



(51) International Patent Classification:

C07D 413/14 (2006.01) A61K 31/444 (2006.01)

A61K 31/4245 (2006.01)

(21) International Application Number:

PCT/US2017/038068

(22) International Filing Date:

19 June 2017 (19.06.2017)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/353,833 23 June 2016 (23.06.2016) US

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(81) Designated States (unless otherwise indicated, for every

kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA,

SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every

kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

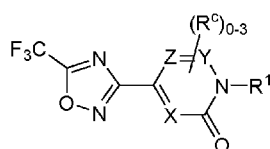
Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

(54) Title: 3- HETEROARYL SUBSTITUTED 5-TRIFLUOROMETHYL OXADIAZOLES AS HISTONE DEACETYLASE 6 (HDAC6) INHIBITORS



(I)

(57) Abstract: The present invention is directed to substituted 5-trifluoromethyl oxadiazole compounds of generic formula (I) (I) or a pharmaceutically acceptable salt thereof. In particular, the invention is directed to a class of heteroaryl substituted 5-trifluoromethyl oxadiazole compounds of formula I which may be useful as HDAC6 inhibitors for treating cellular proliferative diseases, including cancer, neurodegenerative diseases, such as schizophrenia and stroke, as well as other diseases.



TITLE OF THE INVENTION

3- HETEROARYL SUBSTITUTED 5-TRIFLUOROMETHYL OXADIAZOLES AS HISTONE DEACETYLASE 6 (HDAC6) INHIBITORS

5 BACKGROUND OF THE INVENTION

Histone deacetylases (HDACs) and histone acetyl transferases (HATs) determine the pattern of histone acetylation, which together with other dynamic sequential post-translational modifications might represent a 'code' that can be recognised by non-histone proteins forming complexes involved in the regulation of gene expression. This and the ability of histone deacetylases (HDACs) to also modify non-histonic substrates and participate in multi-protein complexes contributes to the regulation of gene transcription, cell cycle progression and differentiation, genome stability and stress responses.

Eleven members of the HDAC family have been identified in humans, which share a conserved catalytic domain and are grouped into two classes: class I (1, 2, 3, 8), homologous to yeast Rpd3; class IIa (4, 5, 7, 9) and IIb (6, 10), homologous to yeast Hda1. HDAC11 shares homologies with both classes, but is at the same time distinct from all the other ten subtypes. Interest in these enzymes is growing because HDAC inhibitors (HDACi) are promising therapeutic agents against cancer and other diseases. The first generation of HDACi were discovered from cell-based functional assays and only later identified as HDAC class I/II inhibitors. Present HDAC inhibitors are pan-specific or poorly selective. Those that entered clinical trials all show similar adverse effects, mainly fatigue, anorexia, hematologic and GI-toxicity, that becomes dose-limiting in clinical trials.

HDAC6 is one of the best characterized deacetylase enzymes regulating many important biological processes via the formation of complexes with specific client proteins. In contrast to other deacetylases, HDAC6 has unique substrate specificity for nonhistone proteins such as α -tubulin, Hsp90, cortactin and peroxiredoxins. The diverse function of HDAD6 in conjunction with published data over the past few years suggest it could serve as a potential therapeutic target for the treatment of a wide range of diseases and may be overexpressed or deregulated in various cancers, neurodegenerative diseases and inflammatory disorders. Despite extensive efforts, very few HDAC6-selective inhibitors have been identified. The majority of the reported compounds use the hydroxamic acid pharmacophore as the zinc-binding group. See WO2013080120, WO2013008162, WO2013066835, WO2013066839, WO2013066831, WO2013066833, WO2013006408, WO2011088192, WO2011088181, J. Kalin et al., J. Med Chem 2013, 56, 6297-6313; and Simoes-Pires, et al., Molecular Neurodegeneration 2013 8:7. See also WO2016031815 containing compounds that have not used the hydroxamic acid pharmacophore as the zinc-binding group.

To date, HDAC inhibitors that have been approved for use by the FDA can be divided into two categories: 1) non-selective pan HDAC inhibitors such as vorinostat (SAHA); and 2) HDAC inhibitors

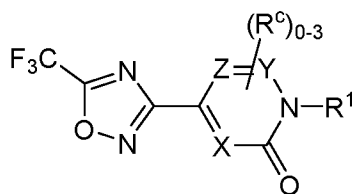
such as entinostat that only target Class I HDACs. The potential advantage of isoform-selective inhibitors over pan-HDAC inhibitors is based both in terms of efficacy and toxicity. The development of potent and highly selective HDAC inhibitors would be critical for better understanding of the cellular pathways related to their therapeutic effects, while also providing a reasonable basis to explore synergistic interactions with other clinically active compounds. It is also valuable because it is expected that the selective inhibition of a mostly cytoplasmic HDAC6 should avoid toxicity resulting from inhibition of other HDACs mainly involved in epigenetic modulation.

SUMMARY OF THE INVENTION

The invention is directed to a class of heteroaryl substituted 5-trifluoromethyl oxadiazole compounds of formula I below, their salts, pharmaceutical compositions comprising them, diagnostic and therapeutic uses and processes for making such compounds. In particular, the invention is directed to a class of heteroaryl substituted 5-trifluoromethyl oxadiazole compounds of formula I which may be useful as HDAC6 inhibitors for treating cellular proliferative diseases, including cancer, neurodegenerative diseases, such as schizophrenia and stroke, as well as other diseases. Uses for the claimed compounds include treating autoimmune diseases and/or inflammatory diseases (e.g., inflammatory bowel disease, rheumatoid arthritis, psoriasis, multiple sclerosis, Sjogren's syndrome, Behcet's disease, systemic erythematodes etc), graft-versus-host disease (GvHD), cellular proliferative diseases, including cancer (e.g., multiple myeloma, leukemia, uterus smooth muscle sarcoma, prostate cancer, intestinal cancer, lung cancer, cachexia, bone marrow fibrosis, etc.), central nervous system diseases, including neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, schizophrenia and stroke, amongst other diseases.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to substituted 5-trifluoromethyl oxadiazole compounds of generic formula (I)



(I)

or a pharmaceutically acceptable salt thereof wherein;

X, Y, and Z independently represent CH, or N;

R^1 represents hydrogen, C_{1-6} alkyl, $-(C(R^2)_2)_pC_{4-10}$ heterocyclyl, $-(C(R^2)_2)_pC_{6-10}$ aryl, $-(C(R^2)_2)_pOC_{6-10}$ aryl, $-(C(R^2)_2)_pNRC(O)(C(R^2)_2)_pC_{6-10}$ aryl, $-(C(R^2)_2)_pNR^2C(O)(C(R^2)_2)_pC_{4-10}$ heterocyclyl, $-(C(R^2)_2)_pNRC(O)N(R^2)_2$, $-(C(R^2)_2)_pN(R^2)_2$, $-(C(R^2)_2)_pOR^a$, $-(C(R^2)_2)_pC(O)R^a$, $-(C(R^2)_2)_pC(O)N(R^2)_2$, or $-(C(R^2)_2)_pC_{3-6}$ cycloalkyl, said alkyl, cycloalkyl, aryl, and heterocyclyl optionally substituted with 1 to 3 groups of R^a ;

R represents hydrogen, or $-C_{1-6}$ alkyl, said alkyl optionally substituted with 1 to 3 groups of R^a ;

each R^2 independently selected from hydrogen, halo, $N(R)_2$, $NHC(O)OR$, $-C(O)ON(R)_2$, $-C(O)OR$, $-(CH_2)_pC_{6-10}$ aryl, $-(CH_2)_pC_{4-10}$ heterocyclyl, $-C(O)C_{4-10}$ heterocyclyl, $-OR$, or $-C_{1-6}$ alkyl, said alkyl, aryl, heterocyclyl, optionally substituted with 1 to 3 groups of R^a ;

R^a is selected from the group consisting of H , $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $=O$, $-C_{3-6}$ cycloalkyl, $-OR$, $-C_{1-6}$ alkylOR, $-O_{0-1}C_{1-4}$ haloalkyl, $-(CH_2)_pC_{6-10}$ aryl; $-(CH_2)_pC_{5-10}$ heterocyclyl, $-C(O)C_{1-6}$ alkyl, $C(O)OR$, $-NHC(O)OC_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $C(O)NH(CH_2)_pC_{6-10}$ aryl, $C(O)(CH_2)_pC_{6-10}$ heterocyclyl, $N(R)_2$, CN , halo, $-SO_{0-2}C_{1-6}$ alkyl, $C(O)N(R)_2$, said alkyl, cycloalkyl, aryl, and heterocyclyl optionally substituted with 1 to 3 groups of R^b ;

R^b is selected from the group consisting of C_{1-6} alkyl, OR , C_{1-4} haloalkyl, $-OC_{1-4}$ haloalkyl, and halo;

R^c is halo or C_{1-6} alkyl and

p represents 0-4.

An embodiment of this invention is realized when X , Y , Z are CH .

An embodiment of this invention is realized when X is N and Y and Z are CH .

An embodiment of this invention is realized when X and Z are CH , and Y is N .

An embodiment of this invention is realized when X and Y are CH and Z is N .

An embodiment of this invention is realized when no more than one of X , Y and Z are N at the same time.

An embodiment of this invention is realized when no more than two of X , Y and Z are N at the same time.

An embodiment of this invention is realized when R^c is not present.

An embodiment of this invention is realized when only 1 R^c is present.

An embodiment of this invention is realized when two R^c are present.

An embodiment of this invention is realized when R^1 is H .

An embodiment of this invention is realized when R^1 is not H .

An embodiment of this invention is realized when R^1 is unsubstituted or substituted C_{1-6} alkyl. A subembodiment of this aspect of the invention is realized when the C_{1-6} alkyl of R^1 is unsubstituted. A

subembodiment of this aspect of the invention is realized when R^1 is substituted with 1 to 3 groups of groups of R^a . Another subembodiment of this aspect of the invention is realized when the R^a substituent on the C_{1-6} alkyl of R^1 is selected from the group consisting of OR, C_{1-6} alkyl, $C(O)OC_{1-6}$ alkyl, and $N(R)_2$, said alkyl, optionally substituted with 1 to 3 groups of R^b .

Another embodiment of this invention is realized when R^1 is $-(C(R^2)_2)_pC(O)R^a$, and the R^a of $-(C(R^2)_2)_pC(O)R^a$ is selected from the group consisting of $-(CH_2)_pC_{6-10}$ aryl, $-(CH_2)_pC_{5-10}$ heterocyclyl, and $N(R)_2$, said aryl and heterocyclyl optionally substituted with 1 to 3 groups of R^b . A subembodiment of this aspect of the invention is realized when the R^a of $-(C(R^2)_2)_pC(O)R^a$ is selected from the group consisting of NH_2 , $NHCH_3$, $N(CH_3)_2$, $NCH_3C(CH_3)_3$, and optionally substituted phenyl, dihydroisoquinoliny, and pyrrolidiny. A subembodiment of this aspect of the invention is realized when the R^a of $-(C(R^2)_2)_pC(O)R^a$ is selected from the group consisting of NH_2 , $NHCH_3$, $N(CH_3)_2$, and $NCH_3C(CH_3)_3$. Another subembodiment of this aspect of the invention is realized when the R^a of $-(C(R^2)_2)_pC(O)R^a$ is optionally substituted phenyl. A subembodiment of this aspect of the invention is realized when the R^a of $-(C(R^2)_2)_pC(O)R^a$ is optionally substituted pyrrolidiny.

Another embodiment of this invention is realized when R^1 is $-(C(R^2)_2)_pOR^a$ and the R^a of $-(C(R^2)_2)_pOR^a$ is selected from the group consisting of $-(CH_2)_pC_{6-10}$ aryl, and $-(CH_2)_pC_{5-10}$ heterocyclyl, said aryl and heterocyclyl optionally substituted with 1 to 3 groups of R^b . A subembodiment of this aspect of the invention is realized when the R^a of $-(C(R^2)_2)_pOR^a$ is selected from the group consisting of unsubstituted or substituted phenyl and naphthaleny.

Another embodiment of this invention is realized when R^1 is $-(C(R^2)_2)_pC_{3-6}$ cycloalkyl, said cycloalkyl unsubstituted or substituted with 1 to 3 groups of R^a . A subembodiment of this aspect of the invention is realized when the cycloalkyl of R^1 is selected from the group consisting of unsubstituted or substituted cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. A subembodiment of this aspect of the invention is realized when the cycloalkyl of R^1 is optionally substituted cyclohexyl. A subembodiment of this aspect of the invention is realized when the cycloalkyl of R^1 is optionally substituted cyclopropyl. A subembodiment of this aspect of the invention is realized when the cycloalkyl of R^1 is optionally substituted cyclopentyl.

An embodiment of this invention is realized when R^1 represents unsubstituted or substituted $-(C(R^2)_2)_pOC_{6-10}$ aryl, $-(C(R^2)_2)_pC_{6-10}$ aryl or $-(C(R^2)_2)_pNRC(O)(C(R^2)_2)_pC_{6-10}$ aryl. A subembodiment of this aspect of the invention is realized when the aryl is selected from the group consisting of unsubstituted or substituted phenyl and naphthyl. A further subembodiment of this aspect of the invention is realized when the aryl is unsubstituted or substituted phenyl. A still further subembodiment of this aspect of the invention is realized when the aryl is unsubstituted or substituted naphthyl. A further subembodiment of this aspect of the invention is realized when the p in $-(C(R^2)_2)_pOC_{6-10}$ aryl, $-(C(R^2)_2)_pC_{6-10}$ aryl and $-(C(R^2)_2)_pNRC(O)(C(R^2)_2)_pC_{6-10}$ aryl is 1, 2, or 3, preferably 1 or 2. A further subembodiment of this aspect of the invention is realized when each R^2 in $-(C(R^2)_2)_pOC_{6-10}$ aryl, $-(C(R^2)_2)_pC_{6-10}$ aryl and $-(C(R^2)_2)_pNRC(O)(C(R^2)_2)_pC_{6-10}$ aryl is selected from

H or CH₃. Another subembodiment of this aspect of the invention is realized when the substituents of $-(C(R^2)_2)_pOC_{6-10}aryl$, $(C(R^2)_2)_pC_{6-10}aryl$ and $-(C(R^2)_2)_pNRC(O)(C(R^2)_2)_pC_{6-10}aryl$ are selected from the group consisting of C₁₋₆alkyl, -O-, -C₃₋₆cycloalkyl, -OR, -C₁₋₆alkylOR, -O₀₋₁C₁₋₄haloalkyl, $-(CH_2)_pC_{6-10}aryl$; $-(CH_2)_pC_{5-10}heterocyclyl$, $-C(O)C_{1-6}alkyl$, $C(O)OC_{1-6}alkyl$, -N(R)₂, halo, -SC₁₋₆alkyl, said alkyl, aryl, and heterocyclyl optionally substituted with 1 to 3 groups of R^b. Still another subembodiment of this aspect of the invention is realized when the substituents of $-(C(R^2)_2)_pOC_{6-10}aryl$, $-(C(R^2)_2)_pC_{6-10}aryl$ and $-(C(R^2)_2)_pNRC(O)(C(R^2)_2)_pC_{6-10}aryl$ are selected from the group consisting of halo, CH₃, CH₂OH, OH, OCH₃, OCF₃, SCH₃, N(CH₃)₂, NH₂, and optionally substituted cyclopropyl, piperidiny, pyrazolyl, pyrimidinyl, imidazolyl, (CH₂)_pphenyl, and pyrrolidinyl. Yet another subembodiment of this aspect of the invention is realized when the substituents of $-(C(R^2)_2)_pOC_{6-10}aryl$, $-(C(R^2)_2)_pC_{6-10}aryl$ and $-(C(R^2)_2)_pNRC(O)(C(R^2)_2)_pC_{6-10}aryl$ are selected from the group consisting of halo, CH₃, OCH₃, OCF₃, N(CH₃)₂, NH₂, and optionally substituted cyclopropyl, and (CH₂)_pphenyl.

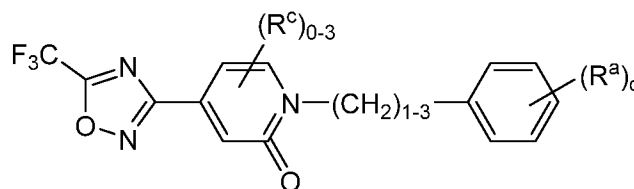
An embodiment of this invention is realized when R¹ represents unsubstituted or substituted $-(C(R^2)_2)_pC_{4-10}heterocyclyl$ or $(C(R^2)_2)_pNR^2C(O)(C(R^2)_2)_pC_{4-10}heterocyclyl$. Another embodiment of this invention is realized when R¹ represents unsubstituted or substituted $-(C(R^2)_2)_pC_{4-10}heterocyclyl$. Still another embodiment of this invention is realized when R¹ represents unsubstituted or substituted $(C(R^2)_2)_pNR^2C(O)(C(R^2)_2)_pC_{4-10}heterocyclyl$. A subembodiment of this aspect of the invention is realized when the heterocyclyl of $-(C(R^2)_2)_pC_{4-10}heterocyclyl$ and $(C(R^2)_2)_pNR^2C(O)(C(R^2)_2)_pC_{4-10}heterocyclyl$ is selected from the group consisting of unsubstituted or substituted indazolyl, quinoxaliny, quinoliny, benzthiazolyl, benzimidazolyl, benztriazolyl, pyrazolyl, indoliny, pyrazolopyridiny, pyraziny, dihydroisobenzofurany, oxadiazolyl, benzdioxalyl, isoxazolyl, thienopyridiny, oxazolyl, thiazolyl, triazolopyridiny, pyridyl, piperidiny, imidazopyridiny, triazolyl, tetrahydropyrany, tetrahydrotriazolyl, pyrimidinyl, pyridazinyl, dihydroisoquinoliny, pyrrolidinyl, morpholiny, imidazolyl, dihydropyrrolotriazolyl, tetrahydroimidazopiperidiny, tetrahydrotriazolopyridiny, imidazolothiazolyl, piperazinyl, indolyl, and oxetany. A further subembodiment of this aspect of the invention is realized when the heterocyclyl is unsubstituted or substituted indazolyl. A further subembodiment of this aspect of the invention is realized when the heterocyclyl is unsubstituted or substituted quinoliny. A further subembodiment of this aspect of the invention is realized when the heterocyclyl is unsubstituted or substituted benzothiazolyl. A further subembodiment of this aspect of the invention is realized when the heterocyclyl is unsubstituted or substituted benzimidazolyl. A further subembodiment of this aspect of the invention is realized when the heterocyclyl is unsubstituted or substituted pyrazolyl. A further subembodiment of this aspect of the invention is realized when the heterocyclyl is unsubstituted or substituted indolyl. A further subembodiment of this aspect of the invention is realized when the heterocyclyl is unsubstituted or substituted pyrazolopyridiny. A further subembodiment of this aspect of the invention is realized when the heterocyclyl is unsubstituted or substituted pyraziny. A further subembodiment of this aspect of the invention is realized when the heterocyclyl is unsubstituted or substituted oxadiazolyl. A further

subembodiment of this aspect of the invention is realized when the heterocyclyl is unsubstituted or substituted isoxazolyl. A further subembodiment of this aspect of the invention is realized when the heterocyclyl is unsubstituted or substituted oxazolyl. A further subembodiment of this aspect of the invention is realized when the heterocyclyl is unsubstituted or substituted pyridinyl. A further subembodiment of this aspect of the invention is realized when the heterocyclyl is unsubstituted or substituted piperidinyl. A further subembodiment of this aspect of the invention is realized when the heterocyclyl is unsubstituted or substituted pyrimidinyl. A further subembodiment of this aspect of the invention is realized when the heterocyclyl is unsubstituted or substituted imidazolyl. A further subembodiment of this aspect of the invention is realized when the heterocyclyl is unsubstituted or substituted pyrrolidinyl. A further subembodiment of this aspect of the invention is realized when the heterocyclyl is unsubstituted or substituted morpholinyl. A further subembodiment of this aspect of the invention is realized when the p in $-(C(R^2)_2)_pC_{4-10}$ heterocyclyl and $(C(R^2)_2)_pNR^2C(O)(C(R^2)_2)_pC_{4-10}$ heterocyclyl is 1, 2, or 3, preferably 1 or 2. A further subembodiment of this aspect of the invention is realized when each R^2 in $-(C(R^2)_2)_pC_{4-10}$ heterocyclyl and $(C(R^2)_2)_pNR^2C(O)(C(R^2)_2)_pC_{4-10}$ heterocyclyl is selected from H or CH_3 . Another subembodiment of this aspect of the invention is realized when the substituents of the heterocyclyl of $-(C(R^2)_2)_pC_{4-10}$ heterocyclyl and $(C(R^2)_2)_pNR^2C(O)(C(R^2)_2)_pC_{4-10}$ heterocyclyl are selected from the group consisting of C_{1-6} alkyl, $-O-$, $-C_{3-6}$ cycloalkyl, $-OR$, $-C_{1-6}$ alkylOR, $-O_{0-1}C_{1-4}$ haloalkyl, $-(CH_2)_pC_{6-10}$ aryl; $-(CH_2)_pC_{5-10}$ heterocyclyl, $-C(O)C_{1-6}$ alkyl, $C(O)OC_{1-6}$ alkyl, $-N(R)_2$, halo, $-SC_{1-6}$ alkyl, said alkyl, aryl, and heterocyclyl optionally substituted with 1 to 3 groups of R^b . Still another subembodiment of this aspect of the invention is realized when the substituents of the heterocyclyl of $-(C(R^2)_2)_pC_{4-10}$ heterocyclyl and $(C(R^2)_2)_pNR^2C(O)(C(R^2)_2)_pC_{4-10}$ heterocyclyl are selected from the group consisting of halo, CH_3 , CH_2OH , OH , OCH_3 , OCF_3 , SCH_3 , $N(CH_3)_2$, NH_2 , and optionally substituted cyclopropyl, piperidinyl, pyrazolyl, pyrimidinyl, imidazolyl, $(CH_2)_p$ phenyl, and pyrrolidinyl. Yet another subembodiment of this aspect of the invention is realized when the substituents of the heterocyclyl of $-(C(R^2)_2)_pC_{4-10}$ heterocyclyl and $(C(R^2)_2)_pNR^2C(O)(C(R^2)_2)_pC_{4-10}$ heterocyclyl are selected from the group consisting of halo, CH_3 , OCH_3 , OCF_3 , $N(CH_3)_2$, NH_2 , and optionally substituted cyclopropyl, and $(CH_2)_p$ phenyl.

An embodiment of this invention is realized when R^1 represents $-(C(R^2)_2)_pNRC(O)N(R^2)_2$.

An embodiment of this invention is realized when R^1 represents $-(C(R^2)_2)_pC(O)N(R^2)_2$.

Another embodiment of the claimed invention of formula I is realized by structural formula II:



II

or a pharmaceutically acceptable salt thereof, wherein q is 0-3.

A subembodiment of the invention of formula II is realized when q is 0 and R^a is absent. Another subembodiment of the invention of formula II is realized when q is 1. Another subembodiment of the invention of formula II is realized when q is 2. Another subembodiment of the invention of formula II is realized when q is 3.

Another subembodiment of the invention of formula II is realized when R^c is absent.

Another subembodiment of the invention of formula II is realized when one R^c is present.

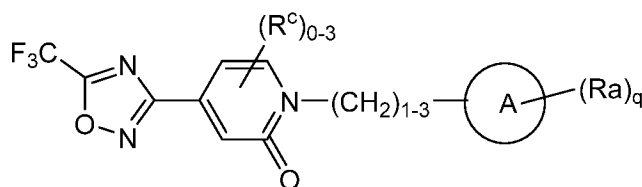
Another subembodiment of the invention of formula II is realized when only one (CH₂) group links the pyridinone and phenyl groups. Still another subembodiment of the invention of formula II is realized when two (CH₂) groups link the pyridinone and phenyl groups. Still another subembodiment of the invention of formula II is realized when three (CH₂) groups link the pyridinone and phenyl groups.

Another subembodiment of the invention of formula II is realized when R^a is selected from the group consisting of halo, CH₃, CH₂OH, OH, OCH₃, OCF₃, SCH₃, N(CH₃)₂, NH₂, and optionally substituted cyclopropyl, piperidinyl, pyrazolyl, pyrimidinyl, imidazolyl, (CH₂)_pphenyl, and pyrrolidinyl.

Still another subembodiment of the invention of formula II is realized when R^a is 1 or 2, one (CH₂) group links the pyridinone and phenyl groups, and R^a is selected from the group consisting of halo, CH₃, CH₂OH, OH, OCH₃, OCF₃, SCH₃, N(CH₃)₂, NH₂, and optionally substituted cyclopropyl, piperidinyl, pyrazolyl, pyrimidinyl, imidazolyl, (CH₂)_pphenyl, and pyrrolidinyl.

Still another subembodiment of the invention of formula II is realized when R^a is 1 or 2, two (CH₂) group link the pyridinone and phenyl groups, and R^a is selected from the group consisting of halo, CH₃, CH₂OH, OH, OCH₃, OCF₃, SCH₃, N(CH₃)₂, NH₂, and optionally substituted cyclopropyl, piperidinyl, pyrazolyl, pyrimidinyl, imidazolyl, (CH₂)_pphenyl, and pyrrolidinyl.

Another embodiment of the claimed invention of formula I is realized by structural formula III:



III

or a pharmaceutically acceptable salt thereof, wherein q is 0-3, R^a is as originally defined and A is C₄-10 heterocyclyl.

Another subembodiment of the invention of formula III is realized when R^c is absent.

Another subembodiment of the invention of formula III is realized when one R^c is present.

A subembodiment of the invention of formula III is realized when A is selected from the group consisting of unsubstituted or substituted indazolyl, quinoxaliny, quinolinyl, benzthiazolyl, benzimidazolyl, benztriazolyl, pyrazolyl, indolinyl, pyrazolopyridinyl, pyrazinyl,

dihydroisobenzofuranyl, oxadiazolyl, benzodioxolyl, isoxazolyl, thienopyridinyl, oxazolyl, thiazolyl, triazolopyridinyl, pyridyl, piperidinyl, imidazopyridinyl, triazolyl, tetrahydropyranyl, tetrahydrotriazolyl, pyrimidinyl, pyridazinyl, dihydroisoquinolinyl, pyrrolidinyl, morpholinyl, imidazolyl, dihydropyrrolotriazolyl, tetrahydroimidazopiperidinyl, tetrahydrotriazolopyridinyl, imidazothiazolyl, piperazinyl, indolyl, and oxetanyl. Still another subembodiment of this aspect of the invention is realized when A is unsubstituted or substituted indazolyl, quinolinyl, benzimidazolyl, pyrazolyl, oxadiazolyl, isoxazolyl, pyridinyl, pyrimidinyl, pyrrolidinyl, and imidazolyl. A further subembodiment of this aspect of the invention is realized when A is unsubstituted or substituted indazolyl. A further subembodiment of this aspect of the invention is realized when A is unsubstituted or substituted quinolinyl. A further subembodiment of this aspect of the invention is realized when A is unsubstituted or substituted benzimidazolyl. A further subembodiment of this aspect of the invention is realized when A is unsubstituted or substituted pyrazolyl. A further subembodiment of this aspect of the invention is realized when A is unsubstituted or substituted oxadiazolyl. A further subembodiment of this aspect of the invention is realized when A is unsubstituted or substituted isoxazolyl. A further subembodiment of this aspect of the invention is realized when A is unsubstituted or substituted pyridinyl. A further subembodiment of this aspect of the invention is realized when A is unsubstituted or substituted pyrimidinyl. A further subembodiment of this aspect of the invention is realized when A is unsubstituted or substituted imidazolyl. A further subembodiment of this aspect of the invention is realized when A is unsubstituted or substituted pyrrolidinyl. Another subembodiment of this aspect of the invention of formula III is realized when the substituent is R^a selected from the group consisting of C_1 -6alkyl, =O, - C_3 -6cycloalkyl, -OR, - C_1 -6alkylOR, - $O_{0-1}C_1$ -4haloalkyl, -(CH₂)_p C_6 -10 aryl; -(CH₂)_p C_5 -10 heterocyclyl, -C(O) C_1 -6alkyl, C(O)OC C_1 -6alkyl, -N(R)₂, halo, -SC C_1 -6alkyl, said alkyl, aryl, and heterocyclyl optionally substituted with 1 to 3 groups of R^b . Still another subembodiment of this aspect of the invention of formula III is realized when the substituent is R^a selected from the group consisting of halo, CH₃, CH₂OH, OH, OCH₃, OCF₃, SCH₃, N(CH₃)₂, NH₂, and optionally substituted cyclopropyl, piperidinyl, pyrazolyl, pyrimidinyl, imidazolyl, (CH₂)_pphenyl, and pyrrolidinyl.

A subembodiment of the invention of formula III is realized when q is 0 and R^a is absent. Another subembodiment of the invention of formula III is realized when q is 1. Another subembodiment of the invention of formula III is realized when q is 2. Another subembodiment of the invention of formula III is realized when q is 3.

Another subembodiment of the invention of formula III is realized when only one (CH₂) group links the pyridinone and A. Still another subembodiment of the invention of formula III is realized when two (CH₂) groups link the pyridinone and A. Still another subembodiment of the invention of formula II is realized when three (CH₂) groups link the pyridinone and A.

Still another subembodiment of the invention of formula III is realized when q is 1 or 2, one (CH₂) group links the pyridinone and A, A is selected from the group consisting of unsubstituted or substituted indazolyl, quinolinyl, benzimidazolyl, pyrazolyl, oxadiazolyl, isoxazolyl, pyridinyl, pyrimidinyl, pyrrolidinyl, morpholinyl, and imidazolyl and R^a is selected from the group consisting of

halo, CH₃, CH₂OH, OH, OCH₃, OCF₃,SCH₃, N(CH₃)₂, NH₂, and optionally substituted cyclopropyl, piperidinyl, pyrazolyl, pyrimidinyl, imidazolyl, (CH₂)_pphenyl, and pyrrolidinyl.

Still another subembodiment of the invention of formula III is realized when q is 1 or 2, two (CH₂) groups link the pyridinone and A, A is selected from the group consisting of unsubstituted or substituted indazolyl, quinolinyl, benzimidazolyl, pyrazolyl, oxadiazolyl, isoxazolyl, pyridinyl, pyrimidinyl, pyrrolidinyl, morpholinyl, and imidazolyl and R^a is selected from the group consisting of halo, CH₃, CH₂OH, OH, OCH₃, OCF₃,SCH₃, N(CH₃)₂, NH₂, and optionally substituted cyclopropyl, piperidinyl, pyrazolyl, pyrimidinyl, imidazolyl, (CH₂)_pphenyl, and pyrrolidinyl.

Still another subembodiment of the invention of formula III is realized when q is 1 or 2, three (CH₂) groups link the pyridinone and A, A is selected from the group consisting of unsubstituted or substituted indazolyl, quinolinyl, benzimidazolyl, pyrazolyl, oxadiazolyl, isoxazolyl, pyridinyl, pyrimidinyl, pyrrolidinyl, morpholinyl, and imidazolyl and R^a is selected from the group consisting of halo, CH₃, CH₂OH, OH, OCH₃, OCF₃,SCH₃, N(CH₃)₂, NH₂, and optionally substituted cyclopropyl, piperidinyl, pyrazolyl, pyrimidinyl, imidazolyl, (CH₂)_pphenyl, and pyrrolidinyl.

