Pyrimidine Compounds

CROSS REFERENCE TO RELATED APPLICATIONS

Pursuant to 35 USC § 119(e), this application claims priority to U.S. Provisional Application Serial No. 60/690,267, filed June 14, 2005, and U.S. Provisional Application Serial No. 60/798,596, filed May 8, 2006, the contents of which are 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. Take CXCR4 receptor for example, it can be activated by Stromal-derived factor-1 or SDF-1, a member of CXC chemokines.

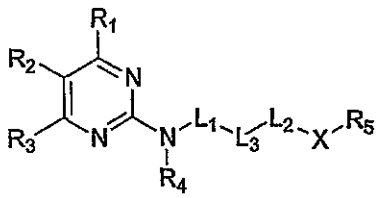
SDF-1 was originally cloned from bone marrow stromal cell lines and found to act as a growth factor for progenitor B cells (Nishikawa et al., Eur. J. Immunol., (1988) 18:1767). SDF-1 also induces bone marrow colonization of hematopoietic precursor cells during embryogenesis (Bleul et al., J. Exp. Med., (1996) 184:1101). 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). CXCR4 receptor and SDF-1 are also found widely expressed in many tissues during embryonic development. 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 pyrimidine compounds are effective in treating inflammatory and immune diseases (e.g., retinopathy), developmental or degenerative diseases, or tissue injuries through their binding to chemokine receptors (e.g., CXCR3 or CXCR4 receptors). In addition, these compounds, when used in combination with G-CSF growth factor, exhibited synergistic effects in stem cells and endothelial progenitor cells mobilization.

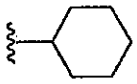
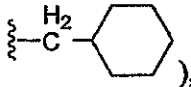
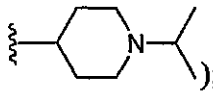
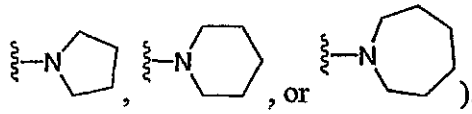
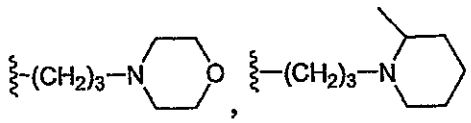
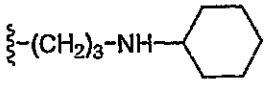
In one aspect, this invention features pyrimidine compounds of formula (I) and their salts:

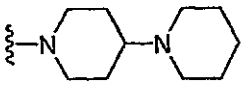
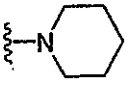
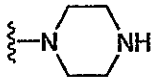
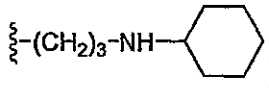


(I).

In this formula, X is $-N(R_a)-$ or $-O-$; or X, together with R_5, is C_3-C_{20} heterocycloalkyl; or X, together with L_2 and L_3, is C_3-C_{20} heterocycloalkyl; each of L_1 and L_2, independently, is C_1-C_{10} alkylene, C_1-C_{10} heteroalkylene, -C(O)-, or deleted; or L_1, together with L_3, R_4, and the nitrogen attached to R_4, is C_3-C_{20} heterocycloalkyl, or L_2, together with L_3 and X, is C_3-C_{20} heterocycloalkyl; L_3 is $-N(R_b)-$, -O-, aryl, heteroaryl, or C_3-C_{20} cycloalkyl; or L_3, together with L_1, R_4, and the nitrogen attached to R_4, is C_3-C_{20} heterocycloalkyl; or

L_3, together with L_2 and X, is C_3-C_{20} heterocycloalkyl; each of R_1, R_2, and R_3, independently, is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_3-C_{20} heterocycloalkyl, aryl, heteroaryl, halo, CN, OR_c, $COOR_c$, $OC(O)R_c$, $C(O)R_c$, $C(O)NR_cR_d$, or NR_cR_d; R_4 is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_3-C_{20} heterocycloalkyl, aryl, or heteroaryl; and R_5 is C_3-C_{20} cycloalkyl, C_3-C_{20} heterocycloalkyl, aryl, heteroaryl, or C_1-C_{10} alkyl substituted with C_3-C_{20} cycloalkyl, C_3-C_{20} heterocycloalkyl, or $N(R_eR_f)$; or R_5, together with X, is C_3-C_{20} heterocycloalkyl; 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_3-C_{20} heterocycloalkyl, aryl, heteroaryl, or -C(O)R; R being H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_3-C_{20} heterocycloalkyl, aryl, or heteroaryl.

Referring to formula (I), a subset of the pyrimidine compounds described above are those in which X can be $-N(R_a)-$, each of L_1 and L_2, independently, can be C_1-C_{10} alkylene, -C(O)-, or deleted; and L_3 can be $-N(R_b)-$, -O-, aryl, or C_3-C_{20} cycloalkyl. As one example, in certain pyrimidine compounds, L_3 is $-N(R_b)-$. In these compounds, R_5 can be C_3-C_{20} cycloalkyl (e.g., ), C_1-C_{10} alkyl substituted with C_3-C_{20} cycloalkyl (e.g., ), or C_3-C_{20} heterocycloalkyl substituted with C_1-C_{10} alkyl (e.g., ); R_b can be C_1-C_{10} alkyl substituted with N(R'R''), in which each of R' and R'', independently, is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_3-C_{20} heterocycloalkyl, aryl, or heteroaryl; and R_1 can be C_3-C_{20} heterocycloalkyl (e.g., ). As another example, in certain pyrimidine compounds, L_3 can be aryl (e.g., phenylene). In these compounds, R_5 can be C_1-C_{10} alkyl substituted with C_3-C_{20} heterocycloalkyl (e.g., ) or C_1-C_{10} alkyl substituted with $N(R_eR_f)$ (e.g., ); or R_5, together with X, is

C_3-C_{20} heterocycloalkyl (e.g., ). R_3 can be H, halo C_1-C_{10} alkyl, OR_c, NR_cR_d, or C_3-C_{20} heterocycloalkyl optionally substituted with C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_3-C_{20} heterocycloalkyl, aryl, OR', C(O)R', COOR', C(O)N(R'R''), SO_2R', C(S)N(R'R''), OSO_3R', or $PO(OR')_2$, in which each of R' and R'', independently, is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_3-C_{20} heterocycloalkyl, aryl, or heteroaryl. For example, R_3 can be H, Cl, CH_3, OPh, ,  optionally substituted with OH,  optionally substituted with C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_3-C_{20} heterocycloalkyl, aryl, OH, C(O)R', COOR', C(O)N(R'R''), SO_2R', C(S)N(R'R''), OSO_3R', $PO(OR')_2$, or NH(R') substituted with OH or NHC(O)R''. As another example, in certain pyrimidine compounds, L_3 can be C_3-C_{20} cycloalkyl (e.g., cyclohexylene). In these compounds, R_5 can be C_1-C_{10} alkyl substituted with $N(R_eR_f)$ (e.g., ) and R_3 can be C_3-C_{20} heterocycloalkyl substituted with C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_3-C_{20} heterocycloalkyl, aryl, OR', C(O)R', COOR', C(O)N(R'R''), SO_2R', or C(S)N(R'R''), in which each of R' and R'', independently, is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_3-C_{20} heterocycloalkyl, aryl, or heteroaryl.

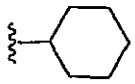
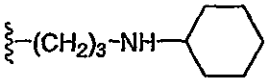
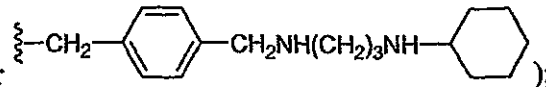
The term "alkyl" refers to a saturated or unsaturated, linear or branched hydrocarbon moiety, such as $-CH_3$, $-CH_2-CH=CH_2$, or branched $-C_3H_7$. The term "alkylene" refers to a divalent, saturated or unsaturated, linear or branched hydrocarbon moiety, such as $-CH_2-$ or -CH=CH-. The term "heteroalkylene" refers to an alkylene moiety having at least one heteroatom (e.g., N, O, or S). The term "cycloalkyl" refers to a saturated or unsaturated, non-aromatic, cyclic hydrocarbon moiety, such as cyclohexyl or cyclohexen-3-yl. The term "heterocycloalkyl" refers to a saturated or unsaturated, non-aromatic, cyclic moiety having at least one ring heteroatom (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,

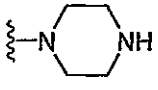
O, or S). Examples of heteroaryl moieties include furyl, furylene, fluorenyl, pyrrolyl, thienyl, oxazolyl, imidazolyl, thiazolyl, pyridyl, pyrimidinyl, quinazolinyl, quinolyl, isoquinolyl and indolyl.

Alkyl, alkylene, heteroalkylene, 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_3-C_{20} heterocycloalkyl, C_3-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, alkylene, or heteroalkylene 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.

In another aspect, this invention features pyrimidine compounds of formula (I) shown above in which X is $-N(R_a)-$ or $-O-$; each of L_1 and L_2, independently, is C_1-C_{10} alkylene, C_1-C_{10} heteroalkylene, -C(O)-, or deleted; L_3 is $-N(R_b)-$, C_3-C_{20} cycloalkyl, aryl, heteroaryl, or deleted; R_1 is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, aryl, heteroaryl, halo, CN, OR_c, $COOR_c$, $OC(O)R_c$, $C(O)R_c$, $C(O)NR_cR_d$, or NR_cR_d; each of R_2 and R_3, independently, is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_3-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; and each of R_4 and R_5, independently, is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_3-C_{20} heterocycloalkyl, aryl, or heteroaryl; or R_4 and R_5 together are C_1-C_{10} alkylene or C_1-C_{10} heteroalkylene; 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_3-C_{20} heterocycloalkyl, aryl, or heteroaryl; or a salt thereof.

Referring to formula (I), a subset of the just-described pyrimidine compounds are those in which X is $-N(R_a)-$; each of L_1 and L_2, independently, is C_1-C_{10} alkylene; L_3 is deleted; R_1 is NR_cR_d; each of R_2 and R_3, independently, is H, C_1-C_{10} alkyl, halo, or C_3-C_{20} cycloalkyl; and each of R_4 and R_5, independently, is H or C_3-C_{20} cycloalkyl; or R_4 and R_5 together are C_1-C_{10} alkylene or C_1-C_{10} heteroalkylene. In these compounds, R_5

can be , or R_4 and R_5 together can be $-CH_2CH_2-$; one of R_c and R_d can be C_1-C_{10} alkyl substituted with N(RR') or aryl, in which each of R and R', independently, is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_3-C_{20} heterocycloalkyl, aryl, or heteroaryl (e.g., one of R_c and R_d being  or );

R_3 can be  substituted with C_1-C_{10} alkyl, which is in turn substituted with C_3-C_{20} heterocycloalkyl or OR, R being H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_3-C_{20} heterocycloalkyl, aryl, or heteroaryl.

In still another aspect, this invention features a method for treating an inflammatory or immune disease, a developmental or degenerative disease, or a tissue injury. The method includes administering to a subject in need thereof an effective amount of one or more pyrimidine compounds of formula (I) shown above.

The term "treating" or "treatment" refers to administering one or more pyrimidine compounds to a subject, who has an above-described disease, a symptom of such a disease, or a predisposition toward such a disease, with the purpose to confer a therapeutic effect, e.g., to cure, relieve, alter, affect, ameliorate, or prevent the above-described disease, the symptom of it, or the predisposition toward it.

An inflammatory disease is characterized by a local or systemic, acute or chronic inflammation. Examples include 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 or ILD, idiopathic pulmonary fibrosis, and ILD associated with rheumatoid arthritis), asthma, and allergic rhinitis.

An immune disease is characterized by a hyper- or hypo-reaction of the immune system. Examples include autoimmune diseases (e.g., rheumatoid arthritis, psoriatic arthritis, systemic lupus erythematosus, myasthenia gravis, juvenile onset diabetes,

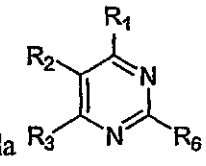
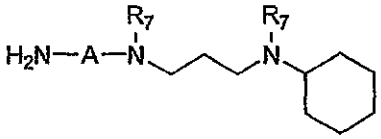
glomerulonephritis, autoimmune throiditis, ankylosing spondylitis, systemic sclerosis, and multiple sclerosis), acute and chronic inflammatory diseases (e.g., systemic anaphylaxia or hypersensitivity responses, drug allergies, insect sting allergies, graft rejection, including allograft rejection, and graft-versus-host disease), Sjogren's syndrome, human immunodeficiency virus infection, cancer (e.g., brain, breast, prostate, colon, kidney, ovary, thyroid, lung, and haematopoietic cancer), and tumor metastasis.

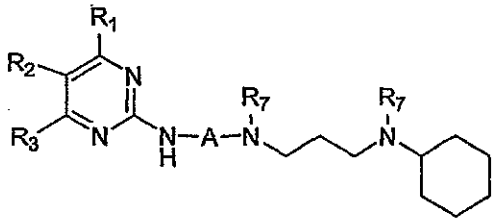
Developmental diseases are growth or differentiation related disorders that lead to loss-of-function or gain-of-function. Degenerative diseases generally refer to change of a tissue to a lower or less functional form. Examples of a developmental or degenerative disease include spinal muscular atrophy, 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, heart injury, liver damage, skeletal muscle injury, kidney damage, pancreatic injury, lung injury, skin injury, and gastrointestinal tract injury.

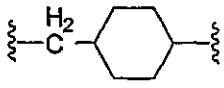
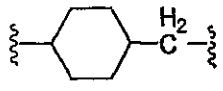
A subject in need of treatment of an above-described disease can also be concurrently administered with a pyrimidine compound described above and one or more other therapeutic agents. Examples of such a therapeutic agent include a G-CSF growth factor, a steroidal or a non-steroidal anti-inflammatory drug, a COX2 inhibitor, a leukotriene receptor inhibitor, a prostaglandin modulator, a TNF modulator, and an immunosuppressive agent (e.g., cyclosporine A). The term "concurrently administered" refers to administering a pyrimidine compound and one or more other therapeutic agents at the same time or at different times during the period of treatment.

In still another aspect, this invention features 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 pyrimidine 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,

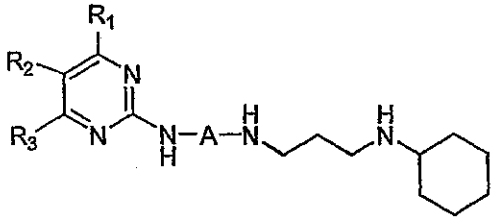
CD34+ cells and CD133+ cells. Preferrably, bone marrow-derived cells are stem cells or endothelial progenitor cells.

In still another aspect, this invention features a chemical synthetic method. The method includes reacting a compound of the formula  with a compound of the formula  to give a compound of formula (II):

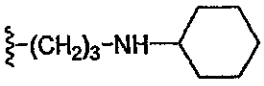
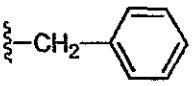
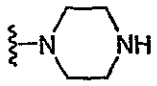


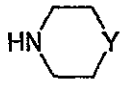
(II). In this formula, A is phenylene, cyclohexylene, , or ; each of R_1, R_2, and R_3, independently, is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_3-C_{20} heterocycloalkyl, aryl, heteroaryl, halo, CN, OR_a, $COOR_a$, $OC(O)R_a$, $C(O)R_a$, $C(O)NR_aR_b$, or NR_aR_b; R_6 is halo; and R_7 is a amino-protecting group (e.g., t-butoxycarbonyl, benzyloxycarbonyl, acetyl, phenylcarbonyl, or trialkylsilyl); in which each of R_a and R_b, independently, is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_3-C_{20} heterocycloalkyl, aryl, heteroaryl, or -C(O)R; R being H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_3-C_{20} heterocycloalkyl, aryl, or heteroaryl.

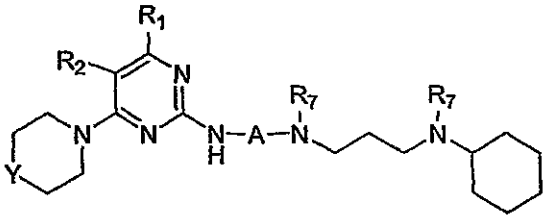
The method can further include deprotecting the compound of formula (II) to give a compound of formula (III):



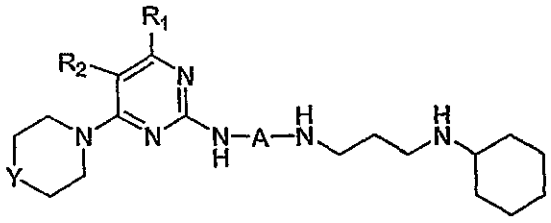
(III). In a subset of compounds of formula (III), R_1 is $N(R_aR_b)$, in which R_a and R_b, independently, is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_3-C_{20} heterocycloalkyl, aryl, or heteroaryl. In these

compounds, one of R_a and R_b can be  or . In another subset of compounds of formula (III), R_3 is  optionally substituted with C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_3-C_{20} heterocycloalkyl, or aryl.

Referring to formula (II), when R_3 is halo, a compound of formula (II) can further react with a compound of the formula  to give a compound of formula (IV):

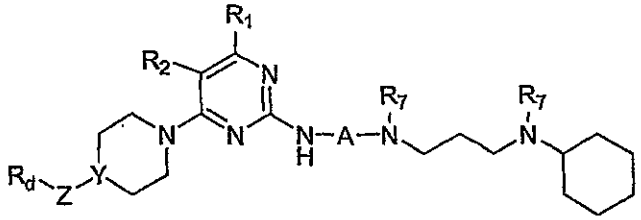


(IV). In this formula, Y is -O-, $-CH_2-$, or $-N(R_c)-$, in which R_c is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_3-C_{20} heterocycloalkyl, aryl, heteroaryl, or halo. The compound of formula (IV) can be deprotected to give a compound of formula (V):

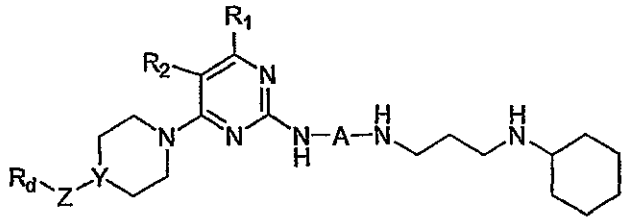
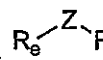
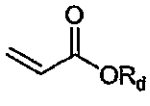


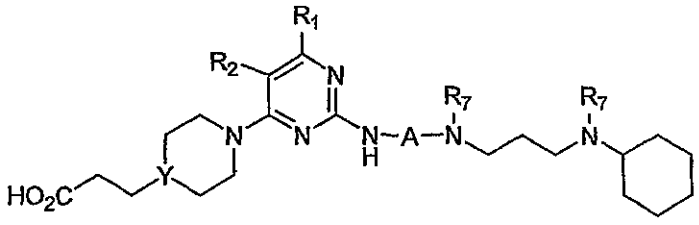
(V).

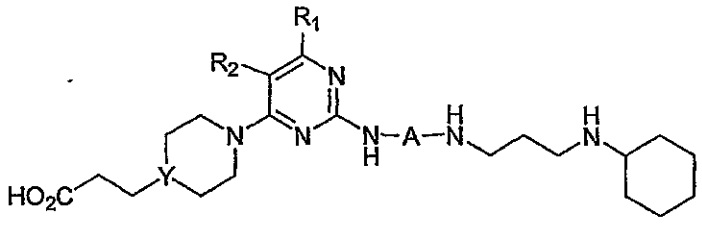
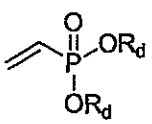
Referring to formula (IV), when Y is NH, a compound of formula (IV) can further react with a compound of the formula  to give a compound of formula (VI):

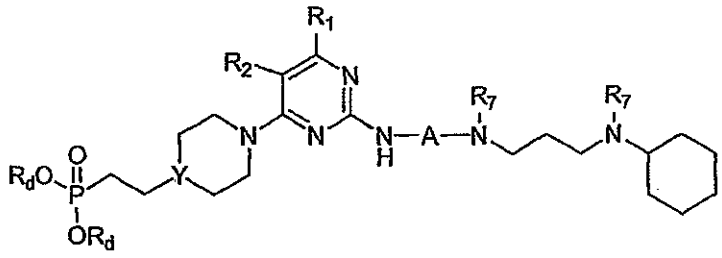


(VI), in which Z is $-CH_2-$ or $-C(O)-$; R_d is C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_3-C_{20} heterocycloalkyl, aryl, or heteroaryl; and R_e is halo. The compound of formula (VI) can be deprotected to give a compound of

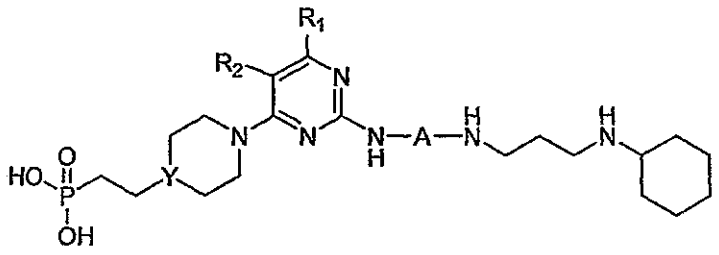
formula (VII):  (VII). As another example, when Y is NH, a compound of formula (IV) can further react with a compound of the formula  to give an imine compound, followed by reducing the imine compound to give a compound of formula (VI).. In the formula , Z is -C(O)-; R_d is C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_3-C_{20} heterocycloalkyl, aryl, or heteroaryl; and R_e is H. As another example, when Y is NH, a compound of formula (IV) can further react with a compound of the formula  to give an ester compound, followed by hydrolyzing the ester compound to give a compound of formula (VIII):

 (VIII), in which R_d is C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_3-C_{20} heterocycloalkyl, aryl, or heteroaryl. The compound of formula (VIII) can be deprotected to give a compound of formula (IX):

 (IX). As a further example, when Y is NH, a compound of formula (IV) can further react with a compound of the formula  to give a compound of formula (X):

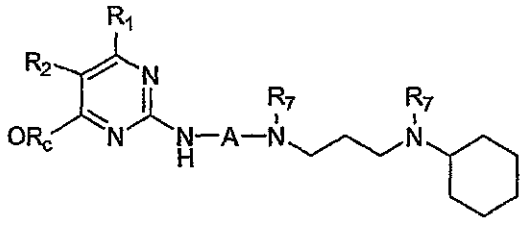


(X), in which R_d is C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_3-C_{20} heterocycloalkyl, aryl, or heteroaryl. The compound of formula (X) can be deprotected to give a deprotected compound, followed by hydrolyzing the deprotected compound to give a compound of formula (XI):

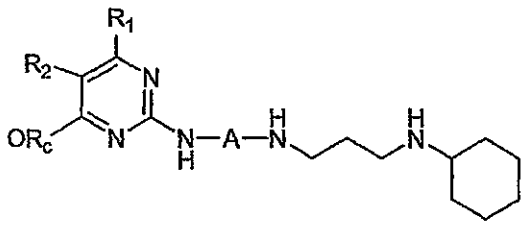


(XI).

Referring to formula (II), when R_3 is halo, a compound of formula (II) can further react with a compound of the formula R_cOH to give a compound of formula (XII):

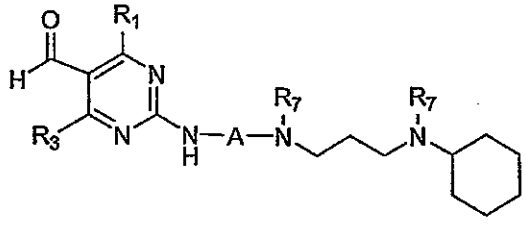


(XII), in which R_c is C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_3-C_{20} heterocycloalkyl, aryl, or heteroaryl. The compound of formula (XII) can be deprotected to give a compound of formula (XIII):

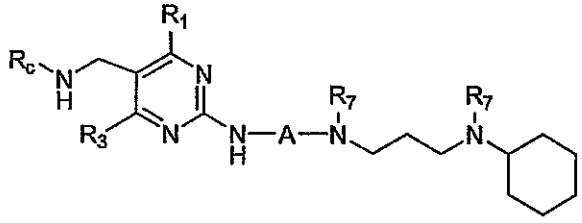


(XIII).

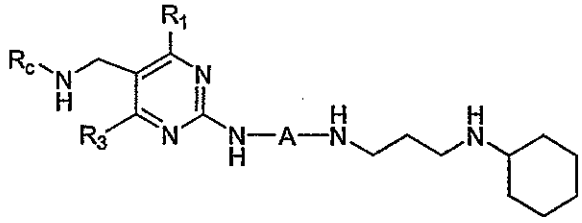
Referring to formula (II), when R_2 is CN, the compound of formula (II) can be reduced to give a compound of formula (XIV):



(XIV). The compound of formula (XIV) can further react with a compound of the formula R_cNH_2 to give an imine compound, followed by reducing the imine compound to give a compound of formula (XV):

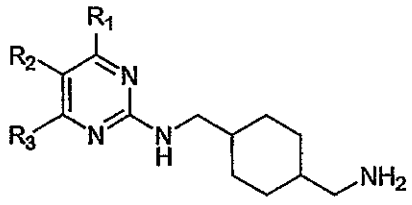


(XV), in which R_c is C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_3-C_{20} heterocycloalkyl, aryl, or heteroaryl. The compound of formula (XV) can be deprotected to give a compound of formula (XVI):

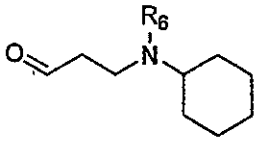


(XVI).

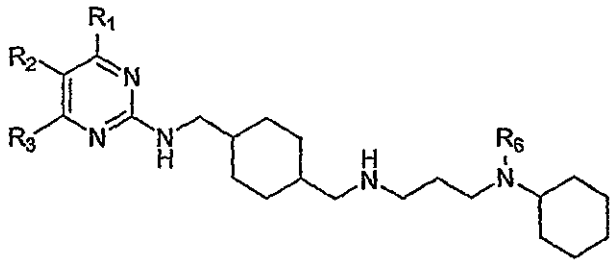
In a further aspect, the invention features a chemical synthetic method that includes reacting a compound of the formula



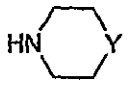
with a compound of the formula



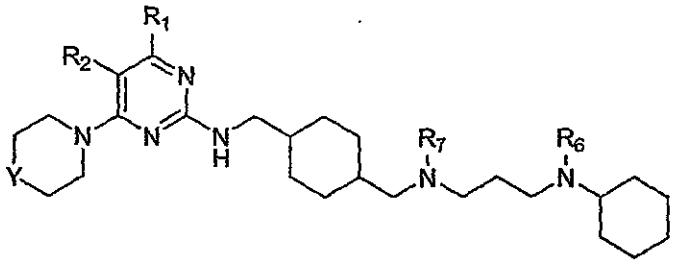
to give a compound of formula (XVII):



(XVII). In formula (XVII), each of R_1 and R_2, independently, is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_3-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_3 is halo; and R_6 is a amino-protecting group; in which each of R_a and R_b, independently, is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_3-C_{20} heterocycloalkyl, aryl, heteroaryl, or -C(O)R; R being H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_3-C_{20} heterocycloalkyl, aryl, or heteroaryl. The method can further include protecting the compound of formula (XX), followed by reacting the protected compound of formula (XVII) with a compound of the formula

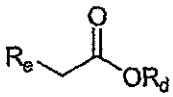


to give a compound of formula (XVIII):

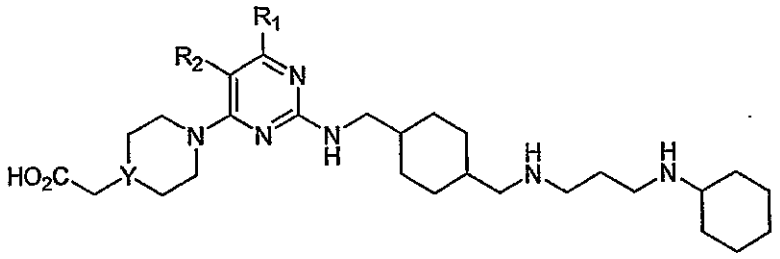


(XVIII). In formula (XVIII), R_7 is a amino-protecting group; and Y is -O-, $-CH_2-$, or $-N(R_c)-$, in which R_c is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_3-C_{20} heterocycloalkyl, aryl, heteroaryl, or halo.

Referring to formula (XVIII), when Y is NH, the method can further include: (1) reacting the compound of formula (XVIII) with a compound of the formula



to give an ester compound; (2) hydrolyzing the ester compound to give an acid compound; and (3) deprotecting the acid compound to give a compound of formula



(XIX): (XIX), in which R_d is C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_3-C_{20} heterocycloalkyl, aryl, or heteroaryl; and R_e is halo.

In addition, this invention encompasses a pharmaceutical composition that contains an effective amount of at least one of the above-mentioned pyrimidine compounds and a pharmaceutically acceptable carrier.

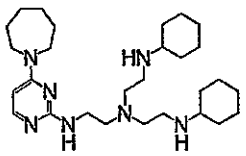
The pyrimidine compounds described above include the compounds themselves, as well as their salts, prodrugs, and solvates, if applicable. A salt, for example, can be formed between an anion and a positively charged group (e.g., amino) on a pyrimidine compound. Suitable anions include chloride, bromide, 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 pyrimidine compound. Suitable cations include sodium ion, potassium ion, magnesium ion, calcium ion, and an ammonium cation such as tetramethylammonium ion. The pyrimidine 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 pyrimidine compounds. A solvate refers to a complex formed between an active pyrimidine compound and a pharmaceutically acceptable solvent. Examples of pharmaceutically acceptable solvents include water, ethanol, isopropanol, ethyl acetate, acetic acid, and ethanolamine.

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

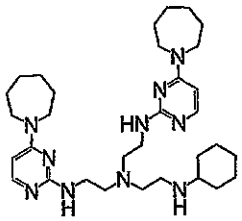
The details of one or more embodiments of the invention are set forth in the description below. Other features, objects, and advantages of the invention will be apparent from the description and from the claims.

DETAILED DESCRIPTION

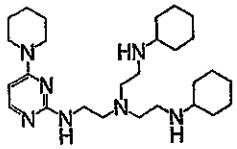
Shown below are exemplary compounds, compounds 1-268, of this invention:



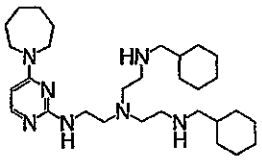
Compound 1



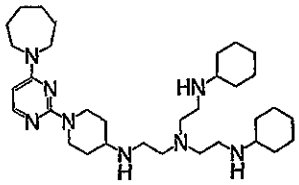
Compound 2



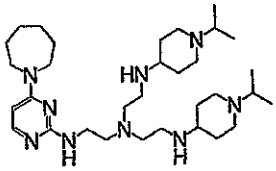
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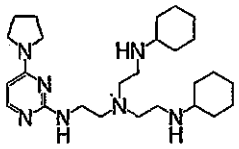
Compound 4



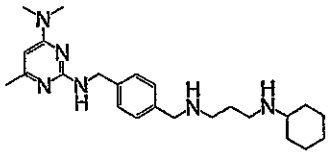
Compound 5



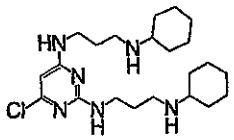
Compound 6



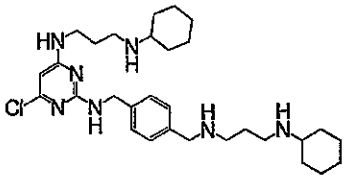
Compound 7



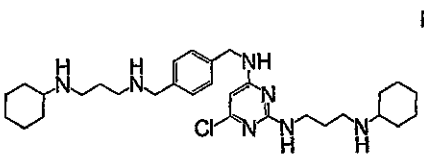
Compound 8



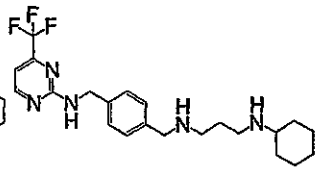
Compound 9



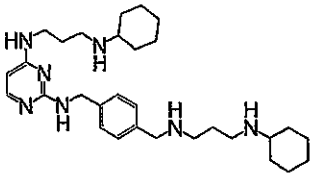
Compound 10



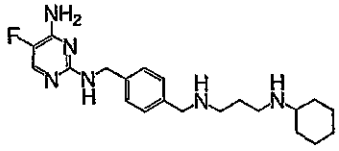
Compound 11



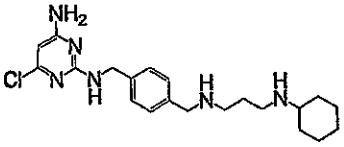
Compound 12



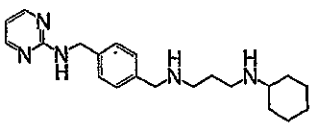
Compound 13



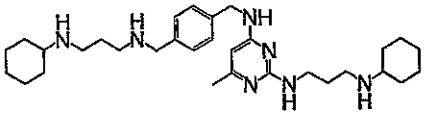
Compound 14



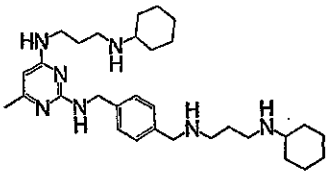
Compound 15



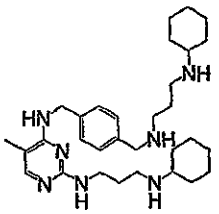
Compound 16



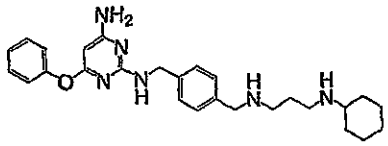
Compound 17



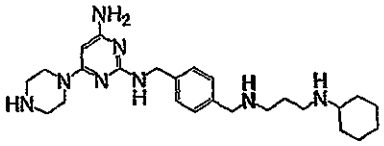
Compound 18



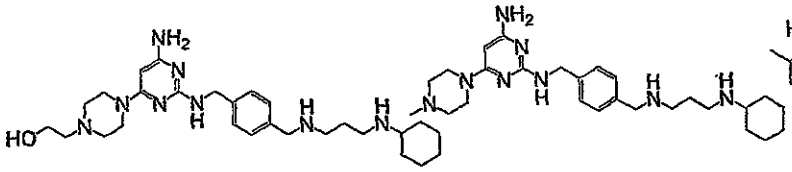
Compound 19



Compound 20

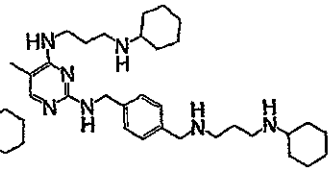


Compound 21

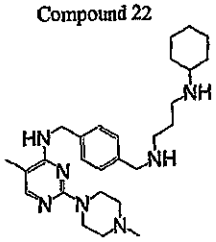


Compound 22

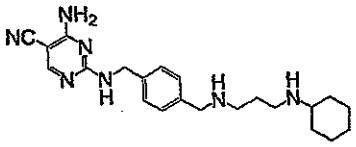
Compound 23



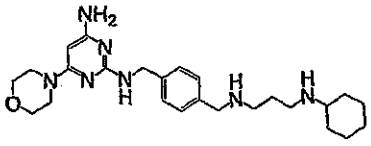
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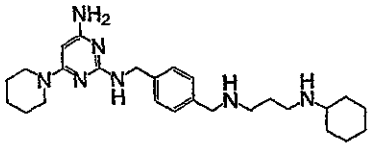
Compound 25



