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(54) **BICYCLIC HETEROARYL INHIBITORS OF PDE4**

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(52) **U.S. Cl.** **514/312; 546/157**

(58) **Field of Classification Search** None
See application file for complete search history.

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(57)

ABSTRACT

The present invention relates to compounds and methods which may be useful as inhibitors of phosphodiesterase 4 (PD E4) for the treatment or prevention of inflammatory diseases and other diseases involving elevated levels of cytokines and proinflammatory mediators.

7 Claims, No Drawings

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BICYCLIC HETEROARYL INHIBITORS OF
PDE4

This application claims the benefit of U.S. Provisional Applications No. 60/819,509, filed Jul. 7, 2006, and No. 60/886,825, filed Jan. 26, 2007, the disclosures of which are hereby incorporated by reference as if written herein in their entireties.

Disclosed herein are potent and selective new bicyclic heteroaryl compounds, certain of which have been found to be useful as inhibitors of phosphodiesterase 4 (PDE4), compositions comprising the same, and their application as pharmaceuticals for the treatment of disease. Methods of inhibition of PDE4 activity are also provided, as well as methods for the treatment of inflammatory diseases and other diseases involving elevated levels of cytokines and proinflammatory mediators.

Chronic inflammation is a multi-factorial disease complication characterized by activation of multiple types of inflammatory cells, for example cells of lymphoid lineage (including T lymphocytes) and myeloid lineage (including granulocytes, macrophages, and monocytes). Proinflammatory mediators, including cytokines, such as tumor necrosis factor (TNF) and interleukin-1 (IL-1), are produced by these activated cells. Accordingly, an agent that suppresses the activation of these cells, or their production of proinflammatory cytokines, would be useful in the therapeutic treatment of inflammatory diseases and other diseases involving elevated levels of cytokines.

Cyclic adenosine monophosphate (cAMP) is a second messenger that mediates the biologic responses of cells to a wide range of extracellular stimuli. When the appropriate agonist binds to specific cell surface receptors, adenylate cyclase is activated to convert adenosine triphosphate (ATP) to cAMP. It is theorized that the agonist induced actions of cAMP within the cell are mediated predominately by the action of cAMP-dependent protein kinases. The intracellular actions of cAMP are terminated by either a transport of the nucleotide to the outside of the cell, or by enzymatic cleavage by cyclic nucleotide phosphodiesterases (PDEs), which hydrolyze the 3'-phosphodiester bond to form 5'-adenosine monophosphate (5'-AMP). 5'-AMP is an inactive metabolite.

The superfamily of PDEs is subdivided into two major classes, class I and class II, which have no recognizable sequence similarity. Class I includes all known mammalian PDEs and is comprised of 11 identified families that are products of separate genes. Some PDEs are highly specific for hydrolysis of cAMP (PDE4, PDE7, PDE8), some are highly cGMP-specific (PDE5, PDE6, PDE9), and some have mixed specificity (PDE1, PDE2, PDE3, PDE10, PDE11). All of the characterized mammalian PDEs are dimeric, but the importance of the dimeric structure for function in each of the PDEs is unknown.

The PDE4 subfamily is comprised of 4 members: PDE4A, PDE4B, PDE4C, and PDE4D. These enzymes possess N-terminal regulatory domains that presumably mediate dimerization, which results in optimally regulated PDE activity. In addition, activity is regulated via cAMP-dependent protein kinase phosphorylation sites in this upstream regulatory domain. PDE4 enzymes are broadly expressed and distributed.

Elevated levels of cAMP in human myeloid and lymphoid lineage cells are associated with the suppression of cell activation. The intracellular enzyme family of PDEs, therefore, regulates the level of cAMP in cells. PDE4 is a predominant PDE isotype in these cells, and is a major contributor to cAMP degradation. Accordingly, the inhibition of PDE function would prevent the conversion of cAMP to the inactive metabolite 5'-AMP and, consequently, maintain higher cAMP levels, and, accordingly, suppress cell activation.

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PDE4 inhibitors have been shown to inhibit production of TNF α and partially inhibit IL-1 β release by monocytes (see Semmler et al., *Int. J. Immunopharmacol.*, 15, pp. 409-413, (1993); Molnar-Kimber et al., *Mediators of Inflammation*, 1, pp. 411-417, (1992)). PDE4 inhibitors also have been shown to inhibit the production of superoxide radicals from human polymorphonuclear leukocytes (see Vergheese et al., *J. Mol. Cell. Cardiol.*, 21 (Suppl. 2), S61 (1989); Nielson et al., *J. Allergy Immunol.*, 86, pp. 801-808, (1990)); to inhibit the release of vasoactive amines and prostanoids from human basophils (see Peachell et al., *J. Immunol.*, 148, pp. 2503-2510, (1992)); to inhibit respiratory bursts in eosinophils (see Dent et al., *J. Pharmacol.*, 103, pp. 1339-1346, (1991)); and to inhibit the activation of human T-lymphocytes (see Robicsek et al., *Biochem. Pharmacol.*, 42, pp. 869-877, (1991)).

Inflammatory cell activation and excessive or unregulated cytokine (e.g., TNF α and IL-1 β) production are implicated in allergic, autoimmune, and inflammatory diseases and disorders, such as rheumatoid arthritis, osteoarthritis, gouty arthritis, spondylitis, thyroid associated ophthalmopathy, Behcet's disease, sepsis, septic shock, endotoxic shock, gram negative sepsis, gram positive sepsis, toxic shock syndrome, asthma, chronic bronchitis, adult respiratory distress syndrome, chronic pulmonary inflammatory disease, such as chronic obstructive pulmonary disease, silicosis, pulmonary sarcoidosis, reperfusion injury of the myocardium, brain, and extremities, fibrosis, cystic fibrosis, keloid formation, scar formation, atherosclerosis, transplant rejection disorders, such as graft vs. host reaction and allograft rejection, chronic glomerulonephritis, lupus, inflammatory bowel disease, such as Crohn's disease and ulcerative colitis, proliferative lymphocyte diseases, such as leukemia, ophthalmologic diseases such as dry eye and ocular pain resulting from inflammation or surgery, and inflammatory dermatoses, such as atopic dermatitis, psoriasis, and urticaria.

Other conditions characterized by elevated cytokine levels include brain injury due to moderate trauma, cardiomyopathies, such as congestive heart failure, cachexia, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), ARC (AIDS related complex), fever myalgias due to infection, cerebral malaria, osteoporosis and bone resorption diseases, keloid formation, scar tissue formation, and pyrexia.

Additionally, several properties of TNF α , such as stimulation of collagenases, stimulation of angiogenesis in vivo, stimulation of bone resorption, and an ability to increase the adherence of tumor cells to endothelium, are consistent with a role for TNF in the development and metastatic spread of cancer in the host. TNF α recently has been directly implicated in the promotion of growth and metastasis of tumor cells (see Orosz et al., *J. Exp. Med.*, 177, pp. 1391-1398, (1993)).

Investigators have shown considerable interest in the use of PDE4 inhibitors as anti-inflammatory agents. Early evidence indicates that PDE4 inhibition has beneficial effects on a variety of inflammatory cells such as monocytes, macrophages, T-cells of the Th-1 lineage, and granulocytes. The synthesis and/or release of many proinflammatory mediators, such as cytokines, lipid mediators, superoxide, and biogenic amines, such as histamine, have been attenuated in these cells by the action of PDE4 inhibitors. The PDE4 inhibitors also affect other cellular functions including T-cell proliferation, granulocyte transmigration in response to chemotoxic substances, and integrity of endothelial cell junctions within the vasculature.

The design, synthesis, and screening of various PDE4 inhibitors have been reported. Methylxanthines, such as caffeine and theophylline, were the first PDE inhibitors discovered, but these compounds are nonselective with respect to which PDE is inhibited. The drug rolipram, an antidepressant agent, was one of the first reported specific PDE4 inhibitors,

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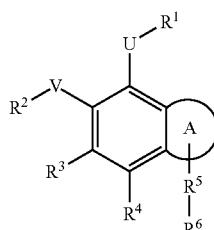
with a reported IC_{50} of about 200 nM with respect to inhibiting recombinant human PDE4.

Investigators have continued to search for PDE4 inhibitors that are more selective with respect to inhibiting PDE4, that have a lower IC_{50} than rolipram, and that avoid the undesirable central nervous system (CNS) side effects, such as retching, vomiting, and sedation, associated with the administration of rolipram. In addition, several companies are now undertaking clinical trials of other PDE4 inhibitors. However, problems relating to efficacy and adverse side effects, such as emesis and central nervous system disturbances, remain unsolved.

Accordingly, compounds that selectively inhibit PDE4, and that reduce or eliminate the adverse side effects associated with prior PDE4 inhibitors, would be useful in the treatment of allergic and inflammatory diseases, and other diseases associated with excessive or unregulated production of cytokines, such as TNF. In addition, selective PDE4 inhibitors would be useful in the treatment of diseases that are associated with elevated cAMP levels or PDE4 function in a particular target tissue.

Novel compounds and pharmaceutical compositions useful as anti-inflammatory agents via the inhibition of PDE4 have been found, together with methods of synthesizing and using the compounds including methods for inhibiting PDE4 in a patient by administering the compounds.

Disclosed herein is a class of compounds, certain of which have been found to be useful in treating PDE4-mediated disorders and conditions, defined by structural Formula I:



wherein:

A is an optionally substituted saturated or unsaturated hydrocarbon chain or a heteroatom-comprising hydrocarbon chain having from 3 to 5 atoms, forming a five- to seven-membered ring;

U, and V are independently selected from the group consisting of O , $N(R^7)$ and SO_q ;

R^1 and R^2 are independently selected from the group consisting of hydrogen, $-(CH_2)_sG^1G^2G^3$, acyl, acylalkyl, carboxyalkyl, cyanoalkyl, alkoxy, alkoxyalkyl, amidoalkyl, amino, alkyl, alkylalkoxy, aminoalkyl, alkenyl, alkynyl, carboxy, carboxyalkyl, ether, heteroalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aralkyl, aryl, guanidine, heteroaryl, heteroaralkyl, hydrogen and hydroxylalkyl, any of which may be optionally substituted;

s is 0-8;

G^1 is selected from the group consisting of alkoxy, amino, amido, carbonyl, hydroxy, ether, an amino acid, and null;

G^2 is selected from the group consisting of alkyl, alkoxy, amino, aryl, halo, haloalkyl, heterocycloalkyl, heteroaryl, carboxylalkylamino, guanidine, an amino acid, and null, any of which may be optionally substituted;

G^3 is selected from the group consisting of alkyl, alkoxy, amino, hydroxy, ether, carboxyl, hydroxamic acid, an amino acid, phosphonate, phosphoamide, and null, any of which may be optionally substituted;

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R^3 and R^4 are each independently selected from the group consisting of hydrogen, halogen, alkoxy and lower alkyl;

R^5 is selected from the group consisting of $-(CR^8R^9)_mW$ $(CR^{10}R^{11})_n$ and $-(CR^{12}R^{13})_p$;

m , n , and q are each independently 0, 1 or 2;

p is 1 or 2;

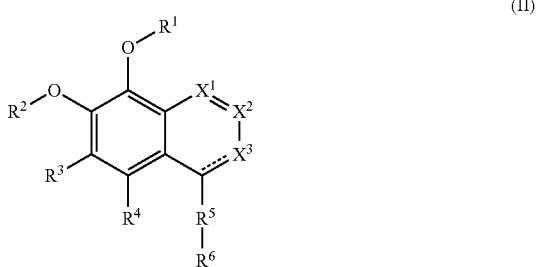
W is selected from the group consisting of O , $N(R^7)$, $C(O)N(R^7)$, and SO_q ;

R^6 is selected from the group consisting of carboxy, alkylcarboxy, amido, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkyl, heteroalkyl, acyl, and hydroxamic acid, any of which may be optionally substituted;

R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , and R^{13} are each independently selected from the group consisting of hydrogen, halogen, hydroxyl, lower alkyl, hydroxylalkyl, haloalkyl, alkoxy, haloalkoxy, amino, aminoalkyl, and aminoalkoxy; and hydrogen and optionally substituted lower alkyl.

Certain compounds according to the present invention possess useful PDE4 inhibiting or modulating activity, and may be used in the treatment or prophylaxis of a disease or condition in which PDE4 plays an active role. Thus, in broad aspect, the certain embodiments of the present invention also provide pharmaceutical compositions comprising one or more compounds disclosed herein together with a pharmaceutically acceptable carrier, as well as methods of making and using the compounds and compositions. Certain embodiments of the present invention provide methods for inhibiting PDE4. Other embodiments of the present invention provide methods for treating a PDE4-mediated disorder in a patient in need of such treatment, comprising administering to said patient a therapeutically effective amount of a compound or composition according to the present invention. Related embodiments disclose the use of certain compounds disclosed herein as therapeutic agents, for example, in treating inflammatory diseases and other diseases involving elevated levels of cytokines and proinflammatory mediators. The present invention also contemplates the use of certain compounds disclosed herein for use in the manufacture of a medicament for the treatment of a disease or condition ameliorated by the inhibition of PDE4.

In further embodiments, compounds of the present invention have structural formula II



wherein:

X^1 is NR^{14} ;

X^2 is selected from the group consisting of $C(O)$, $(CR^{15}R^{16})$ and null;

X^3 is selected from the group consisting of $C(O)$, $N(R^{17})$ and $(CR^{18}R^{19})$;

R^1 and R^2 are independently selected from the group consisting of hydrogen, $-(CH_2)_sG^1G^2G^3$, acyl, acylalkyl, carboxyalkyl, cyanoalkyl, alkoxy, alkoxyalkyl, amidoalkyl, amino, alkyl, alkylalkoxy, aminoalkyl, alkenyl, alkynyl, carboxy, carboxyalkyl, ether, heteroalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl,

aralkyl, aryl, guanidine, heteroaryl, heteroaralkyl, hydrogen and hydroxyalkyl, any of which may be optionally substituted;

s is 0-8;

G¹ is selected from the group consisting of alkoxy, amino, amido, carbonyl, hydroxy, ether, an amino acid, and null;

G² is selected from the group consisting of alkyl, alkoxy, amino, aryl, halo, haloalkyl, heterocycloalkyl, heteroaryl, carboxylalkylamino, guanidine, an amino acid, and null, any of which may be optionally substituted;

G³ is selected from the group consisting of alkyl, alkoxy, amino, hydroxy, ether, carboxyl, hydroxamic acid, an amino acid, phosphonate, phosphoamide, and null, any of which may be optionally substituted;

R³ and R⁴ are independently selected from the group consisting of hydrogen, halogen, alkoxy and lower alkyl;

R⁵ is selected from the group consisting of —(CR⁸R⁹)_mW (CR¹⁰R¹¹)_n— and —(CR¹²R¹³)_p—;

m, n, and q are each independently 0, 1 or 2;

p is 1 or 2;

W is selected from the group consisting of O, N(R⁷), C(O)N(R⁷), and SO_q;

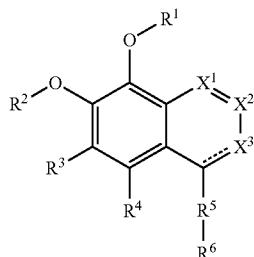
R⁶ is selected from the group consisting of carboxy, alkylcarboxy, amido, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkyl, heteroalkyl, acyl, and hydroxamic acid, any of which may be optionally substituted;

R⁸, R⁹, R¹⁰, R¹¹, R¹² and R¹³ are each independently selected from the group consisting of hydrogen and optionally substituted lower alkyl;

R¹⁴ and R¹⁷ are each independently selected from the group consisting of hydrogen, halogen, hydroxyl, lower alkyl, hydroxyalkyl, haloalkyl, aminoalkyl, and a bond; and

R¹⁵, R¹⁶, R¹⁸ and R¹⁹ are each independently selected from the group consisting of hydrogen, halogen, lower alkyl, haloalkyl, alkoxy, haloalkoxy, amino, aminoalkyl, aminoalkoxy and a bond.

In further embodiments, compounds of the present invention have structural formula III



wherein:

X¹ is NR¹⁴;

X² is selected from the group consisting of C(O) and null;

X³ is selected from the group consisting of C(O) and (CR¹⁸R¹⁹);

R¹ and R² are independently selected from the group consisting of hydrogen, —(CH₂)_sG¹G²G³, acyl, acylalkyl, carboxylalkyl, cyanoalkyl, alkoxy, alkoxyalkyl, amidoalkyl, amino, alkyl, alkylalkoxy, aminoalkyl, alkenyl, alkynyl, carboxyl, carboxylalkyl, ether, heteroalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aralkyl, aryl, guanidine, heteroaryl, heteroaralkyl, hydrogen and hydroxyalkyl, any of which may be optionally substituted;

s is 1-8;

G¹ is selected from the group consisting of alkoxy, amino, amido, carbonyl, hydroxy, ether, an amino acid, and null;

cloalkylalkyl, aralkyl, aryl, guanidine, heteroaryl, heteroaralkyl, hydrogen and hydroxyalkyl, any of which may be optionally substituted;

s is 1-8;

G¹ is selected from the group consisting of alkoxy, amino, amido, carbonyl, hydroxy, ether, an amino acid, and null;

G² is selected from the group consisting of alkyl, alkoxy, amino, aryl, halo, haloalkyl, heterocycloalkyl, heteroaryl, carboxylalkylamino, guanidine, an amino acid, and null, any of which may be optionally substituted;

G³ is selected from the group consisting of alkyl, alkoxy, amino, hydroxy, ether, carboxyl, hydroxamic acid, an amino acid, phosphonate, phosphoamide, and null, any of which may be optionally substituted;

R³ and R⁴ are independently selected from the group consisting of hydrogen, halogen, alkoxy and lower alkyl;

R⁵ is selected from the group consisting of —(CR⁸R⁹)_mW (CR¹⁰R¹¹)_n— and —(CR¹²R¹³)_p—;

m, n, and q are each independently 0, 1 or 2;

p is 1 or 2;

W is selected from the group consisting of O, N(R⁷), C(O)N(R⁷), and SO_q;

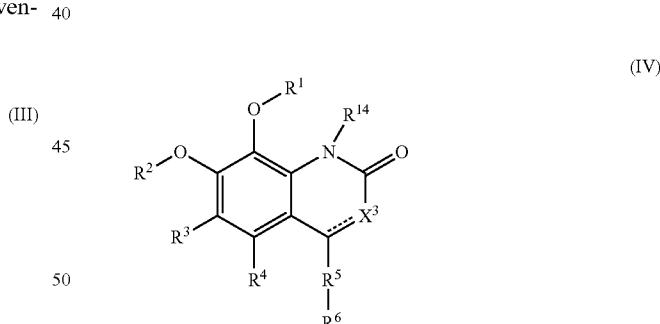
R⁶ is selected from the group consisting of carboxyl, alkylcarboxy, amido, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkyl, heteroalkyl, acyl, and hydroxamic acid, any of which may be optionally substituted;

R⁸, R⁹, R¹⁰, R¹¹, R¹² and R¹³ are each independently selected from the group consisting of hydrogen and optionally substituted lower alkyl;

R⁷ and R¹⁴ are independently selected from the group consisting of hydrogen, halogen, hydroxyl, lower alkyl, hydroxyalkyl, haloalkyl, and aminoalkyl; and

R¹⁵, R¹⁶, R¹⁸ and R¹⁹ are each independently selected from the group consisting of hydrogen, halogen, lower alkyl, haloalkyl, alkoxy, haloalkoxy, amino, aminoalkyl, aminoalkoxy and a bond.

In certain embodiments, compounds of the present invention have structural Formula IV



wherein:

X³ is (CR¹⁸R¹⁹);

R¹ and R² are independently selected from the group consisting of hydrogen, —(CH₂)_sG¹G²G³, acyl, acylalkyl, carboxylalkyl, cyanoalkyl, alkoxy, alkoxyalkyl, amidoalkyl, amino, alkyl, alkylalkoxy, aminoalkyl, alkenyl, alkynyl, carboxyl, carboxylalkyl, ether, heteroalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aralkyl, aryl, guanidine, heteroaryl, heteroaralkyl, hydrogen and hydroxyalkyl, any of which may be optionally substituted;

s is 1-8;

G¹ is selected from the group consisting of alkoxy, amino, amido, carbonyl, hydroxy, ether, an amino acid, and null;

G^2 is selected from the group consisting of alkyl, alkoxy, amino, aryl, halo, haloalkyl, heterocycloalkyl, heteroaryl, carboxylalkylamino, guanidine, an amino acid, and null, any of which may be optionally substituted;

G^3 is selected from the group consisting of alkyl, alkoxy, amino, hydroxy, ether, carboxyl, hydroxamic acid, an amino acid, phosphonate, phosphoamide, and null, any of which may be optionally substituted;

R^3 and R^4 are each independently selected from the group consisting of hydrogen, halogen, alkoxy and lower alkyl;

R^5 is selected from the group consisting of $-(CR^8R^9)_mW(CR^{10}R^{11})_n-$ and $-(CR^{12}R^{13})_p-$;

m , n , and q are each independently 0, 1 or 2;

p is 1 or 2;

W is selected from the group consisting of O, N(R^7), C(O) $N(R^7)$, and SO_q ;

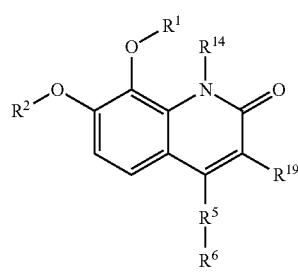
R^6 is selected from the group consisting of carboxyl, alkylcarboxy, amido, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkyl, heteroalkyl, acyl, and hydroxamic acid, any of which may be optionally substituted;

R^8 , R^9 , R^{10} , R^{11} , R^{12} and R^{13} are each independently selected from the group consisting of hydrogen and optionally substituted lower alkyl;

R^7 and R^{14} are independently selected from the group consisting of hydrogen, halogen, hydroxyl, lower alkyl, hydroxyalkyl, haloalkyl, and aminoalkyl; and

R^{18} and R^{19} are each independently selected from the group consisting of hydrogen, halogen, lower alkyl, haloalkyl, alkoxy, haloalkoxy, amino, aminoalkyl, aminoalkoxy and a bond.

In further embodiments, compounds of the present invention have structural Formula V



(V) 35

wherein:

R^1 and R^2 are independently selected from the group consisting of hydrogen, $-(CH_2)_sG^1G^2G^3$, acyl, acylalkyl, carboxylalkyl, cyanoalkyl, alkoxy, alkoxyalkyl, amidoalkyl, amino, alkyl, alkylalkoxy, aminoalkyl, alkenyl, alkynyl, carboxyl, carboxylalkyl, ether, heteroalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aralkyl, aryl, guanidine, heteroaryl, heteroaralkyl, hydrogen and hydroxyalkyl, any of which may be optionally substituted;

s is 1-8;

G^1 is selected from the group consisting of alkoxy, amino, amido, carbonyl, hydroxy, ether, an amino acid, and null;

G^2 is selected from the group consisting of alkyl, alkoxy, amino, aryl, halo, haloalkyl, heterocycloalkyl, heteroaryl, carboxylalkylamino, guanidine, an amino acid, and null, any of which may be optionally substituted;

G^3 is selected from the group consisting of alkyl, alkoxy, amino, hydroxy, ether, carboxyl, hydroxamic acid, an amino acid, phosphonate, phosphoamide, and null, any of which may be optionally substituted;

R^5 is selected from the group consisting of $-(CR^8R^9)_mW(CR^{10}R^{11})_n-$ and $-(CR^{12}R^{13})_p-$;

m , n , and q are each independently 0, 1 or 2;

p is 1 or 2;

W is selected from the group consisting of O, N(R^7), C(O) $N(R^7)$, and SO_q ;

R^6 is selected from the group consisting of carboxyl, alkylcarboxy, amido, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkyl, heteroalkyl, acyl, and hydroxamic acid, any of which may be optionally substituted;

R^7 and R^{14} are independently selected from the group consisting of hydrogen, halogen, hydroxyl, lower alkyl, hydroxyalkyl, haloalkyl, and aminoalkyl; and

R^{19} is selected from the group consisting of hydrogen, halogen, lower alkyl and haloalkyl.

In yet further embodiments are provided compounds wherein R^7 and R^{14} are independently selected from the group consisting of hydrogen, halogen and optionally substituted lower alkyl

In yet further embodiments are provided compounds wherein R^6 is selected from the group consisting of aryl and heteroaryl, either of which may be optionally substituted;

In yet further embodiments are provided compounds wherein R^{19} is hydrogen.

In yet further embodiments are provided compounds wherein R^6 is selected from the group consisting of phenyl, pyridine, pyrimidine, pyridazine, and pyrazine, any of which may be optionally substituted.

In yet further embodiments are provided compounds wherein R^6 is selected from the group consisting of phenyl, pyridine, and pyrimidine, any of which may be optionally substituted.

In yet further embodiments are provided compounds wherein R^{14} is hydrogen.

In yet further embodiments are provided compounds wherein:

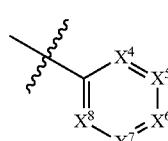
R^5 is $-(CR^8R^9)_mW(CR^{10}R^{11})_n-$;

m and n are both 0;

W is N(R^7); and

R^7 is hydrogen.

In yet further embodiments are provided compounds wherein R^6 has the formula



wherein

X^4 is CR^{20} or N;

X^5 is CR^{21} or N;

X^6 is CR^{22} or N;

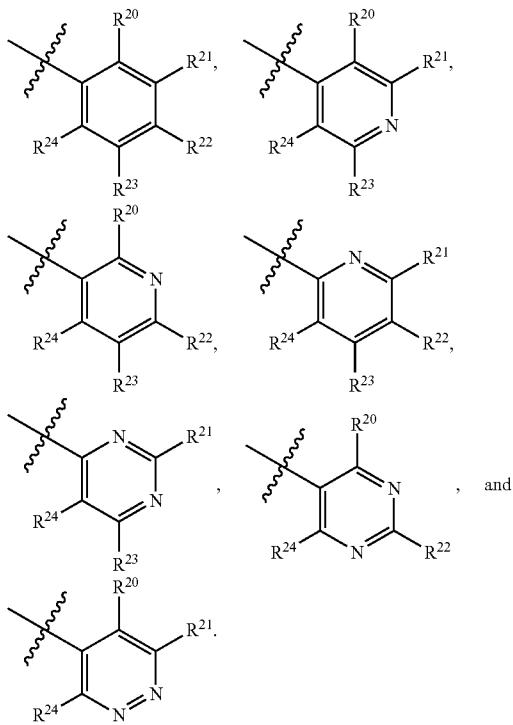
X^7 is CR^{23} or N;

X^8 is CR^{24} or N;

wherein no more than two of X^4 — X^8 may be N; and

R^{20} , R^{21} , R^{22} , R^{23} and R^{24} are independently selected from the group consisting of hydrogen, halogen, hydroxyl, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, amino, and carboxyl.

In yet further embodiments are provided compounds wherein R⁶ has a formula selected from the group consisting of



In yet further embodiments are provided compounds wherein R² is lower alkyl. In yet further embodiments, R² is 35 methyl.

In yet further embodiments are provided compounds wherein:

R¹ is selected from the group consisting of —(CH₂)_sG¹G²G³, lower alkyl, cycloalkyl, cycloalkylalkyl, and heterocycloalkyl, any of which may be optionally substituted;

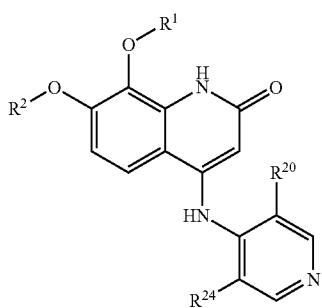
s is 1-6;

G¹ is selected from the group consisting of amino, amido, and null;

G² is selected from the group consisting of alkoxy, aryl, halo, heterocycloalkyl, and null, any of which may be optionally substituted; and

G³ is selected from the group consisting of alkyl, carboxyl, and null, any of which may be optionally substituted.

In further embodiments, compounds of the present invention have structural Formula VI



wherein:

R¹ and R² are independently selected from the group consisting of hydrogen, —(CH₂)_sG¹G²G³, acyl, acylalkyl, carboxyalkyl, cyanoalkyl, alkoxy, alkoxyalkyl, amidoalkyl, amino, alkyl, alkylalkoxy, aminoalkyl, alkenyl, alkynyl, carboxyl, carboxyalkyl, ether, heteroalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aralkyl, aryl, guanidine, heteroaryl, heteroaralkyl, hydrogen and hydroxyalkyl, any of which may be optionally substituted;

s is 1-8;

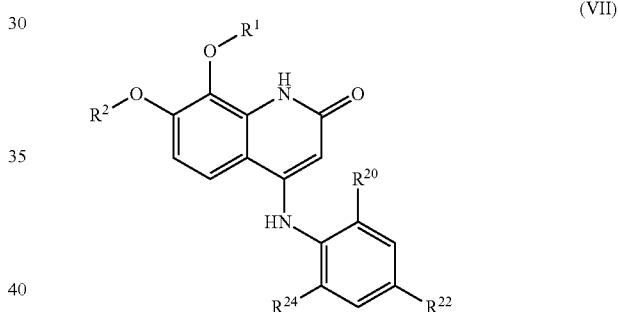
G¹ is selected from the group consisting of alkoxy, amino, amido, carbonyl, hydroxy, ether, an amino acid, and null;

G² is selected from the group consisting of alkyl, alkoxy, amino, aryl, halo, haloalkyl, heterocycloalkyl, heteroaryl, carboxylalkylamino, guanidine, an amino acid, and null, any of which may be optionally substituted;

G³ is selected from the group consisting of alkyl, alkoxy, amino, hydroxy, ether, carboxyl, hydroxamic acid, an amino acid, phosphonate, phosphoamide, and null, any of which may be optionally substituted; and

R²⁰ and R²⁴ are independently selected from the group consisting of hydrogen, halogen, hydroxyl, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, amino, and carboxyl.

In yet further embodiments, compounds of the present invention have structural Formula VII



wherein:

R¹ and R² are independently selected from the group consisting of hydrogen, —(CH₂)_sG¹G²G³, acyl, acylalkyl, carboxyalkyl, cyanoalkyl, alkoxy, alkoxyalkyl, amidoalkyl, amino, alkyl, alkylalkoxy, aminoalkyl, alkenyl, alkynyl, carboxyl, carboxyalkyl, ether, heteroalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aralkyl, aryl, guanidine, heteroaryl, heteroaralkyl, hydrogen and hydroxyalkyl, any of which may be optionally substituted;

s is 1-8;

G¹ is selected from the group consisting of alkoxy, amino, amido, carbonyl, hydroxy, ether, an amino acid, and null;

G² is selected from the group consisting of alkyl, alkoxy, amino, aryl, halo, haloalkyl, heterocycloalkyl, heteroaryl, carboxylalkylamino, guanidine, an amino acid, and null, any of which may be optionally substituted;

G³ is selected from the group consisting of alkyl, alkoxy, amino, hydroxy, ether, carboxyl, hydroxamic acid, an amino acid, phosphonate, phosphoamide, and null, any of which may be optionally substituted; and

R²⁰, R²², and R²⁴ are independently selected from the group consisting of hydrogen, halogen, hydroxyl, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, amino, and carboxyl.

Compounds of the present invention may be selective amongst the PDE4 isoforms PDE4A, PDE4B, PDE4C, and PDE4D in various ways. For example, compounds described herein may be selective for PDE4B and PDE4D over the other two isoforms, be a pan-inhibitor of all the isoforms, or be selective for only one isoform. In certain embodiments, compounds of the present invention may be selective for PDE4B over other isoforms.

The present invention also relates to a method of inhibiting at least one PDE4 function comprising the step of contacting the PDE4 with a compound of Formula I, as described herein. The cell phenotype, cell proliferation, activity of PDE4, change in biochemical output produced by active PDE4, expression of PDE4, or binding of PDE4 with a natural binding partner may be monitored. Such methods may be modes of treatment of disease, biological assays, cellular assays, biochemical assays, or the like.

As used herein, the terms below have the meanings indicated.

When ranges of values are disclosed, and the notation "from $n_1 \dots$ to n_2 " is used, where n_1 and n_2 are the numbers, then unless otherwise specified, this notation is intended to include the numbers themselves and the range between them. This range may be integral or continuous between and including the end values. By way of example, the range "from 2 to 6 carbons" is intended to include two, three, four, five, and six carbons, since carbons come in integer units. Compare, by way of example, the range "from 1 to 3 μM (micromolar)," which is intended to include 1 μM , 3 μM , and everything in between to any number of significant figures (e.g., 1.255 μM , 2.1 μM , 2.9999 μM , etc.).

The term "about," as used herein, is intended to qualify the numerical values which it modifies, denoting such a value as variable within a margin of error. When no particular margin of error, such as a standard deviation to a mean value given in a chart or table of data, is recited, the term "about" should be understood to mean that range which would encompass the recited value and the range which would be included by rounding up or down to that figure as well, taking into account significant figures.

The term "acyl," as used herein, alone or in combination, refers to a carbonyl attached to an alkenyl, alkyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, or any other moiety were the atom attached to the carbonyl is carbon. An "acetyl" group, which is a type of acyl, refers to a $-\text{C}(\text{O})\text{CH}_3$ group. An "alkylcarbonyl" or "alkanoyl" group refers to an alkyl group attached to the parent molecular moiety through a carbonyl group. Examples of such groups include methylcarbonyl and ethylcarbonyl. Examples of acyl groups include 45 formyl, alkanoyl and aroyl.

