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Robert [US/US]; 815 Bush Street, #4, San Francisco, California 94108 (US).

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(74) Agents: **KEZER, William, B.** et al.; Townsend and Townsend and Crew LLP, Two Embarcadero Center, 8th Floor, San Francisco, California 94111 (US).

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(71) Applicant (for all designated States except US): **AXYS PHARMACEUTICALS, INC.** [US/US]; 180 Kimball Way, South San Francisco, California 94080 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **HIRSCHBEIN, Bernard** [US/US]; 1629 York Street, San Francisco, California 94110 (US). **LEE, Chang Sun** [KR/US]; 3751 Norris Canyon Road, San Ramon, California 94583 (US). **LITVAK, Joane** [US/US]; 555 Jean Street, Apt. 626, Oakland, California 94610 (US). **LIU, Weili** [CN/US]; 10580 White Fir Court, Cupertino, California 95014 (US). **SENDZIK, Martin** [DE/US]; 225 42nd Avenue, San Mateo, California 94403 (US). **SHELTON, Emma, J.** [US/US]; 680 Lemon Street, Menlo Park, California 94025 (US). **SPENCER, Jeffrey, R.** [US/US]; 8 Baycrest Way, South San Francisco, California 94080 (US). **SPERANDIO, David** [CH/US]; 3804 Nathan Way, Palo Alto, California 94303 (US). **TAI, Vincent, W-F.** [CN/US]; 49 Darcy Avenue, San Mateo, California 94403 (US). **WINSLOW-LOHMAN, Julia** [US/US]; 420 First Avenue, Half Moon Bay, California 94019 (US). **YEE,**

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(54) Title: INHIBITORS OF TRYPTASE

(57) Abstract: The present invention related to certain inhibitors of tryptase that are inhibitors of tryptase, pharmaceutical composition comprising these compounds and method of treating asthma, allergic rhinitis, and/or Chronic Obstructive Pulmonary Disease utilizing these compounds.

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INHIBITORS OF TRYPTASE

BACKGROUND OF THE INVENTION

Cross Reference to Related Applications

The Applicants claim priority under 35 U.S.C. 119(e) to copending Provisional Application No. 60/651,870 filed on February 10, 2005, the disclosure of which is incorporated herein by reference in its entirety.

Field of the Invention

This invention relates to novel methods and compositions for the treatment of diseases associated with tryptase activity by administration of novel tryptase inhibitors.

State of the Art

Tryptase, the predominant protease secreted from human mast cells, is thought to be involved in neuropeptide processing and tissue inflammation. Elevated levels of tryptase have been detected in a number of diseases, including asthma, allergic conjunctivitis, allergic rhinitis, rheumatoid arthritis, multiple sclerosis, interstitial cystitis (Drugs of the Future **1996**, *21*, 811), and Chronic Obstructive Pulmonary Disease (COPD). In particular, tryptase concentrations are elevated in the bloodstream for several hours following anaphylaxis (Schwartz *et al. N. Eng. J. Med.* **1987**, *316*, 1622-1626) (Shalit, *et al. J. Allergy & Clin. Immunol.* **1990**, *86*, 117-125.), are increased in nasal and lung lavage fluid from atopic subjects following specific antigen challenge (Castells *et al. J. Allerg. Clin. Immunol.* **1988**, *141*, 563-568), and are elevated in lung lavage fluid of atopic asthmatics after endobronchial allergen challenge. Smokers often have striking elevations of bronchoalveolar lavage fluid tryptase levels, a finding that provides some support for the hypothesis that release of proteinase from activated mast cells could contribute to lung destruction in smoker's emphysema. (Celenteron *et al. Chest* **1988**, *94*, 119-123). Animal studies have shown microvascular leakage subsequent to injection of tryptase (He, *et al. Eur J. Pharmacol.* **1997**, *328*, 89-97). In addition, tryptase has been shown to be a potent mitogen for fibroblasts, suggesting that it is involved in pulmonary fibrosis and interstitial lung disease (Ross *et al.* (1991) *J. Clin. Invest.* *88*:493-499).

Asthma is becoming increasingly prevalent, especially in the pediatric population (GINA Workshop Report, Global Strategy for Asthma Management and Prevention -updated April 2002. (Scientific information and recommendations for asthma programs. NIH Publication No. 02-3659)). It is recognized as an inflammatory disorder (Hood *et al.*,

Immunology, Benjamin-Cummings, ed., 2nd ed., 1984) and frequently is characterized by progressive development of hyperresponsiveness of the trachea and bronchi to both immunospecific allergens and generalized chemical or physical stimuli. The disease involves multiple biochemical mediators in both its acute and chronic stages. The hyperresponsiveness of asthmatic bronchiolar tissue is believed to be the result of chronic inflammatory reactions, involving a variety of cells and inflammatory mediators (Busse & Lemanske (2001) *N Engl. J. Med.* 344:350-362) which irritate and damage the epithelium lining the airway wall and promote pathological thickening of the underlying tissue. Bronchial biopsies in patients with only mild asthma have features of inflammation in the airway wall.

Allergic responses to inhaled allergens can initiate the inflammatory sequence. For example, allergens can activate mast cells and basophils, which are present in the epithelium and underlying smooth muscle tissue by binding IgE located on the cell surface. Activated mast cells release a number of preformed or primary chemical mediators (e.g., histamine) of the inflammatory response and generate numerous other secondary mediators of inflammation (e.g., superoxide, lipid derived mediators, etc.) *in situ*. In addition, several large molecules (e.g., proteoglycans, tryptase, chymase, etc.) are released by degranulation of mast cells.

The release of these preformed mediators from mast cells probably accounts for the early bronchiolar constriction in the asthmatic reaction to air borne allergens. The early phase of the asthmatic reaction peaks approximately fifteen minutes after exposure to allergen and is generally followed by recovery over the ensuing one to two hours. Twenty five to thirty five percent of the patient population experience a further decline in respiratory function which maximizes six to twelve hours after exposure. This late reaction phase is accompanied by a marked increase in the number of inflammatory cells (e.g., eosinophils, neutrophils, lymphocytes, etc.) infiltrating the bronchiolar tissue. The infiltrating cells are attracted to the site by release of mast cell derived chemotactic agents and then become activated during the late reaction phase. The late asthmatic response is believed to be a secondary inflammatory reaction mediated in part by the secretory activity of granulocytes.

Tryptase is implicated in the degradation of vasodilating and bronchorelaxing neuropeptides (Caughey *et al. J.Pharmacol. Exp. Ther* **1988**, 244, 133-137; Franconi *et al. J. Pharmacol. Exp. Ther.* **1988**, 248, 947-951; and Tam *et al. Am. J. Respir. Cell Mol. Biol.* **1990**, 3, 27-32) and modulation of bronchial responsiveness to histamine (Sekizawa *et al. J. Clin. Invest.* **1989**, 83, 175-179). These findings suggest that tryptase may increase bronchoconstriction in asthma by destroying bronchodilating peptides. Tryptase activates

prostromelysin (pro-MMP-3) and procollagenase (pro-MMP-1) via MMP-3, which suggests that tryptase is involved in tissue inflammation and remodeling and joint destruction in rheumatoid arthritis. Tryptase was also shown to activate PAR-2 (Molino, *et al. J. Biol. Chem.* **1997**, 272, 4043-4049), a tethered ligand G-protein-coupled receptor that is believed to mediate some of the inflammation and hyperreactivity seen in asthma (Schmidlin, *et al J. Immunol.* **2002**, 169, 5315-5321). Further, administration of tryptase inhibitor protects against development of the late and airway hyperresponsive phases in allergen challenged sheep (Clark *et al. Am. J. Respir. Crit. Care Med.* **1995**, 152, 2076-2083) and inhibits the immediate cutaneous response to intradermal injection of allergen in allergic sheep (Molinari *et al. Amer. Physiol. Soc.* **1995**, 79(6), 1966-1970). Tryptase inhibitor was also found to reduce the acute airway response to allergen in pigs (Dahlback, *et al. Clin. & Exp. Allergy* **2002**, 32, 967-971). Most relevant are results from a clinical trial showing that a tryptase inhibitor reduced allergen-induced late asthmatic response in mild atopic asthmatics (Krishna, *et al. J. Allergy Clin. Immunol.* **2001**, 107, 1039-1045). All of the above-described findings clearly indicate the applicability of tryptase inhibitors as therapeutic agents in treating asthma and other disorders associated with inflammation of the respiratory tract.

Myocardial infarction is associated with an inflammatory response ultimately leading to healing and formation of a scar (Frangogiannis, *et. al. Cardiovasc Res* **2002**, 53, 31-47). Mast cells may regulate this healing process by releasing proteases, particularly tryptase (Somasundaram, *et al. J. of Pathol.* **2005**, 205, 102-111). Tryptase's activation of the PAR-2 receptor (*id.*), a receptor that is believed to mediate some of the inflammation seen in healing myocardial infarctions (*id.*), may be responsible for inducing inflammation and angiogenesis, perhaps partially *via* induction of angiogenic chemokines.

Tryptase has been observed to cleave gelatinase and fibronectin (*J. Cell. Biochem.* **1992**, 50, 337) which suggests that it may function in the normal regulation of extracellular matrix turnover through a direct proteolytic mechanism. Such activity is important for tissue growth and remodeling, cell migration and wound healing, and probably metastasis as well. Tryptase may also have a role in other pathological conditions where pro-matrix metalloproteinase 3 (MMP-3) is implicated because of tryptase's role in activation of MMP-3. Once activated, MMP-3 can degrade proteoglycans, fibronectin, laminin, and type IV and type IX collagen. Such conditions include cartilage degradation as well as collagen deposits in such diseases as arthritis, chronic periodontitis, rheumatoid synovium and sclerosis.

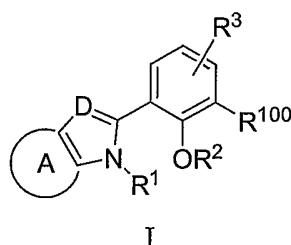
Diseases or conditions that may be mediated by tryptase activity include: metastasis of tumor cells, anaphylaxis, mastocytosis, scleroderma, urticaria, atopic dermatitis, bullous

pemphigoid, psoriasis, pulmonary fibrosis, interstitial pneumonia, nephritis, hepatic fibrosis, hepatitis, hepatic cirrhosis, Crohn's disease, ulcerative colitis, allergic rhinitis, peptic ulcers, gastric disease induced by non-steroidal inflammatory agents, cardiac infarction, disseminated intravascular coagulation, pancreatitis, multi-organ failure, interstitial lung diseases, gingivitis, periodontitis, viral infections, breast cancer, ocular allergy, bladder cancer, fibrotic lung disease, atherosclerosis, cardiomyopathic disorders, rheumatoid arthritis, and Chronic Obstructive Pulmonary Disease (COPD).

The disclosures of these and other documents referred to throughout this application are incorporated herein by reference.

SUMMARY OF THE INVENTION

In first aspect, this invention is directed to a Compound of Formula I:



where

A is optionally substituted benzo, optionally substituted pyridino, optionally substituted pyrimidino, optionally substituted pyrazino, or optionally substituted pyridazino;

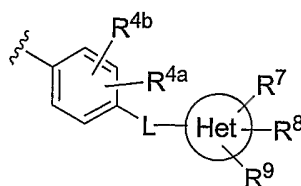
D is =N-, or =CR⁶- where R⁶ is hydrogen, alkyl, halo, alkylcarbonyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkyl, alkoxycarbonylalkyl, or carboxyalkyl;

R¹ is hydrogen, alkylsulfonyl, arylsulfonyl, alkoxycarbonyl, or aralkyloxycarbonyl;

R² is hydrogen, alkyl, alkylsulfonyl, alkylphosphonyl, or alkoxyalkyloxyalkyl;

R³ is hydrogen, alkyl, hydroxy, halo, cyano, haloalkoxy, haloalkyl, alkoxy, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylcarbonylamino, alkylcarbonyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonylamino, alkylaminosulfonyl, dialkylaminosulfonyl, carboxy, alkylcarbonyloxy, amino, alkylamino, dialkylamino, mercaptoalkylaminocarbonylalkyl, R^{10a}R^{10b}NC(O)NR^{10c}- (where R^{10a}, R^{10b}, and R^{10c} are independently hydrogen, alkyl, or substituted alkyl), R^{11a}R^{11b}NC(O)O- (where R^{11a} and R^{11b} are independently hydrogen, alkyl, or substituted alkyl), or R^{12a}OC(O)NR^{12b}- (where R^{12a} and R^{12b} are independently hydrogen, alkyl, or substituted alkyl);

and R^{100} is a group of formula (A1):



(A1)

where

R^{4a} and R^{4b} are independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, hydroxy, halo, alkoxy, acyl, acyloxy, acylamino, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonylamino, alkylaminosulfonyl, dialkylaminosulfonyl, carboxy, alkylcarbonyloxy, amino, alkylamino, dialkylamino, mercaptoalkylaminocarbonylalkyl, $-NR^{19c}C(O)NR^{19a}R^{19b}$ (where R^{19a} , R^{19b} , and R^{19c} are independently hydrogen, alkyl, or substituted alkyl), $-OC(O)NR^{24a}R^{24b}$ (where R^{24a} and R^{24b} are independently hydrogen, alkyl, or substituted alkyl), or $-NR^{25b}C(O)OR^{25a}$ (where R^{25a} and R^{25b} are independently hydrogen, alkyl, or substituted alkyl); and where alkyl, alkenyl, and alkynyl, either alone or as part of another group are independently optionally substituted with one, two, three, four, or five halo; and

L is $-X^1-Y^1-Z^1-$ where X^1 is alkylene, alkenylene, or cycloalkylene and where X^1 is optionally substituted by one or two substituents selected from the group consisting of halo, hydroxy, alkoxy, alkylamino, and dialkylamino; Y^1 is $-O-$, $-NR^{13}-$, $-C(O)-$, $-C(O)O-$, $-C(O)NR^{13}-$, $-NR^{13}C(O)-$, $-C(O)NR^{13}C(O)-$, $-S-$, $-S(O)-$, $-SO_2-$, $-SO_2NR^{13}-$, $-NR^{13}SO_2-$, $-OC(O)-$, $-OC(O)NR^{13}-$, $-NR^{13}C(O)O-$, or $-NR^{13}C(O)NR^{14}-$ (where R^{13} and R^{14} are independently hydrogen, alkyl, or substituted alkyl); and Z^1 is a bond, alkylene, alkenylene, or cycloalkylene;

L is $-X^2-$ where X^2 is alkylene, alkenylene, or cycloalkylene and is optionally substituted by one or two substituents selected from the group consisting of halo, hydroxy, alkoxy, alkylamino, and dialkylamino;

L is $-Y^2-Z^2-$ where Y^2 is $-NR^{15}-$, $-C(O)-$, $-C(O)O-$, $-C(O)NR^{15}-$, $-NR^{15}C(O)-$, $-C(O)NR^{15}C(O)-$, $-S-$, $-S(O)-$, $-SO_2-$, $-SO_2NR^{15}-$, $-NR^{15}SO_2-$, $-OC(O)-$, $-OC(O)NR^{15}-$, $-NR^{15}C(O)O-$, or $-NR^{15}C(O)NR^{16}-$ (where R^{15} and R^{16} are independently hydrogen, alkyl, or substituted alkyl); and where Z^2 is alkylene, alkenylene, or cycloalkylene; and

L is $-Y^3-$ where Y^3 is $-NR^{17}-$, $-C(O)O-$, $-C(O)NR^{17}-$, $-NR^{17}C(O)-$, $-C(O)NR^{17}C(O)-$, $-S-$, $-S(O)-$, $-SO_2-$, $-SO_2NR^{17}-$, $-NR^{17}SO_2-$, $-OC(O)-$, $-OC(O)NR^{17}-$, $-NR^{17}C(O)O-$, or

-NR¹⁷C(O)NR¹⁸- (where R¹⁷ and R¹⁸ are independently hydrogen, alkyl, or substituted alkyl);
or

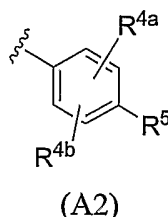
L is -X⁵-Y^{5a}-Z⁵-Y^{5b}- where X⁵ is alkylene, alkenylene, or cycloalkylene and where X⁵ is optionally substituted by one or two substituents selected from the group consisting of halo, hydroxy, alkoxy, alkylamino, and dialkylamino; Y^{5a} is -O-, -NR¹³-, -C(O)-, -C(O)O-, -C(O)NR¹³-, -NR¹³C(O)-, -C(O)NR¹³C(O)-, -S-, -S(O)-, -SO₂-, -SO₂NR¹³-, -NR¹³SO₂-, -OC(O)-, -OC(O)NR¹³-, -NR¹³C(O)O-, or -NR¹³C(O)NR¹⁴- (where R¹³ and R¹⁴ are independently hydrogen, alkyl, or substituted alkyl); Z⁵ is a bond, alkylene, alkenylene, or cycloalkylene where the alkylene or alkenylene are optionally substituted with aralkyloxyalkyl; and Y^{5b} is -C(O)-;

Het is heterocycloalkyl; and

R⁷, R⁸, and R⁹ are independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, acyl, acylamino, acyloxy, acylaminoalkyloxycarbonyl, alkylthio, alkylsulfonyl, alkoxy, alkoxycarbonyl, alkoxyalkylamino, alkoxyalkylaminocarbonyl, alkoxyalkyloxy, alkoxyalkyloxycarbonyl, amino, alkylamino, dialkylamino, aminoalkyloxy, carboxy, carboxyalkylaminocarbonyl where the "alkyl" is optionally substituted with one or two hydroxy, cyano, cyanoalkylaminocarbonyl, aryl, aryloxy, arylsulfonyl, arylthioalkylcarbonyl, aralkyl where the alkyl is optionally substituted with one or two hydroxy, aralkyloxy, aralkyloxycarbonyl, aralkyloxyaminocarbonyl, aralkyloxycarbonylamino, aralkenyl, cycloalkyl, cycloalkyloxy, cycloalkylaminocarbonyl, cycloalkylalkyl where the "alkyl" is optionally substituted with one or two hydroxy, cycloalkylalkylaminocarbonyl, cycloalkylalkyloxycarbonyl, heteroaryl, heteroarylaminocarbonyl, heteroaralkyl, heteroaralkenyl, heteroaralkyloxy, halo, hydroxy, hydroxyalkyloxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, *N*-hydroxyaminocarbonyl, *N*-alkoxyaminocarbonyl, hydroxyalkylaminocarbonyl, dialkylaminoalkyloxycarbonyl, dialkylaminoalkylaminocarbonyl, arylamino, arylaminocarbonyl, alkylsulfonylamino, alkylsulfonylaminocarbonyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkyloxy, optionally substituted heterocycloalkylaminocarbonyl, optionally substituted heterocycloalkylalkyl, optionally substituted heterocycloalkylalkyloxy, optionally substituted heterocycloalkylalkyloxycarbonyl, optionally substituted heterocycloalkylalkylaminocarbonyl, aminocarbonylamino, *N*-aryl-*N*-(alkylcarbonyl)-amino, *N*-(alkylsulfonyl)-*N*-alkyl-amino, alkoxycarbonylalkylaminocarbonyl where the "alkyl" is optionally substituted with one or two hydroxy, or trialkylsilyl; or any two of R⁷, R⁸, and R⁹

attached to the same carbon atom together with the carbon to which they are attached form indanylene or optionally substituted heterocycloalkylene; and where the alkyl, alkenyl, and alkynyl in R^7 , R^8 , and R^9 , either alone or part of another group (for example, the alkyl within the group “alkoxy” or for example, any alkyl or alkenyl within the group “optionally substituted alkenyl”), independently are optionally substituted with one, two, three, four, or five halo; or

R^{100} is a group of formula (A2):



where

R^{4a} and R^{4b} are as defined above;

R^5 is $-Y^{11}-X^{11}-Q^{11}$ where Y^{11} is $-S(O)-$, $-SO_2-$, $-NR^{26a}SO_2-$, $-SO_2NR^{26a}-$, $-C(O)NR^{26a}-$, $-NR^{26a}C(O)-$, $-OC(O)-$, $-OC(O)NR^{26a}-$, $-NR^{26a}C(O)O-$, $-C(O)NR^{26a}C(O)-$, or $-NR^{26a}C(O)NR^{26b}-$, where R^{26a} and R^{26b} are independently hydrogen, alkyl, haloalkyl, hydroxy, alkoxy, haloalkoxy, or acyl, where X^{11} is a bond, alkylene, or alkenylene, (where X^{11} is optionally substituted with hydroxy, alkoxycarbonyl, carboxy), and where Q^{11} is heteroaryl, aryl, aryloxy, or cycloalkyl;

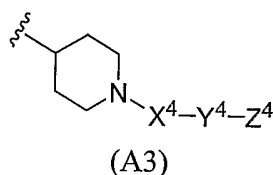
R^5 is $-X^{12a}-Y^{12}-X^{12b}-Q^{12}$ where X^{12a} is alkylene or alkenylene; Y^{12} is $-NR^{26a}-$, $-O-$, $-C(O)-$, $-C(O)O-$, $-S-$, $-S(O)-$, $-SO_2-$, $-NR^{26a}SO_2-$, $-SO_2NR^{26a}-$, $-C(O)NR^{26a}-$, $-NR^{26a}C(O)-$, $-OC(O)-$, $-OC(O)NR^{26a}-$, $-NR^{26a}C(O)O-$, $-C(O)NR^{26a}C(O)-$, or $-NR^{26a}C(O)NR^{26b}-$, where R^{26a} and R^{26b} are as defined above; X^{12b} is a bond, alkylene, or alkenylene where X^{12b} is optionally substituted with one, two, or three groups selected from hydroxy, cyano, halo, heteroaryl, alkylcarbonyl, alkoxycarbonyl, carboxy, $-NR^{27a}R^{27b}$ (where R^{27a} and R^{27b} are independently hydrogen, alkyl, alkoxy, alkoxyalkyl, heteroaryl, or heteroarylamino), $-C(O)NR^{28a}R^{28b}$ (where R^{28a} and R^{28b} are independently hydrogen, alkyl, alkenyl, alkoxy, alkenyloxy, alkoxyalkyl, hydroxy, or heteroaryl), and $-NR^{29a}C(O)OR^{29b}$ (where R^{29a} is hydrogen, alkyl, alkenyl, alkoxy, alkenyloxy, alkoxyalkyl, or hydroxy, and R^{29b} is alkyl); and Q^{12} is aryl, aryloxy, aralkyloxy, heteroaryl, aralkylaminocarbonyl (where the alkyl is optionally substituted with alkoxycarbonyl or carboxy), cycloalkyl, cycloalkylaminocarbonyl, cycloalkylalkyloxy, $-NR^{30a}R^{30b}$ (where R^{30a} is hydrogen or alkyl and R^{30b} is aryl, heteroaryl, or cycloalkylalkyl) or $-S(O)_n-R^{31}$ (where n is 0, 1, or 2 and R^{31} is heteroaryl, cycloalkylalkyl

or aralkyl); where the alkyl within any group in Q^{12} is optionally substituted with alkoxyalkyl);

R^5 is $-X^{13}-Y^{13}-Z^{13}$ where X^{13} is alkylene or alkenylene, where Y^{13} is $-NR^{26a}-$, $-O-$, $-C(O)-$, $-C(O)O-$, $-S-$, $-S(O)-$, $-SO_2-$, $-NR^{26a}SO_2-$, $-SO_2NR^{26a}-$, $-C(O)NR^{26a}-$, $-NR^{26a}C(O)-$, $-OC(O)-$, $-OC(O)NR^{26a}-$, $-NR^{26a}C(O)O-$, $-C(O)NR^{26a}C(O)-$, or $-NR^{26a}C(O)NR^{26b}-$, where R^{26a} and R^{26b} are as defined above, and where Z^{13} is hydrogen, alkyl, or alkenyl (where Z^{13} is optionally substituted with one, two, or three halo, hydroxy, amino, alkoxy, alkoxy carbonyl, carboxy, or alkylcarbonylamino); or

R^5 is $-Y^{14}-Z^{14}$ where Y^{14} is $-S(O)-$, $-NR^{26a}C(O)-$, $-C(O)NR^{26a}-$, $-NR^{26a}C(O)NR^{26b}-$, $-C(O)NR^{26a}C(O)-$, $-NR^{26a}C(O)O-$, $-OC(O)NR^{26a}$, or $-OC(O)-$, where R^{26a} and R^{26b} are as defined above, and where Z^{14} is alkyl or alkenyl (where Z^{14} is optionally substituted with one, two, or three halo, hydroxy, amino, alkoxy, alkoxy carbonyl, carboxy, or alkylcarbonylamino); or

R^{100} is a group of formula (A3):



where

X^4 is alkylene optionally substituted with one, two, three, four, or five halo;

Y^4 is $-C(O)-$, $-NR^{32}C(O)-$, $-S(O)_2-$, or a bond;

Z^4 is heterocycloalkyl optionally substituted with one, two, three, or four groups selected from cycloalkyl, cycloalkylalkyl, alkoxy carbonyl, carboxy, aryl, aralkyl, cyano, arylcarbonyl, alkoxy, and hydroxy; or Z^4 is $-NR^{50a}R^{50b}$ where R^{50a} is hydrogen, alkyl, alkoxy, or hydroxy and R^{50b} is (alkylene)-aryl where the alkylene is optionally substituted with one or two groups selected from halo, alkoxy carbonyl, hydroxy, and carboxy;

or a pharmaceutically acceptable salt thereof.

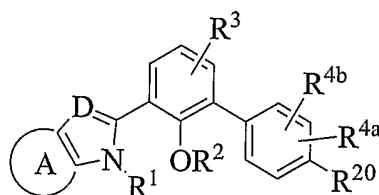
In second aspect, this invention is directed to a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I and a pharmaceutically acceptable excipient.

In a third aspect, this invention is directed to a method of treating a disease, disorder, or syndrome responsive to the inhibition of tryptase in an animal suffering said disease, disorder, or syndrome, comprising administering to said animal a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I.

In a fourth aspect, this invention is directed to a method of treating an immunomediated respiratory disease independently selected from the group consisting of asthma, COPD, and allergic rhinitis, preferably asthma, in an animal which method comprises administering to said animal a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I and a pharmaceutically acceptable excipient in combination with one or more compound(s) independently selected from the group consisting of a β -2 adrenoreceptor agonist, corticosteroid, leukotriene antagonist, phosphodiesterase 4 inhibitor, and antihistamine. Preferably, the compound of Formula I and the pharmaceutically acceptable excipient is administered in combination with one or more compound(s) independently selected from salmeterol, fluticasone, budesonide, montelukast, levalbuterol, and roflumilast.

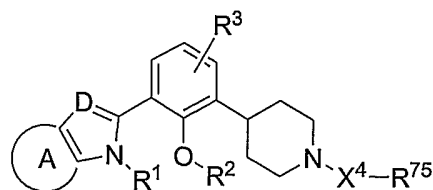
In a fifth aspect, this invention is directed to a method of treating an immunomediated disease independently selected from the group consisting of rheumatoid arthritis, inflammatory bowel disease (IBD) (comprising Crohn's Disease and Ulcerative Colitis), myocardial infarction, and systemic lupus erythematosus (SLE) in an animal which method comprises administering to said animal a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I and a pharmaceutically acceptable excipient in combination with one or more anti-inflammatory compound(s). Preferably, the compound of Formula I and the pharmaceutically acceptable excipient is administered in combination with one or more compound(s) independently selected from azathioprine, plaquenil, prednisone, sulfasalazine, methotrexate, Arava, Remicade, and Enbrel.

In a sixth aspect, this invention is directed to an intermediate of Formula II or III:



II

where R^{20} is $-X^1-OH$, $-X^1-NHR^{13}$, $-X^1-C(O)OH$, $-X^1-SH$, $-X^2-LG$ where LG is a leaving group under alkylating conditions, $-C(O)OH$, $-NHR^{15}$, $-NHR^{17}$, $-X^5-NHR^{13}$, $-X^5-C(O)OH$, $-NHR^{26a}$, $-X^{12a}-C(O)OH$, $-X^{12a}-NHR^{26a}$, $-X^{13}-C(O)OH$, or $-X^{13}-NHR^{26a}$, and all other groups are as defined in the Summary of the Invention; or



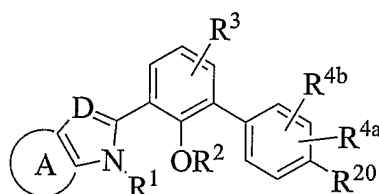
III

where R^{75} is $-X^4-C(O)OH$, $-X^4-LG$ where LG is a leaving group under alkylating conditions, or $-X^4-NHR^{32}$; and all other groups are as defined in the Summary of the Invention.

In a seventh aspect, this invention is directed to *N*-(4-iodo-pyridin-3-yl)-methanesulfonamide.

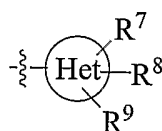
In a eighth aspect, this invention is directed to a process of preparing a compound of Formula I, in which Y^1 is $-C(O)NR^{13}$ or $-NR^{13}C(O)-$ comprising:

- (a) reacting an intermediate of Formula II:



II

where R^{20} is $-X^1-R^{23}$; and R^{23} is $-NHR^{13}$ or $-C(O)OH$, with an intermediate of formula $R^{22}C(O)OH$ or $NHR^{21}R^{22}$, respectively; where R^{21} is R^{13} and R^{22} is $-Z^1-R^{23}$, wherein R^{23} is a moiety of Formula (a):

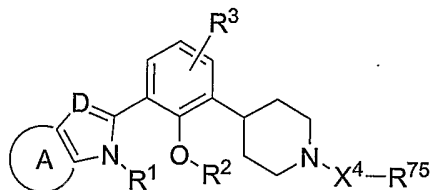


(a)

and each A, R^3 , R^{4a} , R^{4b} , X^1 , Z^1 , R^7 , R^8 , R^9 and R^{13} are as defined in the Summary of the Invention or R^{21} and R^{22} together with the nitrogen atom to which they are attached form a moiety of Formula (a); and

- (b) optionally separating individual isomers; and
 (c) optionally modifying any of the A, D, R^1 , R^2 , R^3 , R^{4a} , and R^{4b} groups; or
 a process of preparing a compound of Formula I, in which Y^{12} is $-C(O)NR^{26a}$ or $-NR^{26a}C(O)-$ comprising:
 (d) reacting an intermediate of Formula II where R^{20} is $-X^{12a}-NHR^{26a}$ or $-X^{12a}-C(O)OH$, with an intermediate of formula $Q^{12}-X^{12b}-C(O)OH$, or $Q^{12}-X^{12b}-NHR^{26a}$, respectively; and

- (e) optionally separating individual isomers; and
- (f) optionally modifying any of the A, D, R¹, R², R³, R^{4a}, and R^{4b} groups; or
- a process of preparing a compound of Formula I, in which Y⁴ is -C(O)- comprising:
- (g) reacting an intermediate of Formula III:



III

where R⁷⁵ is -C(O)OH and all other groups are as defined in the Summary of the Invention, with an intermediate of formula NHR^{50a}R^{50b} or NHR²¹R²² where R²¹ and R²² together with the nitrogen atom to which they are attached form heterocycloalkyl optionally substituted with one, two, three, or four groups selected from cycloalkyl, cycloalkylalkyl, alkoxycarbonyl, carboxy, aryl, aralkyl, cyano, arylcarbonyl, alkoxy, and hydroxy;

- (h) optionally separating individual isomers; and
- (i) optionally modifying any of the A, D, R¹, R², and R³ groups.

DETAILED DESCRIPTION OF THE INVENTION

Abbreviations and Definitions:

Unless otherwise stated, the following terms used in the specification and claims are defined for the purposes of this Application and have the following meanings:

“Acyl” means a -C(O)R radical where R is optionally substituted alkyl, optionally substituted alkenyl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, optionally substituted heterocycloalkyl, or optionally substituted heterocycloalkylalkyl, as defined herein, e.g., acetyl, benzoyl, trifluoromethylcarbonyl, or 2-methoxyethylcarbonyl, and the like.

“Acylamino” means a -NRR’ radical where R is hydrogen, hydroxy, alkyl, or alkoxy and R’ is acyl, as defined herein.

“Acylaminoalkyl” means an alkyl radical substituted with at least one, preferably one or two, acylamino group(s), as defined herein.

“Acylaminoalkyloxycarbonyl” means a -C(O)OR radical where R is an acylaminoalkyl group, as defined herein.

“Acyloxy” means an -OR radical where R is acyl, as defined herein, e.g. cyanomethylcarbonyloxy, and the like.

“Administration” and variants thereof (e.g., “administering” a compound) in reference to a compound of the invention means introducing the compound or a prodrug of the compound into the system of the animal in need of treatment. When a compound of the invention or prodrug thereof is provided in combination with one or more other active agents (e.g., β -2 adrenoreceptor agonists, corticosteroids, leukotriene antagonists, and/or phosphodiesterase 4 inhibitors, etc.), “administration” and its variants are each understood to include concurrent and sequential introduction of the compound or prodrug thereof and other agents.

“Alkenyl” means a linear monovalent hydrocarbon radical of two to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbon atoms containing one or two double bonds e.g., ethenyl, propenyl (including all isomeric forms), 1-methylpropenyl, butenyl (including all isomeric forms), or pentenyl (including all isomeric forms), and the like.

“Alkenylene” means a linear divalent hydrocarbon radical of two to six carbon atoms or a branched divalent hydrocarbon radical of three to six carbon atoms containing at least one, preferably one or two, double bonds e.g., ethen-1,2-diyl, propen-3,3-diyl, propen-1,3-diyl, or 2-methyl-but-2-en-1,4-diyl, and the like.

“Alkoxy” means a radical -OR where R is alkyl as defined herein, e.g., methoxy, ethoxy, propoxy, or 2-propoxy, n-, iso-, or *tert*-butoxy, and the like.

“Alkoxyalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, alkoxy group(s), as defined herein, e.g., 2-methoxyethyl, 1-, 2-, or 3-methoxypropyl, 2-ethoxyethyl, or 3,4-dimethoxybutyl, and the like.

“Alkoxyalkylamino” means an -NR^aR^b where R^a is hydrogen, alkyl, or alkoxyalkyl, as defined herein, and R^b is alkoxyalkyl, as defined herein.

“Alkoxyalkylaminocarbonyl” means the radical -C(O)R where R is alkoxyalkylamino, as defined herein.

“Alkoxyalkyloxy” means a -OR radical where R is alkoxyalkyl, as defined herein.

“Alkoxyalkyloxyalkyl” means an alkyl radical substituted with at least one, preferably one or two, alkoxyalkyloxy group(s), as defined herein.

“Alkoxyalkyloxycarbonyl” means a -C(O)OR radical where R is alkoxyalkyl as defined herein.

“Alkoxyalkyloxycarbonylalkyl” means an alkyl radical substituted with at least one, preferably one or two, alkoxyalkyloxycarbonyl group(s), as defined herein

“Alkoxyaminocarbonyl” means a -C(O)NHR radical where R is alkoxy, as defined

herein, e.g. methoxyaminocarobnyl, and the like.

“Alkoxyacarbonyl” means a radical $-C(O)OR$ where R is alkyl as defined herein, e.g., methoxyacarbonyl, ethoxyacarbonyl, n-propoxyacarbonyl, or 2-propoxyacarbonyl, n-, iso-, or *tert*-butoxyacarbonyl, and the like.

“Alkoxyacarbonylalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, alkoxyacarbonyl group(s), as defined herein, e.g., methoxyacarbonylmethyl or methoxyacarbonylethyl, and the like.

“Alkoxyacarbonylalkylaminocarbonyl” means a $-C(O)NR^aR^b$ radical where R^a is alkoxyacarbonylalkyl, as defined herein, and R^b is hydrogen, alkyl, as defined herein, or alkoxyacarbonylalkyl, as defined herein.

“Alkoxyacarbonylalkyloxy” means an $-OR$ radical where R is alkoxyacarbonylalkyl, as defined herein.

“Alkoxyacarbonylalkyloxyalkyl” means an alkyl radical substituted with at least one, preferably one or two, alkoxyacarbonylalkyloxy group(s), as defined herein.

“Alkoxyacarbonylamino” means a $-NRC(O)OR'$ radical where R is hydrogen or alkyl, as defined herein, and R' is alkyl, as defined herein, e.g., methoxyacarbonylamino, methoxyacarbonyl-*N*-methylamino or isopropoxyacarbonylamino, and the like.

“Alkoxyacarbonylaminoalkyl” means an alkyl radical as defined herein substituted with at least one, preferably one or two, alkoxyacarbonylamino as defined herein, e.g., 2-(methoxyacarbonylamino)ethyl, methoxyacarbonyl-*N*-methylaminomethyl or 2-(isopropoxyacarbonylamino)propyl, and the like.

“Alkyl” means a linear saturated monovalent hydrocarbon radical of one to six carbon atoms or a branched saturated monovalent hydrocarbon radical of three to six carbon atoms, e.g., methyl, ethyl, propyl, 2-propyl, butyl (including all isomeric forms), or pentyl (including all isomeric forms), and the like.

“Alkylamino” means a radical $-NHR$ where R is alkyl as defined herein, or an N-oxide derivative, or a protected derivative thereof, e.g., methylamino, ethylamino, *n*-, *iso*-propylamino, *n*-, *iso*-, *tert*-butylamino, or methylamino-N-oxide, and the like.

“Alkylaminoalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, alkylamino group(s), as defined herein.

“Alkylaminoalkylaminocarbonyl” means a $-C(O)NR'R''$ radical where R' is hydrogen, alkyl, hydroxy, or alkoxy and R'' is alkylaminoalkyl, as defined herein.

“Alkylaminoalkyloxy” means a $-OR$ radical, as defined herein, substituted with at least one, preferably one or two, alkylaminoalkyl group(s), as defined herein.

“Alkylaminoalkyloxyalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, alkylaminoalkyloxy group(s), as defined herein.

“Alkylaminocarbonyl” means a $-C(O)R$ radical where R is alkylamino as defined herein e.g, methylaminocarbonyl or ethylaminocarbonyl, and the like.

“Alkylaminosulfonyl” means a $-S(O)_2NHR$ radical where R is alkyl, as defined herein.

“Alkylcarbonyl” means a $-C(O)R$ radical where R is alkyl as defined herein, e.g., methylcarbonyl, ethylcarbonyl, or 2-propylcarbonyl, and the like.

“Alkylcarbonylamino” means a $-NRR'$ radical, where R is hydrogen or alkyl, as defined herein, and R' is alkylcarbonyl as defined herein, e.g., methylcarbonylamino or ethylcarbonylamino, and the like.

“Alkylcarbonyloxy” means an $-OR$ radical where R is alkylcarbonyl, as defined herein, e.g., methylcarbonyloxy, ethylcarbonyloxy, or n-propylcarbonyloxy, and the like.

“Alkylene” means a linear saturated divalent hydrocarbon radical of one to six carbon atoms or as otherwise indicated or a branched saturated divalent hydrocarbon radical of two to six carbon atoms or as otherwise indicated, e.g., methylene, prop-2,2-diyl, eth-1,2-diyl, prop-1,3-diyl, 1-methylprop-1,3-diyl, 2-methylprop-1,3-diyl, but-1,4-diyl (including all isomers), or pent-1,5-diyl (including all isomers), and the like. Alkylene may contain the number of carbon atoms indicated. For example the term (alkylene)₁₋₃ means alkylene containing from 1 carbon atom, i.e., methylene, to 3 carbon atoms, i.e., eth-1,2-diyl, eth-1,1-diyl, prop-1,3-diyl, 1-methyleth-1,2-diyl-, 2-methyleth-1,2-diyl, prop-1,1-diyl, and prop-2,2-diyl. The term (alkylene)₀ means that a bond is intended.

“Alkylphosphonyl” means a $-OPO(OR)_2$ radical where R is alkyl, as defined herein.

“Alkylsulfinyl” means a $-S(O)R$ radical where R is alkyl as defined herein, e.g., methylsulfinyl, ethylsulfinyl, or propylsulfinyl, and the like.

“Alkylsulfonyl” means a $-SO_2R$ radical where R is alkyl as defined herein, e.g., methylsulfonyl or ethylsulfonyl, and the like.

“N-(alkylsulfonyl)-N-alkyl-amino” means a $-NR^aR^b$ radical where R^a is an alkyl radical as defined herein and R^b is an alkylsulfonyl radical, as defined herein.

“Alkylsulfonylamino” means an $-NHR^a$ radical, where R^a is alkylsulfonyl, as defined herein, e.g., methylsulfonylamino, and the like.

“Alkylsulfonylaminoalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two alkylsulfonylamino group(s), as defined herein.

“Alkylsulfonylaminocarbonyl” means a $-C(O)R$ radical where R is

alkylsulfonylamino, as defined herein.

“Alkylthio” means an -SR radical where R is alkyl as defined herein, e.g., methylthio, ethylthio, propylthio, or butylthio, and the like.

“Alkynyl” means a linear monovalent hydrocarbon radical of two to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbon atoms containing at least one, preferably one or two, triple bond(s), e.g., ethynyl, propynyl (and all isomeric forms) and butynyl (and all isomeric forms), and the like.

“Amino” means a -NH₂ radical or an N-oxide derivative, or a protected derivative thereof such as -NH→O, -NHBoc, or -NHCbz, and the like.

“Aminoalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, -NH₂ group(s), e.g., aminomethyl, aminoethyl, or 1,4-diamino-2-methyl-pentyl, and the like.

“Aminoalkyloxy” means an -OR radical where R is aminoalkyl as defined herein.

“Aminoalkylaminocarbonyl” means a -C(O)NR'R'' radical where R' is hydrogen, alkyl, hydroxy, or alkoxy and R'' is aminoalkyl, as defined herein.

“Aminocarbonyl” means a -CONH₂ radical, or an N-oxide derivative, or a protected derivative thereof.

“Aminocarbonylamino” means a -NRC(O)NH₂ where R is hydrogen or alkyl, as defined herein.

“Aralkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, aryl group(s) as defined herein, e.g., benzyl or phenethyl, and the like.

“Aralkyloxy” means an -OR radical where R is aralkyl as defined above, e.g., benzyloxy, and the like.

“Aralkyloxyaminocarbonyl” means a -C(O)NHOR radical where R is aralkyl, as defined herein.

“Aralkyloxycarbonyl” means a -C(O)R radical where R is aralkyloxy as defined herein.

“Aralkyloxycarbonylalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, aralkyloxycarbonyl group(s), as defined herein.

“Aralkyloxycarbonylamino” means a -NHR radical where R is aralkyloxycarbonyl, as defined herein.

“Aryl” means a monovalent, monocyclic or fused bicyclic hydrocarbon radical of 6 to 12 ring atoms, wherein the ring comprising a monocyclic radical ring is aromatic and wherein

at least one of the fused rings comprising a bicyclic radical is aromatic. Fused bicyclic hydrocarbon radical includes bridged ring systems. Unless otherwise stated, the valency of the group may be located on any atom of any ring within the radical, valency rules permitting. More specifically the term aryl includes, but is not limited to, phenyl, naphthyl, indanyl (including, for example, indan-5-yl, or indan-2-yl, and the like) or tetrahydronaphthyl (including, for example, tetrahydronaphth-1-yl, or tetrahydronaphth-2-yl, and the like), and the like. Unless indicated otherwise, aryl may be substituted on any ring with one, two, or three substituents independently selected from the group consisting of acyl, acylamino, acyloxy, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, alkoxy, alkenyloxy, halo, hydroxy, alkoxycarbonyl, alkenyloxycarbonyl, alkylthio, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, amino, alkylamino, dialkylamino, nitro, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, carboxy, cyano, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, aminoalkoxy, alkoxyalkyloxy, hydroxyalkyloxy, aminoalkyloxy, alkylcarbonylamino, aminoalkylaminocarbonyl, alkylaminoalkylaminocarbonyl, dialkylaminoalkylaminocarbonyl, -CONR^PR^V (where R^P is hydrogen, alkyl, hydroxy, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, optionally substituted heterocycloalkyl, or optionally substituted heterocycloalkylalkyl and R^V is hydrogen, alkyl, alkenyl, hydroxy, or alkoxy), -(alkylene)-SiR₁₋₃ (where R is alkyl), -P(O)OR'R'' (where R' and R'' are alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylalkyl, heteroaryl, or heteroaralkyl), -P(O)R'R'' where R' and R'' are alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylalkyl, heteroaryl, or heteroaralkyl; or R' and R'' together with the P to which they are attached form optionally substituted heterocycloalkyl or heteroaryl), -P(O)(OR')(OR'') (where R' and R'' are alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylalkyl, heteroaryl, or heteroaralkyl), optionally substituted phenyl, optionally substituted phenylalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted heterocycloalkylalkylaminocarbonyl, and heteroaryl; or when two substituents are adjacent to each other they can combine to form methylenedioxy group or aryl is pentafluorophenyl. Within the optional substituents on "aryl", any alkyl, alkenyl, or alkynyl, either alone or as part of another group (including, for example, the alkyl in heteroaralkyl and the alkyl in alkoxy), is independently optionally

substituted with one, two, three, four, or five halo.

“*N*-aryl-*N*-(alkylcarbonyl)-amino” means a -NR^aR^b radical where R^a is aryl, as defined herein and R^b is alkylcarbonyl, as defined herein.

“Arylamino” means a -NR'R” radical where R' is hydrogen, hydroxy, alkyl, alkenyl, alkoxy, or alkenyloxy and R” is aryl, as defined herein.

“Arylaminoalkyl” means an alkyl radical substituted with -NHR where R is aryl, as defined herein.

“Arylaminoalkyl” means an alkyl radical substituted with -NHR where R is aryl, as defined herein.

“Arylcarbonyl” means a -C(O)R radical where R is aryl as defined herein.

“Arylcarbonylamino” means a the radical -NHC(O)R where are is aryl, as defined herein.

“Aryloxy” means a -OR where R is aryl as defined herein.

“Aryloxyalkyl” means an alkyl radical substituted with aryloxy, as defined herein.

“Arylthioalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, -S-aryl group(s).

“Arylthioalkylcarbonyl” means a -C(O)R radical where R is arylthioalkyl, as defined herein.

“Carboxy” means a -C(O)OH radical.

“Carboxyalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, -C(O)OH group(s), e.g., carboxymethyl, carboxyethyl, 1-, 2-, or 3-carboxypropyl, and the like.

“Carboxyalkylaminoalkyl” means an alkyl radical substituted with -NHR where R is carboxyalkyl, as defined herein.

“Carboxyalkylaminocarbonyl” means a -C(O)NHR radical where R is carboxyalkyl as defined herein.

“Carboxyalkylcarbonylamino” means an alkyl radical substituted with -NHC(O)R where R is carboxyalkyl, as defined herein.

“Carboxyalkyloxyalkyl” means an alkyl radical substituted with -OR where R is carboxyalkyl, as defined here.

“Chronic bronchitis” clinically means a daily cough with production of sputum for 3 months, two years in a row. In chronic bronchitis, the lining of the airways becomes inflamed and swells leading to narrowing and obstruction of the airways. The inflammation stimulates production of mucous (sputum), which can cause further obstruction of the airways. Obstruction of the airways, especially with mucus, increases the likelihood of bacterial lung

infections.

“Chronic Obstructive Pulmonary Disease” or “COPD” is a disease comprising primarily chronic bronchitis and/or emphysema and is characterized by chronic obstruction of the flow of air through the airways and out of the lungs. The obstruction generally is permanent and progressive over time, limiting the ability to exhale. Chronic asthma may also develop into COPD where the lungs have become irreversibly damaged and scarred from repeated, untreated asthma flares. There is frequent overlap among COPD patients. Thus, patients with emphysema may have some of the characteristics of chronic bronchitis. Similarly, patients with chronic bronchitis also may have some of the characteristics of emphysema.

“Composition” is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

“Cyanoalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, cyano group(s), e.g., cyanomethyl, 2-cyanoethyl, or 2-cyanopropyl, and the like.

“Cyanoalkylaminocarbonyl” means a $-C(O)NR'R''$ radical where R' is hydrogen, alkyl, hydroxy, or alkoxy and R'' is cyanoalkyl as defined herein.

“Cycloalkyl” means a monocyclic or fused bicyclic, saturated or partially unsaturated, monovalent hydrocarbon radical of three to ten carbon ring atoms. Fused bicyclic hydrocarbon radical includes bridged ring systems. Unless otherwise stated, the valency of the group may be located on any atom of any ring within the radical, valency rules permitting. One or two ring carbon atoms may be replaced by a $-C(O)-$, $-C(S)-$, or $-C(=NH)-$ group. More specifically, the term cycloalkyl includes, but is not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, decahydronaphthyl (including, but not limited to, decahydronaphth-1-yl or decahydronaphth-2-yl, and the like), or cyclohexenyl and the like. The cycloalkyl ring may be substituted with one, two, or three substituents independently selected from acyl, acyloxy, acylamino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, alkoxy, alkoxycarbonyl, alkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonylamino, arylsulfonylamino, halo, hydroxy, amino, alkylamino, dialkylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, nitro, alkoxyalkyloxy, aminoalkoxy, carboxy, cyano, $-P(O)ORR'$ (where R and R' are independently alkyl, cycloalkyl, aryl, or heteroaryl), $-P(O)RR'$ (where R and R' are independently alkyl, cycloalkyl, aryl, or heteroaryl; or R and

R' together with the P to which they are attached form optionally substituted heterocycloalkyl or heteroaryl), aryl, aralkyloxy, and heteroaryl. Within the above optional substituents, the alkyl, alkenyl, and alkynyl, either alone or as part of another substituent on the cycloalkyl ring, are independently optionally substituted with one, two, three, four, or five halo, e.g. haloalkyl, haloalkoxy, haloalkenyloxy, or haloalkylsulfonfyl.

"Cycloalkylalkyl" means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, cycloalkyl group(s) as defined herein, e.g., cyclopropylmethyl, cyclobutylmethyl, cyclopentylethyl, 2-(cyclopropyl)-propyl, or cyclohexylmethyl, and the like.

"Cycloalkylalkyloxycarbonyl" means a -C(O)OR where R is cycloalkylalkyl as defined herein.

"Cycloalkylene" means a monocyclic or fused bicyclic, saturated or partially unsaturated, divalent hydrocarbon radical of three to ten carbon ring atoms. Fused bicyclic hydrocarbon radical includes bridged ring systems. Unless otherwise stated, the valency of the group may be located on any atom of any ring within the radical, valency rules permitting. One or two ring carbon atoms may be replaced by a -C(O)-, -C(S)-, or -C(=NH)- group. More specifically, the term cycloalkylene includes, but is not limited to, cycloprop-1,1-diyl, cyclobut-1,3-diyl, cyclopent-1,4-diyl, cyclohex-1,3-diyl, cyclohex-1,4-diyl, or cyclohex-3-en-1,2-diyl, and the like. The cycloalkylene ring may be substituted with one, two, or three substituents independently selected from the group consisting of acyl, acyloxy, acylamino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, alkoxy, alkoxy carbonyl, alkylthio, alkylsulfanyl, alkylsulfonfyl, aminosulfonfyl, alkylaminosulfonfyl, dialkylaminosulfonfyl, alkylsulfonfylamino, arylsulfonfylamino, halo, hydroxy, amino, alkylamino, dialkylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, nitro, alkoxyalkyloxy, aminoalkoxy, carboxy, cyano, -P(O)ORR' (where R and R' are independently alkyl, cycloalkyl, aryl, or heteroaryl), -P(O)RR' (where R and R' are independently alkyl, cycloalkyl, aryl, or heteroaryl; or R and R' together with the P to which they are attached form heterocycloalkyl or heteroaryl), aryl, and heteroaryl. Within the above optional substituents, the alkyl, alkenyl, and alkynyl, either alone or as part of another substituent on the cycloalkyl ring, are independently optionally substituted with one, two, three, four, or five halo, e.g. haloalkyl, haloalkoxy, haloalkenyloxy, or haloalkylsulfonfyl.

"Cycloalkylalkylaminocarbonyl" means a -C(O)NHR radical where R is cycloalkylalkyl, as defined herein.

“Cycloalkylalkynyl” is an alkynyl radical, as defined herein, substituted with at least one, preferably one or two, cycloalkyl group(s) as defined herein.

“Cycloalkylcarbonyl” means a $-C(O)R$ radical where R is cycloalkyl as defined herein.

“Cycloalkylcarbonylamino” means a $-NR^aR^b$ radical where R^a is cycloalkylcarbonyl, as defined herein and R^b is hydrogen or alkyl, as defined herein.

“Cycloalkylcarbonylaminoalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, cycloalkylcarbonylamino group(s), as defined herein.

“Cycloalkylcarbonyloxy” means a $-OC(O)R$, where R is cycloalkyl, as defined above, e.g., cyclohexylcarbonyloxy, and the like.

“Cycloalkylcarbonyloxyalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, cycloalkylcarbonyloxy group(s), as defined herein.

“Cycloalkyloxy” means a $-OR$ radical where R is cycloalkyl as defined herein.

“Dialkylamino” means a radical $-NRR'$ where R and R' are independently alkyl as defined herein, or an N-oxide derivative, or a protected derivative thereof, e.g., dimethylamino, diethylamino, *N,N*-methylpropylamino or *N,N*-methylethylamino, and the like.

“Dialkylaminoalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, dialkylamino group(s), as defined herein.

“Dialkylaminoalkylaminocarbonyl” means the radical $-C(O)NHR$ where R is dialkylamino, as defined herein.

“Dialkylaminoalkyloxy” means a $-OR$ radical where R is dialkylaminoalkyl, as defined herein.

“Dialkylaminoalkyloxyalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, dialkylaminoalkyloxy group(s), as defined herein.

“Dialkylaminoalkyloxycarbonyl” means a $-C(O)R$ radical where R is dialkylaminoalkyloxy, as defined herein.

“Dialkylaminocarbonyl” means a $-C(O)R$ radical where R is dialkylamino as defined herein, e.g., dimethylaminocarbonyl or methylethylaminocarbonyl, and the like.

“Dialkylaminocarbonylalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, dialkylaminocarbonyl group(s), as defined herein.

“Dialkylaminocarbonylalkyloxy” means an $-OR$ radical where R is dialkylaminocarbonylalkyl, as defined herein.

“Dialkylaminocarbonylalkyloxyalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, dialkylaminocarbonylalkyloxy group(s), as defined herein.

“Dialkylaminosulfonyl” means a -S(O)NR'R'' where R' and R'' are alkyl, as defined herein.

“Emphysema” means a lung condition featuring an abnormal accumulation of air in the lung's alveoli, leading to their enlargement and resulting breakage or damage or formation of scar tissue. Emphysema is associated with smoking cigarettes and also with or worsened by repeated infection of the lungs, such as is seen in chronic bronchitis.

“Halo” means fluoro, chloro, bromo, and iodo, preferably fluoro or chloro.

“Haloalkenyl” means means an alkenyl radical, as defined herein, substituted with at least one, preferably one to five, halogen atoms, preferably fluorine or chlorine, including those substituted with different halogens.

“Haloalkoxy” means a radical -OR where R is haloalkyl as defined herein, e.g., trifluoromethoxy or 2,2,2-trifluoroethoxy, and the like.

“Haloalkoxyalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two haloalkoxy group(s), as defined herein.

“Haloalkoxycarbonyl” means the radical -C(O)R where R is haloalkyl, as defined herein.

“Haloalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one to five halogen atoms, preferably fluorine or chlorine, including those substituted with different halogens, e.g., -CH₂Cl, -CF₃, -CHF₂, -CF₂CF₃, -CF(CH₃)₃, or -CHFCl, and the like.

“Haloalkylamino” means a -NR^aR^b radical where R^a is haloalkyl, as defined herein, and R^b is hydrogen, alkyl, or haloalkyl, as defined herein, e.g. *N*-(trifluoromethyl)-*N*-(2,2-difluoroethyl)-amino.

“Haloalkylaminoalkyl” means an alkyl radical substituted with haloalkylamino, as defined herein.

“Haloalkylaminocarbonyl” means a -C(O)R radical where R is haloalkylamino, as defined herein.

“Heteroarakenyl” means an alkenyl radical, as defined herein, substituted with at least one, preferably, one or two, heteroaryl group(s), as defined herein.

“Heteroaralkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, heteroaryl group(s) as defined herein, e.g., pyridinylmethyl,

furanylmethyl, or chloropyridinylmethyl, and the like.

“Heteroaralkynyl” means an alkynyl radical, as defined herein, substituted with at least one, preferably, one or two, heteroaryl group(s), as defined herein

“Heteroaralkyloxy” means an -OR radical where R is heteroaralkyl as defined herein e.g., furanylmethyloxy or pyridinylethyloxy, and the like.

“Heteroaryl” means a monocyclic, fused bicyclic, or fused tricyclic, monovalent radical of 5 to 14 ring atoms containing one or more, preferably one, two, three, or four ring heteroatoms independently selected from -O-, -S(O)_n- (n is 0, 1, or 2), -N-, -N(R²⁰⁰)-, -Si(alkyl)₂-, -P(=S)(R²⁰¹)-, and -P(=O)(R²⁰¹)-, and the remaining ring atoms being carbon, wherein the ring comprising a monocyclic radical is aromatic and wherein at least one of the fused rings comprising a bicyclic or tricyclic radical is aromatic. One or two ring carbon atoms of any nonaromatic rings comprising a bicyclic or tricyclic radical may be replaced by a -C(O)-, -C(S)-, or -C(=NH)- group. R²⁰⁰ is hydrogen, alkyl, hydroxy, alkoxy, acyl, or alkylsulfonyl. R²⁰¹ is alkyl, aryl, aralkyl, cycloalkyl, or cycloalkylalkyl. Fused bicyclic radical includes bridged ring systems. Unless stated otherwise, the valency may be located on any atom of any ring of the heteroaryl group, valency rules permitting. In particular, when the point of valency is located on a nitrogen or phosphorous atom, R²⁰⁰ or R²⁰¹, respectively, is absent. More specifically, the term heteroaryl includes, but is not limited to, phthalimidyl, pyridinyl, pyrrolyl, imidazolyl, thienyl, furanyl, indolyl, 2,3-dihydro-1*H*-indolyl (including, for example, 2,3-dihydro-1*H*-indol-2-yl or 2,3-dihydro-1*H*-indol-5-yl, and the like), pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isooxazolyl, benzoxazolyl, quinolinyl, isoquinolinyl, tetrahydroisoquinolinyl (including, for example, tetrahydroisoquinolin-4-yl or tetrahydroisoquinolin-6-yl, and the like), pyrrolo[3,2-*c*]pyridinyl (including, for example, pyrrolo[3,2-*c*]pyridin-2-yl or pyrrolo[3,2-*c*]pyridin-7-yl, and the like), benzopyranyl, thiazolyl, methylenedioxyphenyl (including, for example, methylenedioxyphen-5-yl), and the derivatives thereof, or *N*-oxide or a protected derivative thereof. Unless otherwise stated, the heteroaryl ring may be substituted with one, two, or three substituents independently selected from the group consisting of acyl, acylamino, acyloxy, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, alkoxy, alkenyloxy, alkoxycarbonyl, alkylthio, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, aminoalkoxy, optionally substituted heterocycloalkyl, halo, hydroxy, amino, alkylamino, dialkylamino, nitro, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, carboxy, cyano, optionally substituted phenyl,

-CONR^PR^V (where R^P is hydrogen, alkyl, hydroxy, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, optionally substituted heterocycloalkyl, or optionally substituted heterocycloalkylalkyl and R^V is hydrogen, alkyl, alkenyl, hydroxy, or alkoxy), -(alkylene)₁₋₃-SiR₁₋₃ (where R is alkyl), -P(O)ORR' (where R and R' are independently alkyl, cycloalkyl, aryl, or heteroaryl), -P(O)RR' (where R and R' are independently alkyl, cycloalkyl, aryl, or heteroaryl; or R and R' together with the P to which they are attached form optionally heterocycloalkyl or heteroaryl), and heteroaryl substituted with a group independently selected from hydrogen, alkyl, alkoxy, haloalkyl, haloalkoxy, halo, hydroxy, amino, alkylamino, dialkylamino, alkylcarbonyl, alkylcarbonylamino, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, carboxy, and cyano; or when two substituents are adjacent to each other they can combine to form methylenedioxy group. Within R²⁰⁰, R²⁰¹, and the above optional substituents, the alkyl, alkenyl, and alkynyl, either alone or as part of another substituent on the heteroaryl ring, are independently optionally substituted with one, two, three, four, or five halo, e.g. haloalkyl, haloalkoxy, or haloalkylsulfonyl.

"Heteroarylamino" means a -NR'R" radical where R' is hydrogen, hydroxy, alkyl, alkenyl, alkoxy, or alkenyloxy and R" is heteroaryl, as defined herein.

"Heteroarylaminomethyl" means an alkyl radical substituted with heteroarylamino, as defined herein.

"Heteroarylaminocarbonyl" means -C(O)NR^aR^b where R^a is hydrogen or alkyl, as defined herein, and R^b is heteroaryl as defined herein.

"Heteroarylaminocarbonylalkyl" means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, heteroarylaminocarbonyl group(s), as defined herein.

"Heteroaryloxyalkyl" means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, heteroaryloxy group(s) as defined herein, e.g., furanyloxymethyl or pyridinyloxyethyl, and the like.

"Heterocycloalkyl" means a saturated or partially unsaturated monovalent monocyclic group of 3 to 8 ring atoms or a saturated or partially unsaturated monovalent fused bicyclic group of 5 to 12 ring atoms in which one or more, preferably one, two, three, or four ring heteroatoms independently selected from -O-, -S(O)_n- (n is 0, 1, or 2), -N-, -N(R²⁰⁰)-, -Si(alkyl)₂-, -P(=S)(R²⁰¹)-, and -P(=O)(R²⁰¹)-, the remaining ring atoms being carbon. One or two ring carbon atoms may be replaced by a -C(O)-, -C(S)-, or -C(=NH)- group. R²⁰⁰ is hydrogen, alkyl, hydroxy, alkoxy, acyl, or alkylsulfonyl. R²⁰¹ is alkyl, aryl, aralkyl, cycloalkyl, or cycloalkylalkyl. Fused bicyclic radical includes bridged ring systems. Unless

otherwise stated, the valency of the group may be located on any atom of any ring within the radical, valency rules permitting. In particular, when the point of valency is located on a nitrogen or phosphorous atom, R^{200} or R^{201} , respectively, is absent. More specifically the term heterocycloalkyl includes, but is not limited to, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, homopiperazinyl, tetrahydropyranyl, 2-oxopiperidinyl, and thiomorpholinyl, and the derivatives thereof and N-oxide, including the N-oxide of piperazin-1,4-diyl, or a protected derivative thereof.

“Hydroxyalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, hydroxy group(s), provided that if two hydroxy groups are present they are not both on the same carbon atom. Representative examples include, but are not limited to, hydroxymethyl, 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 1-(hydroxymethyl)-2-methylpropyl, 2-hydroxybutyl, 3-hydroxybutyl, 4-hydroxybutyl, 2,3-dihydroxypropyl, 1-(hydroxymethyl)-2-hydroxyethyl, 2,3-dihydroxybutyl, 3,4-dihydroxybutyl and 2-(hydroxymethyl)-3-hydroxypropyl, preferably 2-hydroxyethyl, 2,3-dihydroxypropyl, or 1-(hydroxymethyl)-2-hydroxyethyl, and the like.

“Hydroxyalkyloxy” means an -OR radical where R is hydroxyalkyl, as defined herein.

“Hydroxyalkylaminocarbonyl” means a $-C(O)NR'R''$ where R' is hydroxyalkyl, as defined herein, and R'' is hydrogen, alkyl, or hydroxyalkyl, as defined herein.

“Hydroxyalkyloxyalkyl” means a -OR radical where R is hydroxyalkyloxy, as defined herein.

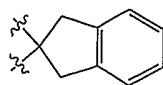
“N-Hydroxyaminocarbonyl” means a $-C(O)NR^aR^b$ where R^a is hydroxy and R^b is hydrogen or alkyl, as defined herein.

“Hyperresponsiveness” means the late phase bronchoconstriction and airway hyperreactivity associated with chronic asthma. Hyper-responsiveness of asthmatic bronchiolar tissue is believed to result from chronic inflammation reactions, which irritate and damage the epithelium lining the airway wall and promote pathological thickening of the underlying tissue.

“Immunomediated inflammatory disorders” means those diseases associated with mast cell mediator release and susceptible to treatment with a tryptase inhibitor [e.g., immunomediated type hypersensitivity diseases such as asthma, allergic rhinitis, Chronic Obstructive Pulmonary Disease (COPD), urticaria and angioedema, eczematous anaphylaxis, dermatitis such as atopic dermatitis, hyperproliferative skin disease, peptic ulcers, inflammatory bowel disorder, ocular and vernal conjunctivitis, rheumatoid arthritis, SLE, Inflammatory Bowel Disease, including Crone’s Disease and Ulcerative Colitis, or

inflammatory skin conditions, and the like].

“2,2,-Indanylene” means a divalent radical having the following structure:



and when used in conjunction with any two of R^7 , R^8 , and R^9 attached to the same carbon ring atom of Het it is intended that any two of R^7 , R^8 , and R^9 attached to the same carbon ring atom together with the heterocycloalkyl they are attached forms a heterospiroalkyl moiety, e.g., indan-2',4-piperidin-1-yl. Unless indicated otherwise, the indanylene ring may be substituted with one, two, or three substituents independently selected from the group consisting of alkyl, alkoxy, alkylthio, haloalkyl, haloalkoxy, halo, hydroxy, amino, alkylamino, dialkylamino, nitro, alkylcarbonyl, alkylcarbonylamino, alkoxy carbonyl, alkoxyalkyl, aminoalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, carboxy, cyano, hydroxyalkyl, oxo, thioxo, imino, and optionally substituted phenyl.