The compounds of the present invention may have asymmetric centers, chiral axes and chiral planes, and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers, including optical isomers, being included in the present invention. (See E.L. Eliel and S.H. Wilen *Stereochemistry of Carbon Compounds* (John Wiley and Sons, New York 1994), in particular pages 1119-1190)

Absolute stereochemistry is illustrated by the use of hashed and solid wedge bonds. As shown in Illus-I and Illus-II. Accordingly, the methyl group of Illus-I is emerging from the page of the paper and the ethyl group in Illus-II is descending into the page, where the cyclohexene ring resides within the plane of the paper. It is assumed that the hydrogen on the same carbon as the methyl group of Illus-I descends into the page and the hydrogen on the same carbon as the ethyl group of Illus-II emerges from the page. The convention is the same where both a hashed and solid rectangle are appended to the same carbon as in Illus-III, the Methyl group is emerging from the plane of the paper and the ethyl group is descending into the plane of the paper with the cyclohexene ring in the plane of the paper.



As is conventional, unless otherwise noted in accompanying text, ordinary "stick" bonds or "wavy" bonds indicate that all possible stereochemistry is represented, including, pure compounds, mixtures of isomers, and racemic mixtures.

As described herein, unless otherwise indicated, the use of a compound in treatment means that an amount of the compound, generally presented as a component of a formulation that comprises other excipients, is administered in aliquots of an amount, and at time intervals, which provides and maintains

at least a therapeutic serum level of at least one pharmaceutically active form of the compound over the time interval between dose administration.

When any variable (e.g. aryl, heterocycle, R¹, R² etc.) occurs more than one time in any constituent, its definition on each occurrence is independent at every other occurrence. Also, combinations of substituents/or variables are permissible only if such combinations result in stable compounds, is chemically feasible and/or valency permits.

As used herein, unless otherwise specified, the terms in the paragraphs immediately below have the indicated meanings.

"Alkoxy" means a moiety of the structure: alkyl-O- (i.e., the bond to the substrate moiety is through the oxygen), wherein the alkyl portion of the moiety is as defined below for alkyl; non-limiting examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy and heptoxy.

"Alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms.

"Halogen" or "halo" means fluoro, chloro, bromo and iodo.

"Cycloalkyl" is intended to include cyclic saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. Preferably, cycloalkyl is C₃-C₁₀ cycloalkyl. Examples of such cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

"Aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic. Examples of such aryl rings include phenyl, naphthyl, tetrahydronaphthyl, indanyl, biphenyl, phenanthryl, anthryl or acenaphthyl.

The term heterocyclyl, heterocycle or heterocyclic represents a stable 5- to 7-membered monocyclic or stable 8- to 14-membered bicyclic or tricyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. The term heterocyclyl, heterocycle or heterocyclic includes heteroaryl moieties. Examples of such heterocyclic elements include, but are not limited to, azepinyl, benzodioxolyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzotriazolyl, benzoxazolyl, chromanyl, cinnolyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, 1,3-dioxolanyl, furyl, furopyridinyl, imidazolidinyl, imidazolyl, indolyl, isochromanyl, isoindolyl, isoquinolyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, 2-oxopiperazinyl, 2-oxopiperdinyl, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl,

pyrazinyl, pyrazolidinyl, pyrazolyl, pyrazolopyridinyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, pyrrolopyridinyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, thienyl, and triazolyl.

5 Preferably, heterocyclyl is selected from furopyridinyl, imidazolyl, indolyl, isoquinolinylisothiazolyl, morpholinyl, naphthyridinyl, oxadiazolyl, piperidyl, piperazinyl, pyridyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyrazolopyridinyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, pyrrolopyridinyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, thienyl, and triazolyl.

10 "Heteroaryl" means any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic and wherein from one to four carbon atoms are replaced by heteroatoms selected from the group consisting of N, O, and S. Examples of such heteroaryl rings include, but are not limited to, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolyl, naphthyridinyl, oxadiazolyl, pyridyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiazolyl, thienofuryl, thienothienyl, thienyl, triazolyl and the like.

"Effective amount" or "therapeutically effective amount" is meant to describe the provision of an amount of at least one compound of the invention or of a composition comprising at least one compound of the invention which is effective in treating or inhibiting a disease or condition described herein, and thus produce the desired therapeutic, ameliorative, inhibitory or preventative effect. For example, in treating cellular proliferative diseases or central nervous system diseases or disorders with one or more of the compounds described herein "effective amount" (or "therapeutically effective amount") means, for example, providing the amount of at least one compound of Formula I that results in a therapeutic response in a patient afflicted with a central nervous system disease or disorder ("condition"), including a response suitable to manage, alleviate, ameliorate, or treat the condition or alleviate, ameliorate, reduce, or eradicate one or more symptoms attributed to the condition and/or long-term stabilization of the condition, for example, as may be determined by the analysis of pharmacodynamic markers or clinical evaluation of patients afflicted with the condition.

30 The phrase "at least one" used in reference to the number of components comprising a composition, for example, "at least one pharmaceutical excipient" means that one member of the specified group is present in the composition, and more than one may additionally be present. Components of a composition are typically aliquots of isolated pure material added to the composition, where the purity level of the isolated material added into the composition is the normally accepted purity level for a reagent of the type.

"at least one" used in reference to substituents on a compound or moiety appended to the core structure of a compound means that one substituent of the group of substituents specified is present, and more than one substituent may be bonded to any of the chemically accessible bonding points of the core.

Whether used in reference to a substituent on a compound or a component of a pharmaceutical composition the phrase "one or more", means the same as "at least one".

As used herein, the term "patient" and "subject" means an animal, such as a mammal (e.g., a human being) and is preferably a human being.

"prodrug" means compounds that are rapidly transformed, for example, by hydrolysis in blood, *in vivo* to the parent compound, e.g., conversion of a prodrug of Formula A to a compound of Formula A, or to a salt thereof; a thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference; the scope of this invention includes prodrugs of the novel compounds of this invention.

Unsatisfied valences in the text, schemes, examples, structural formulae, and any Tables herein is assumed to have a hydrogen atom or atoms of sufficient number to satisfy the valences.

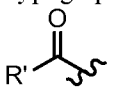
One or more compounds of the invention may also exist as, or optionally be converted to, a solvate. Preparation of solvates is generally known. Thus, for example, M. Caira *et al*, *J. Pharmaceutical Sci.*, 93(3), 601-611 (2004) describe the preparation of the solvates of the antifungal fluconazole in ethyl acetate as well as from water. Similar preparations of solvates, and hemisolvate, including hydrates (where the solvent is water or aqueous-based) and the like are described by E. C. van Tonder *et al*, *AAPS PharmSciTech.*, 5(1), article 12 (2004); and A. L. Bingham *et al*, *Chem. Commun.*, 603-604 (2001). A typical, non-limiting, process involves dissolving the inventive compound in desired amounts of the desired solvent (for example, an organic solvent, an aqueous solvent, water or mixtures of two or more thereof) at a higher than ambient temperature, and cooling the solution, with or without an antisolvent present, at a rate sufficient to form crystals which are then isolated by standard methods. Analytical techniques such as, for example I.R. spectroscopy, show the presence of the solvent (including water) in the crystals as a solvate (or hydrate in the case where water is incorporated into the crystalline form).

The term "substituted" means that one or more of the enumerated substituents can occupy one or more of the bonding positions on the substrate typically occupied by "-H", provided that such substitution does not exceed the normal valency rules for the atom in the bonding configuration presented in the substrate, and that the substitution ultimately provides a stable compound, which is to say that such substitution does not provide compounds with mutually reactive substituents located geminal or vicinal to

each other; and wherein the substitution provides a compound sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture.

Where optional substitution of a moiety is described (e.g. "optionally substituted") the term means that if substituents are present, one or more of the enumerated can be present on the substrate in a bonding position normally occupied by the default substituent, for example, a hydrogen atom, in accordance with the definition of "substituted" presented herein.

As used herein, unless otherwise specified, the preceding terms used to describe moieties, whether comprising the entire definition of a variable portion of a structural representation of a compound of the invention or a substituent appended to a variable portion of a structural representation of a group of compounds of the invention have the following meanings, and unless otherwise specified, the definitions of each term (i.e., moiety or substituent) apply when that term is used individually or as a component of another term (e.g., the definition of aryl is the same for aryl and for the aryl portion of arylalkyl, alkylaryl, arylalkynyl moieties, and the like); moieties are equivalently described herein by structure, typographical representation or chemical terminology without intending any differentiation in meaning, for example, the chemical term "acyl", defined below, is equivalently described herein by the term itself, or by typographical representations

"R'-(C=O)-" or "R'-C(O)-", or by the structural representation: .

The term "pharmaceutical composition" as used herein encompasses both the bulk composition and individual dosage units comprised of more than one (e.g., two) pharmaceutically active agents such as, for example, a compound of the present invention and an additional agent as described herein, along with any pharmaceutically inactive excipients. As will be appreciated by the ordinarily skilled artisan, excipients are any constituent which adapts the composition to a particular route of administration or aids the processing of a composition into a dosage form without itself exerting an active pharmaceutical effect. The bulk composition and each individual dosage unit can contain fixed amounts of the afore-said "more than one pharmaceutically active agents". The bulk composition is material that has not yet been formed into individual dosage units.

This invention also includes the compounds of this invention in isolated and purified form obtained by routine techniques.

Polymorphic forms of the compounds of Formula I, and of the salts, solvates and prodrugs of the compounds of Formula I, are intended to be included in the present invention. Certain compounds of the invention may exist in different isomeric forms (e.g., enantiomers, diastereoisomers, atropisomers). The inventive compounds include all isomeric forms thereof, both in pure form and admixtures of two or more, including racemic mixtures.

In the same manner, unless indicated otherwise, presenting a structural representation of any tautomeric form of a compound which exhibits tautomerism is meant to include all such tautomeric forms of the compound. Accordingly, where compounds of the invention, their salts, and solvates and prodrugs thereof, may exist in different tautomeric forms or in equilibrium among such forms, all such forms of the compound are embraced by, and included within the scope of the invention. Examples of such tautomers include, but are not limited to, ketone/enol tautomeric forms, imine-enamine tautomeric forms, and for example heteroaromatic forms such as the following moieties:



All stereoisomers of the compounds of the invention (including salts and solvates of the inventive compounds and their prodrugs), such as those which may exist due to asymmetric carbons present in a compound of the invention, and including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention. Individual stereoisomers of the compounds of the invention may be isolated in a pure form, for example, substantially free of other isomers, or may be isolated as an admixture of two or more stereoisomers or as a racemate. The chiral centers of the present invention can have the S or R configuration as defined by the IUPAC 1974 Recommendations. The use of the terms “salt”, “solvate” “prodrug” and the like, is intended to equally apply to salts, solvates and prodrugs of isolated enantiomers, stereoisomer pairs or groups, rotamers, tautomers, or racemates of the inventive compounds.

Where diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by known methods, for example, by chiral chromatography and/or fractional crystallization, simple structural representation of the compound contemplates all diastereomers of the compound. As is known, enantiomers may also be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g., hydrolyzing) the individually isolated diastereomers to the corresponding purified enantiomers.

Included in the instant invention is the free base of compounds of Formula I, as well as the pharmaceutically acceptable salts and stereoisomers thereof. The formation of pharmaceutically useful salts from basic (or acidic) pharmaceutical compounds are discussed, for example, by S. Berge et al., Journal of Pharmaceutical Sciences (1977) 66(1) 1-19; P. Gould, International J. of Pharmaceutics (1986) 33 201-217; Anderson et al, The Practice of Medicinal Chemistry (1996), Academic Press, New York; in The Orange Book (Food & Drug Administration, Washington, D.C. on their website); and P. Heinrich

Stahl, Camille G. Wermuth (Eds.), Handbook of Pharmaceutical Salts: Properties, Selection, and Use, (2002) Int'l. Union of Pure and Applied Chemistry, pp. 330-331. These disclosures are incorporated herein by reference.

The present invention contemplates all available salts, including salts which are generally
5 recognized as safe for use in preparing pharmaceutical formulations and those which may be formed presently within the ordinary skill in the art and are later classified as being "generally recognized as safe" for use in the preparation of pharmaceutical formulations, termed herein as "pharmaceutically acceptable salts".

Some of the specific compounds exemplified herein are the protonated salts of amine compounds.

10 Compounds of Formula I with a heterocycle ring containing 2 or more N atoms may be protonated on any one, some or all of the N atoms. The term "free base" refers to the amine compounds in non-salt form.

The encompassed pharmaceutically acceptable salts not only include the salts exemplified for the specific compounds described herein, but also all the typical pharmaceutically acceptable salts of the free form of compounds of Formula I. The free form of the specific salt compounds described may be isolated using
15 techniques known in the art. For example, the free form may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous NaOH, potassium carbonate, ammonia and sodium bicarbonate. The free forms may differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the acid and base salts are otherwise pharmaceutically equivalent to their respective free forms for purposes of the invention.

20 The pharmaceutically acceptable salts of the instant compounds can be synthesized from the compounds of this invention which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts of the basic compounds are prepared either by ion exchange chromatography or by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents. Similarly, the salts of the acidic
25 compounds are formed by reactions with the appropriate inorganic or organic base.

Thus, pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed by reacting a basic instant compound with an inorganic or organic acid. For example, conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric
30 and the like, as well as salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like. Preferably, a pharmaceutically acceptable salt of this invention contains 1 equivalent of a compound of formula (I) and 1, 2 or 3 equivalent of an
35 inorganic or organic acid. More particularly, pharmaceutically acceptable salts of this invention are the trifluoroacetate or the chloride salts, especially the trifluoroacetate salts.

When the compound of the present invention is acidic, suitable "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases

and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N¹-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

It will also be noted that the compounds of the present invention are potentially internal salts or zwitterions, since under physiological conditions a deprotonated acidic moiety in the compound, such as a carboxyl group, may be anionic, and this electronic charge might then be balanced off internally against the cationic charge of a protonated or alkylated basic moiety, such as a quaternary nitrogen atom.

The present invention also embraces isotopically-labeled compounds of the present invention which are structurally identical to those recited herein, but for the fact that a statistically significant percentage of one or more atoms in that form of the compound are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number of the most abundant isotope usually found in nature, thus altering the naturally occurring abundance of that isotope present in a compound of the invention. Examples of isotopes that can be preferentially incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, iodine, fluorine and chlorine, for example, but not limited to: ²H, ³H, ¹¹C, ¹³C, ¹⁴C, ¹³N, ¹⁵N, ¹⁵O, ¹⁷O, ¹⁸O, ³¹P, ³²P, ³⁵S, ¹⁸F, and ³⁶Cl, ¹²³I and ¹²⁵I. It will be appreciated that other isotopes may be incorporated by known means also.

Certain isotopically-labeled compounds of the invention (e.g., those labeled with ³H, ¹¹C and ¹⁴C) are recognized as being particularly useful in compound and/or substrate tissue distribution assays using a variety of known techniques. Tritiated (i.e., ³H) and carbon-14 (i.e., ¹⁴C) isotopes are particularly preferred for their ease of preparation and detection. Further, substitution of a naturally abundant isotope with a heavier isotope, for example, substitution of protium with deuterium (i.e., ²H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labeled compounds of the invention can generally be prepared by following procedures analogous to those disclosed in the reaction Schemes and/or in the Examples herein below, by substituting an appropriate isotopically labeled reagent for a non-isotopically labeled reagent, or by well-known reactions of an appropriately prepared precursor to the compound of the invention which is specifically prepared for such a "labeling" reaction. Such compounds are included also in the present invention.

The compounds of the invention can be used in a method of treatment of the human or animal body by therapy.

The compounds of the invention find use in a variety of applications for human and animal health. The compounds of the invention are histone deacetylase (HDAC) inhibitors useful in the treatment of cancer among other diseases. HDACs catalyse the removal of acetyl groups from lysine residues on proteins, including histones and HDAC inhibitors show diverse biological functions including affecting gene expression, cell differentiation, cell cycle progression, growth arrest, and/or apoptosis. See *J. Med. Chem.* (2003) **46**:5097 and *Curr. Med. Chem.* (2003) **10**:2343.

The compounds of the invention are used to treat cellular proliferation diseases. Disease states which can be treated by the methods and compositions provided herein include, but are not limited to, cancer (further discussed below), neurodegenerative diseases, schizophrenia and stroke.

The compounds, compositions and methods provided herein are particularly deemed useful for the treatment of cancer including solid tumors such as skin, breast, brain, cervical carcinomas, testicular carcinomas, etc. In particular, cancers that may be treated by the compounds, compositions and methods of the invention include, but are not limited to: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochondroma (osteochondilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous

cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma]; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma. Thus, the term "cancerous cell" as provided herein, includes a cell afflicted by any one of the above-identified conditions.

Thus, the present invention provides a compound of formula I for use in the manufacture of a medicament for treating cellular proliferation diseases.

The present invention also provides a method for the treatment of cellular proliferation diseases, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula I or a composition comprising a compound of formula I.

The compounds of the instant invention may also be useful in the treatment or prevention of neurodegenerative diseases, including, but not limited to, poly glutamine-expansion-related neurodegeneration, Huntington's disease, Kennedy's disease, spinocerebellar ataxia, dentatorubral-pallidoluysian atrophy (DRPLA), protein-aggregation-related neurodegeneration, Machado-Joseph's disease, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, spongiform encephalopathy, a prion-related disease and multiple sclerosis (MS).

Thus, the present invention provides a compound of formula I for use in the manufacture of a medicament for treating or preventing neurodegenerative diseases.

The present invention also provides a method for treating or preventing neurodegenerative diseases, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula I or a composition comprising a compound of formula I.

The compounds of the invention may also be useful in the treatment or prevention of mental retardation, in particular "X chromosome-linked mental retardation" and "Rubinstein-Taybi syndrome".

Thus, the present invention provides a compound of formula I for the manufacture of a medicament for treating or preventing mental retardation.

The present invention also provides a method for treating or preventing mental retardation, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula I or a composition comprising a compound of formula I.

The compounds of the invention may also be useful in the treatment or prevention of schizophrenia.

Thus, the present invention provides a compound of formula I for the manufacture of a medicament for treating or preventing schizophrenia.

The present invention also provides a method for treating or preventing schizophrenia, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula I or a composition comprising a compound of formula I.

5 The compounds of the invention may also be useful in the treatment or prevention of inflammatory diseases, including, but not limited to stroke, rheumatoid arthritis, lupus erythematosus, ulcerative colitis and traumatic brain injuries. See Leoni *et al* (2002), *PNAS*, **99**(5):2995-3000, Suuronen *et al.*(2003) *J. Neurochem*, **87**:407-416 and *Drug Discovery Today* (2005), **10**:197-204.

Thus, the present invention provides a compound of formula I for the manufacture of a medicament for treating or preventing inflammatory diseases.

10 The present invention also provides a method for treating or preventing inflammatory diseases, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula I or a composition comprising a compound of formula I.

The compounds of the present invention are also useful in the inhibition of smooth muscle cell proliferation and/or migration and are thus useful in the prevention and/or treatment of restenosis, for
15 example after angioplasty and/or stent implantation.

Thus, the present invention provides a compound of formula I for the manufacture of a medicament for treating or preventing restenosis.

The present invention also provides a method for treating or prevention restenosis, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula I
20 or a composition comprising a compound of formula I.

In one embodiment, smooth muscle cell proliferation and/or migration is inhibited and restenosis is prevented and/or treated by providing a stent device having one or more of the compounds of the instant invention in or on the stent device, e.g. coated onto the stent device. The stent device is designed to controllably release the compounds of the invention, thereby inhibiting smooth muscle cell proliferation
25 and/or migration and preventing and/or treating restenosis.

Stenosis and restenosis are conditions associated with a narrowing of blood vessels. Stenosis of blood vessels generally occurs gradually over time. Restenosis, in contrast, relates to a narrowing of blood vessels following an endovascular procedure, such as balloon angioplasty and/or stent implantation, or a vascular injury.

30 Balloon angioplasty is typically performed to open a stenotic blood vessel; stenting is usually performed to maintain the patency of a blood vessel after, or in combination with, balloon angioplasty. A stenotic blood vessel is opened with balloon angioplasty by navigating a balloon-tipped catheter to the site of stenosis, and expanding the balloon tip effectively to dilate the occluded blood vessel. In an effort to maintain the patency of the dilated blood vessel, a stent may be implanted in the blood vessel to
35 provide intravascular support to the opened section of the blood vessel, thereby limiting the extent to which the blood vessel will return to its occluded state after release of the balloon catheter. Restenosis is typically caused by trauma inflicted during angioplasty, effected by, for example, balloon dilation, atherectomy or laser ablation treatment of the artery. For these procedures, restenosis occurs at a rate of

about 30% to about 60% depending on the vessel location, lesion length and a number of other variables. This reduces the overall success of the relatively non-invasive balloon angioplasty and stenting procedures.

Restenosis is attributed to many factors, including proliferation of smooth muscle cells (SMC).

5 SMC proliferation is triggered by the initial mechanical injury to the intima that is sustained at the time of balloon angioplasty and stent implantation. The process is characterized by early platelet activation and thrombus formation, followed by SMC recruitment and migration, and, finally, cellular proliferation and extracellular matrix accumulation. Damaged endothelial cells, SMCs, platelets, and macrophages secrete cytokines and growth factors which promote restenosis. SMC proliferation represents the final common
10 pathway leading to neointimal hyperplasia. Therefore, anti-proliferative therapies aimed at inhibiting specific regulatory events in the cell cycle may constitute the most reasonable approach to restenosis after angioplasty.

The compounds of the invention may also be used as immunosuppressants or immunomodulators and can accordingly be used in the treatment or prevention of immune response or immune-mediated
15 responses and diseases such as systemic lupus erythematosus (SLE) and acute or chronic transplant rejection in a recipient of an organ, tissue or cell transplant, (see WO O5/013958).

Examples of autoimmune diseases for which the compounds of the invention may be employed include autoimmune hematological disorders (including hemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopenia), systemic lupus erythematosus, thyroiditis, Hashimoto's
20 thyroiditis, polychondritis, sclerodoma, Wegener granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, psoriasis, atopic dermatitis, vasculitis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (including ulcerative colitis and Crohn's disease) endocrine ophthalmopathy, Graves disease, sarcoidosis, multiple sclerosis, primary billiary cirrhosis, juvenile diabetes (diabetes mellitus type I), diabetes type II and the disorders associated therewith, uveitis
25 (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis, glomerulonephritis (with and without nephrotic syndrome, including idiopathic nephrotic syndrome or minimal change nephropathy), juvenile dermatomyositis, infectious, auto-antibody mediated diseases, aplastic anemia, Evan's syndrome, autoimmune hemolytic anemia, infectious diseases causing aberrant immune response and/or activation, such as traumatic or pathogen induced immune
30 disregulation, including for example, that which are caused by hepatitis B and C infections, staphylococcus aureus infection, viral encephalitis, sepsis, parasitic diseases wherein damage is induced by inflammatory response (e.g. leprosy); and circulatory diseases, such as arteriosclerosis, atherosclerosis, polyarteritis nodosa and myocarditis.

Thus, the present invention provides a compound of formula I for the manufacture of a
35 medicament for the treatment or prevention of immune disorders.

The present invention also provides a method for treating or preventing immune disorders, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula I or a composition comprising a compound of formula I.

The compounds of the invention may also be useful in the treatment or prevention of other diseases such as diabetes, cardiovascular disorders, asthma, cardiac hypertrophy and heart failure (see *Cell* (2002), **110**:479-488).

The compounds of this invention may be administered to mammals, preferably humans, either alone or in combination with pharmaceutically acceptable carriers, excipients or diluents, in a pharmaceutical composition, according to standard pharmaceutical practice. In one embodiment, the compounds of this invention may be administered to animals. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

The invention also provides pharmaceutical compositions comprising one or more compounds of this invention and a pharmaceutically acceptable carrier. The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, microcrystalline cellulose, sodium crosscarmellose, corn starch, or alginic acid; binding agents, for example starch, gelatin, polyvinyl-pyrrolidone or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to mask the unpleasant taste of the drug or delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a water soluble taste masking material such as hydroxypropyl-methylcellulose or hydroxypropylcellulose, or a time delay material such as ethyl cellulose, cellulose acetate butyrate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water soluble carrier such as polyethyleneglycol or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic

alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as butylated hydroxyanisole or alpha-tocopherol.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally occurring phosphatides, for example soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavoring agents, preservatives and antioxidants.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, flavoring and coloring agents and antioxidant.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous solutions. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution.

The sterile injectable preparation may also be a sterile injectable oil-in-water microemulsion where the active ingredient is dissolved in the oily phase. For example, the active ingredient may be first dissolved in a mixture of soybean oil and lecithin. The oil solution then introduced into a water and glycerol mixture and processed to form a microemulsion.

The injectable solutions or microemulsions may be introduced into a patient's blood stream by local bolus injection. Alternatively, it may be advantageous to administer the solution or microemulsion

in such a way as to maintain a constant circulating concentration of the instant compound. In order to maintain such a constant concentration, a continuous intravenous delivery device may be utilized. An example of such a device is the Deltec CADD-PLUS™ model 5400 intravenous pump.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension for intramuscular and subcutaneous administration. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butane diol. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compounds of Formula I may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compound of Formula I are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

The compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles and delivery devices, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

When a compound according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, sex and response of the individual patient, as well as the severity of the patient's symptoms.

In one exemplary application, a suitable amount of compound is administered to a mammal undergoing treatment for cancer. Administration generally occurs in an amount between about 0.1 mg/kg of body weight to about 60 mg/kg of body weight per day, preferably of between 0.5 mg/kg of body weight to about 40 mg/kg of body weight per day.

The instant compounds are also useful in combination with known therapeutic agents and anti-cancer agents. Thus, this invention provides combinations of compounds of formula (I) and known therapeutic agents and/or anti-cancer agents for simultaneous, separate or sequential administration. For example, instant compounds are useful in combination with known anti-cancer agents. Combinations of the presently disclosed compounds with other anti-cancer or chemotherapeutic agents are within the scope

of the invention. Examples of such agents can be found in *Cancer Principles and Practice of Oncology* by V.T. Devita and S. Hellman (editors), 6th edition (February 15, 2001), Lippincott Williams & Wilkins Publishers. A person of ordinary skill in the art would be able to discern which combinations of agents would be useful based on the particular characteristics of the drugs and the cancer involved. Such anti-cancer agents include, but are not limited to, the following: other HDAC inhibitors, estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic/cytostatic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors and other angiogenesis inhibitors, inhibitors of cell proliferation and survival signaling, apoptosis inducing agents and agents that interfere with cell cycle checkpoints. The instant compounds are particularly useful when co-administered with radiation therapy.

In an embodiment, the instant compounds are also useful in combination with known anti-cancer agents including the following: other HDAC inhibitors, estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors, HIV protease inhibitors, reverse transcriptase inhibitors, and other angiogenesis inhibitors.

Examples of "other HDAC inhibitors" include suberoylanilide hydroxamic acid (SAHA), LAQ824, LBH589, PXD101, MS275, FK228, valproic acid, butyric acid and CI-994.

"Estrogen receptor modulators" refers to compounds that interfere with or inhibit the binding of estrogen to the receptor, regardless of mechanism. Examples of estrogen receptor modulators include, but are not limited to, tamoxifen, raloxifene, idoxifene, LY353381, LY117081, toremifene, fulvestrant, 4-[7-(2,2-dimethyl-1-oxopropoxy-4-methyl-2-[4-[2-(1-piperidinyl)ethoxy]phenyl]-2H-1-benzopyran-3-yl)-phenyl-2,2-dimethylpropanoate, 4,4'-dihydroxybenzophenone-2,4-dinitrophenyl-hydrazone, and SH646.

"Androgen receptor modulators" refers to compounds which interfere or inhibit the binding of androgens to the receptor, regardless of mechanism. Examples of androgen receptor modulators include finasteride and other 5 α -reductase inhibitors, nilutamide, flutamide, bicalutamide, liarozole, and abiraterone acetate.

"Retinoid receptor modulators" refers to compounds which interfere or inhibit the binding of retinoids to the receptor, regardless of mechanism. Examples of such retinoid receptor modulators include bexarotene, tretinoin, 13-cis-retinoic acid, 9-cis-retinoic acid, α -difluoromethylornithine, ILX23-7553, trans-*N*-(4'-hydroxyphenyl) retinamide, and *N*-4-carboxyphenyl retinamide.

"Cytotoxic/cytostatic agents" refer to compounds which cause cell death or inhibit cell proliferation primarily by interfering directly with the cell's functioning or inhibit or interfere with cell mitosis, including alkylating agents, tumor necrosis factors, intercalators, hypoxia activatable compounds, microtubule inhibitors/microtubule-stabilizing agents, inhibitors of mitotic kinesins, inhibitors of kinases involved in mitotic progression, antimetabolites; biological response modifiers; hormonal/anti-hormonal therapeutic agents, haematopoietic growth factors, monoclonal antibody targeted therapeutic agents, topoisomerase inhibitors, proteasome inhibitors and ubiquitin ligase inhibitors.

Examples of cytotoxic agents include, but are not limited to, serteneft, cachectin, ifosfamide, tasonermin, lonidamine, carboplatin, altretamine, prednimustine, dibromodulcitol, ranimustine, fotemustine, nedaplatin, oxaliplatin, temozolomide, heptaplatin, estramustine, improsulfan tosilate, trofosfamide, nimustine, dibrospidium chloride, pumitepa, lobaplatin, satraplatin, proflomycin, cisplatin, 5 irofulven, dexifosfamide, cis-aminodichloro(2-methyl-pyridine)platinum, benzylguanine, glufosfamide, GPX100, (trans, trans, trans)-bis- μ -(hexane-1,6-diamine)- μ -[diamine-platinum(II)]bis[diamine(chloro)platinum (II)]tetrachloride, diarizidinylspermine, arsenic trioxide, 1-(11-dodecylamino-10-hydroxyundecyl)-3,7-dimethylxanthine, zorubicin, idarubicin, daunorubicin, bisantrene, mitoxantrone, pirarubicin, pinafide, valrubicin, amrubicin, antineoplaston, 3'-deamino-3'-morpholino-13-deoxy-10-hydroxycarminomycin, annamycin, galarubicin, elinafide, MEN10755, and 4-demethoxy-3-deamino-3-aziridinyl-4-methylsulphonyl-daunorubicin.

An example of a hypoxia activatable compound is tirapazamine.

Examples of proteasome inhibitors include but are not limited to lactacystin, bortezomib, epoxomicin and peptide aldehydes such as MG 132, MG 115 and PSI.

15 In an embodiment, the compounds of the present invention may be used in combination with other HDAC inhibitors such as SAHA and proteasome inhibitors.

Examples of microtubule inhibitors/microtubule-stabilising agents include paclitaxel, vindesine sulfate, 3',4'-didehydro-4'-deoxy-8'-norvincal leukoblastine, docetaxol, rhizoxin, dolastatin, mivobulin isethionate, auristatin, cemadotin, RPR109881, BMS184476, vinflunine, cryptophycin, 2,3,4,5,6- 20 pentafluoro-*N*-(3-fluoro-4-methoxyphenyl) benzene sulfonamide, anhydrovinblastine, *N,N*-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl-L-proline-*t*-butylamide, TDX258, the epothilones (see for example U.S. Pat. Nos. 6,284,781 and 6,288,237) and BMS188797.

