甲酸甲酯（1.1g，75%）。

[1754] 步骤 5 ：合成 3-（环戊基（甲基）氨基）-2- 乙烯基苯甲酸甲酯

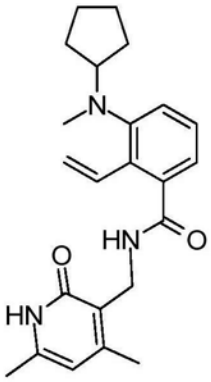
[1755]



[1756] 向搅拌后的2-溴-3-(环戊基(甲基)氨基)苯甲酸甲酯(1equiv.)和4,4,5,5-四甲基-2-乙烯基-1,3,2-二氧杂硼烷(1.2equiv.)的二氧六环/水混合物(5mL+1mL)的溶液中加入 Na_2CO_3(3.6equiv.)，向溶液中通入氩气 15 分钟。然后，加入 $Pd(PPh_3)_4$(0.1equiv.)，通入氩气 10 分钟。反应混合物 100℃加热 2 小时。结束时，反应混合物用水稀释，并用 10%MeOH/DCM 萃取。合并的有机相经 Na_2SO4 干燥，减压除去溶剂，得到粗品，该粗品经硅胶柱层析纯化得到所需的 3-（环戊基（甲基）氨基）-2- 乙烯基苯甲酸甲酯。

[1757] 步骤 6 ：合成 3-（环戊基（甲基）氨基）-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-2- 乙烯基苯甲酰胺

[1758]

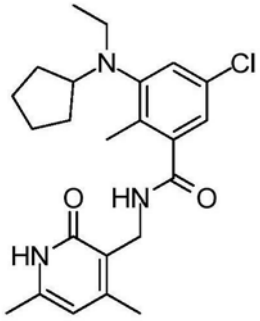


[1759] 向搅拌后的 3-(环戊基(甲基)氨基)-2-乙烯基苯甲酸甲酯(1equiv.)的乙醇(10mL)溶液中加入 NaOH(1.5equiv 溶解在 10mL 水中)水()溶液,在 60℃搅拌反应 4 小时。结束时,减压除去甲醇,残余物用 1N HCl 酸化至 pH 值为 6。将沉淀过滤,用水洗涤,干燥,得到纯净的相应的酸。

[1760] 向该单独的酸(1equiv.)的 DMSO(10mL)溶液中加入 PYBOP(1.5equiv.),在室温下搅拌反应 15 分钟。然后加入 3-(氨基甲基)-4,6-二甲基吡啶-2(1H)-酮(2equiv.),搅拌反应过夜。结束时,加水,将产生的固体过滤,用水洗涤。所得到的固体在乙腈溶液中搅拌 10 分钟,并再次过滤,以得到 3-(环戊基(甲基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-乙烯基苯甲酰胺,其经制备 HPLC 纯化得到三氟乙酸盐(0.045g,10.39%)。LCMS:380.25(M+1)+;HPLC%98.00(@254nm)(Rt;4.323);^{1}H NMR(DMSO-d_6,400MHz)δ11.51(s,1H),8.01(s,1H),7.25(bs,2H),6.81-6.88(m,2H),5.85(s,1H),5.49(d,1H,J=18Hz),5.40(bs,1H),4.34(3H merged in solvent peak),4.19(d,3H,J=4.8Hz),2.17(s,3H),2.10(s,3H),1.61(m,4H),1.47(bs,4H)。

[1761] 实施例 42:合成化合物 64:5-氯-3-(环戊基(乙基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺

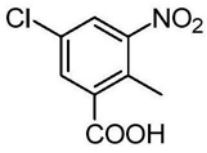
[1762]



化合物 64

[1763] 步骤 1:合成 5-氯-2-甲基-3-硝基苯甲酸

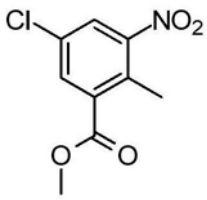
[1764]



[1765] 在 -10℃下，将 5- 氯 -2- 甲基苯甲酸（4g，23.39mmol）分多批加入到冷却的浓硫酸（27mL）中。10 分钟后，在 -10℃下，逐滴滴加硝化混合物［通过混合浓硝酸（3.3g，52.68mmol）与浓硫酸（4.4mL）来制备］。将产生的反应混合物在 -10℃搅拌 30 分钟。结束时，将反应混合物加到冰冷水中，将所产生的固体过滤，用水洗涤并真空干燥，得到所需的 5- 氯 -2- 甲基 -3- 硝基苯甲酸（4.95g，99%）。

[1766] 步骤 2：合成 5- 氯 -2- 甲基 -3- 硝基苯甲酸甲酯

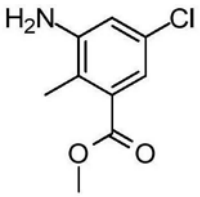
[1767]



[1768] 向搅拌后的 5- 氯 -2- 甲基 -3- 硝基苯甲酸（6.75g，31.25mmol）的 DMF（33mL）溶液中加入碳酸钠（13.23g，125.18mmol）和碘甲烷（17.77g，125.2mmol）。产生的反应混合物在 60℃加热 4 小时。结束时，加水，用 DCM 萃取。将合并的有机相干燥，减压浓缩，硅胶柱层析纯化（60-120 目），得到 5- 氯 -2- 甲基 -3- 硝基苯甲酸甲酯（6g，83.65%）。

[1769] 步骤 3：合成 3- 氨基 -5- 氯 -2- 甲基苯甲酸甲酯

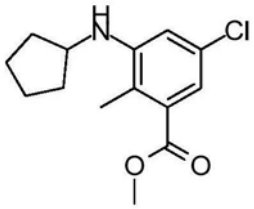
[1770]



[1771] 在搅拌下，向搅拌后的 5- 氯 -2- 甲基 -3- 硝基苯甲酸甲酯（6g，26.13mmol）的乙醇（60mL）溶液中加入溶解于水（60mL）中的氯化铵（6g，112.1mmol）和铁粉（11.88g，208.4mmol）。将产生的反应混合物在 80℃加热 1 小时。结束时，向混合物加水，通过硅藻土过滤。滤液用乙酸乙酯萃取，合并的有机相用水洗涤，干燥，减压浓缩，得到 3- 氨基 -5- 氯 -2- 甲基苯甲酸甲酯，其无需进一步纯化便可使用。

[1772] 步骤 4：合成 5- 氯 -3-（环戊基氨基）-2- 甲基苯甲酸甲酯

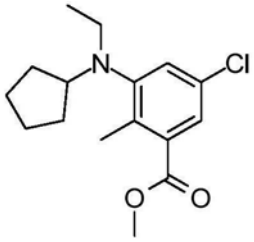
[1773]



[1774] 向搅拌后的 3- 氨基 -5- 氯 -2- 甲基苯甲酸甲酯（1g，5.02mmol）和环戊酮（2.1g，25mmol）的甲醇（10mL）溶液中加入醋酸（0.3g，5.02mmol），室温下搅拌反应 3 小时。然后加入氰基硼氢化钠（0.37g，5.90mmol），并搅拌反应过夜。结束时，减压除去溶剂，粗品经柱层析纯化得到 5- 氯 -3-（环戊基氨基）-2- 甲基苯甲酸甲酯（0.62g，46.2%）。

[1775] 步骤 5：合成 5- 氯 -3-（环戊基（乙基）氨基）-2- 甲基苯甲酸甲酯

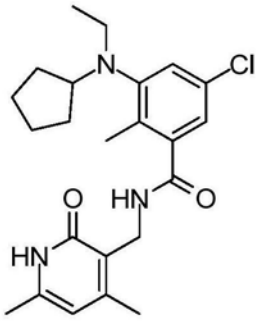
[1776]



[1777] 向搅拌后的 5- 氯 -3-(环戊基氨基)-2- 甲基苯甲酸甲酯(0.62g,2.32mmol)的无水 DMF (10mL) 溶液中加入碳酸铯(3.78g,11.6mmol) 和碘乙烷(5.43g,34.8mmol),所得反应物料在 80℃加热 18 小时。结束时,将反应混合物冷却至室温后过滤。残余物用乙酸乙酯洗涤,滤液经浓缩,柱层析纯化得到所需的 5- 氯 -3-(环戊基 (乙基) 氨基)-2- 甲基苯甲酸甲酯(0.101g,15%)。

[1778] 步骤 6 :合成 5- 氯 -3-(环戊基 (乙基) 氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基苯甲酰胺

[1779]

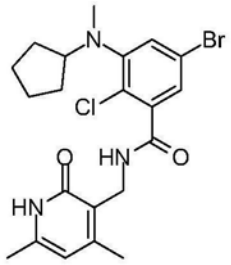


[1780] 将 NaOH (0.1g,2.5mmol) 水溶液加入到 5- 氯 -3-(环戊基 (乙基) 氨基)-2- 甲基苯甲酸甲酯(0.5g,1.69mmol) 的 EtOH (10mL) 溶液中并 60℃搅拌 1 小时。反应结束后,减压除去乙醇,用稀盐酸酸化至 pH 值为 6,再用柠檬酸酸化至 pH 值为 4。用乙酸乙酯施行萃取,将合并的有机相干燥,浓缩后得到单独的酸(0.41g,86%)。

[1781] 将所得酸(0.10g,0.355mmol) 溶解到 DMSO (1.5mL) 中,并向其中加入 3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮(0.104g,0.77mmol)。反应混合物在室温下搅拌 15 分钟后向其中加入 PYBOP(0.277g,0.533mmol),继续搅拌过夜。反应结束后,将混合物加入到冰中,将产生的固体过滤,用乙腈洗涤,再用额外的溶剂洗涤,以得到 5- 氯 -3-(环戊基 (乙基) 氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基苯甲酰胺(0.107g,72%)。LCMS:416.25(M+1)+;HPLC%91.83(@254nm)(Rt;5.021);^{1}H NMR(DMSO-d_6,400MHz) δ 11.45(s,1H),8.21(t,1H),7.19(s,1H),6.95(s,1H),5.85(s,1H),4.23(d,2H,J=4Hz),3.45(t,1H),2.94-2.96(m,2H),2.18(s,3H),2.15(s,3H),2.10(s,3H),1.58-1.64(m,4H),1.47(m,2H),1.32(m,2H),0.77(t,3H,J=6.8Hz)。

[1782] 实施例 43 :合成化合物 19 :5- 溴 -2- 氯 -3-(环戊基 (甲基) 氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基) 苯甲酰胺

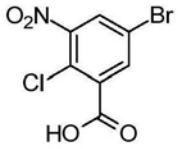
[1783]



化合物 19

[1784] 步骤 1 :合成 5- 溴 -2- 氯 -3- 硝基苯甲酸 :

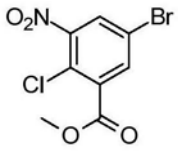
[1785]



[1786] 在 -10℃下,将 5- 溴 -2- 氯苯甲酸(5g,27.3mmol)分小批加入到冷却的浓硫酸(20mL)中。10 分钟后,在 -10℃下逐滴加入硝化混合物 { 通过混合浓硝酸(2.5mL)和浓硫酸(10mL)来制备 }。在 -10℃下搅拌反应混合物 30 分钟。结束时,将反应混合物加入到冰冷水中,通过过滤收集固体。所得固体用水洗涤,并在真空中干燥,得到 5- 溴 -2- 氯 -3- 硝基苯甲酸(3.6g,60.5%)。

[1787] 步骤 2 :合成 5- 溴 -2- 氯 -3- 硝基苯甲酸甲酯

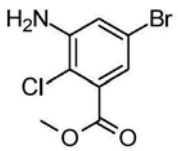
[1788]



[1789] 向搅拌后的 5- 溴 -2- 氯 -3- 硝基苯甲酸(3.6g,12.9mmol)的 DMF (40mL)溶液中加入碳酸钠(4.1g,38.6mmol)和碘甲烷(4ml,64.3mmol)。将反应混合物在 60℃加热 8 小时。结束时,向反应混合物加水,用乙酸乙酯萃取产品。合并的有机相用饱和碳酸氢钠溶液和 5N HCl 洗涤。将有机相干燥,减压浓缩得到 5- 溴 -2- 氯 -3- 硝基苯甲酸甲酯(3.4g,89.9%)。

[1790] 步骤 3 :合成 3- 氨基 -5- 溴 -2- 氯苯甲酸甲酯

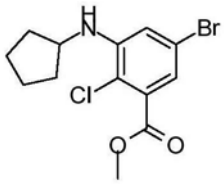
[1791]



[1792] 向搅拌后的 5- 溴 -2- 氯 -3- 硝基苯甲酸甲酯(3.4g,11.6mmol)的乙醇(19mL)溶液中加入溶解于水(30mL)中的氯化铵(3.4g,57.8mmol)和铁粉(5.16g,92.5mmol)。反应混合物在 80℃加热 1 小时。结束时,将反应混合物通过硅藻土过滤,用乙醇和乙酸乙酯洗涤。滤液用乙酸乙酯萃取,合并的有机相用水洗涤,干燥,减压浓缩,得到 3- 氨基 -5- 溴 -2- 氯苯甲酸甲酯(2.8g,92.1%)。

[1793] 步骤 4 :合成 5- 溴 -2- 氯 -3-(环戊基氨基) 苯甲酸甲酯

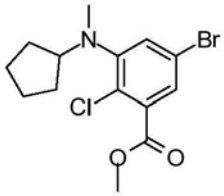
[1794]



[1795] 向搅拌后的 3- 氨基 -5- 溴 -2- 氯苯甲酸甲酯(2.8g,10.6mmol)和环戊酮(4.47g,53.2mmol)的甲醇(20mL)溶液中加入醋酸(1.3ml,21.2mmol),在室温下搅拌反应 3 小时。然后加入氰基硼氢化钠(1.7g,26.6mmol),搅拌反应过夜。结束时,减压除去溶剂,产品经柱层析纯化得到 5- 溴 -2- 氯 -3-(环戊基氨基)苯甲酸甲酯(0.5g,14.2%)。

[1796] 步骤 5 :合成 5- 溴 -2- 氯 -3-(环戊基(甲基)氨基)苯甲酸甲酯

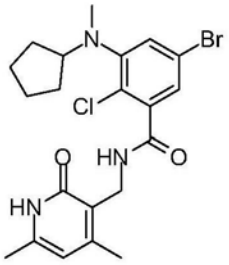
[1797]



[1798] 向搅拌后的 5- 溴 -2- 氯 -3-(环戊基氨基)苯甲酸甲酯(0.550g,1.65mmol)的乙腈(20mL)溶液中加入碳酸铯(1.08g,3.31mmol)和碘甲烷(1.17g,8.25mmol)。反应混合物在 80℃加热 12 小时。结束时,将反应混合物冷却至室温后过滤。残余物用乙酸乙酯洗涤,滤液浓缩后经柱层析纯化得到 5- 溴 -2- 氯 -3-(环戊基(甲基)氨基)苯甲酸甲酯(0.350g,61%)。

[1799] 步骤 6 :合成 5- 溴 -2- 氯 -3-(环戊基(甲基)氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)苯甲酰胺

[1800]



[1801] 将 NaOH (0.06g,1.52mmol)水溶液加入到 5- 溴 -2- 氯 -3-(环戊基(甲基)氨基)苯甲酸甲酯(0.350g,1.01mmol)的乙醇(4mL)和水(1mL)溶液中,并在 60℃搅拌 1 小时。反应结束后,减压除去乙醇,用稀盐酸酸化至 pH 值为 6,再用柠檬酸酸化至 pH 值为 4。用乙酸乙酯萃取产物。合并的有机相经干燥,浓缩得到所需的酸(0.266g,79.4%)。

[1802] 将所得酸(0.265g,0.80mmol)溶解到 DMSO (3mL),并向其中加入 3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮(0.243g,1.60mmol)。反应混合物在室温下搅拌 15 分钟后加入 PYBOP(0.624g,1.20mmol),继续搅拌过夜。反应结束后,将反应混合物加入到冰中以产生固体。将固体过滤并用乙腈洗涤后,经柱层析和制备 HPLC 纯化后得到 5- 溴 -2- 氯 -3-(环戊基(甲基)氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)苯甲酰胺(0.012g,3.22%)。

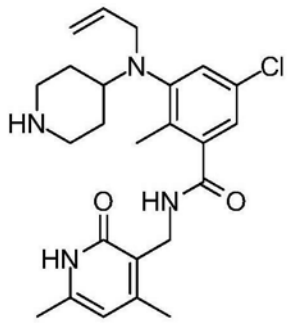
[1803] 分析数据:LCMS:466.05(M+1)+;HPLC:99.28%(@254nm)(Rt;6.917;方法:柱子:YMC ODS-A150mm x4.6mm x5μ;流动相A:0.05%TFA的水溶液/流动相B:0.05%TFA的乙腈溶液;进样量:10μL,柱温:30℃;流速:1.4mL/min.;梯度:0-8min5%B-95%B,保持1.5min,9.51-12min5%B);^{1}H NMR(CD_3OD,400MHz)δ7.42(d,1H,J=2Hz),7.24(d,1H,J=1.6Hz),6.16(s,1H),4.66(s,2H),3.71(m,1H),2.70(s,3H),2.37(s,3H),2.25(s,3H),1.79(m,2H),1.70(m,2H),1.56(m,4H)。

[1804] 实施例44:合成化合物91、92、97、98、102、104、105、117-123、126、127、137、144、157、191、192、205-209、212、213、222、243-245、268、269、273、276-279、282-287、290、301、302、306、308-311、313、315、319-322、328、332-336、339、340、344、347-349、356、386、387、389、390和392-417

[1805] 化合物91、92、97、98、102、104、105、117-123、126、127、137、144、157、191、192、205-209、212、213、222、243-245、268、269、273、276-279、282-287、290、301、302、306、308-311、313、315、319-322、328、332-336、339、340、344、347-349、356、386、387、389、390和392-417用下述方法合成。

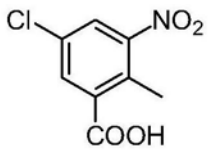
[1806] 化合物91:3-(烯丙基(哌啶-4-基)氨基)-5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺

[1807]



[1808] 步骤1:合成5-氯-2-甲基-3-硝基苯甲酸

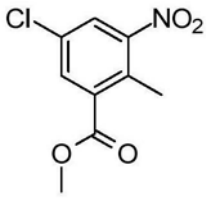
[1809]



[1810] 在-10℃下,将5-氯-2-甲基苯甲酸(4.0g,23mmol)分批加入冷却的浓硫酸(27mL)中。10分钟后,逐滴滴加硝化混合物{由浓硝酸(3.3g,52mmol)和浓硫酸(4.4mL)组成}。在-10℃下搅拌混合物30分钟后,加到冰冷水中。将固体沉淀过滤,用水洗涤,在真空中干燥,得到标题化合物(4.95g,99%)。

[1811] 步骤2:合成5-氯-2-甲基-3-硝基苯甲酸甲酯

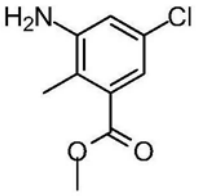
[1812]



[1813] 向搅拌后的 5- 氯 -2- 甲基 -3- 硝基苯甲酸(6.75g,31.3mmol)的 DMF (33mL)溶液中加入碳酸钠(13.23g,125mmol)和碘甲烷(17.77g,125mmol)。混合物在 60℃加热 4 小时。结束时,向反应物料中加水,用 DCM 施行萃取。将合并的有机相干燥,减压浓缩后经硅胶柱层析纯化得到标题化合物(6.0g,83%)。

[1814] 步骤 3 :合成 3- 氨基 -5- 氯 -2- 甲基苯甲酸甲酯

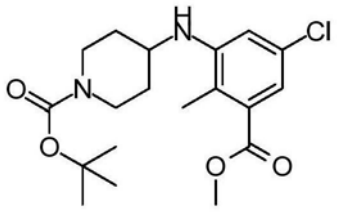
[1815]



[1816] 在搅拌下,向搅拌后的 5- 氯 -2- 甲基 -3- 硝基苯甲酸甲酯(6.0g,26mmol)的乙醇(60mL)溶液加入溶解于水(60mL)中的氯化铵(6.0g,110mmol)和铁粉(11.9g,208mmol)。混合物在 80℃加热 1 小时。结束时,加入水,通过硅藻土过滤反应混合物。滤液用乙酸乙酯萃取。合并的有机相用水洗涤,干燥,减压浓缩得到标题化合物,其无需进一步纯化即可使用。

[1817] 步骤 4 :合成 4-((5- 氯 -3-(甲氧基羰基)-2- 甲基苯基) 氨基) 哌啶 -1- 羧酸叔丁酯

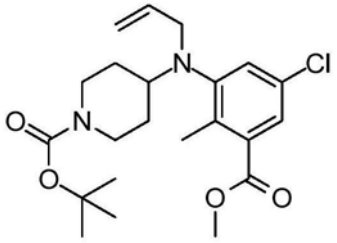
[1818]



[1819] 向搅拌后的 3- 氨基 -5- 氯 -2- 甲基苯甲酸甲酯(5.0g,25mmol)和 4- 氧代哌啶 -1- 羧酸叔丁酯(25.3g,127mmol)的甲醇(50mL)溶液中加入醋酸(1.5g,25mmol),在室温下搅拌反应 8 小时。然后在 0℃加入氰基硼氢化钠(1.89g,30.1mmol),在室温下搅拌反应过夜。结束时,减压除去溶剂,粗品柱层析纯化得到标题化合物(5.0g,52%)。

[1820] 步骤 5 :合成 4-(烯丙基 (5- 氯 -3-(甲氧基羰基)-2- 甲基苯基) 氨基) 哌啶 -1- 羧酸叔丁酯

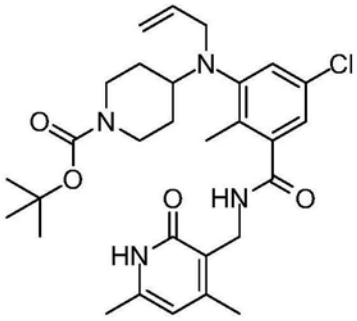
[1821]



[1822] 在 0℃下，向搅拌后的 4-((5- 氯 -3-(甲氧基羰基)-2- 甲基苯基) 氨基) 哌啶 -1- 羧酸叔丁酯 (0.70g,1.82mmol) 的 DMF (7mL) 溶液中加入 NaH(0.052g,2.19mmol)。搅拌 20 分钟后，加入 3- 溴丙 -1- 烯 (0.44g,3.64mmol)，混合物在 80℃加热 15h。结束时，用冰冷水淬灭反应，用 DCM 进行萃取。将合并的有机相干燥，减压浓缩，将残余物柱层析纯化得到标题化合物 (0.3g,39%)。

[1823] 步骤 6：合成 4-(烯丙基 (5- 氯 -3-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基) 氨基甲酰基)-2- 甲基苯基) 氨基) 哌啶 -1- 羧酸叔丁酯

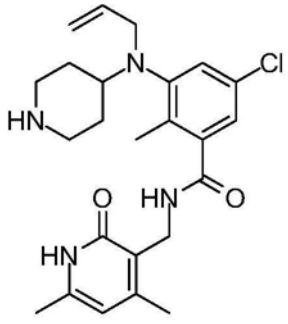
[1824]



[1825] 将 NaOH (0.113g,2.83mmol) 水溶液加入到 4-(烯丙基 (5- 氯 -3-(甲氧基羰基)-2- 甲基苯基) 氨基) 哌啶 -1- 羧酸叔丁酯 (0.60g,1.41mmol) 的乙醇 (15mL) 溶液中。在 60℃下搅拌 1 小时后减压除去乙醇，混合物用稀盐酸酸化至 pH 值为 6，再用柠檬酸酸化至 pH 值为 4。用 DCM 进行萃取。将合并的有机相干燥，浓缩得到单独的酸 (0.5g,86%)。然后将上述酸 (0.5g,1.22mmol) 溶解于 DMSO (5mL) 中，并向其中加入 3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮 (0.37g,2.44mmol)。反应混合物在室温下搅拌 15 分钟后加入 PYBOP (0.95g,1.83mmol)，继续搅拌过夜。将混合物加入到冰中，并用 10%MeOH/DCM 萃取。将合并的有机相干燥，浓缩后经柱层析纯化得到标题化合物 (0.2g,30%)。

[1826] 步骤 7：合成 3-(烯丙基 (哌啶 -4- 基) 氨基)-5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基苯甲酰胺

[1827]

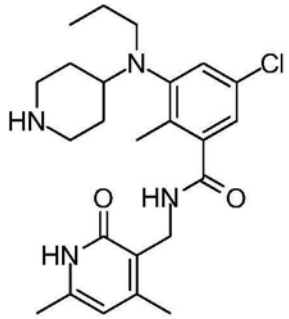


[1828] 将搅拌后的化合物 4-(烯丙基 (5- 氯 -3-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢

吡啶 -3- 基) 甲基) 氨基甲酰基)-2- 甲基苯基) 氨基) 哌啶 -1- 羧酸叔丁酯 (0.2g, 0.36mmol) 的 DCM (5mL) 冷却至 0℃, 并加入 TFA (0.5mL)。将混合物在室温下搅拌 18 小时后, 浓缩至干燥。将残余物用乙醚洗涤, 然后用制备 HPLC 纯化, 以得到标题化合物的三氟乙酸盐 (0.06g, 37%)。LCMS:443.25(M+1)+;HPLC:97.14%(@254nm)(Rt;5.074; 方法 : 色谱柱 :YMC ODS-A150mm x4.6mm x5μ ; 流动相 A:0.05%TFA 的水溶液 / 流动相 B:0.05%TFA 的乙腈溶液 ; 进样量 :10μL, 柱温 :30℃ ; 流速 :1.4mL/min.; 梯度 :0-8min5%B-95%B, 保持 1.5min, 9.51-12min5%B);^{1}H NMR(DMSO-d_6, 400MHz) δ 11.46(s, 1H), 8.38(bs, 1H), 8.21(t, 1H), 8.05(d, 1H), 7.21(d, 1H, J=4.4Hz), 6.97(d, 1H, J=1.6Hz), 5.86(s, 1H), 5.56-5.64(m, 1H), 4.97-5.09(m, 2H), 4.24(d, 2H, J=4.4Hz), 3.62(d, 2H, J=5.2Hz), 3.23(m, 2H), 3.10-3.16(m, 1H), 2.85-2.88(m, 2H), 2.19(s, 3H), 2.18(s, 3H), 2.10(s, 3H), 1.83-1.86(m, 2H), 1.68-1.73(m, 2H)。

[1829] 化合物 97 :5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基 -3-(哌啶 -4- 基 (丙基) 氨基) 苯甲酰胺

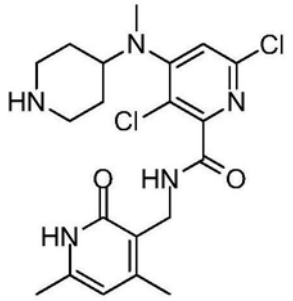
[1830]



[1831] 向搅拌后的 3-(烯丙基 (哌啶 -4- 基) 氨基)-5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基苯甲酰胺 (0.04g, 0.09mmol) 的 MeOH(3mL) 溶液中加入 10%Pd/C(0.01g), 并在氢气氛 (气球压力) 中、在室温下搅拌反应 2 小时。将混合物通过硅藻土过滤, 将滤液减压浓缩, 得到固体粗产物, 该粗产物经制备 HPLC 纯化得到标题化合物的三氟乙酸盐 (0.012g, 40%)。LCMS:445.25(M+1)$^+$;HPLC:95.52%(@254nm)(Rt;5.102; 方法 : 色谱柱 :YMC ODS-A150mm x4.6mm x5μ ; 流动相 :A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液 ; 进样量 :10μL, 柱温 :30℃ ; 流速 :1.4mL/min.; 梯度 :0-8min5%B-95%B, 保持 1.5min, 9.51-12min5%B);^{1}H NMR(DMSO-d_6, 400MHz) δ 11.46(s, 1H), 8.39(bs, 1H), 8.22(t, 1H), 8.03(bs, 1H), 7.25(s, 1H), 6.98(s, 1H), 5.86(s, 1H), 4.24(d, 2H, J=4.8Hz), 3.24-3.27(m, 2H), 3.00(m, 1H), 2.92(m, 2H), 2.83-2.86(m, 2H), 2.18(s, 3H), 2.17(s, 3H), 2.10(s, 3H), 1.79-1.82(m, 2H), 1.67-1.71(m, 2H), 1.18-1.23(m, 2H), 0.75(t, 3H, J=8Hz)。

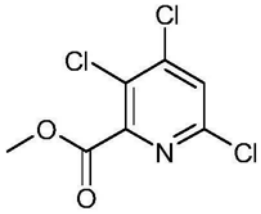
[1832] 化合物 144 :3,6- 二氯 -N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基]-4-[甲基 (哌啶 -4- 基) 氨基] 吡啶 -2- 甲酰胺

[1833]



[1834] 步骤 1 :合成 3,4,6- 三氯吡啶 -2- 羧酸甲酯

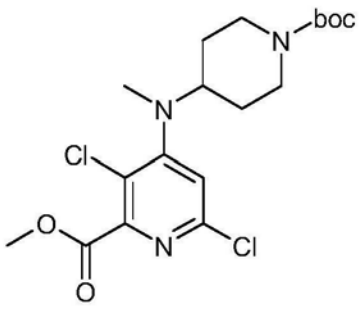
[1835]



[1836] 向搅拌后的 3,6- 二氯吡啶 -2- 羧酸甲酯(0.96g,4.66mmol)的 TFA (5mL)溶液中加入过氧化氢(30%w/w 水溶液,435μl,2.5mmol),反应混合物在 60℃加热 20 小时。然后将反应混合物冷却,并缓慢加到饱和 K_2CO_3(100mL)溶液中,随后用 EtOAc 萃取(2x200mL)水层,用盐水洗涤(2x50mL)合并的有机相,干燥(Na_2SO_4),蒸发。所需的 3,6- 二氯 -2-(甲氧羰基) 吡啶 -1-N- 氧化物(3,6-dichloro-2-(methoxycarbonyl)pyridin-1-ium-1-olate)的粗品未经任何进一步纯化而用于合成的下一步骤中。向 3,6- 二氯 -2-(甲氧羰基) 吡啶 -1-N- 氧化物(约 70% 纯度,2.40g,7.7mmol)中加入 $POCl_3$(3.5ml,38mmol),将溶液加热至 100℃ 4 小时。冷却后在真空中除去 $POCl_3$,以产生白色固体,将该白色固体通过硅胶 (洗脱液为 0%-10% 的 EtOAc 庚烷溶液) 进行层析,以得到的无色针状的标题化合物(340mg,两步 30%)。LC-MS100%,2.20 分钟 (3.5 分钟 LC-MS 法),m/z=239.8/241.7,^{1}H NMR(500MHz,$CDCl_3$) δ 7.51(1H,s),3.92(3H,s)。

[1837] 步骤 2 :合成 4-({1-[(叔丁氧) 羰基] 哌啶 -4- 基 }(甲基) 氨基)-3,6- 二氯吡啶 -2- 羧酸甲酯

[1838]

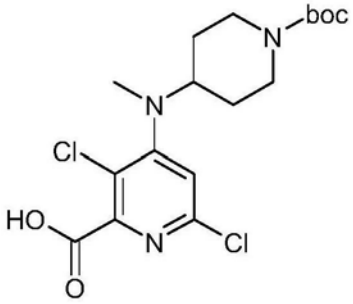


[1839] 向搅拌后的 3,4,6- 三氯吡啶 -2- 羧酸甲酯(310mg,1.29mmol)的 DMF (5mL)溶液中加入 TEA (359μl,2.58mmol),然后加入 4-(甲基氨基) 哌啶 -1- 羧酸叔丁酯(276mg,1.29mmol),反应混合物在 100℃加热 4 小时。然后将反应混合物冷却到室温,倒入水中(50mL),随后将产物萃取到 TBME (3x50mL)中,用盐水(50mL)洗涤合并的有机相,用 Na_2SO_4 干燥,蒸发。粗产品用 10g 硅胶 Isolute 柱(洗脱梯度为 0%-50% 的 EtOAc 庚烷溶液)纯化

得到白色固体状的标题化合物(95mg,18%)。LC-MS95%,2.29 分钟 (3.5 分钟 LC-MS 法),m/z=418.1/419.8,^{1}H NMR(500MHz,$CDCl_3$) δ 6.87(s,1H)4.12-4.34(m,2H)3.99(s,3H)3.69-3.80(m,1H)2.79(s,3H)2.64-2.77(m,2H)1.75(br.s.,4H)1.48(s,9H)。

[1840] 步骤 3:合成 4-({1-[(叔丁氧)羰基]哌啶-4-基}(甲基)氨基)-3,6-二氯吡啶-2-羧酸

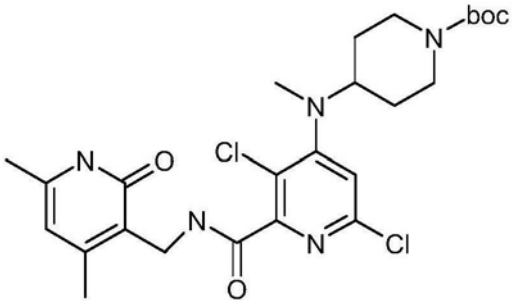
[1841]



[1842] 向搅拌后的 4-({1-[(叔丁氧)羰基]哌啶-4-基}(甲基)氨基)-3,6-二氯吡啶-2-羧酸甲酯(95mg,0.23mmol)的 THF(5mL)溶液中加入 2M NaOH 溶液(2.3ml,4.54mmol)水溶液,反应混合物在室温下搅拌 16 小时,该时间之后,在真空中除去 THF。水相用 10% 的柠檬酸水溶液酸化至 pH 值 5-6,然后用 EtOAc 萃取(3x50mL),合并的有机相用 Na_2SO_4 干燥,蒸发,得到白色粉末状的标题化合物(77mg,84%)。LC-MS100%,2.02 分钟 (3.5 分钟 LC-MS 法),m/z=403.9/405.6,^{1}H NMR(500MHz,Methanol-d4) δ 7.09(s,1H)4.14-4.22(m,2H)3.80-3.89(m,1H)2.84(s,5H)1.74-1.81(m,4H)1.46(s,9H)。

[1843] 步骤 4:合成 4-[(3,6-二氯-2-{[(4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基]氨基甲酰基}吡啶-4-基)(甲基)氨基]哌啶-1-羧酸叔丁酯

[1844]

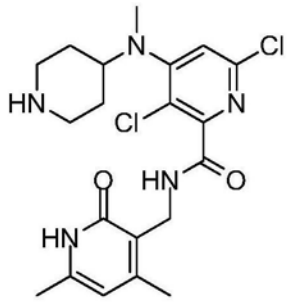


[1845] 将搅拌后的 4-({1-[(叔丁氧)羰基]哌啶-4-基}(甲基)氨基)-3,6-二氯吡啶-2-羧酸(75mg,0.19mmol)的 DMF (2mL)溶液冷却至 0℃后,向其加入 DIPEA (48μl,0.28mmol),然后再加入 PYBOP (116mg,0.22mmol)和 3-(氨基甲基)-4,6-二甲基-1,2-二氢吡啶-2-酮(89% 的纯度,35mg,0.2mmol)。然后将反应混合物室温下搅拌 16 小时,之后将该反应倒入水(30mL)中,用 EtOAc 萃取(3x50mL),之后用盐水(50mL)洗涤合并的有机相,干燥(Na_2SO_4)并蒸发。粗产物用 5g 硅胶 Isolute 柱(洗脱梯度 0%-100% 的 EtOAc 庚烷溶液)纯化,得到的白色固体的标题化合物,通过 NMR 检测其中包含～ 45%w/w 三吡咯烷氧化膦(tripyrrolidinophosphene oxide)-该化合物未经任何进一步纯化而用于合成的下一步骤中。LC-MS93%,1.97 分钟 (3.5 分钟 LC-MS 法),m/z=538.0/539.45/542.05,^{1}HNMR(500MHz,CDCl3) δ 10.03(br.s,1H),8.13-7.97(m,1H),6.79(s,1H),5.87(s

,1H),4.50(d,J=6.1Hz,2H),4.16(br.m,2H),3.78-3.62(m,1H),2.72(s,3H),2.65(br.m,2H),2.35(s,3H),2.22(s,3H),1.73-1.63(m,4H),1.44(s,9H)。

[1846] 步骤5:合成3,6-二氯-N-[(4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基]-4-[甲基(哌啶-4-基)氨基]吡啶-2-甲酰胺盐酸盐

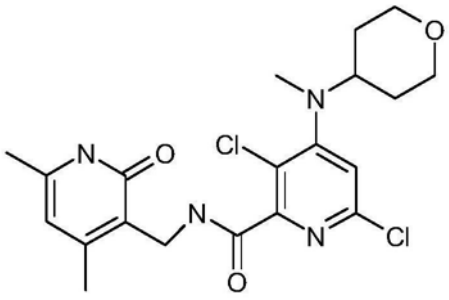
[1847]



[1848] 将4-[(3,6-二氯-2-{[(4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基]氨基甲酰基}吡啶-4-基)(甲基)氨基]哌啶-1-羧酸叔丁酯(310mg,1.29mmol)溶于4M盐酸的人氧六环溶液(3mL)中,在室温下搅拌16小时,然后蒸发除去溶剂,化合物通过制备HPLC纯化得到米黄色粉末状的标题化合物(13mg,14%)。LC-MS100%,2.41分钟(7分钟LC-MS法),m/z=438.1/439.8,^{1}H NMR(500MHz,Methanol-d4)δ7.12(s,1H),6.11(s,1H),4.46(s,2H),4.01-3.81(m,1H),3.45(d,J=12.9Hz,2H),3.12-2.97(m,2H),2.82(s,3H),2.35(s,3H),2.22(s,3H),2.13-1.93(m,4Hz)。

[1849] 化合物386:3,6-二氯-n-[(4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基]-4-[甲基(四氢吡喃-4-基)氨基]吡啶-2-甲酰胺

[1850]

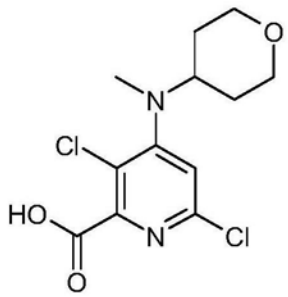


[1851] 步骤1:合成3,6-二氯-4-[甲基(四氢吡喃-4-基)氨基]吡啶-2-羧酸甲酯

[1852] 向搅拌后的3,4,6-三氯吡啶-2-羧酸甲酯(600mg,2.50mmol)的DMF(12mL)溶液中加入TEA(696μl,4.99mmol),随后加入N-甲基四氢吡喃-4-胺(287mg,2.50mmol),反应混合物在100℃加热20小时。然后将反应混合物冷却到室温并倒入水(100mL)中,然后将产物萃取至EtOAc(3x100mL)中,用盐水洗涤(50mL)合并的有机相,用Na_2SO_4干燥并蒸发。粗产物用10g硅胶Isolute柱(洗脱梯度为0%-60%EtOAc/庚烷溶液)纯化得到白色固体状的标题化合物(114mg,14%)。LC-MS100%,1.91分钟(3.5分钟LC-MS法),m/z=319.3/320.9,^{1}H NMR(500MHz,$CDCl_3$)δ6.87(s,1H),4.15-4.00(m,2H),3.98(s,3H),3.93-3.71(m,1H),3.54-3.24(m,2H),2.82(s,3H),1.94(dd,J=12.1,4.7Hz,2H),1.70(d,J=10.2Hz,2H)。(br.s.,4H)1.48(s,9H)。

[1853] 步骤2:合成3,6-二氯-4-[甲基(四氢吡喃-4-基)氨基]吡啶-2-羧酸

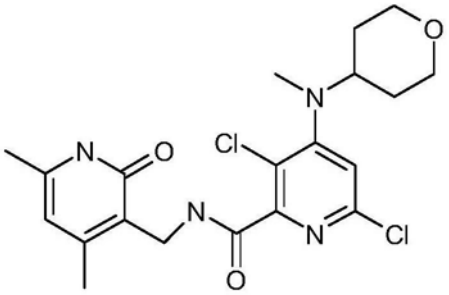
[1854]



[1855] 向搅拌后的 3,6- 二氯 -4-[甲基 (四氢吡喃 -4- 基) 氨基] 吡啶 -2- 羧酸甲酯 (114mg,0.36mmol) 的 THF (5mL) 溶液中加入 2M NaOH 水溶液 (0.89ml,1.79mmol) 中,将反应混合物在室温下搅拌 20 小时,然后在真空中除去 THF。然后用 10% 柠檬酸水溶液酸化水相至 pH 值为 5-6,然后用 EtOAc 萃取 (3x50mL),再用 1:1 的 IPA/$CHCl_3$ 溶液萃取 (2x50mL),然后用盐水 (50mL) 洗涤合并的有机相,用 Na_2SO_4 干燥并蒸发,以得到白色固体状的标题化合物 (85mg,78%)。LC-MS100%,1.47 分钟 (3.5 分钟 LC-MS 法),m/z=305.5/306.9,^1H NMR(500MHz,CD_3OD) δ 7.10(s,1H),4.03(dd,J=11.5,4.4Hz,2H),3.99-3.86(m,1H),3.47(t,J=11.0Hz,2H),2.90(s,3H),2.05-1.90(m,2H),1.74(d,J=12.4Hz,2H)。

[1856] 步骤 3 :合成 3,6- 二氯 -N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基]-4-[甲基 (四氢吡喃 -4- 基) 氨基] 吡啶 -2- 甲酰胺

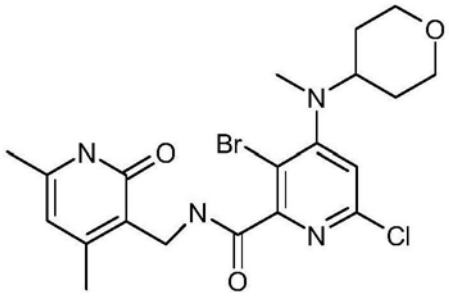
[1857]



[1858] 向搅拌后的 3,6- 二氯 -4-[甲基 (四氢吡喃 -4- 基) 氨基] 吡啶 -2- 羧酸 (85mg,0.28mmol) 的 DMF (2mL) 溶液中加入 DIPEA (73μl,0.42mmol) 和 HATU (127mg,0.33mmol)。在室温下搅拌反应 5 分钟后,加入 3-(氨基甲基)-4,6- 二甲基 -1,2- 二氢吡啶 -2- 酮 (89%,52mg,0.31mmol),在室温下搅拌反应 16 小时。然后将反应混合物倒入 50ml 水中,水相用 EtOAc 萃取 (3x50mL),用盐水洗涤 (50mL),干燥 (Na_2SO_4) 并蒸发以得到油状物。然后将所得产品用 5g 硅胶 Isolute 柱纯化 (洗脱液为 0%-5% 的 DCM/MeOH),蒸发,以得到玻璃状固体,将该固体与乙醚一起研磨,过滤,得到白色粉末状的标题化合物 (50mg,41%)。LC-MS95%,,m/z=439.0/440.8,^1H NMR(500MHz,$CDCl_3$) δ 11.33(br.s,1H),8.20(br.s,1H),6.79(s,1H),5.93(s,1H),4.51(s,2H),4.02(dd,J=11.4,3.8Hz,2H),3.92-3.72(m,1H),3.39(t,J=11.3Hz,2H),2.78(s,3H),2.38(s,3H),2.27(s,3H),1.89(tt,J=12.0,6.2Hz,2H),1.83-1.52(m,2H)。

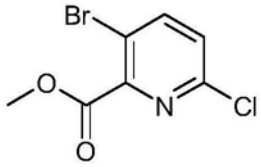
[1859] 化合物 387 :3- 溴 -6- 氯 -N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基]-4-[甲基 (四氢吡喃 -4- 基) 氨基] 吡啶 -2- 甲酰胺

[1860]



[1861] 步骤 1 :合成 3- 溴 -6- 氯吡啶 -2- 羧酸甲酯

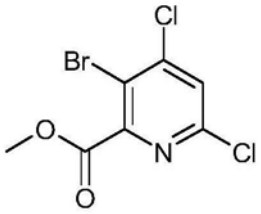
[1862]



[1863] 向搅拌后的 3- 溴 -6- 氯吡啶 -2- 羧酸(2.00g,8.46mmol)的 MeOH(40mL)溶液中加入 H_2SO_4(189μl,3.55mmol),将溶液加热回流 16 小时。将反应混合物冷却后在减压下除去甲醇,将得到的固体溶于 EtOAc (100mL),并用饱和 $NaHCO_3$ 溶液(2x50mL)洗涤,然后用盐水洗涤(50mL),干燥(Na_2SO_4),减压蒸发,以得到的灰白色固体状的标题化合物(1.97g,93%),其无需进一步纯化即可使用。LC-MS98%,m/z=249.8/251.7/253.7。

[1864] 步骤 2 :合成 3- 溴 -4,6- 二氯吡啶 -2- 羧酸甲酯

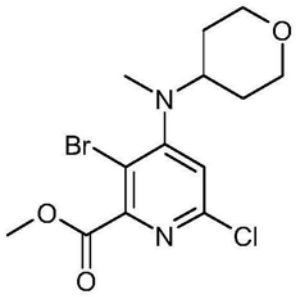
[1865]



[1866] 向搅拌后的 3- 溴 -6- 氯吡啶 -2- 羧酸甲酯(1.92g,7.67mmol)的 TFA (18mL)溶液中加入过氧化氢(30%w/w 水溶液,5.22ml,53.7mmol),反应混合物在 60℃加热 21 小时。然后将反应混合物冷却并慢慢加入饱和 K_2CO_3 溶液(100mL)中,然后用 EtOAc 萃取(3x100mL)水层,用盐水洗涤(2x50mL)合并的有机相,干燥(Na_2SO_4) 并蒸发。所需的 3- 溴 -6- 氯 -2-(甲氧羰基) 吡啶 -1-N- 氧化物(2.61g,～ 75% 纯度) 粗品没有进一步纯化,用于该合成的下一步。向 3- 溴 -6- 氯 -2-(甲氧羰基) 吡啶 -1-N- 氧化物粗品(约 75% 的纯度,2.61g,7.35mmol)中加入 $POCl_3$(3.42ml,36.7mmol),将溶液加热至 100℃ 4 小时。冷却后真空除去 $POCl_3$,得到白色固体,该固体经硅胶柱(用 0%-10% 的 EtOAc 的庚烷溶液洗脱)纯化,得到浅黄色粉末状的标题化合物(1.07g,两步 49%)。LC-MS99%,2.02 分钟 (3.5 分钟 LC-MS 法),m/z=283.7/285.7/287.7,^1H NMR(500MHz,$CDCl_3$) δ ppm7.56(s,1H),4.00(s,3H)。

[1867] 步骤 3 :合成 3- 溴 -6- 氯 -4-[甲基 (四氢吡喃 -4- 基) 氨基] 吡啶 -2- 羧酸甲酯

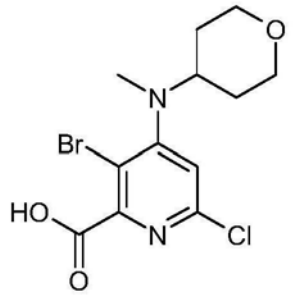
[1868]



[1869] 向搅拌后的 3- 溴 -4,6- 二氯吡啶 -2- 羧酸甲酯(600mg,2.1mmol)的 DMF (5mL)溶液中加入 TEA (587μl,4.21mmol),然后再加入 N- 甲基四氢吡喃 -4- 胺(240mg,2.1mmol),反应混合物在 80℃加热 20 小时。将反应混合物冷却到室温后,倒入水(100mL)中,然后将产物萃取至 EtOAc (3x100mL)中,用盐水(50mL)洗涤合并的有机相,用 Na_2SO_4 干燥并蒸发。然后将所得粗品用 10g 的硅胶 Isolute 柱(洗脱梯度为 0%-100% 的 EtOAc 的庚烷溶液)纯化,得到的白色固体状的标题化合物(110mg,14%)。LC-MS100%,1.94 分钟 (3.5 分钟 LC-MS 法),m/z=362.8/365.2/346.8,^{1}H NMR(250MHz,$CDCl_3$) δ 6.87(s,1H),4.17-3.99(m,2H),3.98(s,3H),3.93-3.70(m,1H),3.41(t,J=10.9Hz,2H),2.81(s,3H),1.93(dd,J=11.9,4.6Hz,2H),1.71(d,J=10.3Hz,2H)。

[1870] 步骤 4 :合成 3- 溴 -6- 氯 -4-[甲基 (四氢吡喃 -4- 基) 氨基] 吡啶 -2- 羧酸

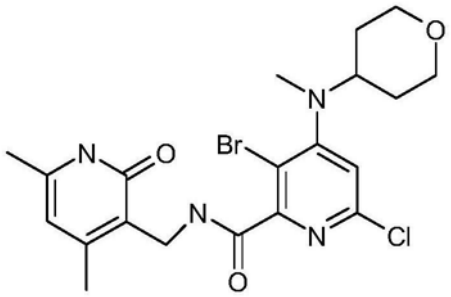
[1871]



[1872] 向搅拌后的 3- 溴 -6- 氯 -4-[甲基 (四氢吡喃 -4- 基) 氨基] 吡啶 -2- 羧酸甲酯(102mg,0.28mmol)的 THF (2mL)溶液中加入 2M NaOH (0.70ml,1.40mmol)水溶液,将反应混合物在室温下搅拌 18 小时后,之后在真空中蒸发除去 THF。水相用 10% 柠檬酸水溶液酸化至 pH 值为 5-6,然后先用 EtOAc 萃取(3x50mL),再用 1:1 的 IPA/$CHCl_3$ 溶液萃取(2x50mL),用盐水洗涤合并的有机相 (50mL),用 Na_2SO_4 干燥,蒸发,得到白色固体状的标题化合物(72mg,73%)。LC-MS100%,1.49 分钟 (3.5 分钟 LC-MS 法),m/z=349.0/351.0/352.9,^{1}H NMR(500MHz,Methanol-d_4) δ 7.07(s,1H),4.02(dd,J=11.3,4.3Hz,2H),3.96-3.87(m,1H),3.46(t,J=11.0Hz,2H),2.85(s,3H),1.96(dd,J=12.3,4.3Hz,2H),1.77(s,2H)。

[1873] 步骤 5 :合成 3- 溴 -6- 氯 -N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基]-4-[甲基 (四氢吡喃 -4- 基) 氨基] 吡啶 -2- 甲酰胺

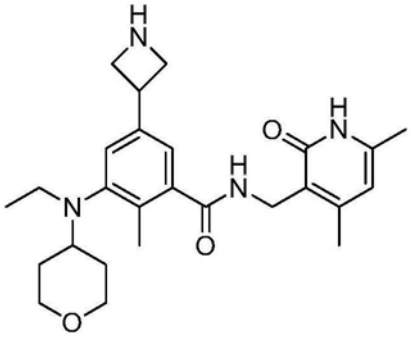
[1874]



[1875] 在0℃下,向搅拌后的3-溴-6-氯-4-[甲基(四氢吡喃-4-基)氨基]吡啶-2-羧酸(73mg,0.21mmol)的DMF(2mL)溶液中加入DIPEA(56μl,0.31mmol)和HATU(95mg,0.25mmol)。在0℃搅拌反应5分钟后,加入3-(氨基甲基)-4,6-二甲基-1,2-二氢吡啶-2-酮(89%,52mg,0.31mmol),在室温下搅拌反应16小时。然后将反应混合物倒入50ml水中,水相用EtOAc萃取(3x50mL),用盐水洗涤(50mL),干燥(Na_2SO_4)并蒸发,得到一个油状物。然后所得产物经5g硅胶柱(用0%-4%的MeOH/DCM洗脱)纯化,蒸发,得到玻璃状固体,将该固体与乙醚一起研磨并过滤,在真空干燥箱中在40℃下干燥24小时,得到白色粉状的标题化合物(50mg,41%)。LC-MS99%,m/z=483.1/485.0/486.9,^1H NMR(500MHz,$CDCl_3$)δ10.94(br.s,1H),8.14-7.98(m,1H),6.83(s,1H),5.92(s,1H),4.55(d,J=6.1Hz,2H),4.15-3.94(m,2H),3.93-3.70(m,1H),3.40(t,J=11.0Hz,2H),2.78(s,3H),2.39(s,3H),2.28(s,3H),1.99-1.82(m,2H),1.79-1.64(m,2H)。

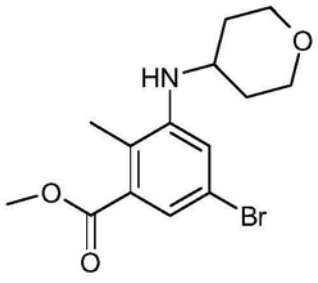
[1876] 化合物213:5-(氮杂环丁烷-3-基)-N-[(4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基]-3-[乙基(四氢吡喃-4-基)氨基]-2-甲基苯甲酰胺

[1877]



[1878] 步骤1:合成5-溴-2-甲基-3-[(四氢吡喃-4-基)氨基]苯甲酸甲酯

[1879]

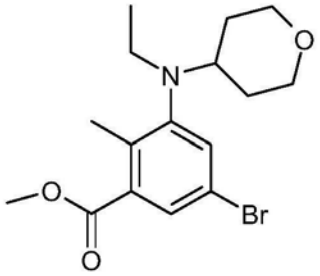


[1880] 在氮气保护下,向搅拌后的3-氨基-2-甲基-5-溴苯甲酸甲酯(4.06g,16.6mmol)的DCE(60mL)溶液中依次加入四氢吡喃酮(3.07ml,33.3mmol)和醋酸(5.71ml,99.8mmol),将反应搅拌5分钟后,加入三乙酰基硼氢化钠(10.6g,49.9mmol)。反应在室温下搅拌3

小时，之后加入蒸馏水（50mL），溶液用固体 $NaHCO_3$ 中和。两相分离，然后水相用 EtOAc（2x100mL）洗涤，合并的有机相用 Na_2SO_4 干燥，过滤并蒸发。残余物经硅胶 FCC（用 10%-40% 的 EtOAc 的庚烷溶液梯度洗脱）纯化，得到灰白色固体状的标题化合物（3.88g，71%）。LC-MS100%，2.10 分钟（3.5 分钟 LC-MS 法），m/z=327.9/329.8，^1H NMR（500MHz，$CDCl_3$）δ 7.23（d，J=1.9Hz，1H），6.84（d，J=1.7Hz，1H），4.02（dt，J=11.7，3.5Hz，2H），3.87（s，3H），3.65（d，J=7.2Hz，1H），3.59 - 3.45（m，3H），2.23（s，3H），2.05（d，J=13.8Hz，2H），1.51-（ddd，J=24.1，10.8，4.2Hz，2H）。

[1881] 步骤 2：合成 5- 溴 -3-[乙基（四氢吡喃 -4- 基）氨基]-2- 甲基苯甲酸甲酯

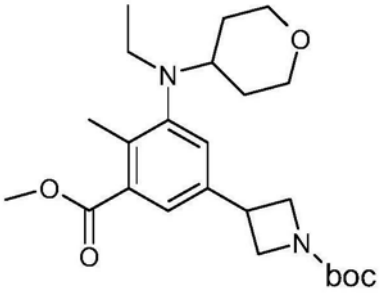
[1882]



[1883] 在氮气气氛下，向搅拌后的 5- 溴 -2- 甲基 -3-[（四氢吡喃 -4- 基）氨基] 苯甲酸甲酯（2.0g，6.1mmol）的 DCE（10mL）溶液中依次加入乙醛（1.0ml，18mmol）和醋酸（2.1ml，37mmol），反应搅拌 5 分钟后，加入三乙酰基硼氢化钠（6.6g，31mmol）。在室温下搅拌反应 16 小时，之后加入乙醛（1.0ml，22mmol）和三乙酰基硼氢化钠（3.0g，14mmol），再搅拌反应 6 小时，之后加入蒸馏水（100mL），并分离两相。水相用 EtOAc（3x100mL）洗涤，合并的有机相用 Na_2SO_4 干燥，过滤，蒸发，得到的无色油状的标题化合物（2.10g，93%），其无需进一步纯化即适合使用。LC-MS96%，2.38 分钟（3.5 分钟 LC-MS 法），m/z=356.1/357.9，^1H NMR（500MHz，$CDCl_3$）δ 7.70（d，J=2.0Hz，1H），7.36（d，J=2.0Hz，1H），3.95（d，J=11.3Hz，2H），3.88（d，J=9.1Hz，3H），3.32（td，J=11.5，2.5Hz，2H），3.04（q，J=7.1Hz，2H），2.98 - 2.87（m，1H），2.44（s，3H），1.77 - 1.55（m，4H），0.86（t，J=7.1Hz，3H）。

[1884] 步骤 3：合成 3-{3-[乙基（四氢吡喃 -4- 基）氨基]-5-（甲氧羰基）-4- 甲基苯基 } 氮杂环丁烷 -1- 羧酸叔丁酯

[1885]

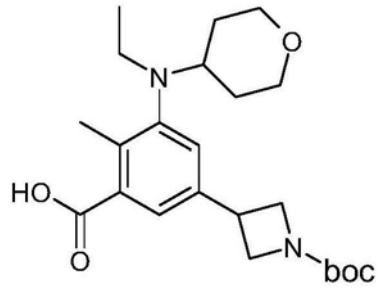


[1886] 向干燥的烧瓶中依次加入锌粉（40mg，0.61mmol）和无水 DMA（2mL），向该容器中通入氮气，同时剧烈搅拌并加热到 65℃。加入 TMS-Cl（9μl，0.07mmol）和 1,2- 二溴乙烷（6μl，0.07mmol），反应在 65℃搅拌 30 分钟，然后逐滴滴加 N-Boc-3- 碘代氮杂环丁烷（133mg，0.47mmol）的无水 DMA（1mL）溶液。将反应冷却至室温，向其加入 5- 溴 -3-[乙基（四氢吡喃 -4- 基）氨基]-2- 甲基苯甲酸甲酯（100mg，0.28mmol）的无水 DMA（2mL）溶液。

所得溶液用氮气进行脱气处理5分钟后，加入固体形式的Pd(dppf)Cl_2.DCM(7mg,0.01mmol)和碘化亚铜(3mg,0.02mmol)。将反应加热至80℃ 16小时，然后冷却到室温，之后加入饱和NH_4Cl溶液(50mL)。水相用EtOAc萃取(3x100mL)，合并的有机相用盐水洗涤(2x50mL)，用Na_2SO_4干燥，过滤并蒸发。残余物经5g Isolute柱(使用10-30%EtOAc的庚烷溶液作为洗脱液)纯化，得到无色油状的标题化合物(77mg,62%)。LC-MS98%,2.19分钟(3.5分钟LC-MS法),m/z=433.2,^{1}H NMR(500MHz,$CDCl_3$) δ 7.49(d,J=1.6Hz,1H),7.16(d,J=1.6Hz,1H),4.31(t,J=8.7Hz,2H),3.94(dd,J=14.4,5.5Hz,4H),3.89(s,3H),3.77－3.64(m,1H),3.31(td,J=11.4,2.7Hz,2H),3.06(q,J=7.0Hz,2H),2.99－2.87(m,1H),2.46(s,3H),1.65(ddd,J=11.1,8.6,6.0Hz,4H),1.46(s,9H),0.85(dd,J=13.1,6.1Hz,3H)。

[1887] 步骤4：合成5-{1-[(叔丁氧)羰基]氮杂环丁烷-3-基}-3-[乙基(四氢吡喃-4-基)氨基]-2-甲基苯甲酸

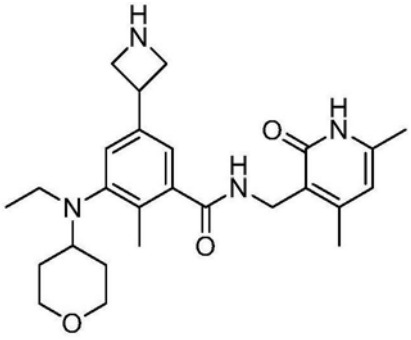
[1888]



[1889] 向搅拌后的3-{3-[乙基(四氢吡喃-4-基)氨基]-5-(甲氧羰基)-4-甲基苯基}氮杂环丁烷-1-羧酸叔丁酯(78mg,0.18mmol)的THF(2mL)和MeOH(0.1mL)溶液中加入2M NaOH溶液(0.9ml,1.8mmol)，在室温下搅拌反应16小时，随后在50℃加热22小时。将反应冷却至室温，真空除去溶剂，之后水溶液用1M HCl调至pH值为5。将产物萃取到DCM中(2x50mL)，用Na_2SO_4干燥，过滤，得到的无色油状的标题化合物(54mg,72%)。LC-MS100%,1.70分钟(3.5分钟LC-MS法),m/z=419.2,^{1}H NMR(500MHz,MeOD) δ 7.77(s,1H),7.55(s,1H),4.36(t,J=8.2Hz,2H),3.90(d,J=27.0Hz,5H),3.71(t,J=6.5Hz,1H),3.36(t,J=11.3Hz,3H),2.55(s,3H),1.92－1.81(m,1H),1.64(d,J=55.8Hz,3H),1.49－1.42(m,10H),0.93(s,3H)。

[1890] 步骤5：合成5-(氮杂环丁烷-3-基)-N-[(4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基]-3-[乙基(四氢吡喃-4-基)氨基]-2-甲基苯甲酰胺

[1891]

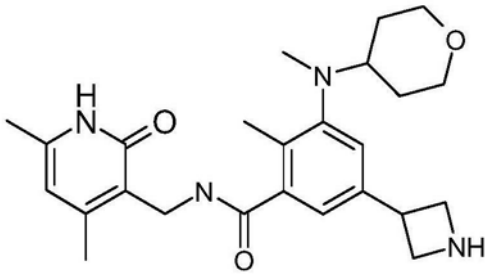


[1892] 将搅拌后的5-{1-[(叔丁氧)羰基]氮杂环丁烷-3-基}-3-[乙基(四氢吡

喃 -4- 基）氨基]-2- 甲基苯甲酸（54mg，0.13mmol）的 DMF（2mL）溶液用冰浴冷却，然后加入 DIPEA（45μl，0.26mmol）和 HATU（59mg，0.15mmol）。反应在 0℃搅拌 5 分钟后，加入 3-（氨基甲基）-4,6- 二甲基 -1,2- 二氢吡啶 -2- 酮（89%，24mg，0.14mmol），在室温下搅拌 16 小时。然后将反应混合物倒入 50ml 水中，水相用 EtOAc（3x50mL）萃取，用盐水（50mL）洗涤，干燥（Na_2SO_4），过滤，蒸发，得到油状物。所得产物再用 5g 硅胶 Isolute 柱（用 0%-2.5% 的 MeOH/DCM 洗脱）纯化，蒸发，得到无色油状的 3-(3-{[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基] 氨基甲酰基 }-5-[乙基（四氢吡喃 -4- 基）氨基]-4- 甲基苯基）氮杂环丁烷 -1- 羧酸叔丁酯（29mg）。LC-MS90%，m/z=553.3。将该原料溶解于 4M HCl 的二氧六环（3mL）溶液中，并在室温下搅拌 90 分钟，之后将溶剂蒸干，化合物通过制备 HPLC 纯化，得到白色固体状的标题化合物（11mg，两步 8%）。LC-MS97%，2.17 分钟（7 分钟 LC-MS 法），m/z=453.2，^{1}H NMR(500MHz，MeOD) δ 7.26(s,1H)，7.18(s,1H)，6.14(s,1H)，4.48(s,2H)，4.39(s,2H)，4.22(s,3H)，3.93(d,J=10.5Hz,2H)，3.40 - 3.33(m,2H)，3.29 - 2.90(m,3H)，2.40(s,3H)，2.31(s,3H)，2.26(s,3H)，1.68(d,J=26.3Hz,4H)，0.87(s,3H)。

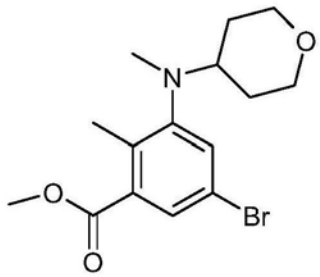
[1893] 化合物 245：5-（氮杂环丁烷 -3- 基）-N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基]-2- 甲基 -3-[甲基（四氢吡喃 -4- 基）氨基] 苯甲酰胺

[1894]



[1895] 步骤 1：合成 5- 溴 -2- 甲基 -3-[甲基（四氢吡喃 -4- 基）氨基] 苯甲酸甲酯

[1896]

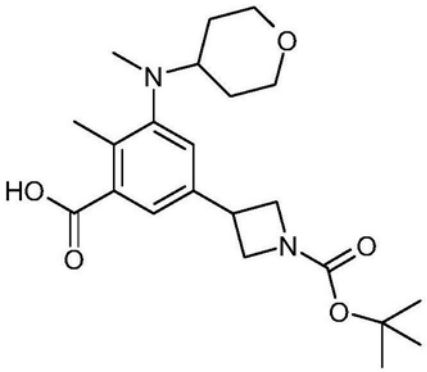


[1897] 在氮气气氛下，向搅拌后的 5- 溴 -2- 甲基 -3-[（四氢吡喃 -4- 基）氨基] 苯甲酸甲酯（1.20g，3.66mmol）的 DCE（10mL）溶液中依次加入多聚甲醛（659mg，21.9mmol）和醋酸（1.26ml，21.9mmol），将反应搅拌 5 分钟后，向其中加入三乙酰基硼氢化钠（4.65g，21.9mmol）。室温下搅拌反应 16 小时，然后加入额外的多聚甲醛（325mg，10.8mmol）和三乙酰基硼氢化钠（2.40g，11.3mmol），继续搅拌 18 小时，届时向其中加入蒸馏水（30mL），加入固体 $NaHCO_3$ 直到水相 pH 值为 7，分离两相，水相用 EtOAc（3x50mL）洗涤，然后合并的有机相用盐水（50mL）洗涤，用 Na_2SO_4 干燥，过滤并蒸发。粗制的残余物经硅胶 FCC（用 0-10%EtOAc 的庚烷溶液洗脱）纯化，得到的无色油状的标题化合物（728mg，52%）。LC-MS87%，m/z=341.9/343.9，^{1}H NMR(500MHz，$CDCl_3$) δ 7.60(d,J=2.0Hz,1H)，7.25(d,J

=1.9Hz,1H),3.92(d,J=11.1Hz,2H),3.82(s,3H),3.27(td,J=11.5,2.0Hz,2H),2.94-2.79(m,1H),2.57(s,3H),2.36(s,3H),1.74-1.52(m,4H)。

[1898] 步骤2:合成5-{1-[(叔丁氧)羰基]氮杂环丁烷-3-基}-2-甲基-3-[甲基(四氢吡喃-4-基)氨基]苯甲酸

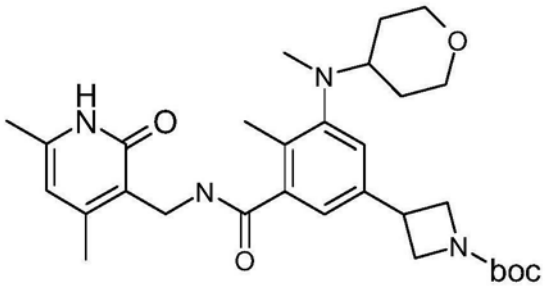
[1899]



[1900] 向干燥的烧瓶中加入锌粉(436mg,6.67mmol),并用热枪将该烧瓶加热几分钟。然后在氮气保护下,将无水DMA(20mL)加入到上述烧瓶中,同时剧烈搅拌并加热到65℃。向其中加入TMS-Cl(102μl,0.8mmol)和1,2-二溴乙烷(70μl,0.8mmol),反应在65℃搅拌30分钟后,随后逐滴滴加N-Boc-3-碘代氮杂环丁烷(1.46g,5.16mmol)的无水DMA(15mL)溶液。然后将反应冷却至室温,添加5-溴-2-甲基-3-[甲基(四氢吡喃-4-基)氨基]苯甲酸甲酯(1.06g,3.09mmol)的无水DMA(15mL)溶液。所得溶液用氮气进行10分钟脱气处理,之后添加固体形式的Pd(dppf)Cl_2.DCM(76mg,0.09mmol)和碘化亚酮(35mg,0.19mmol)。将反应加热至80℃ 90分钟,然后冷却到室温,随后加入蒸馏水(100mL)和饱和NH_4Cl溶液(10mL)。水相用TBME(3x50mL)萃取,然后合并的有机相用Na_2SO_4干燥,过滤,蒸发。残余物经25g Isolute柱(使用0%-40%的EtOAc的庚烷溶液作为洗脱液)纯化,得到浅棕色油状的标题化合物(507mg)。LC-MS97%,m/z=420.0. 向搅拌后的3-[3-(甲氧羰基)-4-甲基-5-[甲基(四氢吡喃-4-基)氨基]苯基]氮杂环丁烷-1-羧酸叔丁酯(85mg,0.2mmol)的THF(2mL)和MeOH(0.1mL)溶液中加入2M NaOH溶液(1.02ml,2.03mmol),在50℃搅拌反应16小时,然后再添加4MNaOH溶液(0.5ml,2,0mmol),再加热反应24小时。将反应冷却至室温,真空除去溶剂,然后用1M HCl将水溶液调至pH值为3。将产物萃取到DCM(2x50mL)中,用盐水(20mL)洗涤,用Na_2SO_4干燥并过滤,得到灰白色固体状的标题化合物(47mg,两步21%)。LC-MS95%,m/z=405.1,^1H NMR(500MHz,$CDCl_3$)δ7.66(t,J=7.0Hz,1H),7.19(d,J=1.3Hz,1H),4.34(t,J=8.7Hz,2H),3.98(dd,J=16.6,10.2Hz,4H),3.79-3.69(m,2H),3.35(dd,J=11.5,10.0Hz,2H),2.97(td,J=10.8,5.3Hz,1H),2.67(s,3H),2.55(d,J=6.6Hz,3H),1.74(ddd,J=15.5,12.1,4.3Hz,2H),1.66(d,J=11.1Hz,2H),1.48(s,9H)。

[1901] 步骤3:合成3-(3-{[(4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基]氨基甲酰基}-4-甲基-5-[甲基(四氢吡喃-4-基)氨基]苯基)氮杂环丁烷-1-羧酸叔丁酯

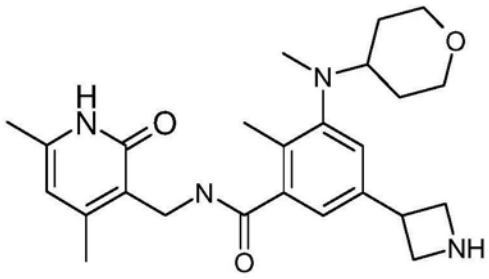
[1902]



[1903] 在 0℃下，向搅拌后的 5-{1-[(叔丁氧)羰基]氮杂环丁烷-3-基}-2-甲基-3-[甲基(四氢吡喃-4-基)氨基]苯甲酸(47mg,0.12mmol)的 DMF (2mL)溶液中加入 DIPEA (40μl,0.23mmol)和 HATU (53mg,0.14mmol)。在 0℃搅拌反应 5 分钟后，向其加入 3-(氨基甲基)-4,6-二甲基-1,2-二氢吡啶-2-酮(89%,22mg,0.13mmol)，在室温下搅拌 16 小时。然后将反应混合物倒入蒸馏水(50mL)中，水相用 DCM (3x50mL)萃取，用盐水(50mL)洗涤，干燥(Na_2SO_4)，过滤，蒸发，得到油状物。然后产物用 5g 硅胶 Isolute 柱(用 0%-5%MeOH/DCM 洗脱)纯化，蒸发，得到无色油状的标题化合物(44mg,67%)。LC-MS96%,m/z=539.4,^{1}H NMR(500MHz,$CDCl_3$) δ 11.68(s,1H),6.95(t,J=5.8Hz,1H),6.92(d,J=4.2Hz,2H),5.88(s,1H),4.47(d,J=5.8Hz,2H),4.20(t,J=8.7Hz,2H),3.90(d,J=11.2Hz,2H),3.86 - 3.73(m,2H),3.62 - 3.50(m,1H),3.26(t,J=10.8Hz,2H),2.89(ddd,J=14.6,10.8,3.7Hz,1H),2.55(s,3H),2.33(s,3H),2.20(s,3H),2.14(s,3H),1.75 - 1.47(m,4H),1.39(d,J=5.7Hz,9H)。

[1904] 步骤 4:合成 5-(氮杂环丁烷-3-基)-N-[(4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基]-2-甲基-3-[甲基(四氢吡喃-4-基)氨基]苯甲酰胺

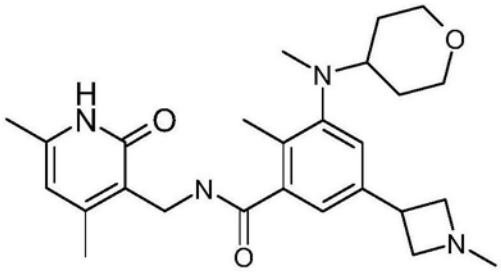
[1905]



[1906] 向搅拌后的 3-(3-{[(4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基]氨基甲酰基}-4-甲基-5-[甲基(四氢吡喃-4-基)氨基]苯基)氮杂环丁烷-1-羧酸叔丁酯(29mg,1.29mmol)的 DCM (4mL)溶液中加入 TFA (1mL)，所得溶液在室温下搅拌 90 分钟，然后蒸发脱去溶剂，添加饱和 $NaHCO_3$ 水溶液至 pH 值为 7-8。水相用 1:1 的 IPA:$CHCl_3$ 混合物(2x50mL)萃取，合并的有机相用盐水(30mL)洗涤，用 Na_2SO_4 干燥，过滤并蒸发。残余物通过制备 HPLC 纯化，得到白色固体状的标题化合物(15mg,42%)。LC-MS100%,m/z=439.3,^{1}H NMR(500MHz,MeOD) δ 7.19(d,J=1.4Hz,1H),7.10(d,J=1.5Hz,1H),6.12(s,1H),4.46(s,2H),4.41 - 4.27(m,2H),4.26 - 4.13(m,3H),3.93(d,J=11.4Hz,2H),3.36(td,J=11.3,3.3Hz,2H),3.06(dq,J=14.6,5.0Hz,1H),2.65(s,3H),2.39(s,3H),2.26(s,3H),2.24(s,3H),1.75 - 1.60(m,4H)。

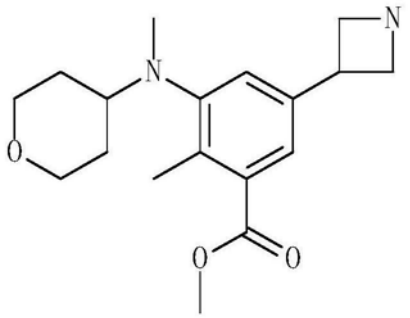
[1907] 化合物 269:N-[(4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基]-2-甲基-3-[甲基(四氢吡喃-4-基)氨基]-5-(1-甲基氮杂环丁烷-3-基)苯甲酰胺

[1908]



[1909] 步骤 1 :合成 5-(氮杂环丁烷 -3- 基)-2- 甲基 -3-[甲基 (四氢吡喃 -4- 基) 氨基] 苯甲酸甲酯

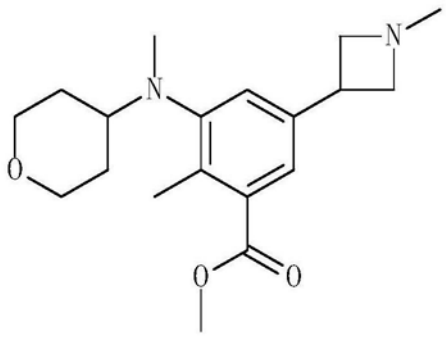
[1910]



[1911] 向搅拌后的 3-[3-(甲氧羰基)-4- 甲基 -5-[甲基 (四氢吡喃 -4- 基) 氨基] 苯基] 氮杂环丁烷 -1- 羧酸叔丁酯 (400mg,0.96mmol) 的 DCM (4mL) 溶液中加入 TFA (1mL),溶液在室温下搅拌 45 分钟,之后将溶剂蒸干,添加饱和 $NaHCO_3$ 水溶液至 pH 值为 7-8。水相用 DCM(3x30mL) 萃取,用盐水 (30mL) 洗涤,用 $MgSO_4$ 干燥,过滤,蒸发,得到橙色油状的标题化合物 (370mg,95%)。LC-MS96%,m/z=319.1,^1H NMR(500MHz,$CDCl_3$) δ 7.49(d,J=1.4Hz,1H),7.20(d,J=1.3Hz,1H),4.32 - 4.10(m,5H),3.98(d,J=11.0Hz,2H),3.90(d,J=8.4Hz,3H),3.34(t,J=10.8Hz,2H),2.99(ddd,J=14.7,10.9,3.8Hz,1H),2.65(d,J=8.3Hz,3H),2.51 - 2.41(m,3H),1.73(ddd,J=15.7,12.1,4.3Hz,2H),1.64(d,J=11.2Hz,2H)。

[1912] 步骤 2 :合成 2- 甲基 -3-[甲基 (四氢吡喃 -4- 基) 氨基]-5-(1- 甲基氮杂环丁烷 -3- 基) 苯甲酸甲酯

[1913]

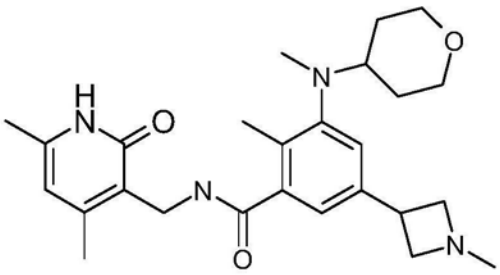


[1914] 在氮气气氛下,向搅拌后的 5-(氮杂环丁烷 -3- 基)-2- 甲基 -3-[甲基 (四氢吡喃 -4- 基) 氨基] 苯甲酸甲酯 (320mg,1.01mmol) 的 DCE (10mL) 溶液中依次加入多聚甲醛 (151mg,5.03mmol) 和醋酸 (0.115ml,2.01mmol),搅拌反应 5 分钟后,加入三乙酰基硼氢化钠 (852mg,4.02mmol)。在室温下搅拌反应 16 小时后,向反应混合物加入额外的多聚

甲醛(21mg)和三乙酰基硼氢化钠(98mg),继续搅拌反应 4 小时,届时添加蒸馏水(20mL),添加固体 $NaHCO_3$ 直到水相 pH 值为 7。两相分离,水相用 DCM (3x20mL)洗涤,合并的有机相用盐水(50mL)洗涤,用 $MgSO_4$ 干燥,过滤,蒸发,得到油状的标题化合物(296mg,89%)。LC-MS100%,m/z=333.1,^1H NMR(500MHz,$CDCl_3$) δ 7.42(d,J=1.4Hz,1H),7.09(s,1H),3.96(d,J=11.2Hz,2H),3.92 - 3.82(m,5H),3.74(d,J=7.2Hz,1H),3.30(dt,J=22.2,15.0Hz,4H),3.00 - 2.89(m,1H),2.62(s,3H),2.49 - 2.39(m,6H),1.75 - 1.59(m,4H)。

[1915] 步骤 3 :合成 N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基]-2- 甲基 -3-[甲基(四氢吡喃 -4- 基)氨基]-5-(1- 甲基氮杂环丁烷 -3- 基)苯甲酰胺

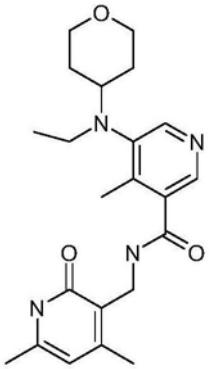
[1916]



[1917] 向搅拌后的 2- 甲基 -3-[甲基(四氢吡喃 -4- 基)氨基]-5-(1- 甲基氮杂环丁烷 -3- 基)苯甲酸甲酯(296mg,0.89mmol)的 THF(10mL)和 MeOH(1mL)溶液中加入 2M NaOH 溶液(4.5ml,8.9mmol),在 50℃搅拌反应 16 小时,之后加入 4M NaOH 溶液(1ml,4.5mmol),反应继续加热 24 小时。将反应冷却至室温,产物用 1M HCl 中和,蒸干,然后通过与甲苯共沸除掉残留的水。所得粗品酸用于下一阶段,而不进行任何纯化。将 2- 甲基 -3-[甲基(四氢吡喃 -4- 基)氨基]-5-(1- 甲基氮杂环丁烷 -3- 基)苯甲酸的粗品悬浮于 DMF (10mL)中,用冰浴冷却溶液,然后向该溶液中加入 DIPEA (433μl,2.49mmol)和 HATU (567mg,1.49mmol)。在 0℃搅拌该反应 5 分钟后,向其加入 3-(氨基甲基)-4,6- 二甲基 -1,2- 二氢吡啶 -2- 酮(89%,221mg,1.29mmol),在室温下搅拌反应 16 小时。然后将反应混合物倒入蒸馏水中(50mL),水相用 DCM (3x50mL)萃取,用盐水(50mL)洗涤,干燥(Na_2SO_4),过滤,蒸发,得到油状物。所得产物再经制备 HPLC 法纯化,蒸干,在乙醚中研磨,过滤,得到的灰白色固体状的标题化合物(51mg,10%)。LC-MS91%,m/z=453.2,^1H NMR(500MHz,MeOD) δ 7.14(d,J=1.7Hz,1H),7.09(d,J=1.7Hz,1H),6.12(s,1H),4.46(s,2H),4.41(t,J=9.2Hz,2H),4.22(t,J=9.3Hz,2H),4.14(dd,J=17.4,8.5Hz,1H),3.98 - 3.89(m,2H),3.36(td,J=11.3,3.4Hz,2H),3.06(ddd,J=14.6,9.8,4.9Hz,1H),2.97(s,3H),2.64(s,3H),2.39(s,3H),2.26(s,3H),2.24(s,3H),1.73 - 1.62(m,4H)。

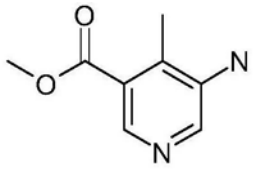
[1918] 化合物 389 :N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基]-5-[乙基(四氢吡喃 -4- 基)氨基]-4- 甲基吡啶 -3- 甲酰胺

[1919]



[1920] 步骤 1 :合成 5- 氨基 -4- 甲基吡啶 -3- 羧酸甲酯

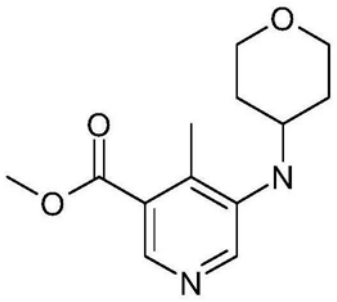
[1921]