“Isomer” or “isomers” means compounds of Formula I having identical molecular formulae but differ in the nature or sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed “stereoisomers”. Stereoisomers that are not mirror images of one another are termed “diastereomers” and stereoisomers that are nonsuperimposable mirror images are termed “enantiomers” or sometimes “optical isomers”. An atom bonded to four nonidentical substituents is termed a “chiral center”. A compound with one chiral center has two enantiomeric forms of opposite chirality; and a mixture of both enantiomeric forms in equal amounts is termed racemic. A compound that has one or more chiral centers has 2^{n-1} enantiomeric pair(s), where n is the number of chiral centers, unless the compound is meso (i.e. the compound has 2 or more asymmetric or chiral centers but which is achiral because it contains an internal plane of symmetry). Compounds with more than one chiral center may exist as either an individual diastereomer or as a mixture of diastereomers, termed a “diastereomeric mixture”. When one chiral center is present a stereoisomer may be characterized by the absolute configuration of that chiral center. Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center. Enantiomers are characterized by the absolute configuration of their chiral centers and described by the *R*- and *S*-sequencing rules of Cahn, Ingold and Prelog. Conventions for stereochemical nomenclature, methods for the determination of stereochemistry and the

separation of stereoisomers are well known in the art (e.g., see "Advanced Organic Chemistry," 4th edition, March, Jerry, John Wiley & Sons, New York, 1992). It is understood that the names and illustration used in this Application to describe compounds of Formula I are meant to be encompassed all possible stereoisomers and any mixture, racemic or otherwise, thereof.

"Mercaptoalkylaminocarbonyl" means a $-C(O)NR^aR^b$ radical where R^a is hydrogen or alkyl and R^b is a mercaptoalkyl radical group.

"Mercaptoalkylaminocarbonylalkyl" means an alkyl radical as defined herein substituted with at least one, preferably one or two, mercaptoalkylaminocarbonyl group(s) as defined herein, e.g., *N*-(mercaptomethyl)-aminocarbonylethyl or *N*-(2-mercapto-*n*-propyl)-aminocarbonylmethyl, and the like.

"Methylene" means a radical $-CH_2-$ and the term $-(methylene)_n-$ wherein *n* means the number of methylenes indicated and when *n* is 0 then a bond is intended.

"Methylenedioxy" means a radical $-O-CH_2-O-$.

"Optionally substituted" or "may be substituted," when modifying a particular group, means that the group the term modifies may, but does not have to, be substituted. Where the term "optionally substituted" or "may be substituted" is used to modify a particular group, this does not mean, unless otherwise stated, that any other groups not so modified cannot also be optionally substituted. Furthermore, where a group is defined as being substituted by one of a number of enumerated alternative substituents, it does not mean, unless otherwise stated, that the group cannot be substituted further with one or more substituents not enumerated. For example, "optionally substituted heterocycloalkyl" means that the heterocycloalkyl may but need not be substituted with the enumerated substituents within the definition of "optionally substituted heterocycloalkyl"; and the description includes situations where the heterocycloalkyl group is substituted and situations where the heterocycloalkyl group is not substituted.

"Optionally substituted alkenyl" means an alkenyl radical, as defined herein, substituted with one or more group(s), preferably one, two, or three groups, independently selected from alkylcarbonyl, alkenylcarbonyl, cycloalkylcarbonyl, cycloalkylcarbonyloxy, cycloalkylcarbonylamino, alkylcarbonyloxy, alkenylcarbonyloxy, amino, alkylamino, dialkylamino, arylamino, aryloxy, hydroxy, hydroxyalkyloxy, heteroaryl amino, heteroaryloxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, cyano, cyanoalkylaminocarbonyl, alkoxy, alkenyloxy, hydroxy, hydroxyalkoxy, carboxy, carboxyalkyloxy, carboxyalkylamino, carboxyalkylcarbonylamino (where the "alkyl" within

“carboxyalkylcarbonylamino” is optionally substituted with one or two amino), alkylcarbonylamino, alkylcarbonyloxy, -S(O)₀₋₂-alkyl, -S(O)₀₋₂-alkenyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, -NR^c-SO₂-alkyl (where R^c is hydrogen, optionally substituted alkyl, optionally substituted alkynyl, hydroxy, alkoxy, alkenyloxy, or cyanoalkyl), alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylaminoalkyloxy, dialkylaminoalkyloxy, alkoxycarbonyl, alkenyloxycarbonyl, alkoxycarbonylamino, alkoxycarbonylalkylcarbonylamino where the “alkyl” within “alkoxycarbonylalkylcarbonylamino” is optionally substituted with one or two hydroxy, alkylaminocarbonylamino, dialkylaminocarbonylamino, dialkylaminoalkylcarbonylamino, dialkylaminocarbonylalkyloxy, alkoxyalkyloxy, alkoxyalkyloxycarbonyl, alkoxycarbonylalkyloxy, aralkyloxycarbonyl, optionally substituted heterocycloalkyloxy, and -C(O)NR^aR^b (where R^a is hydrogen, optionally substituted alkyl, alkenyl, optionally substituted alkynyl, hydroxy, alkoxy, or alkenyloxy, and R^b is hydrogen, optionally substituted alkyl, alkenyl, optionally substituted alkynyl, hydroxy, alkoxy, alkenyloxy, optionally substituted heterocycloalkyl, or heteroaryl, or R^a and R^b together with the nitrogen to which they are attached form optionally substituted heterocycloalkyl).

“Optionally substituted alkyl” means an alkyl radical, as defined herein, substituted with one or more group(s), preferably one, two, or three groups, independently selected from alkylcarbonyl, alkenylcarbonyl, cycloalkylcarbonyl, cycloalkylcarbonyloxy, cycloalkylcarbonylamino, alkylcarbonyloxy, alkenylcarbonyloxy, amino, alkylamino, dialkylamino, arylamino, aryloxy, hydroxy, hydroxyalkyloxy, heteroarylamino, heteroaryloxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, cyano, cyanoalkylaminocarbonyl, alkoxy, alkenyloxy, hydroxy, hydroxyalkoxy, carboxy, carboxyalkyloxy, carboxyalkylamino, carboxyalkylcarbonylamino where the “alkyl” within “carboxyalkylcarbonylamino” is optionally substituted with one or two amino, alkylcarbonylamino, alkylcarbonyloxy, -S(O)₀₋₂-alkyl, -S(O)₀₋₂-alkenyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, -NR^c-SO₂-alkyl (where R^c is hydrogen, alkyl, optionally substituted alkenyl, optionally substituted alkynyl, hydroxy, alkoxy, alkenyloxy, or cyanoalkyl), alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylaminoalkyloxy, dialkylaminoalkyloxy, alkoxycarbonyl, alkenyloxycarbonyl, alkoxycarbonylamino, alkoxycarbonylalkylcarbonylamino where the “alkyl” within “alkoxycarbonylalkylcarbonylamino” is optionally substituted with one or two hydroxy, alkylaminocarbonylamino, dialkylaminocarbonylamino, dialkylaminoalkylcarbonylamino, dialkylaminocarbonylalkyloxy, alkoxyalkyloxy, alkoxyalkyloxycarbonyl,

alkoxycarbonylalkyloxy, aralkyloxycarbonyl, optionally substituted heterocycloalkyloxy, and $-C(O)NR^aR^b$ (where R^a is hydrogen, alkyl, optionally substituted alkenyl, optionally substituted alkynyl, hydroxy, alkoxy, or alkenyloxy, and R^b is hydrogen, alkyl, optionally substituted alkenyl, optionally substituted alkynyl, hydroxy, alkoxy, alkenyloxy, optionally substituted heterocycloalkyl, or heteroaryl, or R^a and R^b together with the nitrogen to which they are attached form optionally substituted heterocycloalkyl).

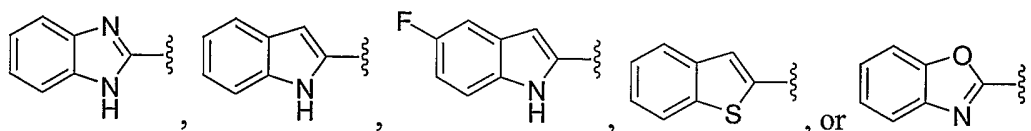
“Optionally substituted alkynyl” means an alkynyl radical, as defined herein, substituted with one or more group(s), preferably one, two, or three groups, independently selected from alkylcarbonyl, alkenylcarbonyl, cycloalkylcarbonyl, cycloalkylcarbonyloxy, cycloalkylcarbonylamino, alkylcarbonyloxy, alkenylcarbonyloxy, amino, alkylamino, dialkylamino, arylamino, aryloxy, hydroxy, hydroxyalkyloxy, heteroarylamino, heteroaryloxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, cyano, cyanoalkylaminocarbonyl, alkoxy, alkenyloxy, hydroxy, hydroxyalkoxy, carboxy, carboxyalkyloxy, carboxyalkylamino, carboxyalkylcarbonylamino where the “alkyl” within “carboxyalkylcarbonylamino” is optionally substituted with one or two amino, alkylcarbonylamino, alkylcarbonyloxy, $-S(O)_{0-2}$ -alkyl, $-S(O)_{0-2}$ -alkenyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, $-NR^c-SO_2$ -alkyl (where R^c is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, alkynyl, hydroxy, alkoxy, alkenyloxy, or cyanoalkyl), alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylaminoalkyloxy, dialkylaminoalkyloxy, alkoxycarbonyl, alkenyloxycarbonyl, alkoxycarbonylamino, alkoxycarbonylalkylcarbonylamino where the “alkyl” within “alkoxycarbonylalkylcarbonylamino” is optionally substituted with one or two hydroxy, alkylaminocarbonylamino, dialkylaminocarbonylamino, dialkylaminoalkylcarbonylamino, dialkylaminocarbonylalkyloxy, alkoxyalkyloxy, alkoxyalkyloxycarbonyl, alkoxycarbonylalkyloxy, aralkyloxycarbonyl, optionally substituted heterocycloalkyloxy, and $-C(O)NR^aR^b$ (where R^a is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, alkynyl, hydroxy, alkoxy, or alkenyloxy, and R^b is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, alkynyl, hydroxy, alkoxy, alkenyloxy, optionally substituted heterocycloalkyl, or heteroaryl, or R^a and R^b together with the nitrogen to which they are attached form optionally substituted heterocycloalkyl).

“Optionally substituted benzo” means a



radical, as represented by the ring labeled A in Formula I, where the points of fusion with the

5-membered ring are indicated by the asterisks and where the benzo ring is optionally substituted with one, two, three, or four substituents independently selected from the group consisting of alkyl, aminocarbonyl, halo, haloalkyl, optionally substituted heterocycloalkyl, cyano, amino, alkylamino, dialkylamino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, and heteroaryl. Examples of ring A together with the 5-membered ring to which A is fused include, but are not limited to,



“Optionally substituted heterocycloalkyl” means a saturated or partially unsaturated monovalent monocyclic group of 3 to 8 ring atoms or a saturated or partially unsaturated monovalent fused bicyclic group of 5 to 12 ring atoms in which one or more, preferably one, two, three, or four ring heteroatoms independently selected from -O-, -S(O)_n- (n is 0, 1, or 2), -N-, -N(R²⁰⁰)-, -Si(alkyl)₂-, -P(=S)(R²⁰¹)-, and -P(=O)(R²⁰¹)-, the remaining ring atoms being carbon. One or two ring carbon atoms may be replaced by a -C(O)-, -C(S)-, or -C(=NH)-group. R²⁰⁰ is hydrogen, alkyl, hydroxy, alkoxy, acyl, or alkylsulfonyl. R²⁰¹ is alkyl, aryl, aralkyl, cycloalkyl, or cycloalkylalkyl. Fused bicyclic radical includes bridged ring systems. Unless otherwise stated, the valency of the group may be located on any atom of any ring within the radical, valency rules permitting. In particular, when the point of valency is located on a nitrogen or phosphorous atom, R²⁰⁰ or R²⁰¹, respectively, is absent. More specifically the term optionally substituted heterocycloalkyl includes, but is not limited to, pyrrolidinyl, 2,5-dihydro-1*H*-pyrrolyl, piperidinyl, morpholinyl, piperazinyl, tetrahydropyranyl, 2-oxopiperidinyl, and thiomorpholinyl, and the derivatives thereof and N-oxide or a protected derivative thereof. Unless stated otherwise, the heterocycloalkyl ring is optionally substituted with one, two, or three substituents independently selected from optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, acyl, acyloxy, acylamino, alkoxy, alkenyloxy, alkoxycarbonyl, alkylthio, halo, hydroxy, hydroxyalkyloxy, aminoalkyloxy, alkoxyalkyloxy, amino, alkylamino, dialkylamino, nitro, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, carboxy, cyano, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonylamino, arylsulfonylamino, aminoalkoxy, optionally substituted phenyl, heterocycloalkyl, heteroaryl, -P(O)ORR' (where R and R' are independently alkyl, cycloalkyl, aryl, or heteroaryl), and -P(O)RR' (where R and R' are independently alkyl, cycloalkyl, aryl, or heteroaryl; or R and R' together with the P to which they are attached

form heterocycloalkyl or heteroaryl). Within R^{200} , R^{201} , and the above optional substituents, the alkyl, alkenyl, and alkynyl, either alone or as part of another substituent on the heterocycloalkyl ring, are independently optionally substituted with one, two, three, four, or five halo, e.g. haloalkyl, haloalkoxy, or haloalkylsulfonyl.

“Optionally substituted heterocycloalkylalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, optionally substituted heterocycloalkyl group(s) as defined herein, e.g., piperazinylmethyl or morpholinylethyl, and the like.

“Optionally substituted heterocycloalkylalkyloxy” means an -OR radical where R is optionally substituted heterocycloalkylalkyl as defined herein, e.g., tetrahydropyranylmethyloxy, and the like.

“Optionally substituted heterocycloalkyloxy” means an -OR radical where R is optionally substituted heterocycloalkyl as defined herein.

“Optionally substituted heterocycloalkylene” means a saturated or partially unsaturated divalent monocyclic group of 3 to 8 ring atoms or a saturated or partially unsaturated divalent fused bicyclic group of 5 to 12 ring atoms in which one or more, preferably one, two, three, or four ring heteroatoms independently selected from -O-, -S(O)_n- (n is 0, 1, or 2), -N-, -N(R^{200})-, -Si(alkyl)₂-, -P(=S)(R^{201})-, and -P(=O)(R^{201})-, the remaining ring atoms being carbon. One or two ring carbon atoms may be replaced by a -C(O)-, -C(S)-, or -C(=NH)- group. R^{200} is hydrogen, alkyl, hydroxy, alkoxy, acyl, or alkylsulfonyl. R^{201} is alkyl, aryl, aralkyl, cycloalkyl, or cycloalkylalkyl. Fused bicyclic radical includes bridged ring systems. Unless otherwise stated, the valency of the group may be located on any atom of any ring within the radical, valency rules permitting. In particular, when the point of valency is located on a nitrogen or phosphorous atom, R^{200} or R^{201} , respectively, is absent. More specifically the term heterocycloalkylene includes, but is not limited to, pyrrolidin-diyl, piperidin-diyl, morpholin-diyl, piperazin-diyl, tetrahydropyran-diyl, 2-oxopiperidin-diyl, and thiomorpholin-diyl, and the derivatives thereof and N-oxide or a protected derivative thereof. Unless stated otherwise, the heterocycloalkylene ring is optionally substituted with one, two, or three substituents independently selected from optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, acyl, acyloxy, acylamino, alkoxy, alkenyloxy, alkoxy carbonyl, alkylthio, halo, hydroxy, hydroxyalkyloxy, aminoalkyloxy, alkoxyalkyloxy, amino, alkylamino, dialkylamino, nitro, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, carboxy, cyano, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonylamino,

arylsulfonylamino, aminoalkoxy, optionally substituted phenyl, heterocycloalkyl, heteroaryl, -P(O)ORR' (where R and R' are independently alkyl, cycloalkyl, aryl, or heteroaryl), and -P(O)RR' (where R and R' are independently alkyl, cycloalkyl, aryl, or heteroaryl; or R and R' together with the P to which they are attached form heterocycloalkyl or heteroaryl). Within R²⁰⁰, R²⁰¹, and the above optional substituents, the alkyl, alkenyl, and alkynyl, either alone or as part of another substituent on the heterocycloalkylene ring, are independently optionally substituted with one, two, three, four, or five halo, e.g. haloalkyl, haloalkoxy, or haloalkylsulfonyl.

"Optionally substituted heterocycloalkyloxyalkyl" means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, optionally substituted heterocycloalkyloxy group(s), as defined herein.

"Optionally substituted heterocycloalkylalkyl" means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, optionally substituted heterocycloalkyl group(s), as defined herein, e.g., piperazinylmethyl or morpholinylethyl, and the like.

"Optionally substituted heterocycloalkylalkylaminocarbonyl" means a the radical -C(O)NHR where R is optionally substituted heterocycloalkylalkyl, as defined herein.

"Optionally substituted heterocycloalkylalkyloxy" means an -OR radical where R is optionally substituted heterocycloalkylalkyl as defined herein, e.g., tetrahydropyranylmethoxy, and the like.

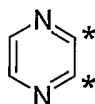
"Optionally substituted heterocycloalkylalkyloxycarbonyl" means a -C(O)R radical where R is optionally substituted heterocycloalkylalkyloxy as defined herein.

"Optionally substituted heterocycloalkylcarbonyl" means a -C(O)R radical where R is optionally substituted heterocycloalkyl as defined herein, e.g. morpholin-4-ylcarbonyl, and the like.

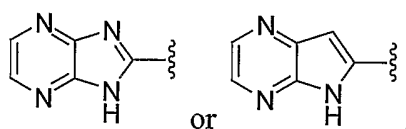
"Optionally substituted heterocycloalkyloxy" means a -OR radical where R is optionally substituted heterocycloalkyl as defined herein.

"Optionally substituted heterocycloalkyloxyalkyl" means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, optionally substituted heterocycloalkyloxy group(s), as defined herein.

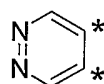
"Optionally substituted pyrazino" means a



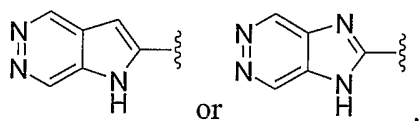
radical, as represented by the ring labeled A in Formula I, where the points of fusion with the 5-membered ring are indicated by the asterisks and where the pyrazino ring is optionally substituted with one or two substituents independently selected from the group consisting of alkyl, aminocarbonyl, halo, haloalkyl, optionally substituted heterocycloalkyl, cyano, amino, alkylamino, dialkylamino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, and heteroaryl. Examples of ring A together with the 5-membered ring to which A is fused include, but are not limited to,



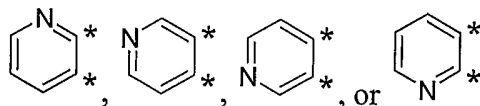
“Optionally substituted pyridazino” means a



radical, as represented by the ring labeled A in Formula I, where the points of fusion with the 5-membered ring are indicated by the asterisks and where the pyridazino ring is optionally substituted with one or two substituents selected from the group consisting of alkyl, aminocarbonyl, halo, haloalkyl, optionally substituted heterocycloalkyl, cyano, amino, alkylamino, dialkylamino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, and heteroaryl. Examples of ring A together with the 5-membered ring to which A is fused include, but are not limited to,

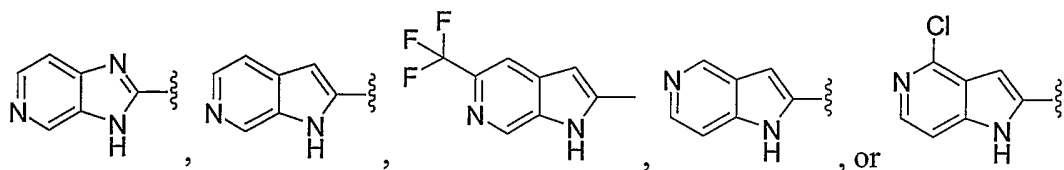


“Optionally substituted pyridino” means a

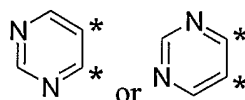


radical, as represented by the ring labeled A in Formula I, where the points of fusion with the 5-membered ring are indicated by the asterisks and where the pyridino ring is optionally substituted with one, two, or three substituents selected from the group consisting of alkyl, aminocarbonyl, halo, haloalkyl, optionally substituted heterocycloalkyl, cyano, amino, alkylamino, dialkylamino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, and heteroaryl. Examples of ring A together with the 5-membered ring to which A is fused include, but are

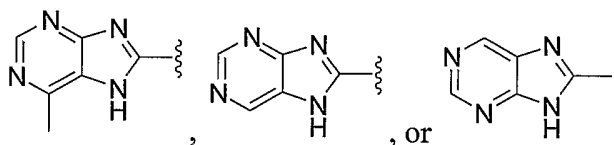
not limited to,



“Optionally substituted pyrimidino” means a



radical, as represented by the ring labeled A in Formula I, where the points of fusion with the 5-membered ring are indicated by the asterisks and where the pyrimidino ring is optionally substituted with one or two substituents selected from the group consisting of alkyl, aminocarbonyl, halo, haloalkyl, optionally substituted heterocycloalkyl, cyano, amino, alkylamino, dialkylamino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, and heteroaryl. Examples of ring A together with the 5-membered ring to which A is fused include, but are not limited to,



“Optionally substituted phenyl” means a phenyl ring optionally substituted with one, two, or three substituents independently selected from alkyl, halo, alkoxy, alkylthio, haloalkyl, haloalkoxy, heteroaryl, optionally substituted heterocycloalkyl, amino, alkylamino, dialkylamino, hydroxy, cyano, nitro, aminocarbonyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, and carboxy; or optionally substituted with five fluorine atoms.

“Optionally substituted phenylalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, optionally substituted phenyl as defined herein e.g., benzyl or phenylethyl, and the like.

“Optionally substituted phenylcarbonylamino” means a $-NR^aC(O)R$ radical where R is optionally substituted phenyl, as defined herein, and R^a is hydrogen or alkyl.

“Optionally substituted phenyloxyalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, $-OR$ radical(s), where R is optionally substituted phenyl, as defined herein.

“Partially unsaturated” describes a group which contains at least one unsaturated bond but does not contain an aromatic ring. For example, partially unsaturated cycloalkylene

includes cyclohexenyl group but not indanyl.

A “pharmaceutically acceptable carrier or excipient” means a carrier or an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes a carrier or an excipient that is acceptable for veterinary use as well as human pharmaceutical use. “A pharmaceutically acceptable carrier/excipient” as used in the specification and claims includes both one and more than one such excipient.

“Substituted,” when modifying a particular group, means that the group the term modifies must be substituted. Where the term “substituted” is used to modify a particular group, this does not mean, unless otherwise stated, that any other groups not so modified cannot be substituted. Furthermore, where a group is defined as being substituted by one of a number of enumerated alternative substituents, it does not mean, unless otherwise stated, that the group cannot be substituted further with one or more substituents not enumerated. For example, the phrase “substituted alkyl” means that the alkyl group referred to must be substituted with one or more of the substituents set forth in the definitions for “substituted alkyl.”

“Sulfonylalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two sulfonyl group(s).

“Syncytial viral infection” means an infection by a virus, such as a respiratory syncytial virus, causing the formation of a cellular protoplasmic mass, i.e. syncytia, via infection.

A “therapeutically effective amount” means the amount of a compound of Formula I that, when administered to an animal for treating a disease, is sufficient to effect such treatment for the disease. The “therapeutically effective amount” will vary depending on the compound, the disease and its severity and the age, weight, etc., of the animal to be treated.

“Treating” or “treatment” of a disease, disorder, or syndrome includes:

- (1) preventing the disease, disorder, or syndrome, i.e. causing the clinical symptoms of the disease, disorder, or syndrome not to develop in an animal that may be exposed to or predisposed to the disease, disorder, or syndrome but does not yet experience or display symptoms of the disease, disorder, or syndrome;
- (2) inhibiting the disease, disorder, or syndrome, i.e., arresting or reducing the development of the disease, disorder, or syndrome or its clinical symptoms; or
- (3) relieving the disease, disorder, or syndrome, i.e., causing regression of the disease, disorder, or syndrome or its clinical symptoms.

“Trialkylsilyl” means a the radical $-\text{Si}(\text{R})_3$ where R at each occurrence is independently an alkyl radical, as defined herein.

The present invention also includes the prodrugs of compounds of Formula I. The term prodrug is intended to represent covalently bonded carriers, which are capable of releasing the active ingredient of Formula I when the prodrug is administered to an animal subject. Release of the active ingredient occurs *in vivo*. Prodrugs can be prepared by techniques known to one skilled in the art. These techniques generally modify appropriate functional groups in a given compound. These modified functional groups however regenerate original functional groups by routine manipulation or *in vivo*. Prodrugs of compounds of Formula I include compounds wherein a hydroxy, amidino, guanidino, amino, carboxylic, or a similar group is modified. Examples of prodrugs include, but are not limited to esters (e.g., acetate, formate, and benzoate derivatives), carbamates (e.g., *N,N*-dimethylaminocarbonyl) of hydroxy or amino functional groups in compounds of Formula I), amides (e.g., trifluoroacetyl amino, acetyl amino, and the like), and the like. Prodrugs of compounds of Formula I are also within the scope of this invention.

The present invention also includes N-oxide derivatives and protected derivatives of compounds of Formula I. For example, when compounds of Formula I contain an oxidizable nitrogen atom, the nitrogen atom can be converted to an N-oxide by methods well known in the art. Also when compounds of Formula I contain groups such as hydroxy, carboxy, thiol or any group containing a nitrogen atom(s), these groups can be protected with a suitable protecting groups. A comprehensive list of suitable protective groups can be found in T.W. Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc. 1991, the disclosure of which is incorporated herein by reference in its entirety. The protected derivatives of compounds of Formula I can be prepared by methods well known in the art.

A “pharmaceutically acceptable salt” of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts include:

acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid,

2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or

salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, *N*-methylglucamine, and the like. It is understood that the pharmaceutically acceptable salts are non-toxic. Additional information on suitable pharmaceutically acceptable salts can be found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, which is incorporated herein by reference.

The compounds of the present invention may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of materials. All chiral, diastereomeric, racemic forms are within the scope of this invention, unless the specific stereochemistry or isomeric form is specifically indicated.

Certain compounds of Formula I can exist as isomers. All possible isomers are within the scope of this invention. Additionally, as used herein the terms alkyl includes all the possible isomeric forms of said alkyl group albeit only a few examples are set forth. Furthermore, when the cyclic groups such as aryl, heteroaryl, heterocycloalkyl are substituted, they include all the positional isomers albeit only a few examples are set forth.

Preferred Embodiments

1. One preferred group of compounds of Formula 1 is where

A is optionally substituted benzo, optionally substituted pyrimidino, or optionally substituted pyridino;

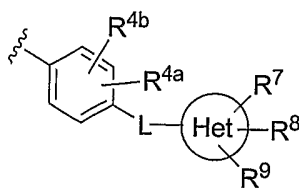
D is =N-, or =CR⁶- where R⁶ is hydrogen, halo, or carboxyalkyl;

R¹ is hydrogen;

R² is hydrogen;

R³ is hydrogen, halo, or mercaptoalkylaminocarbonylalkyl; and

R¹⁰⁰ is a group of formula (A1):



(A1)

where

R^{4a} and R^{4b} are hydrogen;

L is selected from the group consisting of:

-X¹-Y¹-Z¹- where X¹ is alkylene; Y¹ is -C(O)-, -C(O)NH-, or -NHC(O)- and Z¹ is a bond, alkylene, or alkenylene;

-X²- where X² is alkylene;

-Y²-Z²- where Y² is -C(O)NH- or -NHC(O)-; and Z² is alkylene; and

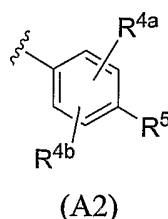
-X⁵-Y^{5a}-Z⁵-Y^{5b}- where X⁵ is alkylene; Y^{5a} is -C(O)NH- or -NHC(O)- (where R¹³ is hydrogen); Z⁵ is alkylene where the alkylene is optionally substituted with aralkyloxyalkyl; and Y^{5b} is -C(O)-;

Het is piperidinyl, piperazinyl, homopiperazinyl, pyrrolidinyl, or 4-oxo-4λ⁵-[1,4]azaphosphinanyl (where the phosphorous atom is substituted with alkyl, aryl, aralkyl, cycloalkyl, or cycloalkylalkyl); and

R⁷, R⁸, and R⁹ are independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, acyl, acylamino, acylaminoalkyloxycarbonyl, alkoxy carbonyl, alkoxyalkylaminocarbonyl, alkoxyalkyloxycarbonyl, amino, carboxy, carboxyalkylaminocarbonyl (where the "alkyl" is optionally substituted with one or two hydroxy), cyano, cyanoalkylaminocarbonyl, aryl, aryloxy, arylsulfonyl, arylthioalkylcarbonyl, aralkyl (where the alkyl is optionally substituted with one or two hydroxy), aralkyloxy, aralkyloxyaminocarbonyl, aralkyloxycarbonylamino, cycloalkylaminocarbonyl, cycloalkylalkyl (where the "alkyl" is optionally substituted with one or two hydroxy), cycloalkylalkylaminocarbonyl, cycloalkylalkyloxycarbonyl, heteroaryl, heteroarylaminocarbonyl, heteroaralkyl, halo, hydroxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, *N*-hydroxyaminocarbonyl, *N*-alkoxyaminocarbonyl, hydroxyalkylaminocarbonyl, dialkylaminoalkyloxycarbonyl, dialkylaminoalkylaminocarbonyl, arylamino, arylaminocarbonyl, alkylsulfonylamino, alkylsulfonylaminocarbonyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylaminocarbonyl, optionally substituted heterocycloalkylalkyl, optionally substituted heterocycloalkylalkyloxycarbonyl, optionally substituted

heterocycloalkylalkylaminocarbonyl, aminocarbonylamino, *N*-aryl-*N*-(alkylcarbonyl)-amino, or alkoxycarbonylalkylaminocarbonyl (where the “alkyl” is optionally substituted with one or two hydroxy); or any two of R^7 , R^8 , and R^9 attached to the same carbon atom together with the carbon to which they are attached form indanylene or optionally substituted heterocycloalkylene; and where the alkyl, alkenyl, and alkynyl in R^7 , R^8 , and R^9 , either alone or part of another group (for example, the alkyl within the group “alkoxy” or for example, any alkyl or alkenyl within the group “optionally substituted alkenyl”), independently are optionally substituted with one, two, three, four, or five halo; or

R^{100} is a group of formula (A2):



where

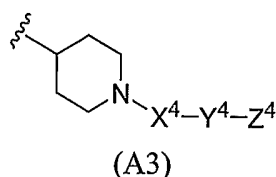
R^{4a} and R^{4b} are hydrogen;

R^5 is selected from the group consisting of:

$-Y^{11}-X^{11}-Q^{11}$ where Y^{11} is $-C(O)NR^{26a}-$, $-NR^{26a}C(O)-$, $-NR^{26a}C(O)O-$, or $-NR^{26a}C(O)NR^{26b}-$, where R^{26a} and R^{26b} are independently hydrogen or hydroxy, where X^{11} is a bond, alkylene, or alkenylene, (where X^{11} is optionally substituted with hydroxy), and where Q^{11} is heteroaryl, aryl, aryloxy, or cycloalkyl;

$-X^{12a}-Y^{12}-X^{12b}-Q^{12}$ where X^{12a} is alkylene; Y^{12} is $-C(O)NH-$, $-NHC(O)-$, or $-NHC(O)NH-$; X^{12b} is a bond, alkylene, or alkenylene where X^{12b} is optionally substituted with one, two, or three groups selected from hydroxy, cyano, halo, heteroaryl, alkoxycarbonyl, carboxy, $-NR^{27a}R^{27b}$ (where R^{27a} and R^{27b} are independently hydrogen or alkyl), $-C(O)NR^{28a}R^{28b}$ (where R^{28a} and R^{28b} are independently hydrogen, alkyl, alkoxy, or heteroaryl), and $-NHC(O)OR^{29b}$ (where R^{29b} is alkyl); and Q^{12} is aryl, aryloxy, aralkyloxy, heteroaryl, aralkylaminocarbonyl (where the alkyl is optionally substituted with alkoxycarbonyl or carboxy), cycloalkyl, cycloalkylaminocarbonyl, cycloalkylalkyloxy, $-NR^{30a}R^{30b}$ (where R^{30a} is hydrogen or alkyl and R^{30b} is aryl, heteroaryl, or cycloalkylalkyl) or $-S(O)_n-R^{31}$ (where n is 0 or 2 and R^{31} is heteroaryl, cycloalkylalkyl or aralkyl); where the alkyl within any group in Q^{12} is optionally substituted with alkoxyalkyl); or

R^{100} is a group of formula (A3):



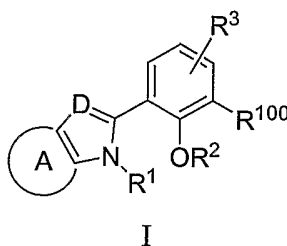
where

X^4 is alkylene;

Y^4 is $-C(O)-$;

Z^4 is heterocycloalkyl optionally substituted with one, two, three, or four groups selected from cycloalkylalkyl, alkoxycarbonyl, carboxy, aralkyl, cyano, acyl, and hydroxy; or Z^4 is $-NHR^{50b}$ where R^{50b} is $-(alkylene)-aryl$ where the alkylene is optionally substituted with one or two groups selected from alkoxycarbonyl, hydroxy, and carboxy.

2. A Compound of Formula I:



where

A is optionally substituted benzo, optionally substituted pyridino, optionally substituted pyrimidino, optionally substituted pyrazino, or optionally substituted pyridazino;

D is $=N-$ or $=CR^6-$ where R^6 is hydrogen, alkyl, halo, alkylcarbonyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkyl, alkoxycarbonylalkyl, or carboxyalkyl;

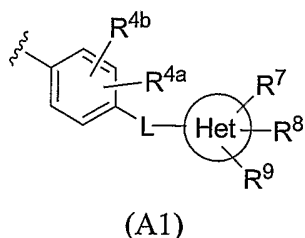
R^1 is hydrogen, alkylsulfonyl, arylsulfonyl, alkoxycarbonyl, or aralkyloxycarbonyl;

R^2 is hydrogen, alkyl, alkylsulfonyl, alkylphosphonyl, or alkoxyalkyloxyalkyl;

R^3 is hydrogen, alkyl, hydroxy, halo, cyano, haloalkoxy, haloalkyl, alkoxy, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylcarbonylamino, alkylcarbonyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonylamino, alkylaminosulfonyl, dialkylaminosulfonyl, carboxy, alkylcarbonyloxy, amino, alkylamino, dialkylamino, mercaptoalkylaminocarbonylalkyl, $R^{10a}R^{10b}NC(O)NR^{10c}-$ (where R^{10a} , R^{10b} , and R^{10c} are independently hydrogen, alkyl, or substituted alkyl), $R^{11a}R^{11b}NC(O)O-$ (where R^{11a} and R^{11b} are independently hydrogen, alkyl, or substituted

alkyl), or $R^{12a}OC(O)NR^{12b}$ - (where R^{12a} and R^{12b} are independently hydrogen, alkyl, or substituted alkyl); and

R^{100} is a group of formula (A1):



where

R^{4a} and R^{4b} are independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, hydroxy, halo, alkoxy, acyl, acyloxy, acylamino, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonylamino, alkylaminosulfonyl, dialkylaminosulfonyl, carboxy, alkylcarbonyloxy, amino, alkylamino, dialkylamino, mercaptoalkylaminocarbonylalkyl, $-NR^{19c}C(O)NR^{19a}R^{19b}$ (where R^{19a} , R^{19b} , and R^{19c} are independently hydrogen, alkyl, or substituted alkyl), $-OC(O)NR^{24a}R^{24b}$ (where R^{24a} and R^{24b} are independently hydrogen, alkyl, or substituted alkyl), or $-NR^{25b}C(O)OR^{25a}$ (where R^{25a} and R^{25b} are independently hydrogen, alkyl, or substituted alkyl); and where alkyl, alkenyl, and alkynyl, either alone or as part of another group are independently optionally substituted with one, two, three, four, or five halo; and

L is $-X^1-Y^1-Z^1$ - where X^1 is alkylene, alkenylene, or cycloalkylene and where X^1 is optionally substituted by one or two substituents selected from the group consisting of halo, hydroxy, alkoxy, alkylamino, and dialkylamino; Y^1 is $-O-$, $-NR^{13}-$, $-C(O)-$, $-C(O)O-$, $-C(O)NR^{13}-$, $-NR^{13}C(O)-$, $-C(O)NR^{13}C(O)-$, $-S-$, $-S(O)-$, $-SO_2-$, $-SO_2NR^{13}-$, $-NR^{13}SO_2-$, $-OC(O)-$, $-OC(O)NR^{13}-$, $-NR^{13}C(O)O-$, or $-NR^{13}C(O)NR^{14}-$ (where R^{13} and R^{14} are independently hydrogen, alkyl, or substituted alkyl); and Z^1 is a bond, alkylene, alkenylene, or cycloalkylene;

L is $-X^2$ - where X^2 is alkylene, alkenylene, or cycloalkylene and is optionally substituted by one or two substituents selected from the group consisting of halo, hydroxy, alkoxy, alkylamino, and dialkylamino;

L is $-Y^2-Z^2$ - where Y^2 is $-NR^{15}-$, $-C(O)-$, $-C(O)O-$, $-C(O)NR^{15}-$, $-NR^{15}C(O)-$, $-C(O)NR^{15}C(O)-$, $-S-$, $-S(O)-$, $-SO_2-$, $-SO_2NR^{15}-$, $-NR^{15}SO_2-$, $-OC(O)-$, $-OC(O)NR^{15}-$, $-NR^{15}C(O)O-$, or $-NR^{15}C(O)NR^{16}-$ (where R^{15} and R^{16} are independently hydrogen, alkyl, or substituted alkyl); and where Z^2 is alkylene, alkenylene, or cycloalkylene; and

L is $-Y^3-$ where Y^3 is $-NR^{17}-$, $-C(O)O-$, $-C(O)NR^{17}-$, $-NR^{17}C(O)-$, $-C(O)NR^{17}C(O)-$, $-S-$, $-S(O)-$, $-SO_2-$, $-SO_2NR^{17}-$, $-NR^{17}SO_2-$, $-OC(O)-$, $-OC(O)NR^{17}-$, $-NR^{17}C(O)O-$, or $-NR^{17}C(O)NR^{18}-$ (where R^{17} and R^{18} are independently hydrogen, alkyl, or substituted alkyl); or

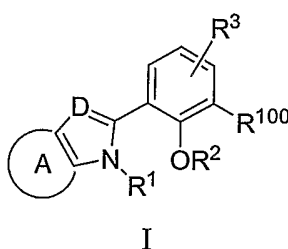
L is $-X^5-Y^{5a}-Z^5-Y^{5b}-$ where X^5 is alkylene, alkenylene, or cycloalkylene and where X^5 is optionally substituted by one or two substituents selected from the group consisting of halo, hydroxy, alkoxy, alkylamino, and dialkylamino; Y^{5a} is $-O-$, $-NR^{13}-$, $-C(O)-$, $-C(O)O-$, $-C(O)NR^{13}-$, $-NR^{13}C(O)-$, $-C(O)NR^{13}C(O)-$, $-S-$, $-S(O)-$, $-SO_2-$, $-SO_2NR^{13}-$, $-NR^{13}SO_2-$, $-OC(O)-$, $-OC(O)NR^{13}-$, $-NR^{13}C(O)O-$, or $-NR^{13}C(O)NR^{14}-$ (where R^{13} and R^{14} are independently hydrogen, alkyl, or substituted alkyl); Z^5 is a bond, alkylene, alkenylene, or cycloalkylene where the alkylene or alkenylene are optionally substituted with aralkyloxyalkyl; and Y^{5b} is $-C(O)-$;

Het is heterocycloalkyl; and

R^7 , R^8 , and R^9 are independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, acyl, acylamino, acyloxy, acylaminoalkyloxycarbonyl, alkylthio, alkylsulfonyl, alkoxy, alkoxycarbonyl, alkoxyalkylamino, alkoxyalkylaminocarbonyl, alkoxyalkyloxy, alkoxyalkyloxycarbonyl, amino, alkylamino, dialkylamino, aminoalkyloxy, carboxy, carboxyalkylaminocarbonyl where the "alkyl" is optionally substituted with one or two hydroxy, cyano, cyanoalkylaminocarbonyl, aryl, aryloxy, arylsulfonyl, arylthioalkylcarbonyl, aralkyl where the alkyl is optionally substituted with one or two hydroxy, aralkyloxy, aralkyloxycarbonyl, aralkyloxyaminocarbonyl, aralkyloxycarbonylamino, aralkenyl, cycloalkyl, cycloalkyloxy, cycloalkylaminocarbonyl, cycloalkylalkyl where the "alkyl" is optionally substituted with one or two hydroxy, cycloalkylalkylaminocarbonyl, cycloalkylalkyloxycarbonyl, heteroaryl, heteroarylaminocarbonyl, heteroaralkyl, heteroaralkenyl, heteroaralkyloxy, halo, hydroxy, hydroxyalkyloxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, *N*-hydroxyaminocarbonyl, *N*-alkoxyaminocarbonyl, hydroxyalkylaminocarbonyl, dialkylaminoalkyloxycarbonyl, dialkylaminoalkylaminocarbonyl, arylamino, arylaminocarbonyl, alkylsulfonylamino, alkylsulfonylaminocarbonyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkyloxy, optionally substituted heterocycloalkylaminocarbonyl, optionally substituted heterocycloalkylalkyl, optionally substituted heterocycloalkylalkyloxy, optionally substituted heterocycloalkylalkyloxycarbonyl, optionally substituted heterocycloalkylalkylaminocarbonyl, aminocarbonylamino, *N*-aryl-*N*-(alkylcarbonyl)-amino,

N-(alkylsulfonyl)-*N*-alkyl-amino, alkoxycarbonylalkylaminocarbonyl where the “alkyl” is optionally substituted with one or two hydroxy, or trialkylsilyl; or any two of R^7 , R^8 , and R^9 attached to the same carbon atom together with the carbon to which they are attached form indanylene or optionally substituted heterocycloalkylene; and where the alkyl, alkenyl, and alkynyl in R^7 , R^8 , and R^9 , either alone or part of another group, independently are optionally substituted with one, two, three, four, or five halo; or a pharmaceutically acceptable salt thereof.

3. A Compound of Formula I:



where

A is optionally substituted benzo, optionally substituted pyridino, optionally substituted pyrimidino, optionally substituted pyrazino, or optionally substituted pyridazino;

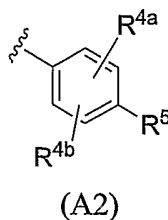
D is =N- or =CR⁶- where R⁶ is hydrogen, alkyl, halo, alkylcarbonyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkyl, alkoxycarbonylalkyl, or carboxyalkyl;

R¹ is hydrogen, alkylsulfonyl, arylsulfonyl, alkoxycarbonyl, or aralkyloxycarbonyl;

R² is hydrogen, alkyl, alkylsulfonyl, alkylphosphonyl, or alkoxyalkyloxyalkyl;

R³ is hydrogen, alkyl, hydroxy, halo, cyano, haloalkoxy, haloalkyl, alkoxy, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylcarbonylamino, alkylcarbonyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonylamino, alkylaminosulfonyl, dialkylaminosulfonyl, carboxy, alkylcarbonyloxy, amino, alkylamino, dialkylamino, mercaptoalkylaminocarbonylalkyl, R^{10a}R^{10b}NC(O)NR^{10c}- (where R^{10a}, R^{10b}, and R^{10c} are independently hydrogen, alkyl, or substituted alkyl), R^{11a}R^{11b}NC(O)O- (where R^{11a} and R^{11b} are independently hydrogen, alkyl, or substituted alkyl), or R^{12a}OC(O)NR^{12b}- (where R^{12a} and R^{12b} are independently hydrogen, alkyl, or substituted alkyl); and

R^{100} is a group of formula (A2):



where

R^{4a} and R^{4b} are as defined above;

R^5 is $-Y^{11}-X^{11}-Q^{11}$ where Y^{11} is $-S(O)-$, $-SO_2-$, $-NR^{26a}SO_2-$, $-SO_2NR^{26a}-$, $-C(O)NR^{26a}-$, $-NR^{26a}C(O)-$, $-OC(O)-$, $-OC(O)NR^{26a}-$, $-NR^{26a}C(O)O-$, $-C(O)NR^{26a}C(O)-$, or $-NR^{26a}C(O)NR^{26b}-$, where R^{26a} and R^{26b} are independently hydrogen, alkyl, haloalkyl, hydroxy, alkoxy, haloalkoxy, or acyl, where X^{11} is a bond, alkylene, or alkenylene, (where X^{11} is optionally substituted with hydroxy, alkoxy, alkoxy, or acyl), and where Q^{11} is heteroaryl, aryl, aryloxy, or cycloalkyl;

R^5 is $-X^{12a}-Y^{12}-X^{12b}-Q^{12}$ where X^{12a} is alkylene or alkenylene; Y^{12} is $-NR^{26a}-$, $-O-$, $-C(O)-$, $-C(O)O-$, $-S-$, $-S(O)-$, $-SO_2-$, $-NR^{26a}SO_2-$, $-SO_2NR^{26a}-$, $-C(O)NR^{26a}-$, $-NR^{26a}C(O)-$, $-OC(O)-$, $-OC(O)NR^{26a}-$, $-NR^{26a}C(O)O-$, $-C(O)NR^{26a}C(O)-$, or $-NR^{26a}C(O)NR^{26b}-$, where R^{26a} and R^{26b} are as defined above; X^{12b} is a bond, alkylene, or alkenylene where X^{12b} is optionally substituted with one, two, or three groups selected from hydroxy, cyano, halo, heteroaryl, alkylcarbonyl, alkoxy, alkoxyalkyl, heteroaryl, or heteroarylamino, $-C(O)NR^{28a}R^{28b}$ (where R^{28a} and R^{28b} are independently hydrogen, alkyl, alkenyl, alkoxy, alkenyloxy, alkoxyalkyl, hydroxy, or heteroaryl), and $-NR^{29a}C(O)OR^{29b}$ (where R^{29a} is hydrogen, alkyl, alkenyl, alkoxy, alkenyloxy, alkoxyalkyl, or hydroxy, and R^{29b} is alkyl); and Q^{12} is aryl, aryloxy, aralkyloxy, heteroaryl, aralkylaminocarbonyl (where the alkyl is optionally substituted with alkoxy, alkoxy, or carboxy), cycloalkyl, cycloalkylaminocarbonyl, cycloalkylalkyloxy, $-NR^{30a}R^{30b}$ (where R^{30a} is hydrogen or alkyl and R^{30b} is aryl, heteroaryl, or cycloalkylalkyl) or $-S(O)_n-R^{31}$ (where n is 0, 1, or 2 and R^{31} is heteroaryl, cycloalkylalkyl or aralkyl); where the alkyl within any group in Q^{12} is optionally substituted with alkoxyalkyl);

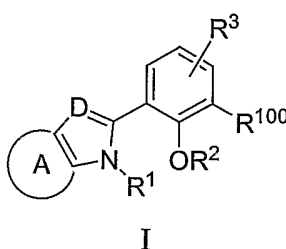
R^5 is $-X^{13}-Y^{13}-Z^{13}$ where X^{13} is alkylene or alkenylene, where Y^{13} is $-NR^{26a}-$, $-O-$, $-C(O)-$, $-C(O)O-$, $-S-$, $-S(O)-$, $-SO_2-$, $-NR^{26a}SO_2-$, $-SO_2NR^{26a}-$, $-C(O)NR^{26a}-$, $-NR^{26a}C(O)-$, $-OC(O)-$, $-OC(O)NR^{26a}-$, $-NR^{26a}C(O)O-$, $-C(O)NR^{26a}C(O)-$, or $-NR^{26a}C(O)NR^{26b}-$, where R^{26a} and R^{26b} are as defined above, and where Z^{13} is hydrogen, alkyl, or alkenyl (where Z^{13} is

optionally substituted with one, two, or three halo, hydroxy, amino, alkoxy, alkoxycarbonyl, carboxy, or alkylcarbonylamino); or

R^5 is $-Y^{14}-Z^{14}$ where Y^{14} is $-S(O)-$, $-NR^{26a}C(O)-$, $-C(O)NR^{26a}-$, $-NR^{26a}C(O)NR^{26b}-$, $-C(O)NR^{26a}C(O)-$, $-NR^{26a}C(O)O-$, $-OC(O)NR^{26a}$, or $-OC(O)-$, where R^{26a} and R^{26b} are as defined above, and where Z^{14} is alkyl or alkenyl (where Z^{14} is optionally substituted with one, two, or three halo, hydroxy, amino, alkoxy, alkoxycarbonyl, carboxy, or alkylcarbonylamino);

or a pharmaceutically acceptable salt thereof.

4. A Compound of Formula I:



where

A is optionally substituted benzo, optionally substituted pyridino, optionally substituted pyrimidino, optionally substituted pyrazino, or optionally substituted pyridazino;

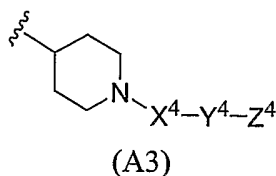
D is $=N-$ or $=CR^6-$ where R^6 is hydrogen, alkyl, halo, alkylcarbonyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkyl, alkoxycarbonylalkyl, or carboxyalkyl;

R^1 is hydrogen, alkylsulfonyl, arylsulfonyl, alkoxycarbonyl, or aralkyloxycarbonyl;

R^2 is hydrogen, alkyl, alkylsulfonyl, alkylphosphonyl, or alkoxyalkyloxyalkyl;

R^3 is hydrogen, alkyl, hydroxy, halo, cyano, haloalkoxy, haloalkyl, alkoxy, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylcarbonylamino, alkylcarbonyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonylamino, alkylaminosulfonyl, dialkylaminosulfonyl, carboxy, alkylcarbonyloxy, amino, alkylamino, dialkylamino, mercaptoalkylaminocarbonylalkyl, $R^{10a}R^{10b}NC(O)NR^{10c}-$ (where R^{10a} , R^{10b} , and R^{10c} are independently hydrogen, alkyl, or substituted alkyl), $R^{11a}R^{11b}NC(O)O-$ (where R^{11a} and R^{11b} are independently hydrogen, alkyl, or substituted alkyl), or $R^{12a}OC(O)NR^{12b}-$ (where R^{12a} and R^{12b} are independently hydrogen, alkyl, or substituted alkyl); and

R^{100} is a group of formula (A3):



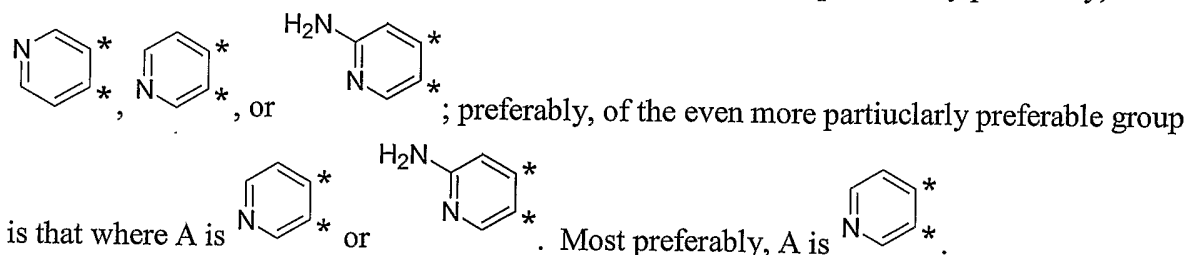
where

X^4 is alkylene optionally substituted with one, two, three, four, or five halo;

Y^4 is $-C(O)-$, $-NR^{32}C(O)-$, $-S(O)_2-$, or a bond;

Z^4 is heterocycloalkyl optionally substituted with one, two, three, or four groups selected from cycloalkyl, cycloalkylalkyl, alkoxycarbonyl, carboxy, aryl, aralkyl, cyano, arylcarbonyl, alkoxy, and hydroxy; or Z^4 is $-NR^{50a}R^{50b}$ where R^{50a} is hydrogen, alkyl, alkoxy, or hydroxy and R^{50b} is $-(alkylene)-aryl$ where the alkylene is optionally substituted with one or two groups selected from halo, alkoxycarbonyl, hydroxy, and carboxy; or a pharmaceutically acceptable salt thereof.

5. Another preferred group of compounds of Formula 1 is where A is optionally substituted benzo, optionally substituted pyridino, optionally substituted pyrimidino, optionally substituted pyrazino, or optionally substituted pyridazino. Preferably, A is optionally substituted benzo, optionally substituted pyridino, or optionally substituted pyrimidino. More preferably, A is unsubstituted pyridino or pyridino substituted with halo, amino, aminocarobnyl, or heteroaryl. Even more preferably, A is unsubstituted pyridino or pyridino substituted with chloro, amino, aminocarobnyl, or 5-methyl-[1,2,4]oxadiazol-3-yl. Particularly preferably, A is unsubstituted pyridino. Even more particularly preferably, A is

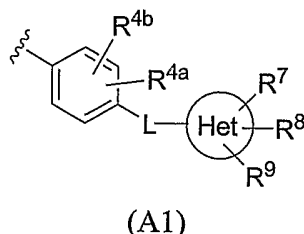


6. Another preferred group of compounds of Formula 1 is where D is $=N-$, or $=CR^6-$ where R^6 is hydrogen, alkyl, halo, alkylcarbonyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkyl, alkoxycarbonylalkyl, or carboxyalkyl. Preferably, D is $=N-$ or $=CR^6-$ where R^6 is hydrogen, halo, or carboxyalkyl. More preferably, D is $=N-$ or $=CH-$. Even more preferably, D is $=CH-$.

7. Another preferred group of compounds of Formula 1 is where R^1 is hydrogen, alkylsulfonyl, arylsulfonyl, alkoxycarbonyl, or aralkyloxycarbonyl. Preferably, R^1 is hydrogen or alkylsulfonyl. More preferably, R^1 is hydrogen or methylsulfonyl. Even more preferably, R^1 is hydrogen.
8. Another preferred group of compounds of Formula 1 is where R^2 is hydrogen, alkyl, alkylsulfonyl, alkylphosphonyl, or alkoxyalkyloxyalkyl. Preferably, R^2 is hydrogen or alkoxyalkyloxyalkyl. More preferably, R^2 is hydrogen or $-\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$. Even more preferably, R^2 is hydrogen.
9. Another preferred group of compounds of Formula 1 is where R^3 is hydrogen, alkyl, hydroxy, halo, cyano, haloalkoxy, haloalkyl, alkoxy, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylcarbonylamino, alkylcarbonyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonylamino, alkylaminosulfonyl, dialkylaminosulfonyl, carboxy, alkylcarbonyloxy, amino, alkylamino, dialkylamino, mercaptoalkylaminocarbonylalkyl, $R^{10a}R^{10b}\text{NC(O)NR}^{10c}$ - (where R^{10a} , R^{10b} , and R^{10c} are independently hydrogen, alkyl, or substituted alkyl), $R^{11a}R^{11b}\text{NC(O)O}$ - (where R^{11a} and R^{11b} are independently hydrogen, alkyl, or substituted alkyl), or $R^{12a}\text{OC(O)NR}^{12b}$ - (where R^{12a} and R^{12b} are independently hydrogen, alkyl, or substituted alkyl). Preferably, R^3 is hydrogen, halo, or mercaptoalkylaminocarbonylalkyl. More preferably, R^3 is hydrogen or chloro. Even more preferably, R^3 is hydrogen.
10. Another preferred group of compounds of Formula 1 is where R^{4a} and R^{4b} are independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, hydroxy, halo, alkoxy, acyl, acyloxy, acylamino, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonylamino, alkylaminosulfonyl, dialkylaminosulfonyl, carboxy, alkylcarbonyloxy, amino, alkylamino, dialkylamino, mercaptoalkylaminocarbonylalkyl, $-\text{NR}^{19c}\text{C(O)NR}^{19a}R^{19b}$ (where R^{19a} , R^{19b} , and R^{19c} are independently hydrogen, alkyl, or substituted alkyl), $-\text{OC(O)NR}^{24a}R^{24b}$ (where R^{24a} and R^{24b} are independently hydrogen, alkyl, or substituted alkyl), or $-\text{NR}^{25b}\text{C(O)OR}^{25a}$ (where R^{25a} and R^{25b} are independently hydrogen, alkyl, or substituted alkyl); and where alkyl, alkenyl, and alkynyl, either alone or as part of another group are independently optionally substituted with

one, two, three, four, or five halo. Preferably, R^{4a} and R^{4b} are hydrogen.

11. Another preferred group of compounds of Formula 1 is where R^{100} is a group of formula (A1):



where

R^{4a} and R^{4b} are independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, hydroxy, halo, alkoxy, acyl, acyloxy, acylamino, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonylamino, alkylaminosulfonyl, dialkylaminosulfonyl, carboxy, alkylcarbonyloxy, amino, alkylamino, dialkylamino, mercaptoalkylaminocarbonylalkyl, $-NR^{19c}C(O)NR^{19a}R^{19b}$ (where R^{19a} , R^{19b} , and R^{19c} are independently hydrogen, alkyl, or substituted alkyl), $-OC(O)NR^{24a}R^{24b}$ (where R^{24a} and R^{24b} are independently hydrogen, alkyl, or substituted alkyl), or $-NR^{25b}C(O)OR^{25a}$ (where R^{25a} and R^{25b} are independently hydrogen, alkyl, or substituted alkyl); and where alkyl, alkenyl, and alkynyl, either alone or as part of another group are independently optionally substituted with one, two, three, four, or five halo; and

L is $-X^1-Y^1-Z^1-$ where X^1 is alkylene, alkenylene, or cycloalkylene and where X^1 is optionally substituted by one or two substituents selected from the group consisting of halo, hydroxy, alkoxy, alkylamino, and dialkylamino; Y^1 is $-O-$, $-NR^{13}-$, $-C(O)-$, $-C(O)O-$, $-C(O)NR^{13}-$, $-NR^{13}C(O)-$, $-C(O)NR^{13}C(O)-$, $-S-$, $-S(O)-$, $-SO_2-$, $-SO_2NR^{13}-$, $-NR^{13}SO_2-$, $-OC(O)-$, $-OC(O)NR^{13}-$, $-NR^{13}C(O)O-$, or $-NR^{13}C(O)NR^{14}-$ (where R^{13} and R^{14} are independently hydrogen, alkyl, or substituted alkyl); and Z^1 is a bond, alkylene, alkenylene, or cycloalkylene;

L is $-X^2-$ where X^2 is alkylene, alkenylene, or cycloalkylene and is optionally substituted by one or two substituents selected from the group consisting of halo, hydroxy, alkoxy, alkylamino, and dialkylamino;

L is $-Y^2-Z^2-$ where Y^2 is $-NR^{15}-$, $-C(O)-$, $-C(O)O-$, $-C(O)NR^{15}-$, $-NR^{15}C(O)-$, $-C(O)NR^{15}C(O)-$, $-S-$, $-S(O)-$, $-SO_2-$, $-SO_2NR^{15}-$, $-NR^{15}SO_2-$, $-OC(O)-$, $-OC(O)NR^{15}-$, $-NR^{15}C(O)O-$, or $-NR^{15}C(O)NR^{16}-$ (where R^{15} and R^{16} are independently hydrogen, alkyl, or

substituted alkyl); and where Z^2 is alkylene, alkenylene, or cycloalkylene; and

L is $-Y^3-$ where Y^3 is $-NR^{17}-$, $-C(O)O-$, $-C(O)NR^{17}-$, $-NR^{17}C(O)-$, $-C(O)NR^{17}C(O)-$, $-S-$, $-S(O)-$, $-SO_2-$, $-SO_2NR^{17}-$, $-NR^{17}SO_2-$, $-OC(O)-$, $-OC(O)NR^{17}-$, $-NR^{17}C(O)O-$, or $-NR^{17}C(O)NR^{18}-$ (where R^{17} and R^{18} are independently hydrogen, alkyl, or substituted alkyl); or

L is $-X^5-Y^{5a}-Z^5-Y^{5b}-$ where X^5 is alkylene, alkenylene, or cycloalkylene and where X^5 is optionally substituted by one or two substituents selected from the group consisting of halo, hydroxy, alkoxy, alkylamino, and dialkylamino; Y^{5a} is $-O-$, $-NR^{13}-$, $-C(O)-$, $-C(O)O-$, $-C(O)NR^{13}-$, $-NR^{13}C(O)-$, $-C(O)NR^{13}C(O)-$, $-S-$, $-S(O)-$, $-SO_2-$, $-SO_2NR^{13}-$, $-NR^{13}SO_2-$, $-OC(O)-$, $-OC(O)NR^{13}-$, $-NR^{13}C(O)O-$, or $-NR^{13}C(O)NR^{14}-$ (where R^{13} and R^{14} are independently hydrogen, alkyl, or substituted alkyl); Z^5 is a bond, alkylene, alkenylene, or cycloalkylene where the alkylene or alkenylene are optionally substituted with aralkyloxyalkyl; and Y^{5b} is $-C(O)-$;

Het is heterocycloalkyl; and

R^7 , R^8 , and R^9 are independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, acyl, acylamino, acyloxy, acylaminoalkyloxycarbonyl, alkylthio, alkylsulfonyl, alkoxy, alkoxycarbonyl, alkoxyalkylamino, alkoxyalkylaminocarbonyl, alkoxyalkyloxy, alkoxyalkyloxycarbonyl, amino, alkylamino, dialkylamino, aminoalkyloxy, carboxy, carboxyalkylaminocarbonyl where the "alkyl" is optionally substituted with one or two hydroxy, cyano, cyanoalkylaminocarbonyl, aryl, aryloxy, arylsulfonyl, arylthioalkylcarbonyl, aralkyl where the alkyl is optionally substituted with one or two hydroxy, aralkyloxy, aralkyloxycarbonyl, aralkyloxyaminocarbonyl, aralkyloxycarbonylamino, aralkenyl, cycloalkyl, cycloalkyloxy, cycloalkylaminocarbonyl, cycloalkylalkyl where the "alkyl" is optionally substituted with one or two hydroxy, cycloalkylalkylaminocarbonyl, cycloalkylalkyloxycarbonyl, heteroaryl, heteroarylaminocarbonyl, heteroaralkyl, heteroaralkenyl, heteroaralkyloxy, halo, hydroxy, hydroxyalkyloxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, *N*-hydroxyaminocarbonyl, *N*-alkoxyaminocarbonyl, hydroxyalkylaminocarbonyl, dialkylaminoalkyloxycarbonyl, dialkylaminoalkylaminocarbonyl, arylamino, arylaminocarbonyl, alkylsulfonylamino, alkylsulfonylaminocarbonyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkyloxy, optionally substituted heterocycloalkylaminocarbonyl, optionally substituted heterocycloalkylalkyl, optionally substituted heterocycloalkylalkyloxy, optionally substituted heterocycloalkylalkyloxycarbonyl, optionally substituted

heterocycloalkylalkylaminocarbonyl, aminocarbonylamino, *N*-aryl-*N*-(alkylcarbonyl)-amino, *N*-(alkylsulfonyl)-*N*-alkyl-amino, alkoxycarbonylalkylaminocarbonyl where the "alkyl" is optionally substituted with one or two hydroxy, or trialkylsilyl; or any two of R⁷, R⁸, and R⁹ attached to the same carbon atom together with the carbon to which they are attached form indanylene or optionally substituted heterocycloalkylene; and where the alkyl, alkenyl, and alkynyl in R⁷, R⁸, and R⁹, either alone or part of another group, independently are optionally substituted with one, two, three, four, or five halo.

Preferably, R^{4a} and R^{4b} are hydrogen; L is -X¹-Y¹-Z¹- where X¹ is alkylene, Y¹ is -C(O)-, -C(O)NH-, or -NHC(O)-, and Z¹ is a bond, alkylene, or alkenylene; or L is -X²- where X² is alkylene; or L is -Y²-Z²- where Y² is -C(O)NH- or -NHC(O)-; and Z² is alkylene; or L is -X⁵-Y^{5a}-Z⁵-Y^{5b}- where X⁵ is alkylene; Y^{5a} is -C(O)NH- or -NHC(O)-; Z⁵ is alkylene where the alkylene is optionally substituted with aralkyloxyalkyl; and Y^{5b} is -C(O)-; Het is piperidinyl, piperazinyl, homopiperazinyl, pyrrolidinyl, or 4-oxo-4λ⁵-[1,4]azaphosphinanyl (where the phosphorous atom is substituted with alkyl, aryl, aralkyl, cycloalkyl, or cycloalkylalkyl); R⁷ and R⁸ are independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, acyl, acylamino, acylaminoalkyloxycarbonyl, alkoxycarbonyl, alkoxyalkylaminocarbonyl, alkoxyalkyloxycarbonyl, amino, carboxy, carboxyalkylaminocarbonyl (where the "alkyl" is optionally substituted with one or two hydroxy), cyano, cyanoalkylaminocarbonyl, aryl, aryloxy, arylsulfonyl, arylthioalkylcarbonyl, aralkyl (where the alkyl is optionally substituted with one or two hydroxy), aralkyloxy, aralkyloxyaminocarbonyl, aralkyloxycarbonylamino, cycloalkylaminocarbonyl, cycloalkylalkyl (where the "alkyl" is optionally substituted with one or two hydroxy), cycloalkylalkylaminocarbonyl, cycloalkylalkyloxycarbonyl, heteroaryl, heteroarylaminocarbonyl, heteroaralkyl, halo, hydroxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, *N*-hydroxyaminocarbonyl, *N*-alkoxyaminocarbonyl, hydroxyalkylaminocarbonyl, dialkylaminoalkyloxycarbonyl, dialkylaminoalkylaminocarbonyl, arylamino, arylaminocarbonyl, alkylsulfonylamino, alkylsulfonylaminocarbonyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylaminocarbonyl, optionally substituted heterocycloalkylalkyl, optionally substituted heterocycloalkylalkyloxycarbonyl, optionally substituted heterocycloalkylalkylaminocarbonyl, aminocarbonylamino, *N*-aryl-*N*-(alkylcarbonyl)-amino, or alkoxycarbonylalkylaminocarbonyl (where the "alkyl" is optionally substituted with one or two hydroxy); or any two of R⁷, R⁸, and R⁹ attached to the same carbon atom together with

the carbon to which they are attached form indanylene or optionally substituted heterocycloalkylene; and where the alkyl, alkenyl, and alkynyl in R^7 , R^8 , and R^9 , either alone or part of another group, independently are optionally substituted with one, two, three, four, or five halo; and R^9 is hydrogen.