The term "alkenyl," as used herein, alone or in combination, refers to a straight-chain or branched-chain hydrocarbon radical having one or more double bonds and containing from 2 to 20 carbon atoms. In certain embodiments, said alkenyl will comprise from 2 to 6 carbon atoms. The term "alkenylene" refers to a carbon-carbon double bond system attached at two or more positions such as ethenylene [$(-\text{CH}=\text{CH}-), (-\text{C}=\text{C}-)$]. Examples of suitable alkenyl radicals include ethenyl, propenyl, 2-methylpropenyl, 1,4-butadienyl and the like. Unless otherwise specified, the term "alkenyl" may include "alkenylene" groups.

The term "alkoxy," as used herein, alone or in combination, refers to an alkyl ether radical, wherein the term alkyl is as defined below. Examples of suitable alkyl ether radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, and the like.

The term "alkyl," as used herein, alone or in combination, refers to a straight-chain or branched-chain alkyl radical containing from 1 to 20 carbon atoms. In certain embodiments, said alkyl will comprise from 1 to 10 carbon atoms. In further 5 embodiments, said alkyl will comprise from 1 to 6 carbon atoms. Alkyl groups may be optionally substituted as defined herein. Examples of alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl, noyl and the like. The term 10 "alkylene," as used herein, alone or in combination, refers to a saturated aliphatic group derived from a straight or branched chain saturated hydrocarbon attached at two or more positions, such as methylene ($-\text{CH}_2-$). Unless otherwise specified, the term "alkyl" may include "alkylene" 15 groups.

The term "alkylamino," as used herein, alone or in combination, refers to an alkyl group attached to the parent molecular moiety through an amino group. Suitable alkylamino groups may be mono- or dialkylated, forming groups such as, 20 for example, N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-ethyldimethylamino and the like.

The term "alkylidene," as used herein, alone or in combination, refers to an alkenyl group in which one carbon atom of the carbon-carbon double bond belongs to the moiety to 25 which the alkenyl group is attached.

The term "alkylthio," as used herein, alone or in combination, refers to an alkyl thioether ($\text{R}-\text{S}-$) radical wherein the term alkyl is as defined above and wherein the sulfur may be singly or doubly oxidized. Examples of suitable alkyl thioether radicals include methylthio, ethylthio, n-propylthio, iso-propylthio, n-butylthio, iso-butylthio, sec-butylthio, tert-butylthio, methanesulfonyl, ethanesulfinyl, and the like.

The term "alkynyl," as used herein, alone or in combination, refers to a straight-chain or branched chain hydrocarbon radical having one or more triple bonds and containing from 35 2 to 20 carbon atoms. In certain embodiments, said alkynyl comprises from 2 to 6 carbon atoms. In further embodiments, said alkynyl comprises from 2 to 4 carbon atoms. The term "alkynylene" refers to a carbon-carbon triple bond attached at two positions such as ethynylene ($-\text{C}::\text{C}-$, $-\text{C}\equiv\text{C}-$). Examples of alkynyl radicals include ethynyl, propynyl, hydroxypropynyl, butyn-1-yl, butyn-2-yl, pentyn-1-yl, 3-methylbutyn-1-yl, hexyn-2-yl, and the like. Unless otherwise specified, the term "alkynyl" may include "alkynylene" 45 groups.

The terms "amido" and "carbamoyl," as used herein, alone or in combination, refer to an amino group as described below attached to the parent molecular moiety through a carbonyl group, or vice versa. The term "C-amido" as used herein, alone or in combination, refers to a $-\text{C}(=\text{O})-\text{N}(\text{R})_2$ group with R as defined herein. The term "N-amido" as used herein, alone or in combination, refers to a $\text{RC}(=\text{O})\text{N}(\text{R}')-$ group, with R and R' as defined herein. The term "acylamino" as used herein, alone or in combination, embraces an acyl group 55 attached to the parent moiety through an amino group. An example of an "acylamino" group is acetylamino ($\text{CH}_3\text{C}(\text{O})\text{NH}-$).

The term "amino," as used herein, alone or in combination, refers to $-\text{N}(\text{R})(\text{R}')$ or $-\text{N}^+(\text{R})(\text{R}')(\text{R}'')$, wherein R, R' and R" are independently selected from the group consisting of hydrogen, alkyl, acyl, heteroalkyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl, any of which may themselves be optionally substituted.

The term "amino acid," as used herein, alone or in combination, means a substituent of the form $-\text{NRCH}(\text{R}')\text{C}(\text{O})\text{OH}$, wherein R is typically hydrogen, but may be cyclized with N (for example, as in the case of the amino acid proline),

and R' is selected from the group consisting of hydrogen, alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, amino, amido, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl, aminoalkyl, amidoalkyl, hydroxyalkyl, thiol, thioalkyl, alkylthioalkyl, and alkylthio, any of which may be optionally substituted. The term "amino acid" includes all naturally occurring amino acids as well as synthetic analogues.

The term "aryl," as used herein, alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as benzyl, phenyl, naphthyl, anthracenyl, phenanthryl, indanyl, indenyl, annulenyl, azulenyl, tetrahydronaphthyl, and biphenyl.

The term "arylalkenyl" or "aralkenyl," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkenyl group.

The term "arylalkoxy" or "aralkoxy," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkoxy group.

The term "arylalkyl" or "aralkyl," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkyl group.

The term "arylalkynyl" or "aralkynyl," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkynyl group.

The term "arylalkanoyl" or "aralkanoyl" or "aryoyl," as used herein, alone or in combination, refers to an acyl radical derived from an aryl-substituted alkanecarboxylic acid such as benzoyl, naphthoyl, phenylacetyl, 3-phenylpropionyl (hydrocinnamoyl), 4-phenylbutyryl, (2-naphthyl)acetyl, 4-chlorohydrocinnamoyl, and the like.

The term aryloxy as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an oxy.

The terms "benzo" and "benz," as used herein, alone or in combination, refer to the divalent radical C_6H_4 derived from benzene. Examples include benzothiophene and benzimidazole.

The term "carbamate," as used herein, alone or in combination, refers to an ester of carbamic acid ($—NHCOO—$) which may be attached to the parent molecular moiety from either the nitrogen or acid end, and which may be optionally substituted as defined herein.

The term "O-carbamyl" as used herein, alone or in combination, refers to a $—OC(O)NRR'$ group, with R and R' as defined herein.

The term "N-carbamyl" as used herein, alone or in combination, refers to a $ROC(O)NR'$ group, with R and R' as defined herein.

The term "carbonyl," as used herein, when alone includes formyl [$—C(O)H$] and in combination is a $—C(O)—$ group.

The term "carboxyl" or "carboxyl," as used herein, refers to $—C(O)OH$, O-carboxy, C-carboxy, or the corresponding "carboxylate" anion, such as is in a carboxylic acid salt. An "O-carboxy" group refers to a $RC(O)O—$ group, where R is as defined herein. A "C-carboxy" group refers to a $—C(O)OR$ groups where R is as defined herein.

The term "cyano," as used herein, alone or in combination, refers to $—CN$.

The term "cycloalkyl," or, alternatively, "carbocycle," as used herein, alone or in combination, refers to a saturated or partially saturated monocyclic, bicyclic or tricyclic alkyl radical wherein each cyclic moiety contains from 3 to 12 carbon atom ring members and which may optionally be a benzo fused ring system which is optionally substituted as

defined herein. In certain embodiments, said cycloalkyl will comprise from 5 to 7 carbon atoms. Examples of such cycloalkyl radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, octahydronaphthyl, 2,3-dihydro-1H-indenyl, adamantly and the like. "Bicyclic" and "tricyclic" as used herein are intended to include both fused ring systems, such as decahydronaphthalene, octahydronaphthalene as well as the multicyclic (multicentered) saturated or partially unsaturated type. The latter type of isomer is exemplified in general by, bicyclo[1,1,1]pentane, camphor, adamantane, and bicyclo[3,2,1]octane.

The term "ester," as used herein, alone or in combination, refers to a carboxyl group bridging two moieties linked at carbon atoms.

The term "ether," as used herein, alone or in combination, typically refers to an oxy group bridging two moieties linked at carbon atoms. "Ether" may also include polyethers, such as, for example, $—RO(CH_2)_2—O—(CH_2)_2—O—(CH_2)_2OR'$, $—RO(CH_2)_2—O—(CH_2)_2OR'$, $—RO(CH_2)_2OR'$, and $—RO(CH_2)_2OH$.

The term "halo," or "halogen," as used herein, alone or in combination, refers to fluorine, chlorine, bromine, or iodine.

The term "haloalkoxy," as used herein, alone or in combination, refers to a haloalkyl group attached to the parent molecular moiety through an oxygen atom.

The term "haloalkyl," as used herein, alone or in combination, refers to an alkyl radical having the meaning as defined above wherein one or more hydrogens are replaced with a halogen. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. "Haloalkylene" refers to a haloalkyl group attached at two or more positions. Examples include fluoromethylene ($—CFH—$), difluoromethylene ($—CF_2—$), chloromethylene ($—CHCl—$) and the like.

The term "heteroalkyl," as used herein, alone or in combination, refers to a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, fully saturated or containing from 1 to 3 degrees of unsaturation, consisting of the stated number of carbon atoms and from one to three heteroatoms selected from the group consisting of O, N, and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S may be placed at any interior position of the heteroalkyl group. Up to two heteroatoms may be consecutive, such as, for example, $—CH_2—NH—OCH_3$. The term heteroalkyl may include ethers.

The term "heteroaryl," as used herein, alone or in combination, refers to 3 to 7 membered unsaturated heteromonocyclic rings, or fused polycyclic rings in which at least one of the fused rings is unsaturated, wherein at least one atom is selected from the group consisting of O, S, and N. In certain embodiments, said heteroaryl will comprise from 5 to 7 carbon atoms. The term also embraces fused polycyclic groups wherein heterocyclic radicals are fused with aryl radicals, wherein heteroaryl radicals are fused with other heteroaryl radicals, or wherein heteroaryl radicals are fused with cycloalkyl radicals. Examples of heteroaryl groups include pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidi-

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nyl, pyrazinyl, pyridazinyl, triazolyl, pyranyl, furyl, thiényl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, thiadiazolyl, isothiazolyl, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, quinoxalinyl, quinazolinyl, indazolyl, benzotriazolyl, benzodioxolyl, benzopyranyl, benzoxazolyl, benzoxadiazolyl, benzothiazolyl, benzothiadiazolyl, benzofuryl, benzothienyl, chromonyl, coumarinyl, benzopyranyl, tetrahydroquinolinyl, tetrazolopyridazinyl, tetrahydroisoquinolinyl, thienopyridinyl, furopyridinyl, pyrrolopyridinyl and the like. Exemplary tricyclic heterocyclic groups include carbazolyl, benzidolyl, phenanthrolinyl, dibenzofuranyl, acridinyl, phenanthridinyl, xanthenyl and the like.

The terms "heterocycloalkyl" and, interchangeably, "heterocycle," as used herein, alone or in combination, each refer to a saturated, partially unsaturated, or fully unsaturated monocyclic, bicyclic, or tricyclic heterocyclic radical containing at least one heteroatom as ring members, wherein each said heteroatom may be independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, said heterocycloalkyl will comprise from 1 to 4 heteroatoms as ring members. In further embodiments, said heterocycloalkyl will comprise from 1 to 2 heteroatoms ring members. In certain embodiments, said heterocycloalkyl will comprise from 3 to 8 ring members in each ring. In further embodiments, said heterocycloalkyl will comprise from 3 to 7 ring members in each ring. In yet further embodiments, said heterocycloalkyl will comprise from 5 to 6 ring members in each ring. "Heterocycloalkyl" and "heterocycle" are intended to include sugars, sulfones, sulfoxides, N-oxides of tertiary nitrogen ring members, and carbocyclic fused and benzo-fused ring systems; additionally, both terms also include systems where a heterocycle ring is fused to an aryl group, as defined herein, or an additional heterocycle group. Examples of heterocycloalkyl groups include aziridinyl, azetidinyl, 1,3-benzodioxolyl, dihydroisoindolyl, dihydroisoquinolinyl, dihydrocinnolinyl, dihydrobenzodioxinyl, dihydro[1,3]oxazolo[4,5-b]pyridinyl, benzothiazolyl, dihydroindolyl, dihydropyridinyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-dioxolanyl, isoindolinyl, morpholinyl, piperazinyl, pyrrolidinyl, tetrahydropyridinyl, piperidinyl, thiomorpholinyl, and the like. The heterocycloalkyl groups may be optionally substituted unless specifically prohibited.

The term "hydrazinyl" as used herein, alone or in combination, refers to two amino groups joined by a single bond, i.e., $-\text{N}=\text{N}-$.

The term "hydroxamic acid" as used herein, refers to $-\text{C}(\text{O})\text{ON}(\text{R})\text{O}(\text{R}')$, wherein R and R' are as defined herein, or the corresponding "hydroxamate" anion, including any corresponding hydroxamic acid salt.

The term "hydroxy," as used herein, alone or in combination, refers to $-\text{OH}$.

The term "hydroxyalkyl," as used herein, alone or in combination, refers to a hydroxy group attached to the parent molecular moiety through an alkyl group.

The term "imino," as used herein, alone or in combination, refers to $=\text{N}-$.

The term "iminohydroxy," as used herein, alone or in combination, refers to $=\text{N}(\text{OH})$ and $=\text{N}-\text{O}-$.

The term "isocyanato" refers to a $-\text{NCO}$ group.

The term "isothiocyanato" refers to a $-\text{NCS}$ group.

The phrase "linear chain of atoms" refers to the longest straight chain of atoms independently selected from carbon, nitrogen, oxygen and sulfur.

The term "lower," as used herein, alone or in combination, means containing from 1 to and including 6 carbon atoms.

The term "mercaptyl" as used herein, alone or in combination, refers to an $\text{RS}-$ group, where R is as defined herein.

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The term "nitro," as used herein, alone or in combination, refers to $-\text{NO}_2$.

The terms "oxy" or "oxa" as used herein, alone or in combination, refer to $-\text{O}-$.

The term "oxo," as used herein, alone or in combination, refers to $=\text{O}$.

The term "perhaloalkoxy" refers to an alkoxy group where all of the hydrogen atoms are replaced by halogen atoms.

The term "perhaloalkyl" as used herein, alone or in combination, refers to an alkyl group where all of the hydrogen atoms are replaced by halogen atoms.

The term "phosphoamide" as used herein, alone or in combination, refers to a phosphate group $[(\text{OH})_2\text{P}(\text{O})\text{O}-]$ in which one or more of the hydroxyl groups has been replaced by nitrogen, amino, or amido.

The term "phosphonate" as used herein, alone or in combination, refers to a group of the form $\text{ROP}(\text{OR}')(\text{OR})\text{O}-$ wherein R and R' are selected from the group consisting of hydrogen, alkyl, acyl, heteroalkyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl, any of which may themselves be optionally substituted. "Phosphonate" includes "phosphate $[(\text{OH})_2\text{P}(\text{O})\text{O}-]$ and related phosphoric acid anions which may form salts.

The terms "sulfonate," "sulfonic acid," and "sulfonic," as used herein, alone or in combination, refers to the $-\text{SO}_3\text{H}$ group and its anion as the sulfonic acid is used in salt formation.

The term "sulfanyl," as used herein, alone or in combination, refers to $-\text{S}-$.

The term "sulfinyl," as used herein, alone or in combination, refers to $-\text{S}(\text{O})-$.

The term "sulfonyl," as used herein, alone or in combination, refers to $-\text{S}(\text{O})_2-$.

The term "N-sulfonamido" refers to a $\text{RS}(\text{O})_2\text{NR}'-$ group with R and R' as defined herein.

The term "S-sulfonamido" refers to a $-\text{S}(\text{O})_2\text{NRR}'$ group, with R and R' as defined herein.

The terms "thia" and "thio," as used herein, alone or in combination, refer to a $-\text{S}-$ group or an ether wherein the oxygen is replaced with sulfur. The oxidized derivatives of the thio group, namely sulfinyl and sulfonyl, are included in the definition of thia and thio.

The term "thiol," as used herein, alone or in combination, refers to an $-\text{SH}$ group.

The term "thiocarbonyl," as used herein, when alone includes thioformyl $-\text{C}(\text{S})\text{H}$ and in combination is a $-\text{C}(\text{S})-$ group.

The term "N-thiocarbamyl" refers to an $\text{ROC}(\text{S})\text{NR}'-$ group, with R and R' as defined herein.

The term "O-thiocarbamyl" refers to a $-\text{OC}(\text{S})\text{NRR}'$ group with R and R' as defined herein.

The term "thiocyanato" refers to a $-\text{CNS}$ group.

The term "trihalomethanesulfonamido" refers to a $\text{X}_3\text{CS}(\text{O})_2\text{NR}'$ group with X is a halogen and R as defined herein.

The term "trihalomethanesulfonyl" refers to a $\text{X}_3\text{CS}(\text{O})_2-$ group where X is a halogen.

The term "trihalomethoxy" refers to a $\text{X}_3\text{CO}-$ group where X is a halogen.

The term "trisubstituted silyl," as used herein, alone or in combination, refers to a silicone group substituted at its three free valences with groups as listed herein under the definition of substituted amino. Examples include trimethylsilyl, tert-butyldimethylsilyl, triphenylsilyl and the like.

Any definition herein may be used in combination with any other definition to describe a composite structural group. By convention, the trailing element of any such definition is that which attaches to the parent moiety. For example, the com-

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posite group alkylamido would represent an alkyl group attached to the parent molecule through an amido group, and the term alkoxyalkyl would represent an alkoxy group attached to the parent molecule through an alkyl group.

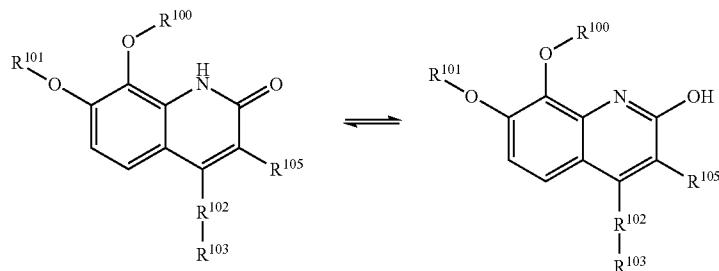
When a group is defined to be "null," what is meant is that said group is absent. A "null" group occurring between two other group may also be understood to be a collapsing of flanking groups. For example, if in $-(CH_2)_sG^1G^2G^3$, the element G^2 were null, said group would become $-(CH_2)_sG^1G^3$.

The term "optionally substituted" means the antecedent group may be substituted or unsubstituted. When substituted, the substituents of an "optionally substituted" group may include, without limitation, one or more substituents independently selected from the following groups or a particular designated set of groups, alone or in combination: lower alkyl, lower alkenyl, lower alkynyl, lower alkanoyl, lower heteroalkyl, lower heterocycloalkyl, lower haloalkyl, lower haloalkenyl, lower haloalkynyl, lower perhaloalkyl, lower perhaloalkoxy, lower cycloalkyl, phenyl, aryl, aryloxy, lower alkoxy, lower haloalkoxy, oxo, lower acyloxy, carbonyl, carboxyl, lower alkylcarbonyl, lower carboxyester, lower carboxamido, cyano, hydrogen, halogen, hydroxy, amino, lower alkylamino, arylamino, amido, nitro, thiol, lower alkylthio, lower haloalkylthio, lower perhaloalkylthio, arylthio, sulfonate, sulfonic acid, trisubstituted silyl, N_3 , SH , SCH_3 , $C(O)CH_3$, CO_2CH_3 , CO_2H , pyridinyl, thiophene, furanyl, lower carbamate, and lower urea. Two substituents may be joined together to form a fused five-, six-, or seven-membered carbocyclic or heterocyclic ring consisting of zero to three heteroatoms, for example forming methylenedioxy or ethylenedioxy. An optionally substituted group may be unsubstituted (e.g., $-CH_2CH_3$), fully substituted (e.g., $-CF_2CF_3$), mono-substituted (e.g., $-CH_2CH_2F$) or substituted at a level anywhere in-between fully substituted and monosubstituted (e.g., $-CH_2CF_3$). Where substituents are recited without

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R' and R'' where $n=(1, 2, 3, \dots, n)$, every substituent, and every term should be understood to be independent of every other in terms of selection from a group. Should any variable, substituent, or term (e.g. aryl, heterocycle, R , etc.) occur more than one time in a formula or generic structure, its definition at each occurrence is independent of the definition at every other occurrence. Those of skill in the art will further recognize that certain groups may be attached to a parent molecule or may occupy a position in a chain of elements from either end as written. Thus, by way of example only, an unsymmetrical group such as $-C(O)N(R)$ may be attached to the parent moiety at either the carbon or the nitrogen.

Asymmetric centers exist in the compounds of the present invention. These centers are designated by the symbols "R" or "S," depending on the configuration of substituents around the chiral carbon atom. It should be understood that the invention encompasses all stereochemical isomeric forms, including diastereomeric, enantiomeric, and epimeric forms, as well as d-isomers and l-isomers, and mixtures thereof. Individual stereoisomers of compounds can be prepared synthetically from commercially available starting materials which contain chiral centers or by preparation of mixtures of enantiomeric products followed by separation such as conversion to a mixture of diastereomers followed by separation or recrystallization, chromatographic techniques, direct separation of enantiomers on chiral chromatographic columns, or any other appropriate method known in the art. Starting compounds of particular stereochemistry are either commercially available or can be made and resolved by techniques known in the art. Additionally, the compounds of the present invention may exist as geometric isomers. The present invention includes all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof. Additionally, compounds may exist as tautomers, including keto-enol tautomers; all tautomeric isomers are provided by this invention. By way of example, the following pairs of tautomers illustrate how both forms are contemplated herein:



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qualification as to substitution, both substituted and unsubstituted forms are encompassed. Where a substituent is qualified as "substituted," the substituted form is specifically intended. Additionally, different sets of optional substituents to a particular moiety may be defined as needed; in these cases, the optional substitution will be as defined, often immediately following the phrase, "optionally substituted with."

The term R or the term R' , appearing by itself and without a number designation, unless otherwise defined, refers to a moiety selected from the group consisting of hydrogen, hydroxyl, halogen, alkyl, cycloalkyl, heteroalkyl, aryl, heteroaryl and heterocycloalkyl, any of which may be optionally substituted. Such R and R' groups should be understood to be optionally substituted as defined herein. Whether an R group has a number designation or not, every R group, including R,

Additionally, the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

The term "bond" refers to a covalent linkage between two atoms, or two moieties when the atoms joined by the bond are considered to be part of larger substructure. A bond may be single, double, or triple unless otherwise specified. A dashed line between two atoms in a drawing of a molecule indicates that an additional bond may be present or absent at that position.

The term "disease" as used herein is intended to be generally synonymous, and is used interchangeably with, the terms "disorder" and "condition" (as in medical condition), in that

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all reflect an abnormal condition of the body or of one of its parts that impairs normal functioning and is typically manifested by distinguishing signs and symptoms.

The term "combination therapy" means the administration of two or more therapeutic agents to treat a therapeutic condition or disorder described in the present disclosure. Such administration encompasses co-administration of these therapeutic agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients or in multiple, separate capsules for each active ingredient. In addition, such administration also encompasses use of each type of therapeutic agent in a sequential manner. In either case, the treatment regimen will provide beneficial effects of the drug combination in treating the conditions or disorders described herein.

"PDE4 inhibitor" is used herein to refer to a compound that exhibits an IC_{50} with respect to PDE4 activity of no more than about 100 μ M and more typically not more than about 50 μ M, as measured in the PDE4 assay described generally hereinbelow. " IC_{50} " is that concentration of inhibitor which reduces the activity of an enzyme (e.g., PDE4) to half-maximal level. Certain representative compounds of the present invention have been discovered to exhibit inhibition against PDE4. In certain embodiments, compounds will exhibit an IC_{50} with respect to PDE4 of no more than about 10 μ M; in further embodiments, compounds will exhibit an IC_{50} with respect to PDE4 of no more than about 5 μ M; in yet further embodiments, compounds will exhibit an IC_{50} with respect to PDE4 of not more than about 1 μ M, as measured in the PDE4 assay described herein. In yet further embodiments, compounds will exhibit an IC_{50} with respect to PDE4 of not more than about 200 nM.

The phrase "therapeutically effective" is intended to qualify the amount of active ingredients used in the treatment of a disease or disorder. This amount will achieve the goal of reducing or eliminating the said disease or disorder.

As used herein, reference to "treatment" of a patient is intended to include prophylaxis. The term "patient" means all mammals including humans. Examples of patients include humans, cows, dogs, cats, goats, sheep, pigs, and rabbits. Preferably, the patient is a human.

The term "prodrug" refers to a compound that is made more active in vivo. Certain of the present compounds can also exist as prodrugs, as described in *Hydrolysis in Drug and Prodrug Metabolism: Chemistry, Biochemistry, and Enzymology* (Testa, Bernard and Mayer, Joachim M. Wiley-VHCA, Zurich, Switzerland 2003). Prodrugs of the compounds described herein are structurally modified forms of the compound that readily undergo chemical changes under physiological conditions to provide the compound. Additionally, prodrugs can be converted to the compound by chemical or biochemical methods in an ex vivo environment. For example, prodrugs can be slowly converted to a compound when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent. Prodrugs are often useful because, in some situations, they may be easier to administer than the compound, or parent drug. They may, for instance, be bioavailable by oral administration whereas the parent drug is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. A wide variety of prodrug derivatives are known in the art, such as those that rely on hydrolytic cleavage or oxidative activation of the prodrug. An example, without limitation, of a prodrug would be a compound which is administered as an ester (the "prodrug"), but then is metabolically hydrolyzed to the carboxylic acid, the active entity. Additional examples include peptidyl derivatives of a compound. The term "therapeutically accept-

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able prodrug," refers to those prodrugs or zwitterions which are suitable for use in contact with the tissues of patients without undue toxicity, irritation, and allergic response, are commensurate with a reasonable benefit/risk ratio, and are effective for their intended use.

The compounds of the present invention can exist as therapeutically acceptable salts. The present invention includes compounds listed above in the form of salts, including acid addition salts. Suitable salts include those formed with both organic and inorganic acids. Such acid addition salts will normally be pharmaceutically acceptable. However, salts of non-pharmaceutically acceptable salts may be of utility in the preparation and purification of the compound in question. Basic addition salts may also be formed and be pharmaceutically acceptable. For a more complete discussion of the preparation and selection of salts, refer to *Pharmaceutical Salts: Properties, Selection, and Use* (Stahl, P. Heinrich. Wiley-VCHA, Zurich, Switzerland, 2002).

The term "therapeutically acceptable salt," as used herein, represents salts or zwitterionic forms of the compounds of the present invention which are water or oil-soluble or dispersible and therapeutically acceptable as defined herein. The salts can be prepared during the final isolation and purification of the compounds or separately by reacting the appropriate compound in the form of the free base with a suitable acid. Representative acid addition salts include acetate, adipate, alginate, L-ascorbate, aspartate, benzoate, benzenesulfonate (besylate), bisulfate, butyrate, camphorate, camphorsulfonate, citrate, digluconate, formate, fumarate, gentisate, glutarate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hippurate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethansulfonate (isethionate), lactate, maleate, malonate, DL-mandelate, mesitylenesulfonate, methanesulfonate, naphthalenesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphonate, picrate, pivalate, propionate, pyroglutamate, succinate, sulfonate, tartrate, L-tartrate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, para-toluenesulfonate (p-tosylate), and undecanoate. Also, basic groups in the compounds of the present invention can be quaternized with methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides; dimethyl, diethyl, dibutyl, and diethyl sulfates; decyl, lauryl, myristyl, and steryl chlorides, bromides, and iodides; and benzyl and phenethyl bromides. Examples of acids which can be employed to form therapeutically acceptable addition salts include inorganic acids such as hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic, succinic, and citric. Salts can also be formed by coordination of the compounds with an alkali metal or alkaline earth ion. Hence, the present invention contemplates sodium, potassium, magnesium, and calcium salts of the compounds disclosed herein, and the like.

Basic addition salts can be prepared during the final isolation and purification of the compounds by reacting a carboxyl group with a suitable base such as the hydroxide, carbonate, or bicarbonate of a metal cation or with ammonia or an organic primary, secondary, or tertiary amine. The cations of therapeutically acceptable salts include lithium, sodium, potassium, calcium, magnesium, and aluminum, as well as nontoxic quaternary amine cations such as ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine, tributylamine, pyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylmorpholine, dicyclohexylamine, procaine, dibenzylamine, N,N-dibenzylphenethylamine, 1-ephenamine, and N,N'-

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dibenzylethylenediamine. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, and piperazine.

While it may be possible for the compounds of the subject invention to be administered as the raw chemical, it is also possible to present them as a pharmaceutical formulation. Accordingly, provided herein are pharmaceutical formulations which comprise one or more of certain compounds of the present invention, or one or more pharmaceutically acceptable salts, esters, prodrugs, amides, or solvates thereof, together with one or more pharmaceutically acceptable carriers thereof and optionally one or more other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Proper formulation is dependent upon the route of administration chosen. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art; e.g., in Remington's Pharmaceutical Sciences. The pharmaceutical compositions disclosed herein may be manufactured in any manner known in the art, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous, intraarticular, and intramedullary), intraperitoneal, transmucosal, transdermal, rectal and topical (including dermal, buccal, sublingual and intraocular) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Typically, these methods include the step of bringing into association a compound of the subject invention or a pharmaceutically acceptable salt, ester, amide, prodrug or solvate thereof ("active ingredient") with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

Pharmaceutical preparations which can be used orally include tablets, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. Tablets may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with binders, inert diluents, or lubricating, surface active or dispersing agents. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein. All formulations for oral administration should be in dosages suitable for such administration. The push-fit capsules can con-

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tain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

The compounds may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in powder form or in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline or sterile pyrogen-free water, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Formulations for parenteral administration include aqueous and non-aqueous (oily) sterile injection solutions of the active compounds which may contain antioxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

For buccal or sublingual administration, the compositions may take the form of tablets, lozenges, pastilles, or gels formulated in conventional manner. Such compositions may comprise the active ingredient in a flavored basis such as sucrose and acacia or tragacanth.

The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter, polyethylene glycol, or other glycerides.

Certain compounds of the present invention may be administered topically, that is by non-systemic administration. This includes the application of a compound of the present inven-

tion externally to the epidermis or the buccal cavity and the instillation of such a compound into the ear, eye and nose, such that the compound does not significantly enter the blood stream. In contrast, systemic administration refers to oral, intravenous, intraperitoneal and intramuscular administration.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as gels, liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose. The active ingredient for topical administration may comprise, for example, from 0.001% to 10% w/w (by weight) of the formulation. In certain embodiments, the active ingredient may comprise as much as 10% w/w. In other embodiments, it may comprise less than 5% w/w. In certain embodiments, the active ingredient may comprise from 2% w/w to 5% w/w. In other embodiments, it may comprise from 0.1% to 1% w/w of the formulation.

Gels for topical or transdermal administration may comprise, generally, a mixture of volatile solvents, nonvolatile solvents, and water. In certain embodiments, the volatile solvent component of the buffered solvent system may include lower (C1-C6) alkyl alcohols, lower alkyl glycols and lower glycol polymers. In further embodiments, the volatile solvent is ethanol. The volatile solvent component is thought to act as a penetration enhancer, while also producing a cooling effect on the skin as it evaporates. The nonvolatile solvent portion of the buffered solvent system is selected from lower alkylene glycols and lower glycol polymers. In certain embodiments, propylene glycol is used. The nonvolatile solvent slows the evaporation of the volatile solvent and reduces the vapor pressure of the buffered solvent system. The amount of this nonvolatile solvent component, as with the volatile solvent, is determined by the pharmaceutical compound or drug being used. When too little of the nonvolatile solvent is in the system, the pharmaceutical compound may crystallize due to evaporation of volatile solvent, while an excess may result in a lack of bioavailability due to poor release of drug from solvent mixture. The buffer component of the buffered solvent system may be selected from any buffer commonly used in the art; in certain embodiments, water is used. A common ratio of ingredients is about 20% of the nonvolatile solvent, about 40% of the volatile solvent, and about 40% water. There are several optional ingredients which can be added to the topical composition. These include, but are not limited to, chelators and gelling agents. Appropriate gelling agents can include, but are not limited to, semisynthetic cellulose derivatives (such as hydroxypropylmethylcellulose) and synthetic polymers, and cosmetic agents.

Lotions include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

Creams, ointments or pastes are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy base. The base may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive

oil; wool fat or its derivatives or a fatty acid such as stearic or oleic acid together with an alcohol such as propylene glycol or a macrogel. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as a sorbitan ester or a polyoxyethylene derivative thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as siliceous silicas, and other ingredients such as lanolin, may also be included.

Drops may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and, in certain embodiments, including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100° C. for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavored basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerin or sucrose and acacia.

For administration by inhalation, compounds may be conveniently delivered from an insufflator, nebulizer pressurized packs or other convenient means of delivering an aerosol spray. Pressurized packs may comprise a suitable propellant such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Alternatively, for administration by inhalation or insufflation, the compounds according to the invention may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form, in for example, capsules, cartridges, gelatin or blister packs from which the powder may be administered with the aid of an inhalator or insufflator.

