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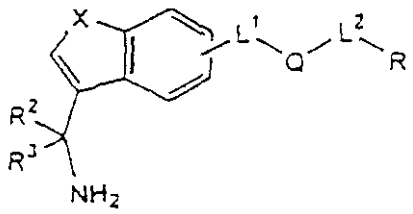
(54) Title: SUBSTITUTED (AMINOIMINOMETHYL OR AMINOMETHYL)BENZOHETEROARYL COMPOUNDS AS FACTOR XA INHIBITORS



(I)

(57) Abstract

This invention is directed to an (aminoiminomethyl or aminomethyl)benzoheteroaryl compound of formula (I): wherein X is O, S or NR^1 which is useful for inhibiting the activity of Factor Xa by combining said compound with a composition containing Factor Xa. The present invention is also directed to compositions containing compounds of formula (I), methods for their preparation, their use, such as in inhibiting the formation of thrombin or for treating a patient suffering from, or subject to, a disease state associated with a physiologically detrimental excess amount of thrombin.

SUBSTITUTED (AMINOIMINOMETHYL OR AMINOMETHYL)BENZOHETEROARYL COMPOUNDS

FIELD OF THE INVENTION

This invention is directed to substituted (aminoiminomethyl or aminomethyl)benzoheteroaryl compounds that inhibit Factor Xa, pharmaceutical compositions comprising these compounds and use of the compounds for inhibiting Factor Xa or otherwise treating a physiological condition in a patient that may be ameliorated by administering these compounds to the patient.

BACKGROUND OF THE INVENTION

Factor Xa is the penultimate enzyme in the coagulation cascade. Both free Factor Xa and Factor Xa assembled in the prothrombinase complex (Factor Xa, Factor Va, calcium and phospholipid) are inhibited by compounds of formula I. Factor Xa inhibition is obtained by direct complex formation between the inhibitor and the enzyme and is therefore independent of the plasma co-factor antithrombin III. Effective Factor Xa inhibition is achieved by administering the compounds either by oral administration, continuous intravenous infusion, bolus intravenous administration or any other parenteral route such that it achieves the desired effect of preventing the Factor Xa induced formation of thrombin from prothrombin.

Anticoagulant therapy is indicated for the treatment and prophylaxis of a variety of thrombotic conditions of both the venous and arterial vasculature. In the arterial system, abnormal thrombus formation is primarily associated with arteries of the coronary, cerebral and peripheral vasculature. The diseases associated with thrombotic occlusion of these vessels principally include acute myocardial infarction (AMI), unstable angina, thromboembolism, acute vessel closure associated with thrombolytic therapy and percutaneous transluminal coronary angioplasty (PTCA), transient ischemic attacks, stroke, intermittent claudication and bypass grafting of the coronary (CABG) or peripheral arteries. Chronic anticoagulant therapy may also be beneficial in preventing the vessel luminal narrowing (restenosis) that often occurs following PTCA and CABG, and in the maintenance of vascular access patency in long-term hemodialysis patients. With respect to the venous vasculature, pathologic thrombus formation frequently occurs in the veins of the lower extremities following abdominal, knee and hip surgery (deep vein thrombosis, DVT). DVT further predisposes the patient to a higher risk of pulmonary thromboembolism. A systemic,

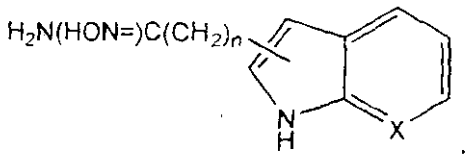
disseminated intravascular coagulopathy (DIC) commonly occurs in both vascular systems during septic shock, certain viral infections and cancer. This condition is characterized by a rapid consumption of coagulation factors and their plasma inhibitors resulting in the formation of life-threatening clots throughout the microvasculature of several organ systems.

Accumulated experimental evidence has also reflected that prothrombin activation is only one of the biological activities of Factor Xa. EPR-1 (effector cell protease receptor-1, recognizing Factor Xa), is believed to mediate several of the vascular wall interactions by Factor Xa. It has been shown to be expressed on human umbilical vein endothelial cells, rat smooth muscle cells and platelets(CR McKenzie, et al., Arterioscler Thromb Vasc Biol 16 1285-91 (1996); also F Bono, et al., J Cell Physiol 172 36-43 (1997), AC Nicholson, et al., J Biol Chem 271 28407-13 (1996),J.M. Herbert, et al., J Clin Invest 101 993-1000 (1998)). This protease-receptor interaction could mediate not only prothrombinase-catalyzed thrombin generation, but also diverse cellular functions such as cell proliferation, release of PDGF and DNA syntheses. The mitogenic effect of Factor Xa has been reported to be dependent on Factor Xa enzymatic activity (F Bono, et al., J Cell Physiol 172 36-43 (1997), J.M. Herbert, et al., J Clin Invest 101 993-1000 (1998)). TAP for example inhibited the mitogenesis of human and rat cultured vascular smooth muscle cells (F Bono, et al., J Cell Physiol 172 36-43 (1997)). In a study of the rabbit carotid artery air-drying injury model, increased EPR-1 expression was detected after vascular injury. Animals treated with the specific Factor Xa inhibitor, DX-9065a, exhibited less neointimal proliferation. The important regulatory role of Factor Xa in the coagulation process coupled with its mitogenic effects points to Factor Xa's involvement in the formation of thrombin at the luminal surface of the vessel wall and contribution to the atherothrombotic process and abnormal proliferation of vascular cells resulting in restenosis or angiogenesis.

In view of the physiological conditions discussed above related to Factor Xa, inhibitors of Factor Xa would be useful in treating those conditions and others that would be ameliorated by a Factor Xa inhibitor.

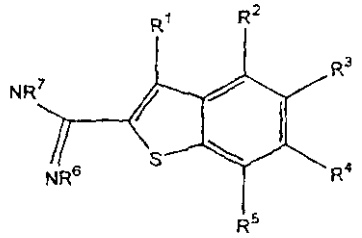
Reported Developments

H. E. Lape, et al, Arch. Int. Pharmacodyn., 171(2) 394414 (1968) disclose the following optionally alkyl substituted indole-(1 or 3)-acetamidoxime compounds wherein X is CH or N, and n is 0-2



A wide range of antihypertensive activity is noted regarding the compounds. There is no disclosure or suggestion that the acetamidoxime compounds exhibit Factor Xa activity.

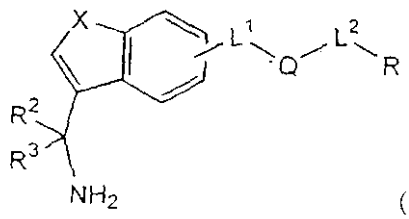
European Patent Application Publication No. 568,289 discloses the following 2-carboxamidine benzothiophene compounds wherein at least one of R^2, R^3, R^4 and R^5 is an organic group



which includes 5 or more carbons, an organic group which contains a sulfur atom or hydroxy, an unsaturated organic group or a cyclic organic group. The compounds are noted to be urokinase inhibitors. European Patent Application Publication No. 568,289 does not disclose or suggest 3-carboxamidine benzothiophene compounds or that the 2-carboxamidine benzothiophene compounds exhibit Factor Xa activity.

SUMMARY OF THE INVENTION

This invention is directed to a compound of formula I:



(I)

wherein

X is O, S or NR^1;

R is hydrogen, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, fused arylcycloalkyl, fused heteroarylcycloalkyl, fused arylcycloalkenyl, fused heteroarylcycloalkenyl, fused arylheterocyclyl, fused heteroarylheterocyclyl, fused arylheterocyclenyl, fused heteroarylheterocyclenyl, aryl, fused cycloalkenylaryl, fused cycloalkylaryl, fused heterocyclylaryl, fused heterocyclenylaryl, heteroaryl, fused cycloalkylheteroaryl, fused cycloalkenylheteroaryl, fused heterocyclenylheteroaryl or fused heterocyclylheteroaryl, provided that when L^2 is a chemical bond, then Q is attached to R through a carbon atom thereof and, when R is hydrogen then L^2 is not a chemical bond;

R^1 is hydrogen, alkyl, aralkyl, heteroaralkyl, acyl, aroyl, heteroaroyl, alkoxycarbonyl, aryloxycarbonyl or heteroaryloxycarbonyl;

R^2 and R^3 are hydrogen, or taken together are $=NR^4$;

R^4 is hydrogen, R^5O_2C-, R^5O-, HO-, cyano, R^5CO-, HCO-, lower alkyl, nitro, or R^6R^7N-;

R^5 is alkyl, aryl, heteroaryl, aralkyl, or heteroaralkyl;

R^6 and R^7 are independently hydrogen or alkyl;

L^1 is alkylene, alkenylene or alkynylene;

L^2 is a chemical bond, alkylene, alkenylene or alkynylene;

Q is $-NR^{8'}-$, -O-, -C(O)-, -C(O)-O-, -O-C(O)-, $-NR^{8'}C(X^1)-$, $-C(X^1)NR^{8'}-$, $-NR^8C(X^1)O-$, $-OC(X^1)NR^8-$, $-NR^8C(X^1)NR^8-$, $-NR^8C(X^1)NR^8-$, $-S(O)_n-$, $-NR^8SO_2-$ or $-SO_2NR^8-$, provided that a nitrogen atom or oxygen atom of Q is not directly bonded to a carbon atom of L^1 or L^2 having a double bond or triple bond, or $Q\text{-}L^2\text{-}R$ is cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, fused arylcycloalkyl, fused heteroarylcycloalkyl, fused arylcycloalkenyl, fused heteroarylcycloalkenyl, fused arylheterocyclyl, fused heteroarylheterocyclyl, fused arylheterocyclenyl, fused heteroarylheterocyclenyl, aryl, fused cycloalkenylaryl, fused cycloalkylaryl, fused heterocyclylaryl, fused heterocyclenylaryl, heteroaryl, fused cycloalkylheteroaryl, fused cycloalkenylheteroaryl, fused heterocyclenylheteroaryl or fused heterocyclylheteroaryl, provided that a nitrogen atom or oxygen atom of Q is not directly bonded to a carbon atom of L^1 having a double bond or triple bond;

X^1 is O or S;

$R^{8'}$ is hydrogen, alkyl, aralkyl, heteroaralkyl, acyl, aroyl, heteroaroyl or alkoxycarbonyl;

R^8 is hydrogen, alkyl, aralkyl, heteroaralkyl, acyl, aroyl or heteroaroyl; and

n is 0, 1 or 2, or

an oxide thereof, a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

DETAILED DESCRIPTION OF THE INVENTION

As used above, and throughout the description of the invention, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

Definitions

"Patient" includes both human and other mammals.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched having about 1 to about 15 carbon atoms in the chain. Preferred alkyl groups have 1 to about 10 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkyl chain. "Lower alkyl" means about 1 to about 4 carbon atoms in the chain which may be straight or branched. The alkyl group may be substituted by one or more halo, hydroxyl, cycloalkyl or cycloalkenyl. Representative alkyl groups include methyl, fluoromethyl, difluoromethyl, trifluoromethyl, cyclopropylmethyl, cyclopentylmethyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl, n-pentyl, 3-pentyl, heptyl, octyl, nonyl, decyl and dodecyl.

"Alkylene" means a straight or branched bivalent hydrocarbon chain having from 1 to about 10 carbon atoms. The preferred alkylene groups are the lower alkylene groups having from 1 to about 4 carbon atoms. The alkylene group may be substituted by one or more halo, hydroxy, acyl, alkoxycarbonyl or carboxy. Exemplary alkylene groups include methylene, ethylene, propylene or butylene; preferred is ethylene.

"Alkenyl" means an aliphatic hydrocarbon group containing a carbon-carbon double bond and which may be straight or branched having about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have 2 to about 10 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkenyl chain. "Lower alkenyl" means about 2 to about 4 carbon atoms in the chain which may be straight or branched. The alkenyl group may be substituted by one or more halo. Representative alkenyl groups include ethenyl, propenyl, n-butenyl, i-butenyl, 3-methylbut-2-enyl, n-pentenyl, heptenyl, octenyl and decenyl.

"Alkenylene" means a straight or branched bivalent hydrocarbon chain having a double bond and from 2 to about 10 carbon atoms. Preferred alkenylene groups are the lower alkenylene groups having from 2 to about 4 carbon atoms. The alkenylene group may be substituted by one or more halo, hydroxy, acyl,

alkoxycarbonyl or carboxy, provided the hydroxy is not substituted at a double bond thereof. Exemplary alkenylene groups include ethenylene, propenylene or butenylene.

"Alkynyl" means an aliphatic hydrocarbon group containing a carbon-carbon triple bond and which may be straight or branched having about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have 2 to about 10 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to about 4 carbon atoms in the chain which may be straight or branched. Representative alkynyl groups include ethynyl, propynyl, n-butynyl, 2-butynyl, 3-methylbutynyl, n-pentynyl, heptynyl, octynyl and decynyl.

"Alkynylene" means a straight or branched bivalent hydrocarbon chain having a double bond and from 2 to about 10 carbon atoms. Preferred alkynylene groups are the lower alkynylene groups having from 2 to about 4 carbon atoms. The alkynylene group may be substituted by one or more halo, hydroxy, acyl, alkoxycarbonyl or carboxy, provided the hydroxy is not substituted at a triple bond thereof. Exemplary alkynylene groups include ethynylene, propynylene or butynylene.

"Carboxy" means a HO(O)C- (carboxylic acid) group.

"Carboxyalkyl" means an HOOC-alkyl- group wherein the alkyl group is as defined herein. Preferred groups include carboxymethyl and carboxyethyl.

"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system of about 3 to about 10 carbon atoms, preferably of about 5 to about 10 carbon atoms. Preferred cycloalkyl rings contain about 5 to about 6 ring atoms. The cycloalkyl is optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Representative monocyclic cycloalkyl include cyclopentyl, cyclohexyl, cycloheptyl, and the like. Representative multicyclic cycloalkyl include 1-decalin, norbornyl, adamantyl, and the like.

"Cycloalkylalkyl" means a cycloalkylalkyl group wherein the cycloalkyl and alkyl groups are as herein defined. Representative cycloalkylalkyl groups include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like

"Cycloalkenyl" means a non-aromatic mono- or multicyclic ring system of about 3 to about 10 carbon atoms, preferably of about 5 to about 10 carbon atoms which contains at least one carbon-carbon double bond. Preferred cycloalkylene rings contain about 5 to about 6 ring atoms. The cycloalkenyl is optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Representative monocyclic cycloalkenyl include cyclopentenyl, cyclohexenyl, cycloheptenyl, and the like. A representative multicyclic cycloalkenyl is norbornylenyl.

"Heterocyclenyl" means a non-aromatic monocyclic or multicyclic ring system of about 3 to about ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is/are element(s) other than carbon, for example nitrogen, oxygen or sulfur atoms, and which contains at least one carbon-carbon double bond or carbon-nitrogen double bond. Preferred heterocyclenyl rings contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before heterocyclenyl means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. The heterocyclenyl is optionally substituted by one or more ring system substituents, wherein "ring system substituent" is as defined herein. The nitrogen or sulphur atom of the heterocyclenyl is optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Representative monocyclic azaheterocyclenyl groups include 4,5-dihydro-[1,2,4]oxadiazyl, 1,2,3,4- tetrahydropyridinyl, 1,2-dihydropyridyl, 1,4-dihydropyridyl, 1,2,3,6-tetrahydropyridinyl, 1,4,5,6-tetrahydropyrimidinyl, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolinyl, 2-pyrazolinyl, and the like. Representative oxaheterocyclenyl groups include 3,4-dihydro-2H-pyran, dihydrofuranyl, fluorodihydrofuranyl, 2,3-dihydropyridazinyl, 1,6-dihydrotriazinyl, and the like. A representative multicyclic oxaheterocyclenyl group is 7-oxabicyclo[2.2.1]heptenyl. Representative monocyclic thiaheterocyclenyl rings include dihydrothiophenyl, dihydrothiopyranyl, and the like. A heterocyclenyl may also be a "lactam" where the heterocyclenyl is an appropriately dioxo substituted azaheterocyclenyl, for example maleimide.

"Heterocyclyl" means a non-aromatic saturated monocyclic or multicyclic ring system of about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is/are element(s) other than carbon, for example nitrogen, oxygen or sulfur. Preferred heterocyclyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before heterocyclyl means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. The heterocyclyl is optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The nitrogen or sulphur atom of the heterocyclyl is optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Representative monocyclic heterocyclyl rings include piperidyl, 2-oxo-hexahydro-pyrimidinyl, imidazolinyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,3-dioxolanyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like. A heterocyclyl may also be a "lactam" where the heterocyclyl is an appropriately dioxo substituted azaheterocyclyl, for example succinimide.

"Heterocyclyloxy" means a heterocyclyl-O- group in which the heterocyclyl group is as previously described. Exemplary heterocyclyloxy groups include quinuclidyloxy, pentamethylenesulfideoxy,

tetrahydropyranyloxy, tetrahydrothiophenyloxy, piperidinyloxy, pyrrolidinyloxy, tetrahydrofuranyloxy or 7-oxabicyclo[2.2.1]heptanyloxy, hydroxytetrahydropyranyloxy and hydroxy-7-oxabicyclo[2.2.1]heptanyloxy.

"Heterocyclyl-alkylene-O-" means a heterocyclyl-alkylene-O- group in which the heterocyclyl and alkylene groups are as previously described. Exemplary heterocyclyl-alkylene-O- groups include pyrrolidinyl-ethoxyl, and piperidinyl-methoxyl.

"Aryl" means an aromatic monocyclic or multicyclic ring system of 6 to about 14 carbon atoms, preferably of about 6 to about 10 carbon atoms. The aryl is optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Representative aryl groups include phenyl, naphthyl, substituted phenyl or substituted naphthyl.

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system of about 5 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is/are element(s) other than carbon, for example nitrogen, oxygen or sulfur. Preferred heteroaryls contain about 5 to about 6 ring atoms. The "heteroaryl" is optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The prefix aza, oxa or thia before heteroaryl means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. A nitrogen atom of a heteroaryl is optionally oxidized to the corresponding N-oxide. Representative heteroaryls include pyrazinyl, furanyl, thienyl, pyridyl, pyrimidinyl, isoxazolyl, furanopyridyl, pyrrolopyrimidinyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl, imidazo[1,2-a]pyridine, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like.

"Fused arylcycloalkenyl" means a radical derived from a fused aryl and cycloalkenyl as defined herein by removal of hydrogen atom from the cycloalkenyl portion. Preferred fused arylcycloalkenyls are those wherein aryl is phenyl and the cycloalkenyl consists of about 5 to about 6 ring atoms. The fused arylcycloalkenyl is optionally substituted by one or more ring system substituents, wherein "ring system substituent" is as defined herein. Representative fused arylcycloalkenyl include 1,2-dihydronaphthylene, indene, and the like, in which the bond to the parent moiety is through a non-aromatic carbon atom.

"Fused cycloalkenylaryl" means a radical derived from a fused arylcycloalkenyl as defined herein by removal of hydrogen atom from the aryl portion. Representative fused cycloalkenylaryl are as described herein for a fused arylcycloalkenyl, except that the bond to the parent moiety is through an aromatic carbon atom.

"Fused arylcycloalkyl" means a radical derived from a fused aryl and cycloalkyl as defined herein by removal of a hydrogen atom from the cycloalkyl portion. Preferred fused arylcycloalkyls are those wherein aryl is phenyl and the cycloalkyl consists of about 5 to about 6 ring atoms. The fused arylcycloalkyl is optionally substituted by one or more ring system substituents, wherein "ring system substituent" is as defined herein. Representative fused arylcycloalkyl includes 1,2,3,4-tetrahydronaphthyl, and the like, in which the bond to the parent moiety is through a non-aromatic carbon atom.

"Fused cycloalkylaryl" means a radical derived from a fused arylcycloalkyl as defined herein by removal of a hydrogen atom from the aryl portion. Representative fused cycloalkylaryl are as described herein for a fused arylcycloalkyl radical, except that the bond to the parent moiety is through an aromatic carbon atom.

"Fused arylheterocyclenyl" means a radical derived from a fused aryl and heterocyclenyl as defined herein by removal of a hydrogen atom from the heterocyclenyl portion. Preferred fused arylheterocyclenyls are those wherein aryl is phenyl and the heterocyclenyl consists of about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclenyl portion of the fused arylheterocyclenyl means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. The fused arylheterocyclenyl is optionally substituted by one or more ring system substituents, wherein "ring system substituent" is as defined herein. The nitrogen or sulphur atom of the heterocyclenyl portion of the fused arylheterocyclenyl is optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Representative fused arylheterocyclenyl include 3H-indolinyl, 1H-2-oxoquinolyl, 2H-1-oxoisoquinolyl, 1,2-dihydroquinolinyl, 3,4-dihydroquinolinyl, 1,2-dihydroisoquinolinyl, 3,4-dihydroisoquinolinyl, and the like, in which the bond to the parent moiety is through a non-aromatic carbon atom.

"Fused heterocyclenylaryl" means a radical derived from a fused arylheterocyclenyl as defined herein by removal of a hydrogen atom from the aryl portion. Representative fused heterocyclenylaryl are as defined herein for a fused arylheterocyclenyl radical, except that the bond to the parent moiety is through an aromatic carbon atom.

"Fused arylheterocyclyl" means a radical derived from a fused aryl and heterocyclyl as defined herein by removal of a hydrogen atom from the heterocyclyl portion. Preferred fused arylheterocyclyls are those wherein aryl is phenyl and the heterocyclyl consists of about 5 to about 6 ring atoms. The prefix aza, oxa or thia before heterocyclyl means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. The fused arylheterocyclyl is optionally substituted by one or more ring system substituents, wherein "ring system substituent" is as defined herein. The nitrogen or sulphur atom of the heterocyclyl portion of the fused arylheterocyclyl is optionally oxidized to the corresponding N-oxide, S-oxide or S,S-

dioxide. Representative preferred fused arylheterocyclyl ring systems include phthalimide, 1,4-benzodioxane, indolinyl, 1,2,3,4-tetrahydroisoquinoline, 1,2,3,4-tetrahydroquinoline, 1H-2,3-dihydroisoindolyl, 2,3-dihydrobenz[f]isoindolyl, 1,2,3,4-tetrahydrobenz[g]isoquinolinyl, and the like, in which the bond to the parent moiety is through a non-aromatic carbon atom.

"Fused heterocyclylaryl" means a radical derived from a fused aryheterocyclyl as defined herein by removal of a hydrogen atom from the heterocyclyl portion. Representative preferred fused heterocyclylaryl ring systems are as described for fused arylheterocyclyl, except that the bond to the parent moiety is through an aromatic carbon atom. A fused heterocyclylaryl may also be a "lactam" where the heterocyclyl is an appropriately dioxo substituted azaheterocyclenyl, for example phthalimide.

"Fused heteroarylcycloalkenyl" means a radical derived from a fused heteroaryl and cycloalkenyl as defined herein by removal of a hydrogen atom from the cycloalkenyl portion. Preferred fused heteroarylcycloalkenyls are those wherein the heteroaryl and the cycloalkenyl each contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before heteroaryl means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. The fused heteroarylcycloalkenyl is optionally substituted by one or more ring system substituents, wherein "ring system substituent" is as defined herein. The nitrogen atom of the heteroaryl portion of the fused heteroarylcycloalkenyl is optionally oxidized to the corresponding N-oxide. Representative fused heteroarylcycloalkenyl include 5,6-dihydroquinolyl, 5,6-dihydroisoquinolyl, 5,6-dihydroquinoxalinyl, 5,6-dihydroquinazolinyl, 4,5-dihydro-1H-benzimidazolyl, 4,5-dihydrobenzoxazolyl, and the like, in which the bond to the parent moiety is through a non-aromatic carbon atom.

"Fused cycloalkenylheteroaryl" means a radical derived from a fused heteroarylcycloalkenyl as defined herein by removal of a hydrogen atom from the heteroaryl portion. Representative fused cycloalkenylheteroaryl are as described herein for fused heteroaylcycloalkenyl, except that the bond to the parent moiety is through an aromatic carbon atom.

"Fused heteroarylcycloalkyl" means a radical derived from a fused heteroaryl and cycloalkyl as defined herein by removal of a hydrogen atom from the cycloalkyl portion. Preferred fused heteroarylcycloalkyls are those wherein the heteroaryl thereof consists of about 5 to about 6 ring atoms and the cycloalkyl consists of about 5 to about 6 ring atoms. The prefix aza, oxa or thia before heteroaryl means that at least a nitrogen, oxygen or sulfur atom is present respectively as a ring atom. The fused heteroarylcycloalkyl is optionally substituted by one or more ring system substituents, wherein "ring system substituent" is as defined herein. The nitrogen atom of the heteroaryl portion of the fused

heteroarylcycloalkyl is optionally oxidized to the corresponding N-oxide. Representative fused heteroarylcycloalkyl include 5,6,7,8-tetrahydroquinolinyl, 5,6,7,8-tetrahydroisoquinolyl, 5,6,7,8-tetrahydroquinoxalinyl, 5,6,7,8-tetrahydroquinazolyl, 4,5,6,7-tetrahydro-1H-benzimidazolyl, 4,5,6,7-tetrahydrobenzoxazolyl, 1H-4-oxa-1,5-diazanaphthalen-2-onyl, 1,3-dihydroimidizole-[4,5]-pyridin-2-onyl, and the like, in which the bond to the parent moiety is through a non-aromatic carbon atom.

"Fused cycloalkylheteroaryl" means a radical derived from a fused heteroarylcycloalkyl as defined herein by removal of a hydrogen atom from the heteroaryl portion. Representative fused cycloalkylheteroaryl are as described herein for fused heteroarylcycloalkyl, except that the bond to the parent moiety is through an aromatic carbon atom.

"Fused heteroarylheterocyclenyl" means a radical derived from a fused heteroaryl and heterocyclenyl as defined herein by the removal of a hydrogen atom from the heterocyclenyl portion. Preferred fused heteroarylheterocyclenyls are those wherein the heteroaryl thereof consists of about 5 to about 6 ring atoms and the heterocyclenyl consists of about 5 to about 6 ring atoms. The prefix aza, oxa or thia before heteroaryl or heterocyclenyl means that at least a nitrogen, oxygen or sulfur atom is present respectively as a ring atom. The fused heteroarylheterocyclenyl is optionally substituted by one or more ring system substituents, wherein "ring system substituent" is as defined herein. The nitrogen atom of the heteroaryl portion of the fused heteroarylheterocyclenyl is optionally oxidized to the corresponding N-oxide. The nitrogen or sulphur atom of the heterocyclenyl portion of the fused heteroarylheterocyclenyl is optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Representative fused heteroarylheterocyclenyl include 7,8-dihydro[1,7]naphthyridinyl, 1,2-dihydro[2,7]naphthyridinyl, 6,7-dihydro-3H-imidazo[4,5-c]pyridyl, 1,2-dihydro-1,5-naphthyridinyl, 1,2-dihydro-1,6-naphthyridinyl, 1,2-dihydro-1,7-naphthyridinyl, 1,2-dihydro-1,8-naphthyridinyl, 1,2-dihydro-2,6-naphthyridinyl, and the like, in which the bond to the parent moiety is through a non aromatic carbon atom.

"Fused heterocyclenylheteroaryl" means a radical derived from a fused heteroarylheterocyclenyl as defined herein by the removal of a hydrogen atom from the heteroaryl portion. Representative fused heterocyclenylheteroaryl are as described herein for fused heteroarylheterocyclenyl, except that the bond to the parent moiety is through an aromatic carbon atom.

"Fused heteroarylheterocyclyl" means a radical derived from a fused heteroaryl and heterocyclyl as defined herein, by removal of a hydrogen atom from the heterocyclyl portion. Preferred fused heteroarylheterocyclyls are those wherein the heteroaryl thereof consists of about 5 to about 6 ring atoms and the heterocyclyl consists of about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heteroaryl or heterocyclyl portion of the fused heteroarylheterocyclyl means that at least a nitrogen, oxygen or sulfur

atom respectively is present as a ring atom. The fused heteroarylheterocyclyl is optionally substituted by one or more ring system substituents, wherein "ring system substituent" is as defined herein. The nitrogen atom of the heteroaryl portion of the fused heteroarylheterocyclyl is optionally oxidized to the corresponding N-oxide. The nitrogen or sulphur atom of the heterocyclyl portion of the fused heteroarylheterocyclyl is optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Representative fused heteroarylheterocyclyl include 2,3-dihydro-1H pyrrol[3,4-b]quinolin-2-yl, 1,2,3,4-tetrahydrobenz [b][1,7]naphthyridin-2-yl, 1,2,3,4-tetrahydrobenz [b][1,6]naphthyridin-2-yl, 1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indol-2yl, 1,2,3,4-tetrahydro-9H-pyrido[4,3-b]indol-2yl, 2,3,-dihydro-1H-pyrrolo[3,4-b]indol-2-yl, 1H-2,3,4,5-tetrahydroazepino[3,4-b]indol-2-yl, 1H-2,3,4,5-tetrahydroazepino[4,3-b]indol-3-yl, 1H-2,3,4,5-tetrahydroazepino[4,5-b]indol-2 yl, 5,6,7,8-tetrahydro[1,7]naphthyridinyl, 1,2,3,4-tetrhydro[2,7]naphthyridyl, 2,3-dihydro[1,4]dioxino[2,3-b]pyridyl, 2,3-dihydro[1,4]dioxino[2,3-b]pyridyl, 3,4-dihydro-2H-1-oxa[4,6]diazanaphthalenyl, 4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridyl, 6,7-dihydro[5,8]diazanaphthalenyl, 1,2,3,4-tetrahydro[1,5] naphthyridinyl, 1,2,3,4-tetrahydro[1,6]naphthyridinyl, 1,2,3,4-tetrahydro[1,7]naphthyridinyl, 1,2,3,4-tetrahydro[1,8]naphthyridinyl, 1,2,3,4-tetrahydro[2,6]naphthyridinyl, and the like, in which the bond to the parent moiety is through a non-aromatic carbon atom.

"Fused heterocyclylheteroaryl" means a radical derived from a fused heteroarylheterocyclyl as defined herein, by removal of a hydrogen atom from the heteroaryl portion. Representative fused heterocyclylheteroaryl are as described herein for fused heterarylheterocyclyl, except that the bond to the parent moiety is through an aromatic carbon atom.

"Aralkyl" means an aryl-alkyl- group in which the aryl and alkyl are as previously described. Preferred aralkyls contain a lower alkyl moiety. Representative aralkyl groups include benzyl, 2-phenethyl and naphthlenemethyl.

"Aralkenyl" means an aryl-alkenyl- group in which the aryl and alkenyl are as previously described. Preferred aralkenyls contain a lower alkenyl moiety. Representative aralkenyl groups include 2-phenethenyl and 2-naphthylethenyl.

"Aralkynyl" means an aryl-alkynyl- group in which the aryl and alkynyl are as previously described. Preferred aralkynyls contain a lower alkynyl moiety. Representative aralkynyl groups include phenacetylenyl and naphthylacetylenyl.

"Heteroaralkyl" means an heteroaryl-alkyl- group in which the heteroaryl and alkyl are as previously described. Preferred heteroaralkyls contain a lower alkyl moiety. Representative aralkyl groups include pyridylmethyl, 2-(furan-3-yl)ethyl and quinolin-3-ylmethyl.

"Heteroaralkenyl" means an heteroaryl-alkenyl- group in which the heteroaryl and alkenyl are as previously described. Preferred heteroaralkenyls contain a lower alkenyl moiety. Representative heteroaralkenyl groups include 2-(pyrid-3-yl)ethenyl and 2-(quinolin-3-yl)ethenyl.

"Heteroaralkynyl" means an heteroaryl-alkynyl- group in which the heteroaryl and alkynyl are as previously described. Preferred heteroaralkynyls contain a lower alkynyl moiety. Representative heteroaralkynyl groups include pyrid-3-ylacetylenyl and quinolin-3-ylacetylenyl.

"Hydroxyalkyl" means a HO-alkyl- group in which alkyl is as previously defined. Preferred hydroxyalkyls contain lower alkyl. Other preferred hydroxyalkyls contain more than one hydroxyl group. Representative hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl.

"Hydroxyalkylene-O-" means a HO-alkylene-O- group in which the alkylene moiety is as previously defined. Preferred hydroxyalkylene-O- groups contain lower alkylene. Representative hydroxyalkylene-O- groups include hydroxymethoxyl and 2-hydroxyethoxyl.

"Acyl" means an H-CO- or alkyl-CO- group in which the alkyl group is as previously described. Preferred acyls contain a lower alkyl. Representative acyl groups include formyl, acetyl, propanoyl, 2-methylpropanoyl, butanoyl and palmitoyl.

"Aroyl" means an aryl-CO- group in which the aryl group is as previously described. Representative groups include benzoyl and 1- and 2-naphthoyl.

"Heteroaroyl" means a heteroaryl-CO- group in which the heteroaryl group is as previously described. Representative groups include nicotinoyl and pyrrol-2-ylcarbonyl and 3-quinolinccarbonyl.

"Alkoxy" means an alkyl-O- group in which the alkyl group is as previously described. Representative alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy and heptoxy.

"Alkoxy-alkylene-O-" means an alkoxy-alkylene-O- group in which the alkoxy and alkylene groups are as previously described. Representative alkoxy-alkylene-O- groups include methoxymethoxy, methoxyethoxy, methoxy-n-propoxy, methoxy-n-butoxy and methoxyheptoxy.

"Aryloxy" means an aryl-O- group in which the aryl group is as previously described. Representative aryloxy groups include phenoxy and naphthoxy.

"Aralkyloxy" means an aralkyl-O- group in which the aralkyl groups is as previously described. Representative aralkyloxy groups include benzyloxy and 1- or 2-naphthalenemethoxy.

"Alkylthio" means an alkyl-S- group in which the alkyl group is as previously described. Representative alkylthio groups include methylthio, ethylthio, i-propylthio and heptylthio.

"Arylthio" means an aryl-S- group in which the aryl group is as previously described. Representative arylthio groups include phenylthio and naphthylthio.

"Aralkylthio" means an aralkyl-S- group in which the aralkyl group is as previously described. A representative aralkylthio group is benzylthio.

"Y^1Y^2N-" means a substituted or unsubstituted amino group, wherein Y^1 and Y^2 are as described herein. Representative groups include amino (H_2N-), methylamino, ethylmethylamino, dimethylamino and diethylamino.

"Alkoxycarbonyl" means an alkyl-O-CO- group. Representative alkoxycarbonyl groups include methoxy- and ethoxycarbonyl.

"Aryloxycarbonyl" means an aryl-O-CO- group. Representative aryloxycarbonyl groups include phenoxy- and naphthoxycarbonyl.

"Aralkoxycarbonyl" means an aralkyl-O-CO- group. A representative aralkoxycarbonyl group is benzyloxycarbonyl.

"Y^1Y^2NCO-" means a substituted or unsubstituted carbamoyl group, wherein Y^1 and Y^2 are as previously described. Representative groups are carbamoyl (H_2NCO-) and dimethylcarbamoyl (Me_2NCO-).

"$Y^1Y^2NSO_2$-" means a substituted or unsubstituted sulfamoyl group, wherein Y^1 and Y^2 are as previously described. Representative groups are sulfamoyl (H_2NSO_2-) and dimethylsulfamoyl (Me_2NSO_2-).

"Sulfo" means an HO-SO_2- group.

"Sulfoalkyl" means an HO-SO_2-alkyl- group wherein the alkyl group is as herein defined. Exemplary HO-SO_2-alkyl- groups include sulfomethyl, sulfoethyl and sulfopropyl.

"Alkylsulfonyl" means an alkyl-SO_2- group. Preferred groups are those in which the alkyl group is lower alkyl.

"Alkylsulfinyl" means an alkyl-SO- group. Preferred groups are those in which the alkyl group is lower alkyl.

"Arylsulfonyl" means an aryl-SO_2- group.

"Arylsulfinyl" means an aryl-SO- group.

"Halo" means fluoro, chloro, bromo, or iodo. Preferred are fluoro, chloro or bromo, and more preferred are fluoro or chloro.

"Ring system substituent" means a substituent which optionally replaces hydrogen on an aromatic or non-aromatic ring system. Ring system substituents are selected from the group consisting of alkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroaralkyl, heteroaralkenyl, heteroaralkynyl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, heterocyclenyloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, hydroxy-alkylene-O-, alkoxy-alkylene-O-, Y^1Y^2NCO-alkylene-O-, Y^1Y^2N-alkylene-O-, heterocyclyl-alkylene-O-, carboxy, carboxyalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, sulfo, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, heterocyclylalkyl, heterocyclenylalkyl, aryldiazo, heteroaryldiazo, amidino, 1-azaheterocyclylcarbonyl, carboxy-alkyl-, Y^1Y^2N-, Y^1Y^2N-alkyl-, (Y^1Y^2N- and hydroxy)alkyl-, Y^1Y^2N-alkenyl-, Y^1Y^2N-alkynyl-, Y^1Y^2NCO-, Y^1Y^2NCO-alkyl-, Y^1Y^2NCONH-, $Y^1Y^2NCO_2$- and $Y^1Y^2NSO_2$-, wherein Y^1 and Y^2 are independently hydrogen, alkyl, alkoxyalkyl, hydroxyalkyl, cycloalkyl, cycloalkyl-alkyl, Y^1Y^2N-alkyl, aryl, aralkyl, heteroaralkyl, heterocyclylalkyl, heterocyclenylalkyl, sulfo-alkyl-, or where the substituent is Y^1Y^2N- or Y^1Y^2N-alkyl-, then one of Y^1 and Y^2 is H-CO-, alkyl-CO-, aryl-CO-, heterocyclyl-CO-, and the other of Y^1 and Y^2 is hydrogen, alkyl, aryl, or aralkyl. When a ring system is saturated or partially saturated, the "ring system substituent" further comprises methylene (H_2C=), oxo (O=) and thioxo (S=).

"Chemical bond" means a direct bond.

"Solvate" means a physical association of a compound with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolable solvates. Representative solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule(s) is/are H_2O.

"Prodrug" means a form of the compound of formula I suitable for administration to a patient without undue toxicity, irritation, allergic response, and the like, and effective for their intended use, including ketal, ester and zwitterionic forms. A prodrug is transformed in vivo to yield the compound of formula I, for example by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A. C. S. Symposium Series, and in Edward B.

Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

"Acid protecting group" means an easily removable group which is known in the art to protect an acid group against undesirable reaction during synthetic procedures and preferably to be selectively removable. The use of acid protecting groups is well known in the art for protecting groups against undesirable reactions during a synthetic procedure and many such protecting groups are known to those skilled in the art, having been extensively used in the protection of carboxyl groups in the penicillin and cephalosporin fields, as described in U.S. Pat. No. 3,840,556 and 3,719,667, the disclosures of which are hereby incorporated herein by reference. For suitable protecting groups see T.W. Green and P.G.M.Wuts in "Protective Groups in Organic Chemistry" John Wiley and Sons, 1991. Examples of carboxylic acid protecting groups include esters such as methoxymethyl, methylthiomethyl, tetrahydropyranyl, substituted and unsubstituted phenacyl, 2,2,2-trichloroethyl, tert-butyl, cinnamyl, dialkylaminoalkyl (e.g., dimethylaminoethyl and the like), trimethylsilyl, and the like, and amides and hydrazides including N,N-dimethyl, 7-nitroindolyl, hydrazide, N-phenylhydrazide, C_1 to C_8 loweralkyl (e.g., methyl, ethyl or tertiary butyl and the like); and substituted derivatives thereof such as alkoxybenzyl or nitrobenzyl groups and the like; alkanoyloxyalkyl groups such as pivaloyloxymethyl or propionyloxymethyl and the like; aroyloxyalkyl, such as benzoyloxyethyl and the like; alkoxycarbonylalkyl, such as methoxycarbonylmethyl, cyclohexyloxy-carbonylmethyl and the like; alkoxycarbonyloxyalkyl, such as t-butyloxycarbonyloxymethyl and the like; alkoxycarbonylaminoalkyl, such as t-butyloxycarbonylaminomethyl and the like; alkylaminocarbonylaminoalkyl, such as methylaminocarbonylaminomethyl and the like; alkanoylaminoalkyl, such as acetylaminomethyl and the like; heterocycliccarbonyloxyalkyl, such as 4-methylpiperazinylcarbonyloxymethyl and the like; dialkylaminocarbonylalkyl, such as dimethylaminocarbonylmethyl and the like; (5-(loweralkyl)-2-oxo-1,3-dioxolen-4-yl)alkyl, such as (5-t-butyl-2-oxo-1,3-dioxolen-4-yl)methyl and the like; and (5-phenyl-2-oxo-1,3-dioxolen-4-yl)alkyl, such as (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methyl and the like.

"Amine protecting group" means an easily removable group which is known in the art to protect an amino group against undesirable reaction during synthetic procedures and preferably to be selectively removable. The use of amine protecting groups is well known in the art for protecting groups against undesirable reactions during a synthetic procedure and many such protecting groups are known, for example, T.H. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 2nd edition, John Wiley & Sons, New York (1991), incorporated herein by reference. Preferred amine protecting groups are acyl, including formyl, acetyl, chloroacetyl, trichloroacetyl, o-nitrophenylacetyl, o-nitrophenoxyacetyl, trifluoroacetyl,

acetoacetyl, 4-chlorobutyryl, isobutyryl, o-nitrocinnamoyl, picolinoyl, acylisothiocyanate, aminocaproyl, benzoyl and the like, and acyloxy including methoxycarbonyl, 9-fluorenylmethoxycarbonyl, 2,2,2-trifluoroethoxycarbonyl, 2-trimethylsilylethxoycarbonyl, vinyloxycarbonyl, allyloxycarbonyl, t-butyloxycarbonyl (BOC), 1,1-dimethylpropynyloxycarbonyl, benzyloxycarbonyl (CBZ), p-nitrobenzyloxycarbony, 2,4-dichlorobenzyloxycarbonyl, and the like.

"Acid labile amine protecting group" means an amine protecting group as defined above which is readily removed by treatment with acid while remaining relatively stable to other reagents. A preferred acid labile amine protecting group is tert-butoxycarbonyl (BOC).

"Hydrogenation labile amine protecting group" means an amine protecting group as defined above which is readily removed by hydrogenation while remaining relatively stable to other reagents. A preferred hydrogenation labile amine protecting group is benzyloxycarbonyl (CBZ).

"Hydrogenation labile acid protecting group" means an acid protecting group as defined above which is readily removed by hydrogenation while remaining relatively stable to other reagents. A preferred hydrogenation labile acid protecting group is benzyl.

"Thiol protecting group" means a thiol protecting group that is readily removed by some reagents while being relatively stable to other reagents. The use of thiol protecting groups is well known in the art for thiol protecting groups against undesirable reactions during a synthetic procedure and many such protecting groups are known, for example, T.H. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 2nd edition, John Wiley & Sons, New York (1991), incorporated herein by reference. Exemplary thiol protecting groups are trityl (Trt), acetamidomethyl (Acm), and the like.

"Hydroxy protecting group" means a hydroxy protecting group that is readily removed by some reagents while being relatively stable to other reagents. The use of hydroxy protecting groups is well known in the art for hydroxy protecting groups against undesirable reactions during a synthetic procedure and many such protecting groups are known, for example, T.H. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 2nd edition, John Wiley & Sons, New York (1991), incorporated herein by reference. Exemplary hydroxy protecting groups are t-butyl, benzyl, tetrahydropyranyl, and the like.

Preferred Embodiments

A preferred embodiment of the invention is a method for treating a physiological condition capable of being modulated by inhibiting the activity of Factor Xa in a patient suffering from said physiological condition by administering to the patient an effective amount of a compound of formula I .

A preferred compound aspect of the invention is a compound of formula I wherein R is aryl, heteroaryl or heterocyclyl; a more preferred R is substituted phenyl.

Another preferred compound aspect of the invention is a compound of formula I wherein R is optionally substituted (phenyl substituted phenyl), optionally substituted (heteroaryl substituted phenyl), optionally substituted (phenyl substituted heteroaryl), optionally substituted (heteroaryl substituted heteroaryl), optionally substituted (phenyl substituted cyclyoalkyl), optionally substituted (heteroaryl substituted cyclyoalkyl), optionally substituted (cyclyoalkyl substituted heteroaryl), optionally substituted (cyclyoalkyl substituted phenyl), optionally substituted (cyclyoalkyl substituted cyclyoalkyl), optionally substituted (phenyl substituted cyclyoalkenyl), optionally substituted (heteroaryl substituted cyclyoalkenyl), optionally substituted (cyclyoalkenyl substituted heteroaryl), optionally substituted (cyclyoalkenyl substituted phenyl), optionally substituted (cyclyoalkenyl substituted cyclyoalkeny), optionally substituted (phenyl substituted heterocyclyl), optionally substituted (heteroaryl substituted heterocyclyl), optionally substituted (cyclyoalkyl substituted heterocyclyl), optionally substituted (heterocyclyl substituted phenyl), optionally substituted (heterocyclyl substituted heterocyclyl), optionally substituted (phenyl substituted heterocyclenyl), optionally substituted (heteroaryl substituted heterocyclenyl), optionally substituted (cyclyoalkenyl substituted heterocyclenyl), optionally substituted (heterocyclenyl substituted phenyl), or optionally substituted (heterocyclenyl substituted heterocyclenyl), wherein the term "optionally substituted" before the term in the parenthesis, denote that the phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocyclyl, or heterocyclenyl, portions thereof could be further substituted as noted per their definitions).

A further preferred compound aspect of the invention is a compound of formula I wherein R is optionally substituted (phenyl substituted phenyl), optionally substituted (heteroaryl substituted phenyl), optionally substituted (phenyl substituted heteroaryl), optionally substituted (heteroaryl substituted heteroaryl), optionally substituted (phenyl substituted heterocyclyl), optionally substituted (heteroaryl substituted heterocyclyl), optionally substituted (cyclyoalkyl substituted heterocyclyl), optionally substituted (heterocyclyl substituted phenyl), optionally substituted (heterocyclyl substituted heterocyclyl), optionally substituted (phenyl substituted heterocyclenyl), optionally substituted (heteroaryl substituted heterocyclenyl), optionally substituted (cyclyoalkenyl substituted heterocyclenyl), optionally substituted (heterocyclenyl substituted phenyl), or optionally substituted (heterocyclenyl substituted heterocyclenyl), wherein the term "optionally substituted" before the term in the parenthesis, denote that the phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocyclyl, or heterocyclenyl, portions thereof could be further substituted as noted per their definitions).

A more preferred compound aspect of the invention is a compound of formula I wherein R is optionally substituted (phenyl substituted heteroaryl), optionally substituted (phenyl substituted heterocyclyl), and optionally substituted (phenyl substituted heterocyclenyl).

Another preferred compound aspect of the invention is a compound of formula I wherein R is optionally substituted (phenyl substituted heteroaryl), optionally substituted (phenyl substituted heterocyclyl), and optionally substituted (phenyl substituted heterocyclenyl); L^2 is bonded to said phenyl in the 1-position of the phenyl moiety and said heterocyclyl, heterocyclenyl, or heteroaryl, is bonded to said phenyl in the 4-position of the phenyl moiety.

Another preferred compound aspect of the invention is a compound of formula I wherein X is NR^1.

Another preferred compound aspect of the invention is a compound of formula I wherein R^1 is hydrogen.

Another preferred compound aspect of the invention is a compound of formula I wherein R^8 is hydrogen.

Another preferred compound aspect of the invention is a compound of formula I wherein R^2 and R^3 taken together are $=NR^4$.

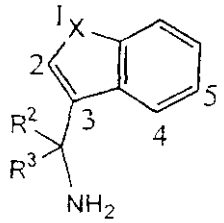
Another preferred compound aspect of the invention is a compound of formula I wherein R^4 is hydrogen or hydroxy, more preferred is hydrogen.

Another preferred compound aspect of the invention is a compound of formula I wherein R^5 is alkyl; more preferred is methyl.

Another preferred compound aspect of the invention is a compound of formula I wherein R^6 and $R^7$are hydrogen.

Another preferred compound aspect of the invention is a compound of formula I wherein L^1 is alkylene; more preferred is ethylene.

Another preferred compound aspect of the invention is a compound of formula I wherein L^1 is



bonded to the 5-position of the moiety.

Another preferred compound aspect of the invention is a compound of formula I wherein L^2 is a chemical bond or alkylene.

Another preferred compound aspect of the invention is a compound of formula I wherein L^2 is

chemical bond.

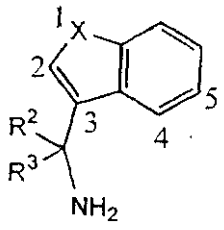
Another preferred compound aspect of the invention is a compound of formula I wherein X^1 is O.

Another preferred compound aspect of the invention is a compound of formula I wherein Q is -NR^8CO-, -$CONR^8$-, -NR^8SO_2- or -SO_2NR^8-; more preferred is -NR^8CO-.

Another preferred compound aspect of the invention is a compound of formula I R^8 and $R^{8'}$ are hydrogen.

Another preferred compound aspect of the invention is a compound of formula I wherein n is 2.

Another preferred compound aspect of the invention is a compound of formula I wherein L^1 is



bonded to the 5-position of the moiety;

R is optionally substituted (phenyl substituted pyridinonyl), optionally substituted (phenyl substituted pyrrolopyrimidinyl), optionally substituted (phenyl substituted pyridazinyl), optionally substituted (phenyl substituted pyridazinonyl), optionally substituted (phenyl substituted pyridyl), or optionally substituted (phenyl substituted pyrimidinyl).

Another preferred compound aspect of the invention is a compound of formula I wherein R is substituted (phenyl substituted pyrimidinyl), said pyrimidinyl is substituted with at least one ring system substituent selected from the group alkoxy, Y^1Y^2N-alkyl-, Y^1Y^2N-, azaheterocyclyl, Y^1Y^2NCO-alkylene-O-, azaheterocyclyl-alkylene-O-, and Y^1Y^2N-alkylene-O-; and

Y^1 and Y^2 are independently hydrogen, alkyl, alkoxyalkyl, hydroxyalkyl, cycloalkyl, cycloalkyl-alkyl, Y^1Y^2N-alkyl, aryl, aralkyl, heteroaralkyl, heterocyclylalkyl, heterocyclenylalkyl, or sulfo-alkyl-; or when Y^1 is H-CO-, alkyl-CO-, aryl-CO-, or heterocyclyl-CO-, then Y^2 is hydrogen, alkyl, aryl, or aralkyl.

Included within the scope of formula I are compounds wherein R^2 and R^3 taken together are $=NR^4$, wherein R^4 is R^5O_2C-, R^5O-, cyano, R^5CO-, optionally substituted lower alkyl, nitro, or R^6R^7N-. Such derivatives may themselves comprise the biologically active compound useful for treating a physiological condition capable of being modulated by inhibiting activity of Factor Xa by its administration to a patient suffering from said physiological condition, or may act as pro-drugs to such biologically active compounds which are formed therefrom under physiological conditions.

Species according to the invention are selected from the following:

N-(2-[3-Carbamimidoyl-5-indolyl]ethyl)-4-pyrid-3-ylbenzamide;

N-(2-[3-Carbamimidoyl-5-indolyl]ethyl)-4-(pyrimidin-5-yl)-benzamide);

5-(Pyrid-2-yl)-thiophene-2-carboxylic acid 2-(3-Carbamimidoyl-5-indolyl)ethyl amide;

N-(2-[3-Carbamimidoylindol-5-yl]ethyl)- 6-morpholin-4-ylnicotinamide4-(5-2[-{3-Carbamimidoylindol-5-yl}ethylcarbamoyl]pyridin-2-yl)piperazine-1-carboxylic acid ethyl ester;

N-(2-[3-Carbamimidoylindol-5-yl]ethyl)- 6-imidazol-1-ylnicotinamide;

N-(2-[3-Carbamimidoylindol-5-yl]ethyl)- 4-imidazol-1-ylbenzamide;

N-(2-[3-Carbamimidoylindol-5-yl]ethyl)- 4-(3H-imidazol-4-yl)benzamide;

N-(2-[3-Carbamimidoylindol-5-yl]ethyl)- 4-(1,2,4)thiadiazol-5-ylbenzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(1-carbamoyl-1-methyl-ethyl-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(1-[N-(2-methoxyethyl)]-carbamoyl-1-methyl-ethyl-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(t-butyl)-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(pyridazin-4-yl)-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-2-methyl-4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzamide

3',4'-Dimethoxybiphenyl-4-carboxylic acid (2-[3-Carbamimidoylindol-5-yl]ethyl)amide;

N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-(6-methoxypyrid-3-yl)benzamide;

N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-(1-oxy-pyrid-4-yl)benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(7H-pyrrolo[2,3-d]pyrimidin-6-yl)-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(1H-pyrrolo[3,2-c]pyridin-2-yl)-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-furo[3,2-c]pyridin-2-yl-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-3-chloro-4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzamide;

N-(2-[3-Carbamimidoyl-1H-indol-5-yl]ethyl)-4-(6-oxo-1,6-dihydro-pyrid-3-yl)benzamide;

4-(3-Amino-1,1-dimethyl-propyl)-N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-2-(4-chloro-phenyl)-acetamide;

5-chloro-thiophene-2-carboxylic acid [2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-amide;

N-(2-[3- Carbamimidoylindol-5-yl]ethyl)-6-(2-hydroxyethylamino)nicotinamide;

N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-6-(1, 2, 4)-triazol-1-ylnicotinamide;

N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-6-pyrrol-1-ylnicotinamide;

N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-6-pyrazol-1-ylnicotinamide;

N-(2-[3-Carbamimidoyl-1-methylindol-5-yl]ethyl)-4-(6-methoxypyrid-3-yl)benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-3-chloro-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-2-(3-chloro-phenyl)-acetamide;

4-(2-Aminomethyl-pyridin-4-yl)-N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-benzamide;

4-{4-[2-(3-Carbamimidoy-1H-indol-5-yl)-ethylcarbamoyl]-phenyl-pyridine-2-carboxylic acid amide;

N-[2-(3-Carbamimidoy-1H-indol-5-yl)-ethyl]-4-(2-(N,N-dimethylaminomethyl)-pyridin-4-yl)benzamide);

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(6-oxo-1,6-dihydro-pyridazin-3-yl)-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(6-methoxy-pyridazin-3-yl)-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[1-(2-dimethylamino-ethyl)-6-oxo-1,6-dihydro-pyridazin-3-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[1-(3-dimethylamino-propyl)-6-oxo-1,6-dihydro-pyridazin-3-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(2-dimethylamino-ethylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-methoxy-pyrimidin-4-yl]-benzamide;

N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-(1-[2-dimethylaminoethyl]-6-oxo-1,6-dihydropyridin-3-yl)benzamide;

N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-(1-carbamoylmethyl-6-oxo-1,6-dihydropyridin-3-yl)benzamide;

4-(3-Amino-[1,2,4]triazin-6-yl)-N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-benzamide;

4-(3-Amino-[1,2,4]triazin-5-yl)-N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]- 4-(3-oxo-2,3-dihydro-[1,2,4]triazin-6-yl)-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5yl)ethyl]-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-benzamide

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl-4-(6-oxo-piperidin-3-yl)-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(morpholin-4yl-ethylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(3-dimethylamino-propylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-([2-dimethylamino-ethyl]-methyl-amino)-pyrimidin-4-yl]-benzamide;

2-[(4-{4-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethylcarbamoyl]-phenyl}-pyrimidin-2-yl)-methyl-amino]-ethanesulfonic acid;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-{2-[methyl-(2(S),3(R),4(R),5(R),6-pentahydroxy-hexyl)-amino]-pyrimidin-4-yl}-benzamide

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-{2-[methyl-(2(S),3(R),4(S),5(R),6-pentahydroxy-hexyl)-amino]-pyrimidin-4-yl}-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(2-hydroxy-1-hydroxymethyl-ethylamino)-pyrimidin-4-yl]-benzamide;

2-[(4-{4-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethylcarbamoyl]-phenyl}-pyrimidin-2-yl)-methyl-amino]-ethanesulfonic acid;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(3-imidazol-1-yl-propylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-{2-[(2-diethylamino-ethyl)-methyl-amino]-pyrimidin-4-yl}-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(2-diisopropylamino-ethylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(2-dibutylamino-ethylamino)-pyrimidin-4-yl]-benzamide

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(3-morpholin-4-yl-propylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(3-diethylamino-propylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(3-piperidin-1-yl-propylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(2-{[2-(ethyl-methyl-amino)-ethyl]-methyl-amino}-pyrimidin-4-yl)-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(5-dimethylamino-pentylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(5-morpholin-4-yl-pentylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(5-piperidin-1-yl-pentylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(5-pyrrolidin-1-yl-pentylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(2-oxo-hexahydro-pyrimidin-5-yl)-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(1,3-dimethyl-2-oxo-hexahydro-pyrimidin-5-yl)-benzamide;

Biphenyl-3,4'-dicarboxylic acid 4'-{[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-amide} 3-[(2-methoxy-ethyl)-amide];

3'-(Morpholine-4-carbonyl)-biphenyl-4-carboxylic acid [2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-amide;

Biphenyl-3,4'-dicarboxylic acid 4'-{[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-amide} 3-[(2-morpholin-4-yl-ethyl)-amide];

Biphenyl-2,4'-dicarboxylic acid 4'-{[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-amide} 2-[(3-diethylamino-propyl)-amide];

Biphenyl-2,4'-dicarboxylic acid 4'-{[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-amide} 2-[(3-morpholin-4-yl-propyl)-amide];

Biphenyl-2,4'-dicarboxylic acid 4'-{[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-amide} 2-[(3-piperidin-1-yl-propyl)-amide];

Biphenyl-2,4'-dicarboxylic acid 4'-{[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-amide} 2-[(4-dimethylamino-butyl)-amide];

Biphenyl-2,4'-dicarboxylic acid 4'-{[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-amide} 2-[(2,3-dihydroxy-propyl)-methyl-amide];

Biphenyl-2,4'-dicarboxylic acid 4'-{[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-amide} 2-[(2,3-dihydroxy-propyl)-amide];

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(4-methylpiperazin-1-yl)pyrimidin-4-yl]benzamide;

4-[(4-{4-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethylcarbamoyl]phenyl}pyrimidin-2-yl)methylamino]butyric acid;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl]benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(2-pyrrolidin-1-ylpyrimidin-4-yl)benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(2-hydroxymethylpyrrolidin-1-yl)-pyrimidin-4-yl]benzamide ;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(carbamoylmethyl-N-methylamino)-pyrimidin-4-yl]benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(6-pyrrolidin-1-yl-hexylamino)pyrimidin-4-yl]benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(6-piperidin-1-ylhexylamino)pyrimidin-4-yl]benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(4-piperidin-1-ylbutylamino)pyrimidin-4-yl]benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(4-diethylaminobutylamino)pyrimidin-4-yl]benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(6-morpholin-4-ylhexylamino)pyrimidin-4-yl]benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(6-dimethylaminohexylamino)pyrimidin-4-yl]benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(4-dimethylaminobutylamino)pyrimidin-4-yl]benzamide;
4-[2-(Bicyclo[2;2;1]hept-2-ylamino)pyrimidin-4-yl]-N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]benzamide;
1-(4-{4-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethylcarbamoyl]phenyl}pyrimidin-2-yl)pyrrolidine-2-carboxylic acid amide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-{2-[(2-hydroxy-ethyl)-N-methylamino]pyrimidin-4-yl}benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(2-morpholin-4-yl-pyrmidin-4-yl)-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(cyclopropylmethyl-amino)-pyrimidin-4-yl]-benzamide;
N-[2-(Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-[(2-methoxy-ethyl)-methyl-amino]-pyrimidin-4-yl]-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(3-hydroxy-propylamino)-pyrimidin-4-yl]-benzamide;
N-[2-(3-Carbamimidoyl -1H-indol-5-yl)-ethyl]-4-[(2-hydroxy-ethyl)-propyl-amino]-pyrimidin-4-yl]-benzamide;
N-[2-(3-Carbamimidoyl-1H-indole-5yl)-ethyl]-4-(2-piperidin-1-yl-pyrimidin-4-yl)-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(ethyl-methyl-amino)-pyrimidin-4-yl]-benzamide;
N-[2-(3-Carbamimidoyl -1H-indol-5-yl)-ethyl]-4-[2-(4-hydroxy-piperidin-1-yl)-pyrimidin-4-yl]-benzamide;
N-[2-(3-Carbamimidoyl -1H-indol-5-yl)-ethyl]-4-[2-(2,3-dihydroxy-propylamino)-pyrimidin-4-yl]-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-[(2,3-dihydroxy-propyl)-methyl-amino]-pyrimidin-4-yl]-benzamide;
N-[2-(3-Carbamimidoyl -1H-indol-5-yl)-ethyl]-4-[2-((s)-2-methoxymethyl-pyrrolidin-1-yl)-pyrimidin-4-yl]-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(2-piperazin-1-yl-pyrimidin-4-yl)-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)- 4-[2-[2-(2-oxo-imidazolidin-1-yl)-ethylamino]-pyrimidin-4-yl]-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(3-methoxy-propylamino)-pyrimidin-4-yl]-benzamide;
4-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(2-hydroxy-ethylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(2-methoxyethoxy)-pyrimidin-4-yl]benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(1-carbamoylethoxy)pyrimidin-4-yl]benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(6-dimethylaminohexyloxy)pyrimidin-4-yl]benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(2-oxopiperidin-3-yloxy)pyrimidin-4-yl]benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(2-pyrrolidin-1-yl-ethoxy)pyrimidin-4-yl]benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(2-dimethylaminoethoxy)pyrimidin-4-yl]benzamide;
3'-(2-Dimethylaminoethoxy)biphenyl-4-carboxylic acid [2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]amide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-(1-oxypyridin-2-yl)benzamide;
2'-(2-Dimethylaminoethoxy)biphenyl-4-carboxylic acid [2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]amide;
2'-(3-Dimethylaminopropoxy)biphenyl-4-carboxylic acid [2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]amide;
3'-(3-Dimethylaminopropoxy)biphenyl-4-carboxylic acid [2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]amide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(1-oxo-pyridin-3-yl)-benzamide;
4-[2-(acetylamino-methyl)-pyridin-4-yl]-N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-benzamide;
Piperidine-4-carboxylic acid (4-[4-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethylcarbamoyl]-phenyl-]-pyridin-2-ylmethyl)-amide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[1-(3-dimethylaminopropyl)-6-oxo-1,6-dihydropyridin-3-yl]benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[6-(3-dimethylaminopropoxy)pyridin-3-yl]benzamide;
(5-{4-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethylcarbamoyl]phenyl}-2-oxo-2H-pyridin-1-yl)acetamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-{1-[(2-dimethylaminoethylcarbamoyl)methyl]-6-oxo-1,6-dihydropyridin-3-yl}benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(4-dimethylamino-piperidin-1-yl)-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[4-(2-dimethylamino-ethylamino)-piperidin-1-yl]-benzamide;
4-(4-Amino-piperidin-1-yl)-N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(4-methoxy-piperidin-1-yl)-benzamide;
4-(4-Acetylamino-piperidin-1-yl)-N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-benzamide;
4-(1-Acetyl-piperidin-4-yl)-N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-benzamide;
4-{4-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethylcarbamoyl]-phenyl}-piperidine-1-carboxylic acid amide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(1-methyl-1-oxy-piperidin-4-yl)-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(1-methyl-piperidin-4-yl)-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(1-methanesulfonyl-piperidin-4-yl)-benzamide;

4-(2-Acetylamino-1,1-dimethyl-ethyl)-N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(2-methanesulfonylamino-1,1-dimethyl-ethyl)-benzamide;
Piperidine-4-carboxylic acid (2-{4-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethylcarbamoyl]-phenyl}-2-methyl-propyl)-amide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(1,1-dimethyl-2-ureido-ethyl)-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(3-ethyl-ureido)-1,1-dimethyl-ethyl]-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(2-dimethylamino-3,4,5,6-tetrahydro-pyrimidin-4-yl)-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(1-oxy-pyridin-4-yloxy)-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(1-methyl-piperidin-4-yloxy)-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-(1,2,3,6-tetrahydropyridin-4-yl)-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-piperidin-4-yl-benzamide;
4-(2-Amino-1,1-dimethylethyl)-N-(2-[3-Carbamimidoylindol-5-yl]ethyl)benzamide;
N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-(6-[2-dimethylaminoethoxy]pyridin-3-yl)benzamide;
N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-pyrid-4-ylbenzamide;
N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-(4-carbamoyl-phenyl)-benzamide;
N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-(4-methoxy-phenyl)-benzamide;
N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-(5-methoxy-indol-2-yl)-carboxamide;
N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-(6-chloro-benzothiophen-2-yl)-carboxamide;
N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-(4-benzyloxy-phenyl)-benzamide;
N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-chloro-benzamide;
N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-(methylsulphonyl)-benzamide;
N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-(amino-sulphonyl)-benzamide;
4-(3-Aminoprop-1-ynyl)-N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-benzamide;
5-{4-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethylcarbamoyl]phenyl}-2-oxo-2H-pyridin-1-yl)acetic acid; and
3-Carbamimidoyl-5-{2-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzoylamino]-propyl}-indole.

More preferred species according to the invention are compounds:
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(pyridazin-4-yl)-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-2-methyl-4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzamide;
N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-(6-methoxypyrid-3-yl)benzamide;
N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-(1-oxy-pyrid-4-yl)benzamide;

N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(7H-pyrrolo[2,3-d]pyrimidin-6-yl)-benzamide;
N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(1H-pyrrolo[3,2-c]pyridin-2-yl)-benzamide;
N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-3-chloro-4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzamide;
N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-(6-oxo-1,6-dihydropyrid-3-yl)benzamide;
4-(3-Amino-1,1-dimethyl-propyl)-N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-benzamide;
4-(2-Aminomethyl-pyridin-4-yl)-N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-benzamide;
4-{4-[2-(3-Carbamimidoy-1H-indol-5-yl)-ethylcarbamoyl]-phenyl-pyridine-2-carboylic acid amide;
N-[2-(3-Carbamimidoy-1H-indol-5-yl-ethyl]-4-(2-(N,N-dimethylaminomethyl)-pyridin-4-yl)benzamide);
N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(6-oxo-1,6-dihydro-pyridazin-3-yl)-benzamide;
N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(6-methoxy-pyridazin-3-yl)-benzamide;
N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[1-(2-dimethylamino-ethyl)-6-oxo-1,6-dihydro-pyridazin-3-yl]-benzamide;
N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[1-(3-dimethylamino-propyl)-6-oxo-1,6-dihydro-pyridazin-3-yl]-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(2-dimethylamino-ethylamino)-pyrimidin-4-yl]-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-methoxy-pyrimidin-4-yl]-benzamide;
N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-(1-[2-dimethylaminoethyl]-6-oxo-1,6-dihydropyridin-3-yl)benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl-4-(6-oxo-piperidin-3-yl)-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(morpholin-4yl-ethylamino)-pyrimidin-4-yl]-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(3-dimethylamino-propylamino)-pyrimidin-4-yl]-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-([2-dimethylamino-ethyl]-methyl-amino)-pyrimidin-4-yl]-benzamide;
2-[(4-{4-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethylcarbamoyl]-phenyl}-pyrimidin-2-yl)-methyl-amino]-ethanesulfonic acid;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-{2-[methyl-(2(S),3(R),4(R),5(R),6-pentahydroxy-hexyl)-amino]-pyrimidin-4-yl}-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-{2-[methyl-(2(S),3(R),4(S),5(R),6-pentahydroxy-hexyl)-amino]-pyrimidin-4-yl}-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(2-hydroxy-1-hydroxymethyl-ethylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(3-imidazol-1-yl-propylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-{2-[(2-diethylamino-ethyl)-methyl-amino]-pyrimidin-4-yl}-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(2-diisopropylamino-ethylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(2-dibutylamino-ethylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(3-morpholin-4-yl-propylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(3-diethylamino-propylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(3-piperidin-1-yl-propylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(2-{[2-(ethyl-methyl-amino)-ethyl]-methyl-amino}-pyrimidin-4-yl)-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(5-dimethylamino-pentylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(5-morpholin-4-yl-pentylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(5-piperidin-1-yl-pentylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(5-pyrrolidin-1-yl-pentylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(2-oxo-hexahydro-pyrimidin-5-yl)-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(1,3-dimethyl-2-oxo-hexahydro-pyrimidin-5-yl)-benzamide;

Biphenyl-3,4'-dicarboxylic acid 4'-{[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-amide} 3-[(2-methoxy-ethyl)-amide];

Biphenyl-3,4'-dicarboxylic acid 4'-{[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-amide} 3-[(2-morpholin-4-yl-ethyl)-amide];

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(4-methylpiperazin-1-yl)pyrimidin-4-yl]benzamide;

4-[(4-{4-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethylcarbamoyl]phenyl}pyrimidin-2-yl)methylamino]butyric acid;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl]benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(2-pyrrolidin-1-ylpyrimidin-4-yl)benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(2-hydroxymethylpyrrolidin-1-yl)-pyrimidin-4-yl]benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(carbamoylmethyl-N-methylamino)-pyrimidin-4-yl]benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(6-pyrrolidin-1-yl-hexylamino)pyrimidin-4-yl]benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(6-piperidin-1-ylhexylamino)pyrimidin-4-yl]benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(4-piperidin-1-ylbutylamino)pyrimidin-4-yl]benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(4-diethylaminobutylamino)pyrimidin-4-yl]benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(6-morpholin-4-ylhexylamino)pyrimidin-4-yl]benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(6-dimethylaminohexylamino)pyrimidin-4-yl]benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(4-dimethylaminobutylamino)pyrimidin-4-yl]benzamide;

4-[2-(Bicyclo[2;2;1]hept-2-ylamino)pyrimidin-4-yl]-N-[2-(3-carbamimidoyl-1H-indol-5-yl)ethyl]benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-{2-[(2-hydroxy-ethyl)-N-methylamino]pyrimidin-4-yl}benzamide;

N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(2-morpholin-4-yl-pyrmidin-4-yl)-benzamide;

N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(cyclopropylmethyl-amino)-pyrimidin-4-yl]-benzamide;

N-[2-(carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-[(2-methoxy-ethyl)-methyl-amino]-pyrimidin-4-yl]-benzamide;

N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(3-hydroxy-propylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-carbamimidoyl -1H-indol-5-yl)-ethyl]-4-[(2-hydroxy-ethyl)-propyl-amino]-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indole-5yl)-ethyl]-4-(2-piperidin-1-yl-pyrimidin-4-yl)-benzamide;

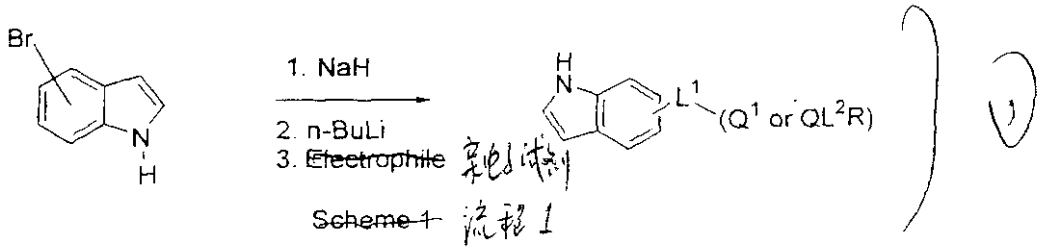
N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(ethyl-methyl-amino)-pyrimidin-4-yl]-benzamide;
N-[2-(3-carbamimidoyl -1H-indol-5-yl)-ethyl]-4-[2-(4-hydroxy-piperidin-1-yl)-pyrimidin-4-yl]-benzamide;
N-[2-(3-carbamimidoyl -1H-indol-5-yl)-ethyl]-4-[2-(2,3-dihydroxy-propylamino)-pyrimidin-4-yl]-benzamide;
N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-[(2,3-dihydroxy-propyl)-methyl-amino]-pyrimidin-4-yl]-benzamide;
N-[2-(3-carbamimidoyl -1H-indol-5-yl)-ethyl]-4-[2-((s)-2-methoxymethyl-pyrrolidin-1-yl)-pyrimidin-4-yl]-benzamide;
N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(2-piperazin-1-yl-pyrimidin-4-yl)-benzamide;
N-[2-(3-carbamimidoyl-1H-indol-5-yl)- 4-[2-[2-(2-oxo-imidazolidin-1-yl)-ethylamino]-pyrimidin-4-yl]-benzamide;
N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(3-methoxy-propylamino)-pyrimidin-4-yl]-benzamide;
4-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(2-hydroxy-ethylamino)-pyrimidin-4-yl]-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(2-methoxyethoxy)-pyrimidin-4-yl]benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(1-carbamoylethoxy)pyrimidin-4-yl]benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(6-dimethylaminohexyloxy)pyrimidin-4-yl]benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(2-pyrrolidin-1-yl-ethoxy)pyrimidin-4-yl]benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(2-dimethylaminoethoxy)pyrimidin-4-yl]benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-(1-oxypyridin-2-yl)benzamide;
2'-(2-Dimethylaminoethoxy)biphenyl-4-carboxylic acid [2-(3-carbamimidoyl-1H-indol-5-yl)ethyl]amide;
2'-(3-Dimethylaminopropoxy)biphenyl-4-carboxylic acid [2-(3-carbamimidoyl-1H-indol-5-yl)ethyl]amide;
N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(1-oxo-pyridin-3-yl)-benzamide;
4-[2-(acetylamino-methyl)-pyridin-4-yl]-N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-benzamide;
Piperidine-4-carboxylic acid (4-[4-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethylcarbamoyl]-phenyl-]-pyridin-2-ylmethyl)-amide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[1-(3-dimethylaminopropyl)-6-oxo-1,6-dihydropyridin-3-yl]benzamide;
4-(2-Amino-1,1-dimethylethyl)-N-(2-[3-carbamimidoylindol-5-yl]ethyl)benzamide; and
N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-pyrid-4-ylbenzamide.

It is to be understood that this invention covers all appropriate combinations of the particular and preferred groupings referred to herein.

Compounds of formula I may be prepared by the application or adaptation of known methods, by which is meant methods used heretofore or described in the literature, or by methods according to the invention described herein.

One aspect of this invention involves the syntheses of variously substituted indole, benzofuran and benzothiophene heterocycles. These syntheses are achieved, for example, by functionalization of specific precursors followed by ring synthesis or by derivatization of a preformed ring system. There are numerous approaches to the synthesis and functionalization of the aforementioned heterocycles in the chemical literature (For reviews, see (a) Katritzky, A.R.; Rees, C.W.; Scriven, E.F.V. Eds. Comprehensive Heterocyclic Chemstry II, Vol 2, 119, 607. Elsevier Science 1996 and references therein. (b) Ketcha, D.M. Prog. Heterocycl. Chem. 1997, 9, 97 and references therein. (c) Hughes, D. L. Org. Prep. Proced. Int. 1993, 25, 607).

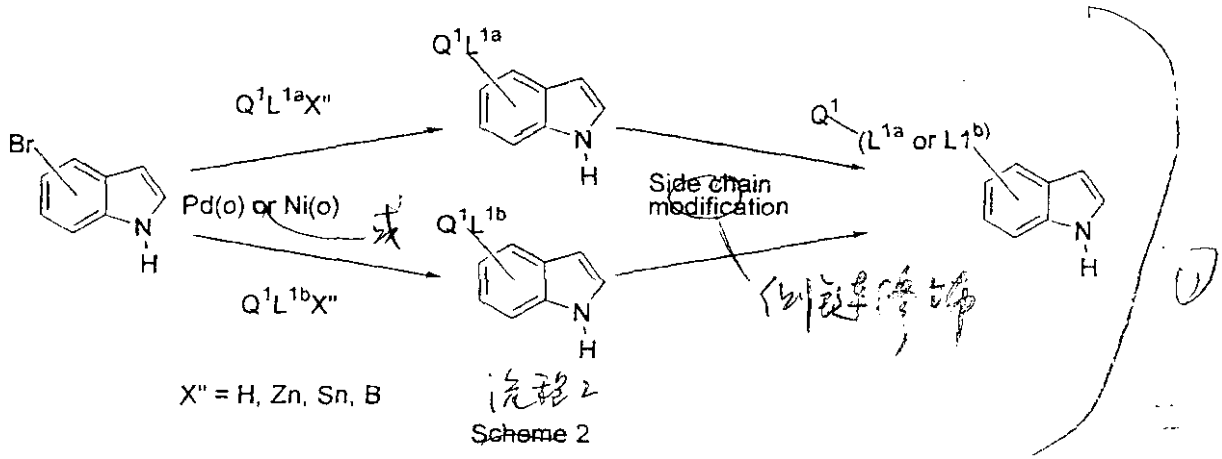
A particularly useful preparative method according to the invention is outlined in Scheme 1. Bromo-indoles can be metalated using sodium hydride or other strong base at or around room temperature followed by treatment (at lower temperature, typically below 0 °C) with an alkyl lithium reagent. Suitable solvents for this method include THF or diethyl ether, either alone or as mixtures with additives such as HMPA, TMEDA or DABCO. The resulting nucleophile is then reacted with a variety of appropriately functionalized/substituted and/or protected electrophiles, for example, such as aldehydes, ketones, alkyl halides, oxiranes, aziridines, ,β-unsaturated carbonyls or ,β-unsaturated esters (Scheme 1) to provide indoles substituted with a variety of functionalized/substituted and/or protected side chains, i.e., wherein Q^1 is -NR^8P^1, -OP^1, -C(O)(H or alkyl), -C(O)-OP^1 or -SP^1, wherein P^1 is hydrogen or a protecting group as defined herein. (For representative examples see Moyer, M.P.; Shiurba, J.F.; Rapaport, H. J. Org. Chem., 1986, 51, 5106).



Scheme 1

Alternatively, as shown in Scheme 2, bromo-indoles are reacted with terminal olefins ($Q^1L^{1b}H$, wherein Q^1 is as defined herein and L^{1b} is an alkenylene having at least a terminal double bond), terminal acetylenes ($Q^1L^{1a}H$, wherein Q^1 is as defined herein and L^{1a} is an alkynylene having at least a terminal triple

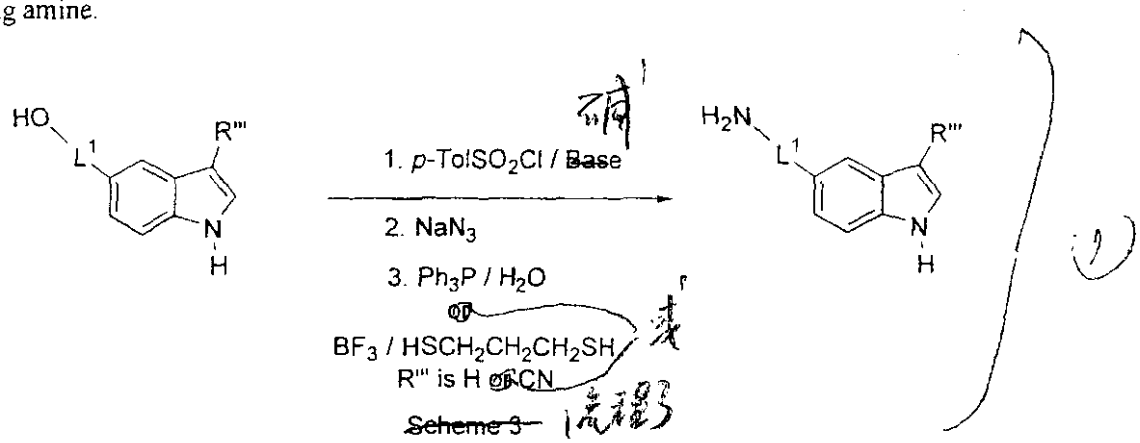
bond), or metalated derivatives thereof (particularly zinc tin and boron), under palladium or nickel catalysis (for examples see J. Tsuji, Palladium Reagents and Catalysts, J. Wiley Publications, 1996. Also Harrington, P.J.; Hegedus, L.S. J. Org. Chem., 1984, 49, 2657), with or without a base, to produce vinyl or acetylenic substituted indoles. The choice of catalyst depends on the substrate employed but is most commonly tetrakistriphenylphosphine palladium, bis(triphenylphosphine)palladium chloride, 1,1'-bis(diphenylphosphino)ferrocene / bis-dibenzylideneacetone palladium or 1,2 bis-(diphenylphosphino)-ethane / bis(acetonitrile)dichloropalladium. In certain cases, addition of a copper (I) salt as co-catalyst is also required (Rossi, R.; Carpita, A.; Bellina, F. Org. Prep. Proced. Int. 1995, 27, 127). These coupling reactions are performed in various solvents, including toluene, THF, DME, DMSO, DMF, dimethylacetamide and HMPA, at about 20 to about 150 °C.



Scheme 2

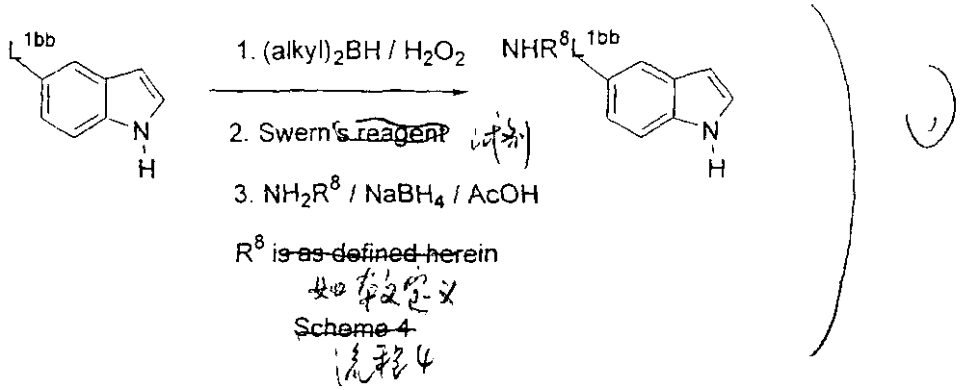
The indole side chains incorporated as described above, can contain, or be converted to, a variety of functional groups (using one or more steps) including amines, alcohols, aldehydes, ketones, carboxylic acids, esters, olefins, amides, imides, urethanes, carbamates, sulfonamides, sulfones, sulfoxides and sulfides. These interconversions employ standard synthetic methods described in the chemical literature (For example, see Larock, C.L. Comprehensive Organic Transformations, VCH Publishers 1989 and Greene, T.W.; Wuts, P.G.M. Protective Groups in Organic Synthesis, John Wiley Publications 1991). In particular, an alcohol in the indole side chain is converted, for example, to the corresponding amine by a sequence (Scheme 3) involving treatment with toluenesulfonyl chloride / DMAP and a base such as triethylamine or diisopropylethylamine in a solvent such as dichloromethane, DMF or pyridine at about room temperature. Alternatively, the alcohol is treated with NBS / Ph_3P, NCS / Ph_3P, I_2 / Ph_3P / imidazole. CBr_4 / Ph_3P to provide the corresponding alkyl halide (For a review see Castro, B.R. Org. React., 1983, 29, 1). The product

is then reacted with sodium azide in a solvent such as DMF, dimethyl acetamide, DMPU or ethanol at about 20 to about 80 °C. The resulting azide is then reduced with a reagent such as triphenylphosphine / water in THF or boron trifluoride etherate / 1,3-propane-dithiol in a solvent such as dichloromethane to the corresponding amine.



Scheme 3

An amino moiety can also be introduced into the indole side chain (Scheme 4) by conversion of an appropriate side chain alkene double bond (L^{1bb} is an alkenylene having at least a double bond at the terminal end thereof distal to its attachment to the indole moiety), first to an alcohol, using a hydroboration oxidation sequence, (For examples see (a) Beletskaya, I; Pelter, A. Tetrahedron, 1997, 53, 4957 and references therein. (b) Brown, H.C.; Kramer, G.W.; Levy, M.B.; Midland, M.M., Organic Synthesis via Boranes, Wiley Interscience, N.Y. 1973.), then oxidation of the alcohol to the corresponding ketone using any of a number of common oxidation reagents such as Swern's reagent. (For a review, see Hudlicky, T. Oxidations in Organic Chemistry, ACS Publications 1990) and finally reductive amination of the ketone (Abdel-Magid, A.F.; Maryanoff, C. A. Reductions in Organic Synthesis, ACS Symp. Ser., 641, p201, ACS Publications 1996) with an appropriate amine and a reducing agent such as sodium cyanoborohydride or sodium triacetoxyborohydride in a solvent such as methanol, THF, acetonitrile, HMPA, or water either alone or as cosolvents. In certain cases, the amine moiety may be part of the indole side chain, in which case, a heterocyclyl can be formed.

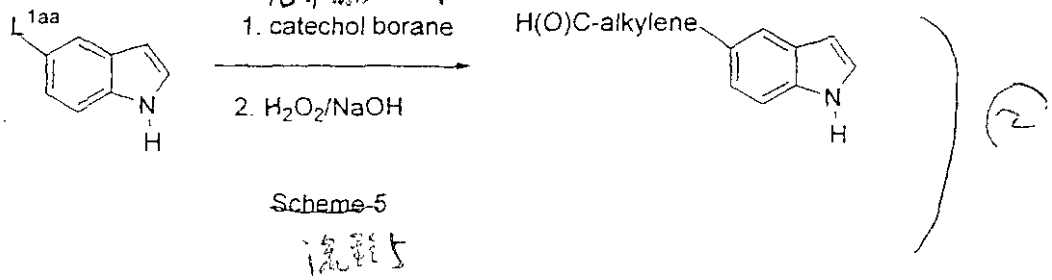


R8 is as defined herein

Scheme 4

Another convenient method for introduction of an amino moiety into the side chain involves treatment of a side chain carboxylic acid with diphenylphosphoryl azide and a base such as triethylamine, diisopropylamine in a solvent such as dichloromethane or THF toluene or benzene usually at about 0 °C to about room temperature. (For a review, see Banthrope, The Chemistry of the Azido Group, S. Patai Ed. Wiley Interscience N.Y. 1971). Subsequent thermolysis of the resulting acyl azide at about room temperature to about 140 °C in the presence of an alcohol such as t-butanol, benzyl alcohol or allyl alcohol provides the corresponding carbamate which can be cleaved to the amine using standard protecting group chemistry. Thermolysis of the acyl azide in the absence of an alcohol produces the corresponding isocyanate which may be subsequently reacted with a variety of amines to provide urethanes (for a modification which also provides a convenient preparation of secondary amines see Pfister, J.R.; Wymann, W.E. Synthesis, 1983, 38). Alternatively, a urethane may be incorporated by reaction of a side chain amino moiety with an appropriate isocyanate.

According to Scheme 5, a ketone may also be incorporated into the side chain by hydroboration of an appropriate alkyne (L^{1aa} is an alkynylene having at least a triple bond at the terminal end thereof distal to its attachment to the indole moiety) with catechol borane in a solvent such as THF at about room temperature to about 67 °C, followed by oxidative cleavage of the resulting product with hydrogen peroxide in the presence of a base such as sodium hydroxide.



Scheme 5

An imide moiety may be incorporated by reaction of a side chain alcohol with a preformed, N-unsubstituted-imide using Mitsunobu's reagent (Mitsunobu. O., Synthesis, 1981, 1, an imide, so formed, can also be converted to the corresponding amine by treatment with hydrazine in a solvent such as ethanol). Alternatively, the imide group may be introduced by acylation of a side chain amide with an acid chloride (or an activated ester) in the presence of a base such as sodium hydride.

An amide linkage may be introduced into the indole side chain by reaction of an amine (incorporated using a method such as described above) with a carboxylic acid. Suitable conditions for effecting this transformation involve activation of the acid with a reagent such as thionyl chloride, isopropyl chloroformate, oxalylchloride / DMF, TBTU, DCC, DICC / HOBT, CDI, BOP, EEDQ or PyBroP (For reviews see (a) Blackburn, C.; Kates, S. A. Methods Enzymol. 1997, 289, 175. (b) Bodanszky, M.; Trost, B.M. Principles of Peptide Synthesis 2nd Ed., Springer Verlag, N.Y. 1993) usually in the presence of a base such as triethylamine, diisopropylethylamine and / or DMAP in a solvent such as dichloromethane, DMF, dimethylacetamide or DMPU at about or above room temperature. The reverse orientation of the amide unit may be prepared by reaction of an indole side chain containing an acid moiety with an amine. An acid moiety may be formed in the side chain by oxidation of a side chain alcohol, first to the aldehyde, then oxidation of the aldehyde to the corresponding carboxylic acid. A particularly suitable reagent for this transformation is sodium chlorate (Lidgren, B.O.; Hilsson, T. Acta. Chem. Scand. 1973, 58, 238). Alternatively, an aldehyde may be generated by oxidation of an olefin using osmium tetroxide with a co-catalyst such as sodium periodate in a solvent such as THF / water or t-butanol / water. A carboxylic acid may also be obtained by hydrolysis of the corresponding ester using standard protecting group methodology.

A sulfonamide linkage may be introduced into the side chain by reaction of a side chain amino functionality with a sulfonyl chloride in the presence of a base such as pyridine, triethylamine, diisopropylethylamine or sodium hydroxide in a solvent such as dichloromethane, pyridine, DMF or an alcohol such as ethanol or isopropanol. The reverse orientation of the sulfonamide linkage may be produced by the method of Liskamp (Moree, W. J.; Van der Marel, G.A.; Liskamp, R.J. J. Org. Chem. 1995, 60, 1995.) from a side chain thioacetate. The thioacetate moiety may be prepared by displacement of a halide or sulfonate with sodium thioacetate in a solvent such as DMF, DMPU, HMPA or DMSO.

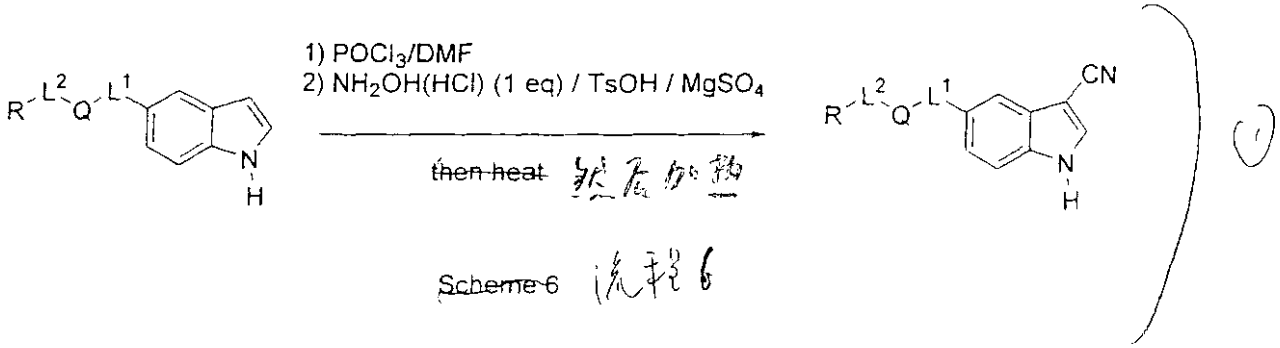
A sulfide linkage may be incorporated into the side chain by saponification of the thioacetate functional group followed by alkylation of the resulting thiol with an appropriate alkyl halide, or sulfonate(such as tosylate, triflate or mesylate). Alternatively, the sulfide linkage may be incorporated by direct reaction of a side chain alkyl chloride, bromide, iodide, tosylate or mesylate with a thiolate ion in a

solvent such as benzene, DMF, DMPU, HMPA or DMSO. In certain cases, a sulfide can be formed from an appropriate disulfide and a side chain alcohol in the presence of tributylphosphine in a solvent such as THF.

The sulfoxide and sulfone linkages may be introduced by mild oxidation of the sulfides with a reagent such as m-chloroperbenzoic acid in dichloromethane chloroform or benzene at about or below room temperature.

An ether linkage (for a review see Comprehensive Organic Chemistry Vol 1, p 799, Ed. Barton, D.; Ollis, W.D., Pergamon Press, 1979) may be prepared from a side chain alcohol and an alkyl halide, sulfonate or unsaturated ketone derivative and a base such as sodium hydride potassium hydride in a solvent such as DMF DMSO THF DMPU or HMPA. Alternatively, an ether linkage may be obtained using a side chain alkyl halide, sulfonate or ,β-unsaturated ketone and an appropriate alcohol under the same conditions. Another method of ether formation involves formation of a thiono-ester from a side chain ester or lactone by reaction with a thionating reagent, such as Lawesson's reagent (For a review see Cava, M. P.; Levinson, M. I. Tetrahedron (1985), 41(22), 5061-87), followed by reduction of the thiono group with a hydride reducing agent such as tributyltin hydride, usually in the presence of a free radical initiator such as AIBN.

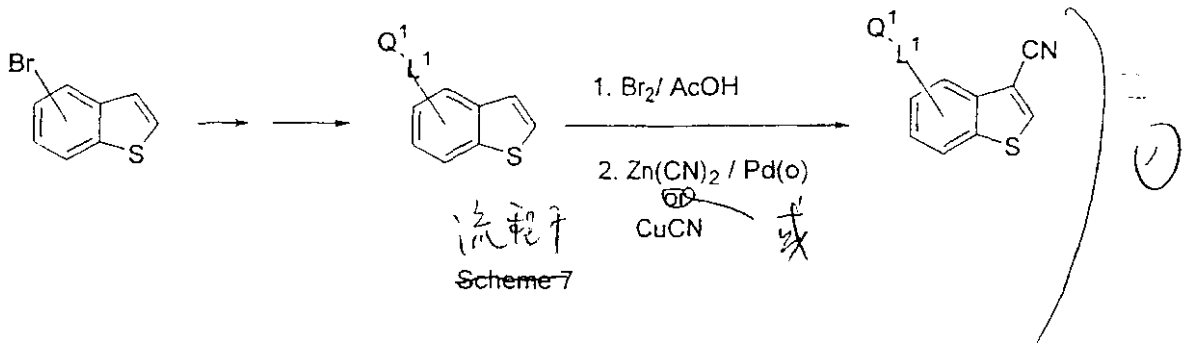
Introduction of a nitrile at C-3 of the indole ring system (Scheme 6) may be accomplished by first formylation at C-3 using a reagent combination such as phosphorous oxychloride in DMF, at or above room temperature, followed by conversion of the resulting aldehyde to the corresponding oxime with hydroxylamine hydrochloride in a solvent such as toluene or xylene in the presence of a catalyst such as toluene sulfonic acid and a desiccant such as magnesium sulfate according to the method of Ganbao and Palomo (Ganbao, I.; Palomo, C. Syn. Commun. 1983, 13, 219. For alternatives to this procedure see Wang, E-C.; Lin, G-J. Tetrahedron Lett. 1998, 39, 4047 and references therein) Heating the oxime with these reagents at about 80 °C to about 150 °C then results in dehydration to form the corresponding nitrile. In certain favorable cases, the formylation conditions described above also result in conversion of a side chain alcohol into the corresponding alkyl chloride.



Scheme 6

Introduction of the C-3 nitrile, as described above, may be carried out either before or after derivatization of the side chain(s) at other positions on the indole ring depending on the nature of the functionality present.

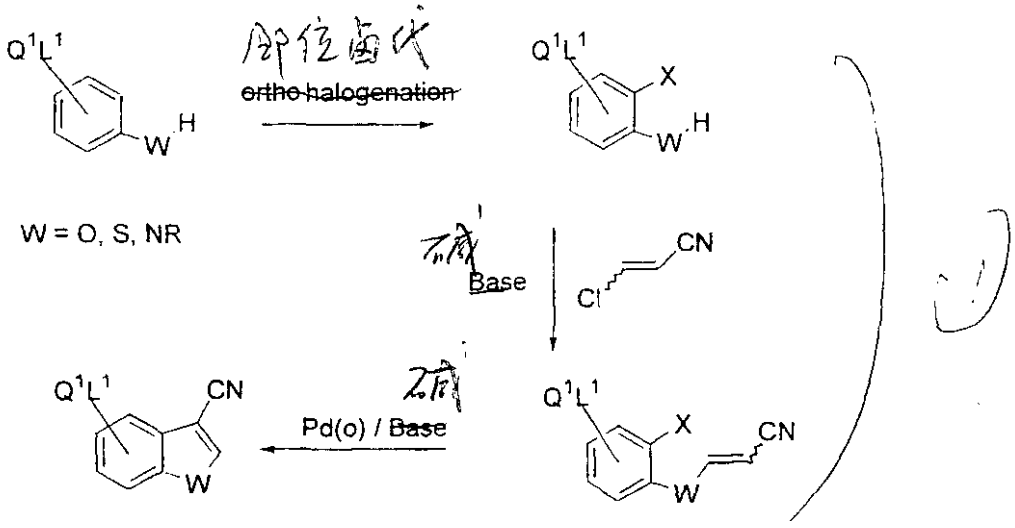
Another embodiment of this invention involves the use of a benzothiophene in place of an indole scaffold. A variety of methods can be applied to the synthesis of benzothiophenes (for examples see Katritzky, A.R.; Rees, C.W.; Scriven, E.F.V. Eds. Comprehensive Heterocyclic Chemistry II, Vol. 2, p 607, Elsevier Science 1996 and references therein). A particularly useful protocol with reference to the current invention is outlined in Scheme 7. Starting from an appropriate bromo-thiophenol, alkylation of the thiol with bromo-acetaldehyde diethyl acetal in the presence of a base such as NaH in a solvent such as DMF, THF, TBTU, DMSO or HMPA followed by cyclization with an acid such as polyphosphoric acid provides the corresponding bromo-benzothiophene (for examples see Titus, R.L.; Choi, M.; Hutt, M.P. J. Heterocycl. Chem. 1967, 4, 651. and Clark, P.D.; Kirk, A.; Yee, J.G.K. J. Org. Chem. 1995, 60, 1936). This structure may be manipulated using many of the same procedures used to install and functionalize the side chain of the indole scaffold described above. Introduction of a nitrile at C-3 of the benzothiophene ring may be effected by treatment with bromine in a solvent such as acetic acid or chloroform. The resulting 3-bromo-benzothiophene can then be converted to the 3-cyano- derivative using zinc cyanide and a palladium catalyst, preferably tetrakis(triphenylphosphine) palladium(o) in DMF at about 70°C to about 90 °C.



Scheme 7

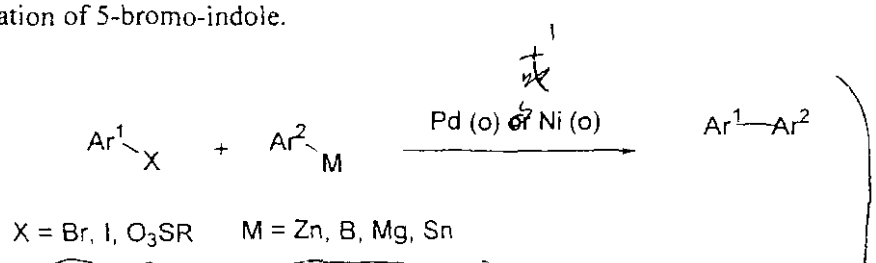
In certain cases, it is convenient to prepare a specifically substituted heteroaryl scaffold by direct ring synthesis. A particularly suitable ring synthesis protocol employs an adaptation of the method of Yamanaka (Sakamoto, K.; Nagano, T.; Kondo, Y.; Yamanaka, H. Synthesis, 1990, 215). In this approach, an appropriately substituted aniline, thiophenol or phenol is first brominated or more preferably, iodinated ortho to the nitrogen / sulfur / oxygen substituent on the ring (Scheme 8). Suitable reagents for effecting this transformation include bromine in the presence of either acid (such as acetic acid) or a base (such as sodium acetate, sodium carbonate, triethylamine or pyridine), iodine or iodine monochloride in the presence of a soft Lewis acid such as silver sulfate or a base such as calcium carbonate, morpholine, dimethylamine or

pyridine. Suitable solvents for this process include water, methanol, ethanol or dichloromethane at about or below room temperature. Addition of the acrylonitrile functionality to the ring heteroatom can be effected following the procedures of Scotti and Frazza (Scotti, F.; Frazza, E.J. J. Org. Chem., 1964, 29, 1800)



Scheme 8

A particular embodiment of the current invention employs indoles / benzothiophenes / benzofurans substituted with a side chain which contains (aryl or heteroaryl)-substituted aryl or heteroaryl appendages. These latter structural motifs can be prepared by cross coupling (Scheme 9) of an appropriately substituted (heteroaryl or aryl)halide or triflate with a (heteroaryl or aryl)aryl organometallic (most commonly zinc, boron, magnesium and tin derivatives) under catalysis by Pd(o) or Ni(o) employing conditions described above for derivatization of 5-bromo-indole.

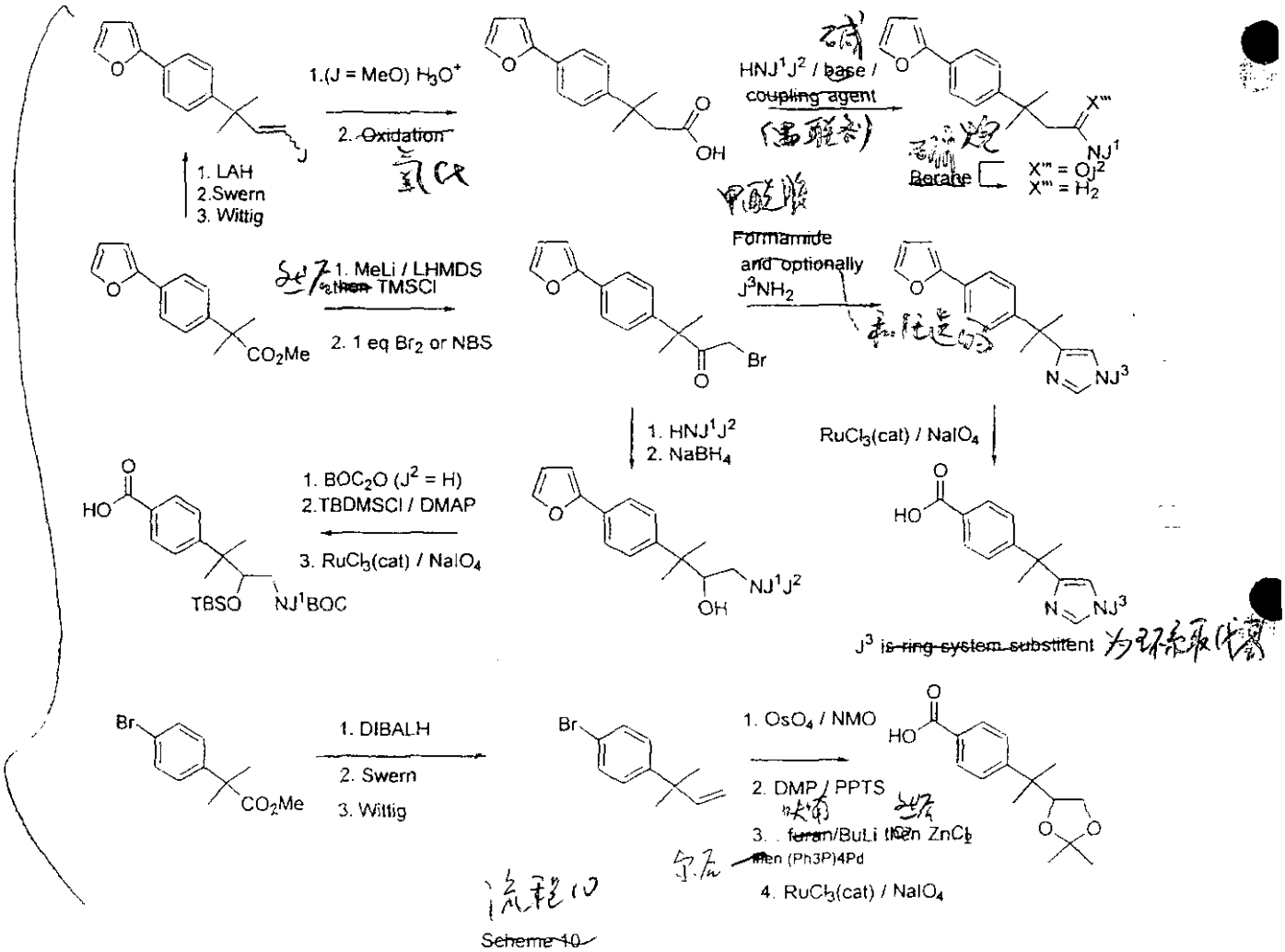


Scheme 9

Aryl and heteroaryl substituted heterocycles can also be prepared by direct ring synthesis. A wide variety of methods and conditions for this kind of process are known in the chemical literature (for

examples see(a) Katritzky, A.R.; Rees, C.W.; Scriven, E.F.V. Eds. Comprehensive Heterocyclic Chemstry II, Elsevier Science 1996).

In another embodiment of this invention the indole / benzothiophene / benzofuran side chain is substituted with a substituted aryl group. One particularly useful aryl substitution comprises of a 1,1-dimethyl alkyl chain further substituted with a heteroatom, a heteroatom cluster (such as a diol or amino-alcohol) or a heteroaryl (such as imidazole). These systems can be prepared from 2-(4-furan-2-yl-phenyl)-2-methyl-propionic acid methyl ester or 2-(4-bromo-phenyl)-2-methyl-propionic acid methyl ester a shown in scheme 10.

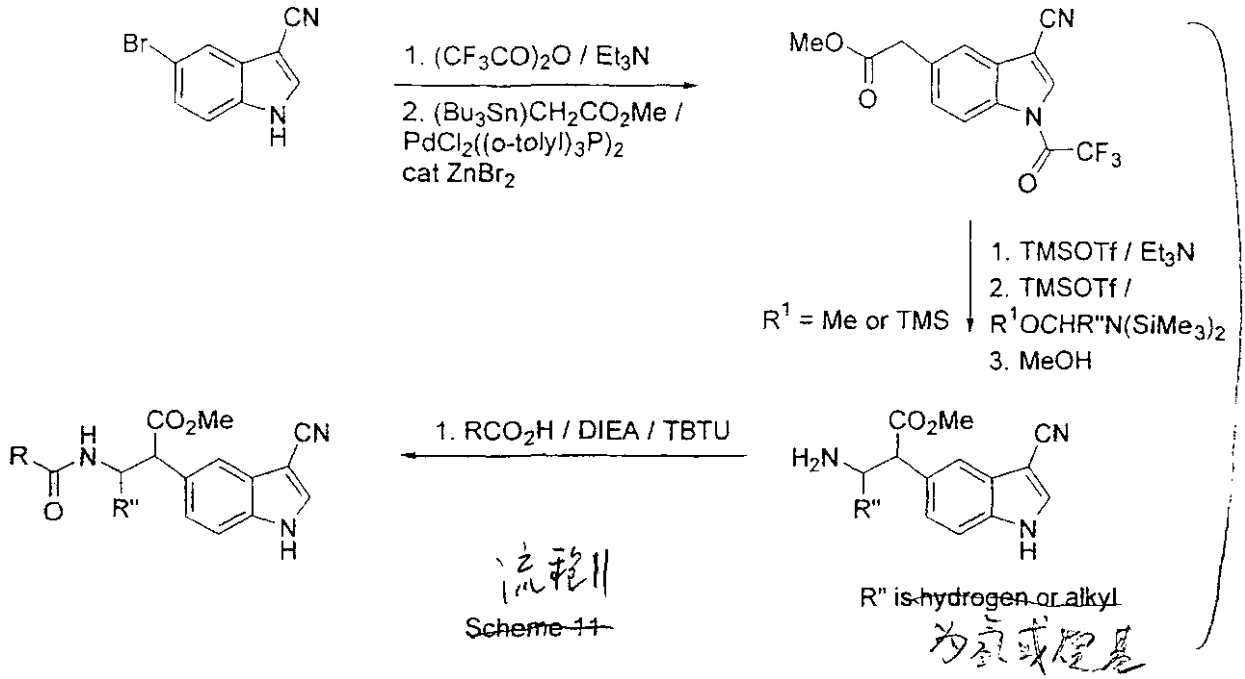


Scheme 10

Treatment of 2-(4-furan-2-yl-phenyl)-2-methyl-propionic acid methyl ester with methyl lithium in the presence of lithium hexamethyldisilazide at about or below room temperature and reaction of the resulting enolate with TMS chloride provides the corresponding silylenol ether. Reaction of this intermediate with 1 eq of bromine at low temperature (typically at about -78 °C) furnishes the α-

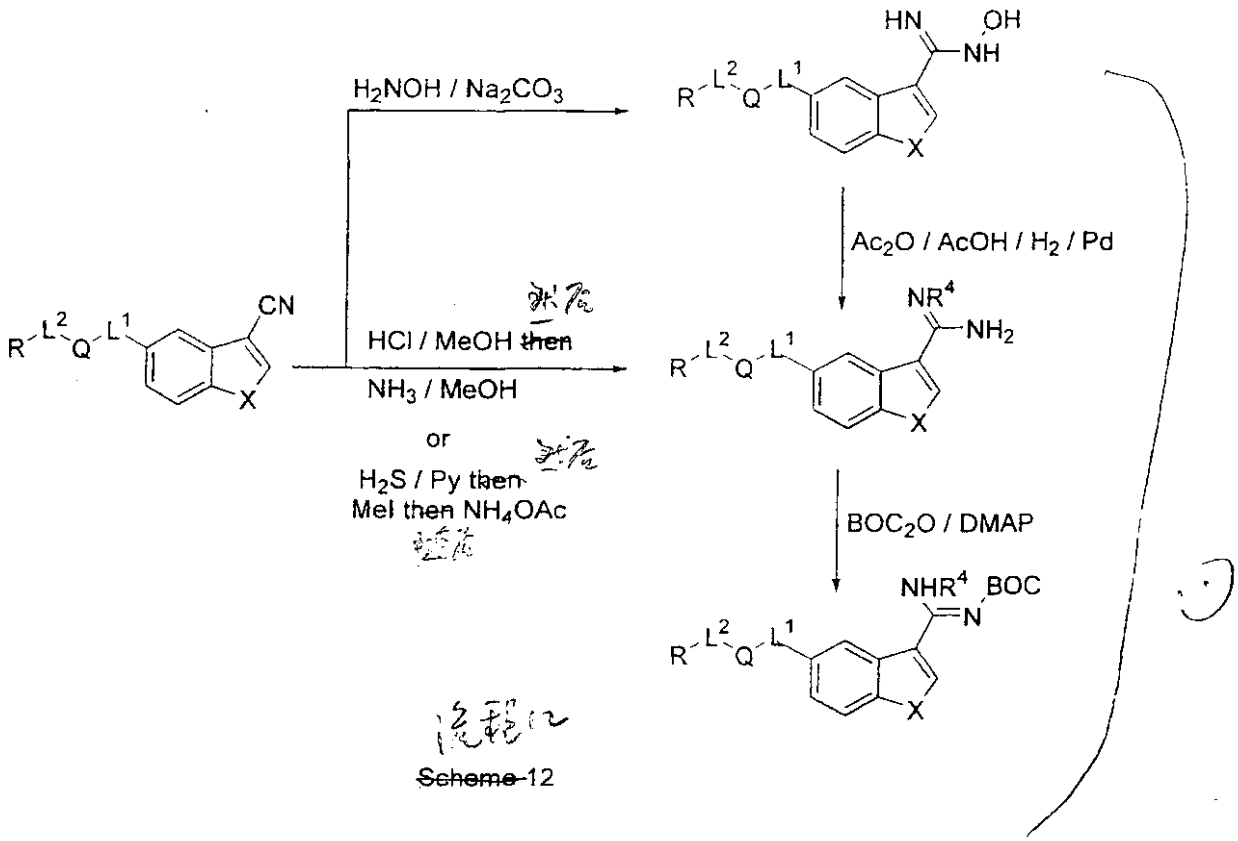
bromoketone. This compound can be treated with formamide at elevated temperatures (from about 50 °C to about 180 °C) to provide imidazole. Alternatively, the bromo ketone can be reacted with sodium azide followed by reduction with sodium borohydride to provide the amino alcohol. After, protection of the amino alcohol as a BOC derivative of the amine and a TBS ether of the alcohol, the furan ring can be oxidatively cleaved to provide the benzoic acid derivative. This unit can then be attached to the heteroaryl scaffold as described above. Reduction of 2-(4-furan-2-yl-phenyl)-2-methyl-propionic acid methyl ester with lithium aluminum hydride in a solvent such as THF followed by oxidation of the resulting primary alcohol to the corresponding aldehyde and Wittig or Horner-Emmons olefin reactions provides access to chain extended alkenes (For a review see Cadogan, J.I.G. Organophosphorus Reagents in Organic Synthesis, Academic Press, 1979). In the case where R = Ome, this system can be hydrolyzed to the corresponding aldehyde with dilute HCl then oxidized to the carboxylic acid as previously described. Amide formation followed by reduction with a reagent such as borane in THF provides a series of amines. Subsequent oxidative cleavage of the furan ring as described above provides a useful functional group for attachment to the heterocyclic scaffold. Additionally, treatment of 2-(4-bromo-phenyl)-2-methyl-propionic acid methyl ester with diisobutylaluminum hydride at -78 °C in dichloromethane followed by Swern oxidation of the resulting alcohol and Wittig reaction on the aldehyde provides the one carbon chain extended olefin. Osmylation of this species, followed by protection of the resulting diol as an acetonide allows oxidation of the furan ring to the carboxylic acid which provides an attachment point for coupling to the heteroaryl scaffold.