[1922] 在 0℃下,向搅拌后的 5- 氨基 -4- 甲基吡啶 -3- 羧酸(0.94g,6.18mmol)的 MeOH(20mL)溶液中逐滴添加二氯亚砜。然后将溶液加热至 50℃ 3.5 小时,再加 10ml MeOH,在 50℃加热反应 5 小时,随后在室温下搅拌 64 小时。然后减压蒸发溶剂,加入饱和 $NaHCO_3$ 溶液直到为 pH 值为 7-8。将产物萃取到 EtOAc (2x50mL)中,合并的有机相用盐水洗涤(50mL),用 Na_2SO_4 干燥,过滤并蒸发,得到灰白色粉末状的标题化合物(824mg,80%),该化合物适合用于下一步骤中,无需任何纯化。LC-MS m/z=167.0,^1H NMR(500MHz,$CDCl_3$) δ 8.52(d,J=34.2Hz,1H),8.16(s,1H),3.95(d,J=4.8Hz,3H),3.78(s,2H),2.42(s,3H)。

[1923] 步骤 2 :合成 4- 甲基 -5-[(四氢吡喃 -4- 基)氨基]吡啶 -3- 羧酸甲酯

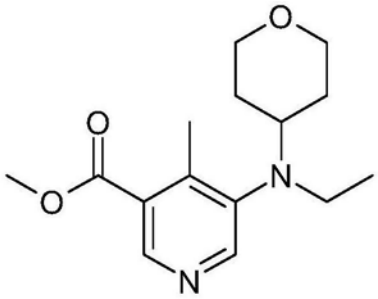
[1924]



[1925] 在氮气气氛下,向搅拌后的 5- 氨基 -4- 甲基吡啶 -3- 羧酸甲酯(805mg,4.84mmol)的 DCE (20mL) 溶液中依次加入四氢吡喃酮(537μl,5.80mmol)和三氟乙酸(742μl,9.69mmol),搅拌反应 5 分钟后,加入三乙酰基硼氢化钠(1.54g,7.27mmol)。在室温下搅拌反应 16 小时,再添加更多的四氢吡喃酮(100μl)和三乙酰基硼氢化钠(300mg),反应继续搅拌 6 小时。向反应混合物加入蒸馏水(20mL)和固体 $NaHCO_3$ 至 pH 值为 8。两相分离,水相用 EtOAc (2x50mL)洗涤,合并的有机相用盐水(50mL)洗涤,用 Na_2SO_4 干燥,过滤并蒸发,得到淡黄色固体状的标题化合物(1.11g,88%),该化合物不经任何进一步的纯化而用于下一步骤中。LC-MS96%,m/z=251.0,^1H NMR(500MHz,$CDCl_3$) δ 8.40(s,1H),8.10(s,1H),4.03(dt,J=11.9,3.5Hz,2H),3.92(s,3H),3.68 - 3.58(m,1H),3.54(tt,J=8.1,4.1Hz,3H),2.35(s,3H),2.12 - 2.05(m,2H),1.53(ddd,J=23.8,11.0,4.3Hz,2H)。

[1926] 步骤 3 :合成 5-[乙基 (四氢吡喃 -4- 基) 氨基]-4- 甲基吡啶 -3- 羧酸甲酯

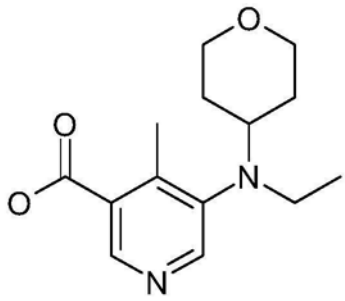
[1927]



[1928] 在氮气气氛下,向搅拌后的 4- 甲基 -5-[(四氢吡喃 -4- 基) 氨基] 吡啶 -3- 羧酸甲酯(600mg,2.40mmol)的 DCE (20mL)溶液中依次加入乙醛(1.07ml,19.2mmol)和三氟乙酸(367μl,4.79mmol),搅拌反应 5 分钟后,添加三乙酰基硼氢化钠(3.05g,14.4mmol)。在室温下搅拌反应 16 小时,之后向反应混合物加入更多的乙醛(500μl)和三乙酰基硼氢化钠(1.0g),继续搅拌反应 16 小时。向反应混合物添加蒸馏水(20mL),并添加固体 $NaHCO_3$ 至 pH 值为 8。两相分离,水相用 DCM (2x50mL)洗涤,合并的有机相用盐水(50mL)洗涤,用 Na_2SO_4 干燥,过滤并蒸发。残余物用 25g Isolate 硅胶柱(用梯度 0-50% 的 EtOAc 的庚烷溶液洗脱)纯化,得到淡黄色油状的标题化合物(418mg,60%)。LC-MS96%,m/z=279.1,^{1}H NMR(500MHz,$CDCl_3$) δ 8.76(s,1H),8.44(s,1H),3.97(d,J=11.0Hz,2H),3.93(s,3H),3.33(td,J=11.6,2.1Hz,2H),3.13(q,J=7.1Hz,2H),3.04(tt,J=10.9,4.0Hz,1H),2.54(s,3H),1.76 - 1.59(m,4H),0.89(t,J=7.1Hz,3H)。

[1929] 步骤 4 :合成 5-[乙基 (四氢吡喃 -4- 基) 氨基]-4- 甲基吡啶 -3- 羧酸

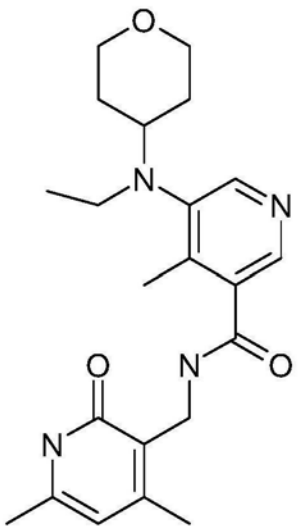
[1930]



[1931] 向搅拌后的 5-[乙基 (四氢吡喃 -4- 基) 氨基]-4- 甲基吡啶 -3- 羧酸甲酯(415mg,1.49mmol)的 THF (7mL)和 MeOH (3mL)溶液中加入 4M NaOH 溶液(932μl,3.73mmol)。在室温下搅拌反应 4.5 小时后,通过添加 1M HCl 来中和溶液,减压除去溶剂,然后添加饱和盐水(10mL)。水相用 1:1 的 IPA:$CHCl_3$ (3×50mL)萃取,合并的有机相用盐水(30mL)洗涤,用 Na_2SO_4 干燥,过滤并蒸发,得到灰白色固体状的标题化合物(305mg,77%),该化合物适合用于下一步骤中,而不经任何进一步的纯化。LC-MS99%,m/z=265.1,^{1}H NMR(500MHz,DMSO-d6) δ 8.57(s,1H),8.46(s,1H),3.82(d,J=11.6Hz,2H),3.25(t,J=10.9Hz,2H),3.16 - 2.99(m,3H),2.45(s,3H),1.64(d,J=11.0Hz,2H),1.48(dt,J=11.9,5.7Hz,2H),0.81(t,J=7.0Hz,3H)。

[1932] 步骤 5 :合成 N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基]-5-[乙基 (四氢吡喃 -4- 基) 氨基]-4- 甲基吡啶 -3- 甲酰胺

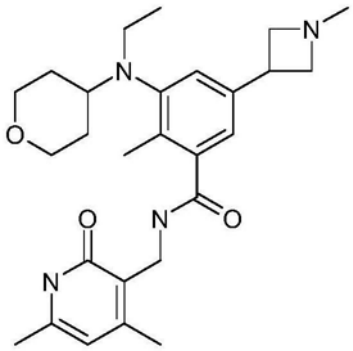
[1933]



[1934] 向搅拌后的 5-[乙基 (四氢吡喃 -4- 基) 氨基]-4- 甲基吡啶 -3- 羧酸(300mg, 1.13mmol)的 DMF(10mL)溶液中加入 DIPEA(395μl,2.27mmol)和 HATU(518mg,1.36mmol)。在室温下搅拌 5 分钟后,加入 3-(氨基甲基)-4,6- 二甲基 -1,2- 二氢吡啶 -2- 酮(89%, 214mg,1.25mmol),在室温下搅拌反应 18 小时。然后将反应混合物倒入 500ml 水,将产物萃取到 EtOAc 中(3x200mL),合并的有机相用盐水洗涤(2x100mL),干燥 (Na_2SO_4),蒸发。粗产物再用制备 HPLC 纯化,所得固体在乙醚中磨碎并过滤分离,得到灰白色固体状的标题化合物(115mg,25%)。LC-MS100%,m/z=399.2,^{1}H NMR(500MHz,Acetone) δ 10.97(s,1H),8.32(s,1H),8.22(s,1H),7.73(s,1H),5.92(s,1H),4.41(d,J=5.3Hz,2H),3.85(dd,J=11.3,3.0Hz,2H),3.28(td,J=11.7,1.9Hz,2H),3.15(q,J=7.1Hz,2H),3.09(ddd,J=11.1,7.2,3.9Hz,1H),2.32(d,J=1.5Hz,6H),2.23(s,3H),1.69(dd,J=12.6,1.7Hz,2H),1.55(ddd,J=24.3,12.2,4.4Hz,2H),0.85(t,J=7.1Hz,3H)。

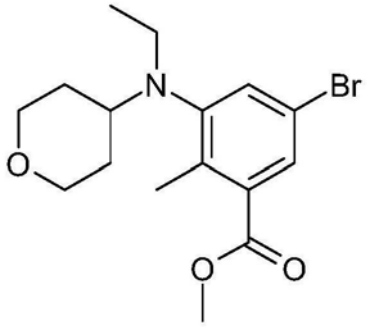
[1935] 化合物 322 :N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基]-3-[乙基 (四氢吡喃 -4- 基) 氨基]-2- 甲基 -5-(1- 甲基氮杂环丁烷 -3- 基) 苯甲酰胺

[1936]



[1937] 步骤 1 :合成 5- 溴 -3-[乙基 (四氢吡喃 -4- 基) 氨基]-2- 甲基苯甲酸甲酯

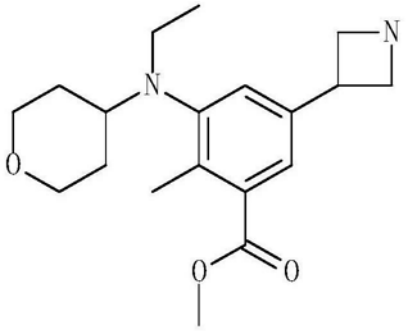
[1938]



[1939] 在氮气气氛下，向搅拌后的 5- 溴 -3-[乙基 (四氢吡喃 -4- 基) 氨基]-2- 甲基苯甲酸甲酯 (622mg，1.90mmol) 的 DCE (10mL) 溶液中依次加入乙醛 (318μl，5.69mmol) 和醋酸 (650μl，11.4mmol)，将反应搅拌 5 分钟后，加入三乙酰基硼氢化钠 (2.00g，9.48mmol)。在室温下搅拌反应 16 小时后，向反应混合物加加入额外的乙醛 (300μl) 和三乙酰基硼氢化钠 (1.2g)。反应搅拌继续 6 小时，然后添加蒸馏水 (100mL)，并添加固体 $NaHCO_3$ 直到水相 pH 值为 7。两相分离，水相用 DCM (2x50mL) 洗涤，合并的有机相用盐水 (100mL) 洗涤，用 Na_2SO_4 干燥，过滤并蒸发。粗产物用硅胶 FCC (用 0-5% 的 EtOAc 的庚烷溶液洗脱) 纯化，得到标淡黄色油状的题化合物 (470mg，70%)。LC-MS100m/z=356.0/357.9.^{1}H NMR(500MHz,CDCl3) δ 7.64(d,J=2.0Hz,1H),7.29(d,J=2.0Hz,1H),3.89(d,J=11.3Hz,2H),3.83(s,3H),3.26(td,J=11.5,2.6Hz,2H),2.98(q,J=7.1Hz,2H),2.86(dd,J=9.7,5.2Hz,1H),2.38(s,3H),1.67-1.52(m,4H),0.80(t,J=7.1Hz,3H)。

[1940] 步骤 2 :合成 5-(氮杂环丁烷 -3- 基)-3-[乙基 (四氢吡喃 -4- 基) 氨基]-2- 甲基苯甲酸甲酯

[1941]

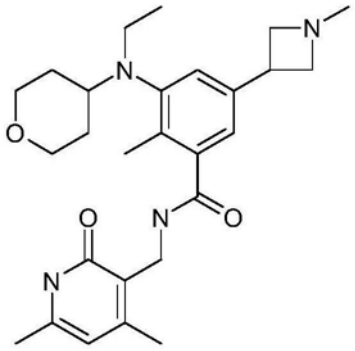


[1942] 向干燥的烧瓶中加入锌粉 (186mg，2.85mmol) 并用热枪将该烧瓶加热几分钟。然后氮气保护下，将无水 DMA (15mL) 加入到上述烧瓶中，同时剧烈搅拌并加热到 65℃。向反应混合物中加入 TMSCl(44μl，0.34mmol) 和 1,2- 二溴乙烷 (30μl，0.34mmol)，反应在 65℃搅拌 30 分钟，随后逐滴滴加 N-Boc-3- 碘代氮杂环丁烷 (624mg，2.20mmol) 的无水 DMA (5mL) 溶液。然后将反应冷却到室温，向反应混合物加入 5- 溴 -3-[乙基 (四氢吡喃 -4- 基) 氨基]-2- 甲基苯甲酸甲酯 (470mg，1.32mmol) 的无水 DMA (10mL) 溶液。将所得溶液用氮气进行脱气处理 10 分钟后，向其加入固体形式的 $Pd(dppf)Cl_2$.DCM (32mg，0.04mmol) 和碘化亚铜 (15mg，0.08mmol)。在 80℃加热反应 60 分钟，然后冷却到室温，加入蒸馏水 (50mL) 和饱和 NH_4Cl 溶液 (10mL)。水相用 EtOAc 萃取 (3x50mL)，然后合并的有机相用盐水洗涤 (20mL)，用 Na_2SO_4 干燥，过滤并蒸干，随后通过与庚烷形成共沸物除去残余的 DMA。残余物经 10g Isolute 柱 (用 0%-25%EtOAc 的庚烷溶液作为洗脱液) 纯化，得到浅棕色油状的标题化合物

(565mg)。LC-MS100%,2.12 分钟 (3.5 分钟 LC-MS 法),m/z=433.2。向该油状物中依次加入 DCM (4mL)和 TFA (1mL),所得溶液在室温下搅拌 2 小时,之后将溶剂蒸发,加饱和 $NaHCO_3$ 水溶液至 pH 值为 7-8。水相用 DCM 萃取(3x30mL),用盐水洗涤(30mL),用 $MgSO_4$ 干燥,过滤并蒸发,得到黄色油状的标题化合物(440mg)。LC-MS100%,m/z=333.1。

[1943] 步骤 3 :合成 N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基]-3-[乙基 (四氢吡喃 -4- 基) 氨基]-2- 甲基 -5-(1- 甲基氮杂环丁烷 -3- 基) 苯甲酰胺

[1944]

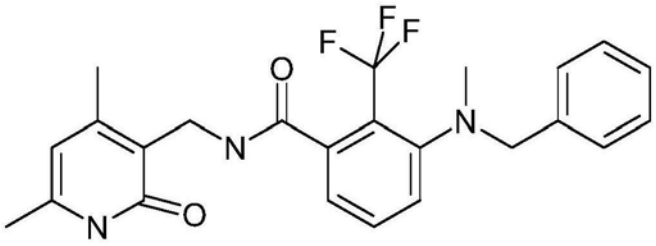


[1945] 在氮气气氛下,向搅拌后的 5-(氮杂环丁烷 -3- 基)-3-[乙基 (四氢吡喃 -4- 基) 氨基]-2- 甲基苯甲酸甲酯(440mg,1.32mmol) 的 DCE (10mL) 溶液中依次加入多聚甲醛 (278mg,9.27mmol) 和醋酸(0.15ml,2.65mmol),搅拌反应 5 分钟后,加三乙酰基硼氢化钠 (1.40g,6.62mmol)。在室温下搅拌反应 16 小时,然后向反应混合物添加蒸馏水(20mL),并添加固体 $NaHCO_3$ 直到水相 pH 值为 8,两相分离,水相用 DCM (3x30mL) 洗涤,合并的有机相用盐水(50mL)洗涤,干燥 Na_2SO_4,过滤,蒸发。残余物经 10g Isolute 层析(用 0-5% 的 MeOH/DCM 洗脱)纯化,蒸发,然后经氧化铝(用 0-1% 的 MeOH/DCM 洗脱)纯化,得到黄色油状的标题化合物,其直接用于合成的下一步。LC-MS77%,1m/z=347.1。

[1946] 将 3-[乙基 (四氢吡喃 -4- 基) 氨基]-2- 甲基 -5-(1- 甲基氮杂环丁烷 -3- 基) 苯甲酸甲酯(103mg,0.30mmol) 溶于 THF (20mL) 和 MeOH (5mL) 的混合溶液中,向该溶液中加入 2M NaOH(1.49ml,2.97mmol)。反应混合物在 50℃搅拌 16 小时,冷却,用 6M HCl 酸化至 pH 值为 4,减压蒸发脱去溶剂,然后残余物在真空干燥箱中在 40℃下干燥 5 小时,得到粗品酸。向所得酸的 DMF (10mL) 溶液中加入 HATU (170mg,0.45mmol) 和 DIPEA (130μl, 0.74mmol)。所得混合物在室温下搅拌 5 分钟后,加 3-(氨基甲基)-4,6- 二甲基 -1,2- 二氢吡啶 -2 酮(89%,66mg,0.39mmol)。反应搅拌 16 小时后,向反应混合物中加入额外的 HATU (80mg)和 3-(氨基甲基)-4,6- 二甲基 -1,2- 二氢吡啶 -2- 酮(30mg),继续搅拌 5 小时。将反应混合物倒入蒸馏水(50mL)中,用 EtOAc 萃取(3x50mL),用盐水洗涤(2x20mL),用 Na_2SO_4 干燥,过滤并蒸发。粗产物经制备 HPLC 纯化,并蒸发,得到灰白色固体的标题化合物(28mg, 三步 5%)。LC-MS95%,m/z=467.3,^{1}H NMR(500MHz,Acetone-d_6) δ 10.73(s,1H),7.61(s,1H), 7.30(s,1H),7.26(s,1H),5.97(s,1H),4.74(t,J=9.9Hz,2H),4.60(t,J=9.6Hz,2H),4.38(q ,J=6.2Hz,3H),3.83(d,J=11.6Hz,2H),3.27(s,3H),3.23(t,J=11.6Hz,2H),3.10(dd,J=14. 1,7.0Hz,2H),3.04 - 2.97(m,1H),2.34(s,3H),2.31(s,3H),2.25(s,3H),1.67(d,J=11.1Hz ,2H),1.56(td,J=11.8,4.1Hz,2H),0.83(t,J=7.0Hz,3H)。

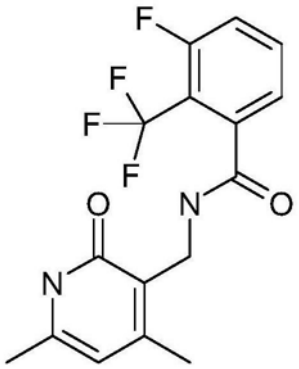
[1947] 化合物 332 :3-[苄基 (甲基) 氨基]-N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基]-2-(三氟甲基) 苯甲酰胺

[1948]



[1949] 步骤 1：合成 N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基]-3- 氟代 -2-（三氟甲基）苯甲酰胺

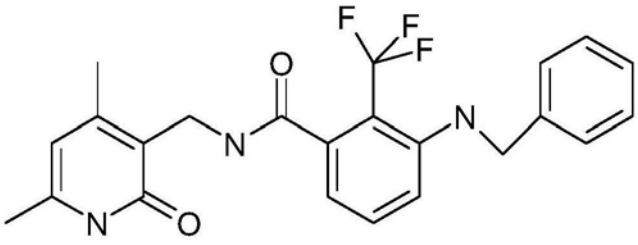
[1950]



[1951] 在冰浴冷却下，向搅拌后的 3- 氟代 -2-（三氟甲基）苯甲酸（1.00g，4.81mmol）的 DMF（25mL）溶液中加入 HATU（2.19g，5.77mmol）和 DIPEA（1.67ml，9.61mmol）。在 0℃搅拌反应 5 分钟后，向反应混合物中加入 3-（氨基甲基）-4,6- 二甲基 -1,2- 二氢吡啶 -2- 酮（89%，904mg，5.29mmol），在室温下搅拌 4 小时。然后将反应混合物倒入蒸馏水（300mL）中并搅拌 1 小时，然后采用微纤维纸通过真空抽滤收集沉淀物。将所得固体在乙醚中磨碎并过滤，得到浅褐色固体状的标题化合物（1.19g，72%）。LC-MS100%，m/z=343.0，^{1}H NMR（500MHz，DMSO）δ 11.48（s，1H），8.54（t，J=4.8Hz，1H），7.71（dd，J=13.3，8.0Hz，1H），7.56 - 7.45（m，1H），7.20（d，J=7.6Hz，1H），5.86（s，1H），4.25（d，J=4.9Hz，2H），2.18（s，3H），2.11（s，3H）。

[1952] 步骤 2：合成 3-（苄基氨基）-N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基]-2-（三氟甲基）苯甲酰胺

[1953]

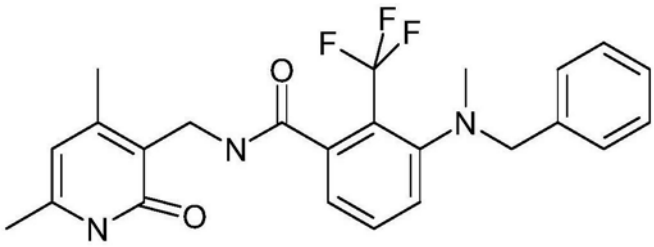


[1954] 将 N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基]-3- 氟代 -2-（三氟甲基）苯甲酰胺（0.80g，2.34mmol）的苄胺（2.6ml，23.4mmol）悬浮液在微波反应器中在 210℃加热 4 小时。冷却后向浆体中加入蒸馏水（20mL），并添加 2M HCl 直到其 pH 值为 5。混合物用 EtOAc 萃取（3x50mL）。合并的有机相依次用 pH 值为 5 的 HCl 溶液（2x50mL）和盐水（30mL）洗涤，用 Na_2SO_4 干燥，过滤并蒸发。所得油状物用 50g Isolute 硅胶柱（用

0-5% 的 MeOH/DCM 洗脱)纯化，得到灰白色固体状的标题化合物(313mg，29%)。LC-MS94%，m/z=430.2，^{1}H NMR(500MHz，Acetone-d_6) δ 7.41 - 7.16(m，8H)，6.69(d，J=8.5Hz，1H)，6.50(d，J=7.4Hz，1H)，5.87(s，1H)，5.84(s，1H)，4.53(d，J=5.7Hz，2H)，4.35(d，J=5.6Hz，2H)，2.28，(d，J=4.0Hz，3H)，2.21(s，3H)。

[1955] 步骤 3：合成 3-[苄基 (甲基) 氨基]-N-[(4，6- 二甲基 -2- 氧代 -1，2- 二氢吡啶 -3- 基) 甲基]-2-(三氟甲基) 苯甲酰胺

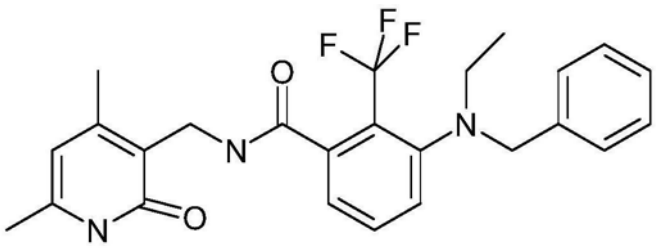
[1956]



[1957] 向 3-(苄基氨基)-N-[(4，6- 二甲基 -2- 氧代 -1，2- 二氢吡啶 -3- 基) 甲基]-2-(三氟甲基) 苯甲酰胺(100mg，0.23mmol)的 DCE(5mL)溶液中依次加入醋酸(27μl，0.47mmol)和多聚甲醛(7mg，0.23mmol)，反应在室温下搅拌 10 分钟。然后向反应混合物中一次性加入三乙酰基硼氢化钠(74mg，0.35mmol)，在室温下搅拌 16 小时。用乙醛(35mg)、三乙酰基硼氢化钠(250mg)和 AcOH(100mL)进行进一步的处理。再过 24 小时后，向反应混合物中再加乙醛(445mg)和三乙酰基硼氢化钠(250mg)，继续搅拌反应 3 小时。然后向反应混合物中加水(20mL)，分批加入 $NaHCO_3$ 来中和水相。水相用 DCM 萃取(2x50mL)，然后合并的有机相用盐水洗涤，干燥(Na_2SO_4) 并蒸发。所得产物用 5g Isolute 经 FCC(用 0-5% 的 MeOH/DCM 洗脱)纯化，得到灰白色粉末状的标题化合物(24mg，22%)。LC-MS95%，4.12 分钟 (7 分钟 LC-MS 法)，m/z=444.2，^{1}H NMR(500MHz，$CDCl_3$) δ 11.10(br. s，1H)，7.44(t，J=7.8Hz，1H)，7.38 - 7.29(m，5H)，7.27 - 7.23(m，1H)，7.12(d，J=7.4Hz，1H)，7.04(t，J=5.6Hz，1H)，5.92(s，1H)，4.52(d，J=5.9Hz，2H)，4.09(s，2H)，2.60(s，3H)，2.38(s，3H)，2.19(s，3H)。

[1958] 化合物 333：3-[苄基 (乙基) 氨基]-N-[(4，6- 二甲基 -2- 氧代 -1，2- 二氢吡啶 -3- 基) 甲基]-2-(三氟甲基) 苯甲酰胺

[1959]

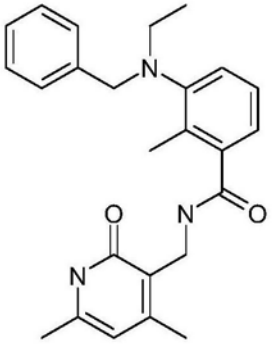


[1960] 向 3-(苄基氨基)-N-[(4，6- 二甲基 -2- 氧代 -1，2- 二氢吡啶 -3- 基) 甲基]-2-(三氟甲基) 苯甲酰胺(198mg，0.46mmol)的 DCE(5mL)溶液中依次加入醋酸(80μl，1.38mmol)和乙醛(129μl，2.31mmol)，反应在室温下搅拌 10 分钟。然后向反应混合物一次性加入三乙酰基硼氢化钠(490mg，2.31mmol)，在室温下搅拌反应 16 小时。3 天之内，用乙醛(4x130μl)和三乙酰基硼氢化钠(4x0.5g)进行进一步的处理以结束反应。然后向反应混合物加水(100mL)，分批加 $NaHCO_3$ 中和水相。水相用 DCM(2x50mL)萃取，然后合并的有机相用

盐水洗涤，干燥（Na_2SO_4），蒸发。所得产物用 5g Isolute FCC（用 0-5% 的 MeOH/DCM 洗脱）纯化，随后通过 RP-HPLC 纯化，得到灰白色粉末状的标题化合物（76mg，34%）。LC-MS100%，m/z=458.3，^1H NMR（500MHz，$CDCl_3$）δ 11.70（s，1H），7.42（t，J=7.8Hz，1H），7.36 - 7.27（m，5H），7.24（d，J=7.1Hz，1H），7.12（d，J=7.4Hz，1H），7.03（d，J=5.4Hz，1H），5.90（s，1H），4.50（d，J=5.7Hz，2H），4.05（s，2H），2.96（q，J=7.1Hz，2H），2.36（s，3H），2.15（s，3H），0.89（t，J=7.1Hz，3H）。

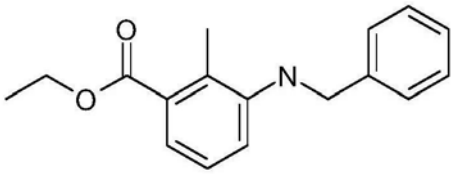
[1961] 化合物 334：3-[苄基（乙基）氨基]-N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基]-2- 甲基苯甲酰胺

[1962]



[1963] 步骤 1：合成 3-（苄基氨基）-2- 甲基苯甲酸乙酯

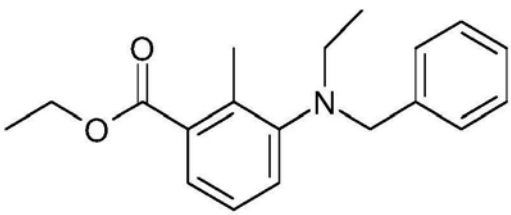
[1964]



[1965] 向搅拌后的 3- 氨基 -2- 甲基苯甲酸乙酯（1.00g，5.58mmol）的 DCE（20mL）溶液中依次加入苯甲醛（569μl，5.58mmol）和醋酸（0.64ml，11.2mmol）。在室温下搅拌反应 1 小时后，然后向反应混合物中加入三乙酰基硼氢化钠（1.77g，8.37mmol），搅拌反应 2 小时。向反应混合物中加入蒸馏水（20mL），并加入固体 $NaHCO_3$ 直至水相 pH 值为 7，两相分离。水相用 DCM 洗涤（2x50mL），合并的有机相用盐水洗涤（50mL），用 Na_2SO_4 干燥，过滤并蒸发，得到黄色油状的标题化合物（1.52g，96%），其未经任何进一步纯化，即用于下一步反应。LC-MS95%，m/z=270.0，^1H NMR（500MHz，$CDCl_3$）δ 7.42 - 7.32（m，4H），7.32 - 7.28（m，1H），7.17 - 7.06（m，2H），6.73（dd，J=7.8，1.1Hz，1H），4.40（s，2H），4.36（q，J=14.3，5.3Hz，2H），4.08（br.s，1H），2.35，（s，3H），1.39（t，3H）。

[1966] 步骤 2：合成 3-[苄基（乙基）氨基]-2- 甲基苯甲酸乙酯

[1967]

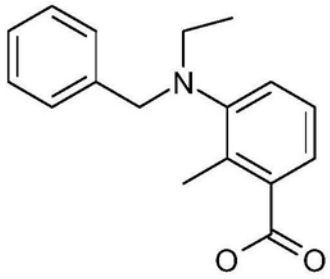


[1968] 向搅拌后的 3-（苄基氨基）-2- 甲基苯甲酸乙酯（396mg，1.47mmol）的 DCE

(10mL)溶液中依次加入乙醛(164μl,2.94mmol)和醋酸(0.17ml,2.94mmol)。在室温下搅拌反应10分钟后,向反应混合物中加入三乙酰基硼氢化钠(0.62g,2.94mmol),搅拌反应16小时。加入蒸馏水(30mL),并加入固体$NaHCO_3$直到水相pH值为7,两相分离,水相用DCM(2x50mL)洗涤,合并的有机相用盐水(50mL)洗涤,用Na_2SO_4干燥,过滤并蒸发。所得残余物再用25g硅胶Isolute柱(用0%-5%的EtOAc的庚烷溶液洗脱)纯化,得到无色油状的标题化合物(372mg,81%)。LC-MS94%,m/z=298.1,^1H NMR(500MHz,$CDCl_3$)δ7.48(dd,J=7.5,1.3Hz,1H),7.29-7.08(m,8H),4.32(q,J=7.1Hz,2H),4.05(s,2H),2.92(q,J=7.1Hz,2H),2.56(s,3H),1.35(t,J=7.1Hz,3H),0.92(t,J=7.1Hz,3H)。

[1969] 步骤3:合成3-[苄基(乙基)氨基]-2-甲基苯甲酸

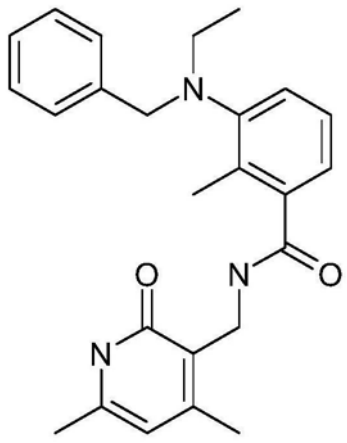
[1970]



[1971] 向搅拌后的3-[苄基(乙基)氨基]-2-甲基苯甲酸乙酯(370mg,1.24mmol)的THF(20mL)和MeOH(5mL)溶液中加入2M NaOH(3.11ml,6.22mmol),反应在50℃搅拌16小时。将反应混合物冷却到室温,真空除去溶剂,用1M HCl将水溶液调至pH值为1。将产品萃取到DCM中(3x50mL),用盐水洗涤(20mL),用Na_2SO_4干燥,过滤并浓缩,得到橙色油状的标题化合物(296mg,80%),其未经任何进一步的纯化,而用于下一步反应中。LC-MS91%,m/z=270.0,^1H NMR(500MHz,$CDCl_3$)δ7.73(d,J=7.5Hz,1H),7.34-7.30(m,4H),7.23(dt,J=15.4,6.9Hz,3H),4.12(d,J=13.5Hz,2H),3.04-2.94(m,2H),2.69(s,3H),0.99(t,J=7.0Hz,3H)。

[1972] 步骤4:合成3-[苄基(乙基)氨基]-N-[(4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基]-2-甲基苯甲酰胺

[1973]

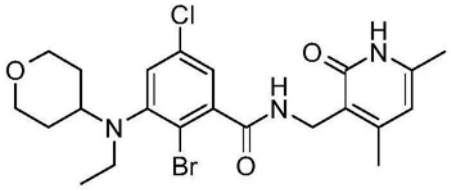


[1974] 向搅拌后的(3-[苄基(乙基)氨基]-2-甲基苯甲酸(纯度为91%,296mg,1.0mmol)的DMF(10mL)溶液中加入DIPEA(440μl,2.5mmol)和HATU(570mg,1.5mmol)。在室温下搅拌5分钟后,向反应混合物中加入3-(氨基甲基)-4,6-二甲基-1,2-二氢吡啶-2-酮

(89%,222mg,1.3mmol),反应在室温下搅拌 16 小时。然后将反应混合物倒入 150ml 水中,并搅拌 20 分钟。将产品过滤,真空干燥,使用 RP-HPLC 纯化。所得固体与乙醚一起研磨并通过过滤分离,得到灰白色固体状的标题化合物(86mg,21%)。LC-MS99%,m/z=404.3,^{1}H NMR(500MHz,$CDCl_3$) δ 12.04(s,1H),7.33 - 7.23(m,4H),7.21(t,J=6.8Hz,1H),7.14 - 7.05(m,3H),7.05 - 6.99(m,1H),5.92(s,1H),4.53(d,J=5.9Hz,2H),4.06(s,2H),2.92(q,J=6.9Hz,2H),2.41(s,3H),2.39(s,3H),2.16(s,3H),0.92(t,J=7.0Hz,3H)。

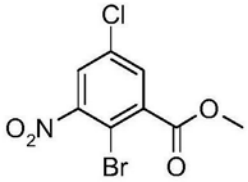
[1975] 化合物 191 :2- 溴 -5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-3-(乙基 (四氢 -2H- 吡喃 -4- 基) 氨基) 苯甲酰胺

[1976]



[1977] 步骤 1 :合成 2- 溴 -5- 氯 -3- 硝基苯甲酸甲酯

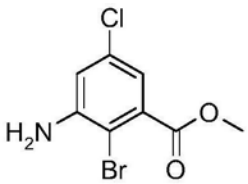
[1978]



[1979] 将 2- 溴 -5- 氯苯甲酸甲酯(10g,40mmol)的浓 H_2SO_4(48ml,910mmol)溶液在空气中的丙酮 / 冰浴中冷却至 -5℃。在 0℃下,在 30 分钟内将浓硝酸(3.35ml,52mmol)和浓硫酸(3.4ml,64mmol)的混合物逐滴滴加到反应混合物中。将黄色的反应混合物在 0℃搅拌 1.5 小时后倒入冰中。加入 EtOAc (150mL),分离两相。有机相依次用去离子水(3x50mL)和盐水(50mL)洗涤。有机相用 $MgSO_4$ 干燥,过滤并减压浓缩,得到淡黄色油状的标题化合物(12.0g,60%),放置固化。所得原料含 40% 的 6- 硝基异构体。所得原料使用时不用进一步纯化。LC-MS91%,m/z= 无电离作用 ,^{1}H NMR(500MHz,$CDCl_3$) δ 7.86(1H,d,J=2.52Hz),7.77(1H,d,J=2.52Hz),3.99(3H,s)。

[1980] 步骤 2 :合成 3- 氨基 -2- 溴 -5- 氯苯甲酸甲酯

[1981]

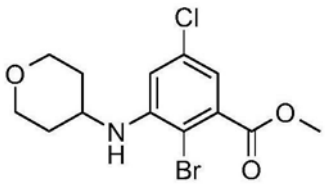


[1982] 在室温下,向 2- 溴 -5- 氯 -3- 硝基苯甲酸甲酯(4.0g,14mmol)的甲醇(130mL)溶液中依次加入氯化铵(7.13g,136mmol)和去离子水(65mL)。在空气中加热混合物到 70℃后,向所得混合物加入铁粉(4.55g,81.5mmol)。反应在 70℃搅拌 3 小时,冷却到室温,通过硅胶过滤。滤饼用 MeOH (65mL)洗涤,滤液减压浓缩。将残余物溶解于饱和 $NaHCO_3$ 溶液(50mL)和 EtOAc (100mL)中。两相分离,有机相用饱和 $NaHCO_3$(aq) (3x50mL)洗涤后用 $MgSO_4$ 干燥,过滤并减压浓缩。残余物通过 FCC (50g 硅胶,Isolute 柱,洗脱梯度为

95:5 至 7:3 的庚烷 :EtOAc）纯化，得到无色油状的标题化合物（1.92g，48%）。LC-MS92%，m/z=268.8/265.8/267.6，^{1}H NMR(500MHz，$CDCl_3$) δ 7.08(1H，d，J=2.36Hz)，6.86(1H，d，J=2.36Hz)，4.34-4.49(2H，m)，3.93(3H，s)。

[1983] 步骤 3 :合成 2- 溴 -5- 氯 -3-（四氢吡喃 -4- 基氨基）苯甲酸甲酯

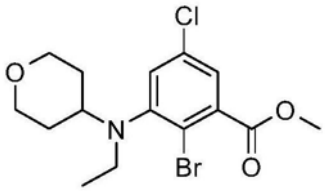
[1984]



[1985] 在室温和氮气保护下，向 3- 氨基 -2- 溴 -5- 氯苯甲酸甲酯（1.0g，3.8mmol）的 1，2- 二氯乙烷（15mL）溶液中依次加入四氢吡喃酮（0.7ml，7.6mmol）和醋酸（1.3ml，23mmol）。在室温下搅拌溶液 5 分钟后，在室温下向反应溶液加入三乙酰基硼氢化钠（2.4g，11mmol）。21 小时后，向反应混合物中加入额外的四氢吡喃酮（0.7ml，7.6mmol），搅拌 10 分钟后，加入三乙酰基硼氢化钠（2.4g，11mmol）。搅拌 20 小时后，加去离子水（30mL），所得混合物用固体 $NaHCO_3$ 中和。两相分离，水层用 EtOAc 萃取（2x30mL）。合并的萃取液用 $MgSO_4$ 干燥，过滤并减压浓缩。残余物通过 FCC（25g 硅胶，Isolute 柱，洗脱液梯度为 9:1 至 8:2 的庚烷 :EtOAc）纯化，得到白色固体状的标题化合物（903mg，68%）。LC-MS92%，2.11 分钟（3 分钟 LC-MS 法），m/z=348.2/350.2/351.9，^{1}H NMR(500MHz，$CDCl_3$) δ 6.94-7.07(1H，m)，6.70(1H，d，J=2.36Hz)，4.72(1H，d，J=7.57Hz)，3.96-4.15(2H，m)，3.87-3.96(3H，m)，3.40-3.67(3H，m)，2.05(2H，d，J=13.08Hz)，1.49-1.69(2H，m)。

[1986] 步骤 4 :合成 2- 溴 -5- 氯 -3-[乙基（四氢吡喃 -4- 基）氨基] 苯甲酸甲酯

[1987]

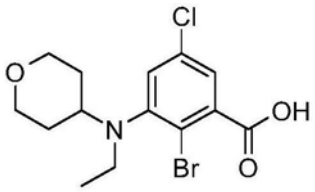


[1988] 在室温和氮气保护下，向 2- 溴 -5- 氯 -3-（四氢吡喃 -4- 基氨基）苯甲酸甲酯（300mg，0.86mmol）的 1，2- 二氯乙烷（3mL）溶液中依次加入乙醛（96μl，1.7mmol）和醋酸（0.3ml，5.16mmol）。在室温下搅拌反应 5 分钟后，在室温下向所得溶液加入三乙酰基硼氢化钠（0.55g，2.6mmol），通过 LCMS 监测反应。22 小时后，向反应混合物中再加入乙醛（96μl，1.7mmol），搅拌 10 分钟后，加入三乙酰基硼氢化钠（0.55g，2.6mmol）。3 天后，反应混合物用 1，2- 二氯乙烷（5mL）稀释。向反应混合物加入乙醛（962μl，17.2mmol），搅拌 10 分钟后，加入三乙酰基硼氢化钠（1.82g，8.6mmol）。15 小时后，向反应混合物再加入乙醛（960μl，17.2mmol），搅拌 10 分钟后，加入三乙酰基硼氢化钠（1.82g，8.6mmol）。反应混合物在室温下再搅拌 22 小时，然后加去离子水（25mL），混合物用固体 $NaHCO_3$ 中和。加入 EtOAc（25mL），两相分离。水层用 EtOAc 萃取（2x25mL），合并的萃取液用 $MgSO_4$ 干燥，过滤并减压浓缩。残余物通过 FCC（10g 硅胶，Isolute 柱，洗脱液梯度为 99:1 至 8:2 的庚烷 :EtOAc）纯化，得到无色油状的标题化合物（122mg，38%）物。LC-MS85%，m/z=376.3/378.2/379.9，^{1}H NMR(500MHz，CDCl3) δ 7.31(d，J=2.5Hz，1H)，7.18(d，J=2.4Hz，1H)，3.98(dd，J=8.7，5.5Hz，

2H),3.94(s,3H),3.35(td,J=11.6,5.5Hz,2H),3.19(t,J=7.1Hz,1H),3.12(q,J=7.1Hz,2H),1.75(td,J=10.1,8.8,3.9Hz,4H),0.92(t,J=7.1Hz,3H)。

[1989] 步骤 5:合成 2-溴-5-氯-3-[乙基(四氢吡喃-4-基)氨基]苯甲酸

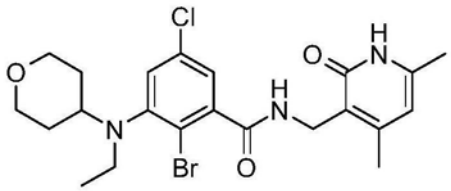
[1990]



[1991] 向 2-溴-5-氯-3-[乙基(四氢吡喃-4-基)氨基]苯甲酸甲酯(122mg,0.32mmol)的四氢呋喃(3mL)溶液中加入 4M NaOH(3.2mL)。反应混合物在 50℃搅拌 20 小时。用 6M HCl 将反应混合物酸化至 pH 值 2-3,用 DCM 萃取(3x100mL)。合并的有机液用 $MgSO_4$ 干燥,过滤并减压浓缩,得到淡黄色泡沫状的 2-溴-5-氯-3-[乙基(四氢吡喃-4-基)氨基]苯甲酸(109mg,93%, 校正产率为 83%)。LC-MS89%,m/z=361.9/364.2/365.8,^{1}H NMR(500MHz,$CDCl_3$) δ 7.50(d,J=2.4Hz,1H),7.23(d,J=2.4Hz,1H),4.00(d,J=11.5Hz,2H),3.49-3.27(m,2H),3.21(t,J=7.4Hz,1H),3.14(q,J=7.0Hz,2H),1.78(dd,J=7.4,3.4Hz,4H),0.93(t,J=7.0Hz,3H)。

[1992] 步骤 6:合成 2-溴-5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(四氢-2H-吡喃-4-基)氨基)苯甲酰胺

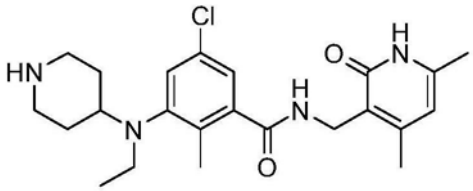
[1993]



[1994] 在室温和氮气保护下,向 2-溴-5-氯-3-[乙基(四氢吡喃-4-基)氨基]苯甲酸(109mg,0.3mmol)的 DMF 溶液(3mL)中依次加入 PYBOP (187mg,0.36mmol)、N-乙基-N-(丙烷-2-基)丙烷-2-胺(78μl,0.45mmol)和 3-(氨基甲基)-4,6-二甲基-1,2-二氢吡啶-2-酮(89%,56mg,0.33mmol)。在室温下搅拌 1 小时后,向反应混合物加入 EtOAc(30mL),然后依次用去离子水(2x10mL)和饱和 $NaHCO_3$(aq)(2x10mL)洗涤。有机相用 $MgSO_4$ 干燥,过滤并减压浓缩。残余物通过 FCC(5g 硅胶,Isolute 柱,洗脱液梯度为 100%DCM 至 98:2 的 DCM:MeOH)进行两次纯化。样品在真空干燥箱干燥 18 小时,得到淡黄色固体状的标题化合物(103mg,65%)。LC-MS94%,m/z=496.0/498.0/500.0,^{1}H NMR(500MHz,$CDCl_3$) δ 11.00(s,1H),7.20-7.10(m,1H),7.10-7.05(m,2H),5.94(s,1H),4.54(d,J=5.9Hz,2H),3.96(d,J=11.4Hz,2H),3.42-3.26(m,2H),3.28-3.12(m,1H),3.09(q,J=7.0Hz,2H),2.39(s,3H),2.23(s,3H),1.72(td,J=8.5,3.8Hz,4H),0.90(t,J=7.0Hz,3H)。

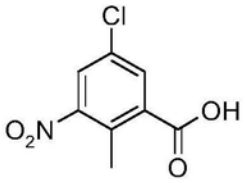
[1995] 化合物 102:5-氯-N-[(4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基]-3-[乙基(哌啶-4-基)氨基]-2-甲基苯甲酰胺

[1996]



[1997] 步骤 1 :合成 5- 氯 -2- 甲基 -3- 硝基苯甲酸

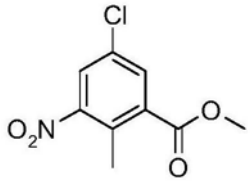
[1998]



[1999] 将 5- 氯 -2- 甲基苯甲酸(9.9g,58mmol)的浓硫酸(70ml,1310mmol)溶液在丙酮 / 冰浴中冷却到 -5℃。在 -5℃下,在 30 分钟内将浓硝酸(4.9ml,75mmol)和浓硫酸(5.0ml,94mmol)的混合物逐滴滴加到反应混合物中。将反应混合物在 -5℃搅拌 2 小时后倒入冰中(150g),过滤收集沉淀物。将所得沉淀物溶解在 EtOAc (100mL)中,用盐水洗涤(100mL),然后用 $MgSO_4$ 干燥,过滤并减压浓缩,得到灰白色固体状的标题化合物(11.9g)。所得原料使用时不用进一步纯化。LC-MS57%,m/z=214.0/216.0,^{1}H NMR(500MHz,$CDCl_3$) δ 10.37(1H,br. s.),8.19(1H,d,J=2.21Hz),7.91(1H,d,J=2.21Hz),2.67(2H,s)。

[2000] 步骤 2 :合成 5- 氯 -2- 甲基 -3- 硝基苯甲酸甲酯

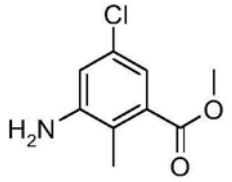
[2001]



[2002] 在室温和氮气保护下,向 5- 氯 -2- 甲基 -3- 硝基苯甲酸(1.17g,5.43mmol)的 DMF 溶液中(11mL)依次加入 Na_2CO_3 (862mg,8.14mmol)和碘乙烷(0.51ml,8.14mmol)。反应混合物在室温下搅拌 19 小时,然后用去离子水(30mL)稀释,并用 EtOAc 萃取(3x30mL)。合并的有机相用饱和 $NaHCO_3$(aq)(30mL)洗涤,用 $MgSO_4$ 干燥,过滤并减压浓缩。残余物通过 FCC(10g 硅胶,Isolute 柱,洗脱液梯度为 99:1-95:5 的庚烷 :EtOAc)纯化,得到淡黄色油状的标题化合物(900mg)。LC-MS89%,m/z= 无电离作用 ,^{1}H NMR(500MHz,$CDCl_3$) δ 8.00(1H,d,J=2.21Hz),7.86(1H,d,J=2.21Hz),3.96(3H,s),2.60(3H,s).

[2003] 步骤 3 :合成 3- 氨基 -5- 氯 -2- 甲基苯甲酸甲酯

[2004]

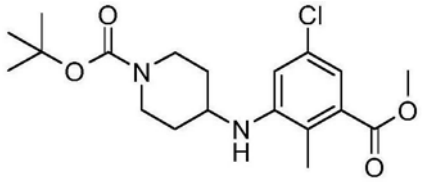


[2005] 在室温下,向 5- 氯 -2- 甲基 -3- 硝基苯甲酸甲酯(9.19g,40mmol)的甲醇(200mL)溶液中依次加入氯化铵(21g,400mmol)和去离子水(100mL)。将混合物加热到 70℃后 ,

向所得混合物加入铁(13.4g,240mmol)。反应混合物在70℃搅拌的2.5小时中,颜色变深。将反应混合物冷却到室温,通过硅胶过滤。滤饼用MeOH(100mL)洗涤,滤液减压浓缩。将残余物溶解于去离子水(100mL)和EtOAc(100mL)中。两相分离,水相用EtOAc萃取(2x100mL)。合并的萃取液用盐水洗涤(100mL),用$MgSO_4$干燥,过滤并减压浓缩,得到粘稠的橙色油状的标题化合物(7.6g),放置固化。所得原料使用时不用进一步纯化。LC-MS63%,m/z=200.3/202.0,^1H NMR(500MHz,$CDCl_3$) δ 7.20(1H,d,J=2.21Hz),6.80(1H,d,J=2.05Hz),3.89(3H,s),3.74-3.87(2H,m),2.30(3H,s)。

[2006] 步骤4:合成4-{[5-氯-3-(甲氧羰基)-2-甲基苯基]氨基}哌啶-1-羧酸叔丁酯

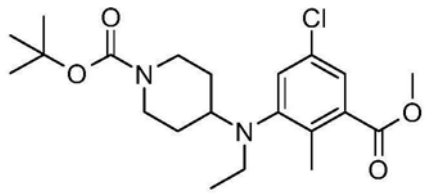
[2007]



[2008] 在室温和氮气保护下,向3-氨基-5-氯-2-甲基苯甲酸甲酯(100mg,0.50mmol)的1,2-二氯乙烷(2.5mL)溶液中依次加入4-氧代哌啶-1-羧酸叔丁酯(200mg,1.0mmol)和醋酸(0.17ml,3.0mmol)。所得溶液在室温下搅拌5分钟后,加入三乙酰基硼氢化钠(0.32g,1.5mmol)。在氮气氛中,搅拌反应混合物20小时。加去离子水(5mL),所得混合物用固体$NaHCO_3$中和。两相分离,水层用EtOAc萃取(2x5mL)。合并的有机萃取液用$MgSO_4$干燥,过滤并减压浓缩。残余物通过FCC(10g硅胶,Isolute柱,洗脱液梯度为99:1至7:3的庚烷:EtOAc)纯化,得到白色固体状的标题化合物(131mg,68%)。LC-MS98%,m/z=405.4/406.9(M+Na),^1H NMR(500MHz,$CDCl_3$) δ ppm7.10(1H,d,J=2.05Hz),6.70(1H,d,J=1.89Hz),3.98-4.16(2H,m),3.88(3H,s),3.58-3.72(1H,m),3.37-3.52(1H,m),2.97(2H,br.t,J=11.50,11.50Hz),2.24(3H,s),2.06(2H,br.d,J=10.60Hz),1.44-1.51(9H,m),1.32-1.44(2H,m)。

[2009] 步骤5:合成4-{[5-氯-3-(甲氧羰基)-2-甲基苯基](乙基)氨基}哌啶-1-羧酸叔丁酯

[2010]

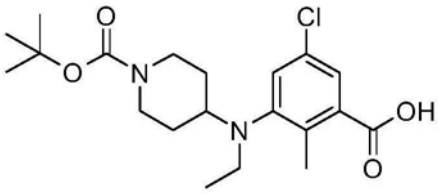


[2011] 在室温和氮气保护下,向4-{[5-氯-3-(甲氧羰基)-2-甲基苯基]氨基}哌啶-1-羧酸叔丁酯(125mg,0.33mmol)的1,2-二氯乙烷(1.6mL)溶液中依次加入乙醛(37μl,0.65mmol)和醋酸(0.11ml,1.96mmol)。所得溶液在室温下搅拌5分钟后,在室温下加入三乙酰基硼氢化钠(0.21g,0.98mmol)。通过LCMS监测反应,4.5小时后向反应混合物中再次加入乙醛(73μl,1.31mmol)和三乙酰基硼氢化钠(0.28g,1.31mmol)。所得混合物继续搅拌18小时,然后加去离子水(10mL),并用固体$NaHCO_3$中和。两相分离,水层用EtOAc萃取(2x10mL)。合并的萃取液用$MgSO_4$干燥,过滤并减压浓缩。残余物通过FCC(10g硅胶,

Isolute 柱，洗脱液梯度为 99:1 至 8:2 的庚烷 :EtOAc)纯化，得到稠密的无色油状的标题化合物（131mg，98%）。LC-MS98%，m/z=433.5/435.1(M+Na)，^{1}H NMR(500MHz，$CDCl_3$) δ ppm7.57(1H，d，J=2.21Hz)，7.22(1H，d，J=2.05Hz)，3.97-4.14(2H，m)，3.90(3H，s)，3.04(2H，q，J=6.99Hz)，2.81-2.91(1H，m)，2.70(2H，br. t，J=11.50，11.50Hz)，2.45(3H，s)，1.69-1.80(2H，m)，1.47-1.56(2H，m)，1.46(9H，s)，0.87(3H，t，J=7.09Hz)。

[2012] 步骤 6 :合成 3-({1-[（叔丁氧）羰基］哌啶 -4- 基}（乙基）氨基)-5- 氯 -2- 甲基苯甲酸

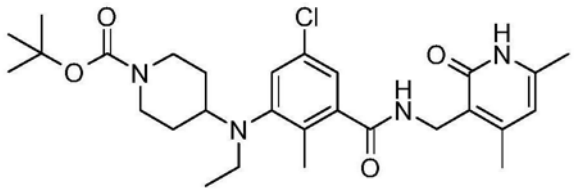
[2013]



[2014] 向 4-{[5- 氯 -3-（甲氧羰基)-2- 甲基苯基］(乙基）氨基} 哌啶 -1- 羧酸叔丁酯（131mg，0.32mmol)的四氢呋喃 (2mL)溶液中加入 LiOH(8.4mg，0.35mmol)的去离子水（2mL）溶液。反应混合物在室温下在空气中搅拌 24 小时。向反应混合物中加入 1M NaOH(3.19mL)，继续搅拌 24 小时。然后将反应混合物升温至 40℃ 25 小时。用 1M HCl 将反应混合物酸化至 pH 值 2-3，并用 EtOAc 萃取（3x20mL)。合并的萃取液用 $MgSO_4$ 干燥，过滤并减压浓缩，得到稠密的橙色油状的标题化合物（122mg)。LC-MS76%，m/z=397.5/399.4，^{1}H NMR(500MHz，$CDCl_3$) δ ppm7.74(1H，s)，7.20-7.35(2H，m)，3.92-4.11(2H，m)，2.97-3.13(2H，m)，2.81-2.95(1H，m)，2.62-2.79(2H，m)，2.53(3H，s)，1.75(2H，br. s.)，1.48-1.61(2H，m)，1.46(9H，s)，0.89(3H，t，J=6.86Hz)。

[2015] 步骤 7 :合成 4-[(5- 氯 -3-{[(4，6- 二甲基 -2- 氧代 -1，2- 二氢吡啶 -3- 基）甲基］氨基甲酰基}-2- 甲基苯基)(乙基）氨基］哌啶 -1- 羧酸叔丁酯

[2016]

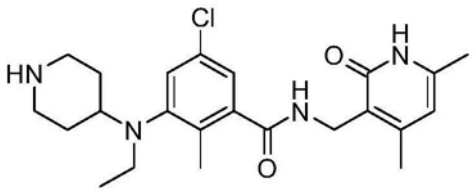


[2017] 在室温和氮气保护下，向 3-({1-[（叔丁氧）羰基］哌啶 -4- 基}（乙基）氨基)-5- 氯 -2- 甲基苯甲酸（60mg，0.15mmol）的 DMF （2mL）溶液中依次加入 PYBOP （94mg，0.18mmol)、N- 乙基 -N-（丙烷 -2- 基）丙烷 -2- 胺（40μl，0.23mmol）和 3-（氨基甲基)-4，6- 二甲基 -1，2- 二氢吡啶 -2- 酮（89%，28mg，0.17mmol)。在室温下搅拌 1 小时后，向反应混合物中加入 EtOAc （30mL)，并依次用去离子水（5mL）和饱和 $NaHCO_3$(aq) （3x5mL）洗涤。有机相用 $MgSO_4$ 干燥，过滤并减压浓缩。残余物通过 FCC（2g 硅胶，Isolute 柱，洗脱液梯度为 100%EtOAc 至 96:4 的 EtOAc :MeOH)纯化，得到淡黄色固体状的标题化合物（71mg，88%)。LC-MS97%，m/z=531.1/533.1，^{1}H NMR(250MHz，$CDCl_3$) δ ppm11.17(1H，br. s.)，7.11-7.18(1H，m)，7.06(2H，dd，J=7.46，2.28Hz)，5.96(1H，s)，4.53(2H，d，J=5.94Hz)，3.93-4.14(2H，m)，2.97-3.08(2H，m)，2.78-2.88(1H，m)，2.68(2H，t，J=11.57Hz)，2.39(3H，s)，2.26(3H

,s),2.24(3H,s),1.71(2H,d,J=11.27Hz),1.52(2H,br.s.),1.45(9H,s),0.86(3H,t,J=6.93Hz)。

[2018] 步骤 8：合成 5- 氯 -N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基]-3-[乙基（哌啶 -4- 基）氨基]-2- 甲基苯甲酰胺

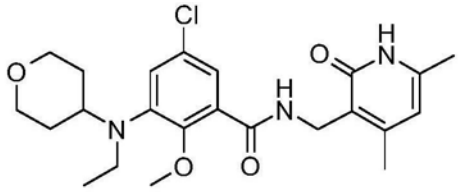
[2019]



[2020] 在室温下，向 4-[(5- 氯 -3-{[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基] 氨基甲酰基 }-2- 甲基苯基)(乙基) 氨基] 哌啶 -1- 羧酸叔丁酯（140mg，0.26mmol）的 1,4- 二氧六环 (5mL) 溶液中加入 4M HCl 的二氧六环溶液（1.32mL）。搅拌很短的时间后形成胶状物，然后将该胶状物溶解于加入的去离子水（2mL）。反应搅拌 21 小时后，减压浓缩得到稠密的油状物。加入 DCM（3mL），形成固体。将所得混合物浓缩得到 105mg 黄色固体，将该固体在 DCM（10mL）中搅拌 1 小时，再进行过滤，在真空干燥箱中在高度真空下干燥 24 小时。然后将所得样品溶解于去离子水（0.2mL）中，再冻干，得到米黄色固体状的标题化合物（86mg，70%）。LC-MS100%,m/z=431.2/433.2,^{1}H NMR(500MHz,$CDCl_3$) δ ppm7.44(bs,1H),7.26(bs,1H),6.69(bs,1H),4.55(s,2H),3.53 - 3.34(m,3H),3.28 - 3.08(m,2H),3.01(t,J=11.8Hz,2H),2.51(s,3H),2.43(s,3H),2.33(s,3H),2.16 - 1.96(m,2H),1.91 - 1.76(m,2H),0.92(t,J=6.9Hz,3H)。

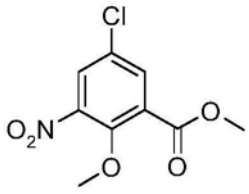
[2021] 化合物 192：5- 氯 -N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基]-3-[乙基（四氢吡喃 -4- 基）氨基]-2- 甲氧基苯甲酰胺

[2022]



[2023] 步骤 1：合成 5- 氯 -2- 甲氧基 -3- 硝基苯甲酸甲酯

[2024]

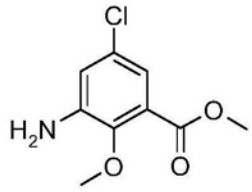


[2025] 在 0℃下，将浓硫酸（90mL）分批加入 5- 氯 -2- 甲基苯甲酸（13.2g，77.6mmol）中。然后在 0℃下，再将浓 HNO_3（10.5g，1740mmol）和浓 H_2SO_4（15mL）的混合物逐滴滴加到上述混合物中，滴加时间约为 1.5 小时。滴加完后，所得混合物在该温度下搅拌 2 小时。将所得混合物在倒入冰水中同时剧烈搅拌，通过过滤收集沉淀。将所得沉淀溶解于 EtOAc，用盐水洗涤，用无水 Na_2SO_4 干燥并浓缩，得到不经进一步的纯化即用于下一步中的标题化合物

(13.2g)。LC-MS95%,m/z=245.9/247.9,^{1}H NMR(500MHz,$CDCl_3$) δ ppm8.01(1H,d,J=2.68Hz),7.91(1H,d,J=2.68Hz),4.01(3H,s),3.97-3.99(3H,s)。

[2026] 步骤 2 :合成 3- 氨基 -5- 氯 -2- 甲氧基苯甲酸甲酯

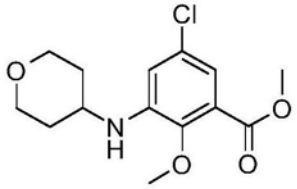
[2027]



[2028] 在室温下,向 5- 氯 -2- 甲氧基 -3- 硝基苯甲酸甲酯(1.21g,4.93mmol)的甲醇(50mL)溶液中依次加入氯化铵(2.59g,49.2mmol)和去离子水(25mL)。将所得混合物加热到 70℃后加入铁(1.65g,29.6mmol)。反应混合物在 70℃搅拌的 2 小时中,颜色变深。将所得混合物冷却到室温并通过硅胶过滤。滤饼用 MeOH (50mL)洗涤,滤液减压浓缩。将残余物溶解于去离子水(25mL)和 EtOAc (25mL)中。两相分离,水相用 EtOAc 萃取(2x25mL)。合并的萃取液用盐水洗涤(25mL),用 $MgSO_4$ 干燥,过滤并减压浓缩,得到粘性的褐色油状的标题化合物(892mg,67%)。所得原料使用时没有进一步纯化。LC-MS89%,1.75 分钟 (3 分钟 LC-MS 方法),m/z=216.3/218.0,^{1}H NMR(500MHz,$CDCl_3$) δ ppm7.16(1H,d,J=2.52Hz),6.87(1H,d,J=2.52Hz),4.03(2H,br.s.),3.89-3.94(3H,m),3.84(3H,s)。

[2029] 步骤 3 :合成 5- 氯 -2- 甲氧基 -3-[(四氢吡喃 -4- 基)氨基]苯甲酸甲酯

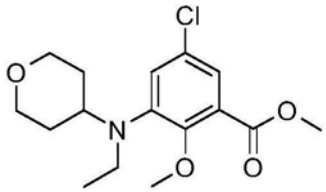
[2030]



[2031] 在室温和氮气保护下,向 3- 氨基 -5- 氯 -2- 甲氧基苯甲酸甲酯(440mg,2mmol)的 1,2- 二氯乙烷(8mL)溶液中依次加入四氢吡喃酮(0.38ml,4.0mmol)和醋酸(0.7ml,12mmol)。在室温下搅拌溶液 5 分钟后,向所得溶液加入三乙酰基硼氢化钠(1.3g,6.1mmol)。搅拌 23 小时后加入去离子水(16mL),混合物用固体 $NaHCO_3$ 中和。两相分离,水层用 EtOAc 萃取(2x16mL)。合并的萃取液用 $MgSO_4$ 干燥,过滤并减压浓缩。残余物通过 FCC(10g 硅胶,Isolute 柱,洗脱液梯度为 9:1 至 7:3 的庚烷 :EtOAc)纯化,得到白色固体状的标题化合物(439mg,72%)。LC-MS97%,m/z=300.3/302.0,^{1}H NMR(500MHz,$CDCl_3$) δ ppm7.06(1H,d,J=2.52Hz),6.73(1H,d,J=2.52Hz),4.38-4.45(1H,m),4.02(2H,dt,J=11.78,3.49Hz),3.91(3H,s),3.81(3H,s),3.54(2H,td,J=11.47,2.13Hz),3.40-3.50(1H,m),2.03(2H,br.d,J=13.70Hz),1.48-1.55(2H,m)。

[2032] 步骤 4 :合成 5- 氯 -3-[乙基 (四氢吡喃 -4- 基) 氨基]-2- 甲氧基苯甲酸甲酯

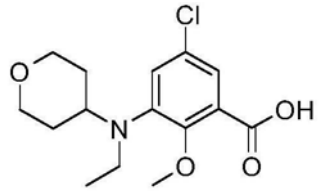
[2033]



[2034] 在室温和氮气保护下，向 5- 氯 -2- 甲氧基 -3-[(四氢吡喃 -4- 基) 氨基] 苯甲酸甲酯 (220mg，0.73mmol) 的 1,2- 二氯乙烷 (2mL) 溶液中依次加入乙醛 (82μl，1.47mmol) 和醋酸 (0.25ml，4.4mmol)。在室温下搅拌 5 分钟后，向所得溶液加入三乙酰基硼氢化钠 (0.47g，2.2mmol)。搅拌 16 小时后，向反应混合物加入乙醛 (82μl，1.47mmol)，搅拌 5 分钟后，加入三乙酰基硼氢化钠 (0.47g，2.2mmol)。搅拌 24 小时后，向反应混合物再加入乙醛 (82μl，1.47mmol)，搅拌 5 分钟后，加入三乙酰基硼氢化钠 (0.47g，2.2mmol)。反应搅拌 24 小时后，加去离子水 (10mL)，并用固体 $NaHCO_3$ 中和。两相分离，水层用 EtOAc 萃取 (2x10mL)。合并的萃取液用 $MgSO_4$ 干燥，过滤并减压浓缩。残余物通过 FCC (10g 硅胶，Isolute 柱，洗脱液梯度为 95:5 至 7:3 的庚烷 :EtOAc) 纯化，得到黄色油状的标题化合物 (127mg，53%)。LC-MS93%，m/z=328.4/330.0，^1H NMR(500MHz，$CDCl_3$) δ ppm7.35(d，J=2.6Hz，1H)，7.09(d，J=2.6Hz，1H)，3.98(dd，J=11.3，4.2Hz，2H)，3.91(s，3H)，3.85(s，3H)，3.48(tt，J=11.6，4.0Hz，1H)，3.36(td，J=11.8，1.9Hz，2H)，3.15(q，J=7.0Hz，2H)，1.78(qd，J=12.2，4.6Hz，2H)，1.72 - 1.59(m，2H)，0.99(t，J=7.0Hz，3H)。

[2035] 步骤 5 :合成 5- 氯 -3-[乙基 (四氢吡喃 -4- 基) 氨基]-2- 甲氧基苯甲酸

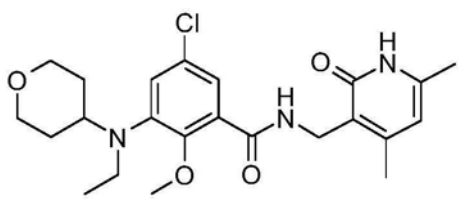
[2036]



[2037] 向 5- 氯 -3-[乙基 (四氢吡喃 -4- 基) 氨基]-2- 甲氧基苯甲酸甲酯 (127mg，0.39mmol) 的 THF (4mL) 溶液中加入 4M NaOH (3.87mL)。反应在 50℃搅拌 24 小时。用 6M HCl 将反应混合物酸化至 pH 值 2-3，用 DCM 萃取 (5x15mL)。合并的萃取液用 $MgSO_4$ 干燥，过滤并减压浓缩，得到黄色油状的标题化合物 (111mg，91%)。LC-MS80%，1.25 分钟 (3 分钟 LC-MS 法)，m/z=314.4/315.9，^1H NMR(500MHz，$CDCl_3$) δ ppm10.02 - 9.55(m，1H)，8.01 - 7.47(m，1H)，7.36 - 6.96(m，1H)，4.15 - 3.86(m，5H)，3.76(t，J=6.6Hz，2H)，3.55 - 3.12(m，3H)，1.95 - 1.59(m，4H)，1.15 - 0.88(m，3H)。

[2038] 步骤 6 :合成 5- 氯 -N-[(4，6- 二甲基 -2- 氧代 -1，2- 二氢吡啶 -3- 基) 甲基]-3-[乙基 (四氢吡喃 -4- 基) 氨基]-2- 甲氧基苯甲酰胺

[2039]

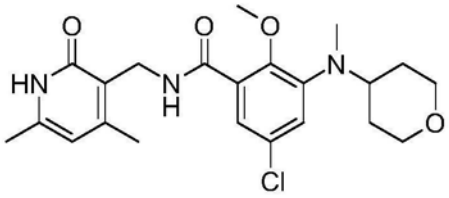


[2040] 在室温和氮气保护下，向 5- 氯 -3-[乙基 (四氢吡喃 -4- 基) 氨基]-2- 甲氧

基苯甲酸(111mg,0.35mmol)的DMF(3mL)溶液中依次加入PYBOP(220mg,0.42mmol)、N-乙基-N-(丙烷-2-基)丙烷-2-胺(92μl,0.53mmol)和3-(氨基甲基)-4,6-二甲基-1,2-二氢吡啶-2-酮(89%,66mg,0.39mmol)。在室温下搅拌1.5小时后,通过LCMS未观测到起始原料。向反应混合物中加入去离子水(20mL),所产生的沉淀经过滤收集。所得固体用去离子水洗涤(3x5mL),然后在空气中干燥。固体通过FCC(5g硅胶,Isolute柱,洗脱液梯度为100%DCM-至97:3的DCM/MeOH)进一步纯化。所得样品在真空干燥箱中干燥18小时,得到白色固体状的标题化合物(105mg,64%)。LC-MS98%,m/z=449.5/452.1,^{1}H NMR(500MHz,$CDCl_3$)δppm11.47(s,1H),8.79(t,J=5.8Hz,1H),7.73(d,J=2.6Hz,1H),7.05(d,J=2.6Hz,1H),5.92(s,1H),4.55(d,J=6.0Hz,2H),3.98(dd,J=11.3,3.8Hz,2H),3.78(s,3H),3.35(t,J=11.6Hz,3H),3.12(q,J=7.0Hz,2H),2.42(s,3H),2.28(s,3H),1.92-1.61(m,4H),0.94(t,J=7.0Hz,3H)。

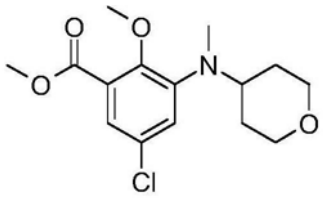
[2041] 化合物212:5-氯-N-[(4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基]-2-甲氧基-3-[甲基(四氢吡喃-4-基)氨基]苯甲酰胺

[2042]



[2043] 步骤1:合成5-氯-2-甲氧基-3-[甲基(四氢吡喃-4-基)氨基]苯甲酸甲酯

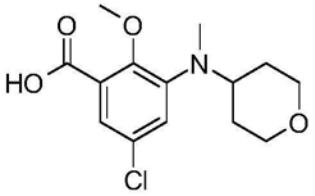
[2044]



[2045] 在室温和氮气保护下,向5-氯-2-甲氧基-3-[(四氢吡喃-4-基)氨基]苯甲酸甲酯(500mg,1.67mmol)的1,2-二氯乙烷(16mL)溶液中依次加入多聚甲醛(300mg,10mmol)和醋酸(0.57ml,10mmol)。搅拌5分钟后,向所得混合物加入三乙酰基硼氢化钠(2.12g,10mmol)。搅拌64小时后加去离子水(30mL),混合物用固体$NaHCO_3$中和,两相分离。水层用EtOAc萃取(3x15mL),合并的有机萃取液用$MgSO_4$干燥,过滤并减压浓缩。残余物通过FCC(10g硅胶,Isolute柱,洗脱液梯度为9:1至7:3的庚烷:EtOAc)纯化,得到431mg无色油状的标题化合物(82%)。LC-MS98%,m/z=314.0/316.0,^{1}H NMR(500MHz,$CDCl_3$)δppm7.30(d,J=2.5Hz,1H),7.04(d,J=2.5Hz,1H),4.00(dd,J=11.3,4.3Hz,2H),3.90(s,3H),3.82(s,3H),3.70(ddt,J=11.7,7.7,3.8Hz,1H),3.39(t,J=11.1Hz,2H),2.71(s,3H),1.84(qd,J=12.3,4.6Hz,2H),1.66-1.55(m,2H)。

[2046] 步骤2:合成5-氯-2-甲氧基-3-[甲基(四氢吡喃-4-基)氨基]苯甲酸

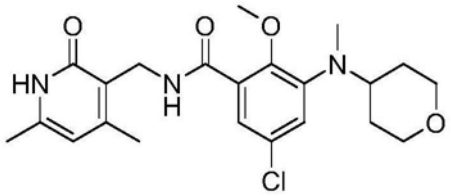
[2047]



[2048] 向 5- 氯 -2- 甲氧基 -3-[甲基 (四氢吡喃 -4- 基) 氨基] 苯甲酸甲酯(413mg,1.32mmol)的 THF(13mL)和 MeOH(2mL)溶液中加入 4M NaOH(13.16mL)。反应混合物在 50℃搅拌 16 小时。用 6M HCl 将反应混合物酸化至 pH 值 2-3,并用 DCM 萃取(5x10mL)。合并的有机萃取液用 $MgSO_4$ 干燥,过滤并减压浓缩,得到稠密的黄色油状的标题化合物(385mg,98%)。LC-MS94%,m/z=300.0/302.0,^1H NMR(500MHz,$CDCl_3$) δ ppm7.74(d,J=2.0Hz,1H),7.30 - 7.12(m,1H),4.11 - 4.02(m,2H),4.01(s,3H),3.54(t,J=11.6Hz,1H),3.40(t,J=11.3Hz,2H),2.76(s,3H),1.97 - 1.78(m,2H),1.63(d,J=11.8Hz,2H)。

[2049] 步骤 3 :合成 5- 氯 -N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基]-2- 甲氧基 -3-[甲基 (四氢吡喃 -4- 基) 氨基] 苯甲酰胺

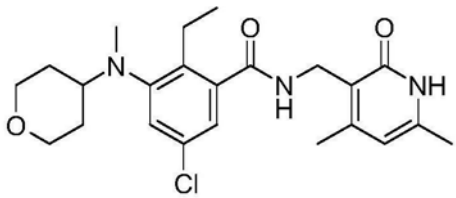
[2050]



[2051] 在室温和氮气保护下,向 5- 氯 -2- 甲氧基 -3-[甲基 (四氢吡喃 -4- 基) 氨基] 苯甲酸(200mg,0.67mmol) 的 DMF (2mL) 溶液中依次加入 HBTU(304mg,0.80mmol)、N- 乙基 -N-(丙烷 -2- 基) 丙烷 -2- 胺(174μl,1.0mmol)和 3-(氨基甲基)-4,6- 二甲基 -1,2- 二氢吡啶 -2- 酮(89%,125mg,0.73mmol)。在室温下搅拌 2 小时后,向反应混合物加入 EtOAc(30mL),然后依次用去离子水(5mL) 和饱和 $NaHCO_3$(aq) (3x5mL) 洗涤。有机相用 $MgSO_4$ 干燥,过滤并减压浓缩。残余物通过 FCC (10g 硅胶,Isolute 柱,洗脱液梯度为 100%DCM 至 96:4 的 DCM/MeOH) 纯化,得到灰白色固体状的标题化合物(182mg,63%)。LC-MS98%,m/z=434.1/436.1,^1H NMR(500MHz,$CDCl_3$) δ ppm12.52(br s,1H),8.76(t,J=5.8Hz,1H),7.69(d,J=2.6Hz,1H),7.01(d,J=2.6Hz,1H),5.94(s,1H),4.56(d,J=6.0Hz,2H),3.99(dd,J=11.2,3.9Hz,2H),3.72(s,3H),3.49(tt,J=11.5,3.7Hz,1H),3.36(t,J=11.2Hz,2H),2.67(s,3H),2.42(s,3H),2.31(s,3H),1.93 - 1.73(m,2H),1.64 - 1.52(m,2H)。

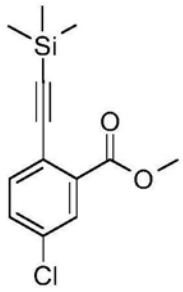
[2052] 化合物 205:5- 氯 -N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基]-2- 乙基 -3-[甲基 (四氢吡喃 -4- 基) 氨基] 苯甲酰胺

[2053]



[2054] 步骤 1 :合成 5- 氯 -2-[2-(三甲基硅基) 乙炔基] 苯甲酸甲酯

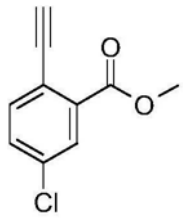
[2055]



[2056] 在室温和氮气保护下，向 2- 溴 -5- 氯苯甲酸甲酯（14.8g，59mmol）的 TEA（124ml，890mmol）溶液中加入碘化亚铜（338mg，1.78mmol）和三苯基膦（778mg，2.97mmol）。向所得混合物中通入氮气 10 分钟后，加入乙炔基（三甲基）硅烷（12.45ml，89mmol）和 $Pd(OAc)_2$（266mg，1.19mmol）。反应混合物在 50℃搅拌 20 小时，然后减压浓缩。将残余物溶解于去离子水（50mL）和 EtOAc（50mL）中，并通过硅藻土过滤。滤饼用 EtOAc 洗涤（50mL），两相分离，水层用 EtOAc 萃取（2x50mL）。合并的有机萃取液用 $MgSO_4$ 干燥，过滤并减压浓缩。残余物通过 FCC（10g 硅胶，Isolute 柱，洗脱液梯度为 99:1-85:15 的庚烷 :EtOAc）纯化，得到橙色油状的标题化合物（16.2g，102.4%），其放置固化且包含残留的庚烷。LC-MS91%，m/z=267.4/268.9，^1H NMR（500MHz，$CDCl_3$）δ ppm7.89（d，J=2.2Hz，1H），7.51（d，J=8.3Hz，1H），7.41（dd，J=8.3，2.3Hz，1H），3.92（s，3H），0.27（s，9H）。

[2057] 步骤 2 :合成 5- 氯 -2- 乙炔基苯甲酸甲酯

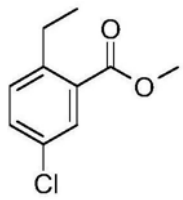
[2058]



[2059] 在室温下，向 5- 氯 -2-[2-（三甲基硅基）乙炔基] 苯甲酸甲酯（10g，37.5mmol）的 MeOH（150mL）溶液中加入 K_2CO_3（10.4g，75mmol）。反应混合物搅拌 1 小时，然后减压浓缩。将残余物溶解于去离子水（50mL）和 EtOAc（50mL）。两相分离，水层用 EtOAc 萃取（2x50mL）。合并的有机萃取液用 $MgSO_4$ 干燥，过滤并减压浓缩。残余物通过 FCC（50g 硅胶，Isolute 柱，洗脱液梯度为 95:5-9:1 的庚烷 :EtOAc）纯化，得到橙色油状的标题化合物（5.75g，55%），放置固化。所得原料包含 30% 的乙醚，未经任何进一步纯化即适合使用。LC-MS38%，m/z=195.0/196.9，^1H NMR（500MHz，$CDCl_3$）δ ppm7.93（d，J=2.2Hz，1H），7.55（d，J=8.3Hz，1H），7.45（dd，J=8.3，2.3Hz，1H），3.94（s，3H），3.43（s，1H）。

[2060] 步骤 3 :合成 5- 氯 -2- 乙基苯甲酸甲酯

[2061]

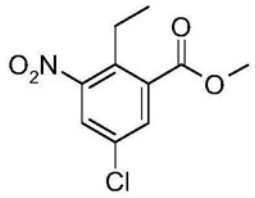


[2062] 向 5- 氯 -2- 乙炔基苯甲酸甲酯（5.34g，27mmol）的乙酸乙酯（135mL）溶液中加入

Pd/C（10%）(50% 水，2.92g，1.37mmol)。反应混合物在氢气氛中在室温下搅拌 3 小时。所得混合物通过硅藻土过滤。滤饼用 EtOAc(50mL)洗涤，滤液减压浓缩，得到棕色油状的标题化合物(5.12g，94%)，其未经任何进一步纯化即适合使用。LC-MS56%，m/z=198.9/200.9，^{1}H NMR(500MHz，$CDCl_3$) δ ppm7.84(d，J=2.3Hz，1H)，7.39(dd，J=8.3，2.3Hz，1H)，7.21(d，J=8.3Hz，1H)，3.90(s，3H)，2.94(q，J=7.5Hz，2H)，1.21(t，J=7.5Hz，3H)。

[2063] 步骤 4：合成 5- 氯 -2- 乙基 -3- 硝基苯甲酸甲酯

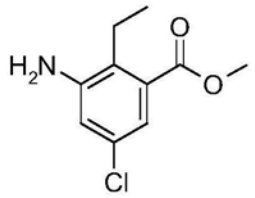
[2064]



[2065] 将 5- 氯 -2- 乙基苯甲酸甲酯(5.12g，25.8mmol)的浓硫酸(31ml，587mmol)溶液在丙酮 / 冰浴中冷却到 -5℃。将浓硝酸(2.15ml，33.5mmol）和浓硫酸(2.0ml，37.5mmol）的混合物逐滴滴加到上述混合物中，滴加时间为 15 分钟。将所得淡黄色反应混合物在 -5℃搅拌 1 小时，然后倒入冰中(500mL)，用 EtOAc 萃取(3x100mL)。合并的有机相依次用去离子水(100mL)和盐水(100mL)洗涤。有机相用 $MgSO_4$ 干燥，过滤并减压浓缩。LCMS 和 NMR 显示了约 30% 的酯水解。将所得原料粗品溶解于甲醇(30mL)中，并在氮气保护下冷却到 0℃，再慢慢滴加 $SOCl_2$(2.25ml，30.93mmol)。然后反应混合物加热回流 6 小时，减压浓缩，得到的含有原料的橙色油状的标题化合物(6.18g，98%)，其是 1:1 的 3- 硝基 :6- 硝基异构体的混合物，并包含一些乙酸乙酯。所得原料适合用于下一步骤，而不经过任何进一步的纯化。