Preferred unit dosage formulations are those containing an effective dose, as herein below recited, or an appropriate fraction thereof of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations described above may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

Compounds may be administered orally or via injection at a dose of from 0.1 to 500 mg/kg per day. The dose range for adult humans is generally from 5 mg to 2 g/day. Tablets or other forms of presentation provided in discrete units may conveniently contain an amount of one or more compounds which is effective at such dosage or as a multiple of the same, for instance, units containing 5 mg to 500 mg, usually around 10 mg to 200 mg.

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The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

The compounds can be administered in various modes, e.g. orally, topically, or by injection. The precise amount of compound administered to a patient will be the responsibility of the attendant physician. 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, diets, time of administration, route of administration, rate of excretion, drug combination, the precise disorder being treated, and the severity of the indication or condition being treated. Also, the route of administration may vary depending on the condition and its severity.

In certain instances, it may be appropriate to administer at least one of the compounds described herein (or a pharmaceutically acceptable salt, ester, or prodrug thereof) in combination with another therapeutic agent. By way of example only, if one of the side effects experienced by a patient upon receiving one of the compounds herein is hypertension, then it may be appropriate to administer an anti-hypertensive agent in combination with the initial therapeutic agent. Or, by way of example only, the therapeutic effectiveness of one of the compounds described herein may be enhanced by administration of an adjuvant (i.e., by itself the adjuvant may only have minimal therapeutic benefit, but in combination with another therapeutic agent, the overall therapeutic benefit to the patient is enhanced). Or, by way of example only, the benefit of experienced by a patient may be increased by administering one of the compounds described herein with another therapeutic agent (which also includes a therapeutic regimen) that also has therapeutic benefit. By way of example only, in a treatment for diabetes involving administration of one of the compounds described herein, increased therapeutic benefit may result by also providing the patient with another therapeutic agent for diabetes. In any case, regardless of the disease, disorder or condition being treated, the overall benefit experienced by the patient may simply be additive of the two therapeutic agents or the patient may experience a synergistic benefit.

In any case, the multiple therapeutic agents (at least one of which is a compound of the present invention) may be administered in any order or even simultaneously. If simultaneously, the multiple therapeutic agents may be provided in a single, unified form, or in multiple forms (by way of example only, either as a single pill or as two separate pills). One of the therapeutic agents may be given in multiple doses, or both may be given as multiple doses. If not simultaneous, the timing between the multiple doses may be any duration of time ranging from a few minutes to four weeks.

Thus, in another aspect, the present invention provides methods for treating PDE4-mediated disorders in a human or animal subject in need of such treatment comprising administering to said subject an amount of a compound of the present invention effective to reduce or prevent said disorder in the subject in combination with at least one additional agent for the treatment of said disorder that is known in the art. In a related aspect, the present invention provides therapeutic compositions comprising at least one compound of the present invention in combination with one or more additional agents for the treatment of PDE4-mediated disorders.

Compounds of the subject invention may be useful in treating PDE4-mediated disease, disorders and conditions. In certain embodiments, said compounds may find use in treating acute and chronic pain and inflammation. The compounds of

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the present invention may be useful to treat patients with neuropathy, neuropathic pain, or inflammatory pain such as reflex sympathetic dystrophy/causalgia (nerve injury), peripheral neuropathy (including diabetic neuropathy), intractable cancer pain, complex regional pain syndrome, and entrapment neuropathy (carpel tunnel syndrome). The compounds may also be useful in the treatment of pain associated with acute herpes zoster (shingles), postherpetic neuralgia (PHN), and associated pain syndromes such as ocular pain. 5 The compounds may further be useful as analgesics in the treatment of pain such as surgical analgesia, or as an anti-pyretic for the treatment of fever. Pain indications include, but are not limited to, post-surgical pain for various surgical procedures including post-cardiac surgery, dental pain/dental extraction, pain resulting from cancer, muscular pain, mastalgia, pain resulting from dermal injuries, lower back pain, headaches of various etiologies, including migraine, and the like. The compounds may also be useful for the treatment of pain-related disorders such as tactile allodynia and hyperalgesia. 10 The pain may be somatogenic (either nociceptive or neuropathic), acute and/or chronic. The PDE4 inhibitors of the subject invention may also be useful in conditions where NSAIDs, morphine or fentanyl opiates and/or other opioid analgesics would traditionally be administered.

Furthermore, compounds of the subject invention may be used in the treatment or prevention of opiate tolerance in patients needing protracted opiate analgesics, and benzodiazepine tolerance in patients taking benzodiazepines, and other addictive behavior, for example, nicotine addiction, alcoholism, and eating disorders. Moreover, the compounds and methods of the present invention may be useful in the treatment or prevention of drug withdrawal symptoms, for example treatment or prevention of symptoms of withdrawal from opiate, alcohol, or tobacco addiction.

In addition, compounds of the subject invention may be used to treat insulin resistance and other metabolic disorders such as atherosclerosis that are typically associated with an exaggerated inflammatory signaling.

The present invention encompasses therapeutic methods 40 using novel selective PDE4 inhibitors to treat or prevent respiratory disease or conditions, including therapeutic methods of use in medicine for preventing and treating a respiratory disease or condition including: asthmatic conditions including allergen-induced asthma, exercise-induced asthma, pollution-induced asthma, cold-induced asthma, and viral-induced-asthma; asthma-related diseases such as airway hyperreactivity and small airway disease; chronic obstructive pulmonary diseases including chronic bronchitis with normal airflow, chronic bronchitis with airway obstruction (chronic obstructive bronchitis), emphysema, asthmatic bronchitis, and bullous disease; and other pulmonary diseases involving inflammation including bronchiolitis, bronchioectasis, cystic fibrosis, pigeon fancier's disease, farmer's lung, acute respiratory distress syndrome, pneumonia, pneumonitis, aspiration or inhalation injury, fat embolism in the lung, acidosis 45 inflammation of the lung, acute pulmonary edema, acute mountain sickness, acute pulmonary hypertension, persistent pulmonary hypertension of the newborn, perinatal aspiration syndrome, hyaline membrane disease, acute pulmonary thromboembolism, heparin-protamine reactions, sepsis, status asthamticus, hypoxia, dyspnea, hypercapnea, hyperinflation, hypoxemia, and cough. Further, compounds disclosed herein would find use in the treatment of allergic disorders such as delayed type hypersensitivity reaction, allergic contact dermatitis, allergic rhinitis, and chronic sinusitis.

Other disorders or conditions which may be treated by the compounds of the present invention include inflammation

and related disorders. The compounds of the present invention may be useful as anti-inflammatory agents with the additional benefit of having significantly less harmful side effects. The compounds may be useful to treat arthritis, including but not limited to rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, juvenile arthritis, acute rheumatic arthritis, enteropathic arthritis, neuropathic arthritis, psoriatic arthritis, reactive arthritis (Reiter's syndrome), and pyogenic arthritis, and autoimmune diseases, including systemic lupus erythematosus, hemolytic syndromes, autoimmune hepatitis, autoimmune neuropathy, vitiligo (autoimmune thyroiditis), Hashimoto's thyroiditis, anemias, myositis including polymyositis, alopecia areata, Goodpasture's syndrome, hypophyseal, and pulmonary fibrosis.

The compounds may also be useful in treating osteoporosis and other related bone disorders.

These compounds may also be used to treat gastrointestinal conditions such as reflux esophagitis, diarrhea, inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome, Graves' disease (hyperthyroidism), necrotizing enterocolitis, and ulcerative colitis. The compounds may also be used in the treatment of pulmonary inflammation, such as that associated with viral infections and cystic fibrosis.

In addition, compounds of invention may also be useful in organ transplant patients either alone or in combination with conventional immunomodulators. Examples of conditions to be treated in said patients include graft vs. host reaction (i.e., graft vs. host disease), allograft rejections (e.g., acute allograft rejection, and chronic allograft rejection), transplant reperfusion injury, and early transplantation rejection (e.g., acute allograft rejection).

Yet further, the compounds of the invention may be useful in the treatment of pruritis and vitiligo.

The compounds of the present invention may also be useful in treating tissue damage in such diseases as vascular diseases, migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodema, rheumatic fever, type I diabetes, neuromuscular junction disease including myasthenia gravis, white matter disease including multiple sclerosis, sarcoidosis, nephritis, nephrotic syndrome, Langerhans' cell histiocytosis, glomerulonephritis, reperfusion injury, pancreatitis, interstitial cystitis, Behcet's syndrome, polymyositis, gingivitis, periodontitis, hypersensitivity, swelling occurring after injury, ischemias including myocardial ischemia, cardiovascular ischemia, and ischemia secondary to cardiac arrest, cirrhosis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, stroke, ischemia reperfusion injury, multi-organ dysfunction, restenosis including restenosis following coronary bypass surgery, and the like.

The compounds of the subject invention may also be useful for the treatment of certain diseases and disorders of the nervous system. Central nervous system disorders in which PDE4 inhibition may be useful include cortical dementias including Alzheimer's disease and mild cognitive impairment (MCI), central nervous system damage resulting from stroke, ischemias including cerebral ischemia (both focal ischemia, thrombotic stroke and global ischemia (for example, secondary to cardiac arrest), and trauma. Neurodegenerative disorders in which PDE4 inhibition may be useful include nerve degeneration or nerve necrosis in disorders such as hypoxia, hypoglycemia, epilepsy, and in cases of central nervous system (CNS) trauma (such as spinal cord and head injury), hyperbaric oxygen convulsions and toxicity, dementia e.g. pre-senile dementia, and AIDS-related dementia, cachexia, Sydenham's chorea, Huntington's disease, Parkinson's Disease, amyotrophic lateral sclerosis (ALS), Kor-

sakoff's syndrome, and imbecility relating to a cerebral vessel disorder. Further disorders in which PDE4 inhibition might prove useful include neuropathies of the central and peripheral nervous system (including, for example, IgA neuropathy, membranous neuropathy and idiopathic neuropathy), chronic inflammatory demyelinating polyneuropathy, transverse myelitis, Gullain-Barre disease, encephalitis, and cancers of the nervous system. Disorders of CNS function in which PDE4 inhibitors may find use include sleeping disorders, schizophrenia, depression, depression or other symptoms associated with Premenstrual Syndrome (PMS), and anxiety.

Furthermore, the compounds of the present invention may also be useful in inhibiting PDE4 activity for the amelioration of systemic disorders including systemic hypotension associated with septic and/or toxic hemorrhagic shock induced by a wide variety of agents; as a therapy with cytokines such as TNF, IL-1 and IL-2; and as an adjuvant to short term immunosuppression in transplant therapy.

Still other disorders or conditions which may be treated by the compounds of the subject invention include the prevention or treatment of cancer, such as colorectal cancer, and cancer of the breast, lung, prostate, bladder, cervix and skin. Compounds of the invention may be used in the treatment and prevention of neoplasias including but not limited to brain cancer, bone cancer, leukemia, lymphoma, epithelial cell-derived neoplasia (epithelial carcinoma) such as basal cell carcinoma, adenocarcinoma, gastrointestinal cancer such as lip cancer, mouth cancer, esophageal cancer, small bowel cancer and stomach cancer, colon cancer, liver cancer, bladder cancer, pancreas cancer, ovary cancer, cervical cancer, lung cancer, breast cancer and skin cancer, such as squamous cell and basal cell cancers, prostate cancer, renal cell carcinoma, and other known cancers that effect epithelial cells throughout the body. The neoplasia can be selected from gastrointestinal cancer, liver cancer, bladder cancer, pancreas cancer, ovary cancer, prostate cancer, cervical cancer, lung cancer, breast cancer and skin cancer, such as squamous cell and basal cell cancers. The present compounds and methods may also be used to treat the fibrosis which occurs with radiation therapy. The present compounds and methods may be used to treat subjects having adenomatous polyps, including those with familial adenomatous polyposis (FAP). Additionally, the present compounds and methods may be used to prevent polyps from forming in patients at risk of FAP.

The compounds of the subject invention may be used in the treatment of ophthalmic diseases, such as dry eye, glaucoma, corneal neovascularization, optic neuritis, Sjogren's syndrome, retinal ganglion degeneration, ocular ischemia, retinitis, retinopathies, uveitis, ocular photophobia, and of inflammation and pain associated with acute injury to the eye tissue. Specifically, the compounds may be used to treat glaucomatous retinopathy and/or diabetic retinopathy. The compounds may also be used to treat post-operative inflammation or pain as from ophthalmic surgery such as cataract surgery and refractive surgery.

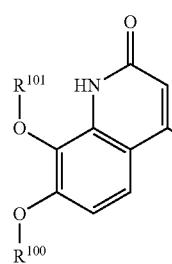
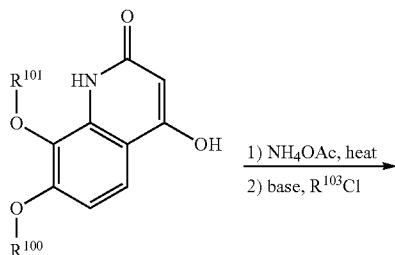
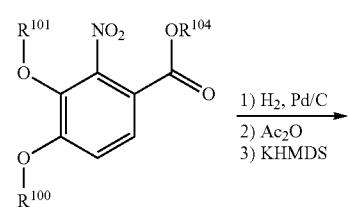
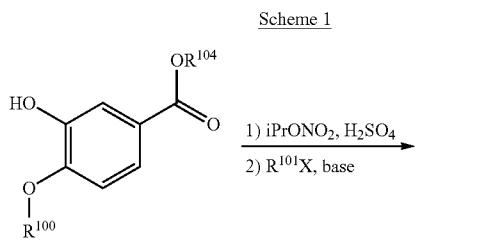
Moreover, compounds of the subject invention may be used in the treatment of menstrual cramps, dysmenorrhea, premature labor, endometriosis, tendonitis, bursitis, skin-related conditions such as psoriasis, eczema, burns, sunburn, dermatitis, pancreatitis, hepatitis, lichen planus, scleritis, scleroderma, dermatomyositis, and the like. Other conditions in which the compounds of the subject invention may be used include diabetes (type I or type II), atherosclerosis, congestive heart failure, myocarditis, atherosclerosis, cerebral ischemia, angiogenesis, pulmonary hypertension, and aortic aneurysm.

The present compounds may also be used in co-therapies, partially or completely, in place of other conventional anti-inflammatory therapies, such as together with steroids, NSAIDs, COX-2 selective inhibitors, 5-lipoxygenase inhibitors, LTB₄ antagonists and LTA₄ hydrolase inhibitors. The compounds of the subject invention may also be used to prevent tissue damage when therapeutically combined with antibacterial or antiviral agents.

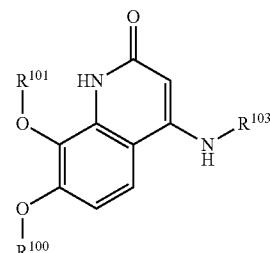
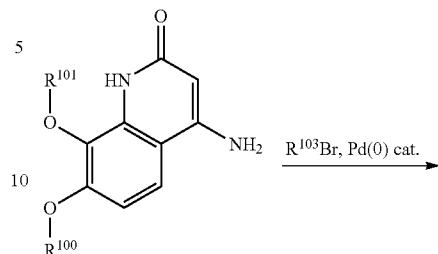
Besides being useful for human treatment, the compounds and formulations of the present invention are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. More preferred animals include horses, dogs, and cats.

General Synthetic Methods for Preparing Compounds

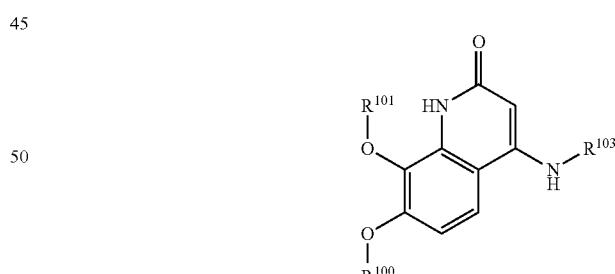
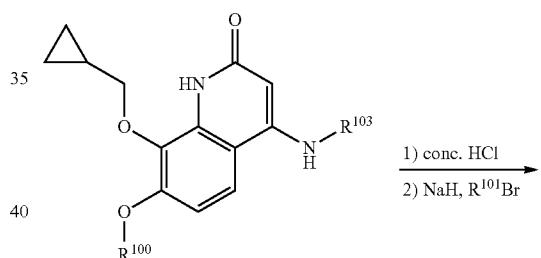
The following schemes can be used to practice the present invention.



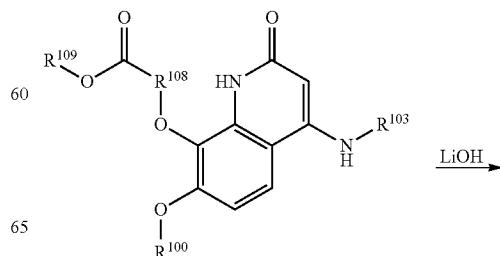
Scheme 2



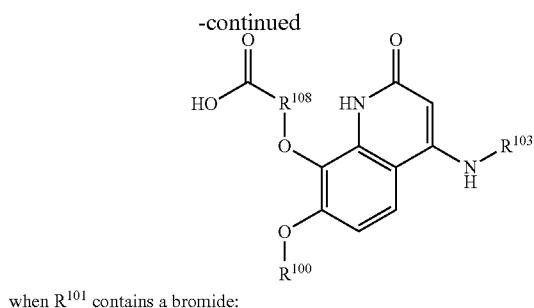
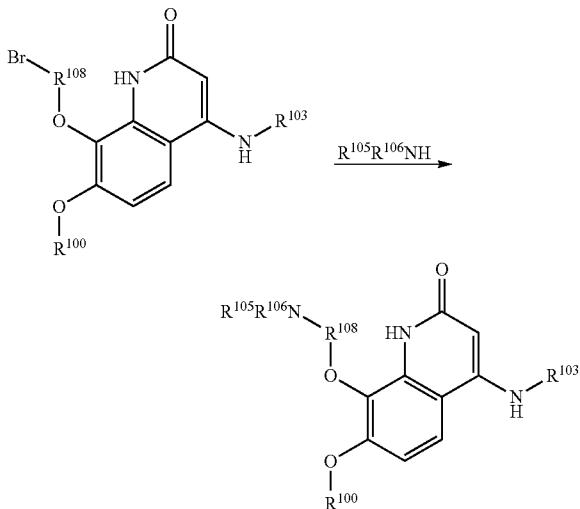
Scheme 3



when R^{101} contains an ester:



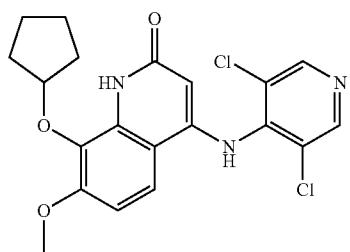
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when R¹⁰¹ contains a bromide:

The invention is further illustrated by the following examples.

EXAMPLE 1

8-(Cyclopentyloxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxyquinolin-2(1H)-one



Step 1

Sulfuric acid (3.0 mL, 56 mmol) was added dropwise over 2 min to a solution of methyl 3-hydroxy-4-methoxybenzoate (3.64 g, 20 mmol), tetrabutylammonium hydrogensulfate (340 mg, 1.0 mmol), isopropyl nitrate (5.0 mL, 50 mmol), and dichloromethane (40 mL) at 0° C. The reaction was allowed to warm to rt, maintained for 45 min, and then quenched with ice water (100 mL). This mixture was extracted with dichloromethane (250 mL×2). The combined extracts were dried, filtered, concentrated, and purified by silica gel chromatography (4:1→3:2; hexanes:ethyl acetate) to give methyl 3-hydroxy-4-methoxy-2-nitrobenzoate: MS (ESI): 228.4.

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Step 2

A mixture of methyl 3-hydroxy-4-methoxy-2-nitrobenzoate (1.14 g, 5.0 mmol), bromocyclopentane (0.7 mL, 6.5 mmol), potassium carbonate (2.0 g, 14 mmol), and anhydrous acetonitrile (15 mL) was refluxed under N₂. After 19 h, the reaction was allowed to cool to rt, concentrated, and purified by silica gel chromatography (4:1→3:2; hexanes:ethyl acetate) to give methyl 3-(cyclopentyloxy)-4-methoxy-2-nitrobenzoate: MS (ESI): 296.5.

Step 3

A mixture of methyl 3-(cyclopentyloxy)-4-methoxy-2-nitrobenzoate (750 mg, 2.54 mmol), 10% Pd/C (50% H₂O, 500 mg, 0.23 mmol Pd), and methanol (10 mL) was stirred vigorously at rt under an atmosphere of H₂. After 21 h, the mixture was filtered through Celite and concentrated to give methyl 2-amino-3-(cyclopentyloxy)-4-methoxybenzoate: MS (ESI): 266.5.

Step 4

A solution of methyl 2-amino-3-(cyclopentyloxy)-4-methoxybenzoate (5.54 g, 20.9 mmol), acetic anhydride (21.0 mL, 222 mmol), and dioxane (35 mL) was heated at 40° C. under N₂ for 17 h and then allowed to cool to rt. Water (10 mL) was added, and after 15 min of stirring, the reaction was concentrated to give methyl 2-acetamido-3-(cyclopentyloxy)-4-methoxybenzoate: MS (ESI): 307.9.

Step 5

A solution of methyl 2-acetamido-3-(cyclopentyloxy)-4-methoxybenzoate (6.42 g, 20.9 mmol) and anhydrous THF (60 mL) was added via syringe pump (1 mL/min) to a solution of KHMDS (150 mL, 0.5M PhMe, 75 mmol) at -78° C. under N₂. The reaction was allowed to slowly warm to rt as the bath expired overnight. After 17 h, the reaction was poured into ice/water (250 mL), let stir for 10 min, and the layers were separated. The aqueous was washed with ether (150 mL), acidified with conc. HCl (7 mL), and filtered to give 8-(cyclopentyloxy)-4-hydroxy-7-methoxyquinolin-2(1H)-one: MS (ESI): 276.0.

Step 6

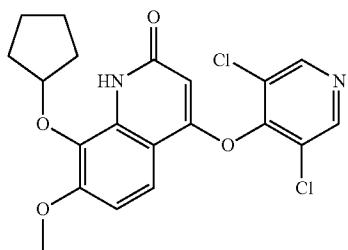
A mixture of 8-(cyclopentyloxy)-4-hydroxy-7-methoxyquinolin-2(1H)-one (350 mg, 1.3 mmol), ammonium acetate (4.0 g, 52 mmol), and anhydrous m-xylene (10 mL) was heated at 150° C. under N₂ for 48 h and then allowed to cool to rt. The mixture was concentrated to dryness, diluted with water (25 mL), stirred for 2 min, sonicated for 1 min, and then stirred for 5 min. The free-flowing solid was filtered, washed with water (25 mL), and pumped to dryness to give 4-amino-8-(cyclopentyloxy)-7-methoxyquinolin-2(1H)-one: MS (ESI): 274.9.

Step 7

4-Amino-8-(cyclopentyloxy)-7-methoxyquinolin-2(1H)-one (340 mg, 1.24 mmol) was added in 3 portions over 5 min to a mixture of sodium hydride (110 mg, 60%, 2.75 mmol) and DMSO (4 mL) at rt under N₂. After 5 min, 3,4,5-trichloropyridine (271 mg, 1.49 mmol) was added. After 19 h, more sodium hydride (100 mg, 60%, 2.5 mmol) was added followed by more 3,4,5-trichloropyridine (250 mg, 1.37 mmol). After an additional 4 h, the reaction was poured into 1M KH₂PO₄ (75 mL) and stirred for 5 min. The solids were filtered, washed with water (25 mL), and then purified by reverse-phase HPLC (3:7→1:0; acetonitrile:water). In some cases, additional purification by silica gel chromatography (1:0→9:1; dichloromethane:methanol) was needed to give 8-(cyclopentyloxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxyquinolin-2(1H)-one: ¹H NMR (400 MHz, DMSO-d₆): δ 9.39 (s, 1H), 8.86 (s, 1H), 8.76 (s, 2H), 7.87 (d, 1H), 7.06 (d, 1H), 4.97 (m, 1H), 4.78 (s, 1H), 3.90 (s, 3H), 1.83–1.48 (m, 8H); MS (ESI): 419.7.

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EXAMPLE 2

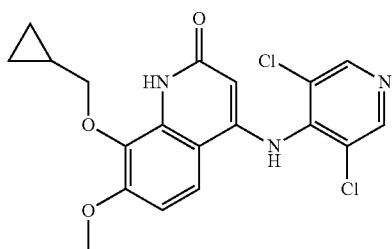
8-(Cyclopentyloxy)-4-(3,5-dichloropyridin-4-yloxy)-7-methoxyquinolin-2(1H)-one



The title compound was isolated from the purification of Example 1, Step 7. ^1H NMR (400 MHz, DMSO-d₆): δ 10.28 (s, 1H), 8.84 (s, 2H), 7.71 (d, 1H), 7.11 (d, 1H), 5.35 (s, 1H), 4.97 (m, 1H), 3.91 (s, 3H), 1.86-1.43 (m, 8H); MS (ESI): 420.7.

EXAMPLE 3

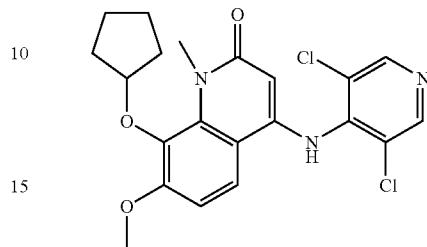
8-(Cyclopropylmethoxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxyquinolin-2(1H)-one



The title compound was prepared from methyl 3-hydroxy-4-methoxy-2-nitrobenzoate (Example 1, Step 1) and (bromomethyl)cyclopropane following the procedures outlined in Example 1. ^1H NMR (400 MHz, DMSO-d₆): δ 9.91 (s, 1H), 8.83 (s, 1H), 8.76 (s, 2H), 7.87 (d, 1H), 7.03 (d, 1H), 4.78 (s, 1H), 3.89 (s, 3H), 3.84 (d, 2H), 1.27 (m, 1H), 0.45 (m, 2H), 0.25 (m, 2H); MS (ESI): 405.8.

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EXAMPLE 4

8-(Cyclopentyloxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-1-methylquinolin-2(1H)-one



Step 1

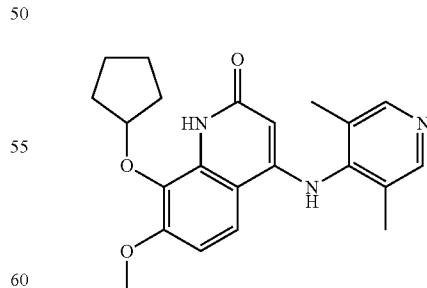
A solution of methyl 2-acetamido-3-(cyclopentyloxy)-4-methoxybenzoate (1.6 g, 5.2 mmol, Example 1, Step 4) and anhydrous THF (30 mL) was added over 5 min to a mixture of sodium hydride (230 mg, 5.75 mmol) and anhydrous THF (10 mL) at 0° C. under N₂. The reaction was allowed to warm to rt and after 20 min, cooled back to 0° C. A solution of iodomethane (1.06 g, 0.0075 mol) and anhydrous THF (10 mL) was added over 3 min. The reaction was allowed to warm to rt and after 30 min, concentrated. The residue was diluted with ethyl acetate (40 mL) and washed with brine (10 mL×2). The organic layer was dried, filtered, and concentrated to give methyl 3-(cyclopentyloxy)-4-methoxy-2-(N-methylacetamido)benzoate: MS (ESI): 322.1.

Step 2

The title compound was prepared from methyl 3-(cyclopentyloxy)-4-methoxy-2-(N-methylacetamido)benzoate following the procedures outlined in Example 1. ^1H NMR (400 MHz, DMSO-d₆): δ 8.75 (s, 1H), 8.74 (s, 2H), 7.92 (d, 1H), 7.13 (d, 1H), 4.92 (s, 1H), 4.53 (m, 1H), 3.90 (s, 3H), 3.59 (s, 3H), 1.80-1.48 (m, 8H); MS (ESI): 433.9.

EXAMPLE 5

8-(Cyclopentyloxy)-4-(3,5-dimethylpyridin-4-ylamino)-7-methoxyquinolin-2(1H)-one



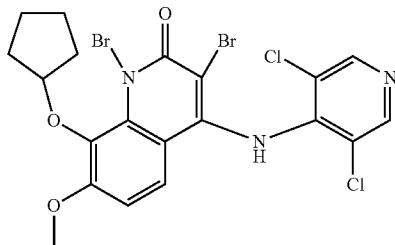
The title compound was prepared from 4-bromo-3,5-dimethylpyridine and 4-amino-8-(cyclopentyloxy)-7-methoxyquinolin-2(1H)-one (Example 1, Step 6) following the procedure outlined in Example 8. ^1H NMR (400 MHz, DMSO-d₆): δ 9.08 (s, 1H), 8.44 (s, 1H), 8.40 (s, 2H), 7.88 (d, 1H), 6.55 (s, 1H).

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7.03 (d, 1H), 4.96 (m, 1H), 4.51 (s, 1H), 3.90 (s, 3H), 2.13 (s, 6H), 1.80-1.54 (m, 8H); MS (ESI): 380.2.

EXAMPLE 6

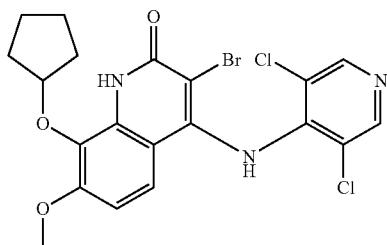
1,3-Dibromo-8-(cyclopentyloxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxyquinolin-2(1H)-one



N-Bromosuccinimide (0.118 g, 0.61 mmol) was added to a solution of 4-(3,5-dichloropyridin-4-ylamino)-8-(cyclopentyloxy)-7-methoxyquinolin-2(1H)-one (0.100 g, 0.240 mmol, Example 1) and anhydrous DMF (2 mL) at 0° C. After 2 h at 0° C., the mixture was poured into water, and the precipitate was filtered to give 1,3-dibromo-8-(cyclopentyloxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxyquinolin-2(1H)-one: ¹H NMR (400 MHz, DMSO-d₆): δ 10.5 (s, 1H), 8.59 (s, 2H), 6.76 (d, 1H), 6.61 (d, 1H), 4.87 (m, 1H), 3.80 (s, 3H), 1.82-1.51 (m, 8H); MS (ESI): 575.8.

EXAMPLE 7

3-Bromo-8-(cyclopentyloxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxyquinolin-2(1H)-one



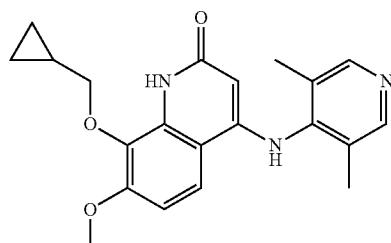
N-Bromosuccinimide (0.104 g, 0.585 mmol) was added to a solution of 4-(3,5-dichloropyridin-4-ylamino)-8-(cyclopentyloxy)-7-methoxyquinolin-2(1H)-one (0.246 g, 0.585 mmol, Example 1) and anhydrous DMF (3 mL) at 0° C. After 4 h at 0° C., the mixture was poured into water, and the precipitate was filtered. Saturated sodium thiosulfate solution (1 mL) was added to a solution of the filter cake and methanol (5 mL). After the dibromo intermediate was consumed by LCMS, the mixture was diluted with water and extracted with EtOAc. The organic extract was dried, filtered, and concentrated to give 3-bromo-8-(cyclopentyloxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxyquinolin-2(1H)-one: ¹H NMR (400 MHz, DMSO-d₆): δ 10.56 (s, 1H), 8.88 (br s, 1H),

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8.42 (s, 2H), 7.62 (d, 1H), 7.04 (d, 1H), 4.98 (m, 1H), 3.89 (s, 3H), 1.84-1.51 (m, 8H); MS (ESI): 497.8.

EXAMPLE 8

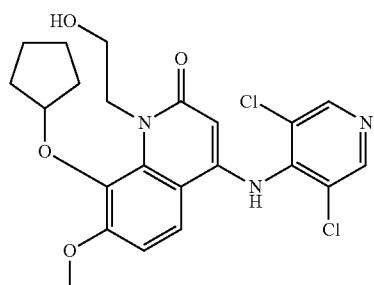
8-(Cyclopropylmethoxy)-4-(3,5-dimethylpyridin-4-ylamino)-7-methoxyquinolin-2(1H)-one



A solution of 4-bromo-3,5-dimethylpyridine (1.16 g, 6.21 mmol) and degassed toluene (5 mL) was added to a mixture of 4-amino-8-(cyclopropylmethoxy)-7-methoxyquinolin-2(1H)-one (1.94 g, 7.45 mmol, intermediate for Example 3), Pd₂(dba)₃ (0.28 g, 0.31 mmol), 2,2-dicyclohexylphosphorane trisopropylbiphenyl (0.59 g, 1.24 mmol), sodium tert-butoxide (1.20 g, 12.4 mmol), and degassed toluene (20 mL) under N₂. The mixture was heated at 110° C. for 2 h, allowed to cool to rt, sonicated until the solids broke up, and then filtered through Celite with EtOAc (500 mL). The filtrate was concentrated, purified by silica gel chromatography (0→8% MeOH/CH₂Cl₂), and then repurified by reverse-phase HPLC (25→100% MeCN/H₂O) to give 8-(cyclopropylmethoxy)-4-(3,5-dimethylpyridin-4-ylamino)-7-methoxyquinolin-2(1H)-one: ¹H NMR (400 MHz, DMSO-d₆): δ 9.64 (s, 1H), 8.43 (s, 1H), 8.42 (s, 2H), 7.89 (d, 1H), 7.03 (d, 1H), 4.54 (s, 1H), 3.91 (s, 3H), 3.85 (d, 2H), 2.15 (s, 6H), 1.28 (m, 1H), 0.47 (m, 2H), 0.28 (m, 2H); MS (ESI): 365.8.