It is often useful to introduce conformational constraints into a linker to optimize the availability of a bioactive conformer. These constraining groups can also interact favorably with a target protein providing an additional advantage. An example of the synthesis of a system which can produce such effects is shown in Scheme 11. Two carbon chain extension of the bromo indole by adaptation of the method of Migata (Kosugi, M; Negishi, Y.; Kameyama, M.; Migata, T.; Bull, Chem. Soc. Jpn., 1985, 58, 3383; Agnelli, F., Sulikowski, G.A. Tetrahedron Letts 1998, 39, 8807) then treatment of the resulting ester with TMS triflate and triethylamine in ether at 0 °C provides the silyl ketene acetal. Reaction of this species with an amine acetal in dichloromethane in the presence of TMS triflate as a catalyst, generates the substituted ,β-amino ester (for representative examples see Okano, K.; Morimoto, T.; Sekiya, M. J. Chem Soc., Chem. Commun., 1984, 883 and Colvin, E.W.; McGarry, D.G.; Nugent, M.J. Tetrahedron, 1988, 44, 4157). Acylation of the amino group then provides access to a variety of amide substituted scaffolds.



~~Scheme 11~~

Transformation of the C-3 nitrile into the corresponding amidine can be carried out employing a number of standard procedures. (for examples see Judkins, B.D.; Allen, D.G.; Cook, T.A.; Evans, B.; Sardharwala, T.E. Syn. Comm. 1996, 26, 4351 and references therein). Treatment of the nitrile (Scheme 12) with HCl in a solvent such as methanol or ethanol at about or above room temperature provides the imidate ester intermediate which can then be converted to the amidine by treatment with ammonia or an alkylamine in a solvent such as methanol or ethanol. Alternatively, reaction of the nitrile with hydrogen sulfide in a solvent such as pyridine, followed by alkylation of the resulting thioamide with an alkylating agent such as methyl iodide in a solvent such as acetone at a temperature at or above room temperature and treatment of this product with ammonia or ammonium acetate in a solvent such as methanol at about or above room temperature provides the final amidine.



Scheme 12

An amidine can also be prepared by addition of hydroxylamine to the nitrile to form the corresponding N-hydroxyamidine followed by acylation and hydrogenolysis of the N-O bond using hydrogen / acetic acid / acetic anhydride in the presence of a catalyst such as palladium on carbon. For certain transformations of the side chain, it may be necessary or preferable to protect the indole nitrogen as an inert derivative (Protective Groups in Organic Synthesis, T.W. Greene and P.G.M. Wuts; John Wiley Publications 1991). A particularly suitable derivative for this purpose is the t-butyloxy-carbamate. This can be prepared by reaction of the appropriate indole with di-t-butyldicarbonate in THF or dichloromethane in the presence of a base such as DMAP / triethylamine or diisopropylethylamine at about or above room temperature. The nitrogen of the amidine functional group can be protected using essentially the same conditions described above for the indole nitrogen. Cleavage of these BOC derivatives can be accomplished by treatment with TFA in dichloromethane or with HCl in ethyl acetate.

It will be apparent to those skilled in the art that certain compounds of formula I can exhibit isomerism, for example geometrical isomerism, e.g., E or Z isomerism, and optical isomerism, e.g., R or S configurations. Geometrical isomers include the cis and trans forms of compounds of the invention having

alkenyl moieties. Individual geometrical isomers and stereoisomers within formula I, and their mixtures, are within the scope of the invention.

Such isomers can be separated from their mixtures, by the application or adaptation of known methods, for example chromatographic techniques and recrystallization techniques, or they are separately prepared from the appropriate isomers of their intermediates, for example by the application or adaptation of methods described herein.

The compounds of the present invention are useful in the form of the free base or acid or in the form of a pharmaceutically acceptable salt thereof. All forms are within the scope of the invention.

Where the compound of the present invention is substituted with a basic moiety, acid addition salts are formed and are simply a more convenient form for use; and in practice, use of the salt form inherently amounts to use of the free base form. The acids which can be used to prepare the acid addition salts include preferably those which produce, when combined with the free base, pharmaceutically acceptable salts, that is, salts whose anions are non-toxic to the patient in pharmaceutical doses of the salts, so that the beneficial inhibitory effects on Factor Xa inherent in the free base are not vitiated by side effects ascribable to the anions. Although pharmaceutically acceptable salts of said basic compounds are preferred, all acid addition salts are useful as sources of the free base form even if the particular salt, per se, is desired only as an intermediate product as, for example, when the salt is formed only for purposes of purification, and identification, or when it is used as intermediate in preparing a pharmaceutically acceptable salt by ion exchange procedures. Pharmaceutically acceptable salts within the scope of the invention are those derived from the following acids: mineral acids such as hydrochloric acid, sulfuric acid, phosphoric acid and sulfamic acid; and organic acids such as acetic acid, citric acid, lactic acid, tartaric acid, malonic acid, methanesufonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, cyclohexylsulfamic acid, quinic acid, and the like. The corresponding acid addition salts comprise the following: hydrohalides, e.g. hydrochloride and hydrobromide, sulfate, phosphate, nitrate, sulfamate, acetate, citrate, lactate, tartarate, malonate, oxalate, salicylate, propionate, succinate, fumarate, maleate, methylene-bis-β-hydroxy-naphthoates, gentisates, mesylates, isethionates, di-p-toluoyltartrates, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, cyclohexylsulfamate and quinate, respectively.

According to a further feature of the invention, acid addition salts of the compounds of this invention are prepared by reaction of the free base with the appropriate acid, by the application or adaptation of known methods. For example, the acid addition salts of the compounds of this invention are prepared either by dissolving the free base in aqueous or aqueous-alcohol solution or other suitable solvents containing the

appropriate acid and isolating the salt by evaporating the solution, or by reacting the free base and acid in an organic solvent, in which case the salt separates directly or can be obtained by concentration of the solution.

The acid addition salts of the compounds of this invention can be regenerated from the salts by the application or adaptation of known methods. For example, parent compounds of the invention can be regenerated from their acid addition salts by treatment with an alkali, e.g. aqueous sodium bicarbonate solution or aqueous ammonia solution.

Where the compound of the invention is substituted with an acidic moiety, base addition salts may be formed and are simply a more convenient form for use; and in practice, use of the salt form inherently amounts to use of the free acid form. The bases which can be used to prepare the base addition salts include preferably those which produce, when combined with the free acid, pharmaceutically acceptable salts, that is, salts whose cations are non-toxic to the animal organism in pharmaceutical doses of the salts, so that the beneficial inhibitory effects on Factor Xa inherent in the free acid are not vitiated by side effects ascribable to the cations. Pharmaceutically acceptable salts, including for example alkali and alkaline earth metal salts, within the scope of the invention are those derived from the following bases: sodium hydride, sodium hydroxide, potassium hydroxide, calcium hydroxide, aluminum hydroxide, lithium hydroxide, magnesium hydroxide, zinc hydroxide, ammonia, ethylenediamine, N-methyl-glucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, diethylamine, piperazine, tris(hydroxymethyl)-aminomethane, tetramethylammonium hydroxide, and the like.

Metal salts of compounds of the present invention may be obtained by contacting a hydride, hydroxide, carbonate or similar reactive compound of the chosen metal in an aqueous or organic solvent with the free acid form of the compound. The aqueous solvent employed may be water or it may be a mixture of water with an organic solvent, preferably an alcohol such as methanol or ethanol, a ketone such as acetone, an aliphatic ether such as tetrahydrofuran, or an ester such as ethyl acetate. Such reactions are normally conducted at ambient temperature but they may, if desired, be conducted with heating.

Amine salts of compounds of the present invention may be obtained by contacting an amine in an aqueous or organic solvent with the free acid form of the compound. Suitable aqueous solvents include water and mixtures of water with alcohols such as methanol or ethanol, ethers such as tetrahydrofuran, nitriles such as acetonitrile, or ketones such as acetone. Amino acid salts may be similarly prepared.

The the compounds of this invention can be regenerated from the salts by the application or adaptation of known methods. For example, parent compounds of the invention can be regenerated from their base addition salts by treatment with an acid, e.g. hydrochloric acid.

Pharmaceutically acceptable salts also include quaternary lower alkyl ammonium salts. The quaternary salts are prepared by the exhaustive alkylation of basic nitrogen atoms in compounds, including nonaromatic and aromatic basic nitrogen atoms, according to the invention, i.e., alkylating the non-bonded pair of electrons of the nitrogen moieties with an alkylating agent such as methylhalide, particularly methyl iodide, or dimethyl sulfate. Quaternarization results in the nitrogen moiety becoming positively charged and having a negative counter ion associated therewith.

As will be self-evident to those skilled in the art, some of the compounds of this invention do not form stable salts. However, acid addition salts are most likely to be formed by compounds of this invention having a nitrogen-containing heteroaryl group and/or wherein the compounds contain an amino group as a substituent. Preferable acid addition salts of the compounds of the invention are those wherein there is not an acid labile group.

As well as being useful in themselves as active compounds, salts of compounds of the invention are useful for the purposes of purification of the compounds, for example by exploitation of the solubility differences between the salts and the parent compounds, side products and/or starting materials by techniques well known to those skilled in the art.

The starting materials and intermediates are prepared by the application or adaptation of known methods, for example methods as described in the Reference Examples or their obvious chemical equivalents, or by methods according to this invention.

The present invention is further exemplified but not limited by the following illustrative examples which illustrate the preparation of the compounds according to the invention.

Experimental Section

Unless otherwise stated, all starting materials are obtained from commercial suppliers and are used without further purification. Reactions are routinely carried out under an inert atmosphere of nitrogen or argon using anhydrous solvents obtained from Aldrich Chemical Company. Flash column chromatography is performed on Merck silica gel (230-400 mesh) eluting with the specified solvent mixture. Reverse phase HPLC is performed using Dynamax C-18 (60A) columns, eluting with a water / acetonitrile gradient (containing a fixed 0.1% v/v trifluoroacetic acid additive) with UV detection (λ = 220, 254, 294 nM). ^{1}H NMR spectra are recorded at a frequency of 300 MHz in the specified deuterated solvent. Chemical shifts are in ppm relative to the resonance frequency of tetramethylsilane δ= 0.00. The following conventions are

used throughout to describe NMR spectra: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. Coupling constants are designated with the symbol J and are measured in Hz.

Example 1a

N-(2-[3-Carbamimidoyl-5-indolyl]ethyl)-4-pyrid-3-ylbenzamide.

A stream of HCl gas is bubbled through a cooled (0 °C) slurry of N-(2-[3-Cyano-5-indolyl]ethyl)-4-pyrid-3-ylbenzamide (reference example 1a) in MeOH (10 mL) for seven minutes, after which the reaction is capped and allowed to stir overnight at room temperature. After purging with a stream of nitrogen, the reaction is concentrated, and 15 mL 7N NH_3 in MeOH is added. After stirring overnight, the reaction is purged with nitrogen and concentrated, The residue is chromatographed (3:1 CH_2Cl_2: 7N NH_3 in MeOH) to afford partially purified product. Further purification by reverse phase HPLC provided 0.298 g of the title compound as a white solid. m.p. 55-58°C; ^{1}H NMR (CD_3OD): δ 3.09 (2H, t, J = 7 Hz), 3.71 (2H, t, J = 7 Hz), 7.26 (1H, d, J = 8 Hz), 7.49 (1H, d, J = 8 Hz), 7.80 (1H, s), 7.87 (2H, d, J = 8 Hz), 7.97 (2H, d, J = 8 Hz), 8.00 (1H, m), 8.09 (1H, s), 8.69 (1H, d, J = 8 Hz), 8.80 (1H, br, m), 9.14 (1H, br, s). MS (ion spray) m/z 384 $(M+H)^+$. Anal. calcd for $C_{23}H_{21}N_5O\cdot(C_2HF_3O_2)_2\cdot(H_2O)_3$: C, 48.7; H, 4.4; N, 10.5. Found: C, 48.5; H, 3.9; N, 10.3.

The following compounds are prepared using essentially the same procedure described in example 1a except using the specified nitrile:

Example 1b

N-(2-[3-Carbamimidoyl-5-indolyl]ethyl)-4-(pyrimidin-5-yl)-benzamide). Using the product from reference example 1b. m.p. 97-100°C; ^{1}H NMR (CD_3OD): δ 3.09 (2H, t, J = 7 Hz), 3.71 (2H, t, J = 7 Hz), 7.26 (1H, d, J = 8 Hz), 7.49 (1H, d, J = 8 Hz), 7.79 (1H, s), 7.82 (2H, d, J = 8 Hz), 7.94 (2H, d, J = 8 Hz), 8.08 (1H, s), 9.23 (3H, br). MS (ion spray) m/z 385 $(M+H)^+$.

Example 1c

5-(Pyrid-2-yl)-thiophene-2-carboxylic acid 2-(3-carbamimidoyl-5-indolyl)ethyl amide. Using the product from reference example 1c. m.p. 198-200°C; ^{1}H NMR (CD_3OD): δ 3.07 (2H, t J = 7 Hz), 3.66 (2H, t, J = 7

Hz), 7.25 (1H, d, J = 8 Hz), 7.33 (1H, m), 7.48 (1H, d, J = 8 Hz), 7.63 (1H, m), 7.66 (1H, m), 7.78 (1H, s), 7.83 (1H, m), 7.87 (1H, m), 8.07 (1H, s), 8.52 (1H, d, J = 5 Hz). MS (ion spray) m/z 390 $(M+H)^+$. Anal. calcd for $C_{21}H_{19}N_5OS\cdot(C_2HF_3O)_2\cdot(H_2O)_{0.5}$: C, 47.9; H, 3.5; N, 11.2. Found: C, 48.1; H, 3.4; N, 11.0.

Example 1d

N-(2-[3-Carbamimidoylindol-5-yl]ethyl)- 6-morpholin-4-ylnicotinamide. Using the product from reference example 1d. m.p. 130-132 °C; ^1H NMR (D_2O): δ 2.88 (2H, t, J = 6 Hz), 3.50 (2H, t, J = 6 Hz), 3.56 (2H, t , J = 4 Hz), 3.73 (2H, t, J = 4 Hz), 7.07-7.12 (2H, m), 7.37 (1H, d, J = 8 Hz), 7.55 (1H, s), 7.88-7.96 (2H, m), 8.00 (1H, s). MS (ion spray) m/z 393 $(M+H)^+$. Anal. calcd. for $C_{21}H_{24}N_6O_2\cdot(C_2HF_3O)_2\cdot(H_2O)_2$: C, 45.1; H, 4.7; N, 12.6. Found: C, 44.9; H, 4.2; N, 12.4.

Example 1e

4-(5-2[-{3-Carbamimidoylindol-5-yl}ethylcarbamoyl]pyridin-2-yl)piperazine-1-carboxylic acid ethyl ester. Using the product from reference example 24b. m.p. 85-87°C. ^1H NMR (CD_3OD): δ 1.28 (3H, t, J = 7 Hz), 3.05 (2H, t, J = 7 Hz), 3.55-3.73 (10H, m), 4.16 (2H, q, J = 7 Hz), 6.97 (1H, d, J = 9 Hz), 7.23 (1H, d, J = 8 Hz), 7.47 (1H, d, J = 8 Hz), 7.76 (1H, s), 8.06 (1H, d, J = 9 Hz), 8.80 (1H, s), 8.50 (1H, d, J = 2 Hz). MS (ion spray) m/z 464 $(M+H)^+$. Anal. calcd. for $C_{24}H_{29}N_7O_3\cdot(C_2HF_3O)_2\cdot(H_2O)_{4.5}$: C, 43.5; H, 5.2; N, 12.7. Found: C, 43.5; H, 4.4; N, 12.6.

Example 1f

N-(2-[3-Carbamimidoylindol-5-yl]ethyl)- 6-imidazol-1-ylnicotinamide. Using the product from reference example 1f. m.p. 94-97°C. ^1H NMR (CD_3OD): δ 3.09 (2H, t, J = 7 Hz), 3.72 (2H, m), 7.26 (1H, d, J = 9 Hz), 7.49 (1H, d, J = 9 Hz), 7.71 (1H, s, br), 7.79 (1H, s), 7.99 (1H, d, J = 9 Hz), 8.09 (1H, s), 8.37 (1H, s, br), 8.43 (1H, d, J = 9 Hz), 8.95 (1H, s), 9.66 (1H, s, br). MS (FAB) m/z 374 $(M+H)^+$. Anal. calcd. for $C_{20}H_{19}N_7O\cdot(C_2HF_3O)_2\cdot(H_2O)_2$: C, 45.2; H, 3.9; N, 15.4. Found: C, 45.2; H, 3.5; N, 15.3.

Example 1g

N-(2-[3-Carbamimidoylindol-5-yl]ethyl)- 4-imidazol-1-ylbenzamide.

Using the product from reference example 1g, m.p. 191-194°C. ^{1}H NMR (CD_3OD): δ 3.09 (2H, m), 3.71 (2H, m), 7.26 (1H, d, J = 8 Hz), 7.48 (1H, d, J = 8Hz), 7.73 (1H, s, br), 7.77-7.86 (3H, m), 8.01-8.16 (4H, m), 9.38 (1H, s, br). MS (ion spray) m/z 373 $(M+H)^+$. Anal. calcd. for $C_{21}H_{20}N_6O\cdot(C_2HF_3O)_2\cdot(H_2O)_5\cdot(CH_3CN)_{0.5}$: C, 43.9; H, 4.7; N, 12.8. Found: C, 43.6; H, 4.0; N, 13.1.

Example 1h

N-(2-[3-Carbamimidoylindol-5-yl]ethyl)- 4-(3H-imidazol-4-yl)benzamide.

Using the product from reference example 1h, m.p. 52-54°C. ^{1}H NMR (D_2O): δ 2.89 (2H, m), 3.52 (2H, m), 7.13 (1H, d, J = 8 Hz), 7.39 (1H, d, J = 8 Hz), 7.49-7.57 (5H, m), 7.65 (1H, s), 7.90 (1H, s), 8.62 (1H, s). MS (ion spray) m/z 373 $(M+H)^+$.

Example 1i

N-(2-[3-Carbamimidoylindol-5-yl]ethyl)- 4-(1,2,4)thiadiazol-5-ylbenzamide. Using the product from reference example 1i m.p. 222-224°C. ^{1}H NMR (DMSO-d_6): δ 2.99 (2H, t, J = 7 Hz), 3.60 (2H, m), 7.20 (1H, d, J = 8 Hz), 7.50 (1H, d, J = 8 Hz), 7.74 (1H, s), 8.01 (2H, d, J = 8 Hz), 8.16 (2H, d, J = 8Hz), 8.20 (1H, d, J = 3 Hz), 9.03 (1H, s). MS (ion spray) m/z 391 $(M+H)^+$. Anal. calcd. for $C_{20}H_{18}N_6OS\cdot C_2HF_3O\cdot(H_2O)_{1.5}$: C, 49.7; H, 4.2; N, 15.8. Found: C, 49.9; H, 4.0; N, 15.7.

Example 1j

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(1-carbamoyl-1-methyl-ethyl-benzamide. Using the product from reference example 1j. ^{1}H NMR (CD_3OD) d 1.56 (s, 6H), 3.06 (t, J = 7Hz, 2H), 3.67 (t, J = 7Hz, 2H), 7.22 (d, J = 8Hz, 1H), 7.48 (m, 3H), 7.76 (m, 3H), 8.07 (s, 1H), 8.28 (bs, 1H), 8.6 (bs, 1H). MS (ion spray) m/z 392 (M+H). Combustion Analysis $C_{22}H_{25}N_5O_2;(C_2HF_3O)_2;(H_2O)$ requires C 52.8, H 5.4, N 13.3. Found C 52.8, H 5.3, N 13.2.

Example 1k

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(1-[N-(2-methoxyethyl)]-carbamoyl-1-methyl-ethyl-benzamide. Using the product from reference example 1k. ^{1}H NMR (CD_3OD) d 1.54 (s, 6H), 3.05 (t, J =

7Hz, 2H), 3.28 (s, 3H), 3.34 (m, 2H), 3.40 (m, 2H), 3.67 (t, J = 7Hz, 2H), 7.22 (dd, J = 7, 1Hz, 1H), 7.44 (m, 3H), 7.75 (m, 3H), 8.07 (s, 1H). MS (ion spray) m/z 450 (M+H). Combustion Analysis $C_{25}H_{31}N_5O_3;(C_2HF_3O_2)_{1.4}$ requires C 54.9, H 5.4, N 11.5. Found C 54.6, H 5.5, N 11.8.

Example 1l

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(t-butyl)-benzamide. Using the product from reference example 1l ^{1}H NMR (DMSO) d 1.29 (s, 9H), 2.96 (t, J = 7Hz, 2H), 3.53 (q, J = 7Hz, 2H), 7.18 (d, J = 8Hz, 1H), 7.45 (m, 3H), 7.75 (m, 3H), 8.21 (s, 1H), 8.52 (bt, 1H), 8.70 (bs, 4H), 12.3 (bs, 1H). MS (ion spray) m/z 363 (M+H). Combustion Analysis $C_{22}H_{26}N_4O;[C_2HF_3O_2]_{1.3}$ requires C 57.8, H 5.4, N 11.0. Found C 57.6, H 5.3, N 11.0.

Example 1m

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(pyridazin-4-yl)-benzamide. Using the product from reference example 1m. ^{1}H NMR (DMSO) d 3.0 (t, J = 7Hz, 2H), 3.60 (q, J = 7Hz, 2H), 7.20 (d, J = 8Hz, 1H), 7.50 (d, J = 8Hz, 1H), 7.74 (s, 1H), 8.04 (m, 5H), 8.20 (d, J = 3Hz, 1H), 8.54 (bs, 2H), 8.70 (bs, 2H), 8.77 (bt, J = 7Hz, 1H), 9.33 (d, J = 5Hz, 1H), 9.71 (s, 1H), 12.28 (bs, 1H). MS (ion spray) m/z 385 (M+H). Combustion Analysis $C_{22}H_{20}N_6O;(C_2HF_3O_2)_2$ requires C 51.0, H 3.6, N 13.7. Found C 50.7, H 4.1, N 13.7.

Example 1n

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-2-methyl-4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzamide. Using the product from reference example 36a. ^{1}H NMR (CD_3OD) d 2.30 (s, 3H), 3.07 (t, J = 7Hz, 2H), 3.69 (t, J = 7Hz, 2H), 6.63 (d, J = 9Hz, 1H), 7.34-7.40 (m, 4H), 7.50 (d, J = 8 Hz, 1H), 7.71 (d, J = 2Hz, 1H), 7.80 (s, 1H), 7.93 (dd, J = 9, 2, 1H), 8.08 (s, 1H). MS (ion spray) m/z 414 (M+H).

Example 1o

3',4'-Dimethoxybiphenyl-4-carboxylic acid (2-[3-carbamimidoylindol-5-yl]ethyl)amide. Using the product from reference example 1o but without HPLC purification. Instead, the crude product is chromatographed on silica gel then washed with distilled water to remove inorganic salts and dried by lyophilization. m.p.

>250°C. ^{1}H NMR (DMSO): δ 2.99 (2H, m), 3.57 (2H, m), 3.80 (3H, s), 3.86 (3H, s), 7.06 (1H, d, J = 9 Hz), 7.20 (1H, d, J = 8 Hz), 7.27-7.29 (2H, m), 7.50 (1H, d, J = 9 Hz), 7.71-7.76 (3H, m), 7.90 (2H, d, J = 8 Hz), 8.23 (1H, d, J = 3 Hz). MS (ion spray) m/z 443 $(M+H)^+$. Anal. calcd. for $C_{26}H_{26}N_4O_3 \cdot HCl \cdot (H_2O)_{1.25}$: C, 62.3; H, 5.9; N, 11.2. Found C, 62.2; H, 5.8; N, 10.9.

Example 1p

N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-(6-methoxypyrid-3-yl)benzamide. Using the product from reference example 1p. m.p. 164-167°C. ^{1}H NMR (3:1 D_2O:CD_3OD): δ 2.81 (2H, m), 3.43 (2H, m), 3.70 (3H, s), 6.76 (1H, d, J = 8 Hz), 7.06 (1H, d, J = 8 Hz), 7.38 (1H, d, J = 8 Hz), 7.35-7.46 (5H, m), 7.78 (1H, m), 7.81 (1H, s), 8.09 (1H, s). MS (FAB) m/z 414 $(M+H)^+$. Anal. calcd. for $C_{24}H_{23}N_5O_2 \cdot C_2HO_2F_3 \cdot (H_2O)_2$: C, 55.4; H, 5.0; N, 12.4. Found C, 55.3; H, 4.5; N, 12.1.

Example 1q

N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-(1-oxy-pyrid-4-yl)benzamide. Using the product from reference example 1q. m.p. 99-101°C. ^{1}H NMR (3:1 D_2O:CD_3OD): δ 2.80 (2H, m), 3.44 (2H, m), 7.03 (1H, d, J = 8 Hz), 7.28 (1H, d, J = 8 Hz), 7.34-7.67 (7H, m), 7.82 (1H, s), 8.13 (2H, br, m). MS (ion spray) m/z 400 $(M+H)^+$.

Example 1r

N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(7H-pyrrolo[2,3-d]pyrimidin-6-yl)-benzamide. Using the product from reference example 1r. ^{1}H NMR (DMSO) δ 2.98 (m, 2H), 3.59 (m, 2H), 7.20 (d, J = 9Hz, 1H), 7.33 (s, 1H), 7.50 (d, J = 8Hz, 1H), 7.74 (s, 1H), 7.96 (d, J = 8Hz, 2H), 8.10 (d, J = 8Hz, 2H), 8.20 (d, J = 3Hz, 1H), 8.68 (m, 4H), 8.95 (s, 1H), 9.19 (bs, 1H), 12.30 (bs, 1H), 13.22 (bs, 1H). MS (ion spray) m/z 424 $(M+H)^+$. Combustion Analysis: $C_{24}H_{21}N_7O;(C_2HF_3O_2)_2;(H_2O)_{0.5}$ requires C 50.9, H 3.7, N 14.8. Found C 50.7, H 3.7, N 14.4

Example 1s

N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(1H-pyrrolo[3,2-c]pyridin-2-yl)-benzamide. Using the product from reference example 1s. ^{1}H NMR (DMSO) δ 3.02 (bt, 2H), 3.58 (m, 2H), 7.22 (s, 1H), 7.52 (d, J = 8Hz, 1H), 7.60 (s, 1H), 7.77 (s, 1H), 7.98 (d, J = 6Hz, 1H), 8.02 (d, J = 8Hz, 2H), 8.13 (d, J = 8Hz, 2H), 8.24 (d, J = 4Hz, 1H), 8.45 (d, J = 7Hz, 1H), 8.76 (m, 5H), 9.31 (s, 1H), 12.36 (s, 1H), MS (ion spray) m/z 423 (M+H)$^+$. Combustion Analysis: $C_{25}H_{22}N_6O;(C_2HF_3O_2)_{2.5};(H_2O)_{3.5}$ requires C 48.8, H 4.4, N 11.8. Found C 48.5, H 4.0, N 11.8.

Example1t

N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-furo[3,2-c]pyridin-2-yl-benzamide. Using the product from reference example 1t. ^{1}H NMR (DMSO) δ 2.98 (bt, 2H), 3.59 (m, 2H), 7.20 (d, J = 8Hz, 1H), 7.50 (d, J = 8Hz, 1H), 7.74 (s, 1H), 7.85 (s, 1H), 8.00 (d, J = 8Hz, 2H), 8.05 (d, J = 6Hz, 1H), 8.10 (d, J = 8Hz, 2H), 8.20 (d, J = 3Hz, 1H), 8.59 (bs, 2H), 8.67 (m, 2H), 8.76 (bt, 1H), 9.24 (s, 1H), 12.29 (bs, 1H), MS (ion spray) m/z 424 (M+H)$^+$. Combustion analysis: $C_{25}H_{21}N_5O_2;(C_2HF_3O_2)_2;(H_2O)_{1.5}$ requires C 51.3, H 3.9, N 10.3. Found C 51.2, H 3.7, N 10.4.

Example 1u

N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-3-chloro-4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzamide. Using the product from reference example 36c. ^{1}H NMR (DMSO) δ 2.98 (bt, 2H), 3.56 (m, 2H), 6.42 (d, J = 9Hz, 1H), 7.20 (d, J = 8Hz, 1H), 7.56 (m, 4H), 7.74 (s, 1H), 7.82 (d, J = 8Hz, 1H), 7.96 (s, 1H), 8.22 (d, J = 3Hz, 1H), 8.54 (bs, 2H), 8.70 (bs, 2H), 8.76 (bt, 1H), 12.28 (bs, 1H). MS (ion spray) m/z 434/436 (M+H)$^+$, Cl.

Example 1v

N-(2-[3-carbamimidoyl-1H-indol-5-yl]ethyl)-4-(6-oxo-1,6-dihydro-pyrid-3-yl)benzamide. Using the product from reference example 36b. m.p. 152-156°C. ^{1}H NMR (CD_3OD): δ 3.08 (2H, m), 3.69 (2H, m), 6.66 (1H, d, J= 9 Hz), 7.26 (1H, d, J = 8 Hz), 7.48 (1H, d, J = 8 Hz), 7.62 (2H, d, J = 8 Hz), 7.78 (1H, s), 7.79 (1H, s),

7.84 (2H, d, J = 8 Hz), 7.99 (1H, d, J = 9 Hz), 8.08 (1H, s). MS (FAB) m/z calcd. for $C_{23}H_{22}N_5O_2$ $(M+H)^+$ 400.1773, found 400.1778.

Example 1w

4-(3-Amino-1,1-dimethyl-propyl)-N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-benzamide. Using the product from reference example 1w. ^1H NMR (DMSO) δ 1.31 (s, 1H), 1.93 (m, 2H), 2.50 (m, 2H), 2.97 (m, 2H), 3.57 (m, 2H), 7.18 (d, J = 8 Hz, 1H), 7.44 (d, J = 8Hz, 2H), 7.50 (d, J = 9Hz, 1H), 7.72 (m, 3H), 7.80 (d, J = 8Hz, 2H), 8.22 (d, J = 3Hz, 1H), 8.59 (bt, 1H), 8.72 (s, 1H), 8.77 (s, 2H), 12.35 (s, 1H). MS (ion spray) m/z 392 $(M+H)^+$. Combustion Analysis: $C_{23}H_{29}N_5O;(C_2HF_3O_2)_{2.5}$ requires C 49.7, H 4.7, N 10.4. Found C 50.0, H 4.8, N 10.7.

Example 1x

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-2-(4-chloro-phenyl)-acetamide. Using the product from reference example 1x. ^1H NMR (CD_3OD) δ 2.94 (t, J = 7Hz, 2H), 3.39 (s, 2H), 3.55 (q, J = 7Hz, 2H), 7.04 (d, J = 8Hz, 2H), 7.14 (m, 3H), 7.44 (d, J = 8Hz, 1H), 7.67 (s, 1H), 8.09 (s, 1H). MS (ion spray) m/z 355 / 357 (M+H, Cl pattern). Combustion analysis: $C_{19}H_{19}N_4OCl;(C_2HF_3O_2)_{1.3}$ requires C 51.6, H 4.1, N 11.1. Found C 51.6, H 4.1, N 11.2.

Example 1y

5-chloro-thiophene-2-carboxylic acid [2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-amide. Using the product from reference example 1y. ^1H NMR (CD_3OD) δ 3.0 (t, J = 7Hz, 2H), 3.61 (q, J = 7Hz, 2H), 6.98 (d, J = 4Hz, 1H), 7.21 (d, J = 8Hz, 1H), 7.46 (m, 2H), 7.75 (s, 1H), 8.07 (s, 1H). MS (ion spray) m/z 347 / 349 (M+H, Cl pattern). Combustion analysis: $C_{16}H_{15}N_4OSCl;(C_2HF_3O_2)_{1.5}$ requires C 44.1, H 3.2, N 10.8. Found C 44.1, H 3.2, N 10.9.

Example 1z

N-(2-[3- Carbamimidoylindol-5-yl]ethyl)-6-(2-hydroxyethylamino)nicotinamide. Using the product from reference example 1z

m.p. 102-105°C. ^{1}H NMR (D_2O): δ 2.88 (2H, t, J = 6.0 Hz), 3.39 (2H, t, J = 4 Hz), 3.49 (2H, t, J = 6.0 Hz), 3.64 (2H, t, J = 4 Hz), 6.88 (1H, d, J = 9 Hz), 7.09 (1H, d, J = 8 Hz), 7.37 (1H, d, J = 8 Hz), 7.54 (1H, s), 7.79 (1H, d, J = 9 Hz), 7.91 (1H, s), 7.92 (1H, s). MS (ion spray) m/z 367 $(M+H)^+$.

Example 1aa

N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-6-(1, 2, 4)-triazol-1-ylnicotinamide. Using the product from reference example 1aa, m.p. 196-199°C. ^{1}H NMR (DMSO-d_6): δ 2.99 (2H, m), 3.59 (2H, m), 7.21 (1H, d, J = 8 Hz), 7.51 (1H, d, J = 8 Hz), 7.74 (1H, s), 7.98 (1H, d, J = 8 Hz), 8.21 (1H, d, J = 3 Hz), 8.37 (1H, s), 8.45 (1H, dd, J = 8, 2 Hz), 8.51 (1H, s, br), 8.71 (2H, s, br), 8.92 (2H, m, br), 9.47 (1H, s). MS (ion spray) m/z 375 $(M+H)^+$. Anal. calcd. for $C_{19}H_{18}N_8O\cdot(C_2HO_2F_3).(H_2O)_{0.5}$: C, 45.2; H, 3.5; N, 18.3. Found: C, 45.0; H, 3.5; N, 18.7.

Example 1ab

N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-6-pyrrol-1-ylnicotinamide. Using the product from reference example 1ab, m.p. 213-214°C. ^{1}H NMR (CD_3OD): δ 3.08 (2H, d, J = 7 Hz), 3.70 (2H, d, J = 7Hz), 6.33 (2H, s), 7.26 (1H, d, J = 7Hz), 7.49 (1H, d, J = 7 Hz), 7.58-7.62 (3H, m), 7.77 (1H, s), 8.07 (1H, s), 8.19 (1H, d, J = 8 Hz), 8.75 (1H, s). MS (ion spray) m/z 373 $(M+H)^+$. Anal. calcd. for $C_{21}H_{20}N_5O\cdot C_2HO_2F_3\cdot(H_2O)_{1.25}$: C, 54.3; H, 4.6; N, 16.5. Found: C, 54.1; H, 4.3; N, 16.3.

Example 1ac

N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-6-pyrazol-1-ylnicotinamide. Using the product from reference example 1ac, m.p. 235-236°C. ^{1}H NMR (CD_3OD): δ 3.08 (2H, m), 3.69 (2H, m), 6.56 (1H, s), 7.26 (1H, d, J = 8 Hz), 7.49 (1H, d, J = 8 Hz), 7.77 (1H, s), 7.80 (1H, s), 7.98 (1H, d, J = 8 Hz), 8.07 (1H, s), 8.24 (1H, d, J = 8 Hz), 8.64 (1H, s), 8.70-8.79 (2H, m). MS (ion spray) m/z 374 $(M+H)^+$. Anal. calcd. for $C_{20}H_{19}N_7O\cdot C_2HO_2F_3\cdot(H_2O)_2$: C, 50.5; H, 4.6; N, 18.7. Found: C, 50.5; H, 4.0; N, 18.5.

Example 1ad

N-(2-[3-Carbamimidoyl-1-methylindol-5-yl]ethyl)-4-(6-methoxypyrid-3-yl)benzamide. Using the product from reference example 55. m.p. 237-238°C. ^{1}H NMR (CD_3OD): δ 3.09 (2H, m), 3.71 (2H, m), 3.92 (3H, s), 3.96 (3H, s), 6.90 (1H, d, J = 9 Hz), 7.32 (1H, d, J = 9 Hz), 7.52 (1H, d, J = 9 Hz), 7.68 (2H, d, J = 8 Hz), 7.79 (1H, s), 7.85 (2H, d, J = 8 Hz), 8.00 (1H, d, J = 9 Hz), 8.02 (1H, s), 8.43 (1H, s), 8.62 (1H, m, br). MS (ion spray) m/z 428 $(M+H)^+$. Anal. calcd. for $C_{25}H_{25}N_5O_2 \cdot C_2HO_2F_3 \cdot (H_2O)_{1.25}$: C, 57.5; H, 5.1%; N, 12.4. Found: C, 57.5; H, 4.8; N, 12.3.

Example 1ae

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-3-chloro-benzamide. Using the product from reference example 1ae. ^{1}H NMR (DMSO) δ 2.96 (t, J = 7Hz, 2H), 3.59 (q, J = 7Hz, 2H), 7.14 (d, J = 8 Hz, 1H), 7.3-7.45 (m, 3H), 7.59 (d, J = 7Hz, 1H), 7.65 (m, 2H), 7.98 (s, 1H), 8.57 (bt, 1H). MS (ion spray) m/z 341 / 343 (M+H Cl pattern). Combustion analysis: $C_{18}H_{17}N_4OCl;(C_2HF_3O_2)_{1.2}$ requires C 51.3, H 3.8, N 11.7. Found C 51.4, H 3.9, N 11.7.

Example 1af

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-2-(3-chloro-phenyl)-acetamide. Using the product from reference example 1af. ^{1}H NMR (DMSO) δ 2.82 (t, J = 7Hz, 2H), 3.35 (q, J = 7Hz, 2H), 3.40 (s, 2H), 7.11 (m, 2H), 7.25 (m, 2H), 7.45 (d, J = 8Hz, 1H), 7.67 (s, 1H), 8.22 (m, 2H), 8.62 (bs, 2H), 8.69 (bs, 2H). MS (ion spray) m/z 355 / 357 (M+H, Cl pattern).

Example 1ag

4-(2-Aminomethyl-pyridin-4-yl)-N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-benzamide. Using the product from reference example 1ag. ^{1}H NMR (DMSO) δ 3.0 (t, J = 7.5Hz, 2H), 3.61 (q, J = 7 Hz, 2H), 4.29 (q, J = 6 Hz, 2H), 7.20 (d, J = 8Hz, 1H), 7.50 (d, J = 8 Hz, 1H), 7.82 (d, J = 5Hz, 1H), 7.93 (m, 3H), 8.0 (m, 2H), 8.22 (d, J = 3Hz, 1H), 8.40 (bs, 3H), 8.7 (m, 6H), 12.34 (bs, 1H). MS (ion spray) m/z 527 $(M+H^+TFA)$, 413 (M+H). Combustion analysis: $C_{24}H_{24}N_5O;(C_2HF_3O_2)_3(NH_4Cl)_{0.3}$ requires C 46.8, H 3.7, N 11.4. Found C 46.6, H 3.9, N 11.5.

Example 1ah

4-{4-[2-(3-Carbamimidoy-1H-indol-5-yl)-ethylcarbamoyl]-phenyl-pyridine-2-carboxylic acid amide. Using the product from reference example 1ah. ^{1}H NMR (DMSO) δ 3.0 (t, J = 7Hz, 2H), 3.61 (q, J = 7Hz, 2H), 7.21 (d, J = 8Hz, 1H), 7.50 (d, J = 8Hz, 1H), 7.75 (m, 2H), 8.0 (m, 4H), 8.23 (m, 2H), 8.35 (bs, 1H), 8.55 (bs, 2H), 8.75 (m, 5H). MS (ion spray) m/z 427 (M+H).

Example 1ai

N-[2-(3-Carbamimidoy-1H-indol-5-yl)-ethyl]-4-(2-(N,N-dimethylaminomethyl)-pyridin-4-yl)benzamide). Using the product from reference example 1ai. ^{1}H NMR (CD_3OD) δ 3.00 (s, 6H), 3.10 (t, J = 7Hz, 2H), 3.70 (t, J = 7Hz, 2H), 4.56 (s, 2H), 7.25 (dd, J = 8, 2Hz, 1H), 7.49 (d, J = 8Hz, 1H), 7.80 (m, 2H), 7.83 (s, 1H), 7.88 (m, 2H), 7.93 (m, 2H), 8.09 (s, 1H), 8.75 (d, J = 5Hz, 1H). MS (ion spray) m/z 441 (M+H). Combustion analysis: $C_{26}H_{28}N_6O;(C_2HF_3O_2)_3$ requires C 49.1, H 4.0, N 10.7. Found C 49.4, H 4.3, N 10.9.

Example 1aj

N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(6-oxo-1,6-dihydro-pyridazin-3-yl)-benzamide. Using the product from reference example 36d. ^{1}H NMR (DMSO) δ 2.98 (bt, 2H), 3.58 (m, 2H), 7.02 (d, J = 9Hz, 1H), 7.20 (d, J = 9Hz, 1H), 7.50 (d, J = 8Hz, 1H), 7.74 (s, 1H), 7.95 (m, 4H), 8.10 (d, J = 10Hz, 1H), 8.21 (s, 1H), 8.60 (bs, 1H), 8.71 (bs, 3H), 12.30 (s, 1H), 13.31 (s, 1H). MS (ion spray) m/z 401 $(M+H)^+$. Combustion Analysis: $C_{22}H_{20}N_6O_2$; $(C_2HF_3O_2)_2;(NH_4Cl)_{1.5}$ requires C 44.1, H 4.0, N 14.8. Found C 44.5, H 4.1, N 14.4.

Example 1ak

N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(6-methoxy-pyridazin-3-yl)-benzamide. Using the product from reference example 1ak. ^{1}H NMR (DMSO) δ 3.00 (bt, 2H), 3.58 (m, 2H), 4.10 (s, 3H), 7.20 (d, J = 9Hz, 1H), 7.36 (d, J = 9Hz, 1H), 7.50 (d, J = 8Hz, 1H), 7.76 (s, 1H), 7.98 (d, J = 8Hz, 2H), 8.17 (d, J = 8Hz, 2H), 8.23 (d, J = 5Hz, 1H), 8.63 (bs, 2H), 8.73 (bs, 3H), 12.32 (bs, 1H). MS (ion spray) m/z 415 $(M+H)^+$. Combustion Analysis: $C_{21}H_{22}N_6O_2;(C_2HF_3O_2)_{2.5};(NH_4Cl)_{0.5}$ requires C 46.3, H 3.7, N 12.5. Found C 46.2, H 3.8, N 12.6.

Example 1al

N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[1-(2-dimethylamino-ethyl)-6-oxo-1,6-dihydro-pyridazin-3-yl]-benzamide. Using the product from reference example 1al. ^{1}H NMR (DMSO) δ 2.88 (bs, 6H), 2.98 (bt, 2H), 3.58 (m, 4H), 4.52 (bt, 2H), 7.14 (d, J = 10Hz, 1H), 7.18 (d, J = 9Hz, 1H), 7.49 (d, J = 8Hz, 1H), 7.74 (s, 1H), 7.94 (d, J = 9Hz, 2H), 8.02 (d, J = 9Hz, 2H), 8.16 (d, J = 10Hz, 1H), 8.22 (d, J = 3Hz, 1H), 8.74 (m, 3H), 9.74 (bs, 1H), 12.34 (d, J = 3Hz, 1H). MS (ion spray) m/z 472 $(M+H)^+$. Combustion Analysis: $C_{26}H_{29}N_7O_2;(C_2HF_3O_2)_3;(NH_4Cl)_{0.1};(H_2O)_2$ requires C 45.0, H 4.0, N 11.6. Found C 45.1, H 3.8, N 11.3.

Example 1am

N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[1-(3-dimethylamino-propyl)-6-oxo-1,6-dihydro-pyridazin-3-yl]-benzamide. Using the product from reference example 1am. ^{1}H NMR (DMSO) δ 2.16 (m, 2H), 2.77 (s, 3H), 2.78 (s, 3H), 2.98 (bt, 2H), 3.15 (m, 2H), 3.56 (m, 2H), 4.22 (bt, 2H), 7.10 (d, J = 10Hz, 1H), 7.18 (d, J = 8Hz, 1H), 7.49 (d, J = 9Hz, 1H), 7.74 (s, 1H), 7.94 (d, J = 8Hz, 2H), 8.00 (d, J = 8Hz, 2H), 8.14 (d, J = 10Hz, 1H), 8.22 (d, J = 3Hz, 1H), 8.74 (m, 3H), 9.72 (bs, 1H), 12.34 (s, 1H). MS (ion spray) m/z 485 $(M+H)^+$. Combustion Analysis: $C_{27}H_{31}N_7O_2;(C_2HF_3O_2)_3;(NH_4Cl)_{0.1};(H_2O)_{0.5}$ requires C 47.1, H 4.2, N 11.8. Found C 46.8, H 4.2, N 11.8.

Example 1an

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(2-dimethylamino-ethylamino)-pyrimidin-4-yl]-benzamide. Using the product from reference example 1an. ^{1}H NMR (CD_3OD) δ 2.97 (s, 6H), 3.08 (t, J = 7Hz, 2H), 3.44 (t, J = 6Hz, 2H), 3.70 (t, J = 7Hz, 2H), 3.87 (bt, J = 6Hz, 2H), 7.28 (m, 2H), 7.49 (d, J = 8Hz, 1H), 7.80 (s, 1H), 7.90 (d, J = 8Hz, 2H), 8.09 (s, 1H), 8.18 (d, J = 8Hz, 2H), 8.44 (bm, 1H). MS (ion spray) m/z 471 $(M+H)^+$. Combustion Analysis: $C_{26}H_{30}N_8O;(C_2HF_3O_2)_{3.2}$ requires C 46.6, H 4.0, N 13.4. Found C 46.6, H 4.1, N 13.7.

Example 1ao

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-methoxy-pyrimidin-4-yl]-benzamide. Using the product from reference example 1ao and purifying by flash chromatography (eluting with 10 % MeOH in CH_2Cl_2 then 20% MeOH / 10 % 7N NH_3 in MeOH / 70 % CH_2Cl_2) isolated as the hydrochloride salt, ^1H NMR (CD_3OD) δ 3.09 (t, J = 7Hz, 2H), 3.70 (t, J = 7Hz, 2H), 4.10 (s, 3H), 7.25 (d, J = 8Hz, 1H), 7.48 (d, J = 8Hz, 1H), 7.63 (d, J = 5Hz, 1H), 7.78 (s, 1H), 7.90 (d, J = 8Hz, 2H), 8.09 (s, 1H), 8.23 (d, J = 8Hz, 2H), 8.61 (d, J = 5Hz, 1H). MS (ion spray) m/z (ion spray) m/z 415 (M+H). Combustion Analysis: $C_{23}H_{22}N_6O_2$;$(HCl)_2$ requires C 56.7, H 5.0, N 17.2. Found C 57.1, H 4.9, N 17.0.

Example 1ap

N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-(1-[2-dimethylaminoethyl]-6-oxo-1,6-dihydropyridin-3-yl)benzamide. Using the product from reference example 1ap, m.p. 94-97°C. ^1H NMR (D_2O): δ 2.61 (2H, m), 2.80 (6H, s), 3.25 (2H, m), 3.32 (2H, m), 4.14 (2H, m), 6.45 (1H, d, J = 9.0 Hz), 6.96 (1H, d, J = 8.2 Hz), 7.22-7.31 (4H, m), 7.40 (2H, d, J = 8.0 Hz), 7.55-7.69 (3H, m), 7.78 (1H, s). MS (ion spray) m/z 471 $(M+H)^+$. Anal. calcd. for $C_{27}H_{30}N_6O_2 \cdot 3C_2HO_2F_3$: C, 48.8; H, 4.1; N, 10.3. Found: C, 48.8; H, 4.1; N, 10.6.

Example 1aq

N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-(1-carbamoylmethyl-6-oxo-1,6-dihydropyridin-3-yl)benzamide. Using the product from reference example 1aq m.p. 244-245°C. ^1H NMR (CD_3OD): δ 2.97 (2H, t, J = 7 Hz), 3.59 (2H, m), 4.67 (2H, s), 6.56 (1H, d, J = 9 Hz), 7.16 (1H, d, J = 8 Hz), 7.38 (1H, d, J = 8 Hz), 7.54 (2H, d, J = 8 Hz), 7.67 (1H, s), 7.73 (2H, d, J = 8 Hz), 7.85 (1H, d, J = 9 Hz), 7.91 (1H, s), 7.98 (1H, s). MS (ion spray) m/z 457 $(M+H)^+$.

Example 1ar

4-(3-Amino-[1,2,4]triazin-6-yl)-N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-benzamide. Using the product from reference example 1ar ^1H NMR (CD_3OD) d 3.09 (2H, t, J = 7 Hz), 3.72 (2H, t, J = 7 Hz), 7.23 (1H, d, J = 8 Hz), 7.49 (1H, d, J = 8 Hz), 7.79 (1H, s), 7.93 (2H, d, J = 7 Hz), 8.13 (1H, s), 8.28 (2H, d, J = 7 Hz), 9.15 (1H, s); MS, m/z (ion spray) 401 $(M + H)^+$.

Example 1as

4-(3-Amino-[1,2,4]triazin-5-yl)-N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-benzamide. Using the product from reference example 1as. ^{1}H NMR (CD_3OD) d 3.08 (2H, t, J = 7 Hz), 3.68 (2H, m), 7.25 (1H, d, J = 9 Hz), 7.49 (1H, d, J = 9 Hz), 7.7-8.3 (7H, m); MS, m/z (ion spray) 401 $(M + H)^+$.

Example 1at

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]- 4-(3-oxo-2,3-dihydro-[1,2,4]triazin-6-yl)-benzamide. Using the product from reference example 1at. ^{1}H NMR (DMSO-d_6) d 2.99 (2H, t, J = 5 Hz), 3.05 (2H, m), 6.58 (1H, m), 7.22 (1H, d, J = 8 Hz). 7.52 (1H, d, J = 8 Hz), 7.75 (1H, d, J = 3 Hz), 7.94 (2H, d, J = 8 Hz), 8.02 (1H, d, J = 3 Hz), 8.04 (2H, d, J =7 Hz), 8.22 (1H, d, J = 3 Hz), 8.49 (1H, s), 8.70 (1H, s), 8.81 (1H, t, J = 5 Hz), 11.12 (1H, s), 12.28 (1H, s); MS, m/z (ion spray) 420 $[(M+18)+H]^+$.

Example 1au

N-[2-(3-Carbamimidoyl-1H-indol-5yl)ethyl]-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-benzamide. Using the product from reference example 1au. ^{1}H NMR (CD_3OD) d 3.11 (2H, t, J = 8 Hz), 3.72 (2H, m), 7.27 (1H, d, J = 9 Hz.), 7.49 (1H, d, J = 9 Hz), 7.78 (1H, s), 7.90 (4H, q, J = 8 Hz, J = 16 Hz), 8.08 (1H, s), 8.76 (1H, m); MS, m/z (ion spray) 391 $[(M+H]^+$.

Example 1av

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl-4-(6-oxo-piperidin-3-yl)-benzamide. Using the product from reference example 64a. ^{1}H NMR (CD_3OD) δ 2.08 (m, 2H), 2.43 (m, 2H), 3.10 (m, 3H), 3.42 (m, 2H), 3.65 (m, 2H), 7.13 (m, 1H), 7.20 (m, 1H), 7.38 (m, 2H), 7.45 (m, 1H), 7.72 (m, 3H), 8.07 (m, 1H); MS (Ion spray) m/z 387 $(M+H)^+$.

Example 1aw

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(morpholin-4yl-ethylamino)-pyrimidin-4-yl]-benzamide. Using the product from reference example 1aw. ^{1}H NMR (DMSO) δ 2.99 (t, J = 7Hz, 2H), 3.40 (m, 2H), 3.53-4.1 (m, 12H), 7.20 (d, J = 8Hz, 1H), 7.34 (d, J = 5Hz, 1H), 7.50 (m, 2H), 7.73 (s, 1H), 7.95 (d, J = 8Hz, 2H), 8.21 (m, 3H), 8.45 (d, J = 5Hz, 1H), 8.52 (bs, 2H), 8.72 (bs, 2H), 8.77 (bt, 1H). MS (ion spray) m/z = 513 $(M+H)^+$.

Example 1ax

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(3-dimethylamino-propylamino)-pyrimidin-4-yl]-benzamide. Using the product from reference example 1ax. ^{1}H NMR (DMSO) δ 1.95 (m, 2H), 2.77 (s, 3H), 2.79 (s, 3H), 3.0 (t, J = 7Hz, 2H), 3.15 (m, 2H), 3.43 (m, 2H), 3.60 (q, J = 7Hz, 2H), 7.21 (d, J = 8Hz, 1H), 7.25 (d, J = 5Hz, 1H), 7.45 (bm, 1H), 7.50 (d, J = 8Hz, 1H), 7.74 (s, 1H), 7.95 (d, J = 8Hz, 2H), 8.20 (d, J = 8Hz, 2H), 8.21 (d, J = 5Hz, 1H), 8.41 (d, J = 5Hz, 1H), 8.70 (bm, 5H). MS (ion spray) m/z 485 $(M+H)^+$.

Example 1ay

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-([2-dimethylamino-ethyl]-methyl-amino)-pyrimidin-4-yl]-benzamide. Using the product from reference example 1ay ^{1}H NMR (DMSO) δ 2.9 (bs, 6H), 3.0 (bt, J = 7Hz, 2H), 3.24 (s, 3H), 3.40 (bm, 2H), 3.59 (bq, J = 7Hz, 2H), 4.05 (bm, 2H), 7.20 (d, J = 8Hz, 1H), 7.35 (d, J = 5Hz, 1H), 7.51 (d, J = 8Hz, 1H), 7.77 (s, 1H), 7.98 (d, J = 8Hz, 2H), 8.24 (m, 3H), 8.52 (d, J = 5Hz, 1H), 8.7 (bm, 5H). MS (ion spray) m/z 485 $(M+H)^+$.

Example 1az

2-[(4-{4-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethylcarbamoyl]-phenyl}-pyrimidin-2-yl)-methyl-amino]-ethanesulfonic acid. Using the product from reference example 92d. ^{1}H NMR (DMSO) δ 2.95 (bm, 4H), 3.17 (s, 3H), 3.48 (m, 2H), 3.96 (bm, 2H), 7.18 (d, J = 8Hz, 1H), 7.24 (dd, J = 5, 1Hz, 1H), 7.47 (dd, J = 8, 1Hz, 1H), 7.81 (bd, 2H), 7.92 (bs, 1H), 8.17 (bt, J = 1Hz, 1H), 8.31 (bd, J = 8Hz, 2H), 8.51 (bs, 1H), 8.61 (bs, 2H), 9.11 (bs, 1H). MS (ion spray) m/z 522 $(M+H)^+$.

Example 1aaa

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-{2-[methyl-(2(S),3(R),4(R),5(R),6-pentahydroxy-hexyl)-amino]-pyrimidin-4-yl}-benzamide. Using the product from reference example 92e. ^{1}H NMR (DMSO) δ 2.99 (t, J = 7Hz, 2H), 3.24 (bs, 3H), 3.38 (m, 1H), 3.42-3.67 (m, 9H), 4.05 (bm), 7.19 (d, J = 8Hz, 1H), 7.22 (d, J = 5Hz, 1H), 7.49 (d, J = 8Hz, 1H), 7.71 (s, 1H), 7.91 (d, J = 8Hz, 2H), 8.20 (m, 3H), 8.45 (m, 3H), 8.70 (m, 3H). MS (ion spray) m/z 578 $(M+H)^+$.

Example 1aab

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-{2-[methyl-(2(S),3(R),4(S),5(R),6-pentahydroxy-hexyl)-amino]-pyrimidin-4-yl}-benzamide. Using the product from reference example 92f. ^{1}H NMR (DMSO) δ 2.99 (t, J = 7Hz, 2H), 3.26 (bs, 3H), 3.39 (m, 3H), 3.55 (m, 3H), 3.63-4.2 (bm, 8H), 7.20 (m, 2H), 7.50 (d, J = 8Hz, 1H), 7.72 (s, 1H), 7.93 (d, J = 8Hz, 2H), 8.20 (m, 3H), 8.42 (m, 3H), 8.70 (m, 3H). MS (ion spray) m/z 578 $(M+H)^+$.

Example 1aac

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(2-hydroxy-1-hydroxymethyl-ethylamino)-pyrimidin-4-yl]-benzamide. Using the product from reference example 92g. ^{1}H NMR (DMSO) δ 2.95 (t, J = 7Hz, 2H), 3.55 (m, 4H), 3.6-4.1 (bm, 5H), 6.75 (bs, 1H), 7.20 (m, 2H), 7.48 (d, J = 8Hz, 1H), 7.70 (s, 1H), 7.90 (d, J = 8Hz, 2H), 8.18 (m, 3H), 8.40 (d, J = 5Hz, 1H), (m, 2H), 8.70 (m, 3H). MS (ion spray) m/z 474 $(M+H)^+$.

Example 1aad

2-[(4-{4-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethylcarbamoyl]-phenyl}-pyrimidin-2-yl)-methyl-amino]-ethanesulfonic acid. Using the product from reference example 92h. The title compound was purified by precipitation from the reaction medium. ^{1}H NMR (DMSO) δ 2.95 (m, 4H), 3.18 (s, 3H), 3.50 (bm, 2H), 4.00 (bm, 2H), 7.18 (d, J = 8Hz, 1H), 7.24 (dd, J = 5, 1Hz, 1H), 7.47 (dd, J = 8, 2Hz, 1H), 7.81 (d, J = 8Hz, 1H), 7.92 (bs, 1H), 8.15 (t, J = 1Hz, 1H), 8.30 (d, J = 8Hz, 2H), 8.40 (dd, J = 8, 2Hz, 1H), 8.52 (m, 1H), 8.64 (bs, 2H), 9.11 (bs, 2H). MS (ion spray) m/z 522 $(M+H)^+$.

Example 1aae

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(3-imidazol-1-yl-propylamino)-pyrimidin-4-yl]-benzamide. Using the product from reference example 92i, ^{1}H NMR (DMSO) δ 2.10 (m, 2H), 2.95 (t, J = 7Hz, 2H), 3.36 (bm, 2H), 3.56 (q, J = 7Hz, 2H), 4.30 (t, J = 7Hz, 2H), 7.18 (d, J = 8Hz, 1H), 7.24 (d, J = 5 Hz, 1H), 7.48 (d, J = 8 Hz, 1H), 7.50 (bs, 1H), 7.70 (s, 1H), 7.75 (s, 1H), 7.82 (s, 1H), 7.94 (d, J = 8Hz, 2H), 8.14 (d, J = 8Hz, 2H), 8.21 (d, J = 1Hz, 1H), 8.39 (d, J = 5 Hz, 1H), 8.75 (m, 5H) 9.15 (s, 1H). MS (ion spray) m/z 508 $(M+H)^+$.

Example 1aaf

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-{2-[(2-diethylamino-ethyl)-methyl-amino]-pyrimidin-4-yl}-benzamide. Using the product from reference example 92j. ^{1}H NMR (DMSO) δ 1.60 (t, J = 7Hz, 6H), 2.95 (t, J = 7Hz, 2H), 3.12-3.4 (m, 9H), 3.59 (q, J = 7Hz, 2H), 4.0 (bt, 2H), 7.18 (d, J = 8Hz, 1H), 7.32 (d, J = 5Hz, 1H), 7.49 (d, J = 8Hz, 1H), 7.75 (s, 1H), 7.94 (d, J = 8Hz, 2H), 8.20 (m, 3H), 8.50 (d, J = 5Hz, 1H), 8.70 (bs, 4H), 8.74 (bt, 1H), 9.40 (bs, 1H). MS (ion spray) m/z 513 $(M+H)^+$.

Example 1aag

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(2-diisopropylamino-ethylamino)-pyrimidin-4-yl]-benzamide. Using the product from reference example 92k. ^{1}H NMR (DMSO) δ 1.29 (d, J = 7Hz, 12H), 2.97 (t, J = 7Hz, 2H), 3.22 (bt, 2H), 3.57 (q, J = 7Hz, 2H), 3.68 (m, 4H), 7.18 (d, J = 8Hz, 1H), 7.39 (d, J = 5Hz, 1H), 7.42 (bm, 1H), 7.48 (d, J = 8Hz, 1H), 7.73 (s, 1H), 7.95 (d, J = 8Hz, 2H), 8.15 (d, J = 8Hz, 2H), 8.20 (d, J = 3Hz, 1H), 8.44 (d, J =5Hz, 1H), 8.71 (bs, 4H), 8.74 (bt, 1H). MS (ion spray) m/z 527 $(M+H)^+$.

Example 1aah

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(2-dibutylamino-ethylamino)-pyrimidin-4-yl]-benzamide. Using the product from reference example 92l. ^{1}H NMR (DMSO) δ 0.85 (t, J = 7Hz, 6H), 1.29 (m, 4H), 1.60 (m, 4H), 2.97 (t, J = 7Hz, 2H), 3.12 (m, 4H), 3.30 (m, 2H), 3.58 (q, J = 7Hz, 2H), 3.73 (m, 2H), 7.17 (d, J = 8Hz, 1H), 7.30 (d, J = 5Hz, 1H), 7.45 (d, J = 8Hz, 2H), 7.48 (d, J = 8Hz, 1H), 7.72 (s, 1H), 7.95 (d, J = 8Hz, 2H), 8.15 (d, J = 8Hz, 2H), 8.20 (d, J = 3Hz, 1H), 8.44 (d, J =5Hz, 1H), 8.65-8.8 (bm, 5H), 8.74 (bs, 1H). MS (ion spray) m/z 555 $(M+H)^+$.

Example 1aai

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(3-morpholin-4-yl-propylamino)-pyrimidin-4-yl]-benzamide. Using the product from reference example 92m. ^{1}H NMR (DMSO) δ 1.95 (m, 2H), 2.9-3.14 (m, 4H), 3.19 (m, 2H), 3.40 (m, 4H), 3.59 (m, 4H), 7.17 (d, J = 8Hz, 1H), 7.21 (d, J = 5Hz, 1H), 7.40 (bt, J = 7Hz, 1H), 7.48 (d, J = 8Hz, 1H), 7.72 (s, 1H), 7.93 (d, J = 8Hz, 2H), 8.14 (m, 3H), 8.44 (d, J =5Hz, 1H), 8.55 (bs, 2H), 8.71 (bm, 3H).

Example 1aaj

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(3-diethylamino-propylamino)-pyrimidin-4-yl]-benzamide. Using the product from reference example 92n. ^{1}H NMR (DMSO) δ 1.15 (t, J = 7Hz, 6H), 2.99 (t, J = 7Hz, 2H), 3.13 (m, 6H), 3.43 (m, 2H), 3.58 (m, 2H), 7.18 (d, J = 8Hz, 1H), 7.21 (d, J = 5Hz, 1H), 7.40 (bt, J = 7Hz, 1H), 7.48 (d, J = 8Hz, 1H), 7.73 (s, 1H), 7.94 (d, J = 8Hz, 2H), 8.16 (m, 3H), 8.40 (d, J =5Hz, 1H), 8.60 (bs, 2H), 8.71 (bm, 3H). MS (ion spray) m/z 513 $(M+H)^+$.

Example 1aak

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(3-piperidin-1-yl-propylamino)-pyrimidin-4-yl]-benzamide. Using the product from reference example 92p. ^{1}H NMR (DMSO) δ 1.50-1.73 (m, 4H), 1.80 (m, 2H), 1.96 (m, 2H), 2.85 (m, 2H), 2.96 (m, 2H), 3.13 (m, 2H), 3.42 (m, 4H), 3.56 (m, 2H), 7.18 (d, J = 8Hz, 1H), 7.22 (d, J = 5Hz, 1H), 7.40 (bt, J = 7Hz, 1H), 7.48 (d, J = 8Hz, 1H), 7.73 (s, 1H), 7.95 (d, J = 8Hz, 2H), 8.16 (m, 3H), 8.38 (d, J =5Hz, 1H), 8.6-8.78 (bm, 5H). MS (ion spray) m/z 525 $(M+H)^+$.

Example 1aal

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(2-{[2-(ethyl-methyl-amino)-ethyl]-methyl-amino}-pyrimidin-4-yl)-benzamide. Using the product from reference example 92q. ^{1}H NMR (DMSO) δ 1.15 (t, J = 7Hz, 3H), 2.77 (s, 3H), 2.78 (s, 3H), 2.96 (t, J = 7Hz, 2H), 3.10 (m, 2H), 3.57 (q, J = 7Hz, 2H), 3.69 (m, 4H), 7.18 (d, J = 8Hz, 1H), 7.24 (d, J = 5Hz, 1H), 7.49 (d, J = 8Hz, 1H), 7.72 (s, 1H), 7.94 (d, J = 8Hz, 2H), 8.18 (m, 3H), 8.38 (d, J =5Hz, 1H), 8.6-8.75 (bm, 5H), 9.6 (bs, 1H).

Example 1aam

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(5-dimethylamino-pentylamino)-pyrimidin-4-yl]-benzamide. Using the product from reference example 92r. ^{1}H NMR (DMSO) δ 1.35 (m, 2H), 1.58 (m, 4H), 2.71 (s, 3H), 2.72 (s, 3H), 3.0 (m, 4H), 3.37 (m, 2H), 3.45-3.8 (bs, solvent), 7.18 (m, 2H), 7.32 (bm, 1H), 7.48 (d, J = 8Hz, 1H), 7.72 (s, 1H), 7.94 (d, J = 8Hz, 2H), 8.15 (m, 3H), 8.37 (d, J =5Hz, 1H), 8.57 (bs, 2H), 8.70 (bm, 3H), 9.35 (bs, 1H). MS (ion spray) m/z 513 $(M+H)^+$.

Example 1aan

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(5-morpholin-4-yl-pentylamino)-pyrimidin-4-yl]-benzamide. Using the product from reference example 92s. ^{1}H NMR (DMSO) δ 1.36 (m, 2H), 1.61 (m, 4H), 2.9-3.1 (m, 8H), 3.35 (m, 4H), 3.5-3.7 (m, 4H), 7.18 (m, 2H), 7.40 (bm, 1H), 7.48 (d, J = 8Hz, 1H), 7.71 (s, 1H), 7.92 (d, J = 8Hz, 2H), 8.15 (m, 3H), 8.38 (d, J =5Hz, 1H), 8.62 (bs, 2H), 8.70 (bm, 3H), 9.85 (bs, 1H). MS (ion spray) m/z 555 $(M+H)^+$.

Example 1aap

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(5-piperidin-1-yl-pentylamino)-pyrimidin-4-yl]-benzamide. Using the product from reference example 92t. ^{1}H NMR (DMSO) δ 1.35 (m, 4H), 1.5-1.95 (m, 8H), 2.80 (m, 2H), 2.95 (m, 4H), 3.38 (m, 4H), 3.55 (q, J = 7Hz, 2H), 7.19 (m, 2H), 7.40 (bm, 1H), 7.46 (d, J = 8Hz, 1H), 7.71 (s, 1H), 7.92 (d, J = 8Hz, 2H), 8.19 (m, 3H), 8.39 (d, J =5Hz, 1H), 8.62-8.80 (bm, 5H), 9.20 (bs, 1H). MS (ion spray) m/z 553 $(M+H)^+$.

Example 1aaq

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(5-pyrrolidin-1-yl-pentylamino)-pyrimidin-4-yl]-benzamide. Using the product from reference example 92u. ^{1}H NMR (DMSO) δ 1.37 (m, 4H), 1.60 (m, 4H), 1.80 (m, 2H), 1.94 (m, 2H), 2.94 (m, 4H), 3.08 (m, 2H), 3.33 (m, 2H), 3.50 (m, 4H), 7.19 (m, 2H), 7.40 (bm, 1H), 7.48 (d, J = 8Hz, 1H), 7.70 (s, 1H), 7.91 (d, J = 8Hz, 2H), 8.15 (m, 3H), 8.36 (d, J =5Hz, 1H), 8.62 (bs, 2H), 8.7 (bm, 3H), 9.60 (bs, 1H). MS (ion spray) m/z 539 $(M+H)^+$.

Example 1aar

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(2-oxo-hexahydro-pyrimidin-5-yl)-benzamide. Using the product from reference example 1aaa. ^{1}H NMR (DMSO) δ 2.91 (t, J = 7Hz, 2H), 3.08 (m, 1H), 3.25 (m, 4H), 3.53 (q, J = 7Hz, 2H), 6.33 (bs, 2H), 7.17 (d, J = 8Hz, 1H), 7.38 (d, J = 8Hz, 2H), 7.46 (d, J = 8Hz, 1H), 7.69 (s, 1H), 7.75 (d, J = 8Hz, 2H), 8.17 (d, J = 3Hz, 1H), 8.42 (bm, 2H), 8.52 (bt, J = 7Hz, 1H), 8.67 (bs, 2H). MS (ion spray) m/z 407 $(M+H)^+$.

Example 1aas

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(1,3-dimethyl-2-oxo-hexahydro-pyrimidin-5-yl)-benzamide. Using the product from reference example 1aab. ^{1}H NMR (CD_3OD) δ 2.95 (s, 6H), 3.06 (t, J = 7Hz, 2H), 3.36-3.55 (m, 5H), 3.66 (m, 2H), 7.23 (d, J = 8Hz, 1H), 7.39 (d, J = 8Hz, 2H), 7.47 (d, J = 8Hz, 1H), 7.77 (m, 3H), 8.07 (d, J = 3Hz, 1H), 8.30 (bm, 2H), 8.52 (bt, J = 7Hz, 1H), 8.68 (bs, 2H). MS (ion spray) m/z 433 $(M+H)^+$.

Example 1aat

Biphenyl-3,4'-dicarboxylic acid 4'-{[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-amide} 3-[(2-methoxy-ethyl)-amide]. Using the product from reference example 99a. ^{1}H NMR (CD_3OD) δ 3.09 (t, J = 7Hz, 2H), 3.40 (s, 3H), 3.60 (bs, 4H), 3.71 (q, J = 7Hz, 2H), 7.28 (d, J = 8Hz, 1H), 7.48 (d, J = 8Hz, 1H), 7.56 (t, J = 8Hz, 1H), 7.77 (m, 3H), 7.87 (m, 4H), 8.07 (s, 1H), 8.13 (s, 1H), 8.65 (bt, 1H). MS (ion spray) m/z 484 $(M+H)^+$.

Example 1aau

3'-(Morpholine-4-carbonyl)-biphenyl-4-carboxylic acid [2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-amide. Using the product from reference example 99b. ^{1}H NMR (DMSO) δ 2.98 (t, J = 7Hz, 2H), 3.3-3.8 (bs, solvent), 7.20 (d, J = 8Hz, 1H), 7.43 (d, J = 8Hz, 1H), 7.50 (d, J = 8Hz, 1H), 7.56 (t, J = 8Hz, 1H), 7.73 (bs, 2H), 7.80 (m, 3H), 7.91 (d, J = 8Hz, 2H), 8.20 (d, J = 1Hz, 1H), 8.50 (bs, 2H), 8.70 (m, 3H). MS (ion spray) m/z 496 $(M+H)^+$.

Example 1aav

Biphenyl-3,4'-dicarboxylic acid 4'-{[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-amide} 3-[(2-morpholin-4-yl-ethyl)-amide]. Using the product from reference example 99c. ^{1}H NMR (CD_3OD) δ 3.08 (t, J = 7Hz, 2H), 3.15-3.3 (bm, 2H), 3.45 (t, J = 7Hz, 2H), 3.70 (m, 2H), 3.6-3.95 (bm, 4H), 3.81 (t, J = 7Hz, 2H), 4.06 (bm, 2H), 7.27 (d, J = 8Hz, 1H), 7.50 (d, J = 8Hz, 1H), 7.61 (t, J = 8Hz, 1H), 7.77 (m, 3H), 7.90 (m, 4H), 8.1 (s, 1H), 8.20 (bs, 1H), 8.7 (bt, 1H). MS (ion spray) m/z 539 $(M+H)^+$.

Example 1aaw

Biphenyl-2,4'-dicarboxylic acid 4'-{[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-amide} 2-[(3-diethylamino-propyl)-amide]. Using the product from reference example 99d. MS (ion spray) m/z 539 $(M+H)^+$.

Example 1aax

Biphenyl-2,4'-dicarboxylic acid 4'-{[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-amide} 2-[(3-morpholin-4-yl-propyl)-amide]. Using the product from reference example 99e. MS (ion spray) m/z 553 $(M+H)^+$.

Example 1aaaa

Biphenyl-2,4'-dicarboxylic acid 4'-{[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-amide} 2-[(3-piperidin-1-yl-propyl)-amide]. Using the product from reference example 99f. MS (ion spray) m/z 551 $(M+H)^+$.

Example 1aaab

Biphenyl-2,4'-dicarboxylic acid 4'-{[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-amide} 2-[(4-dimethylamino-butyl)-amide]. Using the product from reference example 99g. MS (ion spray) m/z 525 $(M+H)^+$.

Example 1aaac

Biphenyl-2,4'-dicarboxylic acid 4'-{[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-amide} 2-[(2,3-dihydroxy-propyl)-methyl-amide]. Using the product from reference example 99h. MS (ion spray) m/z 514 $(M+H)^+$.

Example 1aaad

Biphenyl-2,4'-dicarboxylic acid 4'-{[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-amide} 2-[(2,3-dihydroxy-propyl)-amide]. Using the product from reference example 99i. MS (ion spray) m/z 500 $(M+H)^+$.

Example 1aaae

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(4-methylpiperazin-1-yl)pyrimidin-4-yl]benzamide. Using the product from reference example 92v. m.p. 111-113°C. ^{1}H NMR (DMSO-d_6): δ 2.50 (s, 3H), 2.86 (s, 4H), 2.98 (t, 2H, J=9Hz), 3.30 (t, 2H, J=12Hz), 3.57 (m, 4H), 7.20 (d,1H, J=9Hz), 7.43 (d,1H, J=6Hz), 7.50 (d,1H, J=9Hz), 7.74 (s,1H), 7.97 (d, 2H, J=9Hz), 8.22 (d,1H, J=3Hz), 8.26 (d, 2H, J=9Hz), 8.55 (s, 1H), 8.57 (d,1H, J=6Hz), 8.72 (s, 2H), 8.77 (t,1H, J=6Hz). MS (ion spray) m/z 483 $(M+H)^+$. Anal. calcd for $C_{27}H_{30}N_8O \cdot 3C_2HF_3O_2 \cdot 1.5H_2O$: C, 46.5%; H, 4.3%; N, 13.2%. Found: C, 46.3%; H, 4.1%; N, 13.4%.

Example 1aaaf

4-[(4-{4-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethylcarbamoyl]phenyl}pyrimidin-2-yl)methylamino]butyric acid. Using the product from reference example 92w. m.p. 100-104°C. ^{1}H NMR (DMSO-d_6): δ 1.85(t, 2H, J=6Hz), 2.26 (t, 2H, J=6Hz), 3.00 (t, 2H, J=6Hz), 3.18 (s, 3H), 3.56 (m, 2H), 3.71 (m, 2H), 7.22 (t,1H, J=6Hz), 7.50 (d,1H, J=6Hz), 7.74 (s,1H), 8.00 (d, 2H, J=8Hz), 8.24 (s,1H), 8.25 (d, 2H, J=8Hz), 8.45 (d, 2H, J=6Hz), 8.71 (s, 2H). MS (ion spray) m/z 500 $(M+H)^+$. Anal. calcd for $C_{27}H_{29}N_7O_3 \cdot 2.5C_2HF_3O_2 \cdot 0.5H_2O$: C, 48.4%; H, 4.1%; N, 12.4%. Found: C, 48.7%; H, 4.1%; N, 12.1%.

Example 1aaag

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl]benzamide. Using the product from reference example 92x, m.p. 194-195°C. ^{1}H NMR (DMSO-d_6): δ 3.02 (t, 2H, J=6Hz), 3.60

(m, 2H), 5.10 (d, 1H, J=9Hz), 5.19 (d, 1H, J=9Hz), 7.21 (d,1H, J=9Hz), 7.52 (d,1H, J=9Hz), 7.72 (s,1H), 7.93 (d,1H, J=3Hz), 8.00 (d, 2H, J=6Hz), 8.20 (d,1H, J=3Hz), 8.32 (d, 2H, J=6Hz), 8.44 (s,1H), 8.71 (s, 2H), 8.80 (m, 2H). MS (ion spray) m/z 483 $(M+H)^+$.

Example 1aaah

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(2-pyrrolidin-1-ylpyrimidin-4-yl)benzamide. Using the product from reference example 92y. m.p. 134-136°C. ^{1}H NMR (DMSO-d_6): δ 2.00 (m, 4H), 3.00 (t, 2H, J=6Hz), 3.55 (m, 6H), 7.21 (m, 2H), 7.53 (d,1H, J=6Hz), 7.72 (s,1H), 7.93 (d, 2H, J=6Hz), 8.20 (m, 3H), 8.42 (m, 2H), 8.71 (s, 2H). MS (ion spray) m/z 454 $(M+H)^+$. >98% pure by analytical HPLC.

Example 1aaaj

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(2-hydroxymethylpyrrolidin-1-yl)-pyrimidin-4-yl]benzamide . Using the product from reference example 92z. m.p. 117-120°C. ^{1}H NMR (DMSO-d_6): δ 2.01 (m, 4H), 2.98 (t, 2H, J=6Hz), 3.40 (s,1H), 3.58 (m, 4H), 3.70 (s, 1H), 4.19 (s,1H), 7.20 (d,1H, J=6Hz), 7.25 (d,1H, J=6Hz), 7.50 (d,1H, J=6Hz), 7.73 (s,1H), 7.94 (d, 2H, J=9Hz), 8.21 (t, 3H, J=9Hz), 8.46 (d, 2H, J=6Hz), 8.71 (s, 2H). MS (ion spray) m/z 484 $(M+H)^+$. Anal. calcd for $C_{27}H_{29}N_7O_2 \cdot 2.5C_2HF_3O_2 \cdot 0.5H_2O$: C, 49.4%; H, 4.2%; N, 12.6%. Found: C, 49.2%; H, 4.2%; N, 12.6%.

Example 1aaak

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(carbamoylmethyl-N-methylamino)-pyrimidin-4-yl]benzamide. Using the product from reference example 92aa. m.p. 96-98°C. ^{1}H NMR (DMSO-d_6): δ 2.99 (t, 2H, J=6Hz), 3.23 (s, 3H), 3.59 (m, 2H), 3.80 (s, 2H), 7.21 (d,1H, J=9Hz), 7.30 (m, 1H), 7.50 (d,1H, J=6Hz), 7.74 (s,1H), 7.93 (d, 2H, J=9Hz), 8.20 (m, 3H), 8.45 (s, 2H), 8.71 (s, 2H). MS (ion spray) m/z 471 $(M+H)^+$. Anal. calcd for $C_{25}H_{26}N_8O_2 \cdot 3C_2HF_3O_2 \cdot H_2O$: C, 44.8%; H, 3.8%; N, 13.5%. Found: C, 44.9%; H, 4.0%; N, 13.5%.

Example 1aaal

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(6-pyrrolidin-1-yl-hexylamino)pyrimidin-4-yl]benzamide. Using the product from reference example 92ab. m.p. 159-161°C. ^{1}H NMR (DMSO-d_6): δ 1.38 (m, 4H), 1.62 (m, 4H), 1.87 (m, 2H), 2.02 (m, 2H), 2.53 (m, 4H), 3.00 (m, 2H), 3.12 (m, 2H), 3.38 (m, 2H), 3.57 (m, 2H), 7.20 (m, 2H), 7.30 (m,1H), 7.50 (d,1H, J=6Hz), 7.72 (s, 1H), 7.93 (d, 2H, J=6Hz), 8.19 (m, 3H), 8.40 (d, 1H, J=3Hz), 8.50 (s, 1H), 8.72 (m, 3H). MS (ion spray) m/z 553 $(M+H)^+$. >98% pure by analytical HPLC.

Example 1aaam

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(6-piperidin-1-ylhexylamino)pyrimidin-4-yl]benzamide. Using the product from reference example 92ac. m.p. 110-113°C. ^{1}H NMR (DMSO-d_6): δ 1.36 (m, 4H), 1.63(m, 6H), 1.97 (m, 2H), 1.98 (m, 2H), 2.50 (m, 4H), 2.80 (m, 2H), 2.98 (m, 2H), 3.40 (m, 2H), 3.67 (m, 2H), 7.22 (m, 2H), 7.30 (m, 1H), 7.55 (d, 1H, J=6Hz), 7.70 (s, 1H), 7.97 (d, 2H, J=6Hz), 8.20 (m, 3H), 8.40 (d, 1H, J=3Hz), 8.50 (s, 1H), 8.75 (m, 3H). MS (ion spray) m/z 567 $(M+H)^+$. >99% pure by analytical HPLC.

Example 1aaan

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(4-piperidin-1-ylbutylamino)pyrimidin-4-yl]benzamide. Using the product from reference example 92ad. m.p. 94-96°C. ^{1}H NMR (DMSO-d_6): δ 1.52-1.86 (m, 10H), 2.50 (m, 4H), 2.82 (m, 2H), 2.98 (m, 2H), 3.40 (m, 2H), 3.61 (m, 2H), 7.20 (m, 2H), 7.35 (m, 1H), 7.50 (d, 1H, J=6Hz), 7.75 (s, 1H), 7.95 (d, 2H, J=6Hz), 8.20 (m, 3H), 8.40 (d, 1H, J=3Hz), 8.48 (s, 1H), 8.7 (m, 3H). MS (ion spray) m/z 539 $(M+H)^+$. >99% pure by analytical HPLC.

Example 1aaap

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(4-diethylaminobutylamino)pyrimidin-4-yl]benzamide. Using the product from reference example 92ae. m.p. 73-76°C. ^{1}H NMR (D_2O): δ 1.03 (t, 6H, J=8Hz), 1.60 (s, 4H), 2.81 (m, 2H), 2.97 (m, 6H), 3.45 (m, 4H), 7.08 (d, 1H, J=6Hz), 7.18 (d, 1H, J=3Hz), 7.35 (d, 1H, J=9), 7.42 (s, 1H), 7.55 (m, 3H), 7.86 (s, 1H), 7.98 (m, 2H), 8.10 (m, 1H). MS (ion spray) m/z 527 $(M+H)^+$. >97% pure by analytical HPLC.

Example 1aaaq

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(6-morpholin-4-ylhexylamino)pyrimidin-4-yl]benzamide. Using the product from reference example 92af. m.p. 129-130°C. ^{1}H NMR (DMSO-d_6): δ 1.38 (m, 4H), 1.62 (m , 4H), 2.50 (m, 6H), 3.01 (m, 2H), 3.10 (m, 2H), 3.50 (m, 6H), 7.20 (m, 2H), 7.31 (m, 1H) 7.50 (d, 1H, J=3Hz), 7.65 (s, 1H), 7.95 (d, 2H, J=9Hz), 8.10 (m, 3H), 8.40 (m, 1H), 8.5 (s, 1H), 8.72 (m, 3H). MS (ion spray) m/z 569 $(M+H)^+$. >99% pure by analytical HPLC.

Example 1aaar

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(6-dimethylaminohexylamino)pyrimidin-4-yl]benzamide. Using the product from reference example 92ag. m.p. 89-91°C. ^{1}H NMR (DMSO-d_6): δ 1.36 (m, 4H), 1.59 (m, 4H), 2.75 (s, 3H), 2.76 (s, 3H), 2.95 (m, 4H), 3.28 (m, 2H), 3.60 (m, 2H), 7.21 (m, 2H), 7.32 (m, 1H), 7.51 (d, 1H, J=9Hz), 7.74 (s, 1H), 7.95 (d, 2H, J=9Hz), 8.18 (d, 2H, J=9Hz), 8.21 (d, 1H, J=3Hz), 8.37 (d, 1H, J=6Hz), 8.49 (s, 1H), 8.72 (m, 3H). MS (ion spray) m/z 527 $(M+H)^+$. Anal. calcd for $C_{30}H_{38}N_8O\cdot 3C_2HF_3O_2\cdot 2H_2O$: C, 47.8%; H, 5.0%; N, 12.4%. Found: C, 47.8%; H, 4.6%; N, 12.3%.

Example 1aaas

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(4-dimethylaminobutylamino)pyrimidin-4-yl]benzamide. Using the product from reference example 92ah. m.p. 156-159°C. ^{1}H NMR (DMSO-d_6): δ 1.62 (m, 2H), 1.68 (m, 2H), 2.76 (s, 3H), 2.77 (s, 3H), 2.98 (t, 2H, J=6Hz), 3.07 (m, 2H), 3.99 (m, 2H), 3.59 (m, 2H), 7.21 (m, 2H), 7.32 (m, 1H), 7.52 (d, 1H, J=9Hz), 7.74 (s, 1H), 7.95 (d, 2H, J=9Hz), 8.18 (d, 2H, J=9Hz), 8.21 (d, 1H, J=3Hz), 8.37 (d, 1H, J=6Hz), 8.49 (s, 1H), 8.72 (m, 3H). MS (ion spray) m/z 499 $(M+H)^+$. Anal. calcd for $C_{28}H_{34}N_8O\cdot 3C_2HF_3O_2\cdot 2H_2O$: C, 46.6%; H, 4.7%; N, 12.8%. Found: C, 46.5%; H, 4.5%; N, 12.6%. >99% pure by analytical HPLC.

Example 1aaat

4-[2-(Bicyclo[2.2.1]hept-2-ylamino)pyrimidin-4-yl]-N-[2-(3-carbamimidoyl-1H-indol-5-yl)ethyl]benzamide. Using the product from reference example 92ai. m.p. 152-155°C. ^{1}H NMR (DMSO-d_6): δ 1.14 (m, 2H), 1.33 (m, 2H), 1.46 (m, 2H), 1.63 (m, 1H), 1.97 (m, 1H), 2.20 (m, 2H), 2.97 (t, 2H, J=6Hz),

3.56 (m, 2H), 4.09 (m, 1H), 7.20 (m, 2H), 7.37 (m, 1H), 7.53 (d, 1H, J=9Hz), 7.73 (s, 1H), 7.94 (d, 2H, J=9Hz), 8.19 (d, 2H, J=9Hz), 8.20 (d, 1H, J=3Hz), 8.39 (d, 1H, J=6Hz), 8.45 (s, 1H), 8.70 (m, 3H). MS (ion spray) m/z 494 $(M+H)^+$. Anal. calcd for $C_{29}H_{31}N_7O \cdot 2C_2HF_3O_2 \cdot 1.5H_2O$: C, 52.9%; H, 4.8%; N, 13.1%. Found: C, 53.0%; H, 4.7%; N, 12.9%. >98% pure by analytical HPLC.

Example 1aaau

1-(4-{4-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethylcarbamoyl]phenyl}pyrimidin-2-yl)pyrrolidine-2-carboxylic acid amide. Using the product from reference example 92aj. m.p. 139-141°C. ^{1}H NMR (D_2O): δ 1.98 (m, 2H), 2.28 (m, 1H), 2.81 (t, 2H, J=6Hz), 3.44 (t, 2H, J=6Hz), 3.62 (m, 1H), 4.40 (m, 1H), 7.07 (d, 1H, J=9Hz), 7.12 (m, 1H), 7.38 (d, 1H, J=9Hz), 7.47 (s, 1H), 7.48 (d, 2H, J=9Hz), 7.89 (m, 3H), 8.16 (d, 1H, J=6Hz). MS (ion spray) m/z 497 $(M+H)^+$. Anal. calcd for $C_{27}H_{28}N_8O_2 \cdot 3C_2HF_3O_2 \cdot NH_3$: C, 46.3%; H, 4.0%; N, 14.7%. Found: C, 46.6%; H, 4.0%; N, 14.2%.

Example 1aaav

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-{2-[(2-hydroxy-ethyl)-N-methylamino]pyrimidin-4-yl}benzamide. Using the product from reference example 92ak. m.p. 97-100°C. ^{1}H NMR (DMSO-d_6): δ 2.99 (t, 2H, J=7Hz), 3.24 (s, 3H), 3.58 (m, 2H), 3.64 (t, 2H, J=7Hz), 3.75 (m, 2H), 7.21 (m, 2H), 7.50 (d, 1H, J=9Hz), 7.74 (s, 1H), 7.94 (d, 2H, J=9Hz), 8.21 (m, 3H), 8.44 (d, 1H, J=5Hz), 8.52 (s, 1H), 8.72 (s, 2H). MS (ion spray) m/z 458 $(M+H)^+$. Anal. calcd for $C_{25}H_{27}N_7O_2 \cdot 3C_2HF_3O_2 \cdot NH_3$: C, 47.1%; H, 4.1%; N, 13.7%. Found: C, 47.2%; H, 4.3%; N, 13.7%.

Example 1aaaw

N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(2-morpholin-4-yl-pyrmidin-4-yl)-benzamide. Using the product from reference example 92al. ^{1}H NMR (DMSO) δ 3.0 (bt, 2H); 3.59 (m, 2H); 3.71 (m, 4H); 3.80 (m, 4H); 7.20 (d, 1H, J = 8Hz); 7.32 (d, J = 5Hz, 1H); 7.50 (d, J = 8Hz, 1H); 7.74 (s, 1H); 7.94 (d, 2H, J = 9Hz); 8.22 (m, 3H); 8.51 (m, 2H); 8.73 (m, 3H); 12.28 (bs, 1H). MS (ion spray) m/z 470 $(M+H)^+$.

Example 1aaax

N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(cyclopropylmethyl-amino)-pyrimidin-4-yl]-benzamide. Using the product from reference example 92am. ^{1}H NMR (DMSO) δ 0.26 (m, 2H); 0.43 (d, 2H, J = 7Hz); 1.12 (bt, H); 2.98 (t, 2H, J = 7Hz); 3.25 (bs, 2H); 3.57 (m, 2H); 7.20 (m, 2H); 7.50 (d, 1H, J = 9Hz); 7.74 (s, 1H); 7.94 (d, 2H, J = 9Hz); 8.19 (m, 3H); 8.39 (d, 1H, J = 5Hz); 8.53 (bs, 2H); 8.71 (bs, 3H); 12.28 (bs, 1H). MS (ion spray) m/z 454 $(M+H)^+$.

Example 1aaay

N-[2-(carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-[(2-methoxy-ethyl)-methyl-amino]-pyrimidin-4-yl]-benzamide. Using the product from reference example 92an ^{1}H NMR (DMSO) δ 2.99 (bt, 2H); 3.22 (s, 3H); 3.58 (m, 4H); 3.86 (m, 2H); 7.24 (m, 2H); 7.50 (d, 1H, J = 8Hz); 7.76 (s, 1H); 7.96 (d, 2H, J = 9Hz); 8.46 (d, 1H, J = 5Hz); 8.65 (bs, 1H); 8.76 (bs, 3H); 12.37 (bs, 1H). MS (ion spray) m/z 472 $(M+H)^+$.

Example 1aaaz

N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(3-hydroxy-propylamino)-pyrimidin-4-yl]-benzamide. Using the product from reference example 92ap. ^{1}H NMR (DMSO) δ 1.74 (bt, 2H); 2.98 (bt, 2H); 3.42 (bs, 2H); 3.50 (t, 2H, J = 6Hz); 3.56 (m, 2H); 7.20 (m, 2H); 7.50 (d, 1H, J = 9Hz); 7.74 (s, 1H); 7.94 (d, 2H, J = 8Hz); 8.19 (m, 3H); 8.39 (d, 1H, J = 5Hz); 8.52 (bs, 2H); 8.71 (m, 3H); 12.28 (bs, 1H). MS (ion spray) m/z 458 $(M+H)^+$.

Example 1aaaaa

N-[2-(3-carbamimidoyl -1H-indol-5-yl)-ethyl]-4-[(2-hydroxy-ethyl)-propyl-amino]-pyrimidin-4-yl]-benzamide. Using the product from reference example 92aq. ^{1}H NMR (DMSO) δ .90 (t, 3H); 1.63 (bd, 2H); 2.99 (t, 2H); 3.61 (m, 8H); 4.70 (bs, 1H); 7.20 (m, 2H); 7.49 (d, 1H, J = 8Hz); 7.73 (s, 1H); 7.92 (d, 2H, J = 8Hz); 8.18 (m, 3H); 8.42 (d, 1H, J = 5Hz); 8.50 (bs, 2H); 8.70 (bs, 2H); 12.26 (bs, 1H). MS (ion spray) m/z 469 $(M+H)^+$.

Example 1aaaab

N-[2-(3-Carbamimidoyl-1H-indole-5yl)-ethyl]-4-(2-piperidin-1-yl-pyrimidin-4-yl)-benzamide. Using the product from reference example 92ar. ^{1}H NMR (DMSO) δ 1.61 (m, 6H); 2.98 (m, 2H); 3.57 (m, 2H); 3.84 (m, 4H); 7.20 (m, 2H); 7.50 (m, 2H); 7.74 (s, 1H); 7.94 (d, 2H, J = 8Hz); 8.20 (m, 3H); 8.45 (d, 1H, J = 5Hz); 8.50 (bs, 1H); 8.71 (bs, 3H); 12.28 (bs, 1H). MS (ion spray) m/z 468 $(M+H)^+$.

Example 1aaaac

N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(ethyl-methyl-amino)-pyrimidin-4-yl]-benzamide. Using the product from reference example 92as. ^{1}H NMR (DMSO) δ 1.15 (t, 3H, J = 7Hz); 2.98 (bt, 2H); 3.18 (s, 3H); 3.59 (m, 2H); 3.73 (m, 2H); 7.21 (m, 2H); 7.50 (d, 1H, J = 8Hz); 7.74 (s, 1H); 7.94 (d, 2H, J = 8Hz); 8.21 (m, 3H); 8.45 (d, 1H, J = 5Hz); 8.53 (bs, 1H); 8.72 (bs, 3H); 12.29 (bs, 1H). MS (ion spray) m/z 442 $(M+H)^+$.

Example 1aaaad

N-[2-(3-carbamimidoyl -1H-indol-5-yl)-ethyl]-4-[2-(4-hydroxy-piperidin-1-yl)-pyrimidin-4-yl]-benzamide. Using the product from reference example 92at. ^{1}H NMR (DMSO) δ 1.38 (m, 2H); 1.82 (m, 2H); 2.99 (t, 2H, J = 7Hz); 3.34 (t, 2H, J = 7Hz); 3.58 (m, 2H); 3.76 (m, 1H); 4.39 (bd, 2H); 7.22 (m, 2H); 7.50 (d, 1H, J = 8Hz); 7.75 (s, 1H); 7.94 (d, 2H, J = 8Hz); 8.20 (m, 3H); 8.45 (d, 1H, J = 5Hz); 8.57 (bs, 1H); 8.73 (bs, 3H); 12.29 (bs, 1H). MS (ion spray) m/z 484 $(M+H)^+$.

Example 1aaaae

N-[2-(3-carbamimidoyl -1H-indol-5-yl)-ethyl]-4-[2-(2,3-dihydroxy-propylamino)-pyrimidin-4-yl]-benzamide. Using the product from reference example 92au. ^{1}H NMR (DMSO) δ 2.98 (bt, 2H); 3.3 (m, 1H); 3.39 (m, 2H); 3.57 (m, 3H); 3.70 (bs, 1H); 7.22 (m, 3H); 7.50 (d, 1H, J = 8Hz); 7.74 (s, 1H); 7.94 (d, 2H, J = 9Hz); 8.21 (m, 3H); 8.40 (d, 1H, J = 5Hz); 8.53 (bs, 1H); 8.72 (m, 3H); 12.29 (bs, 1H). MS (ion spray) m/z 474 $(M+H)^+$.

Example 1aaaaf

N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-[(2,3-dihydroxy-propyl)-methyl-amino]-pyrimidin-4-yl]-benzamide. Using the product from reference example 92av. ^{1}H NMR (DMSO) δ 2.98 (t, 2H, J = 7Hz); 3.25 (s, 3H); 3.38 (d, 2H, J = 5Hz); 3.54 (m, 3H); 3.85 (bs, 2H); 7.22 (m, 2H); 7.50 (d, 1H, J = 8Hz); 7.74 (s, 1H); 7.94 (d, 2H, J = 8Hz); 8.22 (m, 3H); 8.45 (d, 1H, J = 5Hz); 8.53 (bs, 1H); 8.71 (bs, 3H); 12.28 (bs, 1H). MS (ion spray) m/z 488 $(M+H)^+$.

Example 1aaaag

N-[2-(3-carbamimidoyl -1H-indol-5-yl)-ethyl]-4-[2-((s)-2-methoxymethyl-pyrrolidin-1-yl)-pyrimidin-4-yl]-benzamide. Using the product from reference example 92aw. ^{1}H NMR (DMSO) δ 2.04 (m, 4H); 2.98 (t, 2H, J = 7Hz); 3.33 (m, 5H); 3.60 (m, 4H); 4.35 (bs, 1H); 7.20 (d,1H, J = 8Hz); 7.28 (d, 1H, J = 8Hz); 7.50 (d, 1H, J = 8Hz); 7.74 (s, 1H); 7.95 (d, 2H, J = 8Hz); 8.22 (m, 3H); 8.47 (d, 1H, J = 5Hz); 8.52 (bs, 1H); 8.72 (bs, 3H); 12.28 (bs, 1H). MS (ion spray) m/z 498 $(M+H)^+$.

Example 1aaaah

N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(2-piperazin-1-yl-pyrimidin-4-yl)-benzamide. Using the product from reference example 92ax. ^{1}H NMR (DMSO) δ 2.98 (bt, 2H, J = 7Hz); 3.24 (bs, 4H); 3.59 (m, 2H); 4.06 (bs, 4H); 7.20 (d, 1H, J = 9Hz); 7.40 (d, 1H, J = 5Hz); 7.50 (d, 1H, J = 8Hz); 7.75 (s, 1H); 7.96 (d, 2H, J = 8Hz); 8.24 (m, 3H); 8.56 (d, 1H, J = 5Hz); 8.63 (bs, 1H); 8.74 (m, 2H); 8.95 (bs, 2H); 12.30 (bs, 1H). MS (ion spray) m/z 469 $(M+H)^+$.

Example 1aaaai

N-[2-(3-carbamimidoyl-1H-indol-5-yl)- 4-[2-[2-(2-oxo-imidazolidin-1-yl)-ethylamino]-pyrimidin-4-yl]-benzamide. Using the product from reference example 92ay. ^{1}H NMR (DMSO) δ 2.98 (bt, 2H); 3.24 (m, 4H); 3.50 (m, 6H); 6.28 (bs, 1H); 7.22 (m, 2H); 7.39 (bs, 1H); 7.50 (d, 1H, J = 8Hz); 7.74 (s, 1H); 7.94 (d, 2H, J = 9Hz); 8.20 (m, 3H); 8.40 (bs, 1H); 8.50 (bs, 2H); 8.73 (m, 3H); 12.28 (bs, 1H). MS (ion spray) m/z 512 $(M+H)^+$.

Example 1aaaaj

N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(3-methoxy-propylamino)-pyrimidin-4-yl]-benzamide. Using the product from reference example 92az. ^{1}H NMR (DMSO) δ 1.80 (m, 2H); 2.98 (t, 2H, J = 7Hz); 3.23 (s, 3H); 3.40 (t, 4H, J = 6Hz); 3.55 (m, 2H); 7.20 (m, 2H); 7.50 (d, 1H, J = 9Hz); 7.73 (s, 1H); 7.94 (d, 2H, J = 9Hz); 8.18 (m, 3H); 8.38 (d, 1H, J = 5Hz); 8.54 (bs, 2H); 8.71 (m, 3H); 12.28 (bs, 1H). MS (ion spray) m/z 472 (M+H)$^+$.

Example 1aaaak

4-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(2-hydroxy-ethylamino)-pyrimidin-4-yl]-benzamide. Using the product from reference example 92aaa. ^{1}H NMR (DMSO) δ 2.98 (t, 2H, J = 7Hz); 3.44 (bs, 2H); 3.56 (m, 4H); 4.80 (bs, 1H); 7.20 (m, 2H); 7.49 (d, 1H, J = 9Hz); 7.72 (s, 1H); 7.93 (d, 2H, J = 8Hz); 8.18 (m, 3H); 8.38 (d, 1H, J = 5Hz); 8.50 (bs, 2H); 8.70 (m, 3H); 12.26 (bs, 1H). MS (ion spray) m/z 444 (M+H)$^+$.

Example 1aaaal

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(2-methoxyethoxy)-pyrimidin-4-yl]benzamide. Using the product from reference example 100a. m.p. 122-124°C. ^{1}H NMR (DMSO-d_6): δ 2.50 (s, 3H), 2.99 (t, 2H, J=9 Hz), 3.59 (m, 2H), 3.74 (m, 2H), 4.51 (m, 2H), 7.22 (d,1H, J=9Hz), 7.50 (d,1H, J=9Hz), 7.73 (s,1H), 7.79 (d,1H, J=6Hz), 7.97 (d, 2H, J=6Hz), 8.20 (d,1H, J=3Hz), 8.28 (d, 2H , J=6Hz), 8.41 (s,1H), 8.71 (m, 3H), 8.76 (t,1H, J=6Hz). MS (ion spray) m/z 459 (M+H)$^+$. Anal. calcd for $C_{25}H_{26}N_6O_3 \cdot 2.5C_2HF_3O_2 \cdot 0.5NH_3$: C, 50.1%; H, 4.3%; N, 13.1%. Found: C, 50.1%; H, 4.5%; N, 13.0%.

Example 1aaaam

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(1-carbamoylethoxy)pyrimidin-4-yl]benzamide. Using the product from reference example 100b. m.p. 159-161°C. ^{1}H NMR (DMSO-d_6): δ 1.52 (d, 3H, J=6Hz), 3.00 (t, 2H, J=6Hz), 3.60 (m, 2H), 5.21 (q,1H, J=6Hz), 7.21 (d,1H, J=6Hz), 7.51 (d, 1H, J=6Hz), 7.60 (s, 1H), 7.82 (d, 2H, J=6Hz), 7.97 (d, 2H, J=9Hz), 8.20 (d, 1H, J=3Hz), 8.29 (d, 2H, J=9Hz), 8.44 (s, 1H), 8.71 (m, 2H), 8.80 (m, 1H). MS (ion spray) m/z 472 (M+H)$^+$.

Example 1aaaan

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(6-dimethylaminohexyloxy)pyrimidin-4-yl]benzamide. Using the product from reference example 100c, m.p. 82-84°C. ^{1}H NMR (DMSO-d_6): δ 1.40 (m, 2H), 1.49 (m, 2H), 1.68 (m, 2H), 1.81 (m, 2H), 2.76 (s, 3H), 2.78 (s, 3H), 3.01 (m, 4H), 3.56 (m, 2H), 7.21 (d, 1H, J=9Hz), 7.50 (d, 1H, J=9Hz), 7.74 (s, 1H), 7.78 (d, 1H, J=6Hz), 7.98 (d, 2H, J= 9Hz), 8.21 (d, 1H, J=3Hz), 8.27 (d, 2H, J= 9Hz), 8.55 (s, 1H), 8.70 (m, 3H), 8.78 (m, 2H). MS (ion spray) m/z 528 $(M+H)^+$. >99% pure by analytical HPLC.

Example 1aaaap

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(2-oxopiperidin-3-yloxy)pyrimidin-4-yl]benzamide. Using the product from reference example 100d, m.p. 145-147°C. ^{1}H NMR (DMSO-d_6): δ 1.92 (m, 2H), 2.20 (m, 1H), 2.25 (m, 1H), 3.00 (t, 2H, J=3Hz), 3.22 (m, 2H), 3.52 (m, 2H), 5.55 (m, 1H), 7.20 (d, 1H, J=6Hz), 7.50 (d, 1H, J=6Hz), 7.70 (s, 1H), 7.75 (d, 1H, J=3Hz), 7.97 (d, 2H, J=9Hz), 8.20 (d, 1H, J=3Hz), 8.26 (d, 2H, J=9Hz), 8.45 (s, 1H), 8.70 (m, 3H), 8.77 (t, 1H, J=3Hz). MS (ion spray) m/z 498 $(M+H)^+$.

Example 1aaaaq

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(2-pyrrolidin-1-yl-ethoxy)pyrimidin-4-yl]benzamide. Using the product from reference example 100e, m.p. 104-105°C. ^{1}H NMR (DMSO-d_6): δ 1.89 (m, 2H), 2.05 (m, 2H), 2.98 (t, 2H, J=3Hz), 3.19 (m, 2H), 3.50-3.66 (m, 6H), 4.73 (m, 2H), 7.22 (d, 1H, J=6Hz), 7.50 (d1H, J=6Hz), 7.73 (s, 1H), 7.88 (d, 2H, J=6Hz), 8.01 (d, 2H, J=9Hz), 8.25 (d, 1H, J=3Hz), 8.30 (d, 2H, J=9Hz), 8.51 (s, 1H), 8.71 (s, 2H), 8.76 (m, 1H), 8.77 (m, 1H). MS (ion spray) m/z 498 $(M+H)^+$. Anal. calcd for $C_{28}H_{31}N_7O_2 \cdot 2.5C_2HF_3O_2 \cdot H_2O$: C, 49.5%; H, 4.5%; N, 12.3%. Found: C, 49.6%; H, 4.4%; N, 12.2%.

Example 1aaaar

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(2-dimethylaminoethoxy)pyrimidin-4-yl]benzamide. Using the product from reference example 100f, m.p. 106-107°C. ^{1}H NMR (DMSO-d_6): δ 2.89 (s, 3H), 2.91 (s, 3H),3.59 (m,4H), 4.75 (t, 2H, J=3Hz), 7.20 (d, 1H, J=6Hz), 7.51 (d, 1H, J=9Hz), 7.74 (s, H), 7.87 (d, 1H,

J=6Hz), 8.00 (d, 2H, J=9Hz), 8.20 (d, 1H, J=3Hz), 8.30 (d, 2H, J=9Hz), 8.45 (s, 1H), 8.72 (s, 2H), 8.77 (d, 1H, J=6Hz), 8.79 (m, 1H). MS (ion spray) m/z 472 $(M+H)^+$. >99% pure by analytical HPLC.

Example 1aaaas

3'-(2-Dimethylaminoethoxy)biphenyl-4-carboxylic acid [2-(3-carbamimidoyl-1H-indol-5-yl)ethyl]amide. Using the product from reference example 1aae. m.p. 99-101°C. ^{1}H NMR (D_2O): δ 2.88 (s, 6H), 2.94 (t, 2H ,J=61Hz), 3.55 (m, 4H), 4.32 (t, 2H, J=3 Hz), 6.99 (d,1H, J=9 Hz), 7.20 (m, 2H), 7.39 (d,1H, J=6 Hz), 7.45(d,1H, J=6 Hz), 7.55(m, 4H), 7.94 (s,1H). MS (ion spray) m/z 470 $(M+H)^+$. >99% pure by analytical HPLC.

Example 1aaaat

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-(1-oxypyridin-2-yl)benzamide. Using the product from reference example 1aaf. m.p. 164-167°C. ^{1}H NMR (DMSO-d_6): δ 2.98 (t, 2H, J=7Hz), 3.58 (m, 2H), 7.20 (d, 1H, J=8Hz), 7.44 (m, 2H), 7.47 (d, 1H, J=8Hz), 7.74 (s, 1H), 7.92 (s, 4H), 8.20 (d, 1H, J=3Hz), 8.37 (m, 1H), 8.45 (s, 1H), 8.71 (s, 2H). MS (ion spray) m/z 400 $(M+H)^+$. Anal. calcd for $C_{23}H_{21}N_5O_2 \cdot 1.5C_2HF_3O_2 \cdot 0.5H_2O$: C, 53.9%; H, 4.1%; N, 12.1%. Found: C, 54.1%; H, 4.6%; N, 12.5%.

Example 1aaaau

2'-(2-Dimethylaminoethoxy)biphenyl-4-carboxylic acid [2-(3-carbamimidoyl-1H-indol-5-yl)ethyl]amide. Using the product from reference example 1aag. m.p. 73-76°C. ^{1}H NMR (D_2O): δ NMR 2.57 (s, 6H), 2.95 (t, 2H, J=3Hz), 3.32 (t, 2H, J=3Hz), 3.60 (t, 2H, J=6Hz), 4.20 (m, 2H), 7.00 (d, 2H, J=6Hz), 7.20 (d, 1H, J=3Hz), 7.25 (d, 1H, J=3Hz), 7.35 (m, 1H), 7.46 (m, 3H), 7.52 (d, 2H, J=6Hz), 7.60 (s, 1H), 7.95 (s, 1H). MS (ion spray) m/z 470 $(M+H)^+$. >94% pure by analytical HPLC.

Example 1aaaav

2'-(3-Dimethylaminopropoxy)biphenyl-4-carboxylic acid [2-(3-carbamimidoyl-1H-indol-5-yl)ethyl]amide. Using the product from reference example 1aah. m.p. 76-78°C. ^{1}H NMR (D_2O): δ 1.95 (m, 2H), 2.45 (s, 6H), 2.88 (t, 2H, J=9Hz), 2.96 (t, 2H, J=9Hz), 3.59 (t, 2H , J=9Hz), 4.00 (t, 2H, J=9Hz), 7.06 (m, 2H), 7.23

(m, 1H), 7.31 (m, 1H), 7.42 (m, 3H), 7.56 (d, 3H, J=9Hz), 7.61 (s, 1H), 7.96 (s, 1H). MS (ion spray) m/z 484 $(M+H)^+$. >98% pure by analytical HPLC.

Example 1aaaaw

3'-(3-Dimethylaminopropoxy)biphenyl-4-carboxylic acid [2-(3-carbamimidoyl-1H-indol-5-yl)ethyl]amide. Using the product from reference example 1aai. m.p. 84-86°C. ^{1}H NMR (D_2O): δ 2.06 (m, 2H), 2.76 (s, 6H), 2.85 (t, 2H, J=6Hz), 3.18 (t, 2H, J=6Hz), 3.47 (t, 2H, J=6Hz), 4.00 (t, 2H, J=6Hz), 6.88 (d,1H, J=6Hz), 7.02 (s,1H), 7.12 (m, 2H), 7.25 (t,1H, J=9Hz), 7.36 (d,1H, J=9Hz), 7.45 (m, 4H), 7.86 (s,1H). MS (ion spray) m/z 484 $(M+H)^+$. 100% pure by analytical HPLC.

Example 1aaaax

N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(1-oxo-pyridin-3-yl)-benzamide. Using the product from reference example 1aaj. ^{1}H NMR (DMSO) δ 3.01 (bt, 2H); 3.56 (m, 2H); 7.20 (d, 1H, J = 9Hz); 7.52 (m, 2H); 7.73 (m, 2H); 7.86 (d, 2H, J = 9Hz); 7.94 (d, 2H, J = 9Hz); 8.20 (s, 1H); 8.27 (d, 1H, J = 7Hz); 8.67 (s, 1H); 8.56 (s, 2H); 8.71 (m, 2H); 12.28 (bs, 1H). MS (ion spray) m/z 400 $(M+H)^+$.

