01640/01/PCT

Substituted Pyrimidinones

Background

Field

This invention relates to substituted pyrimidinones that are useful for treating diseases and conditions caused or exacerbated by unregulated p38 MAP kinase activity. It also relates to Pharmaceutical compositions containing the pyrimidinone compounds, methods of preparing the pyrimidinone compounds and methods of treatment using these compounds.

Description of the Related Art

Numerous cell surface receptors use one or more of the mitogen-activated protein kinase (MAP kinase) cascades during signal transduction. MAP kinases are a family of protein-directed serine/threonine kinases that are activated by dual phosphorylation. One subgroup of the MAP kinases is p38 MAP kinase, which is activated by a variety of signals including proinflammatory cytokines such as tumor necrosis factor (TNF) and interleukin-1 (IL-1), as well as bacterial lipopolysaccharides and environmental stress such as osmotic shock and ultraviolet radiation (Ono, K. and J. Han, Cell Signal. 12: 1, 2000). Within the p38 kinase family, there are four distinct isozymes: p38 alpha, p38 beta, p38 gamma, and p38 delta. The p38 kinase family function downstream of an activating stimulus by phosphorylating and activating transcription factors (e.g. ATF2, CHOP and MEF2C) as well as other kinases (e.g. MAPKAP-2 and MAPKAP-3) (Trends in Cell biology 7, 353-361, 1997;Mol Cell Biology 19, 21-30, 1999; EMBO J 20, 466-479, 2001)Upon activation, the p38 kinase cascade leads to the induction of gene expression of several factors involved in inflammation and immunity including TNF, interleukin-6, granulocyte-macrophage colony stimulating

factor (GM-CSF), and HIV long terminal repeat (Paul et al., Cell Signal. 9: 403-410, 1997). The products of the p38 phosphorylation stimulate the production of inflammatory cytokines and other proteins, including TNF and IL-1, and cyclooxygenase-2, and also possibly modulate the effects of these cytokines on their target cells, and thus stimulate inflammation processes (Lee, J.C. et al, Nature, 372: 376, 1994).

P38 MAP kinases have also been shown to promote apoptosis during ischemia in cardiac myocytes, which suggests that p38 MAP kinase inhibitors can be used to treat ischemic heart disease (J. Biol. Chem. 274, 6272, 1999). They are also required for T-cell HIV-1 replication and may be useful targets for AIDS therapy. P38 pathway inhibitors have been used to increase cancer cell sensitivity to cancer therapy also find use in the treatment of asthma (JPET 293, 281, 2000).

TNF is a cytokine and a potent proinflammatory mediator implicated in inflammatory conditions such as arthritis, asthma, septic shock, non-insulin dependent diabetes mellitus, multiple sclerosis, asthma, and inflammatory bowel disease. Thus inhibitors of p38 MAP kinases (required for TNF production) may be useful for the treatment of inflammatory conditions resulting from excessive cytokine production such as arthritis. (Boehm, J.C. and J.L. Adams, Exp. Opin. Ther. Patents 10: 25, 2000, and references cited therein). TNF has also been implicated in viral infections, such as HIV, influenza virus, and herpes virus including herpes simplex virus type-1 (HSV-1), herpes simplex virus type-2 (HSV-2), cytomegalovirus (CMV), varicella-zoster virus (VZV), Epstein-Barr virus, human herpesvirus-6 (HHV-6), human herpesvirus-7 (HHV-7), human herpesvirus-8 (HHV-8), pseudorabies and rhinotracheitis, among others.

Excessive or unregulated TNF production has also been shown to produce elevated levels of IL-1. Inhibition of TNF, therefore, should reduce levels of IL-1 (European Cytokine Netw 6, 225, 1995) and ameliorate disease states caused by unregulated IL-1 synthesis. Such disease states include rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone resorption diseases, reperfusion injury, graft versus host reaction, alallograft rejections, fever and myalgias due to infection, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS related complex (ARC), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, and pyresis.

IL-1 has also been shown to mediate a variety of biological activities such as the activation of T-helper cells, induction of fever, stimulation of prostaglandin or collagenase production, neutrophil chemotaxis, and the suppression of plasma iron levels (*Rev. Infect. Disease*, 6, 51 (1984)). Elevated levels of IL-1 have also been implicated in mediating or exacerbating a number of disease states including rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis, inflammatory bowel disease, adult respiratory distress syndrome (ARDS), psoriasis, Crohn's disease, ulcerative colitis, anaphylaxis, muscle degeneration, cachexia, Reiter's syndrome, type I and type II diabetes, bone resorption diseases, ischemia reperfusion injury, arteriosclerosis, brain trauma, multiple sclerosis, sepsis, septic shock, and toxic shock syndrome. Viruses sensitive to TNF inhibition, such as HIV-1, HIV-2, HIV-3, are also affected

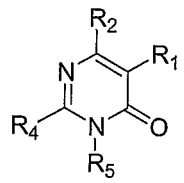
by IL-1 production. In rheumatoid arthritis, both IL-1 and TNF induce collagenase synthesis and ultimately lead to tissue destruction within arthritic joints (*Lymphokine Cytokine Res.* (11): 253-256, (1992) and *Clin. Exp. Immunol.* 989:244-250, (1992)).

IL-6 is another pro-inflammatory cytokine, which is associated with many conditions including inflammation. Consequently, TNF, IL-1 and IL-6 affect a wide variety of cells and tissues and are important inflammatory mediators of a wide variety of disease states and conditions. The inhibition of these cytokines by inhibition or modulation of p38 kinase is of benefit in controlling, reducing and alleviating many of these disease states and conditions. Therefore, the invention concerns finding small molecule inhibitors or modulators of p38 kinase and the p38 kinase pathway.

01640/01/PCT

Summary

In a broad aspect, the invention provides compounds of Formula I (Embodiment I):



(I)

and pharmaceutically acceptable salts thereof, wherein

R_1 is H, halogen, NO_2, alkyl, carboxaldehyde, hydroxyalkyl, dihydroxyalkyl, arylalkoxy, arylalkyl, alkenyl, alkynyl, arylalkynyl, -CN, aryl, alkanoyl, alkoxy, alkoxyalkyl, haloalkyl, haloalkoxy, carboxyl, or arylalkanoyl,

wherein the aryl portion of arylalkoxy, arylalkyl, and arylalkanoyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, nitro, CN, haloalkyl, haloalkoxy or CO_2R;

wherein the alkyl portion of the alkyl, hydroxyalkyl, dihydroxyalkyl, arylalkoxy, arylalkyl, alkanoyl, alkoxy, alkoxyalkyl and arylalkanoyl groups is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, C_1-C_4 alkoxy, C_1-C_4 alkoxycarbonyl, or C_3-C_7 cycloalkyl;

R_2 is H, OH, halogen, $-OSO_2-(C_1-C_6)$ alkyl, $-OSO_2$-aryl, arylalkoxy, aryloxy, arylthio, arylthioalkoxy, arylalkynyl, alkoxy, aryloxy(C_1-C_6)alkyl, alkyl, alkynyl, $-OC(O)NH(CH_2)_n$aryl, $-OC(O)N(alkyl)(CH_2)_n$aryl, alkoxyalkoxy, dialkylamino, alkyl, alkoxy, aryl, arylalkyl, heteroaryl, heteroarylalkyl, arylalkenyl, heterocycloalkyl, heterocycloalkylalkyl, alkoxyalkoxy, NR_8R_9, dialkylamino, or CO_2R, wherein

n is 0, 1, 2, 3, 4, 5 or 6;

each of which groups is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, $-(C_1-C_6)$alkyl-$N(R)-CO_2R_{30}$, haloalkyl, heteroaryl, heteroarylalkyl, $-NR_6R_7$, $R_6R_7N-(C_1-C_6$ alkyl)-, $-C(O)NR_6R_7$, $-(C_1-C_4)$alkyl-$C(O)NR_6R_7$, $-(C_1-C_4$ alkyl)-$NRC(O)NR_{16}R_{17}$, haloalkoxy, alkyl, CN, hydroxyalkyl, dihydroxyalkyl, alkoxy, alkoxycarbonyl, phenyl, $-SO_2$-phenyl wherein the phenyl and $-SO_2$-phenyl groups are optionally substituted with 1, 2, or 3 groups that are independently halogen or NO_2, or $-OC(O)NR_6R_7$, wherein R_{16} and R_{17} are independently H or C_1-C_6 alkyl; or

R_{16}, R_{17} and the nitrogen to which they are attached form a morpholinyl ring;

R_6 and R_7 are independently at each occurrence H, alkyl, hydroxyalkyl, dihydroxyalkyl, alkoxy, alkanoyl, arylalkyl, arylalkoxy, alkoxycarbonyl, $-SO_2$-alkyl, OH, alkoxy, alkoxyalkyl, arylalkoxycarbonyl, $-(C_1-C_4)$alkyl-CO_2-alkyl, heteroarylalkyl, or arylalkanoyl, wherein each is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, OH, SH, heterocycloalkyl, heterocycloalkylalkyl, C_3-C_7 cycloalkyl, alkoxy, NH_2, NH(alkyl), N(alkyl)(alkyl), -O-alkanoyl, alkyl, haloalkyl, carboxaldehyde, or haloalkoxy; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, pyrrolidinyl, thiomorpholinyl, thiomorpholinyl S-oxide, thiomorpholinyl S,S-dioxide, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that

are independently C_1-C_4 alkyl, alkoxycarbonyl, C_1-C_4 alkoxy, hydroxyl, hydroxyalkyl, dihydroxyalkyl, or halogen;

R at each occurrence is independently hydrogen or C_1-C_6 alkyl optionally substituted with 1 or 2 groups that are independently OH, SH, halogen, amino, monoalkylamino, dialkylamino or C_3-C_6 cycloalkyl;

R_{30} is C_1-C_6 alkyl optionally substituted with 1 or 2 groups that are independently OH, SH, halogen, amino, monoalkylamino, dialkylamino or C_3-C_6 cycloalkyl;

each R_8 is independently hydrogen, alkyl, alkanoyl, arylalkyl and arylalkanoyl, wherein each of the above is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, alkoxy, alkoxycarbonyl, halogen, or haloalkyl;

each R_9 is hydrogen, alkyl, alkanoyl, arylalkyl, cycloalkyl, cycloalkylalkyl, alkenyl, heteroaryl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, arylalkanoyl, -SO_2-phenyl, and aryl wherein each of the above is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, alkoxy, alkoxycarbonyl, halogen, or haloalkyl;

R_4 is hydrogen or R_4 is alkyl unsubstituted or substituted with one or two groups that are independently CO_2R, -CO_2-(C_1-C_6)alkyl, -$C(O)NR_6R_7$, -$C(O)R_6$, -$N(R_{30})C(O)NR_{16}R_{17}$, -$N(R_{30})C(O)$-($C_1$-$C_6$)alkoxy, or -$NR_6R_7$, arylalkoxy, arylalkyl, heteroaryl, heteroarylalkyl, hydroxyalkyl, dihydroxyalkyl, haloalkyl, R_6R_7N-(C_1-C_6 alkyl)-, -NR_6R_7, alkoxy, hydroxyalkoxy-, (R_6R_7N)-alkoxy-, $R_6R_7NC(O)$-alkoxy-, $R_6C(O)N(R_7)$alkoxy-, carboxaldehyde, -$C(O)NR_6R_7$, CO_2R,

alkoxyalkyl, or alkoxyalkoxy, wherein the heteroaryl or aryl portions of is the above are unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, hydroxy, alkoxy, alkyl, $-CO_2-(C_1-C_6)$alkyl, $-CONR_6R_7$, $-NR_6R_7$, $R_6R_7N-(C_1-C_6)$alkyl-, nitro, haloalkyl, or haloalkoxy; and

R_5 is H, aryl, arylalkyl, arylthioalkyl, alkyl optionally substituted with 1, 2, or 3 groups that are independently arylalkoxycarbonyl, $-NR_8R_9$, halogen, $-C(O)NR_8R_9$, alkoxycarbonyl, C_3-C_7 cycloalkyl, or alkanoyl, alkoxy, alkoxyalkyl optionally substituted with one trimethylsilyl group, amino, alkoxycarbonyl, hydroxyalkyl, dihydroxyalkyl, alkynyl, $-SO_2$-alkyl, alkoxy optionally substituted with one trimethylsilyl group, heterocycloalkylalkyl, cycloalkyl, cycloalkylalkyl, -alkyl-S-aryl, -alkyl-SO_2-aryl, heteroarylalkyl, heterocycloalkyl, heteroaryl, or alkenyl optionally substituted with alkoxycarbonyl, wherein

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, halogen, alkoxy, hydroxyalkyl, dihydroxyalkyl, arylalkoxy, thioalkoxy, alkoxycarbonyl, arylalkoxycarbonyl, CO_2R, CN, OH, hydroxyalkyl, dihydroxyalkyl, amidinooxime, $-NR_6R_7$, $-NR_8R_9$, $R_6R_7N-(C_1-C_6$ alkyl)-, carboxaldehyde, SO_2alkyl, $-SO_2H$, $-SO_2NR_6R_7$, alkanoyl wherein the alkyl portion is optionally substituted with OH, halogen or alkoxy, $-C(O)NR_6R_7$, $-(C_1-C_4$ alkyl)$-C(O)NR_6R_7$, amidino, haloalkyl, $-(C_1-C_4$ alkyl)$-NR_{15}C(O)NR_{16}R_{17}$, $-(C_1-C_4$ alkyl)$-NR_{15}C(O)R_{18}$, $-O-CH_2-O$, $-O-CH_2CH_2-O-$, or haloalkoxy; wherein

R_{15} is H or C_1-C_6 alkyl; and

R_{18} is C_1-C_6 alkyl optionally substituted with -O-(C_2-C_6 alkanoyl, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl; amino C_1-C_6 alkyl, mono or dialkylamino C_1-C_6 alkyl.

The invention also includes intermediates that are useful in making the compounds of the invention.

The compounds and salts of the invention bind and/or interact with p38 kinase and/or TNF. Preferably, they inhibit the activity of p38 kinase and/or TNF. They are therefore used in treating p38 map kinase or TNF mediated disorders. Preferably they are used in treating p38 alpha or TNF mediated disorders.

The invention also includes pharmaceutical compositions comprising at least one compound or salt of formula I and at least one pharmaceutically acceptable carrier, solvent, adjuvant or excipient.

The invention also includes methods of treating a TNF mediated disorder, a p38 kinase mediated disorder, inflammation and/or arthritis in a subject, the method comprising treating a subject having or susceptible to such disorder or condition with a therapeutically-effective amount of a compound or salt of Formula I.

Detailed Description

In a preferred aspect, the invention provides compounds of formula I wherein:

no more than two of R_1, R_2, R_4, and R_5 are simultaneously hydrogen;

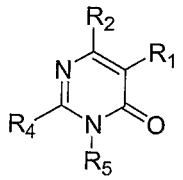
R_6 and R_7 are not simultaneously OH;

when R_2 is OH, R_4 is methyl and R_5 is phenyl, R_1 is not acetyl; and

R_4 and R_5 are not simultaneously hydrogen.

In other aspects and embodiments, the invention provides:

Embodiment 2. Compounds of the formula:



and the pharmaceutically acceptable salts thereof, wherein

R_1 is H, halogen, alkyl, carboxaldehyde, hydroxyalkyl, dihydroxyalkyl, arylalkoxy, arylalkyl, alkenyl, alkynyl, arylalkynyl, CN, alkanoyl, alkoxy, alkoxyalkyl, haloalkyl, carboxyl, or arylalkanoyl,

wherein the aryl portion of arylalkoxy, arylalkyl, and arylalkanoyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, nitro, CN, haloalkyl, haloalkoxy or CO_2R;

wherein the alkyl portion of the alkyl, hydroxyalkyl, dihydroxyalkyl, arylalkoxy, arylalkyl, alkanoyl, alkoxy, alkoxyalkyl and arylalkanoyl groups is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, C_1-C_4 alkoxy, C_1-C_4 alkoxycarbonyl, or cyclopropyl;

R_2 is H, OH, halogen, $-OSO_2-(C_1-C_6)$ alkyl, $-OSO_2$-aryl, arylalkoxy, aryloxy, arylthioalkoxy, arylalkynyl, alkoxy, phenyloxy(C_1-C_6)alkyl, $-OC(O)NH(CH_2)_n$aryl, $-OC(O)N(alkyl)(CH_2)_n$aryl, alkyl, alkynyl, alkoxyalkoxy, dialkylamino, heteroaryl, heterocycloalkyl, aryloxyalkyl, or CO_2R, wherein

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, $-NR_6R_7$, haloalkyl, haloalkoxy, alkyl, heteroaryl, heteroarylalkyl, $-(C_1-C_4)$alkyl$-C(O)NR_6R_7$, $R_6R_7N-(C_1-C_6$ alkyl$)-$, $-C(O)NR_6R_7$, $-(C_1-C_4$ alkyl$)-NRC(O)NR_{16}R_{17}$, CN, hydroxyalkyl, dihydroxyalkyl, $-OC(O)NR_6R_7$, or $-(C_1-C_6)$alkyl$-N(R)-CO_2R_{30}$, wherein

R_{16} and R_{17} are independently H or C_1-C_6 alkyl; or

R_{16}, R_{17} and the nitrogen to which they are attached form a morpholinyl ring;

R_6 and R_7 are independently at each occurrence H, alkyl, hydroxyalkyl, dihydroxyalkyl, alkoxy, alkoxyalkyl, alkanoyl, arylalkyl, arylalkoxy, arylalkoxycarbonyl, or arylalkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, alkoxy, alkyl, OH, SH, carboxaldehyde, haloalkyl, or haloalkoxy; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, thiomorpholinyl S-oxide, thiomorpholinyl S,S-dioxide, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, dihydroxyalkyl, or halogen;

n is 0, 1, 2, 3, 4, 5 or 6;

R at each occurrence is independently H or C_1-C_6 alkyl optionally substituted with 1 or 2 groups that are independently OH, SH, halogen, amino, monoalkylamino, dialkylamino or C_3-C_6 cycloalkyl;

R_{30} is C_1-C_6 alkyl optionally substituted with 1 or 2 groups that are independently OH, SH, halogen, amino, monoalkylamino, dialkylamino or C_3-C_6 cycloalkyl;

R_4 is H, alkyl optionally substituted with one or two groups that are independently CO_2R, $-CO_2$alkyl, $-C(O)NR_6R_7$, $-C(O)R_6$, $-N(R_{30})C(O)NR_{16}R_{17}$, $-N(R_{30})C(O)-(C_1-C_6)$alkoxy, or $-NR_6R_7$, arylalkoxy, heteroaryl, arylalkyl, hydroxyalkyl, dihydroxyalkyl, haloalkyl, $-NR_6R_7$, $-C(O)NR_6R_7$, alkoxy, hydroxyalkoxy-, (R_6R_7N)-alkoxy-, $R_6R_7NC(O)$-alkoxy-, $R_6C(O)N(R_7)$alkoxy-, alkoxyalkyl, or alkoxyalkoxy, wherein the heteroaryl or aryl portions of the above are unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, hydroxy, alkoxy, alkyl, $-CO_2-(C_1-C_6)$alkyl, $-CONR_6R_7$, $-NR_6R_7$, $R_6R_7N-(C_1-C_6)$alkyl-, nitro, haloalkyl, or haloalkoxy; and

R_5 is H, arylalkyl, alkyl optionally substituted with 1, 2, or 3 groups that are independently arylalkoxycarbonyl, $-NR_8R_9$, halogen, $-C(O)NR_8R_9$, alkoxycarbonyl, or alkanoyl, alkoxyalkyl optionally substituted with one trimethylsilyl group, alkoxycarbonyl, amino, hydroxyalkyl, dihydroxyalkyl, alkenyl optionally substituted with alkoxycarbonyl, alkynyl, $-SO_2$-alkyl, aryl, alkoxy optionally substituted with one trimethylsilyl group, heterocycloalkylalkyl, heteroarylalkyl, heterocycloalkyl, or heteroaryl, wherein

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, halogen, alkoxy, arylalkoxy, hydroxyalkyl, dihydroxyalkyl, thioalkoxy, $-SO_2$alkyl, alkoxycarbonyl, arylalkoxycarbonyl, CO_2R, CN, OH, amidinooxime, NR_8R_9, R_6R_7N-(C_1-C_6 alkyl)-, $-C(O)NR_6R_7$, amidino, hydroxyalkyl, dihydroxyalkyl, carboxaldehyde, $-NR_6R_7$, haloalkyl, -(C_1-C_4 alkyl)-$C(O)NR_6R_7$, -(C_1-C_4 alkyl)-CO_2R, -(C_1-C_4 alkyl)-C_1-C_6 alkoxycarbonyl, -(C_1-C_4 alkyl)-CN, -(C_1-C_4 alkyl)-$NR_{15}C(O)R_{18}$, $-O-CH_2-O-$, $-O-CH_2CH_2-O-$, phenyl or haloalkoxy;

R_8 is hydrogen, alkyl, alkanoyl, arylalkyl and arylalkanoyl;

R_9 is alkyl, alkanoyl, arylalkyl, heteroaryl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, and arylalkanoyl.

Embodiment 3. Compounds according to embodiment 2 wherein

R_1 is H, halogen, alkyl optionally substituted with C_1-C_4 alkoxycarbonyl, carboxaldehyde, hydroxyalkyl, dihydroxyalkyl, phenyl(C_1-C_6)alkoxy, phenyl(C_1-C_6)alkyl, CN, alkanoyl, alkoxy, C_2-C_4 alkynyl, C_2-C_6 alkenyl optionally substituted with C_1-C_4 alkoxycarbonyl, alkoxyalkyl, haloalkyl, or phenyl(C_1-C_6)alkanoyl,

wherein the phenyl groups are unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, nitro, CN, CF_3, OCF_3 or CO_2R;

wherein the alkyl groups are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, methoxy, or ethoxy;

R_2 is OH, phenyl(C_1-C_6)alkoxy, phenyloxy, phenyloxy(C_1-C_6)alkyl, phenyl (C_1-C_4) thioalkoxy, C_1-C_8 alkoxy, alkoxyalkoxy, -O-SO_2phenyl, alkynyl, phenyl (C_2-C_4) alkynyl, alkyl, -OC(O)NH$(CH_2)_n$phenyl, -OC(O)N(alkyl)$(CH_2)_n$phenyl, dialkylamino, pyridyl, pyrimidyl, pyridazyl, pyrazolyl, imidazolyl, pyrrolyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, tetrazolyl, pyrazinyl, benzimidazolyl, triazinyl, tetrahydrofuryl, piperidinyl, hexahydropyrimidinyl, thiazolyl, thienyl, or CO_2R, wherein n is 0, 1, 2, 3, 4, 5 or 6;

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, NR_6R_7, haloalkyl, haloalkoxy, hydroxyalkyl, dihydroxyalkyl, alkyl, phenyl, pyridyl, piperidinyl, piperazinyl, -(C_1-C_6)alkyl-N(R)-CO_2R_{30}, R_6R_7N-(C_1-C_6 alkyl)-, -C(O)NR_6R_7, -(C_1-C_4)alkyl-C(O)NR_6R_7, -(C_1-C_4 alkyl)-NRC(O)$NR_{16}R_{17}$, or -OC(O)NR_6R_7, wherein

R_6 and R_7 are independently at each occurrence H, alkyl, (C_1-C_4) hydroxyalkyl, (C_1-C_4) dihydroxyalkyl, (C_1-C_4) alkoxy, (C_1-C_4) alkoxy (C_1-C_4) alkyl, (C_1-C_4) alkanoyl, phenyl (C_1-C_4) alkyl, phenyl (C_1-C_4) alkoxy, phenyl (C_1-C_4) alkoxycarbonyl, or phenyl (C_1-C_4) alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, OH, SH, C_3-C_6 cycloalkyl, (C_1-C_4) alkoxy, (C_1-C_4) alkyl, CF_3, carboxaldehyde, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl (C_1-C_6)alkyl, OCF_3; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2

groups that are independently C_1-C_4 alkyl, hydroxy, hydroxy C_1-C_4 alkyl, C_1-C_4 dihydroxyalkyl, C_1-C_4 alkoxycarbonyl, or halogen; and

R_4 is H, alkyl optionally substituted with one or two groups that are independently CO_2R, $-CO_2$alkyl, $-C(O)NR_6R_7$, $-C(O)R_6$, $-N(R_{30})C(O)NR_{16}R_{17}$, $-N(R_{30})C(O)-(C_1-C_6)$alkoxy, or $-NR_6R_7$, arylalkoxy, heteroaryl, arylalkyl, hydroxyalkyl, dihydroxyalkyl, haloalkyl, $-NR_6R_7$, $-C(O)NR_6R_7$, alkoxy, hydroxyalkoxy-, (R_6R_7N)-alkoxy-, $R_6R_7NC(O)$-alkoxy-, $R_6C(O)N(R_7)$alkoxy-, alkoxyalkyl, or alkoxyalkoxy, wherein the heteroaryl or aryl portions of the above are unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, hydroxy, alkoxy, alkyl, $-CO_2-(C_1-C_6)$alkyl, $-CONR_6R_7$, $-NR_6R_7$, $R_6R_7N-(C_1-C_6)$alkyl-, nitro, haloalkyl, or haloalkoxy; and

R_5 is phenyl(C_1-C_6)alkyl, (C_1-C_6)alkyl optionally substituted with 1, 2, 3, 4, or 5 groups that are independently phenyl C_1-C_4 alkoxycarbonyl, $-NR_8R_9$, halogen, $-C(O)NR_8R_9$, alkoxycarbonyl, or alkanoyl, phenyl, alkoxy, C_2-C_6 alkynyl, C_2-C_6 alkenyl optionally substituted with alkoxycarbonyl, indolyl, quinolinyl, isoquinolinyl, isoindolyl, dihydroindolyl, pyrazolyl, imidazolyl, dihydroisoindolyl, indolon-2-yl, indazolyl, benzimidazolyl, pyridyl, imidazolidine dione, pyrazolyl$(C_1-C_6$ alkyl), imidazolyl$(C_1-C_6$ alkyl), piperidinyl(C_1-C_6)alkyl, pyrrolidinyl(C_1-C_6)alkyl, imidazolidinyl(C_1-C_6)alkyl, tetrahydroisoquinolinyl(C_1-C_6)alkyl, 1H-indazolyl(C_1-C_6)alkyl, dihydroindolon-2-yl$(C_1-C_6$ alkyl), indolinyl$(C_1-C_6$ alkyl), dihydrobenzimidazolyl$(C_1-C_6$ alkyl), or dihydrobenzoimidazolonyl$(C_1-C_6$ alkyl), pyridyl (C_1-C_6)

alkyl, pyridazinyl (C_1-C_6) alkyl, pyrimidinyl (C_1-C_6) alkyl, pyrazinyl (C_1-C_6) alkyl, tetrahydrofuryl(C_1-C_6)alkyl, naphthyl(C_1-C_6)alkyl, morpholinyl (C_1-C_6) alkyl, tetrahydrofuryl (C_1-C_6) alkyl, thienyl (C_1-C_6) alkyl, piperazinyl (C_1-C_6) alkyl, indolyl (C_1-C_6) alkyl, quinolinyl(C_1-C_6) alkyl, isoquinolinyl(C_1-C_6) alkyl, isoindolyl(C_1-C_6) alkyl, dihydroindolyl(C_1-C_6) alkyl, pyrazolyl(C_1-C_4) alkyl, imidazolyl(C_1-C_4) alkyl, dihydroisoindolyl(C_1-C_6) alkyl, indoon-2-yl(C_1-C_6) alkyl, indolon-2-yl(C_1-C_6) alkyl, or morpholinyl C_1-C_6 alkyl, wherein

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, halogen, C_1-C_6 alkoxy, phenyl C_1-C_6 alkoxy, C_1-C_6 thioalkoxy, C_1-C_6 alkoxycarbonyl, CO_2R, CN, $-SO_2(C_1$-$C_6)$alkyl, amidinooxime, NR_8R_9, $-NR_6R_7$, NR_6R_7 C_1-C_6 alkyl, $-C(O)NR_6R_7$, $-(C_1$-$C_4)$alkyl-$C(O)NR_6R_7$, amidino, C_1-C_4 haloalkyl, hydroxy C_1-C_6 alkyl, C_1-C_6 dihydroxyalkyl, or C_1-C_4 haloalkoxy; wherein

R_8 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkanoyl, phenyl C_1-C_6 alkyl and phenyl C_1-C_6 alkanoyl; and

R_9 is aminoalkyl, mono C_1-C_6 alkylamino C_1-C_6 alkyl, di C_1-C_6 alkylamino C_1-C_6 alkyl, C_1-C_6 alkyl, C_1-C_6 alkanoyl, phenyl C_1-C_6 alkyl, indazolyl, and phenyl C_1-C_6 alkanoyl.

Embodiment 4. Compounds according to embodiment 3, wherein

R_1 is H, halogen, C_1-C_4 alkyl optionally substituted with C_1-C_4 alkoxycarbonyl, C_2-C_4 alkenyl optionally substituted with C_1-C_4 alkoxycarbonyl, C_2-C_4 alkynyl, or carboxaldehyde;

R_2 is benzyloxy, OH, phenyloxy, phenyloxy(C_1-C_6)alkyl, phenyl (C_1-C_4) thioalkoxy, or pyridyl; wherein each of the above

is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, -(C_1-C_6)alkyl-N(R)-CO_2R_{30}, NR_6R_7, -(C_1-C_4)alkyl-C(O)NR_6R_7, (C_1-C_4) haloalkyl, -C(O)NR_6R_7, -(C_1-C_4 alkyl)-NRC(O)$NR_{16}R_{17}$, (C_1-C_4) haloalkoxy, hydroxyalkyl, C_1-C_6 dihydroxyalkyl, (C_1-C_6) alkyl, pyridyl, or R_6R_7N-(C_1-C_6 alkyl)-.

Embodiment 4a. Compounds according to embodiment 4, wherein R_1 is H.

Embodiment 4b. Compounds according to embodiment 4, wherein R_1 is halogen.

Embodiment 4c. Compounds according to embodiment 4, wherein R_1 is C_1-C_4 alkyl optionally substituted with C_1-C_4 alkoxycarbonyl.

Embodiment 5. Compounds according to embodiment 4, wherein R_5 is indolyl, pyridyl, pyridazinyl, pyrimidinyl, indazolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, pyrazolyl, imidazolyl, furanyl, quinolinyl, isoquinolinyl, isoindolyl, dihydroindolyl, dihydroisoindolyl, indolon-2-yl, or pyrazinyl, each of which is unsubstituted or substituted with 1, 2, 3, 4 or 5 groups that are independently C_1-C_4 alkyl, halogen, CF_3, OCF_3, -CO_2CH_3, C_1-C_4 hydroxyalkyl, dihydroxyalkyl, C_1-C_4 alkoxy, -CO_2(C_1-C_5 alkyl), benzyloxy, -NR_6R_7, -(C_1-C_4)alkyl-C(O)NR_6R_7, -NR_8R_9, NR_6R_7-(C_1-C_4 alkyl), -C(O)NR_6R_7, or amidinooxime; wherein R_6 and R_7 are independently at each occurrence H, C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, C_1-C_4 alkoxy, C_1-C_4 alkoxy C_1-C_4 alkyl, C_1-C_4 alkanoyl, phenyl C_1-C_4 alkyl, phenyl C_1-C_4 alkoxy, or phenyl C_1-C_4 alkanoyl, wherein each is unsubstituted or substituted with 1, 2, or 3 groups that are

independently, halogen, OH, SH, C_3-C_6 cycloalkyl, aryl, C_1-C_4 alkoxy, C_1-C_4 alkyl, OH, CF_3, or OCF_3; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, hydroxy, hydroxy C_1-C_4 alkyl, C_1-C_4 dihydroxyalkyl, or halogen.

Embodiment 6. Compounds according to embodiment 5, wherein

R_5 is indolyl, pyridyl, pyrimidinyl, pyrazolyl, furanyl, indazolyl, dihydroindolyl, dihydroisoindolyl, indolon-2-yl, or pyrazinyl, each of which is unsubstituted or substituted with 1, 2, 3, or 4 groups that are independently C_1-C_4 alkyl, halogen, CF_3, OCF_3, $-CO_2CH_3$, C_1-C_4 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, C_1-C_4 alkoxy, $-CO_2(C_1$-C_5 alkyl), benzyloxy, $-C(O)NR_6R_7$, $-NR_8R_9$, $-(C_1$-$C_4)$alkyl-$C(O)NR_6R_7$, $-NR_6R_7$, NR_6R_7-$(C_1$-C_4 alkyl)-, and amidinooxime.

Embodiment 7. Compounds according to embodiment 6, wherein

R_5 is indolyl, pyridyl, pyrimidinyl, dihydroindolyl, dihydroisoindolyl, pyrazolyl, or pyrazinyl, each of which is unsubstituted or substituted with 1, 2, 3, or 4 groups that are independently C_1-C_4 alkyl, halogen, CF_3, OCF_3, $-CO_2CH_3$, C_1-C_4 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, C_1-C_4 alkoxy, $-CO_2(C_1$-C_5 alkyl), benzyloxy, $-C(O)NR_6R_7$, NR_8R_9, $-(C_1$-$C_4)$alkyl-$C(O)NR_6R_7$, $-NR_6R_7$, NR_6R_7-$(C_1$-C_4 alkyl)-, or amidinooxime; wherein

R_6 and R_7 are independently at each occurrence H, C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, C_1-C_4

alkoxy, C_1-C_4 alkanoyl, C_1-C_4 alkoxy C_1-C_4 alkyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, OH, CF_3, or OCF_3.

Embodiment 8. Compounds according to embodiment 7, wherein

R_5 is indolyl, pyridyl, pyrimidinyl, dihydroindolyl, dihydroisoindolyl, pyrazolyl, or pyrazinyl, each of which is unsubstituted or substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkyl, halogen, CF_3, OCF_3, C_1-C_4 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, C_1-C_4 alkoxy, $-C(O)NR_6R_7$, $-(C_1$-$C_4)$alkyl$-C(O)NR_6R_7$, NR_8R_9, $-NR_6R_7$, or NR_6R_7-(C_1-C_4 alkyl)-; wherein

R_6 and R_7 are independently at each occurrence H, C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, C_1-C_4 alkanoyl, or C_1-C_4 alkoxy, each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, OH, CF_3, or OCF_3.

Embodiment 9. Compounds according to embodiment 4, wherein

R_5 is phenyl, phenyl$(C_1$-$C_6)$alkyl, or $(C_1$-$C_6)$alkyl, wherein

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, halogen, alkoxy, benzyloxy, hydroxyalkyl, dihydroxyalkyl, thioalkoxy, $-CO_2(C_1$-C_5 alkyl), CO_2R, CN, amidinooxime, $-NR_8R_9$, $-NR_6R_7$, R_6R_7N-$(C_1$-C_6 alkyl)-, $-C(O)NR_6R_7$, $-(C_1$-$C_4)$alkyl$-C(O)NR_6R_7$, amidino, CF_3, or OCF_3;

R_8 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkanoyl, phenyl C_1-C_6 alkyl and phenyl C_1-C_6 alkanoyl; and

R_9 is aminoalkyl, mono C_1-C_6 alkylamino C_1-C_6 alkyl, di C_1-C_6 alkylamino C_1-C_6 alkyl, C_1-C_6 alkyl, C_1-C_6 alkanoyl, phenyl C_1-C_4 alkyl, indazolyl, and phenyl C_1-C_4 alkanoyl.

Embodiment 10. Compounds according to embodiment 4, wherein

R_5 is phenyl, phenyl(C_1-C_6)alkyl, which is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, halogen, alkoxy, benzyloxy, thioalkoxy, -CO_2(C_1-C_5 alkyl), CO_2R, CN, amidinooxime, -NR_8R_9, -NR_6R_7, R_6R_7N-(C_1-C_6 alkyl)-, $R_6R_7NC(O)$-(C_1-C_4 alkyl)-, $R_6R_7NC(O)$-(C_5-C_6 alkyl)-, -$C(O)NR_6R_7$, amidino, CF_3, or OCF_3; wherein

R_6 and R_7 are independently at each occurrence H, C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, C_1-C_4 alkoxy, C_1-C_4 alkoxy C_1-C_4 alkyl, C_1-C_4 alkanoyl, phenyl C_1-C_4 alkyl, phenyl C_1-C_4 alkoxy, or phenyl C_1-C_4 alkanoyl, wherein each is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, OH, SH, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, CF_3, or OCF_3; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, hydroxy, hydroxy C_1-C_4 alkyl, C_1-C_4 dihydroxyalkyl, or halogen;

R_8 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkanoyl, phenyl C_1-C_6 alkyl and phenyl C_1-C_6 alkanoyl; and

R_9 is aminoalkyl, mono C_1-C_6 alkylamino C_1-C_6 alkyl, di C_1-C_6 alkylamino C_1-C_6 alkyl, C_1-C_6 alkyl, C_1-C_6

alkanoyl, phenyl C_1-C_4 alkyl, indazolyl, and phenyl C_1-C_4 alkanoyl.

Embodiment 11. Compounds according to embodiment 10, wherein

R_5 is phenyl, benzyl or phenethyl, wherein each is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, $-NR_6R_7$, $-C(O)NR_6R_7$, $-(C_1$-C_4 alkyl)$-C(O)NR_6R_7$, $-NR_8R_9$, halogen, C_1-C_6 alkoxy, CO_2R, $-(C_1$-C_4 alkyl)$-CO_2R$, C_1-C_6 thioalkoxy, amidinooxime, C_1-C_6 alkoxycarbonyl, $-(C_1$-C_4 alkyl)$-C_1$-C_6 alkoxycarbonyl, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, $-(C_1$-C_4 alkyl)$-CN$, CN, phenyl C_1-C_6 alkoxy, OH, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, $R_6R_7N-(C_1$-C_6 alkyl)-, $-(C_1$-C_4 alkyl)$-NR_{15}C(O)R_{18}$, amidinooxime, $-SO_2(C_1$-C_6 alkyl), $-O-CH_2-O-$, $-O-CH_2CH_2-O-$, phenyl C_1-C_4 alkoxy, or phenyl; wherein

R_6 and R_7 are independently at each occurrence H, C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, C_1-C_4 alkanoyl, or C_1-C_4 alkoxy, each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, OH, CF_3, or OCF_3.

Embodiment 12. Compounds according to embodiment 11, wherein

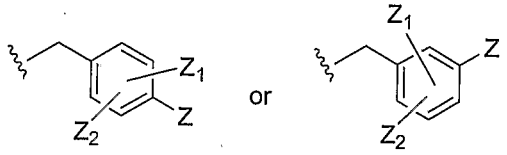
R_5 is phenyl, benzyl or phenethyl, each of which is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently CN, halogen, C_1-C_4 alkoxy, CF_3, OCF_3, C_1-C_4 alkyl, $-NR_8R_9$, $-NR_6R_7$, $R_6R_7N-(C_1$-C_6 alkyl)-, or $-C(O)NR_6R_7$, wherein

R_6 and R_7 are independently at each occurrence H, C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, C_1-C_4 alkanoyl, or C_1-C_4 alkoxy, each of which is

optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, OH, CF_3, or OCF_3.

Embodiment 13. Compounds according to embodiment 4, wherein

the R_5 group is of the formula:



wherein

Z_1 and Z_2 are independently H, halogen, C_1-C_4 alkyl, or CO_2R; and

Z is $-C(O)NR_6R_7$, $-(C_1-C_4)alkyl-C(O)NR_6R_7$, $-(C_1-C_4$ alkyl)-$NR_{15}C(O)R_{18}$, $-NR_6R_7$, $R_6R_7N-(C_1-C_6$ alkyl)-, $-NR_8R_9$, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, C_1-C_6 alkyl, CO_2R, or halogen; wherein

R_6 and R_7 at each occurrence are independently H, OH, C_1-C_6 alkyl, amino C_1-C_4 alkyl, $NH(C_1$-C_6 alkyl)alkyl, $N(C_1$-C_6 alkyl)(C_1-C_6 alkyl) C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, C_1-C_6 alkoxy C_1-C_6 alkyl, or -$SO_2(C_1$-C_6 alkyl) each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, OH, CF_3, or OCF_3;

or

R_6, R_7, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl, thiomorpholinyl, ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy C_1-C_4 alkyl, C_1-C_4 dihydroxyalkyl, or halogen; and

R_{18} is C_1-C_6 alkyl optionally substituted with -O-(C_2-C_6 alkanoyl, C_1-C_6 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl; amino C_1-C_6 alkyl, mono or dialkylamino C_1-C_6 alkyl.

Embodiment 14. Compounds according to embodiment 4, wherein

R_5 is pyrazolyl(C_1-C_6 alkyl), imidazolyl(C_1-C_6 alkyl), thienyl(C_1-C_6 alkyl), furanyl(C_1-C_6 alkyl), piperidinyl(C_1-C_6)alkyl, pyrrolidinyl(C_1-C_6)alkyl, imidazolidinyl(C_1-C_6)alkyl, piperazinyl(C_1-C_6)alkyl, pyridyl(C_1-C_6)alkyl, pyrimidyl(C_1-C_6)alkyl, pyridazyl(C_1-C_6)alkyl, pyrazinyl(C_1-C_6)alkyl, isoquinolinyl(C_1-C_6)alkyl, tetrahydroisoquinolinyl(C_1-C_6)alkyl, indolyl(C_1-C_6)alkyl, 1H-indazolyl(C_1-C_6)alkyl, dihydroindolyl(C_1-C_6 alkyl), dihydroindolon-2-yl(C_1-C_6 alkyl), indolinyl(C_1-C_6 alkyl), dihydroisoindolyl(C_1-C_6 alkyl), dihydrobenzimdazolyl(C_1-C_6 alkyl), or dihydrobenzoimidazolonyl(C_1-C_6 alkyl), wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently (C_1-C_6)alkyl, halogen, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, C_1-C_6 dihydroxyalkyl, phenyl(C_1-C_6)alkoxy, (C_1-C_6)thioalkoxy, (C_1-C_6)alkoxycarbonyl, phenyl(C_1-C_6)alkoxycarbonyl, OH, CO_2R, CN, amidinooxime, $-NR_8R_9$, $-NR_6R_7$, R_6R_7N-(C_1-C_6 alkyl)-, $-C(O)NR_6R_7$, -(C_1-C_4 alkyl)-$C(O)NR_6R_7$, amidino, piperazinyl, morpholinyl, $-SO_2$ (C_1-C_6) alkyl, $-SO_2NH_2$, $-SO_2NH$(C_1-C_6)alkyl, $-SO_2N$(C_1-C_6)alkyl (C_1-C_6)alkyl, (C_1-C_4)haloalkyl, -(C_1-C_4 alkyl)-$NR_{15}C(O)NR_{16}R_{17}$, -(C_1-C_4 alkyl)-$NR_{15}C(O)R_{18}$, $-O-CH_2-O$, $-O-CH_2CH_2-O$-, or (C_1-C_4)haloalkoxy; wherein R_6 and R_7 are independently at each occurrence H, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_1-

C_6)hydroxyalkyl, C_1-C_6 dihydroxyalkyl, -(C_1-C_4)alkyl-CO_2-(C_1-C_6)alkyl, (C_1-C_6)alkanoyl, phenyl(C_1-C_6)alkyl, phenyl(C_1-C_6)alkoxy, or phenyl(C_1-C_6)alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, (C_1-C_4)alkoxy, OH, SH, C_3-C_6 cycloalkyl, NH_2, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)(C_1-C_6 alkyl), (C_1-C_4)alkyl, CF_3 or OCF_3; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, hydroxy, hydroxy C_1-C_4 alkyl, C_1-C_4 dihydroxyalkyl, or halogen; and

R_{18} is C_1-C_6 alkyl optionally substituted with -O-(C_2-C_6 alkanoyl, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl; amino C_1-C_6 alkyl, mono or dialkylamino C_1-C_6 alkyl.

In this embodiment, it is preferred that R_6 and R_7 are not simultaneously OH; and

R_6 and R_7 are not simultaneously -SO_2(C_1-C_6 alkyl).

Embodiment 15. Compounds according to embodiment 14, wherein

R_5 is pyrazolyl(C_1-C_6 alkyl), imidazolyl(C_1-C_6 alkyl), benzimidazolyl(C_1-C_6 alkyl), thienyl(C_1-C_6 alkyl), pyrimidyl(C_1-C_6)alkyl, indolyl(C_1-C_6 alkyl), dihydroindolyl(C_1-C_6 alkyl), dihydroisoindolyl(C_1-C_6 alkyl), dihydroindolon-2-yl(C_1-C_6 alkyl), pyridinyl(C_1-C_6 alkyl), piperazinyl(C_1-C_6 alkyl), or pyrazinyl(C_1-C_6 alkyl)

each of which is optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, halogen, $-C(O)NR_6R_7$, $-(C_1$-C_4 alkyl$)-C(O)NR_6R_7$, C_1-C_6 alkoxycarbonyl, $-NR_6R_7$, $R_6R_7N-(C_1$-C_6 alkyl$)-$, haloalkyl, C_1-C_6 alkanoyl,

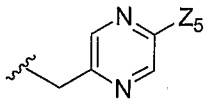
R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy;

or

R_6, R_7, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy C_1-C_4 alkyl, C_1-C_4 dihydroxyalkyl, or halogen.

Embodiment 16. Compounds according to embodiment 15, wherein

R_5 is of the formula:



wherein

Z_5 is C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, halogen, $-C(O)NR_6R_7$, $-(C_1$-C_4 alkyl$)-C(O)NR_6R_7$, C_1-C_6 alkoxycarbonyl, $R_6R_7N-(C_1$-C_6 alkyl$)-$, $-NR_6R_7$, CF_3, or C_1-C_6 alkanoyl, wherein

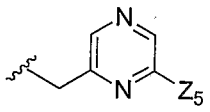
R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy;

or

R_6, R_7, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy C_1-C_4 alkyl, C_1-C_4 dihydroxyalkyl, or halogen.

Embodiment 17. Compounds according to embodiment 15, wherein

R_5 is of the formula:



wherein

Z_5 is C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, halogen, $-C(O)NR_6R_7$, $-(C_1$-C_4 alkyl$)-C(O)NR_6R_7$, C_1-C_6 alkoxycarbonyl, $R_6R_7N-(C_1$-C_6 alkyl$)-$, $-NR_6R_7$, CF_3, or C_1-C_6 alkanoyl, wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy;

or

R_6, R_7, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy C_1-C_4 alkyl, C_1-C_4 dihydroxyalkyl, or halogen.

Embodiment 18. Compounds according to either embodiment 16 or 17, wherein

Z_5 is C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, halogen, C_1-C_6 alkoxycarbonyl, CF_3, or C_1-C_6 alkanoyl.

Embodiment 19. Compounds according to either embodiment 16 or 17, wherein

Z_5 is C_1-C_4 alkyl, -C(O)NR_6R_7, -(C_1-C_4 alkyl)-C(O)NR_6R_7, R_6R_7N-(C_1-C_6 alkyl)-, or -NR_6R_7, CF_3, or C_1-C_4 alkanoyl, wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy;

or

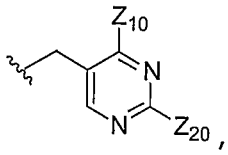
R_6, R_7, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy C_1-C_4 alkyl, C_1-C_4 dihydroxyalkyl, or halogen.

Embodiment 20. Compounds according to embodiment 19, wherein

Z_5 is -C(O)NR_6R_7, -(C_1-C_4 alkyl)-C(O)NR_6R_7, R_6R_7N-(C_1-C_6 alkyl)-, or -NR_6R_7, wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, cyclopropyl, OH, SH, or C_1-C_4 alkoxy.

Embodiment 21. Compounds according to embodiment 15, wherein

R_5 is of the formula:  , wherein

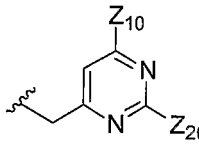
Z_{10} is H or methyl; and

Z_{20} is hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, OH, halogen, haloalkyl, (C_1-C_4)alkyl, OCF_3, -NR_6R_7, R_6R_7N-(C_1-C_6

alkyl)-, -(C_1-C_4 alkyl)-C(O)NR_6R_7, or -C(O)NR_6R_7, wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy.

Embodiment 22. Compounds according to embodiment 15, wherein

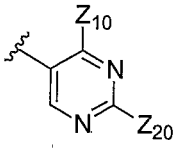
R_5 is of the formula:  , wherein

Z_{10} is H or methyl; and

Z_{20} is hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, OH, halogen, CF_3, (C_1-C_4)alkyl, OCF_3, -NR_6R_7, R_6R_7N-(C_1-C_6 alkyl)-, -(C_1-C_4 alkyl)-C(O)NR_6R_7, or -C(O)NR_6R_7, wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy.

Embodiment 23. Compounds according to embodiment 15, wherein

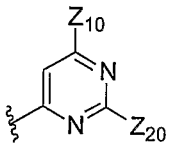
R_5 is of the formula:  , wherein

Z_{10} is H or methyl; and

Z_{20} is hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, OH, halogen, haloalkyl, (C_1-C_4)alkyl, OCF_3, -NR_6R_7, R_6R_7N-(C_1-C_6 alkyl)-, -(C_1-C_4 alkyl)-C(O)NR_6R_7, or -C(O)NR_6R_7, wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy.

Embodiment 24. Compounds according to embodiment 15, wherein

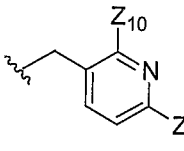
R_5 is of the formula:  , wherein

Z_{10} is H or methyl; and

Z_{20} is hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, OH, halogen, CF_3, (C_1-C_4)alkyl, OCF_3, -NR_6R_7, R_6R_7N-(C_1-C_6 alkyl)-, -(C_1-C_4 alkyl)-C(O)NR_6R_7, or -C(O)NR_6R_7, wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy.

Embodiment 25. Compounds according to embodiment 15, wherein

R_5 is of the formula:  , wherein

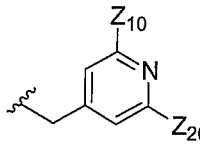
Z_{10} is H or methyl; and

Z_{20} is hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, OH, halogen, haloalkyl, (C_1-C_4)alkyl, OCF_3, -NR_6R_7, R_6R_7N-(C_1-C_6 alkyl)-, -(C_1-C_4 alkyl)-C(O)NR_6R_7, or -C(O)NR_6R_7, wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups

that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy.

Embodiment 26. Compounds according to embodiment 15, wherein

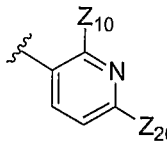
R_5 is of the formula:  , wherein

Z_{10} is H or methyl; and

Z_{20} is hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, OH, halogen, CF_3, (C_1-C_4)alkyl, OCF_3, $-NR_6R_7$, R_6R_7N-(C_1-C_6 alkyl)-, -(C_1-C_4 alkyl)-$C(O)NR_6R_7$, or $-C(O)NR_6R_7$, wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy.

Embodiment 27. Compounds according to embodiment 15, wherein

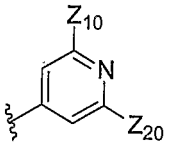
R_5 is of the formula:  , wherein

Z_{10} is H or methyl; and

Z_{20} is hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, OH, halogen, haloalkyl, (C_1-C_4)alkyl, OCF_3, $-NR_6R_7$, R_6R_7N-(C_1-C_6 alkyl)-, -(C_1-C_4 alkyl)-$C(O)NR_6R_7$, or $-C(O)NR_6R_7$, wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy.

Embodiment 28. Compounds according to embodiment 15, wherein

R_5 is of the formula:  , wherein

Z_{10} is H or methyl; and

Z_{20} is hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, OH, halogen, CF_3, (C_1-C_4)alkyl, OCF_3, -NR_6R_7, R_6R_7N-(C_1-C_6 alkyl)-, -(C_1-C_4 alkyl)-$C(O)NR_6R_7$, or -$C(O)NR_6R_7$, wherein R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy.

Embodiment 29. Compounds according to embodiment 4, wherein

R_5 is phenyl, which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_4 alkyl, -$C(O)NR_6R_7$, -(C_1-C_4 alkyl)-$C(O)NR_6R_7$, -NR_6R_7, NR_6R_7(C_1-C_6 alkyl), C_1-C_6 hydroxyalkyl, dihydroxyalkyl, halogen, C_1-C_4 alkoxy, CO_2R, OH, C_1-C_6 alkoxycarbonyl, CF_3, -(C_1-C_4 alkyl)-$NR_{15}C(O)NR_{16}R_{17}$, -(C_1-C_4 alkyl)-$NR_{15}C(O)R_{18}$; wherein

R_{15} is H or C_1-C_6 alkyl;

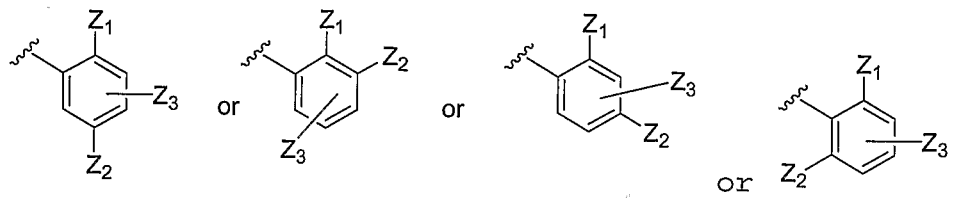
R_{16} and R_{17} are independently H or C_1-C_6 alkyl; or

R_{16}, R_{17}, and the nitrogen to which they are attached form a morpholinyl ring; and

R_{18} is C_1-C_6 alkyl optionally substituted with -O-(C_2-C_6 alkanoyl, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl; amino C_1-C_6 alkyl, mono or dialkylamino C_1-C_6 alkyl.

Embodiment 30. Compounds according to embodiment 29, wherein

R_5 is of the formula:



Z_1 is H, halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, or C_1-C_4 alkoxy; and

Z_2 is C_1-C_4 alkyl, $-C(O)NR_6R_7$, $-(C_1$-C_4 alkyl$)-C(O)NR_6R_7$, $-NR_6R_7$, $NR_6R_7(C_1$-C_6 alkyl), C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, halogen, C_1-C_4 alkoxy, CO_2R, OH, C_1-C_6 alkoxycarbonyl, or C_1-C_4 haloalkyl;

Z_3 is H, C_1-C_4 alkyl, $-C(O)NR_6R_7$, $-(C_1$-C_4 alkyl$)-C(O)NR_6R_7$, $-NR_6R_7$, $NR_6R_7(C_1$-C_6 alkyl), C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, halogen, C_1-C_4 alkoxy, CO_2R, OH, C_1-C_6 alkoxycarbonyl, or C_1-C_4 haloalkyl;

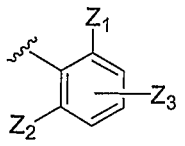
and wherein

R_6 and R_7 at each occurrence are independently H, OH, C_1-C_6 alkyl, amino C_1-C_4 alkyl, $NH(C_1$-C_6 alkyl)alkyl, $N(C_1$-C_6 alkyl$)(C_1$-C_6 alkyl) C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, C_1-C_6 alkoxy C_1-C_6 alkyl, $-SO_2(C_1$-C_6 alkyl), $-SO_2NH_2$, $-SO_2NH(C_1$-C_6 alkyl), $-SO_2N(C_1$-C_6 alkyl$)(C_1$-C_6 alkyl), or C_1-C_6 alkanoyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, OH, CF_3, or OCF_3.

In this embodiment, it is preferred that at least one of Z_1, Z_2, and Z_3 is not hydrogen.

Embodiment 31. Compounds according to embodiment 30, wherein

R_5 is of the formula:



wherein

Z_1 is H, halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, or C_1-C_4 alkoxy; and

Z_2 is C_1-C_4 alkyl, $-C(O)NR_6R_7$, $-(C_1$-C_4 alkyl$)$-$C(O)NR_6R_7$, $-NR_6R_7$, $NR_6R_7(C_1$-C_6 alkyl$)$, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, halogen, C_1-C_4 alkoxy, CO_2R, OH, C_1-C_6 alkoxycarbonyl, or C_1-C_4 haloalkyl;

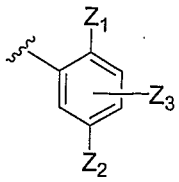
Z_3 is H, C_1-C_4 alkyl, $-C(O)NR_6R_7$, $-(C_1$-C_4 alkyl$)$-$C(O)NR_6R_7$, $-NR_6R_7$, $NR_6R_7(C_1$-C_6 alkyl$)$, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, halogen, C_1-C_4 alkoxy, CO_2R, OH, C_1-C_6 alkoxycarbonyl, or C_1-C_4 haloalkyl, and wherein

R_6 and R_7 at each occurrence are independently H, OH, C_1-C_6 alkyl, amino C_1-C_4 alkyl, $NH(C_1$-C_6 alkyl$)$alkyl, $N(C_1$-C_6 alkyl$)(C_1$-C_6 alkyl$)$ C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, C_1-C_6 alkoxy C_1-C_6 alkyl, $-SO_2(C_1$-C_6 alkyl$)$, $-SO_2NH_2$, $-SO_2NH(C_1$-C_6 alkyl$)$, $-SO_2N(C_1$-C_6 alkyl$)(C_1$-C_6 alkyl$)$, or C_1-C_6 alkanoyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, OH, CF_3, or OCF_3.

In this embodiment, it is preferred that at least one of Z_1, Z_2, and Z_3 is not hydrogen.

Embodiment 32. Compounds according to embodiment 30, wherein

R_5 is of the formula:



wherein

Z_1 is H, halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, or C_1-C_4 alkoxy; and

Z_2 is C_1-C_4 alkyl, $-C(O)NR_6R_7$, $-(C_1$-C_4 alkyl$)$-$C(O)NR_6R_7$, $-NR_6R_7$, $NR_6R_7(C_1$-C_6 alkyl), C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, halogen, C_1-C_4 alkoxy, CO_2R, OH, C_1-C_6 alkoxycarbonyl, or C_1-C_4 haloalkyl;

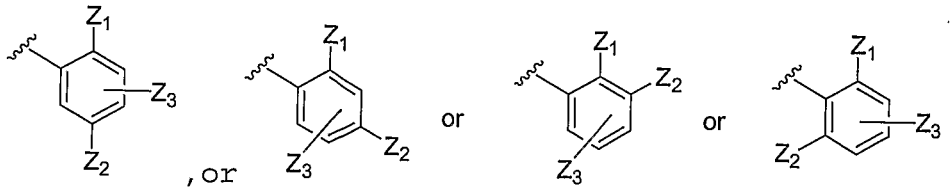
Z_3 is H, C_1-C_4 alkyl, $-C(O)NR_6R_7$, $-(C_1$-C_4 alkyl$)$-$C(O)NR_6R_7$, $-NR_6R_7$, $NR_6R_7(C_1$-C_6 alkyl), C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, halogen, C_1-C_4 alkoxy, CO_2R, OH, C_1-C_6 alkoxycarbonyl, or C_1-C_4 haloalkyl, and wherein

R_6 and R_7 at each occurrence are independently H, OH, C_1-C_6 alkyl, amino C_1-C_4 alkyl, $NH(C_1$-C_6 alkyl$)$alkyl, $N(C_1$-C_6 alkyl$)(C_1$-C_6 alkyl) C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, C_1-C_6 alkoxy C_1-C_6 alkyl, $-SO_2(C_1$-C_6 alkyl), $-SO_2NH_2$, $-SO_2NH(C_1$-C_6 alkyl), $-SO_2N(C_1$-C_6 alkyl$)(C_1$-C_6 alkyl), or C_1-C_6 alkanoyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, OH, CF_3, or OCF_3.

In this embodiment, it is preferred that at least one of Z_1, Z_2, and Z_3 is not hydrogen.

Embodiment 33. Compounds according to embodiment 29, wherein

R_5 is either



wherein

Z_1 is H, halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, or C_1-C_4 alkoxy; and

Z_2 is C_1-C_4 alkyl, $-C(O)NR_6R_7$, $-(C_1$-C_4 alkyl$)-C(O)NR_6R_7$, $-NR_6R_7$, $NR_6R_7(C_1$-C_6 alkyl), C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, halogen, C_1-C_4 alkoxy, CO_2R, C_1-C_6 alkoxycarbonyl, $-(C_1$-C_4 alkyl$)-NR_{15}C(O)NR_{16}R_{17}$, or $-(C_1$-C_4 alkyl$)-NR_{15}C(O)R_{18}$;

Z_3 is H, C_1-C_4 alkyl, $-C(O)NR_6R_7$, $-(C_1$-C_4 alkyl$)-C(O)NR_6R_7$, $-NR_6R_7$, $NR_6R_7(C_1$-C_6 alkyl), C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, halogen, C_1-C_4 alkoxy, CO_2R, C_1-C_6 alkoxycarbonyl, $-(C_1$-C_4 alkyl$)-NR_{15}C(O)NR_{16}R_{17}$, or $-(C_1$-C_4 alkyl$)-NR_{15}C(O)R_{18}$;

R_6, R_7, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy C_1-C_4 alkyl, C_1-C_4 dihydroxyalkyl, or halogen;

R_{15} is H or C_1-C_6 alkyl;

R_{16} and R_{17} are independently H or C_1-C_6 alkyl; or

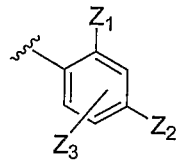
R_{16}, R_{17}, and the nitrogen to which they are attached form a morpholinyl ring; and

R_{18} is C_1-C_6 alkyl optionally substituted with $-O-(C_2$-C_6 alkanoyl, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl; amino C_1-C_6 alkyl, mono or dialkylamino C_1-C_6 alkyl.

In this embodiment, it is preferred that at least one of Z_1, Z_2, and Z_3 is not hydrogen.

Embodiment 34. Compounds according to embodiment 33, wherein

R_5 is of the formula:



Z_1 is H, halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, or C_1-C_4 alkoxy; and

Z_2 is C_1-C_4 alkyl, $-C(O)NR_6R_7$, $-(C_1$-C_4 alkyl$)$-$C(O)NR_6R_7$, $-NR_6R_7$, $NR_6R_7(C_1$-C_6 alkyl$)$, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, halogen, C_1-C_4 alkoxy, CO_2R, C_1-C_6 alkoxycarbonyl, $-(C_1$-C_4 alkyl$)$-$NR_{15}C(O)NR_{16}R_{17}$, or $-(C_1$-C_4 alkyl$)$-$NR_{15}C(O)R_{18}$;

Z_3 is H, C_1-C_4 alkyl, $-C(O)NR_6R_7$, $-(C_1$-C_4 alkyl$)$-$C(O)NR_6R_7$, $-NR_6R_7$, $NR_6R_7(C_1$-C_6 alkyl$)$, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, halogen, C_1-C_4 alkoxy, CO_2R, C_1-C_6 alkoxycarbonyl, $-(C_1$-C_4 alkyl$)$-$NR_{15}C(O)NR_{16}R_{17}$, or $-(C_1$-C_4 alkyl$)$-$NR_{15}C(O)R_{18}$;

R_6, R_7, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy C_1-C_4 alkyl, C_1-C_4 dihydroxyalkyl, or halogen;

R_{15} is H or C_1-C_6 alkyl;

R_{16} and R_{17} are independently H or C_1-C_6 alkyl; or

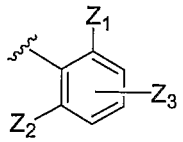
R_{16}, R_{17}, and the nitrogen to which they are attached form a morpholinyl ring; and

R_{18} is C_1-C_6 alkyl optionally substituted with $-O-(C_2$-C_6 alkanoyl, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl; amino C_1-C_6 alkyl, mono or dialkylamino C_1-C_6 alkyl.

In this embodiment, it is preferred that at least one of Z_1, Z_2, and Z_3 is not hydrogen.

Embodiment 35. Compounds according to embodiment 33, wherein

R_5 is of the formula:



wherein

Z_1 is H, halogen, C_1-C_4 alkyl C_1-C_4 haloalkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, or C_1-C_4 alkoxy; and

Z_2 is C_1-C_4 alkyl, $-C(O)NR_6R_7$, $-(C_1$-C_4 alkyl$)-C(O)NR_6R_7$, $-NR_6R_7$, $NR_6R_7(C_1$-C_6 alkyl), C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, halogen, C_1-C_4 alkoxy, CO_2R, C_1-C_6 alkoxycarbonyl, $-(C_1$-C_4 alkyl$)-NR_{15}C(O)NR_{16}R_{17}$, or $-(C_1$-C_4 alkyl$)-NR_{15}C(O)R_{18}$;

Z_3 is H, C_1-C_4 alkyl, $-C(O)NR_6R_7$, $-(C_1$-C_4 alkyl$)-C(O)NR_6R_7$, $-NR_6R_7$, $NR_6R_7(C_1$-C_6 alkyl), C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, halogen, C_1-C_4 alkoxy, CO_2R, C_1-C_6 alkoxycarbonyl, $-(C_1$-C_4 alkyl$)-NR_{15}C(O)NR_{16}R_{17}$, or $-(C_1$-C_4 alkyl$)-NR_{15}C(O)R_{18}$;

R_6, R_7, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring, each of which is optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy C_1-C_4 alkyl, C_1-C_4 dihydroxyalkyl, or halogen;

R_{15} is H or C_1-C_6 alkyl;

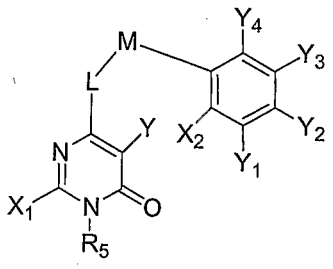
R_{16} and R_{17} are independently H or C_1-C_6 alkyl; or

R_{16}, R_{17}, and the nitrogen to which they are attached form a morpholinyl ring; and

R_{18} is C_1-C_6 alkyl optionally substituted with -O-(C_2-C_6 alkanoyl, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl; amino C_1-C_6 alkyl, mono or dialkylamino C_1-C_6 alkyl.

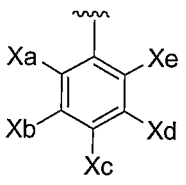
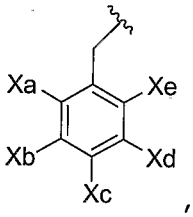
In this embodiment, it is preferred that at least one of Z_1, Z_2, and Z_3 is not hydrogen.

Embodiment 36. A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein

L and M are indepedently selected from -O-, -CH_2-, -S-,-NR-, -N(R)-N(R)-, C(=O)-, -SO_2-;

R_5 is  or  , wherein

X_1, X_2, X_a, X_b, X_c, X_d, and X_e at are independently selected from -C(O)NR_6R_7, -(C_1-C_4 alkyl)-C(O)NR_6R_7, -NR_6R_7, hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, H, OH, halogen, haloalkyl, alkyl, haloalkoxy, heteroaryl, heterocycloalkyl, C_3-C_7 cycloalkyl, R_6R_7N-(C_1-C_6 alkyl)-, -CO_2-(C_1-C_6)alkyl, -N(R)C(O)NR_6R_7, -N(R)C(O)-(C_1-C_6)alkoxy, CO_2R-(C_1-C_6 alkyl)-, or -$SO_2NR_6R_7$; wherein the heteroaryl and heterocycloalkyl groups are optionally substituted with -NR_6R_7, -C(O)NR_6R_7, R_6R_7N-(C_1-C_6 alkyl)-, C_1-C_6 alkyl, C_1-C_6 alkoxy, or halogen; or

R_5 is heteroaryl or heteroarylalkyl, wherein the heteroaryl and heteroaryl groups are optionally substituted with 1,2, 3,

or 4 groups that are independently -C(O)NR_6R_7, -(C_1-C_4 alkyl)-C(O)NR_6R_7, -NR_6R_7, hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, H, OH, halogen, haloalkyl, alkyl, haloalkoxy, R_6R_7N-(C_1-C_6 alkyl)-, -CO_2-(C_1-C_6)alkyl, -N(R)C(O)NR_6R_7, or -N(R)C(O)-(C_1-C_6)alkoxy; wherein

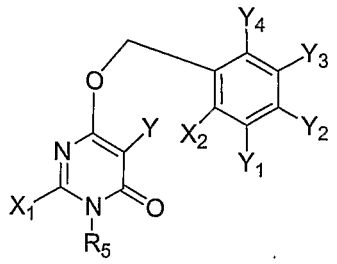
R_6 and R_7 are independently at each occurrence H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl, OH, C_1-C_6 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, C_1-C_6 thiohydroxyalkyl, -(C_1-C_4)alkyl-CO_2-alkyl, pyridyl C_1-C_6 alkyl, C_1-C_6 alkanoyl, benzyl, phenyl C_1-C_6 alkoxy, or phenyl C_1-C_6 alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, piperidinyl C_1-C_6 alkyl, morpholinyl C_1-C_6 alkyl, piperazinyl C_1-C_6 alkyl, OH, SH, NH_2, NH(alkyl), N(alkyl)(alkyl), -O-C_1-C_4 alkanoyl, C_1-C_4 alkyl, CF_3, or OCF_3; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, hydroxy C_1-C_4 alkyl, C_1-C_4 dihydroxyalkyl, or halogen;

R at each occurrence is independently H or C_1-C_6 alkyl; and

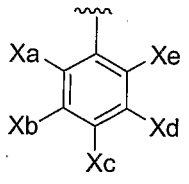
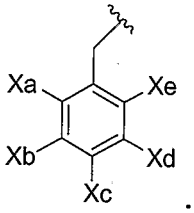
Y, Y_1, Y_2, Y_3, and Y_4 are independently selected from H, halogen, alkyl, carboxaldehyde, hydroxyalkyl, dihydroxyalkyl, alkenyl, alkynyl, CN, alkanoyl, alkoxy, alkoxyalkyl, haloalkyl, and carboxyl.

Embodiment 37. Compounds according to embodiment 36 of the formula



or a pharmaceutically acceptable salt thereof.

Embodiment 38. Compounds according to embodiment 37, wherein

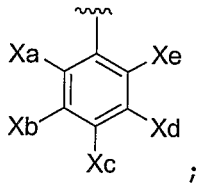
R_5 is  or  .

Embodiment 39. Compounds according to embodiment 31, wherein

Y_2, Y_4, and Y are independently halogen; and

Y_1 and Y_3 are both hydrogen.

Embodiment 40. Compounds according to embodiment 39, wherein

R_5 is  ;

X_1 and X_2 are independently H, methyl, NR_6R_7, -(C_1-C_4 alkyl)-$C(O)NR_6R_7$, R_6R_7N-(C_1-C_6 alkyl)-, -$C(O)NR_6R_7$, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, or -(C_1-C_4 alkyl)-morpholinyl; and

X_a and X_e are independently halogen, NH_2, $NH(C_1$-C_6 alkyl), $N(C_1$-C_6 alkyl)(C_1-C_6 alkyl), methyl, or hydrogen.

In this embodiment, it is preferred that one of X_a and X_e is not hydrogen.

Embodiment 41. Compounds according to embodiment 40, wherein

one of X_b and X_c is hydrogen and the other is $-NR_6R_7$, $R_6R_7N-(C_1-C_6$ alkyl)-, $-C(O)NR_6R_7$, $-SO_2NR_6R_7$, or halogen; where

R_6 and R_7 are independently at each occurrence H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl, OH, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, $-(C_1-C_4)$alkyl-CO_2-alkyl, pyridyl C_1-C_6 alkyl, C_1-C_6 alkanoyl, benzyl, phenyl C_1-C_6 alkoxy, or phenyl C_1-C_6 alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, piperidinyl C_1-C_6 alkyl, morpholinyl C_1-C_6 alkyl, piperazinyl C_1-C_6 alkyl, OH, SH, NH_2, NH(alkyl), N(alkyl)(alkyl), $-O-C_1-C_4$ alkanoyl, C_1-C_4 alkyl, CF_3, or OCF_3; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, hydroxy C_1-C_4 alkyl, C_1-C_4 dihydroxyalkyl, or halogen.

Embodiment 42. Compounds according to embodiment 41, wherein

R_6 and R_7 are independently at each occurrence H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl, OH, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, $-(C_1-C_4)$alkyl-CO_2-alkyl, pyridyl C_1-C_6 alkyl, C_1-C_6 alkanoyl, benzyl, phenyl C_1-C_6 alkoxy, or

phenyl C_1-C_6 alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, piperidinyl C_1-C_6 alkyl, morpholinyl C_1-C_6 alkyl, piperazinyl C_1-C_6 alkyl, OH, NH_2, NH(alkyl), N(alkyl)(alkyl), -O-C_1-C_4 alkanoyl, C_1-C_4 alkyl, CF_3, or OCF_3.

Embodiment 43. Compounds according to embodiment 42, wherein

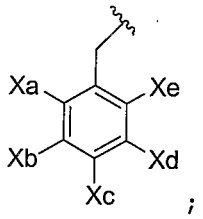
X_a is hydrogen, methyl, fluorine, or chlorine;

X_c and X_d are both hydrogen;

X_b is $-NR_6R_7$, $-(C_1$-C_4 alkyl$)-C(O)NR_6R_7$, $R_6R_7N-(C_1$-C_6 alkyl$)-$, $-C(O)NR_6R_7$; wherein

R_6 and R_7 are independently at each occurrence H, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, or C_1-C_6 alkanoyl, wherein each of the above is optionally substituted with 1, 2, or 3 groups that are independently OH, SH, halogen, or C_3-C_6 cycloalkyl.

Embodiment 44. Compounds according to embodiment 39, wherein

R_5 is 

;

X_a is H, fluoro, chloro, or methyl;

X_e is hydrogen, halogen, or methyl; and

X_b is H;

X_d is H or halogen;

Embodiment 45. Compounds according to embodiment 44, wherein

X_c is $-SO_2NR_6R_7$, or halogen; wherein

R_6 and R_7 are independently at each occurrence H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl, OH, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, -(C_1-C_4)alkyl-CO_2-alkyl, pyridyl C_1-C_6 alkyl, C_1-C_6 alkanoyl, benzyl, phenyl C_1-C_6 alkoxy, or phenyl C_1-C_6 alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, piperidinyl C_1-C_6 alkyl, morpholinyl C_1-C_6 alkyl, piperazinyl C_1-C_6 alkyl, OH, SH, NH_2, NH(alkyl), N(alkyl)(alkyl), -O-C_1-C_4 alkanoyl, C_1-C_4 alkyl, CF_3, or OCF_3; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, hydroxy C_1-C_4 alkyl, C_1-C_4 dihydroxyalkyl, or halogen; or

X_c is fluoro, chloro, $-NH_2$, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)(C_1-C_6 alkyl), $-SO_2NH_2$, $-SO_2NH(C_1$-C_6 alkyl), $-SO_2N(C_1$-C_6 alkyl)(C_1-C_6 alkyl), or piperazinyl, wherein the piperazinyl group is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, hydroxy C_1-C_4 alkyl, C_1-C_4 dihydroxyalkyl, or halogen.

Embodiment 46. Compounds according to embodiment 44, wherein

X_c is $-C(O)NR_6R_7$, $-(C_1-C_6$ alkyl$)-C(O)NR_6R_7$, $-NR_6R_7$, or $R_6R_7N-(C_1-C_6$ alkyl$)-$; wherein

R_6 and R_7 are independently at each occurrence H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl, OH, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, C_1-C_6 dihydroxyalkyl, $-(C_1-C_4)$alkyl-CO_2-alkyl, pyridyl C_1-C_6 alkyl, C_1-C_6 alkanoyl, benzyl, phenyl C_1-C_6 alkoxy, or phenyl C_1-C_6 alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, piperidinyl C_1-C_6 alkyl, morpholinyl C_1-C_6 alkyl, piperazinyl C_1-C_6 alkyl, OH, $-NH_2$, -NH(alkyl), -N(alkyl)(alkyl), $-O-C_1-C_4$ alkanoyl, C_1-C_4 alkyl, CF_3, or OCF_3; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, hydroxy C_1-C_4 alkyl, C_1-C_4 dihydroxyalkyl, or halogen.

Embodiment 47. Compounds according to embodiment 46, wherein

R_6 is hydrogen; and

R_7 is C_1-C_6 alkyl or C_1-C_6 alkanoyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently NH_2, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)(C_1-C_6 alkyl), OH, SH, cyclopropyl, or C_1-C_4 alkoxy;

Embodiment 48. Compounds according to embodiment 47, wherein

X_c is $-C(O)NR_6R_7$.

Embodiment 49. Compounds according to embodiment 47, wherein

X_c is NR_6R_7, or R_6R_7N-(C_1-C_6 alkyl)-.

Embodiment 50. Compounds according to embodiment 38, wherein

X_a is hydrogen;

two of X_b, X_c, and X_d are hydrogen and the other is $-C(O)NR_6R_7$, -(C_1-C_6 alkyl)-$C(O)NR_6R_7$, $-NR_6R_7$, R_6R_7N-(C_1-C_6 alkyl)- or -CO_2-(C_1-C_6)alkyl; wherein

R_6 and R_7 are independently at each occurrence H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl, OH, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, -(C_1-C_4)alkyl-CO_2-alkyl, pyridyl C_1-C_6 alkyl, C_1-C_6 alkanoyl, benzyl, phenyl C_1-C_6 alkoxy, or phenyl C_1-C_6 alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, piperidinyl C_1-C_6 alkyl, morpholinyl C_1-C_6 alkyl, piperazinyl C_1-C_6 alkyl, OH, NH_2, NH(alkyl), N(alkyl)(alkyl), -O-C_1-C_4 alkanoyl, C_1-C_4 alkyl, CF_3, or OCF_3; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, hydroxy C_1-C_4 alkyl, C_1-C_4 dihydroxyalkyl, or halogen; and

X_e is hydrogen, methyl, C_1-C_2 alkoxy, or halogen.

Embodiment 51. Compounds according to embodiment 50, wherein

X_b is $-C(O)NR_6R_7$, $-(C_1-C_6$ alkyl$)-C(O)NR_6R_7$, $-NR_6R_7$, or $R_6R_7N-(C_1-C_6$ alkyl$)-$ wherein

R_6 is hydrogen or C_1-C_4 alkyl;

R_7 is OH, C_1-C_6 alkyl or C_1-C_6 alkanoyl, wherein the alkyl and alkanoyl groups substituted with 1, 2, or 3 groups that are independently NH_2, $NH(C_1-C_6$ alkyl$)$, $N(C_1-C_6$ alkyl$)(C_1-C_6$ alkyl$)$, C_3-C_6 cycloalkyl, OH, or C_1-C_4 alkoxy.

Embodiment 52. Compounds according to embodiment 38, wherein

X_a is halogen or methyl;

X_b is H, $-NR_6R_7$, $R_6R_7N-(C_1-C_6$ alkyl$)-$, $-C(O)NR_6R_7$, or $-CO_2-(C_1-C_6)$alkyl;

X_c is $-NR_6R_7$, $R_6R_7N-(C_1-C_6$ alkyl$)-$, $-C(O)NR_6R_7$, halogen, $-CO_2-(C_1-C_6)$alkyl, NH_2, $NH(C_1-C_6$ alkyl$)$, $N(C_1-C_6$ alkyl$)(C_1-C_6$ alkyl$)$, $-SO_2NH_2$, $-SO_2NH(C_1-C_6$ alkyl$)$, $-SO_2N(C_1-C_6$ alkyl$)(C_1-C_6$ alkyl$)$, or piperazinyl, wherein the piperazinyl group is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, hydroxy C_1-C_4 alkyl, C_1-C_4 dihydroxyalkyl, or halogen;

X_d is hydrogen;

X_e is H, methyl, NH_2, $NH(C_1-C_6$ alkyl$)$ or $N(C_1-C_6$ alkyl$)(C_1-C_6$ alkyl$)$.

Embodiment 53. Compounds according to embodiment 38, wherein

X_1, X_2, X_a, X_b, X_c, X_d, and X_e are independently selected from H, OH, halogen, CF_3, alkyl, OCF_3, pyridyl, pyridazinyl, pyrimidyl, pyrazinyl, thienyl, furyl, pyrrolyl, piperidinyl, piperazinyl, or C_3-C_7 cycloalkyl, wherein each of the above is optionally substituted with $-NR_6R_7$, $-C(O)NR_6R_7$, $-(C_1-C_4$ alkyl$)-C(O)NR_6R_7$, $R_6R_7N-(C_1-C_6$ alkyl$)-$, C_1-C_6 alkyl, C_1-C_6 alkoxy, or halogen.

Embodiment 54. Compounds according to embodiment 37, wherein

R_5 is a heteroaryl or heteroarylalkyl group, where each heteroaryl is pyrazolyl, imidazolyl, furanyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrazolyl, imidazolyl, dihydroindolyl, dihydroisoindolyl, indolon-2-yl, quinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, dihydroisoquinolinyl, or indolyl, each of which is optionally substituted with 1, 2, 3, or 4 groups that are independently $-C(O)NR_6R_7$, $-(C_1-C_4$ alkyl$)-C(O)NR_6R_7$, $-NR_6R_7$, hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, hydrogen, hydroxy, halogen, haloalkyl, alkyl, haloalkoxy, $R_6R_7N-(C_1-C_6$ alkyl$)-$, $-CO_2-(C_1-C_6)$alkyl, $-N(R)C(O)NR_6R_7$, or $-N(R)C(O)-(C_1-C_6)$alkoxy; wherein

R_6 and R_7 are independently at each occurrence H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl, OH, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, C_1-C_6 thiohydroxyalkyl, $-(C_1-C_4)$alkyl-CO_2-alkyl, pyridyl C_1-C_6 alkyl, C_1-C_6 alkanoyl, benzyl, phenyl C_1-C_6 alkoxy, or phenyl C_1-C_6 alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, piperidinyl C_1-C_6 alkyl, morpholinyl C_1-C_6 alkyl, piperazinyl C_1-C_6 alkyl, OH, SH, NH_2, NH(alkyl), N(alkyl)(alkyl), $-O-C_1-C_4$ alkanoyl, C_1-C_4 alkyl, CF_3, or OCF.

Embodiment 55. Compounds according to embodiment 54, wherein

Y_2, Y_4, and Y are independently halogen; and

Y_1 and Y_3 are both hydrogen.

Embodiment 56. Compounds according to embodiment 55, wherein

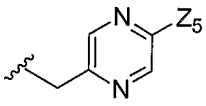
X_1 and X_2 are independently H, methyl, $-NR_6R_7$, $R_6R_7N-(C_1-C_6$ alkyl)-, $-C(O)NR_6R_7$, $-(C_1-C_4$ alkyl)$-C(O)NR_6R_7$, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, or $-(C_1-C_4$ alkyl)-morpholinyl.

Embodiment 57. Compounds according to embodiment 56, wherein

R_5 is pyridyl C_1-C_6 alkyl, pyrimidinyl C_1-C_6 alkyl, or pyrazinyl C_1-C_6 alkyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, OH, halogen, CF_3, (C_1-C_4)alkyl, OCF_3, $-NR_6R_7$, $-(C_1-C_4$ alkyl$)-C(O)NR_6R_7$, $R_6R_7N-(C_1-C_6$ alkyl)-, or $-C(O)NR_6R_7$.

Embodiment 58. Compounds according to embodiment 57, wherein

R_5 is of the formula:



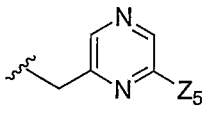
wherein

Z_5 is hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, OH, halogen, CF_3, (C_1-C_4)alkyl, OCF_3, $-NR_6R_7$, $R_6R_7N-(C_1-C_6$ alkyl)-, $-(C_1-C_4$ alkyl$)-C(O)NR_6R_7$, or $-C(O)NR_6R_7$, wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy.

Embodiment 59. Compounds according to embodiment 57, wherein

R_5 is of the formula:

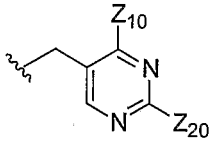


wherein

Z_5 is hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, OH, halogen, CF_3, (C_1-C_4)alkyl, OCF_3, $-NR_6R_7$, R_6R_7N-(C_1-C_6 alkyl)-, -(C_1-C_4 alkyl)-$C(O)NR_6R_7$, or $-C(O)NR_6R_7$, wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy.

Embodiment 60. Compounds according to embodiment 57, wherein

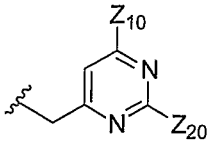
R_5 is of the formula:  , wherein

Z_{10} is H or methyl; and

Z_{20} is -(C_1-C_4 alkyl)-$C(O)NR_6R_7$, hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, OH, halogen, CF_3, (C_1-C_4)alkyl, OCF_3, $-NR_6R_7$, R_6R_7N-(C_1-C_6 alkyl)-, or $-C(O)NR_6R_7$, wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy.

Embodiment 61. Compounds according to embodiment 57, wherein

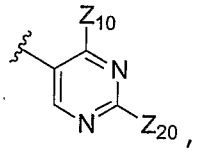
R_5 is of the formula:  , wherein

Z_{10} is H or methyl; and

Z_{20} is $-(C_1\text{-}C_4$ alkyl)$-C(O)NR_6R_7$, hydroxy$(C_1\text{-}C_4)$alkyl, $C_1\text{-}C_4$ dihydroxyalkyl, OH, halogen, CF_3, $(C_1\text{-}C_4)$alkyl, OCF_3, $-NR_6R_7$, $R_6R_7N\text{-}(C_1\text{-}C_6$ alkyl)-, or $-C(O)NR_6R_7$, wherein

R_6 and R_7 at each occurrence are independently H, $C_1\text{-}C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1\text{-}C_4$ alkoxycarbonyl, halogen, $C_3\text{-}C_6$ cycloalkyl, OH, SH, or $C_1\text{-}C_4$ alkoxy.

Embodiment 62. Compounds according to embodiment 57, wherein

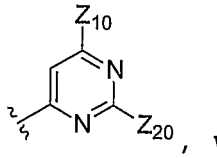
R_5 is of the formula:  , wherein

Z_{10} is H or methyl; and

Z_{20} is $-(C_1\text{-}C_4$ alkyl)$-C(O)NR_6R_7$, hydroxy$(C_1\text{-}C_4)$alkyl, $C_1\text{-}C_4$ dihydroxyalkyl, OH, halogen, CF_3, $(C_1\text{-}C_4)$alkyl, OCF_3, $-NR_6R_7$, $R_6R_7N\text{-}(C_1\text{-}C_6$ alkyl)-, or $-C(O)NR_6R_7$, wherein

R_6 and R_7 at each occurrence are independently H, $C_1\text{-}C_6$ alkyl optionally substituted with 1, 2, or 3 groups that are independently $C_1\text{-}C_4$ alkoxycarbonyl, halogen, $C_3\text{-}C_6$ cycloalkyl, OH, SH, or $C_1\text{-}C_4$ alkoxy.

Embodiment 63. Compounds according to embodiment 57, wherein

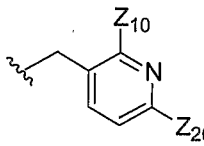
R_5 is of the formula:  , wherein

Z_{10} is H or methyl; and

Z_{20} is $-(C_1-C_4$ alkyl$)-C(O)NR_6R_7$, hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, OH, halogen, CF_3, (C_1-C_4)alkyl, OCF_3, $-NR_6R_7$, $R_6R_7N-(C_1-C_6$ alkyl$)-$, or $-C(O)NR_6R_7$, wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy.

