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— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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(54) Title: HETEROCYCLIC COMPOUNDS

(57) Abstract: This invention relates to heterocyclic compounds of the formulas shown in the specification. It also relates to methods for treating inflammatory diseases or immune diseases, developmental or degenerative diseases, and tissue injuries with one of the heterocyclic compounds

Heterocyclic Compounds

CROSS REFERENCE

This application claims priority to U.S. Provisional Application Serial No. 61/046,496, filed April 21, 2008, the content of which is incorporated herein by reference.

BACKGROUND

Chemokines are a family of cytokines that regulate the adhesion and transendothelial migration of leukocytes during an immune or inflammatory reaction (Mackay C.R., Nat. Immunol., 2001, 2:95; Olson et al., Am. J. Physiol. Regul. Integr. Comp. Physiol., 2002, 283:R7). Chemokines also regulate T cells and B cells trafficking and homing, and contribute to the development of lymphopoietic and hematopoietic systems (Ajuebor et al., Biochem. Pharmacol., 2002, 63:1191). Approximately 50 chemokines have been identified in humans. They can be classified into 4 subfamilies, i.e., CXC, CX3C, CC, and C chemokines, based on the positions of the conserved cysteine residues at the N-terminal (Onuffer et al., Trends Pharmacol Sci., 2002, 23:459). The biological functions of chemokines are mediated by their binding and activation of G protein-coupled receptors (GPCRs) on the cell surface.

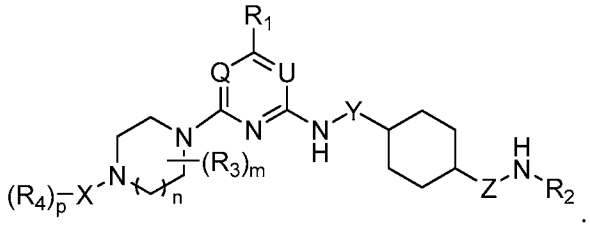
Stromal-derived factor-1 (SDF-1) is a member of CXC chemokines. It is originally cloned from bone marrow stromal cell lines and found to act as a growth factor for progenitor B cells (Nishikawa et al., Eur. J. Immunol., 1988, 18:1767). SDF-1 plays key roles in homing and mobilization of hematopoietic stem cells and endothelial progenitor cells (Bleul et al., J. Exp. Med., 1996, 184:1101; and Gazzit et al., Stem Cells, 2004, 22:65-73). The physiological function of SDF-1 is mediated by CXCR4 receptor. Mice lacking SDF-1 or CXCR4 receptor show lethal abnormality in bone marrow myelopoiesis, B cell lymphopoiesis, and cerebellar development (Nagasawa et al., Nature, 1996, 382:635; Ma et al., Proc. Natl. Acad. Sci., 1998, 95:9448; Zou et al., Nature, 1998, 393:595; Lu et al., Proc. Natl. Acad. Sci., 2002, 99:7090). CXCR4 receptor is expressed broadly in a variety of tissues, particularly in immune and central nervous systems, and has been described as the major co-receptor for HIV-1/2 on T lymphocytes. Although initial interest in CXCR4 antagonism focused on its potential application to AIDS treatment (Bleul et al., Nature, 1996,

382:829), it is now becoming clear that CXCR4 receptor and SDF-1 are also involved in other pathological conditions such as rheumatoid arthritis, asthma, and tumor metastases (Buckley et al., J. Immunol., 2000, 165:3423). Recently, it has been reported that a CXCR4 antagonist and an anticancer drug act synergistically in inhibiting cancer such as acute promuelocutic leukemia (Liesveld et al., Leukemia Research 2007, 31:1553). Further, the CXCR4/SDF-1 pathway has been shown to be critically involved in the regeneration of several tissue injury models. Specifically, it has been found that the SDF-1 level is elevated at an injured site and CXCR4-positive cells actively participate in the tissue regenerating process.

SUMMARY

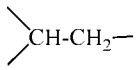
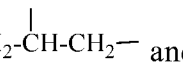
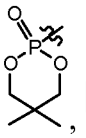
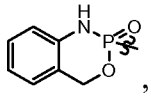
This invention is based on the discovery that certain compounds (1) are effective in inhibiting the binding between SDF-1 and chemokine receptors (e.g., CXCR3 or CXCR4 receptors), and (2) exhibit synergistic effects in stem cells and endothelial progenitor cells mobilization, when used in combination with a granulocyte-colony stimulating factor (G-CSF).

In one aspect, this invention relates to compounds of the following formula:



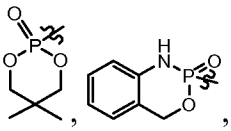
In this formula, each of Q and U is CH or N, provided that at least one of Q and U is N; each of X, Y, and Z, independently, is C_{1-5} alkylene or deleted; m is 0, 1, 2, 3, 4, or 5; n is 0, 1 or 2; p is 1 or 2; R_1 is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, heteroaryl, halo, CN, OR_a, $COOR_a$, $OC(O)R_a$, $C(O)R_a$, $C(O)NR_aR_b$, or NR_aR_b; R_2 is C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, heteroaryl, or C_1-C_{10} alkyl, optionally substituted with C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, or $N(R_cR_d)$; R_3, independently, is C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, heteroaryl, halo, CN, OR_e, $COOR_e$, $OC(O)R_e$, $C(O)R_e$, $C(O)NR_eR_f$, or NR_eR_f; or R_3 is C_{1-5} alkylene bonded to two carbon atoms of the ring to which it is attached or C_{2-8} alkylene bonded to one carbon atom of the ring to which it is attached; and R_4 is $P(=O)(OR_g)(OR_i)$, $P(=O)(NHR_g)(OR_i)$, $P(=O)(NR_g)(NR_i)$, $S(=O)_2OR_g$, or $S(=O)_2R_g$; in which each of R_a, R_b, R_c, R_d, R_e, R_f,

R_g and R_i, independently, is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, heteroaryl, or -C(O)R, R being H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, or heteroaryl; or R_a and R_b are linked and together form C_{2-8} alkylene, R_c and R_d are linked and together form C_{2-8} alkylene, R_e and R_f are linked and together form C_{2-8} alkylene, or R_g and R_i are linked and together form C_{1-5} alkylene.

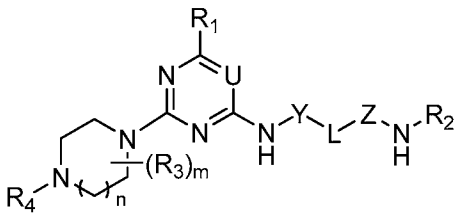
The just-described compounds may have one or more of the following features: U is N; X is $-CH_2-$, $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$ and p is 1, or X is  or  and p is 2; Y is $-CH_2$ or deleted; Z is $-CH_2-$; m is 0, 1, or 2; n is 1 or 2; R_1 is NH_2; R_2 is C_{1-5} alkyl substituted $N(R_cR_d)$, e.g., $-CH_2CH_2-N(R_cR_d)$ or $-CH_2CH_2CH_2-N(R_cR_d)$, in which R_c is H and R_d is C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, or heteroaryl, or R_c and R_d are linked and together form C_{4-6} alkylene; R_3 is C_1-C_3 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 heterocycloalkyl, aryl, heteroaryl, halo, CN, OR_e, or $C(O)NR_eR_f$; or R_3 is C_{1-2} alkylene bonded to two carbon atoms of the ring to which it is attached or C_{2-5} alkylene bonded to one carbon atom of the ring to which it is attached; and R_4 is $P(=O)(OH)_2$, $P(=O)(OH)(OCH_2CH_3)$, $P(=O)(OCH_2CH_3)_2$,  ,  , $S(=O)_2OH$, $S(=O)_2CH_3$, or $S(=O)_2Ph$.

In another aspect, this invention relates to compounds of the above formula, in which each of Q and U is N or CH, provided at least one of them is N; each of X, Y, and Z, independently, is C_{1-5} alkylene or deleted, m is 1, 2, 3, 4, or 5; n is 0, 1 or 2; R_1 is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, heteroaryl, halo, CN, OR_a, $COOR_a$, $OC(O)R_a$, $C(O)R_a$, $C(O)NR_aR_b$, or NR_aR_b; R_2 is C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, heteroaryl, or C_1-C_{10} alkyl, optionally substituted with C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, or $N(R_cR_d)$; R_3 is C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, heteroaryl, halo, CN, OR_e, $COOR_e$, $OC(O)R_e$, $C(O)R_e$, $C(O)NR_eR_f$, or NR_eR_f; or R_3 is C_{1-5} alkylene bonded to two carbon atoms of the ring to which it is attached or C_{2-8} alkylene bonded to one carbon atom of the ring to which it is attached; and R_4 is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, heteroaryl, OR_g, $COOR_g$, $C(O)R_g$, $C(O)NR_gR_i$, $P(=O)(OR_g)(OR_i)$, $P(=O)(NHR_g)(OR_i)$, $P(=O)(NR_g)(NR_i)$, $S(=O)_2OR_g$, or $S(=O)_2R_g$; in which each of R_a, R_b, R_c, R_d, R_e, R_f, R_g and R_i, independently, is H,

C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, heteroaryl, or -C(O)R, R being H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, or heteroaryl; or R_a and R_b are linked and together form C_{2-8} alkylene, R_c and R_d are linked and together form C_{2-8} alkylene, R_e and R_f are linked and together form C_{2-8} alkylene, or R_g and R_i are linked and together form C_{2-8} alkylene.

The just-described compounds may have one or more of the following features: U is N; X is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or deleted; Y is $-CH_2$ or deleted; Z is $-CH_2-$; m is 1 or 2; n is 1 or 2; R_1 is NH_2; R_2 is C_{1-5} alkyl substituted $N(R_cR_d)$, e.g., $-CH_2CH_2-N(R_cR_d)$ or $-CH_2CH_2CH_2-N(R_cR_d)$, in which R_c is H and R_d is C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, or heteroaryl, or R_c and R_d are linked and together form C_{4-6} alkylene; R_3 is C_1-C_3 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 heterocycloalkyl, aryl, heteroaryl, halo, CN, OR_e, or $C(O)NR_eR_f$; or R_3 is C_{1-2} alkylene bonded to two carbon atoms of the ring to which it is attached or C_{2-5} alkylene bonded to one carbon atom of the ring to which it is attached; and R_4 is $P(=O)(OH)_2$, $P(=O)(OH)(OCH_2CH_3)$, $P(=O)(OCH_2CH_3)_2$,  , $S(=O)_2OH$, $S(=O)_2CH_3$, or $S(=O)_2Ph$.

In still another aspect, this invention relates to compounds of the following formula:

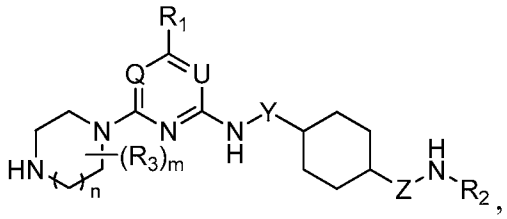


In this formula, U is CH or N; L is C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, or heteroaryl; each of Y and Z, independently, is C_{1-5} alkylene or deleted; m is 0, 1, 2, 3, 4, or 5; n is 0, 1 or 2; R_1 is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, heteroaryl, halo, CN, OR_a, $COOR_a$, $OC(O)R_a$, $C(O)R_a$, $C(O)NR_aR_b$, or NR_aR_b; R_2 is C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, heteroaryl, or C_1-C_{10} alkyl, optionally substituted with C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, or $N(R_cR_d)$; R_3 is C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, heteroaryl, halo, CN, OR_e, $COOR_e$,

$OC(O)R_e$, $C(O)R_e$, $C(O)NR_eR_f$, or NR_eR_f; or R_3 is C_{1-5} alkylene bonded to two carbon atoms of the ring to which it is attached or C_{2-8} alkylene bonded to one carbon atom of the ring to which it is attached; and R_4 is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, heteroaryl, OR_g, $COOR_g$, $C(O)R_g$, or $C(O)NR_gR_i$; in which each of R_a, R_b, R_c, R_d, R_e, R_f, R_g and R_i, independently, is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, heteroaryl, or -C(O)R, R being H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, or heteroaryl; or R_a and R_b are linked and together form C_{2-8} alkylene, R_c and R_d are linked and together form C_{2-8} alkylene, R_e and R_f are linked and together form C_{2-8} alkylene, or R_g and R_i are linked and together form C_{2-8} alkylene.

The just-described compounds may have one or more of the following features: U is N; Y is $-CH_2$ or deleted; Z is $-CH_2-$; m is 1 or 2; n is 1 or 2; L is cyclohexyl; R_1 is NH_2; R_2 is C_{1-5} alkyl substituted $N(R_cR_d)$, e.g., $-CH_2CH_2-N(R_cR_d)$ or $-CH_2CH_2CH_2-N(R_cR_d)$, in which R_c is H and R_d is C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, or heteroaryl, or R_c and R_d are linked and together form C_{4-6} alkylene; R_3 is C_1-C_3 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 heterocycloalkyl, aryl, heteroaryl, halo, CN, OR_e, or $C(O)NR_eR_f$; or R_3 is C_{1-2} alkylene bonded to two carbon atoms of the ring to which it is attached or C_{2-5} alkylene bonded to one carbon atom of the ring to which it is attached; and R_4 is H or C_1-C_3 alkyl optionally substituted with OR_g, CO_2R_g, NR_gR_i, $P(=O)(OR_g)(OR_i)$, $P(=O)(NHR_g)(OR_i)$, $P(=O)(NR_g)(NR_i)$, $S(=O)_2OR_g$, or $S(=O)_2R_g$; in which each of R_g and R_i, independently, is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, heteroaryl, or -C(O)R, R being H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, or heteroaryl; or R_g and R_i are linked and together form C_{1-5} alkylene.

In still another aspect, this invention relates to compounds of the following formula:

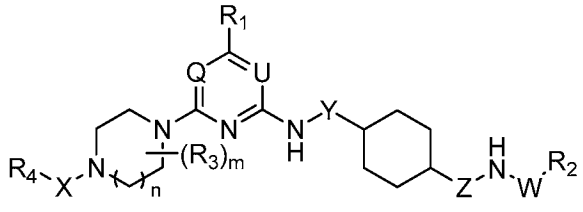


In this formula, each of Q and U is N or CH, provided at least one of them is N; each of Y and Z, independently, is C_{1-5} alkylene or deleted; m is 0, 1, 2, 3, 4, or 5; n is 0, 1

or 2; R_1 is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, heteroaryl, halo, CN, OR_a, $COOR_a$, $OC(O)R_a$, $C(O)R_a$, $C(O)NR_aR_b$, or NR_aR_b; R_2 is C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, heteroaryl, or C_1-C_{10} alkyl, optionally substituted with C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, or $N(R_cR_d)$; and R_3 is C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, heteroaryl, halo, CN, OR_e, $COOR_e$, $OC(O)R_e$, $C(O)R_e$, $C(O)NR_eR_f$, or NR_eR_f; or R_3 is C_{1-5} alkylene bonded to two carbon atoms of the ring to which it is attached or C_{2-8} alkylene bonded to one carbon atom of the ring to which it is attached; in which each of R_a, R_b, R_c, R_d, R_e, and R_f, independently, is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, heteroaryl, or -C(O)R, R being H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, or heteroaryl; or R_a and R_b are linked and together form C_{2-8} alkylene, R_c and R_d are linked and together form C_{2-8} alkylene, or R_e and R_f are linked and together form C_{2-8} alkylene.

The just-described compounds may have one or more of the following features: U is N; Y is $-CH_2$ or deleted; Z is $-CH_2-$; m is 0, 1 or 2; n is 1 or 2; R_1 is NH_2; R_2 is C_{1-5} alkyl substituted $N(R_cR_d)$, e.g., $-CH_2CH_2-N(R_cR_d)$ or $-CH_2CH_2CH_2-N(R_cR_d)$, in which R_c is H and R_d is C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, or heteroaryl, or R_c and R_d are linked and together form C_{4-6} alkylene; R_3 is C_1-C_3 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 heterocycloalkyl, aryl, heteroaryl, halo, CN, OR_e, or $C(O)NR_eR_f$; or R_3 is C_{1-2} alkylene bonded to two carbon atoms of the ring to which it is attached or C_{2-5} alkylene bonded to one carbon atom of the ring to which it is attached;

In still another aspect, this invention relates to compounds of the following formula:



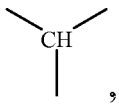
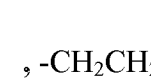
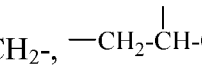
,

In the formula, each of Q and U is N or CH, provided at least one of them is N; each of W, X, Y, and Z, independently, is C_{1-5} alkylene or deleted; m is 0, 1, 2, 3, 4, or 5; n is 0, 1 or 2; R_1 is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, heteroaryl, halo, CN, OR_a, $COOR_a$, $OC(O)R_a$, $C(O)R_a$, $C(O)NR_aR_b$, or NR_aR_b; R_2 is piperidin-1-yl, (bicyclo[2.2.1]heptanyl)amino, (cyclohexylmethyl)amino, (2,3-

dihydro-1H-inden-2-yl)amino, phenylamino, or benzylamino; R_3 is C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, heteroaryl, halo, CN, OR_e, $COOR_e$, $OC(O)R_e$, $C(O)R_e$, $C(O)NR_eR_f$, or NR_eR_f; or R_3 is C_{1-5} alkylene bonded to two carbon atoms of the ring to which it is attached or C_{2-8} alkylene bonded to one carbon atom of the ring to which it is attached; and R_4 is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, heteroaryl, OR_g, $COOR_g$, $C(O)R_g$, or $C(O)NR_gR_i$; in which each of R_a, R_b, R_e, R_f, R_g and R_i, independently, is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, heteroaryl, or -C(O)R, R being H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, or heteroaryl; or R_a and R_b are linked and together form C_{2-8} alkylene, R_e and R_f are linked and together form C_{2-8} alkylene, or R_g and R_i are linked and together form C_{2-8} alkylene.

The just-described compounds may have one or more of the following features: U is N; X is $-CH_2-$, $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$; Y is $-CH_2$ or deleted; Z is $-CH_2-$; W is

$-CH_2CH_2-$; m is 1 or 2; n is 1 or 2; R_1 is NH_2; and R_3 is C_1-C_3 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 heterocycloalkyl, aryl, heteroaryl, halo, CN, OR_e, or $C(O)NR_eR_f$; or R_3 is C_{1-2} alkylene bonded to two carbon atoms of the ring to which it is attached or C_{2-5} alkylene bonded to one carbon atom of the ring to which it is attached.

The term "alkyl" refers to a saturated or unsaturated, linear or branched hydrocarbon moiety, such as $-CH_3$, $-CH_2-CH=CH_2$, or branched $-C_3H_7$. The term "alkylene" refers to a divalent or multivalent, saturated or unsaturated, linear or branched hydrocarbon moiety, such as $-CH_2-$,  , $-CH_2CH_2-$,  , $-CH_2CH_2CH_2-$,  , or $-CH=CH-$. The term "cycloalkyl" refers to a saturated or unsaturated, non-aromatic, monocyclic, bicyclic, tricyclic, or tetracyclic hydrocarbon moiety, such as cyclohexyl, cyclohexen-3-yl, or adamantyl. The term "heterocycloalkyl" refers to a saturated or unsaturated, non-aromatic, monocyclic, bicyclic, tricyclic, or tetracyclic moiety having one or more ring heteroatoms (e.g., N, O, or S), such as 4-tetrahydropyranyl or 4-pyranyl. The term "aryl" refers to a hydrocarbon moiety having one or more aromatic rings. Examples of aryl moieties include phenyl (Ph), phenylene, naphthyl, naphthylene, pyrenyl, anthryl, and phenanthryl. The term "heteroaryl" refers to a moiety having one or more aromatic rings that contain at least one heteroatom (e.g., N, O, or S). Examples of heteroaryl

moieties include furyl, furylene, fluorenyl, pyrrolyl, thienyl, oxazolyl, imidazolyl, thiazolyl, pyridyl, pyrimidinyl, quinazolinyl, quinolyl, isoquinolyl and indolyl.

Alkyl, alkylene, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl mentioned herein include both substituted and unsubstituted moieties, unless specified otherwise. Possible substituents on cycloalkyl, heterocycloalkyl, aryl, and heteroaryl include, but are not limited to, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{20} cycloalkyl, C_3-C_{20} cycloalkenyl, C_1-C_{20} heterocycloalkyl, C_1-C_{20} heterocycloalkenyl, C_1-C_{10} alkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, amino, C_1-C_{10} alkylamino, C_1-C_{20} dialkylamino, arylamino, diarylamino, hydroxyl, halogen, thio, C_1-C_{10} alkylthio, arylthio, C_1-C_{10} alkylsulfonyl, arylsulfonyl, acylamino, aminoacyl, aminothioacyl, amidino, guanidine, ureido, cyano, nitro, acyl, thioacyl, acyloxy, carboxyl, and carboxylic ester. On the other hand, possible substituents on alkyl and alkylene include all of the above-recited substituents except C_1-C_{10} alkyl, C_2-C_{10} alkenyl, and C_2-C_{10} alkynyl. Cycloalkyl, heterocycloalkyl, aryl, and heteroaryl can also be fused with each other.

The compounds described above include the compounds themselves, as well as their salts, prodrugs, and solvates, if applicable. A salt, for example, can be formed between an anion and a positively charged group (e.g., amino) on a compound having one of the above formulas. Suitable anions include chloride, bromide, iodide, sulfate, nitrate, phosphate, citrate, methanesulfonate, trifluoroacetate, acetate, malate, tosylate, tartrate, fumurate, glutamate, glucuronate, lactate, glutarate, and maleate. Likewise, a salt can also be formed between a cation and a negatively charged group (e.g., carboxylate) on a compound having one of the above formulas. Suitable cations include sodium ion, potassium ion, magnesium ion, calcium ion, and an ammonium cation such as tetramethylammonium ion. The compounds also include those salts containing quaternary nitrogen atoms. Examples of prodrugs include esters and other pharmaceutically acceptable derivatives, which, upon administration to a subject, are capable of providing active compounds. A solvate refers to a complex formed between an active compound and a pharmaceutically acceptable solvent. Examples of pharmaceutically acceptable solvents include water, ethanol, isopropanol, ethyl acetate, acetic acid, and ethanolamine.

In still another aspect, this invention relates to a method for treating a medical condition related to CXCR4, such as an inflammatory or immune disease, a

developmental or degenerative disease, a tissue injury, or cancer. The method includes administering to a subject in need thereof an effective amount of one or more compounds of formula (I) shown above.

An inflammatory disease is characterized by a local or systemic, acute or chronic inflammation. Examples include retinopathy (e.g., diabetic retinopathy and proliferative retinopathy), inflammatory dermatoses (e.g., dermatitis, eczema, atopic dermatitis, allergic contact dermatitis, urticaria, necrotizing vasculitis, cutaneous vasculitis, hypersensitivity vasculitis, eosinophilic myositis, polymyositis, dermatomyositis, and eosinophilic fasciitis), inflammatory bowel diseases (e.g., Crohn's disease and ulcerative colitis), hypersensitivity lung diseases (e.g., hypersensitivity pneumonitis, eosinophilic pneumonia, delayed-type hypersensitivity, interstitial lung disease (ILD), idiopathic pulmonary fibrosis, and ILD associated with rheumatoid arthritis), macular edema, asthma, and allergic rhinitis.

An immune disease is characterized by a hyper- or hypo-reaction of the immune system. Examples include, but are not limited to, autoimmune diseases (e.g., rheumatoid arthritis, psoriatic arthritis, systemic lupus erythematosus, myasthenia gravis, Type I diabetes mellitus, glomerulonephritis, autoimmune throiditis, ankylosing spondylitis, systemic sclerosis, and multiple sclerosis), acute and chronic inflammatory diseases (e.g., systemic anaphylaxia or hypersensitivity responses, drug allergies, insect sting allergies, graft rejection, including allograft rejection, and graft-versus-host disease), Sjogren's syndrome, and human immunodeficiency virus infection.

Developmental diseases are growth or differentiation related disorders that lead to loss-of-function or gain-of-function. Degenerative diseases generally refer to change of a tissue to a lower or less functional form. Examples of a developmental or degenerative disease include age-related macular degeneration, corneal neovascularization, iris neovascularization, spinal muscular atrophy, Duchenne muscular dystrophy, Parkinson's disease, and Alzheimer's disease. Tissue injuries can be caused by oxidative stress (e.g., ischemia-reperfusion in stroke or myocardial infarction), complement activation, graft rejection, chemicals (e.g., alcohol-induced liver damage or mucosal tissue injuries in cancer therapy), viral infection (e.g., glomerular injuries associated with hepatitis C infection), and mechanical forces (e.g., sports injury). Examples of tissue injuries include brain injury, nerve injury, heart

injury, liver damage, skeletal muscle injury, kidney damage, pancreatic injury, lung injury, skin injury, limb ischemia, silent ischemia, cardiac ischemia, and gastrointestinal tract injury.

Cancer is a class of diseases in which a group of cells having the capacity for autonomous growth, i.e., an abnormal state or condition characterized by rapidly proliferating cell growth and sometimes tumor metastasis. Examples of cancers include, but are not limited to, carcinoma and sarcoma such as leukemia, sarcomas, osteosarcoma, lymphomas, melanoma, ovarian cancer, skin cancer, testicular cancer, gastric cancer, pancreatic cancer, renal cancer, breast cancer, prostate colorectal cancer, cancer of head and neck, brain cancer, esophageal cancer, bladder cancer, adrenal cortical cancer, lung cancer, bronchus cancer, endometrial cancer, nasopharyngeal cancer, cervical or hepatic cancer, colon cancer, kidney cancer, thyroid cancer, haematopoietic cancer, and cancer of unknown primary site.

A subject in need of the above-described treatment can also be concurrently administered with an effective amount of one of the heterocyclic compounds described above and an effective amound of one or more other therapeutic agents. The therapeutic agents include a G-CSF, a steroidal or a non-steroidal anti-inflammatory drug, a chemotherapeutic agent, an anti-angiogenesis agent, a COX2 inhibitor, a leukotriene receptor inhibitor, a prostaglandin modulator, a TNF modulator, and an immunosuppressive agent (e.g., cyclosporine A). For example, one can use a combination of a compound of this invention and a chemotherapeutic agent to treat cancers, either hematological cancer or solid cancer. Without being bound by theory, in treating hematological cancer (e.g., acute myeloid leukemia and acute lymphoblastic leukemia), the heterocyclic compound acts as a "chemosensitizer" to mobilize cancer cells from bone marrow and the chemotherapeutic agent and then kills these cancer cells, thereby resulting in enhanced treatment effect. Also, without being bound by theory, in treating solid cancer, the heterocyclic compound acts as an anti-angiogenesis agent, and, when used together with a chemotherapeutic agent, enhances treatment effect. As another example, one can use a compound of this invention and another anti-agiogenesis agent to treat retinopathy, age-related macular degeneration, macular edema, corneal neovascularization, or iris neovascularization. G-CSF is a haematopoietic growth factor that stimulates the bone marrow to produce more white blood cells. A chemotherapeutic agent is a drug that inhibits cancer cell

growth or a cytotoxic agent. An anti-angiogenesis agent is a drug that confers its therapeutical effects via inhibiting the angiogenesis process. Examples of angiogenesis agents include, but are not limited to, Avastin, Lucentis, Sunitinib, and Sorafenib. The term "concurrently administered" refers to administering two or more active agents at the same time or at different times during the period of treatment. An example of concurrent administration is to apply a solid or liquid mixture of the two or more active agents to a patient.

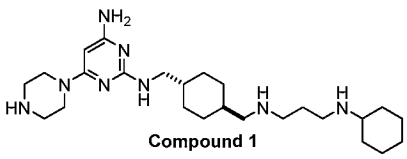
In yet another aspect, this invention relates to a method for enhancing migration of bone marrow-derived cells to blood. The method includes administering to a subject in need thereof an effective amount of one or more compounds of formula (I) shown above. The term "bone marrow-derived cells" refers to cells originating from bone marrow. Examples of bone marrow-derived cells include, but are not limited to, CD34+ cells and CD133+ cells. Preferrably, bone marrow-derived cells are stem cells or endothelial progenitor cells. In this method, an effective amount of a G-CSF growth factor may also be used.

Also within the scope of this invention is a composition containing one or more of the compounds and a pharmaceutically acceptable carrier described above for use in treating an above-described medical condition, and the use of such a composition for the manufacture of a medicament for the just-mentioned treatment.

The details of one or more embodiments of the invention are set forth in the description below. Other features, objects, and advantages of the invention will be apparent from the description and from the claims.