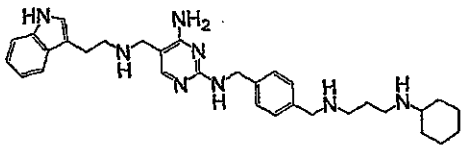
Compound 26



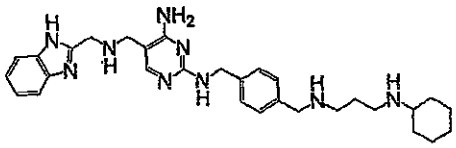
Compound 27



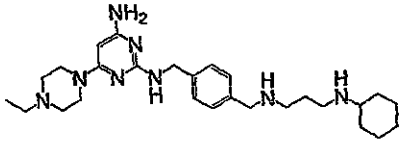
Compound 28



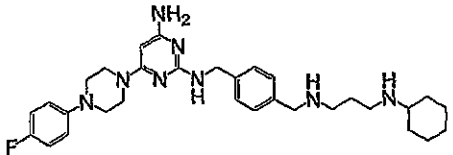
Compound 29



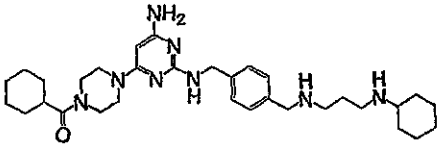
Compound 30



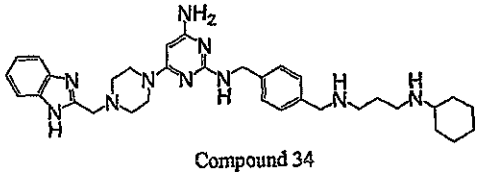
Compound 31



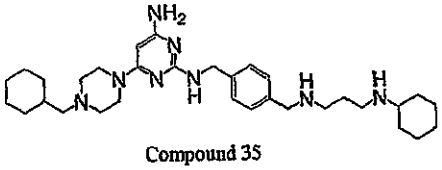
Compound 32



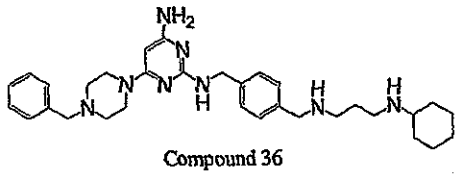
Compound 33



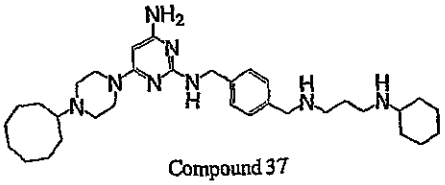
Compound 34



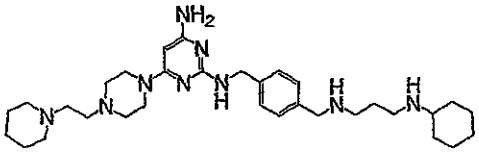
Compound 35



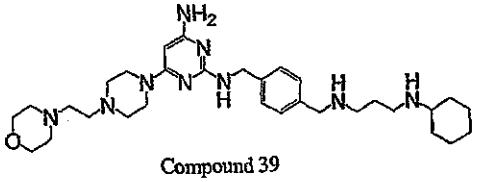
Compound 36



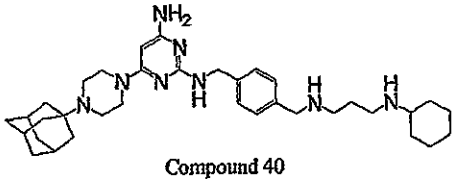
Compound 37



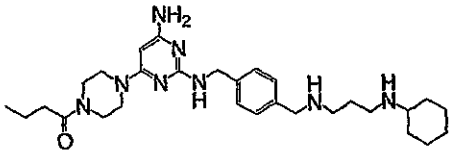
Compound 38



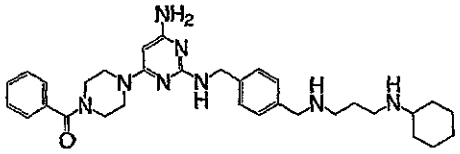
Compound 39



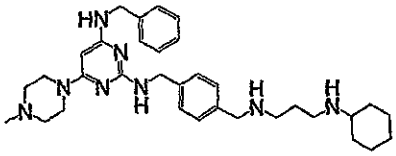
Compound 40



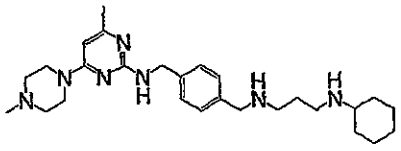
Compound 41



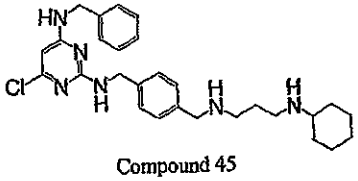
Compound 42



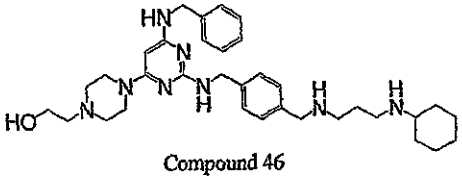
Compound 43



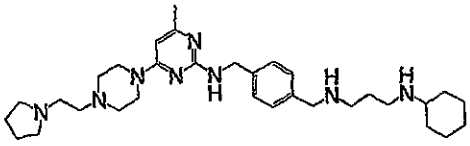
Compound 44



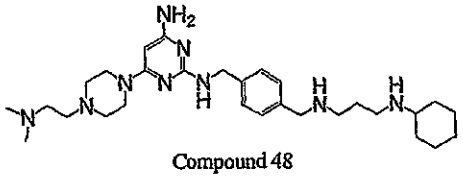
Compound 45



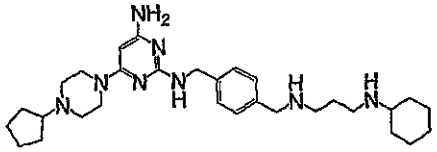
Compound 46



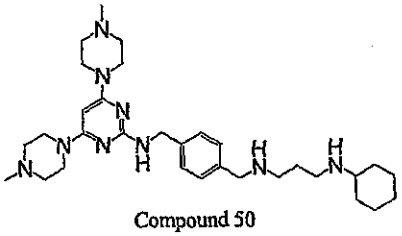
Compound 47



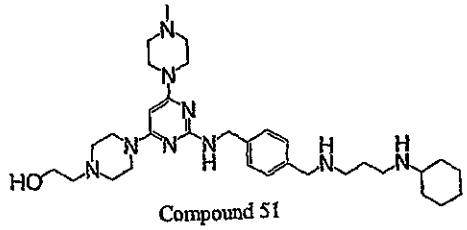
Compound 48



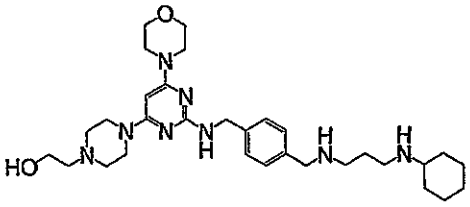
Compound 49



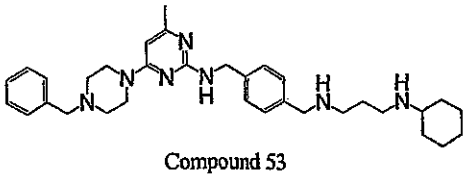
Compound 50



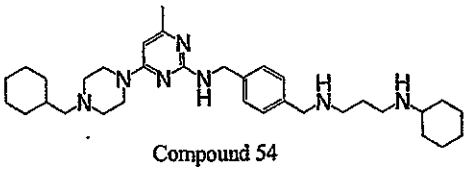
Compound 51



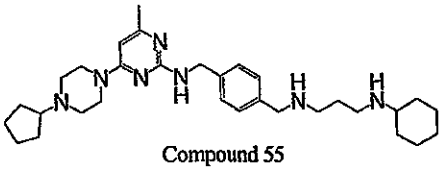
Compound 52



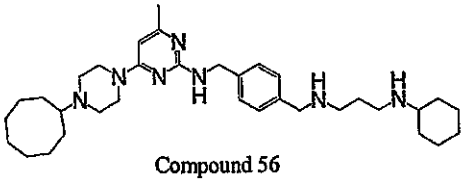
Compound 53



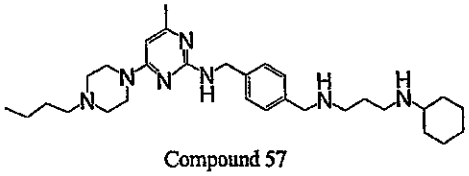
Compound 54



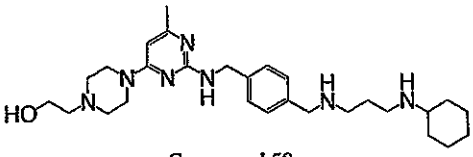
Compound 55



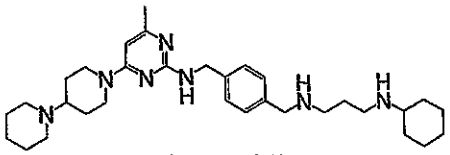
Compound 56



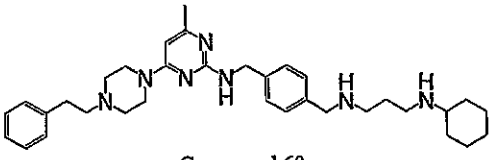
Compound 57



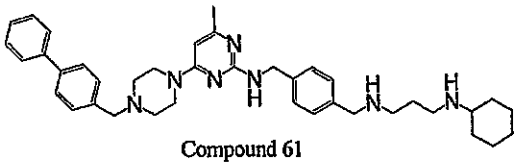
Compound 58



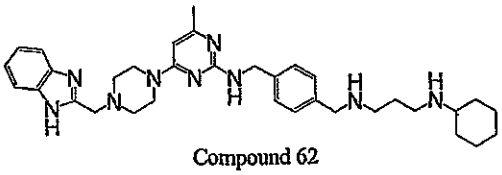
Compound 59



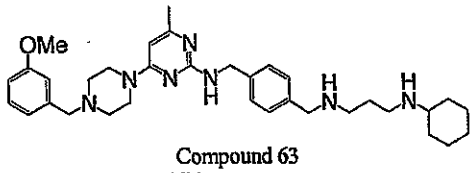
Compound 60



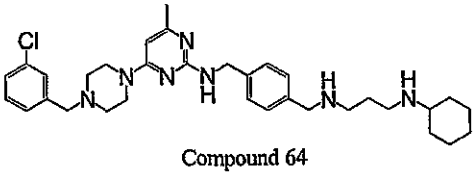
Compound 61



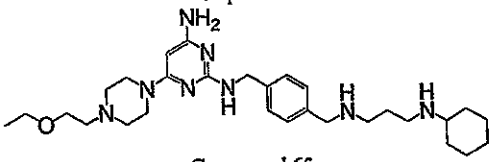
Compound 62



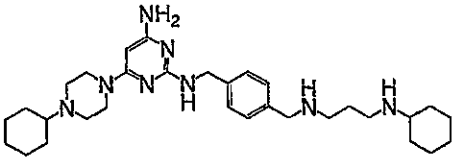
Compound 63



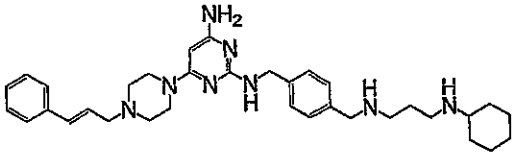
Compound 64



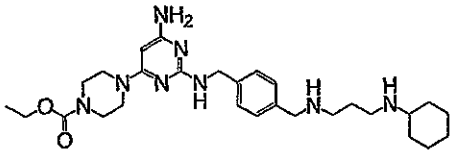
Compound 65



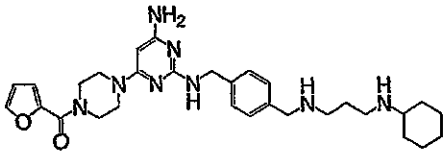
Compound 66



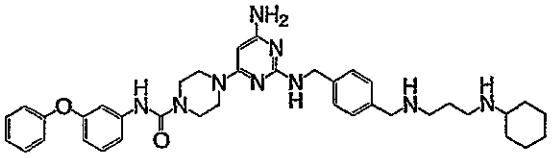
Compound 67



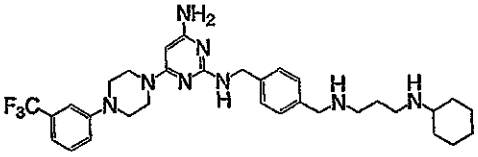
Compound 68



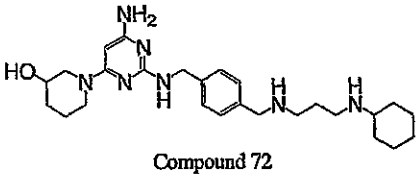
Compound 69



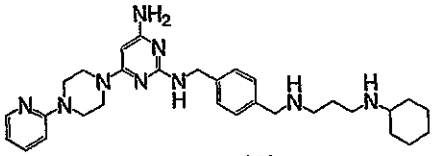
Compound 70



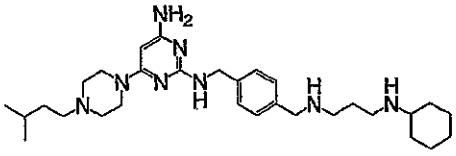
Compound 71



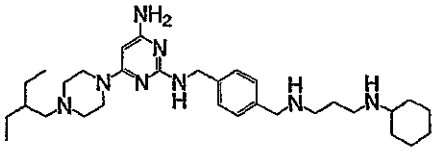
Compound 72



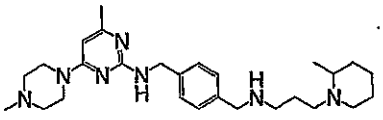
Compound 73



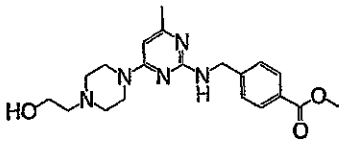
Compound 74



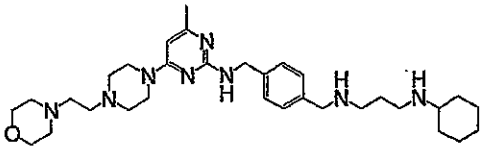
Compound 75



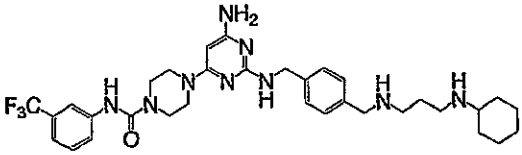
Compound 76



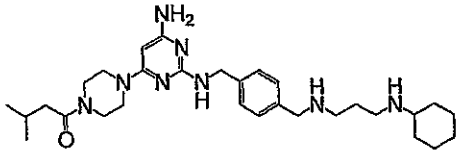
Compound 77



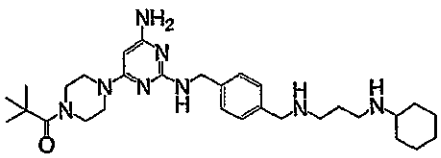
Compound 78



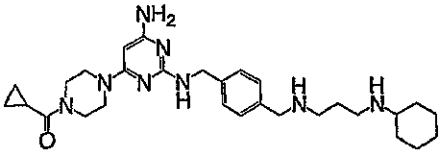
Compound 79



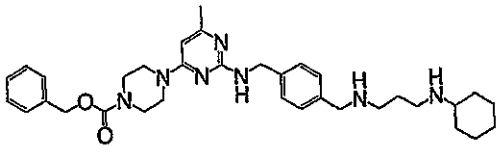
Compound 80



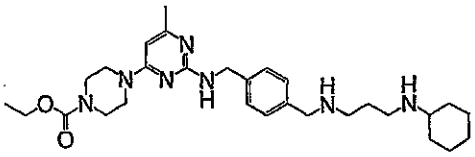
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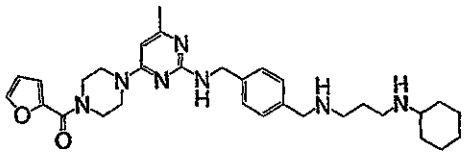
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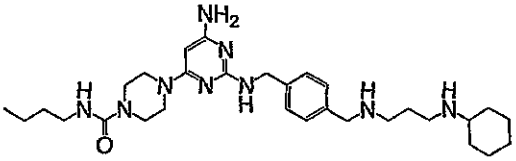
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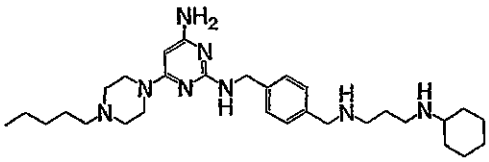
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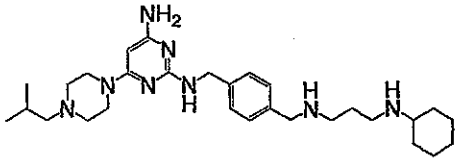
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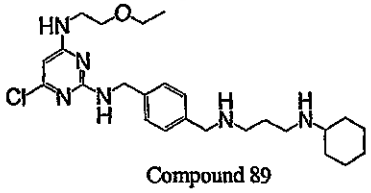
Compound 86



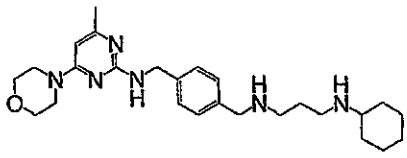
Compound 87



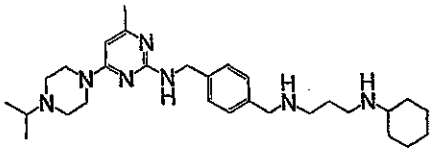
Compound 88



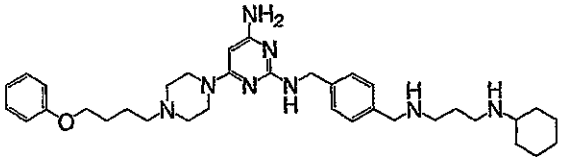
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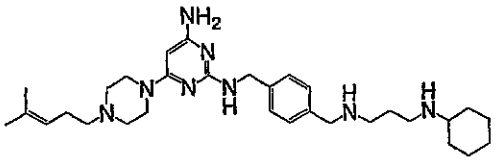
Compound 90



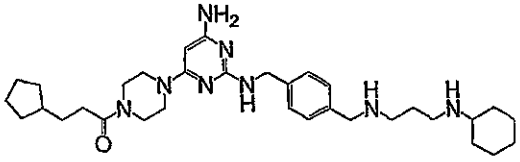
Compound 91



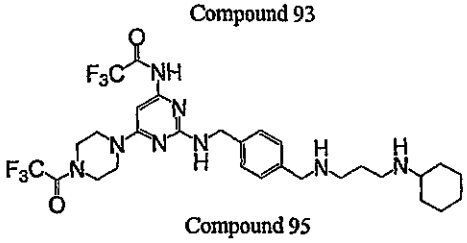
Compound 92



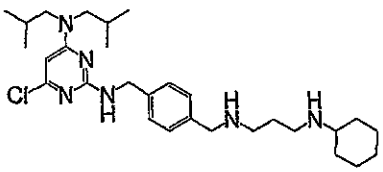
Compound 93



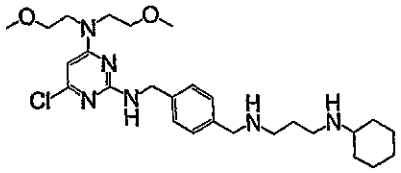
Compound 94



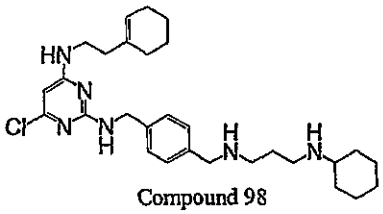
Compound 95



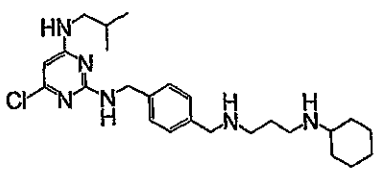
Compound 96



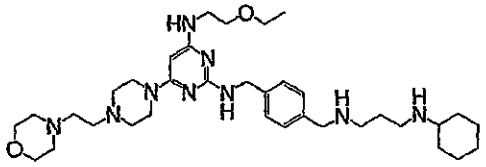
Compound 97



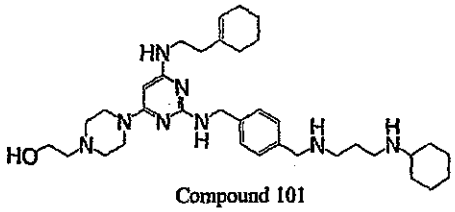
Compound 98



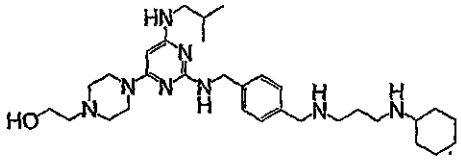
Compound 99



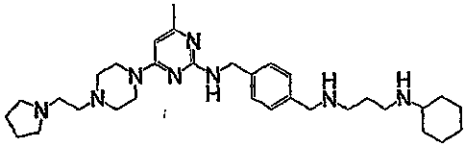
Compound 100



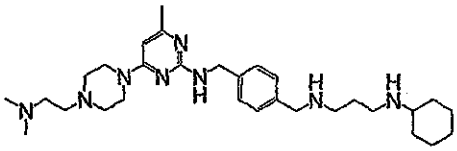
Compound 101



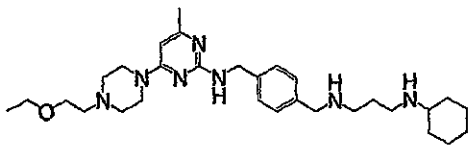
Compound 102



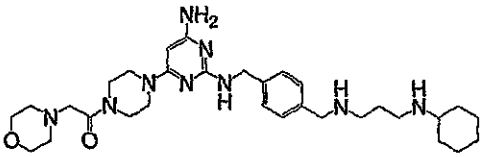
Compound 103



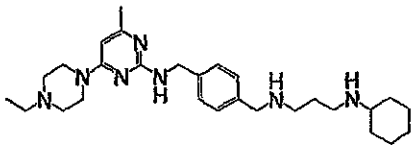
Compound 104



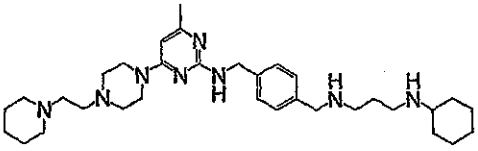
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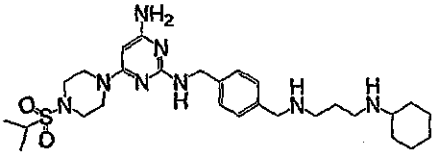
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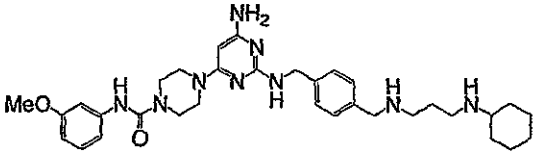
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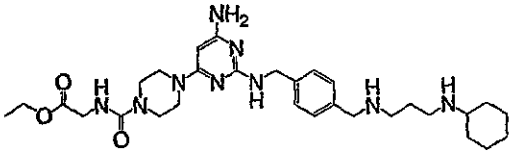
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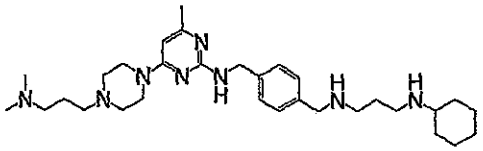
Compound 109



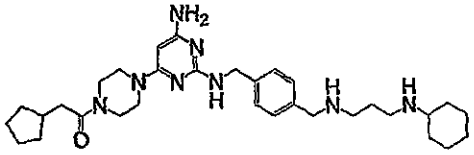
Compound 110



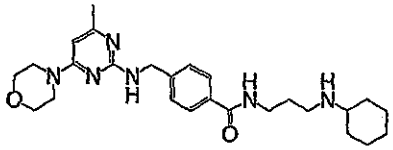
Compound 111



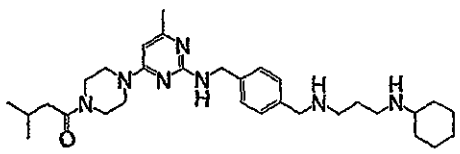
Compound 112



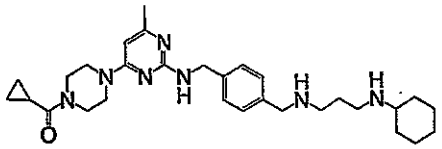
Compound 113



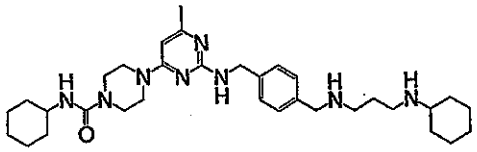
Compound 114



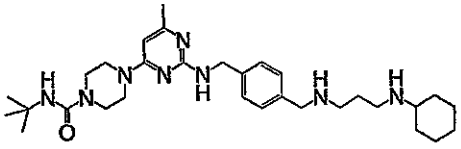
Compound 115



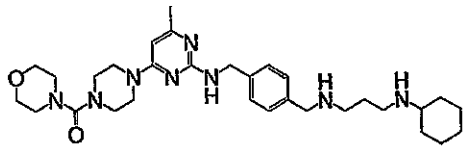
Compound 116



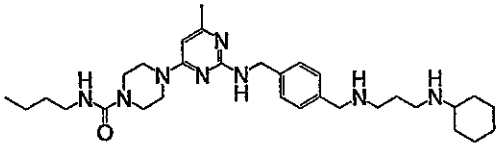
Compound 117



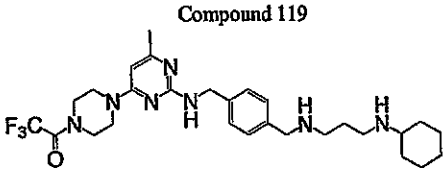
Compound 118



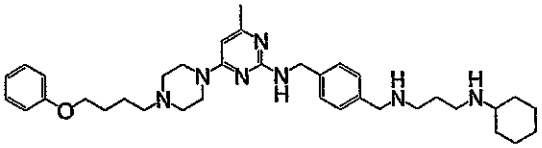
Compound 119



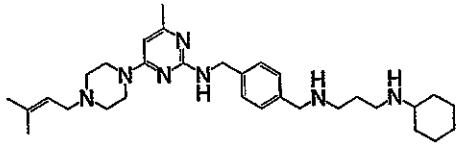
Compound 120



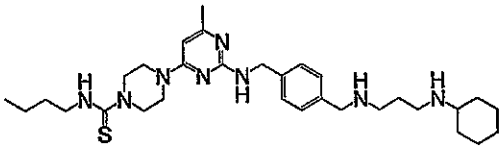
Compound 121



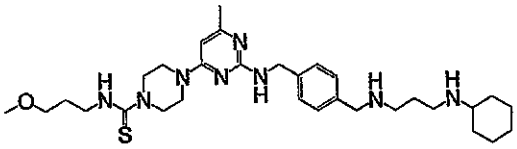
Compound 122



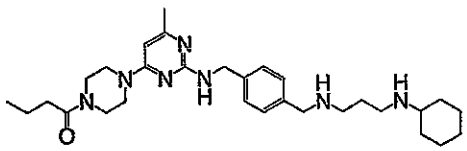
Compound 123



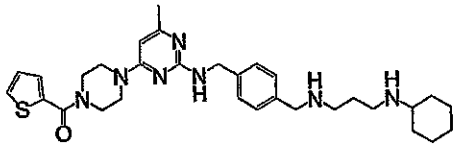
Compound 124



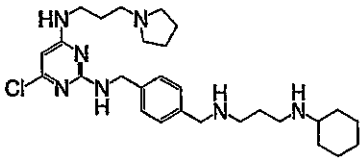
Compound 125



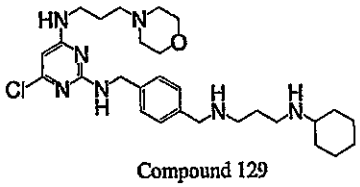
Compound 126



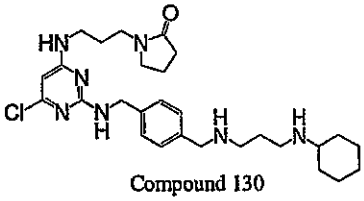
Compound 127



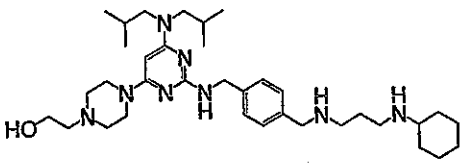
Compound 128



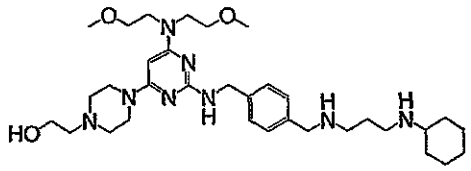
Compound 129



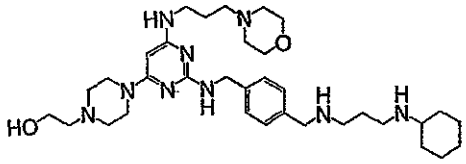
Compound 130



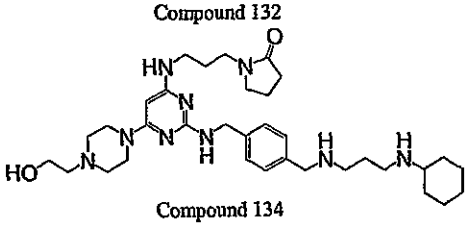
Compound 131



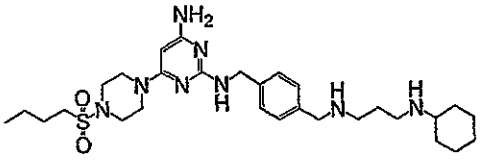
Compound 132



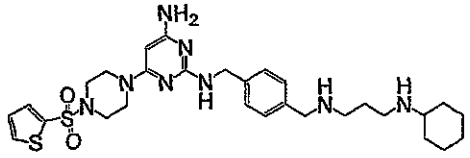
Compound 133



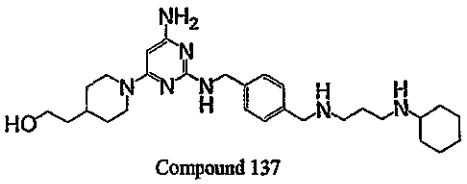
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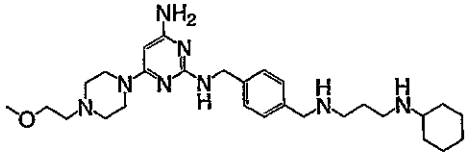
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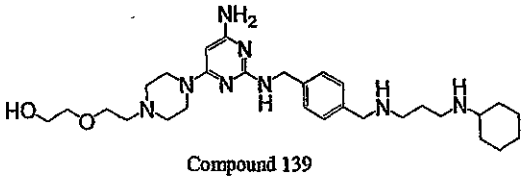
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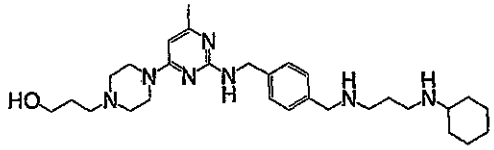
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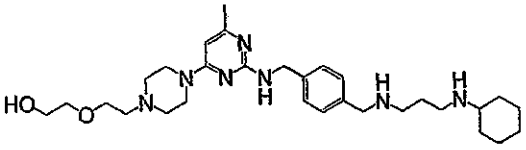
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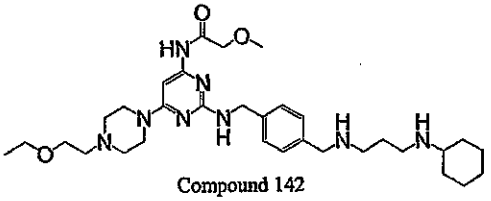
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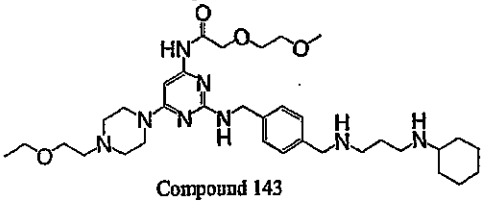
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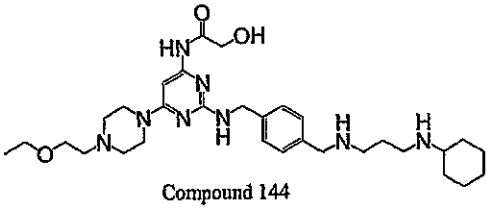
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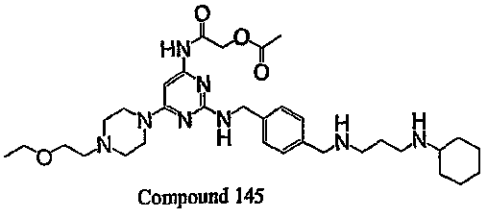
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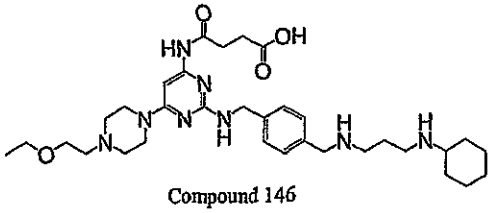
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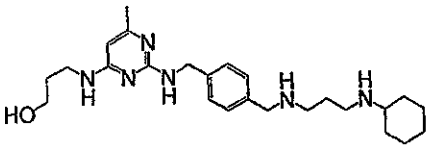
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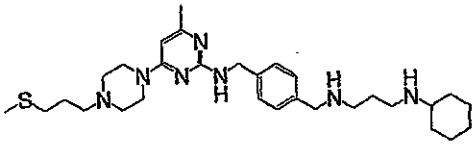
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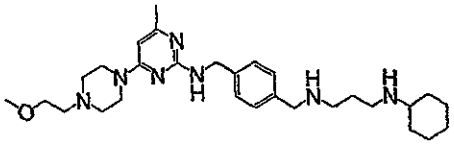
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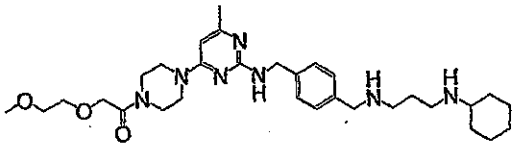
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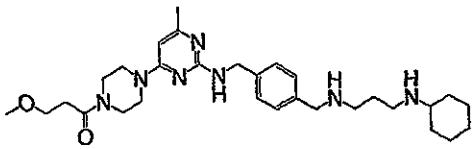
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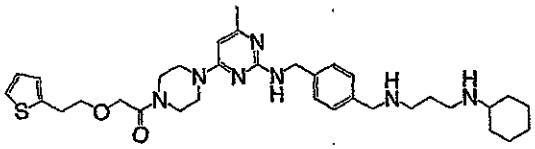
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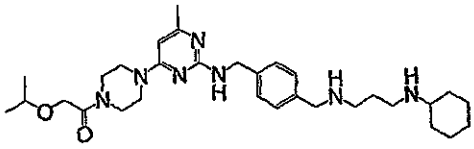
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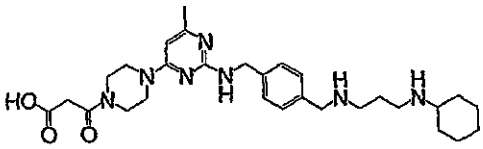
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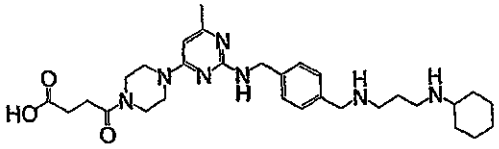
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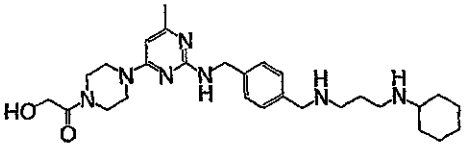
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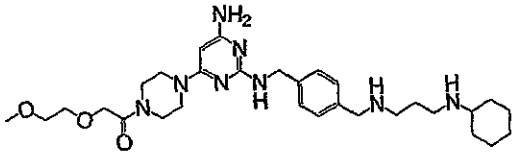
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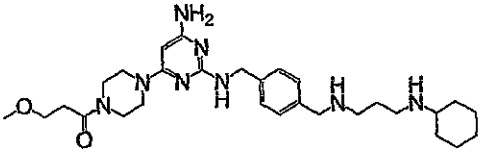
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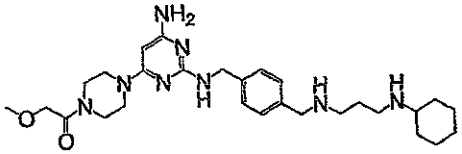
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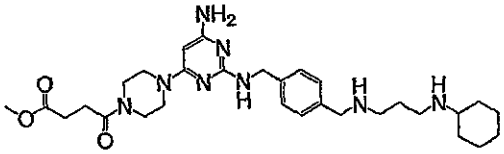
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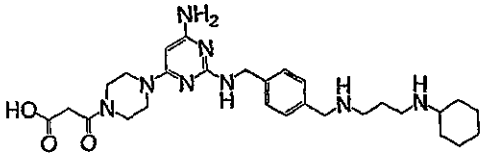
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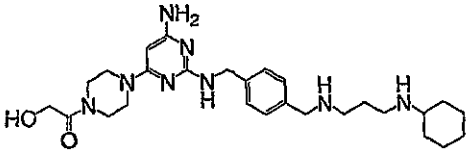
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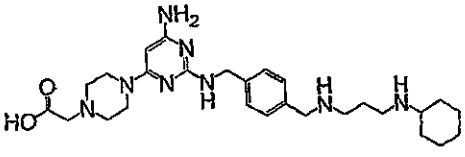
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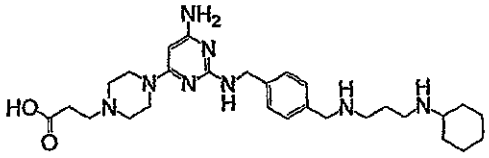
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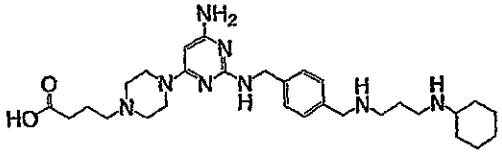
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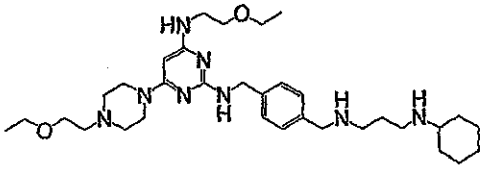
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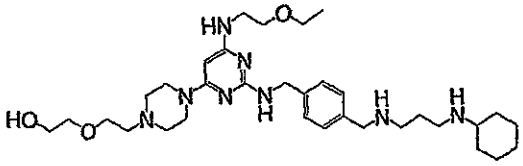
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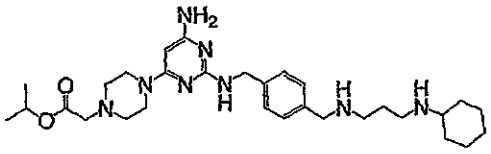
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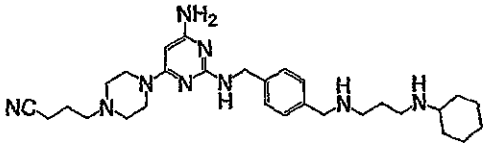
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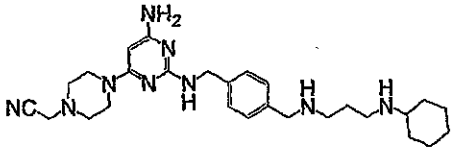
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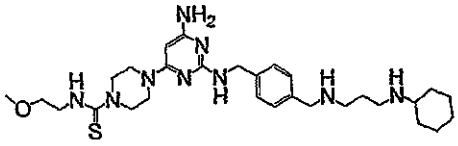
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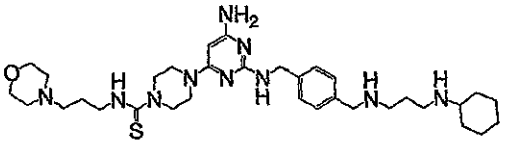
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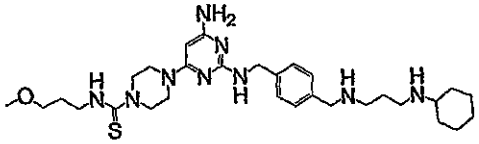
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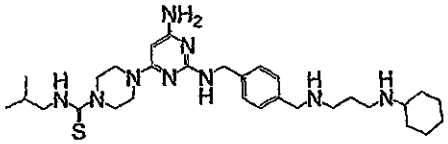
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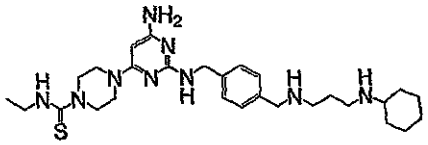
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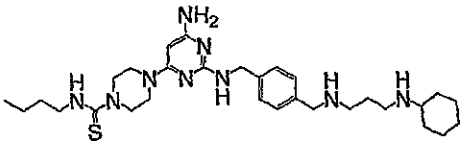
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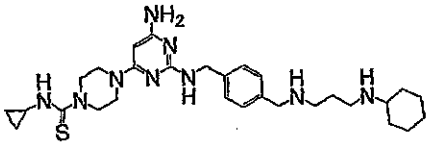
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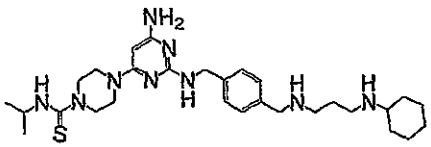
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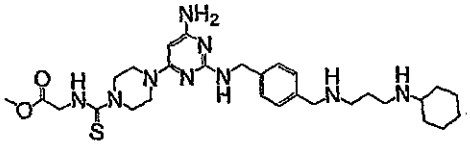
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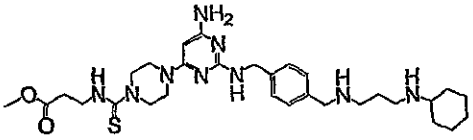
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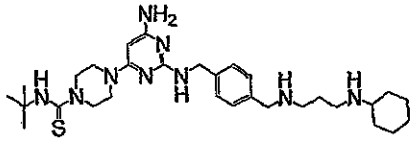
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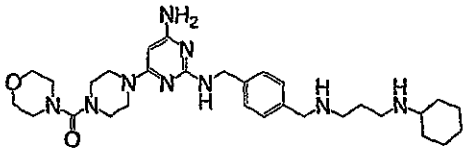
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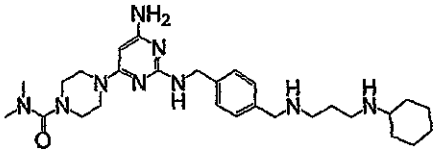
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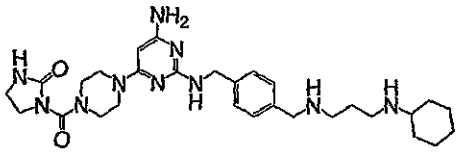
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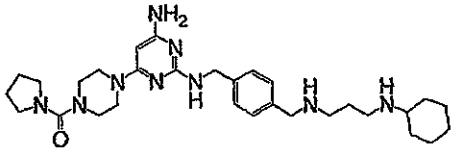
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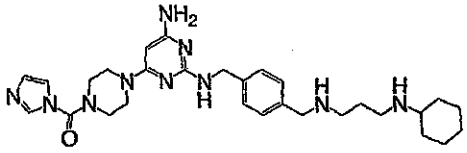
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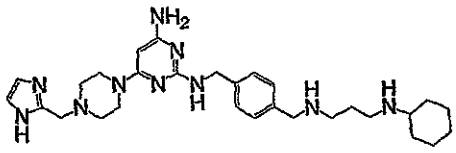
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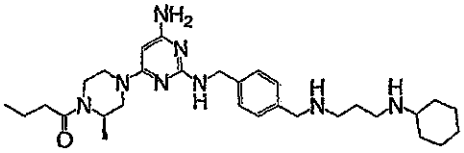
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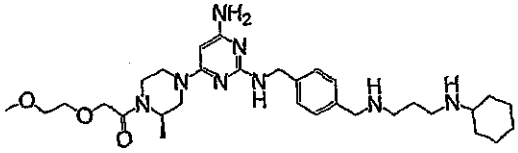
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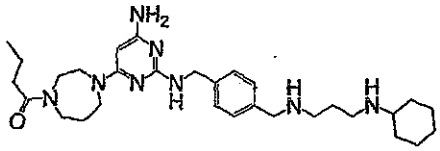
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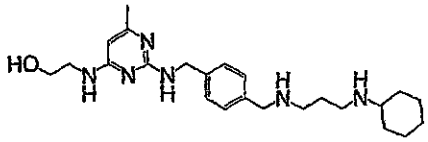
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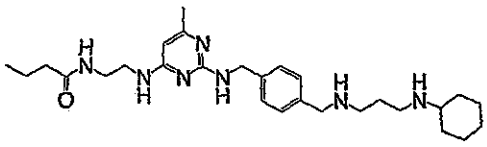
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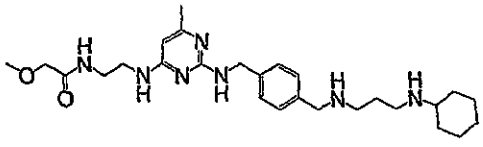
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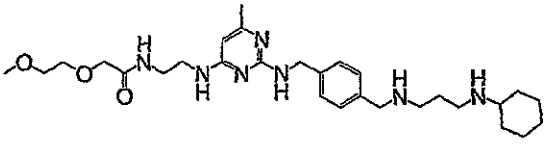
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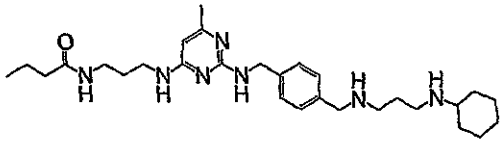
Compound 192



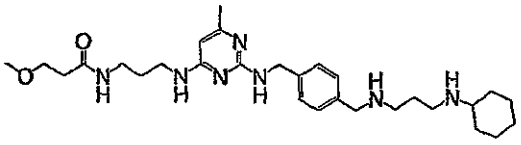
Compound 193



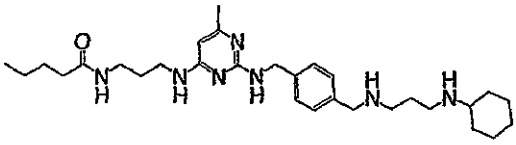
Compound 194



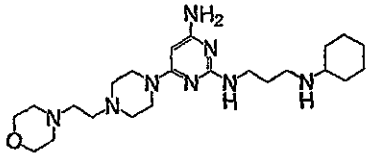
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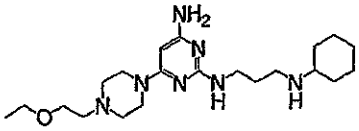
Compound 196



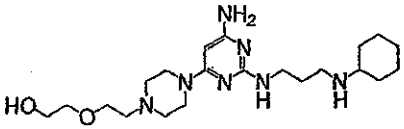
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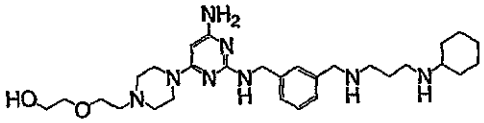
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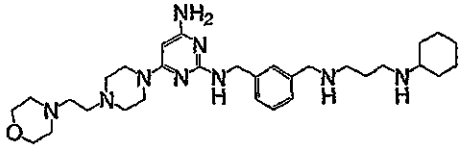
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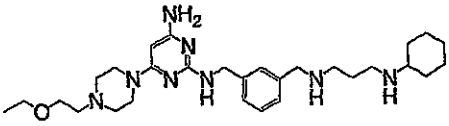
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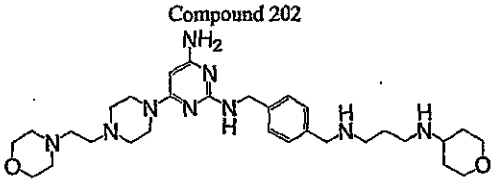
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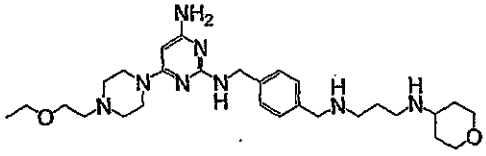
Compound 202