Some examples of topoisomerase inhibitors are topotecan, hycaptamine, irinotecan, rubitecan, 6-ethoxypropionyl-3',4'-*O*-exo-benzylidene-chartreusin, 9-methoxy-*N,N*-dimethyl-5-nitropyrzolo[3,4,5- 25 kl]acridine-2-(6*H*) propanamine, 1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1*H*,12*H*-benzo[de]pyrano[3',4':b,7]-indolizino[1,2b]quinoline-10,13(9*H*,15*H*)dione, lurtotecan, 7-[2-(*N*-isopropylamino)ethyl]-(2*S*)camptothecin, BNP1350, BNPI1100, BN80915, BN80942, etoposide phosphate, teniposide, sobuzoxane, 2'-dimethylamino-2'-deoxy-etoposide, GL331, *N*-[2-(dimethylamino)ethyl]-9-hydroxy-5,6-dimethyl-6*H*-pyrido[4,3-*b*]carbazole-1-carboxamide, asulacrine, 30 (5*a*, 5*aB*, 8*aa*,9*b*)-9-[2-[*N*-[2-(dimethylamino)ethyl]-*N*-methylamino]ethyl]-5-[4-hydroxy-3,5-dimethoxyphenyl]-5,5*a*,6,8,8*a*,9-hexahydrofuro(3',4':6,7)naphtho(2,3-*d*)-1,3-dioxol-6-one, 2,3-(methylenedioxy)-5-methyl-7-hydroxy-8-methoxybenzo[*c*]-phenanthridinium, 6,9-bis[(2-aminoethyl)amino]benzo[*g*]isoguinoline-5,10-dione, 5-(3-aminopropylamino)-7,10-dihydroxy-2-(2-hydroxyethylaminomethyl)-6*H*-pyrazolo[4,5,1-*de*]acridin-6-one, *N*-[1-[2(diethylamino)ethylamino]-7-methoxy-9-oxo-9*H*-thioxanthen-4-ylmethyl]formamide, *N*-(2-(dimethylamino)ethyl)acridine-4- 35 carboxamide, 6-[[2-(dimethylamino)ethyl]amino]-3-hydroxy-7*H*-indeno[2,1-*c*] quinolin-7-one, and dimesna.

Examples of inhibitors of mitotic kinesins, and in particular the human mitotic kinesin KSP, are described in the prior art.

“Inhibitors of kinases involved in mitotic progression” include, but are not limited to, inhibitors of aurora kinase, inhibitors of Polo-like kinases (PLK) (in particular inhibitors of PLK-1), inhibitors of bub-1 and inhibitors of bub-R1.

“Antiproliferative agents” includes antisense RNA and DNA oligonucleotides such as G3139, ODN698, RVASKRAS, GEM231, and INX3001, and antimetabolites such as enocitabine, carmofur, tegafur, pentostatin, doxifluridine, trimetrexate, fludarabine, capecitabine, galocitabine, cytarabine, ocfosfate, fosteabine sodium hydrate, raltitrexed, paltitrexid, emitefur, tiazofurin, decitabine, nolatrexed, pemetrexed, nelzarabine, 2'-deoxy-2'-methylidenecytidine, 2'-fluoromethylene-2'-deoxycytidine, *N*-[5-(2,3-dihydro-benzofuryl)sulfonyl]-*N'*-(3,4-dichlorophenyl)urea, *N*6-[4-deoxy-4-[*N*2-[2(E),4(E)-tetradecadienoyl]glycylamino]-L-glycero-B-L-manno-heptopyranosyl]adenine, aplidine, ecteinascidin, troxacitabine, 4-[2-amino-4-oxo-4,6,7,8-tetrahydro-3*H*-pyrimidino[5,4-*b*][1,4]thiazin-6-yl-(*S*)-ethyl]-2,5-thienoyl-L-glutamic acid, aminopterin, 5-fluorouracil, alanosine, 11-acetyl-8-(carbamoyloxymethyl)-4-formyl-6-methoxy-14-oxa-1,11-diazatetracyclo(7.4.1.0.0)-tetradeca-2,4,6-trien-9-yl acetic acid ester, swainsonine, lometrexol, dexrazoxane, methioninase, 2'-cyano-2'-deoxy-*N*4-palmitoyl-1-*B*-D-arabino furanosyl cytosine and 3-aminopyridine-2-carboxaldehyde thiosemicarbazone.

Examples of monoclonal antibody targeted therapeutic agents include those therapeutic agents which have cytotoxic agents or radioisotopes attached to a cancer cell specific or target cell specific monoclonal antibody. Examples include Bexxar.

“HMG-CoA reductase inhibitors” refers to inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase. Examples of HMG-CoA reductase inhibitors that may be used include but are not limited to lovastatin (MEVACOR[®]), simvastatin (ZOCOR[®]), pravastatin (PRAVACHOL[®]), fluvastatin (LESCOL[®]) and atorvastatin (LIPITOR[®]). The structural formulas of these and additional HMG-CoA reductase inhibitors that may be used in the instant methods are described at page 87 of M. Yalpani, “Cholesterol Lowering Drugs”, *Chemistry & Industry*, pp. 85-89 (5 February 1996) and US Patent Nos. 4,782,084 and 4,885,314. The term HMG-CoA reductase inhibitor as used herein includes all pharmaceutically acceptable lactone and open-acid forms (i.e., where the lactone ring is opened to form the free acid) as well as salt and ester forms of compounds which have HMG-CoA reductase inhibitory activity, and therefore the use of such salts, esters, open-acid and lactone forms is included within the scope of this invention.

“Prenyl-protein transferase inhibitor” refers to a compound which inhibits any one or any combination of the prenyl-protein transferase enzymes, including farnesyl-protein transferase (FPTase), geranylgeranyl-protein transferase type I (GGPTase-I), and geranylgeranyl-protein transferase type-II (GGPTase-II, also called Rab GGPTase). For an example of the role of a prenyl-protein transferase inhibitor on angiogenesis see *European J. of Cancer* (1999), **35(9)**:1394-1401.

“Angiogenesis inhibitors” refers to compounds that inhibit the formation of new blood vessels, regardless of mechanism. Examples of angiogenesis inhibitors include, but are not limited to, tyrosine

kinase inhibitors, such as inhibitors of the tyrosine kinase receptors Flt-1 (VEGFR1) and Flk-1/KDR (VEGFR2), inhibitors of epidermal-derived, fibroblast-derived, or platelet derived growth factors, MMP (matrix metalloprotease) inhibitors, integrin blockers, interferon- α , interleukin-12, pentosan polysulfate, cyclooxygenase inhibitors, including nonsteroidal anti-inflammatories (NSAIDs) like aspirin and ibuprofen as well as selective cyclooxygenase-2 inhibitors like celecoxib and rofecoxib (*PNAS* (1992) **89**:7384; *JNCI* (1982) **69**:475; *Arch. Ophthalmol.* (1990) **108**:573; *Anat. Rec.* (1994) **238**:68; *FEBS Letters* (1995) **372**:83; *Clin. Orthop.* (1995) **313**:76; *J. Mol. Endocrinol.* (1996) **16**:107; *Jpn. J. Pharmacol.* (1997) **75**:105; *Cancer Res.* (1997) **57**:1625 (1997); *Cell* (1998) **93**:705; *Intl. J. Mol. Med.* (1998) **2**:715; *J. Biol. Chem.* (1999) **274**:9116)), steroidal anti-inflammatories (such as corticosteroids, mineralocorticoids, dexamethasone, prednisone, prednisolone, methylpred, betamethasone), carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl-fumagillol, thalidomide, angiostatin, troponin-1, angiotensin II antagonists (see Fernandez *et al* (1985) *J. Lab. Clin. Med.* **105**:141-145), and antibodies to VEGF (see, *Nature Biotechnology* (1999) **17**:963-968; Kim *et al* (1993) *Nature* **362**:841-844; WO 00/44777; and WO 00/61186).

Other therapeutic agents that modulate or inhibit angiogenesis and may also be used in combination with the compounds of the instant invention include agents that modulate or inhibit the coagulation and fibrinolysis systems (see review in *Clin. Chem. La. Med.* (2000) **38**:679-692). Examples of such agents that modulate or inhibit the coagulation and fibrinolysis pathways include, but are not limited to, heparin (see *Thromb. Haemost.* (1998) **80**:10-23), low molecular weight heparins and carboxypeptidase U inhibitors (also known as inhibitors of active thrombin activatable fibrinolysis inhibitor [TAFIa]) (see *Thrombosis Res.* (2001) **101**:329-354). TAFIa inhibitors have been described in PCT Publication WO 03/013,526 and U.S. Ser. No. 60/349,925 (filed January 18, 2002).

“Agents that interfere with cell cycle checkpoints” refer to compounds that inhibit protein kinases that transduce cell cycle checkpoint signals, thereby sensitizing the cancer cell to DNA damaging agents. Such agents include inhibitors of ATR, ATM, the Chk1 and Chk2 kinases and cdk and cdc kinase inhibitors and are specifically exemplified by 7-hydroxystaurosporin, flavopiridol, CYC202 (Cyclacel) and BMS-387032.

“Inhibitors of cell proliferation and survival signaling pathway” refer to pharmaceutical agents that inhibit cell surface receptors and signal transduction cascades downstream of those surface receptors. Such agents include inhibitors of inhibitors of EGFR (for example gefitinib and erlotinib), inhibitors of ERB-2 (for example trastuzumab), inhibitors of IGFR (for example those disclosed in WO 03/059951), inhibitors of cytokine receptors, inhibitors of MET, inhibitors of PI3K (for example LY294002), serine/threonine kinases, inhibitors of Raf kinase (for example BAY-43-9006), inhibitors of MEK (for example CI-1040 and PD-098059) and inhibitors of mTOR (for example Wyeth CCI-779 and Ariad AP23573). Such agents include small molecule inhibitor compounds and antibody antagonists.

“Apoptosis inducing agents” include activators of TNF receptor family members (including the TRAIL receptors).

The invention also encompasses combinations with NSAID's which are selective COX-2 inhibitors. For purposes of this specification NSAID's which are selective inhibitors of COX-2 are defined as those which possess a specificity for inhibiting COX-2 over COX-1 of at least 100 fold as measured by the ratio of IC₅₀ for COX-2 over IC₅₀ for COX-1 evaluated by cell or microsomal assays.

5 Inhibitors of COX-2 that are particularly useful in the instant method of treatment are 5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl)pyridine; or a pharmaceutically acceptable salt thereof.

Compounds that have been described as specific inhibitors of COX-2 and are therefore useful in the present invention include, but are not limited to: parecoxib, CELEBREX[®] and BEXTRA[®] or a
10 pharmaceutically acceptable salt thereof.

Other examples of angiogenesis inhibitors include, but are not limited to, endostatin, ukrain, ranpirnase, IM862, 5-methoxy-4-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-1-oxaspiro[2,5]oct-6-yl(chloroacetyl)carbamate, acetyldinanaline, 5-amino-1-[[3,5-dichloro-4-(4-chlorobenzoyl)phenyl]methyl]-1*H*-1,2,3-triazole-4-carboxamide, CM101, squalamine, combretastatin,
15 RPI4610, NX31838, sulfated mannopentaose phosphate, 7,7-(carbonyl-bis[imino-*N*-methyl-4,2-pyrrolocarbonylimino[*N*-methyl-4,2-pyrrole]-carbonylimino]-bis-(1,3-naphthalene disulfonate), and 3-[(2,4-dimethylpyrrol-5-yl)methylene]-2-indolinone (SU5416).

As used above, "integrin blockers" refers to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha_v\beta_3$ integrin, to compounds which selectively
20 antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha_v\beta_5$ integrin, to compounds which antagonize, inhibit or counteract binding of a physiological ligand to both the $\alpha_v\beta_3$ integrin and the $\alpha_v\beta_5$ integrin, and to compounds which antagonize, inhibit or counteract the activity of the particular integrin(s) expressed on capillary endothelial cells. The term also refers to antagonists of the $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins. The term also refers to antagonists of any
25 combination of $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\beta_5\alpha_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins.

Some specific examples of tyrosine kinase inhibitors include *N*-(trifluoromethylphenyl)-5-methylisoxazol-4-carboxamide, 3-[(2,4-dimethylpyrrol-5-yl)methylidenyl]indolin-2-one, 17-(allylamino)-17-demethoxy geldanamycin, 4-(3-chloro-4-fluorophenylamino)-7-methoxy-6-[3-(4-morpholinyl)propoxyl]quinazoline, *N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine,
30 BIBX1382, 2,3,9,10,11,12-hexahydro-10-(hydroxymethyl)-10-hydroxy-9-methyl-9,12-epoxy-1*H*-diindolo[1,2,3-*fg*:3',2',1'-*kl*]pyrrolo[3,4-*i*][1,6]benzodiazocin-1-one, SH268, genistein, STI571, CEP2563, 4-(3-chlorophenylamino)-5,6-dimethyl-7*H*-pyrrolo[2,3-*d*]pyrimidinemethane sulfonate, 4-(3-bromo-4-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, 4-(4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, SU6668, STI571A, *N*-4-chlorophenyl-4-(4-pyridylmethyl)-1-phthalazinamine,
35 and EMD121974.

Combinations with compounds other than anti-cancer compounds are also encompassed in the instant methods. For example, combinations of the instantly claimed compounds with PPAR- γ (i.e., PPAR-gamma) agonists and PPAR- δ (i.e., PPAR-delta) agonists are useful in the treatment of certain

maligancies. PPAR- γ and PPAR- δ are the nuclear peroxisome proliferator-activated receptors γ and δ . The expression of PPAR- γ on endothelial cells and its involvement in angiogenesis has been reported in the literature (see *J. Cardiovasc. Pharmacol.* (1998) **31**:909-913; *J. Biol. Chem.* (1999) **274**:9116-9121; *Invest. Ophthalmol Vis. Sci.* (2000) **41**:2309-2317). More recently, PPAR- γ agonists have been shown to inhibit the angiogenic response to VEGF in vitro; both troglitazone and rosiglitazone maleate inhibit the development of retinal neovascularization in mice. (*Arch. Ophthalmol.* (2001) **119**:709-717). Examples of PPAR- γ agonists and PPAR- γ/α agonists include, but are not limited to, thiazolidinediones (such as DRF2725, CS-011, troglitazone, rosiglitazone, and pioglitazone), fenofibrate, gemfibrozil, clofibrate, GW2570, SB219994, AR-H039242, JTT-501, MCC-555, GW2331, GW409544, NN2344, KRP297, NP0110, DRF4158, NN622, GI262570, PNU182716, DRF552926, 2-[(5,7-dipropyl-3-trifluoromethyl-1,2-benzisoxazol-6-yl)oxy]-2-methylpropionic acid, and 2(R)-7-(3-(2-chloro-4-(4-fluorophenoxy)phenoxy)propoxy)-2-ethylchromane-2-carboxylic acid.

Another embodiment of the instant invention is the use of the presently disclosed compounds in combination with anti-viral agents (such as nucleoside analogs including ganciclovir for the treatment of cancer.

Another embodiment of the instant invention is the use of the presently disclosed compounds in combination with gene therapy for the treatment of cancer. For an overview of genetic strategies to treating cancer see Hall et al (*Am J Hum Genet* (1997) **61**:785-789) and Kufe et al (*Cancer Medicine*, 5th Ed, pp 876-889, BC Decker, Hamilton 2000). Gene therapy can be used to deliver any tumor suppressing gene. Examples of such genes include, but are not limited to, p53, which can be delivered via recombinant virus-mediated gene transfer (see U.S. Pat. No. 6,069,134, for example), a uPA/uPAR antagonist ("Adenovirus-Mediated Delivery of a uPA/uPAR Antagonist Suppresses Angiogenesis-Dependent Tumor Growth and Dissemination in Mice," *Gene Therapy*, August (1998) **5**(8):1105-13), and interferon gamma (*J Immunol* (2000) **164**:217-222).

The compounds of the instant invention may also be administered in combination with an inhibitor of inherent multidrug resistance (MDR), in particular MDR associated with high levels of expression of transporter proteins. Such MDR inhibitors include inhibitors of p-glycoprotein (P-gp), such as LY335979, XR9576, OC144-093, R101922, VX853 and PSC833 (valspodar).

A compound of the present invention may be employed in conjunction with anti-emetic agents to treat nausea or emesis, including acute, delayed, late-phase, and anticipatory emesis, which may result from the use of a compound of the present invention, alone or with radiation therapy. For the prevention or treatment of emesis, a compound of the present invention may be used in conjunction with other anti-emetic agents, especially neurokinin-1 receptor antagonists, 5HT₃ receptor antagonists, such as ondansetron, granisetron, tropisetron, and zatisetron, GABA_B receptor agonists, such as baclofen, a corticosteroid such as Decadron (dexamethasone), Kenalog, Aristocort, Nasalide, Preferid, Benecorten or others such as disclosed in U.S. Patent Nos. 2,789,118, 2,990,401, 3,048,581, 3,126,375, 3,929,768, 3,996,359, 3,928,326 and 3,749,712, an antidopaminergic, such as the phenothiazines (for example

prochlorperazine, fluphenazine, thioridazine and mesoridazine), metoclopramide or dronabinol. In an embodiment, an anti-emesis agent selected from a neurokinin-1 receptor antagonist, a 5HT₃ receptor antagonist and a corticosteroid is administered as an adjuvant for the treatment or prevention of emesis that may result upon administration of the instant compounds.

5 In an embodiment, the neurokinin-1 receptor antagonist for use in conjunction with the compounds of the present invention is selected from: 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)-4-(3-(5-oxo-1*H*,4*H*-1,2,4-triazolo)methyl)morpholine, or a pharmaceutically acceptable salt thereof.

10 A compound of the instant invention may also be administered with an agent useful in the treatment of anemia. Such an anemia treatment agent is, for example, a continuous erythropoiesis receptor activator (such as epoetin alfa).

A compound of the instant invention may also be administered with an agent useful in the treatment of neutropenia. Such a neutropenia treatment agent is, for example, a hematopoietic growth factor which regulates the production and function of neutrophils such as a human granulocyte colony stimulating factor, (G-CSF). Examples of a G-CSF include filgrastim.

15 A compound of the instant invention may also be administered with an immunologic-enhancing drug, such as levamisole, isoprinosine and Zadaxin.

A compound of the instant invention may also be useful for treating or preventing cancer, including bone cancer, in combination with bisphosphonates (understood to include bisphosphonates, diphosphonates, bisphosphonic acids and diphosphonic acids). Examples of bisphosphonates include but are not limited to: etidronate (Didronel), pamidronate (Aredia), alendronate (Fosamax), risedronate (Actonel), zoledronate (Zometa), ibandronate (Boniva), incadronate or cimadronate, clodronate, EB-1053, minodronate, neridronate, piridronate and tiludronate including any and all pharmaceutically acceptable salts, derivatives, hydrates and mixtures thereof.

25 Thus, the scope of the instant invention encompasses the use of the instantly claimed compounds in combination with a second compound selected from: other HDAC inhibitors, an estrogen receptor modulator, an androgen receptor modulator, retinoid receptor modulator, a cytotoxic/cytostatic agent, an antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an HIV protease inhibitor, a reverse transcriptase inhibitor, an angiogenesis inhibitor, a PPAR- γ agonist, a PPAR- δ agonist, an anti-viral agent, an inhibitor of inherent multidrug resistance, an anti-emetic agent, an agent useful in the treatment of anemia, an agent useful in the treatment of neutropenia, an immunologic-enhancing drug, an inhibitor of cell proliferation and survival signaling, an agent that interferes with a cell cycle checkpoint, an apoptosis inducing agent and a bisphosphonate.

35 The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention means introducing the compound or a prodrug of the compound into the system of the animal in need of treatment. When a compound of the invention or prodrug thereof is provided in combination with one or more other active agents (e.g., a cytotoxic agent, etc.),

"administration" and its variants are each understood to include concurrent and sequential introduction of the compound or prodrug thereof and other agents.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The term "treating cancer" or "treatment of cancer" refers to administration to a mammal afflicted with a cancerous condition and refers to an effect that alleviates the cancerous condition by killing the cancerous cells, but also to an effect that results in the inhibition of growth and/or metastasis of the cancer.

In an embodiment, the angiogenesis inhibitor to be used as the second compound is selected from a tyrosine kinase inhibitor, an inhibitor of epidermal-derived growth factor, an inhibitor of fibroblast-derived growth factor, an inhibitor of platelet derived growth factor, an MMP (matrix metalloprotease) inhibitor, an integrin blocker, interferon- α , interleukin-12, pentosan polysulfate, a cyclooxygenase inhibitor, carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl-fumagillol, thalidomide, angiostatin, troponin-1, or an antibody to VEGF. In an embodiment, the estrogen receptor modulator is tamoxifen or raloxifene.

Also included in the scope of the claims is a method of treating cancer that comprises administering a therapeutically effective amount of a compound of Formula I in combination with radiation therapy and/or in combination with a compound selected from: other HDAC inhibitors, an estrogen receptor modulator, an androgen receptor modulator, retinoid receptor modulator, a cytotoxic/cytostatic agent, an antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an HIV protease inhibitor, a reverse transcriptase inhibitor, an angiogenesis inhibitor, a PPAR- γ agonist, a PPAR- δ agonist, an anti-viral agent, an inhibitor of inherent multidrug resistance, an anti-emetic agent, an agent useful in the treatment of anemia, an agent useful in the treatment of neutropenia, an immunologic-enhancing drug, an inhibitor of cell proliferation and survival signaling, an agent that interferes with a cell cycle checkpoint, an apoptosis inducing agent and a bisphosphonate.

And yet another embodiment of the invention is a method of treating cancer that comprises administering a therapeutically effective amount of a compound of Formula I in combination with paclitaxel or trastuzumab.

The invention further encompasses a method of treating or preventing cancer that comprises administering a therapeutically effective amount of a compound of Formula I in combination with a COX-2 inhibitor.

The instant invention also includes a pharmaceutical composition useful for treating or preventing cancer that comprises a therapeutically effective amount of a compound of Formula I and a compound selected from: other HDAC inhibitors, an estrogen receptor modulator, an androgen receptor modulator, a retinoid receptor modulator, a cytotoxic/cytostatic agent, an antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an HIV protease inhibitor, a reverse transcriptase inhibitor, an angiogenesis inhibitor, a PPAR- γ agonist, a PPAR- δ agonist, an anti-viral

agent, an inhibitor of cell proliferation and survival signaling, an agent that interferes with a cell cycle checkpoint, an apoptosis inducing agent and a bisphosphonate.

These and other aspects of the invention will be apparent from the teachings contained herein.

5 The present invention also provides a method for the synthesis of compounds useful as intermediates in the preparation of compounds of the invention.

10 The compounds described herein can be prepared according to the procedures of the following schemes and examples, using appropriate materials and are further exemplified by the following specific examples. The examples further illustrate details for the preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds.

15 All temperatures are degrees Celsius unless otherwise noted. Mass spectra (MS) were measured by electrospray ion-mass spectroscopy (ESI). ¹H NMR spectra were recorded at 400-500 MHz. Compounds described herein were synthesized as a racemic mixture unless otherwise stated in the experimental procedures.

20 In some cases the final product may be further modified, for example, by manipulation of substituents. These manipulations may include, but are not limited to, reduction, oxidation, alkylation, acylation, and hydrolysis reactions which are commonly known to those skilled in the art. In some cases the order of carrying out the foregoing reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products. The following examples are provided so that the invention might be more fully understood. These examples are illustrative only and should not be construed as limiting the invention in any way.

List of Abbreviations

25	AcOH	=	acetic acid
	Anal.	=	analytical
	aq	=	aqueous
	<i>n</i> -BuLi	=	<i>n</i> -butyl lithium
30	br	=	broad
	calc.	=	calculated
	<i>m</i> -CPBA	=	3-chloroperoxybenzoic acid
	d	=	doublet
	DBAD	=	di-tert-butyl azodicarboxylate
35	DBU	=	1,8-diazabicyclo[5.4.0]undec-7-ene
	DCE	=	dichloroethane

	DCM	=	dichloromethane
	DEA	=	diethylamine
	DIEA	=	<i>N,N</i> -diisopropylethylamine
	DIPEA	=	<i>N,N</i> -diisopropylethylamine
5	DMA	=	<i>N,N</i> -dimethylacetamide
	DMF	=	<i>N,N</i> -dimethylformamide
	DMSO	=	dimethyl sulfoxide
	ESI	=	electrospray ionization
	EtOAc	=	ethyl acetate
10	EtOH	=	ethanol
	HATU	=	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium3-oxid hexafluorophosphate
	Hex	=	hexanes
	HPLC	=	high-pressure liquid chromatography
15	IPA	=	<i>iso</i> -propyl alcohol
	IPAc	=	<i>iso</i> -propyl acetate
	KF	=	Karl-Fischer titration (to determine water content)
	KOt-Bu	=	potassium <i>tert</i> -butoxide
	LCMS	=	liquid chromatography-mass spectrometry
20	LiHMDS	=	lithium hexamethyl silazane
	m	=	multiplet
	MeCN	=	acetonitrile
	MeOH	=	methyl alcohol
	MPa	=	milipascal
25	MS	=	mass spectroscopy
	MTBE	=	methyl <i>tert</i> -butyl ether
	NHS	=	normal human serum
	NMR	=	nuclear magnetic resonance spectroscopy
	PE	=	petroleum ether
30	Piv	=	pivalate, 2,2-dimethylpropanoyl
	Pd/C	=	palladium on carbon
	q	=	quartet
	rt	=	room temperature

s	=	singlet
sat. aq.	=	saturated aqueous
SEM-Cl	=	2-(trimethylsilyl)ethoxymethyl chloride
SFC	=	supercritical fluid chromatography
5 t	=	triplet
THF	=	THF
TFA	=	trifluoroacetic acid
TFAA	=	trifluoroacetic anhydride
TLC	=	thin-layer chromatography
10 <i>p</i> -TsOH	=	<i>para</i> -toluene sulfonic acid
wt%	=	percentage by weight
Xantphos	=	4,5- <i>bis</i> -(diphenylphosphino)-9,9-dimethylxanthene

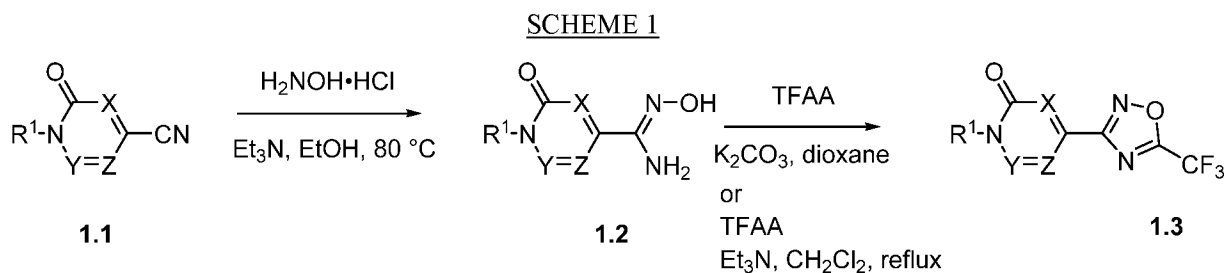
REACTION SCHEMES

15 The compounds of the present invention can be prepared readily according to the following Schemes and specific examples, or modifications thereof, using readily available starting materials, reagents and conventional synthetic procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art but are not mentioned in greater detail. The general procedures for making the compounds claimed in this invention can be readily

20 understood and appreciated by one skilled in the art from viewing the following Schemes.

Scheme 1 illustrates a general strategy for preparing the 5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl compounds of the present invention in which a nitrile intermediate (**1.1**) is heated with hydroxylamine to give the hydroxyamidine product **1.2**. Cyclization of **1.2** with TFAA in the presence of potassium carbonate or Et₃N then provides the 5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl product **1.3**.

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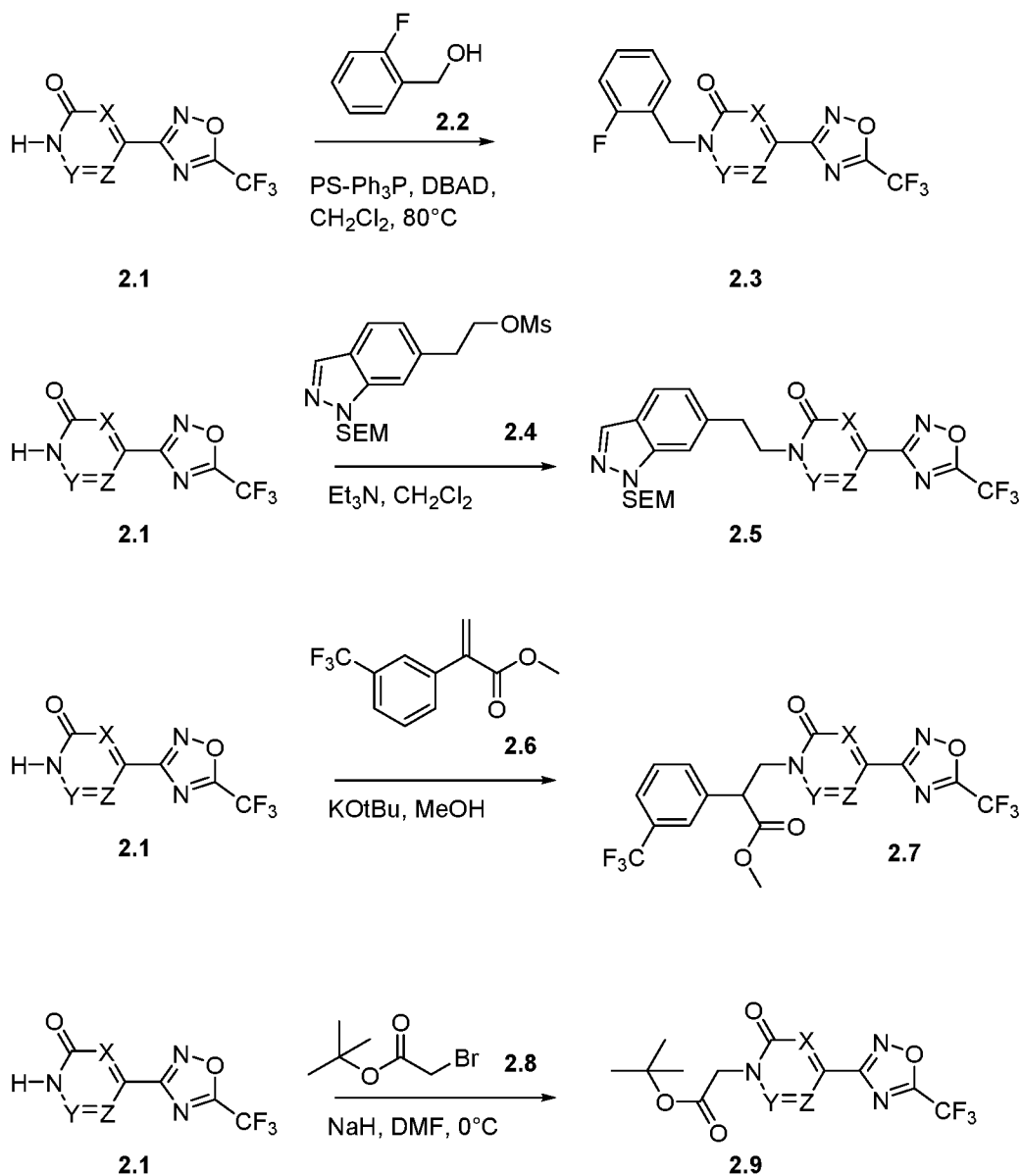


Scheme 2 depicts methods of preparing *N*-alkylated compounds of the present invention. *N*-alkylated compound **2.3** is prepared by a Mitsunobu reaction of pyridone **2.1** with benzyl alcohol **2.2**

30 using PS-Ph₃P and DBAD. For the preparation of *N*-alkylated compound **2.5**, mesylate **2.4** is reacted with pyridone **2.1** in the presence Et₃N. For the preparation of *N*-alkylated compound **2.7**, deprotonation of **2.1**

with KOtBu followed by the addition of ester **2.6** provides **2.7**. Deprotonation of **2.1** with NaH followed by the addition of bromide **2.8** affords *N*-alkylated compound **2.9**.