Example 1aaaay

4-[2-(acetylamino-methyl)-pyridin-4-yl]-N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-benzamide. Using the product from reference example 1aak. ^{1}H NMR (DMSO) δ 1.94 (s, 3H); 2.99 (bt, 2H); 4.49 (d, 2H, J = 5Hz); 7.20 (d, 1H, J = 8Hz); 7.50 (d, 1H, J = 8Hz); 7.74 (s, 1H); 7.83(m, 2H); 7.94 (d, 2H , J = 8Hz); 8.00 (d, 2H, J = 8Hz); 8.22 (d, 1H, J = 3Hz); 8.53 (m, 2H); 8.74 (m, 3H); 12.29 (bs, 1H). MS (ion spray) m/z 455 $(M+H)^+$.

Example 1aaaaz

Piperidine-4-carboxylic acid (4-[4-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethylcarbamoyl]-phenyl-]-pyridin-2-ylmethyl)-amide. Using the product from reference example 1aal. ^{1}H NMR (DMSO) δ 1.75 (m, 2H); 1.94 (m, 2H); 2.58 (m, 1H); 2.94 (m,5H); 3.30 (m, 2H); 3.62 (m, 2H); 4.54 (bd, 2H); 7.20 (d, 1H, J = 8Hz); 7.51

(d, 1H, J = 8Hz); 7.76 (s, H); 7.88 (m, 2H); 7.94 (d, 2H, J = 9Hz); 8.03 (d, 2H, J = 9Hz); 8.24 (s, 1H); 8.44 (bs, 1H); 8.77 (m, 3H); 12.35 (bs, 1H). MS (ion spray) m/z 524 $(M+H)^+$.

Example 1aaaaaa

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[1-(3-dimethylaminopropyl)-6-oxo-1,6-dihydropyridin-3-yl]benzamide. Using the product from reference example 1aam, m.p. 129-130°C. ^{1}H NMR (DMSO-d_6): δ 2.07 (t, 2H, J=6Hz), 2.72 (s, 6H), 2.84 (t, 2H, J=6Hz), 3.03 (t, 2H, J=6Hz), 3.46 (t, 2H, J=6Hz), 3.98 (t, 2H, J= 6Hz), 6.58 (d,1H, J= 12Hz), 7.12 (d,1H, J=9Hz), 7.38 (m, 3H), 7.47 (m, 3H), 7.81 (m, 2H), 7.88 (s,1H). MS (ion spray) m/z 485 $(M+H)^+$. Anal. calcd for $C_{28}H_{32}N_6O_2 \cdot 3C_2HF_3O_2 \cdot 0.5H_2O$: C, 48.9%; H, 4.3%; N, 10.1%. Found: C, 48.6%; H, 4.3%; N, 10.4%.

Example 1aaaaab

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[6-(3-dimethylaminopropoxy)pyridin-3-yl]benzamide. Using the product from reference example 1aan, m.p. 84-86°C. ^{1}H NMR (D_2O): δ 2.11 (m, 2H), 2.78 (s, 6H), 2.90 (t, 2H, J=3Hz), 3.21 (m, 2H,), 3.51 (t, 2H, J=3Hz), 4.23(m, 2H), 6.85 (d,1H, J=6Hz), 7.05 (d,1H, J=6Hz), 7.40 (d, 1H, J=6Hz), 7.48-7.55 (m, 5H), 7.89 (m, 2H), 8.23 (s,1H).
MS (ion spray) m/z 485 $(M+H)^+$. Anal. calcd for $C_{28}H_{32}N_6O_2 \cdot 3C_2HF_3O_2$: C, 49.4%; H, 4.3%; N, 10.2%. Found: C, 49.3%; H, 4.6%; N, 10.4%.

Example 1aaaaac

(5-{4-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethylcarbamoyl]phenyl}-2-oxo-2H-pyridin-1-yl)acetamide. Using the product from reference example 1aap. MS (ion spray) m/z 457 $(M+H)^+$.

Example 1aaaaad

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-{1-[(2-dimethylaminoethylcarbamoyl)methyl]-6-oxo-1,6-dihydropyridin-3-yl}benzamide. Using the product from reference example 1aaq, m.p. 71-75°C. ^{1}H NMR (D_2O): δ 2.75 (s, 6H), 3.16 (m, 2H), 3.37 (m, 2H), 3.50 (m, 2H), 4.55 (s, 2H), 4.63 (m 2H), 6.48 (d, 1H,

J=9Hz), 7.03 (d, 1H, J=9Hz), 7.25 (m, 3H), 7.38 (m, 3H), 7.63 (s, 1H), 7.65 (m,, 1H), 7.79 (s, 1H) MS (ion spray) m/z 528 $(M+H)^+$. >94% pure by analytical HPLC.

Example 1aaaaae

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(4-dimethylamino-piperidin-1-yl)-benzamide. Using the product from reference example 1aas. ^1H NMR (CD_3OD): δ 8.04 (s, 1H0, 7.71 (brs, 1H), 7.59 (d, 2H), 7.47 (d, 1H), 7.19 (dd, 1H), 6.92 (d, 2H), 3.93 (d, 2H), 3.59 (t, 2H), 3.29 (m, 1H), 2.96 (t, 2H), 2.80 (dt, 2H), 2.74 (s, 6H), 2.06 (m, 2H), 1.68 (dq, 2H). MS (ion spray) m/z 433 (M+H)+. 92 % pure by analytical HPLC.

Example 1aaaaaf

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[4-(2-dimethylamino-ethylamino)-piperidin-1-yl]-benzamide. Using the product from reference example 1aat. ^1H NMR (CD_3OD): d 8.04 (s, 1H), 7.86 (d, 1H), 7.71 (s, 1H), 7.68 (d, 1H), 7.59 (d, 1H), 7.19 (d, 1H), 6.91 (d, 2H), 4.02 (d, 2H), 3.64 (t, 2H), 3.56 (brs, 2H); 3.42 (m, 1H), 2.98 (s, 6H), 2.90 (m, 2H), 2.20 (brd, 2H), 1.79 (q, 2H).
MS (ion spray)m/z 476 (M+H)+. > 97% pure by analytical HPLC

Example 1aaaaag

4-(4-Amino-piperidin-1-yl)-N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-benzamide. Using the product from reference example 1aav. ^1H NMR (CD_3OD): δ 8.08 (s, 1H), 7.78 (s, 1H), 7.71 (d, 2H), 7.48 (d, 1H), 7.24 (dd, 1H), 6.99 (d, 2H), 3.96 (brd, 2H), 3.65 (t, 2H), 3.05 (t, 2H), 2.93 (dt, 2H), 2.07 (brd, 2H), 1.70 (dq, 2H). MS (ion spray) m/z 405 (M+H)+. >99 % pure by HPLC.

Example 1aaaaah

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(4-methoxy-piperidin-1-yl)-benzamide. Using the product from reference example 1aaw. ^1H NMR (CD_3OD): d 8.07 (s, H), 7.76 (s, H), 7.72 (d, 2H), 7.46 (d, H), 7.33 (dd, H), 7.08 (d, 2H), 3.60-3.72 (m, 3H), 3.44-3.52 (m, H), 3.29 (s, 3H), 3.10-3.20 (m, 2H), 3.04 (t, 2H), 1.97-2.08 (m, 2H), 1.54-1.65 (m, 2H). MS (Cl) m/z 420 (M+H)+.

Example 1aaaaai

4-(4-Acetylamino-piperidin-1-yl)-N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-benzamide. Using the product from reference example 125. ^{1}H NMR (CD_3OD): δ 8.08 (s, 1H), 7.76 (s, 1H), 7.69 (d, 2H), 7.48 (d, 1H), 7.24 (dd, 1H), 7.01 (d, 2H), 3.83 (brd, 2H), 3.65 (t, 2H), 3.05 (t, 2H), 2.98 (dt, 2H), 1.97 (m, 2H), 1,94 (s, 3H), 1.58 (dq, 2H). MS (CI) m/z 447 (M+H)+.

Example 1aaaaaj

4-(1-Acetyl-piperidin-4-yl)-N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-benzamide. Using the product from reference example 1aay. ^{1}H NMR (CD_3OD): δ 8.06 (s, 1H), 7.76 (d, 2H), 7.47 (d, 1H), 7.32 (d, 2H), 7.23 (dd, 1H), 4.02 (d, 1H), 4,64 (t, 2H), 3.05 (t, 2H), 2.81-2.93 (m, 1H), 2.64-2.75 (dt, 1H), 1.82-1.92 (m, 2H), 1.55-1.75 (m, 2H), 1.37 (m, 1H). MS (ion spray) m/z 432 (M+H)+. > 96 % pure by analytical HPLC.

Example 1aaaaak

4-{4-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethylcarbamoyl]-phenyl}-piperidine-1-carboxylic acid amide. Using the product from reference example 1aaz. ^{1}H NMR (CD_3OD): δ 8.07 (s, 1H), 7.76 (s, 1H), 7.70 (d, 2H), 7.47 (d, 1H), 7.31 (brd, 2H), 7.24 (dd, 2H), 4.14 (m, 2H), 3.66 (t, 2H), 3.08 (t, 2H), 2.80-2.97 (m, 2H), 1.80-1.88 (m, 2H), 1.58-1.68 (m, 2H). MS (ion spray) m/z 433 $(M+H)^+$. 95% pure by analytical HPLC.

Example 1aaaaal

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(1-methyl-1-oxy-piperidin-4-yl)-benzamide. Using the product from reference example 1aaaa. ^{1}H NMR (DMSO): δ 8.69 (brs, 1H), 8.46 (brs, 1H), 8.19 (s, 1H), 7.80 (d, 1H), 7.70 (s, 1H), 7.48 (d, 1H), 7.37 (d, 1H), 7.18 (d, 1H), 3.75 (d, 2H), 3.50 (s, 3H), 3.45-3.72 (m, 8H), 2.94 (m, 1H), 1.97 (m, 1H). MS (ion spray) m/z 420 (M+H)+. 96 % pure by analytical HPLC.

Example 1aaaaam

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(1-methyl-piperidin-4-yl)-benzamide. Using the product from reference example 1aaab. ^{1}H NMR (DMSO): δ 9.55 (brs, 1H), 8.62 (d, 2H), 8.18 (d, 1H), 7.77 (d, 1H),

7.69 (s, 1H), 7.46 (d, 1H), 7.29 (d, 1H), 7.15 (d, 1H), 3.47-3.,52 (m, 2H), 3.02-3.06 (m, 1H), 2.89-2.95 (m, 2H), 2.78-2.80 (m, 4H), 1.97-2.01 (m, 1H), 1,79-1.82 (m, 1H), 1.20-1.24 (m, 1H) MS (ion spray) m/z 404 (M+H)+.

Example 1aaaaan

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(1-methanesulfonyl-piperidin-4-yl)-benzamide. Using the product from reference example 1aaac. ^{1}H NMR (CD_3OD) : d 8.06 (s, 1H), 7.76 (s, 1H), 7.72 (d, 2H), 7.47 (d, 1H), 7.34 (d, 2H), 7.23 (d, 1H), 3.84 (d, 2H), 3.67 (m, 2H), 3.04 (t, 2H), 2.71-2.89 (m, 3H), 2.84 (s, 3H), 1.92 (m, 2H), 1.78 (dq, 2H). MS (ion spray) m/z 468 (M+H)+.

Example 1aaaaao

4-(2-Acetylamino-1,1-dimethyl-ethyl)-N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-benzamide. Using the product from reference example 1aaad. ^{1}H NMR (DMSO) δ 1.24 (s, 6H); 1.77 (s, 3H); 2.96 (t, 2H); 3.27 (d, J = 6Hz); 3.55 (m, 2H); 7.20 (d, J = 9Hz, 1H); 7.44 (d, J = 9Hz, 2H); 7.50 (d, J = 9Hz, 1H); 7.65 (t, 1H); 7.77 (m, 3H); 8.20 (d, J = 3Hz, 1H); 8.52 (m, 2H); 8.70 (bs, 1H); 12.28 (bs, 1H). MS (ion spray) m/z 420 $(M+H)^+$.

Example 1aaaaap

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(2-methanesulfonylamino-1,1-dimethyl-ethyl)-benzamide. Using the product from reference example 106. ^{1}H NMR (DMSO) δ 1.28 (s, 6H); 2.74 (s, 3H); 2.96 (t, J = 7Hz, 2H); 3.11 (d, J = 7Hz, 2H); 3.54 (m, 2H); 6.85 (t, J = 7Hz, 1H); 7.18 (d, J = 9Hz, 1H); 7.48 (m, 3H); 7.76 (m, 3H); 8.20 (d, J = 3Hz, 1H); 8.54 (m, 2H); 8.70 (bs, 1H); 12.27 (d, J = 3Hz, 1H). MS (ion spray) m/z 456 $(M+H)^+$.

Example 1aaaaaq

Piperidine-4-carboxylic acid (2-{4-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethylcarbamoyl]-phenyl}-2-methyl-propyl)-amide. Using the product from reference example 1aaaf. ^{1}H NMR (DMSO) δ 1.24 (s, 6H); 1.68 (m, 4H); 2.42 (m, 1H); 2.84 (m, 2H); 2.96 (m, 2H); 3.28 (m, 4H); 3.54 (m, 2H); 3.90 (bs, 1H); 7.18 (d, J = 8Hz,

1H); 7.44 (d, J = 8Hz, 2H); 7.50 (d, J = 8Hz, 1H); 7.76 (m, 4H); 8.22 (s, 1H); 8.58 (m, 2H); 8.71 (bs, 1H); 12.30 (bs, 1H). MS (ion spray) m/z 489 $(M+H)^+$.

Example 1aaaaar

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(1,1-dimethyl-2-ureido-ethyl)-benzamide. Using the product from reference example 107a. ^{1}H NMR (DMSO) δ 1.23 (s, 6H); 2.96 (t, 2H); 3.23 (d, J = 6Hz, 2H); 3.55 (m, 2H); 4.19 (bs, 2H); 5.72 (t, 1H); 7.19 (d, J = 9Hz, 1H); 7.46 (m, 3H); 7.75 (m, 3H); 8.20 (d, J = 3Hz, 1H); 8.53 (m, 2H); 8.70 (bs, 1H); 12.26 (d, J = 3Hz, 1H). MS (ion spray) m/z 421 $(M+H)^+$.

Example 1aaaaas

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(3-ethyl-ureido)-1,1-dimethyl-ethyl]-benzamide. Using the product from reference example 107b. ^{1}H NMR (DMSO) δ 0.93 (t, J = 7Hz, 3H); 1.22 (s, 6H); 2.96 (m, 4H); 3.25 (m, 2H); 3.56 (m, 2H); 5.54 (bt, 1H); 5.78 (bs, 1H); 7.18 (d, J = 8Hz, 1H); 7.43 (d, J = 8Hz, 2H); 7.72 (d, J = 8Hz, 1H); 7.76 (m, 3H); 8.21 (bs, 1H); 8.51 (m, 2H); 8.70 (bs, 1H); 12.27 (s, 1H). MS (ion spray) m/z 449 $(M+H)^+$.

Example 1aaaaat

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(2-dimethylamino-3,4,5,6-tetrahydro-pyrimidin-4-yl)-benzamide. Using the product from reference example 1aaai. ^{1}H NMR (DMSO) δ 1.88 (m, 1H); 2.11 (m, 1H); 2.98 (m, 10H); 3.33 (m, 1H); 3.57 (m, 2H); 4.80 (bs, 1H); 7.18 (d, J = 9Hz, 1H); 7.42 (d, J = 8Hz, 2H); 7.50 (d, J = 8Hz, 1H); 7.86 (d, J = 8Hz, 2H); 8.05 (s, 1H); 8.22 (d, J = 3Hz, 2H); 8.64 (bs, 2H); 8.71 (bs, 1H); 12.31 (s, 1H). MS (ion spray) m/z 432 $(M+H)^+$.

Example 1aaaaau

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(1-oxy-pyridin-4-yloxy)-benzamide. Using the product from reference example 1aaaj. ^{1}H NMR ($CDCl_3$): δ 8.07 (s, 1H); 7.74 (s, 1H); 7.64 (d, 2H); 7.46 (d, 1H); 7.22 (dd, 2H); 6.79 (d, 2H); 3.63 (t, 2H); 3.03 (t, 2H).
MS (ion spray) m/z 416 (M+H)+.

Example 1aaaaav

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(1-methyl-piperidin-4-yloxy)-benzamide. Using the product from reference example 1aaak. ^{1}H NMR (CD_3OD): d 8.07 (s, 1H), 7.74-7.79 (m, 3H), 7.46 (d, 1H), 7.23 (dd, 1H), 6.99-7.09 (m, 2H), 3.59-3.67 (m, 2H), 3.34-3.45 (m, 2H), 3.12-3.23 (m, 1H), 3.04 (t, 2H), 2.91 (t, 3H), 2.38 (brd, 1H), 2.20-2.26 (m, 2H), 2.06-2.10 (m, 2H), 1.89 (brq, 1H); MS (ion spray) m/z 420 (M+H)+. 94% pure by analytical HPLC.

Example 1aaaaaw and 1aaaaax

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-(1,2,3,6-tetrahydropyridin-4-yl)-benzamide. Using the product from reference example 67b. ^{1}H NMR (300 MHz, DMSO-d_6) d 12.27 (bs, 1H), 8.89 (bs, 2H), 8.70 (bs, 2H), 8.56 (t, 1H), 8.21 (bs, 2H), 8.20 (d, J = 3 Hz, 1H), 7.84 (d, J = 8 Hz, 2H), 7.72 (s, 1H), 7.57 (d, J = 8 Hz, 2H), 7.48 (d, J = 8 Hz, 1H), 7.18 (d, J = 8 Hz, 1H), 6.32 (bs, 1H), 3.78 (bs, 2H), 3.57-3.49 (m, 2H), 3.3 (obsc, 2H), 2.94 (t, J = 8 Hz, 2H), 2.69 (bm, 2H); MS (electrospray) m/z 388 ($M+H^+$).

A solution of N-[2-(3-carbamimidoyl-1H-indol-5-yl)ethyl]-4-(1,2,3,6-tetrahydropyridin-4-yl)-benzamide (5 mg,) in MeOH (2 mL) is purged with N_2 and 10% palladium on carbon (9 mg) added and the reaction again purged with N_2. The reaction is then purged with H_2 and is vigorously stirred 30 minutes. The reaction is purged with N_2, filtered through Celite, washed with MeOH and concentrated to provide N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-piperidin-4-yl-benzamide.: ^{1}H NMR (300 MHz, DMSO-d_6) d 12.31 (bs, 1H), 8.72-8.84 (m, 7H), 8.21 (s, 1H), 7.79 (d, J = 7 Hz, 2H), 7.72 (s, 1H), 7.47 (d, J = 8 Hz, 1H), 7.30 (d, J = 7 Hz, 2H), 7.17 (d, J = 8 Hz, 1H), 3.52 (m, 2H), 3.3 (obsc, 2H), 3.05-3.85 (m, 5H), 1.96-1.72 (m, 4H); MS (ion spray) m/z 390 ($M+H^+$).

Example 1aaaaay

4-(2-Amino-1,1-dimethylethyl)-N-(2-[3-carbamimidoylindol-5-yl]ethyl)benzamide. To a solution of 4-(2-[tert-Butoxycarbonylamino]-1,1-dimethylethyl)-N-(2-[1-tert-butoxycarbonyl-3-tert-butoxycarbonyl-carbamimidoylindol-5-yl]ethyl)benzamide (0.092 g, 0.14 mmol, reference example 1aaal) in CH_2Cl_2 (8 mL) is added distilled water (0.1 mL) and trifluoroacetic acid (2 mL). After stirring six hours, the reaction mixture is concentrated and then placed under high vacuum to give a quantitative yield of the title compound

as a white solid (m.p. 67-70°C). ^{1}H NMR (D_2O): δ 1.29 (6H, s), 2.91 (2H, t, J = 7 Hz), 3.12 (2H, s), 3.53 (2H, t, J = 7 Hz), 7.14 (1H, d, J = 8 Hz), 7.36-7.46 (5H, m), 7.54 (1H, s), 7.93 (1H, s). MS (FAB) m/z 378 $(M+H)^+$. Anal. calcd. for $C_{22}H_{27}N_5O•3C_2HO_2F_3$: C, 46.7; H, 4.2; N, 9.7. Found: C, 46.8; H, 4.5; N, 9.8.

Using essentially the same procedure as used in Example 1aaaaay, except using the specified substrate, there is prepared

Example 1aaaaaz

N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-(6-[2-dimethylaminoethoxy]pyridin-3-yl)benzamide. Using the product from reference example 1aaam. Purified by HPLC (96.8% pure by analytical HPLC). m.p. 57-59°C. ^{1}H NMR (D_2O): δ 2.77-2.89 (8H, m), 3.39-3.54 (4H, m), 4.44 (2H, m), 6.86 (1H, d, J = 9 Hz), 7.09 (1H, d, J = 8 Hz), 7.35 (1H, d, J = 8 Hz), 7.40-7.49 (5H, m), 7.84 (1H, s), 7.88 (1H, d, J = 9 Hz), 8.16 (1H, s). MS (ion spray) m/z 471 $(M+H)^+$.

Example 1aaaaaaa

N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-pyrid-4-ylbenzamide. Using the product from reference example 1aaan. m.p. 113-116°C. ^{1}H NMR (D_2O): δ 2.19 (2H, t, J = 6 Hz), 3.56 (2H, t, J = 6 Hz), 7.16 (1H, d, J = 8 Hz), 7.42 (1H, d, J = 8 Hz), 7.54 (1H, s), 7.62 (2H, d, J = 8 Hz), 7.79 (2H, d, J = 8 Hz), 7.92 (1H, s), 8.19 (2H, m), 8.67 (2H, br, m). MS (ion spray) m/z 384 $(M+H)^+$. Anal. calcd. for $C_{23}H_{21}N_5O•(C_2HO_2F_3)_3(H_2O)_{0.5}$: C, 47.4; H, 3.4; N, 9.5. Found: C, 47.2; H, 3.7; N, 9.8.

Example 1aaaaaab

N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-(4-carbamoyl-phenyl)-benzamide. Using the product from reference example 1aaao. MS m/z 426 (M+H).

Example 1aaaaaac

N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-(4-methoxy-phenyl)-benzamide. Using the product from reference example 1aaap. MS m/z 413 (M+H).

Example 1aaaaaad

N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-(5-methoxy-indol-2-yl)-carboxamide. Using the product from reference example 1aaaq. MS m/z 375 (M+H).

Example 1aaaaaae

N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-(6-chloro-benzothiophen-2-yl)-carboxamide. Using the product from reference example 1aaar. MS m/z 397 (M+H).

Example 1aaaaaaf

N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-(4-benzyloxy-phenyl)-benzamide. Using the product from reference example 1aaas. MS m/z 413 (M+H).

Example 1aaaaaag

N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-chloro-benzamide. Using the product from reference example 1aaat. MS m/z 341 / 343 (M+H, Cl pattern).

Example 1aaaaaah

N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-(methylsulphonyl)-benzamide. Using the product from reference example 1aaau. MS m/z 385 (M+H).

Example 1aaaaaai

N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-(amino-sulphonyl)-benzamide. Using the product from reference example 1aaav. MS m/z 386 (M+H).

Example 1aaaaaaj

4-(3-Aminoprop-1-ynyl)-N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-benzamide. Using the product from reference example 64d. ^{1}H NMR (300 MHz, CD_3OD) d 8.09 (s, 1H) 7.78 (d, J =8 Hz, 3H), 7.56 (d, J = 8 Hz, 2H), 7.48 (d, J = 8 Hz, 1H), 7.24 (d, J = 7 Hz, 1H), 4.06 (s, 2H), 3.67 (t, J = 8 Hz, 2H), 3.05 (t, J = 8 Hz, 2H). MS (ion spray) m/z 360 ($M+H^+$).

Example 1aaaaaak

5-{4-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethylcarbamoyl]phenyl}-2-oxo-2H-pyridin-1-yl)acetic acid. Stirred a solution of (5-{4-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethylcarbamoyl]phenyl}-2-oxo-2H-pyridin-1-yl)acetamide (0.507g, 1.11 mmoles Example 1aaaaac) in 5M HCl (40 mL) and and methanol (20 mL) at 50°C for 42 hours. The reaction mixture was concentrated and taken up in 9:1 H_2O: AcCN (30 mL). The solid impurities were filtered off, and the effluent was purified on an HPLC to give 3.60 mg of the title compound as a white solid. m.p. >250°C. ^{1}H NMR (CD_3OD): δ 3.07 (t, 2H, J=6Hz), 3.68 (m, 2H), 4.82 (m, 2H), 6.68 (d, 1H, 9Hz), 7.26 (d, 1H, J = 9Hz), 7.50 (d, 1H, J=9Hz), 7.63 (d, 2H, J=8Hz), 7.78 (s, 1H), 7.83 (d, 2H, J=8Hz), 7.97 (d, 1H, J=9Hz), 8.07 (m, 2H), 8.65 (m, 1H); MS (ion spray) m/z 458 $(M+H)^+$. >90% pure by analytical HPLC.

Example 2

Using essentially the same procedure used to prepare example 1a except using the product from reference example 67c there is prepared 3-Carbamimidoyl-5-{2-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzoylamino]-propyl}-indole. ^{1}H NMR (300 MHz, DMSO-d_6) d 12.24 (bs, 1H), 8.68 (bs, 2H), 8.49 (bs, 2H), 8.33 (d, J = 8 Hz, 1H), 8.17 (d, J = 3 Hz, 1H), 7.88 (dd, J = 10, 3 Hz, 1H), 7.83-7.81 (m, 3H), 7.72 (s, 1H), 7.63 (d, J = 8 Hz, 2H), 7.45 (d, J = 8 Hz, 1H), 7.19 (d, J = 8 Hz, 1H), 6.44 (d, J = 9 Hz, 1H), 4.34-4.25 (m, 1H), 3.00 (dd, J = 13, 7 Hz, 1H), 2.81 (dd, J = 13, 7 Hz, 1H), 1.15 (d, J = 7 Hz, 3H); MS (ion spray) m/z 414 $(M+H^+)$.

Reference Example 1a

N-(2-[3-Cyano-5-indolyl]ethyl)-4-pyridin-3-ylbenzamide.

To a suspension of 4-pyrid-3-ylbenzoic acid (0.430 g, 2.16 mmol, reference example 11b) and diisopropylethylamine (DIEA) (0.42 mL, 2.4 mmol) in CH_2Cl_2 (10 mL) is added O-Benzotriazol-1yl-N,N,N',N',-tetramethyluronium tetrafluoro-borate (TBTU) (0.706 g, 2.20 mmol). After 30 minutes, 3-cyano-5-(2-aminoethyl)indole (0.4 g, 2.16 mmol, reference example 2) and DIEA (0.42 mL, 2.4 mmol) are

added, followed fifteen minutes later by another portion of DIEA (0.42 mL) in CH_2Cl_2 (5 mL) After stirring overnight the solution is concentrated, and the resulting residue chromatographed (10:1 CH_2Cl_2: MeOH) to provide the product with some DIEA contamination. This crude product is used without further purification. MS (ion spray) m/z 367 $(M+H)^+$.

The following compounds are prepared using essentially the same procedure described in reference example 1a except using the specified acid:

Reference Example 1b

N-(2-[3-Cyano-5-indolyl]ethyl)-4-pyrimid-5-yl-benzamide. Using the product from reference example 11c. Used without further purification. MS (ion spray) m/z 368 $(M+H)^+$.

Reference Example 1c

5-(Pyridin-2-yl)-thiophene-2-carboxylic acid 2-(3-cyano-5-indolyl)ethylamide. Used without further purification. MS (FAB) m/z 373 $(M+H)^+$.

Reference Example 1d

N-(2-[3-Cyanoindol-5-yl]ethyl)- 6-morpholin-4-ylnicotinamide. Using the product from reference example 24a. Used 4:1 methylene chloride: DMF as solvent. Used without further purification. MS (ion spray) m/z 376 $(M+H)^+$.

Reference Example 1e

N-(2-[3-Cyanoindol-5-yl]ethyl)-6-chloronicotinamide. Using commercially available 6-chloronicotinic acid. Used without further purification. MS (EI) m/z 324, 326 $(M[^{35}Cl, ^{37}Cl])^+$.

Reference Example 1f

N-(2-[3-Cyanoindol-5-yl]ethyl)- 6-imidazol-1-yl-nicotinamide. Using commercially available 6-imidazol-1-yl-nicotinic acid. Used without further purification. MS (ion spray) m/z 357 $(M+H)^+$.

Reference Example 1g

N-(2-[3-Cyanoindol-5-yl]ethyl)- 4-imidazol-1-yl-benzamide. Used without further purification. MS (ion spray) m/z 357 $(M+H)^+$.

Reference Example 1h

N-(2-[3-Cyanoindol-5-yl]ethyl)- 4-(3H-imidazol-4-yl)benzamide. Using the product from reference example 35b. Used without further purification. MS (ion spray) m/z 356 $(M+H)^+$.

Reference Example 1i

N-(2-[3-Cyanoindol-5-yl]ethyl)- 4-(1,2,4)thiadiazol-5-ylbenzamide. Using the product from reference example 35a. Used without further purification. MS (ion spray) m/z 374 $(M+H)^+$.

Reference Example 1j

N-[2-(3-Cyano-1H-indol-5-yl)-ethyl]-4-(1-carbamoyl-1-methyl-ethyl-benzamide. Using the product from reference example 25a. ^1H NMR ($CDCl_3$ / CD_3OD) d 1.58 (s, 6H), 3.05 (t, J = 7Hz, 2H), 3.67 (q, J = 7Hz, 2H), 7.21 (d, J = 8Hz, 1H), 7.44 (m, 3H), 7.56 (s, 1H), 7.75 (d, J = 8Hz, 2H), 7.81 (s, 1H), 8.28 (bt, 1H). MS (ion spray) m/z 375 (M+H).

Reference Example 1k

N-[2-(3-Cyano-1H-indol-5-yl)-ethyl]-4-(1-[N-(2-methoxyethyl)]-carbamoyl-1-methyl-ethyl-benzamide. Using the product from reference example 25b. ^1H NMR ($CDCl_3$ / CD_3OD) d 1.58 (s, 6H), 3.05 (t, J = 7Hz, 2H), 3.28 (s, 3H), 3.37 (m, 4H), 3.70 (q, J = 7Hz, 1H), 6.3 (bt, 1H), 7.20 (d, J = 10Hz, 1H), 7.41 (m, 3H), 7.57 (s, 1H), 7.57 (bt, J = 7Hz, 1H), 7.74 (m, 3H). MS (ion spray) m/z 433 (M+H).

Reference Example 1l

N-[2-(3-Cyano-1H-indol-5-yl)-ethyl]-4-(t-butyl)-benzamide. Using commercially available 4-(t-butyl)-benzoic acid. ^{1}H NMR ($CDCl_3$) d 1.30 (s, 9H), 3.04 (t, J = 7Hz, 2H), 3.76 (q, J = 7Hz, 2H), 6.32 (bt, J = 7Hz, 1H), 7.11 (dd, J = 9, 1Hz, 1H), 7.27 (d, J = 9Hz, 1H), 7.42 (m, 2H), 7.65 (m, 4H), 9.9 (bs, 1H). MS (ion spray) m/z 346 (M+H).

Reference Example 1m

N-[2-(3-Cyano-1H-indol-5-yl)-ethyl]-4-(pyridazin-4-yl)-benzamide. Using the product from reference example 11e. ^{1}H NMR (DMSO) d 2.98 (t, J = 7Hz, 2H), 3.59 (q, J = 7Hz, 2H), 7.20 (d, J = 8Hz, 1H), 7.50 (m, 2H), 8.05 (m, 5H), 8.23 (s, 1H), 8.74 (bt, J = 7Hz, 1H), 9.31 (d, J = 5Hz, 1H), 9.7 (bs, 1H). MS (ion spray) m/z 368 (M+H)

Reference Example 1n

N-[2-(3-Cyano-1H-indol-5-yl)-ethyl]-4-(2-methoxy-pyridin-5-yl)-2-methyl-benzamide. Using the product from reference example 33a. ^{1}H NMR (DMSO) d 2.30 (s, 3H), 2.96 (t, J = 7Hz, 2H), 3.52 (q, J = 7Hz, 2H), 3.90 (s, 3H), 6.91 (d, J = 8Hz, 1H), 7.20 (d, J = 8Hz, 1H), 7.32 (d, J = 8Hz, 1H), 7.50 (m, 4H), 8.01 (dd, J = 8, 3 Hz, 1H), 8.21 (d, J = 3 Hz, 1H), 8.33 (t, J = 7Hz, 1H), 8.49 (d, J = 3 Hz, 1H). MS (ion spray) m/z 411 (M+H).

Reference Example 1o

3',4'-Dimethoxybiphenyl-4-carboxylic acid (2-[3-cyanoindol-5-yl]ethyl)amide. Using the product from reference example 33b. Used without further purification. MS (ion spray) m/z 426 $(M+H)^+$.

Reference Example 1p

N-(2-[3-Cyano-1H-indol-5-yl]ethyl)-4-(6-methoxypyrid-3-yl)benzamide. Using the product from reference example 33c. Used without further purification. MS (FAB) m/z 397 $(M+H)^+$.

Reference Example 1q

N-(2-[3-Cyano-1H-indol-5-yl]ethyl)-4-(1-oxy-pyrid-4-yl)benzamide. Using the product from reference example 17a. Used without further purification. MS (ion spray) m/z 383 $(M+H)^+$.

Reference Example 1r

N-[2-(3-Cyano-1H-indol-5-yl)-ethyl]-4-(7H-pyrrolo[2,3-d]pyrimidin-6-yl)-benzamide. Using the product from reference example 42a. ^{1}H NMR (DMSO) δ 2.99 (bt, 2H), 3.56 (m, 2H), 7.20 (m, 2H), 7.50 (m, 2H), 7.94 (d, J = 8Hz, 2H), 8.06 (d, J = 8Hz, 2H), 8.21 (s, 1H), 8.65 (bt, 1H), 8.78 (s, 1H), 9.02 (bs, 1H), 12.13 (bs, 1H), 12.71 (bs, 1H). MS (ion spray) m/z 407 $(M+H)^+$.

Reference Example 1s

N-[2-(3-cyano-1H-indol-5-yl)-ethyl]-4-(1H-pyrrolo[3,2-c]pyridin-2-yl)-benzamide. Using the product from reference example 42b. ^{1}H NMR (DMSO) δ 2.99 (bt, 2H), 3.55 (m, 2H), 7.22 (d, J = 8Hz, 1H), 7.30 (s, 1H), 7.52 (m, 3H), 7.95 (d, J = 9Hz, 2H), 8.02 (d, J = 9Hz, 2H), 8.21 (d, J = 3Hz, 1H), 8.26 (d, J = 6Hz, 1H), 8.66 (bt, 1H), 8.98 (s, 1H), 12.13 (s, 1H), 12.49 (bs, 1H). MS (ion spray) m/z 406 $(M+H)^+$.

Reference Example 1t

N-[2-(3-cyano-1H-indol-5-yl)-ethyl]-4-furo[3,2-c]pyridin-2-yl-benzamide. Using the product from reference example 42c. ^{1}H NMR (DMSO) δ 2.99 (bt, 2H), 3.57 (m, 2H), 7.19 (d, J = 8Hz, 1H), 7.49 (m, 2H), 7.74 (m, 2H), 7.98 (d, J = 8Hz, 2H), 8.06 (d, J = 8Hz, 2H), 8.20 (d, J = 3Hz, 1H), 8.51 (d, J = 5Hz, 1H), 8.71 (bt, 1H), 9.00 (s, 1H), 12.10 (bs, 1H). MS (ion spray) m/z 407 $(M+H)^+$.

Reference Example 1u

N-[2-(3-cyano-1H-indol-5-yl)-ethyl]-3-chloro-4-(6-methoxy-pyridin-3-yl)-benzamide. Using the product from reference example 33d. ^{1}H NMR (DMSO) δ 2.98 (bt, 2H), 3.56 (m, 2H), 3.91 (s, 3H), 6.94 (d, J = 9Hz, 1H), 7.18 (d, J = 8Hz, 1H), 7.48 (d, J = 9Hz, 2H), 7.55 (d, J = 8Hz, 1H), 7.86 (d, J = 9Hz, 2H), 7.99 (s, 1H), 8.20 (s, 1H), 8.27 (s, 1H), 8.74 (bt, 1H), 12.12 (bs, 1H). MS (ion spray) m/z 431 $(M+H)^+$.

Reference Example 1w

(3-{4-[2-(3-cyano-1H-indol-5-yl)-ethylcarbamoyl]-phenyl}-3-methyl-butyl)-carbamic acid tert-butyl ester. Using the product from reference example 25d. ^{1}H NMR (DMSO) δ 1.27 (s, 6H), 1.33 (s, 9H), 1.74 (m, 2H), 2.65 (m, 2H), 2.95 (t, J = 7Hz, 2H), 3.51 (q, J = 7Hz, 2H), 6.67 (bt, 1H), 7.18 (d, J = 8Hz, 1H), 7.42 (d, J = 8Hz, 2H), 7.46 (s, 1H), 7.50 (s, 1H), 7.76 (d, J = 8Hz, 2H), 8.20 (d, J = 3Hz, 1H), 8.50 (bt, 1H), 12.12 (s, 1H). MS (ion spray) m/z 475 (M+H)$^+$.

Reference Example 1x

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-2-(4-chloro-phenyl)-acetamide. Using commercially available 2-(4-chloro-phenyl) acetic acid. ^{1}H NMR (CD_3OD) δ 2.90 (t, J = 7Hz, 2H), 3.40 (s, 2H), 3.48 (q, J = 7Hz, 2H), 7.10 (m, 3H), 7.20 (m, 2H), 7.40 (d, J = 8Hz, 1H), 7.45 (s, 1H), 7.91 (s, 1H). MS (ion spray) m/z 338 / 340 (M+H, Cl pattern).

Reference Example 1y

5-chloro-thiophene-2-carboxylic acid [2-(3-cyano-1H-indol-5-yl)-ethyl]-amide. Using commercially available 5-chloro-thiophene-2-carboxylic acid. ^{1}H NMR (DMSO) δ 2.93 (t, J = 7Hz, 2H), 3.48 (q, J = 7Hz, 2H), 7.16 (m, 2H), 7.50 (m, 2H), 7.61 (d, J = 4Hz, 1H), 8.20 (d, J = 3Hz, 1H), 8.7 (bt, J = 7Hz, 1H), 12.14 (bs, 1H). MS (ion spray) m/z 330 / 332 (M+H, Cl pattern).

Reference Example 1z

N-(2-[3-Cyanoindol-5-yl]ethyl)-6-(2-hydroxyethylamino)nicotinamide. Using the product from reference example 24c MS (ion spray) m/z 350 (M+H)$^+$.

Reference Example 1aa

N-(2-[3-Cyanoindol-5-yl]ethyl)-6-(1, 2, 4)-triazol-1-ylnicotinamide. Using commercially available 6-(1, 2, 4)-triazol-1-ylnicotinic acid. MS (ion spray) m/z 358 (M+H)$^+$.

Reference Example 1ab

N-(2-[3-Cyano-indol-5-yl]ethyl)-6-pyrrol-1-ylnicotinamide. Using commercially available 6-(pyrrol-1-yl)-nicotinic acid. MS (ion spray) m/z 356 $(M+H)^+$.

Reference Example 1ac

N-(2-[3-Cyanoindol-5-yl]ethyl)-6-pyrazol-1-ylnicotinamide). Using commercially available 6-pyrazol-1-ylnicotinic acid. MS (ion spray) m/z 357 $(M+H)^+$.

Reference Example 1ae

N-[2-(3-cyano-1H-indol-5-yl)-ethyl]-3-chloro-benzamide. Using commercially available 3-chloro-benzoic acid. ^1H NMR (DMSO) δ 2.98 (t, J = 7Hz, 2H), 3.53 (q, J = 7Hz, 2H), 7.18 (d, J = 8Hz, 1H), 7.50 (m, 3H), 7.60 (m, 1H), 7.79 (d, J = 8Hz, 1H), 7.82 (s, 1H), 8.20 (d, J = 2Hz, 1H), 8.70 (bt, J = 7Hz, 1H). MS (EI) m/z 323 / 325 (M+, Cl pattern).

Reference Example 1af

N-[2-(3-Cyano-1H-indol-5-yl)-ethyl]-2-(3-chloro-phenyl)-acetamide. Using commercially available 2-(3-chloro-phenyl) acetic acid. ^1H NMR (CD_3OD) δ 2.90 (t, J = 7Hz, 2H), 3.42 (s, 2H), 3.48 (q, J = 7Hz, 2H), 7.10 (m, 2H), 7.21 (m, 3H), 7.40 (d, J = 8Hz, 1H), 7.45 (s, 1H), 7.91 (s, 1H), 8.11 (bs, 1H). MS (ion spray) m/z 338 / 340 (M+H, Cl pattern).

Reference Example 1ag

4-(2-t-Butyloxycarbonylamino-methyl)-pyridin-4-yl)-N-[2-(3-cyano-1H-indol-5-yl)-ethyl]-benzamide. Using the product from reference example 33e. ^1H NMR (DMSO) δ 1.38 (s, 9H), 2.96 (t, J = 7Hz, 2H), 3.55 (q, J = 7Hz, 2H), 4.27 (d, J = 6Hz, 2H), 7.16 (d, J = 8Hz, 1H), 7.45 (m, 3H), 7.59 (m, 2H), 7.80 (d, J = 8Hz, 2H), 7.94 (d, J = 8Hz, 2H), 8.17 (d, J = 3Hz, 1H), 8.55 (d, J = 5Hz, 1H), 8.65 (t, J = 7Hz, 1H). MS (ion spray) m/z 496 (M+H).

Reference Example 1ah

4-{4-[2-(3-Cyano-1H-indol-5-yl)-ethylcarbamoyl]-pyridine-2-carboylic acid amide. Using the product from reference example 33f. ^{1}H NMR (DMSO) δ 3.0 (t, J = 7Hz, 2H), 3.57 (q, J = 7Hz, 2H), 7.19 (d, J = 8Hz, 1H), 7.50 (d, J = 8Hz, 1H), 7.51 (s, 1H), 7.75 (bs, 1H), 8.0 (m, 5H), 8.2 (bs, 2H), 8.35 (s, 1H), 8.73 (m, 2H). MS (ion spray) m/z 410 (M+H).

Reference Example 1ai

N-[2-(3-Cyano-1H-indol-5-yl)-ethyl-]-4-(2-dimethylaminomethyl-pyridin-4-yl)benzamide). Using the product from reference example 33g. ^{1}H NMR (CD_3OD) δ 2.63 (s, 6H), 3.06 (t, J = 7Hz, 2H), 3.67 (t, J = 7Hz, 2H), 4.08 (s, 2H), 7.24 (d, J = 8Hz, 1H), 7.45 (d, J = 8Hz, 1H), 7.55 (s, 1H), 7.70 (d, J = 5Hz, 1H), 7.81 (s, 1H), 7.84 (d, J = 8Hz, 2H), 7.91 (d, J = 8Hz, 2H), 8.64 (d, J = 5Hz, 1H). MS (ion spray) m/z 424 (M+H).

Reference Example 1ak

N-[2-(3-cyano-1H-indol-5-yl)-ethyl]-4-(6-methoxy-pyridazin-3-yl)-benzamide. Using the product from reference example 11f. ^{1}H NMR (DMSO) δ 3.00 (t, J = 7Hz, 2H), 3.57 (m, 2H), 4.10 (s, 3H), 7.20 (d, J = 8Hz, 1H), 7.36 (d, J = 9Hz, 1H), 7.48 (d, J = 8Hz, 1H), 7.52 (s, 1H), 7.96 (d, J = 9Hz, 2H), 8.20 (m, 4H); 8.68 (bt, 1H), 12.10 (bs, 1H). MS (ion spray) m/z 398 $(M+H)^+$.

Reference Example 1al

N-[2-(3-cyano-1H-indol-5-yl)-ethyl]-4-[1-(2-dimethylamino-ethyl)-6-oxo-1,6-dihydro-pyridazin-3-yl]-benzamide. Using the product from reference example 61a. ^{1}H NMR (DMSO) δ 2.49 (s, 6H), 2.98 (bt, 2H), 3.06 (m, 2H), 3.55 (m, 2H), 4.37 (bt, 2H), 7.10 (d, J = 10Hz, 1H), 7.18 (d, J = 8Hz, 1H), 7.48 (d, J = 8Hz, 1H), 7.51 (s, 1H), 7.94 (d, J = 9Hz, 2H), 8.00 (d, J = 9Hz, 2H), 8.12 (d, J = 10Hz, 1H), 8.20 (d, J = 2Hz, 1H), 8.68 (bt, 1H), 12.12 (s, 1H). MS (ion spray) m/z 455 $(M+H)^+$.

Reference Example 1am

N-[2-(3-cyano-1H-indol-5-yl)-ethyl]-4-[1-(3-dimethylamino-propyl)-6-oxo-1,6-dihydro-pyridazin-3-yl]-benzamide. Using the product from reference example 61b. ^{1}H NMR (DMSO) δ 2.05 (m, 2H), 2.51 (s, 6H), 2.79 (bt, 2H), 2.98 (bt, 2H), 3.56 (m, 2H), 4.21 (bt, 2H), 7.10 (d, J = 10Hz, 1H), 7.19 (d, J = 8Hz, 1H), 7.49 (m, 2H), 7.94 (d, J = 8Hz, 2H), 8.00 (d, J = 8Hz, 2H), 8.14 (d, J = 10Hz, 1H), 8.22 (d, J = 3Hz, 1H), 8.68 (m, 1H), 12.12 (bs, 1H). MS (ion spray) m/z 469 $(M+H)^+$.

Reference Example 1an

N-[2-(3-Cyano-1H-indol-5-yl)-ethyl]-4-[2-(2-dimethylamino-ethylamino)-pyrimidin-4-yl]-benzamide. Using the product from reference example 83 ^{1}H NMR (DMSO) δ 2.20 (s, 6H), 2.95 (t, J = 7Hz, 2H), 3.31 (m, 2H), 3.44 (bm, 2H), 3.51 (bm, 2H), 7.07 (t, J = 7Hz, 1H), 7.18 (m, 2H), 7.45 (d, J = 8Hz, 1H), 7.50 (s, 1H), 7.90 (d, J = 8Hz, 2H), 8.17 (d, J = 8Hz, 2H), 8.18 (s, 1H), 8.37 (d, J = 6Hz, 1H), 8.67 (t, J = 7Hz, 1H). MS (ion spray) m/z 454 (M+H).

Reference Example 1ao

N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-methoxy-pyrimidin-4-yl]-benzamide. Using the product from reference example 17b. ^{1}H NMR (DMSO) δ 2.96 (t, J = 7Hz, 2H), 3.54 (q, J = 7Hz, 2H), 4.0 (s, 3H), 7.17 (d, J = 8Hz, 1H), 7.46 (m, 2H), 7.78 (d, J = 5Hz, 1H), 7.95 (d, J = 8Hz, 2H), 8.18 (d, J = 3Hz, 1H), 8.26 (d, J = 8Hz, H), 8.70 (d, J = 5Hz, 1H), 8.75 (t, J = 7Hz, 1H). MS (ion spray) m/z 398 (M+H).

Reference Example 1ap

N-(2-[3-Cyanoindol-5-yl]ethyl)-4-(1-[2-dimethylaminoethyl)-6-oxo-1,6-dihydropyridin-3-yl)benzamide. Using the product from reference example 17c ^{1}H NMR (1:1 CD_3OD: $CDCl_3$): δ 2.46 (6H, s), 2.86 (2H, m), 3.08 (2H, m), 3.70 (2H, m), 4.23 (2H, m), 6.70 (1H, d, J = 9 Hz), 7.24 (1H, d, J = 8 Hz), 7.49 (1H, d, J = 9 Hz), 7.54-7.61 (3H, m), 7.79-7.92 (4H, m), 7.92 (1H, s). MS (ion spray) m/z 454 $(M+H)^+$.

Reference Example 1aq

N-(2-[3-Cyanoindol-5-yl]ethyl)-4-(1-carbamoylmethyl-6-oxo-1,6-dihydropyridin-3-yl)benzamide. Using the product from reference example 17d. MS (ion spray) m/z 440 $(M-H)^-$.

Reference Example 1ar

4-(3-Amino-[1,2,4]triazin-6-yl)-N-[2-(3-cyano-1H-indol-5-yl)-ethyl]-benzamide. Using the appropriate product from reference example 86a, ^{1}H NMR (DMSO-d_6) d 2.98 (2H, t, J = 6 Hz), 3.56 (2H, m), 7.15-7.55 (5H), 7.90-8.35 (6H), 8.75 (1H, t, J = 5 Hz), 9.28 (1H,s); MS, m/z (ion spray) 384 $(M + H)^+$.

Reference Example 1as

4-(3-Amino-[1,2,4]triazin-5-yl)-N-[2-(3-cyano-1H-indol-5-yl)-ethyl]-benzamide. Using the appropriate product from reference example 86a.

Reference Example 1at

N-[2-(3-Cyano-1H-indol-5-yl)-ethyl]- 4-(3-oxo-2,3-dihydro-[1,2,4]triazin-6-yl)-benzamide. Using the product from reference example 86b: MS, m/z (ion spray) 403 $[(M+18)+H]^+$.

Reference Example 1au

N-[2-(3-Cyano-1H-indol-5yl)ethyl]-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-benzamide. Using the product from reference example 86c. MS, m/z (ion spray) 374 $[(M+H]^+$.

Reference Example 1av

Ethyl 4-(1-carbamoylmethyl-6-oxo-1,6-dihydropyridin-3-yl)benzoate. Using the product from reference example 67a as the acid component and ammonia as the amine. ^{1}H NMR (1:2 CD_3OD: $CDCl_3$): δ 1.43 (3H, t, J = 7 Hz), 4.41 (2H, q, J = 7 Hz), 4.72 (2H, s), 6.72 (1H, d, J = 9 Hz), 7.58 (2H, d, J = 8 Hz), 7.82 (1H, d, J = 2 Hz), 7.85 (1H, dd, J = 9, 2 Hz), 8.09 (2H, d, J = 8 Hz). MS (ion spray) m/z 301 $(M+H)^+$.

Reference Example 1aw

N-[2-(3-Cyano-1H-indol-5-yl)-ethyl]-4-[2-(morpholin-4yl-ethylamino)-pyrimidin-4-yl]-benzamide. Using the product from reference example 92a. ^{1}H NMR (DMSO): δ 2.46 (bm, 6H), 2.99 (t, J = 7Hz, 2H), 3.42-3.62 (m, 8H), 7.09 (bt, J = 5Hz, 1H), 7.20 (m, 2H), 7.92 (d, J = 8Hz, 2H), 8.20 (m, 3H), 8.39 (m, 1H), 8.69 (t, J = 5Hz, 1H). MS (ion spray) m/z 496 $(M+H)^+$.

Reference Example 1ax

N-[2-(3-Cyano-1H-indol-5-yl)-ethyl]-4-[2-(3-dimethylamino-propylamino)-pyrimidin-4-yl]-benzamide. Using the product from reference example 92b. ^{1}H NMR (CD_3OD): δ 1.90 (m, 2H), 2.59 (t, J = 7Hz, 2H), 3.05 (t, J = 7Hz, 2H), 3.50 (t, J = 7Hz, 2H), 3.66 (t, J = 7Hz, 2H), 7.13 (d, J = 5Hz, 1H), 7.23 (d, J = 8Hz, 1H), 7.45 (d, J = 8Hz, 1H), 7.56 (s, 1H), 7.86 (d, J = 8Hz, 2H), 7.90 (s, 1H), 8.16 (d, J = 8Hz, 2H), 8.30 (d, J = 5Hz, 1H). MS (ion spray) m/z 468 $(M+H)^+$.

Reference Example 1ay

N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-([2-dimethylamino-ethyl]-methyl-amino)-pyrimidin-4-yl]-benzamide. Using the product from reference example 92c. ^{1}H NMR ($CDCl_3$): δ 2.35 (s, 6H), 2.60 (t, J = 7Hz, 2H), 3.05 (t, J = 7Hz, 2H), 3.23 (s, 3H), 3.77 (q, J = 7Hz, 2H), 3.85 (t, J = 7Hz, 2H), 6.25 (bt, J = 7Hz, 1H), 6.90 (d, J = 5Hz, 1H), 7.17 (bd, J = 8Hz, 1H), 7.36 (bd, J = 8Hz, 1H), 7.61 (bs, 1H), 7.67 (bs, 1H), 7.75 (d, J = 8Hz, 2H), 8.04 (d, J = 8Hz, 2H), 8.35 (d, J = 5Hz, 1H), 9.3 (bs, 1H). MS (ion spray) m/z 468 $(M+H)^+$.

Reference Example 1az

N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide. Using the product from reference example 11g. The crude reaction product was filtered and washed with water dried under vacuum and used without further purification. ^{1}H NMR ($CDCl_3$): δ 2.99 (t, J = 7Hz, 2H), 3.55 (q, J = 7Hz, 2H), 7.18 (d, J = 8Hz, 1H), 7.5 (m, 2H), 8.01 (d, J = 8Hz, 2H), 8.27 (m, 4H), 8.77 (t, J = 7Hz, 1H), 8.87 (d, J = 5Hz, 1H), 12.1 (bs, 1H). MS (ion spray) m/z 402 $(M+H)^+$.

Reference Example 1aaa

N-[2-(3-Cyano-1H-indol-5-yl)-ethyl]-4-(2-oxo-hexahydro-pyrimidin-5-yl)-benzamide. Using the product from reference example 17f. MS (ion spray) m/z 388 $(M+H)^+$.

Reference Example 1aab

N-[2-(3-Cyano-1H-indol-5-yl)-ethyl]-4-(1,3-dimethyl-2-oxo-hexahydro-pyrimidin-5-yl)-benzamide. Using the product from reference example 17g. MS (ion spray) m/z 416 $(M+H)^+$.

Reference Example 1aac

Biphenyl-3,4'-dicarboxylic acid 4'-{[2-(3-cyano-1H-indol-5-yl)-ethyl]-amide} 3-methyl ester. Using the product from reference example 11i. ^{1}H NMR (DMSO): δ 2.96 (t, J = 7Hz, 2H), 3.54 (q, J = 7Hz, 2H), 3.88 (s, 3H), 7.16 (d, J = 8Hz, 1H), 7.46 (m, 2H), 7.64 (t, J = 8Hz, 1H), 7.78 (d, J = 8Hz, 2H), 7.9-8.01 (m, 4H), 8.19 (d, J = 1Hz, 1H), 8.22 (s, 1H), 8.64 (bt, J = 7Hz, 1H). MS (ion spray) m/z 424 $(M+H)^+$.

Reference Example 1aad

Biphenyl-2,4'-dicarboxylic acid 4'-{[2-(3-cyano-1H-indol-5-yl)-ethyl]-amide} 2-methyl ester. Using the product from reference example 11j. ^{1}H NMR (DMSO): δ 2.97 (t, J = 7Hz, 2H), 3.55 (q, J = 7Hz, 2H), 3.60 (s, 3H), 7.20 (d, J = 8Hz, 1H), 7.36 (d, J = 8Hz, 2H), 7.50 (m, 4H), 7.66 (t, J = 8Hz, 1H), 7.80 (d, J = 8Hz, 1H), 7.85 (d, J = 8Hz, 2H), 8.20 (d, J = 1Hz, 1H), 8.65 (bt, J = 7Hz, 1H). MS (ion spray) m/z 424 $(M+H)^+$.

Reference Example 1aae

3'-(2-Dimethylaminoethoxy)biphenyl-4-carboxylic acid [2-(3-cyano-1H-indol-5-yl)-ethyl]amide. Using the product from reference example 101a. MS (ion spray) m/z 453 $(M+H)^+$.

Reference Example 1aaf

N-[2-(3-Cyano-1H-indol-5-yl)ethyl]-4-(1-oxypyridin-2-yl)benzamide. Using the product from reference example 101b. MS (ion spray) m/z 383 $(M+H)^+$.

Reference Example 1aag

2'-(2-Dimethylaminoethoxy)biphenyl-4-carboxylic acid [2-(3-cyano-1H-indol-5-yl)ethyl]amide. Using the product from reference example 101c. MS (ion spray) m/z 453 $(M+H)^+$.

Reference example 1aah

2'-(3-Dimethylaminopropoxy)biphenyl-4-carboxylic acid [2-(3-cyano-1H-indol-5-yl)ethyl]amide. Using the product from reference example 101d. MS (ion spray) m/z 467 $(M+H)^+$.

Reference Example 1aai

3'-(3-Dimethylaminopropoxy)biphenyl-4-carboxylic acid [2-(3-cyano-1H-indol-5-yl)ethyl]amide. Using the product from reference example 101e. MS (ion spray) m/z 467 $(M+H)^+$.

Reference Example 1aaj

N-[2-(3-cyano-1H-indol-5-yl)-ethyl]-4-(1-oxo-pyridin-3-yl)-benzamide. Using the product from reference example 101f ^{1}H NMR (DMSO) δ 2.98 (bt, 2H); 3.56 (m, 2H); 7.18 (d, 1H, J = 9Hz); 7.51 (m, 3H); 7.72 (d, 1H, J = 9Hz); 7.86 (d, 2H, J = 8Hz); 7.94 (d, 2H, J = 8Hz); 8.25 (d, 1H, J = 7Hz); 8.65 (s, 1H); 8.72 (bt, 1H); 12.22 (bs, 1H). MS (ion spray) m/z 383 $(M+H)^+$.

Reference example 1aak

4-[2-(acetylamino-methyl)-pyridin-4-yl]-N-[2-(3-cyano-1H-indol-5-yl)-ethyl]-benzamide. Using the product from reference example 17j ^{1}H NMR (DMSO) δ 1.92 (s, 3H); 3.08 (bt, 2H); 3.55 (m, 2H); 4.42 (d, 2H, J =

6Hz); 7.18 (d, 1H, J = 9Hz); 7.49 (m, 3H); 7.63 (s, 2H); 7.86 (d, 2H, J = 8Hz); 7.96 (d, 2H, J = 8Hz); 8.20 (d, 1H); 8.48 (bt, 1H); 8.58 (m, 1H); 8.70 (bt, 1H); 12.17 (bs, 1H). MS (ion spray) m/z 438 $(M+H)^+$.

Reference Example 1aal

4-[[4-[4-[2-(3-cyano-1H-indol-5-yl)-ethylcarbamoyl]-phenyl-]-pyridin-2-ylmethyl]-carbamoyl]-piperidine-1-carboxylic acid tert-butyl ester. Using the product from reference example 17k. ^{1}H NMR (CD_3OD) δ 1.45 (s, 9H); 1.62 (m, 2H); 1.82 (m, 2H); 2.51 (m, 1H); 2.99 (s, 2H); 3.06 (t, 2H, J = 7Hz); 3.67 (t, 2H, J = 7Hz); 4.12 (m, 2H); 4.54 (s, 2H); 7.22 (d, 1H, J = 8Hz); 4.46 (d, 1H, J = 8Hz); 7.58 (m, 3H); 7.78 (d, 2H, J = 9Hz); 7.90 (m, 3H); 7.97 (s, 2H); 8.54 (d, 1H, J = 5Hz). MS (ion spray) m/z 607 $(M+H)^+$.

Reference Example 1aam

N-[2-(3-Cyano-1H-indol-5-yl)ethyl]-4-[1-(3-dimethylaminopropyl)-6-oxo-1,6-dihydropyridin-3-yl]benzamide. Using the product from reference example 17l. MS (esi loop) m/z 468 $(M+H)^+$.

Reference Example 1aan

N-[2-(3-Cyano-1H-indol-5-yl)ethyl]-4-[6-(3-dimethylaminopropoxy)pyridin-3-yl]benzamide. Using the product from reference example 17m.
MS (ion spray) m/z 468 $(M+H)^+$.

Reference Example 1aap

tert-Butyl (5-{4-[2-(3-cyano-1H-indol-5-yl)ethylcarbamoyl]phenyl}-2-oxo-2H-pyridin-1-yl)acetate. Using the product from reference example 7b. MS (ion spray) m/z 497 $(M+H)^+$.

Reference Example 1aaq

N-[2-(3-Cyano-1H-indol-5-yl)-ethyl]-4-{1-[(2-dimethylaminoethylcarbamoyl)methyl]-6-oxo-1,6-dihydropyridin-3-yl}benzamide. Using the product from reference example 17n. MS (ion spray) m/z 511 $(M+H)^+$.

Reference Example 1aar

Ethyl 4-{1-[(2-dimethylaminoethylcarbamoyl)methyl]-6-oxo-1,6-dihydropyridin-3-yl}benzoate. Using the product from reference Example 103b. MS (ion spray) m/z 372 (M+H)+.

Reference Example 1aas

N-[2-(3-Cyano-1H-indol-5-yl)-ethyl]-4-(4-dimethylamino-piperidin-1-yl)-benzamide. Using the product from reference example 113a. MS (ion spray) m/z 416 (M+H)+.

Reference example 1aat.

N-[2-(3-Cyano-1H-indol-5-yl)-ethyl]-4-[4-(2-dimethylamino-ethyl-tert-butyloxycarbonyl-amino)-piperidin-1-yl]-benzamide. Using the product from reference example 120. MS (ion spray) m/z 559 (M+H)+.

Reference example 1aav

4-(4-Tert-butoxycarbonylamino-piperidin-1-yl)-N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-benzamide. Using the product from reference example 115. MS (ion spray) m/z 488 (M+H)+.

Reference example 1aaw

N-[2-(3-Cyano-1H-indol-5-yl)-ethyl]-4-(4-methoxy-piperidin-1-yl)-benzamide. Using the product from reference example 121 . MS (CI) m/z 403 (M+H)+.

Reference Example 1aay

4-(1-Acetyl-piperidin-4-yl)-N-[2-(3-cyano-1H-indol-5-yl)-ethyl]-benzamide. Using the product from reference example 110 . MS (ion spray) m/z 415 (M+H)+.

Reference example 1aaz

4-{4-[2-(3-Cyano-1H-indol-5-yl)-ethylcarbamoyl]-phenyl}-piperidine-1-carboxylic acid amide. Using the product from reference example 107c. MS (ion spray) m/z 416 $(M+H)^+$.

Reference example 1aaaa

N-[2-(3- Cyano-1H-indol-5-yl)-ethyl]-4-(1-oxo-1-methyl-piperidin-4-yl)-benzamide. Using the product from reference example 112 . MS (ion spray) m/z 403 $(M+H)^+$.

Reference example 1aaab

N-[2-(3- Cyano-1H-indol-5-yl)-ethyl]-4-(1-methyl-piperidin-4-yl)-benzamide. Using the product from reference example 111. MS (ion spray) m/z 387 $(M+H)^+$.

Reference example 1aaac

N-[2-(3-Cyano-1H-indol-5-yl)-ethyl]-4-(1-methanesulfonyl-piperidin-4-yl)-benzamide. Using the product from reference example 17p. MS (ion spray) m/z 451 (M+H)+.

Reference example 1aaad

4-(2-Acetylamino-1,1-dimethyl-ethyl)-N-[2-(3-cyano-1H-indol-5-yl)-ethyl]-benzamide. Using the product from reference example 105 and acetic acid as substrates. MS (ion spray) m/z 403 $(M+H)^+$.

Reference example 1aaaf

N-BOC-Piperidine-4-carboxylic acid (2-{4-[2-(3- cyano -1H-indol-5-yl)-ethylcarbamoyl]-phenyl}-2-methyl-propyl)-amide. Using the product from reference example 105 and N-BOC piperidine-4-carboxylic acid as substrates. MS (ion spray) m/z 572 $(M+H)^+$.

Reference example 1aaai

N-[2-(3-Cyano-1H-indol-5-yl)-ethyl]-4-(2-dimethylamino-3,4,5,6-tetrahydro-pyrimidin-4-yl)-benzamide. Using the product from reference example 108. MS (ion spray) m/z 415 $(M+H)^+$.

Reference example 1aaaj

N-[2-(3- Cyano-1H-indol-5-yl)-ethyl]-4-(1-oxy-pyridin-4-yloxy)-benzamide. Using the product from reference example 118. MS (ion spray) m/z 399 (M+H)+.

Reference example 1aaak

N-[2-(3- Cyano-1H-indol-5-yl)-ethyl]-4-(1-methyl-piperidin-4-yloxy)-benzamide. Using the product from reference example 17o. MS (ion spray) m/z 403 (M+H)+.

Reference Example 1aaal

4-(2-[tert-Butoxycarbonylamino]-1,1-dimethylethyl)-N-(2-[1-tert-butoxycarbonyl-3-tert-butoxycarbonylcarbamimidoylindol-5-yl]ethyl)benzamide. Using the products from reference example 25c and 7a. ^{1}H NMR ($CDCl_3$): δ 1.31 (6H, s), 1.37 (9H, s), 1.56 (9H, s), 1.66 (9H, s), 3.08 (2H, t, J = 6.6 Hz), 3.31 (2H, d, J = 6.2 Hz), 3.81 (2H, m), 4.27 (1H, br, m), 6.18 (1H, br, m), 7.25 (1H, d, J = 8.4 Hz), 7.37 (2H, d, J = 8.2 Hz), 7.64 (2H, d, J = 8.2 Hz), 7.88 (1H, s), 8.17 (1H, d, J = 8.4 Hz), 8.24 (1H, s). MS (ion spray) m/z 678 $(M+H)^+$.

Reference Example 1aaam

N-(2-[1-tert-Butoxycarbonyl-3-tert-butoxycarbonylcarbamimidoylindol-5-yl]ethyl)-4-(6-[2-dimethylamino-ethoxy]pyridin-3-yl)benzamide. Using the product from reference example 7a as the amine component and the product from reference example 17e as the acid component. MS (ion spray) m/z 671 $(M+H)^+$.

Reference example 1aaan

N-(2-[1-tert-Butoxycarbonyl-3-tert-butoxycarbonylcarbamimidoylindol-5-yl]ethyl)-4-pyrid-4-ylbenzamide. Using the product from reference examples 11a and 7a. ^{1}H NMR ($CDCl_3$): δ 1.55 (9H, s), 1.66 (9H, s), 3.10 (2H, t, J = 6.6 Hz), 3.83 (2H, m), 6.32 (1H, br, m), 7.25 (1H, d, J = 8.5 Hz), 7.50 (2H, d, J = 4.9 Hz), 7.65 (2H, d, J = 8.2 Hz), 7.80 (2H, d, J = 8.2 Hz), 7.92 (1H, s), 8.17 (1H, d, J = 8.5 Hz), 8.23 (1H, s), 8.68 (2H, br, m). MS (ion spray) m/z 584 $(M+H)^+$.

Reference Example 1aaao-1aaav

A solution of N-(2-[1-tert-Butoxycarbonyl-3-tert-butoxycarbonylcarbamimidoylindol-5-yl]ethyl)-amine (1 mL, 0.01M in DMF) (reference example 7a) is added to 30 mg of acylated resin (0.5 mmol / g, reference example 54) and the mixture shaken for 48 hours. then filtered. The resin is washed with a further portion of DMF (1 mL) then the combined filtrates concentrated under high vacuum. The residue is used without further purification.

The following compounds are prepared using this procedure:

Reference example 1aaao

N-(2-[1-tert-butoxycarbonyl-3-tert-butoxycarbonylcarbamimidoylindol-5-yl]ethyl)-4-(4-carbamoyl-phenyl)-benzamide.

Reference Example 1aaap

N-(2-[1-tert-butoxycarbonyl-3-tert-butoxycarbonylcarbamimidoylindol-5-yl]ethyl)-4-(4-methoxyl-phenyl)-benzamide.

Reference Example 1aaaq

N-(2-[1-tert-butoxycarbonyl-3-tert-butoxycarbonylcarbamimidoylindol-5-yl]ethyl)-(5-methoxyindol-2-yl)-carboxamide.

Reference Example 1aaar

N-(2-[1-tert-butoxycarbonyl-3-tert-butoxycarbonylcarbamimidoylindol-5-yl]ethyl)-(6-chloro-benzothiophen-2-yl)-carboxamide.

Reference Example 1aaas

4-(4-benzyloxyl-phenyl)-N-(2-[1-tert-butoxycarbonyl-3-tert-butoxycarbonyl-carbamimidoylindol-5-yl]ethyl)- benzamide.

Reference Example 1aaat

N-(2-[1-tert-butoxycarbonyl-3-tert-butoxycarbonylcarbamimidoylindol-5-yl]ethyl)-4-chloro-benzamide.

Reference Example 1aaau

N-(2-[1-tert-butoxycarbonyl-3-tert-butoxycarbonyl-carbamimidoylindol-5-yl]ethyl)- 4-(methylsulphonyl)-benzamide.

Reference Example 1aaav

N-(2-[1-tert-butoxycarbonyl-3-tert-butoxycarbonyl-carbamimidoylindol-5-yl]ethyl)- 4-(amino-sulphonyl)-benzamide.

Reference Example 2

3-Cyano-5-(2-aminoethyl)indole. A solution of 1.01 g (4.78 mmol) 3-cyano-5-(2-azidoethyl)indole (reference example 3) and 1.38 g (5.26 mmol) triphenylphosphine in 20 mL THF is stirred overnight to give a white precipitate. Another 20 mL THF and 1 mL distilled water is added. After stirring overnight the resulting solution is concentrated, and the residue chromatographed (10: 1 CH_2Cl_2: 7N NH_3 in MeOH) to provide 0.870 g of the product as a white solid in 98% yield. ^1H NMR (CD_3OD): δ 2.87-2.97 (4H, m), 7.17 (1H, d, J = 8 Hz), 7.45 (1H, d, J = 8 Hz), 7.50 (1H, s), 7.90 (1H, s). MS (EI) m/z 185 M^+, 169 $(M-NH_3)^+$, 155 $(M-CH_2NH_2)^+$.

Reference Example 3

3-Cyano-5-(2-azidoethyl)indole.

A mixture of 1.92 g (9.38 mmol) 3-cyano-5-(2-chloroethyl)indole (reference example 4) and 1.53 g (23.5 mmol) sodium azide in 10 mL DMF is heated to 80° C for three hours, followed by azeotroping with toluene. The resulting residue is chromatographed (2:1 hexane: ethyl acetate) to provide 1.89 g of the product as a brown solid in 95% yield. ^{1}H NMR ($CDCl_3$): δ 3.03 (2H, t, J = 7.1 Hz), 3.57 (2H, t, J = 7 Hz), 7.20 (1H, dd, J = 8, 1 Hz), 7.43 (1H, d, J = 8 Hz), 7.62 (1H, s), 7.73 (1H, d, J = 3 Hz), 8.81 (1H, br). MS (ion spray) m/z 212 $(M+H)^+$, 169 $(M-N_3)^+$.

Reference Example 4

3-Cyano-5-(2-chloroethyl)indole. A mixture of 3.29 g (15.8 mmol) 5-(2-chloroethyl)indole-3-carboxaldehyde (reference example 5), 1.15 g (16.6 mmol) hydroxylamine hydrochloride, 6.27 g (52.1 mmol) magnesium sulfate, and 0.601 g (3.16 mmol) p-toluenesulfonic acid monohydrate in 10 mL DMF is heated to 150° C for 30 minutes. The reaction mixtue is azeotroped with toluene, and the resulting residue chromatographed (2:1, then 1:1 hexane: ethyl acetate) to provide 3.08 g of product as a white solid in 95% yield. ^{1}H NMR ($CDCl_3$): δ 3.20 (2H, t, J = 7 Hz), 3.77 (2H, t, J = 7 Hz), 7.21 (1H, dd, J = 8, 1 Hz), 7.43 (1H, d, J = 8 Hz), 7.63 (1H, s), 7.73 (1H, d, J = 3 Hz), 8.66 (1H, br). MS (EI) m/z 204, 206 (M[^{35}Cl, ^{37}Cl])$^+$, 155 $(M-CH_2Cl)^+$.

Reference Example 5

5-(2-Chloroethyl)indole-3-carboxaldehyde.

A solution of 1.46 mL (15.7 mmol) phosphorous oxychloride in 5 mL DMF is stirred for 20 minutes. A solution of 2.11 g (13.1 mmol) 5-(2-hydroxyethyl)indole (reference example 6) in 5 mL DMF is added, and the reaction mixture is heated to 80° C for ten minutes. The reaction is quenched with solid sodium bicarbonate and diluted with 250 mL 1:1 CH_2Cl_2: MeOH. The inorganic solids are filtered off, and the filtrate concentrated. The resulting residue is refluxed in 75 mL 1N HCl solution for one hour, then extracted with CH_2Cl_2. The organic extracts are combined and concentrated, and the residue chromatographed (20:1 CH_2Cl_2: MeOH) to provide 2.45 g of the product as a brown solid in 90% yield. ^{1}H

NMR ($CDCl_3$): δ 3.19 (2H, t, J = 7 Hz), 3.76 (2H, t, J =, 7 Hz), 7.20 (1H, dd, J = 8, 1 Hz), 7.40 (1H, d, J =8 Hz), 7.85 (1H, d, J = 3 Hz), 8.19 (1H, s), 8.98 (1H, br), 10.05 (1H, s). MS (EI) m/z 207, 209 ($M[^{35}Cl, ^{37}Cl])^+$, 158 $(M-CH_2Cl)^+$.

Reference Example 6

5-(2-Hydroxyethyl)indole.

To a cooled (0° C) mixture of 1.56 g (38.9 mmol) of a 60% dispersion of sodium hydride in 10 mL THF is slowly added a solution of 5.05 g (25.9 mmol) 5-bromoindole (Acros) in 20 mL THF. After H_2 evolution stopped (~10 min) the mixture is cooled to -78° C, and 25.9 mL (64.8 mmol) of a 2.5 M hexane solution of n-butyllithium is added dropwise. After five minutes, added 16.8 mL (38.9 mmol) of a 2.3 M THF stock solution of ethylene oxide and removed cooling bath. After 90 minutes, quenched with 5 mL distilled water. The organic layer is then poured away from the inorganic salts and concentrated. The resulting residue is chromatographed (1:1 hexane: ethyl acetate) to provide 2.24 g of the product as a yellow oil in 54% yield.

^1H NMR ($CDCl_3$): δ 2.96 (2H, t, J = 6.5 Hz), 3.88 (2H, m), 6.51 (1H, m), 7.06 (1H, dd, J_1 = 8.5 Hz, J_2 = 1.5 Hz), 7.19 (1H, m), 7.33 (1H, d, J = 8.5 Hz), 7.49 (1H, s), 8.19 (1H, br). MS (EI) m/z 161 M^+, 130 $(M-CH_2OH)^+$.

Reference Example 7a

1-tert-Butoxycarbonyl-3-(tert-butoxycarbonylcarbamimidoyl)-5-(2-aminoethyl)indole.

A solution of 1-tert-Butoxycarbonyl-3-(tert-butoxycarbonylcarbamimidoyl)-5-(2-[allyloxycarbonylamino]ethyl)indole (reference example 8) (0.199 g, 0.409 mmol), 50 mg tetrakis(triphenylphosphine)palladium (0), and 0.078 mL (0.90 mmol) morpholine in 20 mL CH_2Cl_2 is stirred for one hour. TLC showed some starting material present, so another 50 mg palladium catalyst is added. After stirring 45 minutes, the reaction mixture is concentrated, and the residue chromatographed (10:1 CH_2Cl_2: 7N NH_3 in MeOH) to provide the product as a yelow solid. ^1H NMR ($CDCl_3$): δ 1.57 (9H, s), 1.64 (9H, s), 2.88 (4H, m), 7.23 (1H, dd, J_1 = 8.7 Hz, J_2 = 1.2 Hz), 7.77 (1H, s), 8.16 (1H, d, J = 8.7 Hz), 8.25 (1H, s). MS (EI) m/z 402 M^+.

Reference Example 7b

4-(1-[tert-Butoxycarbonylmethyl]-2-oxo-2H-pyridin-5-yl)benzoic acid. Prepared using essentially the same procedure used in reference example 7a except using Allyl 4-(1-[tert-butoxycarbonylmethyl]-2-oxo-2H-pyridin-5-yl)benzoate (reference example 85d) as substrate. MS (ion spray) m/z 330 $(M+H)^+$.

Reference Example 8

1-tert-Butoxycarbonyl-3-(tert-butoxycarbonylcarbamimidoyl)-5-(2-[allyloxycarbonylamino]ethyl)indole. A solution of 0.346 g (0.999 mmol) 3-Carbamimidoyl-5-(2-[allyloxycarbonylamino]ethyl)indole (reference example 9) 0.655 g (3.00 mmol) *di-tert-butyl dicarbonate*, and 0.49 mL (3.5 mmol) triethylamine in 40 mL 1:1 CH_2Cl_2: THF is stirred at 40° C for seven hours, then at room temperature overnight, then at 40° C for four more hours, followed by concentration. The resulting residue is chromatographed (2:1 hexane: ethyl acetate) to provide the product as a white solid in 36% yield. ^1H NMR ($CDCl_3$): δ 1.56 (9H, s), 1.66 (9H, s), 2.95 (2H, t, J = 6.5 Hz), 3.56 (2H, m), 4.51 (2H, d, J = 5.4 Hz), 5.21 (2H, m), 5.85 (1H, m), 7.21 (1H, d, J = 8.3 Hz), 7.76 (1H, s), 8.15 (1H, d, J = 8.3 Hz), 8.40 (1H, s). MS (ion spray) m/z 487 $(M+H)^+$.

Reference Example 9

3-Carbamimidoyl-5-(2-[allyloxycarbonylamino]ethyl)indole.

A stream of hydrogen sulfide is bubbled through a solution of 0.392 g (1.11 mmol) 1-Allyloxycarbonyl-3-cyano-5-(2-[allyloxycarbonylamino]ethyl)indole (reference example 10) in 10 mL 9:1 pyridine: triethylamine for fifteen minutes. The reaction is capped and stirred for 36 hours, followed by removal of solvent by distillation. The residue is dissolved in 10 mL acetone, and 1.82 mL iodomethane is added. The reaction vessel is fitted with a cooled condenser and heated to 60° C for one hour. The reaction is concentrated, and 10 mL MeOH and 0.940 g (12.2 mmol) are added. This mixture is stirred at 60° C for four hours, then at room temperature overnight, followed by concentration and chromatography (5:1 CH_2Cl_2: MeOH) to provide the product as the acetate salt in 90% yield. ^1H NMR (CD_3OD): δ 1.98 (3H, s). 2.94 (2H, t, J = 7.2 Hz), 3.41 (2H, t, J = 7.2 Hz), 4.49 (2H, d, J = 4.9 Hz), 5.19 (2H, m), 5.87 (1H, m), 7.20 (1H, d, J = 8.3 Hz), 7.50 (1H, d, J = 8.3 Hz), 7.73 (1H, s), 8.14 (1H, s). MS (ion spray) m/z 287 $(M+H)^+$.

This compound can also be prepared directly, from 3-cyano-5-(2-[allyloxycarbonylamino]ethyl)indole (reference example 23) using essentially the same procedure as described above.

Reference Example 10

1-Allyloxycarbonyl-3-cyano-5-(2-[allyloxycarbonylamino]ethyl)indole.

A solution of 1.89 g (8.95 mmol) 3-cyano-5-(2-azidoethyl)-indole (reference example 3) and 2.58 g (9.85 mmol) triphenylphosphine in 40 mL THF is stirred overnight to give a white precipitate. To this is added 0.32 mL H_2O, and stirring is continued overnight. Then 4.75 g (44.8 mmol) sodium bicarbonate and 15 mL H_2O, followed by 2.1 mL (20 mmol) allyl chloroformate, is added. After stirring overnight another 2 mL allyl chloroformate is added, followed by stirring overnight. The reaction mixture is diluted with ethyl acetate and washed with distilled water. The organic layer is concentrated, and the resulting residue chromatographed (3:1, then 1:1 hexane: ethyl acetate) to provide the product as a white solid in 61.7% yield. ^{1}H NMR ($CDCl_3$): δ 2.96 (2H, t, J = 7.0 Hz), 3.50 (2H, m), 4.56 (2H, d, J = 5.4 Hz), 4.97 (2H, d, J = 5.9 Hz), 5.25 (2H, m), 5.46 (2H, m), 5.91 (1H, m), 6.06 (1H, m), 7.31 (1H, d, J = 8.6 Hz), 7.54 (1H, s), 8.14 (1H, d, J = 8.6 Hz), 8.15 (1H, s). MS (EI) m/z 353 M^+, 268 $(M\text{-}CO_2Allyl)^+$.

Reference Example 11a

4-[Pyridin-4-yl]-Benzoic Acid. To a suspension of 4-[pyridin-4-yl]-benzaldehyde (approx. 2.8g, 15 mmol) (reference example 12a) in t-butanol (100 mL) is added 2-methy-but-2-ene (15mL) followed by a solution comprised of $NaClO_2$ (14.7g, tech. grade) and $NaH_2PO_4.H_2O$ (14.7g, 105 mmol) in H_2O (100 mL). This mixture is stirred for 20 minutes then the precipitated solid filtered off. This solid is washed with water then set aside. The organic phase of the mother liquor is separated, then washed with brine, dried over $MgSO_4$ and concentrated to give a solid. This material is combined with the solid obtained by filtration and dried under vacuum to give 2.34g of the title compound. ^{1}H NMR (DMSO) d 7.77 (d, J = 6Hz, 2H), 7.93 (d, J = 8Hz, 2H), 8.06 (d, J = 8Hz, 2H), 8.70 (d, J = 6Hz, 2H). MS (EI) m/z 199 $(M)^+$.

Reference Example 11b

By employing essentially the same procedure as used in reference example 11a, except using the product from reference example 12b, there is prepared 4-[Pyridin-3-yl]-Benzoic Acid. ^{1}H NMR (DMSO) d 7.52

(dd, J = 8, 5Hz, 1H), 7.87 (d, J = 8Hz, 2H), 8.06 (d, J = 8Hz, 2H), 8.15 (dd, J = 8, 2Hz, 1H), 8.62 (dd, J = 5, 2Hz, 1H), 8.96 (s, 1H), 13.05 (bs, 1H). MS (EI) m/z 199 $(M)^+$.

Reference Example 11c

By employing essentially the same procedure as used in reference example 11a, except using the product from reference example 12c, there is prepared 4-[Pyrimidin-5-yl]-Benzoic Acid. ^{1}H NMR (DMSO) d 7.95 (d, J = 8Hz, 2H), 8.10 (d, J = 8Hz, 2H), 9.23 (s, 2H), 9.25 (s, 1H), MS (EI) m/z 200 $(M)^+$.

Reference Example 11d

By employing essentially the same procedure as used in reference example 11a, except using the product from reference example 12d, there is prepared 4-[Pyridazin-3-yl]-Benzoic Acid. ^{1}H NMR (DMSO) d 7.85 (dd, J = 8, 4Hz. 1H), 8.1 (d, J = 8Hz, 2H), 8.29 (d, J = 8Hz, 2H), 8.31 (d, J = 8Hz, 1H), 9.26 (d, J = 4Hz, 1H). MS (EI) m/z 200 $(M)^+$.

Reference Example 11e

By employing essentially the same procedure as used in reference example 11a, except using the product from reference example 12e, there is prepared 4-[Pyridazin-4-yl]-Benzoic Acid. ^{1}H NMR (DMSO) d 8.10 (m, 5H), 9.33 (d, J = 4Hz, 1H), 9.67 (bs, 1H). MS (EI) m/z 200 $(M)^+$.

Reference Example 11f

By employing essentially the same procedure as used in reference example 11a, except using the product from reference example 12f, there is prepared 4-(6-methoxy-pyridazin-3-yl)-benzoic acid. ^{1}H NMR (DMSO) δ 4.10 (s, 3H), 7.36 (d, J = 9Hz, 1H), 8.08 (d, J = 8Hz, 2H), 8.20 (d, J = 8Hz, 2H), 8.26 (d, J = 9Hz, 1H), 13.00 (bs, 1H). MS (EI) m/z 230 (M^+).

Reference Example 11g

By employing essentially the same procedure as used in reference example 11a, except using the product from reference example 12g, there is prepared 4-[2-chloro-pyrimidin-4-yl]-benzoic acid. ^{1}H NMR (DMSO)

δ 8.09 (d, J = 8Hz, 2H), 8.21 (d, J = 5Hz, 1H), 8.30 (d, J = 8Hz, 2H), 8.88 (d, J = 5Hz, 1H). MS (EI) m/z 234/ 236 (M+, Cl pattern).

Reference Example 11h

By employing essentially the same procedure as used in reference example 11a, except using the product from reference example 97a, there is prepared 4-[2-oxo-pyrimidin-4-yl]-benzoic acid. ^{1}H NMR (DMSO) δ 7.77 (d, J = 8Hz, 2H), 7.97 (d, J = 8Hz, 1H), 8.70 (bs, 2H). MS (EI) m/z 216 $(M)^+$.

Reference Example 11i

By employing essentially the same procedure as used in reference example 11a, except using the product from reference example 97b , there is prepared Biphenyl-3,4'-dicarboxylic acid 3-Methyl ester. ^{1}H NMR (DMSO) δ 3.90 (s, 3H), 7.69 (t, J = 8Hz, 2H), 7.86 (d, J = 8Hz, 2H), 8.0-8.11 (m, 4H), 8.25 (s, 1H). MS (EI) m/z 256 $(M)^+$.

Reference Example 11j

By employing essentially the same procedure as used in reference example 11a, except using the product from reference example 97c , there is prepared Biphenyl-2,4'-dicarboxylic acid 2-Methyl ester. ^{1}H NMR ($CDCl_3$) δ 3.68 (s, 3H), 7.47-7.51 (m, 5H), 8.19 (d, J = 8Hz, 1H). MS (EI) m/z 256 $(M)^+$.

Reference Example 12a

4-[Pyridin-4-yl]-Benzaldehyde. To a cooled (-78 °C) solution of oxalyl chloride in CH_2Cl_2 (15mL, 1M) is added, dropwise, DMSO (3 mL). The resulting solution is stirred for 5 minutes then a solution of 4-[pyridin-4-yl]-benzyl alcohol (2.80 g, 15 mmol) (reference example 13a) in CH_2Cl_2 / DMSO (27 mL, 3:1 CH_2Cl_2 / DMSO) is added dropwise. The resulting mixture is stirred 5 minutes then Et_3N added (15 mL, 108 mmol) in one portion. The cold bath is removed and stirring continued for 15 minutes. The reaction mixture is then diluted with ethyl acetate, washed with water and then brine, dried over $MgSO_4$ and concentrated. The crude, orange solid product is used without further purification.

Reference Example 12b

By employing essentially the same procedure as used in reference example 12a, except using the product from reference example 13b, there is prepared 4-[Pyridin-3-yl]-Benzaldehyde.

Reference Example 12c

By employing essentially the same procedure as used in reference example 12a, except using the product from reference example 13c, there is prepared 4-[Pyrimidin-5-yl]-Benzaldehyde.

Reference Example 12d

By employing essentially the same procedure as used in reference example 12a, except using the product from reference example 14a, there is prepared 4-[Pyridazin-3-yl]-Benzaldehyde.

Reference Example 12e

By employing essentially the same procedure as used in reference example 12a, except using the product from reference example 14b, there is prepared 4-[Pyridazin-4-yl]-Benzaldehyde.

Reference Example 12f

By employing essentially the same procedure as used in reference example 12a, except using the product from reference example 13d, there is prepared 4-(6-methoxy-pyridazin-3-yl)-benzaldehyde. ^{1}H NMR ($CDCl_3$) δ 4.22 (s, 3H), 7.10 (d, J = 9Hz, 1H), 7.86 (d, J = 9Hz, 1H), 8.02 (d, J = 8Hz, 2H). 8.20 (d, J = 8Hz, 2H), 10.10 (s, 1H). MS (EI) m/z 214 (M^+).

Reference Example 12g

By employing essentially the same procedure as used in reference example 12a, except using the product from reference example 14c, there is prepared 4-[2-(2-chloro)-pyrimidin-4-yl]-benzaldehyde. ^{1}H NMR (DMSO) δ 8.10 (d, J = 8Hz, 2H), 8.29 (d, J = 5Hz, 1H), 8.41 (d, J = 8Hz, 2H), 8.94 (d, J = 5Hz, 1H), 10.13 (s, 1H). MS (EI) m/z 218/ 220 (M^+, Cl pattern).

Reference Example 13a

4-[Pyridin-4-yl]-Benzyl alcohol. To a cooled (-78°C) solution of 4-bromo-benzyl-(t-butyldimethylsilyl)-ether (5.46 g, 18 mmol) (reference example 16) in THF (40 mL) is added, dropwise, n-BuLi (8.8 mL, 2.5M in hexanes). On complete addition, the resulting solution is stirred for 10 minutes then $ZnCl_2$ (40 mL, 0.5M in THF) is added. The cold bath is removed and stirring continued for 10 minutes. To this solution is added 4-bromo-pyridine* (approx. 2.2 mL, 22 mmol) in hexanes (25 mL) followed by $(Ph_3P)_4Pd$ (900 mg, 0.77 mmol). The resulting mixture is heated to 60 °C and stirred at this temperature for 1 hour. The reaction mixture is allowed to cool to room temperature then diluted with ether, washed, sequentially, with 5% aqueous ammonium hydroxide solution and brine, dried over $MgSO_4$ and concentrated. The residue is taken up in THF (30 mL) and treated with n-Bu_4NF (25 mL, 1M in THF). The resulting solution is stirred for 25 minutes then diluted with ethyl acetate, washed with water and brine, dried over $MgSO_4$ and concentrated. The residue is triturated with ether, filtered and the solid dried under vacuum to give 2.8g of the title compound as a tan solid.

* 4-bromo-pyridine is obtained from its HCl salt by dissolving the salt in cold 1M NaOH (5% excess) then extracting with cold hexane. The hexane extract is dried over $MgSO_4$ and used without further manipulation.

Reference Example 13b

By employing essentially the same procedure as used in reference example 13a, except using 3-bromo-pyridine, there is prepared 4-[Pyridin-3-yl]-Benzyl alcohol. ^{1}H NMR (DMSO) d 4.55 (d, J = 6 Hz, 2H), 5.25 (t, J = 6Hz, 1H), 7.44 (d, J = 8Hz, 2H), 7.48 (dd, J = 8, 5Hz, 1H), 7.68 (d, J = 8Hz, 2H), 8.07 (dt, J = 8, 2Hz, 1H), 8.56 (dd, J = 5, 2Hz, 1H), 8.88 (d, J = 2Hz, 1H). MS (EI) m/z 185 $(M)^+$.

Reference Example 13c

By employing essentially the same procedure as used in reference example 13a, except using 5-bromo-pyrimidine, there is prepared 4-[Pyrimidin-5-yl] Benzyl Alcohol. ^{1}H NMR ($CDCl_3$) d 2.61 (bs, 1H), 4.80 (d, J = 7Hz, 2H), 7.55 (m, 4H), 8.88 (s, 2H), 9.20 (s, 1H). MS (EI) m/z 186 $(M)^+$.

Reference Example 13d

By employing essentially the same procedure as used in reference example 13a, except using the product from reference example 41b , there is prepared 4-(6-methoxy-pyridazin-3-yl)-benzyl alcohol. ^{1}H NMR ($CDCl_3$) δ 1.85 (bt, 1H), 4.19 (s, 3H), 4.78 (d, J = 5Hz, 2H), 7.06 (d, J = 9Hz, 1H), 7.50 (d, J = 8Hz, 2H), 7.78 (d, J = 9Hz, 1H), 8.01 (d, J = 8Hz, 2H). MS (EI) m/z 216 (M^+).

Reference Example 14a

4-[Pyridazin-3-yl]-Benzyl Alcohol. To a solution of 4-[pyridazin-3-yl]-benzyl-(t-butyldimethylsilyl) ether (2.71g, 9 mmol) (reference example 15, less polar product) is added a solution of tetra-n-butylammonium fluoride in THF (12 mL, 1M). The resulting solution is stirred for 15 minutes then diluted with ethyl acetate. This solution is washed with water then brine. The aqueous washings are back extrated with 10% methanol in CH_2Cl_2. The combined organic extracts are dried over $MgSO_4$ then concentrated. The residue is purified by flash chromatography (eluting with ethyl acetate) to give 1.50g of the title compound as a white solid. ^{1}H NMR ($CDCl_3$) d 2.28 (t, J = 5Hz, 1H), 4.79 (d, J = 5Hz, 2H), 7.50 (m, 3H), 7.85 (dd, J = 8, 1 Hz, 1H), 8.05 (d, J = 8 Hz, 2H), 9.13 (dd, J = 5, 1Hz, 1) MS (EI) m/z 186 (M^+).

Reference Example 14b

By employing essentially the same procedure as used in reference example 14a, except using the more polar product from reference example 15, there is prepared 4-[Pyridazin-4-yl]-Benzyl Alcohol. ^{1}H NMR ($CDCl_3$) d 2.20 (t, J = 6Hz, 1H), 4.79 (d, J = 6 Hz, 2H), 7.53 (d, J = 8Hz, 2H), 7.63 (m, 3H), 9.18 (d, J = 4Hz, 1H), 9.42 (bs, 1H). MS (EI) m/z 186 (M^+).

Reference Example 14c

By employing essentially the same procedure as used in reference example 14a, except using the product from reference example 84, there is prepared 4-[2-(2-chloro)-pyrimidin-4-yl]-benzyl alcohol. ^{1}H NMR (DMSO) d 4.57 (d, J = 5Hz, 2H), 5.34 (t, J = 5Hz, 1H), 7.49 (d, J = 8Hz, 2H), 8.14 (m, 3H), 8.79 (d, J = 5Hz, 1H). MS (EI) m/z 220 / 222 (M+, Cl pattern)

Reference Example 15

4-[Pyridazin-3-yl]-Benzyl-(t-Butyldimethylsilyl) Ether and 4-[Pyridazin-4-yl]-Benzyl-(t-Butyldimethylsilyl) Ether. To a solution cooled (-78°C) of 4-Bromobenzyl(t-butyldimethylsilyl)-ether (9.03g, 30mmol) (reference example 16 in THF (60 mL) is added, dropwise, n-BuLi (12.6 mL, 2.5M in hexanes). The resulting solution is stirred for 5 minutes then pyridazine (2.25mL, 31 mmol) is added in one portion. This solution is stirred for 20 minutes then aqueous HCl added (30 mL, 1M). The reaction mixture is diluted with ether, washed with brine dried over $MgSO_4$ and concentrated. The residue is taken up in acetone (45 mL) and this solution added to a solution of $KMnO_4$ in acetone (9.3g, 60 mmol in approx. 200 mL). On complete addition, the brown colored mixture is stirred 5 minutes then filtered through celite. The mother liquor is concentrated and the residue purified by flash chromatography (eluting with 50% ethyl acetate in hexanes) to give 2.71g of 4-[pyridazin-3-yl]-benzyl-(t-butyldimethylsilyl) ether: ^{1}H NMR ($CDCl_3$) d 0.12 (s, 6H), 0.99 (s, 9H), 4.83 (s, 2H), 7.50 (d, J = 8Hz, 2H), 7.53 (dd, J = 8, 5 Hz, 1H), 7.85 (dd, J = 8, 1Hz, 1H), 8.06 (d, J = 8Hz, 2H), 9.14 (dd, J = 5, 1Hz, 1H). MS (EI) m/z 301 $(M+H)^+$ and 2.0g of 4-[pyridazin-4-yl]-benzyl-(t-butyldimethylsilyl) ether: ^{1}H NMR ($CDCl_3$) d 0.11 (s, 6H), 0.96 (s, 9H), 4.80 (s, 2H), 7.47 (d, J = 8Hz, 2H), 7.63 (m, 3H), 9.20 (d, J = 4Hz, 1H), 9.45 (bs, 1H). MS (EI) m/z 301 $(M+H)^+$.

Reference Example 16

4-Bromobenzyl-(t-butyldimethylsilyl)-ether. To a cooled (0 °C) solution of 4-bromo-benzyl alcohol (3.74g, 20 mmol) in ether (80 mL) is added 2,6-lutidine (2.6mL, 22mmol) followed by t-butyldimethylsilyl trifluoromethanesulphonate (5.05 mL, 22 mmol). The resulting mixture is stirred for 40 minutes then diluted with ether, washed, sequentially, with water and brine, dried over $MgSO_4$ and concentrated. The residue is purified by flash chromatography (eluting with 5% ether in hexanes) to give 6.0g of the title compound as an oil. ^{1}H NMR ($CDCl_3$) d 0.09 (s, 6H), 0.93 (s, 9H), 4.68 (s, 2H), 7.18 (d, J = 8Hz, 2H), 7.44 (d, J = 8Hz, 2H). MS (EI) m/z 300 $(M)^+$.

Reference Example 17a

4-[pyridine-N-oxide-4-yl]-Benzoic Acid. Stirred 0.940 g Methyl 4-[pyridine-N-oxide-4-yl]-benzoate (reference example 18) (4.10 mmol) with 6 mL 1N NaOH and 20 mL 1:1 THF: CH_3OH. After 18 hours,

added another 3 mL NaOH solution. After 24 more hours acidified with 1N HCl. Collected resulting white solid by filtration. Washed with H_2O; air dried. Used without further purification. MS(EI) m/z 215 (M^-), 171 $(M-CO_2)^-$.

Reference Example 17b

Using essentially the same procedure used to prepare reference example 17a except using methyl 4-(2-methoxy-pyrimidin-4-yl)-benzoate (reference example 19b) there is prepared 4-(2-methoxy-pyrimidin-4-yl)-benzoic acid. ^1H NMR (DMSO) d 3.99 (s, 3H), 7.78 (d, J = 5Hz, 1H), 8.06 (d, J = 8Hz, 2H), 8.27 (d, J = 8Hz, 2H), 8.70 (d, J = 5Hz, 1H). MS (EI) m/z 230 (M+).

Reference Example 17c

Using essentially the same procedure used to prepare reference example 17a except using ethyl 4-(1-[2-Dimethylaminoethyl]-6-oxo-1,6-dihydropyridin-3-yl)benzoate (reference example 85a) there is prepared 4-(1-[2-Dimethylaminoethyl]-6-oxo-1,6-dihydropyridin-3-yl)benzoic acid. Purified by HPLC; isolated as the TFA salt. ^1H NMR (D_2O): δ 2.86 (6H, s), 3.47 (2H, m), 4.34 (2H, m), 6.62 (1H, d, J = 8.6 Hz), 7.50 (2H, d, J = 8.4 Hz), 7.82-7.91 (4H, m). MS (ion spray) m/z 287 $(M+H)^+$.

Reference Example 17d

Using essentially the same procedure used to prepare reference example 17a except using ethyl 4-(1-Carbamoylmethyl-6-oxo-1,6-dihydropyridin-3-yl)benzoate (reference example 1av) there is prepared 4-(1-Carbamoylmethyl-6-oxo-1,6-dihydropyridin-3-yl)benzoic acid. MS (ion spray) m/z 273 $(M+H)^+$.

Reference example 17e

Using essentially the same procedure used to prepare reference example 17a except using ethyl 4-(6-[2-Dimethylaminoethoxy]pyridin-3-yl)benzoate (reference example 85a) there is prepared 4-(6-[2-Dimethylaminoethoxy]pyridin-3-yl)benzoic acid. Purified by HPLC; isolated as the TFA salt. ^1H NMR (D_2O): δ 2.84 (6H, s), 3.48 (2H, m), 4.44 (2H, m), 6.81 (1H, d, J = 8.6 Hz), 7.50 (2H, d, J = 8.2 Hz), 7.85 (2H, d, J = 8.2 Hz), 7.88 (1H, m), 8.18 (1H, s). MS (ion spray) m/z 287 $(M+H)^+$.

Reference Example 17f

Using essentially the same procedure used to prepare reference example 17a except using 4-(2-oxo-hexahydro-pyrimidin-5-yl)-benzoic acid methyl ester as substrate (reference example 95) there is prepared 4-(2-oxo-hexahydro-pyrimidin-5-yl)-benzoic acid. ^{1}H NMR (DMSO) δ 3.15 (m, 1H), 3.4 (m, 4H), 6.33 (bs, 2H), 7.45 (d, J = 8Hz, 2H), 7.90 (d, J = 8Hz, 2H).

Reference Example 17g

Using essentially the same procedure used to prepare reference example 17a except using 4-(1,3 dimethyl-2-oxo-hexahydro-pyrimidin-5-yl)-benzoic acid methyl ester as substrate (reference example 98) there is prepared 4-(1,3-dimethyl-2-oxo-hexahydro-pyrimidin-5-yl)-benzoic acid. MS (ion spray) m/z 249 $(M+H)^+$.

Reference Example 17h

Using essentially the same procedure used to prepare reference example 17a except using Biphenyl-3,4'-dicarboxylic acid 4'-{[2-(3-cyano-1H-indol-5-yl)-ethyl]-amide} 3-methyl ester as substrate (reference example 1aac) there is prepared Biphenyl-3,4'-dicarboxylic acid 4'-{[2-(3-cyano-1H-indol-5-yl)-ethyl]-amide}. MS (CI) m/z 410 $(M+H)^+$.

Reference Example 17i

Using essentially the same procedure used to prepare reference example 17a except using Biphenyl-2,4'-dicarboxylic acid 4'-{[2-(3-cyano-1H-indol-5-yl)-ethyl]-amide} 2-methyl ester as substrate (reference example 1aad) there is prepared Biphenyl-2,4'-dicarboxylic acid 4'-{[2-(3-Cyano-1H-indol-5-yl)-ethyl]-amide}. MS (ion spray) m/z 410 $(M+H)^+$.

Reference Example 17j

Using essentially the same procedure used to prepare reference example 17a except using methyl 4-[2-(acetylamino-methyl)-pyridin-4-yl]-benzoate as substrate (reference example 102b) there is prepared 4-[2-(acetylamino-methyl)-pyridin-4-yl]-benzoic acid. MS (ion spray) m/z 271 $(M+H)^+$.

Reference Example 17k

Using essentially the same procedure used to prepare reference example 17a except using 4-[[4-(4-methoxycarbonyl-phenyl)-pyridin-2-ylmethyl]-carbamoyl]-piperidine-1-carboxylic acid tert-butyl ester as substrate (reference example 102a) there is prepared 4-[[4-(4-carboxy-phenyl)-pyridin-2-ylmethyl]-carbamoyl]-piperidine-1-carboxylic acid tert-butyl ester. MS (ion spray) m/z 440 $(M+H)^+$.

Reference Example 17l

Using essentially the same procedure used to prepare reference example 17a, except using Ethyl 4-[1-(3-dimethylaminopropyl)-6-oxo-1,6-dihydropyridin-3-yl]benzoate (reference example 85c) as substrate, there is prepared 4-[1-(3-Dimethylaminopropyl)-6-oxo-1,6-dihydropyridin-3-yl]benzoic acid. MS (ion spray) m/z 301 $(M+H)^+$.

Reference Example 17m

Using essentially the same procedure used to prepare reference example 17a, except using Ethyl 4-[6-(3-dimethylaminopropoxy)pyridin-3-yl]benzoate (reference example 85c) as substrate there is prepared 4-[6-(3-Dimethylaminopropoxy)pyridin-3-yl]benzoic acid.
MS (ion spray) m/z 301 $(M+H)^+$.

Reference Example 17n

Using essentially the same procedure used to prepare reference example 17a, except using Ethyl 4-{1-[(2-dimethylaminoethylcarbamoyl)methyl]-6-oxo-1,6-dihydropyridin-3-yl}benzoate (reference example 1aar) as

substrate there is prepared 4-{1-[(2-dimethylaminoethylcarbamoyl)methyl]-6-oxo-1,6-dihydropyridin-3-yl}benzoic acid. MS (ion spray) m/z 344 $(M+H)^+$.

Reference Example 17o

Using essentially the same procedure used to prepare reference example 17a, except using methyl 4-(1-methyl-piperidin-4-yloxy)-benzoate (reference example 114d) as substrate there is prepared 4-(1-methyl-piperidin-4-yloxy)-benzoic acid.

Reference Example 17p

Using essentially the same procedure used to prepare reference example 17a, except using methyl 4-(1-methanesulphonyl-piperidin-4-yl)-benzoate (reference example 126) as substrate and purifying by reverse phase HPLC, there is prepared 4-(1-methanesulphonyl-piperidin-4-yl)-benzoic acid. ^{1}H NMR (DMSO): d 7.88 (d, 2H), 7.40 (d, 2H), 3.68 (d, 2H), 2.91 (s, 3H), 2.70-2.85 (m, 3H), 1.84-1.93 (m, 2H), 1.68 (dq, 2H).

Reference Example 18

Methyl 4-[pyridine-N-oxide-4-yl]-benzoate. To a cooled (0°C) solution of methyl 4-[pyridin-4-yl]-benzoate (2.1g, 10 mmol) (reference example 19a) in CH_2Cl_2 (41 mL) is added m-CPBA (3.4g, 50-60% technical grade, 10 mmol). The resulting solution is stirred for 1 hour then a further portion of m-CPBA added (1.7g, 5 mmol). This solution is stirred for 1 hour (temperature held between 5-10 °C) then the reaction mixture poured directly onto a silica gel column. Elution with 10% MeOH / 40% EtOAc / 50% CH_2Cl_2 gave 2.0g of the title compound as a tan solid. ^{1}H NMR (CD_3OD) d 3.94 (s, 3H), 7.90 (m, 4H), 8.14 (d, J = 8.5 Hz, 2H), 8.39 (d, J = 7Hz, 2H). MS (EI) m/z 230 $(M)^+$.

Reference Example 19a

Methyl 4-[Pyridin-4-yl]-Benzoate. To a solution of 4-[pyridin-4-yl]-benzoic acid (2.0g, 10mmol) (reference example 11a) in methanol (30 mL) is added conc. H_2SO_4 (4 mL). The resulting solution is warmd to 60 °C and stirred at this temperature for 2.5 hours. The reaction mixture is then allowed to cool to room

temperature then poured into ice. The pH of the resulting solution is adjusted to 7 using a 10 M solution of NaOH. The product is then extracted into ethyl acetate. This solution is washed with brine, dried over $MgSO_4$ and concentrated to give 2.1g of the title compound as a white solid. ^1H NMR ($CDCl_3$) d 3.94 (s, 3H), 7.50 (d, J = 5Hz, 2H), 7.69 (d, J = 8Hz, 2H), 8.13 (d, J = 5Hz, 2H) 8.68 (d, J = 5Hz, 2H). MS (EI) m/z 213 $(M)^+$.

Reference Example 19b

Using essentially the same procedure used to prepare reference example 19a except using 4-(2-chloro-pyrimidin-4-yl)-benzoic acid (reference example 11g) there is prepared methyl 4-(2-methoxy-pyrimidin-4-yl)-benzoate. ^1H NMR ($CDCl_3$) 3.93 (s, 3H), 4.09 (s, 3H), 7.39 (d, J = 5Hz, 1H), 8.13 (d, J = 8Hz, 2H), 8.16 (d, J = 8Hz, 2H), 8.59 (d, J = 5Hz, 1H). MS (EI) m/z 244 (M+).

Reference Example 19c

4-(2-Oxo-pyrimidin-5-yl)-benzoic acid methyl ester. Using essentially the same procedure used to prepare reference example 19a except using 4-(2-Oxo-pyrimidin-5-yl)-benzoic acid (reference example 1h) as substrate. ^1H NMR (CD_3OD) 3.28 (m, 1H), 3.47 (d, J = 7Hz, 4H), 3.90 (s, 3H), 7.44 (d, J = 8Hz, 2H), 7.90 (d, J = 8Hz, 2H).

Reference Example 20

[3-(4-furan-2-yl-phenyl)-3-methyl-butyl]-carbamic acid tert-butyl ester. To a solution of 2-[4-(3-azido-1,1-dimethyl-propyl)-phenyl]-furan (1.06g, 4.2mmol) (reference example 21) in THF (14mL) is added triphenylphosphine (1.21g, 4.6mmol) and the solution stirred for 5 hours then added H_2O (151ul, 8.4mmol) and stirred for 3 hours. To the solution is added di-tert-butyl dicarbonate (3.7g, 16.8mmol), stirred for 16 hours then concentrated. The residue is purified by flash chromatography (eluting with 15% ethyl acetate in hexanes) to give 1.17g of title compound as a colorless oil. ^1H NMR ($CDCl_3$) δ 1.34 (s, 6H), 1.39 (s, 9H), 1.83 (m, 2H), 2.92 (m, 2H), 4.27 (bs, 1H), 6.46 (m, 1H), 6.61 (d, J = 3Hz, 1H), 7.34 (d, J = 9Hz, 2H), 7.45 (d, J = 2Hz, 1H), 7.60 (d, J = 9Hz, 2H). MS (ion spray) m/z 330 $(M+H)^+$.

Reference Example 21

2-[4-(3-azido-1,1-dimethyl-propyl)-phenyl]-furan. To a cooled solution (0°C) of 3-(4-furan-2-yl-phenyl)-3-methyl-butan-1-ol (1.2g, 5.2mmol) (reference example 22) in CH_2Cl_2 (17mL) is added triethylamine (0.86mL, 6.2mmol), p-toluenesulfonyl chloride (1.18g, 6.2mmol) and 4-dimethylaminopyridine (305mg, 2.5mmol). The resulting solution is allowed to warm to 20°C while stirring for 1.5h then diluted with ethyl acetate, washed with water and brine, dried over $MgSO_4$ and concentrated. The residue is dissolved in DMF (17mL), sodium azide (845mg, 13mmol) added and the mixture heated to 60°C and stirred for 3h. The mixture is cooled to 20°C, then diluted with ethyl acetate, washed with water and brine, dried over $MgSO_4$ and concentrated. The residue is purified by flash chromatography (eluting with 10% ethyl acetate in hexanes) to give 1.06g of title compound as a colorless oil. ^1H NMR ($CDCl_3$) δ 1.36 (s, 6H), 1.95 (t, J = 8Hz, 2H), 3.03 (t, J = 8Hz, 2H), 6.46 (m, 1H), 6.62 (m, 1H), 7.34 (d, J = 8Hz, 2H), 7.46 (d, J = 2Hz, 1H), 7.62 (d, J = 8Hz, 2H). MS (ion spray) m/z 256 $(M+H)^+$.

Reference Example 22

3-(4-furan-2-yl-phenyl)-3-methyl-butan-1-ol. To a cooled solution (0°C) of 2-[4-(1,1-dimethyl-allyl)-phenyl]-furan (424mg, 2mmol) (reference example 51) in THF (4mL) is added dropwise (1M)borane-THF complex (2.2mL, 2.2mmol) and the resulting mixture stirred for 1 hour. To the mixture is added 10%NaOH (1.5mL) and 30wt% H_2O_2 (1.5mL) and stirred for 1 hour while allowing to warm to 20°C. The mixture is diluted with ether, washed with water and brine, dried over $MgSO_4$ and concentrated. The residue is purified by flash chromatography (eluting with 25% ethyl acetate in hexanes) to give 341mg of the title compound. ^1H NMR ($CDCl_3$) δ 1.34 (s, 6H), 1.40 (m, 1H), 1.94 (t, J = 8Hz, 2H), 3.48 (t, J = 8Hz, 2H), 6.45 (m, 1H), 6.60 (m, 1H), 7.35 (d, J = 8Hz, 2H), 7.44 (bs, 1H), 6.61 (d, J = 8Hz, 2H). MS (EI) m/z 230 (M+).

Reference Example 23

3-cyano-5- (2-[allyloxy-carbonyl-amino]-ethyl)indole. To a suspension of 5-(2-amino-ethyl)-3-cyano-indole (reference example 2) (925 mg, 5 mmol) in CH_2Cl_2 / THF (20 mL, 1 / 1) is added N,N-diisopropylethylamine (869 mL, 5 mmol) followed by allyl-1-benzotriazolyl carbonate (1.096g, 5 mmol). The resulting mixture is stirred for 25 minutes then concentrated. The residue is purified by flash chromatography (eluting with 7% MeOH in CH_2Cl_2) to give 1.27g of product as a white solid. ^1H NMR ($CDCl_3$) d 2.92 (t, J = 7Hz, 2H), 3.50 (q, J = 7Hz, 2H), 4.53 (d, J = 5Hz, 2H), 4.79 (bs, 1H), 5.18 (d, J = 10

Hz, 1H), 5.26 (d, J = 17Hz, 1H), 5.87 (m, 1H), 7.10 (dd, J = 8,1 Hz, 1H), 7.34 (d, J = 8Hz, 1H), 7.54 (s, 1H), 7.67 (d, J = 1Hz, 1H), 9.08 (bs, 1H). MS (EI) m/z 269 (M+).