DETAILED DESCRIPTION

Shown below are exemplary compounds, compounds 1-150, of this invention: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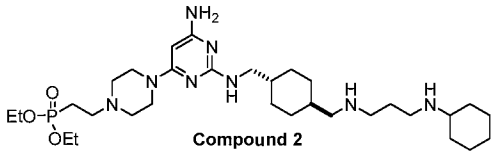
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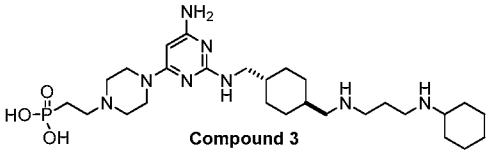
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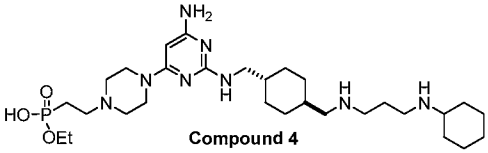
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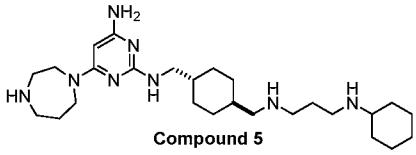
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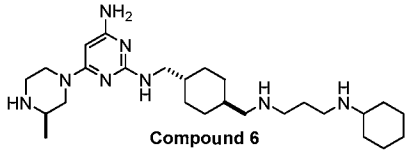
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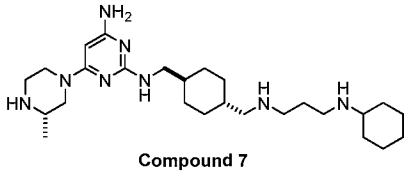
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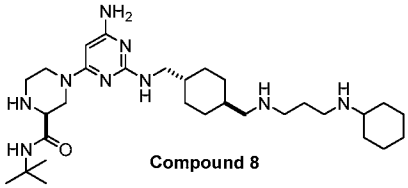
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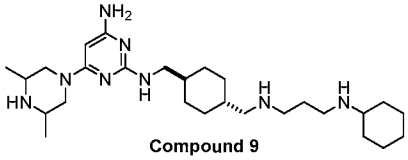
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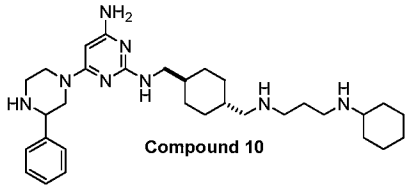
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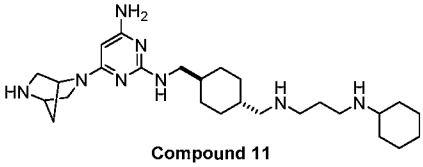
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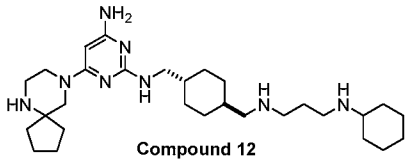
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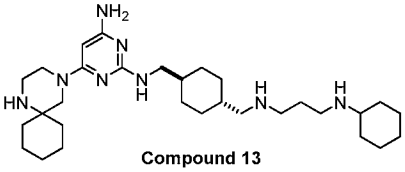
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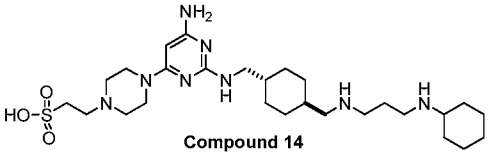
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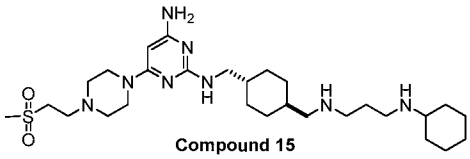
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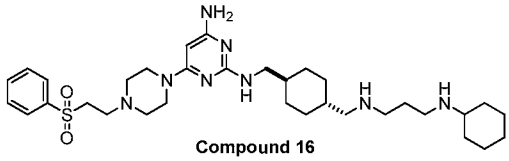
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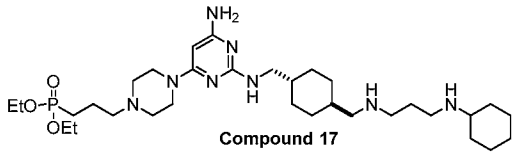
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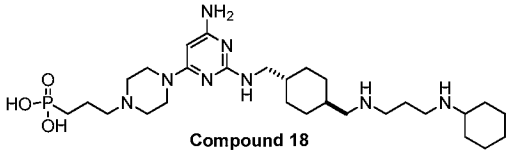
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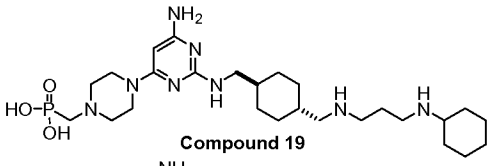
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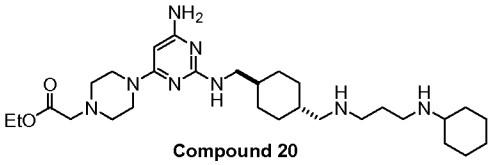
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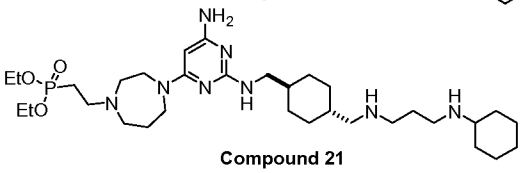
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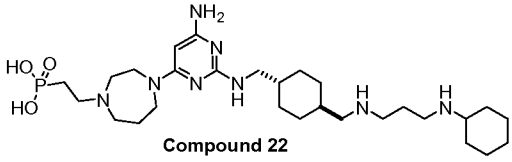
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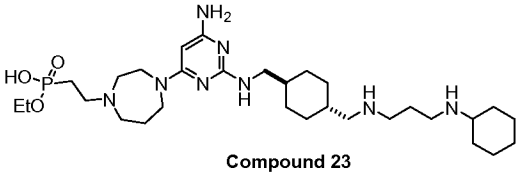
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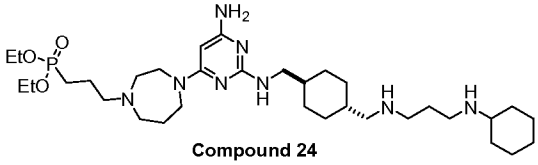
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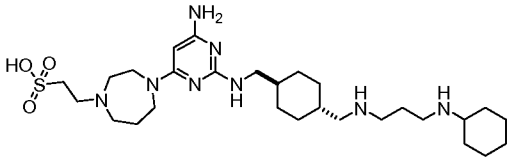
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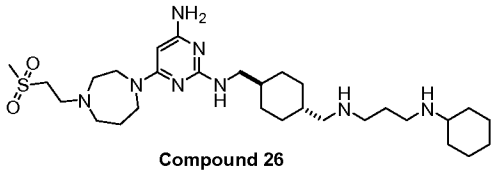
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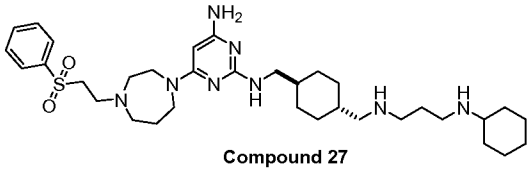
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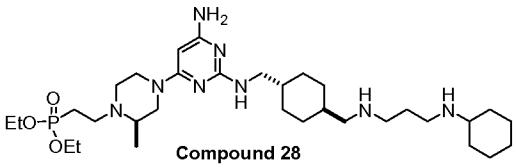
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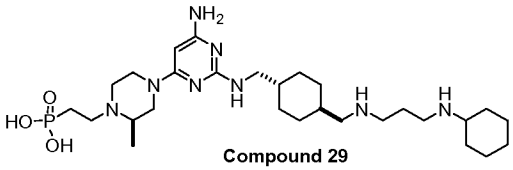
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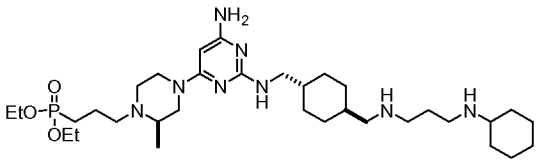
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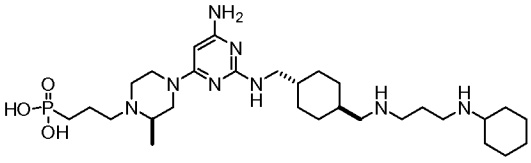
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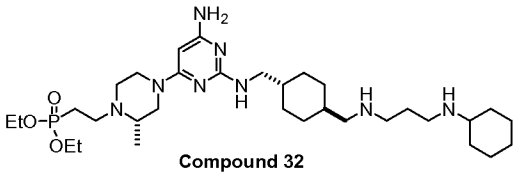
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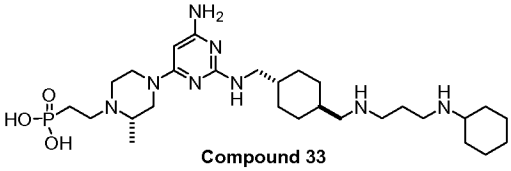
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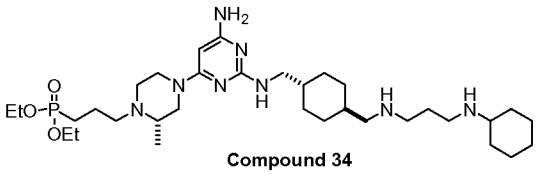
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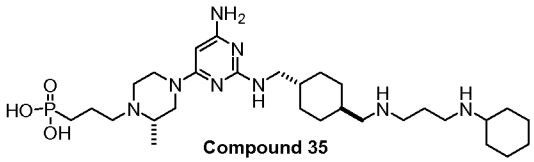
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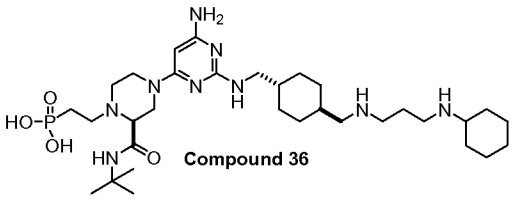
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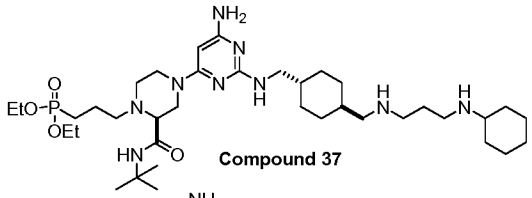
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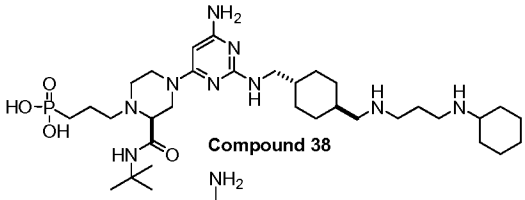
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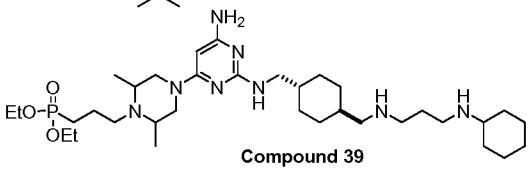
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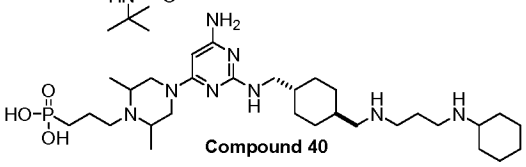
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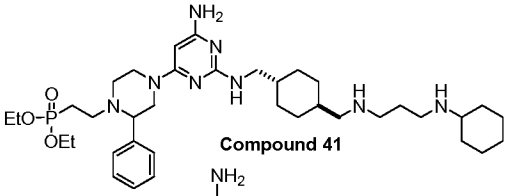
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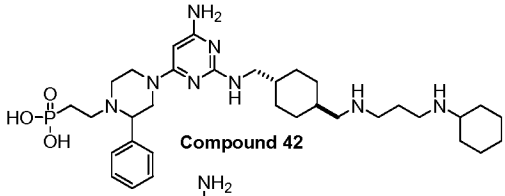
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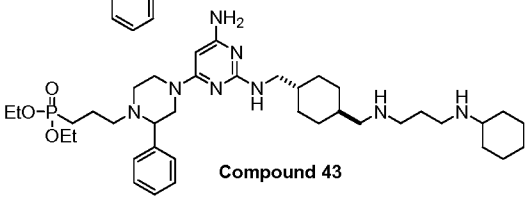
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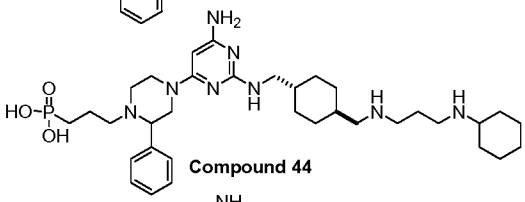
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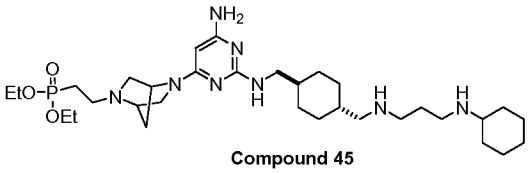
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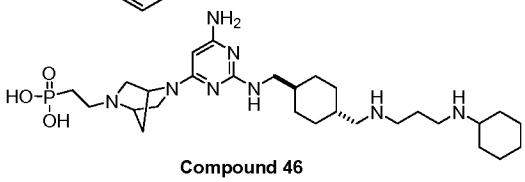
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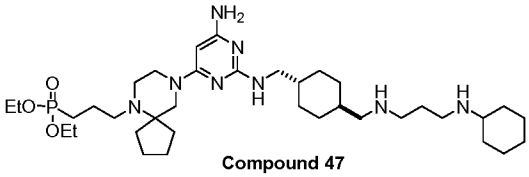
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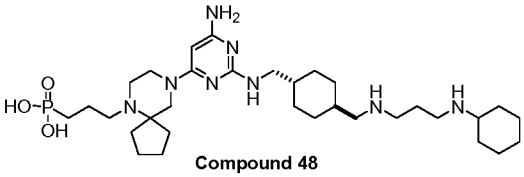
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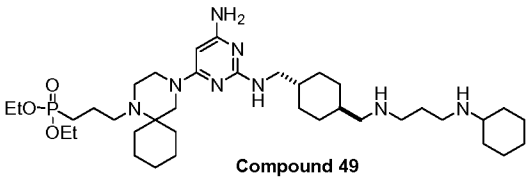
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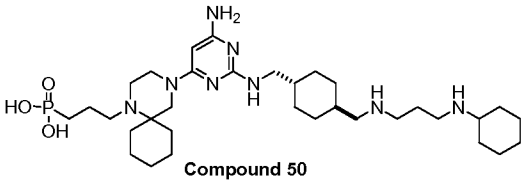
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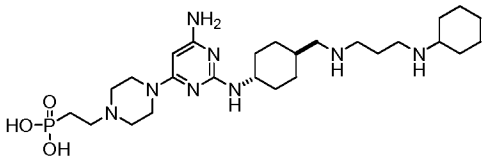
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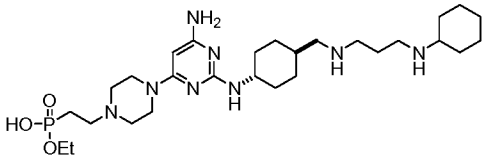
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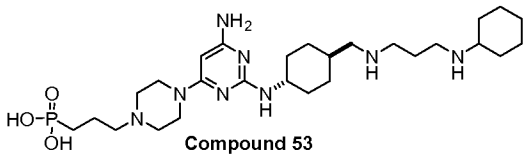
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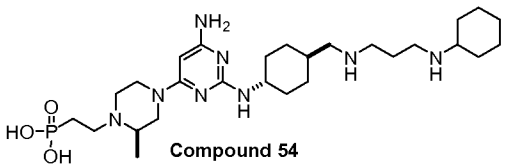
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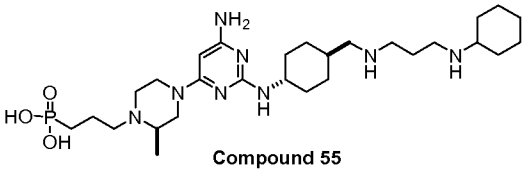
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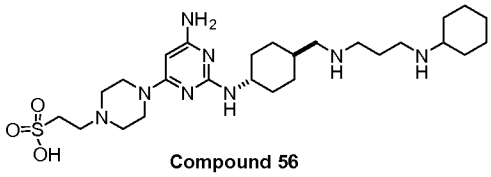
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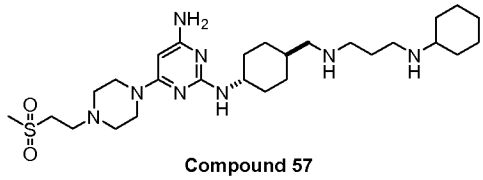
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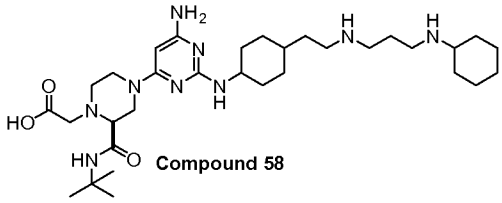
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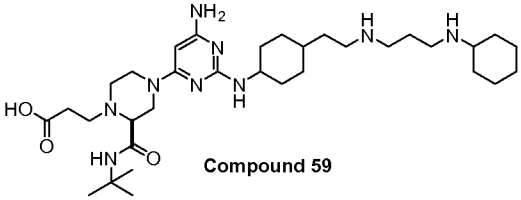
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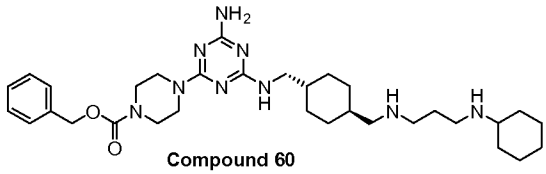
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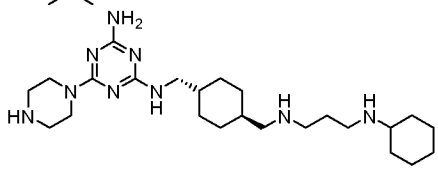
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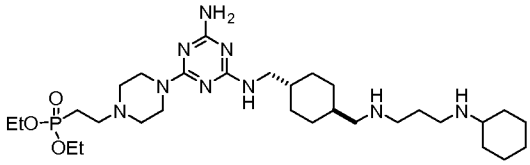
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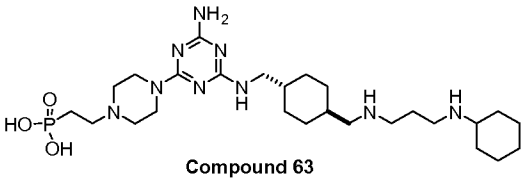
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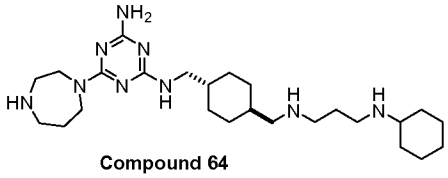
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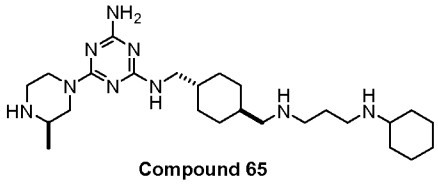
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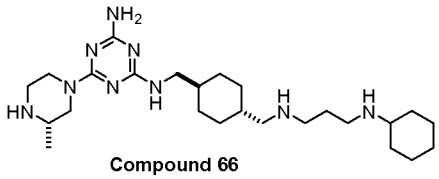
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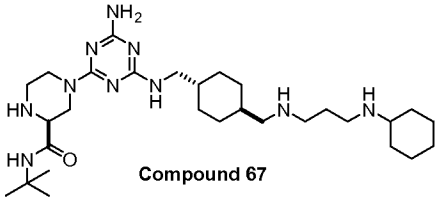
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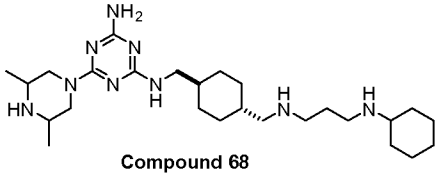
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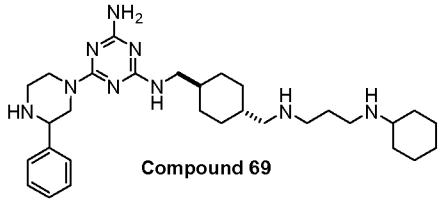
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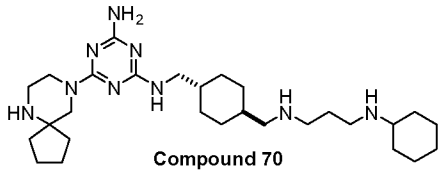
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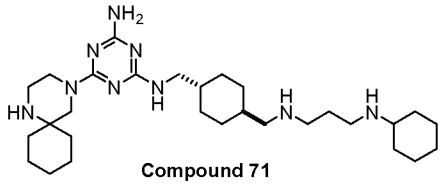
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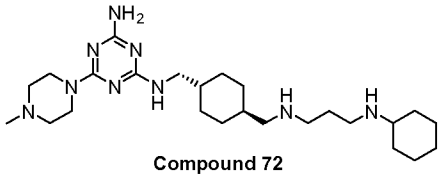
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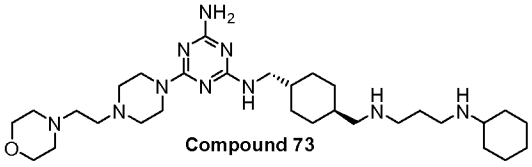
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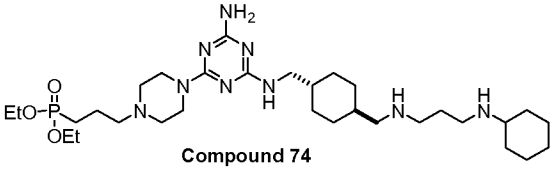
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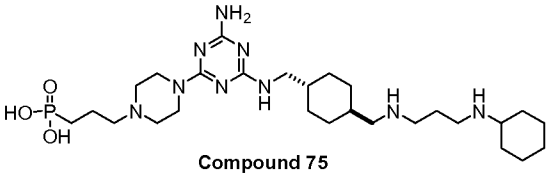
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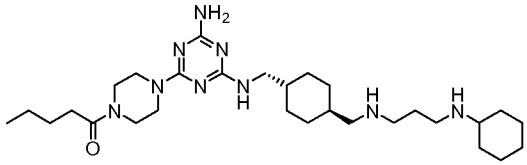
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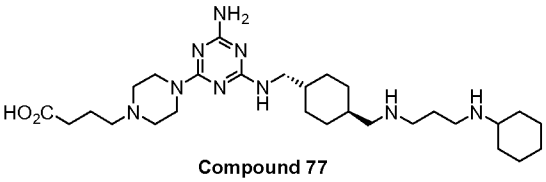
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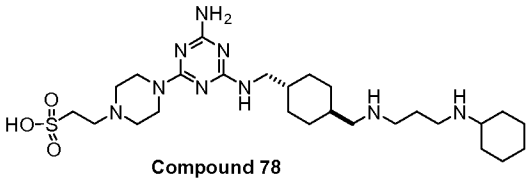
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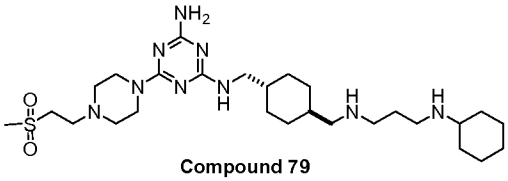
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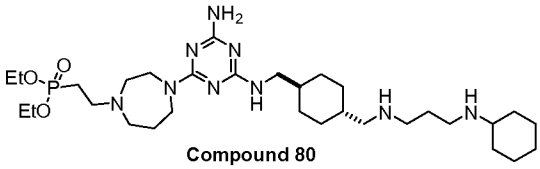
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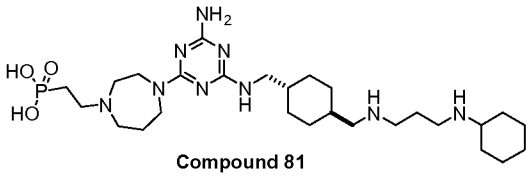
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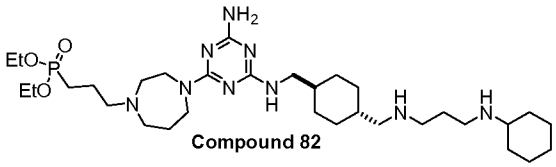
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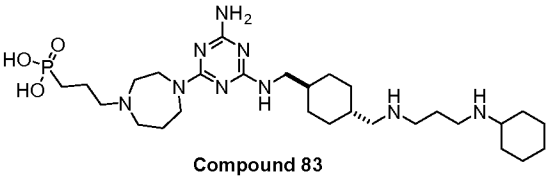
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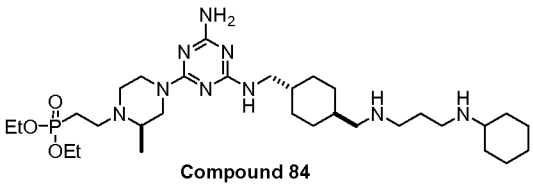
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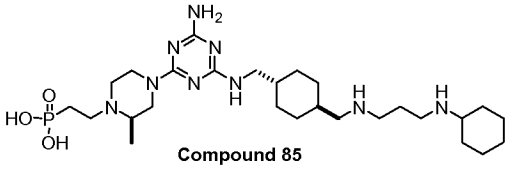
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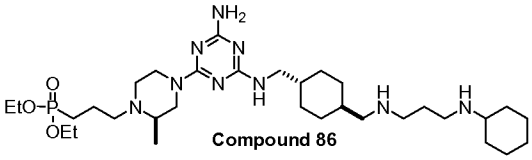
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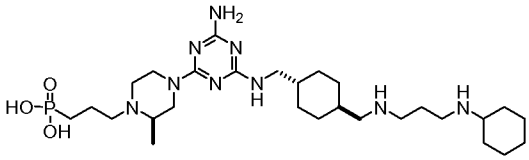
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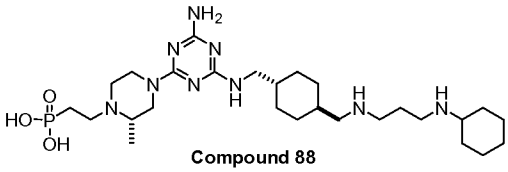
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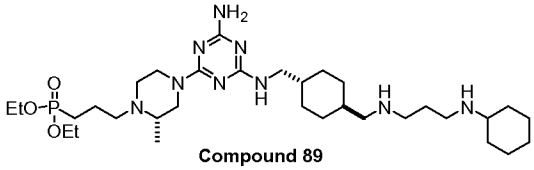
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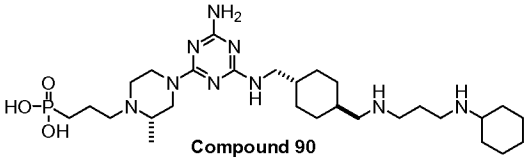
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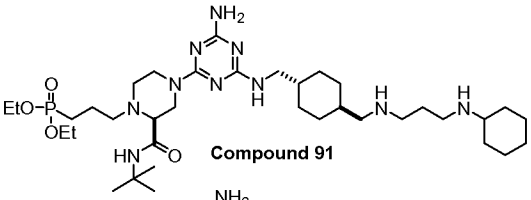
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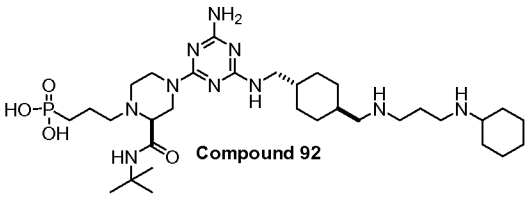
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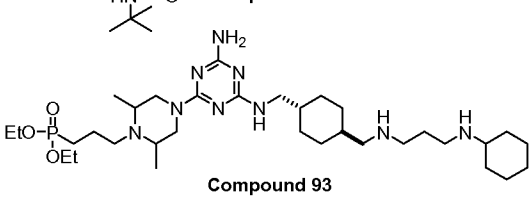
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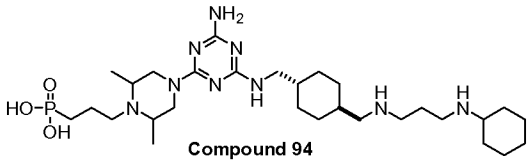
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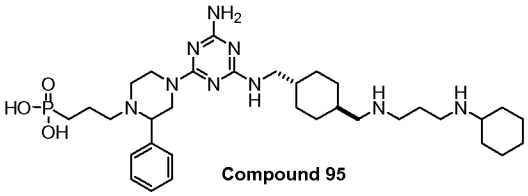
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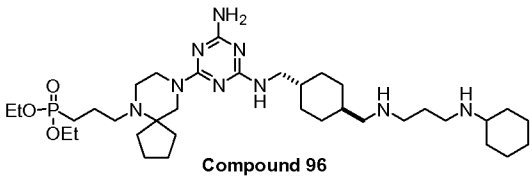
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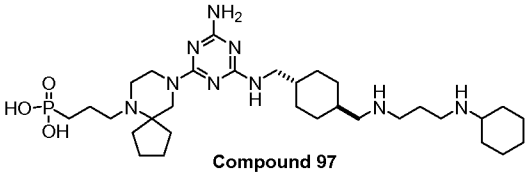
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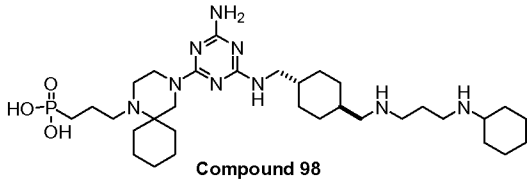
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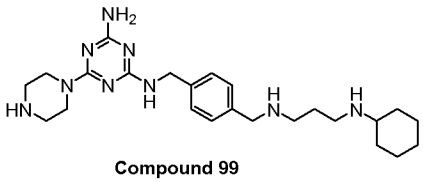
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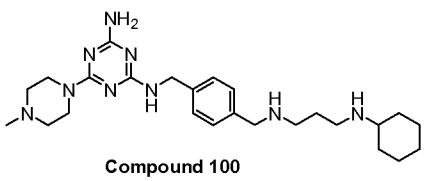
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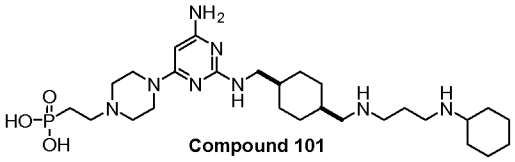
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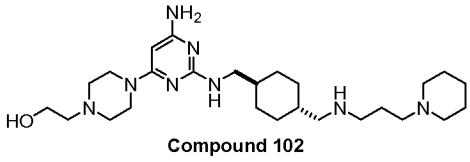
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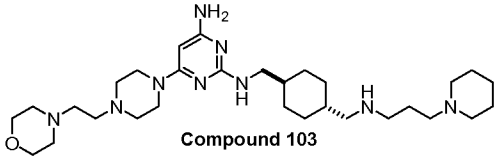
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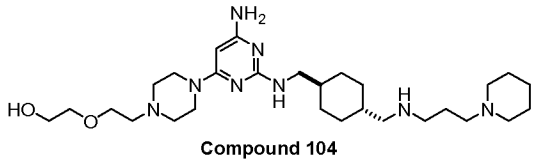
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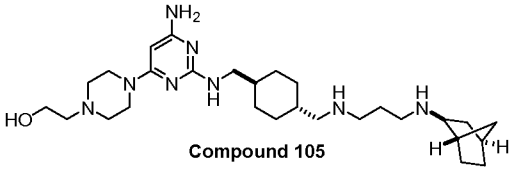
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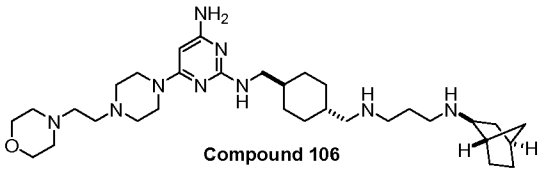
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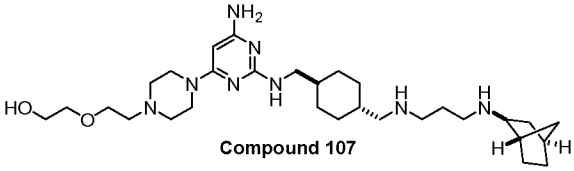
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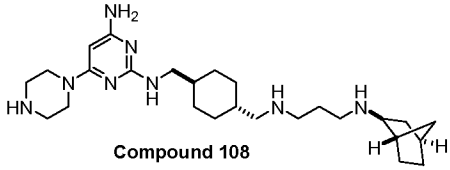
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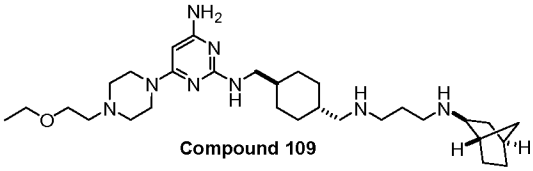
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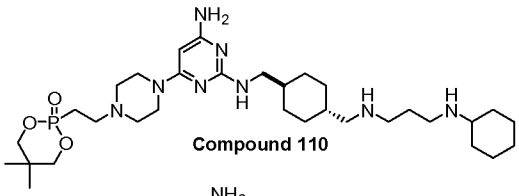
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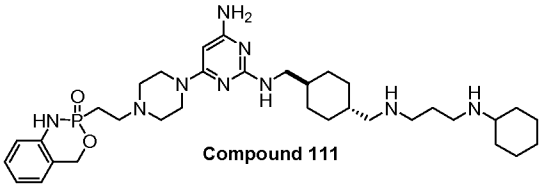
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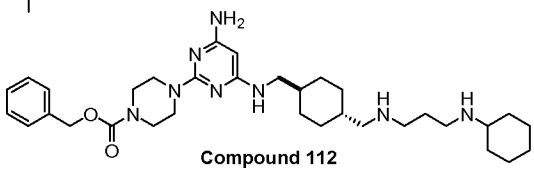
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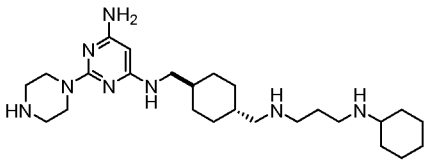
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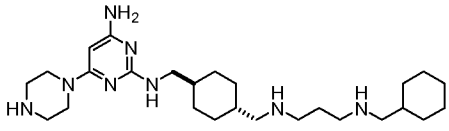
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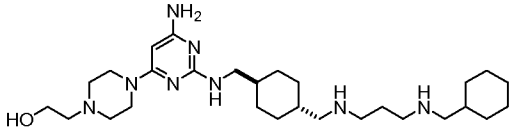
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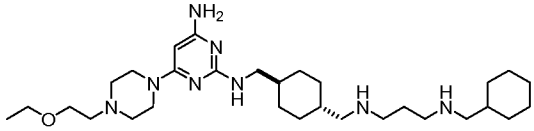
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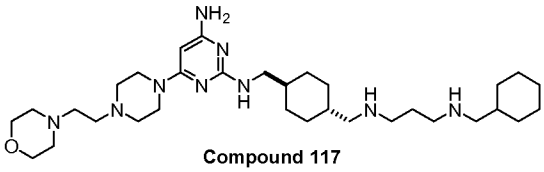