SCHEME 2



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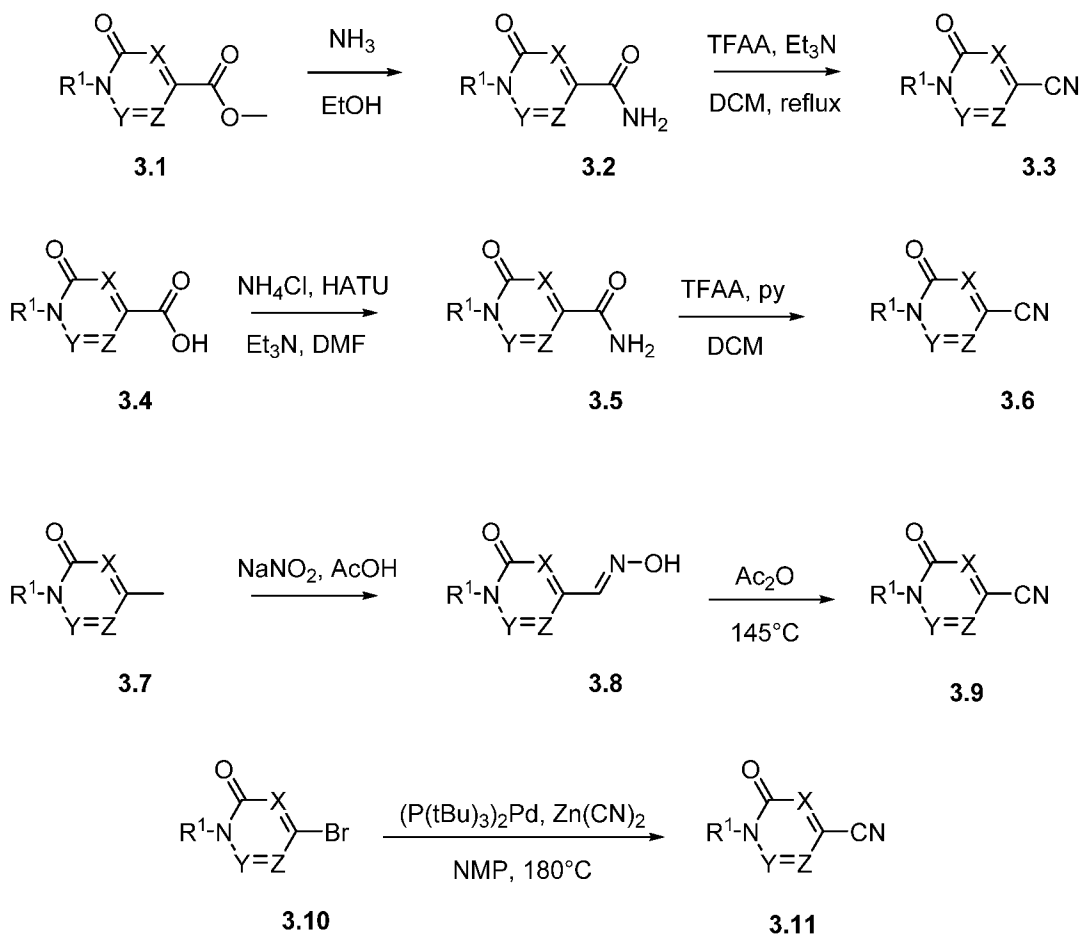
For the preparation of certain nitrile intermediates of the present invention, ester, carboxylic acid, methyl or bromide starting materials are utilized, as illustrated in Scheme 3. For example, in the synthesis of intermediate **3.3**, treatment of **3.1** with ammonia provides amide **3.2**, which is dehydrated with trifluoroacetic anhydride and triethylamine to give nitrile intermediate **3.3**. For the preparation of nitrile intermediate **3.6**, carboxylic acid **3.4** is coupled with ammonia under HATU conditions to furnish amide **3.5**. Dehydration of amide **3.5** using TFAA in the presence of pyridine then affords nitrile **3.6**. For the

10

preparation of nitrile intermediate **3.9**, methyl **3.7** is treated with sodium nitrite in the presence of AcOH to afford oxime **3.8**. Dehydration of oxime **3.8** using acetic anhydride affords nitrile **3.9**. Additionally, cyanation of bromide **3.10** with bis(tri-tert-butylphosphine)palladium and dicyanozinc affords nitrile intermediate **3.11**.

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SCHEME 3



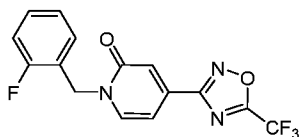
The following examples are presented to further illustrate compounds of the invention, but, with reference to the general formula presented above, they are not presented as limiting the invention to these specifically exemplified compounds. With appropriate modifications known to those skilled in the art, the compounds illustrated in the present application can be made in accordance to the following examples.

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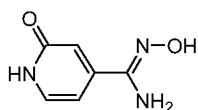
EXAMPLE 1

1-(2-fluorobenzyl)-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one

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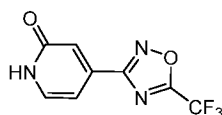


Step A: (Z)-N'-hydroxy-2-oxo-1,2-dihydropyridine-4-carboximidamide



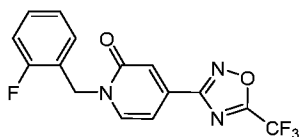
To a solution of 2-oxo-1,2-dihydropyridine-4-carbonitrile (4.35 g, 36.2 mmol) in EtOH (12 mL) was added 50% hydroxyl amine in water (12 mL, 1800 mmol). The resulting mixture was heated at reflux for 2 h and concentrated to give the title compound.

Step B: 4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one



To a solution of (Z)-N'-hydroxy-2-oxo-1,2-dihydropyridine-4-carboximidamide (5500 mg, 35.9 mmol) in CH₂Cl₂ (180 mL) was added Et₃N (15.0 mL, 108 mmol) followed by dropwise addition of TFAA (15.2 mL, 108 mmol). The resulting mixture was stirred at 23 °C for 2 h, and then concentrated. The residue was suspended in CH₂Cl₂, filtered, and washed with CH₂Cl₂ to give the title compound as a powder. MS (ESI) *m/z* [M+H]⁺: 232.1.

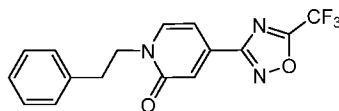
Step C: 1-(2-fluorophenyl)-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one (1-4)



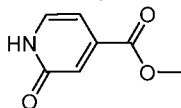
To a suspension of 4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one (500 mg, 2.16 mmol) in THF (20 mL) was added (2-fluorophenyl)methanol (546 mg, 4.33 mmol), PS-Ph₃P (1.97 g, 6.49 mmol), and DBAD (747 mg, 3.24 mmol). The resulting mixture was sonicated for 12 h, filtered, and concentrated. The residue was purified by reverse-phase HPLC to give the title compound. ¹H NMR (500 MHz, DMSO): δ 8.01 (1 H, d, *J* = 7.07 Hz), 7.38 (1 H, d, *J* = 7.84 Hz), 7.18-7.26 (3 H, m), 7.05 (1 H, s), 6.83 (1 H, d, *J* = 7.03 Hz), 5.23 (2 H, s); MS (ESI) *m/z* [M+H]⁺: 340.2.

EXAMPLE 2

1-Phenethyl-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one

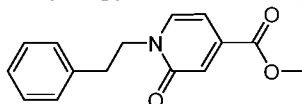


Step A: Methyl 2-oxo-1,2-dihydropyridine-4-carboxylate



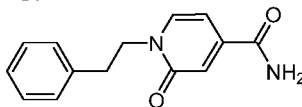
- 5 To a solution of 2-oxo-1,2-dihydropyridine-4-carboxylic acid (2.00 g, 14.4 mmol) in MeOH (80 mL) was added concentrated sulfuric acid (1 mL). The mixture was evacuated and back-filled with nitrogen three times, then and heated at 70 °C for 12 h. The mixture was cooled to room temperature and saturated aqueous sodium bicarbonate solution (200 mL) was added. Methanol was removed under reduced pressure. The resulting aqueous mixture was extracted with ethyl acetate (3 X 200 mL). The combined organic layers were washed with brine (200 mL), dried (Na₂SO₄), and concentrated under reduced pressure to give methyl 2-oxo-1,2-dihydropyridine-4-carboxylate as a solid. MS (ESI) *m/z* [M+H]⁺: 153.8.

Step B: Methyl 2-oxo-1-phenethyl-1,2-dihydropyridine-4-carboxylate



- 15 To a mixture of methyl 2-oxo-1,2-dihydropyridine-4-carboxylate (1.00 g, 6.53 mmol) in DMF (10 mL) was added sodium hydride (0.392 g, 9.80 mmol) (60% in mineral oil) at 0 °C, and after 30 min, a solution of (2-bromoethyl)benzene (1.450 g, 7.84 mmol) in DMF (5 mL) was added. The resulting mixture was stirred at 15 °C for 12 h. The mixture was cooled to 0 °C and saturated aqueous ammonium chloride (100 mL) was added slowly. The water layer was extracted with EtOAc (150 mLx2). The combined organic layers were washed with brine (200 mL) and dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO[®]; 40 g SepaFlash[®] Silica Flash Column, Eluent of 0~15% MeOH/DCM gradient @ 40 mL/min) to give methyl 2-oxo-1-phenethyl-1,2-dihydropyridine-4-carboxylate as a solid. MS (ESI) *m/z* [M+H]⁺: 257.9.

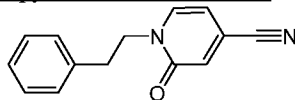
- 25 **Step C:** 2-Oxo-1-phenethyl-1,2-dihydropyridine-4-carboxamide



- A mixture of methyl 2-oxo-1-phenethyl-1,2-dihydropyridine-4-carboxylate (900 mg, 3.50 mmol) in a saturated solution of NH₃ in ethanol (30 mL) was heated at 70 °C for 66 h. After cooling to room temperature, the mixture was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO[®]; 40 g SepaFlash[®] Silica Flash Column, Eluent of 0~15% MeOH/DCM

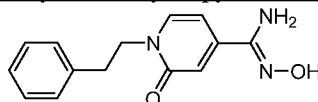
gradient @ 40 mL/min) to give 2-oxo-1-phenethyl-1,2-dihydropyridine-4-carboxamide as a solid. MS (ESI) m/z $[M+H]^+$: 242.8.

Step D: 2-Oxo-1-phenethyl-1,2-dihydropyridine-4-carbonitrile



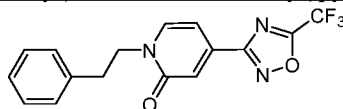
A mixture of TFAC (0.350 mL, 2.48 mmol), pyridine (0.200 mL, 2.48 mmol) and 2-oxo-1-phenethyl-1,2-dihydropyridine-4-carboxamide (300 mg, 1.24 mmol) in THF (6 mL) was stirred at 15 °C for 2 h. After cooling to room temperature, the mixture was diluted with EtOAc (15 mL) and washed with H₂O (15 mL). The water layer was extracted with EtOAc (15 mLx2). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to give 2-oxo-1-phenethyl-1,2-dihydropyridine-4-carbonitrile as an oil. MS (ESI) m/z $[M+H]^+$: 225.1.

Step E: (Z)-N'-hydroxy-2-oxo-1-phenethyl-1,2-dihydropyridine-4-carboximidamide



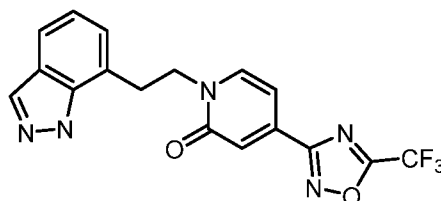
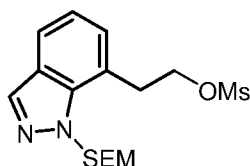
A mixture of 2-oxo-1-phenethyl-1,2-dihydropyridine-4-carbonitrile (300 mg, 1.34 mmol), hydroxylamine hydrochloride (232 mg, 3.34 mmol) and triethylamine (0.559 mL, 4.01 mmol) in EtOH (10 mL) was heated at 80 °C for 2 hours. After cooling to room temperature, the mixture was concentrated under reduced pressure to give a residue, which was diluted with H₂O (20 mL). The aqueous mixture was extracted with EtOAc (30 mLx3). The combined organic layers were washed with brine (25 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to give (Z)-N'-hydroxy-2-oxo-1-phenethyl-1,2-dihydropyridine-4-carboximidamide as a solid. MS (ESI) m/z $[M+H]^+$: 258.1.

Step F: 1-Phenethyl-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one

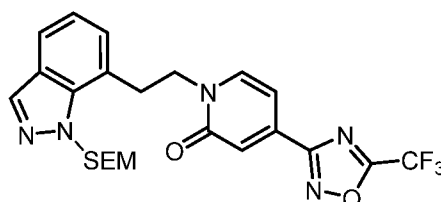


A mixture of potassium carbonate (45.1 mg, 0.326 mmol), methyl 2,2,2-trifluoroacetate (69.7 mg, 0.544 mmol), and (Z)-N'-hydroxy-2-oxo-1-phenethyl-1,2-dihydropyridine-4-carboximidamide (70 mg, 0.272 mmol) in toluene (2 mL) and DMF (0.2 mL) was heated at 80 °C for 16 h. After cooling to the room temperature, the mixture was concentrated and the residue purified by reverse Prep-HPLC (preparative HPLC on a GILSON 281 instrument fitted with Phenomenex Synergi C18 250x21.2mmx4um using water and acetonitrile as the eluents. Mobile phase A: water, mobile phase B: acetonitrile (containing: 0.1%TFA-ACN). Gradient: 40-70%, 0-10 min; 100% B, 10.5-12.5min; 5% B, 13-15min) to give 1-phenethyl-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one as an oil. ¹H NMR (400 MHz, CDCl₃): δ 7.38 (s, 1H), 7.32 - 7.26 (m, 2H), 7.25 - 7.21 (m, 1H), 7.15 (d, J = 6.8 Hz, 2H), 7.00 (d, J = 7.1 Hz, 1H), 6.61 (dd, J = 1.7, 6.9 Hz, 1H), 4.20 (t, J = 6.9 Hz, 2H), 3.10 (t, J = 6.9 Hz, 2H); MS (ESI) m/z $[M+H]^+$: 336.1.

EXAMPLE 3

1-(2-(1H-indazol-7-yl)ethyl)-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one5 **Step A:** 2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-7-yl)ethyl methanesulfonate

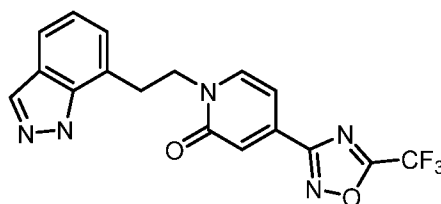
MsCl (0.052 mL, 0.667 mmol) was added to a mixture of Et₃N (0.124 mL, 0.889 mmol) and 2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-7-yl)ethanol (130 mg, 0.445 mmol) in DCM (5 mL) at 15 °C. After the addition was complete, the mixture was stirred at 15 °C for 3 h. The mixture was partitioned between CH₂Cl₂ (20 mL) and H₂O (20 mL), and the aqueous layer was extracted with CH₂Cl₂ (2 x 10 mL). The combined organic layers were washed with brine (20 mL), dried (MgSO₄), and concentrated under reduced pressure to give 2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-7-yl)ethyl methanesulfonate as an oil.

15 **Step B:** 4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)-1-(2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-7-yl)ethyl)pyridin-2(1H)-one

A mixture of 4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one (94.0 mg, 0.405 mmol), potassium carbonate (112 mg, 0.810 mmol) and 2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-7-yl)ethyl methanesulfonate (150 mg, 0.405 mmol) in CH₃CN (5 mL) was heated at 90 °C for 16 h. After cooling to room temperature, the mixture was filtered, the filtered solid washed with EtOAc (50 mL), and the combined filtrate concentrated under reduced pressure. The residue was purified by reverse Prep-HPLC (preparative HPLC on a GILSON 281 instrument fitted with Waters XSELECT C18 150x30mmx5um using water and acetonitrile as the eluents. Mobile phase A: water, mobile phase B: acetonitrile (containing: 0.1%TFA-ACN) Gradient:28-68%, 0-10 min; 100% B, 10.5-12.5min; 5% B, 13-

15min) to give 4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)-1-(2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-7-yl)ethyl)pyridin-2(1H)-one as an oil. ESI-MS m/z $[M + H]^+$: 506.1

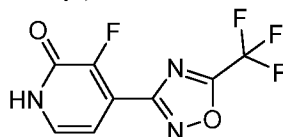
Step C: 1-(2-(1H-indazol-7-yl)ethyl)-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one



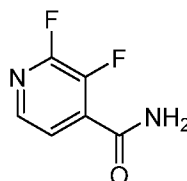
5 A mixture of 4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)-1-(2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-7-yl)ethyl)pyridin-2(1H)-one (75.0 mg, 0.148 mmol) in TFA:DCM = 1:2 (2 mL) was stirred at 15 °C for 6 h. The mixture was concentrated under reduced pressure and the residue was purified by reverse Prep-HPLC (preparative HPLC on a GILSON 281 instrument fitted with Waters XSELECT C18 150x30mmx5um using water and acetonitrile as the eluents. Mobile phase A: water,
10 mobile phase B: acetonitrile (containing: 0.1%TFA-ACN). Gradient: 38-68%, 0-10 min; 100% B, 10.5-12.5min; 5% B, 13-15min) to give 1-(2-(1H-indazol-7-yl)ethyl)-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridine-2(1H)-one as an oil. ^1H NMR (400 MHz, MeOH- d_4) δ : 8.09 (s, 1 H), 7.64 - 7.70 (m, 1 H), 7.46 - 7.52 (m, 1 H), 7.29 (d, J =1.32 Hz, 1 H), 7.10 - 7.15 (m, 1 H), 7.02 - 7.08 (m, 1 H), 6.75 - 6.85 (m, 1 H), 4.39 (s, 2 H), 3.40 (s, 2 H); ESI-MS m/z $[M + H]^+$: 376.0

15 EXAMPLE 4

3-fluoro-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one



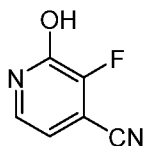
Step A: 2,3-difluoroisonicotinamide



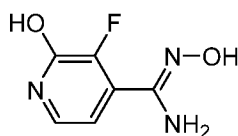
20 NH_4Cl (4.54 g, 85 mmol) was added to a stirred mixture of DIPEA (14.8 mL, 85 mmol), HATU (16.13 g, 42.4 mmol), and 2,3-difluoroisonicotinic acid (4.50 g, 28.3 mmol) in DMF (45 mL) at 17 °C, and the resulting mixture was stirred at 17 °C for 18 h. The reaction mixture was diluted with H_2O (40 mL) and extracted with EtOAc (3x30 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by SiO_2 column
25 chromatography (heptane: EtOAc = 95:5 to 40:60) to give 2,3-difluoroisonicotinamide as a solid.

Step B: 2,3-difluoroisonicotinonitrile

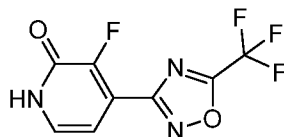
2,2,2-trifluoroacetic anhydride (7.97 g, 37.9 mmol) was added to a stirred mixture of 2,3-difluoroisonicotinamide (3.00 g, 19.0 mmol), and triethylamine (5.76 g, 56.9 mmol) in DCM (30 mL) at 15 °C, and the resulting mixture was stirred at 15 °C for 17 h. The mixture was diluted with H₂O (50 mL). The water layer was extracted with DCM (40 mLx3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by SiO₂ column chromatography (heptane: EtOAc = 95:5 to 40:60) to give 2,3- difluoroisonicotinonitrile as a solid.

Step C: 3-fluoro-2-hydroxyisonicotinonitrile

A mixture of 2,3-difluoroisonicotinonitrile (1.00 g, 7.14 mmol) and aqueous hydrogen chloride solution (2N, 2.68 mL, 5.35 mmol) was placed in a microwave tube and heated at 150 °C for 10 min. The reaction mixture was concentrated under reduced pressure to give 3-fluoro-2-oxo-1, 2- dihydropyridine-4- carbonitrile as a solid and that was used directly without further purification.

Step D: (Z)-3-fluoro-N',2-dihydroxyisonicotinimidamide

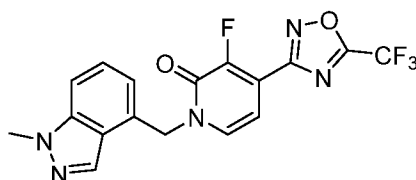
A mixture of 3-fluoro-2-hydroxyisonicotinonitrile (900 mg, 6.52 mmol), hydroxylamine hydrochloride (906 mg, 13.0 mmol) and triethylamine (1.82 mL, 13.0 mmol) in EtOH (20 mL) was heated at 80 °C for 2 h. The contents in the flask were concentrated to give (Z)-3-fluoro-N', 2- dihydroxyisonicotinimidamide as a solid.

Step E: 3-fluoro-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one

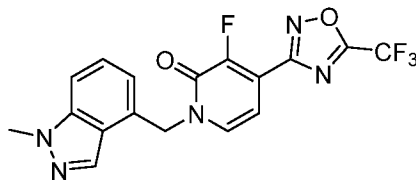
A mixture of (Z)-3-fluoro-N',2-dihydroxyisonicotinimidamide (1115 mg, 6.52 mmol), K₂CO₃ (1081 mg, 7.82 mmol) and TFAA (3.68 mL, 26.1 mmol) in dioxane (20 mL) was stirred for 4 h. The contents in the flask were partitioned between ethyl acetate (30 mL) and water (20 mL). The organic layer was washed with brine (30 mLx2), dried over Na₂SO₄, and concentrated *in vacuo*. The crude product was purified by column chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~10% MeOH/DCM gradient @ 30 mL/min) to give 3-fluoro-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one as a solid. ¹H NMR (400 MHz, MeOD) δ: 7.41 (dd, *J*=1.5, 7.1 Hz, 1H), 6.86 (dd, *J*=5.3, 6.8 Hz, 1H); ESI-MS *m/z* [M + H]⁺: 250.0.

EXAMPLE 5

3-fluoro-1-((1-methyl-1H-indazol-4-yl)methyl)-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one



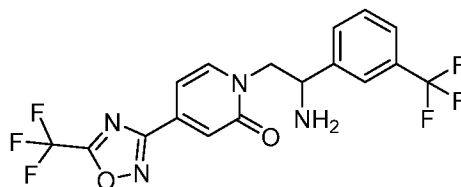
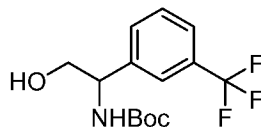
Step A: 3-fluoro-1-((1-methyl-1H-indazol-4-yl)methyl)-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one



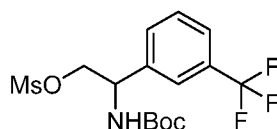
To a solution of 3-fluoro-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one (50.0 mg, 0.201 mmol) in CH₂Cl₂ (2 mL) was added (1-methyl-1H-indazol-4-yl)methanol (48.8 mg, 0.301 mmol), polymer-supported triphenyl phosphine (~3mmol/g, 200 mg, 0.600 mmol), and (E)-di-tert-butyl diazene-1,2-dicarboxylate (92 mg, 0.401 mmol) in CH₂Cl₂ (2 mL). The reaction was sealed and heated at 80 °C for 3 h, then filtered and concentrated. The residue was chromatographed using HPLC purification (19 cm x 150cm C18, 30 min 0-95% acetonitrile-water gradient, 0.05% TFA added) to yield an oil. ¹H NMR (CHCl₃-*d*, 600 MHz): δ 8.11 (1H, s), 8.04 (1H, s), 7.19 (1H, dd, *J* = 7.4, 1.7 Hz), 7.10 (1H, dd, *J* = 21.7, 6.7 Hz), 6.62 (1H, dd, *J* = 7.4, 5.5 Hz), 5.53 (2H, s), 5.02 (1H, s), 4.07 (3H, d, *J* = 1.5 Hz); ESI-MS *m/z* [M + H]⁺: 394.2.

EXAMPLE 6

1-(2-amino-2-(3-(trifluoromethyl)phenyl)ethyl)-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-

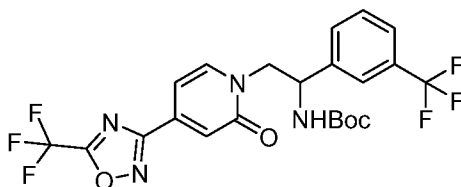
2(1H)-one**Step A:** tert-butyl (2-hydroxy-1-(3-(trifluoromethyl)phenyl)ethyl)carbamate

- 5 Isobutyl chloroformate (141 mg, 1.03 mmol) was added to a mixture of 2-((tert-butoxycarbonyl)amino)-2-(3-(trifluoromethyl)phenyl)acetic acid (300 mg, 0.940 mmol) and 4-methylmorpholine (0.114 mL, 1.034 mmol) in THF (6 mL) at -30 °C under N₂. After the addition was complete, the mixture was stirred at -30 °C for 1 h. NaBH₄ (107 mg, 2.82 mmol) was added to the mixture followed by water (0.15 mL). The resulting mixture was stirred at 0 °C for 1 h, then partitioned
- 10 between water (10 mL) and EtOAc (10 mLx3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~20% MeOH/DCM gradient @ 18 mL/min) to give tert-butyl (2-hydroxy-1-(3-(trifluoromethyl)phenyl)ethyl)carbamate as an oil.

15 **Step B:** 2-((tert-butoxycarbonyl)amino)-2-(3-(trifluoromethyl)phenyl)ethyl

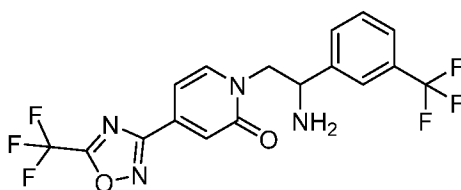
- MsCl (0.123 mL, 1.57 mmol) was added to a mixture of TEA (0.329 mL, 2.36 mmol) and N,N-dimethylpyridin-4-amine (28.8 mg, 0.236 mmol) and tert-butyl (2-hydroxy-1-(3-(trifluoromethyl)phenyl)ethyl)carbamate (240 mg, 0.786 mmol) in DCM (8 mL) at 0 °C. After the
- 20 addition was complete, the mixture was stirred at 0 °C for 1 h. The mixture was partitioned between H₂O (15 mL) and EtOAc (15 mLx3). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to give 2-((tert-butoxycarbonyl)amino)-2-(3-(trifluoromethyl)phenyl)ethyl methanesulfonate as an oil.

25 **Step C:** tert-butyl (2-(2-oxo-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-1(2H)-yl)-1-(3-(trifluoromethyl)phenyl)ethyl)carbamate



A mixture of potassium carbonate (162 mg, 1.17 mmol), 2-((tert-butoxycarbonyl)amino)-2-(3-(trifluoro-methyl)phenyl)ethyl methanesulfonate (150 mg, 0.391 mmol) and 4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one (90.0 mg, 0.391 mmol) in MeCN (5 mL) was stirred at 90 °C for 1 h under N₂. After cooling to room temperature, the mixture was partitioned between H₂O (15 mL) and EtOAc (15 mLx3). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to give tert-butyl (2-(2-oxo-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-1(2H)-yl)-1-(3-(trifluoromethyl)phenyl)ethyl)carbamate as an oil.

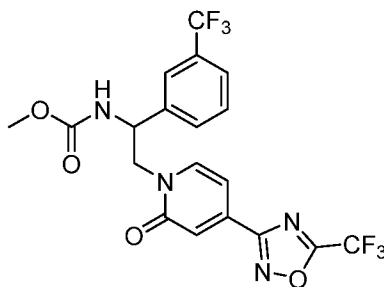
Step D: 1-(2-amino-2-(3-(trifluoromethyl)phenyl)ethyl)-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one



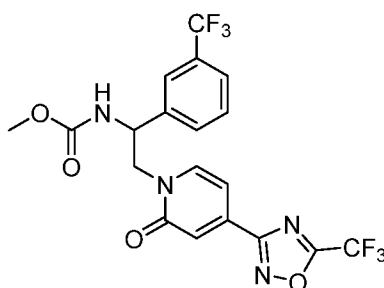
TFA (0.119 mL, 1.543 mmol) was added to a solution of tert-butyl (2-(2-oxo-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-1(2H)-yl)-1-(3-(trifluoromethyl)phenyl)ethyl)carbamate (160 mg, 0.309 mmol) in DCM (2 mL). After the addition was complete, the mixture was stirred at 25 °C for 16 h. The mixture was concentrated under reduced pressure and the residue was purified by reverse Prep-HPLC (preparative HPLC on an EA instrument fitted with a Agela ASB 150 x 25mm x 5um using water and acetonitrile as the eluents. Mobile phase A: water (containing: 0.1%TFA), mobile phase B: acetonitrile. Gradient: 17-37%) to give 1-(2-amino-2-(3-(trifluoromethyl)phenyl)ethyl)-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one as a solid. ¹H NMR (400 MHz, CHCl₃-d) δ ppm 4.39 (br d, *J*=10.56 Hz, 1 H), 4.68 (br s, 1 H), 5.06 (br s, 1 H), 6.72 (br d, *J*=6.71 Hz, 1 H), 7.08 - 7.18 (m, 2 H), 7.49 - 7.56 (m, 1 H), 7.64 (br d, *J*=7.81 Hz, 1 H), 7.71 (br s, 2 H); ESI-MS *m/z* [M + H]⁺: 419.1.

EXAMPLE 7

methyl (2-(2-oxo-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-1(2H)-yl)-1-(3-(trifluoromethyl)phenyl)ethyl)carbamate



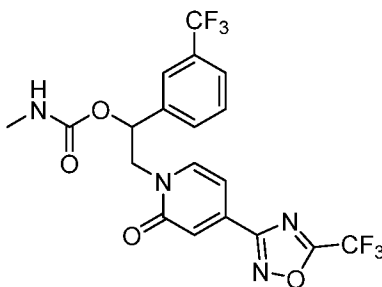
Step A: methyl (2-(2-oxo-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-1(2H)-yl)-1-(3-(trifluoromethyl)phenyl)ethyl)carbamate



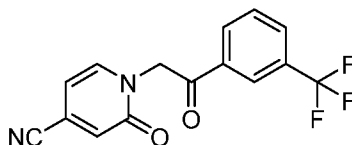
- 5 Methyl carbonochloridate (40.7 mg, 0.430 mmol) was added to a mixture of 1-(2-amino-2-(3-(trifluoromethyl)phenyl)ethyl)-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one (60.0 mg, 0.143 mmol) and TEA (0.100 mL, 0.717 mmol) in DCM (10 mL) under N₂. After the addition was complete, the mixture was stirred at 0 °C for 1 h. The mixture was partitioned between H₂O (15 mL) and EtOAc (15 mLx3). The combined organic layers were washed with brine (15 mL), dried over anhydrous
- 10 Na₂SO₄, and concentrated under reduced pressure. The residue was purified by prep-TLC (SiO₂, PE: EA=2:1) to give methyl (2-(2-oxo-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-1(2H)-yl)-1-(3-(trifluoromethyl)phenyl)ethyl)carbamate as a solid. ¹H NMR (400 MHz, CHCl₃-d) δ ppm 2.90 (s, 1 H) 3.53 (s, 3 H) 3.64 (s, 1 H) 4.10 (br d, *J*=13.45 Hz, 1 H) 4.32 - 4.49 (m, 2 H) 5.04 - 5.14 (m, 1 H) 6.61 - 6.75 (m, 2 H) 7.13 (d, *J*=7.06 Hz, 1 H) 7.36 (d, *J*=1.32 Hz, 1 H) 7.41 - 7.56 (m, 6 H); ESI-MS *m/z* [M +
- 15 H]⁺: 477.1.