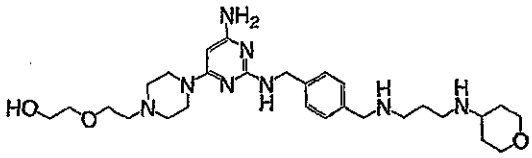
Compound 203



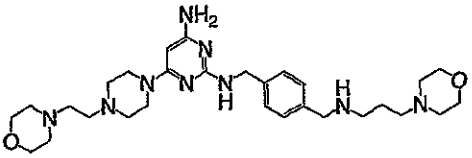
Compound 204



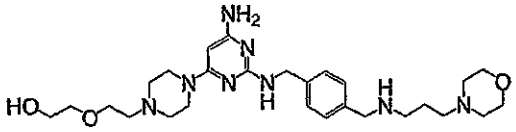
Compound 205



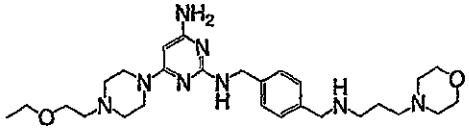
Compound 206



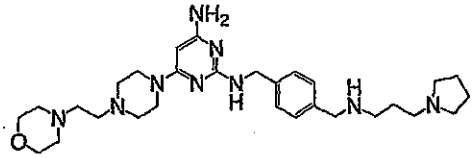
Compound 207



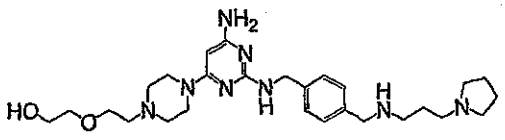
Compound 208



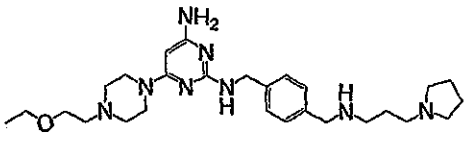
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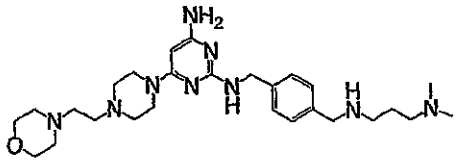
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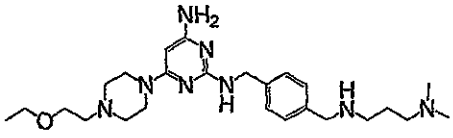
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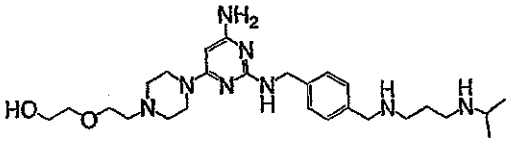
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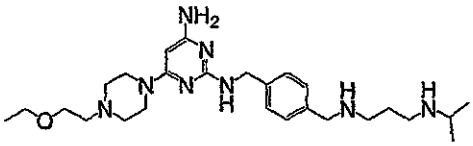
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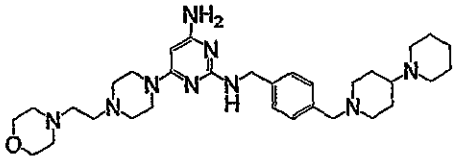
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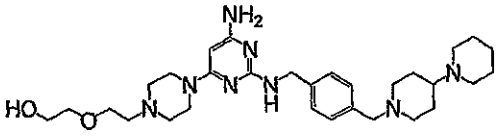
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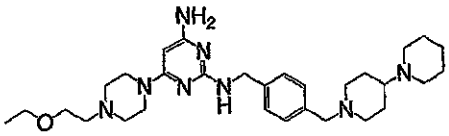
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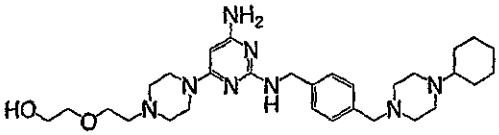
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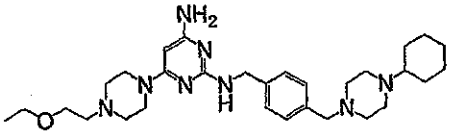
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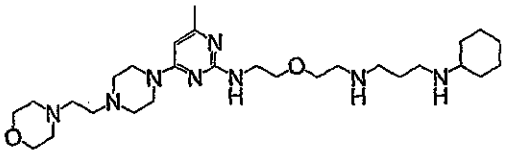
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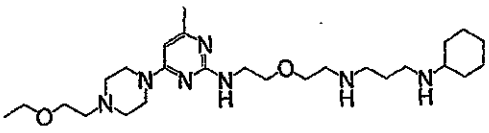
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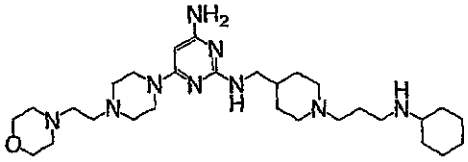
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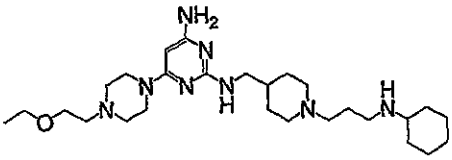
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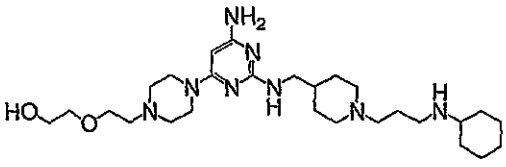
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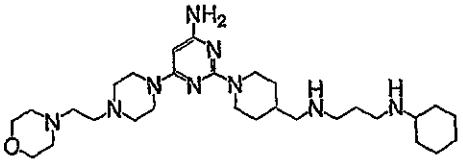
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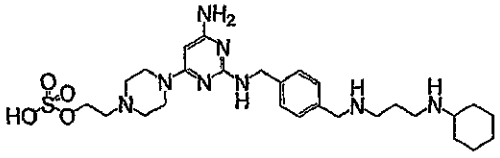
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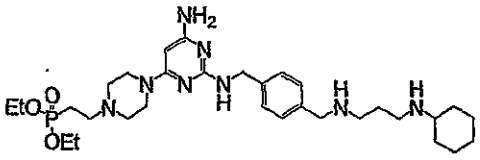
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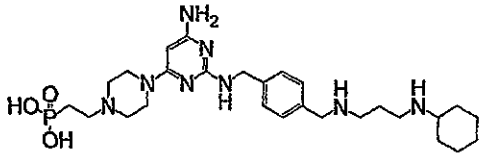
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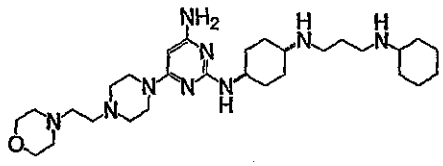
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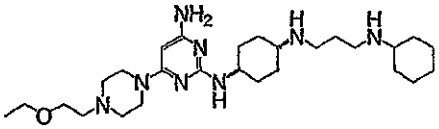
Compound 229



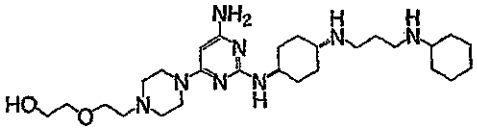
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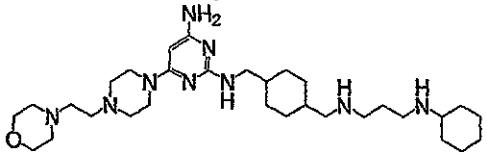
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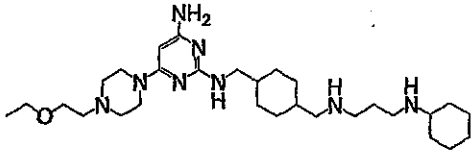
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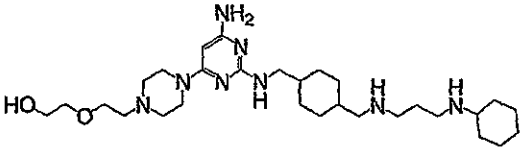
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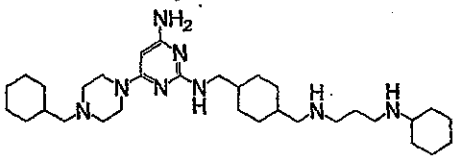
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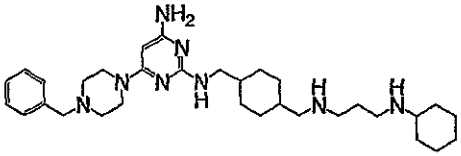
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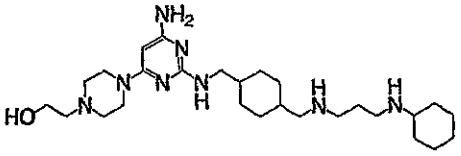
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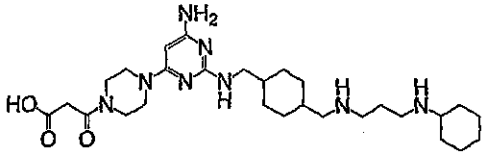
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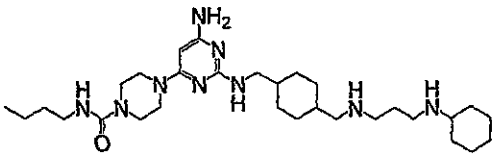
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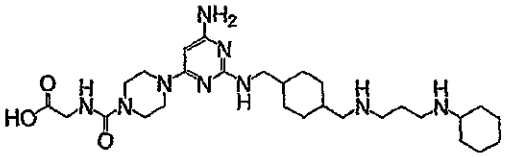
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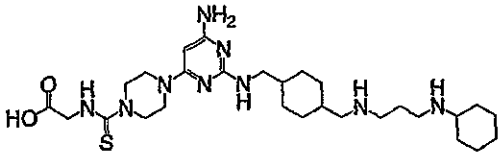
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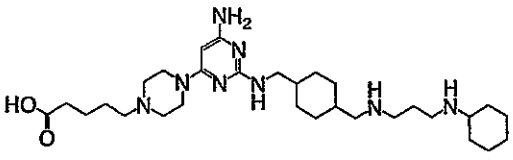
Compound 241



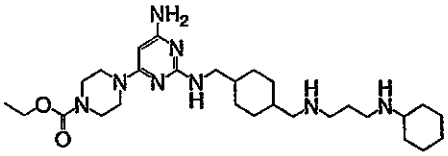
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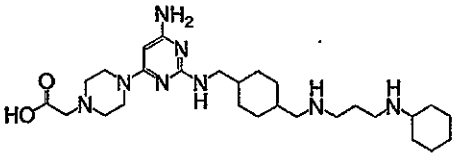
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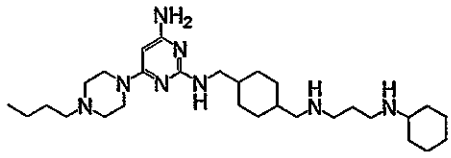
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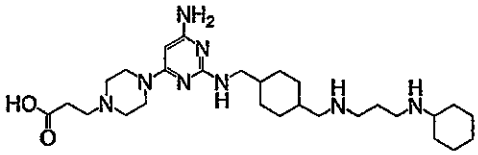
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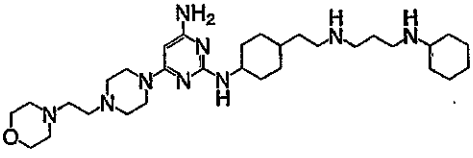
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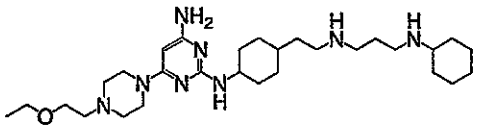
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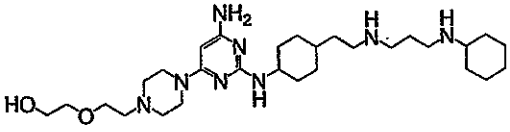
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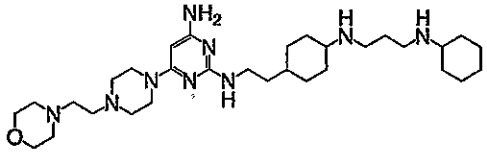
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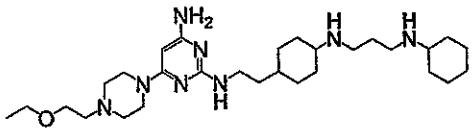
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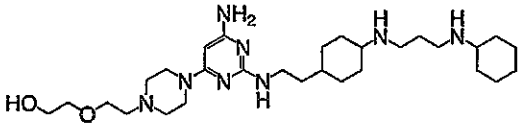
Compound 251



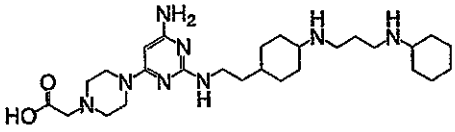
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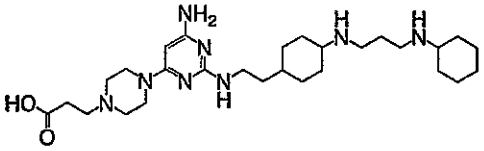
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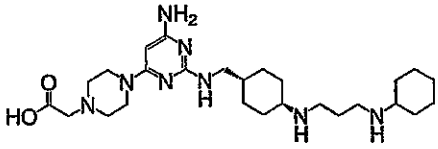
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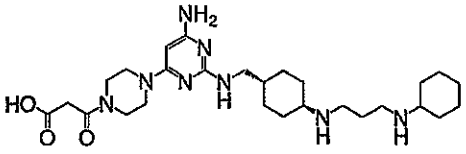
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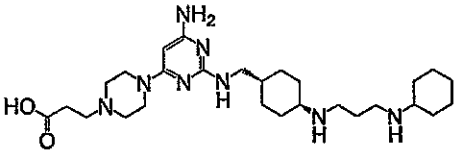
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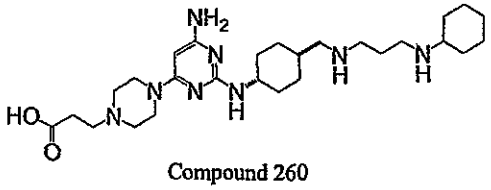
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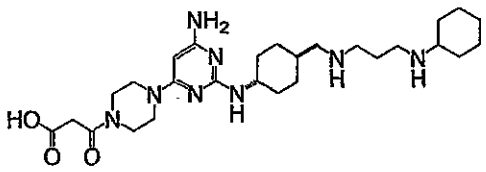
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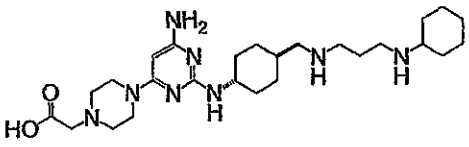
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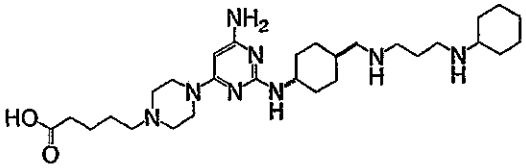
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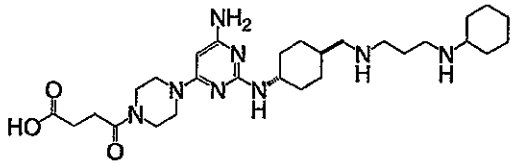
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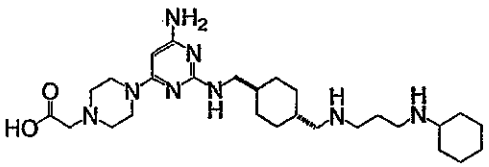
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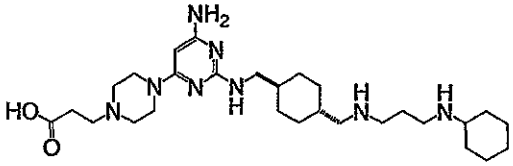
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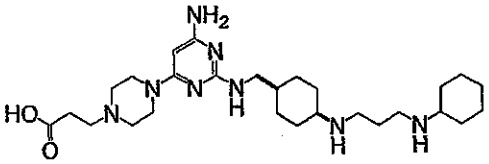
Compound 264



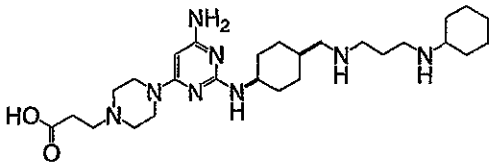
Compound 265



Compound 266



Compound 267

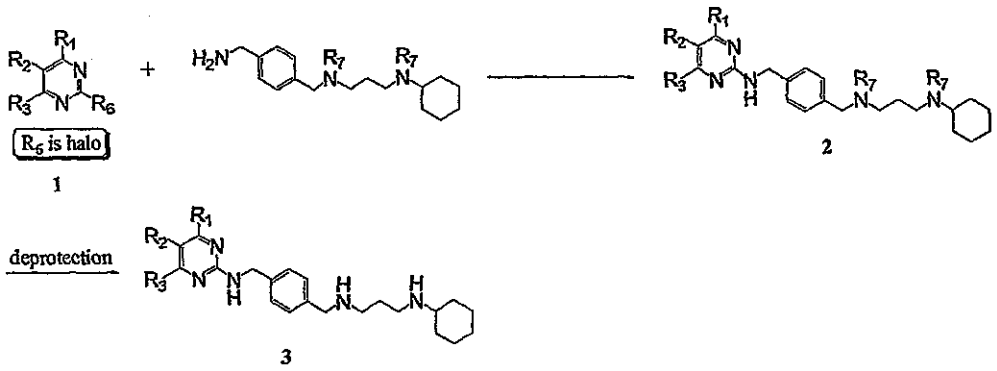


Compound 268

The pyrimidine compounds described above can be prepared by methods well known in the art. Examples 1-268 below provide detailed descriptions of the preparation of compounds 1-268 of this invention.

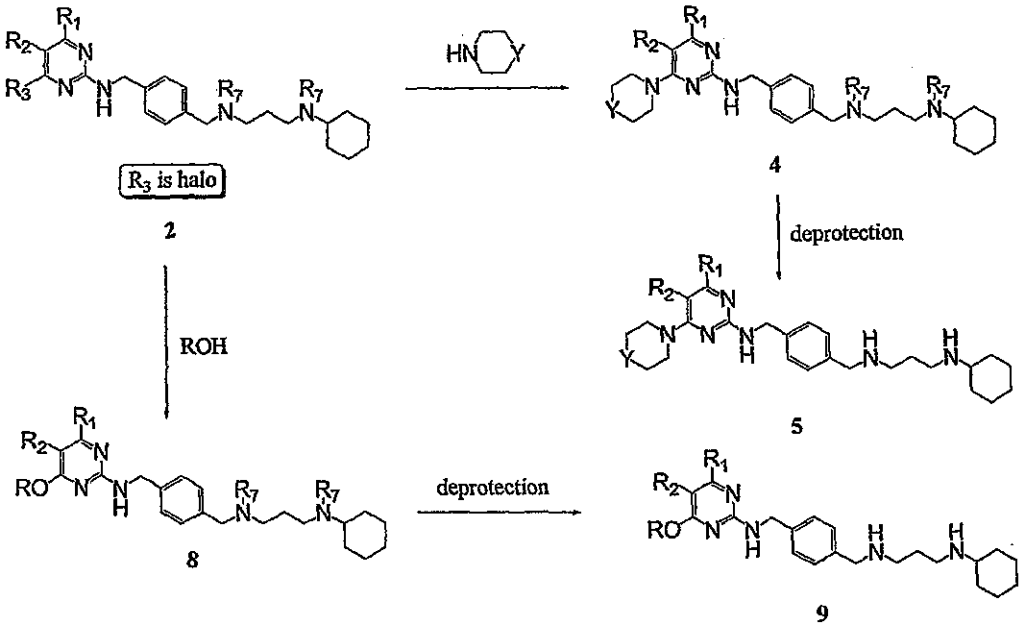
Scheme I shown below depicts a typical synthetic route for synthesizing certain exemplary compounds. In this scheme, R_1, R_2, R_3, R_6, and R_7 are as defined in the Summary section above. Specifically, a pyrimidine compound containing a halo group reacts with a compound containing two protected amino groups and an unprotected primary amino group to give a compound of formula (2), which is subsequently deprotected by removing the amino-protecting group to give a compound of formula (3). Exemplary amino-protecting groups include t-butoxycarbonyl, benzyloxycarbonyl, acetyl, phenylcarbonyl, and trialkylsilyl.

Scheme I



Compounds of formula (2) can be modified in various manners to afford other compounds of this invention. For example, as shown in Scheme II below, when R_3 is halo, a compound of formula (2) reacts with a heterocyclic compound containing a ring nitrogen atom to give a compound of formula (4), which is subsequently deprotected to give a compound of formula (5). As another example, when R_3 is also halo, a compound of formula (2) reacts with an alcohol to give a compound of formula (8), which is subsequently deprotected to give a compound of formual (9).

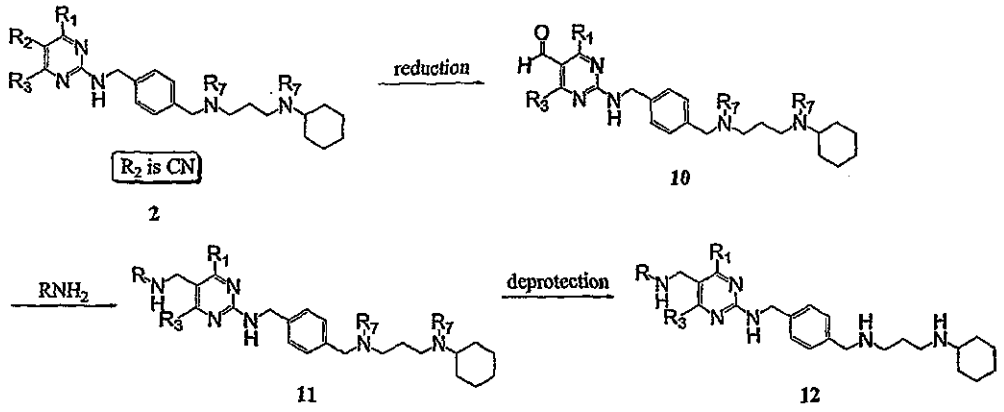
Scheme II



As shown in Scheme III below, when R_2 is CN, a compound of formula (2) can be first reduced to give a compound of formula (10), which contains an aldehyde group. The compound of formula (10) can then react with a primary amine to give a compound

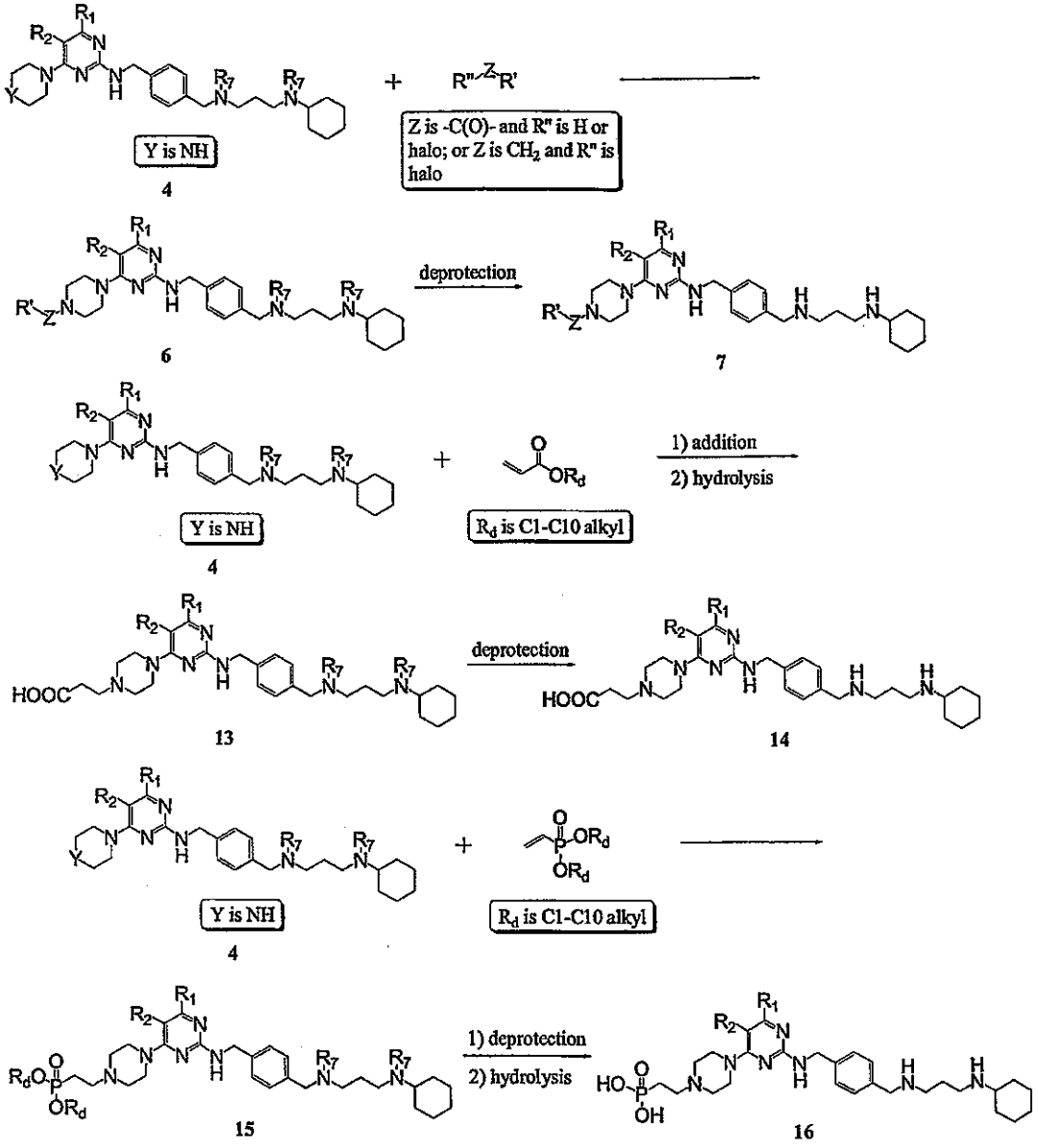
of formula (11), which can be subsequently deprotected to form a compound of formula (12).

Scheme III



Compounds of formula (4) obtained above can be further modified in various manners to give other compounds of this invention. For example, as shown in Scheme IV below, when Y is NH, a compound of formula (4) reacts with a compound containing a halide group, an aldehyde group, or an acyl chloride group to give a compound of formula (6), which is subsequently deprotected to give a compound of formula (7). As another example, when Y is NH, a compound of formula (4) reacts with an α,β-unsaturated ester, followed by hydrolysis to give a compound of formula (13), which is subsequently deprotected to give a compound of formula (14). As another example, when Y is NH, a compound of formula (4) reacts with a vinyl phosphonate to give a compound of formula (15). The compound of formula (15) is then deprotected and hydrolyzed to give a compound of formula (16).

Scheme IV



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

Other pyrimidine compounds can be prepared using other suitable starting materials through the above synthetic routes and others known in the art. The methods described above 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 pyrimidine 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 pyrimidine 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 pyrimidine 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 pyrimidine 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 pyrimidine compounds to a patient having a disease described in the summary section above. This invention also covers a method of administering an effective amount of one or more of the pyrimidine compounds for enhancing migration of bone marrow-derived cells to blood. "An effective amount" refers to the amount of an active pyrimidine compound that is required to confer a therapeutic effect on the treated subject. 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 pyrimidine 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.

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.

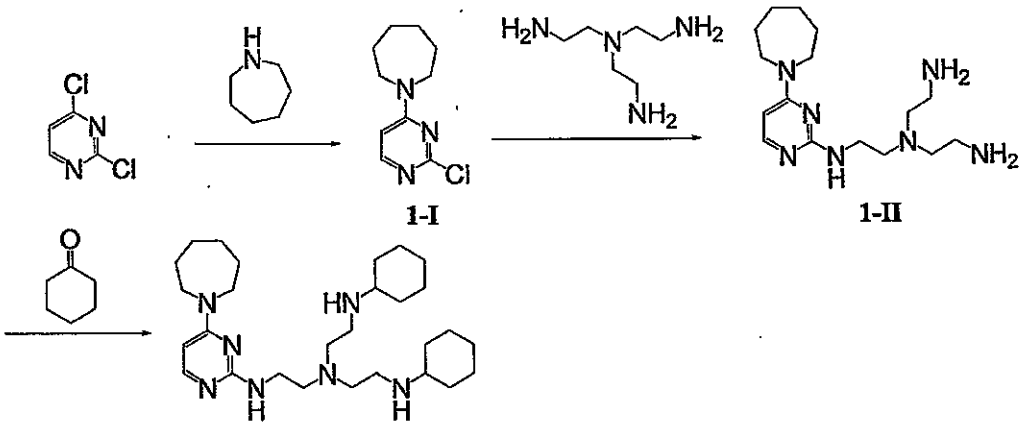
A composition having one or more active pyrimidine compounds can also be administered in the form of suppositories for rectal administration.

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 pyrimidine compound. Examples of other carriers include colloidal silicon oxide, magnesium stearate, cellulose, sodium lauryl sulfate, and D&C Yellow # 10.

The pyrimidine 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.

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 compound 1:



1-I

1-II

Compound 1

Hexamethyleneimine (0.673 g) was slowly added to a stirred solution of 2,4-dichloropyrimidine (1 g) in THF (50 mL) at 0°C. The reaction mixture was stirred at 0°C for 2 hours and the reaction was allowed to warm-up to room temperature overnight. The solution was then concentrated to give a residue, which was purified by chromatography on silica gel (EtOAc/Hexane = 1/5) to afford intermediate 1-I (1.234 g) in a 86% yield.

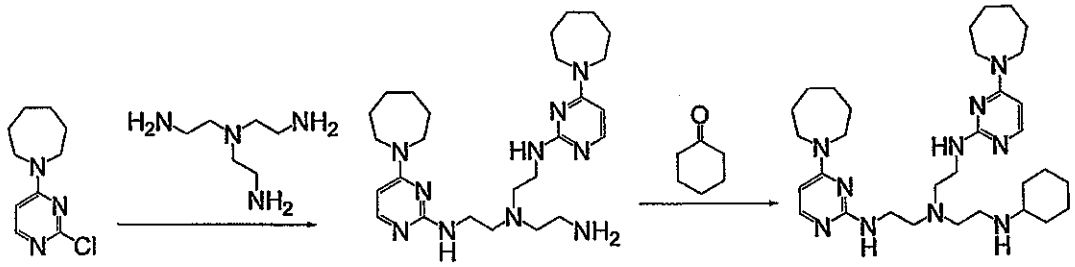
A solution of Intermediate 1-I (0.46 g) and tris-(2-aminoethyl)-amine (1.6 g) in DMSO (2 mL) was heated at 120°C for 8 hours by microwave. The solution was partitioned between CH_2Cl_2 and H_2O. The organic layer was isolated and then concentrated. The residue was purified by chromatography on silica gel (21% NH_3(aq)/MeOH = 1/3) to afford intermediate 1-II (0.454 g) in a 65% yield.

Cyclohexanone (488 mg) and $NaBH(OAc)_3$ (1320 mg) were added to a stirred solution of intermediate 1-II (200 mg) in CH_2Cl_2 (50 mL) at room temperature over a short period of time. The resulting solution was stirred at room temperature for 8 hours, and then quenched with a saturated aqueous $NaHCO_3$ solution. The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic layers were subsequently washed with water, dried, filtered, and concentrated to give a crude residue, which was purified by chromatography on silica gel (21% NH_3(aq)/MeOH = 1/10) to give compound 1 (217 mg) in a 72% yield.

CI-MS (M^++1): 486.4.

1 M hydrochloric acid (6 mL) and CH_2Cl_2 (4 ml) were added to the compound 1 (217 mg). The mixture was stirred for 10 minutes at room temperature. After removing the supernatant, the solid was dried under vacuum to afford the hydrochloride salt of compound 1 (268 mg) in a 95% yield.

Example 2: Preparation of compound 2:



2-I 2-II Compound 2

Intermediate 2-I was obtained during the preparation of compound 1.

A solution of Intermediate 2-I (200 mg) and tris-(2-aminoethyl) amine (70 mg) in DMSO (2 mL) was heated at 120°C for 8 hours by microwave. The solution was partitioned between CH_2Cl_2 and H_2O. The organic layer was isolated and then

concentrated. The residue was purified by chromatography on silica gel (21% NH_3(aq)/MeOH = 1/5) to afford intermediate 2-II (296 mg) in a 63% yield.

Cyclohexanone (234 mg) and $NaBH(OAc)_3$ (506 mg) were added to a stirred solution of intermediate 2-II (296 mg) in CH_2Cl_2 (30 mL) at room temperature over a short period of time. The resulting solution was stirred at room temperature for 8 hours, and then quenched with a saturated aqueous $NaHCO_3$ solution. The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic layers were subsequently washed with water, dried, filtered, and concentrated to give a crude residue, which was purified by chromatography on silica gel (21% NH_3(aq)/MeOH = 1/15) to give compound 2 (266 mg) in a 77% yield.

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

1 M hydrochloric acid (6 mL) and CH_2Cl_2 (4 ml) were added to compound 2 (266 mg). The mixture was stirred for 10 minutes at room temperature. After removing the supernatant, the solid was dried under vacuum to afford the hydrochloride salt of compound 2 (302 mg) in a 91% yield.

Example 3: Preparation of compound 3:

Compound 3 was prepared in a manner similar to that used to prepare compound 1.

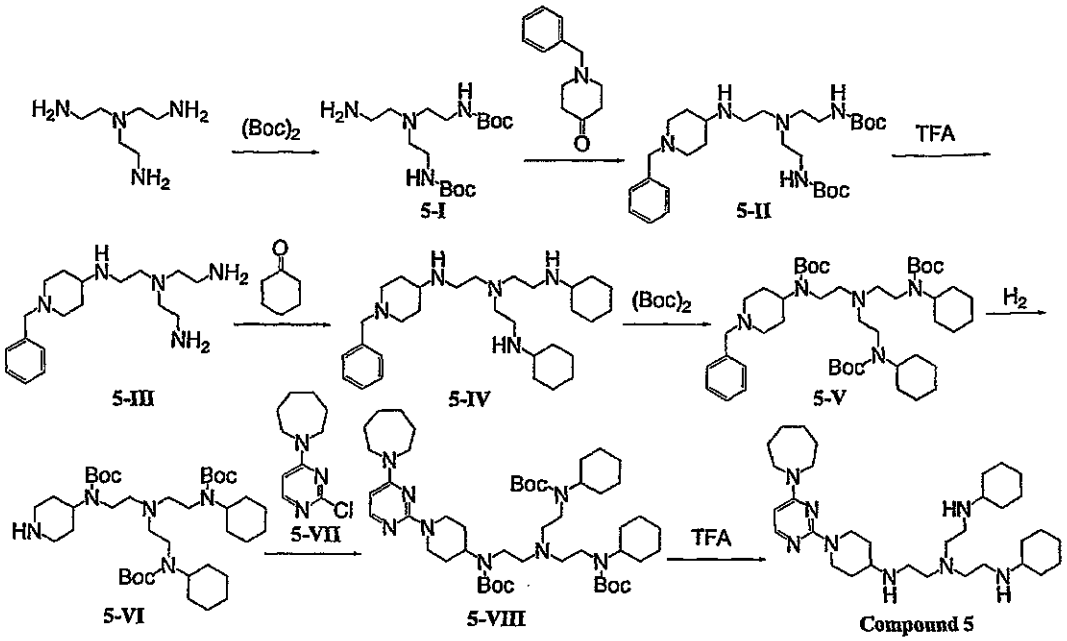
CI-MS (M^++1): 472.4.

Example 4: Preparation of compound 4:

Compound 4 was prepared in a manner similar to that used to prepare compound 1.

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

Example 5: Preparation of compound 5:



A solution of tris-(2-aminoethyl)-amine (2.0 g) and Boc_2O (1.0 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/MeOH = 1/1) to afford intermediate 5-I (2.04 g) in a 43% yield.

1-Benzyl-4-piperidone (2.177 g) and $NaBH(OAc)_3$ (3.665 g) were added to a stirred solution of intermediate 5-I (2.0 g) in MeOH (30 mL) at room temperature over a short period of time. The resulting solution was stirred at room temperature for 8 hours, and then quenched with a saturated aqueous $NaHCO_3$ solution. The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic layers were subsequently washed with water, dried, filtered, and concentrated to give a crude residue, which was purified by chromatography on silica gel (EtOAc/MeOH = 9/1) to afford intermediate 5-II (2.488 g) in a 83% yield.

A solution of 20% TFA/CH_2Cl_2 (20 mL) was added to Intermediate 5-II (1.0 g) in CH_2Cl_2 (10 mL). The reaction mixture was stirred for 5 hours at room temperature and concentrated by removing the solvent. The residue was purified by chromatography on silica gel (21% NH_3(aq)/MeOH = 1/4) to afford intermediate 5-III (0.54 g) in a 88% yield.

Cyclohexanone (1,323 mg) and $NaBH(OAc)_3$ (3,220 mg) were added to a stirred solution of intermediate 5-III (540 mg) in CH_2Cl_2 (30 mL) at room temperature over a short period of time. The resulting solution was stirred at room temperature for 8 hours and then quenched with a saturated aqueous $NaHCO_3$ solution. The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic layers were subsequently washed with water, dried, filtered, and concentrated to give a crude residue, which was purified by chromatography on silica gel (21% NH_3(aq)/MeOH = 1/10) to afford intermediate 5-IV (0.58 g) in a 71% yield.

A solution of intermediate 5-IV (580 mg), Boc_2O (863 mg) and Et_3N (485 mg) in CH_2Cl_2 (150 ml) was stirred at 25°C for 15 hours and then concentrated. The resultant residue was purified by chromatography on silica gel (EtOAc/Hexane = 1/5) to afford intermediate 5-V (865 mg) in a 92% yield.

A mixture of intermediate 5-V (865 mg) and Pd/C (90 mg) in MeOH (20 ml) was stirred under H_2 (balloon) at 25°C for 15 hours and then filtered through a celite column and concentrated. The resultant residue was purified by chromatography on silica gel (EtOAc/ MeOH = 15/1) to afford intermediate 5-VI (681 mg) in a 89% yield.

Diisopropylethylamine (0.1 mL) was added to a solution of 5-VII (30 mg; obtained during preparation of compound 1) and intermediate 5-VI (100 mg) in 1-pentanol (2 mL). The reaction mixture was stirred overnight at 140°C. The solvent was then removed under vacuum and the resultant residue was purified by chromatography on silica gel (EtOAc/Hexane = 1/1) to afford intermediate 5-VIII (76 mg) in a 61% yield.

A solution of 20% TFA/CH_2Cl_2 (2 mL) was added to intermediate 5-VIII (76 mg) in CH_2Cl_2 (1 mL). The reaction mixture was stirred for 5 hours at room temperature and concentrated by removing the solvent. 1 M hydrochloric acid (2 mL) and CH_2Cl_2 (1 mL) were added to the resultant residue. The mixture was stirred for 10 minutes at room temperature. After removal of the supernatant, the solid was dried under vacuum to afford the hydrochloride salt of compound 5 (81 mg) in a 85% yield.

CI-MS (M^++1): 569.5.

Example 6: Preparation of compound 6:

Compound 6 was prepared in a manner similar to that used to prepare compound 1.

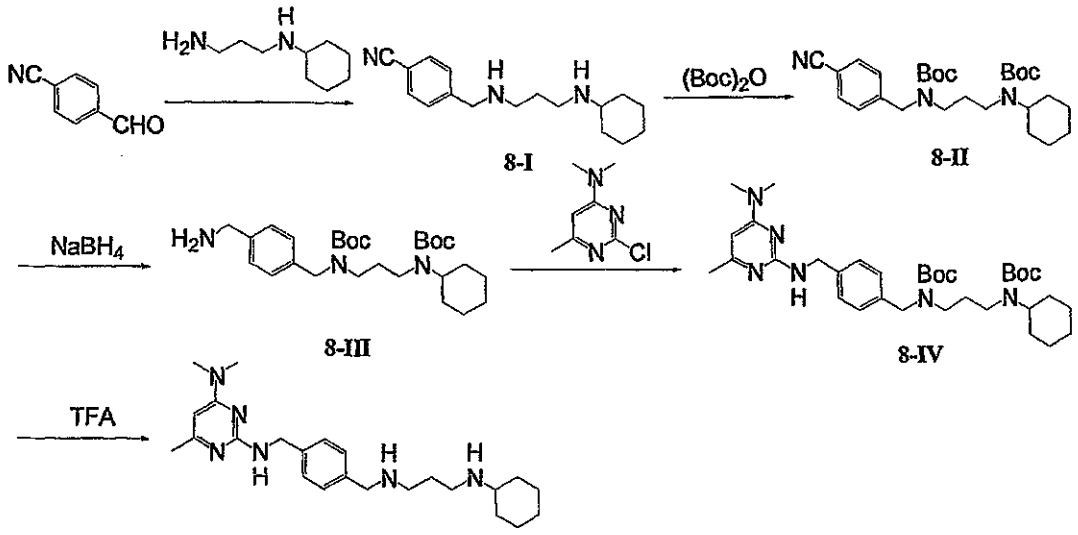
CI-MS (M^++1): 572.5.

Example 7: Preparation of compound 7:

Compound 7 was prepared in a manner similar to that used to prepare compound 1.

CI-MS (M^++1): 458.4.

Example 8: Preparation of compound 8:



A solution of 4-cyanobenzylaldehyde (5 g) and N-cyclohexyl-1,3-propane-diamine (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 above solution. The mixture was stirred for another 30 minutes. The mixture 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 8-I (7.2 g) in a 70% yield.

A solution of Intermediate 8-I (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 8-II as a yellow oil (10.6 g, yield: 85%).

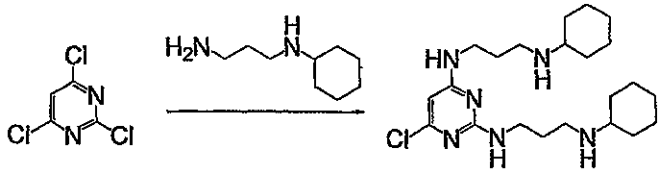
A solution of Intermediate 8-II (4.7 g) and $NiCl_2$ (64 mg) in CH_3OH (100 ml) was first stirred at 25°C. After cooling to 0°C, $NaBH_4$ (1.83 g) was slowly added and the mixture was stirred for another 15 hours. The solution was concentrated, quenched with NH_4Cl (aq), and extracted with CH_2Cl_2. 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 8-III (2.36 g) in a 50% yield.

Diisopropylethylamine (0.1 mL) was added to a solution of 2-chloro-6-methyl-4-dimethylaminopyrimidine (110 mg) and Intermediate 8-III (150 mg) in 1-pentanol (2 mL). The reaction mixture was stirred overnight at 150°C. The solvent was removed under vacuum and the residue was purified by chromatography on silica gel (EtOAc/Hexane = 1/1) to afford Intermediate 8-IV (88 mg) in a 47% yield.

A solution of 20% TFA/CH_2Cl_2 (2 mL) was added to Intermediate 8-IV (88 mg) in CH_2Cl_2 (1 mL). The reaction mixture was stirred for 5 hours at room temperature and concentrated by removing the solvent. 1 M hydrochloric acid (2 mL) and CH_2Cl_2 (1 mL) were added to the resultant residue. The mixture was stirred for 10 minutes at room temperature. After removal of the supernatant, the solid was dried under vacuum to afford the hydrochloride salt of compound 8 (60 mg) in an 80% yield.

CI-MS (M^++1): 411.3.