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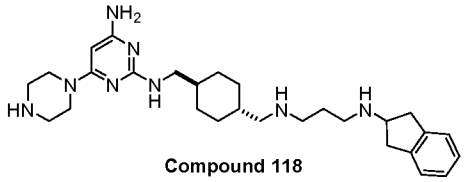

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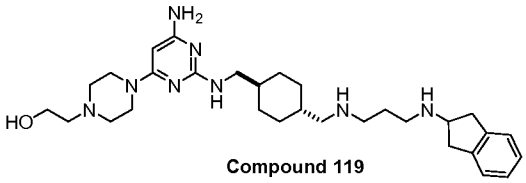

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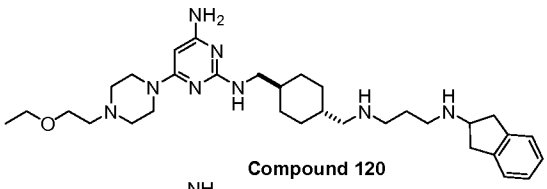

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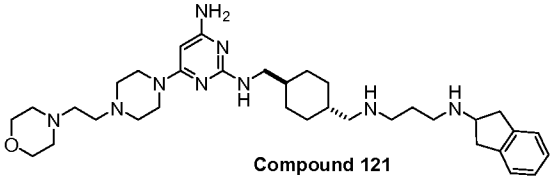

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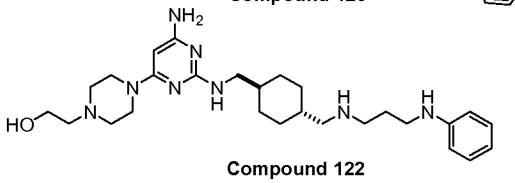

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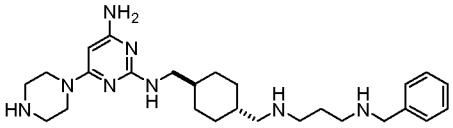

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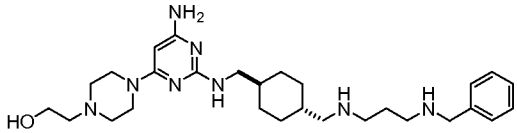

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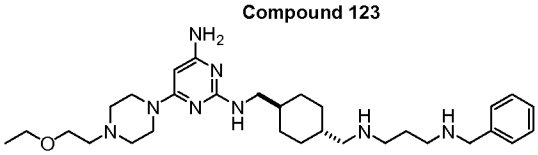

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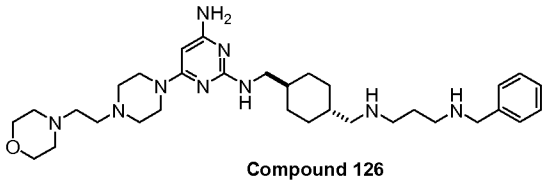

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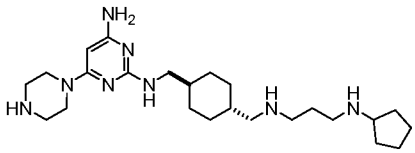

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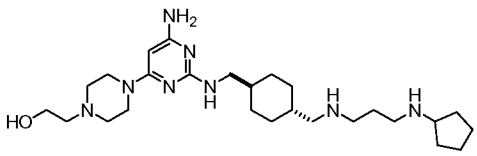

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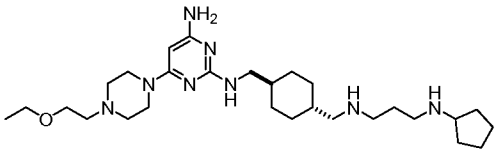

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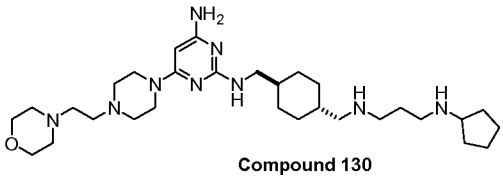

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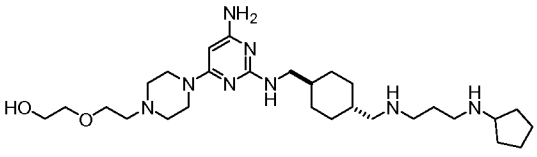

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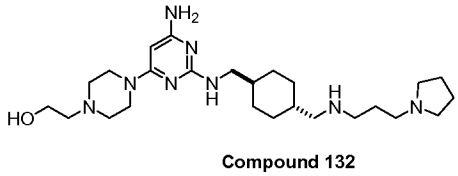

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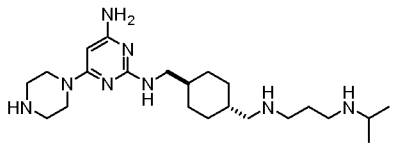

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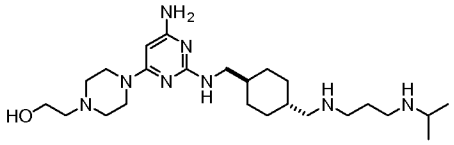

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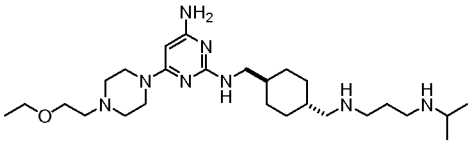

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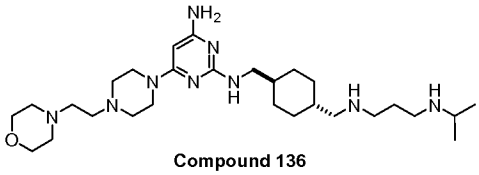

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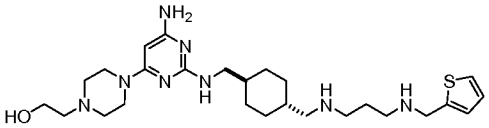

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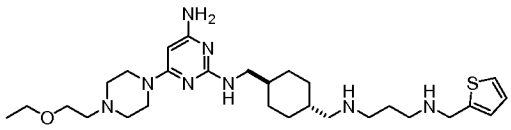

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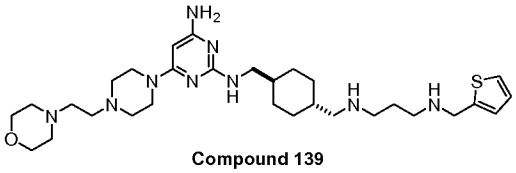

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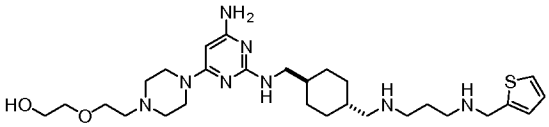

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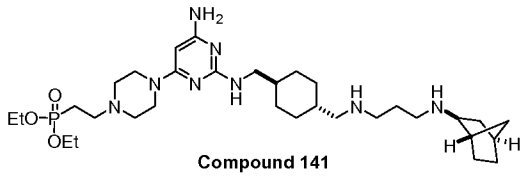

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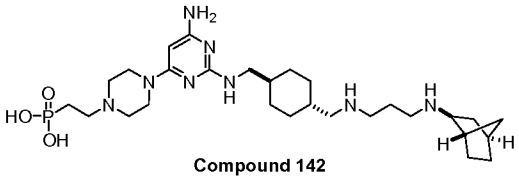

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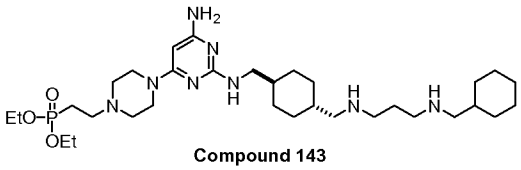

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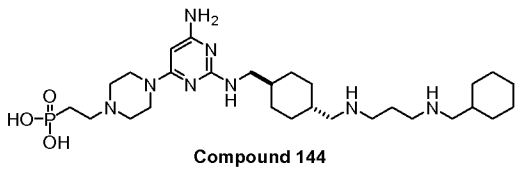

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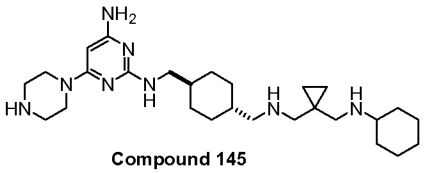

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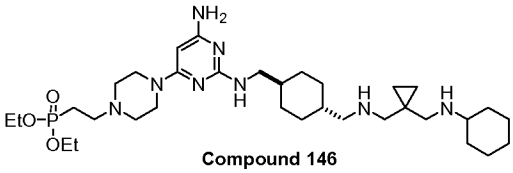

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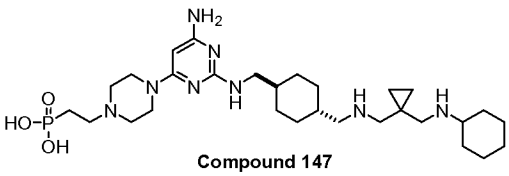

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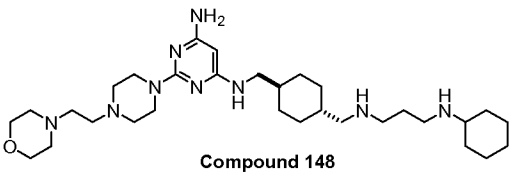
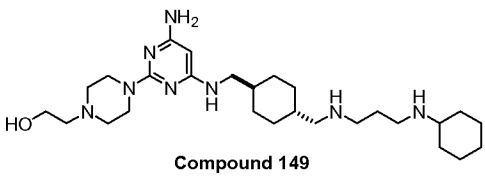
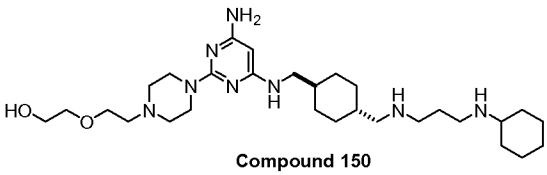


Compound 148



Compound 149

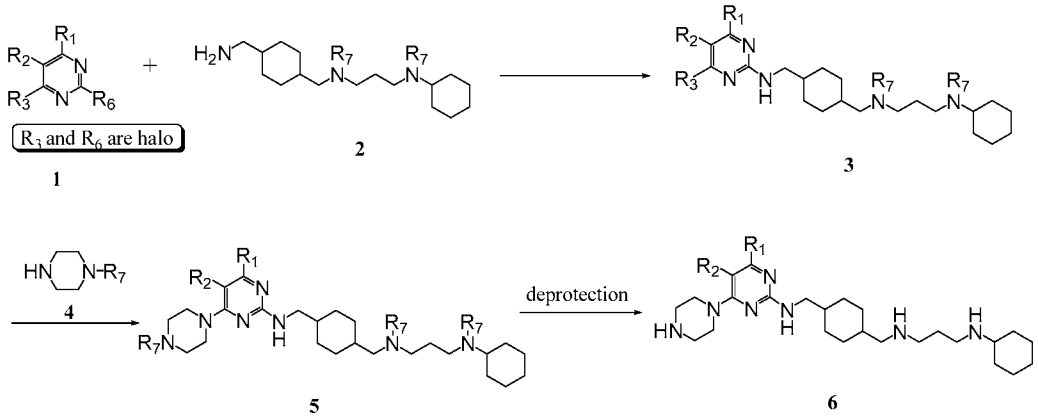


Compound 150

The compounds described above can be prepared by methods well known in the art.

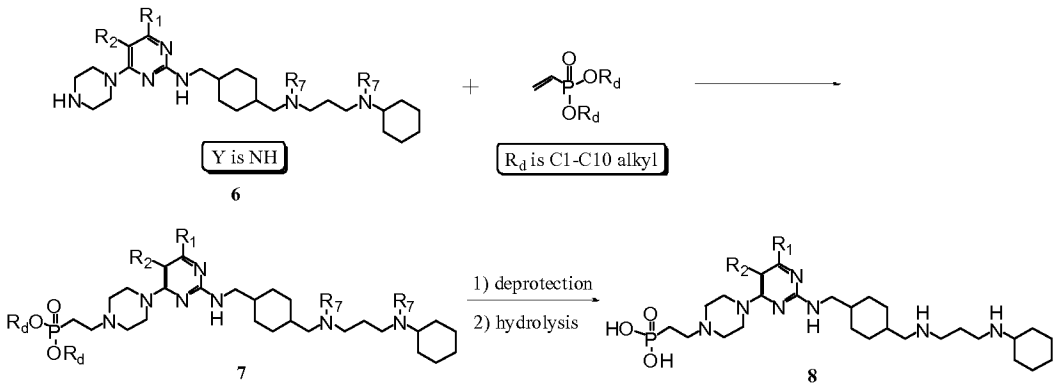
Scheme I below depicts a typical synthetic route for synthesizing certain exemplary compounds. Compound (1) containing two halo groups (R_3 and R_6 are halo) reacts with an amino compound (2) to give a compound of formula (3), which reacts with piperazine compound (4) containing a nitrogen ring atom to give a compound of formula (5). Finally, deprotection of the resultant compound, if necessary, affords a compound of formula (6), which is one of the compounds of this invention.

Scheme I



Scheme I can be modified in various manners to prepare other compounds of this invention. For example, an amino compound different from compound (2) may be used, or piperazine compound (4) can be replaced by an imidazolidine or diazepane compound. As another example, compound (6) can be further modified as shown in Scheme II below to obtain phosphonate compound (7) or phophonic acid (8).

Scheme II



A compound thus synthesized can be purified by a method such as column chromatography, high-pressure liquid chromatography, or recrystallization.

Examples 1-150 below provide detailed descriptions of the preparation of Compounds 1-150 of this invention.

The intermediates used in the methods described above are either commercially available or can be prepared by methods known in the art. The methods may also additionally include steps, either before or after the steps described specifically herein, to add or remove suitable protecting groups in order to ultimately allow synthesis of the compounds. In addition, various synthetic steps may be performed in an alternate sequence or order to give the desired compounds. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing applicable compounds are known in the art and include, for example, those described in R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 2nd Ed., John Wiley and Sons (1991); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995) and subsequent editions thereof.

The compounds mentioned herein may contain a non-aromatic double bond and one or more asymmetric centers. Thus, they can occur as racemates and racemic mixtures, single enantiomers, individual diastereomers, diastereomeric mixtures, and cis- or trans- isomeric forms. All such isomeric forms are contemplated.

Also within the scope of this invention is a pharmaceutical composition containing an effective amount of at least one compound described above and a pharmaceutical acceptable carrier. Further, this invention covers a method of administering an effective amount of one or more of the compounds of this invention to a patient having a disease described in the summary section above for treating the disease. This invention also covers a method of administering an effective amount of one or more of the compounds to a subject for enhancing migration of bone marrow-derived cells to blood.

The term "treating" or "treatment" refers to administering one or more compounds to a subject, who has an above-described medical condition, a symptom

of such a medical condition, or a predisposition toward such a medical condition, with the purpose to confer a therapeutic effect, e.g., to cure, relieve, alter, affect, ameliorate, or prevent the above-described medical condition, the symptom of it, or the predisposition toward it. "An effective amount" refers to the amount of an active compound that is required to confer the therapeutic effect. Effective doses will vary, as recognized by those skilled in the art, depending on the types of diseases treated, route of administration, excipient usage, and the possibility of co-usage with other therapeutic treatment.

To practice the method of the present invention, a composition having one or more compounds can be administered parenterally, orally, nasally, rectally, topically, or buccally. The term "parenteral" as used herein refers to subcutaneous, intracutaneous, intravenous, intrmuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional, or intracranial injection, as well as any suitable infusion technique. The composition can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, microparticles, or nanoparticles. It can be also formulated to achieve controlled-reslease or sustained-release of the active ingradients.

A sterile injectable composition can be a solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are mannitol, water, Ringer's solution, and isotonic sodium chloride solution. In addition, fixed oils are conventionally employed as a solvent or suspending medium (e.g., synthetic mono- or diglycerides). Fatty acid, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions can also contain a long chain alcohol diluent or dispersant, carboxymethyl cellulose, or similar dispersing agents. Other commonly used surfactants such as Tweens or Spans or other similar emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms can also be used for the purpose of formulation.

A composition for oral administration can be any orally acceptable dosage form including capsules, tablets, emulsions and aqueous suspensions, dispersions, and

solutions. In the case of tablets, commonly used carriers include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions or emulsions are administered orally, the active ingredient can be suspended or dissolved in an oily phase combined with emulsifying or suspending agents. If desired, certain sweetening, flavoring, or coloring agents can be added.

A nasal aerosol or inhalation composition can be prepared according to techniques well known in the art of pharmaceutical formulation. For example, such a composition can be prepared as a solution in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

An eye drop or ointment composition can also be prepared and used according to the well-known art.

A composition having one or more active compounds can also be administered in the form of suppositories for rectal administration.

The carrier in the pharmaceutical composition must be "acceptable" in the sense that it is compatible with the active ingredient of the composition (and preferably, capable of stabilizing the active ingredient) and not deleterious to the subject to be treated. One or more solubilizing agents can be utilized as pharmaceutical excipients for delivery of an active compound. Examples of other carriers include colloidal silicon oxide, magnesium stearate, cellulose, sodium lauryl sulfate, and D&C Yellow # 10.

The compounds described above can be preliminarily screened for their efficacy in treating above-described diseases by an *in vitro* assay (See Examples 269 and 270 below) and then confirmed by animal experiments and clinic trials. Other methods will also be apparent to those of ordinary skill in the art.

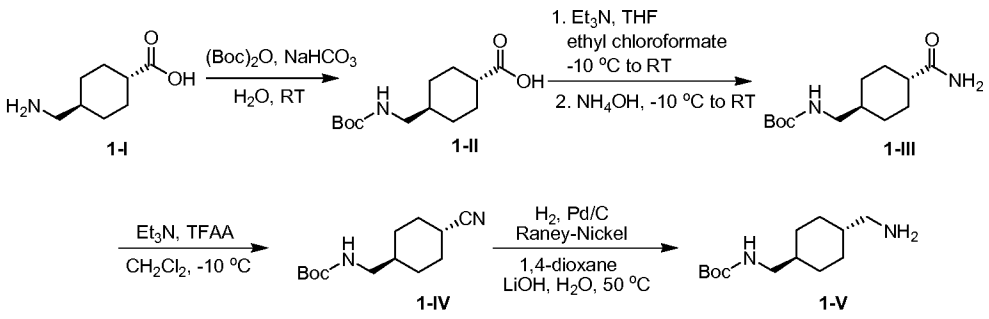
It has been found that the compounds of this invention, acting as the antagonists of CXCR4, compete against its ligand SDF-1 for binding to the receptor and thus block CXCR4/SDF-1 signaling, which is important in the mobilization/homing of stem and progenitor cells. Without being bound by theory, the compounds of this invention may act through the following mechanisms in treating and repairing tissue damage.

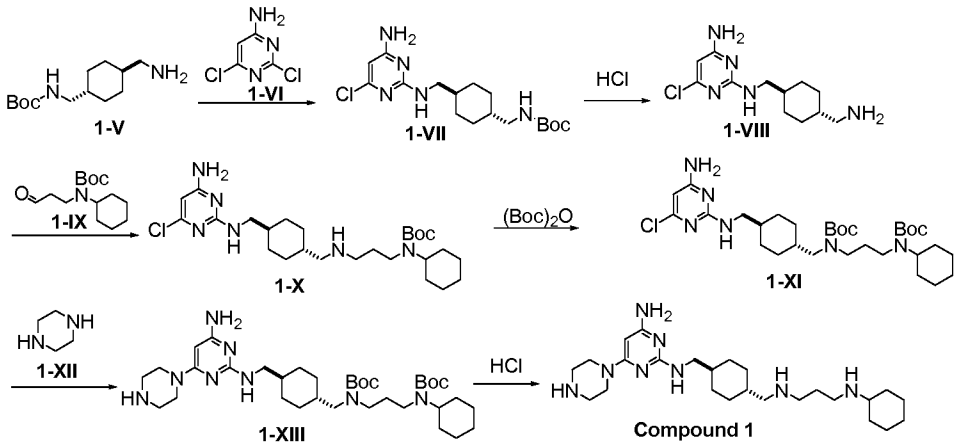
By blocking CXCR4/SDF-1 signaling, the compounds of this invention promote the mobilization of stem and progenitor cells from bone morrow, a reservoir of stem/progenitor cells, to the peripheral blood. More specifically, as SDF-1 is highly expressed in bone marrow, stem and progenitor cells, expressing CXCR4, are trapped in bone morrow via CXCR4-SDF-1 interaction. By blocking this interaction, the compounds of this invention release stem and progenitor cells from bone marrow to the peripheral blood. While circulating in the blood, stem and progenitor cells home to tissues and organs where damage has occurred and repair the damage by differentiating into the type of cells, the loss of which has caused the damage.

In the condition of retinopathy, SDF-1 is highly expressed in vitreous. Binding to CXCR4 expressed in stem and progenitor cells, SDF-1 facilitates these cells to migrate to the retina, resulting in neovascularization, which plays an essential role in retinopathy development and progression. Also by blocking CXCR4/SDF-1 signaling, the compounds of this invention prevent stem and progenitor cells homing to the retina, thus effectively treating retinopathy. The compounds can be applied topically to an eye of a retinopathy patient. Unlike systemic applications, topical application does not mobilize stem/progenitor cells out of bone marrow and therefore does not help the homing of these cells into retina.

The specific examples below are to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever. Without further elaboration, it is believed that one skilled in the art can, based on the description herein, utilize the present invention to its fullest extent. All publications cited herein are hereby incorporated by reference in their entirety.

Example 1: Preparation of Compounds **1**





Water (10.0 L) and $(Boc)_2O$ (3.33 kgg, 15.3 mol) were added to a solution of *trans*-4-aminomethyl-cyclohexanecarboxylic acid (compound **1-I**, 2.0 kg, 12.7 mol) and sodium bicarbonate (2.67 kg, 31.8 mol). The reaction mixture was stirred at ambient temperature for 18 hours. The aqueous layer was acidified with concentrated hydrochloric acid (2.95 L, pH = 2) and then filtered. The resultant solid was collected, washed three times with water (15 L), and dried in a hot box (60 °C) to give *trans*-4-(*tert*-butoxycarbonylamino-methyl)-cyclo-hexanecarboxylic acid (Compound **1-II**, 3.17 kg, 97%) as a white solid. R_f = 0.58 (EtOAc). LC-MS m/e 280 ($M+Na^+$). ^1H NMR (300 MHz, $CDCl_3$) δ 4.58 (brs, 1H), 2.98 (t, J = 6.3 Hz, 2H), 2.25 (td, J = 12, 3.3 Hz, 1H), 2.04 (d, J = 11.1 Hz, 2H), 1.83 (d, J = 11.1 Hz, 2H), 1.44 (s, 9H), 1.35~1.50 (m, 3H), 0.89~1.03 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.31, 156.08, 79.12, 46.41, 42.99, 37.57, 29.47, 28.29, 27.96. M.p. 134.8~135.0 °C.