Embodiment 64. Compounds according to embodiment 57, wherein

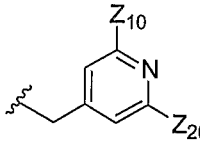
R_5 is of the formula:  , wherein

Z_{10} is H or methyl; and

Z_{20} is $-(C_1-C_4$ alkyl$)-C(O)NR_6R_7$, hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, OH, halogen, CF_3, (C_1-C_4)alkyl, OCF_3, $-NR_6R_7$, $R_6R_7N-(C_1-C_6$ alkyl$)-$, or $-C(O)NR_6R_7$, wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy.

Embodiment 65. Compounds according to embodiment 57, wherein

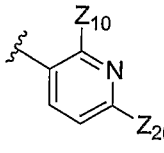
R_5 is of the formula:  , wherein

Z_{10} is H or methyl; and

Z_{20} is $-(C_1-C_4$ alkyl$)-C(O)NR_6R_7$, hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, OH, halogen, CF_3, (C_1-C_4)alkyl, OCF_3, $-NR_6R_7$, $R_6R_7N-(C_1-C_6$ alkyl$)-$, or $-C(O)NR_6R_7$, wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy.

Embodiment 66. Compounds according to embodiment 57, wherein

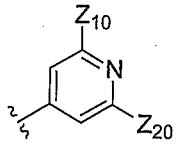
R_5 is of the formula:  , wherein

Z_{10} is H or methyl; and

Z_{20} is -(C_1-C_4 alkyl)-C(O)NR_6R_7, hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, OH, halogen, CF_3, (C_1-C_4)alkyl, OCF_3, -NR_6R_7, R_6R_7N-(C_1-C_6 alkyl)-, or -C(O)NR_6R_7, wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy.

Embodiment 67. Compounds according to embodiment 57, wherein

R_5 is of the formula:  , wherein

Z_{10} is H or methyl; and

Z_{20} is -(C_1-C_4 alkyl)-C(O)NR_6R_7, hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, OH, halogen, CF_3, (C_1-C_4)alkyl, OCF_3, -NR_6R_7, R_6R_7N-(C_1-C_6 alkyl)-, or -C(O)NR_6R_7, wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy.

Embodiment 68. Compounds according to embodiment 3, wherein

R_4 is H, alkyl optionally substituted with one or two groups that are independently CO_2R, $-CO_2$alkyl, $-C(O)NR_6R_7$, $-C(O)R_6$, $-N(R_{30})C(O)NR_{16}R_{17}$, $-N(R_{30})C(O)-(C_1-C_6)$alkoxy, or $-NR_6R_7$, $-C(O)NR_6R_7$, phenyl(C_1-C_6)alkoxy, phenyl(C_1-C_6)alkyl, hydroxyalkyl, dihydroxyalkyl, haloalkyl, alkoxy, hydroxyalkoxy-, (R_6R_7N)-alkoxy-, $R_6R_7NC(O)$-alkoxy-, $R_6C(O)N(R_7)$alkoxy-, alkoxyalkyl, or alkoxyalkoxy, wherein the phenyl groups are unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, hydroxy, alkoxy, alkyl, nitro, CF_3, OCF_3.

Embodiment 69. Compounds according to embodiment 1 wherein

R_1 is H, halogen, alkyl optionally substituted with C_1-C_4 alkoxycarbonyl, C_2-C_6 alkenyl optionally substituted with C_1-C_4 alkoxycarbonyl, C_2-C_4 alkynyl, C_1-C_4 haloalkyl, carboxaldehyde, C_1-C_4 hydroxyalkyl, phenyl(C_1-C_6)alkoxy, benzyl, phenethyl, phenpropyl, CN, or phenyl(C_1-C_6)alkanoyl,

wherein the phenyl groups are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, nitro, CN, CF_3, OCF_3 or CO_2H;

R_2 is OH, benzyloxy, phenyloxy, phenyloxy(C_1-C_6)alkyl, phenyl(C_1-C_4) thioalkoxy, $-OC(O)NH(CH_2)_n$phenyl, $-OC(O)N$(alkyl)$(CH_2)_n$phenyl, di(C_1-C_6)alkylamino, C_2-C_6 alkynyl, pyridyl, pyrimidyl, pyridazyl, pyrazolyl, imidazolyl, pyrrolyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, tetrazolyl, pyrazinyl, benzimidazolyl, triazinyl, tetrahydrofuryl, piperidinyl, hexahydropyrimidinyl, thiazolyl, thienyl, or CO_2H, wherein n is 0, 1, 2, 3, 4, 5 or 6;

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, NR_6R_7, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, (C_1-C_6) alkyl, pyridyl, -(C_1-C_6)alkyl-N(R)-CO_2R_{30}, or NR_6R_7-(C_1-C_6 alkyl)-,

R_4 is H, alkyl optionally substituted with one or two groups that are independently CO_2H, -CO_2alkyl, -C(O)NRR, -$N(R_{30})$C(O)NRR, -$N(R_{30})$C(O)-(C_1-C_6)alkoxy, or -NR_6R_7, phenyl(C_1-C_6)alkoxy, phenyl(C_1-C_6)alkyl, hydroxyalkyl, wherein the phenyl groups are unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, hydroxy, alkoxy, alkyl, nitro, CF_3, or OCF_3; and

R_5 is phenyl(C_1-C_6)alkyl, (C_1-C_6)alkyl, phenyl, piperidinyl(C_1-C_6) alkyl, thienyl(C_1-C_6) alkyl, indolyl, quinolinyl, isoquinolinyl, isoindolyl, indol-2-onyl, indazolyl, indolyl (C_1-C_6) alkyl, quinolinyl(C_1-C_6) alkyl, isoquinolinyl(C_1-C_6) alkyl, isoindolyl(C_1-C_6) alkyl, indol-2-onyl(C_1-C_6) alkyl, naphthyl(C_1-C_6)alkyl, pyridyl(C_1-C_6)alkyl, pyrimidyl(C_1-C_6)alkyl, pyrazinyl(C_1-C_6)alkyl, or wherein

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, halogen, alkoxy, benzyloxy, thioalkoxy, -CO_2(C_1-C_5 alkyl), CO_2H, CN, amidinooxime, NR_8R_9, NR_6R_7-(C_1-C_6 alkyl)-, -C(O)NR_6R_7, amidino, CF_3, or OCF_3;

R_8 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkanoyl, phenyl C_1-C_6 alkyl and phenyl C_1-C_6 alkanoyl; and

R_9 is aminoalkyl, mono C_1-C_6 alkylamino C_1-C_6 alkyl, di C_1-C_6 alkylamino C_1-C_6 alkyl, C_1-C_6 alkyl, C_1-C_6 alkanoyl, phenyl C_1-C_4 alkyl, indazolyl, and phenyl C_1-C_4 alkanoyl.

In this embodiment, it is preferred that when R_2 is benzyloxy, R_4 is H, and R_5 is benzyl or methyl, R_1 is not hydrogen; and

no more than two of R_1, R_2, R_4, and R_5 are simultaneously hydrogen.

Embodiment 70. Compounds according to embodiment 69 wherein

R_1 is H, halogen, C_1-C_4 alkyl optionally substituted with C_1-C_4 alkoxycarbonyl, C_2-C_4 alkenyl optionally substituted with C_1-C_4 alkoxycarbonyl, C_2-C_4 alkynyl, or carboxaldehyde;

R_2 is benzyloxy, OH, phenyloxy, phenyloxy(C_1-C_6)alkyl, phenyl (C_1-C_4) thioalkoxy, or pyridyl; wherein each of the above is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, -(C_1-C_6)alkyl-N(R)-CO_2R_{30}, NR_6R_7, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, (C_1-C_6) alkyl, pyridyl, or NR_6R_7-(C_1-C_6 alkyl)-.

Embodiment 71. Compounds according to embodiment 69 wherein

R_4 is H, (C_1-C_6)alkyl optionally substituted with one or two groups that are independently CO_2H, -CO_2alkyl, -C(O)NRR, -N(R_{30})C(O)NRR, -N(R_{30})C(O)-(C_1-C_6)alkoxy, or -NR_6R_7, phenyl(C_1-C_6)alkoxy, or hydroxy(C_1-C_6)alkyl, wherein the phenyl groups are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, hydroxy, C_1-C_4 alkoxy, C_1-C_4 alkyl, nitro, CF_3, OCF_3; and

R_5 is benzyl, phenethyl, phenpropyl, phenbutyl, (C_1-C_6)alkyl, phenyl, pyridyl, pyrimidyl, indolyl, indazolyl, indolyl (C_1-C_6) alkyl, naphthyl(C_1-C_6)alkyl, thienyl(C_1-C_6)alkyl, pyridyl(C_1-C_6)alkyl, pyrimidyl(C_1-C_6)alkyl, or pyrazinyl(C_1-C_6)alkyl, and wherein

each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently alkyl, halogen, alkoxy, benzyloxy, thioalkoxy, $-CO_2(C_1-C_5$ alkyl), CF_3, OCF_3, CO_2H, CN, amidinooxime.

In this embodiment, it is preferred that when R_2 is benzyloxy, R_4 is H, and R_5 is benzyl or methyl, R_1 is not hydrogen; and

no more than two of R_1, R_2, R_4, and R_5 are simultaneously hydrogen.

Embodiment 72. Compounds according to embodiment 69, wherein

R_4 is H, (C_1-C_4) alkyl optionally substituted with one or two groups that are independently CO_2H, $-CO_2$alkyl, $-C(O)NRR$, $-N(R_{30})C(O)NRR$, $-N(R_{30})C(O)-(C_1-C_6)$alkoxy, or $-NR_6R_7$, phenyl(C_1-C_6)alkoxy, benzyl, phenethyl, phenpropyl, or hydroxy(C_1-C_6)alkyl, wherein

the phenyl groups are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, hydroxy, C_1-C_4 alkoxy, C_1-C_4 alkyl, nitro, CF_3, OCF_3; and

R_5 is indolyl, quinolinyl, isoquinolinyl, isoindolyl, indol-2-onyl, indolyl(C_1-C_6) alkyl, quinolinyl(C_1-C_6) alkyl, isoquinolinyl(C_1-C_6) alkyl, isoindolyl(C_1-C_6) alkyl, indol-2-onyl(C_1-C_6) alkyl, each of which is unsubstituted or substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkyl, halogen, CF_3, OCF_3, $-CO_2CH_3$, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxy, $-CO_2(C_1-C_5$ alkyl), benzyloxy, $-NR_8R_9$, $NR_6R_7-(C_1-C_6$ alkyl)-, $-C(O)NR_6R_7$, or amidinooxime; wherein

R_6 and R_7 are independently at each occurrence H, alkyl, hydroxyalkyl, alkoxy, alkoxyalkyl, alkanoyl, phenylalkyl, phenylalkoxy, or phenylalkanoyl,

wherein each is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, hydroxy, C_1-C_4 alkoxy, OH, SH, C_3-C_6 cycloalkyl, C_1-C_4 alkyl, CF_3, or OCF_3; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, hydroxy, hydroxy C_1-C_4 alkyl, or halogen.

Embodiment 73. Compounds according to embodiment 69 wherein

R_1 is chloro, bromo, iodo, or H; and

R_5 is benzyl, phenethyl, phenpropyl, phenyl, quinolinyl, indolyl, isoquinolinyl, isoindolyl, indol-2-onyl, indolyl(C_1-C_6) alkyl, quinolinyl(C_1-C_6) alkyl, isoquinolinyl(C_1-C_6) alkyl, isoindolyl(C_1-C_6) alkyl, indol-2-onyl(C_1-C_6) alkyl, piperidinyl C_1-C_4 alkyl, thienyl C_1-C_4 alkyl, $-CH_2$-pyridyl, or pyridyl, each of which is unsubstituted or substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkyl, halogen, CF_3, OCF_3, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxy, $-CO_2$(C_1-C_5 alkyl), benzyloxy, NR_8R_9, NR_6R_7 C_1-C_4 alkyl, $-C(O)NR_6R_7$, and amidinooxime; wherein

R_6 and R_7 are independently at each occurrence H, alkyl, hydroxyalkyl, alkoxy, alkoxyalkyl, alkanoyl, phenylalkyl, phenylalkoxy, or phenylalkanoyl, wherein each is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, hydroxy, C_1-C_4 alkoxy, OH, SH, C_3-C_6 cycloalkyl, C_1-C_4 alkyl, CF_3, or OCF_3; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, or piperazinyl ring

which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, hydroxy, hydroxy C_1-C_4 alkyl, or halogen.

Embodiment 74. Compounds according to embodiment 73, wherein

R_5 is benzyl, phenethyl, phenpropyl, or phenyl, each of which is unsubstituted or substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkyl, halogen, CF_3, OCF_3, -CO_2CH_3, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxy, -CO_2(C_1-C_5 alkyl), benzyloxy, NR_8R_9, NR_6R_7 C_1-C_4 alkyl, -C(O)NR_6R_7, and amidinooxime.

Embodiment 75. Compounds according to embodiment 73, wherein

R_5 is quinolinyl, indolyl, isoquinolinyl, isoindolyl, indol-2-onyl, indolyl(C_1-C_6) alkyl, quinolinyl(C_1-C_6) alkyl, isoquinolinyl(C_1-C_6) alkyl, isoindolyl(C_1-C_6) alkyl, indol-2-onyl(C_1-C_6) alkyl, piperidinyl C_1-C_4 alkyl, thienyl C_1-C_4 alkyl, -CH_2-pyridyl, or pyridyl, each of which is unsubstituted or substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkyl, halogen, CF_3, OCF_3, -CO_2CH_3, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxy, -CO_2(C_1-C_5 alkyl), benzyloxy, NR_8R_9, NR_6R_7 C_1-C_4 alkyl, -C(O)NR_6R_7, and amidinooxime.

Embodiment 76. Compounds according to any one of embodiments 73, 74, or 75 wherein

R_2 is benzyloxy, or phenethyloxy;

each of the above is unsubstituted or substituted with 1, 2, or 3, groups that are independently -(C_1-C_6)alkyl-N(R)-CO_2R_{30}, fluoro, chloro, bromo, CF_3, or (C_1-C_4)alkyl.

Embodiment 77. Compounds according to any one of embodiments 73, 74 or 75 wherein

R_2 is phenyloxy(C_1-C_6)alkyl, wherein the phenyl group is unsubstituted or substituted with 1, 2, or 3, groups that are independently -(C_1-C_6)alkyl-N(R)-CO_2R_{30}, fluoro, chloro, bromo, CF_3, or (C_1-C_4)alkyl.

Embodiment 78. Compounds according to embodiment 1 or 69, wherein

R_1 is H, halogen, C_1-C_4 alkyl optionally substituted with C_1-C_4 alkoxycarbonyl, C_2-C_4 alkenyl optionally substituted with C_1-C_4 alkoxycarbonyl, C_2-C_4 alkynyl, or carboxaldehyde.

Embodiment 79. Compounds according to embodiment 78, wherein

R_2 is benzyloxy, OH, phenyloxy, phenyloxy(C_1-C_6)alkyl, or phenyl (C_1-C_4) thioalkoxy, wherein each of the above is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, -(C_1-C_6)alkyl-N(R)-CO_2R_{30}, NR_6R_7, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, (C_1-C_6) alkyl, pyridyl, or NR_6R_7-(C_1-C_6 alkyl)-.

Embodiment 80. Compounds according to embodiment 79, wherein

R_4 is H, or (C_1-C_4) alkyl optionally substituted with one or two groups that are independently CO_2H, -CO_2alkyl, -C(O)NRR, -N(R_{30})C(O)NRR, -N(R_{30})C(O)-(C_1-C_6)alkoxy, OH, or -NR_6R_7.

Embodiment 81. Compounds according to embodiment 80, wherein

R_5 is phenyl, naphthyl, indolyl, pyridyl, quinolinyl, isoquinolinyl, isoindolyl, indol-2-onyl, indolyl(C_1-C_6)

alkyl, quinolinyl(C_1-C_6) alkyl, isoquinolinyl(C_1-C_6) alkyl, isoindolyl(C_1-C_6) alkyl, indol-2-onyl(C_1-C_6) alkyl, pyridazinyl, pyrimidinyl, or pyrazinyl, pyridazinyl(C_1-C_6) alkyl, pyrimidinyl(C_1-C_6) alkyl, or pyrazinyl(C_1-C_6) alkyl; each of which is unsubstituted or substituted with 1, 2, 3, 4 or 5 groups that are independently C_1-C_4 alkyl, halogen, CF_3, OCF_3, $-CO_2CH_3$, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxy, $-CO_2(C_1$-C_5 alkyl), benzyloxy, $-NR_8R_9$, $-C(O)NR_6R_7$, NR_6R_7 C_1-C_4 alkyl, and amidinooxime; wherein

R_6 and R_7 are independently at each occurrence H, C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxy, C_1-C_4 alkoxy C_1-C_4 alkyl, C_1-C_4 alkanoyl, phenyl C_1-C_4 alkyl, phenyl C_1-C_4 alkoxy, or phenyl C_1-C_4 alkanoyl, wherein each is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, hydroxy, C_1-C_4 alkoxy, C_1-C_4 alkyl, OH, SH, C_3-C_6 cycloalkyl, CF_3, or OCF_3; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, hydroxy, hydroxy C_1-C_4 alkyl, or halogen.

Embodiment 82. Compounds according to embodiment 81, wherein

R_1 is H, halogen, methyl, ethyl, C_2-C_4 alkenyl C_2-C_4 alkynyl, or carboxaldehyde;

R_2 is benzyloxy, OH, phenyloxy, phenyloxy(C_1-C_6)alkyl, or phenyl (C_1-C_4) thioalkoxy, wherein each of the above is optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, $-(C_1$-$C_6)$alkyl-N(R)-CO_2R_{30}, NR_6R_7, NR_6R_7 C_1-C_4 alkyl, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, (C_1-C_6) alkyl, or pyridyl; and

R_4 is H, (C_1-C_4) alkyl optionally substituted with one or two groups that are independently CO_2H, $-CO_2$alkyl, $-C(O)NRR$, $-N(R_{30})C(O)NRR$, $-N(R_{30})C(O)-(C_1-C_6)$alkoxy, OH, or $-NR_6R_7$.

Embodiment 83. Compounds according to embodiment 82, wherein

R_5 is phenyl optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C_1-C_6 alkyl, $-NR_{10}R_{11}$, C_1-C_4 alkoxy, $-C(O)NR_{10}R_{11}$, $-CO_2H$, $NR_{10}R_{11}$ C_1-C_4 alkyl, C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxy, CHO, $-SO_2NH_2$, C_1-C_4 haloalkyl, C_1-C_6 hydroxyalkyl, $-C_1-C_4$ alkyl-$NR_{12}C(O)NR_{13}R_{14}$, $-C_1-C_4$ alkyl-$NR_{12}C(O)-(C_1-C_4$ alkyl)-$NR_{13}R_{14}$, $-C_1-C_4$ alkyl-$NR_{12}C(O)OR_{15}$, or $-C_1-C_4$ alkyl-$NR_{12}C(O)-(C_1-C_4$ alkyl)-R_{15}, wherein

R_{10} and R_{11} at each occurrence are independently H, C_1-C_6 alkyl, amino C_1-C_4 alkyl, $NH(C_1-C_6$ alkyl)alkyl, $N(C_1-C_6$ alkyl)$(C_1-C_6$ alkyl) C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy C_1-C_6 alkyl, OH, $-SO_2$ $(C_1-C_6$ alkyl), or C_1-C_6 alkanoyl, or

R_{10}, R_{11}, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring optionally substituted with 1 or 2 groups that are independently alkyl or halogen,

R_{12} is H or C_1-C_6 alkyl;

R_{13} and R_{14} are independently H or C_1-C_6 alkyl; or

R_{13} and R_{14} and the nitrogen to which they are attached form a morpholinyl ring; and

R_{15} is C_1-C_6 alkoxy; $-OC(O)C_1-C_6$ alkyl, OH.

Embodiment 84. Compounds according to embodiment 83, wherein

R_5 is phenyl optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C_1-C_6 alkyl, -

$NR_{10}R_{11}$, $NR_{10}R_{11}$ C_1-C_6 alkyl, C_1-C_4 alkoxy, or -C(O)$NR_{10}R_{11}$, -CO_2H, -C_1-C_4 alkyl-$NR_{10}R_{11}$, C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxy, CHO, -SO_2NH_2, C_1-C_4 haloalkyl, C_1-C_6 hydroxyalkyl, -C_1-C_4 alkyl-NR_{12}C(O)$NR_{13}R_{14}$, -C_1-C_4 alkyl-NR_{12}C(O)-(C_1-C_4 alkyl)-$NR_{13}R_{14}$, -C_1-C_4 alkyl-NR_{12}C(O)OR_{15}, or -C_1-C_4 alkyl-NR_{12}C(O)-(C_1-C_4 alkyl)-R_{15} wherein

R_{10} and R_{11} at each occurrence are independently H, C_1-C_6 alkyl, amino C_1-C_4 alkyl, NH(C_1-C_6 alkyl)alkyl, N(C_1-C_6 alkyl)(C_1-C_6 alkyl) C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy C_1-C_6 alkyl, OH, -SO_2 (C_1-C_6 alkyl), or C_1-C_6 alkanoyl,

R_{12} is H or C_1-C_6 alkyl;

R_{13} and R_{14} are independently H or C_1-C_6 alkyl; or

R_{13} and R_{14} and the nitrogen to which they are attached form a morpholinyl ring; and

R_{15} is C_1-C_6 alkoxy; -OC(O)C_1-C_6 alkyl, OH.

Embodiment 85. Compounds according to embodiment 84, wherein

R_5 is phenyl optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C_1-C_6 alkyl, -$NR_{10}R_{11}$, $NR_{10}R_{11}$ C_1-C_4 alkyl, C_1-C_4 alkoxy, -C(O)$NR_{10}R_{11}$, wherein

R_{10} and R_{11} at each occurrence are independently H, C_1-C_6 alkyl, amino C_1-C_4 alkyl, NH(C_1-C_6 alkyl)alkyl, N(C_1-C_6 alkyl)(C_1-C_6 alkyl) C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy C_1-C_6 alkyl, OH, -SO_2 (C_1-C_6 alkyl), C_1-C_6 alkanoyl.

Embodiment 86. Compounds according to embodiment 85, wherein

R_5 is phenyl optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C_1-C_6 alkyl, -$NR_{10}R_{11}$, or C_1-C_4 alkoxy.

Embodiment 87. Compounds according to embodiment 85, wherein

R_5 is substituted with at least one -$C(O)NR_{10}R_{11}$.

Embodiment 88. Compounds according to embodiment 87, wherein

R_{10} and R_{11} at each occurrence are independently H, C_1-C_6 alkyl, amino C_1-C_4 alkyl, $NH(C_1$-C_6 alkyl)alkyl, $N(C_1$-C_6 alkyl)(C_1-C_6 alkyl) C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy C_1-C_6 alkyl.

Embodiment 89. Compounds according to embodiment 88, wherein

R_{10} is H.

Embodiment 90. Compounds according to embodiment 87, wherein

R_{10} and R_{11} at each occurrence are independently H, C_1-C_6 alkyl, OH, -SO_2 (C_1-C_6 alkyl), C_1-C_6 alkanoyl.

Embodiment 91. Compounds according to embodiment 82, wherein

R_5 is phenyl optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C_1-C_6 alkyl, NH_2, $NH(C_1$-C_6 alkyl), $N(C_1$-C_6 alkyl)(C_1-C_6 alkyl), C_1-C_4 alkoxy, -$C(O)NR_{10}R_{11}$, wherein each of the above alkyl groups is optionally substituted with 1 or 2 groups that are independently OH, or methoxy; wherein

R_{10}, R_{11}, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring optionally substituted with 1 or 2 groups that are independently alkyl or halogen.

Embodiment 92. Compounds according to embodiment 82, wherein

R_5 is phenyl optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, $-CO_2H$, $-C_1$-C_4 alkyl-$NR_{10}R_{11}$, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxy, CHO, $-SO_2NH_2$, C_1-C_4 haloalkyl, C_1-C_6 hydroxyalkyl, $-C_1$-C_4 alkyl-$NR_{12}C(O)NR_{13}R_{14}$, $-C_1$-C_4 alkyl-$NR_{12}C(O)$-(C_1-C_4 alkyl)-$NR_{13}R_{14}$, $-C_1$-C_4 alkyl-$NR_{12}C(O)OR_{15}$, or $-C_1$-C_4 alkyl-$NR_{12}C(O)$-(C_1-C_4 alkyl)-R_{15}, $-OC(O)C_1$-C_6 alkyl, or OH wherein

R_{12} is H or C_1-C_6 alkyl;

R_{13} and R_{14} are independently H or C_1-C_6 alkyl; or

R_{13} and R_{14} and the nitrogen to which they are attached form a morpholinyl ring;

R_{15} is C_1-C_6 alkoxy.

Embodiment 93. Compounds according to embodiment 92, wherein

R_5 is phenyl optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-CO_2H$, C_1-C_4 alkoxycarbonyl, C_1-C_4 alkoxy, CHO, $-SO_2NH_2$, C_1-C_4 haloalkyl, C_1-C_4 hydroxyalkyl.

Embodiment 94. Compounds according to embodiment 92, wherein

R_5 is phenyl optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-CO_2H$, $-C_1$-C_4 alkyl-$NR_{10}R_{11}$, $-C_1$-C_4 alkyl-

$NR_{12}C(O)NR_{13}R_{14}$, $-C_1-C_4$ alkyl-$NR_{12}C(O)-(C_1-C_4$ alkyl)-$NR_{13}R_{14}$, $-C_1-C_4$ alkyl-$NR_{12}C(O)OR_{15}$, or $-C_1-C_4$ alkyl-$NR_{12}C(O)-(C_1-C_4$ alkyl)-R_{15}, or $-OC(O)C_1-C_6$ alkyl, wherein

R_{12} is H or C_1-C_6 alkyl;

R_{13} and R_{14} are independently H or C_1-C_6 alkyl; or

R_{13} and R_{14} and the nitrogen to which they are attached form a morpholinyl ring;

R_{15} is C_1-C_6 alkoxy.

Embodiment 95. Compounds according to embodiment 94, wherein

R_5 is phenyl optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-CO_2H$, $-C_1-C_4$ alkyl-$NR_{10}R_{11}$, $-C_1-C_4$ alkyl-$NR_{12}C(O)NR_{13}R_{14}$, $-C_1-C_4$ alkyl-$NR_{12}C(O)-(C_1-C_4$ alkyl)-$NR_{13}R_{14}$, wherein

R_{12} is H or C_1-C_6 alkyl;

R_{13} and R_{14} are independently H or C_1-C_6 alkyl; or

R_{13} and R_{14} and the nitrogen to which they are attached form a morpholinyl ring.

Embodiment 96. Compounds according to any one of embodiments 92, 93, 94, or 95, wherein the phenyl group is substituted with two groups that are meta to each other.

Embodiment 97. Compounds according to any one of embodiments 92, 93, 94, or 95, wherein the phenyl group is substituted with two groups that are para to each other.

Embodiment 98. Compounds according to embodiment 82, wherein

R_5 is indolyl, pyridyl, pyridazinyl, pyrimidinyl, indazolyl, quinolinyl, isoquinolinyl, isoindolyl, indol-2-onyl,

pyridazinyl, pyrimidinyl, or pyrazinyl, , each of which is unsubstituted or substituted with 1, 2, 3, 4 or 5 groups that are independently C_1-C_4 alkyl, halogen, CF_3, OCF_3, $-CO_2CH_3$, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxy, $-CO_2(C_1$-C_5 alkyl), benzyloxy, NR_8R_9, NR_6R_7 C_1-C_4 alkyl, $-C(O)NR_6R_7$, or amidinooxime; wherein

R_6 and R_7 are independently at each occurrence H, C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxy, C_1-C_4 alkoxy C_1-C_4 alkyl, C_1-C_4 alkanoyl, phenyl C_1-C_4 alkyl, phenyl C_1-C_4 alkoxy, or phenyl C_1-C_4 alkanoyl, wherein each is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, OH, SH, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, OH, CF_3, or OCF_3; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, hydroxy, hydroxy C_1-C_4 alkyl, or halogen.

Embodiment 99. Compounds according to embodiment 98, wherein

R_5 is indolyl, pyridyl, pyrimidinyl, indazolyl, or pyrazinyl, each of which is unsubstituted or substituted with 1, 2, 3, or 4 groups that are independently C_1-C_4 alkyl, halogen, CF_3, OCF_3, $-CO_2CH_3$, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxy, $-CO_2(C_1$-C_5 alkyl), benzyloxy, $-C(O)NR_6R_7$, $-NR_8R_9$, NR_6R_7 C_1-C_4 alkyl, and amidinooxime; wherein

R_6 and R_7 are independently at each occurrence H, C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxy, C_1-C_4 alkoxy C_1-C_4 alkyl, C_1-C_4 alkanoyl, phenyl C_1-C_4 alkyl, phenyl C_1-C_4 alkoxy, or phenyl C_1-C_4 alkanoyl, wherein each is unsubstituted or substituted with 1, 2, or 3

groups that are independently, halogen, OH, SH, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, OH, CF_3, or OCF_3.

Embodiment 100. Compounds according to embodiment 99, wherein

R_5 is indolyl, pyridyl, or pyrazinyl, each of which is unsubstituted or substituted with 1, 2, 3, or 4 groups that are independently C_1-C_4 alkyl, halogen, CF_3, OCF_3, $-CO_2CH_3$, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxy, $-CO_2(C_1$-C_5 alkyl), benzyloxy, $-C(O)NR_6R_7$, NR_8R_9, NR_6R_7-C_1-C_4 alkyl-, and amidinooxime; wherein

R_6 and R_7 are independently at each occurrence H, C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxy, C_1-C_4 alkoxy C_1-C_4 alkyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, OH, CF_3, or OCF_3.

Embodiment 101. Compounds according to embodiment 98, wherein

R_5 is indolyl, pyridyl, pyridazinyl, pyrimidinyl, or pyrazinyl, each of which is unsubstituted or substituted with 1, 2, 3, 4 or 5 groups that are independently C_1-C_4 alkyl, halogen, CF_3, OCF_3, $-CO_2CH_3$, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxy, $-CO_2(C_1$-C_5 alkyl), benzyloxy, $-C(O)NH_2$, $-C(O)NH(C_1$-C_6 alkyl) wherein the alkyl group is optionally substituted with OH or methoxy, $-C(O)N(C_1$-C_6 alkyl) (C_1-C_6 alkyl) wherein each alkyl group is independently and optionally substituted with OH or methoxy, $-C(O)NR_6R_7$, NR_8R_9, NR_6R_7 C_1-C_4 alkyl, $-C_1$-C_4 alkyl-NH_2, $-C_1$-C_4 alkyl-$NH(C_1$-C_6 alkyl) wherein each alkyl group is independently and optionally substituted with OH or methoxy, $-C_1$-C_4

alkyl-N(C_1-C_6 alkyl)(C_1-C_6 alkyl) wherein each alkyl group is independently and optionally substituted with OH or methoxy, and amidinooxime; wherein

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, hydroxy, hydroxy C_1-C_4 alkyl, or halogen.

Embodiment 102. Compounds according to any one of embodiments 98, 99, 100, or 101, , wherein

R_1 is H, halogen, methyl, or carboxaldehyde;

R_2 is benzyloxy, phenyloxy, phenyloxy(C_1-C_6)alkyl, or phenyl (C_1-C_4) thioalkoxy, wherein each of the above is optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, -(C_1-C_6)alkyl-N(R)-CO_2R_{30}, NR_6R_7, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, (C_1-C_6) alkyl, NR_6R_7(C_1-C_6)alkyl, pyridyl, morpholinyl, thiomorpholinyl, piperazinyl pyridyl(C_1-C_6)alkyl, morpholinyl(C_1-C_6)alkyl, thiomorpholinyl(C_1-C_6)alkyl, or piperazinyl(C_1-C_6)alkyl wherein the pyridyl, morpholinyl, thiomorpholinyl, and piperazinyl rings are optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, or halogen; wherein

R_6 and R_7 are independently at each occurrence H, C_1-C_4 alkyl optionally substituted with 1 or two groups that are independently OH, halogen or methoxy, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxy, C_1-C_4 alkoxy C_1-C_4 alkyl, C_1-C_4 alkanoyl, benzyl, benzyloxy, or phenyl C_1-C_4 alkanoyl, wherein each is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, OH, SH, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, CF_3, or OCF_3, and

R_4 is H, (C_1-C_3) alkyl optionally substituted with one or two groups that are independently CO_2H, -CO_2alkyl, -C(O)NRR, -N(R_{30})C(O)NRR, -N(R_{30})C(O)-(C_1-C_6)alkoxy, -NR_6R_7, $NR_6R_7C_1$-C_4 alkyl, or hydroxy(C_1-C_3)alkyl.

Embodiment 103. Compounds according to embodiment 102, wherein

R_1 is H or halogen.

Embodiment 104. Compounds according to embodiment 80, wherein

R_5 is phenyl(C_1-C_6)alkyl, (C_1-C_6)alkyl, piperidinyl(C_1-C_6) alkyl, thienyl(C_1-C_6) alkyl, indolyl (C_1-C_6) alkyl, naphthyl(C_1-C_6)alkyl, pyridyl(C_1-C_6)alkyl, pyrimidyl(C_1-C_6)alkyl, quinolinyl(C_1-C_6) alkyl, isoquinolinyl(C_1-C_6) alkyl, isoindolyl(C_1-C_6) alkyl, indol-2-onyl(C_1-C_6) alkyl, pyridazinyl(C_1-C_6) alkyl, pyrazinyl(C_1-C_6) alkyl, or pyrazinyl(C_1-C_6)alkyl, wherein

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, halogen, alkoxy, benzyloxy, hydroxyalkyl, thioalkoxy, -CO_2(C_1-C_5 alkyl), CO_2H, CN, amidinooxime, NR_8R_9, NR_6R_7-(C_1-C_6 alkyl)-, -C(O)NR_6R_7, amidino, CF_3, or OCF_3;

R_8 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkanoyl, phenyl C_1-C_6 alkyl and phenyl C_1-C_6 alkanoyl; and

R_9 is aminoalkyl, mono C_1-C_6 alkylamino C_1-C_6 alkyl, di C_1-C_6 alkylamino C_1-C_6 alkyl, C_1-C_6 alkyl, C_1-C_6 alkanoyl, phenyl C_1-C_4 alkyl, indazolyl, and phenyl C_1-C_4 alkanoyl.

In this embodiment, it is preferred that when R_2 is benzyloxy, R_4 is H, and R_5 is benzyl or methyl, R_1 is not hydrogen; and

no more than two of R_1, R_2, R_4, and R_5 are simultaneously hydrogen.

Embodiment 105. Compounds according to embodiment 104, wherein

R_5 is phenyl(C_1-C_6)alkyl, which is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, halogen, alkoxy, benzyloxy, thioalkoxy, -CO_2(C_1-C_5 alkyl), CO_2H, CN, amidinooxime, NR_8R_9, NR_6R_7-(C_1-C_6 alkyl)-, -C(O)NR_6R_7, amidino, CF_3, or OCF_3; wherein

R_6 and R_7 are independently at each occurrence H, C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxy, C_1-C_4 alkoxy C_1-C_4 alkyl, C_1-C_4 alkanoyl, phenyl C_1-C_4 alkyl, phenyl C_1-C_4 alkoxy, or phenyl C_1-C_4 alkanoyl, wherein each is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, OH, SH, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, CF_3, or OCF_3; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, hydroxy, hydroxy C_1-C_4 alkyl, or halogen;

R_8 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkanoyl, phenyl C_1-C_6 alkyl and phenyl C_1-C_6 alkanoyl; and

R_9 is aminoalkyl, mono C_1-C_6 alkylamino C_1-C_6 alkyl, di C_1-C_6 alkylamino C_1-C_6 alkyl, C_1-C_6 alkyl, C_1-C_6 alkanoyl, phenyl C_1-C_4 alkyl, indazolyl, and phenyl C_1-C_4 alkanoyl.

Embodiment 106. Compounds according to embodiment 105, wherein

R_5 is phenyl(C_1-C_6)alkyl, which is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently CN, halogen, C_1-C_4 alkoxy, C_1-C_4 thioalkoxy, C_1-C_4 haloalkyl, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, -C(O)$NR_{20}R_{21}$, wherein

R_{20} and R_{21} are independently H, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy C_1-C_6 alkyl, or

R_{20}, R_{21}, and the nitrogen to which they are attached form a piperazinyl, or morpholinyl ring, each of which is optionally substituted with 1 or 2 groups that are independently alkyl or halogen.

Embodiment 107. Compounds according to embodiment 106, wherein

R_5 is phenyl(C_1-C_4)alkyl, which is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently CN, halogen, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 alkyl, C_1-C_4 haloalkoxy, -C(O)$NR_{20}R_{21}$, wherein

R_{20} and R_{21} are independently H, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy C_1-C_6 alkyl, or

R_{20}, R_{21}, and the nitrogen to which they are attached form a piperazinyl, or morpholinyl ring, each of which is optionally substituted with 1 or 2 groups that are independently alkyl or halogen.

Embodiment 108. Compounds according to embodiment 107, wherein

R_5 is benzyl or phenethyl, each of which is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently CN, halogen, C_1-C_4 alkoxy, CF_3, OCF_3, C_1-C_4 alkyl, -C(O)$NR_{20}R_{21}$, wherein

R_{20} and R_{21} are independently H, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy C_1-C_6 alkyl, or

R_{20}, R_{21}, and the nitrogen to which they are attached form a piperazinyl, or morpholinyl ring, each of which is optionally substituted with 1 or 2 groups that are independently alkyl or halogen.

Embodiment 109. Compounds according to embodiment 108, wherein

R_5 is benzyl or phenethyl, each of which is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, methoxy, ethoxy, CF_3, OCF_3, methyl, ethyl, or $-C(O)NR_{20}R_{21}$, wherein

R_{20} and R_{21} are independently H, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy C_1-C_6 alkyl,

Embodiment 110. Compounds according to embodiment 108, wherein

R_5 is benzyl or phenethyl, each of which is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, methoxy, ethoxy, CF_3, OCF_3, methyl, ethyl, or $-C(O)NR_{20}R_{21}$, wherein

R_{20}, R_{21}, and the nitrogen to which they are attached form a piperazinyl, or morpholinyl ring, each of which is optionally substituted with 1 or 2 groups that are independently alkyl or halogen.

Embodiment 111. Compounds according to embodiment 109 or embodiment 110, wherein

R_5 is substituted on the phenyl ring with 1, 2, 3, 4, or 5 groups and wherein there is a group at the para position of the phenyl.

Embodiment 112. Compounds according to embodiment 103, wherein

R_5 is piperidinyl(C_1-C_6) alkyl, thienyl(C_1-C_6) alkyl, indolyl (C_1-C_6) alkyl, pyridyl(C_1-C_6)alkyl, pyrimidyl(C_1-C_6)alkyl, quinolinyl(C_1-C_6) alkyl, isoquinolinyl(C_1-C_6) alkyl, isoindolyl(C_1-C_6) alkyl, indol-2-onyl(C_1-C_6) alkyl, pyridazinyl(C_1-C_6) alkyl, or pyrazinyl(C_1-C_6) alkyl, or pyrazinyl(C_1-C_6)alkyl, or pyrazinyl(C_1-C_6)alkyl, wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, halogen, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, benzyloxy, C_1-C_6 thioalkoxy, -CO_2(C_1-C_5 alkyl), CO_2H, CN, amidinooxime, NR_8R_9, NR_6R_7-(C_1-C_6 alkyl)-, -C(O)NR_6R_7, amidino, CF_3, or OCF_3;

R_8 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkanoyl, phenyl C_1-C_6 alkyl and phenyl C_1-C_6 alkanoyl; and

R_9 is aminoalkyl, mono C_1-C_6 alkylamino C_1-C_6 alkyl, di C_1-C_6 alkylamino C_1-C_6 alkyl, C_1-C_6 alkyl, C_1-C_6 alkanoyl, phenyl C_1-C_4 alkyl, indazolyl, and phenyl C_1-C_4 alkanoyl.

In this embodiment, it is preferred that when R_2 is benzyloxy, R_4 is H, and R_5 is benzyl or methyl, R_1 is not hydrogen; and

no more than two of R_1, R_2, R_4, and R_5 are simultaneously hydrogen.

Embodiment 113. Compounds according to embodiment 112, wherein

R_5 is piperidinyl(C_1-C_4) alkyl, thienyl(C_1-C_4) alkyl, indolyl (C_1-C_4) alkyl, pyridyl(C_1-C_4)alkyl, pyrimidyl(C_1-C_4)alkyl, or pyrazinyl(C_1-C_4)alkyl, each of which is unsubstituted.

Embodiment 114. Compounds according to embodiment 112, wherein

R_5 is indolyl (C_1-C_4) alkyl, pyrimidyl(C_1-C_4)alkyl, or pyrazinyl(C_1-C_4)alkyl, wherein

each of the above is unsubstituted or substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, halogen, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, benzyloxy, C_1-C_6 thioalkoxy, -CO_2(C_1-C_5 alkyl), CO_2H, CN, amidinooxime, NR_8R_9, NR_6R_7-(C_1-C_6 alkyl)-, amidino, -C(O)$NR_{20}R_{21}$, CF_3, or OCF_3; wherein

R_6 and R_7 are independently at each occurrence H, C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxy, C_1-C_4 alkoxy C_1-C_4 alkyl, C_1-C_4 alkanoyl, benzyl, benzyloxy, or phenyl C_1-C_4 alkanoyl, wherein each is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, OH, SH, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, CF_3, or OCF_3; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, hydroxy, hydroxy C_1-C_4 alkyl, or halogen;

R_8 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkanoyl, phenyl C_1-C_4 alkyl and phenyl C_1-C_4 alkanoyl; and

R_9 is aminoalkyl, mono C_1-C_6 alkylamino C_1-C_6 alkyl, di C_1-C_6 alkylamino C_1-C_6 alkyl, C_1-C_6 alkyl, C_1-C_6 alkanoyl, phenyl C_1-C_4 alkyl, indazolyl, and phenyl C_1-C_4 alkanoyl;

R_{20} and R_{21} are independently H, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy C_1-C_6 alkyl, or

R_{20}, R_{21}, and the nitrogen to which they are attached form a piperazinyl, or morpholinyl ring, each of which is optionally substituted with 1 or 2 groups that are independently alkyl or halogen

Embodiment 115. Compounds according to embodiment 114, wherein

R_5 is indolyl (C_1-C_4) alkyl, or pyrazinyl(C_1-C_4)alkyl, wherein each of the above is unsubstituted or substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, halogen, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, benzyloxy, C_1-C_6 thioalkoxy, -CO_2(C_1-C_5 alkyl), CO_2H, CN, -C(O)$NR_{20}R_{21}$, CF_3, or OCF_3; wherein

R_{20} and R_{21} are independently H, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy C_1-C_6 alkyl, or

R_{20}, R_{21}, and the nitrogen to which they are attached form a piperazinyl, or morpholinyl ring, each of which is optionally substituted with 1 or 2 groups that are independently alkyl or halogen.

Embodiment 116. Compounds according to embodiment 102 or embodiment 103, wherein

R_5 is isoquinolinyl, isoindolyl, indol-2-onyl, quinolinyl(C_1-C_6) alkyl, isoquinolinyl(C_1-C_6) alkyl, isoindolyl(C_1-C_6) alkyl, indol-2-onyl(C_1-C_6) alkyl, wherein

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, halogen, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, benzyloxy, C_1-C_6 thioalkoxy, -CO_2(C_1-C_5 alkyl), CO_2H, CN, amidinooxime, NR_8R_9, NR_6R_7-(C_1-C_6 alkyl)-, -C(O)NR_6R_7, amidino, CF_3, or OCF_3.

Embodiment 117. Compounds according to embodiment 1 or 2, wherein

R_1 is H, halogen, methyl, ethyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, or carboxaldehyde;

R_2 is benzyloxy, OH, phenyloxy, phenyloxy(C_1-C_6)alkyl, or phenyl (C_1-C_4) thioalkoxy, wherein each of the above is

optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, -(C_1-C_6)alkyl-N(R)-CO_2R_{30}, NR_6R_7, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, (C_1-C_6) alkyl, pyridyl, or NR_6R_7-(C_1-C_6 alkyl)-; and

R_4 is H, (C_1-C_4) alkyl optionally substituted with one or two groups that are independently CO_2H, -CO_2alkyl, -C(O)NRR, -N(R_{30})C(O)NRR, -N(R_{30})C(O)-(C_1-C_6)alkoxy, or -NR_6R_7, or hydroxy(C_1-C_4)alkyl;

R_5 is C_3-C_7 cycloalkyl or C_3-C_7 cycloalkylalkyl, each of which is optionally substituted with 1 or 2 groups that are independently alkyl, alkoxy, halogen, -NR_6R_7, or NR_6R_7-(C_1-C_6 alkyl)-, wherein each of the alkyl groups is optionally substituted with 1 or 2 groups that are independently OH, methoxy, NH_2, or halogen.

Embodiment 118. Compounds according to embodiment 117, wherein

R_5 is C_3-C_7 cycloalkyl or C_3-C_7 cycloalkyl C_1-C_4 alkyl, each of which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, -NR_6R_7, or NR_6R_7-(C_1-C_6 alkyl)- wherein each of the alkyl groups is optionally substituted with 1 or 2 groups that are independently OH, methoxy, or NH_2;

R_6 and R_7 are independently at each occurrence H, C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxy, C_1-C_4 alkoxy C_1-C_4 alkyl, C_1-C_4 alkanoyl, benzyl, benzyloxy, or phenyl C_1-C_4 alkanoyl, wherein each is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, OH, SH, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, CF_3, or OCF_3; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are

independently C_1-C_4 alkyl, hydroxy, hydroxy C_1-C_4 alkyl, or halogen.

Embodiment 119. Compounds according to embodiment 118, wherein

R_1 is H, halogen, methyl, ethyl;

R_2 is benzyloxy, phenyloxy, phenyloxy(C_1-C_6)alkyl, or phenyl (C_1-C_4) thioalkoxy, wherein each of the above is optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, -(C_1-C_6)alkyl-N(R)-CO_2R_{30}, amino, mono or dialkylamino, -NR_6R_7, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, (C_1-C_6) alkyl, or NR_6R_7-(C_1-C_6 alkyl)-; and

R_4 is H, methyl, (C_1-C_4)alkyl optionally substituted with one or two groups that are independently CO_2H, -CO_2alkyl, -C(O)NRR, -N(R_{30})C(O)NRR, -N(R_{30})C(O)-(C_1-C_6)alkoxy, or -NR_6R_7 or hydroxy(C_1-C_2)alkyl.

Embodiment 120. Compounds according to embodiment 119, wherein

R_2 is substituted with two halogens and is further optionally substituted with 1 or 2 groups that are independently halogen, -(C_1-C_6)alkyl-N(R)-CO_2R_{30}, amino, mono or dialkylamino, -NR_6R_7, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, (C_1-C_6) alkyl, or NR_6R_7-(C_1-C_6 alkyl).

Embodiment 121. Compounds according to embodiment 1 or 2, wherein

R_5 is H, alkyl optionally substituted with 1, 2, or 3 groups that are independently phenylalkoxycarbonyl, -NR_8R_9, halogen, -C(O)NR_8R_9, alkoxycarbonyl, or alkanoyl, alkoxyalkyl optionally substituted with one trimethylsilyl group, alkoxycarbonyl, amino, hydroxyalkyl, alkenyl optionally substituted with

alkoxycarbonyl, alkynyl, -SO_2-alkyl, or alkoxy optionally substituted with one trimethylsilyl group, wherein

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, halogen, alkoxy, phenylalkoxy, thioalkoxy, -SO_2alkyl, alkoxycarbonyl, phenylalkoxycarbonyl, CO_2H, CN, OH, amidinooxime, NR_8R_9, NR_6R_7-(C_1-C_6 alkyl)-, -$C(O)NR_6R_7$, amidino, hydroxyalkyl, carboxaldehyde, -NR_6R_7, haloalkyl, or haloalkoxy;

wherein R_8 is hydrogen, alkyl, alkanoyl, phenylalkyl and arylalkanoyl; and

wherein R_9 is alkyl, alkanoyl, phenylalkyl, heteroaryl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, and arylalkanoyl.

In this embodiment, it is preferred that when R_2 is benzyloxy, R_4 is H, and R_5 is benzyl or methyl, R_1 is not hydrogen; and

no more than two of R_1, R_2, R_4, and R_5 are simultaneously hydrogen.

Embodiment 122. Compounds according to embodiment 1 or 2, wherein

R_5 is H, alkyl optionally substituted with 1, 2, or 3 groups that are independently phenylalkoxycarbonyl, -NR_8R_9, halogen, -$C(O)NR_8R_9$, alkoxycarbonyl, or alkanoyl, alkoxyalkyl optionally substituted with one trimethylsilyl group, alkoxycarbonyl, amino, hydroxyalkyl, alkenyl optionally substituted with alkoxycarbonyl, alkynyl, -SO_2-alkyl, alkoxy optionally substituted with one trimethylsilyl group, wherein

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, halogen, alkoxy, phenylalkoxy, thioalkoxy, -SO_2alkyl,

alkoxycarbonyl, phenylalkoxycarbonyl, CO_2H, CN, OH, amidinooxime, NR_8R_9, NR_6R_7-(C_1-C_6 alkyl)-, $-C(O)NR_6R_7$, amidino, hydroxyalkyl, carboxaldehyde, $-NR_6R_7$, haloalkyl, or haloalkoxy;

wherein R_8 is hydrogen, alkyl, alkanoyl, phenylalkyl and arylalkanoyl; and

wherein R_9 is alkyl, alkanoyl, phenylalkyl, heteroaryl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, and arylalkanoyl.

In this embodiment, it is preferred that when R_2 is benzyloxy, R_4 is H, and R_5 is benzyl or methyl, R_1 is not hydrogen; and

no more than two of R_1, R_2, R_4, and R_5 are simultaneously hydrogen.

Embodiment 123. Compounds according to any one of embodiments 117, 118, 119, 120, 121, or 122, wherein

R_1 is H, halogen, methyl, ethyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, or carboxaldehyde;

R_2 is benzyloxy, OH, phenyloxy, phenyloxy(C_1-C_6)alkyl, or phenyl (C_1-C_4) thioalkoxy, wherein each of the above is optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, -(C_1-C_6)alkyl-N(R)-CO_2R_{30}, NR_6R_7, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, (C_1-C_6) alkyl, pyridyl, or NR_6R_7-(C_1-C_6 alkyl)-; and

R_4 is H, (C_1-C_4) alkyl optionally substituted with one or two groups that are independently CO_2H, $-CO_2$alkyl, -C(O)NRR, -$N(R_{30})C(O)NRR$, $-N(R_{30})C(O)$-(C_1-C_6)alkoxy, or $-NR_6R_7$, or hydroxy(C_1-C_4)alkyl.

Embodiment 123A. Compounds according to embodiment 122, wherein

R_5 is H, alkyl optionally substituted with 1, 2, or 3 groups that are independently phenylalkoxycarbonyl, $-NR_8R_9$, halogen, $-C(O)NR_8R_9$, alkoxycarbonyl, or alkanoyl, alkoxyalkyl optionally substituted with one trimethylsilyl group, alkoxycarbonyl, amino, hydroxyalkyl, alkenyl optionally substituted with alkoxycarbonyl, alkynyl, $-SO_2$-alkyl, alkoxy optionally substituted with one trimethylsilyl group, wherein

wherein R_8 is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkanoyl, phenyl C_1-C_4 alkyl and phenyl C_1-C_4 alkanoyl;

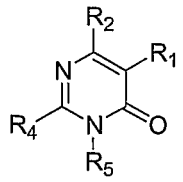
wherein R_9 is C_1-C_4 alkyl, C_1-C_4 alkanoyl, phenyl C_1-C_4 alkyl, pyridyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, and phenyl C_1-C_4 alkanoyl.

Embodiment 124. Compounds according to embodiment 123A, wherein

R_5 is C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently phenyl C_1-C_4 alkoxycarbonyl, NH_2, mono C_1-C_4 alkylamino, di C_1-C_4 alkylamino, halogen, $-C(O)NH_2$, $-C(O)NH(C_1$-C_6 alkyl) wherein the alkyl is optionally substituted with OH, NH_2, or methoxy, $-C(O)N(C_1$-C_6 alkyl) (C_1-C_6 alkyl) wherein each alkyl is optionally substituted with OH, NH_2, or methoxy, C_1-C_4 alkoxycarbonyl, and C_1-C_4 alkanoyl, or

R_5 is C_1-C_4 alkoxy C_1-C_4 alkyl, C_1-C_4 alkoxycarbonyl, amino, C_1-C_4 hydroxyalkyl, C_2-C_4 alkenyl optionally substituted with C_1-C_4 alkoxycarbonyl, C_2-C_4 alkynyl, $-SO_2$- C_1-C_4 alkyl, or C_1-C_4 alkoxy.

Embodiment 125. A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein

R_1 is halogen, NO_2, alkyl, carboxaldehyde, hydroxyalkyl, arylalkoxy, arylalkyl, CN, aryl, alkanoyl, alkoxy, alkoxyalkyl, haloalkyl, or arylalkanoyl,

wherein the aryl portion of arylalkoxy, arylalkyl, and arylalkanoyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, (C_1-C_4)alkyl, (C_1-C_4) alkoxy, nitro, CN, haloalkyl, haloalkoxy or CO_2H;

wherein the alkyl portion of the alkyl, hydroxyalkyl, arylalkoxy, arylalkyl, alkanoyl, alkoxy, alkoxyalkyl and arylalkanoyl groups is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, C_1-C_4 alkoxy, C_1-C_4 alkoxycarbonyl, or spirocyclopropyl;

R_2 is aryl, heteroaryl, arylalkenyl, arylalkoxy, aryloxyalkyl, arylalkyl, OH, alkynyl, aryloxy, aryloxyalkyl, arylthioalkoxy, alkoxy, $-OC(O)NH(CH_2)_n$aryl, $-OC(O)N(alkyl)(CH_2)_n$aryl, $-OSO_2(C_1-C_6)$alkyl, $-OSO_2$aryl, alkyl, alkoxyalkoxy, NR_8R_9, or CO_2H, wherein

n is 0, 1, 2, 3, 4, 5 or 6;

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, $-(C_1-C_6)$alkyl$-N(R)-CO_2R_{30}$, alkoxy, alkoxycarbonyl, CN, NR_6R_7, haloalkyl, haloalkoxy, alkyl, heteroaryl, heteroarylalkyl, $NR_6R_7-(C_1-C_6$ alkyl$)-$, phenyl, $-SO_2-$phenyl wherein the phenyl groups are optionally substituted with 1, 2, or 3 groups that are independently halogen or NO_2; or $-OC(O)NR_6R_7$, wherein

R_6 and R_7 are independently at each occurrence H, alkyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, -SO_2-alkyl, OH, hydroxyalkyl, -(C_1-C_4)alkyl-CO_2-alkyl, heteroarylalkyl, alkanoyl, arylalkyl, arylalkoxy, or arylalkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, alkoxy, heterocycloalkyl, OH, SH, C_3-C_6 cycloalkyl, NH_2, NH(alkyl), N(alkyl)(alkyl), -O-alkanoyl, alkyl, haloalkyl, or haloalkoxy; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, hydroxy C_1-C_4 alkyl, or halogen;

R at each occurrence is independently H or C_1-C_6 alkyl;

R_{30} is C_1-C_6 alkyl optionally substituted with 1 or 2 groups that are independently OH, SH, halogen, amino, monoalkylamino, dialkylamino or C_3-C_6 cycloalkyl;

R_4 is H, alkyl optionally substituted with one or two groups that are independently CO_2H, -CO_2alkyl, -C(O)NRR, -N(R_{30})C(O)NRR, -N(R_{30})C(O)-(C_1-C_6)alkoxy, or -NR_6R_7, arylalkoxy, arylalkyl, hydroxyalkyl, haloalkyl, alkoxy, carboxaldehyde, CO_2H, alkoxyalkyl, or alkoxyalkoxy, wherein

the aryl portion of arylalkoxy, arylalkyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, hydroxy, alkoxy, alkyl, nitro, haloalkyl, or haloalkoxy; and

R_5 is H, arylalkyl, alkyl, aryl, alkoxy, heterocycloalkylalkyl, heteroarylalkyl, heterocycloalkyl, cycloalkyl, cycloalkylalkyl, -alkyl-S-aryl, -alkyl-SO_2-aryl, -(C_1-C_4) alkyl-C(O)-heterocycloalkyl, -SO_2-aryl, or heteroaryl, wherein

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, halogen, alkoxy, aryl, arylalkoxy, thioalkoxy, alkoxycarbonyl, arylalkoxycarbonyl, OH, CO_2H, CN, amidinooxime, NR_8R_9, NR_6R_7-(C_1-C_6 alkyl)-, -C(O)NR_6R_7, -(C_1-C_4 alkyl)-C(O)NR_6R_7, amidino, hydroxyalkyl, -SO_2alkyl, -SO_2H, -$SO_2NR_6R_7$, -NR_6R_7, alkanoyl wherein the alkyl portion is optionally substituted with OH, halogen or alkoxy, haloalkyl, -(C_1-C_4 alkyl)-NR_{15}C(O)$NR_{16}R_{17}$, -(C_1-C_4 alkyl)-NR_{15}C(O)R_{18}, -O-CH_2-O, -O-CH_2CH_2-O-, or haloalkoxy; wherein

R_8 at each occurrence is independently hydrogen, alkyl, alkanoyl, arylalkyl and arylalkanoyl wherein each of the above is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, alkoxy, alkoxycarbonyl, halogen, or haloalkyl; and

R_9 at each occurrence is independently alkyl, alkanoyl, arylalkyl cycloalkyl, alkenyl, heteroaryl, cycloalkylalkyl, arylalkanoyl, -SO_2-phenyl, and aryl wherein each of the above is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, alkoxy, alkoxycarbonyl, halogen, or haloalkyl;

R_{15} is H or C_1-C_6 alkyl;

R_{16} and R_{17} are independently H or C_1-C_6 alkyl; or

R_{16}, R_{17}, and the nitrogen to which they are attached form a morpholinyl ring; and

R_{18} is C_1-C_6 alkyl optionally substituted with -O-(C_2-C_6 alkanoyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl; amino C_1-C_6 alkyl, mono or dialkylamino C_1-C_6 alkyl.

In this embodiment, it is preferred that:

R_6 and R_7 are not simultaneously OH;

R_6 and R_7 are not simultaneously -SO_2(C_1-C_6 alkyl);

when R_2 is OH, R_4 is methyl and R_5 is phenyl, R_1 is not acetyl; and

R_4 and R_5 are not simultaneously hydrogen.

Embodiment 126. Compounds according to embodiment 125 wherein

R_1 is halogen, C_1-C_6 alkyl, phenyl, carboxaldehyde, C_1-C_6 hydroxyalkyl, phenyl C_1-C_6 alkoxy, phenyl C_1-C_6 alkyl, CN, C_1-C_6 alkanoyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, C_1-C_6 haloalkyl, or phenyl C_1-C_6 alkanoyl,

wherein the above phenyl groups are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, (C_1-C_4)alkyl, (C_1-C_4) alkoxy, nitro, CN, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy or CO_2H;

wherein the above alkyl groups are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, methoxy, or ethoxy,

R_2 is phenylalkoxy, OH, phenyloxy, phenyloxy(C_1-C_6)alkyl, phenylthio(C_1-C_4)alkoxy, alkoxy, alkenyl, phenethyl, -OC(O)NH(CH_2)$_n$phenyl, -OC(O)N(alkyl)(CH_2)$_n$phenyl, alkyl, alkoxyalkoxy, NR_8R_9, pyridyl, pyrimidyl, pyridazyl, pyrazolyl, imidazolyl, pyrrolyl, tetrahydroquinolinyl, amino, tetrahydroisoquinolinyl, tetrazolyl, pyrazinyl, benzimidazolyl, triazinyl, tetrahydrofuryl, piperidinyl, hexahydropyrimidinyl, thiazolyl, thienyl, or CO_2H, wherein n is 0, 1, 2, or 3;

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, -(C_1-C_6)alkyl-N(R)-CO_2R_{30}, haloalkyl, haloalkoxy, alkyl, thienyl, pyridyl, or phenyl optionally substituted with 1, 2, or 3 halogens;

R_6 and R_7 are independently at each occurrence H, alkyl, alkoxy, alkoxyalkyl, hydroxyalkyl, alkoxycarbonyl, -(C_1-C_4)alkyl-CO_2-alkyl, alkanoyl, phenylalkyl, phenylalkoxy, or phenylalkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, OH, SH, C_3-C_6 cycloalkyl, alkoxy, NH_2, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)(C_1-C_6 alkyl), alkyl, CF_3 or OCF_3; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, hydroxy, hydroxy C_1-C_4 alkyl, or halogen;

R_4 is H, alkyl optionally substituted with one or two groups that are independently CO_2H, -CO_2alkyl, -C(O)NRR, -N(R_{30})C(O)NRR, -N(R_{30})C(O)-(C_1-C_6)alkoxy, or -NR_6R_7, phenylalkoxy, phenylalkyl, hydroxyalkyl, carboxaldehyde, haloalkyl, alkoxy, alkoxyalkyl, or alkoxyalkoxy, wherein the above phenyl groups are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, hydroxy, alkoxy, alkyl, nitro, haloalkyl, or haloalkoxy; and

R_5 is benzyl, phenethyl, (C_1-C_6)alkyl, phenyl, naphthyl, alkoxy, piperidinyl, pyrrolidinyl, imidazolidinyl, piperazinyl, isoquinolinyl, tetrahydroisoquinolinyl, indolyl, 1H-indazolyl, pyridyl, pyrimidyl, pyridazyl, pyrazinyl, piperidinyl(C_1-C_6)alkyl, pyrrolidinyl(C_1-

C_6)alkyl, imidazolidinyl(C_1-C_6)alkyl, piperazinyl(C_1-C_6)alkyl, pyridyl(C_1-C_6)alkyl, pyrimidyl(C_1-C_6)alkyl, pyridazyl(C_1-C_6)alkyl, pyrazinyl(C_1-C_6)alkyl, isoquinolinyl(C_1-C_6)alkyl, tetrahydroisoquinolinyl(C_1-C_6)alkyl, indolyl(C_1-C_6)alkyl, or 1H-indazolyl(C_1-C_6)alkyl, and wherein

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, halogen, alkoxy, hydroxyalkyl, phenylalkoxy, thioalkoxy, alkoxycarbonyl, phenylalkoxycarbonyl, OH, CO_2H, CN, amidinooxime, NR_8R_9, NR_6R_7-(C_1-C_6 alkyl)-, -C(O)NR_6R_7, amidino, piperazinyl, morpholinyl, -SO_2(C_1-C_6) alkyl, -SO_2NH_2, -SO_2NH(C_1-C_6)alkyl, -SO_2N(C_1-C_6)alkyl (C_1-C_6)alkyl, haloalkyl, or haloalkoxy.

In this embodiment, it is preferred that when R_2 is OH, R_4 is methyl and R_5 is phenyl, R_1 is not acetyl; and

R_4 and R_5 are not simultaneously hydrogen.

Embodiment 127. Compounds according to embodiment 126 wherein

R_1 is halogen, alkyl, carboxaldehyde, hydroxyalkyl, phenylalkoxy, phenyl, benzyl, phenethyl, phenpropyl, phenbutyl, CN, (C_2-C_6)alkanoyl, haloalkyl, or phenylCO-, phenylCH_2CO-, phenylCH_2CH_2CO-,

wherein the above phenyl groups are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, (C_1-C_4)alkyl, (C_1-C_4) alkoxy, nitro, CN, haloalkyl, haloalkoxy or CO_2H;

wherein the above alkyl groups are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, methoxy, or ethoxy,

R_2 is benzyloxy, phenethyloxy, phenpropyloxy, OH, phenyloxy, phenyloxy(C_1-C_6)alkyl, phenylthio(C_1-C_4)alkoxy, NR_8R_9, (C_1-

C_6)alkyl, alkynyl, phenethyl, -OC(O)N(CH_3)CH_2phenyl, alkoxyalkoxy, pyridyl, pyrimidyl, pyridazyl, pyrazolyl, imidazolyl, pyrrolyl, pyrazinyl, piperidinyl, hexahydropyrimidinyl, benzimidazolyl, or thienyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, -(C_1-C_6)alkyl-N(R)-CO_2R_{30}, CF_3, OCF_3, (C_1-C_4)alkyl, thienyl, pyridyl, or phenyl optionally substituted with 1, 2, or 3 halogens;

R_6 and R_7 are independently at each occurrence H, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, hydroxy(C_1-C_6)alkyl, -(C_1-C_4)alkyl-CO_2-alkyl, (C_1-C_6)alkanoyl, phenyl(C_1-C_6)alkyl, phenyl(C_1-C_6)alkoxy, or phenyl(C_1-C_6)alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, (C_1-C_6)alkoxy, NH_2, OH, SH, C_3-C_6 cycloalkyl, (C_1-C_6)alkyl, CF_3 or OCF_3; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, hydroxy, hydroxy C_1-C_4 alkyl, or halogen;

R_4 is H, alkyl optionally substituted with one or two groups that are independently CO_2H, -CO_2alkyl, -C(O)NRR, -N(R_{30})C(O)NRR, -N(R_{30})C(O)-(C_1-C_6)alkoxy, or -NR_6R_7, benzyloxy, phenethyloxy, phenpropyloxy, benzyl, phenethyl, phenpropyl, hydroxyalkyl, halo(C_1-C_4)alkyl, carboxaldehyde, alkoxy, alkoxyalkyl, or alkoxyalkoxy, wherein

the above phenyl groups are unsubstituted or substituted with 1, 2, or 3 groups that are independently

halogen, hydroxy, alkoxy, alkyl, nitro, CF_3 or OCF_3; and

R_5 is benzyl, phenethyl, phenpropyl, phenbutyl, (C_1-C_6)alkyl, phenyl, piperidinyl, pyrrolidinyl, imidazolidinyl, piperidinyl(C_1-C_6)alkyl, pyrrolidinyl(C_1-C_6)alkyl, imidazolidinyl(C_1-C_6)alkyl, pyridyl, pyrimidyl, pyridazyl, pyrazinyl, pyridyl(C_1-C_6)alkyl, pyrimidyl(C_1-C_6)alkyl, pyridazyl(C_1-C_6)alkyl, or pyrazinyl(C_1-C_6)alkyl wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, halogen, haloalkyl, NR_8R_9, NR_6R_7-$(C_1-C_6$ alkyl)-, carboxaldehyde, morpholinyl, SO_2NH_2, SO_2NH(alkyl), SO_2N(alkyl)(alkyl), alkoxy, hydroxyalkyl, benzyloxy, thioalkoxy, OH, CO_2H, CN, $-CO_2(C_1-C_5$ alkyl), phenylalkoxycarbonyl, amidinooxime, amidino, $-C(O)NR_6R_7$, CF_3, CF_2CF_3, $ClCH_2$, or OCF_3.

In this embodiment, it is preferred that when R_2 is OH, R_4 is methyl and R_5 is phenyl, R_1 is not acetyl.

Embodiment 128. Compounds according to embodiment 127 wherein

R_1 is halogen, alkyl, carboxaldehyde, hydroxy(C_1-C_4)alkyl, phenylalkoxy, benzyl, phenethyl, $-C(O)CH_3$, phenylCO-, or phenylCH_2CO-,

wherein the above phenyl groups are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, (C_1-C_4)alkyl, (C_1-C_4) alkoxy, nitro, CN, CF_3, or OCF_3;

wherein the above alkyl groups are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, methoxy, or ethoxy;

R_2 is benzyloxy, phenethyloxy, phenpropyloxy, OH, phenyloxy, phenyloxy(C_1-C_6)alkyl, phenethyl, NR_8R_9, -S-benzyl, or (C_1-C_6)alkyl, wherein

each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, -(C_1-C_6)alkyl-N(R)-CO_2R_{30}, CF_3, OCF_3, alkyl, thienyl, or pyridyl;

R_6 and R_7 are independently at each occurrence H, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, hydroxy(C_1-C_6)alkyl, -(C_1-C_4)alkyl-CO_2-alkyl, (C_1-C_6)alkanoyl, phenyl(C_1-C_6)alkyl, phenyl(C_1-C_6)alkoxy, or phenyl(C_1-C_6)alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, (C_1-C_6)alkoxy, NH_2, OH, SH, C_3-C_6 cycloalkyl, (C_1-C_6)alkyl, CF_3 or OCF_3; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, hydroxy, hydroxy C_1-C_4 alkyl, or halogen;

R_4 is H, alkyl optionally substituted with one or two groups that are independently CO_2H, -CO_2alkyl, -C(O)NRR, -N(R_{30})C(O)NRR, -N(R_{30})C(O)-(C_1-C_6)alkoxy, or -NR_6R_7, benzyloxy, phenethyloxy, phenpropyloxy, benzyl, or hydroxyalkyl, wherein

the above phenyl groups are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, hydroxy, alkoxy, alkyl, nitro, CF_3 or OCF_3; and

R_5 is benzyl, phenethyl, phenpropyl, phenbutyl, (C_1-C_6)alkyl, phenyl, pyridyl, pyrazinyl, pyrimidinyl, pyrazinyl(C_1-

C_6)alkyl, pyrimidinyl(C_1-C_6)alkyl, or pyridyl(C_1-C_4)alkyl, wherein

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, halogen, haloalkyl, morpholinyl, $-SO_2$ (C_1-C_6) alkyl, $-SO_2NH_2$, $-SO_2NH(C_1$-$C_6)$, $-SO_2N(C_1$-$C_6)(C_1$-$C_6)$, (C_1-C_4)alkoxy, phenyl(C_1-C_4)alkoxy, thio(C_1-C_4)alkoxy, (C_1-C_4)alkoxycarbonyl, OH, CO_2H, CN, amidinooxime, amidino, NR_8R_9, NR_6R_7-(C_1-C_6 alkyl)-, hydroxyalkyl, $CONR_6R_7$, CF_3, or OCF_3.

Embodiment 129. Compounds according to embodiment 128 wherein

R_1 is halogen, alkyl, carboxaldehyde, or hydroxyalkyl;

R_2 is benzyloxy, phenethyloxy, phenpropyloxy, OH, phenyloxy, phenyloxy(C_1-C_6)alkyl, phenethyl, phenylthioalkoxy, or (C_1-C_6)alkyl, wherein

each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, -(C_1-C_6)alkyl-N(R)-CO_2R_{30}, CF_3, OCF_3, alkyl, thienyl, or pyridyl;

R_4 is H, (C_1-C_4) alkyl optionally substituted with one or two groups that are independently CO_2H, $-CO_2$alkyl, -C(O)NRR, $-N(R_{30})C(O)NRR$, $-N(R_{30})C(O)$-(C_1-C_6)alkoxy, or $-NR_6R_7$, benzyloxy, or phenethyloxy, wherein

the above phenyl groups are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, hydroxy, (C_1-C_4)alkoxy, (C_1-C_4)alkyl, nitro, CF_3 or OCF_3; and

R_5 is benzyl, phenethyl, (C_1-C_6)alkyl, phenyl, indazolyl, or pyridyl, wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently (C_1-C_4)alkyl, halogen, OH, CO_2H, CN,

(C_1-C_4)alkoxy, -C(O)pyrrolidine, -SO_2 (C_1-C_6) alkyl, benzyloxy, -CO_2(C_1-C_5 alkyl), amidino, thio(C_1-C_4)alkoxy, amidinooxime, CF_3, NR_8R_9, NR_6R_7-(C_1-C_6 alkyl)-, $CONR_6R_7$, or OCF_3.

Embodiment 130. Compounds according to embodiment 129 wherein

R_1 is chloro, bromo, iodo, methyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl; and

R_5 is benzyl, phenethyl, phenpropyl, phenyl, or pyridyl, each of which is unsubstituted or substituted with 1, 2, or 3 groups that are independently alkyl, OH, halogen, alkoxy, NH_2, NH(C_1-C_6)alkyl, N(C_1-C_6)alkyl(C_1-C_6)alkyl, NR_8R_9, NR_6R_7-(C_1-C_6 alkyl)-, $CONR_6R_7$, and amidinooxime; wherein

R_6 and R_7 are independently H, C_1-C_4 alkyl, C_1-C_6 alkanoyl, wherein the alkyl and alkanoyl groups are optionally substituted with 1, 2, or 3 groups that are independently OH, halogen, or C_3-C_7 cyclopropyl.

Embodiment 131. Compounds according to embodiment 130 wherein

R_2 is benzyloxy, phenethyl, phenyloxy(C_1-C_6)alkyl, or phenethyloxy, each of which is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, -(C_1-C_6)alkyl-N(R)-CO_2R_{30}, CF_3, OCF_3, or (C_1-C_4)alkyl.

Embodiment 132. Compounds according to embodiment 125, wherein

R_5 is benzyl, phenethyl, thienyl(C_1-C_6 alkyl), piperidinyl(C_1-C_6)alkyl, pyrrolidinyl(C_1-C_6)alkyl, imidazolidinyl(C_1-C_6)alkyl, piperazinyl(C_1-C_6)alkyl, pyridyl(C_1-C_6)alkyl, pyrimidyl(C_1-C_6)alkyl, pyridazyl(C_1-C_6)alkyl, pyrazinyl(C_1-

C_6)alkyl, isoquinolinyl(C_1-C_6)alkyl, tetrahydroisoquinolinyl(C_1-C_6)alkyl, indolyl(C_1-C_6)alkyl, or 1H-indazolyl(C_1-C_6)alkyl, wherein

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently (C_1-C_6)alkyl, halogen, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, phenyl(C_1-C_6)alkoxy, (C_1-C_6)thioalkoxy, (C_1-C_6)alkoxycarbonyl, phenyl(C_1-C_6)alkoxycarbonyl, OH, CO_2H, CN, amidinooxime, NR_8R_9, NR_6R_7-(C_1-C_6 alkyl)-, -$C(O)NR_6R_7$, amidino, piperazinyl, morpholinyl, -SO_2(C_1-C_6) alkyl, -SO_2NH_2, -SO_2NH(C_1-C_6)alkyl, -SO_2N(C_1-C_6)alkyl (C_1-C_6)alkyl, (C_1-C_4)haloalkyl, -(C_1-C_4 alkyl)-$NR_{15}C(O)NR_{16}R_{17}$, -(C_1-C_4 alkyl)-$NR_{15}C(O)R_{18}$, -O-CH_2-O, -O-CH_2CH_2-O-, or (C_1-C_4)haloalkoxy; wherein

R_6 and R_7 are independently at each occurrence H, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)hydroxyalkyl, -(C_1-C_4)alkyl-CO_2-(C_1-C_6)alkyl, (C_1-C_6)alkanoyl, phenyl(C_1-C_6)alkyl, phenyl(C_1-C_6)alkoxy, or phenyl(C_1-C_6)alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, (C_1-C_4)alkoxy, NH_2, OH, SH, C_3-C_6 cycloalkyl, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)(C_1-C_6 alkyl), (C_1-C_4)alkyl, CF_3 or OCF_3; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, hydroxy, hydroxy C_1-C_4 alkyl, or halogen; and

R_{18} is C_1-C_6 alkyl optionally substituted with -O-(C_2-C_6 alkanoyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl; amino C_1-C_6 alkyl, mono or dialkylamino C_1-C_6 alkyl.

In this embodiment, it is preferred that R_6 and R_7 are not simultaneously OH; and

R_6 and R_7 are not simultaneously -SO_2(C_1-C_6 alkyl).

Embodiment 133. Compounds according to embodiment 132, wherein

R_1 is halogen, methyl, ethyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, or carboxaldehyde;

R_2 is benzyloxy, OH, phenyloxy, phenyloxy(C_1-C_6)alkyl, or phenyl (C_1-C_4) thioalkoxy, wherein each of the above is optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, -(C_1-C_6)alkyl-N(R)-CO_2R_{30}, NR_6R_7, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, (C_1-C_6) alkyl, or pyridyl; and

R_4 is H, (C_1-C_4) alkyl optionally substituted with one or two groups that are independently CO_2H, -CO_2alkyl, -C(O)NRR, -N(R_{30})C(O)NRR, -N(R_{30})C(O)-(C_1-C_6)alkoxy, or -NR_6R_7, or hydroxy(C_1-C_4)alkyl.

Embodiment 134. Compounds according to embodiment 133, wherein

R_5 is benzyl, or phenethyl, wherein each is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently (C_1-C_6)alkyl, halogen, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, phenyl(C_1-C_6)alkoxy, (C_1-C_6)thioalkoxy, (C_1-C_6)alkoxycarbonyl, phenyl(C_1-C_6)alkoxycarbonyl, OH, CO_2H, CN, amidinooxime, NR_8R_9, NR_6R_7-(C_1-C_6 alkyl)-, -C(O)NR_6R_7, -(C_1-C_4 alkyl)-C(O)NR_6R_7amidino, piperazinyl, morpholinyl, -SO_2 (C_1-C_6) alkyl, -SO_2NH_2, -SO_2NH(C_1-

C_6)alkyl, $-SO_2N(C_1-C_6)$alkyl (C_1-C_6)alkyl, (C_1-C_4)haloalkyl, $-(C_1-C_4$ alkyl)$-NR_{15}C(O)R_{18}$, $-O-CH_2-O$, $-O-CH_2CH_2-O-$, or (C_1-C_4)haloalkoxy; wherein

R_6 and R_7 are independently at each occurrence H, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)hydroxyalkyl, $-(C_1-C_4)$alkyl$-CO_2-(C_1-C_6)$alkyl, (C_1-C_6)alkanoyl, phenyl(C_1-C_6)alkyl, phenyl(C_1-C_6)alkoxy, or phenyl(C_1-C_6)alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, (C_1-C_4)alkoxy, NH_2, OH, SH, C_3-C_6 cycloalkyl, $NH(C_1-C_6$ alkyl), $N(C_1-C_6$ alkyl)$(C_1-C_6$ alkyl), (C_1-C_4)alkyl, CF_3 or OCF_3; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, hydroxy, hydroxy C_1-C_4 alkyl, or halogen; and

R_{18} is C_1-C_6 alkyl optionally substituted with $-O-(C_2-C_6$ alkanoyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, amino C_1-C_6 alkyl, or mono or dialkylamino C_1-C_6 alkyl.

In this embodiment, it is preferred that R_6 and R_7 are not simultaneously OH; and

R_6 and R_7 are not simultaneously $-SO_2(C_1-C_6$ alkyl).

Embodiment 135. Compounds according to embodiment 134, wherein

R_5 is benzyl or phenethyl, wherein each is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, $-C(O)NR_6R_7$, $-(C_1-C_4$ alkyl)$-C(O)NR_6R_7$, NR_8R_9, halogen, C_1-C_6 alkoxy, CO_2H, $-(C_1-C_4$

alkyl)-CO_2H, C_1-C_6 thioalkoxy, amidinooxime, C_1-C_6 alkoxycarbonyl, -(C_1-C_4 alkyl)-C_1-C_6 alkoxycarbonyl, C_1-C_6 hydroxyalkyl, -(C_1-C_4 alkyl)-CN, CN, phenyl C_1-C_6 alkoxy, OH, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, NR_6R_7-(C_1-C_6 alkyl)-, -(C_1-C_4 alkyl)-$NR_{15}C(O)R_{18}$, amidinooxime, -SO_2(C_1-C_6 alkyl), -O-CH_2-O-, -O-CH_2CH_2-O-, phenyl C_1-C_4 alkoxy, or phenyl; wherein

R_6 and R_7 at each occurrence are independently H, OH, C_1-C_6 alkyl, amino C_1-C_4 alkyl, NH(C_1-C_6 alkyl)alkyl, N(C_1-C_6 alkyl)(C_1-C_6 alkyl) C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy C_1-C_6 alkyl, -SO_2(C_1-C_6 alkyl) each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, OH, CF_3, or OCF_3;

or

R_6, R_7, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl, thiomorpholinyl, ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy C_1-C_4 alkyl, or halogen,

R_{18} is C_1-C_6 alkyl optionally substituted with -O-(C_2-C_6 alkanoyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl; amino C_1-C_6 alkyl, mono or dialkylamino C_1-C_6 alkyl.

In this embodiment, it is preferred that R_6 and R_7 are not simultaneously OH; and

R_6 and R_7 are not simultaneously -SO_2(C_1-C_6 alkyl).

Embodiment 136. Compounds according to embodiment 135, wherein

R_5 is benzyl or phenethyl, wherein each is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, $-C(O)NR_6R_7$, $-(C_1$-C_4 alkyl)-$C(O)NR_6R_7$, halogen, C_1-C_6 alkoxy, CO_2H, $-(C_1$-C_4 alkyl)-CO_2H, C_1-C_6 thioalkoxy, amidinooxime, C_1-C_6 alkoxycarbonyl, $-(C_1$-C_4 alkyl)-C_1-C_6 alkoxycarbonyl, C_1-C_6 hydroxyalkyl, $-(C_1$-C_4 alkyl)-CN, CN, phenyl C_1-C_6 alkoxy, OH, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, NR_6R_7-(C_1-C_6 alkyl)-, NR_8R_9, $-(C_1$-C_4 alkyl)-$NR_{15}C(O)R_{18}$, amidinooxime, $-SO_2(C_1$-C_6 alkyl), $-O-CH_2-O-$, $-O-CH_2CH_2-O-$, phenyl C_1-C_4 alkoxy, or phenyl; wherein

R_6 and R_7 at each occurrence are independently H, OH, C_1-C_6 alkyl, amino C_1-C_4 alkyl, $NH(C_1$-C_6 alkyl)alkyl, $N(C_1$-C_6 alkyl)(C_1-C_6 alkyl) C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy C_1-C_6 alkyl, $-SO_2(C_1$-C_6 alkyl) each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, OH, CF_3, or OCF_3; and

R_{18} is C_1-C_6 alkyl optionally substituted with $-O-(C_2$-C_6 alkanoyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl; amino C_1-C_6 alkyl, mono or dialkylamino C_1-C_6 alkyl.

In this embodiment, it is preferred that R_6 and R_7 are not simultaneously OH; and

R_6 and R_7 are not simultaneously $-SO_2(C_1$-C_6 alkyl).

Embodiment 137. Compounds according to embodiment 136, wherein

R_5 is benzyl which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_4 alkyl, $-C(O)NR_6R_7$, $-(C_1$-C_4 alkyl)-$C(O)NR_6R_7$, halogen, C_1-C_4 alkoxy, CO_2H, C_1-C_4 thioalkoxy, C_1-C_4 alkoxycarbonyl, C_1-C_6 hydroxyalkyl, CN,

OH, NR_6R_7-(C_1-C_6 alkyl)-, NR_8R_9, -SO_2(C_1-C_6 alkyl), or benzyloxy; wherein

R_6 and R_7 at each occurrence are independently H, OH, C_1-C_6 alkyl, amino C_1-C_4 alkyl, NH(C_1-C_6 alkyl)alkyl, N(C_1-C_6 alkyl)(C_1-C_6 alkyl) C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy C_1-C_6 alkyl, -SO_2(C_1-C_6 alkyl) each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, OH, CF_3, or OCF_3.

In this embodiment, it is preferred that R_6 and R_7 are not simultaneously OH; and

R_6 and R_7 are not simultaneously -SO_2(C_1-C_6 alkyl).

Embodiment 138. Compounds according to embodiment 137, wherein

R_5 is benzyl which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_4 alkyl, -C(O)NR_6R_7, -(C_1-C_4 alkyl)-C(O)NR_6R_7, halogen, C_1-C_4 alkoxy, C_1-C_4 thioalkoxy, C_1-C_4 alkoxycarbonyl, C_1-C_6 hydroxyalkyl, CN, NR_8R_9, or NR_6R_7-(C_1-C_6 alkyl)-; wherein

R_6 and R_7 at each occurrence are independently H, OH, C_1-C_6 alkyl, amino C_1-C_4 alkyl, NH(C_1-C_6 alkyl)alkyl, N(C_1-C_6 alkyl)(C_1-C_6 alkyl) C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, or C_1-C_4 alkoxy C_1-C_4 alkyl each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, OH, CF_3, or OCF_3.

In this embodiment, it is preferred that R_6 and R_7 are not simultaneously OH.

Embodiment 139. Compounds according to embodiment 138, wherein

the R_5 group is disubstituted with two groups that are meta to each other.

Embodiment 140. Compounds according to embodiment 135, wherein

R_5 is benzyl which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_4 alkyl, $-C(O)NR_6R_7$, $-(C_1$-C_4 alkyl$)-C(O)NR_6R_7$, NR_8R_9, $NR_6R_7-(C_1$-C_6 alkyl$)-$, halogen, C_1-C_4 alkoxy, CO_2H, $-(C_1$-C_4 alkyl$)-CO_2H$, $-(C_1$-C_4 alkyl$)-C_1$-C_6 alkoxycarbonyl, $-(C_1$-C_4 alkyl$)-CN$, CN, phenyl C_1-C_6 alkoxy, CF_3, OCF_3, $-(C_1$-C_4 alkyl$)-NR_{15}C(O)R_{18}$, amidinooxime, $-O-CH_2-O-$, $-O-CH_2CH_2-O-$, or phenyl; wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_4 alkyl, amino C_1-C_4 alkyl, $NH(C_1$-C_4 alkyl$)$alkyl, $N(C_1$-C_4 alkyl$)(C_1$-C_4 alkyl$)$ C_1-C_4 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_4 alkoxy C_1-C_4 alkyl, or OH, each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, OH, CF_3, or OCF_3; and

R_{18} is C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, C_1-C_4 alkoxy C_1-C_6 alkyl; amino C_1-C_6 alkyl, mono or dialkylamino C_1-C_6 alkyl.

In this embodiment, it is preferred that R_6 and R_7 are not simultaneously OH.

Embodiment 141. Compounds according to embodiment 135, wherein

R_5 is benzyl or phenethyl, wherein each is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, $-C(O)NR_6R_7$, $-(C_1$-C_4 alkyl$)-C(O)NR_6R_7$, halogen, C_1-C_6 alkoxy, CO_2H, $-(C_1$-C_4 alkyl$)-CO_2H$, C_1-C_6 thioalkoxy, amidinooxime, C_1-C_6 alkoxycarbonyl, $-(C_1$-C_4 alkyl$)-C_1$-C_6 alkoxycarbonyl, C_1-C_6 hydroxyalkyl, $-(C_1$-C_4

alkyl)-CN, CN, phenyl C_1-C_6 alkoxy, OH, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, NR_8R_9, NR_6R_7-(C_1-C_6 alkyl)-, -(C_1-C_4 alkyl)-$NR_{15}C(O)R_{18}$, amidinooxime, -SO_2(C_1-C_6 alkyl), -O-CH_2-O-, -O-CH_2CH_2-O-, phenyl C_1-C_4 alkoxy, or phenyl; wherein

R_6, R_7, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl, thiomorpholinyl, ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy C_1-C_4 alkyl, or halogen,

R_{18} is C_1-C_6 alkyl optionally substituted with -O-(C_2-C_6 alkanoyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl; amino C_1-C_6 alkyl; mono or dialkylamino C_1-C_6 alkyl.

In this embodiment, it is preferred that R_6 and R_7 are not simultaneously OH; and

R_6 and R_7 are not simultaneously -SO_2(C_1-C_6 alkyl).