Example 9: Preparation of compound 9:



Compound 9

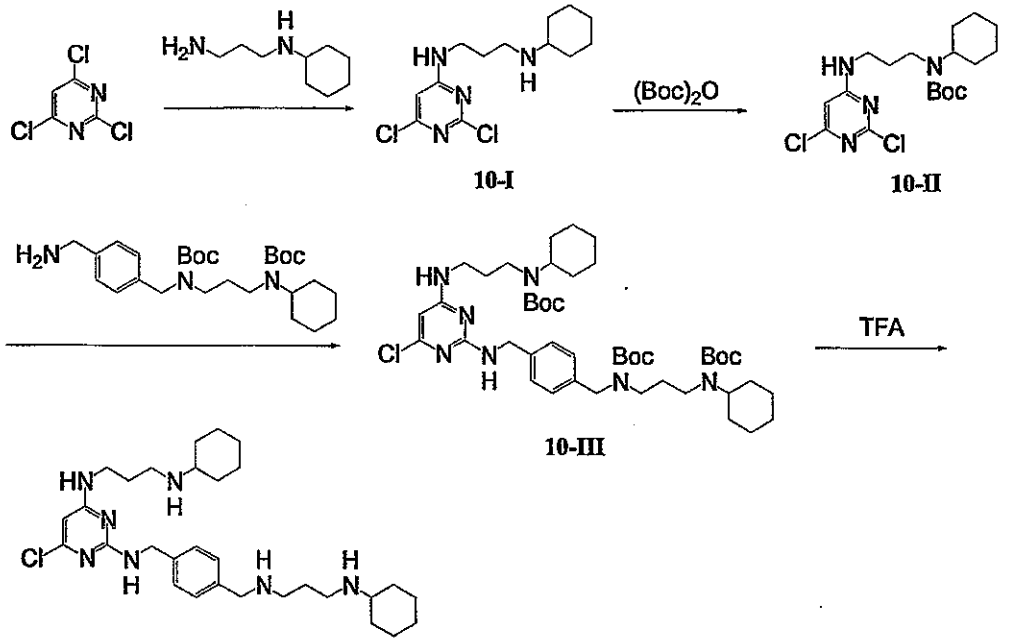
A solution of N-cyclohexyl-1,3-propanediamine (2.6 g), Et_3N (3.8 mL) and 2,4,6-trichloropyrimidine (1 g) in THF (50 mL) was stirred for overnight at 60°C and

concentrated by removing the solvent under vacuum. The residue was purified by chromatography on silica gel (21% NH_3 (aq)/MeOH = 5/95) to afford compound 9 (1.7 g) in a 75% yield.

CI-MS (M^++1): 423.3.

1 M hydrochloric acid (3 mL) and CH_2Cl_2 (2 ml) were added to compound 9 (100 mg). The mixture was stirred for 10 minutes at room temperature. After removing the supernatant, the solid was dried under vacuum to afford the hydrochloride salt of compound 9 (130 mg) in a 97% yield.

Example 10: Preparation of compound 10:



Compound 10

N-cyclohexyl-1,3-propanediamine (0.808 g) was slowly added to a stirred solution of 2,4,6-trichloropyrimidine (1 g) in THF (50 mL) at room temperature. The reaction mixture was stirred at 0°C for 2 hours and the reaction was allowed to warm-up to room temperature overnight. The solution was then concentrated to give a residue, which was purified by chromatography on silica gel (EtOAc/Hexane = 1/2) to afford Intermediate 10-I (1.386 g) in a 60% yield.

A solution of Intermediate 10-I (500 mg) and Boc_2O (770 mg) in CH_2Cl_2 (15 mL) was stirred at 25°C overnight. The solution was then concentrated and the resultant

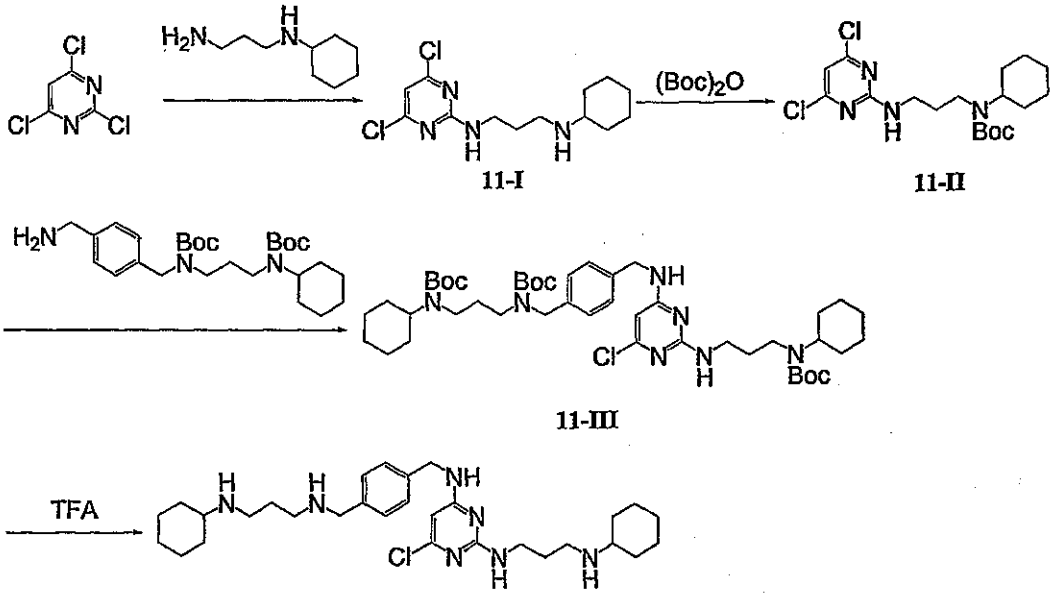
residue was purified by chromatography on silica gel (EtOAc/Hexane = 1/9) to afford Intermediate 10-II (590 mg) in an 80% yield.

Diisopropylethylamine (0.25 mL) was added to a solution of Intermediate 10-II (590 mg), Intermediate 8-III prepared in Example 8 (700 mg), and NaI (260 mg) in 1-pentanol (20 mL). The reaction mixture was stirred for 24 hours at 120°C and then concentrated by removing the solvent under vacuum. The resultant residue was dissolved in CH_2Cl_2, washed with water, dried with anhydrous $MgSO_4$, and concentrated to give a residue. The residue was purified by chromatography on silica gel (EtOAc/Hexane = 1/1) to afford Intermediate 10-III (865 mg) in a 70% yield.

A solution of 20% TFA/CH_2Cl_2 (3 mL) was added to a solution of Intermediate 10-III (150 mg) in CH_2Cl_2 (2 mL). The reaction mixture was stirred for 5 hours at room temperature and concentrated by removing the solvent. 1 M hydrochloric acid (3 mL) and CH_2Cl_2 (2 mL) were added to the residue. The mixture was stirred for another 10 minutes at room temperature. After removing the supernatant, the solid was dried under vacuum to afford the hydrochloride salt of compound 10 (107 mg) in an 80% yield.

CI-MS (M^++1): 542.4.

Example 11: Preparation of compound 11:



N-cyclohexyl-1,3-propanediamine (0.808 g) was slowly added to a stirred solution of 2,4,6-trichloropyrimidine (1 g) in THF (50 mL) at room temperature. The reaction mixture was stirred at 0°C for 2 hours and the reaction was allowed to warm-up to room temperature overnight. The solution was then concentrated to give a residue, which was purified by chromatography on silica gel (EtOAc/Hexane = 1/4) to afford intermediate 11-I (0.349 g) in a 21% yield.

A solution of intermediate 11-I (349 mg) and Boc_2O (540 mg) in CH_2Cl_2 (15 mL) was stirred at 25°C overnight. The solution was then concentrated and the resultant residue was purified by chromatography on silica gel (EtOAc/Hexane = 1/10) to afford intermediate 11-II (400 mg) in an 86% yield (CI-MS (M^++1): 403.4).

Diisopropylethylamine (0.17 mL) was added to a solution of intermediate 11-II (400 mg), intermediate 8-III (prepared in Example 8) (475 mg), and NaI (176 mg) in 1-pentanol (20 mL). The reaction mixture was stirred for 24 hours at 120°C and then concentrated by removing the solvent under vacuum. The resultant residue was dissolved in CH_2Cl_2, washed with water, dried with anhydrous $MgSO_4$, and concentrated to give a residue. The residue was purified by chromatography on silica gel (EtOAc/Hexane = 1/1) to afford Intermediate 11-III (427 mg) in a 51% yield.

A solution of 20% TFA/CH_2Cl_2 (4 mL) was added to a solution of intermediate 11-III (200 mg) in CH_2Cl_2 (2 mL). The reaction mixture was stirred for 5 hours at room temperature and concentrated by removing the solvent. 1 M hydrochloric acid (5 mL) and CH_2Cl_2 (2 mL) were added to the residue. The mixture was stirred for another 10 minutes at room temperature. After removing the supernatant, the solid was dried under vacuum to afford the hydrochloride salt of compound 11 (117 mg) in a 91% yield.

CI-MS (M^++1): 542.4.

Example 12: Preparation of compound 12:

Compound 12 was prepared in a manner similar to that used to prepare compound 8.

CI-MS (M^++1): 422.

Example 13: Preparation of compound 13:

Compound 13 was prepared in a manner similar to that used to prepare compound 10.

CI-MS (M^++1): 508.4.

Example 14: Preparation of compound 14:

Compound 14 was prepared in a manner similar to that used to prepare compound 8.

CI-MS (M^++1): 387.

Example 15: Preparation of compound 15:

Compound 15 was prepared in a manner similar to that used to prepare compound 8.

CI-MS (M^++1): 403.

Example 16: Preparation of compound 16:

Compound 16 was prepared in a manner similar to that used to prepare compound 8.

CI-MS (M^++1): 354.3.

Example 17: Preparation of compound 17:

Compound 17 was prepared in a manner similar to that used to prepare compound 11.

CI-MS (M^++1): 522.4.

Example 18: Preparation of compound 18:

Compound 18 was prepared in a manner similar to that used to prepare compound 10.

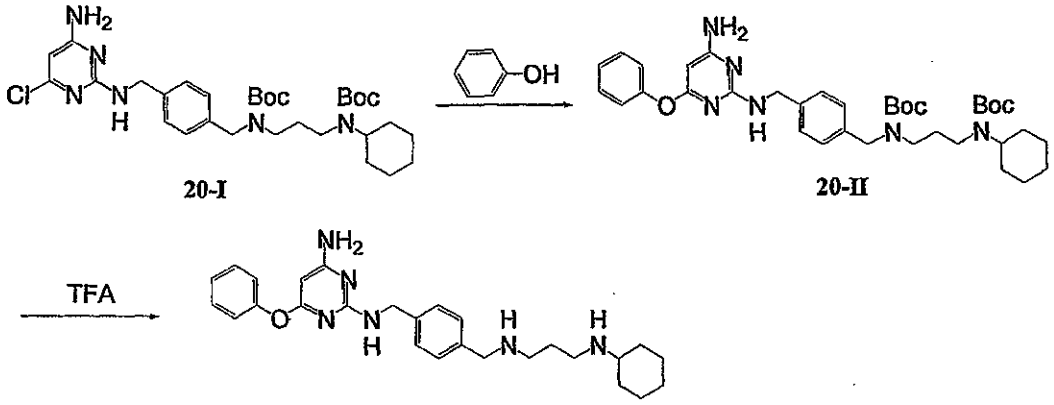
CI-MS (M^++1): 522.4.

Example 19: Preparation of compound 19:

Compound 19 was prepared in a manner similar to that used to prepare compound 11.

CI-MS (M^++1): 522.4.

Example 20: Preparation of compound 20:



Compound 20

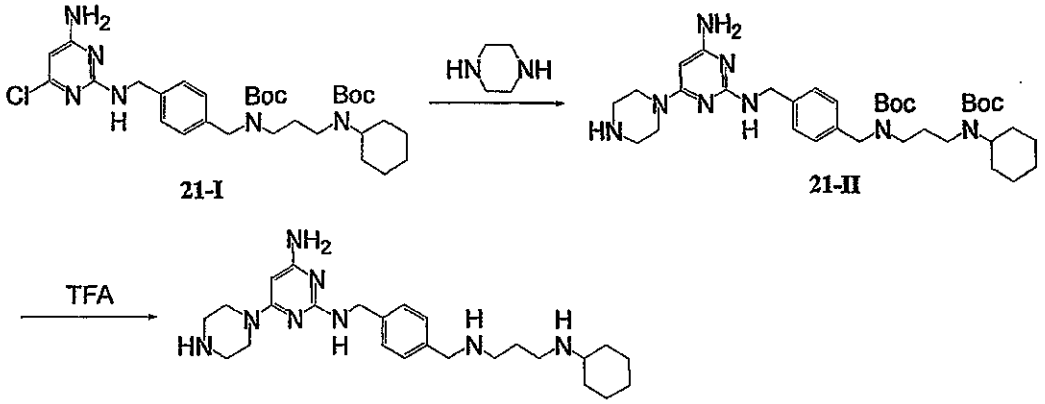
Intermediate 20-I was obtained as an intermediate during the preparation of compound 15.

NaH (110 mg) was added to a solution of the Intermediate 20-I (200 mg) and phenol (250 mg) in DMSO (3 mL). The reaction mixture was stirred at 25°C for 1 hour. The mixture was then heated at 120°C for 8 hours under microwave, cooled to room temperature, and concentrated by removing the solvent. The resultant residue was dissolved in CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, dried with anhydrous $MgSO_4$, and concentrated to give a residue. The residue was purified by chromatography on silica gel (EtOAc/Hexane = 1/1) to afford Intermediate 20-II (65 mg) in a 30% yield.

Intermediate 20-II (65 mg) in CH_2Cl_2 (1 mL) was added to a solution of 20% TFA/CH_2Cl_2 (2 mL). The reaction mixture was stirred for 5 hours at room temperature and concentrated by removing the solvent. 1 M hydrochloric acid (2 mL) and CH_2Cl_2 (1 mL) were subsequently added to the residue. The mixture was stirred for 10 minutes at room temperature. After removing the supernatant, the solid was dried under vacuum to afford the hydrochloride salt of compound 20 (45 mg) in an 80% yield.

CI-MS (M^++1): 461.3.

Example 21: Preparation of compound 21:



21-I

21-II

Compound 21

Intermediate 21-I was obtained as an intermediate during the preparation of compound 20.

A solution of 21-I (2 g) and piperazine (10 g) in 1-pentanol (3 mL) was stirred for 4 hours at 120°C and concentrated by removing the solvent under vacuum. The resultant mixture was dissolved in $CHCl_3$, washed with water, 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 = 1/99) to afford Intermediate 21-II (1.5 g) in a 60% yield.

A solution of 20% TFA/CH_2Cl_2 (3 mL) was added to a solution of Intermediate 20-II (130 mg) in CH_2Cl_2 (2 mL). The reaction mixture was stirred for 5 hours at room temperature and then concentrated by removing the solvent. 1 M hydrochloric acid (3 mL) and CH_2Cl_2 (2 ml) were added to the resultant residue. The mixture was stirred for another 10 minutes at room temperature. After removing the supernatant, the solid was dried under vacuum to afford the hydrochloride salt of compound 21 (90 mg) in an 80% yield.

CI-MS (M^++1): 453.3.

Example 22: Preparation of compound 22:

Compound 22 was prepared in a manner similar to that used to prepare compound 21.

CI-MS (M^++1): 497.4

Example 23: Preparation of compound 23:

Compound 23 was prepared in a manner similar to that used to prepare compound 21.

CI-MS (M^++1): 467.4.

Example 24: Preparation of compound 24:

Compound 24 was prepared in a manner similar to that used to prepare compound 10.

CI-MS (M^++1): 522.4.

Example 25: Preparation of compound 25:

Compound 25 was prepared in a manner similar to that used to prepare compound 11.

CI-MS (M^++1): 466.4.

Example 26: Preparation of compound 26:

Compound 26 was prepared in a manner similar to that used to prepare compound 8.

CI-MS (M^++1): 394.3.

Example 27: Preparation of compound 27:

Compound 27 was prepared in a manner similar to that used to prepare compound 21.

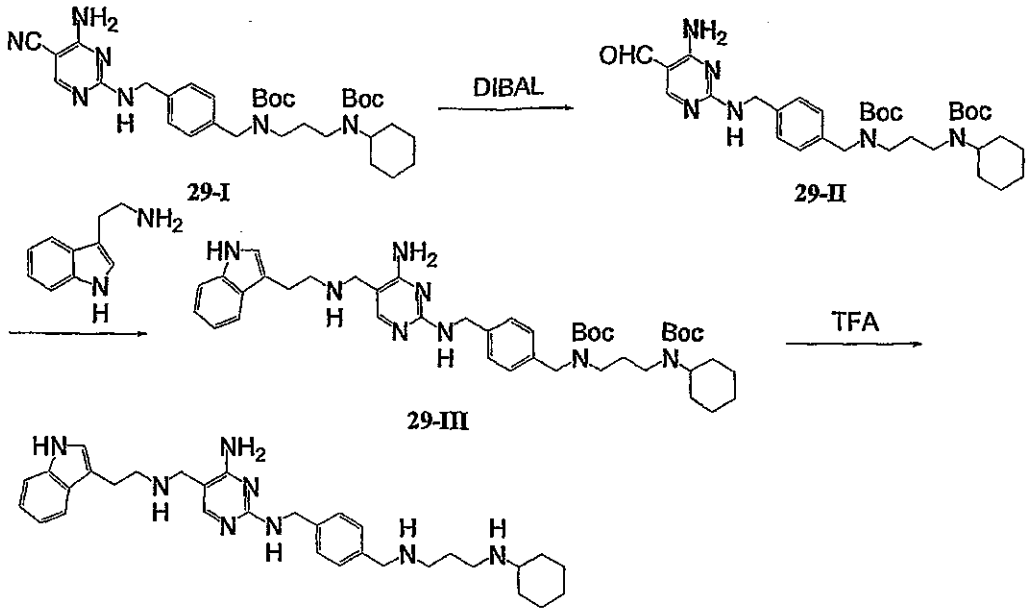
CI-MS (M^++1): 454.3.

Example 28: Preparation of compound 28:

Compound 28 was prepared in a manner similar to that used to prepare compound 21.

CI-MS (M^++1): 452.3.

Example 29: Preparation of compound 29:



Compound 29

Intermediate 29-I was obtained as an intermediate during the preparation of compound 26.

1M DIBAL/ether (8.35 mL) was added to a stirred solution of Intermediate 29-I (1.24 g) in dry toluene (100 mL) at -70~-78°C under N_2 (g). The reaction mixture was stirred for 2 hours at this temperature. 5% HCl (aq) (9 mL) was then added to the solution at -60~-70°C and the mixture was stirred for another 0.5 hour after the reaction temperature was increased to 25°C. To the solution was added CH_2Cl_2 (100 mL) and H_2O. The aqueous layer was extracted with CH_2Cl_2 twice. The organic layers were combined, dried with anhydrous $MgSO_4$, and concentrated by removing the solvent under vacuum. The resultant residue was purified by chromatography on silica gel (EtOAc/Hexane = 1/2) to afford Intermediate 29-II (620 mg) in a 50% yield.

A solution of tryptamine (99 mg) and Intermediate 29-II (170 mg) in CH_3OH (6 mL) was heated at 60°C for 6 hours. After cooling to room temperature, $NaBH_4$ (20 mg) was slowly added to the solution and the mixture was stirred for another 30 minutes. The mixture was concentrated, quenched with NH_4Cl (aq), extracted with CH_2Cl_2. The organic layer was dried with anhydrous $MgSO_4$ and concentrated to give a

residue. The residue was purified by chromatography on silica gel (EtOAc/MeOH = 9/1) to afford Intermediate 29-III (150 mg) in a 70% yield.

Intermediate 29-III (150 mg) in CH_2Cl_2 (2 mL) was added to a solution of 20% TFA/CH_2Cl_2 (3 mL). The reaction mixture was stirred for 5 hours at room temperature and concentrated by removing the solvent. 1 M hydrochloric acid (3 mL) and CH_2Cl_2 (2 mL) were added to the residue obtained above. The mixture was stirred for another 10 minutes at room temperature. After removal of the supernatant, the solid was dried under vacuum to afford the hydrochloride salt of compound 29 (92 mg) in a 70% yield.

CI-MS (M^++1): 541.4.

Example 30: Preparation of compound 30:

Compound 30 was prepared in a manner similar to that used to prepare compound 29.

CI-MS (M^++1): 528.3.

Example 31: Preparation of compound 31:

Compound 31 was prepared in a manner similar to that used to prepare compound 21.

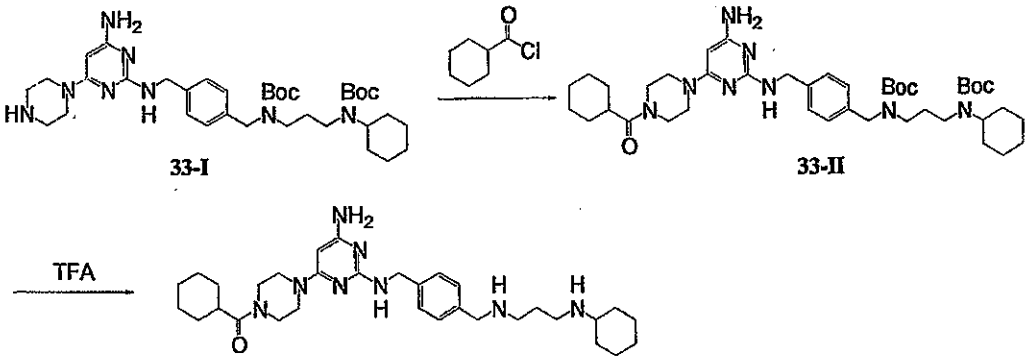
CI-MS (M^++1): 481.4.

Example 32: Preparation of compound 32:

Compound 32 was prepared in a manner similar to that used to prepare compound 21.

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

Example 33: Preparation of compound 33:



Compound 33

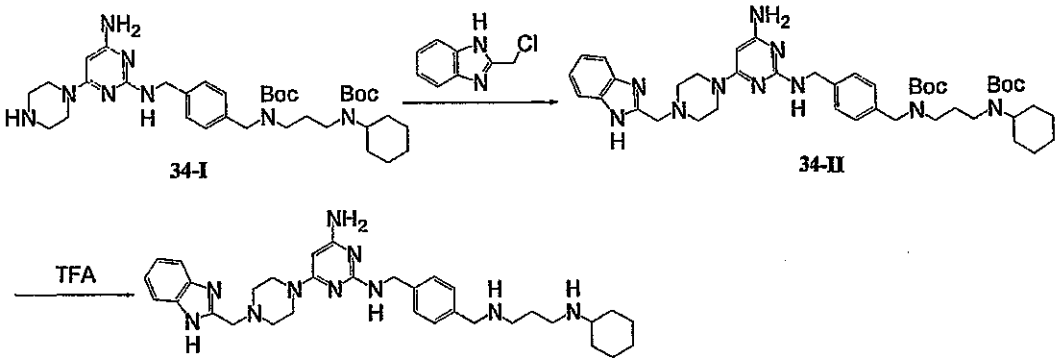
Intermediate 33-I was obtained as an intermediate during the preparation of compound 21.

Diisopropylethylamine (0.1 mL) and cyclohexanecarbonyl chloride (55 mg) were added to a solution of Intermediate 33-I (200 mg) in CH_2Cl_2 (10 mL). The reaction mixture was stirred overnight at room temperature and then concentrated by removing the solvent. The resultant mixture was dissolved in $CHCl_3$, washed with water, dried with anhydrous $MgSO_4$, and concentrated to give a residue. The residue was purified by chromatography on silica gel (EtOAc/Hexane = 1/1) to afford Intermediate 33-II (140 mg) in a 60% yield.

A solution of 20% TFA/CH_2Cl_2 (3 mL) was added to a solution of Intermediate 33-II (140 mg) in CH_2Cl_2 (2 mL). The reaction mixture was stirred for 5 hours at room temperature and concentrated by removing the solvent. 1 M hydrochloric acid (3 mL) and CH_2Cl_2 (2 mL) were added to the residue. The resultant mixture was stirred for another 10 minutes at room temperature. After removal of the supernatant, the solid was dried under vacuum to afford the hydrochloride salt of compound 33 (100 mg) in an 80% yield.

CI-MS (M^++1): 563.4.

Example 34: Preparation of compound 34:

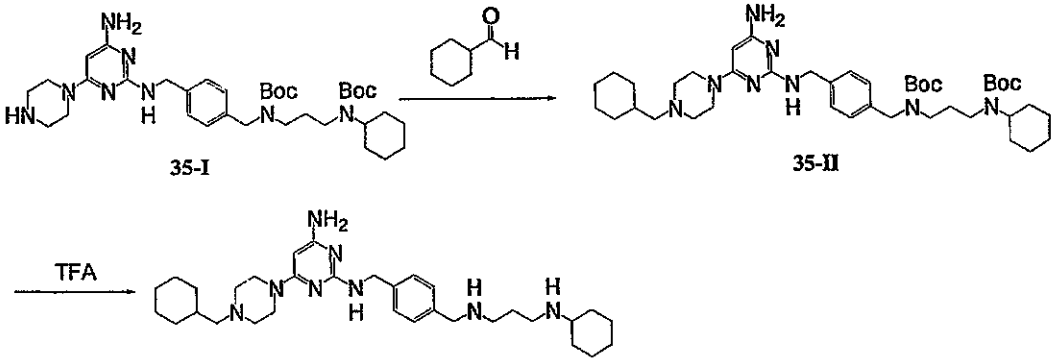


Intermediate 34-I was obtained as an intermediate during the preparation of compound 21. Intermediate 34-I (166 mg) was first dissolved in CH_3CN (10 mL). 2-chloromethylbenzimidazole (42 mg) and K_2CO_3 (79 mg) were then added to the above solution. After the mixture was stirred for 48 hours at room temperature, it was filtered and concentrated. The resultant residue was purified by chromatography on silica gel (EtOAc/MeOH = 10/1) to afford Intermediate 34-II (70 mg) in a 35% yield.

A solution of 20% TFA/CH_2Cl_2 (2 mL) was added to a solution of Intermediate 34-II (70 mg) in CH_2Cl_2 (1 mL). The reaction mixture was stirred for 5 hours at room temperature and concentrated by removing the solvent. 1 M hydrochloric acid (2 mL) and CH_2Cl_2 (1 mL) were added to the resultant residue. The mixture was stirred for another 10 minutes at room temperature. After removal of the supernatant, the solid was dried under vacuum to afford the hydrochloride salt of compound 34 (50 mg) in an 80% yield.

CI-MS (M^++1): 583.4.

Example 35: Preparation of compound 35:



Compound 35

Intermediate 35-I was obtained as an intermediate during the preparation of compound 21.

$NaBH(OAc)_3$ (215 mg) was added to a solution of Intermediate 35-I (166 mg) in MeOH (10 mL) and cyclohexanecarbaldehyde (57 mg). A few drops of acetic acid was then added. The reaction mixture was stirred for 48 hours at room temperature and concentrated by removing the solvent through distillation. The resultant mixture was dissolved in CH_2Cl_2 and quenched with saturated aqueous $NaHCO_3$. The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic layers were subsequently washed with water, dried with anhydrous $MgSO_4$, filtered, and concentrated to give a residue. The residue was purified by chromatography on silica gel (EtOAc/Hexane = 2/1) to give Intermediate 35-II (120 mg) in a 65% yield.

A solution of 20% TFA/CH_2Cl_2 (3 mL) was added to a solution of Intermediate 35-II (120 mg) in CH_2Cl_2 (2 mL). The reaction mixture was stirred for 5 hours at room temperature and concentrated by removing the solvent. 1 M hydrochloric acid (3 mL) and CH_2Cl_2 (2 mL) were added to the residue. The mixture was stirred for another 10 minutes at room temperature. After removal of the supernatant, the solid was dried under vacuum to afford the hydrochloride salt of compound 35 (85 mg) in an 80% yield.

CI-MS (M^++1): 549.4.

Example 36: Preparation of compound 36:

Compound 36 was prepared in a manner similar to that used to prepare compound 35.

CI-MS (M^++1): 543.4.

Example 37: Preparation of compound 37:

Compound 37 was prepared in a manner similar to that used to prepare compound 21.

CI-MS (M^++1): 563.4.

Example 38: Preparation of compound 38:

Compound 38 was prepared in a manner similar to that used to prepare compound 21.

CI-MS (M^++1): 564.4.

Example 39: Preparation of compound 39:

Compound 39 was prepared in a manner similar to that used to prepare compound 21.

CI-MS (M^++1): 566.4.

Example 40: Preparation of compound 40:

Compound 40 was prepared in a manner similar to that used to prepare compound 21.

CI-MS (M^++1): 587.4.

Example 41: Preparation of compound 41:

Compound 41 was prepared in a manner similar to that used to prepare compound 33.

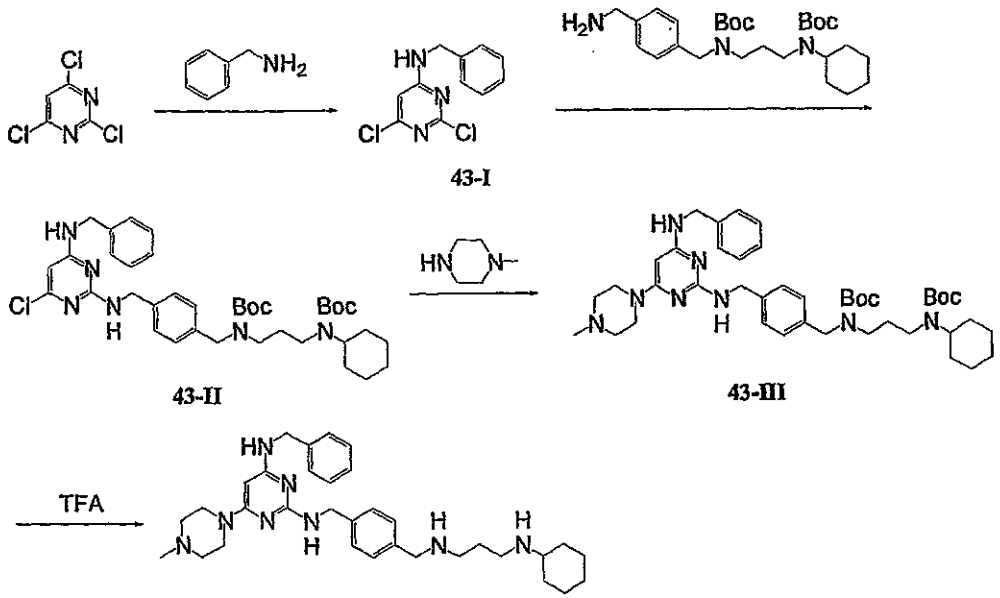
CI-MS (M^++1): 523.4.

Example 42: Preparation of compound 42:

Compound 42 was prepared in a manner similar to that used to prepare compound 33.

CI-MS (M^++1): 557.4.

Example 43: Preparation of compound 43:



Intermediate 43-I was prepared in a 45 % yield in a manner similar to that described in the first paragraph of Example 10 using benzylamine (645 mg) as a starting material.

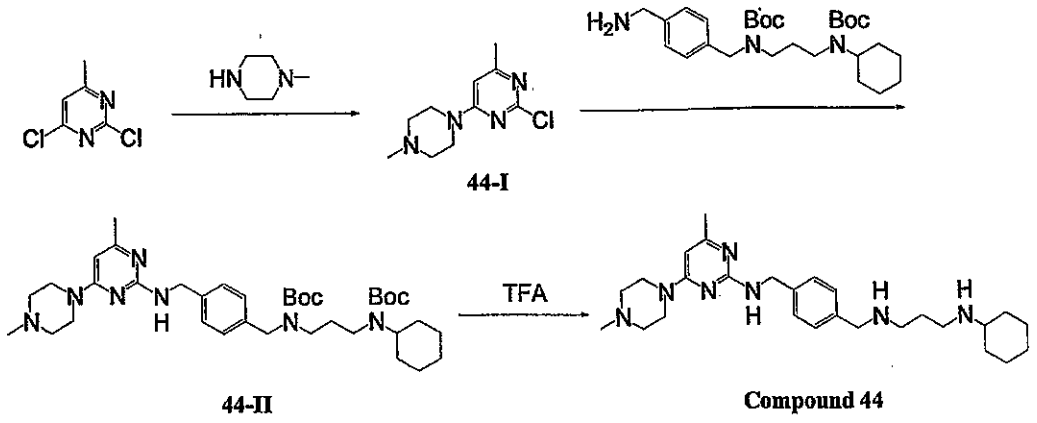
Diisopropylethylamine (0.27 mL) was added to a solution of Intermediate 43-I (625 mg), Intermediate 8-III prepared in Example 8 (741 mg), and NaI (275 mg) in 1-pentanol (20 mL). The reaction mixture was stirred at 120°C for 24 hours and concentrated by removing the solvent under vacuum. The resultant mixture was dissolved in CH_2Cl_2, washed with water, dried with anhydrous $MgSO_4$, and concentrated to give a residue. The residue was purified by chromatography on silica gel (EtOAc/Hexane = 1/3) to afford Intermediate 43-II (1,100 mg) in a 65% yield.

A solution of Intermediate 43-II (200 mg) and N-methylpiperazine (2,000 mg) in 1-pentanol (1 mL) was stirred at 120°C for 4 hours. The solvent was then removed under vacuum. The resultant mixture was dissolved in $CHCl_3$, washed with water, dried with anhydrous $MgSO_4$, and concentrated to give a residue. The residue was purified by chromatography on silica gel (EtOAc/MeOH = 20/1) to afford Intermediate 43-III (215 mg) in a 70% yield.

A solution of 20% TFA/CH_2Cl_2 (4 mL) was added to a solution of Intermediate 43-III (215 mg) in CH_2Cl_2 (2 mL). The reaction mixture was stirred for 5 hours at room temperature and concentrated by removing the solvent. 1 M hydrochloric acid (4 mL) and CH_2Cl_2 (2 mL) were added to the residue. The mixture was stirred for another 10 minutes at room temperature. After removal of the supernatant, the solid was dried under vacuum to afford the hydrochloride salt of compound 43 (150 mg) in an 80% yield.

CI-MS (M^++1): 557.4.

Example 44: Preparation of compound 44:



1-Methylpiperazine (0.76 g) and Et_3N (0.8 mL) were added to a solution of 2,4-dichloro-6-methylpyrimidine (1 g) in EtOH (60 mL). The reaction solution was stirred at 0°C for 1 hour and then was allowed to warm-up to room temperature within 3 hours. The solution was then concentrated to give a residue, which was purified by chromatography on silica gel (EtOAc/MeOH = 6/1) to afford Intermediate 44-I (0.76 g) in a 55% yield.

Diisopropylethylamine (0.25 mL) was added to a solution of Intermeidate 44-I (300 mg), Intermediate 8-III prepared in Example 8 (689 mg), and NaI (260 mg) in 1-pentanol (20 mL). The reaction mixture was stirred for 24 hours at 120°C and concentrated by removing the solvent under vacuum. The resultant mixture was dissolved in CH_2Cl_2, washed with water, dried with anhydrous $MgSO_4$, and concentrated to give a residue. The residue was purified by chromatography on silica gel (EtOAc/MeOH = 5/1) to afford Intermediate 44-II (530 mg) in a 60% yield.

A solution of 20% TFA/CH_2Cl_2 (3 mL) was added to a solution of compound Intermediate 44-II (150 mg) in CH_2Cl_2 (2 mL). The reaction mixture was stirred for 5 hours at room temperature and concentrated by removing the solvent. 1 M hydrochloric acid (3 mL) and CH_2Cl_2 (2 mL) were added to the residue. The mixture was stirred for another 10 minutes at room temperature. After removal of the supernatant, the solid was dried under vacuum to afford the hydrochloride salt of compound 44 (100 mg) in an 80% yield.

CI-MS (M^++1): 466.4.

Example 45: Preparation of compound 45:

Compound 45 was prepared in a manner similar to that used to prepare compound 43.

CI-MS (M^++1): 493.3.

Example 46: Preparation of compound 46:

Compound 46 was prepared in a manner similar to that used to prepare compound 43.

CI-MS (M^++1): 587.4.

Example 47: Preparation of compound 47:

Compound 47 was prepared in a manner similar to that used to prepare compound 21.

CI-MS (M^++1): 549.4.

Example 48: Preparation of compound 48:

Compound 48 was prepared in a manner similar to that used to prepare compound 21.

CI-MS (M^++1): 524.4.

Example 49: Preparation of compound 49:

Compound 49 was prepared in a manner similar to that used to prepare compound 21.

CI-MS (M^++1): 521.4.

Example 50: Preparation of compound 50:

Compound 50 was prepared in a manner similar to that used to prepare compound 43.

CI-MS (M^++1): 550.4.

Example 51: Preparation of compound 51:

Compound 51 was prepared in a manner similar to that used to prepare compound 43.

CI-MS (M^++1): 580.4.

Example 52: Preparation of compound 52:

Compound 52 was prepared in a manner similar to that used to prepare compound 43.

CI-MS (M^++1): 567.4.

Example 53: Preparation of compound 53:

Compound 53 was prepared in a manner similar to that used to prepare compound 44.

CI-MS (M^++1): 542.4.

Example 54: Preparation of compound 54:

Compound 54 was prepared in a manner similar to that used to prepare compound 44.

CI-MS (M^++1): 548.4.

Example 55: Preparation of compound 55:

Compound 55 was prepared in a manner similar to that used to prepare compound 44.

CI-MS (M^++1): 520.4.

Example 56: Preparation of compound 56:

Compound 56 was prepared in a manner similar to that used to prepare compound 44.

CI-MS (M^++1): 562.5.

Example 57: Preparation of compound 57:

Compound 57 was prepared in a manner similar to that used to prepare compound 44.

CI-MS (M^++1): 508.4.

Example 58: Preparation of compound 58:

Compound 58 was prepared in a manner similar to that used to prepare compound 44.

CI-MS (M^++1): 496.4.

Example 59: Preparation of compound 59:

Compound 59 was prepared in a manner similar to that used to prepare compound 44.

CI-MS (M^++1): 534.4.

Example 60: Preparation of compound 60:

Compound 60 was prepared in a manner similar to that used to prepare compound 44.

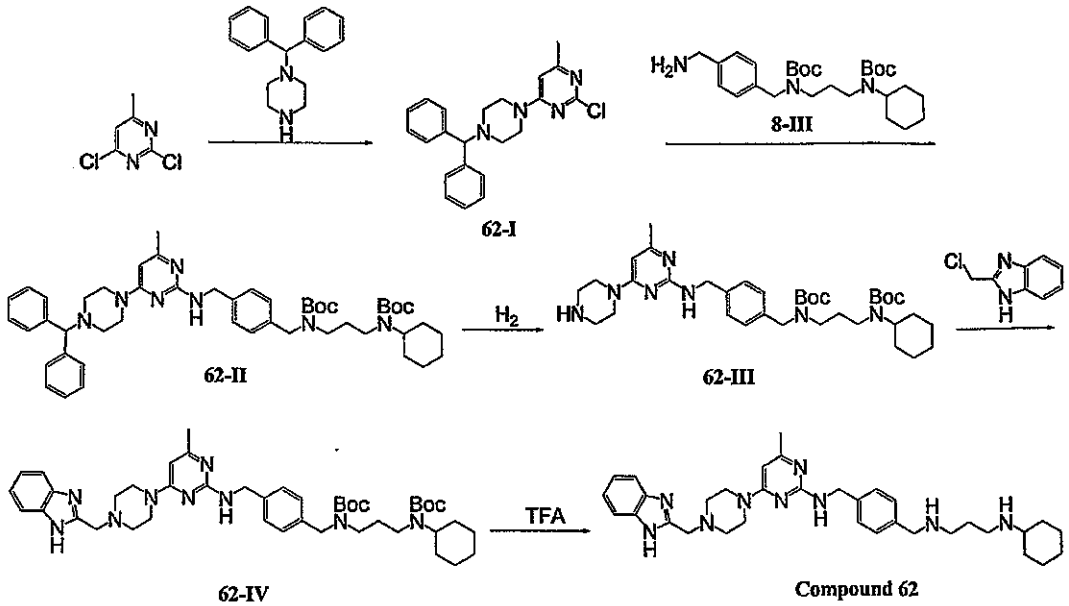
CI-MS (M^++1): 556.4.

Example 61: Preparation of compound 61:

Compound 61 was prepared in a manner similar to that used to prepare compound 44.

CI-MS (M^++1): 618.4.

Example 62: Preparation of compound 62:



1-(Diphenylmethyl)piperazine (3.78 g) and Et_3N (2.3 mL) were added to a solution of 2,4-dichloro-6-methylpyrimidine (2.43 g) in EtOH (200 mL). The reaction mixture was stirred at 0°C for 1 hour and then was allowed to warm-up to room temperature within 15 hours. The solution was then concentrated to give a residue, which was purified by chromatography on silica gel (EtOAc/Hexane = 1/5) to afford intermediate 62-I (4.0 g) in a 70% yield.

Diisopropylethylamine (4.09 g) was added to a solution of intermediate 92-I (4.0 g), intermediate 8-III prepared in Example 8 (5.29 g), and NaI (2.38 g) in 1-pentanol (10 mL). The reaction mixture was stirred for 15 hours at 140°C and concentrated by removing the solvent under vacuum. The resultant mixture was dissolved in CH_2Cl_2, washed with water, dried with anhydrous $MgSO_4$, and concentrated to give a residue. The residue was purified by chromatography on silica gel (EtOAc/Hexane = 1/1) to afford intermediate 62-II (2.7 g) in a 31% yield.

A solution of intermediate 62-II (2.7 g) and Pd/C (2.0 g) in isopropanol (30 ml) was stirred under H_2 (balloon) at 60°C for 3 hours and then filtered through a celite column and concentrated. The resultant residue was purified by chromatography on silica gel (EtOAc/ MeOH = 10/1) to afford intermediate 62-III (1.1 g) in a 50% yield.

Intermediate 62-III (200 mg) was first dissolved in CH_3CN (10 mL). 2-chloromethylbenzimidazole (51 mg) and K_2CO_3 (86 mg) were then added to the above solution. After the mixture was stirred for 48 hours at room temperature, it was filtered and concentrated. The resultant residue was purified by chromatography on silica gel (EtOAc/MeOH = 10/1) to afford intermediate 62-IV (100 mg) in a 42% yield.

A solution of 20% TFA/CH_2Cl_2 (3 mL) was added to a solution of intermediate 62-IV (100 mg) in CH_2Cl_2 (2 mL). The reaction mixture was stirred for 5 hours at room temperature and concentrated by removing the solvent. 1 M hydrochloric acid (3 mL) and CH_2Cl_2 (2 mL) were added to the residue. The mixture was stirred for another 10 minutes at room temperature. After removal of the supernatant, the solid was dried under vacuum to afford the hydrochloride salt of compound 62 (100 mg) in a 84% yield.