A suspension of compound **1-II** (1.0 kg, 3.89 mol) in THF (5 L) was cooled at −10 °C and triethyl amine (1.076 L, 7.78 mol) and ethyl chloroformate (0.441 L, 4.47 mol) were added below −10 °C. The reaction mixture was stirred at ambient temperature for 3 hours. The reaction mixture was then cooled at −10 °C again and NH_4OH (3.6 L, 23.34 mol) was added below −10 °C. The reaction mixture was stirred at ambient temperature for 18 hours and filtered. The solid was collected and washed three times with water (10 L) and dried in a hot box (60°C) to give *trans*-4-(*tert*-butoxycarbonyl-amino-methyl)-cyclohexanecarboxylic acid amide (Compound **1-III**, 0.8 kg, 80%) as a white solid. Rf = 0.23 (EtOAc). LC-MS m/e 279, $M+Na^+$. ^1H NMR (300 MHz, CD_3OD) δ 6.63 (brs, 1H), 2.89 (t, J = 6.3 Hz, 2H), 2.16 (td, J = 12.2, 3.3 Hz, 1H), 1.80~1.89 (m, 4H), 1.43 (s, 9H), 1.37~1.51 (m, 3H), 0.90~1.05 (m,

2H). ^{13}C NMR (75 MHz, CD_3OD) δ 182.26, 158.85, 79.97, 47.65, 46.02, 39.28, 31.11, 30.41, 28.93. M.p. 221.6~222.0 °C.

A suspension of compound **1-III** (1.2 kg, 4.68 mol) in CH_2Cl_2 (8 L) was cooled at −10°C and triethyl amine (1.3 L, 9.36 mol) and trifluoroacetic anhydride (0.717 L, 5.16 mol) were added below −10 °C. The reaction mixture was stirred for 3 hours. After water (2.0 L) was added, the organic layer was separated and washed with water (3.0 L) twice. The organic layer was then passed through silica gel and concentrated. The resultant oil was crystallized by methylene chloride. The crystals were washed with hexane to give *trans*-(4-cyano-cyclohexylmethyl)-carbamic acid *tert*-butyl ester (Compound **1-IV**, 0.95 kg, 85%) as a white crystal. R_f = 0.78 (EtOAc). LC-MS m/e 261, M+Na$^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.58 (brs, 1H), 2.96 (t, J = 6.3 Hz, 2H), 2.36 (td, J = 12, 3.3 Hz, 1H), 2.12 (dd, J = 13.3, 3.3 Hz, 2H), 1.83 (dd, J = 13.8, 2.7 Hz, 2H), 1.42 (s, 9H), 1.47~1.63 (m, 3H), 0.88~1.02 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.96, 122.41, 79.09, 45.89, 36.92, 29.06, 28.80, 28.25, 28.00. M.p. 100.4~100.6°C.

Compound **1-IV** (1.0 kg, 4.196 mol) was dissolved in a mixture of 1,4-dioxane (8.0 L) and water (2.0 L). To the reaction mixture were added lithium hydroxide monohydrate (0.314 kg, 4.191), Raney-nickel (0.4 kg, 2.334 mol), and 10% palladium on carbon (0.46 kg, 0.216 mol) as a 50% suspension in water. The reaction mixture was stirred under hydrogen atmosphere at 50°C for 20 hours. After the catalysts were removed by filtration and the solvents were removed in vacuum, a mixture of water (1.0 L) and CH_2Cl_2 (0.3 L) was added. After phase separation, the organic phase was washed with water (1.0 L) and concentrated to give *trans*-(4-aminomethyl-cyclohexylmethyl)-carbamic acid *tert*- butyl ester (compound **1-V**, 0.97 kg, 95%) as pale yellow thick oil. R_f = 0.20 (MeOH/EtOAc = 9/1). LC-MS m/e 243, M+H$^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.67 (brs, 1H), 2.93 (t, J = 6.3 Hz, 2H), 2.48 (d, J = 6.3 Hz, 2H), 1.73~1.78 (m, 4H), 1.40 (s, 9H), 1.35 (brs, 3H), 1.19~1.21 (m, 1H), 0.77~0.97 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.85, 78.33, 48.27, 46.38, 40.80, 38.19, 29.87, 29.76, 28.07.

A solution of compound **1-V** (806 g) and Et_3N (1010 g, 3 eq) in 1-pentanol (2.7 L) was treated with compound **1-VI**, 540 g, 1 eq) at 90°C for 15 hours. TLC showed that the reaction was completed.

Ethyl acetate (1.5 L) was added to the reaction mixture at 25°C. The solution was stirred for 1 hour. The Et_3NHCl salt was filtered. The filtrate was then concentrated to 1.5 L (1/6 of original volume) by vacuum at 50°C. Then, diethyl ether (2.5 L) was added to the concentrated solution to afford the desired product **1-VII** (841 g, 68% yield) after filtration at 25°C.

A solution of intermediate **1-VII** (841 g) was treated with 4 N HCl/dioxane (2.7 L) in MeOH (8.1 L) and stirred at 25°C for 15 hours. TLC showed that the reaction was completed. The mixture was concentrated to 1.5 L (1/7 of original volume) by vacuum at 50°C. Then, diethyl ether (5 L) was added to the solution slowly, and HCl salt of **1-VIII** (774 g) was formed, filtered, and dried under vacuum (<10 torr). For neutralization, K_2CO_3 (2.5 kg, 8 eq) was added to the solution of HCl salt of **1-VIII** in MeOH (17 L) at 25°C. The mixture was stirred at the same temperature for 3 hours (pH > 12) and filtered (estimated amount of **1-VIII** in the filtrate is 504 g).

Aldehyde **1-IX** (581 g, 1.0 eq based on mole of **1-VII**) was added to the filtrate of **1-VIII** at 0-10°C. The reaction was stirred at 0-10°C for 3 hours. TLC showed that the reaction was completed. Then, $NaBH_4$ (81 g, 1.0 eq based on mole of **1-VII**) was added at less than 10°C and the solution was stirred at 10-15°C for 1h. The solution was concentrated to get a residue, which then treated with CH_2Cl_2 (15 L). The mixture was washed with saturated aq. NH_4Cl solution (300 mL) diluted with H_2O (1.2 L). The CH_2Cl_2 layer was concentrated and the residue was purified by chromatography on silica gel (short column, EtOAc as mobile phase for removing other components; MeOH/28% NH_4OH = 97/3 as mobile phase for collecting **1-X**) afforded crude **1-X** (841 g).

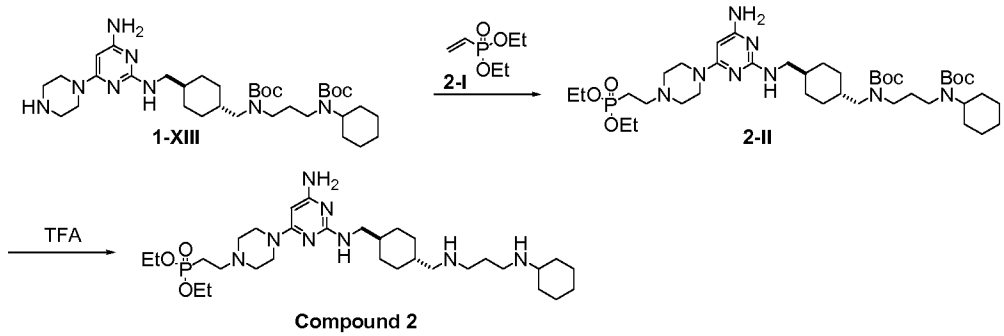
Then Et_3N (167 g, 1eq) and Boc_2O (360 g, 1eq) were added to the solution of **1-X** (841 g) in CH_2Cl_2 (8.4 L) at 25°C. The mixture was stirred at 25°C for 15 hours. After the reaction was completed as evidenced by TLC, the solution was concentrated and EtOAc (5 L) was added to the resultant residue. The solution was concentrated to 3L (1/2 of the original volume) under low pressure at 50°C. Then, *n*-hexane (3 L) was added to the concentrated solution. The solid product formed at 50°C by seeding to afford the desired crude product **1-XI** (600 g, 60% yield) after filtration and evaporation.

To compound **1-XI** (120.0 g) and piperazine (**1-XII**, 50.0 g, 3 eq) in 1-pentanol (360 mL) was added Et_3N (60.0 g, 3.0 eq) at 25°C. The mixture was stirred at 120°C for 8 hours. Ethyl acetate (480 mL) was added to the reaction mixture at 25°C. The solution was stirred for 1h. The Et_3NHCl salt was filtered and the solution was concentrated and purified by silica gel (EtOAc/MeOH = 2:8) to afforded **1-XIII** (96 g) in a 74% yield.

A solution of intermediate **1-XIII** (100 mg) was treated with 4 N HCl/dioxane (2 mL) in CH_2Cl_2 (1 mL) and stirred at 25°C for 15 hours. The mixture was concentrated to give hydrochloride salt of compound **1** (51 mg).

CI-MS ($M^+ + 1$): 459.4

Example 2: Preparation of Compound **2**



Intermediate **1-XIII** was prepared as described in Example 1.

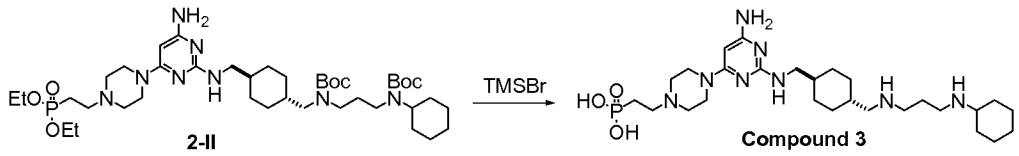
To a solution of **1-XIII** (120 g) in MeOH (2.4 L) were added diethyl vinyl phosphonate (**2-I**, 45 g, 1.5 eq) at 25°C. The mixture was stirred under 65°C for 24 hours. TLC and HPLC showed that the reaction was completed. The solution was concentrated and purified by silica gel ($MeOH/CH_2Cl_2$ = 8/92) to get 87 g of **2-II** (53% yield, purity > 98%, each single impurity <1%) after analyzing the purity of the product by HPLC.

A solution of 20% TFA/CH_2Cl_2 (36 mL) was added to a solution of intermediate **2-II** (1.8 g) in CH_2Cl_2 (5 mL). The reaction mixture was stirred for 15

hours at room temperature and concentrated by removing the solvent to afford trifluoracetic acid salt of compound **2** (1.3 g).

CI-MS ($M^+ + 1$): 623.1

Example 3: Preparation of Compound **3**



2-II **Compound 3**

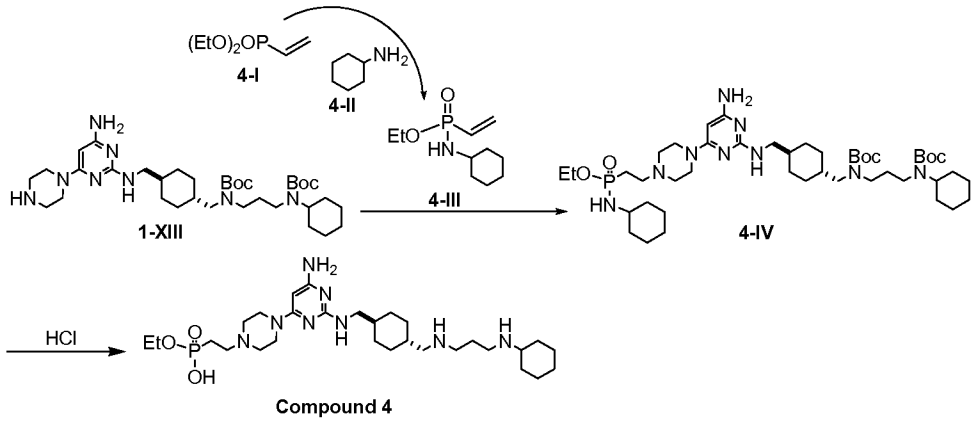
Intermediate **2-II** was prepared as described in Example 2.

To a solution of **2-II** (300 g) in CH_2Cl_2 (1800 mL) was added TMSBr (450 g, 8 eq) at 10-15°C for 1 hour. The mixture was stirred at 25°C for 15 hours. The solution was concentrated to remove TMSBr and solvent under vacuum at 40°C. CH_2Cl_2 was added to the mixture to dissolve the residue. TMSBr and solvent were removed under vacuum again to obtain 360 g crude solid after drying under vacuum (<1 torr) for 3 hours. Then, the crude solid was washed with 7.5 L IPA/MeOH (9/1) to afford compound **3** (280 g) after filtration and drying at 25°C under vacuum (<1 torr) for 3 hours. Crystallization by EtOH gave hydrobromide salt of compound **3** (190g). CI-MS ($M^+ + 1$): 567.0.

The hydrobromide salt of compound **3** (5.27 g) was dissolved in 20 mL water and treated with concentrated aqueous ammonia (pH=9-10), and the mixture was evaporated in vacuo. The residue in water (30 mL) was applied onto a column (100 mL, 4.5x8 cm) of Dowex 50WX8 (H^+ form, 100-200 mesh) and eluted (elution rate, 6 mL/min). Elution was performed with water (2000 mL) and then with 0.2 M aqueous ammonia. The UV-absorbing ammonia eluate was evaporated to dryness to afford ammonia salt of compound **3** (2.41 g). CI-MS ($M^+ + 1$): 567.3.

The ammonia salt of compound **3** (1.5 g) was dissolved in water (8 mL) and alkalified with concentrated aqueous ammonia (pH=11), and the mixture solution was applied onto a column (75 mL, 3x14 cm) of Dowex 1X2 (acetate form, 100-200 mesh) and eluted (elution rate, 3 mL/min). Elution was performed with water (900 mL) and then with 0.1 M acetic acid. The UV-absorbing acetic acid eluate was evaporated, and the residue was codistilled with water (5x50 mL) to afford compound **3** (1.44 g). CI-MS ($M^+ + 1$): 567.4.

Example 4: Preparation of Compound **4**



Intermediate **1-XIII** was obtained during the preparation of compound **1**.

To a solution of diethyl vinyl phosphonate (**4-I**, 4 g) in CH_2Cl_2 (120 mL) was added oxalyl chloride (15.5 g, 5 eq) and the mixture was stirred at 30°C for 36 hours. The mixture were concentrated under vacuum on a rotatory evaporated to give quantitatively the corresponding phosphochloridate, which was added to a mixture of cyclohexyl amine (**4-II**, 5.3 g, 2.2 eq), CH_2Cl_2 (40 mL), and Et_3N (6.2 g, 2.5 eq). The mixture was stirred at 35°C for 36 hours, and then was washed with water. The organic layer was dried ($MgSO_4$), filtered, and evaporated to afford **4-III** (4.7 g, 85% yield) as brown oil.

Compound **4-III** (505 mg) was added to a solution of intermediate **1-XIII** (500 mg) in MeOH (4 mL). The solution was stirred at 45°C for 24 hours. The solution was concentrated and the residue was purified by column chromatography on silica gel (EtOAc/ MeOH = 4:1) to afford intermediate **4-IV** (420 mg) in a 63% yield.

A solution of HCl in ether (5 mL) was added to a solution of intermediate **4-IV** (420 mg) in CH_2Cl_2 (1.0 mL). The reaction mixture was stirred for 12 hours at room temperature and concentrated by removing the solvent. The resultant residue was washed with ether to afford hydrochloride salt of compound **4** (214 mg).

CI-MS ($M^+ + 1$): 595.1

Example 5: Preparation of compound **5**

Compound **5** was prepared in the same manner as that described in Example 1 except that homopiperazine was used instead of piperazine.

CI-MS (M^++1): 473.1

Example 6: Preparation of compound **6**

Compound was prepared in the same manner as that described in Example 1 except that (R)-(-)-2-methylpiperazine was used instead of piperazine.

CI-MS (M^++1): 473.4

Example 7: Preparation of compound **7**

Compound **7** was prepared in the same manner as that described in Example 1 except that (S)-(+)-2-methylpiperazine was used instead of piperazine.

CI-MS (M^++1): 473.4

Example 8: Preparation of compound **8**

Compound **8** was prepared in the same manner as that described in Example 1 except that (S)-(-)-2-*t*-butyl-2-piperazinecarboxamide was used instead of piperazine.

CI-MS (M^++1): 558.4

Example 9: Preparation of compound **9**

Compound **9** was prepared in the same manner as that described in Example 1 except that 2,6-dimethylpiperazine was used instead of piperazine.

CI-MS (M^++1): 487.4

Example 10: Preparation of compound **10**

Compound **10** was prepared in the same manner as that described in Example 1 except that 2-phenylpiperazine was used instead of piperazine.

CI-MS (M^++1): 535.4

Example 11: Preparation of compound **11**

Compound **11** was prepared in the same manner as that described in Example 1 except that (1S,4S)-2,5-diazabicyclo[2.2.1]heptane dihydrobromide was used instead of piperazine.

CI-MS (M^++1): 471.4

Example 12: Preparation of compound **12**

Compound **12** was prepared in the same manner as that described in Example 1 except that 6,9-diaza-spiro[4.5]decane dihydrochloride was used instead of piperazine.

CI-MS (M^++1): 513.4

Example 13: Preparation of compound **13**

Compound **13** was prepared in the same manner as that described in Example 1 except that 1,4-diaza-spiro[5.5]undecane dihydrochloride was used instead of piperazine.

CI-MS (M^++1): 527.5

Example 14: Preparation of Compound **14**

Compound **14** was prepared in the same manner as that described in Example 3 except that sodium 2-bromoethanesulfonate in the presence of Et_3N in DMF at 45°C was used instead of diethyl vinyl phosphonate. Deportations of amino-protecting group by hydrochloride to afford hydrochloride salt of compound **14**.

CI-MS (M^+ + 1): 567.3

Example 15: Preparation of Compound **15**

Compound **15** was prepared in the same manner as that described in Example 3 except that methyl vinyl sulfone in MeOH at 40°C was used instead of diethyl vinyl phosphonate. Deportations of amino-protecting group by hydrochloride to afford hydrochloride salt of compound **15**.

CI-MS (M^++1): 565.4

Example 16: Preparation of Compound **16**

Compound **16** was prepared in the same manner as that described in Example 3 except that phenyl vinyl sulfone was used instead of diethyl vinyl phosphonate.

CI-MS (M^++1): 627.4

Example 17: Preparation of Compound **17**

Compound **17** was prepared in the same manner as that described in Example 2 except that diethyl-1-bromopropylphosphonate in the presence of K_2CO_3 in CH_3CN was used instead of diethyl vinyl phosphonate.

CI-MS (M^+ + 1): 637.5

Example 18: Preparation of Compound **18**

Compound **18** was prepared in the same manner as that described in Example 3 except that diethyl-1-bromopropylphosphonate in the presence of K_2CO_3 in CH_3CN was used instead of diethyl vinyl phosphonate.

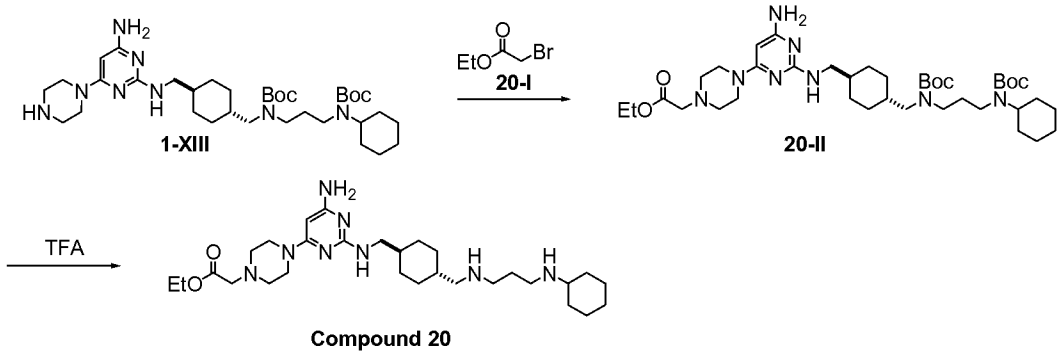
CI-MS (M^+ + 1): 581.4

Example 19: Preparation of Compound **19**

Compound **19** was prepared in the same manner as that described in Example 3 except that diisopropyl-1-bromomethylphosphonate in the presence of K_2CO_3 in CH_3CN was used instead of diethyl vinyl phosphonate.

CI-MS (M^+ + 1): 553.3

Example 20: Preparation of Compound **20**



Intermediate **1-XIII** was prepared as described in Example 1.

To a solution of **1-XIII** (5 g) in CH_3CN (150 mL) were added ethyl bromoacetate (**20-I**, 1.25 g) and K_2CO_3 (3.1 g). The mixture was stirred at room temperature for 2 hours. The solution was filtered, concentrated and purification by silica gel (EtOAc and MeOH as eluant) afforded **20-II** (5 g) in 88% yield.

To a solution of **20-II** (4 g) in CH_2Cl_2 (60 mL) was added 20% TFA/CH_2Cl_2 (40 mL) was added and stirred at room temperature for overnight. The solution was concentrated and the residue in acetone (75 mL) was added HCl (4 N in 1,4-dioxane, 21.5 mL) at room temperature for 0.5 hour. The solvents was removed and the residual was treated with ether to afford hydrochloride salt **20** (3 g).

CI-MS (M^+ + 1): 545.5

Example 21: Preparation of compound **21**

Compound **21** was prepared in the same manner as that described in Example 2 except that homopiperazine was used instead of piperazine.

CI-MS (M^++1): 637.4

Example 22: Preparation of compound **22**

Compound **22** was prepared in the same manner as that described in Example 3 except that homopiperazine was used instead of piperazine.

CI-MS (M^++1): 581.2

Example 23: Preparation of compound **23**

Compound **23** was prepared in the same manner as that described in Example 4 except that homopiperazine was used instead of piperazine.

CI-MS (M^++1): 609.4

Example 24: Preparation of compound **24**

Compound **24** was prepared in the same manner as that described in Example 17 except that homopiperazine was used instead of piperazine.

CI-MS (M^++1): 651.4

Example 25: Preparation of compound **25**

Compound **25** was prepared in the same manner as that described in Example 14 except that homopiperazine was used instead of piperazine.

CI-MS (M^++1): 581.4

Example 26: Preparation of compound **26**

Compound **26** was prepared in the same manner as that described in Example 15 except that homopiperazine was used instead of piperazine.

CI-MS (M^++1): 579.3

Example 27: Preparation of compound **27**

Compound **27** was prepared in the same manner as that described in Example 16 except that homopiperazine was used instead of piperazine.

CI-MS (M^++1): 641.5

Example 28: Preparation of compound **28**

Compound **28** was prepared in the same manner as that described in Example 2 except that (R)-(-)-2-methylpiperazine was used instead of piperazine.

CI-MS (M^++1): 636.8

Example 29: Preparation of compound **29**

Compound **29** was prepared in the same manner as that described in Example 3 except that (R)-(-)-2-methylpiperazine was used instead of piperazine.

CI-MS (M^++1): 581.1

Example 30: Preparation of compound **30**

Compound **30** was prepared in the same manner as that described in Example 17 except that (R)-(-)-2-methylpiperazine was used instead of piperazine.

CI-MS (M^++1): 651.5

Example 31: Preparation of compound **31**

Compound **31** was prepared in the same manner as that described in Example 18 except that (R)-(-)-2-methylpiperazine was used instead of piperazine.

CI-MS (M^++1): 595.4

Example 32: Preparation of compound **32**

Compound **32** was prepared in the same manner as that described in Example 2 except that (S)-(+)-2-methylpiperazine was used instead of piperazine.

CI-MS (M^++1): 637.1

Example 33: Preparation of compound **33**

Compound **33** was prepared in the same manner as that described in Example 3 except that (S)-(+)-2-methylpiperazine was used instead of piperazine.

CI-MS (M^++1): 581.1

Example 34: Preparation of compound **34**

Compound **34** was prepared in the same manner as that described in Example 17 except that (S)-(+)-2-methylpiperazine was used instead of piperazine.

CI-MS (M^++1): 651.5

Example 35: Preparation of compound **35**

Compound **35** was prepared in the same manner as that described in Example 18 except that (S)-(+)-2-methylpiperazine was used instead of piperazine.

CI-MS (M^++1): 595.5

Example 36: Preparation of compound **36**

Compound **36** was prepared in the same manner as that described in Example 3 except that (S)-(-)-2-*t*-butyl-2-piperazinecarboxamide was used instead of piperazine.

CI-MS (M^++1): 666.5

Example 37: Preparation of compound **37**

Compound **37** was prepared in the same manner as that described in Example 17 except that (S)-(-)-2-*t*-butyl-2-piperazinecarboxamide was used instead of piperazine.

CI-MS (M^++1): 736.5

Example 38: Preparation of compound **38**

Compound **38** was prepared in the same manner as that described in Example 18 except that (S)-(-)-2-*t*-butyl-2-piperazinecarboxamide was used instead of piperazine.

CI-MS (M^++1): 680.5

Example 39: Preparation of compound **39**

Compound **39** was prepared in the same manner as that described in Example 17 except that 2,6-dimethylpiperazine was used instead of piperazine.

CI-MS (M^++1): 665.5

Example 40: Preparation of compound **40**

Compound **40** was prepared in the same manner as that described in Example 18 except that 2,6-dimethylpiperazine was used instead of piperazine.

CI-MS (M^++1): 609.5

Example 41: Preparation of compound **41**

Compound **41** was prepared in the same manner as that described in Example 2 except that 2-phenylpiperazine was used instead of piperazine.

CI-MS (M^++1): 699.5

Example 42: Preparation of compound **42**

Compound **42** was prepared in the same manner as that described in Example 3 except that 2-phenylpiperazine was used instead of piperazine.

CI-MS (M^++1): 643.4

Example 43: Preparation of compound **43**

Compound **43** was prepared in the same manner as that described in Example 17 except that 2-phenylpiperazine was used instead of piperazine.

CI-MS (M^++1): 713.5

Example 44: Preparation of compound **44**

Compound **44** was prepared in the same manner as that described in Example 18 except that 2-phenylpiperazine was used instead of piperazine.

CI-MS (M^++1): 657.4

Example 45: Preparation of compound **45**

Compound **45** was prepared in the same manner as that described in Example 2 except that (1S,4S)-2,5-diazabicyclo[2.2.1]heptane dihydrobromide was used instead of piperazine.

CI-MS (M^++1): 635.5

Example 46: Preparation of compound **46**

Compound **46** was prepared in the same manner as that described in Example 3 except that (1S,4S)-2,5-diazabicyclo[2.2.1]heptane dihydrobromide was used instead of piperazine.

CI-MS (M^++1): 579.4

Example 47: Preparation of compound **47**

Compound **47** was prepared in the same manner as that described in Example 17 except that 6,9-diaza-spiro[4.5]decane dihydrochloride was used instead of piperazine.

CI-MS (M^++1): 691.5

Example 48: Preparation of compound **48**

Compound **48** was prepared in the same manner as that described in Example 18 except that 6,9-diaza-spiro[4.5]decane dihydrochloride was used instead of piperazine.

CI-MS (M^++1): 635.5

Example 49: Preparation of compound **49**

Compound **49** was prepared in the same manner as that described in Example 17 except that 1,4-diaza-spiro[5.5]undecane dihydrochloride was used instead of piperazine.

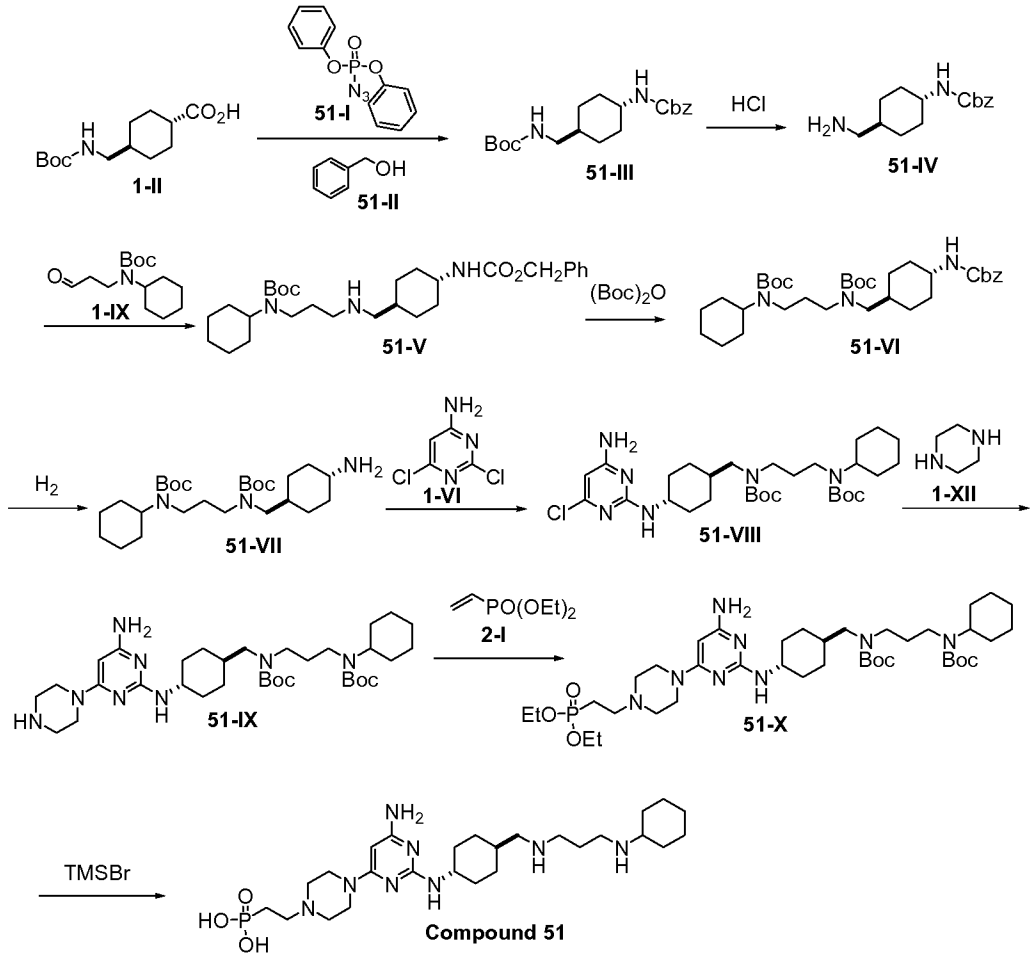
CI-MS (M^++1): 705.5

Example 50: Preparation of compound **50**

Compound **50** was prepared in the same manner as that described in Example 18 except that 1,4-diaza-spiro[5.5]undecane dihydrochloride was used instead of piperazine.