Embodiment 142. Compounds according to embodiment 141, wherein

R_5 is benzyl which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_4 alkyl, -$C(O)NR_6R_7$, -(C_1-C_4alkyl)-$C(O)NR_6R_7$, halogen, C_1-C_4 alkoxy, CO_2H, C_1-C_4 thioalkoxy, C_1-C_4 alkoxycarbonyl, C_1-C_6 hydroxyalkyl, CN, OH, NR_8R_9, NR_6R_7-(C_1-C_6 alkyl)-, -SO_2(C_1-C_6 alkyl), or benzyloxy; and wherein

R_6 and R_7 at each occurrence are independently H, OH, C_1-C_6 alkyl, amino C_1-C_4 alkyl, NH(C_1-C_6 alkyl)alkyl, N(C_1-C_6 alkyl)(C_1-C_6 alkyl) C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy C_1-C_6 alkyl, or -SO_2(C_1-C_6 alkyl), each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, C_3-C_6

cycloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, OH, CF_3, or OCF_3.

In this embodiment, it is preferred that R_6 and R_7 are not simultaneously OH; and

R_6 and R_7 are not simultaneously $-SO_2(C_1$-C_6 alkyl).

Embodiment 143. Compounds according to embodiment 135, wherein

R_5 is benzyl which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_4 alkyl, $-C(O)NR_6R_7$, $-(C_1$-C_4alkyl$)$-$C(O)NR_6R_7$, NR_6R_7-$(C_1$-C_6 alkyl$)$-, NR_8R_9, halogen, C_1-C_4 alkoxy, C_1-C_4 thioalkoxy, C_1-C_4 alkoxycarbonyl, C_1-C_6 hydroxyalkyl, or CN; wherein

R_6 and R_7 at each occurrence are independently H, OH, C_1-C_6 alkyl, amino C_1-C_4 alkyl, $NH(C_1$-C_6 alkyl$)$alkyl, $N(C_1$-C_6 alkyl$)(C_1$-C_6 alkyl$)$ C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, or C_1-C_4 alkoxy C_1-C_4 alkyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, OH, CF_3, or OCF_3.

In this embodiment, it is preferred that R_6 and R_7 are not simultaneously OH.

Embodiment 144. Compounds according to embodiment 143, wherein

the R_5 group is disubstituted with two groups that are meta to each other.

Embodiment 145. Compounds according to embodiment 125, wherein

R_5 is phenyl, which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_4 alkyl, $-C(O)NR_6R_7$, $-NR_6R_7$, $NR_6R_7(C_1$-C_6 alkyl$)$, NR_8R_9, C_1-C_6 hydroxyalkyl,

halogen, C_1-C_4 alkoxy, CO_2H, OH, C_1-C_6 alkoxycarbonyl, carboxaldehyde, C_1-C_4 haloalkyl, -(C_1-C_4 alkyl)-$NR_{15}C(O)NR_{16}R_{17}$, -(C_1-C_4 alkyl)-$NR_{15}C(O)R_{18}$; wherein

R_6 and R_7 at each occurrence are independently H, OH, C_1-C_6 alkyl, amino C_1-C_4 alkyl, NH(C_1-C_6 alkyl)alkyl, N(C_1-C_6 alkyl)(C_1-C_6 alkyl) C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy C_1-C_6 alkyl, -SO_2(C_1-C_6 alkyl), -SO_2NH_2, -SO_2NH(C_1-C_6 alkyl), -SO_2N(C_1-C_6 alkyl)(C_1-C_6 alkyl), or C_1-C_6 alkanoyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, OH, CF_3, or OCF_3; or

R_6, R_7, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy C_1-C_4 alkyl, or halogen,

R_{15} is H or C_1-C_6 alkyl;

R_{16} and R_{17} are independently H or C_1-C_6 alkyl; or

R_{16}, R_{17}, and the nitrogen to which they are attached form a morpholinyl ring;

R_{18} is C_1-C_6 alkyl optionally substituted with -O-(C_2-C_6 alkanoyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl; amino C_1-C_6 alkyl, mono or dialkylamino C_1-C_6 alkyl.

In this embodiment, it is preferred that R_6 and R_7 are not simultaneously OH.

Embodiment 146. Compounds according to embodiment 145, wherein

R_5 is phenyl, which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_4 alkyl, -(C_1-C_4 alkyl)-$C(O)NR_6R_7$, -$C(O)NR_6R_7$, -NR_6R_7, NR_6R_7(C_1-C_6 alkyl),

NR_8R_9, C_1-C_6 hydroxyalkyl, halogen, C_1-C_4 alkoxy, CO_2H, OH, C_1-C_6 alkoxycarbonyl, carboxaldehyde, C_1-C_4 haloalkyl, -(C_1-C_4 alkyl)-$NR_{15}C(O)NR_{16}R_{17}$, -(C_1-C_4 alkyl)-$NR_{15}C(O)R_{18}$; wherein

R_6 and R_7 at each occurrence are independently H, OH, C_1-C_6 alkyl, amino C_1-C_4 alkyl, NH(C_1-C_6 alkyl)alkyl, N(C_1-C_6 alkyl)(C_1-C_6 alkyl) C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy C_1-C_6 alkyl, -SO_2(C_1-C_6 alkyl), -SO_2NH_2, -SO_2NH(C_1-C_6 alkyl), -SO_2N(C_1-C_6 alkyl)(C_1-C_6 alkyl), or C_1-C_6 alkanoyl each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, OH, CF_3, or OCF_3;

R_{15} is H or C_1-C_6 alkyl;

R_{16} and R_{17} are independently H or C_1-C_6 alkyl; or

R_{16}, R_{17}, and the nitrogen to which they are attached form a morpholinyl ring;

R_{18} is C_1-C_6 alkyl optionally substituted with -O-(C_2-C_6 alkanoyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl; amino C_1-C_6 alkyl, mono or dialkylamino C_1-C_6 alkyl.

Embodiment 147. Compounds according to embodiment 146, wherein

R_1 is halogen, methyl, ethyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, or carboxaldehyde;

R_2 is benzyloxy, OH, phenyloxy, phenyloxy(C_1-C_6)alkyl, or phenyl (C_1-C_4) thioalkoxy, wherein each of the above is optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, -(C_1-C_6)alkyl-N(R)-CO_2R_{30}, NR_6R_7, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, (C_1-C_6) alkyl, pyridyl, or NR_6R_7-(C_1-C_6 alkyl)-; and

R_4 is H, (C_1-C_4) alkyl optionally substituted with one or two groups that are independently CO_2H, -CO_2alkyl, -C(O)NRR, -$N(R_{30})$C(O)NRR, -$N(R_{30})$C(O)-(C_1-C_6)alkoxy, or -NR_6R_7, or hydroxy(C_1-C_4)alkyl.

Embodiment 148. Compounds according to embodiment 147, wherein

R_5 is phenyl, which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_4 alkyl, -C(O)NR_6R_7, -(C_1-C_4 alkyl)-C(O)NR_6R_7, -NR_6R_7, NR_6R_7(C_1-C_6 alkyl), C_1-C_6 hydroxyalkyl, halogen, C_1-C_4 alkoxy, CO_2H, OH, C_1-C_6 alkoxycarbonyl, carboxaldehyde, C_1-C_4 haloalkyl, wherein

R_6 and R_7 at each occurrence are independently H, OH, C_1-C_6 alkyl, amino C_1-C_4 alkyl, NH(C_1-C_6 alkyl)alkyl, N(C_1-C_6 alkyl)(C_1-C_6 alkyl) C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy C_1-C_6 alkyl, -SO_2(C_1-C_6 alkyl), -SO_2NH_2, -SO_2NH(C_1-C_6 alkyl), -SO_2N(C_1-C_6 alkyl)(C_1-C_6 alkyl), or C_1-C_6 alkanoyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, OH, SH, C_3-C_6 cycloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkyl, OH, CF_3, or OCF_3.

Embodiment 149. Compounds according to embodiment 125, wherein

R_5 is thienyl(C_1-C_6 alkyl), piperidinyl(C_1-C_6)alkyl, pyrrolidinyl(C_1-C_6)alkyl, imidazolidinyl(C_1-C_6)alkyl, piperazinyl(C_1-C_6)alkyl, pyridyl(C_1-C_6)alkyl, pyrimidyl(C_1-C_6)alkyl, pyridazyl(C_1-C_6)alkyl, pyrazinyl(C_1-C_6)alkyl, isoquinolinyl(C_1-C_6)alkyl, tetrahydroisoquinolinyl(C_1-C_6)alkyl, indolyl(C_1-C_6)alkyl, 1H-indazolyl(C_1-C_6)alkyl, dihydroindolonyl(C_1-C_6 alkyl), indolinyl(C_1-C_6 alkyl), dihydroisoindolyl(C_1-C_6 alkyl), dihydrobenzimdazolyl(C_1-C_6 alkyl), or dihydrobenzoimidazolonyl(C_1-C_6 alkyl), wherein

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently $(C_1$-$C_6)$alkyl, halogen, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$hydroxyalkyl, phenyl$(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$thioalkoxy, $(C_1$-$C_6)$alkoxycarbonyl, phenyl$(C_1$-$C_6)$alkoxycarbonyl, OH, CO_2H, CN, amidinooxime, NR_8R_9, NR_6R_7-$(C_1$-C_6 alkyl)-, -$C(O)NR_6R_7$, -$(C_1$-C_4 alkyl)-$C(O)NR_6R_7$, amidino, piperazinyl, morpholinyl, -SO_2 $(C_1$-$C_6)$ alkyl, -SO_2NH_2, -$SO_2NH(C_1$-$C_6)$alkyl, -$SO_2N(C_1$-$C_6)$alkyl $(C_1$-$C_6)$alkyl, $(C_1$-$C_4)$haloalkyl, -$(C_1$-C_4 alkyl)-$NR_{15}C(O)NR_{16}R_{17}$, -$(C_1$-C_4 alkyl)-$NR_{15}C(O)R_{18}$, -O-CH_2-O, -O-CH_2CH_2-O-, or $(C_1$-$C_4)$haloalkoxy; wherein

R_6 and R_7 are independently at each occurrence H, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxycarbonyl, $(C_1$-$C_6)$hydroxyalkyl, -$(C_1$-$C_4)$alkyl-CO_2-$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkanoyl, phenyl$(C_1$-$C_6)$alkyl, phenyl$(C_1$-$C_6)$alkoxy, or phenyl$(C_1$-$C_6)$alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, $(C_1$-$C_4)$alkoxy, OH, SH, C_3-C_6 cycloalkyl, NH_2, $NH(C_1$-C_6 alkyl), $N(C_1$-C_6 alkyl)$(C_1$-C_6 alkyl), $(C_1$-$C_4)$alkyl, CF_3 or OCF_3; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, hydroxy, hydroxy C_1-C_4 alkyl, or halogen; and

R_{18} is C_1-C_6 alkyl optionally substituted with -O-$(C_2$-C_6 alkanoyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy,

C_1-C_6 alkoxy C_1-C_6 alkyl; amino C_1-C_6 alkyl, mono or dialkylamino C_1-C_6 alkyl.

In this embodiment, it is preferred that R_6 and R_7 are not simultaneously OH; and

R_6 and R_7 are not simultaneously $-SO_2(C_1$-C_6 alkyl).

Embodiment 150. Compounds according to embodiment 149, wherein

R_1 is halogen, methyl, ethyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, or carboxaldehyde;

R_2 is benzyloxy, OH, phenyloxy, phenyloxy$(C_1$-$C_6)$alkyl, or phenyl $(C_1$-$C_4)$ thioalkoxy, wherein each of the above is optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, $-(C_1$-$C_6)$alkyl-N(R)-CO_2R_{30}, NR_6R_7, $(C_1$-$C_4)$ haloalkyl, $(C_1$-$C_4)$ haloalkoxy, $(C_1$-$C_6)$ alkyl, pyridyl, or NR_6R_7-$(C_1$-C_6 alkyl)-; and

R_4 is H, $(C_1$-$C_4)$ alkyl optionally substituted with one or two groups that are independently CO_2H, $-CO_2$alkyl, -C(O)NRR, $-N(R_{30})C(O)NRR$, $-N(R_{30})C(O)-(C_1$-$C_6)$alkoxy, or $-NR_6R_7$, or hydroxy$(C_1$-$C_4)$alkyl.

Embodiment 151. Compounds according to embodiment 150, wherein

R_5 is thienyl$(C_1$-C_6 alkyl), indolyl$(C_1$-C_6 alkyl), pyridinyl$(C_1$-C_6 alkyl), piperazinyl$(C_1$-C_6 alkyl), or pyrazinyl$(C_1$-C_6 alkyl) each of which is optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, halogen, $-C(O)NR_6R_7$, $-(C_1$-C_4 alkyl)$-C(O)NR_6R_7$, C_1-C_6 alkoxycarbonyl, $-NR_6R_7$, NR_6R_7-$(C_1$-C_6 alkyl)-, haloalkyl, C_1-C_6 alkanoyl,

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups

that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy;

or

R_6, R_7, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy C_1-C_4 alkyl, or halogen.

Embodiment 152. Compounds according to embodiment 151, wherein

R_5 is thienyl(C_1-C_6 alkyl), indolyl(C_1-C_6 alkyl), pyridinyl(C_1-C_6 alkyl), piperazinyl(C_1-C_6 alkyl), or pyrazinyl(C_1-C_6 alkyl).

Embodiment 153. Compounds according to embodiment 151, wherein

R_4 is H, methyl, ethyl, or $-CH_2OH$;

R_5 is pyridinyl(C_1-C_6 alkyl), or pyrazinyl(C_1-C_6 alkyl) each of which is optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, halogen, $-C(O)NR_6R_7$, $-(C_1$-C_4 alkyl$)-C(O)NR_6R_7$, C_1-C_6 alkoxycarbonyl, $-NR_6R_7$, $NR_6R_7-(C_1$-C_6 alkyl$)-$, CF_3, C_1-C_6 alkanoyl, wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy;

or

R_6, R_7, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring optionally substituted with 1 or 2

groups that are independently alkyl, hydroxy, hydroxy C_1-C_4 alkyl, or halogen.

Embodiment 154. Compounds according to embodiment 153, wherein

R_4 is H, alkyl substituted with one or two groups that are independently CO_2H, $-CO_2-(C_1-C_6)$alkyl, $-C(O)NRR$, $-N(R_{30})C(O)NRR$, $-N(R_{30})C(O)-(C_1-C_6)$alkoxy, or $-NR_6R_7$.

Embodiment 155. Compounds according to embodiment 16, wherein

R_1 is halogen, or methyl;

R_2 is benzyloxy, which is optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, $-(C_1-C_6)$alkyl-$N(R)-CO_2R_{30}$, CF_3, OCF_3, or (C_1-C_4) alkyl,; and

R_4 is H, methyl, ethyl, $-CH_2OH$, $-CH_2CO_2-(C_1-C_4$ alkyl), or C_2 hydroxyalkyl.

Embodiment 156. Compounds according to any one of embodiments 16, 17, 138, 143, 148, 149, 151 or 153, wherein

R_1 is halogen, or methyl;

R_2 is benzyloxy, which is optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, $-(C_1-C_6)$alkyl-$N(R)-CO_2R_{30}$, CF_3, OCF_3, or (C_1-C_4) alkyl,; and

R_4 is alkyl substituted with one group that is CO_2H, $-CO_2-(C_1-C_6)$alkyl, $-C(O)NRR$, $-N(R_{30})C(O)NRR$, $-N(R_{30})C(O)-(C_1-C_6)$alkoxy, or $-NR_6R_7$.

Embodiment 157. Compounds according to embodiment 125, wherein

R_5 is isoquinolinyl(C_1-C_6 alkyl), tetrahydroisoquinolinyl(C_1-C_6 alkyl), 1H-indazolyl(C_1-C_6 alkyl), dihydroindolonyl(C_1-C_6 alkyl), indolinyl(C_1-C_6 alkyl), dihydroisoindolyl(C_1-C_6

alkyl), dihydrobenzimdazolyl(C_1-C_6 alkyl), dihydrobenzoimidazolonyl(C_1-C_6 alkyl), each of which is unsubstituted or substituted with 1, 2, or 3 groups that are independently alkyl, alkoxy, halogen, C_1-C_6 alkoxycarbonyl, alkanoyl optionally substituted with 1 or 2 groups that are independently selected from the group consisting of OH, NH_2, $NH(C_1$-C_6 alkyl), and $N(C_1$-C_6 alkyl)(C_1-C_6 alkyl), $-C(O)NR_6R_7$, $-(C_1$-C_4 alkyl)$-C(O)NR_6R_7$, NR_6R_7-(C_1-C_6 alkyl)-, $-NR_6R_7$, or SO_2H; or

piperidinyl C_1-C_4 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, $-C(O)NR_6R_7$, $-(C_1$-C_4 alkyl)$-C(O)NR_6R_7$, NR_6R_7-(C_1-C_6 alkyl)-, or $-NR_6R_7$, or C_1-C_6 alkoxycarbonyl.

Embodiment 158. Compounds according to embodiment 157, wherein

R_5 is isoquinolinyl(C_1-C_4 alkyl), piperidinyl C_1-C_4 alkyl, tetrahydroisoquinolinyl(C_1-C_4 alkyl), 1H-indazolyl(C_1-C_4 alkyl), dihydroindolonyl(C_1-C_4 alkyl), indolinyl(C_1-C_4 alkyl), dihydroisoindolyl(C_1-C_4 alkyl), dihydrobenzimdazolyl(C_1-C_4 alkyl), or dihydrobenzoimidazolonyl(C_1-C_4 alkyl).

Embodiment 159. Compounds according to embodiment 157, wherein

R_5 is piperidinyl C_1-C_4 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, or C_1-C_6 alkoxycarbonyl.

Embodiment 160. Compounds according to embodiment 125, wherein

R_5 is pyrimidyl, indolinyl, indolyl, 1H-isoindolyl, isoquinolinyl, tetrahydroisoquinolinyl, benzimidazolyl,

dihydro-1H-benzimidazolyl, pyrrolyl, imidazolyl, or each of which is optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of

C_1-C_6 alkoxycarbonyl, C_1-C_4 thioalkoxy, each of which is unsubstituted or substituted with 1, 2, or 3 groups that are independently $-C(O)NR_6R_7$, $-(C_1$-C_4 alkyl)-$C(O)NR_6R_7$, NR_6R_7-(C_1-C_6 alkyl)-, $-NR_6R_7$, alkyl, alkoxy, halogen, C_1-C_6 alkoxycarbonyl, or alkanoyl optionally substituted with 1 or 2 groups that are independently selected from the group consisting of OH, NH_2, $NH(C_1$-C_6 alkyl), and $N(C_1$-C_6 alkyl) (C_1-C_6 alkyl), and SO_2H; or

pyridyl, pyrazolyl, optionally substituted with 1, 2, or 3 groups that are independently $-C(O)NR_6R_7$, $-(C_1$-C_4 alkyl)-$C(O)NR_6R_7$, NR_6R_7-(C_1-C_6 alkyl)-, $-NR_6R_7$, C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, halogen, C_1-C_6 alkoxycarbonyl, $-NR_6R_7$, NR_6R_7-(C_1-C_6 alkyl)-, CF_3, C_1-C_6 alkanoyl, wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy;

or

R_6, R_7, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy C_1-C_4 alkyl, or halogen.

Embodiment 161. Compounds according to embodiment 160, wherein

R_5 is pyrimidyl, pyrrolyl, imidazolyl, or pyrazolyl, each of which is optionally substituted with 1, 2, or 3 groups independently selected from C_1-C_6 alkoxycarbonyl, C_1-C_4 thioalkoxy, each of which is unsubstituted or substituted with 1, 2, or 3 groups that are independently alkyl, alkoxy, halogen, C_1-C_6 alkoxycarbonyl, $-C(O)NR_6R_7$, $-(C_1$-C_4 alkyl)$-C(O)NR_6R_7$, $NR_6R_7-(C_1$-C_6 alkyl)-, or $-NR_6R_7$, or C_1-C_4 alkanoyl optionally substituted with 1 or 2 groups that are independently selected from the group consisting of OH, NH_2, $NH(C_1$-C_6 alkyl), and $N(C_1$-C_6 alkyl) (C_1-C_6 alkyl), or SO_2H.

Embodiment 162. Compounds according to embodiment 160, wherein

R_5 is pyridyl or pyrazolyl, optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, halogen, $-C(O)NR_6R_7$, $-(C_1$-C_4 alkyl)$-C(O)NR_6R_7$, $NR_6R_7-(C_1$-C_6 alkyl)-, or $-NR_6R_7$, C_1-C_6 alkoxycarbonyl, $-NR_6R_7$, $NR_6R_7-(C_1$-C_6 alkyl)-, CF_3, C_1-C_6 alkanoyl, wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy;

or

R_6, R_7, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy C_1-C_4 alkyl, or halogen.

Embodiment 163. Compounds according to embodiment 162, wherein

R_5 is pyridyl or pyrazolyl, optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, halogen, -C(O)NR_6R_7, -(C_1-C_4 alkyl)-C(O)NR_6R_7, NR_6R_7-(C_1-C_6 alkyl)-, -NR_6R_7, C_1-C_6 alkoxycarbonyl, CF_3, C_1-C_6 alkanoyl, wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy.

Embodiment 164. Compounds according to embodiment 162, wherein

R_5 is pyridyl or pyrazolyl, optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, halogen, -C(O)NR_6R_7, -(C_1-C_4 alkyl)-C(O)NR_6R_7, NR_6R_7-(C_1-C_6 alkyl)-, -NR_6R_7, C_1-C_6 alkoxycarbonyl, CF_3, C_1-C_6 alkanoyl, wherein

R_6, R_7, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy C_1-C_4 alkyl, or halogen.

Embodiment 165. Compounds according to any one of embodiments 157, 158, 159, 160, 161, 162, 163, or 164 wherein

R_1 is halogen, methyl, ethyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, or carboxaldehyde;

R_2 is benzyloxy, OH, phenyloxy, phenyloxy(C_1-C_6)alkyl, or phenyl (C_1-C_4) thioalkoxy, wherein each of the above is optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, -(C_1-C_6)alkyl-N(R)-CO_2R_{30}, NR_6R_7, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, (C_1-C_6) alkyl, pyridyl, or NR_6R_7-(C_1-C_6 alkyl)-; and

R_4 is H, (C_1-C_4) alkyl substituted with one group that is CO_2H, $-CO_2-(C_1-C_6)$alkyl, $-C(O)NRR$, $-N(R_{30})C(O)NRR$, $-N(R_{30})C(O)-(C_1-C_6)$alkoxy, or $-NR_6R_7$, hydroxy(C_1-C_4)alkyl.

Embodiment 166. Compounds according to embodiment 125, wherein

R_5 is C_1-C_6 alkyl optionally substituted with 1 or 2, groups that are independently C_1-C_4 alkoxycarbonyl, or halogen, or

R_5 is C_1-C_4 alkoxy, ethyl, methyl, cyclopropylmethyl, cycloalkyl, or alkynyl, or

R_5 is C_2-C_6 alkenyl optionally substituted with C_1-C_4 alkoxycarbonyl or cyclohexyl.

Embodiment 167. Compounds according to embodiment 166, wherein

R_1 is halogen, methyl, ethyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, or carboxaldehyde;

R_2 is benzyloxy, OH, phenyloxy, phenyloxy(C_1-C_6)alkyl, or phenyl (C_1-C_4) thioalkoxy, wherein each of the above is optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, $-(C_1-C_6)$alkyl$-N(R)-CO_2R_{30}$, NR_6R_7, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, (C_1-C_6) alkyl, pyridyl, or $NR_6R_7-(C_1-C_6$ alkyl$)-$; and

R_4 is H, (C_1-C_4) alkyl substituted with one group that is CO_2H, $-CO_2-(C_1-C_6)$alkyl, $-C(O)NRR$, $-N(R_{30})C(O)NRR$, $-N(R_{30})C(O)-(C_1-C_6)$alkoxy, or $-NR_6R_7$, hydroxy(C_1-C_4)alkyl; wherein

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy;

or

R_6, R_7, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy C_1-C_4 alkyl, or halogen.

Embodiment 168. Compounds according to embodiment 167, wherein

R_5 is C_1-C_6 alkyl optionally substituted with 1 or 2, groups that are independently C_1-C_4 alkoxycarbonyl, or halogen, or

R_5 is C_1-C_4 alkoxy, ethyl, methyl, cyclopropylmethyl, cyclohexyl, cyclopentyl, C_2-C_6 alkynyl, or

R_5 is C_2-C_6 alkenyl optionally substituted with C_1-C_4 alkoxycarbonyl or cyclohexyl.

Embodiment 169. Compounds according to embodiment 125, wherein

R_2 is phenylalkynyl, $-OC(O)NH(CH_2)_n$aryl, $-OC(O)N(alkyl)(CH_2)_n$aryl, $-OSO_2(C_1-C_6)$alkyl, $-OSO_2$aryl, NR_8R_9, or NR_8R_9-(C_1-C_4 alkyl); wherein

n is 0, 1, 2, 3, 4, 5 or 6;

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, $-(C_1-C_6)$alkyl-$N(R)-CO_2R_{30}$, alkoxy, alkoxycarbonyl, CN, NR_6R_7, haloalkyl, haloalkoxy, alkyl, heteroaryl, heteroarylalkyl, NR_6R_7-(C_1-C_6 alkyl)-, phenyl, $-SO_2$-phenyl wherein the phenyl groups are optionally substituted with 1, 2, or 3 groups that are independently halogen or NO_2; or $-OC(O)NR_6R_7$, wherein

R_6 and R_7 are independently at each occurrence H, alkyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, $-SO_2$-alkyl, OH, hydroxyalkyl, $-(C_1-C_4)$alkyl-CO_2-

alkyl, heteroarylalkyl, alkanoyl, arylalkyl, arylalkoxy, or arylalkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, alkoxy, heterocycloalkyl, OH, NH_2, C_3-C_6 cycloalkyl, NH(alkyl), N(alkyl)(alkyl), -O-alkanoyl, alkyl, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, hydroxy C_1-C_4 alkyl, or halogen.

Embodiment 170. Compounds according to embodiment 169, wherein

R_1 is halogen, methyl, ethyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, or carboxaldehyde; and

R_4 is H, (C_1-C_4) alkyl substituted with one group that is CO_2H, -CO_2-(C_1-C_6)alkyl, -C(O)NRR, -N(R_{30})C(O)NRR, -N(R_{30})C(O)-(C_1-C_6)alkoxy, -NR_6R_7, NR_6R_7-(C_1-C_6 alkyl)-, or hydroxy(C_1-C_4)alkyl.

Embodiment 171. Compounds according to embodiment 170, wherein

R_5 is phenyl, optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, CF_3, OCF_3, -(C_1-C_4 alkyl)-C(O)NR_6R_7, NR_6R_7-(C_1-C_6 alkyl)-, -NR_6R_7, or C(O)NR_6R_7, wherein

R_6 and R_7 are independently at each occurrence H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, C_1-C_6

alkoxycarbonyl, OH, C_1-C_6 hydroxyalkyl, -(C_1-C_4)alkyl-CO_2-alkyl, pyridyl C_1-C_6 alkyl, C_1-C_6 alkanoyl, benzyl, phenyl C_1-C_6 alkoxy, or phenyl C_1-C_6 alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, C_1-C_6 alkoxy, piperidinyl C_1-C_6 alkyl, morpholinyl C_1-C_6 alkyl, piperazinyl C_1-C_6 alkyl, OH, SH, C_3-C_6 cycloalkyl, NH_2, NH(alkyl), N(alkyl)(alkyl), -O-C_1-C_4 alkanoyl, C_1-C_4 alkyl, CF_3, or OCF_3; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, hydroxy C_1-C_4 alkyl, or halogen; or

R_5 is benzyl optionally substituted with 1 ,2 ,3 ,4, or 5 groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, CN, CF_3, OCF_3, -(C_1-C_4 alkyl)-C(O)NR_6R_7, NR_6R_7-(C_1-C_6 alkyl)-, -NR_6R_7, or C(O)NR_6R_7.

Embodiment 172. Compounds according to embodiment 171, wherein

R_2 is NR_8R_9, or NR_8R_9-(C_1-C_4 alkyl)-; wherein

R_8 at each occurrence is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 alkanoyl, phenyl(C_1-C_6)alkyl or phenyl(C_1-C_6)alkanoyl wherein each of the above is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxycarbonyl, halogen, or C_1-C_4 haloalkyl; and

R_9 at each occurrence is independently C_1-C_6 alkyl, C_1-C_6 alkanoyl, phenyl(C_1-C_6)alkyl, C_3-C_7 cycloalkyl, C_2-C_6 alkenyl, pyridyl, pyridazinyl, pyrimidinyl,

pyrazinyl, imidazolyl, C_3-C_7 cycloalkyl(C_1-C_6)alkyl, phenyl(C_1-C_6)alkanoyl, -SO_2-phenyl, and phenyl wherein each of the above is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxycarbonyl, halogen, or C_1-C_4 haloalkyl.

Embodiment 173. Compounds according to embodiment 172, wherein

R_8 is H.

Embodiment 174. Compounds according to embodiment 173, wherein

R_2 is -NH-benzyl option substituted with 1, 2, or 3 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, CF_3, OCF_3,

or

R_2 is -NH-C(O)phenyl, wherein the phenyl group is optionally substituted with 1, 2, or 3 groups that are independently halogen, C_1-C_4 alkyl, or C_1-C_4 alkoxy; or

R_2 is -NH-allyl.

Embodiment 175. Compounds according to embodiment 174, wherein

R_1 is chloro, bromo, iodo, or methyl; and

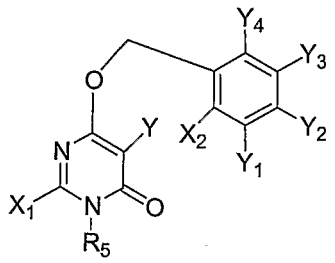
R_5 is benzyl optionally substituted with 1 ,2 ,3 ,4, or 5 groups that are independently halogen, -(C_1-C_4 alkyl)-C(O)NR_6R_7, NR_6R_7-(C_1-C_6 alkyl)-, -NR_6R_7, C_1-C_6 alkyl, C_1-C_6 alkoxy, CN, CF_3, OCF_3, or C(O)NR_6R_7.

Embodiment 176. Compounds according to embodiment 174, wherein

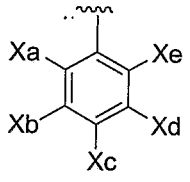
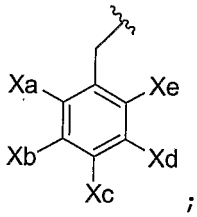
R_1 is chloro, bromo, iodo, or methyl; and

R_5 is phenyl, optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, -(C_1-C_4 alkyl)-$C(O)NR_6R_7$, NR_6R_7-(C_1-C_6 alkyl)-, -NR_6R_7, C_1-C_4 alkyl, C_1-C_4 alkoxy, CF_3, OCF_3, or $C(O)NR_6R_7$.

Embodiment 177. A compound of the formula



or pharmaceutically acceptable salts thereof, wherein

R_5 is  or  ; wherein

X_1, X_2, X_a, X_b, X_c, X_d, and X_e at are independently selected from -$C(O)NR_6R_7$, -NR_6R_7, hydroxy(C_1-C_4)alkyl, H, OH, halogen, haloalkyl, alkyl, haloalkoxy, heteroaryl, heterocycloalkyl, C_3-C_7 cycloalkyl, NR_6R_7-(C_1-C_6 alkyl)-, -CO_2-(C_1-C_6)alkyl, -$N(R)C(O)NR_6R_7$, -$N(R)C(O)$-(C_1-C_6)alkoxy, CO_2H-(C_1-C_6 alkyl)-, or -$SO_2NR_6R_7$; wherein

the heteroaryl and heterocycloalkyl groups are optionally substituted with -NR_6R_7, -$C(O)NR_6R_7$, NR_6R_7-(C_1-C_6 alkyl)-, C_1-C_6 alkyl, C_1-C_6 alkoxy, or halogen;

R_6 and R_7 are independently at each occurrence H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl, OH, C_1-C_6 hydroxyalkyl, C_1-C_6 thiohydroxyalkyl, -(C_1-C_4)alkyl-CO_2-alkyl, pyridyl C_1-C_6 alkyl, C_1-C_6 alkanoyl, benzyl, phenyl C_1-C_6 alkoxy, or phenyl C_1-C_6 alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3

groups that are independently, halogen, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, piperidinyl C_1-C_6 alkyl, morpholinyl C_1-C_6 alkyl, piperazinyl C_1-C_6 alkyl, OH, SH, NH_2, NH(alkyl), N(alkyl)(alkyl), -O-C_1-C_4 alkanoyl, C_1-C_4 alkyl, CF_3, or OCF_3; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, hydroxy C_1-C_4 alkyl, or halogen;

R at each occurrence is independently H or C_1-C_6 alkyl; and

Y, Y_1, Y_2, Y_3, and Y_4 are independently selected from H, halogen, alkyl, carboxaldehyde, hydroxyalkyl, alkenyl, alkynyl, CN, alkanoyl, alkoxy, alkoxyalkyl, haloalkyl, and carboxyl.

Embodiment 178. Compounds according to embodiment 177, wherein

Y_2, Y_4, and Y are independently halogen; and

Y_1 and Y_3 are both hydrogen.

Embodiment 179. Compounds according to embodiment 178, wherein

X_1 is H, methyl, -NR_6R_7, NR_6R_7-(C_1-C_6 alkyl)-, -C(O)NR_6R_7, C_1-C_6 hydroxyalkyl, or -(C_1-C_4 alkyl)-morpholinyl.

Embodiment 180. Compounds according to embodiment 179, wherein

X_a and X_e are independently halogen, is NH_2, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)(C_1-C_6 alkyl) or methyl.

Embodiment 181. Compounds according to embodiment 180, wherein

X_b or X_c is $-NR_6R_7$, NR_6R_7-(C_1-C_6 alkyl)-, $-C(O)NR_6R_7$, $-SO_2NR_6R_7$, or halogen; wherein

R_6 and R_7 are independently at each occurrence H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl, OH, C_1-C_6 hydroxyalkyl, -(C_1-C_4)alkyl-CO_2-alkyl, pyridyl C_1-C_6 alkyl, C_1-C_6 alkanoyl, benzyl, phenyl C_1-C_6 alkoxy, or phenyl C_1-C_6 alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, piperidinyl C_1-C_6 alkyl, morpholinyl C_1-C_6 alkyl, piperazinyl C_1-C_6 alkyl, OH, SH, NH_2, NH(alkyl), N(alkyl)(alkyl), -O-C_1-C_4 alkanoyl, C_1-C_4 alkyl, CF_3, or OCF_3; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, hydroxy C_1-C_4 alkyl, or halogen.

Embodiment 182. Compounds according to embodiment 181, wherein

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, hydroxy C_1-C_4 alkyl, or halogen.

Embodiment 183. Compounds according to embodiment 181, wherein

R_6, R_7, and the nitrogen to which they are attached form a piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, hydroxy C_1-C_4 alkyl, or halogen.

Embodiment 184. Compounds according to embodiment 181, wherein

R_6 and R_7 are independently at each occurrence H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl, OH, C_1-C_6 hydroxyalkyl, -(C_1-C_4)alkyl-CO_2-alkyl, pyridyl C_1-C_6 alkyl, C_1-C_6 alkanoyl, benzyl, phenyl C_1-C_6 alkoxy, or phenyl C_1-C_6 alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, piperidinyl C_1-C_6 alkyl, morpholinyl C_1-C_6 alkyl, piperazinyl C_1-C_6 alkyl, OH, NH_2, NH(alkyl), N(alkyl)(alkyl), -O-C_1-C_4 alkanoyl, C_1-C_4 alkyl, CF_3, or OCF_3.

Embodiment 185. Compounds according to embodiment 181, wherein

R_6 and R_7 are independently at each occurrence H, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, or C_1-C_6 alkanoyl, wherein each of the above is optionally substituted with 1, 2, or 3 groups that are independently OH, SH, halogen, or C_3-C_6 cycloalkyl.

Embodiment 186. Compounds according to embodiment 180, wherein

X_a and X_e are independently fluoro, chloro, or methyl; and

X_c is hydrogen or halogen.

Embodiment 187. Compounds according to embodiment 180, wherein

X_a is halogen;

X_e is NH_2, $NH(C_1\text{-}C_6$ alkyl) or $N(C_1\text{-}C_6$ alkyl)$(C_1\text{-}C_6$ alkyl);

X_b and X_d are both hydrogen.

Embodiment 188. Compounds according to embodiment 187, wherein

X_c is $-NR_6R_7$, NR_6R_7 $C_1\text{-}C_6$ alkyl, $-SO_2NR_6R_7$, or halogen; wherein

R_6 and R_7 are independently at each occurrence H, $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ alkoxy, $C_1\text{-}C_6$ alkoxy $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ alkoxycarbonyl, OH, $C_1\text{-}C_6$ hydroxyalkyl, $-(C_1\text{-}C_4)$alkyl-CO_2-alkyl, pyridyl $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ alkanoyl, benzyl, phenyl $C_1\text{-}C_6$ alkoxy, or phenyl $C_1\text{-}C_6$ alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, $C_3\text{-}C_6$ cycloalkyl, $C_1\text{-}C_6$ alkoxy, piperidinyl $C_1\text{-}C_6$ alkyl, morpholinyl $C_1\text{-}C_6$ alkyl, piperazinyl $C_1\text{-}C_6$ alkyl, OH, SH, NH_2, NH(alkyl), N(alkyl)(alkyl), $-O\text{-}C_1\text{-}C_4$ alkanoyl, $C_1\text{-}C_4$ alkyl, CF_3, or OCF_3; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently $C_1\text{-}C_4$ alkyl, $C_1\text{-}C_4$ alkoxy, hydroxy, hydroxy $C_1\text{-}C_4$ alkyl, or halogen.

Embodiment 189. Compounds according to embodiment 188, wherein

X_c is fluoro, chloro, NH_2, $NH(C_1\text{-}C_6$ alkyl), $N(C_1\text{-}C_6$ alkyl)$(C_1\text{-}C_6$ alkyl), $-SO_2NH_2$, $-SO_2NH(C_1\text{-}C_6$ alkyl), $-SO_2N(C_1\text{-}C_6$ alkyl)$(C_1\text{-}C_6$ alkyl), or piperazinyl, wherein the piperazinyl group

is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, hydroxy C_1-C_4 alkyl, or halogen.

Embodiment 190. Compounds according to either embodiment 180 or 187, wherein

X_c is $-C(O)NR_6R_7$, $-(C_1$-C_6 alkyl$)-C(O)NR_6R_7$, NR_6R_7, or $NR_6R_7-(C_1$-C_6 alkyl$)-$; wherein

R_6 and R_7 are independently at each occurrence H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl, OH, C_1-C_6 hydroxyalkyl, $-(C_1$-$C_4)$alkyl-CO_2-alkyl, pyridyl C_1-C_6 alkyl, C_1-C_6 alkanoyl, benzyl, phenyl C_1-C_6 alkoxy, or phenyl C_1-C_6 alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, piperidinyl C_1-C_6 alkyl, morpholinyl C_1-C_6 alkyl, piperazinyl C_1-C_6 alkyl, OH, NH_2, NH(alkyl), N(alkyl)(alkyl), $-O-C_1$-C_4 alkanoyl, C_1-C_4 alkyl, CF_3, or OCF_3; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, hydroxy C_1-C_4 alkyl, or halogen.

Embodiment 191. Compounds according to embodiment 190, wherein

R_6 is hydrogen; and

R_7 is C_1-C_6 alkyl or C_1-C_6 alkanoyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently

NH_2, $NH(C_1-C_6$ alkyl), $N(C_1-C_6$ alkyl)$(C_1-C_6$ alkyl), OH, SH, cyclopropyl, or C_1-C_4 alkoxy.

Embodiment 192. Compounds according to embodiment 191, wherein

R_7 is C_1-C_6 alkanoyl optionally substituted with 1, 2, or 3 groups that are independently OH, cyclopropyl, or NH_2.

Embodiment 193. Compounds according to embodiment 178, wherein

X_a is hydrogen;

X_b, X_c, or X_d is $-C(O)NR_6R_7$, $-(C_1-C_6$ alkyl$)-C(O)NR_6R_7$, NR_6R_7, $NR_6R_7-(C_1-C_6$ alkyl$)-$ or $-CO_2-(C_1-C_6)$alkyl; wherein

R_6 and R_7 are independently at each occurrence H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl, OH, C_1-C_6 hydroxyalkyl, $-(C_1-C_4)$alkyl-CO_2-alkyl, pyridyl C_1-C_6 alkyl, C_1-C_6 alkanoyl, benzyl, phenyl C_1-C_6 alkoxy, or phenyl C_1-C_6 alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, piperidinyl C_1-C_6 alkyl, morpholinyl C_1-C_6 alkyl, piperazinyl C_1-C_6 alkyl, OH, NH_2, NH(alkyl), N(alkyl)(alkyl), $-O-C_1-C_4$ alkanoyl, C_1-C_4 alkyl, CF_3, or OCF_3; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, hydroxy C_1-C_4 alkyl, or halogen; and

X_e is hydrogen, methyl, C_1-C_2 alkoxy, or halogen.

Embodiment 194. Compounds according to embodiment 193, wherein

X_b is NR_6R_7, or NR_6R_7-(C_1-C_6 alkyl)-, -C(O)NR_6R_7 or -CO_2-(C_1-C_6)alkyl; wherein

R_6 is hydrogen or C_1-C_4 alkyl;

R_7 is OH, C_1-C_6 alkyl or C_1-C_6 alkanoyl, wherein the alkyl and alkanoyl groups substituted with 1, 2, or 3 groups that are independently NH_2, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)(C_1-C_6 alkyl), C_3-C_6 cycloalkyl, OH, or C_1-C_4 alkoxy.

Embodiment 195. Compounds according to embodiment 180, wherein

X_a is halogen;

X_b is NR_6R_7, NR_6R_7-(C_1-C_6 alkyl)-, -C(O)NR_6R_7, or -CO_2-(C_1-C_6)alkyl;

X_c is NR_6R_7, NR_6R_7-(C_1-C_6 alkyl)-, -C(O)NR_6R_7, halogen, -CO_2-(C_1-C_6)alkyl, NH_2, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)(C_1-C_6 alkyl), -SO_2NH_2, -SO_2NH(C_1-C_6 alkyl), -SO_2N(C_1-C_6 alkyl)(C_1-C_6 alkyl), or piperazinyl, wherein the piperazinyl group is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, hydroxy C_1-C_4 alkyl, or halogen;

X_d is hydrogen;

X_e is H, methyl, NH_2, NH(C_1-C_6 alkyl) or N(C_1-C_6 alkyl)(C_1-C_6 alkyl).

Embodiment 196. Compounds according to embodiment 178, wherein

X_1, X_2, X_a, X_b, X_c, X_d, and X_e are independently selected from H, OH, halogen, CF_3, alkyl, OCF_3, pyridyl, pyridazinyl, pyrimidyl, pyrazinyl, thienyl, furyl, pyrrolyl, piperidinyl, piperazinyl, or C_3-C_7 cycloalkyl, wherein each of the above is optionally substituted with -NR_6R_7,

-C(O)NR_6R_7, NR_6R_7-(C_1-C_6 alkyl)-, C_1-C_6 alkyl, C_1-C_6 alkoxy, or halogen.

Embodiment 197. Compounds according to embodiment 196, wherein at least three of X_1, X_2, X_a, X_b, X_c, X_d, and X_e are hydrogen.

In another aspect, the invention provides pharmaceutical compositions comprising at least one pharmaceutically acceptable carrier, solvent, adjuvant or excipient and a compound or salt of formula I, embodiment 118, or embodiment 181. .

The invention further provides pharmaceutical compositions comprising at least one pharmaceutically acceptable carrier, solvent, adjuvant or excipient and compounds according to any of the preceding embodiments.

As noted above, the invention encompasses methods of treating a TNF mediated disorder, a p38 kinase mediated disorder, inflammation and/or arthritis in a subject, the method comprising treating a subject having or susceptible to such disorder or condition with a therapeutically-effective amount of a compound of formula I.

More specifically, the invention provides methods for treating or preventing inflammation; arthritis, rheumatoid arthritis, spondylarthropathies, gouty arthritis, osteoarthritis, systemic lupus erthematosus, juvenile arthritis, and other arthritic conditions; neuroinflammation; allergy, Th2 mediated diseases; pain, neuropathic pain; fever; pulmonary disorders, lung inflammation, adult respiratory distress syndrome, pulmonary sarcoisosis, asthma, silicosis, chronic pulmonary inflammatory disease, and chronic obstructive pulmonary disease (COPD); cardiovascular disease, arteriosclerosis, myocardial infarction (including post-

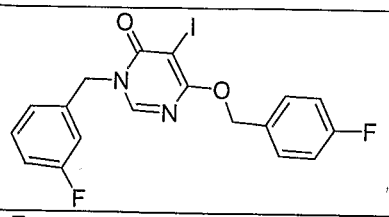
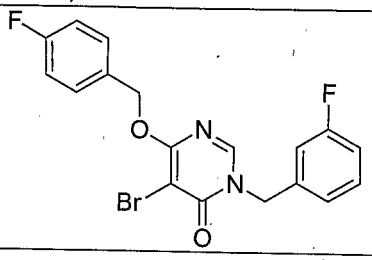
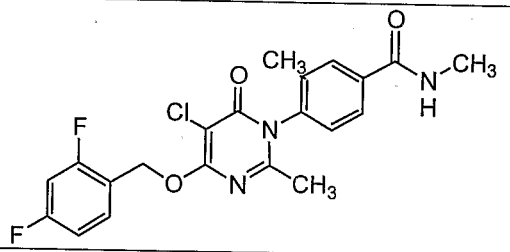
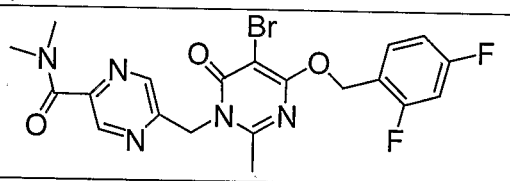
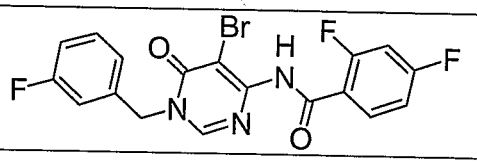
myocardial infarction indications), thrombosis, congestive heart failure, cardiac reperfusion injury, as well as complications associated with hypertension and/or heart failure such as vascular organ damage, restenosis; cardiomyopathy; stroke including ischemic and hemorrhagic stroke; reperfusion injury; renal reperfusion injury; ischemia including stroke and brain ischemia, and ischemia resulting from cardiac/coronary bypass; neurotrauma and brain trauma including closed head injury; brain edema; neurodegenerative disorders; liver disease and nephritis; gastrointestinal conditions, inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome, ulcerative colitis; ulcerative diseases, gastric ulcers; ophthalmic diseases, retinitis, retinopathies, uveitis, ocular photophobia, acute injury to the eye tissue and ocular traumas such as post-traumatic glaucoma, traumatic optic neuropathy, and central retinal artery occlusion (CRAO); periodontal disease; ophthalmological conditions, retinitis, retinopathies (including diabetic retinopathy), uveitis, ocular photophobia, nonglaucomatous optic nerve atrophy, and age related macular degeneration (ARMD) (including ARMD-atrophic form), corneal graft rejection, ocular neovascularization, retinal neovascularization, neovascularization following injury or infection, retrolental fibroplasias, neovascular glaucoma; glaucoma including primary open angle glaucoma (POAG), juvenile onset primary open-angle glaucoma, angle-closure glaucoma, pseudoexfoliative glaucoma, anterior ischemic optic neuropathy (AION), ocular hypertension, Reiger's syndrome, normal tension glaucoma, neovascular glaucoma, ocular inflammation and corticosteroid-induced glaucoma; diabetes; diabetic nephropathy; skin-related conditions, psoriasis, eczema, burns, dermatitis, keloid formation, scar tissue formation, angiogenic disorders; viral and bacterial

infections, sepsis, septic shock, gram negative sepsis, malaria, meningitis, HIV infection, opportunistic infections, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), pneumonia, herpes virus; myalgias due to infection; influenza; endotoxic shock; toxic shock syndrome; autoimmune disease, graft vs. host reaction and allograft rejections; treatment of bone resorption diseases, osteoporosis; multiple sclerosis; disorders of the female reproductive system, endometriosis; hemaginomas, infantile hemagionmas, angiofibroma of the nasopharynx, avascular necrosis of bone; benign and malignant tumors/neoplasia, cancer, colorectal cancer, brain cancer, bone cancer, epithelial call-derived neoplasia (epithelial carcinoma), basal cell carcinoma, adenocarcinoma, gastrointestinal cancer, lip cancer, mouth cancer, esophageal cancer, small bowel cancer, stomach cancer, colon cancer, liver cancer, bladder cancer, pancreas cancer, ovarian cancer, cervical cancer, lung cancer, breast cancer, skin cancer, squamus cell and/or basal cell cancers, prostate cancer, renal cell carcinoma, and other known cancers that affect epithelial cells throughout the body; leukemia; lymphoma; systemic lupus erthrematosis (SLE); angiogenesis including neoplasia; metastasis; central nervous system disorders, central nervous system disorders having an inflammatory or apoptotic component, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, spinal cord injury, and peripheral neuropathy; Canine B-Cell Lymphoma. Compounds of the invention are also useful for preventing the production or expression of cyclooxygenase-2, or cyclooxygenase-2 activity.

In this aspect, the invention encompasses methods of treating a p38 kinase or TNF-alpha mediated disorder comprising administering to a patient in need thereof a

therapeutically effective amount of compounds or salts according to embodiment 1, 118, or 181 and at least one pharmaceutically acceptable carrier, adjuvant, solvent or excipient.

Representative compounds of the invention are:

3-(3-fluorobenzyl)-6-[(4-fluorobenzyl)oxy]-5-iodopyrimidin-4(3H)-one	
5-bromo-3-(3-fluorobenzyl)-6-[(4-fluorobenzyl)oxy]pyrimidin-4(3H)-one	
4-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N,3-dimethylbenzamide	
5-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-N,N-dimethylpyrazine-2-carboxamide	
N-[5-bromo-1-(3-fluorobenzyl)-6-oxo-1,6-dihydropyrimidin-4-yl]-2,4-difluorobenzamide	

Other representative compounds of the invention are

3-(2-bromobenzyl)-5-[(2-bromobenzyl)oxy]pyrimidin-4(3H)-one;
3-benzyl-5-bromo-6-(2-phenylethyl)pyrimidin-4(3H)-one;
3-benzyl-5-bromo-6-(3-phenylpropyl)pyrimidin-4(3H)-one;
3-benzyl-5-bromo-6-[(2,6-dichlorobenzyl)oxy]pyrimidin-4(3H)-one;
3-benzyl-5-bromo-6-[(2-chlorobenzyl)oxy]pyrimidin-4(3H)-one;
3-benzyl-5-bromo-6-[(5-chlorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;

3-benzyl-5-bromo-6-[(4-chlorobenzyl)oxy]pyrimidin-4(3H)-one;
3-benzyl-5-bromo-6-{[2-(trifluoromethyl)benzyl]oxy}pyrimidin-4(3H)-one;
3-benzyl-5-methyl-6-(2-phenylethyl)pyrimidin-4(3H)-one;
3-benzyl-5-methyl-6-(3-phenylpropyl)pyrimidin-4(3H)-one;
3-benzyl-6-(benzyloxy)-5-(hydroxymethyl)pyrimidin-4(3H)-one;
3-benzyl-6-(benzyloxy)-1,5-dibromo-2-methylpyrimidin-4(3H)-one;
3-benzyl-6-(benzyloxy)-1,5-dibromopyrimidin-4(3H)-one;
3-benzyl-6-(benzyloxy)-5-bromopyrimidin-4(3H)-one;
3-benzyl-6-(benzyloxy)-5-chloropyrimidin-4(3H)-one;
3-benzyl-6-(benzyloxy)-5-methylpyrimidin-4(3H)-one;
3-benzyl-6-(benzyloxy)-2-methylpyrimidin-4(3H)-one;
3-benzyl-6-(benzyloxy)pyrimidin-4(3H)-one;
3-benzyl-6-(benzylthio)-5-bromopyrimidin-4(3H)-one;
3-benzyl-6-(benzylthio)-5-methylpyrimidin-4(3H)-one;
3-benzyl-6-(benzylthio)pyrimidin-4(3H)-one;
3-benzyl-6-[(2,6-dichlorobenzyl)oxy]pyrimidin-4(3H)-one;
3-benzyl-6-[(2-chlorobenzyl)oxy]pyrimidin-4(3H)-one;
3-benzyl-6-[(3-chlorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;
3-benzyl-6-[(3-chlorobenzyl)oxy]pyrimidin-4(3H)-one;
3-benzyl-6-hydroxypyrimidin-4(3H)-one;
5-acetyl-6-hydroxy-2-methyl-1-[choro]phenylpyrimidin-4(3H)-one;
5-benzoyl-2-(benzyloxy)-3-methylpyrimidin-4(3H)-one;
5-benzyl-2-(benzyloxy)-3-methylpyrimidin-4(3H)-one;
5-bromo-3-(5-chlorobenzyl)-6-[(4-chlorobenzyl)oxy]pyrimidin-4(3H)-one;
5-bromo-3-(4-chlorobenzyl)-6-[(4-chlorobenzyl)oxy]pyrimidin-4(3H)-one;
5-bromo-3-(4-fluorobenzyl)-6-[(4-fluorobenzyl)oxy]pyrimidin-4(3H)-one;
5-bromo-3-(4-methoxybenzyl)-6-phenoxypyrimidin-4(3H)-one;
5-bromo-3-(4-methylbenzyl)-6-[(4-methylbenzyl)oxy]pyrimidin-4(3H)-one;
5-bromo-6-[(4-chlorobenzyl)oxy]-3-(2-phenylethyl)pyrimidin-4(3H)-one;
5-bromo-6-[(4-chlorobenzyl)oxy]-3-(4-fluorobenzyl)pyrimidin-4(3H)-one;
5-bromo-6-[(4-chlorobenzyl)oxy]-3-(4-methoxybenzyl)pyrimidin-4(3H)-one;
5-bromo-6-[(4-chlorobenzyl)oxy]-3-[2-(phenylthio)ethyl]pyrimidin-4(3H)-one;
5-bromo-6-[(4-fluorobenzyl)oxy]-3-(3-phenylpropyl)pyrimidin-4(3H)-one;
5-bromo-6-hydroxy-3-(4-hydroxybenzyl)pyrimidin-4(3H)-one;
6-(benzyloxy)-3-(2-fluorobenzyl)pyrimidin-4(3H)-one;
6-(benzyloxy)-3-(3-fluorobenzyl)pyrimidin-4(3H)-one;

6-(benzyloxy)-3-(4-bromobenzyl)pyrimidin-4(3H)-one;
6-(benzyloxy)-3-(4-chlorobenzyl)pyrimidin-4(3H)-one;
6-(benzyloxy)-3-(4-fluorobenzyl)pyrimidin-4(3H)-one;
6-(benzyloxy)-3-[6-(benzyloxy)benzyl]-5-bromopyrimidin-4(3H)-one;
6-(benzyloxy)-5-bromo-3-(2-thien-2-ylethyl)pyrimidin-4(3H)-one;
6-(benzyloxy)-5-bromo-3-(4-fluorobenzyl)pyrimidin-4(3H)-one;
6-(benzyloxy)-5-bromo-3-(4-tert-butylbenzyl)pyrimidin-4(3H)-one;
6-(benzyloxy)-5-bromo-3-(piperidin-3-ylmethyl)pyrimidin-4(3H)-one hydrochloride;
6-(benzyloxy)-5-bromo-3-(piperidin-4-ylmethyl)pyrimidin-4(3H)-one hydrochloride;
6-(benzyloxy)-5-bromo-3-[4-(methylthio)benzyl]pyrimidin-4(3H)-one;
6-(benzyloxy)-5-bromo-3-[4-(trifluoromethoxy)benzyl]pyrimidin-4(3H)-one;
6-(benzyloxy)-5-bromo-3-ethylpyrimidin-4(3H)-one;
6-(benzyloxy)-5-bromo-3-methylpyrimidin-4(3H)-one;
6-(benzyloxy)-5-bromo-3-methylpyrimidin-4(3H)-one hydrobromide;
6-amino-3-benzylpyrimidin-4(3H)-one;
1-bromo-3-(2-chloro-6-fluorobenzyl)-5-methylpyrimidin-4(3H)-one;
1-benzyl-4-(benzyloxy)-6-oxo-1,6-dihydropyrimidine-5-carbaldehyde;
1-benzyl-4-chloro-6-oxo-1,6-dihydropyrimidine-5-carbaldehyde;
1-benzyl-4-hydroxy-6-oxo-1,6-dihydropyrimidine-5-carbaldehyde;
1-benzyl-6-oxo-1,6-dihydropyrimidin-4-yl methanesulfonate;
1-benzyl-6-oxo-1,6-dihydropyrimidin-4-yl methyl(phenyl)carbamate;
1-benzyl-6-oxo-4-phenoxy-1,6-dihydropyrimidine-5-carbaldehyde;
1-benzyl-5-bromo-6-oxo-1,6-dihydropyrimidin-4-yl methyl(phenyl)carbamate; or
2-(benzyloxy)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carbonitrile.

Embodiment 203. Compounds according to embodiment 1 embodiment 118, or embodiment 181, which is

3-(2,6-dichlorophenyl)-6-hydroxy-2-methylpyrimidin-4(1H)-one;
3-(3-fluorobenzyl)-6-hydroxy-2-methylpyrimidin-4(3H)-one;
3-(3-fluorobenzyl)-6-hydroxypyrimidin-4(3H)-one;

3-benzyl-5-bromo-6-(phenylethynyl)pyrimidin-4(3H)-one;
3-benzyl-5-bromo-6-[(4-methylbenzyl)oxy]pyrimidin-4(3H)-one;
3-Benzyl-5-bromo-6-[2,6-(dichlorobenzyl)oxy]pyrimidin-4(3H)-one;
3-benzyl-5-bromo-6-hydroxypyrimidin-4(3H)-one;
3-benzyl-6-(benzyloxy)-3-ethylpyrimidin-4(3H)-one;
3-benzyl-6-(benzyloxy)-5-iodopyrimidin-4(3H)-one;
3-benzyl-6-(benzyloxy)-3-vinylpyrimidin-4(3H)-one;
3-Benzyl-6-[2,6-(dichlorobenzyl)oxy]pyrimidin-4(3H)-one;
3-Benzyl-6-[benzylthio]-5-bromopyrimidin-4(3H)-one;
3-benzyl-6-hydroxy-2-methylpyrimidin-4(3H)-one;
5-acetyl-3-(2,6-dichlorophenyl)-6-hydroxy-6-methylpyrimidin-4(3H)-one;
5-acetyl-3-(2-chlorophenyl)-4-hydroxy-2-methylpyrimidin-4(3H)-one;
5-acetyl-6-(benzyloxy)-3-(2-chlorophenyl)-2-methylpyrimidin-4(3H)-one;
5-bromo-3-(3-fluorobenzyl)-6-(2-phenylethyl)pyrimidin-4(3H)-one;
5-bromo-3-(3-fluorobenzyl)-6-(phenylethynyl)pyrimidin-4(3H)-one;
5-bromo-3-(3-fluorobenzyl)-6-hydroxy-2-methylpyrimidin-4(3H)-one;
5-bromo-3-(3-fluorobenzyl)-6-hydroxypyrimidin-4(3H)-one;
5-bromo-3-(3-fluorobenzyl)-2-methyl-6-(2-phenylethyl)pyrimidin-4(3H)-one;
5-bromo-3-(3-fluorobenzyl)-6-methyl-6-(phenylethynyl)pyrimidin-4(3H)-one;
6-(benzylamino)-3-(3-fluorobenzyl)pyrimidin-4(3H)-one;
6-(benzylamino)-5-bromo-3-(3-fluorobenzyl)pyrimidin-4(3H)-one;
6-(benzyloxy)-3-(2,6-dichlorophenyl)-2-methylpyrimidin-4(3H)-one;
6-(benzyloxy)-3-(3-fluorobenzyl)-5-[(trimethylsilyl)ethynyl]pyrimidin-4(3H)-one;
6-(benzyloxy)-3-(3-fluorobenzyl)-5-iodopyrimidin-4(3H)-one;
6-(benzyloxy)-3-(4-methylbenzyl)pyrimidin-4(3H)-one;
6-(benzyloxy)-3-(4-tert-butylbenzyl)pyrimidin-4(3H)-one;
6-(benzyloxy)-3-[4-(trifluoromethoxy)benzyl]pyrimidin-4(3H)-one;
6-(benzyloxy)-3-[4-(trifluoromethyl)benzyl]pyrimidin-4(3H)-one;
6-(benzyloxy)-5-bromo-3-[2-(trifluoromethyl)benzyl]pyrimidin-4(3H)-one;
6-(benzyloxy)-5-bromo-3-[3-(trifluoromethyl)benzyl]pyrimidin-4(3H)-one;
6-(benzyloxy)-5-bromo-3-[4-(trifluoromethyl)benzyl]pyrimidin-4(3H)-one;
6-(benzyloxy)-5-bromopyrimidin-4(3H)-one;
6-(benzyloxy)-3-ethynyl-3-(3-fluorobenzyl)pyrimidin-4(3H)-one;
6-[(2,6-dichlorobenzyl)oxy]pyrimidine-4-one;

1-benzyl-2-methyl-6-oxo-1,6-dihydropyrimidin-4-yl 4-bromobenzenesulfonate;
1-benzyl-5-bromo-6-oxo-1,6-dihydropyrimidin-4-yl trifluoromethanesulfonate;
4-{[4-(benzyloxy)-6-oxopyrimidin-1(6H)-yl]methyl}benzonitrile;
5-bromo-1-(3-fluorobenzyl)-6-oxo-1,6-dihydropyrimidin-4-yl trifluoromethanesulfonate;
5-bromo-1-(3-fluorobenzyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-4-yl trifluoromethanesulfonate;
4-{[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]methyl}-2-methylbenzoate; or
4-{[4-(benzyloxy)-6-oxopyrimidin-1(6H)-yl]methyl}-2-methylbenzoate.

Still other representative compounds of the invention are

3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methylbenzamide;
5-bromo-3-(2,4-difluorobenzyl)-6-[(2,4-difluorobenzyl)oxy]pyrimidin-4(3H)-one;
5-bromo-3-(2,6-dichlorophenyl)-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;
5-bromo-3-(2,6-dichlorophenyl)-6-[(4-fluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;
5-bromo-3-(2,6-dimethylphenyl)-6-[(4-fluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;
5-bromo-3-(3-fluorobenzyl)-6-[(3-methylbenzyl)oxy]pyrimidin-4-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(2-fluorobenzyl)pyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(2-methoxy-2-methylphenyl)-2-methylpyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(3-fluorobenzyl)pyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(3-methoxybenzyl)pyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-(pyridin-3-ylmethyl)pyrimidin-4(3H)-one;
5-bromo-6-[(5-chlorobenzyl)oxy]-3-(3-fluorobenzyl)pyrimidin-4(3H)-one;
5-bromo-6-[(4-fluorobenzyl)oxy]-3-(pyridin-3-ylmethyl)pyrimidin-4(3H)-one;
5-bromo-6-[(4-fluorobenzyl)oxy]-3-(pyridin-4-ylmethyl)pyrimidin-4(3H)-one;
5-bromo-6-[(4-fluorobenzyl)oxy]-2-methyl-3-(pyrimidin-4-ylmethyl)pyrimidin-4(3H)-one;
5-bromo-6-[(4-fluorobenzyl)oxy]-2-methyl-3-(pyridin-3-

ylmethyl)pyrimidin-4(3H)-one;
5-bromo-6-[(4-fluorobenzyl)oxy]-2-methyl-3-(pyridin-4-ylmethyl)pyrimidin-4(3H)-one; or
4-{[5-bromo-4-[(4-fluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}benzonitrile.

Other representative compounds of the invention are

3-(1-acetyl-1H-benzimidazol-5-yl)-5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;
3-(1-acetyl-1H-imidazol-4-yl)-5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;
3-(1-acetyl-1H-indol-5-yl)-5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;
3-(1-acetyl-1H-pyrazol-4-yl)-5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;
3-(1-acetyl-1H-pyrrol-3-yl)-5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;
3-(1-acetyl-2,3-dihydro-1H-indol-5-yl)-5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;
3-(1-acetyl-3-glycoloyl-2,3-dihydro-1H-benzimidazol-5-yl)-5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;
3-(1H-indazol-5-yl)-6-(1H-indazol-5-ylamino)-2-methylpyrimidin-4(3H)-one;
3-(2,6-difluoro-phenyl)-6-methoxy-2-methyl-1-phenethyl-1H-pyrimidin-4-one;
3-(2-acetyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;
3-(2-acetyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;
3-(2-acetyl-2,3-dihydro-1H-isoindol-5-yl)-5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;
3-(2-Chloro-4-hydroxy-phenyl)-6-(2,4-difluoro-benzyloxy)-2-methyl-1H-pyrimidin-4-one;
3-(3-{[Bis-(2-hydroxy-ethyl)-amino]-methyl}-benzyl)-5-bromo-6-(2,4-difluoro-benzyloxy)-2-methyl-1H-pyrimidin-4-one;
3-(3-acetyl-1-glycoloyl-2,3-dihydro-1H-benzimidazol-5-yl)-5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;
3-(3-Aminomethyl-2-fluoro-benzyl)-5-bromo-6-(2,4-difluoro-benzyloxy)-3H-pyrimidin-4-one;
3-(3-Aminomethyl-benzyl)-5-bromo-6-(2,4-difluoro-benzyloxy)-2-methyl-3H-pyrimidin-4-one;
3-(3-Aminomethyl-benzyl)-6-benzyloxy-5-bromo-3H-pyrimidin-4-one;
3-(3-Fluoro-benzyl)-6-(4-fluoro-benzyloxy)-5-iodo-1H-pyrimidin-4-one;
3-(3-fluorobenzyl)-6-(phenylethynyl)pyrimidin-4(3H)-one;

3-(3-fluorobenzyl)-6-[(4-fluorobenzyl)oxy]-5-methylpyrimidin-4(3H)-one;

3-(4-{[Bis-(2-hydroxy-ethyl)-amino]-methyl}-benzyl)-5-bromo-6-(2,4-difluoro-benzyloxy)-2-methyl-3H-pyrimidin-4-one;

3-(4-Aminomethyl-benzyl)-5-bromo-6-(2,4-difluoro-benzyloxy)-2-methyl-3H-pyrimidin-4-one;

3-(4-Aminomethyl-benzyl)-6-benzyloxy-5-bromo-3H-pyrimidin-4-one;

3-(4-Bromo-2,6-difluoro-phenyl)-6-(2,4-difluoro-benzyloxy)-2-methyl-1H-pyrimidin-4-one;

3-(4-bromo-2-methylphenyl)-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;

3-(4-Chloro-benzyl)-3-[3-(4-chloro-phenyl)-[1,2,4]oxadiazol-5-yl]-3H-pyrimidin-4-one;

3-(4-fluorobenzyl)-6-[(4-fluorobenzyl)oxy]pyrimidin-4(3H)-one;

3-(4-methoxybenzyl)-6-phenoxypyrimidin-4(3H)-one;

3-(biphenyl-4-ylmethyl)-5-bromo-6-[(4-fluorobenzyl)oxy]pyrimidin-4(3H)-one;

1,3-diacetyl-5-{[5-chloro-6-[(2,4-difluorobenzyl)oxy]-4-oxopyrimidin-3(3H)-yl]methyl}-1,3-dihydro-2H-benzimidazol-2-one;

3,5-dibenzyl-6-hydroxy-2-methylpyrimidin-4(3H)-one;

3-[(1-acetyl-1H-indol-5-yl)methyl]-5-chloro-6-[(2,4-difluorobenzyl)oxy]pyrimidin-4(3H)-one;

3-[(1-acetyl-2,3-dihydro-1H-benzimidazol-5-yl)methyl]-5-chloro-6-[(2,4-difluorobenzyl)oxy]pyrimidin-4(3H)-one;

3-[(1-acetyl-2,3-dihydro-1H-indol-5-yl)methyl]-5-chloro-6-[(2,4-difluorobenzyl)oxy]pyrimidin-4(3H)-one;

3-[(1-acetyl-3-glycoloyl-2,3-dihydro-1H-benzimidazol-5-yl)methyl]-5-chloro-6-[(2,4-difluorobenzyl)oxy]pyrimidin-4(3H)-one;

3-[(2-acetyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl]-5-chloro-6-[(2,4-difluorobenzyl)oxy]pyrimidin-4(3H)-one;

3-[(2-acetyl-1,2,3,4-tetrahydroisoquinolin-6-yl)methyl]-5-chloro-6-[(2,4-difluorobenzyl)oxy]pyrimidin-4(3H)-one;

3-[(2-acetyl-2,3-dihydro-1H-isoindol-5-yl)methyl]-5-chloro-6-[(2,4-difluorobenzyl)oxy]pyrimidin-4(3H)-one;

3-[(3-acetyl-1-glycoloyl-2,3-dihydro-1H-benzimidazol-5-yl)methyl]-5-chloro-6-[(2,4-difluorobenzyl)oxy]pyrimidin-4(3H)-one;

3-[(3-acetyl-2,3-dihydro-1H-benzimidazol-5-yl)methyl]-5-chloro-6-[(2,4-difluorobenzyl)oxy]pyrimidin-4(3H)-one;

3-[1,3-bis(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]-5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;

3-[1,3-bis(3-hydroxy-5-methylbutanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]-5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;

3-[1,3-bis(3-hydroxypropanoyl)-2,3-dihydro-1H-benzimidazol-5-

yl]-5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;

3-[1,3-bis(methylsulfonyl)-2,3-dihydro-1H-benzimidazol-5-yl]-5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;

3-[1,3-bis(N-methylglycyl)-2,3-dihydro-1H-benzimidazol-5-yl]-5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;

3-[1-acetyl-3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]-5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;

3-[1-acetyl-3-(3-hydroxy-5-methylbutanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]-5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;

3-[1-acetyl-3-(3-hydroxypropanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]-5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;

3-[1-acetyl-3-(methylsulfonyl)-2,3-dihydro-1H-benzimidazol-5-yl]-5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;

3-[1-acetyl-3-(N-methylglycyl)-2,3-dihydro-1H-benzimidazol-5-yl]-5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;

3-[2-(aminomethyl)benzyl]-5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;

3-[2-(aminomethyl)benzyl]-5-bromo-6-[(2,4-difluorobenzyl)oxy]pyrimidin-4(3H)-one;

3-[2-(aminomethyl)benzyl]-6-(benzyloxy)-5-bromopyrimidin-4(3H)-one;

3-[2-chloro-5-(hydroxymethyl)phenyl]-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;

3-[3-(2-aminoethyl)benzyl]-5-bromo-6-[(2,4-difluorobenzyl)oxy]pyrimidin-4(3H)-one trifluoroacetate;

3-[3-(aminomethyl)benzyl]-5-bromo-6-[(2,4-difluorobenzyl)oxy]pyrimidin-4(3H)-one trifluoroacetate;

3-[3-(aminomethyl)benzyl]-5-bromo-6-[(4-fluorobenzyl)oxy]pyrimidin-4(3H)-one trifluoroacetate;

3-[3-(aminomethyl)benzyl]-5-bromo-6-[(4-fluorobenzyl)oxy]pyrimidin-4(3H)-one;

3-[3-(aminomethyl)phenyl]-5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;

3-[3-acetyl-3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]-5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;

3-[3-acetyl-3-(3-hydroxy-5-methylbutanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]-5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;

3-[3-acetyl-3-(3-hydroxypropanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]-5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;

3-[3-acetyl-3-(methylsulfonyl)-2,3-dihydro-1H-benzimidazol-5-

yl]-5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;

3-[3-acetyl-3-(N-methylglycyl)-2,3-dihydro-1H-benzimidazol-5-yl]-5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;

3-{[1,3-bis(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}-5-chloro-6-[(2,4-difluorobenzyl)oxy]pyrimidin-4(3H)-one;

3-{[1,3-bis(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}-5-chloro-6-[(2,4-difluorobenzyl)oxy]pyrimidin-4(3H)-one;

3-{[1,3-bis(3-hydroxypropanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}-5-chloro-6-[(2,4-difluorobenzyl)oxy]pyrimidin-4(3H)-one;

3-{[1,3-bis(methylsulfonyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}-5-chloro-6-[(2,4-difluorobenzyl)oxy]pyrimidin-4(3H)-one;

3-{[1,3-bis(N-methylglycyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}-5-chloro-6-[(2,4-difluorobenzyl)oxy]pyrimidin-4(3H)-one;

3-{[1-acetyl-3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}-5-chloro-6-[(2,4-difluorobenzyl)oxy]pyrimidin-4(3H)-one;

3-{[1-acetyl-3-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}-5-chloro-6-[(2,4-difluorobenzyl)oxy]pyrimidin-4(3H)-one;

3-{[1-acetyl-3-(3-hydroxypropanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}-5-chloro-6-[(2,4-difluorobenzyl)oxy]pyrimidin-4(3H)-one;

3-{[1-acetyl-3-(methylsulfonyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}-5-chloro-6-[(2,4-difluorobenzyl)oxy]pyrimidin-4(3H)-one;

3-{[1-acetyl-3-(N-methylglycyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}-5-chloro-6-[(2,4-difluorobenzyl)oxy]pyrimidin-4(3H)-one;

3-{[3-acetyl-1-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}-5-chloro-6-[(2,4-difluorobenzyl)oxy]pyrimidin-4(3H)-one;

3-{[3-acetyl-1-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}-5-chloro-6-[(2,4-difluorobenzyl)oxy]pyrimidin-4(3H)-one;

3-{[3-acetyl-1-(3-hydroxypropanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}-5-chloro-6-[(2,4-difluorobenzyl)oxy]pyrimidin-4(3H)-one;

3-{[3-acetyl-1-(methylsulfonyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}-5-chloro-6-[(2,4-difluorobenzyl)oxy]pyrimidin-4(3H)-one;

3-{[3-acetyl-1-(N-methylglycyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}-5-chloro-6-[(2,4-difluorobenzyl)oxy]pyrimidin-4(3H)-

one;
1-acetyl-5-{[5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-oxopyrimidin-3(3H)-yl]methyl}-1,3-dihydro-2H-benzimidazol-2-one;
1-acetyl-5-{[5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-oxopyrimidin-3(3H)-yl]methyl}-3-glycoloyl-1,3-dihydro-2H-benzimidazol-2-one;
1-acetyl-5-{[5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-oxopyrimidin-3(3H)-yl]methyl}-3-(2-hydroxy-2-methylpropanoyl)-1,3-dihydro-2H-benzimidazol-2-one;
1-acetyl-5-{[5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-oxopyrimidin-3(3H)-yl]methyl}-3-(N-methylglycyl)-1,3-dihydro-2H-benzimidazol-2-one;
1-acetyl-5-{[5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-oxopyrimidin-3(3H)-yl]methyl}-3-(3-hydroxypropanoyl)-1,3-dihydro-2H-benzimidazol-2-one;
1-acetyl-5-{[5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-oxopyrimidin-3(3H)-yl]methyl}-3-(3-hydroxy-3-methylbutanoyl)-1,3-dihydro-2H-benzimidazol-2-one;
1-acetyl-5-{[5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-oxopyrimidin-3(3H)-yl]methyl}-3-(methylsulfonyl)-1,3-dihydro-2H-benzimidazol-2-one;
1-acetyl-6-{[5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-oxopyrimidin-3(3H)-yl]methyl}-1,3-dihydro-2H-benzimidazol-2-one;
3-allyl-5-(2,4-difluorobenzyl)-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;
3-allyl-5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;
3-Allyl-5-chloro-6-(2,4-difluoro-benzyloxy)-2-methyl-3H-pyrimidin-4-one;
3-Benzenesulfonyl-6-benzyloxy-5-bromo-3H-pyrimidin-4-one;
3-Benzo[1,3]dioxol-5-ylmethyl-5-bromo-6-(2,4-difluoro-benzyloxy)-3H-pyrimidin-4-one;
3-benzyl-5-[(benzylamino)methyl]-6-(benzyloxy)pyrimidin-4(3H)-one;
3-Benzyl-5-bromo-6-(2,4-difluoro-benzyloxy)-2-methyl-1H-pyrimidin-4-one;
3-benzyl-5-bromo-2-methyl-6-{[2-(trifluoromethyl)benzyl]oxy}pyrimidin-4(3H)-one;
3-benzyl-6-(1-naphthylmethoxy)pyrimidin-4(3H)-one;
3-benzyl-6-(benzyloxy)-5-{[(2-cyclohexylethyl)amino]methyl}pyrimidin-4(3H)-one;
3-benzyl-6-(benzyloxy)-5-bromo-2-methylpyrimidin-4(3H)-one;
3-benzyl-6-(benzylthio)-3,5-dibromopyrimidin-4(3H)-one;
3-benzyl-6-[(4-methylbenzyl)oxy]pyrimidin-4(3H)-one;
3-benzyl-6-benzyloxy-5-bromo-1H-pyrimidin-4-one;
3-benzyl-6-benzyloxy-5-bromo-2-methyl-1H-pyrimidin-4-one;
3-benzyl-6-benzyloxy-5-chloro-1H-pyrimidin-4-one;
3-benzyl-6-phenoxypyrimidin-4(3H)-one;
3-Benzyl-1-[5-(3,4-dichloro-benzylsulfanyl)-[1,3,4]oxadiazol-

2-yl]-3H-pyrimidin-4-one;
3-cyclohexyl-6-[(2,4-difluorobenzyl)oxy]-3,6-dimethylpyrimidin-4(3H)-one;
5-benzyl-6-hydroxy-3-(2-phenylethyl)pyrimidin-4(3H)-one;
5-bromo-3-(2,6-dichlorophenyl)-6-[(4-fluorophenyl)ethynyl]-2-methylpyrimidin-4(3H)-one;
5-bromo-3-(2,6-dichlorophenyl)-6-[2-(4-fluorophenyl)ethyl]-2-methylpyrimidin-4(3H)-one;
5-bromo-3-(2,6-difluoro-phenyl)-6-methoxy-2-methyl-1-(4-methyl-benzyl)-3H-pyrimidin-4-one;
5-bromo-3-(2,6-difluoro-phenyl)-6-methoxy-2-methyl-1-phenethyl-1H-pyrimidin-4-one;
5-bromo-3-(2,6-difluoro-phenyl)-6-methoxy-2-methyl-1-styryl-1H-pyrimidin-4-one;
5-bromo-3-(2,6-difluoro-phenyl)-6-methoxy-2-methyl-1-vinyl-3H-pyrimidin-4-one;
5-bromo-3-(2,6-dimethylphenyl)-2-methyl-6-[(2,4,6-trifluorobenzyl)oxy]pyrimidin-4(3H)-one;
5-bromo-3-(3,5-dibromo-2,6-difluoro-4-hydroxyphenyl)-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;
5-bromo-3-(3-fluorobenzyl)-6-(1-phenylethoxy)pyrimidin-4(3H)-one;
5-bromo-3-(3-fluoro-benzyl)-6-(2,3,4-trifluoro-benzyloxy)-3H-pyrimidin-4-one;
5-bromo-3-(3-fluoro-benzyl)-6-(2-hydroxymethyl-benzyloxy)-3H-pyrimidin-4-one;
5-Bromo-3-(3-fluoro-benzyl)-6-(3-isopropyl-phenyl)-3H-pyrimidin-4-one;
5-bromo-3-(3-fluoro-benzyl)-6-(3-methoxy-phenyl)-3H-pyrimidin-4-one;
5-bromo-3-(3-fluoro-benzyl)-6-(5-methyl-benzyloxy)-3H-pyrimidin-4-one;
5-Bromo-3-(3-fluoro-benzyl)-6-(3-trifluoromethyl-phenyl)-3H-pyrimidin-4-one;
5-bromo-3-(3-fluoro-benzyl)-6-(4-fluoro-benzyloxy)-3H-pyrimidin-4-one;
5-bromo-3-(3-fluoro-benzyl)-6-(4-fluoro-phenyl)-3H-pyrimidin-4-one;
5-bromo-3-(3-fluorobenzyl)-6-[(2-methylbenzyl)oxy]pyrimidin-4(3H)-one;
5-bromo-3-(3-fluorobenzyl)-6-[(3,4,5-trimethoxyphenyl)amino]pyrimidin-4(3H)-one;
5-bromo-3-(3-fluorobenzyl)-6-[(3-fluorobenzyl)amino]pyrimidin-4(3H)-one;
5-bromo-3-(3-fluorobenzyl)-6-[(3-fluorobenzyl)oxy]pyrimidin-4(3H)-one;
5-bromo-3-(3-fluorobenzyl)-6-[(3-methoxybenzyl)oxy]pyrimidin-4(3H)-one;
5-bromo-3-(3-fluorobenzyl)-6-[(5-methylbenzyl)oxy]pyrimidin-

4(3H)-one;
5-bromo-3-(3-fluorobenzyl)-6-[(4-methoxybenzyl)oxy]pyrimidin-4(3H)-one;
5-bromo-3-(3-fluorobenzyl)-6-[(E)-2-(4-fluorophenyl)vinyl]pyrimidin-4(3H)-one;
5-bromo-3-(3-fluorobenzyl)-6-[4-(4-fluorophenyl)piperazin-1-yl]pyrimidin-4(3H)-one;
5-bromo-3-(3-fluorobenzyl)-6-{[2-(hydroxymethyl)benzyl]oxy}pyrimidin-4(3H)-one;
5-bromo-3-(3-fluorobenzyl)-6-{[3-(trifluoromethyl)benzyl]amino}pyrimidin-4(3H)-one;
5-bromo-3-(3-fluorobenzyl)-6-{[4-(trifluoromethyl)benzyl]oxy}pyrimidin-4(3H)-one;
5-bromo-3-(3-fluorobenzyl)-6-{[4-fluoro-2-(trifluoromethyl)benzyl]amino}pyrimidin-4(3H)-one;
5-bromo-3-(3-fluoro-benzyl)-6-naphthalen-2-yl-3H-pyrimidin-4-one;
5-bromo-3-(3-fluoro-benzyl)-6-thiophen-3-yl-3H-pyrimidin-4-one;
5'-bromo-3'-(3-fluoro-benzyl)-6-methoxy-3'H-[3,6']bipyrimidinyl-4'-one;
5-bromo-3-(4-bromo-2,6-difluorophenyl)-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;
5-bromo-3-(4-fluoro-benzyl)-6-(4-fluoro-benzyloxy)-3H-pyrimidin-4-one;
5-bromo-3-(4-fluorobenzyl)-6-[(4-fluorobenzyl)amino]-2-methylpyrimidin-4(3H)-one;
5-bromo-3-(4-tert-butylbenzyl)-6-[(2,4-difluorobenzyl)oxy]pyrimidin-4(3H)-one;
5-bromo-3-(4-tert-butylbenzyl)-6-[(4-fluorobenzyl)oxy]pyrimidin-4(3H)-one;
5-bromo-3-(cyclohexylmethyl)-6-[(4-fluorobenzyl)oxy]pyrimidin-4(3H)-one;
5-bromo-3-(cyclopropylmethyl)-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;
5-bromo-3-(cyclopropylmethyl)-6-[(4-fluorobenzyl)oxy]pyrimidin-4(3H)-one;
5-bromo-3-[2-chloro-5-(hydroxymethyl)phenyl]-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;
5-bromo-3-{[5-(chloromethyl)pyrazin-2-yl]methyl}-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;
5-Bromo-6-(2,4-difluoro-benzyloxy)-3-(2,3-dihydro-1H-indol-5-ylmethyl)-3H-pyrimidin-4-one;
5-bromo-6-(2,4-difluoro-benzyloxy)-3-(2-methyl-4-methylamino-pyrimidin-5-ylmethyl)-3H-pyrimidin-4-one;
5-bromo-6-(2,4-difluoro-benzyloxy)-3-(3-dimethylaminomethyl-benzyl)-3H-pyrimidin-4-one;
5-bromo-6-(2,4-difluoro-benzyloxy)-3-(3-dimethylaminomethyl-benzyl)-2-methyl-3H-pyrimidin-4-one;

5-bromo-6-(2,4-difluoro-benzyloxy)-3-(3-fluoro-benzyl)-3H-pyrimidin-4-one;

5-bromo-6-(2,4-difluoro-benzyloxy)-3-(3-hydroxymethyl-benzyl)-2-methyl-3H-pyrimidin-4-one;

5-bromo-6-(2,4-difluoro-benzyloxy)-3-(3-methoxy-benzyl)-3H-pyrimidin-4-one;

5-bromo-6-(2,4-difluoro-benzyloxy)-3-(5-methylaminomethyl-benzyl)-3H-pyrimidin-4-one;

5-bromo-6-(2,4-difluoro-benzyloxy)-3-(4-dimethylaminomethyl-benzyl)-2-methyl-3H-pyrimidin-4-one;

5-bromo-6-(2,4-difluoro-benzyloxy)-3-(4-dimethylaminomethyl-benzyl)-3H-pyrimidin-4-one;

5-bromo-6-(2,4-difluoro-benzyloxy)-3-(4-hydroxy-benzyl)-2-methyl-3H-pyrimidin-4-one;

5-bromo-6-(2,4-difluoro-benzyloxy)-3-(4-hydroxymethyl-benzyl)-2-methyl-3H-pyrimidin-4-one;

5-bromo-6-(2,4-difluoro-benzyloxy)-3-(4-methoxy-benzyl)-2-methyl-3H-pyrimidin-4-one;

5-bromo-6-(2,4-difluoro-benzyloxy)-3-[1-(2-hydroxy-acetyl)-2,3-dihydro-1H-indol-5-ylmethyl]-2-methyl-3H-pyrimidin-4-one;

5-bromo-6-(2,4-difluoro-benzyloxy)-3-[3-(isopropylamino-methyl)-benzyl]-1H-pyrimidin-4-one;

5-bromo-6-(2,4-difluoro-benzyloxy)-3-[3-(isopropylamino-methyl)-benzyl]-2-methyl-3H-pyrimidin-4-one;

5-bromo-6-(2,4-difluoro-benzyloxy)-3-[4-(1-hydroxy-1-methyl-ethyl)-benzyl]-2-methyl-3H-pyrimidin-4-one;

5-bromo-6-(2,4-difluoro-benzyloxy)-3-[4-(isopropylamino-methyl)-benzyl]-2-methyl-3H-pyrimidin-4-one;

5-bromo-6-(2,4-difluoro-benzyloxy)-3-{3-[(2-hydroxy-ethylamino)-methyl]-benzyl}-2-methyl-3H-pyrimidin-4-one;

5-Bromo-6-(2,4-difluoro-benzyloxy)-2-methyl-3-(1H-pyrazol-3-ylmethyl)-3H-pyrimidin-4-one;

5-bromo-6-(2,4-difluoro-benzyloxy)-2-methyl-3-(3-morpholin-4-ylmethyl-benzyl)-3H-pyrimidin-4-one;

5-bromo-6-(2,4-difluoro-benzyloxy)-2-methyl-3-(3-piperazin-1-ylmethyl-benzyl)-3H-pyrimidin-4-one;