EXAMPLE 9

8-(Cyclopentyloxy)-4-(3,5-dichloropyridin-4-ylamino)-1-(2-hydroxyethyl)-7-methoxyquinolin-2(1H)-one



Step 1

Methyl 3-(cyclopentyloxy)-4-methoxy-2-(N-(2-(tetrahydro-2H-pyran-2-yl)ethyl)acetamido)benzoate was prepared from methyl 2-acetamido-3-(cyclopentyloxy)-4-methoxybenzoate (Example 1, Step 4) following the procedure outlined in Example 4 (except: solvent was DMF; temp was 33° C.; time was overnight). MS (ESI): 458.2 (M+Na).

Step 2

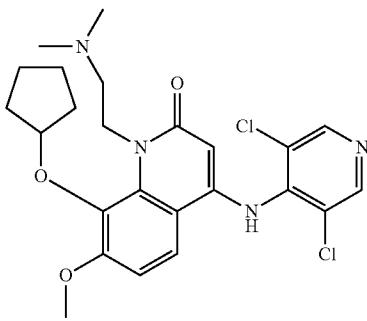
8-(Cyclopentyloxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)quinolin-2(1H)-one was prepared from methyl 3-(cyclopentyloxy)-4-methoxy-2-(N-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)acetamido)benzoate following the procedures outlined in Example 1. MS (ESI): 570 (M+Na).

Step 3

p-Toluenesulfonic acid (172 mg, 1.0 mmol) was added to a solution of 8-(cyclopentyloxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)quinolin-2(1H)-one (2.4 g, 4.4 mmol) and methanol (100 mL). After stirring overnight, the reaction was concentrated, diluted with dichloromethane (100 mL), and then washed with sat'd NaHCO₃ (20 mL) followed by water (20 mL). The organic layer was dried, filtered, concentrated, and recrystallized from dichloromethane/petroleum ether (1:2) to give 8-(cyclopentyloxy)-4-(3,5-dichloropyridin-4-ylamino)-1-(2-hydroxyethyl)-7-methoxyquinolin-2(1H)-one: ¹H NMR (400 MHz, DMSO-d₆): δ 8.74 (s, 2H), 8.73 (s, 1H), 7.91 (d, 1H), 7.11 (d, 1H), 4.92 (s, 1H), 4.65 (t, 2H), 4.59 (m, 1H), 4.50 (t, 1H), 3.90 (s, 3H), 3.32 (m 2H), 1.80-1.48 (m, 8H); MS (ESI): 463.9.

EXAMPLE 10

8-(Cyclopentyloxy)-4-(3,5-dichloropyridin-4-ylamino)-1-(2-(dimethylamino)ethyl)-7-methoxyquinolin-2(1H)-one



Step 1

Dess-Martin periodinane (933 mg, 2.2 mmol) was added to a solution of 8-(cyclopentyloxy)-4-(3,5-dichloropyridin-4-ylamino)-1-(2-hydroxyethyl)-7-methoxyquinolin-2(1H)-one (500 mg, 1.08 mmol, Example 9) and CH₂Cl₂ (30 mL) at 0° C. After 30 min, the mixture was allowed to warm to rt. When the starting material was consumed, the reaction was diluted with dichloromethane (25 mL), washed with aq. NaOH (20 mL×2), and then washed with water (20 mL). The organic layer was dried, filtered, concentrated, and purified by silica gel chromatography (1:2→1:1; ethyl acetate:petroleum ether) to give 2-(8-(cyclopentyloxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2-oxoquinolin-1(2H)-yl)acetaldehyde: MS (ESI): 462.2.

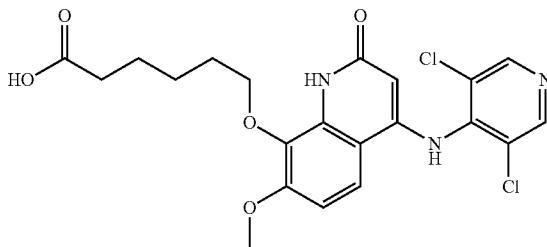
Step 2

Titanium (IV) isopropoxide (496 mg, 1.74 mmol) and 2-(8-(cyclopentyloxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2-oxoquinolin-1(2H)-yl)acetaldehyde (400 mg, 0.87 mmol) were added sequentially to a solution of dimethylamine hydrochloride (144 mg, 1.74 mmol), triethylamine (176 mg, 1.74 mmol), and absolute ethanol (20 mL). After

stirring overnight, sodium borohydride (50 mg, 1.3 mmol) was added. After an additional 3 h, the reaction was poured into aq. ammonia (30 mL) and then filtered—washing with dichloromethane. The filtrate was extracted with dichloromethane (50 mL×3). The combined extracts were dried, filtered, concentrated, and purified by reverse-phase HPLC to give 8-(cyclopentyloxy)-4-(3,5-dichloropyridin-4-ylamino)-1-(2-(dimethylamino)ethyl)-7-methoxyquinolin-2(1H)-one: ¹H NMR (400 MHz, DMSO-d₆): δ 8.75 (s, 1H), 8.73 (s, 2H), 7.91 (d, 1H), 7.12 (d, 1H), 4.94 (s, 1H), 4.71 (t, 2H), 4.58 (m, 1H), 3.90 (s, 3H), 2.22 (m, 2H), 2.04 (s, 6H), 1.80-1.50 (m, 8H); MS (ESI): δ 491.0.

EXAMPLE 11

6-(4-(3,5-Dichloropyridin-4-ylamino)-7-methoxy-2-oxo-1,2-dihydroquinolin-8-yloxy)hexanoic acid



Step 1

Concentrated HCl (15 mL) was added to a solution of 8-(cyclopentylmethoxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxyquinolin-2(1H)-one (1.2 g, 2.90 mmol, Example 3) and methanol (8 mL). The reaction mixture was heated at 50° C. for 4 h and then concentrated. The residue was neutralized with sat'd NaHCO₃, filtered (washed with ethanol and ether), and dried to give 4-(3,5-dichloropyridin-4-ylamino)-8-hydroxy-7-methoxyquinolin-2(1H)-one: MS (ESI): 352.

Step 2

Sodium hydride (54 mg, 1.35 mmol) was added to a solution of 4-(3,5-dichloropyridin-4-ylamino)-8-hydroxy-7-methoxyquinolin-2(1H)-one (380 mg, 1.08 mmol) and DMSO (20 mL) at rt under N₂. After 1 h, ethyl 6-bromohexanoate (770 mg, 3.45 mmol) was added, and the mixture was heated at 30° C. for 5 h. The reaction was quenched with drops of water, poured into 0.5 M KH₂PO₄, and extracted with EtOAc (100 mL×3). The combined extracts were washed with water and then brine, dried, filtered, concentrated, and purified by silica gel chromatography (ethyl acetate: pet. ether) to give ethyl 6-(4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2-oxo-1,2-dihydroquinolin-8-yloxy)hexanoate: MS (ESI): 494.0.

Step 3

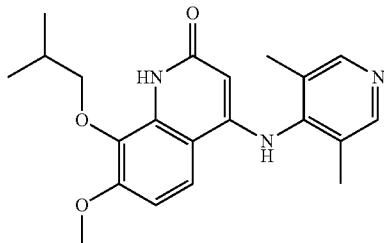
Lithium hydroxide (2.0 mL, 1M, 2.0 mmol) was added to a solution of ethyl 6-(4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2-oxo-1,2-dihydroquinolin-8-yloxy)hexanoate (100 mg, 0.20 mmol), MeOH (2 mL), and THF (8 mL). The mixture was stirred for 24 h, quenched with 1N HCl (30 mL), and extracted with EtOAc (40 mL×2). The organic extracts were dried, filtered, and concentrated to give 6-(4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2-oxo-1,2-dihydroquinolin-8-yloxy)hexanoic acid: ¹H NMR (400 MHz, DMSO-d₆): δ 10.10 (s, 1H), 8.88 (s, 1H), 8.77 (s, 2H), 7.89 (d,

39

1H), 7.06 (d, 1H), 4.80 (s, 1H), 3.95 (t, 2H), 3.90 (s, 3H), 2.22 (t, 2H), 1.76 (m, 2H), 1.55 (m, 2H), 1.39 (m, 2H); MS (ESI): 465.8.

EXAMPLE 12

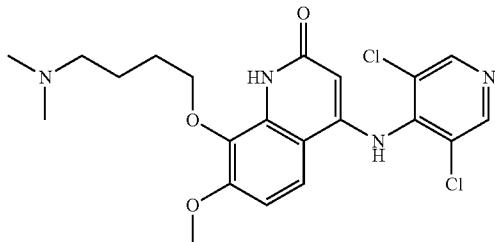
4-(3,5-Dimethylpyridin-4-ylamino)-8-isobutoxy-7-methoxyquinolin-2(1H)-one



The title compound was prepared from methyl 3-hydroxy-4-methoxy-2-nitrobenzoate (Example 1, Step 1) and 1-bromo-2-methylpropane following the procedures outlined in Examples 1 & 8. ¹H NMR (400 MHz, DMSO-d₆): δ 9.39 (s, 1H), 8.42 (s, 1H), 8.39 (s, 2H), 7.89 (d, 1H), 7.03 (d, 1H), 4.51 (s, 1H), 3.89 (s, 3H), 3.74 (d, 2H), 2.13 (s, 6H), 2.13 (m, 1H), 0.97 (d, 6H); MS (ESI): 368.2.

EXAMPLE 13

4-(3,5-Dichloropyridin-4-ylamino)-8-(4-(dimethylamino)butoxy)-7-methoxyquinolin-2(1H)-one



Step 1

8-(4-Bromobutoxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxyquinolin-2(1H)-one was prepared from 4-(3,5-dichloropyridin-4-ylamino)-8-hydroxy-7-methoxyquinolin-2(1H)-one (Example 11, Step 1) and 1,4-dibromobutane following the procedure outlined in Example 11, Step 2. MS (ESI): 485.8.

Step 2

A solution of dimethylamine (1.5 mL, 2M THF, 3 mmol) was added to a solution of 8-(4-bromobutoxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxyquinolin-2(1H)-one (146 mg, 0.3 mmol) and DMSO (3 mL). After 2.5 h, the reaction was poured into 10% K₂CO₃ (30 mL) and extracted with dichloromethane (40 mL×2). The combined extracts were dried, filtered, concentrated, and purified by silical gel chromatography (1:0→4:1; dichlormethane:methanol w/1% conc. NH₄OH solution) and then reverse-phase HPLC (1:9→1:1; acetonitrile:water) to give 4-(3,5-dichloropyridin-4-ylamino)-8-(4-(dimethylamino)butoxy)-7-methoxyquinolin-2(1H)-one (110 mg, 0.17 mmol, 50% yield).

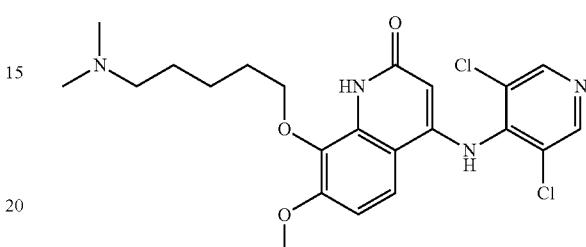
lin-2(H)-one: ¹H NMR (400 MHz, DMSO-d₆): δ 10.29 (s, 1H), 8.81 (s, 1H), 8.75 (s, 2H), 7.87 (d, 1H), 7.04 (d, 1H), 4.77 (s, 1H), 3.99 (t, 2H), 3.90 (s, 3H), 2.27 (t, 2H), 2.13 (s, 6H), 1.73 (m, 2H), 1.54 (m, 2H); MS (ESI): 451.0.

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4-(3,5-Dichloropyridin-4-ylamino)-8-(5-(dimethylamino)pentyloxy)-7-methoxyquinolin-2(1H)-one

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The title compound was prepared from 4-(3,5-dichloropyridin-4-ylamino)-8-hydroxy-7-methoxyquinolin-2(1H)-one (Example 11, Step 1) and 1,5-dibromopentane following the procedures outlined in Example 13. ¹H NMR (400 MHz, DMSO-d₆): δ 9.91 (s, 1H), 8.83 (s, 1H), 8.75 (s, 2H), 7.87 (d, 1H), 7.04 (d, 1H), 4.77 (s, 1H), 3.96 (t, 2H), 3.90 (s, 3H), 2.19 (t, 2H), 2.10 (s, 6H), 1.76 (m, 2H), 1.48-1.32 (m, 4H); MS (ESI): 465.0.

The following compounds can generally be made using the methods described above. It is expected that these compounds when made will have activity similar to those that have been made in the examples above.

The following compounds are represented herein using the Simplified Molecular Input Line Entry System, or SMILES. SMILES is a modern chemical notation system, developed by David Weininger and Daylight Chemical Information Systems, Inc., that is built into all major commercial chemical structure drawing software packages. Software is not needed to interpret SMILES text strings, and an explanation of how to translate SMILES into structures can be found in Weininger, D., *J. Chem. Inf. Comput. Sci.* 1988, 28, 31-36. All SMILES strings used herein were generated using Accelrys's Pipeline Pilot 6.0. Many IUPAC names used herein were generated using CambridgeSoft's ChemDraw 10.0.

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CCCCN(C)C)=C(OC)C=C3
O=C1C=C(NC2=C(C)C=NC=C2C)C3=C(N1)C(OC-
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O=C1C=C(NC2=C(C)C=NC=C2C)C3=C(N1)C(OC-
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cccc23
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cccc3C
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(=CC(=O)Nc23)Nc4c(C)cccc4C
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cccc3F
CCN(C)CCCCOc1c(OCF)ccc2C(=CC(=O)Nc12)Nc3c(C)
cccc3F
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cccc3F
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$\text{Cc1cccc(F)c1NC2=CC(=O)Nc3c(OCCCC(=O)N[C@@H](\text{Cc4c[nH]c5cccc45})\text{C}(=O)\text{O)c(OC(F)F)ccc23}$
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$\text{Cc1cccc(Br)c1NC2=CC(=O)Nc3c(OCC(=O)N[C@@H](\text{CCC}(=O)\text{O})\text{C}(=O)\text{O})\text{c}(OC(F)F)ccc23}$
 $\text{CN(C)CCN(C)\text{C}(=O)CCCCOc1c(OC(F)F)\text{ccc2C}(=CC(=O)\text{Nc12})\text{Nc3c(C)cccc3Br}}$
 $\text{5 CN1CCN(CC1)\text{C}(=O)CCCCOc2c(OC(F)F)\text{ccc3C}(=CC(=O)\text{Nc23})\text{Nc4c(C)cccc4Br}}$
 $\text{COc1ccc2C(=CC(=O)\text{Nc2c1OCCCC(=O)N[C@@H](C(C)\text{C}(=O)\text{O})\text{Nc3c(C)cccc3Br})\text{c}(OC(F)F)ccc2C}(=CC(=O)\text{Nc12})\text{Nc3c(C)cccc3Br}$
 $\text{CN(C)CCN(C)\text{C}(=O)CCCCOc1c(OC(F)F)\text{ccc2C}(=CC(=O)\text{Nc12})\text{Nc3c(C)cccc3Br}}$
 $\text{10 CN(CCC[N+](C)(C)\text{C}(=O)CCCCOc1c(OC(F)F)\text{ccc2C}(=CC(=O)\text{Nc12})\text{Nc3c(C)cccc3Br}}$
 $\text{CN(CCC[N+](C)(C)\text{C}(=O)CCCCOc1c(OC(F)F)\text{ccc2C}(=CC(=O)\text{Nc12})\text{Nc3c(C)cccc3Br}}$
 $\text{15 COc1ccc2C(=CC(=O)\text{Nc2c1OCCCCC(=O)N[C@@H](C(C)\text{C}(=O)\text{O})\text{Nc4c(C)cccc4Br})\text{c}(OC(F)F)ccc2C}(=CC(=O)\text{Nc12})\text{Nc3c(C)cccc3C}$
 $\text{COc1ccc2C(=CC(=O)\text{Nc2c1OCCCCN3CCCC3})\text{Nc4c(C)cc4C}}$
 $\text{Cc1cc(F)cc(C)c1NC2=CC(=O)Nc3c(OCCCCN4CCCC4)\text{c}(OC(F)F)ccc23}$
 $\text{CCCCN(C)CCCCCOc1c(OC)\text{ccc2C}(=CC(=O)\text{Nc12})\text{Nc3c(C)cc(F)cc3C}}$
 $\text{20 Cc1cc(F)cc(C)c1NC2=CC(=O)\text{Nc3c(OCCCCCn4ncen4)\text{c}(OC(F)F)ccc23}$
 $\text{Cc1cc(F)cc(C)c1NC2=CC(=O)\text{Nc3c(OCCCCOc4ccncc4)\text{c}(OC(F)F)ccc23}$
 $\text{Cc1cc(F)cc(C)c1NC2=CC(=O)\text{Nc3c(OCCCCCn4ccncc4)\text{c}(OC(F)F)ccc23}$
 $\text{25 Cc1cc(F)cc(C)c1NC2=CC(=O)\text{Nc3c(OCC(=O)OCC[N+](C)(C)\text{c}(OC(F)F)ccc23}$
 $\text{Cc1cc(F)cc(C)c1NC2=CC(=O)\text{Nc3c(OCCCCOc4ccncc4)\text{c}(OC(F)F)ccc23}$
 $\text{Cc1cc(F)cc(C)c1NC2=CC(=O)\text{Nc3c(OCCCCCn4ccncc4)\text{c}(OC(F)F)ccc23}$
 $\text{30 Cc1cc(F)cc(C)c1NC2=CC(=O)\text{Nc3c(OCC(=O)OCC[N+](C)(C)\text{c}(OC(F)F)ccc23}$
 $\text{Cc1cc(F)cc(C)c1NC2=CC(=O)\text{Nc3c(OCC(=O)OCC[N+](C)(C)\text{c}(OC(F)F)ccc23}$
 $\text{CN(C)CCN(C)\text{C}(=O)CCCCOc1c(OC)\text{ccc2C}(=CC(=O)\text{Nc12})\text{Nc3c(C)cc(F)cc3C}}$
 $\text{35 Cc1cc(F)cc(C)c1NC2=CC(=O)\text{Nc3c(OCCCC(=O)OCC[N+](C)(C)\text{c}(OC(F)F)ccc23}$
 $\text{Cc1cc(F)cc(C)c1NC2=CC(=O)\text{Nc3c(OCCCC(=O)OCC[N+](C)(C)\text{c}(OC(F)F)ccc23}$
 $\text{COc1ccc2C(=CC(=O)\text{Nc2c1OCCCCC(=O)N(C)CCN(C)\text{Nc3c(C)cc(F)cc3C})\text{c}(OC(F)F)ccc23}$
 $\text{40 Cc1cc(F)cc(C)c1NC2=CC(=O)\text{Nc3c(OCCCCC(=O)OCC[N+](C)(C)\text{c}(OC(F)F)ccc23}$
 $\text{Cc1cc(F)cc(C)c1NC2=CC(=O)\text{Nc3c(OCCCCC(=O)OCC[N+](C)(C)\text{c}(OC(F)F)ccc23}$
 $\text{Cc1cc(F)cc(C)c1NC2=CC(=O)\text{Nc3c(OCCCCC(=O)OCC[N+](C)(C)\text{c}(OC(F)F)ccc23}$
 $\text{45 Cc1cc(F)cc(F)c1NC2=CC(=O)\text{Nc3c(OCCCCCn4cnnn4)\text{c}(OC(F)F)ccc23}$
 $\text{Cc1cc(F)cc(F)c1NC2=CC(=O)\text{Nc3c(OCCCCOe4ccncc4)\text{c}(OC(F)F)ccc23}$
 $\text{COc1ccc2C(=CC(=O)\text{Nc2c1OCCCCCOc1c(C@H)O)[C@H]3O)\text{Nc4c(C)cc(F)cc4F}}$
 $\text{50 [C@H](CO)[C@@H](O)[C@H]3O)\text{Nc4c(C)cc(F)cc4F}}$
 $\text{CCCCN(C)CCCCCOc1c(OC(F)F)\text{ccc2C}(=CC(=O)\text{Nc12})\text{Nc3c(C)cc(F)cc3F}}$
 $\text{Cc1cc(F)cc(C)c1NC2=CC(=O)\text{Nc3c(OCCCCC(=O)OCC[N+](C)(C)\text{c}(OC(F)F)ccc23}$
 $\text{55 COc1ccc2C(=CC(=O)\text{Nc2c1OCCCCC(=O)N(C)CCN(C)\text{Nc3c(C)cc(F)cc3F})\text{c}(OC(F)F)ccc23}$
 $\text{Cc1cc(F)cc(F)c1NC2=CC(=O)\text{Nc3c(OCCCCC(=O)OCC[N+](C)(C)\text{c}(OC(F)F)ccc23}$
 $\text{COc1ccc2C(=CC(=O)\text{Nc2c1OCCCCC(=O)N(C)CCN(C)\text{Nc3c(C)cc(F)cc3F})\text{c}(OC(F)F)ccc23}$
 $\text{60 Cc1cc(F)cc(F)c1NC2=CC(=O)\text{Nc3c(OCCCCC(=O)OCC[N+](C)(C)\text{c}(OC(F)F)ccc23}$
 $\text{Cc1cc(F)cc(F)c1NC2=CC(=O)\text{Nc3c(OCCCCC(=O)OCC[N+](C)(C)\text{c}(OC(F)F)ccc23}$
 $\text{CC(C)[C@H](NC(=O)COc1c(OC(F)F)\text{ccc2C}(=CC(=O)\text{Nc12})\text{Nc3c(C)cc(F)cc3F})\text{c}(OC(F)F)ccc23}$
 $\text{65 CC(C)[C@H](NC(=O)COc1c(OC(F)F)\text{ccc2C}(=CC(=O)\text{Nc12})\text{Nc3c(C)cc(F)cc3F})\text{c}(OC(F)F)ccc23}$

COc1ccc2C=CC(=O)Nc2c1OCCCC(=O)N[C@@H]
 (CCCCN)C(=O)O)Nc3c(C)cc(F)cc3F
 CN(C)CCN(C)C(=O)CCCCOc1c(OC(F)F)ccc2C(=CC
 (=O)Nc12)Nc3c(C)cc(F)cc3F
 COc1ccc2C=CC(=O)Nc2c1OCCCCC(=O)
 N3CCNCC3)Nc4c(C)cc(F)cc4F
 Cc1cc(F)cc(F)c1NC2=CC(=O)Nc3c(OCCCCC(=O)N
 [C@@H](Cc4ccc(O)cc4)C(=O)O)e(OC(F)F)ccc23
 Cc1cc(F)cc(F)c1NC2=CC(=O)Nc3c(OCCCCC(=O)N
 [C@@H](CCC(=O)N)C(=O)O)e(OC(F)F)ccc23
 CC(C)C H] (NC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC
 (=O)Nc12)Nc3c(C)cc(F)cc3F)C(=O)O
 Cc1cc(F)cc(F)c1NC2=CC(=O)Nc3c(OCCCCC(=O)N
 [C@@H](Cc4cccc4)C(=O)O)e(OC(F)F)ccc23
 COCCN(C)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)
 Nc3c(C)cc(F)cc3C1
 COc1ccc2C=CC(=O)Nc2c1OCCCCn3ccnc3)Nc4c(C)cc
 (F)cc4C1
 Cc1cc(F)cc(C1)c1NC2=CC(=O)Nc3c
 (OCCCCOc4ccnc4)cc(OC(F)F)ccc23
 COCCN(C)CCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)
 Nc3c(C)cc(F)cc3C1
 Cc1cc(F)cc(C1)c1NC2=CC(=O)Nc3c(OCCCCn4ncnn4)
 cc(OC(F)F)ccc23
 COc1ccc2C=CC(=O)Nc2c1OCCCCCOc3ccnc3)Nc4c
 (C)cc(F)cc4C1
 Cc1cc(F)cc(C1)c1NC2=CC(=O)Nc3c
 (OCCCCCOc4ccnc4)cc(OC(F)F)ccc23
 COCCN(C)CCCCCOc1c(OC)ccc2C(=CC(=O)Nc12)
 Nc3c(C)cc(F)cc3C1
 Cc1cc(F)cc(C1)c1NC2=CC(=O)Nc3c(OCCCCCn4CCC
 (F)C4)cc(OC(F)F)ccc23
 Cc1cc(F)cc(C1)c1NC2=CC(=O)Nc3c
 (OCCCCCCn4cccc4)cc(OC(F)F)ccc23
 Cc1cc(F)cc(C1)c1NC2=CC(=O)Nc3c(OCC(=O)NCC
 (=O)O)e(OC(F)F)ccc23
 Cc1cc(F)cc(C1)c1NC2=CC(=O)Nc3c(OCC(=O)N
 [C@@H](CO)C(=O)O)c(OC(F)F)ccc23
 CN(CCC[N+](C)(C)C(=O)O)CCCCOc1c(OC(F)F)ccc2C
 (=CC(=O)Nc12)Nc3c(C)cc(F)cc3C1
 COc1ccc2C=CC(=O)Nc2c1OCCCC(=O)N[C@@H]
 (CCCCN)C(=O)O)Nc3c(C)cc(F)cc3C1
 Cc1cc(F)cc(C1)c1NC2=CC(=O)Nc3c(OCCCC(=O)N
 [C@@H](CCCCN)C(=O)O)e(OC(F)F)ccc23
 Cc1cc(F)cc(C1)c1NC2=CC(=O)Nc3c(OCCCC(=O)N
 [C@@H](CO)C(=O)O)c(OC(F)F)ccc23
 COc1ccc2C=CC(=O)Nc2c1OCCCC(=O)N[N[C@@H]
 ([C@@H](C)O)C(=O)O)Nc3c(C)cc(F)cc3C1
 Cc1cc(F)cc(C1)c1NC2=CC(=O)Nc3c(OCCCC(=O)N
 [C@@H](CCCCN)C(=O)O)e(OC(F)F)ccc23
 Cc1cc(F)cc(C1)c1NC2=CC(=O)Nc3c(OCCCC(=O)N
 [C@@H](CCCCN)C(=O)O)e(OC(F)F)ccc23
 Cc1cc(F)cc(C1)c1NC2=CC(=O)Nc3c(OCCCCC(=O)
 OCC[N+](C)(C)C(=O)O)Nc3c(C)cc(F)cc3C1
 Cc1cc(F)cc(C1)c1NC2=CC(=O)Nc3c(OCCCCC(=O)N
 [C@@H](CO)C(=O)O)c(OC(F)F)ccc23
 COCCN(C)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)
 Nc12)Nc3c(C)cc(F)cc3Br
 Cc1cc(F)cc(C1)c1NC2=CC(=O)Nc3c(OCCCCn4ccnn4)
 (OC(F)F)ccc23
 COCCN(C)CCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)
 Nc3c(C)cc(F)cc3Br
 COc1ccc2C=CC(=O)Nc2c1OCCCCN3CCC(F)CC3
 Nc4c(C)cc(F)cc4Br
 COCCOCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)
 Nc3c(C)cc(F)cc3Br

Cc1cc(F)cc(Br)c1NC2=CC(=O)Nc3c
 (OCCCCCCN4CCCC(F)F)C4)c(OC(F)F)F)ccc23
 Cc1cc(F)cc(Br)c1NC2=CC(=O)Nc3c
 (OCCCCCCN4ccnc4)cc(OC(F)F)ccc23
 5 Cc1cc(F)cc(Br)c1NC2=CC(=O)Nc3c(OCC(=O)N
 [C@@H](CCC(=O)O)C(=O)O)e(OC(F)F)F)ccc23
 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)N[C@@H]
 (CCC(=O)N)C(=O)O)Nc3c(C)cc(F)cc3Br
 Cc1cc(F)cc(Br)c1NC2=CC(=O)Nc3c(OCCCCC(=O)
 10 OCC[N+](C)(C)C(=O)O)cc(OC(F)F)ccc23
 COc1ccc2C(=CC(=O)Nc2c1OCCCCC(=O)N[C@@H]
 (CCCCN)C(=O)O)Nc3c(C)cc(F)cc3Br
 Cc1cc(F)cc(Br)c1NC2=CC(=O)Nc3c(OCCCCC(=O)N
 [C@@H](CCCCN)C(=O)O)e(OC(F)F)ccc23
 15 Cc1cc(F)cc(Br)c1NC2=CC(=O)Nc3c(OCCCCC(=O)N
 [C@@H](CCCCN)C(=O)O)e(OC(F)F)ccc23
 Cc1cc(F)cc(Br)c1NC2=CC(=O)Nc3c(OCCCCC(=O)
 OCC[N+](C)(C)C(=O)O)cc(OC(F)F)ccc23
 Cc1cc(F)cc(Br)c1NC2=CC(=O)Nc3c(OCCCCC(=O)N
 20 [C@@H](CO)C(=O)O)e(OC(F)F)ccc23
 COc1ccc2C(=CC(=O)Nc2c1OCCCCC(=O)N[C@@H]
 [C@@H](CCCNC(=N)N)C(=O)O)Nc3c(C)cc(F)
 cc3Br
 CCCNCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c
 (C)cc(O)cc3C
 25 Cc1cc(O)cc(C)c1NC2=CC(=O)Nc3c(OCCCCN4CCC(F)
 (F)C4)cc(OC(F)F)ccc23
 COc1ccc2C(=CC(=O)Nc2c1OCCCCn3ccnc3)Nc4c(C)cc
 (O)cc4C
 30 CCCNCCCCCOc1c(OC)ccc2C(=CC(=O)Nc12)Nc3c(C)
 cc(O)cc3C
 Cc1cc(O)cc(C)c1NC2=CC(=O)Nc3c(OCCCCCn4ccnn4)c
 (OC(F)F)ccc23
 Cc1cc(O)cc(C)c1NC2=CC(=O)Nc3c(OCCCCCn4ccnn4)c
 35 (OC(F)F)ccc23
 Cc1cc(O)cc(C)c1NC2=CC(=O)Nc3c
 (OCCCCCOc4ccnc4)cc(OC(F)F)ccc23
 COCCN(C)CCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)
 Nc3c(C)cc(O)cc3C
 40 Cc1cc(O)cc(C)c1NC2=CC(=O)Nc3c
 (OCCCCCCN4CCOCC4)cc(OC(F)F)ccc23
 COc1ccc2C(=CC(=O)Nc2c1OCCCCCN3CCCCC3)
 Nc4c(C)cc(O)cc4C
 Cc1cc(O)cc(C)c1NC2=CC(=O)Nc3c(OCC(=O)N
 45 [C@@H](CC(=O)O)C(=O)O)e(OC(F)F)ccc23
 COc1ccc2C(=CC(=O)Nc2c1OCCCCCN3CCCCC3)
 Nc4c(C)cc(O)cc3C
 Cc1cc(O)cc(C)c1NC2=CC(=O)Nc3c(C)cc(O)cc3C
 CN(C)CCCN(C)C(=O)CCCCOc1c(OC(F)F)ccc2C(=CC
 (=O)Nc12)Nc3c(C)cc(O)cc3C
 50 CN(CCC[N+](C)(C)C(=O)CCCCOc1c(OC(F)F)F)
 ccc2C(=CC(=O)Nc12)Nc3c(C)cc(O)cc3C
 C[C@@H](NC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)
 Nc12)Nc3c(C)cc(O)cc3C)C(=O)O
 COc1ccc2C(=CC(=O)Nc2c1OCCCCC(=O)N
 55 [C@@H](Cc3cccc3)C(=O)O)Nc4c(C)cc(O)cc4C
 Cc1cc(O)cc(C)c1NC2=CC(=O)Nc3c(OCCCCC(=O)N
 [C@@H](CO)C(=O)O)e(OC(F)F)ccc23
 Cc1cc(O)cc(C)c1NC2=CC(=O)Nc3c(OCCCCn4ccnn4)c
 (OC(F)F)ccc23
 60 COCCOCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)
 Nc3c(C)cc(O)cc3F
 CCCN(C)CCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)
 Nc3c(C)cc(O)cc3F
 Cc1cc(O)cc(C)c1NC2=CC(=O)Nc3c(OCCCCn4ccnn4)c
 65 (OC(F)F)ccc23
 Cc1cc(O)cc(C)c1NC2=CC(=O)Nc3c(OCCCCCn4ccnn4)c
 (OC(F)F)ccc23