CI-MS (M^++1): 649.5

Example 51: Preparation of compound **51**



Intermediate **1-II** was prepared as described in Example 1.

To a suspension of the intermediate **1-II** (31.9 g) in toluene (150 mL) were added phosphorazidic acid diphenyl ester (**51-I**, 32.4 g) and Et_3N (11.9 g) at 25°C for 1 hour. The reaction mixture was stirred at 80°C for 3 hours and then cooled to 25°C. After benzyl alcohol (**51-II**, 20 g) was added, the reaction mixture was stirred at 80°C for additional 3 hours and then warmed to 120°C overnight. It was then concentrated and dissolved again in EtOAc and H_2O. The organic layer was collected. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with 2.5 N HCl, saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue thus obtained was purified by column chromatography on silica gel (EtOAc/Hexane = 1:2) to give Intermediate **51-III** (35 g) in a 79% yield.

A solution of intermediate **51-III** (35 g) treated with 4 N HCl/dioxane (210 mL) in MeOH (350 mL) was stirred at room temperature overnight. After ether (700 mL) was added, the solution was filtered. The solid was dried under vacuum. K_2CO_3 was added to a suspension of this solid in CH_3CN and *iso*-propanol at room temperature for 10 minutes. After water was added, the reaction mixture was stirred at room temperature for 2 hours, filtered, dried over anhydrous $MgSO_4$, and concentrated. The resultant residue was purified by column chromatography on silica gel (using CH_2Cl_2 and MeOH as an eluant) to give intermediate **51-IV** (19 g) in a 76% yield.

Intermediate **1-IX** (21 g) was added to a solution of intermediate **51-IV** (19 g) in CH_2Cl_2 (570 mL). The mixture was stirred at 25°C for 2 hours. $NaBH(OAc)_3$ (23 g) was then added at 25°C overnight. After the solution was concentrated, a saturated aqueous $NaHCO_3$ solution was added to the resultant residue. The mixture was then extracted with CH_2Cl_2. The solution was concentrated and the residue was purified by column chromatography on silica gel (using EtOAc and MeOH as an eluant) to afford intermediate **51-V** (23.9 g) in a 66% yield.

A solution of intermediate **51-V** (23.9 g) and Boc_2O (11.4 g) in CH_2Cl_2 (200 mL) was added to Et_3N (5.8 mL) at 25°C for overnight. The solution was then concentrated and the resultant residue was purified by column chromatography on silica gel (using EtOAc and Hexane as an eluant) to give intermediate **51-VI** (22 g) in a 77% yield.

10% Pd/C (2.2 g) was added to a suspension of intermediate **51-VI** (22 g) in MeOH (44 mL). The mixture was stirred at ambient temperature under hydrogen atmosphere overnight, filtered, and concentrated. The residue thus obtained was purified by column chromatography on silica gel (using EtOAc and MeOH as an eluant) to afford intermediate **51-VII** (16.5 g) in a 97% yield.

Intermediate **51-VII** (16.5 g) and Et_3N (4.4 mL) in 1-pentanol (75 mL) was allowed to react with 2,4-dichloro-6-aminopyrimidine (**1-VI**, 21 g) at 120°C overnight. The solvent was then removed and the residue was purified by column chromatography on silica gel (using EtOAc and hexane as an eluant) to afford intermediate **51-VIII** (16.2 g) in a 77% yield.

A solution of intermediate **51-VIII** (16.2 g) and piperazine (**1-XII**, 11.7 g) in 1-pentanol (32 mL) was added to Et_3N (3.3 mL) at 120°C overnight. After the

solution was concentrated, the residue was treated with water and extracted with CH_2Cl_2. The organic layer was collected and concentrated. The residue thus obtained was purified by column chromatography on silica gel (using EtOAc/ MeOH to 28% NH_4OH/MeOH as an eluant) to afford Intermediate **51-IX** (13.2 g) in a 75% yield.

Diethyl vinyl phosphonate (**2-I**) was treated with **51-IX** as described in Example 3 to afford hydrobromide salt of compound **51**.

CI-MS ($M^+ + 1$): 553.3

Example 52: Preparation of Compound **52**

Compound **52** was prepared in the same manner as that described in Example 4 except that intermediate **51-IX** was used instead of intermediate **1-XIII**.

CI-MS ($M^+ + 1$): 581.2

Example 53: Preparation of Compound **53**

Compound **53** was prepared in the same manner as that described in Example 51 except that diethyl-1-bromopropylphosphonate in the presence of K_2CO_3 in CH_3CN was used instead of diethyl vinyl phosphonate.

CI-MS ($M^+ + 1$): 567.2

Example 54: Preparation of Compound **54**

Compound **54** was prepared in the same manner as that described in Example 51 except that (R)-(-)-2-methylpiperazine was used instead of piperazine.

CI-MS ($M^+ + 1$): 566.7

Example 55: Preparation of Compound **55**

Compound **55** was prepared in the same manner as that described in Example 53 except that (R)-(-)-2-methylpiperazine was used instead of piperazine.

CI-MS ($M^+ + 1$): 580.7

Example 56: Preparation of Compound **56**

Compound **56** was prepared in the same manner as that described in Example 51 except that sodium 2-bromoethanesulfonate in the presence of Et_3N in DMF at 45 ^0C was used instead of diethyl vinyl phosphonate.

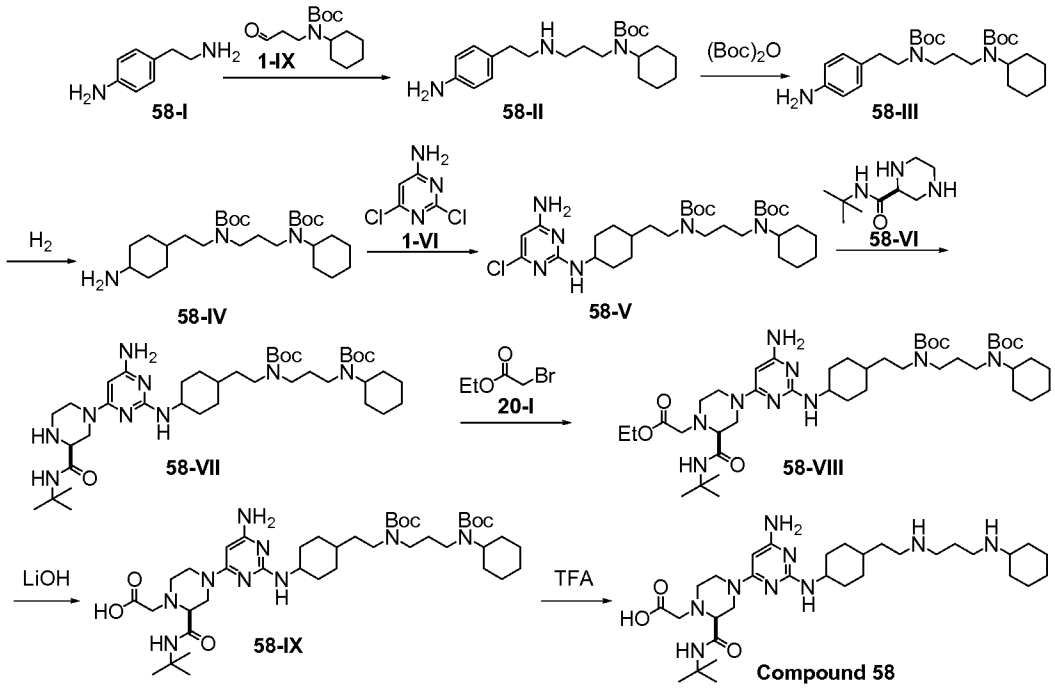
CI-MS ($M^+ + 1$): 553.2

Example 57: Preparation of Compound **57**

Compound **57** was prepared in the same manner as that described in Example 51 except that methyl vinyl sulfone in MeOH at 40 ^{0}C was used instead of diethyl vinyl phosphonate. Deportations of amino-protecting group by hydrochloride to afford hydrochloride salt of compound **57**.

CI-MS (M^+ + 1): 551.3

Example 58: Preparation of Compound **58**



To a solution of 2-aminoethylaniline (**58-1**, 2.92 g) in MeOH (300 mL) was added **1-IX** (4.56 g). The mixture was stirred at 60°C for 8 h. Then, $NaBH_4$ (0.68 g) was added at 0°C for 0.5 hour and concentrated by removing the solvent. To the resultant residue was added an aqueous solution of NH_4Cl (10%, 10 mL). The mixture was extracted with CH_2Cl_2, dried (MgSO4), filtered and evaporated. Purified by chromatography on silica gel (EtOAc/MeOH = 1/1) to afford **58-II** (4.2 g) in a 63% yield.

A solution of **58-II** (4.2 g) and Boc_2O (2.8 g) in CH_2Cl_2 (250 mL) was added Et_3N (1.4 mL) at 25°C for overnight. The solution was then concentrated and the resultant residue was purified by chromatography on silica gel (EtOAc/Hexane = 1/5) to give **58-III** (4 g) in a 75% yield.

Compound **58-III** (4.0 g) in MeOH (20 mL) was hydrogenated at 50 psi at room temperature in the presence of 10% Pd/C (800 mg) and 5% Rh/C (400 mg) for 18 hours. The mixture was then filtered, evaporated, and the residue was purified by chromatography on silica gel (EtOAc/MeOH as eluant) to afford **58-IV** (2.8 g) in a 69% yield.

Compound **58-IV** (900 mg) and Et_3N (0.4 mL) in 1-pentanol (5 mL) was reacted with 2,4-dichloro-6-aminopyrimidine (**1-VI**, 365 mg) at 120°C for 24 hours. The solvent was removed and the residue was purified by chromatography on silica gel (EtOAc/Hexane = 1/1) to afford **58-V** (842 mg) in a 74% yield.

(S)-(-)-2-*t*-butyl-2-piperazinecarboxamide (**58-VI**, 274 mg) was added to **58-V** (300 mg) in 1-pentanol (1 mL) and the mixture was stirred at 120°C for 18 hours. The solution was concentrated to give the residue which was coated with SiO_2 and purified by silica gel (EtOAc/ MeOH = 7/3) to afford **58-VII** (242 mg) in a 65% yield.

To a solution of **58-VII** (200 mg) in CH_3CN (20 mL) were added ethyl bromoacetate (**20-I**, 44 mg) and K_2CO_3 (182 mg). The mixture was stirred at 60°C for 2 hours. The solution was filtered, concentrated and purification by silica gel (EtOAc and MeOH as eluant) afforded **58-VIII** (133 mg) in a 60% yield.

Compound **58-VIII** (500 mg) dissolved in THF (10 mL) was added 0.5 M LiOH (10 mL). The mixture was stirred at room temperature for 15 hours. Then, it was acidified with 2.5 M HCl (PH = 9) and filtered to obtain yellow solid **58-IX**. Purification by silica gel chromatography (EtOAc/MeOH to 21% NH_3 (aq)/MeOH as eluant) afforded intermediate **58-IX** (324 mg) in a 67% yield.

To a solution of **58-IX** (200 mg) in CH_2Cl_2 (2 mL) was added 20% TFA/CH_2Cl_2 (4 mL). The solution was stirred at room temperature for 2 hours. The solvents were removed to afford trifluoracetic acid salt of compound **58** (260 mg).

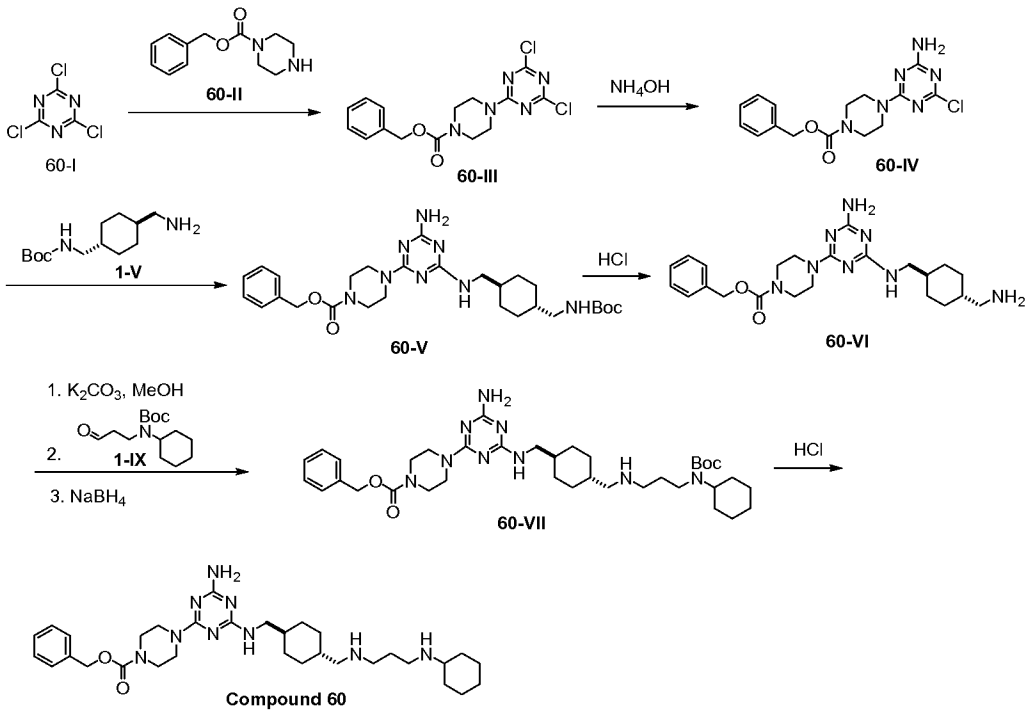
CI-MS (M^+ + 1): 615.8

Example 59: Preparation of Compound **59**

Compound **59** was prepared in the same manner as that described in Example 58 except that ethyl 3-bromopropionate was used instead of ethyl bromoacetate.

CI-MS (M^++1): 629.8

Example 60: Preparation of Compound **60**



Intermediate **1-V** was prepared as described in Example 1.

Benzyl 1-piperazinecarboxylate (**60-II**, 1.3 g) was dissolved in acetone (10 mL) and $NaHCO_3$ (0.5 g) in water (10 mL) was added simultaneously to solution of triazine **60-I** (1.1 g) in acetone (24 mL) and water (36 mL) at 0°C. The solution was stirred at 25°C for 2 hours to obtain a solid. Filtration afforded compound **60-III**, which was used for the next step without purification.

To a solution of compound **60-III** (2.0 g) in acetone (20 mL) was added aq. ammonium hydroxide solution (10 mL) at 25°C. After 15 hours, acetone was removed under reduced pressure and compound **60-IV** was precipitated, filtered, washed with acetone (10 mL), and dried to give 1.9 g of **60-IV** in a 91% overall yield.

A solution of intermediate **1-V** (1.45 g) and Et_3N (1.6 mL) in *iso*-propylalcohol (10 mL) was reacted with compound **60-IV** (1.9 g) at 60°C for overnight. The reaction mixture was evaporated under reduced pressure. The residue thus obtained was purified by column chromatography on silica gel (EtOAc as an eluant) to afford intermediate **60-V** (2.2 g) in a 70% yield.

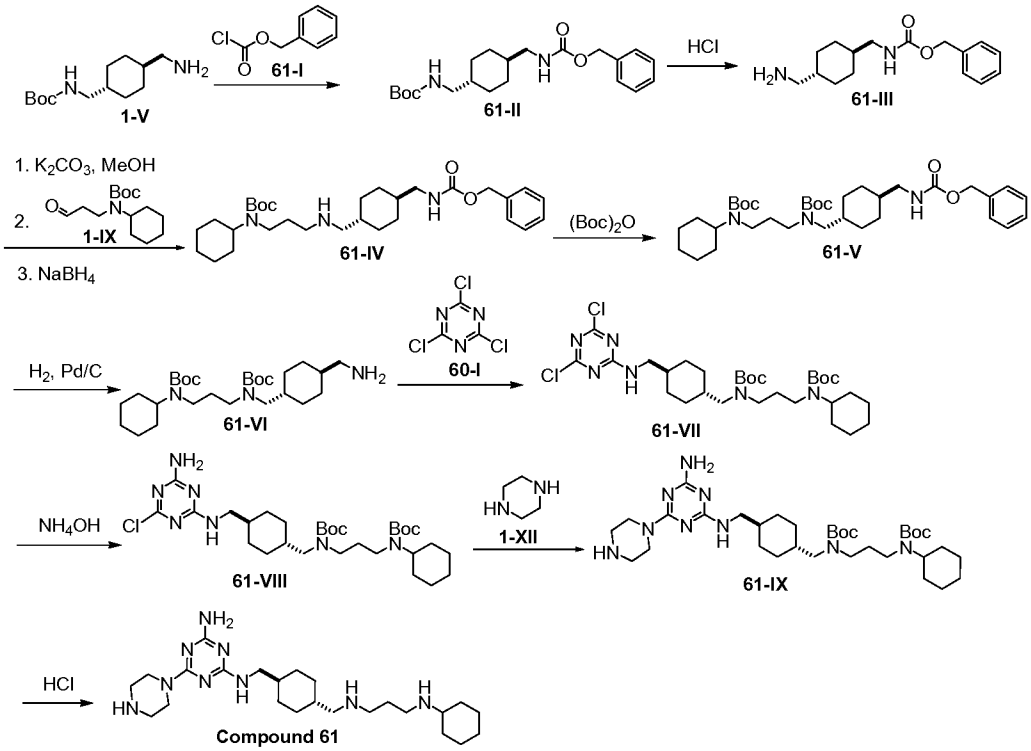
A solution of intermediate **60-V** (17 g) was treated with 4 N HCl/dioxane (160 mL) in MeOH (180 mL) and stirred at room temperature overnight. After ether was added, the solution was filtered. The solid thus obtained was dried under vacuum. To

a solution of the above solid in MeOH was added K_2CO_3 at room temperature. The resultant mixture was stirred for 1 hour and was filtered. Intermediate **1-IX** (7.78 g) was added. The mixture was stirred at 25°C for 2 hours. $NaBH_4$ (1.0 g) was then added at 25°C. The mixture was stirred overnight and then concentrated. A saturated aqueous NH_4Cl solution was added. The mixture was extracted with CH_2Cl_2. The organic layers were collected, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by column chromatography on silica gel (MeOH as an eluant) to afford intermediate **60-VII** (16 g) in a 74% yield.

A solution of HCl in ether (3 mL) was added to a solution of intermediate **60-VII** (200 mg) in CH_2Cl_2 (1.0 mL). The reaction mixture was stirred for 12 hours at room temperature and concentrated by removing the solvent. The resultant residue was washed with ether to afford hydrochloride salt of compound **60** (128 mg).

CI-MS ($M^+ + 1$): 594.2

Example 61: Preparation of Compound **61**



Intermediate **1-V** was prepared as described in Example 1.

A solution of compound **1-V** (120 g) and Et_3N (150 g, 3eq) in CH_2Cl_2 (2.6 L) was reacted with benzylchloroformate (**61-I**, 84 g, 1eq) at -10°C for 15 hours. TLC showed that the reaction was completed.

Intermediate **61-II** (167 g) was treated with 4 N HCl/dioxane (280 mL) in MeOH (1.2 L). The mixture was stirred at room temperature overnight. After ether was added, the solution was filtered. The solid thus obtained was dried under vacuum. To a solution of the above solid in MeOH was added K_2CO_3 at room temperature. After stirred for 1 hour, the solution was filtered and intermediate **1-IX** (101.2 g) was added. The mixture was stirred at 25°C for 2 hours. $NaBH_4$ (12 g) was then added at 25°C and the mixture was stirred overnight. The solution was then concentrated and a saturated aqueous NH_4Cl solution was added. The mixture was extracted with CH_2Cl_2, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue thus obtained was purified by column chromatography on silica gel (MeOH as an eluant) to afford intermediate **61-IV** (100 g) in 32% yield.

Et_3N (29.2 mL) was added to a solution of intermediate **61-IV** (80 g) and Boc_2O (5 g) in CH_2Cl_2 (200 mL) at 25°C. The solution was stirred overnight and then concentrated. The resultant residue was purified by column chromatography on silica gel (EtOAc as an eluant) to give intermediate **61-V** (80 g) in 84% yield.

Catalytic hydrogenation of **61-V** (38 g) with Pd/C (10%, 3.8 g) under H_2 (1 atm) in MeOH afforded intermediate **61-VI** (29 g).

61-VI (26.1 g) dissolved in THF (200 mL) and N,N-disopropylethylamine (7.8 g) dissolved in THF (200 mL) were added simultaneously to solution of triazine **60-I** (10 g) in THF (200 mL) at 0°C. The solution was stirred at 25°C for 2 hours to obtain a solid. Filtration afforded compound **61-VII**, which was used for the next step without purification.

To a solution of compound **61-VII** (30 g) in THF (1000 mL) was added aq. ammonium hydroxide solution (50 mL) at 25°C. After 15 hours, THF was evaporated under reduced pressure and compound **61-VIII** was precipitated, filtered, and dried to give 23.9 g of **61-VIII** in a 70% overall yield.

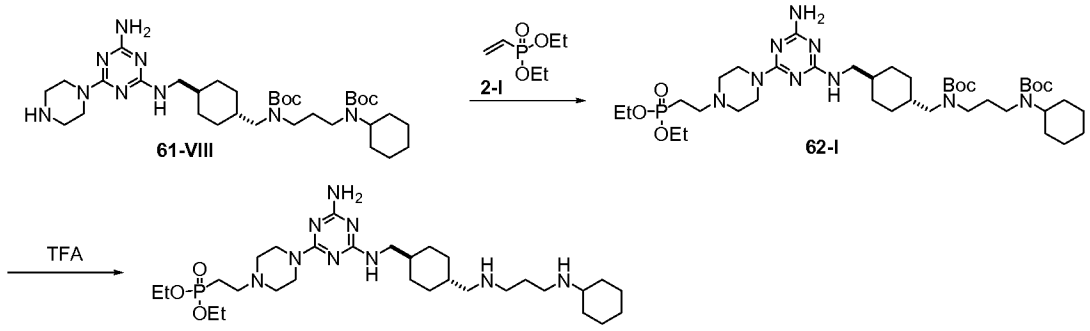
To compound **61-VIII** (2.0 g) and piperazine (**1-XII**, 0.83 g) in 1-pentanol (3 mL) was added Et_3N (0.97 g) at 25°C. The mixture was stirred at 120°C for 8 hours. TLC showed that the reaction was completed. Ethyl acetate (480mL) was added to the reaction mixture at 25°C. The solution was stirred for 1 hour. The Et_3NHCl salt

was filtered and the solution was concentrated and purified by silica gel (EtOAc/ MeOH = 2:8) to afforded **61-IX** (1.0 g) in a 46%yield.

A solution of HCl in ether (5 mL) was added to a solution of intermediate **61-IX** (420 mg) in CH_2Cl_2 (1.0 mL). The reaction mixture was stirred for 12 hours at room temperature and concentrated by removing the solvent. The resultant residue was washed with ether to afford hydrochloride salt of compound **61** (293 mg).

CI-MS (M^+ + 1): 460.0

Example 62: Preparation of Compound **62**



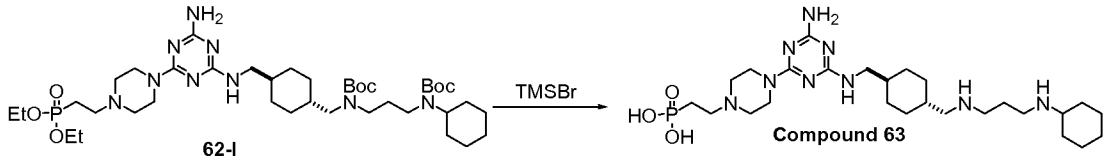
Intermediate **61-VIII** was prepared as described in Example 61.

Diethyl vinylphosphonate (**2-I**, 213 mg) was added to a solution of intermediate **61-VIII** (570 mg) in MeOH (20 mL). The solution was stirred at 25°C for 12 hours. The solution was then concentrated and the residue was purified by column chromatography on silica gel (EA/ MeOH = 5/1) to afford intermediate **62-I** (290 mg) in a 42% yield.

A solution of 20% TFA/CH_2Cl_2 (5 mL) was added to a solution of intermediate **62-I** (430 mg) in CH_2Cl_2 (2 mL). The reaction mixture was stirred for 8 hours at room temperature and concentrated by removing the solvent. The resultant residue was purified by column chromatography on silica gel (EA/MeOH = 1/1) to afford trifluoracetic acid salt of compound **62** (175 mg).

CI-MS (M^++1): 642.4

Example 63: Preparation of Compound **63**



62-I Compound 63

Intermediate **62-I** was prepared as described in Example 62.

A solution of compound **62-I** (610 mg) and trimethylsilyl bromide (1.21 g) in CH_2Cl_2 (30 mL) was stirred at 25°C for 72 hours. The solution was then concentrated in vacuum to yield yellow-orange foam. Crystallization from EtOH gave hydrobromide salt of compound **63** (189 mg).

CI-MS (M^++1): 568.0

Example 64: Preparation of compound **64**

Compound **64** was prepared in the same manner as that described in Example 61 except that homopiperazine was used instead of piperazine.

CI-MS (M^++1): 474.4

Example 65: Preparation of compound **65**

Compound **65** was prepared in the same manner as that described in Example 61 except that (R)-(-)-2-methylpiperazine was used instead of piperazine.

CI-MS (M^++1): 474.4

Example 66: Preparation of compound **66**

Compound **66** was prepared in the same manner as that described in Example 61 except that (S)-(+)-2-methylpiperazine was used instead of piperazine.

CI-MS (M^++1): 474.1

Example 67: Preparation of compound **67**

Compound **67** was prepared in the same manner as that described in Example 61 except that (S)-(-)-2-*t*-butyl-2-piperazinecarboxamide was used instead of piperazine.

CI-MS (M^++1): 559.5

Example 68: Preparation of compound **68**

Compound **68** was prepared in the same manner as that described in Example 61 except that 2,6-dimethylpiperazine was used instead of piperazine.

CI-MS (M^++1): 488.1

Example 69: Preparation of compound **69**

Compound **69** was prepared in the same manner as that described in Example 61 except that 2-phenylpiperazine was used instead of piperazine.

CI-MS (M^++1): 536.4

Example 70: Preparation of compound **70**

Compound **70** was prepared in the same manner as that described in Example 61 except that (1S,4S)-2,5-diazabicyclo[2.2.1]heptane dihydrobromide was used instead of piperazine.

CI-MS (M^++1): 514.4

Example 71: Preparation of compound **71**

Compound **71** was prepared in the same manner as that described in Example 61 except that 6,9-diaza-spiro[4.5]decane dihydrochloride was used instead of piperazine.

CI-MS (M^++1): 528.5

Example 72: Preparation of compound **72**

Compound **72** was prepared in the same manner as that described in Example 61 except that 1-methyl piperazine was used instead of piperazine.

CI-MS (M^++1): 474.4

Example 73: Preparation of compound **73**

Compound **73** was prepared in the same manner as that described in Example 61 except that 1-(2-morpholinoethyl)-piperazine was used instead of piperazine.

CI-MS (M^++1): 573.5

Example 74: Preparation of Compound **74**

Compound **74** was prepared in the same manner as that described in Example 62 except that diethyl-1-bromopropylphosphonate in the presence of K_2CO_3 in CH_3CN was used instead of diethyl vinyl phosphonate.

CI-MS ($M^+ + 1$): 638.2

Example 75: Preparation of Compound **75**

Compound **75** was prepared in the same manner as that described in Example 63 except that diethyl-1-bromopropylphosphonate in the presence of K_2CO_3 in CH_3CN was used instead of diethyl vinyl phosphonate.

CI-MS ($M^+ + 1$): 582.0

Example 76: Preparation of Compound **76**

Compound **76** was prepared in the same manner as that described in Example 63 except that *N*-valeryl chloride in the presence of DIPEA in CH_2Cl_2 was used instead of diethyl vinyl phosphonate. Deportations of amino-protecting group by hydrochloride to afford hydrochloride salt of compound **76**.

CI-MS ($M^+ + 1$): 544.4

Example 77: Preparation of Compound **77**

Compound **77** was prepared in the same manner as that described in Example 63 except that ethyl 4-bromobutyrate in the presence of K_2CO_3 in CH_3CN was used instead of diethyl vinyl phosphonate. Hydrolysis of ether group by LiOH afforded amino acid compound. Removal of amino-protecting group by trifluoracetic acid afforded trifluoracetic acid salt of compound **77**.