EXAMPLE 8

2-(2-oxo-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-1(2H)-yl)-1-(3-(trifluoromethyl)-phenyl)ethyl methylcarbamate

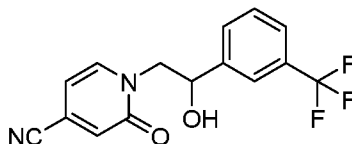


Step A: 2-oxo-1-(2-oxo-2-(3-(trifluoromethyl)phenyl)ethyl)-1,2-dihydropyridine-4-carbonitrile



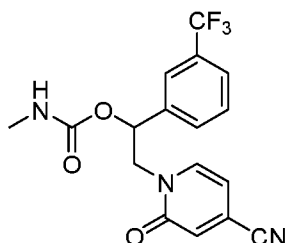
To a solution of 2-oxo-1,2-dihydropyridine-4-carbonitrile (4.50 g, 37.5 mmol) in DMSO (25 mL) and acetonitrile (25 mL) was added 2-bromo-1-(3-(trifluoromethyl)phenyl)ethanone (13.0 g, 48.7 mmol) at 0 °C. The solution was stirred at 0 °C for 10 min before K₂CO₃ (7.77 g, 56.2 mmol) was added. The solution was stirred at 0 °C for 1 h, then partitioned between water (150 mL) and ethyl acetate (3x150 mL). The combined organic layers were washed with brine (150 mL), dried over anhydrous Na₂SO₄, and concentrated to give 2-oxo-1-(2-oxo-2-(3-(trifluoromethyl)phenyl)ethyl)-1,2-dihydropyridine-4-carbonitrile as an oil.

Step B: 1-(2-hydroxy-2-(3-(trifluoromethyl)phenyl)ethyl)-2-oxo-1,2-dihydropyridine-4-carbonitrile



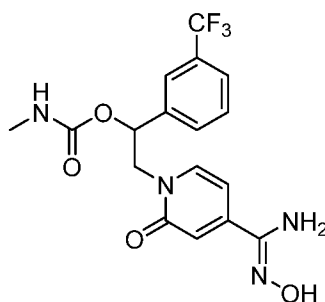
NaBH₄ (1112 mg, 29.4 mmol) was added to a solution of 2-oxo-1-(2-oxo-2-(3-(trifluoromethyl)phenyl)ethyl)-1,2-dihydropyridine-4-carbonitrile (4500 mg, 14.7 mmol) in THF (135 mL) at 0 °C. After the addition was complete, the mixture was stirred at 0 °C for 1 h, then partitioned between H₂O (30 mL) and EtOAc (30 mLx3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~50% EA/PE gradient @ 30 mL/min) to give 1-(2-hydroxy-2-(3-(trifluoromethyl)phenyl)ethyl)-2-oxo-1,2-dihydropyridine-4-carbonitrile as a solid.

Step C: 2-(4-cyano-2-oxopyridin-1(2H)-yl)-1-(3-(trifluoromethyl)phenyl)ethyl methylcarbamate



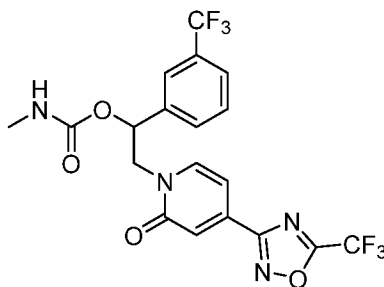
4-nitrophenyl carbonochloridate (785 mg, 3.89 mmol) was added to a mixture of DMAP (15.85 mg, 0.130 mmol), TEA (0.904 mL, 6.49 mmol) and 1-(2-hydroxy-2-(3-(trifluoromethyl)phenyl)ethyl)-2-oxo-1,2-dihydropyridine-4-carbonitrile (400 mg, 1.30 mmol) in DCM (8 mL). After the addition was complete, the mixture was stirred at 25 °C for 2 h, at which point a solution of methylamine (1N, 3.89 mL, 3.89 mmol) was added. The resulting mixture was stirred at 25 °C for 1 h, then partitioned between H₂O (30 mL) and EtOAc (30 mLx3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO[®]; 20 g SepaFlash[®] Silica Flash Column, Eluent of 0~50% EtOAc/pentanes gradient @ 30 mL/min) to give 2-(4-cyano-2-oxopyridin-1(2H)-yl)-1-(3-(trifluoromethyl)phenyl)ethyl methylcarbamate as an oil.

Step D: (Z)-2-(4-(N'-hydroxycarbamimidoyl)-2-oxopyridin-1(2H)-yl)-1-(3-(trifluoromethyl)phenyl)ethyl methylcarbamate



To a solution of 2-(4-cyano-2-oxopyridin-1(2H)-yl)-1-(3-(trifluoromethyl)phenyl)ethyl methylcarbamate (250 mg, 0.684 mmol) in EtOH (12 mL) was added TEA (0.477 mL, 3.42 mmol) and hydroxylamine hydrochloride (143 mg, 2.05 mmol) at 25 °C. The resulting solution was heated at 80 °C for 1 h. The mixture was cooled and concentrated to give (Z)-2-(4-(N'-hydroxycarbamimidoyl)-2-oxopyridin-1(2H)-yl)-1-(3-(trifluoromethyl)phenyl)ethyl methylcarbamate as an oil.

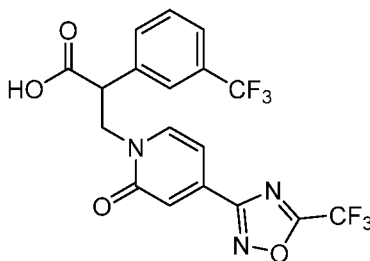
Step E: 2-(2-oxo-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-1(2H)-yl)-1-(3-(trifluoromethyl)phenyl)ethyl methylcarbamate



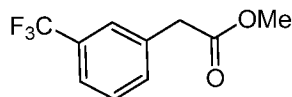
A mixture of K_2CO_3 (312 mg, 2.26 mmol), TFAA (0.319 mL, 2.259 mmol) and (Z)-2-(4-(N'-hydroxycarbamimidoyl)-2-oxopyridin-1(2H)-yl)-1-(3-(trifluoromethyl)phenyl)ethyl methylcarbamate (300 mg, 0.753 mmol) in 1,4-dioxane (10 mL) was stirred at 25 °C for 16 h. The mixture was partitioned between H_2O (20 mL) and EtOAc (20 mLx3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The residue was purified by reverse Prep-HPLC (preparative HPLC on an EF instrument fitted with a Agela ASB 150x25mmx5um using water and acetonitrile as the eluents. Mobile phase A: water (containing: 0.1%TFA), mobile phase B: acetonitrile. Gradient: 42-72%) to give 2-(2-oxo-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-1(2H)-yl)-1-(3-(trifluoromethyl)phenyl)ethyl methylcarbamate as a solid. 1H NMR (400 MHz, $CHCl_3-d$): δ 2.73 (d, $J=4.85$ Hz, 3 H), 3.98 (dd, $J=13.78$, 9.37 Hz, 1 H), 4.52 (dd, $J=13.67$, 3.09 Hz, 1 H), 4.78 (br d, $J=4.41$ Hz, 1 H), 6.13 (br dd, $J=9.04$, 2.87 Hz, 1 H), 6.73 - 6.81 (m, 1 H), 7.34 - 7.42 (m, 2 H), 7.47 - 7.56 (m, 1 H), 7.58 - 7.68 (m, 3 H); ESI-MS m/z $[M + H]^+$: 477.1.

EXAMPLE 9

3-(2-oxo-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-1(2H)-yl)-2-(3-(trifluoromethyl)phenyl)propanoic acid



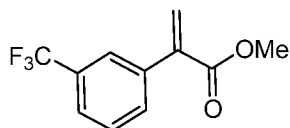
Step A: methyl 2-(3-(trifluoromethyl)phenyl)acetate



A mixture of 2-(3-(trifluoromethyl)phenyl)acetic acid (30.0 g, 147 mmol) and hydrogen chloride solution (4N, 100 mL, 400 mmol) was heated at 75 °C for 3 h. After cooling to room temperature, the mixture was concentrated under reduced pressure. The residue was partitioned between H_2O (300 mL) and

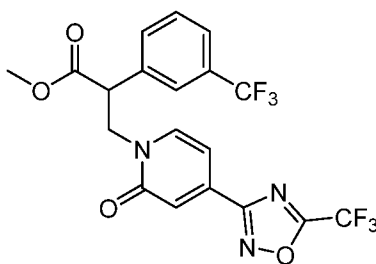
EtOAc (300 mLx3). The combined organic layers were washed with brine (300 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to give methyl 2-(3-(trifluoromethyl)phenyl)acetate as an oil.

Step B: methyl 2-(3-(trifluoromethyl)phenyl)acrylate



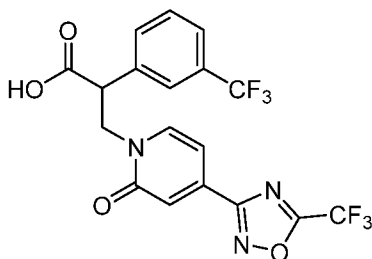
A mixture of tetrabutylammonium iodide (1.22 g, 3.30 mmol), potassium carbonate (36.5 g, 264 mmol), methyl 2-(3-(trifluoromethyl)phenyl)acetate (22.3 g, 743 mmol) and methyl 2-(3-(trifluoromethyl)phenyl)acrylate (18 g, 83 mmol) in toluene (250 mL) was heated at 80 °C for 16 h under N₂. After cooling to room temperature, the mixture was filtered, then partitioned between H₂O (300 mL) and EtOAc (300 mLx3). The combined organic layers were washed with brine (300 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to give methyl 2-(3-(trifluoromethyl)phenyl)acrylate as an oil.

Step C: methyl 3-(2-oxo-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-1(2H)-yl)-2-(3-(trifluoromethyl)phenyl)propanoate



Potassium 2-methylpropan-2-olate (0.049 g, 0.43 mmol) was added to a mixture of methyl 2-(3-(trifluoromethyl)phenyl)acrylate (1.49 g, 6.49 mmol) and 4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one (1.00 g, 4.33 mmol) in MeOH (30 mL). After the addition was complete, the mixture was stirred at 28 °C for 2 h. The mixture was concentrated under reduced pressure, and the residue was partitioned between H₂O (30 mL) and EtOAc (30 mLx3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO[®]; 20 g SepaFlash[®] Silica Flash Column, Eluent of 0~50% EA/PE gradient @ 30 mL/min) to give methyl 3-(2-oxo-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-1(2H)-yl)-2-(3-(trifluoromethyl)phenyl)propanoate as an oil.

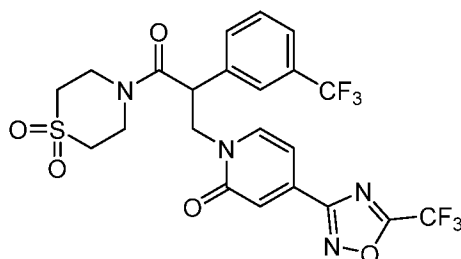
Step C: 2-benzyl-5-phenyl-4-(trifluoromethyl)-4,5-dihydrothiazol-4-ol



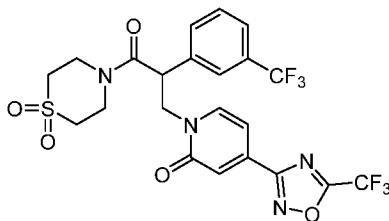
A mixture of methyl 3-(2-oxo-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-1(2H)-yl)-2-(3-(trifluoromethyl)phenyl)propanoate (1.05 g, 2.28 mmol) in AcOH (60 mL) and aqueous hydrochloric acid solution (37%, 30 mL) was heated at 80 °C for 3 h. After cooling to room temperature, the mixture was concentrated under reduced pressure. The residue was partitioned between H₂O (60 mL) and EtOAc (60 mLx3). The combined organic layers were washed with brine (60 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by reverse Prep-HPLC (preparative HPLC on a EF instrument fitted with a Agela ASB 150x25mmx5um using water and acetonitrile as the eluents. Mobile phase A: water(containing: 0.1%TFA), mobile phase B: acetonitrile. Gradient: 39-69%) to give 3-(2-oxo-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-1(2H)-yl)-2-(3-(trifluoromethyl)phenyl)propanoic acid as a solid. ¹H NMR (400 MHz, CHCl₃-d) δ ppm 4.27 (dd, *J*=12.35, 5.07 Hz, 1 H), 4.43 - 4.57 (m, 2 H), 6.75 (dd, *J*=7.17, 1.87 Hz, 1 H), 7.31 (d, *J*=1.54 Hz, 1 H), 7.40 (d, *J*=7.06 Hz, 1 H), 7.44 - 7.50 (m, 1 H), 7.53 - 7.62 (m, 3 H); ESI-MS *m/z* [M + H]⁺: 448.1.

EXAMPLE 10

1-(3-(1,1-dioxidothiomorpholino)-3-oxo-2-(3-(trifluoromethyl)phenyl)propyl)-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one



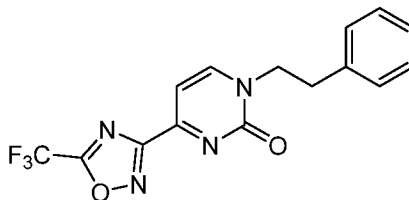
Step A: 1-(3-(1,1-dioxidothiomorpholino)-3-oxo-2-(3-(trifluoromethyl)phenyl)propyl)-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one



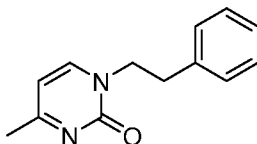
Oxalyl dichloride (0.069 mL, 0.80 mmol) was added to a solution of 3-(2-oxo-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-1(2H)-yl)-2-(3-(trifluoromethyl)phenyl)propanoic acid (300 mg, 0.671 mmol) in DCM (6 mL) at 0 °C. After the addition was complete, DMF (0.01 mL) was added to the mixture and stirring was continued at 0 °C for 15 min. A solution of N-ethyl-N-isopropylpropan-2-amine (0.351 mL, 2.01 mmol) and thiomorpholine 1,1-dioxide (136 mg, 1.01 mmol) in DCM (3 mL) was added to the mixture. The resulting mixture was stirred at 0 °C for 1 h. The mixture was partitioned between H₂O (50 mL) and EtOAc (50 mLx3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by reverse Prep-HPLC on an EF instrument fitted with a Agela ASB 150x25mmx5um using water and acetonitrile as the eluents. Mobile phase A: water (containing: 0.1%TFA), mobile phase B: acetonitrile. Gradient: 40-70%) to give 1-(3-(1,1-dioxidothiomorpholino)-3-oxo-2-(3-(trifluoromethyl)phenyl)propyl)-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one as a solid. ¹H NMR (400 MHz, CHCl₃-d): δ 2.09 - 2.19 (m, 1 H), 2.66 (br d, *J*=14.11 Hz, 1 H), 2.78 - 2.94 (m, 2 H), 3.69 - 3.77 (m, 2 H), 3.79 - 3.89 (m, 1 H), 4.14 - 4.26 (m, 2 H), 4.38 (dd, *J*=12.79, 8.38 Hz, 1 H), 4.76 (dd, *J*=8.38, 5.29 Hz, 1 H), 6.66 (dd, *J*=7.06, 1.76 Hz, 1 H), 7.30 (d, *J*=1.32 Hz, 1 H), 7.34 (d, *J*=7.06 Hz, 1 H), 7.49 (d, *J*=5.07 Hz, 2 H), 7.53 (s, 1 H), 7.58 (br d, *J*=3.75 Hz, 1 H); ESI-MS *m/z* [M + H]⁺: 565.0.

EXAMPLE 11

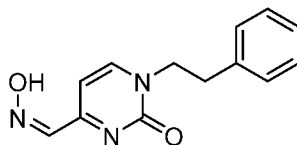
1-phenethyl-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyrimidin-2(1H)-one



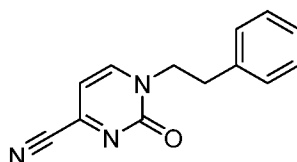
Step A: 4-methyl-1-phenethylpyrimidin-2(1H)-one



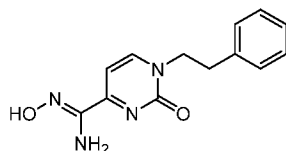
Cs₂CO₃ (5.00 g, 15.4 mmol) was added to a stirred mixture of (2-bromoethyl)benzene (2.08 g, 11.3 mmol) and 4-methylpyrimidin-2-ol hydrochloride (1.50 g, 10.2 mmol) in DMF (15 mL) at 30 °C. The mixture was heated at 90 °C for 16 h under N₂. The mixture was cooled, diluted with EtOAc (50 mL), washed with water (50 mL), dried (Na₂S₂O₄), and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO[®]; 20 g SepaFlash[®] Silica Flash Column, Eluent of 0~10% DCM/MeOH gradient @ 20 mL/min) to give 4-methyl-1-phenethylpyrimidin-2(1H)-one as a solid.

Step B: (Z)-2-oxo-1-phenethyl-1,2-dihydropyrimidine-4-carbaldehyde oxime

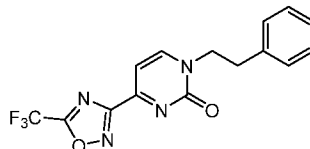
To a solution of 4-methyl-1-phenethylpyrimidin-2(1H)-one (500 mg, 2.33 mmol) in 10 mL of 50% aqueous acetic acid at 0 °C was added sodium nitrite (242 mg, 3.50 mmol). After 30 min the precipitate was filtered to afford (Z)-2-oxo-1-phenethyl-1,2-dihydropyrimidine-4-carbaldehyde oxime as a solid.

Step C: 2-oxo-1-phenethyl-1,2-dihydropyrimidine-4-carbonitrile

(Z)-2-oxo-1-phenethyl-1,2-dihydropyrimidine-4-carbaldehyde oxime (300 mg, 1.23 mmol) was added to acetic anhydride (5 mL) at 30 °C and the resulting mixture was heated at 145 °C for 2 h under N₂. The mixture was added to ice water and stirred for 30 min. The precipitate was collected by filtration to give 2-oxo-1-phenethyl-1,2-dihydropyrimidine-4-carbonitrile as a solid.

Step D: (Z)-N'-hydroxy-2-oxo-1-phenethyl-1,2-dihydropyrimidine-4-carboximidamide

To a solution of 2-oxo-1-phenethyl-1,2-dihydropyrimidine-4-carbonitrile (100 mg, 0.444 mmol) in EtOH (1 mL) was added triethylamine (180 mg, 1.78 mmol) and hydroxylamine hydrochloride (93 mg, 1.33 mmol) at 25 °C. The resulting solution was heated at 60 °C for 2 h, and then concentrated to give (Z)-N'-hydroxy-2-oxo-1-phenethyl-1,2-dihydropyrimidine-4-carboximidamide as an oil. MS (ESI) *m/z* [M+H]⁺: 258.9.

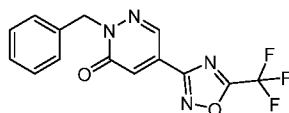
Step E: 1-phenethyl-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyrimidin-2(1H)-one

To a solution of (Z)-N'-hydroxyl-2-oxo-1-phenethyl-1,2-dihydropyrimidine-4-carboximidamide (115 mg, 0.445 mmol) in dioxane (1.5 mL) was added TFAA (0.943 mL, 6.68 mmol) and K₂CO₃ (123

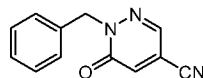
mg, 0.891 mmol). The resulting solution was stirred at 25 °C for 16 h. The mixture was partitioned between water (20 mL) and ethyl acetate (3x20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by prep-HPLC on a GILSON 281 instrument fitted with a Waters XSELECT C18 150x30mmx5um using water and acetonitrile as the eluents. Mobile phase A: water (containing 0.1%TFA, v/v), mobile phase B: acetonitrile. Gradient: 28-58%B,0-10min;100%B,10.5-12.5min;5%B,13-15min to give 1-phenethyl-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyrimidin-2(1H)-one as a solid. ¹H NMR (400 MHz, CDCl₃): δ 3.18 (t, *J*=6.58 Hz, 2 H), 4.23 (t, *J*=6.58 Hz, 2 H), 6.83 (d, *J*=6.58 Hz, 1 H), 7.12 (d, *J*=6.58 Hz, 2 H), 7.29 (br dd, *J*=6.80, 4.17 Hz, 4H); ESI-MS *m/z* [M + H]⁺: 336.9.

EXAMPLE 12

2-benzyl-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridazin-3(2H)-one

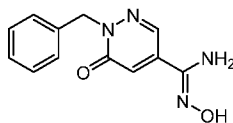


Step A: 1-benzyl-6-oxo-1,6-dihydropyridazine-4-carbonitrile

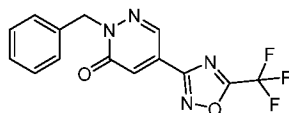


A mixture of bis(tri-*tert*-butylphosphine)palladium (82.0 mg, 0.160 mmol), dicyanozinc (282 mg, 2.403 mmol) and 2-benzyl-5-iodopyridazin-3(2H)-one (500 mg, 1.60 mmol) in NMP (10 mL) was placed in a microwave tube and heated at 180 °C for 30 min. After cooling to room temperature, the mixture was partitioned between H₂O (30 mL) and EtOAc (30 mLx3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, eluent of 0~30% EtOAc/pentanes gradient @ 30 mL/min) to give 1-benzyl-6-oxo-1,6-dihydropyridazine-4-carbonitrile as an oil.

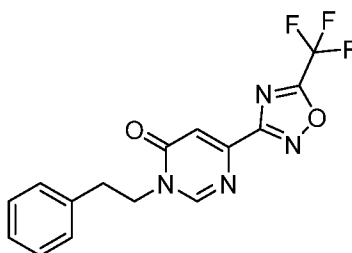
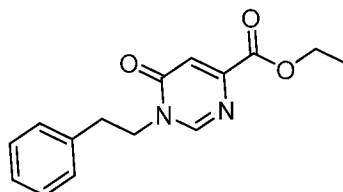
Step B: (Z)-1-benzyl-N'-hydroxy-6-oxo-1,6-dihydropyridazine-4-carboximidamide



A mixture of TEA (0.990 mL, 7.10 mmol), hydroxylamine hydrochloride (296 mg, 4.26 mmol) and 1-benzyl-6-oxo-1,6-dihydropyridazine-4-carbonitrile (300 mg, 1.42 mmol) in EtOH (12 mL) was heated at 80 °C for 2 h. After cooling to room temperature, the mixture was concentrated under reduced pressure to give (Z)-1-benzyl-N'-hydroxy-6-oxo-1,6-dihydropyridazine-4-carboximidamide as a solid.

Step C: 2-benzyl-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridazin-3(2H)-one

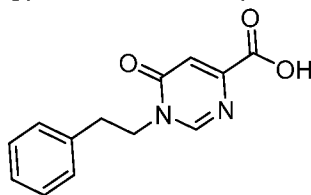
TFAA (2.313 mL, 16.38 mmol) was added to a mixture of K_2CO_3 (905 mg, 6.55 mmol) and (Z)-1-benzyl-N'-hydroxy-6-oxo-1,6-dihydropyridazine-4-carboximidamide (800 mg, 0.00 mmol) in 1,4-dioxane (30 mL) at 20 °C. After the addition was complete, the mixture was stirred at 20 °C for 16 h. The mixture was partitioned between H_2O (30 mL) and EtOAc (30 mLx3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO[®], 12 g SepaFlash[®] Silica Flash Column, eluent of 0~30% EtOAc/pentanes gradient @ 30 mL/min) to give 2-benzyl-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridazin-3(2H)-one as a solid. ¹H NMR (400 MHz, $CHCl_3-d$): δ 5.46 (s, 2 H), 7.29 - 7.36 (m, 3 H), 7.50 - 7.55 (m, 2 H), 7.98 (d, $J=4.19$ Hz, 1 H), 8.04 (d, $J=4.19$ Hz, 1 H); ESI-MS m/z $[M + H]^+$: 323.1.

EXAMPLE 133-phenethyl-6-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyrimidin-4(3H)-one**Step A:** ethyl 6-oxo-1-phenethyl-1,6-dihydropyrimidine-4-carboxylate

Ethyl 6-hydroxypyrimidine-4-carboxylate (100 mg, 0.595 mmol) was dissolved in DMF (3500 μ L) and the resulting solution was cooled to 0 °C. NaH (28.5 mg, 0.714 mmol) was added and the mixture was stirred for 20 min, at which point (2-bromoethyl)benzene (121 μ L, 0.892 mmol) was added. The reaction was allowed to warm to 23 °C and stirred for 16 h. Excess sodium hydride was quenched with water, and the mixture was partitioned between EtOAc. The organic layer was washed twice with

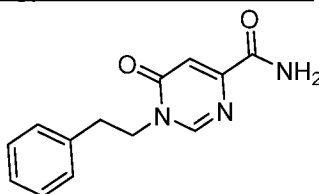
water, dry over magnesium sulfate, and concentrated. The residue was purified by silica gel chromatography (0-100% ethyl acetate/hexanes over 15 min) to obtain the title compound as solid.

Step B: 6-oxo-1-phenethyl-1,6-dihydropyrimidine-4-carboxylic acid



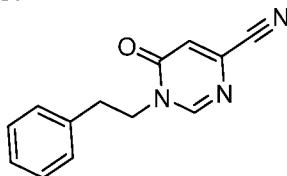
To a solution of ethyl 6-oxo-1-phenethyl-1,6-dihydropyrimidine-4-carboxylate (80.0 mg, 0.294 mmol) in MeOH (1500 μ L) at 23 $^{\circ}$ C was added NaOH (98 μ L, 0.59 mmol), and the resulting mixture was stirred at 23 $^{\circ}$ C for 16 h. The mixture was concentrated, and then diluted with EtOAc and 1N HCl. The resulting aqueous mixture was extracted with EtOAc, and the organic layer was washed with brine, dried over magnesium sulfate, and concentrated to obtain 6-oxo-1-phenethyl-1,6-dihydropyrimidine-4-

Step C: 6-oxo-1-phenethyl-1,6-dihydropyrimidine-4-carboxamide



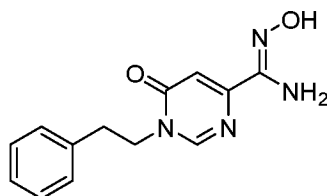
A mixture of 6-oxo-1-phenethyl-1,6-dihydropyrimidine-4-carboxylic acid (70.0 mg, 0.287 mmol), ammonium chloride (23.0 mg, 0.430 mmol), HATU (163 mg, 0.430 mmol), and TEA (120 μ L, 0.860 mmol) in DCM (1500 μ L) was stirred at 23 $^{\circ}$ C for 3 h. The mixture was diluted with DCM, washed with water, washed with brine, dried over magnesium sulfate, and concentrated to obtain 6-oxo-1-phenethyl-1,6-dihydropyrimidine-4-carboxamide as a solid.

Step D: 6-oxo-1-phenethyl-1,6-dihydropyrimidine-4-carbonitrile



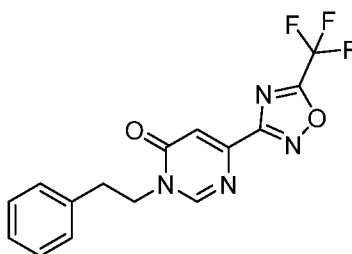
To a suspension of 6-oxo-1-phenethyl-1,6-dihydropyrimidine-4-carboxamide (70.0 mg, 0.288 mmol) in DCM (1500 μ L) at 0 $^{\circ}$ C was added DIEA (126 μ L, 0.719 mmol) and TFAA (44.7 μ L, 0.317 mmol). The resulting mixture was stirred for 3 h, then loaded directly on 4 g ISCO GOLD column for purification via ISCO (0-50% ethyl acetate/hexanes over 56 column volumes) to give 6-oxo-1-phenethyl-1,6-dihydropyrimidine-4-carbonitrile as a solid.

Step E: (Z)-N'-hydroxy-6-oxo-1-phenethyl-1,6-dihydropyrimidine-4-carboximidamide



To a solution of 6-oxo-1-phenethyl-1,6-dihydropyrimidine-4-carbonitrile (35.0 mg, 0.155 mmol) in EtOH (500 μ L) and water (250 μ L) was added hydroxylamine (47.6 μ L, 0.777 mmol). The resulting mixture was heated at 50 $^{\circ}$ C for 2 h. After cooling, the mixture was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated to obtain (Z)-N'-hydroxy-6-oxo-1-phenethyl-1,6-dihydropyrimidine-4-carboximidamide as an oil.

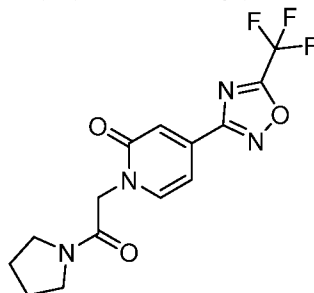
Step F: 3-phenethyl-6-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyrimidin-4(3H)-one



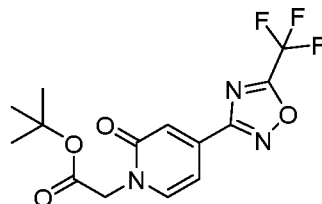
To a suspension of (Z)-N'-hydroxy-6-oxo-1-phenethyl-1,6-dihydropyrimidine-4-carboximidamide (30.9 mg, 0.120 mmol) in DCM (75 mL) at 0 $^{\circ}$ C was added TFAA (0.025 mL, 0.179 mmol) and TEA (0.050 mL, 0.359 mmol). The mixture was allowed to warm to 23 $^{\circ}$ C and stirred for 2 h. The mixture was loaded directly on 4 g ISCO GOLD column for purification (0-50% ethyl acetate/hexanes over 56 column volumes) to obtain 3-phenethyl-6-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyrimidin-4(3H)-one as a solid. 1 H NMR (CHCl_3 -*d*, 600 MHz): δ 7.72 (1H, s), 7.39-7.61 (6H, m), 4.21 (2H, t, J = 6.8 Hz), 3.10 (2H, t, J = 6.8 Hz); ESI-MS m/z $[M + H]^+$: 337.2.

EXAMPLE 14

1-(2-oxo-2-(pyrrolidin-1-yl)ethyl)-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one

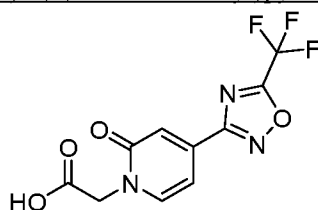


Step A: tert-butyl 2-(2-oxo-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-1(2H)-yl)acetate



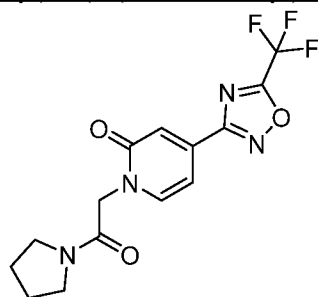
To a solution of 4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-2-ol (1.50 g, 6.49 mmol) in DMF (10 mL) at 0 °C was added NaH (0.389 g, 9.73 mmol). The reaction stirred for 30 min before tert-butyl 2-bromoacetate (1.34 mL, 9.09 mmol) was added. The mixture was allowed to warm to 23 °C, where it was stirred an additional 16 h. The mixture was then cooled to 0 °C and excess NaH was quenched with water. The aqueous mixture was extracted with ether (4x50 mL), and the combined organic extracts were washed with brine, dried over Na₂SO₄, concentrated, and the residue was purified by Isco Rf silica gel column chromatography (80g Isco Gold silica, EtOAc/isohexane 0-50%) to give tert-butyl 2-(2-oxo-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-1(2H)-yl)acetate as a solid.