5-bromo-6-(2,4-difluoro-benzyloxy)-2-methyl-3-(3-piperidin-1-ylmethyl-benzyl)-3H-pyrimidin-4-one;

5-bromo-6-(2,4-difluoro-benzyloxy)-2-methyl-3-(4-methylaminomethyl-benzyl)-3H-pyrimidin-4-one;

5-bromo-6-(2,4-difluoro-benzyloxy)-2-methyl-3-(4-morpholin-4-ylmethyl-benzyl)-3H-pyrimidin-4-one;

5-bromo-6-(2,4-difluoro-benzyloxy)-2-methyl-3-(4-piperazin-1-ylmethyl-benzyl)-3H-pyrimidin-4-one;

5-bromo-6-(2,4-difluoro-benzyloxy)-2-methyl-3-(4-piperidin-1-ylmethyl-benzyl)-3H-pyrimidin-4-one;

5-bromo-6-(2,4-difluoro-benzyloxy)-2-methyl-3-[3-(morpholine-4-carbonyl)-benzyl]-3H-pyrimidin-4-one;

5-bromo-6-(2,4-difluoro-benzyloxy)-2-methyl-3-[3-(piperidine-

1-carbonyl)-benzyl]-3H-pyrimidin-4-one;
5-bromo-6-(2,4-difluoro-benzyloxy)-2-methyl-3-[3-(pyrrolidine-1-carbonyl)-benzyl]-3H-pyrimidin-4-one;
5-bromo-6-(2,4-difluoro-benzyloxy)-2-methyl-3-[4-(4-methyl-piperazine-1-carbonyl)-benzyl]-3H-pyrimidin-4-one;
5-bromo-6-(2,4-difluoro-benzyloxy)-2-methyl-3-[4-(morpholine-4-carbonyl)-benzyl]-3H-pyrimidin-4-one;
5-bromo-6-(2,4-difluoro-benzyloxy)-2-methyl-3-[4-(piperidine-1-carbonyl)-benzyl]-3H-pyrimidin-4-one;
5-bromo-6-(2,4-difluoro-benzyloxy)-2-methyl-3-[4-(pyrrolidine-1-carbonyl)-benzyl]-3H-pyrimidin-4-one;
5-bromo-6-(5-chloro-benzyloxy)-3-(3-fluoro-benzyl)-3H-pyrimidin-4-one;
5-bromo-6-(4-chloro-benzyloxy)-3-(2-phenylsulfanyl-ethyl)-3H-pyrimidin-4-one;
5-bromo-6-[(2,4-difluorobenzyl)amino]-3-(2,6-difluorophenyl)-2-methylpyrimidin-4(3H)-one trifluoroacetate;
5-bromo-6-[(2,4-difluorobenzyl)amino]-3-(3-fluorobenzyl)pyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-({5-[(dimethylamino)methyl]pyrazin-2-yl}methyl)-2-methylpyrimidin-4(3H)-one trifluoroacetate;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(1H-indazol-5-ylmethyl)pyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluoro-4-morpholin-4-ylphenyl)-2-methylpyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluorophenyl)-5-(1,2-dihydroxyethyl)-2-methylpyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluorophenyl)-5-(1,2-dihydroxy-2-phenylethyl)-2-methylpyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluorophenyl)-5-(hydroxymethyl)-2-methylpyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluorophenyl)-1-iodo-2-methylpyrimidin-4(1H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluorophenyl)-2-(hydroxymethyl)pyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluorophenyl)-2-(morpholin-4-ylmethyl)pyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluorophenyl)-2-[(dimethylamino)methyl]pyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluorophenyl)-2-[(ethoxyamino)methyl]pyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluorophenyl)-2-{[(2-methoxyethyl)amino]methyl}pyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluorophenyl)-2-methylpyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluorophenyl)-2-methyl-5-vinylpyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluorophenyl)-2-

methyl-5-oxiran-2-ylpyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluorophenyl)-2-methyl-1-[(E)-2-phenylvinyl]pyrimidin-4(1H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(2,6-dimethylphenyl)-2-methylpyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(pyridin-3-ylmethyl)pyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-[(5-{[(2-hydroxyethyl)(methyl)amino]methyl}pyrazin-2-yl)methyl]-2-methylpyrimidin-4(3H)-one trifluoroacetate (salt);
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-[2-(dimethylamino)-4,6-difluorophenyl]-2-methylpyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-[2-(dimethylamino)-4,6-difluorophenyl]-2-methylpyrimidin-4(3H)-one hydrochloride;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-[2,6-difluoro-4-(4-methylpiperazin-1-yl)phenyl]-2-methylpyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-[2-fluoro-5-(hydroxymethyl)phenyl]-2-methylpyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-[2-fluoro-6-(4-methylpiperazin-1-yl)phenyl]-2-methylpyrimidin-4(3H)-one trifluoroacetate;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-[3-(hydroxymethyl)phenyl]-2-methylpyrimidin-4(3H)-one
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-[4-(dimethylamino)-2,6-difluorophenyl]-2-methylpyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-[4-(hydroxymethyl)-2-methoxyphenyl]-2-methylpyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-[5-(1-hydroxy-1-methylethyl)-2-methylphenyl]-2-methylpyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-[5-(hydroxymethyl)-2-methylphenyl]-2-methylpyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-{[5-(1-hydroxy-1-methylethyl)pyrazin-2-yl]methyl}-2-methylpyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-{[5-(hydroxymethyl)pyrazin-2-yl]methyl}-2-methylpyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-{2,4-difluoro-6-[(2-hydroxyethyl)(methyl)amino]phenyl}-2-methylpyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-{2,6-difluoro-4-[(2-hydroxyethyl)(methyl)amino]phenyl}-2-methylpyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-{3-[(dimethylamino)methyl]phenyl}-2-methylpyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-{5-[(dimethylamino)methyl]-2-methylphenyl}-2-methylpyrimidin-4(3H)-one hydrochloride;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-{5-[(isopropylamino)methyl]-2-methylphenyl}-2-methylpyrimidin-4(3H)-one hydrochloride;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-5'-(1-hydroxy-1-methylethyl)-2-methyl-6H-1,2'-bipyrimidin-6-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-(hydroxymethyl)-3-(2,4,6-trifluorophenyl)pyrimidin-4(3H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-({5-[(4-methylpiperazin-1-yl)carbonyl]pyrazin-2-yl}methyl)pyrimidin-4(3H)-one trifluoroacetate;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-({5-[(methylamino)methyl]pyrazin-2-yl}methyl)pyrimidin-4(3H)-one trifluoroacetate;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-(2,4,6-trifluorophenyl)pyrimidin-4(3H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-(2-morpholin-4-ylethyl)pyrimidin-4(3H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-(tetrahydrofuran-2-ylmethyl)pyrimidin-4(3H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-[(5-methylpyrazin-2-yl)methyl]pyrimidin-4(3H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-[2-(methylthio)pyrimidin-4-yl]pyrimidin-4(3H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-[2-(trifluoromethyl)phenyl]pyrimidin-4(3H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-[2-methyl-5-(morpholin-4-ylcarbonyl)phenyl]pyrimidin-4(3H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-[3-(morpholin-4-ylcarbonyl)phenyl]pyrimidin-4(3H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-[3-(piperazin-1-ylcarbonyl)benzyl]pyrimidin-4(3H)-one hydrochloride;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-[3-(piperidin-1-ylcarbonyl)phenyl]pyrimidin-4(3H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-[3-(pyrrolidin-1-ylcarbonyl)phenyl]pyrimidin-4(3H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-[4-(morpholin-4-ylcarbonyl)phenyl]pyrimidin-4(3H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-[4-(piperazin-1-ylcarbonyl)benzyl]pyrimidin-4(3H)-one hydrochloride;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-[4-(piperazin-1-ylcarbonyl)phenyl]pyrimidin-4(3H)-one hydrochloride;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-[4-(piperidin-1-ylcarbonyl)phenyl]pyrimidin-4(3H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-[4-(pyrrolidin-1-ylcarbonyl)phenyl]pyrimidin-4(3H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-{3-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyrimidin-4(3H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-{4-[(4-methylpiperazin-1-yl)carbonyl]benzyl}pyrimidin-4(3H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;

5-bromo-6-[(2,4-difluorophenyl)amino]-3-(3-fluorobenzyl)pyrimidin-4(3H)-one;

5-bromo-6-[(2,6-difluorobenzyl)oxy]-3-(2,6-dimethylphenyl)-2-

methylpyrimidin-4(3H)-one;
5-bromo-6-[(2,6-difluorobenzyl)oxy]-2-methyl-3-(pyridin-4-ylmethyl)pyrimidin-4(3H)-one;
5-bromo-6-[(3,4-difluorobenzyl)oxy]-3-(3-fluorobenzyl)pyrimidin-4(3H)-one;
5-bromo-6-[(4-chloro-2-fluorobenzyl)amino]-3-(3-fluorobenzyl)pyrimidin-4(3H)-one;
5-bromo-6-[(4-fluorobenzyl)oxy]-3-(4-methoxybenzyl)pyrimidin-4(3H)-one;
5-bromo-6-[(4-fluorobenzyl)oxy]-3-[2-(hydroxymethyl)benzyl]pyrimidin-4(3H)-one;
5-bromo-6-[(4-fluorobenzyl)oxy]-3-[3-(trifluoromethyl)benzyl]pyrimidin-4(3H)-one;
5-bromo-6-[(4-fluorobenzyl)oxy]-3-[4-(trifluoromethyl)benzyl]pyrimidin-4(3H)-one;
5-bromo-6-[(4-tert-butylbenzyl)oxy]-3-(3-fluorobenzyl)pyrimidin-4(3H)-one;
5-bromo-6-hydroxy-3-(4-hydroxybenzyl)pyrimidin-4(3H)-one hydrochloride;
5-bromo-2-methyl-3-(pyridin-4-ylmethyl)-6-[(2,4,6-trifluorobenzyl)oxy]pyrimidin-4(3H)-one;
5-bromo-2-methyl-3-pyridin-3-ylmethyl-6-[(pyridin-3-ylmethyl)-amino]-1H-pyrimidin-4-one;
5-chloro-3-(1,3-diacetyl-2,3-dihydro-1H-benzimidazol-5-yl)-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;
5-chloro-3-(4-fluorobenzyl)-6-[(4-fluorobenzyl)oxy]pyrimidin-4(3H)-one;
5-chloro-3-[(1,3-diacetyl-2,3-dihydro-1H-benzimidazol-5-yl)methyl]-6-[(2,4-difluorobenzyl)oxy]pyrimidin-4(3H)-one;
5-chloro-3-[2-chloro-5-(hydroxymethyl)phenyl]-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;
5-chloro-6-(2,4-difluoro-benzyloxy)-3-(3-fluoro-benzyl)-1H-pyrimidin-4-one;
5-chloro-6-(2,4-difluoro-benzyloxy)-3-(3-methanesulfonyl-benzyl)-3H-pyrimidin-4-one;
5-Chloro-6-(2,4-difluoro-benzyloxy)-3-(5-hydroxymethyl-pyrazin-2-ylmethyl)-2-methyl-3H-pyrimidin-4-one;
5-Chloro-6-(2,4-difluoro-benzyloxy)-3-[4-(1,2-dihydroxy-ethyl)-2-methyl-phenyl]-2-methyl-3H-pyrimidin-4-one;
5-chloro-6-(2,4-difluoro-benzyloxy)-3-[4-(isopropylamino-methyl)-benzyl]-3H-pyrimidin-4-one;
5-Chloro-6-(2,4-difluoro-benzyloxy)-2-methyl-3-(5-methyl-pyrazin-2-ylmethyl)-3H-pyrimidin-4-one;
5-chloro-6-[(2,4-difluorobenzyl)amino]-3-(2,6-difluorophenyl)-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-(1,2,3,4-tetrahydroisoquinolin-5-ylmethyl)pyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-(1,2,3,4-tetrahydroisoquinolin-6-ylmethyl)pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-(1,3-diglycoloyl-2,3-dihydro-1H-benzimidazol-5-yl)-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-(1-glycoloyl-1H-benzimidazol-5-yl)-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-(1-glycoloyl-1H-imidazol-4-yl)-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-(1-glycoloyl-1H-indol-5-yl)-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-(1-glycoloyl-1H-pyrazol-4-yl)-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-(1-glycoloyl-1H-pyrrol-3-yl)-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-(1-glycoloyl-2,3-dihydro-1H-indol-5-yl)-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-(1H-indol-5-ylmethyl)pyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-(2,3-dihydro-1H-benzimidazol-5-ylmethyl)pyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-(2,3-dihydro-1H-indol-5-ylmethyl)pyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-(2,3-dihydro-1H-isoindol-5-ylmethyl)pyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluorophenyl)-6-(hydroxymethyl)pyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluorophenyl)-6-[(dimethylamino)methyl]pyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluorophenyl)-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-(2-glycoloyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-(2-glycoloyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-(2-glycoloyl-2,3-dihydro-1H-isoindol-5-yl)-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-(isoquinolin-5-ylmethyl)pyrimidin-4(3H)-one trifluoroacetate;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-(isoquinolin-6-ylmethyl)pyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[(1,3-diglycoloyl-2,3-dihydro-1H-benzimidazol-5-yl)methyl]pyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[(1-glycoloyl-2,3-dihydro-1H-indol-5-yl)methyl]pyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[(1-glycoloyl-2,3-dihydro-1H-benzimidazol-5-yl)methyl]pyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[(2-glycoloyl-1,2,3,4-tetrahydroisoquinolin-6-yl)methyl]pyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[(2-glycoloyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl]pyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[(2-glycoloyl-2,3-

dihydro-1H-isoindol-5-yl)methyl]pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[(3-glycoloyl-2,3-dihydro-1H-benzimidazol-5-yl)methyl]pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[1-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1H-indol-5-yl]-2-methylpyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[1-(2-hydroxy-2-methylpropanoyl)-1H-indol-5-yl]-2-methylpyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[1-(2-hydroxy-2-methylpropanoyl)-1H-benzimidazol-5-yl]-2-methylpyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[1-(2-hydroxy-2-methylpropanoyl)-3-(N-methylglycyl)-2,3-dihydro-1H-benzimidazol-5-yl]-2-methylpyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[1-(2-hydroxy-2-methylpropanoyl)-3-(3-hydroxypropanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]-2-methylpyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[1-(2-hydroxy-2-methylpropanoyl)-3-(methylsulfonyl)-2,3-dihydro-1H-benzimidazol-5-yl]-2-methylpyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[1-(2-hydroxy-2-methylpropanoyl)-1H-pyrrol-3-yl]-2-methylpyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[1-(2-hydroxy-2-methylpropanoyl)-1H-imidazol-4-yl]-2-methylpyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[1-(2-hydroxy-2-methylpropanoyl)-1H-pyrazol-4-yl]-2-methylpyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[1-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1H-indol-5-yl]-2-methylpyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[1-(3-hydroxy-3-methylbutanoyl)-1H-indol-5-yl]-2-methylpyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[1-(3-hydroxy-3-methylbutanoyl)-1H-benzimidazol-5-yl]-2-methylpyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[1-(3-hydroxy-3-methylbutanoyl)-3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]-2-methylpyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[1-(3-hydroxy-3-methylbutanoyl)-3-(N-methylglycyl)-2,3-dihydro-1H-benzimidazol-5-yl]-2-methylpyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[1-(3-hydroxy-3-methylbutanoyl)-3-(3-hydroxypropanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]-2-methylpyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[1-(3-hydroxy-3-methylbutanoyl)-3-(methylsulfonyl)-2,3-dihydro-1H-benzimidazol-5-yl]-2-methylpyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[1-(3-hydroxy-3-methylbutanoyl)-1H-pyrrol-3-yl]-2-methylpyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[1-(3-hydroxy-3-

methylbutanoyl)-1H-imidazol-4-yl]-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[1-(3-hydroxy-3-methylbutanoyl)-1H-pyrazol-4-yl]-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[1-(3-hydroxypropanoyl)-1H-indol-5-yl]-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[1-(3-hydroxypropanoyl)-1H-benzimidazol-5-yl]-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[1-(3-hydroxypropanoyl)-1H-pyrrol-3-yl]-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[1-(3-hydroxypropanoyl)-1H-imidazol-4-yl]-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[1-(3-hydroxypropanoyl)-1H-pyrazol-4-yl]-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[1-(3-hydroxypropanoyl)-2,3-dihydro-1H-indol-5-yl]-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[1-(3-hydroxypropanoyl)-3-(N-methylglycyl)-2,3-dihydro-1H-benzimidazol-5-yl]-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[1-(3-hydroxypropanoyl)-3-(methylsulfonyl)-2,3-dihydro-1H-benzimidazol-5-yl]-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[1-glycoloyl-3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[1-glycoloyl-3-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[1-glycoloyl-3-(3-hydroxypropanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[1-glycoloyl-3-(methylsulfonyl)-2,3-dihydro-1H-benzimidazol-5-yl]-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[1-glycoloyl-3-(N-methylglycyl)-2,3-dihydro-1H-benzimidazol-5-yl]-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[2-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1H-isoindol-5-yl]-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[2-(2-hydroxy-2-methylpropanoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[2-(2-hydroxy-2-methylpropanoyl)-1,2,3,4-tetrahydroisoquinolin-7-yl]-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[2-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1H-isoindol-5-yl]-2-methylpyrimidin-

4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[2-(3-hydroxy-3-methylbutanoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[2-(3-hydroxy-3-methylbutanoyl)-1,2,3,4-tetrahydroisoquinolin-7-yl]-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[2-(3-hydroxypropanoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[2-(3-hydroxypropanoyl)-1,2,3,4-tetrahydroisoquinolin-7-yl]-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[2-(3-hydroxypropanoyl)-2,3-dihydro-1H-isoindol-5-yl]-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[2,6-difluoro-4-(4-methylpiperazin-1-yl)phenyl]-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[3-(2-hydroxy-2-methylpropanoyl)-1-(N-methylglycyl)-2,3-dihydro-1H-benzimidazol-5-yl]-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[3-(2-hydroxy-2-methylpropanoyl)-1-(3-hydroxypropanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[3-(2-hydroxy-2-methylpropanoyl)-1-(methylsulfonyl)-2,3-dihydro-1H-benzimidazol-5-yl]-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[3-(3-hydroxy-5-methylbutanoyl)-1-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[3-(3-hydroxy-5-methylbutanoyl)-1-(N-methylglycyl)-2,3-dihydro-1H-benzimidazol-5-yl]-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[3-(3-hydroxy-5-methylbutanoyl)-1-(3-hydroxypropanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[3-(3-hydroxy-3-methylbutanoyl)-1-(methylsulfonyl)-2,3-dihydro-1H-benzimidazol-5-yl]-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[3-(3-hydroxypropanoyl)-1-(N-methylglycyl)-2,3-dihydro-1H-benzimidazol-5-yl]-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[3-(3-hydroxypropanoyl)-1-(methylsulfonyl)-2,3-dihydro-1H-benzimidazol-5-yl]-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[3-(hydroxymethyl)phenyl]-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[3-glycoloyl-1-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]-2-

methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[3-glycoloyl-1-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]-2-methylpyrimidin-4(3H)-one;;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[3-glycoloyl-1-(3-hydroxypropanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[3-glycoloyl-1-(methylsulfonyl)-2,3-dihydro-1H-benzimidazol-5-yl]-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[3-glycoloyl-1-(N-methylglycyl)-2,3-dihydro-1H-benzimidazol-5-yl]-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[5-(hydroxymethyl)-2-methylphenyl]-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[1-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1H-indol-5-yl]methyl}pyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[1-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}pyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[1-(2-hydroxy-2-methylpropanoyl)-3-(N-methylglycyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}pyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[1-(2-hydroxy-2-methylpropanoyl)-3-(3-hydroxypropanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}pyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[1-(2-hydroxy-2-methylpropanoyl)-3-(methylsulfonyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}pyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[1-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1H-indol-5-yl]methyl}pyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[1-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}pyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[1-(3-hydroxy-3-methylbutanoyl)-3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}pyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[1-(3-hydroxy-3-methylbutanoyl)-3-(N-methylglycyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}pyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[1-(3-hydroxy-3-methylbutanoyl)-3-(3-hydroxypropanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}pyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[1-(3-hydroxy-3-methylbutanoyl)-3-(methylsulfonyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}pyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[1-(3-

hydroxypropanoyl)-2,3-dihydro-1H-indol-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[1-(3-hydroxypropanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[1-(3-hydroxypropanoyl)-3-(N-methylglycyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[1-(3-hydroxypropanoyl)-3-(methylsulfonyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[1-(methylsulfonyl)-2,3-dihydro-1H-indol-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[1-(methylsulfonyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[1-(N-methylglycyl)-2,3-dihydro-1H-indol-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[1-(N-methylglycyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[1-(N-methylglycyl)-3-(methylsulfonyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[1-glycoloyl-3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[1-glycoloyl-3-(3-hydroxypropanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[1-glycoloyl-3-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[1-glycoloyl-3-(methylsulfonyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[1-glycoloyl-3-(N-methylglycyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[2-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1H-isoindol-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[2-(2-hydroxy-2-methylpropanoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[2-(2-hydroxy-2-methylpropanoyl)-1,2,3,4-tetrahydroisoquinolin-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[2-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1H-isoindol-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[2-(3-hydroxy-3-methylbutanoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[2-(3-hydroxy-3-methylbutanoyl)-1,2,3,4-tetrahydroisoquinolin-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[2-(3-hydroxypropanoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[2-(3-hydroxypropanoyl)-1,2,3,4-tetrahydroisoquinolin-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[2-(3-hydroxypropanoyl)-2,3-dihydro-1H-isoindol-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[2-(methylsulfonyl)-2,3-dihydro-1H-isoindol-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[2-(N-methylglycyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[2-(N-methylglycyl)-1,2,3,4-tetrahydroisoquinolin-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[2-(N-methylglycyl)-2,3-dihydro-1H-isoindol-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[3-(2-hydroxy-2-methylpropanoyl)-1-(N-methylglycyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[3-(2-hydroxy-2-methylpropanoyl)-1-(3-hydroxypropanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[3-(2-hydroxy-2-methylpropanoyl)-1-(methylsulfonyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[3-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[3-(3-hydroxy-3-methylbutanoyl)-1-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[3-(3-hydroxy-3-methylbutanoyl)-1-(N-methylglycyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[3-(3-hydroxy-3-

methylbutanoyl)-1-(methylsulfonyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[3-(3-hydroxy-3-methylbutanoyl)-1-(3-hydroxypropanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[3-(3-hydroxypropanoyl)-1-(N-methylglycyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[3-(3-hydroxypropanoyl)-1-(methylsulfonyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[3-(3-hydroxypropanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[3-(methylsulfonyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[3-(N-methylglycyl)-1-(methylsulfonyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[3-(N-methylglycyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[3-glycoloyl-1-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[3-glycoloyl-1-(3-hydroxypropanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[3-glycoloyl-1-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[3-glycoloyl-1-(methylsulfonyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[3-glycoloyl-1-(N-methylglycyl)-2,3-dihydro-1H-benzimidazol-5-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[5-(hydroxymethyl)pyrazin-2-yl]methyl}-2-methylpyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-1-isoquinolin-7-yl-2-methylpyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-6-(hydroxymethyl)-3-(2,4,6-trifluorophenyl)pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-(2,4,6-trifluorophenyl)pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-[(5-methylpyrazin-2-yl)methyl]pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-[3-(methylsulfonyl)-2,3-dihydro-1H-indol-5-yl]pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-[3-

(methylsulfonyl)-1H-indol-5-yl]pyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-[3-(methylsulfonyl)-1H-benzimidazol-5-yl]pyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-[1-(methylsulfonyl)-1H-pyrrol-3-yl]pyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-[1-(methylsulfonyl)-1H-imidazol-4-yl]pyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-[1-(methylsulfonyl)-1H-pyrazol-4-yl]pyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-[1-(N-methylglycyl)-2,3-dihydro-1H-indol-5-yl]pyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-[1-(N-methylglycyl)-1H-indol-5-yl]pyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-[1-(N-methylglycyl)-1H-benzimidazol-5-yl]pyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-[1-(N-methylglycyl)-3-(methylsulfonyl)-2,3-dihydro-1H-benzimidazol-5-yl]pyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-[1-(N-methylglycyl)-1H-pyrrol-3-yl]pyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-[1-(N-methylglycyl)-1H-imidazol-4-yl]pyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-[1-(N-methylglycyl)-1H-pyrazol-4-yl]pyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-[2-(methylsulfonyl)-2,3-dihydro-1H-isoindol-5-yl]pyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-[2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]pyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-[2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl]pyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-[2-(N-methylglycyl)-2,3-dihydro-1H-isoindol-5-yl]pyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-[2-(N-methylglycyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]pyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-[2-(N-methylglycyl)-1,2,3,4-tetrahydroisoquinolin-7-yl]pyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-[3-(N-methylglycyl)-1-(methylsulfonyl)-2,3-dihydro-1H-benzimidazol-5-yl]pyrimidin-4(3H)-one;
4-({[5-bromo-3-(3-fluorobenzyl)-4-oxo-3,4-dihydropyrimidin-6-yl]oxy}methyl)benzonitrile;
6-(2,4-difluoro-benzyloxy)-3-(3-fluoro-benzyl)-5-iodo-1H-pyrimidin-4-one;
6-(2,4-difluoro-benzyloxy)-2-methyl-3-(2,4,6-trifluoro-

phenyl)-1H-pyrimidin-4-one;
6-(allylamino)-3-(2,6-difluorophenyl)-1-iodo-2-methylpyrimidin-4(3H)-one;
6-(allylamino)-5-bromo-3-(2,6-difluorophenyl)-1-iodo-2-methylpyrimidin-4(3H)-one;
6-(allylamino)-5-bromo-3-(2,6-difluorophenyl)-2-methylpyrimidin-4(3H)-one;
6-(benzylamino)-3-(3-fluorobenzyl)-2-methyl-5-nitropyrimidin-4(3H)-one;
6-(benzylamino)-5-bromo-3-(2,6-difluorophenyl)-1-iodo-2-methylpyrimidin-4(3H)-one;
6-(benzyloxy)-3-(2,2-diethoxyethyl)pyrimidin-4(3H)-one;
6-(benzyloxy)-3-(2-oxopropyl)pyrimidin-4(3H)-one;
6-(benzyloxy)-3-(3-fluorobenzyl)-5-(trifluoromethyl)pyrimidin-4(3H)-one;
6-(benzyloxy)-3-(3-fluorobenzyl)-5-methylpyrimidin-4(3H)-one;
6-(benzyloxy)-3-(piperidin-3-ylmethyl)pyrimidin-4(3H)-one trifluoroacetate;
6-(benzyloxy)-3-[4-(methylsulfonyl)benzyl]pyrimidin-4(3H)-one
6-(benzyloxy)-3-[4-(methylthio)benzyl]pyrimidin-4(3H)-one
6-(benzyloxy)-3-ethylpyrimidin-4(3H)-one
6-(benzyloxy)-5-bromo-3-(2,6-dichlorophenyl)-2-methylpyrimidin-4(3H)-one;
6-(benzyloxy)-5-bromo-3-(2-fluorobenzyl)pyrimidin-4(3H)-one;
6-(benzyloxy)-5-bromo-3-(2-morpholin-4-ylethyl)pyrimidin-4(3H)-one;
6-(benzyloxy)-5-bromo-3-(3-fluorobenzyl)pyrimidin-4(3H)-one;
6-(benzyloxy)-5-bromo-3-(3-morpholin-4-yl-3-oxopropyl)pyrimidin-4(3H)-one;
6-(benzyloxy)-5-bromo-3-(3-oxo-3-piperazin-1-ylpropyl)pyrimidin-4(3H)-one hydrochloride;
6-(benzyloxy)-5-bromo-3-(4-bromobenzyl)pyrimidin-4(3H)-one;
6-(benzyloxy)-5-bromo-3-(4-chlorobenzyl)pyrimidin-4(3H)-one;
6-(benzyloxy)-5-bromo-3-(4-methylbenzyl)pyrimidin-4(3H)-one;
6-(benzyloxy)-5-bromo-3-(piperidin-3-ylmethyl)pyrimidin-4(3H)-one;
6-(benzyloxy)-5-bromo-3-[(6-fluoropyridin-3-yl)methyl]pyrimidin-4(3H)-one;
6-(benzyloxy)-5-bromo-3-[2-(2-thienyl)ethyl]pyrimidin-4(3H)-one;
6-(benzyloxy)-5-bromo-3-[2-(3-thienyl)ethyl]pyrimidin-4(3H)-one;
6-(benzyloxy)-5-bromo-3-[4-(morpholin-4-ylcarbonyl)phenyl]pyrimidin-4(3H)-one;
6-(benzyloxy)-5-bromo-3-piperidin-4-ylpyrimidin-4(3H)-one hydrochloride;
4-(biphenyl-2-ylmethoxy)-5-bromo-3-(3-fluorobenzyl)pyrimidin-4(3H)-one;
6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluoro-4-hydroxyphenyl)-

2-methylpyrimidin-4(3H)-one;
6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluoro-4-morpholin-4-ylphenyl)-2-methylpyrimidin-4(3H)-one;
6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluorophenyl)-6-(hydroxymethyl)pyrimidin-4(3H)-one;;
6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluorophenyl)-2-methylpyrimidin-4(3H)-one;
6-[(2,4-difluorobenzyl)oxy]-3-(3-fluorobenzyl)-4-oxo-3,4-dihydropyrimidine-5-carbonitrile;
6-[(2,4-difluorobenzyl)oxy]-3-(3-fluorobenzyl)-5-methylpyrimidin-4(3H)-one;
6-[(2,4-difluorobenzyl)oxy]-3-(4-methoxybenzyl)-2-methylpyrimidin-4(3H)-one;
6-[(2,4-difluorobenzyl)oxy]-3-[2,6-difluoro-4-(4-methylpiperazin-1-yl)phenyl]-2-methylpyrimidin-4(3H)-one;
6-[(2,4-difluorobenzyl)oxy]-3-[4-(dimethylamino)-2,6-difluorophenyl]-2-methylpyrimidin-4(3H)-one;
6-[(2,4-difluorobenzyl)oxy]-3-[5-(hydroxymethyl)-2-methylphenyl]-2-methylpyrimidin-4(3H)-one;
6-[(2,4-difluorobenzyl)oxy]-3-{2,6-difluoro-4-[(2-hydroxyethyl)(methyl)amino]phenyl}-2-methylpyrimidin-4(3H)-one;
6-[(2,4-difluorobenzyl)oxy]-2-(hydroxymethyl)-3-(2,4,6-trifluorophenyl)pyrimidin-4(3H)-one;
6-[(2,4-difluorobenzyl)oxy]-2-(hydroxymethyl)-3-(pyridin-3-ylmethyl)pyrimidin-4(3H)-one;
6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-(tetrahydrofuran-2-ylmethyl)pyrimidin-4(3H)-one;
6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-[2-(trifluoromethyl)phenyl]pyrimidin-4(3H)-one;
6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-prop-2-yn-1-ylpyrimidin-4(3H)-one;
6-[3-amino-1-(2,4-difluoro-phenyl)-propoxy]-5-bromo-2-methyl-3-pyridin-3-ylmethyl-3H-pyrimidin-4-one;
6-{[2-(aminomethyl)-4-fluorobenzyl]oxy}-5-bromo-3-(2,6-difluorophenyl)-2-methylpyrimidin-4(3H)-one trifluoroacetate;
6-anilino-5-bromo-3-(3-fluorobenzyl)pyrimidin-4(3H)-one;
6-benzo[1,3]dioxol-5-yl-5-bromo-3-(3-fluoro-benzyl)-3H-pyrimidin-4-one;
6-benzyloxy-3-difluoromethyl-3H-pyrimidin-4-one;
6-benzyloxy-3H-pyrimidin-4-one;
6-benzyloxy-5-bromo-3-(2-chloro-phenyl)-2-methyl-3H-pyrimidin-4-one;
6-benzyloxy-5-bromo-3-(3-fluoro-benzyl)-3H-pyrimidin-4-one;
6-benzyloxy-5-bromo-3-(4-bromo-benzyl)-3H-pyrimidin-4-one;
6-benzyloxy-5-bromo-3-(4-chloro-benzyl)-3H-pyrimidin-4-one;
6-benzyloxy-5-bromo-3-(4-fluoro-benzyl)-3H-pyrimidin-4-one;
6-benzyloxy-5-bromo-3-(4-methylsulfanyl-benzyl)-3H-pyrimidin-4-one;
6-benzyloxy-5-bromo-3-methanesulfonyl-3H-pyrimidin-4-one;

6-benzyloxy-5-methyl-3H-pyrimidin-4-one;
6-phenoxy-3-{[2-(trimethylsilyl)ethoxy]methyl}pyrimidin-4(3H)-one;
6-phenoxy-3H-pyrimidin-4-one;
1-[4-(5-chloro-phenyl)-piperazine-1-carbonyl]-3-(3,4-dichloro-benzyl)-3H-pyrimidin-4-one;
1-methyl-3-phenyl-3H-pyrimidin-4-one;
5-bromo-3-(3-fluorobenzyl)-6-(4-methylpiperazin-1-yl)pyrimidin-4(3H)-one trifluoroacetate;
3-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-N,N-dimethylbenzamide;
3-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-N-methylbenzamide;
3-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-N-(2-hydroxyethyl)benzamide;
3-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-N,N-bis(2-hydroxyethyl)benzamide;
3-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-N-isopropylbenzamide;
3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methylbenzaldehyde;
3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-(2-hydroxyethyl)-4-methylbenzamide;
3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-hydroxybenzamide;
3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N,N-dimethylbenzamide;
3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-(2-hydroxyethyl)benzamide;
3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-isopropylbenzamide;
3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N,4-dimethylbenzamide;
3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoic acid;
3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]benzoic acid;
3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-[2-(dimethylamino)ethyl]benzamide;
3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-(2-methoxyethyl)benzamide;
3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-[2-(dimethylamino)ethyl]-N-methylbenzamide;
3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-(2-hydroxyethyl)-N-methylbenzamide;
3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-(2-methoxyethyl)-N-methylbenzamide;
4-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-

oxopyrimidin-1(6H)-yl]-N-(2-hydroxyethyl)benzamide;
4-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]benzoic acid;
2-{[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]methyl}benzonitrile;
2-(3-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}phenyl)acetamide;
2-chloro-N-[3-(2,6-dichlorobenzyl)-4-oxo-5-(trifluoromethyl)-3,4-dihydropyrimidin-1(2H)-yl]-4-fluorobenzamide;
6-oxo-2-(2-phenylethyl)-1,6-dihydropyrimidine-5-carbonitrile;
6-oxo-2-phenyl-1,6-dihydropyrimidine-5-carbonitrile;
methyl 3-{[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]methyl}benzoate;
3-{[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]methyl}benzonitrile;
3-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}benzamide;
3-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzonitrile;
methyl 3-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzoate;
3-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzamide;
3-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-N-hydroxybenzamide;
1-benzyl-5-bromo-2-methyl-6-oxo-1,6-dihydropyrimidin-4-yl methanesulfonate;
1-benzyl-2-methyl-6-oxo-1,6-dihydropyrimidin-4-yl methanesulfonate;
3-benzyl-N-(2-morpholin-4-ylethyl)-4-oxo-3,4-dihydropyrimidine-1(2H)-carboxamide;
N-(4-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzyl)-1-hydroxycyclopropanecarboxamide;
2-({[5-bromo-6-oxo-1-(pyridin-3-ylmethyl)-1,6-dihydropyrimidin-4-yl]oxy}methyl)-5-fluorobenzonitrile;
2-({3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]benzyl}amino)-2-oxoethyl acetate;
2-(2-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}phenyl)acetamide;
2-[({1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-5-bromo-2-methyl-6-oxo-1,6-dihydropyrimidin-4-yl}oxy)methyl]-5-fluorobenzonitrile;
2-[4-(benzyloxy)-6-oxopyrimidin-1(6H)-yl]acetamide;
2-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}benzonitrile;
2-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzonitrile;
2-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-

oxopyrimidin-1(6H)-yl]methyl}benzamide;
2-{[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]methyl}benzamide;
(4-{[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]methyl}phenyl)acetic acid;
[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]acetic acid;
[5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluorophenyl)-2-methyl-4-oxo-3,4-dihydropyrimidin-1(2H)-yl]methyl carbamate;
ethyl [2-({[5-bromo-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-4-yl]oxy}methyl)-5-fluorobenzyl]carbamate;
tert-butyl (3-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}benzyl)carbamate;
ethyl (3-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}phenyl)acetate;
(3-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}phenyl)acetonitrile;
methyl (3-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzyl)carbamate;
tert-butyl (3-{[5-bromo-4-[(4-fluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}benzyl)carbamate;
N'-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]-3-(2,6-dichlorobenzyl)-4-oxo-3,4-dihydropyrimidine-1(2H)-carbohydrazide;
3-(2,6-dichlorobenzyl)-4-oxo-N-[3-(trifluoromethyl)benzyl]-3,4-dihydropyrimidine-1(2H)-carboxamide;
3-(2,6-dichlorobenzyl)-4-oxo-N-[4-(trifluoromethoxy)phenyl]-3,4-dihydropyrimidine-1(2H)-carboxamide;
3-(2,6-dichlorobenzyl)-4-oxo-N-[3-(trifluoromethyl)phenyl]-3,4-dihydropyrimidine-1(2H)-carboxamide;
N-(4-chlorophenyl)-3-(2,6-dichlorobenzyl)-4-oxo-3,4-dihydropyrimidine-1(2H)-carboxamide;
3-(2,6-dichlorobenzyl)-N-[2-(dimethylamino)ethyl]-4-oxo-3,4-dihydropyrimidine-1(2H)-carboxamide;
3-(3,4-dichlorobenzyl)-N-(2,4-difluorophenyl)-4-oxo-3,4-dihydropyrimidine-1(2H)-carboxamide;
1-benzyl-5-bromo-2-methyl-6-oxo-1,6-dihydropyrimidin-4-yl 4-bromobenzenesulfonate;
{4-[({6-(benzyloxy)-5-bromo-3-[4-(carboxymethyl)benzyl]-3,4-dihydropyrimidin-4-yl}oxy)methyl]phenyl}acetic acid;
3-(2,6-dichlorobenzyl)-N-(2,4-difluorophenyl)-4-oxo-3,4-dihydropyrimidine-1(2H)-carboxamide;
3-(2,6-dichlorobenzyl)-N-(2-morpholin-4-ylethyl)-4-oxo-3,4-dihydropyrimidine-1(2H)-carboxamide;
N-benzyl-3-(2,6-dichlorobenzyl)-4-oxo-3,4-dihydropyrimidine-1(2H)-carboxamide;
3-(2,6-dichlorobenzyl)-N-[3-(dimethylamino)propyl]-4-oxo-3,4-dihydropyrimidine-1(2H)-carboxamide;
4-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-hydroxybenzamide;

4-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-methylbenzamide;

4-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N,N-dimethylbenzamide;

4-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N,N-bis(2-hydroxyethyl)benzamide;

4-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-isopropylbenzamide;

4-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]benzamide;

4-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}benzamide;

4-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N,3-dimethylbenzamide;

4-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-1H-imidazole-1-carboxamide;

4-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-1H-pyrazole-1-carboxamide;

4-[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]benzoic acid;

4-[4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-3-methylbenzoic acid;

4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-N,N-dimethylbenzamide

4-{[5-chloro-4-[(2,4-difluorobenzyl)amino]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzonitrile trifluoroacetate;

4-{[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]methyl}benzoic acid;

4-{[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]methyl}benzonitrile;

4-{[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]methyl}-N'-hydroxybenzenecarboximidamide;

3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-methylbenzamide;

3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]benzamide;

3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-(2-methoxyethyl)-4-methylbenzamide;

3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N,N,4-trimethylbenzamide;

methyl 3-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-2-fluorobenzoate;

3-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-2-fluorobenzamide;

3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N,4-dimethylbenzamide;

3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methylbenzamide;

3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-

oxopyrimidin-1(6H)-yl]-4-fluoro-N-methylbenzamide;
3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-fluorobenzamide;
3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]benzoic acid;
3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-2-methylbenzoic acid;
3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-1H-pyrrole-1-carboxamide;
methyl 3-[4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]benzoate;
3-acetyl-5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-1-(3-hydroxy-3-methylbutanoyl)-1,3-dihydro-2H-benzimidazol-2-one;
3-acetyl-5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-2-oxo-2,3-dihydro-1H-benzimidazole-1-carboxamide;
3-acetyl-5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-1-(methylsulfonyl)-1,3-dihydro-2H-benzimidazol-2-one;
3-acetyl-6-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-2,3-dihydro-1H-benzimidazole-1-carboxamide;
3-acetyl-6-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-2,3-dihydro-1H-benzimidazole-1-carboxamide;
3-acetyl-6-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-2-oxo-2,3-dihydro-1H-benzimidazole-1-carboxamide;
2-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-6-methylnicotinonitrile;
6-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]nicotinic acid;
6-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-methylnicotinamide;
6-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-(2-hydroxyethyl)nicotinamide;
6-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-(2-methoxyethyl)nicotinamide;
6-{[5-bromo-1-(5-carboxypyridin-2-yl)-2-methyl-6-oxo-1,6-dihydropyrimidin-4-yl]oxy}nicotinic acid;
4-{[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]methyl}benzamide;
methyl 4-{[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]methyl}benzoate;
4-{[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]methyl}benzoic acid;
4-{[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]methyl}benzonitrile;

4-{[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]methyl}-N'-hydroxybenzenecarboximidamide;

4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}benzamide;

methyl 4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}benzoate;

4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzonitrile;

methyl 4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzoate;

4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzamide;

4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzoic acid;

4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-N-hydroxybenzamide;

4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-N-methylbenzamide;

4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-N,N-dimethylbenzamide;

4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-N-(2-hydroxyethyl)benzamide;

4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-N,N-bis(2-hydroxyethyl)benzamide;

4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-N-isopropylbenzamide;

4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-N-[2-(dimethylamino)ethyl]benzamide;

4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-N-(2-methoxyethyl)benzamide;

4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-N-(2-hydroxyethyl)-N-methylbenzamide;

4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-N-(2-methoxyethyl)-N-methylbenzamide;

5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxo-6H-1,4'-bipyrimidine-2'-carbonitrile;

4-{[5-bromo-4-[(4-fluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}benzonitrile;

4-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-3,5-dichlorobenzenesulfonamide;

3-acetyl-5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-1-glycoloyl-1,3-dihydro-2H-benzimidazol-2-one;

3-acetyl-5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-1-(2-hydroxy-2-methylpropanoyl)-1,3-dihydro-2H-benzimidazol-2-one;

3-acetyl-5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-1-(N-methylglycyl)-1,3-dihydro-2H-benzimidazol-2-one;

3-acetyl-5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-1-(3-hydroxypropanoyl)-1,3-dihydro-2H-benzimidazol-2-one;

3-[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]propanamide;

3-[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]propanoic acid;

3-[4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoic acid;

3-[4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]benzaldehyde;

3-acetyl-5-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-2,3-dihydro-1H-benzimidazole-1-carboxamide;

3-acetyl-5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-2,3-dihydro-1H-benzimidazole-1-carboxamide;

3-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzoic acid;

3-{[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]methyl}benzamide;

3-{[5-chloro-4-[(2,4-difluorobenzyl)amino]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzonitrile;

5-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-N,N-dimethylpyrazine-2-carboxamide;

5-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-N-(2-hydroxyethyl)-N-methylpyrazine-2-carboxamide;

5-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-N-(2,3-dihydroxypropyl)pyrazine-2-carboxamide;

5-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-N-methylpyrazine-2-carboxamide;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-1,3-dihydro-2H-indol-2-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}indoline-1-carboxamide;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-1,3-dihydro-2H-isoindole-2-carboxamide;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-3,4-dihydroisoquinoline-2(1H)-carboxamide;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-2,3-dihydro-1H-benzimidazole-1-carboxamide;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-3-glycoloyl-2,3-dihydro-1H-benzimidazole-1-carboxamide;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-

1(6H)-yl]methyl}-3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1H-benzimidazole-1-carboxamide;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-3-(N-methylglycyl)-2,3-dihydro-1H-benzimidazole-1-carboxamide;

5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyrimidin-1(2H)-yl]methyl}-3-(3-hydroxypropanoyl)-2,3-dihydro-1H-benzimidazole-1-carboxamide;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-3-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1H-benzimidazole-1-carboxamide;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-1H-benzimidazole-1,3(2H)-dicarboxamide;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-3-(methylsulfonyl)-2,3-dihydro-1H-benzimidazole-1-carboxamide;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-1,3-dihydro-2H-benzimidazol-2-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-1-glycoloyl-1,3-dihydro-2H-benzimidazol-2-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-1-(2-hydroxy-2-methylpropanoyl)-1,3-dihydro-2H-benzimidazol-2-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-1-(N-methylglycyl)-1,3-dihydro-2H-benzimidazol-2-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-1-(3-hydroxypropanoyl)-1,3-dihydro-2H-benzimidazol-2-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-1-(3-hydroxy-3-methylbutanoyl)-1,3-dihydro-2H-benzimidazol-2-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-2-oxo-2,3-dihydro-1H-benzimidazole-1-carboxamide;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-1-(methylsulfonyl)-1,3-dihydro-2H-benzimidazol-2-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-1,3-diglycoloyl-1,3-dihydro-2H-benzimidazol-2-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-3-glycoloyl-1-(2-hydroxy-2-methylpropanoyl)-1,3-dihydro-2H-benzimidazol-2-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-3-glycoloyl-1-(N-methylglycyl)-1,3-dihydro-2H-benzimidazol-2-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-3-glycoloyl-1-(3-hydroxypropanoyl)-1,3-dihydro-

2H-benzimidazol-2-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-3-glycoloyl-1-(3-hydroxy-3-methylbutanoyl)-1,3-dihydro-2H-benzimidazol-2-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-3-glycoloyl-2-oxo-2,3-dihydro-1H-benzimidazole-1-carboxamide;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-3-glycoloyl-1-(methylsulfonyl)-1,3-dihydro-2H-benzimidazol-2-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-1-glycoloyl-3-(2-hydroxy-2-methylpropanoyl)-1,3-dihydro-2H-benzimidazol-2-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-1,3-bis(2-hydroxy-2-methylpropanoyl)-1,3-dihydro-2H-benzimidazol-2-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-3-(2-hydroxy-2-methylpropanoyl)-1-(N-methylglycyl)-1,3-dihydro-2H-benzimidazol-2-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-3-(2-hydroxy-2-methylpropanoyl)-1-(3-hydroxypropanoyl)-1,3-dihydro-2H-benzimidazol-2-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-1-(3-hydroxy-3-methylbutanoyl)-3-(2-hydroxy-2-methylpropanoyl)-1,3-dihydro-2H-benzimidazol-2-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-3-(2-hydroxy-2-methylpropanoyl)-2-oxo-2,3-dihydro-1H-benzimidazole-1-carboxamide;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-3-(2-hydroxy-2-methylpropanoyl)-1-(methylsulfonyl)-1,3-dihydro-2H-benzimidazol-2-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-1-glycoloyl-3-(N-methylglycyl)-1,3-dihydro-2H-benzimidazol-2-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-1-(2-hydroxy-2-methylpropanoyl)-3-(N-methylglycyl)-1,3-dihydro-2H-benzimidazol-2-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-1,3-bis(N-methylglycyl)-1,3-dihydro-2H-benzimidazol-2-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-1-(3-hydroxypropanoyl)-3-(N-methylglycyl)-1,3-dihydro-2H-benzimidazol-2-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-1-(3-hydroxy-3-methylbutanoyl)-3-(N-methylglycyl)-1,3-dihydro-2H-benzimidazol-2-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-3-(N-methylglycyl)-2-oxo-2,3-dihydro-1H-benzimidazole-1-carboxamide;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-3-(N-methylglycyl)-1-(methylsulfonyl)-1,3-dihydro-2H-benzimidazol-2-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-1-glycoloyl-3-(3-hydroxypropanoyl)-1,3-dihydro-2H-benzimidazol-2-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-1-(2-hydroxy-2-methylpropanoyl)-3-(3-hydroxypropanoyl)-1,3-dihydro-2H-benzimidazol-2-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-3-(3-hydroxypropanoyl)-1-(N-methylglycyl)-1,3-dihydro-2H-benzimidazol-2-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-1,3-bis(3-hydroxypropanoyl)-1,3-dihydro-2H-benzimidazol-2-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-1-(3-hydroxy-3-methylbutanoyl)-3-(3-hydroxypropanoyl)-1,3-dihydro-2H-benzimidazol-2-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-3-(3-hydroxypropanoyl)-2-oxo-2,3-dihydro-1H-benzimidazole-1-carboxamide;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-3-(3-hydroxypropanoyl)-1-(methylsulfonyl)-1,3-dihydro-2H-benzimidazol-2-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-1-glycoloyl-3-(3-hydroxy-3-methylbutanoyl)-1,3-dihydro-2H-benzimidazol-2-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-3-(3-hydroxy-3-methylbutanoyl)-1-(2-hydroxy-2-methylpropanoyl)-1,3-dihydro-2H-benzimidazol-2-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-3-(3-hydroxy-3-methylbutanoyl)-1-(N-methylglycyl)-1,3-dihydro-2H-benzimidazol-2-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-3-(3-hydroxy-3-methylbutanoyl)-1-(3-hydroxypropanoyl)-1,3-dihydro-2H-benzimidazol-2-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-1,3-bis(3-hydroxy-3-methylbutanoyl)-1,3-dihydro-2H-benzimidazol-2-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-3-(3-hydroxy-3-methylbutanoyl)-2-oxo-2,3-dihydro-1H-benzimidazole-1-carboxamide;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-3-(3-hydroxy-3-methylbutanoyl)-1-(methylsulfonyl)-1,3-dihydro-2H-benzimidazol-2-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-2-oxo-1H-benzimidazole-1,3(2H)-dicarboxamide;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-1-glycoloyl-3-(methylsulfonyl)-1,3-dihydro-2H-

benzimidazol-2-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-1-(2-hydroxy-2-methylpropanoyl)-3-(methylsulfonyl)-1,3-dihydro-2H-benzimidazol-2-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-1-(N-methylglycyl)-3-(methylsulfonyl)-1,3-dihydro-2H-benzimidazol-2-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-1-(3-hydroxypropanoyl)-3-(methylsulfonyl)-1,3-dihydro-2H-benzimidazol-2-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-1-(3-hydroxy-3-methylbutanoyl)-3-(methylsulfonyl)-1,3-dihydro-2H-benzimidazol-2-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-3-(methylsulfonyl)-2-oxo-2,3-dihydro-1H-benzimidazole-1-carboxamide;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-1,3-bis(methylsulfonyl)-1,3-dihydro-2H-benzimidazol-2-one;

4-chloro-3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-methylbenzamide;

5-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]indoline-1-carboxamide;

5-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-1H-indole-1-carboxamide;

5-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-1,3-dihydro-2H-isoindole-2-carboxamide;

5-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-1H-benzimidazole-1-carboxamide;

5-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-3-glycoloyl-2,3-dihydro-1H-benzimidazole-1-carboxamide;

5-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1H-benzimidazole-1-carboxamide;

5-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-3-(N-methylglycyl)-2,3-dihydro-1H-benzimidazole-1-carboxamide;

5-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-3-(3-hydroxypropanoyl)-2,3-dihydro-1H-benzimidazole-1-carboxamide;

5-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-3-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1H-benzimidazole-1-carboxamide;

5-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-1H-benzimidazole-1,3(2H)-dicarboxamide;

5-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-3-(methylsulfonyl)-2,3-dihydro-1H-benzimidazole-1-carboxamide;

5-{[4-(benzyloxy)-6-oxopyrimidin-1(6H)-yl]methyl}-5-methylimidazolidine-2,4-dione;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluorophenyl)-2-[2-(2,4-difluorophenyl)ethyl]-4-oxo-3,4-dihydropyrimidine-1(2H)-carbaldehyde;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluorophenyl)-2-methyl-4-oxo-3,4-dihydropyrimidine-1(2H)-carbaldehyde;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluorophenyl)-2-methyl-4-oxo-3,4-dihydropyrimidine-1(2H)-carbaldehyde oxime;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluorophenyl)-2-methyl-4-oxo-3,4-dihydropyrimidine-1(2H)-carbonitrile;

5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-oxo-1,6-dihydropyrimidine-2-carbaldehyde;

5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-oxo-1,6-dihydropyrimidine-2-carboxylic acid;

5-chloro-3-(2,6-dichlorobenzyl)-N-(2,4-difluorophenyl)-4-oxo-3,4-dihydropyrimidine-1(2H)-carboxamide;

5-chloro-3-(2,6-dichlorobenzyl)-N-methyl-4-oxo-N-phenyl-3,4-dihydropyrimidine-1(2H)-carboxamide;

N-benzyl-5-chloro-3-(2,6-dichlorobenzyl)-4-oxo-3,4-dihydropyrimidine-1(2H)-carboxamide;

6-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-3-glycoloyl-2-oxo-2,3-dihydro-1H-benzimidazole-1-carboxamide;

6-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-3-(2-hydroxy-2-methylpropanoyl)-2-oxo-2,3-dihydro-1H-benzimidazole-1-carboxamide;

6-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-3-(N-methylglycyl)-2-oxo-2,3-dihydro-1H-benzimidazole-1-carboxamide;

6-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-3-(3-hydroxypropanoyl)-2-oxo-2,3-dihydro-1H-benzimidazole-1-carboxamide;

6-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-3-(3-hydroxy-3-methylbutanoyl)-2-oxo-2,3-dihydro-1H-benzimidazole-1-carboxamide;

6-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-3-(methylsulfonyl)-2-oxo-2,3-dihydro-1H-benzimidazole-1-carboxamide;

6-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-1-(methylsulfonyl)-1,3-dihydro-2H-benzimidazol-2-one;

6-oxo-2-pyridin-3-yl-1,6-dihydropyrimidine-5-carbonitrile;

6-oxo-2-pyridin-3-yl-1,6-dihydropyrimidine-5-carboxylic acid;

7-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-3,4-dihydroisoquinoline-2(1H)-carboxamide;

benzyl (5-nitro-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)acetate;

benzyl N-[(benzyloxy)carbonyl]-3-[4-(benzyloxy)-6-

oxopyrimidin-1(6H)-yl]alaninate;
benzyl N-acetyl-3-[4-(benzyloxy)-6-oxopyrimidin-1(6H)-yl]alaninate;
ethyl [4-(benzyloxy)-6-oxopyrimidin-1(6H)-yl]acetate;
ethyl [4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]acetate;
ethyl 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]benzoate;
ethyl 3-[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]propanoate;
ethyl 6-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]nicotinate;
N-(3-aminopropyl)-4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzamide hydrochloride;
N-[3-(2,6-dichlorobenzyl)-4-oxo-5-(trifluoromethyl)-3,4-dihydropyrimidin-1(2H)-yl]-4-isopropoxybenzamide;
N-[5-bromo-1-(3-fluorobenzyl)-6-oxo-1,6-dihydropyrimidin-4-yl]-1-phenylmethanesulfonamide;
N-[5-bromo-1-(3-fluorobenzyl)-6-oxo-1,6-dihydropyrimidin-4-yl]-2,4-difluorobenzamide;
N-[5-bromo-1-(3-fluorobenzyl)-6-oxo-1,6-dihydropyrimidin-4-yl]-2,5-difluorobenzamide;
N-[5-bromo-1-(3-fluorobenzyl)-6-oxo-1,6-dihydropyrimidin-4-yl]-2,6-difluorobenzamide;
N-[5-bromo-1-(3-fluorobenzyl)-6-oxo-1,6-dihydropyrimidin-4-yl]-4-fluorobenzamide;
N-[5-bromo-1-(3-fluorobenzyl)-6-oxo-1,6-dihydropyrimidin-4-yl]benzenesulfonamide;
N-[5-bromo-1-(3-fluorobenzyl)-6-oxo-1,6-dihydropyrimidin-4-yl]-N'-(2,4-difluorophenyl)urea;
N-[1-acetyl-3-(4-chlorobenzyl)-2-methyl-4-oxo-1,2,3,4-tetrahydropyrimidin-5-yl]-4-chlorobenzamide;
N'-{[(3-benzyl-4-oxo-3,4-dihydropyrimidin-1(2H)-yl)carbonyl]oxy}pyridine-4-carboximidamide;
N-(3-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzyl)acetamide;
5-chloro-3-(2,6-dichlorobenzyl)-4-oxo-N-[3-(trifluoromethyl)phenyl]-3,4-dihydropyrimidine-1(2H)-carboxamide;
6-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-3,4-dihydroisoquinoline-2(1H)-carboxamide;
6-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-3-glycoloyl-2,3-dihydro-1H-benzimidazole-1-carboxamide;
6-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1H-benzimidazole-1-carboxamide;
6-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-3-(N-methylglycyl)-2,3-dihydro-1H-benzimidazole-1-carboxamide;
6-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-

oxopyrimidin-1(6H)-yl]-3-(3-hydroxypropanoyl)-2,3-dihydro-1H-benzimidazole-1-carboxamide;

6-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-3-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1H-benzimidazole-1-carboxamide;

6-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-3-(methylsulfonyl)-2,3-dihydro-1H-benzimidazole-1-carboxamide;

6-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-3,4-dihydroisoquinoline-2(1H)-carboxamide;

6-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-2,3-dihydro-1H-benzimidazole-1-carboxamide;

6-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-3-glycoloyl-2,3-dihydro-1H-benzimidazole-1-carboxamide;

6-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-3-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1H-benzimidazole-1-carboxamide;

6-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-3-(N-methylglycyl)-2,3-dihydro-1H-benzimidazole-1-carboxamide;

6-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-3-(3-hydroxypropanoyl)-2,3-dihydro-1H-benzimidazole-1-carboxamide;

6-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-3-(3-hydroxy-3-methylbutanoyl)-2,3-dihydro-1H-benzimidazole-1-carboxamide;

6-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-3-(methylsulfonyl)-2,3-dihydro-1H-benzimidazole-1-carboxamide;

6-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-1-glycoloyl-1,3-dihydro-2H-benzimidazol-2-one;

6-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-1-(2-hydroxy-2-methylpropanoyl)-1,3-dihydro-2H-benzimidazol-2-one;

6-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-1-(N-methylglycyl)-1,3-dihydro-2H-benzimidazol-2-one;

6-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-1-(3-hydroxypropanoyl)-1,3-dihydro-2H-benzimidazol-2-one;

6-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-1-(3-hydroxy-3-methylbutanoyl)-1,3-dihydro-2H-benzimidazol-2-one;

6-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-2-oxo-2,3-dihydro-1H-benzimidazole-1-carboxamide;

N-(3-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzyl)methanesulfonamide;

N-(3-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzyl)-2-hydroxyacetamide;

N'-{3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]benzyl}-N,N-dimethylurea;

N-{3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]benzyl}methanesulfonamide;

N-{3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]benzyl}acetamide;

N-{3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]benzyl}urea;

N-(2-aminoethyl)-4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzamide hydrochloride;

N-(3-aminopropyl)-3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]benzamide hydrochloride;

N-(3-aminopropyl)-3-[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]propanamide hydrochloride;

N-(3-aminopropyl)-3-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzamide hydrochloride;

N-(3-aminopropyl)-4-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]benzamide hydrochloride;

N-{3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]benzyl}-2-methoxyacetamide;

N-{3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]benzyl}-2-hydroxyacetamide;

N-{3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]benzyl}-N'-methylurea;

N-{3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]benzyl}morpholine-4-carboxamide;

N-(4-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}phenyl)-2-hydroxyacetamide;

N-(4-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}phenyl)acetamide;

N^1-{3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]benzyl}glycinamide hydrochloride;

N-allyl-2-[(3-benzyl-4-oxo-3,4-dihydropyrimidin-1(2H)-yl)carbonyl]hydrazinecarbothioamide;

tert-butyl 3-{[4-(benzyloxy)-6-oxopyrimidin-1(6H)-yl]methyl}piperidine-1-carboxylate;

tert-butyl 3-{[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]methyl}piperidine-1-carboxylate;

tert-butyl 4-[5-bromo-1-(3-fluorobenzyl)-6-oxo-1,6-dihydropyrimidin-4-yl]piperazine-1-carboxylate;

tert-butyl 4-[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]piperidine-1-carboxylate;

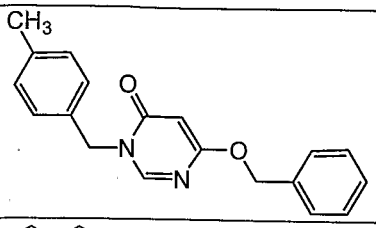
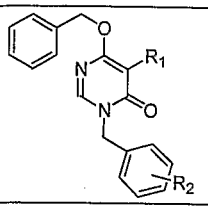
tert-butyl 4-{[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]methyl}piperidine-1-carboxylate;

ethyl 5-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}pyrazine-2-carboxylate;

ethyl 5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-

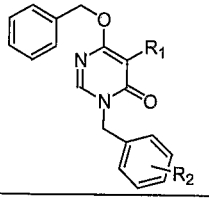
oxopyrimidin-1(6H)-yl]methyl}pyrazine-2-carboxylate;
ethyl N-(5-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-2-methylpyrimidin-4-yl)glycinate trifluoroacetate;
methyl N-acetyl-3-[4-(benzyloxy)-6-oxopyrimidin-1(6H)-yl]alaninate;
N-(2-aminoethyl)-3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]benzamide hydrochloride;
N-(2-aminoethyl)-3-[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]propanamide hydrochloride;
N-(2-aminoethyl)-3-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzamide hydrochloride;
N-(2-aminoethyl)-4-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]benzamide hydrochloride;
methyl 4-{[5-bromo-1-(3-fluorobenzyl)-6-oxo-1,6-dihydropyrimidin-4-yl]amino}benzoate;
methyl 4-{[4-(benzyloxy)-6-oxopyrimidin-1(6H)-yl]methyl}benzoate;
methyl 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoate;
methyl 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-fluorobenzoate;
methyl 3-[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]propanoate;
methyl 3-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}benzoate;
methyl 5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidine-1(6H)-carboxylate;
methyl 3-chloro-4-[4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]benzoate;
methyl 4-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-3-chlorobenzoate;
methyl 4-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]benzoate;
methyl {3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]benzyl}carbamate;
methyl 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]benzoate;
methyl 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoate;
methyl 4-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]benzoate;
methyl (2E)-4-[4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]but-2-enoate;
methyl [2-({[5-bromo-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-4-yl]oxy}methyl)-3,5-difluorobenzyl]carbamate; or
methyl 2-{[5-bromo-4-[(4-fluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}benzoate.

Further representative compounds of the invention are

Example 1	
Examples 3-10	

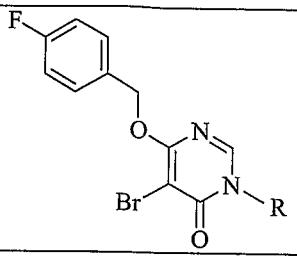
Example No.	R_1	R_2
Ex. 3	-H	4-Br
Ex. 4	-Br	4-Br
Ex. 5	-H	4-Cl
Ex. 6	-Br	4-Cl
Ex. 7	-H	3-F
Ex. 8	-Br	3-F
Ex. 9	-H	2-F
Ex. 10	-Br	2-F

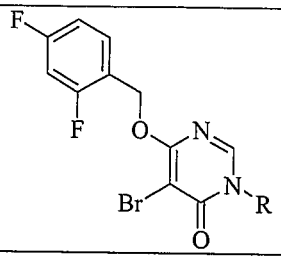
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Examples 12-19	

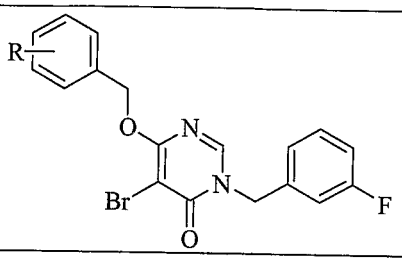
Example No.	R_1	R_2
Ex. 12	-Br	4-benzyloxy
Ex. 13	-H	4-CO_2Me
Ex. 14	-Br	4-CO_2Me
Ex. 15	-Br	4-CO_2H

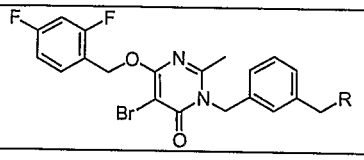
Ex. 16	-H	4-CN
Ex. 17	-Br	4-CN
Ex. 18	-H	4-tButyl
Ex. 19	-Br	4-tButyl

Examples 60-69	
Example No.	R
Ex. 60	pyridin-4-ylmethyl
Ex. 61	pyridin-3-ylmethyl
Ex. 62	4-*tert*-butylbenzyl
Ex. 63	3-trifluoromethylbenzyl
Ex. 64	Biphenyl-2-ylmethyl
Ex. 65	4-methoxybenzyl
Ex. 66	4-cyanobenzyl
Ex. 67	4-trifluoromethylbenzyl
Ex. 68	Biphenyl-4-ylmethyl
Ex. 69	cyclohexylmethyl

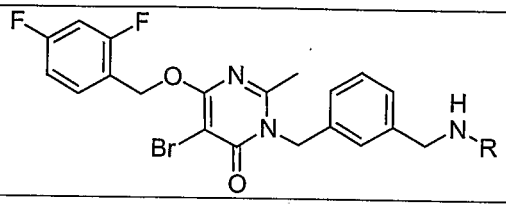
Examples 89-101.	
Example No.	R
Ex. 89	pyridin-3-ylmethyl

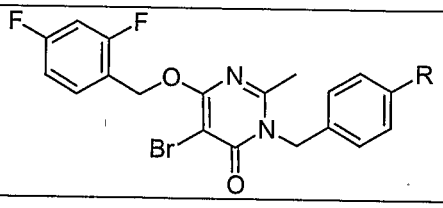
Ex. 90	pyridin-4-ylmethyl
Ex. 91	pyridin-2-ylmethyl
Ex. 92	4-*tert*-butyl)benzyl
Ex. 93	3-methoxybenzyl
Ex. 94	Benzo[1,3]dioxol-5-ylmethyl
Ex. 95	2-fluorobenzyl

Examples 115-123	
Example No.	R
Ex. 115	3-methoxy
Ex. 116	4-*tert*-butyl
Ex. 117	3-methyl
Ex. 118	4-trifluoromethyl
Ex. 119	4-cyano
Ex. 120	2-methyl
Ex. 121	2-phenyl
Ex. 122	4-methoxy
Ex. 123	2-CO_2CH_3

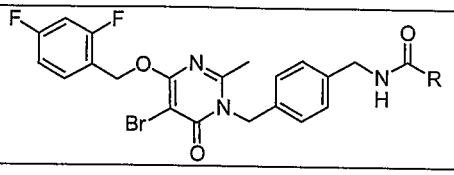
Examples 161-168	
Example No.	R
Ex. 161	-NH_2

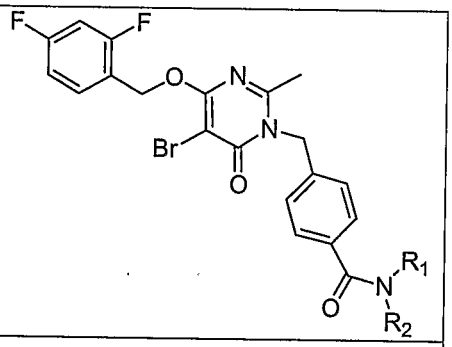
Ex. 162	morpholin-4-yl
Ex. 163	dimethylamino
Ex. 164	isopropylamino
Ex. 165	piperidin-1-yl
Ex. 166	(2-hydroxyethyl)amino
Ex. 167	bis(2-hydroxyethyl)amino
Ex. 168	piperazin-1-yl

Examples 170-174	
Example No.	R
Ex. 170	-C(O)CH_3
Ex. 171	-C(O)OCH_3
Ex. 172	-SO_2CH_3
Ex. 173	-C(O)CH_2OH
Ex. 174	-C(O)NH_2

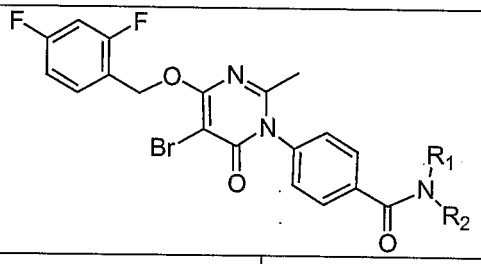
Examples 175-185	
Example No.	R
Ex. 175	-$CH_2NHCH(CH_3)_2$
Ex. 176	morpholin-4-ylmethyl
Ex. 177	-$CH_2N(CH_3)_2$
Ex. 178	piperidin-1-ylmethyl

Ex. 179	[bis(2-hydroxyethyl)amino]methyl
Ex. 180	$-CH_2NHCH_2CH_2OH$
Ex. 181	piperazin-1-ylmethyl
Ex. 182	$-CH_2NHC(O)OCH_3$
Ex. 183	$-CH_2NHC(O)CH_3$
Ex. 184	$-CH_2NHSO_2CH_3$
Ex. 185	$-CH_2NHC(O)NH_2$

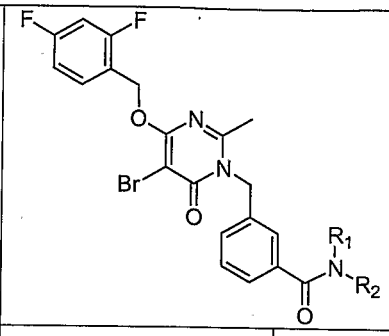
Examples 188-193	
Compound No.	R
Ex. 188	CH_2OCOCH_3
Ex. 189	$C(CH_3)_2OH$
Ex. 190	$C(-CH_2CH_2-)OH$
Ex. 191	CH_2NH_2
Ex. 192	CH_2OH
Ex. 193	$CH_2NHCOCH_3$

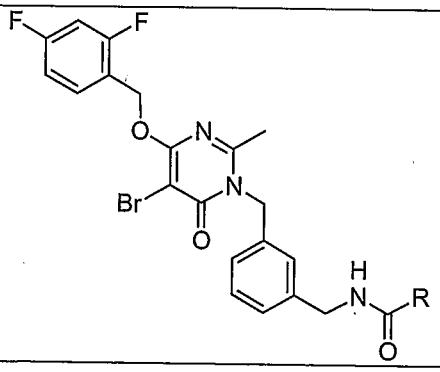
Example 216-231	5-bromo-6-(2,4-difluorobenzyloxy)-2-methyl-3-[4-(aminocarbonyl)benzyl]pyrimidin-4(3H)-ones	
Compound No.	R_1	R_2
Ex. 216	CH_2CH_2NH-	CH_2CH_2NH-
Ex. 217	H	$CH_2CH_2NH_2$
Ex. 218	H	$CH_2CH_2CH_2NH_2$

Ex. 219	H	OH
Ex. 220	H	CH_3
Ex. 221	CH_3	CH_3
Ex. 222	CH_2CH_2O-	CH_2CH_2O-
Ex. 223	CH_2CH_2OH	CH_2CH_2OH
Ex. 224	$CH_2CH_2CH_2$-	$CH_2CH_2CH_2$-
Ex. 225	H	$CH(CH_3)_2$
Ex. 226	CH_2CH_2-	CH_2CH_2-
Ex. 227	$CH_2CH_2N(CH_3)$-	$CH_2CH_2N(CH_3)$-
Ex. 228	H	$CH_2CH_2N(CH_3)_2$
Ex. 229	H	$CH_2CH_2OCH_3$
Ex. 230	CH_3	CH_2CH_2OH
Ex. 231	CH_3	$CH_2CH_2OCH_3$

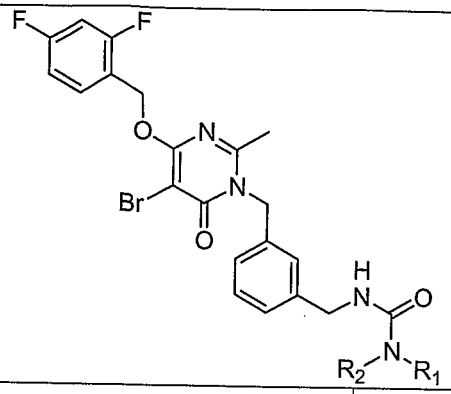
Examples 233-243		
Compound No.	R_1	R_2
Ex. 233	CH_2CH_2NH-	CH_2CH_2NH-
Ex. 234	H	$CH_2CH_2NH_2$
Ex. 235	H	$CH_2CH_2CH_2NH_2$
Ex. 236	H	OH
Ex. 237	H	CH_3
Ex. 238	CH_3	CH_3
Ex. 239	CH_2CH_2O-	CH_2CH_2O-
Ex. 240	CH_2CH_2OH	CH_2CH_2OH
Ex. 241	$CH_2CH_2CH_2$-	$CH_2CH_2CH_2$-
Ex. 242	H	$CH(CH_3)_2$

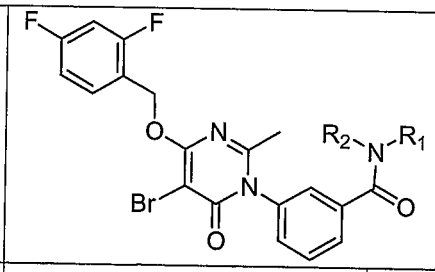
Ex. 243	CH_2CH_2-	CH_2CH_2-

Examples 250-261		
Compound No.	R_1	R_2
Ex. 250	CH_2CH_2NH-	CH_2CH_2NH-
Ex. 251	H	$CH_2CH_2NH_2$
Ex. 252	H	$CH_2CH_2CH_2NH_2$
Ex. 253	H	OH
Ex. 254	CH_3	CH_3
Ex. 255	H	CH_3
Ex. 256	CH_2CH_2O-	CH_2CH_2O-
Ex. 257	H	CH_2CH_2OH
Ex. 258	CH_2CH_2OH	CH_2CH_2OH
Ex. 259	$CH_2CH_2CH_2$-	$CH_2CH_2CH_2$-
Ex. 260	H	$CH(CH_3)_2$
Ex. 261	CH_2CH_2-	CH_2CH_2-

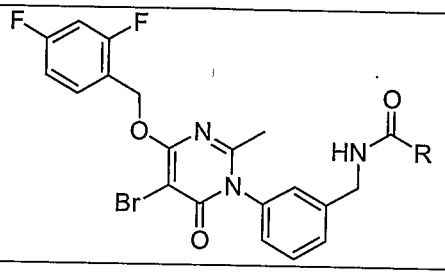
Example 263-265 HCl in dioxane to afford the compounds as hydrochloride salts.	
Compound No.	R

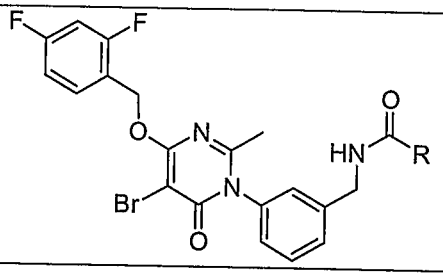
Ex. 263	CH_2NH_2
Ex. 264	$CH_2NHCOCH_3$
Ex. 265	CH_2OCOCH_3

Example 268-270		
Compound No.	R_1	R_2
Ex. 268	CH_2CH_2N-	CH_2CH_2N-
Ex. 269	H	CH_3
Ex. 270	CH_2CH_2O-	CH_2CH_2O-

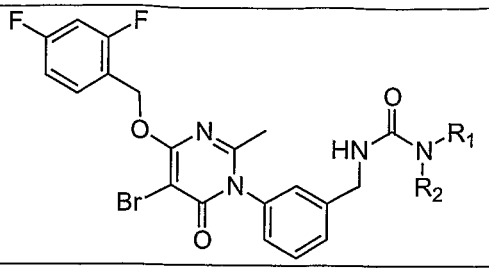
Example 274-289		
Compound No.	R1	R2
Ex. 274	CH2CH2NH-	CH2CH2NH-
Ex. 275	H	CH2CH2NH2
Ex. 276	H	CH2CH2CH2NH2
Ex. 277	H	OH
Ex. 278	CH3	CH3

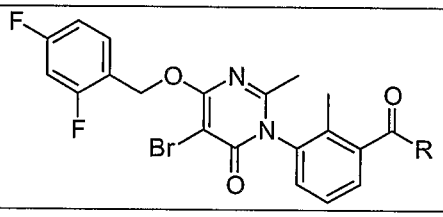
Ex. 279	CH2CH2O-	CH2CH2O-
Ex. 280	H	CH2CH2OH
Ex. 281	CH2CH2CH2-	CH2CH2CH2-
Ex. 282	H	CH(CH3)2
Ex. 283	CH2CH2-	CH2CH2-
Ex. 284	CH2CH2N(CH3)-	CH2CH2N(CH3)-
Ex. 285	H	CH2CH2N(CH3)2
Ex. 286	H	CH2CH2OCH3
Ex. 287	CH3	CH2CH2N(CH3)2
Ex. 288	CH3	CH2CH2OH
Ex. 289	CH3	CH2CH2OCH3

Example 295-296	
Compound No.	R
Ex. 295	CH_3
Ex. 296	OCH_3

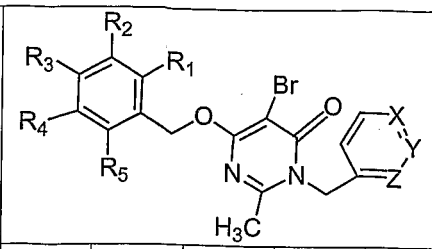
Examples 298-300	
Compound No.	R
Ex. 298	CH_2OCOCH_3
Ex. 299	CH_2NH_2

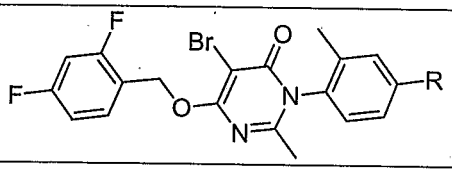
Ex. 300	CH_2OH

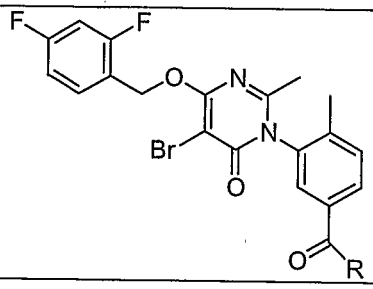
Examples 302-303		
Compound No.	R_1	R_2
Ex. 302	H	CH_3
Ex. 303	CH_2CH_2O-	CH_2CH_2O-

Examples 329-337	
Example No.	R
Ex. 329	$-NHCH_2CH_2OCH_3$
Ex. 330	$-N(CH_3)_2$
Ex. 331	$-NHCH_2CH_2OH$
Ex. 332	$-NHCH_3$
Ex. 333	$-N(CH_3)CH_2CH_2OH$
Ex. 334	4-methylpiperazin-1-yl
Ex. 335	morpholin-4-yl
Ex. 336	$-N(CH_3)CH_2CH_2OCH_3$
Ex. 337	$-NH_2$

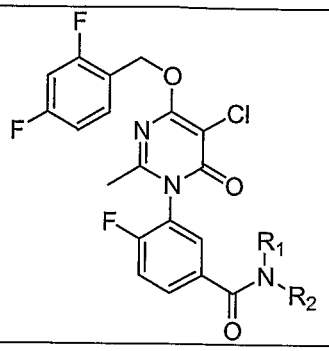
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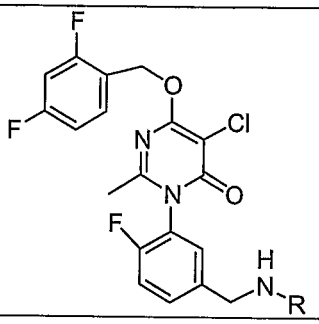
Examples 425-427, 429-435, 436-437								
Ex.No.	R_1	R_2	R_3	R_4	R_5	X	Y	Z
425	H	H	F	H	H	N	CH	CH
426	F	H	F	H	F	N	CH	CH
427	F	H	H	H	F	N	CH	CH
429	H	H	F	H	H	CH	N	CH
430	F	H	F	H	F	CH	N	CH
431	F	H	H	H	H	CH	N	CH
432	F	H	F	F	H	CH	N	CH
433	F	H	Cl	H	H	CH	N	CH
434	Cl	H	F	H	H	CH	N	CH
435	F	H	H	H	F	CH	N	CH
436	H	H	F	H	H	CH	CH	N
437	F	H	F	H	F	CH	CH	N
438	F	H	F	F	H	CH	CH	N

Examples 473-476	
Compound No.	R
Ex. 473	$-CO_2H$
Ex. 474	$-CH_2OH$
Ex. 475	$C(O)NH(CH_2)_2OCH_3$
Ex. 476	$C(O)NHCH_3$

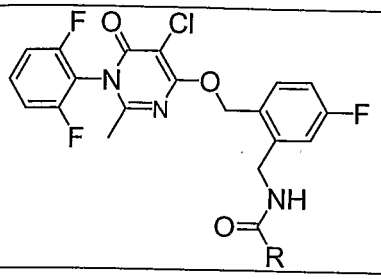
Examples 488-491	
Compound No.	R

Ex. 488	$-NH(CH_2)_2OCH_3$
Ex. 489	$-NHCH_3$
Ex. 490	$-N(CH_3)_2$
Ex. 491	-morpholine

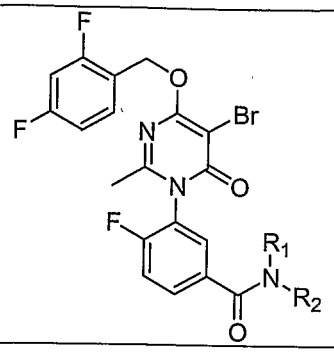
Examples 509-518		
Example No.	R_1	R_2
Ex. 509	CH_3	CH_3
Ex. 510	H	CH_2CH_2OH
Ex. 511	$CH_2CH_2N(CH_3)-$	$CH_2CH_2N(CH_3)-$
Ex. 512	CH_2CH_2O-	CH_2CH_2O-
Ex. 513	H	$CH_2CH_2OCH_3$
Ex. 514	CH_3	CH_2CH_2OH
Ex. 515	H	$CH_2CH_2CH_2OH$
Ex. 516	H	$CH_2CH(OH)CH_2OH$
Ex. 517	H	$C(CH_3)_2CH_2OH-$
Ex. 518	CH_2CH_2NH-	CH_2CH_2NH-

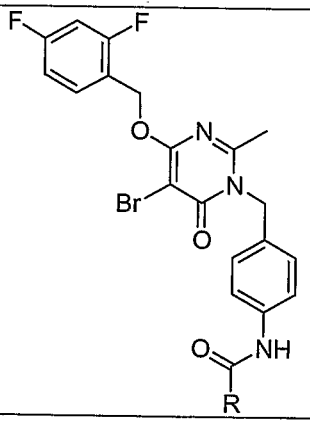
Examples 525-528	
Ex. No.	R

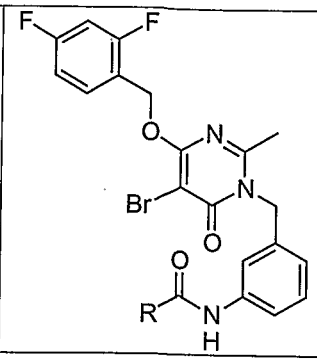
Ex. 525	-C(O)CH_3
Ex. 526	-C(O)CH_2OCH_3
Ex. 527	-SO_2CH_3
Ex. 528	-C(O)NH_2

Examples 531-551	
Compound No.	R
Ex. 531	-OCH_3
Ex. 532	-CF_3
Ex. 533	-O-isopropyl
Ex. 534	-NH-CH_2CH_3
Ex. 535	-O-tetrahydrofuran-3-yl
Ex. 536	-O-propyl
Ex. 537	-O-$CH_2CH=CH_2$
Ex. 538	-O-$CH_2C\equiv CH$
Ex. 539	-O-tButyl
Ex. 540	-NH-tButyl
EX. 541	-$SO_2CH_2CH_2CH_3$
Ex. 542	-$SO_2CH_2CH_3$
Ex. 543	-NH-isopropyl
Ex. 544	-CH_2OCH_3
Ex. 545	-$NHCH_3$
Ex. 546	-N(CH_3)(tButyl)
Ex. 547	-NH(cyclopropyl)
Ex. 548	-$NHCH_2CF_3$
Ex. 549	$NHCH_2$(cyclopropyl)

Ex. 550	-NHCH$_2$(tButyl)
Ex. 551	-N(CH$_3$)$_2$

Example 601-603		
Compound No.	R_1	R_2
Ex. 601	CH_2CH_2O-	CH_2CH_2-
Ex. 602	CH_3	CH_2CH_2OH
Ex. 603	H	$CH_2C(CH_3)_2OH$

Examples 614-616	
Compound No.	R
Ex. 614	CH_2OH
Ex. 615	CH_2OCOCH_3
Ex. 616	$SO_2N(CH_3)_2$

Example 618-620	
Compound No.	R
Ex. 618	CH_2OH
Ex. 619	CH_2OCOCH_3
Ex. 620	$SO_2N(CH_3)_2$

Other representative compounds of the invention are

methyl 3-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}benzoate;

methyl 4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}benzoate;

3-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}benzamide;

4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}benzamide;

3-(3-Aminomethyl-2-fluorobenzyl)-5-bromo-6-(2,4-difluorobenzyloxy)-3H-pyrimidin-4-one;

methyl 3-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-2-fluorobenzoate;

3-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-2-fluorobenzamide;

5-bromo-6-(2,4-difluorobenzyloxy)-3-(3-fluorobenzyl)-3H-pyrimidin-4-one;

5-bromo-3-(3-fluorobenzyl)-6-(2,3,4-trifluorobenzyloxy)-3H-pyrimidin-4-one;

3-[3-(2-aminoethyl) benzyl]-5-bromo-6-(2,4-difluorobenzyloxy)-3H-pyrimidin-4-one;

6-(benzyloxy)-5-bromopyrimidin-4(3H)-one;

5-chloro-6-(2,4-difluorobenzyloxy)-3-(3-fluorobenzyl)-3H-pyrimidin-4-one;

5-bromo-6-(3-chlorobenzyloxy)-3-(3-fluorobenzyl)-3H-pyrimidin-4-one;

5-bromo-6-(3,4-difluorobenzyloxy)-3-(3-fluorobenzyl)-3H-pyrimidin-4-one;

5-bromo-3-(3-fluorobenzyl)-6-(4-fluorobenzyloxy)-3H-pyrimidin-4-one;

5-bromo-3-(3-fluorobenzyl)-6-(3-fluorobenzyloxy)-3H-

pyrimidin-4-one;
5-bromo-3-(3-fluorobenzyl)-6-(2-hydroxymethylbenzyloxy)-3H-pyrimidin-4-one;
2-(2-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}phenyl)acetamide;
ethyl (3-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}phenyl)acetate;
2-(3-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}phenyl)acetamide;
6-(2,4-difluorobenzyloxy)-3-(3-fluorobenzyl)-5-methyl-3H-pyrimidin-4-one;
6-(2,4-difluorobenzyloxy)-3-(3-fluorobenzyl)-5-iodo-3H-pyrimidin-4-one;
4-[(2,4-difluorobenzyl)oxy]-1-(3-fluorobenzyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile;
3-cyclohexyl-6-(2,4-difluorobenzyloxy)-2,5-dimethyl-3H-pyrimidin-4-one;
5-chloro-6-(2,4-difluorobenzyloxy)-2-methyl-3-(1H-pyrazol-4-ylmethyl)-3H-pyrimidin-4-one;
4-{[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]methyl}benzonitrile;
3-{[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]methyl}benzonitrile;
3-[4-(aminomethyl)benzyl]-6-(benzyloxy)-5-bromopyrimidin-4(3H)-one;
3-[3-(aminomethyl)benzyl]-6-(benzyloxy)-5-bromopyrimidin-4(3H)-one;
3-[2-(aminomethyl)benzyl]-6-(benzyloxy)-5-bromopyrimidin-4(3H)-one;
4-{[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]methyl}benzamide;
3-{[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]methyl}benzamide;
2-{[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]methyl}benzamide;
methyl 3-{[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]methyl}benzoate;
methyl 4-{[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]methyl}benzoate;
4-[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]benzonitrile;
2-[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]benzonitrile;
(4-{[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]methyl}phenyl)acetic acid
2-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzonitrile;
3-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzonitrile;