Reference Example 24a

6-Morpholin-4-yl-nicotinic acid. A mixture of 2.00 g (12.7 mmol) 6-chloronicotinic acid and 1.11 mL (12.7 mmol) morpholine is stirred for six hours at 120° C. After cooling, the reaction mixture is flash chromatographed (5:1, then 3:1 methylene chloride: ca 7N NH_3 in MeOH) to provide 0.419 g of product as a tan solid. Contaminated with both staring materials. Used without further purification. MS (ion spray) m/z 209 $(M+H)^+$.

Reference Example 24b

4-(5-2[-{3-Cyanoindol-5-yl}ethylcarbamoyl]pyridin-2-yl)piperazine-1-carboxylic acid ethyl ester. Prepared using essentially the same procedure as for reference example 24a except using N-(2-[3-Cyanoindol-5-yl]ethyl)-6-chloronicotinamide (reference example 1e). ^1H NMR (5:1 $CDCl_3$: CD_3OD): δ 1.30 (3H, t, J = 7.1 Hz), 3.04 (2H, t, J = 7.2 Hz), 3.58-3.73 (10H, m), 4.17 (2H, q, J = 7.1 Hz), 6.68 (1H, d, J= 9.0 Hz), 7.20 (1H, d, J = 8.3 Hz), 7.43 (1H, d, J = 8.3 Hz), 7.58 (1H, s), 7.91 (1H, d, J = 9.0 Hz), 7.98 (1H, s), 8.50 (1H, d, J = 2.4 Hz). MS (ion spray) m/z 447 $(M+H)^+$.

Reference Example 24c

6-(2-Hydroxyethylamino)nicotinic acid. Prepared using essentially the same procedure as for reference example 24a except using 2-amino-ethanol. ^1H NMR (CD_3OD): δ 3.47 (2H, m), 3.72 (2H, m), 6.53 (1H, d, J = 9.3 Hz), 7.92 (1H, d, J = 9.3 Hz), 8.58 (1H, s). MS (ion spray) m/z 183 $(M+H)^+$.

Reference Example 25a

2-(4-(carboxy)-phenyl)-2-methyl-propionamide. To a solution of 2-(4-(furan-2-yl)-phenyl)-2-methyl-propionamide (reference example 26) (124 mg, 0.5 mmol) in CH_3CN / CCl_4 / H_2O (7 mL, 2 / 2 / 3) is added $NaIO_4$ (420mg, 2 mmol) followed by $RuCl_3(H_2O)$ (3 mg). The resulting mixture is stirred vigorously for 1.5h, then diluted with ethyl acetate, washed with water and brine, dried over $MgSO_4$ and concentrated to

give 100mg of the title compound as an orange solid. ^{1}H NMR (CD_3OD) d 1.58 (s, 6H), 7.50 (d, J = 8Hz, 2H), 7.98 (d, J = 8Hz, 2H). MS (EI) m/z 208 (M+H).

Using essentially the same procedure except using the specified furan derivative, there is prepared

Reference Example 25b

N-(2-methoxy-ethyl)-2-(4-(carboxy)-phenyl)-2-methyl-propionamide. Using the product from reference example 27. ^{1}H NMR (CD_3OD) d 1.58 (s, 6H), 3.29 (s, 3H), 3.36 (m, 4H), 6.24 (bs, 1H), 7.45 (m, 2H), 8.05 (m, 2H). MS (EI) m/z 266 (M+).

Reference Example 25c

4-(2-[N-t-Butoxycarbonyl-amino]-1,1-dimethyl-ethyl)-Benzoic Acid. Using the product from reference example 29. ^{1}H NMR ($CDCl_3$) d 1.30 (s, 6H), 1.38 (s, 9H), 3.26 (bs, 1H), 3.33 (d, J = 6Hz, 2H), 7.44 (d, J = 8Hz, 2H), 8.05 (d, J = 8Hz, 2H).

Reference Example 25d

4-(3-tert-butoxycarbonylamino-1,1-dimethyl-propyl)-benzoic acid. Using the product from reference example 20. ^{1}H NMR (DMSO) δ 1.25 (s, 6H), 1.36 (s, 9H), 1.75 (m, 2H), 2.65 (m, 2H), 6.66 (bt, 1H), 7.47 (d, J = 8Hz, 2H), 7.88 (d, J = 8Hz, 2H), 12.79 (bs, 1H). MS (EI) m/z 308 $(M+H)^+$.

Reference Example 26

2-(4-(furan-2-yl)-phenyl)-2-methyl-propionamide. To a solution of 2-(4-(furan-2-yl)-phenyl)-2-methyl-propionic Acid (reference example 28) (115 mg, 0.5 mmol) in CH_2Cl_2 (3 mL) is added DMF (10 mL) followed by oxalyl chloride (0.3 mL, 2M in CH_2Cl_2). The resulting solution is stirred for 2.5 hours then concentrated. The residue is taken up in methanolic ammonia (7N) and stirred for 14.5 hours, then concentrated to give 124 mg of the title compound as a tan solid. ^{1}H NMR ($CDCl_3$) d 1.58 (s, 6H), 5.2 (bs, 1H), 5.3 (bs, 1H), 6.45 (dd, J = 3, 1Hz, 1H), 6.63 (m, 1H), 7.39 (m, 2H), 7.45 (bs, 1H), 7.65 (m, 2H). MS (EI), m/z 229 (M+).

Reference Example 27

N-(2-methoxy-ethyl)-2-(4-(furan-2-yl)-phenyl)-2-methyl-propionamide. To a solution of 2-(4-(furan-2-yl)-phenyl)-2-methyl-propionic Acid (reference example 28) (344mg, 1.5 mmol) in CH_2Cl_2 (4 mL) is added TBTU (528 mg, 1.65 mmol) followed by diisopropylethylamine (280 mL, 1.6mmol). The resulting mixture is stirred for 2h then a further portion of DIEA added (280 mL) along with 2-methoxy-ethylamine (225 mL, 2.6 mmol). The resulting solution is stirred for 90 minutes then concentrated. The residue is purified by flash chromatography (eluting with 10% CH_2Cl_2 / 50% ethyl acetate in hexanes) to give 380mg of product as a white solid. ^{1}H NMR (CD_3OD) d 1.58 (s, 6H), 3.24 (s, 3H), 3.36 (m, 4H), 5.58 (bs, 1H), 6.47 (dd, J = 3, 2Hz, 1H), 6.65 (d, J = 3Hz, 1H), 7.41 (m, 2H), 7.49 (d, J = 2Hz, 1H), 7.65 (m, 2H). MS (EI) m/z 287 (M+).

Reference Example 28

2-(4-(furan-2-yl)-phenyl)-2-methyl-propionic Acid. To a solution of 2-(4-(furan-2-yl)-phenyl)-2-methyl-propionic acid methyl ester (2.0g, 8.2 mmol) (reference example 30a) in MeOH / THF (20 mL, 1 / 1) is added NaOH (2 mL, 6M). The resulting solution is stirred for 1 hour then heated to 65 °C and stirred at this temperature for 2 hours. The reaction mixture is then cooled and acidified (to pH 1) with hydrochloric acid (2 M). The resulting mixture is diluted with ether, washed with water and brine, dried over $MgSO_4$ and concentrated to give 1.78g of the title compound as a solid. ^{1}H NMR ($CDCl_3$) d 1.61 (s, 6H), 6.45 (dd, J = 3, 2 Hz, 1H), 6.62 (d, J = 3 Hz, 1H), 7.42 (m, 2H), 7.45 (d, J = 2 Hz, 1H), 7.64 (m, 2H). MS (EI) m/z 230 (M+)

Reference Example 29.

2-[4-(2-[N-t-Butoxycarbonyl-amino]-1,1-dimethyl-ethyl)-phenyl]-furan. To a cooled (0 °C) solution of lithium aluminum hydride (152 mg, 4 mmol) in THF (6 mL) is added 2-(4-(furan-2-yl)-phenyl)-2-methyl-propionitrile (422mg, 2 mmol) (reference example 30b). On complete addition, the cold bath is removed and stirring continued for 3.5 hours. The resulting mixture is cooled to 0 oC then water (150 mL) NaOH (150 mL, 5M) and water (300 mL) added sequentially. The resulting slurry is diluted with ether then filtered through celite. The filtrate is concentrated then the residue dissolved in THF (5 mL). To this solution is added di-t-butlyl-dicarbonate (480 mg, 2.2mmol). The resulting solution is stirred for 1 hour. then concentrated. the residue is purified by flash chromatography (eluting with 10% ethyl acetate in hexanes) to give 524 mg of product as an oil. ^{1}H NMR ($CDCl_3$) d 1.31 (s, 6H), 1.39 (s, 9H), 3.31 (bd, J = 6Hz, 2H),

6.45 (dd, J = 2, 1Hz, 1H), 6.61 (d, J = 2Hz, 1H), 7.35 (d, J = 8Hz, 2H), 7.44 (d, J = 1Hz, 1H), 7.62 (d, J = 8Hz, 2H). MS (ion spray) m/z 316 $(M+H)^+$.

Reference Example 30a

2-(4-(furan-2-yl)-phenyl)-2-methyl-propionic acid methyl ester. To a cooled (0 °C) solution of furan (5.7 mL, 78 mmol) in TMEDA / THF (81.4 mL, 14 / 86) is added n-buLi (15 mL, 2.5 M in hexanes). The cold bath is removed and the resulting solution stirred for 45 minutes, then a solution of $ZnCl_2$ in THF added (40 mL, 0.5M). To this solution is added $(Ph_3P)_4Pd$ (1.0g, 0.86 mmol) and 2-(4-Bromo-phenyl)-2-methyl-propionic acid methyl ester (4.5g, 17.5 mmol) (reference example 31a). The resulting solution is warmed to 60 °C and stirred for 3 hours. The reaction mixture is then cooled, diluted with ether, washed with hydrochloric acid (2M), then brine, dried over $MgSO_4$ and concentrated. The residue is purified by flash chromatography (eluting with 5% ether in hexanes) to give 3.84g of the title compound as a solid. ^1H NMR ($CDCl_3$) d 1.60 (s, 6H), 3.67 (s, 3H), 6.45 (m, 1H), 6.63 (d, J = 3Hz, 1H), 7.35 (m, 2H), 7.46 (m, 1H), 7.65 (m, 2H). MS (EI) m/z 245 $(M+H)^+$.

Reference Example 30b

2,2-Dimethyl-(4-[Furan-2-yl]-Phenyl)-Acetonitrile. Using essentially the same procedure as in reference example 30a, except using 2-(4-Bromo-phenyl)-2-methyl-propionitrile (referenec example 31b). ^1H NMR ($CDCl_3$) d 1.74 (s, 6H), 6.47 (dd, J = 2, 1Hz, 1H), 6.66 (d, J = 2Hz, 1H), 7.47 (m, 3H), 7.68 (m, 2H),. MS (EI) m/z 211 $(M)^+$.

Reference Example 31a

2-(4-Bromo-phenyl)-2-methyl-propionic Acid Methyl ester. To a cooled (-20 °C) solution of 4-Bromo-phenyl-acetic acid methyl ester (9.1g, 40 mmol) (reference example 32) in THF (80 mL) is added methyl iodide (5.6 mL, 90 mmol) followed by a solution of KOt-Bu in THF (88 mL, 1M). The resulting mixture is stirred for 1 hour then diluted with ether, washed with water, then brine, dried over $MgSO_4$ and concentrated to give 9.8g of the title compound as an oil. ^1H NMR ($CDCl_3$) d 1.55 (s, 6H), 3.63 (s, 3H), 7.2 (m, 2H), 7.43 (m, 2H).

Reference Example 31b

2-(4-bromo-phenyl)-2-methyl-propionitrile. Using essentially the same procedure as in reference example 31a, except using (4-Bromo-phenyl)-acetonitrile. ^{1}H NMR ($CDCl_3$) d 1.70 (s, 6H), 7.34 (d, J = 8Hz, 2H), 7.50 (d, J = 8Hz, 2H). MS (EI) m/z 223, 225 Br pattern $(M)^+$

Reference Example 32

4-Bromo-phenyl-acetic acid methyl ester. To a solution of 4-Bromo-phenyl-acetic acid (8.6g, 40 mmol) in DMF (80 mL) is added K_2CO_3 (6.16g, 44 mmol) followed by methyl iodide (2.8 mL, 45 mmol). The resulting mixture is stirred for 2.5 hours, then diluted with ether, washed with water and brine, dried over $MgSO_4$ and concentrated to give 9.1g of the title compound as an oil. This material is used without further purification. ^{1}H NMR ($CDCl_3$) d 3.58 (s, 2H), 3.69 (s, 3H), 7.13 (d, J = 8Hz, 2H), 7.43 (d, J = 8Hz, 2H). MS (EI) m/z 228 / 230 (M+) Br pattern.

Reference Example 33a

2-Methyl-4- (2-methoxy-pyridin-5-yl)-benzoic Acid. To a solution of Methyl 2-methyl-4- (2-methoxypyridin-5-yl)-benzoate (600mg, 2.6 mmol) (reference example 34a) in THF / MeOH (8 mL, 1 / 1) is added NaOH (3 mL, 1M). The resulting mixture is stirred for 12 hours then acidified with hydrochloric acid (2M, to give pH 5). The mixture is diluted with ether then washed with brine, dried over $MgSO_4$ and concentrated. The residual solid is triturated with ether / hexane (1 / 20). The resulting product (500 mg) is used without further purification. ^{1}H NMR ($CDCl_3$) d 2.71 (s, 3H), 3.98 (s, 3H), 6.82 (d, J = 8Hz, 1H), 7.41 (m, 2H), 7.81 (dd, J = 8, 2Hz, 1H), 8.13 (d, J = 8 Hz, 1H), 8.43 (d, J = 2 Hz, 1H). MS (EI) m/z 243 (M+).

The following compounds are prepared using essentially the same procedure as described for reference example 33a except using the specified ester.

Reference Example 33b

4-(3,4-Dimethoxyphenyl)benzoic acid. Using Ethyl 4-(3,4-Dimethoxyphenyl)benzoate (reference example 34b).

Reference Example 33c

4-(6-methoxy-pyridin-3-yl)-benzoic acid. Using 4-(6-methoxy-pyridin-3-yl)-benzoic acid ethyl ester (reference example 34c). ^{1}H NMR (DMSO) δ 3.92 (s, 3H), 6.95 (d, J = 9Hz, 1H), 7.80 (d, J = 8Hz, 2H), 8.02 (d, J = 8Hz, 2H), 8.10 (dd, J = 9, 2Hz, 1H), 8.58 (d, J = 2Hz, 1H)MS (EI) m/z 229 (M+).

Reference Example 33d

3-chloro-4-(6-methoxy-pyridin-3-yl)-benzoic acid. Using 3-chloro-4-(6-methoxy-pyridin-3-yl)-benzoic acid methyl ester (reference example 38). ^{1}H NMR (DMSO) δ 3.92 (s,3H), 6.96 (d, J = 9 Hz, 1H), 7.60 (d, J = 8Hz, 1H), 7.88 (dd, J = 9, 2Hz, 1H), 7.96 (d, J = 8Hz, 1H), 8.04 (s, 1H), 8.29 (d, J = 2Hz, 1H). MS (EI) m/z 263/265 (M+, Cl).

Reference Example 33e

4-(2-[t-butyloxycarbonylamino-methyl]-pyridin-4-yl)-benzoic acid. Using the product from reference example 56 ^{1}H NMR (DMSO) δ 1.39 (s, 9H), 4.31 (d, J = 6Hz, 2H), 7.47 (bt, J = 6Hz, 1H), 7.65 (m, 2H), 7.86 (d, J = 8Hz, 2H), 8.07 (d, J = 8Hz, 2H), 8.60 (d, J = 5Hz, 1H). MS (ion spray) m/z 329 (M+H).

Reference Example 33f

4-(2-Carbamoyl-pyridin-4-yl)-benzoic acid. Using the product from reference example 58. ^{1}H NMR (DMSO) δ 7.74 (bs, 1H), 7.97 (m, 3H), 8.05 (d, J = 8Hz, 2H), 8.20 (bs, 1H), 8.34 (bs, 1H), 8.73 (d, J = 5Hz, 1H). MS (EI) m/z 242 M+.

Reference Example 33g

4-(2-[N,N-dimethylamino-methyl]-pyridin-4-yl)-benzoic acid. Using the product from reference example 59 and purifying by reverse phase HPLC (0.1% TFA / acetonitrile / water gradient) ^{1}H NMR (DMSO) δ 2.81 (s, 6H), 4.51 (s, 2H), 7.85 (d, J = 5Hz, 1H), 7.93 (s, 1H), 7.94 (d, J = 8Hz, 2H), 8.08 (d, J = 8Hz, 2H), 8.75 (d, J = 5Hz, 1H). MS (ion spray) m/z 257 (M+H).

Reference Example 34a

Methyl 2-methyl-4- (2-methoxy-pyridin-5-yl)-benzoate. To a cooled (-78°C) solution of 2-methoxy-5-bromo-pyridine (1.88g, 10 mmol) in THF (25 mL) is added, dropwise, n-BuLi (4.4 mL, 2.5M in hexanes). On complete addition, the resulting solution is stirred for 10 minutes then $ZnCl_2$ added (21 mL, 0.5M in THF). The cold bath is removed and stirring continued for 15 minutes. To this solution is added a solution comprised of 4-bromo-2-methyl-benzoic acid methyl ester (2.25g, 9.8 mmol) and $(Ph_3P)_4Pd$ (0.56g, 0.48 mmol) in THF (5 mL). The resulting solution is warmed to 60 °C and stirred at this temperature for 2h. The reaction mixture is allowed to cool, then diluted with ethyl acetate, washed with ammonium chloride solution (sat.) and brine, dried over $MgSO_4$ and concentrated. The residue is purified by flash chromatography (eluting with 10% ethyl acetate in hexanes) to give 626 mg of the title compoundas an oil. ^1H NMR ($CDCl_3$) d 2.68 (s, 3H), 3.93 (s, 3H), 3.98 (s, 3H), 6.82 (d, J = 9Hz, 1H), 7.39 (m, 2H), 7.81 (d, J = 9Hz, 1H), 8.00 (d, J = 9 Hz, 1H), 8.40 (d, J = 2 Hz, 1H). MS (EI) m/z 257 (M+).

Using essentially the same procedure as in reference example 34a, except using commercially available 4-bromobenzoic acid ethyl ester and 3,4-dimethoxy-phenyl bromide (in place of 5-bromo-2-methoxy-pyridine) there is prepared:

Reference Example 34b

Ethyl 4-(3,4-Dimethoxyphenyl)benzoate.
^1H NMR($CDCl_3$) δ 1.43 (3H, m), 3.92 (3H, m), 3.98 (3H, m), 6.95 (1H, m), 7.23 (1H, s), 7.20 (1H, m), 7.61 (2H, m), 8.12 (2H, m).

Using essentially the same procedure as in reference example 34a, except using 4-bromobenzoic acid ethyl ester there is prepared:

Reference Example 34c

Ethyl 4-(6-methoxypyrid-3-yl)benzoate. ^1H NMR($CDCl_3$) δ 1.41 (3H, t, J= 7.24 Hz), 3.99 (3H, s), 4.40 (2H, q, J= 7.24 Hz), 8.63 (1H, d, J= 8.63 Hz), 7.60 (2H, d, J= 8.36 Hz), 7.83 (1H, dd, J_1= 8.63 Hz, J_2= 2.58 Hz), 8.12 (2H, d, J= 8.36 Hz), 8.43 (1H, d, J= 2.58 Hz). MS(EI) m/z 257 M^+.

Reference Example 35a

4-(1,2,4)Thiadiazol-5-ylbenzoic acid.

A mixture of 0.500 g (2.17 mmol) 5-(p-trifluoromethylphenyl)-(1,2,4)thiadiazole in 5 mL concentrated sulfuric acid (Fisher) is heated to 150° C for five hours and poured into ice water. A yellow precipitate is collected by filtration, washed with water, and dried to give 0.439 g of the product, as the sulfuric acid salt, as a white solid in 79.3% yield. Used without further purification. MS (EI) m/z 206 M^+.

Reference example 35b

Using essentially the same procedure except starting with 4-(3H-imidazol-4-yl)trifluoromethylbenzene (reference example 37) there is prepared:

4-(3H-imidazol-4-yl)-lbenzenoic acid. Used further purification. MS(EI) m/z 188 (M^+).

Reference Example 36a

N-[2-(3-Cyano-1H-indol-5-yl)-ethyl]-2-methyl-4-(6-oxo-1,6-dihydro-pyridin-5-yl)-benzamide. A mixture of N-[2-(3-Cyano-1H-indol-5-yl)-ethyl]-4-(2-methoxy-pyridin-5-yl)-2-methyl-benzamide (146 mg, 0.35 mmol) (reference example 1n) and pyridinium hydrochloride (3g) is heated to 160 °C and stirred at this temperature for 3 minutes. The liquid is then cooled and mixed with water. The resulting precipitated solid is filtered, washed with water (3x) then dried under vacuum to give 133mg of th title compound as a solid. This material is used without further purification. MS (ion spray) m/z 397 (M+H).

Using esssentially the same procedure except using the specified methoxy-pyridine derivative, there is prepared:

Reference Example 36b

N-[2-(3-Cyano-1H-indol-5-yl)-ethyl]-4-(6-oxo-1,6-dihydro-pyridin-5-yl)-benzamide. Using the product from reference example 1p. MS (ion spray) m/z 383 (M+H).

Reference Example 36c

N-[2-(3-cyano-1H-indol-5-yl)-ethyl]-3-chloro-4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzamide. Using the product from reference example 1u. ^{1}H NMR (DMSO) δ 2.97 (bt, 2H), 3.53 (m, 2H), 6.42 (d, J = 9Hz, 1H), 7.17 (d, J = 9Hz, 1H), 7.54 (m, 4H), 7.82 (d, J = 8Hz, 1H), 7.95 (m, 2H), 8.20 (m, 1H), 8.73 (bt, 1H), 8.88 (m, 1H), 12.15 (bs, 1H). MS (ion spray) m/z 417/419 $(M+H)^+$, Cl.

Reference Example 36d

N-[2-(3-cyano-1H-indol-5-yl)-ethyl]-4-(6-oxo-1,6-dihydro-pyridazin-3-yl)-benzamide. Using the product from reference example 1ak. ^{1}H NMR (DMSO) δ 2.98 (t, J = 7Hz, 2H), 3.55 (m, 2H), 7.02 (d, J = 10Hz, 1H), 7.18 (d, J = 7Hz, 1H), 7.48 (m, 2H), 7.94 (m, 4H), 8.10 (d, J = 10Hz, 1H), 8.20 (d, J = 3Hz, 1H), 8.66 (bt, 1H), 12.11 (s, 1H), 13.29 (s, 1H). MS (ion spray) m/z 384 $(M+H)^+$.

Reference Example 36e

4-(6-oxo-1,6-dihydro-pyridazin-3-yl)-benzoic acid methyl ester. Using the product from reference example 63. ^{1}H NMR (DMSO) δ 3.88 (s, 3H), 7.04 (d, J = 10Hz, 1H), 8.02 (d, J = 8Hz, 2H), 8.06 (d, J = 8Hz, 2H), 8.12 (d, J = 10Hz, 1H), 13.37 (bs, 1H). MS (EI) m/z 230 (M^+).

Reference Example 36f

Ethyl 4-(6-oxo-1,6-dihydropyridin-3-yl)benzoate. Using the product from reference example 34c ^{1}H NMR (5:1 $CDCl_3$:CD_3OD): δ 1.41 (3H, t, J= 7 Hz), 4.40 (2H, q, J = 7 Hz), 6.70 (1H, d, J = 10 Hz), 7.52 (2H, d, J = 8 Hz), 7.63 (1H, d, J = 3 Hz), 7.83 (1H, dd, J = 3 Hz, 10 Hz), 8.09 (2H, d, J = 8 Hz).

Reference Example 37

4-(3H-imidazol-4-yl)-trifluoromethylbenzene. To a solution of 5 g (24 mmol) 4-(trifluoromethyl)benzoyl chloride in 100 mL THF cooled to 0 C is added dropwise 72 mmol diazomethane in 200 mL ethyl ether. After 18 hours at 0 °C, excess diazomethane is destroyed with acetic acid, and the solution is concentrated.

To the resulting residue is added 100 mL THF and 40 mL 1M HCl in ethyl ether. After one hour the reaction is concentrated and then warmed in 25 mL MeOH, and this warm solution is added dropwise to a solution of 8.6 g (47 mmol) copper(II) acetate (Aldrich) in 5 mL 37% aqueous formaldehyde and 100 mL 28% ammonium hydroxide. The reaction is heated to 100 C for 30 minutes and allowed to cool overnight. The resulting solution is decanted away from a brown precipitate, and the precipitate is washed with water and taken up in 150 mL 1:1 EtOH: water. Hydrogen sulfide is bubbled through this solution to give a tan solid; the solution is stirred for two hours and concentrated. The residue is suspended in ethanol/water solution, filtered through Celite, and purified on HPLC to give 2.1 g of the product in 43% yield. MS(EI) m/z 212 (M^+).

Reference Example 38

3-chloro-4-(6-methoxy-pyridin-3-yl)-benzoic acid methyl ester. To a cooled solution (-78°C) of 2-methoxy-5-bromopyridine (1.13g, 6mmol, reference example 41a) inTHF (12mL) is added over 10min (2.5M)n-butyllithium (2.4mL, 6mmol) and the resulting solution stirred for 15min. To this solution is added dropwise (0.5M)zinc chloride (12mL, 6mmol) and the temperature of this arylzinc bromide allowed to warm to 0°C with stirring. To a cooled solution (0°C), in a separate flask, of palladium bis(dibenzylideneacetone) (288mg, 0.5mmol) and 1,1'-bis(diphenylphosphino)ferrocene (276mg, 0.5mmol) in THF (2mL) is added a solution of 3-chloro-4-trifluoromethanesulfonyloxy-benzoic acid methyl ester (1.59g, 5mmol) (reference example 39) in THF (2mL) followed by the arylzinc bromide solution. The resulting solution is heated to 65°C and stirred for 2.5 hours then cooled to 20°C, diluted with ether, washed with sat NH_4Cl soln and brine, dried over $MgSO_4$ and concentrated. The residue is purified by flash chromatography (eluting with 25% ether in hexanes) to give 428mg of title compound as a yellow crystalline solid. ^1H NMR($CDCl_3$) δ 3.95 (s, 3H), 4.00 (s, 3H), 6.84 (d, J = 9Hz, 1H), 7.40 (d, J = 8Hz, 1H), 7.72 (dd, J = 9, 2Hz, 1H), 7.98 (dd, J = 8, 2Hz, 1H), 8.15 (s, 1H), 8.25 (d, J = 2Hz, 1H). MS (EI) m/z 277 (M+).

Reference Example 39

3-chloro-4-trifluoromethanesulfonyloxy-benzoic acid methyl ester. To a cooled mixture (-5°C) of (60%)sodium hydride (1.1g, 27.5mmol) in THF (60mL) is added dropwise a solution of 3-chloro-4-hydroxy-benzoic acid methyl ester (4.66g, 25mmol) (reference example 40) in THF (10mL) and stirred mixture at 0°C for 30min. To this mixture is added a solution of N-phenyltrifluoromethanesulfonimide (13.4g, 37.5mmol) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (20mL) in THF (10mL). The resulting mixture is

allowed to warm to 20°C and stirred for 1 hour, diluted with ether, washed with water and brine, dried over $MgSO_4$ and concentrated. The residue is purified by flash chromatography (eluting with 10% ether in hexanes) to give 6.86g of title compound as a colorless oil. ^1H NMR ($CDCl_3$) δ 3.96 (s, 3H), 7.44 (d, J = 9Hz, 1H), 8.02 (dd, J = 9, 2Hz, 1H), 8.21 (d, J = 2Hz, 1H). MS (EI) m/z 318/320 (M+, Cl).

Reference Example 40

3-chloro-4-hydroxy-benzoic acid methyl ester. To a solution of 3-chloro-4-hydroxy-benzoic acid hemihydrate (9.08g, 50mmol) in methanol (150mL) is added slowly (conc)sulfuric acid (22.5mL). The resulting solution is heated to 55°C and stirred 2 hours then cooled to 20°C. Poured solution into ice and extracted with ether. The organic is washed with brine, dried over $MgSO_4$ and concentrated. The residue is purified by flash chromatography (eluting with 30% ethyl acetate in hexanes) to give 9.5g of title compound as a white crystalline solid. ^1H NMR ($CDCl_3$) δ 3.90 (s, 3H), 7.06 (d, J = 9Hz, 1H), 7.88 (dd, J = 9, 2Hz, 1H), 8.05 (d, J = 2Hz, 1H). MS (EI) m/z 186/188 (M+, Cl).

Reference Example 41a

2-methoxy-5-bromopyridine. To a solution of 2,5-dibromopyridine (20g, 84mmol) in DMSO (84mL) is added (25wt%) sodium methoxide (21.2mL, 93mmol). The resulting solution is heated to 80°C and stirred for 45min then cooled to 20°C, diluted with ether, washed with water and brine, dried over $MgSO_4$ and concentrated. The residue is purified by flash chromatography (eluting with 10% ether in hexanes) to give 14.6g of title compound as a colorless oil. ^1H NMR ($CDCl_3$) δ 3.90 (s, 3H), 6.66 (d, J = 9Hz, 1H), 7.63 (dd, J = 9, 3Hz, 1H), 8.20 (d, J = 3Hz, 1H). MS (EI) m/z 187/189 (M+, Br).

Reference Example 41b

Using essentially the same procedure used to prepare reference example 41a except using the product from reference example 60, there is prepared 3-bromo-6-methoxypyridazine. ^1H NMR ($CDCl_3$) δ 4.11 (s, 3H), 6.87 (d, J = 9Hz, 1H), 7.48 (d, J = 9Hz, 1H). MS (ion spray) m/z 189/191 $(M+H)^+$, Br.

Reference Example 42a

4-(7H-pyrrolo[2,3-d]pyrimidin-6-yl)-benzoic acid. To a solution of 4-(7H-pyrrolo[2,3-d]pyrimidin-6-yl)-benzoic acid methyl ester (0.601 g, 2.4 mmol) (reference example 43a) in 1:1 THF-methanol (10 mL) is added NaOH (10N) (2.4 mL, 24 mmol) and 0.5 ml H_2O. The resulting solution is stirred for 1 hour then cooled to 0°-5°C and adjusted to pH 3 with 2N HCl. The precipitated solid is filtered off, washed with a small volume of water and dried under high vacuum to give 0.355g of title compound as a yellow solid. ^1H NMR (DMSO) δ 7.59 (s, 1H), 8.10 (d, J = 8Hz, 2H), 8.20 (d, J = 8Hz, 2H), 9.22 (s, 1H), 9.50 (bs, 1H), 14.10 (bs, 1H). MS (EI) m/z 239 (M+).

Using essentially the same procedure as in reference example 42a except using the specified ester there is prepared.

Reference Example 42b

4-(1H-pyrrolo[3,2-c]pyridin-2-yl)-benzoic acid. Using the product from reference example 43b, ^1H NMR (DMSO) δ 7.63 (s, 1H), 7.99 (d, J = 6Hz, 1H), 8.16 (m, 4H), 8.46 (d, J = 6Hz,1H), 9.34 (s, 1H), 13.67 (bs, 1H). MS (EI) m/z 238 (M+).

Reference Example 42c

4-furo[3,2-c]pyridin-2-yl-benzoic acid. Using the product from reference example 43c, ^1H NMR (DMSO) δ 7.89 (s, 1H), 8.05 (d, J = 7Hz, 1H), 8.12 (m, 4H), 8.68 (bd, 1H), 9.24 (bs, 1H), 13.20 (bs, 1H). MS (EI) m/z 239 (M+).

Reference Example 43a

4-(7H-pyrrolo[2,3-d]pyrimidin-6-yl)-benzoic acid methyl ester. To a solution of (5-iodo-pyrimidin-4-yl)carbamic acid tert-butyl ester (1.46g, 4.55mmol) (reference example 44a) in DMF (15 mL) is added 4-ethynyl-benzoic acid methyl ester (0.721g, 4.5 mmol)(reference example 46), copper iodide 99.999% (21mg, 0.112mmol), bis(triphenylphosphine)palladium(II)chloride (158mg, 0.225mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.5mL, 10mmol). The resulting solution is heated to 100°C and stirred for 1 hour then cooled to 20°C. The solution is diluted with ethyl acetate, washed with water and brine, dried over $MgSO_4$ and concentrated. The residue is purified by flash chromatography (eluting with 50% ethyl acetate, 5% methanol

in hexanes) to give 601mg of title compound as a yellow crystalline solid. ^{1}H NMR (DMSO) δ 3.89 (s, 3H), 7.24 (s, 1H), 8.06 (d, J = 8Hz, 2H), 8.14 (d, J = 8Hz, 2H), 8.81 (bs, 1H), 9.05 (bs, 1H), 12.79 (bs, 1H). MS (ion spray) m/z 254 $(M+H)^+$.

Using essentially the same procedure as in reference example 43a except using the specified aryl iodide there is prepared.

Reference Example 43b

4-(1H-pyrrolo[3,2-c]pyridin-2-yl)-benzoic acid methyl ester. Using the product from reference example 49. ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 9H), 3.96 (s, 3H), 6.69 (s, 1H), 7.51 (d, J = 8Hz, 2H), 8.08 (d, J = 8Hz, 1H), 8.11 (d, J = 7Hz, 2H), 8.51 (d, J = 6Hz, 1H), 8.90 (s, 1H). MS (EI) m/z 352 (M+).

Reference Example 43c

4-furo[3,2-c]pyridin-2-yl-benzoic acid methyl ester. Using the product from reference example 50. ^{1}H NMR ($CDCl_3$) δ 3.96 (s, 3H), 7.20 (s, 1H), 7.49 (d, J = 5Hz, 1H), 7.94 (d, J = 8Hz, 2H), 8.14 (d, J = 8Hz, 2H), 8.53 (d, J = 5Hz, 1H), 8.97 (s, 1H). MS (EI) m/z 253 (M+).

Reference Example 44a

(5-iodo-pyrimidin-4-yl)carbamic acid tert-butyl ester. To a mixture of 5-iodo-pyrimidin-4-ylamine (3.52g, 15.9mmol) (reference example 45) in THF (100mL) is added pyridine (1.4mL, 17.5mmol) and di-tert-butyl dicarbonate (3.82g, 17.5mmol). The resulting mixture is heated to 50°-55°C and stirred for 2.5 hours then cooled to room temp and concentrated. The residue is purified by flash chromatography (eluting with 20% ethyl acetate, 5% methanol in hexanes) to give 1.46g of title compound as a pale yellow solid. ^{1}H NMR (DMSO) δ 1.48 (s, 9H), 8.87 (s, 1H), 9.01 (s, 1H), 9.60 (bs, 1H). MS (EI) m/z 321 (M+).

Reference Example 44b

using essentially the same procedure as in reference example 44a except using 4-amino-pyridine there is prepared pyridin-4-yl-carbamic acid tert-butyl ester. ^{1}H NMR ($CDCl_3$) δ 1.52 (s, 9H), 6.82 (bs, 1H), 7.30 (d, J = 7Hz, 2H), 8.43 (d, J = 7Hz, 2H).

Reference Example 45

5-iodo-pyrimidin-4-yl amine. (Based on Brown, D.J.; J.S.C.I., 69, December, 1950, pp.353-356) To a solution of 4-aminopyrimidine (2.8g, 29.4mmol) in acetic acid (30mL) is added ICl (3.03mL, 60.4mmol). The solution is heated to 100°C and stirred for 3 hours then poured into H_2O (140mL). The mixture is decolorized with sodium bisulfite then cooled to 0°-5°C and the pH adjusted to 6-7 with NaOH(s). The precipitated product is filtered off, washed with a small volume of H_2O then dried under high vacuum to give 3.52g of title compound as a white solid. ^1H NMR (DMSO) δ 7.09 (bs, 2H), 8.30 (s, 1H), 8.45 (s, 1H). MS (EI) m/z 221 $(M+H)^+$.

Reference Example 46

4-ethynyl-benzoic acid methyl ester. To a solution of 4-trimethylsilanylethynyl-benzoic acid methyl ester (4.65g, 20mmol) (reference example 47) in THF (40mL) is added (1M) tetrabutylammonium fluoride (30mL, 30mmol) and acetic acid (1.9mL, 33mmol). The resulting solution is stirred for 25min, diluted with ethyl acetate, washed with water and brine, dried over $MgSO_4$ and concentrated. The residue is purified by flash chromatography (eluting with 10% ether, 10% dichloromethane in hexanes) to give 2.56g of title compound as a pale yellow solid. ^1H NMR ($CDCl_3$) δ 3.23 (s, 1H), 3.92 (s, 3H), 7.55 (d, J = 8Hz, 2H), 8.00 (d, J = 8Hz, 2H). MS (EI) m/z 160 (M+).

Reference Example 47

4-trimethylsilanylethynyl-benzoic acid methyl ester. To a cooled solution (-78°C) of (trimethylsilyl)acetylene (4.2mL, 30mmol) in THF (25mL) is added dropwise (2.5M) n-butyllithium (11.6mL, 29mmol) and stirred for 30min followed by slow addition of (0.5M) zinc chloride (58mL, 29mmol). The resulting solution is allowed to warm to 20°C followed by addition of 4-iodo-benzoic acid methyl ester (5.24g, 20mmol) (reference example 48) and tetrakis(triphenylphosphine)palladium(0) (1.16g, 1mmol) in THF (10mL). The resulting mixture is heated to 55°C and stirred for 2 hours then cooled to 20°C. The reaction mixture is diluted with ethyl acetate, washed with sat.NH_4Cl soln, water and brine, dried over $MgSO_4$ and concentrated to give 4.65g of title compound. ^1H NMR ($CDCl_3$) δ 0.26 (s, 2H), 3.91 (s, 3H), 7.52 (d, J = 8Hz, 2H), 7.97 (d, J = 8Hz, 2H). MS (EI) m/z 232 (M+).

Reference Example 48

4-iodo-benzoic acid methyl ester. To a solution of 4-iodobenzoic acid (9.92g, 40mmol) in DMF (80mL) is added potassium carbonate (5.8g, 42mmol) and iodomethane (2.6mL, 42mmol). The resulting mixture is stirred for 17 hours, diluted with ethyl acetate, washed with water and brine, dried over $MgSO_4$ and concentrated. The crude solid is recrystallized in ethyl acetate/hexane to give 8.74g of title compound. ^1H NMR ($CDCl_3$) δ 3.91 (s, 3H), 7.74 (d, J = 8Hz, 2H), 7.80 (d, J = 8Hz, 2H). MS (EI) m/z 262 (M+).

Reference Example 49

(3-iodo-pyridin-4-yl)-carbamic acid tert-butyl ester. To a solution of pyridin-4-yl-carbamic acid tert-butyl ester (14.8g, 76.3mmol) (reference example 44b) in THF (300mL) is added N,N,N',N'-tetramethylethylene-diamine (34.5mL, 230mmol) and the solution cooled to -78°C. To this solution is added slowly (2.5M) n-butyllithium (91.5mL, 230mmol), the reaction temperature allowed to rise to -20°C and the resulting mixture stirred for 1.5 hours. The mixture is cooled to -78°C and a solution of iodine (29.04g, 114mmol) in THF (60mL) is added then stirred for 10min. The mixture is warmed to 20°C, stirred 30min then diluted with ethyl acetate, washed with water, sat. sodium thiosulfate and brine, dried over $MgSO_4$ and concentrated. The residue is purified by flash chromatography (eluting with 20% ethyl acetate in hexanes) to give 17.7g of title compound as a light yellow crystalline solid. ^1H NMR ($CDCl_3$) δ 1.54 (s, 9H), 7.03 (bs, 1H), 8.10 (d, J = 6Hz, 1H), 8.34 (d, J = 6Hz, 1H), 8.74 (s,1H). MS (EI) m/z 320 (M+).

Reference Example 50

3-iodo-pyridin-4-ol. To a solution of 4-hydroxypyridine (12g, 126mmol) in H_2O (30mL) is added sodium carbonate (11.32g, 107mmol) and the resulting mixture heated to reflux (100°C) followed by the dropwise addition of a solution of potassium iodide (19.8g, 119mmol) and iodine (18g, 71mmol) in H_2O (50mL). The resulting hot solution is adjusted to pH 6 using 2N HCl soln. and filtered hot through a cintered glass funnel. The filtrate is cooled and the precipitated product collected by filtration. The filtrate is heated to reflux and the above procedure repeated. The crude product is heated to reflux in 0.3M HCl soln. and filtered through a cintered glass funnel. The filtrate is kept near reflux while adjusting pH to 6 with 1N NaOH soln. then cooled to 5°C, the precipitate collected and dried under high vacuum giving 8g of title compound as a yellow

solid. ^{1}H NMR (DMSO) δ 6.16 (d, J = 7Hz, 1H), 7.70 (d, J = 7Hz, 1H), 8.27 (s, 1H), 11.70 (bs, 1H). MS (EI) m/z 221 (M+.).

Reference Example 51

2-[4-(1,1-dimethyl-allyl)-phenyl]-furan. To a cooled slurry (0°C) of methyltriphenylphosphonium bromide (18.8g, 52.6mmol) in THF (60mL) is added dropwise (1M)sodium bis(trimethylsilyl)amide (52.6mL, 52.6mmol) and the resulting mixture stirred for 30min. To the mixture is added a solution of 2-(4-furan-2-yl-phenyl)-2-methyl-propionaldehyde (5.64g, 26.3mmol) (reference example 52) in THF (25mL) and the resulting mixture stirred for 45min. The mixture is diluted with ether, washed with water and brine, dried over $MgSO_4$ and concentrated. The residue is purified by flash chromatography (eluting with 10% ethyl acetate in hexanes) to give 6.2g of title compound as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 6H), 5.03 (s, 1H), 5.08 (d, J = 7Hz, 1H), 6.03 (m, 1H), 6.45 (m, 1H), 6.60 (d, J = 3Hz, 1H), 7.36 (d, J = 8Hz, 2H), 7.44 (s, 1H), 7.60 (d, J = 8Hz, 2H). MS (EI) m/z 212 (M+).

Reference Example 52

2-(4-furan-2-yl-phenyl)-2-methyl-propionaldehyde. To a solution of 2-(4-furan-2-yl-phenyl)-2-methyl-propan-1-ol (6.56g, 30mmol) (reference example 53) in CH_2Cl_2 (200mL) is added Dess-Martin-periodinane (22.5g, 53mmol) and the resulting mixture stirred for 45min then concentrated. The residue is purified by flash chromatography (eluting with 10% ethyl acetate in hexanes) to give 5.64g of title compound. ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 6H), 6.47 (m, 1H), 6.66 (d, J = 3Hz, 1H), 7.30 (d, J = 8Hz, 2H), 7.46 (s, 1H), 7.68 (d, J = 8Hz, 2H), 9.50 (s, 1H). MS (EI) m/z 214 (M+).

Reference Example 53

2-(4-furan-2-yl-phenyl)-2-methyl-propan-1-ol. To a cooled solution (0°C) of (1M)lithium aluminum hydride (13.3mL, 13.3mmol) in THF (27mL) is added a solution of 2-(4-furan-2-yl-phenyl)-2-propionic acid methyl ester (3.1g, 12.7mmol) (reference example 30a) in THF (11mL). The resulting solution is stirred for 15min then added slowly H_2O (0.5mL), 15%NaOH (0.5mL) and H_2O (1.5mL). The resulting slurry is diluted with ether, filtered through a pad of celite and the filtrate concentrated to give 2.7g of title compound as a white

crystalline solid. ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 6H), 3.62 (m, 3H), 6.46 (m, 1H), 6.62 (d, J = 3Hz, 1H), 7.40 (d, J = 8Hz, 2H), 7.46 (bs, 1H), 7.64 (d, J = 8Hz, 2H). MS (EI) m/z 216 (M+).

Reference Example 54

A suspension of TFP resin (United States Patent Application Serial No. 60/090,558) (1g, 0.83 mmol/g) and 4-t-butyl-benzoic acid (295 mg, 1.66 mmol in DMF(10 mL) is shaken for 10 minutes. then DMAP (20 mg, 0.16 mmol) in DMF (1mL) added. To this mixture is added 1,3-diisopropylcarbodiimide (200 mL, 1.6 mmol). The resulting suspension is shaken for 2.5 hours then filtered and the solid washed, sequentially, with approximately 10 mL of each of CH_2Cl_2, DMF, THF, CH_2Cl_2. The resulting acylated resin is dried under vacuum and used without further processing.

A wide range of carboxylic acids can be activated using essentially the same procedure. A representative list of such carboxylic acids includes:

4-(4-carbamoyl-phenyl)-benzoic acid
4-(4-methoxy-phenyl)-benzoic acid
5-methoxy-indol-2-yl-carboxylic acid
6-chloro-benzothiophen-2-yl carboxylic acid
4-(4-benzyloxy-phenyl)-benzoic acid
4-chloro-benzoic acid
4-(methylsulphonyl)-benzoic acid
4-(aminosulphonyl)-benzoic acid

Reference Example 55

N-(2-[3-Cyano-1-methylindol-5-yl]ethyl)-4-(6-methoxypyrid-3-yl)benzamide. A solution of 0.250 g (0.631 mmol) N-(2-[3-Cyano-indol-5-yl]ethyl)-4-(6-methoxypyrid-3-yl)benzamide (reference example 1p) in 5 mL DMF is added to a cooled (0°C) solution of 0.0328 g (0.820 mmol) sodium hydride (60% dispersion in mineral oil) in 2 mL DMF. After ten minutes 0.043 mL (0.69 mmol) iodomethane is added, and the cooling bath removed. After 3 hours, the reaction is quenched with water, concentrated, and the resulting residue flash chromatographed (2:2:1 CH_2Cl_2: EtOAc: hexanes) to provide 0.167 g of the product as a white solid in 65% yield. ^{1}H NMR ($CDCl_3$) δ 3.09 (2H, t, J = 7 Hz), 3.80 (2H, m), 3.86 (3H, s), 3.99 (3H, s), 6.17 (1H, m,

br), 6.83 (1H, d, J = 8 Hz), 7.29 (1H, s), 7.37 (1H, d, J = 8 Hz), 7.55-7.58 (3H, m), 7.64 (1H, s), 7.76-7.82 (3H, m), 8.40 (1H, d, J = 2 Hz). MS (ion spray) m/z 411 $(M+H)^+$.

Reference Example 56

Methyl 4-(2-[t-butyloxycarbonylamino-methyl]-pyridin-4-yl)-benzoate. To a solution of methyl 4-(2-cyano-pyridin-4-yl)-benzoate (1.15g, 4.8 mmol) (reference example 57) in THF (20 mL) is added palladium on carbon (200 mg, 10% Pd by wt) followed by di-t-butyl-dicarbonate (1.12g, 5.1mmol). The resulting mixture is stirred under an atmosphere of hydrogen for 16 hours. Then purged with nitrogen, diluted with ethyl acetate and filtered through celite. The filtrate is concentrated under reduced pressure and the residue purified by flash chrmatography (eluting with 50% ethyl acetate in hexanes to give 534 mg of the title compund as an oil (32%). ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 9H), 3.96 (s, 3H), 4.51 (d, J = 6Hz, 2H), 7.41 (dd, J = 5, 1.4Hz, 1H), 7.50 (bs, 1H), 7.71 (d, J = 8Hz, 2H), 8.16 (d, J = 8Hz, 2H), 8.61 (d, J = 5Hz, 1H). MS (ion spray) m/z 343 (M+H).

Reference Example 57

Methyl 4-(2-cyano-pyridin-4-yl)-benzoate. To a solution of methyl 4-(pyridin-N-oxide-4-yl)-benzoate (1.15g, 5 mmol) (reference example 18) in CH_2Cl_2 (10 mL) is added TMSCN (736 mL, 5.5 mmol) followed by N,N-diethyl carbamoyl chloride (742 mL, 5.8 mmol). The resulting solution is stirred for 116 hours then aqueous K_2CO_3 added (10 mL, 10%). The mixture is diluted with ethyl acetate, washed with brine, dried over $MgSO_4$ and concentrated to give 1.15g of the title compound as a tan solid . This material is used without further purification. ^{1}H NMR ($CDCl_3$) δ 3.86 (s, 3H), 8.05 (m, 2H), 8.08 (m, 2H), 8.12 (dd, J = 5, 2Hz, 1H), 8.49 (bs, 1H), 8.82 (d, J = 5Hz, 1H). MS (EI) m/z 238 M+.

Reference Example 58

Methyl 4-(2-carbamoyl-pyridin-4-yl)-benzoate. A solution of methyl 4-(2-cyano-pyridin-4-yl)-benzoate (400 mg, 1.68 mmol) (reference example 57) in 80% sulphuric acid (3 mL) is stirred at room temperature for 12 hours. The resulting solution is poured onto ice and the mixture brought to pH 8 with sat. sodium bicarbonate solution then extracted with ethyl acetate, washed with brine, dried over MgSO4 and concentrated. The residue is purified by flash chromatography (eluting with 40% ethyl acetate in

chloroform) to give 340 mg of the title compound. ^{1}H NMR ($CDCl_3$) δ 3.94 (s, 3H), 5.72 (bs, 1H), 7.67 (dd, J = 5, 1Hz, 1H), 7.75 (d, J = 8Hz, 2H), 7.9 (bs, 1H), 8.15 (d, J = 8Hz, 2H), 8.46 (bs, 1H), 8.63 (d, J = 5Hz, 1H). MS (EI) m/z 256.

Reference Example 59

Methyl 4-(2-[N,N-dimethylamino-methyl]-pyridin-4-yl)-benzoate. To a solution of Methyl 4-(2-[t-butyloxycarbonylamino-methyl]-pyridin-4-yl)-benzoate (reference example 56) (520 mg, 1.5 mmol) in CH_2Cl_2 (5 mL) is added TFA (1.5 mL) and 2 drops of water (approx. 100 mL). The resulting solution is stirred for 90 minutes. then concentrated under reduced pressure. The residue is dissolved in THF (4 mL) then $NaBH_4$ added (222 mg, 6 mmol) followed by paraformaldehyde (360 mg, 12 mmol). To this mixture is added TFA (4 mL) dropwise. The resulting mixture is stirred for 6 hours then concentrated. The residue is brought to pH 8 with aqueous NaOH (1M) and sat $NaHCO_3$. The mixture is then extracted with ethyl acetate then ethyl acetate methanol (9 / 1). The combined organic extracts are washed with brine dried over $MgSO_4$ and concentrated. The residue is purified by flash chromatography (eluting with 10% methanol in CH_2Cl_2) to give 329 mg of the title compound. ^{1}H NMR (CD_3OD) δ 3.00 (s, 6H), 3.94 (s, 3H), 4.56 (s, 2H), 7.74 (d, J = 5 Hz, 1H), 7.83 (s, 1H), 7.88 (d, J = 8Hz, 2H), 8.17 (d, J = 8Hz, 2H), 8.76 (d, J = 5Hz, 1H). MS (ion spray) m/z 271 (M+H).

Reference Example 60

3,6-dibromopyridazine. To a cooled solution (0°C) of phosphorus tribromide (15.7mL, 165mmol) is added dropwise bromine (8.5mL, 165mmol). The resulting solid is allowed to stand for 10min then quickly mixed thoroughly with a spatula. To the solid PBr_5 is added 3,6-dihydroxypyridazine (16.8g, 150mmol), the solids mixed thoroughly and the flask equipped with a condenser and drying tube. The mixture is heated to 100°C for 3 hours then cooled to 20°C. The solids are transferred in small portions to a cooled (-5°C) 2N NH_4OH soln (200mL). Collected solids by filtration and washed with cold (-5°C) 1N NaOH (120mL) then with H_2O till neutral pH. Dissolved solids in ether, dried over $MgSO_4$, concentrated and dried under high vacuum to give 25.8g of title compound as a pale yellow solid. ^{1}H NMR (DMSO) δ 8.01 (s, 2H). MS (EI) m/z 236/238/240 (M^+), Br_2.

Reference Example 61a

4-[1-(2-dimethylamino-ethyl)-6-oxo-1,6-dihydro-pyridazin-3-yl]-benzoic acid. To a solution of 4-[1-(2-dimethylamino-ethyl)-6-oxo-1,6-dihydro-pyridazin-3-yl]-benzoic acid methyl ester (542mg, 1.8mmol, reference example 62a) in 1:1 THF/methanol (6mL) is added 10N NaOH (1.8mL, 18mmol) followed by H_2O (0.5mL). The resulting solution is stirred for 1.5 hours then cooled to 0°-5°C, adjusted to pH 6 with 2N HCl and concentrated. The residue is purified by reverse phase HPLC (eluting with 15%-40% acetonitrile(0.1%TFA) / H_2O(0.1%TFA) over 20min) to give 487mg of title compound. ^{1}H NMR (DMSO) δ 2.89 (s, 6H), 3.59 (m, 2H), 4.52 (bt, 2H), 7.14 (d, J = 10Hz, 1H), 8.04 (s, 4H), 8.16 (d, J = 10Hz, 1H), 9.63 (bs, 1H). MS (ion spray) m/z 288 $(M+H)^+$.

Reference Example 61b

Using essentially the same procedure used to prepare reference example 61a except using the product from reference example 62b there is prepared 4-[1-(3-dimethylamino-propyl)-6-oxo-1,6-dihydro-pyridazin-3-yl]-benzoic acid. ^{1}H NMR (DMSO) δ 2.17 (m, 2H), 2.78 (s, 3H), 2.79 (s, 3H), 3.16 (m, 2H), 4.24 (bt, 2H), 7.14 (d, J = 10Hz, 1H), 8.05 (s, 4H), 8.16 (d, J = 10Hz, 1H), 9.61 (bs, 1H). MS (EI) m/z 302 $(M+H)^+$.

Reference Example 62a

4-[1-(2-dimethylamino-ethyl)-6-oxo-1,6-dihydro-pyridazin-3-yl]-benzoic acid methyl ester. To DMSO (3.5mL) is added 60% NaH dipersion in mineral oil (84mg, 2.1mmol) and the resulting mixture stirred for 5min. To this solution is added 4-(6-oxo-1,6-dihydro-pyridazin-3-yl)-benzoic acid methyl ester (460mg, 2mmol reference example 36e) and the mixture stirred for 10min (till homogeneous). In a separate flask containing DMSO (3.5mL) is added 60% NaH (101mg, 2.5mmol) and stirred 5min. To this solution is added 2-dimethylaminoethylchloride hydrochloride (346mg, 2.4mmol) and let stir for 5min. This solution is transferred to the reaction solution, heated to 50°C, let stir for 2 hours. Cooled to 20°C, quenched with sat NH_4Cl soln (2mL) and concentrated. The residue is purified by short path flash chromatography (eluting with 10% methanol in dichloromethane) to give 542mg of title compound. ^{1}H NMR (CD_3OD) δ 2.35 (s, 6H), 2.88 (t, J = 7Hz, 2H), 3.93 (s, 3H), 4.42 (t, J = 7Hz, 2H), 7.08 (d, J = 10Hz, 1H), 8.06 (m, 5H). MS (EI) m/z 302 $(M+H)^+$.

Reference Example 62b

Using essentially the same procedure used to prepare reference example 61a except using 3-(dimethyl-amino)-propylchloride hydrochloride, there is prepared 4-[1-(3-dimethylamino-propyl)-6-oxo-1,6-dihydro-pyridazin-3-yl]-benzoic acid methyl ester. ^{1}H NMR (CD_3OD) δ 2.07 (m, 2H), 2.25 (s, 6H), 2.45 (bt, 2H), 3.92 (s, 3H), 4.29 (bt, 2H), 7.07 (d, J = 10Hz, 1H), 8.04 (m, 5H). MS (ion spray) m/z 316 $(M+H)^+$.

Reference Example 63

4-(6-methoxy-pyridazin-3-yl)-benzoic acid methyl ester. To a solution of 4-(6-methoxy-pyridazin-3-yl)-benzoic acid (5.02g, 21.8mmol) (reference example 11f) in methanol (75mL) is added slowly conc. H_2SO_4 (3.75mL). The resulting solution is heated to 50°C and stirred for 1 hour. The solution is then concentrated to one third volume, cooled to 0°-5°C, adjusted to pH 6 with sat $NaHCO_3$ soln and extracted into ethyl acetate. The organic layer is washed with brine, dried over $MgSO_4$ and concentrated. The residue is purified by flash chromatography (eluting with 20% ethyl acetate in dichloromethane) to give 4.26g of title compound as a white crystalline solid. ^{1}H NMR (DMSO) δ 3.90 (s, 3H), 4.10 (s, 3H), 7.38 (d, J = 9Hz, 1H), 8.10 (d, J = 9Hz, 2H), 8.25 (m, 3H). MS (EI) m/z 244 (M^+).

Reference Example 64a

N-[2-(3-cyano-1H-indol-5-yl)-ethyl]-4-(6-oxo-piperidin-3-yl)-benzamide. 4-(6-Oxo-piperidin-3-yl)-benzoic acid (190mg, 0.87 mmol, reference example 65) and 5-(2-amino-ethyl)-1H-indole-3-carbonitrile (161 mg, 0.87 mmol, reference example 2) is dissolved in anhydrous DMF (3 mL). To this solution is added diisopropiyethylamine (330 µl, 1.9 mmol), followed by HBTU (330 mg, 0.87 mmol) and allowed to stir at room temperature overnight (16 hours). The product is isolated by Reverse-Phase chromatography of the crude reaction mixture (Dynamax C-18 60 A (5 x 30 cm), 50 ml/min, λ@ 220 nm, 10-70% B in 15 minutes, A: 0.1% TFA/water, B: 0.1% TFA/acetonitrile). ^{1}H NMR (300 MHz, DMSO) δ 1.94 (m, 2H), 2.26 (m, 2H), 2.92 (t, J = 7.1, 2H), 3.19 (m, 1H), 3.48 (m, 2H), 3.46 (m, 2H), 7.13 (d, J = 8.4, 1H), 7.15 (d, J = 1.4, 2H), 7.36 (d, J = 8.3, 2H), 7.43 (d, J = 8.5, 1H), 7.46 (s, 1H), 7.55 (d, J = 2.5, 1H), 7.73 (d, J = 8.3, 2H), 8.17 (d, J = 3.0, 1H), 8.47 (t, J = 5.5, 1H). MS (Ion spray) m/z 387 $(M+H)^+$.

Reference Example 64b

Using essentially the same procedure used to prepare reference example 64a except using the product from reference example 68 there is prepared N-Boc-3-cyano-5-{2-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzoylamino]-propyl}-indole. ^{1}H NMR (300 MHz, $CDCl_3$) d 8.11 (d, J = 8.7 Hz, 1H), 8.09 (s, 1H), 7.79 (dd, J = 9.4, 2.4 Hz, 1H), 7.76 (d, J = 8.1 Hz, 2H), 7.65 (d, J = 2.4 Hz, 1H), 7.56 (s, 1H), 7.47 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.6 Hz, 1H), 6.71 (d, J = 9.4 Hz, 1H), 6.02 (d, J = 8.1 Hz, 1H), 4.57-4.47 (m, 1H), 3.13-2.96 (m, 2H), 1.68 (s, 9H), 1.27 (d, J = 6.7 Hz, 3H); MS (ion spray) m/z 497 ($M+H^+$).

Reference Example 64c

Using essentially the same procedure used to prepare reference example 64a except using the product from reference example 75 there is prepared tert-Butyl 4-{4-[2-(3-cyano-1H-indol-5-yl)ethylcarbamoyl]-phenyl}-3,6-dihydro-2H-pyridine-1-carboxylate. ^{1}H NMR (300 MHz, $CDCl_3$) d 8.92 (bs, 1H), 7.72-7.64 (m, 4H), 7.42-7.38 (m, 3H), 7.21 (d, J = 6.9 Hz, 1H), 6.17 (bt, 1H), 6.09 (bs, 1H), 4.10-4.06 (m, 2H), 3.78 (dd, J = 12.9, 6.7 Hz, 2H), 3.64 (t, J = 5.7 Hz, 2H), 3.07 (t, J = 6.8 Hz, 2H), 2.55-2.47 (m, 2H), 1.49 (s, 9H); MS (ion spray) m/z 471 ($M+H^+$).

Reference Example 64d

Using essentially the same procedure used to prepare reference example 64a except using the product from reference example 81 there is prepared t-Butyl (3-{4-[2-(3-cyano-1H-indol-5-yl)ethylcarbamoyl]phenyl}-prop-2-ynyl)carbamate. ^{1}H NMR (300 MHz, CD_3OD) d 11.62 (bs, 1H), 8.56 (bs, 1H), 7.90 (d, 1H), 7.71 (m, 2H), 7.55 (s, 1H), 7.50-7.40 (m, 3H), 7.21 (d, 1H), 4.08 (s, 2H), 3.63 (m, 2H), 3.05 (t, 2H).

Reference Example 65

4-(6-Oxo-piperidin-3-yl)-benzoic acid. Ethyl 4-(6-oxo-piperidin-3-yl)-benzoate (320 mg, 1.30 mmol, reference example 66) is dissolved in MeOH (8 mL). To this solution is added 1 N NaOH (1.43 mL, 1.43 mmol) and the resulting solution stirred at room temperature for 1 hour. An additional portion of 1 N NaOH (2mL) is added and the mixture allowed to stir at room temperature overnight (16 hours). 1 N HCl is added until pH 2-3 is reached. A precipitate formed and is filtered, washed with water and placed in a vacuum oven to dry overnight to afford the title compound (250 mg, 88%) as small white crystals (needles). ^{1}H NMR

(300 MHz, DMSO) δ 1.94 (m, 2H), 2.23 (m, 2H), 3.06 (m, 1H), 3.23 (m, 2H), 7.42 (d, J = 8.3, 2H), 7.57 (bs, 1H), 7.87 (d, J = 8.1, 2H); MS (Ion spray) m/z 220 $(M+H)^+$.

Reference Example 66

Ethyl 4-(6-oxo-piperidin-3-yl)-benzoate. Ethyl 4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzoate (450 mg, 1.8 mmol) (reference example 36f)is dissolved in HOAc (15 mL), and the the solution is degassed several times by alternating N_2/vacuum. 50 mg of PtO_2 is added and the mixture is degassed for several minutes before being placed under a H_2 atmosphere. The mixture is stirred at room temperature for 9 hours then degassed several times by alternating N_2/vacuum then filtered through a plug of celite. The plug is washed thoroughly with HOAc and the filtrate concentrated. The residue is chromatographed first on silica gel (3% MeOH/ CH_2Cl_2), and then by Reverse-Phase HPLC to afford 330 mg of the title compound (72%) as a white solid. ^1H NMR ($CDCl_3$) δ 1.39 (t, J = 7 Hz, 3H), 2.12 (m, 2H), 2.56 (m, 2H), 3.13 (m, 1H), 3.41 (dd, J = 11.3, 11.3, 1H), 3.53 (m, 1H), 4.37 (q, J = 7, 2H), 6.78 (bs, 1H), 7.16 (d, J = 8 Hz, 2H), 8.01 (d, J = 8 Hz, 2H). MS (Ion spray) m/z 248 $(M+H)^+$.

Reference Example 67a

Ethyl 4-(1-carboxymethyl-6-oxo-1,6-dihydropyridin-3-yl)benzoate. To a solution of ethyl 4-(1-tert-butoxycarbonylmethyl-6-oxo-1,6-dihydropyridin-3-yl)benzoate [1.03g, 2.88 mmol, reference example 85b] in CH_2Cl_2 [10 ml] and H_2O [0.125 ml] is added trifluoroacetic acid [2.5 ml]. After 18 hours removed solvent in vacuo and triturated the resulting solid with methylene chloride to give 0.815g of the product as a white solid in 93.9% yield. ^1H NMR (1:1 CD_3OD: $CDCl_3$): δ 1.43 (3H, t, J= 7 Hz), 4.40 (2H, q, J = 7 Hz), 4.81 (2H, s), 6.73 (1H, d, J = 9 Hz), 7.60 (2H, d, J = 8 Hz), 7.60 (1H, s), 7.88 (1H, d, J = 9.0 Hz), 8.09 (2H, d, J = 8 Hz). MS (ion spray) m/z 302 $(M+H)^+$.

Reference Example 67b

Using essentially the same procedure used to prepare reference example 67a except using the product from reference example 64c there is prepared N-[2-(3-Cyano-1H-indol-5-yl)ethyl]-4-(1,2,3,6-tetrahydropyridin-4-yl)benzamide. ^1H NMR (300 MHz, DMSO-d_6) d 12.11 (bs, 1H), 8.84 (bs, 2H), 8.57 (t, 1H), 8.19 (d, J = 2.9 Hz, 1H), 7.82 (d, J = 8.3 Hz, 2H), 7.55 (d, J = 8.3 Hz, 2H), 7.47 (s, 1H), 7.46 (d, J = 8.9 Hz, 1H), 7.16 (d, J =

8.9 Hz, 1H), 6.31 (bs, 1H), 3.77 (bm, 2H), 3.55-3.47 (m, 2H), 3.36-3.29 (m, 2H), 2.94 (t, 2H), 2.69 (bm, 2H); MS (ion spray) m/z 371 ($M+H^+$).

Reference Example 67c

3-Cyano-5-{2-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzoylamino]-propyl}-indole. Using essentially the same procedure used in reference example 67a except using the product from reference example 64b afforded the title compound. ^1H NMR (300 MHz, DMSO-d_6) d 12.07 (bs, 1H), 8.30 (d, J = 8.0 Hz, 1H), 8.17 (s, 1H), 7.88 (d, J = 9.5 Hz, 1H), 7.83-7.80 (m, 3H), 7.62 (d, J = 8.4 Hz, 2H), 7.50 (s, 1H), 7.42 (d, J = 8.3 Hz, 1H), 7.17 (d, J = 8.5 Hz, 1H), 6.43 (d, J = 9.6 Hz, 1H), 4.26-4.17 (m, 1H), 3.02-2.82 (m, 2H), 1.16 (d, J = 6.6 Hz, 3H); MS (ion spray) m/z 397 ($M+H^+$).

Reference example 68

N-Boc-5-(2-aminopropyl)-indole-3-carbonitrile. To a solution of N-Boc-5-(2-azidopropyl)-indole-3-carbonitrile (0.33 g, 0.97 mmol reference example 69) in tetrahydrofuran (5 mL) and a drop of water is added triphenylphosphine (1.1 g, 4.2 mmol). The reaction mixture is allowed to stir 3 days, and then concentrated and purified by column chromatography (silica, 3% to 5% MeOH/CH_2Cl_2) to provide 0.12 g of N-Boc-5-(2-aminopropyl)-indole-3-carbonitrile: ^1H NMR (300 MHz, DMSO-d_6) d 8.62 (s, 1H), 8.04 (d, J = 8.6 Hz, 1H), 7.51 (s, 1H), 7.34 (d, J = 8.7 Hz, 1H), 3.13-3.05 (m, 1H), 2.69 (d, J = 6.6 Hz, 2H), 1.64 (s, 9H), 0.97 (d, J = 6.2 Hz, 3H); MS (ion spray) m/z 300 ($M+H^+$).

Reference Example 69

N-Boc-5-(2-azidopropyl)-indole-3-carbonitrile. N-Boc-5-(2-hydroxypropyl)-indole-3-carbonitrile (480 mg, 1.6 mmol, reference example 70) is dissolved in THF (10 mL) and cooled to 0 °C. Triphenylphosphine (0.5 g, 2 mmol), diethylazodicarboxylate (0.3 mL, 2 mmol) and diphenylphosphorylazide (0.41 mL, 2 mmol) are added and the reaction stirred 14 hours. An additional portion (2 mmol) of each of the above reagents is added and the reaction stirred 6 hours. The resulting mixture n is partitioned between ethyl acetate and a saturated solution of sodium bicarbonate. The organic layer is separated, dried ($MgSO_4$), concentrated and purified by column chromatography (silica, 20% EtOAc/petroleum ether to EtOAc) to provide 0.33 g of N-Boc-5-(2-azidopropyl)-indole-3-carbonitrile: ^1H NMR (300 MHz, $CDCl_3$) d 8.11 (d, J = 8.2 Hz, 1H), 8.10

(s, 1H), 7.54 (d, J = 1.0 Hz, 1H), 7.29 (dd, J = 8.7, 1.6 Hz, 1H), 3.81-3.70 (m, 1H), 2.97-2.83 (m, 2H), 1.69 (s, 9H), 1.29 (d, J = 6.5 Hz, 3H).

Reference Example 70

N-Boc-5-(2-hydroxypropyl)-indole-3-carbonitrile. A solution of N-Boc-5-(2-oxopropyl)-indole-3-carbonitrile (0.48 g, 1.6 mmol, reference example 71) in THF (15 mL) and ethanol (15 mL) is cooled to 0 °C and sodium borohydride (95 mg, 2.5 mmol) added in two portions over 15 minutes. After stirring an additional 15 minutes the reaction mixture is partitioned between ethyl acetate (150 mL) and a saturated aqueous ammonium chloride solution (50 mL). The organic layer is dried ($MgSO_4$) and concentrated to provide a semi-pure sample of N-Boc-5-(2-hydroxypropyl)-indole-3-carbonitrile which is used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) d 8.10 (d, J = 8.1 Hz, 1H), 8.09 (s, 1H), 7.56 (s, 1H), 7.30 (dd, J = 8.7, 1.3 Hz, 1H), 4.16-4.04 (m, 1H), 3.7 (bs, 1H), 2.95-2.79 (m, 2H), 1.67 (s, 9H), 1.26 (d, J = 6.4 Hz, 3H); MS (EI) m/z 300 (M^+).

Reference Example 71

N-Boc-5-(2-oxopropyl)-indole-3-carbonitrile. A mixture of N-Boc-5-bromoindole-3-carbonitrile (1.08 g, 3.36 mmol, refererence example 72), tributyltin fluoride (2.1g, 6.7 mmol), bis(tri-o-tolylphosphine) palladium dichloride (66mg, 0.13 mmol), 2-trimethylsilyloxy-propene (1.1 mL, 6.7 mmol) and toluene (25 mL) is degassed and then heated in an 80 °C bath for 3 hours. Additional palladium catalyst (70 mg), 2-trimethylsilyloxy-propene (0.7 mL) and tributyltin fluoride (2.0g) is added and the reaction is heated for an additional 1 hour. The reaction is cooled, and ether (25 mL) and 1N NaOH (25 mL) added followed by vigorous stirring for 10 minutes. The ether layer is separated, dried ($MgSO_4$), concentrated and purified by column chromatography (silica, CH_2Cl_2) to provide 0.48 g of N-Boc-5-(2-oxopropyl)-indole-3-carbonitrile: ^{1}H NMR (300 MHz, DMSO-d_6) d 8.64 (s, 1H), 8.06 (d, J = 8.6 Hz, 1H), 7.54 (s, 1H), 7.30 (d, J = 8.6 Hz, 1H), 3.94 (s, 2H), 2.16 (s, 3H), 1.65 (s, 9H).); MS (EI) m/z 299 ($M+H^+$).

Reference Example 72

N-Boc-5-bromoindole-3-carbonitrile. To a mixture of CH_2Cl_2 (20 mL) and acetone (5 mL) is added to 5-bromoindole-3-carbonitrile (1.23 g, 5.5 mmol, reference example 73) and di-t-butyldicarbonate (1.21 g, 5.5

mmol). N,N-Dimethylaminopyridine (24 mg, 0.2 mmol) is added and the reaction is stirred 1 hour. A precipitate formed which is filtered to provide 0.63 g of N-Boc-5-bromoindole-3-carbonitrile as a white solid. The filtrate is concentrated to provide 1.1 g of semi-pure product. The filtered product provided the following analytical data: ^{1}H NMR (300 MHz, DMSO-d_6) d 8.73 (s, 1H), 8.07 (d, J = 8.9 Hz, 1H), 7.90 (s, 1H), 7.66 (d, J = 8.9 Hz, 1H), 1.64 (s, 9H).

Reference Example 73

5-Bromoindole-3-carbonitrile. Hydroxylamine hydrochloride (4.5 g, 66 mmol) is add to a mixture of 5-bromoindole-3-carbaldehyde (14.7 g, 66 mmol, reference example 74) and methanol (100 mL). After 1 hour toluene (80 mL) and THF (30 mL) are added and the reaction concentrated. Additional toluene (80 mL) is added and the reaction is azeotroped again. The mixture is dissolved in toluene (200 mL) and thionyl chloride (12 mL, 165 mmol) added causing a mild exotherm. The reaction is placed in a 70 °C bath and heated for 45 minutes. The reaction is then cooled and azeotroped with a mixture of CH_2Cl_2 and THF. The crude reaction mixture is dissolved in a mixture of methanol and CH_2Cl_2, adsorbed to silica gel and extracted with CH_2Cl_2 to provide 11.4 g of 5-bromoindole-3-carbonitrile. An analytically pure sample is obtained by recrystallization from toluene: (reddish needles) m.p. 189-191; ^{1}H NMR (300 MHz, DMSO-d_6) d 12.38 (bs, 1H), 8.30 (d, J = 3.0 Hz, 1H), 7.79 (d, J = 1.5 Hz, 1H), 7.52 (d, J = 8.6 Hz, 1H), 7.40 (dd, J = 8.6, 1.6 Hz, 1H); MS (EI) m/z 220 (M^+,Br).

Reference Example 74

5-Bromoindole-3-carbaldehyde. Phosphorous oxychloride (10.5 mL, 112 mmol) is added slowly (over 10 min) to dimethylformamide (15 mL) with water bath cooling. To this solution is added a solution of 5-bromoindole (15 g, 93 mmol) in dimethylformamide (15 mL) over 15 minutes causing a slight exotherm. After 5 minutes the reaction is placed in an 80 °C bath and heated for 10 minutes. The reaction is cooled slightly and water (15 mL) added producing a vigorous exotherm. The reaction is heated in a bath temperature of 90 °C for 1.5 hours. The reaction is cooled and then added very slowly to 0.4 N NaOH (500 mL) forming a brown precipitate which is filtered, dissolved in EtOAc, dried ($MgSO_4$) and concentrated to yield a reddish solid. After sitting overnight the filtrate precipitated additional product which is collected and combined with the first batch to provide semi-pure aldehyde (15.3 g) which is used without further

purification. ^{1}H NMR (300 MHz, DMSO-d_6) d 12.30 (bs, 1H), 9.92 (s, 1H), 8.34 (d, J = 3.0 Hz, 1H), 8.21 (s, 1H), 7.49 (d, J = 8.6 Hz, 1H), 7.38 (dd, J = 8.7, 1.8 Hz, 1H).

Reference Example 75

tert-Butyl 4-(4-Carboxyphenyl)-3,6-dihydro-2H-pyridine-1-carboxylate. To a solution of tert-butyl 1,2,3,6-tetrahydro-4-[(trifluoromethyl)sulfonyloxy]pyridine-1-carboxylate (2.63 g, 7.9 mmol, reference example 76) in dimethoxyethane (21 mL) is added 4-carboxybenzeneboronic acid (1.44 g, 8.7 mmol), 2M aqueous sodium carbonate (17.4 mL) and lithium chloride (0.99 g, 24 mmol). The mixture is degassed and then tetrakis(triphenylphosphine)palladium (450 mg, 0.4 mmol) added, the reaction is degassed again and then heated at reflux 6h. The reaction is filtered and the solid washed with EtOAc. The organic phase is washed with 0.5 N HCl, dried ($MgSO_4$), concentrated and purified by column chromatography (silica, 3% MeOH/CH_2Cl_2/0.1%HOAc) providing a semi-purified product. This material is titurated with ether and a small amount of CH_2Cl_2 to provide 0.27 g of the title compound as a white solid: m.p. 200-209 (dec); ^{1}H NMR (300 MHz, $CDCl_3$) d 8.07 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 6.20 (bs, 1H), 4.15-4.00 (m, 2H), 3.66 (t, J = 5.6 Hz, 2H), 2.60-2.52 (m, 2H), 1.50 (s, 9H); MS (ion spray) m/z 304 ($M+H^+$).

Reference Example 76

tert-Butyl 1,2,3,6-Tetrahydro-4-[(trifluoromethyl)sulfonyloxy]pyridine-1-carboxylate. According to Wustrow and Wise, Synthesis 1991, 993. A solution of diisopropylamine (4.2 g, 29 mmol) in THF (9 mL) is cooled to -78 °C. A solution of n-butyl lithium (11.2 mL, 2.5 M in hexanes) is added at -78 °C and the reaction warmed to 0 °C and then recooled to -78 °C. A solution of tert-butyl 4-oxopiperidine-1-carboxylate (5.4 g, 27 mmol) in THF (15 mL) is added dropwise (5 min). After stirring an additional 25 minutes, a solution of N-phenyltrifluoromethanesulfonimide (10 g, 28 mmol) in THF (25 mL) is added and the reaction allowed to stir at room temperature 2h. The reaction is concentrated, dissolved in CH_2Cl_2 and poured onto a dry pad of alumina (350g). The product is eluted with 10% EtOAc/petroleum ether (1L) and concentrated to provide 8g of the title compound as a low melting solid: ^{1}H NMR (300 MHz, $CDCl_3$) d 5.77 (bs, 1H), 4.06-4.04 (m, 2H), 3.63 (t, J = 5.7 Hz, 2H), 2.46-2.40 (m, 2H), 1.48 (s, 9H).

Reference Example 77

t-Butyl 5-[2-[4-(3-t-butoxycarbonylaminoprop-1-ynyl)-benzoylamino]ethyl}-3-carbamimidoyl-indole-1-carboxylate. t-Butyl 5-[2-[4-(3-t-butoxycarbonylaminoprop-1-ynyl)-benzoylamino]ethyl}-3-thiocarbamoyl-indole-1-carboxylate (73 mg, 0.13mmol, reference example 78) is dissolved in acetone (75 mL) and methyl iodide (5 mL) added. This mixture is heated to reflux. After 15 minutes, the solvent is removed in vacuo giving a yellow residue. MS (ion spray) m/e 591 ($M+H^+$). The residue (80 mg, 0.13mmol) is dissolved in MeOH (15 mL) and ammonium acetate (0.5 g) added and this mixture heated at reflux for 20 minutes. The solvent is removed in vacuo and the residue partitioned between CH_2Cl_2 and water. The aqueous layer is extracted with CH_2Cl_2 and the combined organic layers washed with water, dried over magnesium sulfate and concentrated in vacuo. The crude product is purified by reverse phase HPLC eluting with 30-70%/15 minutes, giving 22 mg. MS (ion spray) m/z 560 ($M+H^+$).

Reference Example 78

t-Butyl 5-[2-[4-(3-t-butoxycarbonylaminoprop-1-ynyl)-benzoylamino]ethyl}-3-thiocarbamoyl-indole-1-carboxylate. t-Butyl 5-[2-[4-(3-t-butoxycarbonylaminoprop-1-ynyl)-benzoylamino]ethyl}-3-cyano-indole-1-carboxylate (80 mg, 0.15 mmol, reference example 79) is dissolved in pyridine (20 mL), triethylamine (2 mL) added. Hydrogen sulfide is bubbled into the reaction for 5 minutes. The reaction is then allowed to stand at R.T. overnight. The solvent is removed in vacuo and the residue is dissolved in CH_2Cl_2, washed with water and dried over magnesium sulfate. The solvent is removed in vacuo, giving 80 mg of residue which is used without further purification: ^1H NMR (300 MHz, $CDCl_3$) d 8.61 (t, J =3.0 Hz, 2H), 8.24 (s, 1H), 8.12-8.06 (m, 2H), 7.71-7.59 (m, 2H), 7.39-7.20 (m, 3H), 6.41 (bs, 1H), 4.89 (bs, 1H), 4.14 (d, J = 5.1 Hz, 2H), 3.78 (q, J = 6.4 Hz, 2H), 3.05 (t, J = 6.6 Hz, 2H), 1.66 (s, 9H), 1.46 (s, 9H).

Reference Example 79

t-Butyl 5-{2-[4-(3-t-butoxycarbonylaminoprop-1-ynyl)-benzoylamino]ethyl}-3-cyano-indole-1-carboxylate. To a suspension of t-Butyl (3-{4-[2-(3-cyano-1H-indol-5-yl)ethylcarbamoyl]phenyl}-prop-2-ynyl)carbamate (95 mg, 0.22mmol, reference example 64d) in acetone (5 mL) is added di-t-butoxy-dicarbonate (47 mg, 0.22 mmol) and DMAP (0.9 mg, 8mmol). Then pyridine (1mL) is added and the mixture stirred at R.T. overnight.The solvent is removed in vacuo and the residue dissolved in CH_2Cl_2 and washed with water, then dried over magnesium sulfate and the solvent removed in vacuo, giving 88 mg of solid residue (75% yield). ^1H NMR: (300 MHz, $CDCl_3$) d 8.63 (bs, 1H), 8.11 (d, J = 9.7 Hz, 1H), 7.72-7.57 (m, 2H), 7.43 (d, J = 8.4

Hz, 2H), 7.34-7.27 (m, 2H), 6.25 (bs, 1H), 4.84 (bs, 1H), 4.15 (d, J = 5.2 Hz, 2H), 3.76 (q, J = 6.6 Hz, 2H), 3.07 (t, J = 6.9 Hz, 2H), 1.69 (s, 9H), 1.47 (s, 9H).

Reference Example 80

4-(3-t-Butoxycarbonylaminoprop-1-ynyl)benzoic acid. Methyl 4-(3-t-butoxycarbonylaminoprop-1-ynyl)benzoate (1.09 g, 38 mmol, reference example 81) is dissolved in MeOH (15 mL) and to this solution added NaOH (0.15 g, 38 mmol) dissolved in water (5 mL). This mixture is heated to reflux. After 5 hours, the solvent is removed in vacuo and CH_2Cl_2 and 1N HCl added to the residue. The organic layer is washed with 1N HCl, water and brine, then dried over magnesium sulfate. The solvent is removed in vacuo to give a white solid (0.60 g, 57% yield): ^{1}H NMR (300 MHz, CD_3OD) d 7.86 (d, 2H), 7.39 (d, 2H), 3.98 (s, 2H), 1.38 (s, 9H).

Reference Example 81

Methyl 4-(3-t-butoxycarbonylaminoprop-1-ynyl)benzoate. Methyl-4-iodobenzoate (1.5 g, 5.7 mmol) and t-butyl prop-2-ynylcarbamate (0.89 g, 5.7 mmol, reference example 82) are dissolved in piperidine (12 mL) and this solution purged with nitrogen. Copper(I) iodide (22 mg, 0.11 mmol) and dichlorobis(triphenylphosphine) palladium (40 mg, 0.057mmol) is added and the mixture is stirred at R.T. After 2 hours, the solvent is removed in vacuo and the residue added to CH_2Cl_2 and washed with 1N HCl, water and brine, then dried over magnesium sulfate. The solvent is removed in vacuo and the residue purified by flash chromatography, eluting with 20% ethyl acetate/hexane to provide the title compound as a white solid (1.1 g, 67% yield): ^{1}H NMR (300 MHz, $CDCl_3$) d 7.98 (d, 2H), 7.48 (d, 2H), 4.79 (bs, 1H), 4.17 (d, 2H), 3.91 (s, 3H), 1.48 (s, 9H).

Reference Example 82

t-Butyl prop-2-ynylcarbamate. Propargylamine (10 g, 0.18 mol) is dissolved in CH_2Cl_2 (40 mL) and cooled in an ice bath. Di-t-butyl dicarbonate (40 g, 0.18 mol), dissolved in CH_2Cl_2 (60 mL), is added over 20 minutes. The cooling bath is removed and the reaction allowed to warm to R.T. and stirred overnight. The solvent is removed in vacuo and the residue used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) d 4.75 (bs, 1H), 3.90 (d, 2H), 2.21 (t, 1H), 1.45 (s, 9H).

Reference Example 83

4-[2-(2-Dimethylamino-ethylamino)-pyrimidin-4-yl]-benzoic acid. To a solution of 4-[2-chloro-pyrimidin-4-yl]-benzoic acid (234 mg, 1 mmol, reference example 11g) in DMSO (2mL) is added 2-(N,N-dimethyl-amino)ethylamine (291 mL, 2 mmol). The resulting solution is heated to 85 °C and stirred at this temperature for 3.5 hours, then cooled and concentrated. The residue is purified by reverese phase HPLC to give 296 mg of the title compound as a TFA salt. ^{1}H NMR (CD_3OD) d 2.97 (s, 6H), 3.45 (t, J = 6Hz, 2H), 3.88 (t, J = 6Hz, 2H), 7.31 (d, J = 5Hz, 1H), 8.13 (d, J = 8Hz, 2H), 8.20 (d, J = 8Hz, 2H), 8.44 (d, J = 5Hz, 1H). MS (ion spray) m/z 286 (M+).

Reference Example 84

4-[2-(2-Chloro)-pyrimidin-4-yl]-benzyl (t-butyldimethylsilyl) Ether. To a cooled (-78 °C) solution of 4-bromo-benzyl t-butyldimethylsilyl ether (3.0g, 10 mmol, reference example 16) in THF (30 mL) is added, dropwise, n-buLi (4.08 mL, 2.5M in hexanes). The resulting solution is stirred for 10 minutes then a solution of 2-chloro-pyrimidine (1.14g, 10 mmol) in THF (30 mL) added in one portion. This solution is warmed to -30 °C and stirred for 20 minutes then a solution comprised of acetic acid (600 mL, 10 mmol) and H_2O (100mL, 5.5 mmol) in THF (5 mL) added. The resulting mixture is warmed to 0 °C then DDQ (2.27g, 10 mmol) in THF (10 mL) added. The cold bath is removed and stirring continued for 10 minutes. To this mixture is added NaOH (10 mL, 1M) then the mixture partitioned between ether and water. The ether fraction is washed with brine, dried over $MgSO_4$, and decolorized with activated charcoal, filtered through celite and the filtrate concentrated. The residue is purified by flash chromatography (eluting with 20% ethyl acetate in hexanes) to give 1.68g of the title compound as an oil which crystallized on standing. ^{1}H NMR ($CDCl_3$) d 0.04 (s, 6H), 0.84 (s, 9H), 4.70 (s, 2H), 7.45 (d, J = 8Hz, 2H), 7.53 (d, J = 5Hz, 1H), 7.96 (d, J = 8Hz, 2H), 8.50 (d, J = 5Hz, 1H). MS (ion spray) m/z 335 (M+H, Cl pattern).

Reference Example 85a

Ethyl 4-(1-[2-dimethylaminoethyl]-6-oxo-1,6-dihydropyridin-3-yl)benzoate and Ethyl 4-(6-[2-dimethyl-aminoethoxy]pyridin-3-yl)benzoate. To a cooled (0°C) slurry of ethyl 4-(6-oxo-1,6-dihydropyridin-3-yl)benzoate [0.500g, 2.06 mmol, reference example 36f] in THF:DMF [30 mL 5:1] is added 60% sodium hydride [0.247g, 6.18 mmol]. After ten minutes added potassium iodide [2 mg] and 2-dimethylaminoethyl-

chloride hydrochloride [Aldrich, 0.386g, 2.68 mmol] and heated to 50°C. After twenty hours, quenched slowly with H_2O [15 ml] and extracted with CH_2Cl_2. The organic extracts are combined and concentrated, then purified on an HPLC (40 to 60% AcCN in water with 0.1% TFA) to give ethyl 4-(1-[2-dimethylamino-ethyl]-6-oxo-1,6-dihydropyridin-3-yl)benzoate [0.337g, 38.2% yield] as the TFA salt and ethyl 4-(6-[2-di-methylaminoethoxy]pyridin-3-yl)benzoate [0.110g, 12.5%] yield as the TFA salt.

For ethyl 4-(1-[2-dimethylaminoethyl]-6-oxo-1,6-dihydropyridin-3-yl)benzoate: ^{1}H NMR (CD_3OD): δ 1.40 (3H, t, J = 7.8 Hz), 3.03 (6H, s), 3.62 (2H, t, J = 5.9 Hz), 4.38 (2H, q, J = 7.8 Hz), 4.49 (2H, t, J = 5.9 Hz), 6.72 (1H, d, J = 9.2 Hz), 7.68 (2H, d, J = 8.8 Hz), 7.98 (1H, dd, J = 9.2 Hz, 3.0 Hz), 8.07 (2H, d, J = 8.8 Hz), 8.13 (1H, d, J = 3.0 Hz). MS (ion spray) m/z 315 $(M+H)^+$.

For ethyl 4-(6-[2-dimethylaminoethoxy]pyridin-3-yl)benzoate: ^{1}H NMR (CD_3OD): δ 1.41 (3H, t, J = 8.1 Hz), 3.02 (6H, s), 3.64 (2H, t, J = 6.1 Hz), 4.39 (2H, q, J = 8.1 Hz), 4.74 (2H, t, J = 6.1 Hz), 7.01 (1H, d, J = 9.4 Hz), 7.73 (2H, d, J = 8.8 Hz), 8.07 (1H, dd, J = 9.4 Hz, 2.5 Hz), 8.10 (2H, d, J = 8.8 Hz), 8.51 (1H, d, J = 2.5 Hz). MS (ion spray) m/z 315 $(M+H)^+$.

Reference example 85b

Using essentially the same conditions used to prepare reference example 85a except using t-butyl bromo-acetate as the alkylating agent there is prepared Ethyl 4-(1-tert-butoxycarbonylmethyl-6-oxo-1,6-dihydropyridin-3-yl)benzoate. ^{1}H NMR ($CDCl_3$): δ 1.41 (3H, t, J = 7.3 Hz), 1.50 (9H, s), 4.40 (2H, q, J = 7.3 Hz), 4.64 (2H, s), 6.70 (1H, d, J = 9.5 Hz), 7.48 (2H, d, J = 8.2 Hz), 7.50 (1H, s), 7.68 (1H, d, J = 9.5 Hz), 8.08 (2H, d, J = 8.2 Hz). MS (ion spray) m/z 358 $(M+H)^+$, 302 $(M-$ tert-Bu$)^+$.

Reference Example 85c

Using essentially the same conditions used to prepare reference example 85a except using 3-dimethylamino-propyl chloride hydrochloride as the alkylating agent there is prepared Ethyl 4-[1-(3-dimethylaminopropyl)-6-oxo-1,6-dihydropyridin-3-yl]benzoate. MS (ion spray) m/z 329 $(M+H)^+$ and Ethyl 4-[6-(3-dimethylaminopropoxy)pyridin-3-yl]benzoate. MS (ion spray) m/z 329 $(M+H)^+$.

Reference example 85d

Using essentially the same conditions used to prepare reference example 85a except using Allyl 4-(2-oxo-2H-pyridin-5-yl)benzoate (reference example 104) and t-butyl bromoacetate as substrates there is prepared Allyl 4-(1-[tert-butoxycarbonylmethyl]-2-oxo-2H-pyridin-5-yl)benzoate. MS (ion spray) m/z 370 $(M+H)^+$.

Reference Example 86a

4-(3-Amino-[1,2,4]triazin-6-yl)benzoic acid and 4-(3-Amino-[1,2,4]triazin-5-yl)benzoic acid. Aqueous NaOH (1N, 8.2 mL, 8.2 mmol) is added to a solution of a 2:1 mixture of the ethyl 4-(3-amino-[1,2,4]triazin-5-yl)benzoate and ethyl 4-(3-amino-[1,2,4]triazin-6-yl)benzoate (0.80 g, 3.3 mmol, reference example 87a) in MeOH (50 mL) and THF (100 mL). After stirring at ambient temperature for 18 hours, the reaction mixture is acidified to pH 4-5 with 2N HCl and partially evaporated. The resulting precipitate is collected, washed with H_2O and dried in vacuo to afford 4-(3-Amino-[1,2,4]triazin-6-yl)benzoic acid containing ~10% 4-(3-Amino-[1,2,4]triazin-5-yl)benzoic acid; yield 0.23 g (32%): ^{1}H NMR (DMSO-d_6) d 8.10 (2H, d, J = 7.3 Hz), 8.27 (2H, d, 7.3 Hz), 9.26 (1H,s); MS, m/z (isomeric mixture, ion spray) 235 $[(M+18)+H]^+$, 217 $(M+H)^+$. Further evaporation of the mother liquor and filtration of the precipitated solid gave 4-(3-Amino-[1,2,4]triazin-5-yl)benzoic acid. yield 0.40 g (56%): ^{1}H NMR (DMSO-d_6) d 7.8-8.2 (4H, m), 8.95 (1H, s):

Reference Example 86b

4-(3-Oxo-2,3-dihydro-[1,2,4]triazin-6-yl)benzoic acid. Using the procedure of example 86a except substituting ethyl 4-(3-oxo-2,3-dihydro-[1,2,4]triazin-6-yl)-benzoate (reference example 87b) for a mixture of ethyl 4-(3-amino-[1,2,4]triazin-5-yl)benzoate and ethyl 4-(3-amino-[1,2,4]triazin-6-yl)benzoate afforded the title compound: ^{1}H NMR (DMSO-d_6) d 3.90 [(0.2H, d, J = 4.9 Hz), (hydrate)], 7.72 (0.80H, s), 8.05 (3.2H, s), 8.11 [(0.4H, d, J = 7.7 Hz), (hydrate)], 8.32 [(0.4H, d, J = 7.7 Hz), (hydrate)], 8.77 [(0.2H, s), (hydrate)].

Reference Example 86c

4-(5-Oxo-4,5-dihydro-[1,2,4]oxaidiazol-3-yl)-benzoic acid. Using the procedure of example 86a except using the product from reference example 89 afforded the title compound: ^{1}H NMR (DMSO-d_6) d 7.93 (2H, d, J = 7.3 Hz), 8.12 (2H, d, J =7.3 Hz).

Reference Example 87a

Ethyl 4-(3-amino-[1,2,4]triazin-5-yl)benzoate and ethyl 4-(3-amino-[1,2,4]triazin-6-yl)benzoate. Using the following modification of the procedure of Loev, B. and Goodman, M. M. (Tetrahedron Lett., 1968, 789) except substituting 4-carboethyoxy phenylglyoxal hydrate for glyoxal hydrate afforded approximately a 2:1 mixture of the ethyl 4-(3-amino-[1,2,4]triazin-5-yl)benzoate and ethyl 4-(3-amino-[1,2,4]triazin-6-yl)benzoate, respectively:

Solid $NaHCO_3$ (0.79 g, 9.4 mmol) is added to a solution of aminoguanidine hydrochloride (1 g, 4.7 mol) in H_2O. The resulting solution is then added to a solution of 4-carboethyoxy phenylglyoxal hydrate (1 g, 4.7 mmol, reference example 88). The reaction mixture is stirred at ambient temperature for 72 hours and the precipitate collected, washed with H_2O and air-dried. The crude product is filtered through a pad of silica gel eluting with 4% CH_2Cl_2 in MeOH. Fractions containing only product are collected and the solvent removed under reduced pressure. The residue is triturated with ether to afford a 2:1 mixture of the title compounds (^{1}H NMR) as a white solid; yield 0.80 g (70%): ^{1}H NMR (DMSO-d_6) d 1.35 (3H, t), 4.35 (1.34H, q), 4.37 (0.66H, q), 7.38 (0.33H, s), 7.56 (0.67H, s), 8.08 (1.34H, d), 8.13 (0.67H, d), 8.18 (1.34H, d), 8.32 (0.67H, d), 8.89 (0.67, s), 9.28 (0.33H, s); MS, m/z (EI) 244 (M^+).

Regiochemically pure ethyl 4-(3-amino-[1,2,4]triazin-5-yl)benzoate is also prepared by the procedure of Lalezari et al. (*J. Het. Chem. 1969, 403*) except substituting ethyl 4-acetyl benzoate for acetophenone facilitating identification of the structures of the respective regioisomers: ^{1}H NMR (DMSO-d_6) d 1.35 (3H, t, J = 7.1 Hz), 4.35 (2H, q, J =7.1 Hz), 7.56 (1H, s), 8.08 (2H, d, J =7.5 Hz), 8.18 (2H, d, J = 7.5 Hz), 8.89 (1H, s); MS, m/z (ion spray) 263 $[(M+18)+H]^+$, 245 $(M + H)^+$.

Reference Example 87b

Ethyl 4-(3-oxo-2,3-dihydro-[1,2,4]triazin-6-yl)-benzoate. Using the procedure of reference example 87a except substituting semicarbazide hydrochloride for aminoguanidine hydrochloride afforded the title compound: ^{1}H NMR (DMSO-d_6) d 1.33 (3H, t, J = 4.6 Hz), 4.38 (2H, q, J = 4.6 Hz), 7.74 (1H, s), 8.10 (4H, s), 11.12 (1H, s); MS, m/z (EI) 264 $[(M+18)+H]^+$, 246 $(M + H)^+$.

Reference Example 88

4-Carboethyoxy phenylglyoxal hydrate. The title compound is prepared using the following modification of an Org. Syn. preparation (vol. 2, 509) of phenylglyoxal and substituting ethyl 4-acetyl benzoate for acetophenone:

Selenium dioxide (2.8 g, 0.026 mol) is added to a solution of ethyl 4-acetyl benzoate (5 g, 0.026 mol) in dioxane (30 mL) and water (1 mL). The reaction mixture is heated to reflux for 18 hours, cooled to ambient temperature and filtered through a pad of celite to remove the precipitated selenium. The filtrate is concentrated under reduced pressure and the residue is vacuum filtered through a pad of silica gel eluting successively with 33% and 50% hexanes in ethyl acetate to afford the title compound as a chromatographically pure yellow oil; yield 4.8 g (87 %). A sample is further purified by trituation with ether to afford a white solid: ^{1}H NMR (DMSO-d_6) d 1.32 (3H, t, J = 6.3 Hz), 4.35 (2H, q, J = 6.3 Hz), 5.67 (1H, t, J = 5.9 Hz), 6.88 (2H, d, J = 5.9 Hz), 8.08 (2H, d, J = 7.1 Hz), 8.17 (2H, d, J = 7.1 Hz).

Reference Example 89

Methyl 4-(5-oxo-4,5-dihydro-[1,2,4]oxaidiazol-3-yl)-benzoate. Ethyl chloroformate (0.23 mL, 0.26 g, 2 mmol) is added to a solution of 4-(carbomethoxy)benzaldehyde amidoxime (0.38 g, 2 mmol, reference example 90) in pyridine (10 mL) at ambient temperature. The reaction mixture is heated to reflux for 5 hours and the solvent evaporated. The residue is poured into H_2O which is partially evaporated until a preciptate began to appear. The solids are collected, washed with H_2O, air-dried and dried in vacuo to afford the title compound as a white solid; yield 0.25 g (57%); ^{1}H NMR ($CDCl_3$ / DMSO-d_6) d 3.95 (3H, s), 7.73 (2H, d, J = 8.0 Hz), 8.13 (2H, d, J = 8.0 Hz); MS, m/z(EI) 220 (M^+).

Reference Example 90

4-(Carbomethoxy)benzaldehyde amidoxime. Chlorine gas is bubbled through a solution of 4-(Carbomethoxy)benzaldehyde oxime (2.7 g, 0.015 mol, reference example 91) in $CHCl_3$ at 0 °C. The reaction mixture turned green followed by a precipitate. Bubbling is continued until the reaction mixture became homogeneous at which time bubbling is ceased and the vessel sealed. After stirring for an additional 1/2 hour at ambient temperature, nitrogen is bubbled through the reaction mixture to remove excess chlorine. The solvent is evaporated and the residue is dissolved in EtOH (100 mL) to which NH_3 in MeOH (7M, 11mL, 110 mmol) is added. After stirring for 1 hour at ambient temperature, the solvent is evaporated and

the residue is vacuum filtered through a pad of silica gel eluting with 4% MeOH in CH_2Cl_2. Fractions containing only product are combined and concentrated. The residue is triturated with ether to afford the title compound as a white solid; yield 0.69 (24%): ^{1}H NMR ($CDCl_3$ / DMSO-d_6) 3.92 (3H, s), 5.24 (2H,s), 7.77 (2H, d, J = 9.1 Hz), 8.02 (2H, d, J = 9.1 Hz), 9.68 (1H, s); MS, m/z(ion spray) 195 $(M+H)^+$.

Reference example 91

4-(Carbomethoxy)benzaldehyde oxime. Sodium ethoxide (2.9 g, 0.43 mol) is added to a solution of hydroxylamine hydrochloride (3.3 g, 0.048 mol) in EtOH (100 mL). The mixture is filtered to remove the precipitated NaCl and 4-(carbomethoxy)benzaldehyde is added at ambient temperature. After stirring at this temperature for 18 hours, the solvent is evaporated and the residue is triturated with H_2O and air-dried to afford the title compound as a white solid; yield 5.3 g (99%): MS (EI) m/z 180 $(M + H)^+$.

Reference Example 92a

4-[2-(morpholin-4yl-ethylamino)-pyrimidin-4-yl]-benzoic acid. To a solution of 4-[2-chloro-pyrimidin-4-yl]-benzoic acid (234 mg, 1 mmol, reference example 11g) in DMF (or DMSO) (3 mL) is added 2-(morpholin-4-yl)-ethyl amine (275 µL , 2.1 mmol). The resulting mixture was warmed to 80 °C and stirred for 4 h. The reaction mixture was then concentrated under a stream of nitrogen and the residue purified by reverse phase HPLC to give 166 mg of the title compound. ^{1}H NMR (DMSO-d_6) 3.18 (m, 2H), 3.40 (m, 2H), 3.50-3.80 (m, 6H), 3.97 (m, 2H) 7.33 (d, J = 5Hz, 1H), 7.53 (bt, 1H), 8.07 (d, J = 8Hz, 2H), 8.25 (d, J = 8Hz, 2H), 8.49 (d, J = 5Hz, 1H), 9.70 (bs, 1H). MS (ion spray) m/z 329 $(M+H)^+$.

The following compounds were prepared using essentially the same procedure employed in reference example 92a except using the cited amine instead of 2-(morpholin-4-yl)-ethyl amine.

Reference Example 92b

4-[2-(3-dimethylamino-propylamino)-pyrimidin-4-yl]-benzoic acid. Using 3-dimethylamino-propylamine. ^{1}H NMR (CD_3OD) 2.1 (m, 2H), 2.88 (s, 6H), 3.28 (t, J = 7Hz, 2H), 3.65 (bm, 2H), 7.33 (d, J = 5Hz, 1H), 8.15 (d, J = 8Hz, 2H), 8.24 (d, J = 8Hz, 2H), 8.40 (d, J = 5Hz, 1H). MS (ion spray) m/z 301 $(M+H)^+$.

Reference Example 92c

4-[2-(2-dimethylamino-ethyl-methyamino)-pyrimidin-4-yl]-benzoic acid. Using 2-(dimethylamino-ethyl)-methyamine. ^{1}H NMR (CD_3OD) 3.0 (s, 6H), 3.31 (s, 3H), 3.50 (t, J = 7Hz, 2H), 4.15 (t, J = 7Hz, 2H), 7.28 (d, J = 5Hz, 1H), 8.14 (d, J = 8Hz, 2H), 8.22 (d, J = 8Hz, 2H), 8.49 (d, J = 5Hz, 1H). MS (ion spray) m/z 301 $(M+H)^+$.

Reference Example 92d

2-[(4-{4-[2-(3-Cyano -1H-indol-5-yl)-ethylcarbamoyl]-phenyl}-pyrimidin-2-yl)-methyl-amino]-ethanesulfonic acid. Using 2-methylamino-ethyl sulphonic acid and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates.

Reference Example 92e

N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-{2-[methyl-(2(S),3(R),4(R),5(R),6-pentahydroxy-hexyl)-amino]-pyrimidin-4-yl}-benzamide. Using N-methyl-(2(S),3(R),4(R),5(R),6-pentahydroxy-hexyl)-amine and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates.

Reference Example 92f

N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-{2-[methyl-(2(S),3(R),4(S),5(R),6-pentahydroxy-hexyl)-amino]-pyrimidin-4-yl}-benzamide. Using N-methyl-(2(S),3(R),4(S),5(R),6-pentahydroxy-hexyl)-amine and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates.

Reference Example 92g

N-[2-(3-cyano -1H-indol-5-yl)-ethyl]-4-[2-(2-hydroxy-1-hydroxymethyl-ethylamino)-pyrimidin-4-yl]-benzamide. Using 2-hydroxy-1-hydroxymethyl-ethylamine and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates. MS (ion spray) m/z 457 $(M+H)^+$.

Reference Example 92h

2-[(4-{4-[2-(3-Cyano-1H-indol-5-yl)-ethylcarbamoyl]-phenyl}-pyrimidin-2-yl)-methyl-amino]-ethanesulfonic acid. Using 2-(N-methyl-amino)-ethanesulfonic acid and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates.

Reference Example 92i

N-[2-(3-Cyano-1H-indol-5-yl)-ethyl]-4-[2-(3-imidazol-1-yl-propylamino)-pyrimidin-4-yl]-benzamide. Using 3-imidazol-1-yl-propylamine and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates.

Reference Example 92j

N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-{2-[(2-diethylamino-ethyl)-methyl-amino]-pyrimidin-4-yl}-benzamide. Using 2-(diethylamino)-ethyl-methyl-amine and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates.

Reference Example 92k

N-[2-(3-Cyano-1H-indol-5-yl)-ethyl]-4-[2-(2-diisopropylamino-ethylamino)-pyrimidin-4-yl]-benzamide. Using 2-(diisopropylamino)-ethylamine and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates.

Reference Example 92l

N-[2-(3-Cyano-1H-indol-5-yl)-ethyl]-4-[2-(2-dibutylamino-ethylamino)-pyrimidin-4-yl]-benzamide. Using 2-(dibutylamino)-ethylamine and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates.

Reference Example 92m

N-[2-(3-Cyano-1H-indol-5-yl)-ethyl]-4-[2-(3-morpholin-4-yl-propylamino)-pyrimidin-4-yl]-benzamide. Using 3-(morpholin-4-yl)-propylamine and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates.

Reference Example 92n

N-[2-(3-Cyano-1H-indol-5-yl)-ethyl]-4-[2-(3-diethylamino-propylamino)-pyrimidin-4-yl]-benzamide. Using 3-(diethylamino)-propylamine and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates.

Reference Example 92p

N-[2-(3-Cyano-1H-indol-5-yl)-ethyl]-4-[2-(3-piperidin-1-yl-propylamino)-pyrimidin-4-yl]-benzamide. Using 3-(piperidin-1-yl)-propylamine and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates.

Reference Example 92q

N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-(2-{[2-(ethyl-methyl-amino)-ethyl]-methyl-amino}-pyrimidin-4-yl)-benzamide. Using [2-(ethyl-methyl-amino)-ethyl]-methyl-amine and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates.

Reference Example 92r

N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-(5-dimethylamino-pentylamino)-pyrimidin-4-yl]-benzamide. Using 5-dimethylamino-pentylamine (reference example 93a) and and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates. MS (ion spray) m/z 496 $(M+H)^+$.

Reference Example 92s

N-[2-(3-Cyano-1H-indol-5-yl)-ethyl]-4-[2-(5-morpholin-4-yl-pentylamino)-pyrimidin-4-yl]-benzamide. Using 5-(morpholin-4-yl)-pentylamine (reference example 93b) and and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates. MS (ion spray) m/z 538 $(M+H)^+$.

Reference Example 92t

N-[2-(3-Cyano-1H-indol-5-yl)-ethyl]-4-[2-(5-piperidin-1-yl-pentylamino)-pyrimidin-4-yl]-benzamide. Using 5-(piperidin-1-yl)-pentylamine (reference example 93c) and and N-[2-(3-Cyano -1H-indol-5-yl)-

ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates. MS (ion spray) m/z 536 $(M+H)^+$.

Reference Example 92u

N-[2-(3-Cyano-1H-indol-5-yl)-ethyl]-4-[2-(5-pyrrolidin-1-yl-pentylamino)-pyrimidin-4-yl]-benzamide. Using 5-(pyrrolidin-1-yl)-pentylamine (reference example 93d) and and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates. MS (ion spray) m/z 522 $(M+H)^+$.

Reference Example 92v

N-[2-(3-Cyano-1H-indol-5-yl)ethyl]-4-[2-(4-methylpiperazin-1-yl)pyrimidin-4-yl]benzamide. Using N-methyl-piperazine and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates. MS (ion spray) m/z 466 $(M+H)^+$.

Reference Example 92w

4-[(4-{4-[2-(3-Cyano-1H-indol-5-yl)ethylcarbamoyl]phenyl}pyrimidin-2-yl)-methylamino]-butyric acid. Using 4-(methylamino)-butyric acid and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates. MS (ion spray) m/z 483 $(M+H)^+$.

Reference Example 92x

N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl]benzamide. Using trifluoroethanol and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates. MS (ion spray) m/z 466 $(M+H)^+$.

Reference Example 92y

N-[2-(3-Cyano-1H-indol-5-yl)-ethyl]-4-(2-pyrrolidin-1-ylpyrimidin-4-yl)benzamide. Using pyrrolidine and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates. MS (ion spray) m/z 437 $(M+H)^+$.

Reference Example 92z

N-[2-(3-Cyano-1H-indol-5-yl)-ethyl]-4-[2-(2-hydroxymethylpyrrolidin-1-yl)-pyrimidin-4-yl]benzamide. Using 2-(hydroxymethyl)-pyrrolidine and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates. MS (ion spray) m/z 467 $(M+H)^+$.

Reference Example 92aa

N-[2-(3-Cyano-1H-indol-5-yl)-ethyl]-4-[2-(carbamoylmethyl-N-methylamino)-pyrimidin-4-yl]benzamide. Using N-methyl glycine amide and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates. MS (ion spray) m/z 454 $(M+H)^+$.

Reference Example 92ab

N-[2-(3-Cyano-1H-indol-5-yl)ethyl]-4-[2-(6-pyrrolidin-1-ylhexylamino)pyrimidin-4-yl]benzamide. Using 6-pyrrolidin-1-ylhexylamine (reference example 93e) and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates. MS (ion spray) m/z 536 $(M+H)^+$.

Reference Example 92ac

N-[2-(3-Cyano-1H-indol-5-yl)ethyl]-4-[2-(6-piperidin-1-ylhexylamino)pyrimidin-4-yl]benzamide. Using 6-piperidin-1-ylhexylamine (reference example 93f) and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates. MS (ion spray) m/z 550 $(M+H)^+$.

Reference Example 92ad

N-[2-(3-Cyano-1H-indol-5-yl)ethyl]-4-[2-(4-piperidin-1-ylbutylamino)pyrimidin-4-yl]benzamide. Using 4-piperidin-1-ylbutylamine (reference example 93g) and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates. MS (ion spray) m/z 522 $(M+H)^+$.

Reference Example 92ae

N-[2-(3-Cyano-1H-indol-5-yl)ethyl]-4-[2-(4-diethylaminobutylamino)pyrimidin-4-yl]benzamide. Using 4-diethylaminobutylamine (reference example 93h) and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates. MS (ion spray) m/z 510 $(M+H)^+$.

Reference Example 92af

N-[2-(3-Cyano-1H-indol-5-yl)ethyl]-4-[2-(6-morpholin-4-ylhexylamino)pyrimidin-4-yl]benzamide. Using 6-morpholin-4-ylhexylamine (reference example 93i) and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates
MS (ion spray) m/z 552 $(M+H)^+$.

Reference Example 92ag

N-[2-(3-Cyano-1H-indol-5-yl)ethyl]-4-[2-(6-dimethylaminohexylamino)pyrimidin-4-yl]benzamide. Using 6-(dimethylamino)-hexylamine and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates. MS (ion spray) m/z 510 $(M+H)^+$.

Reference Example 92ah

N-[2-(3-Cyano-1H-indol-5-yl)ethyl]-4-[2-(4-dimethylaminobutylamino)pyrimidin-4-yl]benzamide. Using 4-(dimethylamino)-butylamine and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates. MS (ion spray) m/z 482 $(M+H)^+$.