Step B: 2-(2-oxo-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-1(2H)-yl)acetic acid



To a solution of tert-butyl 2-(2-oxo-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-1(2H)-yl)acetate (2.10 g, 6.08 mmol) in DCM (10 mL) was added TFA (2.5 mL, 32.4 mmol). The reaction was stirred at 23 °C for 16 h, then concentrated to give 2-(2-oxo-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-1(2H)-yl)acetic acid as an oil.

Step C: 1-(2-oxo-2-(pyrrolidin-1-yl)ethyl)-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one

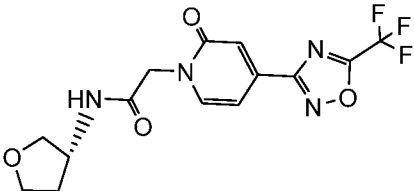
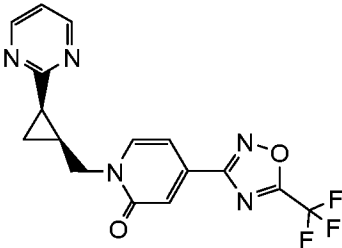
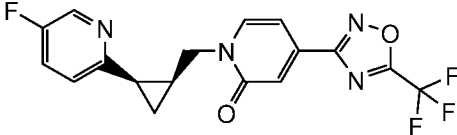


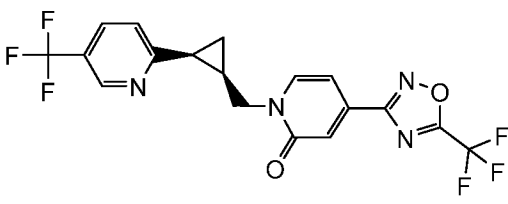
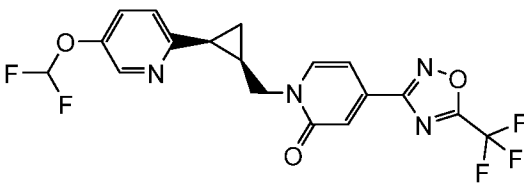
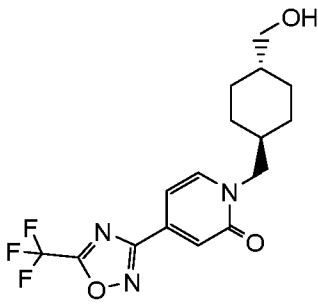
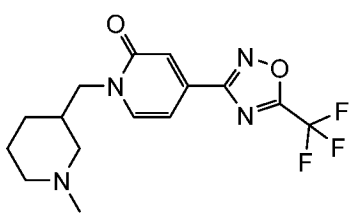
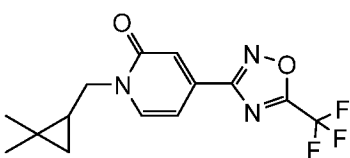
To a solution of 2-(2-oxo-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-1(2H)-yl)acetic acid (50.0 mg, 0.173 mmol) and 2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (131 mg, 0.346 mmol) in DCM (1 mL) was added pyrrolidine (16.0 mg, 0.225 mmol) and triethylamine (0.072 mL, 0.519 mmol). The resulting solution was stirred at 23 °C for 16 h. The mixture was concentrated and the residue purified via Gilson PLC 2020 [SunFire Prep C18 OBD Column, 5µm, 30 x 150 mm, 5-95 Water/ACN(+0.1%TFA) over 25 min] to give 1-(2-oxo-2-(pyrrolidin-1-yl)ethyl)-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one as a solid. ¹H NMR (CH₃OH-

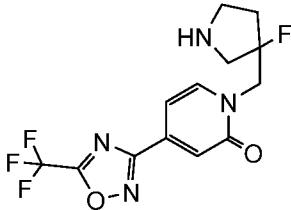
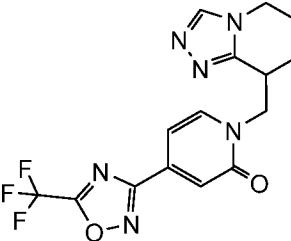
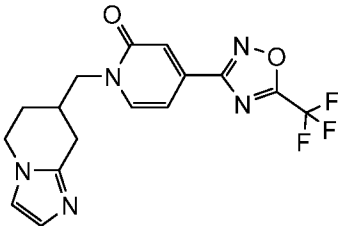
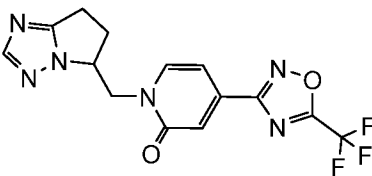
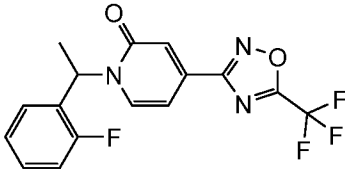
d4, 600 MHz): δ H 7.75 (1H, d, $J = 7.1$ Hz), 7.26 (1H, s), 6.97 (1H, d, $J = 7.1$ Hz), 4.85 (2H, s), 3.63 (2H, t, $J = 6.9$ Hz), 3.45 (2H, t, $J = 7.0$ Hz), 2.04 (2H, t, $J = 6.9$ Hz), 1.91 (2H, t, $J = 6.9$ Hz). ESI-MS m/z [$M + H$] $^+$: 343.2.

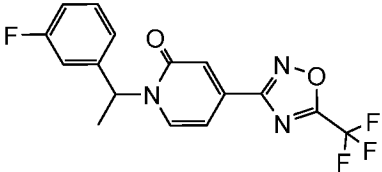
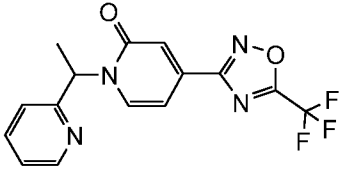
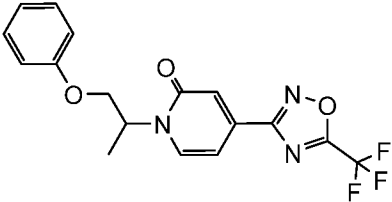
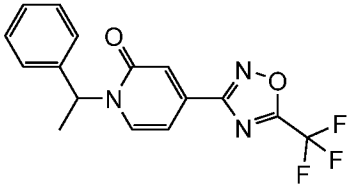
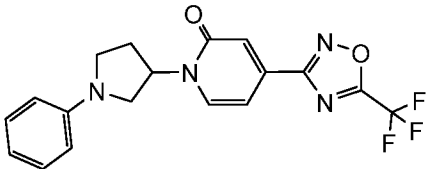
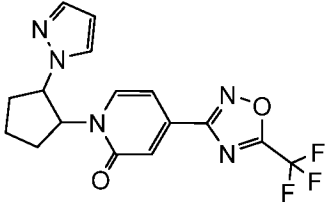
- 5 The following examples are provided to illustrate the invention and are not to be construed as limiting the scope of the invention in any manner. The following examples displayed in TABLE 1 were prepared according to the identified procedures from the examples above using the appropriate commercially available starting materials.

Table 1

Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
15	R		N-[(3R)-oxolan-3-yl]-2-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}acetamide	358.1	358.9
16	R,S		1-{[(1S,2R)-2-pyrimidin-2-ylcyclopropyl]methyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	363.1	364.1
17	R,S		1-{[(1S,2R)-2-(5-fluoropyridin-2-yl)cyclopropyl]methyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	380.1	380.9

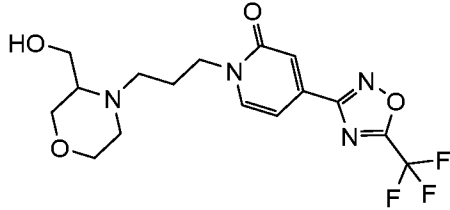
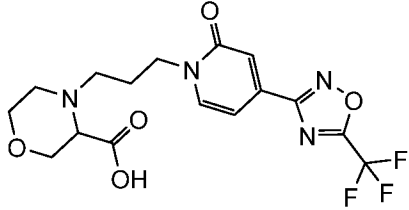
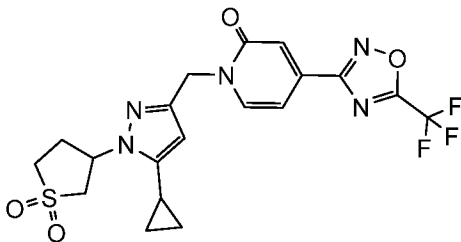
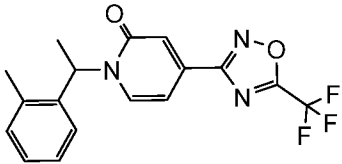
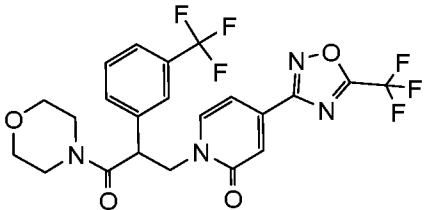
Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
18	R,S		4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]-1-({(1R,2S)-2-[5-(trifluoromethyl)pyridin-2-yl]cyclopropyl}methyl)pyridin-2(1H)-one	430.1	431.1
19	R,S		1-({(1R,2S)-2-[5-(difluoromethoxy)pyridin-2-yl]cyclopropyl}methyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	428.1	428.9
20	RACEMIC		1-({[trans-4-(hydroxymethyl)cyclohexyl]methyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	357.3	358.1
21	RACEMIC		1-[(1-methylpiperidin-3-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	342.3	343.1
22	RACEMIC		1-[(2,2-dimethylcyclopropyl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	313.3	314.1

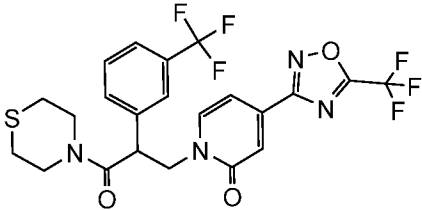
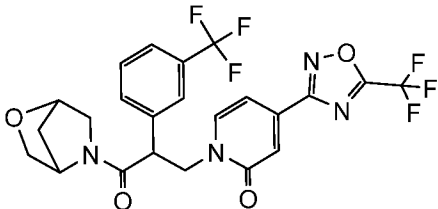
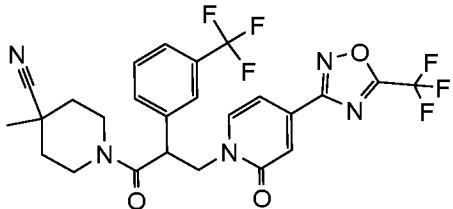
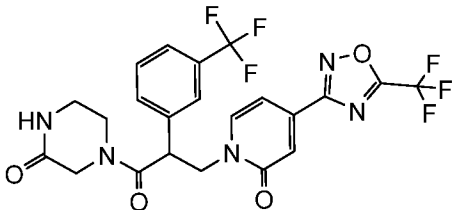
Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
23	RACEMIC		1-[(3-fluoropyrrolidin-3-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	332.3	333.1
24	RACEMIC		1-(5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyridin-8-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	366.3	367.1
25	RACEMIC		1-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-7-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	365.3	366.1
26	RACEMIC		1-(6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazol-5-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	352.3	353.1
27	RACEMIC		1-[1-(2-fluorophenyl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	353.3	354.1

Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
28	RACEMIC		1-[1-(3-fluorophenyl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	353.3	354.1
29	RACEMIC		1-(1-pyridin-2-ylethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	336.3	337.1
30	RACEMIC		1-(1-methyl-2-phenoxyethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	365.3	366.1
31	RACEMIC		1-(1-phenylethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	335.3	336.1
32	RACEMIC		1-(1-phenylpyrrolidin-3-yl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	376.3	377.1
33	RACEMIC		1-[2-(1H-pyrazol-1-yl)cyclopentyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	365.3	366.1

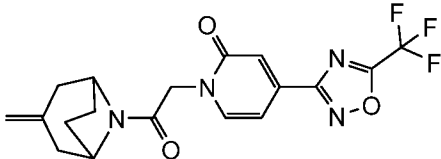
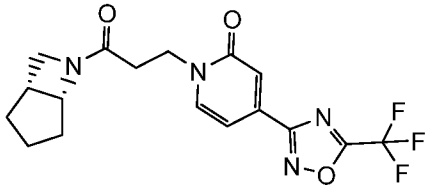
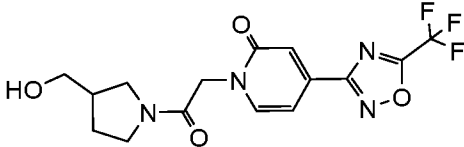
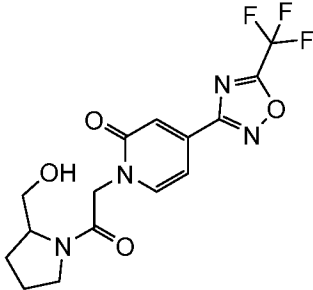
Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
34	RACEMIC		1-[2-(1-methylpiperidin-2-yl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	356.4	357.1
35	RACEMIC		1-[2-(4-methylmorpholin-2-yl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	358.3	359.1
36	RACEMIC		1-(3-hydroxy-2-phenylpropyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	365.3	366.1
37	RACEMIC		1-(3-hydroxycyclopentyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	315.3	316.1
38	RACEMIC		1-(3-methylpiperidin-4-yl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	328.3	329.1

Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
39	RACEMIC		1-[4-(4-bromo-1H-pyrazol-1-yl)tetrahydro-2H-pyran-3-yl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	460.2	460.0
40	RACEMIC		1-(5-hydroxy-3-methylpentyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	331.3	354.1
41	RACEMIC		1-(1-naphthalen-1-ylethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	385.1	386.2
42	RACEMIC		1-(2-methyl-3-morpholin-4-ylpropyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	372.1	373.1
43	RACEMIC		1-(2-fluoro-3-morpholin-4-ylpropyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	376.1	377.1

Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
44	RACEMIC		1-({3-[(hydroxymethyl)morpholin-4-yl]propyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	388.1	389.2
45	RACEMIC		4-(3-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}propyl)morpholine-3-carboxylic acid	402.1	403.2
46	RACEMIC		1-{[5-cyclopropyl-1-(1,1-dioxido-tetrahydrothiophen-3-yl)-1H-pyrazol-3-yl]methyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	469.1	470.3
47	RACEMIC		1-[1-(2-methylphenyl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	349.1	350.2
48	RACEMIC		1-{3-(morpholin-4-yl)-3-oxo-2-[3-(trifluoromethyl)phenyl]propyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	516.1	517.2

Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
49	RACEMIC		1-{3-oxo-3-(thiomorpholin-4-yl)-2-[3-(trifluoromethyl)phenyl]propyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	532.1	533.1
50	RACEMIC		1-{3-(2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-3-oxo-2-[3-(trifluoromethyl)phenyl]propyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	528.1	529.2
51	RACEMIC		4-methyl-1-(3-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}-2-[3-(trifluoromethyl)phenyl]propanoyl)piperidine-4-carbonitrile	553.2	554.2
52	RACEMIC		4-(3-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}-2-[3-(trifluoromethyl)phenyl]propanoyl)piperazin-2-one	529.1	530.5

Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
53	RACEMIC		2-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}-1-[3-(trifluoromethyl)phenyl]ethyl ethylcarbamate	490.1	491.2
54	RACEMIC		cyclobutyl (2-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}-1-[3-(trifluoromethyl)phenyl]ethyl)carbamate	516.1	517.1
55	RACEMIC		1-[2-(2,6-dimethylmorpholin-4-yl)-2-oxoethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	386.1	386.2
56	RACEMIC		1-[2-(3-methoxy-5-methyl-3,6-dihydropyridin-1(2H)-yl)-2-oxoethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	398.1	398.9

Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
57	RACEMIC		1-[2-(3-methyldiene-8-azabicyclo[3.2.1]octan-8-yl)-2-oxoethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	394.1	394.9
58	RACEMIC		1-{3-[(1R,5R)-6-azabicyclo[3.2.0]heptan-6-yl]-3-oxopropyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	382.1	382.9
59	RACEMIC		1-{2-[3-(hydroxymethyl)pyrrolidin-1-yl]-2-oxoethyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	372.1	372.9
60	RACEMIC		1-{2-[2-(hydroxymethyl)pyrrolidin-1-yl]-2-oxoethyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	372.1	373.2

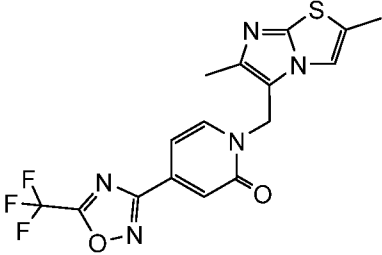
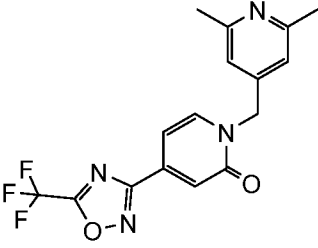
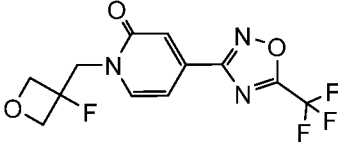
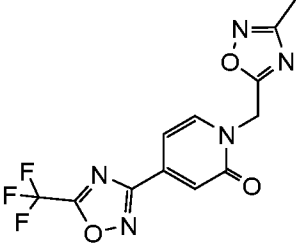
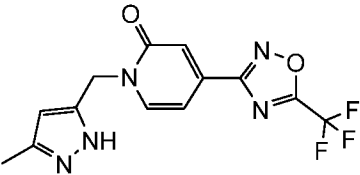
Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
61	RS, SS		1-{{3-[(3S)-3-methylmorpholin-4-yl]-3-oxo-2-[3-(trifluoromethyl)phenyl]propyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	530.1	531.2
62	RS,S		1-[(2S)-2-phenylcyclopentyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	375.4	376.1
63	S		1-[(2S)-5-oxopyrrolidin-2-yl]methyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	328.3	329.1
64	S		1-[(2S)-1-benzylpyrrolidin-2-yl]methyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	404.4	405.1
65	S,R		1-[(1S,2R)-2-(5-fluoropyridin-2-yl)cyclopropyl]methyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	380.1	381.2

Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
66	S,S		1-{2-[(3S,4S)-3,4-difluoropyrrolidin-1-yl]ethyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	364.3	365.1
67	S,S		1-{2-[(2S,6S)-2,6-dimethylmorpholin-4-yl]-2-oxoethyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	386.1	386.9
68			1-[(1-pyridin-3-ylcyclopropyl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	362.3	363.2
69			1-(1,3-dihydro-2-benzofuran-5-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	363.3	364.0
70			1-[(1,3-dimethyl-1H-pyrazol-5-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	339.3	340.1

Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
71			1-[(1,5-dimethyl-1H-benzimidazol-2-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	389.3	390.1
72			1-[(1,5-dimethyl-1H-pyrazol-4-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	339.3	340.1
73			1-[(1-cyclopropyl-1H-imidazol-2-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	351.3	352.0
74			1-(1H-imidazol-2-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	311.2	312.1
75			1-(1H-indazol-3-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	361.3	362.1
76			1-(1H-indazol-5-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	361.3	362.0

Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
77			1-(1H-pyrazol-3-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	311.2	312.1
78			1-(1H-pyrazolo[3,4-b]pyridin-3-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	362.3	363.0
79			1-[(1-methyl-1H-benzotriazol-5-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	376.3	377.1
80			1-[(1-methyl-1H-benzimidazol-2-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	375.3	376.1
81			1-[(1-methyl-1H-benzimidazol-5-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	375.3	376.1

Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
82			1-[(1-methyl-1H-indazol-4-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	375.3	376.2
83			1-[(1-methyl-1H-indazol-5-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	375.3	376.2
84			1-[(1-methyl-1H-indazol-6-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	375.3	376.1
85			1-[(1-methyl-3-phenyl-1H-pyrazol-5-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	401.4	402.1
86			1-[(2,5-dimethyl-1,3-oxazol-4-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	340.3	341.1

Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
87			1-[(2,6-dimethylimidazo[2,1-b][1,3]thiazol-5-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	395.4	396.1
88			1-[(2,6-dimethylpyridin-4-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	350.3	351.1
89			1-[(3-fluorooxetan-3-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	319.2	320.1
90			1-[(3-methyl-1,2,4-oxadiazol-5-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	327.2	328.1
91			1-[(3-methyl-1H-pyrazol-5-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	325.3	326.1

Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
92			1-[(4-chloroquinolin-6-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	406.8	407.1
93	RACEMIC		1-[(4-methylcyclohexyl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	341.3	342.2
94			1-(5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyridin-3-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	366.3	367.1
95			1-[(5-chloro-1-methyl-1H-benzimidazol-2-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	409.8	410.1
96			1-[(5-cyclopropyl-1,2,4-oxadiazol-3-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	353.3	354.0

Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
97			1-[(5-cyclopropylisoxazol-3-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	352.3	353.1
98			1-[(5-fluoropyridin-2-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	340.2	341.0
99			1-[(5-(1-methylethyl)-1,3,4-oxadiazol-2-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	355.3	356.1
100			1-[(5-methoxypyridin-2-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	352.3	353.1
101			1-[(5-methylisoxazol-3-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	326.2	327.0

Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
102			1-[(5-methyl-1,3-oxazol-2-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	326.2	327.1
103			1-[(5-methylpyrimidin-2-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	337.3	338.1
104			1-[(6-chloro-1-methyl-1H-benzimidazol-2-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	409.8	410.1
105			1-[(8-methoxyquinolin-5-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	402.3	403.1
106			1-(biphenyl-4-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	397.4	398.1

Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
107			1-{2-[(2-fluorobenzyl)amino]ethyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	382.3	383.1
108			1-(2-[1,2,4]triazolo[4,3-a]pyridin-3-ylethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	376.3	377.1
109			1-[2-(1H-1,2,4-triazol-1-yl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	326.2	327.0
110			1-[2-(1H-imidazol-1-yl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	325.3	326.1
111			1-[2-(1H-pyrazol-1-yl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	325.3	326.0
112			1-[2-(1-methyl-1H-imidazol-2-yl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	339.3	340.1

Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
113			1-[2-(1-methyl-1H-pyrazol-4-yl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	339.3	340.0
114			1-[2-(1-methyl-1H-pyrazol-5-yl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	339.3	340.2
115			1-[2-(2,2-dimethylpyrrolidin-1-yl)-2-oxoethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	370.3	371.1
116			1-[2-(2-bromo-1,3-thiazol-4-yl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	421.2	422.0
117			1-[2-(2-oxopyrrolidin-1-yl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	342.3	343.1

Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
118			1-[2-(3,4-dihydroisoquinolin-2(1H)-yl)-2-oxoethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	404.4	405.1
119			1-[2-(4H-1,2,4-triazol-4-yl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	326.2	327.0
120			1-[2-(4-methyl-1H-pyrazol-1-yl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	339.3	340.1
121			1-[2-(5-ethylpyridin-2-yl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	364.3	365.1
122			1-[2-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	341.3	342.1

Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
123			1-[2-(6-methylpyridin-2-yl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	350.3	351.1
124			1-[2-(diethylamino)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	330.3	331.1
125			1-[2-(dimethylamino)-2-methylpropyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	330.3	331.1
126			1-[2-(hydroxymethyl)benzyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	351.3	352.1
127			1-[2-(2,3-dihydro-1H-indol-1-yl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	376.3	377.1
128			1-(2-isoxazol-4-ylethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	326.2	327.0

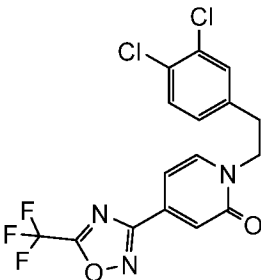
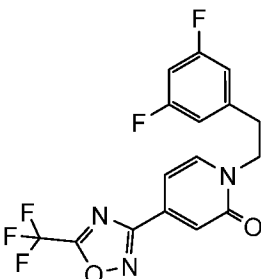
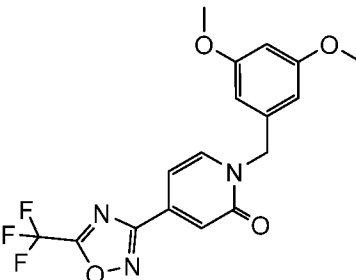
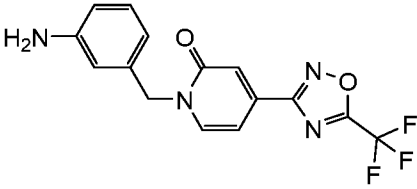
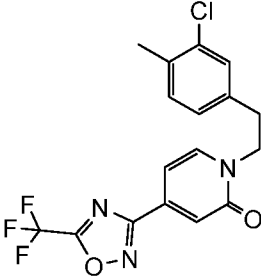
Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
129			1-(2-naphthalen-1-ylethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	385.3	386.1
130			1-[2-(naphthalen-2-yloxy)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	401.4	402.1
131			1-(2-pyridin-4-ylethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	336.3	337.0
132			1-(2-pyrimidin-4-ylethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	337.3	338.1
133			1-(2,3,4-trifluorobenzyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	375.2	376.0

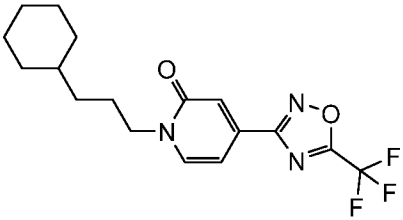
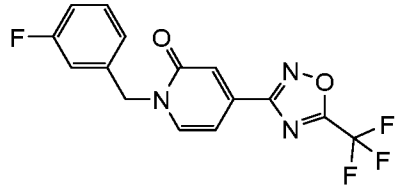
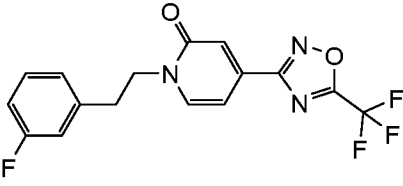
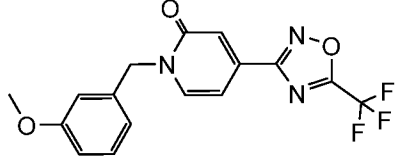
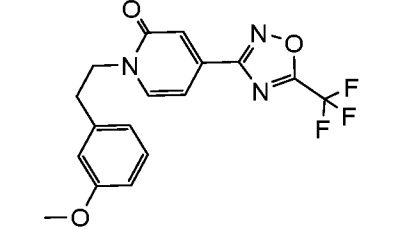
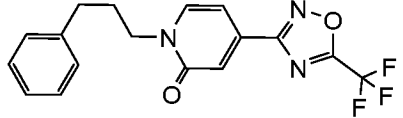
Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
134			1-(2,3-difluorobenzyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	357.2	358.0
135			1-[2-(2,3-difluorophenyl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	371.3	372.0
136			1-(2,3-dimethoxybenzyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	381.3	382.1
137			1-[2-(2,4-dichlorophenyl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	404.2	404.0
138			1-(2,4-difluorobenzyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	357.2	358.0

Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
139			1-(2,4-dimethylbenzyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	349.3	350.3
140			1-(2,5-difluorobenzyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	357.2	358.0
141			1-[2-(2,6-dichlorophenyl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	404.2	404.1
142			1-(2-amino-3-methylbenzyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	350.3	351.1
143			1-(2-amino-5-methylbenzyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	350.3	351.1
144			1-(2-aminobenzyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	336.3	337.1

Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
145			1-(2-benzylbenzyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	411.4	412.2
146			1-[2-(2-chloro-4-fluorophenyl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	387.7	388.0
147			1-(2-chloro-6-fluorobenzyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	373.7	374.1
148			1-[2-(2-fluorophenyl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	353.3	354.0
149			1-(2-morpholin-4-ylethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	344.3	345.1

Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
150			1-[3-(1H-imidazol-1-yl)propyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	339.3	340.1
151			1-[3-(6-methylpyridin-2-yl)propyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	364.3	365.2
152			1-[3-(dimethylamino)benzyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	364.3	365.1
153			1-(3-pyrrolidin-1-ylbenzyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	390.4	391.1
154			1-[3-(trifluoromethoxy)benzyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	405.3	406.1

Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
155			1-[2-(3,4-dichlorophenyl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	404.2	404.0
156			1-[2-(3,5-difluorophenyl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	371.3	372.1
157			1-(3,5-dimethoxybenzyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	381.3	382.0
158			1-(3-aminobenzyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	336.3	337.1
159			1-[2-(3-chloro-4-methylphenyl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	383.8	384.1

Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
160			1-(3-cyclohexylpropyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	355.4	356.1
161			1-(3-fluorobenzyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	339.3	340.0
162			1-[2-(3-fluorophenyl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	353.3	354.0
163			1-(3-methoxybenzyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	351.3	352.1
164			1-[2-(3-methoxyphenyl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	365.3	366.5
165			1-(3-phenylpropyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	349.3	350.1

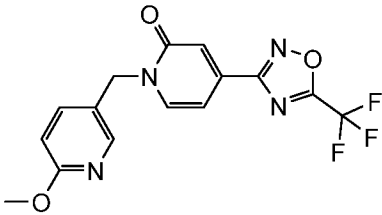
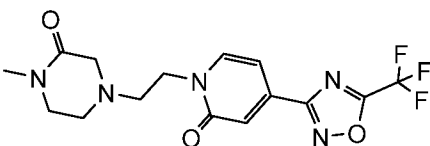
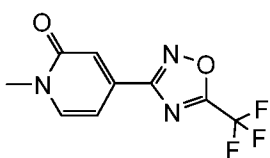
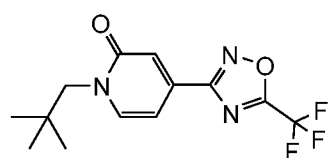
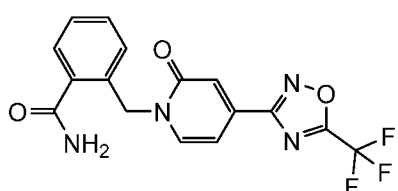
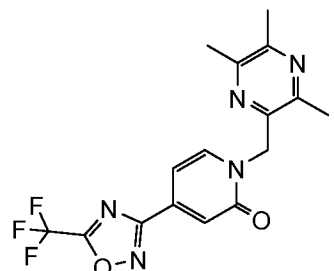
Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
166			1-[4-(1H-imidazol-1-yl)benzyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	387.3	388.1
167			1-[4-(1H-indol-1-yl)butyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	402.4	403.1
168			1-[4-(methylsulfanyl)benzyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	367.4	368.0
169			1-(4-pyrimidin-5-ylbenzyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	399.3	400.1
170			1-[4-(trifluoromethoxy)benzyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	405.3	406.1