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

Example 63: Preparation of compound 63:

Compound 63 was prepared in a manner similar to that used to prepare compound 44.

CI-MS (M^++1): 572.4.

Example 64: Preparation of compound 64:

Compound 64 was prepared in a manner similar to that used to prepare compound 44.

CI-MS (M^++1): 576.4.

Example 65: Preparation of compound 65:

Compound 65 was prepared in a manner similar to that used to prepare compound 21.

CI-MS (M^++1): 525.4.

Example 66: Preparation of compound 66:

Compound 66 was prepared in a manner similar to that used to prepare compound 21.

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

Example 67: Preparation of compound 67:

Compound 67 was prepared in a manner similar to that used to prepare compound 21.

CI-MS (M^++1): 569.4.

Example 68: Preparation of compound 68:

Compound 68 was prepared in a manner similar to that used to prepare compound 21.

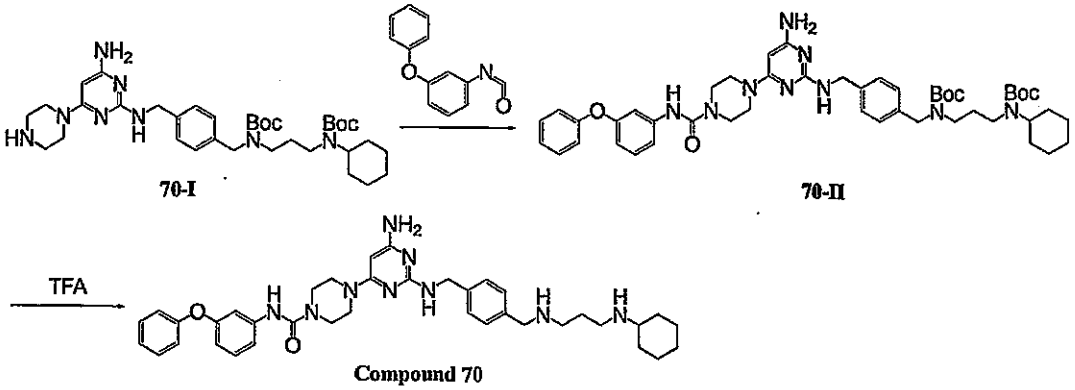
CI-MS (M^++1): 525.4.

Example 69: Preparation of compound 69:

Compound 69 was prepared in a manner similar to that used to prepare compound 21.

CI-MS (M^++1): 547.3.

Example 70: Preparation of compound 70:



Intermediate 70-I was obtained during the preparation of compound 21.

A solution of intermediate 70-I (150 mg), 3-phenoxyphenyl isocyanate (48 mg) and Et_3N (46 mg) in CH_2Cl_2 (15 ml) was stirred at 25°C overnight and then concentrated. The resultant residue was purified by chromatography on silica gel (EtOAc/MeOH = 20/1) to afford Intermediate 70-II (163 mg) in a 82% yield.

A solution of 20% TFA/CH_2Cl_2 (3 mL) was added to a solution of intermediate 70-II (163 mg) in CH_2Cl_2 (2 mL). The reaction mixture was stirred for 5 hours at room temperature and concentrated by removing the solvent. 1 M hydrochloric acid (3 mL) and CH_2Cl_2 (2 mL) were added to the residue. The mixture was stirred for another 10 minutes at room temperature. After removal of the supernatant, the solid was dried under vacuum to afford the hydrochloride salt of compound 70 (164 mg) in a 86% yield.

CI-MS (M^++1): 664.4.

Example 71: Preparation of compound 71:

Compound 71 was prepared in a manner similar to that used to prepare compound 21.

CI-MS (M^++1): 597.4.

Example 72: Preparation of compound 72:

Compound 72 was prepared in a manner similar to that used to prepare compound 21.

CI-MS (M^++1): 468.3.

Example 73: Preparation of compound 73:

Compound 73 was prepared in a manner similar to that used to prepare compound 21.

CI-MS (M^++1): 530.4.

Example 74: Preparation of compound 74:

Compound 74 was prepared in a manner similar to that used to prepare compound 35.

CI-MS (M^++1): 523.4.

Example 75: Preparation of compound 75:

Compound 75 was prepared in a manner similar to that used to prepare compound 35.

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

Example 76: Preparation of compound 76:

Compound 76 was prepared in a manner similar to that used to prepare compound 44.

CI-MS (M^++1): 566.4.

Example 77: Preparation of compound 77:

Compound 77 was prepared in a manner similar to that used to prepare compound 44.

CI-MS (M^++1): 386.

Example 78: Preparation of compound 78:

Compound 78 was prepared in a manner similar to that used to prepare compound 44.

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

Example 79: Preparation of compound 79:

Compound 79 was prepared in a manner similar to that used to prepare compound 70.

CI-MS (M^++1): 640.4.

Example 80: Preparation of compound 80:

Compound 80 was prepared in a manner similar to that used to prepare compound 33.

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

Example 81: Preparation of compound 81:

Compound 81 was prepared in a manner similar to that used to prepare compound 33.

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

Example 82: Preparation of compound 82:

Compound 82 was prepared in a manner similar to that used to prepare compound 33.

CI-MS (M^++1): 521.4.

Example 83: Preparation of compound 83:

Compound 83 was prepared in a manner similar to that used to prepare compound 33.

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

Example 84: Preparation of compound 84:

Compound 84 was prepared in a manner similar to that used to prepare compound 44.

CI-MS (M^++1): 524.4.

Example 85: Preparation of compound 85:

Compound 85 was prepared in a manner similar to that used to prepare compound 44.

CI-MS (M^++1): 546.3.

Example 86: Preparation of compound 86:

Compound 86 was prepared in a manner similar to that used to prepare compound 70.

CI-MS (M^++1): 552.4.

Example 87: Preparation of compound 87:

Compound 87 was prepared in a manner similar to that used to prepare compound 35.

CI-MS (M^++1): 523.4.

Example 88: Preparation of compound 88:

Compound 88 was prepared in a manner similar to that used to prepare compound 35.

CI-MS (M^++1): 509.4.

Example 89: Preparation of compound 89:

Compound 89 was prepared in a manner similar to that used to prepare compound 43.

CI-MS (M^++1): 475.3.

Example 90: Preparation of compound 90:

Compound 90 was prepared in a manner similar to that used to prepare compound 44.

CI-MS (M^++1): 453.4.

Example 91: Preparation of compound 91:

Compound 91 was prepared in a manner similar to that used to prepare compound 44.

CI-MS (M^++1): 494.4.

Example 92: Preparation of compound 92:

Compound 92 was prepared in a manner similar to that used to prepare compound 34.

CI-MS (M^++1): 601.4.

Example 93: Preparation of compound 93:

Compound 93 was prepared in a manner similar to that used to prepare compound 34.

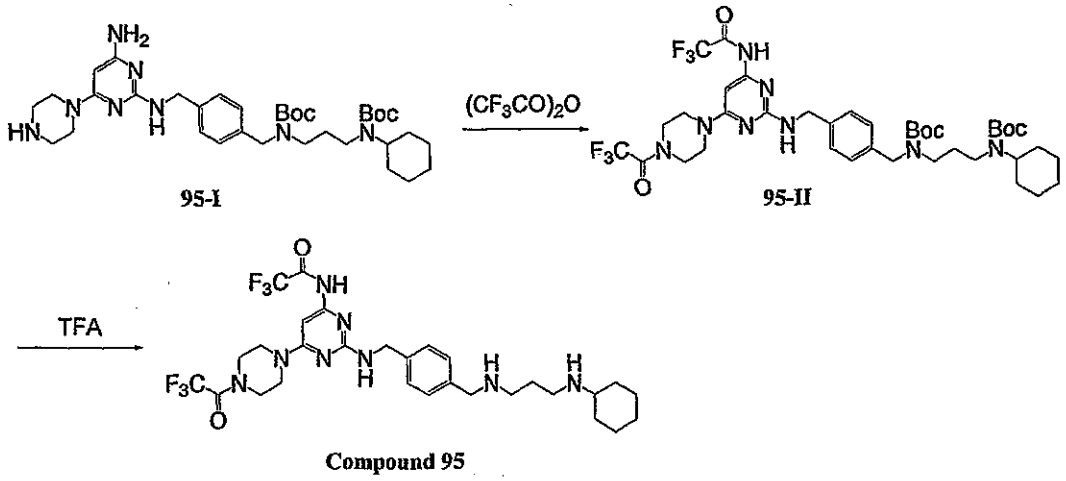
CI-MS (M^++1): 535.4.

Example 94: Preparation of compound 94:

Compound 94 was prepared in a manner similar to that used to prepare compound 33.

CI-MS (M^++1): 577.4.

Example 95: Preparation of compound 95:



Intermediate 95-I was obtained during the preparation of compound 21.

A solution of intermediate 95-I (150 mg), trifluoroacetic anhydride (240 mg), and Et_3N (230 mg) in CH_2Cl_2 (10 ml) was stirred at 25°C overnight and then concentrated. The resultant residue was purified by chromatography on silica gel (EtOAc/MeOH = 20/1) to afford Intermediate 95-II (148 mg) in a 76% yield.

A solution of 20% TFA/CH_2Cl_2 (3 mL) was added to a solution of compound 95-II (148 mg) in CH_2Cl_2 (2 mL). The reaction mixture was stirred for 5 hours at room temperature and concentrated by removing the solvent. 1 M hydrochloric acid (3 mL) and CH_2Cl_2 (2 mL) were added to the residue. The mixture was stirred for another 10

minutes at room temperature. After removal of the supernatant, the solid was dried under vacuum to afford the hydrochloride salt of compound 95 (127 mg) in a 92% yield.

CI-MS (M^++1): 645.3.

Example 96: Preparation of compound 96:

Compound 96 was prepared in a manner similar to that used to prepare compound 43.

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

Example 97: Preparation of compound 97:

Compound 97 was prepared in a manner similar to that used to prepare compound 43.

CI-MS (M^++1): 519.3.

Example 98: Preparation of compound 98:

Compound 98 was prepared in a manner similar to that used to prepare compound 43.

CI-MS (M^++1): 511.3.

Example 99: Preparation of compound 99:

Compound 99 was prepared in a manner similar to that used to prepare compound 43.

CI-MS (M^++1): 459.3.

Example 100: Preparation of compound 100:

Compound 100 was prepared in a manner similar to that used to prepare compound 43.

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

Example 101: Preparation of compound 101:

Compound 101 was prepared in a manner similar to that used to prepare compound 43.

CI-MS (M^++1): 605.5.

Example 102: Preparation of compound 102:

Compound 102 was prepared in a manner similar to that used to prepare compound 43.

CI-MS (M^++1): 553.4.

Example 103: Preparation of compound 103:

Compound 103 was prepared in a manner similar to that used to prepare compound 44.

CI-MS (M^++1): 549.4.

Example 104: Preparation of compound 104:

Compound 104 was prepared in a manner similar to that used to prepare compound 44.

CI-MS (M^++1): 523.4.

Example 105: Preparation of compound 105:

Compound 105 was prepared in a manner similar to that used to prepare compound 44.

CI-MS (M^++1): 524.4.

Example 106: Preparation of compound 106:

Compound 106 was prepared in a manner similar to that used to prepare compound 33.

CI-MS (M^++1): 580.4.

Example 107: Preparation of compound 107:

Compound 107 was prepared in a manner similar to that used to prepare compound 44.

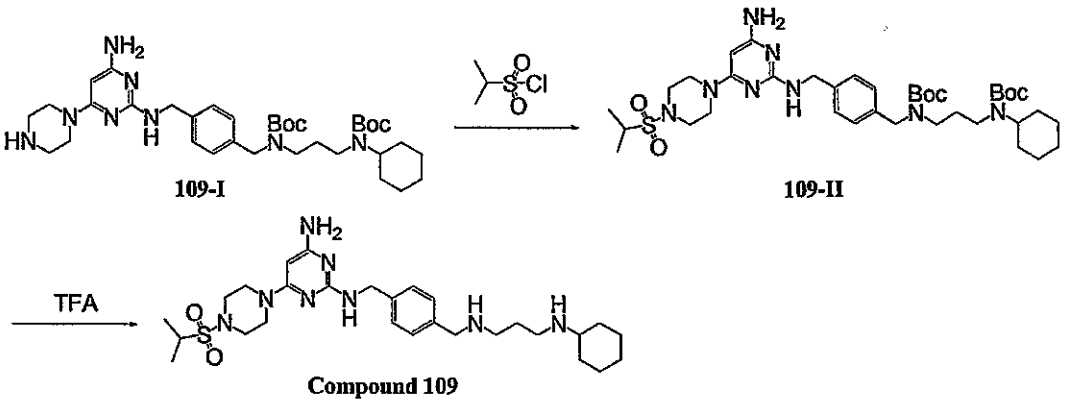
CI-MS (M^++1): 580.4.

Example 108: Preparation of compound 108:

Compound 108 was prepared in a manner similar to that used to prepare compound 44.

CI-MS (M^++1): 563.4.

Example 109: Preparation of compound 109:



Intermediate 109-I was obtained during the preparation of compound 21.

A solution of intermediate 109-I (100 mg), isopropylsulfonyl chloride (35 mg), and Et_3N (30 mg) in CH_2Cl_2 (10 ml) was stirred at 25°C for overnight and then concentrated. The resultant residue was purified by chromatography on silica gel (EtOAc/MeOH = 20/1) to afford intermediate 109-II (100 mg) in a 86% yield.

A solution of 20% TFA/CH_2Cl_2 (3 mL) was added to a solution of compound 109-II (100 mg) in CH_2Cl_2 (2 mL). The reaction mixture was stirred for 5 hours at room temperature and concentrated by removing the solvent. 1 M hydrochloric acid (3 mL) and CH_2Cl_2 (2 mL) were added to the residue. The mixture was stirred for another 10 minutes at room temperature. After removal of the supernatant, the solid was dried under vacuum to afford the hydrochloride salt of compound 109 (80 mg) in a 87% yield.

CI-MS (M^++1): 559.3.

Example 110: Preparation of compound 110:

Compound 110 was prepared in a manner similar to that used to prepare compound 70.

CI-MS (M^++1): 602.4.

Example 111: Preparation of compound 111:

Compound 111 was prepared in a manner similar to that used to prepare compound 70.

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

Example 112: Preparation of compound 112:

Compound 112 was prepared in a manner similar to that used to prepare compound 44.

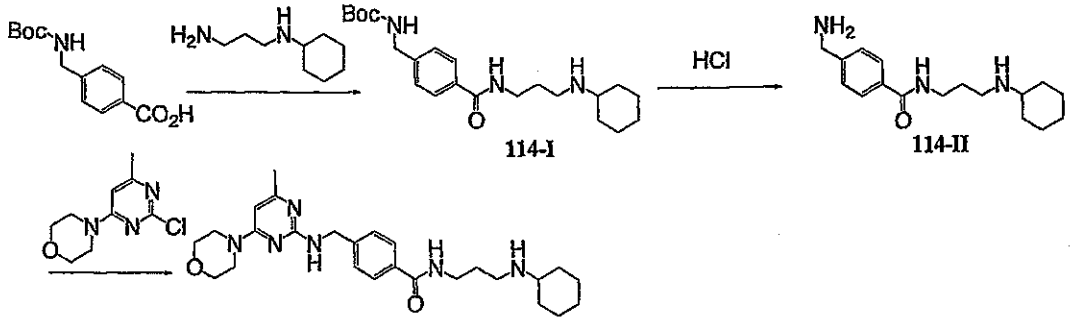
CI-MS (M^++1): 537.4.

Example 113: Preparation of compound 113:

Compound 113 was prepared in a manner similar to that used to prepare compound 33.

CI-MS (M^++1): 563.4.

Example 114: Preparation of compound 114:



Compound 114

4-(tert-butoxycarbonylamino-methyl)benzoic acid (1,000 mg) was dissolved in CH_2Cl_2 (50 mL). N-cyclohexyl-1,3-propanediamine (745 mg), 1-hydroxybenzo-triazole hydrate (HOBt, 645 mg), 4-methylmorpholine (1,607 mg), and 1-(3-(dimethyl-

amino)propyl)-3-ethylcarbodiimide hydrochloride (EDC, 740 mg) were added to the above solution sequentially. The reaction mixture was stirred at 25°C for 18 hours and then was partitioned between water (150 mL) and EtOAc (2×150 mL). The combined organic layers were dried over Na_2SO_4 and were concentrated. The resultant residue was purified by chromatography on silica gel (EtOAc/MeOH = 20/1) to afford intermediate 114-I (1,000 mg) in a 65% yield.

A solution of HCl in ether (1.0 M, 20 mL) was added to a solution of 114-I (1,000 mg) in MeOH (10 mL) at 25 °C. The mixture was stirred for 12 hours at room temperature. After removal of the supernatant, the solid was dried under vacuum to afford the hydrochloride salt of intermediate 114-II (743 mg) in a 73% yield.

Diisopropylethylamine (134 mg) was added to a solution of intermediate 114-II (250 mg), intermediate 90-I prepared in Example 90 (184 mg), and NaI (22 mg) in 1-pentanol (5 mL). The reaction mixture was stirred for 15 hours at 140°C and concentrated by removing the solvent under vacuum. The resultant mixture was dissolved in CH_2Cl_2, washed with water, 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 = 1/15) to give compound 114 (213 mg) in a 53% yield.

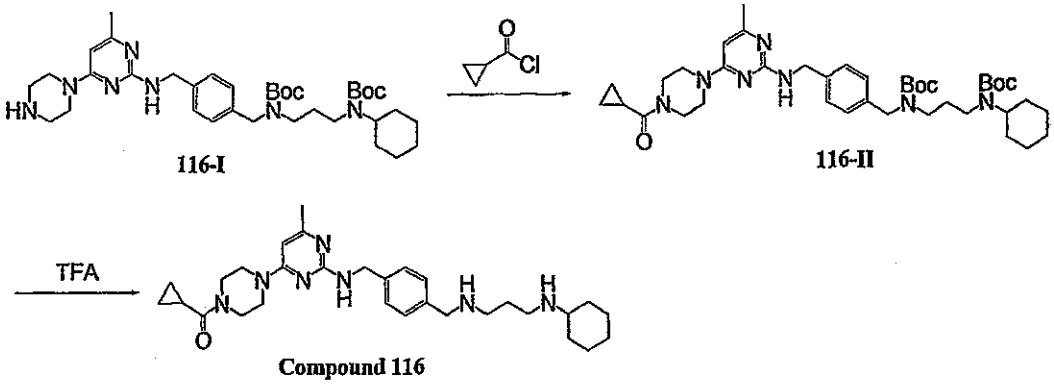
CI-MS (M^++1): 467.3.

Example 115: Preparation of compound 115:

Compound 115 was prepared in a manner similar to that used to prepare compound 44.

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

Example 116: Preparation of compound 116:



116-I 116-II

Compound 116

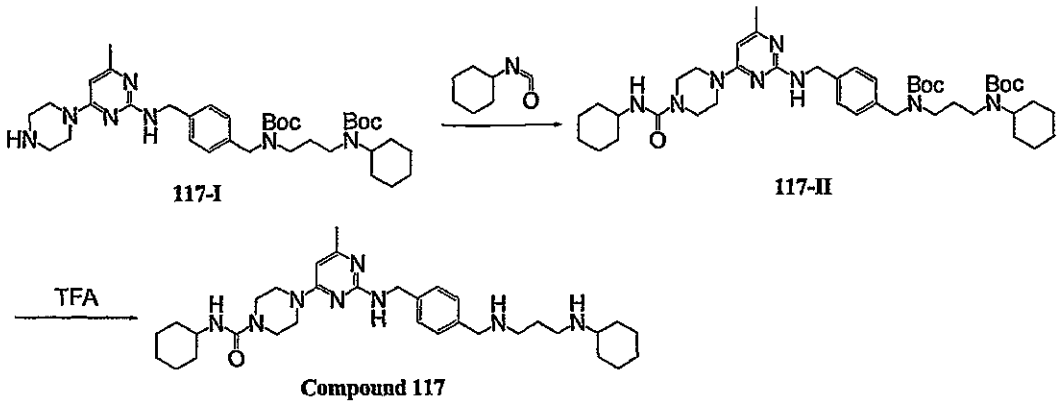
Intermediate 116-I was obtained during the preparation of compound 62.

Et_3N (0.18 mL) and cyclopropylcarbonyl chloride (96 mg) were added to a solution of intermediate 116-I (200 mg) in CH_2Cl_2 (10 mL). The reaction mixture was stirred overnight at room temperature and then concentrated by removing the solvent. The resultant mixture was dissolved in $CHCl_3$, washed with water, dried with anhydrous $MgSO_4$, and concentrated to give a residue. The residue was purified by chromatography on silica gel (EtOAc/Hexane = 1/1) to afford intermediate 116-II (126 mg) in a 57% yield.

A solution of 20% TFA/CH_2Cl_2 (3 mL) was added to a solution of intermediate 116-II (126 mg) in CH_2Cl_2 (2 mL). The reaction mixture was stirred for 5 hours at room temperature and concentrated by removing the solvent. 1 M hydrochloric acid (3 mL) and CH_2Cl_2 (2 mL) were added to the residue. The resultant mixture was stirred for another 10 minutes at room temperature. After removal of the supernatant, the solid was dried under vacuum to afford the hydrochloride salt of compound 116 (93 mg) in an 80% yield.

CI-MS (M^++1): 520.4.

Example 117: Preparation of compound 117:



Intermediate 117-I was obtained during the preparation of compound 62.

A solution of Intermediate 117-I (200 mg), cyclohexyl isocyanate (42 mg), and Et_3N (62 mg) in CH_2Cl_2 (10 ml) was stirred at 25°C for overnight and then concentrated. The resultant residue was purified by chromatography on silica gel (EtOAc/MeOH = 20/1) to afford intermediate 117-II (172 mg) in a 72% yield.

A solution of 20% TFA/CH_2Cl_2 (3 mL) was added to a solution of compound 117-II (172 mg) in CH_2Cl_2 (2 mL). The reaction mixture was stirred for 5 hours at room temperature and concentrated by removing the solvent. 1 M hydrochloric acid (3 mL) and CH_2Cl_2 (2 mL) were added to the residue. The mixture was stirred for another 10 minutes at room temperature. After removal of the supernatant, the solid was dried under vacuum to afford the hydrochloride salt of compound 117 (145 mg) in a 91% yield.

CI-MS (M^++1): 577.4.

Example 118: Preparation of compound 118:

Compound 118 was prepared in a manner similar to that used to prepare compound 117.

CI-MS (M^++1): 551.4.

Example 119: Preparation of compound 119:

Compound 119 was prepared in a manner similar to that used to prepare compound 116.

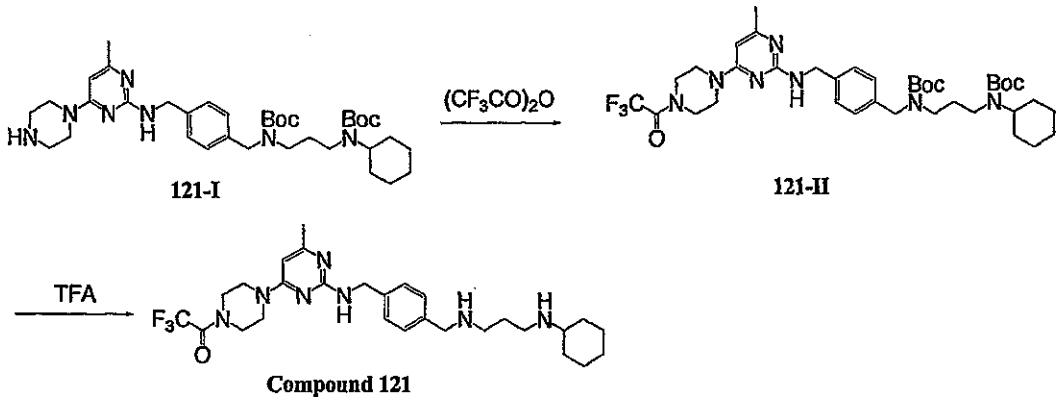
CI-MS (M^++1): 565.4.

Example 120: Preparation of compound 120:

Compound 120 was prepared in a manner similar to that used to prepare compound 117.

CI-MS (M^++1): 551.4.

Example 121: Preparation of compound 121:



Intermediate 121-I was obtained during the preparation of compound 62.

A solution of intermediate 121-I (200 mg), trifluoroacetic anhydride (257 mg), and Et_3N (155 mg) in CH_2Cl_2 (10 ml) was stirred at 25°C for overnight and then concentrated. The resultant residue was purified by chromatography on silica gel (EtOAc/MeOH = 15/1) to afford intermediate 121-II (163 mg) in a 71% yield.

A solution of 20% TFA/CH_2Cl_2 (3 mL) was added to a solution of compound 121-II (163 mg) in CH_2Cl_2 (2 mL). The reaction mixture was stirred for 5 hours at room temperature and concentrated by removing the solvent. 1 M hydrochloric acid (3 mL) and CH_2Cl_2 (2 mL) were added to the residue. The mixture was stirred for another 10 minutes at room temperature. After removal of the supernatant, the solid was dried under vacuum to afford the hydrochloride salt of compound 121 (127 mg) in an 84% yield.

CI-MS (M^++1): 548.3.

Example 122: Preparation of compound 122:

Compound 122 was prepared in a manner similar to that used to prepare compound 62.

CI-MS (M^++1): 600.4.

Example 123: Preparation of compound 123:

Compound 123 was prepared in a manner similar to that used to prepare compound 62.

CI-MS (M^++1): 520.4.

Example 124: Preparation of compound 124:

Compound 124 was prepared in a manner similar to that used to prepare compound 117.

CI-MS (M^++1): 567.4.

Example 125: Preparation of compound 125:

Compound 125 was prepared in a manner similar to that used to prepare compound 117.

CI-MS (M^++1): 583.4.

Example 126: Preparation of compound 126:

Compound 126 was prepared in a manner similar to that used to prepare compound 116.

CI-MS (M^++1): 522.4.

Example 127: Preparation of compound 127:

Compound 127 was prepared in a manner similar to that used to prepare compound 116.

CI-MS (M^++1): 562.3.

Example 128: Preparation of compound 128:

Compound 128 was prepared in a manner similar to that used to prepare compound 43.

CI-MS (M^++1): 514.3.

Example 129: Preparation of compound 129:

Compound 129 was prepared in a manner similar to that used to prepare compound 43.

CI-MS (M^++1): 530.3.

Example 130: Preparation of compound 130:

Compound 130 was prepared in a manner similar to that used to prepare compound 43.

CI-MS (M^++1): 528.3.

Example 131: Preparation of compound 131:

Compound 131 was prepared in a manner similar to that used to prepare compound 43.

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

Example 132: Preparation of compound 132:

Compound 132 was prepared in a manner similar to that used to prepare compound 43.

CI-MS (M^++1): 613.4.

Example 133: Preparation of compound 133:

Compound 133 was prepared in a manner similar to that used to prepare compound 43.

CI-MS (M^++1): 624.5.

Example 134: Preparation of compound 134:

Compound 134 was prepared in a manner similar to that used to prepare compound 43.

CI-MS (M^++1): 622.4.

Example 135: Preparation of compound 135:

Compound 135 was prepared in a manner similar to that used to prepare compound 109.

CI-MS (M^++1): 573.4.

Example 136: Preparation of compound 136:

Compound 136 was prepared in a manner similar to that used to prepare compound 109.

CI-MS (M^++1): 599.3.

Example 137: Preparation of compound 137:

Compound 137 was prepared in a manner similar to that used to prepare compound 21.

CI-MS (M^++1): 496.4.

Example 138: Preparation of compound 138:

Compound 138 was prepared in a manner similar to that used to prepare compound 21.

CI-MS (M^++1): 511.4.

Example 139: Preparation of compound 139:

Compound 139 was prepared in a manner similar to that used to prepare compound 21.

CI-MS (M^++1): 541.4.

Example 140: Preparation of compound 140:

Compound 140 was prepared in a manner similar to that used to prepare compound 21.

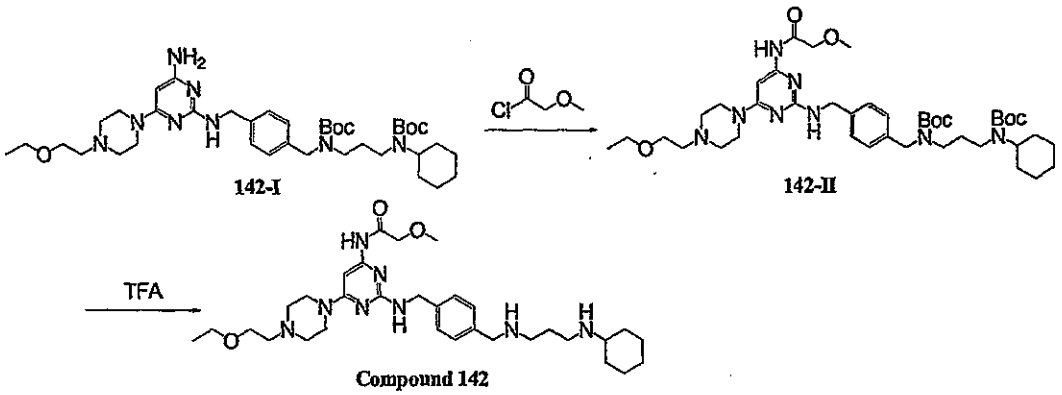
CI-MS (M^++1): 510.4.

Example 141: Preparation of compound 141:

Compound 141 was prepared in a manner similar to that used to prepare compound 44.

CI-MS (M^++1): 540.4.

Example 142: Preparation of compound 142:



Intermediate 142-I was obtained during the preparation of compound 65.

A solution of intermediate 142-I (200 mg), methoxyacetyl chloride (60 mg), and Et_3N (60 mg) in CH_2Cl_2 (10 ml) was stirred at 0°C for 1 hour and then was allowed to warm-up to room temperature within 3 hours. The solution was then concentrated to give a residue, which was purified by chromatography on silica gel (EtOAc/Hexane = 1/1) to afford intermediate 142-II (107 g) in a 48% yield.

A solution of 20% TFA/CH_2Cl_2 (3 mL) was added to a solution of compound 142-II (107 mg) in CH_2Cl_2 (2 mL). The reaction mixture was stirred for 5 hours at room temperature and concentrated by removing the solvent. 1 M hydrochloric acid (3 mL) and CH_2Cl_2 (2 mL) were added to the residue. The mixture was stirred for another 10 minutes at room temperature. After removal of the supernatant, the solid was dried under vacuum to afford the hydrochloride salt of compound 142 (92 mg) in a 93% yield.

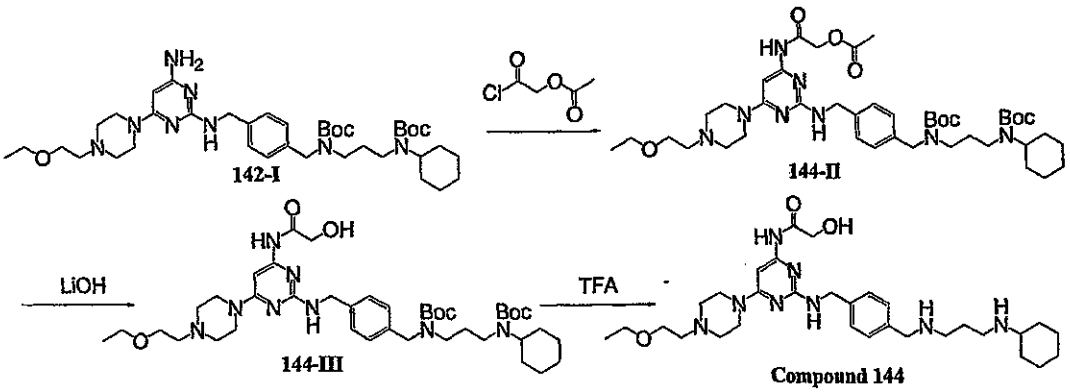
CI-MS (M^++1): 597.4.

Example 143: Preparation of compound 143:

Compound 143 was prepared in a manner similar to that used to prepare compound 142.

CI-MS (M^++1): 641.4.

Example 144: Preparation of compound 144:



Acetyloxyacetyl chloride (304 mg) was added dropwise to a stirred solution of compound 142-I (200 mg) and Et_3N (0.3 mL) in CH_2Cl_2 (10 mL) at 0°C for 2 hours to afford a residue. The resultant residue was purified by chromatography on silica gel (EtOAc/Hexane = 1/1) to afford intermediate 144-II (200 mg) in a 90% yield.

An aqueous solution of 20% LiOH (4 mL) was added to 144-II (200 mg) in THF (5 mL). After stirring for 12 hour, the mixture was acidified with 2M HCl to obtain a crude product. The crude product was purified by chromatography on silica gel (EtOAc/MeOH = 20/1) afforded intermediate 144-III (98 mg) in a 51% yield.

Compound 144-III (98 mg) was treated with 20% TFA/CH_2Cl_2 (2 mL) at room temperature for 12 hours and then concentrated. The resultant residue was purified by chromatography on silica gel (21% NH_3 (aq)/MeOH = 1/19) to afford compound 144 (65 mg) in a 90% yield. Compound 144 was then treated with 1 M HCl (2 mL) in CH_2Cl_2 (2 mL) for 0.5 hour. The solvents were evaporated and the residue was treated with ether and filtered to afford the hydrochloride salt of compound 144.

CI-MS (M^+ + 1): 583.4.

Example 145: Preparation of compound 145:

Compound 145 was prepared in the same manner as that used to prepare intermediate 144-II.

CI-MS ($M^+ + 1$): 625.5.

Example 146: Preparation of compound 146:

Compound 146 was prepared in a manner similar to that used to prepare compound 144.

CI-MS ($M^+ + 1$): 625.5.

Example 147: Preparation of compound 147:

Compound 147 was prepared in a manner similar to that used to prepare compound 44.

CI-MS ($M^+ + 1$): 441.3.

Example 148: Preparation of compound 148:

Compound 148 was prepared in a manner similar to that used to prepare compound 44.

CI-MS ($M^+ + 1$): 654.0.

Example 149: Preparation of compound 149:

Compound 149 was prepared in a manner similar to that used to prepare compound 116.

CI-MS ($M^+ + 1$): 509.8.

Example 150: Preparation of compound 150:

Compound 150 was prepared in a manner similar to that used to prepare compound 116.

CI-MS ($M^+ + 1$): 567.7.

Example 151: Preparation of compound 151:

Compound 151 was prepared in a manner similar to that used to prepare compound 116.

CI-MS ($M^+ + 1$): 537.7.

Example 152: Preparation of compound 152:

Compound 152 was prepared in a manner similar to that used to prepare compound 116.

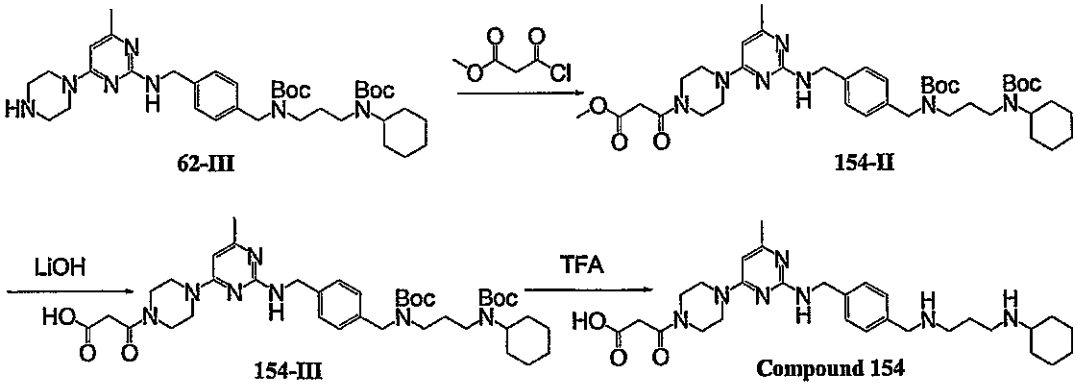
CI-MS ($M^+ + 1$): 620.3.

Example 153: Preparation of compound 153:

Compound 153 was prepared in a manner similar to that used to prepare compound 116.

CI-MS ($M^+ + 1$): 551.8.

Example 154: Preparation of compound 154:



Compound 154 was prepared from compound 62-III in a manner similar to that used to prepare compound 144.

CI-MS ($M^+ + 1$): 538.4.

Example 155: Preparation of compound 155:

Compound 155 was prepared from compound 62-III in a manner similar to that used to prepare compound 144.

CI-MS ($M^+ + 1$): 552.4.

Example 156: Preparation of compound 156:

Compound 156 was prepared from compound 62-III in a manner similar to that used to prepare compound 144.

CI-MS ($M^+ + 1$): 510.3.

Example 157: Preparation of compound 157:

Compound 157 was prepared from compound 109-I in a manner similar to that used to prepare compound 109.

CI-MS ($M^+ + 1$): 569.4.

Example 158: Preparation of compound 158:

Compound 158 was prepared from compound 109-I in a manner similar to that used to prepare compound 109.

CI-MS ($M^+ + 1$): 539.4.

Example 159: Preparation of compound 159:

Compound 159 was prepared from compound 109-I in a manner similar to that used to prepare compound 109.

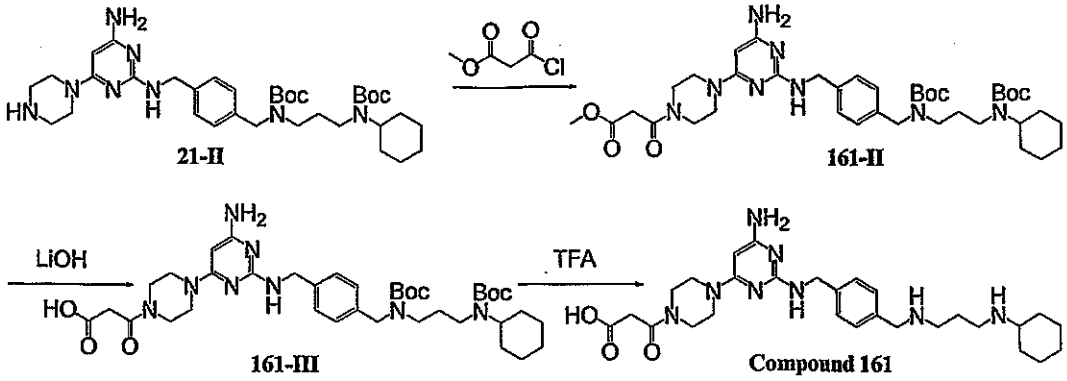
CI-MS ($M^+ + 1$): 525.4.

Example 160: Preparation of compound 160:

Compound 160 was prepared from compound 109-I in a manner similar to that used to prepare compound 109.

CI-MS ($M^+ + 1$): 567.4.

Example 161: Preparation of compound 161:



Compound 161 was prepared from compound 21-II in a manner similar to that used to prepare compound 154.

CI-MS ($M^+ + 1$): 539.3.

Example 162: Preparation of compound 162:

Compound 162 was prepared from compound 21-II in a manner similar to that used to prepare compound 154.

CI-MS ($M^+ + 1$): 511.3.

Example 163: Preparation of compound 163:

Compound 163 was prepared from compound 21-II in a manner similar to that used to prepare compound 154.

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

Example 164: Preparation of compound 164:

Compound 164 was prepared from compound 21-II in a manner similar to that used to prepare compound 154.

CI-MS ($M^+ + 1$): 511.7.

Example 165: Preparation of compound 165:

Compound 165 was prepared from compound 21-II in a manner similar to that used to prepare compound 154.

CI-MS ($M^+ + 1$): 539.4.

Example 166: Preparation of compound 166:

Compound 166 was prepared in a manner similar to that used to prepare compound 43.

CI-MS ($M^+ + 1$): 597.4.

Example 167: Preparation of compound 167:

Compound 167 was prepared in a manner similar to that used to prepare compound 43.

CI-MS ($M^+ + 1$): 613.4.

Example 168: Preparation of compound 168:

Compound 168 was prepared in a manner similar to that used to prepare compound 109.

CI-MS ($M^+ + 1$): 553.4.

Example 169: Preparation of compound 169:

Compound 169 was prepared from compound 34-I in a manner similar to that used to prepare compound 34.

CI-MS ($M^+ + 1$): 520.4.

Example 170: Preparation of compound 170:

Compound 170 was prepared from compound 34-I in a manner similar to that used to prepare compound 34.

CI-MS ($M^+ + 1$): 492.3.

Example 171: Preparation of compound 171:

Compound 171 was prepared from compound 70-I and the corresponding thioisocyanate in a manner similar to that used to prepare compound 70.

CI-MS ($M^+ + 1$): 570.3.

Example 172: Preparation of compound 172:

Compound 172 was prepared from compound 70-I and the corresponding thioisocyanate in a manner similar to that used to prepare compound 70.

CI-MS ($M^+ + 1$): 539.4.

Example 173: Preparation of compound 173:

Compound 173 was prepared from compound 70-I and the corresponding thioisocyanate in a manner similar to that used to prepare compound 70.

CI-MS ($M^+ + 1$): 574.3.

Example 174: Preparation of compound 174:

Compound 174 was prepared from compound 70-I and the corresponding thioisocyanate in a manner similar to that used to prepare compound 70.

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

Example 175: Preparation of compound 175:

Compound 175 was prepared from compound 70-I and the corresponding thioisocyanate in a manner similar to that used to prepare compound 70.

CI-MS ($M^+ + 1$): 553.4.

Example 176: Preparation of compound 176:

Compound 176 was prepared from compound 70-I and the corresponding thioisocyanate in a manner similar to that used to prepare compound 70.

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

Example 177: Preparation of compound 177:

Compound 177 was prepared from compound 70-I and the corresponding thioisocyanate in a manner similar to that used to prepare compound 70.

CI-MS ($M^+ + 1$): 552.2.

Example 178: Preparation of compound 178:

Compound 178 was prepared from compound 70-I and the corresponding thioisocyanate in a manner similar to that used to prepare compound 70.

CI-MS ($M^+ + 1$): 554.2.

Example 179: Preparation of compound 179:

Compound 179 was prepared from compound 70-I and the corresponding thioisocyanate in a manner similar to that used to prepare compound 70.

CI-MS ($M^+ + 1$): 584.3.

Example 180: Preparation of compound 180:

Compound 180 was prepared from compound 70-I and the corresponding thioisocyanate in a manner similar to that used to prepare compound 70.

CI-MS ($M^+ + 1$): 598.5.

Example 181: Preparation of compound 181:

Compound 181 was prepared from compound 70-I and the corresponding thioisocyanate in a manner similar to that used to prepare compound 70.

CI-MS ($M^+ + 1$): 553.4.