CI-MS ($M^+ + 1$): 546.2

Example 78: Preparation of Compound **78**

Compound **78** was prepared in the same manner as that described in Example 63 except that sodium 2-bromoethanesulfonate in the presence of Et_3N in DMF at 45 ^0C was used instead of diethyl vinyl phosphonate. Removal of amino-protecting group by hydrochloride afforded hydrochloride salt of compound **79**.

CI-MS (M^+ + 1): 568.3

Example 79: Preparation of Compound **79**

Compound **79** was prepared in the same manner as that described in Example 78 except that methyl vinyl sulfone in MeOH at 40°C was used instead of diethyl vinyl phosphonate. Deportations of amino-protecting group by hydrochloride to afford hydrochloride salt of compound **79**.

CI-MS (M^++1): 566.2

Example 80: Preparation of compound **80**

Compound **80** was prepared in the same manner as that described in Example 62 except that homopiperazine was used instead of piperazine.

CI-MS (M^++1): 638.5

Example 81: Preparation of compound **81**

Compound **81** was prepared in the same manner as that described in Example 63 except that homopiperazine was used instead of piperazine.

CI-MS (M^++1): 582.4

Example 82: Preparation of compound **82**

Compound **82** was prepared in the same manner as that described in Example 74 except that homopiperazine was used instead of piperazine.

CI-MS (M^++1): 652.5

Example 83: Preparation of compound **83**

Compound **83** was prepared in the same manner as that described in Example 75 except that homopiperazine was used instead of piperazine.

CI-MS (M^++1): 596.4

Example 84: Preparation of compound **84**

Compound **84** was prepared in the same manner as that described in Example 62 except that (R)-(-)-2-methylpiperazine was used instead of piperazine.

CI-MS (M^++1): 638.3

Example 85: Preparation of compound **85**

Compound **85** was prepared in the same manner as that described in Example 63 except that (R)-(-)-2-methylpiperazine was used instead of piperazine.

CI-MS (M^++1): 582.2

Example 86: Preparation of compound **86**

Compound **86** was prepared in the same manner as that described in Example 74 except that (R)-(-)-2-methylpiperazine was used instead of piperazine.

CI-MS (M^++1): 652.5

Example 87: Preparation of compound **87**

Compound **87** was prepared in the same manner as that described in Example 75 except that (R)-(-)-2-methylpiperazine was used instead of piperazine.

CI-MS (M^++1): 596.2

Example 88: Preparation of compound **88**

Compound **88** was prepared in the same manner as that described in Example 63 except that (S)-(+)-2-methylpiperazine was used instead of piperazine.

CI-MS (M^++1): 582.4

Example 89: Preparation of compound **89**

Compound **89** was prepared in the same manner as that described in Example 74 except that (S)-(+)-2-methylpiperazine was used instead of piperazine.

CI-MS (M^++1): 652.5

Example 90: Preparation of compound **90**

Compound **90** was prepared in the same manner as that described in Example 75 except that (S)-(+)-2-methylpiperazine was used instead of piperazine.

CI-MS (M^++1): 596.0

Example 91: Preparation of compound **91**

Compound **91** was prepared in the same manner as that described in Example 74 except that (S)-(-)-2-*t*-butyl-2-piperazinecarboxamide was used instead of piperazine.

CI-MS (M^++1): 737.6

Example 92: Preparation of compound **92**

Compound **92** was prepared in the same manner as that described in Example 75 except that (S)-(-)-2-*t*-butyl-2-piperazinecarboxamide was used instead of piperazine.

CI-MS (M^++1): 681.5

Example 93: Preparation of compound **93**

Compound **93** was prepared in the same manner as that described in Example 74 except that 2,6-dimethylpiperazine was used instead of piperazine.

CI-MS (M^++1): 666.5

Example 94: Preparation of compound **94**

Compound **94** was prepared in the same manner as that described in Example 75 except that 2,6-dimethylpiperazine was used instead of piperazine.

CI-MS (M^++1): 610.4

Example 95: Preparation of compound **95**

Compound **95** was prepared in the same manner as that described in Example 75 except that 2-phenylpiperazine was used instead of piperazine.

CI-MS (M^++1): 658.4

Example 96: Preparation of compound **96**

Compound **96** was prepared in the same manner as that described in Example 74 except that 6,9-diaza-spiro[4.5]decane dihydrochloride was used instead of piperazine.

CI-MS (M^++1): 692.5

Example 97: Preparation of compound **97**

Compound **97** prepared in the same manner as that described in Example 75 except that 6,9-diaza-spiro[4.5]decane dihydrochloride was used instead of piperazine.

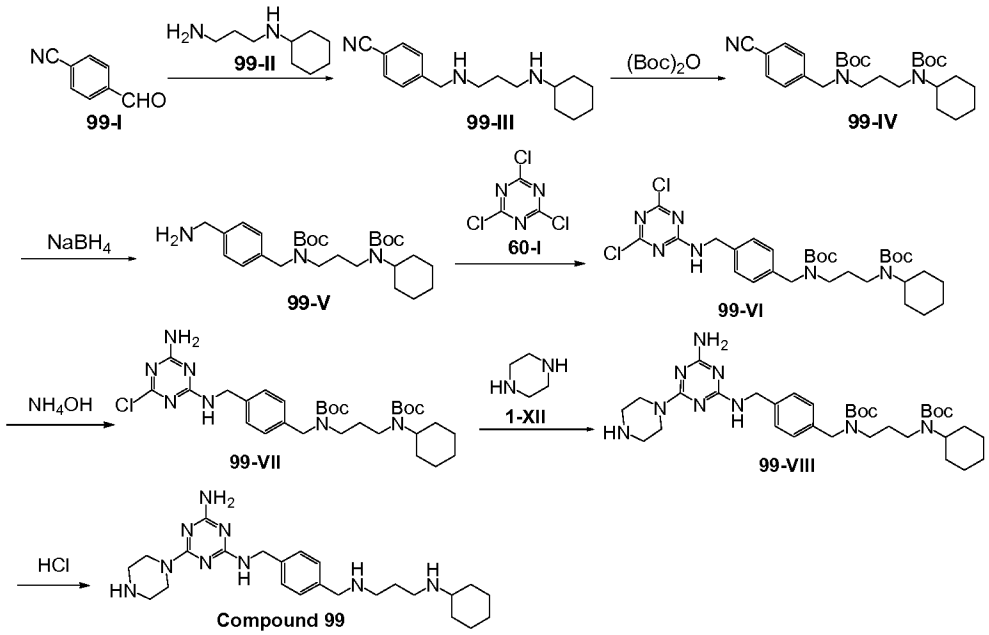
CI-MS (M^++1): 636.5

Example 98: Preparation of compound **98**

Compound **98** was prepared in the same manner as that described in Example 75 except that 1,4-diaza-spiro[5.5]undecane dihydrochloride was used instead of piperazine.

CI-MS (M^++1): 650.5

Example 99: Preparation of compound **99**



A solution of 4-cyanobenzylaldehyde (**99-I**, 5 g) and *N*-cyclohexyl-1,3-propane- diamine (**99-II**, 6 g) in CH_3OH (100 mL) was heated to 60°C for 6 hours. After cooling to room temperature, $NaBH_4$ (2.5 g) was slowly added to the solution. The mixture was stirred for another 30 minutes, and was then concentrated, quenched with NH_4Cl (aq), and extracted with CH_2Cl_2. The organic layers were combined, dried with anhydrous $MgSO_4$, and concentrated to give a residue. The residue was

purified by chromatography on silica gel (EtOAc/Et_3N = 4/1) to afford Intermediate **99-III** (7.2 g) in a 70% yield.

A solution of Intermediate **99-III** (7.2 g) and Boc_2O (17.3 g) in CH_2Cl_2 (280 ml) was stirred at 25°C for 15 hours and then concentrated. The resultant residue was purified by chromatography on silica gel (EtOAc/Hexane = 1/1) to afford Intermediate **99-IV** as a yellow oil (10.6 g, yield: 85%).

A solution of Intermediate **99-IV** (4.7 g) and $NiCl_2$ (64 mg) in CH_3OH (100 ml) was stirred at 25°C. After cooling to 0°C, $NaBH_4$ (1.83 g) was slowly added and the mixture was stirred for another 15 hours. The solution was concentrated, quenched with NH_4Cl (aq), and extracted with CH_2Cl_2. The combined organic layer was washed with water, filtered, dried with anhydrous $MgSO_4$, and concentrated to give a residue. The residue was purified by chromatography on silica gel (21% NH_3(aq)/MeOH = 1/19) to afford Intermediate **99-V** (2.36 g) in a 50% yield.

99-V (3.4 g) dissolved in THF (50 mL) and N,N-disopropylethylamine (0.92 g) dissolved in THF (50 mL) were added simultaneously to triazine **60-I** (1.3 g) in THF (50 mL) at 0°C. The solution was stirred at 25°C for 2 hours to obtain a solid. Filtration afforded compound **99-VI**, which was used for the next step without purification.

To a solution of compound **99-VI** (4.3 g) in THF (100 mL) was added aq. ammonium hydroxide solution (10 mL) at 25°C. After 15 hours, THF was evaporated under reduced pressure and compound **99-VII** was precipitated, filtered, and dried to give 3 g of **99-VII** in a 70% overall yield.

To compound **99-VII** (500 mg) and piperazine (**1-XII**, 211 mg) in 1-pentanol (3 mL) was added Et_3N (248 mg) at 25°C. The mixture was stirred at 120°C for 8 hours. TLC showed that the reaction was completed. Ethyl acetate (120mL) was added to the reaction mixture at 25°C. The solution was stirred for 1 hour. The Et_3NHCl salt was filtered and the solution was concentrated and purified by silica gel (EtOAc/ MeOH = 2:8) to afforded **99-VIII** (460 mg) in a 85%yield.

A solution of HCl in ether (5 mL) was added to a solution of intermediate **99-VIII** (200 mg) in CH_2Cl_2 (1.0 mL). The reaction mixture was stirred for 12 hours at room temperature and concentrated by removing the solvent. The resultant residue was washed with ether to afford hydrochloride salt of compound **99** (110 mg).

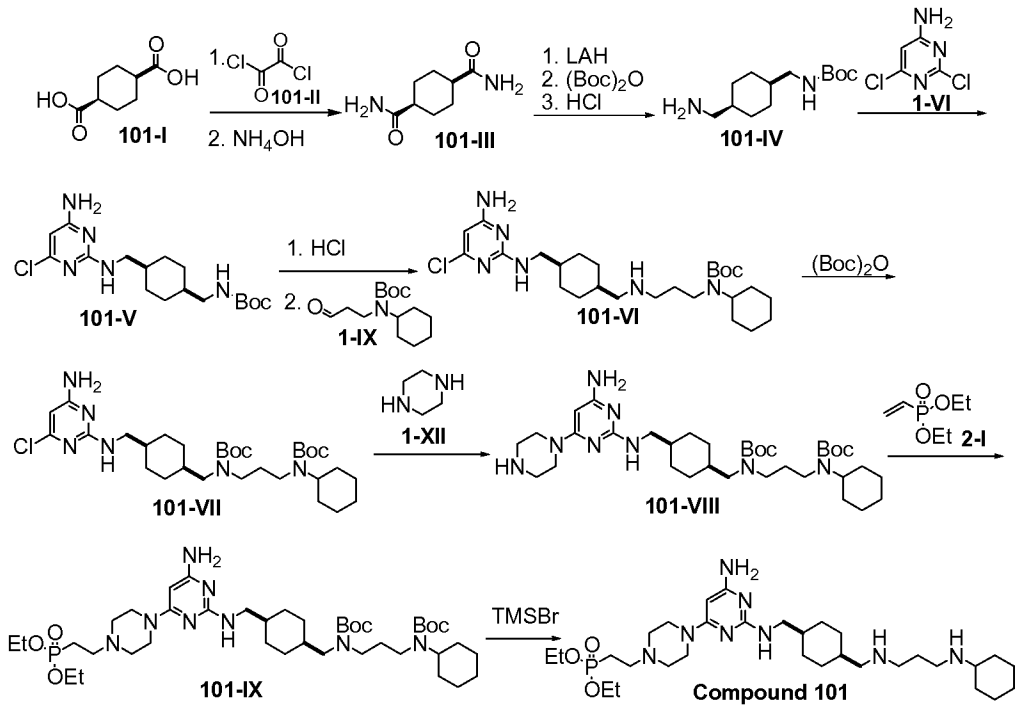
CI-MS (M^+ + 1): 454.1

Example 100: Preparation of compound **100**

Compound **100** was prepared in a manner the same as that described in Example 99 except that 1-methyl piperazine was used instead of piperazine.

CI-MS (M^++1): 468.0

Example 101: Preparation of compound **101**



Cis-1,4-cyclohexanedicarboxylic acid (**101-I**, 10 g) in THF (100 ml) was added oxalyl chloride(**101-II**, 15.5g) at 0°C and then DMF (few drops). The mixture was stirred at room temperature for 15 hours. The solution was concentrated and the residue was dissolved in THF (100 ml). The mixture solution was added to ammonium hydroxide (80 ml) and stirred for 1 hour. The solution was concentrated and filtration to afford crude product **101-III** (7.7 g).

Compound **101-III** (7.7 g) in THF (200 ml) was slowly added to $LiAlH_4$ (8.6 g) in THF (200 ml) solution at 0°C. The mixture solution was stirred at 65°C for 15 hours. $NaSO_4 \cdot 10H_2O$ was added at room temperature and stirred for 1 hours. The resultant mixture was filtered to get filtrate and concentrated. The residue was dissolved in CH_2Cl_2 (100 ml). Et_3N (27 g) and $(Boc)_2O$ (10 g) were added at room temperature. The solution was stirred for 15 h, and then concentrated to get resultant

residue. Ether was added to the resultant residue. Filtration and drying under vacuum afforded solid crude product **101-IV** (8.8 g).

A solution of compound **101-IV** (1.1 g) and Et_3N (1.7 g) in 1-pentanol (10 ml) was reacted with 2,4-dichloro-6-aminopyrimidine (**1-VI**, 910 mg) at 90°C for 15 hours. TLC showed that the reaction was completed. Ethyl acetate (10 mL) was added to the reaction mixture at 25°C. The solution was stirred for 1 hour. The Et_3NHCl salt was removed. The filtrate was concentrated and purified by silica gel (EtOAc/Hex = 1:2) to afford the desired product **101-V** (1.1 g, 65% yield).

A solution of intermediate **101-V** (1.1 g) was treated with 4 N HCl/dioxane (10 ml) in MeOH (10 ml) and stirred at 25°C for 15 hours. TLC showed that the reaction was completed. The mixture was concentrated, filtered, and dried under vacuum (<10 torr). For neutralization, K_2CO_3 (3.2g) was added to the solution of HCl salt in MeOH (20 ml) at 25°C. The mixture was stirred at the same temperature for 3 hours (pH > 12) and filtered. Aldehyde **1-IX** (759 mg) was added to the filtrate at 0-10°C. The reaction was stirred at 0-10°C for 3 hours. TLC showed that the reaction was completed. Then, $NaBH_4$ (112 mg) was added at less than 10°C and the solution was stirred at 10-15°C for 1 hour. The solution was concentrated to get a residue, which was then treated with CH_2Cl_2 (10 mL). T he mixture was washed with saturated NH_4Cl (aq) solution. The CH_2Cl_2 layer was concentrated and the residue was purified by chromatography on silica gel (MeOH/28% NH_4OH = 97/3) to afford intermediate **101-VI** (1.0 g, 66% yield).

Et_3N (600 mg) and Boc_2O (428 mg) were added to the solution of **101-VI** (1.0 g) in CH_2Cl_2 (10 ml) at 25°C. The mixture was stirred at 25°C for 15 hours. TLC showed that the reaction was completed. The solution was concentrated and purified by chromatography on silica gel (EtOAc/Hex = 1:1) to afford intermediate **101-VII** (720 mg, 60% yield).

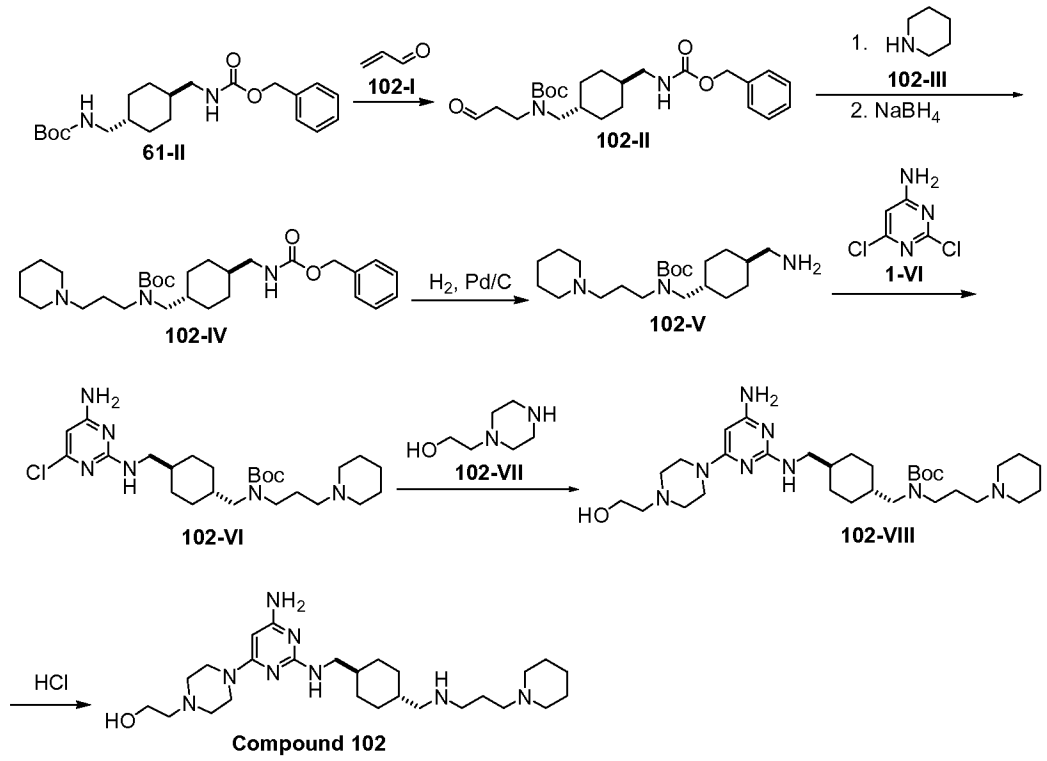
To a solution compound **101-VII** (720 mg) and piperazine (**1-XII**, 1.22 g) in 1-pentanol (10 mL) was added Et_3N (1.43 g) at 25°C. The mixture was stirred at 120°C for 24 hours. TLC showed that the reaction was completed. Ethyl acetate (20 mL) was added at 25°C. The solution was stirred for 1 hour. The Et_3NHCl salt was removed and the solution was concentrated and purified by silica gel (EtOAc/MeOH = 2:8) to afford **101-VIII** (537 mg) in 69% yield.

To a solution of **101-VIII** (537 mg) in MeOH (11 ml) was added diethyl vinyl phosphonate (**2-I,** 201 mg) at 25°C. The mixture was stirred under 65°C for 24 hours. TLC and HPLC showed that the reaction was completed. The solution was concentrated and purified by silica gel (MeOH/CH_2Cl_2 = 1:9) to get **101-IX** (380 mg) in a 57% yield.

To a solution of **101-IX** (210 mg) in CH_2Cl_2 (5 ml) was added TMSBr (312 mg) at 10-15°C for 1 hour. The mixture was stirred at 25°C for 15 hours. The solution was concentrated to remove TMSBr and solvent under vacuum at 40°C, then, CH_2Cl_2 was added to dissolve the residue. Then TMSBr and solvent were further removed under vacuum and CH_2Cl_2 was added for four times repeatedly. The solution was concentrated to get hydrobromide salt of compound **101** (190 mg).

CI-MS (M^+ + 1): 566.9

Example 102: Preparation of compound **102**



Intermediate **61-II** was preared as described in Example 61.

To intermediate **61-II** (1.0 g) and DL-10-camphorsulfonic acid (150 mg) in CH_2Cl_2 (10 ml) was added acrolein (**102-I**, 446 mg) at 0°C. The reaction was stirred

at 25°C for 15 hours. The solution was concentrated and purified by chromatography on silica gel (EtOAc/Hex = 1:1) to give intermediate **102-II** (180 mg) in a 16% yield.

Intermediate **102-II** (1.13 g) and piperidine (**102-III**, 222mg) were dissolved in MeOH (10 mL). The mixture was stirred in 0°C for 3 hours. $NaBH_4$ (119 mg) was added under 0°C and the solution was stirred 1 hour. The solution was concentrated and CH_2Cl_2 was added. The mixture was washed with solution of saturated NH_4Cl (aq) solution. The CH_2Cl_2 layer was concentrated and the residue was purified by chromatography on silica gel (EtOAc/Hex = 1:1) to give intermediate **102-IV** (737 mg) in a 56% yield.

102-IV (737 mg) and Pd/C (10%, 20 mg) in MeOH (10 ml) was stirred under H_2 (1 atm) for 18 hours. Filtration through a celite column and removal of MeOH afforded intermediate **102-V** (580 mg).

A solution of compound **102-V** (580 mg) and Et_3N (480 mg) in 1-pentanol (10 ml) was reacted with 2,4-dichloro-6-aminopyrimidine (**1-VI**, 258 mg) at 120°C for 15 hours. The solution was concentrated and purified by chromatography on silica gel (EtOAc/Hex = 1:2) to give intermediate **102-VI** (420 mg) in 54% yield.

Compound **102-VI** (50 mg) in *N*-(2-hydroxyethyl)piperazine (**102-VII**, 1 ml) was stirred at 120°C for 15 hours. To the mixture was added CH_2Cl_2 (10 ml) at 25°C. The solution was washed with water. After removed of Cl_2CH_2, the residue was purified by chromatography on silica gel (Cl_2CH_2/ MeOH = 9:1) to give intermediate **102-VIII** (15 mg) in a 25% yield.

A solution of HCl in 1,4-dioxane (4N, 2 mL) was added to a solution of intermediate **102-VIII** (15 mg) in CH_2Cl_2 (5.0 mL). The reaction mixture was stirred for 4 hours at room temperature and concentrated by removing the solvent. The resultant residue was washed with ether to afford hydrochloride salt of compound **102** (11 mg).

CI-MS (M^++1): 489.3

Example 103: Preparation of compound **103**

Compound **103** was prepared in the same manner as that described in Example 102 except that 1-(2-morpholinoethyl)-piperazine was used instead of *N*-(2-hydroxyethyl)piperazine.

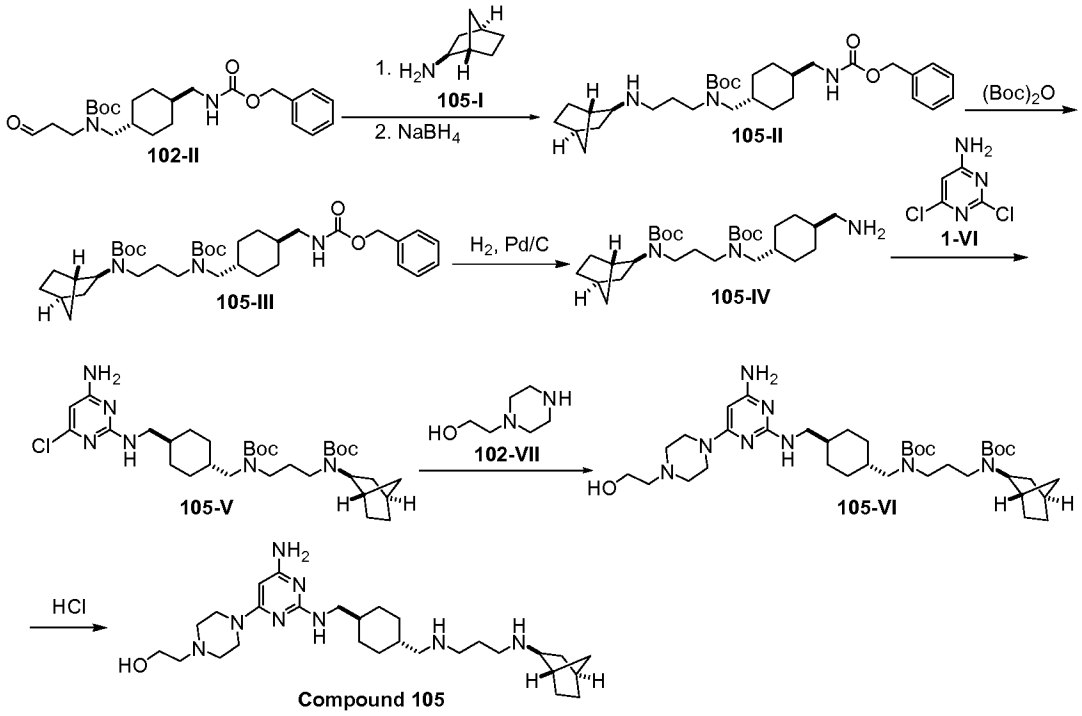
CI-MS (M^++1): 558.5

Example 104: Preparation of compound **104**

Compound **104** was prepared in the same manner as that described in Example 102 except that 1-(2-(2-hydroxyethoxy)ethyl)piperazine was used instead of *N*-(2-hydroxyethyl)piperazine.

CI-MS (M^++1): 533.4

Example 105: Preparation of compound **105**



Intermediate **102-II** was prepared as described in Example 102.

102-II (1000 mg) and *exo*-2-aminonorbornane (**105-I**, 257 mg) in MeOH (10 mL) was stirred at 0°C for 3 hours. $NaBH_4$ (87.5 mg) was then added at 0°C during a period of 1 hour. The solution was concentrated, quenched with NH_4Cl (aq), and extracted with CH_2Cl_2. The organic layers were combined, dried with anhydrous $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (MeOH/28% NH_4OH = 97/3) to afford intermediate **105-II** (1000 mg, 82% yield).

A solution of intermediate **105-II** (1000 mg), Et_3N (210 mg) and Boc_2O (455 mg) in CH_2Cl_2 (10 mL) was stirred at 25°C for 15 hours. The solution was

concentrated and purified by chromatography on silica gel (EtOAcA/ Hexane = 1/1) to afford intermediate **105-III** (907 mg, 76% yield).

A solution of intermediate **105-III** (907 mg) and Pd/C (20 mg) in MeOH (10 mL) was stirred under H_2 (balloon) at 25°C for 18 hours. The filtrate was got by filtration through a celite column and removed MeOH to afford intermediate **105-IV** (740mg).

Et_3N (454 mg) was added to a solution of intermediate **105-IV** (740 mg) and 2,4-dichloro-6-aminopyrimidine (**1-VI**, 246 mg) in 1-pentanol (10 mL). The reaction mixture was stirred at 120°C for 15 hours and concentrated under vacuum. The resultant residue was purified by chromatography on silica gel (EtOAc/ Hexane = 1/2) to afford intermediate **105-V** (420 mg, 45% yield).

A solution of intermediate **105-V** (50 mg) in *N*-(2-hydroxyethyl)piperazine (1 mL) was stirred at 120°C for 15 hours. The reaction was cooled to 25°C and diluted with Cl_2CH_2 (10 mL). The reaction solution was washed with water, dried with anhydrous $MgSO_4$, and concentrated. The residue was purified by chromatography on silica gel (Cl_2CH_2/MeOH = 9/1) to afford intermediate **105-VI** (10mg, 17% yield).

A solution of 4 N HCl in 1,4-dioxane (2 mL) was added to a solution of intermediate **105-VI** (10 mg) in CH_2Cl_2 (5 mL). The reaction mixture was stirred for 4 hours at room temperature and concentrated by removing the solvent. The resultant residue was washed with ether to afford hydrochloride salt of compound **105** (8 mg).

CI-MS (M^++1): 515.4

Example 106: Preparation of compound **106**

Compound **106** was prepared in a manner the same as that descrined in Example 105 except that 1-(2-morpholinoethyl)-piperazine was used instead of *N*-(2-hydroxyethyl)piperazine.

CI-MS (M^++1): 584.5

Example 107: Preparation of compound **107**

Compound **107** was prepared in the same manner as that described in Example 105 except that 1-(2-(2-hydroxyethoxy)ethyl)piperazine was used instead of *N*-(2-hydroxyethyl)piperazine.

CI-MS (M^++1): 559.5

Example 108: Preparation of compound **108**

Compound **108** was prepared in the same manner as that described in Example 105 except that piperazine was used instead of *N*-(2-hydroxyethyl)piperazine.