CNCCCCCOc1c(OCF)ccc2C(=CC(=O)Nc12)Nc3c(C)cc(O)cc3F
 COCCOCCCCCOc1c(OC)ccc2C(=CC(=O)Nc12)Nc3c(C)cc(O)cc3F
 Cc1cc(O)cc(F)c1NC2=CC(=O)Nc3c(OCC(=O)N)c(OC(F)F)ccc23
 COc1ccc2C(=CC(=O)Nc2c1OCC(=O)N[C@@H](CC(C)C(=O)O)Nc3c(C)cc(O)cc3F
 Cc1cc(O)cc(F)c1NC2=CC(=O)Nc3c(OCC(=O)N[C@@H](CO)C(=O)O)c(OCF)ccc23
 Cc1cc(O)cc(F)c1NC2=CC(=O)Nc3c(OCCCC(=O)N4CCNCC4)c(OC(F)F)ccc23
 CN1CCN(CC1)C(=O)CCCCOc2c(OCF)ccc3C(=CC(=O)Nc23)Nc4c(C)cc(O)cc4F
 Cc1cc(O)cc(F)c1NC2=CC(=O)Nc3c(OCCCC(=O)N[C@@H](CCCNC(=N)N)C(=O)O)c(OC(F)F)ccc23
 COc1ccc2C(=CC(=O)Nc2c1OCCCCC(=O)N3CCNCC3)Nc4c(C)cc(O)cc4F
 CC(C)[C@H](NC(=O)CCCCOc1c(OCF)ccc2C(=CC(=O)Nc12)Nc3c(C)cc(O)cc3F
 COc1ccc2C(=CC(=O)Nc2c1OCCCCC(=O)NCC[N+](C)C)Nc3c(C)cc(O)cc3F
 Cc1cc(O)cc(F)c1NC2=CC(=O)Nc3c(OCCCCC(=O)N[C@@H](Cc4ccc(0)cc4)C(=O)O)c(OC(F)F)ccc23
 CCN(CC)CCCCOc1c(OC)ccc2C(=CC(=O)Nc12)Nc3c(C)cc(O)cc3C1
 Cc1cc(O)cc(C1)c1NC2=CC(=O)Nc3c(OCCCCN4CCCC4)e(OC(F)F)ccc23
 Cc1cc(O)cc(C1)c1NC2=CC(=O)Nc3c(OCCCCN4CCC(F)C4)e(OC(F)F)ccc23
 CCNCCCCCOc1c(OCF)ccc2C(=CC(=O)Nc12)Nc3c(C)cc(O)cc3C1
 CCCN(C)CCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C)cc(O)cc3C1
 COc1ccc2C(=CC(=O)Nc2c1OCCCCCn3cnnc3)Nc4c(C)cc(O)cc4C1
 Cc1cc(O)cc(C1)c1NC2=CC(=O)Nc3e(OCCCCCOCCOCOCO)cc(OC(F)F)ccc23
 CCN(CC)CCCCCOc1c(OC)ccc2C(=CC(=O)Nc12)Nc3e(C)cc(O)cc3C1
 Cc1cc(O)cc(C1)c1NC2=CC(=O)Nc3c(OCCCCN4cnnc4)e(OCF)ccc23
 Cc1cc(O)cc(C1)c1NC2=CC(=O)Nc3c(OCC(=O)OCC[N+](C)C)cc(O)cc3C1
 Cc1cc(O)cc(C1)c1NC2=CC(=O)Nc3c(OCC(=O)N4CCCC[C@H]4C(=O)O)c(OCF)ccc23
 C[C@H](NC(=O)CCCCOc1c(OCF)ccc2C(=CC(=O)Nc12)Nc3c(C)cc(O)cc3C1)C(=O)O
 C[C@H](O)[C@H](NC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C)cc(O)cc3C1)C(=O)O
 CN(CCC[N+](C)C)C(=O)CCCCOc1c(OCF)ccc2C(=CC(=O)Nc12)Nc3c(C)cc(O)cc3C1
 Cc1cc(O)cc(C1)c1NC2=CC(=O)Nc3c(OCCCCC(=O)N4CCNCC4)c(OC(F)F)ccc23
 Cc1cc(O)cc(C1)c1NC2=CC(=O)Nc3c(OCCCCCCC(=O)N[C@@H](CO)C(=O)O)c(OC(F)F)ccc23
 COc1ccc2C(=CC(=O)Nc2c1OCCCCC(=O)N[C@@H](CC(=O)N)C(=O)O)Nc3c(C)cc(O)cc3C1
 Cc1cc(O)cc(Br)c1NC2=CC(=O)Nc3c(OCCCCN4cnnc4)c(OC(F)F)ccc23
 COc1ccc2C(=CC(=O)Nc2c1OCCCCOCCOCOCO)Nc3c(C)cc(O)cc3Br
 Cc1cc(O)cc(Br)c1NC2=CC(=O)Nc3c(OCCCCOc4cccc4)c(OC(F)F)ccc23

COc1ccc2C(=CC(=O)Nc2c1OCCCCCOc3ccncc3)Nc4c(C)cc(O)cc4Br
 CCN(C)CCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C)cc(O)cc3Br
 5 Cc1cc(O)cc(Br)c1NC2=CC(=O)Nc3c(OCCCCCn4ncnn4)c(OCF)ccc23
 Cc1cc(O)cc(Br)c1NC2=CC(=O)Nc3c(OCCCCCOCCOCOCO)cc(OC(F)F)ccc23
 CC[C@H](C)[C@H](NC(=O)O)c1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C)cc(O)cc3BrC(=O)O
 Cc1cc(O)cc(Br)c1NC2=CC(=O)Nc3c(OCC(=O)N[C@@H](Cc4ccc(0)cc4)C(=O)O)c(OCF)ccc23
 Cc1cc(O)cc(Br)c1NC2=CC(=O)Nc3c(OCC(=O)N[C@@H](CCCNC(=N)N)C(=O)O)c(OC(F)F)ccc23
 10 Cc1cc(O)cc(Br)c1NC2=CC(=O)Nc3c(OCCCC(=O)N4CCCC[C@H]4C(=O)O)c(OC(F)F)ccc23
 Cc1cc(O)cc(Br)c1NC2=CC(=O)Nc3c(OCCCCn4ncnn4)c(OC(F)F)ccc23
 Cc1cc(O)cc(Br)c1NC2=CC(=O)Nc3c(OCC(=O)N[C@@H](CCCNC(=N)N)C(=O)O)c(OC(F)F)ccc23
 15 Cc1cc(O)cc(Br)c1NC2=CC(=O)Nc3c(OCCCC(=O)N4CCCC[C@H]4C(=O)O)c(OC(F)F)ccc23
 CN(C)CCN(C)C(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C)cc(O)cc3Br
 COc1ccc2C(=CC(=O)Nc2c1OCCCCC(=O)N[C@@H](CC(=O)O)c(OC(F)F)ccc23
 20 Cc1cc(O)cc(Br)c1NC2=CC(=O)Nc3c(OCCCCC(=O)N[C@@H](CCCNC(=N)N)C(=O)O)c(OC(F)F)ccc23
 Cc1cc(cc(C)c1NC2=CC(=O)Nc3c(OCCCCn4ncnn4)c(OC(F)F)ccc23C(=O)O
 Cc1cc(cc(C)c1NC2=CC(=O)Nc3c(OCCCCCn4ncnn4)c(OC(F)F)ccc23C(=O)O
 25 Cc1cc(cc(C)c1NC2=CC(=O)Nc3c(OCCCCn4cnnc4)c(OC(F)F)ccc23C(=O)O
 Cc1cc(cc(C)c1NC2=CC(=O)Nc3c(OCCCCOCCO)c(OC(F)F)ccc23C(=O)O
 COCCOCCOCCOCCCCOc1c(OC)ccc2C(=CC(=O)Nc12)Nc3e(C)cc(cc3C)C(=O)O
 30 Cc1cc(cc(C)c1NC2=CC(=O)Nc3c(OCCCCN4cnnc4)c(OC(F)F)ccc23C(=O)O
 Cc1cc(cc(C)c1NC2=CC(=O)Nc3c(OCCCCN4ccnn4)c(OC(F)F)ccc23C(=O)O
 Cc1cc(cc(C)c1NC2=CC(=O)Nc3c(OCCCCN4ncnn4)c(OC(F)F)ccc23C(=O)O
 35 COc1ccc2C(=CC(=O)Nc2c1OCCCCCOc3ccncc3)Nc4c(C)cc(cc4C)C(=O)O
 Cc1cc(cc(C)c1NC2=CC(=O)Nc3c(OCCCCCN4CCOCC4)c(OC(F)F)ccc23C(=O)O
 Cc1cc(cc(C)c1NC2=CC(=O)Nc3c(OCCCCCOCCO)c(OC(F)F)ccc23C(=O)O
 40 Cc1cc(cc(C)c1NC2=CC(=O)Nc3c(OCCCCCn4ncnn4)c(OC(F)F)ccc23C(=O)O
 CN(C)CCN(=O)Oc1c(OCF)ccc2C(=CC(=O)Nc12)Nc3e(C)cc(cc3C)C(=O)O
 COc1ccc2C(=CC(=O)Nc2c1OCC(=O)N(C)CCN(C)C)Nc3e(C)cc(cc3C)C(=O)O
 45 Cc1cc(cc(C)c1NC2=CC(=O)Nc3c(OCC(=O)N4CCNCC4)c(OC(F)F)ccc23C(=O)O
 Cc1cc(cc(C)c1NC2=CC(=O)Nc3c(OCC(=O)N[C@@H](CO)C(=O)O)c(OC(F)F)ccc23C(=O)O
 Cc1cc(cc(C)c1NC2=CC(=O)Nc3c(OCCCC(=O)N[C@@H](CCCNC(=N)N)C(=O)O)c(OC(F)F)ccc23C(=O)O
 50 Cc1cc(cc(C)c1NC2=CC(=O)Nc3c(OCCCC(=O)N4CCCC[C@H]4C(=O)O)c(OC(F)F)ccc23C(=O)O
 Cc1cc(cc(C)c1NC2=CC(=O)Nc3c(OCCCCN4cnnc4)c(OC(F)F)ccc23C(=O)O
 Cc1cc(cc(C)c1NC2=CC(=O)Nc3c(OCCCCN4ccnn4)c(OC(F)F)ccc23C(=O)O
 55 Cc1cc(cc(C)c1NC2=CC(=O)Nc3c(OCCCC(=O)N4CCNCC4)c(OC(F)F)ccc23C(=O)O
 CN(C)CCNC(=O)CCCCCOc1c(OCF)ccc2C(=CC(=O)Nc12)Nc3e(C)cc(cc3C)C(=O)O
 Cc1cc(cc(F)c1NC2=CC(=O)Nc3c(OCCCCN4cccc4)c(OC(F)F)ccc23C(=O)O
 60 Cc1cc(cc(F)c1NC2=CC(=O)Nc3c(OCCCCOc4cccc4)c(OC(F)F)ccc23C(=O)O
 COc1ccc2C(=CC(=O)Nc2c1OCCCCCOc3ccncc3)Nc4c(C)cc(cc4F)C(=O)O
 Cc1cc(cc(F)c1NC2=CC(=O)Nc3c(OCCCCOc4cccc4)c(OC(F)F)ccc23C(=O)O
 65 CCCNCCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3e(C)cc(cc3F)C(=O)O

Cc1cc(cc(F)c1NC2=CC(=O)Nc3c(OCCCCCCn4cnnc4)(OC(F)F)ccc23)C(=O)O
 Cc1cc(cc(F)c1NC2=CC(=O)Nc3c(OCCCCCCOc4cccc4)(OC(F)c(cc23)C(=O)O
 COc1ecc2C(=CC(=O)Nc2c10CCCCCOc3ecncc3)Nc4c(C)cc(cc4F)C(=O)O
 Cc1cc(cc(F)c1NC2=CC(=O)Nc3c(OCC(=O)N)c(OC(F)F)ccc23)C(=O)O
 Cc1cc(cc(F)c1NC2=CC(=O)Nc3c(OCC(=O)N)[C@@H](Cc4ccc(O)cc4)C(=O)O)c(OC(F)ccc23)C(=O)O
 CN(CC[N+](C)(C)C(=O)CCCCOc1c(OC(F)F)F)ccc2C(=CC(=O)Nc12)Nc3c(C)cc(cc3F)C(=O)O
 COc1ecc2C(=CC(=O)Nc2c10CCCC(=O)N)[C@@H](CC(C)C)C(=O)O)Nc3c(C)cc(cc3F)C(=O)O
 Cc1cc(cc(F)c1NC2=CC(=O)Nc3c(OCCCCCC(=O)N4CCCC[C@H]4C(=O)O)c(OC(F)F)ccc23)C(=O)O
 CN(CC[N+](C)(C)C(=O)CCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C)cc(cc3F)C(=O)O
 CN(CC[N+](C)(C)C(=O)CCCCCOc1c(OC(F)F)F)ccc2C(=CC(=O)Nc12)Nc3c(C)cc(cc3F)C(=O)O
 CC[C@H](C)[C@H](NC(=O)CCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C)cc(cc3F)C(=O)O
 CCCN(C)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C)cc(cc3C1)C(=O)O
 CCCCCN(C)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C)cc(cc3C1)C(=O)O
 COc1ecc2C(=CC(=O)Nc2c10CCCCN3CCCC3)Nc4c(C)cc(cc4C1)C(=O)O
 Cc1cc(cc(C1)c1NC2=CC(=O)Nc3c(OCCCCCCn4cnnc4)(OC(F)ccc23)C(=O)O
 Cc1cc(cc(C1)c1NC2=CC(=O)Nc3c(OCCCCCCn4cccc4)(OC(F)ccc23)C(=O)O
 Cc1cc(cc(C1)c1NC2=CC(=O)Nc3c(OCCCCCCn4cnnc4)(OC(F)F)ccc23)C(=O)O
 COc1ecc2C(=CC(=O)Nc2c10CCCCCn3cnnn3)Nc4c(C)cc(cc4C1)C(=O)O
 CN(C)CCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C)cc(cc3C1)C(=O)O
 CCN(C)CCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C)cc(cc3C1)C(=O)O
 COCCOCCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C)cc(cc3C1)C(=O)O
 Cc1cc(cc(C1)c1NC2=CC(=O)Nc3c(OCCCCCCCOCCOC-COCCO)c(OC(F)F)ccc23)C(=O)O
 CN(CC[N+](C)(C)C(=O)COc1c(OC(F)F)F)ccc2C(=CC(=O)Nc12)Nc3c(C)cc(cc3C1)C(=O)O
 Cc1cc(cc(C1)c1NC2=CC(=O)Nc3c(OCCCC(=O)N4CCNCC4)c(OC(F)F)ccc23)C(=O)O
 Cc1cc(cc(C1)c1NC2=CC(=O)Nc3c(OCCCCCC(=O)NCC(=O)O)c(OC(F)F)ccc23)C(=O)O
 Cc1cc(cc(C1)c1NC2=CC(=O)Nc3c(OCCCCCC(=O)N[C@@H](Cc4cccc4)C(=O)O)c(OC(F)F)ccc23)C(=O)O
 CSCC[C@H](NC(=O)CCCCOc1c(OC(F)F)F)ccc2C(=CC(=O)Nc12)Nc3c(C)cc(cc3C1)C(=O)O
 CN1CCN(CC1)C(=O)CCCCCOc2c(OC(F)F)ccc3C(=CC(=O)Nc23)Nc4c(C)cc(cc4C1)C(=O)O
 COc1ecc2C(=CC(=O)Nc2c10CCCCCCC(=O)N[C@@H](CO)C(=O)O)Nc3c(C)cc(cc3C1)C(=O)O
 CN(C)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C)cc(cc3Br)C(=O)O
 COc1ecc2C(=CC(=O)Nc2c10CCCCCn3CCOCC3)Nc4c(C)cc(cc4Br)C(=O)O
 Cc1cc(cc(Br)c1NC2=CC(=O)Nc3c(OCCCCCCOCCOC-COCCO)c(OC(F)F)ccc23)C(=O)O
 Cc1cc(cc(Br)c1NC2=CC(=O)Nc3c(OCCCCCCN)c(OC(F)F)ccc23)C(=O)O

OCoc1ccc2C(=CC(=O)Nc2c1OCCCCCN3CCCC3)
 Nc4c(C)cc(cc4Br)C(=O)O
 Cc1cc(cc(Br)c1NC2=CC(=O)Nc3c(OCCCCCn4cnnn4)c
 (OC(F)F)ccc23)C(=O)O
 5 COc1ccc2C(=CC(=O)Nc2c1OCC(=O)N[C@H](Cc3c
 [nH]c4cccc34)C(=O)O)Nc5c(C)cc(cc5Br)C(=O)O
 Cc1cc(cc(Br)c1NC2=CC(=O)Nc3c(OCC(=O)N
 [C@H](Cc4c[nH]c5cccc45)C(=O)O)c(OCF)ccc23)
 C(=O)O
 10 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)N3CCN(C
 CC3)Nc4c(C)cc(cc4Br)C(=O)O
 Cc1cc(cc(Br)c1NC2=CC(=O)Nc3c(OCCCCC(=O)N)c
 (OC(F)F)ccc23)C(=O)O
 COc1ccc2C(=CC(=O)Nc2c1OCCCCC(=O)NCC
 15 (=O)O)Nc3c(C)cc(cc3Br)C(=O)O
 C[C@H](NC(=O)CCCCCOc1c(OCF)ccc2C(=CC(=O)
 Nc12)Nc3c(C)cc(cc3Br)C(=O)O)C(=O)O
 Cc1cc(cc(Br)c1NC2=CC(=O)Nc3c(OCCCCC(=O)N
 [C@H](CO)C(=O)O)c(OC(F)F)ccc23)C(=O)O
 20 CCN(CC)CCCCOc1c(OCF)ccc2C(=CC(=O)Nc12)Nc3c
 (F)ccc3F
 NC(=N)NCCCCOc1c(OC(F)F)ccc2C(=CC(=O)
 Nc12)Nc3c(F)cccc3F
 COc1ccc2C(=CC(=O)Nc2c1OCCCCOCCOCCOCCO
 25 Nc3c(F)cccc3F
 FCOc1ccc2C(=CC(=O)Nc2c 1OCCCCN3CCOCC3)
 Nc4c(F)cccc4F
 FC(F)Oc1ccc2C(=CC(=O)Nc2c1OCCCCN3ccnn3)
 Nc4c(F)cccc4F
 30 COCCOCCOCCCCCOc1c2NC(=O)C=C(Nc3c(F)
 cccc3F)c2ccc1OC(F)F
 FC(F)Oc1ccc2C(=CC(=O)Nc2c1OCCCCCn3ccnc3)
 Nc4c(F)cccc4F
 COCCOCCCCCOc1c(OC)ccc2C(=CC(=O)Nc12)Nc3c
 35 (F)cccc3F
 NCCCC[C@H](NC(=O)COc1c(OC(F)F)ccc2C(=CC
 (=O)Nc12)Nc3c(F)cccc3F)C(=O)O
 NC(=N)NCCCC[C@H](NC(=O)COc1c(OCF)ccc2C
 (=CC(=O)Nc12)Nc3c(F)cccc3F)C(=O)O
 40 NC(=O)CC[C@H](NC(=O)COc1c(OC(F)F)ccc2C(=CC
 (=O)Nc12)Nc3c(F)cccc3F)C(=O)O
 NC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c
 (F)cccc3F
 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)N3CCNCC3
 45 Nc4c(F)cccc4F
 NC(=O)CCCCOc1c(OCF)ccc2C(=CC(=O)Nc12)Nc3c
 (F)cccc3F
 C[N+](C)(C)CCNC(=O)CCCCOc1c(OC(F)F)ccc2C
 (=CC(=O)Nc12)Nc3c(F)cccc3F
 50 C[N+](C)(C)CCNC(=O)CCCCOc1c(OC(F)F)ccc2C
 (=CC(=O)Nc12)Nc3c(F)cccc3F
 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)N(C)CC
 [N+](C)(C)Nc3c(F)cccc3F
 NCCCC[C@H](NC(=O)CCCCCOc1c(OCF)ccc2C(=CC
 55 (=O)Nc12)Nc3c(F)cccc3F)C(=O)O
 COc1ccc2C(=CC(=O)Nc2c1OCCCCC(=O)N
 [C@H](Cc3cnc[nH]3)C(=O)O)Nc4c(F)cccc4F
 NCCCCOc1c(OCF)ccc2C(=CC(=O)Nc12)Nc3c(F)
 cccc3Cl
 60 Fe1cccc(C1)c1NC2=CC(=O)Nc3c(OCCCCn4ncnn4)c(OC
 (F)F)ccc23
 COCCOCCOCCOCCCCOc1c(OC(F)F)ccc2C(=CC(=O)
 Nc12)Nc3c(F)cccc3Cl
 COc1ccc2C(=CC(=O)Nc2c1OCCCCN(C)C)Nc3c(F)
 65 cccc3Cl
 Fe1cccc(C1)c1NC2=CC(=O)Nc3c(OCCCCN4CCCC(F)
 (F)C4)c(OC(F)F)ccc23

FCOc1ccc2C(=CC(=O)Nc2c1OCCCCOc3cccc3)Nc4c(F)cccc4C1
 OCCOCCOCCCCCOc1c(OC(F)(F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cccc3C1
 CN(CCC[N+](C)(C)C)(=O)COc1c(OCF)ccc2C(=CC(=O)Nc12)Nc3c(F)cccc3C1
 CN1CCN(CC1)C(=O)COc2c(OC(F)(F)F)ccc3C(=CC(=O)Nc23)Nc4c(F)cccc4C1
 COc1ccc2C(=CC(=O)Nc2c1OCC(=O)N[C@@H](CCCN)C(=O)O)Nc3c(F)cccc3C1
 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)N[C@@H](C)C(=O)O)Nc3c(F)cccc3C1
 OC(=O)[C@H](Cc1ccc(O)cc1)NC(=O)CCCCOc2c(OCF)ccc3C(=CC(=O)Nc23)Nc4c(F)cccc4C1
 C[C@H](O)[C@H](NC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cccc3C1)C(=O)O
 CN(CC[N+](C)(C)C)C(=O)CCCCOc1c(OCF)ccc2C(=CC(=O)Nc12)Nc3c(F)cccc3C1
 OC(=O)CNC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cccc3C1
 C[C@H](O)[C@H](NC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cccc3C1)C(=O)O
 OC(=O)[C@H](Cc1cnc[nH]1)NC(=O)CCCCOc2c(OC(F)F)ccc3C(=CC(=O)Nc23)Nc4c(F)cccc4C1
 NC(=O)C[C@H](NC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cccc3C1)C(=O)O
 COc1ccc2C(=CC(=O)Nc2c1OCCCCOc3cccc3)Nc4c(F)cccc4Br
 FC(F)Oc1ccc2C(=CC(=O)Nc2c1OCCCCN3CCC(F)CC3)Nc4c(F)cccc4Br
 FCOc1ccc2C(=CC(=O)Nc2c1OCCCCOc3cccc3)Nc4c(F)cccc4Br
 CNCCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cccc3Br
 COCCN(C)CCCCCOc1c(OC(F)(F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cccc3Br
 FCOc1ccc2C(=CC(=O)Nc2c1OCCCCN3CCC(F)F)C3)Nc4c(F)cccc4Br
 NC(=O)COc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cccc3Br
 CC[C@H](C)[C@H](NC(=O)COc1c(OCF)ccc2C(=CC(=O)Nc12)Nc3c(F)cccc3Br)C(=O)O
 NC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cccc3Br
 CN(C)CCNC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cccc3Br
 OC(=O)[C@H](Cc1c[nH]c2cccc12)NC(=O)CCCCOc3(OCF)ccc4C(=CC(=O)Nc34)Nc5c(F)cccc5Br
 CCCN(C)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cccc3F
 Fe1cc(F)c(NC2=CC(=O)Nc3c(OCCCCn4ccenc4)c(OC(F)F)ccc23)c(F)c1
 CCCNCCCCOc1c(OC)ccc2C(=CC(=O)Nc12)Nc3c(F)cc(F)cc3F
 NC(=N)NCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cc(F)cc3F
 NC(=N)NCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cc(F)cc3F

FC(F)Oc1ccc2C(=CC(=O)Nc2c1OCCCCN3CCCC(F)C3)Nc4c(F)cc(F)cc4F
 COc1ccc2C(=CC(=O)Nc2c1OCCCCN3ccnc3)Nc4c(F)cc(F)cc4F
 5 CN(C)CCOC(=O)COc1c(OCF)ccc2C(=CC(=O)Nc12)Nc3c(F)cc(F)cc3F
 COc1ccc2C(=CC(=O)Nc2c1OCC(=O)NCC[N+](C)(C)C)Nc3c(F)cc(F)cc3F
 CN(C)CCCN(C)C(=O)COc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cc(F)cc3F
 10 CN(C)CCNC(=O)CCCCOc1c(OCF)ccc2C(=CC(=O)Nc12)Nc3c(F)cc(F)cc3F
 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)N[C@@H](CC(C)C)C(=O)O)Nc3c(F)cc(F)cc3F
 15 C[N+](C)(C)CCOC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cc(F)cc3F
 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)N[C@@H](Cc3ccc(O)cc3)C(=O)O)Nc3c(F)cc(F)cc4F
 20 NC(=O)C[C@H](NC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cc(F)cc3F)C(=O)O
 C[N+](C)(C)CCOC(=O)CCCCOc1c(OCF)ccc2C(=CC(=O)Nc12)Nc3c(F)cc(F)cc3F
 25 OC(=O)[C@H](Cc1c[nH]c2cccc12)NC(=O)CCCCOc3(OC(F)F)ccc4C(=CC(=O)Nc34)Nc5c(F)cc(F)cc5F
 NC(=N)NCCC[C@H](NC(=O)CCCCOc1c(OC(F)F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cc(F)cc3Cl
 30 CCCN(C)CCCCOc1c(OCF)ccc2C(=CC(=O)Nc12)Nc3c(F)cc(F)cc3Cl
 FC(F)Oc1ccc2C(=CC(=O)Nc2c1OCCCCN3CCCC3)Nc4c(F)cc(F)cc4C1
 COc1ccc2C(=CC(=O)Nc2c1OCCCCN3CCCC(F)C3)Nc4c(F)cc(F)cc4C1
 35 CCN(C)CCCCOc1c(OCF)ccc2C(=CC(=O)Nc12)Nc3c(F)cc(F)cc3Cl
 COc1ccc2C(=CC(=O)Nc2c1OCCCCN3CCC(F)F)CC3)Nc4c(F)cc(F)cc4C1
 COCCOCCOCCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cc(F)cc3Cl
 40 Fe1cc(F)c(NC2=CC(=O)Nc3c(OCCCCN4CCCC4)c(OC(F)F)ccc23)c(C1)c1
 COc1ccc2C(=CC(=O)Nc2c1OCCCCN3CCCC3)Nc4c(F)cc(F)cc4C1
 45 NC(=O)COc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cc(F)cc3Cl
 COc1ccc2C(=CC(=O)Nc2c1OCC(=O)N(C)CCN(C)C)Nc3c(F)cc(F)cc3Cl
 CN(C)CCN(C)C(=O)COc1c(OC(F)F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cc(F)cc3Cl
 50 C[N+](C)(C)CCNC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cc(F)cc3Cl
 NC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cc(F)cc3Cl
 55 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)N(C)CCCC[N+](C)(C)Nc3c(F)cc(F)cc3Cl
 C[C@H](NC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cc(F)cc3Cl)C(=O)O
 CN(C)CCOC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cc(F)cc3Cl
 60 CN(C)CCOC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cc(F)cc3Cl
 CN(CCC[N+](C)(C)C(=O)CCCCOc1c(OCF)ccc2C(=CC(=O)Nc12)Nc3c(F)cc(F)cc3Cl
 OC(=O)[C@H](Cc1c[nH]c2cccc12)NC(=O)CCCCOc3(OC(F)F)ccc4C(=CC(=O)Nc34)Nc5c(F)cc(F)cc5C1
 65 FC(F)Oc1ccc2C(=CC(=O)Nc2c1OCCCCN3CCCC3)Nc4c(F)cc(F)cc4Br

FCOc1ccc2C(=CC(=O)Nc2c1OCCCCOc3cccn3)Nc4c
 (F)cc(F)cc4Br
 CCNCCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c
 (F)cc(F)cc3Br
 FCOc1ccc2C(=CC(=O)Nc2c1OCCCCCCOc3ccnc3)
 Nc4c(F)cc(F)cc4Br
 OC[C@H]1O[C@H]1OCCCCCCOc2c(OC(F)F)ccc3C
 (=CC(=O)Nc23)Nc4c(F)cc(F)cc4Br)[C@H](O)
 [C@H](O)[C@H]1O
 COCCOCOCOCOCOCOC1c(OC)ccc2C(=CC(=O)Nc12)
 Nc3c(F)cc(F)cc3Br
 OCCOCOCOCOCOCOC1c(OC(F)(F)F)ccc2C(=CC
 (=O)Nc12)Nc3c(F)cc(F)cc3Br
 COc1ccc2C(=CC(=O)Nc2c1OCC(=O)N[C@H]
 ([C@H](C)O)C(=O)O)Nc3c(F)cc(F)cc3Br
 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)N[C@H]
 (CCSC)C(=O)O)Nc3c(F)cc(F)cc3Br
 NC(=N)NCCC[C@H](NC(=O)CCCOc1c(OC(F)F)
 ccc2C(=CC(=O)Nc12)Nc3c(F)cc(F)cc3Br)C(=O)O
 CN(C)CCNC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)
 Nc12)Nc3c(F)cc(F)cc3Br
 CN(CCC[N+](C)C)C(=O)CCCCOc1c(OC(F)F)ccc2C
 (=CC(=O)Nc12)Nc3c(F)cc(F)cc3Br
 CN(C)CCCCN(C)C(=O)CCCCOc1c(OC(F)F)F)ccc2C
 (=CC(=O)Nc12)Nc3c(F)cc(F)cc3Br
 OC(=O)[C@H](Cc1c[nH]2cccc2)NC(=O)
 CCCCCOc3c(OC(F)F)ccc4C(=CC(=O)Nc34)Nc5c(F)cc
 (F)cc5Br
 COc1ccc2C(=CC(=O)Nc2c1OCCCCC(=O)N
 [C@H](CCCCN)C(=O)O)Nc3c(F)cc(F)cc3Br
 Oc1cc(F)cc(NC2=CC(=O)Nc3c(OCCCCN4CCCC(F)F)
 C4)c(OC(F)F)ccc23)c(F)c1
 COc1ccc2C(=CC(=O)Nc2c1OCCCCOCCO)Nc3c(F)cc
 (O)cc3F
 COCCOCOCOCOC1c(OC(F)F)ccc2C(=CC(=O)
 Nc12)Nc3c(F)cc(O)cc3F
 CN(C)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c
 (F)cc(O)cc3F
 COc1ccc2C(=CC(=O)Nc2c1OCCCCN3CCCC(F)C3)
 Nc4c(F)cc(O)cc4F
 Oc1cc(F)cc(NC2=CC(=O)Nc3c(OCCCCN4CCCC(F)C4)
 c(OC(F)F)ccc23)c(F)c1
 Oc1cc(F)cc(NC2=CC(=O)Nc3c(OCCCCN4ccnc4)C(OC
 (F)F)ccc23)c(F)c1
 Oc1cc(F)cc(NC2=CC(=O)Nc3c(OCCCCCN4CCC(F)F)
 CC4)c(OC(F)F)ccc23)c(F)c1
 COc1ccc2C(=CC(=O)Nc2c1OCCCCCOc3cccn3)
 Nc4c(F)cc(O)cc4F
 C[N+](C)CCOC(=O)COc1c(OC(F)F)ccc2C(=CC(=O)
 Nc12)Nc3c(F)cc(O)cc3F
 COc1ccc2C(=CC(=O)Nc2c1OCC(=O)N[C@H]
 (Cc3cccc3)C(=O)O)Nc4c(F)cc(O)cc4F
 C[N+](C)CCNC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC
 (=O)Nc12)Nc3c(F)cc(O)cc3F
 C[N+](C)CCNC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC
 (=O)Nc12)Nc3c(F)cc(O)cc3F
 CN(CC[N+](C)C)C(=O)CCCCOc1c(OC(F)F)ccc2C
 (=CC(=O)Nc12)Nc3c(F)cc(O)cc3F
 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)OCCN(C)
 C)Nc3c(F)cc(O)cc3F
 C[N+](C)CCNC(=O)CCCCOc1c(OC(F)F)ccc2C
 (=CC(=O)Nc12)Nc3c(F)cc(O)cc3F
 CN(C)CCOC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC
 (=O)Nc12)Nc3c(F)cc(O)cc3F
 COc1ccc2C(=CC(=O)Nc2c1OCCCCC(=O)N
 [C@H](CC(=O)N)C(=O)O)Nc3c(F)cc(O)cc3F