Reference Example 92ai

4-[2-(Bicyclo[2.2.1]hept-2-ylamino)pyrimidin-4-yl]-N-[2-(3-cyano-1H-indol-5-yl)ethyl]benzamide. Using Bicyclo[2.2.1]hept-2-ylamine and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates. MS (ion spray) m/z 477 $(M+H)^+$.

Reference Example 92aj

1-(4-{4-[2-(3-Cyano-1H-indol-5-yl)ethylcarbamoyl]phenyl}pyrimidin-2-yl)pyrrolidine-2-carboxylic acid amide. Using pyrrolidine-2-carboxylic acid amide. and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates. MS (ion spray) m/z 480 $(M+H)^+$.

Reference Example 92ak

N-[2-(3-Cyano-1H-indol-5-yl)ethyl]-4-{2-[(2-hydroxy-ethyl)-N-methylamino]pyrimidin-4-yl}benzamide. Using (2-hydroxy-ethyl)-N-methylamine and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates. MS (ion spray) m/z 441 $(M+H)^+$.

Reference Example 92al

N-[2-(3-cyano-1H-indol-5-yl)-ethyl]-4-(2-morpholin-4-yl-pyrimidin-4-yl)-benzamide. Using morpholine and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates. ^{1}H NMR (DMSO) δ 2.98 (bt, 2H, J = 7Hz); 3.56 (m, 2H); 3.70 (bs, 4H); 3.79 (bs, 4H); 7.18 (d, 1H, J = 9Hz); 7.32 (d, 1H, J = 5Hz); 7.49 (m, 2H); 7.94 (d, 2H, J = 8Hz); 8.22 (m, 3H); 8.50 (d, 1H, J = 5Hz); 8.74 (bt, 1H); 12.20 (bs, 1H). MS (ion spray) m/z 453 $(M+H)^+$.

Reference Example 92am

N-[2-(3-cyano-1H-indol-5-yl)-ethyl]-4-[2-(cyclopropylmethyl-amino)-pyrimidin-4-yl]-benzamide. Using cyclopropylmethyl-amine and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates. ^{1}H NMR (DMSO) δ 0.26 (m, 2H); 0.44 (m, 2H); 3.00 (bt, 2H, J = 7Hz); 3.25 (bs, 2H); 3.56 (m, 2H); 7.20 (m, 2H); 7.36 (bt, 1H); 7.50 (m, 2H); 7.94 (d, 2H, J = 8Hz); 8.29 (m, 3H); 8.38 (d, 1H, J = 5Hz); 8.69 (bt, 1H); 12.15 (bs, 1H). MS (ion spray) m/z 437 $(M+H)^+$.

Reference Example 92an

N-[2-(3-cyano-1H-indol-5-yl)-ethyl]-4-[2-[(2-methoxy-ethyl)-methyl-amino]-pyrimidin-4-yl]-benzamide. Using (2-methoxy-ethyl)-methyl-amine and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates. ^{1}H NMR (DMSO) δ 2.98 (t, 2H, J = 7Hz); 3.22 (s, 3H); 3.28 (s, 3H); 3.58 (m, 4H); 3.85 (m, 2H); 7.21 (m, 2H); 7.50 (m,2H); 7.93 (d, 2H, J = 9Hz); 8.20 (m, 3H); 8.45 (d, 1H, J = 5Hz); 8.69 (bt, 1H); 12.13 (bs, 1H). MS (ion spray) m/z 455 (M+H)$^+$.

Reference Example 92ap

N-[2-(3-cyano-1H-indol-5-yl)-ethyl]-4-[2-(3-hydroxy-propylamino)-pyrimidin-4-yl]-benzamide. Using 3-hydroxy-propylamine and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates. ^{1}H NMR (DMSO) δ 1.73 (t, 2H, J = 7Hz); 2.98 (t, 2H, J = 7Hz); 3.40 (m, 2H); 4.48 (bs, 1H); 7.20 (m, 3H); 7.48 (m, 2H); 7.92 (d, 2H, J = 8Hz); 8.18 (m, 3H); 8.37 (bd, 1H, J = 5Hz); 8.68 (bt, 1H); 12.12 (bs, 1H). MS (ion spray) m/z 441 (M+H)$^+$.

Reference Example 92aq

N-[2-(3-cyano-1H-indol-5-yl)-ethyl]-4-[2-(2-hydroxy-ethyl)-propyl-amino]-pyrimidin-4-yl]-benzamide. Using (2-hydroxy-ethyl)-propyl-amine and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates. ^{1}H NMR (DMSO) δ .90 (t, 3H, J = 7Hz); 1.63 (bd, 2H); 2.98 (t, 2H, J = 7Hz); 3.63 (m, 8H); 4.73 (t, 1H, J = 5Hz); 7.19 (m, 2H); 7.48 (m, 2H); 7.92 (d, 2H, J = 8Hz); 8.19 (m, 3H); 8.43 (d, 1H, J = 5Hz); 8.67 (bt, 1H); 12.11 (bs, 1H). MS (ion spray) m/z 469 (M+H)$^+$.

Reference Example 92ar

N-[2-(3-cyano-1H-indol-5-yl)-ethyl]-4-(2-piperidin-1-yl-pyrimidin-4-yl)-benzamide. Using piperidine and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates. ^{1}H NMR (DMSO) δ 1.6 (m, 6H); 2.98 (m, 2H); 3.55 (m, 2H); 3.84 (m, 4H); 7.19 (m, 2H); 7.49 (m, 2H); 7.93 (d, 2H, J = 8Hz); 8.20 (m, 3H); 8.44 (d, 1H, J = 5Hz); 8.69 (bt, 1H); 12.14 (bs, 1H). MS (ion spray) m/z 451 (M+H)$^+$.

Reference Example 92as

N-[2-(3-cyano-1H-indol-5-yl)-ethyl]-4-[2-(ethyl-methyl-amino)-pyrimidin-4-yl]-benzamide. Using ethylmethylamine and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates. ^{1}H NMR (DMSO) δ 1.15 (t, 3H, J = 7Hz); 2.99 (bt, 2H); 3.17 (s, 3H); 3.56 (m, 2H); 3.73 (m, 2H); 7.20 (m, 2H); 7.50 (m, 2H); 7.94 (d, 2H, J = 7Hz); 8.20 (m, 3H); 8.44 (d, 1H, J = 5Hz); 8.69 (bs, 1H); 12.14 (bs, 1H). MS (ion spray) m/z 425 $(M+H)^+$.

Reference Example 92at

N-[2-(3-cyano-1H-indol-5-yl)-ethyl]-4-[2-(4-hydroxy-piperidin-1-yl)-pyrimidin-4-yl]-benzamide. Using 4-hydroxy-piperidine and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates. ^{1}H NMR (DMSO) δ 1.36 (m, 2H); 1.82 (m, 2H); 2.98 (t, 2H, J = 7Hz); 3.34 (m, 2H); 3.55 (m, 2H); 3.76 (bs, 1H); 4.39 (bd, 2H); 4.75 (bs, 1H); 7.20 (m, 2H); 7.48 (m, 2H); 7.92 (d, 2H, J = 9Hz); 8.20 (m, 3H); 8.45 (d, 1H, J = 5Hz); 8.67 (bt, 1H); 12.12 (bs, 1H). MS (ion spray) m/z 467 $(M+H)^+$.

Reference Example 92au

N-[2-(3-cyano-1H-indol-5-yl)-ethyl]-4-[2-(2,3-dihydroxy-propylamino)-pyrimidin-4-yl]-benzamide. Using 2,3-dihydroxy-propylamine and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates. MS (ion spray) m/z 457 $(M+H)^+$.

Reference Example 92av

N-[2-(3-cyano-1H-indol-5-yl)-ethyl]-4-[2-[(2,3-dihydroxy-propyl)-methyl-amino]-pyrimidin-4-yl]-benzamide. Using 2,3-dihydroxy-propyl-methylamine and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates. MS (ion spray) m/z 471 $(M+H)^+$.

Reference Example 92aw

N-[2-(3-cyano-1H-indol-5-yl)-ethyl]-4-[2-((s)-2-methoxymethyl-pyrrolidin-1-yl)-pyrimidin-4-yl]-benzamide. Using (s)-2-methoxymethyl-pyrrolidine and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates. MS (ion spray) m/z 481 $(M+H)^+$.

Reference Example 92ax

4-[4-[4-[2-(3-cyano-1H-indol-5-yl)-ethylcarbamoyl]-phenyl]-pyrimidin-2-yl]-piperazine-1-carboxylic acid tert-butyl ester. Using piperazine-1-carboxylic acid tert-butyl ester and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates. ^{1}H NMR (DMSO) δ 1.44 (s, 9H); 2.98 (t, 2H, J = 7Hz); 3.45 (bs, 4H); 3.56 (m, 2H); 3.83 (bs, 4H); 7.18 (d, 1H, J = 8Hz); 7.31 (d, 1H, J = 5Hz); 7.48 (d, 1H, J = 8Hz); 7.51 (s, 1H); 7.94 (d, 2H, J = 8Hz); 8.22 (m, 3H); 8.49 (d, 1H, J = 5Hz); 8.70 (bt, 1H); 12.12 (bs, 1H). MS (ion spray) m/z 552 $(M+H)^+$.

Reference Example 92ay

N-[2-(3-cyano-1H-indol-5-yl)-ethyl]-4-[2-[2-(2-oxo-imidazolidin-1-yl)-ethylamino]-pyrimidin-4-yl]-benzamide. Using 2-(2-oxo-imidazolidin-1-yl)-ethylamine and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates. ^{1}H NMR (DMSO) δ 2.96 (bt, 2H); 3.24 (m, 4H); 3.47 (m, 6H); 6.26 (s, 1H); 7.18 (m, 2H); 7.27 (bt, 1H, J = 5Hz); 7.48 (m, 2H); 7.91 (d, 2H, J = 9Hz); 8.19 (m, 3H); 8.36 (bd, 1H); 8.67 (t, 1H, J = 5Hz); 12.10 (bs, 1H). MS (ion spray) m/z 495 $(M+H)^+$.

Reference Example 92az

N-[2-(3-cyano-1H-indol-5-yl)-ethyl]-4-[2-(3-methoxy-propylamino)-pyrimidin-4-yl]-benzamide. Using 3-methoxy-propylamine and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates. ^{1}H NMR (DMSO) δ 1.81 (m, 2H); 2.98 (m, 2H); 3.24 (s, 3H); 3.41 (m, 4H); 3.56 (m, 2H); 7.19 (m, 2H); 7.28 (bs, 1H); 7.50 (m, 2H); 7.92 (m, 2H); 8.18 (m, 3H); 8.38 (bs, 1H); 8.68 (bs, 1H); 12.13 (bs, 1H). MS (ion spray) m/z 455 $(M+H)^+$.

Reference Example 92aaa

N-[2-(3-cyano-1H-indol-5-yl)-ethyl]-4-[2-(2-hydroxy-ethylamino)-pyrimidin-4-yl]-benzamide. Using 2-hydroxy-ethylamine and N-[2-(3-Cyano -1H-indol-5-yl)-ethyl]-4-[2-chloro-pyrimidin-4-yl]-benzamide (reference example 1az) as substrates. ^{1}H NMR (DMSO) δ 2.98 (t, 2H, J = 7Hz); 3.44 (bs, 2H); 3.55 (m, 4H); 4.70 (t, 1H, J = 6Hz); 7.17 (m, 3H); 7.48 (m, 2H); 7.92 (d, 2H, J = 9Hz); 8.18 (m, 3H); 8.38 (d, 1H, J = 5Hz); 8.68 (bt, 1H); 12.12 (bs, 1H). MS (ion spray) m/z 427 $(M+H)^+$.

Reference Example 92aab

4-(2-dimethylamino-pyrimidin-4-yl)-benzoic acid. Using dimethylamine and 4-[2-chloro-pyrimidin-4-yl]-benzoic acid as substrates. MS (ion spray) m/z 244 $(M+H)^+$.

Reference Example 93a

5-Dimethylamino-pentylamine. To a cooled (0°C) solution of lithium aluminum hydride (8 ml, 0.5M in ether) is added, slowly, a solution of 5-(dimethylamino)-pentanenitrile (126 mg, 1 mmol, reference example 94a) in ether (1 mL). On complete addition, the cold bath is removed and stirring continued for 2 h. The reaction mixture is then cooled to 0 °C and quenched by dropwise addition of water (160 mL), sodium hydroxide solution (160 mL, 5M), then a further portion of water (160 mL). The resulting mixture is filtered through celite and the filtrate concentrated under reduced pressure to give an oil which is used without further purification.

The following compounds are prepared using essentially the same procedure as used in reference example 93a, except using the cited nitrile in place of 5-(dimethylamino)-pentanenitrile.

Reference Example 93b

5-(morpholin-4-yl)-pentylamine. Using 5-(morpholino-4-yl)-pentanenitrile (reference example 94b) as substrate.

Reference Example 93c

5-(piperidin-1-yl)-pentylamine. Using 5-(piperidin-1 -yl)-pentanenitrile (reference example 94c) as substrate.

Reference Example 93d

5-(pyrrolidin-1-yl)-pentylamine. Using 5-(pyrrolidin-1 -yl)-pentanenitrile (reference example 94d) as substrate.

Reference Example 93e

6-Pyrrolidin-1-ylhexylamine. Using 6-Pyrrolidin-1-ylhexanenitrile (reference example 94e) as substrate. MS (ion spray) m/z 171 $(M+H)^+$.

Reference Example 93f

6-piperidin-1-ylhexylamine. Using 6-Piperidin-1-ylhexanenitrile (reference example 94f) as substrate. MS (ion spray) m/z 185 $(M+H)^+$.

Reference Example 93g

4-piperidin-1-ylbutylamine. Using 4-Piperidin-1-ylbutanenitrile (reference example 94g) as substrate. MS (ion spray) m/z 157 $(M+H)^+$.

Reference Example 93h

4-(diethylamino)-butylamine. Using 4-(diethylamino)-butanenitrile (reference example 94h) as substrate. MS (ion spray) m/z 145 $(M+H)^+$.

Reference Example 93i

6-morpholin-4-ylhexylamine. Using 6-morpholin-4-ylhexanenitrile (reference example 94i) as substrate. MS (ion spray) m/z 187 $(M+H)^+$.

Reference Example 94a

5-(dimethylamino)-pentanenitrile. A mixture of dimethylamine (4 mL, 40% in water) and 5-bromo-pentanenitrile (2.3 mL, 20 mmol) is stirred for 24 h. The resulting reaction mixture is diluted with sodium hydroxide solution (10 mL, 5M) and extracted with ether. The ether extract is dried over K_2CO_3 and concentrated under reduced pressure to give an oil (1.5g) which is used without further purification.

The following compounds are prepared using essentially the same procedure as used in reference example 94a, except using a solution of the cited amine (2 eq.) in benzene (4 mL) in place of dimethylamine in water.

Reference Example 94b

5-(morpholino-4-yl)-pentanenitrile. Using morpholine as substrate gives 3.5g of oil.

Reference Example 94c.

5-(Piperidin-1-yl)-pentanenitrile. Using piperidine as substrate gives 3.29g of oil.

Reference Example 94d

5-(pyrrolidin-1-yl)-pentanenitrile. Using pyrrolidine as substrate gives 3.32g of oil.

Reference Example 94e.

6-Pyrrolidino-hexanenitrile. Using pyrrolidine and 6-chloro-hexanenitrile as substrates. MS (ion spray) m/z 167 $(M+H)^+$.

Reference Example 94f

6-Piperidin-1-ylhexanenitrile. Using piperidine and 6-chloro-hexanenitrile as substrates. MS (ion spray) m/z 181 $(M+H)^+$.

Reference Example 94g

4-Piperidin-1-ylbutanenitrile. Using piperidine and 4-chloro-butanenitrile as substrates. MS (ion spray) m/z 153

Reference Example 94h

4 (diethylamino)-butanenitrile. Using diethylamine and 4-chloro-butanenitrile as substrates. MS (ion spray) m/z 141.

Reference Example 94i

6-morpholin-4-ylhexanenitrile. Using morpholine and 6-chloro-hexanenitrile as substrates. MS (ion spray) m/z 183.

Reference Example 95

4-(2-oxo-hexahydro-pyrimidin-5-yl)-benzoic acid methyl ester.

To a solution of 4-(2-oxo-pyrimidin-5-yl)-benzoic acid methyl ester (761 mg, 3.3 mmol, reference example 19c) in DMF (20 mL) and methanol (5 mL) was added Pd on carbon (250 mg, 10% w/w). The resulting mixtured was stirred under an atmosphere of hydrogen gas for 3 h. This mixture is purged with nitrogen gas then filtered through celite. The filtrate is concentrated and the residue purified by flash chromatography (eluting with 5% methanol in dichloromethane) to give the title compound (421 mg) as a white solid. ^1H NMR (CD_3OD) 3.28 (m, 1H), 3.47 (d, J = 7Hz, 4H), 3.90 (s, 3H), 7.44 (d, J = 8Hz, 2H), 7.90 (d, J = 8Hz. 2H).

Reference Example 96

4-(2-oxo-pyrimidin-5-yl)-benzaldehyde. To a solution of 4-(2-[t-butyldiphenylsilyloxy]-pyrimidin-5-yl)-benzaldehyde dimethyl ketal (2.28g, 4.7 mmol reference example 97a) in THF (10 mL) is added hydrochloric acid (10 mL, 2M). The resulting mixture is stirred for 1 h. This mixture is concentrated to about half its original volume under reduced pressure. The solid is filtered then washed with water and ether to give the title compound (1.1g) as a white solid. ^{1}H NMR (DMSO) δ 7.88 (d, J = 8Hz, 2H), 7.95 (d, J = 8Hz, 2H), 8.79 (s, 2H), 9.99 (s, 1H).

Reference Example 97a

4-(2-[t-butyldiphenylsilyloxy]-pyrimidin-5-yl)-benzaldehyde dimethyl ketal. To a cooled (-78 °C) solution of 4-bromo-benzaldehyde dimethyl ketal (2.31g 10 mmol) in THF (30 mL) is added, dropwise, n-butyl lithium (4.4 mL, 2.5 M in hexanes). On complete addition, the reaction mixture is stirred for 5 min then $ZnCl_2$ solution (20 mL, 0.5M in THF) is added. The cold bath is removed and stirring continued for 5 min. then a solution comprising of 5-bromo-(2-[t-butyldiphenylsilyloxy]-pyrimidine (4.13g, 10 mmol) and $(Ph_3P)_4Pd$ (1.1g, 1 mmol) in THF (20 mL) is added. This mixture is warmewd to 60 °C and stirred at this temperature for 2h. The resulting solution is cooled to room temperature, diluted with ether, washed, sequentially, with 5% aqueous ammonia solution, water and brine, dried over $MgSO_4$ and concentrated. The residue is purified by flash chromatography (eluting with 10% ethyl acetate, 10% dichloromethane in hexanes) to give 2.28g of the title compound as an oil. ^{1}H NMR ($CDCl_3$) δ 1.18 (s, 9H), 3.35 (s, 6H), 5.44 (s, 1H), 7.38 (m, 6H), 7.44 (d, J = 8Hz, 2H), 7.53 (d, J = 8Hz, 2H), 7.8 (m, 4H), 8.59 (s, 2H).

Reference Example 97b

4-(3-Methoxycarbonyl-phenyl)-Benzaldehyde. Using essentially the same procedure used in reference example 97a except using methyl 3-bromo-benzoate as substrate in place of 5-bromo-(2-[t-butyldiphenylsilyloxy]-pyrimidine and using the following modified workup: On cooling to room temperature, the reaction mixture is diluted with ethyl acetate and washed with hydrochloric acid (2M) then brine, dried over $MgSO_4$ and concentrated. The residue is purified by flash chromatography (eluting with 20% ethyl acetate / 5% dichloromethane in hexanes) to give the title compound as a yellow solid. MS (EI) m/z 240 $(M)^+$.

Reference Example 97c

4-(2-Methoxycarbonyl-phenyl)-Benzaldehyde. Using essentially the same procedure used in reference example 97b except using methyl 2-iodo-benzoate as substrate in place of methyl 3-bromo-benzoate. MS (EI) m/z 240 $(M)^+$.

Reference Example 98

4-(1,3-Dimethyl-2-oxo-hexahydro-pyrimidin-5-yl)-benzoic acid methyl ester. To a cooled (0°C) suspension of sodium hydride dispersion (60% in mineral oil (88mg, 2.2 mmol) in THF (3 mL) is added a solution comprising of 4-(2-oxo-hexahydro-pyrimidin-5-yl)-benzoic acid methyl ester (236 mg, 1 mmol, reference example 95) and methyl iodide (300 μL, 5 mmol) in DMF (4 mL). The resulting mixture is stirred for 16 h. then quenched with water, diluted with ethyl acetate, washed with water and brine, dried over $MgSO_4$ and concentrated to give the title compound (255 mg) as a tan solid. ^1H NMR ($CDCl_3$) δ 2.98 (s, 6H), 3.37-3.53 (m, 5H), 3.93 (s, 3H), 7.32 (d, J = 8Hz, 2H), 8.01 (d, J = 8Hz, 2H). MS (ion spray) m/z 263 $(M+H)^+$.

Reference Example 99a

Biphenyl-3,4'-dicarboxylic acid 4'-{[2-(3-Cyano-1H-indol-5-yl)-ethyl]-amide} 3-[(2-methoxy-ethyl)-amide]. To a solution of Biphenyl-3,4'-dicarboxylic acid 4'-{[2-(3-cyano-1H-indol-5-yl)-ethyl]-amide} (102 mg, 0.25 mmol, reference example 17h) in dichloromethane / DMF (3:1, 1 mL total volume) is added TBTU (88 mg, 0.27 mmol) and diisopropylethylamine (48 mL, 0.28 mmol). The resulting solution is stirred for 2 min. then a further portion of diisopropylethylamine (48 mL) and 2-methoxy-ethylamine (44 mL) is added. This solution is stirred for 35 min. then concentrated under reduced pressure. The residue is suspended in dichloromethane and filtered. The solid is washed with dichloromethane / methanol (3:1) then dried under vacuum to give 121 mg of the title compound. MS (ion spray) m/z 467 $(M+H)^+$.

Reference Example 99b

3'-(Morpholine-4-carbonyl)-biphenyl-4-carboxylic acid [2-(3-cyano-1H-indol-5-yl)-ethyl]-amide. Using essentially the same procedure used in reference example 99a, except using morpholine as substrate in place of 2-methoxy-ethylamine. MS (ion spray) m/z 479 $(M+H)^+$.

Reference Example 99c

Biphenyl-3,4'-dicarboxylic acid 4'-{[2-(3-cyano-1H-indol-5-yl)-ethyl]-amide} 3-[(2-morpholin-4-yl-ethyl)-amide]. Using essentially the same procedure used in reference example 99a, except using 2-(morpholin-4-yl)-ethylamine as substrate in place of 2-methoxy-ethylamine. MS (ion spray) m/z 522 $(M+H)^+$.

Reference Example 99d

Biphenyl-2,4'-dicarboxylic acid 4'-{[2-(3-cyano-1H-indol-5-yl)-ethyl]-amide} 2-[(3-diethylamino-propyl)-amide] . Using essentially the same procedure used in reference example 99a, except using 3-(diethylamino)-propylamine and Biphenyl-2,4'-dicarboxylic acid 4'-{[2-(3-cyano-1H-indol-5-yl)-ethyl]-amide} (reference example 17i) as substrates. MS (ion spray) m/z 522 $(M+H)^+$.

Reference Example 99e

Biphenyl-2,4'-dicarboxylic acid 4'-{[2-(3-cyano-1H-indol-5-yl)-ethyl]-amide} 2-[(3-morpholin-4-yl-propyl)-amide]. Using essentially the same procedure used in reference example 99a, except using 3-(morpholin-4-yl)-propylamine and Biphenyl-2,4'-dicarboxylic acid 4'-{[2-(3-cyano-1H-indol-5-yl)-ethyl]-amide} (reference example 17i) as substrates. MS (ion spray) m/z 536 $(M+H)^+$.

Reference Example 99f

Biphenyl-2,4'-dicarboxylic acid 4'-{[2-(3-cyano-1H-indol-5-yl)-ethyl]-amide} 2-[(3-piperidin-1-yl-propyl)-amide]. Using essentially the same procedure used in reference example 99a, except using 3-(piperidin-1-yl)-propylamine and Biphenyl-2,4'-dicarboxylic acid 4'-{[2-(3-cyano-1H-indol-5-yl)-ethyl]-amide} (reference example 17i) as substrates. MS (ion spray) m/z 534 $(M+H)^+$.

Reference Example 99g

Biphenyl-2,4'-dicarboxylic acid 4'-{[2-(3-cyano-1H-indol-5-yl)-ethyl]-amide} 2-[(4-dimethylamino-butyl)-amide]. Using essentially the same procedure used in reference example 99a, except using 4-(dimethylamino)-butylamine and Biphenyl-2,4'-dicarboxylic acid 4'-{[2-(3-cyano-1H-indol-5-yl)-ethyl]-amide} (reference example 17i) as substrates. MS (ion spray) m/z 508 $(M+H)^+$.

Reference Example 99h

Biphenyl-2,4'-dicarboxylic acid 4'-{[2-(3-cyano-1H-indol-5-yl)-ethyl]-amide} 2-[(2,3-dihydroxy-propyl)-methyl-amide]. Using essentially the same procedure used in reference example 99a, except using (2,3-dihydroxy-propyl)-methyl-amine and Biphenyl-2,4'-dicarboxylic acid 4'-{[2-(3-cyano-1H-indol-5-yl)-ethyl]-amide} (reference example 17i) as substrates. MS (ion spray) m/z 497 $(M+H)^+$.

Reference example 99i

Biphenyl-2,4'-dicarboxylic acid 4'-{[2-(3-cyano-1H-indol-5-yl)-ethyl]-amide} 2-[(2,3-dihydroxy-propyl)-amide]. Using essentially the same procedure used in reference example 99a, except using 2,3-dihydroxy-propyl-amine and Biphenyl-2,4'-dicarboxylic acid 4'-{[2-(3-cyano-1H-indol-5-yl)-ethyl]-amide} (reference example 17i) as substrates. MS (ion spray) m/z 497 $(M+H)^+$.

Reference Example 100a

N-[2-(3-Cyano-1H-indol-5-yl)-ethyl]-4-[2-(2-methoxyethoxy)-pyrimidin-4-yl]benzamide. To a solution of 2-methoxyethanol (0.118 mL, 1.50 mmoles) in DMSO (5 mL) was added sodium hydride (Aldrich, 60% dispersion, 0.0720g, 1.80 mmoles), followed by stirring until H_2 evolution ceased (~ 15 minutes). One milliliter of this alkoxide stock solution was added to N-[2-(3-Cyano-1H-indol-5-yl)-ethyl]-4-[2-chloropyrimidin-4-yl]benzamide (0.147g, 0.249 mmoles, reference example 1az), followed by heating (60°C). After two hours, another 0.5 mL of the alkoxide stock solution was added. After two more hours, the reaction was quenched with water (40 mL) and the resulting precipitate collected by filtration. The precipitate was washed with water and CH_2Cl_2 and dried under vacuum to give the product as a white solid. MS (ion spray) m/z 442 $(M+H)^+$.

The following compounds were prepared using essentially the same procedure used in reference example 100a except using the cited alcohol in place of 2-methoxyethanol.

Reference Example 100b

N-[2-(3-Cyano-1H-indol-5-yl)ethyl]-4-[2-(1-carbamoylethoxy)pyrimidin-4-yl]benzamide. Using 2-hydroxy-propionamide as substrate. MS (ion spray) m/z 455 $(M+H)^+$.

Reference Example 100c

N-[2-(3-Cyano-1H-indol-5-yl)ethyl]-4-[2-(6-dimethylaminohexyloxy)pyrimidin-4-yl]benzamide. Using 6-dimethylaminohexanol as substrate. MS (ion spray) m/z 511 $(M+H)^+$.

Reference Example 100d

N-[2-(3-Cyano-1H-indol-5-yl)ethyl]-4-[2-(2-oxopiperidin-3-yloxy)pyrimidin-4-yl]benzamide. Using 2-hydroxy-valerolactam as substrate. MS (ion spray) m/z 481 $(M+H)^+$.

Reference Example 100e

N-[2-(3-Cyano-1H-indol-5-yl)ethyl]-4-[2-(2-pyrrolidin-1-yl-ethoxy)pyrimidin-4-yl]benzamide. Using 2-(pyrrolidin-1-yl)-ethanol as substrate. MS (ion spray) m/z 481 $(M+H)^+$.

Reference Example 100f

N-[2-(3-Cyano-1H-indol-5-yl)ethyl]-4-[2-(2-dimethylaminoethoxy)pyrimidin-4-yl]benzamide. Using 2-(dimethylamino)-ethanol as substrate. MS (ion spray) m/z 455 $(M+H)^+$.

Reference Example 101a

4-(3-[2-Dimethylaminoethoxy]phenyl)benzoic acid. Stirred a solution of 3-(2-Dimethylaminoethoxy)phenyl iodide (0.495g, 1.70 mmoles), 4-carboxybenzeneboronic acid (Lancaster, 0.282g, 1.70 mmoles), and sodium

carbonate (0.360g, 3.40 mmoles) in 1:1 H_2O: AcCN (20 mL) under vacuum for five minutes, followed by the addition of tetrakis(triphenylphosphine)palladium (0) (0.170g). The reaction mixture was heated (90°C) for three hours, and the catalyst was filtered off through Celite. The effluent was concentrated slightly to remove the AcCN, and the resulting aqueous solution was acidified with 2N HCl and purified on an HPLC to yield 0.462g of the title compound as the TFA salt. MS (ion spray) m/z 286 $(M+H)^+$.

The following compounds were prepared using essentially the same procedure used in reference example 101a except using the specified aryl halide in place of 3-(2-dimethylaminoethoxy)phenyliodide.

Reference Example 101b

4-(1-Oxypyridin-2-yl)benzoic acid. Using 2-bromo-pyridine-N-oxide. MS (ion spray) m/z 216 $(M+H)^+$.

Reference Example 101c

4-(2-[2-Dimethylaminoethoxy]phenyl)benzoic acid. Using 2-(2-Dimethylaminoethoxy]phenyl-iodide as substrate. MS (ion spray) m/z 286 $(M+H)^+$.

Reference Example 101d

4-(2-[3-Dimethylaminopropoxy]phenyl)benzoic acid. Using 2-[3-Dimethylaminopropoxy]phenyl iodide as substrate. MS (ion spray) m/z 300 $(M+H)^+$.

Reference Example 101e

4-(3-[3-Dimethylaminopropoxy]phenyl)benzoic acid. Using 3-[3-Dimethylaminopropoxy]phenyl iodide as substrate. MS (ion spray) m/z 300 $(M+H)^+$.

Reference Example 101f

4-(1-Oxypyridin-3-yl)benzoic acid. Using 3-bromo-pyridine-N-oxide as substrate.

Reference example 102a

4-[[4-(4-methoxycarbonyl-phenyl)-pyridin-2-ylmethyl]-carbamoyl]-piperidine-1-carboxylic acid tert-butyl ester. To a solution of piperidine-1,4-dicarboxylic acid mono-tert-butyl ester (275 mg, 1.2 mmol) in CH_2Cl_2 (2ml) was added diisopropylethylamine (0.23 ml, 1.32 mmol). The resulting solution was stirred for 5 minutes then TBTU (337 mg, 1.26 mmol) was added and stirred for 20 minutes. To the reaction mixture was added a solution of 4-(2-aminomethyl-pyridin-4-yl)-benzoic acid methyl ester trifluoroacetic acid salt (356 mg, 1 mmol, reference example 103a) and diisopropylethylamine (0.192 ml, 1.1 mmol) in CH_2Cl_2 (2 ml). The reaction mixture was stirred 45 minutes then concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with 40% ethyl acetate / 10% methanol / hexanes) to give 455 mg of product as a white foam. MS (ion spray) m/z 454 $(M+H)^+$.

Reference Example 102b

Using essentially the same procedure used to prepare reference example 102a except using acetic acid as substrate in place of piperidine-1,4-dicarboxylic acid mono-tert-butyl ester, there is prepared 4-[2-(acetylamino-methyl)-pyridin-4-yl]-benzoic acid methyl ester. MS (ion spray) m/z 285 $(M+H)^+$.

Reference Example 103a

4-(2-aminomethyl-pyridin-4-yl)-benzoic acid methyl ester trifluoroacetic acid salt. To a solution of 4-[2-(tert-butoxycarbonylamino-methyl)-pyridin-4-yl]-benzoic acid methyl ester (1.96 g, 5.72 mmol, reference example 56) in CH_2Cl_2 (19 ml) was added TFA (6 ml). The reaction solution was stirred 3 hrs then concentrated under reduced pressure. The residue was purified by trituration with ether. The solids were collected by filtration, washed with ether and dried under vacuum to give 1.68 g of product. MS (EI) m/z 243 $(M+H)^+$.

Reference Example 103b

Ethyl 4-(1-[carboxymethyl]-6-oxo-1,6-dihydropyridin-3-yl)benzoate. Prepared using essentially the same procedure used to prepare reference example 103a except using Ethyl 4-{1-[(tert-butoxycarbonyl)methyl]-6-oxo-1,6-dihydropyridin-3-yl}benzoate (reference example 85b). MS (ion spray) m/z 302 $(M+H)^+$.

Reference Example 104

Allyl 4-(2-oxo-2H-pyridin-5-yl)benzoate. To a solution of ethyl 4-(2-oxo-2H-pyridin-5-yl)benzoate (1.24g, 5.10 mmoles, reference example 36f) in allyl alcohol (50 mL) was added titanium (IV) isopropoxide. The resulting mixture was heated to 70°C for seven hours at which point more titanium (IV) isopropoxide (3 mL) was added. After 18 hours the heat was removed and 1N HCl sloution (50 mL) was added followed by extraction with CH_2Cl_2 (200 mL). The organic layer was isolated and concentrated to give the title compound in quantitative yield. MS (ion spray) m/z 256 $(M+H)^+$.

Reference Example 105

4-[2-amino-1,1-dimethyl-ethyl]-N-[2-(3-cyano-1H-indol-5-yl)-ethyl]-benzamide. To a solution of (2-[4-[2-(3-cyano-1H-indol-5-yl)-ethylcarbamoyl]-phenyl]-2-methyl-propyl)-carbamic acid tert-butyl ester (1.16 g, 2.5 mmol) (prepared using the procedure of reference example 1w) in CH_2Cl_2 (8 ml) was added TFA (1.6 ml) and the reaction stirred 2 hrs. Water (50 µL) was add-ed and the reaction concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with 10% 7M NH_3 in CH_3OH / CH_2Cl_2) to give 808 mg of product. MS (ion spray) m/z 361 $(M+H)^+$.

Reference Example 106

N-[2-(3-cyano-1H-indol-5-yl)-ethyl]-4-(2-methanesulfonylamino-1,1-dimethyl-ethyl)-benzamide. To a solution of 4-[2-amino-1,1-dimethyl-ethyl]-N-[2-(3-cyano-1H-indol-5-yl)-ethyl]-benzamide (97 mg, 0.27 mmol) (reference example 105) in CH_2Cl_2 (1 ml) was added pyridine (24 µL, 0.30 mmol) and methane-sulfonyl chloride (23 µL, 0.30 mmol). The reaction was stirred for 5 min then concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with 8% 7M NH_3 in CH_3OH / CH_2Cl_2 to give 95 mg of product. MS (ion spray) m/z 439 $(M+H)^+$.

Reference Example 107a

N-[2-(3-Cyano-1H-indol-5-yl)-ethyl]-4-(1,1-dimethyl-2-ureido-ethyl)-benzamide. To a solution of 4-[2-amino-1,1-dimethyl-ethyl]-N-[2-(3-cyano-1H-indol-5-yl)-ethyl]-benzamide (90 mg, 0.25 mmol) (reference

example 105) in 1,4-dioxane (1 ml) was added trimethylsilyl isocyanate (68 µL, 0.50 mmol). The resulting mixture is stirred for 16h. The precipitated solids are collected by vacuum filtration, washed with a small volume of CH_2Cl_2 and dried under high vacuum to give 99 mg of product. MS (ion spray) m/z 404 $(M+H)^+$.

Reference Example 107b

N-[2-(3-Cyano-1H-indol-5-yl)-ethyl]-4-[2-(3-ethyl-ureido)-1,1-dimethyl-ethyl]-benzamide. Prepared using essentially the same procedure used in reference example 107a except using ethyl isocyanate as substrate. MS (ion spray) m/z 432 $(M+H)^+$.

Reference Example 107c

4-(1-carbamoyl-piperidin-4-yl)-benzoic acid Prepared using essentially the same procedure used in reference example 107a except using 4-(piperidin-4-yl)-benzoic acid (reference example 109) as substrate.

Reference Example 108

4-(2-dimethylamino-3,4,5,6-tetrahydro-pyrimidin-4-yl)-benzoic acid. To a solution of 4-(2-dimethylamino-pyrimidin-4-yl)-benzoic acid (275 mg, 1.13 mmol reference example 92aab) in H_2O (13 ml) was added conc HCl (212 µL, 2.54 mmol) followed by 10% palladium on carbon (366 mg). The resulting mixture was stirred under H_2 for 2.5hrs. The mixture was filtered through a celite pad to remove the catalyst, using CH_2Cl_2 as a wash. The filtrate was concentrated under reduced pressure to give 260 mg of product as the HCl salt. MS (ion spray) m/z 248 $(M+H)^+$.

Reference Example 109

4-(Piperidin-4-yl)-benzoic acid. To the sodium salt of 4-pyridine benzoic acid (500 mg, 2.25 mmol) suspended in 20% AcOH/MeOH (20 ml) was added PtO_2 (250 mg) and the mixture was hydrogenated at 50 psi with agitation (Parr) for 4 h. The solution was filtered through celite, washed with MeOH (3 x 5 ml), evaporated with hexane (4x) to azeotrope the acetic acid. TLC of the crude ($EtOH/H_2O/NH_4OH$ 10:1:1) shows no starting material, but did show 2 more polar spots. After evaporation from hexane, the white solid

(596 mg crude, still with residual HOAc) was dried in a vacuum overnight, and used without further purification in subsequent steps. MS m/z $[M+H]^+$.

Reference Example 110

Preparation of 4-(1-acetyl-piperidin-4-yl)-benzoic acid . To a solution of 4-piperidin-4-yl)-benzoic acid (102 mg, 0.5 mmol, reference example 109) dissolved in pyridine (2 mL) was added acetic anhydride (255 mg, 2.5 mmol) and the reaction stirred overnight at room temperature. The reaction was concentrated in vacuo and residual pyridine partially removed by azeotroping with dichloromethane/methanol 1:1. The crude product was then washed with dichlormethane and the solvent decanted to yield a white solid residue (61 mg, 49%) 4-(1-acetyl-piperidin-4-yl)-benzoic acid. ^{1}H NMR (CD_3OD): δ 7.89 (d, 2H); 7.27 (d, 2H); 4.65 (d, 1H); 4.03 (d, 1H); 3.21 (dt, 2H); 2.68-2.88 (m, 2H); 1.93 (s, 3H); 1.85-2.04 (m, 2H); 1.50-1.75 (m, 3H). MS m/z 248 (M+H)+.

Reference Example 111

4-(1-methyl-piperdin-4-yl)-benzoic acid. 4-piperidin-4yl-benzoic acid (110 mg, 0.54 mmol, reference example 109) was added to paraformaldehyde (180 mg, 6 mmol) in MeOH (10 mL) and $NaCNBH_3$ (120 mg, 1.94 mmol). The reaction was stirred at room temperature for 4 days, at which time HPLC shows no remaining starting material. The solution was acidified to pH 2 with concentrated HCl, evaporated, dissolved in water (20 mL), and extracted with ether (3 x 20 mL). Then the solution was brought to pH 12 with KOH pellets, extracted with dichloromethane (3 x 20 mL) and finally brought to pH5 with acetic acid. The mixture was lyophilized and the solid was extracted with MeOH (3 x 15 mL). The combined methanol extracts were evaporated and the residue chromatographed (reverse-phase HPLC, C18 column, 10-100% CH_3CN/water) to yield, after lyophilization, 72 mg of the desired product (61 %). ^{1}H NMR (CD_3OD): δ 7.98 (d, 2H), 7.38 (d, 2H), 3.60 (m, 2H), 3.18 (t, 2H), 2.94 (s, 3H), 2.85 - 2.95 (m, 2H), 2.08 - 2.18 (m, 2H), 1.90 - 2.02 (m, 2H). MS (ion spray) m/z 220 ($M+H^+$). > 98% pure by analytical HPLC.

Reference Example 112

4-(1-oxo-1-methyl-piperidin-4-yl)-benzoic acid. 4-(1-methyl-piperidin-4-yl)-benzoic acid (47 mg, 0.21 mmol, reference example 111) dissolved in $CHCl_3$ (3 mL) was added to mCPBA (60 mg). After 3 h, HPLC

showed only 1 peak (9 min), which was different from the starting material. The solvent was evaporated and the crude product was partially purified by reverse-phase HPLC (C-18 column, 10-100% CH_3CN/water) to yield the product 4-(1-oxo-1-methyl-piperidin-4-yl)-benzoic acid. (28 mg, 56%) as a solid. ^1H NMR (CD_3OD): δ 7.98 (d, 2H), 7.42 (d, 2H), 3.72-3.88 (m, 4H), 3.58 (s, 3H), 2.91-3.02 (m, 2H), 2.28-2.42 (m, 2H), 2.01-2.07 (m, 2H). MS (ion spray) m/z 236 $[M+H]^+$. > 92% pure by analytical HPLC.

Reference Example 113a

4-(4-Dimethylamino-piperidin-1-yl)-benzoic acid. 280 mg (1.22 mmol) of 4-(4-dimethylamino-piperidin-1-yl)-benzonitrile (reference example 114a) was dissolved in 2 ml of acetic acid, 4ml of 6 N HCl was added and the mixture stirred with reflux for 16 h. After cooling 20 ml of water was added and extracted with DCM (3x). The pH of the aqueous phase was adjusted to 5 with KOH pellets, white solid precipitated which was filtered off, washed and dried to give 257 mg of the title compound (85 % yield). ^1H NMR ($CDCl_3$): δ 7.88 (dd, 2H), 6.98 (dd, 2H), 4.09 (d, 2H), 3.42 (m, 1H), 3.29 (t, 2H), 2.90 (s, 6H), 2.89-2.96 (m, 2H), 2.18 (m, 2H), 1.80 (dq, 2H). MS (ion spray) m/z 249 (M+H)+. 90 % pure by analytical HPLC.

Reference Example 113b

4-(4-Amino-piperidin-1-yl)-benzoic acid. Prepared using essentially the same procedure used in reference example 114a except using 4-(4-Amino-piperidin-1-yl)-benzonitrile (reference example 114b) as substrate. MS (ion spray) m/z 221 (M+H)+.

Reference Example 113c

4-[4-(2-dimethylamino-ethyl-amino)-piperidin-1-yl]-benzoic acid. Prepared using essentially the same procedure used in reference example 114a except using 4-[4-(2-dimethylamino-ethyl-amino)-piperidin-1-yl]-benzonitrile (reference example 114c) as substrate. MS (ion spray) m/z 292 (M+H)+.

Reference Example 113d

4-(4-hydroxy-piperidin-1-yl)-benzoic acid Prepared using essentially the same procedure used in reference example 114a except using 4-[4-(hydroxy)-piperidin-1-yl]-benzonitrile (reference example 122). MS (EI) m/z 221 (M^+)

Reference Example 114a

4-(4-Dimethylamino-piperidin-1-yl)-benzonitrile. A mixture of 4-(4-oxo-piperidin-1-yl)-benzonitrile (100 mg, 0.5 mmol, reference example 116) dimethylamine hydrochloride (408 mg, 5 mmol) and $NaCNBH_3$ (25 mg, 0.4 mmol) was dissolved in MeOH (7 mL) and stirred at room temperature overnight. After 24 h, additional $NaCNBH_3$ (24 mg, 0.38 mmol) was added and the mixture was stirred overnight at room temperature. The pH of the mixture was adjusted to pH 2 with concentrated HCl and extracted with Et_2O (3x). The aqueous phase was adjusted to pH 10 with KOH pellets, and extracted (3x) with Et_2O. The latter combined organic phases were washed with brine, dried with Na_2SO_4, filtered and evaporated. The crude material was taken into the next step without further purification. ^1H NMR ($CDCl_3$): δ 7.44 (d, 2H), 6.83 (d, 2H), 3.86 (m, 2H), 2.86 (dt, 2H), 2.32-2.38 (m, 1H), 2.28 (s, 6H), 1.92 m(m, 2H), 1.54 (dq, 2H). MS (EI) m/z 229 (M+H)+.

Reference Example 114b

4-(4-Amino-piperidin-1-yl)-benzonitrile. Prepared using essentially the same procedure used in reference example 114a except using NH_4OAc as substrate in place of dimethylamine hydrochloride. ^1H NMR ($CDCl_3$): δ 7.45 (d, 2H), 6.84 (d, 2H), 3.80 (d, 3H), 2.92 (m, 2H), 1.92 (d, 2H), 1.28-1.46 (m, 2H). MS (ion spray) m/z 202 (M+H)+.

Reference Example 114c

4-[4-(2-dimethylamino-ethyl-amino)-piperidin-1-yl]-benzonitrile. Prepared using essentially the same procedure used in reference example 114a except using N,N-dimethylethylene diamine as substrate in place of dimethylamine hydrochloride. ^1H NMR ($CDCl_3$): d 7.45 (d, 2H), 6.84 (d, 2H), 3.27 (m, 1H), 2.94 (t, 2H), 2.73 (m, 2H), 2.39 (t, 2H), 2.21 (s, 6H), 1.94 (dd, 2H), 1.62 (brs, 2H), 1.43 (q, 2H). MS (ion spray) m/z 273 (M+H)+.

Reference Example 114d

Methyl 4-(1-methyl-piperidin-4-yloxy)-benzoate. Prepared using essentially the same procedure used in reference example 114a except using formaldehyde and Methyl 4-(piperidin-4-yloxy)-benzoate (reference example 123) as substrates. ^{1}H NMR ($CDCl_3$): d 8.01 (d, 2H), 6.91 (d, 2H), 4.80 (s, 1H), 3.89 (s, 3H), 3.35 (brd, 2H), 3.13 (q, 2H), 2.80 (d, 3H), 2.65 (t, 2H), 2.18 (d, 2H). MS (ion spray) m/z 250 (M+H)+.

Reference Example 115

4-(4-[tert-butoxycarbonylamino]-piperidin-1-yl)-benzoic acid. To a solution of of 4-(4-amino piperidin-1-yl)-benzoic acid (242 mg, 1.1 mmol, reference example 113b) dissolved in 5 ml of dichloromethane is added 300 mg of triethylamine and 305 mg (1.4 mmol) of Boc_2O . The resulting mixture is stirred at room temperature for 16 h. Solvent is evaporated and the mixture separated by chromatography on silica with DCM/MeOH (10%) to give 214 mg of the title compound. ^{1}H NMR (CD_3OD): δ 7.85 (d, 2H), 6.94 (d, 2H), 3.85 (m, 2H), 3.65 (m, 1H), 2.93 (m, 2H), 1.91 (m, 2H), 1.49 (s, 9H), 1.32-1.40 (m, 2H). MS (EI) m/z 320 (M+).

Reference Example 116

4-(4-oxo-piperidin-1-yl)-benzonitrile. To 4-(1,4-dioxa-8-aza-spiro[4.5] dec-8-yl)-benzonitrile (460 mg, 1.88 mmol, reference example 117) dissolved in THF (2 mL) was added 10% H_2SO_4 (4 mL) and the reaction was stirred for 24 h at room temperature. TLC (40% EtOAc in hexanes) shows a small amount of starting material, but mainly a more polar product. The reaction was diluted with water, extracted with dichloromethane (3x), washed with saturated aqueous NaCl solution, dried with Na_2SO_4 , filtered and evaporated. The crude product was chromatographed on silica gel (20-40% EtOAc in hexanes) to afford the title compound (315 mg, 84%). ^{1}H NMR ($CDCl_3$): δ 7.52 (d, 2H), 6.88 (d, 2H), 3.72 (t, 4H), 2.57 (t, 4H). MS (ion spray) m/z 200 (M+).

Reference Example 117

4-(1,4-dioxa-8-aza-spiro[4.5] dec-8-yl)-benzonitrile. A mixture of 4-fluorobenzonitrile (2.49 g, 20.57 mmol (14.73 g, 103 mmol) 1,4-dioxa-8-azaspiro[4.5] decane and K_2CO_3 (4.14 g, 30 mmol) in dioxane (40 mL)

was refluxed for 65 h. The reaction was filtered and the solvent was evaporated. Chromatography on silica gel (10-30% EtOAc in hexanes) provided the desired alkylated product 1,4-dioxa-8-azaspiro[4.5] decane (3.9 g, 79%). ^{1}H NMR ($CDCl_3$): δ 7.47 (d, 2H), 6.86 (d, 2H), 3.98 (s, 4H), 3.48 (t, 4H), 1.78 (t, 4H). MS (ion spray) m/z 245 (M+H)+.

Reference Example 118

4-(1-oxy-pyridin-4-yloxy)-benzoic acid. 246 mg (1 mol) of methyl 4-(1-oxy-pyridin-4-yloxy)-benzoate (reference example 119) was dissolved in 6 ml of ethanol, 4ml of 1N NaOH is added and refluxed for 3h. The mixture was neutralized with conc. HCl, evaporated and purified by preparative HPLC. ^{1}H NMR ($CDCl_3$): d 8.51 (d, 1H); 7.86 (d, 2H); 7.33 (d, 2H); 6.80 (d, 2H). MS (ion spray) m/z 232 (M+H)+.

Reference Example 119

Methyl 4-(1-oxy-pyridin-4-yloxy)-benzoate 304 mg (2 mol) of 4-hydroxy benzoic acid methyl ester, 280 mg (2 mmol) of 4-nitro pyridine oxide (2 mol) and 420 mg (3 mol) of K_2CO_3 were dissolved in 5 ml of dry DMF and stirred for 2h at 110°C. Cooled mixture was poured into brine and extracted with EtOAc (3x), washed with brine, dried with Na_2SO_4 and evaporated to give 246 mg of the title compound. ^{1}H NMR ($CDCl_3$): d 8.18 (d, 2H); 8.10 (d, 2H); 7.89 (d, 1H); 7.12 (d, 1H); 6.93 (d, 1H); 6.88 (d, 1H); 3.92 (s, 3H). MS (EI) m/z 245 (M+H)+.

Reference Example 120

4-[4-(2-dimethylamino-ethyl-tert-butyloxycarbonyl-amino)-piperidin-1-yl]-benzoic Acid. 140 mg (0.48 mmol) of the 4-[4-(2-dimethylamino-ethyl-amino)-piperidin-1-yl]-benzoic acid (reference example 113c) were dissolved in 8ml of THF, 655 mg (3 mol) of Boc_2O was added and stirred 3 days at room temperature. The mixture was diluted with water and extracted with DCM (3x); the combined extracts were washed with brine, dried over Na_2SO_4, filtered and evaporated. The resulting solid was washed with DCM/ether and dried to give 114 mg (61%) of the title compound. ^{1}H NMR ($CDCl_3$): d 7.84 (m, 2H), 6.79 (d, 1H), 3.95 (m, H), 3.70 (m, 4H), 3.18(m, 2H), 2.84 (s, 3H), 2.79 (s, 3H), 2.70 (t, 1H), 1.88 (m, 2H), 1.76 (m, 2H), 1.57 (s, 3H), 1.44 (s, 6H). MS (ion spray) m/z 392 (M+H)+.

Reference Example 121

4-(4-Methoxy-piperidin-1-yl)-Benzoic Acid. 170 mg (0.77 mmol) of 4-(4-hydroxy-piperidin-1-yl)-benzoic acid (reference example 113d) were dissolved in 3 ml of THF and 3 ml of DMSO, 120 mg (1.1 equiv) of methyl iodide and 68 mg (1.69 mmol) of NaH were added and stirred 16h at room temperature. The mixture was poured into brine and extracted with DCM (3x) aqueous phase acidified with HCl to pH 1 and extracted again with DCM (3x). The combined organic extracts were washed with brine, dried with Na_2SO_4, filtered and evaporated. TLC (DCM/MeOH 10%) showed a mixture of the starting material (Rf ~ 0.5) and a new product with Rf ~0.6. The two were separated by chromatography on silica with DCM/MeOH (0-10%) as a mobile phase to give 60 mg of the title compound. ^1H NMR ($CDCl_3$): d 7.95 (d, 2H), 6.87 (d, 2H), 3.68 (m, 2H), 3.63 (m, 1H), 3.38 (s, 3H), 3.14 (m, 2H), 1.98(m, 2H), 1.68 (m, 2H). MS (ion spray) m/z 236 (M+H)+.

Reference Example 122

4-(4-hydroxy-piperidin-1-yl)-benzonitrile. 240 mg (1.2 mmol) of 4-(4-oxo-piperidin-1-yl)-benzonitrile (reference example 116) was dissolved in 5 ml of methanol, 23 mg (0.6 mmol) of $NaBH_4$ was added and stirred 3h at room temperature. A few drops of water were added, methanol evaporated then 20 ml of water were added and extracted with DCM (3x), dried with Na_2SO_4, filtered and evaporated to give 230 mg (95% yield) of the title compound. ^1H NMR ($CDCl_3$): d 7.47 (d, 2H), 6.85 (d, 2H), 3.93 (bs, H), 3.70 (m, 2H), 3.11 (m, 2H), 1.95 (m, 2H), 1.62 (m, 2H). MS (ion spray) m/z 202 (M+H)+.

Reference Example 123

Methyl 4-(piperidin-4-yl-oxy)-benzoate. 266 mg (0.79 mmol) of methyl 4-(N-BOC-piperidin-4-yl-oxy)-benzoate (reference Example 124) was dissolved in 4 ml of DCM to which 4 ml of TFA was added and stirred 1h at room temperature. The mixture was evaporated to dryness and purified by preparative HPLC with the mobile phase water/acetonitrile/0.1 % TFA to give 217 mg of the TFA salt of the title compound. ^1H NMR (CD_3OD): d 7.97 (d, 2H), 7.06 (d, 2H), 4.78-4.85 (m, 1H), 3.86 (s, 3H), 3.19-3.44 (m, 4H), 2.14-2.23 (m, 2H), 2.00-2.08 (m, 2H). MS (ion spray) m/z 236 (M+H)+.

Reference Example 124

Methyl 4-(N-BOC-piperidin-4-yl-oxy)-benzoate. 656 mg (2.5 mmol) of triphenylphosphine and 304 mg (2 mmol) of 4-hydroxy methyl benzoate were dissolved in 3 ml of dry THF at 0°C and a solution of 402 mg (2 mmol) of N-Boc 4-piperidinol and 418 mg (2.4 mmol) of diethylazodicarboxylate in 4 ml of dry THF were added dropwise over 5 min. The mixture was stirred at 0°C for 2 h and then allowed to warm to room temperature and stirred for 3 days.The mixture was separated by chromatography on silica with a gradient of hexane/EtOAc (5-20%) to give 266 mg (40% yield) of the title compound. ^{1}H NMR ($CDCl_3$): 7.96 (d, 2H), 6.90 (d, 2H), 4.52-4.56 (m, 1H), 3.87 (s, 3H), 3.65-3.72 (m, 2H), 3.31-3.39 (m, 2H), 1.83-1.97 (m, 2H), 1.70-1.82 (m, 2H), 1.45 (s, 9H). MS (EI) m/z 184.

Reference Example 125

4-(4-Acetylamino-piperidin-1-yl)-N-[2-(3-Cyano-1H-indol-5-yl)-ethyl]-benzamide. 40 mg (0.09 mmol) of 4-(4-amino-piperidin-1-yl)-N-[2-(3-Cyano-1H-indol-5-yl)-ethyl]-benzamide. (reference Example 1aav) . was dissolved in 2 ml of pyridine, 22 mg (0.22 mmol) of acetic anhydride was added and stirred at room temperature for 16 h. The reaction mixture was evaporated to dryness. MS (CI) 430 $(M+H)^+$.

Reference Example 126

Methyl 4-(1-methanesulphonyl-piperidin-4-yl) Benzoate. 87 mg (0.40 mmol) of Methyl 4-(piperidin-4-yl) Benzoate (reference Example 127) was dissolved in 3 ml of DCM, cooled to 0°C and 55 mg (0.48 mmol) of methanesulfonyl chloride added and stirred for 1h. The mixture was poured into water, extracted with DCM (3x), washed with dilute $NaHCO_3$, dried with Na_2SO_4, filtered and evaporated. The crude was purified by chromatography on silica with hexane/EtOAc as the mobile phase to give 81 mg (61% yield) of the title compound. ^{1}H NMR ($CDCl_3$) : δ7.98 (d, 2H), 7.26 (d, 2H), 3.93 (m, 2H), 3.90 (s, 3H), 2.81 (s, 3H), 2.63-2.78 (m, 3H), 1.76-1.96 (m, 4H). MS (ion spray) m/z 298 $(M+H)^+$.

Reference Example 127

Methyl 4-(piperidin-4-yl) Benzoate. 160 mg (0.78 mmol) of 4-(piperidine-4-yl) benzoic acid (reference example 109) was dissolved in 2 ml of MeOH. 0.5 ml of conc. H_2SO_4 was added dropwise and the mixture was refluxed for 2h. It was cooled, diluted with water, pH adjusted to 12 with KOH pellets and extracted

with DCM (3x). The aqueous phase was purified by preparative HPLC with a 10-100% gradient of water/acetonitrile/ 0.1 % TFA to give 87 mg of the title compound. MS (ion spray) m/z 220 $(M+H)^+$.

The molecules described herein inhibit blood coagulation by virtue of their ability to inhibit the penultimate enzyme in the coagulation cascade, Factor Xa, rather than thrombin. Both free Factor Xa and Factor Xa assembled in the prothrombinase complex (Factor Xa, Factor Va, calcium and phospholipid) are inhibited. Factor Xa inhibition is obtained by direct complex formation between the inhibitor and the enzyme and is therefore independent of the plasma co-factor antithrombin III. Effective Factor Xa inhibition is achieved by administering the compounds either by oral administration, continuous intravenous infusion, bolus intravenous administration or any other parenteral route such that it achieves the desired effect of preventing the Factor Xa induced formation of thrombin from prothrombin.

Anticoagulant therapy is indicated for the treatment and prophylaxis of a variety of physiological thrombotic conditions of both the venous and arterial vasculature. In the arterial system, abnormal thrombus formation is primarily associated with arteries of the coronary, cerebral and peripheral vasculature. The diseases associated with thrombotic occlusion of these vessels principally include acute myocardial infarction (AMI), unstable angina, thromboembolism, acute vessel closure associated with thrombolytic therapy and percutaneous transluminal coronary angioplasty (PTCA), transient ischemic attacks, stroke, intermittent claudication and bypass grafting of the coronary (CABG) or peripheral arteries. Chronic anticoagulant therapy may also be beneficial in preventing the vessel luminal narrowing (restenosis) that often occurs following PTCA and CABG, and in the maintenance of vascular access patency in long-term hemodialysis patients. With respect to the venous vasculature, pathologic thrombus formation frequently occurs in the veins of the lower extremities following abdominal, knee and hip surgery (deep vein thrombosis, DVT). DVT further predisposes the patient to a higher risk of pulmonary thromboembolism. A systemic, disseminated intravascular coagulopathy (DIC) commonly occurs in both vascular systems during septic shock, certain viral infections and cancer. This condition is characterized by a rapid consumption of coagulation factors and their plasma inhibitors resulting in the formation of life-threatening thrombin throughout the microvasculature of several organ systems. The indications discussed above include some, but not all, of the possible clinical situations where anticoagulant therapy is warranted. Those experienced in this field are well aware of the circumstances requiring either acute or chronic prophylactic anticoagulant therapy.

In addition to their use in anticoagulant therapy, Factor Xa inhibitors may find utility in the treatment or prevention of other diseases in which the generation of thrombin has been implicated as playing a physiologic role. For example, thrombin has been proposed to contribute to the morbidity and mortality of

such chronic and degenerative diseases as arthritis, cancer, atherosclerosis and Alzheimer's disease by virtue of its ability to regulate many different cell types through specific cleavage and activation of a cell surface thrombin receptor, mitogenic effects, diverse cellular functions such as cell proliferation, for example, abnormal proliferation of vascular cells resulting in restenosis or angiogenesis, release of PDGF and DNA syntheses. Inhibition of Factor Xa will effectively block thrombin generation and therefore neutralize any physiologic effects of thrombin on various cell types.

Accordingly, the invention provides a method of inhibiting Factor Xa comprising contacting a Factor Xa inhibitory amount of a compound of formula I with a composition containing Factor Xa. According to a further feature of the invention there is provided a method of inhibiting the formation of thrombin comprising contacting Factor Xa inhibitory amount of a compound of formula I with a composition containing Factor Xa.

According to a further feature of the invention there is provided a method for the treatment of a human or animal patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of Factor Xa, for example conditions as hereinbefore described, which comprises the administration to the patient of an effective amount of compound of formula I or a composition containing a compound of formula I. "Effective amount" is meant to describe an amount of compound of the present invention effective in inhibiting Factor Xa and thus producing the desired therapeutic effect.

The present invention also includes within its scope pharmaceutical formulations which comprise at least one of the compounds of Formula I in association with a pharmaceutically acceptable carrier or coating.

In practice, compounds of the present invention may generally be administered parenterally, intravenously, subcutaneously, intramuscularly, colonically, nasally, intraperitoneally, rectally or orally.

The products according to the invention may be presented in forms permitting administration by the most suitable route and the invention also relates to pharmaceutical compositions containing at least one product according to the invention which are suitable for use in human or veterinary medicine. These compositions may be prepared according to the customary methods, using one or more pharmaceutically acceptable adjuvants or excipients. The adjuvants comprise, inter alia, diluents, sterile aqueous media and the various non-toxic organic solvents. The compositions may be presented in the form of tablets, pills, granules, powders, aqueous solutions or suspensions, injectable solutions, elixirs or syrups, and can contain one or more agents chosen from the group comprising sweeteners, flavorings, colorings, and stabilizers in order to obtain pharmaceutically acceptable preparations.

The choice of vehicle and the content of active substance in the vehicle are generally determined in accordance with the solubility and chemical properties of the product, the particular mode of administration and the provisions to be observed in pharmaceutical practice. For example, excipients such as lactose, sodium citrate, calcium carbonate, dicalcium phosphate and disintegrating agents such as starch, alginic acids and certain complex silicates combined with lubricants such as magnesium stearate, sodium lauryl sulfate and talc may be used for preparing tablets. To prepare a capsule, it is advantageous to use lactose and high molecular weight polyethylene glycols. When aqueous suspensions are used they can contain emulsifying agents or agents which facilitate suspension. Diluents such as sucrose, ethanol, polyethylene glycol, propylene glycol, glycerol and chloroform or mixtures thereof may also be used.

For parenteral administration, emulsions, suspensions or solutions of the products according to the invention in vegetable oil, for example sesame oil, groundnut oil or olive oil, or aqueous-organic solutions such as water and propylene glycol, injectable organic esters such as ethyl oleate, as well as sterile aqueous solutions of the pharmaceutically acceptable salts, are used. The solutions of the salts of the products according to the invention are especially useful for administration by intramuscular or subcutaneous injection. The aqueous solutions, also comprising solutions of the salts in pure distilled water, may be used for intravenous administration with the proviso that their pH is suitably adjusted, that they are judiciously buffered and rendered isotonic with a sufficient quantity of glucose or sodium chloride and that they are sterilized by heating, irradiation or microfiltration.

Suitable compositions containing the compounds of the invention may be prepared by conventional means. For example, compounds of the invention may be dissolved or suspended in a suitable carrier for use in a nebulizer or a suspension or solution aerosol, or may be absorbed or adsorbed onto a suitable solid carrier for use in a dry powder inhaler.

Solid compositions for rectal administration include suppositories formulated in accordance with known methods and containing at least one compound of formula I.

The percentage of active ingredient in the compositions of the invention may be varied, it being necessary that it should constitute a proportion such that a suitable dosage shall be obtained. Obviously, several unit dosage forms may be administered at about the same time. The dose employed will be determined by the physician, and depends upon the desired therapeutic effect, the route of administration and the duration of the treatment, and the condition of the patient. In the adult, the doses are generally from about 0.01 to about 100, preferably about 0.01 to about 10, mg/kg body weight per day by inhalation, from about 0.01 to about 100, preferably 0.1 to 70, more especially 0.5 to 10, mg/kg body weight per day by oral administration, and from about 0.01 to about 50, preferably 0.01 to 10, mg/kg body weight per day by

intravenous administration. In each particular case, the doses will be determined in accordance with the factors distinctive to the subject to be treated, such as age, weight, general state of health and other characteristics which can influence the efficacy of the medicinal product.

The products according to the invention may be administered as frequently as necessary in order to obtain the desired therapeutic effect. Some patients may respond rapidly to a higher or lower dose and may find much weaker maintenance doses adequate. For other patients, it may be necessary to have long-term treatments at the rate of 1 to 4 doses per day, in accordance with the physiological requirements of each particular patient. Generally, the active product may be administered orally 1 to 4 times per day. For other patients, it will be necessary to prescribe not more than one or two doses per day.

The compounds of formula (I) may be used alone or in combination with other diagnostic, cardioprotective agents, direct thrombin inhibitors, anticoagulants, antiplatelet or fibrinolytic agents. Often patients are concurrently treated prior, during and after interventional procedures with agents of these classes either in order to safely perform the interventional procedure or to prevent deleterious effects of thrombus formation. Some examples of classes of agents which may be used in combination with a compound of formula (I) are selected from: anti-coagulants such as Factor Xa inhibitors, Factor VIIa inhibitors, warfarin or heparin; synthetic pentasaccharides; anti-platelet agents such as aspirin, piroxicam or ticlopidine; direct thrombin inhibitors (e.g. boroarginine derivatives, hirudin or argatroban (Novastan®)); fibrinogen receptor antagonists; statins / fibrates; or fibrinolytic agents (thrombolytic agents) such as tissue plasminogen activator, anistreplase (Eminase®), urokinase or streptokinase; or combinations thereof.

The term cardioprotective agents as used herein, denotes agents that act to protect myocardium during ischemia. These cardioprotective agents include, but are nor limited to, adenosine agonists, β-blockers and Na/H exchange inhibitors. Adendosine agonists include those compounds disclosed in Spada et al., US Patent No. 5,364,862 and Spada et al., US Patent No. 5,736,554, the disclosures of which are hereby incorporated herein by reference. An example of an adenosine agonists is AMP 579 (Rhone-Poulenc Rorer). An example of a Na/H exchange inhibitor is Cariporide (HOE 642).

The term anti-coagulant agents as used herein, denotes agents that inhibit blood coagulation. Such agents include warfarin (Coumadin®) and heparin.

The term anti-platelet agents as used herein, denotes agents that inhibit platelet function such as by inhibiting the aggregation, adhesion or granular secretion of platelets. Such agents include the various known non-steroidal anti-inflammatory drugs (NSAIDS) such as aspirin, ibuprofen, naproxen, sulindac, indomethacin, mefenamate, droxicam, diclofenac, sulfinpyrazone, and piroxicam (Feldane®), including pharmaceutically acceptable salts or prodrugs thereof. Other suitable anti-platelet agents include ticlopidine

(Ticlid), thromboxane-A2-receptor antagonists and thromboxane-A2-synthetase inhibitors, as well as pharmaceutically acceptable salts or prodrugs thereof.

The phrase direct thrombin inhibitors (i.e. Factor IIa inhibitors), as used herein, denotes inhibitors of the serine protease thrombin. By inhibiting thrombin directly, the inhibition of the cleavage of fibrinogen to fibrin, activation of Factor XIIIa, activation of platelets, and feedback of thrombin to the coagulation cascade to generate more thrombin, occurs. Such direct inhibitors include boroarginine derivatives and boropeptides, hirudin and argatroban (Novastan®), including pharmaceutically acceptable salts and prodrugs thereof. Boroarginine derivatives and boropeptides include N-acetyl and peptide derivatives of boronic acid, such as C-terminal α-aminoboronic acid derivatives of lysine, ornithine, arginine, homoarginine and corresponding isothiouronium analogs thereof. The term hirudin, as used herein, includes suitable derivatives or analogs of hirudin, referred to herein as hirulogs, such as disulfatohirudin.

The phrase fibrinolytic agents (or thrombolytics or fibrinolytics), as used herein, denotes agents that lyse blood clots. Such agents include tissue plasminogen activator, anistreplase (Eminase®), urokinase or streptokinase, including pharmaceutically acceptable salts or prodrugs thereof. Tissue plasminogen activator (tPA) is commercially available from Genentech Inc., South San Francisco, Calif. The term urokinase, as used herein, is intended to denote both dual and single chain urokinase, the latter also being referred to herein as prourokinase.

The compounds described herein may be administered to treat thrombotic complications in a variety of animals such as primates including humans. Inhibition of factor Xa is useful not only in the anticoagulant therapy of individuals having thrombotic conditions but is useful whenever inhibition of blood coagulation is required such as to prevent coagulation of stored whole blood and to prevent coagulation in other biological samples for testing or storage. Thus, any inhibitor of Factor Xa activity can be added to or contacted with any medium containing or suspected of containing Factor Xa and in which it is desired that blood coagulation be inhibited.

The compounds of the present invention may be used in combination with any antihypertensive agent or cholesterol or lipid regulating agent, or concurrently with agents used in the treatment of restenosis, atherosclerosis or high blood pressure. Some examples of agents that are useful in combination with a compound according to the invention in the treatment of high blood pressure include compounds of the following classes: beta-blockers, ACE inhibitors, calcium channel antagonists and alpha-receptor antagonists. Some examples of agents that are useful in combination with a compound according to the invention in the treatment of elevated cholesterol levels or disregulated lipid levels include compounds known to be HMGCoA reductase inhibitors, compounds of the fibrate class.

It is understood that the present invention includes combinations of compounds of the present invention with one or more of the aforementioned therapeutic class agents

Compounds within the scope of the present invention exhibit marked pharmacological activities according to tests described in the literature and below which tests results are believed to correlate to pharmacological activity in humans and other mammals.

Enzyme Assays:

The ability of the compounds of the present invention to act as inhibitors of Factor Xa, thrombin, trypsin, tissue-plasminogen activator (t-PA), urokinase-plasminogen activator (u-PA), plasmin and activated protein C is evaluated by determining the concentration of inhibitor which resulted in a 50% loss in enzyme activity (IC50) using purified enzymes.

All enzyme assays are carried out at room temperature in 96-well microtiter plates using a final enzyme concentration of 1 nM. The concentrations of Factor Xa and thrombin are determined by active site titration and the concentrations of all other enzymes are based on the protein concentration supplied by the manufacturer. Compounds according to the invention are dissolved in DMSO, diluted with their respective buffers and assayed at a maximal final DMSO concentration of 1.25%. Compound dilutions are added to wells containing buffer and enzyme and pre-equilibrated for between 5 and 30 minutes. The enzyme reactions are initiated by the addition of substrate and the color developed from the hydrolysis of the peptide-p-nitroanilide substrates is monitored continuously for 5 minutes at 405 nm on a Vmax microplate reader (Molecular Devices). Under these conditions, less than 10% of the substrate is utilized in all assays. The initial velocities measured are used to calculate the amount of inhibitor which resulted in a 50% reduction of the control velocity (IC_{50}). The apparent Ki values are then determined according to the Cheng-Prusoff equation (IC50 = Ki [1+[S]/Km]) assuming competitive inhibition kinetics.

An additional in vitro assay may be used to evaluate the potency of compounds according to the invention in normal human plasma. The activated partial thromboplastin time is a plasma-based clotting assay that relies on the in situ generation of Factor Xa, its assembly into the prothrombinase complex and the subsequent generation of thrombin and fibrin which ultimately yields the formation of a clot as the assay endpoint. This assay is currently used clinically to monitor the ex vivo effects of the commonly used anticoagulant drug heparin as well as direct acting antithrombin agents undergoing clinical evaluation. Therefore, activity in this in vitro assay is considered as a surrogate marker for in vivo anticoagulant activity.

Human Plasma Based Clotting Assay:

Activated partial thromboplastin clotting times are determined in duplicate on a MLA Electra 800 instrument. A volume of 100 µl of citrated normal human pooled plasma (George King Biomedical) is added to a cuvette containing 100 µl of a compound according to the invention in Tris/NaCl buffer (pH 7.5) and placed in the instrument. Following a 3 minute warming period the instrument automatically adds 100 µl of activated cephaloplastin reagent (Actin, Dade) followed by 100 µl of 0.035 M $CaCl_2$ to initiate the clotting reaction. Clot formation is determined spectrophotometrically and measured in seconds. Compound potency is quantitated as the concentration required to double a control clotting time measured with human plasma in the absence of the compound according to the invention.

Compounds according to the invention may also be evaluated for their in vivo antithrombotic efficacy in two well established animal experimental models of acute vascular thrombosis. A rabbit model of jugular vein thrombosis and a rat model of carotid artery thrombosis are used to demonstrate the antithrombotic activity of these compounds in distinct animal model paradigms of human venous thrombosis and arterial thrombosis, respectively.

Experimental In Vivo Rabbit Venous Thrombosis Model:

This is a well characterized model of fibrin rich venous thrombosis that is validated in the literature and shown to be sensitive to several anticoagulant drugs including heparin (Antithrombotic Effect of Recombinant Truncated Tissue Factor Pathway Inhibitor (TFPI 1-161) in Experimental Venous Thrombosis-a Comparison with Low Molecular Weight Heparin, J. Holst, B. Lindblad, D. Bergqvist, O. Nordfang, P.B. Ostergaard, J.G.L. Petersen, G. Nielsen and U. Hedner. Thrombosis and Haemostasis, 71, 214-219 (1994). The purpose of utilizing this model is to evaluate the ability of compounds to prevent the formation of venous thrombi (clots) in vivo generated at a site of injury and partial stasis in the jugular vein.

Male and female New Zealand white rabbits weighing 1.5-2 kg are anesthetized with 35 mg/kg of ketamine and 5 mg/kg xylazine in a volume of 1 mL/kg (i.m.). The right jugular vein is cannulated for infusion of anesthetic (ketamine/xylazine 17/2.5 mg/kg/hr at a rate of approximately 0.5 mL/hr) and administration of test substances. The right carotid artery is cannulated for recording arterial blood pressure and collecting blood samples. Body temperature is maintained at 39°C with a GAYMAR T-PUMP. The left external jugular vein is isolated and all side branches along an exposed 2-3 cm of vessel are tied off. The internal jugular vein is cannulated, just above the bifurcation of the common jugular, and the tip of the cannula is advanced just proximal to the common jugular vein. A 1 cm segment of the vein is isolated with non-traumatic vascular clamps and a relative stenosis is formed by tying a ligature around the vein with an 18G needle just below the distal most clamp.

This creates a region of reduced flow and partial stasis at the injury site. The isolated segment is gently rinsed with saline 2-3 times via the cannula in the internal jugular. Thereafter the isolated segment is filled with 0.5 mL of 0.5% polyoxyethylene ether (W-1) for 5 minutes. W-1 is a detergent which disrupts the endothelial cell lining of the segment, thus providing a thrombogenic surface for initiating clot formation. After 5 minutes the W-1 is withdrawn from the segment, and the segment is again gently rinsed with saline 2-3 times. The vascular clamps are then removed, restoring blood flow through this portion of the vessel. Clot formation is allowed to form and grow for 30 minutes after which the vein is cut just below the stenotic ligature and inspected for blood flow (the absence of blood flow is recorded as complete occlusion). The entire isolated segment of vein is then ligated and the formed clot is removed and weighed (wet weight). The effect of test agents on final clot weights is used as the primary end point. Animals are maintained for an additional thirty minutes to obtain a final pharmacodynamic measure of anticoagulation. Drug administration is initiated 15 minutes prior to vascular injury with W-1 and continued through the period of clot formation and maturation. Three blood samples (3 mL ea.) are obtained for evaluation of hemostatic parameters: one just prior to administration of W-1; a second 30 minutes after removal of the vascular clamps and a third at the termination of the experiment. Antithrombotic efficacy is expressed as a reduction in the final clot weight in preparations treated with a compound according to the invention relative to vehicle treated control animals.

Experimental In Vivo Rat Arterial Thrombosis Model:

The antithrombotic efficacy of Factor Xa inhibitors against platelet-rich arterial thrombosis may be evaluated using a well characterized rat carotid artery $FeCl_2$-induced thrombosis model (Superior Activity of a Thromboxane Receptor Antagonist as Compared with Aspirin in Rat Models of Arterial and Venous Thrombosis, W.A. Schumacher, C.L. Heran, T.E. Steinbacher, S. Youssef and M.L. Ogletree. Journal of Cardiovascular Pharmacology, 22, 526-533 (1993); Rat Model of Arterial Thrombosis Induced by Ferric Chloride, K.D. Kurtz, B.W. Main, and G.E. Sandusky. Thrombosis Research, 60, 269-280 (1990); The Effect of Thrombin Inhibition in a Rat Arterial Thrombosis Model, R.J. Broersma, L.W. Kutcher and E.F. Heminger. Thrombosis Research 64, 405-412 (1991). This model is widely used to evaluate the antithrombotic potential of a variety of agents including heparin and the direct acting thrombin inhibitors.

Sprague Dawley rats weighing 375-450 g are anesthetized with sodium pentobarbital (50 mg/kg i.p.). Upon reaching an acceptable level of anesthesia, the ventral surface of the neck is shaved and prepared for aseptic surgery. Electrocardiogram electrodes are connected and lead II is monitored throughout the experiment. The right femoral vein and artery are cannulated with PE-50 tubing for administration of a

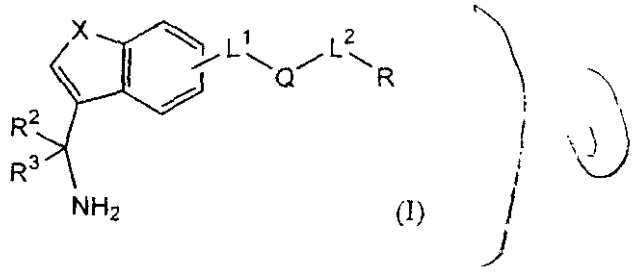
compound according to the invention and for obtaining blood samples and monitoring blood pressure, respectively. A midline incision is made in the ventral surface of the neck. The trachea is exposed and intubated with PE-240 tubing to ensure airway patency. The right carotid artery is isolated and two 4-0 silk sutures are placed around the vessel to facilitate instrumentation. An electromagnetic flow probe (0.95-1 mm lumen) is placed around the vessel to measure blood flow. Distal to the probe a 4x4 mm strip of parafilm is placed under the vessel to isolate it from the surrounding muscle bed. After baseline flow measurements are made, a 2x5 mm strip of filter paper previously saturated in 35% $FeCl_2$ is placed on top of the vessel downstream from the probe for ten minutes and then removed. The $FeCl_2$ is thought to diffuse into the underlying segment of artery and cause deendothelialization resulting in acute thrombus formation. Following application of the $FeCl_2$-soaked filter paper, blood pressure, carotid artery blood flow and heart rate are monitored for an observation period of 60 minutes. Following occlusion of the vessel (defined as the attainment of zero blood flow), or 60 minutes after filter paper application if patency is maintained, the artery is ligated proximal and distal to the area of injury and the vessel is excised. The thrombus is removed and weighed immediately and recorded as the primary end point of the study.

Following surgical instrumentation a control blood sample (B1) is drawn. All blood samples are collected from the arterial catheter and mixed with sodium citrate to prevent clotting. After each blood sample, the catheter is flushed with 0.5 mL of 0.9% saline. A compound according to the invention is administered intravenously (i.v.) starting 5 minutes prior to $FeCl_2$ application. The time between $FeCl_2$ application and the time at which carotid blood flow reached zero is recorded as time to occlusion (TTO). For vessels that did not occlude within 60 minutes, TTO is assigned a value of 60 minutes. Five minutes after application of $FeCl_2$, a second blood sample is drawn (B2). After 10 minutes of $FeCl_2$ exposure, the filter paper is removed from the vessel and the animal is monitored for the remainder of the experiment. Upon reaching zero blood flow blood a third blood sample is drawn (B3) and the clot is removed and weighed. Template bleeding time measurements are performed on the forelimb toe pads at the same time that blood samples are obtained. Coagulation profiles consisting of activated partial thromboplastin time (APTT) and prothrombin time (PT) are performed on all blood samples. In some instances a compound according to the invention may be administered orally. Rats are restrained manually using standard techniques and compounds are administered by intragastric gavage using a 18 gauge curved dosing needle (volume of 5 mL/kg). Fifteen minutes after intragastric dosing, the animal is anesthetized and instrumented as described previously. Experiments are then performed according to the protocol described above.

The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof.

WHAT IS CLAIMED IS:

1. A compound of formula I:



(I)

wherein

X is O, S or NR^1;

R is hydrogen, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, fused arylcycloalkyl, fused heteroarylcycloalkyl, fused arylcycloalkenyl, fused heteroarylcycloalkenyl, fused arylheterocyclyl, fused heteroarylheterocyclyl, fused arylheterocyclenyl, fused heteroarylheterocyclenyl, aryl, fused cycloalkenylaryl, fused cycloalkylaryl, fused heterocyclylaryl, fused heterocyclenylaryl, heteroaryl, fused cycloalkylheteroaryl, fused cycloalkenylheteroaryl, fused heterocyclenylheteroaryl or fused heterocyclylheteroaryl, provided that where L^2 is a chemical bond then Q is attached to R through a carbon atom thereof or where R is hydrogen then L^2 is not a chemical bond;

R^1 is hydrogen, alkyl, aralkyl, heteroaralkyl, acyl, aroyl, heteroaroyl, alkoxycarbonyl, aryloxycarbonyl or heteroaryloxycarbonyl;

R^2 and R^3 are hydrogen, or taken together are $=NR^4$;

R^4 is hydrogen, R^5O_2C-, R^5O-, HO-, cyano, R^5CO-, HCO-, lower alkyl, nitro, or R^6R^7N-;

R^5 is alkyl, aryl, heteroaryl, aralkyl, or heteroaralkyl;

R^6 and R^7 are independently hydrogen or alkyl;

L^1 is alkylene, alkenylene or alkynylene;

L^2 is a chemical bond, alkylene, alkenylene or alkynylene;

Q is $-NR^{8'}$-, -O-, -C(O)-, -C(O)-O-, -O-C(O)-, $-NR^{8'}C(X^1)$-, $-C(X^1)NR^{8'}$-, $-NR^8C(X^1)O$-, $-OC(X^1)NR^8$-, $-NR^8C(X^1)NR^8$-, $-NR^8C(X^1)NR^8$-, $-S(O)_n$-, $-NR^8SO_2$- or $-SO_2NR^8$-, provided that a nitrogen atom or oxygen atom of Q is not directly bonded to a carbon atom of L^1 or L^2 having a double bond or triple bond, or Q-L^2-R is cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, fused arylcycloalkyl, fused heteroarylcycloalkyl, fused arylcycloalkenyl, fused heteroarylcycloalkenyl, fused arylheterocyclyl, fused heteroarylheterocyclyl, fused arylheterocyclenyl, fused heteroarylheterocyclenyl, aryl, fused cycloalkenylaryl, fused cycloalkylaryl, fused heterocyclylaryl, fused heterocyclenylaryl, heteroaryl, fused

cycloalkylheteroaryl, fused cycloalkenylheteroaryl, fused heterocyclenylheteroaryl or fused heterocyclylheteroaryl, provided that a nitrogen atom or oxygen atom of Q is not directly bonded to a carbon atom of L^1 having a double bond or triple bond;

X^1 is O or S;

$R^{8'}$ is hydrogen, alkyl, aralkyl, heteroaralkyl, acyl, aroyl, heteroaroyl or alkoxycarbonyl;

R^8 is hydrogen, alkyl, aralkyl, heteroaralkyl, acyl, aroyl or heteroaroyl; and

n is 0, 1 or 2, or

an oxide thereof, a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

2. The compound of claim 1 wherein R is aryl, heteroaryl or heterocyclyl.

3. The compound of claim 1 wherein R is substituted phenyl.

4. The compound of claim 1 wherein R is optionally substituted (phenyl substituted phenyl), optionally substituted (heteroaryl substituted phenyl), optionally substituted (phenyl substituted heteroaryl), optionally substituted (heteroaryl substituted heteroaryl), optionally substituted (phenyl substituted cyclyoalkyl), optionally substituted (heteroaryl substituted cyclyoalkyl), optionally substituted (cyclyoalkyl substituted heteroaryl), optionally substituted (cyclyoalkyl substituted phenyl), optionally substituted (cyclyoalkyl substituted cyclyoalkyl), optionally substituted (phenyl substituted cyclyoalkenyl), optionally substituted (heteroaryl substituted cyclyoalkenyl), optionally substituted (cyclyoalkenyl substituted heteroaryl), optionally substituted (cyclyoalkenyl substituted phenyl), optionally substituted (cyclyoalkenyl substituted cyclyoalkeny), optionally substituted (phenyl substituted heterocyclyl), optionally substituted (heteroaryl substituted heterocyclyl), optionally substituted (cyclyoalkyl substituted heterocyclyl), optionally substituted (heterocyclyl substituted phenyl), optionally substituted (heterocyclyl substituted heterocyclyl), optionally substituted (phenyl substituted heterocyclenyl), optionally substituted (heteroaryl substituted heterocyclenyl), optionally substituted (cyclyoalkenyl substituted heterocyclenyl), optionally substituted (heterocyclenyl substituted phenyl), or optionally substituted (heterocyclenyl substituted heterocyclenyl).

5. The compound of claim 1 wherein R is optionally substituted (phenyl substituted phenyl), optionally substituted (heteroaryl substituted phenyl), optionally substituted (phenyl substituted heteroaryl), optionally substituted (heteroaryl substituted heteroaryl), optionally substituted (phenyl substituted heterocyclyl), optionally substituted (heteroaryl substituted heterocyclyl), optionally substituted (cyclyoalkyl substituted

heterocyclyl), optionally substituted (heterocyclyl substituted phenyl), optionally substituted (heterocyclyl substituted heterocyclyl), optionally substituted (phenyl substituted heterocyclenyl), optionally substituted (heteroaryl substituted heterocyclenyl), optionally substituted (cyclyoalkenyl substituted heterocyclenyl), optionally substituted (heterocyclenyl substituted phenyl), or optionally substituted (heterocyclenyl substituted heterocyclenyl).

6. The compound of claim 1 wherein R is optionally substituted (phenyl substituted heteroaryl), optionally substituted (phenyl substituted heterocyclyl), and optionally substituted (phenyl substituted heterocyclenyl).

7. The compound of claim 1 wherein R is optionally substituted (phenyl substituted heteroaryl), optionally substituted (phenyl substituted heterocyclyl), and optionally substituted (phenyl substituted heterocyclenyl); L^2 is bonded to said phenyl in the 1-position of the phenyl moiety and said heterocyclyl, heterocyclenyl, or heteroaryl, is bonded to said phenyl in the 4-position of the phenyl moiety.

8. The compound of claim 1 wherein X is NR^1.

9. The compound of claim 1 wherein R^1 is hydrogen.

10. The compound of claim 1 wherein R^8 is hydrogen.

11. The compound of claim 1 wherein R^2 and R^3 taken together are $=NR^4$.

12. The compound of claim 1 wherein R^4 is hydrogen.

13. The compound of claim 1 wherein R^5 is alkyl.

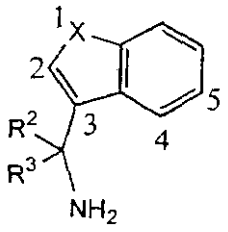
14. The compound of claim 9 wherein R^5 is methyl.

15. The compound of claim 1 wherein R^6 and $R^7$are hydrogen.

16. The compound of claim 1 wherein L^1 is alkylene.

17. The compound of claim 1 wherein L^1 is ethylene.

18. The compound of claim 1 wherein L^1 is



bonded to the 5-position of the moiety

19. The compound of claim 1 wherein L^2 is a chemical bond or alkylene.

20. The compound of claim 14 wherein L^2 is a chemical bond.

21. The compound of claim 1 wherein X^1 is O.

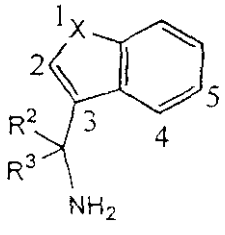
22. The compound of claim 1 wherein Q is $-NR^8CO-$, $-CONR^8-$, $-NR^8SO_2-$ or $-SO_2NR^8-$.

23. The compound of claim 1 wherein Q is $-NR^8CO-$.

24. The compound of claim 1 wherein R^8 and $R^{8'}$ are hydrogen.

25. The compound of claim 1 wherein n is 2.

26. The compound of claim 1 wherein L^1 is



bonded to the 5-position of the moiety;

R is optionally substituted (phenyl substituted pyridinonyl), optionally substituted (phenyl substituted pyrrolopyrimidinyl), optionally substituted (phenyl substituted pyridazinyl), optionally substituted (phenyl

substituted pyridazinonyl), optionally substituted (phenyl substituted pyridyl), or optionally substituted (phenyl substituted pyrimidinyl).

27. The compound of claim 1 wherein R is substituted (phenyl substituted pyrimidinyl), said pyrimidinyl is substituted with at least one ring system substituent selected from the group consisting of alkoxy, Y^1Y^2N-alkyl-, Y^1Y^2N-, azaheterocyclyl, Y^1Y^2NCO-alkylene-O-, azaheterocyclyl-alkylene-O-, and Y^1Y^2N-alkylene-O-; wherein

Y^1 and Y^2 are independently hydrogen, alkyl, alkoxyalkyl, hydroxyalkyl, cycloalkyl, cycloalkyl-alkyl, Y^1Y^2N-alkyl, aryl, aralkyl, heteroaralkyl, heterocyclylalkyl, heterocyclenylalkyl, or sulfo-alkyl-; or when Y^1 is H-CO-, alkyl-CO-, aryl-CO-, or heterocyclyl-CO-, then Y^2 is hydrogen, alkyl, aryl, or aralkyl.

28. A compound according to claim 1 which is

N-(2-[3-Carbamimidoyl-5-indolyl]ethyl)-4-pyrid-3-ylbenzamide;
N-(2-[3-Carbamimidoyl-5-indolyl]ethyl)-4-(pyrimidin-5-yl)-benzamide);
5-(Pyrid-2-yl)-thiophene-2-carboxylic acid 2-(3-Carbamimidoyl-5-indolyl)ethyl amide;
N-(2-[3-Carbamimidoylindol-5-yl]ethyl)- 6-morpholin-4-ylnicotinamide4-(5-2[-{3-Carbamimidoylindol-5-yl}ethylcarbamoyl]pyridin-2-yl)piperazine-1-carboxylic acid ethyl ester;
N-(2-[3-Carbamimidoylindol-5-yl]ethyl)- 6-imidazol-1-ylnicotinamide;
N-(2-[3-Carbamimidoylindol-5-yl]ethyl)- 4-imidazol-1-ylbenzamide;
N-(2-[3-Carbamimidoylindol-5-yl]ethyl)- 4-(3H-imidazol-4-yl)benzamide;
N-(2-[3-Carbamimidoylindol-5-yl]ethyl)- 4-(1,2,4)thiadiazol-5-ylbenzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(1-carbamoyl-1-methyl-ethyl-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(1-[N-(2-methoxyethyl)]-carbamoyl-1-methyl-ethyl-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(t-butyl)-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(pyridazin-4-yl)-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-2-methyl-4-(6-oxo-1.6-dihydro-pyridin-3-yl)-benzamide
3',4'-Dimethoxybiphenyl-4-carboxylic acid (2-[3-Carbamimidoylindol-5-yl]ethyl)amide;
N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-(6-methoxypyrid-3-yl)benzamide;
N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-(1-oxy-pyrid-4-yl)benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(7H-pyrrolo[2,3-d]pyrimidin-6-yl)-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(1H-pyrrolo[3,2-c]pyridin-2-yl)-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-furo[3,2-c]pyridin-2-yl-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-3-chloro-4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzamide;
N-(2-[3-Carbamimidoyl-1H-indol-5-yl]ethyl)-4-(6-oxo-1,6-dihydro-pyrid-3-yl)benzamide;
4-(3-Amino-1,1-dimethyl-propyl)-N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-2-(4-chloro-phenyl)-acetamide;
5-chloro-thiophene-2-carboxylic acid [2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-amide;
N-(2-[3- Carbamimidoylindol-5-yl]ethyl)-6-(2-hydroxyethylamino)nicotinamide;
N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-6-(1, 2, 4)-triazol-1-ylnicotinamide;
N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-6-pyrrol-1-ylnicotinamide;
N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-6-pyrazol-1-ylnicotinamide;
N-(2-[3-Carbamimidoyl-1-methylindol-5-yl]ethyl)-4-(6-methoxypyrid-3-yl)benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-3-chloro-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-2-(3-chloro-phenyl)-acetamide;
4-(2-Aminomethyl-pyridin-4-yl)-N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-benzamide;
4-{4-[2-(3-Carbamimidoy-1H-indol-5-yl)-ethylcarbamoyl]-phenyl-pyridine-2-carboxylic acid amide;
N-[2-(3-Carbamimidoy-1H-indol-5-yl)-ethyl]-4-(2-(N,N-dimethylaminomethyl)-pyridin-4-yl)benzamide);
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(6-oxo-1,6-dihydro-pyridazin-3-yl)-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(6-methoxy-pyridazin-3-yl)-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[1-(2-dimethylamino-ethyl)-6-oxo-1,6-dihydro-pyridazin-3-yl]-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[1-(3-dimethylamino-propyl)-6-oxo-1,6-dihydro-pyridazin-3-yl]-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(2-dimethylamino-ethylamino)-pyrimidin-4-yl]-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-methoxy-pyrimidin-4-yl]-benzamide;
N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-(1-[2-dimethylaminoethyl]-6-oxo-1,6-dihydropyridin-3-yl)benzamide;
N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-(1-carbamoylmethyl-6-oxo-1,6-dihydropyridin-3-yl)benzamide;
4-(3-Amino-[1,2,4]triazin-6-yl)-N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-benzamide;
4-(3-Amino-[1,2,4]triazin-5-yl)-N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]- 4-(3-oxo-2,3-dihydro-[1,2,4]triazin-6-yl)-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5yl)ethyl]-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-benzamide

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl-4-(6-oxo-piperidin-3-yl)-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(morpholin-4yl-ethylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(3-dimethylamino-propylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-([2-dimethylamino-ethyl]-methyl-amino)-pyrimidin-4-yl]-benzamide;

2-[(4-{4-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethylcarbamoyl]-phenyl}-pyrimidin-2-yl)-methyl-amino]-ethanesulfonic acid;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-{2-[methyl-(2(S),3(R),4(R),5(R),6-pentahydroxy-hexyl)-amino]-pyrimidin-4-yl}-benzamide

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-{2-[methyl-(2(S),3(R),4(S),5(R),6-pentahydroxy-hexyl)-amino]-pyrimidin-4-yl}-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(2-hydroxy-1-hydroxymethyl-ethylamino)-pyrimidin-4-yl]-benzamide;

2-[(4-{4-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethylcarbamoyl]-phenyl}-pyrimidin-2-yl)-methyl-amino]-ethanesulfonic acid;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(3-imidazol-1-yl-propylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-{2-[(2-diethylamino-ethyl)-methyl-amino]-pyrimidin-4-yl}-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(2-diisopropylamino-ethylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(2-dibutylamino-ethylamino)-pyrimidin-4-yl]-benzamide

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(3-morpholin-4-yl-propylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(3-diethylamino-propylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(3-piperidin-1-yl-propylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(2-{[2-(ethyl-methyl-amino)-ethyl]-methyl-amino}-pyrimidin-4-yl)-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(5-dimethylamino-pentylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(5-morpholin-4-yl-pentylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(5-piperidin-1-yl-pentylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(5-pyrrolidin-1-yl-pentylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(2-oxo-hexahydro-pyrimidin-5-yl)-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(1,3-dimethyl-2-oxo-hexahydro-pyrimidin-5-yl)-benzamide;

Biphenyl-3,4'-dicarboxylic acid 4'-{[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-amide} 3-[(2-methoxy-ethyl)-amide];

3'-(Morpholine-4-carbonyl)-biphenyl-4-carboxylic acid [2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-amide;

Biphenyl-3,4'-dicarboxylic acid 4'-{[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-amide} 3-[(2-morpholin-4-yl-ethyl)-amide];

Biphenyl-2,4'-dicarboxylic acid 4'-{[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-amide} 2-[(3-diethylamino-propyl)-amide];

Biphenyl-2,4'-dicarboxylic acid 4'-{[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-amide} 2-[(3-morpholin-4-yl-propyl)-amide];

Biphenyl-2,4'-dicarboxylic acid 4'-{[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-amide} 2-[(3-piperidin-1-yl-propyl)-amide];

Biphenyl-2,4'-dicarboxylic acid 4'-{[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-amide} 2-[(4-dimethylamino-butyl)-amide];

Biphenyl-2,4'-dicarboxylic acid 4'-{[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-amide} 2-[(2,3-dihydroxy-propyl)-methyl-amide];

Biphenyl-2,4'-dicarboxylic acid 4'-{[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-amide} 2-[(2,3-dihydroxy-propyl)-amide];

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(4-methylpiperazin-1-yl)pyrimidin-4-yl]benzamide;

4-[(4-{4-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethylcarbamoyl]phenyl}pyrimidin-2-yl)methylamino]butyric acid;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl]benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(2-pyrrolidin-1-ylpyrimidin-4-yl)benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(2-hydroxymethylpyrrolidin-1-yl)-pyrimidin-4-yl]benzamide ;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(carbamoylmethyl-N-methylamino)-pyrimidin-4-yl]benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(6-pyrrolidin-1-yl-hexylamino)pyrimidin-4-yl]benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(6-piperidin-1-ylhexylamino)pyrimidin-4-yl]benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(4-piperidin-1-ylbutylamino)pyrimidin-4-yl]benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(4-diethylaminobutylamino)pyrimidin-4-yl]benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(6-morpholin-4-ylhexylamino)pyrimidin-4-yl]benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(6-dimethylaminohexylamino)pyrimidin-4-yl]benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(4-dimethylaminobutylamino)pyrimidin-4-yl]benzamide;

4-[2-(Bicyclo[2;2;1]hept-2-ylamino)pyrimidin-4-yl]-N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]benzamide;

1-(4-{4-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethylcarbamoyl]phenyl}pyrimidin-2-yl)pyrrolidine-2-carboxylic acid amide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-{2-[(2-hydroxy-ethyl)-N-methylamino]pyrimidin-4-yl}benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(2-morpholin-4-yl-pyrmidin-4-yl)-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(cyclopropylmethyl-amino)-pyrimidin-4-yl]-benzamide;

N-[2-(Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-[(2-methoxy-ethyl)-methyl-amino]-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(3-hydroxy-propylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl -1H-indol-5-yl)-ethyl]-4-[(2-hydroxy-ethyl)-propyl-amino]-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indole-5yl)-ethyl]-4-(2-piperidin-1-yl-pyrimidin-4-yl)-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(ethyl-methyl-amino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl -1H-indol-5-yl)-ethyl]-4-[2-(4-hydroxy-piperidin-1-yl)-pyrimidin-4-yl]-benzamide;
N-[2-(3-Carbamimidoyl -1H-indol-5-yl)-ethyl]-4-[2-(2,3-dihydroxy-propylamino)-pyrimidin-4-yl]-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-[(2,3-dihydroxy-propyl)-methyl-amino]-pyrimidin-4-yl]-benzamide;
N-[2-(3-Carbamimidoyl -1H-indol-5-yl)-ethyl]-4-[2-((s)-2-methoxymethyl-pyrrolidin-1-yl)-pyrimidin-4-yl]-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(2-piperazin-1-yl-pyrimidin-4-yl)-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)- 4-[2-[2-(2-oxo-imidazolidin-1-yl)-ethylamino]-pyrimidin-4-yl]-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(3-methoxy-propylamino)-pyrimidin-4-yl]-benzamide;
4-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(2-hydroxy-ethylamino)-pyrimidin-4-yl]-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(2-methoxyethoxy)-pyrimidin-4-yl]benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(1-carbamoylethoxy)pyrimidin-4-yl]benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(6-dimethylaminohexyloxy)pyrimidin-4-yl]benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(2-oxopiperidin-3-yloxy)pyrimidin-4-yl]benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(2-pyrrolidin-1-yl-ethoxy)pyrimidin-4-yl]benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(2-dimethylaminoethoxy)pyrimidin-4-yl]benzamide;
3'-(2-Dimethylaminoethoxy)biphenyl-4-carboxylic acid [2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]amide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-(1-oxypyridin-2-yl)benzamide;
2'-(2-Dimethylaminoethoxy)biphenyl-4-carboxylic acid [2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]amide;
2'-(3-Dimethylaminopropoxy)biphenyl-4-carboxylic acid [2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]amide;
3'-(3-Dimethylaminopropoxy)biphenyl-4-carboxylic acid [2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]amide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(1-oxo-pyridin-3-yl)-benzamide;
4-[2-(acetylamino-methyl)-pyridin-4-yl]-N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-benzamide;
Piperidine-4-carboxylic acid (4-[4-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethylcarbamoyl]-phenyl-]-pyridin-2-ylmethyl)-amide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[1-(3-dimethylaminopropyl)-6-oxo-1,6-dihydropyridin-3-yl]benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[6-(3-dimethylaminopropoxy)pyridin-3-yl]benzamide;
(5-{4-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethylcarbamoyl]phenyl}-2-oxo-2H-pyridin-1-yl)acetamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-{1-[(2-dimethylaminoethylcarbamoyl)methyl]-6-oxo-1,6-dihydropyridin-3-yl}benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(4-dimethylamino-piperidin-1-yl)-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[4-(2-dimethylamino-ethylamino)-piperidin-1-yl]-benzamide;

4-(4-Amino-piperidin-1-yl)-N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(4-methoxy-piperidin-1-yl)-benzamide;

4-(4-Acetylamino-piperidin-1-yl)-N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-benzamide;

4-(1-Acetyl-piperidin-4-yl)-N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-benzamide;

4-{4-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethylcarbamoyl]-phenyl}-piperidine-1-carboxylic acid amide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(1-methyl-1-oxy-piperidin-4-yl)-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(1-methyl-piperidin-4-yl)-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(1-methanesulfonyl-piperidin-4-yl)-benzamide;

4-(2-Acetylamino-1,1-dimethyl-ethyl)-N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(2-methanesulfonylamino-1,1-dimethyl-ethyl)-benzamide;

Piperidine-4-carboxylic acid (2-{4-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethylcarbamoyl]-phenyl}-2-methyl-propyl)-amide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(1,1-dimethyl-2-ureido-ethyl)-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(3-ethyl-ureido)-1,1-dimethyl-ethyl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(2-dimethylamino-3,4,5,6-tetrahydro-pyrimidin-4-yl)-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(1-oxy-pyridin-4-yloxy)-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(1-methyl-piperidin-4-yloxy)-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-(1,2,3,6-tetrahydropyridin-4-yl)-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-piperidin-4-yl-benzamide;

4-(2-Amino-1,1-dimethylethyl)-N-(2-[3-Carbamimidoylindol-5-yl]ethyl)benzamide;

N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-(6-[2-dimethylaminoethoxy]pyridin-3-yl)benzamide;

N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-pyrid-4-ylbenzamide;

N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-(4-carbamoyl-phenyl)-benzamide;

N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-(4-methoxy-phenyl)-benzamide;

N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-(5-methoxy-indol-2-yl)-carboxamide;

N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-(6-chloro-benzothiophen-2-yl)-carboxamide;

N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-(4-benzyloxy-phenyl)-benzamide;
N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-chloro-benzamide;
N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-(methylsulphonyl)-benzamide;
N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-(amino-sulphonyl)-benzamide;
4-(3-Aminoprop-1-ynyl)-N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-benzamide;
5-{4-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethylcarbamoyl]phenyl}-2-oxo-2H-pyridin-1-yl)acetic acid; and
3-Carbamimidoyl-5-{2-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzoylamino]-propyl}-indole.

29. A compound according to claim 28 which is
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(pyridazin-4-yl)-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-2-methyl-4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzamide;
N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-(6-methoxypyrid-3-yl)benzamide;
N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-(1-oxy-pyrid-4-yl)benzamide;
N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(7H-pyrrolo[2,3-d]pyrimidin-6-yl)-benzamide;
N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(1H-pyrrolo[3,2-c]pyridin-2-yl)-benzamide;
N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-3-chloro-4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzamide;
N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-(6-oxo-1,6-dihydropyrid-3-yl)benzamide;
4-(3-Amino-1,1-dimethyl-propyl)-N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-benzamide;
4-(2-Aminomethyl-pyridin-4-yl)-N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-benzamide;
4-{4-[2-(3-Carbamimidoy-1H-indol-5-yl)-ethylcarbamoyl]-phenyl-pyridine-2-carboylic acid amide;
N-[2-(3-Carbamimidoy-1H-indol-5-yl-ethyl]-4-(2-(N,N-dimethylaminomethyl)-pyridin-4-yl)benzamide);
N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(6-oxo-1,6-dihydro-pyridazin-3-yl)-benzamide;
N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(6-methoxy-pyridazin-3-yl)-benzamide;
N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[1-(2-dimethylamino-ethyl)-6-oxo-1,6-dihydro-pyridazin-3-yl]-benzamide;
N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[1-(3-dimethylamino-propyl)-6-oxo-1,6-dihydro-pyridazin-3-yl]-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(2-dimethylamino-ethylamino)-pyrimidin-4-yl]-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-methoxy-pyrimidin-4-yl]-benzamide;
N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-(1-[2-dimethylaminoethyl]-6-oxo-1,6-dihydropyridin-3-yl)benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl-4-(6-oxo-piperidin-3-yl)-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(morpholin-4yl-ethylamino)-pyrimidin-4-yl]-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(3-dimethylamino-propylamino)-pyrimidin-4-yl]-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-([2-dimethylamino-ethyl]-methyl-amino)-pyrimidin-4-yl}-benzamide;
2-[(4-{4-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethylcarbamoyl]-phenyl}-pyrimidin-2-yl)-methyl-amino]-ethanesulfonic acid;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-{2-[methyl-(2(S),3(R),4(R),5(R),6-pentahydroxy-hexyl)-amino]-pyrimidin-4-yl}-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-{2-[methyl-(2(S),3(R),4(S),5(R),6-pentahydroxy-hexyl)-amino]-pyrimidin-4-yl}-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(2-hydroxy-1-hydroxymethyl-ethylamino)-pyrimidin-4-yl]-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(3-imidazol-1-yl-propylamino)-pyrimidin-4-yl]-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-{2-[(2-diethylamino-ethyl)-methyl-amino]-pyrimidin-4-yl}-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(2-diisopropylamino-ethylamino)-pyrimidin-4-yl]-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(2-dibutylamino-ethylamino)-pyrimidin-4-yl]-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(3-morpholin-4-yl-propylamino)-pyrimidin-4-yl]-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(3-diethylamino-propylamino)-pyrimidin-4-yl]-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(3-piperidin-1-yl-propylamino)-pyrimidin-4-yl]-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(2-{[2-(ethyl-methyl-amino)-ethyl]-methyl-amino}-pyrimidin-4-yl)-benzamide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(5-dimethylamino-pentylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(5-morpholin-4-yl-pentylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(5-piperidin-1-yl-pentylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(5-pyrrolidin-1-yl-pentylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(2-oxo-hexahydro-pyrimidin-5-yl)-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(1,3-dimethyl-2-oxo-hexahydro-pyrimidin-5-yl)-benzamide;

Biphenyl-3,4'-dicarboxylic acid 4'-{[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-amide} 3-[(2-methoxy-ethyl)-amide];

Biphenyl-3,4'-dicarboxylic acid 4'-{[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-amide} 3-[(2-morpholin-4-yl-ethyl)-amide];

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(4-methylpiperazin-1-yl)pyrimidin-4-yl]benzamide;

4-[(4-{4-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethylcarbamoyl]phenyl}pyrimidin-2-yl)methylamino]butyric acid;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl]benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(2-pyrrolidin-1-ylpyrimidin-4-yl)benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(2-hydroxymethylpyrrolidin-1-yl)-pyrimidin-4-yl]benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(carbamoylmethyl-N-methylamino)-pyrimidin-4-yl]benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(6-pyrrolidin-1-yl-hexylamino)pyrimidin-4-yl]benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(6-piperidin-1-ylhexylamino)pyrimidin-4-yl]benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(4-piperidin-1-ylbutylamino)pyrimidin-4-yl]benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(4-diethylaminobutylamino)pyrimidin-4-yl]benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(6-morpholin-4-ylhexylamino)pyrimidin-4-yl]benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(6-dimethylaminohexylamino)pyrimidin-4-yl]benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(4-dimethylaminobutylamino)pyrimidin-4-yl]benzamide;

4-[2-(Bicyclo[2;2;1]hept-2-ylamino)pyrimidin-4-yl]-N-[2-(3-carbamimidoyl-1H-indol-5-yl)ethyl]benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-{2-[(2-hydroxy-ethyl)-N-methylamino]pyrimidin-4-yl}benzamide;

N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(2-morpholin-4-yl-pyrmidin-4-yl)-benzamide;

N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(cyclopropylmethyl-amino)-pyrimidin-4-yl]-benzamide;

N-[2-(carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-[(2-methoxy-ethyl)-methyl-amino]-pyrimidin-4-yl]-benzamide;

N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(3-hydroxy-propylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-carbamimidoyl -1H-indol-5-yl)-ethyl]-4-[(2-hydroxy-ethyl)-propyl-amino]-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indole-5yl)-ethyl]-4-(2-piperidin-1-yl-pyrimidin-4-yl)-benzamide;

N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(ethyl-methyl-amino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-carbamimidoyl -1H-indol-5-yl)-ethyl]-4-[2-(4-hydroxy-piperidin-1-yl)-pyrimidin-4-yl]-benzamide;

N-[2-(3-carbamimidoyl -1H-indol-5-yl)-ethyl]-4-[2-(2,3-dihydroxy-propylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-[(2,3-dihydroxy-propyl)-methyl-amino]-pyrimidin-4-yl]-benzamide;

N-[2-(3-carbamimidoyl -1H-indol-5-yl)-ethyl]-4-[2-((s)-2-methoxymethyl-pyrrolidin-1-yl)-pyrimidin-4-yl]-benzamide;

N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(2-piperazin-1-yl-pyrimidin-4-yl)-benzamide;

N-[2-(3-carbamimidoyl-1H-indol-5-yl)- 4-[2-[2-(2-oxo-imidazolidin-1-yl)-ethylamino]-pyrimidin-4-yl]-benzamide;

N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(3-methoxy-propylamino)-pyrimidin-4-yl]-benzamide;

4-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(2-hydroxy-ethylamino)-pyrimidin-4-yl]-benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)-ethyl]-4-[2-(2-methoxyethoxy)-pyrimidin-4-yl]benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(1-carbamoylethoxy)pyrimidin-4-yl]benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(6-dimethylaminohexyloxy)pyrimidin-4-yl]benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(2-pyrrolidin-1-yl-ethoxy)pyrimidin-4-yl]benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[2-(2-dimethylaminoethoxy)pyrimidin-4-yl]benzamide;

N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-(1-oxypyridin-2-yl)benzamide;

2'-(2-Dimethylaminoethoxy)biphenyl-4-carboxylic acid [2-(3-carbamimidoyl-1H-indol-5-yl)ethyl]amide;

2'-(3-Dimethylaminopropoxy)biphenyl-4-carboxylic acid [2-(3-carbamimidoyl-1H-indol-5-yl)ethyl]amide;
N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-4-(1-oxo-pyridin-3-yl)-benzamide;
4-[2-(acetylamino-methyl)-pyridin-4-yl]-N-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethyl]-benzamide;
Piperidine-4-carboxylic acid (4-[4-[2-(3-carbamimidoyl-1H-indol-5-yl)-ethylcarbamoyl]-phenyl-]-pyridin-2-ylmethyl)-amide;
N-[2-(3-Carbamimidoyl-1H-indol-5-yl)ethyl]-4-[1-(3-dimethylaminopropyl)-6-oxo-1,6-dihydropyridin-3-yl]benzamide;
4-(2-Amino-1,1-dimethylethyl)-N-(2-[3-carbamimidoylindol-5-yl]ethyl)benzamide; and
N-(2-[3-Carbamimidoylindol-5-yl]ethyl)-4-pyrid-4-ylbenzamide.