Example 182: Preparation of compound 182:

Compound 182 was prepared from compound 109-I in a manner similar to that used to prepare compound 109.

CI-MS ($M^+ + 1$): 566.3.

Example 183: Preparation of compound 183:

Compound 183 was prepared from compound 109-I in a manner similar to that used to prepare compound 109.

CI-MS ($M^+ + 1$): 524.3.

Example 184: Preparation of compound 184:

Compound 184 was prepared from compound 109-I in a manner similar to that used to prepare compound 109.

CI-MS ($M^+ + 1$): 565.3.

Example 185: Preparation of compound 185:

Compound 185 was prepared from compound 109-I in a manner similar to that used to prepare compound 109.

CI-MS ($M^+ + 1$): 550.3.

Example 186: Preparation of compound 186:

Compound 186 was prepared from compound 109-I in a manner similar to that used to prepare compound 109.

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

Example 187: Preparation of compound 187:

Compound 187 was prepared from compound 35-I in a manner similar to that used to prepare compound 35.

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

Example 188: Preparation of compound 188:

Compound 188 was prepared from compound 33-I in a manner similar to that used to prepare compound 33.

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

Example 189: Preparation of compound 189:

Compound 189 was prepared from compound 33-I in a manner similar to that used to prepare compound 33.

CI-MS ($M^+ + 1$): 583.4.

Example 190: Preparation of compound 190:

Compound 190 was prepared from compound 33-I in a manner similar to that used to prepare compound 33.

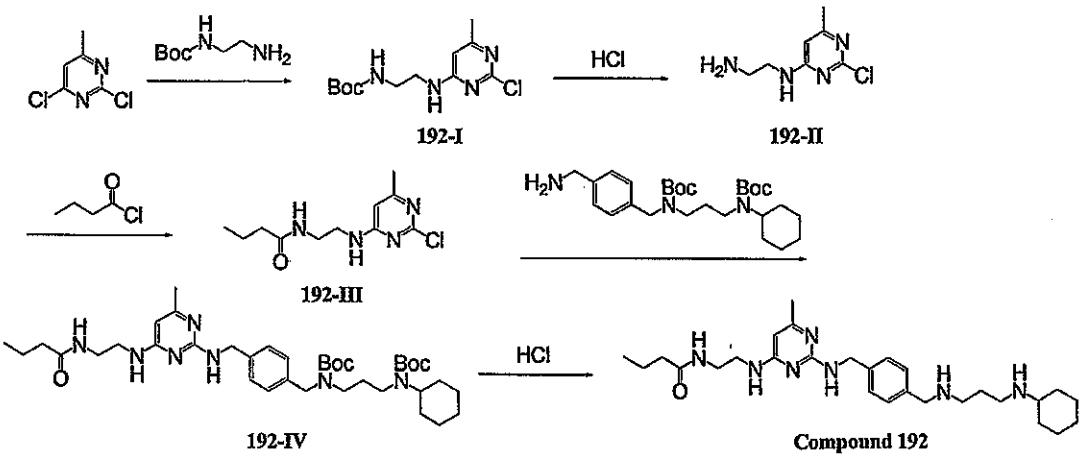
CI-MS ($M^+ + 1$): 537.4.

Example 191: Preparation of compound 191:

Compound 191 was prepared in a manner similar to that used to prepare compound 44.

CI-MS ($M^+ + 1$): 463.2.

Example 192: Preparation of compound 192:



tert-Butoxycarbonylaminoethylamine (5.4 g) was added to a solution of 2,4-dichloro-6-methylpyrimidine (5 g) in THF (350 mL). The reaction mixture was stirred at 0 °C for 1 hour and then was allowed to warm-up to room temperature within 3 hours. After the solution was then concentrated and treated with 1 M HCl (40 mL) in MeOH (50 mL), it was stirred at room temperature for another 8 hours. The solution was then again concentrated. The resultant residue was then neutralization with NH_4OH and extracted with CH_2Cl_2. The solution was concentrated and the residue was purified by chromatography on silica gel (MeOH as eluant) to afford intermediate 192-II (4.6 g) in a 90% yield.

Butyryl chloride (430 mg) was added to a solution of 192-II (680 mg) in CH_2Cl_2 (35 mL). After 1 hour of stirring at room temperature, the solution was concentrated and

1-pentanol (2 mL) was added. Diisopropylethylamine (0.2 mL), intermediate 8-III prepared in example 8 (150 mg), and NaI (110 mg) were also added to this solution, which was then stirred for 24 hours at 120°C. The resultant mixture was dissolved in CH_2Cl_2, washed with water, dried with anhydrous $MgSO_4$ and evaporated to afford 192-IV in a 50% yield after purification by chromatography on silica gel (EtOAc/MeOH = 5/1).

192-IV (950 mg) was treated with 1 M HCl (20 mL) and stirred for overnight. After the supernatant was removed, compound 192 was collected by filtration.

CI-MS ($M^+ + 1$): 498.4.

Example 193: Preparation of compound 193:

Compound 193 was prepared in a manner similar to that used to prepare compound 192.

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

Example 194: Preparation of compound 194:

Compound 194 was prepared in a manner similar to that used to prepare compound 192.

CI-MS ($M^+ + 1$): 542.4.

Example 195: Preparation of compound 195:

Compound 195 was prepared in a manner similar to that used to prepare compound 192.

CI-MS ($M^+ + 1$): 510.4.

Example 196: Preparation of compound 196:

Compound 196 was prepared in a manner similar to that used to prepare compound 192.

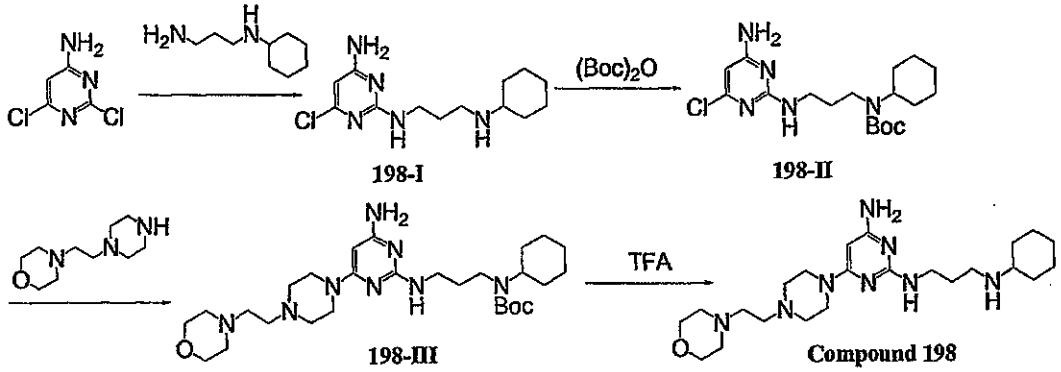
CI-MS ($M^+ + 1$): 526.4.

Example 197: Preparation of compound 197:

Compound 197 was prepared in a manner similar to that used to prepare compound 192.

CI-MS ($M^+ + 1$): 524.4.

Example 198: Preparation of compound 198:



2,4-Dichloro-6-aminopyrimidine (2.0 g) was dissolved in 1-pentanol (10 mL). Cyclohexylaminopropylamine (1.92 g) was then added. The reaction mixture was stirred at 120 °C for 24 hours. The solution was concentrated and the residue was purified by column chromatography on silica gel (EtOAc/Hexane = 1/3) to afford 198-I (1.8 mg) in a 52% yield.

A solution of intermediate 198-I (1.8 g) reacted with $(Boc)_2O$ in CH_2Cl_2 (120 mL) for 8 hours at 25°C. The solution was concentrated and the residue was purified by column chromatography on silica gel (EtOAc/Hexane = 1/9) to give pure 198-II (1.06 g) in a 70% yield.

N^1-Morpholine-N^1-piperazine ethane (0.3 g) was added to 198-II (130 mg). The mixture was stirred at 120°C for 8 hours. The solution was concentrated and the residue was treated with water and extracted with CH_2Cl_2. The organic layer was collected, concentrated to give a crude product, which was purified by column chromatography on silica gel (EtOAc/ MeOH = 10/1) to afford 198-III (100 mg) in a 72% yield.

Compound 198-III (100 mg) was treated with 20% TFA/CH_2Cl_2 (2 mL) for 8 hours and then concentrated. The resultant residue was purified by chromatography on silica gel (21% NH_3 (aq)/MeOH = 1/19) to afford Compound 198 (69 mg) in a 85 % yield. Compound 198 was then treated with 1 M HCl (2 mL) in CH_2Cl_2 (2 mL) for 0.5

hour. After the solvents were evaporated, the residue was treated with ether and filtered to give hydrochloride salt of 198.

CI-MS ($M^+ + 1$): 447.4.

Example 199: Preparation of compound 199:

Compound 199 was prepared in a manner similar to that used to prepare compound 197.

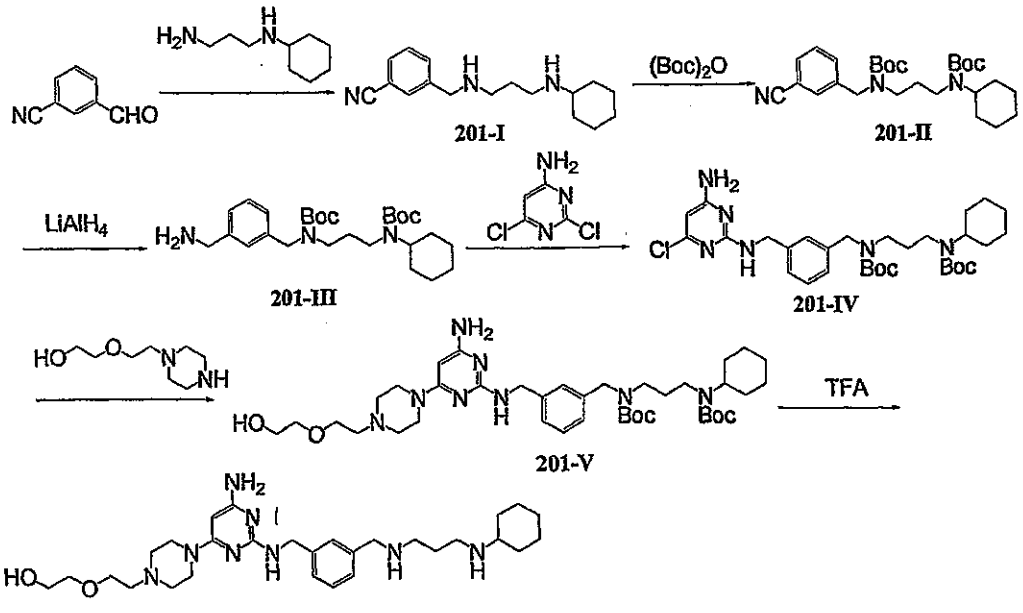
CI-MS ($M^+ + 1$): 408.3.

Example 200: Preparation of compound 200:

Compound 200 was prepared in a manner similar to that used to prepare compound 197.

CI-MS ($M^+ + 1$): 422.2.

Example 201: Preparation of compound 201:



A solution of 3-cyanobenzylaldehyde (1.0 g) and N-cyclohexyl-1,3-propane-diamine (2.4 g) in CH_3OH (150 mL) was heated to 60°C for 18 hours. After cooling to room temperature, $NaBH_4$ (1.5 g) was slowly added to the above solution. The mixture

was stirred for another 30 minutes. The mixture 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 = 7/3) to afford Intermediate 201-I (1.6 g) in a 80% yield.

A solution of Intermediate 201-I (1.6 g) and Boc_2O (3.5 g) in CH_2Cl_2 (160 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 201-II as a yellow oil (2.36 g) in a 85% yield.

A solution of Intermediate 201-II and $LiAlH_4$ (2.3 g) in THF (230 mL) was stirred at 0 °C for 4 hours. After $Na_2SO_4 \cdot 10H_2O$ was added, the solution was stirred at room temperature for 0.5 hour. The solution was then filtered through a celite pad. The filtrate was dried over anhydrous $MgSO_4$ and concentrated to give a residue. The residue was purified by column chromatography on silica gel (using MeOH as an eluant) to afford Intermediate 201-III (1.1 g) in a 50% yield.

Diisopropylethylamine (1.1 mL) was added to a solution of 2,4-dichloro-6-aminopiperidine (0.41 g) and Intermediate 201-III (1.1 g) in 1-pentanol (10 mL). The reaction mixture was stirred overnight at 120°C. The solvent was removed under vacuum and the residue was purified by column chromatography on silica gel (EtOAc/ Hexane = 3/7) to afford 201-IV (1.0 g) in a 65% yield.

To a solution of Intermediate 201-IV (1.0 g) in 1-pentanol (1 mL) was added N^1-hydroxyethoxyethyl piperazine (0.25 g). After the solution was stirred at 120°C for 8 hours, it was concentrated. The residue thus obtained was purified by column chromatography on silica gel (EtOAc/ MeOH = 4/1) to afford Intermediate 201-V (730 mg) in a 60% yield.

A solution of 20% TFA/CH_2Cl_2 (5 mL) was added to a solution of Intermediate 201-V (0.73 g) in CH_2Cl_2 (2 mL). The reaction mixture was stirred for 5 hours at room temperature and concentrated by removing the solvent. The resultant residue was purified by column chromatography on silica gel (21% NH_3 (aq)/MeOH = 1/19) to afford Compound 201 (434 mg) in a 85 % yield. Compound 201 was then treated with 1 M HCl

(4 mL) in CH_2Cl_2 (2 mL) for 0.5 hour. After the solvents were removed, the residue was treated with ether and filtered to give hydrochloride salt of compound 201.

CI-MS ($M^+ + 1$): 541.3.

Example 202: Preparation of compound 202:

Compound 202 was prepared in a manner similar to that used to prepare compound 200.

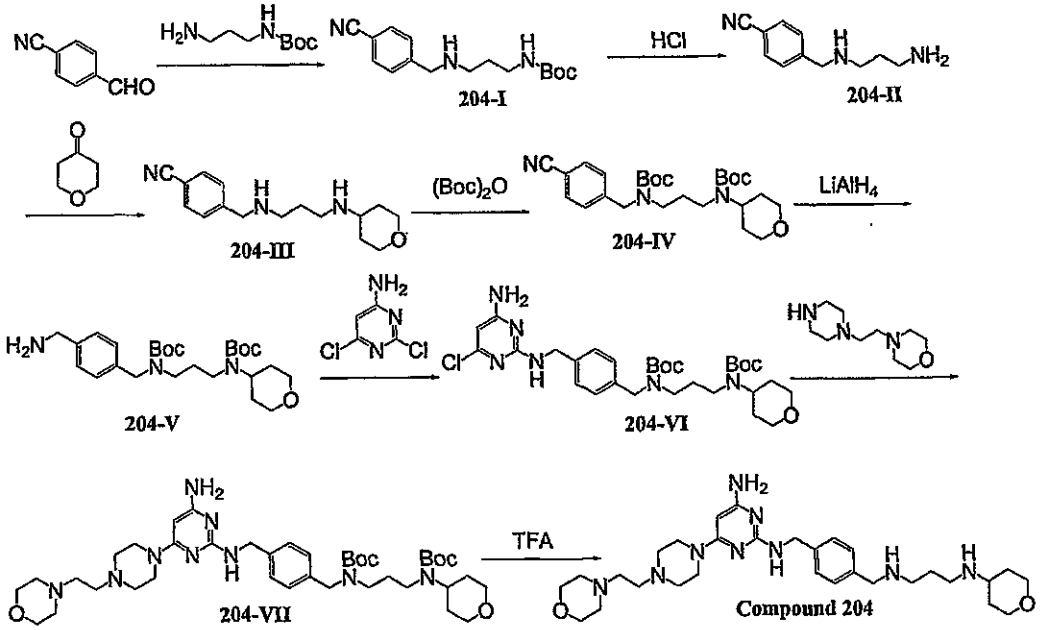
CI-MS ($M^+ + 1$): 566.4.

Example 203: Preparation of compound 203:

Compound 203 was prepared in a manner similar to that used to prepare compound 200.

CI-MS ($M^+ + 1$): 525.4.

Example 204: Preparation of compound 204:



A solution of 4-cyanobenzaldehyde (3.0 g) and *tert*-butoxyaminopropylamine (3.9 g) in MeOH (60 mL) was heated at 60°C for 6 hours. After the solution was cooled to room temperature, $NaBH_4$ (2.5 g) was slowly added. After the mixture was stirred for 30 minutes, it was concentrated, quenched with NH_4Cl (aq.), and extracted with CH_2Cl_2.

The organic layer was separated and concentrated. The residue thus obtained was purified by column chromatography on silica gel (EtOAc/Hexane = 1/3) to afford Intermediate 204-I (5.8 g) in a 88% yield.

A solution of intermediate 204-I (5.8 g) and 1 M HCl (40 mL) in MeOH (50 mL) was stirred at room temperature for 8 hours. The solution was then concentrated and the resultant residue was neutralization with NH_4OH, and extracted with CH_2Cl_2. The organic layer was separated and concentrated. The residue thus obtained was purified by column chromatography on silica gel (using MeOH as an eluant) to afford Intermediate 204-II (3.4 g) in a 90% yield.

To a solution of compound 204-II (3.5 g) in MeOH (50 mL) was added tetrahydro-*4H*-pyran-4-one (2 g). The solution was then heated at 60 °C for 6 hours. After the solution was cooled to room temperature, $NaBH_4$ (1.85 g) was slowly added. After the mixture was stirred 30 minutes, it was concentrated, quenched with NH_4Cl (aq.), and extracted with CH_2Cl_2. The organic layer was separated and concentrated. The residue thus obtained was purified by column chromatography on silica gel (EtOAc/ MeOH = 1/1) to afford Intermediate 204-III (3.5 g) in a 70% yield.

A solution of Intermediate 204-III (12.99 g) and Boc_2O (20.76 g) in 1,4-dioxane (200 ml) and H_2O (100 mL) was stirred at room temperature for 15 hours and then concentrated. The resultant residue was purified by column chromatography on silica gel (EtOAc/Hexane = 1/3) to afford Intermediate 204-IV (21.5 g) in a 95% yield.

LiAlH4 (8.6 g) was added to a solution of Intermediate 204-IV (21.5 g) in THF (500 mL) and ether (500 mL). After the solution was stirred at 0°C for 2 hours, it was treated with saturated aq. NH_4Cl solution, extracted with CH_2Cl_2, and concentrated. The residue thus obtained was purified by column chromatography on silica gel (using MeOH as an eluant) to afford Intermediate 204-V (13.0 g) in a 60% yield.

A solution of Intermediate 204-V (7.6 g) in 1-pentanol (50 mL) was reacted with 2,4-dichloro-6-aminopyrimidine (3.1 g) at 120°C for 12 h. The solvent was then removed and the residue was purified by column chromatography on silica gel (EtOAc/ MeOH = 5/1) to afford Intermediate 204-VI (7.2 g) in a 75% yield.

Intermediate 204-VI (400 mg) was added to N^1-Morpholine-N^1-piperazine ethane (470 mg) in 1-pentanol (1 mL). The reaction mixture was heated at 120°C for 12 hours.

The solvent was then removed under vacuum and the residue was purified by column chromatography on silica gel (EtOAc/ MeOH = 1/1) to afford Intermediate 204-VII (386 mg) in a 76% yield.

A solution of 20% TFA/CH_2Cl_2 (3 mL) was added to a solution of Intermediate 204-VI (386 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 (21% NH_3 (aq)/MeOH = 1/19) to afford Compound 204 (256 mg) in a 85 % yield. Compound 204 was then treated with 1 M HCl (3 mL) in CH_2Cl_2 (1 mL) for 0.5 hour. After the solvents were removed, the residue was treated with ether and filtered to give hydrochloride salt of 204.

CI-MS (M^+ + 1): 568.4.

Example 205: Preparation of compound 205:

Compound 205 was prepared in a manner similar to that used to prepare compound 204.

CI-MS (M^+ + 1): 527.3.

Example 206: Preparation of compound 206:

Compound 206 was prepared in a manner similar to that used to prepare compound 204.

CI-MS (M^+ + 1): 543.3.

Example 207: Preparation of compound 207:

Compound 207 was prepared in a manner similar to that used to prepare compound 204.

CI-MS (M^+ + 1): 554.4.

Example 208: Preparation of compound 208:

Compound 208 was prepared in a manner similar to that used to prepare compound 204.

CI-MS (M^+ + 1): 529.3.

Example 209: Preparation of compound 209:

Compound 209 was prepared in a manner similar to that used to prepare compound 204.

CI-MS ($M^+ + 1$): 513.3.

Example 210: Preparation of compound 210:

Compound 210 was prepared in a manner similar to that used to prepare compound 204.

CI-MS ($M^+ + 1$): 538.4.

Example 211: Preparation of compound 211:

Compound 211 was prepared in a manner similar to that used to prepare compound 204.

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

Example 212: Preparation of compound 212:

Compound 212 was prepared in a manner similar to that used to prepare compound 204.

CI-MS ($M^+ + 1$): 497.3.

Example 213: Preparation of compound 213:

Compound 213 was prepared in a manner similar to that used to prepare compound 204.

CI-MS ($M^+ + 1$): 512.4.

Example 214: Preparation of compound 214:

Compound 214 was prepared in a manner similar to that used to prepare compound 204.

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

Example 215: Preparation of compound 215:

Compound 215 was prepared in a manner similar to that used to prepare compound 204.

CI-MS ($M^+ + 1$): 501.4.

Example 216: Preparation of compound 216:

Compound 216 was prepared in a manner similar to that used to prepare compound 204.

CI-MS ($M^+ + 1$): 485.3.

Example 217: Preparation of compound 217:

Compound 217 was prepared in a manner similar to that used to prepare compound 204.

CI-MS ($M^+ + 1$): 578.4.

Example 218: Preparation of compound 218:

Compound 218 was prepared in a manner similar to that used to prepare compound 204.

CI-MS ($M^+ + 1$): 553.4.

Example 219: Preparation of compound 219:

Compound 219 was prepared in a manner similar to that used to prepare compound 204.

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

Example 220: Preparation of compound 220:

Compound 220 was prepared in a manner similar to that used to prepare compound 204.

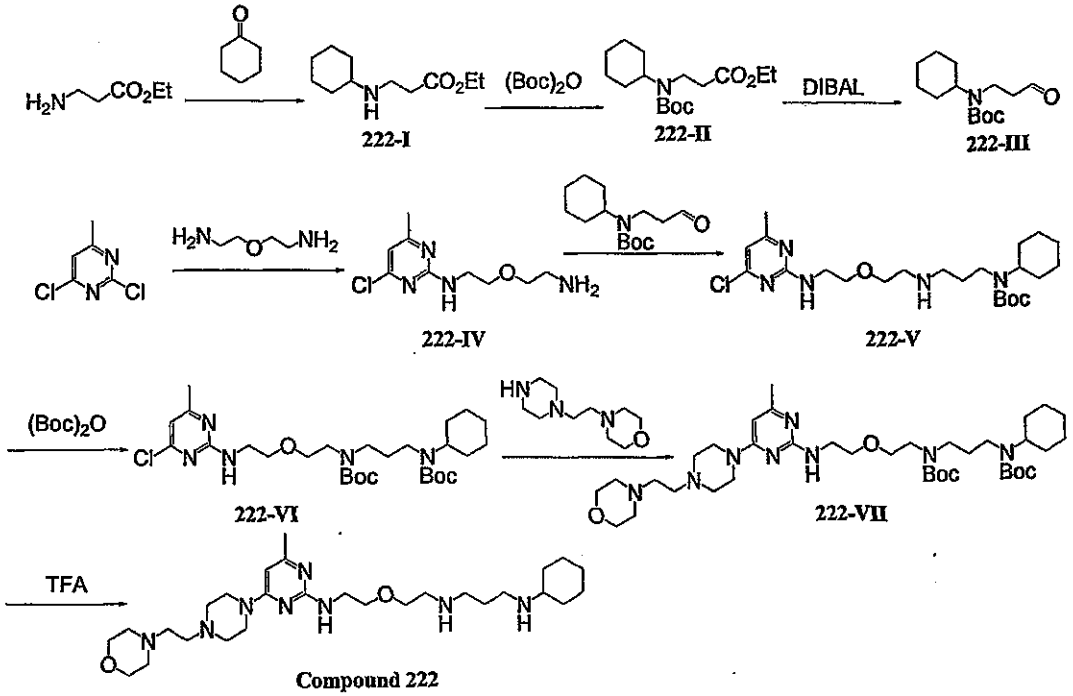
CI-MS ($M^+ + 1$): 553.3.

Example 221: Preparation of compound 221:

Compound 221 was prepared in a manner similar to that used to prepare compound 204.

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

Example 222: Preparation of compound 222:



$NaBH(OAc)_3$ (52.68 g) was added to a solution of ethyl (2-aminomethyl) acetate (25.5 g) and cyclohexanone (24.45 g) in CH_2Cl_2 (200 mL) and MeOH (300 ml). The mixture was stirred at room temperature for 6 hours. After a saturated aq. $NaHCO_3$ solution was added, the mixture was extracted with EtOAc, dried over anhydrous $MgSO_4$, and filtered. The solvent was then removed and the residue was purified by column chromatography on silica gel (EtOAc/ Hexane = 1/1) to afford Intermediate 222-I (32.9 g) in a 76% yield.

A solution of Intermediate 222-I (32.9 g) and Boc_2O (36.0 g) in CH_2Cl_2 (300 mL) was stirred at 25 °C overnight. The solution was then concentrated and the resultant residue was purified by column chromatography on silica gel (EtOAc/ Hexane = 1/9) to give Intermediate 222-II (39.5 g) in a 80% yield.

1M DIBAL/ether (85 mL) was added to a stirred solution of Intermediate 222-II (15 g) in dry toluene (500 mL) at -70~-78°C under N_2 (g). The reaction mixture was stirred for 2 hours at this temperature. After 5% HCl (aq) (85 mL) was then added to the solution at -60~-70°C, the mixture was stirred for another 0.5 hour after the reaction temperature was increased to 25°C. The aqueous layer was extracted with CH_2Cl_2 twice. The organic layers were combined, dried with anhydrous $MgSO_4$, and concentrated by removing the solvent under vacuum. The resultant residue was purified by column chromatography on silica gel (EtOAc/Hexane = 1/5) to afford Intermediate 222-III (7.7 g) in a 60% yield.

Di-2-aminoethylether (1.0 g) was slowly added to a stirred solution of 2,4-dichloro-6-methylpyrimidine (2.0 g) in THF (15 mL) at room temperature. The mixture was stirred at 0°C for 2 hours and the reaction was allowed to warm-up to room temperature overnight. The solution was then concentrated and the resultant residue was purified by column chromatography on silica gel (EtOAc/ MeOH = 1/1) to give Intermediate 222-IV (1.5 g) in a 53% yield.

A solution of Intermediate 222-IV (0.7 g) and Intermediate 222-III (0.77 g) in MeOH (60 mL) was stirred at 60 °C for 8 hours. $NaBH_4$ (0.17 g) was then added the solution at 0 °C. After the solution was stirred for 0.5 hour, a saturated aq. NH_4Cl solution was added and the mixture was extracted with EtOAc, dried over anhydrous $MgSO_4$, and filtered. The solution was then concentrated and the resultant residue was purified by column chromatography on silica gel (EtOAc/ MeOH = 2/1) to afford Intermediate 222-V (356 mg) in a 25% yield.

A solution of Intermediate 222-V (356 mg) and Boc_2O (180 mg) in CH_2Cl_2 (10 mL) was stirred at 25°C overnight. The solution was then concentrated and the resultant residue was purified by column chromatography on silica gel (EtOAc/Hexane = 1/5) to give Intermediate 222-VI (410 mg) in a 95% yield.

N^1-Morpholine-N^1-piperazine ethane (221 mg) was added to a solution of Intermediate 222-VI (210 mg) in 1-pentanol (1 mL). The mixture was stirred at 120°C for 12 hours. It was then concentrated and the resultant residue was purified by column chromatography on silica gel (EtOAc/ MeOH = 10/1) to afford Intermediate 222-VII (100 mg) in a 37% yield.

A solution of 20% TFA/CH_2Cl_2 (2 mL) was added to a solution of Intermediate 222-VII (100 mg) in CH_2Cl_2 (1 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 (21% NH_3 (aq)/MeOH = 1/19) to afford Compound 222 (65 mg) in 90 % yield. Compound 222 was then treated with 1 M HCl (2 mL) in CH_2Cl_2 (1 mL) for 0.5 hour. After the solvents were removed, the residue was treated with ether and filtered to afford hydrochloride salt of 222.

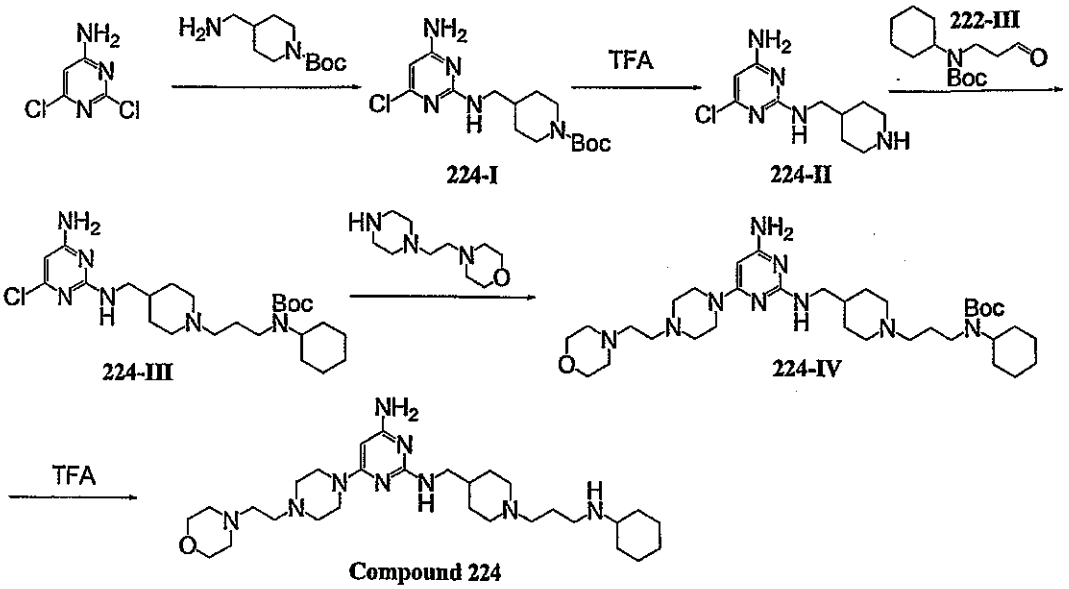
CI-MS (M^+ + 1): 533.4.

Example 223: Preparation of compound 223:

Compound 223 was prepared in a manner similar to that used to prepare compound 222.

CI-MS (M^+ + 1): 528.4.

Example 224: Preparation of compound 224:



N-tert-Butoxycarbonylpiperidinyl-4-methylamine (5.0 g) was slowly added to a stirred solution of 2,4-dichloro-6-aminopyrimidine (5.7 g) in 1-pentanol (20 mL). The solution was stirred at 120°C for 12 hours. The solution was then concentrated and the

resultant residue was purified by column chromatography on silica gel (EtOAc/Hexane = 1/9) to give Intermediate 224-I (3.6 g) in a 45% yield.

Intermediate 224-I (2.4 g) was then dissolved in CH_2Cl_2 (80 mL) and 20% TFA/ CH_2Cl_2 (20 mL) was added. The solution was stirred at room temperature overnight. The solution was then concentrated and the resultant residue was purified by column chromatography on silica gel (21% NH_3 (aq)/MeOH = 1/19) to afford Intermediate 224-II (1.5 g) in a 90% yield.

Intermediate 222-III (3.3 g) prepared in Example 222 was added to a solution of Intermediate 224-II (1.9 g) in MeOH (40 mL). The mixture was stirred at 60°C for 12 hours. $NaBH_4$ (0.3 g) was then added at 0°C. After the mixture was stirred for 1 hour, an aqueous solution of NH_4Cl (10%, 10 mL) was added. The mixture was extracted with EtOAc, dried over anhydrous $MgSO_4$, and filtered. The solution thus obtained was then concentrated. The resultant residue was purified by column chromatography on silica gel (EtOAc/Hexane = 1/1) to afford Intermediate 224-III (1.5 g) in a 40% yield.

N^1-Morpholine-N^1-piperazine ethane (370 mg) was added to Intermediate 224-III (300 mg) in 1-pentanol (1 mL). The mixture was stirred at 120°C for 12 hours. After the solution was concentrated, the residue was treated with water and extracted with CH_2Cl_2. The organic layer was separated and concentrated. The resultant residue was purified by column chromatography on silica gel (EtOAc/Hexane = 1/9) to afford Intermediate 224-IV (281 mg) in a 70% yield.

A solution of 20% TFA/CH_2Cl_2 (3 mL) was added to a solution of Intermediate 224-IV (281 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 (21% NH_3 (aq)/MeOH = 1/19) to afford Compound 224 (200 mg) in a 85 % yield. Compound 224 was then treated with 1 M HCl (4 mL) in CH_2Cl_2 (2 mL) for 0.5 hours. After the solvents were removed, the residue was treated with ether and filtered to give hydrochloride salt of Compound 224.

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

Example 225: Preparation of compound 225:

Compound 225 was prepared in a manner similar to that used to prepare compound 224.

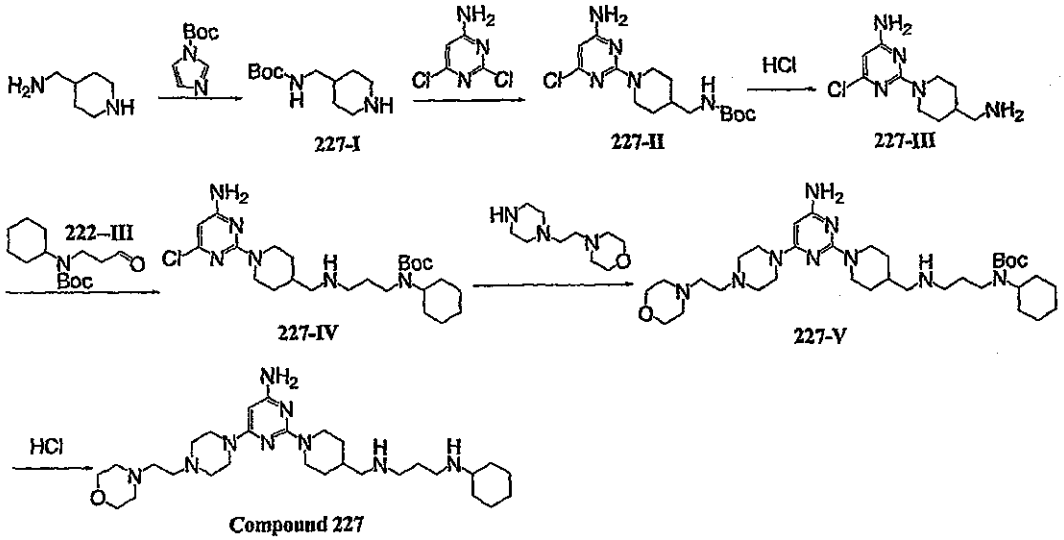
CI-MS ($M^+ + 1$): 503.4.

Example 226: Preparation of compound 226:

Compound 226 was prepared in a manner similar to that used to prepare compound 224.

CI-MS ($M^+ + 1$): 519.4.

Example 227: Preparation of compound 227:



A solution of piperidinyl-4-methylamine (3.6 g) and *N-tert*-butoxycarbonylimidazole (5.3 g) in toluene (80 mL) was stirred at 25°C overnight. The solution was then concentrated and the resultant residue was purified by column chromatography on silica gel (EtOAc/Hexane = 1/2) to give Intermediate 227-I (4.7 g) in a 70% yield.

Intermediate 227-I (4.7 g) and Et_3N (2.7 mL) in 1-pentanol (20 mL) was reacted with 2,4-dichloro-6-aminopyrimidine (5.4 g) at 120°C for 12 hours. After the solvent was removed, the residue was purified by column chromatography on silica gel (EtOAc/Hexane = 1/9) to afford Intermediate 227-II (5.2 g) in a 70% yield.

A solution of Intermediate 227-II (1.0 g) treated with 1 M HCl (20 mL) in CH_2Cl_2 (10 mL) was stirred at room temperature for 8 hours. After the solution was concentrated, the resultant residue was neutralization with NH_4OH, and extracted with CH_2Cl_2. The organic layer was separated and concentrated. The residue thus obtained was purified by column chromatography on silica gel (using MeOH as an eluant) to afford Intermediate 227-III (636 mg) in a 90% yield.

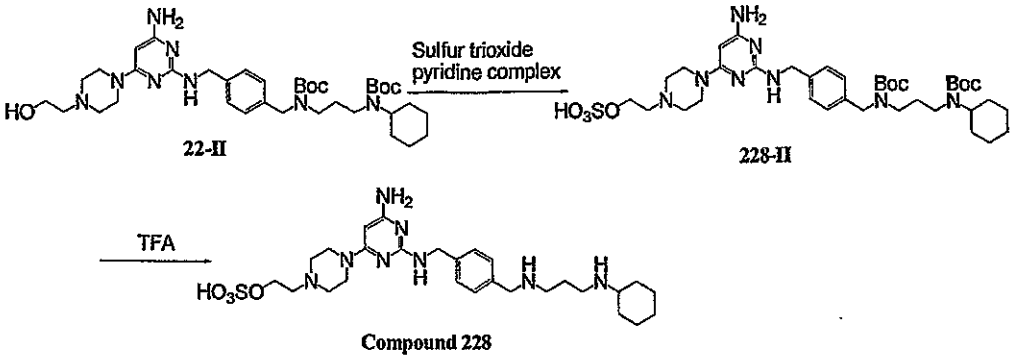
Intermediate 222-III (790 mg) prepared from Example 222 was added to a solution of Intermediate 227-III (450 mg) in MeOH (20 mL). The mixture was stirred at 25°C for 2 hours. $NaBH(OAc)_3$ (2.0 g) was then added at 25°C for 12 hours. After the solution was concentrated, a saturated aq. $NaHCO_3$ solution was added to the resultant residue. The mixture was then extracted with CH_2Cl_2. The organic layer was separated and concentrated. The residue thus obtained was purified by column chromatography on silica gel (using MeOH as an eluant) to afford Intermediate 227-IV (539 mg) in a 60% yield.

N^1-Morpholine-N^1-piperazine ethane (240 mg) was added to a solution of Intermediate 227-IV (160 mg) in 1-pentanol (1 mL). The mixture was stirred at 120°C for 8 hours. The solution was concentrated and the residue was purified by column chromatography on silica gel (EtOAc/ MeOH = 5/1) to afford Intermediate 227-V (85 mg) in a 40% yield.

A solution of 20% TFA/CH_2Cl_2 (1 mL) was added to a solution of Intermediate 227-V (85 mg) in CH_2Cl_2 (1 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 (21% NH_3 (aq)/MeOH = 1/19) to afford Compound 227 (65 mg) in a 90 % yield. Compound 227 was then treated with 1 M HCl (1 mL) in CH_2Cl_2 (1 mL) for 0.5 hour. After the solvents were removed, the residue was treated with ether and filtered to give hydrochloride salt of Compound 227.

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

Example 228: Preparation of compound 228:



22-II 228-II

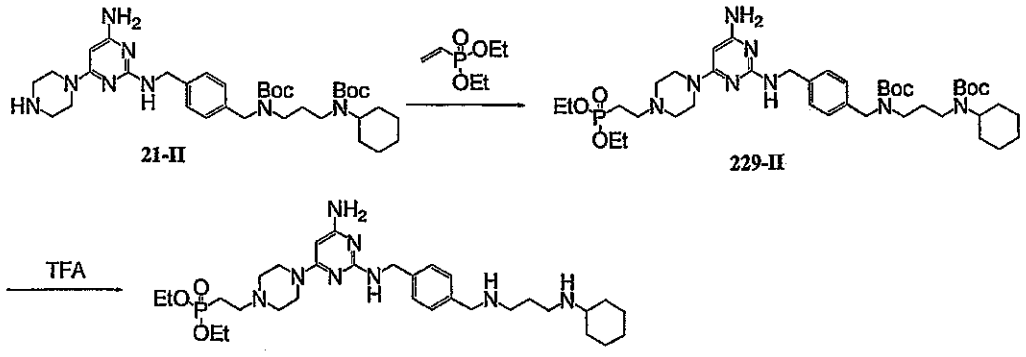
Compound 228

To a solution of 22-II (500 mg) in THF (10 mL) was added sulfur trioxide pyridine complex (457 mg). The mixture was stirred at 25°C for 12 hours. The solution was filtered and concentrated. The resultant residue was purified by column chromatography on silica gel (EA/ MeOH = 10/1) to give Intermediate 228-II (82 mg) in a 10% yield.

A solution of 20% TFA/CH_2Cl_2 (1 mL) was added to a solution of Intermediate 228-II (82 mg) in CH_2Cl_2 (1 mL). The reaction mixture was stirred for 8 hours at room temperature and concentrated by removing the solvent. The resultant residue was purified by chromatography on silica gel (21% NH_3 (aq)/MeOH = 1/19) to afford Compound 228 (54 mg) in 90 % yield. Compound 228 was then treated with 1 M HCl (1 mL) in CH_2Cl_2 (1 mL) for 0.5 hour. After the solvents were removed, the residue was treated with ether and filtered to give hydrochloride salt of Compound 228.

CI-MS (M^+ + 1): 577.2.

Example 229: Preparation of compound 229:



21-II 229-II

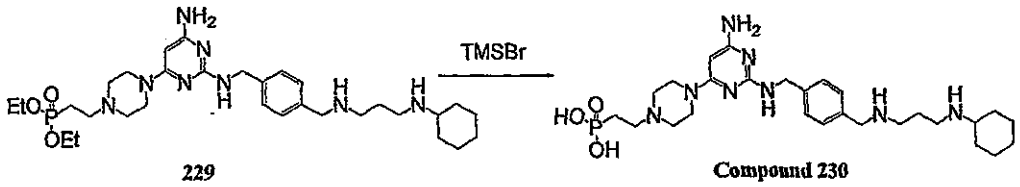
Compound 229

Diethyl vinylphosphonate (377 mg) was added to a solution of Intermediate 21-II (500 mg) prepared from Example 21 in MeOH (10 mL). The solution was stirred at 25°C for 12 hours. The solution was concentrated and the residue was purified by column chromatography on silica gel (EA/ MeOH = 5/1) to afford Intermediate 229-II (438 mg) in a 70% yield.

A solution of 20% TFA/CH_2Cl_2 (5 mL) was added to a solution of Intermediate 229-II (438 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 Compound 229 (165 mg) in a 50 % yield.

CI-MS (M^+ + 1): 617.4.