4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzonitrile;

4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzamide;

methyl 4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzoate;

methyl 3-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzoate;

3-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzamide;

2-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzamide

3-[2-(aminomethyl)benzyl]-5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;

5-bromo-3-[3-(bromomethyl)benzyl]-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;

5-bromo-3-[4-(bromomethyl)benzyl]-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;

3-[4-(aminomethyl)benzyl]-5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;

3-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzoic acid;

4-(4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzoyl)piperazine-1-carboxamide;

N-(4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzyl)-2-methoxyacetamide;

3-{4-[(4-acetylpiperazin-1-yl)carbonyl]benzyl}-5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-(4-{[4-(methylsulfonyl)piperazin-1-yl]carbonyl}benzyl)pyrimidin-4(3H)-one;

methyl 4-[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]benzoate;

4-[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]benzoic acid;

4-[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]benzamide;

3-[4-(aminomethyl)phenyl]-6-(benzyloxy)-5-bromopyrimidin-4(3H)-one;

6-(benzyloxy)-5-bromo-3-(4-methylbenzyl)pyrimidin-4(3H)-one;

6-(benzyloxy)-5-bromo-3-ethylpyrimidin-4(3H)-one;

methyl 4-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]benzoate;

5-bromo-6-[(2,4-diflurorbenzyl)oxy]-3-[3-(hydroxymethyl)phenyl]-2-methylpyrimidin-4(3H)-one;

methyl 4-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]benzoate;

4-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-

oxopyrimidin-1(6H)-yl]benzoic acid;
6-(benzyloxy)-3-(3-fluorobenzyl)-5-(trifluoromethyl)pyrimidin-4(3H)-one;
4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzoic acid;
5-bromo-6-[(2,4-diflurobenzyl)oxy]-3-[4-(hydroxymethyl)benzyl]-2-methylpyrimidin-4(3H)-one;
5-bromo-6-[(2,4-diflurobenzyl)oxy]-3-[4-(1-hydroxy-1-methylethyl)benzyl]-2-methylpyrimidin-4(3H)-one;
5-bromo-6-[(2,4-diflurobenzyl)oxy]- 2-methyl-3-{4-[(methylamino)methyl]benzyl}pyrimidin-4(3H)-one;
6-[(2,4-diflurobenzyl)oxy]-3-(4-methoxybenzyl)-2-methylpyrimidin-4-(3H)-one;
5-bromo-6-hydroxy-3-(4-hydroxybenzyl)pyrimidin-4(3H)-one;
5-bromo-6-[(2,4-diflurobenzyl)oxy]-3-(4-methoxybenzyl)-2-methylpyrimidin-4(3H)-one;
5-bromo-6-[(2,4-diflurobenzyl)oxy]-3-(4-hydroxybenzyl)-2-methylpyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-{4-[(4-hydroxy-4-methylpiperidin-1-yl)carbonyl]benzyl}-2-methylpyrimidin-4(3H)-one;
4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-N-(2-hydroxy-2-methylpropyl)benzamide;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3{4-[(4-hydroxypiperidin-1-yl)carbonyl]benzyl}-2-methylpyrimidin-4(3H)-one;
4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-N-(2-hydroxyethyl)benzamide;
6-(benzyloxy)-5-bromo-3-methylpyrimidin-4(3H)-one hydrobromide;
6-(benzyloxy)-5-bromo-3-methylpyrimidin-4(3H)-one;
4-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-(2-hydroxyethyl)benzamide;
4-{[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]methyl}-N'-hydroxybenzenecarboximidamide;
4-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]benzamide;
6-(benzyloxy)-5-bromo-3-[4-(morpholin-4-ylcarbonyl)phenyl]pyrimidin-4(3H)-one;
6-(Benzyloxy)-5-bromo-3-[4-(piperazin-1-ylcarbonyl)phenyl]pyrimidin-4(3H)-one hydrochloride;
4-[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]-N-hydroxybenzamide;
methyl 4-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzoate;
3-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-N-methylbenzamide;
6-(benzyloxy)-5-bromo-3-(piperidin-4-ylmethyl)pyrimidin-

4(3H)-one hydrochloride;
6-(benzyloxy)-3-[4-(trifluoromethyl)benzyl]pyrimidin-4(3H)-one;
N-(3-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzyl)-2-methoxyacetamide;
N-(3-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzyl)-2-hydroxy-2-methylpropanamide;
N'-(3-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzyl)-N,N-dimethylurea;
N-(3-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzyl)-1-hydroxycyclopropanecarboxamide;
6-(benzyloxy)-5-bromo-3-[4-(trifluoromethyl)benzyl]pyrimidin-4(3H)-one;
3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]benzoic acid;
ethyl 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]benzoate;
3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-methylbenzamide;
6-(benzyloxy)-5-bromo-3-(piperidin-3-ylmethyl)pyrimidin-4(3H)-one hydrochloride;
6-(benzyloxy)-5-bromo-3-(2-thien-3-ylethyl)pyrimidin-4(3H)-one;
3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]benzamide;
3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]benzoic acid;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[3-(hydroxymethyl)phenyl]-2-methylpyrimidin-4(3H)-one;
3-[3-(aminomethyl)phenyl]-5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;
N-{3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]benzyl}methanesulfonamide;
N-{3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]benzyl}-2-methoxyacetamide;
6-(benzyloxy)-5-bromo-3-(2-thien-2-ylethyl)pyrimidin-4(3H)-one;
N'-{3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]benzyl}-N,N-dimethylurea;
N-{3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]benzyl}urea;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-{3-[(dimethylamino)methyl]phenyl}-2-methylpyrimidin-4(3H)-one;
N-{4-[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]benzyl}acetamide;
N-{4-[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]benzyl}-2-hydroxyacetamide;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-(2-morpholin-4-ylethyl)pyrimidin-4(3H)-one;

ethyl 3-[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]propanoate;

6-(benzyloxy)-5-bromo-3-[3-(trifluoromethyl)benzyl]pyrimidin-4(3H)-one;

methyl 3-[4-(benzyloxy)-5-bromo-6-oxopyrimidin-1(6H)-yl]propanoate;

N-[5-bromo-1-(3-fluorobenzyl)-6-oxo-1,6-dihydropyrimidin-4-yl]-2,6-difluorobenzamide;

5-bromo-3-(4-bromo-2,6-difluorophenyl)-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-(2,4,6-trifluorophenyl)pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-(2,4,6-trifluorophenyl)pyrimidin-4(3H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-(hydroxymethyl)-3-(2,4,6-trifluorophenyl)pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-(hydroxymethyl)-3-(2,4,6-trifluorophenyl)pyrimidin-4(3H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluoro-4-morpholin-4-ylphenyl)-2-methylpyrimidin-4(3H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-[2,6-difluoro-4-(4-methylpiperazin-1-yl)phenyl]-2-methylpyrimidin-4(3H)-one;

6-(benzyloxy)-5-bromo-3-[2-(trifluoromethyl)benzyl]pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[2,6-difluoro-4-(4-methylpiperazin-1-yl)phenyl]-2-methylpyrimidin-4(3H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-[4-(dimethylamino)-2,6-difluorophenyl]-2-methylpyrimidin-4(3H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-{2,6-difluoro-4-[(2-hydroxyethyl)(methyl)amino]phenyl}-2-methylpyrimidin-4(3H)-one;

5-bromo-3-(3,5-dibromo-2,6-difluoro-4-hydroxyphenyl)-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;

2-{4-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-3,5-difluorophenoxy}acetamide;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-[2,6-difluoro-4-(2-hydroxyethoxy)phenyl]-2-methylpyrimidin-4(3H)-one;

5-bromo-3-(2,6-difluorophenyl)-6-{[4-fluoro-2-(hydroxymethyl)benzyl]oxy}-2-methylpyrimidin-4(3H)-one;

5-chloro-3-(2,6-difluorophenyl)-6-{[4-fluoro-2-(hydroxymethyl)benzyl]oxy}-2-methylpyrimidin-4(3H)-one;

3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-2-methyl-N-(2-morpholin-4-ylethyl)benzamide;

6-(benzyloxy)-3-[4-(trifluoromethoxy)benzyl]pyrimidin-4(3H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-[3-(hydroxymethyl)-2-methylphenyl]-2-methylpyrimidin-4(3H)-one;

3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-(2-methoxyethyl)-2-methylbenzamide;

6-(benzyloxy)-5-bromo-3-[4-(trifluoromethoxy)benzyl]pyrimidin-4(3H)-one;

3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N,2-dimethylbenzamide;

3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-(2-hydroxyethyl)-2-methylbenzamide;

3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-2-methylbenzamide;

4-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-3,5-difluorobenzonitrile;

3-[4-(aminomethyl)-2,6-difluorophenyl]-5-chloro-6-[(2,4-difluorobenzyl)oxy]pyrimidin-4(3H)-one hydrochloride;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{2,6-difluoro-4-[(methylamino)methyl]phenyl}pyrimidin-4(3H)-one hydrochloride;

5-chloro-3-(4-{[(cyclopropylmethyl)amino]methyl}-2,6-difluorophenyl)-6-[(2,4-difluorobenzyl)oxy]pyrimidin-4(3H)-one hydrochloride;

4-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-3,5-difluoro-N,N-dimethylbenzamide;

4-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-3-fluoro-5-methoxybenzonitrile;

N-{4-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-3,5-difluorobenzyl}urea;

3-benzyl-6-(benzyloxy)-2-methylpyrimidin-4(3H)-one;

2-({4-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-3,5-difluorobenzyl}amino)-1,1-dimethyl-2-oxoethyl acetate;

N-{4-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-3,5-difluorobenzyl}acetamide;

N-{4-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-3,5-difluorobenzyl}-2-methoxyacetamide;

N-{4-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-3,5-difluorobenzyl}-2-furamide;

N-{4-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-3,5-difluorobenzyl}-1H-imidazole-4-carboxamide;

N-{4-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-3,5-difluorobenzyl}prolinamide;

N-{4-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-3,5-difluorobenzyl}-3-hydroxy-3-methylbutanamide;

N-{4-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-3,5-difluorobenzyl}-1-hydroxycyclopropanecarboxamide;

N-{4-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-3,5-difluorobenzyl}-2-hydroxy-2-methylpropanamide;

4-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-3,5-difluorobenzonitrile;

3-benzyl-6-(benzyloxy)-5-bromo-2-methylpyrimidin-4(3H)-one;

5-bromo-3-(3-fluorobenzyl)-2-methyl-6-(2-phenylethyl)pyrimidin-4(3H)-one;

5-bromo-3-(3-fluorobenzyl)-6-(1-phenylethoxy)pyrimidin-4(3H)-one;

5-bromo-3-(3-fluorobenzyl)-6-[(E)-2-(4-fluorophenyl)ethenyl]pyrimidin-4(3H)-one;

6-(benzyloxy)-5-bromo-3-[(6-fluoropyridin-3-yl)methyl]pyrimidin-4(3H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(2,6-dimethylphenyl)-2-methylpyrimidin-4(3H)-one;

5-bromo-3-(2,6-dimethylphenyl)-6-[(4-fluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;

5-bromo-3-(2,6-dimethylphenyl)-2-methyl-6-[(2,4,6-trifluorobenzyl)oxy]pyrimidin-4(3H)-one;

5-bromo-6-[(2,6-difluorobenzyl)oxy]-3-(2,6-dimethylphenyl)-2-methylpyrimidin-4(3H)-one;

5-bromo-3-(2,6-dichlorophenyl)-6-[(4-fluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;

5-bromo-3-(2,6-dichlorophenyl)-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;

3-benzyl-6-(benzyloxy)-1,5-dibromo-2-methylpyrimidin-4(3H)-one;

5-bromo-3-(2,6-dichlorophenyl)-6-[(2,6-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(2-methoxy-2-methylphenyl)-2-methylpyrimidin-4(3H)-one;

4-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-3,5-dichlorobenzenesulfonamide;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluorophenyl)-2-methylpyrimidin-4(3H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluorophenyl)-1-iodo-2-methylpyrimidin-4(1H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-[2-(dimethylamino)-4,6-difluorophenyl]-2-methylpyrimidin-4(3H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-{2,4-difluoro-6-[(2-hydroxyethyl)(methyl)amino]phenyl}-2-methylpyrimidin-4(3H)-one;

2-({[5-bromo-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-4-yl]oxy}methyl)-5-fluorobenzonitrile;

6-{[2-(aminomethyl)-4-fluorobenzyl]oxy}-5-bromo-3-(2,6-difluorophenyl)-2-methylpyrimidin-4(3H)-one trifluoroacetate;

N-[2-({[5-bromo-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-4-yl]oxy}methyl)-5-fluorobenzyl]urea;

3-benzyl-6-[(3-chlorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;

methyl [2-({[5-bromo-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-4-yl]oxy}methyl)-5-fluorobenzyl]carbamate;

N-[2-({[5-bromo-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-4-yl]oxy}methyl)-5-fluorobenzyl]-2-

hydroxyacetamide;

ethyl [2-({[5-chloro-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-4-yl]oxy}methyl)-5-fluorobenzyl]carbamate;

isobutyl [2-({[5-chloro-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-4-yl]oxy}methyl)-5-fluorobenzyl]carbamate;

cyclopropylmethyl [2-({[5-chloro-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-4-yl]oxy}methyl)-5-fluorobenzyl]carbamate;

3-[(4-amino-2-methylpyrimidin-5-yl)methyl]-5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one trifluoroacetate;

3-[(4-amino-2-methylpyrimidin-5-yl)methyl]-5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one hydrochloride;

3-[(4-amino-2-methylpyrimidin-5-yl)methyl]-5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one trifluoroacetate;

3-[(4-amino-2-methylpyrimidin-5-yl)methyl]-5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one hydrochloride;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(1H-indazol-5-ylmethyl)-2-methylpyrimidin-4(3H)-one trifluoroacetate;

3-benzyl-5-bromo-6-[(3-chlorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;

N^1-(5-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-2-methylpyrimidin-4-yl)glycinamide trifluoroacetate;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-{[2-(methylthio)pyrimidin-4-yl]methyl}pyrimidin-4(3H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-{[2-(methylsulfonyl)pyrimidin-4-yl]methyl}pyrimidin-4(3H)-one;

4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}pyrimidine-2-carbonitrile trifluoroacetate;

6-{[2-(aminomethyl)-4-fluorobenzyl]oxy}-5-bromo-3-(2,6-difluorophenyl)-2-methylpyrimidin-4(3H)-one trifluoroacetate;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-[(2-methoxypyrimidin-4-yl)methyl]-2-methylpyrimidin-4(3H)-one trifluoroacetate;

methyl 4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}pyrimidine-2-carboxylate trifluoroacetate;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-[(2-hydroxypyrimidin-4-yl)methyl]-2-methylpyrimidin-4(3H)-one trifluoroacetate;

4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}pyrimidine-2-carboxamide

trifluoroacetate;
methyl [(4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}pyrimidin-2-yl)methyl]carbamate;
3-benzyl-6-[2,6-(dichlorobenzyl)oxy]pyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-[(5-methylpyrazin-2-yl)methyl]pyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-(pyrazin-2-ylmethyl)pyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-{[5-(hydroxymethyl)pyrazin-2-yl]methyl}-2-methylpyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-({5-[(dimethylamino)methyl]pyrazin-2-yl}methyl)-2-methylpyrimidin-4(3H)-one trifluoroacetate;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-[(5-{[(2-hydroxyethyl)(methyl)amino]-methyl}pyrazin-2-yl)methyl]-2-methylpyrimidin-4(3H)-one trifluoroacetate;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-({5-[(4-methylpiperazin-1-yl)carbonyl]pyrazin-2-yl}methyl)pyrimidin-4(3H)-one trifluoroacetate;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-({5-[(4-methylpiperazin-1-yl)carbonyl]pyrazin-2-yl}methyl)pyrimidin-4(3H)-one;
5-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-N-(2-hydroxyethyl)-N-methylpyrazine-2-carboxamide;
5-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-N-(2,3-dihydroxypropyl)pyrazine-2-carboxamide;
5-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-N-(2-hydroxyethyl)pyrazine-2-carboxamide;
3-Benzyl-5-bromo-6-[2,6-(dichlorobenzyl)oxy]pyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-{[5-(methoxymethyl)pyrazin-2-yl]methyl}-2-methylpyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-({5-[(2-methoxyethoxy)methyl]pyrazin-2-yl}methyl)-2-methylpyrimidin-4(3H)-one;
(5-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}pyrazin-2-yl)methyl carbamate;
3-benzyl-5-bromo-4-oxo-3,4-dihydropyrimidin-6-yl methyl(phenyl)carbamate;
6-(benzyloxy)-5-ethynyl-3-(3-fluorobenzyl)pyrimidin-4(3H)-one;
6-(benzylamino)-5-bromo-3-(3-fluorobenzyl)pyrimidin-4(3H)-one;
6-(benzyloxy)-3-(3-fluorobenzyl)-5-methylpyrimidin-4(3H)-

one;
3-(3-fluorobenzyl)-6-[(4-fluorobenzyl)oxy]-5-iodopyrimidin-4(3H)-one;
3-(3-fluorobenzyl)-6-[(4-fluorobenzyl)oxy]-5-methylpyrimidin-4(3H)-one;
3-benzyl-5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;
3-benzyl-6-[(2-chlorobenzyl)oxy]pyrimidin-4(3H)-one;
N-[5-bromo-1-(3-fluorobenzyl)-6-oxo-1,6-dihydropyrimidin-4-yl]-4-fluorobenzamide;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluorophenyl)-2-methylpyrimidin-4(3H)-one;
5-bromo-3-(4-fluorobenzyl)-6-[(4-fluorobenzyl)amino]-2-methylpyrimidin-4(3H)-one;
5-bromo-3-(cyclopropylmethyl)-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-(pyridin-4-ylmethyl)pyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-(pyridin-3-ylmethyl)pyrimidin-4(3H)-one;
3-Benzyl-5-bromo-6-[(2-chlorobenzyl)oxy]pyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-(pyridin-2-ylmethyl)pyrimidin-4(3H)-one;
5-bromo-6-[2-(4-fluorophenyl)ethyl]-2-methyl-3-(pyridin-3-ylmethyl)pyrimidin-4(3H)-one;
3-benzyl-5-bromo-6-[(4-methylbenzyl)oxy]pyrimidin-4(3H)-one;
5-bromo-6-[2-(4-fluorophenyl)ethyl]-2-methyl-3-(pyridin-4-ylmethyl)pyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-(pyridin-3-ylmethyl)pyrimidin-4(3H)-one;
3-[(4-amino-2-methylpyrimidin-5-yl)methyl]-5-bromo-2-methyl-6-[(2,4,6-trifluorobenzyl)oxy]pyrimidin-4(3H)-one trifluoroacetate;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-{[2-methyl-4-(methylamino)pyrimidin-5-yl]methyl}pyrimidin-4(3H)-one trifluoroacetate;
ethyl N-(5-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-2-methylpyrimidin-4-yl)glycinate - trifluoroacetaldehyde (1:1);
N-(5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-2-methylpyrimidin-4-yl)-2-hydroxyacetamide trifluoroacetate;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-[(5-methylpyrazin-2-yl)methyl]pyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-({5-[(methylamino)methyl]pyrazin-2-yl}methyl)pyrimidin-4(3H)-one trifluoroacetate;

ethyl 5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}pyrazine-2-carboxylate;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[5-(hydroxymethyl)pyrazin-2-yl]methyl}-2-methylpyrimidin-4(3H)-one;

3-Benzyl-6-[(3-chlorobenzyl)oxy]pyrimidin-4(3H)-one;

5-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-N,N-dimethylpyrazine-2-carboxamide;

5-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-N-methylpyrazine-2-carboxamide;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-3{[5-(1-hydroxy-1-methylethyl)pyrazin-2-yl]methyl}-2-methylpyrimidin-4(3H)-one;

5-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-N-(2-methoxyethyl)pyrazine-2-carboxamide;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-{[5-(morpholin-4-ylcarbonyl)pyrazin-2-yl]methyl}pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-({5-[(4-hydroxypiperidin-1-yl)carbonyl]pyrazin-2-yl}methyl)-2-methylpyrimidin-4(3H)-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-N-(3-hydroxy-2,2-dimethylpropyl)pyrazine-2-carboxamide;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-N-(2,2,2-trifluoroethyl)pyrazine-2-carboxamide;

3-allyl-5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;

3-allyl-5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;

3-benzyl-6-[benzylthio]-5-bromopyrimidin-4(3H)-one;

methyl (2E)-4-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]but-2-enoate;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-prop-2-ynylpyrimidin-4(3H)-one;

6-[(2,4-difluorobenzyl)oxy]-2-(hydroxymethyl)-3-(pyridin-3-ylmethyl)pyrimidin-4(3H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-(hydroxymethyl)-3-(pyridin-3-ylmethyl)pyrimidin-4(3H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-[(dimethylamino)methyl]-3-(pyridin-3-ylmethyl)pyrimidin-4(3H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluorophenyl)-2-(hydroxymethyl)pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluorophenyl)-2-(hydroxymethyl)pyrimidin-4(3H)-one;

5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-

difluorophenyl)-6-oxo-1,6-dihydropyrimidine-2-carbaldehyde;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluorophenyl)-2-[(dimethylamino)methyl]pyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluorophenyl)-2-(morpholin-4-ylmethyl)pyrimidin-4(3H)-one;
3-Benzyl-5-bromo-6-{[2-(trifluoromethyl)benzyl]oxy}pyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluorophenyl)-2-{[(2-methoxyethyl)amino]methyl}pyrimidin-4(3H)-one;
5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-oxo-1,6-dihydropyrimidine-2-carboxylic acid;
methyl 4-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-3-methylbenzoate;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-(2-methyl-4-vinylphenyl)pyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-[4-(1,2-dihydroxyethyl)-2-methylphenyl]-2-methylpyrimidin-4(3H)-one;
methyl 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-chlorobenzoate;
3-benzyl-6-(benzyloxy)-5-iodopyrimidin-4(3H)-one;
3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-chlorobenzoic acid;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-[5-(hydroxymethyl)-2-methylphenyl]-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[5-(hydroxymethyl)-2-methylphenyl]-2-methylpyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-[5-(hydroxymethyl)-2-methylphenyl]-2-methylpyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-{5-[(dimethylamino)methyl]-2-methylphenyl}-2-methylpyrimidin-4(3H)-one hydrochloride;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-{5-[(isopropylamino)methyl]-2-methylphenyl}-2-methylpyrimidin-4(3H)-one hydrochloride;
3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-(2-hydroxyethyl)-4-methylbenzamide;
3-benzyl-6-(benzyloxy)-5-vinylpyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-[5-(1-hydroxy-1-methylethyl)-2-methylphenyl]-2-methylpyrimidin-4(3H)-one;
methyl 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoate;
methyl 4-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-3-chlorobenzoate;
5-bromo-6-[(2,4-difluorobenzyl)amino]-3-(3-fluorobenzyl)pyrimidin-4(3H)-one;
5-bromo-3-(3-fluorobenzyl)-6-{[3-(trifluoromethyl)benzyl]amino}pyrimidin-4(3H)-one;
5-bromo-3-(3-fluorobenzyl)-6-{[4-fluoro-2-

(trifluoromethyl)benzyl]amino}pyrimidin-4(3H)-one;
5-bromo-6-[(4-chloro-2-fluorobenzyl)amino]-3-(3-fluorobenzyl)pyrimidin-4(3H)-one;
5-bromo-3-(3-fluorobenzyl)-6-[(3-fluorobenzyl)amino]pyrimidin-4(3H)-one;
3-benzyl-6-(benzyloxy)-5-ethylpyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)amino]-2-methyl-3-(pyridin-4-ylmethyl)pyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)amino]-2-methyl-3-(pyridin-3-ylmethyl)pyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)amino]-3-(2,6-difluorophenyl)-2-methylpyrimidin-4(3H)-one;
5-chloro-6-[(2,4-difluorobenzyl)amino]-3-(2,6-difluorophenyl)-2-methylpyrimidin-4(3H)-one;
3-{[5-chloro-4-[(2,4-difluorobenzyl)amino]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzonitrile;
4-{[5-chloro-4-[(2,4-difluorobenzyl)amino]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzonitrile;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-[2-fluoro-5-(hydroxymethyl)phenyl]-2-methylpyrimidin-4(3H)-one;
3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-fluorobenzoic acid;
3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-fluoro-N-methylbenzamide;
5-acetyl-6-(benzyloxy)-3-(2-chlorophenyl)-2-methylpyrimidin-4(3H)-one;
3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-fluorobenzoic acid;
3-benzyl-5-bromo-6-(2-phenylethyl)pyrimidin-4(3H)-one;
3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methoxybenzoic acid;
3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methoxy-N-methylbenzamide;
3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methoxy-N,N-dimethylbenzamide;
3-[5-(aminomethyl)-2-fluorophenyl]-5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one hydrochloride;
3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-fluoro-N-[2-hydroxy-1-(hydroxymethyl)ethyl]benzamide;
2-({[5-chloro-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-4-yl]oxy}methyl)-5-fluorobenzonitrile;
6-{[2-(aminomethyl)-4-fluorobenzyl]oxy}-5-chloro-3-(2,6-difluorophenyl)-2-methylpyrimidin-4(3H)-one trifluoroacetate;
5-bromo-3-(3-fluorobenzyl)-6-(2-phenylethyl)pyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-{[5-(1-hydroxy-1-methylethyl)pyridin-2-yl]methyl}-2-methylpyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-{[5-

(hydroxymethyl)pyridin-2-yl]methyl}-2-methylpyrimidin-4(3H)-one;

6-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-N-(2-hydroxyethyl)-N-methylnicotinamide;

6-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-N-(2-hydroxyethyl)nicotinamide;

6-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-N,N-dimethylnicotinamide;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-[2-(trifluoromethyl)phenyl]pyrimidin-4(3H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluorophenyl)-2-methyl-1-vinylpyrimidin-4(1H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluorophenyl)-1-(1,2-dihydroxyethyl)-2-methylpyrimidin-4(1H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluorophenyl)-1-(hydroxymethyl)-2-methylpyrimidin-4(1H)-one;

6-(benzyloxy)-5-bromo-3-(2,6-difluorophenyl)-2-methylpyrimidin-4(3H)-one;

[5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluorophenyl)-2-methyl-4-oxo-3,4-dihydropyrimidin-1(2H)-yl]methyl carbamate;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluorophenyl)-2-methyl-4-oxo-3,4-dihydropyrimidine-1(2H)-carbaldehyde;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluorophenyl)-2-methyl-4-oxo-3,4-dihydropyrimidine-1(2H)-carbaldehyde oxime;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluorophenyl)-2-methyl-4-oxo-3,4-dihydropyrimidine-1(2H)-carbonitrile;

6-(benzyloxy)-5-bromo-3-(2,6-difluorophenyl)-1-iodo-2-methylpyrimidin-4(1H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluorophenyl)-2-methyl-1-oxiran-2-ylpyrimidin-4(1H)-one;

6-(benzylamino)-5-bromo-3-(2,6-difluorophenyl)-1-iodo-2-methylpyrimidin-4(1H)-one;

6-(benzyloxy)-5-ethynyl-3-(3-fluorobenzyl)pyrimidin-4(3H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluorophenyl)-2-methyl-1-[(E)-2-phenylethenyl]pyrimidin-4(1H)-one;

6-(allylamino)-5-bromo-3-(2,6-difluorophenyl)-1-iodo-2-methylpyrimidin-4(1H)-one;

6-(allylamino)-3-(2,6-difluorophenyl)-1-iodo-2-methylpyrimidin-4(1H)-one;

6-(allylamino)-3-(2,6-difluorophenyl)-1-iodo-2-methylpyrimidin-4(1H)-one;

ethyl 6-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]nicotinate;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-5'-(1-hydroxy-1-methylethyl)-2-methyl-4H-3,2'-bipyrimidin-4-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(2-furylmethyl)-2-methylpyrimidin-4(3H)-one;

6-(benzylamino)-5-bromo-3-(3-fluorobenzyl)pyrimidin-4(3H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-(thien-2-ylmethyl)pyrimidin-4(3H)-one;

5-bromo-3-(2,6-difluorophenyl)-6-(2-furylmethoxy)-2-methylpyrimidin-4(3H)-one;

5-bromo-3-[2-fluoro-6-(3-furylmethoxy)phenyl]-6-(3-furylmethoxy)-2-methylpyrimidin-4(3H)-one;

5-bromo-3-[2-fluoro-6-(thien-3-ylmethoxy)phenyl]-2-methyl-6-(thien-3-ylmethoxy)pyrimidin-4(3H)-one;

methyl 2-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-[(methylamino)carbonyl]benzoate;

3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-(1-hydroxy-1-methylethyl)-N-methylbenzamide;

4{[5-bromo-6-(2-furylmethoxy)-2-methyl-4-oxopyrimidin-3(3H)-yl]methyl}benzamide;

(-)-3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N,4-dimethylbenzamide;

(+)-3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N,4-dimethylbenzamide;

4-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-3-chlorobenzamide;

5-bromo-3-cyclopropylmethyl-6-(4-fluorobenzyloxy)-3H-pyrimidin-4-one;

3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methylbenzamide;

3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N,4-dimethylbenzamide;

N-{3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-fluorobenzyl}propanamide;

N'-{3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-fluorobenzyl}-N,N-dimethylurea;

N-{3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-fluorobenzyl}-2-hydroxyacetamide;

N-{3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-fluorobenzyl}-2-hydroxy-2-methylpropanamide;

N^1-{3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-fluorobenzyl}glycinamide hydrochloride;

3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-fluorobenzamide;

3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-fluoro-N-methylbenzamide;

3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-fluoro-N,N-dimethylbenzamide;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-{2-fluoro-5-[(4-methylpiperazin-1-yl)carbonyl]phenyl}-2-methylpyrimidin-4(3H)-one;

methyl 4-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-3-fluorobenzoate;

4-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzoic acid;

3-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzamide;

3-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-N,N-dimethylbenzamide;

3-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-N-(2-hydroxy-2-methylpropyl)benzamide;

N-{4-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]benzyl}-2-hydroxyacetamide;

3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]benzamide;

3-(4-aminobenzyl)-5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;

3-(3-aminobenzyl)-5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;

N-(4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}phenyl)acetamide;

N-(3-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}phenyl)acetamide;

N-(4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzyl)-N'-methylurea;

N-(4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzyl)-N'-(2-hydroxy-2-methylpropyl)urea;

N-(4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzyl)piperidine-1-carboxamide;

N-(4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzyl)morpholine-4-carboxamide;

N-(4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzyl)piperazine-1-carboxamide;

N-(4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzyl)-N'-(2-hydroxyethyl)urea;

N'-(4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzyl)-N,N-dimethylurea;

N-(4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzyl)-4-hydroxypiperidine-1-carboxamide;

4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-

oxopyrimidin-1(6H)-yl]methyl}-N,N-dimethylbenzenesulfonamide;
4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-N-(2-hydroxyethyl)benzenesulfonamide;
4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-N-(2-hydroxy-2-methylpropyl)benzenesulfonamide;
5-chloro-6-(2,4-difluorobenzyloxy)-2-methyl-3-(1H-pyrazol-3-ylmethyl)-3H-pyrimidin-4-one;
5-chloro-6-(2,4-difluorobenzyloxy)-2-methyl-3-(2,3-dihydro-1H-indol-5-ylmethyl)-3H-pyrimidin-4-one;
5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-1,3-dihydro-2H-indol-2-one;
N-[(5-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}pyrazin-2-yl)methyl]-N-methylmethanesulfonamide;
methyl [(5-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}pyrazin-2-yl)methyl]methylcarbamate;
N-[(5-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}pyrazin-2-yl)methyl]-2-hydroxy-N,2-dimethylpropanamide;
5-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-N-(2-hydroxy-2-methylpropyl)pyrazine-2-carboxamide;
3-[(5-Aminopyrazin-2-yl)methyl]-5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one trifluoroacetate;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-[(3-methyl-1,2,4-triazin-6-yl)methyl]pyrimidin-4(3H)-one trifluoroacetate;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(1H-indazol-5-yl)-2-methylpyrimidin-4(3H)-one;
5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(1H-indazol-6-yl)-2-methylpyrimidin-4(3H)-one;
methyl (2-{[(5-bromo-2-methyl-1-{2-methyl-5-[(methylamino)carbonyl]phenyl}-6-oxo-1,6-dihydropyrimidin-4-yl)oxy]methyl}-5-fluorobenzyl)carbamate;
methyl [2-({[5-bromo-1-(5-{[(2-hydroxyethyl)amino]carbonyl}-2-methylphenyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-4-yl]oxy}methyl)-5-fluorobenzyl]carbamate;
methyl [2-({[5-bromo-1-(5-{[(2-hydroxy-2-methylpropyl)amino]carbonyl}-2-methylphenyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-4-yl]oxy}methyl)-5-fluorobenzyl]carbamate;
methyl [2-({[5-bromo-1-(5-{[(2-methoxyethyl)amino]carbonyl}-2-methylphenyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-4-yl]oxy}methyl)-5-fluorobenzyl]carbamate;
methyl {2-[({1-[5-(aminocarbonyl)-2-methylphenyl]-5-bromo-2-methyl-6-oxo-1,6-dihydropyrimidin-4-yl}oxy)methyl]-5-fluorobenzyl}carbamate;

N-[2-({[5-chloro-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-4-yl]oxy}methyl)-5-fluorobenzyl]-N'-phenylurea;

3-thienylmethyl [2-({[5-chloro-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-4-yl]oxy}methyl)-5-fluorobenzyl]carbamate;

ethyl (2-{[(5-bromo-2-methyl-1-{2-methyl-5-[(methylamino)carbonyl]phenyl}-6-oxo-1,6-dihydropyrimidin-4-yl)oxy]methyl}-5-fluorobenzyl)carbamate;

3-[5-bromo-4-{[2-({[(cyclopropylamino)carbonyl]amino}methyl)-4-fluorobenzyl]oxy}-2-methyl-6-oxopyrimidin-1(6H)-yl]-N,4-dimethylbenzamide;

2-[2-({[5-bromo-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-4-yl]oxy}methyl)-5-fluorophenoxy]-N-ethylacetamide;

methyl 3-[2-[(acetyloxy)methyl]-5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoate;

3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-(hydroxymethyl)-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoic acid;

3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-(hydroxymethyl)-6-oxopyrimidin-1(6H)-yl]-N-(2-hydroxyethyl)-4-methylbenzamide;

3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-(hydroxymethyl)-6-oxopyrimidin-1(6H)-yl]-N,4-dimethylbenzamide;

3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-(hydroxymethyl)-6-oxopyrimidin-1(6H)-yl]-4-methylbenzamide;

(5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{2-methyl-5-[(methylamino)carbonyl]phenyl}-6-oxo-1,6-dihydropyrimidin-2-yl)methyl acetate;

(2E)-4-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-methylbut-2-enamide;

methyl 5-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-2-furoate;

3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-(hydroxymethyl)-N-methylbenzamide;

2-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N,N'-dimethylterephthalamide;

2-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N^4-methylterephthalamide;

methyl 4-(aminocarbonyl)-2-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]benzoate;

2-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N^1,N^1,N^4-trimethylterephthalamide;

2-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-[(methylamino)carbonyl]benzyl carbamate;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(2,6-difluoro-4-vinylphenyl)-2-methylpyrimidin-4(3H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-[4-(1,2-

dihydroxyethyl)-2,6-difluorophenyl]-2-methylpyrimidin-4(3H)-one;

4-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-3,5-difluorobenzaldehyde;

4-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-3,5-difluorobenzyl carbamate;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-[(5-methylpyrazin-2-yl)methyl]pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[5-(hydroxymethyl)pyrazin-2-yl]methyl}-2-methylpyrimidin-4(3H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-(2,3-dihydro-1H-indol-5-ylmethyl)pyrimidin-4(3H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-[(1-glycoloyl-2,3-dihydro-1H-indol-5-yl)methyl]-2-methylpyrimidin-4(3H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-(1H-pyrazol-3-ylmethyl)pyrimidin-4(3H)-one;

3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N,4-dimethylbenzamide;

3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-fluoro-N-methylbenzamide;

4-chloro-3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-methylbenzamide;

3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-fluorobenzamide;

4-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N,3-dimethylbenzamide;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[4-(1,2-dihydroxyethyl)-2-methylphenyl]-2-methylpyrimidin-4(3H)-one;

N-(4-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}phenyl)-2-hydroxyacetamide;

N-(4-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzyl)-1-hydroxycyclopropanecarboxamide;

N-(4-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzyl)-2-hydroxyacetamide;

N-(4-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}phenyl)acetamide;

ethyl [2-({[5-bromo-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-4-yl]oxy}methyl)-5-fluorobenzyl]carbamate;

3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-(2-hydroxyethyl)-6-oxopyrimidin-1(6H)-yl]-N,4-dimethylbenzamide;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-[5-(2-hydroxyethyl)-2-methylphenyl]-2-methylpyrimidin-4(3H)-one;

5-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-2-(2-hydroxyethyl)-N,4-dimethylbenzamide;

3-[2-[(acetylamino)methyl]-5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N,4-

dimethylbenzamide;

3-allyl-5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-(1-methylpiperidin-4-yl)pyrimidin-4(3H)-one;

5-bromo-4-[(2,4-difluorobenzyl)oxy]-2,4'-dimethyl-2'-(methylsulfonyl)-6H-1,5'-bipyrimidin-6-one;

5-bromo-4-[(2,4-difluorobenzyl)oxy]-2,4'-dimethyl-6-oxo-6H-1,5'-bipyrimidine-2'-carbonitrile;

2'-(aminomethyl)-5-bromo-4-[(2,4-difluorobenzyl)oxy]-2,4'-dimethyl-6H-1,5'-bipyrimidin-6-one;

5-bromo-4-[(2,4-difluorobenzyl)oxy]-2'-[(dimethylamino)methyl]-2,4'-dimethyl-6H-1,5'-bipyrimidin-6-one;

N-({5-bromo-4-[(2,4-difluorobenzyl)oxy]-2,4'-dimethyl-6-oxo-6H-1,5'-bipyrimidin-2'-yl}methyl)-2-hydroxyacetamide;

5-bromo-4-[(2,4-difluorobenzyl)oxy]-2,4'-dimethyl-6-oxo-6H-1,5'-bipyrimidine-2'-carboxylic acid;

5-bromo-4-[(2,4-difluorobenzyl)oxy]-2,4'-dimethyl-6-oxo-6H-1,5'-bipyrimidine-2'-carboxamide;

tert-butyl (3-{[5-bromo-4-[(4-fluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}benzyl)carbamate;

5-bromo-4-[(2,4-difluorobenzyl)oxy]-N,2,4'-trimethyl-6-oxo-6H-1,5'-bipyrimidine-2'-carboxamide;

N-(3-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzyl)-2-hydroxyacetamide;

N-(3-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzyl)-1-hydroxycyclopropanecarboxamide;

4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzyl carbamate;

2-[(4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}phenyl)amino]-1-methyl-2-oxoethyl acetate;

2-[(4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}phenyl)amino]-1,1-dimethyl-2-oxoethyl acetate;

{1-[3-(aminocarbonyl)phenyl]-5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxo-1,6-dihydropyrimidin-2-yl}methyl acetate

5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-{[2-(methylthio)pyrimidin-5-yl]methyl}pyrimidin-4(3H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methyl-3-{[2-(methylsulfonyl)pyrimidin-5-yl]methyl}pyrimidin-4(3H)-one;

ethyl [2-({[5-bromo-1-(5-{[(2-hydroxyethyl)amino]carbonyl}-2-methylphenyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-4-yl]oxy}methyl)-5-fluorobenzyl]carbamate;

3-(3-Aminomethylbenzyl)-5-bromo-6-(4-fluorobenzyloxy)-3H-pyrimidin-4-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-[5-(1H-imidazol-2-yl)-2-methylphenyl]-2-methylpyrimidin-4(3H)-one

trifluoroacetate;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-[5-(5-hydroxy-1H-pyrazol-3-yl)-2-methylphenyl]-2-methylpyrimidin-4(3H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-[5-(5-hydroxyisoxazol-3-yl)-2-methylphenyl]-2-methylpyrimidin-4(3H)-one;

3-[4-{[2-({[(cyclopropylamino)carbonyl]amino}methyl)-4-fluorobenzyl]oxy}-2-methyl-6-oxopyrimidin-1(6H)-yl]-N,4-dimethylbenzamide;

methyl 4-{[4-[(2,4-difluorobenzyl)oxy]-2-oxo-2H-pyrido[1,2-a]pyrimidin-1(9aH)-yl]methyl}benzoate;

5-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-2-furamide;

5-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-2-furamide;

3-[3,5-bis(hydroxymethyl)phenyl]-5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;

5-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]isophthalamide;

3-[3,5-bis(1-hydroxy-1-methylethyl)phenyl]-5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one;

methyl 2-{[5-bromo-4-[(4-fluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}benzoate;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-[4-(hydroxymethyl)phenyl]-2-methylpyrimidin-4(3H)-one;

5-bromo-6-[(2,4-difluorobenzyl)oxy]-3-[4-(1-hydroxy-1-methylethyl)phenyl]-2-methylpyrimidin-4(3H)-one

3-(5-amino-2-fluorophenyl)-5-bromo-6-[(2,4-difluorobenzyl)oxy]-2-methylpyrimidin-4(3H)-one hydrochloride;

N-{3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-fluorophenyl}-2-hydroxyacetamide;

N-{3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-fluorophenyl}-2-hydroxy-2-methylpropanamide;

4-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-3-fluoro-N,N-dimethylbenzamide;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[(1-glycoloyl-2,3-dihydro-1H-indol-5-yl)methyl]-2-methylpyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[1-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1H-indol-5-yl]methyl}-2-methylpyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[1-(methoxyacetyl)-2,3-dihydro-1H-indol-5-yl]methyl}-2-methylpyrimidin-4(3H)-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-N,N-dimethylindoline-1-carboxamide;

5-bromo-6-(4-fluorobenzyloxy)-3-(2-hydroxymethylbenzyl)-3H-pyrimidin-4-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[(1-glycoloyl-2,3-dihydro-1H-indol-5-yl)methyl]pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-[(1-glycoloyl-2,3-dihydro-1H-indol-5-yl)methyl]pyrimidin-4(3H)-one;

5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-{[1-(methoxyacetyl)-2,3-dihydro-1H-indol-5-yl]methyl}pyrimidin-4(3H)-one;

5-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}-N,N-dimethylindoline-1-carboxamide;

5-bromo-6-(2,4-difluorobenzyloxy)-3-[(4-dimethylaminomethyl)benzyl]-3H-pyrimidin-4-one;

5-bromo-6-(2,4-difluorobenzyloxy)-3-[3-(isopropylaminomethyl)benzyl]-3H-pyrimidin-4-one;

5-bromo-6-(2,4-difluorobenzyloxy)-3-[(3-dimethylaminomethyl)benzyl]-3H-pyrimidin-4-one;

5-bromo-6-(2,4-difluorobenzyloxy)-3-[(3-methylaminomethyl)benzyl]-3H-pyrimidin-4-one;

tert-butyl (3-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}benzyl)carbamate;

3-[(3-aminomethyl)benzyl]-5-bromo-6-(2,4-difluorobenzyloxy)-3H-pyrimidin-4-one;

5-chloro-6-(2,4-difluorobenzyloxy)-3-[4-(isopropylaminomethyl)benzyl]-3H-pyrimidin-4-one;

5-chloro-6-(2,4-difluorobenzyloxy)-3-[(3-methanesulfonyl)benzyl]-3H-pyrimidin-4-one;

5-chloro-6-(2,4-difluorobenzyloxy)-3-[(4-methanesulfonyl)benzyl]-3H-pyrimidin-4-one;

4-{[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}benzamide;

5-chloro-6-(2,4-difluorobenzyloxy)-3-isoquinolin-5-ylmethyl-3H-pyrimidin-4-one;

5-chloro-6-(2,4-difluorobenzyloxy)-3-(1,2,3,4-tetrahydroisoquinolin-5-ylmethyl)-3H-pyrimidin-4-one;

5-chloro-6-(2,4-difluorobenzyloxy)-3-(1H-indol-5-ylmethyl)-3H-pyrimidin-4-one;

3-(1-acetyl-1H-indol-5-ylmethyl)-5-chloro-6-(2,4-difluorobenzyloxy)-3H-pyrimidin-4-one;

5-chloro-6-(2,4-difluorobenzyloxy)-3-(2,3-dihydro-1H-indol-5-ylmethyl)-3H-pyrimidin-4-one;

5-bromo-6-(2,4-difluorobenzyloxy)-3-(2,4-difluorobenzyl)-3H-pyrimidin-4-one;

(3-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}phenyl)acetonitrile;

2-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]methyl}benzonitrile; or

3-[(2-aminomethyl)benzyl)]-5-bromo-6-(2,4-difluorobenzyloxy)-3H-pyrimidin-4-one.

The above names were generated using ChemDraw Ultra version 6.0.2, which is commercially available from CambridgeSoft.com, Cambridge, MA; or ACD Namepro version 5.09, which is commercially available from ACDlabs.com.

Definitions

As used herein, the term "alkenyl" refers to straight and branched hydrocarbon groups having a designated number of carbon atoms and containing at least one carbon-carbon double bond. Examples of "alkenyl" include vinyl, allyl, and 2-methyl-3-heptene.

The term "alkoxy" represents an alkyl attached to the parent molecular moiety through an oxygen bridge. Examples of alkoxy groups include, for example, methoxy, ethoxy, propoxy and isopropoxy.

The term "thioalkoxy" represents an alkyl attached to the parent molecular moiety through a sulfur atom. Examples of thioalkoxy groups include, for example, thiomethoxy, thioethoxy, thiopropoxy and thioisopropoxy.

As used herein, the term "alkyl" refers to straight and branched chain hydrocarbon chains having the designated number of carbon atoms. Examples of "alkyl" include methyl, ethyl, propyl, isopropyl, butyl, iso-, sec- and tert-butyl, pentyl, hexyl, heptyl, 3-ethylbutyl, and the like. "Cx-Cy alkyl" represents an alkyl group of the specified number of carbons. For example, C_1-C_4 alkyl includes all alkyl groups that include at least one and no more than four carbon atoms. It also contains subgroups, such as, for example, C_2-C_3 alkyl or C_1-C_3 alkyl.

The term "aryl" refers to an aromatic hydrocarbon ring system containing at least one aromatic ring where the

aromatic ring is optionally fused or otherwise attached to other aromatic hydrocarbon rings or non-aromatic hydrocarbon rings. Examples of aryl groups include, for example, phenyl, naphthyl, 1,2,3,4-tetrahydronaphthalene, indanyl, and biphenyl. Preferred examples of aryl groups include phenyl and naphthyl. The most preferred aryl group is phenyl. The aryl groups herein are unsubstituted or, as specified, substituted in one or more substitutable positions with various groups. Thus, such aryl groups can be optionally substituted with groups such as, for example, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, hydroxy, cyano, nitro, amino, mono- or di-(C_1-C_6)alkylamino, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, amino(C_1-C_6)alkyl, mono- or di(C_1-C_6)alkylamino(C_1-C_6)alkyl.

The term "arylalkyl" refers to an aryl group, as defined above, attached to the parent molecular moiety through an alkyl group, as defined above. Preferred arylalkyl groups include, benzyl, phenethyl, phenpropyl, and phenbutyl. More preferred arylalkyl groups include benzyl and phenethyl. The most preferred arylalkyl group is benzyl. The aryl portions of these groups are unsubstituted or, as specified, substituted in one or more substitutable positions with various groups. Thus, such aryl groups can be optionally substituted with groups such as, for example, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, hydroxy, cyano, nitro, amino, mono- or di-(C_1-C_6)alkylamino, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, amino(C_1-C_6)alkyl, mono- or di(C_1-C_6)alkylamino(C_1-C_6)alkyl.

The term "arylalkoxy" refers to an aryl group, as defined above, attached to the parent molecular moiety through an alkoxy group, as defined above. Preferred arylaloxy groups include, benzyloxy, phenethyloxy, phenpropyloxy, and

phenbutyloxy. The most preferred arylalkoxy group is benzyloxy.

The term "cycloalkyl" refers to a C_3-C_8 cyclic hydrocarbon. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. More preferred cycloalkyl groups include cyclopropyl.

The term "cycloalkylalkyl," as used herein, refers to a C_3-C_8 cycloalkyl group attached to the parent molecular moiety through an alkyl group, as defined above. Examples of cycloalkylalkyl groups include cyclopropylmethyl and cyclopentylethyl.

The terms "halogen" or "halo" indicate fluorine, chlorine, bromine, or iodine.

The term "heterocycloalkyl," refers to a non-aromatic ring system containing at least one heteroatom selected from nitrogen, oxygen, and sulfur, wherein the non-aromatic heterocycle is attached to the core. The heterocycloalkyl ring may be optionally fused to or otherwise attached to other heterocycloalkyl rings, aromatic heterocycles, aromatic hydrocarbons and/or non-aromatic hydrocarbon rings. Preferred heterocycloalkyl groups have from 3 to 7 members. Examples of heterocycloalkyl groups include, for example, piperazine, 1,2,3,4-tetrahydroisoquinoline, morpholine, piperidine, tetrahydrofuran, pyrrolidine, and pyrazole. Preferred heterocycloalkyl groups include piperidinyl, piperazinyl, morpholinyl, and pyrolidinyl. The heterocycloalkyl groups herein are unsubstituted or, as specified, substituted in one or more substitutable positions with various groups. Thus, such heterocycloalkyl groups can be optionally substituted with groups such as, for example, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, hydroxy, cyano, nitro, amino, mono- or di-(C_1-

C_6)alkylamino, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, amino(C_1-C_6)alkyl, mono- or di(C_1-C_6)alkylamino(C_1-C_6)alkyl.

The term "heteroaryl" refers to an aromatic ring system containing at least one heteroatom selected from nitrogen, oxygen, and sulfur where the heteroaryl ring is optionally fused or otherwise attached to one or more heteroaryl rings, aromatic or non-aromatic hydrocarbon rings, or heterocycloalkyl rings. Examples of heteroaryl groups include, for example, pyridine, furan, thiophene, 5,6,7,8-tetrahydroisoquinoline and pyrimidine. Preferred examples of heteroaryl groups include thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, benzimidazolyl, furanyl, benzofuranyl, thiazolyl, benzothiazolyl, isoxazolyl, oxadiazolyl, isothiazolyl, benzisothiazolyl, triazolyl, tetrazolyl, pyrrolyl, indolyl, pyrazolyl, and benzopyrazolyl. Preferred heteroaryl groups include pyridyl. The heteroaryl groups herein are unsubstituted or, as specified, substituted in one or more substitutable positions with various groups. Thus, such heteroaryl groups can be optionally substituted with groups such as, for example, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, hydroxy, cyano, nitro, amino, mono- or di-(C_1-C_6)alkylamino, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, amino(C_1-C_6)alkyl, mono- or di(C_1-C_6)alkylamino(C_1-C_6)alkyl.

The term "heteroarylalkyl" refers to a heteroaryl group, as defined above, attached to the parent molecular moiety through an alkyl group, as defined above. Preferred heteroarylalkyl groups include, pyrazolemethyl, pyrazoleethyl, pyridylmethyl, pyridylethyl, thiazolemethyl, thiazoleethyl, imidazolemethyl, imidazoleethyl, thienylmethyl, thienylethyl, furanylmethyl, furanylethyl, isoxazolemethyl, isoxazoleethyl, pyrazinemethyl and pyrazineethyl. More preferred

heteroarylalkyl groups include pyridylmethyl and pyridylethyl. The heteroaryl portions of these groups are unsubstituted or, as specified, substituted in one or more substitutable positions with various groups. Thus, such heteroaryl groups can be optionally substituted with groups such as, for example, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, hydroxy, cyano, nitro, amino, mono- or di-(C_1-C_6)alkylamino, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, amino(C_1-C_6)alkyl, mono- or di(C_1-C_6)alkylamino(C_1-C_6)alkyl.

If two or more of the same substituents are on a common atom, e.g., di(C_1-C_6)alkylamino, it is understood that the nature of each group is independent of the other.

As used herein, the term "p38 mediated disorder" refers to any and all disorders and disease states in which p38 plays a role, either by control of p38 itself, or by p38 causing another factor to be released, such as but not limited to IL-1, IL-6 or IL-8. A disease state in which, for instance, IL-1 is a major component, and whose production or action, is exacerbated or secreted in response to p38, would therefore be considered a disorder mediated by p38.

As TNF-beta has close structural homology with TNF-alpha (also known as cachectin), and since each induces similar biologic responses and binds to the same cellular receptor, the synthesis of both TNF-alpha and TNF-beta are inhibited by the compounds of the invention and thus are herein referred to collectively as "TNF" unless specifically delineated otherwise.

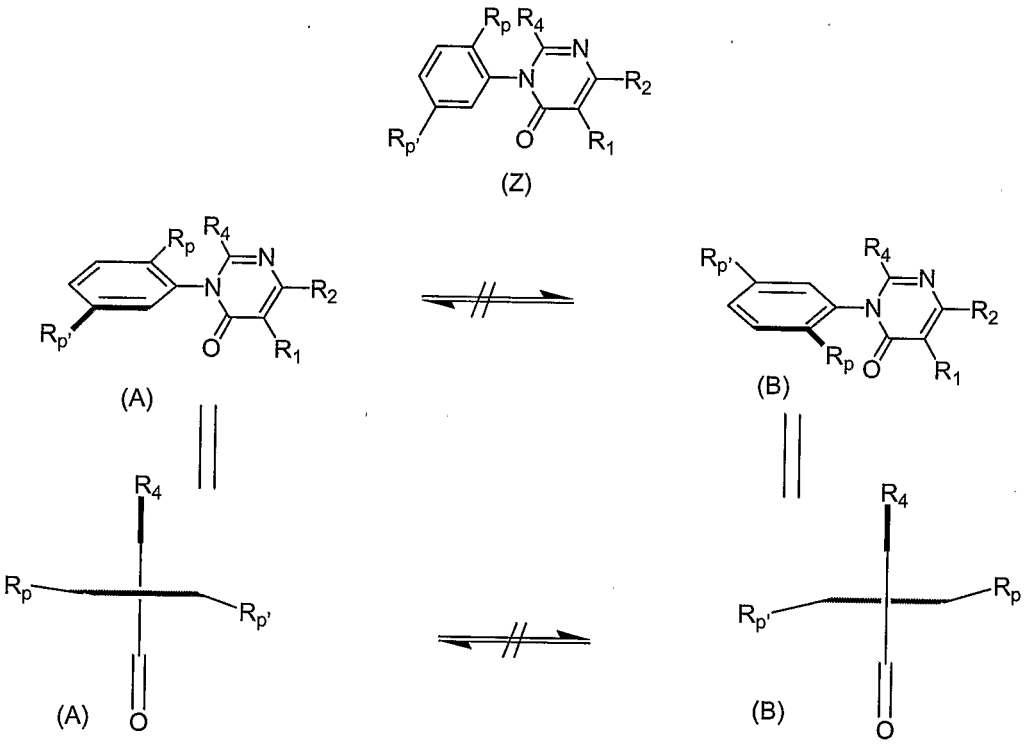
Compounds of invention include the compounds of Formula I and their corresponding pharmaceutically acceptable acid and base addition salts. If the compound of the invention is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt,

particularly a pharmaceutically acceptable acid addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing such addition salts from base compounds.

Non-toxic pharmaceutically acceptable salts include, but are not limited to salts of inorganic acids such as hydrochloric, sulfuric, phosphoric, diphosphoric, hydrobromic, and nitric or salts of organic acids such as formic, citric, malic, maleic, fumaric, tartaric, succinic, acetic, lactic, methanesulfonic, p-toluenesulfonic, 2-hydroxyethylsulfonic, salicylic and stearic. Similarly, pharmaceutically acceptable cations include, but are not limited to sodium, potassium, calcium, aluminum, lithium and ammonium. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.

The compounds of this invention may contain one or more asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. These compounds can be, for example, racemates, chiral non-racemic mixtures or mixtures of diastereomers. In these situations, the single enantiomers, i.e., optically active forms, can be obtained by asymmetric synthesis or by resolution of the racemates or mixtures. Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent; chromatography, using, for example a chiral HPLC column; or derivatizing the racemic mixture with a resolving reagent to generate diastereomers, separating the diastereomers via chromatography or selective crystallization, and removing the resolving agent to generate the original compound in enantiomerically enriched form. Any of the above procedures can be repeated to increase the enantiomeric purity of a compound.

The compounds of the invention may exist as atropisomers, i.e., chiral rotational isomers. The invention encompasses the racemic and the resolved atropisomers. The following illustration generically shows a compound (Z) that can exist as atropisomers as well as its two possible atropisomers (A) and (B). This illustration also shows each of atropisomers (A) and (B) in a Fischer projection. In this illustration, R_1, R_2, and R_4 carry the same definitions as set forth for Formula I, $R_{p'}$ is a substituent within the definition of R_5, and R_p is a non-hydrogen substituent within the definition of R_5.



When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless otherwise specified, it is intended that the compounds include the cis, trans, Z- and E- configurations. Likewise, all tautomeric forms are also intended to be included.

The compounds of general Formula I may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes percutaneous, subcutaneous, intravascular (e.g., intravenous), intramuscular, or intrathecal injection or infusion techniques and the like. In addition, there is provided a pharmaceutical formulation comprising a compound of general Formula I and a pharmaceutically acceptable carrier. One or more compounds of general Formula I may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants, and if desired other active ingredients. The pharmaceutical compositions containing compounds of general Formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, hard or soft capsule, lozenges, dispensable powders, suspension, or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules.

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preservative agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically

acceptable excipients that are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques. In some cases such coatings may be prepared by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monosterate or glyceryl distearate may be employed.

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

Formulations for oral use may also be presented as lozenges.

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

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

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil, or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin, or cetyl alcohol. Sweetening agents and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

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

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil or a mineral oil or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or

partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol, glucose or sucrose. Such formulations may also contain a demulcent, a preservative, and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents that have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of general Formula I may also be administered in the form of suppositories, e.g., for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols.

Compounds of general Formula I may be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives, and buffering agents can be dissolved in the vehicle.

The active ingredient may also be administered by injection (IV, IM, subcutaneous or jet) as a composition wherein, for example, saline, dextrose, or water may be used as a suitable carrier. The pH of the composition may be adjusted, if necessary, with suitable acid, base, or buffer. Suitable bulking, dispersing, wetting or suspending agents, including mannitol and PEG 400, may also be included in the composition. A suitable parenteral composition can also include a compound formulated as a sterile solid substance, including lyophilized powder, in injection vials. Aqueous solution can be added to dissolve the compound prior to injection.

For disorders of the eye or other external tissues, e.g., mouth and skin, the formulations are preferably applied as a topical gel, spray, ointment or cream, or as a suppository, containing the active ingredients in a total amount of, for example, 0.075 to 30% w/w, preferably 0.2 to 20% w/w and most preferably 0.4 to 15% w/w. When formulated in an ointment, the active ingredients may be employed with either paraffinic or a water-miscible ointment base.

Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example at least 30% w/w of a polyhydric alcohol such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol, polyethylene glycol and mixtures thereof. The topical formulation may desirably include a compound, which enhances

absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogs. The compounds of this invention can also be administered by a transdermal device. Preferably topical administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. In either case, the active agent is delivered continuously from the reservoir or microcapsules through a membrane into the active agent permeable adhesive, which is in contact with the skin or mucosa of the recipient. If the active agent is absorbed through the skin, a controlled and predetermined flow of the active agent is administered to the recipient. In the case of microcapsules, the encapsulating agent may also function as the membrane. The transdermal patch may include the compound in a suitable solvent system with an adhesive system, such as an acrylic emulsion, and a polyester patch. The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier, it may comprise a mixture of at least one emulsifier with a fat or oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier, which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make-up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base, which forms the oily, dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers suitable for use in the formulation of the invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate, and sodium lauryl sulfate, among others. The choice of suitable oils or fats for

the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus, the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters may be used. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredients are dissolved or suspended in suitable carrier, especially an aqueous solvent for the active ingredients. The anti-inflammatory active ingredients are preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% and particularly about 1.5% w/w. For therapeutic purposes, the active compounds of this combination invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release

formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

The amount of therapeutically active compounds that are administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the inflammation or inflammation related disorder, the route and frequency of administration, and the particular compound employed, and thus may vary widely. The pharmaceutical compositions may contain active ingredients in the range of about 0.1 to 1000 mg, preferably in the range of about 7.0 to 350 mg. A daily dose of about 0.01 to 100 mg/kg body weight, preferably between about 0.1 and about 50 mg/kg body weight and most preferably between about 0.5 to 30 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day. In the case of skin conditions, it may be preferable to apply a topical preparation of compounds of this invention to the affected area two to four times a day.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of

factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

For administration to non-human animals, the composition may also be added to the animal feed or drinking water. It may be convenient to formulate the animal feed and drinking water compositions so that the animal takes in a therapeutically appropriate quantity of the composition along with its diet. It may also be convenient to present the composition as a premix for addition to the feed or drinking water.

The disclosures in this application of all articles and references, including patents, are incorporated herein by reference.

The invention is illustrated further by the following examples, which are not to be construed as limiting the invention in scope or spirit to the specific procedures described in them.

The starting materials and various intermediates may be obtained from commercial sources, prepared from commercially available compounds, or prepared using well-known synthetic methods.

General Synthetic Procedures

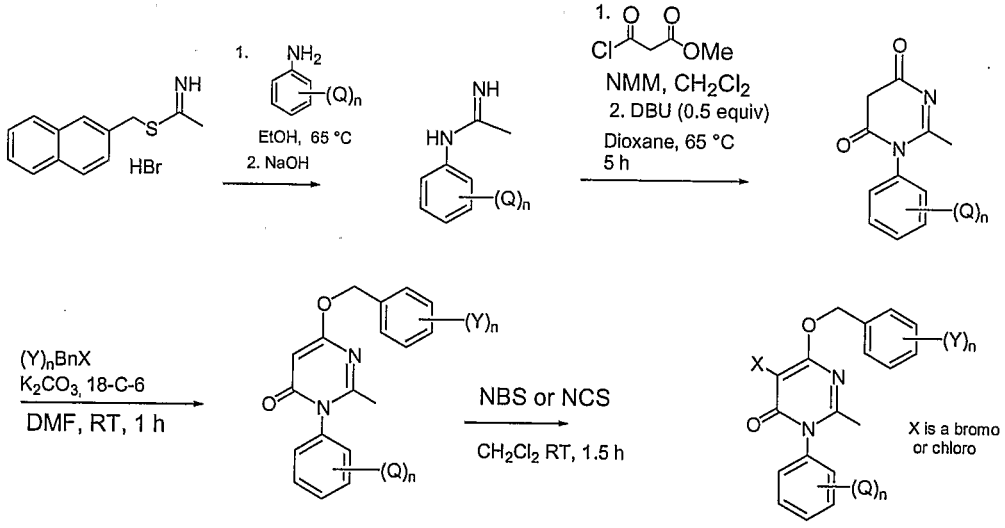
Representative procedures for the preparation of compounds of the invention are outlined below in the Schemes. The starting materials can be purchased or prepared using methods known to those skilled in the art. Similarly, the preparation of the various intermediates can be achieved using methods known in the art. The starting materials may be varied and additional steps employed to produce compounds

encompassed by the invention, as demonstrated by the examples below. In addition, different solvents and reagents can typically be used to achieve the above transformations. Furthermore, in certain situations, it may be advantageous to alter the order in which the reactions are performed. Protection of reactive groups may also be necessary to achieve the above transformations. In general, the need for protecting groups, as well as the conditions necessary to attach and remove such groups, will be apparent to those skilled in the art of organic synthesis. When a protecting group is employed, deprotection will generally be required. Suitable protecting groups and methodology for protection and deprotection such as those described in *Protecting Groups in Organic Synthesis* by Greene and Wuts are known and appreciated in the art.

SCHEMES

The following schemes are representative of the methods that can be used to prepare these compounds.

Scheme 1



In Scheme 1:

Each Q is independently alkyl, halogen, alkoxy, hydroxyalkyl, dihydroxyalkyl, arylalkoxy, thioalkoxy, alkoxycarbonyl, arylalkoxycarbonyl, CO_2R, CN, OH, hydroxyalkyl, dihydroxyalkyl, amidinooxime, $-NR_6R_7$, $-NR_8R_9$, $R_6R_7N-(C_1-C_6$ alkyl)-, carboxaldehyde, SO_2alkyl, $-SO_2H$, $-SO_2NR_6R_7$, alkanoyl wherein the alkyl portion is optionally substituted with OH, halogen or alkoxy, $-C(O)NR_6R_7$, $-(C_1-C_4$ alkyl)$-C(O)NR_6R_7$, amidino, haloalkyl, $-(C_1-C_4$ alkyl)$-NR_{15}C(O)NR_{16}R_{17}$, $-(C_1-C_4$ alkyl)$-NR_{15}C(O)R_{18}$, $-O-CH_2-O$, $-O-CH_2CH_2-O-$, or haloalkoxy; wherein

R_{15} is H or C_1-C_6 alkyl; and

R_{18} is C_1-C_6 alkyl optionally substituted with $-O-(C_2-C_6$ alkanoyl, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl; amino C_1-C_6 alkyl, mono or dialkylamino C_1-C_6 alkyl; and

each Y is independently halogen, $-(C_1-C_6)$alkyl$-N(R)-CO_2R_{30}$, haloalkyl, heteroaryl, heteroarylalkyl, $-NR_6R_7$, $R_6R_7N-(C_1-C_6$ alkyl)-, $-C(O)NR_6R_7$, $-(C_1-C_4)$alkyl$-C(O)NR_6R_7$, $-(C_1-C_4$ alkyl)$-NRC(O)NR_{16}R_{17}$, haloalkoxy, alkyl, CN, hydroxyalkyl, dihydroxyalkyl, alkoxy, alkoxycarbonyl, phenyl, $-SO_2$-phenyl wherein the phenyl and $-SO_2$-phenyl groups are optionally substituted with 1, 2, or 3 groups that are independently halogen or NO_2, or $-OC(O)NR_6R_7$, wherein

R_{16} and R_{17} are independently H or C_1-C_6 alkyl; or

R_{16}, R_{17} and the nitrogen to which they are attached form a morpholinyl ring, wherein

n is 0, 1, 2, 3, 4, or 5.

More preferably, n is 0-4, and even more preferably, n is 0-3.

In a preferred embodiment of Scheme 1, Q and Y carry the following definitions:

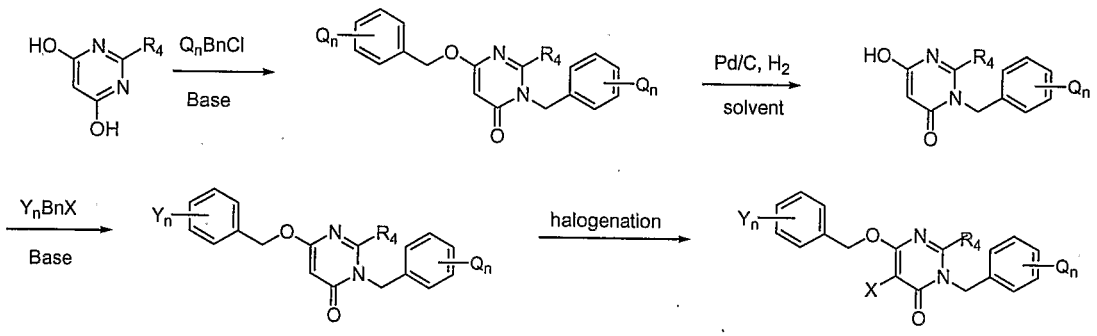
Q at each occurrence is independently alkyl, halogen, alkoxy, arylalkoxy, thioalkoxy, alkoxycarbonyl, arylalkoxycarbonyl, CO_2H, CN, amidinooxime, NR_6R_7, $R_6R_7N(C_1-$

C_6)alkyl, -C(O)NR_6R_7, (C_1-C_4) alkyl-C(O) NR_6R_7, amidino, haloalkyl, or haloalkoxy; and n is 0, 1, 2, 3, 4, or 5;

Y at each occurrence is independently alkyl, halogen, alkoxy, arylalkoxy, thioalkoxy, alkoxycarbonyl, arylalkoxycarbonyl, CO_2H, CN, amidinooxime, NR_6R_7, R_6R_7N(C_1-C_6)alkyl, -C(O)NR_6R_7, (C_1-C_4) alkyl-C(O)NR_6R_7, amidino, haloalkyl, or haloalkoxy; and n is 0, 1, 2, 3, 4, or 5;

X is a halide, preferably Br or Cl.

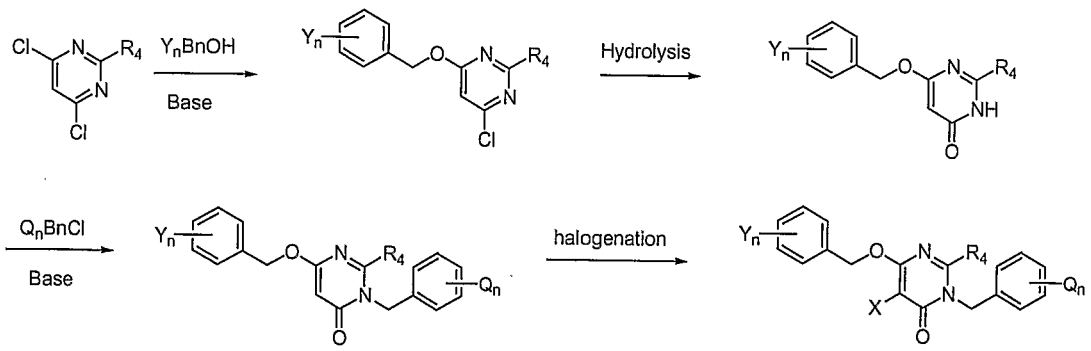
Scheme 2



In Scheme 2:

R_4 is as defined for formula I, and in a preferred embodiment, R_4 is H, halogen, CH_3 or SCH_3. Preferred halogenating reagents include N-bromosuccinimide (NBS), Br_2, N-chlorosuccinimide, and Cl_2.

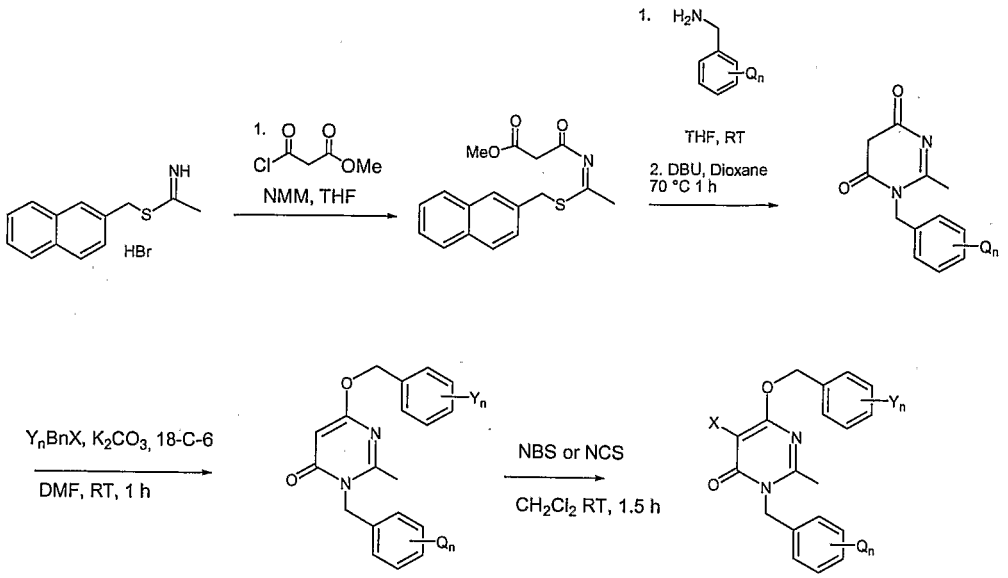
Scheme 3



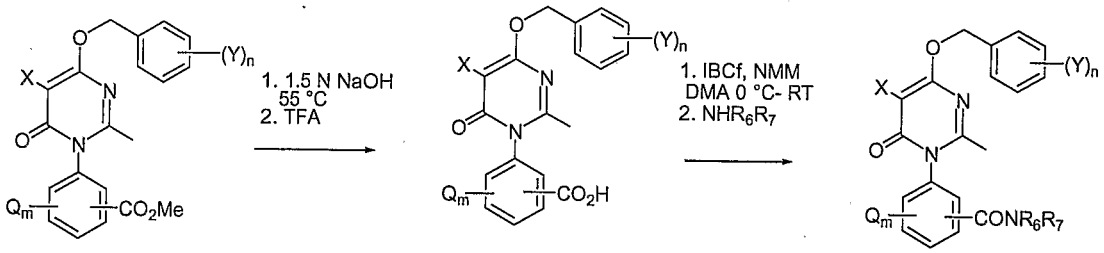
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In Scheme 3, preferred halogenating reagents include N-bromosuccinimide (NBS), Br_2, N-chlorosuccinimide, and Cl_2.

Scheme 4



Scheme 5

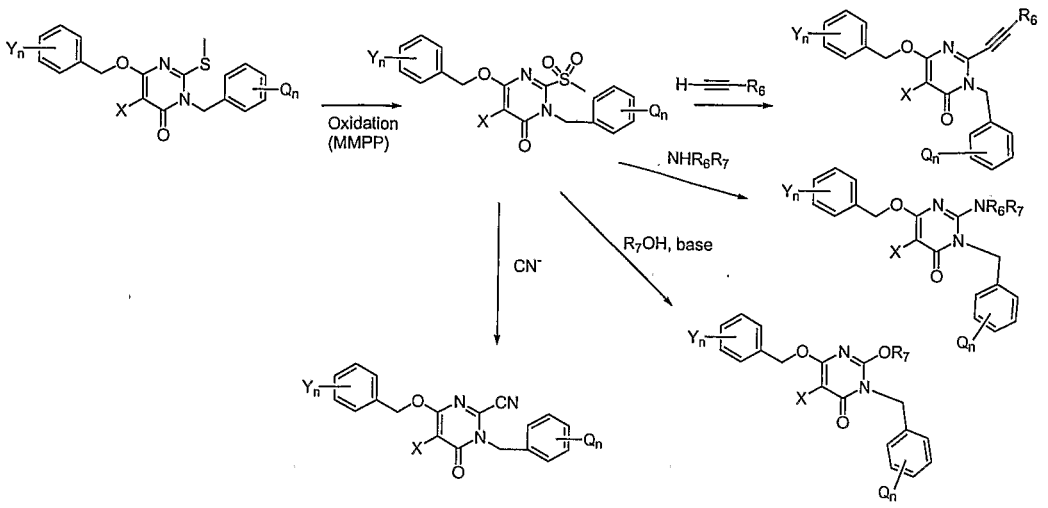


where m is 0,1,2,3 or 4 and

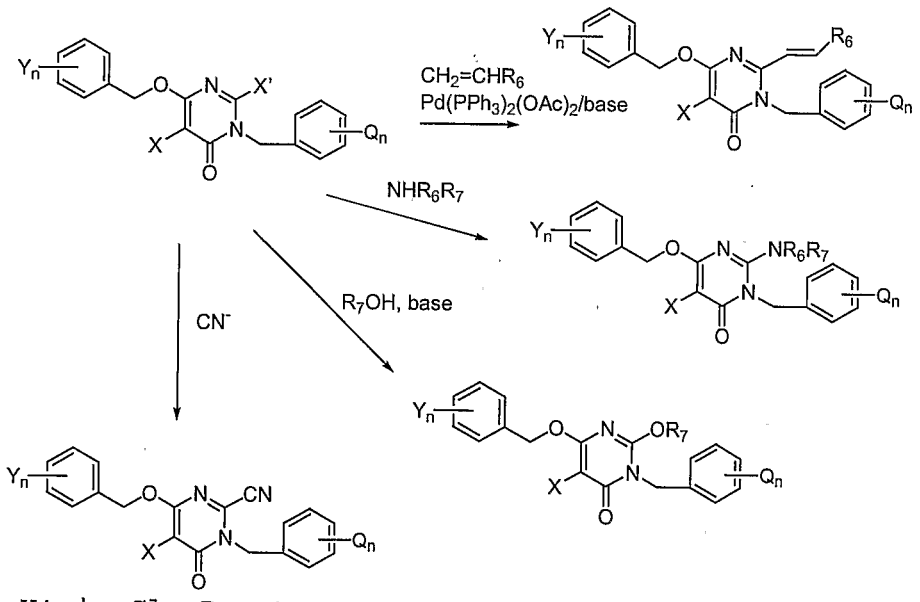
n is 0, 1, 2, 3, 4, or 5.

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Scheme 6



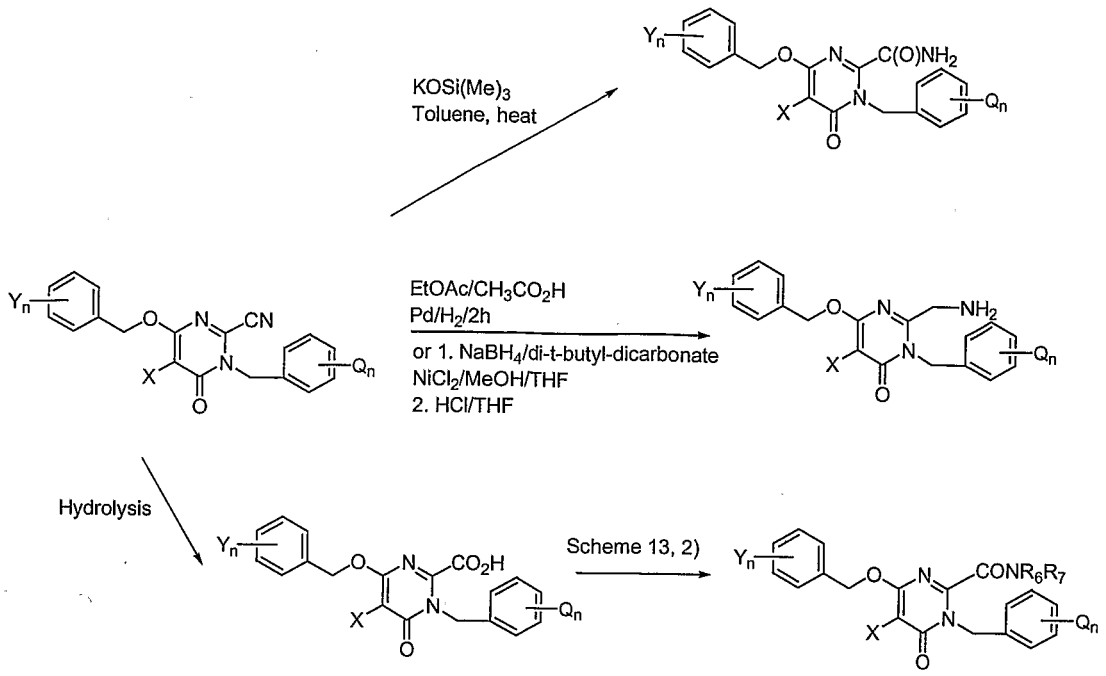
Scheme 7



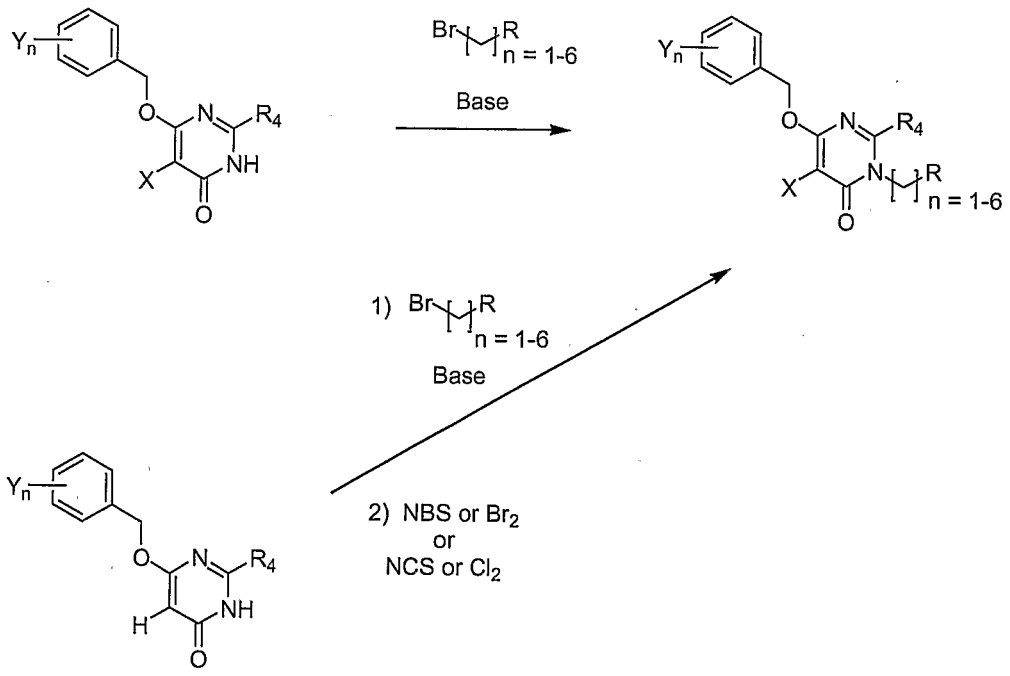
where X' is Cl, Br, I or SR.

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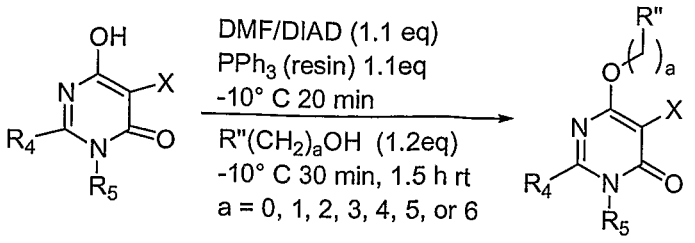
Scheme 8



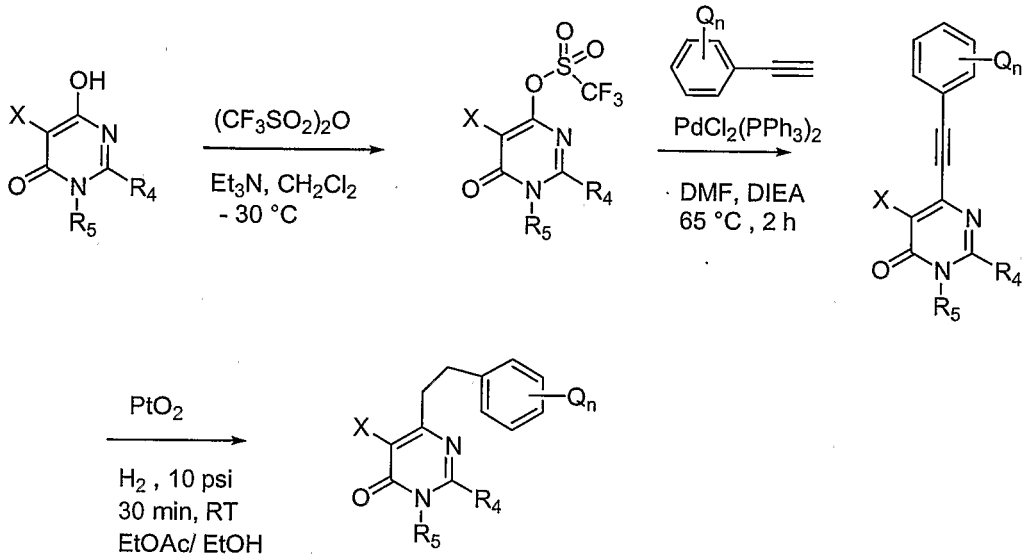
Scheme 9



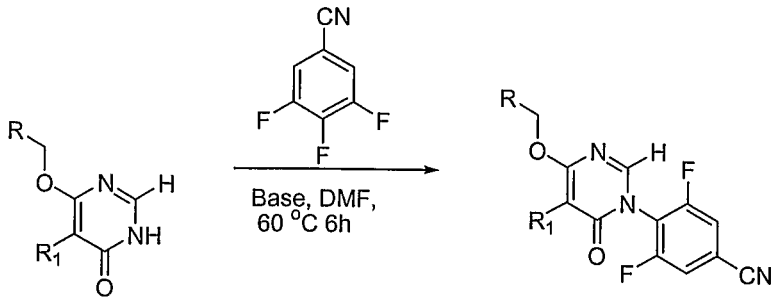
Scheme 10



Scheme 11



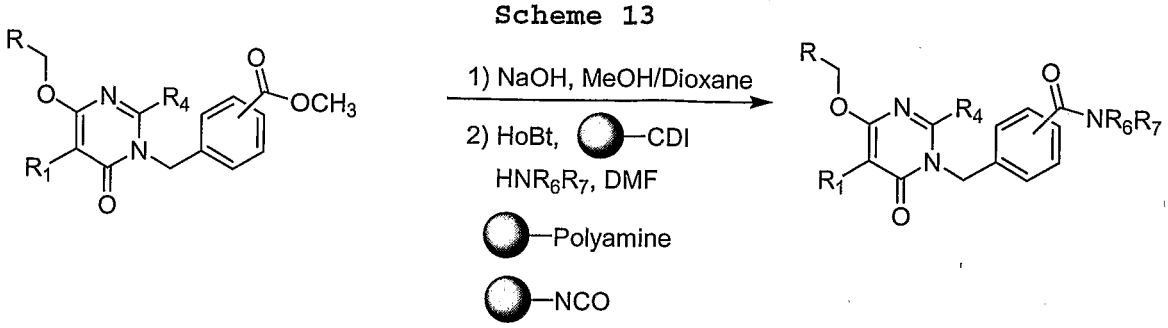
Scheme 12



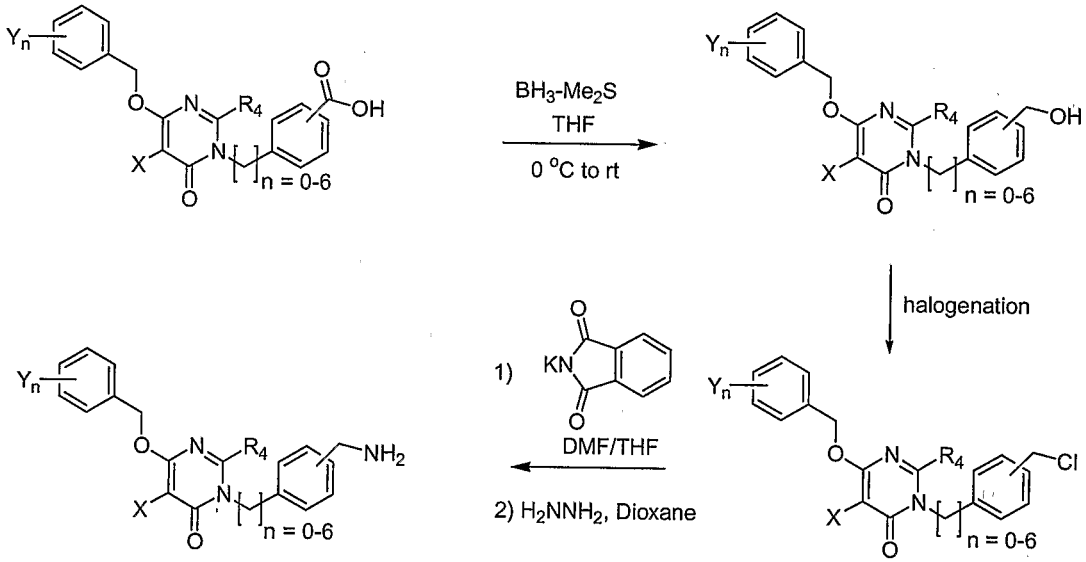
One of skill in the art will appreciate that other halides, such as chloro will work, and that all three halogens are not required. Further, the CN group can be replace with

other activating groups, such as NO_2, CO_2Me, $CONH_2$, and $-CH=CH_2$ will also work.