NC(=O)CC[C@H](NC(=O)CCCCCOc1c(OC(F)F)ccc2C
 (=CC(=O)Nc12)Nc3c(F)cc(O)cc3F)C(=O)O
 COc1ccc2C(=CC(=O)Nc2c1OCCCCN)Nc3c(F)cc(O)
 cc3C1
 5 Oc1cc(F)cc(NC2=CC(=O)Nc3c(OCCCCN4cccc4)C(OC(F)
 (F)F)ccc23)c(C1)c1
 Oc1cc(F)cc(NC2=CC(=O)Nc3c(OCCCCN4ccnc4)C(OC
 (F)F)ccc23)c(C1)c1
 COc1ccc2C(=CC(=O)Nc2c1OCCCCOc3ccnc3)Nc4c
 (F)cc(O)cc4C1
 OCCOCOCOCOCOC1c(OC(F)F)ccc2C(=CC(=O)
 Nc12)Nc3c(F)cc(O)cc3C1
 CCCCCN(C)CCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)
 Nc3c(F)cc(O)cc3C1
 15 Oc1cc(F)cc(NC2=CC(=O)Nc3c(OCCCCN4ncnn4)C(OC
 (F)F)ccc23)c(C1)c1
 CN(C)CCOC(=O)COc1c(OC(F)F)ccc2C(=CC(=O)Nc12)
 Nc3c(F)cc(O)cc3C1
 20 NC(=N)NCCC[C@H](NC(=O)COc1c(OC(F)F)ccc2C
 (=CC(=O)Nc12)Nc3c(F)cc(O)cc3C1)C(=O)O
 CSCC[C@H](NC(=O)CCCCOc1c(OC(F)F)F)ccc2C(=CC
 (=O)Nc12)Nc3c(F)cc(O)cc3C1)C(=O)O
 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)N[C@H]
 (CO)C(=O)O)Nc3c(F)cc(O)cc3C1
 25 OC(=O)[C@H](Cc1c[nH]1)NC(=O)CCCOc2c(OC(F)
 ccc3C(=CC(=O)Nc23)Nc4c(F)cc(O)cc4C1
 CN(C)CCCN(C)C(=O)CCCCOc1c(OC(F)F)ccc2C
 (=CC(=O)Nc12)Nc3c(F)cc(O)cc3C1
 30 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)N[C@H]
 (Cc3c[nH]4cccc34)C(=O)O)Nc5c(F)cc(O)cc5C1
 COc1ccc2C(=CC(=O)Nc2c1OCCCCC(=O)N
 [C@H](CCSC)C(=O)O)Nc3c(F)cc(O)cc3C1
 C[C@H](O)[C@H](NC(=O)CCCCOc1c(OC(F)F)F)
 35 ccc2C(=CC(=O)Nc12)Nc3c(F)cc(O)cc3C1)C(=O)O
 NC(=N)NCCC[C@H](NC(=O)CCCCOc1c(OC(F)F)
 ccc2C(=CC(=O)Nc12)Nc3c(F)cc(O)cc3C1)C(=O)O
 CCNCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c
 (F)cc(O)cc3Br
 40 NC(=N)NCCCCOc1c(OC(F)F)ccc2C(=CC(=O)
 Nc12)Nc3c(F)cc(O)cc3Br
 Oc1cc(F)cc(NC2=CC(=O)Nc3c(OCCCCN4ccnn4)C(OC(F)
 ccc23)c(Br)c1
 COc1ccc2C(=CC(=O)Nc2c1OCCCCN3ncn3)Nc4c(F)
 45 cc(O)cc4Br
 OCCOCOCOCOC1c(OC(F)F)ccc2C(=CC(=O)Nc12)
 Nc3c(F)cc(O)cc3Br
 COc1ccc2C(=CC(=O)Nc2c1OCCCCN3CCC(F)C3)
 Nc4c(F)cc(O)cc4Br
 50 C[N+](C)CCOC(=O)COc1c(OC(F)F)ccc2C(=CC
 (=O)Nc12)Nc3c(F)cc(O)cc3Br
 OC(=O)[C@H](Cc1cccc1)NC(=O)COc2c(OC(F)F)ccc3C
 (=CC(=O)Nc23)Nc4c(F)cc(O)cc4Br
 COc1ccc2C(=CC(=O)Nc2c1OCC(=O)N[C@H]
 55 (Cc3ccc(O)c3)C(=O)O)Nc4c(F)cc(O)cc4Br
 OC(=O)CC[C@H](NC(=O)COc1c(OC(F)F)ccc2C(=CC
 (=O)Nc12)Nc3c(F)cc(O)cc3Br)C(=O)O
 NCCCC[C@H](NC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC
 (=O)Nc12)Nc3c(F)cc(O)cc3Br)C(=O)O
 60 OC(=O)CC[C@H](NC(=O)CCCOc1c(OC(F)F)
 ccc2C(=CC(=O)Nc12)Nc3c(F)cc(O)cc3Br)C(=O)O
 CN(CC[N+](C)C)C(=O)CCCCOc1c(OC(F)F)ccc2C
 (=CC(=O)Nc12)Nc3c(F)cc(O)cc3Br
 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)N[C@H]
 65 (CCCNC(=N)C(=O)O)Nc3c(F)cc(O)cc3Br
 COc1ccc2C(=CC(=O)Nc2c1OCCCCC(=O)N)Nc3c(F)
 cc(O)cc3Br

Oc1cc(F)c(NC2=CC(=O)Nc3c(OCCCCCC(=O)
 N4CCNCC4)c(OCF)ccc23)c(Br)c1
 CN1CCN(CC1)C(=O)CCCCCOc2c(OC(F)F)F)ccc3C
 (=CC(=O)Nc23)Nc4c(F)cc(O)cc4Br
 CSCC[C@H](NC(=O)CCCCCOc1c(OC(F)F)ccc2C
 (=CC(=O)Nc12)Nc3c(F)cc(O)cc3Br)C(=O)O
 CCCCCN(C)CCCCOc1c(OC(F)F)F)ccc2C(=CC(=O)
 Nc12)Nc3c(F)cc(ec3F)C(=O)O
 COc1ccc2C(=CC(=O)Nc2c1OCCCCOCCOCCO)Nc3c
 (F)cc(ec3F)C(=O)O
 COCCOCOCOCOCOCOCOC1c(OC(F)F)ccc2C(=CC(=O)
 Nc12)Nc3c(F)cc(ec3F)C(=O)O
 OC(=O)c1cc(F)c(NC2=CC(=O)Nc3c(OCCCCCCn4ccn4)
 c(OC(F)F)ccc23)c(F)c1
 OC(=O)c1cc(F)c(NC2=CC(=O)Nc3c(OCCCCCCn4ccn4)
 c(OC(F)F)ccc23)c(F)c1
 COCCOCOCOCOCOCOCOC1c(OC)ccc2C(=CC(=O)
 Nc12)Nc3c(F)cc(ec3F)C(=O)O
 COc1ccc2C(=CC(=O)Nc2c1OCCCCCN3CCOCC3)
 Ne4c(F)cc(ec4F)C(=O)O
 OC(=O)c1cc(F)c(NC2=CC(=O)Nc3c
 (OCCCCCCn4CCOC4)c(OC(F)F)ccc23)c(F)c1
 COc1ccc2C(=CC(=O)Nc2c1OCC(=O)NCC[N+](C)(C)
 C)Nc3c(F)cc(ec3F)C(=O)O
 CN(C)CCN(C)C(=O)COc1c(OCF)ccc2C(=CC(=O)
 Nc12)Nc3c(F)cc(ec3F)C(=O)O
 CN(CCC[N+](C)(C)C(=O)CCCOc1c(OC(F)F)F
 ccc2C(=CC(=O)Nc12)Nc3c(F)cc(ec3F)C(=O)O
 OC(=O)c1cc(F)c(NC2=CC(=O)Nc3c(OCCC(=O)
 N4CCNCC4)c(OC(F)F)ccc23)c(F)c1
 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)N
 [C@H](CO)C(=O)O)Nc3c(F)cc(ec3F)C(=O)O
 OC(=O)[C@H]1CCCN1C(=O)CCCCOc2c(OC(F)F)
 ccc3C(=CC(=O)Nc23)Nc4c(F)cc(ec4F)C(=O)O
 C[C@H](O)[C@H](NC(=O)CCCCOc1c(OC(F)F)F)
 ccc2C(=CC(=O)Nc12)Nc3c(F)cc(ec3F)C(=O)O)C
 (=O)O
 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)N
 [C@H](CC(C)C)C(=O)O)Nc3c(F)cc(ec3F)C(=O)O
 CSCC[C@H](NC(=O)CCCCOc1c(OC(F)F)F)ccc2C
 (=CC(=O)Nc12)Nc3c(F)cc(ec3F)C(=O)O)C(=O)O
 CSCC[C@H](NC(=O)CCCCOc1c(OC(F)F)F)ccc2C
 (=CC(=O)Nc12)Nc3c(F)cc(ec3F)C(=O)O)C(=O)O
 COc1ccc2C(=CC(=O)Nc2c1OCCCCN3ncn3)Nc4c(F)cc
 (cc4C1)C(=O)O
 OCCOCCCCOc1c(OC(F)F)F)ccc2C(=CC(=O)Nc12)
 Ne3c(F)cc(cc3Cl)C(=O)O
 OC(=O)c1cc(F)c(NC2=CC(=O)Nc3c(OCCCCCCn4CC
 (F)F)CC4)c(OC(F)F)ccc23)c(C1)cl
 COc1ccc2C(=CC(=O)Nc2c1OCCCCN3ccn3)Nc4c(F)
 cc(cc4Cl)C(=O)O
 C(=O)c1cc(F)c(NC2=CC(=O)Nc3c
 (OCCCCCCOc4ccncc4)c(OCF)ccc23)c(C1)c1
 C(=O)c1cc(F)c(NC2=CC(=O)Nc3c
 (OCCCCCCn4CCCC(F)F)C4)c(OC(F)F)ccc23)c
 (C1)c1
 C(=O)c1cc(F)c(NC2=CC(=O)Nc3c(OCCCCCCn4ncn4)
 c(OC(F)F)ccc23)c(C1)c1
 COCCOCOCOCOCOCOC1c(OC(F)F)ccc2C(=CC(=O)
 Nc12)Nc3c(F)cc(cc3Cl)C(=O)O
 COc1ccc2C(=CC(=O)Nc2c1OCC(=O)N3CCNCC3)
 Ne4c(F)cc(cc4C1)C(=O)O
 CSCC[C@H](NC(=O)COc1c(OC(F)F)ccc2C(=CC(=O)
 Nc12)Nc3c(F)cc(cc3Cl)C(=O)O
 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)NCC(=O)O)
 Ne3c(F)cc(cc3Cl)C(=O)O

C[C@H](O)[C@H](NC(=O)CCCOc1c(OCF)ccc2C
 (=CC(=O)Nc12)Nc3c(F)cc(cc3C1)C(=O)O)C(=O)O
 NC(=N)NCCCC[C@H](NC(=O)CCCOc1c(OC(F)(F)F)
 ccc2C(=CC(=O)Nc12)Nc3c(F)cc(cc3C1)C(=O)O)C
 (=O)O
 OC(=O)[C@H](Cc1cnc[nH]1)NC(=O)CCCOc2c(OC(F)
 F)ccc3C(=CC(=O)Nc23)Nc4c(F)cc(cc4C1)C(=O)O
 C[N+](C)(C)CCNC(=O)CCCCOc1c(OC(F)F)ccc2C
 (=CC(=O)Nc12)Nc3c(F)cc(cc3C1)C(=O)O
 10 CN(C)CCCN(C)C(=O)CCCCOc1c(OC(F)(F)F)ccc2C
 (=CC(=O)Nc12)Nc3c(F)cc(cc3C1)C(=O)O
 CCCCN(C)CCCCOc1c(OC(F)(F)F)ccc2C(=CC(=O)Nc12)
 Nc3c(F)cc(cc3Br)C(=O)O
 COc1ccc2C(=CC(=O)Nc2c1OCCCCN3CCOCC3)Nc4c
 (F)cc(cc4Br)C(=O)O
 OC(=O)c1cc(F)c(NC2=CC(=O)Nc3c(OCCCCn4cccc4)c
 (OC(F)F)ccc23)c(Br)c1
 CCN(CC)CCCCCOc1c(OCF)ccc2C(=CC(=O)Nc12)
 Nc3c(F)cc(cc3Br)C(=O)O
 20 OC(=O)c1cc(F)c(NC2=CC(=O)Nc3c(OCCCCn4ccnn4)c
 (OC(F)F)ccc23)c(Br)c1
 C(=O)c1cc(F)c(NC2=CC(=O)Nc3c(OCCCCn4cnen4)c
 (OC(F)F)F)ccc23)c(Br)c1
 OC(=O)c1cc(F)c(NC2=CC(=O)Nc3c
 (OCCCCCCn4ccnn4)c(OC(F)(F)F)ccc23)c(Br)c1
 25 COc1ccc2C(=CC(=O)Nc2c1OCCCCCOCCOCCO)
 Nc3c(F)cc(cc3Br)C(=O)O
 CC(C)C[C@H](NC(=O)COc1c(OCF)ccc2C(=CC(=O)
 Nc12)Nc3c(F)cc(cc3Br)C(=O)O)C(=O)O
 30 COc1ccc2C(=CC(=O)Nc2c1OCC(=O)N[C@H]
 (Cc3ccc(O)cc3)C(=O)O)Nc4c(F)cc(cc4Br)C(=O)O
 NC(=O)C[C@H](NC(=O)COc1c(OC(F)F)ccc2C(=CC
 (=O)Nc12)Nc3c(F)cc(cc3Br)C(=O)O)C(=O)O
 CC(C)[C@H](NC(=O)CCCCOc1c(OC(F)F)ccc2C
 (=CC(=O)Nc12)Nc3c(F)cc(cc3Br)C(=O)O)C(=O)O
 35 NCCCC[C@H](NC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC
 (=O)Nc12)Nc3c(F)cc(cc3Br)C(=O)O)C(=O)O
 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)N[C@H]
 (CC(=O)N)C(=O)O)Nc3c(F)cc(cc3Br)C(=O)O
 40 COc1ccc2C(=CC(=O)Nc2c1OCCCCC(=O)
 N3CCNCC3)Nc4c(F)cc(cc4Br)C(=O)O
 CC(C)C[C@H](NC(=O)CCCCOc1c(OC(F)F)ccc2C
 (=CC(=O)Nc12)Nc3c(F)cc(cc3Br)C(=O)O)C(=O)O
 CC[C@H](C)[C@H](NC(=O)CCCCOc1c(OC(F)(F)F)
 45 ccc2C(=CC(=O)Nc12)Nc3c(F)cc(cc3Br)C(=O)O)C
 (=O)O
 CN(C)CCOC(=O)CCCCCOc1c(OC(F)(F)F)ccc2C(=CC
 (=O)Nc12)Nc3c(F)cc(cc3Br)C(=O)O)O
 C[C@H](O)[C@H](NC(=O)CCCCCOc1c(OC(F)F)ccc2C
 (=CC(=O)Nc12)Nc3c(F)cc(cc3Br)C(=O)O)C(=O)O
 50 COc1ccc2C(=CC(=O)Nc2c1OCCCCC(=O)N
 [C@H](CC(=O)N)C(=O)O)Nc3c(F)cc(cc3Br)C
 (=O)O
 CCCNCCCCOc1c(OC)ccc2C(=CC(=O)Nc12)Nc3c(C1)
 55 cccc3C1
 CCCNCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c
 (C1)cccc3C1
 CCCNCCCCOc1c(OC(F)(F)F)ccc2C(=CC(=O)Nc12)
 Nc3c(C1)cccc3C1
 60 OCCOCCOCCOCCCCOc1c(OCF)ccc2C(=CC(=O)
 Nc12)Nc3c(C1)cccc3C1
 COc1ccc2C(=CC(=O)Nc2c1OCCCCNC(=N)N)Nc3c
 (C1)cccc3C1
 FC(F)(F)Oc1ccc2C(=CC(=O)
 65 Nc2c1OCCCCN3CCOCC3)Nc4c(C1)cccc4C1
 FCOc1ccc2C(=CC(=O)Nc2c1OCCCCn3cccc3)Nc4c
 (C1)cccc4C1

CCCCN(C)CCCCCOc1c(OC(F)F)ccc2C(=CC(=O)
Nc12)Nc3c(C1)cccc3C1
FCOc1ccc2C(=CC(=O)Nc2c1OCCCCCOc3ccnc3)
Nc4c(C1)cccc4C1
CN(C)CCOC(=O)COc1c(OC(F)F)ccc2C(=CC(=O)Nc12)
Nc3c(C1)cccc3C1
COc1ccc2C(=CC(=O)Nc2c1OCC(=O)N(C)CCCN(C)
C)Nc3c(C1)cccc3C1
OC(=O)[C@H](Cc1cccc1)NC(=O)COc2c(OC(F)F)
ccc3C(=CC(=O)Nc23)Nc4c(C1)cccc4C1
NC(=O)CC[C@H](NC(=O)COc1c(OC(F)F)F)ccc2C
(=CC(=O)Nc12)Nc3c(C1)cccc3C1)C(=O)O
C[C@H](O)[C@H](NC(=O)CCCCOc1c(OC(F)F)F)ccc2C
(=CC(=O)Nc12)Nc3c(C1)cccc3C1)C(=O)O
C[C@H](NC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)
Nc12)Nc3c(C1)cccc3C1)C(=O)O
CC[C@H](C)[C@H](NC(=O)CCCCCOc1c(OC(F)F)
ccc2C(=CC(=O)Nc12)Nc3c(C1)cccc3C1)C(=O)O
OC(=O)[C@H](Cc1ccc(O)cc1)NC(=O)CCCCOc2c
(OC(F)ccc3C(=CC(=O)Nc23)Nc4c(C1)cccc4C1
NCCCC[C@H](NC(=O)CCCCOc1c(OC(F)F)F)ccc2C
(=CC(=O)Nc12)Nc3c(C1)cccc3C1)C(=O)O
COc1ccc2C(=CC(=O)Nc2c1OCCCCN3ccnc3)
[C@H](CCC(=O)O)C(=O)O)Nc3c(C1)cccc3C1
NC(=N)NCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)
Nc3c(C1)cccc3Br
FC1cCCN(CCCCCOc2c(OC(F)F)F)ccc3C(=CC(=O)
Nc23)Nc4c(C1)cccc4Br)C1
COc1ccc2C(=CC(=O)Nc2c1OCCCCN3ccnc3)Nc4c(C1)
cccc4Br
FCOc1ccc2C(=CC(=O)Nc2c1OCCCCN3CC(F)CC3)
Nc4c(C1)cccc4Br
COc1ccc2C(=CC(=O)Nc2c1OCCCCN3ccnn3)Nc4c
(C1)cccc4Br
FC(F)Oc1ccc2C(=CC(=O)Nc2c1OCCCCN3ccnn3)
Nc4c(C1)cccc4Br
CNCCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)
Nc3c(C1)cccc3Br
CCCCN(C)CCCCCOc1c(OC(F)F)ccc2C(=CC(=O)
Nc12)Nc3c(C1)cccc3Br
FCOc1ccc2C(=CC(=O)Nc2c1OCCCCN3ccnc3)Nc4c
(C1)cccc4Br
COCCOCCCCCOc1c(OC)ccc2C(=CC(=O)Nc12)Nc3c
(C1)cccc3Br
C[N+]C(C)CCNC(=O)COc1c(OC(F)F)ccc2C(=CC(=O)
Nc12)Nc3c(C1)cccc3Br
COc1ccc2C(=CC(=O)Nc2c1OCC(=O)NCC(=O)O)
Nc3c(C1)cccc3Br
NC(=O)CC[C@H](NC(=O)COc1c(OC(F)F)ccc2C(=CC
(=O)Nc12)Nc3c(C1)cccc3Br)C(=O)O
CN(C)CCNC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)
Nc12)Nc3c(C1)cccc3Br
CC(C)C[C@H](NC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC
(=O)Nc12)Nc3c(C1)cccc3Br)C(=O)O
COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)N[C@H]
(C)C(=O)O)Nc3c(C1)cccc3Br
C[C@H](NC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)
Nc12)Nc3c(C1)cccc3Br)C(=O)O
C(=O)C[C@H](NC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC
(=O)Nc12)Nc3c(C1)cccc3Br)C(=O)O
CN(CC) [N+]C(C)C(=O)CCCCOc1c(OC(F)F)F)
ccc2C(=CC(=O)Nc12)Nc3c(C1)cccc3Br
COCCOCCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)
Nc3c(C1)cc(F)cc3C1
COc1ccc2C(=CC(=O)Nc2c1OCCCCOCCOCCOCCO)
Nc3c(C1)cc(F)cc3C1

Fc1cc(C1)c(NC2=CC(=O)Nc3c(OCCCCN4CCC(F)F)
C4c(OC(F)F)ccc23)c(C1)c1
FCOc1ccc2C(=CC(=O)Nc2c1OCCCCN3ccn3)Nc4c
(C1)cc(F)cc4C1
5 OCCOCCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)
Nc3c(C1)cc(F)cc3C1
COc1ccc2C(=CC(=O)Nc2c1OCCCCNC(=N)N)
Nc3c(C1)cc(F)cc3C1
FCOc1ccc2C(=CC(=O)Nc2c1OCCCCN3ccn3)Nc4c
(C1)cc(F)cc4C1
Fc1cc(C1)c(NC2=CC(=O)Nc3c(OCCCCN4ccnn4)c
(OC(F)F)ccc23)c(C1)c1
CN(C)CCOC(=O)COc1c(OC(F)F)ccc2C(=CC(=O)Nc12)
Nc3c(C1)cc(F)cc3C1
15 OC(=O)CNC(=O)COc1c(OC(F)F)ccc2C(=CC(=O)
Nc12)Nc3c(C1)cc(F)cc3C1
OC(=O)[C@H](Cc1cccc1)NC(=O)COc2c(OC(F)F)
ccc3C(=CC(=O)Nc23)Nc4c(C1)cc(F)cc4C1
20 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)N3CCNCC3)
Nc4c(C1)cc(F)cc4C1
OC(=O)[C@H]1CCCC1C(=O)CCCOc2c(OC(F)F)F
ccc3C(=CC(=O)Nc23)Nc4c(C1)cc(F)cc4C1
OC[C@H](NC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)
25 Nc12)Nc3c(C1)cc(F)cc3C1)C(=O)O
Fc1cc(C1)c(NC2=CC(=O)Nc3c(OCCCC(=O)
N4CCNCC4)c(OC(F)F)ccc23)c(C1)c1
NC(=O)C[C@H](NC(=O)CCCCOc1c(OC(F)F)ccc2C
(=CC(=O)Nc12)Nc3c(C1)cc(F)cc3C1)C(=O)O
30 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)N3CC
[C@H]3C(=O)O)Nc4c(C1)cc(F)cc4C1
OC(=O)[C@H] (Cc1cccc1)NC(=O)CCCCOc2c(OC
(F)F)ccc3C(=CC(=O)Nc23)Nc4c(C1)cc(F)cc4C1
OC(=O)[C@H](Cc1c[nH]c2cccc12)NC(=O)
CCCCCOc3c(OC(F)F)ccc4C(=CC(=O)Nc34)Nc5c(C1)
cc(F)cc5C1
35 CCCN(C)CCCCOc1c(OC)ccc2C(=CC(=O)Nc12)Nc3c
(C1)cc(F)cc3Br
40 COCCOCCOCCOCCCOc1c(OC(F)F)ccc2C(=CC(=O)
Nc12)Nc3c(C1)cc(F)cc3Br
CCN(C)CCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c
(C1)cc(F)cc3Br
COc1ccc2C(=CC(=O)Nc2c1OCCCCN3CCCC(F)C3)
45 Nc4c(C1)cc(F)cc4Br
CCN(CC)CCCCCOc1c(OC(F)F)ccc2C(=CC(=O)
Nc12)Nc3c(C1)cc(F)cc3Br
FC1cCN(CCCCCCOc2c(OC(F)F)F)ccc3C(=CC(=O)
Nc23)Nc4c(C1)cc(F)cc4Br)CC1
50 COc1ccc2C(=CC(=O)Nc2c1OCCCCCOc3ccnc3)
Nc4c(C1)cc(F)cc4Br
FCOc1ccc2C(=CC(=O)Nc2c1OCCCCN3ccn3)Nc4c
(C1)cc(F)cc4Br
NCCCC[C@H](NC(=O)COc1c(OC(F)F)ccc2C(=CC
(=O)Nc12)Nc3c(C1)cc(F)cc3Br)C(=O)O
55 CN(C)CCOC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)
Nc12)Nc3c(C1)cc(F)cc3Br
CSCC[C@H](NC(=O)CCCCOc1c(OC(F)F)F)ccc2C(=CC
(=O)Nc12)Nc3c(C1)cc(F)cc3Br)C(=O)O
60 C[N+]C(C)CCNC(=O)CCCCOc1c(OC(F)F)F)ccc2C
(=CC(=O)Nc12)Nc3c(C1)cc(F)cc3Br
COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)N(C)CCCN
(C)C)Nc3c(C1)cc(F)cc3Br
CN(C)CCCN(C)C(=O)CCCCOc1c(OC(F)F)ccc2C(=CC
(=O)Nc12)Nc3c(C1)cc(F)cc3Br
65 NC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)
Nc3c(C1)cc(F)cc3Br

NC(=N)NCCC[C@H](NC(=O)CCCCCOc1c(OC(F)(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C1)cc(F)cc3Br)C
 (=O)O
 Oc1cc(C1)c(OC2=CC(=O)Nc3e(OCCCCn4ncen4)c(OCF)ccc23)c(C1)c1
 OCCOCCOCOCOC1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3e(C1)cc(O)cc3C1
 NCCCCCOc1c(OCF)ccc2C(=CC(=O)Nc12)Nc3c(C1)cc(O)cc3C1
 CCN(CC)CCCCCOc1c(OC(F)(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C1)cc(O)cc3C1
 CN(C)CCCCCOc1c(OCF)ccc2C(=CC(=O)Nc12)Nc3c(C1)cc(O)cc3C1
 CCCNCCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3e(C1)cc(O)cc3C1
 COc1ccc2C(=CC(=O)Nc2c1OCCCCCN3CCC(F)CC3)Nc4e(C1)cc(O)cc4C1
 Oc1cc(C1)c(OC2=CC(=O)Nc3c(OCCCCCOc4ccen4)c(OC(F)(F)F)ccc23)c(C1)c1
 COc1ccc2C(=CC(=O)Nc2c1OCC(=O)OCN(C)C)Nc3e(C1)cc(O)cc3C1
 OC(=O)CNC(=O)COc1c(OC(F)(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C1)cc(O)cc3C1
 CS[C@H](NC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3e(C1)cc(O)cc3C1)C(=O)O
 NCCCC[C@H](NC(=O)CCCCOc1c(OC(F)(F)F)ccc2C(=CC(=O)Nc12)Nc3e(C1)cc(O)cc3C1)C(=O)O
 OC(=O)[C@H](Cc1cnc[nH]1)NC(=O)CCCCOc2c(OCF)ccc3C(=CC(=O)Nc23)Nc4e(C1)cc(O)cc4C1
 NC(=O)CCCCOc1c(OCF)ccc2C(=CC(=O)Nc12)Nc3c(C1)cc(O)cc3C1
 OC(=O)CNC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3e(C1)cc(O)cc3C1
 C[N+](C)(C)CCNC(=O)CCCCCOc1c(OCF)ccc2C(=CC(=O)Nc12)Nc3c(C1)cc(O)cc3C1
 COc1ccc2C(=CC(=O)Nc2c1OCCCCCCC(=O)NCC(=O)O)Nc3e(C1)cc(O)cc3C1
 OC(=O)[C@H](Cc1cccc1)NC(=O)CCCCOc2c(OC(F)F)ccc3C(=CC(=O)Nc23)Nc4e(C1)cc(O)cc4C1
 CCN(CC)CCCCOc1c(OCF)ccc2C(=CC(=O)Nc12)Nc3c(C1)cc(O)cc3Br
 COc1ccc2C(=CC(=O)Nc2c1OCCCCN3CCC(F)CC3)Nc4e(C1)cc(O)cc4Br
 Oc1cc(C1)c(OC2=CC(=O)Nc3c(OCCCCOc4ccen4)c(OC(F)(F)F)ccc23)c(Br)c1
 COc1ccc2C(=CC(=O)Nc2c1OCCCCN)Nc3c(C1)cc(O)cc3Br
 Oc1cc(C1)c(OC2=CC(=O)Nc3c(OCCCCN4CCCC(F)C4)c(OC(F)F)ccc23)c(Br)c1
 COCCOCCCCCOc1c(OCF)ccc2C(=CC(=O)Nc12)Nc3c(C1)cc(O)cc3Br
 CCCN(C)CCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3e(C1)cc(O)cc3Br
 Oc1cc(C1)c(OC2=CC(=O)Nc3c(OCCCCCOc4ccen4)c(OCF)ccc23)c(Br)c1
 Oc1cc(C1)c(OC2=CC(=O)Nc3e(OCC(=O)N4CCNCC4)c(OC(F)F)ccc23)c(Br)c1
 COc1ccc2C(=CC(=O)Nc2c1OCC(=O)N[C@H](CCSC)C(=O)O)Nc3c(C1)cc(O)cc3Br
 C(=O)CC[C@H](NC(=O)COc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3e(C1)cc(O)cc3Br)C(=O)O
 CN1CCN(CC1)C(=O)CCCCOc2c(OC(F)(F)F)ccc3C(=CC(=O)Nc23)Nc4e(C1)cc(O)cc4Br
 CoC1ccc2C(=CC(=O)Nc2c1OCCCC(=O)N[C@H](C)C(=O)O)Nc3c(C1)cc(O)cc3Br

CN(C)CCCN(C)C(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C1)cc(O)cc3Br
 OC(=O)CNC(=O)CCCCOc1c(OCF)ccc2C(=CC(=O)Nc12)Nc3c(C1)cc(O)cc3Br
 5 CoC1ccc2C(=CC(=O)Nc2c1OCCCCC(=O)N[C@H](CCC(=O)O)C(=O)O)Nc3c(C1)cc(O)cc3Br
 CN(C)CCN(C)C(=O)CCCCOc1c(OCF)ccc2C(=CC(=O)Nc12)Nc3c(C1)cc(O)cc3Br
 CN(CCC[N+](C)(C)C(=O)CCCCCOc1c(OC(F)(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C1)cc(O)cc3Br
 10 OC(=O)[C@H](Cc1cccc1)NC(=O)CCCCOc2c(OC(F)F)ccc3C(=CC(=O)Nc23)Nc4e(C1)cc(O)cc4Br
 CoC1ccc2C(=CC(=O)Nc2c1OCCCN(C)C)Nc3c(C1)cc(O)cc3C1)C(=O)O
 OC(=O)c1cc(C1)c(OC2=CC(=O)Nc3c
 (OC(OC)Oc4ccen4)c(OC(F)(F)F)ccc23)c(C1)c1
 COCCOCCOCOCOCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3e(C1)cc(O)cc3C1)C(=O)O
 15 OC(=O)c1cc(C1)cc(O)cc3C1)C(=O)O
 COc1ccc2C(=CC(=O)Nc2c1OCCCCN3CCCC(F)CC3)Nc4e(C1)cc(O)cc4C1
 OC(=O)c1cc(C1)cc(O)cc3C1)C(=O)O
 20 NC(=N)NCCCCCOc1c(OCF)ccc2C(=CC(=O)Nc12)Nc3e(C1)cc(O)cc3C1)C(=O)O
 COc1ccc2C(=CC(=O)Nc2c1OCCCCN3CCCC(F)CC3)Nc4e(C1)cc(O)cc4C1
 OC(=O)c1cc(C1)cc(O)cc3C1)C(=O)O
 25 CNCCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C1)cc(O)cc3C1)C(=O)O
 CCN(C)CCCCCOc1c(OC(F)(F)F)ccc2C(=CC(=O)Nc12)Nc3e(C1)cc(O)cc3C1)C(=O)O
 COCCOCCCCCOc1c(OC)ccc2C(=CC(=O)Nc12)Nc3c(C1)cc(O)cc3C1)C(=O)O
 30 COC1ccc2C(=CC(=O)Nc2c1OCC(=O)N3CCC[C@H]3C(=O)O)Nc4e(C1)cc(O)cc4C1
 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)NCC(=O)O)Nc3c(C1)cc(O)cc3C1)C(=O)O
 35 OC(=O)[C@H](Cc1cccc1)NC(=O)CCCOc2c(OCF)ccc3C(=CC(=O)Nc23)Nc4e(C1)cc(O)cc4C1
 CN(C)CCN(C)C(=O)CCCCOc1c(OCF)ccc2C(=CC(=O)Nc12)Nc3e(C1)cc(O)cc3C1)C(=O)O
 OC(=O)[C@H](Cc1cccc1)NC(=O)CCCCOc2c(OCF)ccc3C(=CC(=O)Nc23)Nc4e(C1)cc(O)cc4C1
 40 COc1ccc2C(=CC(=O)Nc2c1OCCCCC(=O)N[C@H](CC(C)C)C(=O)O)Nc3c(C1)cc(O)cc3C1)C(=O)O
 C[C@H](NC(=O)CCCCCOc1c(OCF)ccc2C(=CC(=O)Nc12)Nc3e(C1)cc(O)cc3C1)C(=O)O
 COc1ccc2C(=CC(=O)Nc2c1OCCCCNC(=N)N)Nc3c(C1)cc(O)cc3Br)C(=O)O
 45 OC(=O)c1cc(C1)c(OC2=CC(=O)Nc3c(OCCCCN4CCCC(F)C4)c(OC(F)F)ccc23)c(Br)c1
 CN(C)CCCCCOc1c(OC(F)(F)F)ccc2C(=CC(=O)Nc12)Nc3e(C1)cc(O)cc3Br)C(=O)O
 50 COc1ccc2C(=CC(=O)Nc2c1OCCCCN3CCOCC3)Nc4e(C1)cc(O)cc4Br)C(=O)O
 OC(=O)c1cc(C1)c(OC2=CC(=O)Nc3c
 (OCCCCN4ccen4)c(OCF)ccc23)c(Br)c1
 COCCOCCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3e(C1)cc(O)cc3Br)C(=O)O
 55 NC(=O)CoC1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C1)cc(O)cc3Br)C(=O)O
 NC(=O)CoC1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C1)cc(O)cc3Br)C(=O)O
 CN(CCC[N+](C)(C)C(=O)CoC1c(OCF)ccc2C(=CC(=O)Nc12)Nc3c(C1)cc(O)cc3Br)C(=O)O
 60 CN1CCN(CC1)C(=O)CoC2c(OC(F)F)ccc3C(=CC(=O)Nc23)Nc4e(C1)cc(O)cc4Br)C(=O)O
 C[N+](C)(C)CCNC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3e(C1)cc(O)cc3Br)C(=O)O
 CN(C)CCCN(C)C(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3e(C1)cc(O)cc3Br)C(=O)O
 65 OC(=O)[C@H](Cc1cccc1)NC(=O)CCCCOc2c(OCF)ccc3C(=CC(=O)Nc23)Nc4e(C1)cc(O)cc4Br)C(=O)O