Example 230: Preparation of compound 230:

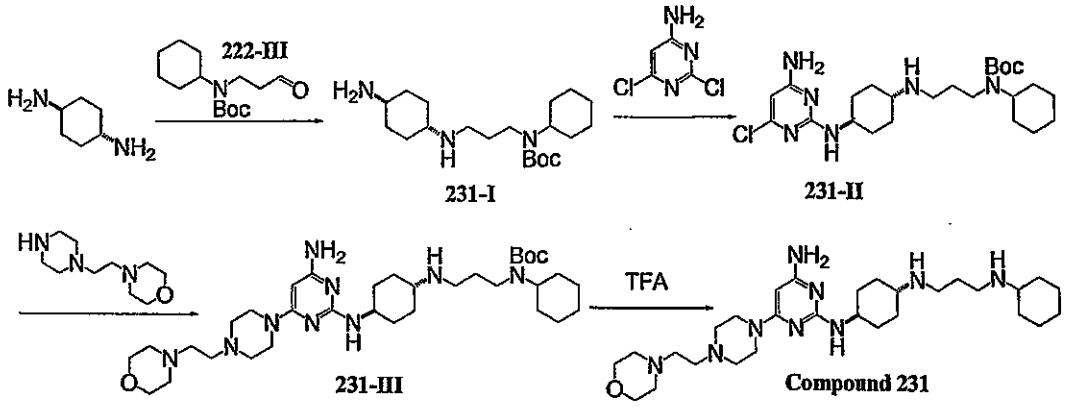


229 Compound 230

A solution of Compound 229 (600 mg) and trimethylsilyl bromide (1.19 g) in CH_2Cl_2 (30 mL) was stirred at 25°C for 72 hours. The solution was then concentrated in vacuo to yield a yellow-orange foam, which was re-dissolved in water (50 mL). The solution was washed with ether (3 X 35 mL) and then concentrated in vacuo to yield a solid. The solid was purified through a column of cation exchange resin (Dowex AG50X8) by eluting the column first with water (ca. 500 mL), and then with 0.2 M aqueous ammonia to afford ammonium salt of Compound 230 (58 mg) in a 10% yield.

CI-MS (M^+ + 1): 561.1.

Example 231: Preparation of compound 231:



Intermediate 222-III (4.5 g) was added to a solution of *trans*-1,4-diaminocyclohexane (3 g) in MeOH (200 mL). The mixture was stirred at 60°C for 8 hours. After $NaBH_4$ (0.7 g) was added at 0°C, the mixture was stirred for 0.5 hour and then concentrated by removing the solvent. An aqueous solution of NH_4Cl (10%, 10 mL) was added to the resultant residue. The mixture was extracted with CH_2Cl_2, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography on silica gel (using MeOH as an eluant) to afford Intermediate 231-I (6.0 g) in a 65% yield.

Intermediate 231-I (6.0 g) and Et_3N (6.0 mL) in 1-pentanol (30 mL) was reacted with 2,4-dichloro-6-aminopyrimidine (2.7 g) at 120°C for 12 hours. The solvent was then removed and the residue was purified by column chromatography on silica gel (EtOAc/Hexane = 1/1) to afford Intermediate 231-II (5.7 g) in a 70% yield.

N^1-Morpholine-N^1-piperazine ethane (620 mg) was added to Intermediate 231-II (500 mg) in 1-pentanol (5 mL). The mixture was stirred at 120°C for 8 hours and then concentrated. The residue thus obtained was treated with water and extracted with CH_2Cl_2 to afford Intermediate 231-III (468 mg) in a 70% yield, which was purified by column chromatography on silica gel using 21% NH_3 (aq) and MeOH as eluants.

A solution of 20% TFA/CH_2Cl_2 (5 mL) was added to a solution of Intermediate 231-III (468 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 (21% NH_3 (aq)/MeOH = 1/19) to afford

Compound 231 (356 mg) in a 90 % yield. Compound 231 was then treated with 1 M HCl (4 mL) in CH_2Cl_2 (2 mL) for 0.5 hour. After the solvents were removed, the residue was treated with ether and filtered to give hydrochloride salt of Compound 231.

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

Example 232: Preparation of compound 232:

Compound 232 was prepared in a manner similar to that used to prepare compound 231.

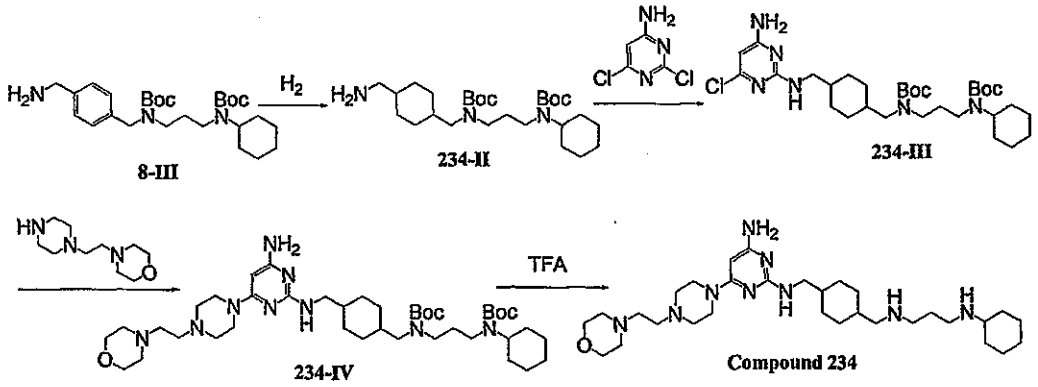
CI-MS ($M^+ + 1$): 503.4.

Example 233: Preparation of compound 233:

Compound 233 was prepared in a manner similar to that used to prepare compound 231.

CI-MS ($M^+ + 1$): 519.4.

Example 234: Preparation of compound 234:



Compound 8-III (1.0 g) prepared in Example 8 in MeOH (20 mL) was hydrogenated in the presence of 10% Pd/C (200 mg) at 50 psi at room temperature for 18 hours. The mixture was then filtered and concentrated to afford Intermediate 234-II (500 mg) without further purification.

Crude Intermediate 234-II (0.5 g) in 1-pentanol (3 mL) was reacted with 2,4-dichloro-6-aminopyrimidine (0.2 g) at 120°C for 15 hours. The solution was then

concentrated and the resultant residue was purified by column chromatography on silica gel (EtOAc/Hexane = 3/7) to give Intermediate 234-III (0.3 g) in a 65% yield.

N^1-Morpholine-N^1-piperazine ethane (0.3 g) was added to Intermediate 234-III (0.5 g) in 1-pentanol (1 mL). The mixture was stirred at 120°C for 18 hours. The solution was concentrated to give the residue, which was then coated with SiO_2 and purified by column chromatography on silica gel (EtOAc/ MeOH = 7/3) to afford Intermediate 234-IV (0.23 g) in a 60% yield.

A solution of 20% TFA/CH_2Cl_2 (5 mL) was added to a solution of Intermediate 234-IV (230 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 (21% NH_3 (aq)/MeOH = 1/19) to afford Compound 234 (192 mg) in a 85 % yield. Compound 234 was then treated with 1 M HCl (4 mL) in CH_2Cl_2 (2 mL) for 0.5 hour. After the solvents were removed, the residue was treated with ether and filtered to give hydrochloride salt of Compound 234.

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

Example 235: Preparation of compound 235:

Compound 235 was prepared in a manner similar to that used to prepare compound 234.

CI-MS ($M^+ + 1$): 531.4.

Example 236: Preparation of compound 236:

Compound 236 was prepared in a manner similar to that used to prepare compound 234.

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

Example 237: Preparation of compound 237:

Compound 237 was prepared in a manner similar to that used to prepare compound 234.

CI-MS ($M^+ + 1$): 555.5.

Example 238: Preparation of compound 238:

Compound 238 was prepared in a manner similar to that used to prepare compound 234.

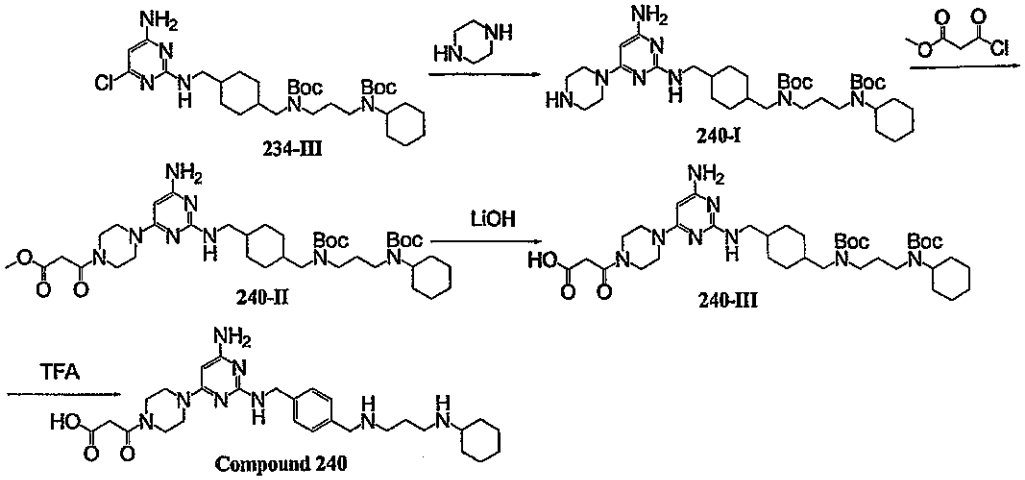
CI-MS (M^+ + 1): 549.4.

Example 239: Preparation of compound 239:

Compound 239 was prepared in a manner similar to that used to prepare compound 234.

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

Example 240: Preparation of compound 240:



Intermediate 234-III (1.0 g) prepared from Example 3 was added to a stirred solution of piperazine (0.36 g) in 1-pentanol (1.0 mL). The solution was stirred at 120°C for 18 hours. It was concentrated to give a residue, which was coated with SiO_2 and purified by column chromatography on silica gel (EtOAc/MeOH = 9/1) to afford Intermediate 240-I (0.82 g) in a 75% yield.

Methoxycarbonylacetyl chloride (0.2 g) was added to a solution of Intermediate 240-I (0.82 g) in CH_2Cl_2 (50 mL) and Et_3N (0.3 g) at 0°C. The mixture was stirred at 0°C for 1 hour and then concentrated. The residue thus obtained was treated with water and extracted with CH_2Cl_2. The organic layer was separated and concentrated. The resultant residue was purified by column chromatography on silica gel (EtOAc/Et_3N = 9/1) to give Intermediate 240-II (0.73 g) in a 80% yield.

Intermediate 240-II (0.5 g) dissolved in THF (10 mL) was added to 0.5 M of an LiOH aqueous solution (10 mL). The mixture was stirred at room temperature for 2 hours. It was then acidified with 2M HCl to obtain a crude product, which was purified by column chromatography on silica gel (EtOAc/MeOH = 20/1) to afford Intermediate 240-III (170 mg) in a 35% yield.

Intermediate 240-III (170 mg) was treated with 20% TFA/CH_2Cl_2 (5 mL) at room temperature for 12 hours and then concentrated. The resultant residue was purified by column chromatography on silica gel (21% NH_3 (aq)/MeOH = 1/19) to afford Compound 240 (100 mg) in a 85 % yield. Compound 240 was then treated with 1 M HCl (3 mL) in CH_2Cl_2 (2 mL) for 0.5 hour. After the solvents were removed, the residue was treated with ether and filtered to give hydrochloride salt of Compound 240.

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

Example 241: Preparation of compound 241:

Compound 241 was prepared in a manner similar to that used to prepare compound 240.

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

Example 242: Preparation of compound 242:

Compound 242 was prepared in a manner similar to that used to prepare compound 240.

CI-MS ($M^+ + 1$): 560.4.

Example 243: Preparation of compound 243:

Compound 243 was prepared in a manner similar to that used to prepare compound 240.

CI-MS ($M^+ + 1$): 576.4.

Example 244: Preparation of compound 244:

Compound 244 was prepared in a manner similar to that used to prepare compound 240.

CI-MS ($M^+ + 1$): 559.4.

Example 245: Preparation of compound 245:

Compound 245 was prepared in a manner similar to that used to prepare compound 240.

CI-MS ($M^+ + 1$): 531.4.

Example 246: Preparation of compound 246:

Compound 246 was prepared in a manner similar to that used to prepare compound 240.

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

Example 247: Preparation of compound 247:

Compound 247 was prepared in a manner similar to that used to prepare compound 240.

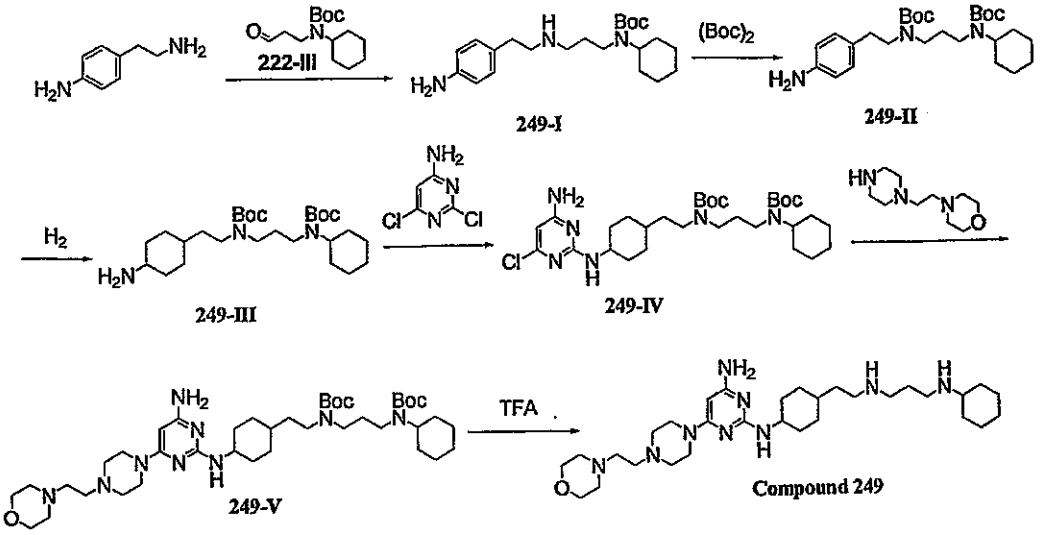
CI-MS ($M^+ + 1$): 515.4.

Example 248: Preparation of compound 248:

Compound 248 was prepared in a manner similar to that used to prepare compound 240.

CI-MS ($M^+ + 1$): 531.4.

Example 249: Preparation of compound 249:



Intermediate 222-III (4.56 g) was added to a solution of 2-aminoethylaniline (2.92 g) in MeOH (300 mL). The mixture was stirred at 60°C for 8 hours. $NaBH_4$ (0.68 g) was then added at 0 °C for 0.5 hour and the mixture was concentrated by removing the solvent. An aqueous solution of NH_4Cl (10%, 10 mL) was added to the resultant residue. 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 (EtOAc/MeOH = 1/1) to afford Intermediate 249-I (4.2 g) in a 63% yield.

A solution of Intermediate 249-I (4.2 g) and Boc_2O (2.8 g) in CH_2Cl_2 (250 mL) was added to Et_3N (1.4 mL) at 25 °C overnight. The solution was then concentrated and the resultant residue was purified by column chromatography on silica gel (EtOAc/Hexane = 1/5) to give Intermediate 249-II (4 g) in a 75% yield.

Intermediate 249-II (4.0 g) in MeOH (20 mL) was hydrogenated in the presence of 10% Pd/C (800 mg) and 5% Rh/C (400 mg) at 50 psi at room temperature for 18 hours. The mixture was then filtered and concentrated. The residue was purified by column chromatography on silica gel (using EtOAc/MeOH as an eluant) to afford Intermediate 249-III (2.8 g) in a 69% yield.

Intermediate 249-III (900 mg) and Et_3N (0.4 mL) in 1-pentanol (5 mL) was reacted with 2,4-dichloro-6-aminopyrimidine (365 mg) at 120°C for 24 hours. The solvent was then removed and the resultant residue was purified by column

chromatography on silica gel (EtOAc/Hexane = 1/1) to afford Intermediate 249-IV (842 mg) in a 74% yield.

N^1-Morpholine-N^1-piperazine ethane (300 mg) was added to Intermediate 249-IV (300 mg) in 1-pentanol (1 mL). The mixture was stirred at 120°C for 18 hours. The solution was concentrated to give a residue, which was then coated with SiO_2 and purified by column chromatography on silica gel (EtOAc/ MeOH = 7/3) to afford Intermediate 249-V (243 mg) in a 64% yield.

A solution of 20% TFA/CH_2Cl_2 (5 mL) was added to a solution of Intermediate 249-V (243 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 (21% NH_3 (aq)/MeOH = 1/19) to afford Compound 249 (151 mg) in a 84 % yield. Compound 249 was t\hen treated with 1 M HCl (4 mL) in CH_2Cl_2 (2 mL) for 0.5 hour. After the solvents were removed, the residue was treated with either and filtered to give hydrochloride salt of Compound 249.

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

Example 250: Preparation of compound 250:

Compound 250 was prepared in a manner similar to that used to prepare compound 249.

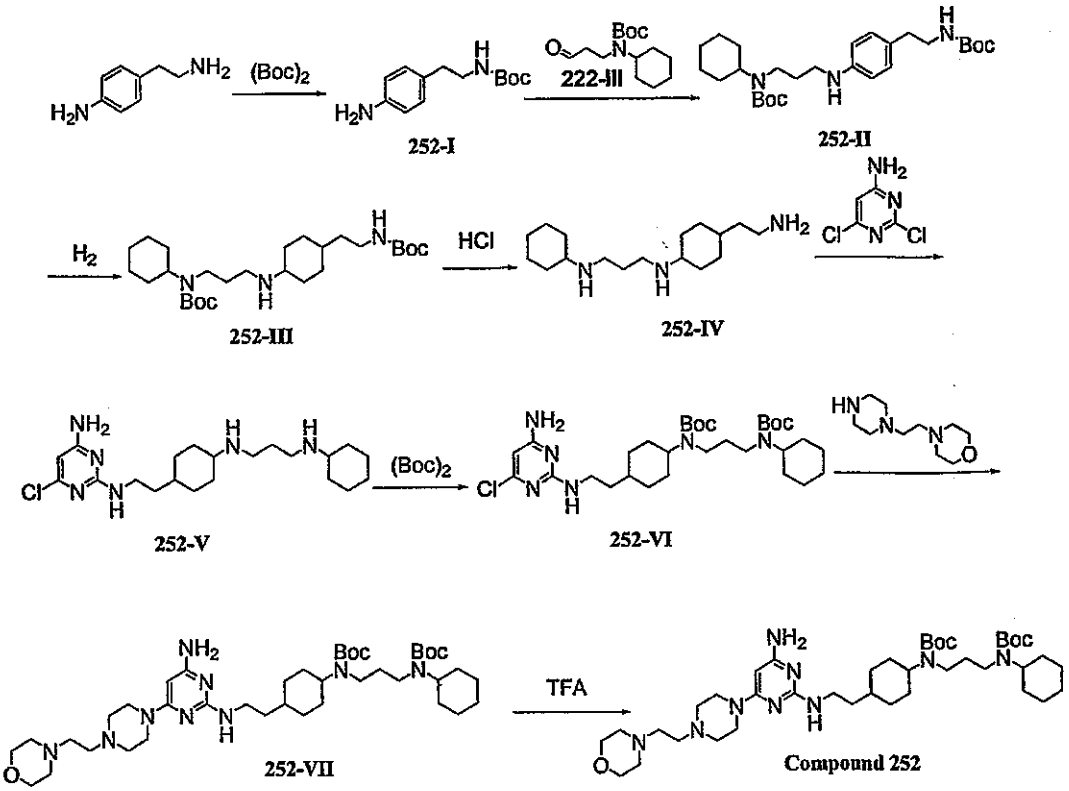
CI-MS (M^+ + 1): 531.4.

Example 251: Preparation of compound 251:

Compound 251 was prepared in a manner similar to that used to prepare compound 249.

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

Example 252: Preparation of compound 252:



A solution of 2-aminoethylaniline (5.0 g) and Boc_2O (6.8 g) in CH_2Cl_2 (200 mL) was stirred at 25 °C overnight. The solution was then concentrated and the resultant residue was purified by column chromatography on silica gel (EtOAc/Hexane = 1:1 as eluant) to give Intermediate 252-I (6.8 g) in a 83% yield.

222-III (7.3 g) prepared from Example 222 was added to a solution of Intermediate 252-I (6.8 g) in CH_2Cl_2 (250 mL). The mixture was stirred at 25°C for 1.5 hour. $NaBH(OAc)_3$ (6.0 g) and a small amount of MeOH were added at 0°C. The mixture was stirred at room temperature overnight. After the solution was concentrated, a saturated solution of $NaHCO_3$ (250 mL) was added. The mixture was extracted with EtOAc, dried over anhydrous $MgSO_4$, filtered, and cocnetrated to afford crude Intermediate 252-II (6.0 g).

Crude Intermediate 252-II (3.0 g) in MeOH (15 mL) was hydrogenated in the presence of 5% Rh/C (300 mg) and 10% Pd/C (300 mg) at 50 psi at room temperature for 72 hours. The mixture was then filtered and concentrated. The resultant residue was

purified by column chromatography on silica gel (EtOAc/MeOH = 1:1) to afford Intermediate 252-III (2.6 g) in a 87% yield.

A solution of intermediate 252-III (1.5 g) treated with 1M HCl in ether (52 mL) and MeOH (10 mL) was stirred at room temperature for 8 hours. After ddditional ether was added, the solution was filtered. The solid thus obtained was dried under vacuum. K_2CO_3 was added to a suspension of the solid in CH_3CN 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 to afford crude Intermediate 252-IV (1.5 g).

Intermediate 252-IV (1.5 g) and Et_3N (0.5 mL) in 1-pentanol (14 mL) was allowed to react with 2,4-dichloro-6-aminopyrimidine (1.0 g) at 120°C overnight. The solvent was then removed to afford crude Intermediate 252-V (2.0 g).

A solution of Intermediate 252-V (2.0 g) and Boc_2O (2.1 g) in CH_2Cl_2 (250 mL) was added to Et_3N (1.0 mL) at 25 °C overnight. The solution was then concentrated and the resultant residue was purified by column chromatography on silica gel (EtOAc/Hexane = 1:1) to give Intermediate 252-VI (1.7 g) in a 56% yield.

N^1-Morpholine-N^1-piperazine ethane (300 mg) was added to Intermediate 252-VI (300 mg) in 1-pentanol (1 mL). The mixture was stirred at 120°C overnight and then concentrated. The residue thus obtained was coated with SiO_2 and purified by column chromatography on silica gel (EtOAc/ MeOH = 1/1) to afford Intermediate 252-VII (260 mg) in a 70% yield.

A solution of 20% TFA/CH_2Cl_2 (5 mL) was added to a solution of Intermediate 252-VII (260 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 (21% NH_3 (aq)/MeOH = 1/19) to afford Compound 252 (175 mg) in a 91 % yield. Compound 252 was then treated with 1 M HCl (4 mL) in CH_2Cl_2 (2 mL) for 0.5 hours. After the solvents were removed, the residue was treated with ether and filtered to give hydrochloride salt of Compound 252.

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

Example 253: Preparation of compound 253:

Compound 253 was prepared in a manner similar to that used to prepare compound 252.

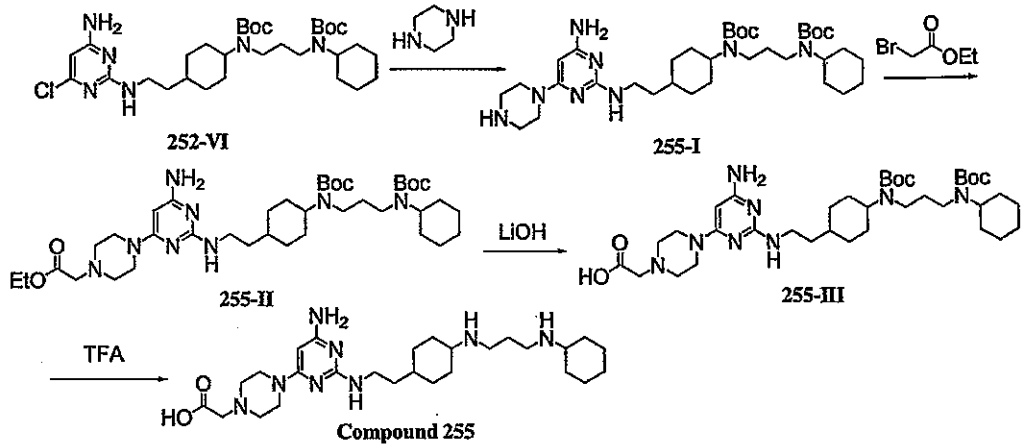
CI-MS ($M^+ + 1$): 531.4.

Example 254: Preparation of compound 254:

Compound 254 was prepared in a manner similar to that used to prepare compound 252.

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

Example 255: Preparation of compound 255:



A solution of Intermediate 252-VI (1.0 g) and piperazine (0.42 g) in 1-pentanol (8 mL) was stirred 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 separated and concentrated. The residue thus obtained was purified by column chromatography on silica gel (EtOAc/ MeOH = 2/1) to afford Intermediate 255-I (0.9 g) in a 84% yield.

To a solution of Intermediate 255-I (0.4 g) in CH_3CN (6 mL) were added ethyl bromoacetate (100 mg) and K_2CO_3 (400 mg). The mixture was stirred at 60°C for 3 hours. After the solution was filtered and concentrated, the residue was purified by column chromatography on silica gel (EtOAc/MeOH = 4/1) to afford Intermediate 255-II (0.17 g) in a 38% yield.

Intermediate 255-II (0.17 g) dissolved in THF (2 mL) was added to 0.5 M of an LiOH aqueous solution (2 mL). The mixture was stirred at room temperature for 15 hours. It was acidified with 2.5 M HCl (PH = 9) and filtered to obtain yellow solid. The yellow solid was purified by column chromatography on silica gel (EtOAc/MeOH = 1/5) to afford Intermediate 255-III (0.1 g) in a 61% yield.

20% TFA/CH_2Cl_2 (3 mL) was added to a solution of Intermediate 255-III (100 mg) in CH_2Cl_2 (2 mL). The solution was stirred at room temperature for 2 hours and then concentrated. The residue in acetone (3 mL) was added to HCl (4 M in dioxane, 1 mL) at room temperature and the mixture was stirred for 30 minutes. After the solvents were removed, the residue was treated with ether and filtered to give hydrochloride salt of Compound 255 (62 mg).

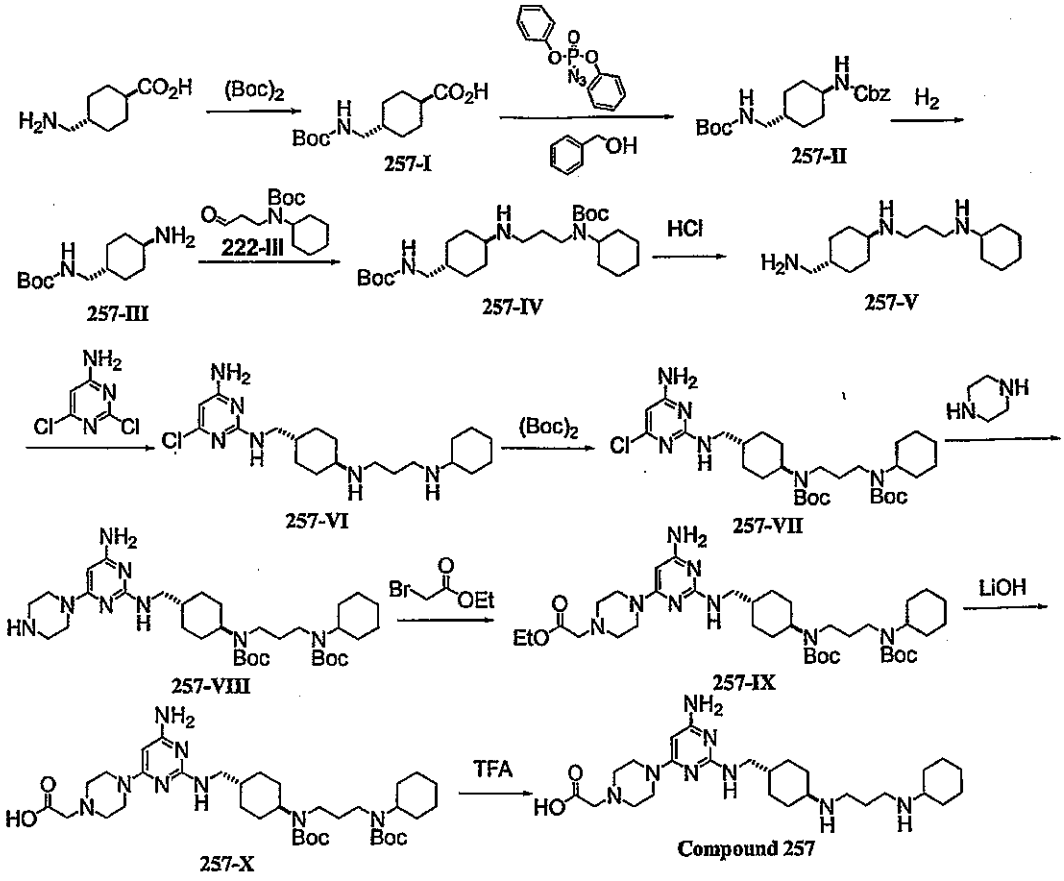
CI-MS ($M^+ + 1$): 517.4.

Example 256: Preparation of compound 256:

Compound 256 was prepared in a manner similar to that used to prepare compound 255.

CI-MS ($M^+ + 1$): 531.7.

Example 257: Preparation of compound 257:



KOH (14 g) and Boc_2O (33.3 g) were added to a solution of *trans*-4-(Aminomethyl)cyclohexane-carboxylic acid (20 g) in dioxane (112 mL) at 0°C. The reaction was stirred at 25°C overnight. The solution was concentrated to half of the original volume under vacuum, acidified with 2.5 N HCl (PH = 3), and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to give a white solid Intermediate 257-I (31.9 g).

To a suspension of the above solid in toluene (150 mL) were added phosphorazidic acid diphenyl ester (32.4 g) and Et_3N (11.9 g) at 25 °C for 1.0 hour. The reaction mixture was warmed to 80 °C for 3.0 hours and then cooled to 25°C. After benzyl alcohol (20 g) was added, the reaction mixture was stirred at 80°C for another 3.0 hours and then warmed to 120 °C overnight. It was then concentrated and dissolved again in EtOAc and H_2O. The organic layer was then collected. The aqueous layer was

extracted with EtOAc. The combined organic layer was 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 257-II (35 g) in a 79% yield.

To a suspension of Intermediate 257-II (1.9 g) in MeOH (10 mL) was added 10% Pd/C (190 mg). The mixture was stirred at ambient temperature under hydrogen atmosphere for 4.0 hours, filtered, and concentrated. The residue thus obtained was purified by column chromatography on silica gel (using EtOAc and MeOH as an eluant) to give Intermediate 257-III (750 mg) in a 60% yield.

222-III (1,198 mg) prepared from Example 222 was added to a solution of Intermediate 257-III (750 mg) in CH_2Cl_2 (30 mL). The mixture was stirred at 25°C for 2 hours. $NaBH(OAc)_3$ (1,046 mg) was then added at 25°C for 12 hours. After the solution was concentrated, a saturated aqueous $NaHCO_3$ solution was added to the resultant residue. The mixture was 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 and MeOH as an eluant) to afford Intermediate 257-IV (1,200 mg) in a 78% yield.

A solution of Intermediate 257-IV (5.2 g) treated with 4 N HCl/dioxane (39 mL) in MeOH (52 mL) was stirred at room temperature for 8 hours. After ether (104 mL) was added, the solution was filtered. The solid thus obtained was dried under vacuum. K_2CO_3 (21 g) was added to a suspension of this solid in CH_3CN (230 mL) at room temperature for 10 minutes. After water (9 mL) was added, the reaction mixture was stirred at room temperature for 2 hours. The mixture was then filtered, dried over anhydrous $MgSO_4$, and concentrated to afford crude Intermediate 257-V (2.8 g).

Crude Intermediate 257-V (2.8 g) and Et_3N (1.3 mL) in 1-pentanol (11.3 mL) was allowed to react with 2,4-dichloro-6-aminopyrimidine (1,633 mg) at 100°C for 12 hours. The solvent was then removed and the residue was purified by column chromatography on silica gel (21% NH_3 (aq)/MeOH = 1/19) to afford Intermediate 257-VI (3.3 g) in a 75% yield.

A solution of Intermediate 252-VI (3.3 g) and Boc_2O (4.189 g) in CH_2Cl_2 (60 mL) was added to Et_3N (1.0 mL) at 25°C 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 257-VII (3.2 g) in a 64% yield.

Intermediate 257-VII (2.6 g) and piperazine (1.127 g) in 1-pentanol (5.2 mL) was added to Et_3N (0.5 mL) at 120°C for 18 hours. 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 21% NH_3 (aq)/MeOH as an eluant) to afford Intermediate 257-VIII (1.8 g) in a 64% yield.

To a solution of Intermediate 257-VIII (200 mg) in CH_3CN (20 mL) were added ethyl bromoacetate (52 mg) and K_2CO_3 (128 mg). The mixture was stirred at 60°C for 2 hours. The solution was filtered and concentrated. The residue was purified by column chromatography on silica gel (using EtOAc and MeOH as an eluant) to afford Intermediate 257-IX (140 mg) in a 62% yield.

0.5 M of a LiOH aqueous solution (10 mL) was added to Intermediate 257-IX (500 mg) dissolved in THF (10 mL). The mixture was stirred at room temperature for 15 hours. It was then acidified with 2.5 M HCl (pH = 9) and filtered to obtain a yellow solid. The yellow solid was purified by column chromatography on silica gel (using EtOAc/MeOH to 21% NH_3 (aq)/MeOH as an eluant) to afford Intermediate 257-X (337 mg) in a 70% yield.

20% TFA/CH_2Cl_2 (10 mL) was added to a solution of Intermediate 257-X (400 mg) in CH_2Cl_2 (8 mL). The solution was stirred at room temperature for 2 hours and then concentrated. To the residue in acetone (7 mL) was added HCl (4 M in dioxane, 1.3 mL) at room temperature for 30 minutes. After the solvents were removed, the residue was treated with ether and filtered to give hydrochloride salt of Compound 257 (257 mg).

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

Example 258: Preparation of compound 258:

Compound 258 was prepared in a manner similar to that used to prepare compound 257.

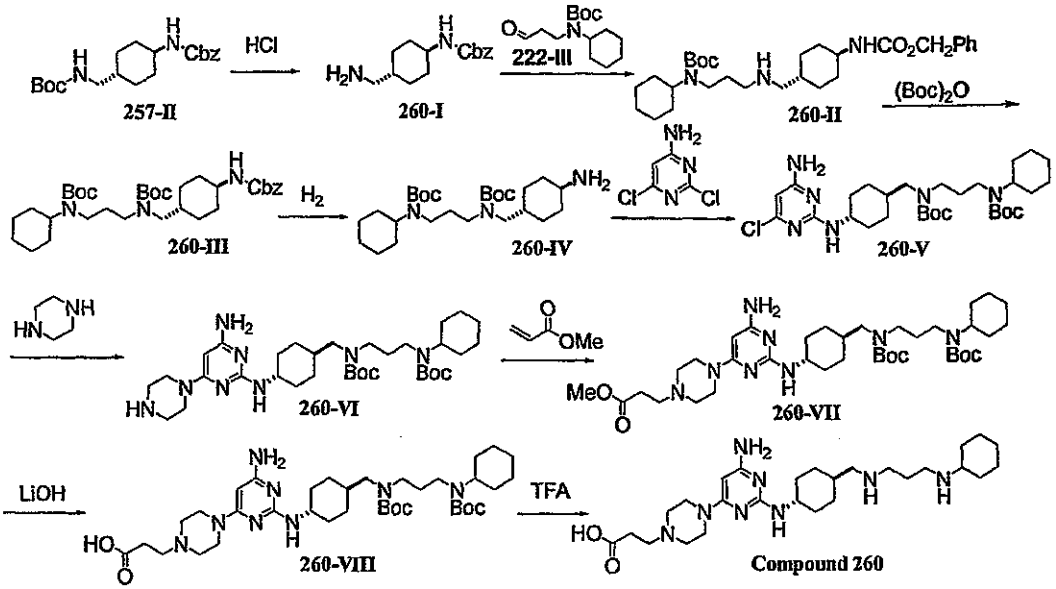
CI-MS ($M^+ + 1$): 531.4.

Example 259: Preparation of compound 259:

Compound 259 was prepared in a manner similar to that used to prepare compound 257.

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

Example 260: Preparation of compound 260:



A solution of Intermediate 257-II (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 thus obtained 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 260-I (19 g) in a 76% yield.

Intermediate 222-III (21 g) prepared from Example 222 was added to a solution of Intermediate 260-I (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 260-II (23.9 g) in a 66% yield.

A solution of Intermediate 260-II (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 260-III (22 g) in a 77% yield.

10% Pd/C (2.2 g) was added to a suspension of Intermediate 260-III (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 260-IV (16.5 g) in a 97% yield.

Intermediate 260-IV (16.5 g) and Et_3N (4.4 mL) in 1-pentanol (75 mL) was allowed to react with 2,4-dichloro-6-aminopyrimidine (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 260-V (16.2 g) in a 77% yield.

Intermediate 260-V (16.2 g) and piperazine (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 21% NH_3 (aq)/MeOH as an eluant) to afford Intermediate 260-VI (13.2 g) in a 75% yield.

Methylacrylate (532 mg) was added to a solution of Intermediate 260-VI (4 g) in MeOH (200 mL) at 25°C for 5 hours. The solution was then concentrated and the resultant residue was purification by column chromatography on silica gel (using EtOAc and MeOH as an eluant) to afford Intermediate 260-VII (3 g) in a 66% yield.

Intermediate 260-VII (3 g) dissolved in THF (60 mL) was added 0.5 M of a LiOH aqueous solution (60 mL). The mixture was stirred at room temperature for 15 hours. It was then acidified with 2.5 M HCl (pH = 8) and filtered to obtain a yellow solid. The

yellow solid was purified by column chromatography on silica gel (using CH_2Cl_2 and MeOH as an eluant) to afford Intermediate 260-VIII (1.4 g) in a 48% yield

20% TFA/CH_2Cl_2 (34 mL) was added to a solution of Intermediate 260-VIII (1.4 g) in CH_2Cl_2 (17 mL). The solution was stirred at room temperature for 5 hours and then concentrated. To the residue in acetone (20 mL) was added HCl (4 M in dioxane, 4 mL) at room temperature for 30 minutes. After the solvents were removed, the residue was treated with ether and (20 mL) and filtered to give hydrochloride salt of Compound 260 (1.4 g).

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

Example 261: Preparation of compound 261:

Compound 261 was prepared in a manner similar to that used to prepare compound 260.

CI-MS ($M^+ + 1$): 531.4.

Example 262: Preparation of compound 262:

Compound 262 was prepared in a manner similar to that used to prepare compound 260.

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

Example 263: Preparation of compound 263:

Compound 263 was prepared in a manner similar to that used to prepare compound 260.

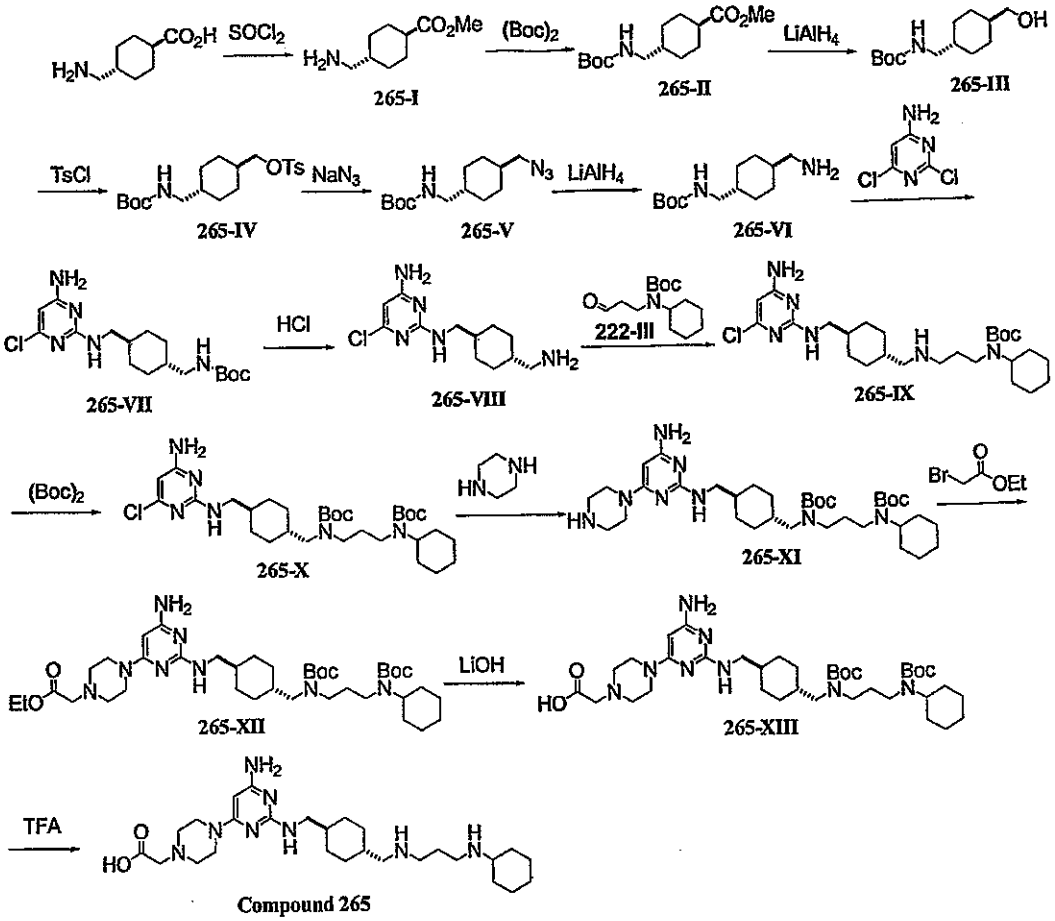
CI-MS ($M^+ + 1$): 545.4.

Example 264: Preparation of compound 264:

Compound 264 was prepared in a manner similar to that used to prepare compound 260.