More preferably, R^{4a} and R^{4b} are hydrogen; L is $-X^1-Y^1-Z^1-$ where X^1 is alkylene, Y^1 is $-C(O)-$ or $-C(O)NH-$, and Z^1 is a bond or alkylene; Het is piperidiny, piperaziny, *N*-oxide of piperaziny, pyrrolidiny, or 4-oxo-4 λ^5 -[1,4]azaphosphinany (where the phosphorous atom is substituted with alkyl, aralkyl, or cycloalkylalkyl); R^7 and R^8 are independently hydrogen, optionally substituted alkyl (preferably alkyl substituted with one or two alkoxyalkyloxycarbonyl, dialkylaminoalkyloxy, hydroxy or carboxy), optionally substituted alkenyl (preferably alkenyl), alkoxy, carboxy, aralkyl, aralkyloxy, heteroaryl, heteroaralkyl, hydroxy, alkylsulfonylaminocarbonyl, alkoxyalkylaminocarbonyl, optionally substituted heterocycloalkyl, cycloalkylalkyl, amino, acyl (preferably optionally substituted heterocycloalkylcarbonyl), alkoxyalkyloxycarbonyl, dialkylaminoalkyloxycarbonyl, optionally substituted heterocycloalkylalkyloxycarbonyl, dialkylaminoalkylaminocarbonyl, or cyano; and R^9 is hydrogen.

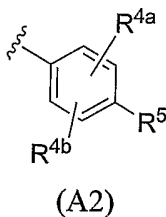
Even more preferably, R^{4a} and R^{4b} are hydrogen; L is $-CH_2C(O)-$; Het is piperidiny, *N*-oxide of piperaziny, or 4-oxo-4 λ^5 -[1,4]azaphosphinany (where the phosphorous atom is substituted with aralkyl or cycloalkylalkyl); R^7 and R^8 are independently hydrogen, phenylmethyl, methoxycarbonyl, carboxy, fluorophenylmethyl, fluorophenylmethyl, thienyl, methylsulfonylaminocarbonyl, 2-oxo-1,3-dihydro-benzoimidazol-1-yl, allyl, hydroxy, tetrazolyl, fluorophenylmethoxy, *N*-(methoxycarbonylmethyl)-aminocarbonyl, 5-oxo-4*H*-[1,2,4]oxadiazolyl, amino, pyrrolidinylcarbonyl, 2-(methoxy)-ethyloxycarbonyl, 2-(methoxy)-ethyloxycarbonylmethyl, 2-(*N,N*-diethylamino)-ethyloxycarbonyl, 2-(morpholin-4-yl)-ethyloxycarbonyl, 2-(*N,N*-diethylamino)-ethylaminocarbonyl, cyano, 2-(*N,N*-diethylamino)-ethyloxymethyl, cyclopropylmethyl, or carboxyalkyl where the alkyl is substituted with hydroxy; and R^9 is hydrogen.

Particularly preferably, R^{4a} and R^{4b} are hydrogen; L is $-CH_2C(O)-$; Het is piperidiny, *N*-oxide of piperaziny, or 4-oxo-4 λ^5 -[1,4]azaphosphinany (where the phosphorous atom is substituted with fluorophenylalkyl); R^7 and R^8 are independently hydrogen, phenylmethyl, methoxycarbonyl, carboxy, 2-fluorophenylmethyl, 3-fluorophenylmethyl, 4-fluorophenylmethyl, 3,4-difluorophenylmethyl, thien-3-yl, hydroxy, methylsulfonylaminocarbonyl, 2-oxo-1,3-dihydro-benzoimidazol-1-yl, allyl, tetrazolyl,

4-fluorophenylmethoxy, *N*-(methoxycarbonylmethyl)-aminocarbonyl, 5-oxo-4*H*-[1,2,4]oxadiazolyl, amino, pyrrolidinylcarbonyl, 2-(methoxy)-ethyloxycarbonyl, 2-(methoxy)-ethyloxycarbonylmethyl, 2-(*N,N*-diethylamino)-ethyloxycarbonyl, 2-(morpholin-4-yl)-ethyloxycarbonyl, 2-(*N,N*-diethylamino)-ethylaminocarbonyl, cyano, 2-(*N,N*-diethylamino)-ethyloxymethyl, cyclopropylmethyl, 1-carboxy-1-hydroxymethyl; and R^9 is hydrogen. More preferably, R^7 and R^8 are independently hydrogen, 3,4-difluorophenylmethyl, carboxy, cyclopropylmethyl, cyano, or 4-fluorophenylmethyl; and R^9 is hydrogen.

Even more particularly preferably, -Het(R^7)(R^8) is 4-carboxy-4-(3,4-difluorophenylmethyl)-piperidin-1-yl, 4-carboxy-4-(cyclopropylmethyl)-piperidin-1-yl, 4-cyano-4-(cyclopropylmethyl)-piperidin-1-yl, 4-(4-fluorophenylmethyl)-4-oxo-4 λ^5 -[1,4]azaphosphinanyl, or 4-(4-fluorophenylmethyl)-4-oxy-piperazin-1-yl.

12. Another preferred group of compounds of Formula 1 is where R^{100} is a group of formula (A2):



where

R^{4a} and R^{4b} are independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, hydroxy, halo, alkoxy, acyl, acyloxy, acylamino, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonylamino, alkylaminosulfonyl, dialkylaminosulfonyl, carboxy, alkylcarbonyloxy, amino, alkylamino, dialkylamino, mercaptoalkylaminocarbonylalkyl, $-NR^{19c}C(O)NR^{19a}R^{19b}$ (where R^{19a} , R^{19b} , and R^{19c} are independently hydrogen, alkyl, or substituted alkyl), $-OC(O)NR^{24a}R^{24b}$ (where R^{24a} and R^{24b} are independently hydrogen, alkyl, or substituted alkyl), or $-NR^{25b}C(O)OR^{25a}$ (where R^{25a} and R^{25b} are independently hydrogen, alkyl, or substituted alkyl); and where alkyl, alkenyl, and alkynyl, either alone or as part of another group are independently optionally substituted with one, two, three, four, or five halo; and

R^5 is $-Y^{11}-X^{11}-Q^{11}$ where Y^{11} is $-S(O)-$, $-SO_2-$, $-NR^{26a}SO_2-$, $-SO_2NR^{26a}-$, $-C(O)NR^{26a}-$, $-NR^{26a}C(O)-$, $-OC(O)-$, $-OC(O)NR^{26a}-$, $-NR^{26a}C(O)O-$, $-C(O)NR^{26a}C(O)-$, or

$-\text{NR}^{26a}\text{C}(\text{O})\text{NR}^{26b}-$, where R^{26a} and R^{26b} are independently hydrogen, alkyl, haloalkyl, hydroxy, alkoxy, haloalkoxy, or acyl, where X^{11} is a bond, alkylene, or alkenylene, (where X^{11} is optionally substituted with hydroxy, alkoxy, carbonyl, carboxy), and where Q^{11} is heteroaryl, aryl, aryloxy, or cycloalkyl;

R^5 is $-\text{X}^{12a}-\text{Y}^{12}-\text{X}^{12b}-\text{Q}^{12}$ where X^{12a} is alkylene or alkenylene; Y^{12} is $-\text{NR}^{26a}-$, $-\text{O}-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})-$, $-\text{SO}_2-$, $-\text{NR}^{26a}\text{SO}_2-$, $-\text{SO}_2\text{NR}^{26a}-$, $-\text{C}(\text{O})\text{NR}^{26a}-$, $-\text{NR}^{26a}\text{C}(\text{O})-$, $-\text{OC}(\text{O})-$, $-\text{OC}(\text{O})\text{NR}^{26a}-$, $-\text{NR}^{26a}\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{O})\text{NR}^{26a}\text{C}(\text{O})-$, or $-\text{NR}^{26a}\text{C}(\text{O})\text{NR}^{26b}-$, where R^{26a} and R^{26b} are as defined above; X^{12b} is a bond, alkylene, or alkenylene where X^{12b} is optionally substituted with one, two, or three groups selected from hydroxy, cyano, halo, heteroaryl, alkylcarbonyl, alkoxy, alkoxyalkyl, heteroaryl, or heteroarylaminocarbonyl), $-\text{C}(\text{O})\text{NR}^{28a}\text{R}^{28b}$ (where R^{28a} and R^{28b} are independently hydrogen, alkyl, alkenyl, alkoxy, alkenyloxy, alkoxyalkyl, hydroxy, or heteroaryl), and $-\text{NR}^{29a}\text{C}(\text{O})\text{OR}^{29b}$ (where R^{29a} is hydrogen, alkyl, alkenyl, alkoxy, alkenyloxy, alkoxyalkyl, or hydroxy, and R^{29b} is alkyl); and Q^{12} is aryl, aryloxy, aralkyloxy, heteroaryl, aralkylaminocarbonyl (where the alkyl is optionally substituted with alkoxy, carbonyl, or carboxy), cycloalkyl, cycloalkylaminocarbonyl, cycloalkylalkyloxy, $-\text{NR}^{30a}\text{R}^{30b}$ (where R^{30a} is hydrogen or alkyl and R^{30b} is aryl, heteroaryl, or cycloalkylalkyl) or $-\text{S}(\text{O})_n-\text{R}^{31}$ (where n is 0, 1, or 2 and R^{31} is heteroaryl, cycloalkylalkyl or aralkyl); where the alkyl within any group in Q^{12} is optionally substituted with alkoxyalkyl);

R^5 is $-\text{X}^{13}-\text{Y}^{13}-\text{Z}^{13}$ where X^{13} is alkylene or alkenylene, where Y^{13} is $-\text{NR}^{26a}-$, $-\text{O}-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})-$, $-\text{SO}_2-$, $-\text{NR}^{26a}\text{SO}_2-$, $-\text{SO}_2\text{NR}^{26a}-$, $-\text{C}(\text{O})\text{NR}^{26a}-$, $-\text{NR}^{26a}\text{C}(\text{O})-$, $-\text{OC}(\text{O})-$, $-\text{OC}(\text{O})\text{NR}^{26a}-$, $-\text{NR}^{26a}\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{O})\text{NR}^{26a}\text{C}(\text{O})-$, or $-\text{NR}^{26a}\text{C}(\text{O})\text{NR}^{26b}-$, where R^{26a} and R^{26b} are as defined above, and where Z^{13} is hydrogen, alkyl, or alkenyl (where Z^{13} is optionally substituted with one, two, or three halo, hydroxy, amino, alkoxy, alkoxy, carbonyl, carboxy, or alkylcarbonylamino); or

R^5 is $-\text{Y}^{14}-\text{Z}^{14}$ where Y^{14} is $-\text{S}(\text{O})-$, $-\text{NR}^{26a}\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{NR}^{26a}-$, $-\text{NR}^{26a}\text{C}(\text{O})\text{NR}^{26b}-$, $-\text{C}(\text{O})\text{NR}^{26a}\text{C}(\text{O})-$, $-\text{NR}^{26a}\text{C}(\text{O})\text{O}-$, $-\text{OC}(\text{O})\text{NR}^{26a}$, or $-\text{OC}(\text{O})-$, where R^{26a} and R^{26b} are as defined above, and where Z^{14} is alkyl or alkenyl (where Z^{14} is optionally substituted with one, two, or three halo, hydroxy, amino, alkoxy, alkoxy, carbonyl, carboxy, or alkylcarbonylamino).

Preferably, R^{4a} and R^{4b} are hydrogen; and

R^5 is $-\text{Y}^{11}-\text{X}^{11}-\text{Q}^{11}$ where Y^{11} is $-\text{C}(\text{O})\text{NR}^{26a}-$, $-\text{NR}^{26a}\text{C}(\text{O})-$, $-\text{NR}^{26a}\text{C}(\text{O})\text{O}-$, or $-\text{NR}^{26a}\text{C}(\text{O})\text{NR}^{26b}-$, where R^{26a} and R^{26b} are independently hydrogen or hydroxy, where X^{11} is

a bond, alkylene, or alkenylene, (where X^{11} is optionally substituted with hydroxy), and where Q^{11} is heteroaryl, aryl, aryloxy, or cycloalkyl; or

R^5 is $-X^{12a}-Y^{12}-X^{12b}-Q^{12}$ where X^{12a} is alkylene; Y^{12} is $-C(O)NH-$, $-NHC(O)-$, or $-NHC(O)NH-$; X^{12b} is a bond, alkylene, or alkenylene where X^{12b} is optionally substituted with one, two, or three groups selected from hydroxy, cyano, halo, heteroaryl, alkoxycarbonyl, carboxy, $-NR^{27a}R^{27b}$ (where R^{27a} and R^{27b} are independently hydrogen or alkyl), $-C(O)NR^{28a}R^{28b}$ (where R^{28a} and R^{28b} are independently hydrogen, alkyl, alkoxy, or heteroaryl), and $-NHC(O)OR^{29b}$ (where R^{29b} is alkyl); and Q^{12} is aryl, aryloxy, aralkyloxy, heteroaryl, aralkylaminocarbonyl (where the alkyl is optionally substituted with alkoxycarbonyl or carboxy), cycloalkyl, cycloalkylaminocarbonyl, cycloalkylalkyloxy, $-NR^{30a}R^{30b}$ (where R^{30a} is hydrogen or alkyl and R^{30b} is aryl, heteroaryl, or cycloalkylalkyl) or $-S(O)_n-R^{31}$ (where n is 0 or 2 and R^{31} is heteroaryl, cycloalkylalkyl or aralkyl); where the alkyl within any group in Q^{12} is optionally substituted with alkoxyalkyl).

More preferably, R^{4a} and R^{4b} are hydrogen; and R^5 is $-X^{12a}-Y^{12}-X^{12b}-Q^{12}$ where X^{12a} is alkylene, Y^{12} is $-C(O)NH-$, X^{12b} is alkylene or alkenylene where X^{12b} is optionally substituted with one or two groups selected from alkoxycarbonyl, carboxy, $-C(O)NHR^{28b}$ (where R^{28b} is alkyl), and hydroxy; and Q^{12} is aryl, aryloxy, aralkyloxy, $-S(O)_2-R^{31}$ (where R^{31} is aryl).

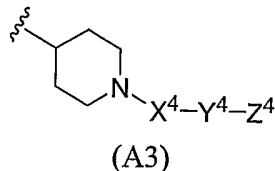
Even more preferably, R^{4a} and R^{4b} are hydrogen; and R^5 is $-X^{12a}-Y^{12}-X^{12b}-Q^{12}$ where X^{12a} is $-CH_2-$, Y^{12} is $C(O)NH$, X^{12b} is eth-1,2-diyl optionally substituted with methoxycarbonyl, carboxy, or *N*-methylaminocarbonyl, or X^{12b} is buten-diyl optionally substituted with methoxycarbonyl, carboxy, or X^{12b} is prop-diyl optionally substituted with methoxycarbonyl, carboxy, hydroxy, or X^{12b} is but-diyl optionally substituted with carboxy, or X^{12b} is meth-diyl optionally substituted with methoxycarbonyl; and Q^{12} is phenylmethyloxy, fluorophenylmethyloxy, phenyl, phenyloxy, indanyl, phenylmethylsulfonyl, chlorophenyl, or methoxyphenyl.

Particularly preferably, R^{4a} and R^{4b} are hydrogen; and R^5 is $-X^{12a}-Y^{12}-X^{12b}-Q^{12}$ where X^{12a} is $-CH_2-$, Y^{12} is $C(O)NH$, X^{12b} is $-CH_2CH_2-$, $-CH[C(O)OCH_3]CH_2-$, $-CH(COOH)CH_2-$, $-CH[C(O)NHCH_3]CH_2-$, $-CH(COOH)CH_2-CH=CH-$, $-CH(COOH)CH_2CH_2-$, $-CH[C(O)OCH_3]CH_2CH_2-$, $-CH[C(O)OCH_2CH_3]CH_2-CH=CH-$, $-CH_2CH(OH)CH_2CH_2-$, $-CH_2CH(OH)CH_2-$, $-CH[C(O)OCH_2CH_3]CH_2CH_2-$, $-CH(CH_2COOH)CH_2CH_2-$, $-CH[CH_2C(O)OCH_3]CH_2CH_2-$, $-CH[C(O)OCH_3]-$, or $-CH(COOH)CH_2CH_2CH_2-$; and Q^{12} is phenylmethyloxy, 4-fluorophenylmethyloxy, phenyl, phenyloxy, indan-1-yl, phenylmethylsulfonyl, 4-chlorophenyl, or 4-methoxyphenyl.

Even more particularly preferably, R^{4a} and R^{4b} are hydrogen; and R^5 is

-CH₂C(O)NHCH₂CH₂; and Q¹² is 4-fluorophenylmethoxy.

13. Another preferred group of compounds of Formula 1 is where R¹⁰⁰ is a group of formula (A3):



where

X⁴ is alkylene optionally substituted with one, two, three, four, or five halo;

Y⁴ is -C(O)-, -NR³²C(O)-, -S(O)₂-, or a bond;

Z⁴ is heterocycloalkyl optionally substituted with one, two, three, or four groups selected from cycloalkyl, cycloalkylalkyl, alkoxycarbonyl, carboxy, aryl, aralkyl, cyano, arylcarbonyl, alkoxy, and hydroxy; or Z⁴ is -NR^{50a}R^{50b} where R^{50a} is hydrogen, alkyl, alkoxy, or hydroxy and R^{50b} is -(alkylene)-aryl where the alkylene is optionally substituted with one or two groups selected from halo, alkoxycarbonyl, hydroxy, and carboxy.

Preferably, X⁴ is alkylene; Y⁴ is -C(O)-; and Z⁴ is heterocycloalkyl optionally substituted with one, two, three, or four groups selected from cycloalkylalkyl, alkoxycarbonyl, carboxy, aralkyl, cyano, acyl, and hydroxy; or Z⁴ is -NR^{50a}R^{50b} where R^{50a} is hydrogen and R^{50b} is -(alkylene)-aryl where the alkylene is optionally substituted with one or two groups selected from alkoxycarbonyl, hydroxy, and carboxy.

More preferably, X⁴ is -CH₂-; Y⁴ is -C(O)-; and Z⁴ is piperidinyl, piperazinyl, or 4-oxo-4λ⁵-[1,4]azaphosphinanyl (where the phosphorous atom is substituted with alkyl, aryl, aralkyl, cycloalkyl, or cycloalkylalkyl) and where Z⁴ is optionally substituted with one or two cyclopropylmethyl, methoxycarbonyl, carboxy, phenethyl, phenylmethyl, cyano, fluorophenylmethyl, phenylcarbonyl, or hydroxy; or Z⁴ is -NHR^{50b} where R^{50b} is -(alkylene)-aryl where the alkylene is optionally substituted with one or two groups selected from methoxycarbonyl, ethoxycarbonyl, hydroxy, and carboxy. Even more preferably -(alkylene)-aryl is -CH[C(O)CH₂CH₃]CH₂CH₂CH₂-phenyl, -CH₂CH(OH)CH₂CH₂-phenyl, -CH₂CH₂CH₂CH₂-phenyl, -CH₂CH[C(O)CH₂CH₃]CH₂CH₂-phenyl, or -CH₂CH₂CH₂-phenyl.

Even more preferably, X⁴ is -CH₂-; Y⁴ is -C(O)-; and Z⁴ is piperidinyl substituted with cyano and 4-fluorophenylmethyl.

14. Another preferred group of compounds of Formula 1 is where

L is $-X^1-Y^1-Z^1$ where X^1 is alkylene, alkenylene, or cycloalkylene and where X^1 is optionally substituted by one or two substituents selected from the group consisting of halo, hydroxy, alkoxy, alkylamino, and dialkylamino; Y^1 is $-O-$, $-NR^{13}-$, $-C(O)-$, $-C(O)O-$, $-C(O)NR^{13}-$, $-NR^{13}C(O)-$, $-C(O)NR^{13}C(O)-$, $-S-$, $-S(O)-$, $-SO_2-$, $-SO_2NR^{13}-$, $-NR^{13}SO_2-$, $-OC(O)-$, $-OC(O)NR^{13}-$, $-NR^{13}C(O)O-$, or $-NR^{13}C(O)NR^{14}-$ (where R^{13} and R^{14} are independently hydrogen, alkyl, or substituted alkyl); and Z^1 is a bond, alkylene, alkenylene, or cycloalkylene;

L is $-X^2-$ where X^2 is alkylene, alkenylene, or cycloalkylene and is optionally substituted by one or two substituents selected from the group consisting of halo, hydroxy, alkoxy, alkylamino, and dialkylamino;

L is $-Y^2-Z^2-$ where Y^2 is $-NR^{15}-$, $-C(O)-$, $-C(O)O-$, $-C(O)NR^{15}-$, $-NR^{15}C(O)-$, $-C(O)NR^{15}C(O)-$, $-S-$, $-S(O)-$, $-SO_2-$, $-SO_2NR^{15}-$, $-NR^{15}SO_2-$, $-OC(O)-$, $-OC(O)NR^{15}-$, $-NR^{15}C(O)O-$, or $-NR^{15}C(O)NR^{16}-$ (where R^{15} and R^{16} are independently hydrogen, alkyl, or substituted alkyl); and where Z^2 is alkylene, alkenylene, or cycloalkylene; and

L is $-Y^3-$ where Y^3 is $-NR^{17}-$, $-C(O)O-$, $-C(O)NR^{17}-$, $-NR^{17}C(O)-$, $-C(O)NR^{17}C(O)-$, $-S-$, $-S(O)-$, $-SO_2-$, $-SO_2NR^{17}-$, $-NR^{17}SO_2-$, $-OC(O)-$, $-OC(O)NR^{17}-$, $-NR^{17}C(O)O-$, or $-NR^{17}C(O)NR^{18}-$ (where R^{17} and R^{18} are independently hydrogen, alkyl, or substituted alkyl); or

L is $-X^5-Y^{5a}-Z^5-Y^{5b}-$ where X^5 is alkylene, alkenylene, or cycloalkylene and where X^5 is optionally substituted by one or two substituents selected from the group consisting of halo, hydroxy, alkoxy, alkylamino, and dialkylamino; Y^{5a} is $-O-$, $-NR^{13}-$, $-C(O)-$, $-C(O)O-$, $-C(O)NR^{13}-$, $-NR^{13}C(O)-$, $-C(O)NR^{13}C(O)-$, $-S-$, $-S(O)-$, $-SO_2-$, $-SO_2NR^{13}-$, $-NR^{13}SO_2-$, $-OC(O)-$, $-OC(O)NR^{13}-$, $-NR^{13}C(O)O-$, or $-NR^{13}C(O)NR^{14}-$ (where R^{13} and R^{14} are independently hydrogen, alkyl, or substituted alkyl); Z^5 is a bond, alkylene, alkenylene, or cycloalkylene where the alkylene or alkenylene are optionally substituted with aralkyloxyalkyl; and Y^{5b} is $-C(O)-$.

Preferably, L is $-X^1-Y^1-Z^1$ where X^1 is alkylene, Y^1 is $-C(O)-$, $-C(O)NH-$, or $-NHC(O)-$ and Z^1 is a bond, alkylene, or alkenylene; L is $-X^2-$ where X^2 is alkylene; L is $-Y^2-Z^2-$ where Y^2 is $-C(O)NH-$ or $-NHC(O)-$, and Z^2 is alkylene; or L is $-X^5-Y^{5a}-Z^5-Y^{5b}-$ where X^5 is alkylene, Y^{5a} is $-C(O)NH-$ or $-NHC(O)-$, Z^5 is alkylene where the alkylene is optionally substituted with aralkyloxyalkyl, and Y^{5b} is $-C(O)-$. More preferably
More preferably, L is $-CH_2C(O)-$, $-CH_2C(O)NHCH_2CH_2CH_2-$, $-CH_2C(O)NH-$, $-CH_2NHC(O)CH_2-$, $-CH_2C(O)-$, $-C(CH_3)_2C(O)-$, $-CH_2CH_2-$, or $-NHC(O)CH_2-$.

Within the above preferred groups, a more preferred group is that where L is

-X¹-Y¹-Z¹- where X¹ is alkylene, Y¹ is -C(O)-, -C(O)NH-, or -NHC(O)- and Z¹ is a bond, alkylene, or alkenylene. Even more preferably, L is -CH₂C(O)-.

15. Another preferred group of compounds of Formula 1 is where Het is heterocycloalkyl. Preferably, Het is piperidinyl, piperazinyl, N-oxide of piperazinyl, homopiperazinyl, pyrrolidinyl, or 4-oxo-4λ⁵-[1,4]azaphosphinanyl (where the phosphorous atom is substituted with alkyl, aryl, aralkyl, cycloalkyl, or cycloalkylalkyl). More preferably, Het is piperidinyl, N-oxide of piperazinyl, or 4-oxo-4λ⁵-[1,4]azaphosphinanyl (where the phosphorous atom is substituted with aralkyl or cycloalkylalkyl). Even more preferably, Het is piperidinyl.

16. Another preferred group of compounds of Formula 1 is where R⁷, R⁸, and R⁹ are independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, acyl, acylamino, acyloxy, acylaminoalkyloxycarbonyl, alkylthio, alkylsulfonyl, alkoxy, alkoxycarbonyl, alkoxyalkylamino, alkoxyalkylaminocarbonyl, alkoxyalkyloxy, alkoxyalkyloxycarbonyl, amino, alkylamino, dialkylamino, aminoalkyloxy, carboxy, carboxyalkylaminocarbonyl where the "alkyl" is optionally substituted with one or two hydroxy, cyano, cyanoalkylaminocarbonyl, aryl, aryloxy, arylsulfonyl, arylthioalkylcarbonyl, aralkyl where the alkyl is optionally substituted with one or two hydroxy, aralkyloxy, aralkyloxycarbonyl, aralkyloxyaminocarbonyl, aralkyloxycarbonylamino, aralkenyl, cycloalkyl, cycloalkyloxy, cycloalkylaminocarbonyl, cycloalkylalkyl where the "alkyl" is optionally substituted with one or two hydroxy, cycloalkylalkylaminocarbonyl, cycloalkylalkyloxycarbonyl, heteroaryl, heteroarylaminocarbonyl, heteroaralkyl, heteroaralkenyl, heteroaralkyloxy, halo, hydroxy, hydroxyalkyloxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, *N*-hydroxyaminocarbonyl, *N*-alkoxyaminocarbonyl, hydroxyalkylaminocarbonyl, dialkylaminoalkyloxycarbonyl, dialkylaminoalkylaminocarbonyl, arylamino, arylaminocarbonyl, alkylsulfonylamino, alkylsulfonylaminocarbonyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkyloxy, optionally substituted heterocycloalkylaminocarbonyl, optionally substituted heterocycloalkylalkyl, optionally substituted heterocycloalkylalkyloxy, optionally substituted heterocycloalkylalkyloxycarbonyl, optionally substituted heterocycloalkylalkylaminocarbonyl, aminocarbonylamino, *N*-aryl-*N*-(alkylcarbonyl)-amino, *N*-(alkylsulfonyl)-*N*-alkyl-amino, alkoxycarbonylalkylaminocarbonyl where the "alkyl" is

optionally substituted with one or two hydroxy, or trialkylsilyl; or any two of R^7 , R^8 , and R^9 attached to the same carbon atom together with the carbon to which they are attached form indanylene or optionally substituted heterocycloalkylene; and where the alkyl, alkenyl, and alkynyl in R^7 , R^8 , and R^9 , either alone or part of another group, independently are optionally substituted with one, two, three, four, or five halo.

Preferably, R^7 and R^8 are independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, acyl, acylamino, acylaminoalkyloxycarbonyl, alkoxy carbonyl, alkoxyalkylaminocarbonyl, alkoxyalkyloxycarbonyl, amino, carboxy, carboxyalkylaminocarbonyl (where the "alkyl" is optionally substituted with one or two hydroxy), cyano, cyanoalkylaminocarbonyl, aryl, aryloxy, arylsulfonyl, arylthioalkylcarbonyl, aralkyl (where the alkyl is optionally substituted with one or two hydroxy), aralkyloxy, aralkyloxyaminocarbonyl, aralkyloxycarbonylamino, cycloalkylaminocarbonyl, cycloalkylalkyl (where the "alkyl" is optionally substituted with one or two hydroxy), cycloalkylalkylaminocarbonyl, cycloalkylalkyloxycarbonyl, heteroaryl, heteroarylaminocarbonyl, heteroaralkyl, halo, hydroxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, *N*-hydroxyaminocarbonyl, *N*-alkoxyaminocarbonyl, hydroxyalkylaminocarbonyl, dialkylaminoalkyloxycarbonyl, dialkylaminoalkylaminocarbonyl, arylamino, arylaminocarbonyl, alkylsulfonylamino, alkylsulfonylaminocarbonyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylaminocarbonyl, optionally substituted heterocycloalkylalkyl, optionally substituted heterocycloalkylalkyloxycarbonyl, optionally substituted heterocycloalkylalkylaminocarbonyl, aminocarbonylamino, *N*-aryl-*N*-(alkylcarbonyl)-amino, or alkoxy carbonylalkylaminocarbonyl (where the "alkyl" is optionally substituted with one or two hydroxy); or any two of R^7 , R^8 , and R^9 attached to the same carbon atom together with the carbon to which they are attached form indanylene or optionally substituted heterocycloalkylene; and where the alkyl, alkenyl, and alkynyl in R^7 , R^8 , and R^9 , either alone or part of another group, independently are optionally substituted with one, two, three, four, or five halo; and R^9 is hydrogen.

More preferably, R^7 and R^8 are independently hydrogen, optionally substituted alkyl (preferably alkyl substituted with one or two alkoxyalkyloxycarbonyl, dialkylaminoalkyloxy, hydroxy or carboxy), optionally substituted alkenyl (preferably alkenyl), alkoxy carbonyl, carboxy, aralkyl, aralkyloxy, heteroaryl, heteroaralkyl, hydroxy, alkylsulfonylaminocarbonyl, alkoxy carbonylalkylaminocarbonyl, optionally substituted heterocycloalkyl, cycloalkylalkyl, amino, acyl (preferably optionally substituted heterocycloalkylcarbonyl),

alkoxyalkyloxycarbonyl, dialkylaminoalkyloxycarbonyl, optionally substituted heterocycloalkylalkyloxycarbonyl, dialkylaminoalkylaminocarbonyl, or cyano; and R⁹ is hydrogen.

Even more preferably, R⁷ and R⁸ are independently hydrogen, phenylmethyl, methoxycarbonyl, carboxy, fluorophenylmethyl, difluorophenylmethyl, thienyl, methylsulfonylaminocarbonyl, 2-oxo-1,3-dihydro-benzoimidazol-1-yl, allyl, hydroxy, tetrazolyl, fluorophenylmethoxy, *N*-(methoxycarbonylmethyl)-aminocarbonyl, 5-oxo-4*H*-[1,2,4]oxadiazolyl, amino, pyrrolidinylcarbonyl, 2-(methoxy)-ethyloxycarbonyl, 2-(methoxy)-ethyloxycarbonylmethyl, 2-(*N,N*-diethylamino)-ethyloxycarbonyl, 2-(morpholin-4-yl)-ethyloxycarbonyl, 2-(*N,N*-diethylamino)-ethylaminocarbonyl, cyano, 2-(*N,N*-diethylamino)-ethyloxymethyl, cyclopropylmethyl, or carboxyalkyl where the alkyl is substituted with hydroxy; and R⁹ is hydrogen.

Particularly preferably, R⁷ and R⁸ are independently hydrogen, phenylmethyl, methoxycarbonyl, carboxy, 2-fluorophenylmethyl, 3-fluorophenylmethyl, 4-fluorophenylmethyl, 3,4-difluorophenylmethyl, thien-3-yl, hydroxy, methylsulfonylaminocarbonyl, 2-oxo-1,3-dihydro-benzoimidazol-1-yl, allyl, tetrazolyl, 4-fluorophenylmethoxy, *N*-(methoxycarbonylmethyl)-aminocarbonyl, 5-oxo-4*H*-[1,2,4]oxadiazolyl, amino, pyrrolidinylcarbonyl, 2-(methoxy)-ethyloxycarbonyl, 2-(methoxy)-ethyloxycarbonylmethyl, 2-(*N,N*-diethylamino)-ethyloxycarbonyl, 2-(morpholin-4-yl)-ethyloxycarbonyl, 2-(*N,N*-diethylamino)-ethylaminocarbonyl, cyano, 2-(*N,N*-diethylamino)-ethyloxymethyl, cyclopropylmethyl, 1-carboxy-1-hydroxymethyl; and R⁹ is hydrogen.

More particularly preferably, R⁷ and R⁸ are independently hydrogen, 3,4-difluorophenylmethyl, carboxy, cyclopropylmethyl, cyano, or 4-fluorophenylmethyl; and R⁹ is hydrogen.

17. Another preferred group of compounds of Formula 1 is where

R⁵ is -Y¹¹-X¹¹-Q¹¹ where Y¹¹ is -S(O)-, -SO₂-, -NR^{26a}SO₂-, -SO₂NR^{26a}-, -C(O)NR^{26a}-, -NR^{26a}C(O)-, -OC(O)-, -OC(O)NR^{26a}-, -NR^{26a}C(O)O-, -C(O)NR^{26a}C(O)-, or -NR^{26a}C(O)NR^{26b}-, where R^{26a} and R^{26b} are independently hydrogen, alkyl, haloalkyl, hydroxy, alkoxy, haloalkoxy, or acyl, where X¹¹ is a bond, alkylene, or alkenylene, (where X¹¹ is optionally substituted with hydroxy, alkoxy, carboxy), and where Q¹¹ is heteroaryl, aryl, aryloxy, or cycloalkyl;

R⁵ is -X^{12a}-Y¹²-X^{12b}-Q¹² where X^{12a} is alkylene or alkenylene; Y¹² is -NR^{26a}-, -O-,

-C(O)-, -C(O)O-, -S-, -S(O)-, -SO₂-, -NR^{26a}SO₂-, -SO₂NR^{26a}-, -C(O)NR^{26a}-, -NR^{26a}C(O)-, -OC(O)-, -OC(O)NR^{26a}-, -NR^{26a}C(O)O-, -C(O)NR^{26a}C(O)-, or -NR^{26a}C(O)NR^{26b}-, where R^{26a} and R^{26b} are as defined above; X^{12b} is a bond, alkylene, or alkenylene where X^{12b} is optionally substituted with one, two, or three groups selected from hydroxy, cyano, halo, heteroaryl, alkylcarbonyl, alkoxycarbonyl, carboxy, -NR^{27a}R^{27b} (where R^{27a} and R^{27b} are independently hydrogen, alkyl, alkoxy, alkoxyalkyl, heteroaryl, or heteroarylamino), -C(O)NR^{28a}R^{28b} (where R^{28a} and R^{28b} are independently hydrogen, alkyl, alkenyl, alkoxy, alkenyloxy, alkoxyalkyl, hydroxy, or heteroaryl), and -NR^{29a}C(O)OR^{29b} (where R^{29a} is hydrogen, alkyl, alkenyl, alkoxy, alkenyloxy, alkoxyalkyl, or hydroxy, and R^{29b} is alkyl); and Q¹² is aryl, aryloxy, aralkyloxy, heteroaryl, aralkylaminocarbonyl (where the alkyl is optionally substituted with alkoxycarbonyl or carboxy), cycloalkyl, cycloalkylaminocarbonyl, cycloalkylalkyloxy, -NR^{30a}R^{30b} (where R^{30a} is hydrogen or alkyl and R^{30b} is aryl, heteroaryl, or cycloalkylalkyl) or -S(O)_n-R³¹ (where n is 0, 1, or 2 and R³¹ is heteroaryl, cycloalkylalkyl or aralkyl); where the alkyl within any group in Q¹² is optionally substituted with alkoxyalkyl);

R⁵ is -X¹³-Y¹³-Z¹³ where X¹³ is alkylene or alkenylene, where Y¹³ is -NR^{26a}-, -O-, -C(O)-, -C(O)O-, -S-, -S(O)-, -SO₂-, -NR^{26a}SO₂-, -SO₂NR^{26a}-, -C(O)NR^{26a}-, -NR^{26a}C(O)-, -OC(O)-, -OC(O)NR^{26a}-, -NR^{26a}C(O)O-, -C(O)NR^{26a}C(O)-, or -NR^{26a}C(O)NR^{26b}-, where R^{26a} and R^{26b} are as defined above, and where Z¹³ is hydrogen, alkyl, or alkenyl (where Z¹³ is optionally substituted with one, two, or three halo, hydroxy, amino, alkoxy, alkoxycarbonyl, carboxy, or alkylcarbonylamino); or

R⁵ is -Y¹⁴-Z¹⁴ where Y¹⁴ is -S(O)-, -NR^{26a}C(O)-, -C(O)NR^{26a}-, -NR^{26a}C(O)NR^{26b}-, -C(O)NR^{26a}C(O)-, -NR^{26a}C(O)O-, -OC(O)NR^{26a}-, or -OC(O)-, where R^{26a} and R^{26b} are as defined above, and where Z¹⁴ is alkyl or alkenyl (where Z¹⁴ is optionally substituted with one, two, or three halo, hydroxy, amino, alkoxy, alkoxycarbonyl, carboxy, or alkylcarbonylamino).

Preferably, R⁵ is -Y¹¹-X¹¹-Q¹¹ where Y¹¹ is -C(O)NR^{26a}-, -NR^{26a}C(O)-, -NR^{26a}C(O)O-, or -NR^{26a}C(O)NR^{26b}-, where R^{26a} and R^{26b} are independently hydrogen or hydroxy, where X¹¹ is a bond, alkylene, or alkenylene, (where X¹¹ is optionally substituted with hydroxy), and where Q¹¹ is heteroaryl, aryl, aryloxy, or cycloalkyl; or R⁵ is -X^{12a}-Y¹²-X^{12b}-Q¹² where X^{12a} is alkylene, Y¹² is -C(O)NH-, -NHC(O)-, or -NHC(O)NH-, X^{12b} is a bond, alkylene, or alkenylene where X^{12b} is optionally substituted with one, two, or three groups selected from hydroxy, cyano, halo, heteroaryl, alkoxycarbonyl, carboxy, -NR^{27a}R^{27b} (where R^{27a} and R^{27b} are independently hydrogen or alkyl), -C(O)NR^{28a}R^{28b} (where R^{28a} and R^{28b} are

independently hydrogen, alkyl, alkoxy, or heteroaryl), and -NHC(O)OR^{29b} (where R^{29b} is alkyl), and Q^{12} is aryl, aryloxy, aralkyloxy, heteroaryl, aralkylaminocarbonyl (where the alkyl is optionally substituted with alkoxycarbonyl or carboxy), cycloalkyl, cycloalkylaminocarbonyl, cycloalkylalkyloxy, $\text{-NR}^{30a}R^{30b}$ (where R^{30a} is hydrogen or alkyl and R^{30b} is aryl, heteroaryl, or cycloalkylalkyl) or $\text{-S(O)}_n\text{-R}^{31}$ (where n is 0 or 2 and R^{31} is heteroaryl, cycloalkylalkyl or aralkyl) and where the alkyl within any group in Q^{12} is optionally substituted with alkoxyalkyl).

More preferably, R^5 is $\text{-X}^{12a}\text{-Y}^{12}\text{-X}^{12b}\text{-Q}^{12}$ where X^{12a} is alkylene, Y^{12} is -C(O)NH- , X^{12b} is alkylene or alkenylene where X^{12b} is optionally substituted with one or two groups selected from alkoxycarbonyl, carboxy, -C(O)NHR^{28b} (where R^{28b} alkyl), and hydroxy; and Q^{12} is aryl, aryloxy, aralkyloxy, $\text{-S(O)}_2\text{-R}^{31}$ (where R^{31} is aryl).

Even more preferably, R^5 is $\text{-X}^{12a}\text{-Y}^{12}\text{-X}^{12b}\text{-Q}^{12}$ where X^{12a} is $\text{-CH}_2\text{-}$, Y^{12} is C(O)NH , X^{12b} is eth-1,2-diyl optionally substituted with methoxycarbonyl, carboxy, or *N*-methylaminocarbonyl, or X^{12b} is buten-diyl optionally substituted with methoxycarbonyl, carboxy, or X^{12b} is prop-diyl optionally substituted with methoxycarbonyl, carboxy, hydroxy, or X^{12b} is but-diyl optionally substituted with carboxy, or X^{12b} is meth-diyl optionally substituted with methoxycarbonyl; and Q^{12} is phenylmethyloxy, fluorophenylmethyloxy, phenyl, phenyloxy, indanyl, phenylmethylsulfonyl, chlorophenyl, or methoxyphenyl.

Particularly preferably, R^5 is $\text{-X}^{12a}\text{-Y}^{12}\text{-X}^{12b}\text{-Q}^{12}$ where X^{12a} is $\text{-CH}_2\text{-}$, Y^{12} is C(O)NH , X^{12b} is $\text{-CH}_2\text{CH}_2\text{-}$, $\text{-CH[C(O)OCH}_3\text{]CH}_2\text{-}$, $\text{-CH(COOH)CH}_2\text{-}$, $\text{-CH[C(O)NHCH}_3\text{]CH}_2\text{-}$, $\text{-CH(COOH)CH}_2\text{-CH=CH-}$, $\text{-CH(COOH)CH}_2\text{CH}_2\text{-}$, $\text{-CH[C(O)OCH}_3\text{]CH}_2\text{CH}_2\text{-}$, $\text{-CH[C(O)OCH}_2\text{CH}_3\text{]CH}_2\text{-CH=CH-}$, $\text{-CH}_2\text{CH(OH)CH}_2\text{CH}_2\text{-}$, $\text{-CH}_2\text{CH(OH)CH}_2\text{-}$, $\text{-CH[C(O)OCH}_2\text{CH}_3\text{]CH}_2\text{CH}_2\text{-}$, $\text{-CH(CH}_2\text{COOH)CH}_2\text{CH}_2\text{-}$, $\text{-CH[CH}_2\text{C(O)OCH}_3\text{]CH}_2\text{CH}_2\text{-}$, $\text{-CH[C(O)OCH}_3\text{]-}$, or $\text{-CH(COOH)CH}_2\text{CH}_2\text{CH}_2\text{-}$; and Q^{12} is phenylmethyloxy, 4-fluorophenylmethyloxy, phenyl, phenyloxy, indan-1-yl, phenylmethylsulfonyl, 4-chlorophenyl, or 4-methoxyphenyl.

Even more particularly preferably, R^5 is $\text{-CH}_2\text{C(O)NHCH}_2\text{CH}_2\text{-}$; and Q^{12} is 4-fluorophenylmethyloxy.

18. Another preferred group of compounds of Formula 1 is where Z^4 is heterocycloalkyl optionally substituted with one, two, three, or four groups selected from cycloalkyl, cycloalkylalkyl, alkoxycarbonyl, carboxy, aryl, aralkyl, cyano, arylcarbonyl, alkoxy, and hydroxy; or Z^4 is $\text{-NR}^{50a}R^{50b}$ where R^{50a} is hydrogen, alkyl, alkoxy, or hydroxy and R^{50b} is (alkylene)-aryl where the alkylene is optionally substituted with one or two groups selected

from halo, alkoxycarbonyl, hydroxy, and carboxy.

Preferably, Z^4 is heterocycloalkyl optionally substituted with one, two, three, or four groups selected from cycloalkylalkyl, alkoxycarbonyl, carboxy, aralkyl, cyano, acyl, and hydroxy; or Z^4 is $-NR^{50a}R^{50b}$ where R^{50a} is hydrogen and R^{50b} is $-(alkylene)-aryl$ where the alkylene is optionally substituted with one or two groups selected from alkoxycarbonyl, hydroxy, and carboxy.

More preferably, Z^4 is piperidinyl, piperazinyl, or 4-oxo-4 λ^5 -[1,4]azaphosphinanyl (where the phosphorous atom is substituted with alkyl, aryl, aralkyl, cycloalkyl, or cycloalkylalkyl) and where Z^4 is optionally substituted with one or two cyclopropylmethyl, methoxycarbonyl, carboxy, phenethyl, phenylmethyl, cyano, fluorophenylmethyl, phenylcarbonyl, or hydroxy; or Z^4 is $-NHR^{50b}$ where R^{50b} is $-(alkylene)-aryl$ where the alkylene is optionally substituted with one or two groups selected from methoxycarbonyl, ethoxycarbonyl, hydroxy, and carboxy. Even more preferably $-(alkylene)-aryl$ is $-CH[C(O)CH_2CH_3]CH_2CH_2CH_2$ -phenyl, $-CH_2CH(OH)CH_2CH_2$ -phenyl, $-CH_2CH_2CH_2CH_2$ -phenyl, $-CH_2CH[C(O)CH_2CH_3]CH_2CH_2$ -phenyl, or $-CH_2CH_2CH_2$ -phenyl.

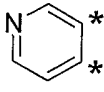
Even more preferably, Z^4 is piperidinyl substituted with cyano and 4-fluorophenylmethyl.

19. Another preferred group of compounds of Formula 1 is where A is optionally substituted pyridino; D is $=CH-$; and R^1 , R^2 , and R^3 are hydrogen.
20. Within the preferred group 2, a more preferred group is that where L is $-CH_2C(O)-$.
21. Within the preferred group 2, a more preferred group is that wherein Het is piperidinyl where L is attached at the 1-position and R^7 and R^8 are attached at the 4-position or where Het is piperazinyl and L is attached at the 1-position and R^7 is attached at the 4-position.
22. Within the preferred group 2, a more preferred group is that where R^7 is carboxy, R^8 is aralkyl, and R^9 is hydrogen; R^7 is alkoxycarbonyl, R^8 is aralkyl, and R^9 is hydrogen; R^7 is carboxy, R^8 is heteroaralkyl, and R^9 is hydrogen; R^7 is alkoxycarbonyl, R^8 is cycloalkylalkyl, and R^9 is hydrogen; R^7 is carboxy, R^8 is cycloalkylalkyl, and R^9 is hydrogen; R^7 is cyano, R^8 is cycloalkylalkyl, and R^9 is hydrogen; or R^7 and R^9 are hydrogen and R^8 is aralkyl.
 Preferably, R^7 is carboxy, R^8 is aralkyl, and R^9 is hydrogen; R^7 is carboxy, R^8 is

cycloalkylalkyl, and R^9 is hydrogen; R^7 is cyano, R^8 is cycloalkylalkyl, and R^9 is hydrogen; or R^7 and R^9 are hydrogen and R^8 is aralkyl.

Within the above preferred groups in 22, another more preferred group is that where Het is piperidiny1 or piperazinyl, and R^7 and R^8 are located at the 4-position of Het and L is located at the 1-position of Het; and R^9 is hydrogen.

23. Within the preferred group 3, a more preferred group is that where X^{12a} is alkylene, preferably $-\text{CH}_2-$; Y^{12} is $-\text{C}(\text{O})\text{NH}-$; and X^{12b} is alkylene optionally substituted with one or two hydroxy, carboxy, or alkoxycarbonyl.

24. Within the preferred group 3, a more preferred group is that where A is  or  and D is $=\text{CH}-$.

25. Within the preferred group 3, a more preferred group is that where R^5 is $-\text{Y}^{11}-\text{X}^{11}-\text{Q}^{11}$ where Y^{11} is $-\text{S}(\text{O})-$, $-\text{SO}_2-$, $-\text{NR}^{26a}\text{SO}_2-$, $-\text{SO}_2\text{NR}^{26a}-$, $-\text{C}(\text{O})\text{NR}^{26a}-$, $-\text{NR}^{26a}\text{C}(\text{O})-$, $-\text{OC}(\text{O})-$, $-\text{OC}(\text{O})\text{NR}^{26a}-$, $-\text{NR}^{26a}\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{O})\text{NR}^{26a}\text{C}(\text{O})-$, or $-\text{NR}^{26a}\text{C}(\text{O})\text{NR}^{26b}-$, where R^{26a} and R^{26b} are independently hydrogen, alkyl, haloalkyl, hydroxy, alkoxy, haloalkoxy, or acyl, where X^{11} is a bond, alkylene, or alkenylene, (where X^{11} is optionally substituted with hydroxy, alkoxycarbonyl, carboxy), and where Q^{11} is heteroaryl, aryl, aryloxy, or cycloalkyl; or R^5 is $-\text{X}^{12a}-\text{Y}^{12}-\text{X}^{12b}-\text{Q}^{12}$ where X^{12a} is alkylene or alkenylene; Y^{12} is $-\text{NR}^{26a}-$, $-\text{O}-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})-$, $-\text{SO}_2-$, $-\text{NR}^{26a}\text{SO}_2-$, $-\text{SO}_2\text{NR}^{26a}-$, $-\text{C}(\text{O})\text{NR}^{26a}-$, $-\text{NR}^{26a}\text{C}(\text{O})-$, $-\text{OC}(\text{O})-$, $-\text{OC}(\text{O})\text{NR}^{26a}-$, $-\text{NR}^{26a}\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{O})\text{NR}^{26a}\text{C}(\text{O})-$, or $-\text{NR}^{26a}\text{C}(\text{O})\text{NR}^{26b}-$, where R^{26a} and R^{26b} are as defined above; X^{12b} is a bond, alkylene, or alkenylene where X^{12b} is optionally substituted with one, two, or three groups selected from hydroxy, cyano, halo, heteroaryl, alkylcarbonyl, alkoxycarbonyl, carboxy, $-\text{NR}^{27a}\text{R}^{27b}$ (where R^{27a} and R^{27b} are independently hydrogen, alkyl, alkoxy, alkoxyalkyl, heteroaryl, or heteroarylamino carbonyl), $-\text{C}(\text{O})\text{NR}^{28a}\text{R}^{28b}$ (where R^{28a} and R^{28b} are independently hydrogen, alkyl, alkenyl, alkoxy, alkenyloxy, alkoxyalkyl, hydroxy, or heteroaryl), and $-\text{NR}^{29a}\text{C}(\text{O})\text{OR}^{29b}$ (where R^{29a} is hydrogen, alkyl, alkenyl, alkoxy, alkenyloxy, alkoxyalkyl, or hydroxy, and R^{29b} is alkyl); and Q^{12} is aryl, aryloxy, aralkyloxy, heteroaryl, aralkylaminocarbonyl (where the alkyl is optionally substituted with alkoxycarbonyl or carboxy), cycloalkyl, cycloalkylaminocarbonyl,

cycloalkylalkyloxy, $-\text{NR}^{30a}\text{R}^{30b}$ (where R^{30a} is hydrogen or alkyl and R^{30b} is aryl, heteroaryl, or cycloalkylalkyl) or $-\text{S}(\text{O})_n-\text{R}^{31}$ (where n is 0, 1, or 2 and R^{31} is heteroaryl, cycloalkylalkyl or aralkyl); where the alkyl within any group in Q^{12} is optionally substituted with alkoxyalkyl).

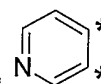
Even more preferably, R^5 is $-\text{X}^{12a}-\text{Y}^{12}-\text{X}^{12b}-\text{Q}^{12}$

26. Within the preferred group 25, a more preferred group is that where Q^{12} is aryl, aryloxy, aralkyloxy, or $-\text{S}(\text{O})_2-\text{R}^{31}$ where R^{31} is aryl. Even more preferably, Q^{12} is aryl or aralkyloxy. Particularly preferably, Q^{12} is phenyl, phenyloxy, phenylmethyloxy, 4-methoxyphenyl, indanyl, phenylmethylsulfonyl, or 4-chlorophenyl.

27. Within the preferred groups 2 or 3, a more preferred group is that wherein R^{4a} and R^{4b} are hydrogen.

28. Within the the preferred group 4, a more preferred group is that where X^4 is $-\text{CH}_2-$ and Y^4 is $-\text{C}(\text{O})-$. Even more preferably, Z^4 is heterocycloalkyl optionally substituted with one, two, three, or four groups selected from cycloalkyl, cycloalkylalkyl, alkoxy, carboxy, aryl, aralkyl, cyano, arylcarbonyl, alkoxy, and hydroxy. Particularly preferably, Z^4 is heterocycloalkyl substituted with one or two cyano or aralkyl.

29. Within the the preferred group 4, a more preferred group is that where A is



and D is $=\text{CH}-$.

30. Yet another preferred group is that wherein this invention is directed to a method of treating an immunomediated inflammatory disease responsive to the inhibition of tryptase in an animal suffering said disease, comprising administering to said animal a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I.

Preferably the immunomediated inflammatory disease is one associated with the respiratory tract, such as asthma, the hyperresponsiveness phase associated with chronic asthma, allergic rhinitis, and Chronic Obstructive Pulmonary Disease (COPD) or is one associated with mast cells, such as conjunctivitis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, inflammatory bowel disease (IBD), peptic ulcers

and various skin conditions, and particularly rheumatoid arthritis.

More preferably, the disease is asthma, allergic rhinitis, COPD, rheumatoid arthritis, or IBD. Even more preferably the disease is asthma or allergic rhinitis. Particularly preferably the disease is asthma.

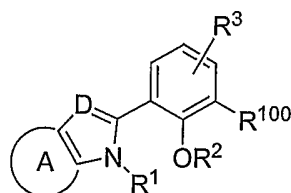
31. Yet another preferred group is that wherein this invention is directed A method of treating an immunomediated respiratory disease independently selected from the group consisting of asthma, COPD, and allergic rhinitis, in an animal which method comprises administering to said animal a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I and a pharmaceutically acceptable excipient in combination with one or more compound(s) independently selected from the group consisting of a β -2 adrenoreceptor agonist, corticosteroid, leukotriene antagonist, phosphodiesterase 4 inhibitor, and antihistamine.

Preferably, the β -2 adrenoreceptor agonist is salmeterol or levalbuterol, the corticosteroid is budesonide or fluticasone, the leukotriene D4 antagonist is montelukast, and the phosphodiesterase 4 inhibitor is roflumilast.

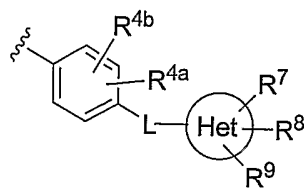
Reference to the preferred embodiments set forth above is meant to include all combinations of particular and preferred groups unless stated otherwise. A person of ordinary skill in the art would recognize that certain groups listed above in the preferred embodiments can exist as geometric or stereoisomers. The present invention includes individual stereoisomers and geometric isomers and mixtures thereof.

Representative compounds of Formula I

Selected compounds of the invention are provided in Table 1, having Formula I



where R^1 , R^2 , and R^3 are hydrogen; D is $=CR^6$ - where R^6 is hydrogen; and R^{100} is

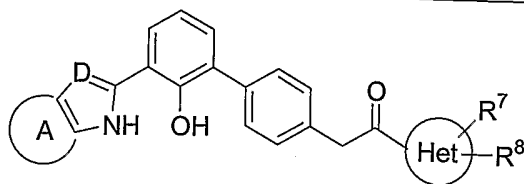


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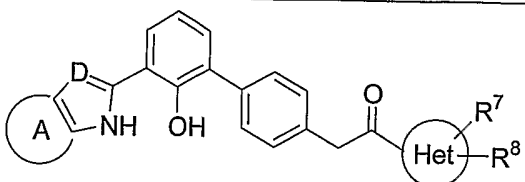
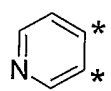
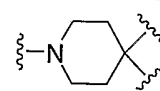
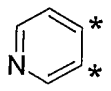
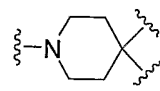
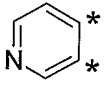
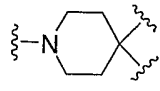
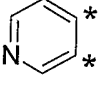
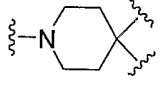
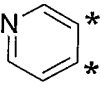
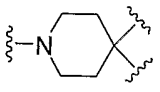
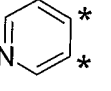
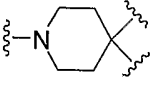
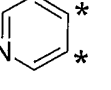
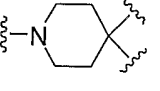
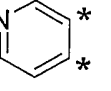
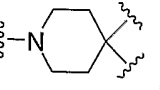
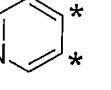
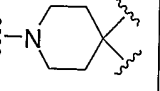
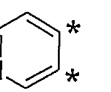
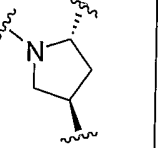
where R^{4a} , R^{4b} , and R^9 are hydrogen; L is $-X^1-Y^1-Z^1-$ where X^1 is $-\text{CH}_2-$, Y^1 is $-\text{C}(\text{O})-$, and Z^1 is a bond; and all other groups are as defined below:

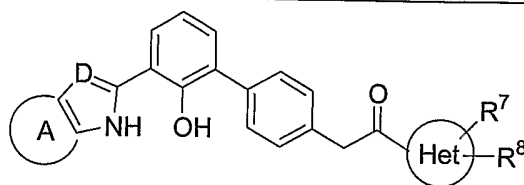
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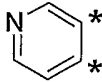
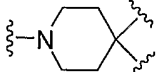
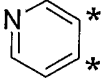
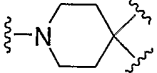
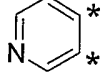
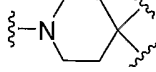
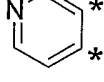
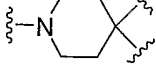
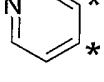
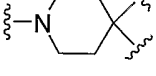
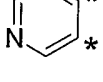
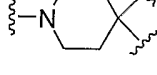
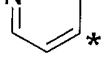
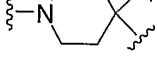
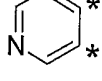
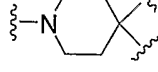
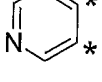
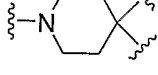
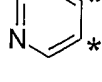
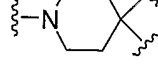
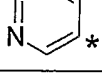
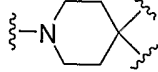
Cmpd. No.	A	D	Het	R^7	R^8
1		$=\text{CH}-$		carboxy	4-fluorophenylmethyl
2		$=\text{CH}-$		carboxy	3,4-difluorophenylmethyl
3		$=\text{CH}-$		carboxy	3-fluorophenylmethyl
4		$=\text{CH}-$		methylsulfonyl-aminocarbonyl	phenylmethyl
5		$=\text{CH}-$		cyano	phenylmethyl
6		$=\text{CH}-$		tetrazol-5-yl	phenylmethyl
7		$=\text{CH}-$		N-hydroxy-aminocarbonyl	4-fluorophenylmethyl
8		$=\text{CH}-$		methoxycarbonyl	phenylmethyl

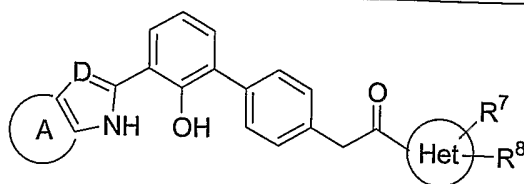


Cmpd. No.	A	D	Het	R ⁷	R ⁸
9		=CH-		aminocarbonyl	4-fluorophenylmethyl
10		=CH-		4,5-dihydrothiazol-2-ylaminocarbonyl	phenylmethyl
11		=CH-		methoxycarbonyl	3,4-difluorophenylmethyl
12		=CH-		methoxycarbonyl	3-fluorophenylmethyl
13		=CH-		methoxycarbonyl	4-fluorophenylmethyl
14		=CH-		carboxy	phenylmethyl
15		=CH-		carboxymethyl-aminocarbonyl	4-fluorophenylmethyl
16		=CH-		methylaminocarbonyl	4-fluorophenylmethyl
17		=CH-		methoxycarbonyl	thien-3-ylmethyl
18		=CH-		carboxy	2-fluorophenylmethyl
19		=CH-		carboxy	thien-3-ylmethyl

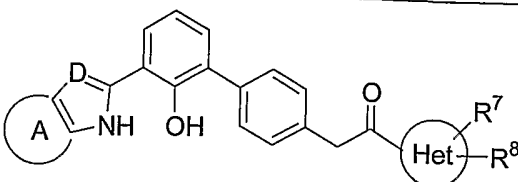
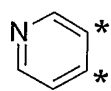
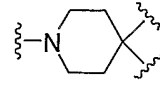
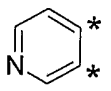
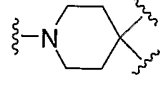
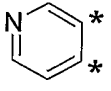
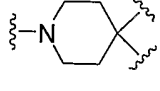
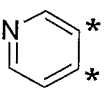
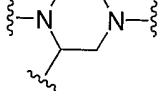
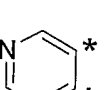
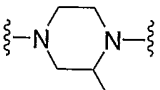
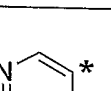
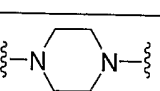
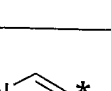
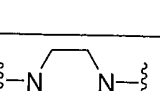
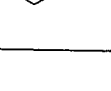
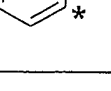
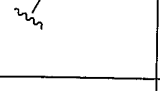
					
Cmpd. No.	A	D	Het	R ⁷	R ⁸
20		=CH-		N-(methoxycarbonylmethyl)-aminocarbonyl	4-fluorophenylmethyl
21		=CH-		methylcarbonyloxy	phenylmethyl
22		=CH-		2,2,2-trifluoroethyl-aminocarbonyl	phenylmethyl
23		=CH-		hydroxy	4-fluorophenylmethyl
24		=CH-		carboxy	3,4-difluorophenylmethyl
25		=CH-		phenylmethyloxy-aminocarbonyl	4-fluorophenylmethyl
26		=CH-		hydroxy	phenylmethyl
27		=CH-		carboxy	4-fluorophenylmethyl
28		=CH-		methoxycarbonyl	2-fluorophenylmethyl
29		=CH-		4-(4-fluorophenylmethoxy)	2-(methoxycarbonyl)

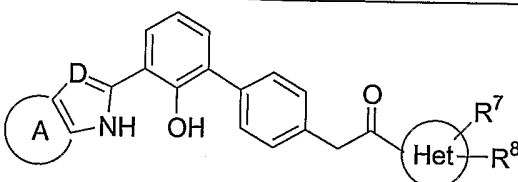
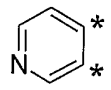
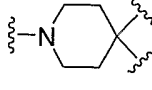
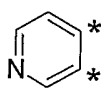
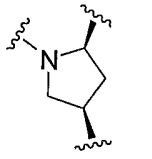
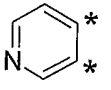
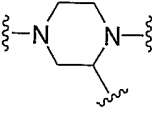
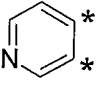
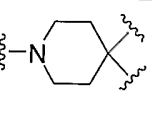
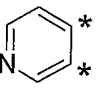
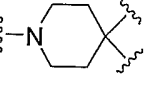
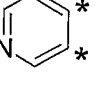
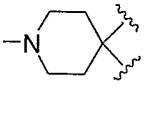
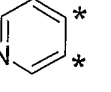
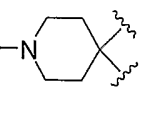
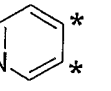
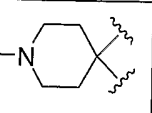
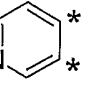
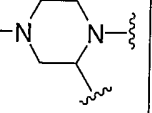
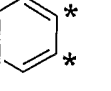
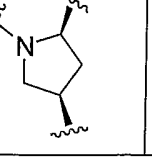


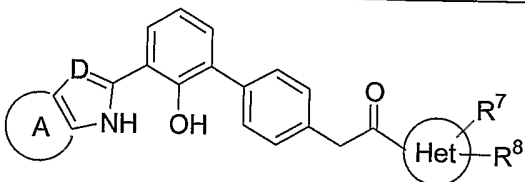
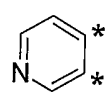
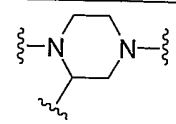
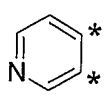
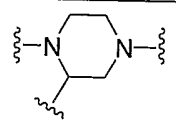
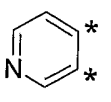
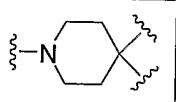
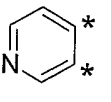
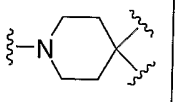
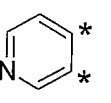
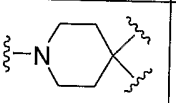
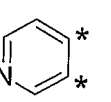
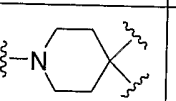
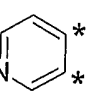
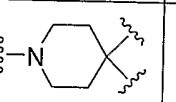
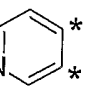
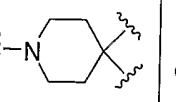
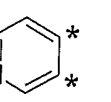
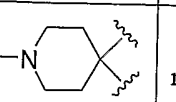
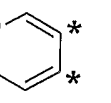
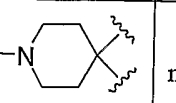
Cmpd. No.	A	D	Het	R ⁷	R ⁸
30		=CH-		methoxycarbonyl	4-fluorophenylmethyl
31		=CH-		methoxycarbonyl	3,4-difluoro-phenylmethyl
32		=CH-		tetrazol-5-ylaminocarbonyl	phenylmethyl
33		=CH-		methoxycarbonyl	phenylmethyl
34		=CH-		carboxy	phenylmethyl
35		=CH-		dimethylaminocarbonyl	phenylmethyl
36		=CH-		methoxycarbonyl	2-fluorophenylmethyl
37		=CH-		thiazol-2-ylaminocarbonyl	phenylmethyl
38		=CH-		fluoro	phenylmethyl
39		=CH-		methoxycarbonyl	allyl
40		=CH-		carboxy	allyl