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COc1ccc2C(=CC(=O)Nc2c1OCCCCCCC(=O)N
 [C@@@H](CCCNC(=N)N)C(=O)O)Nc3c(C1)cc
 (cc3Br)C(=O)O
 CCCN(C)CCCCOc1c(OC)ccc2C(=CC(=O)Nc12)Nc3c
 (Br)cccc3Br
 FC(F)(F)Oc1ccc2C(=CC(=O)Nc2c1OCCCCn3cncn3)
 Ne4c(Br)cccc4Br
 COCCOCOCOCOCOCOC1c(OC(F)F)ccc2C(=CC(=O)
 Nc12)Nc3c(Br)cccc3Br
 FCo1ccc2C(=CC(=O)Nc2c1OCCCCCN3CCOCC3)
 Ne4c(Br)cccc4Br
 COCCOCOCOCOC1c(OC)ccc2C(=CC(=O)Nc12)Nc3c
 (Br)cccc3Br
 CCN(CC)CCCCCOc1c(OC(F)F)ccc2C(=CC(=O)
 Nc12)Nc3c(Br)cccc3Br
 FC(F)(F)Oc1ccc2C(=CC(=O)
 Ne2c1OCCCCCN3CCOCC3)Ne4c(Br)cccc4Br
 FCo1ccc2C(=CC(=O)Nc2c1OCCCCCN3ccen3)Ne4c
 (Br)cccc4Br
 CN1CCN(CC1)C(=O)COc2c(OC(F)F)ccc3C(=CC(=O)
 Nc23)Nc4c(Br)cccc4Br
 C[C@H](NC(=O)Oc1c(OCF)ccc2C(=CC(=O)Nc12)
 Nc3c(Br)cccc3Br)C(=O)O
 C[N+](C)(C)CCNC(=O)CCCCOc1c(OCF)ccc2C(=CC
 (=O)Nc12)Nc3c(Br)cccc3Br
 C[C@H](NC(=O)CCCOc1c(OC(F)F)ccc2C(=CC(=O)
 Nc12)Nc3c(Br)cccc3Br)C(=O)O
 OC(=O)[C@H](Cc1c[nH]1c2cccc12)NC(=O)CCCOc3c
 (OC(F)F)ccc4C(=CC(=O)Nc34)Nc5c(Br)cccc5Br
 C[N+](C)(C)CCNC(=O)CCCCOc1c(OCF)ccc2C(=CC
 (=O)Nc12)Nc3c(Br)cccc3Br
 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)N[C@@H]
 (CC(C)C)(=O)O)Nc3c(Br)cccc3Br
 CN(C)CCN(C)C(=O)CCCCCOc1c(OC(F)F)ccc2C
 (=CC(=O)Nc12)Nc3c(Br)cccc3Br
 CN(CC[N+](C)(C)C(=O)CCCCOc1c(OC(F)F)ccc2C
 (=CC(=O)Nc12)Nc3c(Br)cccc3Br
 FCo1ccc2C(=CC(=O)Nc2c1OCCCCCCC(=O)
 N3CCNCC3)Nc4c(Br)cccc4Br
 COc1ccc2C(=CC(=O)Nc2c1OCCCCCCC(=O)N
 [C@@H](CC(=O)N)C(=O)O)Nc3c(Br)cccc3Br
 FCo1ccc2C(=CC(=O)Nc2c1OCCCCN3CCCC(F)(F)
 C3)Nc4c(Br)cc(F)cc4Br
 FC(F)Oc1ccc2C(=CC(=O)Nc2c1OCCCCN3CCC(F)(F)
 CC3)Nc4c(Br)cc(F)cc4Br
 COCCN(C)CCCCCOc1c(OC(F)F)ccc2C(=CC(=O)
 Nc12)Nc3c(Br)cc(F)cc3Br
 COc1ccc2C(=CC(=O)Nc2c1OCCCCN3CCOCC3)
 Ne4c(Br)cc(F)cc4Br
 Fe1cc(Br)c(NC2=CC(=O)Nc3c(OCCCCN4cccc4)c(OC
 (F)F)ccc23)c(Br)c1
 FCo1ccc2C(=CC(=O)Nc2c1OCCCCN3ccnn3)Nc4c
 (Br)cc(F)cc4Br
 CNCCCCCOc1c(OCF)ccc2C(=CC(=O)Nc12)Nc3c(Br)
 cc(F)cc3Br
 FC(F)Oc1ccc2C(=CC(=O)Nc2c1OCCCCCCCn3ccnn3)
 Nc4c(Br)cc(F)cc4Br
 NCCCC[C@H](NC(=O)Oc1c(OCF)ccc2C(=CC(=O)
 Nc12)Nc3c(Br)cc(F)cc3Br)C(=O)O
 C(=O)[C@H](Cc1c[nH]1)NC(=O)Oc2c(OC(F)F)ccc3C
 (=CC(=O)Nc23)Nc4c(Br)cc(O)cc4Br
 OC(=O)CNC(=O)CCCOc1c(OC(F)F)ccc2C(=CC
 (=O)Nc12)Nc3c(Br)cc(O)cc3Br
 CSCC[CH](NC(=O)CCCOc1c(OCF)ccc2C(=CC(=O)
 Nc12)Nc3c(Br)cc(O)cc3Br)C(=O)O
 NC(=N)NCCC[C@H](NC(=O)CCCOc1c(OC(F)F)
 ccc2C(=CC(=O)Nc12)Nc3c(Br)cc(O)cc3Br)C(=O)O
 50 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)N[C@@H]
 (CC(=O)N)C(=O)O)Nc3c(Br)cc(O)cc3Br
 CN(C)CCNC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)
 Nc12)Nc3c(Br)cc(O)cc3Br
 C[C@H](O)[C@H](NC(=O)CCCCOc1c(OCF)ccc2C
 (=CC(=O)Nc12)Nc3c(Br)cc(O)cc3Br)C(=O)O
 OC(=O)[C@H](Cc1c[nH]1)NC(=O)CCCOc2c(OC
 (F)F)ccc3C(=CC(=O)Nc23)Nc4c(Br)cc(O)cc4Br
 CNCCCCOc1c(OCF)ccc2C(=CC(=O)Nc12)Nc3c(Br)cc
 (cc3Br)C(=O)O
 60 CCN(C)CCCCOc1c(OC)ccc2C(=CC(=O)Nc12)Nc3c
 (Br)cc(cc3Br)C(=O)O
 OC(=O)c1cc(Br)c(NC2=CC(=O)Nc3c(OCCCCN4CCC
 (F)C4)c(OC(F)F)ccc23)c(Br)c1
 OC(=O)c1cc(Br)c(NC2=CC(=O)Nc3c
 (OCCCCN4CCCC(F)F)C4)c(OCF)ccc23)c(Br)c1
 65 OC(=O)c1cc(Br)c(NC2=CC(=O)Nc3c
 (OCCCCN4cccc4)c(OC(F)F)ccc23)c(Br)c1

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NC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)
 Nc3c(Br)cc(F)cc3Br
 CN(C)CCNC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC
 (=O)Nc12)Nc3c(Br)cc(F)cc3Br
 5 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)N3CCN(C)
 CC3)Nc4c(Br)cc(F)cc4Br
 OC(=O)CNC(=O)CCCCOc1c(OCF)ccc2C(=CC(=O)
 Nc12)Nc3c(Br)cc(F)cc3Br
 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)
 N3CCNCC3)Nc4c(Br)cc(F)cc4Br
 C[C@H](O)[C@H](NC(=O)CCCCOc1c(OC(F)F)
 ccc2C(=CC(=O)Nc12)Nc3c(Br)cc(F)cc3Br)C(=O)O
 OC(=O)[C@H](Cc1c[nH]1)NC(=O)CCCOc2c
 (OCF)ccc3C(=CC(=O)Nc23)Nc4c(Br)cc(F)cc4Br
 15 CCNCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c
 (Br)cc(O)cc3Br
 Oc1cc(Br)c(NC2=CC(=O)Nc3c(OCCCCN4CCCC4)c(OC
 (F)F)ccc23)c(Br)c1
 COc1ccc2C(=CC(=O)Nc2c1OCCCCN3CCC(F)CC3)
 Ne4c(Br)cc(O)cc4Br
 Oc1cc(Br)c(NC2=CC(=O)Nc3c(OCCCCN4CCCC4)c
 (OC(F)F)ccc23)c(Br)c1
 25 COc1ccc2C(=CC(=O)Nc2c1OCCCCN3CCC(F)F)C3)
 Ne4c(Br)cc(O)cc4Br
 Oc1cc(Br)c(NC2=CC(=O)Nc3c(OCCCCN4CCCC4)c
 (OC(F)F)ccc23)c(Br)c1
 CN(C)CCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)
 Nc3c(Br)cc(O)cc3Br
 Oc1cc(Br)c(NC2=CC(=O)Nc3c(OCCCCN4CCOCC4)
 c(OCF)ccc23)c(Br)c1
 Oc1cc(Br)c(NC2=CC(=O)Nc3c(OCCCCN4cccc4)c
 (OC(F)F)ccc23)c(Br)c1
 35 CN(C)CCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)
 Nc3c(Br)cc(O)cc3Br
 CN1CCN(CC1)C(=O)COc2c(OC(F)F)ccc3C(=CC
 (=O)Nc23)Nc4c(Br)cc(O)cc4Br
 40 NCCCC[C@H](NC(=O)Oc1c(OC(F)F)ccc2C(=CC
 (=O)Nc12)Nc3c(Br)cc(O)cc3Br)C(=O)O
 C(=O)[C@H](Cc1c[nH]1)NC(=O)Oc2c(OCF)ccc3C
 (=CC(=O)Nc23)Nc4c(Br)cc(O)cc4Br
 OC(=O)CNC(=O)CCCOc1c(OC(F)F)ccc2C(=CC
 (=O)Nc12)Nc3c(Br)cc(O)cc3Br
 45 CSCC[CH](NC(=O)CCCOc1c(OCF)ccc2C(=CC(=O)
 Nc12)Nc3c(Br)cc(O)cc3Br)C(=O)O
 NC(=N)NCCC[C@H](NC(=O)CCCOc1c(OC(F)F)
 ccc2C(=CC(=O)Nc12)Nc3c(Br)cc(O)cc3Br)C(=O)O
 50 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)N[C@@H]
 (CC(=O)N)C(=O)O)Nc3c(Br)cc(O)cc3Br
 CN(C)CCNC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)
 Nc12)Nc3c(Br)cc(O)cc3Br
 C[C@H](O)[C@H](NC(=O)CCCCOc1c(OCF)ccc2C
 (=CC(=O)Nc12)Nc3c(Br)cc(O)cc3Br)C(=O)O
 OC(=O)[C@H](Cc1c[nH]1)NC(=O)CCCOc2c(OC
 (F)F)ccc3C(=CC(=O)Nc23)Nc4c(Br)cc(O)cc4Br
 CNCCCCOc1c(OCF)ccc2C(=CC(=O)Nc12)Nc3c(Br)cc
 (cc3Br)C(=O)O
 60 CCN(C)CCCCOc1c(OC)ccc2C(=CC(=O)Nc12)Nc3c
 (Br)cc(cc3Br)C(=O)O
 OC(=O)c1cc(Br)c(NC2=CC(=O)Nc3c(OCCCCN4CCC
 (F)C4)c(OC(F)F)ccc23)c(Br)c1
 OC(=O)c1cc(Br)c(NC2=CC(=O)Nc3c
 (OCCCCN4CCCC(F)F)C4)c(OCF)ccc23)c(Br)c1
 65 OC(=O)c1cc(Br)c(NC2=CC(=O)Nc3c
 (OCCCCN4cccc4)c(OC(F)F)ccc23)c(Br)c1

COCCOCCOCCCCCOc1c(OC(F)(F)F)ccc2C(=CC(=O)Nc12)Nc3c(Br)cc(cc3Br)C(=O)O
 CNCCCCCOc1c(OC(F)(F)F)ccc2C(=CC(=O)Nc12)Nc3c(Br)cc(cc3Br)C(=O)O
 COCCN(C)CCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(Br)cc(cc3Br)C(=O)O
 COc1ccc2C(=CC(=O)Nc2c1OCCCCCN3CCCC(F)(F)C3)Nc4c(Br)cc(cc4Br)C(=O)O
 OCCOCCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(Br)cc(cc3Br)C(=O)O
 CN(C)CCNC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(Br)cc(cc3Br)C(=O)O
 OC(=O)c1cc(Br)c(NC2=CC(=O)Nc3c(OCCCC(=O)N4CCNCC4)c(OC(F)F)ccc23)c(Br)c1
 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)N[C@@H](CO)C(=O)O)Nc3c(Br)cc(cc3Br)C(=O)O
 CN(C)CCNC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(Br)cc(cc3Br)C(=O)O
 CN(CC[N+](C)(C)C)C(=O)CCCCOc1c(OC(F)(F)F)ccc2C(=CC(=O)Nc12)Nc3c(Br)cc(cc3Br)C(=O)O
 C[C@H](NC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(Br)cc(cc3Br)C(=O)O
 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)N[C@@H](CCCN)C(=O)O)Nc3c(Br)cc(cc3Br)C(=O)O
 CCN(CC)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C)cncc3C
 CCCCCN(C)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C)cncc3C
 COc1ccc2C(=CC(=O)Nc2c1OCCCCN3CCCC(F)(F)C3)Nc4c(C)cncc4C
 Cc1cnec(C)c1NC2=CC(=O)Nc3c(OCCCCn4ccn4)c(OC(F)F)ccc23
 Cc1cnec(C)c1NC2=CC(=O)Nc3c(OCCCCn4ccn4)c(OC(F)(F)F)ccc23
 CNCCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C)cncc3C
 COCCN(C)CCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C)cncc3C
 COc1ccc2C(=CC(=O)Nc2c1OCCCCN3CCC(F)CC3)Nc4c(C)cncc4C
 Cc1cnec(C)c1NC2=CC(=O)Nc3c(OCCCCn4ccn4)c(OC(F)F)ccc23
 Cc1cnec(C)c1NC2=CC(=O)Nc3c(OCCCCn4ccn4)c(OC(F)(F)F)ccc23
 COc1ccc2C(=CC(=O)Nc2c1OCCCCCCN(C)C)Nc3c(C)cncc3C
 CCNCCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C)cncc3C
 CCN(C)CCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C)cncc3C
 CCCCCN(C)CCCCCOc1c(OC(F)(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C)cncc3C
 C[C@H](NC(=O)COc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C)cncc3C)C(=O)O
 Cc1cnec(C)c1NC2=CC(=O)Nc3c(OCCCCOc1c(OC(F)F)ccc23)C(=O)O
 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)N[C@@H](O)[C@H](NC(=O)COc1c(OC(F)F)ccc23)C(=O)O
 Cc1cnec(C)c1NC2=CC(=O)Nc3c(OCCCC(=O)N[C@@H](O)[C@H](NC(=O)COc1c(OC(F)F)ccc23)C(=O)O
 CN(CC[N+](C)(C)C)C(=O)CCCCOc1c(OC(F)(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C)cncc3C
 CN(C)CCCN(C)C(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C)cncc3C

COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)N3CN(C)CC3)Nc4c(C)cncc4C
 Cc1cncc(C)c1NC2=CC(=O)Nc3c(OCCCC(=O)N)c(OC(F)F)ccc23
 5 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)N3CCNCC3)Nc4c(C)cncc4C
 Cc1cncc(C)c1NC2=CC(=O)Nc3c(OCCCC(=O)N)[C@@H](CO)C(=O)O)c(OC(F)F)ccc23
 C[C@H](O)[C@H](NC(=O)CCCCOc1c(OC(F)(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C)cncc3C)C(=O)O
 Cc1cncc(C)c1NC2=CC(=O)Nc3c(OCCCC(=O)N4CCNCC4)C(=O)O)c(OC(F)F)ccc23
 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)NCC(=O)Nc3c(C)cncc3C
 15 Cc1cncc(C)c1NC2=CC(=O)Nc3c(OCCCC(=O)N4CCC[C@H](NC(=O)O)c(OC(F)F)ccc23
 CSCC[C@H](NC(=O)CCCCOc1c(OC(F)(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C)cncc3C)C(=O)O
 20 Cc1cnec(F)c1NC2=CC(=O)Nc3c(OCCCCN4CCCC4)c(OC(F)F)ccc23
 COc1ccc2C(=CC(=O)Nc2c1OCCCCN3CCC(F)(F)CC3)Nc4c(C)cncc4F
 COCCOCCOCCOCCCCOc1c2NC(=O)C=C(Nc3c(C)cncc3F)e2ccc10CF
 25 COCCOCCOCCOCCCCOc1c(OC(F)(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C)cncc3F
 Cc1cnec(F)c1NC2=CC(=O)Nc3c(OCCCCN4CCC(F)F)CC4)c(OC(F)F)ccc23
 Cc1cncc(F)c1NC2=CC(=O)Nc3c(OCCCCN4ccn4)c(OC(F)(F)F)ccc23
 COc1ccc2C(=CC(=O)Nc2c1OCCCCOCCO)Nc3c(C)cncc3F
 30 CNCCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C)cncc3F
 CCN(CC)CCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C)cncc3F
 35 COc1ccc2C(=CC(=O)Nc2c1OCCCCCOCCO)Nc3c(C)cncc3F
 CNCCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C)cncc3F
 Cc1cnec(F)c1NC2=CC(=O)Nc3c(OCC(=O)OCC[N+](C)C)C(=O)O)Nc3c(C)cncc3F
 40 Cc1cnec(F)c1NC2=CC(=O)Nc3c(OCC(=O)OCC[N+](C)C)C(=O)O)Nc3c(C)cncc3F
 COCCOCCOCCCCCOc1c(OC)ccc2C(=CC(=O)Nc12)Nc3c(C)cncc3F
 Cc1cnec(F)c1NC2=CC(=O)Nc3c(OCC(=O)OCC[N+](C)C)C(=O)O)Nc3c(C)cncc3F
 45 CN1CCN(CC1)C(=O)COc2c(OC(F)F)ccc3C(=CC(=O)Nc23)Nc4c(C)cncc4F
 COc1ccc2C(=CC(=O)Nc2c1OCC(=O)N[C@@H](C(C)C(=O)O)Nc3c(C)cncc3F
 Cc1cnec(F)c1NC2=CC(=O)Nc3c(OCC(=O)N[C@@H](C(C)C(=O)O)Nc3c(C)cncc3F
 50 CN1CCN(CC1)C(=O)COc2c(OC(F)F)ccc3C(=CC(=O)Nc23)Nc4c(C)cncc4F
 Cc1cnec(F)c1NC2=CC(=O)Nc3c(OCC(=O)N[C@@H](C(C)C(=O)O)Nc3c(C)cncc3F
 CN1CCN(CC1)C(=O)COc2c(OC(F)F)ccc3C(=CC(=O)Nc23)Nc4c(C)cncc4F
 55 CN1CCN(CC1)C(=O)COc2c(OC(F)F)ccc3C(=CC(=O)Nc23)Nc4c(C)cncc4F
 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)N[C@@H](O)[C@H](NC(=O)COc2c(OC(F)F)ccc3C(=O)Nc12)Nc3c(C)cncc3F
 60 CN(C)CCN(C)C(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C)cncc3F
 CN(CC[N+](C)(C)C(=O)CCCCOc1c(OC(F)(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C)cncc3F
 CN1CCN(CC1)C(=O)COc2c(OC(F)F)ccc3C(=CC(=O)Nc23)Nc4c(C)cncc4F
 65 CSCC[C@H](NC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C)cncc3F)C(=O)O

$\text{Coc1ccc2C(=CC(=O)Nc2c1OCCCCC(=O)N[C@@H](CCC(=O)N)C(=O)O)Nc3c(C)cncc3F}$
 $\text{CN(C)CCN(C)C(=O)CCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C)cncc3F}$
 $\text{Cc1cenc(F)c1NC2=CC(=O)Nc3c(OCCCCCC(=O)N[C@@H](CO)C(=O)O)c(OCF)ccc23}$
 $\text{Cc1cenc(F)c1NC2=CC(=O)Nc3c(OCCCCCC(=O)N[C@@H](CO)C(=O)O)c(OC(F)F)ccc23}$
 $\text{Coc1ccc2C(=CC(=O)Nc2c1OCCCCC(=O)N[C@@H](CCCCN)C(=O)O)Nc3c(C)cncc3F}$
 $\text{Cc1cenc(C1)c1NC2=CC(=O)Nc3c(OCCCCN4CCOCC4)c(OC(F)F)ccc23}$
 $\text{Cc1cenc(C1)c1NC2=CC(=O)Nc3c(OCCCCN4CCC(F)CC4)c(OC(F)F)ccc23}$
 $\text{Coc1ccc2C(=CC(=O)Nc2c1OCCCCN3CCC(F)(F)C3)Nc4c(C)cncc4C1}$
 $\text{Cc1cenc(C1)c1NC2=CC(=O)Nc3c(OCCCCOc4cccne4)c(OC(F)F)ccc23}$
 $\text{CCN(CC)CCCCCOc1c(OC(F)F)F)ccc2C(=CC(=O)Nc12)Nc3c(C)cncc3C1}$
 $\text{Cc1cenc(C1)c1NC2=CC(=O)Nc3c(OCCCCCCn4ccnc4)c(OC(F)F)ccc23}$
 $\text{Coc1ccc2C(=CC(=O)Nc2c1OCCCCCn3ccnn3)Nc4c(C)cncc4C1}$
 $\text{Cc1cenc(C1)c1NC2=CC(=O)Nc3c(OCCCCCOc4ccncc4)c(OC(F)F)ccc23}$
 $\text{CNCCCCCOc1c(OC)ccc2C(=CC(=O)Nc12)Nc3c(C)cncc3C1}$
 $\text{Cc1cenc(C1)c1NC2=CC(=O)Nc3c(OCCCCCN4CCCC(F)F)C4)c(OC(F)F)ccc23}$
 $\text{Cc1cenc(C1)c1NC2=CC(=O)Nc3c(OCCCCCCOc4ccncc4)c(OC(F)F)ccc23}$
 $\text{Cc1cenc(C1)c1NC2=CC(=O)Nc3c(OCCCCCOCCO)c(OC(F)F)ccc23}$
 $\text{Coc1ccc2C(=CC(=O)Nc2c1OCC(=O)OCCN(C)C)Nc3c(C)cncc3C1}$
 $\text{Cc1cenc(C1)c1NC2=CC(=O)Nc3c(OCC(=O)OCC[N+](C)(C)C)c(OC(F)F)ccc23}$
 $\text{Cc1cenc(C1)c1NC2=CC(=O)Nc3c(OCC(=O)OCC[N+](C)(C)C)c(OC(F)F)ccc23}$
 $\text{C[C@@H](O)[C@H](NC(=O)COc1c(OCF)ccc2C(=CC(=O)Nc12)Nc3c(C)cncc3C1)C(=O)O}$
 $\text{CN(C)CCN(C)C(=O)CCCCOc1c(OC(F)F)F)ccc2C(=CC(=O)Nc12)Nc3c(C)cncc3C1}$
 $\text{CN(CCC[N+](C)(C)C)C(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C)cncc3C1}$
 $\text{Coc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)N[C@@H](C(C)C)C(=O)O)Nc3c(C)cncc3C1}$
 $\text{Cc1cenc(C1)c1NC2=CC(=O)Nc3c(OCCCC(=O)N[C@@H](CCC(=O)N)C(=O)O)c(OCF)ccc23}$
 $\text{CN(C)CCNC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C)cncc3C1}$
 $\text{Coc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)NCC[N+](C)(C)C)Nc3c(C)cncc3C1}$
 $\text{Cc1cenc(C1)c1NC2=CC(=O)Nc3c(OCCCC(=O)N[C@@H](CCCNC(=N)N)C(=O)O)c(OCF)ccc23}$
 $\text{Cc1cenc(C1)c1NC2=CC(=O)Nc3c(OCCCCC(=O)N[C@@H](CC(=O)O)C(=O)O)c(OC(F)F)ccc23}$
 $\text{CN(C)CCOC(=O)CCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(C)cncc3C1}$
 $\text{Cc1cenc(C1)c1NC2=CC(=O)Nc3c(OCCCCCC(=O)NCC[N+](C)(C)C)Nc3c(C)cncc3C1}$
 $\text{C[C@H](NC(=O)CCCCOc1c(OC(F)F)F)ccc2C(=CC(=O)Nc12)Nc3c(C)cncc3C1)C(=O)O}$
 $\text{Cc1cenc(C1)c1NC2=CC(=O)Nc3c(OCCCCCC(=O)N[C@@H](C(C)C)Nc3c(C)cncc3C1)C(=O)O}$

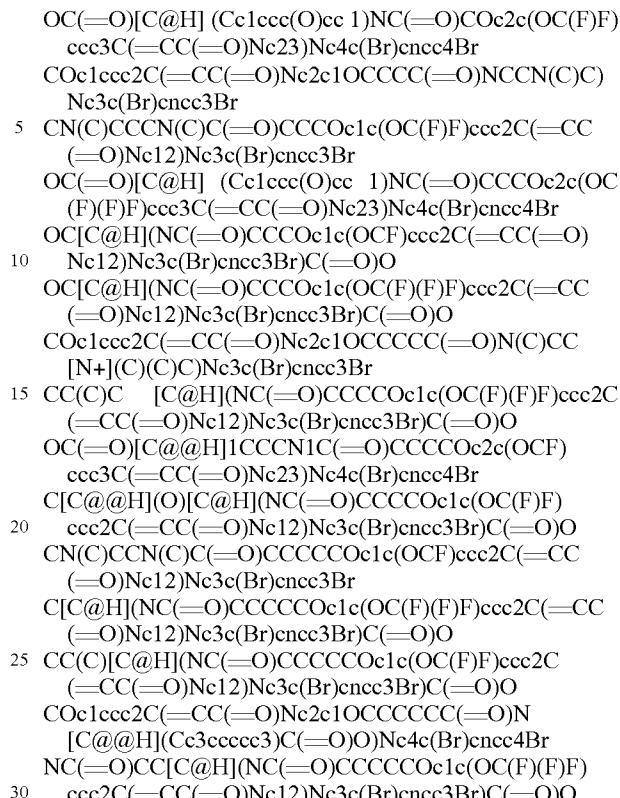
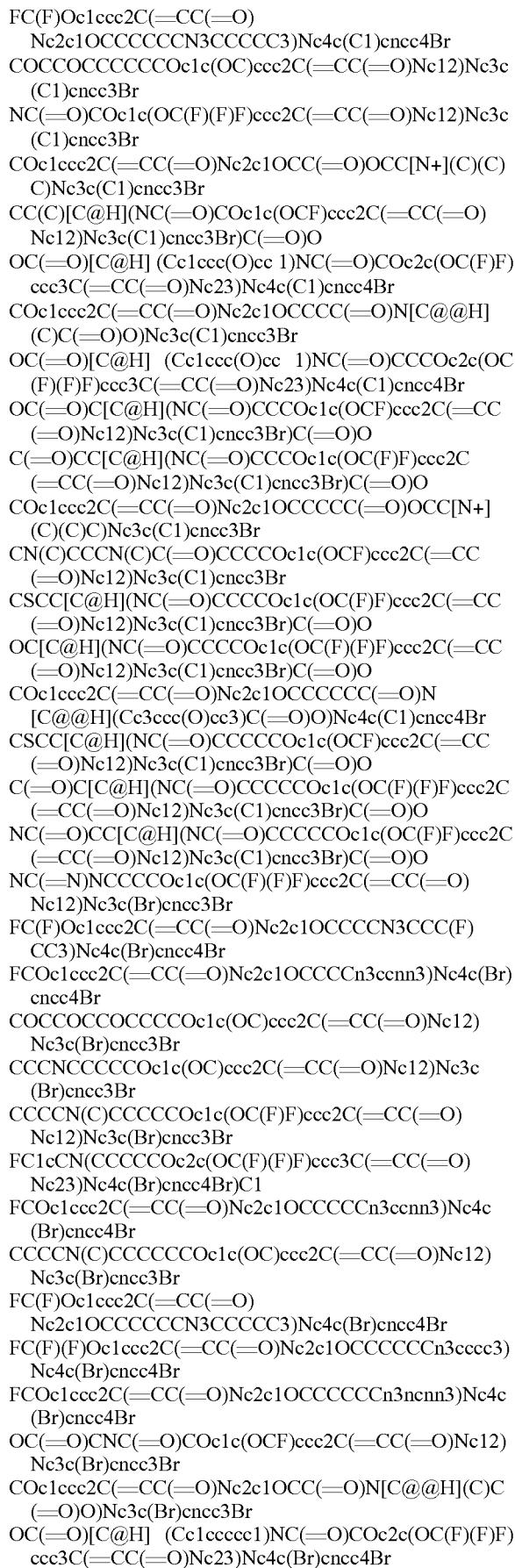
COc1ccc2C(=CC(=O)Nc2c1OCCCCC(=O)N
 [C@H](Cc3cnc[nH]3)C(=O)O)Nc4c(C)cncc4C1
 Cc1nc(C1)c1NC2=CC(=O)Nc3c(OCCCCC(=O)N
 [C@H](Cc4cnc[nH]4)C(=O)O)e(OC(F)F)ccc23
 5 Cc1nc(CBr)c1NC2=CC(=O)Nc3c(OCCCN4CCCC(F)
 C4)c(OC(F)(F)F)ccc23
 Cc1nc(CBr)c1NC2=CC(=O)Nc3c(OCCCN4CCCC(F)
 (F)C4)c(OC(F)F)ccc23
 10 Cc1nc(CBr)c1NC2=CC(=O)Nc3c(OCCCN4CCC(F)
 C4)c(OC(F)ccc23
 Cc1nc(CBr)c1NC2=CC(=O)Nc3c(OCCCOc4ccncc4)c
 (OCF)ccc23
 COc1ccc2C(=CC(=O)Nc2c1OCCCCOCCO)Nc3c(C)
 cncc3Br
 15 CN(C)CCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)
 Nc3c(C)cncc3Br
 CCN(CC)CCCCCOc1c(OCF)ccc2C(=CC(=O)Nc12)
 Nc3c(C)cncc3Br
 20 CCCCCN(C)CCCCCOc1c(OC)ccc2C(=CC(=O)Nc12)
 Nc3c(C)cncc3Br
 Cc1nc(CBr)c1NC2=CC(=O)Nc3c
 (OCCCCN4CCOCC4)c(OC(F)(F)F)ccc23
 COCCOCCOCCOCCCCCOc1c(OC(F)F)ccc2C(=CC
 25 (=O)Nc12)Nc3c(C)cncc3Br
 Cc1nc(CBr)c1NC2=CC(=O)Nc3c(OCCCCN4CCC(F)
 CC4)c(OCF)ccc23
 Cc1nc(CBr)c1NC2=CC(=O)Nc3c(OCCCCN4CCCC
 (F)F)C4)c(OC(F)F)ccc23
 30 COc1ccc2C(=CC(=O)Nc2c1OCCCCCn3ccnn3)Nc4c
 (C)cncc4Br
 Cc1nc(CBr)c1NC2=CC(=O)Nc3c
 (OCCCCCOc4ccncc4)c(OC(F)F)ccc23
 COCCOCCOCCCCCOc1c(OC(F)F)F)ccc2C(=CC
 35 (=O)Nc12)Nc3c(C)cncc3Br
 CN(C)CCOC(=O)Oc1c(OCF)ccc2C(=CC(=O)Nc12)
 Nc3c(C)cncc3Br
 COc1ccc2C(=CC(=O)Nc2c1OCC(=O)N(C)CC[N+](C)
 (C)Nc3c(C)cncc3Br
 40 Cc1nc(CBr)c1NC2=CC(=O)Nc3c(OCC(=O)N[C@H]
 (Cc4c[nH]c5cccc45)C(=O)O)e(OC(F)(F)F)ccc23
 Cc1nc(CBr)c1NC2=CC(=O)Nc3c(OCC(=O)N[C@H]
 (CC(=O)O)C(=O)O)c(OC(F)F)ccc23
 CC[C@H](C)[C@H](NC(=O)CCCOc1c(OC(F)F)ccc2C
 45 (=CC(=O)Nc12)Nc3c(C)cncc3Br)C(=O)O
 CC[C@H](C)[C@H](NC(=O)CCCOc1c(OC(F)(F)F)
 ccc2C(=CC(=O)Nc12)Nc3c(C)encc3Br)C(=O)O
 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)N3CCC
 [C@H]3C(=O)O)Nc4c(C)cncc4Br
 50 Cc1nc(CBr)c1NC2=CC(=O)Nc3c(OCCCC(=O)N
 [C@H](CCCNC(=N)N)C(=O)O)e(OCF)ccc23
 CC(C)[C@H](NC(=O)CCCOc1c(OCF)F)ccc2C(=CC
 (=O)Nc12)Nc3c(C)cncc3Br)C(=O)O
 C[C@H](O)[C@H](NC(=O)CCCOc1c(OC(F)F)
 55 ccc2C(=CC(=O)Nc12)Nc3c(C)cncc3Br)C(=O)O
 C[C@H](O)[C@H](NC(=O)CCCOc1c(OC(F)(F)F)
 ccc2C(=CC(=O)Nc12)Nc3c(C)encc3Br)C(=O)O
 COc1ccc2C(=CC(=O)Nc2c1OCCCCC(=O)N[C@H]
 (Cc3cnc[nH]3)C(=O)O)Nc4c(C)cncc4Br
 60 CN(C)CCNC(=O)CCCCOc1c(OC(F)(F)F)ccc2C(=CC
 (=O)Nc12)Nc3c(C)cncc3Br
 CN(CCC[N+](C)(C)C(=O)CCCCOc1c(OC(F)F)
 ccc2C(=CC(=O)Nc12)Nc3c(C)encc3Br
 Cc1nc(CBr)c1NC2=CC(=O)Nc3c(OCCCCC(=O)
 65 N4CCNCC4)c(OCF)ccc23
 COc1ccc2C(=CC(=O)Nc2c1OCCCCC(=O)N3CCC
 [C@H]3C(=O)O)Nc4c(C)cncc4Br