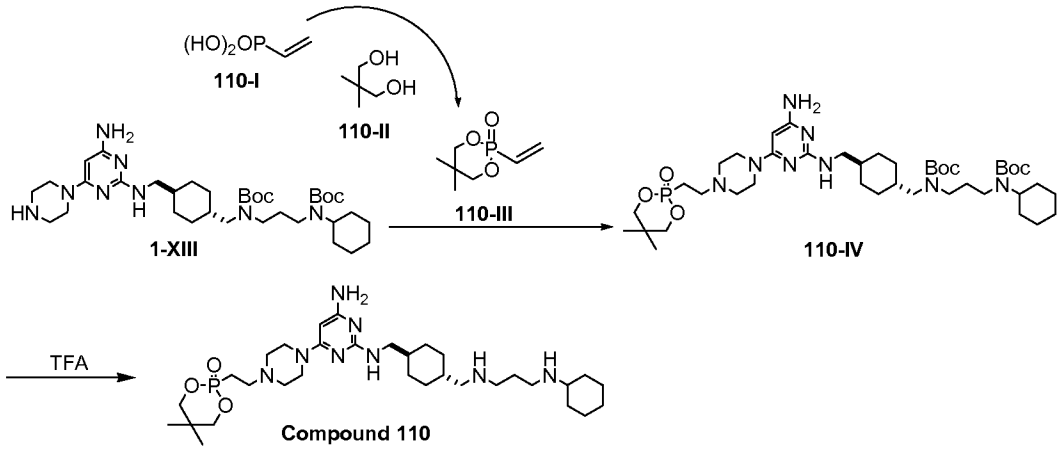
CI-MS (M^++1): 471.4

Example 109: Preparation of compound **109**

Compound **109** was prepared in the same manner as that described in Example 105 except that 1-(2-ethoxyethyl)piperazine was used instead of *N*-(2-hydroxyethyl)piperazine.

CI-MS (M^++1): 543.1

Example 110: Preparation of compound **110**



Intermediate **1-XIII** was prepared as described in Example 1.

To a solution of vinylphosphonic acid (**110-I**, 550 mg) in dry CH_2Cl_2 (17 mL) was slowly added oxalyl chloride (3.9 g) and DMF (0.4 mL) at 0°C. The mixture was refluxed for 3 hours, and concentrated to give quantitatively the corresponding phosphochloridate. The phosphochloridate was added to a mixture of 2,2-dimethyl-1,3-propanediol (**110-II**, 530 mg), dry CH_2Cl_2 (17 mL), and Et_3N (3.1 g) at -70°C. The mixture was slowly warmed to room temperature and stirred at for 15 hours. It was then washed with water. The organic layer was dried ($MgSO_4$), filtered, and evaporated. The residue was purified by column chromatography on silica gel (EtOAc/ MeOH = 9:1) to afford **110-III** (65 mg, 7% yield) as brown oil.

Compound **110-III** (65 mg) was added to a solution of intermediate **1-XIII** (202 mg) in MeOH (4 mL). The solution was stirred at 65°C for 24 hours. The solution was concentrated and the residue was purified by column chromatography on silica gel (CH_2Cl_2/ MeOH = 9:1) to afford intermediate **110-IV** (147 mg) in a 48% yield.

A solution of 20% TFA/CH_2Cl_2 (3 mL) was added to a solution of intermediate **110-IV** (147 mg) in CH_2Cl_2 (2.0 mL). The reaction mixture was stirred for 12 hours at room temperature and concentrated to afford trifluoracetic acid salt of compound **110** (267 mg).

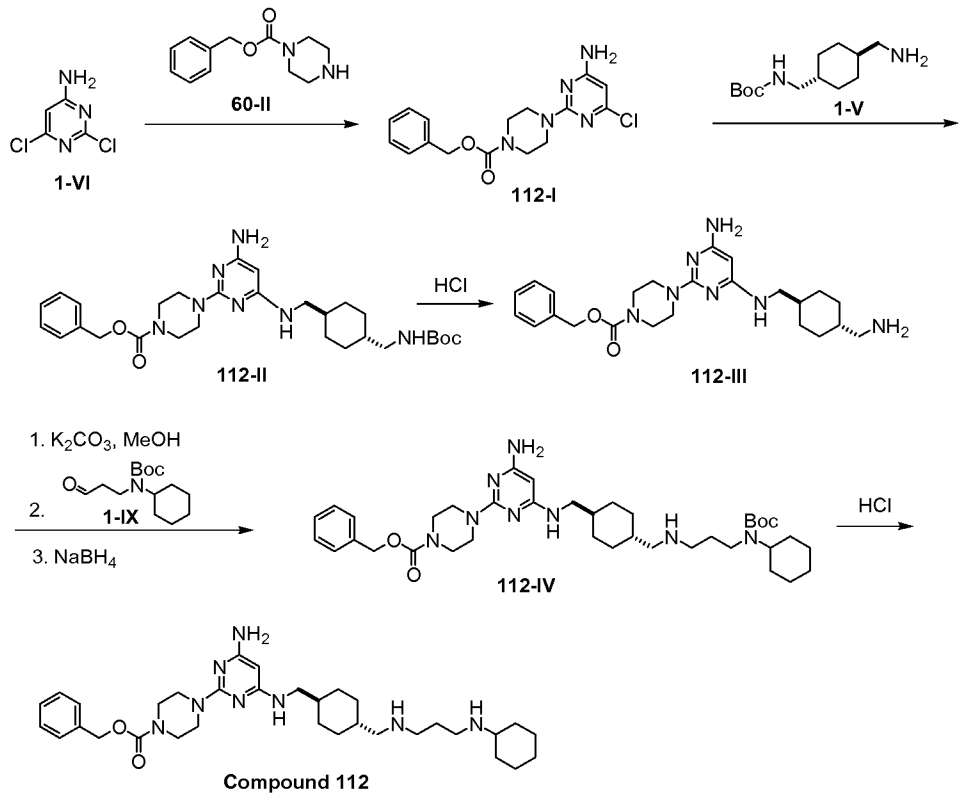
CI-MS (M^++1): 635.4

Example 111: Preparation of compound **111**

Compound **111** was prepared in the same manner as that described in Example 110 except that 2-aminobenzyl alcohol was used instead of 2,2-dimethyl-1,3-propanediol.

CI-MS (M^++1): 654.4

Example 112: Preparation of compound **112**



Intermediate **1-V** was prepared as described in Example 1.

A solution of compound **60-II** (27 g) and Et_3N (37 g, 3 eq) in 1-pentanol (80 mL) was reacted with 2,4-dichloro-6-aminopyrimidine (**1-VI**, 20 g, 1 eq) at 90°C for 15 hours. TLC showed that the reaction was completed. Ethyl acetate (55 mL) was added at 25°C. The solution was stirred for 1 hour. After Et_3NHCl salt was removed, the filtrate was concentrated to 23 mL (1/6 of original volume) at 50°C. Then, diethyl ether (70 mL) was added to the concentrated solution to afford the desired intermediate **112-I** (25 g, 60% yield) after filtration at 25°C.

A solution of intermediate **1-V** (500 mg, 1.2 eq) and *N,N'*-diisopropylethyl amine (DIPEA, 446 mg, 2 eq) and KI (29 mg, 0.1 eq) in 1-pentanol (1.8 mL) was reacted with compound **112-I** (600 mg) at 140°C for 24 hours. The reaction mixture was concentrated under reduced pressure. The residue thus obtained was purified by column chromatography on silica gel ($MeOH/CH_2Cl_2$ = 5/95) to afford intermediate **112-II** (645 mg) in a 67% yield.

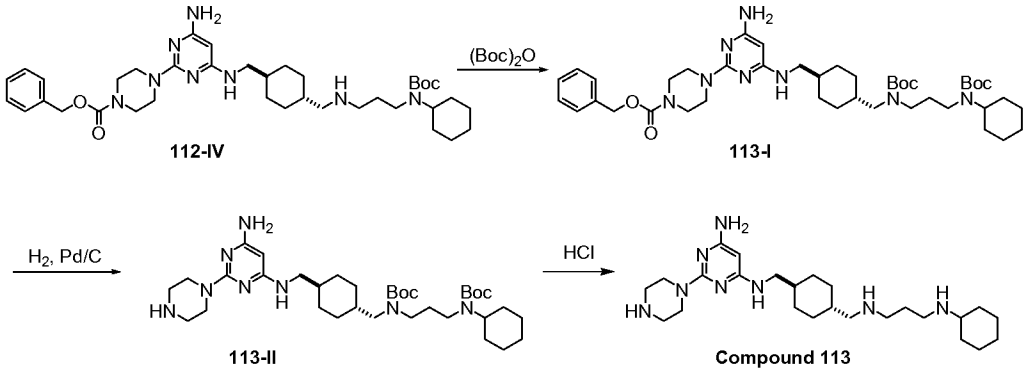
Intermediate **112-II** (645 mg) was treated with 4 N HCl/dioxane (1.7 mL) in MeOH (6.5 mL). The mixture was stirred at room temperature overnight. After ether was added, the solution was filtered. The HCl salt of **112-III** thus obtained was dried under vacuum. To a solution of HCl salt of **112-III** in MeOH (15 mL) was added

K_2CO_3 (1.3 g) at room temperature and stirred for 3 hours (pH > 12). The mixture was filtered. Aldehyde **1-IX** (300 mg, 1.0 eq based on mole of **112-II**) was added to the filtrate of **112-III** at 0-10°C. The reaction was stirred at 0-10°C for 3 hours. TLC showed that the reaction was completed. Then, $NaBH_4$ (70 mg, 1.5 eq based on mole of **112-II**) was added at <10°C. The solution was stirred at 10-15°C for 1 hour and concentrated to provide a residue, which was then treated with CH_2Cl_2 (30 mL). The mixture was washed with saturated NH_4Cl (aq) solution (15 mL). The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (short column, EtOAc as mobile phase for removing other components; MeOH/28% NH_4OH = 97/3 as mobile phase for collecting **112-IV**) to afford intermediate **112-IV** (214 mg) in 30% yield.

A solution of HCl in ether (4 mL) was added to a solution of intermediate **112-IV** (200 mg) in CH_2Cl_2 (1.0 mL). The reaction mixture was stirred for 12 hours at room temperature and concentrated. The resultant residue was washed with ether to afford hydrochloride salt of compound **112** (120 mg).

CI-MS (M^+ + 1): 593.3

Example 113: Preparation of Compound **113**



Intermediate **112-IV** was prepared as described in Example 112.

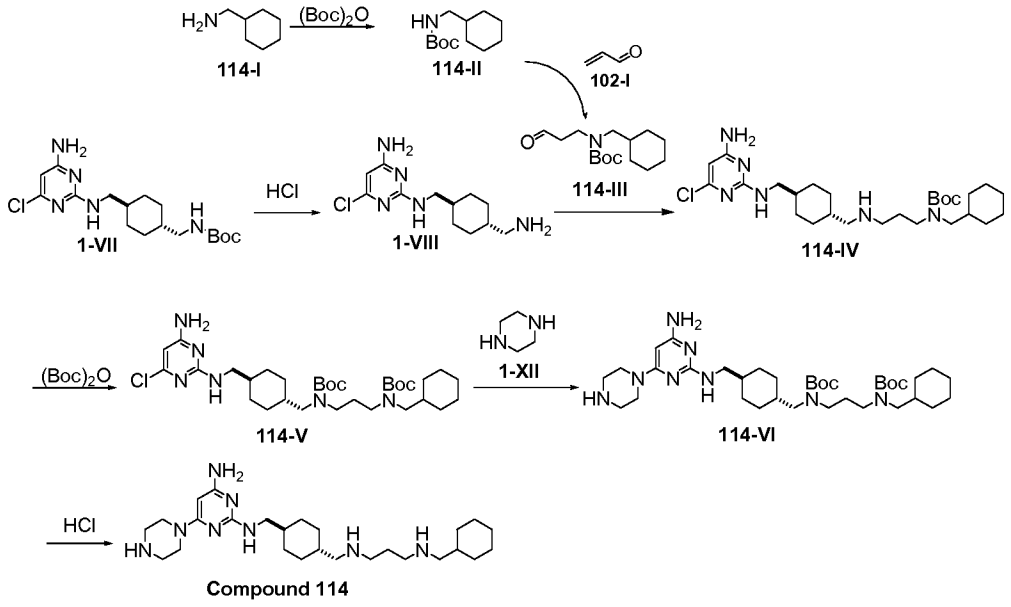
Et_3N (65μL) was added to a solution of intermediate **112-IV** (214 mg) and Boc_2O (81 mg) in CH_2Cl_2 (10 mL) at 25°C. The solution was stirred overnight and then concentrated. The resultant residue was purified by column chromatography on silica gel (EtOAc as an eluant) to give intermediate **113-I** (196 mg) in a 80% yield.

113-I (150 mg) and Pd/C (10%, 20 mg) in MeOH was stirred under H_2 (balloon) at 25°C for 18 hours. The mixture was passed through a celite column. Removal of MeOH afforded intermediate **113-II** (112 mg) in a 90% yield.

A solution of HCl in ether (2 mL) was added to a solution of intermediate **113-II** (100 mg) in CH_2Cl_2 (1.0 mL). The reaction was stirred for 12 hours at room temperature and concentrated. The resultant residue was washed with ether to afford hydrochloride salt of compound **113** (93 mg).

CI-MS (M^+ + 1): 459.4

Example 114: Preparation of Compound **114**



Intermediate **1-VII** was prepared as described in Example 1.

A solution of compound cyclohexylmethanamine (**114-I**, 3.0 g) and Boc_2O (7.7 g) in CH_2Cl_2 (30 mL) was added to Et_3N (5.0 mL) at 25°C for 15 hours. The solution was then concentrated and the resultant residue was purified by column chromatography on silica gel (using EtOAc and Hexane as an eluant) to give intermediate **114-II** (6.5 g) in a 49% yield.

To intermediate **114-I** (3.0 g) and DL-10-camphorsulfonic acid (450 mg) in CH_2Cl_2 (30 ml) was added acrolein (**102-I**, 2.72 g) at 0°C. The reaction was stirred at 25°C for 15 hours. The solution was concentrated and purified by chromatography on silica gel (EtOAc/Hex = 4:1) to give intermediate **114-III** (2.4 g) in a 63% yield.

A solution of intermediate **1-VII** (1.0 g) was treated with 4 N HCl/dioxane (5 mL) in MeOH (20 mL) and stirred at 25°C for 15 hours. TLC showed that the reaction was completed. The mixture was concentrated and HCl salt of **1-VIII** was formed, filtered, and dried under vacuum (<10torr). For neutralization, K_2CO_3 (1.5 g) was added to the solution of HCl salt of **1-VIII** in MeOH (20 mL) at 25°C. The mixture was stirred at the same temperature for 3 hours (pH > 12) and filtered.

Aldehyde **114-III** (728 mg) was added to the filtrate at 0-10 °C. The mixture was stirred at 0-10 °C for 3 hours. TLC showed that the reaction was completed. Then, $NaBH_4$ (103 mg) was added at less than 10°C and the solution was stirred at 10-15°C for 1 h. The solution was concentrated to provide a residue, which was then treated with CH_2Cl_2 (10 mL). The mixture was washed with saturated aq. NH_4Cl solution. The CH_2Cl_2 layer was concentrated and the residue was purified by chromatography on silica gel (short column, EtOAc as mobile phase for removing other components; MeOH/28% NH_4OH = 97/3 as mobile phase for collecting **114-IV**) to afford crude **114-IV** (870 mg).

Et_3N (820 mg) and Boc_2O (470 mg) were added to the solution of **114-IV** (870 mg) in CH_2Cl_2 (10 mL) at 25°C. The mixture was stirred at 25°C for 15 hours. TLC showed that the reaction was completed. The solution was concentrated and purified by chromatography on silica gel (EtOAc/Hex = 1:1) to give intermediate **114-V** (940 g) in a 91% yield.

To compound **114-V** (200 mg) and piperazine (**1-XII**, 116 mg) in 1-pentanol (2 mL) was added Et_3N (194 mg) at 25 °C. The mixture was stirred at 120°C for 8 hours. TLC showed that the reaction was completed. The solution was concentrated and purified by chromatography on silica gel (EtOAc/MeOH = 3:7) to give intermediate **114-VI** (120 mg) in a 56% yield.

A solution of intermediate **114-VI** (120 mg) was treated with 4 N HCl/dioxane (5 mL) in CH_2Cl_2 (10 mL) and stirred at 25°C for 15 hours. The mixture was concentrated to give hydrochloride salt of compound **114** (60 mg).

CI-MS ($M^+ + 1$): 473.4

Example 115: Preparation of compound **115**

Compound **115** was prepared in the same manner as that described in Example 114 except that *N*-(2-hydroxyethyl)piperazine was used instead of piperazine.

CI-MS (M^++1): 517.4

Example 116: Preparation of compound **116**

Compound **116** was prepared in the same manner as that described in Example 114 except that 1-(2-ethoxyethyl)piperazine was used instead of piperazine.

CI-MS (M^++1): 545.4

Example 117: Preparation of compound **117**

Compound **117** was prepared in the same manner as that described in Example 114 except that 1-(2-morpholinoethyl)-piperazine was used instead of piperazine.

CI-MS (M^++1): 586.5

Example 118: Preparation of compound **118**

Compound **118** was prepared in the same manner as that described in Example 114 except that 2-aminoindan was used instead of cyclohexyl-methanamine.

CI-MS (M^++1): 493.4

Example 119: Preparation of compound **119**

Compound **119** was prepared in the same manner as that described in Example 114 except that 2-aminoindan was used instead of cyclohexyl-methanamine.

CI-MS (M^++1): 537.4

Example 120: Preparation of compound **120**

Compound **120** was prepared in the same manner as that described in Example 116 except that 2-aminoindan was used instead of cyclohexyl-methanamine.

CI-MS (M^++1): 565.4

Example 121: Preparation of compound **121**

Compound **121** was prepared in the same manner as that described in Example 117 except that 2-aminoindan was used instead of cyclohexyl-methanamine.

CI-MS (M^++1): 606.4

Example 122: Preparation of compound **122**

Compound **122** was prepared in the same manner as that described in Example 115 except that aniline was used instead of cyclohexyl-methanamine.

CI-MS (M^++1): 497.0

Example 123: Preparation of compound **123**

Compound **123** was prepared in the same manner as that described in Example 114 except that benzylamine was used instead of cyclohexyl-methanamine.

CI-MS (M^++1): 467.1

Example 124: Preparation of compound **124**

Compound **124** was prepared in the same manner as that described in Example 123 except that *N*-(2-hydroxyethyl)piperazine was used instead of piperazine.

CI-MS (M^++1): 511.1

Example 125: Preparation of compound **125**

Compound **125** was prepared in the same manner as that described in Example 123 except that 1-(2-ethoxyethyl)piperazine was used instead of piperazine.

CI-MS (M^++1): 539.0

Example 126: Preparation of compound **126**

Compound **126** was prepared in the same manner as that described in Example 123 except that 1-(2-morpholinoethyl)-piperazine was used instead of piperazine.

CI-MS (M^++1): 580.1

Example 127: Preparation of compound **127**

Compound **127** was prepared in the same manner as that described in Example 114 except that cyclopentylamine was used instead of cyclohexylmethanamine.

CI-MS (M^++1): 445.1

Example 128: Preparation of compound **128**

Compound **128** was prepared in the same manner as that described in Example 115 except that cyclopentylamine was used instead of cyclohexylmethanamine.

CI-MS (M^++1): 489.1

Example 129: Preparation of compound **129**

Compound **129** was prepared in the same manner as that described in Example 116 except that cyclopentylamine was used instead of cyclohexylmethanamine.

CI-MS (M^++1): 517.1

Example 130: Preparation of compound **130**

Compound **130** was prepared in the same manner as that described in Example 117 except that cyclopentylamine was used instead of cyclohexylmethanamine.

CI-MS (M^++1): 558.5

Example 131: Preparation of compound **131**

Compound **131** was prepared in the same manner as that described in Example 128 except that 1-(2-(2-hydroxyethoxy)ethyl)piperazine was used instead of *N*-(2-hydroxyethyl)piperazine.

CI-MS (M^++1): 533.4

Example 132: Preparation of compound **132**

Compound **132** was prepared in the same manner as that described in Example 102 except that pyrrolidine was used instead of piperidine.

CI-MS (M^++1): 475.4

Example 133: Preparation of compound **133**

Compound **133** was prepared in the same manner as that described in Example 114 except that *iso*-propylamine was used instead of cyclohexylmethanamine.

CI-MS (M^++1): 419.1

Example 134: Preparation of compound **134**

Compound **134** was prepared in the same manner as that described in Example 115 except that *iso*-propylamine was used instead of cyclohexylmethanamine.

CI-MS (M^++1): 463.1

Example 135: Preparation of compound **135**

Compound **135** was prepared in the same manner as that described in Example 116 except that *iso*-propylamine was used instead of cyclohexylmethanamine.

CI-MS (M^++1): 491.1

Example 136: Preparation of compound **136**

Compound **136** was prepared in the same manner as that described in Example 117 except that *iso*-propylamine was used instead of cyclohexylmethanamine.

CI-MS (M^++1): 532.1

Example 137: Preparation of compound **137**

Compound **137** was prepared in the same manner as that described in Example 115 except that thiophene-2-methylamine was used instead of cyclohexylmethanamine.

CI-MS (M^++1): 517.4

Example 138: Preparation of compound **138**

Compound **138** was prepared in the same manner as that described in Example 116 except that thiophene-2-methylamine was used instead of cyclohexylmethanamine.

CI-MS (M^++1): 545.4

Example 139: Preparation of compound **139**

Compound **139** was prepared in the same manner as that described in Example 117 except that thiophene-2-methylamine was used instead of cyclohexylmethanamine.

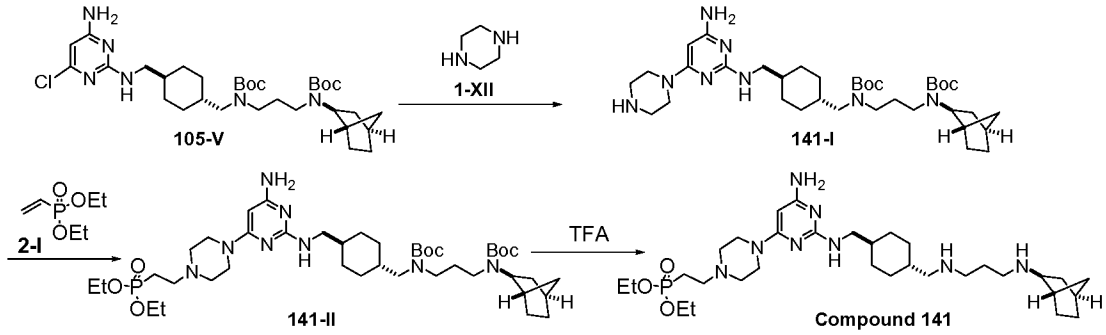
CI-MS (M^++1): 586.4

Example 140: Preparation of compound **140**

Compound **140** was prepared in the same manner as that described in Example 137 except that 1-(2-(2-hydroxyethoxy)ethyl)piperazine was used instead of *N*-(2-hydroxyethyl)piperazine.

CI-MS (M^++1): 561.4

Example 141: Preparation of compound **141**



Intermediate **105-V** was prepared as described in Example 105.

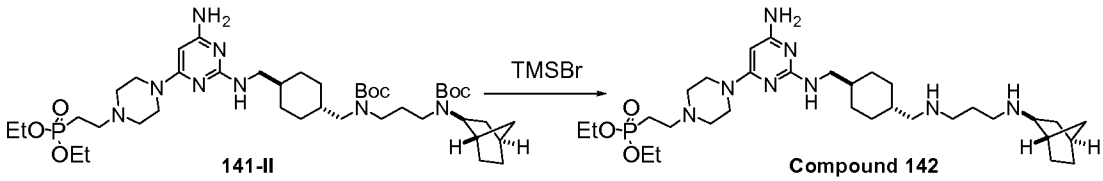
To compound **105-V** (1.7 g) and piperazine (**1-XII**, 1.4 g, 6 eq) in 1-pentanol (30 mL) was added Et_3N (1.66 g, 6.0 eq) at 25°C. The mixture was stirred at 120°C for 15 hours. The solution was concentrated and purified by silica gel (EtOAc/MeOH = 8:2) to afford **141-I** (1.5 g) in a 82% yield.

To a solution of **141-I** (1.5 g) in MeOH (30 mL) was added diethyl vinyl phosphonate (**2-I**, 0.556 g, 1.5 eq) at 25°C. The mixture was stirred under 65°C for 24 hours. TLC and HPLC showed that the reaction was completed. The solution was concentrated and purified by silica gel (MeOH/CH_2Cl_2 = 8/92) to get 1.1 g of **141-II** in a 59% yield.

TFA (0.2 mL) was added to a solution of intermediate **141-II** (100 mg) in CH_2Cl_2 (0.8 mL). The reaction mixture was stirred for 15 hours at room temperature and concentrated by removing the solvent to afford trifluoracetic acid salt of compound **141** (40 mg).

CI-MS (M^+ + 1): 635.4

Example 142: Preparation of compound **142**



Intermediate **141-II** was prepared as described in Example 141.

To a solution of **142-II** (1.0 g) in CH_2Cl_2 (5 mL) was added TMSBr (1.46 g, 8 eq) at 10-15°C for 1 hour. The mixture was stirred at 25°C for 15 hours. The solution was concentrated to remove TMSBr and the solvent under vacuum at 40°C. CH_2Cl_2 was added to the mixture to dissolve the residue. TMSBr and the solvent were removed under vacuum again to obtain a crude solid, which was washed with IPA/MeOH (9/1) to afford compound **142** after filtration and drying at 25°C under vacuum (<1 torr) for 3 hours. Crystallization in EtOH gave hydrobromide salt of compound **142** (530 mg).

CI-MS (M^+ + 1): 579.4

Example 143: Preparation of compound **143**

Compound **143** was prepared in the same manner as that described in Example 141 except that cyclohexylmethanamine was used instead of *exo*-2-aminonorborane.

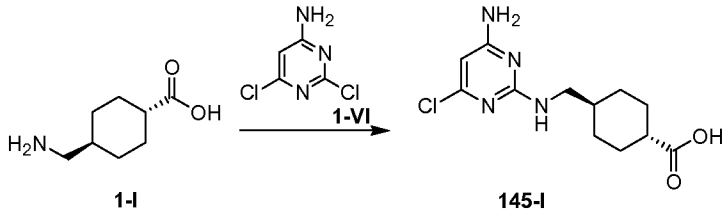
CI-MS (M^++1): 637.5

Example 144: Preparation of compound **144**

Compound **144** was prepared in the same manner as that described in Example 142 except that cyclohexylmethanamine was used instead of *exo*-2-aminonorborane.

CI-MS (M^++1): 581.4

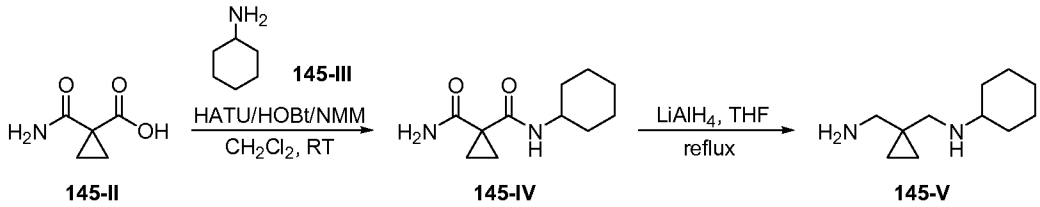
Example 145: Preparation of compound **145-I**



Compound **1-I** (2.11 g, 1.1 eq) and K_2CO_3 (8.5 g, 5 eq) were dissolved in CH_3CN/ H_2O (1:2, 30 mL), and *tetra*-butyl ammonium iodide was added as a catalyst. The mixture was reacted with 2,4-dichloro-6-aminopyrimidine (**1-VI**, 2 g, 1 eq.) at 90°C for 15 hours. The reaction was completed as evidenced TLC. The mixture was evaporated under reduced pressure to remove the organic solvent, and the aqueous layer was acidified with concentrated hydrochloric acid (pH = 4~5) and then filtered. The resultant solid was collected, washed three times with water (15 mL), and dried under vacuum to give compound **145-I** (2.8 g) as a white solid in 80% yield.

CI-MS (M^+ + 1): 285.1

Example 146: Preparation of compound **145-V**



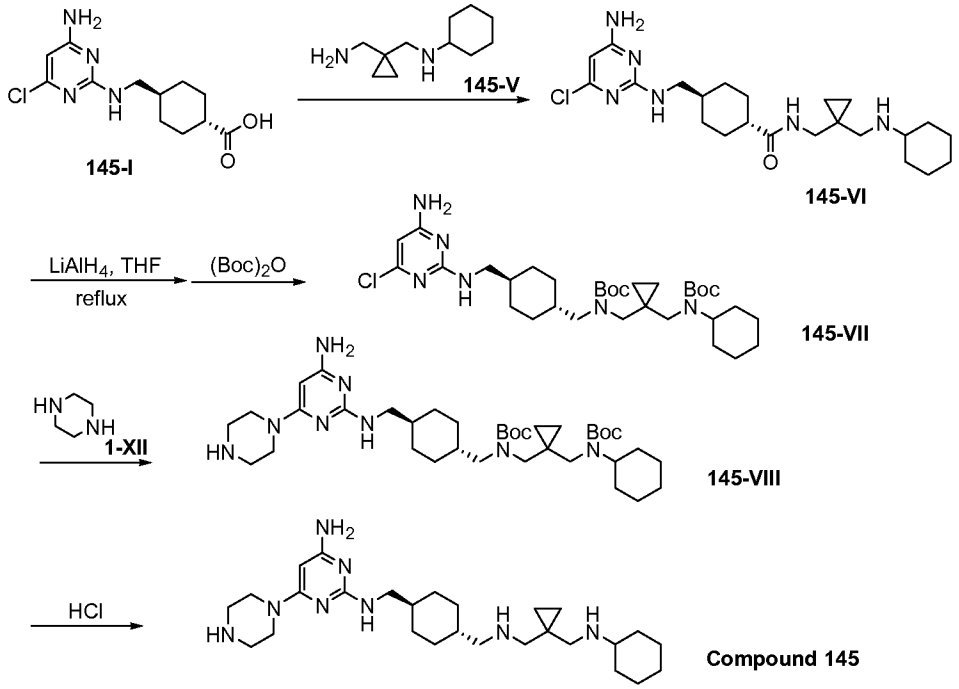
The compound 1-carbamoyl-cyclopropanecarboxylic acid (**145-II**, 5 g, 1eq), *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'-tetra*-methyluronium *hexa*-fluorophosphate (**HATU**, 22.85 g, 1.6 eq), and 1-hydroxybenzotriazole (**HOBt**, 8.12 g, 1.6eq) were suspended in CH_2Cl_2 (150 mL) at an ice-water bath. *N*-methylmorpholine (**NMM**, 16.5 mL, 4eq) and cyclohexyl amine (**145-III**, 5.2 mL, 1.2 eq) were added into the solution at 0~10°C with stirring. After the addition was completed, the reaction mixture was further stirred at room temperature for 15 hours. The reaction was completed as evidenced by TLC.