[2066] 步骤 5：合成 3- 氨基 -5- 氯 -2- 乙基苯甲酸甲酯

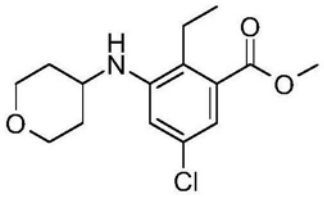
[2067]



[2068] 在室温下，向 5- 氯 -2- 乙基 -3- 硝基苯甲酸甲酯(6.18g，25.4mmol）的甲醇(250mL）溶液中依次加入氯化铵(13.3g，253mmol）和去离子水(125mL)。将所得混合物加热到 70℃后加入铁(8.50g，152mmol)。反应混合物在 70℃搅拌的 2.5 小时中，颜色变深。将所得混合物冷却至室温并通过硅胶过滤。滤饼用 MeOH（250mL）洗涤，滤液减压浓缩。将残余物溶解于饱和 $NaHCO_3$(aq)（50mL）和 EtOAc（150mL）中。两相分离，有机相用饱和 $NaHCO_3$(aq)（2x50mL）洗涤，用 $MgSO_4$ 干燥，过滤并减压浓缩。残余物通过 FCC（50g 硅胶，Isolute 柱，洗脱液梯度为 95:5-75:25 的庚烷 :EtOAc）纯化，得到 2.42g 黄色油状的 3- 氨基 -5- 氯 -2- 乙基苯甲酸甲酯粗品。所得原料用于下一步骤，没有进一步纯化。LC-MS31%，m/z=295.0，^{1}H NMR(500MHz，$CDCl_3$) δ ppm7.17(d，J=2.1Hz，1H)，6.79(d，J=2.1Hz，1H)，3.87(s，3H)，3.86 - 3.81(m，2H)，2.74(q，J=7.5Hz，2H)，1.20(t，J=7.5Hz，3H)。

[2069] 步骤 6：合成 5- 氯 -2- 乙基 -3-[（四氢吡喃 -4- 基）氨基] 苯甲酸甲酯

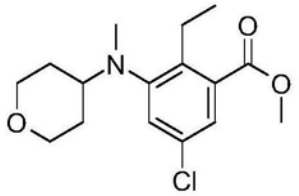
[2070]



[2071] 在室温和氮气保护下，向 3- 氨基 -5- 氯 -2- 乙基苯甲酸甲酯（1.5g，7.02mmol）的 1,2- 二氯乙烷（28mL）溶液中依次加入四氢吡喃酮（1.3ml，14.mmol）和醋酸（2.41ml，42mmol）。所得溶液在室温下搅拌 5 分钟后，加入三乙酰基硼氢化钠（4.46g，21mmol）。搅拌 20 小时后，向混合物中加入去离子水（28mL），并用固体 $NaHCO_3$ 中和。两相分离，水层用 EtOAc 萃取（2x28mL）。合并的有机萃取液用 $MgSO_4$ 干燥，过滤并减压浓缩。残余物通过 FCC（50g 硅胶，Isolute 柱，洗脱液梯度为 95:5-8:2 的庚烷 :EtOAc）纯化，得到白色固体状的 1.76g5- 氯 -2- 乙基 -3-[（四氢吡喃 -4- 基）氨基］苯甲酸甲酯粗品。所得原料用于下一步骤，没有进一步纯化。LC-MS60%，m/z=298.0/300.0，^1H NMR(500MHz，$CDCl_3$) δ ppm7.07(d，J=2.0Hz，1H)，6.71(d，J=1.9Hz，1H)，4.01(dt，J=11.8，3.4Hz，2H)，3.87(s，3H)，3.82 - 3.76(m，1H)，3.64 - 3.47(m，3H)，2.79 - 2.63(m，2H)，2.06(d，J=13.2Hz，2H)，1.55 - 1.46(m，2H)，1.18(t，J=7.5Hz，3H)。

[2072] 步骤 7 :合成 5- 氯 -2- 乙基 -3-［甲基（四氢吡喃 -4- 基）氨基］苯甲酸甲酯

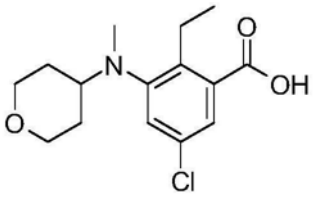
[2073]



[2074] 在室温和氮气保护下，向 5- 氯 -2- 乙基 -3-[（四氢吡喃 -4- 基）氨基］苯甲酸甲酯（350mg，1.18mmol）的 1,2- 二氯乙烷（10mL）溶液中依次加入多聚甲醛（212mg，7.05mmol）和醋酸（0.4ml，7.05mmol）。搅拌 5 分钟后，向所得混合物加入三乙酰基硼氢化钠（1.49g，7.05mmol）。搅拌 23 小时后，向反应混合物再加入多聚甲醛（212mg，7.05mmol），搅拌 10 分钟后，加入三乙酰基硼氢化钠（1.49g，7.05mmol）。搅拌 3 小时后，加入去离子水（15mL），所得混合物用固体 $NaHCO_3$ 中和，分离两相。水层用 EtOAc 萃取（2x15mL），合并的有机萃取液用 $MgSO_4$ 干燥，过滤并减压浓缩。残余物通过 FCC（10g 硅胶，Isolute 柱，洗脱液梯度为 99:1-85:15 的庚烷 :EtOAc）纯化，得到无色油状的标题化合物（334mg）。所得的产品包含约 22% 的乙酸乙酯。所得原料用于下一步骤，没有进一步纯 化。LC-MS56%，m/z=312.0/314.0，^1H NMR(500MHz，$CDCl_3$) δ ppm7.52(d，J=2.2Hz，1H)，7.24(d，J=2.2Hz，1H)，4.01 - 3.93(m，2H)，3.89(s，3H)，3.34(td，J=11.7，2.3Hz，2H)，3.06 - 2.96(m，2H)，2.94 - 2.85(m，1H)，2.61(s，3H)，1.76 - 1.59(m，4H)，1.10(t，J=7.4Hz，3H)。

[2075] 步骤 8 :合成 5- 氯 -2- 乙基 -3-［甲基（四氢吡喃 -4- 基）氨基］苯甲酸

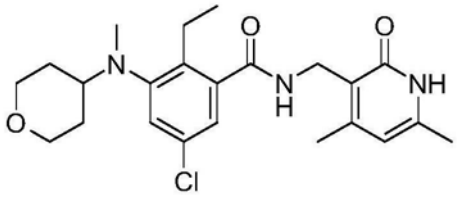
[2076]



[2077] 向 5- 氯 -2- 乙基 -3-[甲基 (四氢吡喃 -4- 基) 氨基] 苯甲酸甲酯(334mg, 1.07mmol)的 THF (11mL)溶液中加入 4M NaOH (10.7mL)。反应混合物在 50℃下搅拌 27 小时。向反应混合物中加入 MeOH (5mL),继续在 50℃搅拌 21 小时。用 6MHCl 将反应混合物酸化至 pH 值 2-3,用 DCM 萃取(5x10mL)。合并的有机萃取液用 $MgSO_4$ 干燥,过滤并减压浓缩,得到 311mg 为橙色油状物的标题化合物,放置固化。所得原料用于下一步骤,没有进一步纯化。LC-MS79%,2.01 分钟 (3 分钟 LC-MS 法),m/z=298.0/300.0,^{1}H NMR(500MHz,$CDCl_3$) δ ppm7.72(d,J=2.1Hz,1H),7.37 - 7.27(m,1H),4.00(brd,J=11.1Hz,2H),3.36(td,J=11.6,2.0Hz,2H),3.11(q,J=7.4Hz,2H),2.94(t,J=10.6Hz,1H),2.64(s,3H),1.78 - 1.56-(m,4H),1.15(t,J=7.4Hz,3H)。

[2078] 步骤 9 :合成 5- 氯 -N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基]-2- 乙基 -3-[甲基 (四氢吡喃 -4- 基) 氨基] 苯甲酰胺

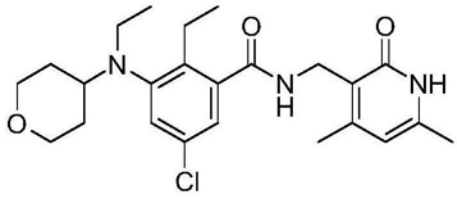
[2079]



[2080] 在室温和氮气保护下,向 5- 氯 -2- 乙基 -3-[甲基 (四氢吡喃 -4- 基) 氨基] 苯甲酸(100mg,0.34mmol) 的 DMF (2mL) 溶液中依次加入 HBTU(153mg,0.4mmol)、N- 乙基 -N-(丙烷 -2- 基) 丙烷 -2- 胺(88μl,0.5mmol)和 3-(氨基甲基)-4,6- 二甲基 -1,2- 二氢吡啶 -2- 酮(89%,63mg,0.37mmol)。在室温下搅拌 3 小时后,向反应混合物加入 EtOAc (30mL),依次用去离子水(5mL) 和饱和 $NaHCO_3$(aq) (3x5mL) 洗涤。有机相用 $MgSO_4$ 干燥,过滤并减压浓缩。残余物通过 FCC (5g 硅胶 , Isolute 柱,洗脱液梯度为 100%DCM 至 96:4 的 DCM :MeOH) 纯化,得到灰白色固体状的标题化合物(94mg,65%)。LC-MS95%,m/z=432.1/434.1,^{1}H NMR(500MHz,$CDCl_3$) δ ppm11.34(s,1H),7.14 - 7.08(m,2H),7.03(d,J=2.0Hz,1H),5.95(s,1H),4.52(d,J=5.8Hz,2H),3.96(d,J=11.2Hz,2H),3.33(td,J=11.4,2.3Hz,2H),2.96 - 2.85(m,1H),2.79(q,J=7.4Hz,2H),2.58(s,3H),2.39(s,3H),2.23(s,3H),1.73 - 1.62(m,4H),1.05(t,J=7.4Hz,3H)。

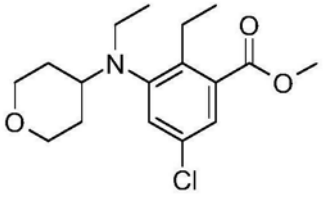
[2081] 化合物 206 :5- 氯 -N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基]-2- 乙基 -3-[乙基 (四氢吡喃 -4- 基) 氨基] 苯甲酰胺

[2082]



[2083] 步骤 1 :合成 5- 氯 -2- 乙基 -3-[乙基 (四氢吡喃 -4- 基) 氨基] 苯甲酸甲酯

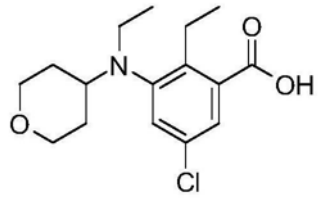
[2084]



[2085] 在室温和氮气保护下,向 5- 氯 -2- 乙基 -3-[(四氢吡喃 -4- 基) 氨基] 苯甲酸甲酯 (350mg,1.18mmol) 的 1,2- 二氯乙烷 (10mL) 溶液中依次加入乙醛 (0.66ml,11.8mmol) 和醋酸 (0.4ml,7.05mmol)。在室温下搅拌 5 分钟后,向所得溶液加入三乙酰基硼氢化钠 (2.49g,11.8mmol)。搅拌 23 小时后,向该深色的反应混合物中加入乙醛 (0.66ml,11.8mmol),搅拌 10 分钟后,添加三乙酰基硼氢化钠 (2.49g,11.8mmol)。搅拌 3 小时后,向所得混合物中加入去离子水 (15mL),用固体 $NaHCO_3$ 中和。两相分离,水层用 EtOAc 萃取 (2x15mL)。合并的有机萃取液用 $MgSO_4$ 干燥,过滤并减压浓缩。残余物通过 FCC(10g 硅胶,Isolute 柱,洗脱液梯度为 99:1-85:15 的庚烷 :EtOAc) 纯化,得到无色油状的标题化合物 (317mg)。所得产品包含 ~ 25% 乙酸乙酯。所得原料用于下一步骤,没有进一步纯化。LC-MS55%,2m/z=326.0/328.0,^1H NMR(500MHz,$CDCl_3$) δ ppm7.52(d,J=2.2Hz,1H),7.23(d,J=2.2Hz,1H),3.97(d,J=11.1Hz,2H),3.90(s,3H),3.32(td,J=11.6,2.5Hz,2H),3.04(q,J=7.1Hz,4H),2.93(ddd,J=15.1,10.8,4.3Hz,1H),1.76 - 1.62(m,4H),1.08(t,J=7.4Hz,3H),0.88(t,J=7.1Hz,3H)。

[2086] 步骤 2 :合成 5- 氯 -N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基]-2- 乙基 -3-[乙基 (四氢吡喃 -4- 基) 氨基] 苯甲酰胺

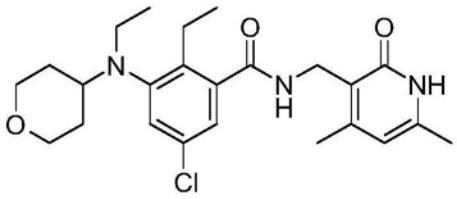
[2087]



[2088] 向 5- 氯 -2- 乙基 -3-[乙基 (四氢吡喃 -4- 基) 氨基] 苯甲酸甲酯 (317mg,0.97mmol) 的 THF (10mL) 溶液中加入 4M NaOH (9.73mL)。反应混合物在 50℃搅拌 27 小时。向反应混合物加入 MeOH (5mL),在 50℃继续搅拌 21 小时。用 6M HCl 将反应混合物酸化至 pH 值 2-3,用 DCM 萃取 (5x10mL)。合并的有机萃取液用 $MgSO_4$ 干燥,过滤并减压浓缩,得到橙色油状的标题化合物 (289mg),放置固化。所得原料用于下一步骤,没有进一步纯化。LC-MS79%,m/z=311.95/313.95,^1H NMR(500MHz,$CDCl_3$) δ ppm7.73(d,J=1.7Hz,1H),7.29(d,J=1.8Hz,1H),3.99(d,J=11.0Hz,2H),3.38 - 3.29(m,2H),3.20 - 3.03(m,4H),3.02 - 2.91(m,1H),1.78 - 1.61(m,4H),1.13(t,J=7.4Hz,3H),0.91(t,J=7.0Hz,3H)。

[2089] 步骤 3 :合成 5- 氯 -N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基]-2- 乙基 -3-[乙基 (四氢吡喃 -4- 基) 氨基] 苯甲酰胺

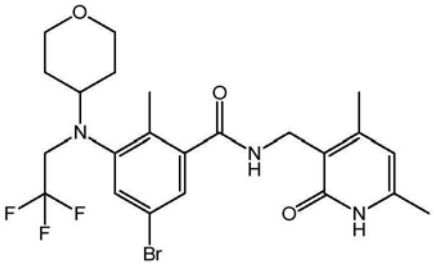
[2090]



[2091] 在室温和氮气保护下，向 5- 氯 -2- 乙基 -3-[乙基（四氢吡喃 -4- 基）氨基] 苯甲酸（100mg，0.32mmol）的 DMF（2mL）溶液中依次加入 HBTU(146mg，0.38mmol)、N- 乙基 -N-（丙烷 -2- 基）丙烷 -2- 胺（84μl，0.48mmol)和 3-（氨基甲基）-4,6- 二甲基 -1,2- 二氢吡啶 -2- 酮（89%，60.3mg，0.35mmol)。在室温下搅拌 3 小时后，向反应混合物加入 EtOAc（30mL)，依次用去离子水（5mL）和饱和 $NaHCO_3$(aq)（3x5mL）洗涤。有机相用 $MgSO_4$ 干燥，过滤并减压浓缩。残余物通过 FCC（5g 硅胶，Isolute 柱，洗脱液梯度为 100%EtOAc 至 97:3 的 EtOAc :MeOH）纯化，得到白色固体状的标题化合物（90mg，63%)。LC-MS97%，m/z=446.1/448.2，^{1}H NMR(500MHz，$CDCl_3$) δ ppm11.93(s,1H)，7.14(t,J=5.7Hz,1H)，7.10(d,J=2.0Hz,1H)，7.04(d,J=2.0Hz,1H)，5.95(s,1H)，4.52(d,J=5.8Hz,2H)，3.95(d,J=11.2Hz,2H)，3.30(td,J=11.3,3.6Hz,2H)，3.01(q,J=7.0Hz,2H)，2.93(ddd,J=15.3,10.0,5.3Hz,1H)，2.83(q,J=7.4Hz,2H)，2.38(s,3H)，2.22(s,3H)，1.71 - 1.63(m,4H)，1.02(t,J=7.5Hz,3H)，0.86(t,J=7.0Hz,3H)。

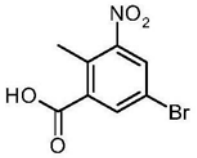
[2092] 化合物 243 :5- 溴 -N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基]-2- 甲基 3-[（四氢吡喃 -4- 基）(2,2,2- 三氟乙基）氨基] 苯甲酰胺

[2093]



[2094] 步骤 1 :合成 5- 溴 -2- 甲基 -3- 硝基苯甲酸

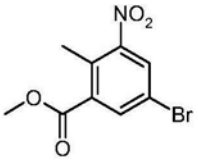
[2095]



[2096] 将 5- 溴 -2- 甲基苯甲酸（5.0g，23mmol）的浓硫酸（27ml，512mmol）溶液在丙酮 / 冰浴中冷却至 -5℃。在 -5 至 0℃下，向反应混合物中逐滴滴加浓硝酸（1.9ml，30mmol)和浓硫酸（2.8ml，52mmol)的混合物，滴加时间为 15 分钟。所得黄色反应混合物在 -5℃搅拌 2 小时，在此期间形成黄色沉淀。将反应混合物倒入冰中（150g)，沉淀物经过滤收集。将所得沉淀物在空气中晾干，得到淡黄色固体状的标题化合物（5.5g，52%)。^{1}H NMR(500MHz，DMSO-d_6) δ ppm8.29(s,1H)8.13(d,J=1.58Hz,1H)2.43(s,3H)。

[2097] 步骤 2 :合成 5- 溴 -2- 甲基 -3- 硝基苯甲酸甲酯

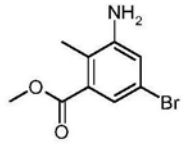
[2098]



[2099] 在氮气保护下，向 5- 溴 -2- 甲基 -3- 硝基苯甲酸（5.5g，21mmol）的 DMF（42mL）溶液中依次加入 Na_2CO_3（3.4g，32mmol）和碘甲烷（2.0ml，32mmol）。反应混合物在室温下搅拌 2 小时。所得混合物用去离子水（150mL）稀释，用 EtOAc 萃取（4x50mL）。合并的有机相用饱和 $NaHCO_3$(aq)（2x50mL)洗涤，用 $MgSO_4$ 干燥，过滤并真空浓缩，得到黄色油状的标题化合物（6.3g，61%）。^1H NMR(500MHz,$CDCl_3$) δ ppm7.38(d,J=2.05Hz,1H)7.23(d,J=2.05Hz,1H)3.20(s,3H)1.82(s,3H)。

[2100] 步骤 3 ：合成 3- 氨基 -5- 溴 -2- 甲基苯甲酸甲酯

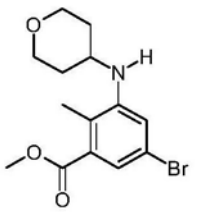
[2101]



[2102] 向 5- 溴 -2- 甲基 -3- 硝基苯甲酸甲酯（6.3g，21mmol）的甲醇（150mL）溶液中依次加入氯化铵（11.0g，210mmol）和去离子水（75mL）。将所得混合物加热到 70℃后，向其加入铁（7.0g，125mmol）。将反应混合物在 70℃搅拌 2 小时，冷却到室温，通过硅胶过滤。滤饼用 MeOH（150mL）洗涤，滤液在真空中浓缩。将残余物溶解于饱和 $NaHCO_3$(aq)（50mL）和 EtOAc（150mL）中。两相分离，有机相用饱和 $NaHCO_3$(aq)（3x50mL）洗涤，用 $MgSO_4$ 干燥，过滤并在真空中浓缩。残余物通过快速柱层析（50g 硅胶 Isolute 柱，5-20% 的 EtOAc ：庚烷）纯化，得到稠密的淡黄色油状的标题化合物（3.0g，51%）。LC-MS87%,m/z=243.9,244.9,245.9,246.9;^1H NMR(500MHz,$CDCl_3$) δ ppm7.34(d,J=1.89Hz,1H)6.95(d,J=1.89Hz,1H)3.88(s,3H)3.80(br.s.,2H)2.29(s,3H)。

[2103] 步骤 4 ：合成 5- 溴 -2- 甲基 -3-[（四氢吡喃 -4- 基）氨基］苯甲酸甲酯

[2104]

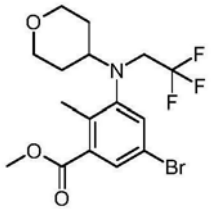


[2105] 在氮气保护下，向 3- 氨基 -5- 溴 -2- 甲基苯甲酸甲酯（3.0g，12mmol）的 1,2- 二氯乙烷（48mL）溶液中依次加入四氢吡喃酮（2.3ml，25mmol）和醋酸（4.2ml，74mmol）。搅拌 5 分钟后，向反应混合物加入三乙酰基硼氢化钠（7.8g，37mmol）。搅拌 64 小时后，向混合物中加入去离子水（100mL），用固体 $NaHCO_3$ 中和。两相分离，水层用 EtOAc（4x50mL）萃取。合并的有机萃取液用 $MgSO_4$ 干燥，过滤并在真空中浓缩。残余物通过快速柱层析（50g 硅胶，Isolute 柱，10－30%EtOAc: 庚烷）纯化，得到白色固体状的标题化合物（3.5g85%）。LC-MS99.8m/z=327.9,328.9,329.9,330.9;^1H NMR(500MHz,$CDCl_3$) δ ppm7.24(d,J=1.73Hz,1H)6.85(d,J=1.58Hz,1H)4.03(dt,J=11.82,3.31Hz,2H)3.88(s,3H)3.66(br.s.,1H)3.56(

td,J=11.55,1.97Hz,2H)3.47-3.55(m,1H)2.24(s,3H)2.06(d,J=13.56Hz,2H)1.47-1.60(m,2H)。

[2106] 步骤5:合成5-溴-2-甲基-3-[(四氢吡喃-4-基)(2,2,2-三氟乙基)氨基]苯甲酸甲酯

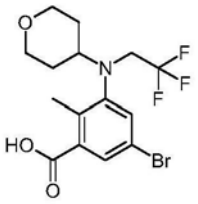
[2107]



[2108] 在5分钟中分批向5-溴-2-甲基-3-[(四氢吡喃-4-基)氨基]苯甲酸甲酯(500mg,1.5mmol)和TFA(15mL)的溶液中加入$NaBH_4$(1.0g,26mmol)。反应混合物在室温下搅拌2小时,然后加热至50℃ 3小时,并在25分钟内用另一小份$NaBH_4$(300mg)处理。然后反应混合物在60℃加热2小时,在室温下搅拌17小时。用TFA(5mL)和$NaBH_4$(200mg)处理该反应混合物,并再加热至60℃ 3.5小时。然后在15分钟中,加入另一小份$NaBH_4$(200mg)和TFA(5mL),并继续加热3小时,在室温中放置过夜。将反应混合物倒入冰(75mL)中,并搅拌直到冰融化。然后向反应混合物加入6M NaOH(aq)(40mL)进行碱化,然后用1M HCl(aq)(40mL)将pH值调到7。所得白色悬浮液经过滤来收集,所得固体用水洗涤(20mL),并在40℃下真空干燥3小时,得到白色固体状的标题化合物(577mg,91%)。LC-MS98%,),m/z=409.90,410.9,411.90,412.9;^{1}H NMR(500MHz,$CDCl_3$)δppm7.80(d,J=1.73Hz,1H)7.41(d,J=1.73Hz,1H)4.01(dd,J=11.51,4.10Hz,2H)3.91(s,3H)3.64(d,J=5.20Hz,2H)3.32(t,J=11.82Hz,2H)2.99(tt,J=11.43,3.63Hz,1H)2.48(s,3H)1.80(dd,J=12.53,1.50Hz,2H)1.54-1.62(m,2H)。

[2109] 步骤6:合成5-溴-2-甲基-3-[(四氢吡喃-4-基)(2,2,2-三氟乙基)氨基]苯甲酸

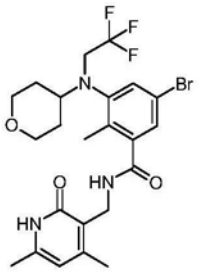
[2110]



[2111] 向搅拌后的5-溴-2-甲基-3-[(四氢吡喃-4-基)(2,2,2-三氟乙基)氨基]苯甲酸甲酯(572mg,1.4mmol)的THF(14mL)和MeOH(2.1mL)的混合溶液中加入4M NaOH(aq)(13.9mL)。反应混合物在50℃搅拌5.5小时后,再室温下搅拌17小时。在真空中浓缩除去THF,含水残余物用6M HCl(9.5mL)酸化至pH值4。所得悬浮液在室温中放置20分钟,过滤收集固体。滤饼用水(20mL)洗涤后在高度真空中干燥2小时,得到白色固体状的标题化合物(507mg,90%)。LC-MS98%,m/z=395.9,396.9,397.9,398.9;^{1}H NMR(500MHz,$CDCl_3$)δppm7.97(d,J=1.73Hz,1H)7.48(d,J=1.73Hz,1H)4.02(dd,J=11.35,3.94Hz,2H)3.65(br.s,2H)3.33(t,J=11.59Hz,2H)3.00(tt,J=11.49,3.80Hz,1H)2.55(s,3H)1.82(d,J=11.98Hz,2H)1.55-1.69(m,2H)。观察不到OH。

[2112] 步骤 7 :合成 5- 溴 -N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基]-2- 甲基 -3-[(四氢吡喃 -4- 基)(2,2,2- 三氟乙基) 氨基] 苯甲酰胺

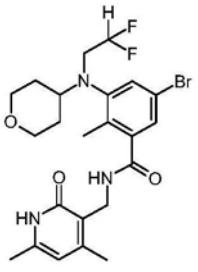
[2113]



[2114] 在 0℃和氮气保护下,向搅拌后的 5- 溴 -2- 甲基 -3-[(四氢吡喃 -4- 基)(2,2,2- 三氟乙基) 氨基] 苯甲酸甲酯(250mg,0.63mmol)的无水 DMF (3.0mL)溶液中逐滴加入 HATU (288mg,0.76mmol)和 DIPEA (220μl,1.3mmol)。搅拌 5 分钟后,向所得溶液加入 3-(氨基甲基)-4,6- 二甲基 -1,2- 二氢吡啶 -2- 酮(89%,119mg,0.69mmol)。所得悬浮液在 0℃搅拌 20 分钟,然后室温下搅拌 16.5 小时。向反应混合物中加入 3-(氨基甲基)-4,6- 二甲基 -1,2- 二氢吡啶 -2- 酮(30mg)。继续搅拌 23 小时,反应混合物在水(30mL)和 CH_2Cl_2 (20mL)之间分配。两相分离,水相 CH_2Cl_2 (3x20mL)萃取。合并的有机相依次用饱和 $NaHCO_3$ 溶液(50mL)、水(60mL)和盐水(2x40mL)洗涤,用 $MgSO_4$ 干燥,过滤并真空浓缩。粗制残余物经快速柱层析(10g SNAP 柱, Isolera,0-10%MeOH/CH_2Cl_2)纯化,在乙醚(10mL)中超声波研磨。所得沉淀物经过滤收集,真空干燥,得到白色固体状的标题化合物(249mg,74%)。LC-MS100%,m/z=530.0,531.0,532.0,533.0;^{1}H NMR(500MHz, 氘代丙酮) δ 10.67(s,1H),7.55(d,J=1.8Hz,2H),7.27(d,J=1.9Hz,1H),5.90(s,1H),4.40(d,J=5.5Hz,2H),3.90(dd,J=11.2,4.6Hz,4H),3.28(t,J=11.6Hz,2H),3.07 - 2.97(m,1H),2.32(s,3H),2.29(s,3H),2.24(s,3H),1.76(dd,J=12.3,1.6Hz,2H),1.61(qd,J=12.0,4.5Hz,2H)。

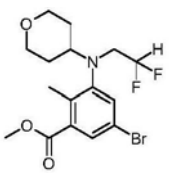
[2115] 化合物 244 :5- 溴 -3-[(2,2- 二氟乙基)(四氢吡喃 -4- 基) 氨基]-N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基]-2- 甲基苯甲酰胺

[2116]



[2117] 步骤 1 :合成 5- 溴 -3-[(2,2- 二氟乙基)(四氢吡喃 -4- 基) 氨基]-2- 甲基苯甲酸甲酯

[2118]

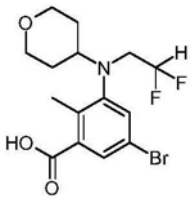


[2119] 在 0℃时,在 12 分钟内向搅拌后的 5- 溴 -2- 甲基 -3-[(四氢吡喃 -4- 基)

氨基]苯甲酸甲酯(500mg,1.5mmol)的二氟醋酸(15mL)溶液中分批加入硼氢化钠(1000mg,26mmol)。将反应混合物升温至50℃并搅拌4小时。将反应混合物冷却到室温,倒入冰中(130mL),保持5分钟。向所得混合物加入6M NaOH(aq)(35mL)进行碱化,再用1M HCl(aq)(20mL)将pH值调至7。所得悬浮液放置直到溶液澄清,过滤收集固体,在40℃真空中干燥,得到白色固体状的标题化合物(572mg,96%)。LC-MS100%,m/z=391.9,392.9,393.9,394.9;^{1}H NMR(500MHz,$CDCl_3$)δppm7.79(d,J=1.89Hz,1H)7.44(d,J=1.89Hz,1H)5.44-5.71(m,1H)4.00(dd,J=11.51,4.10Hz,2H)3.91(s,3H)3.41(td,J=13.99,4.18Hz,2H)3.32(t,J=11.27Hz,2H)2.97(tt,J=11.37,3.84Hz,1H)2.47(s,3H)1.72-1.81(m,2H)1.59-1.67(m,2H)。

[2120] 步骤2:合成5-溴-3-[(2,2-二氟乙基)(四氢吡喃-4-基)氨基]-2-甲基苯甲酸

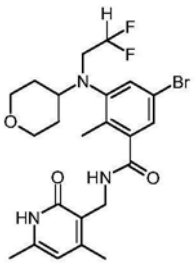
[2121]



[2122] 向搅拌后的5-溴-3-[(2,2-二氟乙基)(四氢吡喃-4-基)氨基]-2-甲基苯甲酸甲酯(571mg,1.5mmol)的THF(14.6mL)和MeOH(2.2mL)的混合溶液中加入4M NaOH(14.6mL)。反应混合物在50℃搅拌7小时。停止加热,反应混合物在室温下搅拌16.5小时。在真空中除去THF,用6M HCl(aq)(10mL)将剩余水溶液酸化至pH值4,同时加冰冷却。过滤收集固体,用水洗涤(20mL),真空干燥,得到淡米色固体状的标题化合物(526mg,96%)。LC-MS100%,m/z=377.9,378.9,379.9,380.9;^{1}H NMR(500MHz,$CDCl_3$)δppm7.91(d,J=1.58Hz,1H)7.49(d,J=1.58Hz,1H)5.43-5.75(m,1H)4.01(dd,J=11.43,3.55Hz,2H)3.42(td,J=13.95,3.78Hz,2H)3.32(t,J=11.35Hz,2H)2.98(tt,J=11.37,3.53Hz,1H)2.52(s,3H)1.77(d,J=10.88Hz,2H)1.56-1.69(m,2H)。观察不到OH。

[2123] 步骤3:合成5-溴-3-[(2,2-二氟乙基)(四氢吡喃-4-基)氨基]-N-[(4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基]-2-甲基苯甲酰胺

[2124]

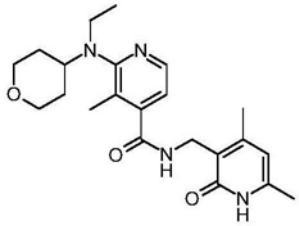


[2125] 在0℃和氮气保护下,向搅拌后的5-溴-3-[(2,2-二氟乙基)(四氢吡喃-4-基)氨基]-2-甲基苯甲酸(250mg,0.66mmol)的无水DMF(3.0mL)溶液中逐滴加入HATU(327mg,0.86mmol)和DIPEA(230μl,1.3mmol)。搅拌5分钟后,向所得溶液加入3-(氨基甲基)-4,6-二甲基-1,2-二氢吡啶-2-酮(89%,136mg,0.79mmol)。所得悬浮液在0℃搅拌20分钟,然后在室温下搅拌过夜。18小时后,向反应液加入3-(氨基甲基)-4,6-二

甲基 -1,2- 二氢吡啶 -2- 酮(25mg),继续搅拌 25 小时。反应混合物用水(30mL)和 CH_2Cl_2(30mL)稀释。两相分离,水相用 CH_2Cl_2(3x15mL)萃取。合并的有机相依次用饱和 $NaHCO_3$(aq)(45mL)、水(2x50mL)和盐水(2x50mL)洗涤,干燥($MgSO_4$),过滤并真空浓缩。残余物通过柱层析(10g SNAP 柱,Isolera,0-3%MeOH:CH_2Cl_2)纯化,然后用乙醚研磨。固体通过过滤收集,在 40℃的真空中干燥,得到灰白色固体状的标题化合物(259mg,77%)。LC-MS100%,m/z=512.0,513.0,514.0,515.0;^{1}H NMR(500MHz, 氘代丙酮)δ 10.71(s,1H),7.57 - 7.49(m,2H),7.25(d,J=1.9Hz,1H),5.91(s,1H),5.76(tt,J=56.2,4.3Hz,1H),4.40(d,J=5.5Hz,2H),3.88(dd,J=11.3,4.2Hz,2H),3.52(td,J=14.6,4.2Hz,2H),3.33 - 3.23(m,2H),3.02(tt,J=11.6,3.9Hz,1H),2.32(s,3H),2.28(s,3H),2.24(s,3H),1.73(dd,J=12.4,1.9Hz,2H),1.59(qd,J=12.2,4.5Hz,2H)。

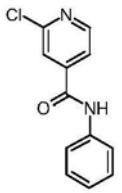
[2126] 化合物 328 :N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基]-2-[乙基(四氢吡喃 -4- 基)氨基]-3- 甲基吡啶 -4- 甲酰胺

[2127]



[2128] 步骤 1 :合成 2- 氯 -N- 苯基吡啶 -4- 甲酰胺

[2129]

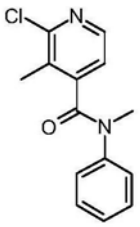


[2130] 在氮气保护下,向搅拌后的 2- 氯异烟酸(5.0g,0.03mol)的无水甲苯(100mL)和 4 滴 DMF 的悬浮液中逐滴滴加二氯亚砜(7.4ml,0.10mol)。反应混合物在 60℃搅拌 2.5 小时,在 1.5 小时内将温度逐渐增加到 100℃,并在此温度下搅拌 2 小时。反应混合物在室温下搅拌 65 小时,然后加入另外当量的二氯亚砜(2.3mL),并加热至 95℃ 40 分钟。将反应冷却到室温,然后在真空中浓缩至干燥,同无水甲苯共沸(2x10mL),得到黄色流性油状物,其直接用于下一步骤,没有进一步纯化。

[2131] 向搅拌后的苯胺(2.9ml,0.03mol)和 N- 乙基 -N-(丙烷 -2- 基)丙烷 -2- 胺(13.6ml,83mmol)的无水 THF (50mL)溶液中逐滴滴加上述制备的酸的氯代物。反应混合物在氮气氛中搅拌 19 小时。向反应混合物加入碳酸氢钠饱和溶液 (aq) (100mL)淬灭反应,并搅拌 35 分钟。两相分离,水相用乙酸乙酯萃取(3x55mL)。合并的有机萃取液依次用水(3x66mL)和盐水(80mL)洗涤,干燥($MgSO_4$),过滤并真空浓缩。将残余物悬浮于乙醚(100mL)中,进行短暂的超声处理,过滤收集产品。在室温下在高度真空中干燥 3 小时,然后在真空中放置过夜,得到白色固体状的标题化合物(6.1g,83%)。LC-MS100%,m/z=233.0,234.9;^{1}H NMR(500MHz,$CDCl_3$) δ ppm8.58(d,J=5.04Hz,1H)7.81(br. s.,1H)7.77(s,1H)7.63(d,J=7.41Hz,3H)7.42(t,J=7.96Hz,2H)7.19-7.26(m,1H)。

[2132] 步骤 2 :合成 2- 氯 -N,3- 二甲基 -N- 苯基吡啶 -4- 甲酰胺

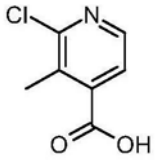
[2133]



[2134] 在 -78℃和氮气保护下,向搅拌后的 2- 氯 -N- 苯基吡啶 -4- 甲酰胺(2.0g,8.6mmol)的无水 THF (40mL)溶液中逐滴滴加 1.6M 丁基锂的正己烷溶液(11.8ml,18.9mmol),滴加时间为 24 分钟。反应混合物在 -78℃搅拌 50 分钟,然后逐滴滴加碘甲烷(1.8ml,28mmol),滴加时间为 8 分钟。反应混合物在 -78℃搅拌 1 小时,然后慢慢升至室温并搅拌 20 小时。加入水(20mL)淬灭反应,两相分离。水相用 CH_2Cl_2 (3x20mL)萃取。合并的有机相用盐水洗涤(60mL),干燥($MgSO_4$),过滤,真空浓缩,得到稠密的棕色油状的标题化合物(2.2g,93%)。LC-MS95%,m/z=261.0,263.0;^1H NMR(500MHz,$CDCl_3$) δ ppm8.03(d,J=4.89Hz,1H)7.23(d,J=7.88Hz,2H)7.16-7.21(m,1H)7.02(d,J=7.25Hz,2H)6.89(d,J=4.89Hz,1H)3.51(s,3H)2.34(s,3H)。

[2135] 步骤 3 :合成 2- 氯 -3- 甲基吡啶 -4- 羧酸

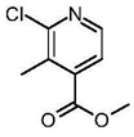
[2136]



[2137] 将 2- 氯 -N,3- 二甲基 -N- 苯基吡啶 -4- 甲酰胺(2.2g,8.5mmol)加入到浓硫酸(23.2mL)和水(16.8mL)的混合溶液中,然后加热到 130℃,保持 46 小时。之后将反应混合物升至室温并倒入冰中(200mL),同时搅拌直到冰融化。向所得混合物中分批加入固体 Na_2CO_3 (50.3g)以将其碱化 (pH 值 8)。将悬浮液过滤,加入 6M HCl(aq) (～ 1.5mL)将滤液酸化至 pH 值为 3。通过过滤收集固体,用水洗涤(20mL),在 40℃真空中干燥 10 小时,得到粉色固体状的标题化合物(779mg,54%)。LC-MS100%,m/z=171.9,173.9;^1H NMR(500MHz,MeOD) δ ppm8.30(d,J=4.89Hz,1H)7.64(d,J=5.04Hz,1H)2.58(s,3H)。

[2138] 步骤 4 :合成 2- 氯 -3- 甲基吡啶 -4- 羧酸甲酯

[2139]

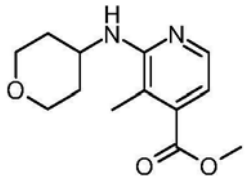


[2140] 向搅拌后的 2- 氯 -3- 甲基吡啶 -4- 羧酸(780mg,4.5mmol)的无水 DMF (5.0mL)溶液中加入碳酸钾(1.25g,9.1mmol),然后逐滴滴加碘甲烷(0.42ml,6.8mmol)。再将 4ml DMF 加入到反应混合物中,在氮气氛中在室温下搅拌 18.5 小时。在真空中除去溶剂,然后将残余物在 CH_2Cl_2 (20mL)和水(20mL)中分配。两相分离,水层用 CH_2Cl_2 萃取(3x15mL)。合并的有机相依次用水(2x30mL)和盐水(40mL)洗涤,干燥($MgSO_4$),过滤并真空浓缩。残余物通

过柱层析(10g SNAP 柱,Isolera,0-6% 乙酸乙酯 : 庚烷)纯化,得到无色油状的标题化合物(591mg,59%)。LC-MS84%,m/z=185.9,187.9;^{1}H NMR(500MHz,$CDCl_3$) δ ppm8.33(d,J=5.04Hz,1H)7.54(d,J=5.04Hz,1H)3.95(s,3H)2.60(s,3H)。

[2141] 步骤 5 :合成 3- 甲基 -2-[(四氢吡喃 -4- 基) 氨基] 吡啶 -4- 羧酸甲酯

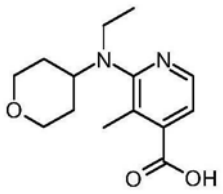
[2142]



[2143] 将氮气净化过的 $Pd(OAc)_2$(77mg,0.34mmol) 和 1,1'- 联二萘 -2,2'- 双 (二苯基膦)(430mg,0.69mmol)的 1,4- 二氧六环 (11mL)的悬浮溶液在 40℃加热 1 小时。然后向上述悬浮液加入四氢吡喃 -4- 胺(237μl,2.3mmol)、2- 氯 -3- 甲基吡啶 -4- 羧酸甲酯(213mg,1.2mmol)的经过除气的二氧六环 (2mL)溶液和 Cs_2CO_3(562mg,1.7mmol),所得红色悬浮液在 100℃加热 6 小时。冷却到室温后,反应混合物用 CH_2Cl_2(30mL) 和水(20mL) 稀释。两相分离,水相用 CH_2Cl_2 萃取(3x15mL)。合并的有机相用盐水洗涤(25mL),干燥($MgSO_4$),过滤并真空浓缩。粗制的残余物依次通过柱层析(25g SNAP 柱,Isolera,0-28% 乙酸乙酯 : 庚烷)和制备 HPLC(MeCN/Water) 纯化,得到白色晶体状的标题化合物(112mg,39%)。LC-MS100%,m/z=251.0;^{1}H NMR(500MHz,MeOD) δ ppm7.91(d,J=5.20Hz,1H)6.77(d,J=5.36Hz,1H)4.07-4.17(m,1H)3.98(dd,J=12.06,1.81Hz,2H)3.88(s,3H)3.55(td,J=11.78,1.66Hz,2H)2.22(s,3H)1.97(dd,J=12.69,1.97Hz,2H)1.62(qd,J=12.03,4.41Hz,2H)。观察不到到 NH。

[2144] 步骤 6 :合成 2-[乙基 (四氢吡喃 -4- 基) 氨基]-3- 甲基吡啶 -4- 羧酸

[2145]



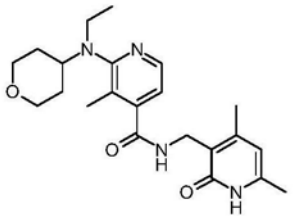
[2146] 在 0℃和氮气保护下,向搅拌后的氢化钠(60% 分散在矿物油中,16mg,0.4mmol)的无水 DMF(0.3mL)悬浮溶液中加入 3- 甲基 -2-[(四氢吡喃 -4- 基) 氨基] 吡啶 -4- 羧酸甲酯(67mg,0.27mmol)的无水 DMF (1.0mL)溶液。将反应混合物升至室温并搅拌 30 分钟。然后向反应混合物中加入碘乙烷(16μl,0.20mmol),搅拌 30 分钟,再次加入碘乙烷(16μl,0.20mmol),继续搅拌 30 分钟。在 0℃下,将反应混合物加到氢化钠(16mg,0.4mmol)的 DMF(0.3mL) 悬浮液中。一旦加完后,将所得反应混合物升至室温并搅拌 1 小时,然后加碘乙烷(2x16μl,0.40mmol)。将反应混合物继续搅拌 30 分钟。向反应混合物中加入氢化钠(16mg,0.4mmol),搅拌 45 分钟后加入碘乙烷(2x16μl,0.40mmol),搅拌 15 分钟,然后在氮气氛中、冷却条件下,加入到 4M HCl/ 二样六环 (5.0mL) 溶液中。

[2147] 然后将反应混合物在 40℃真空中浓缩,用 1M NaOH(aq)(5mL)处理,并冷却条件下加入 10 个 NaOH 小球将溶液碱化至 pH 值 12。通过添加 6M HCl 将溶液 pH 值再调到 10。所得溶液在室温下搅拌 18 小时。通过添加 1M HCl(80 滴) 将反应混合物酸化至 pH 值为 5。所得溶液用 $CHCl_3$/IPA(1:1) 萃取(6x10mL)。合并的萃取液在真空中浓缩,得到黄色油状的

标题化合物粗品(207mg)。LC-MS100%,m/z=265.1。所得原料直接用于下文所述的偶联反应。

[2148] 步骤 7 :合成 N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基]-2-[乙基 (四氢吡喃 -4- 基) 氨基]-3- 甲基吡啶 -4- 甲酰胺

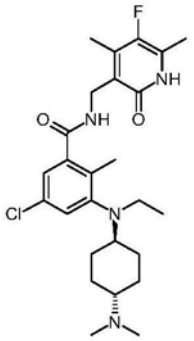
[2149]



[2150] 在 0℃和氮气保护下,向搅拌后的 2-[乙基 (四氢吡喃 -4- 基) 氨基]-3- 甲基吡啶 -4- 羧酸(20mg,0.08mmol)的无水 DMF (1.0mL)溶液中逐滴加入 HATU (37mg,0.1mmol)和 DIPEA (26μl,0.15mmol)。搅拌 10 分钟后,向所得溶液加入 3-(氨基甲基)-4,6- 二甲基 -1,2- 二氢吡啶 -2- 酮(89%,15mg,0.09mmol)。所得悬浮液在 0℃搅拌 20 分钟,然后在室温下搅拌 18.5 小时。将反应混合物冷却到 0℃,向其中加入 HATU (120mg,0.31mmol)和 DIPEA (84μl,0.48mmol)。搅拌 10 分钟后,向反应混合物加入 3-(氨基甲基)-4,6- 二甲基 -1,2- 二氢吡啶 -2- 酮(89%,49mg,0.29mmol)。反应混合物在 0℃搅拌 1 小时,去掉冰浴,在室温下搅拌 48 小时。反应混合物用水(20mL)和 CH_2Cl_2 (20mL)稀释。两相分离,水相用 CH_2Cl_2 萃取(3x15mL)。合并的有机相依次用水(2x25mL)和盐水(2x25mL)洗涤,干燥($MgSO_4$),过滤并真空浓缩。粗制的残余物通过柱层析(10g SNAP 柱,Isolera,0-40%MeOH:CH_2Cl_2 和 0-25%MeOH (包含 10%NH_4OH):CH_2Cl_2)纯化,得到的灰白色固体状标题化合物(6.7mg,产率 22%)。LC-MS100%,m/z=399.1;^1H NMR(250MHz,DMSO-d_6) δ 11.49(s,1H),8.32(t,J=4.9Hz,1H),8.14(d,J=4.9Hz,1H),6.84(d,J=4.9Hz,1H),5.86(s,1H),4.26(d,J=4.7Hz,2H),3.84(dd,J=10.3,3.5Hz,2H),3.21(dt,J=13.6,4.6Hz,5H),2.19(s,3H),2.15(s,3H),2.11(s,3H),1.62(dt,J=21.1,6.6Hz,4H),0.80(t,J=6.9Hz,3H)。

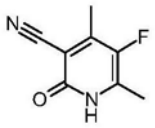
[2151] 化合物 356 :5- 氯 -3-{ 乙基 [(1r,4r)-4-(二甲基氨基) 环己基] 氨基 }-N-[(5- 氟代 -4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基]-2- 甲基苯甲酰胺

[2152]



[2153] 步骤 1 :合成 5- 氟代 -4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 甲腈

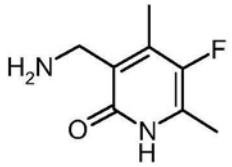
[2154]



[2155] 在 75℃下，向搅拌后的 2- 氰基乙酰胺（689mg，8.2mmol）的无水 EtOH（7.0mL）溶液中依次加入 3- 氟戊烷 -2,4- 二酮（880mg，7.5mmol）和哌啶（96μl，0.97mmol）。反应混合物在此温度下搅拌 3 小时，冷却到室温，然后在冰箱中保藏 4 天。通过过滤收集米黄色固体，用冷的 EtOH（4x0.4mL）冲洗至滤液澄清。所得浅褐色固体在 40℃真空中干燥 5 小时，得到米黄色固体状的标题化合物（733mg，58%）。LC-MS97%，m/z=166.9，^{1}H NMR（500MHz，$CDCl_3$）δ ppm13.67（br. s.，1H）2.46（d，J=2.05Hz，3H）2.45（d，J=2.84Hz，3H）。

[2156] 步骤 2：合成 3-（氨基甲基）-5- 氟代 -4,6- 二甲基 -1,2- 二氢吡啶 -2- 酮

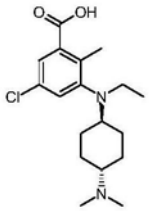
[2157]



[2158] 将 0.05M5- 氟代 -4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 甲腈（731mg，4.4mmol）的 1.75M NH_3/MeOH（87mL）溶液在 80℃和 50bar 下，以 1ml/min 的流速通过 H-Cube 流动氢化器。将所得溶液真空浓缩。将所得固体分为 2 批，将其中 350mg 粗产品通过柱层析（25g SNAP 柱，Isolera，0-25%MeOH（包含 10%NH_4OH）:CH_2Cl_2）纯化，得到灰白色固体状的标题化合物（307mg，20%）和产品：起始原料为 1:1 的混合物。LC-MS（ELS）100%，m/z=170.9，^{1}H NMR（500MHz，$CDCl_3$）δ ppm3.79（s，2H）2.31（d，J=2.84Hz，3H）2.25（d，J=2.05Hz，3H）。

[2159] 步骤 3：合成 5- 氯 -3-{ 乙基 [(1r,4r)-4-（二甲基氨基）环己基] 氨基 }-2- 甲基苯甲酸

[2160]

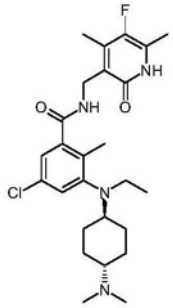


[2161] 向搅拌后的 5- 氯 -3-{ 乙基 [(1r,4r)-4-（二甲基氨基）环己基] 氨基 }-2- 甲基苯甲酸甲酯（1.0g，2.8mmol）的 THF（21mL）溶液依次加入 4M NaOH（aq）（21.3ml，85.0mmol）和 MeOH（8.0mL）。所得溶液在 50℃搅拌 16.5 小时，然后冷却到室温。在真空中除去有机溶剂，剩余的水相用 6M HCl（aq）（14mL）调至 pH 值至 7，再用 0.1M HCl（aq）（24mL）调至 pH 值至 4。所得混合物用乙酸乙酯萃取（3x35mL）。水相萃取液再用 $CHCl_3$:IPA（1:1）的混合液萃取（3x30mL）。将合并的 $CHCl_3$:IPA 萃取液干燥（$MgSO_4$），过滤并真空浓缩，然后在高度真空下彻底干燥。将所得固体同甲苯共沸（3x20mL）。将 CH_2Cl_2（10mL）加入到样品中，真空浓缩并在高度真空下进一步干燥数小时。得到白色固体状的标题化合物（831mg，88%）。LC-MS92m/z=339.0，341.0；^{1}H NMR（500MHz，$CDCl_3$）δ ppm12.21（s，1H）7.69（d，J=2.05Hz，1H）7.22-7.26（m，1H）2.99-3.11（m，3H）2.69-2.79（m，7H）2.47（s，3H）2.28（d，J=11.98Hz，2H）2.

05(d,J=13.08Hz,2H)1.35-1.65(m,4H)0.88(t,J=7.01Hz,3H)。

[2162] 步骤 4：合成 5- 氯 -3-{ 乙基 [(1r,4r)-4-(二甲基氨基) 环己基] 氨基 }-N-[(5- 氟代 -4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基]-2- 甲基苯甲酰胺

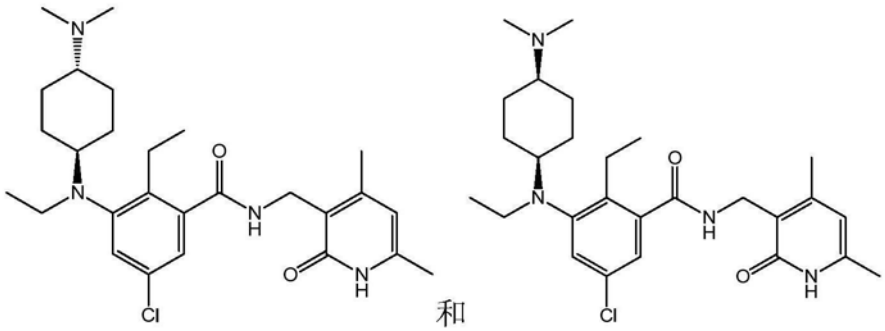
[2163]



[2164] 在 0℃和氮气保护下，向搅拌后的 5- 氯 -3-{ 乙基 [(1r,4r)-4-(二甲基氨基) 环己基] 氨基 }-2- 甲基苯甲酸（100mg，0.27mmol）的无水 DMF（2.0mL）溶液中逐滴加入 HATU（121mg，0.32mmol）和 DIPEA（93μl，0.53mmol）。搅拌 10 分钟后，向所得溶液加入 3-(氨基甲基)-5- 氟代 -4,6- 二甲基 -1,2- 二氢吡啶 -2- 酮（50%，99mg，0.29mmol）。所得悬浮液在 0℃搅拌 1 小时，再在室温下搅拌 17 小时。将反应混合物在水（15mL）和 CH_2Cl_2（20mL）之间分配。两相分离，水相用 CH_2Cl_2 萃取（2x15mL）。合并的有机相依次用饱和 $NaHCO_3$(aq)（30mL）、水（2x25mL）和盐水（20mL）洗涤，干燥（$MgSO_4$），过滤并真空浓缩。残留的粗品通过快速柱层析（10g SNAP 柱，Isolera，0-29%MeOH:CH_2Cl_2）纯化，得到浅褐色固体状的标题化合物（68mg，52%）。LC-MS99%，m/z=491.1，493.1；^{1}H NMR(500MHz,MeOD-d4) δ 7.17(d,J=1.9Hz,1H),7.02(d,J=2.0Hz,1H),4.59(s,1H),4.44(s,2H),3.06(q,J=7.0Hz,2H),2.69(tt,J=12.1,3.2Hz,1H),2.41 - 2.29(m,10H),2.24(d,J=2.8Hz,3H),2.20(s,3H),1.91(dd,J=27.7,12.2Hz,4H),1.44(q,J=12.3,11.1Hz,2H),1.30 - 1.20(m,2H),0.83(t,J=7.0Hz,3H)。一个质子被假定为与溶剂峰一致。

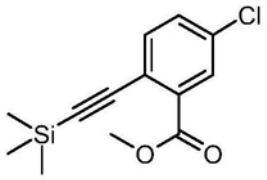
[2165] 化合物 347：5- 氯 -N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基]-2- 乙基 -3-{ 乙基 [(1r,4r)-4-(二甲基氨基) 环己基] 氨基 } 苯甲酰胺和化合物 348：5- 氯 -N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基]-2- 乙基 -3-{ 乙基 [(1s,4s)-4-(二甲基氨基) 环己基] 氨基 } 苯甲酰胺

[2166]



[2167] 步骤 1：合成 5- 氯 -2-[2-(三甲基硅基) 乙炔基] 苯甲酸甲酯

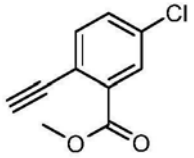
[2168]



[2169] 在室温和氮气保护下，向搅拌后的2-溴-5-氯苯甲酸甲酯(14.8g，59mmol)的三乙胺(124ml，890mmol)溶液中加入碘化铜(339mg，1.8mmol)和三苯基膦(778mg，3.0mmol)。所得混合物用氮气净化后，向其加入乙炔基(三甲基)硅烷(12.5ml，89mmol)和$Pd(OAc)_2$(266mg，1.2mmol)。反应混合物在50℃搅拌20小时，并真空浓缩。将残余物溶解于去离子水(50mL)和EtOAc(50mL)中，并通过硅藻土过滤。滤饼用EtOAc洗涤(50mL)，然后两相分离，水层用EtOAc萃取(2x50mL)。合并的有机萃取液用$MgSO_4$干燥，过滤并在真空中浓缩。残余物通过柱层析(10g硅胶，Isolute柱，1-15%EtOAc:庚烷)纯化，得到橙色固体状的标题化合物(16.2g，93%)。LC-MS91%，m/z=267.4，268.9；^1H NMR(500MHz，$CDCl_3$) δ ppm7.90(d，J=2.21Hz，1H)7.52(d，J=8.35Hz，1H)7.42(dd，J=8.28，2.29Hz，1H)3.93(s，3H)0.28(s，9H)。

[2170] 步骤2：合成5-氯-2-乙炔基苯甲酸甲酯

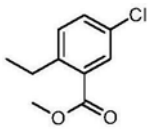
[2171]



[2172] 在氮气保护下搅拌碳酸钾(5.0g，36mmol)的甲醇(20mL)悬浮液，同时向其中加入5-氯-2-[2-(三甲基硅基)乙炔基]苯甲酸甲酯(4.8g，18.0mmol)的甲醇(50mL)溶液。所得混合物在20℃搅拌2小时。将反应混合物过滤，固体用甲醇洗涤。将滤液真空浓缩后再溶解于甲醇(50mL)中，向所得溶液中小心地加入乙酰氯(4.0mL)。反应混合物搅拌过夜，并在真空中浓缩。向残余物中加入TBME(50mL)，将所得悬浮液过滤。滤液用饱和$NaHCO_3$溶液洗涤(40mL)。两相分离，水相用TBME萃取(3x40mL)。合并的有机相用$MgSO_4$干燥，过滤并真空浓缩。残留的粗品通过快速柱层析(50g Isolute柱，0-10%TBME:庚烷)纯化，得到白色固体状的标题化合物(1.2g，33%)。LC-MS93%，m/z=194.9，196.9；^1H NMR(500MHz，$CDCl_3$) δ ppm7.94(s，1H)，7.56(d，J=8.4Hz，1H)，7.46(d，J=8.4Hz，1H)，3.95(s，3H)，3.44(s，1H)。

[2173] 步骤3：合成5-氯-2-乙基苯甲酸甲酯

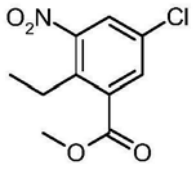
[2174]



[2175] 向5-氯-2-乙炔基苯甲酸甲酯(1.13g，5.8mmol)的TBME(50mL)溶液中加入Pd/C(10%)(50%水，0.61g，0.29mmol)。反应混合物在氢气氛中搅拌130分钟。混合物通过硅藻土过滤，滤饼用TBME洗涤。将滤液在真空中浓缩，得到浅棕色油状的标题化合物(1.08g，74%)。LC-MS79%，m/z=198.9/200.9；^1H NMR(500MHz，$CDCl_3$) δ ppm7.85(s，1H)7.40(d，J=8.20Hz，1H)7.22(d，J=8.20Hz，1H)3.91(s，3H)2.95(q，J=7.46Hz，2H)1.22(t，J=7.49Hz，3H)。

[2176] 步骤4：合成5-氯-2-乙基-3-硝基苯甲酸甲酯

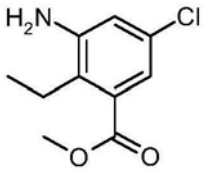
[2177]



[2178] 将 5- 氯 -2- 乙基苯甲酸甲酯(1.08g,5.4mmol)的浓硫酸(7.0mL)溶液在丙酮 / 冰浴中冷却到 -5℃。将 70% 硝酸(0.45ml,7.1mmol)和浓硫酸(0.5mL)的混合物在 -5℃逐滴滴加到反应混合物中,滴加时间为 15 分钟。将所得淡黄色反应混合物在 -5℃搅拌 1 小时后,然后倒入冰中(100mL),并用 CH_2Cl_2 萃取(3x20mL)。合并的有机相依次用去离子水(20mL)和盐水(20mL)洗涤,用 Na_2SO_4 干燥,过滤并真空浓缩。将所得油状物在 0℃下加入到包含甲醇(25mL)和二氯亚砜(0.75mL)的溶液中。加完后,将混合物加热并温和回流 6 小时,然后冷却到室温并真空浓缩,得到橙色油状的标题化合物(1.2g),其用于下一步骤,而没有进一步纯化。

[2179] 步骤 5 :合成 3- 氨基 -5- 氯 -2- 乙基苯甲酸甲酯

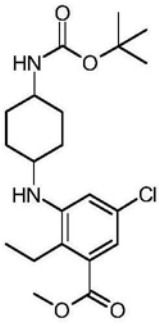
[2180]



[2181] 向 5- 氯 -2- 乙基 -3- 硝基苯甲酸甲酯(1.2g,5.0mmol)的甲醇(50mL)和去离子水(25mL)溶液中加入氯化铵(2.6g,50mmol)。将混合物加热到 70℃后加入铁(1.7g,30mmol)。反应混合物在 70℃搅拌 3.5 小时,通过硅藻土热过滤,滤饼用 MeOH (20mL) 洗涤。将滤液真空浓缩,将残留水溶液溶解于饱和 $NaHCO_3$(aq) (50mL) 和 EtOAc (100mL) 中。两相分离,有机相依次用饱和 $NaHCO_3$(aq) (2x65mL) 和盐水(30mL)洗涤,用 $MgSO_4$ 干燥,过滤并真空浓缩。残余物通过柱层析(25g SNAP 柱,Isolera,0-11% 乙酸乙酯 / 庚烷)纯化,得到黄色油状的标题化合物(372mg,33%)。LC-MS94%,m/z=213.9,215.9;^{1}H NMR(500MHz,$CDCl_3$)d ppm7.18(d,J=2.21Hz,1H)6.80(d,J=2.05Hz,1H)3.88(s,3H)3.85(d,J=2.52Hz,2H)2.75(q,J=7.57Hz,2H)1.21(t,J=7.49Hz,3H)。

[2182] 步骤 6 :合成 3-[(4-{[(叔丁氧)羰基]氨基}环己基)氨基]-5- 氯 -2- 乙基苯甲酸甲酯

[2183]

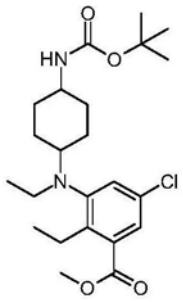


[2184] 在氮气保护下,向搅拌后的 3- 氨基 -5- 氯 -2- 乙基苯甲酸甲酯(365mg,1.7mmol)

的 1,2- 二氯乙烷（20mL）溶液中加入 (4- 氧代环己基) 氨基甲酸叔丁酯（364mg,1.7mmol）和醋酸（587μl,10.3mmol）。搅拌 10 分钟后，在 1 小时内向溶液中分批加入三乙酰基硼氢化钠（1.09g,5.1mmol）。所得溶液在室温下搅拌 17 小时，然后再向其加入 (4- 氧代环己基) 氨基甲酸叔丁酯（364mg,1.7mmol）。反应混合物搅拌 30 分钟后，在 2.5 小时内向其加入三乙酰基硼氢化钠（1.09g,5.1mmol）。反应混合物继续在室温下搅拌 26 小时，然后加入去离子水（40mL）。混合物用固体 $NaHCO_3$（2.95g）中和，用乙酸乙酯萃取（3x50mL）。合并的有机萃取液用盐水洗涤（35mL），干燥（$MgSO_4$），过滤并真空浓缩。残留的粗品通过柱层析（25g SNAP 柱，Isolera，0-18%EtOAc/ 庚烷）纯化，得到油状的标题化合物（623mg,85%），其为顺 / 反异构体的混合物。LC-MS46.1%,2.61 分钟 (3.5 分钟 LC-MS 法),m/z=411.1,413.1 和 50.2%,2.66 分钟 (3.5 分钟 LC-MS 法),m/z=411.1,413.1;^{1}H NMR(500MHz,$CDCl_3$)d ppm7.05(dd,J=7.09,2.05Hz,1H)6.68(t,J=2.36Hz,1H)4.36-4.63(m,1H)3.88(d,J=3.31Hz,3H)3.62-3.78(m,1H)3.49(br.s.,1H)3.23(br.s.,1H)2.63-2.76(m,2H)2.07-2.18(m,2H)1.77-1.89(m,2H)1.69(br.s.,1H)1.46(s,9H)1.27(m,3H)1.13-1.24(m,3H)。

[2185] 步骤 7 :合成 3-[(4-{[(叔丁氧) 羰基] 氨基 } 环己基)(乙基) 氨基]-5- 氯 -2- 乙基苯甲酸甲酯

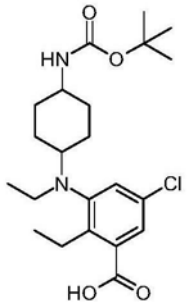
[2186]



[2187] 向搅拌后的 3-[(4-{[(叔丁氧) 羰基] 氨基 } 环己基) 氨基]-5- 氯 -2- 乙基苯甲酸甲酯（200mg,0.49mmol）的无水 1,2- 二氯乙烷（5.0mL）溶液中加入乙醛（54μl,1.0mmol）和醋酸（167μl,2.9mmol）。将反应混合物搅拌 50 分钟后，在 2 小时内分批加完三乙酰基硼氢化钠（309mg,1.5mmol），反应搅拌 20 小时。向反应混合物加入乙醛（54μl,1.0mmol），搅拌 1 小时后，在 2 小时内分批加入三乙酰基硼氢化钠（309mg,1.5mmol）。继续搅拌 22 小时后，向反应混合物中再加入乙醛（136μl,2.4mmol），搅拌 1 小时后，在 1.5 小时内加入三乙酰基硼氢化钠（516mg,2.4mmol），搅拌 22 小时。向反应混合物加入乙醛（109μl,2.0mmol），搅拌 1.5 小时后，在 2 小时内加入三乙酰基硼氢化钠（413mg,2.0mmol），同时加入二氯乙烷（5.0mL）以帮助搅拌。反应混合物搅拌 19 小时后，加入乙醛（82μl,1.5mmol），搅拌 1.5 小时后，45 分钟内加入三乙酰基硼氢化钠（309mg,1.5mmol）。将反应混合物继续搅拌 70 小时，用水（20mL）稀释，逐渐加入固体 $NaHCO_3$(2.53g) 将溶液 pH 值调至 8。两相分离，水层 CH_2Cl_2 萃取（3x20mL）。合并的有机相用盐水洗涤（60mL），干燥（$MgSO_4$），过滤并真空浓缩。残留的粗产物通过快速柱层析（10g SNAP 柱，Isolera，0-30%EtOAc/ 庚烷）纯化，得到黄色油状的标题化合物（163mg,73%）和顺 / 反异构体的混合物。LC-MS100%,5.83 分钟 (7 分钟 LC-MS 法),m/z=439.2,441.2;^{1}H NMR(500MHz,$CDCl_3$) δ ppm7.45-7.55(m,1H)7.22(dd,J=4.33,2.13Hz,1H)4.25-4.67(m,1H)3.90(d,J=2.21Hz,3H)3.29-3.76(m,1H)2.95-3.11(m,4H)2.58-2.96(m,1H)1.62-2.03(m,4H)1.38-1.53(m,11H)1.01-1.14(m,4H)0.81-0.94(m,4H)。

[2188] 步骤 8 :合成 3-[(4-{[(叔丁氧)羰基]氨基}环己基)(乙基)氨基]-5-氯-2-乙基苯甲酸

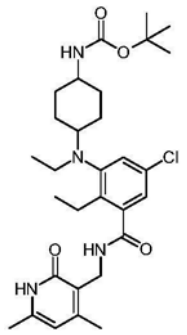
[2189]



[2190] 向搅拌后的 3-[(4-{[(叔丁氧)羰基]氨基}环己基)(乙基)氨基]-5-氯-2-乙基苯甲酸甲酯(156mg,0.36mmol)的 THF(4.0mL)和 MeOH(0.29mL)溶液中加入 4M NaOH(aq)(2.7ml,10.7mmol)。所得溶液在 50℃搅拌 17 小时。向反应混合物加入 4M NaOH(aq)(0.5ml,2.0mmol),并继续在 50℃搅拌 32 小时。停止加热,反应混合物在室温下搅拌 65 小时。向反应混合物加入 4M NaOH(aq)(1.0ml,4.0mmol),并重新加热到 50℃并保持 24 小时。在真空中除去有机溶剂,向水相中加入 0.5M 柠檬酸溶液(20mL)将 pH 值调到 4/5。产物用乙酸乙酯(3x25mL)萃取。合并的有机相用盐水洗涤(30mL),干燥($MgSO_4$),过滤并真空浓缩,再在高真空度下进一步干燥 4 小时,得到白色固体状的标题化合物(142mg,92%)为和顺 / 反异构体的混合物。LC-MS98%,5.49 分钟 (7 分钟 LC-MS 法),m/z=425.1,427.1。^1H NMR 显示顺 / 反异构体的混合物。

[2191] 步骤 9 :合成 N-{4-[(5-氯-3-{[(4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基]氨基甲酰基}-2-乙基苯基)(乙基)氨基]环己基}氨基甲酸叔丁酯

[2192]

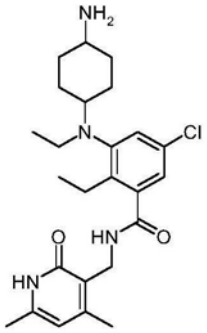


[2193] 在 0℃和氮气保护下,向搅拌后的 3-[(4-{[(叔丁氧)羰基]氨基}环己基)(乙基)氨基]-5-氯-2-乙基苯甲酸(139mg,0.33mmol)的无水 DMF (2.0mL)溶液中加入 HATU(149mg,0.39mmol)和 DIPEA (114μl,0.65mmol)。将所得溶液搅拌 10 分钟后,加入 3-(氨基甲基)-4,6-二甲基-1,2-二氢吡啶-2-酮(89%,61mg,0.36mmol)。所得悬浮液在 0℃搅拌 1 小时,然后再在室温下搅拌 98.5 小时。向反应混合物加入 HATU(37mg,0.1mmol),搅拌 1 小时后加入 3-(氨基甲基)-4,6-二甲基-1,2-二氢吡啶-2-酮(89%,11mg,0.07mmol)。反应混合物继续在室温下搅拌 23 小时,然后将其在水(20mL)和 CH_2Cl_2 (20mL)之间分配。两相分离,水相用 CH_2Cl_2 萃取(3x10mL)。合并的有机相依次用饱和 $NaHCO_3$(aq) (40mL)、水(20mL)和盐水(2x20mL)洗涤,干燥($MgSO_4$),过滤并真空浓缩。残留的粗品通过快速柱层析

(10g SNAP 柱，Isolera，0-13%MeOH/CH_2Cl_2)纯化，在乙醚 / 庚烷(2.0mL)中通过超声磨碎，倾析液体。余下的固体在高度真空中干燥，得到米黄色固体状的标题化合物(101mg，52%)。LC-MS93%，4.54 分钟 (7 分钟 LC-MS 法)，m/z=559.2，561.2。^{1}H NMR 显示顺 / 反异构体的混合物。

[2194] 步骤 10：合成 3-[(4- 氨基环己基)(乙基)氨基]-5- 氯 -N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基]-2- 乙基苯甲酰胺

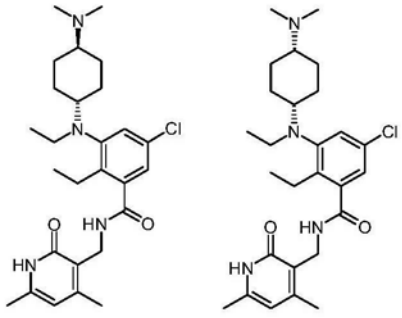
[2195]



[2196] 在 0℃下，向搅拌后的 N-{4-[(5- 氯 -3-{[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基]氨基甲酰基}-2- 乙基苯基)(乙基)氨基]环己基}氨基甲酸叔丁酯(100mg，0.18mmol)的 CH_2Cl_2(4.0mL)溶液中加入三氟乙酸(1.0mL)。反应混合物在 0℃搅拌 40 分钟，然后在室温下搅拌 2 小时。将反应混合物真空浓缩，残余物用饱和 $NaHCO_3$ 溶液 (aq) (10mL)碱化至 pH 值为 8。残留的水溶液用 20%MeOH/CH_2Cl_2 萃取(4x15mL)。将合并的有机相干燥($MgSO_4$)，过滤并真空浓缩，得到黄色固体状的标题化合物(108mg，113%)。LC-MS48%，2.88 分钟 (7 分钟 LC-MS 法)，m/z=459.1 和 39%，2.96 分钟 (7 分钟 LC-MS 法)，m/z=459.1。^{1}H NMR 显示顺 / 反异构体的混合物。

[2197] 步骤 11：合成 5- 氯 -N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基]-2- 乙基 -3-{ 乙基 [(1r,4r)-4-(二甲基氨基)环己基]氨基} 苯甲酰胺和 5- 氯 -N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基]-2- 乙基 -3-{ 乙基 [(1s,4s)-4-(二甲基氨基)环己基]氨基} 苯甲酰胺

[2198]



[2199] 向搅拌后的 3-[(4- 氨基环己基)(乙基)氨基]-5- 氯 -N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基]-2- 乙基苯甲酰胺(80mg，0.18mmol)的 1,2- 二氯乙烷(3.0mL)溶液中加入醋酸(60μl，1.0mmol)和多聚甲醛(31mg，1.0mmol)。将反应混合物在氮气氛中搅拌 35 分钟后，加入三乙酰基硼氢化钠(222mg，1.0mmol)。将反应混合物搅拌 16.5 小时后加入多聚甲醛(16mg，0.52mmol)，并继续搅拌 1 小时，再加入三乙酰基硼氢化

钠(111mg,0.52mmol)。反应混合物继续搅拌 6 小时,然后加入多聚甲醛(10mg,0.35mmol),搅拌 10 分钟后加入三乙酰基硼氢化钠(74mg,0.35mmol)和 1,2- 二氯乙烷(1.0mL),继续搅拌 89 小时。反应混合物用水(20mL)稀释,用固体 $NaHCO_3$(1.45g) 碱化至 pH 值为 8。加入 CH_2Cl_2 (20mL),两相分离。水相用 CH_2Cl_2 萃取(3x10mL)。合并有机相用盐水洗涤(30mL),干燥($MgSO_4$),过滤并真空浓缩。残留的粗品通过制备 HPLC(MeCN/ 水 +0.2% 氢氧化铵)纯化,得到白色固体状的纯净的反式异构体,即标题化合物 347:5- 氯 -N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基]-2- 乙基 -3-{ 乙基 [(1r,4r)-4-(二甲基氨基)环己基]氨基} 苯甲酰胺(22mg,26%),和白色固体状的纯净的顺式异构体,即标题化合物 348:5- 氯 -N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基]-2- 乙基 -3-{ 乙基 [(1s,4s)-4-(二甲基氨基)环己基]氨基} 苯甲酰胺(18mg,21%)。

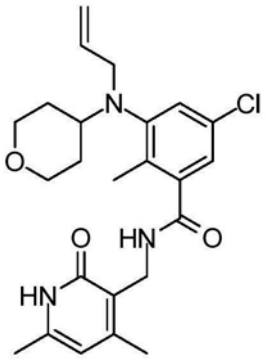
[2200] 5- 氯 -N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基]-2- 乙基 -3-{ 乙基 [(1r,4r)-4-(二甲基氨基)环己基]氨基} 苯甲酰胺

[2201] LC-MS100%,3.07 分钟 (7 分钟 LC-MS 法),m/z=487.2,489.2;^{1}H NMR(500MHz,$CDCl_3$) δ 11.09(s,1H),7.11 - 7.04(m,2H),7.00(d,J=2.1Hz,1H),5.94(s,1H),4.51(d,J=5.9Hz,2H),3.00(q,J=7.0Hz,2H),2.79(q,J=7.4Hz,2H),2.65(t,J=11.5Hz,1H),2.38(s,3H),2.24(s,6H),2.22(s,3H),2.14(t,J=11.4Hz,1H),1.87(d,J=10.3Hz,4H),1.37(q,J=12.1Hz,2H),1.17(q,J=11.5Hz,2H),1.02(t,J=7.4Hz,3H),0.85(t,J=7.0Hz,3H)。

[2202] 5- 氯 -N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基]-2- 乙基 -3-{ 乙基 [(1s,4s)-4-(二甲基氨基)环己基]氨基} 苯甲酰胺 LC-MS100%,3.13 分钟 (7 分钟 LC-MS 法),m/z=487.2,489.2;^{1}H NMR(500MHz,$CDCl_3$) δ 10.72(s,1H),7.09(d,J=2.0Hz,2H),7.01(d,J=2.1Hz,1H),5.93(s,1H),4.51(d,J=5.9Hz,2H),3.01(q,J=6.7Hz,3H),2.89(q,J=7.4Hz,2H),2.39(s,3H),2.23(s,9H),2.06(s,1H),1.87 - 1.72(m,4H),1.43(td,J=8.3,3.8Hz,2H),1.33(dd,J=12.6,9.2Hz,2H),1.01(t,J=7.5Hz,3H),0.84(t,J=7.0Hz,3H)。

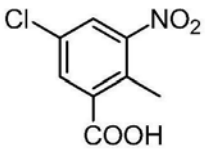
[2203] 化合物 92 :3-(烯丙基 (四氢 -2H- 吡喃 -4- 基)氨基)-5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)-2- 甲基苯甲酰胺

[2204]



[2205] 步骤 1 :合成 5- 氯 -2- 甲基 -3- 硝基苯甲酸

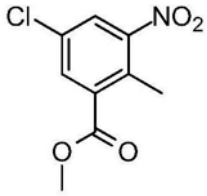
[2206]



[2207] 在 -10℃下，将 5- 氯 -2- 甲基苯甲酸（4.0g，23mmol）分批加入到冷却的浓 H_2SO_4（27mL）中。10 分钟后，将硝化混合物｛通过混合浓 HNO_3（3.3g，52.68mmol）和浓 H_2SO_4（4.4mL）来制备｝在 -10℃下逐滴滴加到上述混合物中。所得反应物料在 -10℃搅拌 30 分钟。结束时，将反应混合物倒入冰冷水中，将析出的固体过滤，用水洗涤并真空干燥，得到标题化合物（4.95g，99%）。

[2208] 步骤 2 ：合成 5- 氯 -2- 甲基 -3- 硝基苯甲酸甲酯

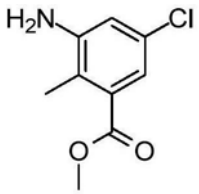
[2209]



[2210] 向搅拌后的 5- 氯 -2- 甲基 -3- 硝基苯甲酸（6.75g，31.3mmol）的 DMF （33mL）溶液中加入碳酸钠（13.2g，125mmol）和碘甲烷（17.8g，125mmol）。混合物在 60℃加热 4 小时。结束时，向反应物料中加水，并用 DCM 萃取。将合并的有机相干燥，减压浓缩，通过硅胶柱层析纯化得到标题化合物（6.0g，83%）。

[2211] 步骤 3 ：合成 3- 氨基 -5- 氯 -2- 甲基苯甲酸甲酯

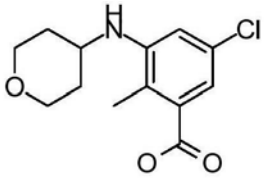
[2212]



[2213] 向搅拌后的 5- 氯 -2- 甲基 -3- 硝基苯甲酸甲酯（6.0g，26mmol）的乙醇（60mL）溶液中加入溶解于水（60mL）中的氯化铵（6.0g，110mmol）和铁粉（11.9g，208mmol）。将所得反应物料在 80℃加热 1 小时。结束时，向反应物料中加入水，通过硅藻土过滤，滤液用乙酸乙酯萃取。合并的有机相用水洗涤，干燥，减压浓缩，得到照现状使用的标题化合物。

[2214] 步骤 4 ：合成 5- 氯 -2- 甲基 -3-（（四氢 -2H- 吡喃 -4- 基）氨基）苯甲酸甲酯

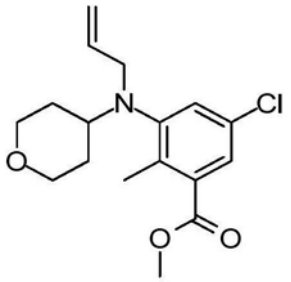
[2215]



[2216] 向搅拌后的 3- 氨基 -5- 氯 -2- 甲基苯甲酸甲酯（5.0g，19mmol）和二氢 -2H- 吡喃 -4(3H)- 酮（2.86g，28.6mmol）的甲醇（50mL）溶液中加入醋酸（2.3g，38mmol），反应在室温下搅拌 8 小时。在 0℃下，向反应混合物加入氰基硼氢化钠（3.0g，48mmol），在室温下搅拌反应过夜。结束时，减压除去溶剂，粗产物通过柱层析纯化得到标题化合物（3.0g，42%）。

[2217] 步骤 5 ：合成 3-（烯丙基（四氢 -2H- 吡喃 -4- 基）氨基）-5- 氯 -2- 甲基苯甲酸甲酯

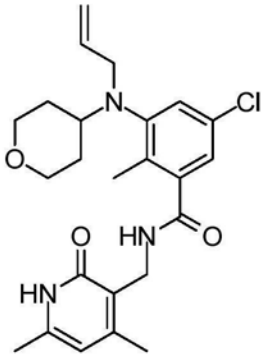
[2218]



[2219] 在 0℃下，向搅拌后的 5- 氯 -2- 甲基 -3-((四氢 -2H- 吡喃 -4- 基）氨基）苯甲酸甲酯(1.0g,3.3mmol)的 DMF (10mL)溶液中加入 NaH (0.25g,10mmol)，混合物搅拌 20 分钟。向反应混合物中加入 3- 溴丙 -1- 烯 (1.7g,14.13mmol)，并在 80℃加热 15 小时。结束时，用冰冷水淬灭反应，用 DCM 萃取。将合并的有机相干燥，浓缩，得到的粗产物经柱层析纯化得到标题化合物(0.50g,44%)。

[2220] 步骤 6：合成 3-(烯丙基(四氢 -2H- 吡喃 -4- 基）氨基)-5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基)-2- 甲基苯甲酰胺

[2221]