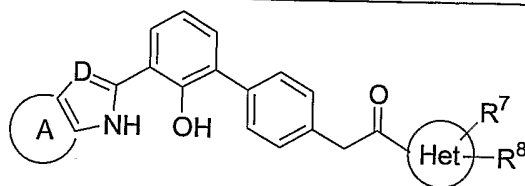


Cmpd. No.	A	D	Het	R ⁷	R ⁸
41		=CH-		carboxy	2-fluorophenylmethyl
42		=CH-		hydroxy	phenylmethyl
43		=CH-		4-(phenylmethoxy)	2-(methoxycarbonyl)
44		=CH-		fluoro	phenylmethyl
45		=CH-		dimethylaminocarbonyl	phenylmethyl
46		=CH-		4-(phenylmethoxy)	2-carboxy
47		=CH-		amino	phenylmethyl
48		=CH-		hydroxy	phenyl
49		=CH-		3-hydroxy	4-(3-trifluoromethylphenyl)
50		=CH-		hydroxy	4-chlorophenyl

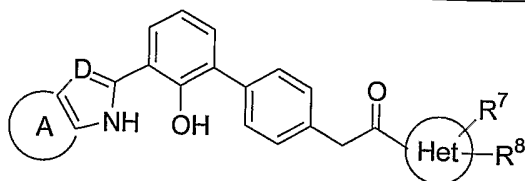
					
Cmpd. No.	A	D	Het	R ⁷	R ⁸
51		=CH-		hydroxy	3-trifluoromethylphenyl
52		=CH-		methoxycarbonyl	methyl
53		=CH-		phenylmethoxy-carbonylamino	phenylmethyl
54		=CH-		2-hydroxymethyl	4-phenylmethyl
55		=CH-		3-(methoxycarbonyl)	4-(phenylmethyl)
56		=CH-		2-(methoxycarbonyl)	4-(phenylmethyl)
57		=CH-		3-carboxy	4-(phenylmethyl)
58		=CH-		2-carboxy	4-(phenylmethyl)
59		=CH-		2-carboxy	4-(4-fluoro-phenylmethoxy)

					
Cmpd. No.	A	D	Het	R ⁷	R ⁸
60		=CH-		[1,2,4]triazol-3-ylaminocarbonyl	phenylmethyl
61		=CH-		2-(methoxycarbonyl)	4-(4-fluoro-phenylmethoxy)
62		=CH-		3-(methoxycarbonyl)	4-(phenylmethyl)
63		=CH-		hydroxy	phenyl
64		=CH-		hydroxy	4-chlorophenyl
65		=CH-		morpholin-4-ylcarbonyl	phenylmethyl
66		=CH-		methoxyaminocarbonyl	4-fluorophenylmethyl
67		=CH-		5-methyl-[1,2,4]triazol-3-yl	4-fluorophenylmethyl
68		=CH-		3-carboxy	4-phenylmethyl
69		=CH-		2-carboxy	4-(4-fluoro-phenylmethoxy)

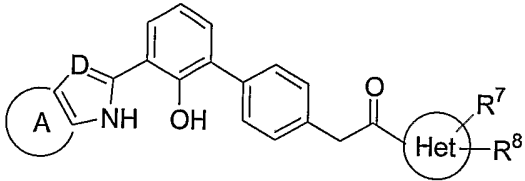
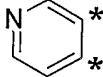
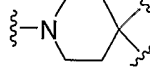
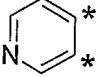
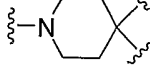
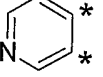
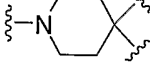
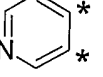
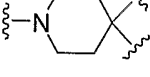
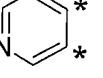
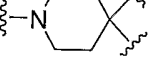
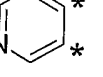
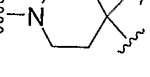
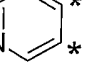
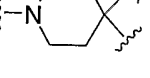
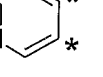
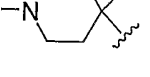
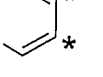
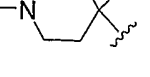
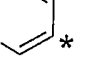
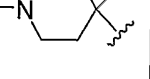
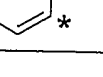
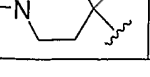
					
Cmpd. No.	A	D	Het	R ⁷	R ⁸
70		=CH-		2-(methoxycarbonyl)	4-(phenylmethyl)
71		=CH-		2-carboxy	4-phenylmethyl
72		=CCl-		hydroxy	phenylmethyl
73		=CH-		cyclopropylmethyl-aminocarbonyl	4-phenylmethyl
74		=CH-		4 <i>H</i> -5-oxo-[1,2,4]oxadiazol-3-yl	phenylmethyl
75		=CH-		4-(2,2,2-trifluoroethyl-aminocarbonyl)	4-fluorophenylmethyl
76		=CH-		phenylmethyloxycarbonylmethyl	4-fluorophenylmethyl
77		=CH-		carboxymethyl	4-fluorophenylmethyl
78		=CH-		methylsulfonylamino	4-fluorophenylmethyl
79		=N-		methoxycarbonyl	4-fluorophenylmethyl

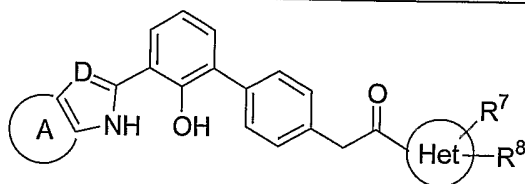


Cmpd. No.	A	D	Het	R ⁷	R ⁸
80		=N-		hydroxy	phenylmethyl
81		=CH-		aminocarbonylamino	4-fluorophenylmethyl
82		=CCl-		[1,2,3,4]tetrazol-5-yl	phenylmethyl
83		=N-		carboxy	4-fluorophenylmethyl
84		=CH-		4,5-dihydrothiazol-2-yl	4-fluorophenylmethyl
85		=CH-		methylcarbonylamino	4-fluorophenylmethyl
86		=CH-		[1,2,3]triazol-4-yl	4-fluorophenylmethyl
87		=CH-		cyclopropylmethylaminocarbonyl	4-fluorophenylmethyl
88		=CH-		phenylmethyloxycarbonylamino	phenylmethyl
89		=CH-		methoxycarbonyl	cyclopropylmethyl
90		=CH-		carboxy	cyclopropylmethyl

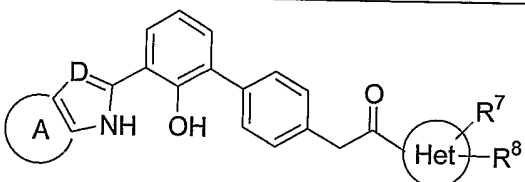
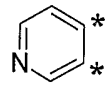
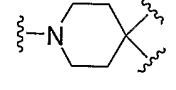
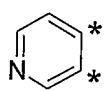
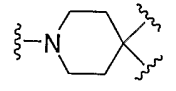
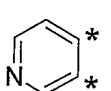
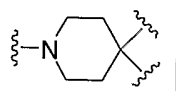
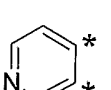
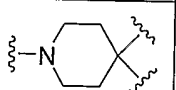
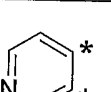
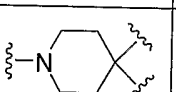
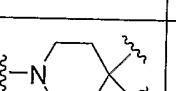
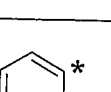
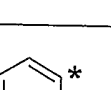
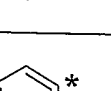
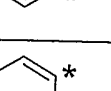


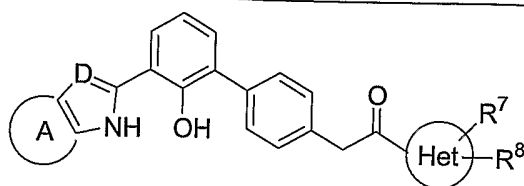
Cmpd. No.	A	D	Het	R ⁷	R ⁸
91		=CH-		amino	phenylmethyl
92		=N-		hydroxy	4-fluorophenylmethyl
93		=CH-		2-(<i>N,N</i> -diethylamino)-ethyloxycarbonyl	4-fluorophenylmethyl
94		=N-		dimethylaminocarbonyl	phenylmethyl
95		=CH-		hydroxymethyl	4-fluorophenylmethyl
96		=N-		hydroxymethyl	4-fluorophenylmethyl
97		=CH-		cyano	4-fluorophenylmethyl
98		=CH-		hydroxymethyl	cyclopropylmethyl
99		=N-		methoxycarbonyl	phenylmethyl
100		=N-		methoxycarbonyl	4-fluorophenylmethyl

					
Cmpd. No.	A	D	Het	R ⁷	R ⁸
101		=N-		hydroxy	3-trifluoromethylphenyl
102		=CH-		methoxycarbonyl	cyclopentylmethyl
103		=CH-		methoxycarbonyl	isobutyl
104		=CH-		cyclopropylcarbonyloxymethyl	4-fluorophenylmethyl
105		=CH-		methoxycarbonyl	3,3-difluoroprop-2-enyl
106		=CH-		methylsulfonylamino methyl	4-fluorophenylmethyl
107		=CH-		cyclopropylcarbonylamino methyl	4-fluorophenylmethyl
108		=CH-		methoxycarbonyl	2,2,2-trifluoroethyl
109		=CH-		cyano	cyclopropylmethyl
110		=CH-		aminocarbonyl	cyclopropylmethyl
111		=CH-		<i>N,N</i> -dimethylamioncarbonyl	cyclopropylmethyl



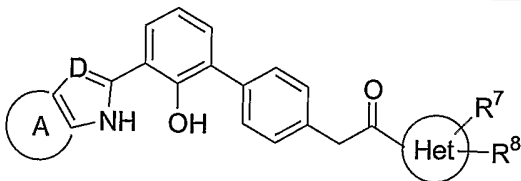
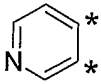
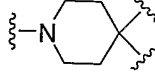
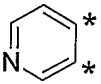
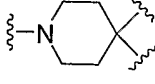
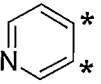
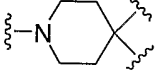
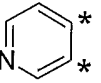
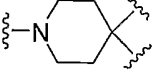
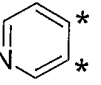
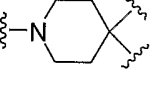
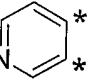
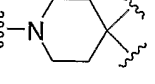
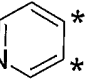
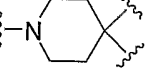
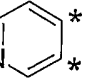
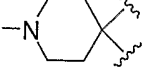
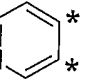
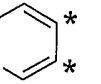
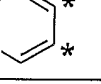
Cmpd. No.	A	D	Het	R ⁷	R ⁸
112		=CH-		oxazol-2-methyl	carboxy
113		=CH-		oxazol-2-methyl	methoxycarbonyl
114		=CH-		phenylamino	cyano
115		=CH-		phenylamino	aminocarbonyl
116		=CH-		4-fluorobenzyl	aminomethyl
117		=CH-		4-fluorobenzyl	2,2,2-trifluoro-1-hydroxyethyl
118		=CH-		4-fluorobenzyl	2-glycolic acid
119		=CH-		4-fluorobenzyl	ethoxycarbonyl
120		=CH-		4-fluorobenzyl	methoxycarbonylmethyl
121		=CH-		4-fluorobenzyl	2-glycolic acid methyl ester

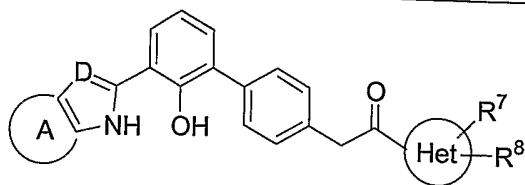
					
Cmpd. No.	A	D	Het	R ⁷	R ⁸
122		=CH-		4-fluorobenzyl	carboxymethoxy-methyl
123		=CH-		4-fluorobenzyl	2-carboxy-1-hydroxyethyl
124		=CH-		4-fluorobenzyl	methoxyethoxy-carbonyl
125		=CH-		4-fluorobenzyl	methoxyethylamino-carbonyl
126		=CH-		4-fluorobenzyl	2-hydroxy-1-hydroxymethyl-ethylamino
127		=CH-		4-fluorobenzyl	ethoxycarbonyl-methoxymethyl
128		=CH-		4-fluorobenzyl	methoxyethoxycarbonyl-methyl
129		=CH-		4-fluorobenzyl	1-hydroxy-2-ethoxycarbonyl-ethyl
130		=CH-		4-fluorobenzyl	2-hydroxy-3-carboxyprop-1-ylaminocarbonyl
131		=CH-		4-fluorobenzyl	(S)-3-hydroxy-3-carboxyprop-1-ylaminocarbonyl
132		=CH-		4-fluorobenzyl	N,N-dimethyl-aminoacetyl-aminomethyl



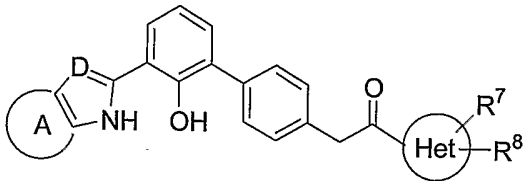
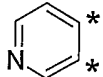
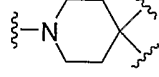
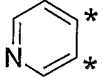
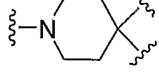
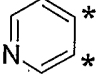
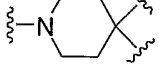
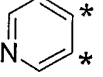
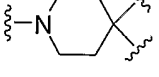
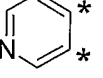
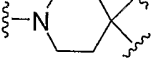
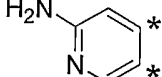
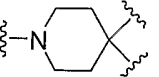
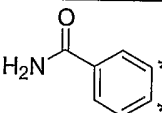
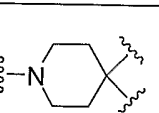
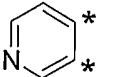
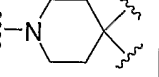
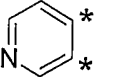
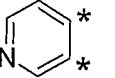
Cmpd. No.	A	D	Het	R ⁷	R ⁸
133		=CH-		4-fluorobenzyl	<i>N,N</i> -dimethyl-aminoethylaminocarbonyl
134		=CH-		4-fluorobenzyl	(<i>S</i>)-2-aminosuccinamoyl-aminomethyl
135		=CH-		4-fluorobenzyl	(<i>S</i>)-3-methoxycarbonyl-3-hydroxypropyl-aminocarbonyl
136		=CH-		4-fluorobenzyl	(2-hydroxy-3-methoxycarbonyl)-prop-1-yl-aminocarbonyl
137		=CH-		4-fluorobenzyl	(<i>S</i>)-2-hydroxy-2-methoxycarbonylethyl-aminomethyl
138		=CH-		4-fluorobenzyl	(<i>R</i>)-2-hydroxy-2-methoxycarbonylethyl-aminomethyl
139		=CH-		4-fluorobenzyl	<i>N,N</i> -diethylaminoethoxymethyl
140		=CH-		4-fluorobenzyl	<i>N,N</i> -diethylaminocarbonylmethoxymethyl
141		=CH-		4-fluorobenzyl	<i>N,N</i> -diethylaminoethylaminocarbonyl
142		=CH-		1-methyl-cyclopropylmethyl	benzyloxycarbonyl

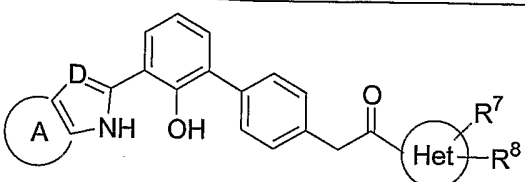
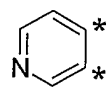
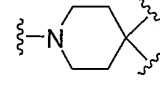
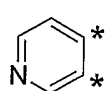
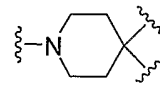
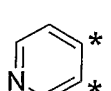
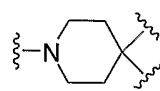
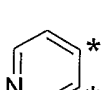
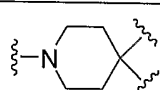
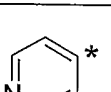
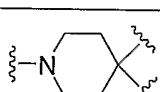
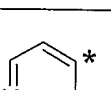
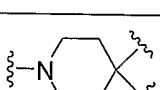
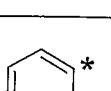
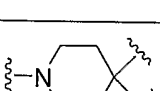
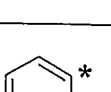
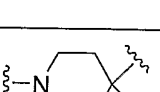
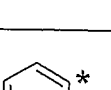
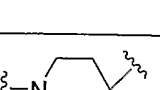
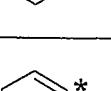
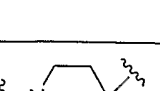
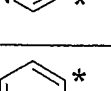
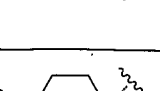
Cmpd. No.	A	D	Het	R ⁷	R ⁸
143		=CH-		4-fluorobenzyl	morpholin-4-ylethoxycarbonyl
144		=CH-		4-fluorobenzyl	morpholin-4-ylethylaminocarbonyl
145		=CH-		4-fluorobenzyl	piperidin-1-ylethylaminocarbonyl
146		=CH-		4-fluorobenzyl	1 <i>H</i> -tetrazol-5-yl-aminocarbonyl
147		=CH-		4-fluorobenzyl	4-trimethylsilyl-1 <i>H</i> -[1,2,3]triazol-4-yl
148		=CH-		4-fluorobenzyl	benzoxazol-2-yl-aminomethyl
149		=N-		4-fluorobenzyl	cyano
150		=N-		benzyl	amino
151		=N-		benzyl	carboxy
152		=N-		4-fluorobenzyl	<i>N,N</i> -diethylaminoethoxy-carbonyl
153		=N-		4-fluorobenzyl	morpholin-4-ylethoxycarbonyl

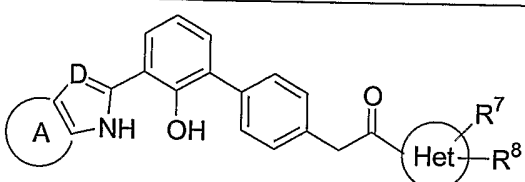
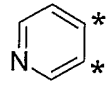
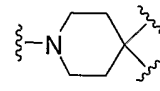
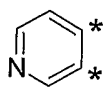
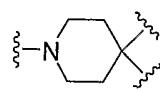
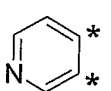
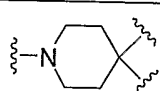
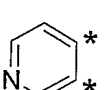
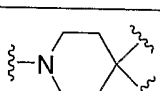
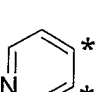
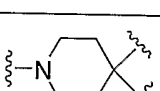
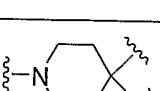
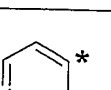
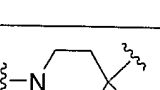
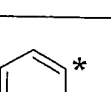
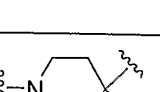
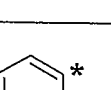
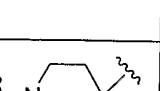
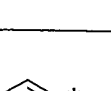
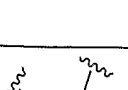
					
Cmpd. No.	A	D	Het	R ⁷	R ⁸
154		=N-		4-fluorobenzyl	5-methyl-2 <i>H</i> -[1,2,4]triazol-3-yl
155		=CH-		carboxy	2,2-difluoroethyl
156		=CH-		carboxy	2,2,2-difluoroethyl
157		=CH-		carboxy	methylsulfonylmethyl
158		=CH-		methoxycarbonyl	2,2-difluoroethyl
159		=CH-		carboxy	3,3-difluoropropyl
160		=CH-		carboxy	2-methoxyethyl
161		=CH-		methoxycarbonyl	methylsulfonylmethyl
162		=CH-		carboxy	2-methylprop-3-enyl
163		=CH-		carboxy	isobutyl
164		=CH-		methoxycarbonyl	3,3-difluoropropyl

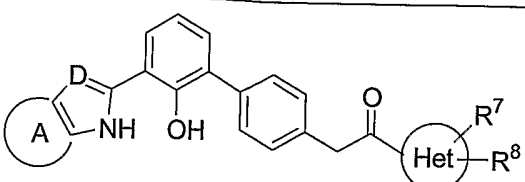
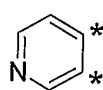
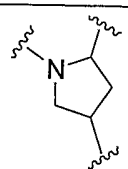
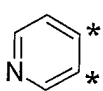
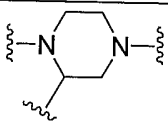
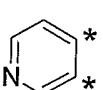
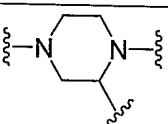
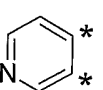
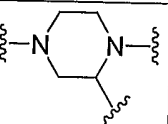


Cmpd. No.	A	D	Het	R ⁷	R ⁸
165		=CH-		methoxycarbonyl	2-methoxyethyl
166		=CH-		methoxycarbonyl	2-methylprop-3-enyl
167		=CH-		methoxycarbonyl	isopentyl
168		=CCl-		carboxy	cyclopropylmethyl
169		=CH-		carboxy	2,2-difluorocyclopropylmethyl
170		=CH-		carboxy	1-cyclopropyl-1-hydroxy-methyl
171		=CH-		carboxy	cyclopropylmethyl
172		=CH-		cyano	cyclopropylmethyl
173		=CH-		methylthiomethyl	cyclopropylmethyl
174		=CCl-		methoxycarbonyl	cyclopropylmethyl

					
Cmpd. No.	A	D	Het	R ⁷	R ⁸
175		=CH-		methoxycarbonyl	2,2-difluorocyclopropylmethyl
176		=CH-		methylsulfonylmethyl	cyclopropylmethyl
177		=CH-		methoxycarbonyl	1-cyclopropyl-1-hydroxy-methyl
178		=CH-		methylaminocarbonyl	cyclopropylmethyl
179		=CH-		cyanomethylaminocar-bonyl	cyclopropylmethyl
180		=CH-		methoxycarbonyl	cyclopropylmethyl
181		=N-		carboxy	cyclopropylmethyl
182		=CH-		ethoxycarbonyl	cyclopropylmethyl
183		=CH-		methoxycarbonyl	1-methylcyclopropylmethyl
184		=CH-		2-carboxy-1-hydroxyethyl	cyclopropylmethyl

					
Cmpd. No.	A	D	Het	R ⁷	R ⁸
185		=CH-		2,2,2-trifluoroethylaminomethyl	cyclopropylmethyl
186		=CH-		2,2,2-trifluoroethylaminocarbonyl	cyclopropylmethyl
187		=C(CH ₂ COOH)-		cyano	cyclopropylmethyl
188		=CH-		2-ethoxycarbonyl-1-hydroxyethyl	cyclopropylmethyl
189		=CH-		N-(2-methoxyethyl)N-methylaminocarbonyl	cyclopropylmethyl
190		=CH-		2-(methylcarbonylamino)-ethoxycarbonyl	cyclopropylmethyl
191		=CH-		3-carboxy-2-hydroxy-propylaminocarbonyl	cyclopropylmethyl
192		=CH-		3-carboxy-3(R)-hydroxy-propylaminocarbonyl	cyclopropylmethyl
193		=CH-		3-methoxycarbonyl-3(R)-hydroxy-propylaminocarbonyl	cyclopropylmethyl
194		=CH-		3-methoxycarbonyl-2-hydroxy-propylaminocarbonyl	cyclopropylmethyl
195		=CH-		carboxy	cyclobutylmethyl

					
Cmpd. No.	A	D	Het	R ⁷	R ⁸
196		=CH-		methoxycarbonyl	cyclobutylmethyl
197		=CH-		carboxy	cyclopentylmethyl
198		=CH-		methoxycarbonyl	tetrahydrofuranylmethyl
199		=CH-		1-cyanocyclopropylaminocarbonyl	cyclopropylmethyl
200		=CH-		cyclopropylaminocarbonyl	cyclopropylmethyl
201		=CH-		cyclopropylcarbonylamino	cyclopropylmethyl
202		=CH-		tetrahydrofuranylmethoxy carbonyl	cyclopropylmethyl
203		=CH-		2-(pyrrolidinyl)-ethyloxycarbonyl	cyclopropylmethyl
204		=CH-		N-methylpyrrolidin-2-ylmethyloxycarbonyl	cyclopropylmethyl
205		=N-		4-benzyloxy	2-carboxy

					
Cmpd. No.	A	D	Het	R ⁷	R ⁸
206		=N-		4-benzyloxy	2-methoxycarbonyl
207		=N-		N-phenylmethyl	2-carboxy
208		=N-		N-phenylmethyl	3-carboxy
209		=N-		N-phenylmethyl	3-(methoxycarbonyl)

and Compounds 1-154 are named:

4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylic acid;

4-(3,4-difluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylic acid;

4-(3-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylic acid;

N-(4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carbonyl)-methanesulfonamide;

4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carbonitrile;

4-(1*H*-tetrazol-5-yl)-4-(phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

N-hydroxy-4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxamide;

methyl 4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-

biphenyl-4-yl]-acetyl}-piperidine-4-carboxylate;
4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxamide;
N-(4,5-dihydro-thiazol-2-yl)-4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxamide;
methyl 4-(3,4-difluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylate;
methyl 4-(3-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylate;
methyl 4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylate;
4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylic acid;
[(4-(4-fluoro-benzyl)-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carbonyl)-amino]-acetic acid;
4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-*N*-methyl-piperidine-4-carboxamide;
methyl 1-{2-[2'-hydroxy-3'-(1H-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-4-thiophen-3-ylmethyl-piperidine-4-carboxylate;
4-(2-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylic acid;
1-{2-[2'-hydroxy-3'-(1H-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-4-thiophen-3-ylmethyl-piperidine-4-carboxylic acid;
methyl [(4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carbonyl)-amino]-acetate;
4-(methylcarbonyloxy)-4-(phenylmethyl)-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;
N-(2,2,2-trifluoro-ethyl)-4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxamide;
4-(hydroxy)-4-(4-fluorophenylmethyl)-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;
4-(3,4-difluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[3,2-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylic acid;

N-phenylmethoxy-4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxamide;

4-(hydroxy)-4-(phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylic acid;

methyl 4-(2-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylate;

methyl 4*R*-(4-fluoro-phenylmethoxy)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-pyrrolidine-2*S*-carboxylate;

methyl 4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylate;

methyl 4-(3,4-difluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylate;

N-(1*H*-tetrazol-5-yl)-4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxamide;

methyl 4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylate;

4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylic acid;

N,N-dimethyl-4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxamide;

methyl 4-(2-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylate;

N-thiazol-2-yl-4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxamide;

4-(fluoro)-4-(phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

methyl 4-allyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylate;

4-allyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylic acid;

4-(2-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylic acid;

4-(hydroxy)-4-(phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

methyl 4-phenylmethoxy-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-pyrrolidine-2-carboxylate;

4-fluoro-4-(phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

N-dimethyl-4-Phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxamide;

4-phenylmethoxy-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-pyrrolidine-2-carboxylic acid;

4-amino-4-(phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

4-hydroxy-4-phenyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

3-hydroxy-4-(3-trifluoromethyl-phenyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

4-hydroxy-4-(4-chlorophenyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

4-hydroxy-4-(3-trifluoromethyl-phenyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

4-methyl-4-(methoxycarbonyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

4-phenylmethyl-4-[(phenylmethoxy)-carbonylamino]-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

4-phenylmethyl-2-(hydroxymethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

methyl 1-phenylmethyl-4-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine-2-carboxylate;

methyl 4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine-2-carboxylate;

1-phenylmethyl-4-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine-2-carboxylic acid;

4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine-2-carboxylic acid;

4(R)-(4-fluoro-phenylmethoxy)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-pyrrolidine-2(*S*)-carboxylic acid;

N-(1*H*-[1,2,4]triazol-3-yl)-4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxamide;

methyl 4*R*-(4-fluoro-phenylmethoxy)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-pyrrolidine-2*R*-carboxylate;

methyl 1-phenylmethyl-4-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine-2-carboxylate;

4-hydroxy-4-phenyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

4-hydroxy-4-(4-chlorophenyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

4-(morpholin-4-ylcarbonyl)-4-(phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

N-methoxy-4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxamide;

4-(5-methyl-[1,2,4]triazol-3-yl)-4-(4-fluorophenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

1-phenylmethyl-4-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine-2-carboxylic acid;

4(R)-(4-fluoro-phenylmethoxy)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-pyrrolidine-2(*R*)-carboxylic acid;

2-(methoxycarbonyl)-4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

2-carboxy-4-(phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-hydroxy-4-(phenylmethyl)-1-{2-[2'-hydroxy-3'-(3-chloro-1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

N-cyclopropylmethyl-4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxamide;

4-(4*H*-5-oxo-[1,2,4]oxadiazol-3-yl)-4-(phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

N-(2,2,2-trifluoro-ethyl)-4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxamide;

phenylmethyl (4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidin-4-yl)-acetate;

(4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidin-4-yl)-acetic acid;

N-(4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidin-4-yl)-methanesulfonamide;

methyl 4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-imidazo[4,5-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylate;

4-hydroxy-4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-imidazo[4,5-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

(4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidin-4-yl)-urea;

4-(1*H*-tetrazol-5-yl)-4-phenylmethyl-1-{2-[2'-hydroxy-3'-(3-chloro-1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-imidazo[4,5-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylic acid;

4-(4,5-dihydro-thiazol-2-yl)-4-(4-fluorophenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

N-(4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidin-4-yl)-acetamide;

4-(1*H*-[1,2,3]triazol-4-yl)-4-(4-fluorophenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

N-cyclopropylmethyl-4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxamide;

phenylmethyl (4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidin-4-yl)-carbamate;

methyl 4-cyclopropylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylate;

4-cyclopropylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylic acid;

4-amino-4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

4-hydroxy-4-(4-fluorophenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

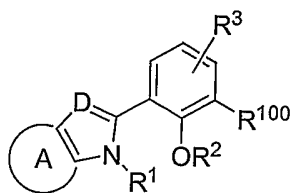
- 2-diethylamino-ethyl 4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylate;
- N,N*-dimethyl-4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[3,2-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxamide;
- 4-(*N,N*-dimethylaminocarbonyl)-4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-imidazo[4,5-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;
- 4-(hydroxymethyl)-4-(4-fluorophenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;
- 4-(hydroxymethyl)-4-(4-fluorophenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-imidazo[4,5-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;
- 4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carbonitrile;
- 4-(hydroxymethyl)-4-(cyclopropylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;
- methyl 4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-imidazo[4,5-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylate;
- methyl 1-{2-[3'-(5,7-dihydro-4*H*-purin-8-yl)-2'-hydroxy-biphenyl-4-yl]-acetyl}-4-(4-fluoro-phenylmethyl)-piperidine-4-carboxylate;
- 4-hydroxy-4-(3-trifluoromethylphenyl)-1-{2-[2'-hydroxy-3'-(1*H*-imidazo[4,5-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;
- methyl 4-cyclopentylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylate;
- methyl 1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-4-isobutyl-piperidine-4-carboxylate;
- 4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidin-4-ylmethyl cyclopropanecarboxylate;
- methyl 4-(3,3-difluoro-allyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylate;
- N*-(4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidin-4-ylmethyl)-methanesulfonamide;
- N*-(4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidin-4-ylmethyl)-cyclopropanecarboxamide;
- methyl 1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-4-(2,2,2-trifluoro-ethyl)-piperidine-4-carboxylate;

- 4-cyano-4-(cyclopropylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;
- 4-(aminocarbonyl)-4-(cyclopropylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;
- 4-(*N,N*-dimethylamioncarbonyl)-4-(cyclopropylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine
- 1-{[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-4-oxazol-2-ylmethyl-piperidine-4-carboxylic acid;
- 1-{[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-4-oxazol-2-ylmethyl-piperidine-4-carboxylic acid methyl ester;
- 1-{[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-4-phenylamino-piperidine-4-carbonitrile;
- 1-{[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-4-phenylamino-piperidine-4-carboxylic acid amide;
- 1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-4-(4-fluorobenzyl)-4-aminomethyl-piperidine;
- 1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-4-(4-fluorobenzyl)-4-(2,2,2-trifluoro-1-hydroxyethyl)-piperidine;
- (4-(4-fluoro-benzyl)-1-{[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidin-4-yl)-hydroxy-acetic acid;
- 4-(4-fluoro-benzyl)-1-{[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylic acid ethyl ester;
- (4-(4-fluoro-benzyl)-1-{[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidin-4-yl)-acetic acid methyl ester;
- (4-(4-fluoro-benzyl)-1-{[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidin-4-yl)-hydroxy-acetic acid methyl ester;
- (4-(4-fluoro-benzyl)-1-{[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidin-4-ylmethoxy)-acetic acid;
- 3-(4-(4-fluoro-benzyl)-1-{[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidin-4-yl)-3-hydroxy-propionic acid;
- 4-(4-fluoro-benzyl)-1-{[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylic acid 2-methoxy-ethyl ester;
- 4-(4-fluoro-benzyl)-1-{[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylic acid (2-methoxy-ethyl)-amide;

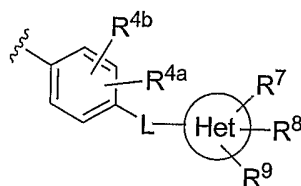
- 4-(4-fluoro-benzyl)-1-{[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylic acid (2-hydroxy-1-hydroxymethyl-ethyl)-amide;
- (4-(4-fluoro-benzyl)-1-{[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidin-4-ylmethoxy)-acetic acid ethyl ester;
- (4-(4-fluoro-benzyl)-1-{[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidin-4-yl)-acetic acid 2-methoxy-ethyl ester;
- 3-(4-(4-fluoro-benzyl)-1-{[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidin-4-yl)-3-hydroxy-propionic acid ethyl ester;
- 4-[(4-(4-fluoro-benzyl)-1-{[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carbonyl)-amino]-3-hydroxy-butyric acid;
- 4-[(4-(4-fluoro-benzyl)-1-{[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carbonyl)-amino]-(*S*)-2-hydroxy-butyric acid;
- 2-dimethylamino-*N*-(4-(4-fluoro-benzyl)-1-{[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidin-4-ylmethyl)-acetamide;
- 4-(4-fluoro-benzyl)-1-{[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylic acid (2-dimethylamino-ethyl)-amide;
- (*S*)-3-amino-*N*-(4-(4-fluoro-benzyl)-1-{[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidin-4-ylmethyl)-succinamic acid;
- 4-[(4-(4-fluoro-benzyl)-1-{[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carbonyl)-amino]-(*S*)-2-hydroxy-butyric acid methyl ester;
- 4-[(4-(4-fluoro-benzyl)-1-{[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carbonyl)-amino]-3-hydroxy-butyric acid methyl ester;
- N*-(4-(4-fluoro-benzyl)-1-{[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidin-4-ylmethyl)-(*S*)-2-hydroxy-succinamic acid methyl ester;
- N*-(4-(4-fluoro-benzyl)-1-{[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidin-4-ylmethyl)-(*R*)-2-hydroxy-succinamic acid methyl ester;
- 1-{[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-4-(4-fluorobenzyl)-4-(2-dimethylamino-ethoxymethyl)-piperidine;
- N,N*-Diethyl-2-(4-(4-fluoro-benzyl)-1-{[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidin-4-ylmethoxy)-acetamide;
- 4-(4-fluoro-benzyl)-1-{[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylic acid (2-diethylamino-ethyl)-amide;
- 1-{[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-4-(1-methyl-cyclopropylmethyl)-piperidine-4-carboxylic acid benzyl ester;

- 4-(4-fluoro-benzyl)-1-{{2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylic acid 2-morpholin-4-yl-ethyl ester;
- 4-(4-fluoro-benzyl)-1-{{2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylic acid (2-morpholin-4-yl-ethyl)-amide;
- 4-(4-fluoro-benzyl)-1-{{2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylic acid (2-piperidin-1-yl-ethyl)-amide;
- 4-(4-fluoro-benzyl)-1-{{2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylic acid (1*H*-tetrazol-5-yl)-amide;
- 1-{{2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-4-(4-fluorobenzyl)-4-[5-(trimethylsilanyl)-1*H*-[1,2,3]triazol-4-yl]-piperidine;
- 1-{{2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-4-(4-fluorobenzyl)-4-(benzoxazol-2-ylaminomethyl)-piperidine;
- 4-(4-fluoro-benzyl)-1-{{2'-hydroxy-3'-(3*H*-imidazo[4,5-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carbonitrile;
- 1-{{2'-hydroxy-3'-(3*H*-imidazo[4,5-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-4-amino-4-benzyl-piperidine;
- 4-benzyl-1-{{2'-hydroxy-3'-(3*H*-imidazo[4,5-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylic acid;
- 4-(4-fluoro-benzyl)-1-{{2'-hydroxy-3'-(3*H*-imidazo[4,5-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylic acid 2-diethylamino-ethyl ester;
- 4-(4-fluoro-benzyl)-1-{{2'-hydroxy-3'-(3*H*-imidazo[4,5-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylic acid 2-morpholin-4-yl-ethyl ester;
- 1-{{2'-hydroxy-3'-(3*H*-imidazo[4,5-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-4-(4-fluorobenzyl)-4-(5-methyl-2*H*-[1,2,4]triazol-3-yl)-piperidine;
- 4-benzyloxy-1-{{2'-hydroxy-3'-(3*H*-imidazo[4,5-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-pyrrolidine-2-carboxylic acid;
- 4-benzyloxy-1-{{2'-hydroxy-3'-(3*H*-imidazo[4,5-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-pyrrolidine-2-carboxylic acid methyl ester
- 4-benzyl-1-{{2'-hydroxy-3'-(3*H*-imidazo[4,5-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine-2-carboxylic acid;
- 1-benzyl-4-{{2'-hydroxy-3'-(3*H*-imidazo[4,5-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine-2-carboxylic acid; and
- 1-benzyl-4-{{2'-hydroxy-3'-(3*H*-imidazo[4,5-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine-2-carboxylic acid methyl ester.

Another selected group of compounds of the invention are provided in Table 2, having Formula I



where R^1 , R^2 , and R^3 are hydrogen; and R^{100} is

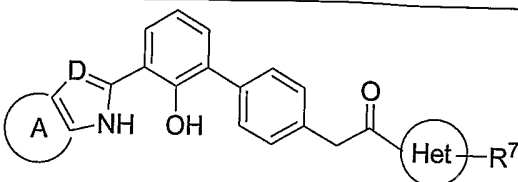
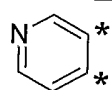
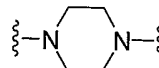
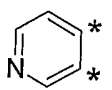
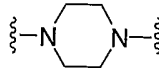
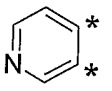
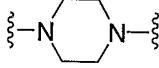
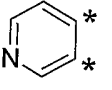
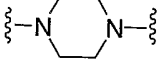
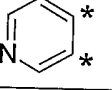
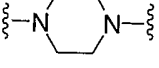
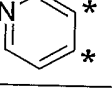
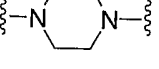
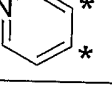
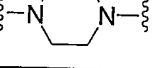
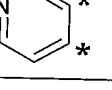
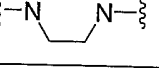
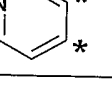
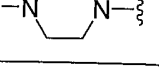
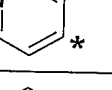
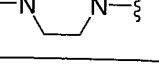
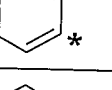
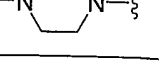
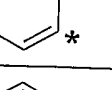
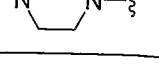
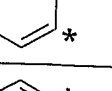
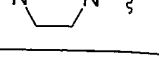
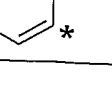
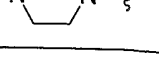


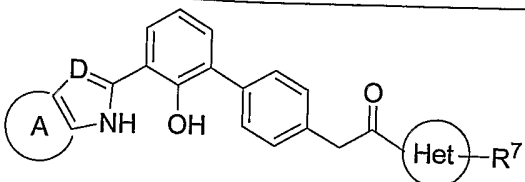
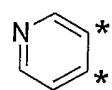
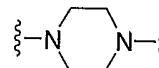
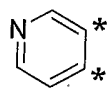
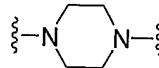
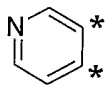
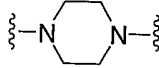
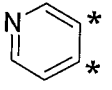
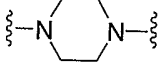
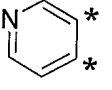
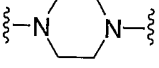
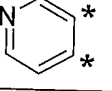
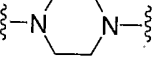
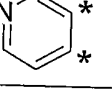
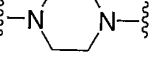
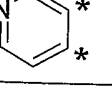
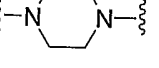
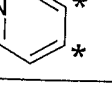
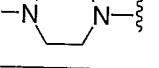
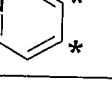
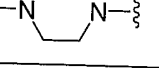
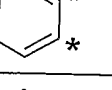
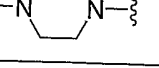
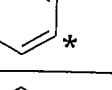
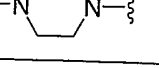
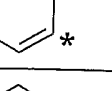
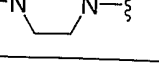
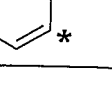
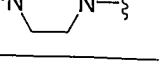
(A1)

where R^{4a} , R^{4b} , R^8 , and R^9 are hydrogen; L is $-X^1-Y^1-Z^1-$ where X^1 is $-CH_2-$, Y^1 is $-C(O)-$, and Z^1 is a bond; and all other groups are as defined below:

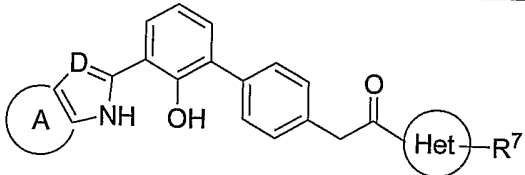
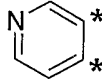
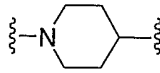
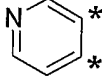
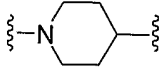
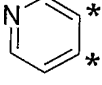
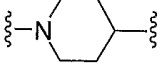
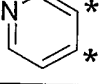
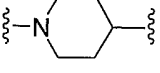
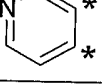
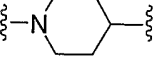
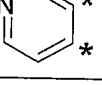
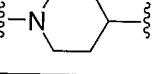
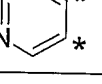
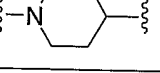
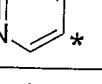
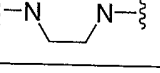
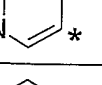
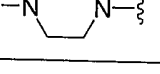
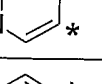
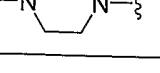
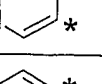
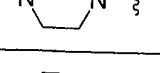
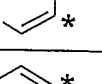
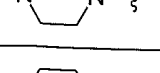
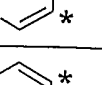
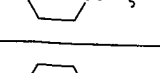
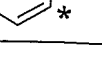
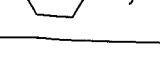
Table 2.

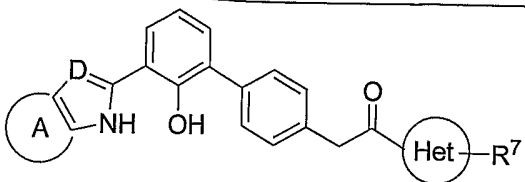
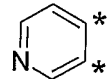
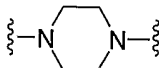
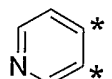
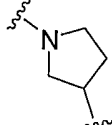
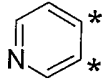
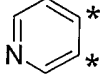
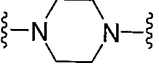
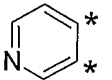
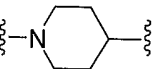
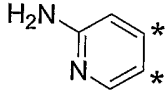
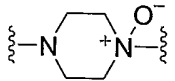
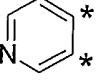
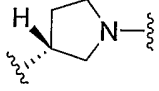
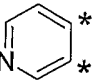
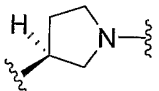
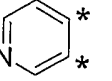
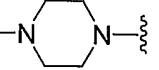
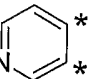
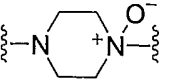
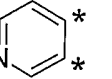
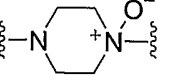
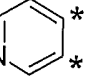
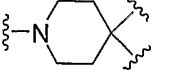
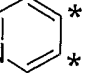
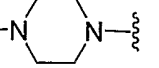
Cm pd. No.	A	D	Het	R^7
210		$=CH-$		2-fluorophenylmethyl
211		$=CH-$		phenylmethyl
212		$=CH-$		phenyl
213		$=CH-$		1-methylbutyl
214		$=CH-$		ethyl
215		$=CH-$		pyridin-4-yl

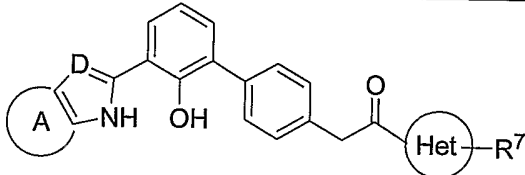
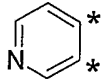
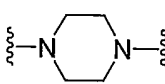
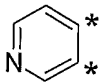
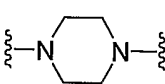
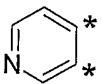
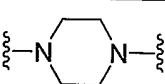
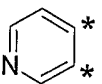
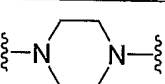
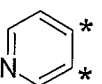
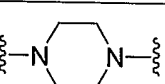
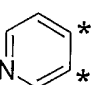
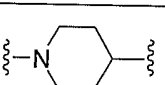
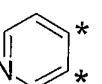
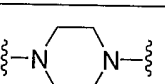
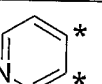
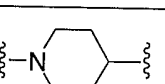
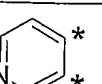
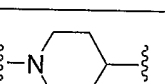
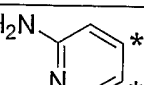
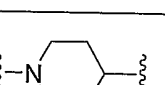
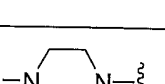
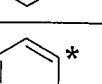
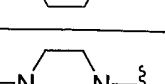
				
Cm pd. No.	A	D	Het	R ⁷
216		=CH-		isopropyl
217		=CH-		phenylmethyl
218		=CH-		(thien-2-yl)methyl
219		=CH-		4-fluorophenylmethyl
220		=CH-		4-chlorophenylmethyl
221		=CH-		2-fluorophenylmethyl
222		=CH-		(thien-2-yl)methyl
223		=CH-		phenylmethyl
224		=CH-		4-chlorophenylmethyl
225		=CH-		thien-3-ylmethyl
226		=CH-		3-fluorophenylmethyl
227		=CH-		3-chlorophenylmethyl
228		=CH-		4-methylpyridin-2-yl
229		=CH-		2-(thien-2-yl)ethyl

				
Cm pd. No.	A	D	Het	R ⁷
230		=CH-		4-fluorophenylmethyl
231		=CH-		2-chloro-4-fluorophenylmethyl
232		=CH-		2-chlorophenylmethyl
233		=CH-		3-carboxyphenylmethyl
234		=CH-		2-methylphenylmethyl
235		=CH-		phenethyl
236		=CH-		pyridin-4-ylmethyl
237		=CH-		pyridin-3-ylmethyl
238		=CH-		phenylaminocarbonyl
239		=CH-		pyridin-2-yl
240		=CH-		3-methoxycarbonyl-phenylmethyl
241		=CH-		3-methylpyridin-2-yl
242		=CH-		4-fluorophenylaminocarbonyl
243		=CH-		isobutyl

Cm pd. No.	A	D	Het	R ⁷
244		=CH-		phenylthiomethylcarbonyl
245		=CH-		phenylmethyl
246		=CH-		3,4-dichlorophenylmethyl
247		=CH-		4-fluorophenyl
248		=CH-		pyridin-2-ylmethyl
249		=CH-		cyclohexylmethyl
250		=CH-		isopentyl
251		=CH-		isopropylaminocarbonyl
252		=CH-		1-phenyleth-1-yl
253		=CH-		phenylmethyl
254		=CH-		phenylmethyl
255		=CH-		2-oxo-1,3-dihydro- benzimidazol-1-yl
256		=CH-		2-methyl-benzimidazol-1-yl

				
Cm pd. No.	A	D	Het	R ⁷
257		=CH-		phenylcarbonyl
258		=CH-		phenoxy
259		=CH-		1-hydroxy-1-phenyl-methyl
260		=CH-		hydroxy
261		=CH-		phenylmethyl
262		=CH-		3,4-difluorophenylmethyl
263		=CH-		benzimidazol-1-yl
264		=CH-		thieno[3,2-d]pyrimidin-7-yl
265		=CH-		2-methyl-pyridin-5-yl
266		=CH-		2-(morpholin-4-yl)-ethyl
267		=CH-		pyridin-4-yl
268		=CH-		phenylaminocarbonyl
269		=CH-		pyridin-2-ylaminocarbonylmethyl
270		=CH-		1-phenyl-eth-1-yl

				
Cm pd. No.	A	D	Het	R ⁷
271		=CH-		ethylaminocarbonyl
272		=CH-		3-(4-chloro-phenylmethoxy)
273		=CH-		<i>N</i> -(ethylcarbonyl)- <i>N</i> -phenyl-amino
274		=CH-		cyclopentylcarbonyl
275		=CH-		methoxyethyloxycarbonylmethyl
276		=CH-		4-fluorophenylmethyl
277		=CH-		benzyl
278		=CH-		benzyl
279		=CH-		<i>N</i> -(pyridin-2-yl)methyl
280		=CH-		benzyl
281		=CH-		4-fluorobenzyl
282		=CH-		benzyl
283		=CH-		<i>N</i> -phenethyl

				
Cm pd. No.	A	D	Het	R ⁷
284		=N-		N-phenylsulfonyl
285		=N-		N-(Pyridin-2-yl)methyl
286		=N-		N-Benzyl
287		=N-		N-4-chlorobenzyl
288		=N-		4-fluorobenzyl
289		=CH-		carboxy
290		=CH-		<i>N,N</i> -dimethylaminocarbonyl
291		=CH-		cyclopropylaminocarbonyl
292		=CH-		cyclopropylmethylaminocarbonyl
293		=CH-		cyclopropylmethyloxycarbonyl
294		=CH-		piperidinylcarbonyl
295		=CH-		benzoxazol-2-yl

and are named as:

4-(2-fluorophenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-(phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-

acetyl}-3,6-dihydro-2*H*-pyridine;

4-(phenyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-(1-methylbutyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-ethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-(pyridin-4-yl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-(isopropyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-(phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-[(thien-2-yl)methyl]-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-(4-chloro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-(2-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-[(thien-2-yl)methyl]-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-(4-chlorophenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-[(thien-3-yl)methyl]-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-(3-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-(3-chloro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-(4-methylpyridin-2-yl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-

biphenyl-4-yl]-acetyl}-piperazine;
4-[2-(thien-2-yl)ethyl]-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;
4-(4-fluorophenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;
4-(2-chloro-4-fluorophenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;
4-(2-chlorophenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;
4-(3-carboxyphenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;
4-(2-methylphenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;
4-(phenethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;
4-(pyridin-4-ylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;
4-(pyridin-3-ylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;
4-(phenylaminocarbonyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;
4-(pyridin-2-yl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;
4-(3-methoxycarbonylphenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;
4-(3-methylpyridin-2-yl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;
4-(4-fluorophenylaminocarbonyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;
4-isobutyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;
4-(phenylthiomethylcarbonyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;
4-(phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-

acetyl}-homopiperazine;

4-(3,4-dichloro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-(4-fluoro-phenyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-(pyridin-2-ylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-(cyclohexylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-(isopentyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-(isopropylaminocarbonyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-(1-phenyl-eth-1-yl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-(phenylmethyl)-1-{2-[2'-hydroxy-3'-(4-chloro-1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-(phenylmethyl)-1-{2-[2'-hydroxy-3'-(6-chloro-1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-(2-oxo-1,3-dihydro-benzoimidazol-1-yl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

4-(2-methyl-benzoimidazol-1-yl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

4-(phenylcarbonyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

4-(phenoxy)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

4-(1-hydroxy-1-phenyl-methyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

4-hydroxy-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

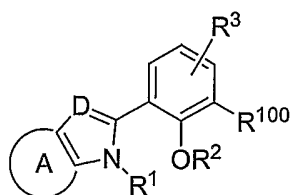
4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

4-(3,4-difluorophenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-

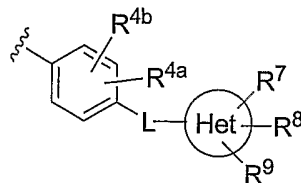
biphenyl-4-yl]-acetyl}-piperidine;
4-(benzoimidazol-1-yl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-
biphenyl-4-yl]-acetyl}-piperidine;
4-(thieno[3,2-*d*]pyrimidin-7-yl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-
biphenyl-4-yl]-acetyl}-piperazine;
4-(2-methyl-pyridin-5-yl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-
biphenyl-4-yl]-acetyl}-piperazine;
4-[2-(morpholin-4-yl)-ethyl]-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-
biphenyl-4-yl]-acetyl}-piperazine;
4-(pyridin-4-yl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-
acetyl}-piperazine;
4-(phenylaminocarbonyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-
biphenyl-4-yl]-acetyl}-piperazine;
4-(pyridin-2-ylaminocarbonylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-
2-yl)-biphenyl-4-yl]-acetyl}-piperazine;
4-(1-phenyl-eth-1-yl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-
4-yl]-acetyl}-piperazine;
4-(ethylaminocarbonyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-
biphenyl-4-yl]-acetyl}-piperazine;
3-(4-chloro-phenylmethyloxy)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-
biphenyl-4-yl]-acetyl}-pyrrolidine;
4-[*N*-(ethylcarbonyl)-*N*-phenyl-amino]-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-
c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;
4-(cyclopentanecarbonyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-
biphenyl-4-yl]-acetyl}-piperazine;
4-(methoxyethyloxycarbonylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-
2-yl)-biphenyl-4-yl]-acetyl}-piperidine;
1-[3'-(5-amino-1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-2'-hydroxy-biphenyl-4-yl]-4-(4-
fluorobenzyl)-4-oxy-piperazine;
(*R*) *N*-(1-benzyl-pyrrolidin-3-yl)-2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-
biphenyl-4-yl]-acetamide;
(*S*) *N*-(1-benzyl-pyrrolidin-3-yl)-2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-
biphenyl-4-yl]-acetamide;

- 1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-4-(pyridin-2-ylmethyl)-piperazine;
- 1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-4-benzyl-4-oxy-piperazine;
- 1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-4-(4-fluorobenzyl)-4-oxy-piperazine;
- 1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-4-benzyl-piperidine;
- 1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-4-phenethyl-piperazine
- 1-{[2'-hydroxy-3'-(3*H*-imidazo[4,5-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-4-phenylsulfonyl-piperazine;
- 1-{[2'-hydroxy-3'-(3*H*-imidazo[4,5-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-4-(pyridin-2-ylmethyl)-piperazine;
- 1-{[2'-hydroxy-3'-(3*H*-imidazo[4,5-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-4-benzyl-piperazine;
- 1-{[2'-hydroxy-3'-(3*H*-imidazo[4,5-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-4-(4-chlorobenzyl)-piperazine;
- 1-{[2'-hydroxy-3'-(3*H*-imidazo[4,5-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-4-(4-fluorobenzyl)-piperazine;
- 4-carboxy-{[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;
- 4-(*N,N*-dimethylaminocarbonyl)-{[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;
- 4-(cyclopropylaminocarbonyl)-{[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;
- 4-(cyclopropylmethylaminocarbonyl)-{[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;
- 4-(cyclopropylmethyloxycarbonyl)-{[2'-hydroxy-3'-(5-amino-1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;
- 4-(piperidinylcarbonyl)-{[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine; and
- 1-{[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-4-(benzoxazol-2-yl)-piperazine.

Another selected group of compounds of the invention are provided in Table 3, having Formula I



where R^1 , R^2 , and R^3 are hydrogen; D is $=CR^6$ - where R^6 is hydrogen; and R^{100} is

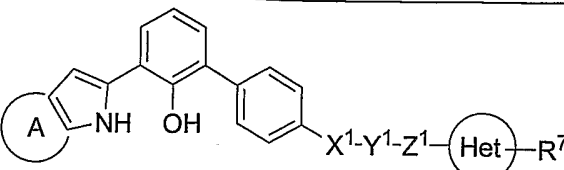
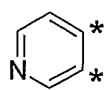
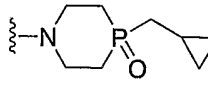
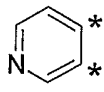
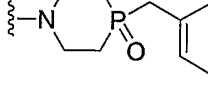


(A1)

where R^{4a} , R^{4b} , R^8 , and R^9 are hydrogen; L is $-X^1-Y^1-Z^1-$; and all other groups are as defined below:

Table 3.

Cmpd. No.	A	X^1	Y^1	Z^1	Het	R^7
296		CH_2	$C(O)NH$	$CH_2CH_2CH_2$		hydrogen
297		CH_2	$C(O)NH$	bond		phenylmethyl
298		CH_2	$NHC(O)$	CH_2		phenylmethyl
299		CH_2	$C(O)$	bond		hydrogen
300		CH_2	$C(O)$	bond		hydrogen
301		$-C(C H_3)_2-$	$C(O)$	bond		benzyl

						
Cmpd. No.	A	X ¹	Y ¹	Z ¹	Het	R ⁷
302		CH ₂	C(O)	bond		hydrogen
303		CH ₂	C(O)	bond		hydrogen

and are named as:

2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-*N*-(3-pyrrolidin-1-yl-propyl)-acetamide;

N-(1-phenylmethyl-pyrrolidin-3-yl)-2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetamide;

N-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-ylmethyl]-4-phenylmethyl-piperazine-1-carboxamide;

4-phenyl-4-oxo-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-4λ⁵-[1,4]azaphosphinane;

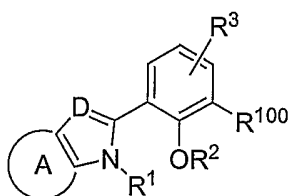
4-methyl-4-oxo-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-4λ⁵-[1,4]azaphosphinane;

1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-dimethylacetyl}-4-benzyl-piperazine;

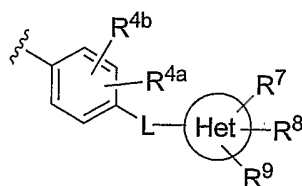
4-(cyclopropylmethyl)-4-oxo-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-4λ⁵-[1,4]azaphosphinane; and

4-(4-fluorobenzyl)-4-oxo-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-4λ⁵-[1,4]azaphosphinane.

Another selected group of compounds of the invention are provided in Table 4, having Formula I



where R^1 , R^2 , and R^3 are hydrogen; D is $=CR^6$ - where R^6 is hydrogen; and R^{100} is



(A1)

where R^{4a} , R^{4b} , and R^9 are hydrogen; L is $-X^1-Y^1-Z^1-$; and all other groups are as defined below:

Table 4.

Cmpd. No.	A	X^1	Y^1	Z^1	Het	R^7 and R^8
304		CH_2	$C(O)$	bond		
305		CH_2	$C(O)$	bond		
306		CH_2	$C(O)$	bond		
307		CH_2	$C(O)$	bond		
308		CH_2	$C(O)$	bond		

and are named:

N-[2'-Hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-ylmethylcarbonyl]-1,3-dihydrospiro(indene-2,4-piperidine);

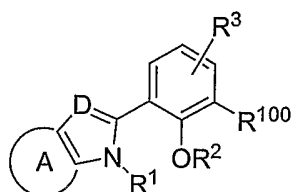
N-[2'-Hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-ylmethylcarbonyl]-1,3-dihydrospiro(indene-2,4-piperidine);

3-ethyl-1-(methoxycarbonyl)-8-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-2-oxa-8-aza-spiro[4.5]decane;

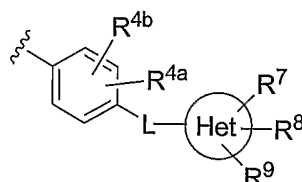
3(*R*)-ethyl-1(*R*)-(methoxycarbonyl)-8-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-2-oxa-8-aza-spiro[4.5]decane; and

3-ethyl-1-(carboxy)-8-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-2-oxa-8-aza-spiro[4.5]decane.

Another selected group of compounds of the invention are provided in Table 5, having Formula I



where R^1 , R^2 , and R^3 are hydrogen; D is $=CR^6$ - where R^6 is hydrogen; and R^{100} is



(A1)

where R^{4a} , R^{4b} , R^8 , and R^9 are hydrogen; L is $-X^2-$; and all other groups are as defined below:

Table 5.

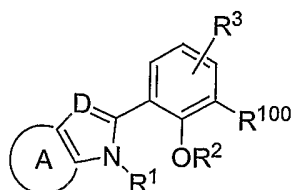
Cmpd. No.	A	X^2	Het	R^7
309		CH_2CH_2		phenylmethyl
310		CH_2CH_2		4-fluorophenyl

and are named as:

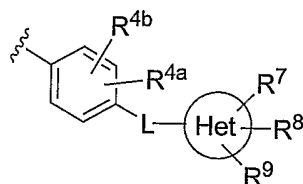
4'-[2-(4-phenylmethyl-piperazin-1-yl)-ethyl]-3-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-2-ol; and

4'-{2-[4-(4-Fluoro-phenyl)-piperazin-1-yl]-ethyl}-3-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-2-ol.

Another selected group of compounds of the invention are provided in Table 6, having Formula I



where R^1 , R^2 , and R^3 are hydrogen; D is $=CR^6$ - where R^6 is hydrogen; and R^{100} is



(A1)

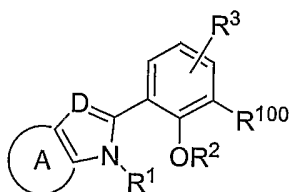
where R^{4a} , R^{4b} , R^8 , and R^9 are hydrogen; L is $-Y^2-Z^2-$; and all other groups are as defined below:

Table 6.

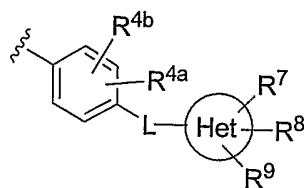
Cmpd. No.	A	Y^2	Z^2	Het	R^7
311		NHC(O)	CH ₂		phenylmethyl

and is named as 2-(4-phenylmethyl-piperazin-1-yl)-N-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetamide.

Another selected group of compounds of the invention are provided in Table 7, having Formula I



where R^1 , R^2 , and R^3 are hydrogen; and R^{100} is



(A1)

where R^{4a} , R^{4b} , and R^9 are hydrogen; L is $-Y^2-Z^2-$; and all other groups are as defined below:

Table 7.

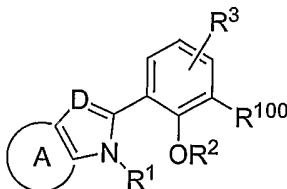
Cmpd. No.	A	D	Het	R^3	R^7	R^8
312		=CH-		Cl	hydroxy	phenylmethyl
313		=CH-		Cl	methoxycarbonyl	4-fluorophenylmethyl

and are named as:

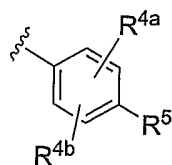
4-(phenylmethyl)-4-hydroxy-1-{2-[5'-chloro-2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine; and

methyl 1-{2-[5'-chloro-2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-4-(4-fluoro-phenylmethyl)-piperidine-4-carboxylate.

Another selected group of compounds of the invention are provided in Table 8, having Formula I:



where R^1 , R^2 , and R^3 are hydrogen; and R^{100} is

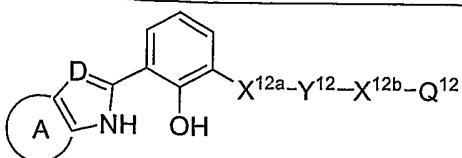
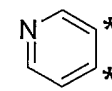
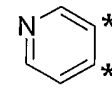
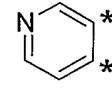
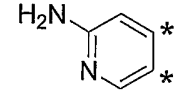
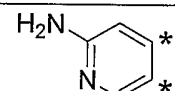
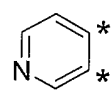


(A2)

where R^{4a} and R^{4b} are hydrogen, R^5 is $X^{12a}-Y^{12}-X^{12b}-Q^{12}$, and all other groups are as defined below:

Table 8.