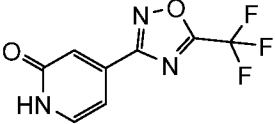
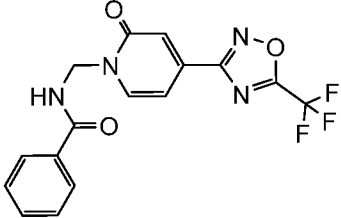
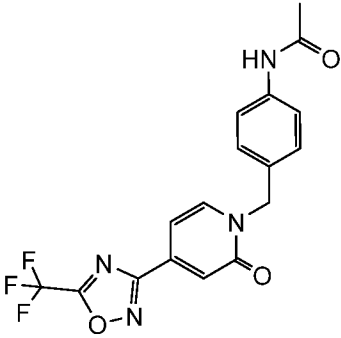
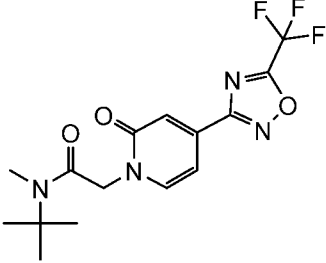
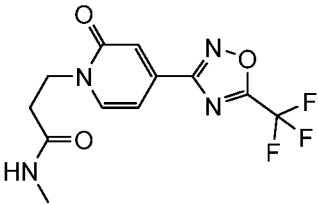
Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
171			1-(4-chloro-2-fluorobenzyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	373.7	374.0
172			1-[2-(4-chlorophenyl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	369.7	370.0
173			1-[2-(4-fluorophenyl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	353.3	354.1
174			1-(4-methoxybenzyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	351.3	352.1
175			1-(1,3-benzodioxol-5-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	365.3	366.0
176			1-(1,3-benzothiazol-2-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	378.3	379.0

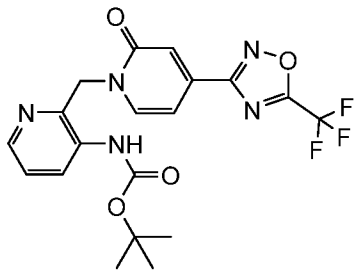
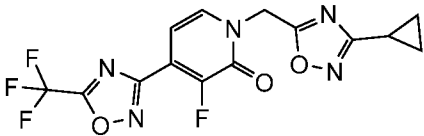
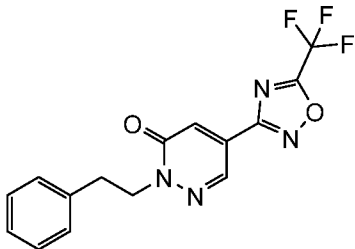
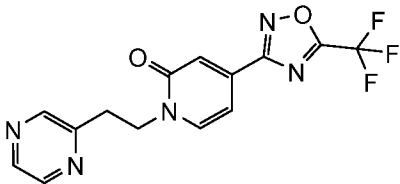
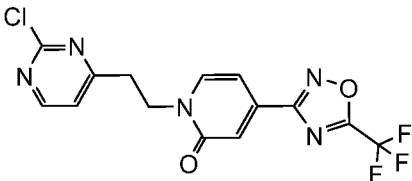
Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
177			1-(1,3-benzothiazol-6-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	378.3	379.0
178			1-(imidazo[1,2-a]pyridin-8-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	361.3	362.2
179			1-(isoxazol-4-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	312.2	313.1
180			1-(naphthalen-1-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	371.3	372.1
181			1-(naphthalen-2-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	371.3	372.1
182			1-(pyrazolo[1,5-a]pyridin-2-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	361.3	362.1

Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
183			1-(pyridazin-3-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	323.2	324.1
184			1-(pyrimidin-2-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	323.2	324.1
185			1-(pyrimidin-5-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	323.2	324.0
186			1-(quinolin-3-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	372.3	373.1
187			1-(quinolin-4-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	372.3	373.0
188			1-(quinolin-5-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	372.3	373.0

Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
189			1-(quinolin-6-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	372.3	373.0
190			1-(quinolin-8-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	372.3	373.0
191			1-(quinoxalin-6-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	373.3	374.0
192			1-(thieno[2,3-b]pyridin-2-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	378.3	379.0
193			1-[(2-methoxypyridin-3-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	352.3	353.1
194			1-[(6-methoxypyridin-2-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	352.3	353.1

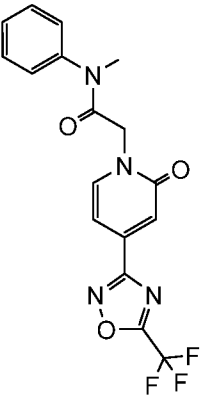
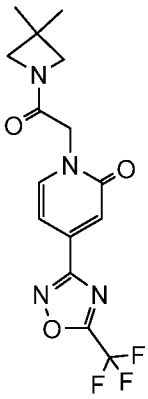
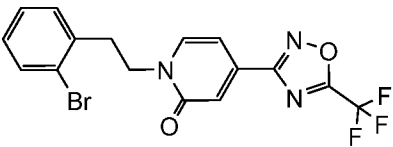
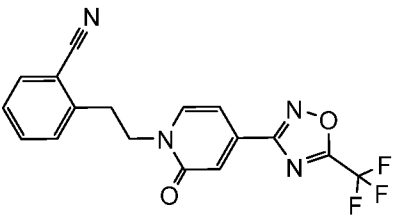
Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
195			1-[(6-methoxypyridin-3-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	352.3	353.0
196			1-methyl-4-(2-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}ethyl)piperazin-2-one	371.3	372.1
197			1-methyl-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	245.2	246.1
198			1-(2,2-dimethylpropyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	301.3	302.1
199			2-({2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}methyl)benzamide	364.3	365.1
200			4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]-1-[(3,5,6-trimethylpyrazin-2-yl)methyl]pyridin-2(1H)-one	365.3	366.1

Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
201			4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	231.1	232.1
202			N-({2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}methyl)benzamide	364.3	365.1
203			N-[4-({2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}methyl)phenyl]acetamide	378.3	379.2
204			N-tert-butyl-N-methyl-2-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}acetamide	358.3	359.1
205			N-methyl-3-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}propanamide	316.2	317.1

Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
206			tert-butyl [2-({2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}methyl)pyridin-3-yl]carbamate	437.4	438.2
207			1-[(3-cyclopropyl-1,2,4-oxadiazol-5-yl)methyl]-3-fluoro-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	371.1	372.2
208			2-(2-phenylethyl)-5-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridazin-3(2H)-one	336.3	337.2
209			1-(2-pyrazin-2-ylethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	337.1	338.0
210			1-[2-(2-chloropyrimidin-4-yl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	371.0	372.0

Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
211			1-[(5-cyclopropyl-1-methyl-1H-pyrazol-3-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	365.1	366.2
212			1-{2-[4-methyl-6-(trifluoromethyl)pyrimidin-2-yl]ethyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	419.1	420.2
213			1-[(1-methyl-1H-indazol-3-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	375.1	376.2
214			1-[(1,4-dimethyl-1H-pyrazol-3-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	339.1	340.2
215			1-{[1-(difluoromethyl)-1H-pyrazol-3-yl]methyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	361.1	362.2

Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
216			1-[(2-methylpyridin-3-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	336.1	337.1
217			1-[(4,6-dimethylpyridin-2-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	350.1	351.3
218			1-(2-pyridin-3-ylethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	336.1	337.0
219			1-[2-(1H-indazol-4-yl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	375.1	376.0
220			N-(2,2-dimethylpropyl)-N-methyl-2-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}acetamide	372.1	373.2

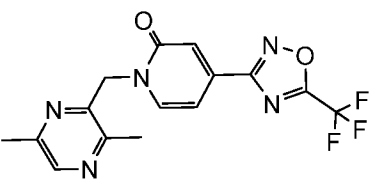
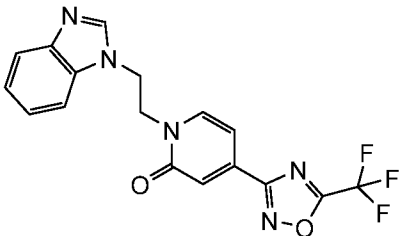
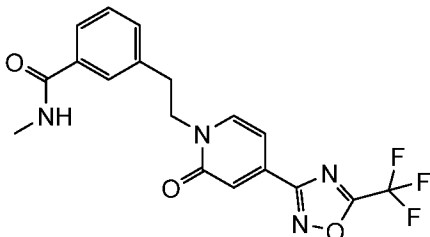
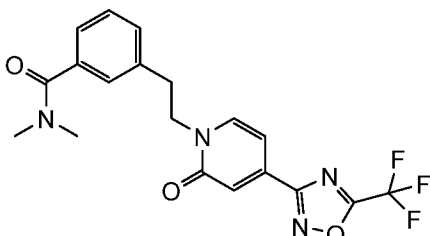
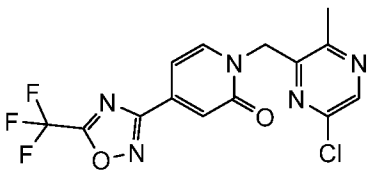
Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
221			N-methyl-2-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}-N-phenylacetamide	378.1	379.2
222			1-[2-(3,3-dimethylazetidin-1-yl)-2-oxoethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	356.1	357.2
223			1-[2-(2-bromophenyl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	413.0	414.1
224			2-(2-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}ethyl)benzonitrile	360.1	361.2

Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
225			4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]-1-{2-[2-(trifluoromethyl)phenyl]ethyl}pyridin-2(1H)-one	403.1	404.2
226			1-{[1-(3-fluorophenyl)-1H-pyrazol-5-yl]methyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	405.1	406.3
227			1-[(3-cyclopropyl-1,2,4-oxadiazol-5-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	353.1	354.2
228			1-[(4,6-dimethylpyrimidin-2-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	351.1	352.2
229			1-[(5-methylpyrazin-2-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	337.1	338.2

Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
230			1-[(6-chloropyrazin-2-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	357.0	358.2
231			1-[(3-fluoropyridin-2-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	340.1	341.2
232			1-[(4-chloro-3-methylpyridin-2-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	370.0	370.9
233			1-[(5-cyclopropyl-1-(2,2,2-trifluoroethyl)-1H-pyrazol-3-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	433.1	434.3
234			1-[(1-cyclopropyl-1H-pyrazol-3-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	351.1	352.2

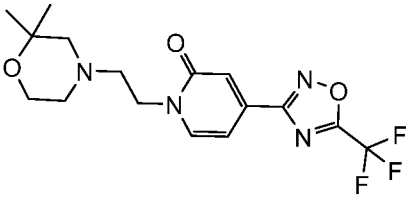
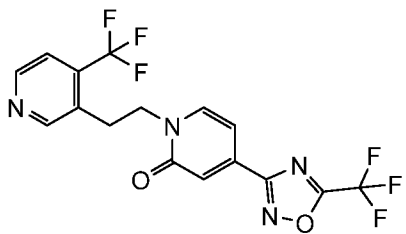
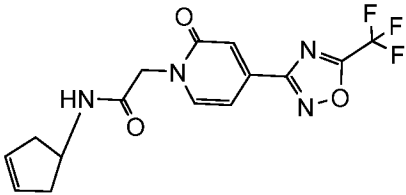
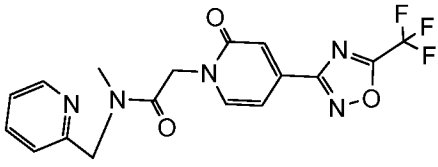
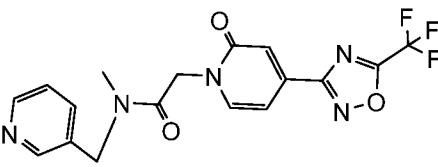
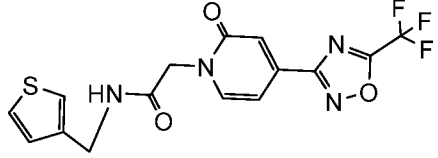
Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
235			1-[2-(3-methylphenyl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	349.1	350.1
236			1-[2-(2-methylphenyl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	349.1	350.1
237			1-[2-(2-chlorophenyl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	369.0	370.1
238			4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]-1-{[6-(trifluoromethyl)pyridin-2-yl]methyl}pyridin-2(1H)-one	390.1	391.2
239			1-[(3,6-dichloropyridin-2-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	390.0	391.1

Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
240			1-{2-[2-(methoxymethyl)phenyl]ethyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	379.1	380.0
241			1-{[3-chloro-6-(trifluoromethyl)pyridin-2-yl]methyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	424.0	425.2
242			1-{[4-(dimethylamino)-6-methylpyrimidin-2-yl]methyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	380.1	381.3
243			1-{2-[2-(hydroxymethyl)phenyl]ethyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	365.1	366.0
244			1-{2-[3-(hydroxymethyl)phenyl]ethyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	365.1	366.0

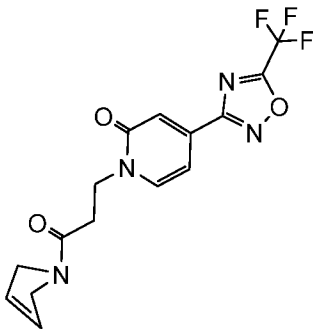
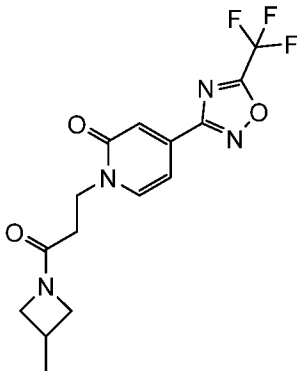
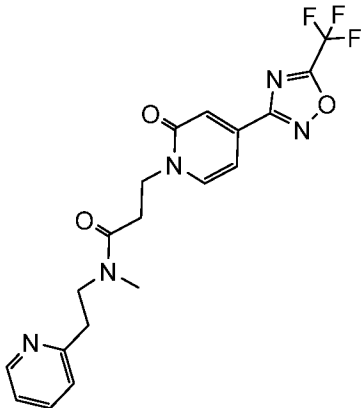
Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
245			1-[(3,6-dimethylpyrazin-2-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	351.1	352.3
246			1-[2-(1H-benzimidazol-1-yl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	375.1	376.0
247			N-methyl-3-(2-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}ethyl)benzamide	392.1	393.0
248			N,N-dimethyl-3-(2-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}ethyl)benzamide	406.1	407.0
249			1-[(6-chloro-3-methylpyrazin-2-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	371.0	372.2

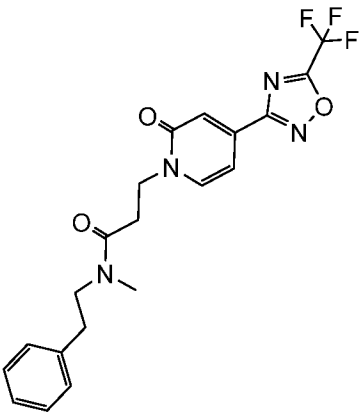
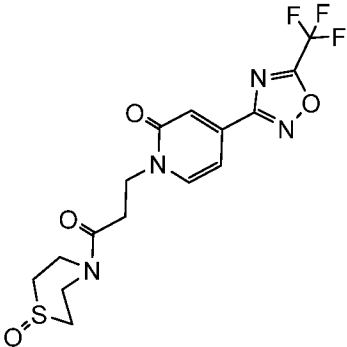
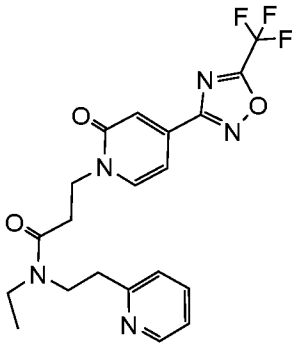
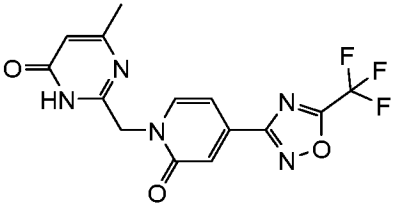
Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
250			1-[(4,5-dimethyl-1,3-oxazol-2-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	340.1	341.2
251			1-[2-(4-methylpyridin-3-yl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	350.1	351.0
252			1-{2-[3-(morpholine-4-carbonyl)phenyl]ethyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	448.1	449.1
253			methyl 3-({2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}methyl)pyrazine-2-carboxylate	381.1	382.2
254			1-[2-(4,5-dimethylpyridin-3-yl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	364.1	365.1

Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
255			1-{2-[2-(1,3-oxazol-2-yl)phenyl]ethyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	402.1	403.0
256			1-[(3-methoxypyrazin-2-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	353.1	354.2
257			1-[(4,6-dimethoxypyrimidin-2-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	383.1	384.3
258			1-(2-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}ethyl)-1,3-dihydro-2H-benzimidazol-2-one	391.1	392.0
259			1-[2-(2,5-dimethylpyridin-3-yl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	364.1	365.0

Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
260			1-[2-(2,2-dimethylmorpholin-4-yl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	372.1	373.5
261			4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]-1-{2-[4-(trifluoromethyl)pyridin-3-yl]ethyl}pyridin-2(1H)-one	404.1	405.0
262			N-(cyclopent-3-en-1-yl)-2-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}acetamide	354.1	354.9
263			N-methyl-2-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}-N-[(pyridin-2-yl)methyl]acetamide	393.1	393.9
264			N-methyl-2-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}-N-[(pyridin-3-yl)methyl]acetamide	393.1	393.9
265			2-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}-N-[(thiophen-3-yl)methyl]acetamide	384.1	384.8

Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
266			1-[2-(5-fluoro-1,3-dihydro-2H-isoindol-2-yl)-2-oxoethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	408.1	408.9
267			N-[(4-fluorophenyl)methyl]-N-methyl-2-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}acetamide	410.1	410.9
268			N-[(3-fluorophenyl)methyl]-N-methyl-2-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}acetamide	410.1	410.9
269			2-({2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}methyl)quinazolin-4(3H)-one	389.1	390.1
270			4-(2-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}ethyl)-2,3-dihydro-1H-isoindol-1-one	390.1	391.1

Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
271			1-[3-(2,5-dihydro-1H-pyrrol-1-yl)-3-oxopropyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	354.1	354.9
272			1-[3-(3-methylazetidin-1-yl)-3-oxopropyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one	356.1	356.9
273			N-methyl-3-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}-N-[2-(pyridin-2-yl)ethyl]propanamide	421.1	421.9

Compound #	Stereo-chem	Structure	Name	Molecular Weight	MS (M+1)
274			N-methyl-3-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}-N-(2-phenylethyl)propanamide	420.1	421.9
275			4-(3-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}propanoyl)-1,4-thiazinan-1-one	404.1	404.9
276			N-ethyl-3-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}-N-[2-(pyridin-2-yl)ethyl]propanamide	435.2	435.9
277			6-methyl-2-({2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}methyl)pyrimidin-4(3H)-one	353.1	353.9

AssayMethods for HDAC Enzymatic Assays:

Compound potencies were determined versus HDAC 1, 5, 6, and 8 isoforms with in vitro assays that measured inhibition of cleavage of a Fluor-de-Lys substrate.

HDAC1 and 6 reagents: FLAG-tagged HDACs 1 and 6 were prepared in-house by protein expression in HEK293F cells followed by anti-FLAG affinity purification. Assays were performed with buffer containing 20 mM HEPES, pH 8.0 [Boston BioProducts, catalog #BB-104, 1M stock], 137 mM NaCl [Sigma, catalog #S5150, 5M stock], 2.7 mM KCl [BioChemika, catalog #87526, 4M stock], 1 mM MgCl₂ [Fluka, catalog #63020, 1M stock], and 0.05% BSA (Fraction V) [Invitrogen, catalog #15260, 7.5% stock]. In addition to the above buffer ingredients, TCEP [CalBiochem, catalog #580561, 500 mM stock] was added at a final concentration of 0.5 mM to the buffer for the HDAC6 assays. HDAC 1, 2, 3, and 6 enzymes were run at the final concentrations of 0.3 nM, 1.5 nM, 0.3 nM, and 1.333 nM, respectively. Fluor-de-Lys substrate [BioMol Research Laboratories, catalog #KI-104], used to evaluate enzyme activity, was added at the final concentrations of 20 uM, 40 uM, 20 uM, and 2.5 uM for HDACs 1, 2, 3, and 6. To enable detection of the signal, Developer [BioMol Research Laboratories, catalog #KI-105] was added at a 1:250 dilution to the stop solution, which also included 10 uM SAHA [Sigma, catalog # SML0061] to ensure complete termination of the reaction.

HDAC5 reagents: N-terminal GST tagged HDAC5 was purchased from BPS Bioscience [catalog # 50045]. Assays were performed with buffer containing 20 mM HEPES, pH 8.0 [Boston BioProducts, catalog #BB-104, 1M stock], 137 mM NaCl [Sigma, catalog #S5150, 5M stock], 2.7 mM KCl [BioChemika, catalog #87526, 4M stock], 1 mM MgCl₂ [Fluka, catalog #63020, 1M stock], and 0.05% BSA (Fraction V) [Invitrogen, catalog #15260, 7.5% stock]. The HDAC5 enzyme was run at the final concentration of 0.447 nM. Boc-Lys(TFA)-AMC substrate [Bachem, catalog #I-1985.0050], used to evaluate enzyme activity, was added at the final concentration of 60 uM. To enable detection of the signal, Developer II [BioMol Research Laboratories, catalog #KI-176] was added at a 1:200 dilution to the stop solution, which also included 20 uM trichostatin A (TSA) [Sigma, catalog # T8552] to ensure complete termination of the reaction.

HDAC8 reagents: HDAC8 was purchased from Enzo Life Sciences [catalog # BML-SE145]. Assays were performed with buffer containing 20 mM HEPES, pH 8.0 [Boston BioProducts, catalog #BB-104, 1M stock], 100 mM NaCl [Sigma, catalog #S5150, 5M stock], 20 mM KCl [BioChemika, catalog #87526, 4M stock], 1 mM MgCl₂ [Fluka, catalog #63020, 1M stock], 0.05% BSA (Fraction V) [Invitrogen, catalog #15260, 7.5% stock], and 0.1% n-Octyl- β -D-glucopyranoside (N-OG) [Anatrace, catalog #O311, 10% stock]. The HDAC8 enzyme was run at the final concentration of 1.333 nM. Fluor-de-Lys substrate [BioMol Research Laboratories, catalog #KI-178], used to evaluate enzyme activity, was added at the final concentration of 200 uM. To enable detection of the signal, Developer II [BioMol Research Laboratories, catalog #KI-176] was added at a 1:200 dilution to the stop solution, which also included 20 uM SAHA [Sigma, catalog # SML0061] to ensure complete termination of the reaction.

Assay protocol: In brief, compounds were titrated in 100% DMSO via acoustic dispensing directly to the assay plate using the ECHO 550 [Labcyte]. HDAC enzymes at the concentrations indicated above were added in assay buffer to the assay plates containing the compounds using a Combi [Thermo Scientific]. The wells were mixed, and the plates were allowed to pre-incubate at room temperature for 3 hours. After the 3 hours, the appropriate substrate, at the concentrations indicated above, was added to the wells using a Combi. The wells were mixed, and the plates were allowed to incubate at room temperature for 1 hour. After the 1 hour, the appropriate Developer/stop solution was added to the wells using a Combi. The wells were mixed, and the plates were allowed to incubate at room temperature for 1 hour. The plates were then read on the EnVision [Perkin Elmer] using 380 nm excitation and 460 nm emission. Data were analyzed using 4P curve fitting with Activity Base [IDBS] software.

TABLE 2 displays the HDAC inhibitory activity of representative HDAC isoforms for the illustrated examples.

Table 2

Compound #	HDAC6 IC50	HDAC1 IC50	HDAC5 IC50	HDAC8 IC50
1	16	1100	95	1200
2	19	3200	500	4600
3	6.8	260	180	1100
4	110	9200	1900	3600
5	22	35000	370	4800
6	25	1400	1600	5600
7	29	1600	440	4500
8	41	4600	2300	>45000
9	50	6400		22000
10	47	>45000		37000
11	63	18000	13000	>45000
12	150	2000	7500	6300
13	370			
14	91	29000	2800	6900
15	64	27000	1900	7600
16	16	1900		4500
17	18	390	69	1600
18	37	350	210	900
19	7.7	210	110	850
20	35	6800	330	6900
21	56	880		1500
22	36	1100		550
23	76	2600		2400
24	34	2000		1000
25	94	4900		2400

Compound #	HDAC6 IC50	HDAC1 IC50	HDAC5 IC50	HDAC8 IC50
26	67	4500		3300
27	41	7800	130	7700
28	62	3000		9500
29	140			
30	14			
31	110	1300		10000
32	63			
33	120		2300	
34	29	1300	750	580
35	120			
36	30	3000		14000
37	91	5700		2500
38	61	4500		2300
39	34	1100		360
40	33	3700		1300
41	17	24000		24000
42	25	5400		2700
43	20	6300		2100
44	37	3700		3700
45	55	16000		8100
46	7.9	990		5300
47	39	26000		
48	40	34000	4900	37000
49	64	>45000	4400	>45000
50	62	21000	5100	25000
51	77	15000	5000	15000
52	49	18000	3800	14000
53	60	6800	3200	15000
54	84	4500	4500	450
55	41	>45000	1600	5200
56	38	27000	1000	6300
57	67	>45000	1500	7800
58	38	4200	3900	5500
59	93	>45000	1900	14000
60	50	10000	1400	3400
61	31	34000	6500	32000
62	180			
63	62	6500		2100
64	150	30000		3800
65	5.8	300	140	1900
66	120	8500		12000
67	97	>45000	3300	900

Compound #	HDAC6 IC50	HDAC1 IC50	HDAC5 IC50	HDAC8 IC50
68	230	6300		2700
69	12	1000		3000
70	21	4900	320	3600
71	48			
72	53	24000		7500
73	58	3700		2300
74	100	4500		2900
75	3.6		52	
76	9.9	110	79	1200
77	51	3400		2100
78	11	660		3300
79	9.8	1200		3500
80	89	30000		20000
81	8.1	650		1900
82	12	910		1600
83	12	2300	190	3200
84	7.3	790		2400
85	16			
86	94	11000		5200
87	110			
88	28	2300		1900
89	140			
90	37	2600		7400
91	10	880	170	1800
92	5.7	370	100	1800
93	18	3300		630
94	79	26000		6500
95	80	700	210	
96	15	1300	420	7000
97	15	940		3500
98	50	5800		4900
99	27	5200		15000
100	34	2000		4600
101	38	4500		5000
102	13	1700		3700
103	62	17000		8400
104	21	3100		3900
105	16	1500		2300
106	58			
107	40			
108	20	1100		1100
109	63	5000		6000

Compound #	HDAC6 IC50	HDAC1 IC50	HDAC5 IC50	HDAC8 IC50
110	85	10000		2800
111	47	4200		6000
112	100	4300		3400
113	99	14000		6000
114	130			
115	110	>45000	3000	12000
116	17	2700		4200
117	150			
118	51	7700		3900
119	34	2500		1400
120	38	5900	1000	14000
121	86	5500		4600
122	66	7100	2400	8700
123	24	3400	1500	2700
124	20	2100	830	1300
125	52	4800		1700
126	39	5600		2400
127	11	2900	500	1800
128	36	4000		1400
129	26	4000		4500
130	77			
131	39	2500	410	3000
132	46	1600		4300
133	26	2500		1700
134	15	2000		1400
135	8.8	7200		6500
136	50	3500		2900
137	140			
138	29	3100		1800
139	37	9000	370	3300
140	13	1900		1900
141	76	15000		12000
142	23	6700	650	2600
143	27	8800		9000
144	43	16000		5600
145	120			
146	19	15000	2200	9400
147	55	16000		2200
148	23	13000		7900
149	60	6500	1900	5800
150	61	5000		3500
151	43	2700		1400

Compound #	HDAC6 IC50	HDAC1 IC50	HDAC5 IC50	HDAC8 IC50
152	15	2500		3900
153	28	1700		1800
154	12	550		3000
155	32	2900		9800
156	13	6200		19000
157	9.4	440		2800
158	17	3200		2200
159	120			
160	12	1100		3000
161	20	2500		4600
162	28	12000		10000
163	6.5	530	190	2100
164	21			
165	7.6	470	190	1300
166	23			
167	130			
168	13			
169	12			
170	24			
171	20	1300		1500
172	41	4300		21000
173	9.7	3000		3300
174	13			
175	15	530		2600
176	20			
177	7.1			
178	29	2300		1400
179	57	3900		3900
180	9.1	2900		2800
181	10			
182	16	1300		5800
183	48	3300		2100
184	72	24000		13000
185	76	13000		9600
186	5.7	160		2000
187	18	4600	89	3300
188	14	3800		2900
189	6.8			
190	21	1700		2000
191	4	340		2100
192	16	250		3800
193	66	5900		5200

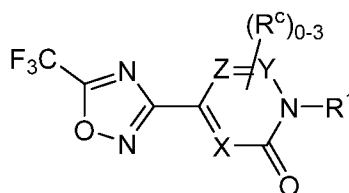
Compound #	HDAC6 IC50	HDAC1 IC50	HDAC5 IC50	HDAC8 IC50
194	41	7900	1800	8000
195	21	1100		3700
196	120			
197	41	1600	730	960
198	50	2000		460
199	48	5300		3100
200	53	7000	400	8400
201	39	4000		1600
202	9.7			
203	19	690		2800
204	89	>45000	1500	3900
205	49	2600	1000	2800
206	54	4000		870
207	12	1900	190	10000
208	40	2800		4100
209	52	6000		7300
210	36	8100		9400
211	7.4	630		4600
212	48	5700		14000
213	9.8	1600	250	3500
214	71	26000		
215	21	910		3500
216	74	10000		
217	19	4300		7800
218	30	6800		4700
219	88	23000		28000
220	94	>45000		
221	44	37000		13000
222	87	>45000		
223	32	35000		4100
224	29	24000		3300
225	18	42000		4000
226	71	8700		
227	20	960		4300
228	11	5600	1800	9100
229	31	3300		3800
230	14	670		2700
231	61	7200		
232	41	11000		
233	3.7	270		5300
234	43	4400		8500
235	21	2300		12000

Compound #	HDAC6 IC50	HDAC1 IC50	HDAC5 IC50	HDAC8 IC50
236	17	5900		6600
237	23	2500		3500
238	16	1800		4100
239	13	1400		2700
240	37	5000		4100
241	6.8	930		3700
242	36	13000	1800	12000
243	15	4200	490	3600
244	15	1300	350	1600
245	55	6800	760	11000
246	27	4500	780	1600
247	22	750	300	1500
248	28	5400	730	800
249	6.4	900	73	2500
250	37	2200	520	8100
251	31	6900	1000	3300
252	38	7300	930	3300
253	36	8100	180	4400
254	54	7100	2500	5500
255	62	4300	2000	3600
256	75	15000		13000
257	51	15000	2100	5000
258	60	5300	2200	3500
259	83	11000	2000	6600
260	34	3200	1100	2800
261	17	29000	720	>45000
262	20	23000	620	2000
263	59	8700	1200	6800
264	39	14000	1600	6100
265	23	4800	500	1300
266	33	15000	670	8400
267	47	19000	1000	7600
268	48	5500	880	6100
269	6.6	810	310	4600
270	16	3200	680	4600
271	20	920	1100	3900
272	79	2200	2200	4800
273	56	1700	2700	2200
274	28	650	870	1400
275	99	3000	2200	7400
276	40	1400	2500	2300
277	22	3200	1400	1600

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without
5 departing from the spirit and scope of the invention. It is intended, therefore, that the invention be defined by the scope of the claims that follow and that such claims be interpreted as broadly as is reasonable.