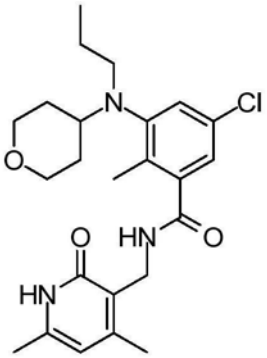


[2222] 向 3-(烯丙基(四氢 -2H- 吡喃 -4- 基）氨基)-5- 氯 -2- 甲基苯甲酸甲酯(0.50g,1.54mmol)的乙醇(15mL)溶液加入 NaOH (0.092g,2.32mmol)水溶液，混合物在 60℃搅拌 1 小时。反应结束后，减压除去乙醇，剩余的水溶液用稀 HCl 酸化至 pH 值为 6，再用柠檬酸酸化至 pH 值为 4。用 DCM 进行萃取。将合并的有机相干燥，浓缩，得到单独的酸(0.47g,98%)。

[2223] 将上述酸(0.47g,1.52mmol)溶解到 DMSO (5mL)溶液中，并向其中加入 3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮(0.462g,3.04mmol)。在室温下搅拌 15 分钟后，向反应混合物加入 PYBOP (1.18g,2.28mmol)，继续搅拌过夜。反应结束后，将反应混合物倒入冰中以获得固体，将该固体过滤，干燥得到标题化合物(0.40g,59%)。LCMS:444.25(M+1)$^+$;HPLC:96.85%(@254nm)(R_t;6.310; 方法：色谱柱 :YMC ODS-A150mm x4.6mm x5μ；流动相 :A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液；进样量 :10μL, 柱温 :30℃；流速 :1.4mL/min.；梯度 :0-8min5%B-95%B, 保持 1.5min,9.51-12min5%B);^{1}H NMR(DMSO-d_6,400MHz) δ 11.47(s,1H),8.22(t,1H),7.16(s,1H),6.93(s,1H),5.85(s,1H),5.56-5.62(m,1H),5.02-5.07(m,1H),4.94-4.96(m,1H),4.23(d,2H,J=3.6Hz),3.83(d,2H,J=9.6Hz),3.64(d,2H,J=4Hz),3.23(t,2H,J=10Hz),2.97(m,1H),2.18(s,3H),2.17(s,3H),2.10(s,3H),1.54-1.60(m,4H)。

[2224] 化合物 98：5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基)-2- 甲基 -3-(丙基(四氢 -2H- 吡喃 -4- 基）氨基）苯甲酰胺

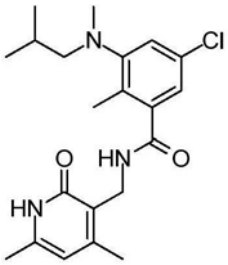
[2225]



[2226] 向搅拌后的 3-(烯丙基(四氢-2H-吡喃-4-基)氨基)-5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺(0.10g)的 MeOH(10mL)溶液中加入 10%Pd/C(0.03g),反应混合物在氢气氛中(气球压力)在室温下搅拌 2 小时。结束时,反应混合物通过硅藻土过滤,滤液在减压下浓缩,得到固体粗品,将该固体粗品通过柱层析纯化得到标题化合物(0.02g,20%)。LCMS:445.25(M+1)$^+$;HPLC:90.40%(@254nm)(Rt;5.609;方法:色谱柱:YMC ODS-A150mm x4.6mm x5μ;流动相:A;0.05%TFA 的水溶液/B;0.05%TFA 的乙腈溶液;进样量:10μL,柱温:30℃;流速:1.4mL/min.;梯度:0-8min5%B-95%B,保持 1.5min,9.51-12min5%B);^{1}H NMR(DMSO-d_6,400MHz)δ11.47(s,1H),8.23(t,1H),7.19(s,1H),6.93(d,1H,J=1.6Hz),5.88(s,1H),4.24(d,2H,J=4.4Hz),3.83(d,2H,J=10.4Hz),3.22-3.25(m,2H),2.94(t,2H,J=7.2Hz),2.88-2.90(m,1H),2.18(s,3H),2.15(s,3H),2.10(s,3H),1.56(m,4H),1.14-1.23(m,2H),0.75(t,3H,J=8Hz)。

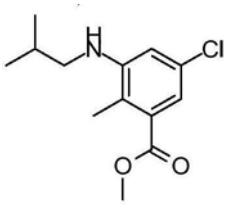
[2227] 化合物 104:5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(异丁基(甲基)氨基)-2-甲基苯甲酰胺

[2228]



[2229] 步骤 1:合成 5-氯-3-(异丁基氨基)-2-甲基苯甲酸甲酯

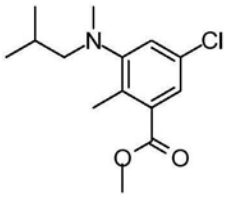
[2230]



[2231] 向搅拌后的 3-氨基-5-氯-2-甲基苯甲酸甲酯(5.0g,25mmol)和异丁醛(4.5g,62mmol)的甲醇(50mL)溶液中加入醋酸(3.0g,50mmol),反应在室温下搅拌 2 小时。在 0℃向反应混合物中加入氰基硼氢化钠(3.94g,62mmol),在室温下搅拌过夜。结束时,减压除去溶剂,粗产物通过柱层析纯化得到标题化合物(6.0g,94%)。

[2232] 步骤 2：合成 5- 氯 -3-（异丁基（甲基）氨基）-2- 甲基苯甲酸甲酯

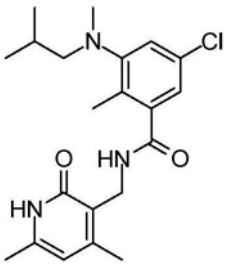
[2233]



[2234] 向搅拌后的 5- 氯 -3-（异丁基氨基）-2- 甲基苯甲酸甲酯（1.0g，3.9mmol）的无水乙腈（10mL）溶液中加入碳酸铯（2.55g，7.8mmol）和碘甲烷（5.55g，39mmol）。所得混合物在 80℃加热 12 小时。结束时，将混合物冷却到室温，过滤。残余物用乙酸乙酯洗涤，滤液经浓缩得到标题化合物（1.0g，95%）。

[2235] 步骤 3：合成 5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-3-（异丁基（甲基）氨基）-2- 甲基苯甲酰胺

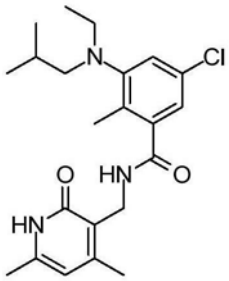
[2236]



[2237] 向 5- 氯 -3-（异丁基（甲基）氨基）-2- 甲基苯甲酸甲酯（1.0g，3.7mmol）的 EtOH（5mL）溶液中加入 NaOH（0.22g，5.5mmol）水溶液，混合物在 60℃搅拌 1 小时。反应结束后，减压除去乙醇。残余物用稀 HCl 酸化至 pH 值为 6，再用柠檬酸调至 pH 值为 4。用乙酸乙酯进行萃取。将合并的有机层干燥，浓缩得到单独的酸（0.900g，95%）。然后将该酸（0.30g，1.17mmol）溶解到 DMSO（1.5mL）中，并向其中加入 3-（氨基甲基）-4,6- 二甲基吡啶 -2(1H)- 酮（0.357g，2.34mmol）。在室温下搅拌反应 15 分钟后，向其中加入 PYBOP（0.915g，1.76mmol），继续搅拌过夜。反应结束后，将反应物料倒入冰中以获得固体，过滤得到的固体，并通过柱层析纯化，得到标题化合物（0.245g，53%）。LCMS:390.25(M+1)$^+$;HPLC:97.59%(@254nm)(Rt;6.063; 方法：色谱柱：YMC ODS-A150mm x4.6mm x5μ；流动相：A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液；进样量：10μL，柱温：30℃；流速：1.4mL/min.；梯度：0-8min5%B-95%B，保持 1.5min,9.51-12min5%B);^{1}H NMR(DMSO-d_6,400MHz) δ 11.47(s,1H),8.20(t,1H),7.07(s,1H),6.90(s,1H),5.85(s,1H),4.23(d,2H,J=4.4Hz),2.63(d,2H,J=7.2Hz),2.54(s,3H),2.18(s,3H),2.16(s,3H),2.10(s,3H),1.75-1.78(m,1H),0.85(d,6H,J=6Hz)。

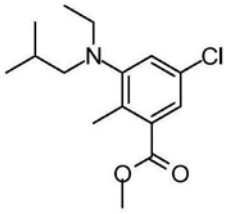
[2238] 化合物 105：5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-3-（乙基（异丁基）氨基）-2- 甲基苯甲酰胺

[2239]



[2240] 步骤 1 :合成 5- 氯 -3-(乙基 (异丁基) 氨基)-2- 甲基苯甲酸甲酯

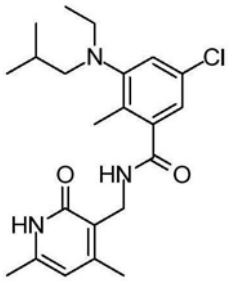
[2241]



[2242] 向搅拌后的 5- 氯 -3-(异丁基氨基)-2- 甲基苯甲酸甲酯(1.0g,3.9mmol)的无水 DMF (10mL) 溶液中加入碳酸铯(2.55g,7.82mmol) 和碘乙烷(6.09g,39.1mmol)。所得反应物料在 80℃加热 12 小时。结束时,将反应物料冷却到室温,过滤。残余物用乙酸乙酯洗涤,滤液经浓缩得到照现状用于下一步中的原料粗品(1.0g,91%)。

[2243] 步骤 2 :合成 5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-3-(乙基 (异丁基) 氨基)-2- 甲基苯甲酰胺

[2244]



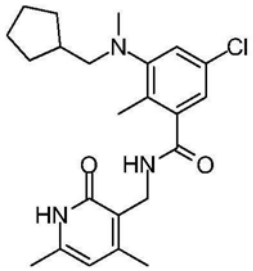
[2245] 向化合物 7(1.0g,3.50mmol)的 EtOH (5mL)溶液中加入 NaOH (0.212g,5.28mmol) 水溶液,在 60℃搅拌 1 小时。反应结束后,减压除去乙醇,用稀 HCl 酸化至 pH 值为 6,并用柠檬酸调至 pH 值为 4。用乙酸乙酯进行萃取。将合并的有机层干燥,浓缩得到单独的酸 (0.900g)。

[2246] 将所得酸(0.90g,3.33mmol) 溶剂于 DMSO (4.5mL) 中,并向其中加入 3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮(1.01g,6.67mmol)。在室温下搅拌 15 分钟后,向反应混合物加入 PYBOP (2.60g,4.9mmol),继续搅拌过夜。将混合物倒入冰中以产生固体,将该固体过滤,并通过乙腈和乙醚洗涤纯化得到标题化合物(1.0g,75%)。LCMS:404.25(M+1)$^+$;HPLC:90.28%(@254nm)(R_t;6.063; 方法 : 色谱柱 :YMC ODS-A150mm x4.6mm x5μ ; 流动相 :A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液 ; 进样量 :10μL, 柱温 :30℃ ; 流速 :1.4mL/min. ; 梯度 :0-8min5%B-95%B, 保持 1.5min,9.51-12min5%B);^{1}H NMR(DMSO-d_6,400MHz) δ 11.45(s,1H),8.19(t,1H),7.10(s,1H),6.90(s,1H),5.85(s,1H), 4.24(d,2H,J=4.8Hz),2.86(q,2H,J=7.2Hz),2.73(d,2H,J=7.6Hz),2.18(s,3H),2.16(s,3H

),2.10(s,3H),1.57-1.61(m,1H),0.91(t,3H,J=6.8Hz),0.82(d,6H,J=6.4Hz)。

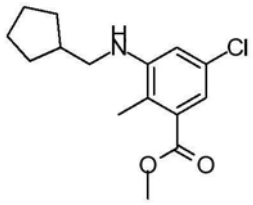
[2247] 化合物 117 :5- 氯 -3-((环戊基甲基)(甲基)氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)-2- 甲基苯甲酰胺

[2248]



[2249] 步骤 1 :合成 5- 氯 -3-((环戊基甲基)氨基)-2- 甲基苯甲酸甲酯

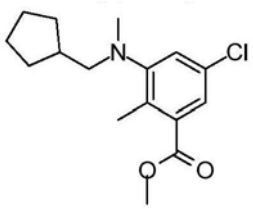
[2250]



[2251] 向搅拌后的 3- 氨基 -5- 氯 -2- 甲基苯甲酸甲酯(3.0g,15mmol)和环戊基甲醛(2.2g,22mmol)的甲醇(30mL)溶液中加入醋酸(1.8g,30mmol),反应混合物在室温下搅拌 8 小时。然后在 0℃下,向反应混合物中加入氰基硼氢化钠(2.4g,37mmol),在室温下搅拌反应过夜。结束时,减压除去溶剂,粗产物通过柱层析纯化得到标题化合物(4.2g,99%)。

[2252] 步骤 2 :合成 5- 氯 -3-((环戊基甲基)(甲基)氨基)-2- 甲基苯甲酸甲酯

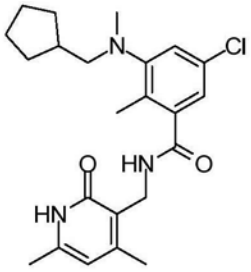
[2253]



[2254] 向搅拌后的 5- 氯 -3-((环戊基甲基)氨基)-2- 甲基苯甲酸甲酯(1.0g,3.5mmol)的乙腈(10mL)溶液中加入碳酸铯(2.3g,7.1mmol)和碘甲烷(5.0g,35mmol)。所得混合物在 80℃加热 12 小时。冷却到室温,过滤。残余物用乙酸乙酯洗涤,滤液经浓缩后通过柱层析纯化,得到标题化合物(1.0g,95%)。

[2255] 步骤 3 :合成 5- 氯 -3-((环戊基甲基)(甲基)氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)-2- 甲基苯甲酰胺

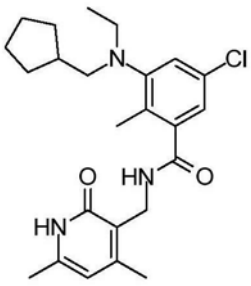
[2256]



[2257] 向 5- 氯 -3-((环戊基甲基)(甲基)氨基)-2- 甲基苯甲酸甲酯(1.0g,3.38mmol)的乙醇(10mL)溶液中加入 NaOH (0.206g,15.1mmol)水溶液,所得混合物在 60℃搅拌 1 小时。减压除去乙醇,残余物用稀 HCl 酸化至 pH 值为 6,并用柠檬酸将 pH 值调至 4。用 DCM 进行萃取。将合并的有机层干燥,浓缩后得到单独的酸(0.9g)。将上述酸(0.3g,1.06mmol)溶解到 DMSO(1.5mL)中,并向其中加入 3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮(0.324g,2.12mmol)。在室温下搅拌 15 分钟后,向反应混合物加入 PYBOP (0.831g,1.57mmol),继续搅拌过夜。将所得混合物倒入冰中以得到固体,将该固体过滤,用乙腈洗涤,得到标题化合物(0.25g,56%)。LCMS:416.15(M+1)$^+$;HPLC:92.58%(@254nm)(R_t;6.169; 方法:色谱柱:YMC ODS-A150mm x4.6mm x5μ;流动相:A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液;进样量:10μL, 柱温:30℃;流速:1.4mL/min.;梯度:0-8min5%B-95%B, 保持 1.5min,9.51-12min5%B);^{1}H NMR(DMSO-d_6,400MHz) δ 11.45(s,1H),8.19(t,1H),7.08(s,1H),6.89(s,1H),5.85(s,1H),4.23(d,2H,J=4.4Hz),2.77(d,2H,J=7.2Hz),2.57(s,3H),2.18(s,3H),2.15(s,3H),2.10(s,3H),2.04-2.06(m,1H),1.63-1.65(m,2H),1.49-1.52(m,2H),1.45-1.46(m,2H),1.15-1.18(m,2H)。

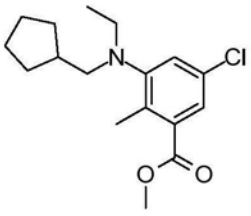
[2258] 化合物 118:5- 氯 -3-((环戊基甲基)(乙基)氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)-2- 甲基苯甲酰胺

[2259]



[2260] 步骤 1:合成 5- 氯 -3-((环戊基甲基)(乙基)氨基)-2- 甲基苯甲酸甲酯

[2261]

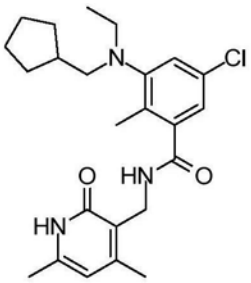


[2262] 向搅拌后的 5- 氯 -3-((环戊基甲基)氨基)-2- 甲基苯甲酸甲酯(1.0g,3.54mmol)的 DMF (10mL)溶液中加入碳酸铯(2.31g,7.09mmol)和碘乙烷(5.53g,35.4mmol)。所得反应物料在 80℃加热 12 小时。将所得混合物冷却到室温,过滤。残余物用乙酸乙酯洗涤,将

滤液浓缩，得到的残余物通过柱层析纯化得到标题化合物（1.0g，91%）。

[2263] 步骤 2：合成 5- 氯 -3-((环戊基甲基)(乙基)氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)-2- 甲基苯甲酰胺

[2264]

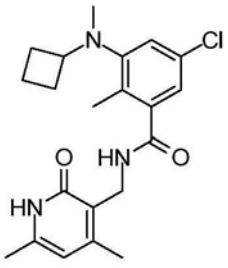


[2265] 向 5- 氯 -3-((环戊基甲基)(乙基)氨基)-2- 甲基苯甲酸甲酯（1.0g，3.22mmol）的乙醇（10mL）溶液加入 NaOH（0.193g，15.1mmol）水溶液，混合物在 60℃搅拌 1 小时。反应结束后，减压除去乙醇，残余物用稀 HCl 酸化至 pH 值为 6，用柠檬酸调至 pH 值为 4。用 DCM 进行萃取。将合并的有机层干燥，浓缩，得到单独的酸（0.9g）。

[2266] 将上述酸（0.3g，1.01mmol）溶解到 DMSO（1.5mL）中，并向其中加入 3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮（0.308g，2.12mmol）。在室温中搅拌 15 分钟后，向反应混合物加入 PYBOP（0.791g，1.52mmol），继续搅拌过夜。反应结束后，将反应物料倒入冰中以获得固体，将固体过滤，用乙腈洗涤得到标题化合物（0.25g，57%）。LCMS:430.2(M+1)$^+$;HPLC:91.54%(@210nm)(R_t;9.378; 方法：色谱柱：YMC ODS-A150mm x4.6mm x5μ；流动相：A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液；进样量：10μL，柱温：30℃；流速：1.4mL/min.；梯度：0-8min5%B-95%B，保持 1.5min,9.51-12min5%B);^{1}H NMR(DMSO-d_6,400MHz) δ 11.46(s,1H),8.20(t,1H),7.12(s,1H),6.91(s,1H),5.85(s,1H),4.23(d,2H,J=3.6Hz),2.83-2.89(m,4H),2.18(s,3H),2.14(s,3H),2.10(s,3H),1.85-1.89(m,1H),1.51-1.58(m,4H),1.41-1.46(m,2H),1.14-1.15(m2H),0.91(t,3H,J=8Hz)。

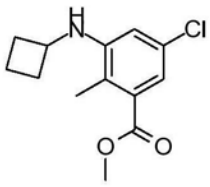
[2267] 化合物 123：5- 氯 -3-(环丁基(甲基)氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)-2- 甲基苯甲酰胺

[2268]



[2269] 步骤 1：合成 5- 氯 -3-(环丁基氨基)-2- 甲基苯甲酸甲酯

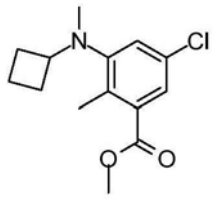
[2270]



[2271] 向搅拌后的 3- 氨基 -5- 氯 -2- 甲基苯甲酸甲酯(2.0g,10mmol)和环丁酮(1.4g,20mmol)的二氯乙烷(20mL)溶液中加入醋酸(3.6g,60mmol),在室温下搅拌 10 分钟。然后在 0℃下向所得混合物中加入三乙酰基硼氢化钠(6.3g,30mmol),在室温下搅拌 3 小时。结束时,减压除去溶剂,粗产物通过柱层析纯化得到标题化合物(1.4g,56%)。

[2272] 步骤 2 :合成 5- 氯 -3-(环丁基 (甲基) 氨基)-2- 甲基苯甲酸甲酯

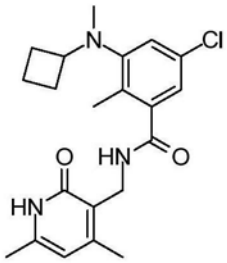
[2273]



[2274] 向搅拌后的 5- 氯 -3-(环丁基氨基)-2- 甲基苯甲酸甲酯(0.7g,2.8mmol)的乙腈(10mL)溶液中加入碳酸铯(2.2g,6.8mmol)和碘甲烷(3.9g,28mmol)。所得反应混合物在 80℃加热 8 小时。结束时,将反应混合物冷却到室温,过滤。残余物用乙酸乙酯洗涤,滤液经浓缩得到标题化合物(0.62g,84%)。

[2275] 步骤 3 :5- 氯 -3-(环丁基 (甲基) 氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基苯甲酰胺

[2276]

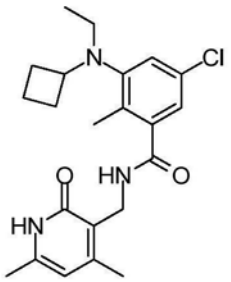


[2277] 向 5- 氯 -3-(环丁基 (甲基) 氨基)-2- 甲基苯甲酸甲酯(0.60g,2.23mmol)的乙醇(10mL)溶液中加入 NaOH (0.134g,3.34mmol)水溶液,所得混合物在 60℃搅拌 1 小时。反应结束后,减压除去乙醇,残余物用稀 HCl 酸化至 pH 值为 6,用柠檬酸将 pH 值调至 4。用 DCM 萃取。将合并的有机层干燥,浓缩得到单独的酸(0.5g)。

[2278] 将上述酸(0.25g,0.98mmol)溶解于 DMSO (5mL)中,并向其中加入 3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮(0.22g,1.41mmol)。在室温下搅拌 15 分钟后,向反应混合物加入 PYBOP(0.767g,1.47mmol),继续搅拌过夜。反应结束后,将反应物料倒入冰中,用 10%MeOH/DCM 萃取。合并的有机层用硫酸钠干燥,减压浓缩,然后得到的粗产物通过柱层析纯化得到标题化合物(0.36g,95%)。LCMS:388.09(M+1)$^+$;HPLC:96.62%(@254nm)(R_t;5.461;方法 : 色谱柱 :YMC ODS-A150mm x4.6mm x5μ ; 流动相 :A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液 ; 进样量 :10μL, 柱温 :30℃ ; 流速 :1.4mL/min. ; 梯度 :0-8min5%B-95%B, 保持 1.5min,9.51-12min5%B);^{1}H NMR(DMSO-d_6,400MHz) δ 11.44(s,1H),8.18(t,1H),6.90(d,2H,J=7.2Hz),5.85(s,1H),4.24(d,2H,J=4.4Hz),3.65(m,1H),2.45(s,3H),2.18(s,3H),2.15(s,3H),2.10(s,3H),2.03(bs,2H),1.76-1.81(m,2H),1.61-1.62(m,2H)。

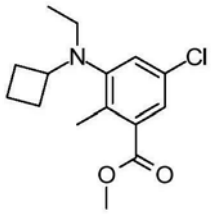
[2279] 化合物 137 :5- 氯 -3-(环丁基 (乙基) 氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基苯甲酰胺

[2280]



[2281] 步骤 1 :合成 5- 氯 -3-(环丁基 (乙基) 氨基)-2- 甲基苯甲酸甲酯

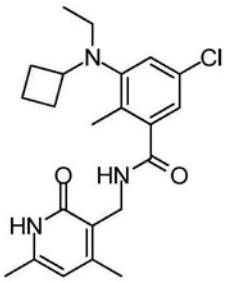
[2282]



[2283] 向搅拌后的 5- 氯 -3-(环丁基氨基)-2- 甲基苯甲酸甲酯(0.70g,2.73mmol) 和乙醛(0.36g,8.20mmol) 的二氯乙烷(15mL) 溶液加入醋酸(0.98g,16.4mmol),反应混合物在室温下搅拌 10 分钟。然后在 0℃下向反应混合物中加入三乙酰基硼氢化钠(1.7g,8.2mmol),在室温下搅拌反应 3 小时。结束时,减压除去溶剂得到标题化合物(0.71g,91%)。

[2284] 步骤 2 :合成 5- 氯 -3-(环丁基 (乙基) 氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基苯甲酰胺

[2285]



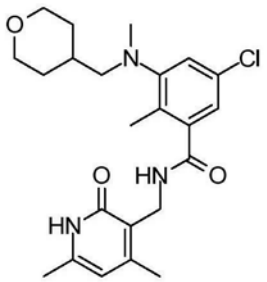
[2286] 向 5- 氯 -3-(环丁基 (乙基) 氨基)-2- 甲基苯甲酸甲酯(0.70g,2.48mmol) 的乙醇(10mL) 溶液加入 NaOH (0.149g,3.7mmol) 水溶液,所得混合物在 60℃搅拌 1 小时。反应结束后,减压除去乙醇,残余物用稀 HCl 酸化至 pH 值为 6,用柠檬酸调至 pH 值为 4。用 DCM 萃取。将合并的有机层干燥,浓缩得到单独的酸(0.6g)。

[2287] 将上述酸(0.6g,2.2mmol) 溶解在 DMSO (5mL) 中,并向其中加入 3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮(0.67g,4.44mmol)。在室温下搅拌 15 分钟后,向反应混合物加入 PYBOP(1.7g,3.33mmol),继续搅拌过夜。反应结束后,将反应物料倒入到冰中 ;用 10%MeOH/DCM 萃取。合并的有机层用硫酸钠干燥,减压浓缩,得到的粗产物再通过溶剂洗涤纯化得到标题化合物(0.45g,50%)。LCMS:402.20(M+1)$^+$;HPLC:98.73%(@254nm)(R_t;4.096; 方法 : 色谱柱 :YMC ODS-A150mm x4.6mm x5μ ; 流动相 :A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液 ; 进样量 :10μL, 柱温 :30℃ ; 流速 :1.4mL/min.; 梯度 :0-8min5%B-95%B, 保持 1.5min,9.51-12min5%B);^{1}H NMR(DMSO-d_6,400MHz) δ 11.47(s,1H),8.22(t,1H,J=4.4Hz)

,6.97(s,1H),6.92(s,1H),5.85(s,1H),4.23(d,2H,J=4.4Hz),3.75-3.79(m,1H),2.87-2.93(m,2H),2.18(s,3H),2.15(s,3H),2.10(s,3H),1.99(m,2H),1.58-1.69(m,4H),0.77(t,3H,J=6.8Hz)。

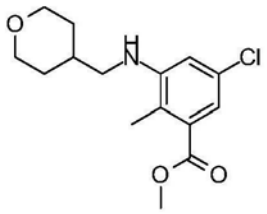
[2288] 化合物126:5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(甲基((四氢-2H-吡喃-4-基)甲基)氨基)苯甲酰胺

[2289]



[2290] 步骤1:合成5-氯-2-甲基-3-(((四氢-2H-吡喃-4-基)甲基)氨基)苯甲酸甲酯

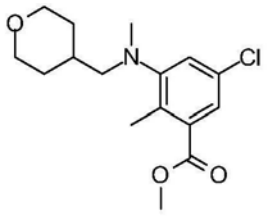
[2291]



[2292] 向搅拌后的3-氨基-5-氯-2-甲基苯甲酸甲酯(2.0g,10mmol)和四氢-2H-吡喃-4-甲醛(1.71g,15mmol)的甲醇(20mL)溶液中加入醋酸(1.2g,20mmol),反应混合物在室温下搅拌8小时。然后在0℃向反应混合物加入氰基硼氢化钠(2.11g,25.1mmol),在室温下搅拌过夜。结束时,减压除去溶剂,粗产物通过柱层析纯化得到标题化合物(1.8g,60%)。

[2293] 步骤2:合成5-氯-2-甲基-3-(甲基((四氢-2H-吡喃-4-基)甲基)氨基)苯甲酸甲酯

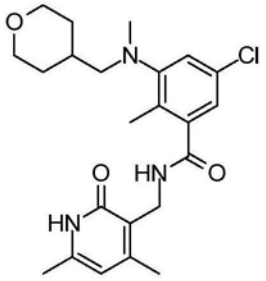
[2294]



[2295] 向搅拌后的5-氯-2-甲基-3-(((四氢-2H-吡喃-4-基)甲基)氨基)苯甲酸甲酯(0.80g,2.71mmol)的乙腈(20mL)溶液中加入碳酸铯(1.75g,5.42mmol)和碘甲烷(1.93g,13.6mmol)。所得反应混合物在80℃下加热8小时。结束时,将混合物冷却到室温,过滤。残余物用乙酸乙酯洗涤,滤液经浓缩得到粗产物,将该粗产物通过柱层析纯化得到标题化合物(0.70g,84%)。

[2296] 步骤3:合成5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-(甲基((四氢-2H-吡喃-4-基)甲基)氨基)苯甲酰胺

[2297]

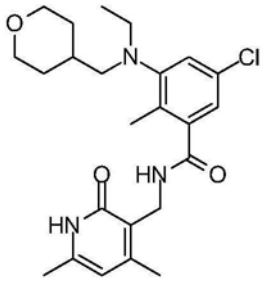


[2298] 向 5- 氯 -2- 甲基 -3-(甲基 ((四氢 -2H- 吡喃 -4- 基) 甲基) 氨基) 苯甲酸甲酯 (0.70g,2.25mmol) 的乙醇 (10mL) 溶液加入 NaOH (0.18g,4.5mmol) 水溶液,所得混合物在 60℃搅拌 1 小时。减压除去乙醇,残余物用稀 HCl 酸化至 pH 值为 6,用柠檬酸调至 pH 值为 4。用 DCM 萃取。将合并的有机层干燥,浓缩得到单独的酸 (0.2g)。

[2299] 将上述酸 (0.2g,0.68mmol) 溶解到 DMSO (0.5mL) 中,并向其中加入 3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮 (0.206g,1.35mmol)。在室温下搅拌 15 分钟后,向反应混合物加入 PYBOP (0.528g,1.01mmol),继续搅拌过夜。将所得混合物倒入冰中,用 10%MeOH/DCM 萃取。将合并的有机层用硫酸钠干燥,减压浓缩,得到粗产物,将该粗产物通过柱层析纯化得到标题化合物 (0.2g,69%)。LCMS:432.25(M+1)$^+$;HPLC:99.95%(@254nm)(Rt;5.750; 方法 : 色谱柱 :YMC ODS-A150mm x4.6mm x5μ ; 流动相 :A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液 ; 进样量 :10μL, 柱温 :30℃ ; 流速 :1.4mL/min.; 梯度 :0-8min5%B-95%B, 保持 1.5min,9.51-12min5%B);^{1}H NMR(DMSO-d_6,400MHz) δ 11.45(s,1H),8.19(t,1H),7.10(d,1H,J=1.6Hz),6.90(d,1H,J=2Hz),5.85(s,1H),4.23(d,2H,J=4.8Hz),3.80(d,2H,J=8.4Hz),3.21-3.27(m,2H),2.73(d,2H,J=7.2Hz),2.55(s,3H),2.18(s,3H),2.15(s,3H),2.10(s,3H),1.74-1.75(m,1H),1.58-1.61(m,2H),1.07-1.16(m,2H)。

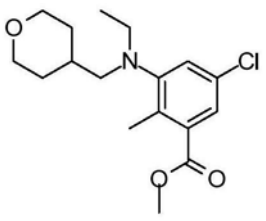
[2300] 化合物 127 :5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-3-(乙基 ((四氢 -2H- 吡喃 -4- 基) 甲基) 氨基)-2- 甲基苯甲酰胺

[2301]



[2302] 步骤 1 :合成 5- 氯 -3-(乙基 ((四氢 -2H- 吡喃 -4- 基) 甲基) 氨基)-2- 甲基苯甲酸甲酯

[2303]

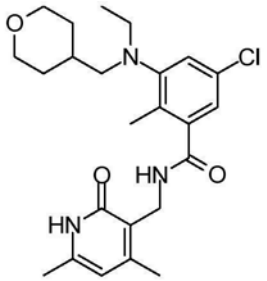


[2304] 向搅拌后的 5- 氯 -2- 甲基 -3-(((四氢 -2H- 吡喃 -4- 基) 甲基) 氨基) 苯甲

酸甲酯(0.40g,1.35mmol)和乙醛(0.120g,2.71mmol)的二氯乙烷(5mL)溶液中加入醋酸(0.48g,8.1mmol),在室温下搅拌10分钟。然后在0℃下向反应混合物加入三乙酰基硼氢化钠(0.663g,4.05mmol),在室温下搅拌3小时。结束时,减压除去溶剂,粗产物通过柱层析纯化得到标题化合物(0.38g,86%)。

[2305] 步骤2:合成5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基((四氢-2H-吡喃-4-基)甲基)氨基)-2-甲基苯甲酰胺

[2306]

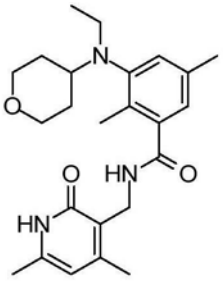


[2307] 向5-氯-3-(乙基((四氢-2H-吡喃-4-基)甲基)氨基)-2-甲基苯甲酸甲酯(0.38g,1.2mmol)的乙醇(20mL)溶液中加入NaOH(0.099g,2.46mmol)水溶液,混合物在60℃搅拌1小时。反应结束后,减压除去乙醇,残余物用稀HCl酸化至pH值为6,用柠檬酸调至pH值为4。用DCM萃取。将合并的有机层干燥,浓缩得到单独的酸(0.2g)。

[2308] 将上述酸(0.2g,0.64mmol)溶解在DMSO(2mL)中,并向其中加入3-(氨基甲基)-4,6-二甲基吡啶-2(1H)-酮(0.196g,1.29mmol)。在室温下搅拌15分钟后,向反应混合物加入PYBOP(0.504g,0.97mmol),继续搅拌过夜。将混合物倒入冰中,用10%MeOH/DCM萃取。合并的有机层用硫酸钠干燥,减压浓缩,得到的粗产物通过柱层析纯化得到标题化合物(0.15g,52%)。LCMS:446.20$(M+1)^+$;HPLC:99.89%(@254nm)(R_t;5.381;方法:色谱柱:YMC ODS-A150mm x4.6mm x5μ;流动相:A;0.05%TFA的水溶液/B;0.05%TFA的乙腈溶液;进样量:10μL,柱温:30℃;流速:1.4mL/min.;梯度:0-8min5%B-95%B,保持1.5min,9.51-12min5%B);^{1}H NMR(DMSO-d_6,400MHz)δ11.47(s,1H),8.21(t,1H),7.14(s,1H),6.91(s,1H),5.85(s,1H),4.23(d,2H,J=4.4Hz),3.78(d,2H,J=8.8Hz),3.18(t,2H,J=11.6Hz),2.82-2.89(m,4H),2.18(s,3H),2.13(s,3H),2.10(s,3H),1.54-1.57(m,3H),1.09-1.15(m,2H),0.91(t,3H,J=6.8Hz)。

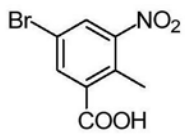
[2309] 化合物157:N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(四氢-2H-吡喃-4-基)氨基)-2,5-二甲基苯甲酰胺

[2310]



[2311] 步骤1:合成5-溴-2-甲基-3-硝基苯甲酸

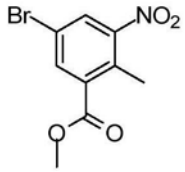
[2312]



[2313] 在室温下，向搅拌后的 2- 甲基 -3- 硝基苯甲酸（50g，276mmol）的浓 H_2SO_4（200mL）溶液中分批加入 1,3- 二溴 -5,5- 二甲基 -2,4- 咪唑烷二酮（43.4g，152mmol）。将所得混合物在室温下搅拌 5 小时，然后倒入冰冷水中。将沉淀物过滤，用水洗涤，真空干燥得到标题化合物（71g，99%）。

[2314] 步骤 2 ：合成 5- 溴 -2- 甲基 -3- 硝基苯甲酸甲酯

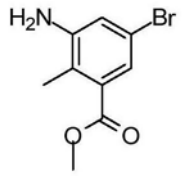
[2315]



[2316] 向搅拌后的 5- 溴 -2- 甲基 -3- 硝基苯甲酸（287g，1100mmol）的 DMF （150mL）溶液中加入碳酸钠（468g，4415mmol）和碘甲烷（627g，4415mmol）。所得混合物在 60℃加热 8 小时。将沉淀物过滤，用乙醚洗涤（5 次）。将合并的有机层干燥，减压浓缩，得到标题化合物（302g，99%），其可直接用于下一步骤，没有进一步纯化。

[2317] 步骤 3 ：合成 3- 氨基 -5- 溴 -2- 甲基苯甲酸甲酯

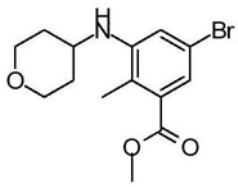
[2318]



[2319] 向搅拌后的 5- 溴 -2- 甲基 -3- 硝基苯甲酸甲酯（150g，544mmol）的乙醇（750mL）溶液加入溶解于水（750mL）中的氯化铵（150g，2777mmol）和铁粉（93.3g，1636mmol）。反应混合物在 80℃加热 7 小时，然后通过硅藻土过滤，所得固体用水和乙酸乙酯洗涤，合并的滤液用乙酸乙酯萃取。将合并的有机层干燥，减压浓缩，得到标题化合物（175g），其可以使用，不用进一步纯化。

[2320] 步骤 4 ：合成 5- 溴 -2- 甲基 -3-（（四氢 -2H- 吡喃 -4- 基）氨基）苯甲酸甲酯

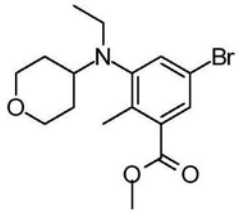
[2321]



[2322] 向搅拌后的 3- 氨基 -5- 溴 -2- 甲基苯甲酸甲酯（15g，61mmol）和二氢 -2H- 吡喃 -4(3H)- 酮（9.2g，92mmol）的二氯乙烷（300mL）溶液中加入醋酸（22g，368.4mmol），反应混合物在室温下搅拌 2 小时。然后在 0℃下，向反应混合物中加入三乙酰基硼氢化钠（39g，184mmol），在室温下搅拌过夜。减压除去溶剂，粗产物通过柱层析纯化得到标题化合物（14g，69%）。

[2323] 步骤 5 :合成 5- 溴 -3-(乙基 (四氢 -2H- 吡喃 -4- 基) 氨基)-2- 甲基苯甲酸甲酯

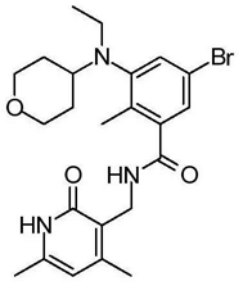
[2324]



[2325] 向搅拌后的 5- 溴 -2- 甲基 -3-((四氢 -2H- 吡喃 -4- 基) 氨基) 苯甲酸甲酯(14g,43mmol)和乙醛(3.75g,85mmol)的二氯乙烷(150mL)溶液中加入醋酸(15.4g,256mmol),反应在室温下搅拌 20 分钟。然后在 0℃下,向反应混合物中加入三乙酰基硼氢化钠(27.0g,128mmol),在室温下搅拌反应 2 小时。减压除去溶剂,向残余物加水。用 DCM 萃取,合并的有机层用硫酸钠干燥,减压浓缩,得到粗产物,将该粗产物通过柱层析纯化得到标题化合物(14g,93%)。

[2326] 步骤 6 :合成 5- 溴 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-3-(乙基 (四氢 -2H- 吡喃 -4- 基) 氨基)-2- 甲基苯甲酰胺

[2327]

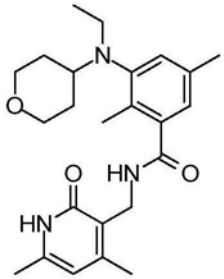


[2328] 向 5- 溴 -3-(乙基 (四氢 -2H- 吡喃 -4- 基) 氨基)-2- 甲基苯甲酸甲酯(14g,39mmol) 的乙醇(100mL) 溶液中加入 NaOH (2.36g,59mmol) 水溶液,所得混合物在 60℃搅拌 1 小时。减压除去乙醇,残余物用稀 HCl 酸化至 pH 值为 6,用柠檬酸调至 pH 值为 4。用乙酸乙酯进行萃取。将合并的有机层干燥并浓缩得到单独的酸(13.9g)。

[2329] 然后将上述酸(10g,29mmol) 溶解在 DMSO (25mL) 中,并向其中加入 3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮(8.8g,58mmol)和三乙胺(5.6g,58mmol)。在室温下搅拌 15 分钟后,向反应混合物加入 PYBOP (22g,43.8mmol),继续搅拌过夜。将所得混合物倒入冰中,用 10%MeOH/DCM 萃取。将合并的有机层干燥,浓缩,得到原料粗品,将该原料粗品通过溶剂洗涤纯化得到标题化合物(14g,74%)。

[2330] 步骤 7 :合成 N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-3-(乙基 (四氢 -2H- 吡喃 -4- 基) 氨基)-2,5- 二甲基苯甲酰胺

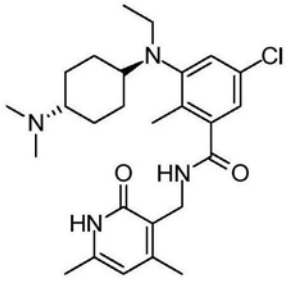
[2331]



[2332] 向搅拌后的5-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(四氢-2H-吡喃-4-基)氨基)-2-甲基苯甲酰胺(0.30g,0.63mmol)的DMF(2mL)溶液中依次加入二氯二(三苯基膦)钯(II)(0.028g,0.034mmol)和四甲基锡(0.124g,0.69mmol)。所得混合物在微波反应器中在160℃下加热30分钟。加水淬灭反应,用10%MeOH/DCM萃取。将合并的有机层干燥并浓缩得到粗产物。将粗产物通过柱层析和然后通过制备HPLC纯化,得到标题化合物相应的三氟乙酸盐(0.15g,57.7%)。LCMS:412.15(M+1)$^+$;HPLC:94.29%(@254nm)(R_t;4.245;方法:色谱柱:YMC ODS-A150mm x4.6mm x5μ;流动相:A;0.05%TFA的水溶液/B;0.05%TFA的乙腈溶液;进样量:10μL,柱温:30℃;流速:1.4mL/min.;梯度:0-8min5%B-95%B,保持1.5min,9.51-12min5%B);^{1}H NMR(CD_3OD,400MHz)δ7.54(s,1H),7.33(s,1H),6.13(s,1H),4.47(s,2H),3.95-3.98(m,4H),3.74(bs,2H),3.37(m,1H),2.42(s,3H),2.38(s,3H),2.37(s,3H),2.24(s,3H),1.61-1.91(bs,4H),1.01(t,3H,J=3.2Hz)。

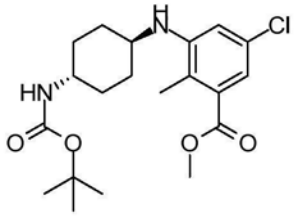
[2333] 化合物222:5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((1s,4s)-4-(二甲基氨基)环己基)(乙基)氨基)-2-甲基苯甲酰胺

[2334]



[2335] 步骤1:合成3-(((1r,4r)-4-((叔丁氧羰基)氨基)环己基)氨基)-5-氯-2-甲基苯甲酸甲酯

[2336]

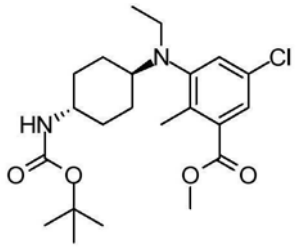


[2337] 在室温下,向搅拌后的3-氨基-5-氯-2-甲基苯甲酸甲酯(5.0g,25mmol)和(4-氧代环己基)氨基甲酸叔丁酯(6.95g,32.6mmol)的25ml二氯乙烷溶液中加入醋酸(9.0ml,450.75mmol)。将反应混合物冷却,加三乙酰基硼氢化钠(22.8g,108mmol),所得混合物室温下搅拌过夜。用饱和$NaHCO_3$溶液中和反应混合物,并用DCM萃取。合并的有机相用Na_2SO_4干

燥，减压浓缩，通过硅胶（100-200）柱层析分离产物异构体得到极性较小的反式异构体，即3-(((1s,4s)-4-((叔丁氧羰基）氨基）环己基）氨基)-5-氯-2-甲基苯甲酸甲酯（5.2g，52%），和极性较大的标题化合物反式异构体，即3-(((1r,4r)-4-((叔丁氧羰基）氨基）环己基）氨基)-5-氯-2-甲基苯甲酸甲酯（3.5g，35%）。

[2338] 步骤2：合成3-(((1r,4r)-4-((叔丁氧羰基）氨基）环己基)(乙基）氨基)-5-氯-2-甲基苯甲酸甲酯

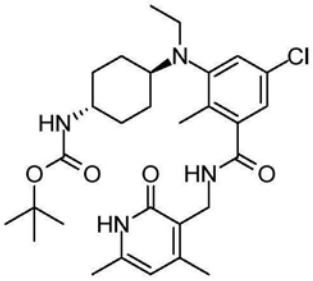
[2339]



[2340] 向搅拌后的3-(((1r,4r)-4-((叔丁氧羰基）氨基）环己基）氨基)-5-氯-2-甲基苯甲酸甲酯（3.0g，7.6mmol）和乙醛（0.66g，15mmol）的15ml二氯乙烷溶液中加入醋酸（2.72ml，45.45mmol），所得混合物在室温下搅拌20分钟。将反应混合物冷却到0℃，加三乙酰基硼氢化钠（4.81g，22.72mmol），在室温下搅拌过夜。反应混合物用饱和$NaHCO_3$溶液中和，用DCM萃取。合并的有机相用Na_2SO_4干燥，减压浓缩，粗产物通过硅胶（100-200）柱层析纯化得到标题化合物（3.5g，96%）。

[2341] 步骤3：合成((1r,rs)-4-((5-氯-3-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基）甲基）氨基甲酰基)-2-甲基苯基)(乙基）氨基）环己基）氨基甲酸叔丁酯

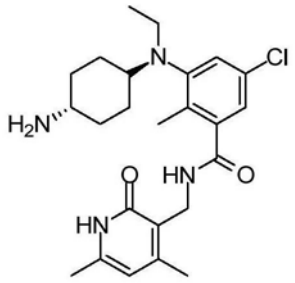
[2342]



[2343] 将3-(((1r,4r)-4-((叔丁氧羰基）氨基）环己基)(乙基）氨基)-5-氯-2-甲基苯甲酸甲酯（3.5g，8.2mmol）和NaOH（0.49g，12mmol）的20ml乙醇：水（4:1）溶液在70℃加热2小时。将反应混合物冷却到0℃，用1N HCl酸化至pH值为6。将混合物浓缩，残余物在水和乙酸乙酯之间分配。有机层用Na_2SO_4干燥，减压浓缩得到3.2g粗品酸。所得粗品酸（3.2g，7.8mmol）、3-(氨基甲基)-4,6-二甲基吡啶-2(1H)-酮（2.36mg，15.5mmol）和PYBOP（6.07mg，11.7mmol）的混合物在15ml DMSO中在室温下搅拌过夜。反应混合物用水稀释，并用10%MeOH/DCM萃取。有机层用Na_2SO_4干燥，减压浓缩，残余物通过硅胶（100-200）柱层析纯化得到标题化合物（3.0g，71%）。

[2344] 步骤4：合成3-(((1r,4r)-4-氨基环己基)(乙基）氨基)-5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基）甲基)-2-甲基苯甲酰胺

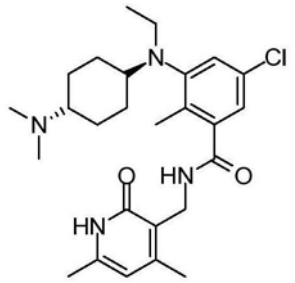
[2345]



[2346] 向冷却的((1r,4r)-4-((5-氯-3-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰)-2-甲基苯基)(乙基)氨基)环己基)氨基甲酸叔丁酯(400mg,0.73mmol)的5ml DCM溶液中加入2ml TFA,反应混合物在室温下搅拌2小时。将反应混合物减压浓缩干。将所得粗产物溶解于10%MeOH/DCM,依次用饱和$NaHCO_3$溶液、水和盐水洗涤。有机相用Na_2SO_4干燥,减压浓缩得到标题化合物(320mg,98%)。

[2347] 步骤5:合成5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-2-甲基苯甲酰胺

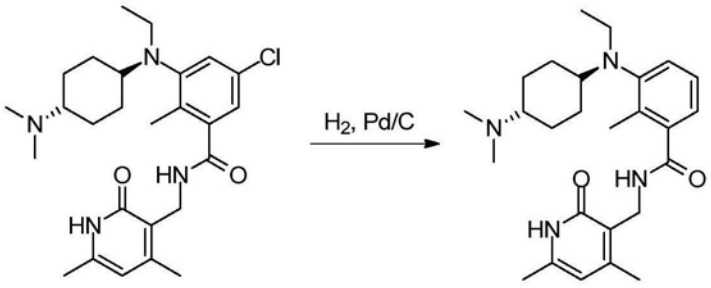
[2348]



[2349] 在0℃下,向搅拌后的3-(((1r,4r)-4-氨基环己基)(乙基)氨基)-5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺(300mg,0.67mmol)和甲醛(0.5ml38%溶液,6.75mmol)的3ml甲醇溶液中加入三乙酰基硼氢化钠(83.0mg,1.35mmol),混合物在室温下搅拌3小时。将反应混合物浓缩至干燥,将残余物在水和10%MeOH的DCM溶液之间分配。有机层用Na_2SO_4干燥,减压浓缩,所得粗品通过碱性氧化铝纯化得到标题化合物(120mg,32%)。

[2350] 化合物268:N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-2-甲基苯甲酰胺

[2351]



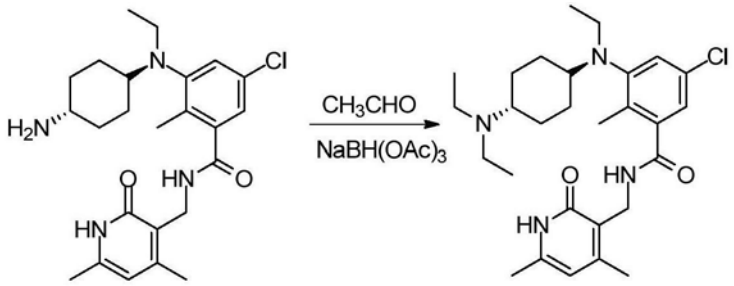
[2352] 向5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-2-甲基苯甲酰胺(80mg,0.16mmol)的5ml甲醇溶液中加入催化量的10%钯碳。所得混合物在气球压力的氢气氛中

搅拌 13 小时。反应混合物通过硅藻土床层过滤，减压浓缩，得到的粘性油状物经乙醚洗涤后得到灰白色固体状的标题化合物（40mg，54%）。

[2353] LCMS:439.25(M+1)$^+$;HPLC:88.61%(@254nm)(R_t4.084; 方法：色谱柱：YMC ODS-A150mm x4.6mm x5μ；流动相：A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液；进样量：10μL，柱温：30℃；流速：1.4mL/min.；梯度：0-8min5%B-95%B，保持 1.5min，9.51-12min5%B)；^{1}H NMR(DMSO-d_6，400MHz) δ 11.46(bs,1H),8.03(t,1H),7.15-7.13m,2H),6.94(d,1H),4.26(d,2H,J=4.4Hz),3.02(d,2H,J=6.8Hz),2.61(s,6H),2.18(s6H),2.10(s,3H),1.97-1.83(m,4H),1.39(m,4H),0.8(t,3H,J=6.8Hz),(3H 合并在溶剂峰中）。

[2354] 化合物 273：5- 氯 -3-(((1s,4s)-4-（二乙基氨基）环己基）（乙基）氨基）-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-2- 甲基苯甲酰胺

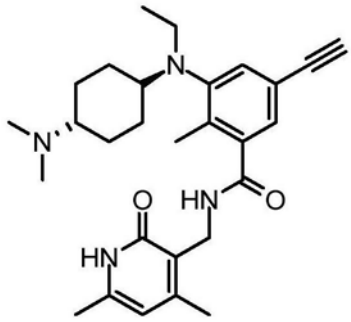
[2355]



[2356] 向搅拌后的 3-(((1r,4r)-4- 氨基环己基）（乙基）氨基）-5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-2- 甲基苯甲酰胺（150mg，0.33mmol）和乙醛（0.15ml，2.70mmol）的 5ml 二氯乙烷溶液中加入醋酸（0.14ml，2.36mmol），所得混合物在室温下搅拌 20 分钟。将反应混合物冷却到 0℃，向其加入三乙酰基硼氢化钠（286mg，1.35mmol），并在室温下搅拌过夜。反应混合物用饱和 $NaHCO_3$ 溶液中和，用 DCM 萃取，用 Na_2SO_4 干燥，减压浓缩得到残余物。所得残余物通过制备 HPLC 纯化得到标题化合物（100mg，59%）。LCMS:501.50(M+1)$^+$;HPLC:93.90%(@210-370nm)(R_t;4.543; 方法：色谱柱：YMC ODS-A150mm x4.6mm x5μ；流动相：A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液；进样量：10μL，柱温：30℃；流速：1.4mL/min.；梯度：0-8min5%B-95%B，保持 1.5min，9.51-12min5%B)；^{1}H NMR(DMSO-d_6，400MHz) δ 11.45(bs,1H),8.21(t,1H),7.13(s,1H),6.92(s,1H),5.85(s,1H),4.25(d,2H,J=3.6Hz),3.03-3.01(m,2H),2.67-2.61(m,2H),2.42-2.33(m,4H),2.19(s,3H),2.14(s,3H),2.11(s,3H),1.73(m,4H),1.39-1.19(m,4H),0.92(m,6H),0.78(t,3H)。

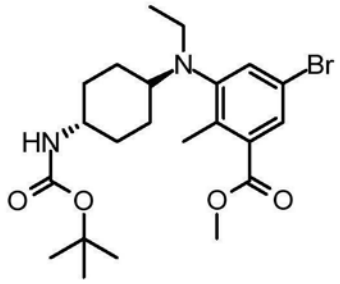
[2357] 化合物 277：N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-3-(((1r,4r)-4-（二甲基氨基）环己基）（乙基）氨基）-5- 乙炔基 -2- 甲基苯甲酰胺

[2358]



[2359] 步骤 1：合成 5- 溴 -3-(((1r,4r)-4-((叔丁氧羰基）氨基）环己基)(乙基）氨基)-2- 甲基苯甲酸甲酯

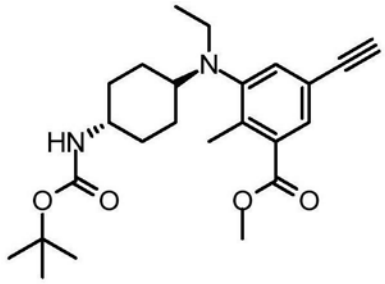
[2360]



[2361] 向搅拌后的 5- 溴 -3-(((1r,4r)-4-((叔丁氧羰基）氨基）环己基）氨基)-2- 甲基苯甲酸甲酯 6.0g,13.0mmol)和乙醛(1.5ml,27.0mmol)的二氯乙烷(60mL)溶液加入醋酸(5.4ml,82mmol),在室温下搅拌 20 分钟。在 0℃下,向反应混合物加入三乙酰基硼氢化钠(8.6g,41mmol),在室温下搅拌混合物 2 小时。反应混合物用饱和 $NaHCO_3$ 溶液中和,用 DCM 萃取。合并的有机相用 Na_2SO_4 干燥,减压浓缩。粗产物通过硅胶(100-200)柱层析纯化得到标题化合物(5.0g,79%)。

[2362] 步骤 2 和 3：合成 3-(((1r,4r)-4-((叔丁氧羰基）氨基）环己基)(乙基）氨基)-5- 乙炔基 -2- 甲基苯甲酸甲酯

[2363]

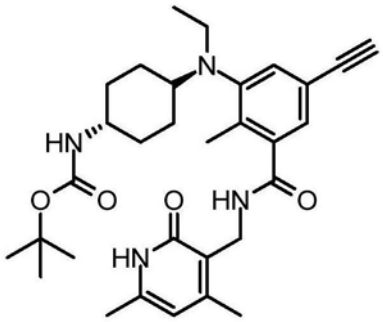


[2364] 将 5- 溴 -3-(((1r,4r)-4-((叔丁氧羰基）氨基）环己基)(乙基）氨基)-2- 甲基苯甲酸甲酯(1.5g,3.20mmol)、三甲基硅基乙炔 (0.52ml,3.84mmol)、碘化铜 (12mg,0.06mmol)和 N,N- 二异丙基胺(1.0ml,8.38mmol)的 20ml 甲苯溶液用氩气净化。将二氯 - 二(三苯基膦）钯 (II)(44mg,0.06mmol)加入到反应混合物中,在 80℃加热 16 小时。将反应混合物冷却到室温,用乙酸乙酯释稀,用水洗涤。有机层用 Na_2SO_4 干燥,减压浓缩得到 1.8g 硅基保护的化合物粗品。将所得粗品溶解于 15ml THF,在室温下向该溶液中加入四丁基氟化铵(7.5ml1M 的 THF 溶液,7.40mmol)。将混合物搅拌 2 小时,用乙酸乙酯稀释,用水洗涤。有机层用 Na_2SO_4 干燥,减压浓缩,残余物通过硅胶(100-200)柱层析纯化得到标题化合物

(800mg,52%)。

[2365] 步骤 4 和 5：合成((1r,4r)-4-((3-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)氨基甲酰基)-5- 乙炔基 -2- 甲基苯基)(乙基)氨基)环己基)氨基甲酸叔丁酯

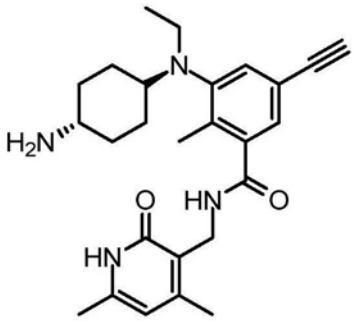
[2366]



[2367] 将 3-(((1r,4r)-4-((叔丁氧羰基)氨基)环己基)(乙基)氨基)-5- 乙炔基 -2- 甲基苯酸甲酯(800mg,1.92mmol)和 NaOH(115mg,2.89mmol)在 12ml 乙醇：水(3:1)中的混合物在 70℃下加热 2 小时。将反应混合物浓缩干,将残余物在水和 DCM 之间分配。有机层用 Na_2SO_4 干燥,减压浓缩得到 700mg 粗品酸。将所得粗品酸(700mg,1.75mmol)、3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮(532mg,3.5mmol)和 PYBOP(1.36g,2.62mmol)在 7ml DMSO 中在室温下搅拌过夜。反应混合物用水稀释,过滤沉淀的产物,通过硅胶柱层析纯化得到标题化合物(750mg,80%)。

[2368] 步骤 6：合成 3-(((1r,4r)-4- 氨基环己基)(乙基)氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)-5- 乙炔基 -2- 甲基苯甲酰胺

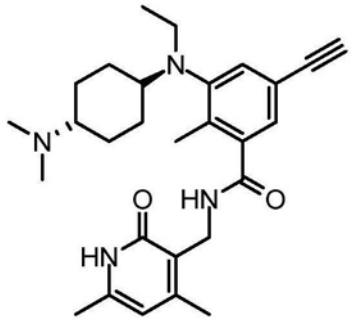
[2369]



[2370] 向冷却的((1r,4r)-4-((3-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)氨基甲酰)-5- 乙炔基 -2- 甲基苯基)(乙基)氨基)环己基)氨基甲酸叔丁酯(750mg,1.40mmol)的 10ml DCM 溶液中加入 3ml TFA。所得混合物在室温下搅拌 2 小时,减压浓缩干。将残余物溶解于 10% 的 MeOH/DCM 中,并依次用饱和 $NaHCO_3$ 溶液、水和盐水洗涤。有机相用 Na_2SO_4 干燥,减压浓缩得到标题化合物粗品(600mg,98%)。

[2371] 步骤 7：合成 N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-5- 乙炔基 -2- 甲基苯甲酰胺

[2372]

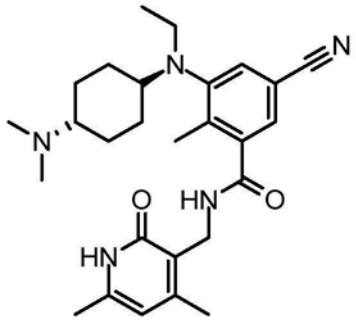


[2373] 在 0℃下，向搅拌后的 3-(((1r,4r)-4- 氨基环己基)(乙基)氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)-5- 乙炔基 -2- 甲基苯甲酰胺粗品(600mg，1.38mmol)和甲醛(0.4ml38% 溶液，6.75mmol)的 10ml 二氯乙烷溶液中加入三乙酰基硼氢化钠(731mg，3.45mmol)。反应混合物在室温下搅拌 3 小时，然后将其在水和 10%MeOH/DCM 之间分配。分离有机层，用 Na_2SO_4 干燥，减压浓缩。残余物经碱性氧化铝纯化得到标题化合物(450mg，70%)。

[2374] N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-5- 乙炔基 -2- 甲基苯甲酰胺 - 三氟乙酸盐的分析数据 :LCMS:463.65(M+1)$^+$;HPLC:92.65%(@254nm)(R_t;4.748; 方法：色谱柱 :YMC ODS-A150mm x4.6mm x5μ；流动相 :A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液；进样量 :10μL，柱温 :30℃；流速 :1.4mL/min.；梯度 :0-8min5%B-95%B, 保持 1.5min,9.51-12min5%B);^{1}H NMR(DMSO-d_6,400MHz) δ 11.46(bs,1H),9.43(bs,1H),8.23(t,1H),7.36(s,1H),7.12(s,1H),5.87(s,1H),4.26(d,2H,J=4.0Hz),3.17-3.03(m,4H),2.69-2.68(m,6H),2.50(1H 合并在溶剂峰中),2.21(s,3H),2.19(s,3H),2.11(s,3H),1.96-1.84(m,4H),1.43(m,4H),0.79(t,3H)。

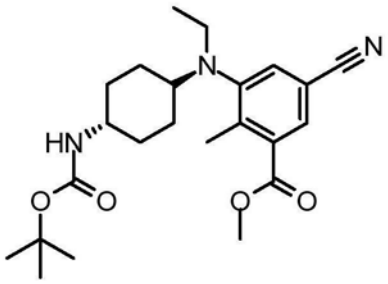
[2375] 化合物 278 :5- 氰基 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-2- 甲基苯甲酰胺

[2376]



[2377] 步骤 1 :合成 3-(((1s,4s)-4-((叔丁氧羰基)氨基)环己基)(乙基)氨基)-5- 氰基 -2- 甲基苯甲酸甲酯

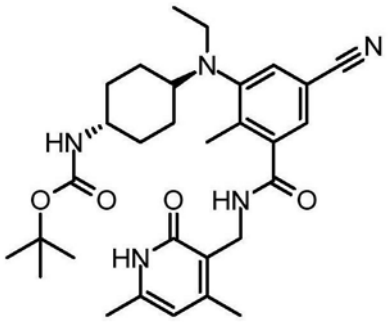
[2378]



[2379] 向化合物 5- 溴 -3-(((1r,4r)-4-((叔丁氧羰基)氨基)环己基)(乙基)氨基)-2- 甲基苯甲酸甲酯(1.0gm,2.13mmol)和 $Zn(CN)_2$(370mg,3.19mmol)的 6ml DMF 溶液中通入氩气脱气 20 分钟后加入 $Pd(PPh_3)_4$(240mg,0.21mmol)。反应混合物在 100℃加热过夜,用水稀释,用乙酸乙酯萃取。合并的有机层用 Na_2SO_4 干燥,浓缩,残余物通过硅胶柱层析纯化得到标题化合物(280mg,82%)。

[2380] 步骤 2 和 3 :合成 ((1r,4r)-4-((5- 氰基 -3-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)氨基甲酰基)-2- 甲基苯基)(乙基)氨基)环己基)氨基甲酸叔丁酯

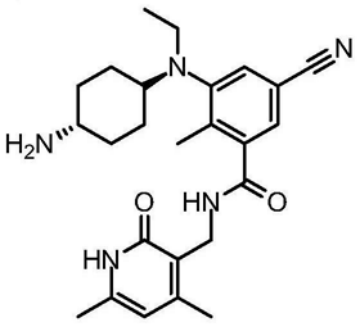
[2381]



[2382] 将 3-(((1r,4r)-4-((叔丁氧羰基)氨基)环己基)(乙基)氨基)-5- 氰基 -2- 甲基苯甲酸甲酯(735mg,1.78mmol)和 NaOH (85mg,2.13mmol)在 12ml 乙醇 : 水(3:1)中的混合物在 70℃加热 2 小时。将所得混合物浓缩干,将粗产物在水和 DCM 之间分配。有机层用 Na_2SO_4 干燥,减压浓缩得到 380mg 粗品酸。将所得粗品酸(380mg,0.94mmol)、3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮(287mg,1.89mmol)和 PYBOP (737mg,1.41mmol)在 4ml DMSO 中的混合物在室温下搅拌过夜。反应混合物用水稀释,用 10%MeOH/DCM 萃取。合并的有机相用 Na_2SO_4 干燥,减压浓缩,残余物通过硅胶柱层析纯化得到标题化合物(350mg,75%)。

[2383] 步骤 4 :合成 3-(((1r,4r)-4- 氨基环己基)(乙基)氨基)-5- 氰基 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)-2- 甲基苯甲酰胺

[2384]

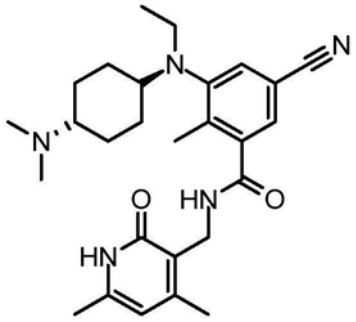


[2385] 向冷却后的化合物((1r,4r)-4-((5- 氰基 -3-(((4,6- 二甲基 -2- 氧代 -1,2- 二

氢吡啶 -3- 基) 甲基) 氨基甲酰基)-2- 甲基苯基)(乙基) 氨基) 环己基) 氨基甲酸叔丁酯(350mg,0.80mmol)在 5ml DCM 中的溶液加入 1ml TFA。将所得混合物搅拌 2 小时,减压浓缩至干燥。将残余物溶解于 10%MeOH/DCM 中,依次用饱和 $NaHCO_3$ 溶液、水和盐水洗涤。有机相用 Na_2SO_4 干燥,减压浓缩得到 284mg 标题化合物的粗品。

[2386] 步骤 5 : 合成 5- 氰基 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)-3-(((1r,4r)-4-(二甲基氨基) 环己基)(乙基) 氨基)-2- 甲基苯甲酰胺

[2387]

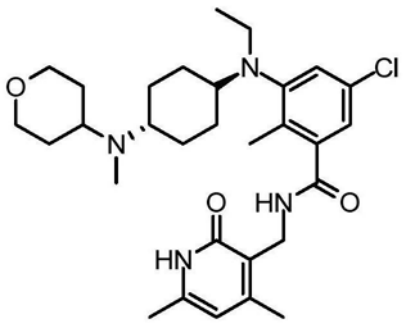


[2388] 在 0℃下,向搅拌后的 3-(((1r,4r)-4- 氨基环己基)(乙基) 氨基)-5- 氰基 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基苯甲酰胺粗品(325mg,0.74mmol)和甲醛(0.3ml38% 溶液,3.72mmol)的甲醇(10ml)溶液中加入氰基硼氢化钠(100mg,1.49mmol)。将混合物在室温下搅拌 4 小时,并将其在水和 10%MeOH/DCM 中分配。有机层用 Na_2SO_4 干燥,减压浓缩,残余物通过碱性氧化铝柱纯化得到标题化合物(75mg,22%)。

[2389] 5- 氰基 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-3-(((1s,4s)-4-(二甲基氨基) 环己基)(乙基) 氨基)-2- 甲基苯甲酰胺的分析数据 :LCMS:464.30(M+1)$^+$;HPLC:87.24%(@254nm)(R_t;4.540; 方法 : 色谱柱 :YMC ODS-A150mm x4.6mm x5μ ; 流动相 :A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液 ; 进样量 :10μL, 柱温 :30℃ ; 流速 :1.4mL/min. ; 梯度 :0-8min5%B-95%B, 保持 1.5min,9.51-12min5%B);^{1}H NMR(DMSO-d_6,400MHz) δ 11.47(bs,1H),8.31(t,1H),7.61(s,1H),7.35(s,1H),5.87(s,1H),4.26(d,2H,J=4.4Hz),3.07-3.05(m,3H),2.73-2.63(m,7H),2.25(s,3H),2.20(s,3H),2.11(s,3H),1.96-1.82(m,4H),1.41-1.37(m,4H),0.78(t,3H)。

[2390] 化合物 279 :5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-3-(乙基 ((1r,4r)-4-(甲基 (四氢 -2H- 吡喃 -4- 基) 氨基) 环己基) 氨基)-2- 甲基苯甲酰胺

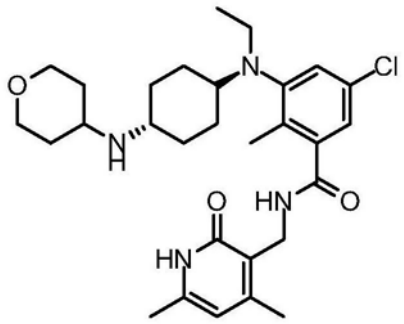
[2391]



[2392] 步骤 1 : 合成 5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲

基)-3-(乙基((1r,4r)-4-(甲基(四氢-2H-吡喃-4-基)氨基)环己基)氨基)-2-甲基苯甲酰胺

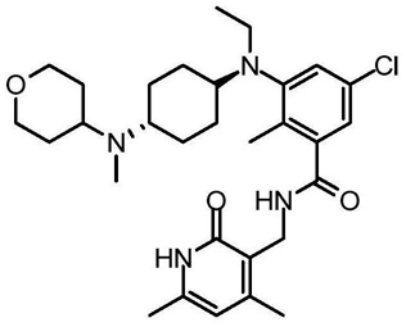
[2393]



[2394] 向搅拌后的3-(((1r,4r)-4-氨基环己基)(乙基)氨基)-5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺(300mg,0.67mmol)和二氢-2H-吡喃-4(3H)-酮(99mg,1.01mmol)的二氯乙烷(5ml)溶液中加入醋酸(0.24ml,4.05mmol),混合物在室温下搅拌20分钟。将所得混合物冷却到0℃,加三乙酰基硼氢化钠(429mg,2.02mmol),在室温下搅拌反应过夜。反应混合物用饱和$NaHCO_3$溶液中和,用DCM萃取。合并有机相Na_2SO_4干燥,减压浓缩,残余物通过硅胶柱层析纯化得到标题化合物(175mg,57%)。

[2395] 步骤2:合成5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基((1r,4r)-4-(甲基(四氢-2H-吡喃-4-基)氨基)环己基)氨基)-2-甲基苯甲酰胺

[2396]



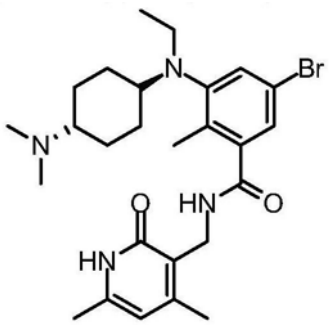
[2397] 在0℃下,向搅拌后的5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基((1r,4r)-4-((四氢-2H-吡喃-4-基)氨基)环己基)氨基)-2-甲基苯甲酰胺(175mg,0.33mmol)和福尔马林(99mg,3.31mmol)的甲醇(2ml)溶液中加入氰基硼氢化钠(41mg,0.66mmol)。混合物在室温下搅拌过夜,用饱和$NaHCO_3$溶液中和,用DCM萃取。合并的有机相用Na_2SO_4干燥,减压浓缩,残余物通过制备HPLC纯化得到标题化合物(70mg,39%)。

[2398] LCMS:543.65$(M+1)^+$;HPLC:98.19%(@210-370nm)(R_t;4.515;方法:色谱柱:YMC ODS-A150mm x4.6mm x5μ;流动相:A;0.05%TFA的水溶液/B;0.05%TFA的乙腈溶液;进样量:10μL,柱温:30℃;流速:1.4mL/min.;梯度:0-8min5%B-95%B,保持1.5min,9.51-12min5%B);^1H NMR(DMSO-d_6,400MHz)δ11.45(bs,1H),8.21(t,1H),7.13(s,1H),6.92(s,1H),5.85(s,1H),4.25(d,2H,J=4Hz),3.84-3.82(m,2H),3.26-3.23(m,3H),3.0

3-3.01(m,2H),2.67-2.53(m,2H),2.19(s,3H),2.14(s,3H),2.11(s,6H),1.75-1.57(m,6H),1.41-1.24(m,6H),0.78(t,3H)。

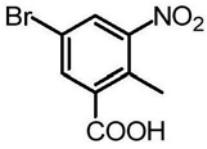
[2399] 化合物276:合成化合物5-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-2-甲基苯甲酰胺

[2400]



[2401] 步骤1:合成5-溴-2-甲基-3-硝基苯甲酸

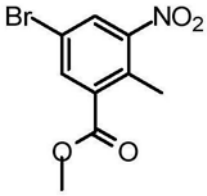
[2402]



[2403] 在室温下,向搅拌后的化合物2-甲基-3-硝基苯甲酸(50.0g,276mmol)的浓H_2SO_4(200mL)分批加入1,3-二溴-5,5-二甲基-2,4-咪唑烷二酮(43.4g,152mmol),继续搅拌5小时。结束时,将反应混合物倒入冰冷水中,将固体沉淀物过滤,用水洗涤,真空干燥,得到标题化合物粗品(71.7g,99.9%),其使用时没有进一步纯化。

[2404] 步骤2:合成5-溴-2-甲基-3-硝基苯甲酸甲酯

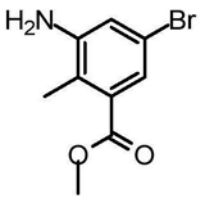
[2405]



[2406] 向搅拌后的5-溴-2-甲基-3-硝基苯甲酸粗品(287g,1103mmol)的DMF(150mL)溶液中加入碳酸钠(468g,4415mmol)和碘甲烷(626g,4415mmol)。所得混合物在60℃加热8小时,冷却到室温。将固体沉淀物过滤,用乙醚洗涤(5次)。将合并的有机层干燥,减压浓缩得到标题化合物(302g,99%),其可直接使用。

[2407] 步骤3:合成3-氨基-5-溴-2-甲基苯甲酸甲酯

[2408]

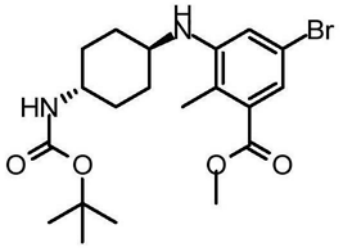


[2409] 在剧烈搅拌条件下,向上述化合物5-溴-2-甲基-3-硝基苯甲酸甲酯粗品(150g,

0.54mol)的乙醇(750mL)溶液中依次加入溶解于水(750mL)中的氯化铵(150g,2.78mol)和铁粉(93.3g,1.64mol)。所得混合物在80℃加热7小时,通过硅藻土过滤。滤饼用水和乙酸乙酯洗涤,滤液用乙酸乙酯萃取。合并的有机层用Na_2SO_4干燥,减压浓缩得到标题化合物(175g粗品)。

[2410] 步骤4:合成5-溴-3-(((1r,4r)-4-((叔丁氧羰基)氨基)环己基)氨基)-2-甲基苯甲酸甲酯

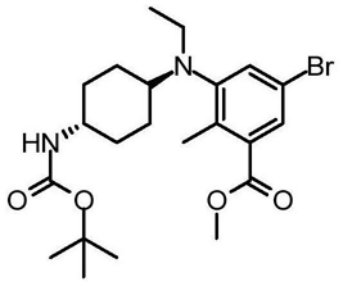
[2411]



[2412] 向搅拌后的3-氨基-5-溴-2-甲基苯甲酸甲酯粗品(15g,62mmol)和(4-氧代环己基)氨基甲酸叔丁酯(17g,8mmol)的二氯乙烷(200mL)溶液中加入醋酸(23ml,368mmol),反应在室温下搅拌10分钟。然后在0℃下,将三乙酰基硼氢化钠(40g,185mmol)加到反应混合物中,在室温下搅拌过夜。反应混合物用饱和$NaHCO_3$溶液中和,用DCM萃取。合并的有机相用Na_2SO_4干燥,减压浓缩。通过柱层析分离异构混合物粗品得到所需的标题化合物(6.0g,22%)。

[2413] 步骤5:合成5-溴-3-(((1r,4r)-4-((叔丁氧羰基)氨基)环己基)(乙基)氨基)-2-甲基苯甲酸甲酯

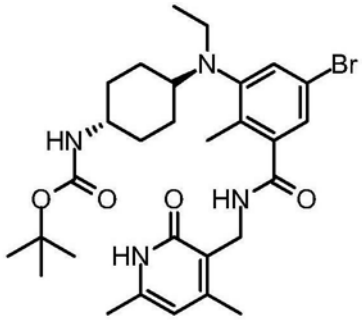
[2414]



[2415] 向搅拌后的5-溴-3-(((1r,4r)-4-((叔丁氧羰基)氨基)环己基)氨基)-2-甲基苯甲酸甲酯(6.0g,13.0mmol)和乙醛(1.5ml,27.0mmol)的二氯乙烷(60mL)溶液中加入醋酸(5.4ml,82mmol),在室温下搅拌20分钟。在0℃下,向反应混合物中加入三乙酰基硼氢化钠(8.6g,40.9mmol),在室温下搅拌2小时。反应混合物用饱和$NaHCO_3$溶液中和,并用DCM萃取。合并的有机相用Na_2SO_4干燥,减压浓缩。将粗产物通过硅胶柱层析得到标题化合物(5.0g,79%)。

[2416] 步骤6和7:合成((1r,4r)-4-((5-溴-3-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰基)-2-甲基苯基)(乙基)氨基)环己基)氨基甲酸叔丁酯

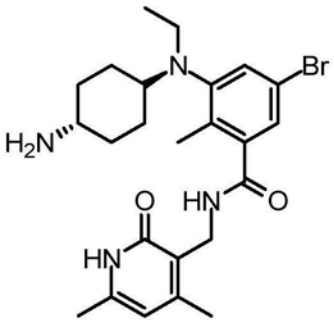
[2417]



[2418] 将 5- 溴 -3-(((1r,4r)-4-((叔丁氧羰基)氨基)环己基)(乙基)氨基)-2- 甲基苯甲酸甲酯(1.00g,2.13mmol)和 NaOH (102mg,2.56mmol)在 6ml 乙醇 : 水(2:1)中的混合物在 70℃加热 2 小时。将反应混合物浓缩干,将残余物在水和 DCM 之间分配。有机层用 Na_2SO_4 干燥,减压浓缩得到 1.0g 粗品酸。将所述粗品酸(1.0g,2.20mmol)、3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮(669mg,4.40mmol)、PYBOP (1.71g,3.30mmol)和 1ml 三乙胺在 2ml DMSO 中在室温下搅拌过夜。反应混合物用水稀释,并用 DCM 萃取。合并的有机层用 Na_2SO_4 干燥,减压浓缩,残余物通过硅胶柱层析纯化得到标题化合物(1.0g,83%)。

[2419] 步骤 8 :合成 3-(((1r,4r)-4- 氨基环己基)(乙基)氨基)-5- 溴 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)-2- 甲基苯甲酰胺

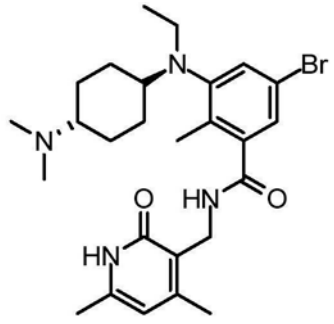
[2420]



[2421] 向冷却的化合物((1r,4r)-4-((5- 溴 -3-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)氨基甲酰基)-2- 甲基苯基)(乙基)氨基)环己基)氨基甲酸叔丁酯(1.0g,1.60mmol)的 DCM (10ml)溶液加入 2ml TFA。反应混合物在室温下搅拌 2 小时,减压浓缩干。将残余物溶解于 10%MeOH/DCM 中,依次用饱和 $NaHCO_3$ 溶液、水和盐水洗涤。有机相用 Na_2SO_4 干燥,减压浓缩得到标题化合物的粗品(650mg,81%)。

[2422] 步骤 9 :合成 5- 溴 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-2- 甲基苯甲酰胺

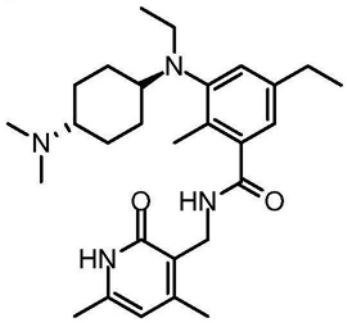
[2423]



[2424] 在 0 ℃ 下，向搅拌后的 3-(((1r,4r)-4- 氨基环己基)(乙基)氨基)-5- 溴 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)-2- 甲基苯甲酰胺粗品(650mg,1.32mmol)和甲醛(0.5ml38% 溶液,13.3mmol)的甲醇(10ml)溶液中加入氰基硼氢化钠(82mg,1.32mmol),混合物在室温下搅拌过夜。将反应混合物在水和 10%MeOH/DCM 之间分配。有机层用 Na_2SO_4 干燥,减压浓缩。残余物通过碱性氧化铝柱纯化得到标题化合物(450mg,65%)。5- 溴 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-2- 甲基苯甲酰胺的分析数据 :LCMS:519.30(M+1)$^+$;HPLC:98.35%(@254nm)(Rt;4.392); 方法 : 色谱柱 :YMC ODS-A150mm x4.6mm x5μ ; 流动相 :A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液 ; 进样量 :10μL, 柱温 :30℃ ; 流速 :1.4mL/min. ; 梯度 :0-8min5%B-95%B, 保持 1.5min,9.51-12min5%B);^{1}H NMR(DMSO-d_6,400MHz) δ 11.46(bs,1H),9.39(bs,1H),8.23(t,1H),7.30(s,1H),7.09(s,1H),5.86(s,1H),4.25(d,2H,J=4.0Hz),3.03-3.01(m,3H),2.69-2.69(m,6H),2.50(1H merged in solvent peak),2.18(s,3H),2.14(s,3H),2.11(s,3H),1.94-1.84(m,4H),1.42(m,4H),0.79(t,3H,J=6.8Hz)。