30. A pharmaceutical composition comprising a pharmaceutically acceptable amount of a compound according to claim 1 and a pharmaceutically acceptable carrier.

31. A method for treating a patient suffering from a physiological condition capable of being modulated by inhibiting activity of Factor Xa comprising administering to said patient a pharmaceutically effective amount of a compound according to claim 1.

32. The method according to claim 31 wherein the physiological condition is venous vasculature, arterial vasculature, abnormal thrombus formation, acute myocardial infarction, unstable angina, thromboembolism, acute vessel closure associated with thrombolytic therapy, percutaneous transluminal coronary angioplasty, transient ischemic attacks, stroke, intermittent claudication or bypass grafting of the coronary or peripheral arteries, vessel luminal narrowing, restenosis post coronary or venous angioplasty, maintenance of vascular access patency in long-term hemodialysis patients, pathologic thrombus formation occurring in the veins of the lower extremities following abdominal, knee or hip surgery, a risk of pulmonary thromboembolism, or of disseminated systemic intravascular coagulopathy occurring in vascular systems during septic shock, certain viral infections or cancer.

33. The method according to claim 31 wherein the physiological condition is abnormal thrombus formation, acute myocardial infarction, unstable angina, thromboembolism, acute vessel closure associated with thrombolytic therapy, transient ischemic attacks, intermittent claudication or bypass grafting of the coronary or peripheral arteries, restenosis post coronary or venous angioplasty, pathologic thrombus

formation occurring in the veins of the lower extremities following abdominal, knee and hip surgery or a risk of pulmonary thromboembolism.

34. The method according to claim 31 wherein the physiological condition is stroke, vessel luminal narrowing, maintenance of vascular access patency in long-term hemodialysis patients, or disseminated systemic intravascular coagulopathy occurring in vascular systems during septic shock, certain viral infections or cancer.

35. A method of inhibiting Factor Xa comprising contacting a Factor Xa inhibitory amount of a compound according to claim 1 with a composition containing Factor Xa.

36. A method of inhibiting the formation of thrombin comprising contacting a Factor Xa inhibitory amount of a compound according to claim 1 with a composition containing Factor Xa.

INTERNATIONAL SEARCH REPORT

Interr ıal Application No
PCT/US 99/30623

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/12 C07D403/12 A61K31/33 A61P7/02 C07D209/42
C07D409/14 C07D417/12 C07D409/12 C07D403/14 C07D401/14
C07D413/12 C07D487/04 C07D471/04 C07D491/04 C07D521/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 01428 A (THE DU PONT MERCK PHARMACEUTICAL COMPANY) 15 January 1998 (1998-01-15) page 4; claim 1	1,30,35
A	WO 97 24118 A (RHÔNE-POULENC RORER PHARMACEUTICALS INC.) 10 July 1997 (1997-07-10) claims 1,13	1,30,35

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 June 2000	18/07/2000

Name and mailing address of the ISA
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INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 99/30623

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 //(C07D487/04,239:00,209:00),(C07D471/04,221:00,209:00),
(C07D491/04,307:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 99/30623

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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C07D401/12
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C07D401/14 C07D413/12
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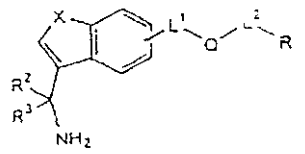
权利要求书23页 说明书220页 附图页数0页

[54]发明名称 取代的(氨基亚氨基甲基或氨基甲基)苯并杂芳基化合物

[57]摘要

本发明涉及式(Ⅰ)的(氨基亚氨基甲基或氨基甲基)苯并杂芳基 化合物,其中X为O、S或NR^1,这种化合物通过与含Xa因子的制品结 合而用于抑制Xa因子的活性。本发明还涉及含有式(Ⅰ)化合物的组 合物、它们的制备方法、它们的用途,如用于抑制凝血酶的形成或用 于治疗患有或易患与凝血酶的生理有害过量有关的疾病状态。


(1)

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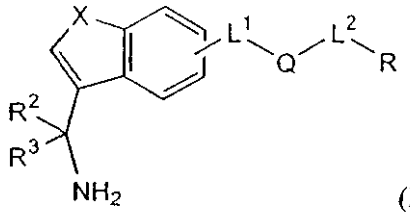
权 利 要 求 书

1. 式 I 化合物或其氧化物、可药用盐、溶剂化物或前药:



(I)

其中

X 为 O，S 或 NR^1;

R 为氢，环烷基，环烯基，杂环基，杂环烯基，稠合芳基环烷基，稠合杂芳基环烷基，稠合芳基环烯基，稠合杂芳基环烯基，稠合芳基杂环基，稠合杂芳基杂环基，稠合芳基杂环烯基，稠合杂芳基杂环烯基，芳基，稠合环烯基芳基，稠合环烷基芳基，稠合杂环基芳基，稠合杂环烯基芳基，杂芳基，稠合环烷基杂芳基，稠合环烯基杂芳基，稠合杂环烯基杂芳基或稠合杂环基杂芳基，条件是当 L^2 为化学键时，则 Q 通过其碳原子与 R 连接，或者当 R 为氢时，则 L^2 不能为化学键;

R^1 为氢，烷基，芳烷基，杂芳烷基，酰基，芳酰基，杂芳酰基，烷氧基羰基，芳氧基羰基或杂芳氧基羰基;

R^2 和 R^3 为氢，或者一起表示=NR^4;

R^4 为氢，R^5O_2C-，R^5O-，HO-，氰基，R^5CO-，HCO-，低级烷基，硝基，或 R^6R^7N-;

R^5 为烷基，芳基，杂芳基，芳烷基，或杂芳烷基;

R^6 和 R^7 独立地为氢或烷基;

L^1 为亚烷基，亚烯基或亚炔基;

L^2 为化学键，亚烷基，亚烯基或亚炔基;

Q 为-$NR^{8'}$-，-O-，-C(O)-，-C(O)-O-，-O-C(O)-，-$NR^{8'}C(X^1)$-，-$C(X^1)NR^{8'}$-，-$NR^8C(X^1)O$-，-$OC(X^1)NR^8$-，-$NR^8C(X^1)NR^8$-，-$NR^8C(X^1)NR^8$-，-$S(O)_n$-，-NR^8SO_2-或-SO_2NR^8-，条件是 Q 的氮原子或氧原子不能与具有双键或三键的 L^1 或 L^2 的碳原子直接键连，或者 Q-L^2-R 为环烷基，环烯

基，杂环基，杂环烯基，稠合芳基环烷基，稠合杂芳基环烷基，稠合芳基环烯基，稠合杂芳基环烯基，稠合芳基杂环基，稠合杂芳基杂环基，稠合芳基杂环烯基，稠合杂芳基杂环烯基，芳基，稠合环烯基芳基，稠合环烷基芳基，稠合杂环基芳基，稠合杂环烯基芳基，杂芳基，稠合环烷基杂芳基，稠合环烯基杂芳基，稠合杂环烯基杂芳基或稠合杂环基杂芳基，条件是 Q 的氮原子或氧原子不能与具有双键或三键的 L^1 的碳原子直接键连；

X^1 为 O 或 S；

$R^{8'}$ 为氢，烷基，芳烷基，杂芳烷基，酰基，芳酰基，杂芳酰基或烷氧基羰基；

R^8 为氢，烷基，芳烷基，杂芳烷基，酰基，芳酰基或杂芳酰基；和

n 为 0、1 或 2。

2. 权利要求 1 的化合物，其中 R 为芳基，杂芳基或杂环基。

3. 权利要求 1 的化合物，其中 R 为取代苯基。

4. 权利要求 1 的化合物，其中 R 为任选取代的（苯基取代苯基），任选取代的（杂芳基取代苯基），任选取代的（苯基取代杂芳基），任选取代的（杂芳基取代杂芳基），任选取代的（苯基取代环烷基），任选取代的（杂芳基取代环烷基），任选取代的（环烷基取代杂芳基），任选取代的（环烷基取代苯基），任选取代的（环烷基取代环烷基），任选取代的（苯基取代环烯基），任选取代的（杂芳基取代环烯基），任选取代的（环烯基取代杂芳基），任选取代的（环烯基取代苯基），任选取代的（环烯基取代环烯基），任选取代的（苯基取代杂环基），任选取代的（杂芳基取代杂环基），任选取代的（环烷基取代杂环基），任选取代的（杂环基取代苯基），任选取代的（杂环基取代杂环基），任选取代的（苯基取代杂环烯基），任选取代的（杂芳基取代杂环烯基），

任选取代的（环烯基取代杂环烯基），任选取代的（杂环烯基取代苯基），或任选取代的（杂环烯基取代杂环烯基）。

5. 权利要求 1 的化合物，其中 R 为任选取代的（苯基取代苯基），任选取代的（杂芳基取代苯基），任选取代的（苯基取代杂芳基），任选取代的（杂芳基取代杂芳基），任选取代的（苯基取代杂环基），任选取代的（杂芳基取代杂环基），任选取代的（环烷基取代杂环基），任选取代的（杂环基取代苯基），任选取代的（杂环基取代杂环基），任选取代的（苯基取代杂环烯基），任选取代的（杂芳基取代杂环烯基），任选取代的（环烯基取代杂环烯基），任选取代的（杂环烯基取代苯基），或任选取代的（杂环烯基取代杂环烯基）。

6. 权利要求 1 的化合物，其中 R 为任选取代的（苯基取代杂芳基），任选取代的（苯基取代杂环基），和任选取代的（苯基取代杂环烯基）。

7. 权利要求 1 的化合物，其中 R 为任选取代的（苯基取代杂芳基），任选取代的（苯基取代杂环基），和任选取代的（苯基取代杂环烯基）；L^2 与所述苯基在苯基部分的 1-位上键连，而所述杂环基、杂环烯基或杂芳基则与所述苯基在苯基部分的 4-位上键连。

8. 权利要求 1 的化合物，其中 X 为 NR^1。

9. 权利要求 1 的化合物，其中 R^1 为氢。

10. 权利要求 1 的化合物，其中 R^8 为氢。

11. 权利要求 1 的化合物，其中 R^2 与 R^3 一起表示=NR^4。

12. 权利要求 1 的化合物，其中 R^4 为氢。

13. 权利要求 1 的化合物，其中 R^5 为烷基。

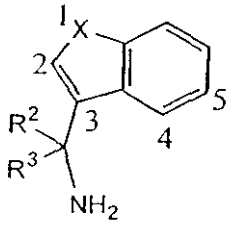
14. 权利要求 9 的化合物，其中 R^5 为甲基。

15. 权利要求 1 的化合物，其中 R^6 和 R^7 均为氢。

16. 权利要求 1 的化合物，其中 L^1 为亚烷基。

17. 权利要求 1 的化合物，其中 L^1 为 1,2-亚乙基。

18. 权利要求 1 的化合物，其中 L^1 键连在



部分的 5-位上。

19. 权利要求 1 的化合物，L^2 为化学键或亚烷基。

20. 权利要求 14 的化合物，其中 L^2 为化学键。

21. 权利要求 1 的化合物，其中 X^1 为 O。

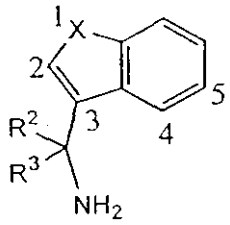
22. 权利要求 1 的化合物，其中 Q 为 $-NR^8CO-$，$-CONR^8-$，$-NR^8SO_2-$ 或 $-SO_2NR^8-$。

23. 权利要求 1 的化合物，其中 Q 为 $-NR^8CO-$。

24. 权利要求 1 的化合物，其中 R^8 和 $R^{8'}$ 均为氢。

25. 权利要求 1 的化合物，其中 n 为 2。

26. 权利要求 1 的化合物，其中 L^1 与：



部分的 5-位键连；R 为任选取代的（苯基取代吡啶酮基），任选取代的（苯基取代吡咯并嘧啶基），任选取代的（苯基取代哒嗪基），任选取代的（苯基取代哒嗪酮基），任选取代的（苯基取代吡啶基），或任选取代的（苯基取代嘧啶基）。

27. 权利要求 1 的化合物，其中 R 为取代的（苯基取代嘧啶基），所述嘧啶基被至少一个选自烷氧基、Y^1Y^2N-烷基-、Y^1Y^2N-、氮杂杂环基、Y^1Y^2NCO-亚烷基-O-、氮杂杂环基-亚烷基-O-、和 Y^1Y^2N-亚烷基-O－的环系取代基所取代；其中

Y^1 和 Y^2 独立地为氢，烷基，烷氧基烷基，羟基烷基，环烷基，环烷基-烷基，Y^1Y^2N-烷基，芳基，芳烷基，杂芳烷基，杂环基烷基，杂环烯基烷基，或磺基-烷基-；或者当 Y^1 为 H-CO-，烷基-CO-，芳基-CO-，或杂环基-CO-时，则 Y^2 为氢，烷基，芳基，或芳烷基。

28. 根据权利要求 1 的化合物，所述化合物为：

N-(2-[3-脒基-5-吲哚基]乙基)-4-吡啶-3-基苯甲酰胺；

N-(2-[3-脒基-5-吲哚基]乙基)-4-(嘧啶-5-基)-苯甲酰胺)；

5-(吡啶-2-基)-噻吩-2-羧酸 2-(3-脒基-5-吲哚基)乙基酰胺；

N-(2-[3-脒基吲哚-5-基]乙基)-6-吗啉-4-基烟酰胺 4-(5-2[-{3-脒基吲哚-5-基}乙基氨基甲酰基]吡啶-2-基)哌嗪-1-羧酸乙酯；

N-(2-[3-脒基吲哚-5-基]乙基)-6-咪唑-1-基烟酰胺；

N-(2-[3-脒基吲哚-5-基]乙基)-4-咪唑-1-基苯甲酰胺;

N-(2-[3-脒基吲哚-5-基]乙基)-4-(3H-咪唑-4-基)苯甲酰胺;

N-(2-[3-脒基吲哚-5-基]乙基)-4-(1,2,4)噻二唑-5-基苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(1-氨基甲酰基-1-甲基-乙基-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(1-[N-(2-甲氧基乙基)]-氨基甲酰基-1-甲基-乙基-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(叔丁基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(哒嗪-4-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-2-甲基-4-(6-氧代-1,6-二氢-吡啶-3-基)-苯甲酰胺;

3′, 4′-二甲氧基联苯-4-羧酸(2-[3-脒基吲哚-5-基]乙基)酰胺;

N-(2-[3-脒基吲哚-5-基]-乙基)-4-(6-甲氧基吡啶-3-基)-苯甲酰胺;

N-(2-[3-脒基吲哚-5-基]-乙基)-4-(1-氧化-吡啶-4-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(7H-吡咯并[2,3-d]嘧啶-6-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(1H-吡咯并[3,2-c]吡啶-2-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-呋喃并[3,2-c]吡啶-2-基-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-3-氯-4-(6-氧代-1,6-二氢-吡啶-3-基)-苯甲酰胺;

N-(2-[3-脒基-1H-吲哚-5-基]-乙基)-4-(6-氧代-1,6-二氢-吡啶-3-基)-苯甲酰胺;

4-(3-氨基-1,1-二甲基-丙基)-N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-2-(4-氯-苯基)-乙酰胺;

5-氯-噻吩-2-羧酸[2-(3-脒基-1H-吲哚-5-基)-乙基]-酰胺;

N-(2-[3-脒基吲哚-5-基]乙基)-6-(2-羟基乙基氨基)烟酰胺;

N-(2-[3-脒基吲哚-5-基]乙基)-6-(1,2,4)-三唑-1-基烟酰胺;

N-(2-[3-脒基吲哚-5-基]乙基)-6-吡咯-1-基烟酰胺;

N-(2-[3-脒基吲哚-5-基]乙基)-6-吡唑-1-基烟酰胺;

N-(2-[3-脒基-1-甲基吲哚-5-基]乙基)-4-(6-甲氧基吡啶-3-基)苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-3-氯-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-2-(3-氯-苯基)-乙酰胺;

4-(2-氨基甲基-吡啶-4-基)-N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-苯甲酰胺;

4-{4-[2-(3-脒基-1H-吲哚-5-基)-乙基氨基甲酰基]-苯基-吡啶-2-羧酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(2-(N,N-二甲氨基甲基)-吡啶-4-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(6-氧代-1,6-二氢-哒嗪-3-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(6-甲氧基-哒嗪-3-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[1-(2-二甲氨基-乙基)-6-氧代-1,6-二氢-哒嗪-3-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[1-(3-二甲氨基-丙基)-6-氧代-1,6-二氢-哒嗪-3-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-(2-二甲氨基-乙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-甲氧基-嘧啶-4-基]-苯甲酰胺;

N-(2-[3-脒基吲哚-5-基]乙基)-4-(1-[2-二甲氨基乙基]-6-氧代

-1,6-二氢吡啶-3-基)苯甲酰胺;

N-(2-[3-脒基吲哚-5-基]乙基)-4-(1-氨基甲酰基甲基-6-氧代-1,6-二氢吡啶-3-基)苯甲酰胺;

4-(3-氨基-[1,2,4]三嗪-6-基)-N-[2-(3-脒基-1H-吲哚-5-基]乙基)-苯甲酰胺;

4-(3-氨基-[1,2,4]三嗪-5-基)-N-[2-(3-脒基-1H-吲哚-5-基]乙基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(3-氧代-2,3-二氢-[1,2,4]三嗪-6-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(5-氧代-4,5-二氢-[1,2,4]噁二唑-3-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(6-氧代-哌啶-3-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(吗啉-4-基-乙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(3-二甲氨基-丙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-([2-二甲氨基-乙基]-甲基-氨基)-嘧啶-4-基]-苯甲酰胺;

2-[(4-{4-[2-(3-脒基-1H-吲哚-5-基)-乙基氨基甲酰基]-苯基}-嘧啶-2-基)-甲基-氨基]-乙磺酸;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-{2-[甲基-2(S),3(R),4(R),5(R),6-五羟基-己基)-氨基]-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-{2-[甲基-2(S),3(R),4(S),5(R),6-五羟基-己基)-氨基]-嘧啶-4-基}-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2-羟基-1-羟甲基-乙基氨基)-嘧啶-4-基]-苯甲酰胺;

2-[(4-{4-[2-(3-脒基-1H-吲哚-5-基)-乙基氨基甲酰基]-苯基}-嘧啶-2-基)-甲基-氨基]-乙烷磺酸;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(3-咪唑-1-基-丙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-{2-[(2-二乙基氨基-乙基)-甲基-氨基]-嘧啶-4-基}-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2-二异丙基氨基-乙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2-二丁基氨基-乙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(3-吗啉-4-基-丙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(3-二乙基氨基-丙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(3-哌啶-1-基-丙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(2-{[2-(乙基-甲基-氨基)-乙基]-甲基-氨基}-嘧啶-4-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(5-二甲氨基-戊基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(5-吗啉-4-基-戊基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(5-哌啶-1-基-戊基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(5-吡咯烷-1-基-戊基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(2-氧代-六氢-嘧啶-5-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(1,3-二甲基-2-氧代-六

氢-嘧啶-5-基)-苯甲酰胺;

联苯-3,4′-二羧酸 4′-{[2-(3-脒基-1H-吲哚-5-基)-乙基]-酰胺}3-[(2-甲氧基-乙基)-酰胺];

3′-(吗啉-4-羰基)-联苯-4-羧酸[2-(3-脒基-1H-吲哚-5-基)-乙基]-酰胺;

联苯-3,4′-二羧酸 4′-{[2-(3-脒基-1H-吲哚-5-基)-乙基]-酰胺}3-[(2-吗啉-4-基-乙基)-酰胺];

联苯-2,4′-二羧酸 4′-{[2-(3-脒基-1H-吲哚-5-基)-乙基]-酰胺}2-[(3-二乙基氨基-丙基)-酰胺];

联苯-2,4′-二羧酸 4′-{[2-(3-脒基-1H-吲哚-5-基)-乙基]-酰胺}2-[(3-吗啉-4-基-丙基)-酰胺];

联苯-2,4′-二羧酸 4′-{[2-(3-脒基-1H-吲哚-5-基)-乙基]-酰胺}2-[(3-哌啶-1-基-丙基)-酰胺];

联苯-2,4′-二羧酸 4′-{[2-(3-脒基-1H-吲哚-5-基)-乙基]-酰胺}2-[(4-二甲氨基-丁基)-酰胺];

联苯-2,4′-二羧酸 4′-{[2-(3-脒基-1H-吲哚-5-基)-乙基]-酰胺}2-[(2,3-二羟基-丙基)-甲基-酰胺];

联苯-2,4′-二羧酸 4′-{[2-(3-脒基-1H-吲哚-5-基)-乙基]-酰胺}2-[(2,3-二羟基-丙基)-酰胺];

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(4-甲基哌嗪-1-基)-嘧啶-4-基]-苯甲酰胺;

4-[(4-{4-[2-(3-脒基-1H-吲哚-5-基)乙基氨基甲酰基]苯基}-嘧啶-2-基)甲基氨基]丁酸;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2,2,2-三氟乙氧基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(2-吡咯烷-1-基嘧啶-4-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2-羟甲基吡咯烷-1-基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(氨基甲酰基甲基-N-甲基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(6-吡咯烷-1-基-己基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(6-哌啶-1-基-己基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(4-哌啶-1-基丁基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(4-二乙基氨基丁基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(6-吗啉-4-基-己基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(6-二甲氨基己基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(4-二甲氨基丁基氨基)-嘧啶-4-基]-苯甲酰胺;

4-[2-(二环[2;2;1]庚-2-基氨基)嘧啶-4-基]-N-[2-(3-脒基-1H-吲哚-5-基)乙基]苯甲酰胺;

1-(4-{4-[2-(3-脒基-1H-吲哚-5-基)乙基氨基甲酰基]苯基}-嘧啶-2-基]-吡咯烷-2-羧酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-{2-[(2-羟基-乙基)-N-甲基氨基]-嘧啶-4-基}-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(2-吗啉-4-基-嘧啶-4-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(环丙基甲基-氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(脒基-1H-吲哚-5-基)乙基]-4-[2-[(2-甲氧基-乙基)-甲基-氨基]-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(3-羟基-丙基氨基)-

嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[(2-羟基-乙基)-丙基-氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(2-哌啶-1-基-嘧啶-4-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(乙基-甲基-氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(4-羟基-哌啶-1-基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2,3-二羟基-丙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-[(2,3-二羟基-丙基)-甲基-氨基]-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-((s)-2-甲氧基甲基-吡咯烷-1-基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(2-哌嗪-1-基-嘧啶-4-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-[2-(2-氧代-咪唑烷-1-基)-乙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(3-甲氧基-丙基氨基)-嘧啶-4-基]-苯甲酰胺;

4-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2-羟基-乙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2-甲氧基乙氧基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(1-氨基甲酰基乙氧基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(6-二甲氨基己氧基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2-氧代哌啶-3-基氧基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2-吡咯烷-1-基-乙氧基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2-二甲氨基乙氧基)-嘧啶-4-基]-苯甲酰胺;

3′-(2-二甲氨基乙氧基)联苯-4-羧酸[2-(3-脒基-1H-吲哚-5-基)乙基]酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(1-氧吡啶-2-基)-苯甲酰胺;

2′-(2-二甲氨基乙氧基)联苯-4-羧酸[2-(3-脒基-1H-吲哚-5-基)乙基]酰胺;

2′-(3-二甲氨基丙氧基)联苯-4-羧酸[2-(3-脒基-1H-吲哚-5-基)乙基]酰胺;

3′-(3-二甲氨基丙氧基)联苯-4-羧酸[2-(3-脒基-1H-吲哚-5-基)乙基]酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(1-氧代-吡啶-3-基)-苯甲酰胺;

4-[2-(乙酰氨基-甲基)-吡啶-4-基]-N-[2-(3-脒基-1H-吲哚-5-基)乙基]-苯甲酰胺;

哌啶-4-羧酸(4-[4-[2-(3-脒基-1H-吲哚-5-基)乙基氨基甲酰基]-苯基-]-吡啶-2-基甲基)-酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[1-(3-二甲氨基丙基)-6-氧代-1,6-二氢吡啶-3-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[6-(3-二甲氨基丙氧基)-吡啶-3-基]-苯甲酰胺;

(5-{4-[2-(3-脒基-1H-吲哚-5-基)乙基氨基甲酰基]苯基}-2-氧代-2H-吡啶-1-基)乙酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-{1-[(2-二甲氨基乙基氨

基甲酰基)甲基]-6-氧代-1,6-二氢吡啶-3-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(4-二甲氨基-哌啶-1-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[4-(2-二甲氨基-乙基氨基)-哌啶-1-基]-苯甲酰胺;

4-(4-氨基-哌啶-1-基)-N-[2-(3-脒基-1H-吲哚-5-基)乙基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(4-甲氧基-哌啶-1-基)-苯甲酰胺;

4-(4-乙酰氨基-哌啶-1-基)-N-[2-(3-脒基-1H-吲哚-5-基)乙基]-苯甲酰胺;

4-(1-乙酰基-哌啶-4-基)-N-[2-(3-脒基-1H-吲哚-5-基)乙基]-苯甲酰胺;

4-{4-[2-(3-脒基-1H-吲哚-5-基)乙基氨基甲酰基]-苯基}-哌啶-1-羧酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(1-甲基-1-氧-哌啶-4-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(1-甲基-哌啶-4-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(1-甲磺酰基-哌啶-4-基)-苯甲酰胺;

4-(2-乙酰氨基-1,1-二甲基-乙基)-N-[2-(3-脒基-1H-吲哚-5-基)乙基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(2-甲磺酰氨基-1,1-二甲基-乙基)-苯甲酰胺;

哌啶-4-羧酸(2-{4-[2-(3-脒基-1H-吲哚-5-基)乙基氨基甲酰基]-苯基}-2-甲基丙基)-酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(1,1-二甲基-2-脲基-乙基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(3-乙基脲基)-1,1-二甲基-乙基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(2-二甲氨基-3,4,5,6-四氢-嘧啶-4-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(1-氧-吡啶-4-基氧基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(1-甲基-哌啶-4-基氧基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(1,2,3,6-四氢吡啶-4-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-哌啶-4-基-苯甲酰胺;

4-(2-氨基-1,1-二甲基乙基)-N-(2-[3-脒基吲哚-5-基]乙基)苯甲酰胺;

N-(2-[3-脒基吲哚-5-基]乙基)-4-(6-[2-二甲氨基乙氧基]吡啶-3-基)-苯甲酰胺;

N-(2-[3-脒基吲哚-5-基]乙基)-4-吡啶-4-基苯甲酰胺;

N-(2-[3-脒基吲哚-5-基]乙基)-4-(4-氨基甲酰基-苯基)-苯甲酰胺;

N-(2-[3-脒基吲哚-5-基]乙基)-4-(4-甲氧基-苯基)-苯甲酰胺;

N-(2-[3-脒基吲哚-5-基]乙基)-(5-甲氧基-吲哚-2-基)-甲酰胺;

N-(2-[3-脒基吲哚-5-基]乙基)-(6-氯-苯并噻吩-2-基)-甲酰胺;

N-(2-[3-脒基吲哚-5-基]乙基)-4-(4-苄氧基-苯基)-苯甲酰胺;

N-(2-[3-脒基吲哚-5-基]乙基)-4-氯苯甲酰胺;

N-(2-[3-脒基吲哚-5-基]乙基)-4-(甲磺酰基)-苯甲酰胺;

N-(2-[3-脒基吲哚-5-基]乙基)-4-(氨基-磺酰基)-苯甲酰胺;

4-(3-氨基丙-1-炔基)-N-[2-(3-脒基-1H-吲哚-5-基)乙基]-苯甲酰胺;

5-{4-[2-(3-脒基-1H-吲哚-5-基)乙基氨基甲酰基]-苯基}-2-氧代-2H-吡啶-1-基)乙酸; 和

3-脒基-5-{2-[4-(6-氧代-1,6-二氢-吡啶-3-基)-苯甲酰基氨基]-丙基}-吲哚。

29. 根据权利要求 28 的化合物，所述化合物为:

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(哒嗪-4-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-2-甲基-4-(6-氧代-1,6-二氢-吡啶-3-基)-苯甲酰胺;

N-(2-[3-脒基吲哚-5-基]乙基)-4-(6-甲氧基吡啶-3-基)-苯甲酰胺;

N-(2-[3-脒基吲哚-5-基]乙基)-4-(1-氧-吡啶-4-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(7H-吡咯并[2,3-d]嘧啶-6-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(1H-吡咯并[3,2-c]吡啶-2-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-3-氯-4-(6-氧代-1,6-二氢-吡啶-3-基)-苯甲酰胺;

N-(2-[3-脒基吲哚-5-基]乙基)-4-(6-氧代-1,6-二氢吡啶-3-基)-苯甲酰胺;

4-(3-氨基-1,1-二甲基-丙基)-N-[2-(3-脒基-1H-吲哚-5-基)乙基]-苯甲酰胺;

4-(2-氨基甲基-吡啶-4-基)-N-[2-(3-脒基-1H-吲哚-5-基)乙基]-苯甲酰胺;

4-{4-[2-(3-脒基-1H-吲哚-5-基)乙基氨基甲酰基]-苯基-吡啶-2-羧酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(2-(N,N-二甲氨基甲基)-吡啶-4-基)-苯甲酰胺);

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(6-氧代-1,6-二氢-哒嗪-3-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(6-甲氧基-哒嗪-3-基)-

苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[1-(2-二甲氨基-乙基)-6-氧代-1,6-二氢-哒嗪-3-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[1-(3-二甲氨基-丙基)-6-氧代-1,6-二氢-哒嗪-3-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2-二甲氨基-乙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-甲氧基-嘧啶-4-基]-苯甲酰胺;

N-(2-[3-脒基吲哚-5-基]乙基)-4-(1-[2-二甲氨基乙基]-6-氧代-1,6-二氢吡啶-3-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(6-氧代-哌啶-3-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(吗啉-4-基-乙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(3-二甲氨基-丙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-([2-二甲氨基-乙基]-甲基-氨基)-嘧啶-4-基]-苯甲酰胺;

2-[(4-{4-[2-(3-脒基-1H-吲哚-5-基)乙基氨基甲酰基]-苯基}-嘧啶-2-基)-甲基-氨基]-乙烷磺酸;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-{2-[甲基-2(S),3(R),4(R),5(R),6-五羟基-己基)-氨基]-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-{2-[甲基-2(S),3(R),4(S),5(R),6-五羟基-己基)-氨基]-嘧啶-4-基}-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2-羟基-1-羟甲基-乙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(3-咪唑-1-基-丙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-{2-[(2-二乙基氨基-乙基)-甲基-氨基]-嘧啶-4-基}-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2-二异丙基氨基-乙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2-二丁基氨基-乙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(3-吗啉-4-基-丙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(3-二乙基氨基-丙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(3-哌啶-1-基-丙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(2-{[2-(乙基-甲基-氨基)-乙基]-甲基-氨基}-嘧啶-4-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(5-二甲氨基-戊基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(5-吗啉-4-基-戊基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(5-哌啶-1-基-戊基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(5-吡咯烷-1-基-戊基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(2-氧代-六氢-嘧啶-5-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(1,3-二甲基-2-氧代-六氢-嘧啶-5-基)-苯甲酰胺;

联苯-3,4′-二羧酸 4′-{[2-(3-脒基-1H-吲哚-5-基)-乙基]-酰胺}

3-[(2-甲氧基-乙基)-酰胺]；

联苯-3,4'-二羧酸 4'-{[2-(3-脒基-1H-吲哚-5-基)-乙基]-酰胺}3-[(2-吗啉-4-基-乙基)-酰胺]；

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(4-甲基哌嗪-1-基)-嘧啶-4-基]-苯甲酰胺；

4-[(4-{4-[2-(3-脒基-1H-吲哚-5-基)乙基氨基甲酰基]苯基}-嘧啶-2-基)甲基氨基]丁酸；

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2,2,2-三氟乙氧基)-嘧啶-4-基]-苯甲酰胺；

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(2-吡咯烷-1-基嘧啶-4-基)-苯甲酰胺；

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2-羟甲基吡咯烷-1-基)-嘧啶-4-基]-苯甲酰胺；

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(氨基甲酰基甲基-N-甲基氨基)-嘧啶-4-基]-苯甲酰胺；

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(6-吡咯烷-1-基-己基氨基)-嘧啶-4-基]-苯甲酰胺；

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(6-哌啶-1-基-己基氨基)-嘧啶-4-基]-苯甲酰胺；

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(4-哌啶-1-基丁基氨基)-嘧啶-4-基]-苯甲酰胺；

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(4-二乙基氨基丁基氨基)-嘧啶-4-基]-苯甲酰胺；

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(6-吗啉-4-基-己基氨基)-嘧啶-4-基]-苯甲酰胺；

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(6-二甲氨基己基氨基)-嘧啶-4-基]-苯甲酰胺；

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(4-二甲氨基丁基氨基)-嘧啶-4-基]-苯甲酰胺；

4-[2-(二环[2;2;1]庚-2-基氨基)嘧啶-4-基]-N-[2-(3-脒基-1H-吲哚-5-基)乙基]苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-{2-[(2-羟基-乙基)-N-甲基氨基]-嘧啶-4-基}-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(2-吗啉-4-基-嘧啶-4-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(环丙基甲基-氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(脒基-1H-吲哚-5-基)乙基]-4-[2-[(2-甲氧基-乙基)-甲基-氨基]-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(3-羟基-丙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[(2-羟基-乙基)-丙基-氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(2-哌啶-1-基-嘧啶-4-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(乙基-甲基-氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(4-羟基-哌啶-1-基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2,3-二羟基-丙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-[(2,3-二羟基-丙基)-甲基-氨基]-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-((s)-2-甲氧基甲基-吡咯烷-1-基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(2-哌嗪-1-基-嘧啶-4-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-[2-(2-氧代-咪唑烷

-1-基)-乙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(3-甲氧基-丙基氨基)-嘧啶-4-基]-苯甲酰胺;

4-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2-羟基-乙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2-甲氧基乙氧基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(1-氨基甲酰基乙氧基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(6-二甲氨基己氧基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2-吡咯烷-1-基-乙氧基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2-二甲氨基乙氧基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(1-氧吡啶-2-基)-苯甲酰胺;

2′-(2-二甲氨基乙氧基)联苯-4-羧酸[2-(3-脒基-1H-吲哚-5-基)乙基]酰胺;

2′-(3-二甲氨基丙氧基)联苯-4-羧酸[2-(3-脒基-1H-吲哚-5-基)乙基]酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(1-氧代-吡啶-3-基)-苯甲酰胺;

4-[2-(乙酰氨基-甲基)-吡啶-4-基]-N-[2-(3-脒基-1H-吲哚-5-基)乙基]-苯甲酰胺;

哌啶-4-羧酸(4-[4-[2-(3-脒基-1H-吲哚-5-基)乙基氨基甲酰基]-苯基-]-吡啶-2-基甲基)-酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[1-(3-二甲氨基丙基)-6-氧代-1,6-二氢吡啶-3-基]-苯甲酰胺;

4-(2-氨基-1,1-二甲基乙基)-N-(2-[3-脒基吲哚-5-基]乙基)苯甲酰胺；和

N-(2-[3-脒基吲哚-5-基]乙基)-4-吡啶-4-基苯甲酰胺。

30. 一种药物组合物，其包括可药用量的权利要求 1 的化合物以及可药用载体。

31. 一种治疗患有通过抑制 Xa 因子的活性而能调控的生理性病症的患者的方法，它包括对所述患者给药药学有效量的权利要求 1 的化合物。

32. 根据权利要求 31 的方法，其中的生理性病症为静脉脉管系统，动脉脉管系统，异常血栓形成，急性心肌梗塞，不稳定性心绞痛，血栓栓塞，与溶栓治疗有关的急性血管闭合，经皮经管腔动脉血管成形术，暂短性缺血发作，中风，间歇性跛行或冠状或外周动脉的旁路移植，血管腔缩小，冠状动脉或静脉血管成形术后的再狭窄，长期血液透析患者脉管通路开放的维持，发生于腹、膝和髋部外科手术之后低肢端静脉中的病理性血栓形成，高危肺血栓栓塞，或发生于脓毒性休克、某些病毒感染和癌症期间血管系统的全身弥散性血管内凝血病。

33. 根据权利要求 31 的方法，其中的生理性病症为异常血栓形成，急性心肌梗塞，不稳定性心绞痛，血栓栓塞，与溶栓治疗有关的急性血管闭合，暂短性缺血发作，间歇性跛行或冠状或外周动脉的旁路移植，冠状动脉或静脉血管成形术后的再狭窄，发生于腹、膝和髋部外科手术之后低肢端静脉中的病理性血栓形成或高危肺血栓栓塞。

34. 根据权利要求 31 的方法，其中的生理性病症为中风，血管腔缩小，长期血液透析患者脉管通路开放的维持，或发生于脓毒性休克、某些病毒感染和癌症期间血管系统的全身弥散性血管内凝血病。

35. 一种抑制 Xa 因子的方法，该方法包括使 Xa 因子抑制量的权利要求 1 的化合物与含 Xa 因子的制品接触。

36. 一种抑制凝血酶产生的方法，该方法包括使 Xa 因子抑制量的权利要求 1 的化合物与含 Xa 因子的制品接触。

说　　明　　书

取代的（氨基亚氨基甲基或氨基甲基）苯并杂芳基化合物

发明领域

本发明涉及能够抑制 Xa 因子的取代的(氨基亚氨基甲基或氨基甲基）苯并杂芳基化合物，包含这些化合物的药物组合物以及这些化合物的用途，即用于抑制 Xa 因子或者用于治疗患有通过给药这些化合物而能够改善的生理病症的患者。

发明背景

Xa 因子是凝固级联中的次末级酶。式 I 化合物能够抑制游离的 Xa 因子以及组装在前凝血酶复合物（Xa 因子、Va 因子、钙和磷脂）中的 Xa 因子。通过在抑制剂与酶之间直接形成复合物而能实现对 Xa 因子的抑制，因此 Xa 因子的抑制不取决于血浆辅因子抗凝血酶 III。通过口服、连续静脉输注、药团输注或任何其它肠胃外途径施用化合物能够有效地抑制 Xa 因子，从而防止 Xa 因子诱导凝血酶原形成凝血酶而达到所需的效果。

抗凝疗法用于治疗和预防各种静脉和动脉血管系统的血栓症状。在动脉系统中，异常血栓的形成最初与冠状、大脑和外周血管系统的动脉有关。与这些血管的血栓闭合有关的疾病主要包括急性心肌梗塞(AMI)、不稳定性心绞痛、血栓栓塞、与溶栓治疗和经皮经管腔动脉血管成形术(PTCA)有关的急性血管闭合、暂时缺血性发作、中风、间歇性跛行和冠状或外周动脉旁路移植(CABG)。慢性抗凝疗法也有益于预防通常发生于 PTCA 和 CABG 之后的血管腔缩小（再狭窄），并有益于维持长期血液透析患者的脉管通路开放。就静脉脉管系统而言，病理性血栓形成常发生于腹、膝和髋部外科手术之后的的较低肢端静脉（深静脉血栓形成，DVT）。DVT 进一步使患者易患高危肺血栓栓塞。全身、

弥散性血管内凝血病(DIC)常发生于脓毒性休克、某些病毒感染和癌症期间的血管系统。这种病症的特征在于凝血因子以及它们的血浆抑制剂的迅速消耗，导致在一些器官系统的整个微脉管系统中形成威胁生命的凝块。

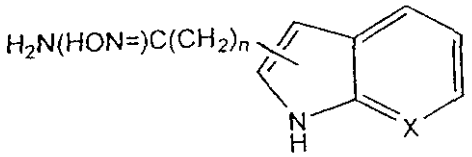
累积的试验资料也已经反映说明凝血酶原的激活只是 Xa 因子的一种生物活性。据信 EPR-1 (效应细胞蛋白酶受体-1，识别 Xa 因子)通过 Xa 因子介导一些血管壁相互作用。它已经通过在人脐静脉内皮细胞、大鼠平滑肌细胞和血小板上表达证明(CR McKenzie 等，Arterioscler Thromb Vasc Biol 16 1285-91 (1996)；还有 F Bono 等，J Cell Physiol 172 36-43 (1997)，AC Nicholson 等，J Biol Chem 271 28407-13 (1996)，J.M. Herbert 等，J Clin Invest 101 993-1000 (1998))。这种蛋白酶-受体相互作用不仅能够介导前凝血酶催化的凝血酶生成，而且还介导各种细胞功能如细胞增殖、释放 PDGF 和 DNA 的合成。据报道 Xa 因子的促细胞分裂作用取决于 Xa 因子的酶活性(F Bono 等，J Cell Physiol 172 36-43 (1997)，J. M. Herbert 等，J Clin Invest 101 993-1000 (1998))。例如，TAP 抑制人和大鼠的培养血管平滑肌细胞的分裂(F Bono 等，J Cell Physiol 172 36-43 (1997))。在兔颈动脉风干损伤模型的研究中，发现血管损伤后 EPR-1 表达增强。用特异性 Xa 因子抑制剂 DX-9065a 处理的动物表现出较低的新血管内膜增殖。Xa 因子在伴随有其促分裂作用的凝血过程中的重要调节作用表明 Xa 因子参与血管壁腔表面上的血栓形成并且影响导致再狭窄或血管生成的动脉粥样硬化血栓形成过程与血管细胞的异常增殖。

由于 Xa 因子与上述生理病症有关，因此 Xa 因子的抑制剂将适用于治疗这些病症以及 Xa 因子抑制剂能缓解的其它病症。

报道进展

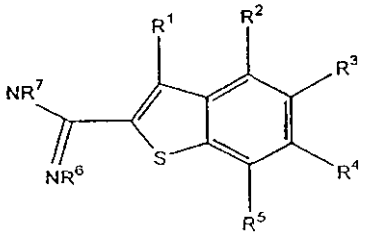
H.E. Lape 等(Arch. Int. Pharmacodyn., 171(2) 394414 (1968))公开了下列任选被烷基取代的吲哚-(1 或 3)-乙酰胺肟化合物，其中 X

为 CH 或 N，且 n 为 0-2：



并且指出这些化合物具有各种抗高血压活性。但其中并没有公开或暗示这些乙酰胺肪化合物具有能够抑制 Xa 因子的活性。

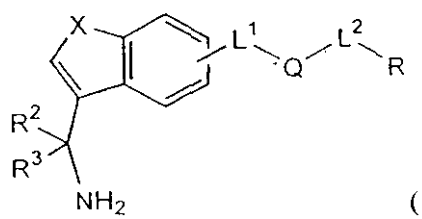
公开号为 568,289 的欧洲专利申请公开了下列 2-甲脒苯并噻吩化合物：



其中 R^2、R^3、R^4和 R^5中至少一个为包含 5 个或更多个碳原子的有机基团，包含硫原子或羟基的有机基团，不饱和有机基团或环状有机基团。据说这些化合物为尿激酶抑制剂。但上述欧洲专利申请公开 568,289 中没有揭示或暗示 3-甲脒苯并噻吩化合物或 2-甲脒苯并噻吩化合物具有 Xa 因子活性。

发明概述

本发明涉及式 I 化合物或其氧化物、可药用盐、溶剂化物或前药：



(I)

其中

X 为 O，S 或 NR^1；

R 为氢，环烷基，环烯基，杂环基，杂环烯基，稠合芳基环烷基，稠合杂芳基环烷基，稠合芳基环烯基，稠合杂芳基环烯基，稠合芳基杂环基，稠合杂芳基杂环基，稠合芳基杂环烯基，稠合杂芳基杂环烯基，芳基，稠合环烯基芳基，稠合环烷基芳基，稠合杂环基芳基，稠合杂环烯基芳基，杂芳基，稠合环烷基杂芳基，稠合环烯基杂芳基，稠合杂环烯基杂芳基或稠合杂环基杂芳基，条件是当 L^2 为化学键时，则 Q 通过其碳原子与 R 连接，以及当 R 为氢时，则 L^2 不能为化学键；

R^1 为氢，烷基，芳烷基，杂芳烷基，酰基，芳酰基，杂芳酰基，烷氧基羰基，芳氧基羰基或杂芳氧基羰基；

R^2 和 R^3 为氢，或者一起表示=NR^4；

R^4 为氢，R^5O_2C-，R^5O-，HO-，氰基，R^5CO-，HCO-，低级烷基，硝基，或 R^6R^7N-；

R^5 为烷基，芳基，杂芳基，芳烷基，或杂芳烷基；

R^6 和 R^7 独立地为氢或烷基；

L^1 为亚烷基，亚烯基或亚炔基；

L^2 为化学键，亚烷基，亚烯基或亚炔基；

Q 为 $-NR^{8'}-$，-O-，$-C(O)-$，$-C(O)-O-$，$-O-C(O)-$，$-NR^{8'}C(X^1)-$，$-C(X^1)NR^{8'}-$，$-NR^8C(X^1)O-$，$-OC(X^1)NR^8-$，$-NR^8C(X^1)NR^8-$，$-NR^8C(X^1)NR^8-$，$-S(O)_n-$，$-NR^8SO_2-$或$-SO_2NR^8-$，条件是 Q 的氮原子或氧原子不能直接与具有双键或三键的 L^1 或 L^2 的碳原子键连，或者 $Q-L^2-R-$为环烷基，环烯基，杂环基，杂环烯基，稠合芳基环烷基，稠合杂芳基环烷基，稠合芳基环烯基，稠合杂芳基环烯基，稠合芳基杂环基，稠合杂芳基杂环基，稠合芳基杂环烯基，稠合杂芳基杂环烯基，芳基，稠合环烯基芳基，稠合环烷基芳基，稠合杂环基芳基，稠合杂环烯基芳基，杂芳基，稠合环烷基杂芳基，稠合环烯基杂芳基，稠合杂环烯基杂芳基或稠合杂环烷基杂芳基，条件是 Q 的氮原子或氧原子不能直接与具有双键或三键的 L^1 的碳原子键连；

X^1为O或S；

$R^{8'}$为氢，烷基，芳烷基，杂芳烷基，酰基，芳酰基，杂芳酰基或烷氧基羰基；

R^8为氢，烷基，芳烷基，杂芳烷基，酰基，芳酰基或杂芳酰基；和

n为0、1或2。

发明详述

上文所用的以及遍及本发明说明书中的下列术语除另有说明外均应理解为具有下列含义：

定义

"患者"包括人和其它哺乳动物。

"烷基"是指链中具有大约1-大约15个碳原子的直链或支链脂族烃基。优选链中具有1至大约10个碳原子的烷基。支链是指有一个或多个低级烷基（如甲基、乙基或丙基）连接在直链烷基链上。"低级烷基"是指链中含有大约1-大约4个碳原子并且可以是直链或支链的烷基。烷基可以被一个或多个卤素、羟基、环烷基或环烯基取代。代表性的烷基基团包括甲基、氟甲基、二氟甲基、三氟甲基、环丙基甲基、环戊基甲基、乙基、正丙基、异丙基、正丁基、叔丁基、正戊基、3-戊基、庚基、辛基、壬基、癸基和十二烷基。

"亚烷基"是指具有1-大约10个碳原子的直链或支链二价烃链。优选的亚烷基基团为具有1-大约4个碳原子的低级亚烷基。亚烷基可以被一个或多个卤素、羟基、酰基、烷氧基羰基或羧基取代。亚烷基基团的实例包括亚甲基、1,2-亚乙基、1,2-亚丙基或亚丁基；优选1,2-亚乙基。

"链烯基"是指含有碳-碳双键并且链中具有大约2-大约15个碳原子的直链或支链脂族烃基。优选链中具有大约2-大约10个碳原子的链烯基；更优选链中具有大约2-大约4个碳原子的链烯基。支

链是指有一个或多个低级烷基（如甲基、乙基或丙基）连接在直链链烯基链上。“低级链烯基”是指其链中具有大约 2 - 大约 4 个碳原子并且可以是直链或支链的链烯基。链烯基基团可以被一个或多个卤素取代。代表性的链烯基基团包括乙烯基、丙烯基、正丁烯基、异丁烯基、3-甲基丁-2-烯基、正戊烯基、庚烯基、辛烯基和癸烯基。

“亚烯基”是指具有双键并且含 2 - 大约 10 个碳原子的直链或支链二价烃链。优选的亚烯基基团为具有 2 - 大约 4 个碳原子的低级亚烯基。亚烯基基团可以被一个或多个卤素、羟基、酰基、烷氧基羰基或羧基取代，条件是羟基不能取代在其双键上。亚烯基的实例包括亚乙烯基，亚丙烯基或亚丁烯基。

“炔基”是指含有碳-碳三键并且链中具有大约 2 - 大约 15 个碳原子的直链或支链脂族烃基。优选链中具有大约 2 - 大约 10 个碳原子的炔基；更优选链中具有大约 2 - 大约 4 个碳原子的炔基。支链是指有一个或多个低级烷基（如甲基、乙基或丙基）连接在直链炔基链上。“低级炔基”是指其链中具有大约 2 - 大约 4 个碳原子并且可以是直链或支链的炔基。代表性的炔基基团包括乙炔基、丙炔基、正丁炔基、2 - 丁炔基、3-甲基丁炔基、正戊炔基、庚炔基、辛炔基和癸炔基。

“亚炔基”是指具有双键并且含 2 - 大约 10 个碳原子的直链或支链二价烃链。优选的亚炔基基团为具有 2 - 大约 4 个碳原子的低级亚炔基。亚炔基基团可以被一个或多个卤素、羟基、酰基、烷氧基羰基或羧基取代，条件是羟基不能取代在其三键上。亚炔基的实例包括亚乙炔基，亚丙炔基或亚丁炔基。

“羧基”是指 HO(O)C-（羧酸）基团。

“羧基烷基”是指 HOOC-烷基-基团，其中的烷基如本文所定义。优选的基团包括羧甲基和羧乙基。

“环烷基”是指具有大约 3 - 大约 10 个碳原子，优选大约 5 - 大约 10 个碳原子的非芳族单-或多环环系。优选的环烷基环包含大约 5 - 大约 6 个环原子。环烷基任选地被一个或多个“环系取代基”取代，其中的“环系取代基”可以相同或不同，并且如本文所定义。代表性

的单环环烷基包括环戊基、环己基、环庚基等。代表性的多环环烷基包括 1-萘烷基、降冰片基、金刚烷基等。

"环烷基烷基"是指其中环烷基和烷基均如本文所定义的环烷基烷基。代表性的环烷基烷基基团包括环丙基、环戊基、环己基、环庚基等。

"环烯基"是指含有至少一个碳-碳双键和大约 3 - 大约 10 个碳原子（优选大约 5 - 大约 10 个碳原子）的非芳族单-或多环环系。优选的环烯基环包含大约 5 - 大约 6 个环原子。环烯基任选地被一个或多个可以相同或不同并且如本文所定义的 "环系取代基"取代。代表性的单环环烯基包括环戊烯基，环己烯基，环庚烯基等。代表性的多环环烯基为降冰片烯基。

"杂环烯基"是指含有大约 3 - 大约环原子（优选大约 5 - 大约 10 个环原子）的非芳族单环或多环环系，其中环系中的一个或多个原子为非碳元素，例如为氮、氧或硫原子，并且其中包含至少一个碳-碳双键或碳-氮双键。优选的杂环烯基环包含大约 5 - 大约 6 个环原子。杂环烯基前的前缀氮杂、氧杂或硫杂分别表示至少存在一个氮、氧或硫原子作为环原子。杂环烯基任选地被一个或多个环系取代基取代，其中的 "环系取代基"如本文所定义。杂环烯基的氮或硫原子任选地被氧化成相应的 N-氧化物，S-氧化物或 S,S-二氧化物。代表性的单环氮杂杂环烯基包括 4,5-二氢-[1,2,4]噁二唑基，1,2,3,4-四氢吡啶基，1,2-二氢吡啶基，1,4-二氢吡啶基，1,2,3,6-四氢吡啶基，1,4,5,6-四氢嘧啶基，2-吡咯啉基，3-吡咯啉基，2-咪唑啉基，2-吡唑啉基等。代表性的氧杂杂环烯基基团包括 3,4-二氢-2H-吡喃，二氢呋喃基，氟代二氢呋喃基，2,3-二氢哒嗪基，1,6-二氢三嗪基等。代表性的多环氧杂杂环烯基为 7-氧杂二环[2.2.1]庚烯基。代表性的单环硫杂杂环烯基环包括二氢噻吩基，二氢噻喃基等。杂环烯基还可以为 "内酰胺"，其中杂环烯基为适当二氧代取代的氮杂杂环烯基，例如马来酰亚胺。

"杂环基"是指具有大约 3 - 大约 10 个环原子（优选大约 5 - 大

约 10 个环原子）的非芳族饱和单环或多环环系，其中环系中的一个或多个原子为非碳元素，例如为氮、氧或硫。优选的杂环基包含大约 5 - 大约 6 个环原子。杂环基前的前缀氮杂、氧杂或硫杂分别表示至少存在一个氮、氧或硫原子作为环原子。杂环基任选地被一个或多个可以相同或不同并且如本文所定义的“环系取代基”所取代。杂环基的氮或硫原子可以任选地氧化成相应的 N-氧化物，S-氧化物或 S，S-二氧化物。代表性的单环杂环基环包括哌啶基、2-氧代-六氢-嘧啶基、咪唑烷基、吡咯烷基、哌嗪基、吗啉基、硫代吗啉基、噻唑烷基、1，3-二氧戊环基、1，4-二噁烷基、四氢呋喃基、四氢噻吩基、四氢噻喃基等。杂环基还可以为“内酰胺”，其中杂环基为适当二氧代取代的氮杂杂环基，例如琥珀酰亚胺。

“杂环氧基”是指杂环基-O-基团，其中的杂环基如前所述。典型的杂环氧基包括奎宁环氧基，硫己环氧基，四氢吡喃氧基，四氢噻吩氧基，哌啶氧基，吡咯烷氧基，四氢呋喃氧基或 7-氧杂二环[2.2.1]庚烷氧基，羟基四氢吡喃氧基和羟基-7-氧杂二环[2.2.1]庚烷氧基。

“杂环基-亚烷基-O-”是指杂环基-亚烷基-O-基团，其中的杂环基和亚烷基如前所述。典型的杂环基-亚烷基-O-基团包括吡咯烷基-乙氧基和哌啶基-甲氧基。

“芳基”是指具有 6 - 大约 14 个碳原子（优选大约 6 - 大约 10 个碳原子）的芳香性单环或多环环系。芳基任选地被一个或多个可以相同或不同并且如本文所定义的“环系取代基”取代。代表性的芳基包括苯基、萘基、取代苯基或取代萘基。

“杂芳基”是指具有大约 5 - 大约 14 个环原子（优选大约 5 - 大约 10 个环原子）的芳香性单环或多环环系，其中环系中的一个或多个原子为非碳原子，例如为氮、氧或硫。优选的杂芳基包含大约 5 - 大约 6 个环原子。“杂芳基”任选地被一个或多个可以相同或不同并且如本文所定义的“环系取代基”取代，杂芳基前的前缀氮杂、氧杂或硫杂分别表示至少存在一个氮、氧或硫原子作为环原子。杂芳基的氮原子可以任选地氧化成相应的 N-氧化物。代表性的杂芳基包括吡嗪基，

呋喃基，噻吩基，吡啶基，嘧啶基，异噁唑基，呋喃并吡啶基，吡咯并嘧啶基，异噻唑基，噁唑基，噻唑基，吡唑基，呋唑基，吡咯基，吡唑基，三唑基，1,2,4-噻二唑基，吡嗪基，哒嗪基，喹喔啉基，2,3-二氮杂萘基，咪唑并[1,2-a]吡啶，咪唑并[2,1-b]噻唑基，苯并呋喃基，吲哚基，氮杂吲哚基，苯并咪唑基，苯并噻吩基，喹啉基，咪唑基，噻吩并吡啶基，喹唑啉基，噻吩并嘧啶基，吡咯并吡啶基，咪唑并吡啶基，异喹啉基，苯并氮杂吲哚基，1,2,4-三嗪基，苯并噻唑基等。

"稠合芳基环烯基"是指通过去除环烯基部分的氢原子而由稠合的本文所定义的芳基和环烯基衍生得到的基团。优选的稠合芳基环烯基为这些基团，其中的芳基为苯基，而环烯基包括大约 5- 大约 6 个环原子。稠合芳基环烯基任选地被一个或多个环系取代基取代，其中"环系取代基"如本文所定义。代表性的稠合芳基环烯基包括 1,2-二氢萘、茚等，其中连接于母体部分的键经非芳香碳原子键连。

"稠合环烯基芳基"是指通过去除芳基部分的氢原子而由本文所定义的稠合芳基环烯基衍生得到的基团。代表性的稠合环烯基芳基如本文稠合芳基环烯基所述，只是其中连接于母体部分的键经芳香碳原子键连。

"稠合芳基环烷基"是指通过去除环烷基部分的氢原子而由稠合的本文所定义的芳基和环烷基衍生形成的基团。优选的稠合芳基环烷基为这些基团，其中的芳基为苯基，而环烷基包括大约 5- 大约 6 个环原子。稠合芳基环烷基可任选地被一个或多个环系取代基取代，其中的"环系取代基"如本文所定义。代表性的稠合芳基环烷基包括 1,2,3,4-四氢萘基等，其中键连于母体部分的键经非芳香碳原子连接。

"稠合环烷基芳基"是指通过去除芳基部分的氢原子而由本文所定义的稠合芳基环烷基衍生得到的基团。代表性的稠合环烷基芳基如本文稠合芳基环烷基部分所述，只是其中连接于母体部分的键经芳香碳原子键连。

"稠合芳基杂环烯基"是指通过去除杂环烯基部分的氢原子而由

稠合的本文所定义的芳基和杂环烯基衍生得到的基团。优选的稠合芳基杂环烯基为这些基团，其中的芳基为苯基，而杂环烯基包括大约 5 - 大约 6 个环原子。杂环烯基部分前的前缀氮杂、氧杂或硫杂分别表示至少存在一个氮、氧或硫原子作为环原子。这种稠合芳基杂环烯基可任选地被一个或多个环系取代基取代，其中的“环系取代基”如本文所定义。稠合芳基杂环烯基中杂环烯基部分的氮或硫原子可任选地氧化成相应的 N-氧化物，S-氧化物或 S,S-二氧化物。代表性的稠合芳基杂环烯基包括 3H-二氢吲哚基，1H-2-氧代喹啉基，2H-1-氧代异喹啉基，1,2-二氢喹啉基，3,4-二氢喹啉基，1,2-二氢异喹啉基，3,4-二氢异喹啉基等，其中连接于母体部分的键经非芳香碳原子连接。

“稠合杂环烯基芳基”是指通过去除芳基部分的氢原子而由本文所定义的稠合芳基杂环烯基衍生得到的基团。代表性的稠合杂环烯基芳基如本文稠合芳基杂环烯基部分所述，只是其中连接于母体部分的键经芳香碳原子键连。

“稠合芳基杂环基”是指通过去除杂环基部分的氢原子而由稠合的本文所定义的芳基与杂环基衍生得到的基团。优选的稠合芳基杂环基为这些基团，其中的芳基为苯基，而杂环基包括大约 5 - 大约 6 个环原子。杂环基前的前缀氮杂、氧杂或硫杂分别表示至少存在一个氮、氧或硫原子作为环原子。这种稠合芳基杂环基可任选地被一个或多个环系取代基取代，其中的“环系取代基”如本文所定义。稠合芳基杂环基中杂环基部分的氮或硫原子可任选地氧化成相应的 N-氧化物，S-氧化物或 S,S-二氧化物。代表性的稠合芳基杂环基环系包括邻苯二甲酰亚胺，1,4-苯并二噁烷，二氢吲哚基，1,2,3,4-四氢异喹啉，1,2,3,4-四氢喹啉，1H-2,3-二氢异吲哚基，2,3-二氢苯并[f]异吲哚基，1,2,3,4-四氢苯并[g]异喹啉基等，其中键连于母体部分的键经非芳香碳原子连接。

“稠合杂环基芳基”是指通过去除杂环基部分的氢原子而由本文所定义的稠合芳基杂环基衍生得到的基团。代表性的稠合杂环基芳基环系如本文稠合芳基杂环基部分所述，只是其中连接于母体部分的键

经芳香碳原子键连。稠合的杂环基芳基还可以为“内酰胺”，其中的杂环基为适当二氧代取代的氮杂杂环烯基，例如邻苯二甲酰亚胺。

“稠合杂芳基环烯基”是指通过去除环烯基部分的氢原子而由稠合的本文所定义的杂芳基和环烯基衍生得到的基团。优选的稠合杂芳基环烯基为这些基团，其中的杂芳基和环烯基各自包含大约5-大约6个环原子。杂芳基前的前缀氮杂、氧杂或硫杂分别表示至少存在一个氮、氧或硫原子作为环原子。这种稠合杂芳基环烯基可任选地被一个或多个环系取代基取代，其中的“环系取代基”如本文所定义。稠合杂芳基环烯基中杂芳基部分的氮原子可任选地氧化成相应的N-氧化物。代表性的稠合杂芳基环烯基包括5,6-二氢喹啉基，5,6-二氢异喹啉基，5,6-二氢喹喔啉基，5,6-二氢喹唑啉基，4,5-二氢-1H-苯并咪唑基，4,5-二氢苯并噁唑基等，其中键连于母体部分的键经非芳香碳原子连接。

“稠合环烯基杂芳基”是指通过去除杂芳基部分的氢原子而由本文所定义的稠合杂芳基环烯基衍生得到的基团。代表性的稠合环烯基杂芳基如本文稠合杂芳基环烯基部分所述，只是其中连接于母体部分的键经芳香碳原子键连。

“稠合杂芳基环烷基”是指通过去除环烷基部分的氢原子而由稠合的本文所定义的杂芳基和环烷基衍生得到的基团。优选的稠合杂芳基环烷基为这些基团，即，其中的杂芳基包括大约5-大约6个环原子，而环烷基也包括大约5-大约6个环原子。杂芳基前的前缀氮杂、氧杂或硫杂分别表示至少存在一个氮、氧或硫原子作为环原子。这种稠合杂芳基环烷基可任选地被一个或多个环系取代基取代，其中的“环系取代基”如本文所定义。稠合杂芳基环烷基中杂芳基部分的氮原子可任选地氧化成相应的N-氧化物。代表性的稠合杂芳基环烷基包括5,6,7,8-四氢喹啉基，5,6,7,8-四氢异喹啉基，5,6,7,8-四氢喹喔啉基，5,6,7,8-四氢喹唑啉基，4,5,6,7-四氢-1H-苯并咪唑基，4,5,6,7-四氢苯并噁唑基，1H-4-氧杂-1,5-二氮杂萘-2-酮基，1,3-二氢咪唑-[4,5]-吡啶-2-酮基等，其中键连于母体部分的键经非芳香碳原子连

接。

"稠合环烷基杂芳基"是指通过去除杂芳基部分的氢原子而由本文所定义的稠合杂芳基环烷基衍生得到的基团。代表性的稠合环烷基杂芳基如本文稠合杂芳基环烷基部分所述，只是其中连接于母体部分的键经芳香碳原子键连。

"稠合杂芳基杂环烯基"是指通过去除杂环烯基部分的氢原子而由稠合的本文所定义的杂芳基和杂环烯基衍生得到的基团。优选的稠合杂芳基杂环烯基为这些基团，其中的杂芳基包括大约 5 - 大约 6 个环原子而杂环烯基也包括大约 5 - 大约 6 个环原子。杂芳基或杂环烯基前的前缀氮杂、氧杂或硫杂分别表示至少存在一个氮、氧或硫原子作为环原子。这种稠合杂芳基杂环烯基可任选地被一个或多个环系取代基取代，其中的"环系取代基"如本文所定义。稠合杂芳基杂环烯基中杂芳基部分的氮原子可任选地氧化成相应的 N-氧化物。稠合杂芳基杂环烯基中杂环烯基部分的氮或硫原子可任选地氧化成相应的 N-氧化物，S-氧化物或 S,S-二氧化物。代表性的稠合杂芳基杂环烯基包括 7,8-二氢[1,7]萘啶基，1,2-二氢[2,7]萘啶基，6,7-二氢-3H-咪唑并[4,5-c]吡啶基，1,2-二氢-1,5-萘啶基，1,2-二氢-1,6-萘啶基，1,2-二氢-1,7-萘啶基，1,2-二氢-1,8-萘啶基，1,2-二氢-2,6-萘啶基等，其中键连于母体部分的键经非芳香碳原子连接。

"稠合杂环烯基杂芳基"是指通过去除杂芳基部分的氢原子而由本文所定义的稠合杂芳基杂环烯基衍生得到的基团。代表性的稠合杂环烯基杂芳基如本文稠合杂芳基杂环烯基部分所述，只是其中连接于母体部分的键经芳香碳原子键连。

"稠合杂芳基杂环基"是指通过去除杂环基部分的氢原子而由稠合的本文所定义的杂芳基和杂环基衍生得到的基团。优选的稠合杂芳基杂环基为这些基团，其中的杂芳基包括大约 5 - 大约 6 个环原子而杂环基也包括大约 5 - 大约 6 个环原子。稠合杂芳基杂环基部分中杂芳基或杂环基前的前缀氮杂、氧杂或硫杂分别表示至少存在一个氮、氧或硫原子作为环原子。这种稠合杂芳基杂环基可任选地被一个或多

个环系取代基取代，其中的“环系取代基”如本文所定义。稠合芳基杂环基中杂芳基部分的氮原子可任选地氧化成相应的N-氧化物。稠合杂芳基杂环基中杂环基部分的氮或硫原子可任选地氧化成相应的N-氧化物，S-氧化物或S,S-二氧化物。代表性的稠合杂芳基杂环基包括2,3-二氢-1H-吡咯并[3,4-b]喹啉-2-基，1,2,3,4-四氢苯并[b][1,7]萘啶-2-基，1,2,3,4-四氢苯并[b][1,6]萘啶-2-基，1,2,3,4-四氢-9H-吡啶并[3,4-b]吲哚-2-基，1,2,3,4-四氢-9H-吡啶并[4,3-b]吲哚-2-基，2,3-二氢-1H-吡咯并[3,4-b]吲哚-2-基，1H-2,3,4,5-四氢吖庚因并[3,4-b]吲哚-2-基，1H-2,3,4,5-四氢吖庚因并[4,3-b]吲哚-3-基，1H-2,3,4,5-四氢吖庚因并[4,5-b]吲哚-2-基，5,6,7,8-四氢[1,7]萘啶基，1,2,3,4-四氢[2,7]萘啶基，2,3-二氢[1,4]二氧杂环己烯并[2,3-b]吡啶基，2,3-二氢[1,4]二氧杂环己烯并[2,3-b]吡啶基，3,4-二氢-2H-1-氧杂[4,6]二氮杂萘基，4,5,6,7-四氢-3H-咪唑并[4,5-c]吡啶基，6,7-二氢[5,8]二氮杂萘基，1,2,3,4-所[1,5]萘啶基，1,2,3,4-四氢[1,6]萘啶基，1,2,3,4-四氢[1,7]萘啶基，1,2,3,4-四氢[1,8]萘啶基，1,2,3,4-四氢[2,6]萘啶基等，其中键连于母体部分的键经非芳香碳原子连接。

“稠合杂环基杂芳基”是指通过去除杂芳基部分的氢原子而由本文所定义的稠合杂芳基杂环基衍生得到的基团。代表性的稠合杂环基杂芳基如本文稠合杂芳基杂环基部分所述，只是其中连接于母体部分的键经芳香碳原子键连。

“芳烷基”是指芳基-烷基-基团，其中的芳基和烷基均如前所述。优选的芳烷基包含低级烷基部分。代表性的芳烷基包括苄基、2-苯乙基和萘甲基。

“芳烯基”是指芳基-链烯基-基团，其中的芳基和链烯基均如前所述。优选的芳烯基包含低级链烯基部分。芳烯基的实例包括2-苯乙烯基和2-萘乙烯基。

“芳炔基”是指芳基-炔基-基团，其中的芳基和炔基均如前所述。优选的芳炔基包含低级炔基部分。典型的芳炔基包括苯乙炔基和萘乙

炔基。

“杂芳烷基”是指杂芳基-烷基-基团，其中的杂芳基和烷基均如前所述。优选的杂芳烷基包含低级烷基部分。代表性的杂芳烷基包括吡啶甲基、2-(呋喃-3-基)乙基和喹啉-3-基甲基。

“杂芳烯基”是指杂芳基-链烯基-基团，其中的杂芳基和链烯基均如前所述。优选的杂芳烯基包含低级链烯基部分。杂芳烯基的实例包括 2-(吡啶-3-基)乙烯基和 2-(喹啉-3-基)乙烯基。

“杂芳炔基”是指杂芳基-炔基-基团，其中的杂芳基和炔基均如前所述。优选的杂芳炔基包含低级炔基部分。典型的杂芳炔基包括吡啶-3-基乙炔基和喹啉-3-基乙炔基。

“羟基烷基”是指 HO-烷基-基团，其中的烷基如前所述。优选的羟基烷基包含低级烷基。其它优选的羟基烷基含有一个以上的羟基。代表性的羟基烷基基团包括羟甲基和 2-羟基乙基。

“烷基亚烷基-O-”是指 HO-亚烷基-O-基团，其中的亚烷基部分如前所述。优选的羟基亚烷基-O-基团包含低级亚烷基。代表性的羟基亚烷基-O-基团包括羟基甲氧基和 2-羟基乙氧基。

“酰基”是指 H-CO-或烷基-CO-基团，其中的烷基如前所述。优选的酰基含有低级烷基。代表性的酰基包括甲酰基、乙酰基、丙酰基、2-甲基丙酰基、丁酰基和棕榈酰基。

“芳酰基”是指芳基-CO-基团，其中的芳基如前所述。代表性的基团包括苯甲酰基和 1-和 2-萘甲酰基。

“杂芳酰基”是指杂芳基-CO-基团，其中的杂芳基如前所述。代表性的基团包括烟酰基和吡咯-2-基羰基和 3-喹啉羰基。

“烷氧基”是指烷基-O-基团，其中的烷基如前所述。代表性的烷氧基包括甲氧基、乙氧基、正丙氧基、异丙氧基、正丁氧基和庚氧基。

“烷氧基-亚烷基-O-”是指烷氧基-亚烷基-O-基团，其中的烷氧基和亚烷基如前所述。代表性的烷氧基-亚烷基-O-基团包括甲氧基甲氧基，甲氧基乙氧基，甲氧基-正丙氧基，甲氧基-正丁氧基和甲氧基庚氧基。

"芳氧基"是指芳基-O-基团，其中的芳基如前所述。代表性的芳氧基包括苯氧基和萘氧基。

"芳烷氧基"是指芳烷基-O-基团，其中的芳烷基如前所述。代表性的芳烷氧基包括苄氧基和 1-或 2-萘甲氧基。

"烷硫基"是指烷基-S-基团，其中的烷基如前所述。代表性的烷硫基包括甲硫基、乙硫基、正丙硫基、异丙硫基和庚硫基。

"芳硫基"是指芳基-S-基团，其中的芳基如前所述。代表性的芳硫基包括苯硫基和萘硫基。

"芳烷硫基"是指芳烷基-S-基团，其中的芳烷基如前所述。代表性的芳烷硫基包括苄硫基。

"Y^1Y^2N-"是指取代的或未取代的氨基，其中 Y^1 和 Y^2 如本文所定义。代表性的基团包括氨基(H_2N-)，甲氨基，乙基甲基氨基，二甲氨基和二乙基氨基。

"烷氧基羰基"是指烷基-O-CO-基团。代表性的烷氧基羰基包括甲氧基-和乙氧基羰基。

"芳氧基羰基"是指芳基-O-CO-基团。代表性的芳氧基羰基基团包括苯氧基-和萘氧基羰基。

"芳烷氧基羰基"是指芳烷基-O-CO-基团。代表性的芳烷氧基羰基为苄氧基羰基。

"Y^1Y^2NCO-"是指取代或未取代的氨基甲酰基，其中 Y^1 和 Y^2 如本文所定义。代表性的基团为氨基甲酰基(H_2NCO-)和二甲氨基甲酰基(Me_2NCO-)。

"$Y^1Y^2NSO_2-$"是指取代或未取代的氨磺酰基，其中 Y^1 和 Y^2 如本文所定义。代表性的基团为氨磺酰基(H_2NSO_2-)和二甲氨基磺酰基(Me_2NSO_2-)。

"磺基"是指 $HO-SO_2-$基团。

"磺基烷基"是指 $HO-SO_2-$烷基-基团，其中的烷基如本文所定义。$HO-SO_2-$烷基-基团的实例包括磺基甲基，磺基乙基和磺基丙基。

"烷基磺酰基"是指烷基-SO_2-基团。优选的基团为其中烷基为低

级烷基的基团。

"烷基亚磺酰基"是指烷基-SO-基团。优选的基团是其中烷基为低级烷基的那些基团。

"芳基磺酰基"是指芳基-SO_2-基团。

"芳基亚磺酰基"是指芳基-SO-基团。

"卤素"是指氟、氯、溴或碘。优选氟、氯或溴，并且更优选氟或氯。

"环系取代基"是指任选置换了芳族或非芳族环系上氢原子的取代基。环系取代基选自烷基、芳基、杂芳基、芳烷基、芳烯基、芳炔基、杂芳烷基、杂芳烯基、杂芳炔基、羟基、羟基烷基、烷氧基、芳氧基、杂芳氧基、杂环基氧基、杂环烯基氧基、芳烷氧基、酰基、芳酰基、卤素、硝基、氰基、羟基-亚烷基-O-、烷氧基-亚烷基-O-、Y^1Y^2NCO-亚烷基-O-、Y^1Y^2N-亚烷基-O-、杂环基-亚烷基-O-、羧基、羧基烷基、烷氧基羰基、芳氧基羰基、芳烷氧基羰基、磺基、烷基磺酰基、芳基磺酰基、杂芳基磺酰基、烷基亚磺酰基、芳基亚磺酰基、杂芳基亚磺酰基、烷硫基、芳硫基、杂芳硫基、芳烷硫基、杂芳烷硫基、环烷基、环烯基、杂环基、杂环烯基、杂环基烷基、杂环烯基烷基、芳基重氮基、杂芳基重氮基、脒基、1-氮杂杂环基羰基、羧基-烷基-、Y^1Y^2N-、Y^1Y^2N-烷基-、(Y^1Y^2N-和羟基)烷基-、Y^1Y^2N-链烯基、Y^1Y^2N-炔基-、Y^1Y^2NCO-、Y^1Y^2NCO-烷基-、Y^1Y^2NCONH-、$Y^1Y^2NCO_2$-和$Y^1Y^2NSO_2$-，其中Y^1和Y^2独立地为氢，烷基，烷氧基烷基，羟基烷基，环烷基，环烷基-烷基，Y^1Y^2N-烷基，芳基，芳烷基，杂芳烷基，杂环基烷基，杂环烯基烷基，磺基-烷基-，或者当取代基为Y^1Y^2N-或Y^1Y^2N-烷基-时，则Y^1和Y^2之一为H-CO-，烷基-CO-，芳基-CO-，杂环基-CO-，而Y^1和Y^2中的另一个为氢，烷基，芳基，或芳烷基。当环系为饱和或部分饱和状态时，"环系取代基"进一步包括亚甲基(H_2C=)，氧代(O=)和硫代(S=)。

"化学键"是指直接键。

"溶剂化物"是指化合物与一个或多个溶剂分子的物理缔合。这种物理缔合涉及不同程度的离子和共价键(包括氢键)。在某些情况下，

溶剂化物能够分离，例如当一个或多个溶剂分子掺入到结晶固体的晶格内时。"溶剂化物"包括溶液相和可分离的溶剂化物。代表性的溶剂化物包括乙醇化物，甲醇化物等。"水合物"是其中溶剂分子为水的溶剂化物。

"前药"是指适于给药患者且无不当毒性、刺激作用、过敏反应等性质，并且对其预期用途有效的式 I 化合物的形式，包括缩酮、酯和两性离子形式。前药在体内转化生成式 I 化合物，例如在血液中通过水解完成。下列文献对此进行了详细论述：T. Higuchi 和 V. Stella, Pro-drugs as Novel Delivery Systems, 14 卷, A.C.S. Symposium Series, 以及 Edward B. Roche 编辑的 Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, 这两篇文献内容在此并入引作参考。

"酸保护基"是指本领域公知的易除去基团，在合成步骤中用于保护酸基避免发生不希望的反应，并且优选能选择性除去。本领域技术人员熟知，在合成过程中为保护酸基避免发生不希望的反应，可以使用酸保护基，并且许多这种保护基均是本领域已知的，如美国专利 3840556 和 3719667 所述在青霉素和头孢菌素领域中广泛用于羧基保护的基团，这两篇文献内容在此并入引作参考。适宜的保护基参见 T.W. Green 和 P.G.M. Wuts 的 "Protective Groups in Organic Chemistry" John Wiley and Sons, 1991。羧酸保护基的实例包括酯如甲氧基甲基、甲硫基甲基、四氢吡喃基、取代和未取代的苯甲酰甲基、2,2,2-三氯乙基、叔丁基、肉桂基、二烷基氨基烷基（如二甲氨基乙基等）、三甲基甲硅烷基等，以及酰胺和酰肼，包括 N,N-二甲基、7-硝基吲哚基、酰肼、N-苯基酰肼，C_1-C_8 低级烷基（如甲基、乙基或叔丁基等）；及其取代衍生物，如烷氧基苄基或硝基苄基等；烷酰氧基烷基如新戊酰氧基甲基或丙酰氧基甲基等；芳酰氧基烷基如苯甲酰氧基乙基等；烷氧基羰基烷基如甲氧基羰基甲基，环己氧基羰基甲基等；烷氧基羰氧基烷基如叔丁氧基羰氧基甲基等；烷氧基羰基氨基烷基如叔丁氧羰基氨基甲基等；烷基氨基羰基氨基烷基，如甲氨基羰基氨基甲基等；

烷酰基氨基烷基，如乙酰氨基甲基等；杂环羰氧基烷基，如 4－甲基哌嗪羰氧基甲基等；二烷基氨基羰基烷基，如二甲氨基羰基甲基等；(5-(低级烷基)-2-氧代-1,3-间二氧杂环戊烯-4-基)烷基，如(5-叔丁基-2-氧代-1,3-间二氧杂环戊烯-4-基)甲基等；以及(5-苯基-2-氧代-1,3-间二氧杂环戊烯-4-基)烷基，如(5-苯基-2-氧代-1,3-间二氧杂环戊烯-4-基)甲基等。

"胺保护基"是指本领域公知的易除去基团，在合成步骤中用于保护氨基避免发生不希望的反应，并且优选能选择性除去。在合成过程中为保护氨基避免发生不希望的反应，使用胺保护基是本领域技术人员熟知的，并且许多这种保护基均是本领域已知的，例如，参见 T.H. Greene 和 P.G.M. Wuts, Protective Groups in Organic Synthesis, 第 2 版，John Wiley & Sons, New York (1991)，该文献的内容在此并入本文引作参考。优选的胺保护基有酰基，包括甲酰基、乙酰基、氯乙酰基、三氯乙酰基、邻-硝基苯基乙酰基、邻-硝基苯氧基乙酰基、三氟乙酰基、4-氯丁酰基、异丁酰基、邻-硝基肉桂酰基、吡啶甲酰基、酰基异硫氰酸(acylisothiocyanate)、氨基己酰基、苯甲酰基等，以及酰氧基，包括甲氧基羰基、9-芴基甲氧基羰基、2,2,2-三氟乙氧基羰基、2-三甲基甲硅烷基乙氧基羰基、乙烯氧基羰基、烯丙氧基羰基、叔丁氧羰基(BOC)、1,1-二甲基丙炔氧基羰基、苄氧基羰基(CBZ)、对-硝基苄氧基羰基、2,4-二氯苄氧基羰基等。

"酸不稳定胺保护基"是指在用酸处理时易除去的上述胺保护基，但它们对其它试剂仍保持相对稳定。优选的酸不稳定胺保护基为叔丁氧羰基(BOC)。

"氢化不稳定胺保护基"是指加氢易除去但对其它试剂仍保持相对稳定的上述胺保护基。优选的氢化不稳定胺保护基为苄氧基羰基(CBZ)。

"氢化不稳定酸保护基"是指加氢易除去但对其它试剂仍保持相对稳定的上述酸保护基。优选的氢化不稳定酸保护基为苄基。

"硫醇保护基"是指用某些试剂处理时易除去但对其它试剂相对

稳定的硫醇保护基。在合成过程中为保护硫醇避免发生不希望的反应，使用硫醇保护基是本领域技术人员熟知的，并且许多这种保护基也均是本领域已知的，例如，参见 T. H. Greene 和 P. G. M. Wuts, Protective Groups in Organic Synthesis, 第 2 版, John Wiley & Sons, New York (1991)，该文献的内容在此并入本文引作参考。典型的硫醇保护基为三苯甲基(Trt)、乙酰氨基甲基(Acm)等。

"羟基保护基"是指用某些试剂处理时易除去但对其它试剂相对稳定的羟基保护基。在合成过程中为保护羟基避免发生不希望的反应，羟基保护基的使用是本领域技术人员熟知的，并且许多这种保护基也是本领域公知的，例如，参见 T. H. Greene 和 P. G. M. Wuts, Protective Groups in Organic Synthesis, 第 2 版, John Wiley & Sons, New York (1991)，该文献的内容在此并入本文引作参考。典型的羟基保护基为叔丁基、苄基、四氢吡喃基等。

优选实施方案

本发明的优选实施方案涉及通过给药有效量的式 I 化合物治疗患有通过抑制 Xa 因子的活性而能调节的生理病症的患者的方法。

本发明一方面优选的化合物为式 I 化合物，其中 R 为芳基、杂芳基或杂环基；更优选 R 为取代苯基。

本发明另一方面优选的化合物为式 I 化合物，其中 R 为任选取代的（苯基取代苯基），任选取代的（杂芳基取代苯基），任选取代的（苯基取代杂芳基），任选取代的（杂芳基取代杂芳基），任选取代的（苯基取代环烷基），任选取代的（杂芳基取代环烷基），任选取代的（环烷基取代杂芳基），任选取代的（环烷基取代苯基），任选取代的（环烷基取代环烷基），任选取代的（苯基取代环烯基），任选取代的（杂芳基取代环烯基），任选取代的（环烯基取代杂芳基），任选取代的（环烯基取代苯基），任选取代的（环烯基取代环烯基），任选取代的（苯基取代杂环基），任选取代的（杂芳基取代杂环基），任选取代的（环烷基取代杂环基），任选取代的（杂环基取代苯基），任选取代的（杂环基取代杂环基），任选取代的（苯基取代杂环烯基），任选取代的

（杂芳基取代杂环烯基），任选取代的（环烯基取代杂环烯基），任选取代的（杂环烯基取代苯基），或任选取代的（杂环烯基取代杂环烯基），其中圆括号前的术语“任选取代的”表示苯基、杂芳基、环烷基、环烯基、杂环基或杂环烯基、这些基团部分可进一步如其各自定义所述被进一步取代）。

本发明再一方面优选的化合物为式 I 化合物，其中 R 为任选取代的（苯基取代苯基），任选取代的（杂芳基取代苯基），任选取代的（苯基取代杂芳基），任选取代的（杂芳基取代杂芳基），任选取代的（苯基取代杂环基），任选取代的（杂芳基取代杂环基），任选取代的（环烷基取代杂环基），任选取代的（杂环基取代苯基），任选取代的（杂环基取代杂环基），任选取代的（苯基取代杂环烯基），任选取代的（杂芳基取代杂环烯基），任选取代的（环烯基取代杂环烯基），任选取代的（杂环烯基取代苯基），或任选取代的（杂环烯基取代杂环烯基），其中圆括号前的术语“任选取代的”表示苯基、杂芳基、环烷基、环烯基、杂环基、或杂环烯基、这些基团可进一步如其各自定义所述被进一步取代）。

本发明更优选的化合物为式 I 化合物，其中 R 为任选取代的（苯基取代杂芳基），任选取代的（苯基取代杂环基），和任选取代的（苯基取代杂环烯基）。

本发明另一方面优选的化合物为式 I 化合物，其中 R 为任选取代的（苯基取代杂芳基），任选取代的（苯基取代杂环基），和任选取代的（苯基取代杂环烯基）；L^2 与所述苯基在苯基部分的 1-位上键连，而所述杂环基、杂环烯基或杂芳基则与所述苯基在苯基部分的 4-位上键连。

本发明另一方面优选的化合物为其中 X 为 NR^1 的式 I 化合物。

本发明另一方面优选的化合物为其中 R^1 为氢的式 I 化合物。

本发明另一方面优选的化合物为其中 R^8 为氢的式 I 化合物。

本发明另一方面优选的化合物为其中 R^2 与 R^3 一起表示=NR^4 的式 I 化合物。

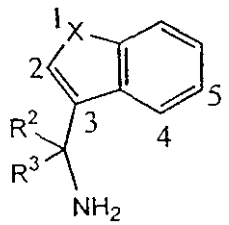
本发明另一方面优选的化合物为式 I 化合物，其中 R^4 为氢或羟基，更优选为氢。

本发明另一方面优选的化合物为式 I 化合物，其中 R^5 为烷基；更优选为甲基。

本发明另一方面优选的化合物为其中 R^6 和 R^7 均为氢的式 I 化合物。

本发明另一方面优选的化合物为式 I 化合物，其中 L^1 为亚烷基；更优选为亚乙基。

本发明另一方面优选的化合物为式 I 化合物，其中 L^1 与：



部分的 5-位键连。

本发明另一方面优选的化合物为其中 L^2 为化学键或亚烷基的式 I 化合物。

本发明另一方面优选的化合物为其中 L^2 为化学键的式 I 化合物。

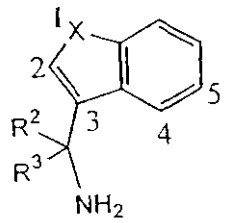
本发明另一方面优选的化合物为其中 X^1 为 O 的式 I 化合物。

本发明另一方面优选的化合物为式 I 化合物，其中 Q 为 $-NR^8CO-$，$-CONR^8-$，$-NR^8SO_2-$ 或 $-SO_2NR^8-$；更优选为 $-NR^8CO-$。

本发明另一方面优选的化合物为其中 R^8 和 $R^{8'}$ 均为氢的式 I 化合物。

本发明另一方面优选的化合物为其中 n 为 2 的式 I 化合物。

本发明另一方面优选的化合物为式 I 化合物，其中 L^1 与：



部分的 5-位键连；R 为任选取代的（苯基取代吡啶酮基），任选取代的

（苯基取代吡咯并嘧啶基），任选取代的（苯基取代哒嗪基），任选取代的（苯基取代哒嗪酮基），任选取代的（苯基取代吡啶基），或任选取代的（苯基取代嘧啶基）。

本发明另一方面优选的化合物为式 I 化合物，其中 R 为取代的（苯基取代嘧啶基），所述嘧啶基被至少一个选自烷氧基、Y^1Y^2N-烷基-、Y^1Y^2N-、氮杂杂环基、Y^1Y^2NCO-亚烷基-O-、氮杂杂环基-亚烷基-O-、和Y^1Y^2N-亚烷基-O 的环系取代基所取代；并且 Y^1 和 Y^2 独立地为氢，烷基，烷氧基烷基，羟基烷基，环烷基，环烷基-烷基，Y^1Y^2N-烷基，芳基，芳烷基，杂芳烷基，杂环基烷基，杂环烯基烷基，或磺基-烷基-；或者当 Y^1 为 H-CO-，烷基-CO-，芳基-CO-，或杂环基-CO-时，则 Y^2 为氢，烷基，芳基，或芳烷基。

包含在式 I 范围内的还有这些化合物，其中 R^2 和 R^3 一起表示=NR^4，其中的 R^4 为 R^5O_2C-，R^5O-，氰基，R^5CO-，任选取代的低级烷基，硝基，或 R^6R^7N-。这些衍生物本身可构成用于治疗通过抑制 Xa 因子的活性而能够调节的病症的生物活性化合物，治疗通过将它们给药于患有所述生理病症的患者来进行；或者它们还可用作在生理病症条件下形成这些生物活性化合物的前药。

本发明化合物选自：

N-(2-[3-脒基-5-吲哚基]乙基)-4-吡啶-3-基苯甲酰胺；

N-(2-[3-脒基-5-吲哚基]乙基)-4-(嘧啶-5-基)-苯甲酰胺)；

5-(吡啶-2-基)-噻吩-2-羧酸 2-(3-脒基-5-吲哚基)乙基酰胺；

N-(2-[3-脒基吲哚-5-基]乙基)-6-吗啉-4-基烟酰胺 4-(5-2[-{3-脒基吲哚-5-基}乙基氨基甲酰基]吡啶-2-基)哌嗪-1-羧酸乙酯；

N-(2-[3-脒基吲哚-5-基]乙基)-6-咪唑-1-基烟酰胺；

N-(2-[3-脒基吲哚-5-基]乙基)-4-咪唑-1-基苯甲酰胺；

N-(2-[3-脒基吲哚-5-基]乙基)-4-(3H-咪唑-4-基)苯甲酰胺；

N-(2-[3-脒基吲哚-5-基]乙基)-4-(1,2,4)噻二唑-5-基苯甲酰胺；

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(1-氨基甲酰基-1-甲基-乙基-苯甲酰胺；

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(1-[N-(2-甲氧基乙基)]-氨基甲酰基-1-甲基-乙基-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(叔丁基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(哒嗪-4-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-2-甲基-4-(6-氧代-1,6-二氢-吡啶-3-基)-苯甲酰胺;

3′, 4′-二甲氧基联苯-4-羧酸(2-[3-脒基吲哚-5-基]乙基)酰胺;

N-(2-[3-脒基吲哚-5-基]-乙基)-4-(6-甲氧基吡啶-3-基)-苯甲酰胺;

N-(2-[3-脒基吲哚-5-基]-乙基)-4-(1-氧-吡啶-4-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(7H-吡咯并[2,3-d]嘧啶-6-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(1H-吡咯并[3,2-c]吡啶-2-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-呋喃并[3,2-c]吡啶-2-基-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-3-氯-4-(6-氧代-1,6-二氢-吡啶-3-基)-苯甲酰胺;

N-(2-[3-脒基-1H-吲哚-5-基]-乙基)-4-(6-氧代-1,6-二氢-吡啶-3-基)-苯甲酰胺;

4-(3-氨基-1,1-二甲基-丙基)-N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-2-(4-氯-苯基)-乙酰胺;

5-氯-噻吩-2-羧酸 N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-酰胺;

N-(2-[3-脒基吲哚-5-基]乙基)-6-(2-羟基乙基氨基)烟酰胺;

N-(2-[3-脒基吲哚-5-基]乙基)-6-(1,2,4)-三唑-1-基烟酰胺;

N-(2-[3-脒基吲哚-5-基]乙基)-6-吡咯-1-基烟酰胺;

N-(2-[3-脒基吲哚-5-基]乙基)-6-吡唑-1-基烟酰胺;

N-(2-[3-脒基-1-甲基吲哚-5-基]乙基)-4-(6-甲氧基吡啶-3-基)苯

甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-3-氯-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-2-(3-氯-苯基)-乙酰胺;

4-(2-氨基甲基-吡啶-4-基)-N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-苯甲酰胺;

4-{4-[2-(3-脒基-1H-吲哚-5-基)-乙基氨基甲酰基]-苯基-吡啶-2-羧酸酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(2-(N,N-二甲氨基甲基)-吡啶-4-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(6-氧代-1,6-二氢-哒嗪-3-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(6-甲氧基-哒嗪-3-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[1-(2-二甲氨基-乙基)-6-氧代-1,6-二氢-哒嗪-3-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[1-(3-二甲氨基-丙基)-6-氧代-1,6-二氢-哒嗪-3-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-(2-二甲氨基-乙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-甲氧基-嘧啶-4-基]-苯甲酰胺;

N-(2-[3-脒基吲哚-5-基]乙基)-4-(1-[2-二甲氨基乙基]-6-氧代-1,6-二氢吡啶-3-基)苯甲酰胺;

N-(2-[3-脒基吲哚-5-基]乙基)-4-(1-氨基甲酰基甲基-6-氧代-1,6-二氢吡啶-3-基)苯甲酰胺;

4-(3-氨基-[1,2,4]三嗪-6-基)-N-[2-(3-脒基-1H-吲哚-5-基]乙基)-苯甲酰胺;

4-(3-氨基-[1,2,4]三嗪-5-基)-N-[2-(3-脒基-1H-吲哚-5-基]乙基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(3-氧代-2,3-二氢-[1,2,4]三嗪-6-基)-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(5-氧代-4,5-二氢-[1,2,4]噁二唑-3-基)-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(6-氧代-哌啶-3-基)-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(吗啉-4-基-乙基氨基)-嘧啶-4-基]-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(3-二甲氨基-丙基氨基)-嘧啶-4-基]-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-([2-二甲氨基-乙基]-甲基-氨基)-嘧啶-4-基]-苯甲酰胺;
2-[(4-{4-[2-(3-脒基-1H-吲哚-5-基)-乙基氨基甲酰基]-苯基}-嘧啶-2-基)-甲基-氨基]-乙磺酸;
N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-{2-[甲基-(2(S),3(R),4(R),5(R),6-五羟基-己基)-氨基]-嘧啶-4-基}-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-{2-[甲基-(2(S),3(R),4(S),5(R),6-五羟基-己基)-氨基]-嘧啶-4-基}-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2-羟基-1-羟甲基-乙基氨基)-嘧啶-4-基]-苯甲酰胺;
2-[(4-{4-[2-(3-脒基-1H-吲哚-5-基)-乙基氨基甲酰基]-苯基}-嘧啶-2-基)-甲基-氨基]-乙烷磺酸;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(3-咪唑-1-基-丙基氨基)-嘧啶-4-基]-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-{2-[(2-二乙基氨基-乙基)-甲基-氨基]-嘧啶-4-基}-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2-二异丙基氨基-乙基氨

基)-嘧啶-4-基]-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2-二丁基氨基-乙基氨基)-嘧啶-4-基]-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(3-吗啉-4-基-丙基氨基)-嘧啶-4-基]-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(3-二乙基氨基-丙基氨基)-嘧啶-4-基]-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(3-哌啶-1-基-丙基氨基)-嘧啶-4-基]-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(2-{[2-(乙基-甲基-氨基)-乙基]-甲基-氨基}-嘧啶-4-基)-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(5-二甲氨基-戊基氨基)-嘧啶-4-基]-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(5-吗啉-4-基-戊基氨基)-嘧啶-4-基]-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(5-哌啶-1-基-戊基氨基)-嘧啶-4-基]-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(5-吡咯烷-1-基-戊基氨基)-嘧啶-4-基]-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(2-氧代-六氢-嘧啶-5-基)-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(1,3-二甲基-2-氧代-六氢-嘧啶-5-基)-苯甲酰胺;
联苯-3,4'-二羧酸 4'-{[2-(3-脒基-1H-吲哚-5-基)-乙基]-酰胺}3-[(2-甲氧基-乙基)-酰胺];
3'-(吗啉-4-羰基)-联苯-4-羧酸[2-(3-脒基-1H-吲哚-5-基)-乙基]-酰胺;
联苯-3,4'-二羧酸 4'-{[2-(3-脒基-1H-吲哚-5-基)-乙基]-酰胺}3-[(2-吗啉-4-基-乙基)-酰胺];

联苯-2,4′-二羧酸 4′-{[2-(3-脒基-1H-吲哚-5-基)-乙基]-酰胺}2-[(3-二乙基氨基-丙基)-酰胺];

联苯-2,4′-二羧酸 4′-{[2-(3-脒基-1H-吲哚-5-基)-乙基]-酰胺}2-[(3-吗啉-4-基-丙基)-酰胺];

联苯-2,4′-二羧酸 4′-{[2-(3-脒基-1H-吲哚-5-基)-乙基]-酰胺}2-[(3-哌啶-1-基-丙基)-酰胺];

联苯-2,4′-二羧酸 4′-{[2-(3-脒基-1H-吲哚-5-基)-乙基]-酰胺}2-[(4-二甲氨基-丁基)-酰胺];

联苯-2,4′-二羧酸 4′-{[2-(3-脒基-1H-吲哚-5-基)-乙基]-酰胺}2-[(2,3-二羟基-丙基)-甲基-酰胺];

联苯-2,4′-二羧酸 4′-{[2-(3-脒基-1H-吲哚-5-基)-乙基]-酰胺}2-[(2,3-二羟基-丙基)-酰胺];

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(4-甲基哌嗪-1-基)-嘧啶-4-基]-苯甲酰胺;

4-[(4-{4-[2-(3-脒基-1H-吲哚-5-基)乙基氨基甲酰基]苯基}-嘧啶-2-基)甲基氨基]丁酸;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2,2,2-三氟乙氧基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(2-吡咯烷-1-基嘧啶-4-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2-羟甲基吡咯烷-1-基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(氨基甲酰基甲基-N-甲基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(6-吡咯烷-1-基-己基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(6-哌啶-1-基-己基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(4-哌啶-1-基丁基氨基)-

嘧啶-4-基]-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(4-二乙基氨基丁基氨基)-嘧啶-4-基]-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(6-吗啉-4-基-己基氨基)-嘧啶-4-基]-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(6-二甲氨基己基氨基)-嘧啶-4-基]-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(4-二甲氨基丁基氨基)-嘧啶-4-基]-苯甲酰胺;
4-[2-(二环[2;2;1]庚-2-基氨基)嘧啶-4-基]-N-[2-(3-脒基-1H-吲哚-5-基)乙基]苯甲酰胺;
1-(4-{4-[2-(3-脒基-1H-吲哚-5-基)乙基氨基甲酰基]苯基}-嘧啶-2-基]-吡咯烷-2-羧酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-{2-[(2-羟基-乙基)-N-甲基氨基]-嘧啶-4-基}-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(2-吗啉-4-基-嘧啶-4-基)-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(环丙基甲基-氨基)-嘧啶-4-基]-苯甲酰胺;
N-[2-(脒基-1H-吲哚-5-基)乙基]-4-[2-[(2-甲氧基-乙基)-甲基-氨基]-嘧啶-4-基]-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(3-羟基-丙基氨基)-嘧啶-4-基]-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[(2-羟基-乙基)-丙基-氨基)-嘧啶-4-基]-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(2-哌啶-1-基-嘧啶-4-基)-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(乙基-甲基-氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(4-羟基-哌啶-1-基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2,3-二羟基-丙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-[(2,3-二羟基-丙基)-甲基-氨基]-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-((s)-2-甲氧基甲基-吡咯烷-1-基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(2-哌嗪-1-基-嘧啶-4-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-[2-(2-氧代-咪唑烷-1-基)-乙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(3-甲氧基-丙基氨基)-嘧啶-4-基]-苯甲酰胺;

4-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2-羟基-乙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2-甲氧基乙氧基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(1-氨基甲酰基乙氧基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(6-二甲氨基己氧基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2-氧代哌啶-3-基氧基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2-吡咯烷-1-基-乙氧基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2-二甲氨基乙氧基)-嘧啶-4-基]-苯甲酰胺;

3′-(2-二甲氨基乙氧基)联苯-4-羧酸[2-(3-脒基-1H-吲哚-5-基)乙基]

酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(1-氧吡啶-2-基)-苯甲酰胺;
2′-(2-二甲氨基乙氧基)联苯-4-羧酸[2-(3-脒基-1H-吲哚-5-基)乙基]酰胺;
2′-(3-二甲氨基丙氧基)联苯-4-羧酸[2-(3-脒基-1H-吲哚-5-基)乙基]酰胺;
3′-(3-二甲氨基丙氧基)联苯-4-羧酸[2-(3-脒基-1H-吲哚-5-基)乙基]酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(1-氧代-吡啶-3-基)-苯甲酰胺;
4-[2-(乙酰氨基-甲基)-吡啶-4-基]-N-[2-(3-脒基-1H-吲哚-5-基)乙基]-苯甲酰胺;
哌啶-4-羧酸(4-[4-[2-(3-脒基-1H-吲哚-5-基)乙基氨基甲酰基]-苯基-]-吡啶-2-基甲基)-酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[1-(3-二甲氨基丙基)-6-氧代-1,6-二氢吡啶-3-基]-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[6-(3-二甲氨基丙氧基)-吡啶-3-基]-苯甲酰胺;
(5-{4-[2-(3-脒基-1H-吲哚-5-基)乙基氨基甲酰基]苯基}-2-氧代-2H-吡啶-1-基)乙酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-{1-[(2-二甲氨基乙基氨基甲酰基)甲基]-6-氧代-1,6-二氢吡啶-3-基}-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(4-二甲氨基-哌啶-1-基)-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[4-(2-二甲氨基-乙基氨基)-哌啶-1-基]-苯甲酰胺;
4-(4-氨基-哌啶-1-基)-N-[2-(3-脒基-1H-吲哚-5-基)乙基]-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(4-甲氧基-哌啶-1-基)-苯甲

酰胺;
4-(4-乙酰氨基-哌啶-1-基)-N-[2-(3-脒基-1H-吲哚-5-基)乙基]-苯甲酰胺;
4-(1-乙酰基-哌啶-4-基)-N-[2-(3-脒基-1H-吲哚-5-基)乙基]-苯甲酰胺;
4-{4-[2-(3-脒基-1H-吲哚-5-基)乙基氨基甲酰基]-苯基}-哌啶-1-羧酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(1-甲基-1-氧-哌啶-4-基)-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(1-甲基-哌啶-4-基)-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(1-甲磺酰基-哌啶-4-基)-苯甲酰胺;
4-(2-乙酰氨基-1,1-二甲基-乙基)-N-[2-(3-脒基-1H-吲哚-5-基)乙基]-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(2-甲磺酰基氨基-1,1-二甲基-乙基)-苯甲酰胺;
哌啶-4-羧酸(2-{4-[2-(3-脒基-1H-吲哚-5-基)乙基氨基甲酰基]-苯基}-2-甲基丙基)-酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(1,1-二甲基-2-脲基-乙基)-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(3-乙基脲基)-1,1-二甲基-乙基]-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(2-二甲氨基-3,4,5,6-四氢-嘧啶-4-基)-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(1-氧-吡啶-4-基氧基)-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(1-甲基-哌啶-4-基氧基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(1,2,3,6-四氢吡啶-4-基)-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-哌啶-4-基-苯甲酰胺;
4-(2-氨基-1,1-二甲基乙基)-N-(2-[3-脒基吲哚-5-基]乙基)苯甲酰胺;
N-(2-[3-脒基吲哚-5-基]乙基)-4-(6-[2-二甲氨基乙氧基]吡啶-3-基)-苯甲酰胺;
N-(2-[3-脒基吲哚-5-基]乙基)-4-吡啶-4-基苯甲酰胺;
N-(2-[3-脒基吲哚-5-基]乙基)-4-(4-氨基甲酰基-苯基)-苯甲酰胺;
N-(2-[3-脒基吲哚-5-基]乙基)-4-(4-甲氧基-苯基)-苯甲酰胺;
N-(2-[3-脒基吲哚-5-基]乙基)-(5-甲氧基-吲哚-2-基)-甲酰胺;
N-(2-[3-脒基吲哚-5-基]乙基)-(6-氯-苯并噻吩-2-基)-甲酰胺;
N-(2-[3-脒基吲哚-5-基]乙基)-4-(4-苄氧基-苯基)-苯甲酰胺;
N-(2-[3-脒基吲哚-5-基]乙基)-4-氯苯甲酰胺;
N-(2-[3-脒基吲哚-5-基]乙基)-4-(甲磺酰基)-苯甲酰胺;
N-(2-[3-脒基吲哚-5-基]乙基)-4-(氨基-磺酰基)-苯甲酰胺;
4-(3-氨基丙-1-炔基)-N-[2-(3-脒基-1H-吲哚-5-基)乙基]-苯甲酰胺;
5-{4-[2-(3-脒基-1H-吲哚-5-基)乙基氨基甲酰基]-苯基}-2-氧代-2H-吡啶-1-基)乙酸; 和
3-脒基-5-{2-[4-(6-氧代-1,6-二氢-吡啶-3-基)-苯甲酰基氨基]-丙基}-吲哚。

更优选的本发明化合物为下列化合物:
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(哒嗪-4-基)-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-2-甲基-4-(6-氧代-1,6-二氢-吡啶-3-基)-苯甲酰胺;
N-(2-[3-脒基吲哚-5-基]乙基)-4-(6-甲氧基吡啶-3-基)-苯甲酰胺;
N-(2-[3-脒基吲哚-5-基]乙基)-4-(1-氧-吡啶-4-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(7H-吡咯并[2,3-d]嘧啶-6-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(1H-吡咯并[3,2-c]吡啶-2-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-3-氯-4-(6-氧代-1,6-二氢-吡啶-3-基)-苯甲酰胺;

N-(2-[3-脒基吲哚-5-基]乙基)-4-(6-氧代-1,6-二氢吡啶-3-基)-苯甲酰胺;

4-(3-氨基-1,1-二甲基-丙基)-N-[2-(3-脒基-1H-吲哚-5-基)乙基]-苯甲酰胺;

4-(2-氨基甲基-吡啶-4-基)-N-[2-(3-脒基-1H-吲哚-5-基)乙基]-苯甲酰胺;

4-{4-[2-(3-脒基-1H-吲哚-5-基)乙基氨基甲酰基]-苯基-吡啶-2-羧酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(2-(N,N-二甲氨基甲基)-吡啶-4-基)-苯甲酰胺);

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(6-氧代-1,6-二氢-哒嗪-3-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(6-甲氧基-哒嗪-3-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[1-(2-二甲氨基-乙基)-6-氧代-1,6-二氢-哒嗪-3-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[1-(3-二甲氨基-丙基)-6-氧代-1,6-二氢-哒嗪-3-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2-二甲氨基-乙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-甲氧基-嘧啶-4-基]-苯甲酰胺;

N-(2-[3-脒基吲哚-5-基]乙基)-4-(1-[2-二甲氨基乙基]-6-氧代

-1,6-二氢吡啶-3-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(6-氧代-哌啶-3-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(吗啉-4-基-乙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(3-二甲氨基-丙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-([2-二甲氨基-乙基]-甲基-氨基)-嘧啶-4-基]-苯甲酰胺;

2-[(4-{4-[2-(3-脒基-1H-吲哚-5-基)乙基氨基甲酰基]-苯基}-嘧啶-2-基)-甲基-氨基]-乙烷磺酸;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-{2-[甲基-(2(S),3(R),4(R),5(R),6-五羟基-己基)-氨基]-嘧啶-4-基}-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-{2-[甲基-(2(S),3(R),4(S),5(R),6-五羟基-己基)-氨基]-嘧啶-4-基}-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2-羟基-1-羟甲基-乙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(3-咪唑-1-基-丙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-{2-[(2-二乙基氨基-乙基)-甲基-氨基]-嘧啶-4-基}-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2-二异丙基氨基-乙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2-二丁基氨基-乙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(3-吗啉-4-基-丙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(3-二乙基氨基-丙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(3-哌啶-1-基-丙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(2-{[2-(乙基-甲基-氨基)-乙基]-甲基-氨基}-嘧啶-4-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(5-二甲氨基-戊基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(5-吗啉-4-基-戊基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(5-哌啶-1-基-戊基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(5-吡咯烷-1-基-戊基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(2-氧代-六氢-嘧啶-5-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(1,3-二甲基-2-氧代-六氢-嘧啶-5-基)-苯甲酰胺;

联苯-3,4'-二羧酸 4'-{[2-(3-脒基-1H-吲哚-5-基)-乙基]-酰胺}3-[(2-甲氧基-乙基)-酰胺];

联苯-3,4'-二羧酸 4'-{[2-(3-脒基-1H-吲哚-5-基)-乙基]-酰胺}3-[(2-吗啉-4-基-乙基)-酰胺];

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(4-甲基哌嗪-1-基)-嘧啶-4-基]-苯甲酰胺;

4-[(4-{4-[2-(3-脒基-1H-吲哚-5-基)乙基氨基甲酰基]苯基}-嘧啶-2-基)甲基氨基]丁酸;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2,2,2-三氟乙氧基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(2-吡咯烷-1-基嘧啶-4-基)-

苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2-羟甲基吡咯烷-1-基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(氨基甲酰基甲基-N-甲基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(6-吡咯烷-1-基-己基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(6-哌啶-1-基-己基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(4-哌啶-1-基丁基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(4-二乙基氨基丁基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(6-吗啉-4-基-己基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(6-二甲氨基己基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(4-二甲氨基丁基氨基)-嘧啶-4-基]-苯甲酰胺;

4-[2-(二环[2;2;1]庚-2-基氨基)嘧啶-4-基]-N-[2-(3-脒基-1H-吲哚-5-基)乙基]苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-{2-[(2-羟基-乙基)-N-甲基氨基]-嘧啶-4-基}-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(2-吗啉-4-基-嘧啶-4-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(环丙基甲基-氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(脒基-1H-吲哚-5-基)乙基]-4-[2-[(2-甲氧基-乙基)-甲基-氨基]-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(3-羟基-丙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[(2-羟基-乙基)-丙基-氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(2-哌啶-1-基-嘧啶-4-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(乙基-甲基-氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(4-羟基-哌啶-1-基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2,3-二羟基-丙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-[(2,3-二羟基-丙基)-甲基-氨基]-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-((s)-2-甲氧基甲基-吡咯烷-1-基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(2-哌嗪-1-基-嘧啶-4-基)-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-[2-(2-氧代-咪唑烷-1-基)-乙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(3-甲氧基-丙基氨基)-嘧啶-4-基]-苯甲酰胺;

4-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2-羟基-乙基氨基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2-甲氧基乙氧基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(1-氨基甲酰基乙氧基)-嘧啶-4-基]-苯甲酰胺;

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(6-二甲氨基己氧基)-嘧

啶-4-基]-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2-吡咯烷-1-基-乙氧基)-嘧啶-4-基]-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[2-(2-二甲氨基乙氧基)-嘧啶-4-基]-苯甲酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(1-氧吡啶-2-基)-苯甲酰胺;
2′-(2-二甲氨基乙氧基)联苯-4-羧酸[2-(3-脒基-1H-吲哚-5-基)乙基]酰胺;
2′-(3-二甲氨基丙氧基)联苯-4-羧酸[2-(3-脒基-1H-吲哚-5-基)乙基]酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-(1-氧代-吡啶-3-基)-苯甲酰胺;
4-[2-(乙酰氨基-甲基)-吡啶-4-基]-N-[2-(3-脒基-1H-吲哚-5-基)乙基]-苯甲酰胺;
哌啶-4-羧酸(4-[4-[2-(3-脒基-1H-吲哚-5-基)乙基氨基甲酰基]-苯基-]-吡啶-2-基甲基)-酰胺;
N-[2-(3-脒基-1H-吲哚-5-基)乙基]-4-[1-(3-二甲氨基丙基)-6-氧代-1,6-二氢吡啶-3-基]-苯甲酰胺;
4-(2-氨基-1,1-二甲基乙基)-N-(2-[3-脒基吲哚-5-基]乙基)苯甲酰胺; 和
N-(2-[3-脒基吲哚-5-基]乙基)-4-吡啶-4-基苯甲酰胺。