FCOc1ccc2C(=CC(=O)Nc2c1OCCCCN3CCCCC3)Nc4c(F)cnc4F
 FC(F)Oc1ccc2C(=CC(=O)Nc2c1OCCCCN3CCCC(F)C3)Nc4c(F)cnc4F
 FC1cCN(CCCCCOc2c(OC(F)F)F)ccc3C(=CC(=O)Nc23)Nc4c(F)cnc4F
 COc1ccc2C(=CC(=O)Nc2c1OCCCCn3nccn3)Nc4c(F)cnc4F
 CCCNCCCCOc1c(OC(F)F)F)ccc2C(=CC(=O)Nc12)Nc3e(F)cnc3F
 CCN(C)CCCCCOc1c(OC(F)F)F)ccc2C(=CC(=O)Nc12)Nc3e(F)cnc3F
 COCCN(C)CCCCCOc1c(OC)ccc2C(=CC(=O)Nc12)Nc3e(F)cnc3F
 FCOc1ccc2C(=CC(=O)Nc2c1OCCCCn3nccn3)Nc4c(F)cnc4F
 COCCN(C)CCCCCOc1c(OC)ccc2C(=CC(=O)Nc12)Nc3e(F)cnc3F
 FCOc1ccc2C(=CC(=O)Nc2c1OCCCCCN3CCC(F)CC3)Nc4c(F)cnc4F
 Fc1cnc(F)c1NC2=CC(=O)Nc3c(OCCCCCn4ncnn4)c(OC(F)F)ccc23
 FC(F)Oc1ccc2C(=CC(=O)Nc2c1OCCCCCOc3ccccn3)Nc4c(F)cnc4F
 COCCOCCCCCOc1c(OC)ccc2C(=CC(=O)Nc12)Nc3e(F)cnc3F
 C[N+]C(C)CCNC(=O)COc1c(OC)ccc2C(=CC(=O)Nc12)Nc3c(F)cnc3F
 COc1ccc2C(=CC(=O)Nc2c1OCC(=O)N(C)CCC[N+](C)(C)C)Nc3c(F)cnc3F
 CC(C)C[C@H](NC(=O)COc1c(OC(F)F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cnc3F
 C(=O)[C@H](C)C1c[nH]c2cccc12)NC(=O)COc3c(OC(F)ccc4C(=CC(=O)Nc34)Nc5c(F)cnc5F
 OC(=O)[C@H](Cc1cnc[nH]1)NC(=O)COc2c(OC(F)F)ccc3C(=CC(=O)Nc23)Nc4c(F)cnc4F
 NC(=O)CC[C@H](NC(=O)COc1c(OC(F)F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cnc3F
 CC(C)C[C@H](NC(=O)CCCCOc1c(OC(F)F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cnc3F
 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)N3CCC
 [C@H]3C(=O)O)Nc4c(F)cnc4FOC(=O)[C@H](Cc1[nH]c2cccc12)NC(=O)CCCOc3c(OC(F)ccc4C(=CC(=O)Nc34)Nc5c(F)cnc5F
 OC(=O)[C@H](Cc1cnc[nH]1)NC(=O)CCCOc2c(OC(F)F)ccc3C(=CC(=O)Nc23)Nc4c(F)cnc4F
 NC(=O)CC[C@H](NC(=O)CCCOc1c(OC)ccc2C(=CC(=O)Nc12)Nc3c(F)cnc3F
 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)NCCN(C)C)Nc3c(F)cnc3F
 CC[C@H](C)C[C@H](NC(=O)CCCOc1c(OC(F)F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cnc3F
 CSCC[C@H](NC(=O)CCCOc1c(OC)ccc2C(=CC(=O)Nc12)Nc3c(F)cnc3F
 CSCC[C@H](NC(=O)CCCOc1c(OC(F)F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cnc3F
 NC(=O)CCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cnc3F
 CN(C)CCN(C)C(=O)CCCCCOc1c(OC)ccc2C(=CC(=O)Nc12)Nc3c(F)cnc3F
 NCCCC[C@H](NC(=O)CCCCCOc1c(OC(F)F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cnc3F
 CCCN(C)CCCOc1c(OC)ccc2C(=CC(=O)Nc12)Nc3c(F)cnc3F
 NCCCC[C@H](NC(=O)CCCCCOc1c(OC(F)F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cnc3F
 CCCN(C)CCCOc1c(OC)ccc2C(=CC(=O)Nc12)Nc3c(F)cnc3F

CCCCCN(C)CCCCOc1c(OC)ccc2C(=CC(=O)Nc12)Nc3c(F)cnc3C1
 FC(F)Oc1ccc2C(=CC(=O)Nc2c1OCCCCn3nccn3)Nc4c(F)cnc4C1
 5 COCCOCCCCOc1c(OC)ccc2C(=CC(=O)Nc12)Nc3c(F)cnc3C1
 OCCOCCOCCCCOc1c(OC(F)F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cnc3C1
 COc1ccc2C(=CC(=O)Nc2c1OCCCCN(C)C)Nc3c(F)cnc3C1
 10 CN(C)CCCCCOc1c(OC(F)F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cnc3C1
 CCN(C)CCCCCOc1c(OC)ccc2C(=CC(=O)Nc12)Nc3c(F)cnc3C1
 15 CCN(C)CCCCCOc1c(OC(F)F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cnc3C1
 NC(=N)NCCCCCOc1c(OC(F)F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cnc3C1
 COc1ccc2C(=CC(=O)Nc2c1OCCCCCn3cccc3)Nc4c(F)cnc4C1
 20 Fc1cnc(C1)c1NC2=CC(=O)Nc3c(OCCCCCOc4cccc4)c(OC(F)F)F)ccc23
 COCCOCCCCCOc1c(OC)ccc2C(=CC(=O)Nc12)Nc3c(F)cnc3C1
 25 C[C@H](NC(=O)COc1c(OC)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cnc3C1
 COc1ccc2C(=CC(=O)Nc2c1OCC(=O)N[C@@H](CC(C)C(=O)O)Nc3c(F)cnc3C1
 NCCCC[C@H](NC(=O)COc1c(OC(F)F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cnc3C1
 30 NC(=N)NCCC[C@H](NC(=O)COc1c(OC(F)F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cnc3C1
 NC(=N)NCCC[C@H](NC(=O)COc1c(OC(F)F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cnc3C1
 35 CN(C)CCN(C)C(=O)CCCOc1c(OC(F)F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cnc3C1
 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)N[C@@H](CC(C)C(=O)O)Nc3c(F)cnc3C1
 OC(=O)[C@H]1CCCCN1C(=O)CCCOc2c(OC)F)ccc3C(=CC(=O)Nc23)Nc4c(F)cnc4C1
 40 NC(=O)C[C@H](NC(=O)CCCOc1c(OC(F)F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cnc3C1
 OC(=O)[C@H]1CCCCN1C(=O)CCCOc2c(OC(F)F)F)ccc3C(=CC(=O)Nc23)Nc4c(F)cnc4C1
 45 OC(=O)[C@H](Cc1cccc1)NC(=O)CCCOc2c(OC(F)F)F)ccc3C(=CC(=O)Nc23)Nc4c(F)cnc4C1
 OC(=O)[C@H](Cc1cnc[nH]1)NC(=O)CCCOc2c(OC)F)ccc3C(=CC(=O)Nc23)Nc4c(F)cnc4C1
 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)N[C@@H](CC(C)C(=O)O)Nc3c(F)cnc3C1
 50 NC(=O)CCCOc1c(OC)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cnc3C1
 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)N[C@@H](CC(C)C(=O)O)Nc3c(F)cnc3C1
 NC(=O)CCCOc1c(OC)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cnc3C1
 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)N[C@@H](CC(C)C(=O)O)Nc3c(F)cnc3C1
 55 C(=O)[C@H](Cc1cnc[nH]1)NC(=O)CCCOc2c(OC)F)ccc3C(=CC(=O)Nc23)Nc4c(F)cnc4C1
 OC(=O)C[C@H](NC(=O)CCCOc1c(OC(F)F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cnc3C1
 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)N[C@@H](CC(C)C(=O)O)Nc3c(F)cnc3C1
 60 Fc1cnc(Br)c1NC2=CC(=O)Nc3c(OCCCCN4CCCCC4)c(OC(F)F)F)ccc23
 COc1ccc2C(=CC(=O)Nc2c1OCCCCn3nccn3)Nc4c(F)cnc4Br
 COCCOCCOCCCCOc1c(OC(F)F)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cnc3Br
 65 OCCOCCOCCOCCCCOc1c(OC)F)ccc2C(=CC(=O)Nc12)Nc3c(F)cnc3Br

COc1ccc2C(=CC(=O)Nc2c1OCCCCN(C)C)Nc3c(F)
 cncc3Br
 Fc1cncc(Br)c1NC2=CC(=O)Nc3c(OCCCCN4CCCC4)c
 (OC(F)(F)F)ccc23
 FCo1ccc2C(=CC(=O)Nc2c1OCCCCN3CCC(F)(F)
 C3)Nc4c(F)cncc4Br
 FC(F)Oc1ccc2C(=CC(=O)Nc2c1OCCCCOc3cncc3)
 Nc4c(F)cncc4Br
 OCCOCCOCCCCOc1c(OCF)ccc2C(=CC(=O)Nc12)
 Nc3e(F)cncc3Br
 NCCCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c
 (F)cncc3Br
 COc1ccc2C(=CC(=O)Nc2c1OCCCCNC(=N)N)
 Nc3e(F)cncc3Br
 Fc1encc(Br)c1NC2=CC(=O)Nc3c
 (OCCCCN4CCCC4)c(OC(F)(F)F)ccc23
 FCo1ccc2C(=CC(=O)Nc2c1OCCCCOc3cncc3)
 Nc4c(F)cncc4Br
 COc1ccc2C(=CC(=O)Nc2c1OCC(=O)NCC[N+](C)(C)
 C)Nc3c(F)cncc3Br
 CC(C)C [C@H](NC(=O)COc1c(OCF)ccc2C(=CC(=O)
 Nc12)Nc3c(F)cncc3Br)C(=O)O
 CC[C@H](C)[C@H](NC(=O)COc1c(OC(F)(F)F)ccc2C
 (=CC(=O)Nc12)Nc3c(F)cncc3Br)C(=O)O
 OC(=O)[C@H](Cc1cccc1)NC(=O)COc2c(OC(F)F)
 ccc3C(=CC(=O)Nc23)Nc4c(F)cncc4Br
 NCCCC[C@H](NC(=O)COc1c(OCF)ccc2C(=CC(=O)
 Nc12)Nc3c(F)cncc3Br)C(=O)O
 CN(CC[N+](C)(C)C)C(=O)CCCCOc1c(OCF)ccc2C(=CC
 (=O)Nc12)Nc3c(F)cncc3Br
 CC(C)[C@H](NC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC
 (=O)Nc12)Nc3c(F)cncc3Br)C(=O)O
 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)N[C@H](
 CCCNC(=N)N)C(=O)O)Nc3c(F)cncc3Br
 NC(=O)C[C@H](NC(=O)CCCCOc1c(OC(F)(F)F)ccc2C
 (=CC(=O)Nc12)Nc3c(F)cncc3Br)C(=O)O
 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)N(C)CCC
 [N+](C)(C)C)Nc3c(F)cncc3Br
 C[C@H](NC(=O)CCCCOc1c(OCF)ccc2C(=CC(=O)
 Nc12)Nc3c(F)cncc3Br)C(=O)O
 C[C@H](NC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)
 Nc12)Nc3c(F)cncc3Br)C(=O)O
 CC(C)C[C@H](NC(=O)CCCCOc1c(OC(F)(F)F)ccc2C
 (=CC(=O)Nc12)Nc3c(F)cncc3Br)C(=O)O
 C[N+](C)(C)CCOC(=O)CCCCOc1c(OCF)ccc2C(=CC
 (=O)Nc12)Nc3c(F)cncc3Br
 CN(C)CCNC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC
 (=O)Nc12)Nc3c(F)cncc3Br
 COc1ccc2C(=CC(=O)Nc2c1OCCCCC(=O)NCC[N+]
 (C)(C)C)Nc3c(F)cncc3Br
 C[N+](C)(C)CCNC(=O)CCCCOc1c(OC(F)(F)F)ccc2C
 (=CC(=O)Nc12)Nc3c(F)cncc3Br
 CN(C)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)Nc3c
 (C1)cncc3C1
 COc1ccc2C(=CC(=O)Nc2c1OCCCCOCCO)Nc3c(C1)
 cncc3C1
 OCCOCCCCOc1c(OCF)ccc2C(=CC(=O)Nc12)Nc3c
 (C1)cncc3C1
 OCCOCCCCOc1c(OC(F)(F)F)ccc2C(=CC(=O)Nc12)
 Nc3c(C1)cncc3C1
 COc1ccc2C(=CC(=O)Nc2c1OCCCCN)Nc3c(C1)
 cncc3C1
 FC(F)(F)Oc1ccc2C(=CC(=O)Nc2c1OCCCCN3CCCC
 (F)(F)C3)Nc4c(C1)cncc4C1
 FC(F)Oc1ccc2C(=CC(=O)Nc2c1OCCCCN3CCC(F)
 C3)Nc4c(C1)cncc4C1

FCo1ccc2C(=CC(=O)Nc2c1OCCCCN3nccn3)Nc4c
 (C1)cncc4C1
 COc1ccc2C(=CC(=O)Nc2c1OCCCCN3cnne3)Nc4c
 (C1)cncc4C1
 5 FC1cCN(CCCCCOc2c(OC(F)(F)F)ccc3C(=CC(=O)
 Nc23)Nc4c(C1)cncc4C1)C1
 FC(F)Oc1ccc2C(=CC(=O)Nc2c1OCCCCN3CCC(F)
 (F)C3)Nc4c(C1)cncc4C1
 OCCOCCCCOc1c(OCF)ccc2C(=CC(=O)Nc12)
 10 Nc3c(C1)cncc3C1
 COc1ccc2C(=CC(=O)
 Nc2c1OCCCCCOCCOCCOCCO)Nc3c(C1)cncc3C1
 CN(C)CCOC(=O)COc1c(OC(F)(F)F)ccc2C(=CC(=O)
 Nc12)Nc3c(C1)cncc3C1
 15 C[N+](C)(C)CCNC(=O)COc1c(OC(F)F)ccc2C(=CC
 (=O)Nc12)Nc3c(C1)cncc3C1
 FCo1ccc2C(=CC(=O)Nc2c1OCC(=O)N3CCNCC3)
 Nc4c(C1)cncc4C1
 20 COc1ccc2C(=CC(=O)Nc2c1OCC(=O)N[C@H](Cc3c
 [nH]c4cccc34)C(=O)O)Nc5c(C1)encc5C1
 OC(=O)[C@H](Cc1c[nH]c2cccc12)NC(=O)COc3c(OC
 (F)F)ccc4C(=CC(=O)Nc34)Nc5c(C1)encc5C1
 C(=O)[C@H](Cc1c[nH]c2cccc12)NC(=O)CCCOc3c
 25 (OCF)ccc4C(=CC(=O)Nc34)Nc5c(C1)encc5C1
 OC[C@H](NC(=O)CCCOc1c(OC(F)(F)F)ccc2C(=CC
 (=O)Nc12)Nc3c(C1)cncc3C1)C(=O)O
 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)N[C@H]
 ([C@H](C)O)C(=O)O)Nc3c(C1)cncc3C1
 30 OC(=O)C[C@H](NC(=O)CCCOc1c(OC(F)F)ccc2C
 (=CC(=O)Nc12)Nc3c(C1)encc3C1)C(=O)O
 OC(=O)CNC(=O)CCCCOc1c(OC(F)(F)F)ccc2C(=CC
 (=O)Nc12)Nc3c(C1)cncc3C1
 NCCCC[C@H](NC(=O)CCCOc1c(OCF)ccc2C(=CC
 (=O)Nc12)Nc3c(C1)cncc3C1)C(=O)O
 35 C(=O)CC[C@H](NC(=O)CCCOc1c(OC(F)F)ccc2C
 (=CC(=O)Nc12)Nc3c(C1)cncc3C1)C(=O)O
 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)N[C@H]
 (CCC(=O)N)C(=O)O)Nc3c(C1)cncc3C1
 40 NC(=O)CCCCOc1c(OCF)ccc2C(=CC(=O)Nc12)Nc3c
 (C1)cncc3C1
 COc1ccc2C(=CC(=O)Nc2c1OCCCC(=O)OCCN(C)
 C)Nc3c(C1)cncc3C1
 C[C@H](O)[C@H](NC(=O)CCCCOc1c(OC(F)F)
 45 ccc2C(=CC(=O)Nc12)Nc3c(C1)cncc3C1)C(=O)O
 NC(=O)C[C@H](NC(=O)CCCCOc1c(OC(F)(F)F)
 ccc2C(=CC(=O)Nc12)Nc3c(C1)cncc3C1)C(=O)O
 CCCCC(C)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Nc12)
 Nc3c(C1)cncc3Br
 50 FC1cCN(CCCCOc2c(OC(F)(F)F)ccc3C(=CC(=O)Nc23)
 Nc4c(C1)cncc4Br)C1
 COc1ccc2C(=CC(=O)Nc2c1OCCCCN3cccc3)Nc4c(C1)
 cncc4Br
 FCo1ccc2C(=CC(=O)Nc2c1OCCCCN3ccnc3)Nc4c
 (C1)cncc4Br
 55 FC1cCN(CCCCOc2c(OC(F)(F)F)ccc3C(=CC(=O)
 Nc23)Nc4c(C1)cncc4Br)C1
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 (C1)cncc4Br
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 (C1)cncc4Br
 COCCOCCOCCCCOc1c(OC(F)(F)F)ccc2C(=CC(=O)
 Nc12)Nc3c(C1)cncc3Br
 NCCCCCOc1c(OCF)ccc2C(=CC(=O)Nc12)Nc3c(C1)
 65 cncc3Br
 COCCN(C)CCCCCOc1c(OC(F)(F)F)ccc2C(=CC(=O)
 Nc12)Nc3c(C1)cncc3Br



35 Novel PDE/AK Biological Activity Assay Protocol

Phosphodiesterases regulate the activity of the second messenger cyclic adenosine monophosphate (cAMP) by hydrolyzing cAMP to adenosine monophosphate (AMP). We developed a novel coupled PDE/AK bioluminescent high-throughput assay to measure the activity of phosphodiesterases. In the PDE/AK assay, the AMP produced from the hydrolysis of cAMP by phosphodiesterase is converted to adenine diphosphate (ADP) by the phosphotransferase activity of adenylate kinase (also known as ADK or myokinase). Adenylate kinase will catalyze the conversion of 1 mole of AMP and 1 mole of ATP into 2 moles of ADP. Thus the conversion of AMP to ADP will result in the subsequent loss of ATP. The decrease in ATP concentration can be monitored as light output using luciferase in a reaction that requires ATP to produce light. The PDE/AK assay uses luciferase, which catalyzes the production of light from ATP present in the reaction mix. The amount of emitted light is inversely proportional to the level of AMP present in the reaction. Test compounds are incubated with the phosphodiesterases and phosphodiesterase inhibitors will decrease the rate of cAMP hydrolysis and decrease the subsequent production of AMP. Thus phosphodiesterase inhibitors will decrease the conversion of ATP to ADP and result in the greatest emission of light.

Compounds may be screened for functional potency in *in vitro* biochemical assays for their ability to inhibit the activity of phosphodiesterase (PDE) enzymes. A novel coupled PDE/AK assay was utilized to measure the inhibitory activity of compounds on PDE isoforms. The catalytic domain of PDE4B was fused to an amino-terminus hex-histidine affinity tag and purified. PDE4B enzyme was incubated with com-

pounds for 10 minutes. Cyclic AMP substrate, ATP and adenylate kinase were then added to the PDE enzyme mix and incubated for 45 minutes at room temperature. A commercial ATP detection assay, Perkin Elmer's easyLite ATP detection reagent, was then added to measure the relative amount of ATP present in the reaction. After minute incubation, the luminescent signal was quantitated with either the Perkin Elmer Viewlux or Molecular Devices Acquest or Analyst. Roflumilast and Rolipram are the positive controls used in the assay.

The PDE/AK assay can be performed with any cAMP dependent phosphodiesterase, and can be performed in 96-, 384-, or 1536-well plates. Unlike other phosphodiesterase activity assays, the PDE/AK assay does not require radioactive substrates, modified substrates, beads, or antibodies, which each have disadvantages. Specifically, the use of radioactive substrates in a phosphodiesterase activity assay requires special protocols for handling and waste disposal, and reduced throughput. Modified substrates add the additional complexity of potentially altering the binding to the phosphodiesterase catalytic site. Fluorescently modified substrates may cause fluorescence artifacts that may interfere in the interpretation of assay results. The use of beads that selectively bind to either the cAMP or AMP may cause an additional complexity in reagent handling. The use of antibodies that selectively bind to either cAMP or AMP can be extremely costly with a relatively small signal to noise ratio. Therefore, the novel PDE/AK assay represents a simple, cost-effective alternative to known methods.

Additionally, the PDE/AK assay's mechanism offers advantages which make it useful for comparison to other phosphodiesterase activity assays. In conventional assays in which cAMP concentration is inversely proportional to the output of bioluminescence (such as Cambrex Biosciences's PDELight), phosphodiesterase catalyzes the hydrolysis of cAMP to AMP that is subsequently converted to ATP, consumed by a luciferase enzyme, and results in an increased bioluminescent output. A phosphodiesterase inhibitor prevents the hydrolysis of cAMP to AMP and consequently results in a decreased bioluminescent output. However, compounds which exhibit luciferase inhibition activity would score as a false positive for PDE inhibition in the conventional assay. In contrast, the novel PDK/AK assay would not score luciferase inhibitors as false positive for PDE inhibition because inhibition of PDE activity would result in increased bioluminescence. However, compounds that are capable of inhibiting both PDE and luciferase would be false negatives. Compounds that inhibit adenylate kinase would score as false positives in the novel PDE/AK assay. Use of both types of assay, and comparison of the data from both, would yield a richer and more reliable data set.

Accordingly, contemplated herein is a method for the detection and quantitation of PDE inhibition which uses adenylate kinase coupled to an ATP-depleting assay.

In certain embodiments, said method comprises the steps of:

1. A first incubation, of PDE, or an isolated isoform thereof, with a compound to be tested;
2. Addition of ATP, cAMP, and AK substrates;
3. A second incubation of said PDE;
4. Coupling to a means for readout of ATP-depletion; and
5. Readout.

In further embodiments, said first incubation is for between about 5 and about 15 minutes; in yet further embodiments, said first incubation is for about 10 minutes.

In further embodiments, said second incubation is for longer than about 30 minutes; in yet further embodiments,

said sufficient length of time is between about 30 minutes and about one hour; in even further embodiments, sufficient length of time is about 45 minutes.

In further embodiments, said readout means is a luciferase assay. In yet further embodiments, said luciferase assay is a Perkin Elmer easyLite assay.

In further embodiments, said readout is done on a machine for detecting a luminescent signal. In yet further embodiments, said machine is selected from the group consisting of a Perkin Elmer Viewlux, a Molecular Devices Acquest, and a Molecular Devices Analyst.

Results are shown below in Table 1.

TABLE 1

Biological Activity		
Example No.	IC ₅₀	
1	+	
2	+	
3	+	
4	+	
5	+	
6	+	
7	+	
8	+	
9	+	
10	+	
11	+	
12	+	
13	+	
14	+	

+ indicates $\leq 1 \mu\text{M}$

- indicates $> 1 \mu\text{M}$

In Vivo Assay Lacrimal Gland Inflammation-Induced Dry Eye in Rabbits

A more detailed description of the assay used herein may be found in Naglehout, T J et al. 2005, "Preservation of Tear Film Integrity and Inhibition of Corneal Injury by Dexamethasone in a Rabbit Model of Lacrimal Gland Inflammation-Induced Dry Eye," *J. Ocular Pharm. Ther.*, 21:2. 139-148, the disclosure of which is hereby incorporated by reference as if written herein in its entirety.

Initiation of Dry Eye and Treatment

Rabbits (n=4/group) were randomized into treatment groups and dosed topically BID with maxidex vehicle or test drug beginning one day prior to initiation of dry eye. Each rabbit received bilateral lacrimal gland injections of saline or ConA (300 $\mu\text{g}/30 \mu\text{l}$) and topical ocular dosing was continued BID throughout the study.

Corneal Staining

Desiccation was initiated 1-2 hours following lacrimal gland injection by placing conscious rabbits in the environmental chamber (10-15% humidity/72° F.). Following 72 consecutive hours of exposure to this dry environment, the animals were anesthetized and sutures were placed in each upper and lower eyelid and lifted to form a corneal/conjunctival cup. Methylene blue dye (1 mL, 1% in dH₂O) was added to the cup for three minutes and the excess removed by washing with 200 mL BSS®. The contralateral eye was then stained using the same procedure. Rabbits were euthanized immediately following the staining procedure and the eyes were excised. The corneas were isolated with a trephine and the 9.5-mm punch of the cornea was placed in 2 mL acetone/saturated sodium sulfate (7:3, vol./vol.). Absorbance of the extracted dye was determined at 660 nm.

Tear Breakup Time (TBUT)

TBUT was quantified in a separate group of treated animals. TBUT was determined by instilling 5 μ L sodium fluorescein into the cul de sac and manually blinking the lids to distribute the fluorescein within the tear film. Under slit lamp observation, the eye was held open and the time whereby one or more black spots or streaks appeared in the precorneal tear film was recorded. The rabbits were euthanized 3 days following ConA injection.

Data reported as NT refers to the example having been not tested.

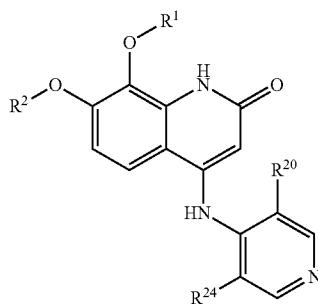
TABLE 2

Example	In Vivo Activity						
	Activity at Percent Concentration Tested						
No.	1×10^{-6}	1×10^{-5}	1×10^{-4}	1×10^{-3}	1×10^{-2}	1×10^{-1}	1
1	NT	NT	NT	NT	Inactive	Inactive	Inactive
5	Inactive	NT	Inactive	NT	Inactive	NT	NT
8	Inactive	NT	Inactive	NT	Inactive	NT	NT

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

What is claimed is:

1. A compound of structural Formula VI



or a salt thereof, wherein:

R^1 and R^2 are independently selected from the group consisting of $-(CH_2)_sG^1G^2G^3$, acyl, acylalkyl, carboxyalkyl, cyanoalkyl, alkoxy, alkoxyalkyl, amidoalkyl, amino, alkyl, alkylalkoxy, aminoalkyl, alkenyl, alkynyl, carboxyl, carboxyalkyl, ether, heteroalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aralkyl, aryl, guanidine, heteroaryl, heteroaralkyl, and hydroxyalkyl, any of which may be optionally substituted;

s is 1-8;

G^1 is selected from the group consisting of alkoxy, amino, amido, carbonyl, hydroxy, ether, an amino acid, and null;

G^2 is selected from the group consisting of alkyl, alkoxy, amino, aryl, halo, haloalkyl, heterocycloalkyl, heteroaryl, carboxylalkylamino, guanidine, an amino acid, and null, any of which may be optionally substituted;

G^3 is selected from the group consisting of alkyl, alkoxy, amino, hydroxy, ether, carboxyl, hydroxamic acid, an

amino acid, phosphonate, phosphoamide, and null, any of which may be optionally substituted; and R^{20} and R^{24} are independently selected from the group consisting of hydrogen, halogen, hydroxyl, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, amino, and carboxyl.

2. The compound as recited in claim 1, wherein R^{20} and R^{24} are independently selected from the group consisting of hydrogen, halogen, and lower alkyl.

3. The compound as recited in claim 2, wherein R^2 is lower alkyl.

4. The compound as recited in claim 3, wherein:

R^1 is selected from the group consisting of $-(CH_2)_sG^1G^2G^3$, lower alkyl, cycloalkyl, cycloalkylalkyl, and heterocycloalkyl, any of which may be optionally substituted;

s is 1-6;

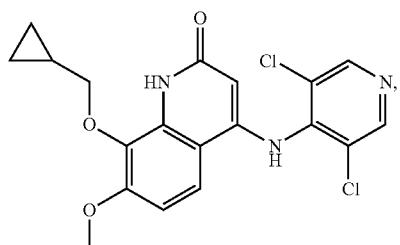
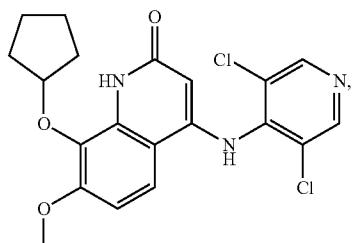
G^1 is selected from the group consisting of amino, amido, and null;

G^2 is selected from the group consisting of alkoxy, aryl, halo, heterocycloalkyl, and null, any of which may be optionally substituted; and

G^3 is selected from the group consisting of alkyl, carboxyl, and null, any of which may be optionally substituted.

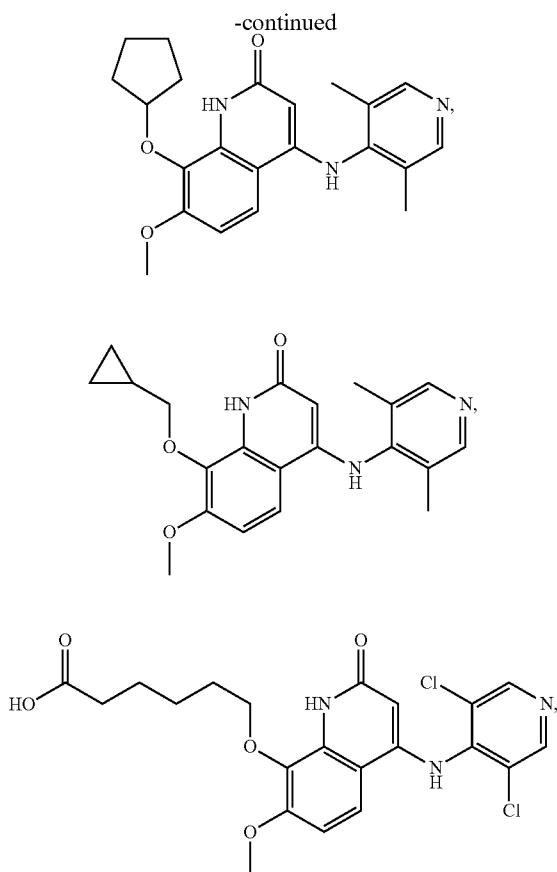
5. The compound as recited in claim 4, wherein R^2 is methyl.

6. A compound selected from the group consisting of:



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-continued

**78**

-continued

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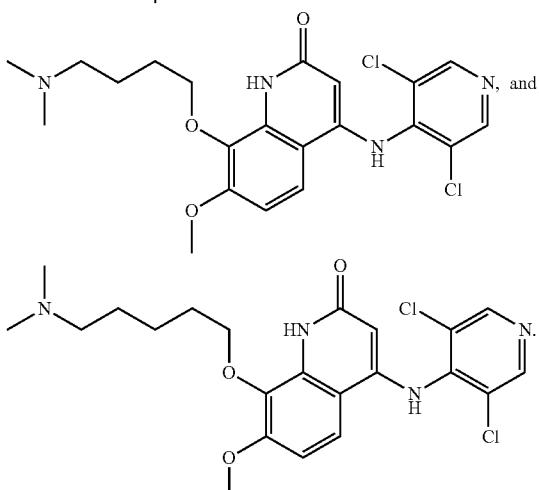
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25

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7. A pharmaceutical composition comprising as recited in claim 1, together with a pharmaceutically acceptable carrier.

* * * * *