Scheme 13

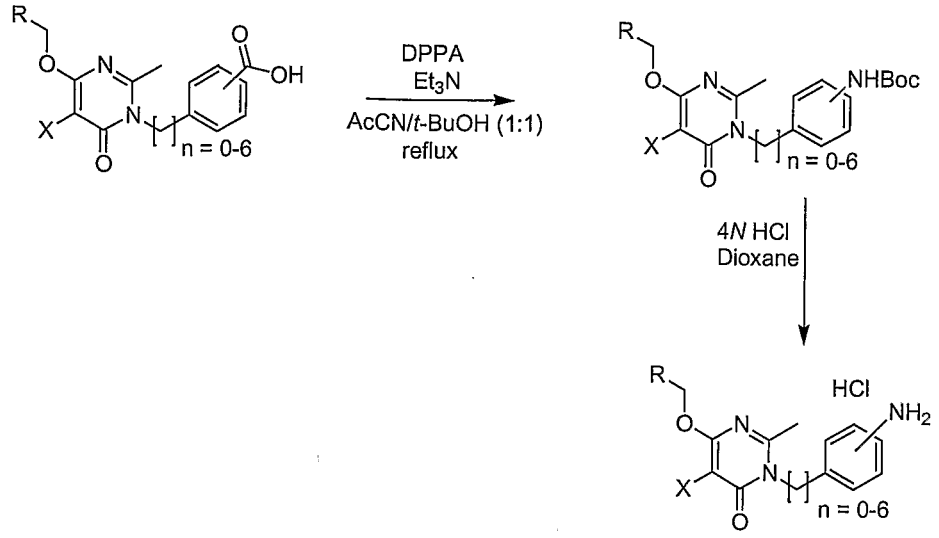


Scheme 14

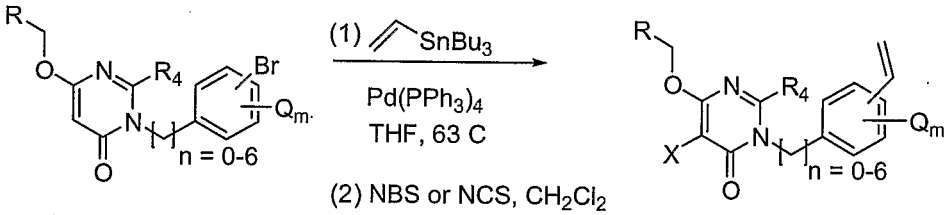


While the halogenation in Scheme 14 can be carried out using a variety of different halogenation reagents, or protocols, a preferred halogenation method includes using 2, 4, 6-trichloro-1, 3, 5-triazine (which is also known as cyanuric chloride) in DMF/CH_2Cl_2.

Scheme 15

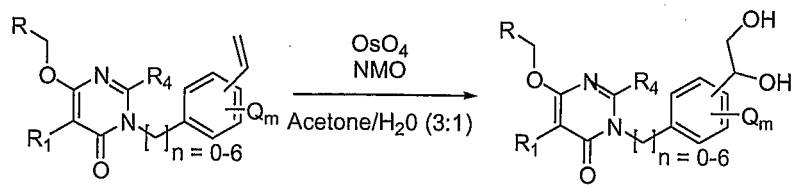


Scheme 16

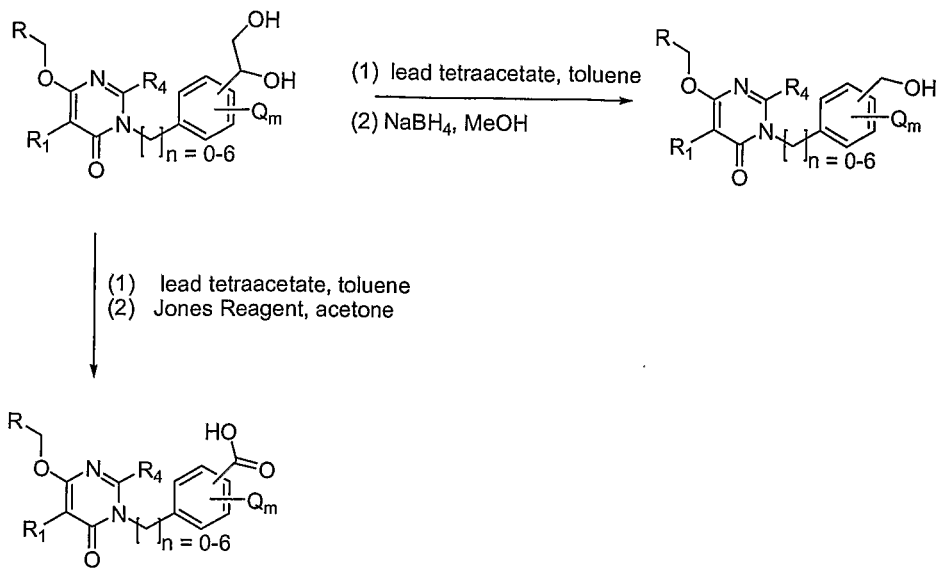


where m is 0, 1, 2, 3, or 4.

Scheme 17

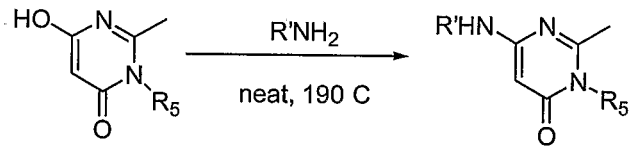


Scheme 18

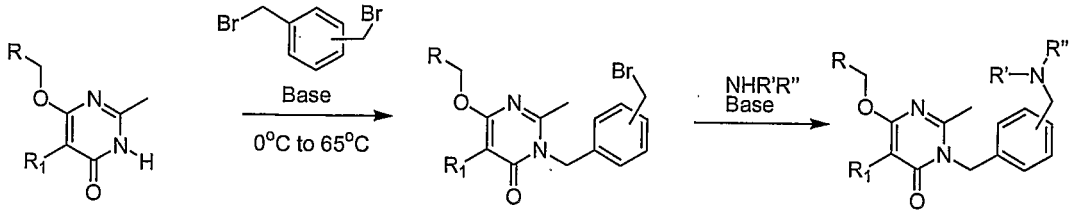


One of skill in the art will appreciate that periodic acid may also be used to affect the desired cleavage of the diol shown in Scheme 18. Further, one of skill in the art will recognize that after cleavage of the diol, the resulting aldehyde may be further elaborated using methods well known in the art, including for example, reductive amination.

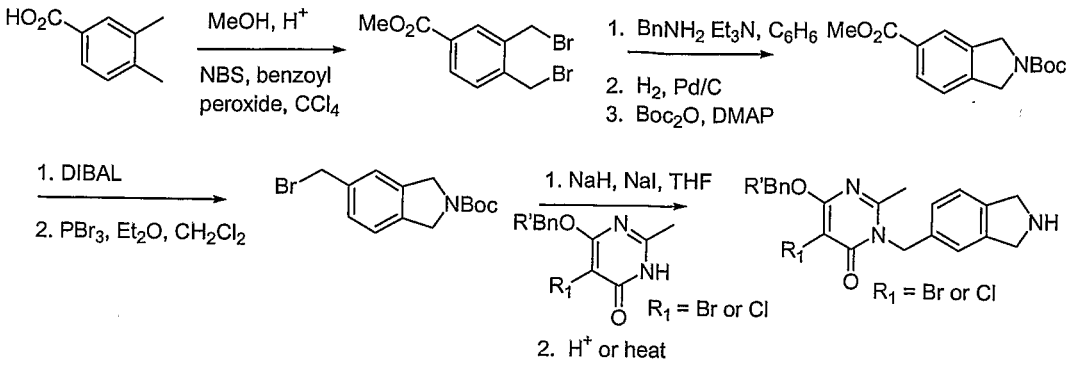
Scheme 19



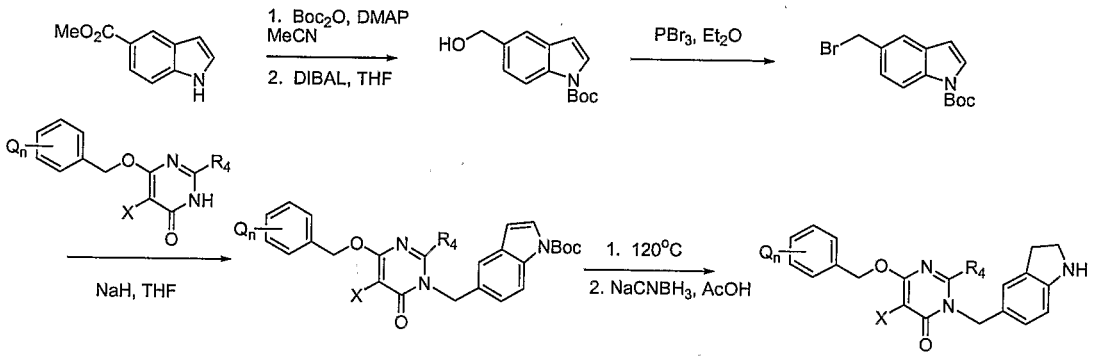
Scheme 20



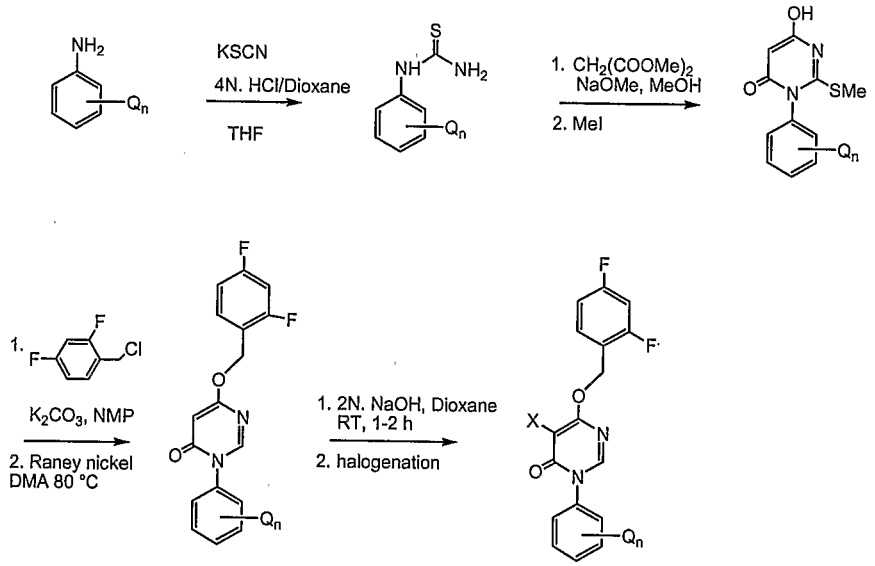
Scheme 21



Scheme 22

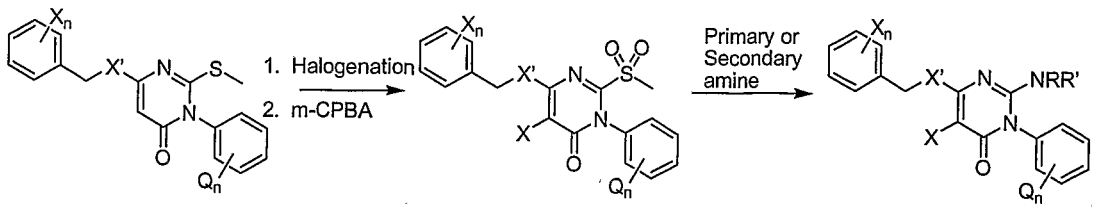


Scheme 23

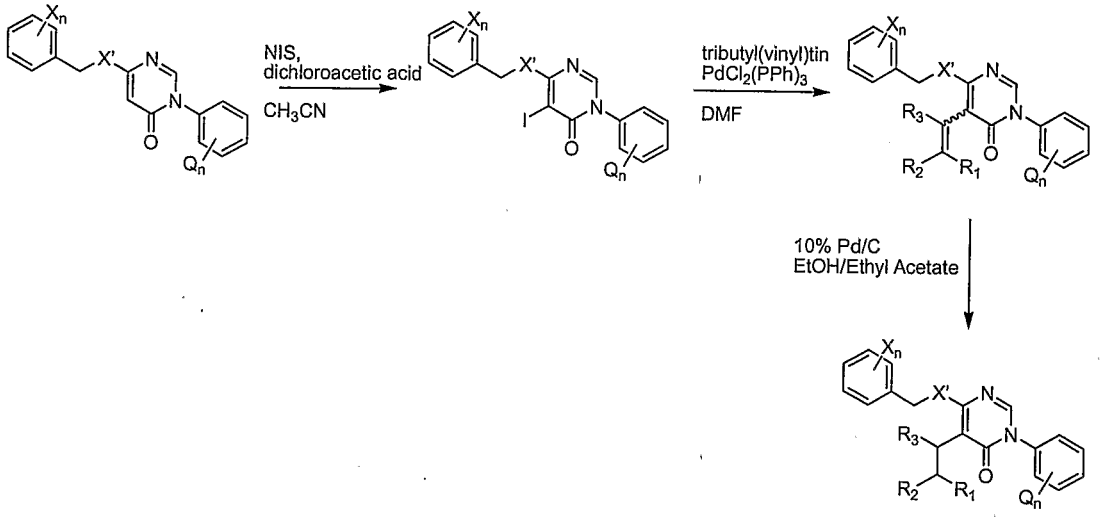


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Scheme 24

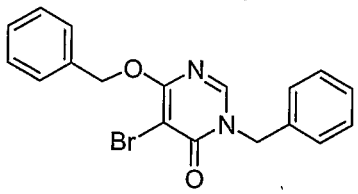


Scheme 25

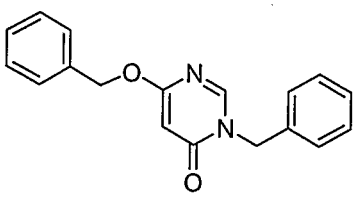


EXPERIMENTAL PROCEDURES

Preparation of 3-benzyl-6-(benzyloxy)-5-bromopyrimidin-4(3H)-one



Step 1: Preparation of 3-benzyl-6-(benzyloxy)-pyrimidin-4(3H)-one



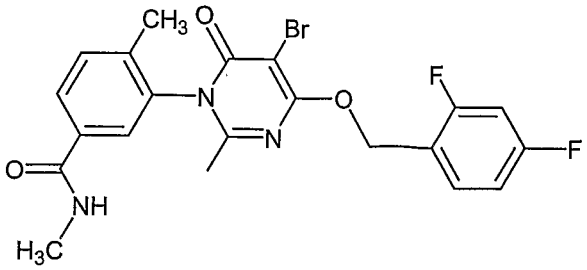
4,6-dihydroxypyrimidine (25.0 g, 0.223 mol) and potassium carbonate (65.1 g, 0.471 mol) are combined in 0.5 L anhydrous dimethylformamide. Benzyl chloride (55.7 g, 0.439 mol) is added dropwise over 30 minutes with stirring. After 4 h the solution is filtered, and the filtrate concentrated in vacuo. The residue is washed with acetonitrile, and the product is collected as a white solid by filtration (44.6 g, 68%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.06 (m, 2 H), 7.61 (quartet, J = 8.45 Hz, 1H), 7.30 (t, J = 10.37 Hz,1H), 7.12, (t, J = 8.45 Hz, 1H), 7.09 (d, J = 5.06 Hz, 2H), 5.14 (s, 2H). LC/MS t_r = 5.29 minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS m/z 293 (M+H).

Step 2: Preparation of the title compound

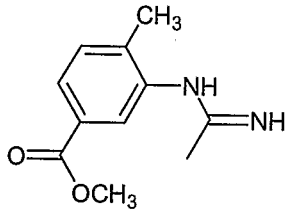
3-benzyl-6-(benzyloxy)-pyrimidin-4(3H)-one (from Step 1) (5.00 g , 17.1 mmol) and *N*-bromosuccinimide (3.15 g, 17.7 mmol) are strirred in 100 ml anhydrous dimethylformamide for 20 hours. The solution is poured onto 1 L of ice with stirring and allowed to come to room temperature, when the product is collected by filtration. (5.97 g). The product is recrystalized from 60 mL hot acetonitrile (4.75 g, 75%) ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.92 (s, 1H), 7.28-7.44 (overlapping m, 9H), 7.24 (s, 1H), 5.43 (s, 2H), 5.12 (s, 2H). LC/MS t_r = 5.89 minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 254 nm, at 50°C) ES-MS m/z 371 (M+H). HRMS m/z 371 (M+H) 371.0399, calc. 371.0395.

Preparation of 3-[5-Bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N,4-dimethylbenzamide

01640/01/PCT

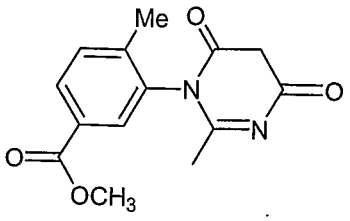


Step 1: Preparation of methyl 3-(Ethanimidoylamino)-4-methylbenzoate



A mixture of 2-naphthylmethyl ethanimidothioate hydrobromide (20.0 g, 0.068mol, (Tetrahedron Letters 38, 179-182, 1997) and methyl 3-amino-4-methylbenzoate (11.3 g, 0.068mol) in ethanol (125 mL) is stirred at room temperature for 1 h and then heated at 65 °C for 2 h under argon atmosphere. The resulting clear solution is concentrated under reduced pressure and the residue is partitioned between water (100 ml) and ether (50 mL). The aqueous portion is washed with ether (2 x 50 mL) and lyophilized to give a white powder (12.0 g). This is suspended in water (25 mL), cold 0.5 N NaOH (90.0 mL) is added, and the mixture is extracted with EtOAc (3 x 50 mL). The combined EtOAc extracts are washed with brine, dried (anhy. Na_2SO_4), filtered, and concentrated to dryness to afford methyl 3-(ethanimidoylamino)-4-methylbenzoate (5.9 g, 42 %) as a white powder. ^1H NMR (CD_3OD/ 400 MHz) δ 7.61 (m, 1H), 7.40 (s, 1H), 7.26 (m, 1H), 3.85 (s, 3H), and 2.17 (s, 3H); ES-HRMS *m/z* 207.1128 (M+H calcd for $C_{11}H_{15}N_2O_2$ requires 207.1104).

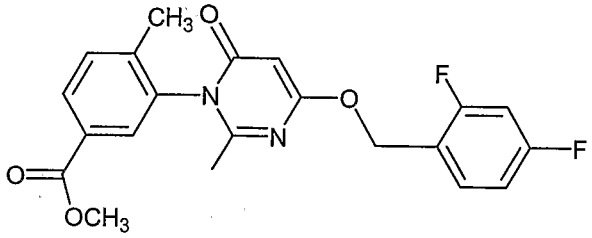
Step 2: Preparation of methyl 4-methyl-3-(2-methyl-4,6-dioxo-5,6-dihydropyrimidin-1(4H)-yl)benzoate



To a solution of methyl 3-(ethanimidoylamino)-4-methylbenzoate (2.5 g, 0.012 mol) in dichloromethane (25 mL) at -10 °C, is added *N*-methylmorpholine (1.84 g, 0.018 mol) followed by the dropwise addition of a solution of methylmalonylchloride (2.54 g, 0.18 mol) in dichloromethane (8.0 mL). The resulting mixture is allowed to warm to room temperature over a period of 16 h. The reaction mixture is then cooled to -10 °C and additional *N*-methylmorpholine (0.37 g, 0.0036 mol) is added, followed by a solution of methylmalonylchloride (0.51 g, 0.0037 mol) in dichloromethane (5.0 mL). After stirring the reaction mixture at room temperature for 1 h, it is cooled to 0 °C and cold 5% $NaHCO_3$ (25 mL) is added. The organic phase is washed with water (2 x 15 mL), dried (Na_2SO_4), filtered, and concentrated to dryness to give a yellow syrup which is purified by silica gel flash chromatography using 35% EtOAc in hexanes. The appropriate fractions (MH^+, m/z = 307) are pooled and concentrated to give a pale yellow syrup (1.8 g). The syrup (0.2 g, 0.00065 mol) is dissolved in dioxane (3.0 mL), DBU is added (0.05 g, 0.00033 mol) and the mixture is heated at 65 °C under argon atmosphere for 5 h. The reaction mixture is concentrated and the residue is purified by reverse-phase HPLC using 10-90% CH_3CN/Water gradient (40 min) at a flow rate of 80 mL/min. The appropriate fractions (MH^+ , m/z = 275) are combined and freeze-dried to afford the title compound (0.11 g, 61%) as a

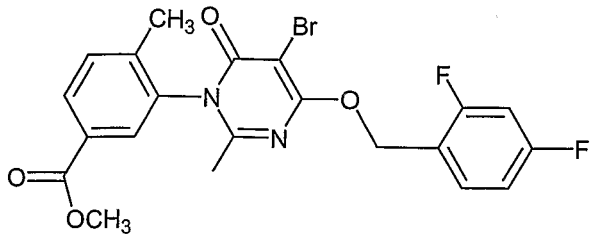
white powder: ^{1}H NMR (CD_3OD/ 400 MHz) δ 8.04 (d, 1H, *J* = 1.6 Hz), 7.87 (d, 1H, *J* = 1.6 Hz), 7.56 (m, 1H), 5.46 (s, 1H) 3.89 (s, 3H), and 2.16 (s, 3H), 2.1 (s, 3H); ES-HRMS *m/z* 275.1045 (M+H calcd for $C_{14}H_{15}N_2O_4$ requires 275.1026).

Step 3: Preparation of Methyl 3-[4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoate



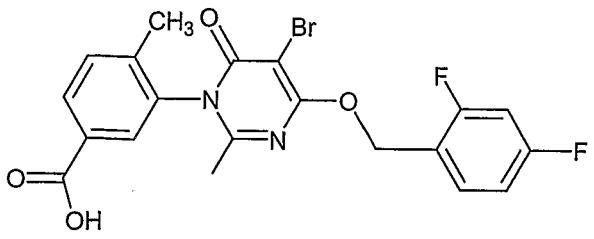
A mixture of methyl 4-methyl-3-(2-methyl-4,6-dioxo-5,6-dihydropyrimidin-1(4H)-yl)benzoate (0.1 g, 0.00036 mol, from Step 2), K_2CO_3 (0.075 g, 0.00054 mol) and 2,4 difluorobenzylbromide (0.075 g, 0.00036 mol) in DMF (2.0 mL) containing 18-crown-6 (0.005 g) is stirred at room temperature for 1 h under argon atmosphere. DMF is distilled *in vacuo* and the residue is purified by reverse-phase HPLC using 10-90% CH_3CN/Water gradient (40 min) at a flow rate of 80 mL/min. The appropriate fractions (MH^+, *m/z* = 401) are combined and concentrated to a small volume (~ 20 mL). After cooling, 5% $NaHCO_3$ solution (10 mL) is added and the solution is extracted with dichloromethane (3 x 20 mL). The combined organic extracts are dried (Na_2SO_4), filtered, and concentrated to dryness to afford the title compound (0.12 g, 82%) as a white amorphous substance: ^{1}H NMR (CD_3OD/ 400 MHz) δ 8.04 (d, 1H, *J* = 1.6 Hz), 7.87 (d, 1H, J = 1.16 Hz), 7.55 (m, 2H), 7.00 (m, 2H), 5.79 (s, 1H), 5.38 (s, 2H), 3.89 (s, 3H), 2.14 (s, 3H), and 2.12 (s, 3H); ES-HRMS *m/z* 401.1346 (M+H calcd for $C_{21}H_{19}N_2O_4F_2$ requires 401.1307).

Step 4: Preparation of Methyl 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoate



A mixture of methyl 3-[4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoate (0.41g, 0.001 mol, from Step 3) and NBS (0.2 g, 0.0011 mol) in dichloromethane (5.0 mL) is stirred at room temperature for 1.5 h under argon atmosphere. The reaction mixture is purified by flash chromatography using 30% EtOAc in hexanes to furnish the title compound (0.37 g, 75%) as a white amorphous powder: ^{1}H NMR (CD_3OD/ 400 MHz) δ 8.04 (d, 1H, *J* = 1.6 Hz), 7.89 (d, 1H, J = 1.6 Hz), 7.62 (m, 2H), 7.01 (m, 2H), 5.56 (s, 2H), 3.89 (s, 3H), 2.15 (s, 3H), and 2.133 (s, 3H); ES-HRMS *m/z* 479.0412 (M+H calcd for $C_{21}H_{18}N_2O_4F_2Br$ requires 479.0413). ^{19}F NMR(CD_3OD/ 400 MHz) -111.870(m) and -115.95 (m).

Step 5: Preparation of 3-[5-Bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoic acid



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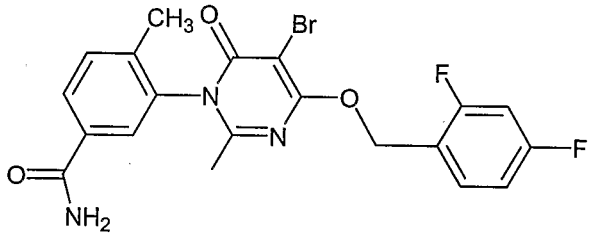
A mixture of methyl 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoate (0.40g, 0.00084 mol, from Step 4), and 1.5 N NaOH (0.7 mL, 0.042 g, 0.001 mol) containing dioxane (0.5 mL) is stirred at 55 °C for 30 min. The resulting clear brown solution is cooled in an ice bath, diluted with water (3 mL), acidified with trifluoroacetic acid, and the product is purified by reverse-phase HPLC using 10-90% CH_3CN/Water gradient (40 min) at a flow rate of 80 mL/min. The appropriate fractions (MH^+, m/z = 465) are combined and freeze-dried to afford the title compound (0.17 g, 44%) as a white powder: ^1H NMR (CD_3OD/ 400 MHz) δ 8.04 (d, 1H, J = 1.6 Hz), 7.87 (d, 1H, J = 1.6 Hz), 7.54 (m, 2H), 6.99 (m 2H), 5.56 (s, 2H), 2.15 (s, 3H), and 2.13 (s, 3H); ES-HRMS m/z 465.0256 (M+H calcd for $C_{20}H_{16}N_2O_4F_2Br$ requires 465.0256); ^{19}F NMR(CD_3OD/ 400 MHz) -111.89(m) and -115.95 (m).

Step 6: Preparation of title compound.

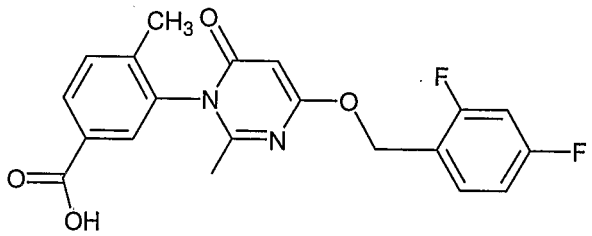
To a solution of 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoic acid (0.16 g, 0.00034 mol, obtained from Step 5) at 0 °C is added isobutylchloroformate (0.063 g, 0.00046 mol) followed by the addition of *N*-methylmorpholine (0.064 g, 0.00064 mol). The resulting reaction mixture is stirred for 5 minutes under an argon atmosphere. The ice bath is then removed, the reaction mixture is stirred at room temperature for 20 minutes, then the reaction mixture is recooled to 0 °C, and *N*-methylamine (0.5 mL of 2.0 M soln in THF) is added. The resulting mixture is stirred at room temperature for 10 min, concentrated *in vacuo*, and the residue is purified by reverse-phase HPLC using 10-90% CH_3CN/Water gradient (40 min) at a flow rate of 80

mL/min. The appropriate fractions (MH^+, m/z = 478) are combined, concentrated to a small volume (~ 20 mL), cooled, 5% $NaHCO_3$ solution (10 mL) is added and then the combined fractions are extracted with dichloromethane (3 x 20 mL). The combined organic extracts are dried (Na_2SO_4), filtered, and concentrated to dryness to afford the title compound (0.16 g, 96%) as a white amorphous substance: ^1H NMR (CD_3OD/ 400 MHz) δ 7.87 (dd 1H, J = 8.0 Hz), 7.64 (d, 1H, J = 1.6 Hz), 7.61 (m, 1H), 7.53 (d, 1H, J = 8.0 Hz), 7.01 (m, 2H), 5.55 (m, 2H), 2.89 (s, 3H), 2.16 (s, 3H), and 2.12 (s, 3H); ES-HRMS m/z 478.0586 (M+H calcd for $C_{21}H_{19}N_2O_4F_2$ requires 478.0572). ^{19}F NMR(CD_3OD/ 400 MHz) -111.84(m) and -115.91 (m).

Preparation of 3-[5-Bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methylbenzamide



Step 1: Preparation of 3-[5-Bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoic acid



A mixture of methyl 3-[4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoate (0.20g, 0.0005 mol) and 2N NaOH (0.4 mL, 0.0008 mol) in dioxane (0.25

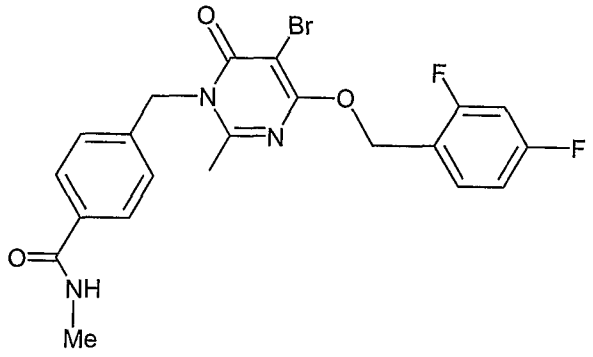
mL) is stirred at room temperature for 45 min. The resulting clear solution is diluted with water (5.0 mL), acidified with acetic acid and extracted with dichloromethane (2 x 10 mL). The combined organic extracts are washed with water (2 x 10 mL), dried (Na_2SO_4), filtered, and concentrated to dryness to afford the title compound (0.15 g, 78%) as a white powder: ^1H NMR (CD_3OD/ 400 MHz) δ 8.08 (m,1H), 7.85 (d, 1H, *J* = 1.6 Hz), 7.55 (m, 2H), 7.00 (m, 2H), 5.80 (s, 1H), 5.38 (s, 2H), 2.14 (s, 3H), and 2.13 (s, 3H); ES-HRMS *m/z* 387.1166 (M+H calcd for $C_{20}H_{17}N_2O_4F_2$ requires 387.1151). ^{19}F NMR(CD_3OD/ 400 MHz) -107.75(m) and-112.08 (m).

Step 2. Preparation of title compound

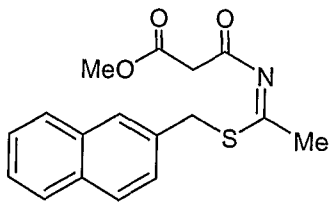
To a suspension of 3-[5-Bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoic acid (0.15 g, 0.00039 mol, obtained from step 1) in dichloromethane (5.0 mL) and dioxane (1.0 mL) is added NBS (0.075 g, 0.00042 mol). The resulting reaction mixture is stirred at room temperature for 1 hour and then concentrated to dryness. The residue is dried in a desiccator for 1 hour, dissolved in dimethylacetamide (2.5 mL), isobutylchloroformate (0.075 mL, 0.00058 mol) is added, *N*-methylmorpholine (0.14 mL, 0.0013 mol) is then added, and the reaction mixture is stirred at 0 °C for 5 min under argon. After stirring the reaction mixture at room temperature for 30 min, it is cooled to 0 °C, a solution of ammonia in isopropanol (1.2 mL of 2M ammonia in isopropanol) is added and the resulting reaction mixture is stirred at 0 °C for 30 min. The resulting mixture is concentrated to dryness under reduced pressure and the residue is purified by reverse-phase HPLC using 10-90% CH_3CN/Water gradient (40 min) at a flow rate of 80 mL/min. The

appropriate fractions (MH^+, m/z = 464) are combined and concentrated to a small volume (~ 25 mL), cooled, 5% $NaHCO_3$ solution (5.0 mL) is added and then the mixture is extracted with dichloromethane (2 x 20 mL). The combined organic extracts are dried (Na_2SO_4), filtered, and concentrated to dryness to afford the desired product (0.115 g, 77%) as a white powder: ^1H NMR (CD_3OD/ 400 MHz) δ 7.95 (m 1H), 7.12 (d, 1H J = 1.6 Hz), 7.62 (m 1H), 7.61 (m, 1H), 7.01 (m, 2H), 5.58 (m, 2H), 2.16 (s, 3H), and 2.12 (s, 3H); ES-HRMS m/z 464.0436 (M+H calcd for $C_{20}H_{17}N_3O_3F_2Br$ requires 464.0416). ^{19}F NMR(CD_3OD/ 400 MHz) -111.85(m) and -115.92 (m).

Preparation of 4-{[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}-N-methylbenzamide



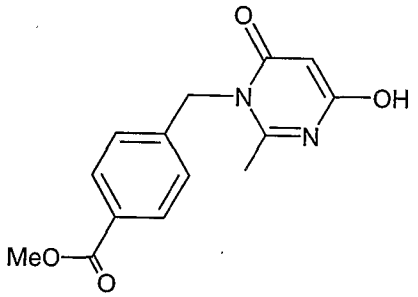
Step 1: Preparation of Methyl 3-({(1Z)-1-[(2-naphthylmethyl)thio]ethylidene}amino)-3-oxopropanoate



To a suspension of 2-naphthylmethyl ethanimidothioate hydrobromide (3.0 g, 0.01mol) in THF (20.0 mL) at 0 °C, is added N-methylmorpholine (2.4 mL. 0.022 mol), followed by the

dropwise addition of a solution of methyl malonyl chloride (1.2 mL, 0.011 mol) in THF (5.0 mL). The resulting mixture is stirred at 0 °C for 30 min, and at room temperature for an additional 30 min. The mixture is diluted with cold water, (25 mL) and extracted with dichloromethane (2 x 20 mL). The combined organic extracts are washed with water, dried (Na_2SO_4), filtered and concentrated to dryness under reduced pressure to give a yellow syrup, which is purified by flash chromatography using 25 % EtOAc in hexanes to give the title compound (1.9 g, 59%) as colorless syrup: ES-HR MS *m/z* 316.0993(M+H calcd for $C_{17}H_{18}NO_3SN$ requires 316.1002).

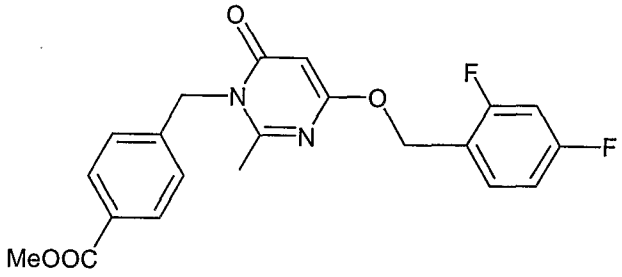
Step 2: Preparation of methyl 4-[(4-hydroxy-2-methyl-6-oxopyrimidin-1(6H)-yl)methyl]benzoate



To a solution of methyl 3-({(1Z)-1-[(2-naphthylmethyl)thio]ethylidene}amino)-3-oxopropanoate (1.9 g, 0.006 mol, from step 1) in THF (25.0 mL), at 0 °C, is added methyl-4-aminomethylbenzoate (1.1 g, 0.0067 mol). The reaction mixture is stirred at room temperature for 1 hour, and then concentrated to dryness. The resulting residue is dissolved in dioxane (20 .0 mL), DBU (0.1 mL) is added, and the resulting reaction mixture is heated at 70 °C for 1 h under an argon atmosphere. After removing the solvent under reduced pressure, the residue is purified by reverse-phase HPLC using 10-90% CH_3CN/Water gradient (40 min) at a flow rate

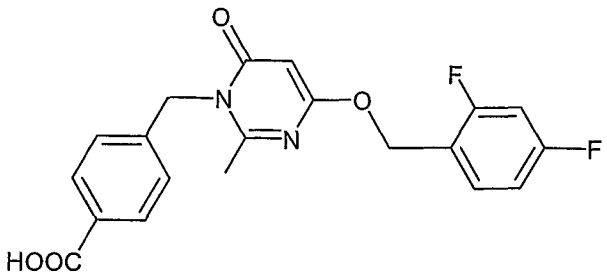
of 80 mL/min. The appropriate fractions (MH^+, m/z = 275) are combined and freeze-dried to afford the title compound (0.33 g) as a white powder: ^1H NMR (CD_3OD/ 400 MHz) δ 7.99 (d 2H, J = 8.4 Hz), 7.29 (d, 2H, J = 8.4 Hz), 5.42 (s, 1H), 5.36 (s, 2H), 3.88 (s, 3H), and 2.42 (s, 3H); ES-HRMS m/z 275.1021 (M+H calcd for $C_{14}H_{15}N_2O_4$ requires 275.1026).

Step 3. Preparation of methyl 4-{[4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzoate



A mixture of methyl 4-[(4-hydroxy-2-methyl-6-oxopyrimidin-1(6H)-yl)methyl]benzoate(0.2 g, 0.00073 mol, from step 2), potassium carbonate (0.15 g, 0.001 mol), 2,4 difluorobenzylbromide (0.15 g, 0.00073 mol), and 18-crown-6 (0.011 g) in DMF is stirred at room temperature for 1 h under argon atmosphere. The DMF was distilled *in vacuo* and the residue is partitioned between dichloromethane (20 mL) and water (20 mL). The organic phase is washed with water, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting residue is purified by silica gel flash chromatography using 35% EtOAc in hexanes to afford the title compound (0.20 g, 69%) as a white powder: ^1H NMR (CD_3OD/ 400 MHz) δ 7.98 (d 2H, J = 8.4 Hz), 7.54 (m, 1H), 7.27 (d, 2H, J = 8.4 Hz), 6.98 (m, 2H), 5.78 (s, 1H), 5.38 (s, 2H), 5.32 (s, 2H), 3.88 (s, 3H), and 2.44 (s, 3H); ES-HRMS m/z 401.1308 (M+H calcd for $C_{21}H_{19}N_2O_4F_2$ requires 401.1307). ^{19}F NMR(CD_3OD/ 400 MHz) -111.77 (m), 116.06 (m).

Step 4: Preparation of 4-{[4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzoic acid



A mixture of methyl 4-{[4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzoate (0.20g, 0.0005 mol, from step 3) and 2N NaOH (0.4 mL, 0.0008 mol) in dioxane (0.25 mL) is stirred at room temperature for 45 min. The resulting clear solution is diluted with water (5.0 mL), acidified with acetic acid and extracted with dichloromethane (2 x 10 mL). The combined organic extracts are washed with water (2 x 10 mL), dried (Na_2SO_4), filtered and concentrated to dryness to afford the title compound (0.15 g, 78%) as a white powder: ^1H NMR (CD_3OD/ 400 MHz) δ 7.99 (d, 2H, J = 8.0 Hz), 7.54 (m, 1H,), 7.27 (d, 2H, J = 8.0 Hz), 6.00 (m, 2H), 5.78 (s, 1H), 5.39 (s, 2H), 5.32 (s, 2H), 2.45 (s, 3H), and 2.13 (s, 3H); ES-HRMS m/z 387.1134 (M+H calcd for $C_{20}H_{17}N_2O_4F_2$ requires 387.1151). ^{19}F NMR(CD_3OD/ 400 MHz) -111.79(m) and -116.08 (m).

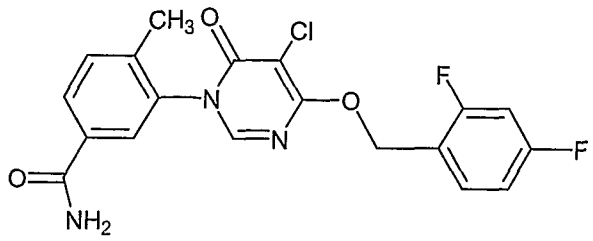
Step 5: Preparation of the title compound.

To a suspension of 4-{[4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]methyl}benzoic acid (0.18 g, 0.00047 mol, from step 4) in dichloromethane (3.0 mL) and dioxane (1.0 mL) is added NBS (0.09 g, 0.0005 mol). The

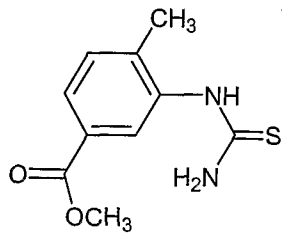
resulting reaction mixture is stirred at room temperature for 3 hours, concentrated to dryness, and the residue is then dried in a desiccator for 2 h. This residue is dissolved in dimethylacetamide (2.5 mL), isobutylchloroformate (0.08 mL, 0.00062 mol) is added, *N*-methylmorpholine (0.0.08 mL, 0.00073 mol) is then added, and the reaction mixture is stirred at 0 °C for 5 min under argon. The reaction mixture is then stirred at room temperature for 30 min, it is recooled to 0 °C, a solution of *N*-methylamine in THF(1.1 mL of 2M inTHF) is then added , and the resulting reaction mixture is stirred at 0 °C for 30 min. The resulting mixture is concentrated to dryness under reduced pressure and the residue is purified by reverse-phase HPLC using 10-90% CH_3CN/Water gradient (40 min) at a flow rate of 80 mL/min. The appropriate fractions (MH^+, *m/z* = 478) are combined and concentrated to a small volume (~ 25 mL), cooled added 5% $NaHCO_3$ solution (5.0 mL) and extracted with dichloromethane (2 x 20 mL). The combined organic extracts are dried (Na_2SO_4), filtered and concentrated to dryness to afford the title compound (0.14 g, 64%) as a white powder: ^1H NMR (CD_3OD/ 400 MHz) δ 7.77 (d 2H, *J* = 8.4 Hz), 7.58 (m, 1H), 7.26 (d, 2H, *J* = 8.4 Hz), 7.01 (m, 2H), 5.49 (s, 2H), 5.42 (s, 2H), 2.89 (s, 3H), and 2.48 (s, 3H); ES-HRMS *m/z* 478.0596 (M+H calcd for $C_{21}H_{19}N_3O_3F_2Br$ requires 478.0572). ^{19}F NMR(CD_3OD/ 400 MHz) -111.99(m) and -115.99 (m).

Preparation of 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-(methylthio)-6-oxopyrimidin-1(6H)-yl]-4-methylbenzamide.

01640/01/PCT



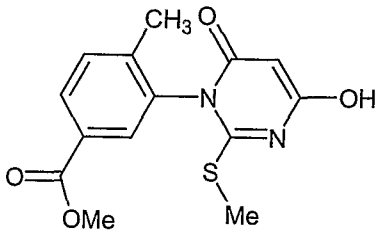
Step 1: Preparation of methyl 3-[(aminocarbonothioyl)amino]-4-methylbenzoate



To a mixture of methyl-3-aminomethyl benzoate (5.7 g, 0.035 mol) and potassiumthiocyanate (5.0 g, 0.05 mol) in THF at 0 °C, was added 4N HCl in dioxane (9.0 mL) and the resulting mixture was heated at 80 °C under argon for 20 h. After the removal of the solvents under educed pressure, the residue was triturated with water and filtered the precipitate. It was washed thoroughly washed with water and air dried to give a pale yellow substance. This material was further washed with hot ethylacetate (200 mL) and dried to give the title compound (3.85 g) as a white powder: ^{1}H NMR (CD_3OD/ 400 MHz) δ7.85 (m, 2H), 7.38 (m, (1H), 3.89 (s, 3H), and 2.33 (s, 3H); ES-HRMS *m/z* 225.0672 (M+H calcd for $C_{10}H_{13}N_2O_2S$ requires 225.0692).

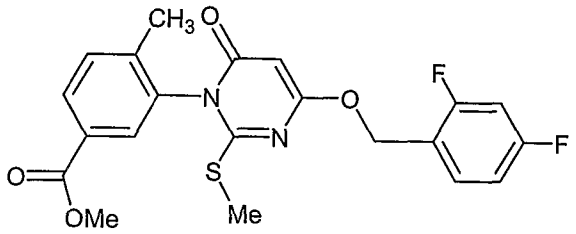
Step 2: Preparation of methyl 3-[4-hydroxy-2-(methylthio)-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoate

01640/01/PCT



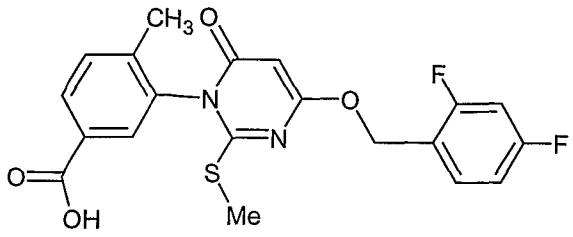
To a suspension of 3-[(aminocarbonothioyl)amino]-4-methylbenzoate (1.5 g, 0.067 mol)in methanol (15.0 mL) at 0 °C, was added iodomethane (0.5 mL. 0.0077 mol) and stirred at room temperature for 30 min. The reaction mixture was then heated to reflux for 15 min, when a clear solution was obtained. It was concentrated under reduced pressure, the residue was dried *in vacuo* for 1 h and dissolved in dichloromethane (25.0 mL). This solution was cooled to -5 °C, added N-methylmorpholine (1.38 g, 0.0136 mol) followed by the dropwise addition of a solution of methylmalonyl chloride (1.36 g, 0.01 mol) in dichloromethane (5.0 mL) and the resulting mixture was stirred at room temperature overnight under argon atmosphere. The mixture was cooled to - 5°C and added an additional amount of N-methylmorpholine (0.46 g, 0.0046 mol) followed by the addition of methylmalonyl chloride (0.62 g, 0.0045 mol) and stirred at room temperature for 2 h. The reaction mixture was then cooled to 10 °C, added water (25 mL) and dichloromethane (25 mL) and the mixture was stirred for 30 min. The interfacial solid was filtered, washed with water and dried in a desicctor to give 1.1 g (55%) of the title compound as a white powder: ^{1}H NMR (CD_3OD/ 400 MHz) δ 8.05 (d, 1H, J = 8.4 Hz), 7.80 (s, 1H), 7.52 (d, 1H, J = 8.4 Hz), 5.44 (s, 1H), 3.89 (s, 3H), 2.46 (s, 3H), and 2.15 (s, 3H); ES-HRMS *m/z* 307.0769 (M+H calcd for $C_{14}H_{15}N_2O_4S$ requires 307.0747).

Step 3: Preparation of methyl 3-[4-[(2,4-difluorobenzyl)oxy]-2-(methylthio)-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoate



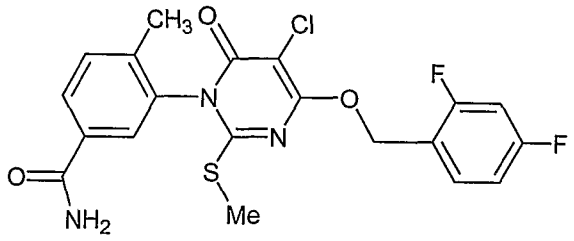
To a solution of methyl 3-[4-hydroxy-2-(methylthio)-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoate (1.0 g, 0.0033 mol) in DMF (10. 0 mL) obtained from step 2, was added potassium carbonate (0.7 g, 0.005 mol) followed by the addition of 2,4 difluorobenzyl bromide (0.8 g, 0.0039 mol) and stirred at 0 °C for 15 min. After stirring at room temperature for 30 min, DMF was distilled *in vacuo* and the residue was portioned between EtOAc (25 mL) and water (25 mL). The organic phase was washed with water, (2 x 20 mL), dried (Na_2SO_4) and concentrated. The resulting material was purified by flash chromatography using EtOAc/hexane (1:1 v/v) to afford the title compound (0.9 g, 64%) as a white powder: ^1H NMR (CD_3OD/ 400 MHz) δ 8.08 (dd, 1H, J = 8.4 Hz, & 1.6 Hz), 7.83 (d, 1H, J = 1.6 Hz), 7.55 (m, 2H), 6.99 (m 2H), 5.64 (s, 1H), 5.48 (s, 2H), 3.89 (s, 3H), 2.50 (s, 3H), and 2.15 (s, 3H); ES-HRMS m/z 433.1016 (M+H calcd for $C_{21}H_{19}N_2O_4SF_2$ requires 433.1028).

Step 4: Preparation of 3-[4-[(2,4-difluorobenzyl)oxy]-2-(methylthio)-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoic acid



A mixture of the ester (0.4 g, 0.0009 mol) obtained from step 3, in 2N NaOH (0.9 mL) and dioxane (0.5 mL) was stirred at room temperature for 1,5 h. The resulting clear solution was diluted with water (5.0 mL), acidified with 5% citric acid and extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with water (2 x15 mL), dried (Na_2SO_4), and concentrated to afford the title compound (0.38 g) as a white powder: ^1H NMR (CD_3OD/ 400 MHz) δ 8.06 (d, 1H, J = 8.0 Hz), 7.81 (s, 1H), 7.51 (m, 2H), 6.99 (m 2H), 5.64 (s, 1H), 5.48 (s, 2H), 2.50 (s, 3H), and 2.15 (s, 3H); ES-HRMS m/z 419.0892(M+H calcd for $C_{20}H_{17}N_2O_4SF_2$ requires 419.0872).

Step 5: Preparation of 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-(methylthio)-6-oxopyrimidin-1(6H)-yl]-4-methylbenzamide



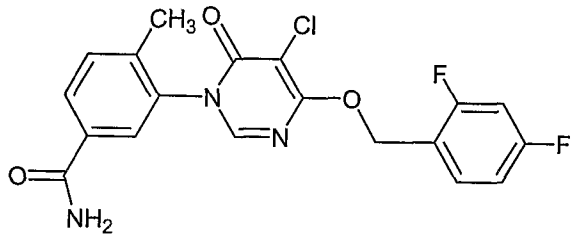
A mixture of 3-[4-[(2,4-difluorobenzyl)oxy]-2-(methylthio)-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoic acid

(0.5 g, 0.001 mol, from step 4), N-chlorosuccinimide (0.14 g, 0.001 mol) in dichloroethane containing dichloroacetic acid (0.2 mL) was heated at 65 °C for 3 h under argon atmosphere. An additional amount of N-chlorosuccinimide (0.05 g) was added and heating was continued for an additional 16 h. The reaction mixture was concentrated under reduced pressure and the residue was partitioned between EtOAc (25 mL) and water (30 mL). The organic phase was washed with water (2 x10 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure.

The resulting material was dried *in vacuo* for 3 h, dissolved in DMF (3.0 mL), added N-methylmorpholine (0.22 g, 0.0022 mol) followed by the addition of isobutylchloroformate (0.23 g, 0.0017 mol) and stirred at 0 °C under argon atmosphere. After 5min, the mixture was stirred at room temperature for 30 min, cooled to 0 °C and added a solution of ammonia (1.8 mL of 2M soln in isopropanol) and the mixture was stirred at room temperature . After 30 min, an additional 1.0 mL of ammonia solution I isopropanol was added and continued stirring for another 30 min. After the removal of the solvents under reduced pressure the residue was purified by reverse-phase HPLC using 10-90% CH_3CN/Water gradient (40 min) at a flow rate of 80 mL/min. The appropriate fractions (MH^+, m/z = 452) were combined and concentrated to a small volume (~ 20 mL), cooled added 5% sod. bicarbonate (10 mL) and extracted with dichloromethane (3 x 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to dryness to afford the title compound (0.15 g,) as a white powder: ^1H NMR (CD_3OD/ 400 MHz) δ 7.87 (dd 1H, J = 2.0 Hz & 8.0 Hz), 7.74 (d, 1H, J = 2.0 Hz)

7.58 (m, 2H), 7.03 (m, 2H), 5.63 (m 2H), 2.53 (s, 3H), and 2.14 (s, 3H); ES-HRMS *m/z* 452.0633(M+H calcd for $C_{20}H_{17}N_3O_3F_2ClS$ requires 452.0642); ^{19}F NMR(CD_3OD/ 400 MHz) -111.75(m) and-115.99(m).

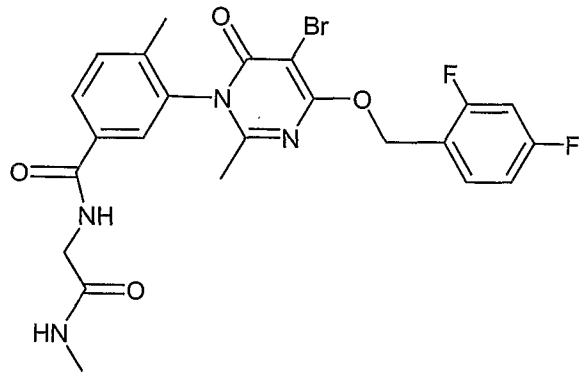
Step 6: Preparation of the title compound 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-4-methylbenzamide



A mixture of 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-(methylthio)-6-oxopyrimidin-1(6H)-yl]-4-methylbenzamide (0.15 g, 0.00033 mol from step 5), and Raney nickel (0.8 mL, 50% slurry in water) in ethanol (15.0 mL) was refluxed under argon atmosphere. After 12 h, added an additional 0.4 mL of Raney nickel and continued refluxing for another 4 h. The reaction mixture was cooled and the supernatant was decanted off. The catalyst was washed with ethanol, the combined ethanol washings and the supernatant were concentrated under reduced pressure and the resulting residue was purified by reverse-phase HPLC using 10-90% CH_3CN/Water gradient (40 min) at a flow rate of 80 mL/min. The appropriate fractions (MH^+, *m/z* = 406) were combined and concentrated to a small volume (~ 20 mL), cooled added 5% sod. bicarbonate (10 mL) and extracted with dichloromethane (3 x 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to dryness to afford the title compound (0.075 g,) as a white powder: ^1H NMR (CD_3OD/ 400 MHz) δ 8.31 (s, 1H), 7.94 (dd, 1H. *J* = 2.0 Hz & 8.0 Hz), 7.79

(d, 1H, J = 2.0 Hz), 7.62 (m, 1H), 7.53 (m, 1H), 7.02 (m, 2H), 5.59 (m, 2H), and 2.19 (s, 3H); ES-HRMS m/z 406.0774(M+H calcd for $C_{19}H_{15}N_3O_3F_2Cl$ requires 406.0765); ^{19}F NMR(CD_3OD/ 400 MHz) -111.62(m) and-115.94(m).

Preparation of (±) 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methyl-N-{1-[(methylamino)carbonyl]methyl}benzamide.

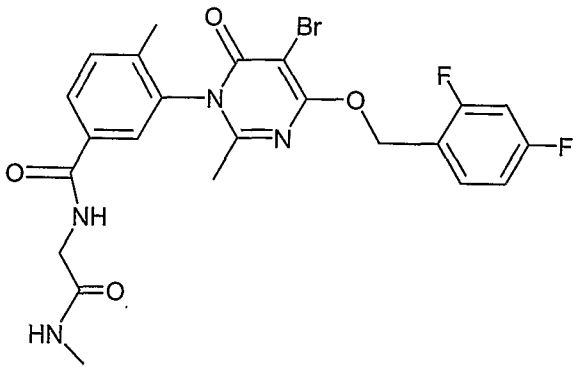


To a solution of 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoic acid (1.0 g, 0.022 mol) in dimethylacetamide (10.0 mL) at -20 °C was added isobutylchloroformate (0.36 g, 0.0028 mol), followed by dropwise addition of *N*-methylmorpholine (0.30 g, 0.003 mol) and stirred for 10 min under nitrogen atmosphere. The reaction mixture was then stirred at room temperature for 20 min, cooled to 0 °C, and added *N*-methylmorpholine (0.30 g, 0.003 mol) followed by the addition of *N*-methylglycine amide hydrochloride (0.35 g, 0.0028 mol) and DMAP (0.025 g). The reaction mixture was stirred at room temperature for 4 h, and concentrated *in vacuo*. The resulting the residue was purified by reverse-phase HPLC using 10-90% CH_3CN/Water gradient (40 min) at a flow rate of 80 mL/min. The appropriate fractions

(MH^+, m/z = 535) were combined, and freeze-dried to give a white solid. This was dissolved in dichloromethane (25 mL), washed successively with 5% sodium bicarbonate (2 x 20 mL), water (2 x 20 mL), dried (Na_2SO_4), and concentrated to dryness to afford the racemic title compound (0.75 g, 65%) as a white amorphous substance: ^1H NMR (CD_3OD/ 400 MHz) δ 7.96 (dd 1H, J = 1.6 Hz, 8.0 Hz), 7.72 (d, 1H, J = 1.6 Hz), 7.62 (m, 1H), 7.56 (d, 1H, J = 8.0 Hz), 7.01 (m, 2H), 5.55 (abq, 2H), 3.99 (s, 2H), 2.74 (s, 3H), 2.18 (s, 3H), and 2.14 (s, 3H); ES-HRMS m/z 535.0792 (M+H calcd for $C_{23}H_{22}N_4O_4F_2$ Br requires 535.0787). ^{19}F NMR(CD_3OD/ 400 MHz) -111.85(m) and

-115.91 (m).

Preparation of (-) 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methyl-N-{1-[(methylamino)carbonyl]methyl}benzamide.

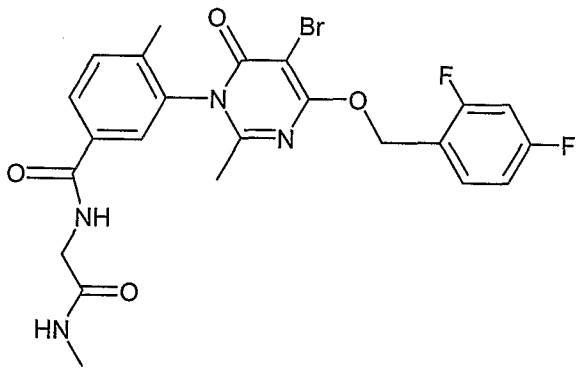


The racemic compound (1.9 g) was resolved using a Chiralpak AD-H column, 21 X 250 mm. The sample was dissolved in EtOH/MeOH (50/50v/v, 25 mg/mL) and 2.7 mL of the solution was injected into the column and eluted with EtOH/MeOH (80/20

v/v) at a flow rate of 12 mL/min. Fractions with negative optical rotation were pooled together and concentrated under reduced pressure to give 0.69g of the (-) isomer as a white solid:

^{1}H NMR (CD_3OD/ 400 MHz) δ 7.96 (dd 1H, J = 2.0 Hz, 8.0 Hz), 7.72 (d, 1H, J = 2.0 Hz), 7.62 (m, 1H), 7.55 (d, 1H, J = 8.0 Hz), 7.01 (m, 2H), 5.55 (abq, 2H), 3.99 (s, 2H), 2.74 (s, 3H), 2.18 (s, 3H), and 2.14 (s, 3H); ES-HRMS m/z 535.0824 (M+H calcd for $C_{23}H_{22}N_4O_4F_2$ Br requires 535.0787). ^{19}F NMR(CD_3OD/ 400 MHz) -111.85(m) and -115.90 (m).

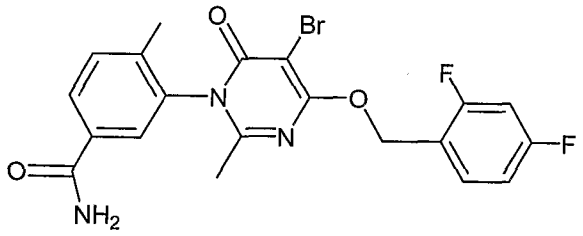
Preparation of (+) 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methyl-N-{1-[(methylamino)carbonyl]methyl}benzamide.



The title compound was isolated from the racemic material (1.9 g) according to the resolution procedure described for (-) 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methyl-N-{1-[(methylamino)carbonyl]methyl}benzamide. Fractions with

positive optical rotation were pooled together and concentrated under reduced pressure to give 0.82 g of the (+) isomer as an amorphous white solid: ^{1}H NMR (CD_3OD/ 400 MHz) δ 7.95 (dd 1H, *J* = 1.6 Hz, 8.0 Hz), 7.72 (d, 1H, *J* = 2.0 Hz), 7.62 (m, 1H), 7.55 (d, 1H, *J* = 8.4 Hz), 7.01 (m, 2H), 5.55 (abq, 2H), 3.98 (s, 2H), 2.74 (s, 3H), 2.18 (s, 3H), and 2.14 (s, 3H); ES-HRMS *m/z* 535.0770 (M+H calcd for $C_{23}H_{22}N_4O_4F_2$ Br requires 535.0787). ^{19}F NMR(CD_3OD/ 400 MHz) -111.84(m) and -115.89 (m).

Preparation of (-) 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methylbenzamide.

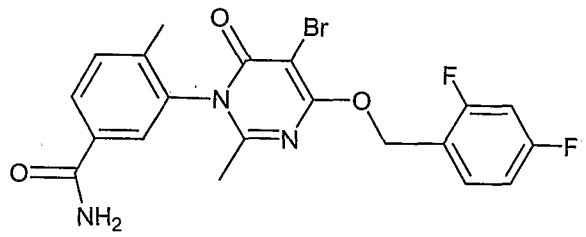


The racemic compound 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methylbenzamide (90.0 mg) was resolved using a Chiralpak AD column, 4.5 X 250 mm. The sample was dissolved in 30% EtOH in hexane and 30 □L of the solution was injected into the column and eluted with 30%EtOH in hexane at a flow rate of 1.5 mL/min. Fractions with negative optical rotation were pooled together and concentrated under reduced pressure to give 39 mg of the (-) isomer as a white solid:

^{1}H NMR (CD_3OD/ 400 MHz) δ 7.94 (dd 1H, *J* = 1.6 Hz, 8.0 Hz), 7.72 (d, 1H, *J* = 1.6 Hz), 7.63 (m, 1H), 7.55 (d, 1H, *J* = 8.0

Hz), 7.01 (m, 2H), 5.55 (abq, 2H), 2.17 (s, 3H), and 2.13 (s, 3H); ES-HRMS *m/z* 464.0439(M+H calcd for $C_{20}H_{17}N_3O_3F_2$ Br requires 464.0416). ^{19}F NMR(CD_3OD/ 400 MHz) -111.86(m) and -115.92 (m).

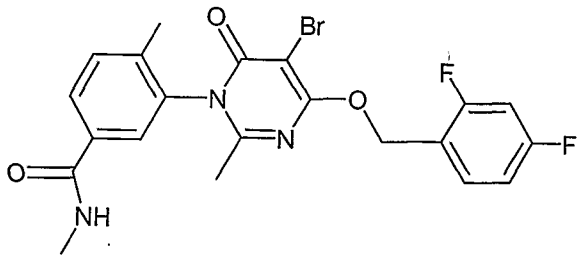
Preparation of (+)3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4- methylbenzamide.



The title compound was isolated from the racemic material (90.0 mg) according to the resolution procedure described for (-) 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methylbenzamide. Fractions with positive optical rotation were pooled together and concentrated under reduced pressure to give 38.5 mg of the (+) isomer as a white solid: ^1H NMR (CD_3OD/ 400 MHz) δ 7.95 (dd 1H, *J* = 2.0Hz, 8.0 Hz), 7.72 (d, 1H, *J* = 2.0 Hz), 7.63 (m, 1H), 7.55 (d, 1H, *J* = 8.0 Hz), 7.01 (m, 2H), 5.55 (abq, 2H), 2.17(s, 3H), and 2.13 (s, 3H); ES-HRMS *m/z* 535. (M+H); ^{19}F NMR(CD_3OD/ 400 MHz) -111.84(m) and -115.90 (m); ES-HRMS *m/z* 464.0410(M+H calcd for $C_{20}H_{17}N_3O_3F_2$ Br requires 464.0416). ^{19}F NMR(CD_3OD/ 400 MHz) -111.86(m) and -115.92 (m).

Preparation of (-) 3-[5-Bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N,4-dimethylbenzamide.

01640/01/PCT



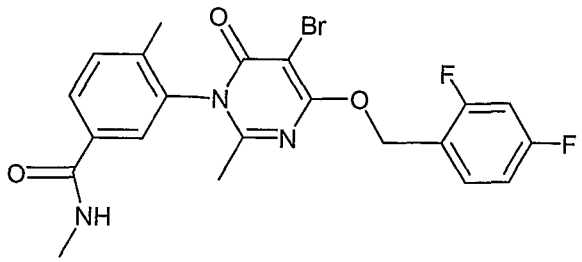
The racemic compound 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N,4-dimethylbenzamide (82.0 mg) was resolved using a Chiralpak AD column, 4.5 X 250 mm. The sample was dissolved in 30%EtOH in hexane and 30 □L of the solution was injected into the column and eluted with 30%EtOH in hexane at a flow rate of 1.5 mL/min. Fractions with negative optical rotation were pooled together and concentrated under reduced pressure to give 37.6 mg of (-) isomer as a white solid:

^{1}H NMR ($CDCl_3$/ 400 MHz) δ 7.81 (dd 1H, *J* = 1.6 Hz, 8.0 Hz), 7.54 (m, 1H), 7.48(d, 1H *J* = 1.6 Hz), 7.40 (d, 1H, *J* = 8.0 Hz), 6.86 (m, 2H), 6.31(br, 1H), 5.48 (abq, 2H), 2.78 (d, 3H, *J* = 4.8 Hz), 2.14 (s, 3H), and 2.09 (s, 3H); ES-HRMS m/z 478.0580(M+H calcd for $C_{21}H_{19}N_3O_3F_2$ Br requires 478.0572). ^{19}F NMR(CD_3OD/ 400 MHz) -109.96(m) and

-114.02 (m).

Preparation of (+) 3-[5-Bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N,4-dimethylbenzamide.

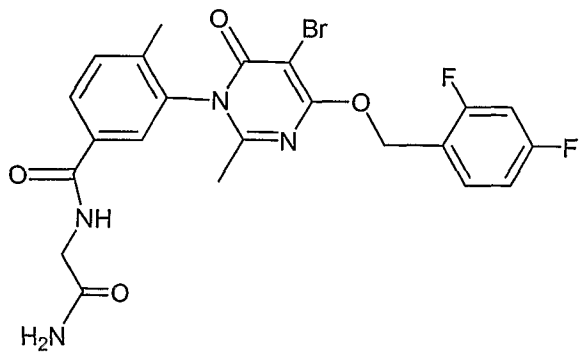
01640/01/PCT



The title compound was isolated from the racemic material (82.0 mg) according to the resolution procedure described for (-) 3-[5-Bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N,4-dimethylbenzamide. Fractions with positive optical rotation were pooled together and concentrated under reduced pressure to give 39.8 mg of (+) isomer as a white solid: ^{1}H NMR ($CDCl_3$/ 400 MHz) δ 7.81 (dd 1H, *J* = 1.6Hz, 8.0 Hz), 7.52 (m, 1H), 7.48 (d, 1H, *J* = 1.6 Hz), 7.41 (dd, 1H, *J* = 8.0 Hz), 6.85 (m, 2H), 6.28 (br, 1H), 5.50 (abq, 2H), 2.81(d, 3H, *J* = 4.4 Hz), and 2.14 (s, 3H), and 2.09 (s, 3H); ES-HRMS *m/z* 478.0577(M+H calcd for $C_{21}H_{19}N_3O_3F_2$ Br requires 478.0572). ^{19}F NMR(CD_3OD/ 400 MHz) -109.97(m) -114.03.

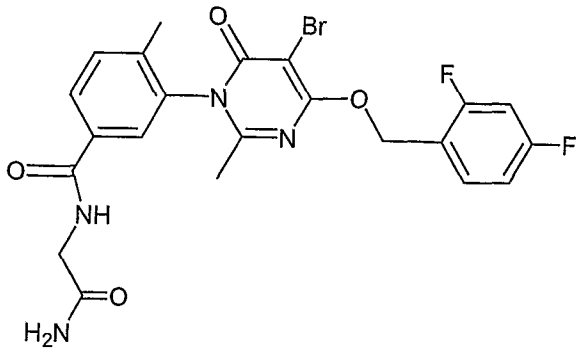
Preparation of (-) 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methyl-N-{1-[aminocarbonyl]methyl}benzamide.

01640/01/PCT



The racemic compound 3-(4-(2,4-difluorobenzyloxy)-5-bromo-2-methyl-6-oxopyrimidin-1(6H)-yl)-N-(carbamoylmethyl)-4-methylbenzamide (3.0 g) was resolved using a Chiralcel OJ-H column, 21 X 250 mm. The compound was dissolved in methanol (15 mg/mL), and injected 5 mL of the solution and eluted with methanol at a flow rate of 20.0 mL/min. Fractions with negative optical rotation were pooled together and concentrated under reduced pressure to give 1.42 g of the (-) isomer as a white solid: ^{1}H NMR (CD_3OD/ 400 MHz) δ 7.96 (dd 1H, J = 2.4 Hz, 10.4 Hz), 7.74 (d, 1H, J = 2.4 Hz), 7.64 (m, 1H), 7.56 (d, 1H, J = 11.2 Hz), 7.012(m, 2H), 5.58 (abq, 2H), 4.02 (s, 2H), 2.19 (s, 3H), 2.15 (s, 3H); ES-HRMS *m/z* 521.0615 (M+H calcd for $C_{22}H_{20}N_4O_4F_2$ Br requires 521.0630). ^{19}F NMR(CD_3OD/ 400 MHz) -111.85(m) and -115.90 (m).

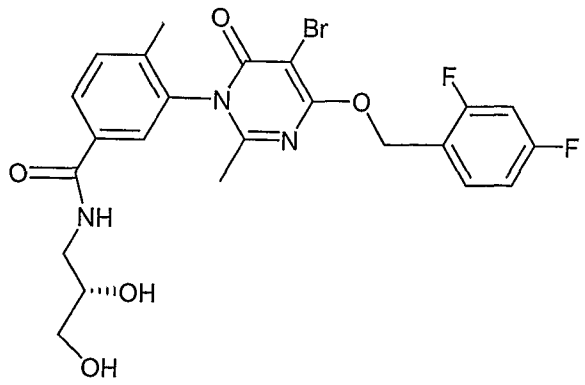
Preparation of (+) 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methyl-N-{1-[aminocarbonyl]methyl}benzamide.



The title compound was isolated from the racemic material (3.0 g) according to the resolution procedure described for (-) 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methyl-N-{1-[aminocarbonyl]methyl}benzamide. Fractions with positive optical rotation were pooled together and concentrated under reduced pressure to give 1.52 g of the (+) isomer as a white solid: ^{1}H NMR (CD_3OD/ 400 MHz) δ 7.96 (dd 1H, J = 2.4 Hz, 10.4 Hz), 7.74 (d, 1H, J = 2.4 Hz), 7.62 (m, 1H), 7.56 (d, 1H, J = 10.4 Hz), 7.02 (m, 2H), 5.58 (abq, 2H), 4.03 (s, 2H), 2.19 (s, 3H), 2.15 (s, 3H); ES-HRMS m/z 521.0670 (M+H calcd for $C_{22}H_{20}N_4O_4F_2$ Br requires 521.0630). ^{19}F NMR(CD_3OD/ 400 MHz) -111.84(m) and
-115.90 (m).

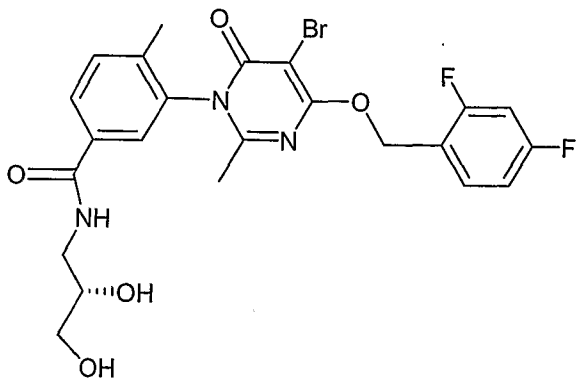
Preparation of (±) 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-[(2S)-2,3-dihydroxypropyl]-4-methylbenzamide.

01640/01/PCT



To a solution of 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoic acid (0.3 g, 0.65 mmol) in dimethylformamide (3.0 mL) at -10 °C was added isobutylchloroformate (0.13 g, 0.92 mmol) followed by the addition of *N*-methylmorpholine (0.130 g, 1.28 mmol). The mixture was stirred for 10 min. under argon atmosphere. The reaction mixture was then stirred at room temperature for 30 min, cooled to 0 °C, and added *S* -3-amino-1,2 propanediol (0.118 g, 1.3 mmol). The resulting mixture was stirred at room temperature for 1.5 h, concentrated *in vacuo*, and the residue was purified by reverse-phase HPLC using 10-90% CH_3CN/Water gradient (40 min) at a flow rate of 80 mL/min. The appropriate fractions (MH^+, *m/z* = 538) were combined, and freeze-dried to give a white solid. This was dissolved in dichloromethane (20 mL), washed successively with 5% sodium bicarbonate (2 x 15 mL), water (2 x 20 mL), dried (Na_2SO_4), and concentrated to dryness to afford the racemic title compound (0.15 g, 43%) as a white amorphous substance: ^1H NMR (CD_3OD/ 400 MHz) δ 7.89 (dd 1H, *J* = 1.6 Hz, 8.0 Hz), 7.66 (d, 1H, *J* = 1.6 Hz), 7.60 (m, 1H), 7.52 (d, 1H, *J* = 8.0 Hz), 7.01 (m, 2H), 5.54 (abq, 2H), 3.77 (m, 1H), 3.51 (m,3H), 3.38 (m, 1H), 2.74 (s, 3H), and 2.11(s, 3H); ES-HRMS *m/z* 538.0782 (M+H calcd for $C_{23}H_{23}N_3O_5F_2$ Br requires 538.0784). ^{19}F NMR(CD_3OD/ 400 MHz) -111.85(m) and-115.91 (m).

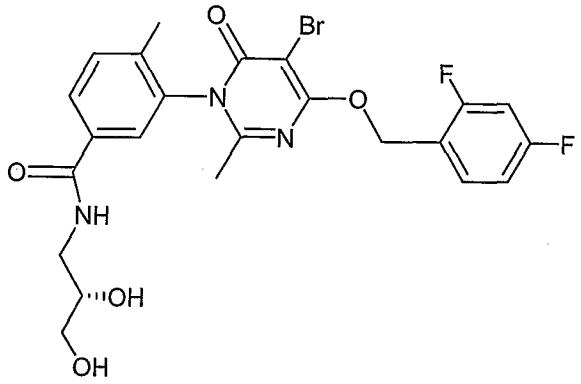
Preparation of (-) 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-[(2*S*)-2,3-dihydroxypropyl]-4-methylbenzamide.



The diastereomeric mixture (±) 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-[(2S)-2,3-dihydroxypropyl]-4-methylbenzamide (0.15 g) was resolved using a ChiralPak AD column, 21 X 250 mm. The compound was dissolved in ethanol and eluted with ethanol containing 20% hexane at a flow rate of 8.0 mL/min. Fractions with negative optical rotation were pooled together and concentrated under reduced pressure to give 70 mg of the (-) isomer as a white solid: ^{1}H NMR (CD_3OD/ 400 MHz) δ 7.90 (dd 1H, *J* = 2.0 Hz, 8.0 Hz), 7.68 (d, 1H, *J* = 2.0 Hz), 7.60 (m, 1H), 7.56 (d, 1H, *J* = 8.0 Hz), 7.012(m, 2H), 5.56 (abq, 2H), 3.80 (m, 1H), 3.52 (m, 3H), 3.38 (m, 1H), 2.16(s, 3H), and 2.12 (s, 3H); ES-HRMS *m/z* 538.0793 (M+H calcd for $C_{23}H_{23}N_3O_5F_2$ Br requires 538.0784). ^{19}F NMR(CD_3OD/ 400 MHz) -111.87(m) and -115.92 (m).

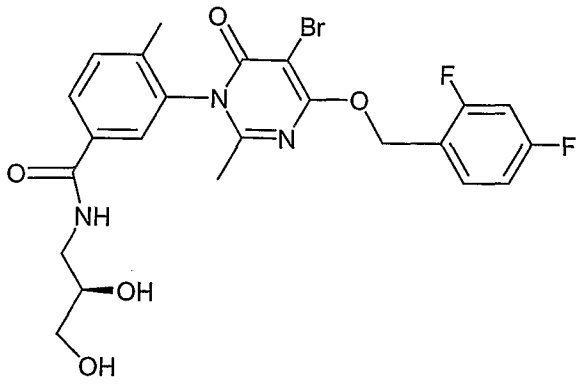
01640/01/PCT

Preparation of (+) 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-[(2*S*)-2,3-dihydroxypropyl]-4-methylbenzamide.



The title compound was isolated from the diastereomeric mixture (0.15 g) according to the resolution procedure described for (-) 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-[(2*S*)-2,3-dihydroxypropyl]-4-methylbenzamide. Fractions with positive optical rotation were pooled together and concentrated under reduced pressure to give 69.8 mg of the (+) isomer as a white solid: ^{1}H NMR (CD_3OD/ 400 MHz) δ 7.90 (dd 1H, *J* = 2.0 Hz, 8.0 Hz), 7.67 (d, 1H, *J* = 2.0 Hz), 7.60 (m, 1H), 7.56 (d, 1H, *J* = 8.0 Hz), 7.012(m, 2H), 5.55 (abq, 2H), 3.81 (m, 1H), 3.52 (m, 3H), 3.38 (m, 1H), 2.16(s, 3H), and 2.12 (s, 3H); ES-HRMS *m/z* 538.0751 (M+H calcd for $C_{23}H_{23}N_3O_5F_2$ Br requires 538.0784). ^{19}F NMR(CD_3OD/ 400 MHz) -111.87(m) and -115.92 (m).

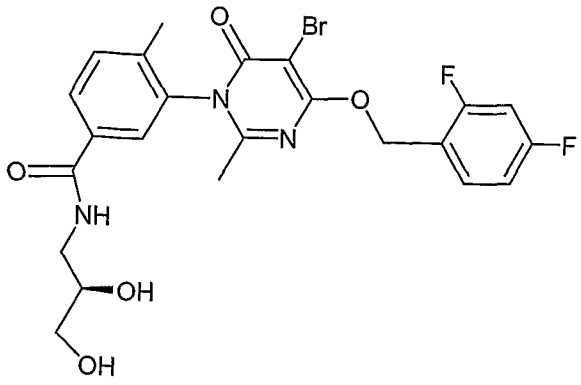
Preparation of (±) 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-[(2*R*)-2,3-dihydroxypropyl]-4-methylbenzamide.



The title compound was prepared by employing a similar procedure as described for (±) 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-[(2S)-2,3-dihydroxypropyl]-4-methylbenzamide, substituting *R* -3-amino-1,2 propanediol for *S* -3-amino-1,2 propanediol.

Yield 46% : ^{1}H NMR (CD_3OD/ 400 MHz) δ 7.91 (dd 1H, *J* = 1.6 Hz, 8.0 Hz), 7.67 (d, 1H, *J* = 1.6 Hz), 7.60 (m, 1H), 7.56 (d, 1H, *J* = 8.0 Hz), 6.97 (m, 2H), 5.54 (abq, 2H), 3.80 (m, 1H), 3.52 (m, 3H), 3.38 (m, 1H), 2.15 (s, 3H), and 2.11 (s, 3H); ES-HRMS *m/z* 538.0803 (M+H calcd for $C_{23}H_{23}N_3O_5F_2$ Br requires 538.0784). ^{19}F NMR(CD_3OD/ 400 MHz) -111.86(m) and -115.92 (m).

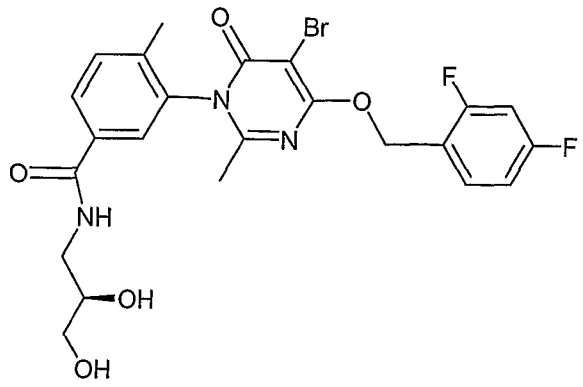
Preparation of (-) 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-[(2*R*)-2,3-dihydroxypropyl]-4-methylbenzamide.



The diastereomeric compound (±) 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-[(2*R*)-2,3-dihydroxypropyl]-4-methylbenzamide (0.24 g) was resolved using a ChiralPak AD column, 21 X 250 mm. The compound was dissolved in ethanol and eluted with ethanol containing 20% hexane at a flow rate of 8.0 mL/min. Fractions with negative optical rotation were pooled together and concentrated under reduced pressure to give 0.101g of the (-) isomer as a white solid: ^{1}H NMR (CD_3OD/ 400 MHz) δ 7.89 (dd 1H, *J* = 2.0 Hz, 8.0 Hz), 7.67 (d, 1H, *J* = 2.0 Hz), 7.60 (m, 1H), 7.53 (d, 1H, *J* = 8.4 Hz), 6.98 (m, 2H), 5.56 (abq, 2H), 3.80 (m, 1H), 3.52 (m, 3H), 3.38 (m, 1H), 2.16(s, 3H), and 2.12 (s, 3H); ES-HRMS *m/z* 538.0740 (M+H calcd for $C_{23}H_{23}N_3O_5F_2$ Br requires 538.0784). ^{19}F NMR(CD_3OD/ 400 MHz) -111.87(m) and -115.92 (m).

Preparation of (+) 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-[(2*R*)-2,3-dihydroxypropyl]-4-methylbenzamide.

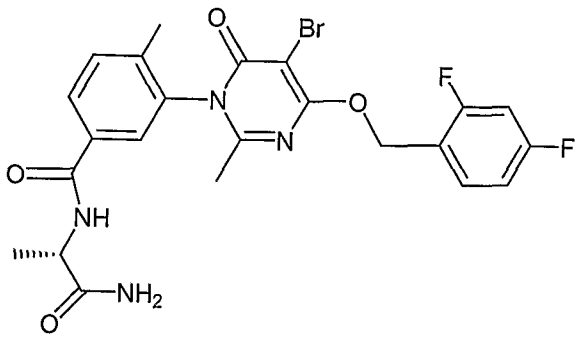
01640/01/PCT



The title compound was isolated from the diastereomeric mixture (0.24 g) according to the resolution procedure described for (-) 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-[(2*R*)-2,3-dihydroxypropyl]-4-methylbenzamide. Fractions with positive optical rotation were pooled together and concentrated under reduced pressure to give 0.105 g of the (+) isomer as a white solid: ^{1}H NMR (CD_3OD/ 400 MHz) δ 7.90 (dd 1H, *J* = 2.0 Hz, 8.0 Hz), 7.68 (d, 1H, *J* = 2.0 Hz), 7.60 (m, 1H), 7.54 (d, 1H, *J* = 8.0 Hz), 6.99 (m, 2H), 5.56 (abq, 2H), 3.81 (m, 1H), 3.53 (m, 3H), 3.38 (m, 1H), 2.16(s, 3H), and 2.12 (s, 3H); ES-HRMS *m/z* 538.0739 (M+H calcd for $C_{23}H_{23}N_3O_5F_2$ Br requires 538.0784). ^{19}F NMR(CD_3OD/ 400 MHz) -111.87(m) and -115.92 (m).

Preparation of (±) N-[(1S)-1-(aminocarbonyl)ethyl]-3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methylbenzamide.

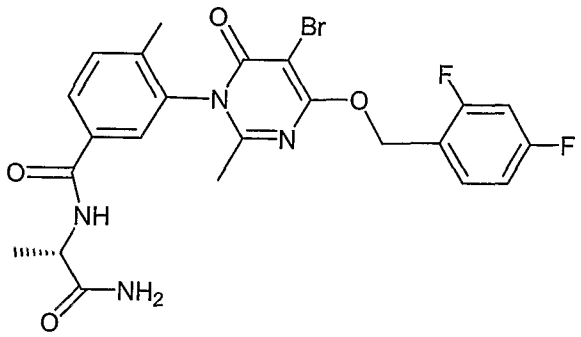
01640/01/PCT



The title compound was prepared by employing a similar procedure as described for (±) 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methyl-N-{1-[(methylamino)carbonyl]methyl}benzamide, substituting *S* -alanineamide hydrochloride for N-methylglycineamide hydrochloride. Yield 45% : ^{1}H NMR (CD_3OD/ 400 MHz) δ 7.96 (m,1H), 7.73 (dd, 1H, *J* = 2.0 Hz), 7.62 (m, 1H), 7.55 (d, 1H, *J* = 8.0 Hz), 7.01 (m, 2H), 5.56 (abq, 2H), 4.55 (ab q, 1H), 2.18 (s, 3H), 2.14 (s, 3H), and 1.45 (d, 3H, *J* = 7.2Hz); ES-HRMS *m/z* 535.0757 (M+H calcd for $C_{23}H_{22}N_4O_4F_2$ Br requires 535.0787). ^{19}F NMR(CD_3OD/ 400 MHz) -111.86(m) and -115.90 (m).

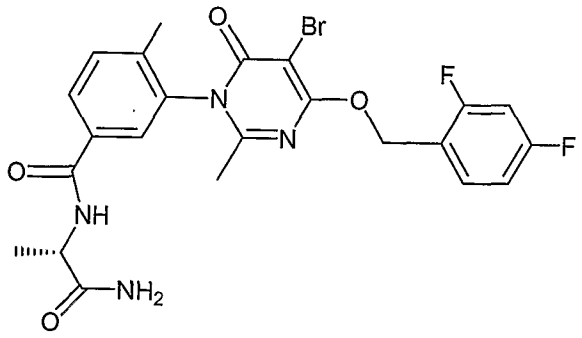
Preparation of (-) N-[(1S)-1-(aminocarbonyl)ethyl]-3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methylbenzamide.