What is claimed is:

1. A compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof wherein;

X, Y, and Z independently represent CH, or N, provided X, Y, and Z are not all nitrogen at the same;

R¹ represents hydrogen, C₁₋₆ alkyl, -(C(R²)₂)_pC₄₋₁₀heterocyclyl, -(C(R²)₂)_pC₆₋₁₀aryl, -(C(R²)₂)_pOC₆₋₁₀aryl, -(C(R²)₂)_pNRC(O)(C(R²)₂)_pC₆₋₁₀aryl, -(C(R²)₂)_pNR²C(O)(C(R²)₂)_pC₄₋₁₀heterocyclyl, -(C(R²)₂)_pNRC(O)N(R²)₂, -(C(R²)₂)_pN(R²)₂, -(C(R²)₂)_pOR^a, -(C(R²)₂)_pC(O)R^a, -(C(R²)₂)_pC(O)N(R²)₂, or -(C(R²)₂)_pC₃₋₆ cycloalkyl, said alkyl, cycloalkyl, aryl, and heterocyclyl optionally substituted with 1 to 3 groups of R^a;

R represents hydrogen, or -C₁₋₆alkyl, said alkyl optionally substituted with 1 to 3 groups of R^a;

each R² independently selected from hydrogen, halo, N(R)₂, NHC(O)OR, -C(O)ON(R)₂, -C(O)OR, -(CH₂)_pC₆₋₁₀aryl, -(CH₂)_pC₄₋₁₀heterocyclyl, -C(O)C₄₋₁₀heterocyclyl, -OR, or -C₁₋₆alkyl, said alkyl, aryl, heterocyclyl, optionally substituted with 1 to 3 groups of R^a;

R^a is selected from the group consisting of H, -C₁₋₆alkyl, -C₂₋₆alkenyl, =O, -C₃₋₆cycloalkyl, -OR, -C₁₋₆alkylOR, -O₀₋₁C₁₋₄haloalkyl, -(CH₂)_pC₆₋₁₀aryl; -(CH₂)_pC₅₋₁₀heterocyclyl, -C(O)C₁₋₆alkyl, C(O)OR, -NHC(O)OC₁₋₆alkyl, -NHC(O)C₁₋₆alkyl, C(O)NH(CH₂)_pC₆₋₁₀aryl, C(O)(CH₂)_pC₆₋₁₀heterocyclyl, N(R)₂, CN, halo, -SO₀₋₂C₁₋₆alkyl, C(O)N(R)₂, said alkyl, cycloalkyl, aryl, and heterocyclyl optionally substituted with 1 to 3 groups of R^b;

R^b is selected from the group consisting of C₁₋₆alkyl, OR, C₁₋₄haloalkyl, -OC₁₋₄haloalkyl, and halo; R^c is halo or C₁₋₆alkyl and

p represents 0-4.

2. The compound according to claim 1 wherein X, Y, and Z are CH.

3. The compound according to claim 1 wherein R¹ is unsubstituted or substituted C₁₋₆alkyl, or a pharmaceutically acceptable salt thereof.

4. The compound according to claim 1 wherein R^1 is $-(C(R^2)_2)_pC(O)R^a$, or a pharmaceutically acceptable salt thereof.

5. The compound according to claim 1 wherein R^1 is $-(C(R^2)_2)_pOR^a$, or a pharmaceutically acceptable salt thereof.

6. The compound according to any one of claims 1, 2, 3, 4 and 5 wherein the R^a is selected from the group consisting of $-(C(R^2)_2)_pC_{6-10}$ aryl, $-(C(R^2)_2)_pC_{5-10}$ heterocyclyl, and $N(R)_2$, said aryl and heterocyclyl optionally substituted with 1 to 3 groups of R^b , or a pharmaceutically acceptable salt thereof.

7. The compound according to claim 1 wherein R^1 is $-(C(R^2)_2)_pC_{3-6}$ cycloalkyl, said cycloalkyl unsubstituted or substituted with 1 to 3 groups of R^a , or a pharmaceutically acceptable salt thereof.

8. The compound according to any one of claims 1 and 7 wherein R^1 is selected from the group consisting of unsubstituted or substituted cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, or a pharmaceutically acceptable salt thereof.

9. The compound according to claim 1 wherein R^1 represents unsubstituted or substituted $-(C(R^2)_2)_pC_{6-10}$ aryl, or a pharmaceutically acceptable salt thereof.

10. The compound according to any one of claims 1 and 9 wherein aryl is selected from the group consisting of unsubstituted or substituted phenyl and naphthyl, or a pharmaceutically acceptable salt thereof.

11. The compound according to any one of claims 1, 9, and 10 wherein aryl is unsubstituted or substituted phenyl, or a pharmaceutically acceptable salt thereof.

12. The compound according to claim 1 wherein R^1 represents unsubstituted or substituted $-(C(R^2)_2)_pC_{5-10}$ heterocyclyl, or a pharmaceutically acceptable salt thereof.

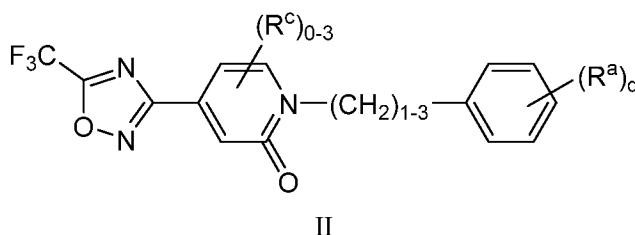
13. The compound according to any one of claims 1 and 12 wherein R^1 is a heterocyclyl selected from the group consisting of unsubstituted or substituted indazolyl, quinoxaliny, quinoliny, benzthiazolyl, benzimidazolyl, benztriazolyl, pyrazolyl, indoliny, pyrazolopyridiny, pyrazinyl, dihydroisobenzofuranyl, oxadiazolyl, benzdioxalyl, isoxazolyl, thienopyridiny, oxazolyl, thiazolyl, triazolopyridiny, pyridyl, piperidiny, imidazopyridiny, triazolyl, tetrahydropyranyl, tetrahydrotriazolyl, pyrimidiny, pyridazinyl, dihydroisoquinoliny, pyrrolidiny, morpholiny, imidazolyl, dihydropyrrolotriazolyl, tetrahydroimidazopiperidiny, tetrahydrotriazolopyridiny, imidazolothiazolyl, piperazinyl, indolyl, and oxetanyl, or a pharmaceutically acceptable salt thereof.

14. The compound according to any one of claims 1, 12, and 13 wherein R^1 is an heterocyclyl selected from the group consisting of unsubstituted or substituted unsubstituted or substituted indazolyl, quinoliny, benzimidazolyl, pyrazolyl, oxadiazolyl, isoxazolyl, pyridiny, pyrimidiny, pyrrolidiny, and imidazolyl, or a pharmaceutically acceptable salt thereof.

15. The compound according to any one of claims 1-14 wherein the R^a substituent is selected from the group consisting of C_{1-6} alkyl, $-O-$, $-C_{3-6}$ cycloalkyl, $-OR$, $-C_{1-6}$ alkylOR, $-O_{0-1}C_{1-4}$ haloalkyl, $-($

CH₂)_pC₆₋₁₀ aryl; -(CH₂)_pC₅₋₁₀ heterocyclyl, -C(O)C₁₋₆alkyl, C(O)OC₁₋₆alkyl, -N(R)₂, halo, -SC₁₋₆alkyl, said alkyl, aryl, and heterocyclyl optionally substituted with 1 to 3 groups of R^b, or a pharmaceutically acceptable salt thereof.

16. The compound according to any one of claims 1, 9, 10, and 11 represented by structural formula II:

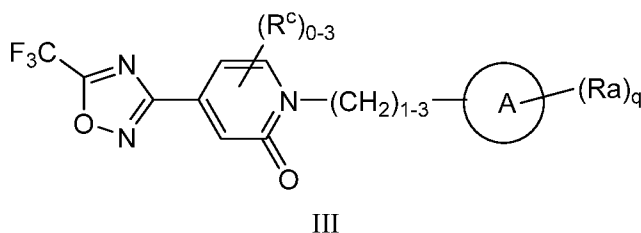


or a pharmaceutically acceptable salt thereof, wherein q is 0-3.

17. The compound according to any one of claims 16 wherein R^a is 1 or 2, one (CH₂) group links the pyridinone and phenyl groups, and R^a is selected from the group consisting of halo, CH₃, CH₂OH, OH, OCH₃, OCF₃, SCH₃, N(CH₃)₂, NH₂, and optionally substituted cyclopropyl, piperidinyl, pyrazolyl, pyrimidinyl, imidazolyl, (CH₂)_pphenyl, and pyrrolidinyl, or a pharmaceutically acceptable salt thereof.

18. The compound according to any one of claims 16 wherein R^a is 1 or 2, two (CH₂) group link the pyridinone and phenyl groups, and R^a is selected from the group consisting of halo, CH₃, CH₂OH, OH, OCH₃, OCF₃, SCH₃, N(CH₃)₂, NH₂, and optionally substituted cyclopropyl, piperidinyl, pyrazolyl, pyrimidinyl, imidazolyl, (CH₂)_pphenyl, and pyrrolidinyl, or a pharmaceutically acceptable salt thereof.

19. The compound according to any one of claims 1, 12, 13, and 14 represented by structural formula III:



or a pharmaceutically acceptable salt thereof, wherein q is 0-3, R^a is as originally defined and A is C₄₋₁₀ heterocyclyl.

20. The compound according to claim 19 wherein A is selected from the group consisting of unsubstituted or substituted indazolyl, quinoxaliny, quinolinyl, benzthiazolyl, benzimidazolyl, benztriazolyl, pyrazolyl, indoliny, pyrazolopyridinyl, pyrazinyl, dihydroisobenzofuranyl, oxadiazolyl,

benzdioxaoxy, isoxazoly, thienopyridiny, oxazoly, thiazoly, triazolopyridiny, pyridy, piperidiny, imidazopyridiny, triazoly, tetrahydropyrany, tetrahydrotriazoly, pyrimidiny, pyridaziny, dihydroisoquinoliny, pyrrolidiny, morpholiny, imidazoly, dihydropyrrolotriazoly, tetrahydroimidazopiperidiny, tetrahydrotriazolopyridiny, imidazolothiazoly, piperaziny, indoly, and oxetany. Still another subembodiment of this aspect of the invention is realized when A is unsubstituted or substituted indazoly, quinoliny, benzimidazoly, pyrazoly, oxadiazoly, isoxazoly, pyridiny, pyrimidiny, pyrrolidiny, and imidazoly, or a pharmaceutically acceptable salt thereof.

21. The compound according to any one of claims 19 and 20 wherein R^a is 1 or 2, one (CH₂) group links the pyridinone and A, A is selected from the group consisting of unsubstituted or substituted indazoly, quinoliny, benzimidazoly, pyrazoly, oxadiazoly, isoxazoly, pyridiny, pyrimidiny, pyrrolidiny, and imidazoly and R^a is selected from the group consisting of halo, CH₃, CH₂OH, OH, OCH₃, OCF₃, SCH₃, N(CH₃)₂, NH₂, and optionally substituted cyclopropyl, piperidiny, pyrazoly, pyrimidiny, imidazoly, (CH₂)_pphenyl, and pyrrolidiny, or a pharmaceutically acceptable salt thereof.

22. The compound according to any one of claims 19, and 20 wherein R^a is 1 or 2, two (CH₂) group link the pyridinone and A, A is selected from the group consisting of unsubstituted or substituted indazoly, quinoliny, benzimidazoly, pyrazoly, oxadiazoly, isoxazoly, pyridiny, pyrimidiny, pyrrolidiny, and imidazoly and R^a is selected from the group consisting of halo, CH₃, CH₂OH, OH, OCH₃, OCF₃, SCH₃, N(CH₃)₂, NH₂, and optionally substituted cyclopropyl, piperidiny, pyrazoly, pyrimidiny, imidazoly, (CH₂)_pphenyl, and pyrrolidiny, or a pharmaceutically acceptable salt thereof.

23. A compound which is:

methyl (2-(2-oxo-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-1(2H)-yl)-1-(3-(trifluoromethyl)phenyl)ethyl)carbamate

2-(2-oxo-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-1(2H)-yl)-1-(3-(trifluoromethyl)-phenyl)ethyl methylcarbamate,

3-(2-oxo-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-1(2H)-yl)-2-(3-(trifluoromethyl)phenyl)propanoic acid,

1-(3-(1,1-dioxidothiomorpholino)-3-oxo-2-(3-(trifluoromethyl)phenyl)propyl)-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one,

1-phenethyl-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyrimidin-2(1H)-one,

2-benzyl-5-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridazin-3(2H)-one,

3-phenethyl-6-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyrimidin-4(3H)-one,

1-(2-oxo-2-(pyrrolidin-1-yl)ethyl)-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one,

N-[(3R)-oxolan-3-yl]-2-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}acetamide,

1-{[(1S,2R)-2-pyrimidin-2-ylcyclopropyl]methyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,

1-{[(1S,2R)-2-(5-fluoropyridin-2-yl)cyclopropyl]methyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,

4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]-1-({(1R,2S)-2-[5-(trifluoromethyl)pyridin-2-yl]cyclopropyl}methyl)pyridin-2(1H)-one,

1-({(1R,2S)-2-[5-(difluoromethoxy)pyridin-2-yl]cyclopropyl}methyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,

1-{{trans-4-(hydroxymethyl)cyclohexyl}methyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,

1-[(1-methylpiperidin-3-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,

1-[(2,2-dimethylcyclopropyl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,

1-[(3-fluoropyrrolidin-3-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,

1-(5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyridin-8-yl)methyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,

1-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-7-yl)methyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,

1-(6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazol-5-yl)methyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,

1-[1-(2-fluorophenyl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,

1-[1-(3-fluorophenyl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(1-pyridin-2-ylethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(1-methyl-2-phenoxyethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(1-phenylethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(1-phenylpyrrolidin-3-yl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[2-(1H-pyrazol-1-yl)cyclopentyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[2-(1-methylpiperidin-2-yl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[2-(4-methylmorpholin-2-yl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(3-hydroxy-2-phenylpropyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(3-hydroxycyclopentyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(3-methylpiperidin-4-yl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[4-(4-bromo-1H-pyrazol-1-yl)tetrahydro-2H-pyran-3-yl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(5-hydroxy-3-methylpentyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(1-naphthalen-1-ylethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(2-methyl-3-morpholin-4-ylpropyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(2-fluoro-3-morpholin-4-ylpropyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-{3-[3-(hydroxymethyl)morpholin-4-yl]propyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
4-{3-[2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl]propyl}morpholine-3-carboxylic acid,
1-{[5-cyclopropyl-1-(1,1-dioxidotetrahydrothiophen-3-yl)-1H-pyrazol-3-yl]methyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[1-(2-methylphenyl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-{3-(morpholin-4-yl)-3-oxo-2-[3-(trifluoromethyl)phenyl]propyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-{3-oxo-3-(thiomorpholin-4-yl)-2-[3-(trifluoromethyl)phenyl]propyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-{3-(2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-3-oxo-2-[3-(trifluoromethyl)phenyl]propyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
4-methyl-1-(3-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}-2-[3-(trifluoromethyl)phenyl]propanoyl)piperidine-4-carbonitrile,

4-(3-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}-2-[3-(trifluoromethyl)phenyl]propanoyl)piperazin-2-one,

2-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}-1-[3-(trifluoromethyl)phenyl]ethyl ethyl carbamate,

cyclobutyl (2-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}-1-[3-(trifluoromethyl)phenyl]ethyl)carbamate,

1-[2-(2,6-dimethylmorpholin-4-yl)-2-oxoethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,

1-[2-(3-methoxy-5-methyl-3,6-dihydropyridin-1(2H)-yl)-2-oxoethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,

1-[2-(3-methylidene-8-azabicyclo[3.2.1]octan-8-yl)-2-oxoethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,

1-{3-[(1R,5R)-6-azabicyclo[3.2.0]heptan-6-yl]-3-oxopropyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,

1-{2-[3-(hydroxymethyl)pyrrolidin-1-yl]-2-oxoethyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,

1-{2-[2-(hydroxymethyl)pyrrolidin-1-yl]-2-oxoethyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,

1-{3-[(3S)-3-methylmorpholin-4-yl]-3-oxo-2-[3-(trifluoromethyl)phenyl]propyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,

1-[(2S)-2-phenylcyclopentyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,

1-{[(2S)-5-oxopyrrolidin-2-yl]methyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,

1-{[(2S)-1-benzylpyrrolidin-2-yl]methyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,

1-{[(1S,2R)-2-(5-fluoropyridin-2-yl)cyclopropyl]methyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,

1-{2-[(3S,4S)-3,4-difluoropyrrolidin-1-yl]ethyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,

1-{2-[(2S,6S)-2,6-dimethylmorpholin-4-yl]-2-oxoethyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,

1-[(1-pyridin-3-ylcyclopropyl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,

1-(1,3-dihydro-2-benzofuran-5-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,

1-[(1,3-dimethyl-1H-pyrazol-5-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,

1-[(1,5-dimethyl-1H-benzimidazol-2-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,

1-[(1,5-dimethyl-1H-pyrazol-4-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,

1-[(1-cyclopropyl-1H-imidazol-2-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,

1-(1H-imidazol-2-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,

1-(1H-indazol-3-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(1H-indazol-5-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(1H-pyrazol-3-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(1H-pyrazolo[3,4-b]pyridin-3-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[(1-methyl-1H-benzotriazol-5-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[(1-methyl-1H-benzimidazol-2-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[(1-methyl-1H-benzimidazol-5-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[(1-methyl-1H-indazol-4-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[(1-methyl-1H-indazol-5-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[(1-methyl-1H-indazol-6-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[(1-methyl-3-phenyl-1H-pyrazol-5-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[(2,5-dimethyl-1,3-oxazol-4-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[(2,6-dimethylimidazo[2,1-b][1,3]thiazol-5-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[(2,6-dimethylpyridin-4-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[(3-fluorooxetan-3-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[(3-methyl-1,2,4-oxadiazol-5-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[(3-methyl-1H-pyrazol-5-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[(4-chloroquinolin-6-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[(4-methylcyclohexyl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyridin-3-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[(5-chloro-1-methyl-1H-benzimidazol-2-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[(5-cyclopropyl-1,2,4-oxadiazol-3-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[(5-cyclopropylisoxazol-3-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[(5-fluoropyridin-2-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[[5-(1-methylethyl)-1,3,4-oxadiazol-2-yl]methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[(5-methoxypyridin-2-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[(5-methylisoxazol-3-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,

1-[(5-methyl-1,3-oxazol-2-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[(5-methylpyrimidin-2-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[(6-chloro-1-methyl-1H-benzimidazol-2-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[(8-methoxyquinolin-5-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(biphenyl-4-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-{2-[(2-fluorobenzyl)amino]ethyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(2-[1,2,4]triazolo[4,3-a]pyridin-3-ylethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[2-(1H-1,2,4-triazol-1-yl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[2-(1H-imidazol-1-yl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[2-(1H-pyrazol-1-yl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[2-(1-methyl-1H-imidazol-2-yl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[2-(1-methyl-1H-pyrazol-4-yl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[2-(1-methyl-1H-pyrazol-5-yl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[2-(2,2-dimethylpyrrolidin-1-yl)-2-oxoethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[2-(2-bromo-1,3-thiazol-4-yl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[2-(2-oxopyrrolidin-1-yl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[2-(3,4-dihydroisoquinolin-2(1H)-yl)-2-oxoethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[2-(4H-1,2,4-triazol-4-yl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[2-(4-methyl-1H-pyrazol-1-yl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[2-(5-ethylpyridin-2-yl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[2-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[2-(6-methylpyridin-2-yl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[2-(diethylamino)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[2-(dimethylamino)-2-methylpropyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[2-(hydroxymethyl)benzyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[2-(2,3-dihydro-1H-indol-1-yl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(2-isoxazol-4-ylethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(2-naphthalen-1-ylethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,

1-[2-(naphthalen-2-yloxy)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(2-pyridin-4-ylethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(2-pyrimidin-4-ylethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(2,3,4-trifluorobenzyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(2,3-difluorobenzyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[2-(2,3-difluorophenyl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(2,3-dimethoxybenzyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[2-(2,4-dichlorophenyl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(2,4-difluorobenzyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(2,4-dimethylbenzyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(2,5-difluorobenzyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[2-(2,6-dichlorophenyl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(2-amino-3-methylbenzyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(2-amino-5-methylbenzyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(2-aminobenzyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(2-benzylbenzyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[2-(2-chloro-4-fluorophenyl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(2-chloro-6-fluorobenzyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[2-(2-fluorophenyl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(2-morpholin-4-ylethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[3-(1H-imidazol-1-yl)propyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[3-(6-methylpyridin-2-yl)propyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[3-(dimethylamino)benzyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(3-pyrrolidin-1-ylbenzyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[3-(trifluoromethoxy)benzyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[2-(3,4-dichlorophenyl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[2-(3,5-difluorophenyl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(3,5-dimethoxybenzyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,

1-(3-aminobenzyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[2-(3-chloro-4-methylphenyl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(3-cyclohexylpropyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(3-fluorobenzyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[2-(3-fluorophenyl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(3-methoxybenzyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[2-(3-methoxyphenyl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(3-phenylpropyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[4-(1H-imidazol-1-yl)benzyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[4-(1H-indol-1-yl)butyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[4-(methylsulfanyl)benzyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(4-pyrimidin-5-ylbenzyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[4-(trifluoromethoxy)benzyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(4-chloro-2-fluorobenzyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[2-(4-chlorophenyl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[2-(4-fluorophenyl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(4-methoxybenzyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(1,3-benzodioxol-5-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(1,3-benzothiazol-2-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(1,3-benzothiazol-6-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(imidazo[1,2-a]pyridin-8-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(isoxazol-4-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(naphthalen-1-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(naphthalen-2-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(pyrazolo[1,5-a]pyridin-2-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(pyridazin-3-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(pyrimidin-2-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(pyrimidin-5-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,

1-(quinolin-3-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(quinolin-4-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(quinolin-5-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(quinolin-6-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(quinolin-8-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(quinoxalin-6-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(thieno[2,3-b]pyridin-2-ylmethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[(2-methoxypyridin-3-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[(6-methoxypyridin-2-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[(6-methoxypyridin-3-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-methyl-4-(2-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}ethyl)piperazin-2-one,
1-methyl-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(2,2-dimethylpropyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
2-({2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}methyl)benzamide,
4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]-1-[(3,5,6-trimethylpyrazin-2-yl)methyl]pyridin-2(1H)-one,
4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
N-({2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}methyl)benzamide,
N-[4-({2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}methyl)phenyl]acetamide,
N-tert-butyl-N-methyl-2-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}acetamide,
N-methyl-3-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}propanamide,
tert-butyl [2-({2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}methyl)pyridin-3-yl]carbamate,
1-[(3-cyclopropyl-1,2,4-oxadiazol-5-yl)methyl]-3-fluoro-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
2-(2-phenylethyl)-5-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridazin-3(2H)-one,
1-(2-pyrazin-2-ylethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[2-(2-chloropyrimidin-4-yl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[(5-cyclopropyl-1-methyl-1H-pyrazol-3-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-{2-[4-methyl-6-(trifluoromethyl)pyrimidin-2-yl]ethyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[(1-methyl-1H-indazol-3-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,

1-[(1,4-dimethyl-1H-pyrazol-3-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-{[1-(difluoromethyl)-1H-pyrazol-3-yl]methyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[(2-methylpyridin-3-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[(4,6-dimethylpyridin-2-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(2-pyridin-3-ylethyl)-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[2-(1H-indazol-4-yl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
N-(2,2-dimethylpropyl)-N-methyl-2-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}acetamide,
N-methyl-2-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}-N-phenylacetamide,
1-[2-(3,3-dimethylazetidin-1-yl)-2-oxoethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[2-(2-bromophenyl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
2-(2-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}ethyl)benzonitrile,
4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]-1-{2-[2-(trifluoromethyl)phenyl]ethyl}pyridin-2(1H)-one,
1-{[1-(3-fluorophenyl)-1H-pyrazol-5-yl]methyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[(3-cyclopropyl-1,2,4-oxadiazol-5-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[(4,6-dimethylpyrimidin-2-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[(5-methylpyrazin-2-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[(6-chloropyrazin-2-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[(3-fluoropyridin-2-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[(4-chloro-3-methylpyridin-2-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-{[5-cyclopropyl-1-(2,2,2-trifluoroethyl)-1H-pyrazol-3-yl]methyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[(1-cyclopropyl-1H-pyrazol-3-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[2-(3-methylphenyl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[2-(2-methylphenyl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-[2-(2-chlorophenyl)ethyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]-1-{[6-(trifluoromethyl)pyridin-2-yl]methyl}pyridin-2(1H)-one,
1-[(3,6-dichloropyridin-2-yl)methyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-{2-[2-(methoxymethyl)phenyl]ethyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,

1-{{3-chloro-6-(trifluoromethyl)pyridin-2-yl}methyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-{{4-(dimethylamino)-6-methylpyrimidin-2-yl}methyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-{{2-[2-(hydroxymethyl)phenyl]ethyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-{{2-[3-(hydroxymethyl)phenyl]ethyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-{{3,6-dimethylpyrazin-2-yl}methyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-{{2-(1H-benzimidazol-1-yl)ethyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
N-methyl-3-(2-{{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}ethyl}benzamide,
N,N-dimethyl-3-(2-{{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}ethyl}benzamide,
1-{{6-chloro-3-methylpyrazin-2-yl}methyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-{{4,5-dimethyl-1,3-oxazol-2-yl}methyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-{{2-(4-methylpyridin-3-yl)ethyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-{{2-[3-(morpholine-4-carbonyl)phenyl]ethyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
methyl 3-{{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}methyl}pyrazine-2-carboxylate,
1-{{2-(4,5-dimethylpyridin-3-yl)ethyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-{{2-[2-(1,3-oxazol-2-yl)phenyl]ethyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-{{3-methoxypyrazin-2-yl}methyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-{{4,6-dimethoxypyrimidin-2-yl}methyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-(2-{{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}ethyl}-1,3-dihydro-2H-benzimidazol-2-one,
1-{{2-(2,5-dimethylpyridin-3-yl)ethyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
1-{{2-(2,2-dimethylmorpholin-4-yl)ethyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,
4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]-1-{{2-[4-(trifluoromethyl)pyridin-3-yl]ethyl}pyridin-2(1H)-one,
N-(cyclopent-3-en-1-yl)-2-{{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}acetamide,
N-methyl-2-{{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}-N-[(pyridin-2-yl)methyl]acetamide,
N-methyl-2-{{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}-N-[(pyridin-3-yl)methyl]acetamide,
2-{{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}-N-[(thiophen-3-yl)methyl]acetamide,
1-{{2-(5-fluoro-1,3-dihydro-2H-isoindol-2-yl)-2-oxoethyl}-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,

N-[(4-fluorophenyl)methyl]-N-methyl-2-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}acetamide,

N-[(3-fluorophenyl)methyl]-N-methyl-2-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}acetamide,

2-({2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}methyl)quinazolin-4(3H)-one,

4-(2-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}ethyl)-2,3-dihydro-1H-isoindol-1-one,

1-[3-(2,5-dihydro-1H-pyrrol-1-yl)-3-oxopropyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,

1-[3-(3-methylazetidin-1-yl)-3-oxopropyl]-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2(1H)-one,

N-methyl-3-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}-N-[2-(pyridin-2-yl)ethyl]propanamide,

N-methyl-3-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}-N-(2-phenylethyl)propanamide,

4-(3-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}propanoyl)-1 λ 4-thiazinan-1-one,

N-ethyl-3-{2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}-N-[2-(pyridin-2-yl)ethyl]propanamide,

6-methyl-2-({2-oxo-4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-1(2H)-yl}methyl)pyrimidin-4(3H)-one,

1-(2-fluorobenzyl)-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one,

1-Phenethyl-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one,

1-(2-(1H-indazol-7-yl)ethyl)-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one,

5 3-fluoro-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one,

3-fluoro-1-((1-methyl-1H-indazol-4-yl)methyl)-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one,

1-(2-amino-2-(3-(trifluoromethyl)phenyl)ethyl)-4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-

2(1H)-one,

10 or a pharmaceutically acceptable salt thereof.

24. A pharmaceutical composition comprising a compound of any previous claim, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

15 25. The compound of any one of claims 1 to 23, or a pharmaceutically acceptable salt thereof for use in therapy.

26. The use of a compound of any one of claims 1 to 23 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating or preventing a disease ameliorated by

20 modulating HDAC activity.

27. The use of a compound of any one of claims 1 to 23 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating or preventing cellular proliferation diseases, neurodegenerative diseases, mental retardation, schizophrenia, inflammatory diseases, restenosis, immune disorders, diabetes, cardiovascular disorders or asthma.

28. A method for treating or preventing cellular proliferation diseases, neurodegenerative diseases, mental retardation, schizophrenia, inflammatory diseases, restenosis, immune disorders, diabetes, cardiovascular disorders or asthma, which method comprises administration to a patient in need thereof of an effective amount of a compound or composition of any one of claims 1 to 23.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 17/38068

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C07D 413/14, A61K 31/4245, A61K 31/444 (2017.01)

CPC - C07D 413/04, A61K 31/506, A61K 31/4439, C07D 413/14

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)

See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2012/011592 A1 (TAKEDA PHARMACEUTICAL COMPANY LIMITED) 26 January 2012 (26.01.2012); para [0745]	1-2
A	US 5,763,461 A (Aldous et al.) 09 June 1998 (09.06.1998); col 13, ln 8-10	1-2
A	WO 2013/008162 A1 (NOVARTIS AG) 17 January 2013 (17.01.2013); entire document	1-2
A	WO 2013/080120 A1 (NOVARTIS AG) 06 June 2013 (06.06.2013); entire document	1-2
A	US 8,981,084 B2 (Baloglu et al.) 17 March 2015 (17.03.2015); entire document	1-2

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"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

09 October 2017 (09.10.2017)

Date of mailing of the international search report

30 OCT 2017

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

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PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

--continued from Box No. III--

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

Group I+: Claims 1-10, 12-13 and 23 directed to compounds having the general formula of claim 1, formula (I). The compound of claim 1 will be searched to the extent that it encompasses the first species of claim 1, represented by the first formula of claim 1, formula (I), wherein X, Y, and Z are CH; R1 is hydrogen; and the variable for Rc is 0. It is believed that claims 1-2 read on this first named invention, and thus these claims will be searched without fee. Applicant is invited to elect additional compounds of claim 1, wherein each additional compound elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected compound. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the '+' group(s) will result in only the first claimed invention to be searched. Additionally, an exemplary election wherein different actual variables are selected is suggested. An exemplary election would be a compound of claim 1, represented by the first formula of claim 1, formula (I), wherein X, Y, and Z are CH; R1 is unsubstituted C1 alkyl; and the variable for Rc is 0 (i.e., claims 1-3).

The group of inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features:

Group I+ includes the technical feature of a unique compound of formula I, which is not required by any other invention of Group I+.

Common technical features:

The inventions of Group I+ share the technical feature of a compound of formula I.

These shared technical features, however, do not provide a contribution over the prior art, as being obvious over WO 2012/011592 A1 to TAKEDA PHARMACEUTICAL COMPANY LIMITED (hereinafter Takeda). Takeda discloses a compound of formula I wherein X and Y are CH; Z is N; R1 is C(R2)2pC6 aryl, said aryl substituted with 1 Ra, wherein Ra is O1C2 haloalkyl; Rc is a substituted C3 alkyl; p is 0 and the variable for Rc is 1 (para [0745]: Table 1: compound 115), but does not disclose wherein Rc is an unsubstituted C3 alkyl. However, Takeda further discloses similar compounds wherein Rc is an unsubstituted C3 alkyl (para [0745]: Table 1: compound 90). It would have been obvious to one with skill in the art to prepare further derivatives of the compounds disclosed varying haloalkyl and alkyl substituents as utilized in the disclosed compounds in order to optimize the compounds pharmacological properties.

As said compound and compositions were known in the art at the time of the invention, these cannot be considered special technical features that would otherwise unify the inventions of Groups I+. The inventions of Group I+ thus lack unity under PCT Rule 13.

Note: Claims 11, 14-22 and 24-28 have been found to be unsearchable because they are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 17/38068

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 11, 14-22, 24-28
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
--see supplemental page--

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-2

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.