Cmpd. No.	A	D	X^{12a}	Y^{12}	X^{12b}	Q^{12}
314		=N-	CH_2	C(O)NH	$CH_2CH_2CH_2$	phenyl
315		=CH-	CH_2	C(O)NH	$CH_2CH_2CH_2$	phenyl
316		=CH-	CH_2	C(O)NH	$CH_2CH_2CH_2$	phenyl
317		=CH-	CH_2	C(O)NH	$CH_2CH_2CH_2$	phenyl
318		=N-	CH_2	C(O)NH	$CH(COOH)CH_2$	phenylmethyloxy
319		=N-	CH_2	C(O)NH	$CH(COOCH_3)CH_2$	phenylmethyloxy
320		=N-	CH_2	C(O)NH	$CH(COOH)CH_2CH_2$	phenyl
321		=N-	CH_2	C(O)NH	$CH[C(O)OCH_2CH_3]CH_2$ $CH=CH$	phenyl
322		=N-	CH_2	C(O)NH	$CH(COOH)CH_2CH=CH$	phenyl

						
Cmpd. No.	A	D	X ^{12a}	Y ¹²	X ^{12b}	Q ¹²
323		=N-	CH ₂	C(O)NH	CH(COOCH ₂ CH ₃)CH ₂ CH ₂	phenyl
324		=N-	CH ₂	C(O)NH	CH ₂ CH ₂	2-carboxyphenyl
325		=N-	CH ₂	C(O)NH	CH(COOH)CH ₂ CH ₂ CH ₂	phenyl
326		=CH-	CH ₂	C(O)NH	CH[C(O)OCH ₂ CH ₃]CH ₂ CH ₂	phenyl
327		=CH-	CH ₂	C(O)NH	CH(COOH)CH ₂ CH ₂ CH ₂	phenyl
328		=CCl-	CH ₂	C(O)NH	CH[C(O)OCH ₃]C(CH ₃) ₂	phenylmethylsulfonyl

and are named:

2-[2'-hydroxy-3'-(1*H*-imidazo[4,5-*c*]pyridin-2-yl)-biphenyl-4-yl]-*N*-(3-phenyl-propyl)-acetamide;

2-{2'-hydroxy-3'-[5-(5-methyl-[1,2,4]oxadiazol-3-yl)-1*H*-indol-2-yl]-biphenyl-4-yl}-*N*-(3-phenyl-propyl)-acetamide;

2-[3'-(4-chloro-1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-2'-hydroxy-biphenyl-4-yl]-*N*-(3-phenyl-propyl)-acetamide;

2-[3'-(6-chloro-1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-2'-hydroxy-biphenyl-4-yl]-*N*-(3-phenyl-propyl)-acetamide;

3-phenylmethoxy-2-{2-[2'-hydroxy-3'-(1*H*-imidazo[4,5-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl-amino}-propionic acid;

3-phenylmethoxy-2-{2-[2'-hydroxy-3'-(1*H*-imidazo[4,5-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl-amino}-propionic acid methyl ester;

2-{2-[2'-hydroxy-3'-(1*H*-imidazo[4,5-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl-amino}-4-phenyl-butyric acid;

2-{2-[2'-hydroxy-3'-(1*H*-imidazo[4,5-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-5-phenyl-pent-4-enoic acid ethyl ester;

2-{2-[2'-hydroxy-3'-(1*H*-imidazo[4,5-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-5-phenyl-pent-4-enoic acid;

2-{2-[2'-hydroxy-3'-(1*H*-imidazo[4,5-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-5-phenyl-pentanoic acid ethyl ester;

2-(2-{2-[2'-hydroxy-3'-(1*H*-imidazo[4,5-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-ethoxy)-benzoic acid];

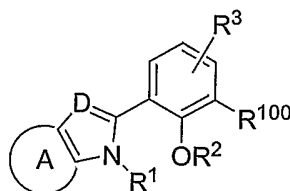
2-{2-[2'-hydroxy-3'-(1*H*-imidazo[4,5-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-5-phenyl-pentanoic acid;

2-{2-[3'-(5-amino-1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-2'-hydroxy-biphenyl-4-yl]-acetylamino}-5-phenyl-pentanoic acid ethyl ester;

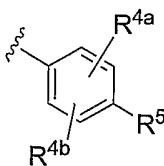
2-{2-[3'-(5-amino-1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-2'-hydroxy-biphenyl-4-yl]-acetylamino}-5-phenyl-pentanoic acid; and

2-{2-[3'-(3-chloro-1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-2'-hydroxy-biphenyl-4-yl]-acetylamino}-3-methyl-3-phenylmethanesulfonyl-butyric acid methyl ester.

Another selected group of compounds of the invention are provided in Table 9, having Formula I:



where R^1 , R^2 , and R^3 are hydrogen; D is $=CR^6$ - wherein R^6 is hydrogen; and R^{100} is



(A2)

where R^{4a} and R^{4b} are hydrogen; and R^5 is $-Y^{11}-X^{11}-Q^{11}$; and all other groups are as defined below:

Table 9.

Cmpd. No.	A	Y ¹¹	X ¹¹	Q ¹¹
329		-NHC(O)-	CH ₂ CH ₂ CH ₂ CH ₂	thien-2-yl
330		-NHC(O)-	CH ₂ CH ₂	phenyl
331		-NHC(O)-	CH(OH)CH ₂	phenyl
332		-NHC(O)-	CH ₂ CH ₂ CH ₂	phenyloxy
333		-NHC(O)NH-	CH ₂	phenyl
334		-NHC(O)-	CH ₂ CH ₂	phenyloxy
335		-NHC(O)-	CH=CH	phenyl
336		-NHC(O)NH-	CH ₂ CH ₂	phenyl
337		-NHC(O)-	bond	quinolin-3-yl
338		-NHC(O)O-	CH ₂	phenyl
339		-NHC(O)-	bond	4-phenylphen-1-yl
340		-C(O)NH-	CH[C(O)OCH ₃]CH ₂	phenylmethyloxy
341		-C(O)NH-	CH ₂ CH(OH)CH ₂	phenoxy

and are named as follows:

5-thiophen-2-yl-pentanoic acid [2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-amide;

N-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-3-phenyl-propionamide;

2-hydroxy-*N*-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-3-phenyl-propionamide;

N-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-4-phenoxy-butylamide;

1-phenylmethyl-3-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-urea;

N-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-3-phenoxy-propionamide;

N-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-3-phenyl-acrylamide;

1-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-3-phenethyl-urea;

quinoline-3-carboxylic acid [2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-amide;

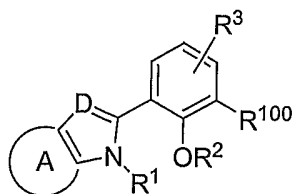
[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-carbamic acid benzyl ester;

biphenyl-4-carboxylic acid [2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-amide;

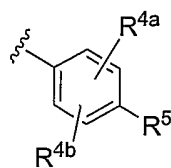
3-phenylmethoxy-2-{[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-carbonyl]-amino}-propionic acid methyl ester; and

2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-carboxylic acid (2-hydroxy-3-phenoxy-propyl)-amide.

Another selected group of compounds of the invention are provided in Table 10, having Formula I:



where R^1 , R^2 , and R^3 are hydrogen; D is $=CR^6$ - wherein R^6 is hydrogen; the A ring is a fused pyridine ring; and R^{100} is



(A2)

where R^{4a} and R^{4b} are hydrogen, R^5 is $X^{12a}-Y^{12}-X^{12b}-Q^{12}$, and all other groups are as defined below:

Table 10.

Cmpd. No.	X^{12a}	Y^{12}	X^{12b}	Q^{12}
342	CH_2	$-C(O)NH-$	$CH(COOH)CH_2$	phenylmethyloxy
343	CH_2	$-C(O)NH-$	$CH(C(O)OCH_3)CH_2$	phenylmethyloxy
344	CH_2	$-C(O)NH-$	$CH(R-COOCH_3)CH_2CH_2$	phenyl
345	CH_2	$-C(O)NH-$	$CH(S-COOCH_3)CH_2CH_2$	phenyl
346	CH_2	$-C(O)NH-$	$CH(COOH)CH_2CH_2$	phenyl
347	CH_2	$-C(O)NH-$	$CH(COOCH_2CH_3)CH_2CH=CH$	phenyl
348	CH_2	$-C(O)N(OH)-$	$CH_2CH_2CH_2$	phenyl
349	CH_2	$-C(O)NH-$	$CH(COOCH_3)CH_2$	indan-2-ylamino
350	CH_2	$-C(O)NH-$	$CH(COOCH_3)CH_2$	benzoxal-2-ylamino
351	CH_2	$-C(O)NH-$	CH_2	
352	CH_2	$-C(O)NH-$	$CH(COOCH_3)CH_2$	indol-3-yl

are named as follows:

3-phenylmethyloxy-2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-propionic acid;

3-phenylmethyloxy-2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-propionic acid methyl ester;

(*R*)-2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-4-phenyl-butyric acid methyl ester;

(*S*)-2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-4-phenyl-butyric acid methyl ester;

2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-4-phenyl-butyrlic acid;

2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-5-phenyl-pent-4-enoic acid ethyl ester;

N-hydroxy-2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-*N*-(3-phenyl-propyl)-acetamide;

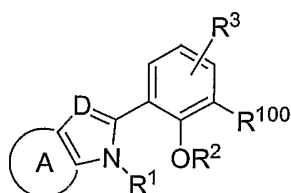
2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-3-(indan-2-ylamino)-propionic acid methyl ester;

3-(benzoxazol-2-ylamino)-2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-propionic acid methyl ester;

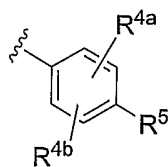
2-(2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-acetylamino)-3-phenyl-propionic acid methyl ester; and

2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-3-(1*H*-indol-3-yl)-propionic acid methyl ester.

Another selected group of compounds of the invention are provided in Table 11, having Formula I:



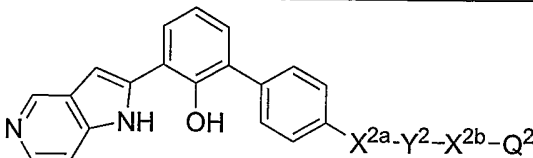
where R^1 , R^2 , and R^3 are hydrogen; D is $=CR^6$ - wherein R^6 is hydrogen; the A ring is a fused pyrido ring; and R^{100} is

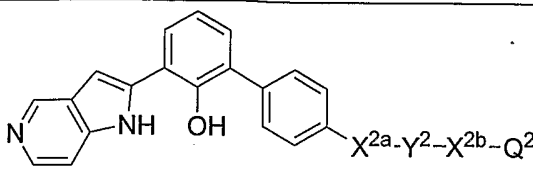


(A2)

where R^{4a} and R^{4b} are hydrogen, R^5 is $X^{12a}-Y^{12}-X^{12b}-Q^{12}$, and all other groups are as defined below:

Table 11.

				
Cmpd. No.	X ^{12a}	Y ¹²	X ^{12b}	Q ¹²
353	CH ₂	-C(O)NH-	CH(<i>R,S</i> -COOCH ₃)CH ₂ CH ₂	phenyl
354	CH ₂	-C(O)NH-	CH(<i>S</i> -COOCH ₃)CH ₂ CH ₂	phenyl
355	CH ₂	-C(O)NH-	CH(COOCH ₃)CH ₂	phenylmethoxy
356	CH ₂	-C(O)NH-	CH(COOH)CH ₂	phenylmethoxy
357	CH ₂	-C(O)NH-	CH(COOCH ₃)CH ₂ CH ₂	phenyl
358	CH ₂	-C(O)NH-	CH ₂ CH=CH	phenyl
359	CH ₂	-C(O)NH-	CH(CH ₂ COOCH ₃)CH ₂ C H ₂	phenyl
360	CH ₂	-C(O)NH-	CH(COOH)CH ₂ CH ₂	phenyl
361	CH ₂	-C(O)NH-	CH ₂ CH ₂	4-fluorophenyl
362	CH ₂	-C(O)NH-	CH(COOH)CH ₂ CH ₂	phenyl
363	CH ₂	-C(O)NH-	CH ₂ CH ₂	benzoxazol-2-ylamino
364	CH ₂	-NHC(O)NH-	CH ₂ CH ₂	phenyl
365	CH ₂	-C(O)NH-	CH(COOH)CH ₂	naphth-2-yl
366	CH ₂	-C(O)NH-	CH(COOCH ₃)CH ₂	naphth-2-yl
367	CH ₂	-C(O)NH-	CH(COOH)CH ₂ CH ₂	phenyl
368	CH ₂	-C(O)NH-	CH ₂ CH ₂	1,3-dihydro-isoindol-2-yl
369	CH ₂	-C(O)NH-	CH ₂ CH ₂	phenyloxy
370	CH ₂	-C(O)NH-	bond	2-phenyl-cycloprop-1-yl
371	CH ₂	-C(O)NH-	CH ₂	2-phenyl-cycloprop-1-yl
372	CH ₂	-C(O)NH-	CH(COOH)CH ₂ CH ₂	phenyl
373	CH ₂	-C(O)NH-	CH(CH ₃)CH ₂ CH ₂	phenyl
374	CH ₂	-C(O)NH-	CH ₂ CH ₂	2-methoxycarbonyl-phenyloxy
375	CH ₂	-NHC(O)-	CH ₂ CH=CH	phenyl
376	CH ₂	-C(O)NH-	CH ₂ CH ₂	2-carboxyphenyloxy
377	CH ₂	-C(O)NH-	CH ₂	3,4-dichlorophenylmethyl
378	CH ₂	-C(O)NH-	CH ₂ CH ₂	1,2,3,4-tetrahydro-isoquinolin-2-yl
379	CH ₂	-C(O)NH-	CH ₂ CH ₂ CH ₂	benzimidazol-2-yl
380	CH ₂	-C(O)NH-	CH ₂ CH ₂	2-[2-(dimethylamino)-ethyl]aminocarbonyl-phenyloxy

				
Cmpd. No.	X ^{12a}	Y ¹²	X ^{12b}	Q ¹²
381	CH ₂	-NHC(O)-	CH ₂ CH ₂ CH ₂	phenyl
382	CH ₂	-NHC(O)-	CH ₂ CH ₂ CH ₂	phenyloxy
383	CH ₂	-C(O)NH-	CH(COOCH ₃)CH ₂	phenyl
384	CH ₂	-C(O)NH-	CH ₂ CH ₂	2-{[2-(piperidin-1-yl)-ethyl]aminocarbonyl}-phenyloxy
385	CH ₂	-C(O)NH-	CH ₂ CH ₂	indol-3-yl
386	CH ₂	-C(O)NH-	bond	2-(phenylmethyloxy)-cyclopent-1-yl
387	CH ₂	-C(O)NH-	CH ₂ CH ₂	4-methyl-[1,2,3]thiadiazol-5-ylthio
388	CH ₂	-C(O)NH-	CH ₂ CH ₂	2-aminocarbonyl-phenyloxy
389	CH ₂	-C(O)NH-	CH(COOCH ₃)CH ₂	naphth-2-yl
390	CH ₂	-C(O)NH-	CH ₂ CH ₂ CH ₂	imidazol-1-yl
391	CH ₂	-C(O)NH-	CH ₂ CH ₂	3,4-dichlorophenyl
392	CH ₂	-C(O)NH-	CH(COOH)CH ₂	naphth-2-yl
393	CH ₂	-C(O)NH-	CH ₂ CH ₂	pyridin-4-yl
394	CH ₂	-C(O)NH-	CH ₂ CH ₂	thien-2-yl
395	CH ₂	-NHC(O)-	bond	2-(4-aminomethylphenyl)oxazol-4-yl
396	CH ₂	-NHC(O)-	CH ₂ CH(NH ₂)	phenyl
397	CH ₂	-C(O)NH-	CH ₂ CH ₂	3-bromophenyl
398	CH ₂	-C(O)NH-	CH ₂ CH ₂	pyridin-2-yl
399	CH ₂	-C(O)NH-	CH ₂	thien-2-yl
400	CH ₂	-C(O)NH-	CH ₂ CH ₂	1,3-dioxo-isoindol-2-yl
401	CH ₂	-NHC(O)-	CH ₂ CH ₂	indol-3-yl
402	CH ₂	-C(O)NH-	CH ₂ CH ₂ CH ₂	phenyl

and are named:

2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl-amino}-4-phenyl-butyric acid methyl ester;

(*S*)-2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl-amino}-4-phenyl-butyric acid methyl ester;

3-phenylmethoxy-2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetamino}-propionic acid methyl ester;

3-phenylmethoxy-2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetamino}-propionic acid;

2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetamino}-4-phenyl-butyric acid methyl ester;

2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-*N*-(3-phenyl-allyl)-acetamide;

3-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetamino}-5-phenyl-pentanoic acid methyl ester;

2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetamino}-4-phenyl-butyric acid;

N-[2-(4-fluoro-phenoxy)-ethyl]-2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetamide;

2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetamino}-4-phenyl-butyric acid;

N-[2-(benzooxazol-2-ylamino)-ethyl]-2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetamide;

1-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-ylmethyl]-3-phenethyl-urea;

2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetamino}-3-naphthalen-2-yl-propionic acid;

2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetamino}-3-naphthalen-2-yl-propionic acid methyl ester;

2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetamino}-4-phenyl-butyric acid;

N-[2-(1,3-dihydro-isoindol-2-yl)-ethyl]-2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetamide;

2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-*N*-(2-phenoxy-ethyl)-acetamide;

2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-*N*-(2-phenyl-cyclopropyl)-acetamide;

2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-*N*-(2-phenyl-cyclopropylmethyl)-acetamide;

2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-4-phenyl-butyric acid;

2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-*N*-(1-methyl-3-phenyl-propyl)-acetamide;

2-(2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-ethoxy)-benzoic acid methyl ester;

4-phenyl-but-3-enoic acid [2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-ylmethyl]-amide;

2-(2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-ethoxy)-benzoic acid;

N-(3,4-dichloro-phenylmethyl)-2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetamide;

N-[2-(3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetamide;

N-[3-(1*H*-benzoimidazol-2-yl)-propyl]-2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetamide;

N-(2-dimethylamino-ethyl)-2-(2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-ethoxy)-benzamide;

N-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-ylmethyl]-4-phenyl-butyramide;

N-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-ylmethyl]-4-phenoxy-butyramide;

2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-3-phenyl-propionic acid methyl ester;

2-(2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-ethoxy)-*N*-(2-piperidin-1-yl-ethyl)-benzamide;

2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-*N*-[2-(1*H*-indol-3-yl)-ethyl]-acetamide;

N-(2-phenylmethyloxy-cyclopentyl)-2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetamide;

2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-*N*-[2-(4-methyl-[1,2,3]thiadiazol-5-ylsulfanyl)-ethyl]-acetamide;

2-(2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-ethoxy)-benzamide;

2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl-amino}-3-naphthalen-2-yl-propionic acid methyl ester;

2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-*N*-(3-imidazol-1-yl-propyl)-acetamide;

N-[2-(3,4-dichloro-phenyl)-ethyl]-2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetamide;

2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl-amino}-3-naphthalen-2-yl-propionic acid;

2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-*N*-(2-pyridin-4-yl-ethyl)-acetamide;

2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-*N*-(2-thiophen-2-yl-ethyl)-acetamide;

2-(4-aminomethyl-phenyl)-oxazole-4-carboxylic acid [2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-ylmethyl]-amide;

3-amino-*N*-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-ylmethyl]-3-phenyl-propionamide;

N-[2-(3-bromo-phenyl)-ethyl]-2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetamide;

2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-*N*-(2-pyridin-2-yl-ethyl)-acetamide;

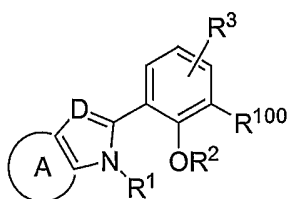
2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-*N*-thiophen-2-ylmethyl-acetamide;

N-[2-(1,3-dioxo-1,3-dihydro-isindol-2-yl)-ethyl]-2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetamide;

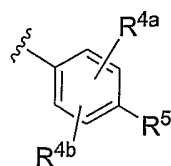
N-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-ylmethyl]-3-(1*H*-indol-3-yl)-propionamide; and

2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-*N*-(3-phenyl-propyl)-acetamide.

Another selected group of compounds of the invention are provided in Table 12, having Formula I:



where R^1 and R^2 are hydrogen; D is $=CR^6$ - wherein R^6 is hydrogen; the A ring is a fused pyrido ring; and R^{100} is



(A2)

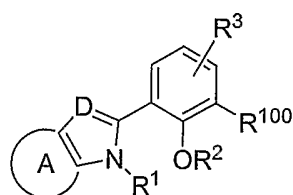
where R^{4a} and R^{4b} are hydrogen, R^5 is $X^{12a}-Y^{12}-X^{12b}-Q^{12}$, and all other groups are as defined below:

Table 12.

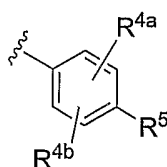
Cmpd. No.	R^3	X^{12a}	Y^{12}	X^{12b}	Q^{12}
403	2-mercaptoethylaminocarbonylmethyl	CH_2	$C(O)NH$	$CH_2CH_2CH_2$	phenyl

and is named *N*-[3-(4-fluoro-phenyl)-propyl]-2-[2'-hydroxy-5'-[(2-mercapto-ethylcarbamoyl)-methyl]-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetamide.

Another selected group of compounds of the invention are provided in Table 13, having Formula I:



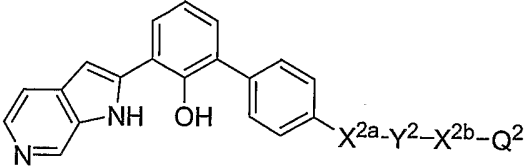
where R^1 , R^2 , and R^3 are hydrogen; D is $=CR^6$ - wherein R^6 is hydrogen; the A ring is a fused pyrido ring; and R^{100} is

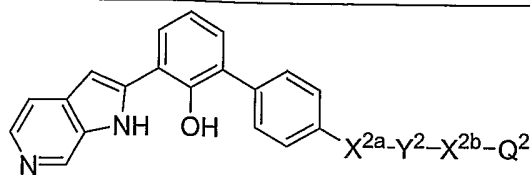


(A2)

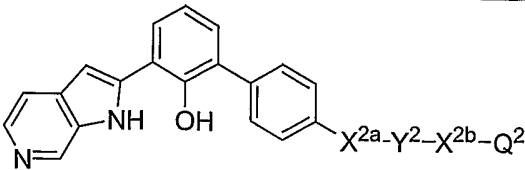
where R^{4a} and R^{4b} are hydrogen, R^5 is $X^{12a}-Y^{12}-X^{12b}-Q^{12}$, and all other groups are as defined below:

Table 13.

				
Cmpd. No.	X ^{12a}	Y ¹²	X ^{12b}	Q ¹²
404	CH ₂	C(O)NH	CH(COOH)CH ₂ CH ₂	phenyl
405	CH ₂	C(O)NH	CH(COOCH ₃)CH ₂	phenylmethylsulfonyl
406	CH ₂	C(O)NH	CH(COOH)CH=CH	phenyl
407	CH ₂	C(O)NH	bond	2-methoxycarbonyl-1,2,3,4-tetrahydronaphth-2-yl
408	CH ₂	C(O)NH	CH(COOCH ₃)	indan-1-yl
409	CH ₂	C(O)NH	CH(CN)CH ₂ CH ₂	4-chlorophenyl
410	CH ₂	C(O)NH	CH[C(O)NH(CH ₃)]CH ₂	phenylmethyloxy
411	CH ₂	C(O)NH	CH(CH ₂ COOCH ₃)CH ₂ CH ₂	phenyl
412	CH ₂	C(O)NH	CH(COOCH ₃)CH ₂	naphth-2-yl
413	CH ₂	C(O)NH	CH ₂ CH=CH	phenyl
414	CH ₂	C(O)NH	CH(CH ₂ COOH)CH ₂ CH ₂	phenyl
415	CH ₂	C(O)NH	CH(tetrazol-5-yl)CH ₂ CH ₂	4-chlorophenyl
416	CH ₂	C(O)NH	CH(COOH)CH ₂	naphth-2-yl
417	CH ₂	C(O)NH	CH(COOCH ₃)CH ₂ CH ₂	4-methoxyphenyl
418	CH ₂	C(O)NH	CH(COOH)CH ₂ CH ₂	4-methoxyphenyl
419	CH ₂	C(O)NH	CH ₂ CH ₂	4-fluorophenoxy
420	CH ₂	C(O)NH	CH ₂ CH ₂	benzoxazol-2-ylamino
421	CH ₂	C(O)NH	CH ₂ CH(OH)CH ₂	phenoxy
422	CH ₂	C(O)NH	CH[C(O)OCH ₂ CH ₃]CH ₂ CH ₂	phenoxy
423	CH ₂	C(O)NH	CH[C(O)OCH ₂ CH ₃]CH ₂ CH ₂ CH ₂	phenoxy
424	CH ₂	C(O)NH	CH[C(O)NH(1,3,4-thiadiazol-2-yl)]CH ₂ CH ₂	phenyl
425	CH ₂	C(O)NH	CH(COOH)CH ₂ CH ₂	phenoxy
426	CH ₂	C(O)NH	CH(COOH)CH ₂ CH ₂ CH ₂	phenoxy
427	CH ₂	C(O)NH	CH[C(O)NH(1,3-thiazol-2-yl)]CH ₂ CH ₂	phenyl
428	CH ₂	C(O)NH	CH(COOCH ₃)CH ₂ CH ₂	phenyl
429	CH ₂	C(O)NH	CH(COOCH ₃)CH ₂ CH ₂	4-chlorophenyl
430	CH ₂	C(O)NH	CH[C(O)OCH ₂ CH ₃]CH ₂ CH ₂	4-fluorophenoxy
431	CH ₂	C(O)NH	CH(COOH)CH ₂ CH ₂	4-chlorophenyl
432	CH ₂	C(O)NH	CH(COOH)CH ₂ CH ₂	4-fluorophenoxy
433	CH ₂	C(O)NH	CH[C(O)OCH ₂ CH ₃]CH ₂ CH ₂ CH ₂	phenyl



Cmpd. No.	X ^{12a}	Y ¹²	X ^{12b}	Q ¹²
434	CH ₂	C(O)NH	CH(COOH)CH ₂ CH ₂ CH ₂	phenyl
435	CH ₂	C(O)NH	CH[C(O)OCH ₃]CH ₂	cyclopropylmethylthio
436	CH ₂	C(O)NH	CH[C(O)OCH ₃]CH ₂	cyclopropylmethylsulfonyl
437	C(CH ₃) ₂	C(O)NH	CH(COOH)CH ₂ CH ₂ CH ₂	phenyl
438	CH ₂	C(O)NH	CH(COOH)CH ₂	cyclopropylmethylthio
439	CH ₂	C(O)NH	CH(COOH)CH ₂	cyclopropylmethylsulfonyl
440	CH ₂	C(O)NH	CH[C(O)OCH ₃]CH ₂	cyclopropylmethyloxy
441	CH ₂	C(O)NH	CH(COOH)CH ₂	cyclopropylmethyloxy
442	CH ₂	C(O)NH	CH[CH(OH)(CF ₃)]CH ₂ CH ₂ CH ₂	phenyl
443	CH ₂	C(O)NH	CH[CO(O)CH ₃]CH ₂	cyclopropylmethylamino
444	CH ₂	C(O)NH	CH ₂ CH(OH)CH ₂ CH ₂	phenyl
445	CH ₂	C(O)NH	CH(COOH)CH ₂	cyclopropylmethylamino
446	CH ₂	C(O)NH	CH(COOH)CH ₂	cyclopropylaminocarbonyl
447	CH ₂	C(O)NH	CH[C(O)OCH ₃]CH ₂ CH ₂	phenylmethyloxy
448	CH ₂	C(O)NH	CH[C(O)OCH ₃]CH ₂	<i>N</i> -cyclopropylmethyl- <i>N</i> -methylamino
449	CH ₂	C(O)NH	CH(COOH)CH ₂ CH ₂	phenylmethyloxy
450	CH ₂	C(O)NH	CH[C(O)OCH ₃]CH ₂	cyclobutylmethyloxy
451	CH ₂	C(O)NH	CH[C(O)OCH ₃]CH(CH ₃)	phenylmethyloxy
452	CH ₂	C(O)NH	CH(COOH)CH ₂	cyclobutylmethyloxy
453	CH ₂	C(O)NH	CH(COOH)CH(CH ₃)	phenylmethyloxy
454	CH ₂	C(O)NH	CH[C(O)OCH ₃]C(CH ₃) ₂	phenylmethylthio
455	CH ₂	C(O)NH	CH(COOH)CH ₂	<i>N</i> -cyclopropylmethyl- <i>N</i> -methylamino
456	CH ₂	C(O)NH	CH ₂ CH[C(O)OCH ₂ CH ₃]CH ₂ CH ₂	phenyl
457	CH ₂	C(O)NH	CH ₂ CH(COOH)CH ₂ CH ₂	phenyl
458	CH ₂	C(O)NH	CH[C(O)OCH ₃]C(CH ₃) ₂	phenylmethylsulfonyl
459	CH ₂	C(O)NH	CH[C(O)OCH ₃]CH ₂ CH ₂	cyclopropylmethyloxy
460	CH ₂	C(O)NH	CH(COOH)CH ₂ CH ₂	cyclopropylmethyloxy
461	CH ₂	C(O)NH	CH ₂ CH(CH ₂ OH)CH ₂ CH ₂	phenyl
462	CH ₂	C(O)NH	CH(COOH)C(CH ₃) ₂	phenylmethylthio
463	CH ₂	C(O)NH	CH(<i>N,N</i> -dimethylaminocarbonyl)CH ₂	phenylmethyloxy
464	CH ₂	C(O)N[CH(	CH ₂ CH(OH)CH ₂	phenoxy

				
Cmpd. No.	X ^{12a}	Y ¹²	X ^{12b}	Q ¹²
		CH ₃) ₂]		
465	CH ₂	C(O)O	CH ₂ CH ₂ CH ₂ CH ₂	phenyl
466	CH ₂	C(O)NH	CH(COOH)C(CH ₃) ₂	phenylmethylsulfonyl
467	CH ₂	C(O)NH	CH[N-(2-methoxyethyl)aminocarbonyl]CH ₂	phenylmethyloxy
468	CH ₂	C(O)NH	CH(N-methoxyaminocarbonyl)CH ₂	phenylmethyloxy
469	CH ₂	C(O)NH	CH ₂ CH ₂ CH ₂ CH ₂	phenyl
470	CH ₂	C(O)NH	CH ₂ CH ₂ CH ₂	phenyl
471	CH ₂	C(O)N(CH ₃)	CH ₂ CH(OH)CH ₂	phenoxy
472	CH ₂	C(O)NH	CH ₂ CH ₂	phenoxy
473	CH ₂	NHC(O)	CH(NHCO ₂ tBu)CH ₂	phenylmethyloxy
474	CH ₂	NHC(O)	CH(NH ₂)CH ₂	phenylmethyloxy
475	CH ₂	C(O)NH	CH(CON(CH ₃) ₂)CH ₂ CH ₂ CH ₂	phenyl
476	CH ₂	C(O)NH	CH ₂ CH ₂	4-fluorophenylmethyloxy
477	CH ₂	C(O)NH	CH(CH ₂ OH)CH ₂	phenylmethyloxy
478	CH ₂	NHC(O)	CH ₂ CH ₂ CH ₂ CH ₂	phenyl
479	CH ₂	C(O)NH	CH ₂ CH ₂	phenylmethyloxy
480	CH ₂	C(O)NH	CH(CON(CH ₃) ₂)CH ₂ CH ₂	phenyl
481	CH ₂	C(O)N(CH ₃)	CH(CON(CH ₃) ₂)CH ₂	phenylmethyloxy
482	CH ₂	C(O)NH	CH(CH ₂ N(CH ₃) ₂)CH ₂	phenylmethyloxy
483	CH ₂	C(O)NH	CH(CH ₂ OH)CH ₂ CH ₂	phenyl
484	CH ₂	C(O)NH	CH(CO ₂ CH ₃)CH ₂	4-fluorophenylmethyloxy
485	CH ₂	C(O)NH	CH(CO ₂ H)CH ₂	4-fluorophenylmethyloxy
486	CH ₂	C(O)NH	CH(CON(CH ₃) ₂)CH ₂	4-fluorophenylmethyloxy
487	CH ₂	C(O)NH	CH(CH ₂ OH)CH ₂	4-fluorophenylmethyloxy

and are named:

2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl-amino}-4-phenyl-butyric acid;

2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl-amino}-3-phenylmethanesulfonyl-propionic acid methyl ester;

2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-4-phenyl-but-3-enoic acid;

2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-1,2,3,4-tetrahydro-naphthalene-2-carboxylic acid methyl ester;

{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-indan-1-yl-acetic acid methyl ester;

N-[3-(4-chloro-phenyl)-1-cyano-propyl]-2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetamide;

3-phenylmethyloxy-2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-*N*-methyl-propionamide;

3-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-5-phenyl-pentanoic acid methyl ester;

2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-3-naphthalen-2-yl-propionic acid methyl ester;

2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-*N*-(3-phenyl-allyl)-acetamide;

3-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-5-phenyl-pentanoic acid;

N-[3-(4-chloro-phenyl)-1-(1*H*-tetrazol-5-yl)-propyl]-2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetamide;

2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-3-naphthalen-2-yl-propionic acid;

2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-4-(4-methoxy-phenyl)-butyric acid methyl ester;

2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-4-(4-methoxy-phenyl)-butyric acid;

N-[2-(4-fluoro-phenoxy)-ethyl]-2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetamide;

N-[2-(benzoxazol-2-ylamino)-ethyl]-2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetamide;

N-(2-hydroxy-3-phenoxy-propyl)-2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetamide;

2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-4-phenoxy-butyric acid ethyl ester;

- 2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-5-phenoxy-pentanoic acid ethyl ester;
- 2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-4-phenyl-N-[1,3,4]thiadiazol-2-yl-butylamide;
- 2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-4-phenoxy-butyric acid;
- 2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-5-phenoxy-pentanoic acid;
- 2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-4-phenyl-N-thiazol-2-yl-butylamide;
- 2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-4-phenyl-butyric acid methyl ester;
- 4-(4-chloro-phenyl)-2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-butyric acid methyl ester;
- 4-(4-fluoro-phenoxy)-2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-butyric acid ethyl ester;
- 4-(4-chloro-phenyl)-2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-butyric acid;
- 4-(4-fluoro-phenoxy)-2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-butyric acid;
- 2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-5-phenyl-pentanoic acid ethyl ester;
- 2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-5-phenyl-pentanoic acid;
- 3-cyclopropylmethylsulfanyl-2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-propionic acid methyl ester;
- 3-cyclopropylmethanesulfonyl-2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-propionic acid methyl ester;
- 2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-2-methyl-propionylamino}-5-phenyl-pentanoic acid;
- 3-cyclopropylmethylsulfanyl-2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-propionic acid;
- 3-Cyclopropylmethanesulfonyl-2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-propionic acid;

3-cyclopropylmethoxy-2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-propionic acid methyl ester;

3-cyclopropylmethoxy-2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-propionic acid;

2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-*N*-[4-phenyl-1-(2,2,2-trifluoro-1-hydroxy-ethyl)-butyl]-acetamide;

3-(cyclopropylmethyl-amino)-2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-propionic acid methyl ester;

N-(2-hydroxy-4-phenyl-butyl)-2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetamide;

3-(cyclopropylmethyl-amino)-2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-propionic acid;

N-cyclopropyl-2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino-succinamic acid;

4-phenylmethyloxy-2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino-butyric acid methyl ester;

3-[*N*-(cyclopropylmethyl)-*N*-methyl-amino]-2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-propionic acid methyl ester;

4-phenylmethyloxy-2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-butyric acid;

3-cyclobutylmethoxy-2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino-propionic acid methyl ester;

3-phenylmethyloxy-2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino-butyric acid methyl ester;

3-cyclobutylmethoxy-2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-propionic acid;

3-phenylmethyloxy-2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-butyric acid;

3-benzylsulfanyl-2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-3-methyl-butyric acid methyl ester;

3-[*N*-(cyclopropylmethyl)-*N*-methyl-amino]-2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-propionic acid;

2-({2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-methyl)-4-phenyl-butyric acid ethyl ester;

2-({2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-methyl)-4-phenyl-butyric acid;

2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-3-methyl-3-phenylmethanesulfonyl-butyric acid methyl ester;

4-cyclopropylmethoxy-2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-butyric acid methyl ester;

4-cyclopropylmethoxy-2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-butyric acid;

N-(2-hydroxymethyl-4-phenyl-butyl)-2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetamide;

3-benzylsulfonyl-2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-3-methyl-butyric acid;

3-phenylmethyloxy-2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-*N,N*-dimethyl-propionamide;

N-(2-hydroxymethyl-3-phenoxy-propyl)-2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-*N*-isopropyl-acetamide;

[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetic acid 4-phenyl-butyl ester;

2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-3-methyl-3-phenylmethanesulfonyl-butyric acid;

3-phenylmethyloxy-2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-*N*-(2-methoxy-ethyl)-propionamide;

3-phenylmethyloxy-2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-*N*-methoxy-propionamide;

2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-*N*-(4-phenyl-butyl)-acetamide;

2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-*N*-(3-phenyl-propyl)-acetamide;

N-(2-hydroxy-3-phenoxy-propyl)-2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-*N*-methyl-acetamide;

2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-*N*-(2-phenoxy-ethyl)-acetamide;

(2-phenylmethyloxy-1-{[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-ylmethyl]-carbonyl}-ethyl)-carbamic acid tert-butyl ester;

2-amino-3-phenylmethyloxy-*N*-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-ylmethyl]-propionamide;

2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-5-phenyl-pentanoic acid dimethylamide;

N-[2-(4-fluoro-phenylmethyloxy)-ethyl]-2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetamide;

N-(2-phenylmethyloxy-1-hydroxymethyl-ethyl)-2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetamide;

5-phenyl-pentanoic acid [2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-ylmethyl]-amide;

N-(2-phenylmethyloxy-ethyl)-2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetamide;

2-({2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-methyl-amino)-*N,N*-dimethyl-4-phenyl-butylamide;

3-phenylmethyloxy-2-({2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-methyl-amino)-*N,N*-dimethyl-propionamide;

N-(2-phenylmethyloxy-1-dimethylaminomethyl-ethyl)-2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetamide;

N-(1-hydroxymethyl-3-phenyl-propyl)-2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetamide;

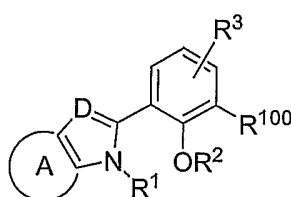
3-(4-fluoro-phenylmethyloxy)-2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-propionic acid methyl ester;

3-(4-fluoro-phenylmethyloxy)-2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-propionic acid;

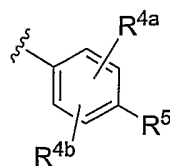
3-(4-fluoro-phenylmethyloxy)-2-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetylamino}-*N,N*-dimethyl-propionamide; and

N-[2-(4-fluoro-phenylmethyloxy)-1-hydroxymethyl-ethyl]-2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetamide.

Another selected group of compounds of the invention are provided in Table 14, having Formula I:



where R^1 , R^2 , and R^3 are hydrogen; D is $=CR^6$ - wherein R^6 is hydrogen; and R^{100} is



(A2)

where R^{4a} and R^{4b} are hydrogen, R^5 is $X^{12a}-Y^{12}-X^{12b}-Q^{12}$, and all other groups are as defined below:

Table 14.

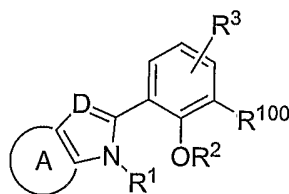
Cmpd. No.	A	X^{12a}	Y^{12}	X^{12b}	Q^{12}
488		CH_2	$C(O)NH$	CH_2CH_2O	4-fluorophenylmethyl
489		CH_2	$C(O)NH$	$CH_2CH_2CH_2$	3-phenylpropyl

and are named:

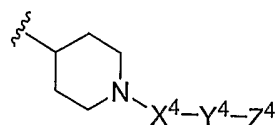
N-[2-(4-Fluoro-phenylmethoxy)-ethyl]-2-[2'-hydroxy-3'-(5-amino-1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetamide; and

N-(3-phenylpropyl)-2-[2'-hydroxy-3'-(5-amino-1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetamide.

Another selected group of compounds of the invention are provided in Table 15, having Formula I:



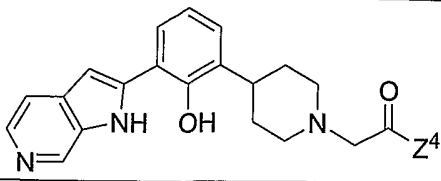
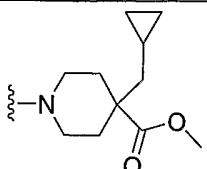
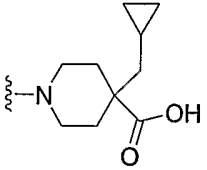
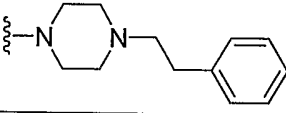
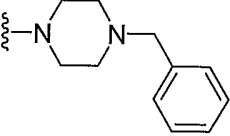
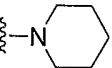
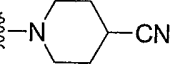
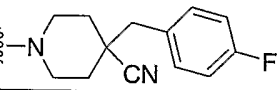
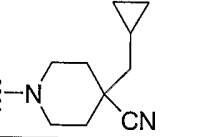
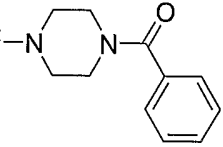
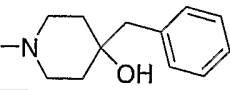
where R^1 , R^2 , and R^3 are hydrogen; D is $=CR^6$ - where R^6 is hydrogen; and R^{100} is

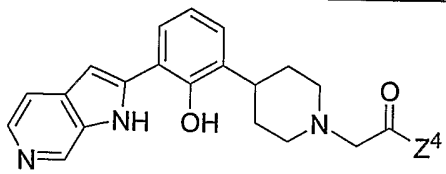
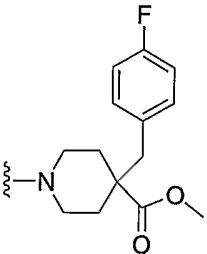
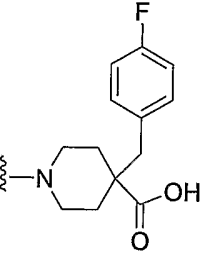
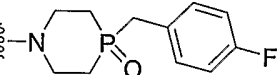
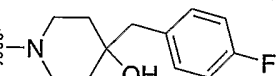


(A3),

where X^4 , Y^4 , and Z^4 are as defined below:

Table 15.

	
Cmpd. No.	Z ⁴
490	
491	
492	
493	
494	
495	
496	
497	
498	
499	

	
Cmpd. No.	Z ⁴
500	
501	
502	
503	

and are named:

methyl 4-(cyclopropylmethyl)-{4-[2-hydroxy-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-phenyl]-piperidin-1-ylacetyl}-piperidine-4-carboxylate;

4-(cyclopropylmethyl)-{4-[2-hydroxy-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-phenyl]-piperidin-1-ylacetyl}-piperidine-4-carboxylic acid;

4-(phenethyl)-{4-[2-hydroxy-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-phenyl]-piperidin-1-ylacetyl}-piperazine;

4-(phenylmethyl)-{4-[2-hydroxy-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-phenyl]-piperidin-1-ylacetyl}-piperazine;

{4-[2-hydroxy-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-phenyl]-piperidin-1-ylacetyl}-piperidine;

4-cyano-{4-[2-hydroxy-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-phenyl]-piperidin-1-ylacetyl}-piperidine;

4-(4-fluorophenylmethyl)-4-cyano-{4-[2-hydroxy-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-phenyl]-piperidin-1-ylacetyl}-piperidine;

4-(cyclopropylmethyl)-4-cyano-{4-[2-hydroxy-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-phenyl]-piperidin-1-ylacetyl}-piperidine;

4-(phenylcarbonyl)-{4-[2-hydroxy-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-phenyl]-piperidin-1-ylacetyl}-piperazine;

4-(phenylmethyl)-4-hydroxy-{4-[2-hydroxy-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-phenyl]-piperidin-1-ylacetyl}-piperidine;

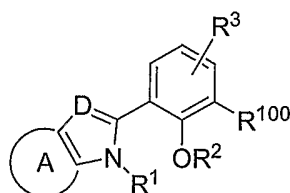
methyl 4-(4-fluorophenylmethyl)-{4-[2-hydroxy-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-phenyl]-piperidin-1-ylacetyl}-piperidine-4-carboxylate;

4-(4-fluorophenylmethyl)-{4-[2-hydroxy-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-phenyl]-piperidin-1-ylacetyl}-piperidine-4-carboxylic acid;

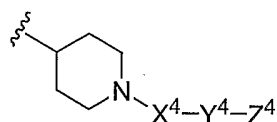
4-(4-fluorophenylmethyl)-4-oxo-{4-[2-hydroxy-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-phenyl]-piperidin-1-ylacetyl}-4 λ^5 -[1,4]azaphosphinane; and

4-(4-fluorophenylmethyl)-4-hydroxy-{4-[2-hydroxy-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-phenyl]-piperidin-1-ylacetyl}-piperidine.

Another selected group of compounds of the invention are provided in Table 16, having Formula I



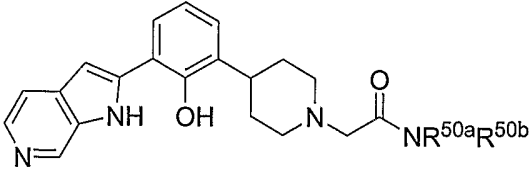
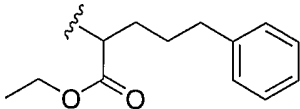
where R^1 , R^2 , and R^3 are hydrogen; D is $=CR^6$ - where R^6 is hydrogen; and R^{100} is

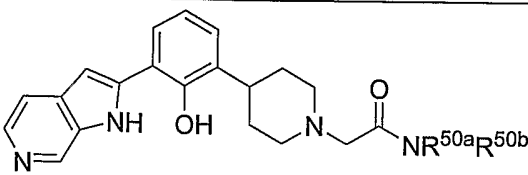
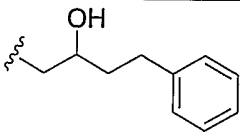
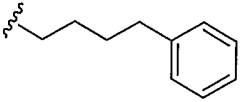
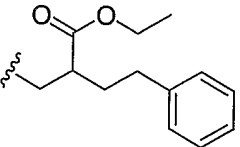
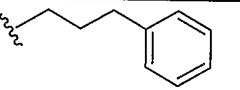


(A3),

where Z^4 is $-NR^{50a}R^{50b}$ and R^{50a} , R^{50b} , X^4 , and Y^4 , are as defined below:

Table 16.

		
Cmpd. No.	R^{50a}	R^{50b}
504	hydrogen	

		
Cmpd. No.	R ^{50a}	R ^{50b}
505	hydrogen	
506	hydrogen	
507	hydrogen	
508	hydrogen	

and are named:

N-[4-phenyl-1-(ethoxycarbonyl)-butyl]-2-{4-[2-hydroxy-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-phenyl]-piperidin-1-yl}-acetamide;

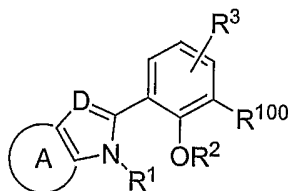
N-(2-hydroxy-4-phenyl-butyl)-2-{4-[2-hydroxy-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-phenyl]-piperidin-1-yl}-acetamide;

N-(4-phenyl-butyl)-2-{4-[2-hydroxy-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-phenyl]-piperidin-1-yl}-acetamide;

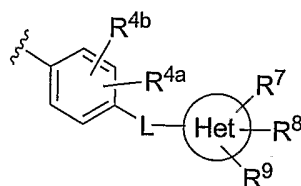
N-[4-phenyl-2-(ethoxycarbonyl)-butyl]-2-{4-[2-hydroxy-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-phenyl]-piperidin-1-yl}-acetamide; and

N-(3-phenyl-propyl)-2-{4-[2-hydroxy-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-phenyl]-piperidin-1-yl}-acetamide.

Another selected group of compounds of the invention are provided in Table 17, having Formula I



where R¹, R², and R³ are hydrogen; D is =CR⁶ - where R⁶ is hydrogen; and R¹⁰⁰ is



(A1)

where R^{4a} , R^{4b} , and R^9 are hydrogen; L is $-X^5-Y^{5a}-Z^5-Y^{5b}-$; and all other groups are as defined below:

Table 17.

Cmpd. No.	A	X^5	Y^{5a}	Z^5	Y^{5b}	Het
509		CH_2	$C(O)NH$	$-CH(CH_2OCH_2phenyl)$	$-C(O)-$	

and is named *N*-(1-benzyloxymethyl-2-oxo-2-pyrrolidin-1-yl-ethyl)-2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetamide.

GENERAL SYNTHESIS

Compounds of this invention can be made by the synthetic procedures described below.

The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as Aldrich Chemical Co. (Milwaukee, Wis.), or Bachem (Torrance, Calif.), or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's *Reagents for Organic Synthesis*, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's *Chemistry of Carbon Compounds*, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989); *Organic Reactions*, Volumes 1-40 (John Wiley and Sons, 1991), March's *Advanced Organic Chemistry*, (John Wiley and Sons, 4th Edition) and Larock's *Comprehensive Organic Transformations* (VCH Publishers Inc., 1989). In particular, 2-chloro-oxazole-4-carboxylic acid ethyl ester can be prepared according to methods described in K.J. Hodgetts, M.T. Kershaw, *Org. Lett.*, **2002**, 4, 2905-7. These schemes are merely illustrative of some methods by which the compounds of this invention can be synthesized, and various modifications to these schemes can be made and will be suggested to one skilled in the art having referred to

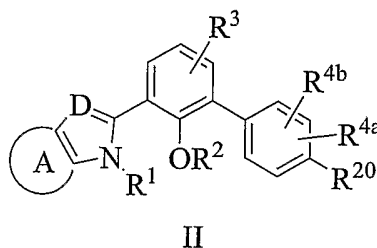
this disclosure.

The starting materials and the intermediates of the reaction may be isolated and purified if desired using conventional techniques, including but not limited to filtration, distillation, crystallization, chromatography and the like. Such materials may be characterized using conventional means, including physical constants and spectral data.

Unless specified to the contrary, the reactions described herein take place at atmospheric pressure over a temperature range from about -78 °C to about 150 °C, more preferably from about 0 °C. to about 125 °C. and most preferably at about room (or ambient) temperature, e.g., about 20 °C. Unless otherwise stated (as in the case of an hydrogenation), all reactions are performed under an atmosphere of nitrogen.

Compounds of Formula I that may be prepared through the syntheses described herein may exist as a single isomer or a mixture of isomers.

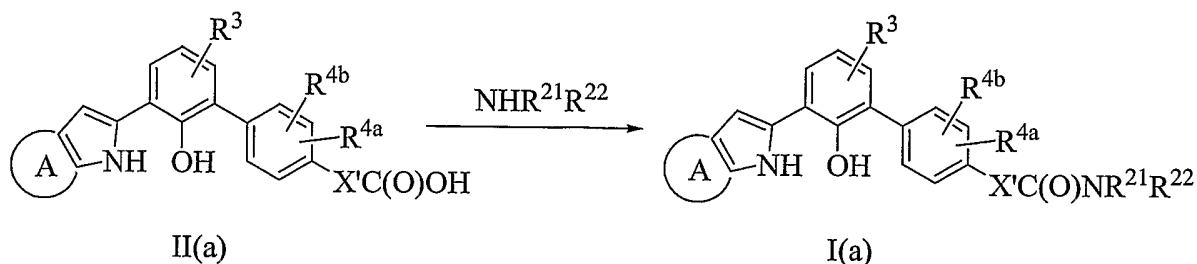
Compounds of Formula I, where each A, D, R¹, R², R³, R^{4a} and R^{4b} are as defined in the Summary of the Invention, can be prepared by reacting a compound of Formula II:



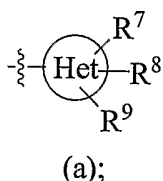
where R²⁰ is a substituent that contains a reactive functional group, e.g., -COOH or -NH₂, with an intermediate that contains a complementary reactive group, e.g., -NHR or -COOH, respectively, to form the group L where R¹⁰⁰ is a group of formula (A1), or to form the groups Y¹¹, Y¹², Y¹³, or Y¹⁴ when R¹⁰⁰ is a group of formula (A2), or to form -Y⁴-Z⁴ when R¹⁰⁰ is a group of formula (A3). Preferably R²⁰ is a reactive functional group containing a protecting group that can be removed by methods known in the art. The reactive group is preferably amino, alkylamino, dialkylamino, hydroxy, carboxy, and thio. The reactive group can be made to react under conditions known to those skilled in the art with a complementary reactive group.

For example, compounds of Formula I in which D is =CH-; R¹ is hydrogen; A, R³, R^{4a}, and R^{4b} are as defined in the Summary of the Invention; R¹⁰⁰ is a group of formula (A1), and L is -X¹-Y¹-Z¹- (where Y¹ is -C(O)NR¹³- and Z¹ is as defined in the Summary of the Invention; or Y¹ is -C(O)- and Z¹ is a bond), or L is -Y²-Z²- (where Y² is -C(O)NR¹⁵- and Z² is as defined in the Summary of the Invention) can be prepared by reacting a deprotected carboxylic acid of Formula II(a) with a primary or secondary amine or amine salt, e.g., an

amine of the formula $\text{NHR}^{21}\text{R}^{22}$ as in the following reaction scheme:



where X' in the above scheme is a bond or $-\text{X}^1-$; R^{21} is R^{13} or R^{15} , as applicable; and R^{22} is $-\text{Z}^1-\text{R}^{23}$ or $-\text{Z}^2-\text{R}^{23}$, as applicable, and R^{23} is a moiety of Formula (a):



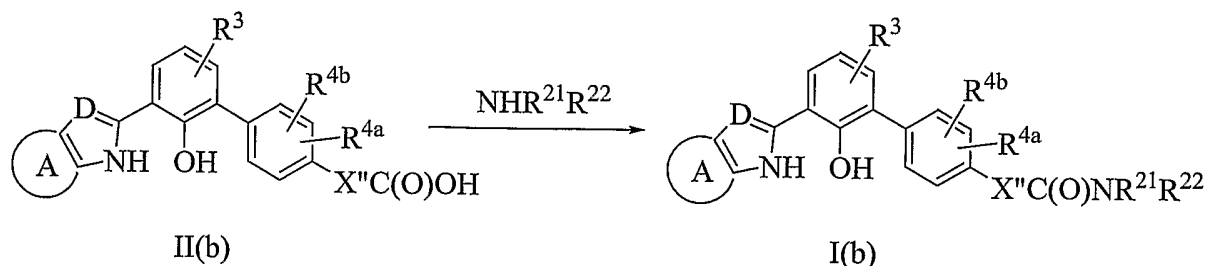
or R^{21} and R^{22} together with the nitrogen atom to which they are attached form a moiety of Formula (a) and R^7 , R^8 and R^9 are as defined in the Summary of the Invention.

The reaction can be carried out with an acid halide of the carboxylic acid in the presence of a suitable base, such as triethylamine, *N,N*-diethylaniline, diisopropylethylamine and the like, in a suitable reaction solvent, such as THF, DMF and the like. The acid halide can be prepared by methods known to those of skill in the art. For example the acid chloride can be prepared by reacting the acid with a halogenating agent, such as oxalyl chloride, thionyl chloride, phosphorous oxychloride, and the like.

The reaction can be carried out with the acid in the presence of a coupling agent such as benzotriazole-1-yloxytrispyrrolidino-phosphonium hexafluorophosphate (PyBOP®), bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBrop®), *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyl-uronium hexafluorophosphate (HBTU), *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU), or 1,3-dicyclohexylcarbodiimide (DCC) or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) optionally in the presence of 1-hydroxybenzotriazole (HOBT). As appropriate, a base such as *N,N*-diisopropylethylamine, triethylamine, or *N*-methylmorpholine can be used. The reaction is carried out in suitable organic solvents, such as DMF and the like. Suitable amines and amine salts are either commercially available or they can be prepared from commercially available starting materials by methods known in the art.

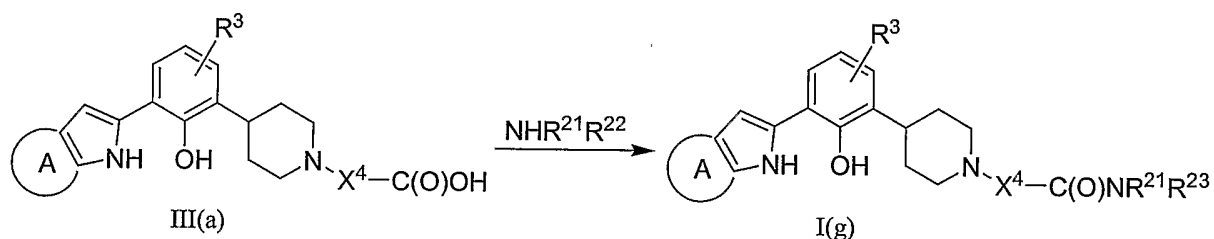
Similarly, for example, compounds of Formula I in which D is $=\text{CH}-$, R^1 is hydrogen,

R^{100} is a group of formula (A2), and Y^{11} , Y^{12} , Y^{13} , or Y^{14} is $-C(O)NR^{26a}$ - can be prepared using conventional amide forming reactants and conditions as in the following reaction scheme:



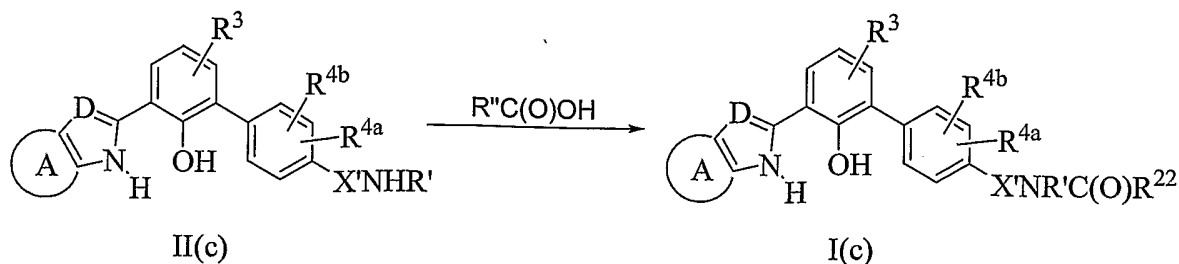
where X'' in the above scheme is a bond, X^{12a} , or X^{13} ; R^{21} is R^{26a} ; and R^{22} is $-X^{11}-Q^{11}$, $-X^{12b}-Q^{12}$, $-Z^{13}$, or $-Z^{14}$, respectively, and each A, R^3 , R^{4a} , R^{4b} , X^{12a} , X^{13} , R^{26a} , X^{12b} , Q^{12} , Z^{13} , and Z^{14} are as defined in the Summary of the Invention.

Similarly, for example, compounds of Formula I in which D is $=CH-$, R^1 is hydrogen, R^{100} is a group of formula (A3), Y^4 is $-C(O)-$, and A, R^3 , and X^4 are as defined in the Summary of the Invention can be prepared using conventional amide forming reactants and conditions as in the following reaction scheme:

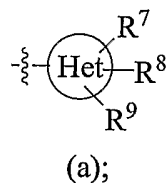


When Z^4 is $-NR^{50a}R^{50b}$, R^{21} is R^{50a} and R^{22} is R^{50b} . When Z^4 is heterocycloalkyl, R^{21} and R^{22} together with the nitrogen atom to which they are attached form heterocycloalkyl optionally substituted with one, two, three, or four groups selected from cycloalkyl, cycloalkylalkyl, alkoxycarbonyl, carboxy, aryl, aralkyl, cyano, arylcarbonyl, alkoxy, and hydroxy.

A compound of Formula I in which D is $=CH-$; R^1 is hydrogen; A, R^3 , R^{4a} , and R^{4b} are as defined in the Summary of the Invention; R^{100} is a group of formula (A1), and L is $-X^1-Y^1-Z^1$ - (where Y^1 is $-NR^{13}C(O)-$ and Z^1 is as defined in the Summary of the Invention), or L is $-Y^3$ - where $-Y^3$ is $-NR^{17}C(O)-$, or L is $-Y^2-Z^2$ - (where Y^2 is $-C(O)NR^{15}-$ and Z^2 is as defined in the Summary of the Invention) can be prepared using conventional amide forming reactants and conditions by reacting a deprotected amine of Formula II(e) with a carboxylic acid or carboxylic acid salt, e.g., an intermediate of the formula $R''C(O)OH$, as in the following reaction scheme:

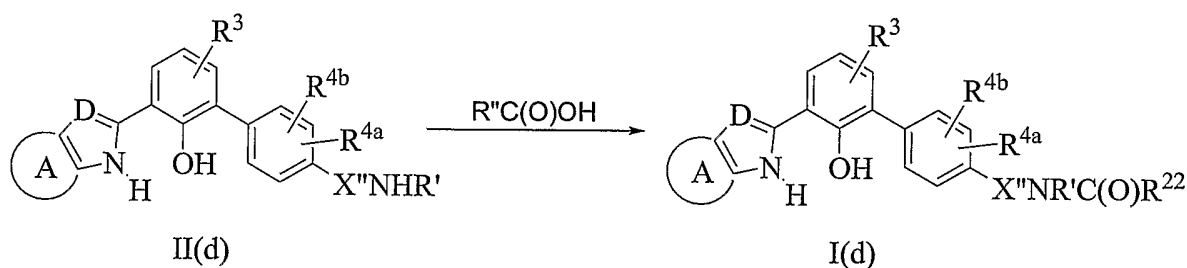


where A, D, R^3 , R^{4a} , and R^{4b} are as defined in the Summary of the Invention and R'' in the above scheme is $-Z^1-R^{23}$, $-Z^2-R^{23}$, or $-R^{23}$, as applicable, and R^{23} is a moiety of Formula (a):



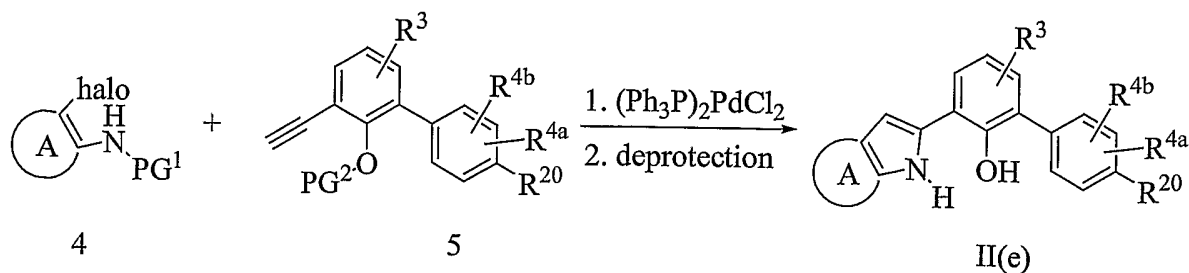
where R^7 , R^8 and R^9 are as defined in the Summary of the Invention. The reaction can also be carried out with a sulfonylating agent instead of the carboxylic acid, preferably a sulfonyl halide, in the presence of a suitable base, such as triethylamine, *N,N*-diethylaniline, diisopropylethylamine and the like, in a suitable reaction solvent, such as methylene chloride and the like.

Similarly, for example, compounds of Formula I in which D is $=CH-$, R^1 is hydrogen, R^{100} is a group of formula (A2), and Y^{11} , Y^{12} , Y^{13} , or Y^{14} is $-NR^{26a}C(O)-$ can be prepared using conventional amide forming reactants and conditions as in the following reaction scheme:



where X'' in the above scheme is a bond, X^{12a} , or X^{13} ; R'' is $-X^{11}-Q^{11}$, $-X^{12b}-Q^{12}$, $-Z^{13}$, or $-Z^{14}$, respectively, and each A, R^3 , R^{4a} , R^{4b} , X^{12a} , X^{13} , R^{26a} , X^{12b} , Q^{12} , Z^{13} , and Z^{14} are as defined in the Summary of the Invention. The reaction can also be carried out with a sulfonylating agent instead of the carboxylic acid, preferably a sulfonyl halide, in the presence of a suitable base, such as triethylamine, *N,N*-diethylaniline, diisopropylethylamine and the like, in a suitable reaction solvent, such as methylene chloride and the like.

Intermediates of Formula II, wherein R^1 is hydrogen and D is $=CH-$ can be prepared by the following reaction scheme:



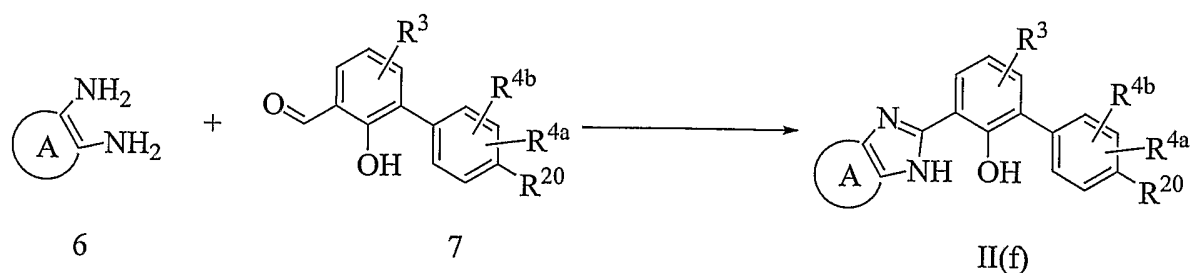
wherein PG^1 and PG^2 are a nitrogen-protecting and oxygen-protecting group, respectively, and A, R^3 , R^{4a} , and R^{4b} are as defined in the Summary of the Invention and R^{20} is, for example, $-\text{X}^1\text{-NHPG}^1$, $-\text{X}^1\text{C(O)OPG}^3$, $-\text{X}^{12a}\text{-NHPG}^1$, $-\text{X}^{12a}\text{-C(O)OPG}^3$, $-\text{X}^{13}\text{-NHPG}^1$, $-\text{X}^{13}\text{-C(O)OPG}^3$, $-\text{X}^4\text{-NHPG}^1$, $-\text{X}^4\text{-C(O)OPG}^3$, $-\text{NHPG}^1$, or $-\text{C(O)OPG}^3$ where PG^1 is as described above, PG^3 is an acid-protecting group, and all other groups are as defined in the Summary of the Invention.

Intermediates of Formula II can be prepared by reacting a compound of Formula 4 with a compound of Formula 5 and then deprotecting. The reaction can be carried out in the presence of acetonitrile, dichloro-bis(triphenylphosphine)palladium (II), copper iodide, and a base, such as triethylamine, at 50 to 100 °C and requires 1 to 8 hours to complete.

The protecting groups represented by PG^2 , PG^1 and PG^3 can be removed in the presence of acid or base, preferably 4 M aqueous hydrochloric acid for the deprotection of PG^2 where PG^2 is methoxyethoxymethyl. 4 M Aqueous hydrochloric acid also is preferred for the removal of PG^3 which is typically an ester or a *tert*-butoxycarbonyl group. Preferably, when PG^1 is methanesulfonyl, aqueous sodium hydroxide or tetrabutylammonium fluoride is used to remove the group.

Compounds of Formula 5 can be prepared from the corresponding aldehyde of Formula 6 by treating the aldehyde with 1-diazo-2-oxopropyl)phosphonate and potassium carbonate or cesium carbonate as described in Ohira, S. *Synth. Commun.* **1989**, 19, 561.