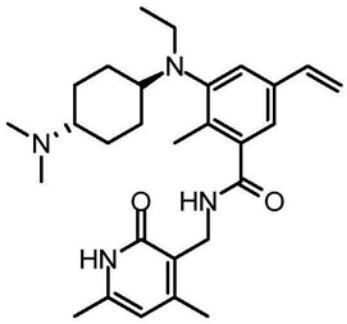
[2425] 化合物 282 :N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-5- 乙基 -2- 甲基苯甲酰胺

[2426]



[2427] 步骤 1 : 合成 N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-2- 甲基 -5- 乙烯基苯甲酰胺

[2428]

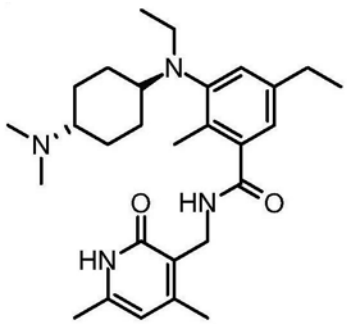


[2429] 5- 溴 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-2- 甲基苯甲酰胺(200mg,0.38mmol)、4,4,5,5- 四甲基 -2- 乙烯基 -1,3,2- 二氧杂硼烷(71mg,0.46mmol)和碳酸钠(147mg,1.39mmol)在 10ml 二氧六环中的混合物用氩气进行 20 分钟脱气处理,然后向上述溶液加 $Pd(PPh_3)_4$(44mg,0.04mmol),所得混合物在 100℃加热过夜。将反应混合物冷却到室

温，用水稀释。混合物用 10%MeOH/DCM 萃取，合并的有机相用 Na_2SO_4 干燥，浓缩。残余物通过硅胶层析纯化得到标题化合物（150mg，83%）。

[2430] 步骤 2：合成 N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-3-(((1r,4r)-4-（二甲基氨基）环己基）（乙基）氨基）-5- 乙基 -2- 甲基苯甲酰胺

[2431]

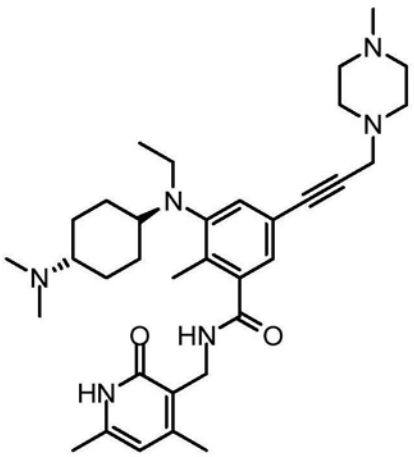


[2432] 向化合物 N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-3-(((1r,4r)-4-（二甲基氨基）环己基）（乙基）氨基）-2- 甲基 -5- 乙烯基苯甲酰胺（150mg，0.32mmol）的甲醇（5mL）溶液中加入催化量的 10% 钯碳。所得混合物在气球压力的氢气氛中搅拌 12 小时，通过硅藻土过滤，减压浓缩。残余物通过制备 HPLC 纯化得到标题化合物的三氟乙酸盐（65mg，43%）。

[2433] LCMS:467.35(M+1)$^+$;HPLC:93.41%(@254nm)(Rt;10.946; 方法：色谱柱：YMC ODS-A150mm x4.6mm x5μ；流动相：A;10m M 甲酸铵水溶液 +0.1%NH_3,B; 乙腈 +5% 溶剂 A+0.1%NH_3; 进样量：10μL, 柱温：30 ℃；流速：1.0mL/min.；梯度：0-6.0min15%B-95%B,6.0-8.0min 保持，在 8.5min15%B 保持到 15min);^{1}H NMR(DMSO-d_6,400MHz) δ 11.47(bs,1H),9.45(s,1H),8.38(s,1H),8.03(s,2H),7.26-6.84(m,2H),5.87(s,1H),4.26(d,J=4.0Hz,2H),3.17-2.89(m,3H),2.70,2.68(2s,6H),2.19,2.11(3s,9H),1.96-1.87(m,4H),1.42(m,4H),1.15(t,J=7.2Hz,3H),0.80(s,3H)。

[2434] 化合物 283：N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-3-(((1r,4r)-4-（二甲基氨基）环己基）（乙基）氨基）-2- 甲基 -5-(3-(4- 甲基哌嗪 -1- 基）丙 -1- 炔 -1- 基）苯甲酰胺

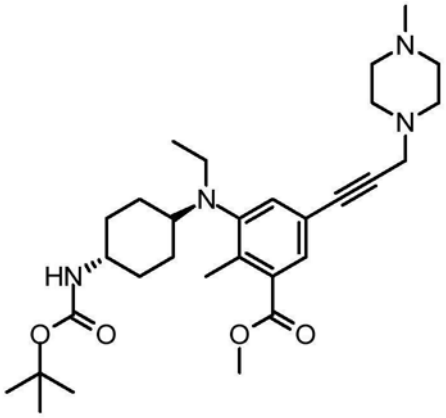
[2435]



[2436] 步骤 1：合成 3-(((1r,4r)-4-((叔丁氧羰基）氨基）环己基）（乙基）氨基）-2- 甲

基-5-(3-(4-甲基哌嗪-1-基)丙-1-炔-1-基)苯甲酸甲酯

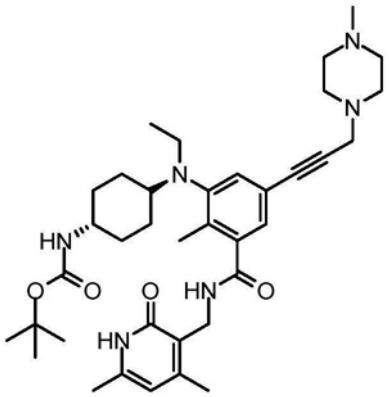
[2437]



[2438] 5-(3-溴丙-1-炔-1-基)-3-(((1r,4r)-4-((叔丁氧羰基)氨基)环己基)(乙基)氨基)-2-甲基苯甲酸甲酯(500mg,1.0mmol)和1-甲基哌嗪(0.49ml,4.9mmol)的DMF(5ml)溶液在室温下搅拌过夜。反应混合物用水稀释,并用DCM萃取。合并的有机相用Na_2SO_4干燥,减压浓缩得到标题化合物(550mg)。

[2439] 步骤2和3:合成((1r,4r)-4-((3-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰基)-2-甲基-5-(3-(4-甲基哌嗪-1-基)丙-1-炔-1-基)苯基)(乙基)氨基)环己基)氨基甲酸叔丁酯

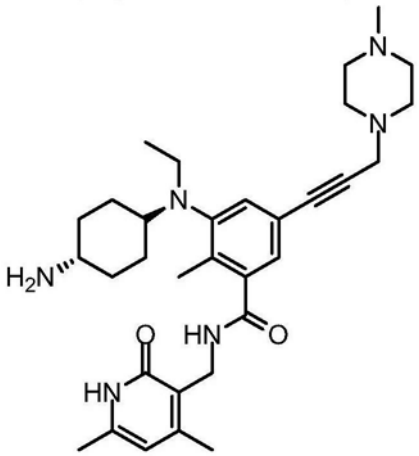
[2440]



[2441] 将化合物3-(((1r,4r)-4-((叔丁氧羰基)氨基)环己基)(乙基)氨基)-2-甲基-5-(3-(4-甲基哌嗪-1-基)丙-1-炔-1-基)苯甲酸甲酯(550mg,1.0mmol)和NaOH(83mg,2.1mmol)在8ml乙醇:水(3:1)中的混合物在70℃加热2小时。将反应混合物浓缩干,将残余物在水和DCM之间分配。有机层用Na_2SO_4干燥,减压浓缩得到470mg酸。将所得粗品酸(470mg,0.92mmol)、3-(氨基甲基)-4,6-二甲基吡啶-2(1H)-酮(279mg,1.83mmol)、PYBOP(716mg,1.37mmol)和三乙胺(0.38ml,2.75mmol)的混合物在5ml DMSO中在室温下搅拌过夜。反应混合物用水稀释,将化合物萃取到10%MeOH/DCM中。有机层用Na_2SO_4干燥,减压浓缩,残余物通过硅胶柱层析纯化得到标题化合物(350mg,50%)。

[2442] 步骤4:合成3-(((1r,4r)-4-氨基环己基)(乙基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-5-(3-(4-甲基哌嗪-1-基)丙-1-炔-1-基)苯甲酰胺

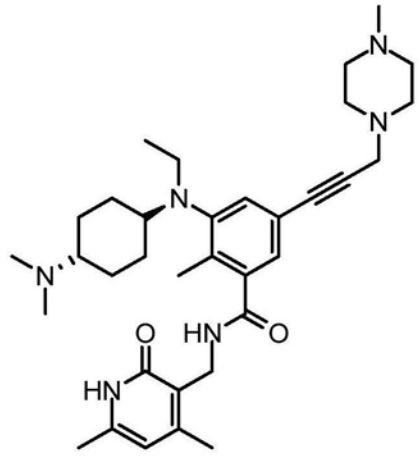
[2443]



[2444] 向冷却的((1r,4r)-4-((3-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰基)-2-甲基-5-(3-(4-甲基哌嗪-1-基)丙-1-炔-1-基)苯基)(乙基)氨基)环己基)氨基甲酸叔丁酯(350mg,0.54mmol)的DCM(5ml)溶液中加入2ml TFA。反应混合物在室温下搅拌2小时,减压浓缩干。将残余物溶解于10%MeOH/DCM中,依次用饱和$NaHCO_3$溶液、水和盐水洗涤。有机相用Na_2SO_4干燥,减压浓缩得到标题化合物粗品(250mg,84%)。

[2445] 步骤5:合成N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-2-甲基-5-(3-(4-甲基哌嗪-1-基)丙-1-炔-1-基)苯甲酰胺

[2446]



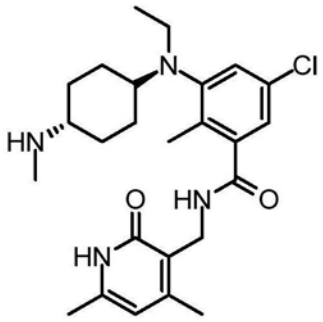
[2447] 在0℃下,向搅拌后的3-(((1r,4r)-4-氨基环己基)(乙基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-5-(3-(4-甲基哌嗪-1-基)丙-1-炔-1-基)苯甲酰胺粗品(250mg,0.45mmol)和甲醛(0.35ml38%溶液,4.56mmol)的甲醇(3ml)溶液中加入氰基硼氢化钠(85mg,1.37mmol)。将所得混合物在室温下搅拌4小时,并将其在水和10%MeOH/DCM之间分配。分离有机层,用Na_2SO_4干燥,减压浓缩。残余物通过制备HPLC纯化得到标题化合物的三氟乙酸盐(40mg,15%)。

[2448] LCMS:575.45(M+1)$^+$;HPLC:99.30%(@254nm)(R_t;3.849;方法:色谱柱:YMC ODS-A150mm x4.6mm x5μ;流动相:A;0.05%TFA的水溶液/B;0.05%TFA的乙腈溶液;进样量:10μL,柱温:30℃;流速:1.4mL/min.;梯度:0-8min5%B-95%B,保持

1.5min,9.51-12min5%B);^{1}H NMR(D_2O,400MHz) δ 7.75(s,1H),7.60(s,1H),6.28(s,1H),4.45(d,J=4.0Hz,2H),3.80-3.63(m,5H),3.40-3.21(m,9H),2.92(s,3H),2.79(2s,6H),2.35(m,3H),2.32(s,3H),2.26(s,3H),2.19-2.05(m,4H),1.65-1.57(m,4H),0.97(t,J=7.2Hz,3H)。

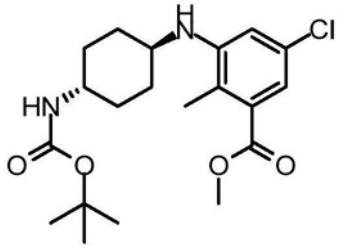
[2449] 化合物284:5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基((1r,4r)-4-(甲基氨基)环己基)氨基)-2-甲基苯甲酰胺

[2450]



[2451] 步骤1:合成3-(((1r,4r)-4-((叔丁氧羰基)氨基)环己基)氨基)-5-氯-2-甲基苯甲酸甲酯

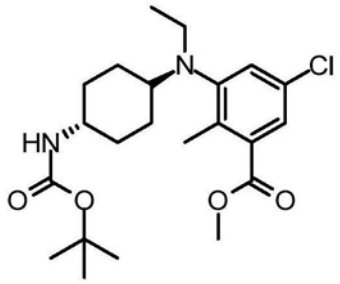
[2452]



[2453] 向搅拌后的3-氨基-5-氯-2-甲基苯甲酸甲酯(5.0g,25mmol)和(4-氧代环己基)氨基甲酸叔丁酯(6.95g,32.7mmol)的二氯乙烷(25mL)溶液中加入醋酸(9.0ml,450mmol),并在室温下搅拌10分钟。混合物冷却到室温后,向反应混合物中加入三乙酰基硼氢化钠(22.8g,108mmol),搅拌过夜。混合物用饱和$NaHCO_3$溶液中和,并用DCM萃取。合并的有机相用Na_2SO_4干燥,减压浓缩,残余物经硅胶柱层析纯化得到标题化合物极性较大的反式异构体3-(((1r,4r)-4-((叔丁氧羰基)氨基)环己基)氨基)-5-氯-2-甲基苯甲酸甲酯(3.5g,35%),以及极性较小的顺式异构体3-(((1s,4s)-4-((叔丁氧羰基)氨基)环己基)氨基)-5-氯-2-甲基苯甲酸甲酯(5.2g,52%)。

[2454] 步骤2:合成3-(((1r,4r)-4-((叔丁氧羰基)氨基)环己基)(乙基)氨基)-5-氯-2-甲基苯甲酸甲酯

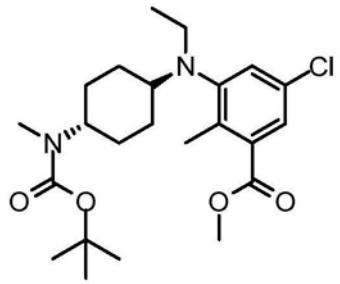
[2455]



[2456] 向搅拌后的 3-(((1r,4r)-4-((叔丁氧羰基)氨基)环己基)氨基)-5-氯-2-甲基苯甲酸甲酯(3.0g,7.6mmol)和乙醛(0.66g,15mmol)的二氯乙烷(15mL)溶液中加入醋酸(2.7ml,45mmol),混合物在室温下搅拌 20 分钟。将反应混合物冷却到 0℃,向其加入三乙酰基硼氢化钠(4.8g,22mmol),在室温下搅拌过夜。混合物用饱和 $NaHCO_3$ 溶液中和,并用 DCM 萃取。合并的有机相用 Na_2SO_4 干燥,减压浓缩。残余物经硅胶柱纯化得到标题化合物(3.5g,96%)。

[2457] 步骤 3:合成 3-(((1r,4r)-4-((叔丁氧羰基)(甲基)氨基)环己基)(乙基)氨基)-5-氯-2-甲基苯甲酸甲酯

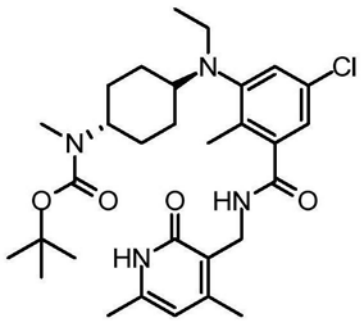
[2458]



[2459] 向冷却后的 3-(((1r,4r)-4-((叔丁氧羰基)氨基)环己基)(乙基)氨基)-5-氯-2-甲基苯甲酸甲酯(1.1g,3.3mmol)的 THF (12mL)溶液中依次加入氢化钠(410mg,10mmol)和碘甲烷(2.1ml,34mmol)。将混合物在室温下搅拌过夜,通过缓慢加入冰水来淬灭反应,再用柠檬酸溶液酸化。用 10%MeOH/DCM 萃取,将合并的有机相干燥,减压浓缩,得到标题化合物(1.0g,88%)。

[2460] 步骤 4 和 5:合成((1r,4r)-4-((5-氯-3-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰基)-2-甲基苯基)(乙基)氨基)环己基)(甲基)氨基甲酸叔丁酯

[2461]

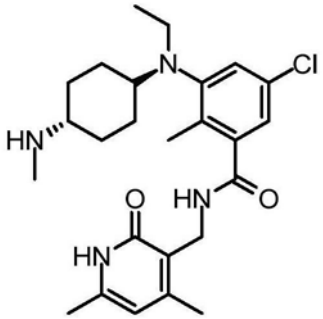


[2462] 将 3-(((1r,4r)-4-((叔丁氧羰基)(甲基)氨基)环己基)(乙基)氨基)-5-氯-2-甲基苯甲酸甲酯(1.0g,2.4mmol)和 NaOH (140mg,3.5mmol)在 10ml 乙醇:

水(4:1)中的混合物在70℃加热2小时。将反应混合物浓缩干,将残余物在水和DCM之间分配。有机层用Na_2SO_4干燥,减压浓缩得到1.0g的粗品酸。将所得粗品酸(1.0g,2.4mmol)、3-(氨基甲基)-4,6-二甲基吡啶-2(1H)-酮(716mg,4.71mmol)、PYBOP(1.83g,3.53mmol)和三乙胺(2mL)的DMSO(5ml)溶液在室温下搅拌过夜。将所得混合物用水稀释,用10%MeOH/DCM萃取。合并的有机层用Na_2SO_4干燥,减压浓缩,残余物通过硅胶柱层析纯化得到标题化合物(700mg,53%)。

[2463] 步骤6:合成5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基((1r,4r)-4-(甲基氨基)环己基)氨基)-2-甲基苯甲酰胺

[2464]

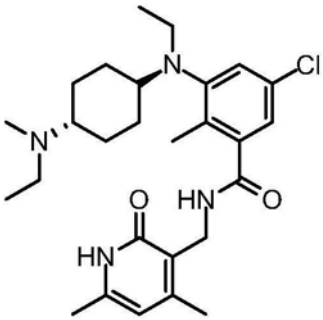


[2465] 向冷却后的((1s,4s)-4-((5-氯-3-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰基)-2-甲基苯基)(乙基)氨基)环己基)(甲基)氨基甲酸叔丁酯(700mg,1.25mmol)的DCM(20ml)溶液中加入TFA(3mL)。反应混合物在室温下搅拌2小时,减压浓缩干。将残余物溶解于10%MeOH/DCM,依次用饱和$NaHCO_3$溶液、水和盐水洗涤。有机相用Na_2SO_4干燥,减压浓缩,残余物经制备HPLC纯化得到标题化合物的三氟乙酸盐(500mg,87%)。

[2466] LCMS:459.35$(M+1)^+$;HPLC:97.63%(@254nm)(Rt;4.565;方法:色谱柱:YMC ODS-A150mm x4.6mm x5μ;流动相:A;0.05%TFA的水溶液/B;0.05%TFA的乙腈溶液;进样量:10μL,柱温:30℃;流速:1.4mL/min.;梯度:0-8min5%B-95%B,保持1.5min,9.51-12min5%B);^1H NMR(DMSO-D_6,400MHz)δ11.46(bs,1H),8.32(s,2H),8.22(m,1H),7.20(s,1H),7.00(s,1H),5.86(s,1H),4.25(d,J=4.0Hz,2H),3.74(m,3H),3.03-3.01(m,3H),2.67(m,1H),2.19(s,3H),2.14(s,3H),2.11(s,3H),1.33(m,2H),1.82-1.80(m,2H),1.42-1.23(m,2H+2H),0.78(t,J=7.2Hz,3H)。

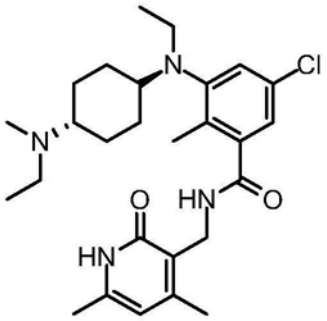
[2467] 化合物285:5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基((1r,4r)-4-(乙基(甲基)氨基)环己基)氨基)-2-甲基苯甲酰胺

[2468]



[2469] 步骤 1：合成 5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-3-（乙基 ((1r,4r)-4-（乙基（甲基）氨基）环己基）氨基）-2- 甲基苯甲酰胺

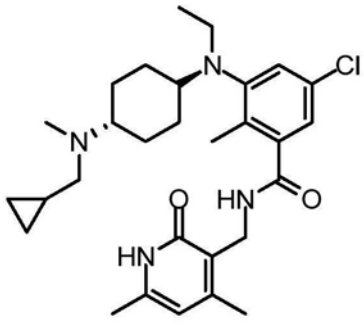
[2470]



[2471] 向搅拌后的化合物 5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-3-（乙基 ((1r,4r)-4-（甲基氨基）环己基）氨基）-2- 甲基苯甲酰胺（200mg，0.43mmol）和乙醛（0.03ml，0.43mmol）的二氯乙烷（5mL）溶液中加入醋酸（0.15ml，2.62mmol），混合物在室温下搅拌 20 分钟。混合物冷却到 0℃后，向反应混合物加入三乙酰基硼氢化钠（0.28g，1.31mmol），混合物在室温下搅拌过夜。反应混合物用饱和 $NaHCO_3$ 中和，并用 DCM 萃取。合并的有机层用 Na_2SO_4 干燥，减压浓缩，残余物通过制备 HPLC 纯化标题化合物的三氟乙酸盐（80mg，37%）。LCMS:487.35(M+1)$^+$;HPLC:99.87%(@254nm)(Rt;4.711; 方法：色谱柱 :YMC ODS-A150mm x4.6mm x5μ；流动相 :A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液；进样量 :10μL, 柱温 :30℃；流速 :1.4mL/min.；梯度 :0-8min5%B-95%B, 保持 1.5min,9.51-12min5%B);^{1}H NMR(DMSO-D_6,400MHz) δ 11.47(bs,1H),9.15(s,1H),8.22(s,1H),7.19(s,1H),6.97(s,1H),5.86(s,1H),4.24(d,J=4.0Hz,2H),3.16-3.01(m,5H),2.64-2.63(m,4H),2.19(s,3H),2.15(s,3H),2.10(s,3H),1.91-1.83(m,4H),1.47(m,4H),1.19(m,3H),0.79(t,J=7.2Hz,3H)。

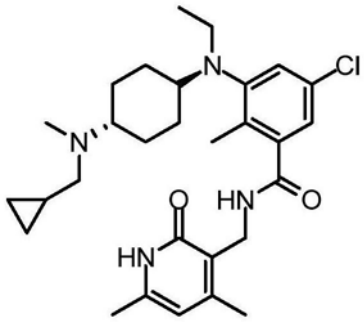
[2472] 化合物 286:5- 氯 -3-(((1r,4r)-4-((环丙基甲基）（甲基）氨基）环己基）（乙基）氨基）-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-2- 甲基苯甲酰胺

[2473]



[2474] 步骤 1：合成 5- 氯 -3-(((1r,r)-4-((环丙基甲基）（甲基）氨基）环己基）（乙基）氨基）-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-2- 甲基苯甲酰胺

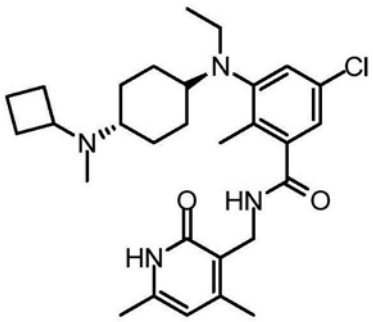
[2475]



[2476] 向搅拌后的5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基((1r,4r)-4-(甲基氨基)环己基)氨基)-2-甲基苯甲酰胺(200mg,0.43mmol)和环丙基甲醛(0.03gm,0.43mmol)的二氯乙烷(5mL)溶液中加入醋酸(0.15ml,2.62mmol),所得混合物在室温下搅拌20分钟。将混合物冷却到0℃,并添加三乙酰基硼氢化钠(0.277g,1.31mmol),混合物在室温下搅拌过夜。所得混合物用饱$NaHCO_3$中和,并用DCM萃取。合并的有机相用Na_2SO_4干燥,减压浓缩,残余物通过制备HPLC纯化得到标题化合物的三氟乙酸盐(100mg,44%)。LCMS:513.40$(M+1)^+$;HPLC:94.81%(@254nm)(Rt;4.924;方法:色谱柱:YMC ODS-A150mm x4.6mm x5μ;流动相:A;0.05%TFA的水溶液/B;0.05%TFA的乙腈溶液;进样量:10μL,柱温:30℃;流速:1.4mL/min.;梯度:0-8min5%B-95%B,保持1.5min,9.51-12min5%B);^1H NMR(DMSO-D_6,400MHz)δ11.47(bs,1H),9.09(s,1H),8.21(s,1H),7.18(s,1H),6.97(s,1H),5.86(s,1H),4.25(d,J=4.0Hz,2H),3.24(m,1H),3.03-3.01(m,3H),2.89-2.87(m,1H),2.71-2.70(m,4H),2.18(s,3H),2.15(s,3H),2.10(s,3H),1.93-1.83(m,4H),1.46-1.44(m,4H),1.05(m,1H),0.79(t,J=7.2Hz,3H),0.63(m,2H),0.38-0.31(m,2H)。

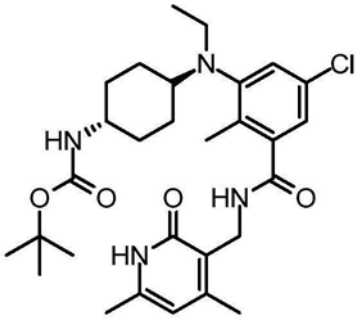
[2477] 化合物287:合成化合物5-氯-3-(((1r,4r)-4-(环丁基(甲基)氨基)环己基)(乙基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺

[2478]



[2479] 步骤1和2:合成((1r,4r)-4-((5-氯-3-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰基)-2-甲基苯基)(乙基)氨基)环己基)氨基甲酸叔丁酯

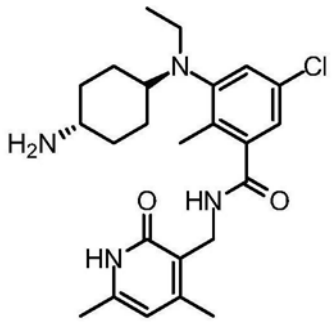
[2480]



[2481] 将化合物 3-(((1r,4r)-4-((叔丁氧羰基)氨基)环己基)(乙基)氨基)-5-氯-2-甲基苯甲酸甲酯(3.5g,8.2mmol)和 NaOH (0.5g,12mmol)在 20ml 乙醇:水(4:1)中的混合物在 70℃加热 2 小时。将反应混合物冷却到 0℃,用 1N HCl 酸化至 pH 值为 6,然后浓缩。将残余物在水和乙酸乙酯之间分配,有机层用 Na_2SO_4 干燥,减压浓缩,得到 3.2g 粗品酸。将所得粗品酸(3.2g,7.8mmol)、3-(氨基甲基)-4,6-二甲基吡啶-2(1H)-酮(2.36mg,15.6mmol)和 PYBOP (6.1mg,11mmol)在 15ml DMSO 中室温下搅拌过夜。反应混合物用水稀释,用 10%MeOH/DCM 萃取,合并的有机层用 Na_2SO_4 干燥,减压浓缩,残余物经硅胶柱层析得到标题化合物(3.0g,71%)。

[2482] 步骤 3:合成 3-(((1r,4r)-4-氨基环己基)(乙基)氨基)-5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺

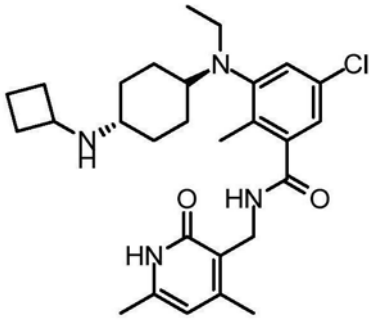
[2483]



[2484] 向冷却后的((1s,4s)-4-((5-氯-3-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰基)-2-甲基苯基)(乙基)氨基)环己基)氨基甲酸叔丁酯(400mg,0.73mmol)的 DCM (5mL)溶液中加入 2ml TFA。反应混合物在室温下搅拌 2 小时,减压浓缩干。将残余物溶解于 10%MeOH/DCM 中,依次用饱和 $NaHCO_3$、水和盐水洗涤。有机相用 Na_2SO_4 干燥,减压浓缩得到标题化合物(320mg,98%)。

[2485] 步骤 4:合成 5-氯-3-(((1r,4r)-4-(环丁基氨基)环己基)(乙基)氨基)-N-((4,6-二甲基-2-氧代-12-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺

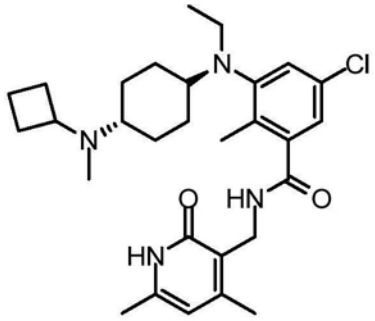
[2486]



[2487] 在 0 ℃ 下，向搅拌后的 3-(((1r,4r)-4- 氨基环己基)(乙基)氨基)-5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)-2- 甲基苯甲酰胺(300mg,0.67mmol)和环丁酮(141mg,2.02mmol)的甲醇(20mL)溶液中加入氰基硼氢化钠(127mg,2.02mmol)。混合物在室温下搅拌过夜，用饱和 $NaHCO_3$ 中和，用 DCM 萃取。合并的有机相用 Na_2SO_4 干燥，减压浓缩得到标题化合物粗品(260mg,77%)。

[2488] 步骤 5：合成 5- 氯 -3-(((1r,4r)-4-(环丁基(甲基)氨基)环己基)(乙基)氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)-2- 甲基苯甲酰胺

[2489]

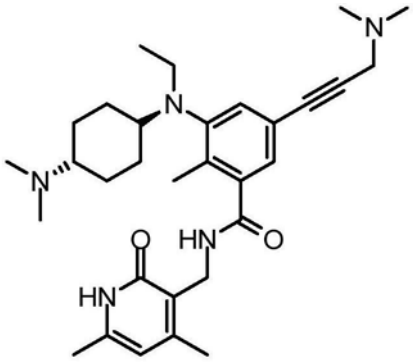


[2490] 在 0℃下，向搅拌后的 5- 氯 -3-(((1r,4r)-4-(环丁基氨基)环己基)(乙基)氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)-2- 甲基苯甲酰胺(230mg,0.46mmol)和福尔马林(138mg,4.61mmol)的甲醇(10ml)溶液中加入氰基硼氢化钠(43mg,0.69mmol)。混合物在室温下搅拌过夜，用饱和溶液 $NaHCO_3$ 中和，并用 DCM 萃取。合并的有机相用 Na_2SO_4 干燥，减压浓缩，残余物经硅胶柱层析纯化得到标题化合物(150mg,63%)。

[2491] 5- 氯 -3-(((1r,4r)-4-(环丁基(甲基)氨基)环己基)(乙基)氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)-2- 甲基苯甲酰胺 - 三氟乙酸盐的分析数据：LCMS:513.25(M+1)$^+$;HPLC:96.89%(@254nm)(Rt;4.886; 方法：色谱柱：YMC ODS-A150mm x4.6mm x5μ；流动相：A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液；进样量：10μL, 柱温：30℃；流速：1.4mL/min.；梯度：0-8min5%B-95%B, 保持 1.5min,9.51-12min5%B);^{1}H NMR(DMSO-D_6,400MHz) δ 11.45(bs,1H),9.40(s,1H),8.21(s,1H),7.18(s,1H),6.97(s,1H),5.86(s,1H),4.25(d,J=4.0Hz,2H),3.77-3.75(m,1H),3.12-3.02(m,3H),2.69(m,1H),2.50(4H 合并在溶剂峰中),2.18,2.15,2.11(3s,6 小时 +3H+3H),1.83-1.44(m,10H),0.78(t,3H)。

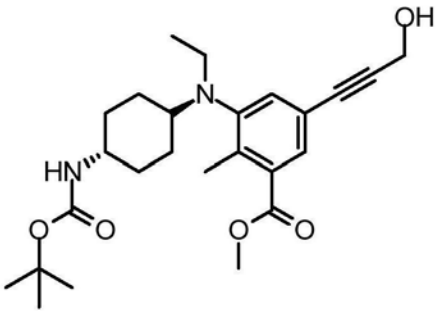
[2492] 化合物 290：N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-5-(3-(二甲基氨基)丙 -1- 炔 -1- 基)-2- 甲基苯甲酰胺

[2493]



[2494] 步骤 1 和 2：合成 3-(((1r,4r)-4-((叔丁氧羰基)氨基)环己基)(乙基)氨基)-5-(3-羟丙-1-炔-1-基)-2-甲基苯甲酸甲酯

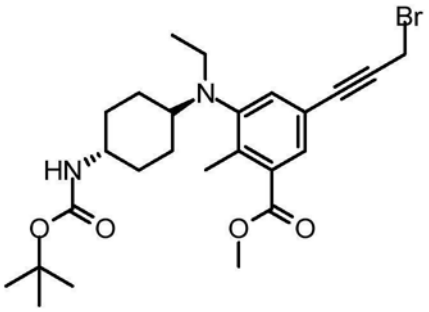
[2495]



[2496] 将 5-溴-3-(((1r,4r)-4-((叔丁氧羰基)氨基)环己基)(乙基)氨基)-2-甲基苯甲酸甲酯(1.5g,3.2mmol)、叔丁基二甲基(丙-2-炔-1-基氧基)硅烷(1.6g,9.6mmol)、碘化铜(183mg,0.96mmol)和三乙胺(1.30ml,9.60mmol)的 DMF(10ml)溶液用氩气净化 20 分钟。向反应混合物中加入四-(三苯基膦)钯(369mg,0.32mmol),所得混合物在 100℃加热 5 小时,然后冷却到室温。所得混合物用乙酸乙酯稀释,用水洗涤,有机层用 Na_2SO_4 干燥,减压浓缩,得到 1.9g 硅基保护的中间体产物的粗品。在室温下,将所得产品溶解于 15ml THF 中,并加入四丁基氟化铵(6.81ml1M 的 THF 溶液,6.81mmol),将所得混合物搅拌 2 小时。反应混合物用乙酸乙酯稀释,用水洗涤。有机层 Na_2SO_4 干燥,减压浓缩,残余物经硅胶柱层析纯化得到标题化合物(950mg,630%)。

[2497] 步骤 3：合成 5-(3-溴丙-1-炔-1-基)-3-(((1r,4r)-4-((叔丁氧羰基)氨基)环己基)(乙基)氨基)-2-甲基苯甲酸甲酯

[2498]

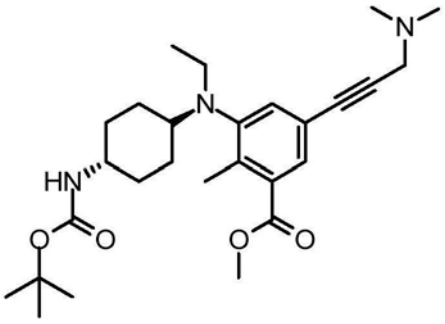


[2499] 在室温下,向 3-(((1r,4r)-4-((叔丁氧羰基)氨基)环己基)(乙基)氨基)-5-(3-羟丙-1-炔-1-基)-2-甲基苯甲酸甲酯(950mg,2.14mmol)的 DCM(13ml)溶

液中加入三苯基膦(840mg,3.21mmol)和四溴化碳(1.06gm,3.21mmol)。所得混合物搅拌 3 小时,用 DCM 稀释,用水洗涤。有机层用 Na_2SO_4 干燥,减压浓缩,残余物经硅胶柱纯化得到标题化合物(900mg,82%)。

[2500] 步骤 4:合成 3-(((1r,4r)-4-((叔丁氧羰基)氨基)环己基)(乙基)氨基)-5-(3-(二甲基氨基)丙-1-炔-1-基)-2-甲基苯甲酸甲酯

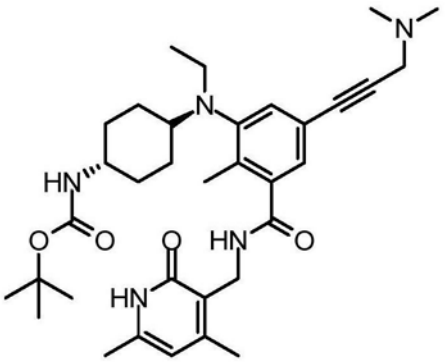
[2501]



[2502] 将 5-(3-溴丙-1-炔-1-基)-3-(((1r,4r)-4-((叔丁氧羰基)氨基)环己基)(乙基)氨基)-2-甲基苯甲酸甲酯(500mg,0.98mmol)和 2M N,N-二甲基胺(2.5ml,4.9mmol)的 THF 溶液的 DMF (5mL)溶液在室温下搅拌过夜。所得混合物减压浓缩,用水稀释,用 DCM 萃取。合并的有机相用 Na_2SO_4 干燥,在真空下浓缩,得到标题化合物(450mg,96%)。

[2503] 步骤 5 和 6:合成((1r,4r)-4-((3-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰基)-5-(3-(二甲基氨基)丙-1-炔-1-基)-2-甲基苯基)(乙基)氨基)环己基)氨基甲酸叔丁酯

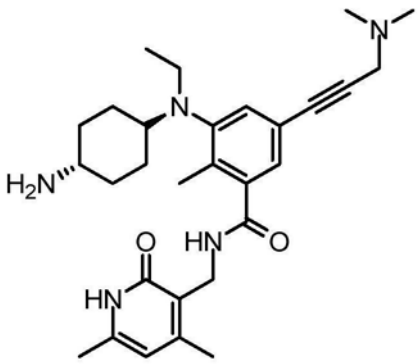
[2504]



[2505] 3-(((1r,4r)-4-((叔丁氧羰基)氨基)环己基)(乙基)氨基)-5-(3-(二甲基氨基)丙-1-炔-1-基)-2-甲基苯甲酸甲酯(450mg,0.95mmol)和 NaOH (57mg,1.40mmol)在 10ml 乙醇:水(4:1)中的混合物在 70℃加热 2 小时。将反应混合物浓缩干,将残余物在水和 DCM 之间分配。有机层用 Na_2SO_4 干燥,减压浓缩得到 430mg 酸。将所得粗品酸(430mg,0.94mmol)、3-(氨基甲基)-4,6-二甲基吡啶-2(1H)-酮(280mg,1.88mmol)、PYBOP(733mg,1.40mmol)和三乙胺(0.1ml,0.94mmol)在 7ml DMSO 中在室温下搅拌过夜。反应混合物用水稀释,将沉淀的化合物过滤,真空干燥,得到标题化合物的粗品(450mg,81%)。

[2506] 步骤 7:合成 3-(((1r,4r)-4-氨基环己基)(乙基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-5-(3-(二甲基氨基)丙-1-炔-1-基)-2-甲基苯甲酰胺

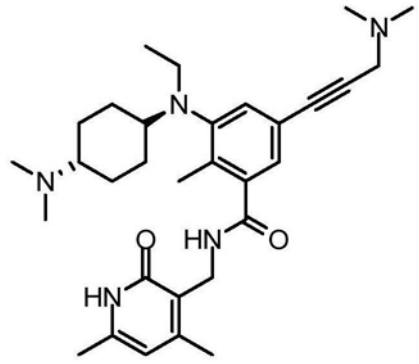
[2507]



[2508] 向冷却后的3-(((1r,4r)-4-((叔丁氧羰基)氨基)环己基)(乙基)氨基)-5-(3-(二甲基氨基)丙-1-炔-1-基)-2-甲基苯甲酸甲酯(450mg,0.76mmol)的DCM(6ml)溶液中加入1ml TFA。反应混合物在室温下搅拌2小时,减压浓缩干。将残余物溶解于10%MeOH/DCM,依次用饱和$NaHCO_3$、水和盐水洗涤。有机相用Na_2SO_4干燥,减压浓缩,得到标题化合物的粗品(350mg,93%)。

[2509] 步骤8:合成N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-5-(3-(二甲基氨基)丙-1-炔-1-基)-2-甲基苯甲酰胺

[2510]

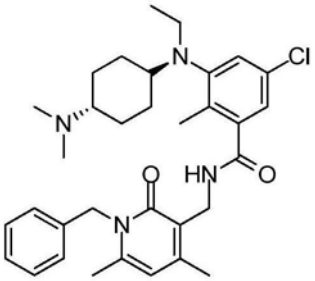


[2511] 在0℃下,向搅拌后的化合物3-(((1r,4r)-4-氨基环己基)(乙基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-5-(3-(二甲基氨基)丙-1-炔-1-基)-2-甲基苯甲酰胺粗品(350mg,0.71mmol)和甲醛(0.56ml38%的溶液,7.10mmol)的甲醇(8ml)溶液中加入氰基硼氢化钠(132mg,2.10mmol)。所得混合物在室温下搅拌4小时,将其在水和10%MeOH/DCM之间分配。有机层用Na_2SO_4干燥,减压浓缩。残余物通过碱性氧化铝柱层析纯化得到标题化合物(120mg,32%)。

[2512] LCMS:520.6(M+1)$^+$;HPLC:92.27%(@254nm)(Rt;3.886;方法:色谱柱:YMC ODS-A150mm x4.6mm x5μ;流动相:A;0.05%TFA的水溶液/B;0.05%TFA的乙腈溶液;进样量:10μL,柱温:30℃;流速:1.4mL/min.;梯度:0-8min5%B-95%B,保持1.5min,9.51-12min5%B);^{1}H NMR(DMSO-d_6,400MHz)δ11.45(bs,1H),8.18(t,1H),7.15(s,1H),6.96(s,1H),5.86(s,1H),4.25(d,2H),3.02-3.00(m,2H),2.50(13质子合并在溶剂峰中),2.33(s,3H),2.23(s,3H),2.18(s,3H),2.11(s,3H),1.82(m,4H),1.39-1.28(m,4H),0.77(t,3H)。

[2513] 化合物 301 :N-((1- 苄基 -4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-5- 氯 -3-(((1r,4r)-4-(二甲基氨基) 环己基)(乙基) 氨基)-2- 甲基苯甲酰胺

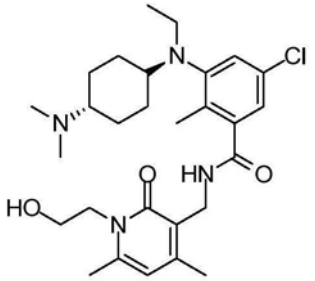
[2514]



[2515] 将 5- 氯 -3-(((1r,4r)-4-(二甲基氨基) 环己基)(乙基) 氨基)-2- 甲基苯甲酸 (1eq)溶解于 DMSO 中,然后将 3-(氨基甲基)-1-(2- 羟乙基)-4,6- 二甲基吡啶 -2(1H)- 酮 (2eq) 和三乙胺 (1eq) 加入到上述溶液。反应混合物在室温下搅拌 15 分钟,向其中加入 PYBOP (1.5eq),继续搅拌过夜。将反应混合物倒入冰中,用 10%MeOH/DCM 萃取。将合并的有机层干燥,浓缩,得到粗产品,将该粗产品用制备 HPLC 纯化得到标题化合物的三氟乙酸盐 (0.011g,16%)。LCMS:563.40(M+1)$^+$;HPLC:90.27%(@210nm-370nm)(Rt;6.122; 方法 : 色谱柱 :YMC ODS-A150mm x4.6mm x5μ; 流动相 :A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液 ; 进样量 :10μL, 柱温 :30℃ ; 流速 :1.4mL/min.; 梯度 :0-8min5%B-95%B, 保持 1.5min,9.51-12min5%B);^{1}H NMR(MeOD,400MHz) δ ,7.31-7.26(m,2H),7.24-7.04(m,5H),6.23(s,1H),5.40(d,2H),4.50(s,2H),3.34(1 个质子合并在溶剂峰中),3.11-3.08(m,2H+1H),2.81(s,3H+3H),2.42(s,3H),2.29(s,3H),2.21(s,3H),2.08-1.99(m,2H+2H),1.52-1.49(m,4H),0.86(t,3H J=7.2Hz)。

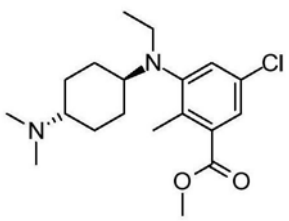
[2516] 化合物 302 :5- 氯 -3-(((1r,4r)-4-(二甲基氨基) 环己基)(乙基) 氨基)-N-((1-(2- 羟乙基)-4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基苯甲酰胺

[2517]



[2518] 步骤 1 :合成 5- 氯 -3-(((1r,4r)-4-(二甲基氨基) 环己基)(乙基) 氨基)-2- 甲基苯甲酸甲酯

[2519]

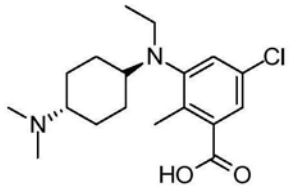


[2520] 向搅拌后的3-(((1r,4r)-4-((叔丁氧羰基)氨基)环己基)(乙基)氨基)-5-氯-2-甲基苯甲酸乙酯(3.4g,8.0mmol)的DCM(35mL)溶液中加入TFA(10mL)。所得混合物在室温下搅拌1小时,减压除去溶剂,添加饱和$NaHCO_3$溶液。用10%MeOH/DCM萃取,合并的有机层依次用水和盐水洗涤,用无水Na_2SO_4干燥。在减压下蒸发除去溶剂得到3-(((1r,4r)-4-氨基环己基)(乙基)氨基)-5-氯-2-甲基苯甲酸甲酯(2.5g,96%)。

[2521] 将上述化合物(2.4g,7.4mmol)溶解于甲醇(25mL)中,将所得混合物冷却到0℃。向所得混合物中加入福尔马林(2.21g,73.95mmol),在同一温度下搅拌20分钟。向反应混合物中加入氰基硼氢化钠(0.92g,14.8mmol),在室温下搅拌1小时。减压除去溶剂,向残余物中加水,用10%MeOH/DCM萃取。将合并的有机层干燥,减压浓缩,得到标题化合物(2.3g,88),其没有进一步纯化即用于下一步骤中。

[2522] 步骤2:合成5-氯-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-2-甲基苯甲酸

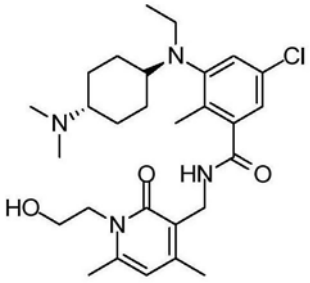
[2523]



[2524] 向5-氯-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-2-甲基苯甲酸乙酯(2.3g,9.1mmol)的乙醇(25mL)溶液中加入NaOH(0.73g,18.35mmol)水溶液,所得混合物在60℃搅拌1小时。减压除去乙醇,残余物用稀HCl酸化至pH值为6,并用柠檬酸调至pH值为4。用乙酸乙酯进行萃取。合并的有机层经干燥,浓缩得到标题化合物(2.0g,92%)。

[2525] 步骤3:合成5-氯-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-N-((1-(2-羟乙基)-4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺

[2526]

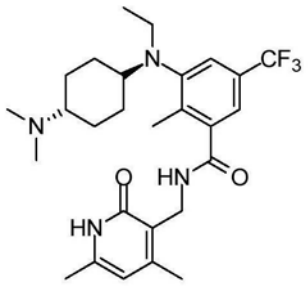


[2527] 将5-氯-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-2-甲基苯甲酸(1eq)溶解于DMSO中,并将3-(氨基甲基)-1-(2-羟乙基)-4,6-二甲基吡啶-2(1H)-酮(2eq)和三乙胺(1eq)加入上述溶液中。在室温下搅拌15分钟后,向反应混合物加入PYBOP(1.5eq),继续搅拌过夜。结束后,将反应混合物倒入冰中,并用10%MeOH/DCM萃取。将合并的有机层干燥并浓缩,得到粗产物,将该粗产物经制备HPLC纯化得到标题化合物的三氟乙酸盐(0.07g,20%)。LCMS:517.35$(M+1)^+$;HPLC:91.15%(@254nm)(R_t;5.134;方法:色谱柱:YMC ODS-A150mm x4.6mm x5μ;流动相:A;0.05%TFA的水溶液/B;0.05%TFA的乙腈溶液;进样量:10μL,柱温:30℃;流速:1.4mL/min.;梯度:0-8min5%B-95%B,保持

1.5min,9.51-12min5%B);^{1}H NMR(DMSO-D_2O 交换,400MHz)δ7.17(s,1H),6.94(s,1H),6.01(s,1H),4.26(m,2H),3.99(s,2H),3.01-2.99(m,3H),2.67(s,3H+3H),2.35(1 个质子合并在溶剂峰中),2.33(m,2H+2H),2.19(s,3H),2.12(s,3H),1.94-1.81(m,5H)1.40(m,4H),0.77(t,3H)。

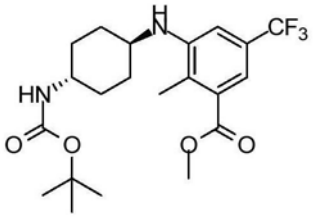
[2528] 化合物 306:N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-2-甲基-5-(三氟甲基)苯甲酰胺

[2529]



[2530] 步骤 1:合成 3-(((1r,4r)-4-((叔丁氧羰基)氨基)环己基)氨基)-2-甲基-5-(三氟甲基)苯甲酸甲酯

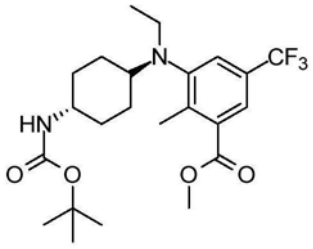
[2531]



[2532] 向搅拌后的 3-氨基-2-甲基-5-(三氟甲基)苯甲酸甲酯(2.0g,9.1mmol)和(4-氧代环己基)氨基甲酸叔丁酯(2.52g,11.87mmol)的二氯乙烷(20mL)溶液中加入醋酸(3.28g,54.8mmol),反应混合物在室温搅拌 10 分钟。然后,在 0℃下向反应混合物中加三乙酰基硼氢化钠(5.80g,27.4mmol),反应混合物在室温下搅拌过夜。结束时,用碳酸氢钠水溶液淬灭反应。将有机相分离,水相用二氯甲烷萃取。合并的有机层用水洗涤,干燥并减压浓缩。原料粗品通过柱层析纯化得到标题化合物(2.8g,82%)。

[2533] 步骤 2:合成 3-(((1r,4r)-4-((叔丁氧羰基)氨基)-环己基)(乙基)氨基)-2-甲基-5-(三氟甲基)苯甲酸甲酯

[2534]

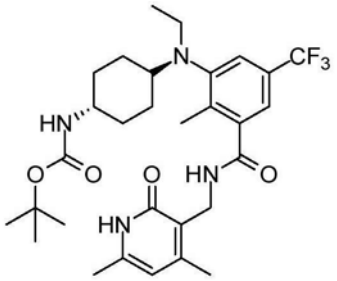


[2535] 向搅拌后的 3-(((1r,4r)-4-((叔丁氧羰基)氨基)环己基)氨基)-2-甲基-5-(三氟甲基)苯甲酸甲酯(0.9g,2.40mmol)和乙醛(0.21g,4.80mmol)的二氯乙烷(10mL)溶液中加入醋酸(0.85g,14.2mmol),反应混合物在室温下搅拌 20 分钟。然后在 0℃

下，向反应混合物中加入三乙酰基硼氢化钠（1.53g，7.21mmol），在室温下搅拌过夜。用碳酸氢钠水溶液淬灭反应，将有机相分离，水相用二氯甲烷萃取。合并的有机层用水洗涤，干燥，减压浓缩，原料粗品通过柱层析纯化得到标题化合物（0.8g，83%）。

[2536] 步骤 3：合成 ((1r,4r)-4-((3-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）氨基甲酰基）-2- 甲基 -5-（三氟甲基）苯基）（乙基）氨基）环己基）氨基甲酸叔丁酯

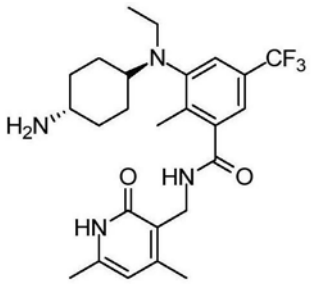
[2537]



[2538] 向化合物 3-(((1r,4r)-4-((叔丁氧羰基）氨基）环己基）（乙基）氨基）-2- 甲基 -5-（三氟甲基）苯甲酸甲酯（0.80g，1.98mmol）的乙醇（8mL）溶液中加入氢氧化钠（0.12g，2.97mmol）水溶液，所得混合物在 60℃搅拌 1 小时。反应结束后，减压除去乙醇，残余物用稀 HCl 酸化至 pH 值为 6，再用柠檬酸调至 pH 值为 4。用 10%MeOH/DCM 萃取。将合并的有机层干燥浓缩得到单独的酸（0.7g）。将所得酸（0.7g，1.8mmol）溶解于 DMSO（10mL）中，并将 3-（氨基甲基）-4,6- 二甲基吡啶 -2(1H)- 酮（0.54g，3.59mmol）加入到上述溶液中。在室温下搅拌 15 分钟后，向反应混合物加入 PYBOP（1.40g，2.69mmol），继续搅拌过夜。反应结束后，将反应混合物倒入冰中，用 10%MeOH/DCM 萃取。将合并的有机层干燥，浓缩，得到的粗产物用乙腈洗涤纯化得到标题化合物（0.7g，74%）。

[2539] 步骤 4：合成 3-(((1r,4r)-4- 氨基环己基）（乙基）氨基）-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-2- 甲基 -5-（三氟甲基）苯甲酰胺

[2540]

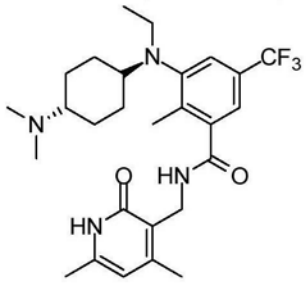


[2541] 向 ((1r,4r)-4-((3-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）氨基甲酰）-2- 甲基 -5-（三氟甲基）苯基）（乙基）氨基）环己基）氨基甲酸叔丁酯（0.7g，1.3mmol）的 DCM（10mL）溶液中加入 TFA（3mL），反应混合物在室温下搅拌 1 小时。反应结束后，减压除去溶剂，加入饱和 $NaHCO_3$ 溶液。用 10%MeOH/DCM 萃取；合并的有机层用水和盐水洗涤；用无水 Na_2SO_4 干燥；过滤并减压浓缩得到标题化合物（0.56g，98%），其直接用于下一步骤。

[2542] 步骤 5：合成 N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-3-(((1r,4r)-4-（二甲基氨基）环己基）（乙基）氨基）-2- 甲基 -5-（三氟甲基）苯

甲酰胺

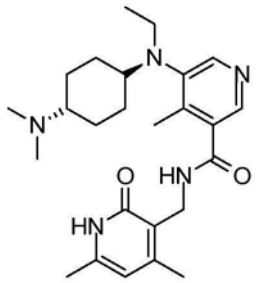
[2543]



[2544] 在0℃下，向3-(((1r,4r)-4-氨基环己基)(乙基)氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-5-(三氟甲基)苯甲酰胺(0.5g,1.2mmol)的DCM(5mL)溶液中加入福尔马林(0.124g,4.13mmol)。反应混合物在0℃搅拌20分钟后加三乙酰基硼氢化钠(0.63g,2.95mmol)，反应混合物在室温下搅拌1小时。结束后，加水并用10%MeOH/DCM萃取。将合并的有机层干燥并减压浓缩。所得固体粗品用乙腈和乙醚洗涤后得到标题化合物(0.4g,67%)。LCMS:507.45(M+1)$^+$;HPLC:96.81%(@210-370nm)(R_t;4.857;方法：色谱柱:YMC ODS-A150mm x4.6mm x5μ；流动相:A;0.05%TFA的水溶液/B;0.05%TFA的乙腈溶液；进样量:10μL，柱温:30℃；流速:1.4mL/min.；梯度:0-8min5%B-95%B，保持1.5min,9.51-12min5%B);^{1}H NMR(DMSO-d6,400MHz)δ11.46(bs,1H),8.34(s,1H),7.38(s,1H),7.20(s,1H),5.86(s,1H),4.27(d,2H),3.08(m,2H),2.67(m,1H),2.40(s,6H),2.24(s,3H),2.19(s,3H),2.10(s,3H),1.85(m,2H),1.80(m,2H),1.42(m,2H),1.25(m,2H),0.78(t,3H)。

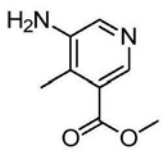
[2545] 化合物390:N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-5-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-4-甲基烟酰胺

[2546]



[2547] 步骤1:合成5-氨基-4-甲基烟酸甲酯

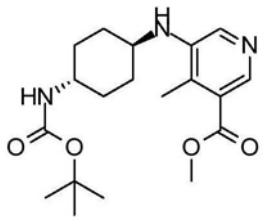
[2548]



[2549] 在室温下，向搅拌后的5-氨基-4-甲基烟酸(5.0g,32mmol)的甲醇(75mL)溶液中慢慢加入浓H_2SO_4(5mL)。所得混合物在70℃搅拌12小时。结束时，减压除去溶剂，残余物用饱和$NaHCO_3$溶液中和。用EtOAc萃取；合并的有机层用水和盐水洗涤，用无水Na_2SO_4干燥，减压浓缩，得到标题化合物(4.1g,75%)，所述化合物使用时不用进一步纯化。

[2550] 步骤 2 :合成 5-(((1r,4r)-4-((叔丁氧羰基)氨基)环己基)氨基)-4- 甲基烟酸甲酯

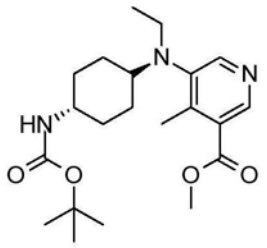
[2551]



[2552] 向搅拌后的 5- 氨基 -4- 甲基烟酸甲酯(1.20g,7.22mmol)和 (4- 氧代环己基)氨基甲酸叔丁酯(2.30g,10.8mmol)的二氯乙烷(20mL)溶液中加入醋酸(2.59g,43mmol),所得混合物在室温下搅拌 10 分钟。然后在 0℃下向反应混合物加入三乙酰基硼氢化钠(4.59g,21.56mmol),反应混合物在室温下搅拌过夜。结束时,用碳酸氢钠溶液淬灭反应,分离有机相,水相用二氯甲烷萃取。合并的有机层用无水硫酸钠干燥,减压浓缩。化合物粗品通过硅胶柱层析纯化得到标题化合物(0.65g,25%)。

[2553] 步骤 3 :合成 5-(((1r,4r)-4-((叔丁氧羰基)- 氨基)- 环己基)-(乙基)- 氨基)-4- 甲基烟酸甲酯

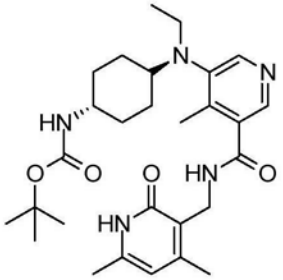
[2554]



[2555] 向搅拌后的 5-(((1r,4r)-4-((叔丁氧羰基)氨基)环己基)氨基)-4- 甲基烟酸甲酯(0.65g,1.79mmol)和乙醛(0.39g,8.95mmol)的二氯乙烷(20mL)溶液中加入醋酸(0.64g,10.7mmol),所得混合物在室温下搅拌 10 分钟。然后在 0℃下向反应混合物加入三乙酰基硼氢化钠(1.13g,5.33mmol),在室温下搅拌过夜。结束时,用碳酸氢钠溶液淬灭反应,分离有机相,水相用二氯甲烷萃取。合并的有机层用无水硫酸钠干燥,减压浓缩,得到标题化合物(0.55g,79%)。

[2556] 步骤 4 :合成 ((1r,4r)-4-((5-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)氨基甲酰基)-4- 甲基吡啶 -3- 基)(乙基)氨基)环己基)氨基甲酸叔丁酯

[2557]

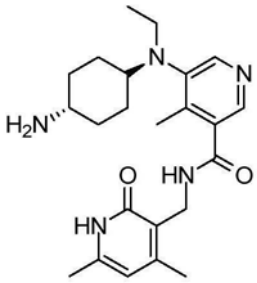


[2558] 向 5-(((1r,4r)-4-((叔丁氧羰基)- 氨基)- 环己基)-(乙基)- 氨基)-4- 甲基烟酸甲酯(0.55g,1.40mmol)的乙醇(7mL)溶液中加入 NaOH (0.11g,2.81mmol)水溶液,

所得混合物在 60℃搅拌 1 小时。反应结束后，减压除去乙醇，所得混合物用稀 HCl 酸化至 pH 值为 6，用柠檬酸酸化至 pH 值为 4。用乙酸乙酯进行萃取。将合并的有机层干燥，浓缩得到单独的酸（0.5g）。将上述酸（0.5g，1.3mmol）溶解于 DMSO（5mL）中，并将 3-（氨基甲基）-4,6- 二甲基吡啶 -2(1H)- 酮（0.48g，2.65mmol)加入到上述溶液中。在室温下搅拌 15 分钟后，向反应混合物加入 PYBOP（1.02g，1.58mmol)，继续搅拌过夜。反应结束后，将反应混合物倒入冰中，用 10%MeOH/DCM 萃取。将合并的有机层干燥，浓缩，残余物通过硅胶层析纯化得到标题化合物（0.5g，74%）。

[2559] 步骤 5：合成 5-(((1r,r)-4- 氨基环己基）（乙基）氨基）-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-4- 甲基烟酰胺

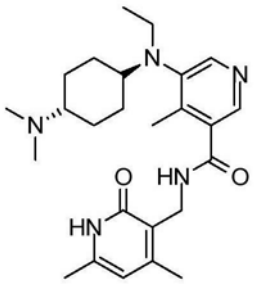
[2560]



[2561] 向搅拌后的 ((1r,4r)-4-((5-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）氨基甲酰基）-4- 甲基吡啶 -3- 基）（乙基）氨基）环己基）氨基甲酸叔丁酯（0.5g，0.97mmol）的 DCM（10mL）溶液中加入 TFA（2mL）。所得混合物在室温下搅拌 1 小时，减压除去溶剂。向残余物中添加饱和 $NaHCO_3$，用 10%MeOH/DCM 萃取。合并的有机层用水和盐水洗涤；用无水 Na_2SO_4 干燥；过滤并减压浓缩，得到标题化合物（0.35g，88%）。

[2562] 步骤 6：合成 N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-5-(((1r,4r)-4-（二甲基氨基）环己基）（乙基）氨基）-4- 甲基烟酰胺

[2563]

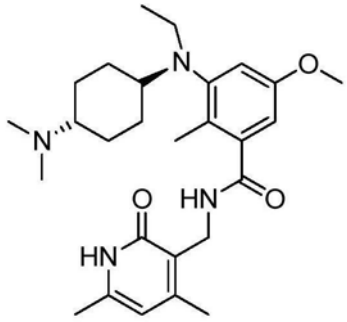


[2564] 将 5-(((1r,4r)-4- 氨基环己基）（乙基）氨基）-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-4- 甲基烟酰胺（0.35g，0.85mmol）溶解于 DCM（5mL）中，在 0℃下向所得溶液中加入福尔马林 (0.089g，2.96mmol)。将所得混合物搅拌 20 分钟后，向混合物中加入三乙酰基硼氢化钠（0.45g，2.12mmol)，混合物在室温下搅拌 1 小时。结束后，混合物用水稀释，用 10%MeOH/DCM 萃取。将合并的有机层干燥并减压浓缩。得到的固体经乙腈和乙醚洗涤进一步纯化得到标题化合物（0.3g，80%）。LCMS:440.45(M+1)$^+$；HPLC:73.44%&21.34%(@210-370nm)(R_t;3.769&3.965)；方法：色谱柱 :YMC ODS-A150mm x4.6mm x5μ；流动相 :A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液；进样量 :10μL，柱温 :30℃；流速 :1.4mL/min.；梯度 :0-8min5%B-95%B, 保持 1.5min,9.51-12min5%B)；^{1}H

NMR(DMSO-d6,400MHz) δ 11.45(bs,1H),8.34(s,1H),8.29(s,1H),8.07(s,1H),5.86(s,1H),4.27(d,2H),3.18(m,1H),3.01(m,2H),2.22(s,3H),2.19(s,3H),2.12(s,6H),2.10(s,3H),1.74(m,2H),1.64(m,2H),1.40-1.20(m,4H),0.81(t,3H)。

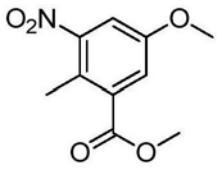
[2565] 化合物308:N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-5-甲氧基-2-甲基苯甲酰胺

[2566]



[2567] 步骤1:合成5-甲氧基-2-甲基-3-硝基苯甲酸甲酯

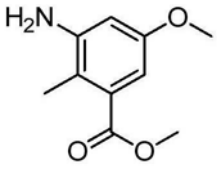
[2568]



[2569] 向搅拌后的5-羟基-2-甲基-3-硝基苯甲酸(1.50g,7.61mmol)的DMF(15mL)溶液中加入碳酸钠(3.23g,30.5mmol)和碘甲烷(1.88ml,30.5mmol)。所得反应混合物在60℃加热8小时。结束时,反应混合物用水稀释,用乙酸乙酯萃取。将合并的有机层干燥并减压浓缩,得到标题化合物粗品(1.7g),其直接用于下一步骤。

[2570] 步骤2:合成3-氨基-5-甲氧基-2-甲基苯甲酸甲酯

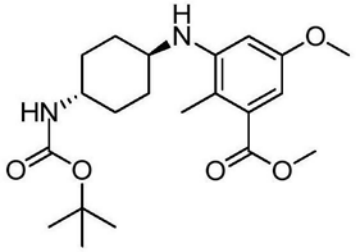
[2571]



[2572] 向搅拌后的5-甲氧基-2-甲基-3-硝基苯甲酸甲酯(1.7g,7.6mmol)的乙醇(20mL)溶液中加入溶解于水(20mL)中的氯化铵(1.7g,32mmol)和铁粉(3.38g,60.44mmol)。混合物在80℃加热3小时,过滤,残余物用热乙醇充分洗涤。将滤液浓缩,残余物用碳酸氢钠水溶液碱化。水相用乙酸乙酯萃取。合并的有机层用水洗涤,干燥并减压浓缩,得到标题化合物(1.2g),其直接用于下一步骤。

[2573] 步骤3:合成3-(((1r,4r)-4-((叔丁氧羰基)氨基)环己基)氨基)-5-甲氧基-2-甲基苯甲酸甲酯

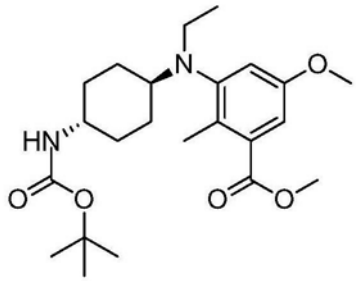
[2574]



[2575] 向搅拌后的 3- 氨基 -5- 甲氧基 -2- 甲基苯甲酸甲酯(1.2g,6.15mmol)和 (4- 氧代环己基) 氨基甲酸叔丁酯(1.70g,7.99mmol) 的二氯乙烷(20mL) 溶液中加入醋酸(2.21g,36.8mmol)。反应在室温下搅拌 20 分钟。在 0℃下向反应混合物加入三乙酰基硼氢化钠(3.91g,18.4mmol),在室温下搅拌过夜。结束时,用碳酸氢钠水溶液淬灭反应,分离有机相,水相用二氯甲烷萃取。合并的有机层用水洗涤,干燥并减压浓缩。所得原料粗品经柱层析纯化得到标题化合物(0.35g,14%)。

[2576] 步骤 4 :合成 3-(((1r,4r)-4-((叔丁氧羰基) 氨基) 环己基)-(乙基) 氨基)-5- 甲氧基 -2- 甲基苯甲酸甲酯

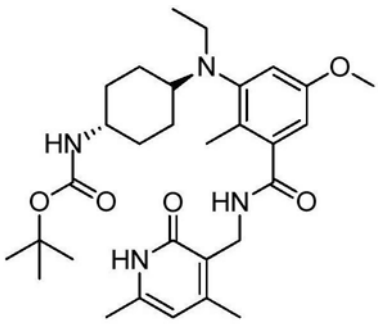
[2577]



[2578] 向搅拌后的 3-(((1r,4r)-4-((叔丁氧羰基) 氨基) 环己基) 氨基)-5- 甲氧基 -2- 甲基苯甲酸甲酯(0.35g,0.89mmol)和乙醛(0.2g,4.46mmol)的二氯乙烷(5mL)溶液中加入醋酸(0.32g,5.35mmol),反应混合物在室温下搅拌 20 分钟。然后在 0℃下向反应混合物中加入三乙酰基硼氢化钠(0.57g,2.67mmol),在室温下搅拌 2 小时。结束时,用碳酸氢钠水溶液淬灭反应,分离有机相,水相用二氯甲烷萃取。合并的有机层用水洗涤,干燥并减压浓缩。所得原料粗品经色谱柱层析纯化得到标题化合物(0.3g,80%)。

[2579] 步骤 5 :合成 ((1r,4r)-4-((3-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基) 氨基甲酰)-5- 甲氧基 -2- 甲基苯基)(乙基) 氨基) 环己基) 氨基甲酸叔丁酯

[2580]



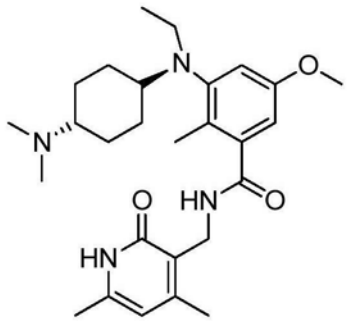
[2581] 向 3-(((1r,4r)-4-((叔丁氧羰基) 氨基) 环己基)(乙基) 氨基)-5- 甲氧基 -2- 甲基苯甲酸甲酯(0.3g,0.71mmol) 的乙醇(4mL) 溶液中加 NaOH (0.06g,1.42mmol)

水溶液，所得混合物在 60℃搅拌 1 小时。反应结束后，减压除去乙醇，残余物用稀 HCl 酸化至 pH 值为 6，并用柠檬酸酸化至 pH 值为 4。用乙酸乙酯萃取。将合并的有机层干燥并浓缩后得到粗品酸（0.25g）。

[2582] 将上述酸（0.25g，0.62mmol）溶解于 DMSO（3mL）中，并将 3-（氨基甲基）-4,6- 二甲基吡啶 -2(1H)- 酮（0.19g，1.23mmol）加入到上述溶液中。反应混合物在室温搅拌 15 分钟后，将 PYBOP（0.48g，0.92mmol）加到反应混合物中，搅拌过夜。将反应物倒入冰中以淬灭反应，所得混合物用 10%MeOH/DCM 萃取。合并的有机层用水洗涤，用无水 Na_2SO_4 干燥，过滤并减压浓缩，得到原料粗品，其经柱层析纯化得到标题化合物（0.2g，60%）。

[2583] 步骤 6：合成 N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-3-(((1r,4r)-4-（二甲基氨基）环己基）（乙基）氨基）-5- 甲氧基 -2- 甲基苯甲酰胺

[2584]

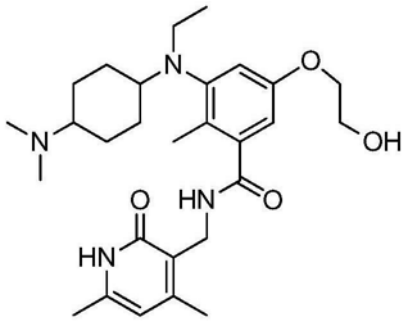


[2585] 向 ((1r,4r)-4-((3-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）氨基甲酰基）-5- 甲氧基 -2- 甲基苯基）（乙基）氨基）环己基）氨基甲酸叔丁酯（0.2g，0.37mmol）的 DCM（4mL）溶液中加入 TFA（2mL），反应混合物在室温搅拌 1 小时。反应结束后，减压除去溶剂，向残余物中加入饱和 $NaHCO_3$ 溶液。用 10%MeOH/DCM 萃取；合并的有机层用水和盐水洗涤；用无水 Na_2SO_4 干燥；过滤并减压浓缩得到 Boc- 去保护的化合物（0.15g，）。

[2586] 将所得 Boc- 去保护的化合物（0.15g，0.34mmol）溶解于 DCM（2mL）中，并在 0℃下向该溶液加入福尔马林（0.035g，1.19mmol）。所得反应混合物在 0℃搅拌 10 分钟。加入三乙酰基硼氢化钠（0.18g，0.85mmol），所得混合物在室温下搅拌 1 小时。反应结束时，加水，用 10%MeOH/DCM 进行萃取。将合并的有机层干燥并减压浓缩，得到的原料粗品经制备 HPLC 纯化获得标题化合物的三氟乙酸盐（0.02g，12%）。LCMS:469.80(M+1)$^+$;HPLC:96.80%(@210-370nm)(R_t;3.802)；方法：色谱柱：YMC ODS-A150mm x4.6mm x5μ；流动相：A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液；进样量：10μL，柱温：30℃；流速：1.4mL/min.；梯度：0-8min5%B-95%B，保持 1.5min，9.51-12min5%B)；^{1}H NMR(DMSO-d6,400MHz) δ 11.46(s,1H),9.42(s,1H),8.06(s,1H),6.75(s,1H),6.58(s,1H),5.86(s,1H),4.26(d,2H,J=4Hz),3.72(s,3H),3.09(m,3H),2.69(s,3H),2.68(s,3H),2.19(s,3H),2.10(s,6H),1.95(m,2H),1.87(m,2H),1.41(m,4H),0.801(t,3H)。

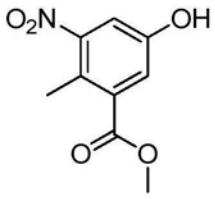
[2587] 化合物 309：N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-3-((4-（二甲基氨基）环己基）（乙基）氨基）-5-(2- 羟基乙氧基）-2- 甲基苯甲酰胺

[2588]



[2589] 步骤 1 :合成 5- 羟基 -2- 甲基 -3- 硝基苯甲酸甲酯

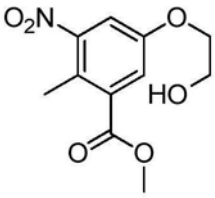
[2590]



[2591] 在 0℃下,向搅拌后的 5- 羟基 -2- 甲基 -3- 硝基苯甲酸(3.50g,17.8mmol)的甲醇(40mL)溶液中加入二氯亚砜(3.9ml,53mmol)。将反应混合物加热回流 3 小时。结束时,减压除去溶剂。向残余物加入碳酸氢钠水溶液,随后用乙酸乙酯萃取。合并的有机层用水洗涤,干燥并减压浓缩。所得原料粗品通过柱层析纯化得到标题化合物(3.0g,80%)。

[2592] 步骤 2 :合成 5-(2- 羟基乙氧基)-2- 甲基 -3- 硝基苯甲酸甲酯

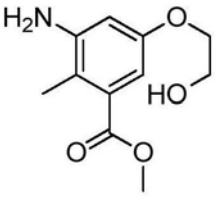
[2593]



[2594] 向搅拌后的 5- 羟基 -2- 甲基 -3- 硝基苯甲酸甲酯(1.5g,7.1mmol)的 ACN (15mL)溶液中加入碳酸铯 (4.6g,14mmol)和 2- 溴乙醇(2.5ml,35mmol)。所得反应混合物在 80℃加热过夜。结束时,反应混合物用水稀释,用乙酸乙酯萃取。合并的有机层用水洗涤,干燥并减压浓缩。所得原料粗品通过硅胶柱层析纯化得到标题化合物(1.35g,74%)。

[2595] 步骤 3 :合成 3- 氨基 -5-(2- 羟基乙氧基)-2- 甲基苯甲酸甲酯

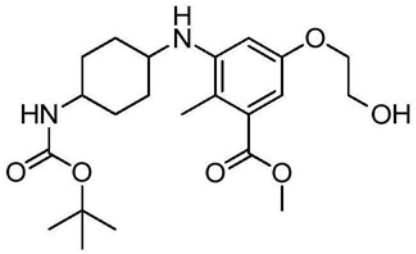
[2596]



[2597] 向搅拌后的 5-(2- 羟基乙氧基)-2- 甲基 -3- 硝基苯甲酸甲酯(1.5g,5.88mmol)的乙醇溶液(20mL)加入溶解于水(20mL)中的氯化铵(1.5g,28mmol)和铁粉(1.3g,23mmol)。所得反应混合物在 80℃加热 3 小时。结束时,将反应混合物过滤,残余物用热乙醇充分洗涤。将滤液浓缩,残余物用碳酸氢钠水溶液碱化。水相用乙酸乙酯萃取。合并的有机层用水洗涤,干燥并减压浓缩,得到标题化合物(1.3g),其可直接使用。

[2598] 步骤 4 :合成 3-((4-((叔丁氧羰基)氨基)-环己基)氨基)-5-(2-羟基乙氧基)-2-甲基苯甲酸甲酯

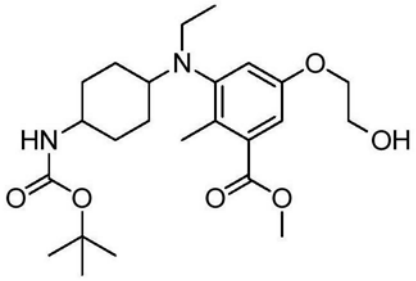
[2599]



[2600] 向搅拌后的 3-氨基-5-(2-羟基乙氧基)-2-甲基苯甲酸甲酯(1.3g,5.77mmol)和(4-氧代环己基)氨基甲酸叔丁酯(1.6g,7.5mmol)的二氯乙烷(20mL)溶液中加入醋酸(2.07g,34.66mmol),反应混合物在室温下搅拌 20 分钟。然后在 0℃下将三乙酰基硼氢化钠(3.7g,17mmol)加入反应混合物中,在室温下搅拌过夜。结束时,用碳酸氢钠水溶液淬灭反应,分离有机相,水相用二氯甲烷萃取。合并的有机层用水洗涤,干燥并减压浓缩。所得原料粗品通过硅胶柱层析纯化,得到作为为顺/反异构体的混合物的标题化合物(2.0g,82%),其继续作为混合物直到最终的化合物 309,所述化合物 309 也是作为顺/反异构体的分离物。。

[2601] 步骤 5 :合成 3-((4-((叔丁氧羰基)氨基)环己基)-(乙基)氨基)-5-(2-羟基乙氧基)-2-甲基苯甲酸甲酯

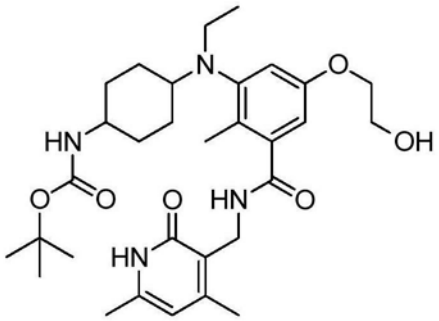
[2602]



[2603] 向搅拌后的 3-((4-((叔丁氧羰基)氨基)环己基)氨基)-5-(2-羟基乙氧基)-2-甲基苯甲酸甲酯(2.0g,4.7mmol)和乙醛(0.63g,14.2mmol)的二氯乙烷(20mL)溶液中加入醋酸(1.7g,28mmol),反应混合物在室温下搅拌 20 分钟。然后在 0℃下,向反应混合物中加入三乙酰基硼氢化钠(3.0g,14.2mmol),反应在室温下搅拌 2 小时。结束时,用碳酸氢钠水溶液淬灭反应,分离有机相,水相用二氯甲烷萃取。合并的有机层用水洗涤,干燥并减压浓缩 ;所得原料粗品经柱层析纯化得到标题化合物(1.9g,89%)。

[2604] 步骤 6 :合成(4-((3-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰基)-5-(2-羟基乙氧基)-2-甲基苯基)-(乙基)-氨基)环己基)氨基甲酸叔丁酯

[2605]

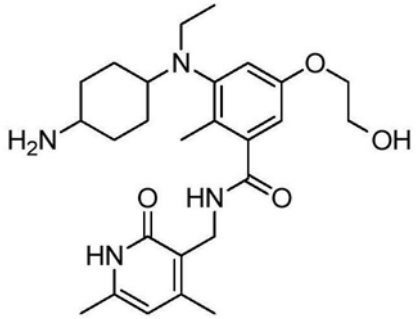


[2606] 向 3-((4-((叔丁氧羰基)氨基)环己基)-(乙基)氨基)-5-(2-羟基乙氧基)-2-甲基苯甲酸甲酯(1.9g,4.2mmol)的乙醇溶液(20mL)中加入NaOH(0.25g,6.33mmol)水溶液,混合物在60℃搅拌1小时。反应结束后,减压除去乙醇,用稀HCl酸化至pH值为6,用柠檬酸酸化至pH值为4。用乙酸乙酯萃取。将合并的有机层干燥并浓缩得到相应的粗品酸(1.8g)。

[2607] 然后将上述酸(1.8g,4.1mmol)溶解到DMSO(15mL)中,并向其中加入3-(氨基甲基)-4,6-二甲基吡啶-2(1H)-酮(1.25g,8.25mmol)。反应混合物在室温搅拌15分钟后,向其加入PYBOP(3.22g,6.19mmol),继续搅拌过夜。反应结束后,将反应混合物倒入冰中,用10%MeOH/DCM萃取。合并的有机层用水洗涤,用无水Na_2SO_4干燥,过滤并减压浓缩,得到的原料粗品通过柱层析纯化得到标题化合物(1.4g,59%)。

[2608] 步骤7:合成3-((4-氨基环己基)-(乙基)-氨基)-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-5-(2-羟基乙氧基)-2-甲基苯甲酰胺

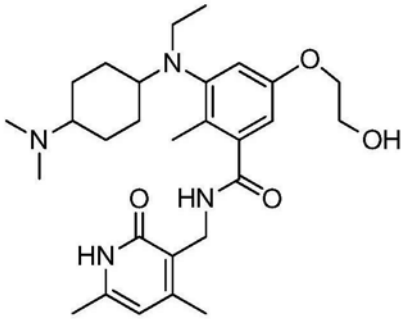
[2609]



[2610] 向(4-((3-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰基)-5-(2-羟基乙氧基)-2-甲基苯基)-(乙基)-氨基)环己基)氨基甲酸叔丁酯(0.80g,1.40mmol)的DCM(5mL)溶液中加入TFA(2mL),反应混合物在室温下搅拌1小时。反应结束后,减压除去溶剂,向残余物加入饱和$NaHCO_3$溶液。用10%MeOH/DCM萃取;合并的有机层用水和盐水洗涤;用无水Na_2SO_4干燥;过滤并减压浓缩得到标题化合物(0.5g,76%)。