01640/01/PCT



The diastereomeric mixture (±) N-[(1S)-1-(aminocarbonyl)ethyl]-3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methylbenzamide (2.0 g) was resolved using a Chiralcel AD-H column, 21 X 250 mm. The compound was dissolved in methanol (10 mg/mL), and injected 5 mL of the solution and eluted with methanol at a flow rate of 20.0 mL/min. Fractions with negative optical rotation were pooled together and concentrated under reduced pressure to give 1.01 g of the (-) isomer as an amorphous white solid: ^{1}H NMR (CD_3OD/ 400 MHz) δ 7.96 (dd 1H, *J* = 1.6 Hz, 8.0 Hz), 7.73 (d, 1H, *J* = 2.0 Hz), 7.64 (m, 1H), 7.55 (d, 1H, *J* = 8.0 Hz), 7.012(m, 2H), 5.56 (abq, 2H), 4.53 (abq, 1H), 2.19 (s, 3H), 2.13 (s, 3H), and 1.44 (d, 3H, *J* = 7.2 Hz); ES-HRMS *m/z* 535.0750 (M+H calcd for $C_{23}H_{22}N_4O_4F_2$ Br requires 535.0787). ^{19}F NMR(CD_3OD/ 400 MHz) -111.88(m) and -115.91 (m).

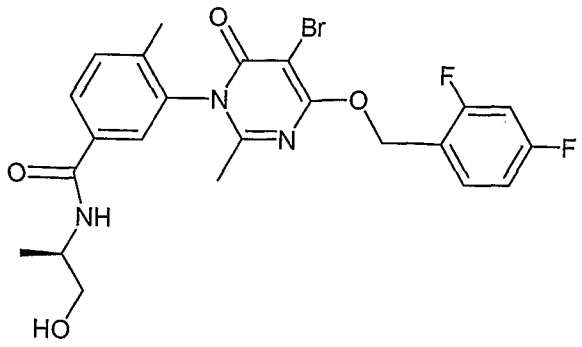
Preparation of (+) N-[(1S)-1-(aminocarbonyl)ethyl]-3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methylbenzamide



The title compound was isolated from the diastereomeric mixture (2.0 g) according to the resolution procedure described for (-) N-[(1S)-1-(aminocarbonyl)ethyl]-3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methylbenzamide. Fractions with positive optical rotation were pooled together and concentrated under reduced pressure to give 0.94 g of the (+) isomer as an amorphous white solid: ^{1}H NMR (CD_3OD/ 400 MHz) δ 7.95 (dd 1H, J = 2.0 Hz, 8.0 Hz), 7.75 (d, 1H, J = 2.0 Hz), 7.64 (m, 1H), 7.54 (d, 1H, J = 8.0 Hz), 7.01(m, 2H), 5.56 (abq, 2H), 4.53 (abq, 1H), 2.19 (s, 3H), 2.13 (s, 3H), and 1.44 (d, 3H, J = 7.2 Hz); ES-HRMS m/z 535.0742(M+H calcd for $C_{23}H_{22}N_4O_4F_2$ Br requires 535.0787). ^{19}F NMR(CD_3OD/ 400 MHz) -111.85(m) and -115.90 (m).

Preparation of (±) 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-[(1R)-2-hydroxy-1-methylethyl]-4-methylbenzamide.

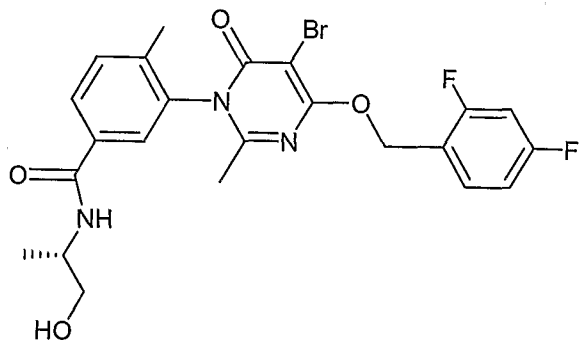
01640/01/PCT



To a solution of 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoic acid (4.0g, 0.0086 mol) in dimethylacetamide (10.0 mL) at -20 °C was added N-methylmorpholine (1.2 g, 0.012 mol), followed by the dropwise addition of a solution of isobutylchloroformate (1.58 g, 0.012 mmol) in dichloromethane (5. 0 mL). The reaction mixture was stirred for 10 min. under argon atmosphere after which it was stirred at room temperature for 20 min. The reaction mixture was then cooled to 0 °C, and added *R* -2-amino-1-propanol (0.97 g, 1.01 mol). The resulting mixture was stirred at room temperature for 1.5 h, concentrated *in vacuo*, and the residue was purified by reverse-phase HPLC using 10-90% CH_3CN/Water gradient (40 min) at a flow rate of 80 mL/min. The appropriate fractions (MH^+, *m/z* = 522) were combined, and freeze-dried to give a white solid. This was dissolved in dichloromethane (20 mL), washed successively with 5% sodium bicarbonate (2 x 15 mL), water (2 x 20 mL), dried (Na_2SO_4), and concentrated to dryness to afford the racemic title compound (2.2 g, 49%) as a white amorphous substance: ^1H NMR (CD_3OD/ 400 MHz) δ 7.91(dd, 1H, *J* = 1.6 Hz, & 6.4 Hz), 7.68 (d, 1H, *J* = 1.6 Hz), 7.60 (m, 1H), 7.53 (d, 1H, *J* = 8.4 Hz), 7.01 (m, 2H), 5.57 (abq, 2H), 4.18 (m, 1H), 3.56 (m, 2H), 2.17 (s, 3H), 2.13 (s, 3H), and 1.22(d, 3H, *J* = 6.8 Hz); ES-HRMS *m/z*

522.0860 (M+H calcd for $C_{23}H_{23}N_3O_4F_2$ Br requires 522.0835). ^{19}F NMR(CD_3OD/ 400 MHz) -111.85(m) and-115.90 (m).

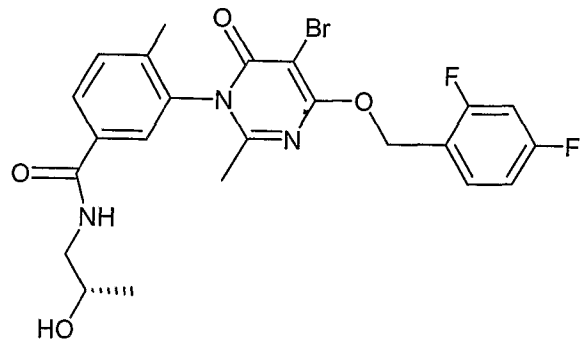
Preparation of (±) 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-[(1S)-2-hydroxy-1-methylethyl]-4-methylbenzamide.



The title compound was prepared in a similar manner as described for (±) 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-[(1R)-2-hydroxy-1-methylethyl]-4-methylbenzamide substituting *R* -2-amino-1-propanol with *S*-2-amino-1-propanol. Yield 42%. ^1H NMR (CD_3OD/ 400 MHz). δ 7.93(d, 1H, J = 1.6 Hz, & 6.4 Hz), 7.68 (s, 1H), 7.60 (m, 1H), 7.53 (d, 1H, J = 8.0 Hz), 7.01 (m, 2H), 5.57 (abq, 2H), 4.18 (m, 1H), 3.56 (m,2H), 2.17 (s, 3H), 2.13 (s, 3H), and 1.22(d, 3H, J = 6.8 Hz); ES-HRMS *m/z* 522.0821 (M+H calcd for $C_{23}H_{23}N_3O_4F_2$ Br requires 522.0835). ^{19}F NMR(CD_3OD/ 400 MHz) -111.85(m) and-115.90 (m).

01640/01/PCT

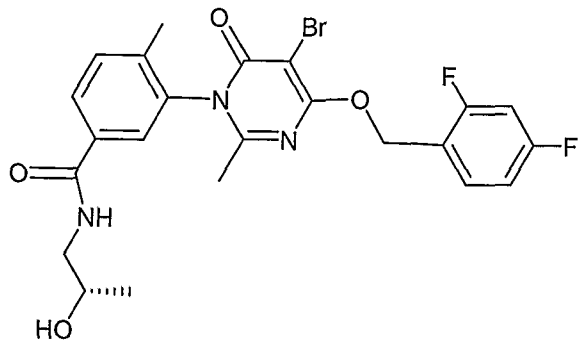
Preparation of (±)3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-[(2S)-2-hydroxypropyl]-4-methylbenzamide.



The title compound was prepared in a similar manner as described for (±) 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-[(1R)-2-hydroxy-1-methylethyl]-4-methylbenzamide substituting *R* -2-amino-1-propanol with *S*-1-amino-2-propanol. Yield 47%. ^{1}H NMR (CD_3OD/ 400 MHz) δ 7.90(d, 1H, J = 1.6 Hz), 7.69 (d, 1H, J = 2.0 Hz), 7.60 (m, 1H), 7.54 (d, 1H, J = 8.0 Hz), 7.01 (m, 2H), 5.57 (abq, 2H), 4.18 (m, 1H), 3.39 (m,1H), 3.31 (m, 1H), 2.17 (s, 3H), 2.13 (s, 3H), and 1.17(d, 3H, J = 6.4 Hz); ES-HRMS *m/z* 522.0863 (M+H calcd for $C_{23}H_{23}N_3O_4F_2$ Br requires 522.0835). ^{19}F NMR(CD_3OD/ 400 MHz) -111.85(m), and-115.9.

Preparation of (-)3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-[(2S)-2-hydroxypropyl]-4-methylbenzamide.

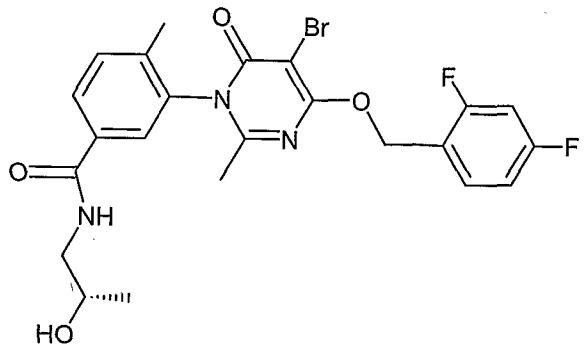
01640/01/PCT



The diastereomeric mixture (2.0 g) was resolved using a Chiralpak AD-H column, 21 X 250 mm. The compound was dissolved in ethanol(15 mg/mL), and injected 4 mL of the solution and eluted with methanol at a flow rate of 10.0 mL/min. Fractions with negative optical rotation were pooled together and concentrated under reduced pressure to give 0.95 g of the (-) isomer as a white amorphous white solid: ^{1}H NMR (CD_3OD/ 400 MHz) δ 7.93(d, 1H, J = 2.0Hz, & 6.8 Hz), 7.70 (s, 1H), 7.60 (m, 1H), 7.55 (d, 1H, J = 11.2 Hz, Hz), 7.01 (m, 2H), 5.57 (abq, 2H), 3.90 (abq, 1H), 3.38 (m,1H), 3.31 (m, 1H), 2.18 (s, 3H), 2.14 (s, 3H), and 1.18(d, 3H, J = 8.4 Hz); ES-HRMS m/z 522.0821 (M+H calcd for $C_{23}H_{23}N_3O_4F_2$ Br requires 522.0835). ^{19}F NMR(CD_3OD/ 400 MHz) -111.85(m) and-115.9.

Preparation of (+)3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-[(2S)-2-hydroxypropyl]-4-methylbenzamide.

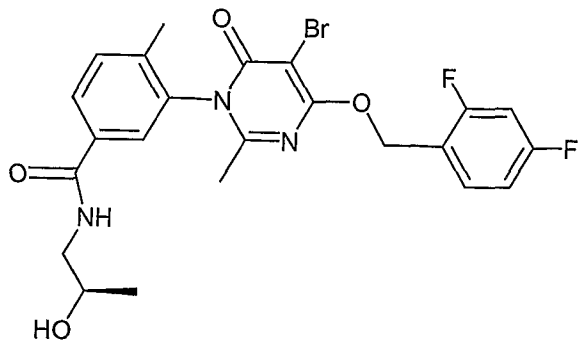
01640/01/PCT



The title compound was isolated from the diastereomeric mixture (2.0 g) according to the resolution procedure described for (-)3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-[(2S)-2-hydroxypropyl]-4-methylbenzamide. Fractions with positive optical rotation were pooled together and concentrated under reduced pressure to give 0.9g of the (+) isomer as a white amorphous white solid: ^{1}H NMR (CD_3OD/ 400 MHz) δ 7.91(d, 1H, J = 1.6 Hz, & 8.0 Hz), 7.70 (s, 1H), 7.60 (m, 1H), 7.54 (d, 1H, J = 8.0 Hz, Hz), 7.01 (m, 2H), 5.57 (abq, 2H), 3.93 (m, 1H), 3.40 (m,1H), 3.28 (m, 1H), 2.17 (s, 3H), 2.14 (s, 3H), and 1.17(d, 3H, J = 6.8 Hz); ES-HRMS m/z 522.0820 (M+H calcd for $C_{23}H_{23}N_3O_4F_2$ Br requires 522.0835). ^{19}F NMR(CD_3OD/ 400 MHz) -111.85(m) and-115.9.

Preparation of (±)3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-[(2R)-2-hydroxypropyl]-4-methylbenzamide.

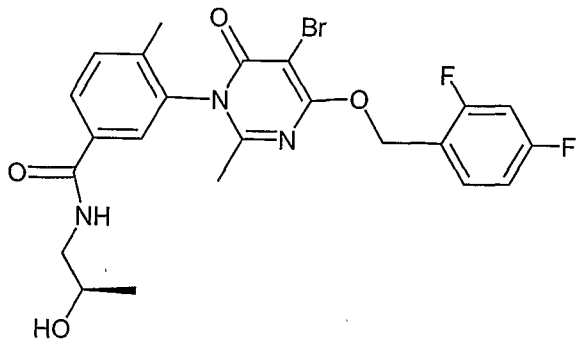
01640/01/PCT



The title compound was prepared in a similar manner as described for (±) 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-[(1R)-2-hydroxy-1-methylethyl]-4-methylbenzamide substituting *R* -2-amino-1-propanol with *R*-1-amino-2-propanol. Yield 48%. ^{1}H NMR (CD_3OD/ 400 MHz) δ 7.91(d, 1H, *J* = 1.6 Hz, & 8.0 Hz), 7.69 (d, 1H, *J* = 1.6 Hz), 7.60 (m, 1H), 7.54 (d, 1H, *J* = 8.0 Hz), 7.01 (m, 2H), 5.57 (abq, 2H), 3.90 (abq, 1H), 3.32 (m,1H), 3.31 (m, 1H), 2.17 (s, 3H), 2.13 (s, 3H), and 1.17(d, 3H, *J* = 6.8 Hz); ES-HRMS *m/z* 522.0869 (M+H calcd for $C_{23}H_{23}N_3O_4F_2$ Br requires 522.0835).^{19}F NMR(CD_3OD/ 400 MHz) -111.85(m), and-115.90.

Preparation of (-)3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-[(2R)-2-hydroxypropyl]-4-methylbenzamide.

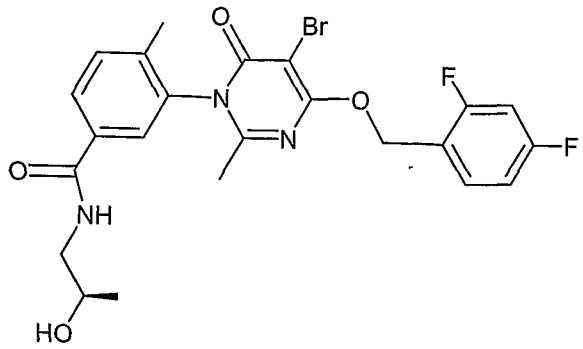
01640/01/PCT



The diastereomeric compound (2.01g) was resolved using a Chiralpak AD-H column, 21 X 250 mm. The compound was dissolved in ethanol (40 mg/mL), and injected 1.8 mL of the solution and eluted with ethanol at a flow rate of 10.0 mL/min. Fractions with negative optical rotation were pooled together and concentrated under reduced pressure to give 1.01 g of the (-) isomer as a white amorphous solid: ^{1}H NMR (CD_3OD/ 400 Mz) 7.91 (d, 1H, J = 1.6 Hz, 8.0 Hz), 7.69 (d, 1H, J = 1.6 Hz), 7.60 (m, 1H), 7.01 (m, 2H), 5.57 (abq, 2H), 3.90 (abq, 1H), 3.40 (m,1H), 3.31 (m, 1H), 2.17 (s, 3H), 2.13 (s, 3H), and 1.18(d, 3H, J = 6.4 Hz); ES-HRMS m/z 522.0831 (M+H calcd for $C_{23}H_{23}N_3O_4F_2$ Br requires 522.0835). ^{19}F NMR(CD_3OD/ 400 MHz) -111.86(m), and-115.9.

Preparation of (+)3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-[(2R)-2-hydroxypropyl]-4-methylbenzamide.

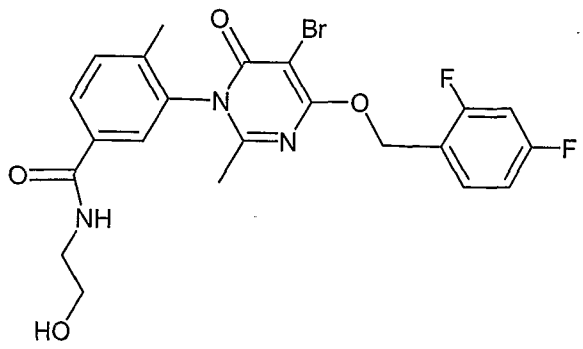
01640/01/PCT



The title compound was isolated from the diastereomeric material (2.1 g) according to the resolution procedure described for 3-[3-bromo-6-methyl-2-oxo-4-[(2,4,6-trifluorobenzyl)oxy]pyridin-1(2H)-yl]-N-[(1S)-2-hydroxy-1-methylethyl]-4-methylbenzamide. Fractions with positive optical rotation were pooled together and concentrated under reduced pressure to give 1.0 g of the (+) isomer as a white amorphous white solid: ^{1}H NMR (CD_3OD/ 400 MHz) δ 7.91(d, 1H, *J* = 1.6 Hz, & 8.0 Hz), 7.70 (s, 1H), 7.60 (m, 1H), 7.54 (d, 1H, *J* = 8.0 Hz), 7.01 (m, 2H), 5.57 (abq, 2H), 3.93 (m, 1H), 3.40 (m,1H), 3.28 (m, 1H), 2.17 (s, 3H), 2.14 (s, 3H), and 1.18(d, 3H, *J* = 6.4 Hz); ES-HRMS *m/z* 522.0830 (M+H calcd for $C_{23}H_{23}N_3O_4F_2Br$ requires 522.0835). ^{19}F NMR(CD_3OD/ 400 MHz) -111.85(m) and-115.9.

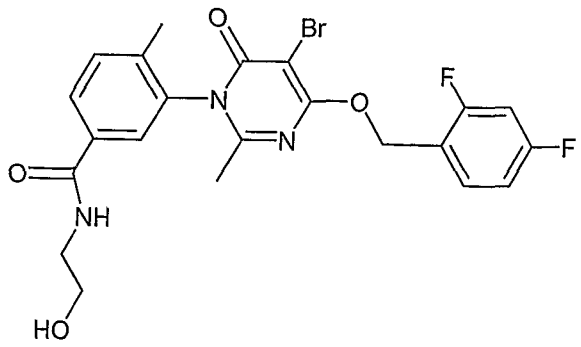
Preparation of (±) 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-(2-hydroxyethyl)-4-methylbenzamide.

01640/01/PCT



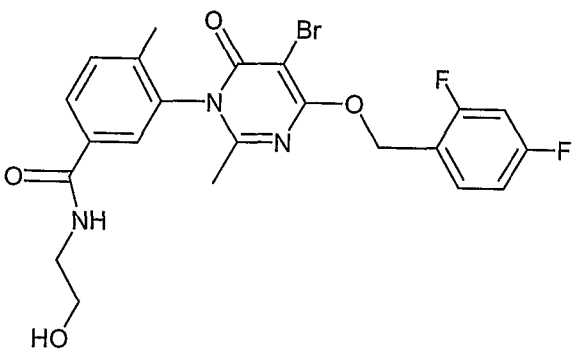
The title compound was prepared in a similar manner as described for (±) 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-[(1R)-2-hydroxy-1-methylethyl]-4-methylbenzamide substituting *R* -2-amino-1-propanol with 2-aminoethanol. Yield 70%. ^{1}H NMR (CD_3OD/ 400 MHz) δ 7.91 (d, 1H,*J* = 1.6 Hz, & 6.4 Hz), 7.68 (d, 1H, *J* = 2.0 Hx), 7.60 (m, 1H), 7.54 (d, 1H, *J* = 8.0 Hz), 7.01 (m, 2H), 5.57 (abq, 2H), 3.67 (t, 2H, *J* = 6.0 Hz), 3.49(t, 2H, *J* = 6.0 Hz), 2.17 (s, 3H), and 2.13 (s, 3H); ES-HRMS *m/z* 508.0659 (M+H calcd for $C_{22}H_{21}N_3O_4F_2$ Br requires 508.0678). ^{19}F NMR(CD_3OD/ 400 MHz) -111.85(m) and-115.90 (m).

Preparation of (-) 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-(2-hydroxyethyl)-4-methylbenzamide.



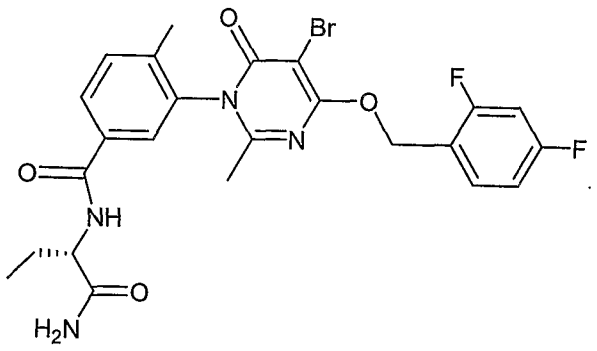
The racemic compound (3.0g) was resolved using a Chiralpak AD-H column, 21 X 250 mm. The compound was dissolved in ethanol (15 mg/mL), and injected 4.0 mL of the solution and eluted with ethanol at a flow rate of 10.0 mL/min. Fractions with negative optical rotation were pooled together and concentrated under reduced pressure to give 1.18 g of the (-) isomer as a white amorphous solid: ^{1}H NMR (CD_3OD/ 400 MHz) δ 7.91 (d, 1H, *J* = 1.6 Hz, & 6.4 Hz), 7.68 (d, 1H, *J* = 2.0 Hz), 7.60 (m, 1H), 7.54 (d, 1H, *J* = 8.0 Hz), 7.01 (m, 2H), 5.57 (abq, 2H), 3.69 (t, 2H, *J* = 5.6 Hz), 3.49(t, 2H, *J* = 5.6 Hz), 2.17 (s, 3H), and 2.13 (s, 3H); ES-HRMS *m/z* 508.0636 (M+H calcd for $C_{22}H_{21}N_3O_4F_2$ Br requires 508.0678). ^{19}F NMR(CD_3OD/ 400 MHz) -111.86(m), and-115.90

Preparation of (+) 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-(2-hydroxyethyl)-4-methylbenzamide.



The title compound was isolated from the racemic material (3.0 g) according to the resolution procedure described for (-) 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-(2-hydroxyethyl)-4-methylbenzamide. Fractions with positive optical rotation were pooled together and concentrated under reduced pressure to give 1.35 g of the (+) isomer as a white amorphous white solid: ^{1}H NMR (CD_3OD/ 400 MHz) δ 7.91 (d, 1H, *J* = 2.0 Hz, & 8.0 Hz), 7.68 (d, 1H, *J* = 2.0 Hz), 7.60 (m, 1H), 7.54 (d, 1H, *J* = 8.0 Hz), 7.01 (m, 2H), 5.57 (abq, 2H), 3.69 (t, 2H, *J* = 5.6 Hz), 3.49(t, 2H, *J* = 5.6 Hz), 2.17 (s, 3H), and 2.13 (s, 3H); ES-HRMS *m/z* 508.0664 (M+H calcd for $C_{22}H_{21}N_3O_4F_2$ Br requires 508.0678). ^{19}F NMR(CD_3OD/ 400 MHz) -111.86(m), and-115.90.

Preparation of (±) N-[(1S)-1-(aminocarbonyl)propyl]-3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methylbenzamide.

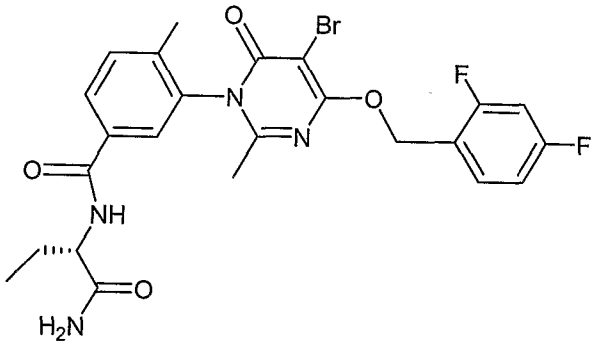


The title compound was prepared in a similar manner as described for (±) 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-

methyl-6-oxopyrimidin-1(6H)-yl]-N-[(1R)-2-hydroxy-1-methylethyl]-4-methylbenzamide substituting *R* -2-amino-1-propanol with *S*-alpha- aminobutyricacid amide. Yield 49%.

^{1}H NMR (CD_3OD/ 400 MHz) δ 8.38 (br, 1H), 7.95 (m, 1H), 7.73 (d, 1H, *J* = 2.0 Hz), 7.60 (m, 1H), 7.55 (d, 1H, *J* = 8.0 Hz), 7.02 (m, 2H), 5.57 (abq, 2H), 4.44 (m 1H), 2.18 (s, 3H), and 2.13 (s, 3H), 1.90 (m, 1H), 1.78 (m, 1H), and 1.01 (t, 3H, *J* =7.2 Hz); ES-HRMS *m/z* 549.0904 (M+H calcd for $C_{24}H_{24}N_4O_4F_2$ Br requires 549.0943). ^{19}F NMR(CD_3OD/ 400 MHz) -111.86(m) and-115.89 (m).

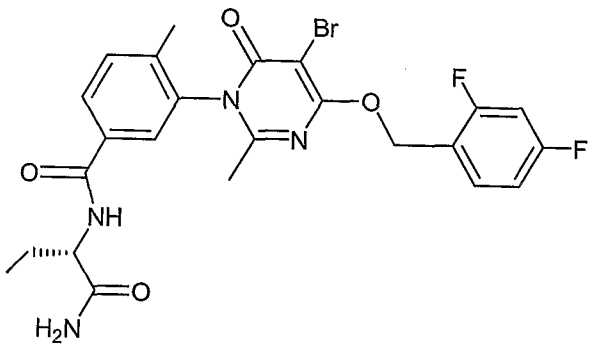
Preparation of (-) N-[(iS)-1-(aminocarbonyl)propyl]-3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methylbenzamide.



The diastereomeric mixture (0.9g) was resolved using a Chiralpak AD-H column, 21 X 250 mm. The compound was dissolved in methanol (15 mg/mL), and injected 2.7 mL of the solution and eluted with ethanol at a flow rate of 20.0

mL/min. Fractions with negative optical rotation were pooled together and concentrated under reduced pressure to give 0.4 g of the (-) isomer as a white amorphous solid: ^{1}H NMR (CD_3OD/ 400 MHz) δ 7.95 (dd, 1H, J = 2.0 Hz, and 8.0 Hz), 7.73 (d, 1H, J = 1.6 Hz), 7.60 (m, 1H), 7.55 (d, 1H, J = 8.0 Hz), 7.01 (m, 2H), 5.57 (abq, 2H), 4.43 (m 1H), 2.18 (s, 3H), and 2.13 (s, 3H), 1.85 (m, 1H), 1.79 (m, 1H), and 1.01 (t, 3H, J = 7.6 Hz); ES-HRMS m/z 549.0928 (M+H calcd for $C_{24}H_{24}N_4O_4F_2$ Br requires 549.0943). ^{19}F NMR(CD_3OD/ 400 MHz) -111.86(m) and -115.89 (m).

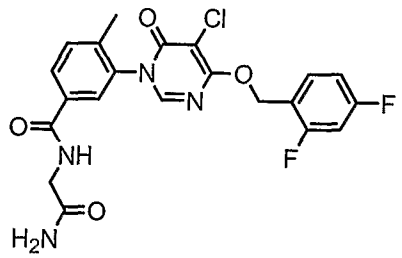
Preparation of (+) N-[(1S)-1-(aminocarbonyl)propyl]-3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methylbenzamide.



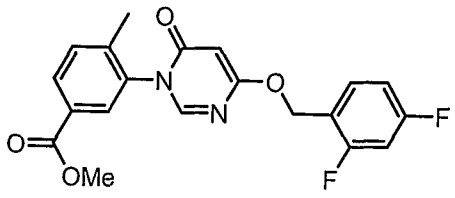
The title compound was isolated from the diastereomeric material (0.9 g) according to the resolution procedure described for (-) N-[(1S)-1-(aminocarbonyl)propyl]-3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methylbenzamide. Fractions with positive optical rotation

were pooled together and concentrated under reduced pressure to give 0.52 g of the (+) isomer as an amorphous white solid: ^{1}H NMR (CD_3OD/ 400 MHz) δ 7.93 (dd, 1H, J = 2.0 Hz, and 8.0 Hz), 7.75 (d, 1H, J = 2.0 Hz), 7.60 (m, 1H), 7.55 (d, 1H, J = 8.0 Hz), 7.01 (m, 2H), 5.56 (abq, 2H), 4.44 (m 1H), 2.18 (s, 3H), 2.14 (s, 3H), 1.85 (m, 1H), 1.79 (m, 1H), and 1.01 (t, 3H, J = 7.2 Hz); ES-HRMS m/z 549.0928(M+H calcd for $C_{24}H_{24}N_4O_4F_2$ Br requires 549.0943). ^{19}F NMR(CD_3OD/ 400 MHz) -111.86(m), and-115.89 (m).

Preparation of 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N-[1-(aminocarbonyl)methyl]-4-methylbenzamide.



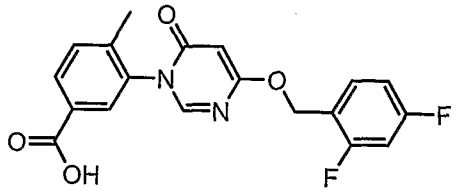
Step 1: Preparation of methyl 3-[4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoate



Methyl 3-[4-[(2,4-difluorobenzyl)oxy]-2-(methylthio)-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoate (87 g, 0.20 mol) was dissolved in N,N-dimethylacetamide (870 mL) and heated to

80°C. Raney Ni was added and slight exotherm and off-gasing were observed. Reaction was complete. Heat and stirring were turned off. Since product had begun to precipitate from the cooled reaction mixture, heat was turned back on to 70°C and stirring resumed. After redissolving the precipitate, the reaction mixture was allowed to cool for 15 min and then filtered through celite. Rinsed with 50°C DMA and water, being careful not to let the celite pad go dry. The filtrate was added to 2L of water and stirred. Product filtered, rinsed with water, and dried in the vacuum oven. When found to still be wet with DMA, slurried with water and stirred 1h before filtering and redrying. Obtained the product as a white solid (63 g, 81%). ^{1}H NMR (CD_3OD/ 400MHz) δ8.28 (s, 1H), 8.04 (m, 1H), 7.90 (s, 1H), 7.55 (m, 2H), 6.99 (m, 2H), 5.87 (s, 1H), 5.39 (s, 2H), 3.88 (s, 3H), 2.19 (s, 3H). ESHRMS *m/z* 387.1195 (M+H calculated for $C_{20}H_{17}F_2N_2O_4$ requires 387.1151).

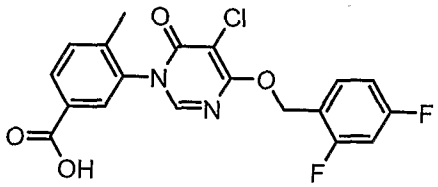
Step 2: Preparation of 3-[4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoic acid



To a solution of methyl 3-[4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoate (from Step 1) (7.56 g, 19.6 mmol) in dioxane (30 mL) was added 2N NaOH (14.7 mL). Stirred at ambient temperature for 1h. Concentrated to ~20 mL under reduced pressure. Cooled to 0°C and added 5% citric acid to precipitate solid, filtered the precipitate, rinsed with water, and dried in vacuo overnight. Obtained product as an

orange solid (6.62 g, 91%). Used without further purification. ^{1}H NMR (CD_3OD/ 400MHz) δ8.28 (s, 1H), 8.04 (m, 1H), 7.88 (s, 1H), 7.56 (q, 1H, J = 8.4 Hz), 7.50 (d, 1H, J = 8.0 Hz), 6.99 (m, 2H), 5.87 (s, 1H), 5.39 (s, 2H), 2.19 (s, 3H). ESHRMS m/z 373.1001 (M+H calculated for $C_{19}H_{15}F_2N_2O_4$ requires 373.0994).

Step 3: Preparation of 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoic acid



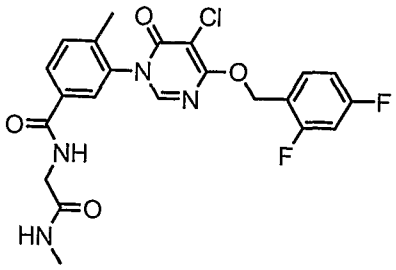
3-[4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoic acid (from Step 2) (6.62 g, 17.8 mmol), N-chlorosuccinimide (2.85 g, 21.3 mmol), and dichloroacetic acid (4 mL) are combined in dichloroethane (50 mL) and heated at 65°C for 65h. The reaction mixture is cooled to 0°C and the precipitate is filtered, washed with cold dichloroethane, and dried in vacuo. Product obtained as a white solid (3.47 g, 48%). Used without further purification. ^{1}H NMR (CD_3OD/ 300MHz) δ8.32 (s, 1H), 8.09 (m, 1H), 7.94 (s, 1H), 7.62 (q, 1H, J = 8.4 Hz), 7.54 (d, 1H, J = 7.8 Hz), 7.03 (m, 2H), 5.61 (s, 2H), 2.21 (s, 3H).

Step 4: Preparation of the title compound (3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N-[1-(aminocarbonyl)methyl]-4-methylbenzamide)

To a cooled (0°C) solution of 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoic acid (from Step 3) (0.25 g, 0.61 mmol) in DMA (2 mL) was added isobutyl chloroformate (0.96 mL stock solution prepared 0.1 mL in 0.9 mL DCM, 0.74 mmol) and 4-methylmorpholine (0.88 mL stock solution prepared 0.1 mL in 0.9 mL DMA, 0.80 mmol). Stirred at 0°C for 5 min, ambient temperature for 30 min. Added NMM (0.1 mL, 0.92 mmol), glycineamide HCl (0.10 g, 0.92 mmol), and DMAP (0.01 g, 0.06 mmol) and stirred at ambient temperature for 1.5h. Removed DMA under reduced pressure. Purified crude product by preparatory HPLC using a 10-90% CH_3CN/H_2O (30 min) gradient containing 0.5% TFA at a flow rate of 80 mL/min. Appropriate fractions (M+H *m/z* = 463) were combined and concentrated to approximately 20 mL under reduced pressure. Added 5% $NaHCO_3$ (20 mL) and extracted with DCM (3 x 15 mL). The organic extracts were dried over Na_2SO_4, filtered, concentrated under reduced pressure, and dried *in vacuo* to give the desired product as an off-white solid (77 mg, 27%). ^1H NMR (CD_3OD/ 400MHz) δ8.32 (s, 1H), 7.96 (m, 1H), 7.80 (s, 1H), 7.61 (m, 1H), 7.54 (m, 1H), 7.01 (m, 2H), 5.60 (m, 2H), 4.01 (s, 2H), 2.20 (s, 3H). ESHRMS *m/z* 463.0990 (M+H calculated for $C_{21}H_{18}ClF_2N_4O_4$ requires 463.0979).

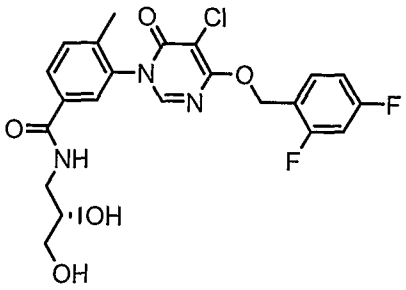
Preparation of 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-4-methyl-N-{1-[(methylamino)carbonyl]methyl}benzamide.

01640/01/PCT



The title compound was prepared using a procedure similar to that used in Step 4 of the synthesis of 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N-[1-(aminocarbonyl)methyl]-4-methylbenzamide by substituting glycine methyl amide HCl for glycineamide HCl. ^{1}H NMR (CD_3OD/400MHz) δ8.32 (s, 1H), 7.96 (m, 1H), 7.81 (s, 1H), 7.61 (q, 1H, *J* = 8.4 Hz), 7.55 (d, 1H, *J* = 8.0 Hz), 7.02 (m, 2H), 5.60 (m, 2H), 3.99 (s, 2H), 2.74 (s, 3H), 2.21 (s, 3H). ESHRMS *m/z* 477.1141 (M+H calculated for $C_{22}H_{20}ClF_2N_4O_4$ requires 477.1136).

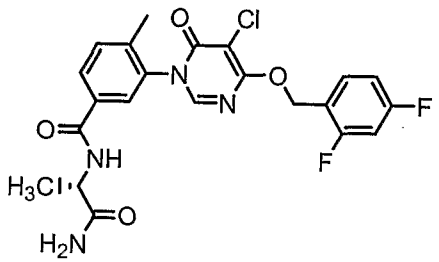
Preparation of 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N-[(2S)-2,3-dihydroxypropyl]-4-methylbenzamide.



The title compound was prepared using a procedure similar to that used in Step 4 of the synthesis of 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N-[1-

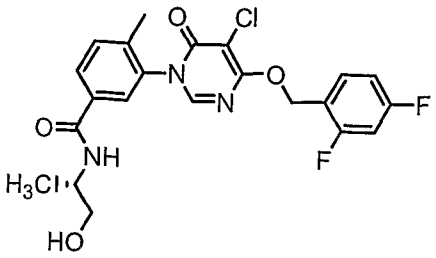
(aminocarbonyl)methyl]-4-methylbenzamide by substituting (*S*)-(-)-3-amino-1,2-propanediol for glycineamide HCl. ^{1}H NMR (CD_3OD/ 400MHz) δ8.32 (s, 1H), 7.92 (m, 1H), 7.77 (s, 1H), 7.61 (q, 1H, *J* = 8.4 Hz), 7.53 (d, 1H, *J* = 8.0 Hz), 7.02 (m, 2H), 5.60 (m, 2H), 3.81 (m, 1H), 3.55 (m, 3H), 3.39 (m, 1H), 2.20 (s, 3H). ESHRMS *m/z* 480.1131 (M+H calculated for $C_{22}H_{21}ClF_2N_3O_5$ requires 480.1132).

Preparation of N-[(1S)-1-(aminocarbonyl)ethyl]-3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-4-methylbenzamide.



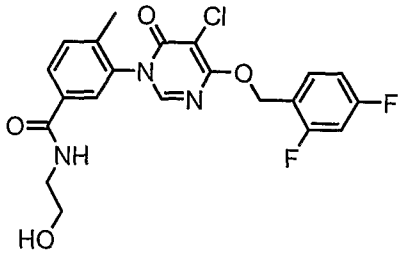
The title compound was prepared using a procedure similar to that used in Step 4 of the synthesis of 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N-[1-(aminocarbonyl)methyl]-4-methylbenzamide by substituting L-alaninamide HCl for glycineamide HCl. ^{1}H NMR (CD_3OD/ 400MHz) δ8.32 (s, 1H), 7.96 (m, 1H), 7.82 (m, 1H), 7.61 (q, 1H, *J* = 6.4 Hz), 7.53 (d, 1H, *J* = 8.0 Hz), 7.02 (m, 2H), 5.60 (m, 2H), 4.55 (q, 1H, *J* = 6.0 Hz), 2.20 (s, 3H), 1.45 (d, 3H, *J* = 6.0 Hz). ESHRMS *m/z* 477.1141 (M+H calculated for $C_{22}H_{20}ClF_2N_4O_4$ requires 477.1136).

Preparation of 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N-[(1S)-2-hydroxy-1-methylethyl]-4-methylbenzamide.



The title compound was prepared using a procedure similar to that used in Step 4 of the synthesis of 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N-[1-(aminocarbonyl)methyl]-4-methylbenzamide by substituting (*S*)-(+)-2-amino-1-propanol for glycineamide HCl. ^{1}H NMR (CD_3OD/ 400MHz) δ8.32 (s, 1H), 7.92 (m, 1H), 7.77 (s, 1H), 7.61 (q, 1H, *J* = 8.4 Hz), 7.52 (d, 1H, *J* = 8.0 Hz), 7.02 (m, 2H), 5.60 (m, 2H), 4.16 (m, 1H), 3.58 (m, 2H), 2.20 (s, 3H), 1.22 (d, 3H, *J* = 6.0 Hz). ESHRMS *m/z* 464.1198 (M+H calculated for $C_{22}H_{21}ClF_2N_3O_4$ requires 464.1183).

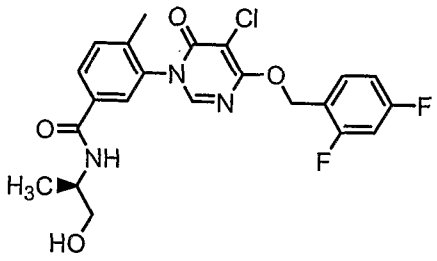
Preparation of 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N-(2-hydroxyethyl)-4-methylbenzamide.



The title compound was prepared using a procedure similar to that used in Step 4 of the synthesis of 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N-[1-(aminocarbonyl)methyl]-4-methylbenzamide by substituting ethanolamine for glycineamide HCl. ^{1}H NMR (CD_3OD/ 400MHz)

δ8.32 (s, 1H), 7.92 (m, 1H), 7.77 (s, 1H), 7.61 (q, 1H, *J* = 8.0 Hz), 7.53 (d, 1H, *J* = 8.0 Hz), 7.02 (m, 2H), 5.60 (m, 2H), 3.69 (t, 2H, *J* = 5.6 Hz), 3.49 (t, 2H, *J* = 5.6 Hz), 2.20 (s, 3H). ESHRMS *m/z* 450.1029 (M+H calculated for $C_{21}H_{19}ClF_2N_3O_4$ requires 450.1027).

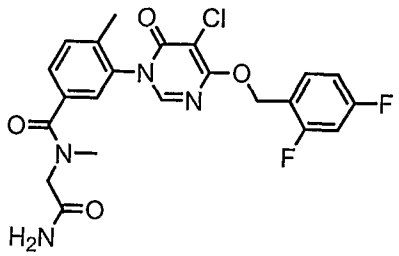
Preparation of 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N-[(1R)-2-hydroxy-1-methylethyl]-4-methylbenzamide.



The title compound was prepared using a procedure similar to that used in Step 4 of the synthesis of 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N-[1-(aminocarbonyl)methyl]-4-methylbenzamide by substituting (*R*)-(-)-2-amino-1-propanol for glycineamide HCl. ^{1}H NMR (CD_3OD/400MHz) δ8.32 (s, 1H), 7.92 (m, 1H), 7.77 (s, 1H), 7.61 (q, 1H, *J* = 8.0 Hz), 7.52 (d, 1H, *J* = 8.0 Hz), 7.02 (m, 2H), 5.60 (m, 2H), 4.16 (q, 1H, *J* = 6.4 Hz), 3.56 (m, 2H), 2.20 (s, 3H), 1.22 (d, 3H, *J* = 6.0 Hz). ESHRMS *m/z* 464.1186 (M+H calculated for $C_{22}H_{21}ClF_2N_3O_4$ requires 464.1183).

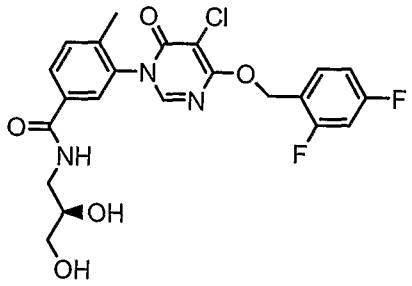
Preparation of 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N-[1-(aminocarbonyl)methyl]-N,4-dimethylbenzamide.

01640/01/PCT



The title compound was prepared using a procedure similar to that used in Step 4 of the synthesis of 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N-[1-(aminocarbonyl)methyl]-4-methylbenzamide by substituting sarcosinamide HCl for glycineamide HCl. ^{1}H NMR (CD_3OD/ 400MHz) δ8.31 (m, 1H), 7.61 (m, 2H), 7.52 (m, 2H), 7.02 (m, 2H), 5.59 (m, 2H), 4.19 (s, 1H), 4.01 (s, 1H), 3.07 (s, 3H), 2.18 (m, 3H). ESHRMS *m/z* 477.1158 (M+H calculated for $C_{22}H_{20}ClF_2N_4O_4$ requires 477.1136).

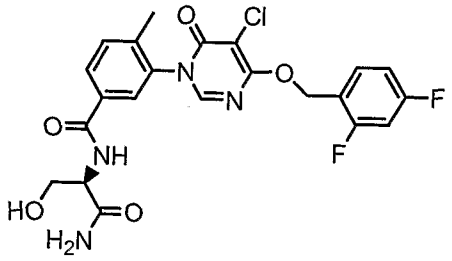
Preparation of 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N-[(2R)-2,3-dihydroxypropyl]-4-methylbenzamide.



The title compound was prepared using a procedure similar to that used in Step 4 of the synthesis of 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N-[1-(aminocarbonyl)methyl]-4-methylbenzamide by substituting (*R*)-(+)-3-amino-1,2-propanediol for glycineamide HCl. ^{1}H NMR (CD_3OD/ 400MHz) δ8.32 (s, 1H), 7.92 (m, 1H), 7.77 (s, 1H), 7.61

(q, 1H, J = 8.0 Hz), 7.53 (d, 1H, J = 8.0 Hz), 7.02 (m, 2H), 5.60 (m, 2H), 3.81 (m, 1H), 3.54 (m, 3H), 3.39 (m, 1H), 2.20 (s, 3H). ESHRMS m/z 480.1117 (M+H calculated for $C_{22}H_{21}ClF_2N_3O_5$ requires 480.1132).

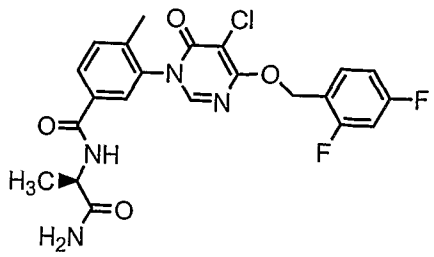
Preparation of N-[(1R)-1-(aminocarbonyl)-2-hydroxyethyl]-3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-4-methylbenzamide.



The title compound was prepared using a procedure similar to that used in Step 4 of the synthesis of 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N-[1-(aminocarbonyl)methyl]-4-methylbenzamide by substituting L-serinamide HCl for glycineamide HCl. ^{1}H NMR (CD_3OD/ 400MHz) δ8.32 (s, 1H), 7.98 (m, 1H), 7.85 (m, 1H), 7.61 (q, 1H, J = 8.4 Hz), 7.55 (d, 1H, J = 8.0 Hz), 7.01 (m, 2H), 5.60 (m, 2H), 4.63 (m, 1H), 3.89 (d, 2H, J = 5.6 Hz), 2.21 (s, 3H). ESHRMS m/z 493.1129 (M+H calculated for $C_{22}H_{20}ClF_2N_4O_5$ requires 493.1085).

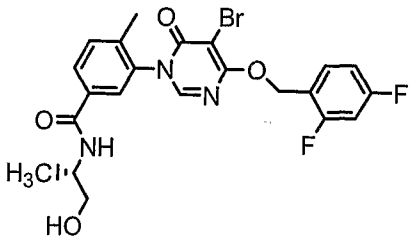
Preparation of N-[(1R)-1-(aminocarbonyl)ethyl]-3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-4-methylbenzamide.

01640/01/PCT



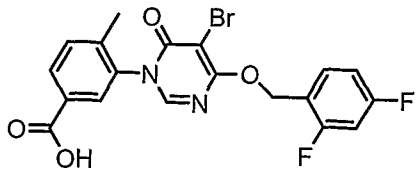
The title compound was prepared using a procedure similar to that used in Step 4 of the synthesis of 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N-[1-(aminocarbonyl)methyl]-4-methylbenzamide by substituting D-alanine amide HCl for glycineamide HCl. ^{1}H NMR (CD_3OD/ 400MHz) δ8.32 (s, 1H), 7.96 (m, 1H), 7.82 (m, 1H), 7.61 (q, 1H, J = 8.4 Hz), 7.53 (d, 1H, J = 8.0 Hz), 7.02 (m, 2H), 5.60 (m, 2H), 4.54 (q, 1H, J = 6.0 Hz), 2.20 (s, 3H), 1.45 (d, 3H, J = 6.0 Hz). ESHRMS m/z 477.1104 (M+H calculated for $C_{22}H_{20}ClF_2N_4O_4$ requires 477.1136).

Preparation of 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N-[(1S)-2-hydroxy-1-methylethyl]-4-methylbenzamide.



Step 1: Preparation of 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoic acid

01640/01/PCT



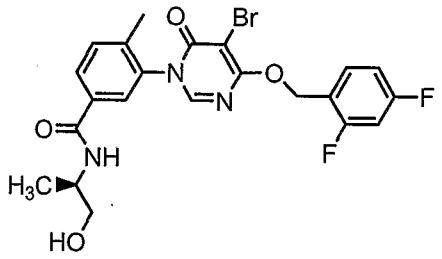
To a cooled (0°C) solution of 3-[4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoic acid (5.76 g, 15.5 mmol) in DCM (35 mL) was added NBS (2.48 g, 13.9 mmol). Allowed reaction to warm to ambient temperature. After 5h, cooled (0°C) reaction mixture, filtered solid, washed with cold DCM and cold hexane, and dried in vacuo. Obtained product as orange solid (5.57 g, 80%). Used without further purification. ^{1}H NMR (CD_3OD/ 400MHz) δ8.29 (s, 1H), 8.05 (m, 1H), 7.91 (s, 1H), 7.60 (q, 1H, J = 8.0 Hz), 7.51 (d, 1H, J = 8.0 Hz), 6.99 (m, 2H), 5.57 (s, 2H), 2.17 (s, 3H). ESHRMS m/z 451.0095 (M+H calculated for $C_{19}H_{14}BrF_2N_2O_4$ requires 451.0100).

Step 2: Preparation of the title compound 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N-[(1S)-2-hydroxy-1-methylethyl]-4-methylbenzamide

To a cooled (0°C) solution of 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoic acid (from Step 1) (0.80 g, 1.77 mmol) in DMA (3.2 mL) was added isobutyl chloroformate (0.28 mL, 2.13 mmol) and 4-methylmorpholine (0.25 mL, 2.30 mmol). Stirred at 0°C for 5 min, ambient temperature for 30 min. Added (*S*)-(+)-2-amino-1-propanol (0.21 mL, 2.66 mmol) and DMAP (0.02 g, 0.18 mmol). Stirred at ambient temperature overnight. Purified crude product by preparatory HPLC using a 10-90% CH_3CN/H_2O (30 min) gradient containing 0.5% TFA at a flow rate of 80 mL/min. Appropriate fractions (M+H m/z = 509) were combined and concentrated to approximately 20 mL under reduced pressure.

Added 5% $NaHCO_3$ (20 mL) and extracted with DCM (3 x 15 mL). The organic extracts were dried over Na_2SO_4, filtered, concentrated under reduced pressure, and dried *in vacuo* to give the desired product as a pale yellow foam (0.61 g, 67%). ^1H NMR (CD_3OD/ 400MHz) δ8.32 (s, 1H), 7.92 (m, 1H), 7.76 (s, 1H), 7.61 (q, 1H, *J* = 8.0 Hz), 7.52 (d, 1H, *J* = 8.0 Hz), 7.01 (m, 2H), 5.60 (m, 2H), 4.16 (m, 1H), 3.57 (m, 2H), 2.19 (s, 3H), 1.22 (d, 3H, *J* = 5.6 Hz). ESHRMS *m/z* 508.0666 (M+H calculated for $C_{22}H_{21}BrF_2N_3O_4$ requires 508.0678).

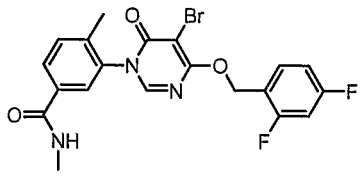
Preparation of 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N-[(1R)-2-hydroxy-1-methylethyl]-4-methylbenzamide.



The title compound was prepared using a procedure similar to that used in Step 4 of the synthesis of 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N-[(1S)-2-hydroxy-1-methylethyl]-4-methylbenzamide by substituting (*R*)-(-)-2-amino-1-propanol for (*S*)-(-)-2-amino-1-propanol HCl. ^1H NMR (CD_3OD/ 400MHz) δ8.32 (s, 1H), 7.92 (m, 1H), 7.76 (s, 1H), 7.61 (q, 1H, *J* = 8.0 Hz), 7.52 (d, 1H, *J* = 8.0 Hz), 7.01 (m, 2H), 5.59 (m, 2H), 4.16 (m, 1H), 3.57 (m, 2H), 2.19 (s, 3H),

1.22 (d, 3H, J = 6.0 Hz). ESHRMS m/z 508.0684 (M+H calculated for $C_{22}H_{21}BrF_2N_3O_4$ requires 508.0678).

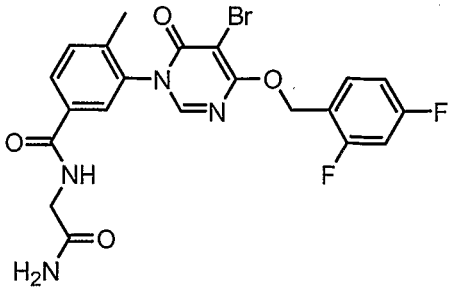
Preparation of 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N,4-dimethylbenzamide.



The title compound was prepared using a procedure similar to that used in Step 2 of the synthesis of 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N-[(1S)-2-hydroxy-1-methylethyl]-4-methylbenzamide by substituting methylamine for (*S*)-(+)-2-amino-1-propanol. ^{1}H NMR (CD_3OD/400MHz) δ8.31 (s, 1H), 7.88 (m, 1H), 7.72 (s, 1H), 7.61 (q, 1H, J = 8.0 Hz), 7.51 (d, 1H, J = 8.0 Hz), 7.01 (m, 2H), 5.58 (m, 2H), 2.89 (s, 3H), 2.18 (s, 3H). ESHRMS m/z 481.0684 (M+H calculated for $C_{20}H_{16}BrF_2N_3O_3\,NH_4$ requires 481.0681).

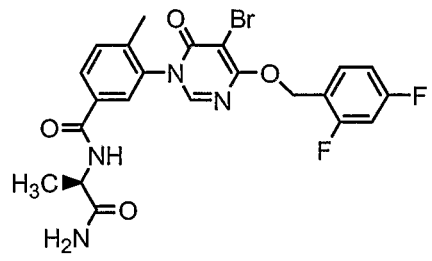
Preparation of N-[1-(aminocarbonyl)methyl]-3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-4-methylbenzamide.

01640/01/PCT



The title compound was prepared using a procedure similar to that used in Step 2 of the synthesis of 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N-[(1S)-2-hydroxy-1-methylethyl]-4-methylbenzamide by substituting glycineamide HCl for (*S*)-(+)-2-amino-1-propanol. ^{1}H NMR (CD_3OD/ 400MHz) δ8.32 (s, 1H), 7.95 (m, 1H), 7.80 (s, 1H), 7.61 (q, 1H, *J* = 8.4 Hz), 7.53 (d, 1H, *J* = 8.0 Hz), 7.01 (m, 2H), 5.58 (m, 2H), 4.01 (s, 2H), 2.20 (s, 3H). ESHRMS *m/z* 507.0474 (M+H calculated for $C_{21}H_{18}BrF_2N_4O_4$ requires 507.0474).

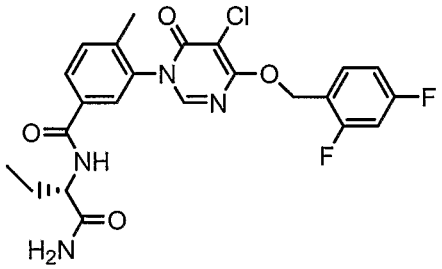
Preparation of N-[(1R)-1-(aminocarbonyl)ethyl]-3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-4-methylbenzamide.



01640/01/PCT

The title compound was prepared using a procedure similar to that used in Step 2 of the synthesis of 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N-[(1S)-2-hydroxy-1-methylethyl]-4-methylbenzamide by substituting D-alanine amide HCl for (*S*)-(+)-2-amino-1-propanol. ^{1}H NMR (CD_3OD/ 400MHz) δ8.32 (s, 1H), 7.96 (m, 1H), 7.82 (m, 1H), 7.62 (q, 1H, *J* = 8.0 Hz), 7.53 (d, 1H, *J* = 8.0 Hz), 7.01 (m, 2H), 5.59 (m, 2H), 4.54 (q, 1H, *J* = 6.0 Hz), 2.20 (s, 3H), 1.45 (d, 3H, *J* = 6.0 Hz). ESHRMS *m/z* 521.0593 (M+H calculated for $C_{22}H_{20}BrF_2N_4O_4$ requires 521.0630).

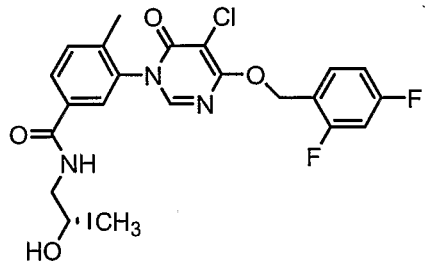
Preparation of N-[(1S)-1-(aminocarbonyl)propyl]-3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-4-methylbenzamide.



The title compound was prepared using a procedure similar to that used in Step 4 of the synthesis of 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N-[1-(aminocarbonyl)methyl]-4-methylbenzamide by substituting L-alpha-aminobutyric acid amide for glycineamide HCl. ^{1}H NMR (CD_3OD/ 400MHz) δ8.32 (s, 1H), 7.95 (m, 1H), 7.83 (m, 1H), 7.61 (q, 1H, *J* = 8.0 Hz), 7.54 (d, 1H, *J* = 8.0 Hz), 7.01 (m, 2H), 5.60 (m, 2H), 4.45 (m, 1H), 2.20 (s, 3H), 1.93 (m, 1H), 1.79

(m, 1H), 1.01 (t, 3H, J = 7.6 Hz). ESHRMS m/z 491.1303 (M+H calculated for $C_{23}H_{22}ClF_2N_4O_4$ requires 491.1292).

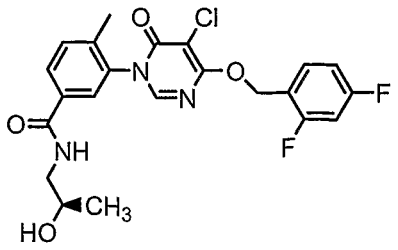
Preparation of 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N-[(2S)-2-hydroxypropyl]-4-methylbenzamide.



The title compound was prepared using a procedure similar to that used in Step 4 of the synthesis of 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N-[1-(aminocarbonyl)methyl]-4-methylbenzamide by substituting (*S*)-(+)-1-amino-2-propanol for glycineamide HCl. ^{1}H NMR (CD_3OD/400MHz) δ8.32 (s, 1H), 7.92 (m, 1H), 7.77 (s, 1H), 7.61 (q, 1H, J = 8.0 Hz), 7.53 (d, 1H, J = 8.0 Hz), 7.02 (m, 2H), 5.60 (m, 2H), 3.93 (m, 1H), 3.39 (m, 2H), 2.20 (s, 3H), 1.18 (d, 3H, J = 6.4 Hz). ESHRMS m/z 464.1154 (M+H calculated for $C_{22}H_{21}ClF_2N_3O_4$ requires 464.1183).

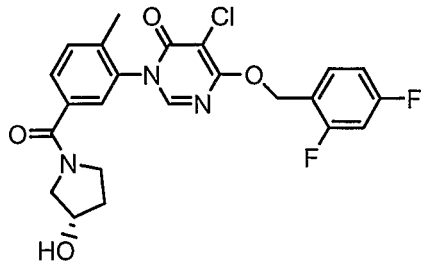
Preparation of 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N-[(2R)-2-hydroxypropyl]-4-methylbenzamide.

01640/01/PCT



The title compound was prepared using a procedure similar to that used in Step 4 of the synthesis of 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N-[1-(aminocarbonyl)methyl]-4-methylbenzamide by substituting (*R*)-(-)-1-amino-2-propanol for glycineamide HCl. ^{1}H NMR (CD_3OD/400MHz) δ8.32 (s, 1H), 7.92 (m, 1H), 7.77 (s, 1H), 7.61 (q, 1H, *J* = 8.0 Hz), 7.53 (d, 1H, *J* = 8.0 Hz), 7.02 (m, 2H), 5.60 (m, 2H), 3.94 (m, 1H), 3.30 (m, 2H), 2.20 (s, 3H), 1.18 (s, 3H). ESHRMS *m/z* 464.1167 (M+H calculated for $C_{22}H_{21}ClF_2N_3O_4$ requires 464.1183).

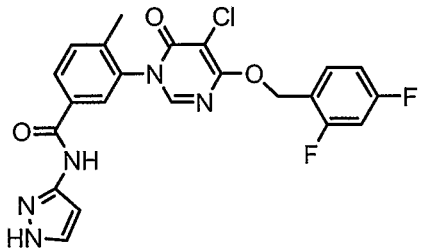
Preparation of 5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-(5-{[(3S)-3-hydroxypyrrolidin-1-yl]carbonyl}-2-methylphenyl)pyrimidin-4(3H)-one.



The title compound was prepared using a procedure similar to that used in Step 4 of the synthesis of 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N-[1-

(aminocarbonyl)methyl]-4-methylbenzamide by substituting (*S*)-3-hydroxypyrrolidine for glycineamide HCl. ^{1}H NMR (CD_3OD/ 400MHz) δ8.31 (d, 1H, *J* = 7.6 Hz), 7.62 (m, 2H), 7.52 (m, 2H), 7.01 (m, 2H), 5.59 (m, 2H), 4.42 (m, 1H), 3.64 (m, 4H), 2.19 (s, 3H), 2.00 (m, 2H). ESHRMS *m/z* 476.1147 (M+H calculated for $C_{23}H_{21}ClF_2N_3O_4$ requires 476.1183).

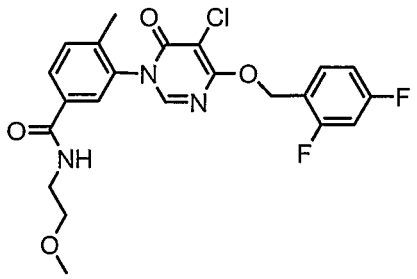
Preparation of 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-4-methyl-N-1H-pyrazol-3-ylbenzamide.



The title compound was prepared using a procedure similar to that used in Step 4 of the synthesis of 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N-[1-(aminocarbonyl)methyl]-4-methylbenzamide by substituting 3-aminopyrazole for glycineamide HCl. ^{1}H NMR (CD_3OD/ 400MHz) δ8.37 (s, 1H), 8.14 (m, 2H), 8.08 (s, 1H), 7.60 (m, 2H), 7.01 (m, 2H), 6.06 (d, 1H, *J* = 3.2 Hz), 5.60 (s, 2H), 2.23 (s, 3H).

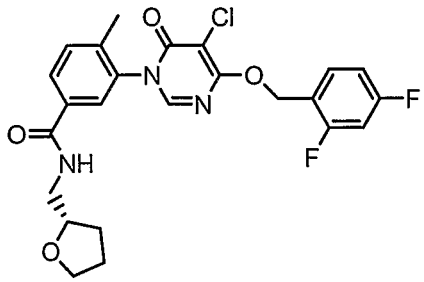
Preparation of 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N-(2-methoxyethyl)-4-methylbenzamide.

01640/01/PCT



The title compound was prepared using a procedure similar to that used in Step 4 of the synthesis of 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N-[1-(aminocarbonyl)methyl]-4-methylbenzamide by substituting 2-methoxyethylamine for glycineamide HCl. ^{1}H NMR (CD_3OD/ 400MHz) δ8.32 (s, 1H), 7.91 (m, 1H), 7.75 (s, 1H), 7.61 (q, 1H, *J* = 8.4 Hz), 7.52 (d, 1H, *J* = 8.0 Hz), 7.02 (m, 2H), 5.60 (m, 2H), 3.55 (s, 4H), 3.35 (s, 3H), 2.19 (s, 3H). ESHRMS *m/z* 464.1142 (M+H calculated for $C_{22}H_{21}ClF_2N_3O_4$ requires 464.1183).

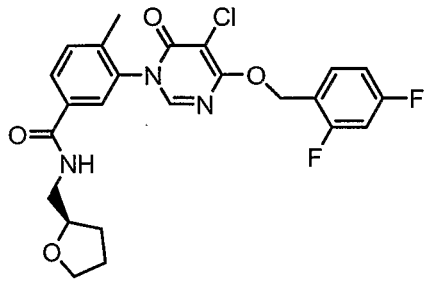
Preparation of 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-4-methyl-N-[(2S)-tetrahydrofuran-2-ylmethyl]benzamide.



The title compound was prepared using a procedure similar to that used in Step 4 of the synthesis of 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N-[1-(aminocarbonyl)methyl]-4-methylbenzamide by substituting (*S*)-

(+)-tetrahydrofurfurylamine for glycineamide HCl. ^{1}H NMR (CD_3OD/ 400MHz) δ8.32 (s, 1H), 7.91 (m, 1H), 7.76 (s, 1H), 7.61 (q, 1H, *J* = 8.0 Hz), 7.52 (d, 1H, *J* = 8.4 Hz), 7.01 (m, 2H), 5.60 (m, 2H), 4.08 (m, 1H), 3.87 (q, 1H, *J* = 6.8 Hz), 3.74 (q, 1H, *J* = 7.6 Hz), 3.49 (m, 1H), 3.39 (m, 1H), 2.19 (s, 3H), 2.01 (m, 1H), 1.91 (m, 2H), 1.64 (m, 1H). ESHRMS *m/z* 490.1308 (M+H calculated for $C_{24}H_{23}ClF_2N_3O_4$ requires 490.1340).

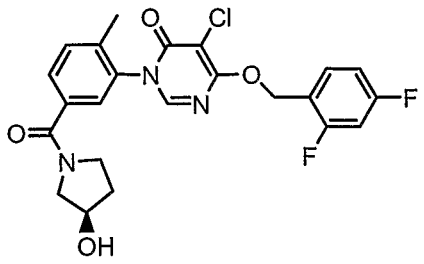
Preparation of 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-4-methyl-N-[(2R)-tetrahydrofuran-2-ylmethyl]benzamide.



The title compound was prepared using a procedure similar to that used in Step 4 of the synthesis of 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N-[1-(aminocarbonyl)methyl]-4-methylbenzamide by substituting (*R*)-(-)-tetrahydrofurfurylamine for glycineamide HCl. ^{1}H NMR (CD_3OD/ 400MHz) δ8.32 (s, 1H), 7.91 (m, 1H), 7.76 (s, 1H), 7.61 (q, 1H, *J* = 8.4 Hz), 7.52 (d, 1H, *J* = 8.0 Hz), 7.02 (m, 2H), 5.59 (m, 2H), 4.08 (m, 1H), 3.87 (q, 1H, *J* = 6.8 Hz), 3.74 (q, 1H, *J* = 7.6 Hz), 3.49 (m, 1H), 3.39 (m, 1H), 2.19 (s, 3H), 2.01 (m, 1H), 1.93 (m, 2H), 1.64 (m, 1H). ESHRMS *m/z* 490.1366 (M+H calculated for $C_{24}H_{23}ClF_2N_3O_4$ requires 490.1340).

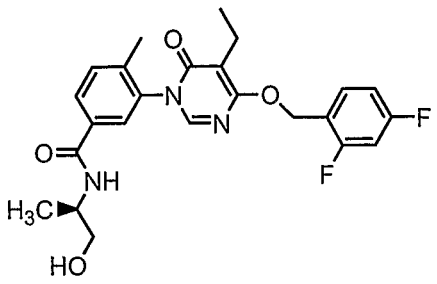
01640/01/PCT

Preparation of 5-chloro-6-[(2,4-difluorobenzyl)oxy]-3-(5-{[(3R)-3-hydroxypyrrolidin-1-yl]carbonyl}-2-methylphenyl)pyrimidin-4(3H)-one.



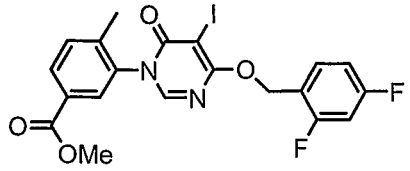
The title compound was prepared using a procedure similar to that used in Step 4 of the synthesis of 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N-[1-(aminocarbonyl)methyl]-4-methylbenzamide by substituting (R)-(+)-3-pyrrolidinol for glycineamide HCl. ^{1}H NMR (CD_3OD/400MHz) δ8.31 (d, 1H, J = 7.6 Hz), 7.62 (m, 2H), 7.52 (m, 2H), 7.01 (m, 2H), 5.51 (m, 2H), 4.42 (m, 1H), 3.65 (m, 4H), 2.19 (s, 3H), 2.00 (m, 2H). ESHRMS m/z 476.1175 (M+H calculated for $C_{23}H_{21}ClF_2N_3O_4$ requires 476.1183).

Preparation of 3-[4-[(2,4-difluorobenzyl)oxy]-5-ethyl-6-oxopyrimidin-1(6H)-yl]-N-[(1R)-2-hydroxy-1-methylethyl]-4-methylbenzamide.



01640/01/PCT

Step 1: Preparation of methyl 3-[4-[(2,4-difluorobenzyl)oxy]-5-iodo-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoate



To a suspension of methyl 3-[4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoate (2.53 g, 6.55 mmol) and dichloroacetic acid (0.27 mL, 3.27 mmol) in acetonitrile (20 mL) was added N-iodosuccinimide (1.62 g, 7.20 mmol). Stirred at ambient temperature for 3.5h. Cooled reaction mixture (0°C), filtered solid, washed with cold acetonitrile, and dried *in vacuo* overnight. Obtained product as white solid (2.72 g, 81%). ^{1}H NMR (CD_3OD/ 400MHz) δ8.24 (s, 1H), 8.07 (m, 1H), 7.93 (s, 1H), 7.63 (q, 1H, J = 8.4 Hz), 7.54 (d, 1H, J = 8.0 Hz), 7.01 (t, 2H, J = 8.4 Hz), 5.57 (s, 2H), 3.90 (s, 3H), 2.19 (s, 3H). ESHRMS *m/z* 513.0143 (M+H calculated for $C_{20}H_{16}F_2IN_2O_4$ requires 513.0117).

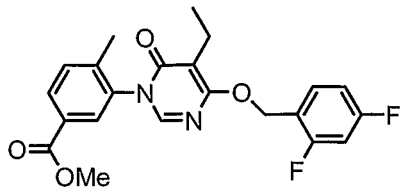
Step 2: Preparation of methyl 3-[4-[(2,4-difluorobenzyl)oxy]-6-oxo-5-vinylpyrimidin-1(6H)-yl]-4-methylbenzoate

A round bottom flask containing methyl 3-[4-[(2,4-difluorobenzyl)oxy]-5-iodo-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoate (2.50 g, 4.88 mmol) in N, N-dimethylformamide was evacuated and flushed with argon. Tributyl(vinyl)tin (2.3 g, 7.3 mmol) and dichlorobis(triphenylphosphine) palladium (II) (0.34 g, 0.49 mmol) were added in the nitrogen atmosphere of a glove box. Heated at 60°C under argon overnight. Added additional tin (0.7 mL) and palladium (0.17 g) reagents and continued over weekend. No progress observed. Distilled DMF, washed crude product with ethyl acetate, and filtered through

01640/01/PCT

celite. The filtrate was concentrated and purified by flash column using 25% ethyl acetate in hexane as eluent. Used without further purification.

Step 3: Preparation of methyl 3-[4-[(2,4-difluorobenzyl)oxy]-5-ethyl-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoate



A solution of methyl 3-[4-[(2,4-difluorobenzyl)oxy]-6-oxo-5-vinylpyrimidin-1(6H)-yl]-4-methylbenzoate (from Step2) (1.0 g) in EtOH (20 mL) was purged with N_2. 10% Pd/C (0.22 g) was added and the chamber was alternately evacuated and purged with H_2 (3x). Reaction at 25 psi was checked by mass spectrometry at 4h but no product was detected. Added additional 10% Pd/C (0.36 g) and stirred at 32 psi overnight. Very little starting material remained. Crude product was filtered through celite, rinsed with ethyl acetate, and concentrated. This residue was dissolved in a small amount of ethyl acetate by heating; hexane was added and the mixture left in the fridge overnight. The precipitate was filtered and washed with cold ethyl acetate and hexane. The product was obtained as a yellow solid (0.58 g, 58%) and used without further purification. ^{1}H NMR (CD_3OD/ 400MHz) δ8.17 (s, 1H), 8.06 (m, 1H), 7.90 (s, 1H), 7.57 (q, 1H, J = 8.4 Hz), 7.53 (d, 1H, J = 8.0 Hz), 7.00 (m, 2H), 5.52 (s, 2H), 3.90 (s, 3H), 2.51 (q, 2H, J = 7.6 Hz), 2.18 (s, 3H), 1.06 (t, 3H, J = 7.6 Hz). ESHRMS m/z 415.1460 (M+H calculated for $C_{22}H_{21}F_2N_2O_4$ requires 415.1464).

Step 4: Preparation of 3-[4-[(2,4-difluorobenzyl)oxy]-5-ethyl-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoic acid

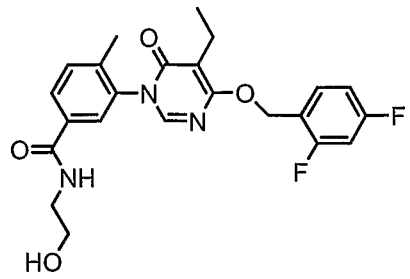
To a suspension of methyl 3-[4-[(2,4-difluorobenzyl)oxy]-5-ethyl-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoate (from Step 3) (0.58 g, 1.40 mmol) in dioxane (2 mL) was added 2N NaOH (1.05 mL, 2.10 mmol). Stirred at ambient temperature for 2h. Cooled reaction mixture (0°C), added 5% citric acid to precipitate the product, filtered solid, washed with water, and dried *in vacuo*. Obtained the product as a pale yellow solid (0.53 g, 95%). Used without further purification.

Step 5: Preparation of the title compound

To a cooled solution (0°C) of 3-[4-[(2,4-difluorobenzyl)oxy]-5-ethyl-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoic acid (from Step 4) (0.25 g, 0.62 mmol) and 4-methylmorpholine (0.10 mL, 0.94 mmol) in DMA (2 mL) was added isobutyl chloroformate (0.12 mL, 0.94 mmol). Stirred 5 min at 0°C, 30 min at ambient temperature. Added (*R*)-(-)-2-amino-1-propanol (0.07 mL, 0.94 mmol) and DMAP (0.02 g, 0.12 mmol) to the cooled (0°C) reaction mixture. Stirred at ambient temperature for 3h. Purified crude product by preparatory HPLC using a 10-90% CH_3CN/H_2O (30 min) gradient containing 0.5% TFA at a flow rate of 80 mL/min. Appropriate fractions (M+H m/z = 458) were combined and concentrated to approximately 20 mL under reduced pressure. Added 5% $NaHCO_3$ (20 mL) and extracted with DCM (3 x 15 mL). The organic extracts were dried over Na_2SO_4, filtered, concentrated under reduced pressure, and dried *in vacuo* to give the desired product as an off-white foam (0.20 g, 70%). ^1H NMR (CD_3OD/ 400MHz) δ8.18 (s, 1H), 7.90 (m, 1H), 7.73 (m, 1H), 7.57 (q, 1H, J = 8.4 Hz),

7.50 (d, 1H, *J* = 8.0 Hz), 7.01 (m, 2H), 5.52 (q, 2H, *J* = 12.4 Hz), 4.16 (m, 1H), 3.57 (m, 2H), 2.21 (q, 2H, *J* = 7.6 Hz), 2.17 (s, 3H), 1.22 (m, 3H), 1.05 (t, 3H, *J* = 7.2 Hz). ESHRMS *m/z* 458.1855 (M+H calculated for $C_{24}H_{26}F_2N_3O_4$ requires 458.1886).

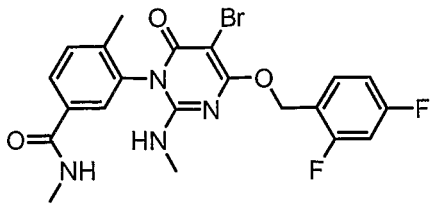
Preparation of 3-[4-[(2,4-difluorobenzyl)oxy]-5-ethyl-6-oxopyrimidin-1(6H)-yl]-N-(2-hydroxyethyl)-4-methylbenzamide.



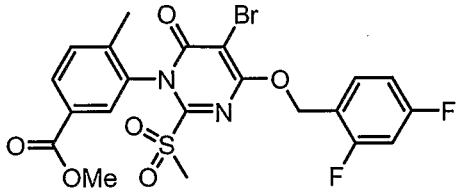
The title compound was prepared using a procedure similar to that used in Step 5 of the synthesis of 3-[4-[(2,4-difluorobenzyl)oxy]-5-ethyl-6-oxopyrimidin-1(6H)-yl]-N-[(1R)-2-hydroxy-1-methylethyl]-4-methylbenzamide by substituting ethanolamine for (*R*)-(-)-2-amino-1-propanol. ^{1}H NMR (CD_3OD/400MHz) δ8.19 (s, 1H), 7.90 (m, 1H), 7.73 (s, 1H), 7.57 (q, 1H, *J* = 8.4 Hz), 7.51 (d, 1H, *J* = 8.0 Hz), 7.00 (m, 2H), 5.51 (q, 2H, *J* = 12.4 Hz), 3.69 (t, 2H, *J* = 6.0 Hz), 3.48 (t, 2H, *J* = 5.6 Hz), 2.51 (q, 2H, *J* = 7.6 Hz), 2.17 (s, 3H), 1.05 (t, 3H, *J* = 7.6 Hz). ESHRMS *m/z* 444.1704 (M+H calculated for $C_{23}H_{24}F_2N_3O_4$ requires 444.1729).

Preparation of 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-(methylamino)-6-oxopyrimidin-1(6H)-yl]-N,4-dimethylbenzamide.

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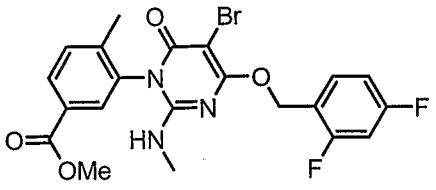
Step 1: Preparation of methyl 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-(methylsulfonyl)-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoate



To a mixture of methyl 3-[4-[(2,4-difluorobenzyl)oxy]-2-(methylthio)-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoate (0.99 g, 2.29 mmol) in DCM (5 mL) was added NBS (0.43 g, 2.40 mmol). After 2h at ambient temperature, added mCPBA (0.40 g, 2.29 mmol). Added an additional aliquot of mCPBA (0.40 g, 2.29 mmol) after 30 min. After another 1.5h, added additional mCPBA (0.20 g, 1.14 mmol) and stirred overnight at ambient temperature. Washed with water (~10 mL) and extracted in DCM. Crude extracts purified by flash column chromatography using 50% ethyl acetate/hexane as eluent. Appropriate fractions combined, concentrated under reduced pressure, and dried in vacuo to give the desired product as a yellow foam (0.89 g, 72%). ^{1}H NMR (CD_3OD/ 400MHz) δ8.04 (m, 1H), 7.94 (s, 1H), 7.60 (q, 1H, J = 8.0 Hz), 7.46 (d, 1H, J = 8.0 Hz), 7.02 (m, 2H), 5.59 (s, 2H), 3.87 (s, 3H), 3.13 (s, 3H), 2.16 (s, 3H). ESHRMS m/z 543.0030 (M+H calculated for $C_{21}H_{18}BrF_2N_2O_6S$ requires 543.0032).

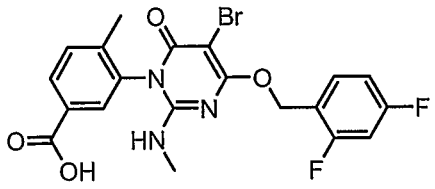
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Step 2: Preparation of methyl 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-(methylamino)-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoate



Methyl 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-(methylsulfonyl)-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoate (from Step 1) (0.35 g, 0.64 mmol), DMAP (0.01 g, 0.06 mmol), and methylamine (0.97 mL of a 2M solution in THF, 1.93 mmol) were combined and stirred at ambient temperature. Reaction complete after 4h. Washed with 5% citric acid, extracted in DCM, dried over Na_2SO_4, filtered, concentrated, and dried *in vacuo* to give a brown film. Dissolved in a small amount of DCM, added hexane, and cooled. Filtered precipitate and washed with a solution of cold 50% DCM/hexane. Dried resulting white solid *in vacuo* (0.22 g, 69%). ^{1}H NMR (CD_3OD/400MHz) δ8.04 (m, 1H), 7.77 (s, 1H), 7.58 (q, 1H, J = 8.8 Hz), 7.53 (d, 1H, J = 8.4 Hz), 6.99 (m, 2H), 5.52 (s, 2H), 3.87 (s, 3H), 2.84 (s, 3H), 2.10 (s, 3H). ESHRMS *m/z* 494.0523 (M+H calculated for $C_{21}H_{19}BrF_2N_3O_4$ requires 494.0522).

Step 3: Preparation of methyl 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-(methylamino)-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoate



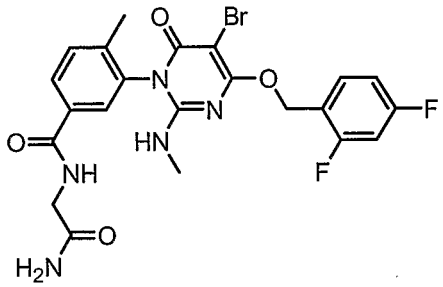
To a mixture of methyl 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-(methylamino)-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoate (from Step 2) (0.25 g, 0.51 mmol) in dioxane (2 mL) was added 2N NaOH (0.76 mmol). The reaction mixture was stirred at ambient temperature for 1.5h, cooled (0°C), and solid precipitated by the addition of 5% citric acid. The precipitate was filtered, washed with water, and dried *in vacuo* to give the desire product as a beige solid (0.21 g, 84%). ^{1}H NMR (CD_3OD/ 400MHz) δ8.05 (m, 1H), 7.76 (s, 1H), 7.58 (q, 1H, J = 8.8 Hz), 7.51 (d, 1H, J = 8.0 Hz), 6.99 (m, 2H), 5.52 (s, 2H), 2.84 (s, 3H), 2.10 (s, 3H). ESHRMS *m/z* 480.0403 (M+H calculated for $C_{20}H_{17}BrF_2N_3O_4$ requires 480.0365).

Step 4: Preparation of the title compound

To a cooled (0°C) solution of methyl 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-(methylamino)-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoate (from Step 3) (0.18 g, 0.38 mmol) in N, N-dimethylacetamide (2 mL) was added isobutyl chloroformate (0.60 mL of a stock solution prepared 0.1 mL in 0.9 mL DCM, 0.46 mmol) and 4-methylmorpholine (0.55 mL of a stock solution prepared 0.1mL in 0.9 mL DMA, 0.50 mmol). Stirred at 0°C for 35 min. Added methylamine (0.29 mL of 2M solution in THF, 0.57 mmol). After 1h, distilled DMA and purified the crude product by preparatory HPLC using a 10-90% CH_3CN/H_2O (30 min) gradient containing 0.5% TFA at a flow rate of 80 mL/min. Appropriate fractions (M+H *m/z* = 494) were combined and concentrated to approximately 20 mL under reduced pressure. Added 5% $NaHCO_3$ (20 mL) and extracted with DCM (3 x 15 mL). The organic extracts were dried over Na_2SO_4, filtered, concentrated under reduced pressure, and dried *in vacuo* to give the desired product as a white solid (77 mg, 27%). ^{1}H NMR

(CD_3OD/ 400MHz) δ7.86 (m, 1H), 7.58 (m, 2H), 7.51 (d, 1H, *J* = 8.0 Hz), 6.98 (m, 2H), 5.52 (q, 2H, *J* = 12.8 Hz), 2.87 (s, 3H), 2.84 (s, 3H), 2.09 (s, 3H). ESHRMS *m/z* 493.0659 (M+H calculated for $C_{21}H_{20}BrF_2N_4O_3$ requires 493.0681).

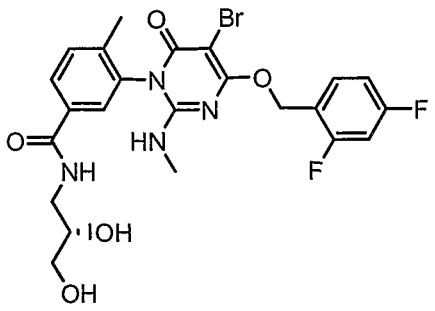
Preparation of N-[1-(aminocarbonyl)methyl]-3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-(methylamino)-6-oxopyrimidin-1(6H)-yl]-4-methylbenzamide.



The title compound was prepared using a procedure similar to that used in Step 4 of the synthesis of 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-(methylamino)-6-oxopyrimidin-1(6H)-yl]-N,4-dimethylbenzamide by substituting glycineamide HCl for methylamine. ^1H NMR (CD_3OD/ 400MHz) δ7.94 (m, 1H), 7.68 (s, 1H), 7.59 (q, 1H, *J* = 8.4 Hz), 7.55 (d, 1H, *J* = 8.0 Hz), 7.00 (m, 2H), 5.54 (q, 2H, *J* = 11.6 Hz), 4.00 (s, 2H), 2.86 (s, 3H), 2.12 (s, 3H). ESHRMS *m/z* 536.0743 (M+H calculated for $C_{22}H_{21}BrF_2N_5O_4$ requires 536.0739).

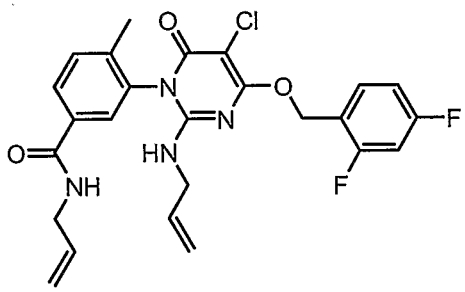
Preparation of 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-(methylamino)-6-oxopyrimidin-1(6H)-yl]-N-[(2S)-2,3-dihydroxypropyl]-4-methylbenzamide.

01640/01/PCT



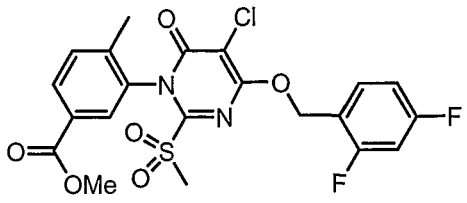
The title compound was prepared using a procedure similar to that used in Step 4 of the synthesis of 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-2-(methylamino)-6-oxopyrimidin-1(6H)-yl]-N,4-dimethylbenzamide by substituting (*S*)-(-)-3-amino-1,2-propanediol for methylamine. ^{1}H NMR (CD_3OD/ 400MHz) δ7.89 (m, 1H), 7.56 (m, 3H), 6.98 (m, 2H), 5.52 (q, 2H, *J* = 12.0 Hz), 3.77 (quintet, 1H, *J* = 5.2 Hz), 3.50 (m, 3H), 3.36 (m, 1H), 2.83 (s, 3H), 2.10 (s, 3H). ESHRMS *m/z* 553.0875 (M+H calculated for $C_{23}H_{24}BrF_2N_4O_5$ requires 553.0893).