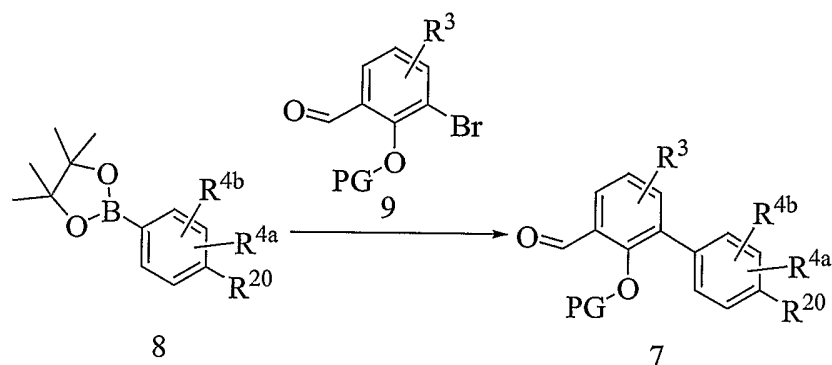
Intermediates of Formula II, wherein R^1 is hydrogen and D is =N- can be prepared by the following reaction scheme:



wherein A, R^3 , R^{4a} , and R^{4b} are as defined in the Summary of the Invention and R^{20} is, for example, $-\text{X}^1\text{-NHPG}^1$, $-\text{X}^1\text{C(O)OPG}^3$, $-\text{X}^{12a}\text{-NHPG}^1$, $-\text{X}^{12a}\text{-C(O)OPG}^3$, $-\text{X}^{13}\text{-NHPG}^1$,

$-X^{13}-C(O)OPG^3$, $-X^4-NHPG^1$, $-X^4-C(O)OPG^3$, $-NHPG^1$, or $-C(O)OPG^3$ where PG^1 is as described above, PG^3 is an acid-protecting group, and all other groups are as defined in the Summary of the Invention. The aldehyde of Formula 7 is reacted with a diamino of Formula 6 in the presence of *N,N*-dimethylformamide and sodium metabisulfite at about 130 °C for approximately 24 to 48 hours.

The aldehyde of Formula 7 can be prepared by the following reaction scheme:

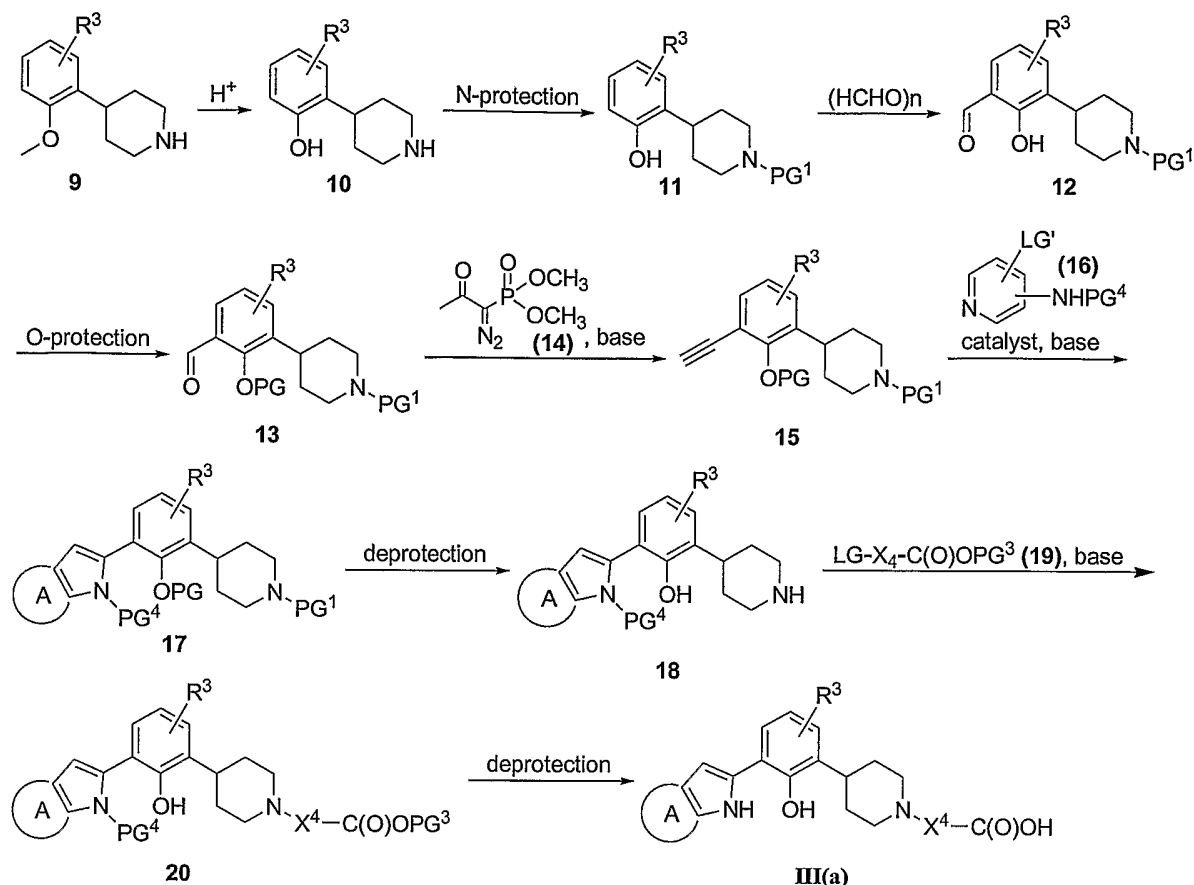


wherein A, R^3 , R^{4a} , and R^{4b} are as defined in the Summary of the Invention and R^{20} is, for example, $-X^1-NHPG^1$, $-X^1-C(O)OPG^3$, $-X^{12a}-NHPG^1$, $-X^{12a}-C(O)OPG^3$, $-X^{13}-NHPG^1$, $-X^{13}-C(O)OPG^3$, $-X^4-NHPG^1$, $-X^4-C(O)OPG^3$, $-NHPG^1$, or $-C(O)OPG^3$ where PG^1 is as described above, PG^3 is an acid-protecting group, and all other groups are as defined in the Summary of the Invention.

The reaction illustrated in the above scheme is carried out with a boronate ester or acid of Formula 6, potassium carbonate, tetrakis(triphenylphosphine)palladium (0), and solvent DME and water at 50 to 100 °C and takes 3 to 5 hours to complete. The aldehyde of Formula 7 where PG is a protecting group such as alkyl or alkyloxyalkyl can be prepared from the compound where PG is hydrogen by methods known in the art. For example, the compound where PG is hydrogen can be reacted in the presence of MEM-Cl, cesium chloride and DMF at 0 to 20 °C and requires approximately 1 to 4 hours to complete. Aldehydes of Formula 7 where PG is hydrogen can be obtained commercially or preferably can be prepared from corresponding 2-halophenols in the presence of THF, paraformaldehyde, triethylamine, and magnesium chloride at ambient temperature and requires 8 to 10 hours to complete.

Boronates of Formula 9 can be obtained from commercially available aryl halides by treating with 1,4-dioxane, potassium acetate, *bis*(pinacolato)diboron, and a catalyst, preferably [1,1'-bis-(diphenylphosphino)ferrocene]dichloropalladium(II)•CH₂Cl₂ complex.

Intermediates of Formula III(a) where A, X^4 , and R^3 are as defined in the Summary of the Invention can be prepared by the following reaction scheme:



The methoxy group in an intermediate of formula 9, which is commercially available or can be prepared by one of ordinary skill in the art, is converted to the hydroxy of an intermediate of formula 10 using a strong acid such as aqueous HBr at reflux temperature. The nitrogen is then protected. For example PG¹ is a CBz which is installed under basic conditions using solvent(s) such as acetonitrile and water. The aldehyde of formula 12 is prepared by reacting 11 with paraformaldehyde in the presence of MgCl₂ and a base such as triethylamine. The reaction is carried out in a solvent such as THF. The reaction is then quenched with phosphoric acid.

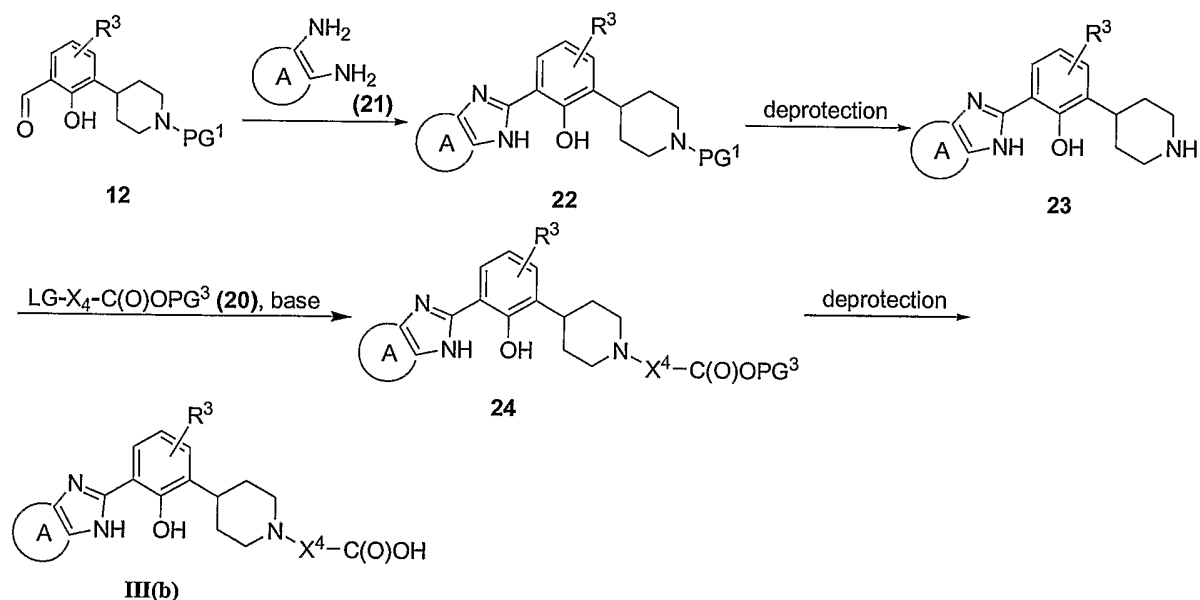
The hydroxy group is then protected. This can be accomplished by reacting in the presence of MEM-Cl, a base such as cesium chloride and a solvent such as DMF at 0 to 20 °C. The reaction is allowed to proceed for approximately 1 to 4 hours yielding the O-protected product 13. The alkyne 15 is prepared by reacting 14 in the presence of Ohira-Bestmann's reagent (14) and a base such as cesium carbonate in a solvent such as ethanol under an inert atmosphere at approximately 0 °C. The reaction is then quenched with a mixture of 5% NaHCO₃ and ethyl acetate.

An intermediate of formula 17 can be prepared by reacting an intermediate of formula 15 with an intermediate of formula 16 where PG⁴ is a nitrogen-protecting group (orthogonal

to PG¹) and LG' is a leaving group, such as halo; and where LG' and NHPG⁴ are attached on adjacent carbon atoms. The reaction is carried out under an inert atmosphere in the presence of copper halide, such as copper iodide, and a catalyst such as PdCl₂(PPh₃)₂ and a base such as triethylamine, in a solvent such as acetonitrile and heated to approximately 75 °C.

The piperidine protecting group is then removed. Where PG¹ is CBz the intermediate is treated with a strong acid such as HBr (a solution in acetic acid) in a solvent such as methylene chloride to yield the intermediate 18. In a solvent such as acetonitrile, 18 is then treated with a base such as *N,N*-diisopropylethylamine, and with LG-X⁴-C(O)OPG³ (20) where LG is a leaving group, such as halo, and PG³ is a carboxy-protecting group. The reaction is then neutralized with an acid such as 1N HCl. Preferably, PG³ and PG⁴ can both be removed under the same conditions, e.g. PG⁴ is methansulfonyl and PG³ is methyl or ethyl, and are removed under basic conditions. The deprotection under basic conditions can be carried out using a base such as sodium hydroxide in a solvent such as THF and heating to approximately 65 °C to yield an intermediate of formula III(a).

Intermediates of Formula III(b) where A, X⁴, and R³ are as defined in the Summary of the Invention can be prepared by the following reaction scheme:



The intermediate of formula 12, prepared as described above, is reacted with an intermediate of formula 21 to yield 22. The reaction is carried out in the presence of *N,N*-dimethylformamide and sodium metabisulfite at about 130 °C for approximately 24 to 48 hours. PG¹ is removed using conditions, known to one of ordinary skill in the art, depending on the type of protecting group used. 23 is then reacted with 20 using conditions described

above and 24 is subsequently deprotected to yield an intermediate of formula III(b).

UTILITY

The compounds of this invention are tryptase inhibitors. As such the compounds of Formula I are useful for treating diseases, particularly immunomediated inflammatory diseases in which tryptase activity contributes to the pathology and/or symptomatology of the disease. For example, immunomediated inflammatory diseases in which tryptase activity contributes to its pathology and/or symptomatology include asthma, allergic rhinitis, rheumatoid spodylitis, osteoarthritis, gouty arthritis, rheumatoid arthritis, arthritic conditions in general, urticaria, angioedema, eczematous dermatitis, anaphylaxis, hyper proliferative skin disease, peptic ulcers, inflammatory bowel disease, ocular and vernal conjunctivitis, inflammatory skin conditions, chronic obstructive pulmonary disease, and the like.

Suitable *in vitro* assays for measuring tryptase activity and the inhibition thereof by compounds are known (e.g., see Sturzebecher *et al.*, *Biol. Chem. Hoppe-Seyler*, **1992**, 373, 1025-1030). Typically, the assay will measure tryptase induced hydrolysis of peptide base substrate. For further details of an *in vitro* assay for measuring tryptase activity see Biological Examples, Example 1 *infra*.

Assays for measurement of efficacy in treatment of skin diseases, ulcers, and Syncytial Virus Infection are described in Biological Examples, Example 3, 5, and 6, *infra*.

Suitable *in vivo* models of inflammation are known to those of ordinary skill in the art. For example, *in vivo* models for asthma are described by Larsen (1991) *Experimental Models of Reversible Airway Obstruction*. In: West *et al.*, eds. *The Lung: Scientific Foundations* Raven Press, New York). Further, *in vivo* models of inflammatory skin conditions (Walsh *et al. Br. J. Pharmacol.*, **1995**, 114, 1343-1350; and Armstrong *et al. Prostaglandins*, **1995**, 49, 205-224), arthritic conditions (Peacock *et al. Cell Immunol.*, **1995**, 160, 178-184; and Houri *et al. Curr. Opin. Rheumatol.*, **1995**, 7, 201-205) and gastrointestinal diseases (Anthony *et al. Int. J. Exp. Pathol.*, **1995**, 76, 215-224.; and Carter *et al. Dig. Dis. Sci.*, **1995**, 40, 192-197) are known. For further details of *in vivo* assays see Biological Examples 2 and 4, *infra*.

ADMINISTRATION AND PHARMACEUTICAL COMPOSITIONS

In general, the compounds of this invention will be administered in a therapeutically effective amount by any of the accepted modes of administration for agents that serve similar

utilities. The actual amount of the compound of this invention, i.e., the active ingredient, will depend upon numerous factors such as the severity of the disease to be treated, the age and relative health of the subject, the potency of the compound used, the route and form of administration, and other factors.

Therapeutically effective amounts of compounds of Formula I may range from approximately 0.1-50 mg per kilogram body weight of the recipient per day; preferably about 0.5-20 mg/kg/day. Thus, for administration to a 70 kg person, the dosage range would most preferably be about 35 mg to 1.4 g per day. If a known β -2 adrenoreceptor agonist(s), corticosteroid(s), leukotriene antagonist(s), and/or phosphodiesterase 4 inhibitor(s) is also administered, each is administered in an amount which is effective to achieve its intended purpose. The amounts of such known β -2 adrenoreceptor agonist(s), corticosteroid(s), leukotriene antagonist(s), and/or phosphodiesterase 4 inhibitor(s) effective for asthma are well known to those of skill in the art.

Therapeutic agents that may be useful for administration in combination with compounds of Formula I in treating asthma include β -2 adrenoreceptor agonists (e.g., salmeterol, albuterol, terbutaline, formoterol, fenoterol, prenaline and the like), methylxanthines (e.g., caffeine, theophylline, aminophylline, theobromine and the like), cromoglycates (e.g., cromolyn, nedocromil, and the like), corticosteroids (e.g., budesonide, fluticasone, beclomethasone, triamcinolone, flurisolide, dexamethasone and the like), leukotriene D4 antagonists (e.g., montelukast and the like), and phosphodiesterase 4 inhibitors (e.g., roflumilast and the like). In general, one of ordinary skill in the art, acting in reliance upon personal knowledge and the disclosure of this application, will be able to ascertain a therapeutically effective amount of a compound of Formula I for treating a given inflammatory disease.

Therapeutic agents that may be useful for administration in combination with compounds of Formula I in treating COPD include corticosteroid(s), xanthines (e.g., theophylline), anticholinergic compounds (e.g., ipratropium, tiotropium), biologics, small molecule immunomodulators, and beta receptor agonists/bronchodilators (e.g., albuterol sulfate, bitolterol mesylate, epinephrine, formoterol fumarate, isoproterenol, levalbuterol hydrochloride, metaproterenol sulfate, pirbuterol scetate, salmeterol xinafoate, and terbutaline).

In general, compounds of this invention will be administered as pharmaceutical compositions by any one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository), or parenteral (e.g., intramuscular, intravenous or subcutaneous)

administration. The preferred manner of administration is oral or parenteral using a convenient daily dosage regimen, which can be adjusted according to the degree of affliction. Oral compositions can take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate compositions.

The choice of formulation depends on various factors such as the mode of drug administration (e.g., for oral administration, formulations in the form of tablets, pills or capsules are preferred) and the bioavailability of the drug substance. Recently, pharmaceutical formulations have been developed especially for drugs that show poor bioavailability based upon the principle that bioavailability can be increased by increasing the surface area i.e., decreasing particle size. For example, U.S. Pat. No. 4,107,288 describes a pharmaceutical formulation having particles in the size range from 10 to 1,000 nm in which the active material is supported on a crosslinked matrix of macromolecules. U.S. Pat. No. 5,145,684 describes the production of a pharmaceutical formulation in which the drug substance is pulverized to nanoparticles (average particle size of 400 nm) in the presence of a surface modifier and then dispersed in a liquid medium to give a pharmaceutical formulation that exhibits remarkably high bioavailability.

The compositions are comprised of in general, a compound of Formula I in combination with at least one pharmaceutically acceptable excipient. Acceptable excipients are non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the compound of Formula I. Such excipient may be any solid, liquid, semi-solid or, in the case of an aerosol composition, gaseous excipient that is generally available to one of skill in the art.

Solid pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk and the like. Liquid and semisolid excipients may be selected from glycerol, propylene glycol, water, ethanol and various oils, including those of petroleum, animal, vegetable or synthetic origin, e.g., peanut oil, soybean oil, mineral oil, sesame oil, etc. Preferred liquid carriers, particularly for injectable solutions, include water, saline, aqueous dextrose, and glycols.

Compressed gases may be used to disperse a compound of this invention in aerosol form. Inert gases suitable for this purpose are nitrogen, carbon dioxide, etc.

Other suitable pharmaceutical excipients and their formulations are described in Remington's Pharmaceutical Sciences, edited by E. W. Martin (Mack Publishing Company, 18th ed., 1990).

The amount of the compound in a formulation can vary within the full range employed by those skilled in the art. Typically, the formulation will contain, on a weight percent (wt %) basis, from about 0.01-99.99 wt % of a compound of Formula I based on the total formulation, with the balance being one or more suitable pharmaceutical excipients. Preferably, the compound is present at a level of about 1-80 wt %. Representative pharmaceutical formulations containing a compound of Formula I are described below.

The compounds of this invention can be administered in combination with known asthma, COPD, and/or allergic rhinitis agents. Such known asthma, COPD, and/or allergic rhinitis agents include β -2 adrenoreceptor agonists, corticosteroids, leukotriene antagonists, and phosphodiesterase 4 inhibitors. Preferred β -2 adrenoreceptor agonists include salmeterol. Preferred corticosteroids include budesonide and fluticasone. Preferred leukotriene antagonists include montelukast. Preferred phosphodiesterase 4 inhibitors include roflumilast.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described above and the other pharmaceutically active agent(s) within its approved dosage range. Compounds of the instant invention may alternatively be used sequentially with known pharmaceutically acceptable agent(s) when a combination formulation is inappropriate.

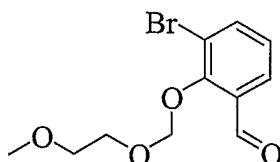
EXAMPLES

The following preparations and examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be considered as limiting the scope of the invention, but merely as being illustrative and representative thereof.

Synthetic Examples

Reference 1

Synthesis of 3-Bromo-2-(methoxyethoxymethoxy)-benzaldehyde



Step 1

2-Bromophenol (97 g, 0.56 mol), THF (1.0 L), and paraformaldehyde, prilled (84.0 g, 2.80 mol) were charged to a 5 L 3-neck round-bottom flask. Triethylamine (TEA) (400 mL)

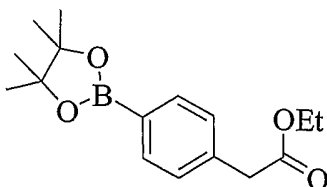
was added, followed by MgCl_2 (200 g, 2.10 mmol) added portionwise over a 90 minutes, while stirring with an overhead stirrer. The reaction was white, cloudy, and viscous, and turned bright yellow on addition of the MgCl_2 . The reaction was allowed to stir overnight under a nitrogen atmosphere. The reaction was neutralized cautiously with phosphoric acid (300 mL) and brine (500 mL) diluted with ethyl acetate (500 mL). The organic layer was separated and washed with water (500 mL X 3) and brine (500 mL), and dried over Na_2SO_4 . The solvents were evaporated and the residue was dissolved in ethyl acetate. The solution was filtered through 6 x 4 inch silica gel plug with ethyl acetate (1.5 L) as eluant. The solution was concentrated to give crude 3-bromo-2-hydroxy-benzaldehyde. (107g, 96%). ^1H NMR (400 MHz, DMSO) δ ppm 11.28 (s, 1H), 10.06 (s, 1H), 7.89 (dd, 1H, $J = 1.6, 7.8$ Hz), 7.78 (dd, 1H, $J = 1.6, 7.4$ Hz), 7.02 (t, 1H, $J = 7.8$ Hz).

Step 2

A 3 L round bottom flask was charged with 3-bromo-2-hydroxy-benzaldehyde (80.00 g, 398.0 mmol) and DMF (300 mL). Cs_2CO_3 (155.6 g, 475.7 mmol) was added and the solution was stirred for 15 minutes. Methoxyethoxymethylchloride (54.53 mL, 477 mmol) was added dropwise via an addition funnel. The reaction solution became a bright yellow, viscous mixture. The reaction mixture turned to a white/light beige, viscous solution as the reaction progressed. When the reaction was complete, the solid was filtered from the reaction solution. Hexane (750 mL) and ether (750 mL) were added to the filtrate. The organic layer was washed with water (3 X 700 mL) and brine (2 X 500 mL), dried over Na_2SO_4 , and concentrated to give 3-bromo-2-(methoxyethoxymethoxy)-benzaldehyde (crude yield of 105g) which was used in Reference 23 without further purification. ^1H NMR (400 MHz, DMSO) δ 10.22 (d, 1H, $J = 0.8$ Hz), 7.97 (dd, 1H, $J = 2, 7.8$ Hz), 7.75 (dd, 1H, $J = 1.6, 7.8$ Hz), 7.27 (dt, 1H, $J = 0.7, 7.8$ Hz), 5.26 (s, 2H), 3.87 (m, 2H), 3.46 (m, 2H), 3.22 (s, 3H).

Reference 2

Ethyl [4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-acetate

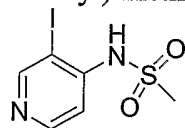


Ethyl (4-bromophenyl)-acetate (100 g, 411 mmol) *bis*-(pinacolato)diboron (125.4 g, 493.7 mmol) and potassium acetate (125.4 g, 493.7 mmol) were charged to a 2 L round bottom flask. 1,4-Dioxane (1 L) was added and the mixture was stirred under a nitrogen

atmosphere for 15 minutes. [1,1'-*bis*-(Diphenylphosphino)-ferrocene]dichloropalladium(II) CH_2Cl_2 complex (1:1) (3.36 g, 4.11 mmol) was added and the reaction was heated in an 100 °C oil bath for 2 hours. The reaction was determined complete by analytical HPLC. The solution was concentrated under reduced pressure to remove the dioxane and the residue was dissolved in ethyl acetate. The solution was filtered through a 6 x 4 inch silica gel plug with ethyl acetate (1.5 L) as eluant to give ethyl [4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-acetate (117 g, 98%). ^1H NMR (400 MHz, DMSO) δ ppm 7.63 (d, 2H, $J = 8$ Hz), 7.27 (d, 2H, $J = 8$ Hz), 4.07 (q, 2H, $J = 7$ Hz), 3.68 (s, 2H), 1.28 (s, 12H), 1.16 (t, 3H, $J = 7$ Hz).

Reference 3

N-(3-Iodo-pyridin-4-yl)-methanesulfonamide



Step 1

4-Aminopyridine (40.5 g, 0.4303 mol) was placed in a 1 L 3-neck flask and then Na_2CO_3 (22.78 g, 0.2150 mmol) and water (100 mL) was added. The mixture was heated to reflux and stirred for 5 minutes. Iodine (81.84 g, 0.3224 mol) and potassium iodide (71.36 g, 0.4301 mol) were dissolved in water (500 mL) and placed in an addition funnel. The iodide/potassium iodide/water mixture was added to the reaction dropwise while the mixture continued to be heated and stirred. An additional 0.25 equiv of the iodide/potassium iodide/water mixture was prepared and added to the reaction mixture. The mixture was heated and stirred for 8 hours and then allowed to cool to room temperature. Ethyl acetate was added and the mixture was washed with water, $\text{Na}_2\text{S}_2\text{O}_3$, and brine. The organic layer was separated, dried (Na_2SO_4), filtered, and concentrated. The residue was dissolved in dichloromethane and filtered using a silica plug (30% EtOAc / 70% hexane system, followed by 100% EtOAc system). The filtrate was dried under reduced pressure to give 4-amino-3-iodopyridine (27.0 g, 29%) as a beige solid.

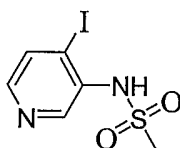
Step 2

4-Amino-3-iodopyridine (20.00 g, 90.87 mmol) was placed in a 500 mL round-bottom flask. Dichloromethane (150 mL) and triethylamine (12.67 mL, 90.87 mmol) were added with stirring under nitrogen. The mixture was cooled to 5 °C and stirred under nitrogen while methanesulfonyl chloride (7.01 mL, 90.9 mmol) was added dropwise. The mixture formed a white precipitate as the reaction progressed and after 5 hours additional

triethylamine (15.2 mL, 109 mmol) and methanesulfonyl chloride (8.41 mL, 109 mmol) were added and the reaction was allowed to proceed for an additional 2 hours. The white precipitate was filtered from the reaction solution and dissolved in THF (400 mL) and water (200 mL). The solution was heated to reflux for 30 minutes and then the THF was then removed under reduced pressure. Solids precipitated out of the aqueous residue and were collected to give *N*-(3-iodo-pyridin-4-yl)-methanesulfonamide (21 g).

Reference 4

Synthesis of 4-iodo-3-(methanesulfonylamino)-pyridine



Step 1

N-(4-Iodo-pyridin-3-yl)-2,2-dimethyl-propionamide (20.00 g, 65.76 mmol) was charged to a 2 L round-bottom flask and 24% sulfuric acid in water (640 mL) was added carefully. The mixture was heated to 100 °C for 4 hours. The reaction was determined complete by analytical HPLC. The mixture was allowed to cool to room temperature and then carefully adjusted to pH 7-8 with 4N NaOH (approximately 700 mL). Saturated sodium bicarbonate was added to the mixture and the product extracted into dichloromethane (3 X 500 mL). The organic layers were combined and concentrated to give 3-amino-4-iodo-pyridine (13.3 g, 92%).

Step 2

3-Amino-4-iodo-pyridine (15.0 g, 68.2 mmol) was charged to a 1 L round-bottom flask and then dichloromethane (200 mL) and triethylamine (21.1 mL, 152 mmol) were added. The mixture was cooled to 5 °C in an ice bath and methanesulfonyl chloride (11.61 mL, 17.18 g) was added via an addition funnel. The reaction was determined greater than 95% after 30 minutes by analytical HPLC. The mixture was quenched with saturated NH₄Cl (300 mL) and extracted with ethyl acetate (1 L). The organic layer was filtered through a silica gel plug with ethyl acetate as eluant and concentrated to give crude 4-iodo-3-(*bis*-methanesulfonylamino)-pyridine (25.0 g, 97%) which was used in the next step without purification. ¹H NMR (400 MHz, DMSO) δ 8.25 (d, 1H, *J* = 5.5 Hz), 8.07 (d, 1H, *J* = 0.8 Hz), 7.68 (dd, 1H, *J* = 0.8, 5.5 Hz).

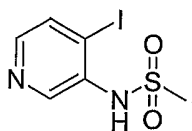
Step 3

N-(4-Iodo-pyridin-3-yl)-*N*-methanesulfonyl-methanesulfonamide (25.64 g, 68.16

mmol), THF (300 mL), water (100 mL) and 4 N NaOH (75 mL) were sequentially added to a 2 L round-bottom flask and the mixture was warmed in a 75 °C oil bath overnight. The reaction was determined complete by analytical HPLC. The THF was removed under reduced pressure and the aqueous layer was adjusted to a pH of 7 using 4 M hydrochloric acid (approximately 75 mL) caustiously added. A solid precipitated out of the mixture, which was collected by filtration to give 4-iodo-3-(methylsulfonylamino)-pyridine (16.5 g, 81%) as an off-white solid. ¹H NMR (400 MHz, DMSO) δ ppm 9.64 (s, 1H), 8.46 (s, 1H), 8.07 (d, 1H, *J* = 5.1 Hz), 7.99 (d, 1H, *J* = 5.1 Hz), 3.12 (s, 3H).

Reference 5

Synthesis of 4-iodo-3-(methylsulfonylamino)-pyridine



Step 1

3-(*tert*-Butylcarbonylamino)-4-iodo-pyridine (20.00 g, 65.76 mmol) was charged to a 2 L round-bottom flask, and sulfuric acid, 24% in water (640 mL) was carefully added. The reaction was heated to 100 °C. After 4 hours, the reaction was shown to be complete as determined by HPLC. After cooling to room temperature, the solution was carefully neutralized with 4 M NaOH until a pH of 7-8 was achieved. Saturated bicarbonate was added to the reaction mixture, and the product extracted into dichloromethane (3 X 500 mL). The organic layers were combined and concentrated to give 13.3 g of 3-amino-4-iodo-pyridine.

Step 2

3-Amino-4-iodo-pyridine (15.0 g, 68.2 mmol) was charged to a 1 L round-bottom flask, and dichloromethane (200 mL) and triethylamine (21.1 mL, 152 mmol) were added. The mixture was cooled to 5 °C in an ice bath, and methanesulfonyl chloride (11.61 mL, 17.18 g) was added via an addition funnel to give a cloudy, viscous, pumpkin-colored solution, which changed to a cream-colored viscous mixture. After 30 minutes the reaction was shown to be >95% complete by analytical HPLC. The reaction was quenched with saturated NH₄Cl (300 mL) and extracted with EtOAc (1 L). The organic fraction was passed through a silica gel plug and concentrated to give 25.0 g of crude 4-iodo-3-(*bis*-methylsulfonylamino)-pyridine. ¹H NMR (400 MHz, DMSO) δ 8.25 (d, 1H, *J* = 5.5 Hz), 8.07 (d, 1H, *J* = 0.8 Hz), 7.68 (dd, 1H, *J* = 0.8, 5.5 Hz).

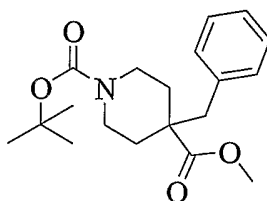
Step 3

To a 2 L round-bottom flask was added 4-iodo-3-(*bis*-methylsulfonylamino)-pyridine

(25.64 g, 68.16 mmol), followed by addition of THF (300 mL), water (100 mL) and 4 M NaOH (75 mL). The reaction solution was stirred at room temperature overnight, at which time HPLC showed the reaction to be complete. THF was removed under reduced pressure, and the aqueous layer was neutralized to a pH of 7. The product precipitated out of the reaction mixture and was collected by filtration, giving 4-iodo-3-(methylsulfonylamino)-pyridine with a purity > 98 % by HPLC. ^1H NMR (400 MHz, DMSO) δ 9.64 (s, 1H), 8.46 (s, 1H), 8.07 (d, 1H, $J = 5.1$ Hz), 7.99 (d, 1H, $J = 5.1$ Hz), 3.12 (s, 3H).

Reference 6

Methyl 1-*tert*-butoxycarbonyl-4-phenylmethyl-piperidine-4-carboxylate

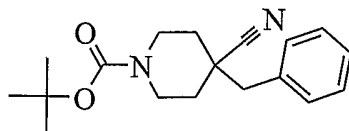


Step 1

1-*tert*-Butoxycarbonyl-4-phenylmethyl-piperidine-4-carboxylic acid (310 mg, 0.97 mmol) was dissolved in methanol (10 mL) and benzene (10 mL). TMS-diazomethane (2 M solution in hexanes, 1.2 mL, 2.4 mmol) was added to the solution via a syringe under a nitrogen atmosphere and the mixture was stirred at room temperature for 4 hours. The mixture was concentrated under reduced pressure and ethyl ether (30 mL) was added. The mixture was washed with saturated ammonium chloride and brine, dried over Na_2SO_4 and concentrated to give methyl 1-*tert*-butoxycarbonyl-4-phenylmethyl-piperidine-4-carboxylate, 350 mg (quant.)

Reference 7

tert-Butyl 4-phenylmethyl-4-cyano-piperidine-1-carboxylate



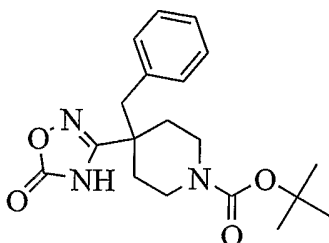
tert-Butyl 4-cyano-piperidine-1-carboxylate (630 mg, 3 mmol) was dissolved in THF (20 mL). The solution was cooled in an ice bath and then potassium bis(trimethylsilyl) amide (0.50 M solution in toluene (12 mL, 6.0 mmol) was added. The mixture was stirred under nitrogen in the ice bath for 45 minutes and then benzyl bromide (0.40 mL, 3.3 mmol) in THF (1 mL) was added slowly dropwise via a syringe at 0 °C. The reaction was monitored by both

analytical HPLC and LCMS and upon the completion of the reaction (approximately 2.5 hours) ether (200 mL), water (50 mL) and saturated ammonium chloride aqueous solution (50 mL) were added. The mixture was stirred vigorously for 15 minutes at room temperature. The organic layer was separated, washed with saturated ammonium chloride aqueous solution, water, and brine, dried over MgSO_4 , and concentrated to give *tert*-butyl 4-phenylmethyl-4-cyano-piperidine-1-carboxylate as a pale yellow-colored solid (quantitative yield). LCMS: $(\text{M}+23)^+$ 323.

One of ordinary skill in the art would know procedures to remove the Boc-protecting group.

Reference 8

tert-Butyl 4-phenylmethyl-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-piperidine-1-carboxylate



Step 1

tert-Butyl 4-phenylmethyl-4-cyano-piperidine-1-carboxylate (100 mg, 0.33 mmol) was dissolved in ethanol (4 mL) and a small amount of powder 4Å molecular sieve and hydroxylamine (50% wt. % solution in water, 1.0 mL, 30 mmol) were added sequentially. The mixture was stirred at 55 °C. The reaction was monitored by both analytical HPLC and LCMS and upon completion of the reaction (approximately 72 hours) the insoluble molecular sieve was filtered off. The product was separated by preparative HPLC and lyophilized to give *tert*-butyl 4-phenylmethyl-4-(*N*-hydroxycarbamimidoyl)-piperidine-1-carboxylate (75 mg, 70%) as a white solid. MS(ES) m/z 334.3 (MH^+); MS calcd: 333.4 (M).

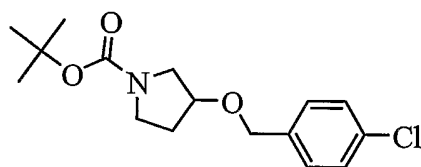
Step 2

A mixture of *tert*-butyl 4-phenylmethyl-4-(*N*-hydroxycarbamimidoyl)-piperidine-1-carboxylate hydrochloride (70 mg, 0.21 mmol) and triethylamine (0.3 mL, 2 mmol) was dissolved in acetonitrile (1 mL) and dioxane (1.5 mL). *N,N*-Carbonyldiimidazole (243 mg, 1.50 mmol) was added to the solution and the mixture was stirred at room temperature. The progress of the reaction was followed by analytical HPLC and LCMS and upon completion (approximately 72 hours), the solvent was removed *in vacuo* and ethyl acetate (50 mL) was added. The organic layer was washed with HCl solution (1 N), water and brine, dried over

MgSO₄ and then concentrated to give *tert*-butyl 4-phenylmethyl-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-piperidine-1-carboxylate (58 mg, 76%) as a pale yellow solid. MS(ES) *m/z* 382 (M+Na); MS calcd: 359.4 (M).

Reference 9

tert-Butyl 3-(4-chloro-phenylmethoxy)-pyrrolidine-1-carboxylate



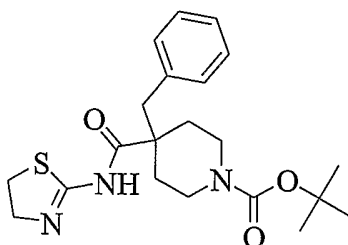
Step 1

Pyrrolidin-3-ol (1.09 g, 12.5 mmol) was dissolved in dichloromethane (20 mL), cooled to 0 °C in an ice bath. Triethylamine (1.93 mL, 13.8 mmol), di-*tert*-butyl dicarbonate (3.06 g, 13.8 mmol) and dimethylaminopyridine (153 mg, 1.25 mmol) were added. The reaction mixture was allowed to warm up to room temperature while stirring. Progress of the reaction was monitored by TLC (silica gel, hexane: EtOAc (1:1, v/v) stained by ninhydrin and upon completion (approximately 3.5 hours) 1 M NaOH aqueous solution (10 mL) was added. The mixture was stirred vigorously for 5-10 minutes and the organic layer was separated, washed with saturated sodium bicarbonate (twice), saturated ammonium chloride and brine, dried over MgSO₄, concentrated. Product was purified from the residue by flash column chromatography (50% hexanes / ethyl acetate) to give *tert*-3-hydroxy-pyrrolidine-1-carboxylate (2.3 g, 98%) as a white solid.

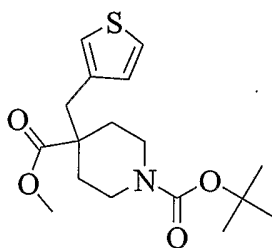
Step 2

Sodium hydride (60% dispersed in mineral oil, 92 mg, 5.8 mmol) in THF (1 mL) was cooled to 0 °C in an ice bath under nitrogen. *tert*-3-Hydroxy-pyrrolidine-1-carboxylate (212 mg, 1.13 mmol) in THF (4 mL) was added slowly via a syringe. The mixture was stirred for 30 minutes at 0 °C and 4-chlorobenzylbromide (257 mg, 1.25 mmol) in THF was added dropwise. The mixture was kept in ice bath for another 30 minutes then stirred at room temperature overnight. Ether (50mL) was added to the reaction mixture and then water (10 mL) was added to quench the reaction. The mixture was stirred for 15-20 minutes and then the organic layer was separated, washed with water and brine, dried over MgSO₄ and concentrated. Product was purified from the residue by flash column chromatography (80% hexanes / ethyl acetate) to give *tert*-butyl 3-(4-chloro-phenylmethoxy)-pyrrolidine-1-carboxylate (250 g, 71.0%) as a colorless oil. MS(ES) *m/z* 334.1 (M+Na); MS calcd: 311.8

(M).

Reference 10*tert*-Butyl 4-phenylmethyl-4-(4,5-dihydro-thiazol-2-ylcarbamoyl)-piperidine-1-carboxylate

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (23 mg, 0.12 mmol), 1-hydroxybenzotriazole hydrate (16 mg, 0.12 mmol), 2-amino-2-thiazoline (12 mg, 0.12 mmol) and di-isopropylethylamine (45 μ L, 0.25 mmol) were added to a solution of 1-*tert*-butoxycarbonyl-4-phenylmethyl-piperidine-4-dicarboxylic acid (31 mg, 0.097 mmol) in 1 mL DMF. The reaction was allowed to proceed for 20 hours at room temperature and then the mixture was acidified. Product was purified by preparative reversed phase HPLC to give *N-tert*-butoxycarbonyl-4-(4,5-dihydro-thiazol-2-ylaminocarbonyl)-4-(phenylmethyl)-piperidine (16 mg, 37 %). MS(ES) m/z 404.2(MH^+); MS calcd: 403.19 (M).

Reference 111-*tert*-Butyl 4-methyl 4-thiophen-3-ylmethyl-piperidine-1,4-dicarboxylate**Step 1**

A solution of phosphorus tribromide (2.24 g, 8.23 mmol) in 10 mL DCM was added dropwise to a solution of 3-thiophenemethanol (0.66 g, 5.8 mmol) in DCM (30 mL) at 0 °C. The mixture was stirred at room temperature for 3 hours and then poured onto ice. The layers were separated and the organic phase was washed with saturated $NaHCO_3$ solution, dried over sodium sulfate and concentrated to give 3-bromomethylthiophene (1.1 g) as a clear liquid, which was used in the next step without further purification.

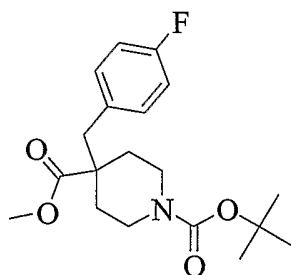
Step 2

A solution of lithium diisopropylamide in heptane/THF/ethylbenzene (2.0 M, 1.1 mL,

2.0 mmol) was added dropwise to a solution of 1-*tert*-butyl 4-methyl piperidine-1,4-dicarboxylate (320 mg, 1.31 mmol) in THF (15 mL) at -78 °C. The mixture was maintained at -78 °C for 15 minutes and then stirred at -20 and -30 °C for 1 hour. A solution of 3-bromomethylthiophene (242 mg, 1.37 mmol) in THF (2 mL) was added dropwise to the chilled mixture and the mixture was maintained at this temperature for 1 hour. The mixture was then allowed to slowly warm to 0 °C and then the reaction was quenched with saturated aqueous NH₄Cl (10 mL). The aqueous phase was separated and extracted with ethyl acetate (20 mL). The combined organic layer was washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a crude yellow oil. The crude oil was flash chromatographed [n-hex/EtOAc (9:1 v/v)] to give 1-*tert*-butyl 4-methyl 4-thiophen-3-ylmethyl-piperidine-1,4-dicarboxylate (100 mg, 23%) as a light yellow oil. MS(ES) *m/z* 362.4 (MNa⁺); MS calcd: 339.15 (M).

Reference 12

1-*tert*-Butyl 4-methyl 4-(4-fluoro-phenylmethyl)-piperidine-1,4-dicarboxylate



Step 1

A solution of trimethylsilyl diazomethane in hexanes (2.00 M, 52.9 mL, 106 mmol) was added dropwise to a suspension of 1-*tert*-butoxycarbonyl-piperidine-4-carboxylic acid (12.14 g, 52.95 mmol) in acetonitrile (100 mL) and methanol (10 mL) at 0 °C. The mixture let stand for 30 minutes and then was stirred at room temperature for 3 hours. The solvent was removed under reduced pressure and product was purified from the residue by column chromatography [n-hex/EtOAc (4.5:1 v/v)] to give 1-*tert*-butyl 4-methyl piperidine-1,4-dicarboxylate as an oil (11.5 g, 90%). ¹H NMR (400 MHz, d₆-DMSO) δ 4.02 (dt, 2H, *J* = 3.5, 13.7 Hz), 3.69 (s, 3H), 2.82 (ddd, 2H, *J* = 3, 11.5, 14.5 Hz), 2.45 (tt, 1H, *J* = 3.9, 11.5 Hz), 1.90-1.84 (m, 2H), 1.67-1.57 (m, 2H), 1.45 (s, 9H). MS(ES) *m/z* 265.8 (MNa⁺); MS calcd: 243.1 (M).

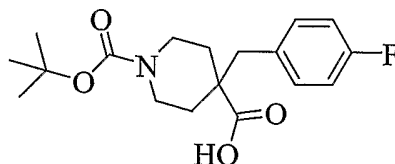
Step 2

A solution of lithium diisopropylamide in heptane/THF/ethylbenzene (2.0 M, 35.5

mL, 71.1 mmol) was added dropwise through an addition funnel over 30 minutes to a solution of 1-*tert*-butyl 4-methyl piperidine-1,4-dicarboxylate (11.53 g, 47.39 mmol) in THF (200 mL) at -78 °C. The mixture was let stand for 15 minutes and then was stirred at 20-30 °C for 50 minutes. The mixture was cooled to -20 °C and then 4-fluorobenzyl bromide (6.50 mL, 52.13 mmol) was added. The mixture was allowed to slowly warm to 0 °C over 2.5 hours and the reaction was quenched with saturated aqueous NH₄Cl (100 mL). The aqueous phase was separated and extracted with ethyl acetate (100 mL). The combined organic layer was washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a crude orange oil (18.77 g). Product was purified from the crude oil by flash chromatography [n-hex/EtOAc (8:1 v/v)] to give 1-*tert*-butyl 4-methyl 4-(4-fluorophenylmethyl)-piperidine-1,4-dicarboxylate (13.5 g, 81%) as a light yellow oil. ¹H NMR (400 MHz, d₆-DMSO) δ 7.11-7.06 (m, 4H), 3.77 (brd, 2H, *J* = 13.3 Hz), 3.59 (s, 3H), 2.74 (brs, 2H), 1.88 (brd, 2H, *J* = 13.3 Hz), 1.43-1.36 (m, 2H), 1.38 (s, 9H). MS(ES) *m/z* 374.1 (MNa⁺); MS calcd: 351.2 (M).

Reference 13

1-*tert*-Butoxycarbonyl-4-(4-fluoro-phenylmethyl)-piperidine-4-carboxylic acid



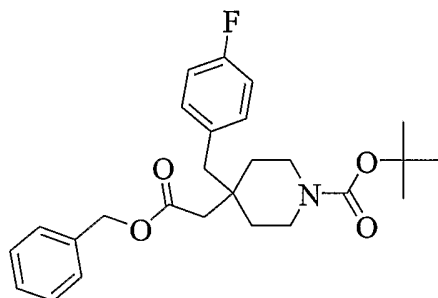
Step 1

A solution of lithium hydroxide monohydrate (11.2 g, 267 mmol) in water (50 mL) was added to a solution of 1-*tert*-butyl 4-methyl 4-(4-fluorophenylmethyl)-piperidine-1,4-dicarboxylate (9.37 g, 26.7 mmol), prepared using procedures similar to those in Reference 12, in THF/MeOH (200 mL, 1:1 v/v). The mixture then was heated to 65 °C for 1 day. The mixture was allowed to cool to room temperature and a solution of sodium hydroxide (1 M, 100 mL) and ether (300 mL) was added. The aqueous phase was separated and acidified with conc. hydrochloric acid (~35 mL) to pH 1. The aqueous phase was extracted with ethyl acetate (200 mL, 100 mL) and the organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The ethereal layer was acidified with conc. hydrochloric acid and the aqueous phase separated. The ethereal layer then was dried over Na₂SO₄, filtered to give 1-*tert*-butoxycarbonyl-4-(4-fluoro-phenylmethyl)-piperidine-4-

carboxylic acid as a white powder (8.16 g). ^1H NMR (400 MHz, d_6 -DMSO) δ 1.29-1.39 (m, 2H), 1.37 (s, 9H), 1.84 (brd, 2H, $J = 13.2$ Hz), 2.78 (brs, 4H), 3.77 (brd, 2H, $J = 13.2$ Hz), 7.06-7.16 (m, 4H), 12.58 (brs, 1H). MS(ES) m/z 336.4 ($\text{M}-1$) $^-$; MS calcd: 337.2 (M).

Reference 14

tert-Butyl 4-phenylmethyloxycarbonylmethyl-4-(4-fluoro-phenylmethyl)-piperidine-1-carboxylate



Step 1

A solution of oxalyl chloride in DCM (2.00 M, 889 μL , 1.78 mmol) and followed by a drop of DMF was added to a suspension of 1-*tert*-butoxycarbonyl-4-(4-fluoro-phenylmethyl)-piperidine-4-carboxylic acid (150 mg, 0.445 mmol), which can be prepared as in Reference 13, in DCM (4 mL). The reaction was allowed to proceed for 2.5 hours and then the mixture was concentrated under reduced pressure to give *tert*-butyl 4-chlorocarbonyl-4-(4-fluoro-phenylmethyl)-piperidine-1-carboxylate as an oil. To the crude reaction mixture in THF/ACN (4 mL, 1:1 v/v) was added a solution of trimethylsilyl diazomethane in hexanes (2.00 M, 445 μL , 0.890 mmol). The mixture was stirred for 2.5 hours at room temperature followed by evaporation of solvent under reduced pressure to give *tert*-butyl 4-(2-diazo-acetyl)-4-(4-fluoro-phenylmethyl)-piperidine-1-carboxylate (145 mg) which was used in the next step without further purification. MS(ES) m/z 384 (MNa^+); MS calcd: 361.2 (M).

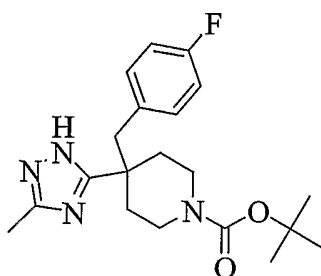
Step 2

2,4,6-Collidine (0.3 mL, 2 mmol) and benzyl alcohol (0.3 mL, 3 mmol) was added to crude *tert*-butyl 4-(2-diazo-acetyl)-4-(4-fluoro-phenylmethyl)-piperidine-1-carboxylate (144.6 mg, 0.4 mmol) in in a sealed tube and the mixture was heated at 180 $^{\circ}\text{C}$ for 10 minutes. The mixture was allowed to cool to room temperature and then was diluted with acetonitrile/water. Product was purified by reversed phase HPLC purification to give *tert*-butyl 4-phenylmethyloxycarbonylmethyl-4-(4-fluoro-phenylmethyl)-piperidine-1-carboxylate (34.8 mg, 18% for 2 steps) as a brown oil. ^1H NMR (400 MHz, d_6 -DMSO) δ 7.41-7.35 (m,

5H), 7.19-7.04 (m, 4H), 5.13 (s, 2H), 3.54-3.49 (m, 2H), 3.19 (brs, 2H), 2.71 (s, 2H), 2.29 (s, 2H), 1.42-1.29 (m, 4H), 1.37 (s, 9H). MS(ES) m/z 464.4 (MNa^+); MS calcd: 441.2 (M).

Reference 15

tert-Butyl 4-(4-fluorophenylmethyl)-4-(5-methyl-2H-[1,2,4]triazol-3-yl)-piperidine-1-carboxylate



Step 1

O-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (676 mg, 1.78 mmol) and *N,N*-diisopropylethylamine (1.55 mL, 8.89 mmol) was added to a solution of 1-*tert*-butoxycarbonyl-4-(4-fluorophenylmethyl)-piperidine-4-dicarboxylic acid (500 mg, 1.48 mmol), which can be prepared as described in Example 12, and NH_4Cl (119 mg, 2.22 mmol) in DMF (8 mL) at room temperature and the reaction was allowed to proceed for 13.5 hours. The mixture was diluted with ethyl acetate (100 mL) and washed with an aqueous solution of hydrochloric acid (1N, 2 x 50 mL), saturated aqueous solution of $NaHCO_3$ (2 x 50 mL), and brine (50 mL). The organic layer then was dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give *tert*-butyl 4-carbamoyl-4-(4-fluorophenylmethyl)-piperidine-1-carboxylate (514.5 mg, quantitative) as a white solid. ^1H NMR (400 MHz, d_6 -DMSO) δ 1.23-1.30 (m, 2H), 1.37 (s, 9H), 1.88 (brd, 2H, $J = 13.3$ Hz), 2.75 (s, 2H), 2.82 (brs, 2H), 3.69 (brd, 2H, $J = 13.3$ Hz), 7.04-7.16 (m, 5H), 7.28 (s, 1H). MS(ES) m/z 337.2 (MH^+); MS calcd: 336.2 (M).

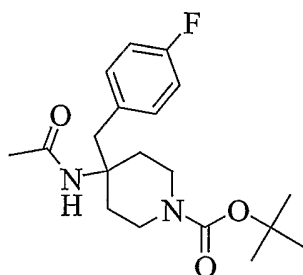
Step 2

A solution of *tert*-butyl 4-carbamoyl-4-(4-fluorophenylmethyl)-piperidine-1-carboxylate (200 mg, 0.595 mmol) was heated in *N,N*-dimethylacetamide dimethyl acetal at 100 °C for 2 hours. The mixture was allowed to cool, diluted with ethyl acetate (50 mL) and washed with water (2 x 50 mL) and then brine (15 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a brown oil. A premixed solution of hydrazine (47 μ L, 1.5 mmol) and glacial acetic acid (5 mL) was added to the

crude oil. The mixture was then heated at 90 °C for 2 hours. The mixture was allowed to cool and poured into water (50 mL). The mixture was extracted with ethyl acetate (50 mL) and the organic layer was separated and washed successively with water (50 mL), saturated aqueous solution of NaHCO₃ (50 mL) and brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give *tert*-Butyl 4-(4-fluoro-phenylmethyl)-4-(5-methyl-2H-[1,2,4]triazol-3-yl)-piperidine-1-carboxylate (232.4 mg, quantitative) as an orange semi-solid. ¹H NMR (400 MHz, d₆-DMSO) δ 1.36 (s, 9H), 1.46-1.64 (m, 2H), 2.06 (brd, 2H, *J* = 12.5 Hz), 2.21 (s, 1H), 2.34 (s, 2H), 2.60-2.85 (brs, 2H), 2.81 (brs, 2H), 3.74 (brs, 2H), 6.66-6.98 (m, 4H), 13.09 (s, 0.34H), 13.20 (s, 0.66H). MS(ES) *m/z* 375.1 (MH⁺); MS calcd: 374.2 (M).

Reference 16

4-Acetylamino-4-(4-fluoro-phenylmethyl)-piperidine-1-carboxylic acid



Step 1

Triethylamine (0.23 mL, 1.6 mmol) and diphenylphosphoryl azide (0.320 mL, 1.48 mmol) was added to a solution of *tert*-butoxycarbonyl-4-(4-fluoro-phenylmethyl)-piperidine-4-carboxylic acid (0.500 g, 1.48 mmol), which can be prepared as in Reference 13, in toluene (10 mL) under nitrogen. The solution was heated to 90 °C for five hours and then benzyl alcohol (0.770 mL, 7.40 mmol) was added. The reaction was allowed to proceed at 90 °C for 3 hours and then the mixture was diluted with ethyl acetate (75 mL). The mixture was washed successively with saturated aqueous solution of NaHCO₃ (50 mL), water (50 mL), and brine (15 mL). Organic extracts were dried over MgSO₄, filtered and concentrated under reduced pressure. Product was purified from the residue by flash chromatography [n-hexanes/EtOAc (4:1 v/v)] to give *tert*-butyl 4-phenylmethylanino-4-(4-fluoro-phenylmethyl)-piperidine-1-carboxylate (530 mg, 81%) as a colorless oil. MS(ES) *m/z* 465.4 (MNa⁺); MS calcd: 442.2 (M).

Step 2

A mixture of *tert*-butyl 4-phenylmethylanino-4-(4-fluoro-phenylmethyl)-piperidine-

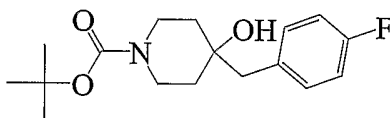
1-carboxylate (0.30 g, 0.68 mmol) and 10% Pd/C (0.03 g) in ethanol (20 mL) was stirred under H₂ at atmospheric pressure for three hours. The mixture was filtered through Celite into a flask containing a solution of hydrochloride in 1,4-dioxane (4 M, 0.34 mL). Concentration of the mixture under reduced pressure yielded *tert*-butyl 4-amino-4-(4-fluoro-phenylmethyl)-piperidine-1-carboxylate hydrochloride (208 mg, 89%) as a grainy oil. MS(ES) *m/z* 342.9 (M-1)⁺; MS calcd: 344.2 (M).

Step 3

Acetic anhydride (40 μ L, 0.44 mmol) and triethylamine (66 μ L, 0.48 mmol) was added to a solution of *tert*-butyl 4-amino-4-(4-fluoro-phenylmethyl)-piperidine-1-carboxylate hydrochloride (0.15 g, 0.44 mmol) in dichloromethane (5 mL). The reaction was allowed to proceed for 1 hour and the mixture was diluted with ethyl acetate (50 mL). The mixture was washed successively with water (50 mL), aqueous hydrochloric acid (0.1 M, 50 mL), and saturated aqueous solution of NaHCO₃ (25 mL). The organic layer was dried over MgSO₄, filtered and concentrated under reduced pressure to give 4-acetylamino-4-(4-fluoro-phenylmethyl)-piperidine-1-carboxylic acid (152 mg, quantitative) as a tan oil.

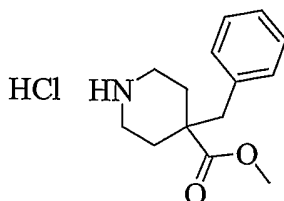
Reference 17

tert-Butyl 4-(4-fluoro-phenylmethyl)-4-hydroxy-piperidine-1-carboxylate



Step 1

4-Fluorobenzyl magnesium bromide (0.24 M THF solution, 18 mL, 4.5 mmol) was added slowly to a solution of *N*-*tert*-butoxycarbonyl-4-piperidone (600 mg, 3.00 mmol) in THF (20 mL) at 0 °C. The mixture was stirred for 2 hours at room temperature and quenched with 1 mL of saturated NH₄Cl. The mixture was diluted with ether (20 mL) and washed with saturated NH₄Cl solution and saturated sodium chloride. The organic phase was concentrated under reduced pressure. The residue was purified by column chromatography (30% EtOAc/n-hexanes) to give *tert*-butyl 4-(4-fluoro-phenylmethyl)-4-hydroxy-piperidine-1-carboxylate (350 mg, 38%). MS(ES) *m/z* 332.3 (M+Na); MS calcd: 309.4 (M), ¹H NMR (400 MHz, CDCl₃): δ 7.17 (m, 2H), 7.00 (m, 2H), 3.85 (m, 2H), 3.08 (m, 2H), 2.74 (s, 2H), 1.58 (m, 2H), 1.50 (s, 9H), 1.46 (m, 2H).

Reference 18**Methyl 4-phenylmethyl-piperidine-4-carboxylate hydrochloride**

Methyl 1-*tert*-butoxycarbonyl-4-phenylmethyl-piperidine-4-carboxylate was dissolved in ethanol (5 mL) and EtOAc (5 mL), and a solution of HCl in dioxane (4N, 1 mL, 4 eq) was added, and the solution warmed at 50 °C until complete by HPLC. 4-(methoxycarbonyl)-4-(phenylmethyl)-piperidine hydrochloride (crop 1, 210 mg, 77%) crystallized as white needles, and was collected by filtration and washed with ether and pentane. MS(ES) *m/z* 243.0 (MH⁺); MS calc: 233.31 (M).

Proceeding as in Reference 18, but substituting *N*-*tert*-butoxycarbonyl-4-cyano-4-(phenylmethyl)-piperidine, gave 4-cyano-4-phenylmethyl-piperidine hydrochloride.

Proceeding as in Reference 18, but substituting *N*-*tert*-butoxycarbonyl-4-(phenylmethyl)-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-piperidine gave 4-(phenylmethyl)-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-piperidine hydrochloride.

Proceeding as in Reference 18, but substituting *N*-*tert*-butoxycarbonyl-3-(4-chlorophenylmethyloxy)-pyrrolidine, gave 3-(4-chlorophenylmethyloxy)-pyrrolidine hydrochloride.

Proceeding as in Reference 18, but substituting *N*-*tert*-butoxycarbonyl-4-(4,5-dihydro-thiazol-2-ylaminocarbonyl)-4-(phenylmethyl)-piperidine gave 4-(4,5-dihydro-thiazol-2-ylaminocarbonyl)-4-(phenylmethyl)-piperidine hydrochloride. MS(ES) *m/z* 304.3(MH⁺); MS cald: 303.19 (M).

Proceeding as in Reference 18, but substituting 4-thiophen-3-ylmethyl-piperidine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-methyl ester, gave 4-methoxycarbonyl-4-(thien-3-ylmethyl)-piperidine hydrochloride. MS(ES) *m/z* 240.9 (M-H⁺); MS cald: 239.1 (M).

Proceeding as in Reference 18, but substituting 4-(4-fluoro-phenylmethyl)-piperidine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-methyl ester gave 4-(4-fluoro-phenylmethyl)-piperidine-4-carboxylic acid methyl ester hydrochloride. MS(ES) *m/z* 251.8 (MH⁺); MS calc: 251.3 (M).

Proceeding as in Reference 18, but substituting 1-*tert*-butoxycarbonyl-4-(4-fluoro-phenylmethyl)-piperidine-4-carboxylic acid, gave 4-(4-fluoro-phenylmethyl)-piperidine-4-

carboxylic acid.

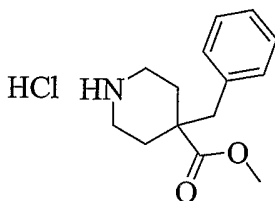
Proceeding as in Reference 18, but substituting 4-phenylmethyloxycarbonylmethyl-4-(4-fluoro-phenylmethyl)-piperidine-1-carboxylic acid tert-butyl ester gave [4-(4-fluoro-phenylmethyl)-piperidin-4-yl]-acetic acid phenylmethyl ester hydrochloride. MS(ES) m/z 341.7 (MH^+); MS calcd: 341.2 (M).

Proceeding as in Reference 18, but substituting 4-(4-fluoro-phenylmethyl)-4-(5-methyl-2H-[1,2,4]triazol-3-yl)-piperidine-1-carboxylic acid tert-butyl ester gave 4-(4-fluoro-phenylmethyl)-4-(5-methyl-2H-[1,2,4]triazol-3-yl)-piperidine hydrochloride. ^1H NMR (400 MHz, d_6 -DMSO) δ 1.83-1.91 (m, 2H), 2.29 (d, 2H, $J = 14$ Hz), 2.47 (s, 3H), 2.72 (brq, 2H, $J = 11$ Hz), 2.93 (s, 2H), 3.22 (brd, 2H, $J = 13$ Hz), 6.80-7.04 (m, 4H), 8.56-8.70 (m, 1H), 8.90-9.00 (brs, 1H). MS(ES) m/z 275.3 (MH^+); MS calcd: 274.2 (M).

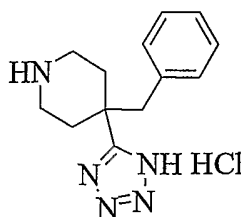
Proceeding as in Reference 18, but substituting 4-acetylamino-4-(4-fluoro-phenylmethyl)-piperidine-1-carboxylic acid tert-butyl ester, gave N-[4-(4-fluoro-phenylmethyl)-piperidin-4-yl]-acetamide hydrochloride. MS(ES) m/z 251.1 (MH^+), 248.8 ($M-1$); MS calcd: 250.2 (M).

Reference 19

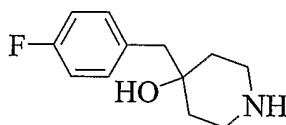
Methyl 4-phenylmethyl-piperidine-4-carboxylate hydrochloride



1-tert-Butyl 4-methyl 4-phenylmethyl-piperidine-1,4-dicarboxylate was dissolved in methanol, saturated with HCl gas, and the reaction was allowed to proceed overnight at room temperature. The solvent was evaporated and the residue was treated with ether to form a white crystalline solid. The crystals were collected by filtration, washed with ether, and dried to give methyl 4-phenylmethyl-piperidine-4-carboxylate (0.31 mg). MS(ES) m/z 234.1(MH^+); MS calcd: 233.14 (M).

Reference 20**4-Phenylmethyl-4-(1*H*-tetrazol-5-yl)-piperidine hydrochloride**

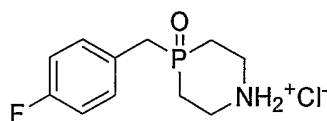
A mixture of *tert*-butyl 4-phenylmethyl-4-cyano-piperidine-1-carboxylate (120 mg, 0.399 mmol), sodium azide (260 mg, 4.00 mmol) and zinc bromide (104 mg, 0.462 mmol) in a mixed solvent of isopropanol (1.5 mL) and water (1.5 mL) was heated to 150 °C in a microwave reactor for 16 hours. The product was separated by preparative HPLC and further lyophilized to give 4-phenylmethyl-4-(1*H*-tetrazol-5-yl)-piperidine hydrochloride (60 mg, 54%) as a fluffy white solid. LCMS: (M+1)⁺ 244.