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

Example 265: Preparation of compound 265:



A suspension of *cis*-4-amino-cyclohexanecarboxylic acid (20 g) in MeOH (300 mL) was cooled to 0°C. Thionyl chloride (12.2 mL) was added dropwise to the suspension. The mixture was stirred at room temperature overnight and concentrated. To the he residue in CH_3CN was added K_2CO_3 at room temperature for 10 minutes. After water was added, the mixture was stirred at room temperature for 2 hours, filtered, dried over anhydrous $MgSO_4$, concentrated to give a white solid Intermediate 265-I (25 g).

Boc_2O (31.8 g) was added to a suspension of the crude Intermediate 265-I (25 g) in CH_2Cl_2 (300 mL) at 0°C for 0.5 hour. The reaction mixture was stirred at 25°C overnight and poured into water. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was collected, dried over anhydrous $MgSO_4$, filtered, and concentrated to give crude Intermediate 265-II (38 g).

A solution of crude Intermediate 265-II (38 g) in Et_2O (100 mL) was added to a suspension of $LiAlH_4$ (6.7 g) in Et_2O (400 mL) below 0 °C. The reaction mixture was stirred at room temperature overnight. The mixture was quenched with $Na_2SO_4 \cdot 10H_2O$, and filtered through a pad of celite. The filtrate was dried over anhydrous $MgSO_4$, filtered, dried under reduced pressure. The residue thus obtained was purified by column chromatography on silica gel (using CH_2Cl_2 and MeOH as an eluant) to afford Intermediate 265-III (28 g) in a 90% yield.

To a solution of Intermediate 265-III (28 g) in CH_2Cl_2 (300 mL) were added Et_3N (30 mL), DMPA (0.7 g), and *p*-toluenesulfonyl chloride (25.8 g). The reaction mixture was stirred at 25°C overnight. The resulting solution was concentrated and the residue was re-dissolved in EtOAc. The solution was then washed with water and extracted with EtOAc. The organic layer was collected, dried over anhydrous $MgSO_4$, concentrated to give Intermediate 265-IV (50 g).

NaN_3 (24 g) was added to a solution of Intermediate 265-IV (50 g) in DMF (300 mL). The resulting mixture was stirred at 60°C overnight, filtered, and concentrated. The residue in CH_2Cl_2 was washed with a saturated aq. $NaHCO_3$ solution. The organic solution collected, dried, and concentrated to give a residue. The residue was purified by column chromatography on silica gel (using EtOAc as an eluant) to afford Intermediate 265-V (30 g) in a 97% yield.

To a suspension of $LiAlH_4$ (5.4 g) in Et_2O (400 mL) was added a solution of crude Intermediate 265-V (30 g) in Et_2O (100 mL) below 0 °C. The reaction mixture was stirred at room temperature overnight. The reaction was quenched with $Na_2SO_4 \cdot 10H_2O$, filtered through a pad of celite. The filtrate was dried over anhydrous $MgSO_4$, filtered, and dried under reduced pressure. The residue thus obtained was purified by column chromatography on silica gel (MeOH as an eluant) to afford Intermediate 265-VI (24.5 g) in a 90% yield.

A solution of Intermediate 265-VI (24.5 g) and Et_3N (13 mL) in 1-pentanol (75 mL) was reacted with 2,4-dichloro-6-aminopyrimidine (19.6 g) at 120 °C overnight. The reaction mixture was stirred at 150°C for 3 hours, filtered, and dried under reduced pressure. The residue thus obtained was purified by column chromatography on silica gel (EtOAc as an eluant) to afford Intermediate 265-VII (26.2 g) in a 68% yield.

A solution of Intermediate 265-VII (26.2 g) treated with 4 N HCl/dioxane (160 mL) in MeOH (200 mL) was stirred at room temperature overnight. After ether was added, the solution was filtered. The solid thus obtained was dried by vacuum. To a suspension of the above solid in CH_3CN and *iso*-propanol was added K_2CO_3 at room temperature for 10 minutes. After water was added at room temperature for 2 hours, the reaction mixture was filtered, dried over anhydrous $MgSO_4$, filtered, and concentrated and to give Intermediate 265-VIII (15 g).

To a solution of Intermediate 265-VIII (15 g) in CH_2Cl_2 (500 mL) was added Intermediate 222-III (18.6 g). The mixture was stirred at 25 °C for 2 hours. $NaBH(OAc)_3$ (11.7 g) was then added at 25°C and the mixture was stirred overnight. The solution was then concentrated and a saturated aqueous $NaHCO_3$ solution was added. The mixture was extracted with CH_2Cl_2. The organic layer was collected, dried over anhydrous $MgSO_4$, concentrated. The residue thus obtained was purified by column chromatography on silica gel (MeOH as an eluant) to afford Intermediate 265-IX (14.1 g) in a 39% yield.

Et_3N (2.2 mL) was added to a solution of Intermediate 265-IX (14.1 g) and Boc_2O (6.6 g) in CH_2Cl_2 (150 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 265-X (12 g) in a 71% yield.

Et_3N (2.4 mL) was added to a mixture of Intermediate 265-X (12 g) and piperazine (5.1 g) in 1-pentanol (24 mL) 120°C. The solution was stirred overnight and then concentrated. The residue was treated with water and extracted with CH_2Cl_2. The organic layer was collected, dried over anhydrous $MgSO_4$. The residue thus obtained was purified by column chromatography on silica gel (MeOH as eluant) to afford Intermediate 265-XI (9.6 g) in a 74% yield.

To a solution of Intermediate 265-XI (500 mg) in CH_3CN (50 mL) were added ethyl bromoacetate (127 mg) and K_2CO_3 (314 mg). The mixture was stirred at 60°C for 2 hours. The solution was filtered and concentrated. The residue thus obtained was purified by column chromatography on silica gel (EtOAc as an eluant) to afford Intermediate 265-XII (230 mg) in a 41% yield.

0.5 M LiOH (5 mL) was added to a solution of Intermediate 265-XII (230 mg) in THF (10 mL). The mixture was stirred at room temperature for 15 hours. It was then acidified with 2.5 M HCl (pH = 8) and filtered to obtain a yellow solid, which was purified by column chromatography on silica gel (MeOH as an eluant) to afford Intermediate 265-XIII (150 mg) in a 68% yield.

To a solution of Intermediate 265-XIII (150 mg) in CH_2Cl_2 (2 mL) was added 20% TFA/CH_2Cl_2 (3 mL). The solution was stirred at room temperature for 5 hours and then concentrated. HCl (4 M in dioxane, 2 mL) was added in the residue in acetone at room temperature for 30 minutes. After solvents were removed, the residue was treated with ether and filtered to give hydrochloride salt of compound 265 (94 mg).

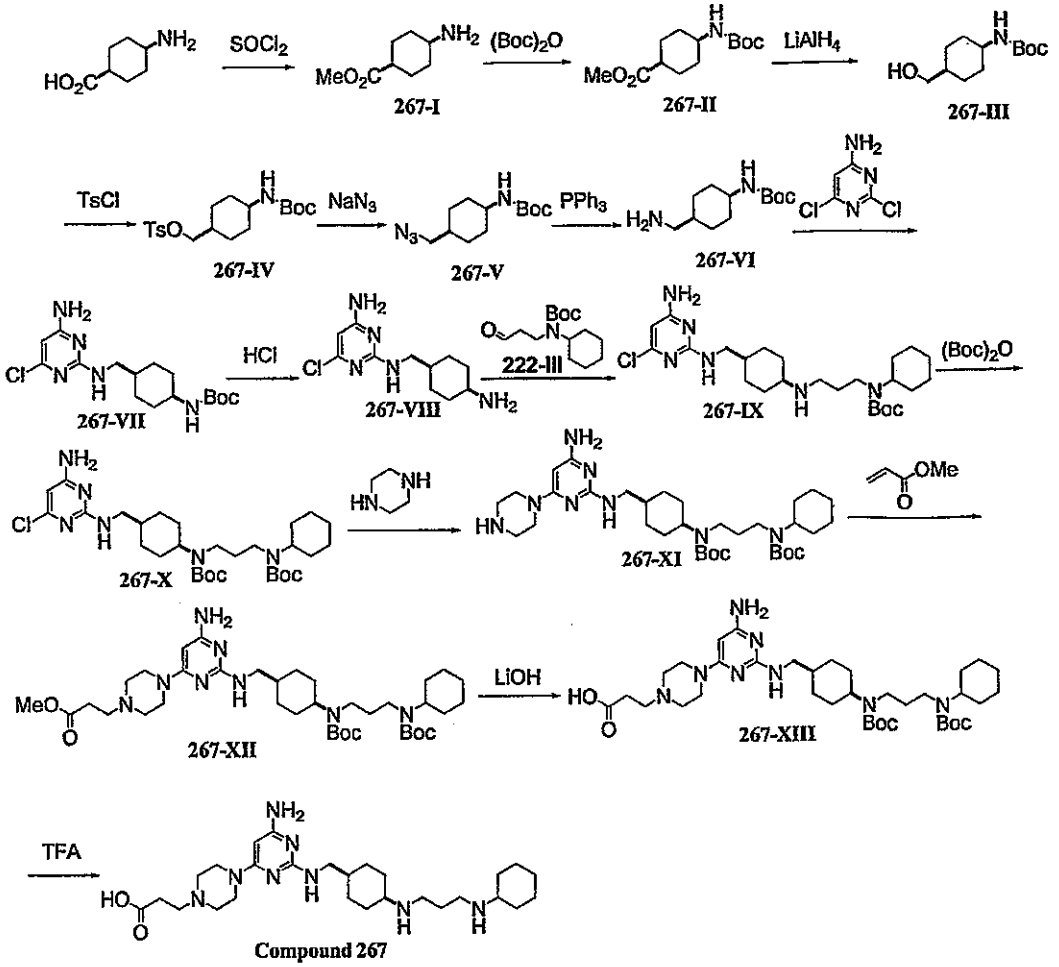
CI-MS ($M^+ + 1$): 517.4.

Example 266: Preparation of compound 266:

Compound 266 was prepared in a manner similar to that used to prepare compound 265 (see example 264).

CI-MS ($M^+ + 1$): 531.4.

Example 267: Preparation of compound 267:



A suspension of *cis*-4-amino-cyclohexanecarboxylic acid (30 g) in MeOH (500 mL) was cooled to 0°C. Thionyl chloride (30.5 mL) was added dropwise. The mixture was stirred at room temperature overnight and concentrated to give a white solid Intermediate 267-I (32.6 g).

To a suspension of Intermediate 267-I (32.6 g) obtained above in CH_2Cl_2 (500 mL) were added Et_3N (18 mL) and Boc_2O (50 g) sequentially. The reaction mixture was stirred at 25°C overnight and poured into water. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried over anhydrous $MgSO_4$, filtered, concentrated to give crude Intermediate 267-II (53.4 g).

A solution of crude Intermediate 267-II (53.4 g) in Et_2O (100 mL) was added to a suspension cooled at 0°C of $LiAlH_4$ (11 g) in Et_2O (500 mL) below 0 °C. The reaction

mixture was stirred at room temperature overnight. The resulting solution was cooled in ice-bath, quenched with cold water, filtered through a pad of celite. The filtrate was dried over anhydrous $MgSO_4$, filtered, washed with hexane, and dried under reduced pressure to give crude Intermediate 267-III (43.21 g).

Et_3N (32 mL), DMPA (4.6 g) and *p*-toluenesulfonyl chloride (40 g) were added to a solution of Intermediate 267-III (43.21 g) in CH_2Cl_2 (400 mL). The reaction mixture was stirred at 25°C overnight. The resulting solution was concentrated and the residue was dissolved in EtOAc. The solution was washed with water and extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, and concentrated to give a residue. The residue was purified by column chromatography on silica gel (EtOAc/Hexane = 1/4) to afford Intermediate 267-IV (57.34 g) in a 71% yield.

NaN_3 (29 g) was added to a solution of Intermediate 267-IV (57.34 g) in DMF (200 mL). The resulting mixture was stirred at 40°C overnight, filtered, and concentrated. The residue was dissolved in CH_2Cl_2 and was washed with a saturated aqueous $NaHCO_3$ solution. The solution was concentrated to give a residue, which was purified by column chromatography on silica gel (EtOAc/Hexane = 1/6) to afford Intermediate 267-V (30.48 g) in a 80% yield.

PPh_3 (12.9 g) and H_2O (0.9 mL) were added to a solution of Intermediate 267-V (11.37 g) in THF (200 mL). After the solution was stirred at 25 °C overnight, the solution was concentrated to give a residue, which was purified by column chromatography on silica gel (EtOAc/MeOH = 15/1) to afford Intermediate 267-VI (9.44 g) in a 93% yield.

A solution of Intermediate 267-VI (9.44 g) and Et_3N (4 mL) in 1-pentanol (40 mL) was reacted with 2,4-dichloro-6-aminopyrimidine (7.5 g). The solution was stirred at 120°C overnight. The solvent was removed and the residue thus obtained was purified by column chromatography on silica gel (EtOAc/MeOH = 1/2) to afford Intermediate 267-VII (10.5 g) in a 71% yield.

A solution of Intermediate 267-VII (2.0 g) treated with 4 N HCl/dioxane (10 mL) in MeOH (20 mL) was stirred at room temperature overnight. After ether was added, the solution was filtered. The solid was dried under vacuum. To a suspension of the above solid in CH_3CN and *iso*-propanol was added K_2CO_3 at room temperature and was stirred

for 10 minutes. After water was added to the reaction mixture at room temperature, it was stirred for another 2 hours. The mixture was then filtered, dried over anhydrous $MgSO_4$, filtered, and concentrated. The resultant residue was purified by column chromatography on silica gel (CH_2Cl_2 and MeOH as eluant) to give Intermediate 267-VIII (1.1 g) in a 77% yield.

Intermediate 222-III (1.58 g) was added to a solution of Intermediate 267-VIII (1.10 g) in CH_2Cl_2 (40 mL). The mixture was stirred at 25°C for 2 hours. $NaBH(OAc)_3$ (907 mg) was then added at 25°C and the mixture was stirred overnight. The mixture was then concentrated and a saturated aqueous $NaHCO_3$ solution was added to the resultant residue. The mixture was extracted with CH_2Cl_2. The organic layer was collected and concentrated. The residue thus obtained was purified by column chromatography on silica gel (EtOAc and MeOH as eluant) to afford Intermediate 267-IX (1.30 g) in a 61% yield.

Et_3N (0.3 mL) was added to a solution of Intermediate 267-IX (1.30 g) and Boc_2O (0.63 g) in CH_2Cl_2 (150 mL) at 25°C. The solution was stirred overnight and then concentrated. The resultant residue was purified by column chromatography on silica gel (EtOAc/Hexane = 1/1) to give Intermediate 267-X (1.30 g) in a 83% yield.

Et_3N (0.2 mL) was added to a solution of Intermediate 267-X (800 mg) and piperazine (347 mg) in 1-pentanol (2 mL) at 120°C. The solution was stirred overnight and then 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 (EtOAc/ MeOH = 1/1) to afford Intermediate 267-XI (700 mg) in a 81% yield.

Methylacrylate (93 mg) was added to a solution of Intermediate 267-XI (700 mg) in MeOH (7 mL) at 30°C. The solution was stirred for 5 hours and then concentrated. The residue was purified by silica gel (EtOAc and MeOH as eluant) to afford Intermediate 267-XII (460 mg) in a 58% yield.

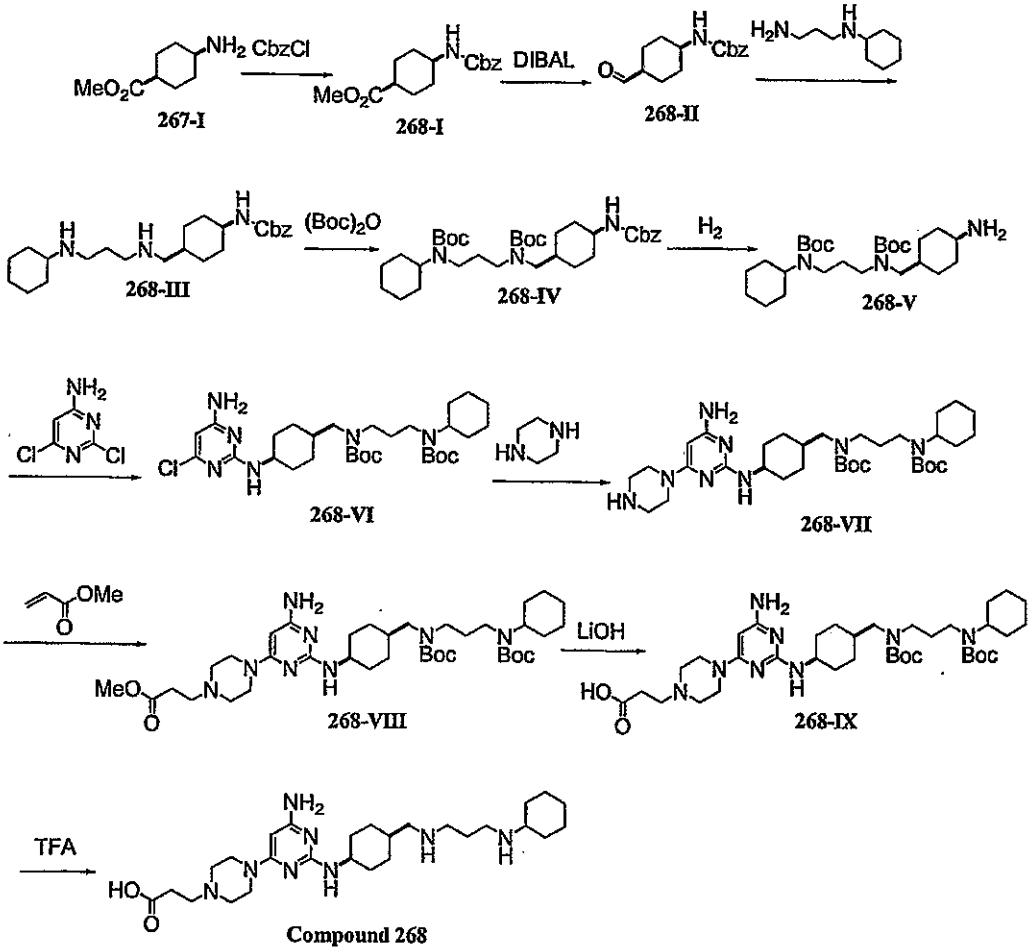
0.5 M LiOH (9.2 mL) was added to a solution of Intermediate 267-XII (460 mg) in THF (5 mL). The mixture was stirred at room temperature for 15 hours. It was then acidified with 2.5 M HCl (pH = 8) and filtered to obtain a yellow solid. The solid was

purified by column chromatography on silica gel (CH_2Cl_2 and MeOH as eluant) to afford Intermediate 267-XIII (266 mg) in a 59% yield

20% TFA/CH_2Cl_2 (5 mL) was added to a solution of Intermediate 267-XIII (266 mg) in CH_2Cl_2 (3 mL). The solution was stirred at room temperature for 5 hours. The solution was concentrated. HCl (4 M in dioxane, 3 mL) was added to the residue in acetone. The mixture was stirred at room temperature for 30 minutes. After solvents were removed, the residue was treated with ether and filtered to give the hydrochloride salt of Compound 267 (153 mg).

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

Example 268: Preparation of compound 268:



A solution of methyl *cis*-4-(amino)cyclohexylcarboxylate (267-I, 5.0 g) and $PhCH_2OCOCl$ (6.5 g) in CH_2Cl_2 (64 mL) was stirred at 0°C for 1 hour. The solution was allowed to warm-up to room temperature and stirred for another 12 hours. It was then concentrated and the residue was purified by column chromatography on silica gel (EtOAc/Hexane = 1/4) to afford Intermediate 268-I (5.56 g) in a 60% yield.

DIBAL (1.0 M in Hexane, 34 mL) was added to a stirred solution of Intermediate 268-I (5.0 g) in dry toluene (170 mL) at -70~-78°C under N_2 (g). The reaction mixture was stirred for 2 hours at this temperature. 5% HCl (aq) (34 mL) was then added to the solution at -60~-70°C and the mixture was stirred for another 0.5 hour after the reaction temperature was increased to 25°C. The aqueous layer was extracted with CH_2Cl_2 twice. The organic layers were combined, dried with anhydrous $MgSO_4$, and concentrated by removing the solvent under vacuum to afford curd 268-II (3.14 g).

Intermediate 268-II (3.0 g) was then reacted at room temperature with cyclohexylaminopropylamine (1.8 g) in MeOH (30 mL). The mixture was stirred at 60°C for 12 hours. $NaBH_4$ (0.43 g) was added at 0°C. After being stirred for 0.5 hour, an aqueous solution of NH_4Cl (10%, 20 mL) was added and the mixture was extracted with CH_2Cl_2. The organic layer was collected, dried over anhydrous $MgSO_4$, filtered, and concentrated to afford a residue. The residue was purified by column chromatography on silica gel (EtOAc/Hexane = 4/1) to afford Intermediate 268-III (2.54 g) in a 55% yield.

A solution of Intermediate 268-III (2.5 g) and Boc_2O (3.0 g) in CH_2Cl_2 (130 mL) was stirred at 25°C overnight. The solution was then concentrated and the resultant residue was purified by column chromatography on silica gel (EtOAc/Hexane = 1/9) to give Intermediate 268-IV (3.2 g) in a 85% yield.

10% Pd/C (570 mg) was added to a suspension of Intermediate 268-IV (3.2 g) in EtOH (18 mL). The mixture was stirred at ambient temperature under hydrogen atmosphere for 2.0 hours, filtered, and concentrated to give crude Intermediate 268-V (2.4 g).

A solution of crude Intermediate 268-V (2.4 g) and Et_3N (0.85 mL) in 1-pentanol (17 mL) was reacted with 2,4-dichloro-6-aminopyrimidine (1.0 g) at 120°C for 15 hours.

The solvent was removed and the residue was purified by column chromatography on silica gel (EtOAc/Hexane = 3/1) to afford Intermediate 268-VI (2.4 g) in a 80% yield.

Piperazine (1.0 g) was added to Intermediate 268-VI (2.4 g) in 1-pentanol (8 mL). The mixture was stirred at 120°C for 15 hours. The solution was concentrated and the residue was treated with water and extracted with CH_2Cl_2. The organic layer was collected and concentrated to afford crude Intermediate 268-VII (2.2 g).

Methyl acrylate (0.1 mL) was added to a solution of crude Intermediate 268-VII (700 mg) in MeOH (10 mL). The mixture was stirred at 30°C for 12 hours. After the mixture was concentrated, the residue was treated with water and extracted with CH_2Cl_2. The organic layer was collected and concentrated to give a residue, which was purified by column chromatography on silica gel (EtOAc/MeOH = 4/1) to afford Intermediate 268-VIII (530 mg) in a 67% yield.

0.5 M LiOH (7.2 mL) was added to a solution of Intermediate 268-VIII (530 mg) in THF (7.2 mL). The mixture was stirred at room temperature for 2 hours. It was then acidified with 2M HCl (pH = 8) and filtered to obtain a yellow solid, which was purifed by column chromatography on silica gel (EtOAc/MeOH = 1/9) to afford Intermediate 268-IX (470 mg) in a 90% yield.

Intermediate 268-IX (470 mg) was dissolved in CH_2Cl_2 (8 mL). TFA (2 mL) was added and the solution was stirred at room temperature overnight. The solution was then concentrated and HCl (4 M in dioxane, 1.3 mL) was added to the residue in acetone (7 mL) at room temperature for 30 minutes. After the solvents were removed, the residue was treated with ether and filtered to give a hydrochloride salt of compound 268 (390 mg).

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

Example 269: *in vitro* assay

143 of the above-mentioned compounds were tested for their efficacy in binding to 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 agonists. Eu-GTP, obtained from Wallac Oy, was used in this assay to allow

monitoring of agonist-dependent activation of G-protein. Stimulation of CXCR4 receptor by SDF-1 leads to the replacement of GDP by GTP on the α-subunit of G-protein. This GTP-Gα complex represents the activated form of G-protein. Eu-GTP, a non-hydrolysable analog of GTP, can be used to quantify the amount of activated G-protein. (Peltonen et al., Eur. J. Pharmacol. (1998) 355:275.)

Plasma membrane of CXCR4-expressing HEK293 cells was suspended in an assay buffer (50 mM NaCl, 100 μg/mL saponin, 3 mM $MgCl_2$, 3 μM 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 the addition of the test compounds (10 μM in 0.1% DMSO) and stromal-derived factor-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 was added to each well and the plate was incubated again for 60 minutes. The assay was terminated by washing the plate twice with a wash solution provided in the assay kit. Binding of Eu-GTP was determined based on the fluorescence signal from a Victor 2 multi-label reader.

Unexpectedly, 196 of the tested compounds showed IC_{50} values between 0.003 μM and 0.1 μM; 56 of the tested compounds showed IC_{50} values between 0.1 μM and 1 μM, and 16 of the test compounds showed IC_{50} values between 1 μM and 5 μM.

Example 270: Radioligand binding assay

Competition binding assays between test compounds human stromal-derived factor-1 were carried out using glass fiber filter plates (Millipore, Billerica, MA). 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 a 70 μl 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 solution and 10 μl of a [^{125}I]-SDF-1 solution (each having a final concentration 150 pM) in U-bottom assay plates (Corning, Corning, NY). After the membranes were incubated at room temperature for 120 minutes, the incubation was terminated by transferring 80 μl of

each reaction mixture to each glass fiber plate well and filtered by vacuum filtration (MultiScreen Vacuum Maniford, Millipore). Each plate was washed 4 times with 80 µl/well of a wash buffer (20 mM HEPES, pH 7.4 and 90 mM NaCl) and then air dried overnight. After 35 µl/well of a Supermix cocktail to each plate, the radioactivity retained on the plate was counted with Trilux MicroBeta (PerkinElmer, Boston, MA).

The 196 compounds with IC_{50} values between 0.003 µM and 0.1 µM in GTP-binding assay were further screened in radioligand binding assay. The results show that they exhibited inhibitory activities in the range of 10-1200 nM.

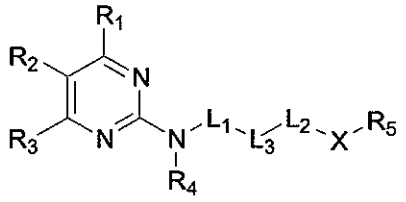
OTHER EMBODIMENTS

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 formula (I):



(I),

wherein

X is $-N(R_a)-$;

L_1 is C_1-C_{10} alkylene or -C(O)-;

L_2 is deleted or C_1-C_{10} alkylene;

L_3 is C_3-C_{20} cycloalkyl;

each of R_1, R_2, and R_3, independently, is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_3-C_{20} heterocycloalkyl, aryl, heteroaryl, halo, CN, OR_c, $COOR_c$, $OC(O)R_c$, $C(O)R_c$, $C(O)NR_cR_d$, or NR_cR_d;

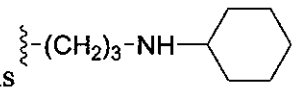
R_4 is H; and

R_5 is C_3-C_{20} cycloalkyl, C_3-C_{20} heterocycloalkyl, aryl, heteroaryl, or C_1-C_{10} alkyl substituted with C_3-C_{20} cycloalkyl, C_3-C_{20} heterocycloalkyl, or $N(R_eR_f)$; 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_3-C_{20} heterocycloalkyl, aryl, heteroaryl, or -C(O)R; R being H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_3-C_{20} heterocycloalkyl, aryl, or heteroaryl;

or a salt thereof.

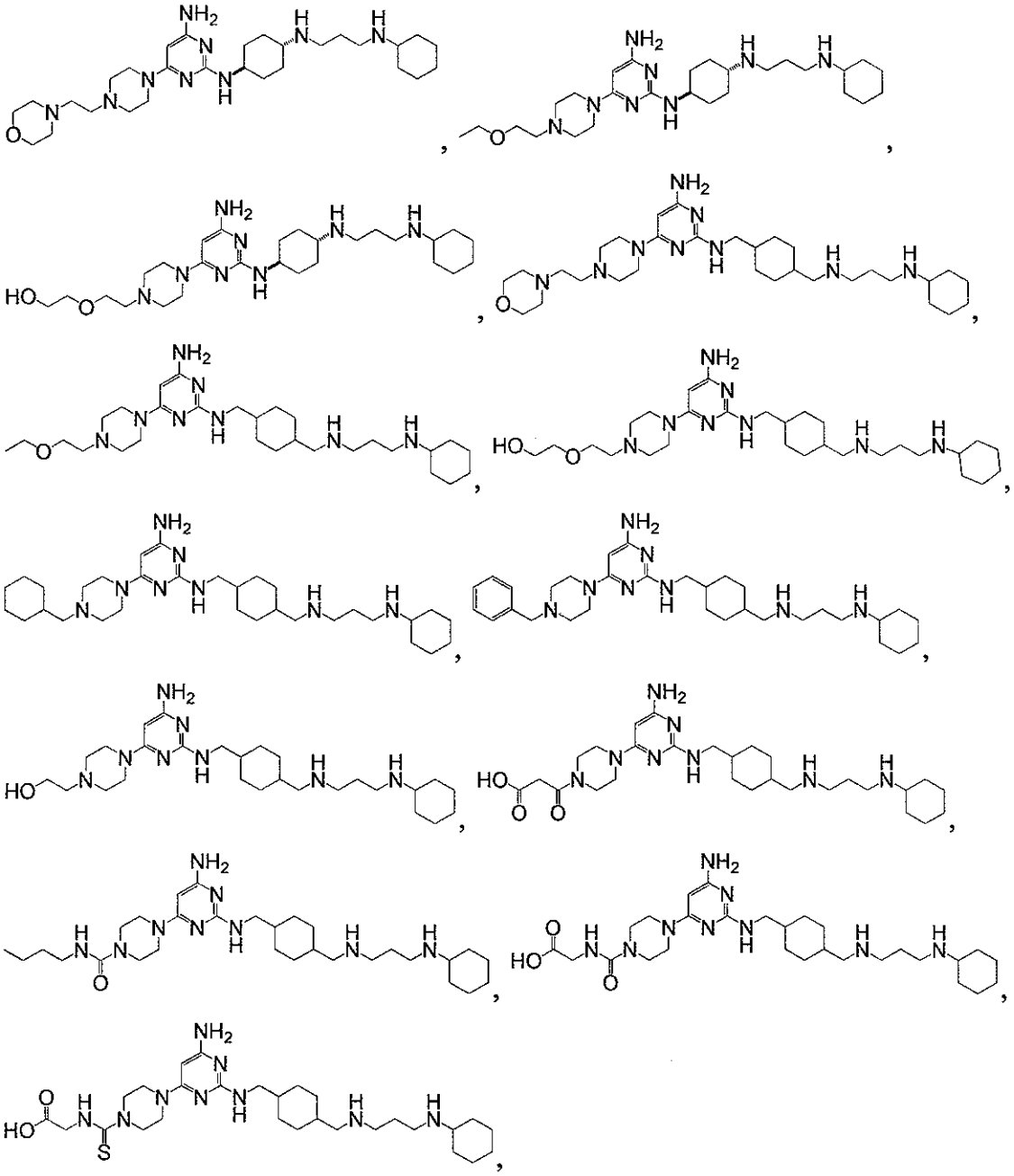
2. The compound of claim 1, wherein L_3 is cyclohexylene.

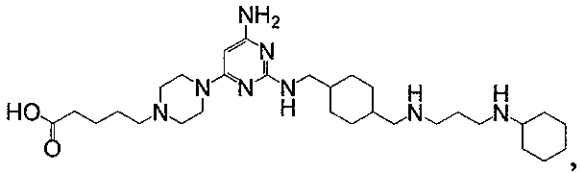
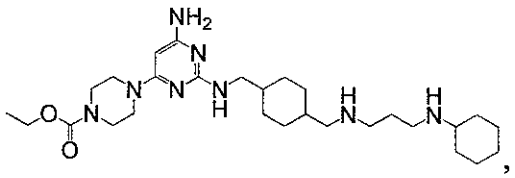
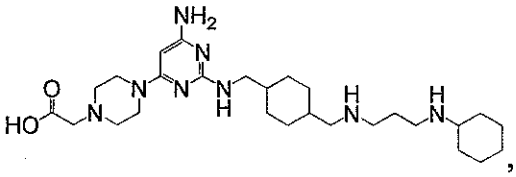
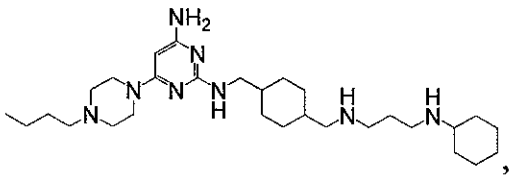
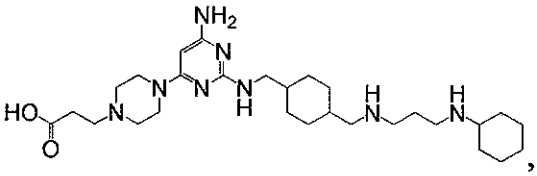
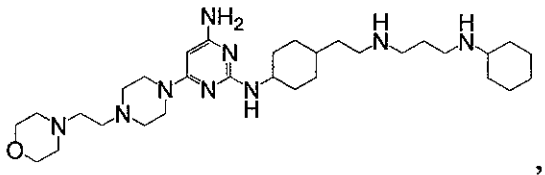
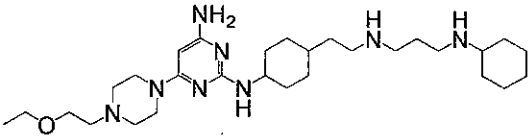
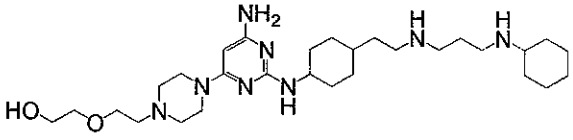
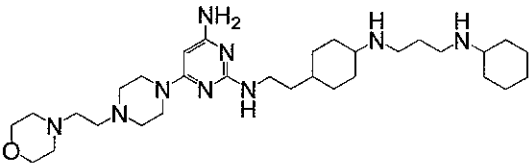
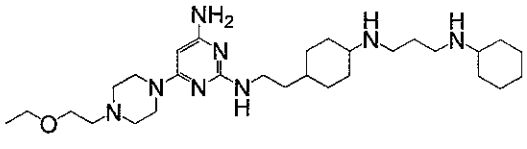
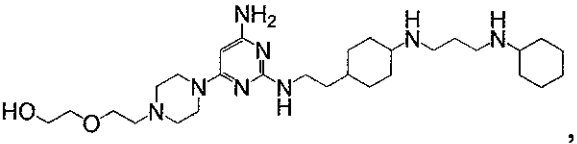
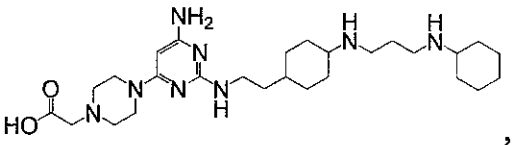
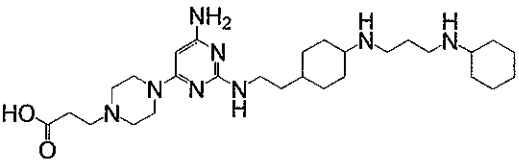
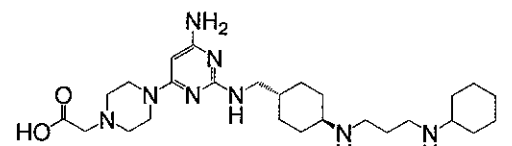
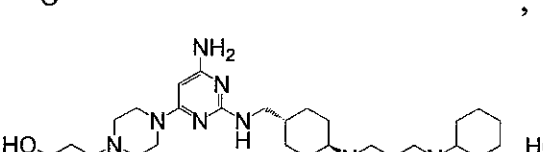
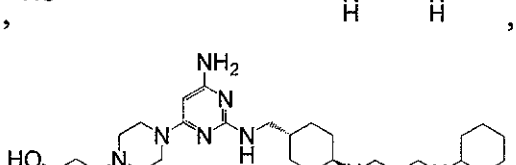
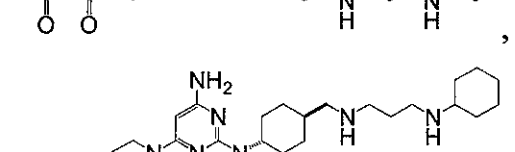
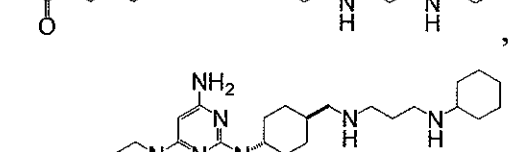
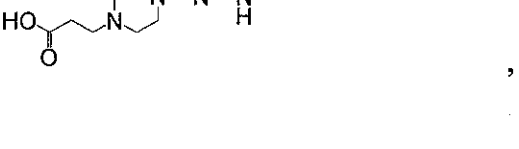
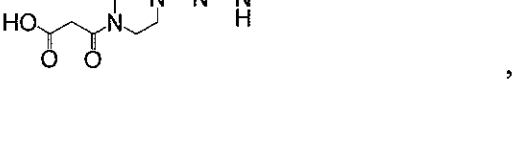
3. The compound of claim 1, wherein R_5 is C_1-C_{10} alkyl substituted with $N(R_eR_f)$.

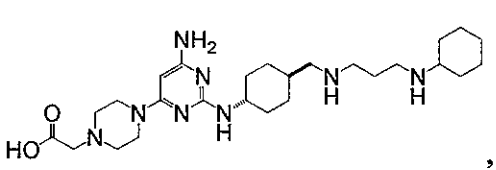
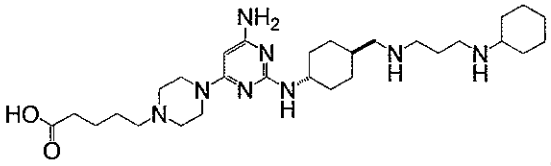
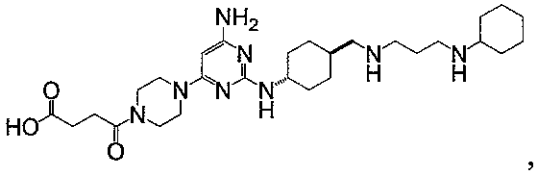
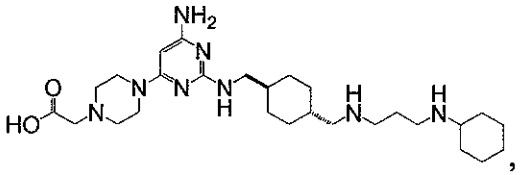
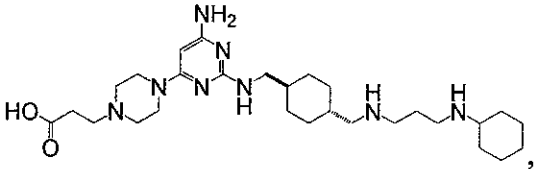
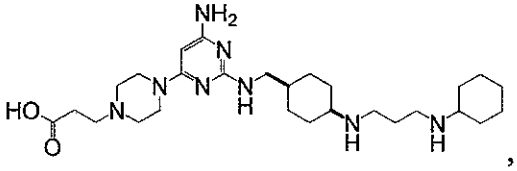
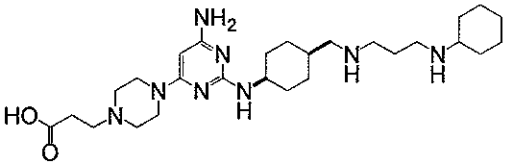
4. The compound of claim 3, R_5 is .

5. The compound of claim 1, R_3 is C_3-C_{20} heterocycloalkyl substituted with C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_3-C_{20} heterocycloalkyl, aryl, OR', C(O)R', COOR', C(O)N(R'R''), SO_2R', or C(S)N(R'R''), in which each of R' and R'', independently, is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_3-C_{20} heterocycloalkyl, aryl, or heteroaryl.

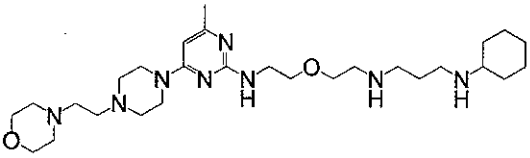
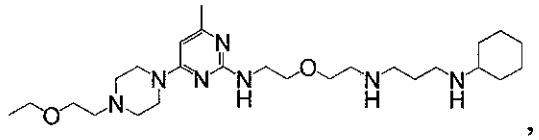
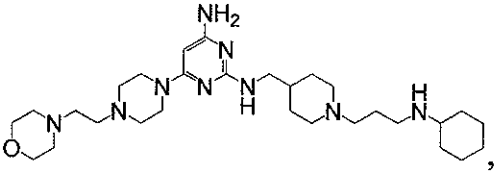
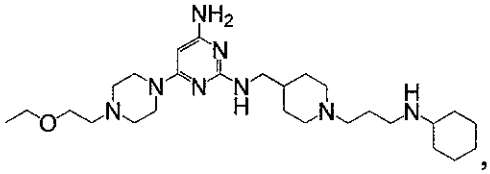
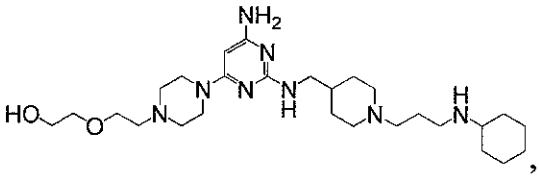
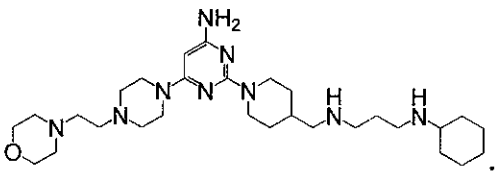
6. A compound, wherein the compound is



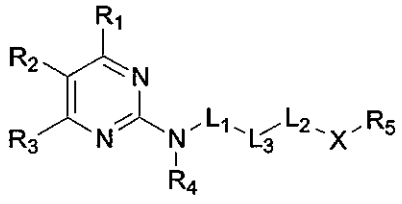

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7. A compound, wherein the compound is


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8. A compound of formula (I):



(I),

wherein

X is -N(R_a)-;

L_1 is C_1-C_{10} alkylene or -C(O)-;

L_2 is deleted or C_1-C_{10} alkylene;

L_3 is C_3-C_{20} cycloalkyl;

R_1 is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, aryl, heteroaryl, halo, CN, OR_c, $COOR_c$, $OC(O)R_c$, $C(O)R_c$, $C(O)NR_cR_d$, or NR_cR_d;

each of R_2 and R_3, independently, is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_3-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;

R_4 is H; and

R_5 is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_3-C_{20} heterocycloalkyl, aryl, or heteroaryl; or R_4 and R_5 together are C_1-C_{10} alkylene or C_1-C_{10} heteroalkylene;

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_3-C_{20} heterocycloalkyl, aryl, or heteroaryl;

or a salt thereof.