Preparation of N-allyl-3-[2-(allylamino)-5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-4-methylbenzamide.



Step 1: Preparation of methyl 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-(methylsulfonyl)-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoate

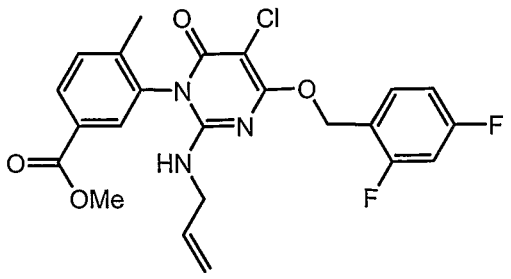
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A mixture of methyl 3-[4-[(2,4-difluorobenzyl)oxy]-2-(methylthio)-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoate (2.48 g, 5.73 mmol), NCS (0.84 g, 6.31 mmol), and dichloroacetic acid (~20 drops) in dichloroethane (20 mL) was heated at 60°C overnight. Added mCPBA (0.99 g, 5.73 mmol) and stirred at ambient temperature for 1h. Then, added second equivalent mCPBA (0.99 g, 5.73 mmol). Stirred overnight. Added additional mCPBA (0.49 g, 2.87 mmol) and stirred for ~65h. Added additional mCPBA (0.49 g, 2.87 mmol) and stirred overnight at ambient temperature again. Reaction found to be complete. Washed with 5%$NaHCO_3$, extracted in DCM, dried over Na_2SO_4, filtered, concentrated, and dried *in vacuo*. Purifired by flash column chromatography using 50% ethyl acetate/hexane as eluent. Obtained clean product as a white solid (1.56 g, 55%). ^1H NMR (CD_3OD/ 400MHz) δ8.07 (m, 1H), 7.96 (s, 1H), 7.62 (q, 1H, J = 8.0 Hz), 7.48 (d, 1H, J = 8.0 Hz), 7.05 (m, 2H), 5.62 (s, 2H), 3.89 (s, 3H), 3.45 (s, 3H), 2.18 (s, 3H). ESHRMS m/z 499.0514 (M+H calculated for $C_{21}H_{18}ClF_2N_2O_6S$ requires 499.0537).

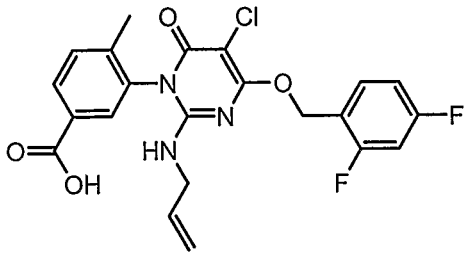
Step 2: Preparation of methyl 3-[2-(allylamino)-5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoate

01640/01/PCT



A mixture of methyl 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-(methylsulfonyl)-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoate (from Step 1) (3.02 g, 6.05 mmol), allyl amine (0.55 mL, 7.26 mmol), and DMAP (0.07 g, 0.61 mmol) in dioxane (8 mL) was stirred at ambient temperature overnight. Observed product and impurity (1:1 ratio). Added ethyl acetate (4 mL), cooled (0°C) the reaction mixture, filtered the precipitate, and dried *in vacuo* to give the product as a white solid (1.17g, 41%). ^{1}H NMR (CD_3OD/ 400MHz) δ8.08 (m, 1H), 7.82 (s, 1H), 7.57 (m, 2H), 7.00 (t, 2H, J = 8.8 Hz), 5.80 (m, 1H), 5.51 (m, 2H), 5.07 (m, 2H), 4.56 (s, 1H), 3.93 (m, 1H), 3.89 (s, 3H), 3.65 (s, 3H). ESHRMS *m/z* 476.1184 (M+H calculated for $C_{23}H_{21}ClF_2N_3O_4$ requires 476.1183).

Step 3: Preparation of 3-[2-(allylamino)-5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoic acid



To a suspension of methyl 3-[2-(allylamino)-5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-4-

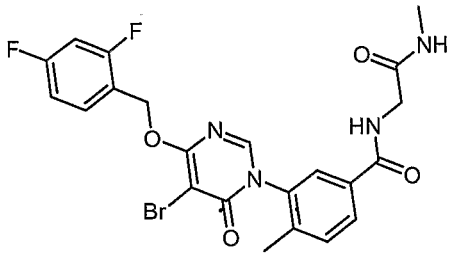
methylbenzoate (from Step 2) (1.59 g, 3.34 mmol) in dioxane (7 mL) was added 2N NaOH (2.51 mL, 5.01 mmol). Stirred at ambient temperature for 1h, cooled (0°C), added 5% citric acid to precipitate the product, filtered precipitate, and dried *in vacuo* to give the desired compound as a white solid (1.30 g, 84%). ^{1}H NMR (CD_3OD/ 400MHz) δ8.08 (m, 1H), 7.81 (s, 1H), 7.56 (m, 2H), 7.00 (t, 2H, J = 8.4 Hz), 5.80 (m, 1H), 5.51 (s, 2H), 5.07 (m, 2H), 3.93 (m, 2H), 2.14 (s, 3H). ESHRMS *m/z* 462.1006 (M+H calculated for $C_{22}H_{19}ClF_2N_3O_4$ requires 462.1027).

Step 4: Preparation of the title compound

To a cooled (0°C) solution of 3-[2-(allylamino)-5-chloro-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoic acid (from Step 3) (0.37 g, 0.80 mmol) in N,N-dimethylacetamide (2 mL) was added isobutyl chloroformate (0.12 mL, 0.96 mmol) and 4-methylmorpholine (0.11 mL, 1.04 mmol). Stirred at 0°C for 5 min, ambient temperature for 30 min. Added allyl amine (0.09 mL, 1.20 mmol). Stirred at ambient temperature for 2h. Purified by preparatory HPLC using a 10-90% CH_3CN/H_2O (30 min) gradient containing 0.5% TFA at a flow rate of 80 mL/min. Appropriate fractions (M+H *m/z* = 494) were combined, freeze-dried, and lyophilized. Washed with 5% $NaHCO_3$ (20 mL) and extracted with DCM (3 x 15 mL). The organic extracts were dried over Na_2SO_4, filtered, concentrated under reduced pressure, and dried *in vacuo* to give the desired product as a white solid (0.24 g, 60%). ^{1}H NMR (CD_3OD/ 400MHz) δ7.93 (m, 1H), 7.67 (s, 1H), 7.55 (q, 2H, J = 8.0 Hz), 7.00 (t, 2H, J = 8.8 Hz), 5.90 (m, 1H), 5.80 (m, 1H), 5.51 (m, 2H), 5.21 (m, 1H), 5.09 (m, 3H), 3.95 (m, 4H), 2.14 (s, 3H). ESHRMS *m/z* 501.1520 (M+H calculated for $C_{25}H_{24}ClF_2N_4O_3$ requires 501.1500).

01640/01/PCT

Preparation of 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-4-methyl-N-{1-[(methylamino)carbonyl]methyl}benzamide.

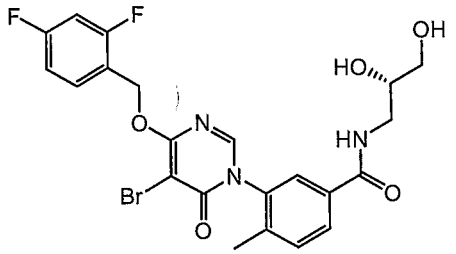


To a cold solution of 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoic acid (0.8 g, 1.7 mmol) in anhydrous dimethylacetamide (3.2 mL) was added isobutyl chloroformate (0.23 mL, 1.7 mmol) followed by N-methylmorpholine (0.25 mL, 2.2 mmol). The reaction mixture stirred under argon atmosphere at 0° C for 10 min and then at room temperature for 30 min. At which time another equivalent of N-methylmorpholine (0.29 mL, 2.5 mmol) was added to reaction mixture, followed by the addition of glycine methyl amide HCl (0.33 g, 2.5 mmol) and DMAP (ca.). The reaction mixture stirred for 2h at room temperature and then diluted with acetonitrile/water (2:1 v/v) to be purified by reverse phase HPLC using a 10-90% acetonitrile in water containing 0.5% TFA (30 min) gradient at a 80 mL/min flow rate. The appropriate fractions (M+H *m/z* = 521) were collected and concentrated to a reduced volume. The resulting suspension was diluted with dichloromethane (30 mL) and washed with 5% $NaHCO_3$ (2 X 50 mL). The organic extracts were washed with water (2 X 25 mL) and dried over Na_2SO_4 (anhydrous). The organic extracts were concentrated under reduced pressure and dried *in vacuo* to afford the desired product (364.4 mg, 37%) as a white solid. ^{1}H-NMR (CD_3OD, 400 MHz) δ 8.32 (s, 1H), 7.96

01640/01/PCT

(dd, 1H, *J*= 2 Hz), 7.80 (d, 1H, *J*= 2 Hz), 7.62 (m, 1H), 7.55 (d, 1H, *J*= 8.4 Hz), 7.01 (m, 2H), 5.60 (q, 2H, *J*= 12.4 Hz), 3.98 (s, 2H), 2.74 (s, 3H), 2.20 (s, 3H); ES-HRMS *m/z* 521.0650 (M+H $C_{22}H_{20}BrF_2N_4O_4$ requires 521.0630).

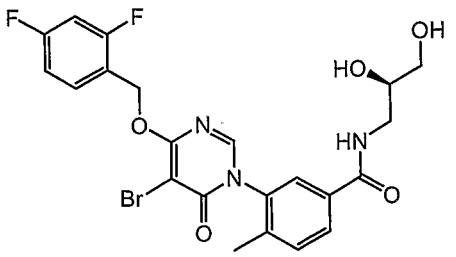
Preparation of 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N-[(2S)-2,3-dihydroxypropyl]-4-methylbenzamide.



The title compound was prepared by a procedure similar to the one described for 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-4-methyl-N-{1-[(methylamino)carbonyl]methyl}benzamide using (S)-(-)-3-amino-1, 2-propanediol (0.162 g 2.5 mmol) as the amine and without the addition of a second equivalent of N-methylmorpholine. After reverse phase HPLC purification, the organic extracts were concentrated under reduced pressure and dried *in vacuo* to afford the desired product (404.3 mg, 43%) as beige solid. ^{1}H-NMR (CD_3OD, 400 MHz) δ 8.31 (s, 1H), 7.92 (dd, 1H, *J*= 2 Hz), 7.76 (d, 1H, *J*= 1.6 Hz), 7.62 (m, 1H), 7.55 (d, 1H, *J*= 8 Hz), 7.01 (m, 2H), 5.59 (q, 2H, *J*= 12.4 Hz), 3.80 (m, 1H), 3.53 (m, 3H), 3.39 (m, 1H), 2.19 (s, 3H); ES-HRMS *m/z* 524.0630 (M+H $C_{22}H_{21}BrF_2N_3O_5$ requires 524.0627).

01640/01/PCT

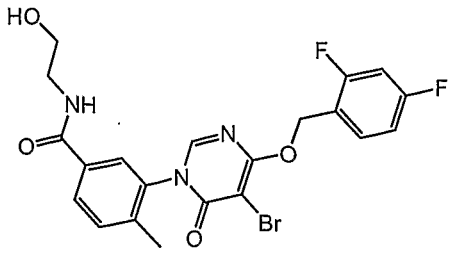
Preparation of 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N-[(2R)-2,3-dihydroxypropyl]-4-methylbenzamide.



The title compound was prepared by a procedure similar to the one described for 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-4-methyl-N-{1-[(methylamino)carbonyl]methyl}benzamide using (R)-(+)-3-amino-1, 2-propanediol (0.162 g 2.5 mmol) as the amine and without the addition of a second equivalent of N-methylmorpholine. After reverse phase HPLC purification, the organic extracts were concentrated under reduced pressure and dried *in vacuo* to afford the desired product (374.5 mg, 40%) as beige solid. ^{1}H-NMR (CD_3OD, 400 MHz) δ 8.32 (s, 1H), 7.92 (dd, 1H, *J*= 2 Hz), 7.77 (d, 1H, *J*= 2 Hz), 7.62 (m, 1H), 7.55 (d, 1H, *J*= 8.4 Hz), 7.04 (m, 2H), 5.60 (q, 2H, *J*= 12.4 Hz), 3.80 (m, 1H), 3.53 (m, 3H), 3.39 (m, 1H), 2.19 (s, 3H); ES-HRMS *m/z* 524.0649 (M+H $C_{22}H_{21}BrF_2N_3O_5$ requires 524.0627).

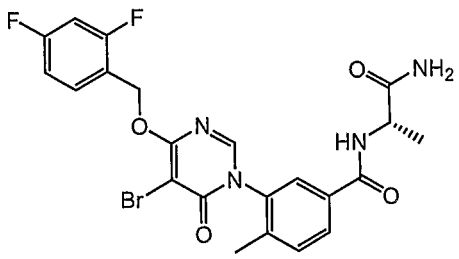
Preparation of 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N-(2-hydroxyethyl)-4-methylbenzamide.

01640/01/PCT



The title compound was prepared by a procedure similar to the one described for 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-4-methyl-N-{1-[(methylamino)carbonyl]methyl}benzamide using ethanolamine (0.16 mL 2.5 mmol) as the amine and without the addition of a second equivalent of N-methylmorpholine. After reverse phase HPLC purification, the organic extracts were concentrated under reduced pressure and dried *in vacuo* to afford the desired product (551.7 mg, 63%) as white solid. ^{1}H-NMR (CD_3OD, 400 MHz) δ 8.32 (s, 1H), 7.92 (dd, 1H, *J*= 2 Hz), 7.77 (d, 1H, *J*= 2 Hz), 7.62 (m, 1H), 7.53 (d, 1H, *J*= 8 Hz), 7.01 (m, 2H), 5.60 (q, 2H, *J*= 12.4 Hz), 3.68 (t, 2H), 3.48 (t, 2H), 2.19 (s, 3H); ES-HRMS *m/z* 494.0518 (M+H $C_{21}H_{19}BrF_2N_3O_4$ requires 494.0522).

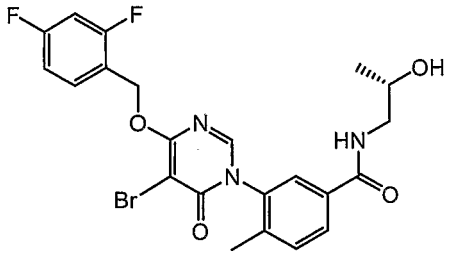
Preparation of N-[(1S)-1-(aminocarbonyl)ethyl]-3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-4-methylbenzamide.



01640/01/PCT

The title compound was prepared by a procedure similar to the one described for 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-4-methyl-N-{1-[(methylamino)carbonyl]methyl}benzamide using L-alaninamide HCl (0.33 g 2.5 mmol) as the amine. After reverse phase HPLC purification, the organic extracts were concentrated under reduced pressure and dried *in vacuo* to afford the desired product (370 mg, 40%) as beige solid. ^{1}H-NMR (CD_3OD, 400 MHz) δ 8.32 (s, 1H), 7.95 (m, 1H), 7.83 (dd, 1H, *J*= 2 Hz), 7.62 (m, 1H), 7.54 (d, 1H, *J*= 8.4 Hz), 7.01 (m, 2H), 5.60 (q, 2H, *J*= 12.4 Hz), 4.55 (m, 1H), 2.19 (s, 3H), 1.46 (dd, 3H *J*=1.2) ES-HRMS *m/z* 521.0598 (M+H $C_{22}H_{20}BrF_2N_4O_4$ requires 521.0630).

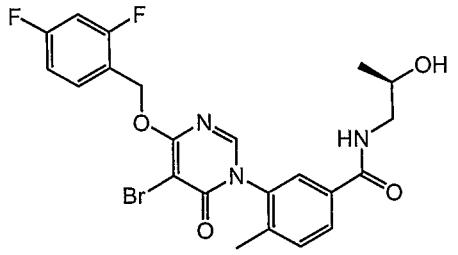
Preparation of 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N-[(2S)-2-hydroxypropyl]-4-methylbenzamide.



The title compound was prepared by a procedure similar to the one described for 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-4-methyl-N-{1-[(methylamino)carbonyl]methyl}benzamide using (S)-(+)-1-amino-2-propanol (0.16 mL 2.5 mmol) as the amine and without the addition of a second equivalent of N-methylmorpholine. After reverse phase HPLC purification, the organic extracts were concentrated under reduced pressure and dried *in vacuo* to afford the desired product (387.8 mg, 57%) as beige solid. ^{1}H-NMR (CD_3OD, 400 MHz) δ 8.32 (s, 1H), 7.92 (dd, 1H, *J*= 1.6 Hz),

7.77 (d, 1H, *J*= 2 Hz), 7.62 (m, 1H), 7.53 (d, 1H, *J*= 8.4 Hz), 7.01 (m, 2H), 5.59 (q, 2H, *J*= 12.4 Hz), 3.92 (m, 1H), 3.32 (m, 2H), 2.19 (s, 3H), 1.18 (d, 3H, *J*= 6.4 Hz); ES-HRMS *m/z* 508.0661 (M+H $C_{22}H_{21}BrF_2N_3O_4$ requires 508.0678).

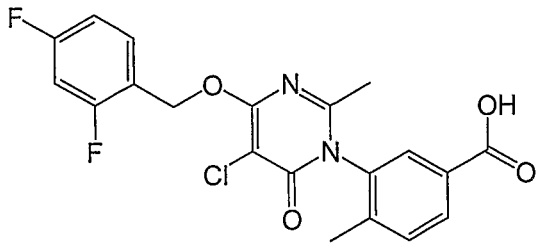
Preparation of 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-N-[(2R)-2-hydroxypropyl]-4-methylbenzamide.



The title compound was prepared by a procedure similar to the one described for 3-[5-bromo-4-[(2,4-difluorobenzyl)oxy]-6-oxopyrimidin-1(6H)-yl]-4-methyl-N-{1-[(methylamino)carbonyl]methyl}benzamide using (R)-(-)-1-amino-2-propanol (0.16 mL 2.5 mmol) as the amine and without the addition of a second equivalent of N-methylmorpholine. After reverse phase HPLC purification, the organic extracts were concentrated under reduced pressure and dried *in vacuo* to afford the desired product (377.8 mg, 55%) as beige solid. ^{1}H-NMR (CD_3OD, 400 MHz) δ 8.32 (s, 1H), 7.93 (dd, 1H, *J*= 1.6 Hz), 7.77 (d, 1H, *J*= 1.6 Hz), 7.62 (m, 1H), 7.53 (d, 1H, *J*= 8 Hz), 7.01 (m, 2H), 5.60 (q, 2H, *J*= 12.4 Hz), 3.93 (m, 1H), 3.32 (m, 2H), 2.19 (s, 3H), 1.18 (d, 3H, *J*= 6.4 Hz); ES-HRMS *m/z* 508.0687 (M+H $C_{22}H_{21}BrF_2N_3O_4$ requires 508.0678).

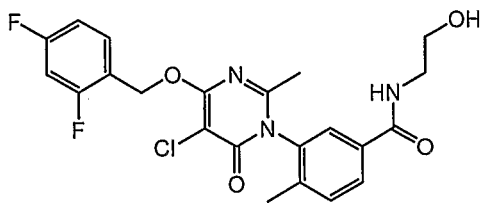
Preparation of 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoic acid.

01640/01/PCT



To a suspension of 3-[4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methylbenzoic acid (1.0 g, 2.6 mmol) in anhydrous acetonitrile (15 mL) was added N-chlorosuccinimide (0.38g, 2.9 mmol) and dichloroacetic acid (0.2 mL, 2.6 mmol). The reaction was heated in oil bath (70° C) overnight under nitrogen. The reaction mixture was concentrated under reduced pressure to remove acetonitrile. The resulting residue was washed with water for 30 min, filtered, and rinsed with water. The white solid (830 mg, 82%) was dried *in vacuo*. ^{1}H-NMR (CD_3OD, 400 MHz) δ 8.09 (dd, 1H, *J*= 1.6 Hz), 7.88 (d, 1H, *J*= 2 Hz), 7.56 (m, 2H), 7.01 (m, 2H), 5.57 (s, 2H), 2.16 (s, 3H), 2.13(s, 3H); ES-HRMS *m/z* 421.0753 (M+H $C_{20}H_{16}ClF_2N_2O_4$ requires 421.0761).

Preparation of (±) 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-(2-hydroxyethyl)-4-methylbenzamide.

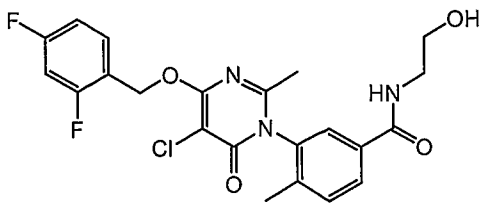


To a cold solution of 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-

methylbenzoic acid (4.0 g, 9.5 mmol) in anhydrous dimethylacetamide (20 mL, -20° C) and N-methylmorpholine (1.56 mL, 14.25 mmol) was added a solution of isobutyl chloroformate (1.84 mL, 14.25 mmol) in anhydrous dichloromethane (5 mL). The reaction mixture stirred under nitrogen atmosphere at -20° C for 10 min and then at room temperature for 30 min. At which time it was cooled back down to 0° C and ethanolamine (0.86 mL, 14.25 mmol) and DMAP (ca.) were added. The reaction mixture stirred for 30 min at 0° C, then at room temperature overnight. The solvent was removed by vacuum distillation and the residue was diluted with acetonitrile/water (1:1 v/v) to be purified by reverse phase HPLC using a 10-90% acetonitrile in water containing 0.5% TFA (30 min) gradient at a 80 mL/min flow rate. The appropriate fractions (M+H *m/z* = 464) were collected, concentrated to a reduced volume, freeze-dried and lyophilized. The resulting white solid was diluted with dichloromethane (30 mL) and washed with 5% $NaHCO_3$ (2 X 50 mL). The organic extracts were washed with water (2 X 25 mL) and dried over Na_2SO_4 (anhydrous). The organic extracts were concentrated under reduced pressure and dried *in vacuo* to afford the desired product (2.625 g, 59%) as a white solid. ^{1}H-NMR (CD_3OD, 400 MHz) δ 7.9 (dd, 1H, *J*= 2 Hz), 7.69 (d, 1H, *J*= 2 Hz), 7.62 (m, 1H), 7.55 (d, 1H, *J*= 8.4 Hz), 7.01 (m, 2H), 5.58 (q, 2H, *J*= 12.4 Hz), 3.68 (t, 2H, *J*= 5.6 Hz), 3.46 (t, 2H, *J*= 5.6 Hz), 2.17 (s, 3H), 2.12 (s, 3H); ES-HRMS *m/z* 464.1153 (M+H $C_{22}H_{21}ClF_2N_3O_4$ requires 464.1183).

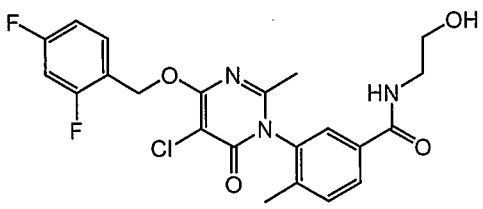
Preparation of (-) 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-(2-hydroxyethyl)-4-methylbenzamide.

01640/01/PCT



Racemic compound, (±) 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-(2-hydroxyethyl)-4-methylbenzamide (2.5 g), was resolved using a Chiralpak AD-H column, 21 X 250 mm. The sample was dissolved in EtOH (15 mg/mL). The injection volume was 4 mL and the material was eluted using EtOH with a flow rate of 10 mL/min. The fractions with (-) rotation were combined and reduced *in vacuo* to obtain the desired product (1.12g) as a white solid. ^{1}H-NMR (CD_3OD, 400 MHz) δ 7.92 (dd, 1H, *J*= 2 Hz), 7.69 (d, 1H, *J*= 2 Hz), 7.62 (m, 1H), 7.56 (d, 1H, *J*= 8.4 Hz), 7.01 (m, 2H), 5.59 (q, 2H, *J*= 12.4 Hz), 3.70 (t, 2H, *J*= 5.6 Hz), 3.48 (t, 2H, *J*= 5.6 Hz), 2.17 (s, 3H), 2.13 (s, 3H); ES-HRMS *m/z* 464.1166 (M+H $C_{22}H_{21}ClF_2N_3O_4$ requires 464.1183).

Preparation of (+) 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-(2-hydroxyethyl)-4-methylbenzamide.

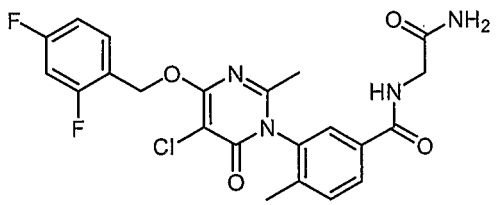


The title compound was isolated from racemic material, (±) 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-(2-hydroxyethyl)-4-methylbenzamide (2.5g) according to resolution procedure for (-) 3-[5-chloro-

01640/01/PCT

4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-(2-hydroxyethyl)-4-methylbenzamide. The fractions with (+) rotation were combined and reduced *in vacuo* to obtain the desired product (1.32g) as beige solid. ^{1}H-NMR (CD_3OD, 400 MHz) δ 7.92 (dd, 1H, *J*= 2 Hz), 7.69 (d, 1H, *J*= 2 Hz), 7.62 (m, 1H), 7.56 (d, 1H, *J*= 8.4 Hz), 7.01 (m, 2H), 5.59 (q, 2H, *J*= 12.4 Hz), 3.70 (t, 2H, *J*= 5.6 Hz), 3.48 (t, 2H, *J*= 5.6 Hz), 2.17 (s, 3H), 2.13 (s, 3H); ES-HRMS *m/z* 464.1166 (M+H $C_{22}H_{21}ClF_2N_3O_4$ requires 464.1183).

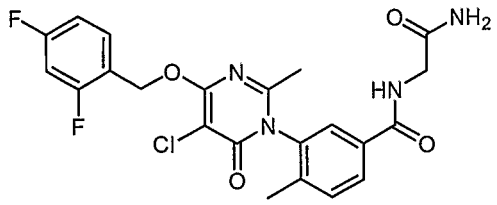
Preparation of (±) 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methyl-N-{1-[aminocarbonyl]methyl}benzamide.



The title compound was prepared by a procedure similar to the one described for (±) 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-(2-hydroxyethyl)-4-methylbenzamide using glycine amide HCl (1.2 g, 10.95 mmol) as the amine and with an addition of a second equivalent of N-methylmorpholine. After reverse phase HPLC purification, the organic extracts were concentrated under reduced pressure and dried *in vacuo* to afford the desired product (1.79 g, 52%) as white solid. ^{1}H-NMR (CD_3OD, 400 MHz) δ 7.97 (dd, 1H, *J*= 1.6 Hz), 7.73 (d, 1H, *J*= 1.6 Hz), 7.62 (m, 1H), 7.53 (d, 1H, *J*= 8 Hz), 7.01 (m, 2H), 5.59 (q, 2H, *J*= 12.4 Hz), 4.01 (d, 2H, *J*= 1.6 Hz), 2.18 (s, 3H), 2.13 (s, 3H); ES-HRMS *m/z* 477.1128 (M+H $C_{22}H_{20}ClF_2N_4O_4$ requires 477.1136).

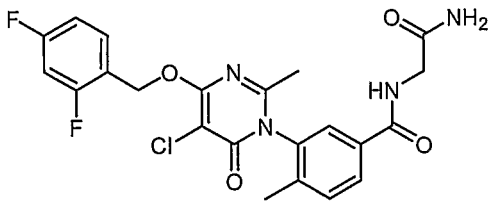
01640/01/PCT

Preparation of (-)3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methyl-N-{1-[aminocarbonyl]methyl}benzamide.



Racemic compound, (±) 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methyl-N-{1-[aminocarbonyl]methyl}benzamide (1.7 g), was resolved using a Chiralpak AD-H column, 21 X 250 mm. The sample was dissolved in MeOH (10 mg/mL). The injection volume was 4 mL and the material was eluted using EtOH/hexane (80/20 v/v) with a flow rate of 8 mL/min. The fractions with (-) rotation were combined and reduced *in vacuo* to obtain the desired product (0.50g) as beige solid. ^{1}H-NMR (CD_3OD, 400 MHz) δ 7.97 (dd, 1H, *J*= 1.6 Hz), 7.73 (d, 1H, *J*= 1.6 Hz), 7.62 (m, 1H), 7.57 (d, 1H, *J*= 8 Hz), 7.01 (m, 2H), 5.59 (q, 2H, *J*= 12.4 Hz), 4.01 (d, 2H, *J*= 1.6 Hz), 2.18 (s, 3H), 2.13 (s, 3H), ES-HRMS *m/z* 477.1141 (M+H $C_{22}H_{20}ClF_2N_4O_4$ requires 477.1136).

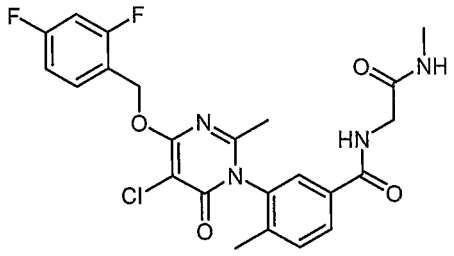
Preparation of (+) 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methyl-N-{1-[aminocarbonyl]methyl}benzamide.



01640/01/PCT

The title compound was isolated from racemic material, (±) 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methyl-N-{1-[aminocarbonyl]methyl}benzamide (1.7g) according to resolution procedure for 3-(4-(2,4-difluorobenzyloxy)-5-chloro-2-methyl-6-oxopyrimidin-1(6H)-yl)-N-(carbamoylmethyl)-4-methylbenzamide. The fractions with (+) rotation were combined and reduced *in vacuo* to obtain the desired product (0.57g) as beige solid. ^{1}H-NMR (CD_3OD, 400 MHz) δ 7.97 (dd, 1H, *J*= 1.6 Hz), 7.73 (d, 1H, *J*= 1.6 Hz), 7.62 (m, 1H), 7.57 (d, 1H, *J*= 8 Hz), 7.01 (m, 2H), 5.59 (q, 2H, *J*= 12.4 Hz), 4.01 (d, 2H, *J*= 1.6 Hz), 2.18 (s, 3H), 2.13 (s, 3H), ES-HRMS *m/z* 477.1125 (M+H $C_{22}H_{20}ClF_2N_4O_4$ requires 477.1136).

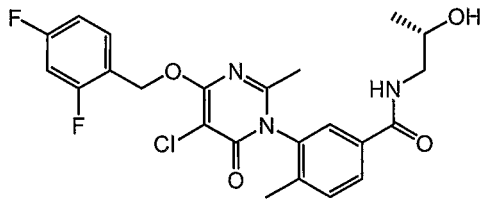
Preparation of (±) 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-4-methyl-N-{1-[(methylamino)carbonyl]methyl}benzamide.



The title compound was prepared by a procedure similar to the one described for (±) 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-(2-hydroxyethyl)-4-methylbenzamide using glycine methyl amide HCl (1.77 g, 14.25 mmol) as the amine and with an addition of a second equivalent of N-methylmorpholine. After reverse phase HPLC purification, the organic extracts were concentrated

under reduced pressure and dried *in vacuo* to afford the desired product (1.55 g, 33%) as white solid. ^{1}H-NMR (CD_3OD, 400 MHz) δ 7.97 (dd, 1H, *J*= 1.6 Hz), 7.73 (d, 1H, *J*= 1.6 Hz), 7.62 (m, 1H), 7.57 (d, 1H, *J*= 8 Hz), 7.01 (m, 2H), 5.59 (q, 2H, *J*= 12.4 Hz), 3.98 (s, 2H), 2.74 (s, 3H), 2.18 (s, 3H), 2.14 (s, 3H); ES-HRMS *m/z* 491.1262 (M+H $C_{23}H_{22}ClF_2N_4O_4$ requires 491.1292). Both (+) and (-) atropomers will be resolved and characterized.

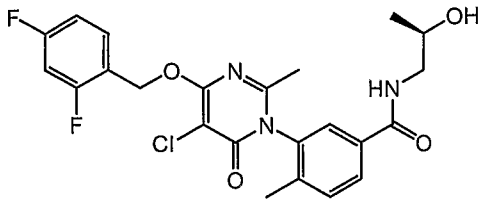
Preparation of ± 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-[(2S)-2-hydroxypropyl]-4-methylbenzamide.



The title compound was prepared by a procedure similar to the one described for (±) 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-(2-hydroxyethyl)-4-methylbenzamide using (S)-(+)-1-amnio-2-propanol (0.98 mL, 12.45 mmol) as the amine. After reverse phase HPLC purification, the organic extracts were concentrated under reduced pressure and dried *in vacuo* to afford the desired product (2.13 g, 53%) as white solid. ^{1}H-NMR (CD_3OD, 400 MHz) δ 7.93 (dd, 1H, *J*= 1.6 Hz), 7.69 (d, 1H, *J*= 1.6 Hz), 7.62 (m, 1H), 7.56 (d, 1H, *J*= 8 Hz), 7.01 (m, 2H), 5.59 (q, 2H, *J*= 12.4 Hz), 3.94 (m, 1H), 3.39 (m, 2H), 2.18 (s, 3H), 2.13 (s, 3H), 1.9 (d, 3H, *J*= 6.4 Hz); ES-HRMS *m/z* 478.1308 (M+H $C_{23}H_{23}ClF_2N_3O_4$ requires 478.1340). Both (+) and (-) atropomers will be resolved and characterized.

01640/01/PCT

Preparation of ± 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-[(2R)-2-hydroxypropyl]-4-methylbenzamide.



The title compound was prepared by a procedure similar to the one described for (±) 3-[5-chloro-4-[(2,4-difluorobenzyl)oxy]-2-methyl-6-oxopyrimidin-1(6H)-yl]-N-(2-hydroxyethyl)-4-methylbenzamide using (R)-(-)-1-amnio-2-propanol (0.98 mL, 12.45 mmol) as the amine. After reverse phase HPLC purification, the organic extracts were concentrated under reduced pressure and dried *in vacuo* to afford the desired product (2.70 g, 58%) as beige solid. ^{1}H-NMR (CD_3OD, 400 MHz) δ 7.93 (dd, 1H, *J*= 1.6 Hz), 7.69 (d, 1H, *J*= 1.6 Hz), 7.62 (m, 1H), 7.56 (d, 1H, *J*= 8 Hz), 7.01 (m, 2H), 5.59 (q, 2H, *J*= 12.4 Hz), 3.94 (m, 1H), 3.39 (m, 2H), 2.18 (s, 3H), 2.13 (s, 3H), 1.9 (d, 3H, *J*= 6.4 Hz); ES-HRMS *m/z* 478.1322 (M+H $C_{23}H_{23}ClF_2N_3O_4$ requires 478.1340). Both (+) and (-) atropomers will be resolved and characterized.

BIOLOGICAL EVALUATION

p38 Kinase Assay

Cloning of human p38a:

The coding region of the human p38a cDNA is obtained by PCR-amplification from RNA isolated from the human monocyte cell line THP.1. First strand CDNA is synthesized from total RNA as follows: 2 µg of RNA is annealed to 100 ng of random

hexamer primers in a 10 µl reaction by heating to 70° C. for 10 minutes followed by 2 minutes on ice. cDNA is then synthesized by adding 1 µl of RNAsin (Promega, Madison Wis.), 2 µl of 50 mM dNTP's, 4 µl of 5X buffer, 2 µl of 100 mM DTT and 1 µl (200 U) of Superscript II™ AMV reverse transcriptase. Random primer, dNTP's and Superscript II™ reagents are all purchased from Life-Technologies, Gaithersburg, Mass. The reaction is incubated at 42° C. for 1 hour. Amplification of p38 cDNA is performed by aliquoting 5 µl of the reverse transcriptase reaction into a 100 µl PCR reaction containing the following: 80 µl dH.sub.2 O, 2 . µl 50 mM dNTP's, 1 µl each of forward and reverse primers (50 pmol/µl), 10 µl of 10X buffer and 1 µl Expand™ polymerase (Boehringer Mannheim). The PCR primers incorporated Bam HI sites onto the 5' and 3' end of the amplified fragment, and are purchased from Genosys. The sequences of the forward and reverse primers were 5'-GATCGAGGATTCATGTCTCAGGAGAGGCCCA-3' and 5'GATCGAGGATTCTCAGGACTCCATCTCTTC-3' respectively. The PCR amplification is carried out in a DNA Thermal Cycler (Perkin Elmer) by repeating 30 cycles of 94° C. for 1 minute, 60° C. for 1 minute and 68° C. for 2 minutes. After amplification, excess primers and unincorporated dNTP's is removed from the amplified fragment with a Wizard™ PCR prep (Promega) and digested with Bam HI (New England Biolabs). The Bam HI digested fragment is ligated into BamHI digested pGEX 2T plasmid DNA (PharmaciaBiotech) using T-4 DNA ligase (New England Biolabs) as described by T. Maniatis, Molecular Cloning: A Laboratory Manual, 2nd ed. (1989). The ligation reaction is transformed into chemically competent E. coli DH10B cells purchased from Life-Technologies following the manufacturer's instructions. Plasmid DNA is isolated from the resulting bacterial colonies using a Promega Wizard™ miniprep

kit. Plasmids containing the appropriate Bam HI fragment are sequenced in a DNA Thermal Cycler (Perkin Elmer) with Prism™ (Applied Biosystems Inc.). cDNA clones are identified that coded for both human p38a isoforms (Lee et al. Nature 372, 739). One of the clones that contained the cDNA for p38a-2 (CSB-2) inserted in the cloning site of PGEX 2T, 3' of the GST coding region is designated pMON 35802. The sequence obtained for this clone is an exact match of the cDNA clone reported by Lee et al. This expression plasmid allows for the production of a GST-p38a fusion protein.

Expression of human p38a

GST/p38a fusion protein is expressed from the plasmid pMON 35802 in E. coli, stain DH10B (Life Technologies, Gibco-BRL). Overnight cultures are grown in Luria Broth (LB) containing 100 mg/ml ampicillin. The next day, 500 ml of fresh LB is inoculated with 10 ml of overnight culture, and grown in a 2 liter flask at 37° C. with constant shaking until the culture reached an absorbance of 0.8 at 600 nm. Expression of the fusion protein is induced by addition of isopropyl b-D-thiogalactosidase (IPTG) to a final concentration of 0.05 mM. The cultures are shaken for three hours at room temperature, and the cells are harvested by centrifugation. The cell pellets are stored frozen until protein purification.

Purification of P38 Kinase-alpha

All chemicals are from Sigma Chemical Co. unless noted. Twenty grams of E. coli cell pellet collected from five 1 L shake flask fermentations is resuspended in a volume of PBS (140 mM NaCl, 2.7 mM KCl, 10 mM Na.sub.2 HPO.sub.4, 1.8 mM KH.sub.2 PO.sub.4, pH 7.3) up to 200 ml. The cell suspension is adjusted to 5 mM DTT with 2 M DTT and then split equally into five 50 ml Falcon conical tubes. The cells are

sonnicated (Ultrasonics model W375) with a 1 cm probe for 3x1 minutes (pulsed) on ice. Lysed cell material is removed by centrifugation (12,000 x g, 15 minutes) and the clarified supernatant applied to glutathione-sepharose resin (Pharmacia).

Glutathione-Sepharose Affinity Chromatography

Twelve ml of a 50% glutathione sepharose-PBS suspension is added to 200 ml clarified supernatant and incubated batchwise for 30 minutes at room temperature. The resin is collected by centrifugation (600 x g, 5 min) and washed with 2 x 150 ml PBS/1% Triton X-100, followed by 4 x 40 ml PBS. To cleave the p38 kinase from the GST-p38 fusion protein, the glutathione-sepharose resin is resuspended in 6 ml PBS containing 250 units thrombin protease (Pharmacia, specific activity >7500 units/mg) and mixed gently for 4 hours at room temperature. The glutathione-sepharose resin is removed by centrifugation (600.times.g, 5 min) and washed 2 x 6 ml with PBS. The PBS wash fractions and digest supernatant containing p38 kinase protein are pooled and adjusted to 0.3 mM PMSF.

Mono Q Anion Exchange Chromatography

The thrombin-cleaved p38 kinase is further purified by FPLC-anion exchange chromatography. Thrombin-cleaved sample is diluted 2-fold with Buffer A (25 mM HEPES, pH 7.5, 25 mM beta-glycerophosphate, 2 mM DTT, 5% glycerol) and injected onto a Mono Q HR 10/10 (Pharmacia) anion exchange column equilibrated with Buffer A. The column is eluted with a 160 ml 0.1 M-0.6 M NaCl/Buffer A gradient (2 ml/minute flowrate). The p38 kinase peak eluting at 200 mM NaCl is collected and concentrated to 3-4 ml with a Filtron 10 concentrator (Filtron Corp.).

Sephacryl S100 Gel Filtration Chromatography

The concentrated Mono Q- p38 kinase purified sample is purified by gel filtration chromatography (Pharmacia HiPrep 26/60 Sephacryl S100 column equilibrated with Buffer B (50 mM HEPES, pH 7.5, 50 mM NaCl, 2 mM DTT, 5% glycerol)). Protein is eluted from the column with Buffer B at a 0.5 ml/minute flowrate and protein is detected by absorbance at 280 nm. Fractions containing p38 kinase (detected by SDS-polyacrylamide gel electrophoresis) are pooled and frozen at -80° C. Typical purified protein yields from 5 L E. coli shake flasks fermentations are 35 mg p38 kinase.

In Vitro Assay

The ability of compounds to inhibit human p38 kinase alpha is evaluated using two in vitro assay methods. In the first method, activated human p38 kinase alpha phosphorylates a biotinylated substrate, PHAS-I (phosphorylated heat and acid stable protein-insulin inducible), in the presence of gamma ^{32}P-ATP (^{32}P-ATP). PHAS-I is biotinylated prior to the assay and provides a means of capturing the substrate, which is phosphorylated during the assay. p38 Kinase is activated by MKK6. Compounds were tested in 10 fold serial dilutions over the range of 100 µM to 0.001 µM using 1% DMSO. Each concentration of inhibitor is tested in triplicate.

All reactions are carried out in 96 well polypropylene plates. Each reaction well contains 25 mM HEPES pH 7.5, 10 mM magnesium acetate and 50 µM unlabeled ATP. Activation of p38 is required to achieve sufficient signal in the assay. Biotinylated PHAS-I is used at 1-2 µg per 50 µl reaction volume, with a final concentration of 1.5 µM. Activated human p38 kinase alpha is used at 1 µg per 50 µl reaction volume representing a final concentration of 0.3 µM. Gamma ^{32}P-ATP is used to follow the phosphorylation of PHAS-I. ^{32}P-ATP has a

specific activity of 3000 Ci/mmol and is used at 1.2 µCi per 50 µl reaction volume. The reaction proceeds either for one hour or overnight at 30° C.

Following incubation, 20 µl of reaction mixture is transferred to a high capacity streptavidin coated filter plate (SAM-streptavidin-matrix, Promega) prewetted with phosphate buffered saline. The transferred reaction mix is allowed to contact the streptavidin membrane of the Promega plate for 1-2 minutes. Following capture of biotinylated PHAS-I with ^{32}P incorporated, each well is washed to remove unincorporated ^{32}P-ATP three times with 2M NaCl, three washes of 2M NaCl with 1% phosphoric, three washes of distilled water and finally a single wash of 95% ethanol. Filter plates are air-dried and 20 µl of scintillant is added. The plates are sealed and counted.

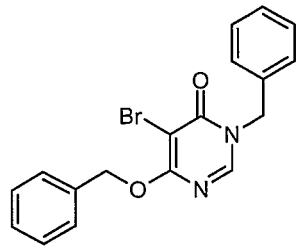
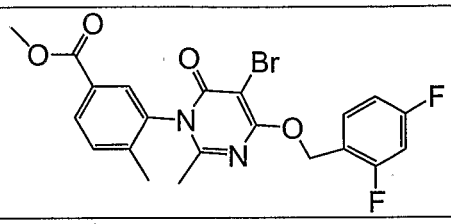
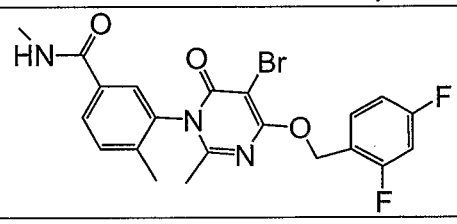
A second assay format is also employed that is based on p38 kinase alpha induced phosphorylation of EGFRP (epidermal growth factor receptor peptide, a 21 mer) in the presence ^{33}P-ATP. Compounds are tested in 10 fold serial dilutions over the range of 100 µM to 0.001 µM in 1% DMSO. Each concentration of inhibitor is tested in triplicate. Compounds were evaluated in 50 µl reaction volumes in the presence of 25 mM Hepes pH 7.5, 10 mM magnesium acetate, 4% glycerol, 0.4% bovine serum albumin, 0.4mM DTT, 50 µM unlabeled ATP, 25 µg EGFRP (200 µM), and 0.05 µCi ^{33}P-ATP. Reactions are initiated by addition of 0.09 µg of activated, purified human GST-p38 kinase alpha. Activation is carried out using GST-MKK6 (5:1,p38:MKK6) for one hour at 30° C. in the presence of 50 µM ATP. Following incubation for 60 minutes at room temperature, the reaction is stopped by addition of 150 µl of AG 1 x 8 resin in 900 mM sodium formate buffer, pH 3.0 (1 volume resin to 2 volumes buffer). The mixture is mixed three times with pipetting and

the resin is allowed to settle. A total of 50 µl of clarified solution head volume is transferred from the reaction wells to Microlite-2 plates. 150 µl of Microscint 40 is then added to each well of the Microlite plate, and the plate is sealed, mixed, and counted.

Preferred compounds of the invention exhibit IC50 values of 25 micromolar or less. More preferred compounds of the invention exhibit IC50 values of 10 micromolar or less. Even more preferred compounds of the invention exhibit IC50 values of 5 micromolar or less. Especially preferred compounds of the invention exhibit IC50 values of 1 micromolar or less.

Some representative examples with IC50 values are shown below.

01640/01/PCT

Structure	p38 Alpha Avg. IC50 (uM)
	<5.00
	<5.00
	<5.00

TNF Cell Assays

Method of Isolation of Human Peripheral Blood Mononuclear Cells:

Human whole blood is collected in Vacutainer tubes containing EDTA as an anticoagulant. A blood sample (7 ml) is carefully layered over 5 ml PMN Cell Isolation Medium (Robbins Scientific) in a 15 ml round bottom centrifuge tube. The sample is centrifuged at 450-500 x g for 30-35 minutes in a swing out rotor at room temperature. After centrifugation, the top band of cells are removed and washed 3 times with PBS w/o calcium or magnesium. The cells are centrifuged at 400 times gravity for 10 minutes at room temperature. The cells are resuspended in Macrophage Serum Free Medium (Gibco BRL) at a concentration of 2 million cells/mi.

LPS Stimulation of Human PBMs

PBM cells (0.1 ml, 2 million/ ml) are co-incubated with 0.1 ml compound (10-0.41 µM, final concentration) for 1 hour in flat bottom 96 well microtiter plates. Compounds are dissolved in DMSO initially and diluted in TCM for a final concentration of 0.1% DMSO. LPS (Calbiochem, 20 ng/ml, final concentration) is then added at a volume of 0.010 ml. Cultures are incubated overnight at 37° C. Supernatants are then removed and tested by ELISA for TNF-a and IL1-b. Viability is analyzed using MTS. After 0.1 ml supernatant is collected, 0.020 ml MTS is added to remaining 0.1 ml cells. The cells are incubated at 37° C. for 2-4 hours, then the O.D. is measured at 490-650 nM.

Maintenance and Differentiation of the U937 Human Histiocytic Lymphoma Cell Line

U937 cells (ATCC) are propagated in RPMI 1640 containing 10% fetal bovine serum, 100 IU/ml penicillin, 100 µg/ml streptomycin, and 2 mM glutamine (Gibco). Fifty million cells in 100 ml media are induced to terminal monocytic differentiation by 24 hour incubation with 20 ng/ml phorbol 12-myristate 13-acetate (Sigma). The cells are washed by centrifugation (200 x g for 5 min) and resuspended in 100 ml fresh medium. After 24-48 hours, the cells are harvested, centrifuged, and resuspended in culture medium at 2 million cells/ml.

LPS Stimulation of TNF production by U937 Cells

U937 cells (0.1 ml, 2 million/ml) are incubated with 0.1 ml compound (0.004-50 µM, final concentration) for 1 hour in 96 well microtiter plates. Compounds are prepared as 10 mM stock solutions in DMSO and diluted in culture medium to yield a final DMSO concentration of 0.1% in the cell assay. LPS (E

coli, 100 ng/ml final concentration) is then added at a volume of 0.02 ml. After 4 hour incubation at 37° C., the amount of TNF-alpha released in the culture medium is quantitated by ELISA. Inhibitory potency is expressed as IC50 (μM).

Rat Assay

The efficacy of the novel compounds in blocking the production of TNF also is evaluated using a model based on rats challenged with LPS. Male Harlen Lewis rats [Sprague Dawley Co.] are used in this model. Each rat weighed approximately 300 g and is fasted overnight prior to testing. Compound administration is typically by oral gavage (although intraperitoneal, subcutaneous and intravenous administration are also used in a few instances) 1 to 24 hours prior to the LPS challenge. Rats are administered 30 μg/kg LPS [salmonella typhosa, Sigma Co.] intravenously via the tail vein. Blood is collected via heart puncture 1 hour after the LPS challenge. Serum samples are stored at -20° C. until quantitative analysis of TNF-alpha by Enzyme Linked-Immuno-Sorbent Assay ("ELISA") [Biosource]. Additional details of the assay are set forth in Perretti, M., et al., Br. J. Pharmacol. (1993), 110, 868-874, which is incorporated by reference in this application.

Mouse Assay

Mouse Model of LPS-Induced TNF Alpha Production

TNF alpha is induced in 10-12 week old BALB/c female mice by tail vein injection with 100 ng lipopolysaccharide (from S. Typhosa) in 0.2 ml saline. One hour later mice are bled from the retroorbital sinus and TNF concentrations in serum from clotted blood are quantified by ELISA. Typically, peak levels of serum TNF ranged from 2-6 ng/ml one hour after LPS injection.

The compounds tested are administered to fasted mice by oral gavage as a suspension in 0.2 ml of 0.5% methylcellulose and 0.025% Tween 20 in water at 1 hour or 6 hours prior to LPS injection. The 1 hour protocol allows evaluation of compound potency at Cmax plasma levels whereas the 6 hour protocol allows estimation of compound duration of action. Efficacy is determined at each time point as percent inhibition of serum TNF levels relative to LPS injected mice that received vehicle only.

Induction and Assessment of Collagen-Induced Arthritis in Mice

Arthritis is induced in mice according to the procedure set forth in J. M. Stuart, Collagen Autoimmune Arthritis, Annual Rev. Immunol. 2:199 (1984), which is incorporated herein by reference. Specifically, arthritis is induced in 8-12 week old DBA/1 male mice by injection of 50 µg of chick type II collagen (CII) (provided by Dr. Marie Griffiths, Univ. of Utah, Salt Lake City, Utah) in complete Freund's adjuvant (Sigma) on day 0 at the base of the tail. Injection volume is 100 µl. Animals are boosted on day 21 with 50 µg of CII in incomplete Freund's adjuvant (100 µl volume). Animals are evaluated several times each week for signs of arthritis. Any animal with paw redness or swelling is counted as arthritic. Scoring of arthritic paws is conducted in accordance with the procedure set forth in Wooley et al., Genetic Control of Type II Collagen Induced Arthritis in Mice: Factors Influencing Disease Suspectibility and Evidence for Multiple MHC Associated Gene Control., Trans. Proc., 15:180 (1983). Scoring of severity is carried out using a score of 1-3 for each paw (maximal score of 12/mouse). Animals displaying any redness or swelling of digits or the paw are scored as 1. Gross swelling of the whole paw or deformity is scored as 2.

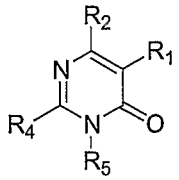
Ankylosis of joints is scored as 3. Animals are evaluated for 8 weeks. 8-10 animals per group are used.

The invention and the manner and process of making and using it, are now described in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same. It is to be understood that the foregoing describes preferred embodiments of the invention and that modifications may be made therein without departing from the spirit or scope of the invention as set forth in the claims. To particularly point out and distinctly claim the subject matter regarded as invention, the following claims conclude this specification.

01640/01/PCT

What is claimed is:

1. A compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein

R_1 is H, halogen, NO_2, alkyl, carboxaldehyde, hydroxyalkyl, dihydroxyalkyl, arylalkoxy, arylalkyl, alkenyl, alkynyl, arylalkynyl, -CN, aryl, alkanoyl, alkoxy, alkoxyalkyl, haloalkyl, haloalkoxy, carboxyl, or arylalkanoyl,

wherein the aryl portion of arylalkoxy, arylalkyl, and arylalkanoyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, nitro, CN, haloalkyl, haloalkoxy or CO_2R;

wherein the alkyl portion of the alkyl, hydroxyalkyl, dihydroxyalkyl, arylalkoxy, arylalkyl, alkanoyl, alkoxy, alkoxyalkyl and arylalkanoyl groups is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, C_1-C_4 alkoxy, C_1-C_4 alkoxycarbonyl, or C_3-C_7 cycloalkyl;

R_2 is H, OH, halogen, $-OSO_2-(C_1-C_6)$ alkyl, $-OSO_2$-aryl, arylalkoxy, aryloxy, arylthio, arylthioalkoxy, arylalkynyl, alkoxy, aryloxy(C_1-C_6)alkyl, alkyl, alkynyl, $-OC(O)NH(CH_2)_n$aryl, $-OC(O)N(alkyl)(CH_2)_n$aryl, alkoxyalkoxy, dialkylamino, alkyl, alkoxy, aryl, arylalkyl, heteroaryl, heteroarylalkyl, arylalkenyl, heterocycloalkyl, heterocycloalkylalkyl, alkoxyalkoxy, NR_8R_9, dialkylamino, or CO_2R, wherein

n is 0, 1, 2, 3, 4, 5 or 6;

each of which groups is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently

halogen, -(C_1-C_6)alkyl-N(R)-CO_2R_{30}, haloalkyl, heteroaryl, heteroarylalkyl, -NR_6R_7, R_6R_7N-(C_1-C_6 alkyl)-, -C(O)NR_6R_7, -(C_1-C_4)alkyl-C(O)NR_6R_7, -(C_1-C_4 alkyl)-NRC(O)$NR_{16}R_{17}$, haloalkoxy, alkyl, CN, hydroxyalkyl, dihydroxyalkyl, alkoxy, alkoxycarbonyl, phenyl, -SO_2-phenyl wherein the phenyl and -SO_2-phenyl groups are optionally substituted with 1, 2, or 3 groups that are independently halogen or NO_2, or -OC(O)NR_6R_7, wherein R_{16} and R_{17} are independently H or C_1-C_6 alkyl; or

R_{16}, R_{17} and the nitrogen to which they are attached form a morpholinyl ring;

R_6 and R_7 are independently at each occurrence H, alkyl, hydroxyalkyl, dihydroxyalkyl, alkoxy, alkanoyl, arylalkyl, arylalkoxy, alkoxycarbonyl, -SO_2-alkyl, OH, alkoxy, alkoxyalkyl, arylalkoxycarbonyl, -(C_1-C_4)alkyl-CO_2-alkyl, heteroarylalkyl, or arylalkanoyl, wherein each is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, OH, SH, heterocycloalkyl, heterocycloalkylalkyl, C_3-C_7 cycloalkyl, alkoxy, NH_2, NH(alkyl), N(alkyl)(alkyl), -O-alkanoyl, alkyl, haloalkyl, carboxaldehyde, or haloalkoxy; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, pyrrolidinyl, thiomorpholinyl, thiomorpholinyl S-oxide, thiomorpholinyl S,S-dioxide, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, alkoxycarbonyl,

C_1-C_4 alkoxy, hydroxyl, hydroxyalkyl, dihydroxyalkyl, or halogen;

R at each occurrence is independently hydrogen or C_1-C_6 alkyl optionally substituted with 1 or 2 groups that are independently OH, SH, halogen, amino, monoalkylamino, dialkylamino or C_3-C_6 cycloalkyl;

R_{30} is C_1-C_6 alkyl optionally substituted with 1 or 2 groups that are independently OH, SH, halogen, amino, monoalkylamino, dialkylamino or C_3-C_6 cycloalkyl;

each R_8 is independently hydrogen, alkyl, alkanoyl, arylalkyl and arylalkanoyl, wherein each of the above is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, alkoxy, alkoxycarbonyl, halogen, or haloalkyl;

each R_9 is hydrogen, alkyl, alkanoyl, arylalkyl, cycloalkyl, cycloalkylalkyl, alkenyl, heteroaryl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, arylalkanoyl, -SO_2-phenyl, and aryl wherein each of the above is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, alkoxy, alkoxycarbonyl, halogen, or haloalkyl;

R_4 is hydrogen or R_4 is alkyl unsubstituted or substituted with one or two groups that are independently CO_2R, -CO_2-(C_1-C_6)alkyl, -$C(O)NR_6R_7$, -$C(O)R_6$, -$N(R_{30})C(O)NR_{16}R_{17}$, -$N(R_{30})C(O)$-($C_1$-$C_6$)alkoxy, or -$NR_6R_7$, arylalkoxy, arylalkyl, heteroaryl, heteroarylalkyl, hydroxyalkyl, dihydroxyalkyl, haloalkyl, R_6R_7N-(C_1-C_6 alkyl)-, -NR_6R_7, alkoxy, hydroxyalkoxy-, (R_6R_7N)-alkoxy-, $R_6R_7NC(O)$-alkoxy-, $R_6C(O)N(R_7)$alkoxy-, carboxaldehyde, -$C(O)NR_6R_7$, CO_2R, alkoxyalkyl, or alkoxyalkoxy, wherein the heteroaryl or

aryl portions of is the above are unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, hydroxy, alkoxy, alkyl, $-CO_2-(C_1-C_6)$alkyl, $-CONR_6R_7$, $-NR_6R_7$, $R_6R_7N-(C_1-C_6)$alkyl-, nitro, haloalkyl, or haloalkoxy; and

R_5 is H, aryl, arylalkyl, arylthioalkyl, alkyl optionally substituted with 1, 2, or 3 groups that are independently arylalkoxycarbonyl, $-NR_8R_9$, halogen, $-C(O)NR_8R_9$, alkoxycarbonyl, C_3-C_7 cycloalkyl, or alkanoyl, alkoxy, alkoxyalkyl optionally substituted with one trimethylsilyl group, amino, alkoxycarbonyl, hydroxyalkyl, dihydroxyalkyl, alkynyl, $-SO_2$-alkyl, alkoxy optionally substituted with one trimethylsilyl group, heterocycloalkylalkyl, cycloalkyl, cycloalkylalkyl, -alkyl-S-aryl, -alkyl-SO_2-aryl, heteroarylalkyl, heterocycloalkyl, heteroaryl, or alkenyl optionally substituted with alkoxycarbonyl, wherein

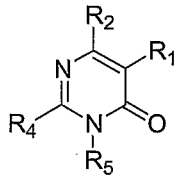
each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, halogen, alkoxy, hydroxyalkyl, dihydroxyalkyl, arylalkoxy, thioalkoxy, alkoxycarbonyl, arylalkoxycarbonyl, CO_2R, CN, OH, hydroxyalkyl, dihydroxyalkyl, amidinooxime, $-NR_6R_7$, $-NR_8R_9$, $R_6R_7N-(C_1-C_6$ alkyl)-, carboxaldehyde, SO_2alkyl, $-SO_2H$, $-SO_2NR_6R_7$, alkanoyl wherein the alkyl portion is optionally substituted with OH, halogen or alkoxy, $-C(O)NR_6R_7$, $-(C_1-C_4$ alkyl)$-C(O)NR_6R_7$, amidino, haloalkyl, $-(C_1-C_4$ alkyl)$-NR_{15}C(O)NR_{16}R_{17}$, $-(C_1-C_4$ alkyl)$-NR_{15}C(O)R_{18}$, $-O-CH_2-O$, $-O-CH_2CH_2-O-$, or haloalkoxy; wherein

R_{15} is H or C_1-C_6 alkyl; and

R_{18} is C_1-C_6 alkyl optionally substituted with $-O-(C_2-C_6$ alkanoyl, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl,

C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl; amino C_1-C_6 alkyl, mono or dialkylamino C_1-C_6 alkyl.

2. A compound according to claim 1, of the formula:



or a pharmaceutically acceptable salt thereof, wherein

R_1 is H, halogen, alkyl, carboxaldehyde, hydroxyalkyl, dihydroxyalkyl, arylalkoxy, arylalkyl, alkenyl, alkynyl, arylalkynyl, CN, alkanoyl, alkoxy, alkoxyalkyl, haloalkyl, carboxyl, or arylalkanoyl,

wherein the aryl portion of arylalkoxy, arylalkyl, and arylalkanoyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, nitro, CN, haloalkyl, haloalkoxy or CO_2R;

wherein the alkyl portion of the alkyl, hydroxyalkyl, dihydroxyalkyl, arylalkoxy, arylalkyl, alkanoyl, alkoxy, alkoxyalkyl and arylalkanoyl groups is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, C_1-C_4 alkoxy, C_1-C_4 alkoxycarbonyl, or cyclopropyl;

R_2 is H, OH, halogen, $-OSO_2-(C_1-C_6)$ alkyl, $-OSO_2$-aryl, arylalkoxy, aryloxy, arylthioalkoxy, arylalkynyl, alkoxy, phenyloxy(C_1-C_6)alkyl, $-OC(O)NH(CH_2)_n$aryl, $-OC(O)N(alkyl)(CH_2)_n$aryl, alkyl, alkynyl, alkoxyalkoxy, dialkylamino, heteroaryl, heterocycloalkyl, aryloxyalkyl, or CO_2R, wherein

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, $-NR_6R_7$, haloalkyl, haloalkoxy, alkyl, heteroaryl,

heteroarylalkyl, -(C_1-C_4)alkyl-C(O)NR_6R_7, R_6R_7N-(C_1-C_6 alkyl)-, -C(O)NR_6R_7, -(C_1-C_4 alkyl)-NRC(O)$NR_{16}R_{17}$, CN, hydroxyalkyl, dihydroxyalkyl, -OC(O)NR_6R_7, or -(C_1-C_6)alkyl-N(R)-CO_2R_{30}, wherein

R_{16} and R_{17} are independently H or C_1-C_6 alkyl; or

R_{16}, R_{17} and the nitrogen to which they are attached form a morpholinyl ring;

R_6 and R_7 are independently at each occurrence H, alkyl, hydroxyalkyl, dihydroxyalkyl, alkoxy, alkoxyalkyl, alkanoyl, arylalkyl, arylalkoxy, arylalkoxycarbonyl, or arylalkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, alkoxy, alkyl, OH, SH, carboxaldehyde, haloalkyl, or haloalkoxy; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, thiomorpholinyl S-oxide, thiomorpholinyl S,S-dioxide, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, dihydroxyalkyl, or halogen;

n is 0, 1, 2, 3, 4, 5 or 6;

R at each occurrence is independently H or C_1-C_6 alkyl optionally substituted with 1 or 2 groups that are independently OH, SH, halogen, amino, monoalkylamino, dialkylamino or C_3-C_6 cycloalkyl;

R_{30} is C_1-C_6 alkyl optionally substituted with 1 or 2 groups that are independently OH, SH, halogen, amino, monoalkylamino, dialkylamino or C_3-C_6 cycloalkyl;

R_4 is H, alkyl optionally substituted with one or two groups that are independently CO_2R, $-CO_2$alkyl, $-C(O)NR_6R_7$, $-C(O)R_6$, $-N(R_{30})C(O)NR_{16}R_{17}$, $-N(R_{30})C(O)-(C_1-C_6)$alkoxy, or $-NR_6R_7$, arylalkoxy, heteroaryl, arylalkyl, hydroxyalkyl, dihydroxyalkyl, haloalkyl, $-NR_6R_7$, $-C(O)NR_6R_7$, alkoxy, hydroxyalkoxy-, (R_6R_7N)-alkoxy-, $R_6R_7NC(O)$-alkoxy-, $R_6C(O)N(R_7)$alkoxy-, alkoxyalkyl, or alkoxyalkoxy, wherein the heteroaryl or aryl portions of the above are unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, hydroxy, alkoxy, alkyl, $-CO_2-(C_1-C_6)$alkyl, $-CONR_6R_7$, $-NR_6R_7$, $R_6R_7N-(C_1-C_6)$alkyl-, nitro, haloalkyl, or haloalkoxy; and

R_5 is H, arylalkyl, alkyl optionally substituted with 1, 2, or 3 groups that are independently arylalkoxycarbonyl, $-NR_8R_9$, halogen, $-C(O)NR_8R_9$, alkoxycarbonyl, or alkanoyl, alkoxyalkyl optionally substituted with one trimethylsilyl group, alkoxycarbonyl, amino, hydroxyalkyl, dihydroxyalkyl, alkenyl optionally substituted with alkoxycarbonyl, alkynyl, $-SO_2$-alkyl, aryl, alkoxy optionally substituted with one trimethylsilyl group, heterocycloalkylalkyl, heteroarylalkyl, heterocycloalkyl, or heteroaryl, wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, halogen, alkoxy, arylalkoxy, hydroxyalkyl, dihydroxyalkyl, thioalkoxy, $-SO_2$alkyl, alkoxycarbonyl, arylalkoxycarbonyl, CO_2R, CN, OH, amidinooxime, NR_8R_9, $R_6R_7N-(C_1-C_6$ alkyl)-, $-C(O)NR_6R_7$, amidino, hydroxyalkyl, dihydroxyalkyl, carboxaldehyde, $-NR_6R_7$, haloalkyl, $-(C_1-C_4$ alkyl)-$C(O)NR_6R_7$, $-(C_1-C_4$ alkyl)-CO_2R, $-(C_1-C_4$ alkyl)-C_1-C_6 alkoxycarbonyl, $-(C_1-C_4$ alkyl)-CN, $-(C_1-C_4$ alkyl)-

$NR_{15}C(O)R_{18}$, $-O-CH_2-O-$, $-O-CH_2CH_2-O-$, phenyl or haloalkoxy;

R_8 is hydrogen, alkyl, alkanoyl, arylalkyl and arylalkanoyl;

R_9 is alkyl, alkanoyl, arylalkyl, heteroaryl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, and arylalkanoyl.

3. A compound according to claim 2 wherein

R_1 is H, halogen, alkyl optionally substituted with C_1-C_4 alkoxycarbonyl, carboxaldehyde, hydroxyalkyl, dihydroxyalkyl, phenyl(C_1-C_6)alkoxy, phenyl(C_1-C_6)alkyl, CN, alkanoyl, alkoxy, C_2-C_4 alkynyl, C_2-C_6 alkenyl optionally substituted with C_1-C_4 alkoxycarbonyl, alkoxyalkyl, haloalkyl, or phenyl(C_1-C_6)alkanoyl,

wherein the phenyl groups are unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, nitro, CN, CF_3, OCF_3 or CO_2R;

wherein the alkyl groups are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, methoxy, or ethoxy;

R_2 is OH, phenyl(C_1-C_6)alkoxy, phenyloxy, phenyloxy(C_1-C_6)alkyl, phenyl (C_1-C_4) thioalkoxy, C_1-C_8 alkoxy, alkoxyalkoxy, $-O-SO_2$phenyl, alkynyl, phenyl (C_2-C_4) alkynyl, alkyl, $-OC(O)NH(CH_2)_n$phenyl, $-OC(O)N$(alkyl)$(CH_2)_n$phenyl, dialkylamino, pyridyl, pyrimidyl, pyridazyl, pyrazolyl, imidazolyl, pyrrolyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, tetrazolyl, pyrazinyl, benzimidazolyl, triazinyl, tetrahydrofuryl, piperidinyl, hexahydropyrimidinyl, thiazolyl, thienyl, or CO_2R, wherein n is 0, 1, 2, 3, 4, 5 or 6;

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, NR_6R_7, haloalkyl, haloalkoxy, hydroxyalkyl, dihydroxyalkyl, alkyl, phenyl, pyridyl, piperidinyl, piperazinyl, $-(C_1-C_6)alkyl-N(R)-CO_2R_{30}$, $R_6R_7N-(C_1-C_6$ alkyl)-, $-C(O)NR_6R_7$, $-(C_1-C_4)alkyl-C(O)NR_6R_7$, $-(C_1-C_4$ alkyl)$-NRC(O)NR_{16}R_{17}$, or $-OC(O)NR_6R_7$, wherein

R_6 and R_7 are independently at each occurrence H, alkyl, (C_1-C_4) hydroxyalkyl, (C_1-C_4) dihydroxyalkyl, (C_1-C_4) alkoxy, (C_1-C_4) alkoxy (C_1-C_4) alkyl, (C_1-C_4) alkanoyl, phenyl (C_1-C_4) alkyl, phenyl (C_1-C_4) alkoxy, phenyl (C_1-C_4) alkoxycarbonyl, or phenyl (C_1-C_4) alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, OH, SH, C_3-C_6 cycloalkyl, (C_1-C_4) alkoxy, (C_1-C_4) alkyl, CF_3, carboxaldehyde, NH_2, $NH(C_1-C_6)alkyl$, $N(C_1-C_6)alkyl$ $(C_1-C_6)alkyl$, OCF_3; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, hydroxy, hydroxy C_1-C_4 alkyl, C_1-C_4 dihydroxyalkyl, C_1-C_4 alkoxycarbonyl, or halogen; and

R_4 is H, alkyl optionally substituted with one or two groups that are independently CO_2R, $-CO_2alkyl$, $-C(O)NR_6R_7$, $-C(O)R_6$, $-N(R_{30})C(O)NR_{16}R_{17}$, $-N(R_{30})C(O)-(C_1-C_6)alkoxy$, or $-NR_6R_7$, arylalkoxy, heteroaryl, arylalkyl, hydroxyalkyl, dihydroxyalkyl, haloalkyl, $-NR_6R_7$, $-C(O)NR_6R_7$, alkoxy,

hydroxyalkoxy-, (R_6R_7N)-alkoxy-, $R_6R_7NC(O)$-alkoxy-, $R_6C(O)N(R_7)$alkoxy-, alkoxyalkyl, or alkoxyalkoxy, wherein the heteroaryl or aryl portions of the above are unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, hydroxy, alkoxy, alkyl, $-CO_2-(C_1-C_6)$alkyl, $-CONR_6R_7$, $-NR_6R_7$, $R_6R_7N-(C_1-C_6)$alkyl-, nitro, haloalkyl, or haloalkoxy; and

R_5 is phenyl(C_1-C_6)alkyl, (C_1-C_6)alkyl optionally substituted with 1, 2, 3, 4, or 5 groups that are independently phenyl C_1-C_4 alkoxycarbonyl, $-NR_8R_9$, halogen, $-C(O)NR_8R_9$, alkoxycarbonyl, or alkanoyl, phenyl, alkoxy, C_2-C_6 alkynyl, C_2-C_6 alkenyl optionally substituted with alkoxycarbonyl, indolyl, quinolinyl, isoquinolinyl, isoindolyl, dihydroindolyl, pyrazolyl, imidazolyl, dihydroisoindolyl, indolon-2-yl, indazolyl, benzimidazolyl, pyridyl, imidazolidine dione, pyrazolyl$(C_1-C_6$ alkyl), imidazolyl$(C_1-C_6$ alkyl), piperidinyl(C_1-C_6)alkyl, pyrrolidinyl(C_1-C_6)alkyl, imidazolidinyl(C_1-C_6)alkyl, tetrahydroisoquinolinyl(C_1-C_6)alkyl, 1H-indazolyl(C_1-C_6)alkyl, dihydroindolon-2-yl$(C_1-C_6$ alkyl), indolinyl$(C_1-C_6$ alkyl), dihydrobenzimidazolyl$(C_1-C_6$ alkyl), or dihydrobenzoimidazolonyl$(C_1-C_6$ alkyl), pyridyl (C_1-C_6) alkyl, pyridazinyl (C_1-C_6) alkyl, pyrimidinyl (C_1-C_6) alkyl, pyrazinyl (C_1-C_6) alkyl, tetrahydrofuryl(C_1-C_6)alkyl, naphthyl(C_1-C_6)alkyl, morpholinyl (C_1-C_6) alkyl, tetrahydrofuryl (C_1-C_6) alkyl, thienyl (C_1-C_6) alkyl, piperazinyl (C_1-C_6) alkyl, indolyl (C_1-C_6) alkyl, quinolinyl(C_1-C_6) alkyl, isoquinolinyl(C_1-C_6) alkyl, isoindolyl(C_1-C_6) alkyl, dihydroindolyl(C_1-C_6) alkyl, pyrazolyl(C_1-C_4) alkyl, imidazolyl(C_1-C_4) alkyl, dihydroisoindolyl(C_1-C_6) alkyl, indoon-2-yl(C_1-C_6) alkyl,

indolon-2-yl(C_1-C_6) alkyl, or morpholinyl C_1-C_6 alkyl, wherein

each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, halogen, C_1-C_6 alkoxy, phenyl C_1-C_6 alkoxy, C_1-C_6 thioalkoxy, C_1-C_6 alkoxycarbonyl, CO_2R, CN, $-SO_2(C_1$-$C_6)$alkyl, amidinooxime, NR_8R_9, $-NR_6R_7$, NR_6R_7 C_1-C_6 alkyl, $-C(O)NR_6R_7$, $-(C_1$-$C_4)$alkyl-$C(O)NR_6R_7$, amidino, C_1-C_4 haloalkyl, hydroxy C_1-C_6 alkyl, C_1-C_6 dihydroxyalkyl, or C_1-C_4 haloalkoxy; wherein

R_8 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkanoyl, phenyl C_1-C_6 alkyl and phenyl C_1-C_6 alkanoyl; and

R_9 is aminoalkyl, mono C_1-C_6 alkylamino C_1-C_6 alkyl, di C_1-C_6 alkylamino C_1-C_6 alkyl, C_1-C_6 alkyl, C_1-C_6 alkanoyl, phenyl C_1-C_6 alkyl, indazolyl, and phenyl C_1-C_6 alkanoyl.

4. A compound according to claim 3, wherein

R_1 is H, halogen, C_1-C_4 alkyl optionally substituted with C_1-C_4 alkoxycarbonyl, C_2-C_4 alkenyl optionally substituted with C_1-C_4 alkoxycarbonyl, C_2-C_4 alkynyl, or carboxaldehyde;

R_2 is benzyloxy, OH, phenyloxy, phenyloxy(C_1-C_6)alkyl, phenyl (C_1-C_4) thioalkoxy, or pyridyl; wherein each of the above is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, $-(C_1$-$C_6)$alkyl-$N(R)$-CO_2R_{30}, NR_6R_7, $-(C_1$-$C_4)$alkyl-$C(O)NR_6R_7$, (C_1-C_4) haloalkyl, $-C(O)NR_6R_7$, $-(C_1$-C_4 alkyl)-$NRC(O)NR_{16}R_{17}$, (C_1-C_4) haloalkoxy, hydroxyalkyl, C_1-C_6 dihydroxyalkyl, (C_1-C_6) alkyl, pyridyl, or R_6R_7N-(C_1-C_6 alkyl)-.

5. A compound according to claim 4, wherein

R_5 is pyrazolyl(C_1-C_6 alkyl), imidazolyl(C_1-C_6 alkyl), thienyl(C_1-C_6 alkyl), furanyl(C_1-C_6 alkyl), piperidinyl(C_1-C_6)alkyl, pyrrolidinyl(C_1-C_6)alkyl, imidazolidinyl(C_1-C_6)alkyl, piperazinyl(C_1-C_6)alkyl, pyridyl(C_1-C_6)alkyl, pyrimidyl(C_1-C_6)alkyl, pyridazyl(C_1-C_6)alkyl, pyrazinyl(C_1-C_6)alkyl, isoquinolinyl(C_1-C_6)alkyl, tetrahydroisoquinolinyl(C_1-C_6)alkyl, indolyl(C_1-C_6)alkyl, 1H-indazolyl(C_1-C_6)alkyl, dihydroindolyl(C_1-C_6 alkyl), dihydroindolon-2-yl(C_1-C_6 alkyl), indolinyl(C_1-C_6 alkyl), dihydroisoindolyl(C_1-C_6 alkyl), dihydrobenzimdazolyl(C_1-C_6 alkyl), or dihydrobenzoimidazolonyl(C_1-C_6 alkyl), wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently (C_1-C_6)alkyl, halogen, (C_1-C_6)alkoxy, (C_1-C_6)hydroxyalkyl, C_1-C_6 dihydroxyalkyl, phenyl(C_1-C_6)alkoxy, (C_1-C_6)thioalkoxy, (C_1-C_6)alkoxycarbonyl, phenyl(C_1-C_6)alkoxycarbonyl, OH, CO_2R, CN, amidinooxime, $-NR_8R_9$, $-NR_6R_7$, R_6R_7N-(C_1-C_6 alkyl)-, $-C(O)NR_6R_7$, -(C_1-C_4 alkyl)-$C(O)NR_6R_7$, amidino, piperazinyl, morpholinyl, $-SO_2$ (C_1-C_6) alkyl, $-SO_2NH_2$, $-SO_2NH$(C_1-C_6)alkyl, $-SO_2N$(C_1-C_6)alkyl (C_1-C_6)alkyl, (C_1-C_4)haloalkyl, -(C_1-C_4 alkyl)-$NR_{15}C(O)NR_{16}R_{17}$, -(C_1-C_4 alkyl)-$NR_{15}C(O)R_{18}$, $-O-CH_2-O$, $-O-CH_2CH_2-O-$, or (C_1-C_4)haloalkoxy; wherein R_6 and R_7 are independently at each occurrence H, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)hydroxyalkyl, C_1-C_6 dihydroxyalkyl, -(C_1-C_4)alkyl-CO_2-(C_1-C_6)alkyl, (C_1-C_6)alkanoyl, phenyl(C_1-C_6)alkyl, phenyl(C_1-C_6)alkoxy, or phenyl(C_1-C_6)alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, (C_1-C_4)alkoxy, OH, SH, C_3-C_6 cycloalkyl, NH_2, NH(C_1-

C_6 alkyl), N(C_1-C_6 alkyl)(C_1-C_6 alkyl), (C_1-C_4)alkyl, CF_3 or OCF_3; or

R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, hydroxy, hydroxy C_1-C_4 alkyl, C_1-C_4 dihydroxyalkyl, or halogen; and

R_{18} is C_1-C_6 alkyl optionally substituted with -O-(C_2-C_6 alkanoyl, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl; amino C_1-C_6 alkyl, mono or dialkylamino C_1-C_6 alkyl,

6. A compound according to claim 5, wherein

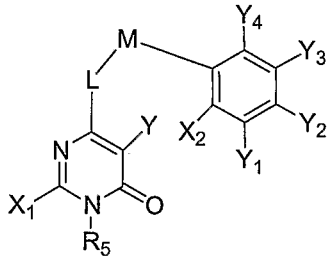
R_5 is pyrazolyl(C_1-C_6 alkyl), imidazolyl(C_1-C_6 alkyl), benzimidazolyl(C_1-C_6 alkyl), thienyl(C_1-C_6 alkyl), pyrimidyl(C_1-C_6)alkyl, indolyl(C_1-C_6 alkyl), dihydroindolyl(C_1-C_6 alkyl), dihydroisoindolyl(C_1-C_6 alkyl), dihydroindolon-2-yl(C_1-C_6 alkyl), pyridinyl(C_1-C_6 alkyl), piperazinyl(C_1-C_6 alkyl), or pyrazinyl(C_1-C_6 alkyl) each of which is optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, halogen, -C(O)NR_6R_7, -(C_1-C_4 alkyl)-C(O)NR_6R_7, C_1-C_6 alkoxycarbonyl, -NR_6R_7, R_6R_7N-(C_1-C_6 alkyl)-, haloalkyl, C_1-C_6 alkanoyl,

R_6 and R_7 at each occurrence are independently H, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkoxycarbonyl, halogen, C_3-C_6 cycloalkyl, OH, SH, or C_1-C_4 alkoxy;

or

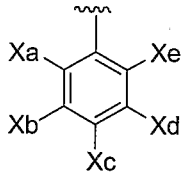
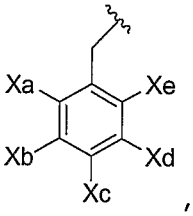
R_6, R_7, and the nitrogen to which they are attached form a piperidinyl, pyrrolidinyl, piperazinyl, or a morpholinyl ring optionally substituted with 1 or 2 groups that are independently alkyl, hydroxy, hydroxy C_1-C_4 alkyl, C_1-C_4 dihydroxyalkyl, or halogen.

7. A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein

L and M are indepedently selected from -O-, $-CH_2-$, -S-,-NR-, -N(R)-N(R)-, C(=O)-, $-SO_2-$;

R_5 is  or  , wherein

X_1, X_2, X_a, X_b, X_c, X_d, and X_e at are independently selected from -C(O)NR_6R_7, -(C_1-C_4 alkyl)-C(O)NR_6R_7, -NR_6R_7, hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, H, OH, halogen, haloalkyl, alkyl, haloalkoxy, heteroaryl, heterocycloalkyl, C_3-C_7 cycloalkyl, R_6R_7N-(C_1-C_6 alkyl)-, $-CO_2$-(C_1-C_6)alkyl, -N(R)C(O)NR_6R_7, -N(R)C(O)-(C_1-C_6)alkoxy, CO_2R-(C_1-C_6 alkyl)-, or $-SO_2NR_6R_7$; wherein the heteroaryl and heterocycloalkyl groups are optionally substituted with -NR_6R_7, -C(O)NR_6R_7, R_6R_7N-(C_1-C_6 alkyl)-, C_1-C_6 alkyl, C_1-C_6 alkoxy, or halogen; or

R_5 is heteroaryl or heteroarylalkyl, wherein the heteroaryl and heteroaryl groups are optionally substituted with 1,2, 3,

or 4 groups that are independently $-C(O)NR_6R_7$, $-(C_1-C_4$ alkyl)$-C(O)NR_6R_7$, $-NR_6R_7$, hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, H, OH, halogen, haloalkyl, alkyl, haloalkoxy, $R_6R_7N-(C_1-C_6$ alkyl$)-$, $-CO_2-(C_1-C_6)$alkyl, $-N(R)C(O)NR_6R_7$, or $-N(R)C(O)-(C_1-C_6)$alkoxy; wherein

R_6 and R_7 are independently at each occurrence H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl, OH, C_1-C_6 hydroxyalkyl, C_1-C_4 dihydroxyalkyl, C_1-C_6 thiohydroxyalkyl, $-(C_1-C_4)$alkyl-CO_2-alkyl, pyridyl C_1-C_6 alkyl, C_1-C_6 alkanoyl, benzyl, phenyl C_1-C_6 alkoxy, or phenyl C_1-C_6 alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, piperidinyl C_1-C_6 alkyl, morpholinyl C_1-C_6 alkyl, piperazinyl C_1-C_6 alkyl, OH, SH, NH_2, NH(alkyl), N(alkyl)(alkyl), $-O-C_1-C_4$ alkanoyl, C_1-C_4 alkyl, CF_3, or OCF_3; or

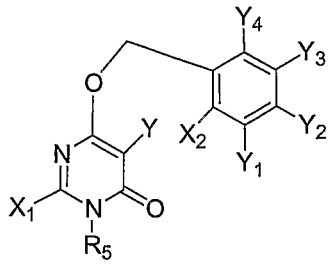
R_6, R_7, and the nitrogen to which they are attached form a morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl ring which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, hydroxy C_1-C_4 alkyl, C_1-C_4 dihydroxyalkyl, or halogen;

R at each occurrence is independently H or C_1-C_6 alkyl; and

Y, Y_1, Y_2, Y_3, and Y_4 are independently selected from H, halogen, alkyl, carboxaldehyde, hydroxyalkyl, dihydroxyalkyl, alkenyl, alkynyl, CN, alkanoyl, alkoxy, alkoxyalkyl, haloalkyl, and carboxyl.

8. A compound according to claim 7 of the formula

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or a pharmaceutically acceptable salt thereof.

9. A compound according to claim 8, wherein

R_5 is a heteroaryl or heteroarylalkyl group, where each heteroaryl is pyrazolyl, imidazolyl, furanyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrazolyl, imidazolyl, dihydroindolyl, dihydroisoindolyl, indolon-2-yl, quinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, dihydroisoquinolinyl, or indolyl, each of which is optionally substituted with 1, 2, 3, or 4 groups that are independently $-C(O)NR_6R_7$, $-(C_1-C_4$ alkyl$)-C(O)NR_6R_7$, $-NR_6R_7$, hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, hydrogen, hydroxy, halogen, haloalkyl, alkyl, haloalkoxy, $R_6R_7N-(C_1-C_6$ alkyl$)-$, $-CO_2-(C_1-C_6)$alkyl, $-N(R)C(O)NR_6R_7$, or $-N(R)C(O)-(C_1-C_6)$alkoxy; wherein

R_6 and R_7 are independently at each occurrence H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl, OH, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, C_1-C_6 thiohydroxyalkyl, $-(C_1-C_4)$alkyl-CO_2-alkyl, pyridyl C_1-C_6 alkyl, C_1-C_6 alkanoyl, benzyl, phenyl C_1-C_6 alkoxy, or phenyl C_1-C_6 alkanoyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently, halogen, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, piperidinyl C_1-C_6 alkyl, morpholinyl C_1-C_6

alkyl, piperazinyl C_1-C_6 alkyl, OH, SH, NH_2, NH(alkyl), N(alkyl)(alkyl), -O-C_1-C_4 alkanoyl, C_1-C_4 alkyl, CF_3, or OCF.

10. A compound according to claim 9, wherein
Y_2, Y_4, and Y are independently halogen; and
Y_1 and Y_3 are both hydrogen.

11. A compound according to claim 10, wherein
X_1 and X_2 are independently H, methyl, -NR_6R_7, R_6R_7N-(C_1-C_6 alkyl)-, -$C(O)NR_6R_7$, -(C_1-C_4 alkyl)-$C(O)NR_6R_7$, C_1-C_6 hydroxyalkyl, C_1-C_6 dihydroxyalkyl, or -(C_1-C_4 alkyl)-morpholinyl.

12. A compound according to claim 11, wherein
R_5 is pyridyl C_1-C_6 alkyl, pyrimidinyl C_1-C_6 alkyl, or pyrazinyl C_1-C_6 alkyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently hydroxy(C_1-C_4)alkyl, C_1-C_4 dihydroxyalkyl, OH, halogen, CF_3, (C_1-C_4)alkyl, OCF_3, -NR_6R_7, -(C_1-C_4 alkyl)-$C(O)NR_6R_7$, R_6R_7N-(C_1-C_6 alkyl)-, or -$C(O)NR_6R_7$.