[2611] 步骤8:合成N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-((4-(二甲基氨基)环己基)(乙基)氨基)-5-(2-羟基乙氧基)-2-甲基苯甲酰胺

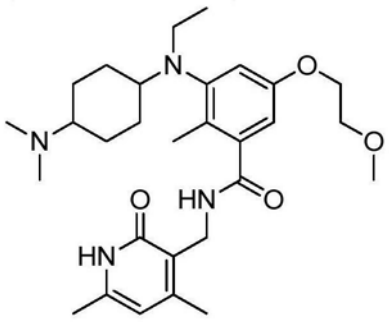
[2612]



[2613] 在 0℃下，向 3-((4- 氨基环己基)-(乙基)- 氨基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-5-(2- 羟基乙氧基)-2- 甲基苯甲酰胺(0.30g,0.63mmol)的 DCM（3mL）溶液中加入福尔马林(0.07g,2.23mmol)。所得反应混合物在 0℃搅拌 20 分钟。向反应混合物加入三乙酰基硼氢化钠(0.34g,1.59mmol),在室温下搅拌 1 小时。结束后,减压除去溶剂,向残余物中加水,用 10%MeOH/DCM 萃取。将合并的有机层干燥并减压浓缩。所得固体通过用乙腈和乙醚洗涤进一步纯化,得到作为顺 / 反异构体的混合物的标题化合物 N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-3-((4-(二甲基氨基) 环己基)(乙基) 氨基)-5-(2- 羟基乙氧基)-2- 甲基苯甲酰胺(0.25g,78%).LCMS:499.55(M+1)$^+$;HPLC:51.61&47.78%(@210-370nm)(R_t;3.539&3.751)；方法：色谱柱：YMC ODS-A150mm x4.6mm x5μ；流动相：A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液；进样量：10μL,柱温：30℃；流速：1.4mL/min.；梯度：0-8min5%B-95%B, 保持 1.5min,9.51-12min5%B)；^{1}H NMR(DMSO-d6,400MHz) δ 11.45(bs,1H),8.04(s,1H),6.68(s,1H),6.51(s,1H),5.85(s,1H),4.25(d,2H),3.92(t,2H),3.67(t,2H),2.97(m,2H),2.18(s,3H),2.16(s,3H),2.12(s,3H),2.10(s,3H),2.08(s,3H),1.89(s,3H),1.76(m,3H),1.65(bs,1H),1.33(m,3H),1.10(m,1H),0.788(bs,3H)。

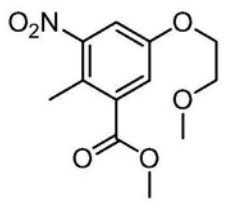
[2614] 化合物 310：N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-3-((4-(二甲基氨基) 环己基)-(乙基)- 氨基)-5-(2- 甲氧基乙氧基)-2- 甲基苯甲酰胺

[2615]



[2616] 步骤 1：合成 5-(2- 甲氧基乙氧基)-2- 甲基 -3- 硝基苯甲酸甲酯

[2617]

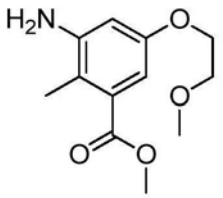


[2618] 向搅拌后的 5- 羟基 -2- 甲基 -3- 硝基苯甲酸甲酯(1.50g,7.61mmol)的 ACN(15mL)

溶液中加入碳酸铯(4.96g,15.2mmol)和 1- 溴 -2- 甲氧基乙烷(1.57g,11.4mmol)。所得反应混合物在 80℃加热过夜。结束时,反应混合物用水稀释,用乙酸乙酯萃取。合并的有机层用水洗涤,干燥并减压浓缩。所得原料粗品通过柱层析纯化得到标题化合物(1.3g,68)。

[2619] 步骤 2 :合成 3- 氨基 -5-(2- 甲氧基乙氧基)-2- 甲基苯甲酸甲酯

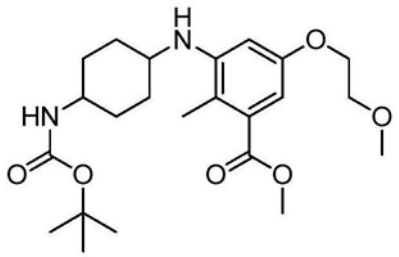
[2620]



[2621] 向搅拌后的 5-(2- 甲氧基乙氧基)-2- 甲基 -3- 硝基苯甲酸甲酯(1.35g,4.83mmol)的乙醇(20mL)溶液中加入溶解于水(20mL)中的氯化铵(1.35g,25.0mmol)和铁粉(1.07g,19.3mmol)。所得反应混合物在 80C 加热 3 小时。结束时,将反应混合物过滤,残余物用热乙醇充分洗涤。将滤液浓缩,残余物用碳酸氢钠水溶液碱化。水相用乙酸乙酯萃取。合并的有机层用水洗涤,干燥,减压浓缩,得到的标题化合物粗产物(1.23g),其直接用于下一步骤。

[2622] 步骤 3 :合成 3-((4-((叔丁氧羰基) 氨基) 环己基) 氨基)-5-(2- 甲氧基乙氧基)-2- 甲基苯甲酸甲酯

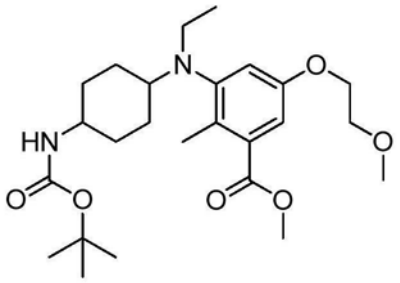
[2623]



[2624] 向搅拌后的 3- 氨基 -5-(2- 甲氧基乙氧基)-2- 甲基苯甲酸甲酯(1.23g,5.14mmol)和 (4- 氧代环己基) 氨基甲酸叔丁酯(1.42g,6.69mmol)的二氯乙烷(15mL)溶液中加入醋酸(1.8g,31mmol),反应混合物在室温下搅拌 20 分钟。然后在 0℃下向反应混合物中加入三乙酰基硼氢化钠(3.2g,15mmol),反应在室温下搅拌过夜。结束时,用碳酸氢钠水溶液淬灭反应,分离有机相,水相用二氯甲烷萃取。合并的有机层用水洗涤,干燥并减压浓缩。所得原料粗品通过柱层析纯化,得到作为顺 / 反异构体的混合物的标题化合物(1.6g,72%),其继续使用直到作为顺 / 反异构体混合物的最终的化合物。

[2625] 步骤 4 :合成 3-((4-((叔丁氧羰基) 氨基) 环己基)-(乙基)- 氨基)-5-(2- 甲氧基乙氧基)-2- 甲基苯甲酸甲酯

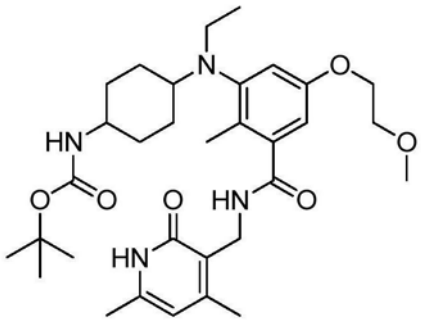
[2626]



[2627] 向搅拌后的 3-((4-((叔丁氧羰基)氨基)环己基)氨基)-5-(2-甲氧基乙氧基)-2-甲基苯甲酸甲酯(1.60g,3.67mmol)和乙醛(0.48g,10.9mmol)的二氯乙烷(20mL)溶液中加入醋酸(1.3g,22mmol),反应混合物在室温下搅拌 20 分钟。然后在 0℃下向反应混合物中加入三乙酰基硼氢化钠(2.33g,11.0mmol),反应在室温下搅拌 2 小时。用碳酸氢钠水溶液淬灭反应,分离有机相,水相用二氯甲烷萃取。合并的有机层用水洗涤,干燥并减压浓缩,所得原料粗品通过柱层析纯化得到标题化合物(1.6g,94%)。

[2628] 步骤 5:合成 (4-((3-(((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)氨基甲酰基)-5-(2-甲氧基乙氧基)-2-甲基苯基)-(乙基)-氨基)-环己基)氨基甲酸叔丁酯

[2629]

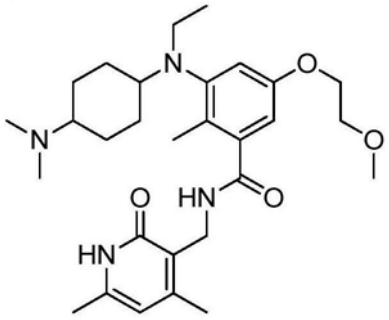


[2630] 向 3-((4-((叔丁氧羰基)氨基)环己基)-(乙基)-氨基)-5-(2-甲氧基乙氧基)-2-甲基苯甲酸甲酯(1.6g,3.5mmol)的乙醇(20mL)溶液中加入 NaOH (0.2g,5.3mmol)水溶液,并在 60℃搅拌 1 小时。反应结束后,减压除去乙醇,用稀 HCl 酸化至 pH 值为 6,并用柠檬酸酸化至 pH 值为 4。用乙酸乙酯萃取。将合并的有机层浓缩后得到相应的粗品酸(1.4g)。

[2631] 将上述酸(1.4g,3.1mmol)溶解到 DMSO (15mL)中,并向其中加入 3-(氨基甲基)-4,6-二甲基吡啶-2(1H)-酮(0.95g,6.2mmol)。反应混合物在室温下搅拌 15 后,向其加入 PYBOP (2.4g,4.6mmol),进行搅拌过夜。将反应混合物倒入冰中,用 10%MeOH/DCM 萃取。合并的有机层用水洗涤,用无水 Na_2SO_4 干燥,过滤并减压浓缩,将得到的原料粗品通过柱层析纯化得到标题化合物(1.9g,95%)。

[2632] 步骤 5:合成 N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-((4-(二甲基氨基)环己基)-(乙基)-氨基)-5-(2-甲氧基乙氧基)-2-甲基苯甲酰胺

[2633]

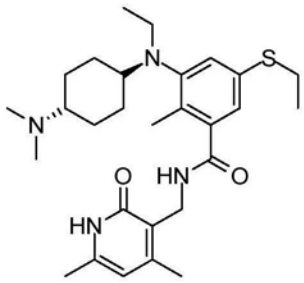


[2634] 向 3-((4-((叔丁氧羰基)氨基)环己基)-(乙基)-氨基)-5-(2-甲氧基乙氧基)-2-甲基苯甲酸甲酯(1.2g,2.67mmol)的 DCM (10mL)溶液中加入 TFA (2mL),反应混合物在室温下搅拌 1 小时。反应结束后,减压除去溶剂,向残余物中加入饱和 $NaHCO_3$ 溶液。用 10%MeOH/DCM 萃取;合并的有机层用水和盐水洗涤;用无水 Na_2SO_4 干燥;过滤并减压浓缩得到 Boc 脱保护的化合物(0.78g,)。

[2635] 将上述 Boc 脱保护的化合物(0.30g,0.62mmol)溶解于 DCM (3mL)中,并在 0℃下向该溶液中加入福尔马林(0.07g,2.33mmol)。将所得反应混合物在 0℃下搅拌 20 分钟。然后向反应混合物中加入三乙酰基硼氢化钠(0.33g,1.56mmol),在室温下搅拌 1 小时。结束后,减压除去溶剂,向残余物中加水,用 10%MeOH/DCM 萃取。将合并的有机层干燥并减压浓缩,得到的原料粗品通过制备 HPLC 纯化得到作为顺/反异构体的混合物的标题化合物 N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-((4-(二甲基氨基)环己基)-(乙基)-氨基)-5-(2-甲氧基乙氧基)-2-甲基苯甲酰胺(0.02g,6.3%)。LCMS:513.60(M+1)$^+$;HPLC:44.48%&50.77%(@210-370nm)(Rt;3.879&4.316);方法:色谱柱:YMC ODS-A150mm x4.6mm x5μ;流动相:A;0.05%TFA 的水溶液/B;0.05%TFA 的乙腈溶液;进样量:10μL,柱温:30℃;流速:1.4mL/min.;梯度:0-8min5%B-95%B,保持 1.5min,9.51-12min5%B);^{1}H NMR(DMSO-d6,400MHz) δ 11.45(s,1H),8.04(s,1H),6.68(s,1H),6.52(s,1H),5.85(s,1H),4.25(d,2H,J=4.4Hz),4.03(bs,2H),3.61(bs,2H),3.28(s,3H),3.10(m,1H),2.95(m,2H),2.18(s,6H),2.12(s,3H),2.10(s,3H),2.08(s,3H),1.77(m,2H),1.65(bs,2H),1.33(m,3H),1.15(m,1H),0.78(t,3H,J=4Hz)。

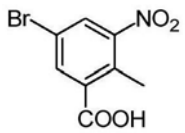
[2636] 化合物 311:N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)-(乙基)-氨基)-5-(乙基硫代)-2-甲基苯甲酰胺

[2637]



[2638] 步骤 1:合成 5-溴-2-甲基-3-硝基苯甲酸

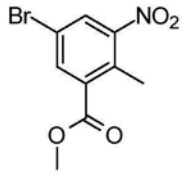
[2639]



[2640] 在室温下向搅拌后的 2- 甲基 -3- 硝基苯甲酸(50.0g,276mmol)的浓 H_2SO_4(200mL)溶液中分批加入 1,3- 二溴 -5,5- 二甲基 -2,4- 咪唑烷二酮(43.4g,151.8mmol),反应混合物在室温下搅拌 5 小时。结束时,将反应混合物倒入冷冰水中,将所得沉淀物过滤,用水洗涤并真空干燥,得到所需标题化合物粗品(71.7g,99.9%),其直接用于下一步骤。

[2641] 步骤 2 :合成 5- 溴 -2- 甲基 -3- 硝基苯甲酸甲酯

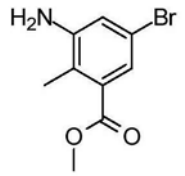
[2642]



[2643] 在室温下向搅拌后的 5- 溴 -2- 甲基 -3- 硝基苯甲酸(285g,1104mmol)的 DMF(2.8L)溶液中依次加入碳酸钠(468g,4415mmol)和碘甲烷(626g,4415mmol)。所得反应混合物在 60℃加热 8 小时。结束后,将反应混合物过滤,用乙酸乙酯洗涤。合并的滤液用水洗涤,水相用乙酸乙酯来回萃取。合并的有机层用无水硫酸钠干燥,过滤并减压浓缩,得到灰白色固体状的标题化合物(290g,97% 的产率)。所得单独的化合物直接用于下一步骤。

[2644] 步骤 3 :合成 3- 氨基 -5- 溴 -2- 甲基苯甲酸甲酯

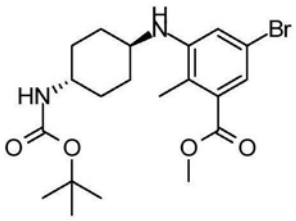
[2645]



[2646] 向搅拌后的 5- 溴 -2- 甲基 -3- 硝基苯甲酸甲酯(290g,1060mmol)的乙醇(1.5L)溶液中加入溶解于水(1.5L)中的氯化铵(283g,5290mmol),将所得混合物搅拌并在 80℃下加热,随后向其分批加入铁粉(472g,8450mmol)。所得反应混合物在 80℃加热 12 小时。结束后,将反应混合物通过硅藻土进行热过滤,并且硅藻土床层依次用甲醇(5L)和 30%MeOH/DCM (5L)洗涤。合并的滤液真空浓缩,得到的残余物用碳酸氢钠水溶液稀释,并用乙酸乙酯萃取。合并的有机层用无水硫酸钠干燥,过滤并减压浓缩,得到棕色固体状的标题化合物(220g,89% 的产率)。

[2647] 步骤 4 :合成 5- 溴 -3-(((1R,4R)-4-((叔丁氧羰基)- 氨基)- 环己基)氨基)-2- 甲基苯甲酸甲酯

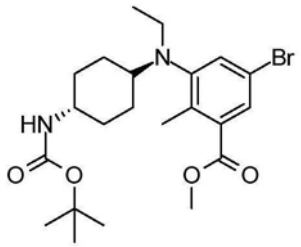
[2648]



[2649] 向搅拌后的 3- 氨基 -5- 溴 -2- 甲基苯甲酸甲酯(15.0g,617mmol)和 (4- 氧代环己基)氨基甲叔丁酯(17.1g,80.2mmol)的二氯乙烷(150mL)溶液中加入醋酸(22.2g,370mmol),反应混合物在室温下搅拌 10 分钟。然后在 0℃下向反应混合物中加入三乙酰基硼氢化钠(39.3g,185mmol),在室温下搅拌过夜。结束时,用碳酸氢钠水溶液淬灭反应,分离有机相,水相用二氯甲烷萃取。合并的有机层用水洗涤,干燥并减压浓缩。所得原料粗品通过柱层析纯化得到标题化合物 5- 溴 -3-(((1r,4r)-4-((叔丁氧羰基)- 氨基)- 环己基)氨基)-2- 甲基苯甲酸甲酯(10.5g,39%)。

[2650] 步骤 5:合成 5- 溴 -3-(((1r,4r)-4-((叔丁氧羰基)- 氨基)- 环己基)-(乙基)- 氨基)-2- 甲基苯甲酸甲酯

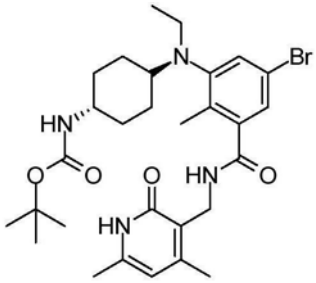
[2651]



[2652] 向搅拌后的5- 溴 -3-(((1r,4r)-4-((叔丁氧羰基)- 氨基)- 环己基)氨基)-2- 甲基苯甲酸甲酯(10.0g,22.7mmol)和乙醛(2.99g,68mmol)的二氯乙烷(100mL)溶液中加入醋酸(8.18g,136mmol),反应混合物在室温下搅拌 20 分钟。然后在 0℃下向反应混合物中加入三乙酰基硼氢化钠(14.5g,68.1mmol),在室温下搅拌过夜。结束时,用碳酸氢钠水溶液淬灭反应,分离有机相,水相用二氯甲烷萃取。合并的有机层用水洗涤,干燥并减压浓缩。所得原料粗品通过柱层析纯化得到标题化合物(9.0g,84%)。

[2653] 步骤 6:合成 ((1r,4r)-4-((5- 溴 -3-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)氨基甲酰基)-2- 甲基苯基)-(乙基)- 氨基)- 环己基)氨基甲酸叔丁酯

[2654]



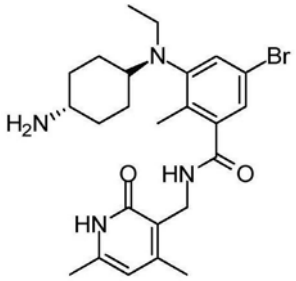
[2655] 向 5- 溴 -3-(((1r,4r)-4-((叔丁氧羰基)- 氨基)- 环己基)-(乙基)- 氨基)-2- 甲基苯甲酸甲酯(9.0g,19mmol)的乙醇(100mL)溶液中加入 NaOH(1.15g,28.8mmol)水溶液,混合物在 60℃搅拌 1 小时。反应结束后,减压除去乙醇,残余物用稀 HCl 酸化至 pH 值为 6,并用柠檬酸调至 pH 值为 4。用 10%MeOH/DCM 萃取。将合并的有机层干燥并浓缩得到粗品酸(8.6g,)。

[2656] 将上述酸(8.6g,19mmol)溶解到 DMSO (10mL)中,并向其中加入 3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮(5.74g,37.8mmol)。反应混合物在室温下搅拌 15 分钟后,

向其加入 PYBOP（14.7g,2845mmol),继续搅拌过夜。将反应混合物倒入冰中,用 10%MeOH/DCM 萃取。将合并的有机层干燥,浓缩,得到的原料粗品用乙腈洗涤纯化得到标题化合物(10.2g,92%)。

[2657] 步骤 7 :合成 3-(((1r,4r)-4- 氨基环己基)-(乙基)- 氨基)-5- 溴 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基苯甲酰胺

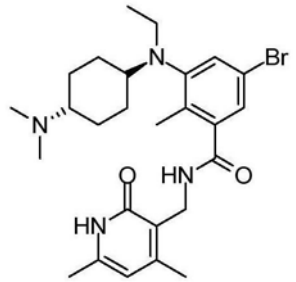
[2658]



[2659] 向 ((1r,4r)-4-((5- 溴 -3-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基) 氨基甲酰基)-2- 甲基苯基)-(乙基)- 氨基)- 环己基) 氨基甲酸甲酯(3.0g,5.10mmol)的 DCM（20mL)溶液中加入 TFA（5mL),反应混合物在室温下搅拌 1 小时。反应结束后,减压除去溶剂,向残余物中加入饱和 $NaHCO_3$ 溶液。用 10%MeOH/DCM 萃取 ;合并的有机层用水和盐水洗涤 ;用无水 Na_2SO_4 干燥 ;过滤并减压浓缩,得到标题化合物(2.2g,88%),其直接用于下一步骤。

[2660] 步骤 8 : 合成 5- 溴 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-3-(((1r,4r)-4-(二甲基氨基) 环己基)-(乙基)- 氨基)-2- 甲基苯甲酰胺

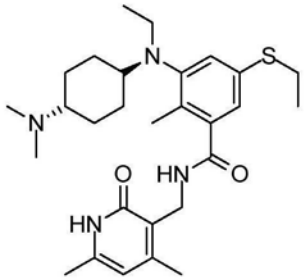
[2661]



[2662] 在 0℃下,向 3-(((1r,4r)-4- 氨基环己基)-(乙基)- 氨基)-5- 溴 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基苯甲酰胺(2.20g,4.50mmol)的 DCM(25mL)溶液中加入福尔马林(0.49g,16.3mmol)。所得反应混合物在 0℃搅拌 20 分钟。向反应混合物中加入三乙酰基硼氢化钠(2.39g,11.2mmol),在室温下搅拌 1 小时。结束后,加水,用 10%MeOH/DCM 萃取。将合并的有机层干燥并减压浓缩,得到标题化合物(2.3g,98%),其直接用于下一步骤。

[2663] 步骤 9 : 合成 N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-3-(((1r,4r)-4-(二甲基氨基) 环己基)-(乙基)- 氨基)-5-(乙基硫代)-2- 甲基苯甲酰胺

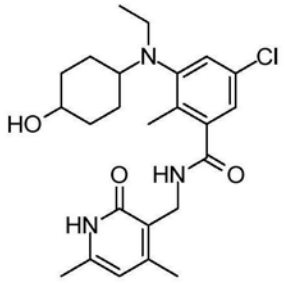
[2664]



[2665] 向搅拌后的5-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)-(乙基)-氨基)-2-甲基苯甲酰胺(0.40g,0.77mmol)的二氧六环溶液中加入乙硫醇(0.048g,0.77mmol)和DIPEA(2.70ml,1.55mmol),然后向反应混合物通入氩气10分钟。然后,将$Pd(OAc)_2$(0.009g,0.038mmol)和4,5-双二苯基膦-9,9-二甲基氧杂蒽(Xantphos)(0.045g,0.077mmol)加入到反应混合物中,并在100℃搅拌过夜。反应结束后,加水并用乙酸乙酯萃取。合并的有机层用水洗涤,用无水Na_2SO_4干燥,过滤并减压浓缩,得到的原料粗品通过柱层析纯化得到标题化合物(0.17g,44%)。LCMS:499.55$(M+1)^+$;HPLC:99.30%(在210-370nm)(R_t;4.264);方法:色谱柱:YMC ODS-A150mm x4.6mm x5μ;流动相:A;0.05%TFA的水溶液/B;0.05%TFA的乙腈溶液;进样量:10μL,柱温:30℃;流速:1.4mL/min.;梯度:0-8min5%B-95%B,保持1.5min,9.51-12min5%B);^1H NMR(DMSO-d6,400MHz)δ11.46(bs,1H),9.37(s,1H),8.14(s,1H),7.08(s,1H),6.89(s,1H),5.86(s,1H),4.25(d,2H,J=4Hz),3.15-2.90(m,6H),2.69(s,3H),2.68(s,3H),2.18(s,3H),2.14(s,3H),2.10(s,3H),1.94(m,2H),1.85(m,2H),1.41(m,4H),1.20(t,3H,J=7.2),0.78(t,3H,J=6Hz)。

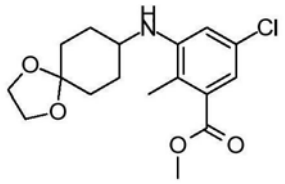
[2666] 化合物313:5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(4-羟基环己基)-氨基)-2-甲基苯甲酰胺

[2667]



[2668] 步骤1:合成3-(1,4-二氧杂螺[4.5]癸-8-基氨基)-5-氯-2-甲基苯甲酸甲酯

[2669]

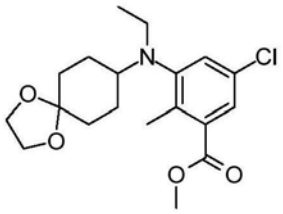


[2670] 向搅拌后的3-氨基-5-氯-2-甲基苯甲酸甲酯(5.0g,25mmol)和1,4-二氧杂螺[4.5]癸-8-酮(5.86g,37.8mmol)的二氯乙烷(50mL)溶液中加入醋酸(9.0g,150mmol),反应混合物在室温下搅拌10分钟。然后在0℃下向反应混合物中加入三乙酰基硼氢化钠

(15.9g,752mmol),在室温下搅拌过夜。结束时,用碳酸氢钠水溶液淬灭反应,分离有机相,水相用二氯甲烷萃取。合并的有机层用水洗涤,干燥并减压浓缩。所得原料粗品通过柱层析纯化得到标题化合物(6.6g,76%)。

[2671] 步骤 2 :合成 5- 氯 -3-(乙基 (1,4- 二氧杂螺 [4.5] 癸 -8- 基) 氨基)-2- 甲基苯甲酸甲酯

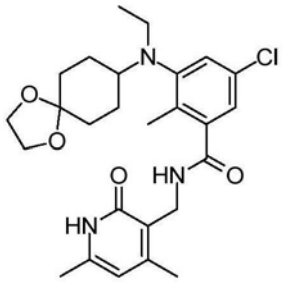
[2672]



[2673] 向搅拌后的 3-(1,4- 二氧杂螺 [4.5] 癸 -8- 基氨基)-5- 氯 -2- 甲基苯甲酸甲酯(6.6g,19mmol) 和乙醛(2.56g,58.4mmol) 的二氯乙烷(70mL) 溶液中加入醋酸(7.0g,120mmol),反应混合物在室温下搅拌 10 分钟。然后在 0℃下向反应混合物中加入三乙酰基硼氢化钠(12g,57mmol),在室温下搅拌过夜。结束时,用碳酸氢钠水溶液淬灭反应,分离有机相,水相用二氯甲烷萃取。合并的有机层用水洗涤,无水硫酸钠干燥并减压浓缩。所得原料粗品通过柱层析纯化得到标题化合物(4.0g,56%)。

[2674] 步骤 3 :合成 5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-3-(乙基 (1,4- 二氧杂螺 [4.5] 癸 -8- 基) 氨基)-2- 甲基苯甲酰胺

[2675]

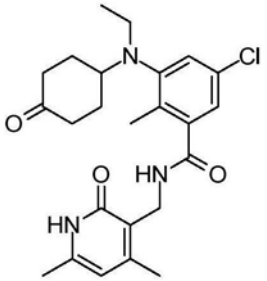


[2676] 向 5- 氯 -3-(乙基 (1,4- 二氧杂螺 [4.5] 癸 -8- 基) 氨基)-2- 甲基苯甲酸甲酯 (6.9g,19mmol) 的乙醇(70mL) 溶液中加入 NaOH (1.5g,38mmol) 水溶液,混合物在 60℃搅拌 1 小时。反应结束后,减压除去乙醇,残余物用稀 HCl 酸化至 pH 值为 6,并用柠檬酸调至 pH 值为 4。用乙酸乙酯萃取。将合并的有机层干燥并浓缩得到粗品酸(6.5g)。

[2677] 将上述酸(6.5g,18mmol) 溶解在 DMSO (50mL) 中,并向其中加入 3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮(5.6g,37mmol)。反应混合物在室温下搅拌 15 分钟后,加入 PYBOP (14.3g,27.5mmol),继续搅拌过夜。反应混合物倒入冰中,用 10%MeOH/DCM 萃取。合并的有机层用水洗涤,干燥,过滤并减压浓缩,得到标题化合物(5.9g66%),其直接用于下一步骤。

[2678] 步骤 4 :合成 5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-3-(乙基 (4- 氧代环己基) 氨基)-2- 甲基苯甲酰胺

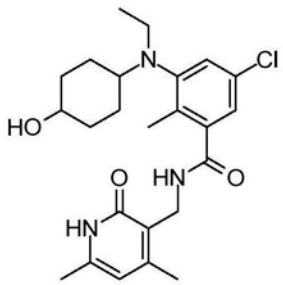
[2679]



[2680] 向搅拌后的5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(1,4-二氧杂螺[4.5]癸-8-基)氨基)-2-甲基苯甲酰胺(2.0g,4.1mmol)的丙酮:水(14mL+6mL)溶液中加入PTSA(3.1g,16mmol)。所得反应混合物在70℃搅拌过夜。结束时,减压除去溶剂,残余物用碳酸氢钠水溶液碱化。水相用乙酸乙酯萃取。合并的有机层用水洗涤,干燥,减压浓缩,得到标题化合物(1.5g,83%),其直接用于下一步骤。

[2681] 步骤5:合成5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(4-羟基环己基)-氨基)-2-甲基苯甲酰胺

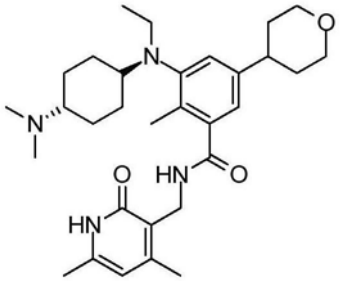
[2682]



[2683] 在0℃下向搅拌后的5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(4-氧代环己基)氨基)-2-甲基苯甲酰胺(0.30g,0.68mmol)的MeOH溶液中慢慢加入$NaBH_4$(0.038g,1.01mmol)。所得反应混合物在0℃搅拌2小时。结束时,用水淬灭反应,用乙酸乙酯萃取。合并的有机层用水洗涤,干燥,减压浓缩,得到的原料粗品通过乙腈和乙醚洗涤纯化,得到作为异构体的混合物的标题化合物(175mg,58%)。LCMS:446.35(M+1)$^+$;HPLC:74.32%&24.18%(@210-370nm)(Rt;5.157&5.276);方法:色谱柱:YMC ODS-A150mm x4.6mmx5μ;流动相:A;0.05%TFA的水溶液/B;0.05%TFA的乙腈溶液;进样量:10μL,柱温:30℃;流速:1.4mL/min.;梯度:0-8min5%B-95%B,保持1.5min,9.51-12min5%B);^{1}H NMR(DMSO-d6,400MHz)δ11.49(s,1H),8.25(s,1H),7.17(s,1H),6.96(s,1H),5.86(s,1H),4.25(d,2H,J=4Hz),3.33(m,1H),3.04(m,2H),2.19(s,3H),2.14(s,3H),2.10(s,3H),1.78(m,2H),1.66(m,2H),1.38(m,3H),1.10(m,2H),0.78(t,3H)。

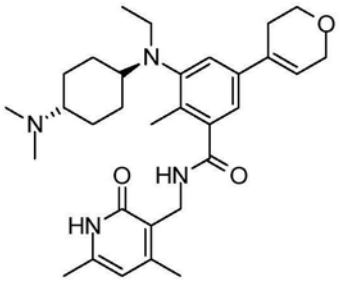
[2684] 化合物315:N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-2-甲基-5-(四氢-2H-吡喃-4-基)苯甲酰胺

[2685]



[2686] 步骤 1 :合成 5-(3,6- 二氢 -2H- 吡喃 -4- 基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-3-(((1r,4r)-4-(二甲基氨基) 环己基)(乙基) 氨基)-2- 甲基苯甲酰胺

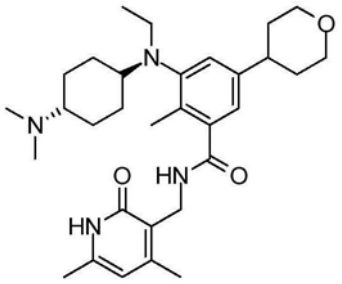
[2687]



[2688] 向搅拌后的 5- 溴 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-3-(((1r,4r)-4-(二甲基氨基) 环己基)(乙基) 氨基)-2- 甲基苯甲酰胺 (0.30g,0.58mmol) 和 2-(3,6- 二氢 -2H- 吡喃 -4- 基)-4,4,5,5- 四甲基 -1,3,2- 二氧杂环戊硼烷 (0.18g,0.88mmol) 的二氧六环 - 水混合溶液中加入 Na_2CO_3(0.22g,2.07mmol)。向溶液通入氩气 15 分钟后加入 $Pd(PPh_3)_4$ (0.067g,0.05mmol),继续向溶液通入氩气 10 分钟。反应混合物在 100℃加热 3 小时。结束时,反应混合物用水稀释,用 10%MeOH/DCM 萃取。合并的有机层 Na_2SO_4 干燥,减压除去溶剂得到标题化合物 (0.30g,98%)。

[2689] 步骤 2 : 合成 N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-3-(((1r,4r)-4-(二甲基氨基) 环己基)(乙基) 氨基)-2- 甲基 -5-(四氢 -2H- 吡喃 -4- 基) 苯甲酰胺

[2690]



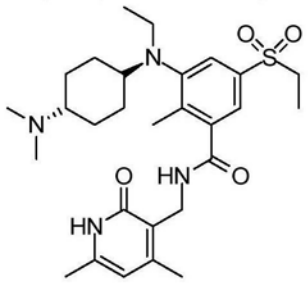
[2691] 向搅拌后的 5-(3,6- 二氢 -2H- 吡喃 -4- 基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-3-(((1r,4r)-4-(二甲基氨基) 环己基)(乙基) 氨基)-2- 甲基苯甲酰胺 (0.3g,0.576mmol) 的甲醇溶液中加入催化量的 10%Pd/C。反应混合物在气球压力的氢气气氛中在室温下搅拌 1 小时。结束时,反应混合物通过硅藻土床层过滤,用甲醇洗涤硅藻土,将滤液减压浓缩,得到的化合物粗品通过制备 HPLC 纯化得到目标化合物 N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-3-(((1s,4s)-4-(二甲基氨基) 环己基)(乙

基）氨基）-2- 甲基 -5-（四氢 -2H- 吡喃 -4- 基）苯甲酰胺的三氟乙酸盐（0.08g，26%）。

[2692] LCMS:523.60(M+1)$^+$;HPLC:48.41+51.05%(@210nm-370nm)(R_t;3.93&3.99)；方法：色谱柱 :YMC ODS-A150mm x4.6mm x5μ；流动相 :A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液；进样量 :10μL，柱温 :30℃；流速 :1.4mL/min.；梯度 :0-8min5%B-95%B，保持 1.5min,9.51-12min5%B);^{1}H NMR(DMSO-d_6,,400MHz) δ 11.47(bs,1H),8.39(t,1H),8.08(s,1H),7.07(s,1H),6.86(s,1H),5.87(s,1H),4.26(d,2H,J=2.8Hz),3.94-3.92(m,2H),3.41(m,2H),3.09-2.89(m,3H),2.69(s,3H+3H),2.19(s,3H+3H),2.11(s,3H),1.99-1.86(m,5H),1.64(m,4H),1.42(m,3H),1.25(m,2H),0.79(t,3H)。

[2693] 化合物 319:N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-3-(((1r,4r)-4-（二甲基氨基）环己基）（乙基）氨基）-5-（乙基磺酰基）-2- 甲基苯甲酰胺

[2694]

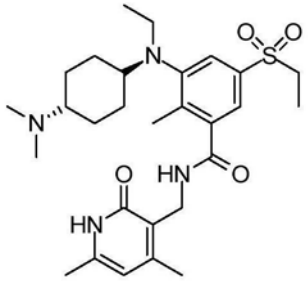


[2695] 步骤 1：合成 N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-3-(((1r,4r)-4-（二甲基氨基）环己基）（乙基）氨基）-5-（乙基硫代）-2- 甲基苯甲酰胺

[2696] 向搅拌后的 5- 溴 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-3-(((1r,4r)-4-（二甲基氨基）环己基）（乙基）氨基）-2- 甲基苯甲酰胺（0.4g，0.77mmol)的二氧六环溶液中加入乙硫醇（0.048g，0.77mmol)和 DIPEA（2.7ml，1.55mmol)。向溶液通入氩气 10 分钟后加入 $Pd(OAc)_2$(0.009g，0.038mmol)和 4,5- 双二苯基膦 -9,9- 二甲基氧杂蒽（0.045g，0.077mmol)，继续向该溶液通入氩气 10 分钟。反应混合物在 100℃搅拌过夜，加水，用乙酸乙酯萃取。合并的有机层用水洗涤，用无水 Na_2SO_4 干燥，过滤并减压浓缩，得到的原料粗品经柱层析纯化得到标题化合物（0.17g，44%)。LCMS:499.55(M+1)$^+$;HPLC:99.30%(@210-370nm)(R_t;4.264)；方法：色谱柱 :YMC ODS-A150mm x4.6mm x5μ；流动相 :A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液；进样量 :10μL，柱温 :30℃；流速 :1.4mL/min.；梯度 :0-8min5%B-95%B，保持 1.5min,9.51-12min5%B);^{1}H NMR(DMSO-d6,400MHz) δ 11.46(bs,1H),9.37(s,1H),8.14(s,1H),7.08(s,1H),6.89(s,1H),5.86(s,1H),4.25(d,2H,J=4Hz),3.15-2.90(m,6H),2.69(s,3H),2.68(s,3H),2.18(s,3H),2.14(s,3H),2.10(s,3H),1.94(m,2H),1.85(m,2H),1.41(m,4H),1.20(t,3H,J=7.2),0.78(t,3H,J=6Hz)。

[2697] 步骤 2：合成 N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-3-(((1r,4r)-4-（二甲基氨基）环己基）（乙基）氨基）-5-（乙基磺酰基）-2- 甲基苯甲酰胺

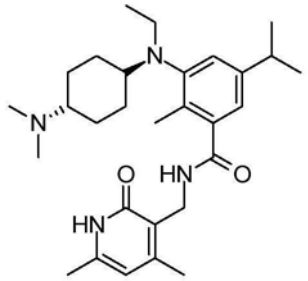
[2698]



[2699] 在室温下向搅拌后的N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-5-(乙基硫代)-2-甲基苯甲酰胺(0.085g,0.17mmol)的甲醇溶液中加入硫酸氢钾(0.105g,0.34mmol)。反应混合物在室温下搅拌4小时,加水,用10%MeOH/DCM萃取。合并的有机层用水洗涤,用无水Na_2SO_4干燥,过滤并减压浓缩,得到的原料粗品通过制备HPLC纯化得到标题化合物的三氟乙酸盐(0.07g,77%)。LCMS:531.60(M+1)$^+$;HPLC:89.24%(@210nm-370nm)(R_t;4.082;方法:色谱柱:YMC ODS-A150mm x4.6mm x5μ;流动相:A;0.05%TFA的水溶液/B;0.05%TFA的乙腈溶液;进样量:10μL,柱温:30℃;流速:1.4mL/min.;梯度:0-8min5%B-95%B,保持1.5min,9.51-12min5%B);^{1}H NMR(DMSO-d_6,,400MHz)δ11.47(s,1H),9.36(s,1H),8.36(s,1H),7.53(s,1H),7.38(s,1H),7.22(m,1H),7.09(s,1H),6.96(s,1H),5.87(s,1H),4.29-4.28(d,2H,J=4.8Hz),3.0-3.20(m,4H),2.60-2.80(m,8H),2.27(s,9H),2.20(s,3H),2.11(s,3H),1.90-2.0(m,2H),1.80-1.90(m,2H),1.40-1.50(m,4H),1.05-1.15(t,3H,J=7.6Hz),0.75-0.85(t,3H,J=6.8Hz)。

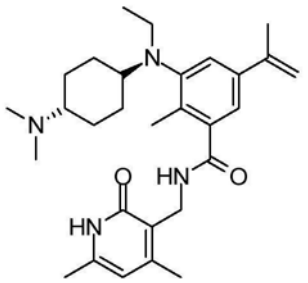
[2700] 化合物320:N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-5-异丙基-2-甲基苯甲酰胺

[2701]



[2702] 步骤1:合成N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-2-甲基-5-(丙-1-烯-2-基)苯甲酰胺

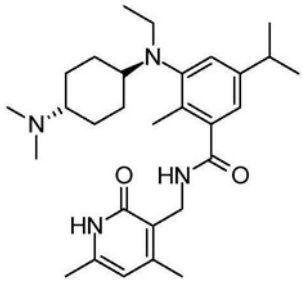
[2703]



[2704] 向搅拌后的5-溴-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-2-甲基苯甲酰胺(0.30g,0.58mmol)和4,4,5,5-四甲基-2-(丙-1-烯-2-基)-1,3,2-二氧杂环戊硼烷(0.147g,0.875mmol)的二氧六环/水的混合溶液中加入Na_2CO_3(0.22g,2.07mmol),向溶液通入氩气15分钟。然后加入$Pd(PPh_3)_4$(0.067g,0.058mmol),继续通入氩气10分钟。反应混合物在100℃加热2小时,用水稀释,用10%MeOH/DCM萃取。合并的有机层用Na_2SO_4干燥,减压除去溶剂,得到的原料粗品通过硅胶柱层析纯化得到标题化合物(0.20g,71%)。

[2705] 步骤2:N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-5-异丙基-2-甲基苯甲酰胺

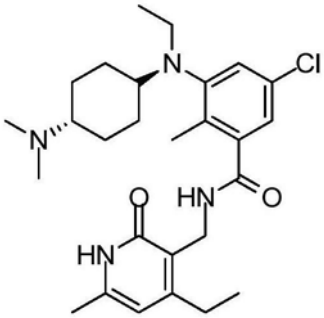
[2706]



[2707] 向搅拌后的N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(((1r,4r)-4-(二甲基氨基)环己基)(乙基)氨基)-2-甲基-5-(丙-1-烯-2-基)苯甲酰胺(0.20g,0.41mmol)的甲醇溶液中加入催化量的10%Pd/C。反应混合物在氢气气氛中(气球压力)在室温下搅拌2小时。所得混合物通过硅藻土床层过滤,用甲醇洗涤,滤液减压浓缩。所得化合物粗品通过制备HPLC纯化得到标题化合物的三氟乙酸盐(0.07g,35%)。LCMS:481.40$(M+1)^+$;HPLC:97.01%(@210nm-370nm)(R_t;3.996;方法:色谱柱:YMC ODS-A150mm x4.6mm x5μ;流动相:A;0.05%TFA的水溶液/B;0.05%TFA的乙腈溶液;进样量:10μL,柱温:30℃;流速:1.4mL/min.;梯度:0-8min5%B-95%B,保持1.5min,9.51-12min5%B);^1H NMR(DMSO-d_6,400MHz)δ11.46(bs,1H),9.37(bs,1H),8.00(s,1H),7.01(s,1H),6.83(s,1H),5.86(s,1H),4.26-4.25(d,2H,J=4.0Hz),3.0-3.25(m,3H),2.70-2.8(m,1H),2.60-2.75(m,6H),2.19(s,3H),2.15(s,3H),2.10(s,3H),1.90-2.0(m,2H),1.80-1.90(m,2H),1.35-1.50(m,4H),1.16-1.20(d,6H,J=6.8Hz),0.75-0.85(t,3H)。

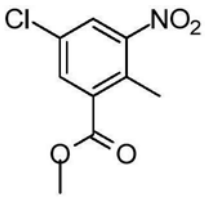
[2708] 化合物321:5-氯-3-(((1r,4r)-4-(二甲基氨基)环己基)-(乙基)-氨基)-N-((4-乙基-6-甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺

[2709]



[2710] 步骤1:合成5-氯-2-甲基-3-硝基苯甲酸甲酯

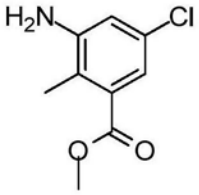
[2711]



[2712] 向搅拌后的 5- 氯 -2- 甲基 -3- 硝基苯甲酸(126g,0.59mol)的 DMF (1.0L)溶液中加入碳酸钠(249g,2.34mol)和碘甲烷(145ml,2.34mol)。反应混合物在 60℃加热 4 小时。结束时,将反应混合物过滤,残余物用 DCM 洗涤。分离水相,用 DCM 萃取。将合并的有机层干燥,减压浓缩,通过硅胶柱层析(洗脱液为乙酸乙酯 :己烷)纯化得到标题化合物(85g,63%)。^{1}H NMR(DMSO-d_6,400MHz):δ 8.25(d,1H),8.05(s,1H),3.9(s,1H),2.4(s,1H)。

[2713] 步骤 2 :合成 3- 氨基 -5- 氯 -2- 甲基苯甲酸甲酯

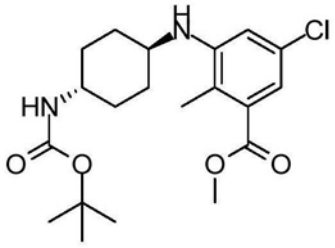
[2714]



[2715] 向搅拌后的 5- 氯 -2- 甲基 -3- 硝基苯甲酸甲酯(85g,0.37mol)的乙醇(425mL)溶液加入溶解于水(425mL)中的氯化铵(85g,112mmol)和铁粉(169g,2.96mol)。所得反应混合物在 80℃加热 16 小时,过滤,残余物用热乙醇充分洗涤。将滤液浓缩,残余物用碳酸氢钠水溶液碱化。水相用乙酸乙酯萃取。合并的有机层用水洗涤,干燥,减压浓缩,得到标题化合物(70g),其直接使用。^{1}H NMR(DMSO-d_6,400MHz):δ 6.8(s,2H),5.45(s,2H),3.75(s,3H),2.15(s,3H)。

[2716] 步骤 3 :合成 3-(((1r,4r)-4-((叔丁氧羰基)氨基)环己基)氨基)-5- 氯 -2- 甲基苯甲酸甲酯

[2717]

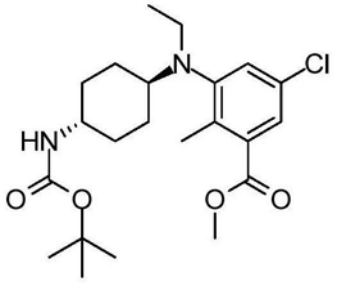


[2718] 向搅拌后的 3- 氨基 -5- 氯 -2- 甲基苯甲酸甲酯(12g,60mmol)和 (4- 氧代环己基)氨基甲酸叔丁酯(15.4g,72mmol)的二氯乙烷(120mL)溶液中加入醋酸(21g,360mmol),反应混合物在室温下搅拌 10 分钟。然后向反应混合物中加入三乙酰基硼氢化钠(38.2g,180mmol),在室温下搅拌 2 小时。结束时,向反应混合物中加水,用 DCM 萃取。合并的有机层用碳酸氢钠溶液洗涤,用硫酸钠干燥并减压浓缩,得到的原料粗品再通过柱纯化得到标题化合物的反式异构体 3-(((1r,4rs)-4-((叔丁氧羰基)氨基)环己基)氨基)-5- 氯 -2- 甲基苯甲酸甲酯(8.0g,33%)。

[2719] 步骤 4 :合成 3-(((1r,4r)-4-((叔丁氧羰基)氨基)- 环己基)-(乙基)氨

基)-5- 氯 -2- 甲基苯甲酸甲酯

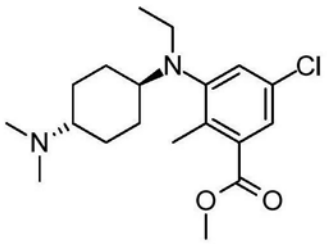
[2720]



[2721] 向搅拌后的 3-(((1r,4r)-4-((叔丁氧羰基)氨基)环己基)氨基)-5- 氯 -2- 甲基苯甲酸甲酯(11.4g,28.8mmol)和乙醛(2.5g,56mmol)的二氯乙烷(120mL)溶液中加入醋酸(10.7g,169mmol),反应混合物在室温下搅拌 10 分钟。然后向反应混合物中加入三乙酰基硼氢化钠(17.95g,84.6mmol),在室温下搅拌 2 小时。结束时,向反应混合物加水,用 DCM 萃取。合并的有机层用碳酸氢钠溶液洗涤,用硫酸钠干燥并减压浓缩,得到的原料粗品再通过柱纯化得到标题化合物(9.8g,80%)。

[2722] 步骤 5:合成 5- 氯 -3-(((1r,4r)-4-(二甲基氨基)- 环己基)-(乙基)氨基)-2- 甲基苯甲酸甲酯

[2723]

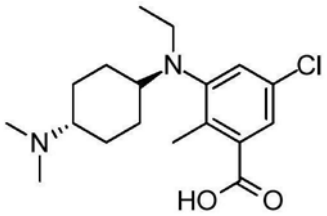


[2724] 在 0℃下,向搅拌后的 3-(((1r,4r)-4-((叔丁氧羰基)氨基)环己基)氨基)-5- 氯 -2- 甲基苯甲酸甲酯(9.8g,23mmol)的 DCM (50mL)溶液中加入 TFA (10mL),反应混合物在室温下搅拌 2 小时。结束后,将反应混合物浓缩干。再用饱和碳酸氢钠溶液(100mL)将残余物碱化至 pH 值为 8,水层用 20% 甲醇 /DCM 萃取(100mL x4)。合并的有机层用 Na_2SO_4 干燥,减压除去溶剂,得到胺的粗品(7.4g),其直接用于下一步反应。

[2725] 在 0℃下,向搅拌后的上述胺(7.4g,23mmol)的 DCM (70mL)溶液中加入 37-41% 福尔马林水溶液 (2.4g,81mmol),反应混合物在室温下搅拌 10 分钟。然后向反应混合物中加入 $NaBH(OAc)_3$ (12.1g,57mmol),搅拌 2 小时。结束时,用水淬灭反应。加入 MeOH (8mL),两相分离。用 10%MeOH/DCM 萃取,将合并的有机相干燥并浓缩。残余物通过碱性氧化铝柱纯化得到标题化合物(8.0g,99%)。

[2726] 步骤 6:合 5- 氯 -3-(((1r,4r)-4-(二甲基氨基)环己基)-(乙基)- 氨基)-2- 甲基 - 苯甲酸

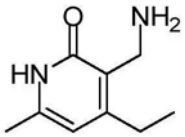
[2727]



[2728] 向化合物 3-(((1r,4r)-4-((叔丁氧羰基)氨基)-环己基)-(乙基)氨基)-5-氯-2-甲基苯甲酸甲酯(8.0g,23mmol)的乙醇(70mL)溶液中加入 NaOH (1.8g,45mmol/7mL H_2O)水溶液,在 60℃搅拌 1 小时。反应结束后,减压除去乙醇,残余物用稀 HCl 酸化至 pH 值为 6,并用柠檬酸调至 pH 值为 4。用 10%MeOH/DCM 萃取。合并的有机层用 Na_2SO_4 干燥并浓缩得到标题化合物(7.6g,99%)。

[2729] 步骤 7:合成 3-(氨基甲基)-4-乙基-6-甲基吡啶-2(1H)-酮

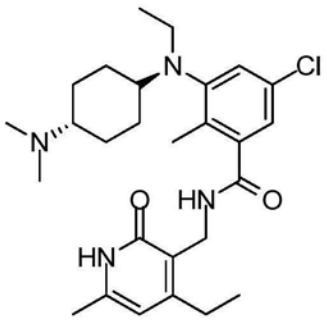
[2730]



[2731] 向 4-乙基-6-甲基-2-氧代-1,2-二氢吡啶-3-甲腈(1eq)的甲醇和氨水(9:1)溶液中加入催化量的雷尼镍。反应混合物在氢气气氛(气球压力)和室温条件下搅拌 2-5 小时。反应结束时,通过硅藻土床层过滤,将滤液减压浓缩得到标题化合物。

[2732] 步骤 8:合成 5-氯-3-(((1r,4r)-4-(二甲基氨基)环己基)-(乙基)-氨基)-N-((4-乙基-6-甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺

[2733]

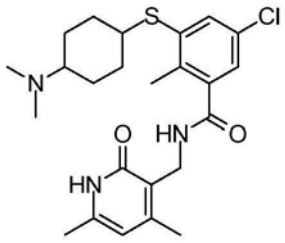


[2734] 将上述酸和 5-氯-3-(((反式)-4-(二甲基氨基)环己基)-(乙基)-氨基)-2-甲基-苯甲酸(1eq)溶解于 DMSO 中,并将 3-(氨基甲基)-4-乙基-6-甲基吡啶-2(1H)-酮(2eq.)加入到上述溶液中。反应混合物在室温下搅拌 15 分钟后加入 PYBOP (1.5eq.)和三乙胺(1eq.)。反应混合物搅拌过夜。然后将反应混合物倒入冰中,用 10%MeOH/DCM 萃取。将合并的有机层干燥并浓缩,得到的产物再依次经柱层析和制备 HPLC 纯化得到标题化合物的三氟乙酸盐(0.1g,70%)。LCMS:487.45(M+1)$^+$;HPLC:96.17%(@254nm)(R_t;6.026;方法:色谱柱:YMC ODS-A150mm x4.6mm x5μ;流动相:A;0.05%TFA 的水溶液/B;0.05%TFA 的乙腈溶液;进样量:10μL,柱温:30℃;流速:1.4mL/min.;梯度:0-8min5%B-95%B,保持 1.5min,9.51-12min5%B);^{1}H NMR(DMSO-d_6,400MHz) δ 11.46(bs,1H),9.33(s,1H),8.22(s,1H),7.19(s,1H),6.97(s,1H),5.88(s,1H),4.20-4.25(d,2H),3.0-3.15(m,1H+2H),2.60-2.75(m,1H+3H+3H),2.35-2.45(m,2H),2.20(s,3H),2.15(s,3H),1.90-2.0(m,2H),1.80-1.

90(m,2H),1.35-1.50(m,4H),1.10-1.20(t,3H,J=7.2Hz),0.75-0.85(t,3H)。

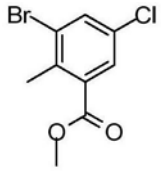
[2735] 化合物335:5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-((4-(二甲基氨基)环己基)硫代)-2-甲基苯甲酰胺

[2736]



[2737] 步骤1:合成3-溴-5-氯-2-甲基苯甲酸甲酯

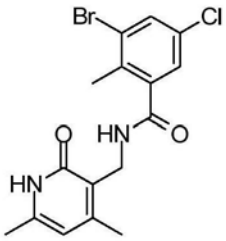
[2738]



[2739] 在0℃下,向搅拌后的$CuBr_2$(12.3g,55.3mmol)的乙腈(150mL)溶液中加入亚硝酸叔丁酯(7.77g,75.4mmol),然后加入3-氨基-5-氯-2-甲基苯甲酸甲酯(10.0g,50.3mmol)的乙腈溶液。所得反应混合物在0℃搅拌2小时,然后在室温18小时。结束时,反应混合物用水稀释,用乙酸乙酯萃取。合并的有机层干燥,减压浓缩,并通过硅胶柱层析纯化得到标题化合物(6.6g,50%)。

[2740] 步骤2:合成3-溴-5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)-甲基)-2-甲基苯甲酰胺

[2741]

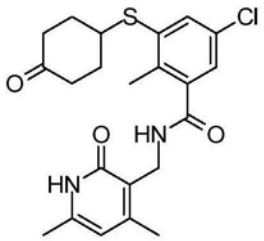


[2742] 向3-溴-5-氯-2-甲基苯甲酸甲酯(2.0g,7.6mmol)的EtOH(20mL)溶液中加入NaOH(0.45g,11.4mmol)水溶液,所得混合物在60℃搅拌1小时。反应结束后,减压除去乙醇,残余物用稀HCl酸化至pH值为8,再用柠檬酸酸化至pH值为6。水相用10%甲醇/DCM萃取。将合并的有机层干燥并浓缩得到单独的粗品酸中间体(1.5g)。

[2743] 将上述酸(1.5g,6.2mmol)溶解在DMSO(15mL)中,并向其中加入3-(氨基甲基)-4,6-二甲基吡啶-2(1H)-酮(1.67g,12.43mmol)和三乙胺(0.61g,6.01mmol)。反应混合物在室温下搅拌15分钟后加入PYBOP(4.81g,9.26mmol),在室温继续搅拌过夜。结束后,将反应混合物倒入冰水中。过滤收集悬浮的固体,用水充分洗涤并干燥。所得固体通过乙腈洗涤进一步纯化得到标题化合物(2.18g,92%)。

[2744] 步骤3:合成5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-3-((4-氧代环己基)硫代)苯甲酰胺

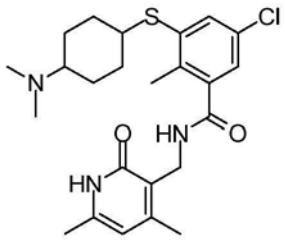
[2745]



[2746] 向 3- 溴 -5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)- 甲基)-2- 甲基苯甲酰胺(0.35g,0.91mmol.)、4- 巯基环己酮(0.142g,1.09mmol)和 DIPEA(0.235g,1.82mmol)的二氧六环溶液通入氩气 10 分钟。然后加入 $Pd(OAc)_2$(0.01g,0.044mmol)和 4,5- 双二苯基膦 -9,9- 二甲基氧杂蒽(0.052g,0.089mmol),继续通入氩气 10 分钟。反应混合物在 100℃搅拌过夜。反应结束后,加水,用乙酸乙酯萃取。合并的有机层用水洗涤,用无水 Na_2SO_4 干燥,过滤并减压浓缩,得到的原料粗品通过柱层析纯化得到标题化合物(0.50g,88%)。

[2747] 步骤 4:合成 5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-3-((4-(二甲基氨基) 环己基) 硫代)-2- 甲基苯甲酰胺

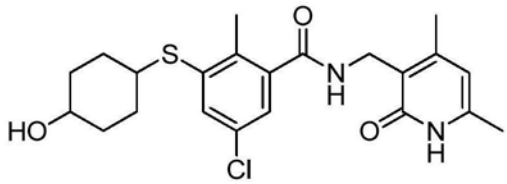
[2748]



[2749] 向搅拌后的 5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基 -3-((4- 氧代环己基) 硫代) 苯甲酰胺(0.45g,1.03mmol)和二甲基胺(0.14g,3.11mmol)的二氯乙烷(5mL)溶液中加入醋酸(0.37g,6.16mmol),所得混合物在室温下搅拌 20 分钟。然后在 0℃下,向反应混合物中加入三乙酰基硼氢化钠(0.66g,3.11mmol),在室温下搅拌过夜。反应结束时,减压除去溶剂。向残余物中加水,用 5%MeOH/DCM 萃取。将合并的有机层干燥并浓缩,得到的原料粗品通过柱层析纯化得到标题化合物(0.016g,3.3%)。分析数据:LCMS:462.35(M+1)$^+$;HPLC:89.00%(@210-370nm)(R_t;4.949; 方法 : 色谱柱 :YMC ODS-A150mm x4.6mm x5μ ; 流动相 :A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液 ; 进样量 :10μL, 柱温 :30℃ ; 流速 :1.4mL/min.; 梯度 :0-8min5%B-95%B, 保持 1.5min,9.51-12min5%B);^{1}H NMR(DMSO-d_6,400MHz) δ 7.44(s,1H),7.16(s,1H),6.10(s,1H),4.44(s,2H),3.63(m,1H),3.13(m,1H),2.38(s,3H),2.36(s,3H),2.35(s,3H),2.31(s,3H),2.24(s,3H),1.75-2.08(m,8H)。

[2750] 化合物 336:5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-3-((4- 羟基环己基) 硫代)-2- 甲基苯甲酰胺

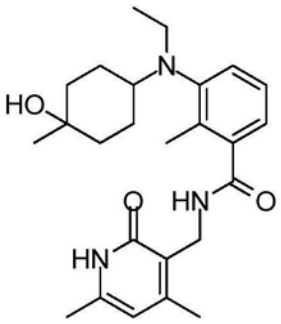
[2751]



[2752] 该化合物作为附加产物也从化合物 335（0.235g,50%）的纯化过程中分离出来，分析数据：LCMS:435.30(M+1)$^+$;HPLC:99.37%(@210-370nm)(R_t;5.900; 方法：色谱柱：YMC ODS-A150mm x4.6mm x5μ；流动相：A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液；进样量：10μL, 柱温：30℃；流速：1.4mL/min.；梯度：0-8min5%B-95%B, 保持 1.5min,9.51-12min5%B)；^{1}H NMR(DMSO-d_6,400MHz) δ 11.46(bs,1H),8.31(t,1H),7.72-7.68(m,1H),7.41(s,1H),7.07(s,1H),5.85(s,1H),4.58(d,1H,J=4Hz),4.24(d,2H,J=4Hz),4.13(m,1H),3.43(m,1H),2.20(s,3H),2.18(s,3H),2.10(s,3H),1.95-1.80(m,1H),1.75-1.55(m,1H),1.40-1.20(m,4H),0.87(m,2H)。

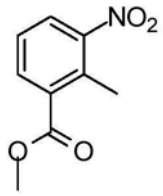
[2753] 化合物 339：N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-3-（乙基(4- 羟基 -4- 甲基环己基）氨基）-2- 甲基苯甲酰胺

[2754]



[2755] 步骤 1：合成 2- 甲基 -3- 硝基苯甲酸甲酯

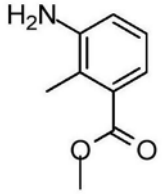
[2756]



[2757] 在室温下向 2- 甲基 -3- 硝基苯甲酸（10.0g,55.0mmol）的 120ml 甲醇溶液中加入浓 H_2SO_4(15mL)，所得混合物在 60℃搅拌过夜。将所得混合物减压浓缩，原料粗品用饱和 $NaHCO_3$ 中和并用乙酸乙酯萃取。有机相用 Na_2SO_4 干燥并减压浓缩得到标题化合物（10g）。

[2758] 步骤 2：合成 3- 氨基 -2- 甲基苯甲酸甲酯

[2759]

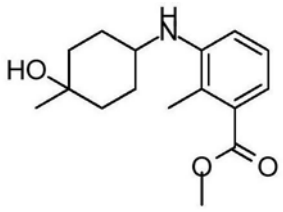


[2760] 向搅拌后的 2- 甲基 -3- 硝基苯甲酸甲酯（10.0g,56.4mmol）的 60ml 乙醇溶液中

加入溶解于水(60mL)中的氯化铵(18.0g,338mmol)和铁粉(18.8g,338.2mmol)。所得反应混合物在80℃加热3小时。向反应混合物中加水,通过硅藻土过滤。滤液用乙酸乙酯萃取。合并的有机层用水洗涤,用Na_2SO_4干燥,减压浓缩得到标题化合物(7.0g,83%)。

[2761] 步骤3:合成3-((4-羟基-4-甲基环己基)氨基)-2-甲基苯甲酸甲酯

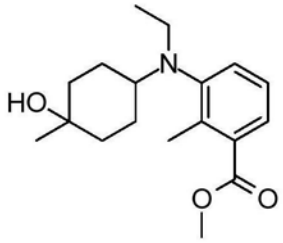
[2762]



[2763] 向搅拌后的3-氨基-2-甲基苯甲酸甲酯(1.5g,9.1mmol)和4-羟基-4-甲基环己酮(1.51ml,11.8mmol)的二氯乙烷(10ml)溶液中加入醋酸(3.2ml,55mmol),反应混合物在室温下搅拌20分钟。将反应混合物冷却至0℃,然后加入三乙酰基硼氢化钠(5.78g,27.3mmol),所得混合物室温下搅拌过夜。用饱和$NaHCO_3$中和反应混合物,用DCM萃取,用Na_2SO_4干燥,减压浓缩,并通过硅胶柱层析纯化,得到的标题化合物作为顺反异构体的混合物(1.4g,56%)继续向后续步骤推进。

[2764] 步骤4:合成3-(乙基(4-羟基-4-甲基环己基)氨基)-2-甲基苯甲酸甲酯

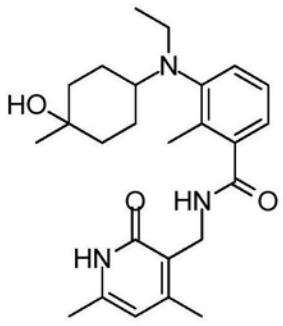
[2765]



[2766] 向搅拌后的3-((4-羟基-4-甲基环己基)氨基)-2-甲基苯甲酸甲酯(1.4g,5.05mmol)和乙醛(0.7ml,13mmol)的二氯乙烷(20ml)溶液中加入醋酸(1.7ml,30mmol),反应混合物在室温下搅拌20分钟。将反应混合物冷却至0℃,并加入三乙酰基硼氢化钠(3.2g,15mmol),所得混合物在室温下搅拌过夜。用饱和$NaHCO_3$中和反应混合物,用DCM萃取,用Na_2SO_4干燥,减压浓缩,残余物通过硅胶柱层析纯化得到标题化合物(1.42g,94%)。

[2767] 步骤5:合成N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(4-羟基-4-甲基环己基)氨基)-2-甲基苯甲酰胺

[2768]

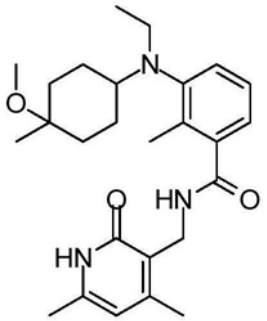


[2769] 3-(乙基(4-羟基-4-甲基环己基)氨基)-2-甲基苯甲酸甲酯(300mg,0.98mmol)

和 NaOH（58mg，1.47mmol）在乙醇 / 水（3:2)(5mL）中的混合物在 70℃加热 2 小时。将反应混合物浓缩干，将残余物在水和乙酸乙酯之间分配。将有机层用 Na_2SO_4 干燥并减压浓缩得到 270mg 粗品酸。将所得粗品酸（270g，0.92mmol）、3-（氨基甲基）-4,6- 二甲基吡啶 -2(1H)- 酮（282mg，1.85mmol）、PYBOP（717mg，1.38mmol）和三乙胺（0.12ml，0.92mmol）在 3ml DMSO 中在室温下搅拌过夜。反应混合物用水稀释，用 10%MeOH/DCM 萃取。合并的有机相用 Na_2SO_4 干燥，浓缩，残余物通过硅胶柱层析纯化，得到作为异构体的混合物的标题化合物 N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-3-（乙基 (4- 羟基 -4- 甲基环己基）氨基）-2- 甲基苯甲酰胺（120mg，30%）。LCMS:426.45(M+1)$^+$;HPLC:62.09&33.24%(@210-370nm)(R_t;3.982&4.164; 方法：色谱柱 :YMC ODS-A150mm x4.6mm x5μ；流动相 :A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液；进样量 :10μL，柱温 :30℃；流速 :1.4mL/min.；梯度 :0-8min5%B-95%B，保持 1.5min，9.51-12min5%B);^{1}H NMR(DMSO-d_6，400MHz) δ 11.44(s,1H),8.04(m,1H),7.12(s,2H),6.91(m,1H),5.85(s,1H),4.25(d,2H,J=4Hz),4.15(m,1H),3.00(m,2H),2.84(m,1H),2.18(s,6H),2.10(s,3H),1.75-1.60(m,2H),1.55-1.35(m,4H),1.35-1.15(m,4H),1.08&1.03(s,3H),0.87&0.77(t,3H)。

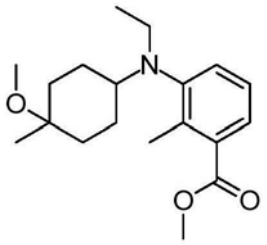
[2770] 化合物 340 :N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-3-（乙基 (4- 甲氧基 -4- 甲基环己基）氨基）-2- 甲基苯甲酰胺

[2771]



[2772] 步骤 1 :合成 3-（乙基 (4- 甲氧基 -4- 甲基环己基）氨基）-2- 甲基苯甲酸甲酯

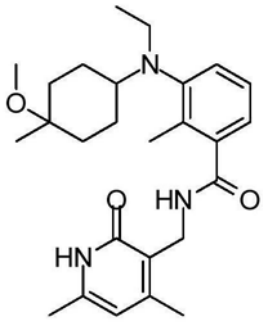
[2773]



[2774] 向冷却后的 3-（乙基 (4- 羟基 -4- 甲基环己基）氨基）-2- 甲基苯甲酸甲酯（300mg，0.98mmol）的 THF（5mL）溶液中分批加入氢化钠（235mg，5.89mmol），然后再加入碘甲烷（0.61ml，9.8mmol）。所得混合物在室温下搅拌 1 小时，冷却至 0℃后用冷冰水淬灭，用乙酸乙酯萃取。合并的有机层用 Na_2SO_4 干燥并减压浓缩，得到 300mg 标题化合物粗品。

[2775] 步骤 2 :合成 N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）-3-（乙基 (4- 甲氧基 -4- 甲基环己基）氨基）-2- 甲基苯甲酰胺

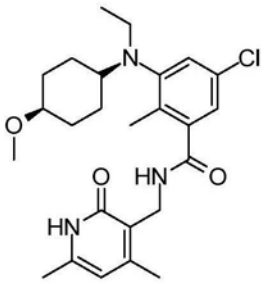
[2776]



[2777] 将 3-(乙基(4-甲氧基-4-甲基环己基)氨基)-2-甲基苯甲酸甲酯(300mg,0.94mmol)和 NaOH(56mg,1.41mmol)在乙醇/水(4:1)(5mL)中的混合物在 70℃加热 2 小时。将反应混合物浓缩干,将残余物在水和乙酸乙酯之间分配。将有机层用 Na_2SO_4 干燥并减压浓缩得到 280mg 粗品酸。将所得粗品酸(280mg,0.91mmol)、3-(氨基甲基)-4,6-二甲基吡啶-2(1H)-酮(279mg,1.83mmol)、PYBOP(716mg,1.37mmol)和三乙胺(0.12ml,0.91mmol)的混合物的 DMSO(3mL)溶液在室温下搅拌过夜。反应混合物用水稀释,并用 10%MeOH/DCM 萃取,用 Na_2SO_4 干燥,浓缩,残余物通过硅胶柱层析纯化,得到作为异构体混合物的标题化合物 N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基(4-甲氧基-4-甲基环己基)氨基)-2-甲基苯甲酰胺(70mg,17%)。LCMS:440.45(M+1)$^+$;HPLC:45.77&48.47%(@210-370nm)(R_t;4.297&4.430;方法:色谱柱:YMC ODS-A150mmx4.6mmx5μ;流动相:A;0.05%TFA 的水溶液/B;0.05%TFA 的乙腈溶液;进样量:10μL,柱温:30℃;流速:1.4mL/min.;梯度:0-8min5%B-95%B,保持 1.5min,9.51-12min5%B);^{1}H NMR(DMSO-d_6,400MHz)δ11.45(s,1H),8.03(bs,1H),7.15(bs,2H),6.91(s,1H),5.85(s,1H),4.25(d,2H,J=2.8Hz),3.10-2.90(m,7H),2.19(s,6H),2.10(s,3H),1.72-1.10(m,8H),1.08&0.99(s,3H),0.77(t,3H)。

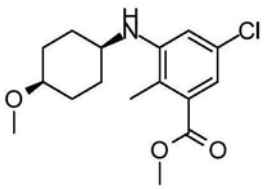
[2778] 化合物 344:5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-3-(乙基((1s,4s)-4-甲氧基环己基)氨基)-2-甲基苯甲酰胺

[2779]



[2780] 步骤 1:合成 5-氯-3-(((1s,4s)-4-甲氧基环己基)氨基)-2-甲基苯甲酸甲酯

[2781]

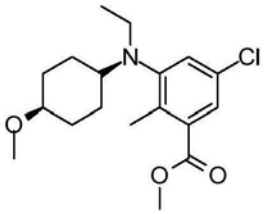


[2782] 向搅拌后的 3-氨基-5-氯-2-甲基苯甲酸甲酯(1.0g,5.0mmol)和 4-甲氧基环己酮(1.28g,10.0mmol)的二氯乙烷(10mL)溶液中加入醋酸(1.8g,30mmol),所得混合物在室

温下搅拌 10 分钟。然后在 0℃下向反应混合物中加入三乙酰基硼氢化钠(3.2g,15mmol),在室温下搅拌过夜。结束时,用碳酸氢钠水溶液淬灭反应,分离有机相,水相用二氯甲烷萃取。合并的有机层用无水硫酸钠干燥并减压浓缩。得到的原料粗品通过硅胶柱层析纯化,分离得到的标题化合物的顺式异构体为极性较小的异构体产物(0.60g,38%)。其反式异构体也可以继续向后续反应推进以生成相应的反式的最终产物化合物 343。

[2783] 步骤 2 :合成 5- 氯 -3-(乙基 ((1s,4s)-4- 甲氧基环己基) 氨基)-2- 甲基苯甲酸甲酯

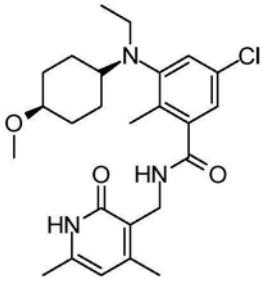
[2784]



[2785] 向搅拌后的 5- 氯 -3-(((1s,4s)-4- 甲氧基环己基) 氨基)-2- 甲基苯甲酸甲酯(0.60g,1.92mmol)和乙醛(0.25g,5.78mmol)的二氯乙烷(10mL)溶液中加入醋酸(0.69g,11.6mmol),所得混合物在室温下搅拌 10 分钟。然后在 0℃下向反应混合物中加入三乙酰基硼氢化钠(1.22g,5.78mmol),在室温下搅拌过夜。结束时,用碳酸氢钠水溶液淬灭反应,分离有机相,水相用二氯甲烷萃取。合并的有机层用无水硫酸钠干燥并减压浓缩,粗产物通过硅胶柱层析纯化得到标题化合物(0.60g,92%)。

[2786] 步骤 3 :合成 5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-3-(乙基 ((1s,4s)-4- 甲氧基环己基) 氨基)-2- 甲基苯甲酰胺

[2787]



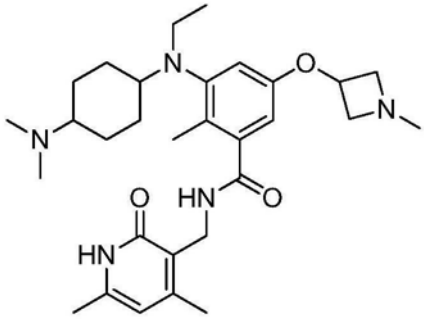
[2788] 向 5- 氯 -3-(乙基 ((1r,4r)-4- 甲氧基环己基) 氨基)-2- 甲基苯甲酸甲酯(0.4g,1.17mmol)的乙醇(5mL)溶液中加入 NaOH (0.07g,1.76mmol)水溶液,所得混合物在 60℃搅拌 1 小时。反应结束后,减压除去乙醇,用稀 HCl 酸化至 pH 值为 6 并用柠檬酸调至 pH 值为 4。用乙酸乙酯萃取,将合并的有机层干燥浓缩得到单独的粗品酸(0.35g)。

[2789] 将上述粗品酸(0.35g,1.1mmol)溶解于 DMSO (4mL)中,并将 3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮(0.33g,2.14mmol)加入到上述溶液中。反应混合物在室温下搅拌 15 分钟后加入 PYBOP(0.84g,1.61mmol),继续搅拌过夜。反应结束后,将所得混合物倒入冰中,用 10%MeOH/DCM 萃取。合并的有机层用无水硫酸钠并干燥减压浓缩,产生的粗产物通过硅胶柱层析纯化得到标题化合物(0.55g,79%)。LCMS:460.30(M+1)$^+$;HPLC:97.37%(@ 210-370nm)(R_t;5.026; 方法 : 色谱柱 :YMC ODS-A150mm x4.6mm x5μ ; 流动相 :A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液 ; 进样量 :10μL, 柱温 :30℃ ; 流速 :1.4mL/min.; 梯

度 :0-8min5%B-95%B, 保持 1.5min,9.51-12min5%B);^{1}H NMR(DMSO-d_6,400MHz) δ 11.44(bs,1H),8.21(t,1H),7.13(s,1H),6.93(s,1H),5.85(s,1H),4.25(d,2H,J=3.2Hz),3.27(m,1H),3.18(s,3H),2.99(q,2H),2.79(m,1H),2.18(s,3H),2.14(s,3H),2.10(s,3H),1.77(m,2H),1.60(m,2H),1.45(m,2H),1.33(m,2H),0.78(t,3H,J=6Hz)。

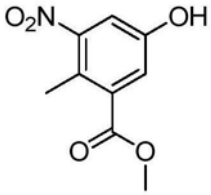
[2790] 化合物 349 :N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-3-((4-(二甲基氨基) 环己基)(乙基) 氨基)-2- 甲基 -5-((1- 甲基氮杂环丁烷 -3- 基) 氧基) 苯甲酰胺

[2791]



[2792] 步骤 1 :合成 5- 羟基 -2- 甲基 -3- 硝基苯甲酸甲酯

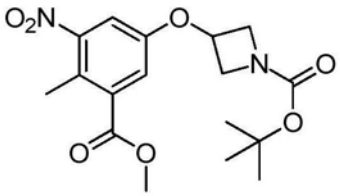
[2793]



[2794] 在 0℃下,向搅拌后的 5- 羟基 -2- 甲基 -3- 硝基苯甲酸(3.50g,17.8mmol)的甲醇(40mL)溶液中加入二氯亚砜(3.9ml,53mmol)。将所得混合物加热回流 3 小时,然后减压浓缩。向残余物中加入碳酸氢钠水溶液,用乙酸乙酯萃取。合并的有机层用水洗涤,干燥并减压浓缩。原料粗品通过柱层析纯化得到标题化合物(3.0g,80%)。

[2795] 步骤 2 :合成 3-(3-(甲氧羰基)-4- 甲基 -5- 硝基苯氧基) 氮杂环丁烷 -1- 羧酸叔丁酯

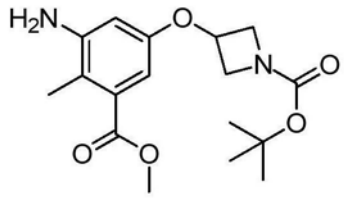
[2796]



[2797] 向搅拌后的 5- 羟基 -2- 甲基 -3- 硝基苯甲酸酯(1.5g,7.1mmol)的 ACN (15mL)溶液中加入碳酸铯(4.64g,14.2mmol)和 3- 碘代氮杂环丁烷 -1- 羧酸叔丁酯(3.0g,11mmol)。所得混合物在 80℃加热过夜。结束时,反应混合物用水稀释,并用乙酸乙酯萃取。合并的有机层用水洗涤,干燥并减压浓缩。原料粗品通过柱层析纯化得到标题化合物(1.2g,46%)。

[2798] 步骤 3 :合成 3-(3- 氨基 -5-(甲氧羰基)-4- 甲基苯氧基) 氮杂环丁烷 -1- 羧酸叔丁酯

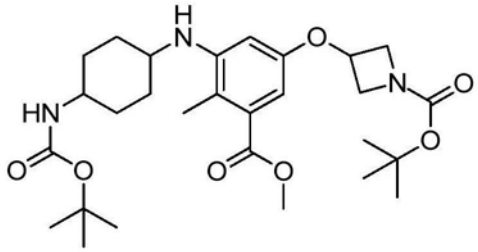
[2799]



[2800] 向搅拌后的 3-(3-(甲氧羰基)-4-甲基-5-硝基苯氧基)氮杂环丁烷-1-羧酸叔丁酯(1.0g,2.7mmol)的甲醇(10mL)溶液中加入催化量的 10%Pd/C。所得混合物在室温和氢气气氛中(气球压力)搅拌 3 小时。结束时,反应混合物通过硅藻土床层过滤,用甲醇洗涤硅藻土床层。合并的滤液减压浓缩得到标题化合物(0.90g,98%)。

[2801] 步骤 4:合成 3-(3-((4-((叔丁氧羰基)氨基)环己基)氨基)-5-(甲氧羰基)-4-甲基苯氧基)氮杂环丁烷-1-羧酸叔丁酯

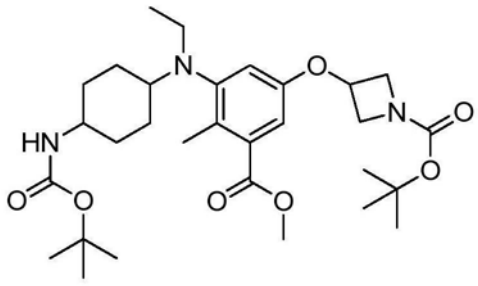
[2802]



[2803] 向搅拌后的 3-(3-氨基-5-(甲氧羰基)-4-甲基苯氧基)氮杂环丁烷-1-羧酸叔丁酯(0.90g,2.67mmol)和(4-氧代环己基)氨基甲酸叔丁酯(0.741g,3.47mmol)的二氯乙烷(10mL)溶液中加入醋酸(0.96g,16.1mmol),所得混合物在室温下搅拌 20 分钟。然后在 0℃下向反应混合物中加入三乙酰基硼氢化钠(1.7g,8.0mmol),在室温下搅拌 2 小时。结束时,用碳酸氢钠水溶淬灭液反应,分离有机相,水相用二氯甲烷萃取。合并的有机层用水洗涤,干燥,减压浓缩,原料粗品通过柱层析纯化,得到的标题化合物(0.9g,63%)为顺反异构体的混合物。

[2804] 步骤 5:合成 3-(3-((4-((叔丁氧羰基)氨基)环己基)(乙基)氨基)-5-(甲氧羰基)-4-甲基苯氧基)氮杂环丁烷-1-羧酸叔丁酯

[2805]

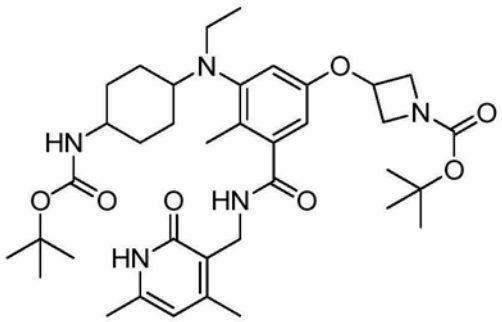


[2806] 向搅拌后的 3-(3-((4-((叔丁氧羰基)氨基)环己基)氨基)-5-(甲氧羰基)-4-甲基苯氧基)氮杂环丁烷-1-羧酸叔丁酯(0.90g,1.69mmol)和乙醛(0.22g,5.06mmol)的二氯乙烷(10mL)溶液中加入醋酸(0.61g,10mmol),反应混合物在室温搅拌 20 分钟。然后在 0℃下向反应混合物中加入三乙酰基硼氢化钠(1.07g,5.05mmol),反应在室温下搅拌 2 小时。结束时,用碳酸氢钠水溶淬灭液反应,分离有机相,水相用二氯甲烷萃取。