Reference 21**4-(4-Fluoro-phenylmethyl)-piperidin-4-ol****Step 1**

4-Fluorophenylmethyl Grignard reagent was added to a solution of *tert*-butyl 4-oxo-piperidine-1-carboxylate (199 mg, 1 mmol) in THF (2 mL) at 0 °C. The mixture was stirred for 1 hour at room temperature, quenched by 1 mL of NH₄Cl and then diluted with ether (20 mL). The mixture was washed with sat. NH₄Cl solution and brine and concentrated under reduced pressure. Product was purified from the residue by column chromatography (20% EtOAc/n-hexanes) to give 4-(4-fluoro-phenylmethyl)-piperidin-4-ol magnesium bromide (135 mg). LCMS (M+Na)⁺ 332.3, ¹H NMR (400 MHz, CDCl₃): δ 7.17 (m, 2H), 7.00 (m, 2H), 3.85 (m, 2H), 3.08 (m, 2H), 2.74 (s, 2H), 1.58 (m, 2H), 1.50 (s, 9H), 1.46 (m, 2H).

Step 2

4 N Hydrochloric acid in dioxane (0.2 mL) was added to a solution of the 4-(4-fluoro-phenylmethyl)-piperidin-4-ol magnesium bromide (50 mg, 0.16 mmol) in dichloromethane (1 mL) and ACN (1 mL). The mixture was stirred for 1 hour at room temperature and concentrated under reduced pressure to give 4-(4-fluoro-phenylmethyl)-piperidin-4-ol.

Reference 22**4-(4-Fluorophenylmethyl)-[1,4]azaphosphinane 4-oxide hydrochloride****Step 1**

4-fluorobenzyl bromide (25 mL, 0.20 mol) was added to a stirred solution of trimethyl phosphite (35.9 mL, 0.30 mol) at ambient temperature, under a nitrogen atmosphere. The resulting solution was heated at 110 °C for six hours, and then at 90 °C overnight. The reaction mixture was allowed to cool to ambient temperature and then ethyl acetate (350 mL) was added. The solution was washed with saturated sodium bicarbonate (350 mL) and then with saturated brine (2 x 350 mL). The organic phase was dried with magnesium sulfate, filtered, and concentrated by rotary evaporation. The resulting crude product was purified by flash silica chromatography using 0-35% acetonitrile in ethyl acetate as eluant to yield (4-fluoro-benzyl)-phosphonic acid dimethyl ester (29.44 g, 135 mmol, 66% yield) as a colorless oil. ¹H NMR (400 MHz, DMSO) δ 7.33-7.28 (m, 2H); 7.17-7.12 (d of d, 2H); 3.61-3.58 (d, 6H); 3.31-3.24 (d, 2H); ESMS (*m/z*): (M+1)⁺ found, 219.

Step 2

Bromotrimethylsilane (6.0 mL, 45.4 mmol) was added dropwise to (4-fluoro-benzyl)-phosphonic acid dimethyl ester (4.57 g, 20.95 mmol) and stirred in a reaction flask chilled to 0 °C. The resulting solution was allowed to warm to ambient temperature and stirred for an additional hour, then concentrated by rotary evaporation to remove volatiles yielding crude (4-fluoro-benzyl) phosphonic acid bis(trimethylsilyl) ester which was used without further purification.

Step 3

To the (4-fluoro-benzyl) phosphonic acid bis(trimethylsilyl) ester was added 25 mL of dry methylene chloride, 12 drops of dry DMF, then dropwise 6 mL of oxalyl chloride (68.3 mmol). The resulting solution was stirred overnight at ambient temperature as gas was generated. The reaction was concentrated by rotary evaporation to yield 5.2 g of a yellow waxy solid that was purified by distillation at reduced pressure to yield 1.71 g (37%) of 4-fluorobenzyl phosphonic dichloride as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.37-7.31 (m, 2H); 7.11-7.05 (m, 2H); 3.93-3.87 (d, 2H).

Step 4

4-Fluorobenzyl phosphonic dichloride (1.71 g, 7.82 mmol) was dissolved in 10 mL of dry THF, under a nitrogen atmosphere, and chilled to -70°C . To this stirred solution was added dropwise vinyl magnesium bromide in THF (18.3 mL, 1M). The resulting solution was stirred for 30 minutes at -70°C . An aqueous solution of ammonium chloride (100 mL, 2M) was chilled to 0°C and stirred rapidly while the cold reaction mixture was added. The product was extracted into dichloromethane and washed with saturated aqueous sodium bicarbonate, and then with water. The organic phase was dried with sodium sulfate, filtered, and concentrated by rotary evaporation to yield 1.375 g of (4-fluorophenylmethyl) divinyl phosphine oxide (6.55 mmol, 84%) as a white solid. ^1H NMR (400 MHz, CDCl_3) 7.20-7.14 (m, 2H); 7.01-6.95 (m 2H); 6.29-6.08 (m, 6H); 3.20-3.15 (d, 2H); ESMS (m/z): $(\text{M}+1)^+$ found, 211.

Step 5

Divinyl-(4-Fluorophenylmethyl)-phosphine oxide (0.719g, 3.42 mmol) and benzylamine (0.45 mL, 4.11 mmol) were dissolved in a mixture of THF (15 mL) and deionized water (15 mL). The reaction mixture was heated at 82°C for 22 hours. The reaction was not complete and so an additional 0.04 mL of benzylamine was added and the reaction mixture was heated for an additional six hours at 90°C . The reaction mixture was concentrated by rotary evaporation and the product was extracted into dichloromethane and washed with saturated brine. The organic phase was dried with sodium sulfate, filtered, and concentrated by rotary evaporation. The crude product was taken up in 1:1 ethyl acetate:dichloromethane and passed through a plug of silica. The product was then eluted from the silica with a solution of 10% methanol in ethyl acetate. The solvents were removed by rotary evaporation to yield 0.84g of 1-benzyl-4-(4-fluorophenylmethyl)-[1,4]azaphosphinane 4-oxide (2.65 mmol, 77%). ^1H NMR (400 MHz, CDCl_3) 7.34-7.25 (m, 5H); 7.25-7.20 (m, 2H); 7.04-6.98. (m, 2H); 3.6 (s, 2H); 3.17-3.12 (d, 2H); 3.00-2.85 (m, 2H); 2.81-2.66 (m, 2H); 1.98-1.75 (m, 4H).

Step 6

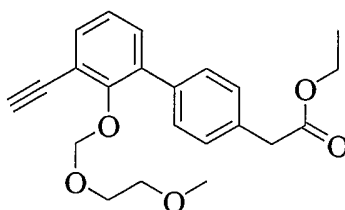
The material from Step 5 was dissolved in ethanol (100 mL). Aqueous HCl (5.2 mL, 1M) and of water (20 mL) were added. The solution was degassed with a stream of nitrogen and then palladium on carbon (10%, 0.5 g) was added. The mixture was hydrogenated on a Parr shaker overnight at 60 psi. The mixture was filtered through Celite and all solvents were removed under reduced pressure. The product was recrystallized from methanol/diethyl ether to yield 0.659g (2.50 mmol, 93%) of 4-(4-fluorophenylmethyl)-[1,4]azaphosphinane 4-oxide hydrochloride as a white crystalline solid. ^1H NMR (400 MHz, DMSO) δ 7.38-7.32 (m, 2H);

7.23-7.18 (m, 2H) 3.46-3.36 (m, 6H); 2.10-1.96 (m, 4H); ESMS (m/z): ($M+1$)⁺ found, 228; ($M+23$)⁺ found, 250.

The free base of 4-(4-fluorophenylmethyl-[1,4]azaphosphinane 4-oxide hydrochloride was prepared. The free base can be obtained by treating with MP-carbonate resin in an appropriate solvent followed by filtration to remove the resin and then concentrating to remove the solvent.

Reference 23

Ethyl [3'-ethynyl-2'-(2-methoxyethoxymethoxy)-biphenyl-4-yl]-acetate



Step 1

3-Bromo-2-(2-methoxyethoxymethoxy)-benzaldehyde (40.0 g, 154 mmol), which was prepared using procedures similar to those described in Reference 1, was dissolved in ethylene glycol dimethyl ether (DME) (100mL) in a 1 L round-bottom flask. Ethyl [4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-acetate (40 g, 138 mmol), which can be prepared as described in Reference 2, was dissolved in DME (200 mL) and the solution was added to the flask. A suspension of K₂CO₃ (38.26 g, 277 mmol) in water (75 mL) was added to the flask and the mixture was degassed under nitrogen for 30 minutes.

Tetrakis(triphenylphosphine)palladium (0) (400 mg, 0.346 mmol) was added and the mixture was heated in an 85 °C oil bath and stirred for 4 hours under nitrogen. The reaction was determined complete by analytical HPLC. The DME was removed under reduced pressure and the residue was dissolved in ethyl acetate (1 L). The solution was washed with 5% citric acid (2 X 200 mL) and brine (2 X 200 mL), dried over Na₂SO₄, and concentrated. Product was purified from the crude mixture by silica flash chromatography [n-Hexane/EtOAc (4:1 v/v)] to give ethyl 2-[3'-formyl-2'-(2-methoxyethoxymethoxy)-biphenyl-4-yl]-acetate (34.5 g, 67 %). MS(ES) m/z 373.1 (MH^+); MS calc: 372.41 (M). ¹H NMR (400 MHz, DMSO) δ ppm d 1.20 (t, 3H, $J = 7$ Hz), 3.12 (s, 3H), 3.20 (m, 2H), 3.41 (m, 2H), 3.73 (s, 2H), 4.10 (q, 2H, $J = 7$ Hz), 4.79 (s, 2H), 7.37-7.43 (m, 3H), 7.51 (brd, 2H, $J = 8.2$ Hz), 7.70 (dd, 1H, $J = 2, 7.4$ Hz), 7.78 (dd, 1H, $J = 2, 7.8$ Hz), 10.34 (s, 1H).

Step 2

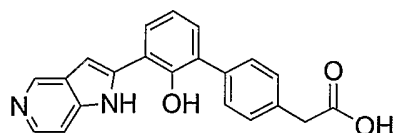
Ethyl [3'-formyl-2'-(2-methoxyethoxymethoxy)-biphenyl-4-yl]-acetate (19.0 g, 51.0 mmol) and ethanol (200 mL) was added to a 2 L round bottom flask and then CS_2CO_3 (41.6 g, 128 mmol) suspended in ethanol (100 mL) was added to the mixture. The mixture was degassed with nitrogen for 15 minutes while stirring at room temperature and then cooled to 5 °C in an ice bath. 1-Diazo-2-oxopropylphosphonate (12.8 g, 66.3 mmol) was dissolved in ethanol (50 mL) and the solution added dropwise to the mixture via an addition funnel and then the ice bath was removed. The mixture was stirred for 45 minutes of stirring at room temperature and the diethylether (1 L) was added. The mixture was filtered to remove solids and the organic layer was separated and washed with 5% citric acid (3 X 150 mL), brine (1 X 200 mL), dried over Na_2SO_4 , and concentrated. Product was purified from the residue by silica flash chromatography [n-Hexane/EtOAc (4:1 v/v)] to give ethyl [3'-ethynyl-2'-(2-methoxy-ethoxymethoxy)-biphenyl-4-yl]-acetate (15.6 g, 83 %). MS(ES) m/z 391.3 (MNa^+); MS calc: 368.42 (M). ^1H NMR (400 MHz, DMSO) δ ppm 1.19 (t, 3H, $J = 7$ Hz), 1.99 (s, 1H), 3.10 (m, 2H), 3.10 (s, 3H), 3.23 (m, 2H), 3.70 (s, 2H), 4.09 (q, 2H, $J = 7$ Hz), 4.93 (s, 2H), 7.22 (t, 1H, $J = 7.8$ Hz), 7.34 (brd, 2H, $J = 8.2$ Hz), 7.39 (dd, 1H, $J = 2, 7.4$ Hz), 7.44 (brd, 2H, $J = 8.2$ Hz), 7.50 (dd, 1H, $J = 2, 7.4$ Hz).

Reference 24

Proceeding as in Reference 23, but substituting 3-bromo-2-(2-methoxyethoxymethoxy)-benzaldehyde and *N-tert*-butoxycarbonyl-4-aminomethyl-phenylboronic acid, gave *tert*-butyl [3'-ethynyl-2'-(2-methoxy-ethoxymethoxy)-biphenyl-4-ylmethyl]-carbamate. MS(ES) m/z 434.2($\text{M}+\text{Na}$); MS cald: 411.2(M).

Reference 25

[2'-Hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetic acid



Step 1

N-(3-Iodo-pyridin-4-yl)-methanesulfonamide (1.61 g, 5.40 mmol), which was prepared using procedures as described in Reference 3, was dissolved in acetonitrile (10 mL) and triethylamine (3.9 mL, 28 mmol). The solution was evacuated and purged with nitrogen. Ethyl [3'-ethynyl-2'-(2-methoxyethoxymethoxy)-biphenyl-4-yl]-acetate (1.9 g, 5.3 mmol), which was prepared using procedures similar to those described in Reference 23, was

dissolved in acetonitrile (10 mL) and added to the reaction mixture, followed by dichloro-*bis*-(triphenylphosphine) palladium (87 mg, 0.12 mmol) and copper iodide (50.4 mg, 0.265 mmol). The reaction mixture was purged with a mixture of nitrogen / hydrogen after each addition. The reaction was then heated to 70 °C for 2 hours. The solution was concentrated, then partitioned between ethyl acetate (100 mL) and 5% citric acid (100 mL). After washing with brine (100 mL), the organic layer was concentrated to a brownish syrup to give [2'-(2-methoxyethoxymethoxy)-3'-(1-methylsulfonyl-1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetic acid ethyl ester. MS(ES) *m/z* 538.5 (MH^+); MS calc: 538.61 (M).

Step 2

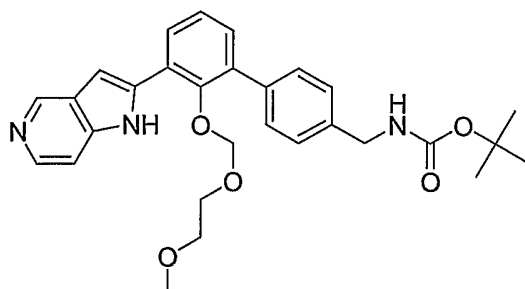
[2'-(2-Methoxyethoxymethoxy)-3'-(1-methylsulfonyl-1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetic acid ethyl ester (from the above step) was dissolved in THF (5 mL). Tetrabutylammonium fluoride (TBAF) in THF solution (1 M, 5.3 mL, 5.3 mmol) was added, and the reaction allowed to stir at room temperature. After 2 hours the reaction was concentrated, then flash chromatographed on silica gel [EtOAc/MeOH (9:1 v/v)] to give [2'-(2-methoxyethoxymethoxy)-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetic acid ethyl ester as a brownish oil. MS(ES) *m/z* 461.2 (MH^+); *m/z* 459.2 (MH^-); MS calc: 460.52 (M).

Step 3

[2'-(2-Methoxyethoxymethoxy)-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetic acid ethyl ester (from the previous step) was dissolved in acetonitrile (5 mL) and THF (5 mL), and mercaptoethylaminomethyl polystyrene scavenger resin (2.0 mmol/g loading, 9 mmol) was added, followed by aqueous HCl (4 N, 6 mL, 24 mmol). The mixture was heated to 50 °C for 24 hours, cooled, and filtered to remove resin. The resin was washed with THF, ACN, and water. The product was then purified by reverse-phase preparative HPLC to give [2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetic acid (727 mg, 39% yield over three steps). MS(ES) *m/z* 344.8 (MH^+); *m/z* 342.5 (MH^-); MS calc: 344.36 (M). ¹H NMR (400 MHz, DMSO) δ 12.36 (brs, 1H), 9.24 (s, 1H), 8.38 (dd, 1H, *J* = 0.8, 6.6 Hz), 7.95 (d, 1H, *J* = 6.6 Hz), 7.80 (dd, 1H, *J* = 1.6, 7.8 Hz), 7.53 (brd, 2H, *J* = 8.2 Hz), 7.46 (d, 1H, *J* = 0.8 Hz), 7.38 (brd, 2H, *J* = 8.2 Hz), 7.34 (dd, 1H, *J* = 1.6, 7.4 Hz), 7.16 (t, 1H, *J* = 7.4 Hz), 3.64 (s, 2H).

Reference 26

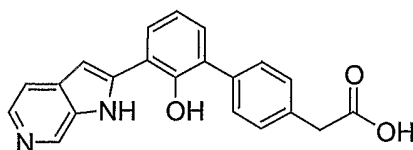
tert-Butyl [2'-(2-methoxyethoxymethoxy)-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-ylmethyl]-carbamate



Proceeding as in Reference 25, but substituting *tert*-butyl [3'-ethynyl-2'-(2-methoxyethoxymethoxy)-biphenyl-4-ylmethyl]-carbamate, gave *tert*-butyl [2'-(2-methoxyethoxymethoxy)-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-ylmethyl]-carbamate. MS(ES) *m/z* 504.0 (*MH*⁺); MS calcd: 503.24(*M*).

Reference 27

[2'-Hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetic acid

**Step 1**

N-(3-Iodo-pyridin-4-yl)-methanesulfonamide (3.00 g, 10.1 mmol), which can be prepared as described in Reference 3, was suspended in acetonitrile (10 ml) and then ethyl [3'-ethynyl-2'-(2-methoxy-ethoxymethoxy)-biphenyl-4-yl]-acetate (3.68 g, 10.9 mmol), as a suspension in acetonitrile (10 ml), was added to the sulfonamide suspension. The mixture was stirred at room temperature and then triethylamine (7 mL, 49.8 mmol) was added. The mixture was purged with nitrogen for 15 minutes and dichloro-bis(triphenylphosphine)palladium (III), (212 mg, 0.0302 mmol) was added. Copper iodide (57 mg, 0.18 mmol) was added and the mixture was placed under a hydrogen/nitrogen atmosphere and heated at 75 °C for 2 hours. The reaction was determined complete by analytical HPLC. The mixture was concentrated and eluted through a 3 x 3 inch silica flash plug with ethyl acetate as aluant (100 mL) and concentrated to give ethyl [2'-(2-methoxyethoxymethoxy)-3'-(1-methanesulfonyl-1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetate, which was used in the Step 2 without further purification.

Step 2

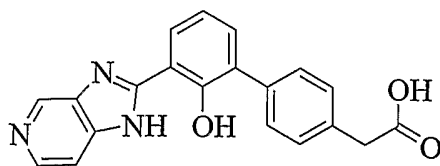
Ethyl [[2'-(2-methoxy-ethoxymethoxy)-3'-(1-methanesulfonyl-1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetate (21.0 g, 40.1 mmol) was suspended in acetonitrile (600 mL) and L-cysteine (9.7 g, 0.080 mmol) and aqueous 4 N HCl (200 mL, 0.8 mol) were added to the suspension. The mixture was heated to 70 °C and stirred for 3 hours. The reaction was determined complete by analytical HPLC. The acetonitrile was evaporated and the subsequent aqueous residue was adjusted to pH 5 with aqueous 4 N NaOH (approximately 200 mL). A solid precipitated out of solution and was collected and dried to give [2'-hydroxy-3'-(1-methanesulfonyl-1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetic acid (16.9 g, 99 %. ¹H NMR (400 MHz, DMSO) δ ppm 9.19 (s, 1H), 8.43 (d, 1H, *J* = 5.5 Hz), 7.69 (d, 1H, *J* = 5.5 Hz), 7.49 (brd, 2H, *J* = 8.2 Hz), 7.35-7.32 (m, 3H), 7.30 (dd, 1H, *J* = 2, 7.4 Hz), 7.01 (t, 1H, *J* = 7.4 Hz), 6.85 (s, 1H), 3.61 (s, 2H), 3.51 (s, 3H).

Step 3

A 1 L round-bottom flask was charged with [2'-hydroxy-3'-(1-methanesulfonyl-1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetic acid (13.4 g, 31.7 mmol) and then THF (30 ml) was added forming a suspension. The suspension was stirred at room temperature for 10 minutes and NaOH (6.34 g, 159 mmol) in water (150 mL) was added forming a clear, yellow solution. The mixture was warmed in an oil bath at 70 °C for 3 hour. The reaction was determined complete by HPLC analysis. The THF was removed under reduced pressure and aqueous residue adjusted to pH 3-4 by addition of aqueous 6N hydrochloric acid (approximately 25 mL). Solids precipitated out of solution and were collected by filtration to give [2'-Hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetic acid (10.9 g, 99 %). MS(ES) *m/z* 345.0 (MH⁺); MS calc: 344.43 (M). ¹H NMR (400 MHz, DMSO) δ ppm 12.8 (br s, 1H), 8.89 (s, 1H), 8.05 (d, 1H, *J* = 6 Hz), 7.91 (d, 1H, *J* = 4 Hz), 7.86 (d, 1H, *J* = 6.4 Hz), 7.59 (d, 2H, *J* = 6 Hz), 7.38 (d, 2H, *J* = 8.4 Hz), 7.35 (d, 1H, *J* = 4 Hz), 7.28 (s, 1H), 7.10 (t, 1H, *J* = 8.0 Hz), 3.65 (s, 2H).

Reference 28

[2'-Hydroxy-3'-(1*H*-imidazo[4,5-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetic acid



Step 1

Pyridine-3,4-diamine (140 mg, 1.28 mmol), methyl 2-(3'-formyl-2'-hydroxy-biphenyl-

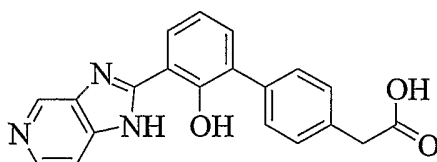
4-yl)-acetate (182 mg, 0.673 mmol) and sodium metabisulfite (418 mg, 2.20 mmol) were combined and dissolved in DMF (4 mL) and heated at 130 °C until addition and cyclization were complete as determined by HPLC, LCMS, and TLC [EtOAc/MeOH (9:1 v/v) and CH₂Cl₂/MeOH (9:1 v/v)], 36 hours. The solution was partitioned between EtOAc (50 mL) and saturated sodium bicarbonate (50 mL), the organic layer washed again with brine (50 mL), and concentrated. The residue was purified by silica column chromatography [EtOAc/MeOH (9:1 v/v)] to give methyl 2-[2'-hydroxy-3'-(1*H*-imidazo[4,5-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetate. MS(ES) *m/z* 360.1 (MH⁺); *m/z* 358.1 (MH⁻); MS calc: 359.38 (M).

Step 2

Methyl [2'-hydroxy-3'-(1*H*-imidazo[4,5-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetate was dissolved in methanol (3 mL) and acetonitrile (3 mL) and aq. 4 M KOH (0.30 mL, 1.2 mmol) was added. The solution was warmed to 50 °C for 2 hours and then adjusted to pH 3 with aq. 4 N HCl. A precipitate was collected, washed with water and dried to give [2'-hydroxy-3'-(1*H*-imidazo[4,5-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetic acid (195 mg, 84%). MS(ES) *m/z* 346.0 (MH⁺); *m/z* 343.6 (MH⁻); MS calc: 345.35 (M).

Reference 29

[2'-Hydroxy-3'-(1*H*-imidazo[4,5-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetic acid



Step 1

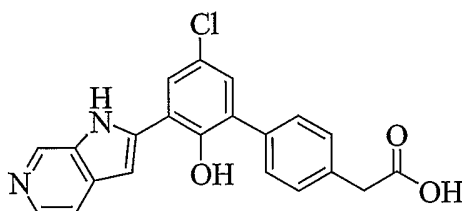
Pyridine-3,4-diamine (430 mg, 3.94 mmol), Ethyl [3'-formyl-2'-(2-methoxyethoxymethoxy)-biphenyl-4-yl]-acetate (1.1 g, 3.0 mmol), which was prepared using procedures similar to those in Reference 23, Steps 1, and sodium metabisulfite (1.54 g, 8.10 mmol) were combined and dissolved in DMF (4 mL). The mixture was heated at 130 °C until reactions were complete as determined by HPLC, LCMS, and TLC [EtOAc/MeOH (9:1 v/v)] and [CH₂Cl₂/MeOH (9:1 v/v)] at 36 hours. The solution was partitioned between EtOAc (50 mL) and saturated sodium bicarbonate (50 mL). The organic layer was separated and washed with brine (50 mL) and concentrated. Product was purified from the residue by silica column chromatography [EtOAc/MeOH (9:1 v/v)] to give ethyl [3'-(1*H*-imidazo[4,5-*c*]pyridin-2-yl)-2'-(2-methoxyethoxymethoxy)-biphenyl-4-yl]-acetate (800 mg, 1.73 mmol, 57 %). MS(ES) *m/z* 462.3 (MH⁺); *m/z* 460.0 (MH⁻); MS calc: 461.51 (M).

Step 2

Ethyl [3'-(1*H*-imidazo[4,5-*c*]pyridin-2-yl)-2'-(2-methoxyethoxymethoxy)-biphenyl-4-yl]-acetate (800 mg, 1.73 mmol) was dissolved in acetonitrile (10 mL) and aq. 4 N hydrochloric acid (4 mL) and the solution was heated at 60 °C for 8 hours. The mixture was allowed to cool to room temperature. A precipitate was collected, washed with acetone and acetonitrile, and dried to give [3'-(1*H*-imidazo[4,5-*c*]pyridin-2-yl)-2'-hydroxy-biphenyl-4-yl]-acetic acid (600 mg, quantitative). MS(ES) m/z 345.8 (MH^+); m/z 343.8 (MH^-); MS calc: 345.35 (M).

Reference 30

[5'-Chloro-2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetic acid



Step 1

4 N hydrogen chloride in dioxane (5 mL) was added to a solution of [2'-hydroxy-3'-(1-methanesulfonyl-1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetic acid (248 mg, 0.587 mmol), prepared as in Reference 27, in MeOH (15 mL). The mixture was stirred for 1 hour at 60 °C and concentrated under reduced pressure. The residue was dissolved in ethyl acetate (100 mL) and the solution was washed with sat. $NaHCO_3$ solution and then brine, dried over $MgSO_4$ and concentrated under reduced pressure to give crude methyl 2-[2'-hydroxy-3'-(1-methanesulfonyl-1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetate.

Step 2

N-Chlorosuccinimide (102 mg, 0.764 mmol) was added to a solution of methyl [2'-hydroxy-3'-(1-methanesulfonyl-1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetate in THF (6 mL). The mixture was stirred for 2 hours at 50 °C and then diluted with ethyl acetate (30 mL). The mixture was washed with sat. $NaHCO_3$ solution and then brine, dried over $MgSO_4$ and concentrated under reduced pressure. Product was purified from the crude residue by column chromatography (10% EtOAc/*n*-hexanes) to give methyl 2-[5'-chloro-2'-hydroxy-3'-(1-methanesulfonyl-1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetate (96 mg, 35%) as a pale yellow viscous oil. LCMS ($M+1$)⁺ 471.1; ^1H NMR (400 MHz, $CDCl_3$): δ

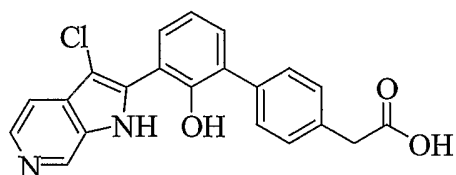
9.16 (s, 1H), 8.30 (d, 1H), 7.52 (d, 2H), 7.48 (d, 1H), 7.41 (d, 2H), 7.38 (d, 1H), 7.31 (d, 1H), 7.30 (s, 1H), 6.72 (s, 1H), 3.74 (s, 3H), 3.70 (s, 2H), 3.23 (s, 3H).

Step 3

0.21 M aq. Sodium hydroxide (3 mL) was added to a solution of methyl [5'-chloro-2'-hydroxy-3'-(1-methanesulfonyl-1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetate (100 mg, 0.21 mmol) in THF (5 mL). The mixture was stirred for 6 hours at 65 °C and then the THF was removed under reduced pressure. The aqueous solution was adjusted to pH 6 to give a precipitate. The precipitate was collected by filtration, washed with water several times and dried under vacuum to give [5'-chloro-2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetic acid (80 mg, quantitative) as a pale yellow solid. LCMS (M+1)⁺ 378.7; ¹H NMR (400 MHz, DMSO-*d*₃): δ 8.75 (s, 1H), 7.89 (d, 1H), 7.82 (d, 1H), 7.63 (d, 1H), 7.60 (d, 2H), 7.31 (d, 2H), 7.25 (d, 1H), 7.16 (s, 1H), 3.61 (s, 2H).

Reference 31

[3'-(3-Chloro-1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-2'-hydroxy-biphenyl-4-yl]-acetic acid



Step 1

N-Chlorosuccinimide (70 mg, 0.52 mmol) was added to a solution of ethyl [2'-(2-methoxyethoxymethoxy)-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetate (200 mg, 0.43 mmol) in THF (8 mL). The mixture was stirred for 5 hours at ambient temperature and then diluted with ether (30 mL) and ethyl acetate (30 mL). The mixture was washed with sat. NaHCO₃, and brine, dried over MgSO₄ and concentrated under reduced pressure. Product was purified from the crude residue by column chromatography (80% EtOAc/*n*-hexanes) to give ethyl [2'-(2-methoxyethoxymethoxy)-3'-(3-chloro-1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetate (135 mg, 63%) as a pale yellow viscous oil. LCMS (M+1)⁺ 495.3, ¹H NMR (400 MHz, CDCl₃) δ 8.88 (s, 1H), 8.36 (s, 1H), 7.92 (m, 1H), 7.62 (d, 1H), 7.56 (d, 2H), 7.48 (m, 1H), 7.40 (m, 3H), 4.70 (s, 2H), 4.23 (q, 2H), 3.71 (s, 2H), 3.34 (m, 4H), 3.29 (s, 3H), 1.31 (t, 3H).

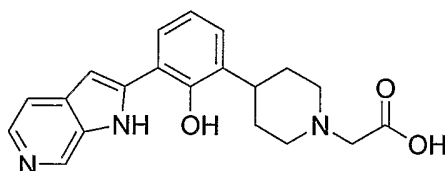
Step 2

Cysteine (75 mg, 0.62 mmol) and 4 N hydrogen chloride in dioxane (1 mL) was

added to a solution of ethyl [2'-(2-methoxyethoxymethoxy)-3'-(3-chloro-1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetate (128 mg, 0.259 mmol) in acetonitrile (5 mL). The mixture was stirred for 2 hours at 60 °C and then concentrated under reduced pressure and adjusted to a pH of 6 to give 2-[2'-hydroxy-3'-(3-chloro-1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetic acid as a pale yellow solid (80 mg). LCMS (M+1)⁺ 379.1, ¹H NMR (400 MHz, DMSO-*d*₃) δ 8.80 (s, 1H), 8.02(s, 1H), 7.59 (d, 2H), 7.56 (d, 1H), 7.35 (d, 1H), 7.33 (m, 3H), 7.03 (dd, 1H), 3.63 (s, 2H).

Reference 32

{4-[2-Hydroxy-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-phenyl]-piperidin-1-yl}-acetic acid



Step 1

A suspension of commercially available 4-(2-methoxyphenyl)-piperidine (5.0 g, 26.1 mmol) in 48% HBr, aq. (20 mL) was heated at reflux for 2 h. After cooling to room temperature, the mixture was concentrated under reduced pressure to give 4-(2-hydroxyphenyl)-piperidine which was used in the next step without further purification.

Step 2

To a solution of 4-(2-hydroxyphenyl)-piperidine in acetonitrile (65 mL) and water (65 mL) at ambient temperature was added NaOH (20 mL, 1M solution, 20.0 mmol) and benzyl chloroformate (2.25 mL, 16.0 mmol). After stirring for 10 min, the reaction was extracted into methylene chloride and washed with acidified aq. NH₄Cl (pH 2). The aqueous layer was separated and extracted with methylene chloride (3×100 mL). The organic layers were combined, washed with brine (50 mL), dried over Na₂SO₄, and concentrated. The residue was purified by flash column chromatography (hexanes/ethyl acetate, 3:1) to give 4-(2-hydroxy-phenyl)-piperidine-1-carboxylic acid benzyl ester (2.9 g, 42% over Steps 1 and 2): ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.44-7.35 (m, 5H), 7.16-7.09 (m, 2H), 6.93 (dt, *J* = 7.6, 1.2 Hz, 1H), 6.80 (dd, *J* = 8.4, 1.2 Hz, 1H), 5.86 (s, 1H), 5.21 (s, 2H), 4.37 (s, 2H), 3.12 (tt, *J* = 12.4, 3.6 Hz, 1H), 2.96 (m, 2H), 1.90 (d, *J* = 12.8, 2H), 1.73-1.67 (m, 2H), MS (calc): 311.2; MS: 312.5 (M+H)⁺, 310.8 (M-H)⁻.

Step 3

To a solution of 4-(2-hydroxy-phenyl)-piperidine-1-carboxylic acid benzyl ester (2.2

g, 7.07 mmol) in THF (12 mL) was added triethylamine (5.2 mL), paraformaldehyde (prilled, 1.07 g, 35.4 mmol) and MgCl_2 (2.55 g, 26.5 mmol). The resulting mixture was heated at 60 °C for 24 h, and was cooled to room temperature. The reaction was quenched with slow addition of phosphoric acid, and the product extracted into ethyl acetate (3×100 mL). The organic layers were combined, washed with water (50 mL), brine (50 mL), dried over Na_2SO_4 , and concentrated. The residue was purified by flash column chromatography (hexanes/ethyl acetate, 2:1) to give 4-(3-formyl-2-hydroxy-phenyl)-piperidine-1-carboxylic acid benzyl ester (1.7 g, 71%) as a white solid: ^1H NMR (400 MHz, CDCl_3) δ (ppm) 11.46 (s, 1H), 9.92 (s, 1H), 7.48-7.30 (m, 7H), 7.28 (t, $J = 7.6$ Hz, 1H), 5.20 (s, 2H), 4.38 (s, 2H), 3.22 (tt, $J = 12.0, 3.6$ Hz, 1H), 2.98 (bs, 2H), 1.90 (d, $J = 12.4$ Hz, 2H), 1.25 (m, 2H).

Step 4

To a solution of 4-(3-formyl-2-hydroxy-phenyl)-piperidine-1-carboxylic acid benzyl ester (1.70 g, 5.17 mmol) in DMF (5.0 mL) at 0 °C was added Cs_2CO_3 (2.02 g, 6.20 mmol) and methoxyethoxymethylchloride (0.71 mL, 6.20 mmol). After stirring at room temperature for 1 h, the mixture was added to water and ethyl acetate. The aqueous layer was separated and was extracted with ethyl acetate (3×75 mL). The organic layers were combined, washed with brine (40 mL), dried and concentrated to give 4-[3-formyl-2-(2-methoxy-ethoxymethoxy)-phenyl]-piperidine-1-carboxylic acid benzyl ester which was used in the next step without further purification.

Step 5

To a solution of 4-[3-formyl-2-(2-methoxy-ethoxymethoxy)-phenyl]-piperidine-1-carboxylic acid benzyl ester in ethanol (25 mL) was added Cs_2CO_3 (4.21 g, 12.91 mmol). The resulting suspension was purged with argon for 10 min. To this mixture at 0 °C was added a solution of dimethyl-1-diazo-2-oxopropylphosphonate [Ohira, S. *Synth. Commun.* **1989**, *19*, 561-54] (1.49 g, 7.76 mmol) in EtOH (3 mL), and the reaction was warmed to ambient temperature. After 40 min of stirring at ambient temperature, the reaction was quenched with a mixture of 5% NaHCO_3 and ethyl acetate. The aqueous layer was separated and extracted with ethyl acetate (3×75 mL), the organic layer was combined, washed with brine (40 mL), dried and concentrated. The residue was purified by flash column chromatography (hexanes/ethyl acetate, 2:1) to give 4-[3-ethynyl-2-(2-methoxy-ethoxymethoxy)-phenyl]-piperidine-1-carboxylic acid benzyl ester (1.40 g, 64% over Steps 3 and 4) as a colorless liquid. ^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.43-7.35 (m, 6H), 7.21 (dd, $J = 7.6, 1.6$ Hz, 1H), 7.08 (t, $J = 7.6$ Hz, 1H), 5.37 (s, 2H), 5.19 (s, 2H), 4.36 (bs, 2H),

3.99-3.96 (m, 2H), 3.63-3.61 (m, 2H), 3.42 (s, 3H), 3.33-3.26 (m, 1H), 2.97 (bs, 2H), 2.08 (s, 1H), 1.86-1.83 (m, 2H), 1.62 (m, 2H). MS (calc): 423.2; MS: 424.2 (M+H)⁺.

Step 6

To a suspension of 4-[3-ethynyl-2-(2-methoxy-ethoxymethoxy)-phenyl]-piperidine-1-carboxylic acid benzyl ester (1.40 g, 3.31 mmol) and *N*-(4-iodo-pyridin-3-yl)-methanesulfonamide (1.0 g, 3.34 mmol), prepared using procedures as described in Reference 4, in acetonitrile (8 mL) was added triethylamine (2.31 mL, 16.55 mmol). The solution was purged with argon for 10 min. PdCl₂(PPh₃)₂ (0.07 g, 0.1 mmol) and CuI (0.019 g, 0.1 mmol) were added. After purging with argon for an additional 10 min, the reaction was heated at 75 °C for 2 h. The solution was concentrated, and the residue was purified by flash column chromatography (methylene chloride/MeOH, 40:1) to give 4-[3-(1-methanesulfonyl-1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-2-(2-methoxy-ethoxymethoxy)-phenyl]-piperidine-1-carboxylic acid benzyl ester (1.75 g, 89%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.44-7.23 (m, 11H), 6.72 (s, 1H), 5.20 (s, 2H), 4.93 (bs, 1H), 4.81 (bs, 1H), 4.39 (bs, 2H), 3.62 (m, 1H), 3.44 (m, 1H), 3.32-3.21 (m, 10 H), 2.93 (bs, 2H), 1.80-1.60 (m, 3H). MS (calc): 593.2; MS: 594.2 (M+H)⁺, 592.2 (M-H)⁻.

Step 7

To a solution of 4-[3-(1-methanesulfonyl-1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-2-(2-methoxy-ethoxymethoxy)-phenyl]-piperidine-1-carboxylic acid benzyl ester (1.60 g, 2.70 mmol) in methylene chloride (8.5 mL) at ambient temperature was added HBr (30% in acetic acid, 2.1 mL). After stirring for 10 min, ether was added. The resulting precipitate was isolated by filtration and dried to give 2-(1-methanesulfonyl-1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-6-piperidin-4-yl-phenol as the HBr salt (1.45 g, 97%) which was used without further purification.

Step 8

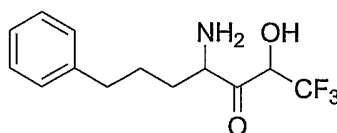
To a suspension of 2-(1-methanesulfonyl-1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-6-piperidin-4-yl-phenol as the HBr salt (1.35 g, 2.50 mmol) in acetonitrile (12.5 mL) at ambient temperature was added *N,N*-diisopropylethylamine (0.178 mL, 10.0 mmol) and ethyl bromoacetate (0.28 mL, 2.5 mmol). The solution gradually turned to clear. After stirring for 10 min, the mixture was concentrated, and the residue was dissolved in 1N HCl (50 mL), extracted with ether (2×20 mL). The aqueous layer was then lyophilized to give {4-[2-hydroxy-3-(1-methanesulfonyl-1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-phenyl]-piperidin-1-yl}-acetic acid ethyl ester. MS (calc): 457.2; MS: 458.0 (M+H)⁺, 456.1 (M-H)⁺.

Step 9

To a solution of {4-[2-hydroxy-3-(1-methanesulfonyl-1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-phenyl]-piperidin-1-yl}-acetic acid ethyl ester in THF (2.2 mL) and H₂O (11.0 mL) was added solid NaOH (1.2 g, 30 mmol). The mixture was heated at 65 °C for 2 h. After cooling to room temperature, the solvent was removed under reduced pressure. The residue was purified by preparative hplc to give {4-[2-hydroxy-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-phenyl]-piperidin-1-yl}-acetic acid (0.6 g, 60 % over Steps 7-9). ¹H NMR (400 MHz, DMSO) δ (ppm) 8.96 (s, 1H), 8.15 (d, *J* = 6.8 Hz, 1H), 7.97 (d, *J* = 6.4 Hz, 1H), 7.74 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.31 (s, 1H), 7.25 (d, *J* = 7.2 Hz, 1H), 7.05 (t, *J* = 7.2 Hz, 1H), 4.09 (s, 2H), 3.57-3.16 (m, 8 H), 2.01-1.89 (m, 4H). MS (calc): 351.2; MS: 352.5 (M+H)⁺, 350.3 (M-H)⁻.

Reference 33

3-Amino-1,1,1-trifluoro-6-phenyl-hexan-2-ol

Step 1

To a solution of 2-*tert*-butoxycarbonylamino-5-phenyl-pentanoic acid (330 mg, 1.12 mmol) in DCM (4 mL) was added at room temperature 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (260 mg, 1.35 mmol), 1-hydroxybenzotriazol hydrate (182 mg, 1.35 mmol), *N*-methoxy-*N*-methylamine hydrochloride (163 mg, 1.68 mmol) and *N,N*-diisopropylethylamine (608 μ L, 3.36 mmol). After stirring for 1 hour, the mixture was diluted with ethyl acetate, washed with 1 N HCl, sat. NaHCO₃, and brine. The organic layers were collected and dried over Na₂SO₄. Ethyl acetate was removed under vacuo, and the residue was purified by column chromatography (hexanes / ethyl acetate, 3:1) to provide [1-(methoxy-methylcarbamoyl)-4-phenylbutyl] carbamic acid *tert*-butyl ester (210 mg, 56%). MS (ES) *m/z*: 359.1(M+23)⁺; MS calcd: 336.20 (M).

Step 2

To a solution of [1-(methoxy-methylcarbamoyl)-4-phenylbutyl] carbamic acid *tert*-butyl ester (200 mg, 0.613 mmol) in ether (6 mL) at -40 °C was added LiAlH₄ in ether (1 M, 1.23 mL, 1.23 mmol). The mixture was gradually warmed to 0 °C and stirred for additional 10 minutes at 0 °C. The reaction was diluted with ethyl acetate, washed with acidified sat. NH₄Cl solution, sat NaHCO₃, and brine. The organic layer were collected, dried over

Na₂SO₄, and concentrated to yield crude (1-formyl-4-phenyl-butyl)-carbamic acid tert-butyl ester, which was used directly in the next step.

Step 3

To a solution of (1-formyl-4-phenyl-butyl)-carbamic acid tert-butyl ester, from Step 2, in THF (4 mL) at 0 °C was added trimethyltrifluoromethylsilane (144 µL, 0.92 mmol) and tetrabutylammonium fluoride in THF (1 M, catalytic amount). After stirring for 10 minutes at 0 °C, the reaction mixture was diluted with ethyl acetate, washed with sat. NaHCO₃, and brine. The organic layers were collected, dried over Na₂SO₄, and concentrated to yield 3-*tert*-butoxycarbonylamino-1,1,1-trifluoro-6-phenyl-hexan-2-ol.

Step 4

The product from Step 3 was dissolved in DCM (2 mL) and was treated with HCl in dioxane (4 M, 2 mL). After stirring overnight, the mixture was concentrated to give crude 3-amino-1,1,1-trifluoro-6-phenyl-hexan-2-ol.

Example 1

4-Hydroxy-4-phenylmethyl-1-{2-[5'-chloro-2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine

4-Phenylmethyl-piperidin-4-ol (30 mg, 0.16 mmol), EDCI (38 mg, 0.19 mmol), HOBT (24 mg, 0.16 mmol) and DIPEA (0.07 mL, 0.40 mmol) were added to a solution of [5'-chloro-2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetic acid (59 mg, 0.16 mmol) in DMF (1 mL) in an ice bath. The mixture was stirred for 24 hours and diluted with ethyl acetate (50 mL). The mixture was washed with sat. NaHCO₃, and brine, dried over MgSO₄ and concentrated under reduced pressure. Product was purified from the crude residue by preparative HPLC and lyophilized to give 4-hydroxy-4-phenylmethyl-1-{2-[5'-chloro-2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine (40 mg, 45% yield) as pale yellow solid. LCMS (M+1)⁺ 552.3.

Examples 2-24

Proceeding as in Example 1, but substituting [2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetic acid and 4-phenylmethyl-piperidin-4-ol, gave 4-hydroxy-4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine. MS(ES) Cald. 517.62. MS(ES) Obsd. m/z 518.4. MS(ES) Obsd. m/z 518.4.

Proceeding as in Example 1, but substituting [2'-hydroxy-3'-(1*H*-pyrrolo[3,2-

c]pyridin-2-yl)-biphenyl-4-yl]-acetic acid and 1-benzyl-piperazine, gave 4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine.

MS(ES) Cald. 502.61. MS(ES) Obsd. *m/z* 503.1 (*MH*⁺); *m/z* 501.3 (*MH*⁻).

Proceeding as in Example 1, but substituting [2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetic acid and methyl 4-phenylmethyl-piperidine-4-carboxylate, gave 4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylic acid methyl ester. MS(ES) Cald. 559.65. MS(ES) Obsd. *m/z* 559.8 (*MH*⁺); *m/z* 558.4 (*MH*⁻).

Proceeding as in Example 1, but substituting [2'-hydroxy-3'-(1-methanesulfonyl-1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetic acid and 4-cyano-4-phenylmethyl-piperidine, and then deprotecting gave *N*-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-ylmethylcarbonyl]-4-(cyano)-4-(phenylmethyl)-piperidine.

Proceeding as in Example 1, but substituting [2'-hydroxy-3'-(1-methanesulfonyl-1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetic acid and 4-(phenylmethyl)-4-(1*H*-tetrazol-5-yl)-piperidine hydrochloride, gave 4-phenylmethyl-4-(1*H*-tetrazol-5-yl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine.

Proceeding as in Example 1, but substituting [2'-hydroxy-3'-(1-methanesulfonyl-1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetic acid and 4-(phenylmethyl)-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-piperidine, and then deprotecting gave 3-(4-Phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidin-4-yl)-4*H*-[1,2,4]oxadiazol-5-one.

Proceeding as in Example 1, but substituting [2'-hydroxy-3'-(1-methanesulfonyl-1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetic acid and 3-(4-chlorophenylmethyloxy)-pyrrolidine gave 3-(4-chloro-phenylmethyloxy)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-pyrrolidine.

Proceeding as in Example 1, but substituting [2'-hydroxy-3'-(3-chloro-1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetic acid (19 mg, 0.050 mmol) and 4-(phenylmethyl)-4-(1*H*-tetrazol-5-yl)-piperidine (12 mg, 0.049 mmol) gave 4-phenylmethyl-4-(1*H*-tetrazol-5-yl)-1-{2-[2'-hydroxy-3'-(3-chloro-1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine (13 mg, 43% yield). LCMS (*M*+1)⁺ 604.3.

Proceeding as in Example 1, but substituting [2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetic acid (55 mg, 0.16 mmol) and 4-(4-fluorophenylmethyl)-piperidin-4-ol in DMF (2 mL) gave 4-(4-fluorophenylmethyl)-4-hydroxy-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine (31 mg,

36% yield). LCMS (M+1)⁺ 536.1, ¹H NMR (400 MHz, DMSO-d₃): δ 13.25 (br, 1H), 9.65 (br, 1H), 9.03 (s, 1H), 8.30 (d, 1H), 8.08 (d, 1H), 7.90 (d, 1H), 7.50 (d, 2H), 7.42 (s, 1H), 7.39 (d, 1H), 7.31 (d, 2H), 7.22 (m, 3H), 7.05 (dd, 2H), 4.12 (m, 1H), 3.73 (m, 3H), 2.85 (m, 1H), 2.67 (s, 2H), 1.45 (m, 4H).

Proceeding as in Example 1, but substituting [2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetic acid (190 mg, 0.551 mmol) and methyl 4-phenylmethyl-piperidine-4-carboxylate hydrochloride (150 mg, 0.55 mmol) gave methyl 4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylate (130 mg, 46%). ¹H NMR (400 MHz, d₆-DMSO) δ 9.04 (s, 1H), 8.26 (d, 1H, *J* = 6.8 Hz), 8.08 (d, 1H, *J* = 6.0 Hz), 7.90 (dd, 1H, *J* = 1.6, 7.8 Hz), 7.52 (brd, 2H, *J* = 8.0 Hz), 7.42 (s, 1H), 7.41 (dd, 1H, *J* = 1.6, 6.4 Hz), 7.35 (brd, 2H, *J* = 8.2 Hz), 7.31-7.19 (brm, 4H), 7.04 (d, 2H, *J* = 8.4 Hz), 4.22 (brd, 1H, *J* = 13 Hz), 3.95 (brd, 1H, *J* = 13 Hz), 3.78 (dd, 2H, *J* = 15 Hz), 3.60 (s, 3H), 3.06 (t, 1H, *J* = 12 Hz), 2.84 (d, 2H, *J* = 3.2), 2.69 (brt, 1H, *J* = 12 Hz), 1.96 (brt, 2H, *J* = 13 Hz), 1.44 (brq, 2H, *J* = 11 Hz); MS(ES) *m/z* 560.0(MH⁺); MS calcd: 559.25 (M).

Proceeding as in Example 1, but substituting [2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetic acid (15 mg, 0.044 mmol) and *N*-(4,5-dihydro-thiazol-2-yl)-4-phenylmethyl-piperidine-4-carboxamide hydrochloride (12 mg, 0.035 mmol) gave *N*-(4,5-dihydro-thiazol-2-yl)-4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxamide (10 mg, 40% yield). MS(ES) *m/z* 630.4(MH⁺); MS calcd: 629.25 (M).

Proceeding as in Example 1, but substituting [2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetic acid (50 mg, 0.13 mmol) and methyl 4-thiophen-3-ylmethyl-piperidine-4-carboxylate hydrochloride (38 mg, 0.14 mmol) gave methyl 1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-4-thiophen-3-ylmethyl-piperidine-4-carboxylate (60 mg, 82%). MS(ES) *m/z* 566.2(MH⁺); MS calcd: 665.20 (M).

Proceeding as in Example 1, but substituting [2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetic acid (25 mg, 0.073 mmol) and 1-piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one (16 mg, 0.072 mmol) gave 1-(1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one (21 mg, 65%). MS(ES) *m/z* 544.2(MH⁺); MS calcd: 543.23 (M).

Proceeding as in Example 1, but substituting [2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetic acid (30 mg, 0.087 mmol) and 4-piperazinothieno[3,2-

d]pyrimidine (25 mg, 0.093 mmol) gave 4-(thieno[3,2-*d*]pyrimidin-7-yl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine (30 mg, 64%). MS(ES) *m/z* 547.5MH⁺; MS calcd: 546.18 (M).

Proceeding as in Example 1, but substituting [2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetic acid (23.4 mg, 0.0680 mmol) and 4-(phenylmethyloxycarbonylmethyl)-4-(4-fluorophenylmethyl)-piperidine hydrochloride (47.7 mg, 0.0747 mmol), and then deprotecting gave 4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidin-4-yl)-acetic acid (22 mg, 67%). ¹H NMR (400 MHz, *d*₆-DMSO) δ 9.02 (s, 1H), 8.24 (d, 1H, *J* = 6.5 Hz), 8.06 (d, 1H, *J* = 6.5 Hz), 7.89 (dd, 1H, *J* = 1.5, 7.5 Hz), 7.41 (s, 1H), 7.52 (d, 2H, *J* = 8 Hz), 7.39 (dd, 1H, *J* = 1.5, 7.9 Hz), 7.33 (d, 2H, *J* = 8Hz), 7.25-7.21 (m, 2H), 7.18 (t, 1H, *J* = 7.9 Hz), 7.11 (brt, 2H, *J* = 9Hz), 3.84-3.70 (m, 2H), 3.76 (s, 2H), 3.46-3.25 (m, 2H), 2.77 (s, 2H), 2.19 (s, 2H), 1.50-1.30 (m, 4H). MS(ES) *m/z* 578.2 (MH⁺); MS calcd: 577.2 (M).

Proceeding as in Example 1, but substituting [2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetic acid (86 mg, 0.25 mmol) and 4-(5-methyl-2*H*-[1,2,4]triazol-3-yl)-4-(4-fluorophenylmethyl)-piperidine hydrochloride (101 mg, 0.325 mmol) gave 4-(4-fluoro-phenylmethyl)-4-(5-methyl-2*H*-[1,2,4]triazol-3-yl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine (62.0 mg, 41%). ¹H NMR (400 MHz, *d*₆-DMSO) δ 13.04 (s, 1H), 9.64 (s, 1H), 9.03 (s, 1H), 8.26 (d, 1H, *J* = 6.3 Hz), 8.07 (d, 1H, *J* = 6.3 Hz), 7.90 (dd, 1H, *J* = 1.6, 7.8 Hz), 7.50 (brd, 2H, *J* = 8.2 Hz), 7.42 (s, 1H), 7.39 (dd, 1H, *J* = 1.6, 7.4 Hz), 7.31 (brd, 2H, *J* = 8.2 Hz), 7.19 (t, 1H, *J* = 7.4 Hz), 6.98 (t, 2H, *J* = 9 Hz), 6.74 (dd, 2H, *J* = 5.5, 8.6 Hz), 4.22 (brd, 1H, *J* = 13 Hz), 3.92 (brd, 1H, *J* = 13 Hz), 3.82 (d, 1H, *J* = 15 Hz), 3.72 (d, 1H, *J* = 15 Hz), 3.00 (t, 1H, *J* = 12 Hz), 2.89 (s, 2H), 2.62 (brt, 1H, *J* = 12 Hz), 2.42 (s, 3H), 2.15 (brd, 2H, *J* = 13 Hz), 1.59 (brq, 2H, *J* = 11 Hz). MS(ES) *m/z* 601.4 (MH⁺); MS calcd: 600.3 (M).

Proceeding as in Example 1, but substituting [2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetic acid (119 mg, 0.346 mmol) and N-[4-(4-fluoro-phenylmethyl)-piperidin-4-yl]-acetamide hydrochloride salt (122 mmol, 0.424 mmol) gave N-(4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidin-4-yl)-acetamide (24 mg, 10%). ¹H NMR (400 MHz, *d*₆-DMSO) δ 9.02 (s, 1H), 8.24 (d, 1H, *J* = 6.3 Hz), 8.06 (d, 1H, *J* = 6.3 Hz), 7.90 (dd, 1H, *J* = 1.7, 8 Hz), 7.52 (brd, 2H, *J* = 8.2 Hz), 7.42 (s, 1H), 7.39 (dd, 1H, *J* = 1.8, 7.7 Hz), 7.25 (s, 1H), 7.18 (t, 1H, *J* = 7.7 Hz), 7.14-7.06 (m, 4H), 4.17 (brd, 1H, *J* = 14.3 Hz), 3.82 (brd, 2H, *J* = 15.5 Hz),

3.72 (d, 1H, $J = 15.5$ Hz), 3.11 (brt, 1H, $J = 12$ Hz), 2.98 (d, 1H, $J = 13$ Hz), 2.93 (d, 1H, $J = 13$ Hz), 2.73 (brt, 1H, $J = 12$ Hz), 2.06-1.97 (m, 2H), 1.84 (s, 3H), 1.40-1.30 (m, 2H).

MS(ES) m/z 577.3 (MH^+); MS cald: 576.3 (M).

Proceeding as in Example 1, but substituting [2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetic acid (50 mg, 0.145 mmol) and 4-(4-fluoro-phenylmethyl)-piperidine-4-carboxylate hydrochloride (50 mg, 0.173 mmol, 1.2 eq) gave methyl 4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylate (69.8 mg, 83 % yield). MS(ES) m/z 578.0 (MH^+); m/z 576.3 (MH); MS calc: 577.64 (M).

Proceeding as in Example 1, but substituting [3'-(1*H*-imidazo[4,5-*c*]pyridin-2-yl)-2'-hydroxy-biphenyl-4-yl]-acetic acid and methyl 4-(4-fluoro-phenylmethyl)-piperidine-4-carboxylate hydrochloride, gave methyl 4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-imidazo[4,5-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylate. MS(ES) m/z 579.1 (MH^+); m/z 577.4 (MH); MS calc: 578.63 (M).

Proceeding as in Example 1, but substituting [2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetic acid and methyl 4-phenylmethyl-piperidine-4-carboxylate hydrochloride, gave 4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylic acid. MS(ES) m/z 546.5 (MH^+); m/z 544.0 (MH); MS calc: 545.63 (M).

Proceeding as in Example 1, but substituting [2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetic acid and 1-phenyl-piperazine, gave 4-phenyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine.

Proceeding as in Example 1, but substituting 4'-aminomethyl-3-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-2-ol hydrochloride and (4-phenylmethyl-piperazin-1-yl)-acetic acid, gave 2-(4-phenylmethyl-piperazin-1-yl)-*N*-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-ylmethyl]-acetamide. MS(ES) m/z 532.4 (MH^+); MS cald: 531.26(M).

Proceeding as in Example 1, but substituting 4'-amino-3-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-2-ol hydrochloride and (4-phenylmethyl-piperazin-1-yl)-acetic acid, gave 2-(4-phenylmethyl-piperazin-1-yl)-*N*-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetamide. MS(ES) m/z 518.5 (MH^+); MS cald: 517.25(M).

Examples 25-183

Proceeding as in Example 1 the following compounds of Formula I were made:

4-(3,4-difluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylic acid;

4-(3-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylic acid;

N-(4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carbonyl)-methanesulfonamide;

N-hydroxy-4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxamide;

methyl 4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylate;

4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxamide;

methyl 4-(3,4-difluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylate;

methyl 4-(3-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylate;

[(4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carbonyl)-amino]-acetic acid;

4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-N-methyl-piperidine-4-carboxamide;

4-(2-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylic acid;

methyl [(4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carbonyl)-amino]-acetate;

N-(4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-yl)-acetate;

N-(2,2,2-trifluoro-ethyl)-4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxamide;

4-(3,4-difluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[3,2-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylic acid;

N-phenylmethoxy-4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxamide;

4-phenylmethyl-4-hydroxy-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[3,2-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylic acid;

methyl 4-(2-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylate;

methyl 4*R*-(4-fluoro-phenylmethoxy)-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-pyrrolidine-2*S*-carboxylate;

methyl 4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[3,2-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylate;

methyl 4-(3,4-difluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[3,2-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylate;

N-(1H-tetrazol-5-yl)-4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxamide;

N,N-dimethyl-4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxamide;

methyl 4-(2-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylate;

N-thiazol-2-yl-4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxamide;

4-fluoro-4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

methyl 4-allyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylate;

4-allyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylic acid;

4-(2-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylic acid;

methyl 4-phenylmethoxy-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-pyrrolidine-2-carboxylate;

4-fluoro-4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

N-dimethyl-4-Phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxamide;

4-phenylmethoxy-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-pyrrolidine-2-carboxylic acid;

4-amino-4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

4-hydroxy-4-phenyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

3-hydroxy-4-(3-trifluoromethyl-phenyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

4-(4-chlorophenyl)-4-hydroxy-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

4-hydroxy-4-(3-trifluoromethyl-phenyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

methyl 1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-4-methyl-piperidine-4-carboxylate;

phenylmethyl (4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidin-4-yl)-carbamate;

2-(hydroxymethyl)-4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

methyl 1-phenylmethyl-4-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine-2-carboxylate;

methyl 4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine-2-carboxylate;

1-phenylmethyl-4-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine-2-carboxylic acid;

4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine-2-carboxylic acid;

4*R*-(4-fluoro-phenylmethoxy)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-pyrrolidine-2*S*-carboxylic acid;

N-(1*H*-[1,2,4]triazol-3-yl)-4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxamide;

methyl 4*R*-(4-fluoro-phenylmethoxy)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-pyrrolidine-2*R*-carboxylate;

methyl 1-phenylmethyl-4-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine-2-carboxylate;

4-hydroxy-4-phenyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

4-hydroxy-4-(4-chlorophenyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

4-phenylmethyl-4-(morpholin-4-ylcarbonyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

N-methoxy-4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxamide;

1-phenylmethyl-4-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine-2-carboxylic acid;

4*R*-(4-fluoro-phenylmethoxy)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-pyrrolidine-2*R*-carboxylic acid;

N-methoxy-4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine-2-carboxamide;

4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine-2-carboxylic acid;

4-hydroxy-4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine

N-cyclopropylmethyl-4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxamide;

N-(2,2,2-trifluoro-ethyl)-4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxamide;

phenylmethyl (4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidin-4-yl)-acetate;

N-(4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidin-4-yl)-methanesulfonamide;

4-phenylmethyl-4-hydroxy-1-{2-[2'-hydroxy-3'-(1*H*-imidazo[4,5-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

(4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidin-4-yl)-urea;

4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-imidazo[4,5-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylic acid;

4-(4,5-dihydro-thiazol-2-yl)-4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

4-(4-fluoro-phenylmethyl)-4-(1*H*-[1,2,3]triazol-4-yl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

N-cyclopropylmethyl-4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxamide;

phenylmethyl (4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidin-4-yl)-carbamate;

methyl 4-cyclopropylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylate;

4-cyclopropylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylic acid;

4-(4-fluoro-phenylmethyl)-4-hydroxy-1-{2-[2'-hydroxy-3'-(1*H*-imidazo[4,5-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

2-diethylamino-ethyl 4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylate;

N,N-dimethyl-4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxamide;

4-(4-fluoro-phenylmethyl)-4-hydroxymethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

4-(4-fluoro-phenylmethyl)-4-hydroxymethyl-1-{2-[2'-hydroxy-3'-(1*H*-imidazo[4,5-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carbonitrile;

4-cyclopropylmethyl-4-hydroxymethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

methyl 4-benzyl-1-{2-[2'-hydroxy-3'-(1*H*-imidazo[4,5-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylate;

methyl 1-{2-[3'-(5,7-dihydro-4*H*-purin-8-yl)-2'-hydroxy-biphenyl-4-yl]-acetyl}-4-(4-fluoro-benzyl)-piperidine-4-carboxylate;

4-hydroxy-4-(3-trifluoromethyl-phenyl)-1-{2-[2'-hydroxy-3'-(1*H*-imidazo[4,5-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

methyl 4-cyclopentylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylate;

methyl 1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-4-isobutyl-piperidine-4-carboxylate;

4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidin-4-ylmethyl cyclopropanecarboxylate;

methyl 4-(3,3-difluoro-allyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylate;

N-(4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidin-4-ylmethyl)-methanesulfonamide;

N-(4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidin-4-ylmethyl)-cyclopropanecarboxamide;

methyl 1-{2-[2'-hydroxy-3'-(1H-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-4-(2,2,2-trifluoro-ethyl)-piperidine-4-carboxylate;

4-(2-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[3,2-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-3,6-dihydro-2H-pyridine;

4-phenyl-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[3,2-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-(1-methyl-butyl)-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[3,2-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-ethyl-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[3,2-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-(pyridin-4-yl)-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[3,2-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-isopropyl-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[3,2-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-(thiophen-2-ylmethyl)-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-(4-chloro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[2,3-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-(2-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[3,2-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-(thiophen-2-ylmethyl)-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[3,2-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-(4-chloro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1H-pyrrolo[3,2-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-(thiophen-3-ylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-(3-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-(3-chloro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-(4-methyl-pyridin-2-yl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-[2-(thiophen-2-yl)-ethyl]-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-(2-chloro-4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-(2-chloro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-(3-carboxyphenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-oxo-4-phenyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-4λ⁵-[1,4]azaphosphinane;

4-(2-methyl-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-phenethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-(pyridin-4-ylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-(pyridin-3-ylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

N-phenyl-4-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine-1-carboxamide;

4-(pyridin-2-yl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

methyl 3-(4-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazin-1-ylmethyl)-benzoate;

- 4-(3-methyl-pyridin-2-yl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;
- N*-(4-fluoro-phenyl)-4-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine-1-carboxamide;
- 4-isobutyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;
- 4-(phenylthiomethylcarbonyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;
- 4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-homopiperazine;
- 4-(3,4-dichloro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;
- 4-(4-fluoro-phenyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;
- 4-(pyridin-2-ylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;
- 4-(cyclohexylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;
- 4-(3-methyl-butyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;
- 4-(*N*-isopropylaminocarbonylamino)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;
- 4-(1-phenyl-eth-1-yl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;
- 4-(phenylmethyl)-1-{2-[2'-hydroxy-3'-(4-chloro-1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;
- 4-methyl-4-oxo-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-4 λ^5 -[1,4]azaphosphinane;
- 4-(phenylmethyl)-1-{2-[2'-hydroxy-3'-(6-chloro-1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;
- 4-(2-methyl-benzimidazol-1-yl)-1-{2-[2'-hydroxy-3'-(6-chloro-1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;
- 4-(phenylmethylcarbonyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

4-phenoxy-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

4-(1-hydroxy-1-phenyl-methyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

4-hydroxy-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

4-(3,4-difluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

4-(benzoimidazol-1-yl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

4-(6-methyl-pyridin-3-yl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine;

4-[2-(morpholin-4-yl)-ethyl]-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-(pyridin-4-yl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine-1-carboxylic acid phenylamide;

2-(4-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazin-1-yl)-*N*-pyridin-2-yl-acetamide;

4-(1-phenyl-eth-1-yl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

4-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine-1-carboxylic acid ethylamide;

N-(1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidin-4-yl)-*N*-phenyl-propionamide;

4-(cyclopentylcarbonyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine;

2-methoxy-ethyl (1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidin-4-yl)-acetate;

2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-*N*-(3-pyrrolidin-1-yl-propyl)-acetamide;

N-(1-phenylmethyl-pyrrolidin-3-yl)-2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetamide;

N-[2'-Hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-ylmethylcarbonyl]-1,3-dihydrospiro(indene-2,4-piperidine);

N-[2'-Hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-ylmethylcarbonyl]-1,3-dihydrospiro(indene-2,4-piperidine); and

methyl 1-{2-[5'-chloro-2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-4-(4-fluoro-phenylmethyl)-piperidine-4-carboxylate.