The mixture was poured into a saturated aqueous NH_4Cl (100 mL) solution. After separation, the organic layer was successively washed with brine and saturated aqueous $NaHCO_3$ (100 mL each), dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/Hexane = 4:1) to afford compound **145-IV** (6.3 g) as an orange oil in 80% yield.

Under nitrogen, $LiAlH_4$ (4.8 g, 4 eq) was added in small portions to a solution of **145-IV** (6.3 g) in anhydrous THF (150 mL), while the temperature was kept between 0°C and 10°C. The mixture was stirred at room temperature for 1 hour and then heated with reflux for another 4 hours. The mixture was cooled and quenched with saturated aqueous NH_4Cl (15 mL) solution at 0°C. It was allowed to warm up to room temperature and stirred for 1 hour. The mixture was filtered through a pad of celite, and the filtrate was concentrated under reduced pressure to give product **145-V** (4.4 g) as a yellow oil in 80% yield.

CI-MS ($M^+ + 1$): 183.1

Example 147: Preparation of compound **145**



The compound **145-I** (3.95 g, 1 eq), HATU (8.44 g, 1.6 eq), and HOBt (3.0 g, 1.6 eq) were suspended in CH_2Cl_2 (55 mL) at an ice-water bath. NMM (6.1 mL, 4eq) and *N*-(1-(aminomethyl)cyclopropyl)cyclohexanamine (**145-V**, 3.1 g, 1.2 eq) were added at 0~10°C with stirring. After the addition was completed, the reaction mixture was further stirred at room temperature for 15 hours. The reaction was completed as evidenced by TLC.

The mixture was poured into a saturated aqueous NH_4Cl (50 mL). After separation, the organic layer was successively washed with brine and saturated aqueous $NaHCO_3$ (50 mL each), dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/MeOH = 7:3) to afford compound **145-VI** (1.5 g) as a yellow oil in 30% yield.

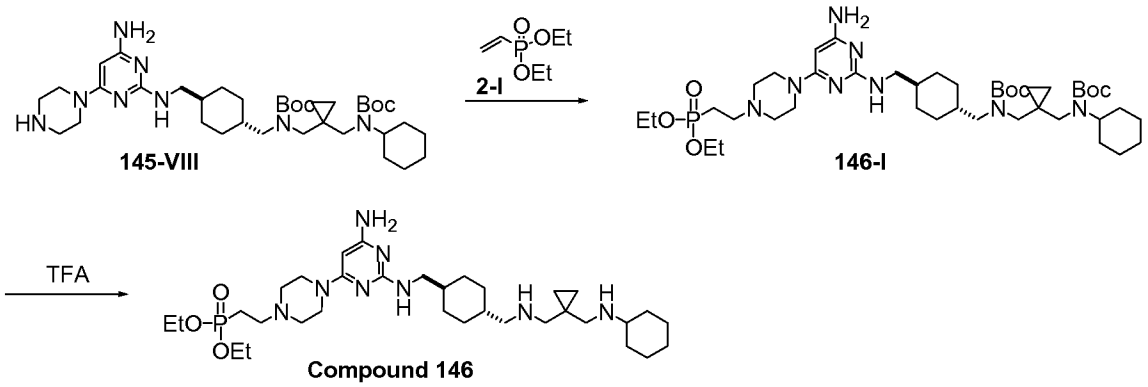
Under nitrogen, $LiAlH_4$ (267 mg, 2 eq) was added in small portions to a solution of **145-VI** (1.5 g) in anhydrous THF (20 mL), while the temperature was kept between 0°C and 10°C. The mixture was stirred at room temperature for 1 hour and then heated with reflux for another 4 hours. It was cooled and quenched with saturated aqueous NH_4Cl (1 mL) solution at 0°C. It was then allowed to warm up to room temperature and stirred for 1 hour. The mixture was filtered through a pad of celite, and then Et_3N (1.0 g, 3 eq) and $(Boc)_2O$ (1.8 g, 2.5 eq) were added to the filtrate at 25°C. After stirred at 25°C for 15 hours, the solution was concentrated and purified by silica gel column chromatography (EtOAc/Hexane = 4:1) to afford compound **145-VII** (940 mg) as a yellow oil in 69% yield.

To compound **145-VII** (940 mg) and piperazine (**1-XII**, 382 mg, 3 eq) in 1-pentanol (3 mL) was added Et_3N (450 mg, 3 eq) at 25°C. The mixture was stirred at 120°C for 8 hours at which time the reaction was completed as evidenced by TLC. Ethyl acetate (5 mL) was added to the reaction mixture at 25°C. The solution was stirred for 1 hour and, after removal of the Et_3NHCl salt by filtration, concentrated and purified by silica gel (EtOAc/MeOH = 7:3) to afford **145-VIII** (570 mg) in 56% yield.

A solution of intermediate **145-VIII** (100 mg) was treated with 4 N HCl/dioxane (2 mL) in CH_2Cl_2 (1 mL) and stirred at 25°C for 15 hours. The reaction was completed as evidenced by TLC. The mixture was concentrated to give hydrochloride salt of compound **145** (55 mg).

CI-MS (M^+ + 1): 485.0

Example 148: Preparation of compound **146**



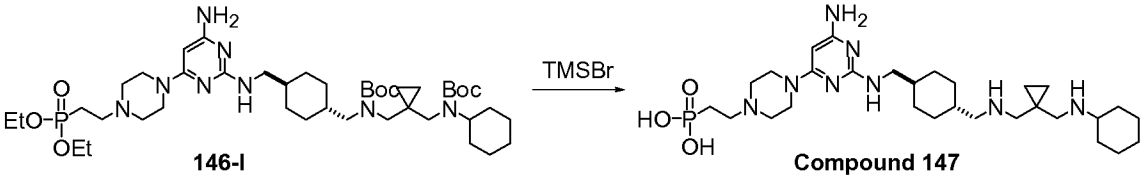
Intermediate **145-VIII** was obtained during the preparation of compound **145**.

To a solution of **145-VIII** (520 mg) in MeOH (8 mL) was added diethyl vinyl phosphonate (**2-I,** 187 mg, 1.5 eq) at 25°C. The mixture was stirred at 65°C for 24 hours. The reaction was completed as evidenced by TLC. The solution was concentrated and purified by silica gel (MeOH/CH_2Cl_2 = 8/92) to afford compound **146-I** (317 mg) as a pale yellow foamy solid in 50% yield.

A solution of 20% TFA/CH_2Cl_2 (2 mL) was added to a solution of intermediate **146-I** (100 mg) in CH_2Cl_2 (1 mL). The reaction mixture was stirred for 15 hours at room temperature and concentrated by removing the solvent to afford trifluoracetic acid salt of compound **146** (80 mg).

CI-MS (M^+ + 1): 649.3

Example 149: Preparation of compound **147**



Intermediate **146-I** was obtained during the preparation of compound **146**.

To a solution of **146-I** (200 mg) in CH_2Cl_2 (1 mL) was added TMSBr (0.3 mL, 8 eq) at 10~15°C for 1 hour. The mixture was stirred at 25°C for 15 hours and then concentrated to remove TMSBr and the solvent under vacuum at 40°C. CH_2Cl_2 was

added to dissolve the residue. The mixture was vacuumed again to obtain hydrobromide salt of compound **147** (150 mg).

CI-MS ($M^+ + 1$): 593.3

Example 150: Preparation of compound **148**

Compound **148** was prepared in the same manner as that described in Example 112 except that 1-(2-morpholinoethyl)-piperazine was used instead of compound **60-II**.

CI-MS (M^++1): 572.5

Example 151: Preparation of compound **149**

Compound **149** was prepared in the same manner as that described in Example 112 except that *N*-(2-hydroxyethyl)piperazine was used instead of compound **60-II**.

CI-MS (M^++1): 503.4

Example 152: Preparation of compound **150**

Compound **150** was prepared in the same manner as that described in Example 112 except that 1-(2-(2-hydroxyethoxy)ethyl)piperazine was used instead of compound **60-II**.

CI-MS (M^++1): 547.4

Example 153: GTP-binding assay

Compounds 1-150 were tested for their efficacy in binding to the CXCR4 receptor using a DELFIA GTP-binding kit (Wallac Oy, Turku, Finland). The DELFIA GTP-binding assay is a time-resolved fluorometric assay based on GDP-GTP exchange on G-protein subunits followed by activation of a G protein-coupled receptor by its agonist. Eu-GTP, a non-hydrolysable analogue of GTP, is used to monitor agonist-dependent activation of G-protein. Note that stimulation of CXCR4 receptor by SDF-1 leads to replacement of GDP by GTP on the α-subunit of G-protein. The resultant GTP-Gα complex represents the activated form of G-protein. See Peltonen et al., Eur. J. Pharmacol. (1998) 355:275.

Plasma membrane derived from CXCR4-expressing HEK293 cells was suspended in an assay buffer (50 mM NaCl, 100 mg/mL saponin, 3 mM $MgCl_2$, 3 mM GDP, 5% BSA, 50 mM HEPES, pH 7.4). An aliquot (4 μg protein) was added to each well of an AcroPlate (Pall Life Sciences, Ann Arbor, MI). After addition of test compounds (10 mM in 0.1% DMSO) and SDF-1 (4 nM in the assay buffer), the assay plate was incubated in the dark at room temperature with slow shaking for 10 minutes. Eu-GTP, obtained from Wallac Oy Eu-GTP, was added to each well. The plate was incubated again for 60 minutes and then washed twice with a wash solution provided in the assay kit to terminate the assay. Binding of Eu-GTP was determined based on the fluorescence signal detected by a Victor 2 multi-label reader.

Unexpectedly, 28 test compounds showed IC_{50} (concentration required to inhibit SDF-1 stimulated GTP-Gα binding by 50%) at 20 nM, 83 test compounds showed IC_{50} between at nM, 37 test compounds showed IC_{50} at 100-1000 nM.

Example 154: Radioligand binding assay

Binding competition between each of 114 test compounds and human SDF-1 was determined using glass fiber filter plates (Millipore, Billerica, MA) as follows:

The glass fiber filter plates were pre-coated with 90 μl of 0.2% polyethyleneimine for 30 minutes and rinsed with 100 μl of distilled water for four times to reduce non-specific binding. Membranes of human CXCR4-transfected HEK293 cells (5-10 μg protein/well) in 70 μl of assay buffer (50 mM HEPES, pH 7.4, 0.5% bovine serum albumin, 90 mM NaCl, 5 mM $MgCl_2$, 1 mM $CaCl_2$) were incubated with 20 μl of a test compound and 10 μl of [^{125}I]-SDF-1 (final concentration 150 pM) in U-bottom assay plates (Corning, Corning, NY). After 120 minutes at room temperature, the incubation was terminated by transferring the reaction mixture to glass fiber plate wells (80 μl/well) and filtered by vacuum filtration (MultiScreen Vacuum Maniford, Millipore). The plate was washed 4 times with 80 μl/well of wash buffer (20 mM HEPES, pH 7.4 and 90 mM NaCl) and then air dried overnight. After 35 μl of a Supermix cocktail was added to each well of plate, the radioactivity retained on the plate was counted with Trilux MicroBeta (PerkinElmer, Boston, MA).

50 test compounds showed IC_{50} (concentration required to inhibit binding of [^{125}I]-SDF-1 to the receptor by 50%) at less than 20 nM, 43 test compounds showed IC_{50} at 20-100 nM, and 21 test compounds showed IC_{50} at 100-1000 nM.

Example 155: Stem cell mobilization

The efficacy of five compounds in enhancing stem cell mobilization was tested as follows:

Each compound was dissolved in saline. The solutions were each administered to BALB/c mice intravenously at 4 ml/kg. Whole blood was collected 1, 2, 3, 6, 18, and 24 hours after intravenous injection by cardiac puncture. Mice receiving saline were used as control. Blood samples of the same group (N = 3 in each group) were pooled and total leukocyte numbers were counted using trypan blue exclusion. Hematopoietic stem cells ($CD34^+$) and endothelial progenitor cells ($CD133^+$) were measured using antibody surface staining and flow cytometry (Beckman Coulter, Miami, FL). Statistical significance was determined using a one-way ANOVA. Differences were considered significant if *P* values were <0.05.

The results indicated that all of the test compounds enhanced mobilization of $CD34^+$ hematopoietic stem cells and $CD133^+$ endothelial progenitor cells into peripheral blood in a dose-dependent manner. Within 13 hours after a single injection, the compounds increased circulating $CD34^+$ cells up to 6.2-14.5 folds and $CD133^+$ cells up to 5.2-10.7 folds.

Example 156: Synergistic effect in mobilization of stem cells and endothelial progenitor cells

The efficacy of G-CSF alone and a combination of G-CSF and a test compound in mobilizing stem cells and endothelial progenitor cells was also tested in a manner similar to that described in Example 129. The results indicate that the combination exerted synergistic effect in enhancing $CD34^+$ and $CD133^+$ mobilization. Circulating $CD34^+$ was increased to up to about 18.5 folds and circulating $CD133^+$ up to about 64.2 folds.

Example 157: Oxygen-induced retinopathy (diabetic retinopathy model)

Newborn rats were placed under air containing 50% oxygen and air containing 10% oxygen alternately in a cycle of 24 hours from birth through 14 days to induce robust retinal angiogenesis. These rats were used as a diabete retinopathy model.

A test compound was dissolved in water. The solutions at the concentrations of 0.1-10 μM were administered to the rats via intravitreal injection (2 μl/eye). Oxygen-induced retinopathy rats without injection of any test compound or injected with vehicle were used as control. All of the rats were then placed under normal air for six days before sacrifice. Neovascularization was assessed using ADPase histochemistry and computer-assisted image analysis techniques.

The results indicate that the test compound effectively inhibited retinal neovascularization.

Example 158: Choroidal neovascularization (age-related macular degeneration model)

Choroidal neovascularization (CNV) was generated by laser-induced rupture of Bruch's membrane in 4- to 6-week-old, male C57BL/6J mice. With a hand-held cover slide as a contact lens, an argon laser photocoagulator (532 nm) mounted on a slit-lamp was used to create four lesions centered around the optic nerve head in the retinal mid-periphery (50 μm spot size, 0.07 sec duration, 260 mW). A test compound was dissolved in water. The solutions at the concentrations of 1 to 100 μM were administered to the CNV mice via intravitreal injection (1 or 2 μl/eye) immediately following laser treatment. CNV mice without treatment of test compounds were used as controal. Fourteen days after the laser treatment, all of the mice were sacrificed and CNV growth at the Bruch's membrane rupture sites was assessed using fluorescently stained choroid-sclera-RPE flat-mounts via computer-assisted image analysis.

The results indicate that the test compound reduced the neovascularization area by 34%-59%, compared with control.

Example 159: Limb ischemia model

The efficacy of three compounds in treating ischemia was tested using a limb ischemia model.

Ischemia was induced in the left hindlimb of each BALB/c mouse as follows: The femoral artery was ligated and transected in two places of 0.20-0.30 cm length proximal and distal to the ligature. Any other large blood vessels that were visible and distal to the ligature were also transected.

Each compound was dissolved in saline and administrated intravenously to the limb ischemia mice on day 4 and day 8 post-surgery at the dosage ranging from 0.5 mg/kg to the maximum tolerated dose. The contralateral right hindlimbs and mice receiving saline were used as control. The animals were observed using two semiquantitative ischemia indexes three times each week. The extent of blood-flow restoration was measured on days 1, 7, 14, 21, and 28 post-surgery using a laser Doppler imager (PeriScan PIM II), which detects the flux (blood/(area×time)) of blood. In addition, the muscle strength was measured using a Digital Grip Strength Meter (0167-005L, Columbus Instruments) new vessel formation in leg muscles collected immediately after sacrifice on day 18 post-surgery was assessed. For capillary density analysis, CD31 immunohistochemistry staining was performed. Positive stained newly-formed endothelial cells in 10 fields were counted under microscopy, and the data presented as positive cells/per high power field. Statistical signgicance was determined using one-way ANOVA. Differences were considered significant if P values were <0.05.

All of the test compounds exhibited efficacy in improving hindlimb function, appearance, and muscle strength, restoring blood flow, and increasing formation of new vessel.

OTHER EMBODIMENTS

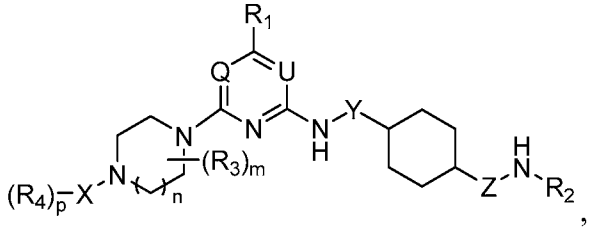
All of the features disclosed in this specification may be combined in any combination. Each feature disclosed in this specification may be replaced by an alternative feature serving the same, equivalent, or similar purpose. Thus, unless expressly stated otherwise, each feature disclosed is only an example of a generic series of equivalent or similar features.

From the above description, one skilled in the art can easily ascertain the essential characteristics of the present invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to

adapt it to various usages and conditions. Thus, other embodiments are also within the scope of the following claims.

WHAT IS CLAIMED IS:

1. A compound of the following formula:



wherein

each Q and U is CH or N, provided that at least one of Q and U is N;

each of X, Y, and Z, independently, is C_{1-5} alkylene or deleted;

m is 0, 1, 2, 3, 4, or 5;

n is 0, 1 or 2;

p is 1 or 2;

R_1 is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, heteroaryl, halo, CN, OR_a, $COOR_a$, $OC(O)R_a$, $C(O)R_a$, $C(O)NR_aR_b$, or NR_aR_b;

R_2 is C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, heteroaryl, or C_1-C_{10} alkyl, optionally substituted with C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, or $N(R_cR_d)$;

R_3, independently, is C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, heteroaryl, halo, CN, OR_e, $COOR_e$, $OC(O)R_e$, $C(O)R_e$, $C(O)NR_eR_f$, or NR_eR_f; or R_3 is C_{1-5} alkylene bonded to two carbon atoms of the ring to which it is attached or C_{2-8} alkylene bonded to one carbon atom of the ring to which it is attached; and

R_4 is $P(=O)(OR_g)(OR_i)$, $P(=O)(NHR_g)(OR_i)$, $P(=O)(NR_g)(NR_i)$, $S(=O)_2OR_g$, or $S(=O)_2R_g$;

in which each of R_a, R_b, R_c, R_d, R_e, R_f, R_g and R_i, independently, is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, heteroaryl, or -C(O)R, R being H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, or heteroaryl; or R_a and R_b are linked and together form C_{2-8} alkylene, R_c and R_d are linked and together form C_{2-8} alkylene, R_e and R_f are linked and together form C_{2-8} alkylene, or R_g and R_i are linked and together form C_{1-5} alkylene.

2. The compound of claim 1, wherein Q is CH or N and U is N.

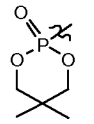
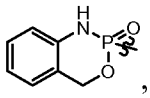
3. The compound of claim 1, wherein X is $-CH_2-$, $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$ and p is 1.

4. The compound of claim 1, wherein Y is $-CH_2$ or deleted and Z is $-CH_2-$.

5. The compound of claim 1, wherein R_2 is C_{1-5} alkyl substituted $N(R_cR_d)$.

6. The compound of claim 5, wherein R_2 is $-CH_2CH_2CH_2-N(R_cR_d)$, in which R_c is H and R_d is C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, or heteroaryl, or R_c and R_d are linked and together form C_{4-6} alkylene.

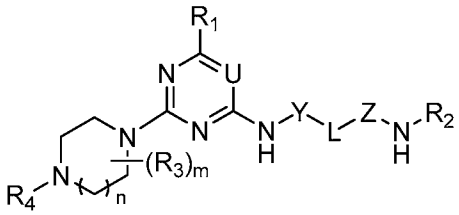
7. The compound of claim 1, wherein m is 0, 1, or 2; n is 1 or 2; R_1 is NH_2; and R_3 is C_1-C_3 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 heterocycloalkyl, aryl, heteroaryl, halo, CN, OR_e, or $C(O)NR_eR_f$; or R_3 is C_{1-2} alkylene bonded to two carbon atoms of the ring to which it is attached or C_{2-5} alkylene bonded to one carbon atom of the ring to which it is attached.

8. The compound of claim 1, wherein R_4 is $P(=O)(OH)_2$, $P(=O)(OH)(OCH_2CH_3)$, $P(=O)(OCH_2CH_3)_2$,  ,  , $S(=O)_2OH$, $S(=O)_2CH_3$, or $S(=O)_2Ph$.

9. The compound of claim 8, wherein m is 0, 1, or 2; n is 1; p is 1; X is $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$; Y is $-CH_2$ or deleted and Z is $-CH_2-$; R_1 is NH_2; R_2 is C_{1-5} alkyl substituted $N(R_cR_d)$; and R_3 is C_1-C_3 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 heterocycloalkyl, aryl, heteroaryl, halo, CN, OR_e, or $C(O)NR_eR_f$; or R_3 is C_{1-2} alkylene bonded to two carbon atoms of the ring to which it is attached or C_{2-5} alkylene bonded to one carbon atom of the ring to which it is attached.

10. The compound of claim 1, wherein the compound is selected from the groups consisting of compounds 2-4, 14-19, 21-57, 62, 63, 74, 75, 78-98, 101, 110, 111, 141-144, 146, and 147.

11. A compound of the following formula:



,

wherein

U is CH or N,

L is C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, or heteroaryl;

each of Y and Z, independently, is C_{1-5} alkylene or deleted;

m is 0, 1, 2, 3, 4, or 5;

n is 0, 1 or 2;

R_1 is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, heteroaryl, halo, CN, OR_a, $COOR_a$, $OC(O)R_a$, $C(O)R_a$, $C(O)NR_aR_b$, or NR_aR_b;

R_2 is C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, heteroaryl, or C_1-C_{10} alkyl, optionally substituted with C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, or $N(R_cR_d)$;

R_3 is C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, heteroaryl, halo, CN, OR_e, $COOR_e$, $OC(O)R_e$, $C(O)R_e$, $C(O)NR_eR_f$, or NR_eR_f; or R_3 is C_{1-5} alkylene bonded to two carbon atoms of the ring to which it is attached or C_{2-8} alkylene bonded to one carbon atom of the ring to which it is attached; and

R_4 is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, heteroaryl, OR_g, $COOR_g$, $C(O)R_g$, or $C(O)NR_gR_i$;

in which each of R_a, R_b, R_c, R_d, R_e, R_f, R_g and R_i, independently, is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, heteroaryl, or -C(O)R, R being H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, or heteroaryl; or R_a and R_b are linked and together form C_{2-8} alkylene, R_c and R_d are linked and together form C_{2-8} alkylene, R_e and R_f are linked and together form C_{2-8} alkylene, or R_g and R_i are linked and together form C_{2-8} alkylene.

12. The compound of claim 11, wherein U is N.

13. The compound of claim 11, wherein Y is -CH_2 or deleted and Z is -CH_2-.

14. The compound of claim 11, wherein R_2 is C_{1-5} alkyl substituted $N(R_cR_d)$.

15. The compound of claim 14, wherein R_2 is -$CH_2CH_2CH_2$-$N(R_cR_d)$, in which R_c is H and R_d is C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, or heteroaryl, or R_c and R_d are linked and together form C_{4-6} alkylene.

16. The compound of claim 15, wherein m is 1 or 2; n is 1 or 2; L is cyclohexyl; R_1 is NH_2; R_3 is C_1-C_3 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 heterocycloalkyl, aryl, heteroaryl, halo, CN, OR_e, or $C(O)NR_eR_f$; or R_3 is C_{1-2} alkylene bonded to two carbon atoms of the ring to which it is attached or C_{2-5} alkylene bonded to one carbon atom of the ring to which it is attached; and R_4 is H or C_1-C_3 alkyl optionally substituted with OR_g, CO_2R_g, NR_gR_i, $P(=O)(OR_g)(OR_i)$, $P(=O)(NHR_g)(OR_i)$, $P(=O)(NR_g)(NR_i)$, $S(=O)_2OR_g$, or $S(=O)_2R_g$; in which each of R_g and R_i, independently, is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, heteroaryl, or -C(O)R, R being H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, or heteroaryl; or R_g and R_i are linked and together form C_{1-5} alkylene.

17. The compound of claim 11, wherein the compound is selected from the groups consisting of compounds 60-100, 112, 113, and 148-150.

18. A method for treating a medical condition related to CXCR4, comprising administering to a subject in need thereof an effective amount of a compound of claim 1, wherein the condition is inflammatory or immune disease, a developmental or degenerative disease, or tissue injury.

19. The method of claim 18, wherein the medical condition is diabetic retinopathy, proliferative retinopathy, age-related macular degeneration, macular edema, corneal neovascularization, or iris neovascularization.

20. The composition of claim 19, wherein the composition is formulated as eye drop, ointment, injectable fluid, microparticles, or sustained release form.

21. The method of claim 18, wherein the medical condition is brain injury, nerve injury, heart injury, liver damage, skeletal muscle injury, kidney damage, pancreatic injury, lung injury, skin injury, limb ischemia, silent ischemia, cardiac ischemia, or gastrointestinal tract injury.

22. The method of claim 18, wherein the medical condition is Type I diabetes mellitus.

23. The method of claim 18, further comprising administering to the subject an effective amount of a G-CSF growth factor.

24. A method for treating cancer, comprising administering to a subject in need thereof an effective amount of a compound of claim 1 and an effective amound of a chemotherapeutic agent.

25. A method for treating a medical condition related to CXCR4, comprising administering to a subject in need thereof an effective amount of a compound of claim 11, wherein the condition is inflammatory or immune disease, a developmental or degenerative disease, or tissue injury.

26. The method of claim 25, wherein the medical condition is diabetic retinopathy, proliferative retinopathy, age-related macular degeneration, macular edema, corneal neovascularization, or iris neovascularization.

27. The method of claim 25, wherein the medical condition is brain injury, nerve injury, heart injury, liver damage, skeletal muscle injury, kidney damage, pancreatic injury, lung injury, skin injury, limb ischemia, silent ischemia, cardiac ischemia, or gastrointestinal tract injury.

28. The method of claim 25, wherein the medical condition is Type I diabetes mellitus.

29. The method of claim 25, further comprising administering to the subject an effective amount of a G-CSF growth factor.

30. A method for treating cancer, comprising administering to a subject in need thereof an effective amount of a compound of claim 11 and an effective amound of a chemotherapeutic agent.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2008/082202

A. CLASSIFICATION OF SUBJECT MATTER

C07D 403/04(2006.01)i, C07D 403/02(2006.01)i

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)

IPC 8 as above

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

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

eKIPASS(KIPO internal), PubMed, NCBI, Esp@snet, PAJ, USPTO, Google

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2006-293324 A1 (FISH & RICHARDSON PC) Dec. 28, 2006 See pages 1-60	1-17
X	US 2006-281712 A1 (FISH & RICHARDSON PC) Dec. 14, 2006 See pages 1-58	1-17
A	WO 2001-047897 A1 (PHARMACOPEIA, INC) July 5, 2001 See page 3, formula I	1-17
A	EP 834507 A1 (JANSSEN PHARMACEUTICA N.V.) Aug. 4, 1998 See the abstract and formula (I)	1-17
A	WO 1998-024782 A2 (AMGEN INC.) June 11, 1998 See page 6, formula I	1-17

☐ 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 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	Date of mailing of the international search report
29 MAY 2009 (29.05.2009)	**29 MAY 2009 (29.05.2009)**
Name and mailing address of the ISA/KR Korean Intellectual Property Office Government Complex-Daejeon, 139 Seonsa-ro, Seo-gu, Daejeon 302-701, Republic of Korea Facsimile No. 82-42-472-7140	Authorized officer YANG, In Soo Telephone No. 82-42-481-5049

Form PCT/ISA/210 (second sheet) (July 2008)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2008/082202

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.: 18-30
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 18-30 pertain to methods for treatment of the human body by therapy, as well as diagnostic methods, and thus relate to a subject matter which this International Searching Authority is not required to search under PCT Article 17(2)(a)(i) and Rule 39.1(iv).

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.:
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:

1. ☐ As all required addtional 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 an additional fee, this Authority did not invite payment of any additional fee.

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.:

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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2008/082202

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2008/082202

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