合并的有机层用水洗涤，干燥，减压浓缩，得到标题化合物（0.85g），其使用时不用进一步纯化。

[2807] 步骤 6：合成 3-(3-((4-((叔丁氧羰基）氨基）环己基)(乙基）氨基)-5-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）氨基甲酰基)-4- 甲基苯氧基）氮杂环丁烷 -1- 羧酸叔丁酯

[2808]

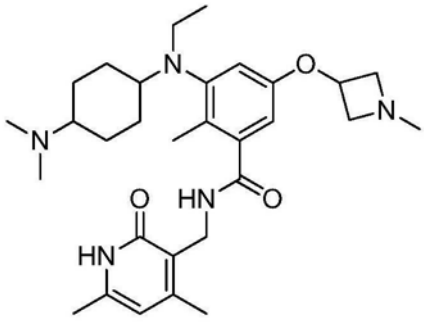


[2809] 向 3-(3-((4-((叔丁氧羰基）氨基）环己基)(乙基）氨基)-5-(甲氧羰基)-4- 甲基苯氧基）氮杂环丁烷 -1- 羧酸叔丁酯（0.85g，1.52mmol）的乙醇（10mL）溶液中加入 NaOH（0.12g，3.03mmol）水溶液，所得混合物在 60℃搅拌 1 小时。反应结束后，减压除去乙醇，用稀 HCl 酸化至 pH 值为 6，用柠檬酸调至 pH 值为 4。用乙酸乙酯萃取。合并的有机层干燥并浓缩后得到单独的酸（0.75g）。

[2810] 然后将上述酸（0.75g，1.37mmol）溶解于 DMSO（7mL）中，并将 3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮（0.42g，2.74mmol）加入到上述溶液中。反应混合物在室温搅拌 15 分钟后加入 PYBOP（1.06g，2.05mmol），继续搅拌过夜。结束后，将反应混合物倒入冰中，用 10%MeOH/DCM 萃取。合并的有机层用水洗涤，用无水 Na_2SO_4 干燥，过滤并减压浓缩得到标题化合物（0.80g，85%）。

[2811] 步骤 7：合成 N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基)-3-((4-(二甲基氨基）环己基)(乙基）氨基)-2- 甲基 -5-((1- 甲基氮杂环丁烷 -3- 基）氧基）苯甲酰胺

[2812]



[2813] 向冷却并搅拌后的 3-(3-((4-((叔丁氧羰基）氨基）环己基)(乙基）氨基)-5-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）氨基甲酰基)-4- 甲基苯氧基）氮杂环丁烷 -1- 羧酸叔丁酯（0.80g，1.17mmol）的 DCM（10mL）溶液中加入 TFA（2mL）。所得混合物在室温下搅拌 1 小时，减压浓缩，向残余物加入饱和 $NaHCO_3$ 溶液。用 10%MeOH/DCM 萃取，合并的有机层用水和盐水洗涤，用无水 Na_2SO_4 干燥。减压除去溶剂得到 Boc 脱保

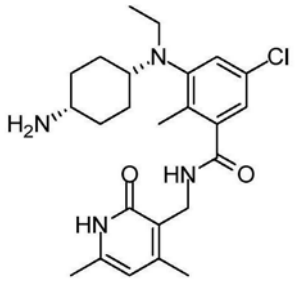
护的中间体化合物(0.5g)。

[2814] 将上述中间体(0.5g,1.0mmol)溶解于MeOH(3mL)中,并在0℃加入福尔马林(0.16g,5.33mmol)。所得混合物在相同温度搅拌20分钟。然后加入三乙酰基硼氢化钠(0.55g,2.59mmol),所得混合物在室温下搅拌1小时。结束后,减压除去溶剂,向残余物中加水。用10%MeOH/DCM萃取。将合并的有机层干燥并减压浓缩,得到的原料粗品通过柱层析纯化得到标题化合物(0.03g,5.5%)。

[2815] LCMS:524.55(M+1)$^+$;HPLC:37.93+61.46%(@210-370nm)(Rt;3.462and3.810; 方法:色谱柱:YMC ODS-A150mm x4.6mm x5μ;流动相:A;0.05%TFA的水溶液/B;0.05%TFA的乙腈溶液;进样量:10μL,柱温:30℃;流速:1.4mL/min.;梯度:0-8min5%B-95%B,保持1.5min,9.51-12min5%B);^{1}H NMR(DMSO-d_6,400MHz)δ11.45(bs,1H),8.05(bs,1H),6.56(s,1H),6.36(s,1H),5.85(s,1H),4.69(bs,1H),4.24(bs,2H),3.67(m,2H),3.08-2.92(m,4H),2.33-2.11(m,20H),1.73-1.65(m,4H),1.35-1.29(m,4H),0.77(t,3H)。

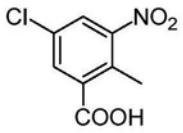
[2816] 化合物119:3-(((1s,4s)-4-氨基环己基)(乙基)氨基)-5-氯-N-((4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺

[2817]



[2818] 步骤1:合成5-氯-2-甲基-3-硝基苯甲酸

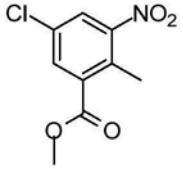
[2819]



[2820] 在-10℃下,向搅拌后的5-氯-2-甲基苯甲酸(4.0g,24mmol)的浓硫酸(27mL)溶液中加入浓缩HNO_3(3.3g,53mmol)溶解于浓硫酸(4.4mL)中组成的硝化溶液。所得混合物在-10℃搅拌3小时,然后倒入冰水中。将产生的沉淀物过滤,用水洗涤并真空干燥得到标题化合物(4.95g,99%)。

[2821] 步骤2:合成5-氯-2-甲基-3-硝基苯甲酸甲酯

[2822]

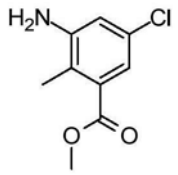


[2823] 向搅拌后的5-氯-2-甲基-3-硝基苯甲酸(6.75g,31.3mmol)的DMF(33mL)溶液中加入碳酸钠(13.2g,125mmol)和碘甲烷(17.8g,125mmol)。所得混合物在60℃加热4小时。向反应混合物中加水,用二氯甲烷萃取。合并的有机萃取液用硫酸钠干燥,过滤并减

压浓缩。所得粗产物通过硅胶柱层析纯化得到标题化合物(6.0g,84%)。

[2824] 步骤 3 :合成 3- 氨基 -5- 氯 -2- 甲基苯甲酸甲酯

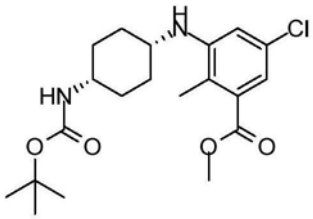
[2825]



[2826] 向搅拌后的 5- 氯 -2- 甲基 -3- 硝基苯甲酸甲酯(6.0g,26mmol)的乙醇(60mL)溶液中加入氯化铵 (6.0g,112mmol)的水(60mL)溶液和铁粉(11.9g,208mmol)。所得混合物在 80℃加热 1 小时。加水,所得混合物通过硅藻土过滤,用乙酸乙酯萃取。合并的有机层用水洗涤,用硫酸钠干燥并减压浓缩得到标题化合物粗品(5.0g)。

[2827] 步骤 4 :合成 3-(((1s,4s)-4-((叔丁氧羰基)氨基)环己基)氨基)-5- 氯 -2- 甲基苯甲酸甲酯

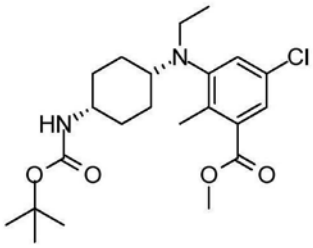
[2828]



[2829] 在室温下,向搅拌后的 3- 氨基 -5- 氯 -2- 甲基苯甲酸甲酯(5.0g,25mmol)和 (4- 氧代环己基)氨基甲酸叔丁酯(6.95g,32.7mmol)的二氯乙烷(25mL)溶液中加入醋酸(9.0g,150mmol)。然后再加入三乙酰基硼氢化钠(15.97g,75.4mmol),反应混合物在室温下搅拌 1 小时。减压除去溶剂,原料粗品纯化硅胶柱层析得到 5.2g(52%)首先被洗脱下来的标题化合物的顺式异构体产物 3-(((1s,4s)-4-((叔丁氧羰基)氨基)环己基)氨基)-5- 氯 -2- 甲基苯甲酸甲酯和 3.5g(35%)极性较大的反式异构体产物 3-(((1r,4r)-4-((叔丁氧羰基)氨基)环己基)氨基)-5- 氯 -2- 甲基苯甲酸甲酯。

[2830] 步骤 5 :合成 3-(((1s,4s)-4-((叔丁氧羰基)氨基)环己基)(乙基)氨基)-5- 氯 -2- 甲基苯甲酸甲酯

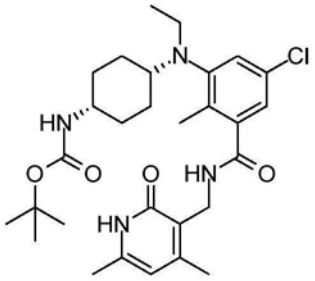
[2831]



[2832] 在室温下,向搅拌后的 3-(((1s,4s)-4-((叔丁氧羰基)氨基)环己基)氨基)-5- 氯 -2- 甲基苯甲酸甲酯(5.20g,13.1mmol)和乙醛(1.15g,26.3mmol)的二氯乙烷(15mL)溶液中加入醋酸(4.72g,78.8mmol)。然后向反应混合物中加入三乙酰基硼氢化钠(8.35g,39.4mmol),搅拌 1 小时。向混合物加水,用二氯甲烷萃取。合并的有机层干燥硫酸钠并减压浓缩。粗产物通过硅胶柱层析纯化得到标题化合物(5.3g,99%)。

[2833] 步骤 6：合成 ((1s,4s)-4-((5- 氯 -3-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）氨基甲酰基)-2- 甲基苯基)(乙基）氨基）环己基）氨基甲酸叔丁酯

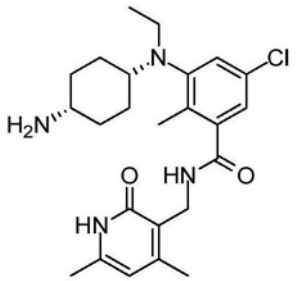
[2834]



[2835] 向搅拌后的 3-(((1s,4s)-4-((叔丁氧羰基）氨基)- 环己基)(乙基）氨基)-5- 氯 -2- 甲基苯甲酸甲酯 (5.20g,12.2mmol) 的乙醇 (15mL) 溶液中加入 NaOH (0.73g,18.4mmol) 水溶液。混合物在 60℃搅拌 1 小时，减压浓缩，然后依次用稀 HCl 和柠檬酸酸化至 pH 值为 4。所得混合物用乙酸乙酯萃取，将合并的萃取液干燥并减压浓缩得到相应的粗品酸 (4.4g)。在 0℃下，向搅拌后的上述酸 (4.4g,10.7mmol)、3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮 (3.25g,21.4mmol) 和三乙胺 (1.08g,10.70mmol) 的 DMSO (15mL) 溶液中加入 PYBOP (8.34g,16.05mmol)。在室温下搅拌过夜后，将所得混合物倒入冰中，并用 10%MeOH/CH_2Cl_2 萃取。合并的有机层用硫酸钠干燥并减压浓缩，得到的原料粗品通过硅胶柱层析纯化得到标题化合物 (4.20g,72%)。LCMS:548.40(M+1)$^+$;HPLC:98.62%(@254nm)(R_t;5.736; 方法：色谱柱 :YMC ODS-A150mm x4.6mm x5μ; 流动相 :A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液；进样量 :10μL, 柱温 :30℃；流速 :1.4mL/min.；梯度 :0-8min5%B-95%B, 保持 1.5min,9.51-12min5%B);^{1}H NMR(DMSO-d_6,400MHz) δ 11.45(s,1H),8.20(t,1H),7.13(s,1H),6.91(m,2H),5.85(s,1H),4.22(d,2H),3.47(bs,1H),3.00-3.02(m,3H),2.18(s,3H),2.16(s,3H),2.10(s,3H),1.71(m,2H),1.53(m,2H),1.39(m,4H),1.37(s,9H),0.78(t,3H,J=6.8Hz)。

[2836] 步骤 7：合成 3-(((1s,4s)-4- 氨基环己基)(乙基）氨基)-5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基)-2- 甲基苯甲酰胺

[2837]

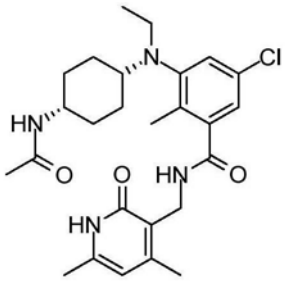


[2838] 在 0℃下，向搅拌后的 ((1s,4s)-4-((5- 氯 -3-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）氨基甲酰)-2- 甲基苯基)(乙基）氨基）环己基）氨基甲酸叔丁酯 (0.60g,1.10mmol) 的 CH_2Cl_2 (10mL) 溶液中加入三氟乙酸 (2mL)。所得混合物在室温下搅拌 2 小时，浓缩干。将残余物溶解于碳酸氢钠水溶液中，用 20%MeOH/CH_2Cl_2 萃取。合并的有机层用硫酸钠干燥并减压浓缩，得到的残余物经研磨得到标题化合物 (0.5g,100%)。LCMS:445.30(M+1)$^+$;HPLC:99.3%(@254nm)(R_t;4.524; 方法：色谱柱 :YMC ODS-A150mm

x4.6mm x5μ；流动相：A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液；进样量：10μL，柱温：30℃；流速：1.4mL/min.；梯度：0-8min5%B-95%B，保持 1.5min,9.51-12min5%B)；^{1}H NMR(DMSO-d_6,400MHz) δ8.21(t,1H),7.13(s,1H),6.91(d,1H,J=1.6Hz),5.85(s,1H),4.24(d,2H,J=4.8Hz),2.99-3.04(m,2H),2.82-2.85(m,2H),2.18(s,3H),2.15(s,3H),2.10(s,3H),1.75-1.77(m,2H),1.36-1.39(m,6H),0.79(t,3H,J=6.8Hz)。

[2839] 化合物 121：3-(((1s,4s)-4- 乙酰氨基环己基)(乙基)氨基)-5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)-2- 甲基苯甲酰胺

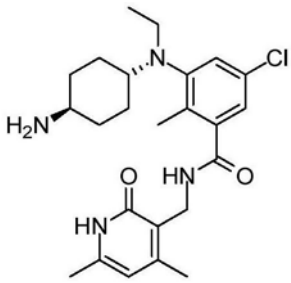
[2840]



[2841] 在室温下，向搅拌后的 3-(((1s,4s)-4- 氨基环己基)(乙基)氨基)-5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)-2- 甲基苯甲酰胺(0.30g,0.68mmol)和 EDCI.HCl(0.194g,1.01mmol)的 DMF (5mL)溶液中加入 HOBt(0.091g,0.675mmol)和醋酸(0.081g,1.35mmol)。搅拌 18 小时后加水，所得混合物用 10%MeOH/CH_2Cl_2 萃取。合并的有机层用硫酸钠干燥并浓缩，得到的残余物纯化通过硅胶柱层析纯化得到标题化合物(0.10g,30%)。LCMS:487.30(M+1)$^+$;HPLC:91.72%(@254nm)(R_t;4.585; 方法：色谱柱：YMC ODS-A150mm x4.6mm x5μ；流动相：A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液；进样量：10μL，柱温：30℃；流速：1.4mL/min.；梯度：0-8min5%B-95%B，保持 1.5min,9.51-12min5%B)；^{1}H NMR(DMSO-d_6,400MHz) δ8.22(t,1H),7.75(d,1H,J=7.2Hz),7.15(s,1H),6.93(s,1H),5.85(s,1H),4.24(d,2H,J=4.4Hz),3.69(bs,1H),3.01-3.03(m,2H),2.94(m,1H),2.18(s,6H),2.10(s,3H),1.80(s,3H),1.69-1.71(m,2H),1.37-1.51(m,6H),0.79(t,3H,J=6.8Hz)。

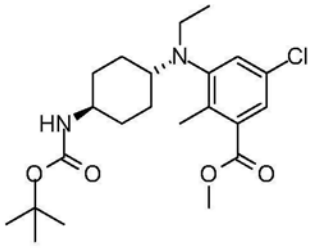
[2842] 化合物 120：3-(((1r,4r)-4- 氨基环己基)(乙基)氨基)-5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)-2- 甲基苯甲酰胺

[2843]



[2844] 步骤 1：合成 3-(((1r,4r)-4-((叔丁氧羰基)氨基)环己基)(乙基)氨基)-5- 氯 -2- 甲基苯甲酸甲酯

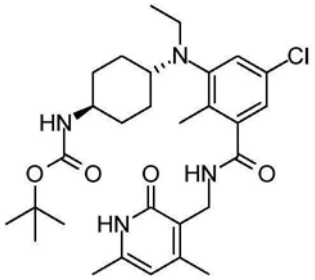
[2845]



[2846] 在室温下，向搅拌后的上述制备的 3-(((1r,4r)-4-((叔丁氧羰基）氨基）环己基）氨基)-5- 氯 -2- 甲基苯甲酸甲酯(3.5g,8.8mmol）和乙醛(0.77g,17.7mmol）的二氯乙烷(15mL）溶液中加入醋酸(3.17g,53mmol)。搅拌 10 分钟后，向反应混合物加入三乙酰基硼氢化钠(5.61g,26.5mmol)，反应在室温下搅拌 1 小时。加水，所得混合物用二氯甲烷萃取。合并的有机层用硫酸钠干燥并减压浓缩，得到的原料粗品通过硅胶柱层析纯化得到标题化合物(3.5g,93%)。

[2847] 步骤 2：合成 ((1r,4r)-4-((5- 氯 -3-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）氨基甲酰基)-2- 甲基苯基)(乙基）氨基）环己基）氨基甲酸叔丁酯

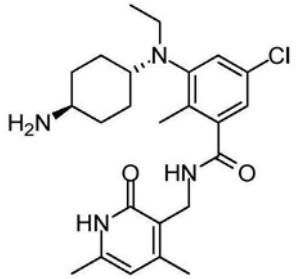
[2848]



[2849] 向搅拌后的 3-(((1r,4r)-4-((叔丁氧羰基）氨基）环己基)(乙基）氨基)-5- 氯 -2- 甲基苯甲酸甲酯(3.50g,8.23mmol)的乙醇(15mL)溶液中加入 NaOH(0.49g,12.4mmol)水溶液。所得混合物在 60℃搅拌 1 小时，减压浓缩并依次用稀 HCl 和柠檬酸水溶液酸化至 pH 值为 4。所得混合物用乙酸乙酯萃取，将合并的有机层干燥，减压浓缩得到相应的粗品酸(3.2g)。在 0℃下，向搅拌后的上述酸(3.2g,7.8mmol)、3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮(2.36g,15.6mmol)和三乙胺(0.79g,7.8mmol)的 DMSO (15mL)溶液中加入 PYBOP (6.07g,11.7mmol)。在室温下搅拌过夜，然后将混合物倒入冰中，并用 10%MeOH/CH_2Cl_2 萃取。合并的有机层用硫酸钠干燥并减压浓缩，得到的原料粗品硅胶柱层析纯化得到标题化合物(3.0g,70%)。分析数据：LCMS:545.25(M+1)$^+$;HPLC:99.92%(@254nm)(R_t;5.677;方法：色谱柱：YMC ODS-A150mm x4.6mm x5μ；流动相：A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液；进样量：10μL, 柱温：30℃；流速：1.4mL/min.；梯度：0-8min5%B-95%B, 保持 1.5min,9.51-12min5%B)；^{1}H NMR(DMSO-d_6,400MHz) δ 11.46(s,1H),8.23(t,1H),7.14(s,1H),6.92(s,1H),6.65(d,1H,J=7.2Hz),5.85(s,1H),4.23(d,2H,J=4Hz),3.14(bs,1H),3.00-3.02(m,2H),2.18(s,3H),2.11(s,3H),2.10(s,3H),1.67-1.76(m,4H),1.40(m,2H),1.35(m,9H),1.04-1.13(m,2H),0.77(t,3H,J=6Hz)。

[2850] 步骤 3：合成 3-(((1r,4r)-4- 氨基环己基)(乙基）氨基)-5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基)-2- 甲基苯甲酰胺

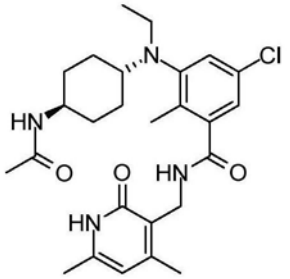
[2851]



[2852] 在 0℃下，向搅拌后的 ((1r,4r)-4-((5- 氯 -3-(((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基）氨基甲酰基)-2- 甲基苯基)（乙基）氨基）环己基）氨基甲酸叔丁酯(0.6g,1.10mmol)的二氯甲烷(2mL)溶液中加入 TFA (2mL)。所得混合物在室温下搅拌 2 小时，浓缩干。将残余物溶解于碳酸氢钠水溶液并用 20%MeOH/CH_2Cl_2 萃取。合并的有机层用硫酸钠干燥并减压浓缩，得到的粗产品通过硅胶柱层析纯化得到标题化合物(0.40g,81%)。LCMS:445.18(M+1)$^+$;HPLC:98.13%(@254nm)(R_t;4.096; 方法：色谱柱 :YMC ODS-A150mm x4.6mm x5μ；流动相 :A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液；进样量 :10μL, 柱温 :30℃；流速 :1.4mL/min.；梯度 :0-8min5%B-95%B, 保持 1.5min,9.51-12min5%B);^{1}H NMR(DMSO-d_6,400MHz) δ 8.22(t,1H),7.13(s,1H),6.92(s,1H),5.85(s,1H),4.23(d,2H,J=4Hz),3.00-3.01(m,2H),2.59(m,1H),2.18(s,3H),2.12(s,3H),2.10(s,3H),1.73-1.76(m,2H),1.65-1.68(m,2H),1.36-1.39(m,2H),0.97-1.00(m,2H),0.77(t,3H,J=6Hz)。[1H 合并在溶剂峰中]。

[2853] 化合物 122 :3-(((1r,4r)-4- 乙酰氨基环己基)（乙基）氨基)-5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基)-2- 甲基苯甲酰胺

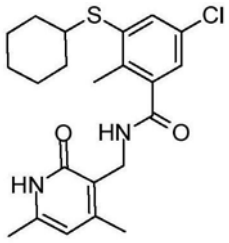
[2854]



[2855] 在室温下，向搅拌后的 3-(((1r,4r)-4- 氨基环己基)（乙基）氨基)-5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基）甲基)-2- 甲基苯甲酰胺 (0.30g,0.68mmol) 和 EDCI.HCl(0.19g,1.0mmol) 的 DMF (5mL) 溶液中加入 HOBt(0.09g,0.68mmol) 和醋酸 (0.081g,1.35mmol)。搅拌 18 小时后，加水，所得混合物用 10%MeOH/DCM 萃取。合并的有机层干燥并浓缩，得到的原料粗品经硅胶柱层析纯化得到标题化合物 (0.10g,30%)。LCMS:487.25(M+1)$^+$;HPLC:92.95%(@254nm)(R_t;4.445; 方法：色谱柱 :YMC ODS-A150mm x4.6mm x5μ；流动相 :A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液；进样量 :10μL, 柱温 :30℃；流速 :1.4mL/min.；梯度 :0-8min5%B-95%B, 保持 1.5min,9.51-12min5%B);^{1}H NMR(DMSO-d_6,400MHz) δ 11.45(s,1H),8.21(t,1H),7.64(d,1H,J=7.6Hz),7.14(s,1H),6.92(s,1H),5.85(s,1H),4.24(d,2H,J=4.8Hz),3.41-3.43(m,1H),3.01-3.03(m,2H),2.61(m,1H),2.18(s,3H),2.13(s,3H),2.10(s,3H),1.74(t,7H,J=18Hz),1.40-1.43(m,2H),1.07-1.12(m,2H),0.77(t,3H,J=6.8Hz)。

[2856] 化合物 207 :5- 氯 -3-(环己基硫代)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基苯甲酰胺

[2857]



[2858] 步骤 1 :合成 3- 溴 -5- 氯 -2- 甲基苯甲酸甲酯

[2859] 在 0℃下,向搅拌后的 $CuBr_2$(12.3g,55.3mmol) 的乙腈 (100mL) 溶液中加入亚硝酸叔丁酯 (7.79g,75.4mmol)。向该溶液中加入 3- 氨基 -5- 氯 -2- 甲基苯甲酸甲酯 (10g,50.3mmol) 的乙腈 (50mL) 溶液,并在 0℃搅拌 2 小时,室温下搅拌过夜。结束时,加水,用乙酸乙酯萃取产物。有机层用 NH_4Cl 水溶液洗涤,用硫酸钠干燥,再减压浓缩。经硅胶柱纯化得到标题化合物 (6.6g,50%)。

[2860] 步骤 2 :合成 5- 氯 -3-(环己基硫代)-2- 甲基苯甲酸甲酯

[2861] 向搅拌后的 3- 溴 -5- 氯 -2- 甲基苯甲酸甲酯 (1.0g,3.79mmol) 的 1,4- 二氧六环溶液中加入 N,N- 二异丙基乙基胺 (0.98g,7.59mmol)。向反应混合物中通入氩气 20 分钟。然后向反应混合物中依次加入 $Pd(OAc)_2$(0.042g,0.189mmol)、4,5- 双二苯基膦 -9,9- 二甲基氧杂蒽 (0.22g,0.38mmol) 和环己基硫醇 (0.44g,3.79mmol),再次通入氩气 10 分钟。将反应混合物回流 16 小时。结束时,加水,产物用乙酸乙酯萃取。有机层用硫酸钠干燥,产物通过硅胶柱纯化得到标题化合物 (1.0g,83%)。

[2862] 步骤 3 :合成 5- 氯 -3-(环己基硫代)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基苯甲酰胺

[2863] 向 5- 氯 -3-(环己基硫代)-2- 甲基苯甲酸甲酯 (1.0g,3.35mmol) 的乙醇 (10mL) 溶液中加入 NaOH (0.2g 在 2.5mL H_2O 中 ,5.02mmol) 水溶液,溶液在 60℃搅拌 1 小时。反应结束后,减压除去乙醇,水层用稀 HCl 酸化至 pH 值为 6,再用柠檬酸酸化至 pH 值为 4。产物用 10% 甲醇 /DCM 萃取。将合并的有机层干燥并浓缩得到单独的酸 (0.91g,95%)。

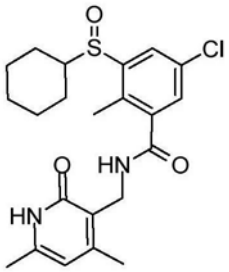
[2864] 将上述酸 (0.91g,3.2mmol) 溶解于 DMSO (2mL) 中,并将 3-(氨基甲基)-4,6- 二甲基吡啶 -2(1H)- 酮 (0.974g,6.41mmol) 和三乙胺 (0.65g,3.2mmol) 加入到上述溶液中。反应混合物在室温下搅拌 15 分钟后加入 PYBOP (2.5g,4.8mmol),继续搅拌过夜。反应结束后,将溶液倒入冰中,用 10%MeOH/DCM 萃取产物。将合并的有机层干燥并浓缩,得到的粗产品通过溶剂洗涤纯化得到标题化合物 (1.3g,93%)。

[2865] 分析数据 :LCMS:419.2(M+1)$^+$;HPLC:98.38%(@254nm)(R_t:7.989; 方法 : 色谱柱 :YMC ODS-A150mm x4.6mm x5μ ; 流动相 :A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液 ; 进样量 :10μL, 柱温 :30℃ ; 流速 :1.4mL/min.; 梯度 :0-8min5%B-95%B, 保持 1.5min,9.51-12min5%B);^{1}H NMR(DMSO-d_6,400MHz) δ 11.47(bs,1H),8.32(t,1H),7.40(s,1H),7.07(s,1H),5.85(s,1H),4.24-4.25(d,1H,J=4Hz),2.21(s,3H),2.18(s,3H),2.11(s,3H),1.88-1.91(m,2H),1.56-1.69(m,3H),1.25-1.38(m,5H),2 个质子合并在溶剂峰中。

[2866] 化合物 208 :5- 氯 -3-(环己基亚磺酰基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二

氢 - 吡啶 -3- 基) 甲基)-2- 甲基苯甲酰胺

[2867]

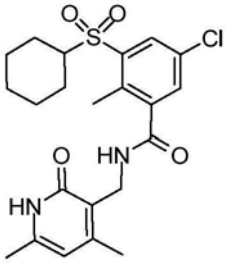


[2868] 在 0℃下，向搅拌后的 5- 氯 -3-(环己基硫代)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基苯甲酰胺 (0.2g,0.48mmol) 的 DCM (7mL) 溶液中加入 m-CPBA(0.098g,0.57mmol)，并在 0℃搅拌 2 小时。通过 TLC 监测反应。结束后，反应混合物用 DCM 稀释，用 $NaHCO_3$ 水溶液洗涤。产物通过溶剂洗涤纯化得到标题化合物 (0.17g,82.3%)。

[2869] 分析数据 :LCMS:435.1(M+1)$^+$;HPLC:92.68%(@220nm)(Rt;5.996; 方法 : 色谱柱 :YMC ODS-A150mm x4.6mm x5μ; 流动相 :A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液 ; 进样量 :10μL, 柱温 :30℃ ; 流速 :1.4mL/min.; 梯度 :0-8min5%B-95%B, 保持 1.5min,9.51-12min5%B);^{1}H NMR($CDCl_3$,400MHz) δ 11.44(bs,1H),7.82(s,1H),7.45(t,1H),7.39(s,1H),5.97(s,1H),4.52(bs,2H),2.53-2.59(m,1H),2.38(s,3H),2.34(s,3H),2.23(s,3H),1.85-1.93(m,3H),1.65(m,2H),1.20-1.29(m,3H)。

[2870] 化合物 209 :5- 氯 -3-(环己基磺酰基)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢 - 吡啶 -3- 基) 甲基)-2- 甲基苯甲酰胺

[2871]



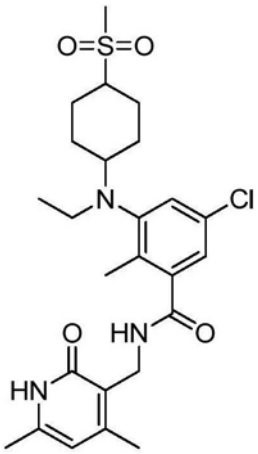
[2872] 在 0℃下，向搅拌后的 5- 氯 -3-(环己基硫代)-N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基苯甲酰胺 (0.1g,0.238mmol) 的 DCM (4mL) 溶液中加入 m-CPBA(0.082g,0.48mmol)，并在室温下搅拌 2 小时。通过 TLC 监测反应。结束后，反应混合物用 DCM 稀释，用 $NaHCO_3$ 水溶液洗涤。产物通过制备 HPLC 纯化得到标题化合物 (0.075g,23%)。

[2873] 分析数据 :LCMS:451.1(M+1)$^+$;HPLC:83.44%(@254nm)(R_t;6.547; 方法 : 色谱柱 :YMC ODS-A150mm x4.6mm x5μ; 流动相 :A;0.05%TFA 的水溶液 /B;0.05%TFA 的乙腈溶液 ; 进样量 :10μL, 柱温 :30℃ ; 流速 :1.4mL/min.; 梯度 :0-8min5%B-95%B, 保持 1.5min,9.51-12min5%B);^{1}H NMR(CDC13,400MHz) δ 11.44(bs,1H),7.98(s,1H),7.50(s,1H),7.45(t,1H),5.97(s,1H),4.51(d,2H,J=4Hz),2.94-3.00(m,1H),2.62(s,3H),2.38(s,3H),2.21(s,3H),1.88-1.95(m,4H),1.70(m,1H),1.52-1.55(m,2H),1.21(m,3H)。

[2874] 化合物 416 :5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲

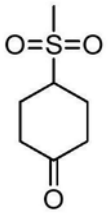
基)-3-(乙基((1s,4s)-4-(甲基磺酰基)环己基)氨基)-2-甲基苯甲酰胺

[2875]



[2876] 步骤1:合成4-甲磺酰基环己基-1-酮

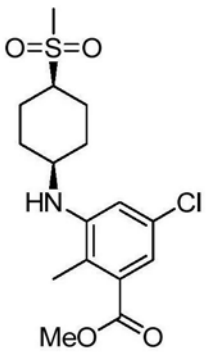
[2877]



[2878] 向包含(丁-1,3-二烯-2-基氧基)(三甲基)硅烷(12.5ml,70.7mmol)的甲苯(50mL)溶液中加入(甲基磺酰基)乙烯(4.1ml,47.1mmol),并加热回流76小时。然后,将反应混合物冷却至室温,并真空浓缩得到黄色油状物。将所得油状物溶解于CH_2Cl_2(120mL)中,并通过硅藻土(Celite®)过滤。将滤液真空浓缩,再将所得残余物在(冰/水)冷却条件下溶解于MeOH(8mL)溶液中。再加入TFA(2.0mL)。反应混合物在0℃继续搅拌10分钟,再在室温下搅拌25小时。将反应混合物真空浓缩,残余物通过Biotage Isolera100g SNAP快速柱层析(0-10%MeOH/CH_2Cl_2)纯化,得到稠密的黄色油状的标题化合物1.2g(14%)。LC-MS94%,0.39分钟(3.5分钟LC-MS法),m/z=177.0(仅ELS可见).^{1}H NMR(500MHz,$CDCl_3$)δppm3.24-3.32(m,1H),2.94(s,3H),2.62-2.70(m,2H),2.50-2.56(m,2H),2.38-2.45(m,2H),2.07-2.18(m,2H)。

[2879] 步骤2:合成5-氯-2-甲基-3-(((1s,4s)-4-(甲基磺酰基)环己基)氨基)苯甲酸甲酯

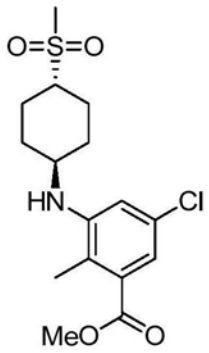
[2880]



[2881] 在氮气气球下，向搅拌后的 4- 甲磺酰基环己基 -1- 酮（94%，0.56g，3.0mmol）的 1，2- 二氯乙烷（10mL）溶液中依次加入 3- 氨基 -5- 氯 -2- 甲基苯甲酸甲酯（0.60g，3.0mmol）和醋酸（1.0ml，18.0mmol）。溶液搅拌 50 分钟后，在 4 小时内向该溶液中分批加入三乙酰基硼氢化钠（1.9g，9.0mmol）。所得悬浮液搅拌过夜后，在 2.5 小时内向其加入 4- 甲磺酰基环己基 -1- 酮（0.28g，1.5mmol）的 1，2- 二氯乙烷（1.5mL）溶液和三乙酰基硼氢化钠（0.96g，4.5mmol）。反应混合物继续搅拌 67 小时，然后向其加入去离子水（40mL），逐渐加入 $NaHCO_3$ 固体（4.8g）中和反应混合物（pH 值为 8）。用 CH_2Cl_2（3x25mL）萃取混合物。合并的有机萃取液用盐水洗涤（40mL），用 $MgSO_4$ 干燥，过滤并真空浓缩。将残余物预先吸附到硅胶上并通过 Biotage Isolera100g SNAP 快速柱层析（0-55% 乙酸乙酯 / 庚烷）纯化得到标题化合物（131mg，12%）。LC-MS96%，2.09 分钟 (3.5 分钟 LC-MS 法)，m/z=359.85，360.85，361.90，362.85；^1H NMR（500MHz，$CDCl_3$）δ ppm7.12（br.s.，1H），6.68（br.s.，1H），3.89（s，3H），3.82（br.s.，1H），3.71（br.s.，1H），2.93-3.02（m，1H），2.89（s，3H），2.29（s，3H），2.03-2.18（m，4H），1.91-2.02（m，2H），1.71-1.83（m，2H）。

[2882] 另一个异构体 5- 氯 -2- 甲基 -3-（((1r，4r)-4-（ 甲基磺酰基 ） 环己基 ） 氨基 ） 苯甲酸甲酯同样被分离。

[2883]

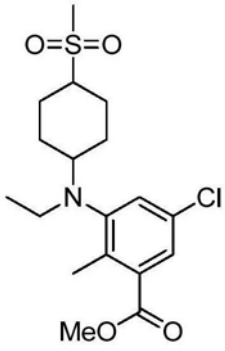


[2884] （92mg，8%），LC-MS96%，2.06 分 钟 (3.5 分 钟 LC-MS 法)，m/z=359.85，360.90，361.90，362.85；^1H NMR（500MHz，$CDCl_3$）δ ppm7.11（br.s，1H），6.68（br.s.，1H），3.89（s，3H），3.62（br.s.，1H），3.27-3.36（m，1H），2.84-2.95（m，4H），2.32-2.42（m，4H），2.24（br.s.，3H），1.72-1.85（m，2H），1.27-1.35（m，2H）。

[2885] 从进一步的 NMR 实验得到顺式和反式的分配是不能实现的，分配是任意的。

[2886] 步骤 3 ：合成 5- 氯 -3-（ 乙基 ((1s，4s)-4-（ 甲基磺酰基 ） 环己基 ） 氨基)-2- 甲基苯甲酸甲酯

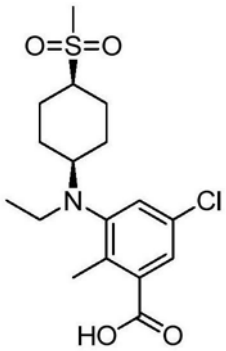
[2887]



[2888] 向搅拌后的 5- 氯 -2- 甲基 -3-(((1s,4s)-4-(甲基磺酰基) 环己基) 氨基) 苯甲酸甲酯(246mg,0.68mmol)的无水 1,2- 二氯乙烷(6.0mL)溶液中依次加入乙醛(115μl,2.1mmol)和醋酸(235μl,4.1mmol)。反应搅拌 35 分钟后,在 50 分钟内向反应混合物分批加入三乙酰基硼氢化钠(435mg,2.1mmol),反应搅拌过夜,加乙醛(115μl,2.1mmol)。反应混合物搅拌 1 小时后,在 1 小时内分批加三乙酰基硼氢化钠(435mg,2.1mmol),反应混合物搅拌过夜。加乙醛(229μl,4.1mmol),反应混合物搅拌 2.5 小时后,在 1.5 小时内再分批加三乙酰基硼氢化钠(869mg,4.1mmol),继续搅拌过夜。加入乙醛(229μl,4.1mmol),同时加入 1,2- 二氯乙烷 (4.0mL)以帮助溶解,所得反应混合物搅拌 4 小时。在 2 小时内分批加入三乙酰基硼氢化钠(869mg,4.1mmol),继续搅拌整个周末。加入乙醛(229μl,4.1mmol),所得反应混合物搅拌 1.5 小时后,在 1 小时内等量分批地加入三乙酰基硼氢化钠(869mg,4.1mmol),同时加入 1,2- 二氯乙烷(5.0mL),继续搅拌过夜。加入乙醛(382μl,6.8mmol),所得反应混合物搅拌 2.5 小时后,在 4 小时内等量分批地加入三乙酰基硼氢化钠(1.4g,6.8mmol),同时加入 1,2- 二氯乙烷(10mL),继续搅拌过夜。反应混合物用水(40mL)稀释,逐渐加固体 $NaHCO_3$(5.79g)中和至 pH 值为 8。两相分离,水层用 CH_2Cl_2 (3x25mL)萃取。合并的有机相用盐水洗涤(20mL),干燥($MgSO_4$),过滤并真空浓缩。将剩余产物预先吸附在硅胶上,通过 Biotage Isolera10g SNAP 柱层析(0-50%EtOAc/ 庚烷)纯化,得到无色玻璃状固体状的题述化合物(140mg,51%)。LC-MS97%,2.29 分钟 (3 分钟 LC-MS 法),m/z=387.95,388.95,389.90,390.95.^{1}H NMR(500MHz,$CDCl_3$) δ ppm7.59(d,J=1.89Hz,1H),7.21(d,J=1.89Hz,1H),3.91(s,3H),3.45(br.s.,1H),3.01(m,2H),2.86-2.95(m,1H),2.82(s,3H),2.52(s,3H),2.08(br.s.,2H),1.94(br.s.,2H),1.86(br.s.,2H),1.46-1.54(m,2H),0.89(t,J=7.01Hz,3H)。

[2889] 步骤 4 :合成 5- 氯 -3-(乙基 ((1s,4s)-4-(甲基磺酰基) 环己基) 氨基)-2- 甲基苯甲酸

[2890]

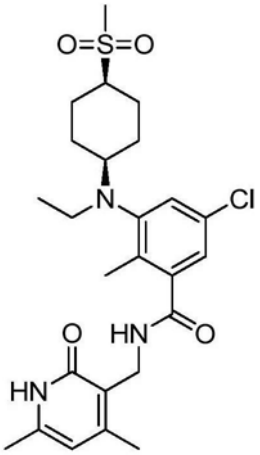


[2891] 向搅拌后的5-氯-3-(乙基((1s,4s)-4-(甲基磺酰基)环己基)氨基)-2-甲基苯甲酸甲酯(140mg,0.36mmol)的 THF(5.0mL)和 MeOH(0.3mL)溶液中加入 4M NaOH(2.7mL)溶液。所得溶液在50℃搅拌21小时,然后再加入4M NaOH(0.9ml,3.6mmol)并继续加热4小时。之后,将反应混合物冷却到室温,然后真空浓缩。所得剩余的水溶液用 CH_2Cl_2(20mL)和乙醚(20mL)萃取。用 1M HCl(aq)(13mL)将水相的 pH 值调至 3-4,并用乙酸乙酯萃取(3x25mL)。合并的乙酸乙酯萃取液用 $MgSO_4$ 干燥,过滤并真空浓缩,得到淡黄色固体状的标题化合物(122mg,产率为80%)。LC-MS89%,4.03 分钟 (7 分钟LC-MS 法),m/z=373.95,374.90,375.95,377.00.^{1}H NMR(500MHz,$CDCl_3$) δ ppm7.77(d,J=1.89Hz,1H),3.47(br.s.,1H),3.03(br.s.,

2H)2.88-2.97(m,1H),2.84(s,3H),2.60(s,3H),2.12(br.s,2H),1.96(br.s,2H),1.88(br.s.,2H),1.55(br.s.,2H),0.91(t,J=7.01Hz,3H)。1 个 ArH 被认为掩盖在 $CDCl_3$ 峰中,并且也看不到 CO_2H 峰。

[2892] 步骤 5:合成 5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)-3-(乙基((1s,4s)-4-(甲基磺酰基)环己基)氨基)-2- 甲基苯甲酰胺

[2893]

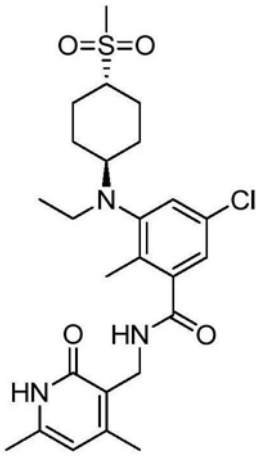


[2894] 在 0℃和氮气气球下,向搅拌后的 5- 氯 -3-(乙基((1s,4s)-4-(甲基磺酰基)环己基)氨基)-2- 甲基苯甲酸(90%,122mg,0.29mmol)的无水 DMF (2.0mL)溶液中逐滴加入 HATU (134mg,0.35mmol)和 DIPEA (102μl,0.59mmol)。所得溶液搅拌 10 分钟后,向其加入 3-(氨基甲基)-4,6- 二甲基 -1,2- 二氢吡啶 -2- 酮(89%,60mg,0.35mmol)。所得悬浮液在 0℃搅拌 15 分钟,然后在室温下搅拌整个周末。将反应混合物在水(10mL)和 CH_2Cl_2 (10mL)之间分配。两相分离,水相用 CH_2Cl_2 萃取(3x15mL)。合并的有机相依次用 $NaHCO_3$(aq)(10mL)饱和溶液、水(40mL)和盐水(2x25mL)洗涤,干燥($MgSO_4$),过滤并真空浓缩。残余物通过 Biotage Isolera10g SNAP 柱层析(0-9%MeOH/CH_2Cl_2)纯化,得到灰白色固体状的标题化合物(120mg,产率为 76%)。LC-MS:95%,3.71 分钟 (7 分钟 LC-MS 法),m/z=508.10,509.10,510.10,511.10.^{1}H NMR(500MHz,$CDCl_3$) δ 10.84(s,1H),7.07(s,2H),7.00(m,1H),6.10(s,1H),4.53(d,J=5.8Hz,2H),3.45(s,1H),3.07 - 2.95(m,2H),2.93 - 2.85(m,1H),2.81(s,3H),2.45(s,3H),2.31(s,3H),2.29(s,3H),2.14 - 2.01(m,2H),1.97-1.89(m,2H),1.87-1.80(m,2H),1.50(br s,2H),0.88(t,J=5.9Hz,3H)。

[2895] 化合物 417:5- 氯 -N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基)-3-(乙基((1r,4r)-4-(甲基磺酰基)环己基)氨基)-2- 甲基苯甲酰胺

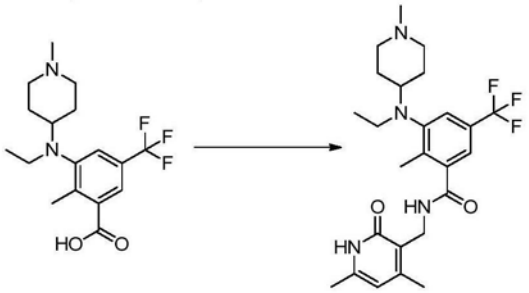
[2896] 通过以制备化合物 416 类似的方法采用在步骤 2 中得到的其他异构体来制备该化合物。

[2897]



[2898] 化合物 392 :N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基]-3-[乙基 (1- 甲基哌啶 -4- 基) 氨基]-2- 甲基 -5-(三氟甲基) 苯甲酰胺

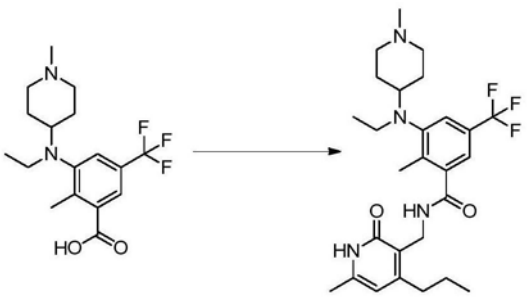
[2899]



[2900] 向搅拌后的 3-[乙基 (1- 甲基哌啶 -4- 基) 氨基]-2- 甲基 -5-(三氟甲基) 苯甲酸(原料粗品 ,580mg,1.68mmol) 和 3-(氨基甲基)-4,6- 二甲基 -1,2- 二氢吡啶 -2- 酮盐酸盐(477mg,2.53mmol) 的 DMSO (6mL) 溶液中加入 PYBOP (1.57g,3.02mmol) 和 hunig 碱 (650mg,5.04mmol)。反应混合物在 23℃搅拌 20 小时。用水淬灭反应,收集产生的沉淀物。所得固体通过硅胶柱层析(NH-SiO_2 乙酸乙酯 /MeOH=25/1) 纯化,得到白色无定形的标题化合物(386mg,产率为 48%)。^{1}HNMR(400MHz,$CDCl_3$) δ ppm;7.31(s,1H),7.27(s,1H),7.18(t,J=5.7Hz,1H),5.95(s,1H),4.55(d,J=5.9Hz,2H),3.17(dq,J=6.4,3.3Hz,2H),3.08(q,J=7.0Hz,2H),2.81(m,2H),2.70(m,1H),2.40(s,3H),2.33(s,3H),2.23(s,3H),2.21(s,3H),1.78-1.93(m,2H),1.70(m,2H),0.84(t,J=7.0Hz,3H);MS(ES)[M+H]479.2,[M+Na]501.3;HPLC 纯度为 96.8%。

[2901] 化合物 393 :3-[乙基 (1- 甲基哌啶 -4- 基) 氨基]-2- 甲基 -N-[(6- 甲基 -2- 氧代 -4- 丙基 -1,2- 二氢吡啶 -3- 基) 甲基]-5-(三氟甲基) 苯甲酰胺

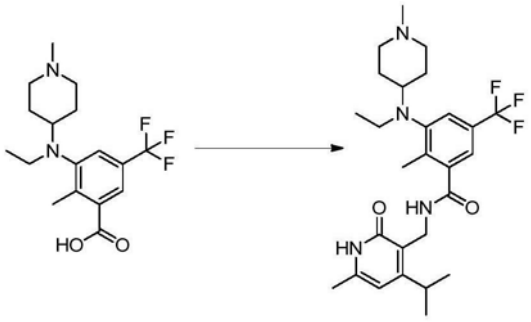
[2902]



[2903] 向搅拌后的 3-[乙基 (1- 甲基哌啶 -4- 基) 氨基]-2- 甲基 -5-(三氟甲基) 苯甲酸(原料粗品 ,680mg,1.97mmol)和 3-(氨基甲基)-6- 甲基 -4- 丙基 -1,2- 二氢吡啶 -2- 酮盐酸盐(642mg,2.96mmol)的 DMSO (7mL)溶液中加入 PYBOP (1.85g,3.55mmol)和 hunig 碱(764mg,5.91mmol)。反应混合物在 23℃搅拌 20 小时。用水淬灭反应,收集产生的沉淀物。所得固体通过硅胶柱层析(NH-SiO_2 乙酸乙酯 /MeOH=20/1)纯化,得到白色固体状的标题化合物(224mg,产率为 22%)。^{1}H-NMR(400MHz,$CDCl_3$) δ ppm;7.31(s,1H),7.26(s,1H),7.16(m,1H),5.94(s,1H),4.55(d,J=5.9Hz,2H),3.08(q,J=7.0Hz,2H),2.82(m,2H),2.66-2.73(m,3H),2.33(s,3H),2.24(s x2,6H),1.79-1.98(m,2H),1.67-1.75(m,4H),1.59-1.66(m,2H),1.02(t,J=7.2Hz,3H),0.84(t,J=7.0Hz,3H);MS(ES)[M-H]505.2;HPLC 纯度为 98.1%。

[2904] 化合物 394 :3-[乙基 (1- 甲基哌啶 -4- 基) 氨基]-2- 甲基 -N-{[6- 甲基 -2- 氧代 -4-(丙 -2- 基)-1,2- 二氢吡啶 -3- 基] 甲基 }-5-(三氟甲基) 苯甲酰胺

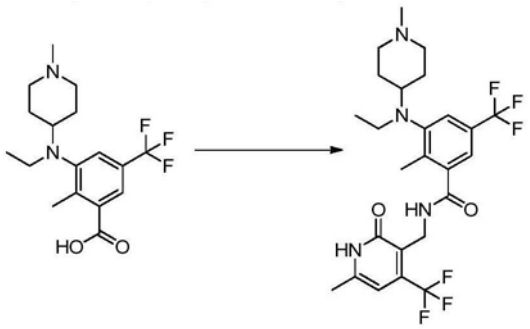
[2905]



[2906] 向搅拌后的 3-[乙基 (1- 甲基哌啶 -4- 基) 氨基]-2- 甲基 -5-(三氟甲基) 苯甲酸(原料粗品 , ～ 0.313mmol)和 3-(氨基甲基)-6- 甲基 -4-(丙 -2- 基)-1,2- 二氢吡啶 -2- 酮盐酸盐(88.0mg,0.407mmol)的 DMSO(2.4mL)溶液中加入 PYBOP(244mg,0.470mmol)和 hunig 碱(164μl,0.939mmol)。反应混合物在室温下搅拌 16 小时。用水淬灭反应,用乙酸乙酯稀释。水层用二氯甲烷萃取。合并的有机层用盐水洗涤,用 Na_2SO_4 干燥,过滤并浓缩。残余物通过硅胶柱层析(NH-SiO_2 乙酸乙酯 /MeOH=20/1+5% 三乙胺)纯化。将化合物粗品溶解于 DMSO 中,用水稀释。收集沉淀的固体,用乙酸乙酯 /TBME/ 己烷研磨,得到白色固体状的标题化合物(80.0mg,产率为 51%)。^{1}H-NMR(400MHz,$CDCl_3$) δ ppm;7.31(s,1H),7.26(s,1H),7.03-7.10(m,1H),6.04(s,1H),4.59(d,J=6.0Hz,2H),3.49-3.55(m,1H),3.09(q,J=6.8Hz,2H),2.81-2.84(m,2H),2.70-2.78(m,1H),2.32(s,3H),2.26(s,3H),2.24(s,3H),1.86-1.89(m,2H),1.68-1.71(m,4H),1.22(d,J=6.4Hz,6H),0.84(t,J=6.8Hz,3H);MS(ES)[M+H]507.2,[M+Na]529.2;HPLC 纯度为 97.7%。

[2907] 化合物 395 :3-[乙基 (1- 甲基哌啶 -4- 基) 氨基]-2- 甲基 -N-{[6- 甲基 -2- 氧代 -4-(三氟甲基)-1,2- 二氢吡啶 -3- 基] 甲基 }-5-(三氟甲基) 苯甲酰胺

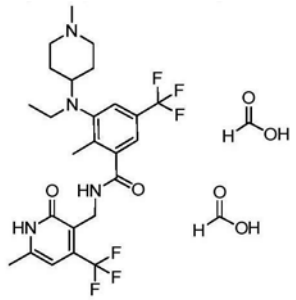
[2908]



[2909] 向搅拌后的 3-[乙基 (1- 甲基哌啶 -4- 基) 氨基]-2- 甲基 -5-(三氟甲基) 苯甲酸(原料粗品 , ～ 0.313mmol) 和 3-(氨基甲基)-6- 甲基 -4-(三氟甲基)-1,2- 二氢吡啶 -2- 酮盐酸盐(100mg,0.91mmol)的 DMSO (2.4mL)溶液中加入 PYBOP (248mg,1.05mmol) 和 hunig 碱(166ul,2.10mmol)。反应混合物在室温下搅拌 16 小时。用水淬灭反应,收集产生的沉淀物。所得固体在乙酸乙酯 / 己烷中研磨。所得固体通过硅胶柱层析(NH-SiO_2 乙酸乙酯 /MeOH=10/1+10% 三乙胺) 纯化。将化合物粗品在乙酸乙酯 / 己烷中研磨并干燥,得到白色固体状的标题化合物(75.0mg,产率为 44%)。^{1}H-NMR(400MHz,$CDCl_3$) δ ppm;7.32(s,1H),7.26(s,1H),6.86-6.89(m,1H),6.34(s,1H),4.73(d,J=6.4Hz,2H),3.08(q,J=7.2Hz,2H),2.80-2.85(m,2H),2.70-2.78(m,1H),2.37(s,3H),2.35(s,3H),2.24(s,3H),1.85-1.89(m,2H),1.69-1.72(m,4H),0.84(t,J=7.2Hz,3H);MS(ES)[M+H]533.1,[M+Na]555.2;HPLC 纯度为 95.8%。

[2910] 化合物 395 :3-(乙基 (1- 甲基哌啶 -4- 基) 氨基)-2- 甲基 -N-((6- 甲基 -2- 氧代 -4-(三氟甲基)-1,2- 二氢吡啶 -3- 基) 甲基)-5-(三氟甲基) 苯甲酰胺二甲酸盐

[2911]

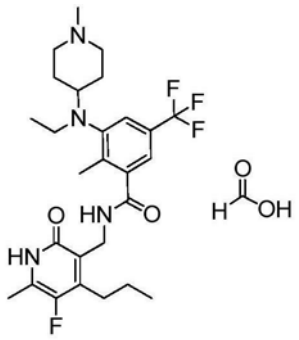


[2912] ^{1}H NMR(400MHz,CD_3OD) δ ppm8.39(s,2H),7.48(s,1H),7.36(s,1H),6.36(s,1H),4.52(s,2H),3.38(br,2H),3.18(br,m,1H),3.11(q,J=7.2Hz,2H),2.96(br,m,2H),2.77(s,3H),2.35(s,3H),2.31(s,3H),1.97(br,d,J=12.0Hz,2H),1.83(br,m,2H),0.84(t,J=7.2Hz,3H);MS(ES)(M+H)=533.53。

[2913] 根据与上述 3-[乙基 (1- 甲基哌啶 -4- 基) 氨基]-2- 甲基 -N-{[6- 甲基 -2- 氧代 -4-(三氟甲基)-1,2- 二氢吡啶 -3- 基] 甲基 }-5-(三氟甲基) 苯甲酰胺相同的制备方法,用相应的羧酸和胺制备下面的类似物,并通过反相 HPLC (包含 0.1% 的甲酸的 ACN-H_2O) 纯化。

[2914] 化合物 396 :3-(乙基 (1- 甲基哌啶 -4- 基) 氨基)-N-((5- 氟 -6- 甲基 -2- 氧代 -4- 丙基 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基 -5-(三氟甲基) 苯甲酰胺甲酸盐

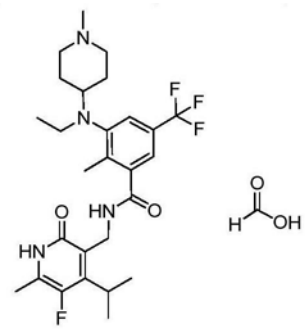
[2915]



[2916] ^{1}H NMR(400MHz,CD_3OD) δ ppm8.31(s,1H),7.49(s,1H),7.34(s,1H),4.45(s,2H),3.39(br,2H),3.17(br,1H),3.10(q,J=7.2Hz,2H),2.97(br,m,2H),2.77(s,3H),2.74(br,m,2H),2.33(s,3H),2.22(d,J=2.8Hz,3H),1.97(br,m,2H),1.85(br,m,2H),1.60(m,2H),1.02(t,J=7.2Hz,3H),0.84(t,J=6.8Hz,3H);MS(ES)(M+H)=525.58。

[2917] 化合物 397 :3-(乙基(1-甲基哌啶-4-基)氨基)-N-((5-氟代-4-异丙基-6-甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-5-(三氟甲基)苯甲酰胺甲酸盐

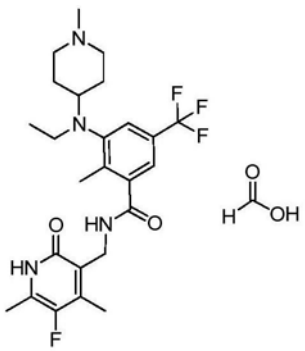
[2918]



[2919] LCMS ES+(M+1)=525.58.^{1}H NMR(400MHz,CD_3OD) δ ppm8.31(s,1H),7.50(s,1H),7.34(s,1H),4.49(s,2H),3.48(m,1H),3.39(br,2H),3.18(br,m,1H),3.09(q,J=6.8Hz,2H),2.97(br,m,2H),2.78(s,3H),2.34(s,3H),2.21(d,J=3.2Hz,3H),1.96(br,d,J=12.0Hz,2H),1.86(br,m,2H),1.32(dd,J=1.6Hz,J=7.2Hz,6H),0.84(t,J=6.8Hz,3H);MS(ES)(M+H)=525.58。

[2920] 化合物 398 :3-(乙基(1-甲基哌啶-4-基)氨基)-N-((5-氟代-4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基-5-(三氟甲基)苯甲酰胺甲酸盐

[2921]

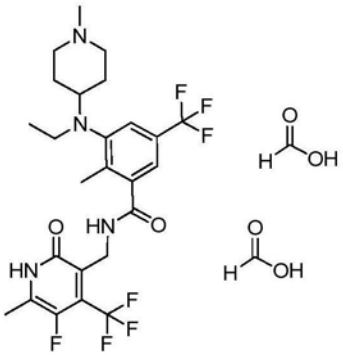


[2922] ^{1}H NMR(400MHz,CD_3OD) δ ppm8.29(s,1H),7.49(s,1H),7.35(s,1H),4.45(s,2H),3.39(br,2H),3.19(br,1H),3.09(q,J=7.2Hz,2H),2.97(br,m,2H),2.77(s,3H),2.34(d,J=2

.4Hz,3H),2.33(s,3H),2.22(d,J=3.2Hz,3H),1.97(br,m,2H),1.86(br,m,2H),0.84(t,J=6.8Hz,3H);MS(ES)(M+H)=497.51。

[2923] 化合物399:3-(乙基(1-甲基哌啶-4-基)氨基)-N-((5-氟代-6-甲基-2-氧代-4-(三氟甲基)-1,2-二氢吡啶-3-基)甲基)-2-甲基-5-(三氟甲基)苯甲酰胺二甲酸盐

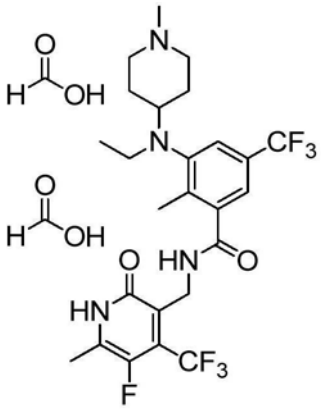
[2924]



[2925] ^{1}H NMR(400MHz,CD_3OD) δ ppm8.32(s,2H),7.50(s,1H),7.34(s,1H),4.59(s,2H),3.40(br,2H),3.18(br,m,2H),3.09(q,J=6.8,2H),2.96(br,m,2H),2.78(s,3H),2.35(s,3H),2.29(d,J=3.2Hz,3H),1.98(br,d,J=13.2Hz,2H),1.86(m,1H),1.80(br,m,2H),0.84(t,J=6.8Hz,3H);MS(ES)(M+H)=551.53。

[2926] 化合物399:3-(乙基(1-甲基哌啶-4-基)氨基)-N-((5-氟代-6-甲基-2-氧代-4-(三氟甲基)-1,2-二氢吡啶-3-基)甲基)-2-甲基-5-(三氟甲基)苯甲酰胺二甲酸盐

[2927]

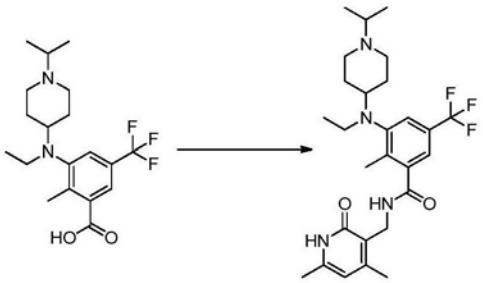


[2928] 采用上述5-氟代-4-异丙基-6-甲基-2-氧代-1,2-二氢吡啶-3-甲腈的方法将6-甲基-2-氧代-4-(三氟甲基)-1,2-二氢吡啶-3-甲腈氟化。产物分离为6-甲基-2-氧代-4-(三氟甲基)-1,2-二氢吡啶-3-甲腈(起始原料)与5-氟代-6-甲基-2-氧代-4-(三氟甲基)-1,2-二氢吡啶-3-甲腈为3:1的混合物。对于5-氟代-6-甲基-2-氧代-4-(三氟甲基)-1,2-二氢吡啶-3-甲腈,LCMS E-S(M+H)=221.2。将该腈类混合物采用上述制备3-(氨基甲基)-5-氟代-4-异丙基-6-甲基吡啶-2(1H)-酮的还原条件还原。氟化化合物LCMS(ES)(M+H)显示225.2,非氟化的类似物的LCMS(ES)(M+H)显示为207.2。用没有进一步纯化的胺的混合物粗品进行随后的偶联反应。3-(乙基(1-甲基哌啶-4-基)氨基)-N-((5-氟代-6-甲基-2-氧代-4-(三氟甲基)-1,2-二氢吡啶-3-基)甲基)-2-甲

基-5-(三氟甲基)苯甲酰胺二甲酸盐;^{1}HNMR(400MHz,CD_3OD)δppm8.32(s,2H),7.50(s,1H),7.34(s,1H),4.59(s,2H),3.40(br,2H),3.18(br,m,1H),3.09(q,J=6.8,2H),2.96(br,m,2H),2.78(s,3H),2.35(s,3H),2.29(d,J=3.2Hz,3H),1.98(br,d,J=13.2Hz,2H),1.80(br,m,2H),0.84(t,J=6.8Hz,3H);MS(ES)(M+H)551.5。

[2929] 化合物400:N-[(4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基]-3-{乙基[1-(丙-2-基)哌啶-4-基]氨基}-2-甲基-5-(三氟甲基)苯甲酰胺

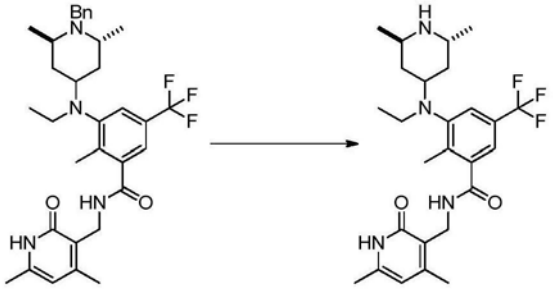
[2930]



[2931] 向搅拌后的3-{乙基[1-(丙烷-2-基)哌啶-4-基]氨基}-2-甲基-5-(三氟甲基)苯甲酸(原料粗品,510mg,0.569mmol)和3-(氨基甲基)-4,6-二甲基-1,2-二氢吡啶-2-酮盐酸盐(161mg,0.854mmol)的DMSO(2mL)溶液中加入PYBOP(534mg,1.02mmol)和hunig碱(220mg,1.71mmol)。反应混合物在23℃搅拌20小时。用水淬灭反应,收集产生的沉淀物。所得固体通过硅胶柱层析(NH-SiO_2乙酸乙酯/MeOH=20/1)纯化,得到白色固体状的标题化合物(129mg,产率为44%)。^{1}H-NMR(400MHz,$CDCl_3$)δppm;7.30(s,1H),7.26(s,1H),7.22(t,J=5.9Hz,1H),5.95(s,1H),4.54(d,J=5.9Hz,2H),3.16(m,2H),3.08(q,J=7.0Hz,2H),2.85(m,2H),2.62-2.74(m,1H),2.38(s,3H),2.33(s,3H),2.19(s,3H),2.00-2.09(m,1H),1.81(m,2H),1.58-1.76(m,2H),0.99(s x2,6H),0.83(t,J=7.0Hz,3H);MS(ES)[M+H]507.2,[M+Na]529.3;HPLC纯度为97.2%。

[2932] 化合物401:N-[(4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基]-3-{[(2R*,6R*)-2,6-二甲基哌啶-4-基](乙基)氨基}-2-甲基-5-(三氟甲基)苯甲酰胺

[2933]

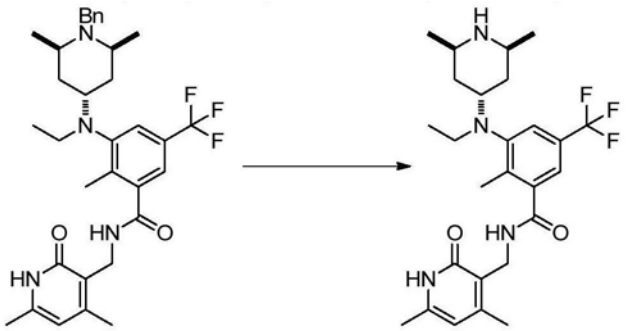


[2934] 向搅拌后的3-{[(2R,6R)-1-苄基-2,6-二甲基哌啶-4-基](乙基)氨基}-N-[(4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基]-2-甲基-5-(三氟甲基)苯甲酰胺(267mg,0.459mmol)的MeOH(5mL溶液中)加入Pd/C(250mg)。反应混合物在室温和氢气气氛中搅拌2小时。将反应混合物过滤,滤液真空浓缩。残余物通过硅胶柱层析(1.Nagara Science Co.,Ltd.生产的NAM-300H硅胶,乙酸乙酯/MeOH=4/1～乙酸乙酯/MeOH/三乙胺=1/1/0.01,2.NH-SiO_2,庚烷/乙酸乙酯=30/1～8/1)纯化,得到白

色固体状的标题化合物(127mg,产率为 56%)。^{1}H-NMR(400MHz,$CDCl_3$) δ ppm;7.30(s,1H),7.26(s,1H),7.14(t,J=6.1Hz,1H),5.94(s,1H),4.54(dd,J=5.9,1.6Hz,2H),3.41-3.49(m,1H),3.01-3.13(m,3H),2.85-2.92(m,1H),2.40(s,3H),2.32(s,3H),2.22(s,3H),1.63-1.80(m,4H),1.13(d,J=7.0Hz,3H),1.02(d,J=6.2Hz,3H),0.83(t,J=7.0Hz,3H);LC-MS:m/z[M+H]493.1,[M+Na]515.3;HPLC; 纯度为 97.2%。

[2935] 化合物 402:N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基]-3-{[(2R*,4R*,6S*)-2,6- 二甲基哌啶 -4- 基](乙基)氨基}-2- 甲基 -5-(三氟甲基)苯甲酰胺

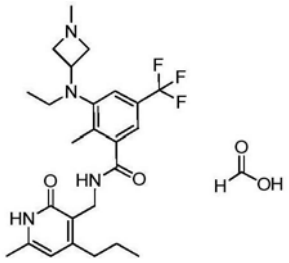
[2936]



[2937] 向搅拌后的 3-{[(2R,4R,6S)-1- 苄基 -2,6- 二甲基哌啶 -4- 基](乙基)氨基}-N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基)甲基]-2- 甲基 -5-(三氟甲基)苯甲酰胺(35.6mg,0.0611mmol)的 MeOH (3.0mL)溶液中加入 Pd/C (120mg)。反应混合物在室温和氢气气氛中搅拌 30 分钟。用氮气置换后,将反应混合物过滤,滤液真空浓缩。残余物通过两次制备 TLC(TLC 硅胶 60F254,MERCK,MeOH/Et_3N=100/1)纯化,得到白色固体状的标题化合物(4.4mg,产率为 15%)。^{1}HNMR(400MHz,$CDCl_3$) δ ppm;7.33(s,1H),7.30(s,1H),7.18(m,1H),5.96(s,1H),4.54(d,J=6.0Hz,2H),3.73(m,1H),3.26-2.69(m,4H),2.40(s,3H),2.38(s,3H),2.23(s,3H),1.90-1.10(m,4H),1.10-0.86(m,6H),0.83(t,J=7.2Hz,3H)。(-2H);LC-MS:m/z[M+H]493.2,[M+Na]515.3;HPLC; 纯度为 88.8%。

[2938] 化合物 403:3-(乙基(1- 甲基氮杂环丁烷 -3- 基)氨基)-2- 甲基 -N-((6- 甲基 -2- 氧代 -4- 丙基 -1,2- 二氢吡啶 -3- 基)甲基)-5-(三氟甲基)苯甲酰胺甲酸盐

[2939]

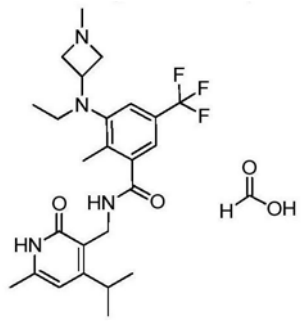


[2940] ^{1}H NMR(400MHz,CD_3OD) δ ppm8.33(s,1H),7.37(s,1H),7.26(s,1H),6.11(s,1H),4.46(s,2H),4.42(br,m,1H),4.21(br,2H),3.82(br,2H),3.00(q,J=6.8Hz,2H),2.88(s,3H),2.65(m,2H),2.40(s,3H),2.22(s,3H),1.61(m,2H),0.99(t,J=7.2Hz,3H),0.86(t,J=6.8Hz,3H);MS(ES)(M+1)480.53。

[2941] 化合物 404:3-(乙基(1- 甲基氮杂环丁烷 -3- 基)氨基)-N-((4- 异丙基 -6- 甲

基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基 -5-(三氟甲基) 苯甲酰胺甲酸盐

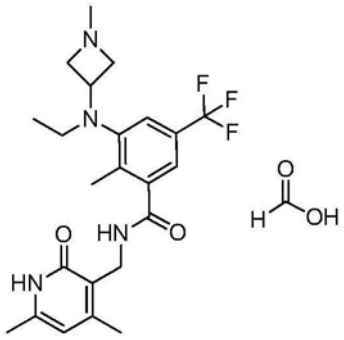
[2942]



[2943] ^{1}H NMR(400MHz,CD_3OD) δ ppm8.31(s,1H),7.37(s,1H),7.27(s,1H),6.21(s,1H),4.50(s,2H),4.41(br,1H0,4.21(br,2H),3.81(br,2H),3.38(m,1H),3.00(q,J=6.8Hz,2H),2.87(s,3H),2.40(s,3H),2.24(s,3H),1.20(d,J=6.4Hz,6H),0.86(t,J=6.8Hz,3H);MS(ES)(M+1)479.54。

[2944] 化合物 405 :N-((4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-3-(乙基 (1- 甲基氮杂环丁烷 -3- 基) 氨基)-2- 甲基 -5-(三氟甲基) 苯甲酰胺甲酸盐

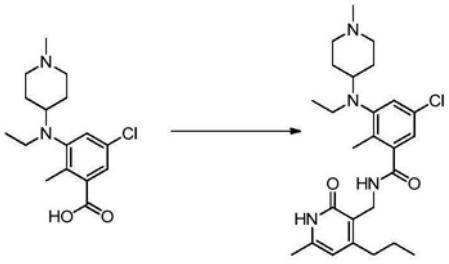
[2945]



[2946] ^{1}H NMR(400MHz,CD_3OD) δ ppm8.32(s,1H),7.39(s,1H),7.26(s,1H),6.08(s,1H),4.44(s,2H),4.41(br,m,1H),4.21(br,2H),3.82(br,2H),3.00(q,J=6.8Hz,2H),2.88(s,3H),2.39(s,3H),2.34(d,J=1.2Hz,3H),2.21(s,3H),0.86(t,J=6.8Hz,3H);MS(ES)(M+1)451.49。

[2947] 化合物 406 :5- 氯 -3-[乙基 (1- 甲基哌啶 -4- 基) 氨基]-2- 甲基 -N-[(6- 甲基 -2- 氧代 -4- 丙基 -1,2- 二氢吡啶 -3- 基) 甲基] 苯甲酰胺

[2948]

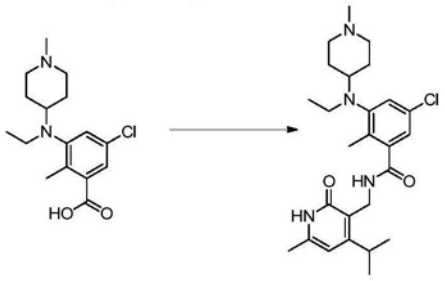


[2949] 向搅拌后的 5- 氯 -3-[乙基 (1- 甲基哌啶 -4- 基) 氨基]-2- 甲基苯甲酸(原料粗品 ,1.80g,3.26mmol) 和 3-(氨基甲基)-6- 甲基 -4- 丙基 -1,2- 二氢吡啶 -2- 酮盐酸盐(916mg,4.24mmol) 的 DMSO (10mL) 溶液中加入 PYBOP (3.10g,5.87mmol) 和 hunig 碱

(1.20g,9.78mmol)。在反应混合物在23℃搅拌16小时。用水淬灭反应,收集产生的沉淀物。所得固体通过硅胶柱层析(NH-SiO_2乙酸乙酯/MeOH=10/1)纯化,得到白色固体状的标题化合物(264mg,产率为17%)。^{1}H-NMR(400MHz,$CDCl_3$)δppm;7.20(t,J=5.9Hz,1H),7.06(d,J=2.0Hz,1H),7.02(d,J=2.0Hz,1H),5.96(s,1H),4.54(d,J=5.9Hz,2H),3.02(q,J=7.0Hz,2H),2.81(m,2H),2.64-2.71(m,3H),2.21-2.27(s x3,9H),1.84-1.94(m,2H),1.55-1.65(m,6H),1.00(t,J=7.4Hz,3H),0.84(t,J=7.0Hz,3H);MS(ES)[M+H]473.1,[M+Na]495.3;HPLC纯度为94.7%。

[2950] 化合物407:5-氯-3-[乙基(1-甲基哌啶-4-基)氨基]-2-甲基-N-{[6-甲基-2-氧代-4-(丙烷-2-基)-1,2-二氢吡啶-3-基]甲基}苯甲酰胺

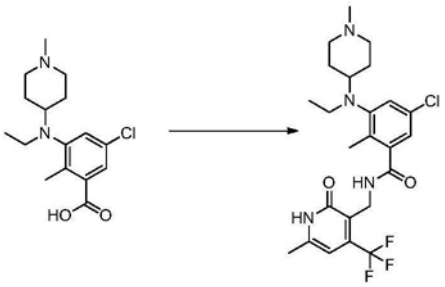
[2951]



[2952] 向搅拌后的5-氯-3-[乙基(1-甲基哌啶-4-基)氨基]-2-甲基苯甲酸(原料粗品,~0.7mmol)和3-(氨基甲基)-6-甲基-4-(丙烷-2-基)-1,2-二氢吡啶-2-酮的盐酸盐(200mg,0.91mmol)的DMSO(5.3mL)溶液中加入PYBOP(550mg,1.05mmol)和hunig碱(366ul,2.10mmol)。反应混合物在23℃搅拌7小时。用水淬灭反应,收集生成的沉淀物。所得固体通过硅胶柱层析(NH-SiO_2乙酸乙酯/MeOH=10/1+10%三乙胺)纯化。将化合物粗品在乙酸乙酯/己烷中研磨,干燥,得到白色固体状的标题化合物(166mg,产率为50%)。^{1}H-NMR(400MHz,$CDCl_3$)δppm;7.06(d,J=2.4Hz,1H),7.01-7.05(m,1H),7.00(d,J=2.4Hz,1H),6.04(s,1H),4.57(d,J=6.0Hz,2H),3.49-3.57(m,1H),3.02(q,J=6.8Hz,2H),2.80-2.84(m,2H),2.61-2.69(m,1H),2.29(s,3H),2.23(s,3H),2.23(s,3H),1.86-1.90(m,2H),1.66-1.70(m,4H),1.21(d,J=6.8Hz,6H),0.84(t,J=6.8Hz,3H);MS(ES)[M+Na]495.2;HPLC纯度为95.7%。

[2953] 化合物408:5-氯-3-[乙基(1-甲基哌啶-4-基)氨基]-2-甲基-N-{[6-甲基-2-氧代-4-(三氟甲基)-1,2-二氢吡啶-3-基]甲基}苯甲酰胺

[2954]



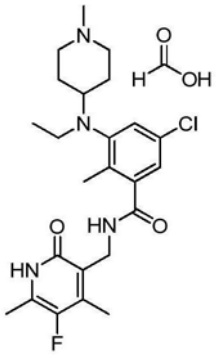
[2955] 向搅拌后的5-氯-3-[乙基(1-甲基哌啶-4-基)氨基]-2-甲基苯甲酸(原料粗品,~0.7mmol)和3-(氨基甲基)-6-甲基-4-(三氟甲基)-1,2-二氢吡啶-2-酮的盐酸盐(200mg,0.91mmol)的DMSO(5.3mL)溶液中加入PYBOP(550mg,1.05mmol)和hunig碱

(366ul,2.10mmol)。反应混合物在23℃搅拌7小时。反应用水淬灭,用乙酸乙酯稀释。水层用二氯甲烷萃取。合并的有机层用盐水洗涤,用Na_2SO_4干燥,过滤并浓缩。残余物通过硅胶柱层析(SiO_2,乙酸乙酯/MeOH=10/1+5%三乙胺)纯化。所得化合物粗品用乙酸乙酯/己烷研磨并干燥,得到白色固体状的标题化合物(145mg,产率为42%)。^{1}H-NMR(400MHz,$CDCl_3$)δppm;7.08(d,J=2.4Hz,1H),7.03(d,J=2.4Hz,1H),6.81-6.85(m,1H),6.35(s,1H),4.71(d,J=5.2Hz,2H),3.03(q,J=6.8Hz,2H),2.81-2.85(m,2H),2.68-2.72(m,1H),2.39(s,3H),2.27(s,3H),2.24(s,3H),1.88-1.94(m,2H),1.67-1.72(m,4H),0.85(t,J=6.8Hz,3H);MS(ES)[M+H]499.1,[M+Na]521.1;HPLC纯度为96.0%。

[2956] 根据与上述5-氯-3-[乙基(1-甲基哌啶-4-基)氨基]-2-甲基-N-{[6-甲基-2-氧代-4-(三氟甲基)-1,2-二氢吡啶-3-基]甲基}苯甲酰胺相同的制备方法,用之前所述的相应的吡啶酮片段制备下列类似物,并通过反相HPLC/MS(ACN-H_2O,包含0.1%甲酸)纯化。

[2957] 化合物409:5-氯-3-(乙基(1-甲基哌啶-4-基)氨基)-N-((5-氟代-4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺甲酸盐

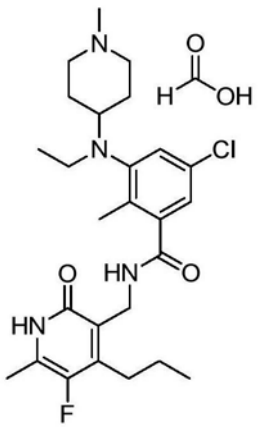
[2958]



[2959] ^{1}H-NMR(500MHz,CD_3OD)δppm8.45-8.25(br,1H),7.30(d,J=2.0Hz,1H),7.13(d,J=2.0Hz,1H),4.47(s,2H),3.50-3.38(br,2H),3.25-3.15(br,1H),3.08(q,J=7.0Hz,2H),3.06-2.98(br,2H),2.83(s,3H),2.38(d,J=2.0Hz,3H),2.27(s,3H),2.26(d,J=2.0Hz,3H),2.03(bd,J=14.75Hz,2H),1.90-1.77(br,2H),0.89(t,J=7.0Hz,3H);MS(ES)(M+H)463.50。

[2960] 化合物410:5-氯-3-(乙基(1-甲基哌啶-4-基)氨基)-N-((5-氟代-6-甲基-2-氧代-4-丙基-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺甲酸盐

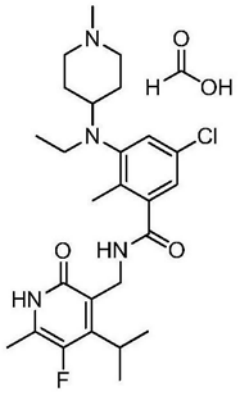
[2961]