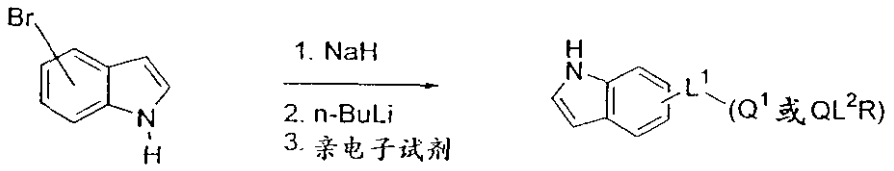
应当理解，本发明包括本文所述的具体与优选组基团的所有适当组合。

式 I 化合物可以使用或采纳已知方法（即指迄今使用过或文献中记载过的方法），或按照本文所述方法制备。

本发明的一个方面涉及各种取代的吲哚、苯并呋喃和苯并噻吩杂环化合物的合成。这些合成可通过例如官能化特定前体继而进行环合成或者衍生化预形成的环体系实现。化学文献中已经介绍了多种合成

和官能化上述杂环的方法(有关综述参见:(a) Katritzky, A.R.; Rees, C.W.; Scriven, E.F.V. Eds.《杂环化学大全 II》(Comprehensive Heterocyclic Chemistry II), 2卷, 119, 607. Elsevier Science 1996及其中的引用文献. (b) Ketcha, D.M.《杂环化学进展》(Prog. Heterocycl. Chem.)1997, 9, 97及其中的引用文献. (c) Hughes, D.L. Org. Prep. Proced. Int. 1993, 25, 607)。

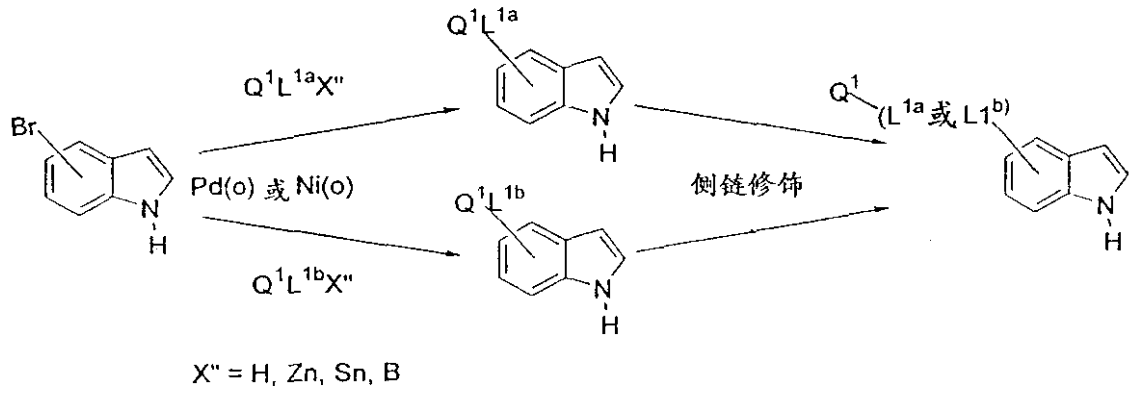
流程1概述了本发明一种特别有用的制备方法。溴代-吲哚可以在大约室温下用氢化钠或其它强碱处理，接着（在较低温度下，通常低于0℃）再用烷基锂试剂处理而金属化。适合此方法用的适宜溶剂包括THF或乙醚,这些溶剂可以单独使用,或者以与添加剂如HMPA、TMEDA或DABCO形成的混合物形式使用。所产生的亲核体然后可以与各种适当的官能化/取代的和/或保护的亲电试剂反应，例如醛、酮、烷基卤、环氧乙烷类化合物、氮丙啶类化合物、β-不饱和羰基化物或β-不饱和酯(流程 1)，生成带有不同官能化/取代的和/或被护侧链的吲哚化合物,亦即其中的Q^1为$-NR^8P^1$, $-OP^1$, -C(O)(H或烷基), $-C(O)-OP^1$或$-SP^1$,其中P^1为氢或如本文所述的保护基。(代表性的实例参见Moyer, M.P.; Shiurba, J.F.; Rapaport, H.《有机化学杂志》(J. Org. Chem.), 1986, 51, 5106]。



流程1

另一方面，如流程2所示，在有或无碱存在下，溴代-吲哚化合物还可以与端烯烃($Q^1L^{1b}H$, 其中Q^1如本文定义，而L^{1b}为具有至少一个端双键的亚烯基)、端炔类($Q^1L^{1a}H$, 其中Q^1如本文定义，而L^{1a}为具有至少一个端三键的亚炔基)、或它们的金属化衍生物(特别是锌、锡和硼)在钯或镍催化剂存在的条件下反应（例如参见: J. Tsuji,)《钯试剂

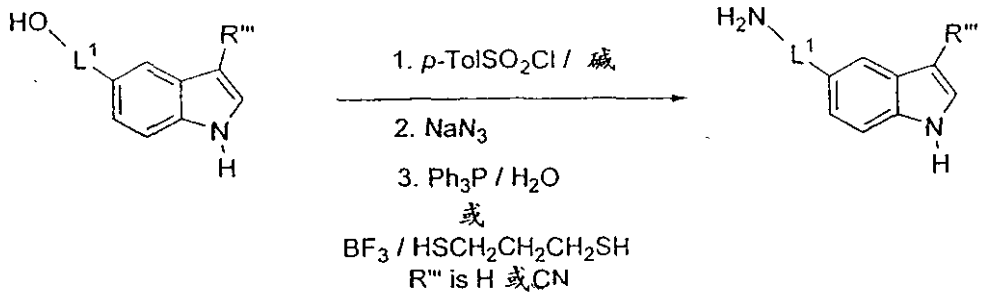
和催化剂》(Palladium Reagents and Catalysts, J. Wiley Publications), 1996, 以及Harrington, P.J.; Hegedus, L.S. 《有机化学杂志》(J. Org. Chem.), 1984, 49, 2657), 生成烯基或炔基取代的吲哚。催化剂的选择取决于所用底物, 但最常用的为四(三苯膦)合钯, 氯化双(三苯膦)合钯, 1,1'-双(二苯基膦基)二茂铁/双-二亚苄基丙酮合钯或1, 2-双(二苯基膦基)乙烷/双(乙腈)二氯合钯。在某些情况下, 还需要加入铜(I)盐作为助催化剂(Rossi, R.; Carpita, A.; Bellina, F. Org. Prep. Proced. Int. 1995, 27, 127)。这些偶联反应可以在大约20-大约25℃下于各种不同溶剂中进行, 包括甲苯、THF、DME、DMSO、DMF、二甲基乙酰胺和HMPA。



流程2

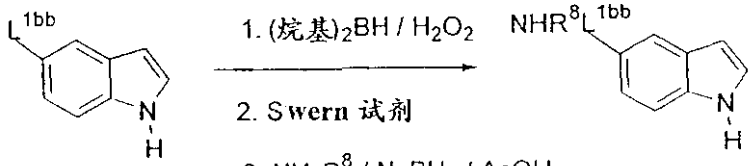
如上所述引入的吲哚侧链可以含有或者可以转化成各种官能团(采用一步或多步步骤), 包括胺、醇、醛、酮、羧酸、酯、烯烃、酰胺、酰亚胺、尿烷、氨基甲酸酯、磺酰胺、砜、亚砜和硫醚。这些相互转化采用化学文献中所述的标准合成方法(例如参见: Larock, C.L. 《有机转化大全》(Comprehensive Organic Transformations), VCH Publishers 1989和Greene, T. W.; Wuts, P.G.M. 《有机合成中的保护基》(Protective Groups in Organic Synthesis), John Wiley Publications 1991)。特别是, 例如醇可以通过下述反应顺序(流程3)而转化为相应的胺: 约室温下, 在溶剂如二氯甲烷、DMF或吡啶中用甲苯磺酰氯/DMAP和碱如三乙胺或二异丙基乙胺进行处理; 或者将醇用NBS/Ph_3P, NCS/Ph_3P, I_2/Ph_3P/咪唑, CBr_4/Ph_3P处理而产生相应

的烷基卤（有关综述参见Castro, B.R. Org. React. 1983, 29, 1). 产物然后在大约20－大约80℃的温度下与叠氮化钠在溶剂如DMF、二甲基乙酰胺、DMPU或乙醇中反应。所生成的叠氮化物随后用试剂如三苯膦/水在 THF 中或用三氟化硼乙醚合物/1,3-丙烷-二硫醇在诸如二氯甲烷之类的溶剂中还原，生成相应的胺:



流程3

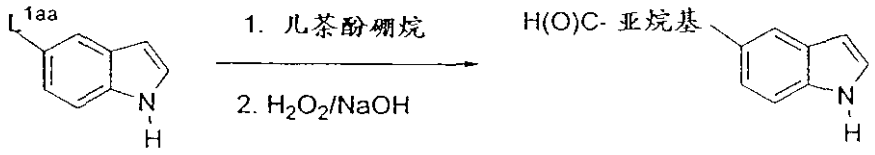
氨基部分也可以按下所述引入到吲哚侧链上（流程4）：首先利用硼氢化氧化反应顺序将适当侧链烯烃双键（L^{1bb}为在其与吲哚部分连接端远侧的末端具有至少一个双键的亚烯基）转化为醇,（例如可参见(a) Beletskaya, I; Pelter, A.《四面体》（Tetrahedron）, 1997, 53, 4957 及其中的引用文献. (b) Brown, H.C.; Kramer, G.W.; Levy, M.B.; Midland, M.M.,《经由硼烷的有机合成》（Organic Synthesis via Boranes）, Wiley Interscience, N.Y. 1973.), 然后使用各种常见氧化试剂（如 Swern 试剂）将醇氧化成相应的酮（有关综述参见 Hudlicky, T.《有机化学中的氧化》（Oxidations in Organic Chemistry）, ACS Publications 1990), 最后用合适的胺和还原剂如氰基硼氢化钠或三乙酰氧基硼氢化钠在溶剂如甲醇、THF、乙腈、HMPA、或水（水可以单独使用或作为助溶剂）中还原胺化所述酮（Abdel-Magid, A.F.; Maryanoff, C.A.《有中成中的还原》（Reductions in Organic Synthesis）, ACS Symp. Ser., 641, p201, ACS Publications 1996）。在某些情况下，胺部分可能是吲哚链的一部分，这时可以形成杂环基。



流程 4

向侧链中引入氨基基团的另一种简便方法包括在溶剂如二氯甲烷或 THF 甲苯或苯中用二苯基磷酰叠氮和碱如三乙胺、二异丙基胺处理侧链羧酸，反应温度通常为大约 0℃ - 大约室温。（有关综述参见 Banthrope, 《叠氮基化学》（The Chemistry of the Azido Group），S. Patai 编辑, Wiley Interscience N.Y. 1971）。随后在醇如叔丁醇、苄醇或烯丙醇存在下，在大约室温 - 大约 140℃下热解所产生的酰基叠氮，得到相应的氨基甲酸酯，进而它可以使用标准的保护基化学裂解形成胺。无醇存在的情况下热解酰基叠氮则生成相应的异氰酸酯，它随后可以与各种胺反应形成尿烷(能同时提供简便制备仲胺的修饰反应，参见 Pfister, J.R.; Wymann, W.E. 《合成》（Synthesis），1983, 38)。另一方面，尿烷也可以通过侧链氨基基团与合适的异氰酸酯反应引入。

根据流程 5，也可以按下所述向侧链中引入酮：在大约室温 - 大约 67℃下，在溶剂如 THF 中用儿茶酚硼烷硼氢化适当炔烃（L^{1aa} 为在其与吲哚部分连接端远侧的末端具有至少一个三键的亚炔基），接着在碱如氢氧化钠存在下用过氧化氢氧化裂解所得产物。



流程 5

利用 Mitsunobu 试剂(Mitsunobu. O.,《合成》(Sythesis), 1981, 1), 使侧链醇与预先形成的 N- 未取代的酰亚胺反应, 可以引入酰亚胺部分(如此形成的酰胺通过在溶剂如乙醇中用肼处理还可以转化为相应的胺)。另一方面, 酰亚胺基团还可以通过用酰氯(或活化酯)在碱如氢化钠存在下酰化侧链酰胺而引入。

酰胺连接基可以通过胺(胺的引入可采用上述方法)与羧酸反应而引入到吲哚侧链上。实现这一转化的适宜条件包括在大约或高于室温的温度下, 在溶剂如二氯甲烷、DMF、二甲基乙酰胺或 DMPU 中用下列试剂活化羧酸: 例如亚硫酰氯、氯甲酸异丙酯、草酰氯/DMF、TBTU、DCC、DICC/HOBT、CDI、BOP、EEDQ 或 PyBroP (有关综述参见(a) Blackburn, C.; Kates, S.A. Methods Enzymol. 1997, 289, 175. (b) Bodanszky, M.; Trost, B.M. Principles of Peptide Synthesis 第二版, Springer Verlag, N.Y. 1993), 该反应通常在碱如三乙胺、二异丙基乙胺和/或 DMAP 下进行。反向酰胺单元可通过含酸部分的吲哚侧链与胺反应制备。通过先将侧链醇氧化为醛, 进而再将醛氧化为相应羧酸而可以在侧链上形成酸部分。用于该转化的特别合适试剂为氯酸钠(Lidgren, B.O.; Hilsson, T. Acta. Chem. Scand, 1973, 58, 238)。另一方面, 在溶剂如 THF/水或叔丁醇/水中用四氧化锇和诸如高碘酸钠之类助催化剂氧化烯烃可以生成醛。羧酸还可以通过用标准保护基方法学水解相应的酯获得。

在碱如吡啶、三乙胺、二异丙基乙胺或氢氧化钠存在下, 在溶剂如二氯甲烷、吡啶、DMF 或醇(如乙醇或异丙醇)中使侧链氨基官能物与磺酰氯反应, 可以在侧链中引入磺酰胺连接基。反向磺酰胺连接基可以按照 Liskamp 的方法(Moree, W.J.; Van der Marel, G.A.; Liskamp, R.J. J.Org.Chem. 1995, 60, 1995)由侧链硫代乙酸酯形成。硫代乙酸酯部分可以通过在溶剂如 DMF、DMPU、HMPA 或 DMSO 中用硫代乙酸钠置换卤素或磺酸酯来制备。

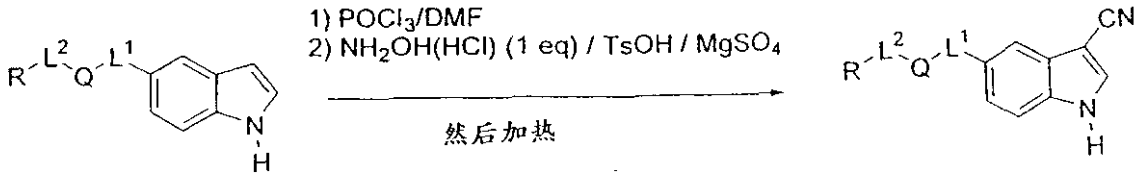
通过皂化硫代乙酸酯官能团, 继而用适当烷基卤或磺酸酯(如甲苯磺酸酯、三氟甲磺酸酯或甲磺酸酯)烷基化所得硫醇, 可以在侧链中引入硫醚官能团。另一方面, 硫醚官能团也可以使侧链烷基氯、烷基溴、

烷基碘、甲苯磺酸烷基酯或甲磺酸烷基酯与硫醇离子在溶剂(如苯、DMF、DMPU、HMPA 或 DMSO)中直接反应引入。在一些情况下，硫醚可由合适的二硫化物和侧链醇在三丁基膦的存在下于溶剂(如 THF)中形成。

在大约室温或低于室温下，在二氯甲烷、氯仿或苯中用诸如间-氯过苯甲酸之类试剂温和氧化硫醚，可以引入亚砜和砜连接基。

醚连接基(有关综述参见《有机化学大全第 1 卷》(Comprehensive Organic Chemistry Vol 1)，799 页，Ed. Barton, D.; Ollis, W.D., Pergamon Press, 1979)的制备可以由侧链醇和烷基卤、磺酸酯或不饱和酮衍生物和碱如氢化钠、氢化钾在溶剂如 DMF、DMSO、THF、DMPU 或 HMPA 中完成。另一方面，醚连接基还可以在相同条件下使用侧链烷基卤、磺酸酯或β-不饱和酮和适当醇制得。成醚的另一种方法包括先使侧链酯或内酯与硫化试剂如 Lawesson 试剂(有关综述参见 Cava, M.P.; Levinson, M.I. 《四面体》(1985), 41 (22), 5061-87)反应生成硫羰酯，接着用氢化物还原剂如氢化三丁基锡还原硫羰基(该反应通常在游离基引发剂如 AIBN 存在下进行)。

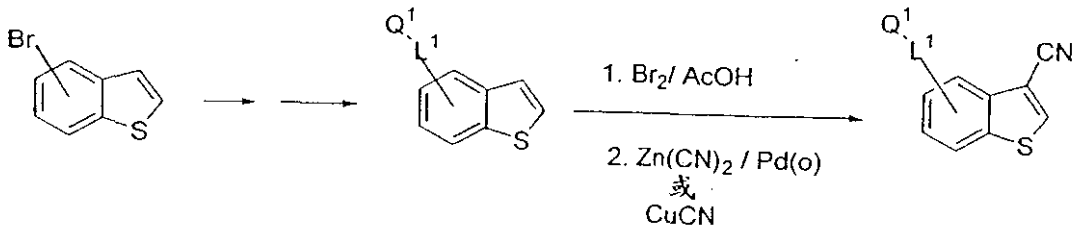
在吲哚环系的 C-3 位引入腈的反应(流程 6)可按下述方式实现：首先在室温或高于室温下，用复合试剂如磷酰氯/DMF 在 C-3 位进行甲酰化，然后按照 Ganbao 和 Palomo 的方法(Ganbao, I.; Palomo, C. Syn. Commun. 1983, 13, 219. 有关该方法的替代方法参见 Wang, E-C.; Lin, G-J, 《四面体通信》1998, 39, 4047 及其中的引用文献)，在催化剂如甲苯磺酸和干燥剂如硫酸镁存在下，在溶剂如甲苯或二甲苯中将所产生的醛用盐酸羟胺转化为相应的肟。然后在大约 80℃ - 大约 150℃下加热肟与这些试剂，脱水生成相应的腈。在某些有利情况下，上述甲酰化条件还会导致侧链醇转化为相应的烷基氯。



流程 6

上述 C-3 腈的引入反应可以在吲哚环其它位置上的侧链衍生化之前或之后进行，它取决于所存在的官能团的性质。

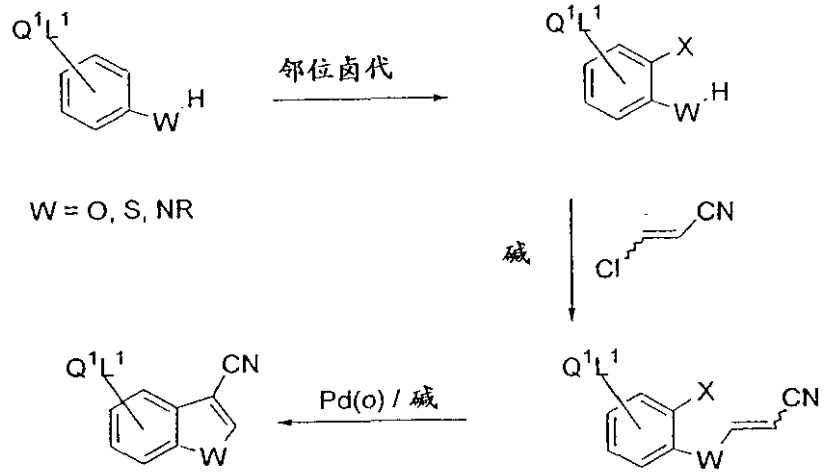
本发明的另一实施方案涉及使用苯并噻吩代替吲哚骨架。苯并噻吩化合物的合成可以使用多种方法（例如参见 Katritzky, A.R.；Rees, C.W.；Scriven, E.F.V.Eds.《杂环化学大全 II》（Comprehensive Heterocyclic Chemistry II, 第二卷, 607 页, Elsevier Science 1996 及其中的引用文献）。特别适用于本发明的方法见流程 7 所示。以适当溴-苯硫酚为原料，在碱如 NaH 存在下在溶剂如 DMF、THF、TBTU、DMSO 或 HMPA 中用溴-乙醛缩二乙醇烷基化所述硫酚，接着用酸如多磷酸进行环化，从而生成相应的溴-苯并噻吩（例如参见 Titus, R.L.；Choi, M.；Hutt, M.P. 《杂环化学杂志》（J. Heterocycl. Chem.）1967, 4, 651, 和 Clark, P.D.；Kirk, A.；Yee, J.G.K.《有机化学杂志》（J. Org. Chem.）1995, 60, 1936）。这一结构可应用上文引入和官能化吲哚骨架侧链所用的相同方法进行处理。苯并噻吩环 C-3 位腈的引入可通过在溶剂如乙酸或氯仿中用溴处理来进行。然后在大约 70℃-大约 90℃下在 DMF 中利用氰化锌和钯催化剂（优选四(三苯膦)钯(0)）将所得 3-溴苯并噻吩转化为 3-氰基-衍生物。



流程 7

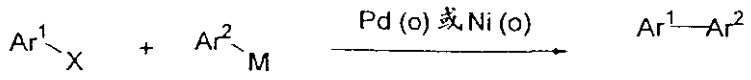
在某些情况下，通过直接环合成能够方便地制备特定取代的杂芳基骨架。特别适宜的环合成方法采用改进的 Yamanaka 方法（Sakamoto, K.；Nagano, T.；Kondo, Y.；Yamanaka, H. 《合成》Synthesis, 1990, 215）。在这一方法中，首先在适当取代的苯胺、苯硫酚或苯酚环的氮/硫/氧取代基的邻位进行溴化或（更优选）碘化反应（流程 8）。适合这种转化用的适宜试剂包括溴+酸（如乙酸）或碱（如乙酸钠、碳酸钠、

三乙胺或吡啶），碘或一氯化碘+软路易斯酸（如硫酸银）或碱（如碳酸钙、吗啉、二甲胺或吡啶）。用于此方法的适宜溶剂包括水、甲醇、乙醇或二氯甲烷，并且反应温度为大约室温或低于室温。丙烯腈官能物与环杂原子的加成可按照Scotti和Frazza的方法进行(Scotti, F.; Frazza, E.J.《有机化学杂志》J. Org. Chem., 1964, 29, 1800)。



流程 8

本发明的一种具体实施方案采用被含有（芳基或杂芳基）-取代的芳基或杂芳基附加基团的侧链取代的吲哚/苯并噻吩/苯并呋喃化合物。其中所述的附加基团结构部分可采用上文衍生化 5-溴-吲哚所述的条件，在Pd(0)或Ni(0)催化下交叉偶联（流程9）适当取代的（杂芳基或芳基）卤或三氟甲磺酸酯与（杂芳基或芳基）芳基有机金属化物（最常用的为锌、硼、镁和锡衍生物）制备。



X = Br, I, O_3SR　　M = Zn, B, Mg, Sn

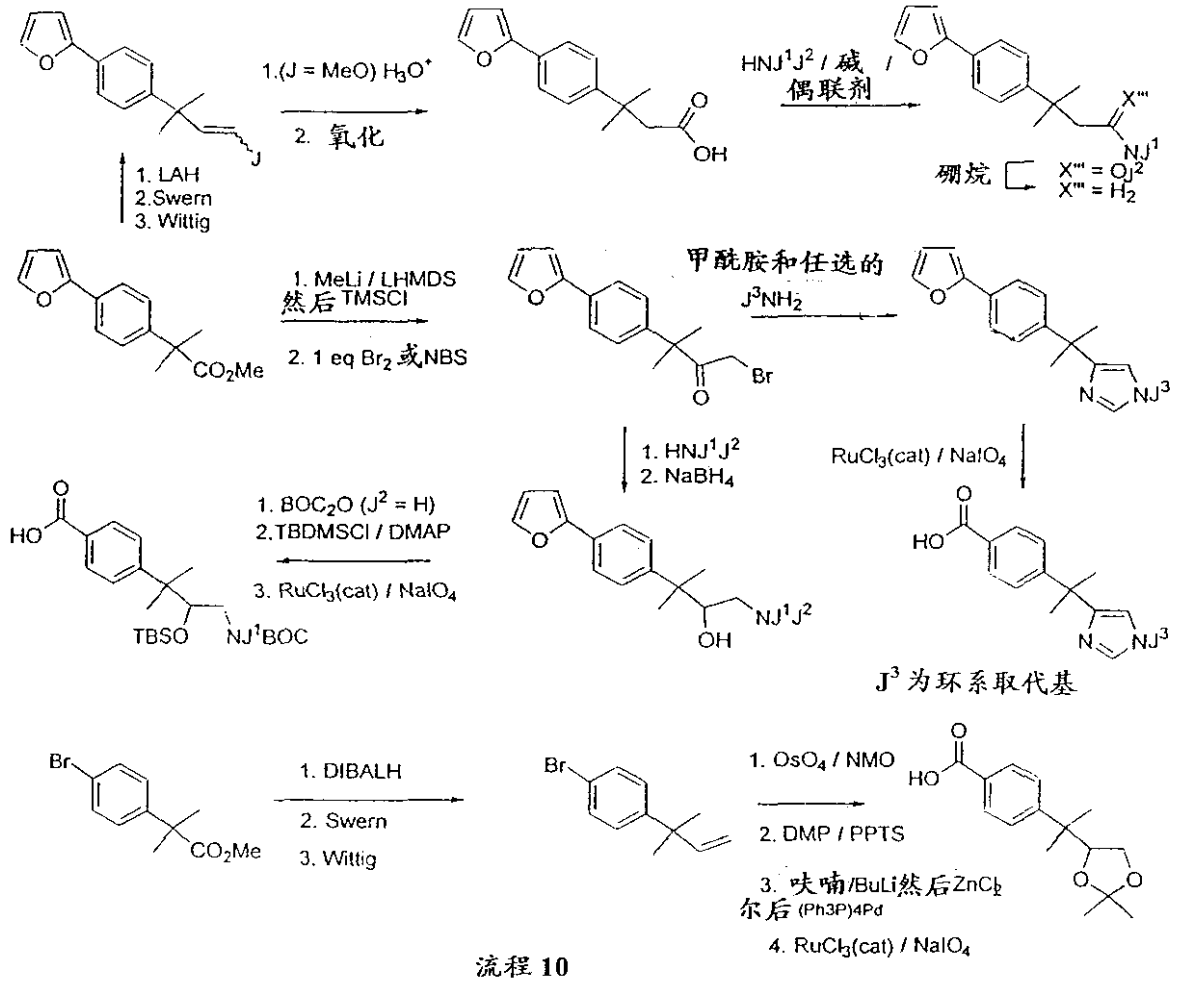
Ar^1 和 Ar^2 为适当取代的芳基或杂芳基

流程 9

芳基和杂芳基取代的杂环化合物还可以通过直接环合成制备。适合这种操作的各种方法与条件均是化学文献中已知的（例如参见(a) Katritzky, A.R.; Rees, C.W.; Scriven, E.F.V. Eds.《杂环化学大全》Comprehensive Heterocyclic Chemistry II, Elsevier Science 1996）。

在本发明的另一实施方案中，吲哚/苯并噻吩/苯并呋喃侧链被取代

的芳基基团取代。一种特别有用的芳基取代基包括进一步被杂原子、杂原子簇(如二醇或氨基-醇)或杂芳基(如咪唑)取代的 1,1-二甲基烷基链。如流程 10 所示，这些体系可以由 2-（4-呋喃-2-基-苯基）-2-甲基-丙酸甲酯或 2-（4-溴-苯基）-2-甲基-丙酸甲酯制备。

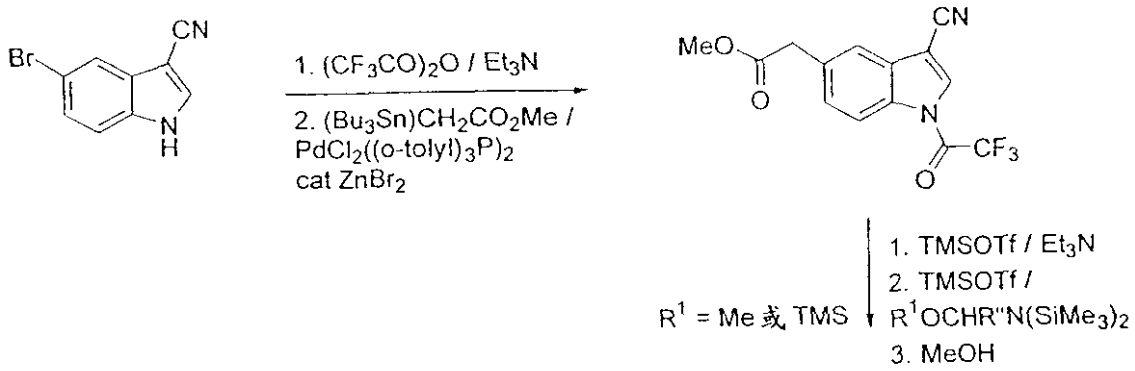


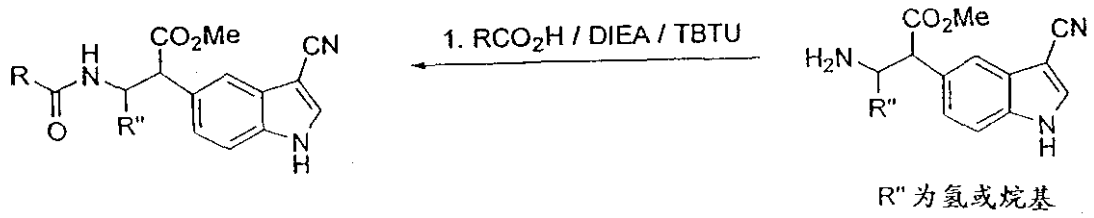
流程 10

在大约室温或低于室温下，在六甲基二硅烷基氨化锂存在下用甲基锂处理 2-（4-呋喃-2-基-苯基）-2-甲基-丙酸甲酯，进而将所得烯醇盐与氯化 TMS 反应，生成相应的甲硅烷基烯醇醚。将该中间体在低温（通常为大约-78℃）下与 1 当量溴反应，生成α-溴酮。在高温（大约 50℃-大约 180℃）下用甲酰胺处理此化合物得到咪唑。另一方面，溴酮也可以与叠氮化钠反应接着用硼氢化钠还原而得到氨基醇。在将氨基醇保护成胺的 BOC 衍生物和醇的 TBS 醚之后，还可以氧化裂解呋喃环得到苯甲酸衍生物。该单元然后可如上所述连接到杂芳基骨架上。在溶剂如 THF 中用氢化铝锂还原 2-（4-呋喃-2-基-苯基）-2-甲基-丙酸甲酯，接着氧化所得伯醇形成相应的醛，再

进行 Wittig 或 Horner-Emmons 烯烃反应，从而提供了获得链增长烯烃的方法（有关综述参见 Cadogan, J. I. G.《有机合成中的有机磷试剂》Organophosphorus Reagents in Organic Synthesis, Academic Press, 1979）。在其中 R = Ome 的情形下，该体系可以用稀盐酸水解成相应的醛，然后再如前所述氧化成羧酸。形成酰胺接着用试剂如硼烷在 THF 中反应可得到一系列胺。随后如上所述氧化裂解呋喃环得到用于与杂环骨架连接的有用官能团。另外，-78℃下在二氯甲烷中用二异丁基氢化铝处理 2-（4-溴-苯基）-2-甲基-丙酸甲酯，接着 Swern 氧化所得醇，再对醛进行 Wittig 反应，从而得到一碳链增长烯烃。锇化该物质，接着将所得二醇保护成丙酮化合物，从而能使呋喃环氧化为羧酸，后者提供了一种与杂芳基骨架偶联的连接点。

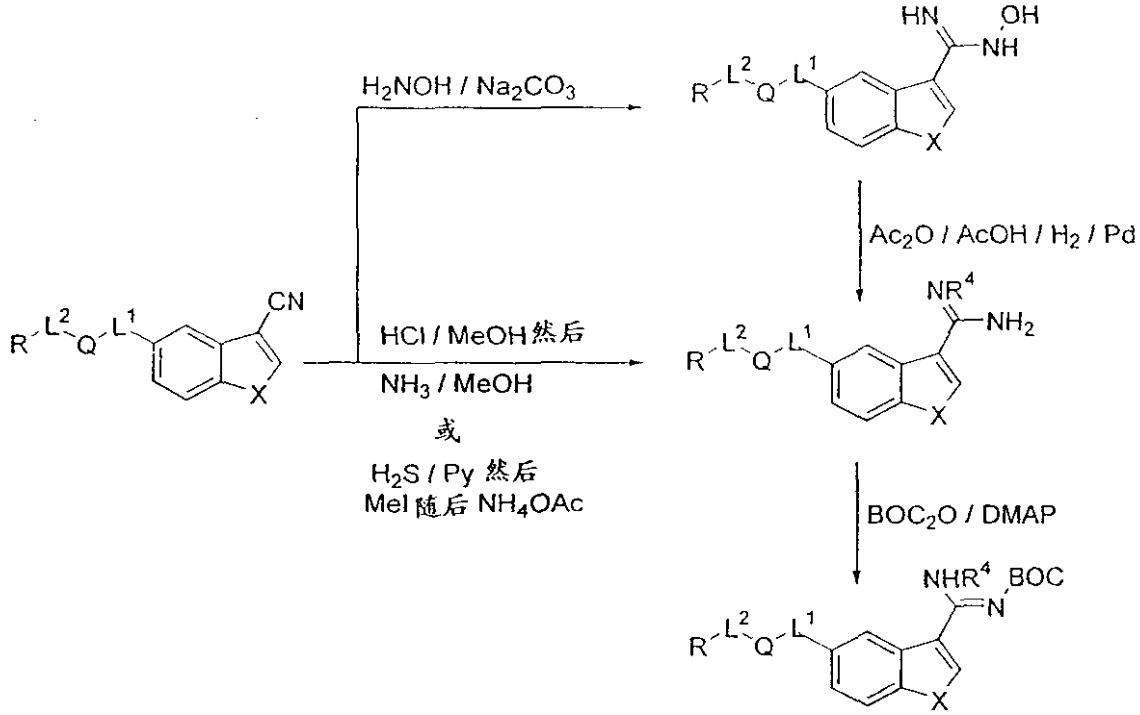
为了优先获得生物活性构象异构体，向连接基中引入构象限制通常是有效的。这些限制基团还可以与能提供其它优点的靶蛋白发生有利的相互作用。流程 11 给出了合成能产生这种作用的体系实例。采用改进的 Migata 方法(Kosugi, M; Negishi, Y.; Kameyama, M.; Migata, T.; Bull. Chem. Soc. Jpn., 1985, 58, 3383; Agnelli, F., Slikowski, G. A.《四面体通信》(Tetrahedron Letts)1998, 39, 8807)对溴吲哚进行两碳链增长反应，然后于 0℃下在乙醚中用 TMS 三氟甲磺酸酯和三乙胺处理所得酯，得到甲硅烷基乙烯酮缩醛。在作为催化剂的 TMS 三氟甲磺酸酯存在下，在二氯甲烷中使该物质与胺缩醛反应，生成取代的β-氨基酯（代表性的实例参见 Okano, K.; Morimoto, T.; Sekiya, M. J. Chem. Soc., Chem. Commun., 1984, 883 和 Colvin, E. W.; McGarry, D. G.; Nugent, M. J. 四面体 Tetrahedron, 1988, 44, 4157）。然后酰化氨基得到各种酰胺取代骨架。





流程 11

C-3 腈转化为相应脒的反应可以采用多种标准方法进行（例如参见 Judkins, B. D. ; Allen, D. G. ; Cook, T. A. ; Evans, B. ; Sardharwala, T. E. 《合成通信》Syn. Comm. 1996, 26, 4351 及其中的引用文献）。在大约或高于室温的温度下，在溶剂如甲醇或乙醇中用 HCl 处理腈（流程 12）得到亚氨酸酯中间体，后者然后可通过在溶剂如甲醇或乙醇中经氨或烷基胺处理而转化为脒。另一方面，使腈与硫化氢在溶剂如吡啶中反应，接着用烷基化剂如甲基碘在溶剂如丙酮中于大于等于室温的温度下烷基化所得硫代酰胺，进而再在溶剂如甲醇中于大约或高于室温的温度下用氨或乙酸铵处理这一产物，从而得到最终的脒。



流程 12

向腈中加入羟胺形成相应的 N-羟基脒，接着在催化剂如钯-碳存在下采用氢/乙酸/乙酐酰化并氢解 N-O 键，也可以制备脒。对于侧链的某些转化，可能需要或者优选将吲哚氮保护成惰性衍生物（《有机合成中的保护基》Portective Groups in Organic Synthesis, T. W. Greene 和 P. G. M. Wuts; John Wiley Publications 1991）。特别适

合此目的的衍生物为叔丁氧基-氨基甲酸酯。在大约或高于室温下，在碱如 DMAP/三乙胺或二异丙基乙胺存在下使合适的吲哚与二碳酸二叔丁酯反应可以制得这一化合物。脒官能团的氮可以使用与上面吲哚氮所述基本相同的条件加以保护。这些 BOC 衍生物的裂解可以通过在二氯甲烷中用 TFA 处理或者在乙酸乙酯中用 HCl 处理完成。

本领域技术人员不难理解某些式 I 化合物能够显示异构现象，例如几何异构现象（如 E 或 Z 异构）和旋光异构（如 R 或 S 构型）。几何异构体包括顺式和反式具有链烯基基团的本发明化合物。式 I 的单一几何异构体和立体异构体以及它们的混合物均在本发明范围内。

通过使用或改进已知方法（例如色谱技术和重结晶技术）能够从它们的混合物中分离出这些异构体，或者通过例如使用本文所述的方法或其改进方法从适当的中间体异构体分别制备它们。

本发明化合物以游离碱或酸的形式或其可药用盐的形式使用。所有这些形式均在本发明范围之内。

当本发明化合物被碱性基团取代时，可以形成酸加成盐并且这种酸加成盐是更简单方便的使用形式；实际上，使用盐形式本质上相当于使用游离碱形式。能够用于制备酸加成盐的酸优选包括这些，即当它们与游离碱结合时能生成可药用盐，也就是说这些盐的阴离子在盐的药物剂量下对患者是无毒的，因而阴离子的副作用不会损害游离碱固有的对 Xa 因子的有益抑制效果。虽然优选所述碱性化合物的可药用盐，但所有酸加成盐均可用作有机碱的形式的来源，即使是仅需要具体盐本身作为中间产物，例如当仅仅是为了纯化与鉴定目的而形成盐时或者当通过离子交换过程制备可药用盐时而用作中间体时也都如此。本发明范围内的可药用盐为衍生自下列酸的盐：无机酸如盐酸、硫酸、磷酸和氨基磺酸；以及有机酸如乙酸、柠檬酸、乳酸、酒石酸、丙二酸、甲磺酸、乙磺酸、苯磺酸、对-甲苯磺酸、环己基氨基磺酸、奎尼酸等。相应的酸加成盐分别包括下列：氢卤酸盐如盐酸盐和氢溴酸盐，硫酸盐，磷酸盐，硝酸盐，氨基磺酸盐，乙酸盐，柠檬酸盐，乳酸盐，酒石酸盐，丙二酸盐，草酸盐，水杨酸盐，丙酸盐，琥珀酸

盐，富马酸盐，马来酸盐，亚甲基-双-β-羟基-萘甲酸盐，龙胆酸盐，甲磺酸盐，羟乙基磺酸盐，二-对甲苯甲酰基酒石酸盐，甲磺酸盐，乙磺酸盐，苯磺酸盐，对-甲苯磺酸盐，环己基氨基磺酸盐和奎尼酸盐。

根据本发明的另一特征，本发明化合物的酸加成盐系使用或采用已知方法由游离碱与合适的酸反应制得。例如，本发明化合物的酸加成盐可如下制备：将游离碱溶于含有适当酸的水或水－醇溶液或其它适宜溶剂中，通过蒸发所得溶液分离所要盐；或者使游离碱与酸在有机溶剂中反应，在该情形下可以直接分离盐或者通过浓缩溶液能够得到盐。

本发明化合物的酸加成盐可以使用或采用已知方法由盐再生。例如，通过用碱如碳酸氢钠水溶液或氨水溶液处理能够由其酸加成盐再生形成本发明母体化合物。

当本发明化合物被酸性基团取代时，可以形成碱加成盐并且这种碱加成盐是更简单方便的使用形式；而且，在实践中使用盐形式本质上相当于使用游离酸形式。能够用于制备碱加成盐的碱优选包括这些，即当它们与游离酸结合时能生成可药用盐，也就是说这些盐的阳离子在盐的药物剂量下对动物机体是无毒的，从而阳离子的副作用不会损害游离酸固有的对 Xa 因子的有益抑制效果。在本发明范围内，包括例如碱金属和碱土金属盐在内的可药用盐为衍生自下列碱的盐：氢化钠，氢氧化钠，氢氧化钾，氢氧化钙，氢氧化铝，氢氧化锂，氢氧化镁，氢氧化锌，氨，乙二胺，N-甲基-葡糖胺，赖氨酸，精氨酸，乌氨酸，胆碱，N,N′-二苄基乙二胺，氯普鲁卡因，二乙醇胺，普鲁卡因，N-苄基苯乙胺，二乙胺，哌嗪，三(羟甲基)-氨基甲烷，氢氧化四甲铵等。

通过在水性或有机溶剂中使选定金属的氢化物、氢氧化物、碳酸盐或类似的反应性化合物与游离酸形式的本发明化合物反应，能够获得本发明化合物的金属盐。所用水性溶剂可以是水或者可以是水与有机溶剂的混合物，其中的有机溶剂优选醇如甲醇或乙醇，酮如丙酮，脂族醚如四氢呋喃，或酯如乙酸乙酯。这类反应通常在室温下进行，但如果需要它们也可以在加热下进行。

本发明化合物的胺盐可以通过在水性或有机溶剂中使胺与游离酸形式的本发明化合物接触制得。适宜的水性溶剂包括水以及水与醇如甲醇或乙醇、醚如四氢呋喃、腈如乙腈、或酮如丙酮的混合物。氨基酸盐可类似地制备。

本发明化合物可以使用或采用已知方法由盐再生。例如，通过用酸如盐酸处理，能够由其碱加成盐再生形成本发明母体化合物。

可药用盐还包括四低级烷基铵盐。这种季盐通过彻底烷基化本发明化合物中的碱性氮原子（包括非芳香性和芳香性碱性氮原子在内）制备，亦即用烷基化剂如甲基卤（特别是甲基碘）或硫酸二甲酯烷基化带有非键合电子对的氮部分。季铵化作用导致氮部分变为正电性，从而带有与其结合的抗衡阳离子。

本发明的一些化合物不能形成稳定盐对本领域技术人员是不言而喻的。但是，酸加成盐多半由带有含氮杂芳基的本发明化合物和/或其中含有氨基基团作为取代基的化合物形成。优选的本发明化合物的酸加成盐为其中不含酸不稳定基团的盐。

除本身用作活性化合物外，本发明化合物的盐还用于纯化化合物之目的，例如按照本领域技术人员熟知的技术，利用盐与母体化合物、副产物和/或起始原料之间溶解度的差异进行纯化。

起始原料和中间体的制备使用或采用已知方法（例如参考实施例中所述的方法或它们明显的化学等同方法）或本发明方法完成。

本发明通过下列举例上面本发明化合物制备的实施例进一步说明，但并不局限于此。

试验部分

除另有说明外，所有起始原料均由供货商提供，并且未进一步纯化而直接使用。反应通常使用购自 Aldrich Chemical Company 的无水溶剂在氮气或氩气惰性气氛中进行。快速柱色谱在 Merck 硅胶(230-400 目)上进行，以指定的溶剂混合物洗脱。反相 HPLC 采用 Dynamax C-18 (60A)柱进行，以水/乙腈梯度液（含固定的 0.1% v/v

三氟乙酸添加物）洗脱，UV 检测(λ=220，254，294nM)。^{1}H NMR 光谱在 300MHz 频率下记录，使用指定的氘代溶剂。化学位移相对于四甲基硅烷的共振频率δ=0.00 以 ppm 表示。NMR 光谱的描述中使用下列常用术语：s=单峰，d=双重峰，t=三重峰，q=四重峰，m=多重峰，b=宽峰。偶合常数以符号 J 表示，并且以 Hz 为单位测量。

实施例 1a

N-(2-[3-脒基-5-吲哚基]乙基)-4-吡啶-3-基苯甲酰胺

向 N-(2-[3-氰基-5-吲哚基]乙基)-4-吡啶-3-基苯甲酰胺(参考实施例 1a)在甲醇(10mL)的冷浆液(0℃)中通 HCl 气流 7 分钟，然后密封反应物，室温搅拌过夜。反应物经氮气流净化后加以浓缩，随后加入 15mL 7N NH_3 甲醇溶液。搅拌过夜后，再用氮气净化反应物并浓缩。层析(3:1 CH_2Cl_2:7N NH_3/MeOH)残留物，得部分纯化产物。进一步用反相 HPLC 纯化，得 0.298g 白色固体标题化合物，m.p. 55-58℃.

^{1}H NMR (CD_3OD): δ 3.09 (2H, t, J = 7 Hz), 3.71 (2H, t, J = 7 Hz), 7.26 (1H, d, J = 8 Hz), 7.49 (1H, d, J = 8 Hz), 7.80 (1H, s), 7.87 (2H, d, J = 8 Hz), 7.97 (2H, d, J = 8 Hz), 8.00 (1H, m), 8.09 (1H, s), 8.69 (1H, d, J = 8 Hz), 8.80 (1H, br, m), 9.14 (1H, br, s).

MS （离子喷雾） m/z 384 $(M+H)^+$.

元素分析 $C_{23}H_{21}N_5O\bullet(C_2HF_3O_2)_2\bullet(H_2O)_3$:

计算值： C，48.7；H，4.4；N，10.5.

实测值： C，48.5；H，3.9；N，10.3.

下列化合物采用和实施例 1a 所述基本相同的方法制备，只是其中使用指定的腈：

实施例 1b

N-(2-[3-脒基-5-吲哚基]乙基)-4-(嘧啶-5-基)-苯甲酰胺). 使用参考实施例 1b 的产物。

m.p. 97-100°C; ^{1}H NMR (CD_3OD): δ 3.09 (2H, t, J = 7 Hz), 3.71 (2H, t, J = 7 Hz), 7.26 (1H, d, J = 8 Hz), 7.49 (1H, d, J = 8 Hz), 7.79 (1H, s), 7.82 (2H, d, J = 8 Hz), 7.94 (2H, d, J = 8 Hz), 8.08 (1H, s), 9.23 (3H, br).

MS （离子喷雾） m/z 385 $(M+H)^+$.

实施例 1c

5-(吡啶-2-基)-噻吩-2-羧酸 2-(3-脒基-5-吲哚基)乙基酰胺. 使用参考实施例 1c 的产物。

m.p. 198-200°C; ^{1}H NMR (CD_3OD): δ 3.07 (2H, t J = 7 Hz), 3.66 (2H, t, J = 7 Hz), 7.25 (1H, d, J = 8 Hz), 7.33 (1H, m), 7.48 (1H, d, J = 8 Hz), 7.63 (1H, m), 7.66 (1H, m), 7.78 (1H, s), 7.83 (1H, m), 7.87 (1H, m), 8.07 (1H, s), 8.52 (1H, d, J = 5 Hz).

MS （离子喷雾） m/z 390 $(M+H)^+$.

元素分析 $C_{21}H_{19}N_5OS\bullet(C_2HF_3O)_2\bullet(H_2O)_{0.5}$:

计算值： C, 47.9; H, 3.5; N, 11.2.

实测值： C, 48.1; H, 3.4; N, 11.0.

实施例 1d

N-(2-[3-脒基吲哚-5-基]乙基)-6-吗啉-4-基烟酰胺. 使用参考实施例 1d 的产物。

m.p. 130-132 °C; ^{1}H NMR (D_2O): δ 2.88 (2H, t, J = 6 Hz), 3.50 (2H, t, J = 6 Hz), 3.56 (2H, t , J = 4 Hz), 3.73 (2H, t, J = 4 Hz), 7.07-7.12 (2H, m), 7.37 (1H, d, J = 8 Hz), 7.55 (1H, s), 7.88-7.96 (2H, m), 8.00 (1H, s).

MS （离子喷雾） m/z 393 $(M+H)^+$.

元素分析 $C_{21}H_{24}N_6O_2\bullet(C_2HF_3O)_2\bullet(H_2O)_2$:

计算值： C, 45.1; H, 4.7; N, 12.6.

实测值： C, 44.9; H, 4.2; N, 12.4.

实施例 1e

4-(5-2[-{3-脒基吲哚-5-基}乙基氨基甲酰基]吡啶-2-基)哌嗪-1-羧

酸乙酯. 使用参考实施例 24b 的产物。

m.p. 85-87°C. ^{1}H NMR (CD_3OD): δ 1.28 (3H, t, J = 7 Hz), 3.05 (2H, t, J = 7 Hz), 3.55-3.73 (10H, m), 4.16 (2H, q, J = 7 Hz), 6.97 (1H, d, J = 9 Hz), 7.23 (1H, d, J = 8 Hz), 7.47 (1H, d, J = 8 Hz), 7.76 (1H, s), 8.06 (1H, d, J = 9 Hz), 8.80 (1H, s), 8.50 (1H, d, J = 2 Hz).

MS (离子喷雾) m/z 464 $(M+H)^+$.

元素分析 $C_{24}H_{29}N_7O_3 \bullet (C_2HF_3O)_2 \bullet (H_2O)_{4.5}$:

计算值: C, 43.5; H, 5.2; N, 12.7.

实测值: C, 43.5; H, 4.4; N, 12.6.

实施例 1f

N-(2-[3-脒基吲哚-5-基]乙基)-6-咪唑-1-基烟酰胺. 使用参考实施例 1f 的产物。

m.p. 94-97°C. ^{1}H NMR (CD_3OD): δ 3.09 (2H, t, J = 7 Hz), 3.72 (2H, m), 7.26 (1H, d, J = 9 Hz), 7.49 (1H, d, J = 9 Hz), 7.71 (1H, s, br), 7.79 (1H, s), 7.99 (1H, d, J = 9 Hz), 8.09 (1H, s), 8.37 (1H, s, br), 8.43 (1H, d, J = 9 Hz), 8.95 (1H, s), 9.66 (1H, s, br). MS (FAB) m/z 374 $(M+H)^+$.

元素分析 $C_{20}H_{19}N_7O \bullet (C_2HF_3O)_2 \bullet (H_2O)_2$:

计算值: C, 45.2; H, 3.9; N, 15.4.

实测值: C, 45.2; H, 3.5; N, 15.3.

实施例 1g

N-(2-[3-脒基吲哚-5-基]乙基)-4-咪唑-1-基苯甲酰胺

使用参考实施例 1g 的产物。

m.p. 191-194°C. ^{1}H NMR (CD_3OD): δ 3.09 (2H, m), 3.71 (2H, m), 7.26 (1H, d, J = 8 Hz), 7.48 (1H, d, J = 8Hz), 7.73 (1H, s, br), 7.77-7.86 (3H, m), 8.01-8.16 (4H, m), 9.38 (1H, s, br).

MS (离子喷雾) m/z 373 $(M+H)^+$.

元素分析 $C_{21}H_{20}N_6O \bullet (C_2HF_3O)_2 \bullet (H_2O)_5 \bullet (CH_3CN)_{0.5}$:

计算值: C, 43.9; H, 4.7; N, 12.8.

实测值: C, 43.6; H, 4.0; N, 13.1.

实施例 1h

N-(2-[3-脒基吲哚-5-基]乙基)-4-(3H-咪唑-4-基)苯甲酰胺

使用参考实施例 1h 的产物。

m.p. 52-54°C. ^{1}H NMR (D_2O): δ 2.89 (2H, m), 3.52 (2H, m), 7.13 (1H, d, J = 8 Hz), 7.39 (1H, d, J = 8 Hz), 7.49-7.57 (5H, m), 7.65 (1H, s), 7.90 (1H, s), 8.62 (1H, s).

MS （离子喷雾） m/z 373 $(M+H)^+$.

实施例 1i

N-(2-[3-脒基吲哚-5-基]乙基)-4-(1,2,4)噻二唑-5-基苯甲酰胺.

使用参考实施例 1i 的产物。

m.p. 222-224°C. ^{1}H NMR (DMSO-d_6): δ 2.99 (2H, t, J = 7 Hz), 3.60 (2H, m), 7.20 (1H, d, J = 8 Hz), 7.50 (1H, d, J = 8 Hz), 7.74 (1H, s), 8.01 (2H, d, J = 8 Hz), 8.16 (2H, d, J = 8Hz), 8.20 (1H, d, J = 3 Hz), 9.03 (1H, s).

MS （离子喷雾） m/z 391 $(M+H)^+$.

元素分析 $C_{20}H_{18}N_6OS \bullet C_2HF_3O \bullet (H_2O)_{1.5}$:

计算值： C, 49.7; H, 4.2; N, 15.8.

实测值： C, 49.9; H, 4.0; N, 15.7.

实施例 1j

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(1-氨基甲酰基-1-甲基-乙基-苯甲酰胺. 使用参考实施例 1j 的产物。

^{1}H NMR (CD_3OD) d 1.56 (s, 6H), 3.06 (t, J = 7Hz, 2H), 3.67 (t, J = 7Hz, 2H), 7.22 (d, J = 8Hz, 1H), 7.48 (m, 3H), 7.76 (m, 3H), 8.07 (s, 1H), 8.28 (bs, 1H), 8.6 (bs, 1H).

MS （离子喷雾） m/z 392 (M+H).

燃烧分析 $C_{22}H_{25}N_5O_2 \bullet (C_2HF_3O)_2 \bullet (H_2O)$:

计算值： C, 52.8; H, 5.4; N, 13.3.

实测值： C, 52.8; H, 5.3; N, 13.2.

实施例 1k

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(1-[N-(2-甲氧基乙基)]-氨基甲酰基-1-甲基-乙基-苯甲酰胺. 使用参考实施例 1k 的产物。

^{1}H NMR (CD_3OD) d 1.54 (s, 6H), 3.05 (t, J = 7Hz, 2H), 3.28 (s, 3H), 3.34 (m, 2H), 3.40 (m, 2H), 3.67 (t, J = 7Hz, 2H), 7.22 (dd, J = 7, 1Hz, 1H), 7.44 (m, 3H), 7.75 (m, 3H), 8.07 (s, 1H).

MS (离子喷雾) m/z 450 (M+H).

燃烧分析 $C_{25}H_{31}N_5O_3$; $(C_2HF_3O_2)_{1.4}$:

计算值: C, 54.9; H, 5.4; N, 11.5.

实测值: C, 54.6; H, 5.5; N, 11.8.

实施例 11

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(叔丁基)-苯甲酰胺. 使用参考实施例 11 的产物。

^{1}H NMR (DMSO) d 1.29 (s, 9H), 2.96 (t, J = 7Hz, 2H), 3.53 (q, J = 7Hz, 2H), 7.18 (d, J = 8Hz, 1H), 7.45 (m, 3H), 7.75 (m, 3H), 8.21 (s, 1H), 8.52 (bt, 1H), 8.70 (bs, 4H), 12.3 (bs, 1H).

MS (离子喷雾) m/z 363 (M+H).

燃烧分析 $C_{22}H_{26}N_4O$; $[C_2HF_3O_2]_{1.3}$:

计算值: C, 57.8; H, 5.4; N, 11.0.

实测值: C, 57.6; H, 5.3; N, 11.0.

实施例 1m

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(哒嗪-4-基)-苯甲酰胺. 使用参考实施例 1m 的产物。

^{1}H NMR (DMSO) d 3.0 (t, J = 7Hz, 2H), 3.60 (q, J = 7Hz, 2H), 7.20 (d, J = 8Hz, 1H), 7.50 (d, J = 8Hz, 1H), 7.74 (s, 1H), 8.04 (m, 5H), 8.20 (d, J = 3Hz, 1H), 8.54 (bs, 2H), 8.70 (bs, 2H), 8.77 (bt, J = 7Hz, 1H), 9.33 (d, J = 5Hz, 1H), 9.71 (s, 1H), 12.28 (bs, 1H).

MS (离子喷雾) m/z 385 (M+H).

燃烧分析 $C_{22}H_{20}N_6O;(C_2HF_3O_2)_2$:

计算值： C，51.0；H，3.6；N，13.7.

实测值： C，50.7；H，4.1；N，13.7.

实施例 1n

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-2-甲基-4-(6-氧代-1,6-二氢-吡啶-3-基)-苯甲酰胺. 使用参考实施例 36a 的产物。

^{1}H NMR (CD_3OD) d 2.30 (s, 3H), 3.07 (t, J = 7Hz, 2H), 3.69 (t, J = 7Hz, 2H), 6.63 (d, J = 9Hz, 1H), 7.34-7.40 (m, 4H), 7.50 (d, J = 8 Hz, 1H), 7.71 (d, J = 2Hz, 1H), 7.80 (s, 1H), 7.93 (dd. J = 9, 2, 1H), 8.08 (s, 1H).

MS （离子喷雾） m/z 414 (M+H).

实施例 1o

3′,4′-二甲氧基联苯-4-羧酸(2-[3-脒基吲哚-5-基]乙基)-酰胺. 使用参考实施例 1o 的产物，但未进行 HPLC 纯化。而代之以将粗产物通过硅胶层析，然后用蒸馏水洗涤以除去无机盐，随后冷冻干燥。m.p. >250℃.

^{1}H NMR (DMSO): δ 2.99 (2H, m), 3.57 (2H, m), 3.80 (3H, s), 3.86 (3H, s), 7.06 (1H, d, J = 9 Hz), 7.20 (1H, d, J = 8 Hz), 7.27-7.29 (2H, m), 7.50 (1H, d, J = 9 Hz), 7.71-7.76 (3H, m), 7.90 (2H, d, J = 8 Hz), 8.23 (1H, d, J = 3 Hz).

MS （离子喷雾） m/z 443 $(M+H)^+$.

元素分析 $C_{26}H_{26}N_4O_3 \bullet HCl \bullet (H_2O)_{1.25}$:

计算值： C，62.3；H，5.9；N，11.2.

实测值： C，62.2；H，5.8；N，10.9.

实施例 1p

N-(2-[3-脒基吲哚-5-基]乙基)-4-(6-甲氧基吡啶-3 基)苯甲酰胺. 使用参考实施例 1p 的产物。

m.p. 164-167°C. ^{1}H NMR (3:1 D_2O:CD_3OD): δ 2.81 (2H, m), 3.43 (2H, m), 3.70 (3H, s), 6.76 (1H, d, J = 8 Hz), 7.06 (1H, d, J = 8 Hz), 7.38 (1H, d, J = 8 Hz), 7.35-7.46 (5H, m), 7.78 (1H, m), 7.81 (1H, s), 8.09 (1H, s). MS (FAB) m/z 414 $(M+H)^+$.

元素分析 $C_{24}H_{23}N_5O_2 \bullet C_2HO_2F_3 \bullet (H_2O)_2$:

计算值: C, 55.4; H, 5.0; N, 12.4.

实测值: C, 55.3; H, 4.5; N, 12.1.

实施例 1q

N-(2-[3-脒基吲哚-5-基]乙基)-4-(1-氧-吡啶-4-基)苯甲酰胺. 使用参考实施例 1q 的产物。

m.p. 99-101°C. ^{1}H NMR (3:1 D_2O:CD_3OD): δ 2.80 (2H, m), 3.44 (2H, m), 7.03 (1H, d, J = 8 Hz), 7.28 (1H, d, J = 8 Hz), 7.34-7.67 (7H, m), 7.82 (1H, s), 8.13 (2H, br, m).

MS (离子喷雾) m/z 400 $(M+H)^+$.

实施例 1r

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(7H-吡咯并[2, 3-d]嘧啶-6-基)-苯甲酰胺. 使用参考实施例 1r 的产物。

^{1}H NMR (DMSO) δ 2.98 (m, 2H), 3.59 (m, 2H), 7.20 (d, J = 9Hz, 1H), 7.33 (s, 1H), 7.50 (d, J = 8Hz, 1H), 7.74 (s, 1H), 7.96 (d, J = 8Hz, 2H), 8.10 (d, J = 8Hz, 2H), 8.20 (d, J = 3Hz, 1H), 8.68 (m, 4H), 8.95 (s, 1H), 9.19 (bs, 1H), 12.30 (bs, 1H), 13.22 (bs, 1H).

MS (离子喷雾) m/z 424 $(M+H)^+$.

燃烧分析 $C_{24}H_{21}N_7O$; $(C_2HF_3O_2)_2$; $(H_2O)_{0.5}$:

计算值: C, 50.9; H, 3.7; N, 14.8.

实测值: C, 50.7; H, 3.7; N, 14.4.

实施例 1s

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(1H-吡咯并[3, 2-c]吡啶-2-基)-苯甲酰胺. 使用参考实施例 1s 的产物。

^{1}H NMR (DMSO) δ 3.02 (bt, 2H), 3.58 (m, 2H), 7.22 (s, 1H), 7.52 (d, J = 8Hz, 1H), 7.60 (s, 1H), 7.77 (s, 1H), 7.98 (d, J = 6Hz, 1H), 8.02 (d, J = 8Hz, 2H), 8.13 (d, J = 8Hz, 2H), 8.24 (d, J = 4Hz, 1H), 8.45 (d, J = 7Hz, 1H), 8.76 (m, 5H), 9.31 (s, 1H), 12.36 (s, 1H), 13.64 (s, 1H).

MS (离子喷雾) m/z 423 $(M+H)^+$.

燃烧分析 $C_{25}H_{22}N_6O$; $(C_2HF_3O_2)_2$; $(H_2O)_{3.5}$:

计算值: C, 48.8; H, 4.4; N, 11.8.

实测值: C, 48.5; H, 4.0; N, 11.8.

实施例 1t

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-呋喃并[3,2-c]吡啶-2-基-苯甲酰胺. 使用参考实施例 1t 的产物。

^{1}H NMR (DMSO) δ 2.98 (bt, 2H), 3.59 (m, 2H), 7.20 (d, J = 8Hz, 1H), 7.50 (d, J = 8Hz, 1H), 7.74 (s, 1H), 7.85 (s, 1H), 8.00 (d, J = 8Hz, 2H), 8.05 (d, J = 6Hz, 1H), 8.10 (d, J = 8Hz, 2H), 8.20 (d, J = 3Hz, 1H), 8.59 (bs, 2H), 8.67 (m, 2H), 8.76 (bt, 1H), 9.24 (s, 1H), 12.29 (bs, 1H)

MS (离子喷雾) m/z 424 $(M+H)^+$.

燃烧分析 $C_{25}H_{21}N_5O_2$; $(C_2HF_3O_2)_2$; $(H_2O)_{1.5}$:

计算值: C, 51.3; H, 3.9; N, 10.3.

实测值: C, 51.2; H, 3.7; N, 10.4.

实施例 1u

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-3-氯-4-(6-氧代-1,6-二氢-吡啶-3-基)-苯甲酰胺. 使用参考实施例 36c 的产物。

^{1}H NMR (DMSO) δ 2.98 (bt, 2H), 3.56 (m, 2H), 6.42 (d, J = 9Hz, 1H), 7.20 (d, J = 8Hz, 1H), 7.56 (m, 4H), 7.74 (s, 1H), 7.82 (d, J = 8Hz, 1H), 7.96 (s, 1H), 8.22 (d, J = 3Hz, 1H), 8.54 (bs, 2H), 8.70 (bs, 2H), 8.76 (bt, 1H), 12.28 (bs, 1H).

MS (离子喷雾) m/z 434/436 $(M+H)^+$, CI.

实施例 1v

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(6-氧代-1,6-二氢-吡啶-3-

基)-苯甲酰胺. 使用参考实施例 36b 的产物。

m.p. 152-156°C. ^{1}H NMR (CD_3OD): δ 3.08 (2H, m), 3.69 (2H, m), 6.66 (1H, d, J= 9 Hz), 7.26 (1H, d, J = 8 Hz), 7.48 (1H, d, J = 8 Hz), 7.62 (2H, d, J = 8 Hz), 7.78 (1H, s), 7.79 (1H, s), 7.84 (2H, d, J = 8 Hz), 7.99 (1H, d, J = 9 Hz), 8.08 (1H, s).

MS (FAB) m/z $C_{23}H_{22}N_5O_2$ $(M+H)^+$的计算值 400.1773, 实测值 400.1778

实施例 1w

4-(3-氨基-1,1-二甲基-丙基)-N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-苯甲酰胺. 使用参考实施例 1w 的产物。

^{1}H NMR (DMSO) δ 1.31 (s, 1H), 1.93 (m, 2H), 2.50 (m, 2H), 2.97 (m, 2H), 3.57 (m, 2H), 7.18 (d, J = 8 Hz, 1H), 7.44 (d, J = 8Hz, 2H), 7.50 (d, J = 9Hz, 1H), 7.72 (m, 3H), 7.80 (d, J = 8Hz, 2H), 8.22 (d, J = 3Hz, 1H), 8.59 (bt, 1H), 8.72 (s, 1H), 8.77 (s, 2H), 12.35 (s, 1H).

MS (离子喷雾) m/z 392 $(M+H)^+$.

燃烧分析 $C_{23}H_{29}N_5O$; $(C_2HF_3O_2)_{2.5}$:

计算值: C, 49.7; H, 4.7; N, 10.4.

实测值: C, 50.0; H, 4.8; N, 10.7.

实施例 1x

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-2-(4-氯-苯基)-乙酰胺. 使用参考实施例 1x 的产物。

^{1}H NMR (CD_3OD) δ 2.94 (t, J = 7Hz, 2H), 3.39 (s, 2H), 3.55 (q, J = 7Hz, 2H), 7.04 (d, J = 8Hz, 2H), 7.14 (m, 3H), 7.44 (d, J = 8Hz, 1H), 7.67 (s, 1H), 8.09 (s, 1H).

MS (离子喷雾) m/z 355/357 (M+H, Cl 图案).

燃烧分析 $C_{19}H_{19}N_4OCl$; $(C_2HF_3O_2)_{1.3}$:

计算值: C, 51.6; H, 4.1; N, 11.1.

实测值: C, 51.6; H, 4.1; N, 11.2.

实施例 1y

5-氯-噻吩-2-羧酸[2-(3-脒基-1H-吲哚-5-基)-乙基]-酰胺. 使用参考实施例 1y 的产物。

^{1}H NMR (CD_3OD) δ 3.0 (t, J = 7Hz, 2H), 3.61 (q, J = 7Hz, 2H), 6.98 (d, J = 4Hz, 1H), 7.21 (d, J = 8Hz, 1H), 7.46 (m, 2H), 7.75 (s, 1H), 8.07 (s, 1H).

MS (离子喷雾) m/z 347/349 (M+H, Cl 图案).

燃烧分析 $C_{16}H_{15}N_4OSCl$; $(C_2HF_3O_2)_{1.5}$:

计算值: C, 44.1; H, 3.2; N, 10.8.

实测值: C, 44.1; H, 3.2; N, 10.9.

实施例 1z

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-6-(2-羟基乙基氨基)-烟酰胺. 使用参考实施例 1z 的产物。

m.p. 102-105°C. ^{1}H NMR (D_2O): δ 2.88 (2H, t, J = 6.0 Hz), 3.39 (2H, t, J = 4 Hz), 3.49 (2H, t, J = 6.0 Hz), 3.64 (2H, t, J = 4 Hz), 6.88 (1H, d, J = 9 Hz), 7.09 (1H, d, J = 8 Hz), 7.37 (1H, d, J = 8 Hz), 7.54 (1H, s), 7.79 (1H, d, J = 9 Hz), 7.91 (1H, s), 7.92 (1H, s).

MS (离子喷雾) m/z 367 $(M+H)^+$.

实施例 1aa

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-6-(1,2,4)-三唑-1-基烟酰胺. 使用参考实施例 1aa 的产物。

m.p. 196-199°C. ^{1}H NMR (DMSO-d_6): δ 2.99 (2H, m), 3.59 (2H, m), 7.21 (1H, d, J = 8 Hz), 7.51 (1H, d, J = 8 Hz), 7.74 (1H, s), 7.98 (1H, d, J = 8 Hz), 8.21 (1H, d, J = 3 Hz), 8.37 (1H, s), 8.45 (1H, dd, J = 8, 2 Hz), 8.51 (1H, s, br), 8.71 (2H, s, br), 8.92 (2H, m, br), 9.47 (1H, s).

MS (离子喷雾) m/z 375 $(M+H)^+$.

元素分析 $C_{19}H_{18}N_8O$; $(C_2HO_2F_3)_2$; $(H_2O)_{0.5}$:

计算值: C, 45.2; H, 3.5; N, 18.3.

实测值: C, 45.0; H, 3.5; N, 18.7.

实施例 1ab

N-(2-[3-脒基吲哚-5-基]-乙基)-6-吡咯-1-基烟酰胺. 使用参考实施例 1ab 的产物。

m.p. 213-214°C. ^{1}H NMR (CD_3OD): δ 3.08 (2H, d, J = 7 Hz), 3.70 (2H, d, J = 7Hz), 6.33 (2H, s), 7.26 (1H, d, J = 7Hz), 7.49 (1H, d, J = 7 Hz), 7.58-7.62 (3H, m), 7.77 (1H, s), 8.07 (1H, s), 8.19 (1H, d, J = 8 Hz), 8:75 (1H, s).

MS (离子喷雾) m/z 373 $(M+H)^+$.

元素分析 $C_{21}H_{20}N_5O \cdot C_2HO_2F_3 \cdot (H_2O)_{1.25}$:

计算值: C, 54.3; H, 4.6; N, 16.5.

实测值: C, 54.1; H, 4.3; N, 16.3.

实施例 1ac

N-(2-[3-脒基吲哚-5-基]-乙基)-6-吡唑-1-基烟酰胺. 使用参考实施例 1ac 的产物。

m.p. 235-236°C. ^{1}H NMR (CD_3OD): δ 3.08 (2H, m), 3.69 (2H, m), 6.56 (1H, s), 7.26 (1H, d, J = 8 Hz), 7.49 (1H, d, J = 8 Hz), 7.77 (1H, s), 7.80 (1H, s), 7.98 (1H, d, J = 8 Hz), 8.07 (1H, s), 8.24 (1H, d, J = 8 Hz), 8.64 (1H, s), 8.70-8.79 (2H, m).

MS (离子喷雾) m/z 374 $(M+H)^+$.

元素分析 $C_{20}H_{19}N_7O \cdot C_2HO_2F_3 \cdot (H_2O)_2$:

计算值: C, 50.5; H, 4.6; N, 18.7.

实测值: C, 50.5; H, 4.0; N, 18.5.

实施例 1ad

N-(2-[3-脒基-1-甲基吲哚-5-基]-乙基)-4-(6-甲氧基吡啶-3-基)苯甲酰胺. 使用参考实施例 55 的产物。

m.p. 237-238°C. ^{1}H NMR (CD_3OD): δ 3.09 (2H, m), 3.71 (2H, m), 3.92 (3H, s), 3.96 (3H, s), 6.90 (1H, d, J = 9 Hz), 7.32 (1H, d, J = 9 Hz), 7.52 (1H, d, J = 9 Hz), 7.68 (2H, d, J = 8 Hz), 7.79 (1H, s), 7.85 (2H, d, J = 8 Hz), 8.00 (1H, d, J = 9 Hz), 8.02 (1H, s), 8.43 (1H, s), 8.62 (1H, m, br).

MS (离子喷雾) m/z 428 $(M+H)^+$.

元素分析 $C_{25}H_{25}N_5O_2 \cdot C_2HO_2F_3 \cdot (H_2O)_{1.25}$:

计算值： C, 57.5; H, 5.1%; N, 12.4.
实测值： C, 57.5; H, 4.8; N, 12.3.

实施例 1ae
N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-3-氯-苯甲酰胺. 使用参考实施例 1ae 的产物。

^{1}H NMR (DMSO) δ 2.96 (t, J = 7Hz, 2H), 3.59 (q, J = 7Hz, 2H), 7.14 (d, J = 8 Hz, 1H), 7.3-7.45 (m, 3H), 7.59 (d, J = 7Hz, 1H), 7.65 (m, 2H), 7.98 (s, 1H), 8.57 (bt, 1H).

MS (离子喷雾) m/z 341/343 (M+H, Cl 图案).
燃烧分析 $C_{18}H_{17}N_4OCl$; $(C_2HF_3O_2)_{1.2}$:
计算值： C, 51.3; H, 3.8; N, 11.7.
实测值： C, 51.4; H, 3.9; N, 11.7.

实施例 1af
N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-2-(3-氯-苯基)-乙酰胺. 使用参考实施例 1af 的产物。

^{1}H NMR (DMSO) δ 2.82 (t, J = 7Hz, 2H), 3.35 (q, J = 7Hz, 2H), 3.40 (s, 2H), 7.11 (m, 2H), 7.25 (m, 2H), 7.45 (d, J = 8Hz, 1H), 7.67 (s, 1H), 8.22 (m, 2H), 8.62 (bs, 2H), 8.69 (bs, 2H).

MS (离子喷雾) m/z 355/357 (M+H, Cl 图案).

实施例 1ag
4-(2-氨基甲基-吡啶-4-基)-N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-苯甲酰胺. 使用参考实施例 1ag 的产物。

^{1}H NMR (DMSO) δ 3.0 (t, J = 7.5Hz, 2H), 3.61 (q, J = 7 Hz, 2H), 4.29 (q, J = 6 Hz, 2H), 7.20 (d, J = 8Hz, 1H), 7.50 (d, J = 8 Hz, 1H), 7.82 (d, J = 5Hz, 1H), 7.93 (m, 3H), 8.0 (m, 2H), 8.22 (d, J = 3Hz, 1H), 8.40 (bs, 3H). 8 7 (m, 6H), 12.34 (bs, 1H).

MS (离子喷雾) m/z 527 (M+H$^+$TFA), 413 (M+H).

燃烧分析 $C_{24}H_{24}N_6O;(C_2HF_3O_2)_3(NH_4Cl)_{0.3}$ ：

计算值： C, 46.8; H, 3.7; N, 11.4.

实测值： C, 46.6; H, 3.9; N, 11.5.

实施例 1ah

4-{4-[2-(3-脒基-1H-吲哚-5-基)-乙基氨基甲酰基]-苯基-吡啶-2-羧酰胺. 使用参考实施例 1ah 的产物。

^{1}H NMR (DMSO) δ 3.0 (t, J = 7Hz, 2H), 3.61 (q, J = 7Hz, 2H), 7.21 (d, J = 8Hz, 1H), 7.50 (d, J = 8Hz, 1H), 7.75 (m, 2H), 8.0 (m, 4H), 8.23 (m, 2H), 8.35 (bs, 1H), 8.55 (bs, 2H), 8.75 (m, 5H).

MS （离子喷雾） m/z 427 (M+H).

实施例 1ai

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(2-(N,N-二甲基氨基甲基)-吡啶-4-基)-苯甲酰胺. 使用参考实施例 1ai 的产物。

^{1}H NMR (CD_3OD) δ 3.00 (s, 6H), 3.10 (t, J = 7Hz, 2H), 3.70 (t, J = 7Hz, 2H), 4.56 (s, 2H), 7.25 (dd, J = 8, 2Hz, 1H), 7.49 (d, J = 8Hz, 1H), 7.80 (m, 2H), 7.83 (s, 1H), 7.88 (m, 2H), 7.93 (m, 2H), 8.09 (s, 1H), 8.75 (d, J = 5Hz, 1H).

MS （离子喷雾） m/z 441 (M+H).

燃烧分析 $C_{26}H_{28}N_6O;(C_2HF_3O_2)_3$ ：

计算值： C, 49.1; H, 4.0; N, 10.7.

实测值： C, 49.4; H, 4.3; N, 10.9.

实施例 1aj

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(6-氧代-1,6-二氢-哒嗪-3-基)-苯甲酰胺. 使用参考实施例 36d 的产物。

^{1}H NMR (DMSO) δ 2.98 (bt, 2H), 3.58 (m, 2H), 7.02 (d, J = 9Hz, 1H), 7.20 (d, J = 9Hz, 1H), 7.50 (d, J = 8Hz, 1H), 7.74 (s, 1H), 7.95 (m, 4H), 8.10 (d, J = 10Hz, 1H), 8.21 (s, 1H), 8.60 (bs, 1H), 8.71 (bs, 3H), 12.30 (s, 1H), 13.31 (s, 1H).

MS （离子喷雾） m/z 401 $(M+H)^+$.

燃烧分析 $C_{22}H_{20}N_6O_2$; $(C_2HF_3O_2)_2$; $(NH_4Cl)_{1.5}$:

计算值： C, 44.1; H, 4.0; N, 14.8.

实测值： C, 44.5; H, 4.1; N, 14.4.

实施例 1ak

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(6-甲氧基-哒嗪-3-基)-苯甲酰胺. 使用参考实施例 1ak 的产物。

^{1}H NMR (DMSO) δ 3.00 (bt, 2H), 3.58 (m, 2H), 4.10 (s, 3H), 7.20 (d, J = 9Hz, 1H), 7.36 (d, J = 9Hz, 1H), 7.50 (d, J = 8Hz, 1H), 7.76 (s, 1H), 7.98 (d, J = 8Hz, 2H), 8.17 (d, J = 8Hz, 2H), 8.23 (d, J = 5Hz, 1H), 8.63 (bs, 2H), 8.73 (bs, 3H), 12.32 (bs, 1H).

MS （离子喷雾） m/z 415 $(M+H)^+$.

燃烧分析 $C_{23}H_{22}N_6O_2$; $(C_2HF_3O_2)_{2.5}$; $(NH_4Cl)_{0.5}$:

计算值： C, 46.3; H, 3.7; N, 12.5.

实测值： C, 46.2; H, 3.8; N, 12.6.

实施例 1al

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[1-(2-二甲氨基-乙基)-6-氧代-1,6-二氢-哒嗪-3-基]-苯甲酰胺. 使用参考实施例 1al 的产物。

^{1}H NMR (DMSO) δ 2.88 (bs, 6H), 2.98 (bt, 2H), 3.58 (m, 4H), 4.52 (bt, 2H), 7.14 (d, J = 10Hz, 1H), 7.18 (d, J = 9Hz, 1H), 7.49 (d, J = 8Hz, 1H), 7.74 (s, 1H), 7.94 (d, J = 9Hz, 2H), 8.02 (d, J = 9Hz, 2H), 8.16 (d, J = 10Hz, 1H), 8.22 (d, J = 3Hz, 1H), 8.74 (m, 3H), 9.74 (bs, 1H), 12.34 (d, J = 3Hz, 1H).

MS （离子喷雾） m/z 472 $(M+H)^+$.

燃烧分析 $C_{26}H_{29}N_7O_2$; $(C_2HF_3O_2)_3$; $(H_2O)_2$:

计算值： C, 45.0; H, 4.0; N, 11.6.

实测值： C, 45.1; H, 3.8; N, 11.3.

实施例 1am

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[1-(3-二甲氨基-丙基)-6-

氧代-1,6-二氢-哒嗪-3-基]-苯甲酰胺. 使用参考实施例 1am 的产物。

^{1}H NMR (DMSO) δ 2.16 (m, 2H), 2.77 (s, 3H), 2.78 (s, 3H), 2.98 (bt, 2H), 3.15 (m, 2H), 3.56 (m, 2H), 4.22 (bt, 2H), 7.10 (d, J = 10Hz, 1H), 7.18 (d, J = 8Hz, 1H), 7.49 (d, J = 9Hz, 1H), 7.74 (s, 1H), 7.94 (d, J = 8Hz, 2H), 8.00 (d, J = 8Hz, 2H), 8.14 (d, J = 10Hz, 1H), 8.22 (d, J = 3Hz, 1H), 8.74 (m, 3H), 9.72 (bs, 1H), 12.34 (s, 1H).

MS (离子喷雾) m/z 485 $(M+H)^+$.

燃烧分析 $C_{27}H_{31}N_7O_2$; $(C_2HF_3O_2)_3$; $(NH_4Cl)_{0.1}$; $(H_2O)_{0.5}$:

计算值: C, 47.1; H, 4.2; N, 11.8.

实测值: C, 46.8; H, 4.2; N, 11.8.

实施例 1an

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-(2-二甲氨基-乙基氨基)-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 1an 的产物。

^{1}H NMR (CD_3OD) δ 2.97 (s, 6H), 3.08 (t, J = 7Hz, 2H), 3.44 (t, J = 6Hz, 2H), 3.70 (t, J = 7Hz, 2H), 3.87 (bt, J = 6Hz, 2H), 7.28 (m, 2H), 7.49 (d, J = 8Hz, 1H), 7.80 (s, 1H), 7.90 (d, J = 8Hz, 2H), 8.09 (s, 1H), 8.18 (d, J = 8Hz, 2H), 8.44 (bm, 1H).

MS (离子喷雾) m/z 471 $(M+H)^+$.

燃烧分析 $C_{26}H_{30}N_8O$; $(C_2HF_3O_2)_{3.2}$:

计算值: C, 46.6; H, 4.0; N, 13.4.

实测值: C, 46.6; H, 4.1; N, 13.7.

实施例 1ao

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-甲氧基-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 1ao 的产物，并通过快速色谱纯化（依次用 10% MeOH/CH_2Cl_2、20% MeOH/10% 7N NH_3 甲醇溶液/70%CH_2Cl_2 洗脱），分离得到其盐酸盐。 ^{1}H NMR (CD_3OD) δ 3.09 (t, J = 7Hz, 2H), 3.70 (t, J = 7Hz, 2H), 4.10 (s, 3H), 7.25 (d, J = 8Hz, 1H), 7.48 (d, J = 8Hz, 1H), 7.63 (d, J = 5Hz, 1H), 7.78 (s, 1H), 7.90 (d, J = 8Hz, 2H), 8.09 (s, 1H), 8.23 (d, J = 8Hz, 2H), 8.61 (d, J = 5Hz, 1H).

MS (离子喷雾) m/z (离子喷雾) m/z 415 (M+H).

燃烧分析 $C_{23}H_{22}N_6O_2$; $(HCl)_2$:

计算值: C, 56.7; H, 5.0; N, 17.2.

实测值: C, 57.1; H, 4.9; N, 17.0.

实施例 1ap

N-(2-[3-脒基吲哚-5-基]-乙基)-4-(1-[2-二甲氨基乙基]-6-氧代-1,6-二氢吡啶-3-基)-苯甲酰胺. 使用参考实施例 1ap 的产物。

m.p. 94-97°C. ^{1}H NMR (D_2O): δ 2.61 (2H, m), 2.80 (6H, s), 3.25 (2H, m), 3.32 (2H, m), 4.14 (2H, m), 6.45 (1H, d, J = 9.0 Hz), 6.96 (1H, d, J = 8.2 Hz), 7.22-7.31 (4H, m), 7.40 (2H, d, J = 8.0 Hz), 7.55-7.69 (3H, m), 7.78 (1H, s).

MS (离子喷雾) m/z 471 $(M+H)^+$.

燃烧分析 $C_{27}H_{30}N_6O_2 \cdot 3C_2HO_2F_3$:

计算值: C, 48.8; H, 4.1; N, 10.3.

实测值: C, 48.8; H, 4.1; N, 10.6.

实施例 1aq

N-(2-[3-脒基吲哚-5-基]-乙基)-4-(1-氨基甲酰基甲基-6-氧代-1,6-二氢吡啶-3-基)-苯甲酰胺. 使用参考实施例 1aq 的产物。

m.p. 244-245°C. ^{1}H NMR (CD_3OD): δ 2.97 (2H, t, J = 7 Hz), 3.59 (2H, m), 4.67 (2H, s), 6.56 (1H, d, J = 9 Hz), 7.16 (1H, d, J = 8 Hz), 7.38 (1H, d, J = 8 Hz), 7.54 (2H, d, J = 8 Hz), 7.67 (1H, s), 7.73 (2H, d, J = 8 Hz), 7.85 (1H, d, J = 9 Hz), 7.91 (1H, s), 7.98 (1H, s).

MS (离子喷雾) m/z 457 $(M+H)^+$.

实施例 1ar

4-(3-氨基-[1,2,4]三嗪-6-基)-N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-苯甲酰胺. 使用参考实施例 1ar 的产物。

^{1}H NMR (CD_3OD) d 3.09 (2H, t, J = 7 Hz), 3.72 (2H, t, J = 7 Hz), 7.23 (1H, d, J = 8 Hz), 7.49 (1H, d, J = 8 Hz), 7.79 (1H, s), 7.93 (2H, d, J = 7 Hz), 8.13 (1H, s), 8.28 (2H, d, J = 7 Hz), 9.15 (1H, s);

MS （离子喷雾） m/z 401 $(M+H)^+$.

实施例 1as

4-(3-氨基-[1,2,4]三嗪-5-基)-N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-苯甲酰胺. 使用参考实施例 1as 的产物。

^{1}H NMR (CD_3OD) d 3.08 (2H, t, J = 7 Hz), 3.68 (2H, m), 7.25 (1H, d, J = 9 Hz), 7.49 (1H, d, J = 9 Hz), 7.7-8.3 (7H, m);

MS （离子喷雾） m/z 401 $(M+H)^+$.

实施例 1at

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(3-氧代-2,3-二氢-[1,2,4]三嗪-6-基)-苯甲酰胺. 使用参考实施例 1at 的产物。

^{1}H NMR (DMSO-d_6) d 2.99 (2H, t, J = 5 Hz), 3.05 (2H, m), 6.58 (1H, m), 7.22 (1H, d, J = 8 Hz), 7.52 (1H, d, J = 8 Hz), 7.75 (1H, d, J = 3 Hz), 7.94 (2H, d, J = 8 Hz), 8.02 (1H, d, J = 3 Hz), 8.04 (2H, d, J =7 Hz), 8.22 (1H, d, J = 3 Hz), 8.49 (1H, s), 8.70 (1H, s), 8.81 (1H, t, J = 5 Hz), 11.12 (1H, s), 12.28 (1H, s);

MS （离子喷雾） m/z 420 $[(M+18)+H]^+$.

实施例 1au

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(5-氧代-4,5-二氢-[1,2,4]噁二唑-3-基)-苯甲酰胺. 使用参考实施例 1au 的产物。

^{1}H NMR (CD_3OD) d 3.11 (2H, t, J = 8 Hz), 3.72 (2H, m), 7.27 (1H, d, J = 9 Hz), 7.49 (1H, d, J = 9 Hz), 7.78 (1H, s), 7.90 (4H, q, J = 8 Hz, J = 16 Hz), 8.08 (1H, s), 8.76 (1H, m);

MS （离子喷雾） m/z 391 $[(M+H]^+$.

实施例 1av

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(6-氧代-哌啶-3-基)-苯甲酰胺. 使用参考实施例 64a 的产物。

^{1}H NMR (CD_3OD) δ 2.08 (m, 2H), 2.43 (m, 2H), 3.10 (m, 3H), 3.42 (m, 2H), 3.65 (m, 2H), 7.13 (m, 1H), 7.20 (m, 1H), 7.38 (m, 2H), 7.45 (m, 1H), 7.72 (m, 3H), 8.07 (m, 1H).

MS （离子喷雾） m/z 387 $(M+H)^+$.

实施例 1aw

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-(吗啉-4-基-乙基氨基)-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 1aw 的产物。

^{1}H NMR (DMSO) δ 2.99 (t, J = 7Hz, 2H), 3.40 (m, 2H), 3.53-4.1 (m, 12H), 7.20 (d, J = 8Hz, 1H), 7.34 (d, J = 5Hz, 1H), 7.50 (m, 2H), 7.73 (s, 1H), 7.95 (d, J = 8Hz, 2H), 8.21 (m, 3H), 8.45 (d, J = 5Hz, 1H), 8.52 (bs, 2H), 8.72 (bs, 2H), 8.77 (bt, 1H).

MS （离子喷雾） m/z 513 $(M+H)^+$.

实施例 1ax

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-(3-二甲氨基-丙基氨基)-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 1ax 的产物。

^{1}H NMR (DMSO) δ 1.95 (m, 2H), 2.77 (s, 3H), 2.79 (s, 3H), 3.0 (t, J = 7Hz, 2H), 3.15 (m, 2H), 3.43 (m, 2H), 3.60 (q, J = 7Hz, 2H), 7.21 (d, J = 8Hz, 1H), 7.25 (d, J = 5Hz, 1H), 7.45 (bm, 1H), 7.50 (d, J = 8Hz, 1H), 7.74 (s, 1H), 7.95 (d, J = 8Hz, 2H), 8.20 (d, J = 8Hz, 2H), 8.21 (d, J = 5Hz, 1H), 8.41 (d, J = 5Hz, 1H), 8.70 (bm, 5H).

MS （离子喷雾） m/z 485 $(M+H)^+$.

实施例 1ay

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-([2-二甲氨基-乙基]-甲基-氨基)-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 1ay 的产物。

^{1}H NMR (DMSO) δ 2.9 (bs, 6H), 3.0 (bt, J = 7Hz, 2H), 3.24 (s, 3H), 3.40 (bm, 2H), 3.59 (bq, J = 7Hz, 2H), 4.05 (bm, 2H), 7.20 (d, J = 8Hz, 1H), 7.35 (d, J = 5Hz, 1H), 7.51 (d, J = 8Hz, 1H), 7.77 (s, 1H), 7.98 (d, J = 8Hz, 2H), 8.24 (m, 3H), 8.52 (d, J = 5Hz, 1H), 8.7 (bm, 5H).

MS （离子喷雾） m/z 485 $(M+H)^+$.

实施例 1az

2-[(4-{4-[2-(3-脒基-1H-吲哚-5-基)-乙基氨基甲酰基]-苯基}-嘧啶-2-基)-甲基-氨基]-乙磺酸. 使用参考实施例 92d 的产物。

^{1}H NMR (DMSO) δ 2.95 (bm, 4H), 3.17 (s, 3H), 3.48 (m, 2H), 3.96 (bm, 2H), 7.18 (d, J = 8Hz, 1H), 7.24 (dd, J = 5, 1Hz, 1H), 7.47 (dd, J = 8, 1Hz, 1H), 7.81 (bd, 2H), 7.92 (bs, 1H), 8.17 (bt, J = 1Hz, 1H), 8.31 (bd, J = 8Hz, 2H), 8.51 (bs, 1H), 8.61 (bs, 2H), 9.11 (bs, 1H).

MS (离子喷雾) m/z 522 $(M+H)^+$.

实施例 1aaa

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-{2-[甲基-(2(S),3(R),4(R),5(R),6-五羟基-己基)-氨基]-嘧啶-4-基}-苯甲酰胺. 使用参考实施例 92e 的产物。

^{1}H NMR (DMSO) δ 2.99 (t, J = 7Hz, 2H), 3.24 (bs, 3H), 3.38 (m, 1H), 3.42-3.67 (m, 9H), 4.05 (bm), 7.19 (d, J = 8Hz, 1H), 7.22 (d, J = 5Hz, 1H), 7.49 (d, J = 8Hz, 1H), 7.71 (s, 1H), 7.91 (d, J = 8Hz, 2H), 8.20 (m, 3H), 8.45 (m, 3H), 8.70 (m, 3H).

MS (离子喷雾) m/z 578 $(M+H)^+$.

实施例 1aab

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-{2-[甲基-(2(S),3(R),4(S),5(R),6-五羟基-己基)-氨基]-嘧啶-4-基}-苯甲酰胺. 使用参考实施例 92f 的产物。

^{1}H NMR (DMSO) δ 2.99 (t, J = 7Hz, 2H), 3.26 (bs, 3H), 3.39 (m, 3H), 3.55 (m, 3H), 3.63-4.2 (bm, 8H), 7.20 (m, 2H), 7.50 (d, J = 8Hz, 1H), 7.72 (s, 1H), 7.93 (d, J = 8Hz, 2H), 8.20 (m, 3H), 8.42 (m, 3H), 8.70 (m, 3H).

MS (离子喷雾) m/z 578 $(M+H)^+$.

实施例 1aac

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-(2-羟基-1-羟甲基-乙基氨基)-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 92g 的产物。

^{1}H NMR (DMSO) δ 2.95 (t, J = 7Hz, 2H), 3.55 (m, 4H), 3.6-4.1 (bm, 5H), 6.75 (bs, 1H), 7.20 (m, 2H), 7.48 (d, J = 8Hz, 1H), 7.70 (s, 1H), 7.90 (d, J = 8Hz, 2H), 8.18 (m, 3H), 8.40 (d, J = 5Hz, 1H), (m, 2H), 8.70 (m, 3H).

MS （离子喷雾） m/z 474 $(M+H)^+$.

实施例 1aad

2-[(4-{4-[2-(3-脒基-1H-吲哚-5-基)-乙基氨基甲酰基]-苯基}-嘧啶-2-基)-甲基-氨基]-乙烷磺酸. 使用参考实施例 92h 的产物。标题化合物通过从反应介质中沉淀析出加以纯化。

^{1}H NMR (DMSO) δ 2.95 (m, 4H), 3.18 (s, 3H), 3.50 (bm, 2H), 4.00 (bm, 2H), 7.18 (d, J = 8Hz, 1H), 7.24 (dd, J = 5, 1Hz, 1H), 7.47 (dd, J = 8, 2Hz, 1H), 7.81 (d, J = 8Hz, 1H), 7.92 (bs, 1H), 8.15 (t, J = 1Hz, 1H), 8.30 (d, J = 8Hz, 2H), 8.40 (dd, J = 8, 2Hz, 1H), 8.52 (m, 1H), 8.64 (bs, 2H). 9.11 (bs, 2H).

MS （离子喷雾） m/z 522 $(M+H)^+$.

实施例 1aae

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-(3-咪唑-1-基-丙基氨基)-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 92i 的产物。

^{1}H NMR (DMSO) δ 2.10 (m, 2H), 2.95 (t, J = 7Hz, 2H), 3.36 (bm, 2H), 3.56 (q, J = 7Hz, 2H), 4.30 (t, J = 7Hz, 2H), 7.18 (d, J = 8Hz, 1H), 7.24 (d, J = 5 Hz, 1H), 7.48 (d, J = 8 Hz, 1H), 7.50 (bs, 1H), 7.70 (s, 1H), 7.75 (s, 1H), 7.82 (s, 1H), 7.94 (d, J = 8Hz, 2H), 8.14 (d, J = 8Hz, 2H), 8.21 (d, J = 1Hz, 1H), 8.39 (d, J = 5 Hz, 1H), 8.75 (m, 5H) 9.15 (s, 1H).

MS （离子喷雾） m/z 508 $(M+H)^+$.

实施例 1aaf

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-{2-[(2-二乙基氨基-乙基)-甲基-氨基]-嘧啶-4-基}-苯甲酰胺. 使用参考实施例 92j 的产物。

^{1}H NMR (DMSO) δ 1.60 (t, J = 7Hz, 6H), 2.95 (t, J = 7Hz, 2H), 3.12-3.4 (m, 9H), 3.59 (q, J = 7Hz, 2H), 4.0 (bt, 2H), 7.18 (d, J = 8Hz, 1H), 7.32 (d, J = 5Hz, 1H), 7.49 (d, J = 8Hz, 1H), 7.75 (s, 1H), 7.94 (d, J = 8Hz, 2H), 8.20 (m, 3H), 8.50 (d, J = 5Hz, 1H), 8.70 (bs, 4H), 8.74 (bt, 1H), 9.40 (bs, 1H).

MS （离子喷雾） m/z 513 $(M+H)^+$.

实施例 1aag

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-(2-二异丙基氨基-乙基氨基)-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 92k 的产物。

^{1}H NMR (DMSO) δ 1.29 (d, J = 7Hz, 12H), 2.97 (t, J = 7Hz, 2H), 3.22 (bt, 2H), 3.57 (q, J = 7Hz, 2H), 3.68 (m, 4H), 7.18 (d, J = 8Hz, 1H), 7.39 (d, J = 5Hz, 1H), 7.42 (bm, 1H), 7.48 (d, J = 8Hz, 1H), 7.73 (s, 1H), 7.95 (d, J = 8Hz, 2H), 8.15 (d, J = 8Hz, 2H), 8.20 (d, J = 3Hz, 1H), 8.44 (d, J =5Hz, 1H), 8.71 (bs, 4H), 8.74 (bt, 1H).

MS (离子喷雾) m/z 527 $(M+H)^+$.

实施例 1aah

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-(2-二丁基氨基-乙基氨基)-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 921 的产物。

^{1}H NMR (DMSO) δ 0.85 (t, J = 7Hz, 6H), 1.29 (m, 4H), 1.60 (m, 4H), 2.97 (t, J = 7Hz, 2H), 3.12 (m, 4H), 3.30 (m, 2H), 3.58 (q, J = 7Hz, 2H), 3.73 (m, 2H), 7.17 (d, J = 8Hz, 1H), 7.30 (d, J = 5Hz, 1H), 7.45 (d, J = 8Hz, 2H), 7.48 (d, J = 8Hz, 1H), 7.72 (s, 1H), 7.95 (d, J = 8Hz, 2H), 8.15 (d, J = 8Hz, 2H), 8.20 (d, J = 3Hz, 1H), 8.44 (d, J =5Hz, 1H), 8.65-8.8 (bm, 5H), 8.74 (bs, 1H).

MS (离子喷雾) m/z 555 $(M+H)^+$.

实施例 1aai

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-(3-吗啉-4-基-丙基氨基)-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 92m 的产物。

^{1}H NMR (DMSO) δ 1.95 (m, 2H), 2.9-3.14 (m, 4H), 3.19 (m, 2H), 3.40 (m, 4H), 3.59 (m, 4H), 7.17 (d, J = 8Hz, 1H), 7.21 (d, J = 5Hz, 1H), 7.40 (bt, J = 7Hz, 1H), 7.48 (d, J = 8Hz, 1H), 7.72 (s, 1H), 7.93 (d, J = 8Hz, 2H), 8.14 (m, 3H), 8.44 (d, J =5Hz, 1H), 8.55 (bs, 2H), 8.71 (bm, 3H).

实施例 1aaj

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-(3-二乙基氨基-丙基氨基)-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 92n 的产物。

^{1}H NMR (DMSO) δ 1.15 (t, J = 7Hz, 6H), 2.99 (t, J = 7Hz, 2H), 3.13 (m, 6H), 3.43 (m, 2H), 3.58 (m, 2H), 7.18 (d, J = 8Hz, 1H), 7.21 (d, J = 5Hz, 1H), 7.40 (bt, J = 7Hz, 1H), 7.48 (d, J = 8Hz, 1H), 7.73 (s, 1H), 7.94 (d, J = 8Hz, 2H), 8.16 (m, 3H), 8.40 (d, J =5Hz, 1H), 8.60 (bs, 2H), 8.71 (bm, 3H).

MS (离子喷雾) m/z 513 $(M+H)^+$.

实施例 1aak

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-(3-哌啶-1-基-丙基氨基)-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 92p 的产物。

^{1}H NMR (DMSO) δ 1.50-1.73 (m, 4H), 1.80 (m, 2H), 1.96 (m, 2H), 2.85 (m, 2H), 2.96 (m, 2H), 3.13 (m, 2H), 3.42 (m, 4H), 3.56 (m, 2H), 7.18 (d, J = 8Hz, 1H), 7.22 (d, J = 5Hz, 1H), 7.40 (bt, J = 7Hz, 1H), 7.48 (d, J = 8Hz, 1H), 7.73 (s, 1H), 7.95 (d, J = 8Hz, 2H), 8.16 (m, 3H), 8.38 (d, J =5Hz, 1H), 8.6-8.78 (bm, 5H).

MS (离子喷雾) m/z 525 $(M+H)^+$.

实施例 1aal

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(2-{[2-(乙基-甲基-氨基)-乙基]-甲基-氨基}-嘧啶-4-基)-苯甲酰胺. 使用参考实施例 92q 的产物。

^{1}H NMR (DMSO) δ 1.15 (t, J = 7Hz, 3H), 2.77 (s, 3H), 2.78 (s, 3H), 2.96 (t, J = 7Hz, 2H), 3.10 (m, 2H), 3.57 (q, J = 7Hz, 2H), 3.69 (m, 4H), 7.18 (d, J = 8Hz, 1H), 7.24 (d, J = 5Hz, 1H), 7.49 (d, J = 8Hz, 1H), 7.72 (s, 1H), 7.94 (d, J = 8Hz, 2H), 8.18 (m, 3H), 8.38 (d, J =5Hz, 1H), 8.6-8.75 (bm, 5H), 9.6 (bs, 1H).

实施例 1aam

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-(5-二甲氨基-戊基氨基)-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 92r 的产物。

^{1}H NMR (DMSO) δ 1.35 (m, 2H), 1.58 (m, 4H), 2.71 (s, 3H), 2.72 (s, 3H), 3.0 (m, 4H), 3.37 (m, 2H), 3.45-3.8 (bs, solvent), 7.18 (m, 2H), 7.32 (bm, 1H), 7.48 (d, J = 8Hz, 1H), 7.72 (s, 1H), 7.94 (d, J = 8Hz, 2H), 8.15 (m, 3H), 8.37 (d, J =5Hz, 1H), 8.57 (bs, 2H), 8.70 (bm, 3H), 9.35 (bs, 1H).

MS (离子喷雾) m/z 513 $(M+H)^+$.

实施例 1aan

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-(5-吗啉-4-基-戊基氨基)-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 92s 的产物。

^{1}H NMR (DMSO) δ 1.36 (m, 2H), 1.61 (m, 4H), 2.9-3.1 (m, 8H), 3.35 (m, 4H), 3.5-3.7 (m, 4H), 7.18 (m, 2H), 7.40 (bm, 1H), 7.48 (d, J = 8Hz, 1H), 7.71 (s, 1H), 7.92 (d, J = 8Hz, 2H), 8.15 (m, 3H), 8.38 (d, J =5Hz, 1H), 8.62 (bs, 2H), 8.70 (bm, 3H), 9.85 (bs, 1H).

MS （离子喷雾） m/z 555 $(M+H)^+$.

实施例 1aap

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-(5-哌啶-1-基-戊基氨基)-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 92t 的产物。

^{1}H NMR (DMSO) δ 1.35 (m, 4H), 1.5-1.95 (m, 8H), 2.80 (m, 2H), 2.95 (m, 4H), 3.38 (m, 4H), 3.55 (q, J = 7Hz, 2H), 7.19 (m, 2H), 7.40 (bm, 1H), 7.46 (d, J = 8Hz, 1H), 7.71 (s, 1H), 7.92 (d, J = 8Hz, 2H), 8.19 (m, 3H), 8.39 (d, J =5Hz, 1H), 8.62-8.80 (bm, 5H), 9.20 (bs, 1H).

MS （离子喷雾） m/z 553 $(M+H)^+$.

实施例 1aaq

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-(5-吡咯烷-1-基-戊基氨基)-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 92u 的产物。

^{1}H NMR (DMSO) δ 1.37 (m, 4H), 1.60 (m, 4H), 1.80 (m, 2H), 1.94 (m, 2H), 2.94 (m, 4H), 3.08 (m, 2H), 3.33 (m, 2H), 3.50 (m, 4H), 7.19 (m, 2H), 7.40 (bm, 1H), 7.48 (d, J = 8Hz, 1H), 7.70 (s, 1H), 7.91 (d, J = 8Hz, 2H), 8.15 (m, 3H), 8.36 (d, J =5Hz, 1H), 8.62 (bs, 2H), 8.7 (bm, 3H), 9.60 (bs, 1H).

MS （离子喷雾） m/z 539 $(M+H)^+$.

实施例 1aar

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(2-氧代-六氢-嘧啶-5-基)-苯甲酰胺. 使用参考实施例 1aaa 的产物。

^{1}H NMR (DMSO) δ 2.91 (t, J = 7Hz, 2H), 3.08 (m, 1H), 3.25 (m, 4H), 3.53 (q, J = 7Hz, 2H), 6.33 (bs, 2H), 7.17 (d, J = 8Hz, 1H), 7.38 (d, J = 8Hz, 2H), 7.46 (d, J = 8Hz, 1H), 7.69 (s, 1H), 7.75 (d, J = 8Hz, 2H), 8.17 (d, J = 3Hz, 1H), 8.42 (bm, 2H), 8.52 (bt, J = 7Hz, 1H), 8.67 (bs, 2H).

MS （离子喷雾） m/z 407 $(M+H)^+$.

实施例 1aas

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(1,3-二甲基-2-氧代-六氢-嘧啶-5-基)-苯甲酰胺. 使用参考实施例 1aab 的产物。

^{1}H NMR (CD_3OD) δ 2.95 (s, 6H), 3.06 (t, J = 7Hz, 2H), 3.36-3.55 (m, 5H), 3.66 (m, 2H), 7.23 (d, J = 8Hz, 1H), 7.39 (d, J = 8Hz, 2H), 7.47 (d, J = 8Hz, 1H), 7.77 (m, 3H), 8.07 (d, J = 3Hz, 1H), 8.30 (bm, 2H), 8.52 (bt, J = 7Hz, 1H), 8.68 (bs, 2H).

MS （离子喷雾） m/z 433 $(M+H)^+$.

实施例 1aat

联苯-3,4′-二羧酸 4′-{[2-(3-脒基-1H-吲哚-5-基)-乙基]-酰胺}3-[(2-甲氧基乙基)酰胺]. 使用参考实施例 99a 的产物。

^{1}H NMR (CD_3OD) δ 3.09 (t, J = 7Hz, 2H), 3.40 (s, 3H), 3.60 (bs, 4H), 3.71 (q, J = 7Hz, 2H), 7.28 (d, J = 8Hz, 1H), 7.48 (d, J = 8Hz, 1H), 7.56 (t, J = 8Hz, 1H), 7.77 (m, 3H), 7.87 (m, 4H), 8.07 (s, 1H), 8.13 (s, 1H), 8.65 (bt, 1H).

MS （离子喷雾） m/z 484 $(M+H)^+$.

实施例 1aau

3′-(吗啉-4-羰基)-联苯-4-羧酸[2-(3-脒基-1H-吲哚-5-基)-乙基]-酰胺. 使用参考实施例 99b 的产物。

^{1}H NMR (DMSO) δ 2.98 (t, J = 7Hz, 2H), 3.3-3.8 (bs, 溶剂), 7.20 (d, J = 8Hz, 1H), 7.43 (d, J = 8Hz, 1H), 7.50 (d, J = 8Hz, 1H), 7.56 (t, J = 8Hz, 1H), 7.73 (bs, 2H), 7.80 (m, 3H), 7.91 (d, J = 8Hz, 2H), 8.20 (d, J = 1Hz, 1H), 8.50 (bs, 2H), 8.70 (m, 3H).

MS （离子喷雾） m/z 496 $(M+H)^+$.

实施例 1aav

联苯-3,4′-二羧酸 4′-{[2-(3-脒基-1H-吲哚-5-基)-乙基]酰胺}3-[(2-吗啉-4-基-乙基)-酰胺]. 使用参考实施例 99c 的产物。

^{1}H NMR (CD_3OD) δ 3.08 (t, J = 7Hz, 2H), 3.15-3.3 (bm, 2H), 3.45 (t, J = 7Hz, 2H), 3.70 (m, 2H), 3.6-3.95 (bm, 4H), 3.81 (t, J = 7Hz, 2H), 4.06 (bm, 2H), 7.27 (d, J = 8Hz, 1H), 7.50 (d, J = 8Hz, 1H), 7.61 (t, J = 8Hz, 1H), 7.77 (m, 3H), 7.90 (m, 4H), 8.1 (s, 1H), 8.20 (bs, 1H), 8.7 (bt, 1H).

MS （离子喷雾） m/z 539 $(M+H)^+$.

实施例 1aaw

联苯-2,4′-二羧酸 4′-{[2-(3-脒基-1H-吲哚-5-基)-乙基]-酰胺}3-[(2-二乙基氨基丙基)酰胺]. 使用参考实施例 99d 的产物。MS (离子喷雾) m/z 539 $(M+H)^+$.

实施例 1aax

联苯-2,4′-二羧酸 4′-{[2-(3-脒基-1H-吲哚-5-基)-乙基]-酰胺}2-[(3-吗啉-4-基-丙基)酰胺]. 使用参考实施例 99e 的产物。MS (离子喷雾) m/z 553 $(M+H)^+$.

实施例 1aaaa

联苯-2,4′-二羧酸 4′-{[2-(3-脒基-1H-吲哚-5-基)-乙基]-酰胺}2-[(3-哌啶-1-基丙基)酰胺]. 使用参考实施例 99f 的产物。MS (离子喷雾) m/z 551 $(M+H)^+$.

实施例 1aaab

联苯-2,4′-二羧酸 4′-{[2-(3-脒基-1H-吲哚-5-基)-乙基]-酰胺}2-[(4-二甲氨基-丁基)酰胺]. 使用参考实施例 99g 的产物。MS (离子喷雾) m/z 525 $(M+H)^+$.

实施例 1aaac

联苯-2,4′-二羧酸 4′-{[2-(3-脒基-1H-吲哚-5-基)-乙基]-酰胺}2-[(2,3-二羟基-丙基)-甲基-酰胺]. 使用参考实施例 99h 的产物。MS (离子喷雾) m/z 514 $(M+H)^+$.

实施例 1aaad

联苯-2,4′-二羧酸 4′-{[2-(3-脒基-1H-吲哚-5-基)-乙基] - 酰胺}2-[(2,3-二羟基丙基)酰胺]. 使用参考实施例 99i 的产物。MS (离子喷雾) m/z 500 $(M+H)^+$.

实施例 1aaae

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-(4-甲基哌嗪-1-基)-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 92v 的产物。

m.p. 111-113°C. ^{1}H NMR (DMSO-d_6): δ 2.50 (s, 3H), 2.86 (s, 4H), 2.98 (t, 2H, J=9Hz), 3.30 (t, 2H, J=12Hz), 3.57 (m, 4H), 7.20 (d,1H, J=9Hz), 7.43 (d,1H, J=6Hz), 7.50 (d,1H, J=9Hz), 7.74 (s,1H), 7.97 (d, 2H, J=9Hz), 8.22 (d,1H, J=3Hz), 8.26 (d, 2H, J=9Hz), 8.55 (s, 1H), 8.57 (d,1H, J=6Hz), 8.72 (s, 2H), 8.77 (t,1H, J=6Hz).

MS (离子喷雾) m/z 483 $(M+H)^+$.

元素分析 $C_{27}H_{30}N_8O \cdot 3C_2HF_3O_2 \cdot 1.5H_2O$:

计算值: C, 46.5%; H, 4.3%; N, 13.2%.

实测值: C, 46.3%; H, 4.1%; N, 13.4%.

实施例 1aaaf

4-[(4-{4-[2-(3-脒基-1H-吲哚-5-基)-乙基氨基甲酰基]苯基}-嘧啶-2-基)甲基氨基]-丁酸. 使用参考实施例 92w 的产物。

m.p. 100-104°C. ^{1}H NMR (DMSO-d_6): δ 1.85(t, 2H, J=6Hz), 2.26 (t, 2H, J=6Hz), 3.00 (t, 2H, J=6Hz), 3.18 (s, 3H), 3.56 (m, 2H), 3.71 (m, 2H), 7.22 (t,1H, J=6Hz), 7.50 (d,1H, J=6Hz), 7.74 (s,1H), 8.00 (d, 2H, J=8Hz), 8.24 (s,1H), 8.25 (d, 2H, J=8Hz), 8.45 (d, 2H, J=6Hz), 8.71 (s, 2H).

MS (离子喷雾) m/z 500 $(M+H)^+$.

元素分析 $C_{27}H_{29}N_7O_3 \cdot 2.5C_2HF_3O_2 \cdot 0.5H_2O$:

计算值: C, 48.4%; H, 4.1%; N, 12.4%.

实测值: C, 48.7%; H, 4.1%; N, 12.1%.

实施例 1aaag

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-(2,2,2-三氟乙氧基)-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 92x 的产物。

m.p. 194-195°C. ^{1}H NMR (DMSO-d_6): δ 3.02 (t, 2H, J=6Hz), 3.60 (m, 2H), 5.10 (d, 1H, J=9Hz), 5.19 (d, 1H, J=9Hz), 7.21 (d,1H, J=9Hz), 7.52 (d,1H, J=9Hz), 7.72 (s,1H), 7.93 (d,1H, J=3Hz), 8.00 (d, 2H, J=6Hz), 8.20 (d,1H, J=3Hz), 8.32 (d, 2H, J=6Hz), 8.44 (s,1H), 8.71 (s, 2H), 8.80 (m, 2H)

MS (离子喷雾) m/z 483 $(M+H)^+$.