Example 184

4-Phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylic acid

2 M Potassium hydroxide (1 mL) was added to a solution of methyl 4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylate (40 mg, 0.071 mmol) in methanol-acetonitrile mixture (v/v, 1:1) (3 mL). The mixture was heated at 60 °C for 20 hours and then acidified with conc. hydrochloric acid. Product was purified by preparative reversed phase HPLC to give 4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylic acid (25 mg, 65%). MS(ES) *m/z* 546.1 (MH⁺); MS calcd: 545.23 (M).

Examples 185-187

Proceeding as in Example 184, but substituting methyl 1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-4-thiophen-3-ylmethyl-piperidine-4-carboxylate, gave 1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-4-thiophen-3-ylmethyl-piperidine-4-carboxylic acid. MS(ES) *m/z* 552.0 (MH⁺); MS calcd: 551.19 (M).

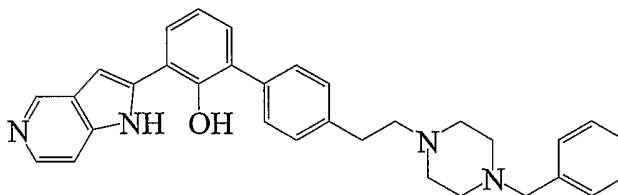
Proceeding as in Example 184, but substituting methyl 4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylate, gave 4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylic acid. MS(ES) *m/z* 563.7 (MH⁺); *m/z* 561.5 (MH⁻); MS calc: 563.6 (M).

Proceeding as in Example 184, but substituting methyl 4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1*H*-imidazo[4,5-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-

carboxylate, gave 4-(4-fluoro-phenylmethyl)-1-{2-[2'-hydroxy-3'-(1H-imidazo[4,5-c]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperidine-4-carboxylic acid. MS(ES) m/z 565.3 (MH^+); m/z 562.9 (MH^-); MS calc: 564.61 (M).

Example 188

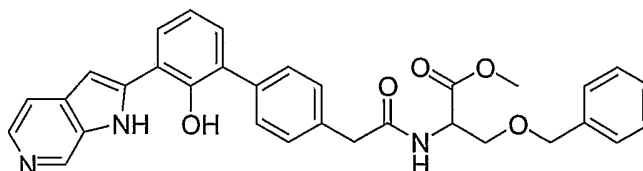
4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-ethyl}-piperazine



4-Phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetyl}-piperazine (20 mg, 0.04 mmol) was dissolved in THF (2 ml) and the solution was heated under nitrogen to 70 °C. Borane-dimethylsulfide (10 M in THF, 0.05 ml, 0.5 mmol) was added and the mixture was heated for 2 hours. 4 N aq. Hydrochloric acid (2 ml) was added carefully under nitrogen and the mixture heated at 60 °C for 2 hours. The mixture was concentrated and product was purified from the residue by preparative TLC (1 x 2000 micron silica gel plate, [CH_2Cl_2 /MeOH (9:1 v/v)]). The product was taken up in 0.1 M hydrochloric acid and dried by lyophilization to give 4-phenylmethyl-1-{2-[2'-hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-ethyl}-piperazine hydrochloride (6.6 mg). MS(ES) m/z 489.2 (MH^+); m/z 487.1 (MH^-); MS calc: 488.62 (M).

Example 189

Synthesis of *N*-[2'-Hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-ylmethylcarbonyl]-*N*-[2-(phenylmethoxy)-1-(methoxycarbonyl)-ethyl]-amine



Step 1

To a solution of commercially available 2-amino-3-benzyloxy-*N*-butoxycarbonyl-propionic acid (340 mg, 1.15 mmol) in methanol (10 mL) and benzene (10 mL) at 20 °C was added dropwise a solution of trimethylsilyl diazomethane in hexanes (2.0 M, 1.3 mL, 2.6 mmol), the reaction was allowed to stir at room temperature for 1 h then the solvent was

removed under reduced pressure to give 2-amino-3-benzyloxy-*N*-*tert*-butoxycarbonyl-propionic acid methyl ester as a clear oil (355 mg). MS(ES) m/z 332.2 (MNa^+); MS cald: 309.16 (M).

Step 2

2-amino-3-benzyloxy-*N*-*tert*-butoxycarbonyl-propionic acid methyl ester from above was dissolved in EtOAc (1 mL), 4 N HCl in dioxane (1 mL, 4 mmol) was added. After 2 h at room temperature the solvent was removed and the residue was treated with ether and dried to give 2-amino-3-benzyloxy-propionic acid methyl ester hydrochloride (260 mg, 92%). MS(ES) m/z 209.9 (MH^+); MS cald: 209.11 (M).

Step 3

[2'-Hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetic acid (80 mg, 0.23 mmol), which was prepared using procedures as described in Reference 8, and 2-amino-3-benzyloxy-propionic acid methyl ester hydrochloride (103 mg, 0.419 mmol) from Step 2, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC, 80 mg, 0.42 mmol), and 1-hydroxybenzotriazole hydrate (HOBt, 57 mg, 0.42 mmol) was added DMF (2 mL) and di-isopropylethylamine (140 μ L, 0.8 mmol) at room temperature. After 20 hours, the reaction mixture was purified by HPLC to yield *N*-[2'-Hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-ylmethylcarbonyl]-*N*-[2-(phenylmethoxy)-1-(methoxycarbonyl)-ethyl]-amine (62 mg, 64%). MS (ES) m/z 535.7 (MH^+); MS cald: 535.21 (M).

Examples 190-192

Example 2

Proceeding as above in Example 189, Step 3, but replacing 2-amino-3-benzyloxy-propionic acid methyl ester hydrochloride with 2-amino-3-(cyclopropylmethyl-amino)-propionic acid methyl ester, *N*-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-ylmethylcarbonyl]-*N*-{2-[*N*-(cyclopropylmethyl)-amino]-1-(methoxycarbonyl)-ethyl}-amine was prepared.

Example 3

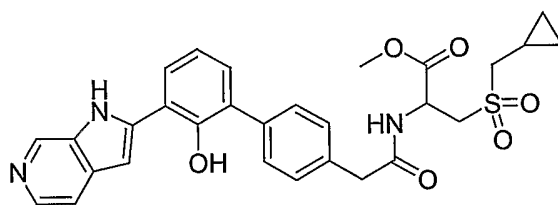
Proceeding as above in Example 189, Step 3, but replacing 2-amino-3-benzyloxy-propionic acid methyl ester hydrochloride with 2-amino-3-[(cyclopropylmethyl)-oxy]-propionic acid methyl ester, *N*-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-ylmethylcarbonyl]-*N*-{2-[(cyclopropylmethyl)-oxy]-1-(methoxycarbonyl)-ethyl}-amine was prepared. ESMS (m/z): found, 500.0 ($M+1$)⁺; cald, 499.56 (M).

Example 4

Proceeding as above in Example 189, Step 3, but replacing 2-amino-3-benzyloxy-propionic acid methyl ester hydrochloride with 3-amino-1,1,1-trifluoro-6-phenyl-hexan-2-ol, which was prepared as described in Reference 12, the product *N*-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-yl-methylcarbonyl]-*N*-(5-phenyl-1-hydroxy-1-trifluoromethyl-pent-2-yl)-amine was prepared. ESMS (*m/z*): found, 573.9 (*M*+1)⁺; calcd., 573.2 (*M*).

Example 193

Synthesis of *N*-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-ylmethylcarbonyl]-*N*-{2-[(cyclopropylmethyl)-sulfonyl]-1-(methoxycarbonyl)-ethyl}-amine



Step 1

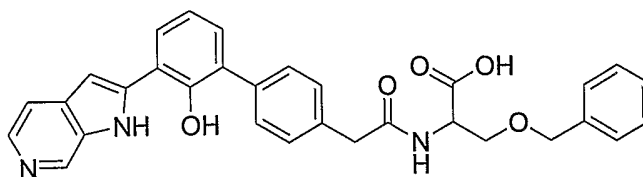
Proceeding as in Example 189, Step 3, but replacing 2-amino-3-benzyloxy-propionic acid methyl ester hydrochloride with 2-amino-3-cyclopropylmethylsulfonyl-propionic acid methyl ester, *N*-[2'-hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-ylmethylcarbonyl]-*N*-{2-[(cyclopropylmethyl)-sulfonyl]-1-(methoxycarbonyl)-ethyl}-amine was prepared. ESMS (*m/z*): found, 516.3 (*M*+1)⁺; calcd., 515.6 (*M*).

Step 2

The product from Step 1 (65 mg, 0.126 mmol) was dissolved in MeOH (3 mL) and oxone (239 mg, 0.39 mmol) in H₂O (3 mL) was added. The suspension was stirred for 1 hour at room temperature. The crude reaction mixture was purified by preparative HPLC afforded the product (20 mg, 29%). ESMS (*m/z*): found, 548.4 (*M*+1)⁺; calcd., 547.6 (*M*).

Example 194

Synthesis of *N*-[2'-Hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-ylmethylcarbonyl]-*N*-[2-(phenylmethoxy)-1-carboxyethyl]-amine

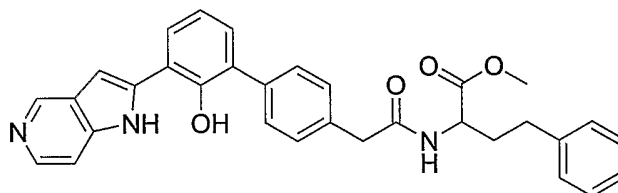


Step 1

A mixture of *N*-[2'-Hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-ylmethylcarbonyl]-*N*-[2-(phenylmethoxy)-1-(methoxycarbonyl)-ethyl]-amine (32 mg, 0.060 mmol), lithium hydroxide monohydrate (7.0 mg, 0.17 mmol), acetonitrile (3 mL) and water (1 mL) was heated at 60 °C for 1 h. The reaction was acidified with 4 N HCl and purified by HPLC to give *N*-[2'-Hydroxy-3'-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-biphenyl-4-ylmethylcarbonyl]-*N*-[1-carboxy-2-(phenylmethoxy)-ethyl]-amine (24 mg, 77 %) as a white solid; MS (ES) *m/z* 521.9 (MH⁺); MS calcd: 521.2 (M).

Example 195

Synthesis of *N*-[2'-Hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-ylmethylcarbonyl]-*N*-[1-(methoxycarbonyl)-3-phenylpropyl]-amine

Step 1

D,L-2-Amino-4-phenyl-butyric acid (248 mg, 1.38 mmol) was suspended in MeOH (5 mL), conc. H₂SO₄ (0.1 mL) was added, and the mixture heated to reflux. After 48 hours the reaction was cooled to room temperature, and basified with 4 M NaOH. The product was extracted with EtOAc (50 mL), and the organic layer washed with brine. 4 N HCl in dioxane solution (0.5 mL) was added, followed by ethyl ether (20 mL) and hexane (20 mL). D,L-2-Amino-4-phenyl-butyric acid methyl ester precipitated as white needles and was collected by filtration and dried to give 130 mg (crop 1). MS(ES) *m/z* 193.5 (MH⁺); MS calc: 193.25 (M)

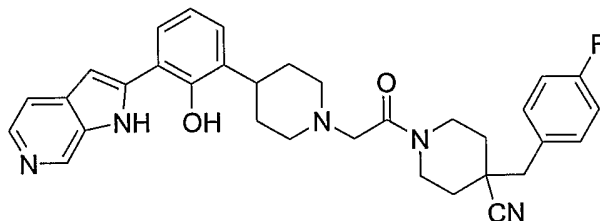
Step 2

[2'-Hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-yl]-acetic acid (40 mg, 0.116 mmol), prepared using the procedures described in Reference 7, was dissolved in DMF (2 mL). EDC-HCl (26 mg, 0.132 mmol), HOBt (18.0 mg, 0.132 mmol), and *N,N*-diisopropylethylamine (0.266 mL, 1.52 mmol) were added, followed by D,L-2-Amino-4-phenylbutyric acid methyl ester HCl (26.1 mg, 0.114 mmol). The reaction was allowed to stir overnight at room temperature. Methylene chloride (98 mL) was added, and the organic layer extracted three times with water (5 mL portions) and brine (5 mL), then dried over sodium hydrogen sulfate. The organic layer was concentrated and the residue purified by silica gel chromatography, using methylene chloride-methanol (19:1) as eluent. *N*-[2'-

Hydroxy-3'-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-biphenyl-4-ylmethylcarbonyl]-*N*-[1-(methoxycarbonyl)-3-phenylpropyl]-amine was obtained (33.5 mg, 56%). MS(ES) (*m/z*) 519.9 (*M*+1)⁺; (*m/z*) 517.8 (*M*-1)⁻; MS calc: 519.59 (*M*).

Example 196

4-(4-fluorophenylmethyl)-4-cyano-4-[2-hydroxy-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-phenyl]-piperidin-1-ylacetyl}-piperidine



To a solution of {4-[2-hydroxy-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)-phenyl]-piperidin-1-yl}-acetic acid (0.035 g, 0.08 mmol), prepared using procedures similar to those in Reference 32, in DMF (0.8 mL) was added at ambient temperature *tert*-butyl 4-fluorophenylmethyl-4-cyano-piperidine, prepared using procedures similar to those described in Reference 7 (except by replacing benzyl bromide with 4-fluorobenzyl bromide), (0.024 g, 0.096 mmol), PyBOP (0.041 g, 0.096 mmol) and DIPEA (0.071 mL, 0.40 mmol). After stirring for 30 min, the reaction was diluted with ethyl acetate, washed with sat. NaHCO₃, brine, dried and concentrated. The residue was then purified by preparative HPLC to give 14 (7 mg, 12%): ¹H NMR (400 MHz, DMSO) δ (ppm) 8.95 (s, 1H), 8.16 (s, 1H), 8.0 (s, 1H), 7.72 (d, *J* = 6.8 Hz, 1H), 7.28 (m, 5H), 7.15 (m, 6H), 4.37 (m, 2H), 3.80 (m, 1H), 3.53 (m, 2H), 3.22 (m, 1H), 3.10 (m, 2H), 2.87 (s, 2H), 2.61 (m, 2H), 2.60 (m, 1H), 2.43 (m, 1H), 2.26 (m, 1H), 2.0 (m, 1H), 1.85 (m, 2H), 1.65 (m, 1H). MS (calc): 551.3; MS: 552.8 (*M*+H)⁺, 550.6 (*M*-H)⁻.

Proceeding as above in Example 196, Table 15 and Table 16 compounds were prepared using the following procedure.

Biological Examples

Example 1

Inhibitory Activity Against Human Tryptase

The following protocol represents an assay for determination of inhibition of tryptase under physiological conditions (pH 7.4). Human skin Beta-1 tryptase can be purchased from Promega. Tosyl-Gly-Pro-Lys-para-nitroanilide (tos-GPK-pNa) can be purchased from Centerchem, Inc. Inhibitor profiles were generated by incubating each enzyme in the

presence of inhibitor (various concentrations) or 10% DMSO (vehicle control) for 30 minutes in 96 well clear polystyrene plates at room temperature prior to the addition of substrate. Specifically, 400 μ M tos-GPK-pNa was added to 1 nM enzyme in 50 mM Tris (7.4), 150 mM NaCl, 0.02% Tween-20, 1 mM EDTA, 50 μ g/mL heparin. Enzyme activity can be measured by monitoring the hydrolysis of the synthetic substrate tos-GPK-pNa at 405 nM over 5 minutes using a UV/MAX kinetic plate reader (Molecular Devices). The apparent inhibition constants (K_i , app) can be calculated from the progress curves using the software package BatchKi (BioKin, Ltd.). BatchKi uses nonlinear least-squares regression to fit experimental data to the Morrison equation for tight binding inhibitors.

Example 2

Identification of Compounds with Anti-inflammatory Efficacy

The efficacy of the compounds of the present invention for the treatment of immunomediated inflammatory disorders can be evaluated by either in vitro or in vivo procedures. Thus, the anti-inflammatory efficacy of the compounds of the present invention can be demonstrated by assays well known in the art, for example, the Reversed Passive Arthus Reaction technique (see US Patent 5,126,352).

Example 3

Identification of Compounds with Efficacy in Treatment of Skin Diseases

Assays for determining the therapeutic value of compounds in the treatment of various skin conditions, such as hyperproliferative skin disease, are well known in the art, for example, the Arachidonic Acid Mouse ear Test.

Example 4

Primate Acute Asthma Model

A primate acute asthma model may be employed for the in vivo evaluation of the compounds of the invention as antiasthmatics.

Example 5

Identification of Compounds with Anti-ulcer Efficacy

The compounds of the present invention can be evaluated for their antiulcer activity according to the procedures described in Chiu, *Archives Internationales de Pharmacodynamie et de Therapie*, **1984**, 270, 128-140.

Example 6**Identification of Compounds with Activity Against Syncytial Virus Infection**

The efficacy of the compounds of the present invention in blocking cell fusion caused by a syncytial virus infection can be evaluated by the methods generally set forth in Tidwell, *J. Med. Chem.*, **1983**, 26, 294-298.

Pharmaceutical Composition Examples

The following are representative pharmaceutical formulations containing a compound of Formula I.

Tablet Formulation

The following ingredients are mixed intimately and pressed into single scored tablets.

Ingredient	Quantity per tablet, mg
compound of this invention	400
Cornstarch	50
croscarmellose sodium	25
Lactose	120
magnesium stearate	5

Capsule Formulation

The following ingredients are mixed intimately and loaded into a hard-shell gelatin capsule.

Ingredient	Quantity per tablet, mg
compound of this invention	200
lactose, spray-dried	148
magnesium stearate	2

Suspension Formulation

The following ingredients are mixed to form a suspension for oral administration.

Ingredient	Amount
compound of this invention	1.0 g
fumaric acid	0.5 g
sodium chloride	2.0 g
methyl paraben	0.15 g
propyl paraben	0.05 g
granulated sugar	25.5 g
sorbitol (70% solution)	12.85 g
Veegum K (Vanderbilt Co.)	1.0 g
Flavoring	0.035 mL

Colorings	0.5 mg
distilled water	q.s. to 100 mL

Injectable Formulation

The following ingredients are mixed to form an injectable formulation.

Ingredient	Amount
compound of this invention	1.2 g
sodium acetate buffer solution	0.4 M 2.0 mL
HCl (1 N) or NaOH (1 M)	q.s. to suitable pH
water (distilled, sterile)	q.s. to 20 mL

All of the above ingredients, except water, are combined and heated to 60-70.degree. C. with stirring. A sufficient quantity of water at 60.degree. C. is then added with vigorous stirring to emulsify the ingredients, and water then added q.s. to 100 g.

Suppository Formulation

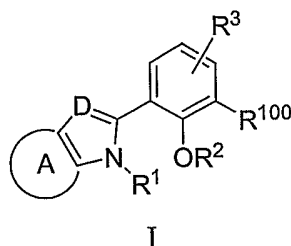
A suppository of total weight 2.5 g is prepared by mixing the compound of the invention with Witepsol.RTM. H-15 (triglycerides of saturated vegetable fatty acid; Riches-Nelson, Inc., New York), and has the following composition:

Ingredient	Quantity per tablet, mg
compound of this invention	500
Witepsol® H-15	balance

The foregoing invention has been described in some detail by way of illustration and example, for purposes of clarity and understanding. It will be obvious to one of skill in the art that changes and modifications may be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled. All patents, patent applications and publications cited in this application are hereby incorporated by reference in their entirety for all purposes to the same extent as if each individual patent, patent application or publication were so individually denoted.

WE CLAIM:

1. A Compound of Formula I:



where

A is optionally substituted benzo, optionally substituted pyridino, optionally substituted pyrimidino, optionally substituted pyrazino, or optionally substituted pyridazino;

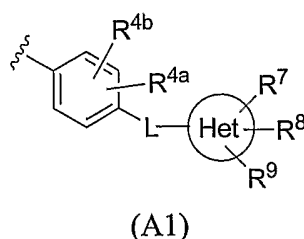
D is =N- or =CR⁶- where R⁶ is hydrogen, alkyl, halo, alkylcarbonyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkyl, alkoxyalkylalkyl, or carboxyalkyl;

R¹ is hydrogen, alkylsulfonyl, arylsulfonyl, alkoxyalkyl, or aralkyloxyalkyl;

R² is hydrogen, alkyl, alkylsulfonyl, alkylphosphonyl, or alkoxyalkyloxyalkyl;

R³ is hydrogen, alkyl, hydroxy, halo, cyano, haloalkoxy, haloalkyl, alkoxy, alkoxyalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylcarbonylamino, alkylcarbonyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonylamino, alkylaminosulfonyl, dialkylaminosulfonyl, carboxy, alkylcarbonyloxy, amino, alkylamino, dialkylamino, mercaptoalkylaminocarbonylalkyl, R^{10a}R^{10b}NC(O)NR^{10c}- (where R^{10a}, R^{10b}, and R^{10c} are independently hydrogen, alkyl, or substituted alkyl), R^{11a}R^{11b}NC(O)O- (where R^{11a} and R^{11b} are independently hydrogen, alkyl, or substituted alkyl), or R^{12a}OC(O)NR^{12b}- (where R^{12a} and R^{12b} are independently hydrogen, alkyl, or substituted alkyl);

and R¹⁰⁰ is a group of formula (A1):



where

R^{4a} and R^{4b} are independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, hydroxy, halo, alkoxy, acyl, acyloxy, acylamino, alkoxyalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl,

alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonylamino, alkylaminosulfonyl, dialkylaminosulfonyl, carboxy, alkylcarbonyloxy, amino, alkylamino, dialkylamino, mercaptoalkylaminocarbonylalkyl, $-\text{NR}^{19c}\text{C}(\text{O})\text{NR}^{19a}\text{R}^{19b}$ (where R^{19a} , R^{19b} , and R^{19c} are independently hydrogen, alkyl, or substituted alkyl), $-\text{OC}(\text{O})\text{NR}^{24a}\text{R}^{24b}$ (where R^{24a} and R^{24b} are independently hydrogen, alkyl, or substituted alkyl), or $-\text{NR}^{25b}\text{C}(\text{O})\text{OR}^{25a}$ (where R^{25a} and R^{25b} are independently hydrogen, alkyl, or substituted alkyl); and where alkyl, alkenyl, and alkynyl, either alone or as part of another group are independently optionally substituted with one, two, three, four, or five halo; and

L is $-\text{X}^1-\text{Y}^1-\text{Z}^1-$ where X^1 is alkylene, alkenylene, or cycloalkylene and where X^1 is optionally substituted by one or two substituents selected from the group consisting of halo, hydroxy, alkoxy, alkylamino, and dialkylamino; Y^1 is $-\text{O}-$, $-\text{NR}^{13}-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{O})\text{NR}^{13}-$, $-\text{NR}^{13}\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{NR}^{13}\text{C}(\text{O})-$, $-\text{S}-$, $-\text{S}(\text{O})-$, $-\text{SO}_2-$, $-\text{SO}_2\text{NR}^{13}-$, $-\text{NR}^{13}\text{SO}_2-$, $-\text{OC}(\text{O})-$, $-\text{OC}(\text{O})\text{NR}^{13}-$, $-\text{NR}^{13}\text{C}(\text{O})\text{O}-$, or $-\text{NR}^{13}\text{C}(\text{O})\text{NR}^{14}-$ (where R^{13} and R^{14} are independently hydrogen, alkyl, or substituted alkyl); and Z^1 is a bond, alkylene, alkenylene, or cycloalkylene;

L is $-\text{X}^2-$ where X^2 is alkylene, alkenylene, or cycloalkylene and is optionally substituted by one or two substituents selected from the group consisting of halo, hydroxy, alkoxy, alkylamino, and dialkylamino;

L is $-\text{Y}^2-\text{Z}^2-$ where Y^2 is $-\text{NR}^{15}-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{O})\text{NR}^{15}-$, $-\text{NR}^{15}\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{NR}^{15}\text{C}(\text{O})-$, $-\text{S}-$, $-\text{S}(\text{O})-$, $-\text{SO}_2-$, $-\text{SO}_2\text{NR}^{15}-$, $-\text{NR}^{15}\text{SO}_2-$, $-\text{OC}(\text{O})-$, $-\text{OC}(\text{O})\text{NR}^{15}-$, $-\text{NR}^{15}\text{C}(\text{O})\text{O}-$, or $-\text{NR}^{15}\text{C}(\text{O})\text{NR}^{16}-$ (where R^{15} and R^{16} are independently hydrogen, alkyl, or substituted alkyl); and where Z^2 is alkylene, alkenylene, or cycloalkylene; and

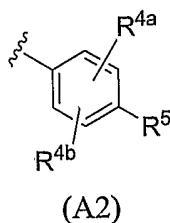
L is $-\text{Y}^3-$ where Y^3 is $-\text{NR}^{17}-$, $-\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{O})\text{NR}^{17}-$, $-\text{NR}^{17}\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{NR}^{17}\text{C}(\text{O})-$, $-\text{S}-$, $-\text{S}(\text{O})-$, $-\text{SO}_2-$, $-\text{SO}_2\text{NR}^{17}-$, $-\text{NR}^{17}\text{SO}_2-$, $-\text{OC}(\text{O})-$, $-\text{OC}(\text{O})\text{NR}^{17}-$, $-\text{NR}^{17}\text{C}(\text{O})\text{O}-$, or $-\text{NR}^{17}\text{C}(\text{O})\text{NR}^{18}-$ (where R^{17} and R^{18} are independently hydrogen, alkyl, or substituted alkyl); or

L is $-\text{X}^5-\text{Y}^{5a}-\text{Z}^5-\text{Y}^{5b}-$ where X^5 is alkylene, alkenylene, or cycloalkylene and where X^5 is optionally substituted by one or two substituents selected from the group consisting of halo, hydroxy, alkoxy, alkylamino, and dialkylamino; Y^{5a} is $-\text{O}-$, $-\text{NR}^{13}-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{O})\text{NR}^{13}-$, $-\text{NR}^{13}\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{NR}^{13}\text{C}(\text{O})-$, $-\text{S}-$, $-\text{S}(\text{O})-$, $-\text{SO}_2-$, $-\text{SO}_2\text{NR}^{13}-$, $-\text{NR}^{13}\text{SO}_2-$, $-\text{OC}(\text{O})-$, $-\text{OC}(\text{O})\text{NR}^{13}-$, $-\text{NR}^{13}\text{C}(\text{O})\text{O}-$, or $-\text{NR}^{13}\text{C}(\text{O})\text{NR}^{14}-$ (where R^{13} and R^{14} are independently hydrogen, alkyl, or substituted alkyl); Z^5 is a bond, alkylene, alkenylene, or cycloalkylene where the alkylene or alkenylene are optionally substituted with aralkyloxyalkyl; and Y^{5b} is $-\text{C}(\text{O})-$;

Het is heterocycloalkyl; and

R^7 , R^8 , and R^9 are independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, acyl, acylamino, acyloxy, acylaminoalkyloxycarbonyl, alkylthio, alkylsulfonyl, alkoxy, alkoxycarbonyl, alkoxyalkylamino, alkoxyalkylaminocarbonyl, alkoxyalkyloxy, alkoxyalkyloxycarbonyl, amino, alkylamino, dialkylamino, aminoalkyloxy, carboxy, carboxyalkylaminocarbonyl where the “alkyl” is optionally substituted with one or two hydroxy, cyano, cyanoalkylaminocarbonyl, aryl, aryloxy, arylsulfonyl, arylthioalkylcarbonyl, aralkyl where the alkyl is optionally substituted with one or two hydroxy, aralkyloxy, aralkyloxycarbonyl, aralkyloxyaminocarbonyl, aralkyloxycarbonylamino, aralkenyl, cycloalkyl, cycloalkyloxy, cycloalkylaminocarbonyl, cycloalkylalkyl where the “alkyl” is optionally substituted with one or two hydroxy, cycloalkylalkylaminocarbonyl, cycloalkylalkyloxycarbonyl, heteroaryl, heteroarylaminocarbonyl, heteroaralkyl, heteroaralkenyl, heteroaralkyloxy, halo, hydroxy, hydroxyalkyloxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, *N*-hydroxyaminocarbonyl, *N*-alkoxyaminocarbonyl, hydroxyalkylaminocarbonyl, dialkylaminoalkyloxycarbonyl, dialkylaminoalkylaminocarbonyl, arylamino, arylaminocarbonyl, alkylsulfonylamino, alkylsulfonylaminocarbonyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkyloxy, optionally substituted heterocycloalkylaminocarbonyl, optionally substituted heterocycloalkylalkyl, optionally substituted heterocycloalkylalkyloxy, optionally substituted heterocycloalkylalkyloxycarbonyl, optionally substituted heterocycloalkylalkylaminocarbonyl, aminocarbonylamino, *N*-aryl-*N*-(alkylcarbonyl)-amino, *N*-(alkylsulfonyl)-*N*-alkyl-amino, alkoxycarbonylalkylaminocarbonyl where the “alkyl” is optionally substituted with one or two hydroxy, or trialkylsilyl; or any two of R^7 , R^8 , and R^9 attached to the same carbon atom together with the carbon to which they are attached form indanylene or optionally substituted heterocycloalkylene; and where the alkyl, alkenyl, and alkynyl in R^7 , R^8 , and R^9 , either alone or part of another group, independently are optionally substituted with one, two, three, four, or five halo; or

R^{100} is a group of formula (A2):



where

R^{4a} and R^{4b} are as defined above;

R^5 is $-Y^{11}-X^{11}-Q^{11}$ where Y^{11} is $-S(O)-$, $-SO_2-$, $-NR^{26a}SO_2-$, $-SO_2NR^{26a}-$, $-C(O)NR^{26a}-$, $-NR^{26a}C(O)-$, $-OC(O)-$, $-OC(O)NR^{26a}-$, $-NR^{26a}C(O)O-$, $-C(O)NR^{26a}C(O)-$, or $-NR^{26a}C(O)NR^{26b}-$, where R^{26a} and R^{26b} are independently hydrogen, alkyl, haloalkyl, hydroxy, alkoxy, haloalkoxy, or acyl, where X^{11} is a bond, alkylene, or alkenylene, (where X^{11} is optionally substituted with hydroxy, alkoxycarbonyl, carboxy), and where Q^{11} is heteroaryl, aryl, aryloxy, or cycloalkyl;

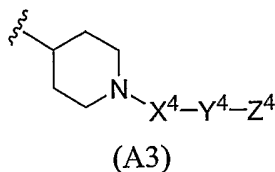
R^5 is $-X^{12a}-Y^{12}-X^{12b}-Q^{12}$ where X^{12a} is alkylene or alkenylene; Y^{12} is $-NR^{26a}-$, $-O-$, $-C(O)-$, $-C(O)O-$, $-S-$, $-S(O)-$, $-SO_2-$, $-NR^{26a}SO_2-$, $-SO_2NR^{26a}-$, $-C(O)NR^{26a}-$, $-NR^{26a}C(O)-$, $-OC(O)-$, $-OC(O)NR^{26a}-$, $-NR^{26a}C(O)O-$, $-C(O)NR^{26a}C(O)-$, or $-NR^{26a}C(O)NR^{26b}-$, where R^{26a} and R^{26b} are as defined above; X^{12b} is a bond, alkylene, or alkenylene where X^{12b} is optionally substituted with one, two, or three groups selected from hydroxy, cyano, halo, heteroaryl, alkylcarbonyl, alkoxy carbonyl, carboxy, $-NR^{27a}R^{27b}$ (where R^{27a} and R^{27b} are independently hydrogen, alkyl, alkoxy, alkoxyalkyl, heteroaryl, or heteroarylaminocarbonyl), $-C(O)NR^{28a}R^{28b}$ (where R^{28a} and R^{28b} are independently hydrogen, alkyl, alkenyl, alkoxy, alkenyloxy, alkoxyalkyl, hydroxy, or heteroaryl), and $-NR^{29a}C(O)OR^{29b}$ (where R^{29a} is hydrogen, alkyl, alkenyl, alkoxy, alkenyloxy, alkoxyalkyl, or hydroxy, and R^{29b} is alkyl); and Q^{12} is aryl, aryloxy, aralkyloxy, heteroaryl, aralkylaminocarbonyl (where the alkyl is optionally substituted with alkoxy carbonyl or carboxy), cycloalkyl, cycloalkylaminocarbonyl, cycloalkylalkyloxy, $-NR^{30a}R^{30b}$ (where R^{30a} is hydrogen or alkyl and R^{30b} is aryl, heteroaryl, or cycloalkylalkyl) or $-S(O)_n-R^{31}$ (where n is 0, 1, or 2 and R^{31} is heteroaryl, cycloalkylalkyl or aralkyl); where the alkyl within any group in Q^{12} is optionally substituted with alkoxyalkyl);

R^5 is $-X^{13}-Y^{13}-Z^{13}$ where X^{13} is alkylene or alkenylene, where Y^{13} is $-NR^{26a}$ -, $-O$ -, $-C(O)$ -, $-C(O)O$ -, $-S$ -, $-S(O)$ -, $-SO_2$ -, $-NR^{26a}SO_2$ -, $-SO_2NR^{26a}$ -, $-C(O)NR^{26a}$ -, $-NR^{26a}C(O)$ -, $-OC(O)$ -, $-OC(O)NR^{26a}$ -, $-NR^{26a}C(O)O$ -, $-C(O)NR^{26a}C(O)$ -, or $-NR^{26a}C(O)NR^{26b}$ -, where R^{26a} and R^{26b} are as defined above, and where Z^{13} is hydrogen, alkyl, or alkenyl (where Z^{13} is optionally substituted with one, two, or three halo, hydroxy, amino, alkoxy, alkoxycarbonyl, carboxy, or alkylcarbonylamino); or

R⁵ is -Y¹⁴-Z¹⁴ where Y¹⁴ is -S(O)-, -NR^{26a}C(O)-, -C(O)NR^{26a}-, -NR^{26a}C(O)NR^{26b}-, -C(O)NR^{26a}C(O)-, -NR^{26a}C(O)O-, -OC(O)NR^{26a}, or -OC(O)-, where R^{26a} and R^{26b} are as defined above, and where Z¹⁴ is alkyl or alkenyl (where Z¹⁴ is optionally substituted with one, two, or three halo, hydroxy, amino, alkoxy, alkoxycarbonyl, carboxy, or

alkylcarbonylamino); or

R^{100} is a group of formula (A3):



where

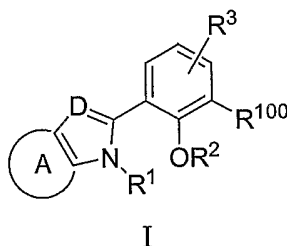
X^4 is alkylene optionally substituted with one, two, three, four, or five halo;

Y^4 is $-C(O)-$, $-NR^{32}C(O)-$, $-S(O)_2-$, or a bond;

Z^4 is heterocycloalkyl optionally substituted with one, two, three, or four groups selected from cycloalkyl, cycloalkylalkyl, alkoxycarbonyl, carboxy, aryl, aralkyl, cyano, arylcarbonyl, alkoxy, and hydroxy; or Z^4 is $-NR^{50a}R^{50b}$ where R^{50a} is hydrogen, alkyl, alkoxy, or hydroxy and R^{50b} is $-(alkylene)-aryl$ where the alkylene is optionally substituted with one or two groups selected from halo, alkoxycarbonyl, hydroxy, and carboxy;

or a pharmaceutically acceptable salt thereof.

2. A Compound of Formula I:



where

A is optionally substituted benzo, optionally substituted pyridino, optionally substituted pyrimidino, optionally substituted pyrazino, or optionally substituted pyridazino;

D is $=N-$ or $=CR^6-$ where R^6 is hydrogen, alkyl, halo, alkylcarbonyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkyl, alkoxycarbonylalkyl, or carboxyalkyl;

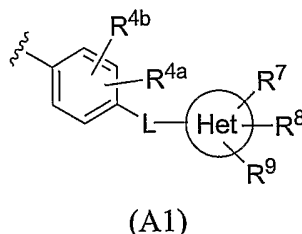
R^1 is hydrogen, alkylsulfonyl, arylsulfonyl, alkoxycarbonyl, or aralkyloxycarbonyl;

R^2 is hydrogen, alkyl, alkylsulfonyl, alkylphosphonyl, or alkoxyalkyloxyalkyl;

R^3 is hydrogen, alkyl, hydroxy, halo, cyano, haloalkoxy, haloalkyl, alkoxy, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylcarbonylamino, alkylcarbonyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonylamino, alkylaminosulfonyl, dialkylaminosulfonyl, carboxy, alkylcarbonyloxy, amino, alkylamino, dialkylamino, mercaptoalkylaminocarbonylalkyl, $R^{10a}R^{10b}NC(O)NR^{10c}-$

(where R^{10a} , R^{10b} , and R^{10c} are independently hydrogen, alkyl, or substituted alkyl), $R^{11a}R^{11b}NC(O)O-$ (where R^{11a} and R^{11b} are independently hydrogen, alkyl, or substituted alkyl), or $R^{12a}OC(O)NR^{12b}-$ (where R^{12a} and R^{12b} are independently hydrogen, alkyl, or substituted alkyl); and

R^{100} is a group of formula (A1):



where

R^{4a} and R^{4b} are independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, hydroxy, halo, alkoxy, acyl, acyloxy, acylamino, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonylamino, alkylaminosulfonyl, dialkylaminosulfonyl, carboxy, alkylcarbonyloxy, amino, alkylamino, dialkylamino, mercaptoalkylaminocarbonylalkyl, $-NR^{19c}C(O)NR^{19a}R^{19b}$ (where R^{19a} , R^{19b} , and R^{19c} are independently hydrogen, alkyl, or substituted alkyl), $-OC(O)NR^{24a}R^{24b}$ (where R^{24a} and R^{24b} are independently hydrogen, alkyl, or substituted alkyl), or $-NR^{25b}C(O)OR^{25a}$ (where R^{25a} and R^{25b} are independently hydrogen, alkyl, or substituted alkyl); and where alkyl, alkenyl, and alkynyl, either alone or as part of another group are independently optionally substituted with one, two, three, four, or five halo; and

L is $-X^1-Y^1-Z^1-$ where X^1 is alkylene, alkenylene, or cycloalkylene and where X^1 is optionally substituted by one or two substituents selected from the group consisting of halo, hydroxy, alkoxy, alkylamino, and dialkylamino; Y^1 is $-O-$, $-NR^{13}-$, $-C(O)-$, $-C(O)O-$, $-C(O)NR^{13}-$, $-NR^{13}C(O)-$, $-C(O)NR^{13}C(O)-$, $-S-$, $-S(O)-$, $-SO_2-$, $-SO_2NR^{13}-$, $-NR^{13}SO_2-$, $-OC(O)-$, $-OC(O)NR^{13}-$, $-NR^{13}C(O)O-$, or $-NR^{13}C(O)NR^{14}-$ (where R^{13} and R^{14} are independently hydrogen, alkyl, or substituted alkyl); and Z^1 is a bond, alkylene, alkenylene, or cycloalkylene;

L is $-X^2-$ where X^2 is alkylene, alkenylene, or cycloalkylene and is optionally substituted by one or two substituents selected from the group consisting of halo, hydroxy, alkoxy, alkylamino, and dialkylamino;

L is $-Y^2-Z^2-$ where Y^2 is $-NR^{15}-$, $-C(O)-$, $-C(O)O-$, $-C(O)NR^{15}-$, $-NR^{15}C(O)-$, $-C(O)NR^{15}C(O)-$, $-S-$, $-S(O)-$, $-SO_2-$, $-SO_2NR^{15}-$, $-NR^{15}SO_2-$, $-OC(O)-$, $-OC(O)NR^{15}-$,

$-\text{NR}^{15}\text{C}(\text{O})\text{O}-$, or $-\text{NR}^{15}\text{C}(\text{O})\text{NR}^{16}-$ (where R^{15} and R^{16} are independently hydrogen, alkyl, or substituted alkyl); and where Z^2 is alkylene, alkenylene, or cycloalkylene; and

L is $-\text{Y}^3-$ where Y^3 is $-\text{NR}^{17}-$, $-\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{O})\text{NR}^{17}-$, $-\text{NR}^{17}\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{NR}^{17}\text{C}(\text{O})-$, $-\text{S}-$, $-\text{S}(\text{O})-$, $-\text{SO}_2-$, $-\text{SO}_2\text{NR}^{17}-$, $-\text{NR}^{17}\text{SO}_2-$, $-\text{OC}(\text{O})-$, $-\text{OC}(\text{O})\text{NR}^{17}-$, $-\text{NR}^{17}\text{C}(\text{O})\text{O}-$, or $-\text{NR}^{17}\text{C}(\text{O})\text{NR}^{18}-$ (where R^{17} and R^{18} are independently hydrogen, alkyl, or substituted alkyl); or

L is $-\text{X}^5-\text{Y}^{5a}-\text{Z}^5-\text{Y}^{5b}-$ where X^5 is alkylene, alkenylene, or cycloalkylene and where X^5 is optionally substituted by one or two substituents selected from the group consisting of halo, hydroxy, alkoxy, alkylamino, and dialkylamino; Y^{5a} is $-\text{O}-$, $-\text{NR}^{13}-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{O})\text{NR}^{13}-$, $-\text{NR}^{13}\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{NR}^{13}\text{C}(\text{O})-$, $-\text{S}-$, $-\text{S}(\text{O})-$, $-\text{SO}_2-$, $-\text{SO}_2\text{NR}^{13}-$, $-\text{NR}^{13}\text{SO}_2-$, $-\text{OC}(\text{O})-$, $-\text{OC}(\text{O})\text{NR}^{13}-$, $-\text{NR}^{13}\text{C}(\text{O})\text{O}-$, or $-\text{NR}^{13}\text{C}(\text{O})\text{NR}^{14}-$ (where R^{13} and R^{14} are independently hydrogen, alkyl, or substituted alkyl); Z^5 is a bond, alkylene, alkenylene, or cycloalkylene where the alkylene or alkenylene are optionally substituted with aralkyloxyalkyl; and Y^{5b} is $-\text{C}(\text{O})-$;

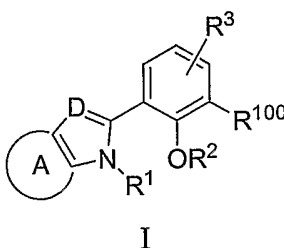
Het is heterocycloalkyl; and

R^7 , R^8 , and R^9 are independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, acyl, acylamino, acyloxy, acylaminoalkyloxycarbonyl, alkylthio, alkylsulfonyl, alkoxy, alkoxycarbonyl, alkoxyalkylamino, alkoxyalkylaminocarbonyl, alkoxyalkyloxy, alkoxyalkyloxycarbonyl, amino, alkylamino, dialkylamino, aminoalkyloxy, carboxy, carboxyalkylaminocarbonyl where the "alkyl" is optionally substituted with one or two hydroxy, cyano, cyanoalkylaminocarbonyl, aryl, aryloxy, arylsulfonyl, arylthioalkylcarbonyl, aralkyl where the alkyl is optionally substituted with one or two hydroxy, aralkyloxy, aralkyloxycarbonyl, aralkyloxyaminocarbonyl, aralkyloxycarbonylamino, aralkenyl, cycloalkyl, cycloalkyloxy, cycloalkylaminocarbonyl, cycloalkylalkyl where the "alkyl" is optionally substituted with one or two hydroxy, cycloalkylalkylaminocarbonyl, cycloalkylalkyloxycarbonyl, heteroaryl, heteroarylaminocarbonyl, heteroaralkyl, heteroaralkenyl, heteroaralkyloxy, halo, hydroxy, hydroxyalkyloxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, *N*-hydroxyaminocarbonyl, *N*-alkoxyaminocarbonyl, hydroxyalkylaminocarbonyl, dialkylaminoalkyloxycarbonyl, dialkylaminoalkylaminocarbonyl, arylamino, arylaminocarbonyl, alkylsulfonylamino, alkylsulfonylaminocarbonyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkyloxy, optionally substituted heterocycloalkylaminocarbonyl, optionally substituted heterocycloalkylalkyl, optionally substituted heterocycloalkylalkyloxy, optionally substituted

heterocycloalkylalkyloxycarbonyl, optionally substituted heterocycloalkylalkylaminocarbonyl, aminocarbonylamino, *N*-aryl-*N*-(alkylcarbonyl)-amino, *N*-(alkylsulfonyl)-*N*-alkyl-amino, alkoxycarbonylalkylaminocarbonyl where the “alkyl” is optionally substituted with one or two hydroxy, or trialkylsilyl; or any two of R^7 , R^8 , and R^9 attached to the same carbon atom together with the carbon to which they are attached form indanylene or optionally substituted heterocycloalkylene; and where the alkyl, alkenyl, and alkynyl in R^7 , R^8 , and R^9 , either alone or part of another group, independently are optionally substituted with one, two, three, four, or five halo;

or a pharmaceutically acceptable salt thereof.

3. A Compound of Formula I:



where

A is optionally substituted benzo, optionally substituted pyridino, optionally substituted pyrimidino, optionally substituted pyrazino, or optionally substituted pyridazino;

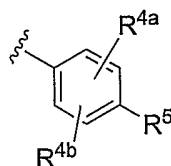
D is =N- or =CR⁶- where R⁶ is hydrogen, alkyl, halo, alkylcarbonyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkyl, alkoxycarbonylalkyl, or carboxyalkyl;

R¹ is hydrogen, alkylsulfonyl, arylsulfonyl, alkoxycarbonyl, or aralkyloxycarbonyl;

R² is hydrogen, alkyl, alkylsulfonyl, alkylphosphonyl, or alkoxyalkyloxyalkyl;

R³ is hydrogen, alkyl, hydroxy, halo, cyano, haloalkoxy, haloalkyl, alkoxy, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylcarbonylamino, alkylcarbonyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonylamino, alkylaminosulfonyl, dialkylaminosulfonyl, carboxy, alkylcarbonyloxy, amino, alkylamino, dialkylamino, mercaptoalkylaminocarbonylalkyl, R^{10a}R^{10b}NC(O)NR^{10c}- (where R^{10a}, R^{10b}, and R^{10c} are independently hydrogen, alkyl, or substituted alkyl), R^{11a}R^{11b}NC(O)O- (where R^{11a} and R^{11b} are independently hydrogen, alkyl, or substituted alkyl), or R^{12a}OC(O)NR^{12b}- (where R^{12a} and R^{12b} are independently hydrogen, alkyl, or substituted alkyl); and

R¹⁰⁰ is a group of formula (A2):



(A2)

where

R^{4a} and R^{4b} are as defined above;

R⁵ is -Y¹¹-X¹¹-Q¹¹ where Y¹¹ is -S(O)-, -SO₂-, -NR^{26a}SO₂-, -SO₂NR^{26a}-, -C(O)NR^{26a}-, -NR^{26a}C(O)-, -OC(O)-, -OC(O)NR^{26a}-, -NR^{26a}C(O)O-, -C(O)NR^{26a}C(O)-, or -NR^{26a}C(O)NR^{26b}-, where R^{26a} and R^{26b} are independently hydrogen, alkyl, haloalkyl, hydroxy, alkoxy, haloalkoxy, or acyl, where X¹¹ is a bond, alkylene, or alkenylene, (where X¹¹ is optionally substituted with hydroxy, alkoxycarbonyl, carboxy), and where Q¹¹ is heteroaryl, aryl, aryloxy, or cycloalkyl;

R⁵ is -X^{12a}-Y¹²-X^{12b}-Q¹² where X^{12a} is alkylene or alkenylene; Y¹² is -NR^{26a}-, -O-, -C(O)-, -C(O)O-, -S-, -S(O)-, -SO₂-, -NR^{26a}SO₂-, -SO₂NR^{26a}-, -C(O)NR^{26a}-, -NR^{26a}C(O)-, -OC(O)-, -OC(O)NR^{26a}-, -NR^{26a}C(O)O-, -C(O)NR^{26a}C(O)-, or -NR^{26a}C(O)NR^{26b}-, where R^{26a} and R^{26b} are as defined above; X^{12b} is a bond, alkylene, or alkenylene where X^{12b} is optionally substituted with one, two, or three groups selected from hydroxy, cyano, halo, heteroaryl, alkylcarbonyl, alkoxycarbonyl, carboxy, -NR^{27a}R^{27b} (where R^{27a} and R^{27b} are independently hydrogen, alkyl, alkoxy, alkoxyalkyl, heteroaryl, or heteroarylamino), -C(O)NR^{28a}R^{28b} (where R^{28a} and R^{28b} are independently hydrogen, alkyl, alkenyl, alkoxy, alkenyloxy, alkoxyalkyl, hydroxy, or heteroaryl), and -NR^{29a}C(O)OR^{29b} (where R^{29a} is hydrogen, alkyl, alkenyl, alkoxy, alkenyloxy, alkoxyalkyl, or hydroxy, and R^{29b} is alkyl); and Q¹² is aryl, aryloxy, aralkyloxy, heteroaryl, aralkylaminocarbonyl (where the alkyl is optionally substituted with alkoxycarbonyl or carboxy), cycloalkyl, cycloalkylaminocarbonyl, cycloalkylalkyloxy, -NR^{30a}R^{30b} (where R^{30a} is hydrogen or alkyl and R^{30b} is aryl, heteroaryl, or cycloalkylalkyl) or -S(O)_n-R³¹ (where n is 0, 1, or 2 and R³¹ is heteroaryl, cycloalkylalkyl or aralkyl); where the alkyl within any group in Q¹² is optionally substituted with alkoxyalkyl);

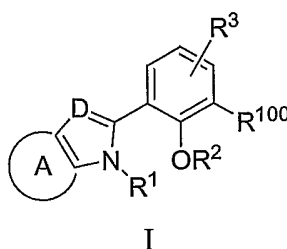
R⁵ is -X¹³-Y¹³-Z¹³ where X¹³ is alkylene or alkenylene, where Y¹³ is -NR^{26a}-, -O-, -C(O)-, -C(O)O-, -S-, -S(O)-, -SO₂-, -NR^{26a}SO₂-, -SO₂NR^{26a}-, -C(O)NR^{26a}-, -NR^{26a}C(O)-, -OC(O)-, -OC(O)NR^{26a}-, -NR^{26a}C(O)O-, -C(O)NR^{26a}C(O)-, or -NR^{26a}C(O)NR^{26b}-, where R^{26a} and R^{26b} are as defined above, and where Z¹³ is hydrogen, alkyl, or alkenyl (where Z¹³ is

optionally substituted with one, two, or three halo, hydroxy, amino, alkoxy, alkoxycarbonyl, carboxy, or alkylcarbonylamino); or

R^5 is $-Y^{14}-Z^{14}$ where Y^{14} is $-S(O)-$, $-NR^{26a}C(O)-$, $-C(O)NR^{26a}-$, $-NR^{26a}C(O)NR^{26b}-$, $-C(O)NR^{26a}C(O)-$, $-NR^{26a}C(O)O-$, $-OC(O)NR^{26a}$, or $-OC(O)-$, where R^{26a} and R^{26b} are as defined above, and where Z^{14} is alkyl or alkenyl (where Z^{14} is optionally substituted with one, two, or three halo, hydroxy, amino, alkoxy, alkoxycarbonyl, carboxy, or alkylcarbonylamino);

or a pharmaceutically acceptable salt thereof.

4. A Compound of Formula I:



where

A is optionally substituted benzo, optionally substituted pyridino, optionally substituted pyrimidino, optionally substituted pyrazino, or optionally substituted pyridazino;

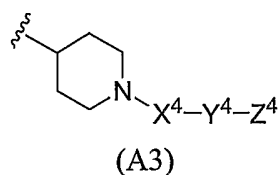
D is $=N-$ or $=CR^6-$ where R^6 is hydrogen, alkyl, halo, alkylcarbonyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkyl, alkoxycarbonylalkyl, or carboxyalkyl;

R^1 is hydrogen, alkylsulfonyl, arylsulfonyl, alkoxycarbonyl, or aralkyloxycarbonyl;

R^2 is hydrogen, alkyl, alkylsulfonyl, alkylphosphonyl, or alkoxyalkyloxyalkyl;

R^3 is hydrogen, alkyl, hydroxy, halo, cyano, haloalkoxy, haloalkyl, alkoxy, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylcarbonylamino, alkylcarbonyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonylamino, alkylaminosulfonyl, dialkylaminosulfonyl, carboxy, alkylcarbonyloxy, amino, alkylamino, dialkylamino, mercaptoalkylaminocarbonylalkyl, $R^{10a}R^{10b}NC(O)NR^{10c}-$ (where R^{10a} , R^{10b} , and R^{10c} are independently hydrogen, alkyl, or substituted alkyl), $R^{11a}R^{11b}NC(O)O-$ (where R^{11a} and R^{11b} are independently hydrogen, alkyl, or substituted alkyl), or $R^{12a}OC(O)NR^{12b}-$ (where R^{12a} and R^{12b} are independently hydrogen, alkyl, or substituted alkyl); and

R^{100} is a group of formula (A3):



where

X^4 is alkylene optionally substituted with one, two, three, four, or five halo;

Y^4 is $-C(O)-$, $-NR^{32}C(O)-$, $-S(O)_2-$, or a bond;

Z^4 is heterocycloalkyl optionally substituted with one, two, three, or four groups selected from cycloalkyl, cycloalkylalkyl, alkoxycarbonyl, carboxy, aryl, aralkyl, cyano, arylcarbonyl, alkoxy, and hydroxy; or Z^4 is $-NR^{50a}R^{50b}$ where R^{50a} is hydrogen, alkyl, alkoxy, or hydroxy and R^{50b} is $-(alkylene)-aryl$ where the alkylene is optionally substituted with one or two groups selected from halo, alkoxycarbonyl, hydroxy, and carboxy; or a pharmaceutically acceptable salt thereof.

5. The compound of Claim 1 where

A is optionally substituted benzo, optionally substituted pyrimidino, or optionally substituted pyridino;

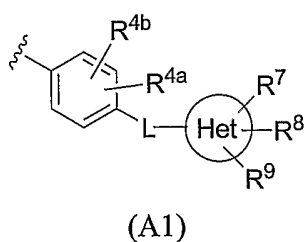
D is $=N-$ or $=CR^6-$ where R^6 is hydrogen, halo, or carboxyalkyl;

R^1 is hydrogen;

R^2 is hydrogen;

R^3 is hydrogen, halo, or mercaptoalkylaminocarbonylalkyl; and

R^{100} is a group of formula (A1):



where

R^{4a} and R^{4b} are hydrogen;

L is $-X^1-Y^1-Z^1-$ where X^1 is alkylene; Y^1 is $-C(O)-$, $-C(O)NH-$, or $-NHC(O)-$ and Z^1 is a bond, alkylene, or alkenylene;

L is $-X^2-$ where X^2 is alkylene;

L is $-Y^2-Z^2-$ where Y^2 is $-C(O)NH-$ or $-NHC(O)-$; and Z^2 is alkylene; or

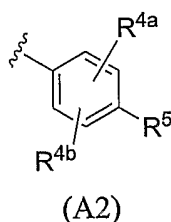
L is $-X^5-Y^{5a}-Z^5-Y^{5b}-$ where X^5 is alkylene; Y^{5a} is $-C(O)NH-$ or $-NHC(O)-$; Z^5 is alkylene where the alkylene is optionally substituted with aralkyloxyalkyl; and Y^{5b} is $-C(O)-$;

Het is piperidinyl, piperazinyl, homopiperazinyl, pyrrolidinyl, or 4-oxo-4 λ^5 -[1,4]azaphosphinanyl; and

R⁷ and R⁸ are independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, acyl, acylamino, acylaminoalkyloxycarbonyl, alkoxy carbonyl, alkoxyalkylaminocarbonyl, alkoxyalkyloxycarbonyl, amino, carboxy, carboxyalkylaminocarbonyl (where the "alkyl" is optionally substituted with one or two hydroxy), cyano, cyanoalkylaminocarbonyl, aryl, aryloxy, arylsulfonyl, arylthioalkylcarbonyl, aralkyl (where the alkyl is optionally substituted with one or two hydroxy), aralkyloxy, aralkyloxyaminocarbonyl, aralkyloxycarbonylamino, cycloalkylaminocarbonyl, cycloalkylalkyl (where the "alkyl" is optionally substituted with one or two hydroxy), cycloalkylalkylaminocarbonyl, cycloalkylalkyloxycarbonyl, heteroaryl, heteroarylaminocarbonyl, heteroaralkyl, halo, hydroxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, *N*-hydroxyaminocarbonyl, *N*-alkoxyaminocarbonyl, hydroxyalkylaminocarbonyl, dialkylaminoalkyloxycarbonyl, dialkylaminoalkylaminocarbonyl, arylamino, arylaminocarbonyl, alkylsulfonylamino, alkylsulfonylaminocarbonyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylaminocarbonyl, optionally substituted heterocycloalkylalkyl, optionally substituted heterocycloalkylalkyloxycarbonyl, optionally substituted heterocycloalkylalkylaminocarbonyl, aminocarbonylamino, *N*-aryl-*N*-(alkylcarbonyl)-amino, or alkoxy carbonylalkylaminocarbonyl (where the "alkyl" is optionally substituted with one or two hydroxy); or any two of R⁷, R⁸, and R⁹ attached to the same carbon atom together with the carbon to which they are attached form indanylene or optionally substituted heterocycloalkylene; and where the alkyl, alkenyl, and alkynyl in R⁷, R⁸, and R⁹, either alone or part of another group, independently are optionally substituted with one, two, three, four, or five halo; and

R⁹ is hydrogen; or

R¹⁰⁰ is a group of formula (A2):



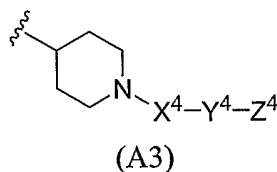
where

R^{4a} and R^{4b} are hydrogen;

R^5 is $-Y^{11}-X^{11}-Q^{11}$ where Y^{11} is $-C(O)NR^{26a}-$, $-NR^{26a}C(O)-$, $-NR^{26a}C(O)O-$, or $-NR^{26a}C(O)NR^{26b}-$, where R^{26a} and R^{26b} are independently hydrogen or hydroxy, where X^{11} is a bond, alkylene, or alkenylene, (where X^{11} is optionally substituted with hydroxy), and where Q^{11} is heteroaryl, aryl, aryloxy, or cycloalkyl; or

R^5 is $-X^{12a}-Y^{12}-X^{12b}-Q^{12}$ where X^{12a} is alkylene; Y^{12} is $-C(O)NH-$, $-NHC(O)-$, or $-NHC(O)NH-$; X^{12b} is a bond, alkylene, or alkenylene where X^{12b} is optionally substituted with one, two, or three groups selected from hydroxy, cyano, halo, heteroaryl, alkoxycarbonyl, carboxy, $-NR^{27a}R^{27b}$ (where R^{27a} and R^{27b} are independently hydrogen or alkyl), $-C(O)NR^{28a}R^{28b}$ (where R^{28a} and R^{28b} are independently hydrogen, alkyl, alkoxy, or heteroaryl), and $-NR^{29a}C(O)OR^{29b}$ (where R^{29a} is hydrogen and R^{29b} is alkyl); and Q^{12} is aryl, aryloxy, aralkyloxy, heteroaryl, aralkylaminocarbonyl (where the alkyl is optionally substituted with alkoxycarbonyl or carboxy), cycloalkyl, cycloalkylaminocarbonyl, cycloalkylalkyloxy, $-NR^{30a}R^{30b}$ (where R^{30a} is hydrogen or alkyl and R^{30b} is aryl, heteroaryl, or cycloalkylalkyl) or $-S(O)_n-R^{31}$ (where n is 0 or 2 and R^{31} is heteroaryl, cycloalkylalkyl or aralkyl); where the alkyl within any group in Q^{12} is optionally substituted with alkoxyalkyl); or

R^{100} is a group of formula (A3):



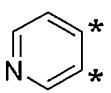
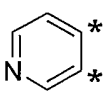
where

X^4 is alkylene;

Y^4 is $-C(O)-$;

Z^4 is heterocycloalkyl optionally substituted with one, two, three, or four groups selected from cycloalkylalkyl, alkoxycarbonyl, carboxy, aralkyl, cyano, acyl, and hydroxy; or Z^4 is $-NR^{50a}R^{50b}$ where R^{50a} is hydrogen and R^{50b} is $-(alkylene)-aryl$ where the alkylene is optionally substituted with one or two groups selected from alkoxycarbonyl, hydroxy, and carboxy.

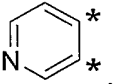
6. The Compound of Claim 1 where A is optionally substituted pyridino; D is $=CH-$; and and R^1 , R^2 , R^3 , R^{4a} and R^{4b} are hydrogen.

7. The Compound of Claim 6 where A is .
8. The Compound of Claim 2 where A is  and R¹, R², and R³ are hydrogen.
9. The Compound of Claim 2 where L is -CH₂C(O)-.
10. The Compound of Claim 2 where Het is piperidinyl, the N-oxide of piperazinyl, or 4-oxo-4λ⁵-[1,4]azaphosphinanyl (where the phosphorous atom is substituted with alkyl, aryl, aralkyl, cycloalkyl, or cycloalkylalkyl).
11. The Compound of Claim 10 where Het is piperidinyl and L is attached at the 1-position and R⁷ and R⁸ are attached at the 4-position; Het is piperazinyl and L is attached at the 1-position and R⁷ is attached at the 4-position; or Het is 4-oxo-4λ⁵-[1,4]azaphosphinanyl where the phosphorous atom is substituted with alkyl, aryl, aralkyl, cycloalkyl, or cycloalkylalkyl.
12. The Compound of Claim 11 where Het is piperidinyl where L is attached at the 1-position and R⁷ and R⁸ are attached at the 4-position.
13. The Compound of Claim 2 where R⁷ and R⁸ are independently hydrogen, optionally substituted alkyl (preferably alkyl substituted with one or two alkoxyalkyloxycarbonyl, dialkylaminoalkyloxy, hydroxy or carboxy), optionally substituted alkenyl (preferably alkenyl), alkoxycarbonyl, carboxy, aralkyl, aralkyloxy, heteroaryl, heteroaralkyl, hydroxy, alkylsulfonylaminocarbonyl, alkoxycarbonylalkylaminocarbonyl, optionally substituted heterocycloalkyl, cycloalkylalkyl, amino, acyl (preferably optionally substituted heterocycloalkylcarbonyl), alkoxyalkyloxycarbonyl, dialkylaminoalkyloxycarbonyl, optionally substituted heterocycloalkylalkyloxycarbonyl, dialkylaminoalkylaminocarbonyl, or cyano; and R⁹ is hydrogen.
14. The Compound of Claim 13 where R⁷ is hydrogen, cyano, carboxy, or alkoxycarbonyl and R⁸ is aralkyl, heteroaralkyl, or cycloalkylalkyl; and R⁹ is hydrogen.

15. The Compound of Claim 13 where R^7 is carboxy, R^8 is aralkyl, and R^9 is hydrogen; R^7 is alkoxycarbonyl, R^8 is aralkyl, and R^9 is hydrogen; R^7 is carboxy, R^8 is heteroaralkyl, and R^9 is hydrogen; R^7 is alkoxycarbonyl, R^8 is cycloalkylalkyl, and R^9 is hydrogen; R^7 is carboxy, R^8 is cycloalkylalkyl, and R^9 is hydrogen; R^7 is cyano, R^8 is cycloalkylalkyl, and R^9 is hydrogen; or R^7 and R^9 are hydrogen and R^8 is aralkyl.

16. The Compound of Claim 15 where R^7 is carboxy, R^8 is aralkyl, and R^9 is hydrogen; R^7 is carboxy, R^8 is cycloalkylalkyl, and R^9 is hydrogen; R^7 is cyano, R^8 is cycloalkylalkyl, and R^9 is hydrogen; or R^7 and R^9 are hydrogen and R^8 is aralkyl.

17. The Compound of Claim 3 where A is optionally substituted pyridino; D is =CH-; and R^1 , R^2 , R^3 , R^{4a} and R^{4b} are hydrogen.

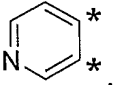
18. The Compound of Claim 17 where A is .

19. The Compound of Claim 3 where R^5 is $-Y^{11}-X^{11}-Q^{11}$ or $-X^{12a}-Y^{12}-X^{12b}-Q^{12}$.

20. The Compound of Claim 19 where R^5 is $-X^{12a}-Y^{12}-X^{12b}-Q^{12}$ and Q^{12} is aryl, aryloxy, aralkyloxy, or $-S(O)_2-R^{31}$ where R^{31} is aryl.

21. The Compound of Claim 20 where Q^{12} is phenyl, phenyloxy, phenylmethyloxy, 4-methoxyphenyl, indanyl, phenylmethylsulfonyl, or 4-chlorophenyl.

22. The Compound of Claim 4 where A is optionally substituted pyridino; D is =CH-; and R^1 , R^2 , and R^3 are hydrogen.

23. The Compound of Claim 22 where A is .

24. The Compound of Claim 4 where X^4 is $-CH_2-$ and Y^4 is $-C(O)-$.

25. The Compound of Claim 24 where Z^4 is heterocycloalkyl optionally substituted with one, two, three, or four groups selected from cycloalkyl, cycloalkylalkyl, alkoxycarbonyl, carboxy, aryl, aralkyl, cyano, arylcarbonyl, alkoxy, and hydroxy.
26. The compound named *N*-(4-iodo-pyridin-3-yl)-methanesulfonamide.
27. A method of treating a disease, disorder, or syndrome responsive to the inhibition of tryptase in an animal suffering said disease, disorder, or syndrome, comprising administering to said animal a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I.
28. The method of Claim 27 wherein said animal is human.
29. The method of Claim 27 wherein the syndrome is asthma.
30. A method of treating an immunomediated respiratory disease independently selected from the group consisting of asthma, COPD, and allergic rhinitis, in an animal which method comprises administering to said animal a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I and a pharmaceutically acceptable excipient in combination with one or more compound(s) independently selected from the group consisting of a β -2 adrenoreceptor agonist, corticosteroid, leukotriene antagonist, phosphodiesterase 4 inhibitor, and antihistamine.
31. The method of Claim 30 wherein the β -2 adrenoreceptor agonist is salmeterol or levalbuterol, the corticosteroid is budesonide or fluticasone, the leukotriene D4 antagonist is montelukast, and the phosphodiesterase 4 inhibitor is roflumilast.
32. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I and a pharmaceutically acceptable excipient.