[2962] ^{1}H-NMR(500MHz,CD_3OD) δ ppm8.43-8.26(br,1H),7.30(d,J=2.0Hz,1H),7.12(d,J=2.0Hz,1H),4.47(s,2H),3.47-3.39(br,2H),3.23-3.15(br,1H),3.08(q,J=7.0Hz,2H),3.05-2.96(br,2H),2.82(s,3H),2.79(bd,J=8.2Hz,2H),2.28-2.26(br,6H),2.06-1.99(br,2H),1.93-1.82(br,2H),1.68-1.59(m,2H),1.06(t,J=7.5Hz,3H),0.89(t,J=7.0Hz,3H);MS(ES)(M+H)491.52。

[2963] 化合物 411 :5- 氯 -3-(乙基 (1- 甲基哌啶 -4- 基) 氨基)-N-((5- 氟代 -4- 异丙基 -6- 甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基)-2- 甲基苯甲酰胺甲酸盐

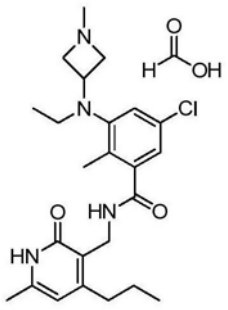
[2964]



[2965] ^{1}H-NMR(500MHz,CD_3OD) δ ppm8.48-8.34(br,1H),7.35(d,J=2.0Hz,1H),7.16(d,J=2.0Hz,1H),4.57(s,2H),3.61-3.53(m,1H),3.52-3.44(br,2H),3.30-3.20(br,1H),3.13(q,J=7.0Hz,2H),3.10-3.01(br,2H),2.87(s,3H),2.33(s,3H),2.31(d,J=2.8Hz,3H),2.10-2.04(br,2H),1.98-1.87(br,2H),1.41(d,J=6.5Hz,6H),0.93(t,J=7.0Hz,3H);MS(ES)(M+H)491.51。

[2966] 化合物 412 :5- 氯 -3-(乙基 (1- 甲基氮杂环丁烷 -3- 基) 氨基)-2- 甲基 -N-((6- 甲基 -2- 氧代 -4- 丙基 -1,2- 二氢吡啶 -3- 基) 甲基) 苯甲酰胺甲酸盐

[2967]

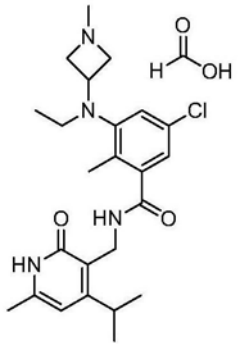


[2968] 根据与从其相应的羧酸酯制备 3-{ 乙基 [1-(丙烷 -2- 基) 哌啶 -4- 基] 氨基 }-2- 甲基 -5-(三氟甲基) 苯甲酸相同的制备方法,将 5- 氯 -3-(乙基 (1- 甲基氮杂环丁烷 -3- 基) 氨基)-2- 甲基苯甲酸甲酯水解为 5- 氯 -3-(乙基 (1- 甲基氮杂环丁烷 -3- 基) 氨基)-2- 甲基苯甲酸。将 5- 氯 -3-(乙基 (1- 甲基氮杂环丁烷 -3- 基) 氨基)-2- 甲基苯甲酸的粗品与之前制备的 3-(氨基甲基)-6- 甲基 -4- 丙基 -1,2- 二氢吡啶 -2- 酮的盐酸盐偶联,其中 3-(氨基甲基)-6- 甲基 -4- 丙基 -1,2- 二氢吡啶 -2- 酮的盐酸盐根据所述制备 N-[(4,6- 二甲基 -2- 氧代 -1,2- 二氢吡啶 -3- 基) 甲基]-3-[乙基 (1- 甲基哌啶 -4- 基) 氨基]-2- 甲基 -5-(三氟甲基) 苯甲酰胺的方法制备。通过反相 HPLC/MS(包含 0.1% 甲酸的

CAN-H_2O)纯化获得标题化合物。^{1}H-NMR(500MHz,CD_3OD) δ ppm8.58-8.24(br,1H),7.15(d,J=2.0Hz,1H),7.08(d,J=2.0Hz,1H),6.14(s,1H),4.48(s,2H),4.41-4.34(m,1H),4.25(br,2H),3.85(br,2H),3.00(q,J=7.0Hz,2H),2.92(s,3H),2.72-2.66(m,2H),2.34(s,3H),2.26(s,3H),1.70-1.61(m,2H),1.04(t,J=7.2Hz,3H),0.91(t,J=7.0Hz,3H);MS(ES)(M+H)445.48。

[2969] 化合物413:5-氯-3-(乙基(1-甲基氮杂环丁烷-3-基)氨基)-N-((4-异丙基-6-甲基-2-氧代-1,2-二氢吡啶-3-基)甲基)-2-甲基苯甲酰胺甲酸盐

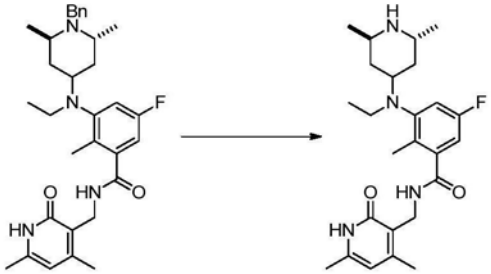
[2970]



[2971] 采用与之前制备的化合物5-氯-3-(乙基(1-甲基氮杂环丁烷-3-基)氨基)-2-甲基-N-((6-甲基-2-氧代-4-丙基-1,2-二氢吡啶-3-基)甲基)苯甲酰胺甲酸盐相同的制备方法,用5-氯-3-(乙基(1-甲基氮杂环丁烷-3-基)氨基)-2-甲基苯甲酸和3-(氨基甲基)-6-甲基-4-(丙烷-2-基)-1,2-二氢吡啶-2-酮的盐酸盐制备标题化合物。通过反相HPLC/MS(包含0.1%甲酸的CAN-H_2O)纯化后,得到标题化合物。^{1}H-NMR(500MHz,CD_3OD) δ ppm8.43-8.25(br,1H),7.15(d,J=2.0Hz,1H),7.08(d,J=2.0Hz,1H),6.25(s,1H),4.52(s,2H),4.40-4.34(m,1H),4.29-4.21(br,2H),3.90-3.79(br,2H),3.48-3.40(m,1H),3.00(q,J=7.0Hz,2H),2.92(s,3H),2.34(s,3H),2.28(s,3H),1.24(d,J=7.0Hz,6H),0.90(t,J=7.0Hz,3H)。MS(ES)(M+H)445.47。

[2972] 化合物414:N-[(4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基]-3-{[(2R,6R)-2,6-二甲基哌啶-4-基](乙基)氨基}-5-氟代-2-甲基苯甲酰胺

[2973]

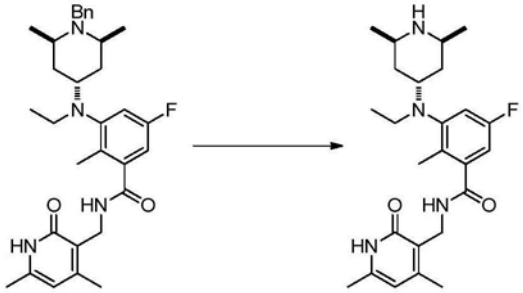


[2974] 向搅拌后的3-{[(2R,6R)-1-苄基-2,6-二甲基哌啶-4-基](乙基)氨基}-N-[(4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基]-5-氟代-2-甲基苯甲酰胺(378mg,0.709mmol)的MeOH(7mL)溶液中加入Pd/C(150mg)。反应混合物在23℃和氢气气氛中搅拌1小时。将反应混合物过滤,滤液真空浓缩,残余物通过硅胶柱层析(1.Nagara Science Co.,Ltd.生产的NAM-300H硅胶,乙酸乙酯/MeOH=4/1～乙酸乙酯/MeOH/三乙胺=1/1/0.01,2.NH-SiO_2,庚烷/乙酸乙酯=30/1～8/1)纯化,得到白色固体状的标题化合物(235mg,产率为75%)。^{1}HNMR(400MHz,$CDCl_3$) δ ppm;7.08(t,J=6.2Hz,1H),

6.82(dd,J=10.7,2.5Hz,1H),6.75(dd,J=8.2,2.7Hz,1H),5.93(s,1H),4.51(d,J=6.2Hz,2H),3.40-3.48(m,1H),2.95-3.09(m,3H),2.83-2.92(m,1H),2.39(s,3H),2.22(s x2,6H),1.63-1.78(m,4H),1.13(d,J=7.0Hz,3H),1.02(d,J=6.2Hz,3H),0.84(t,J=7.0Hz,3H);MS(ES)[M+H]443.1,[M+Na]465.2;HPLC;纯度为 99.3%。

[2975] 化合物 415:N-[(4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基]-3-{[(2R,4R,6S)-2,6-二甲基哌啶-4-基](乙基)氨基}-5-氟代-2-甲基苯甲酰胺

[2976]



[2977] 向搅拌后的 3-{[(2R,4R,6S)-1-苄基-2,6-二甲基哌啶-4-基](乙基)氨基}-N-[(4,6-二甲基-2-氧代-1,2-二氢吡啶-3-基)甲基]-5-氟代-2-甲基苯甲酰胺(50.1mg,0.0860mmol)的 MeOH(2mL)溶液中加入 Pd/C(100mg)。反应混合物在 23℃和氢气气氛中搅拌 3 小时。用氮气净化后,将所得混合物过滤,滤液真空浓缩,残余物通过硅胶柱层析(Nagara Science Co.,Ltd. 生产的 NAM-300H 硅胶,乙酸乙酯/MeOH=4/1 ～乙酸乙酯/MeOH/三乙胺=1/1/0.01)纯化。收集目标部分,并在真空中浓缩。残余物通过硅胶柱层析(NH-SiO_2,乙酸乙酯/MeOH=30/1 ～ 20/1 ～ 8/1)纯化。收集目标部分并在真空中浓缩。残余物用制备 TLC(TLC 硅胶 60F_{254},MERCK,MeOH/Et_3N=100/1)纯化,得到白色固体状的标题化合物(17.2mg,产率为 45%)。^{1}HNMR(400MHz,$CDCl_3$) δ ppm;7.10(m,1H),6.81(m,2H),5.91(s,1H),4.52(d,J=6.0Hz,2H),3.61(m,1H),3.23-2.73(m,4H),2.40(s,3H),2.28(s,3H),2.24(s,3H),1.64-1.05(m,4H),1.05-0.86(m,6H),0.82(t,J=7.2Hz,3H)。(-2H);LC-MS:m/z[M+H]443.2,[M+Na]465.3;HPLC;纯度为 97.4%。

[2978] 实施例 45:合成化合物 6、9、11-12、19、22、24、27、29、34-35、37-47、65-90、93-96、99-101、103、106-116、124、125、128-136、138-143、145-156、158-190、193-204、210、211、214-221、223-242、244-267、270-272、274、275、280、281、288、289、291-300、303-305、307、312、314、316-318、323-327、329-331、337、338、341-343、345、346、350-355、357-385、388、391 和 418

[2979] 通过与在实施例 1-44 中描述的类似方法或者通过在一般方案中描述的反应方案来合成化合物 6、9、11-12、19、22、24、27、29、34-35、37-47、65-90、93-96、99-101、103、106-116、124、125、128-136、138-143、145-156、158-190、193-204、210、211、214-221、223-242、244-267、270-272、274、275、280、281、288、289、291-300、303-305、307、312、314、316-318、323-327、329-331、337、338、341-343、345、346、350-355、357-385、388、391 和 418。

[2980] 实施例 46:生物试验方案和一般方法

[2981] 野生型和突变型的 PRC2 酶的实验方案

[2982] 一般材料。

[2983] 从 Sigma-Aldrich 公司购买可能的最高纯度的 S- 腺苷甲硫氨酸(S-adenosylmethionine，SAM)、S- 腺苷同型半胱氨酸(S-adenosylhomocyteine，SAH)、N- 二甘氨酸(bicine)、KCl、吐温 20（Tween20)、二甲基亚砜(DMSO)和牛皮胶(BSG)。二硫苏糖醇(dithiothreitol,DTT)购自 EMD。^{3}H-SAM 购自 American Radiolabeled Chemicals，其特异性活性为 80Ci/mmol。384 孔链霉亲和素闪光板(Flashplates)购自 PerkinElmer。

[2984] 底物

[2985] 人体组蛋白 H3 氨基酸残基 21-44 的代表性肽是由 21st Century Biochemicals 公司用 C 端 G(K- 生物素)连接 - 亲和标签结构域和 C 端酰胺帽合成的，其要么包括未修饰过的赖氨酸 27（H3K27me0)要么包括二甲基化的赖氨酸 27（H3K27me2)。通过高效液相色谱(HPLC)将此肽纯化至 95% 以上的纯度，通过液相色谱 - 质谱联用(LC-MS)来确认。序列列出如下：

[2986] H3K27me0:ATKAARKSAPATGGVKKPHRYRPGGK(生物素)- 酰胺 (SEQ ID NO:1)

[2987] H3K27me2:ATKAARK(me2)SAPATGGVKKPHRYRPGGK(生物素)- 酰胺 (SEQ ID NO:2)

[2988] 鸡红细胞寡聚核小体根据已确定的程序从鸡血中纯化。

[2989] 重组 PRC2 酶

[2990] 人类 PRC2 酶作为 4- 组分酶复合物纯化，其利用一种杆状病毒表达系统在草地贪夜蛾(Spodoptera frugiperda,sf9)细胞中共表达。表达的亚基为野生型 EZH2(NM_004456)或从野生型 EZH2 构造产生的突变型 EZH2Y641F、Y641N、Y641H、Y641S 或 Y641C、EED(NM_003797)、Suz12（NM_015355)和 RbAp48（NM_005610)。EED 亚基包含 N 端 FLAG 标签，其用于纯化来自于 sf9 细胞裂解物的整个 4- 组分复合物。通过 SDS-PAGE 和安捷伦生物分析仪(Agilent Bioanalyzer)分析来确定复合物的纯度满足或超过 95％。使用布拉德福德(Bradford)法、以牛血清白蛋白(BSA)标准液作为对照来确定酶浓缩母液的浓度(通常为 0.3-1.0mg/mL)。

[2991] 对多肽底物的 PRC2 酶试验的一般程序

[2992] 所有的试验均在由 20mM 的 N- 二甘氨酸(pH 值 =7.6)、0.5mM 的 DTT、0.005％的 BSG 和 0.002％的吐温 20 构成的缓冲液中进行，缓冲液在使用当天制备。用配有 384 通道吸量管头的板伴侣(Platemate)2×3（Thermo 公司)将在 100％ DMSO（1μL)中的化合物点到 384 孔聚丙烯 V 形底板(Greiner 公司)中。作为最大信号对照，将二甲基亚砜(1μL)加入到列 11、12、23、24，行 A-H 的孔中，作为最小信号对照，将 SAH（PRC2 的已知的产物和抑制剂)（1μL)加入到列 11、12、23、24，行 I-P 的孔中。含有野生型 PRC2 酶和 H3K27me0 肽或是 Y641 的任意突变型酶和 H3K27me2 肽的混合物(40μL)通过 Multidrop Combi 分液器 (Thermo 公司) 加入。在 25℃下将化合物和 PRC2 一起孵育 30 分钟，然后加入包含非放射性和 ^{3}H-SAM 的混合物的混合物(10μL)以引发反应(最终体积 =51μL)。在所有情况下，终浓度如下：野生型或突变型 PRC2 酶是 4nM，SAH 在最小信号对照孔中为 1mM，DMSO 浓度为 1％。其余组分的终浓度显示于下表 2 中。通过加入非放射性的 SAM（10μL)至终浓度为 600μm 来终止该试验，这样 ^{3}H - SAM 被稀释到不再检测到其并入肽底物的程度。然后将 384 孔聚丙烯板中的 50μL 的反应物转移到 384 孔闪光板中，将生物素化的肽结合到链亲和素表面至少 1 小时，之后在 Biotek ELx405 洗板机中用 0.1％的吐温 20 洗涤三次。然后将板在 PerkinElmer TopCount 读板器上读数以测定结合到闪光板表面的 ^{3}H- 标记的肽的量，其

是以每分钟衰变(dpm)或者被称为每分钟计数(cpm)来测量。表 2:基于 EZH2 同一性的每一个试验变化(野生型或 Y641 突变的 EZH2)的组分的终浓度

[2993]

PRC2 酶 (表现为 EZH2 同一性)	肽 (nM)	非放射性 SAM (nM)	^{3}H-SAM (nM)
野生型	185	1800	150
Y641F	200	850	150
Y641N	200	850	150
Y641H	200	1750	250

[2994]

Y641S	200	1300	200
Y641C	200	3750	250

[2995] 对寡聚核小体底物的野生型 PRC2 酶试验的一般步骤

[2996] 该试验是在由 20mM 的 N- 二甘氨酸(pH 值 =7.6)、0.5mM 的 DTT、0.005％的 BSG、100mM 的 KCl 和 0.002％的吐温 20 组成的缓冲液中进行,其在使用当天制备。用配有 384 通道吸量管头的板伴侣 2×3 (Thermo 公司)将在 100％的 DMSO (1μL)中的化合物点到 384 孔聚丙烯 V 形底板(Greiner 公司)中。作为最大信号对照,将二甲基亚砜(1μL)加入到列 11、12、23、24,行 A-H 的孔中,作为最小信号对照,将 SAH (PRC2 的已知的产物和抑制剂)(1μL)加入到列 11、12、23、24,行 I-P 的孔中。将含有野生型 PRC2 酶和鸡红细胞寡聚核小体的混合物(40μL)通过 Multidrop Combi 分液器 (Thermo 公司) 加入。将化合物和 PRC2 一起在 25℃孵育 30 分钟,然后加入包含非放射性和 ^{3}H-SAM 的混合物的混合物(10μL)以引发反应(终体积 =51μL)。终浓度如下:野生型 PRC2 酶是 4nM,非放射性的 SAM 是 430nM,^{3}H-SAM 为 120nm,鸡红细胞寡聚核小体为 120nm,SAH 的最小信号对照孔为 1mM,二甲基亚砜浓度为 1％。通过加入非放射性的 SAM (10μL)至终浓度为 600μM 来终止该反应,^{3}H - SAM 被稀释到不能再检测到其并入鸡红细胞寡聚核小体底物的程度。然后将 384- 孔聚丙烯板中的 50μL 的反应物转移到 384 孔闪光板,将鸡红细胞核小体固定至板表面,之后在 Biotek ELx405 洗板机中用 0.1％的吐温 20 洗涤三次。然后将板在 PerkinElmer TopCount 读板器上读数以测定结合到闪光板表面的 ^{3}H 标记的鸡红细胞寡聚核小体的量,其是以每分钟衰变(dpm)或者被称为每分钟计数(cpm)来测量。

[2997] ％抑制率(inh)计算

[2998] $$\%\ \text{inh}=100-\left(\frac{\text{dpm}_{\text{cmpd}}-\text{dpm}_{\text{min}}}{\text{dpm}_{\text{max}}-\text{dpm}_{\text{min}}}\right)\ \text{x}100$$

[2999] 其中,dpm= 每分钟衰变,cmpd= 试验孔信号,min 和 max 分别是最小和最大信号对照。

[3000] 4 参数 IC_{50} 拟合

[3001]

$$Y=\text{底部}+\frac{(\text{顶部}-\text{底部})}{1+(\frac{X}{IC_{50}})^{\text{Hill 系数}}}$$

[3002] 其中，顶部和底部通常允许浮动，但也可以在 3 参数拟合中分别固定为 100 或 0。Hill 系数通常允许浮动，但也可以在 3 参数拟合中固定为 1。Y 为抑制率%，X 是化合物浓度。

[3003] 对肽底物(例如，EZH2 野生型和 Y641F)的 PRC2 酶试验的 IC_{50} 值列于下表 3 中。

[3004] WSU-DLCL2 甲基化试验

[3005] WSU-DLCL2 悬浮细胞从 DSMZ (德国微生物菌种保藏中心，Braunschweig，德国)购买。RPMI/Glutamax 培养基、青霉素－链霉素、热灭活胎牛血清和 D-PBS 购自 Life Technologies 公司(Grand Island，纽约州，美国)。提取缓冲液和中和缓冲液(5X)购自 Active Motif 公司(Carlsbad，加利福尼亚州，美国)。兔抗组蛋白 H3 抗体购自 Abcam 公司(Cambridge，马萨诸塞州，美国)。兔抗 H3K27me3 和结合了 HRP 的抗兔 IgG 购自 Cell Signaling Technology 公司(Danvers，马萨诸塞州，美国)。TMB“超级敏感”底物来自 BioFX 实验室(Owings Mills，马里兰州，美国)。无 IgG 的牛血清白蛋白购自 Jackson ImmunoResearch 公司(West Grove，宾夕法尼亚州，美国)。含 Tween 的 PBS(10X PBST)从 KPL 公司(Gaithersburg，马里兰州，美国)购买。硫酸购自 Ricca Chemical 公司(Arlington，德克萨斯州，美国)。Immulon ELISA 板购自 Thermo 公司(Rochester，纽约州，美国)。V 形底细胞培养板购自 Corning 公司(Corning，纽约州，美国)。V 形底聚丙烯板购自 Greiner Bio-One 公司(Monroe，北卡罗来纳州，美国)。

[3006] WSU-DLCL2 悬浮细胞维持在生长培养基中(补充有 10% v/v 的热灭活的胎牛血清和 100 单位 /mL 的青霉素－链霉素的 RPMI1640)，在 37℃、5% CO_2 中培养。根据试验条件，细胞在板振荡器上、在分析培养基中(补充有 20% v/v 的热灭活的胎牛血清和 100 单位 /mL 的青霉素－链霉素的 RPMI1640)、在 37℃、5% CO_2 中孵育。

[3007] WSU-DLCL2 细胞在分析培养基中以每毫升 50000 个细胞的浓度向 96 孔 V 形底细胞培养板中以每孔 200μL 的量接种。将 96 孔源板的化合物(1μL)直接加入到 V 形底细胞板中。将板在 37℃、5% CO_2 下在滴度板摇床上孵育 96 小时。孵育四天后，将板以 241×g 转速离心五分钟，将培养基从细胞板的每个孔中轻轻地吸出，而不干扰细胞沉淀。将沉淀重悬于 200μL 的 DPBS，然后将板再次以 241×g 转速离心五分钟。将上清液吸出，将冷(4℃)提取缓冲液(100μL)加入到每个孔中。在 4℃下，将板在定轨摇床上孵育 2 小时。将平板以 3427×g 的转速离心 10 分钟。将上清液(每孔 80μL)转移到其在 96 孔 V 形底聚丙烯板上的相应的孔中。把 5× 中和缓冲液(每孔 20μL)加入到含有上清液 V 形底聚丙烯板中。含粗蛋白制剂(CHP)的 V 形底聚丙烯板在定轨摇床上孵育五分钟。将粗组蛋白制剂(每孔 2μL)分别加入到包含 100μL 包被缓冲液(1×PBS+BSA0.05% w/v)的重复的 96 孔 ELISA 板的孔中。将平板密封并在 4℃下孵育过夜。第二天，将板用每孔 300μL 的 1×PBST 洗涤三次。以每孔 300μL ELISA 稀释剂((PBS (1×)的 BSA (2% w/v)和吐温 20 (0.05% v/v))将孔阻断两小时。将板用 1×PBST 洗涤三次。对于组蛋白 H3 检测板，加入 100μL/ 每孔的在 ELISA 稀释剂中以 1:10000 稀释的抗组蛋白 H3 抗体(Abcam 公司，ab1791)。对于 H3K27

三甲基化检测板，加入 100μL/ 每孔的在 ELISA 稀释剂中以 1:2000 稀释的抗 H3K27me3。板在室温下孵育 90 分钟。用每孔 300μL 的 1×PBST 将板洗涤三次。对于组蛋白 H3 的检测，向每孔加入 100μL 的在 ELISA 稀释剂中以 1:6000 稀释的结合 HRP 的抗兔 IgG 抗体。对于 H3K27me3 的检测，向每孔加入 100μL 在 ELISA 稀释剂中以 1:4000 稀释的结合 HRP 的抗兔 IgG 抗体。将板在室温下孵育 90 分钟。用每孔 300μl1×PBST 将板洗涤四次。每孔中加入 100μL 的 TMB 底物。将组蛋白 H3 板在室温下孵育 5 分钟。将 H3K27me3 板在室温下孵育 10 分钟。用硫酸 1N（每孔 100μL）使反应停止。每个板的吸光度在 450nm 处读数。

[3008] 首先，每个孔的比率通过下式确定：$\left(\frac{H3K27me3\ OD450\ 值}{Histone\ H3\ OD450\ 值}\right)$。

[3009] 每个板包括八个只有 DMSO 处理的对照孔（最小抑制），以及八个作为最大抑制的对照孔（背景孔）。

[3010] 计算每种对照类型的比值的平均值，将其用于确定板上每个测试孔的抑制百分数。从 25μM 开始，将测试化合物在 DMSO 中连续地三倍稀释，以获得一共十组测试浓度。确定抑制百分数，用每浓度的化合物的重复孔来产生 IC_{50} 曲线。该试验的 IC_{50} 值列于下表 3。

[3011]

$$抑制百分数=100-\left(\left(\frac{(个体测试样本比率)-(背景平均比率)}{(最小抑制比率)-(背景平均比率)}\right)*100\right)$$

[3012] 细胞增殖分析

[3013] WSU-DLCL2 悬浮细胞从 DSMZ（德国微生物菌种保藏中心，Braunschweig，德国）购买。RPMI/Glutamax 培养基、青霉素－链霉素、热灭活胎牛血清购自 Life Techonologies 公司（Grand Island，纽约州，美国）。V 形底聚丙烯 384 孔板购自 Greiner Bio-One 公司（Monroe，北卡罗来纳州，美国）。细胞培养 384 孔白色不透明板购自 Perkin Elmer 公司（Waltham，马萨诸塞州，美国）。Cell-Titer Glo®购自 Promega 公司（Madison，威斯康星州，美国）。SpectraMax M5 酶标仪器购自 Molecular Devices LLC 公司（Sunnyvale，加利福尼亚州，美国）。

[3014] WSU-DLCL2 悬浮细胞维持在生长培养基（补充有 10％ v/v 的热灭活的胎牛血清的 RPMI1640）中，在 37℃、5％ CO_2 中培养。在试验条件下，细胞在分析培养基（补充有 20％ v/v 的热灭活的胎牛血清和 100units/mL 的青霉素－链霉素的 RPMI1640）中、在 37℃、5％ CO_2 中孵育。

[3015] 为了评估化合物对 WSU-DLCL2 细胞系的增殖的效果，将指数生长的细胞在最终体积为 50μl 的分析培养基中以 1250 个细胞 /ml 的密度接种于 384 孔白色不透明板中。通过在 DMSO 中从 10mM（在试验中化合物的最高终浓度为 20μM，DMSO 为 0.2％）开始进行一式三份的九点的连续 3 倍稀释来制备化合物源板。将来自于化合物储存板的 100nL 的等分加入到细胞板中其各自的孔中。100％抑制对照由终浓度为 200nM 的十字孢碱处理的细胞组成，0％抑制对照由用 DMSO 处理的细胞组成。加入化合物后，将分析板于 37℃、5％ CO_2、相对湿度 >90％的条件下孵育 6 天。向细胞板加入 35μl 的 Cell Titer Glo®试剂，通过存在于细胞培养物中 ATP 的量化来测量细胞的存活率。在 Spectramax M5 中读取发光值。抑制 50％细胞存活率的浓度通过使用的标准化的剂量响应曲线的 4 参数拟合来确定。该试验的 IC_{50} 值也列于下表 3 中。

[3016] 表 3

[3017]

化合物编号	野生型 EZH2 IC_{50} (μM)	突变型 Y641F IC_{50} (μM)	H3K27Me3 ELISA IC_{50} (μM)	WSU 增殖 IC_{50} (μM)
1	0.0199			3.09728
2	0.02348			0.62109
3	0.04011			
4	0.02231			0.54412
5	0.02389			2.19558
6	0.02703			0.50577
7	0.03317			
8	0.03622	0.02506		
9	0.03501			
10	0.03978			
11	0.04682			
12	0.05026			
13	0.06396			
14	0.04353			
15	0.07173			
16	0.10471			
17	0.08438			
18	0.1603			
19	0.10845			
20	0.16251			
21	0.17104			
22	0.20549			
23	0.17755			
24	0.22919			
25	0.23			
26	0.29374			
27	0.48381			
28	0.54889			
29	0.62173			
30	0.62615			
31	0.6324			
32	0.63441			

[3018]

[3019]

化合物编号	野生型 EZH2 IC_{50} (μM)	突变型 Y641F IC_{50} (μM)	H3K27Me3 ELISA IC_{50} (μM)	WSU 增殖 IC_{50} (μM)
33	0.65963			
35	0.82442			
36	0.91712			
37	1.00379			
38	1.0545			
39	1.07137			
40	1.09168			
41	1.13408			
42	2.59043			
43	2.67651			
44	4.32369			
45	25.22746			
46	26.53597			
47	39.133			
48	0.24998			
49	3.59887			
50	0.30813			
51	0.37599			
52	0.04814			
53	0.41267			
54	0.50073			
55	0.01626			3.91279
56	0.01519			0.21216
57	0.02987			7.72974
58	0.05639			
59	0.03149			
60	0.05852			
61	0.01585			0.33187
62	0.09429			
63	0.05709			
64	0.02472			2.06774
65	1.07044			

[3020]

化合物编号	野生型 EZH2 IC_{50} (μM)	突变型 Y641F IC_{50} (μM)	H3K27Me3 ELISA IC_{50} (μM)	WSU 增殖 IC_{50} (μM)
66	1.71172			
67	3.61905			
68	1.3267			
69	4.71695			
70	0.90608			
71	1.21512			
72	1.01436			
73	4.14125			
74	0.07113			
75	0.3843			
76	1.24461			
77	0.14901			
78	0.14362			
79	0.02465	0.02116		
80	1.64878			
82	4.20192			
83	0.18011	0.09576		
84	0.11391	0.10243		
85	0.10754	0.07626		
86	2.57252			
87	0.09019	0.10057		
88	0.03758	0.02817		
89	0.07342	0.08298		
90	0.0998	0.1002		
91	0.02271	0.0176		2.5696
92	0.01655	0.02341		1.23721
93	1.18036	1.08352		
94	3.80992	5.5015		
95	0.35125	0.33255		
96	0.38143	0.40305		
97	0.02024	0.0292		2.4644
98	0.0174	0.03732		1.75896

[3021]

化合物编号	野生型 EZH2 IC_{50} (μM)	突变型 Y641F IC_{50} (μM)	H3K27Me3 ELISA IC_{50} (μM)	WSU 增殖 IC_{50} (μM)
99	0.01481	0.01028		3.86397
100	0.03203	0.01966		
101	0.00711	0.00717		1.07296
102	0.01545	0.00727		0.61272
103	0.072	0.06724		
104	0.03077	0.0318		9.05638
105	0.01728	0.01229		6.47052
106	0.2446	0.19119		
107	0.05396	0.10057		
108	0.02003	0.0175		4.42418
109	0.01112	0.01094		0.44691
110	0.04792	0.06226		
111	0.05328	0.02875		
112	0.0587	0.02666		
113	0.18895	0.17503		
114	0.1051	0.11091		
115	0.06117	0.05267		
116	0.06276	0.0452		
117	0.02807	0.02213		
118	0.01759	0.01615		8.60536
119	0.00951	0.00748		1.40617
120	0.00911	0.01085		0.36889
121	0.01385	0.0133		0.5035
122	0.01511	0.01932		0.18096
123	0.09153	0.06041		
124	0.16779	0.11113		
125	0.04721	0.0315		
126	0.04784	0.03472		
127	0.01691	0.01923		1.50101
128	0.04911	0.0438		
129	0.11098	0.08998		
130	0.01722	0.01508		2.3697

[3022]

化合物编号	野生型 EZH2 IC_{50} (μM)	突变型 Y641F IC_{50} (μM)	H3K27Me3 ELISA IC_{50} (μM)	WSU 增殖 IC_{50} (μM)
131	0.02287	0.00778		1.65122
132	0.06337	0.0717		
133	0.04829	0.03059		
134	0.02562	0.02189		1.08958
135	0.04667	0.02555		4.14394
136	0.11517	0.0957		
137	0.01602	0.00604		3.29434
138	0.03495	0.04493		> 20.0 uM
139	0.0204	0.01392		1.79898
140	1.66626	0.91482		
141	0.06632	0.18147		
142	0.02672	0.02005		3.72097
143	0.13711	0.05828		
144	2.294	1.3667		
145	0.10444	0.07112		
146	0.32313	0.28854		
147	0.14779	0.25593		
148	0.10411	0.0887		
149	0.04469	0.03168		
150	0.02894	0.02965		0.57037
151	0.01594	0.0157		0.52874
152	0.02585	0.02197		1.40549
153	0.08502	0.09128		
154	0.013	0.01062		1.16887
155	0.02133	0.02385		0.46034
156	0.0588	0.01936		
157	0.00315	0.02001		0.71676
158	0.00901	0.00955		0.65779
159	0.02579	0.02495		0.58237
160	0.01766	0.02255		6.6023
161	0.01969	0.01299		1.59243
162	0.01532	0.01819		1.18391

[3023]

化合物编号	野生型 EZH2 IC_{50} (μM)	突变型 Y641F IC_{50} (μM)	H3K27Me3 ELISA IC_{50} (μM)	WSU 增殖 IC_{50} (μM)
163	0.46447	0.26959		
164	0.0546	0.06284		
165	0.02452	0.01895		0.84174
166	0.01495	0.01835		0.69533
167	0.0131	0.00987		0.10896
168	0.00808	0.00611		0.82333
169	0.09611	0.1054		
170	0.01635	0.01145		4.16823
171	0.07652	0.0652		
172	0.65963			
173	1.13408			
174	0.0199			3.09728
175	15.49647			
176	35.36685			
177	4.13196			
178	4.13196			
179	2.875			
180	2.31858			
181	1.18357			
182	0.13256			
183	7.67584			
184	1.07044			
186	1.64878			
187	2.57252			
188	0.15624	0.16162		
189	3.80992	5.5015		
190	0.2839	0.21448		
191	0.0109	0.00548		0.43262
192	0.13004	0.09414		
193	0.0822	0.05193		
194	0.01771	0.00919		0.41697
195	0.01654	0.01113		1.45306

[3024]

化合物编号	野生型 EZH2 IC_{50} (μM)	突变型 Y641F IC_{50} (μM)	H3K27Me3 ELISA IC_{50} (μM)	WSU 增殖 IC_{50} (μM)
196	0.01817	0.01479		0.35933
197	0.01822	0.00537		1.05176
198	0.20387	0.13976		
199	1.38563	0.99179		
200	0.00624	0.00596		0.2826
201	1.33026	1.11031		
202	0.04811	0.03758		3.12395
203	0.02138	0.0142		0.47667
204	0.22175	0.21976		
205	0.0077	0.00479	0.82074	
206	0.01284	0.01106		0.63322
207	0.10198	0.11905		> 20.0 uM
208	1.31405	1.19521		
209	1.487	1.18544		
210				1.26697
211	0.00679	0.0147		0.54832
212	1.05201	0.98451		
213	0.05325	0.0438		14.71083
214	0.07475	0.06722		2.45231
215	0.01551	0.02167		0.80033
216	0.02489	0.04884		1.54705
217	0.18259	0.34753		
218	0.02083	0.02903		1.27027
219	0.1748	0.16449		
220	0.0205	0.04357		1.04201
221	0.0191	0.01616		1.11978
222	0.00078	0.00225	0.18533	0.13712
223	0.0136	0.02689		1.54605
224	0.03257	0.03334		1.76879
225	0.00695	0.01342		0.20778
226	0.03426	0.06624		0.23132
227	0.00365	0.00622		0.21515

[3025]

化合物编号	野生型 EZH2 IC_{50} (μM)	突变型 Y641F IC_{50} (μM)	H3K27Me3 ELISA IC_{50} (μM)	WSU 增殖 IC_{50} (μM)
228	0.0144	0.02015		1.27869
229	0.02235	0.02847		1.54848
230	0.34423	0.25475		
231	0.29712	0.15945		> 20.0 uM
232	0.15485	0.0881		8.04526
233	1.42344	0.5799		
234	1.97267	1.62693		
235	0.0632	0.05138		3.79895
236	0.61213	0.83099		14.62129
237	2.18156	1.47293		
238	1.40428	0.80506		
239	4.95504	4.77826		
240	6.94031	6.8594		
241	6.57787			
242	0.1998	0.12679		8.4057
243	0.06318			6.47336
244	0.03749			3.06427
245	0.33295			
246				
247	0.01787	0.02136		3.19941
248	0.03458	0.0601		4.57081
249				11.45613
250	0.15959	0.20744		4.58295
251				13.11386
252				> 20.0 uM
253	0.45669	0.28936		14.42495
254				
255	0.01095	0.009		1.63338
256	0.00648	0.00738		1.69149
257	0.02224	0.07406		4.49758
258	1.90754			
259	0.58066	0.60207		> 20.0 uM

[3026]

化合物编号	野生型 EZH2 IC_{50} (μM)	突变型 Y641F IC_{50} (μM)	H3K27Me3 ELISA IC_{50} (μM)	WSU 增殖 IC_{50} (μM)
260	0.01282	0.01164		1.08525
261	0.01426	0.02069		0.9055
262	0.00961	0.00523		1.89119
263	0.03631	0.02181		4.89099
264	0.04094	0.04072		8.72536
265	0.02507	0.01843		5.09483
266	0.19847	0.08014		8.72547
267	0.16128			> 20.0 uM
268	0.00131	0.0024		0.38531
269	0.09984	0.11108		14.2318
270	9.47417	> 10.0 uM		
271	0.05109	0.02565		5.32683
272	0.11472	0.06925		
273	0.00328	0.00537		0.28489
274	7.76353	> 10.0 uM		> 20.0 uM
275	0.90643	3.32337		> 20.0 uM
276	0.00152	0.00407		0.18228
277	0.0023	0.00264		2.47797
278	0.00493	0.01117		0.61255
279	0.01143	0.01999		0.78715
280	0.00139	0.00556		0.43228
281	> 10.0 uM	> 10.0 uM		
282	0.00492	0.00985		0.21356
283	0.00316	0.0177		0.27638
284	0.008	0.0119		0.26282
285	0.00211	0.00506		0.21307
286	0.00122	0.00272		0.46721
287	0.00882	0.01141		1.35674
288	0.00694	0.00732		0.53484
289	0.14621	0.09339		
290	0.00743			0.53732

[3027]

化合物编号	野生型 EZH2 IC_{50} (μM)	突变型 Y641F IC_{50} (μM)	H3K27Me3 ELISA IC_{50} (μM)	WSU 增殖 IC_{50} (μM)
291	0.00951			0.71974
292	0.01046			1.21021
293	0.01737	0.01158		1.29406
294	0.02412			2.16178
295	0.01161	0.01056		2.51445
296	0.00655	0.01825		4.33357
297	0.03337	0.02251		11.2951
298	0.0371	0.04303		6.54579
299	0.00324	0.00307		0.25937
300	0.02277	0.01709		4.94656
301	0.00497	0.00507		
302	0.01217	0.01607		1.97477
303	0.03293	0.04119		3.89541
304	0.01722	0.0126		2.14418
305	0.00254	0.00785		0.28787
306	0.00942	0.00922		0.17284
307	0.0402	0.10188		3.85437
308	0.00997	0.01169		0.16744
309	0.00817			
310	0.00596			0.60994
311	0.00323			0.16549
312	0.01507			
313	0.00818			
314	2.90826	4.7092		
315	0.00973	0.00922		
316		0.01202		1.40268
317	1.37527	1.96382		
318	1.06978	0.91775		9.7596
319	0.0108	0.01137		2.95728
320	0.01694	0.01579		0.17566
321	0.00783	0.01144		
322	0.03101	0.02239		3.59961

[3028]

化合物编号	野生型 EZH2 IC_{50} (μM)	突变型 Y641F IC_{50} (μM)	H3K27Me3 ELISA IC_{50} (μM)	WSU 增殖 IC_{50} (μM)
323	0.05148	0.03445		4.15894
324	0.40349	0.15525		16.80211
325	0.13585	0.21534		13.3829
326	0.0206	0.0095		1.43256
327	0.23134	0.09407		3.11887
328	0.84894			> 20.0 uM
329	0.00755	0.00371		0.88119
330	0.03576	0.0368		1.20313
331	0.03891	0.01805		0.19105
332	0.27993	0.45426		> 20.0 uM
333	0.30257	0.54098		> 20.0 uM
334	0.05384	0.11977		
335	0.01004	0.0027		0.97124
336	0.03144	0.02075		
337	4.32339	3.56167		> 20.0 uM
338	0.49234	0.19347		> 20.0 uM
339	0.00858	0.00734		0.97312
340	0.01056	0.00412		1.59354
341	0.00592	0.00552		2.28944
342	0.03972	0.01592		1.9859
343	0.01081	0.00912		0.63289
344	0.00623	0.00396		1.30672
345	0.02228	0.01819		1.2346
346	0.00428	0.00245		0.12639
347	0.00654	0.00328		0.13526
348	0.00566	0.00363		0.32865
349	0.00872	0.00153		
350	0.01244	0.00357		0.38084
351	0.00911	0.00138		4.85151
352	0.13195			5.54765
353	0.00792	0.00463		0.14599
354	0.01312	0.01039	0.14232	0.15832

[3029]

化合物编号	野生型 EZH2 IC_{50} (μM)	突变型 Y641F IC_{50} (μM)	H3K27Me3 ELISA IC_{50} (μM)	WSU 增殖 IC_{50} (μM)
355	0.08966	0.06081		
356	0.03629	0.00721		
357	0.00437	0.00456	0.14928	
358	0.17315	0.06636		
359	0.00729	0.00554		
360	0.00883	0.00841		
361	0.00661	0.00423		
362	0.01388	0.00491		
363	0.00394	0.00206		
364	0.00943	0.00687		
365	0.00609	0.00665	0.23299	
366	0.03483	0.02934	> 25.0 uM	
367	0.33336	0.16784	> 25.0 uM	
368	0.02799	0.03855	> 25.0 uM	
369	0.07146	0.02755	3.7881	
370	0.02998	0.01113		
371	0.01181	0.00537		
372	0.00801	0.0081	0.3659	
373	0.00694	0.00369		
374	0.00319	0.00831		
375	0.01661	0.04182		
376	0.01641	0.01977		
377	0.07647	0.02552		
378	0.00296	0.0031	> 25.0 uM	
379	0.00516	0.00322	> 25.0 uM	
380	0.02778	0.04196	> 25.0 uM	
381	0.05627	0.05243	> 25.0 uM	
382	0.00341	0.02167	4.16185	
383	0.03974	0.04428	> 25.0 uM	
384	0.00206	0.00156	1.53716	
385	0.06573	0.03511	> 25.0 uM	
386	2.42146	1.15144		

[3030]

化合物编号	野生型 EZH2 IC_{50} (μM)	突变型 Y641F IC_{50} (μM)	H3K27Me3 ELISA IC_{50} (μM)	WSU 增殖 IC_{50} (μM)
387	0.74351	0.39771		
388	0.00728	0.00396	2.29835	
389	0.01564	0.0177		
390	0.01251	0.01037		1.32773
391	0.04809	0.06404	> 25.0 uM	
392	0.048	0.039		
393	0.12932	0.10995		
394	0.29421	0.23058		
395	0.30434	0.17359		
396	4.42445	6.6822		
397	3.37221	2.39173		
398	2.61756	2.00394		
399	> 10.0 uM	8.31018		
400	0.025	0.018		
401	0.01466	0.01426		
402	> 10.0 uM	8.0921		
403	0.53602	0.58786		
404	2.27552	1.40203		
405	0.172	0.107		
406	0.017	0.053		
407	0.0861	0.04069		
408	0.1656	0.0936		
409	0.45616	0.3404		
410	2.28273	2.85881		
411	1.19988	1.40119		
412	0.22183	0.21475		
413	0.76484	0.64167		
414	0.00692	0.0084		

[3031]

化合物编号	野生型 EZH2 IC_{50} (μM)	突变型 Y641F IC_{50} (μM)	H3K27Me3 ELISA IC_{50} (μM)	WSU 增殖 IC_{50} (μM)
415	1.5555	0.89979		
416	0.016	0.015		

[3032] 实施例 47 :最低细胞毒性浓度(Lowest Cytotoxic Concentration,LCC)的偏差

[3033] 已经确认,细胞增殖通过细胞分裂发生,细胞分裂导致相对于分裂之前细胞的数量分裂后细胞的数量增加一倍。在固定的环境条件(例如,pH、离子强度、温度、细胞密度、蛋白质和生长因子的培养基含量等)下,细胞将根据下面的方程、通过连续的倍增(即分裂)来增殖,条件是有足够的营养物和其他必需的因子可用。

[3034] $$N_t = N_0 \times 2^{\frac{t}{t_D}} \qquad (A.1)$$

[3035] 其中,N_t 是观察期开始后在时间点 (t) 的细胞数量,N_0 是观察期开始时的细胞数量,t 是观察期开始后的时间,t_D 是细胞倍增所需的时间间隔,也称作倍增时间。方程 A.1 可以被转换成以 e 为底数的指数方程的更方便的形式,其利用等式 0.693=ln(2)。

[3036] $$N_t = N_0 e^{\frac{0.693t}{t_D}} \qquad (A.2)$$

[3037] 如下所示,细胞增殖的速率常数 (k_p) 与倍增时间呈倒数相关

[3038] $$k_p = \frac{0.693}{t_D} \qquad (A.3)。$$

[3039] 合并方程 A.2 和 A.3 得到

[3040] $$N_t = N_0 e^{k_p t} \qquad (A.4)。$$

[3041] 因此,根据方程 A.4 细胞数预计在被称为对数生长期的细胞生长的初期随时间指数性地增加(图 1A)。指数方程,如方程 A.4,可以通过对两边取自然对数来进行线性化处理

[3042] $\ln(N_t)=\ln(N_0)+k_p t$ (A.5)

[3043] 因此,作为时间函数的 ln(Nt) 的图预计产生上升的直线,其斜率等于 k_p,y 轴截距等于 $\ln(N_0)$,如图 1B 所示。

[3044] 环境条件的变化可以导致细胞增殖速率的变化,细胞增殖速率的变化可通过增殖速率常数 k_p 的变化来量化。可能会导致增殖速率的变化的条件有在观察期的开始(即在 t=0)时向系统引入抗增殖化合物。当抗增殖化合物对细胞增殖有立即的影响时,期望作为时间函数的 $\ln(N_t)$ 的图会继续在所有化合物浓度下呈线性,随着化合物浓度的增加 k_p 值递减。

[3045] 根据抗增殖作用的机理基础,一些化合物可能不会立即造成增殖速率的变化。相反,在化合物的作用实现前可能会有一段潜伏时间。在这些情况下,作为时间的函数的 $\ln(N_t)$ 曲线图呈现出两个阶段,化合物的作用开始的时间点可以作为两个阶段之间的拐点

被确定(图2)。不管化合物对增殖的作用是即时的或是在潜伏期后开始的,在各化合物浓度下的增殖的速率常数最好由 $\ln(N_t)$ 对从化合物的作用开始的时间点到该实验的观察期的结束的时间图的斜率来定义。

[3046] 用于生长细胞的化合物可能会以两种普遍方式之一来影响所观察的增殖:通过抑制进一步的细胞分裂(细胞生长抑制)或通过杀死细胞(细胞毒性)。如果化合物是抑制细胞生长的,那么增加化合物的浓度会降低 k_p 值直到没有进一步的细胞分裂。这时,细胞生长的速率、从而 k_p 的值将会是 0。另一方面,如果该化合物是细胞毒性的,那么 k_p 的值将会由两个速率常数组成:在化合物存在下连续的细胞生长的速率常数 (k_g) 和细胞被化合物杀死的速率常数 (k_d)。因此在化合物的固定浓度下增殖的总速率常数将是这些相反的速率常数的绝对值的差。

[3047] $$k_p=|k_g|-|k_d| \qquad (A.6)$$

[3048] 在细胞生长速率超过杀死细胞速率的化合物浓度下,k_p 值将会是正值(即 $k_p>0$)。在细胞生长速率小于杀死细胞速率时的化合物浓度下,k_p 值将会是负值(即 $k_p<0$),并且细胞数量将随着时间的推移减少,其表明很强的细胞毒性。当 k_g 与 k_d 恰好相等时,那么总增殖速率常数 k_p 的值将会是 0。因此我们可以将最低细胞毒性浓度 (LCC) 定义为导致 k_p 值等于 0 的化合物浓度,由于大于该浓度的任何浓度将导致明显的可观察到的细胞毒性。注意:在 LCC 以下的浓度有可能发生细胞杀死,但发生在小于剩余的细胞增殖速率的速率。这里的处理不是为了限定化合物作用的生物学细节。相反,这里的目标是仅限定一个实际参数,其用来客观量化细胞杀死速率超过新细胞生长速率时的化合物浓度。事实上,LCC 表示拐点或临界浓度,高于此浓度时可以观察到明显的细胞毒性,而非表示细胞毒性浓度本身。就这一点而言,LCC 可以被看作类似于其他物理拐点的指标,如临界胶束浓度 (CMC),其被用于定义脂质、清洁剂或其他表面活性剂种类的浓度,在此浓度以上的所有分子并入胶束结构中。

[3049] 传统上,抗增殖化合物对细胞生长的作用最常被 IC_{50} 值量化,其被定义为将细胞增殖速率降低到在化合物不存在(即载剂或溶剂对照样品;图 2)时观察的速率的一半时的化合物浓度。但是 IC_{50} 不能使研究者区分开细胞抑制化合物和细胞毒性化合物。相反,LCC 很容易使人能做出这样的区分,并进一步量化在转变为很强的细胞毒性行为发生时的浓度。

[3050] 如果将观察时间期限限定为作用开始(如在上文和在图 2 中所定义的)到实验结束之间,那么当为作为时间的函数的 $\ln(Nt)$ 作图时(见上文),数据通常与线性方程较好地拟合。在该类型的拟合中,k_p 值可以在所测试化合物的各个浓度下确定。作为化合物浓度 ([I]) 的函数的 k_p 值的重新画图将有一个下降的等温线的形式,在 [I]=0 时有最大值 k_{max} (通过载剂或溶剂对照样品定义),在无限大的化合物浓度时有最小值 k_{min} (图 3)。

[3051] $$k_p=\frac{(k_{max}-k_{min})}{1+\frac{[I]}{I_{mid}}}+k_{min} \qquad (A.7)$$

[3052] 其中,I_{mid} 为产生在 k_{max} 和 k_{min} 之间的中间值的 k_p 值的化合物的浓度(注意 I_{mid} 值与 IC_{50} 值并不一样,除了彻底且仅仅为抑制细胞生长的化合物的情况外)。因此,向方程 A.7

重新画图数据拟合提供了 k_{max}、k_{min} 和 I_{mid} 的估值。如果化合物是抑制细胞生长的（如此处定义的），k_{min} 值不能小于零。对于细胞毒性化合物，k_{min} 将小于零，k_{min} 的绝对值与化合物在杀死细胞方面的效果直接相关。

[3053] 来自方程 A.7 的拟合值也可以用于确定 LCC 值。按照定义，当 [I]=LCC 时，k_p=0。因此，在这些条件下方程 A.7 变为

[3054]
$$0=\frac{\left(k_{\max}-k_{\min}\right)}{1+\frac{LCC}{I_{mid}}}+k_{\min} \qquad (A.8)。$$

[3055] 方程 A.8 的代数重排产生对于 LCC 的方程

[3056]
$$LCC=I_{mid}\left[\left(\frac{k_{\max}-k_{\min}}{-k_{\min}}\right)-1\right] \qquad (A.9)$$

[3057] 用非线性曲线拟合软件实现该分析很简单，可以应用在整个药物发现和开发过程中的化合物活性的细胞分析。用这种方式，LCC 可以提供对化合物 SAR 的评估的有价值的指标（构效关系）。

[3058] 下表 4 提供本发明的某些化合物对 WSU-DLCL2 细胞的 LCC 和 IC_{50} 数据。

[3059] 表 4

[3060]

化合物编号	WSU-DLCL2 11 天 LCC (μM)	WSU-DLCL2 11 天 IC50 (μM)
8	0.207	0.076
56	0.442	0.0097
88	1.27	0.035
101	2.59	0.25
120	0.343	0.006
121	0.0597	0.0094
222	0.0268	0.0043
261	0.556	0.051
277	0.037	0.0024
354	0.043	0.013
357	0.026	0.0095

[3061] 实施例 48：体内试验

[3062] 小鼠

[3063] 雌性 Fox Chase SCID® 小鼠（CB17/Icr-Prkdcscid/IcrIcoCrl，Charles River Laboratories 公司）或胸腺缺失的裸鼠（Crl:NU(Ncr)-Foxn1nu，Charles River Laboratories 公司）是 8 周大，在研究第一天（D1）体重（BW）范围为 16.0－21.1g。以让其随意饮水（反向渗透 1ppm Cl）、喂 NIH31 经修饰且具有辐射处理过的 Lab Diet®（由 18.0% 的粗蛋白、5.0%

粗脂肪和 5.0% 粗纤维组成）的方式来给动物喂食。此小鼠在静态微分离器中的辐射过的 Enrich-o'cobs™ 垫上经 12 小时光照周期、在 20-22℃ (68 - 72° F) 和 40-60% 的湿度下饲养。在约束、饲养、手术治疗、饲料和液体管理和医疗照顾方面的所有的程序符合 Guide for Care and Use of Laboratory Animals 的建议。

[3064] 肿瘤细胞培养

[3065] 人淋巴瘤细胞系从不同来源 (ATCC, DSMZ) 获得，在包含 100units/mL 的青霉素 G 钠盐、100g/mL 的链霉素和 25g/mL 的庆大霉素的 RPMI-1640 培养基中作为悬浮培养液的 Piedmont 中维持细胞系。所述培养基补充有 10% 的胎牛血清和 2mM 的谷氨酰胺。细胞在加湿的培养器中的组织培养瓶中、在 37℃、5%CO_2 和 95% 空气的气氛中培养。

[3066] 体内肿瘤移植

[3067] 收获在对数生长中期阶段的人淋巴瘤细胞系，重悬于含 50%Matrigel™ (BD Biosciences 公司) 的 PBS 中。每只小鼠在右侧经皮下地接受 $1x10^7$ 个细胞（0.2mL 细胞悬浮液）。随着肿瘤的平均体积接近所需的 80 - 120mm^3 的范围时，在两个维度来测量肿瘤以监控其增长。肿瘤大小（以 mm^3 为单位）通过下式计算：

[3068]

$$\text{肿瘤体积} = \frac{w^2 \times l}{2}$$

[3069] 其中 w 为肿瘤的宽度，l 为肿瘤的长度，以 mm 为单位。肿瘤重量可以基于以下假设估算出来：1mg 等同于肿瘤体积的 $1mm^3$。10-30 天（根据所用的细胞系）后，长有 108 - 126mm^3 大小的肿瘤的小鼠被分选到平均肿瘤体积为 117 - 119mm^3 的八组中。

[3070] 供试品

[3071] 测试化合物在室温下避光保存。在每一个治疗日，通过将粉末悬浮于含 0.5% 的羧甲基纤维素钠 (NaCMC) 和 0.1% 的Tween® 80 的去离子水中来制备新鲜的化合物制剂。EM10 载剂（在去离子水中 0.5% 的 NaCMC 和 0.1% 的Tween® 80）以相同的时间表用于处理对照组。给药之前制剂在 4℃避光保存。

[3072] 处理计划

[3073] 以范围为 1 - 1000mg/kg 的化合物剂量和各种天数的 TID（每日三次，每 8 小时一次）、BID（每日两次，每 12 小时一次）或 QD（每日一次）的时间表，通过口腔喂食或通过静脉内、腹膜内或皮下途径注射来处理小鼠。每一种剂量以 0.2mL/20g 小鼠（10mL/kg）的体积输送，根据最后记录的动物个体的重量进行调节。最大治疗时间长度为 28 天。

[3074] 中值肿瘤体积 (MTV) 和肿瘤生长抑制 (TGI) 分析

[3075] 疗效在处理的最后一天确定。为各组确定 MTV(n)，即此动物数量 n 的中值肿瘤体积，n 可在最后一天被评估。肿瘤生长抑制百分数 (%TGI) 可以以几种方式定义。首先，指定对照组的 MTV(n) 和药物处理组的 MTV(n) 之间的差值被表达为对照组的 MTV(n) 的百分比：

[3076]

$$\%TGI = \left(\frac{MTV(n)_{\text{对照}} - MTV(n)_{\text{处理}}}{MTV(n)_{\text{对照}}} \right) \times 100$$

[3077] 计算 %TGI 的另外一种方法是考虑从第 1 天到第 n 天肿瘤大小的变化，n 为处理的最后一天。

[3078]

$$\%TGI = \left(\frac{\Delta MTV_{对照} - \Delta MTV_{处理}}{\Delta MTV_{对照}}\right) \times 100$$

[3079]

$$\Delta MTV_{对照} = MTV(n)_{对照} - MTV(1)_{对照}$$

[3080]

$$\Delta MTV_{处理} = MTV(n)_{处理} - MTV(1)_{处理}$$

[3081] 肿瘤生长延迟分析

[3082] 可选地，为了肿瘤生长延迟分析，使小鼠在最后治疗日之后继续存活。肿瘤用测径器每周测量两次，当其瘤达到 2000mm^3 的终点体积时或在预先规定的研究的最后一天对每只试验用动物实施安乐死，无论哪一个先到。每只小鼠的到终点的时间 (TTE) 从下面的方程计算 ：

[3083]

$$TTE\ (\text{天数}) = \frac{log_{10}(\text{终点体积}, mm^3) - b}{m}$$

[3084] 其中，b 是截距，m 是通过肿瘤生长数据集的对数变换的线性回归获得的线的斜率。所述数据集由对超过研究终点体积的首次观察和三个连续的对直接领先达到的终点体积的观察组成。没有达到终点体积的动物被分配的 TTE 值等于研究的最后一天(预先规定的)。任何被分类为处理相关 (TR) 死亡的动物被分配的 TTE 值等于死亡日。任何被分类为非处理相关 (NTR) 死亡的动物从 TTE 计算和所有进一步的分析中排除。

[3085] 处理效果从肿瘤生长延迟 (TGD) 来确定，肿瘤生长延迟被定义为处理组与对照组相比的中值 TTE 的增加 ：

[3086] TGD ＝ T － C

[3087] 以天数或对照组的中值 TTE 的百分比表示 ：

[3088] $$\%TGD = \frac{T - C}{C} \times 100$$

[3089] 其中 ：

[3090] T= 处理组中值 TTE

[3091] C= 对照组中值 TTE

[3092] 毒性

[3093] 在第 1 - 5 天每天为动物称重，之后每周两次为动物称重直到研究结束。针对任何不利的、治疗相关的副作用的明显迹象对小鼠进行频繁地检查，并记录下来。对最大耐受剂量 (maximum tolerated dose，MTD) 的可接受的毒性定义为在试验期间由于 TR 死亡造成的、少于 20%、不多于 10% 的死亡率的组均体重损失。如果死亡归因于由临床症状和 / 或尸体剖检证明的处理副作用，或由于在给药期间的不明原因，那么死亡被归类为 TR。如果有证据表明死亡与处理副作用无关，那么死亡被归类为 NTR。给药间隔期间的 NTR 死亡通常将归

类为 NTRa（由于意外或人为失误)或 NTRm（由于尸体剖检确认的肿瘤通过入侵和 / 或转移散播)。当群组表现不支持 TR 分类且尸体解剖以排除给药剂量错误不可行时，在给药期间死于不明原因的口服处理的动物可以分为 NTRu。

[3094] 采样

[3095] 在研究期的数天以预先规定的方式对小鼠采样。取样包括在未麻醉条件下从下颌静脉采非末端血 (0.25mL) 和在 CO_2 麻醉条件下经末端心脏穿刺进行全血采集。对血液样本用 K2-EDTA 作为阻凝剂进行处理以获得血浆。在进行化合物水平的生物分析之前，将血浆样品在 -80℃下冷冻和保存。

[3096] 在无 RNA 酶的条件下从指定的小鼠收获肿瘤，并将其分为两份。将来自于每个肿瘤的一半的 2mm 厚度的切片用福尔马林固定 24h，转移到 70% 的乙醇中。固定的肿瘤组织嵌入石蜡。将来自于每只动物的剩下的肿瘤组织在液氮中快速冷冻，用研钵和研杵研磨成粉末。

[3097] 对特定的小鼠进行取样以获得替代组织，所述取代组织包括脾脏、皮肤、骨髓和腮须。将每个组织分离并固定和 / 或快速冷冻。

[3098] 统计和图形分析

[3099] 用 Windows 系统 Prism3.03（GraphPad）软件进行全部的统计和图形分析。采用了几种分析方法。中值 D29 肿瘤体积用克鲁斯卡尔 - 沃利斯(Kruskal-Wallis）检验和事后 Dunn 多项比较检验(post hoc Dunn's multiple comparison test)相比较。将这些检验进行三次。

[3100] 在 P=0.05 时进行双尾统计分析。Prism 以在 P>0.05 时为非显著的 (ns)，在 0.01<P<0.05 时为显著的（用符号“*”表示），在 0.001<P<0.01 时为非常显著的（“**”），在 P<0.001 时极其显著的（“***”）来报告结果。

[3101] 为了检验在整个处理期间对照组和处理组之间的统计显著性，采用重复测量方差分析(ANOVA）检验，然后再 Dunnets 多重比较效果检验或两因素方差分析检验。

[3102] 为了以图形表示，构建“盒须图”(“box and whiskers”）以显示每组的个体肿瘤体积的分布。盒代表观察值的 25% 至 75%，水平线对应中值，须线表明最大和最小值。中值或平均的 (±SEM) 肿瘤体积用作为时间函数的半对数图或线性图表示。在研究期间的组平均 BW 变化被绘制为从 D1 开始的变化百分数，±SEM。

[3103] 通过组构建散点图以显示 TTE 值。TTE 图包括从所有的其它图形分析中排除的 NTR 死亡。当动物由于肿瘤大小退出研究时，为动物记录的最终肿瘤体积包括在用于在随后的时间点计算中值体积的数据中。在研究中每组剩余的动物百分比对时间呈现在 Kaplan-Meier 存活图中。

[3104] 组蛋白提取

[3105] 为了组蛋白的分离，将 60-90mg 的肿瘤组织在 1.5ml 的核提取缓冲液(10mM Tris-HCl，10mM $MgCl_2$，25mM KCl，1%Triton X-100，8.6% 蔗糖，加上 Roche 蛋白酶抑制剂片剂 1836145）中匀浆，在冰上孵育 5 分钟。细胞核通过在 4℃、600g 的转速下离心 5 分钟收集，在 PBS 中洗涤一次。去除上清液，提取组蛋白一小时(每 15 分钟用 0.4N 冷硫酸震荡一次)。通过在 4℃、10000g 的转速下离心 10 分钟来净化提取物，转移到包括 10 倍体积的冰冷丙酮的新鲜的微量离心管中。在 -20℃下组蛋白沉淀 2 小时 - 过夜，通过在 10000g 的转

速下离心 10 分钟来获得沉淀并重悬于水。

[3106] 蛋白质印迹(Western Blot)分析

[3107] 酸提取的组蛋白的蛋白质浓度通过 BCA 法 (Pierce) 测定。400-800ng 的每种溶解物在 10-20% 的三甘氨酸凝胶 (Biorad 公司) 分离,用 iBlot(在程序 3 上 7 分钟,硝酸纤维素转移膜) 转移,用下列 Odyssey 封闭液中的抗体探测 :兔抗 H3K27me3 (CST9733 ;1:20000 稀释)和鼠抗总 H3 (CST3638 ;1:20000 稀释)。一抗孵育后,膜用 IRDye800CW 驴抗鼠 IgG(LiCOR#926-32212) 和 Alexa Fluor680 羊抗兔 IgG(Invitrogen 公司 #A-21076) 二抗进行探测,然后利用 LiCOR Odyssey 系统成像。

[3108] 酶联免疫吸附测定(ELISA)

[3109] 组蛋白在包被缓冲液(PBS+0.05%BSA)中以相同的浓度制备,得到了 0.5ng/μl 的样品,将 100μl 的样品或标准物成对地加入到两个 96 孔 ELISA 板(Thermo Labsystems 公司,Immulon4HBX#3885)中。将板密封,在 4℃孵育过夜。第二天,在 Bio Tek 洗板机中将板用 300μl/ 孔的 PBST (PBS+0.05% 吐温 20 ;10×PBST,KPL#51-14-02)洗涤 3 次。将板中反应用 300μl/ 孔的稀释剂(PBS+2%BSA+0.05% 吐温 20) 阻断,在室温下孵育 2 小时,用 PBST 洗涤 3 次。所有的抗体在稀释剂中稀释。将 100μl/ 孔的抗 H3K27me3 (CST#9733,50% 甘油母液 1:1000) 或抗总 H3 (Abcam ab1791,50% 甘油 1:10000) 加入到每个板中。在室温下将板孵育 90 分钟,用 PBST 洗涤 3 次。将 100μl/ 孔的抗 Rb-IgG-HRP (Cell Signaling Technology 公司,7074) 以 1:2000 加入到 H3K27Me3 板中,以 1:6000 加入到 H3 板中,并在室温下孵育 90 分钟。用 PBST 洗涤板 4 次。为了检测,加入 100μl/ 孔的 TMB 底物(BioFx Laboratories,#TMBS),将板在黑暗、室温下孵育 5 分钟。用 100μl/ 孔的 1N H2SO4 终止反应。在 SpectaMax M5 酶标仪上读取在 450nm 处的吸光度

[3110] 化合物 222 的体内试验结果在图 4 和图 5 中显示。图 4 显示具有 WSU-DLCL2 异种移植肿瘤的小鼠用化合物 222 处理 27 天后的肿瘤生长。在全部的 3 种剂量(100mg/kg(b.i.d.,27 天)、200mg/kg(b.i.d.,27 天) 和 400mg/kg(400mg/kg b.i.d.7 天,0mg/kg7 天和 300mg/kg b.i.d.,13 天)) 中观察到肿瘤生长抑制。图 5 显示在 WSU-DLCL2 肿瘤中对全局 H3K27me3 甲基化,所述肿瘤来自于用化合物 222 或载剂处理 27 天的小鼠。该图显示每一剂量组的 H3K27Me3 标记的减少。

[3111] 引用结合

[3112] 在此提及的所有专利文件和科学论文的全部公开内容通过引用结合于本文中以用于所有目的。

[3113] 等同

[3114] 本发明可以以其他具体形式体现而不脱离其精神或本质特征。因此,上述实施方式在所有方面都应认为是具有启示性的,而不仅限于在此描述的发明。因此,本发明的范围由所附的权利要求而不是前面的描述所表示,此外在权利要求的等同方案的含义和范围内的所有变化都将包含在本发明的范围内。

[0001]

YH1360824USP 序 列 表

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<150> 61/474,825
<151> 2011-04-13

<150> 61/505,676
<151> 2011-07-08

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<223> 其中生物素和酰胺是共轭的

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1 5 10 15

[0002]

Lys Pro His Arg Tyr Arg Pro Gly Gly Lys
20 25

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<223> 其中生物素和酰胺是共轭的

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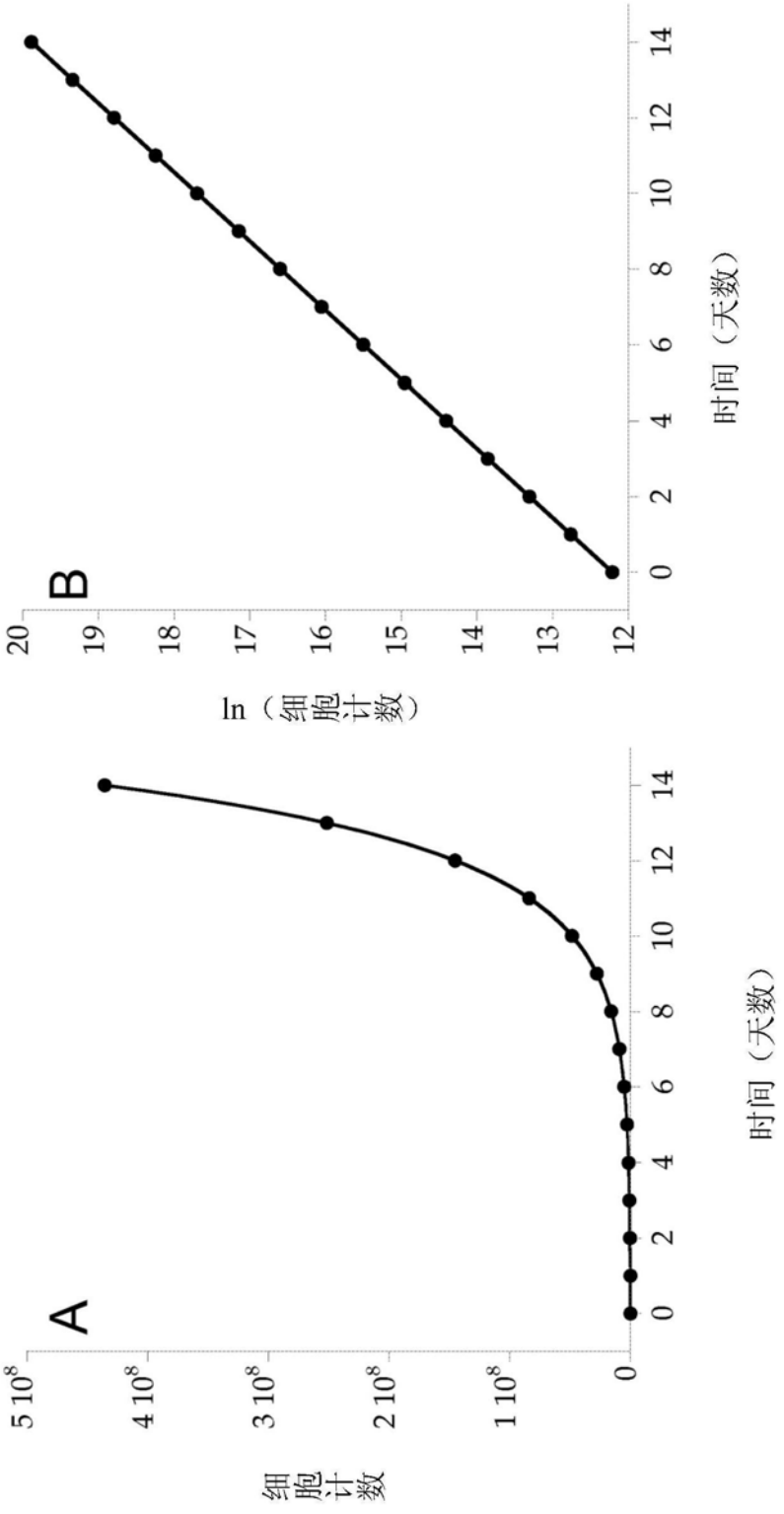
1 5 10 15

Lys Pro His Arg Tyr Arg Pro Gly Gly Lys
20 25


B
20
19
18
17
16
15
14
13
12
ln（细胞计数）
0
2
4
6
8
10
12
14
时间（天数）
A
5 10^8
4 10^8
3 10^8
2 10^8
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细胞计数
0
2
4
6
8
10
12
14
时间（天数）

图 1

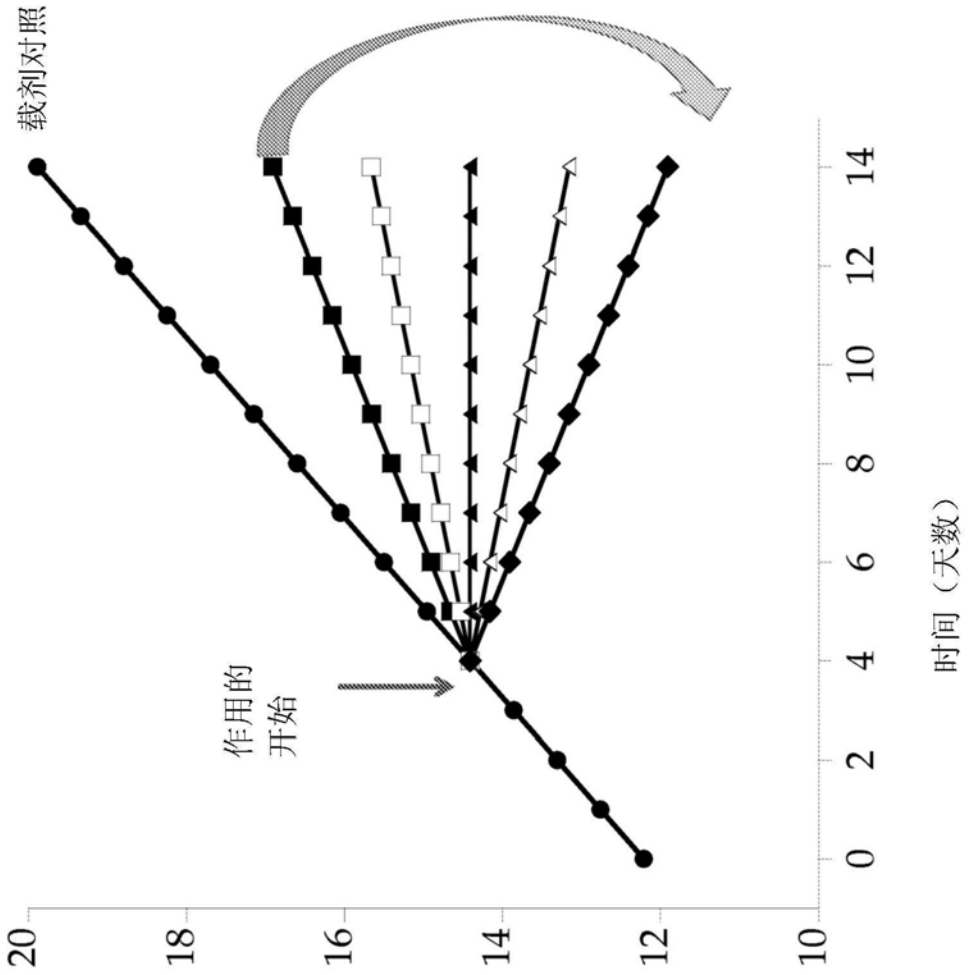
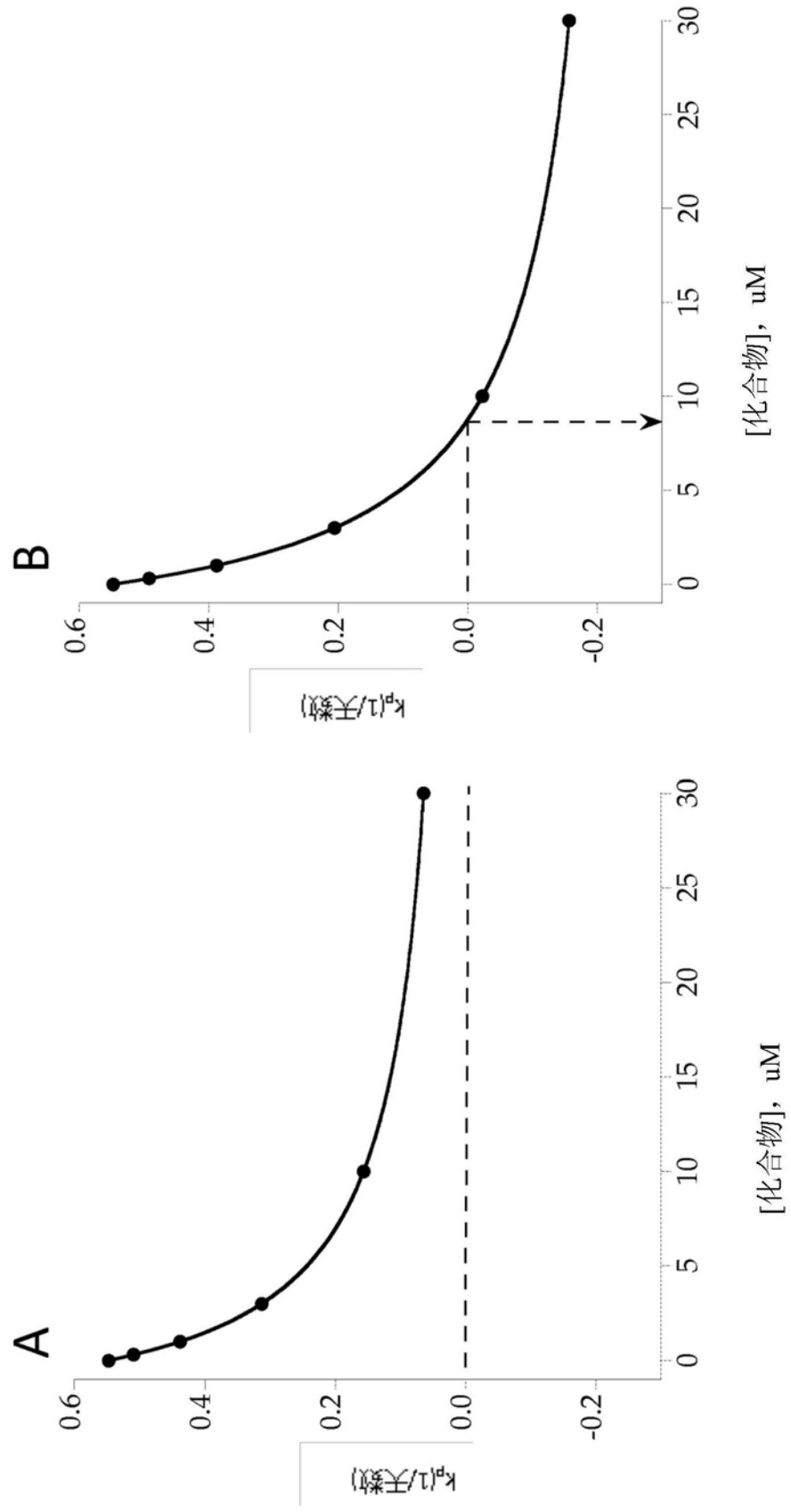


图 2



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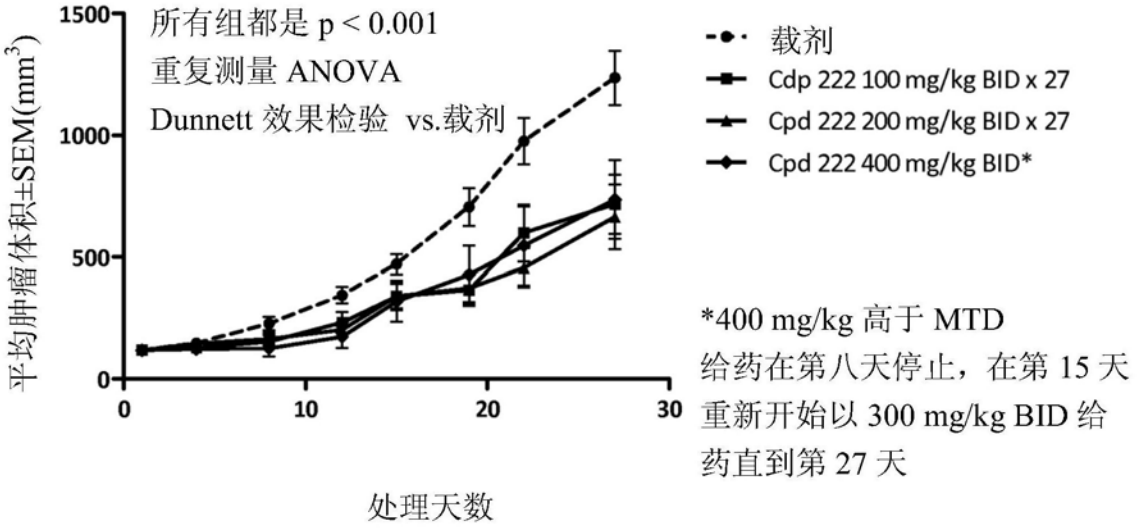
所有组都是 p < 0.001
重复测量 ANOVA
Dunnett 效果检验 vs.载剂
平均肿瘤体积±SEM(mm3)
1500
1000
500
0
0
10
20
30
处理天数
载剂
Cdp 222 100 mg/kg BID x 27
Cpd 222 200 mg/kg BID x 27
Cpd 222 400 mg/kg BID*
*400 mg/kg 高于 MTD
给药在第八天停止，在第 15 天
重新开始以 300 mg/kg BID 给
药直到第 27 天

图 4

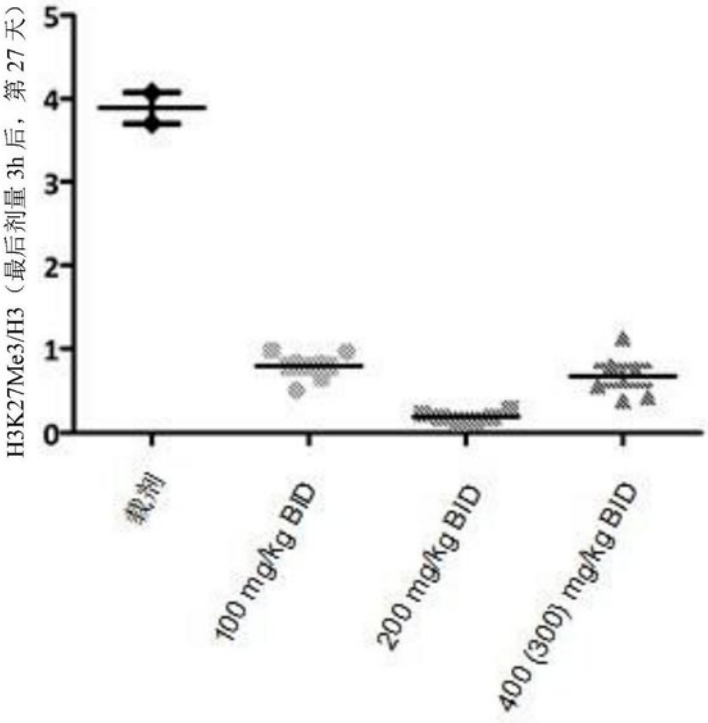
H3K27Me3/H3（最后剂量 3h 后，第 27 天）
5
4
3
2
1
0
载剂
100 mg/kg BID
200 mg/kg BID
400 (300) mg/kg BID

图 5

Abstract

The present invention relates to substituted benzene compounds. The present invention also relates to pharmaceutical compositions containing these compounds and methods of treating cancer by administering these compounds and pharmaceutical compositions to subjects in need thereof. The present invention also relates to the use of such compounds for research or other non-therapeutic purposes.