实施例 1aaah

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(2-吡咯烷-1-基-嘧啶-4-基)-苯甲酰胺. 使用参考实施例 92y 的产物。

m.p. 134-136°C. ^{1}H NMR (DMSO-d_6): δ 2.00 (m, 4H), 3.00 (t, 2H, J=6Hz), 3.55 (m, 6H), 7.21 (m, 2H), 7.53 (d,1H, J=6Hz), 7.72 (s,1H), 7.93 (d, 2H, J=6Hz), 8.20 (m, 3H), 8.42 (m, 2H), 8.71 (s, 2H).

MS (离子喷雾) m/z 454 $(M+H)^+$. >98%纯度(分析 HPLC).

实施例 1aaaj

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-(2-羟甲基吡咯烷-1-基)-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 92z 的产物。

m.p. 117-120°C. ^{1}H NMR (DMSO-d_6): δ 2.01 (m, 4H), 2.98 (t, 2H, J=6Hz), 3.40 (s,1H), 3.58 (m, 4H), 3.70 (s, 1H), 4.19 (s,1H), 7.20 (d,1H, J=6Hz), 7.25 (d,1H, J=6Hz), 7.50 (d,1H, J=6Hz), 7.73 (s,1H), 7.94 (d, 2H, J=9Hz), 8.21 (t, 3H, J=9Hz), 8.46 (d, 2H, J=6Hz), 8.71 (s, 2H).

MS (离子喷雾) m/z 484 $(M+H)^+$.

元素分析 $C_{27}H_{29}N_7O_2 \cdot 2.5C_2HF_3O_2 \cdot 0.5H_2O$:

计算值: C, 49.4%; H, 4.2%; N, 12.6%.

实测值: C, 49.2%; H, 4.2%; N, 12.6%.

实施例 1aaak

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-(氨基甲酰基甲基-N-甲基氨基)-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 92aa 的产物。

m.p. 96-98°C. ^{1}H NMR (DMSO-d_6): δ 2.99 (t, 2H, J=6Hz), 3.23 (s, 3H), 3.59 (m, 2H), 3.80 (s, 2H), 7.21 (d,1H, J=9Hz), 7.30 (m, 1H), 7.50 (d,1H, J=6Hz), 7.74 (s,1H), 7.93 (d, 2H, J=9Hz), 8.20 (m, 3H), 8.45 (s, 2H), 8.71 (s, 2H).

MS (离子喷雾) m/z 471 $(M+H)^+$.

元素分析 $C_{25}H_{26}N_8O_2 \cdot 3C_2HF_3O_2 \cdot H_2O$:

计算值: C, 44.8%; H, 3.8%; N, 13.5%.

实测值: C, 44.9%; H, 4.0%; N, 13.5%.

实施例 1aaal

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-(6-吡咯烷-1-基-己基氨基)-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 92ab 的产物。

m.p. 159-161°C. ^{1}H NMR (DMSO-d_6): δ 1.38 (m, 4H), 1.62 (m, 4H), 1.87 (m, 2H), 2.02 (m, 2H), 2.53 (m, 4H), 3.00 (m, 2H), 3.12 (m, 2H), 3.38 (m, 2H), 3.57 (m, 2H), 7.20 (m, 2H), 7.30 (m,1H), 7.50 (d,1H, J=6Hz), 7.72 (s, 1H), 7.93 (d, 2H, J=6Hz), 8.19 (m, 3H), 8.40 (d, 1H, J=3Hz), 8.50 (s, 1H), 8.72 (m, 3H).

MS (离子喷雾) m/z 553 $(M+H)^+$. >98%纯度(分析 HPLC).

实施例 1aaam

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-(6-哌啶-1-基己基氨基)-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 92ac 的产物。

m.p. 110-113°C. ^{1}H NMR (DMSO-d_6): δ 1.36 (m, 4H), 1.63(m, 6H), 1.97 (m, 2H), 1.98 (m, 2H), 2.50 (m, 4H), 2.80 (m, 2H), 2.98 (m, 2H), 3.40 (m, 2H), 3.67 (m, 2H), 7.22 (m, 2H), 7.30 (m, 1H), 7.55 (d, 1H, J=6Hz), 7.70 (s, 1H), 7.97 (d, 2H, J=6Hz), 8.20 (m, 3H), 8.40 (d, 1H, J=3Hz), 8.50 (s, 1H), 8.75 (m, 3H).

MS (离子喷雾) m/z 567 $(M+H)^+$. >99%纯度(分析 HPLC).

实施例 1aaan

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-(4-哌啶-1-基丁基氨基)-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 92ad 的产物。

m.p. 94-96°C. ^{1}H NMR (DMSO-d_6): δ 1.52-1.86 (m, 10H), 2.50 (m, 4H), 2.82 (m, 2H), 2.98 (m, 2H), 3.40 (m, 2H), 3.61 (m, 2H), 7.20 (m, 2H), 7.35 (m, 1H), 7.50 (d, 1H, J=6Hz), 7.75 (s, 1H), 7.95 (d, 2H, J=6Hz), 8.20 (m, 3H), 8.40 (d, 1H, J=3Hz), 8.48 (s, 1H), 8.7 (m, 3H).

MS (离子喷雾) m/z 539 $(M+H)^+$. >99%纯度(分析 HPLC).

实施例 1aaap

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-(4-二乙基氨基丁基氨基)-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 92ae 的产物。

m.p. 73-76°C ^{1}H NMR (D_2O): δ 1.03 (t, 6H, J=8Hz), 1.60 (s, 4H), 2.81 (m, 2H), 2.97 (m, 6H), 3.45 (m, 4H), 7.08 (d, 1H, J=6Hz), 7.18 (d, 1H, J=3Hz), 7.35 (d, 1H, J=9), 7.42 (s, 1H), 7.55 (m, 3H), 7.86 (s, 1H), 7.98 (m, 2H), 8.10 (m, 1H).

MS （离子喷雾） m/z 527 $(M+H)^+$. >97%纯度(分析 HPLC).

实施例 1aaaq

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-(6-吗啉-4-基-己基氨基)-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 92af 的产物。

m.p. 129-130°C. ^{1}H NMR (DMSO-d_6): δ 1.38 (m, 4H), 1.62 (m , 4H), 2.50 (m, 6H), 3.01 (m, 2H), 3.10 (m, 2H), 3.50 (m, 6H), 7.20 (m, 2H), 7.31 (m, 1H) 7.50 (d, 1H, J=3Hz), 7.65 (s, 1H), 7.95 (d, 2H, J=9Hz), 8.10 (m, 3H), 8.40 (m, 1H), 8.5 (s, 1H), 8.72 (m, 3H).

MS （离子喷雾） m/z 569 $(M+H)^+$. >99%纯度(分析 HPLC).

实施例 1aaar

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-(6-二甲氨基己基氨基)-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 92ag 的产物。

m.p. 89-91°C. ^{1}H NMR (DMSO-d_6): δ 1.36 (m, 4H), 1.59 (m, 4H), 2.75 (s, 3H), 2.76 (s, 3H), 2.95 (m, 4H), 3.28 (m, 2H), 3.60 (m, 2H), 7.21 (m, 2H), 7.32 (m, 1H), 7.51 (d, 1H, J=9Hz), 7.74 (s, 1H), 7.95 (d, 2H, J=9Hz), 8.18 (d, 2H, J=9Hz), 8.21 (d, 1H, J=3Hz), 8.37 (d, 1H, J=6Hz), 8.49 (s, 1H), 8.72 (m, 3H).

MS （离子喷雾） m/z 527 $(M+H)^+$.

元素分析 $C_{30}H_{38}N_8O \cdot 3C_2HF_3O_2 \cdot 2H_2O$:

计算值： C, 47.8%; H, 5.0%; N, 12.4%.

实测值： C, 47.8%; H, 4.6%; N, 12.3%.

实施例 1aaas

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-(4-二甲氨基丁基氨基)-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 92ah 的产物。

m.p. 156-159°C. ^{1}H NMR (DMSO-d_6): δ 1.62 (m, 2H), 1.68 (m, 2H), 2.76 (s, 3H), 2.77 (s, 3H), 2.98 (t, 2H, J=6Hz), 3.07 (m, 2H), 3.99 (m, 2H), 3.59 (m, 2H), 7.21 (m, 2H), 7.32 (m, 1H), 7.52 (d, 1H, J=9Hz), 7.74 (s, 1H), 7.95 (d, 2H, J=9Hz), 8.18 (d, 2H, J=9Hz), 8.21 (d, 1H, J=3Hz), 8.37 (d, 1H, J=6Hz), 8.49 (s, 1H), 8.72 (m, 3H),

MS （离子喷雾） m/z 499 $(M+H)^+$.

元素分析 $C_{28}H_{34}N_8O \cdot 3C_2HF_3O_2 \cdot 2H_2O$:

计算值： C, 46.6%; H, 4.7%; N, 12.8%.

实测值： C, 46.5%; H, 4.5%; N, 12.6%.

>99%纯度(分析 HPLC).

实施例 1aaat

4-[2-(二环[2.2.1]庚-2-基氨基)嘧啶-4-基]-N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-苯甲酰胺. 使用参考实施例 92ai 的产物。

m.p. 152-155°C. ^{1}H NMR (DMSO-d_6): δ 1.14 (m, 2H), 1.33 (m, 2H), 1.46 (m, 2H), 1.63 (m, 1H), 1.97 (m, 1H), 2.20 (m, 2H), 2.97 (t, 2H, J=6Hz), 3.56 (m, 2H), 4.09 (m, 1H), 7.20 (m, 2H), 7.37 (m, 1H), 7.53 (d, 1H, J=9Hz), 7.73 (s, 1H), 7.94 (d, 2H, J=9Hz), 8.19 (d, 2H, J=9Hz), 8.20 (d, 1H, J=3Hz), 8.39 (d, 1H, J=6Hz), 8.45 (s, 1H), 8.70 (m, 3H),

MS (离子喷雾) m/z 494 $(M+H)^+$.

元素分析 $C_{29}H_{31}N_7O \cdot 2C_2HF_3O_2 \cdot 1.5H_2O$:

计算值： C, 52.9%; H, 4.8%; N, 13.1%.

实测值： C, 53.0%; H, 4.7%; N, 12.9%.

>98%纯度(分析 HPLC).

实施例 1aaau

1-(4-{4-[2-(3-脒基-1H-吲哚-5-基)-乙基氨基甲酰基]-苯基}嘧啶-2-基)吡咯烷-2-羧酰胺. 使用参考实施例 92aj 的产物。

m.p. 139-141°C. ^{1}H NMR (D_2O): δ 1.98 (m, 2H), 2.28 (m, 1H), 2.81 (t, 2H, J=6Hz), 3.44 (t, 2H, J=6Hz), 3.62 (m, 1H), 4.40 (m, 1H), 7.07 (d, 1H, J=9Hz), 7.12 (m, 1H), 7.38 (d, 1H, J=9Hz), 7.47 (s, 1H), 7.48 (d, 2H, J=9Hz), 7.89 (m, 3H), 8.16 (d, 1H, J=6Hz).

MS (离子喷雾) m/z 497 $(M+H)^+$.

元素分析 $C_{27}H_{28}N_8O_2 \cdot 3C_2HF_3O_2 \cdot NH_3$:

计算值： C, 46.3%; H, 4.0%; N, 14.7%.

实测值： C, 46.6%; H, 4.0%; N, 14.2%.

实施例 1aaav

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-{2-[(2-羟基-乙基)-N-甲基

氨基]-嘧啶-4-基}-苯甲酰胺. 使用参考实施例 92ak 的产物。

m.p. 97-100°C. ^{1}H NMR (DMSO-d_6): δ 2.99 (t, 2H, J=7Hz), 3.24 (s, 3H), 3.58 (m, 2H), 3.64 (t, 2H, J=7Hz), 3.75 (m, 2H), 7.21 (m, 2H), 7.50 (d, 1H, J=9Hz), 7.74 (s, 1H), 7.94 (d, 2H, J=9Hz), 8.21 (m, 3H), 8.44 (d, 1H, J=5Hz), 8.52 (s, 1H), 8.72 (s, 2H).

MS (离子喷雾) m/z 458 $(M+H)^+$.

元素分析 $C_{25}H_{27}N_7O_2 \cdot 3C_2HF_3O_2 \cdot NH_3$:

计算值: C, 47.1%; H, 4.1%; N, 13.7%.

实测值: C, 47.2%; H, 4.3%; N, 13.7%.

实施例 1aaaw

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(2-吗啉-4-基-嘧啶-4-基)-苯甲酰胺. 使用参考实施例 92al 的产物。

^{1}H NMR (DMSO) δ 3.0 (bt, 2H); 3.59 (m, 2H); 3.71 (m, 4H); 3.80 (m, 4H); 7.20 (d, 1H, J = 8Hz); 7.32 (d, J = 5Hz, 1H); 7.50 (d, J = 8Hz, 1H); 7.74 (s, 1H); 7.94 (d, 2H, J = 9Hz); 8.22 (m, 3H); 8.51 (m, 2H); 8.73 (m, 3H); 12.28 (bs, 1H),

MS (离子喷雾) m/z 470 $(M+H)^+$.

实施例 1aaax

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-(环丙基甲基氨基)-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 92am 的产物。

^{1}H NMR (DMSO) δ 0.26 (m, 2H); 0.43 (d, 2H, J = 7Hz); 1.12 (bt, H); 2.98 (t, 2H, J = 7Hz); 3.25 (bs, 2H); 3.57 (m, 2H); 7.20 (m, 2H); 7.50 (d, 1H, J = 9Hz); 7.74 (s, 1H); 7.94 (d, 2H, J = 9Hz); 8.19 (m, 3H); 8.39 (d, 1H, J = 5Hz); 8.53 (bs, 2H); 8.71 (bs, 3H); 12.28 (bs, 1H).

MS (离子喷雾) m/z 454 $(M+H)^+$.

实施例 1aaay

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-[(2-甲氧基-乙基)-甲基-氨基]-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 92an 的产物。

^{1}H NMR (DMSO) δ 2.99 (bt, 2H); 3.22 (s, 3H); 3.58 (m, 4H); 3.86 (m, 2H); 7.24 (m, 2H); 7.50 (d, 1H, J = 8Hz); 7.76 (s, 1H); 7.96 (d, 2H, J = 9Hz); 8.46 (d, 1H, J = 5Hz); 8.65 (bs, 1H); 8.76 (bs, 3H); 12.37 (bs, 1H).

MS （离子喷雾） m/z 472 $(M+H)^+$.

实施例 1aaaz

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-(3-羟基-丙基氨基)-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 92ap 的产物。

^{1}H NMR (DMSO) δ 1.74 (bt, 2H); 2.98 (bt, 2H); 3.42 (bs, 2H); 3.50 (t, 2H, J = 6Hz); 3.56 (m, 2H); 7.20 (m, 2H); 7.50 (d, 1H, J = 9Hz); 7.74 (s, 1H); 7.94 (d, 2H, J = 8Hz); 8.19 (m, 3H); 8.39 (d, 1H, J = 5Hz); 8.52 (bs, 2H); 8.71 (m, 3H); 12.28 (bs, 1H).

MS （离子喷雾） m/z 458 $(M+H)^+$.

实施例 1aaaaa

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[(2-羟基-乙基)-丙基-氨基]-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 92aq 的产物。

^{1}H NMR (DMSO) δ .90 (t, 3H); 1.63 (bd, 2H); 2.99 (t, 2H); 3.61 (m, 8H); 4.70 (bs, 1H); 7.20 (m, 2H); 7.49 (d, 1H, J = 8Hz); 7.73 (s, 1H); 7.92 (d, 2H, J = 8Hz); 8.18 (m, 3H); 8.42 (d, 1H, J = 5Hz); 8.50 (bs, 2H); 8.70 (bs, 2H); 12.26 (bs, 1H).

MS （离子喷雾） m/z 469 $(M+H)^+$.

实施例 1aaaab

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(2-哌啶-1-基-嘧啶-4-基)-苯甲酰胺. 使用参考实施例 92ar 的产物。

^{1}H NMR (DMSO) δ 1.61 (m, 6H); 2.98 (m, 2H); 3.57 (m, 2H); 3.84 (m, 4H); 7.20 (m, 2H); 7.50 (m, 2H); 7.74 (s, 1H); 7.94 (d, 2H, J = 8Hz); 8.20 (m, 3H); 8.45 (d, 1H, J = 5Hz); 8.50 (bs, 1H); 8.71 (bs, 3H); 12.28 (bs, 1H).

MS （离子喷雾） m/z 468 $(M+H)^+$.

实施例 1aaaac

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-(乙基-甲基-氨基)-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 92as 的产物。

^{1}H NMR (DMSO) δ 1.15 (t, 3H, J = 7Hz); 2.98 (bt, 2H); 3.18 (s, 3H); 3.59 (m, 2H); 3.73 (m, 2H); 7.21 (m, 2H); 7.50 (d, 1H, J = 8Hz); 7.74 (s, 1H); 7.94 (d, 2H, J = 8Hz); 8.21 (m, 3H); 8.45 (d, 1H, J = 5Hz); 8.53 (bs, 1H); 8.72 (bs, 3H); 12.29 (bs, 1H)

MS (离子喷雾) m/z 442 $(M+H)^+$.

实施例 1aaaad

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-(4-羟基-哌啶-1-基)-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 92at 的产物。

^{1}H NMR (DMSO) δ 1.38 (m, 2H); 1.82 (m, 2H); 2.99 (t, 2H, J = 7Hz); 3.34 (t, 2H, J = 7Hz); 3.58 (m, 2H); 3.76 (m, 1H); 4.39 (bd, 2H); 7.22 (m, 2H); 7.50 (d, 1H, J = 8Hz); 7.75 (s, 1H); 7.94 (d, 2H, J = 8Hz); 8.20 (m, 3H); 8.45 (d, 1H, J = 5Hz); 8.57 (bs, 1H); 8.73 (bs, 3H); 12.29 (bs, 1H).

MS (离子喷雾) m/z 484 $(M+H)^+$.

实施例 1aaaae

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-(2,3-二羟基-丙基氨基)-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 92au 的产物。

^{1}H NMR (DMSO) δ 2.98 (bt, 2H); 3.3 (m, 1H); 3.39 (m, 2H); 3.57 (m, 3H); 3.70 (bs, 1H); 7.22 (m, 3H); 7.50 (d, 1H, J = 8Hz); 7.74 (s, 1H); 7.94 (d, 2H, J = 9Hz); 8.21 (m, 3H); 8.40 (d, 1H, J = 5Hz); 8.53 (bs, 1H); 8.72 (m, 3H); 12.29 (bs, 1H)

MS (离子喷雾) m/z 474 $(M+H)^+$.

实施例 1aaaaf

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-[(2,3-二羟基-丙基)-甲基-氨基]-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 92av 的产物。

^{1}H NMR (DMSO) δ 2.98 (t, 2H, J = 7Hz); 3.25 (s, 3H); 3.38 (d, 2H, J = 5Hz); 3.54 (m, 3H); 3.85 (bs, 2H); 7.22 (m, 2H); 7.50 (d, 1H, J = 8Hz); 7.74 (s, 1H); 7.94 (d, 2H, J = 8Hz); 8.22 (m, 3H); 8.45 (d, 1H, J = 5Hz); 8.53 (bs, 1H); 8.71 (bs, 3H); 12.28 (bs, 1H).

MS （离子喷雾） m/z 488 $(M+H)^+$.

实施例 1aaaag

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-((s)-2-甲氧基甲基-吡咯烷-1-基)-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 92aw 的产物。

^{1}H NMR (DMSO) δ 2.04 (m, 4H); 2.98 (t, 2H, J = 7Hz); 3.33 (m, 5H); 3.60 (m, 4H); 4.35 (bs, 1H); 7.20 (d,1H, J = 8Hz); 7.28 (d, 1H, J = 8Hz); 7.50 (d, 1H, J = 8Hz); 7.74 (s, 1H); 7.95 (d, 2H, J = 8Hz); 8.22 (m, 3H); 8.47 (d, 1H, J = 5Hz); 8.52 (bs, 1H); 8.72 (bs, 3H); 12.28 (bs, 1H).

MS （离子喷雾） m/z 498 $(M+H)^+$.

实施例 1aaaah

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(2-哌嗪-1-基-嘧啶-4-基)-苯甲酰胺. 使用参考实施例 92ax 的产物。

^{1}H NMR (DMSO) δ 2.98 (bt, 2H, J = 7Hz); 3.24 (bs, 4H); 3.59 (m, 2H); 4.06 (bs, 4H); 7.20 (d, 1H, J = 9Hz); 7.40 (d, 1H, J = 5Hz); 7.50 (d, 1H, J = 8Hz); 7.75 (s, 1H); 7.96 (d, 2H, J = 8Hz); 8.24 (m, 3H); 8.56 (d, 1H, J = 5Hz); 8.63 (bs, 1H); 8.74 (m, 2H); 8.95 (bs, 2H); 12.30 (bs, 1H).

MS （离子喷雾） m/z 469 $(M+H)^+$.

实施例 1aaaai

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-[2-(2-氧代-咪唑烷-1-基)-乙基氨基]-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 92ay 的产物。

^{1}H NMR (DMSO) δ 2.98 (bt, 2H); 3.24 (m, 4H); 3.50 (m, 6H); 6.28 (bs, 1H); 7.22 (m, 2H); 7.39 (bs, 1H); 7.50 (d, 1H, J = 8Hz); 7.74 (s, 1H); 7.94 (d, 2H, J = 9Hz); 8.20 (m, 3H); 8.40 (bs, 1H); 8.50 (bs, 2H); 8.73 (m, 3H); 12.28 (bs, 1H).

MS （离子喷雾） m/z 512 $(M+H)^+$.

实施例 1aaaaj

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-(3-甲氧基-丙基氨基)-

嘧啶-4-基]-苯甲酰胺. 使用参考实施例 92az 的产物。

^{1}H NMR (DMSO) δ 1.80 (m, 2H); 2.98 (t, 2H, J = 7Hz); 3.23 (s, 3H); 3.40 (t, 4H, J = 6Hz); 3.55 (m, 2H); 7.20 (m, 2H); 7.50 (d, 1H, J = 9Hz); 7.73 (s, 1H); 7.94 (d, 2H, J = 9Hz); 8.18 (m, 3H); 8.38 (d, 1H, J = 5Hz); 8.54 (bs, 2H); 8.71 (m, 3H); 12.28 (bs, 1H).

MS (离子喷雾) m/z 472 $(M+H)^+$.

实施例 1aaaak

4-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-(2-羟基-乙基氨基)-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 92aaa 的产物。

^{1}H NMR (DMSO) δ 2.98 (t, 2H, J = 7Hz); 3.44 (bs, 2H); 3.56 (m, 4H); 4.80 (bs, 1H); 7.20 (m, 2H); 7.49 (d, 1H, J = 9Hz); 7.72 (s, 1H); 7.93 (d, 2H, J = 8Hz); 8.18 (m, 3H); 8.38 (d, 1H, J = 5Hz); 8.50 (bs, 2H); 8.70 (m, 3H); 12.26 (bs, 1H).

MS (离子喷雾) m/z 444 $(M+H)^+$.

实施例 1aaal

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-(2-甲氧基乙氧基)-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 100a 的产物。

m.p. 122-124°C. ^{1}H NMR (DMSO-d_6): δ 2.50 (s, 3H), 2.99 (t, 2H, J=9 Hz), 3.59 (m, 2H), 3.74 (m, 2H), 4.51 (m, 2H), 7.22 (d,1H, J=9Hz), 7.50 (d,1H, J=9Hz), 7.73 (s,1H), 7.79 (d,1H, J=6Hz), 7.97 (d, 2H, J=6Hz), 8.20 (d,1H, J=3Hz), 8.28 (d, 2H , J=6Hz), 8.41 (s,1H), 8.71 (m, 3H), 8.76 (t,1H, J=6Hz).

MS (离子喷雾) m/z 459 $(M+H)^+$.

元素分析 $C_{25}H_{26}N_6O_3 \cdot 2.5C_2HF_3O_2 \cdot 0.5NH_3$:

计算值: C, 50.1%; H, 4.3%; N, 13.1%.

实测值: C, 50.1%; H, 4.5%; N, 13.0%.

实施例 1aaaam

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-(1-氨基甲酰基乙氧基)-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 100b 的产物。

m.p. 159-161°C. ^{1}H NMR (DMSO-d_6): δ 1.52 (d, 3H, J=6Hz), 3.00 (t, 2H, J=6Hz), 3.60 (m, 2H), 5.21 (q,1H, J=6Hz), 7.21 (d,1H, J=6Hz), 7.51 (d, 1H, J=6Hz), 7.60 (s, 1H), 7.82 (d, 2H, J=6Hz), 7.97 (d, 2H, J=9Hz), 8.20 (d, 1H, J=3Hz), 8.29 (d, 2H, J=9Hz), 8.44 (s, 1H), 8.71 (m, 2H), 8.80 (m, 1H).

MS （离子喷雾） m/z 472 $(M+H)^+$.

实施例 1aaaan

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-(6-二甲氨基己氧基)-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 100c 的产物。

m.p. 82-84°C. ^{1}H NMR (DMSO-d_6): δ 1.40 (m, 2H), 1.49 (m, 2H), 1.68 (m, 2H), 1.81 (m, 2H), 2.76 (s, 3H), 2.78 (s, 3H), 3.01 (m, 4H), 3.56 (m, 2H), 7.21 (d, 1H, J=9Hz), 7.50 (d, 1H, J=9Hz), 7.74 (s, 1H), 7.78 (d, 1H, J=6Hz), 7.98 (d, 2H, J= 9Hz), 8.21 (d, 1H, J=3Hz), 8.27 (d, 2H, J= 9Hz), 8.55 (s, 1H), 8.70 (m, 3H), 8.78 (m, 2H).

MS （离子喷雾） m/z 528 $(M+H)^+$. >99%纯度(分析 HPLC).

实施例 1aaaap

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-(2-氧代哌啶-3-基氧基)-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 100d 的产物。

m.p. 145-147°C. ^{1}H NMR (DMSO-d_6): δ 1.92 (m, 2H), 2.20 (m, 1H), 2.25 (m, 1H), 3.00 (t, 2H, J=3Hz), 3.22 (m, 2H), 3.52 (m, 2H), 5.55 (m, 1H), 7.20 (d, 1H, J=6Hz), 7.50 (d, 1H, J=6Hz), 7.70 (s, 1H), 7.75 (d, 1H, J=3Hz), 7.97 (d, 2H, J=9Hz), 8.20 (d, 1H, J=3Hz), 8.26 (d, 2H, J=9Hz), 8.45 (s, 1H), 8.70 (m, 3H), 8.77 (t, 1H, J=3Hz).

MS （离子喷雾） m/z 498 $(M+H)^+$.

实施例 1aaaaq

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-(2-吡咯烷-1-基-乙氧基)-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 100e 的产物。

m.p. 104-105°C. ^{1}H NMR (DMSO-d_6): δ 1.89 (m, 2H), 2.05 (m, 2H), 2.98 (t, 2H, J=3Hz), 3.19 (m, 2H), 3.50-3.66 (m, 6H), 4.73 (m, 2H), 7.22 (d, 1H, J=6Hz), 7.50 (d1H, J=6Hz), 7.73 (s, 1H), 7.88 (d, 2H, J=6Hz), 8.01 (d, 2H, J=9Hz), 8.25 (d, 1H, J=3Hz), 8.30 (d, 2H, J=9Hz), 8.51 (s, 1H), 8.71 (s, 2H), 8.76 (m, 1H), 8.77 (m, 1H).

MS （离子喷雾） m/z 498 $(M+H)^+$.

元素分析 $C_{28}H_{31}N_7O_2 \cdot 2.5C_2HF_3O_2 \cdot H_2O$:

计算值： C, 49.5%; H, 4.5%; N, 12.3%.

实测值： C, 49.6%; H, 4.4%; N, 12.2%.

实施例 1aaaar

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-(2-二甲氨基乙氧基)-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 100f 的产物。

m.p. 106-107°C. ^{1}H NMR (DMSO-d_6): δ 2.89 (s, 3H), 2.91 (s, 3H),3.59 (m,4H), 4.75 (t, 2H, J=3Hz), 7.20 (d, 1H, J=6Hz), 7.51 (d, 1H, J=9Hz), 7.74 (s, H), 7.87 (d, 1H, J=6Hz), 8.00 (d, 2H, J=9Hz), 8.20 (d, 1H, J=3Hz), 8.30 (d, 2H, J=9Hz), 8.45 (s, 1H), 8.72 (s, 2H), 8.77 (d, 1H, J=6Hz), 8.79 (m, 1H).

MS (离子喷雾) m/z 472 $(M+H)^+$. >99%纯度(分析 HPLC).

实施例 1aaaas

3′-(2-二甲氨基乙氧基)联苯-4-羧酸[2-(3-脒基-1H-吲哚-5-基)-乙基]酰胺. 使用参考实施例 1aae 的产物。

m.p. 99-101°C. ^{1}H NMR (D_2O): δ 2.88 (s, 6H), 2.94 (t, 2H ,J=61Hz), 3.55 (m, 4H), 4.32 (t, 2H, J=3 Hz), 6.99 (d,1H, J=9 Hz), 7.20 (m, 2H), 7.39 (d,1H, J=6 Hz), 7.45(d,1H, J=6 Hz), 7.55(m, 4H), 7.94 (s,1H).

MS (离子喷雾) m/z 470 $(M+H)^+$. >99%纯度(分析 HPLC).

实施例 1aaaat

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(1-氧化吡啶-2-基)-苯甲酰胺. 使用参考实施例 1aaf 的产物。

m.p. 164-167°C. ^{1}H NMR (DMSO-d_6): δ 2.98 (t, 2H, J=7Hz), 3.58 (m, 2H), 7.20 (d, 1H, J=8Hz), 7.44 (m, 2H), 7.47 (d, 1H, J=8Hz), 7.74 (s, 1H), 7.92 (s, 4H), 8.20 (d, 1H, J=3Hz), 8.37 (m, 1H), 8.45 (s, 1H), 8.71 (s, 2H).

MS (离子喷雾) m/z 400 $(M+H)^+$.

元素分析 $C_{23}H_{21}N_5O_2 \cdot 1.5C_2HF_3O_2 \cdot 0.5H_2O$:

计算值： C, 53.9%; H, 4.1%; N, 12.1%.

实测值： C, 54.1%; H, 4.6%; N, 12.5%.

实施例 1aaaau

2′-(2-二甲氨基乙氧基)联苯-4-羧酸[2-(3-脒基-1H-吲哚-5-基)-乙基]酰胺. 使用参考实施例 1aag 的产物。

m.p. 73-76°C. ^{1}H NMR (D_2O): δ NMR 2.57 (s, 6H), 2.95 (t, 2H, J=3Hz), 3.32 (t, 2H, J=3Hz), 3.60 (t, 2H, J=6Hz), 4.20 (m, 2H), 7.00 (d, 2H, J=6Hz), 7.20 (d, 1H, J=3Hz), 7.25 (d, 1H, J=3Hz), 7.35 (m, 1H), 7.46 (m, 3H), 7.52 (d, 2H, J=6Hz), 7.60 (s, 1H), 7.95 (s, 1H).

MS (离子喷雾) m/z 470 $(M+H)^+$. >94%纯度(分析 HPLC).

实施例 1aaaav

2′-(3-二甲氨基丙氧基)联苯-4-羧酸[2-(3-脒基-1H-吲哚-5-基)-乙基]酰胺. 使用参考实施例 1aah 的产物。

m.p. 76-78°C. ^{1}H NMR (D_2O): δ 1.95 (m, 2H), 2.45 (s, 6H), 2.88 (t, 2H, J=9Hz), 2.96 (t, 2H, J=9Hz), 3.59 (t, 2H , J=9Hz), 4.00 (t, 2H, J=9Hz), 7.06 (m, 2H), 7.23 (m, 1H), 7.31 (m, 1H), 7.42 (m, 3H), 7.56 (d, 3H, J=9Hz), 7.61 (s, 1H), 7.96 (s, 1H).

MS (离子喷雾) m/z 484 $(M+H)^+$. >98%纯度(分析 HPLC).

实施例 1aaaaw

3′-(3-二甲氨基丙氧基)联苯-4-羧酸[2-(3-脒基-1H-吲哚-5-基)-乙基]酰胺. 使用参考实施例 1aai 的产物。

m.p. 84-86°C. ^{1}H NMR (D_2O): δ 2.06 (m, 2H), 2.76 (s, 6H), 2.85 (t, 2H, J=6Hz), 3.18 (t, 2H, J=6Hz), 3.47 (t, 2H, J=6Hz), 4.00 (t, 2H, J=6Hz), 6.88 (d,1H, J=6Hz), 7.02 (s,1H), 7.12 (m, 2H), 7.25 (t,1H, J=9Hz), 7.36 (d,1H, J=9Hz), 7.45 (m, 4H), 7.86 (s,1H).

MS (离子喷雾) m/z 484 $(M+H)^+$. 100%纯度(分析 HPLC).

实施例 1aaaax

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(1-氧代-吡啶-3-基)苯甲酰胺. 使用参考实施例 1aaj 的产物。

^{1}H NMR (DMSO) δ 3.01 (bt, 2H); 3.56 (m, 2H); 7.20 (d, 1H, J = 9Hz); 7.52 (m, 2H); 7.73 (m, 2H); 7.86 (d, 2H, J = 9Hz); 7.94 (d, 2H, J = 9Hz); 8.20 (s, 1H); 8.27 (d, 1H, J = 7Hz); 8.67 (s, 1H); 8.56 (s, 2H); 8.71 (m, 2H); 12.28 (bs, 1H).

MS （离子喷雾） m/z 400 $(M+H)^+$.

实施例 1aaaay

4-[2-(乙酰氨基-甲基)-吡啶-4-基]-N-[2-(3-脒基-1H-吲哚-5-基)-乙基]苯甲酰胺. 使用参考实施例 1aak 的产物。

^{1}H NMR (DMSO) δ 1.94 (s, 3H); 2.99 (bt, 2H); 4.49 (d, 2H, J = 5Hz); 7.20 (d, 1H, J = 8Hz); 7.50 (d, 1H, J = 8Hz); 7.74 (s, 1H); 7.83(m, 2H); 7.94 (d, 2H , J = 8Hz); 8.00 (d, 2H, J = 8Hz); 8.22 (d, 1H, J = 3Hz); 8.53 (m, 2H); 8.74 (m, 3H); 12.29 (bs, 1H)

MS （离子喷雾） m/z 455 $(M+H)^+$.

实施例 1aaaaz

哌啶-4-羧酸(4-[4-[2-(3-脒基-1H-吲哚-5-基)-乙基氨基甲酰基]-苯基]-吡啶-2-基甲基)-酰胺. 使用参考实施例 1aal 的产物。

^{1}H NMR (DMSO) δ 1.75 (m, 2H); 1.94 (m, 2H); 2.58 (m, 1H); 2.94 (m,5H); 3.30 (m, 2H); 3.62 (m, 2H); 4.54 (bd, 2H); 7.20 (d, 1H, J = 8Hz); 7.51 (d, 1H, J = 8Hz); 7.76 (s, H); 7.88 (m, 2H); 7.94 (d, 2H, J = 9Hz); 8.03 (d, 2H, J = 9Hz); 8.24 (s, 1H); 8.44 (bs, 1H); 8.77 (m, 3H); 12.35 (bs, 1H).

MS （离子喷雾） m/z 524 $(M+H)^+$.

实施例 1aaaaaa

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[1-(3-二甲氨基丙基)-6-氧代-1,6-二氢吡啶-3-基]-苯甲酰胺. 使用参考实施例 1aam 的产物。

m.p. 129-130°C. ^{1}H NMR (DMSO-d_6): δ 2.07 (t, 2H, J=6Hz), 2.72 (s, 6H), 2.84 (t, 2H, J=6Hz), 3.03 (t, 2H, J=6Hz), 3.46 (t, 2H, J=6Hz), 3.98 (t, 2H, J= 6Hz), 6.58 (d,1H, J= 12Hz), 7.12 (d,1H, J=9Hz), 7.38 (m, 3H), 7.47 (m, 3H), 7.81 (m, 2H), 7.88 (s,1H).

MS （离子喷雾） m/z 485 $(M+H)^+$.

元素分析 $C_{28}H_{32}N_6O_2 \cdot 3C_2HF_3O_2 \cdot 0.5H_2O$:

计算值： C, 48.9%; H, 4.3%; N, 10.1%.

实测值： C, 48.6%; H, 4.3%; N, 10.4%.

实施例 1aaaaab

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[6-(3-二甲氨基丙氧基)-吡啶-3-基]-苯甲酰胺. 使用参考实施例 1aan 的产物。

m.p. 84-86°C. ^{1}H NMR (D_2O): δ 2.11 (m, 2H), 2.78 (s, 6H), 2.90 (t, 2H, J=3Hz), 3.21 (m, 2H,), 3.51 (t, 2H, J=3Hz), 4.23(m, 2H), 6.85 (d,1H, J=6Hz), 7.05 (d,1H, J=6Hz), 7.40 (d, 1H, J=6Hz), 7.48-7.55 (m, 5H). 7.89 (m, 2H), 8.23 (s,1H).

MS (离子喷雾) m/z 485 $(M+H)^+$.

元素分析 $C_{28}H_{32}N_6O_2 \cdot 3C_2HF_3O_2$:

计算值: C, 49.4%; H, 4.3%; N, 10.2%.

实测值: C, 49.3%; H, 4.6%; N, 10.4%.

实施例 1aaaaac

(5-{4-[2-(3-脒基-1H-吲哚-5-基)-乙基氨基甲酰基]苯基}-2-氧代-2H-吡啶-1-基)乙酰胺. 使用参考实施例 1aap 的产物。MS (离子喷雾) m/z 457 $(M+H)^+$.

实施例 1aaaaad

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-{1-[(2-二甲氨基乙基氨基甲酰基)甲基]-6-氧代-1,6-二氢吡啶-3-基}-苯甲酰胺. 使用参考实施例 1aaq 的产物。

m.p. 71-75°C. ^{1}H NMR (D_2O): δ 2.75 (s, 6H), 3.16 (m, 2H), 3.37 (m, 2H), 3.50 (m, 2H), 4.55 (s, 2H), 4.63 (m 2H), 6.48 (d, 1H, J=9Hz), 7.03 (d, 1H, J=9Hz), 7.25 (m, 3H), 7.38 (m, 3H), 7.63 (s, 1H), 7.65 (m,, 1H), 7.79 (s, 1H)

MS (离子喷雾) m/z 528 $(M+H)^+$. >94%纯度(分析 HPLC).

实施例 1aaaaae

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(4-二甲氨基-哌啶-1-基)-苯甲酰胺. 使用参考实施例 1aas 的产物。

^{1}H NMR (CD_3OD): δ 8.04 (s, 1H0, 7.71 (brs, 1H), 7.59 (d, 2H), 7.47 (d, 1H), 7.19 (dd, 1H), 6.92 (d, 2H), 3.93 (d, 2H), 3.59 (t, 2H), 3.29 (m, 1H), 2.96 (t, 2H), 2.80 (dt, 2H), 2.74 (s, 6H), 2.06 (m, 2H), 1.68 (dq, 2H).

MS （离子喷雾） m/z 433 $(M+H)^+$. 92%纯度(分析 HPLC).

实施例 1aaaaaf

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[4-(2-二甲氨基-乙基氨基)-哌啶-1-基]-苯甲酰胺. 使用参考实施例 1aat 的产物。

^{1}H NMR (CD_3OD): d 8.04 (s, 1H), 7.86 (d, 1H), 7.71 (s, 1H), 7.68 (d, 1H), 7.59 (d, 1H), 7.19 (d, 1H), 6.91 (d, 2H), 4.02 (d, 2H), 3.64 (t, 2H), 3.56 (brs, 2H); 3.42 (m, 1H), 2.98 (s, 6H), 2.90 (m, 2H), 2.20 (brd, 2H), 1.79 (q, 2H).

MS （离子喷雾） m/z 476 $(M+H)^+$. >97%纯度(分析 HPLC).

实施例 1aaaaag

4-(4-氨基-哌啶-1-基)-N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-苯甲酰胺. 使用参考实施例 1aav 的产物。

^{1}H NMR (CD_3OD): δ 8.08 (s, 1H), 7.78 (s, 1H), 7.71 (d, 2H), 7.48 (d, 1H), 7.24 (dd, 1H), 6.99 (d, 2H), 3.96 (brd, 2H), 3.65 (t, 2H), 3.05 (t, 2H), 2.93 (dt, 2H), 2.07 (brd, 2H), 1.70 (dq, 2H).

MS （离子喷雾） m/z 405 $(M+H)^+$. >99%纯度(HPLC).

实施例 1aaaaah

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(4-甲氧基-哌啶-1-基)-苯甲酰胺. 使用参考实施例 1aaw 的产物。

^{1}H NMR (CD_3OD): d 8.07 (s, H), 7.76 (s, H), 7.72 (d, 2H), 7.46 (d, H), 7.33 (dd, H), 7.08 (d, 2H), 3.60-3.72 (m, 3H), 3.44-3.52 (m, H), 3.29 (s, 3H), 3.10-3.20 (m, 2H), 3.04 (t, 2H), 1.97-2.08 (m, 2H), 1.54-1.65 (m, 2H). MS (CI) m/z 420 (M+H)+.

实施例 1aaaaai

4-(4-乙酰氨基-哌啶-1-基)-N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-

苯甲酰胺. 使用参考实施例 125 的产物。

^{1}H NMR (CD_3OD): δ 8.08 (s, 1H), 7.76 (s, 1H), 7.69 (d, 2H), 7.48 (d, 1H), 7.24 (dd, 1H), 7.01 (d, 2H), 3.83 (brd, 2H), 3.65 (t, 2H), 3.05 (t, 2H), 2.98 (dt, 2H), 1.97 (m, 2H), 1,94 (s, 3H), 1.58 (dq, 2H). MS (CI) m/z 447 (M+H)+.

实施例 1aaaaaj

4-(1-乙酰基-哌啶-4-基)-N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-苯甲酰胺. 使用参考实施例 1aay 的产物。

^{1}H NMR (CD_3OD): δ 8.06 (s, 1H), 7.76 (d, 2H), 7.47 (d, 1H), 7.32 (d, 2H), 7.23 (dd, 1H), 4.02 (d, 1H), 4,64 (t, 2H), 3.05 (t, 2H), 2.81-2.93 (m, 1H), 2.64-2.75 (dt. 1H), 1.82-1.92 (m, 2H), 1.55-1.75 (m, 2H), 1.37 (m, 1H).

MS (离子喷雾) m/z 432 $(M+H)^+$. >96%纯度(分析 HPLC).

实施例 1aaaaak

4-{4-[2-(3-脒基-1H-吲哚-5-基)-乙基氨基甲酰基]-苯基}-哌啶-1-羧酰胺. 使用参考实施例 1aaz 的产物。

^{1}H NMR (CD_3OD): δ 8.07 (s, 1H), 7.76 (s, 1H), 7.70 (d, 2H), 7.47 (d, 1H), 7.31 (brd, 2H), 7.24 (dd, 2H), 4.14 (m, 2H), 3.66 (t, 2H), 3.08 (t, 2H), 2.80-2.97 (m, 2H), 1.80-1.88 (m, 2H), 1.58-1.68 (m, 2H).

MS (离子喷雾) m/z 433 $(M+H)^+$. 95%纯度(分析 HPLC).

实施例 1aaaaal

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(1-甲基-1-氧化-哌啶-4-基)-苯甲酰胺. 使用参考实施例 1aaaa 的产物。

^{1}H NMR (DMSO): δ 8.69 (brs, 1H), 8.46 (brs, 1H), 8.19 (s, 1H), 7.80 (d, 1H), 7.70 (s, 1H), 7.48 (d, 1H), 7.37 (d, 1H), 7.18 (d, 1H), 3.75 (d, 2H), 3.50 (s, 3H), 3.45-3.72 (m, 8H), 2.94 (m, 1H), 1.97 (m, 1H).

MS (离子喷雾) m/z 420 $(M+H)^+$. 96%纯度(分析 HPLC).

实施例 1aaaaam

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(1-甲基-哌啶-4-基)苯甲酰胺. 使用参考实施例 1aaab 的产物。

^{1}H NMR (DMSO): δ 9.55 (brs, 1H), 8.62 (d, 2H), 8.18 (d, 1H), 7.77 (d, 1H), 7.69 (s, 1H), 7.46 (d, 1H), 7.29 (d, 1H), 7.15 (d, 1H), 3.47-3.,52 (m, 2H), 3.02-3.06 (m, 1H), 2.89-2.95 (m, 2H), 2.78-2.80 (m, 4H), 1.97-2.01 (m, 1H), 1,79-1.82 (m, 1H), 1.20-1.24 (m, 1H),

MS (离子喷雾) m/z 404 $(M+H)^+$.

实施例 1aaaaan

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(1-甲磺酰基-哌啶-4-基)-苯甲酰胺. 使用参考实施例 1aaac 的产物。

^{1}H NMR (CD_3OD) : d 8.06 (s, 1H), 7.76 (s, 1H), 7.72 (d, 2H), 7.47 (d, 1H), 7.34 (d, 2H), 7.23 (d, 1H), 3.84 (d, 2H), 3.67 (m, 2H), 3.04 (t, 2H), 2.71-2.89 (m, 3H), 2.84 (s, 3H), 1.92 (m, 2H), 1.78 (dq, 2H).

MS (离子喷雾) m/z 468 $(M+H)^+$.

实施例 1aaaaao

4-(2-乙酰氨基-1,1-二甲基-乙基)-N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-苯甲酰胺. 使用参考实施例 1aaad 的产物。

^{1}H NMR (DMSO) δ 1.24 (s, 6H); 1.77 (s, 3H); 2.96 (t, 2H); 3.27 (d, J = 6Hz); 3.55 (m, 2H); 7.20 (d, J = 9Hz, 1H); 7.44 (d, J = 9Hz, 2H); 7.50 (d, J = 9Hz, 1H); 7.65 (t, 1H); 7.77 (m, 3H); 8.20 (d, J = 3Hz, 1H); 8.52 (m, 2H); 8.70 (bs, 1H); 12.28 (bs, 1H),

MS (离子喷雾) m/z 420 $(M+H)^+$.

实施例 1aaaaap

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(2-甲磺酰氨基-1,1-二甲基-乙基)苯甲酰胺. 使用参考实施例 106 的产物。

^{1}H NMR (DMSO) δ 1.28 (s, 6H); 2.74 (s, 3H); 2.96 (t, J = 7Hz, 2H); 3.11 (d, J = 7Hz, 2H); 3.54 (m, 2H); 6.85 (t, J = 7Hz, 1H); 7.18 (d, J = 9Hz, 1H); 7.48 (m, 3H); 7.76 (m, 3H); 8.20 (d, J = 3Hz, 1H); 8.54 (m, 2H); 8.70 (bs, 1H); 12.27 (d, J = 3Hz, 1H)

MS （离子喷雾） m/z 456 $(M+H)^+$.

实施例 1aaaaaq

哌啶-4-羧酸(2-{4-[2-(3-脒基-1H-吲哚-5-基)乙基氨基甲酰基]-苯基}-2-甲基-丙基)-酰胺. 使用参考实施例 1aaaf 的产物。

^{1}H NMR (DMSO) δ 1.24 (s, 6H); 1.68 (m, 4H); 2.42 (m, 1H); 2.84 (m, 2H); 2.96 (m, 2H); 3.28 (m, 4H); 3.54 (m, 2H); 3.90 (bs, 1H); 7.18 (d, J = 8Hz, 1H); 7.44 (d, J = 8Hz, 2H); 7.50 (d, J = 8Hz, 1H); 7.76 (m, 4H); 8.22 (s, 1H); 8.58 (m, 2H); 8.71 (bs, 1H); 12.30 (bs, 1H).

MS （离子喷雾） m/z 489 $(M+H)^+$.

实施例 1aaaaar

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(1,1-二甲基-2-脲基-乙基)苯甲酰胺. 使用参考实施例 107a 的产物。

^{1}H NMR (DMSO) δ 1.23 (s, 6H); 2.96 (t, 2H); 3.23 (d, J = 6Hz, 2H); 3.55 (m, 2H); 4.19 (bs, 2H); 5.72 (t, 1H); 7.19 (d, J = 9Hz, 1H); 7.46 (m, 3H); 7.75 (m, 3H); 8.20 (d, J = 3Hz, 1H); 8.53 (m, 2H); 8.70 (bs, 1H); 12.26 (d, J = 3Hz, 1H).

MS （离子喷雾） m/z 421 $(M+H)^+$.

实施例 1aaaaas

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-[2-(3-乙基-脲基)-1,1-二甲基-乙基]苯甲酰胺. 使用参考实施例 107b 的产物。

^{1}H NMR (DMSO) δ 0.93 (t, J = 7Hz, 3H); 1.22 (s, 6H); 2.96 (m, 4H); 3.25 (m, 2H); 3.56 (m, 2H); 5.54 (bt, 1H); 5.78 (bs, 1H); 7.18 (d, J = 8Hz, 1H); 7.43 (d, J = 8Hz, 2H); 7.72 (d, J = 8Hz, 1H); 7.76 (m, 3H); 8.21 (bs, 1H); 8.51 (m, 2H); 8.70 (bs, 1H); 12.27 (s, 1H).

MS （离子喷雾） m/z 449 $(M+H)^+$.

实施例 1aaaaat

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(2-二甲氨基-3,4,5,6-四氢-嘧啶-4-基)苯甲酰胺. 使用参考实施例 1aaai 的产物。

^{1}H NMR (DMSO) δ 1.88 (m, 1H); 2.11 (m, 1H); 2.98 (m, 10H); 3.33 (m, 1H); 3.57 (m, 2H); 4.80 (bs, 1H); 7.18 (d, J = 9Hz, 1H); 7.42 (d, J = 8Hz, 2H); 7.50 (d, J = 8Hz, 1H); 7.86 (d, J = 8Hz, 2H); 8.05 (s, 1H); 8.22 (d, J = 3Hz, 2H); 8.64 (bs, 2H); 8.71 (bs, 1H); 12.31 (s, 1H).

MS （离子喷雾） m/z 432 $(M+H)^+$.

实施例 1aaaaau

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(1-氧化-吡啶-4-基氧基)苯甲酰胺. 使用参考实施例 1aaaj 的产物。

^{1}H NMR ($CDCl_3$): δ 8.07 (s, 1H); 7.74 (s, 1H); 7.64 (d, 2H); 7.46 (d, 1H); 7.22 (dd, 2H); 6.79 (d, 2H); 3.63 (t, 2H); 3.03 (t, 2H).

MS （离子喷雾） m/z 416 $(M+H)^+$.

实施例 1aaaaav

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(1-甲基-哌啶-4-基氧基)苯甲酰胺. 使用参考实施例 1aaak 的产物。

^{1}H NMR (CD_3OD): d 8.07 (s, 1H), 7.74-7.79 (m, 3H), 7.46 (d, 1H), 7.23 (dd, 1H), 6.99-7.09 (m, 2H), 3.59-3.67 (m, 2H), 3.34-3.45 (m, 2H), 3.12-3.23 (m, 1H), 3.04 (t, 2H), 2.91 (t, 3H), 2.38 (brd, 1H), 2.20-2.26 (m, 2H), 2.06-2.10 (m, 2H), 1.89 (brq, 1H).

MS （离子喷雾） m/z 420 $(M+H)^+$. 94%纯度(分析 HPLLC).

实施例 1aaaaaw 和 1aaaaax

N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(1,2,3,6-四氢吡啶-4-基)苯甲酰胺. 使用参考实施例 67b 的产物。

^{1}H NMR (300 MHz, DMSO-d_6) d 12.27 (bs, 1H), 8.89 (bs, 2H), 8.70 (bs, 2H), 8.56 (t, 1H), 8.21 (bs, 2H), 8.20 (d, J = 3 Hz, 1H), 7.84 (d, J = 8 Hz, 2H), 7.72 (s, 1H), 7.57 (d, J = 8 Hz, 2H), 7.48 (d, J = 8 Hz, 1H), 7.18 (d, J = 8 Hz, 1H), 6.32 (bs, 1H), 3.78 (bs, 2H), 3.57-3.49 (m, 2H), 3.3 (obsc, 2H), 2.94 (t, J = 8 Hz, 2H), 2.69 (bm, 2H);

MS （电喷雾） m/z 388 $(M+H)^+$.

将 N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-(1,2,3,6-四氢吡啶

-4-基)苯甲酰胺(5mg)的 MeOH (2mL)溶液用 N_2 净化，然后加入 10%钯-碳(9mg)，并再次用氮气净化反应物。反应物随后用氢气净化，并剧烈搅拌 30 分钟。用氮气净化反应物，然后通过 Celite 过滤，用 MeOH 洗涤，浓缩后得到 N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-4-哌啶-4-基-苯甲酰胺.

^{1}H NMR (300 MHz, DMSO-d_6) d 12.31 (bs, 1H), 8.72-8.84 (m, 7H), 8.21 (s, 1H), 7.79 (d, J = 7 Hz, 2H), 7.72 (s, 1H), 7.47 (d, J = 8 Hz, 1H), 7.30 (d, J = 7 Hz, 2H), 7.17 (d, J = 8 Hz, 1H), 3.52 (m, 2H), 3.3 (obsc, 2H), 3.05-3.85 (m, 5H), 1.96-1.72 (m, 4H);

MS (离子喷雾) m/z 390 $(M+H)^+$.

实施例 1aaaaay

4-(2-氨基-1,1-二甲基乙基)-N-(2-[3-脒基吲哚-5-基]乙基)苯甲酰胺

向 4-(2-[叔丁氧羰基氨基]-1,1-二甲基乙基)-N-(2-[1-叔丁氧羰基-3-叔丁氧羰基脒基吲哚-5-基]乙基)苯甲酰胺(0.092g, 0.14 mmol, 参考实施例 1aaa1)的二氯甲烷(8ml)溶液中加入蒸馏水(0.1mL)和三氟乙酸(2mL)。搅拌 6 小时后，浓缩反应混合物，然后置于高真空下，从而以定量产率得到白色固体标题化合物(m.p. 67-70℃).

^{1}H NMR (D_2O): δ 1.29 (6H, s), 2.91 (2H, t, J = 7 Hz), 3.12 (2H, s), 3.53 (2H, t, J = 7 Hz), 7.14 (1H, d, J = 8 Hz), 7.36-7.46 (5H, m), 7.54 (1H, s), 7.93 (1H, s). MS (FAB) m/z 378 $(M+H)^+$.

元素分析 $C_{22}H_{27}N_5O \cdot 3C_2HO_2F_3$:

计算值: C, 46.7; H, 4.2; N, 9.7.

实测值: C, 46.8; H, 4.5; N, 9.8.

采用与参考实施例 1aaaaay 所用基本相同的方法，但其中使用指定的底物，从而制得:

实施例 1aaaaaz

N-(2-[3-脒基吲哚-5-基]-乙基)-4-(6-[2-二甲氨基乙氧基]吡啶-3-基)苯甲酰胺.

使用参考实施例 1aaam 的产物。用 HPLC 纯化(分析 HPLC 检测: 96.8%纯度).

m.p. 57-59°C. ^{1}H NMR (D_2O): δ 2.77-2.89 (8H, m), 3.39-3.54 (4H, m), 4.44 (2H, m), 6.86 (1H, d, J = 9 Hz), 7.09 (1H, d, J = 8 Hz), 7.35 (1H, d, J = 8 Hz), 7.40-7.49 (5H, m), 7.84 (1H, s), 7.88 (1H, d, J = 9 Hz), 8.16 (1H, s).

MS (离子喷雾) m/z 471 $(M+H)^+$.

实施例 1aaaaaaa

N-(2-[3-脒基吲哚-5-基]乙基)-4-吡啶-4-基苯甲酰胺. 使用参考实施例 1aaan 的产物。

m.p. 113-116°C. ^{1}H NMR (D_2O): δ 2.19 (2H, t, J = 6 Hz), 3.56 (2H, t, J = 6 Hz), 7.16 (1H, d, J = 8 Hz), 7.42 (1H, d, J = 8 Hz), 7.54 (1H, s), 7.62 (2H, d, J = 8 Hz), 7.79 (2H, d, J = 8 Hz), 7.92 (1H, s), 8.19 (2H, m), 8.67 (2H, br, m).

MS (离子喷雾) m/z 384 $(M+H)^+$.

元素分析 $C_{23}H_{21}N_5O \cdot (C_2HO_2F_3)_3(H_2O)_{0.5}$:

计算值: C, 47.4; H, 3.4; N, 9.5.

实测值: C, 47.2; H, 3.7; N, 9.8.

实施例 1aaaaaab

N-(2-[3-脒基吲哚-5-基]乙基)-4-(4-氨基甲酰基-苯基)-苯甲酰胺. 使用参考实施例 1aaao 的产物。MS m/z 426 $(M+H)^+$.

实施例 1aaaaaac

N-(2-[3-脒基吲哚-5-基]乙基)-4-(4-甲氧基-苯基)-苯甲酰胺. 使用参考实施例 1aaap 的产物。MS m/z 413 $(M+H)^+$.

实施例 1aaaaaad

N-(2-[3-脒基吲哚-5-基]乙基)-(5-甲氧基-吲哚-2-基)-甲酰胺. 使用参考实施例 1aaaq 的产物。MS m/z 375 (M+H).

实施例 1aaaaaaae

N-(2-[3-脒基吲哚-5-基]乙基)-(6-氯-苯并噻吩-2-基)-甲酰胺. 使用参考实施例 1aaar 的产物。MS m/z 397 (M+H).

实施例 1aaaaaaf

N-(2-[3-脒基吲哚-5-基]乙基)-4-(4-苄氧基-苯基)-苯甲酰胺. 使用参考实施例 1aaas 的产物。MS m/z 413 (M+H).

实施例 1aaaaaag

N-(2-[3-脒基吲哚-5-基]乙基)-4-氯-苯甲酰胺. 使用参考实施例 1aaat 的产物。MS m/z 341 / 343 (M+H, Cl 图案).

实施例 1aaaaaah

N-(2-[3-脒基吲哚-5-基]乙基)-4-(甲磺酰基)-苯甲酰胺. 使用参考实施例 1aaau 的产物。MS m/z 385 (M+H).

实施例 1aaaaaai

N-(2-[3-脒基吲哚-5-基]乙基)-4-(氨基-磺酰基)-苯甲酰胺. 使用参考实施例 1aaav 的产物。MS m/z 386 (M+H).

实施例 1aaaaaaj

4-(3-氨基丙-1-炔基)-N-[2-(3-脒基-1H-吲哚-5-基)乙基]-苯甲酰胺. 使用参考实施例 64d 的产物。

^{1}H NMR (300 MHz, CD_3OD) d 8.09 (s, 1H) 7.78 (d, J =8 Hz, 3H), 7.56 (d, J = 8 Hz, 2H), 7.48 (d, J = 8 Hz, 1H), 7.24 (d, J = 7 Hz, 1H), 4.06 (s, 2H), 3.67 (t, J = 8 Hz, 2H), 3.05 (t, J = 8 Hz, 2H).

MS (离子喷雾) m/z 360 ($M+H^+$).

实施例 1aaaaaak

5-{4-[2-(3-脒基-1H-吲哚-5-基)乙基氨基甲酰基]苯基}-2-氧代-2H-吡啶-1-基)乙酸

在 50℃，搅拌(5-{4-[2-(3-脒基-1H-吲哚-5-基)乙基氨基甲酰基]苯基}-2-氧代-2H-吡啶-1-基)乙酰胺(0.507g，1.11 mmol，实施例 1aaaaac)在 5M HCl (40mL)和甲醇(20mL)中的溶液 42 小时。浓缩反应混合物，接着溶于 9:1 H_2O: AcCN (30mL)。滤除固体杂质，滤液用 HPLC 纯化，得 3.60mg 白色固体标题化合物。

m.p. >250°C. ^{1}H NMR (CD_3OD): δ 3.07 (t, 2H, J=6Hz), 3.68 (m, 2H), 4.82 (m, 2H), 6.68 (d, 1H, 9Hz), 7.26 (d, 1H, J = 9Hz), 7.50 (d, 1H, J=9Hz), 7.63 (d, 2H, J=8Hz), 7.78 (s, 1H), 7.83 (d, 2H, J=8Hz), 7.97 (d, 1H, J=9Hz), 8.07 (m, 2H), 8.65 (m, 1H);

MS (离子喷雾) m/z 458 $(M+H)^+$. >90%纯度(分析 HPLC).

实施例 2

采用与制备实施例 1a 所用基本相同的方法，只是其中使用参考实施例 67c 的产物，从而制得 3-脒基-5-{2-[4-(6-氧代-1,6-二氢-吡啶-3-基)-苯甲酰基氨基]丙基}-吲哚。

^{1}H NMR (300 MHz, DMSO-d_6) d 12.24 (bs, 1H), 8.68 (bs, 2H), 8.49 (bs, 2H), 8.33 (d, J = 8 Hz, 1H), 8.17 (d, J = 3 Hz, 1H), 7.88 (dd, J = 10, 3 Hz, 1H), 7.83-7.81 (m, 3H), 7.72 (s, 1H), 7.63 (d, J = 8 Hz, 2H), 7.45 (d, J = 8 Hz, 1H), 7.19 (d, J = 8 Hz, 1H), 6.44 (d, J = 9 Hz, 1H), 4.34-4.25 (m, 1H), 3.00 (dd, J = 13, 7 Hz, 1H), 2.81 (dd, J = 13, 7 Hz, 1H), 1.15 (d, J = 7 Hz, 3H);

MS (离子喷雾) m/z 414 $(M+H^+)$.

参考实施例 1a

N-(2-[3-氰基-5-吲哚基]乙基)-4-吡啶-3-基苯甲酰胺

向 4-吡啶-3-基苯甲酸(0.430g，2.16 mmol，参考实施例 11b)和二异丙基乙胺(DIEA) (0.42mL，2.4 mmol)在二氯甲烷(10mL)中的悬浮液内加入 O-苯并三唑-1-基-N,N,N′,N′-四甲基脲四氟硼酸盐(TBTU) (0.706g，2.20 mmol)。30 分钟后，加入 3-氰基-5-(2-氨基乙基)吲哚(0.4g，2.16 mmol，参考实施例 2)和 DIEA (0.42mL，2.4 mmol)，

经历 15 分钟后，再加入另一份 DIEA (0.42mL)在 CH_2Cl_2 (5mL)中的溶液。搅拌过夜后，浓缩溶液，层析(10:1 CH_2Cl_2:MeOH)残留物，得含有一些 DIEA 杂质的产物。该粗产物无需进一步纯化而直接使用。
MS (离子喷雾) m/z 367 $(M+H)^+$.

下列化合物采用与参考实施例 1a 所述基本相同的方法制备，但其中使用指定的酸:

参考实施例 1b
N-(2-[3-氰基-5-吲哚基]乙基)-4-嘧啶-5-基-苯甲酰胺. 使用参考实施例 11c 的产物。所得产物无需进一步纯化可直接使用。MS (离子喷雾) m/z 368 $(M+H)^+$.

参考实施例 1c
5-(吡啶-2-基)-噻吩-2-羧酸 2-(3-氰基-5-吲哚基)乙基酰胺. 所得产物无需进一步纯化可直接使用。MS (FAB) m/z 373 $(M+H)^+$.

参考实施例 1d
N-(2-[3-氰基吲哚-5-基]乙基)-6-吗啉-4-基烟酰胺. 使用参考实施例 24a 的产物。采用 4:1 的二氯甲烷: DMF 作为溶剂。所得产物无需进一步纯化而直接使用。MS (离子喷雾) m/z 376 $(M+H)^+$.

参考实施例 1e
N-(2-[3-氰基吲哚-5-基]乙基)-6-氯烟酰胺. 使用市售的 6-氯烟酸。所得产物无需进一步纯化可直接使用。MS (EI) m/z 324, 326 (M[^{35}Cl, ^{37}Cl])$^+$.

参考实施例 1f
N-(2-[3-氰基吲哚-5-基]乙基)-6-咪唑-1-基-烟酰胺. 使用市售的

6-咪唑-1-基-烟酸。所得产物无需进一步纯化可直接使用。MS（离子喷雾）m/z 357 $(M+H)^+$.

参考实施例 1g

N-(2-[3-氰基吲哚-5-基]乙基)-4-咪唑-1-基-苯甲酰胺. 所得产物直接使用无需进一步纯化。MS（离子喷雾）m/z 357 $(M+H)^+$.

参考实施例 1h

N-(2-[3-氰基吲哚-5-基]乙基)-4-(3H-咪唑-4-基)苯甲酰胺. 使用参考实施例 35b 的产物。所得产物无需进一步纯化而直接使用。MS（离子喷雾）m/z 356 $(M+H)^+$.

参考实施例 1i

N-(2-[3-氰基吲哚-5-基]乙基)-4-(1,2,4)噻二唑-5-基苯甲酰胺. 使用参考实施例 35a 的产物。所得产物无需进一步纯化而直接使用。MS（离子喷雾）m/z 374 $(M+H)^+$.

参考实施例 1j

N-[2-(3-氰基-1H-吲哚-5-基)乙基]-4-(1-氨基甲酰基-1-甲基-乙基-苯甲酰胺. 使用参考实施例 25a 的产物。

^{1}H NMR ($CDCl_3$ / CD_3OD) d 1.58 (s, 6H), 3.05 (t, J = 7Hz, 2H), 3.67 (q, J = 7Hz, 2H), 7.21 (d, J = 8Hz, 1H), 7.44 (m, 3H), 7.56 (s, 1H), 7.75 (d, J = 8Hz, 2H), 7.81 (s, 1H), 8.28 (bt, 1H).

MS（离子喷雾）m/z 375 (M+H).

参考实施例 1k

N-[2-(3-氰基-1H-吲哚-5-基)乙基]-4-(1-[N-(2-甲氧基乙基)]-氨基甲酰基-1-甲基-乙基-苯甲酰胺. 使用参考实施例 25b 的产物。

^{1}H NMR ($CDCl_3$ / CD_3OD) d 1.58 (s, 6H), 3.05 (t, J = 7Hz, 2H), 3.28 (s, 3H), 3.37 (m, 4H), 3.70 (q, J = 7Hz, 1H), 6.3 (bt, 1H), 7.20 (d, J = 10Hz, 1H), 7.41 (m, 3H), 7.57 (s, 1H), 7.57 (bt, J = 7Hz, 1H), 7.74 (m, 3H).

MS （离子喷雾） m/z 433 (M+H).

参考实施例 11

N-[2-(3-氰基-1H-吲哚-5-基)乙基]-4-(叔丁基)-苯甲酰胺. 使用市售 4-(叔丁基)苯甲酸。

^{1}H NMR ($CDCl_3$) d 1.30 (s, 9H), 3.04 (t, J = 7Hz, 2H), 3.76 (q, J = 7Hz, 2H), 6.32 (bt, J = 7Hz, 1H), 7.11 (dd, J = 9, 1Hz, 1H), 7.27 (d, J = 9Hz, 1H), 7.42 (m, 2H), 7.65 (m, 4H), 9.9 (bs, 1H).

MS （离子喷雾） m/z 346 (M+H).

参考实施例 1

N-[2-(3-氰基-1H-吲哚-5-基)乙基]-4-(哒嗪-4-基)-乙基-苯甲酰胺. 使用参考实施例 11e 的产物。

^{1}H NMR (DMSO) d 2.98 (t, J = 7Hz, 2H), 3.59 (q, J = 7Hz, 2H), 7.20 (d, J = 8Hz, 1H), 7.50 (m, 2H), 8.05 (m, 5H), 8.23 (s, 1H), 8.74 (bt, J = 7Hz, 1H), 9.31 (d, J = 5Hz, 1H), 9.7 (bs, 1H),

MS （离子喷雾） m/z 368 (M+H).

参考实施例 1n

N-[2-(3-氰基-1H-吲哚-5-基)乙基]-4-(2-甲氧基-吡啶-5-基)-2-甲基-苯甲酰胺. 使用参考实施例 33a 的产物。

^{1}H NMR (DMSO) d 2.30 (s, 3H), 2.96 (t, J = 7Hz, 2H), 3.52 (q, J = 7Hz, 2H), 3.90 (s, 3H), 6.91 (d, J = 8Hz, 1H), 7.20 (d, J = 8Hz, 1H), 7.32 (d, J = 8Hz, 1H), 7.50 (m, 4H), 8.01 (dd, J = 8, 3 Hz, 1H), 8.21 (d, J = 3 Hz, 1H), 8.33 (t, J = 7Hz, 1H), 8.49 (d, J = 3 Hz, 1H).

MS （离子喷雾） m/z 411 (M+H).

参考实施例 1o

3',4'-二甲氧基联苯-4-羧酸(2-[3-氰基吲哚-5-基]乙基)酰胺. 使用参考实施例 33b 的产物。所得产物无需进一步纯化而直接使用。MS（离子喷雾） m/z 426 $(M+H)^+$.

参考实施例 1p

N-(2-[3-氰基-1H-吲哚-5-基]乙基)-4-(6-甲氧基吡啶-3-基)苯甲酰胺. 使用参考实施例 33c 的产物。所得产物无需进一步纯化而直接使用。MS (FAB) m/z 397 $(M+H)^+$.

参考实施例 1q

N-(2-[3-氰基-1H-吲哚-5-基]乙基)-4-(1-氧化吡啶-4-基)苯甲酰胺. 使用参考实施例 17a 的产物。所得产物无需进一步纯化而直接使用。MS (离子喷雾) m/z 283 $(M+H)^+$.

参考实施例 1r

N-[2-(3-氰基-1H-吲哚-5-基)乙基]-4-(7H-吡咯并[2,3-d]嘧啶-6-基)苯甲酰胺. 使用参考实施例 42a 的产物。

^{1}H NMR (DMSO) δ 2.99 (bt, 2H), 3.56 (m, 2H), 7.20 (m, 2H), 7.50 (m, 2H), 7.94 (d, J = 8Hz, 2H), 8.06 (d, J = 8Hz, 2H), 8.21 (s, 1H), 8.65 (bt, 1H), 8.78 (s, 1H), 9.02 (bs, 1H), 12.13 (bs, 1H), 12.71 (bs, 1H).

MS (离子喷雾) m/z 407 $(M+H)^+$.

参考实施例 1s

N-[2-(3-氰基-1H-吲哚-5-基)乙基]-4-(1H-吡咯并[3,2-c]吡啶-2-基)苯甲酰胺. 使用参考实施例 42b 的产物。

^{1}H NMR (DMSO) δ 2.99 (bt, 2H), 3.55 (m, 2H), 7.22 (d, J = 8Hz, 1H), 7.30 (s, 1H), 7.52 (m, 3H), 7.95 (d, J = 9Hz, 2H), 8.02 (d, J = 9Hz, 2H), 8.21 (d, J = 3Hz, 1H), 8.26 (d, J = 6Hz, 1H), 8.66 (bt, 1H), 8.98 (s, 1H), 12.13 (s, 1H), 12.49 (bs, 1H).

MS (离子喷雾) m/z 406 $(M+H)^+$.

参考实施例 1t

N-[2-(3-氰基-1H-吲哚-5-基)乙基]-4-呋喃并[3,2-c]吡啶-2-基-苯甲酰胺. 使用参考实施例 42c 的产物。

^{1}H NMR (DMSO) δ 2.99 (bt, 2H), 3.57 (m, 2H), 7.19 (d, J = 8Hz, 1H), 7.49 (m, 2H), 7.74 (m, 2H), 7.98 (d, J = 8Hz, 2H), 8.06 (d, J = 8Hz, 2H), 8.20 (d, J = 3Hz, 1H), 8.51 (d, J = 5Hz, 1H), 8.71 (bt, 1H), 9.00 (s, 1H), 12.10 (bs, 1H).

MS (离子喷雾) m/z 407 $(M+H)^+$.

参考实施例 1u

N-[2-(3-氰基-1H-吲哚-5-基)乙基]-3-氯-4-(6-甲氧基-吡啶-3-基)-苯甲酰胺. 使用参考实施例 33d 的产物。

^{1}H NMR (DMSO) δ 2.98 (bt, 2H), 3.56 (m, 2H), 3.91 (s, 3H), 6.94 (d, J = 9Hz, 1H), 7.18 (d, J = 8Hz, 1H), 7.48 (d, J = 9Hz, 2H), 7.55 (d, J = 8Hz, 1H), 7.86 (d, J = 9Hz, 2H), 7.99 (s, 1H), 8.20 (s, 1H), 8.27 (s, 1H), 8.74 (bt, 1H), 12.12 (bs, 1H).

MS (离子喷雾) m/z 431 $(M+H)^+$.

参考实施例 1w

(3-{4-[2-(3-氰基-1H-吲哚-5-基)乙基氨基甲酰基]-苯基}-3-甲基-丁基)-氨基甲酸叔丁酯. 使用参考实施例 25d 的产物。

^{1}H NMR (DMSO) δ 1.27 (s, 6H), 1.33 (s, 9H), 1.74 (m, 2H), 2.65 (m, 2H), 2.95 (t, J = 7Hz, 2H), 3.51 (q, J = 7Hz, 2H), 6.67 (bt, 1H), 7.18 (d, J = 8Hz, 1H), 7.42 (d, J = 8Hz, 2H), 7.46 (s, 1H), 7.50 (s, 1H), 7.76 (d, J = 8Hz, 2H), 8.20 (d, J = 3Hz, 1H), 8.50 (bt, 1H), 12.12 (s, 1H).

MS (离子喷雾) m/z 475 $(M+H)^+$.

参考实施例 1x

N-[2-(3-脒基-1H-吲哚-5-基)乙基]-2-(4-氯-苯基)-乙酰胺. 使用市售的 2-(4-氯-苯基)乙酸。

^{1}H NMR (CD_3OD) δ 2.90 (t, J = 7Hz, 2H), 3.40 (s, 2H). 3.48 (q, J = 7Hz, 2H), 7.10 (m, 3H), 7.20 (m, 2H), 7.40 (d, J = 8Hz, 1H), 7.45 (s, 1H), 7.91 (s, 1H).

MS (离子喷雾) m/z 338/340 (M+H, Cl 图案).

参考实施例 1y

5-氯-噻吩-2-羧酸[2-(3-氰基-1H-吲哚-5-基)乙基]-酰胺. 使用市售的 5-氯-噻吩-2-羧酸。 ^{1}H NMR (DMSO) δ 2.93 (t, J = 7Hz, 2H), 3.48 (q, J = 7Hz, 2H), 7.16 (m, 2H), 7.50 (m, 2H), 7.61 (d, J = 4Hz, 1H), 8.20 (d, J = 3Hz, 1H), 8.7 (bt, J = 7Hz, 1H), 12.14 (bs, 1H).

MS (离子喷雾) m/z 330/332 (M+H, Cl 图案).

参考实施例 1z

N-(2-[3-氰基吲哚-5-基]乙基)-6-(2-羟基乙基氨基)烟酰胺. 使用参考实施例 24c 的产物。MS (离子喷雾) m/z 350 $(M+H)^+$.

参考实施例 1aa

N-(2-[3-氰基吲哚-5-基]乙基)-6-(1,2,4)-三唑-1-基烟酰胺. 使用市售的 6-(1,2,4)-三唑-1-基烟酰胺。MS (离子喷雾) m/z 358 $(M+H)^+$.

参考实施例 1ab

N-(2-[3-氰基吲哚-5-基]乙基)-6-吡咯-1-基烟酰胺. 使用市售的 6-(吡咯-1-基)-烟酸。MS (离子喷雾) m/z 356 $(M+H)^+$.

参考实施例 1ac

N-(2-[3-氰基吲哚-5-基]乙基)-6-吡唑-1-基烟酰胺). 使用市售的 6-吡唑-1-基烟酸。MS (离子喷雾) m/z 357 $(M+H)^+$.

参考实施例 1ae

N-[2-(3-氰基-1H-吲哚-5-基)乙基]-3-氯-苯甲酰胺. 使用市售的 3-氯-苯甲酸。

^{1}H NMR (DMSO) δ 2.98 (t, J = 7Hz, 2H), 3.53 (q, J = 7Hz, 2H), 7.18 (d, J = 8Hz, 1H), 7.50 (m, 3H), 7.60 (m, 1H), 7.79 (d, J = 8Hz, 1H), 7.82 (s, 1H), 8.20 (d, J = 2Hz, 1H), 8.70 (bt, J = 7Hz, 1H).

MS (EI) m/z 323/325 (M^+, Cl 图案).

参考实施例 1af

N-[2-(3-氰基-1H-吲哚-5-基)乙基]-2-(3-氯-苯基)-乙酰胺. 使用市售的 2-(3-氯-苯基)乙酸。

^{1}H NMR (CD_3OD) δ 2.90 (t, J = 7Hz, 2H), 3.42 (s, 2H), 3.48 (q, J = 7Hz, 2H), 7.10 (m, 2H), 7.21 (m, 3H), 7.40 (d, J = 8Hz, 1H), 7.45 (s, 1H), 7.91 (s, 1H), 8.11 (bs, 1H).

MS (离子喷雾) m/z 338/340 (M+H, Cl 图案).

参考实施例 1ag

4-(2-叔丁氧羰基氨基-甲基)-吡啶-4-基)-N-[2-(3-氰基-1H-吲哚-5-基)乙基]-苯甲酰胺. 使用参考实施例 33e 的产物。

^{1}H NMR (DMSO) δ 1.38 (s, 9H), 2.96 (t, J = 7Hz, 2H), 3.55 (q, J = 7Hz, 2H), 4.27 (d, J = 6Hz, 2H), 7.16 (d, J = 8Hz, 1H), 7.45 (m, 3H), 7.59 (m, 2H), 7.80 (d, J = 8Hz, 2H), 7.94 (d, J = 8Hz, 2H), 8.17 (d, J = 3Hz, 1H), 8.55 (d, J = 5Hz, 1H), 8.65 (t, J = 7Hz, 1H).

MS (离子喷雾) m/z 496 (M+H).

参考实施例 1ah

4-{4-[2-(3-氰基-1H-吲哚-5-基)乙基氨基甲酰基]-吡啶-2-羧酰胺. 使用参考实施例 33f 的产物。

^{1}H NMR (DMSO) δ 3.0 (t, J = 7Hz, 2H), 3.57 (q, J = 7Hz, 2H), 7.19 (d, J = 8Hz, 1H), 7.50 (d, J = 8Hz, 1H), 7.51 (s, 1H), 7.75 (bs, 1H), 8.0 (m, 5H), 8.2 (bs, 2H), 8.35 (s, 1H), 8.73 (m, 2H).

MS (离子喷雾) m/z 410 (M+H).

参考实施例 1ai

N-[2-(3-氰基-1H-吲哚-5-基)乙基]-4-(2-二甲氨基甲基-吡啶-4-基)-苯甲酰胺. 使用参考实施例 33g 的产物。

^{1}H NMR (CD_3OD) δ 2.63 (s, 6H), 3.06 (t, J = 7Hz, 2H), 3.67 (t, J = 7Hz, 2H), 4.08 (s, 2H), 7.24 (d, J = 8Hz, 1H), 7.45 (d, J = 8Hz, 1H), 7.55 (s, 1H), 7.70 (d, J = 5Hz, 1H), 7.81 (s, 1H), 7.84 (d, J = 8Hz, 2H), 7.91 (d, J = 8Hz, 2H), 8.64 (d, J = 5Hz, 1H).

MS (离子喷雾) m/z 424 (M+H).

参考实施例 1ak

N-[2-(3-氰基-1H-吲哚-5-基)乙基]-4-(6-甲氧基-哒嗪-3-基)-苯甲酰胺. 使用参考实施例 11f 的产物。

^{1}H NMR (DMSO) δ 3.00 (t, J = 7Hz, 2H), 3.57 (m, 2H), 4.10 (s, 3H), 7.20 (d, J = 8Hz, 1H), 7.36 (d, J = 9Hz, 1H), 7.48 (d, J = 8Hz, 1H), 7.52 (s, 1H), 7.96 (d, J = 9Hz, 2H), 8.20 (m, 4H), 8.68 (bt, 1H), 12.10 (bs, 1H).

MS (离子喷雾) m/z 398 $(M+H)^+$.

参考实施例 1al

N-[2-(3-氰基-1H-吲哚-5-基)乙基]-4-[1-(2-二甲氨基-乙基)-6-氧代-1,6-二氢-哒嗪-3-基]-苯甲酰胺. 使用参考实施例 61a 的产物。

^{1}H NMR (DMSO) δ 2.49 (s, 6H), 2.98 (bt, 2H), 3.06 (m, 2H), 3.55 (m, 2H), 4.37 (bt, 2H), 7.10 (d, J = 10Hz, 1H), 7.18 (d, J = 8Hz, 1H), 7.48 (d, J = 8Hz, 1H), 7.51 (s, 1H), 7.94 (d, J = 9Hz, 2H), 8.00 (d, J = 9Hz, 2H), 8.12 (d, J = 10Hz, 1H), 8.20 (d, J = 2Hz, 1H), 8.68 (bt, 1H), 12.12 (s, 1H).

MS (离子喷雾) m/z 455 $(M+H)^+$.

参考实施例 1am

N-[2-(3-氰基-1H-吲哚-5-基)乙基]-4-[1-(3-二甲氨基-丙基)-6-氧代-1,6-二氢-哒嗪-3-基]-苯甲酰胺. 使用参考实施例 61b 的产物。

^{1}H NMR (DMSO) δ 2.05 (m, 2H), 2.51 (s, 6H), 2.79 (bt, 2H), 2.98 (bt, 2H), 3.56 (m, 2H), 4.21 (bt, 2H), 7.10 (d, J = 10Hz, 1H), 7.19 (d, J = 8Hz, 1H), 7.49 (m, 2H), 7.94 (d, J = 8Hz, 2H), 8.00 (d, J = 8Hz, 2H), 8.14 (d, J = 10Hz, 1H), 8.22 (d, J = 3Hz, 1H), 8.68 (m, 1H), 12.12 (bs, 1H)

MS (离子喷雾) m/z 469 $(M+H)^+$.

参考实施例 1an

N-[2-(3-氰基-1H-吲哚-5-基)乙基]-4-[2-(2-二甲氨基-乙基氨基)-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 83 的产物。

^{1}H NMR (DMSO) δ 2.20 (s, 6H), 2.95 (t, J = 7Hz, 2H), 3.31 (m, 2H), 3.44 (bm, 2H), 3.51 (bm, 2H), 7.07 (t, J = 7Hz, 1H), 7.18 (m, 2H), 7.45 (d, J = 8Hz, 1H), 7.50 (s, 1H), 7.90 (d, J = 8Hz, 2H), 8.17 (d, J = 8Hz, 2H), 8.18 (s, 1H), 8.37 (d, J = 6Hz, 1H), 8.67 (t, J = 7Hz, 1H).

MS (离子喷雾) m/z 454 (M+H).

参考实施例 1ao

N-[2-(3-氰基-1H-吲哚-5-基)乙基]-4-[2-甲氧基-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 17b 的产物。

^{1}H NMR (DMSO) δ 2.96 (t, J = 7Hz, 2H), 3.54 (q, J = 7Hz, 2H), 4.0 (s, 3H), 7.17 (d, J = 8Hz, 1H), 7.46 (m, 2H), 7.78 (d, J = 5Hz, 1H), 7.95 (d, J = 8Hz, 2H), 8.18 (d, J = 3Hz, 1H), 8.26 (d, J = 8Hz, H), 8.70 (d, J = 5Hz, 1H), 8.75 (t, J = 7Hz, 1H).

MS (离子喷雾) m/z 398 (M+H).

参考实施例 1ap

N-(2-[3-氰基吲哚-5-基]乙基)-4-(1-[2-二甲氨基乙基)-6-氧代

-1,6-二氢-吡啶-3-基)苯甲酰胺. 使用参考实施例 17c 的产物。

^{1}H NMR (1:1 CD_3OD: $CDCl_3$): δ 2.46 (6H, s), 2.86 (2H, m), 3.08 (2H, m), 3.70 (2H, m), 4.23 (2H, m), 6.70 (1H, d, J = 9 Hz), 7.24 (1H, d, J = 8 Hz), 7.49 (1H, d, J = 9 Hz), 7.54-7.61 (3H, m), 7.79-7.92 (4H, m), 7.92 (1H, s).

MS (离子喷雾) m/z 454 $(M+H)^+$.

参考实施例 1aq

N-(2-[3-氰基吲哚-5-基]乙基)-4-(1-氨基甲酰基甲基-6-氧代-1,6-二氢-吡啶-3-基)苯甲酰胺. 使用参考实施例 17d 的产物。MS (离子喷雾) m/z 440 $(M+H)^+$.

参考实施例 1ar

4-(3-氨基-[1,2,4]三嗪-6-基)-N-[2-(3-氰基-1H-吲哚-5-基)乙基]-苯甲酰胺. 使用参考实施例 86a 的适当产物。

^{1}H NMR (DMSO-d_6) d 2.98 (2H, t, J = 6 Hz), 3.56 (2H, m), 7.15-7.55 (5H), 7.90-8.35 (6H), 8.75 (1H, t, J = 5 Hz), 9.28 (1H,s):

MS (离子喷雾) m/z 384 $(M+H)^+$.

参考实施例 1as

4-(3-氨基-[1,2,4]三嗪-5-基)-N-[2-(3-氰基-1H-吲哚-5-基)乙基]-苯甲酰胺. 使用参考实施例 86a 的适当产物。

参考实施例 1at

N-[2-(3-氰基-1H-吲哚-5-基)乙基]-4-(3-氧代-2,3-二氢-[1,2,4]三嗪-6-基)-苯甲酰胺. 使用参考实施例 86b 的产物。MS, m/z (离子喷雾) 403 $[(M+18)+H]^+$.

参考实施例 1au

N-[2-(3-氰基-1H-吲哚-5-基)乙基]-4-(5-氧代-4,5-二氢-[1,2,4]噁二唑-3-基)-苯甲酰胺. 使用参考实施例 86c 的产物。MS, m/z(离子

喷雾) 374 [(M+H]$^+$.

参考实施例 1av

4-(1-氨基甲酰基甲基-6-氧代-1,6-二氢吡啶-3-基)苯甲酸乙酯. 使用参考实施例 67a 的产物作为酸组分并使用氨作为胺。

^{1}H NMR (1:2 CD_3OD: $CDCl_3$): δ 1.43 (3H, t, J = 7 Hz), 4.41 (2H, q, J = 7 Hz), 4.72 (2H, s), 6.72 (1H, d, J = 9 Hz), 7.58 (2H, d, J = 8 Hz), 7.82 (1H, d, J = 2 Hz), 7.85 (1H, dd, J = 9, 2 Hz), 8.09 (2H, d, J = 8 Hz).

MS (离子喷雾) m/z 301 (M+H)$^+$.

参考实施例 1aw

N-[2-(3-氰基-1H-吲哚-5-基)乙基]-4-[2-(吗啉-4-基-乙基氨基)-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 92a 的产物。

^{1}H NMR (DMSO): δ 2.46 (bm, 6H), 2.99 (t, J = 7Hz, 2H), 3.42-3.62 (m, 8H), 7.09 (bt, J = 5Hz, 1H), 7.20 (m, 2H), 7.92 (d, J = 8Hz, 2H), 8.20 (m, 3H), 8.39 (m, 1H), 8.69 (t, J = 5Hz, 1H).

MS (离子喷雾) m/z 496 (M+H)$^+$.

参考实施例 1ax

N-[2-(3-氰基-1H-吲哚-5-基)乙基]-4-[2-(3-二甲氨基-丙基氨基)-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 92b 的产物。

^{1}H NMR (CD_3OD): δ 1.90 (m, 2H), 2.59 (t, J = 7Hz, 2H), 3.05 (t, J = 7Hz, 2H), 3.50 (t, J = 7Hz, 2H), 3.66 (t, J = 7Hz, 2H), 7.13 (d, J = 5Hz, 1H), 7.23 (d, J = 8Hz, 1H), 7.45 (d, J = 8Hz, 1H), 7.56 (s, 1H), 7.86 (d, J = 8Hz, 2H), 7.90 (s, 1H), 8.16 (d, J = 8Hz, 2H), 8.30 (d, J = 5Hz, 1H).

MS (离子喷雾) m/z 468 (M+H)$^+$.

参考实施例 1ay

N-[2-(3-氰基-1H-吲哚-5-基)乙基]-4-[2-([2-二甲氨基-乙基]-甲基-氨基)-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 92c 的产物。

^{1}H NMR ($CDCl_3$): δ 2.35 (s, 6H), 2.60 (t, J = 7Hz, 2H), 3.05 (t, J = 7Hz, 2H), 3.23 (s, 3H), 3.77 (q, J = 7Hz, 2H), 3.85 (t, J = 7Hz, 2H), 6.25 (bt, J = 7Hz, 1H), 6.90 (d, J = 5Hz, 1H), 7.17 (bd, J = 8Hz, 1H), 7.36 (bd, J = 8Hz, 1H), 7.61 (bs, 1H), 7.67 (bs, 1H), 7.75 (d, J = 8Hz, 2H), 8.04 (d, J = 8Hz, 2H), 8.35 (d, J = 5Hz, 1H), 9.3 (bs, 1H).

MS (离子喷雾) m/z 468 (M+H)$^+$.

参考实施例 1az

N-[2-(3-氰基-1H-吲哚-5-基)乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺. 使用参考实施例 11g 的产物。过滤反应粗产物并用水洗涤，真空干燥后直接使用无需进一步纯化。

^{1}H NMR ($CDCl_3$): δ 2.99 (t, J = 7Hz, 2H), 3.55 (q, J = 7Hz, 2H), 7.18 (d, J = 8Hz, 1H), 7.5 (m, 2H), 8.01 (d, J = 8Hz, 2H), 8.27 (m, 4H), 8.77 (t, J = 7Hz, 1H), 8.87 (d, J = 5Hz, 1H), 12.1 (bs, 1H).

MS (离子喷雾) m/z 402 $(M+H)^+$.

参考实施例 1aaa

N-[2-(3-氰基-1H-吲哚-5-基)乙基]-4-[2-氧代-六氢-嘧啶-5-基]-苯甲酰胺. 使用参考实施例 17f 的产物。MS (离子喷雾) m/z 388 $(M+H)^+$.

参考实施例 1aab

N-[2-(3-氰基-1H-吲哚-5-基)乙基]-4-(1,3-二甲基-2-氧代-六氢-嘧啶-5-基)-苯甲酰胺. 使用参考实施例 17g 的产物。MS (离子喷雾) m/z 416 $(M+H)^+$.

参考实施例 1aac

联苯-3,4′-二羧酸 4′-{[2-(3-氰基-1H-吲哚-5-基)乙基]-酰胺}3-甲基酯. 使用参考实施例 11i 的产物。

^{1}H NMR (DMSO): δ 2.96 (t, J = 7Hz, 2H), 3.54 (q, J = 7Hz, 2H), 3.88 (s, 3H), 7.16 (d, J = 8Hz, 1H), 7.46 (m, 2H), 7.64 (t, J = 8Hz, 1H), 7.78 (d, J = 8Hz, 2H), 7.9-8.01 (m, 4H), 8.19 (d, J = 1Hz, 1H), 8.22 (s, 1H), 8.64 (bt, J = 7Hz, 1H).

MS (离子喷雾) m/z 424 $(M+H)^+$.

参考实施例 1aad

联苯-2,4′-二羧酸 4′-{[2-(3-氰基-1H-吲哚-5-基)乙基]-酰胺}2-甲基酯. 使用参考实施例 11j 的产物。

^{1}H NMR (DMSO): δ 2.97 (t, J = 7Hz, 2H), 3.55 (q, J = 7Hz, 2H), 3.60 (s, 3H), 7.20 (d, J = 8Hz, 1H), 7.36 (d, J = 8Hz, 2H), 7.50 (m, 4H), 7.66 (t, J = 8Hz, 1H), 7.80 (d, J = 8Hz, 1H), 7.85 (d, J = 8Hz, 2H), 8.20 (d, J = 1Hz, 1H), 8.65 (bt, J = 7Hz, 1H).

MS（离子喷雾）m/z 424 $(M+H)^+$.

参考实施例 1aae

3′-(2-二甲氨基乙氧基)联苯-4-羧酸[2-(3-氰基-1H-吲哚-5-基)乙基]-酰胺. 使用参考实施例 101a 的产物。MS（离子喷雾）m/z 453 $(M+H)^+$.

参考实施例 1aaf

N-[2-(3-氰基-1H-吲哚-5-基)乙基]-4-(1-氧化吡啶-2-基)苯甲酰胺. 使用参考实施例 101b 的产物。MS（离子喷雾）m/z 383 $(M+H)^+$.

参考实施例 1aag

2′-(2-二甲氨基乙氧基)联苯-4-羧酸[2-(3-氰基-1H-吲哚-5-基)乙基]-酰胺. 使用参考实施例 101c 的产物。MS（离子喷雾）m/z 453 $(M+H)^+$.

参考实施例 1aah

2′-(3-二甲氨基丙氧基)联苯-4-羧酸[2-(3-氰基-1H-吲哚-5-基)乙基]-酰胺. 使用参考实施例 101d 的产物。MS（离子喷雾）m/z 467 $(M+H)^+$.

参考实施例 1aai

3′-(3-二甲氨基丙氧基)联苯-4-羧酸[2-(3-氰基-1H-吲哚-5-基)乙基]-酰胺. 使用参考实施例 101e 的产物。MS（离子喷雾）m/z 467 $(M+H)^+$.

参考实施例 1aaj

N-[2-(3-氰基-1H-吲哚-5-基)乙基]-4-(1-氧代-吡啶-3-基)-苯甲酰胺. 使用参考实施例 101f 的产物.

^{1}H NMR (DMSO) δ 2.98 (bt, 2H); 3.56 (m, 2H); 7.18 (d, 1H, J = 9Hz); 7.51 (m, 3H); 7.72 (d, 1H, J = 9Hz); 7.86 (d, 2H, J = 8Hz); 7.94 (d, 2H, J = 8Hz); 8.25 (d, 1H, J = 7Hz); 8.65 (s, 1H); 8.72 (bt, 1H); 12.22 (bs, 1H).
MS （离子喷雾） m/z 383 $(M+H)^+$.

参考实施例 1aak

4-[2-(乙酰氨基-甲基)-吡啶-4-基]-N-[2-(3-氰基-1H-吲哚-5-基)乙基]-苯甲酰胺. 使用参考实施例 17j 的产物。
^{1}H NMR (DMSO) δ 1.92 (s, 3H); 3.08 (bt, 2H); 3.55 (m, 2H); 4.42 (d, 2H, J = 6Hz); 7.18 (d, 1H, J = 9Hz); 7.49 (m, 3H); 7.63 (s, 2H); 7.86 (d, 2H, J = 8Hz); 7.96 (d, 2H, J = 8Hz); 8.20 (d, 1H); 8.48 (bt, 1H); 8.58 (m, 1H); 8.70 (bt, 1H); 12.17 (bs, 1H).
MS （离子喷雾） m/z 438 $(M+H)^+$.

参考实施例 1aal

4-[[4-[4-[2-(3-氰基-1H-吲哚-5-基)乙基氨基甲酰基]-苯基]-吡啶-2-基甲基]-氨基甲酰基]-哌啶-1-羧酸叔丁酯. 使用参考实施例 17k 的产物。^{1}H NMR (CD_3OD) δ 1.45 (s, 9H); 1.62 (m, 2H); 1.82 (m, 2H); 2.51 (m, 1H); 2.99 (s, 2H); 3.06 (t, 2H, J = 7Hz); 3.67 (t, 2H, J = 7Hz); 4.12 (m, 2H); 4.54 (s, 2H); 7.22 (d, 1H, J = 8Hz); 4.46 (d, 1H, J = 8Hz); 7.58 (m, 3H); 7.78 (d, 2H, J = 9Hz); 7.90 (m, 3H); 7.97 (s, 2H); 8.54 (d, 1H, J = 5Hz).
MS （离子喷雾） m/z 607 $(M+H)^+$.

参考实施例 1aam

N-[2-(3-氰基-1H-吲哚-5-基)乙基]-4-[1-(3-二甲氨基丙基)-6-氧代-1,6-二氢吡啶-3-基]苯甲酰胺. 使用参考实施例 171 的产物。MS (静电环(esi loop)) m/z 468 $(M+H)^+$.

参考实施例 1aan

N-[2-(3-氰基-1H-吲哚-5-基)乙基]-4-[6-(3-二甲氨基丙氧基)吡啶-3-基]-苯甲酰胺. 使用参考实施例 17m 的产物。
MS （离子喷雾） m/z 468 $(M+H)^+$.

参考实施例 1aap

(5-{4-[2-(3-氰基-1H-吲哚-5-基)乙基氨基甲酰基]苯基}-2-氧代-2H-吡啶-1-基)乙酸叔丁酯. 使用参考实施例 7b 的产物。MS (离子喷雾) m/z 497 $(M+H)^+$.

参考实施例 1aaq

N-[2-(3-氰基-1H-吲哚-5-基)乙基]-4-{1-[(2-二甲氨基乙基氨基甲酰基)甲基]-6-氧代-1,6-二氢吡啶-3-基}-苯甲酰胺. 使用参考实施例 17n 的产物。MS (离子喷雾) m/z 511 $(M+H)^+$.

参考实施例 1aar

4-{1-[(2-二甲氨基乙基氨基甲酰基)甲基]-6-氧代-1,6-二氢吡啶-3-基}苯甲酸乙酯. 使用参考实施例 103b 的产物。MS (离子喷雾) m/z 372 $(M+H)^+$.

参考实施例 1aas

N-[2-(3-氰基-1H-吲哚-5-基)乙基]-4-(4-二甲氨基-哌啶-1-基)-苯甲酰胺. 使用参考实施例 113a 的产物。MS (离子喷雾) m/z 416 $(M+H)^+$.

参考实施例 1aat

N-[2-(3-氰基-1H-吲哚-5-基)乙基]-4-[4-(2-二甲氨基-乙基-叔丁氧羰基-氨基)-哌啶-1-基]-苯甲酰胺. 使用参考实施例 120 的产物。MS (离子喷雾) m/z 559 $(M+H)^+$.

参考实施例 1aav

4-(4-叔丁氧羰基氨基-哌啶-1-基)-N-[2-(3-脒基-1H-吲哚-5-基)-乙基]-苯甲酰胺. 使用参考实施例 115 的产物。MS (离子喷雾) m/z 488 $(M+H)^+$.

参考实施例 1aaw

N-[2-(3-氰基-1H-吲哚-5-基)乙基]-4-(4-甲氧基-哌啶-1-基)-苯甲酰胺. 使用参考实施例 121 的产物。MS (CI) m/z 403 $(M+H)^+$.

参考实施例 1aay

4-(1-乙酰基-哌啶-4-基)-N-[2-(3-氰基-1H-吲哚-5-基) - 乙基]-苯甲酰胺. 使用参考实施例 110 的产物。MS (离子喷雾) m/z 415 $(M+H)^+$.

参考实施例 1aaz

4-{4-[2-(3-氰基-1H-吲哚-5-基)乙基氨基甲酰基]苯基}-哌啶-1-羧酰胺. 使用参考实施例 107c 的产物。MS (离子喷雾) m/z 416 $(M+H)^+$.

参考实施例 1aaaa

N-[2-(3-氰基-1H-吲哚-5-基)乙基]-4-(1-氧代-1-甲基-哌啶-4-基)-苯甲酰胺. 使用参考实施例 112 的产物。MS (离子喷雾) m/z 403 $(M+H)^+$.

参考实施例 1aaab

N-[2-(3-氰基-1H-吲哚-5-基)乙基]-4-(1-甲基-哌啶-4-基)-苯甲酰胺. 使用参考实施例 111 的产物。MS (离子喷雾) m/z 387 $(M+H)^+$.

参考实施例 1aaac

N-[2-(3-氰基-1H-吲哚-5-基)乙基]-4-(1-甲磺酰基-哌啶-4-基)-苯甲酰胺. 使用参考实施例 17p 的产物。MS (离子喷雾) m/z 451 $(M+H)^+$.

参考实施例 1aaad

4-(2-乙酰氨基-1,1-二甲基-乙基)-N-[2-(3-氰基-1H-吲哚-5-基)乙基]-苯甲酰胺. 使用参考实施例 105 的产物和乙酸作为底物。MS (离子喷雾) m/z 403 $(M+H)^+$.

参考实施例 1aaaf

N-BOC-哌啶-4-羧酸(2-{4-[2-(3-氰基-1H-吲哚-5-基)乙基氨基甲酰基]苯基}-2-甲基-丙基)-酰胺. 使用参考实施例 105 的产物和 N-BOC 哌啶-4-羧酸作为底物。MS (离子喷雾) m/z 572 $(M+H)^+$.

参考实施例 1aaai

N-[2-(3-氰基-1H-吲哚-5-基)乙基]-4-(2-二甲氨基-3,4,5,6-四氢-嘧啶-4-基)-苯甲酰胺. 使用参考实施例 108 的产物。MS (离子喷雾) m/z 415 $(M+H)^+$.

参考实施例 1aaaj

N-[2-(3-氰基-1H-吲哚-5-基)乙基]-4-(1-氧化-吡啶-4-基氧基)-苯甲酰胺. 使用参考实施例 118 的产物。MS (离子喷雾) m/z 399 $(M+H)^+$.

参考实施例 1aaak

N-[2-(3-氰基-1H-吲哚-5-基)乙基]-4-(1-甲基-哌啶-4-基氧基)-苯甲酰胺. 使用参考实施例 17o 的产物。MS (离子喷雾) m/z 403 $(M+H)^+$.

参考实施例 1aaal

4-(2-[叔丁氧羰基氨基]-1,1-二甲基乙基)-N-(2-[1-叔丁氧羰基-3-叔丁氧羰基脒基吲哚-5-基]乙基)苯甲酰胺. 使用参考实施例 25c 的产物。

^{1}H NMR ($CDCl_3$): δ 1.31 (6H, s), 1.37 (9H, s), 1.56 (9H, s), 1.66 (9H, s), 3.08 (2H, t, J = 6.6 Hz), 3.31 (2H, d, J = 6.2 Hz), 3.81 (2H, m), 4.27 (1H, br, m), 6.18 (1H, br, m), 7.25 (1H, d, J = 8.4 Hz), 7.37 (2H, d, J = 8.2 Hz), 7.64 (2H, d, J = 8.2 Hz), 7.88 (1H, s), 8.17 (1H, d, J = 8.4 Hz), 8.24 (1H, s).

MS (离子喷雾) m/z 678 $(M+H)^+$.

参考实施例 1aaam

N-(2-[1-叔丁氧羰基-3-叔丁氧羰基脒基吲哚-5-基]乙基)-4-(6-[2-二甲氨基乙氧基]吡啶-3-基)苯甲酰胺. 使用参考实施例 7a 的产物作为胺组分以及使用参考实施例 17e 的产物作为酸组分。MS (离子喷雾)

m/z 671 $(M+H)^+$.

参考实施例 1aaan

N-(2-[1-叔丁氧羰基-3-叔丁氧羰基脒基吲哚-5-基]乙基)-4-吡啶-4-基苯甲酰胺. 使用参考实施例 11a 和 7a 的产物。

^{1}H NMR ($CDCl_3$): δ 1.55 (9H, s), 1.66 (9H, s), 3.10 (2H, t, J = 6.6 Hz), 3.83 (2H, m), 6.32 (1H, br, m), 7.25 (1H, d, J = 8.5 Hz), 7.50 (2H, d, J = 4.9 Hz), 7.65 (2H, d, J = 8.2 Hz), 7.80 (2H, d, J = 8.2 Hz), 7.92 (1H, s), 8.17 (1H, d, J = 8.5 Hz), 8.23 (1H, s), 8.68 (2H, br, m).

MS (离子喷雾) m/z 584 $(M+H)^+$.

参考实施例 1aaao-1aaav

将 N-(2-[1-叔丁氧羰基-3-叔丁氧羰基脒基吲哚-5-基]乙基)-胺溶液(1mL, 0.01M 的 DMF 溶液) (参考实施例 7a)加到 30mg 酰化树脂(0.5mmol/g, 参考实施例 54)中，摇动混合物 48 小时，然后过滤。树脂用另一份 DMF(1ml)洗涤，然后在高真空下浓缩合并的滤液。残留物无需进一步纯化可直接使用。

应用该方法制备下列化合物:

参考实施例 1aaao

N-(2-[1-叔丁氧羰基-3-叔丁氧羰基脒基吲哚-5-基]乙基)-4-(4-氨基甲酰基-苯基)-苯甲酰胺

参考实施例 1aaap

N-(2-[1-叔丁氧羰基-3-叔丁氧羰基脒基吲哚-5-基]乙基)-4-(4-甲氧基-苯基)-苯甲酰胺

参考实施例 1aaaq

N-(2-[1-叔丁氧羰基-3-叔丁氧羰基脒基吲哚-5-基]乙基)- (5-甲氧基吲哚-2-基)-甲酰胺

参考实施例 1aaar

N-(2-[1-叔丁氧羰基-3-叔丁氧羰基脒基吲哚-5-基]乙基)-(6-氯苯并噻吩-2-基)-甲酰胺

参考实施例 1aaas

4-(4-苄氧基-苯基)-N-(2-[1-叔丁氧羰基-3-叔丁氧羰基-脒基吲哚-5-基]乙基)-苯甲酰胺

参考实施例 1aaat

N-(2-[1-叔丁氧羰基-3-叔丁氧羰基脒基吲哚-5-基]乙基)-4-氯-苯甲酰胺

参考实施例 1aaau

N-(2-[1-叔丁氧羰基-3-叔丁氧羰基-脒基吲哚-5-基]乙基)-4-(甲磺酰基)-苯甲酰胺

参考实施例 1aaav

N-(2-[1-叔丁氧羰基-3-叔丁氧羰基-脒基吲哚-5-基]乙基)-4-(氨基磺酰基)-苯甲酰胺

参考实施例 2

3-氰基-5-(2-氨基乙基)吲哚

搅拌 1.01g (4.78 mmol) 3-氰基-5-(2-叠氮基乙基)吲哚(参考实施例 3)和 1.38g (5.26 mmol)三苯膦在 20mL THF 中的溶液过夜，产生白色沉淀物。再加入 20mL THF 和 1mL 蒸馏水。搅拌过夜后浓缩所得溶液，进而层析(10:1 CH_2Cl_2:7N NH_3/MeOH)残留物，得到 0.870g 白色固体产物，产率 98%。

^{1}H NMR (CD_3OD): δ 2.87-2.97 (4H, m), 7.17 (1H, d, J = 8 Hz), 7.45 (1H, d, J = 8 Hz), 7.50 (1H, s), 7.90 (1H, s). MS (EI) m/z 185 M^+, 169 $(M-NH_3)^+$, 155 $(M-CH_2NH_2)^+$.

参考实施例 3

3-氰基-5-(2-叠氮基乙基)吲哚

加热 1.92g (9.38mmol) 3-氰基-5-(2-氯乙基)吲哚（参考实施例 4）与 1.53g (23.5 mmol)叠氮化钠在 10mL DMF 中的混合物至 80℃反应 3 小时，然后与甲苯一起共沸。层析(2:1 己烷:乙酸乙酯)所得残留物，从而获得 1.89g 棕色固体产物，产率 95%。

^{1}H NMR ($CDCl_3$): δ 3.03 (2H, t, J = 7.1 Hz), 3.57 (2H, t, J = 7 Hz), 7.20 (1H, dd, J = 8, 1 Hz), 7.43 (1H, d, J = 8 Hz), 7.62 (1H, s), 7.73 (1H, d, J = 3 Hz), 8.81 (1H, br).

MS (离子喷雾) m/z 212 $(M+H)^+$, 169 $(M-N_3)^+$.

参考实施例 4

3-氰基-5-(2-氯乙基)吲哚

加热 3.29g (15.8 mmol) 5-(2-氯乙基)吲哚-3-甲醛（参考实施例 5）、1.15g (16.6 mmol)盐酸羟胺、6.27g (52.1 mmol)硫酸镁以及 0.601g (3.16 mmol)对-甲苯磺酸一水合物在 10mL DMF 中的混合物至 150℃持续 30 分钟。将反应混合物与甲苯一起共沸，进而层析(依次为 2:1 和 1:1 己烷:乙酸乙酯)所得残留物，从而得到 3.08g 白色固体产物，产率 95%.

^{1}H NMR ($CDCl_3$): δ 3.20 (2H, t, J = 7 Hz), 3.77 (2H, t, J = 7 Hz), 7.21 (1H, dd, J = 8, 1 Hz), 7.43 (1H, d, J = 8 Hz), 7.63 (1H, s), 7.73 (1H, d, J = 3 Hz), 8.66 (1H, br). MS (EI) m/z 204, 206 ($M[^{35}Cl, ^{37}Cl]$)$^+$, 155 ($M-CH_2Cl$)$^+$.

参考实施例 5

5-(2-氯乙基)吲哚-3-甲醛

搅拌 1.46mL (15.7 mmol)磷酰氯的 5ml DMF 溶液 20 分钟。加入 2.11g (13.1 mmol) 5-(2-羟基乙基)吲哚（参考实施例 6）的 5mL DMF 溶液，加热反应混合物到 80℃持续 10 分钟。反应通过加固体碳酸氢钠终止，然后用 250mL CH_2Cl_2:MeOH 稀释。滤除无机固体物，并浓缩滤液。将所得残留物在 75mL 1N HCl 溶液中回流 1 小时，然后用二氯甲烷提取。合并有机提取物并加以浓缩，进而层析(20:1 CH_2Cl_2: MeOH)

残留物，得到 2.45g 棕色固体产物，产率 90%. ^{1}H NMR ($CDCl_3$): δ 3.19 (2H, t, J = 7 Hz), 3.76 (2H, t, J =, 7 Hz), 7.20 (1H, dd, J = 8, 1 Hz), 7.40 (1H, d, J =8 Hz), 7.85 (1H, d, J = 3 Hz), 8.19 (1H, s), 8.98 (1H, br), 10.05 (1H, s). MS (EI) m/z 207, 209 ($M[^{35}Cl, ^{37}Cl]$)$^+$, 158 ($M-CH_2Cl$)$^+$.

参考实施例 6

5-(2-羟基乙基)吲哚

向 1.56g (38.9 mmol) 60%氢化钠分散物在 10mL THF 中的冷(0℃)混合物内缓慢加入 5.05g (25.9 mmol) 5-溴吲哚(Acros)在 20mL THF 中的溶液。待氢气逸出停止后(~10 分钟)，冷却混合物至-78℃，滴加入 25.9mL (64.8 mmol) 2.5M 正丁基锂的己烷溶液。5 分钟后，加入 16.8mL (38.9 mmol) 2.3M 环氧乙烷的 THF 储液，移去冷却浴。90 分钟后，加 5ml 蒸馏水终止反应。然后倒出有机层与无机盐分离开，进而浓缩。层析(1:1 己烷:乙酸乙酯)所得残留物，从而得到 2.24g 黄色油状产物，产率 54%。

^{1}H NMR ($CDCl_3$): δ 2.96 (2H, t, J = 6.5 Hz), 3.88 (2H, m), 6.51 (1H, m), 7.06 (1H, dd, J_1 = 8.5 Hz, J_2 = 1.5 Hz), 7.19 (1H, m), 7.33 (1H, d, J = 8.5 Hz), 7.49 (1H, s), 8.19 (1H, br). MS (EI) m/z 161 M$^+$, 130 ($M-CH_2OH$)$^+$.

参考实施例 7a

1-叔丁氧羰基-3-(叔丁氧羰基脒基)-5-(2-氨基乙基)吲哚

搅拌 1-叔丁氧羰基-3-(叔丁氧羰基脒基)-5-(2-[烯丙氧羰基氨基]乙基)吲哚(参考实施例 8) (0.199g, 0.409 mmol)、50mg 四(三苯膦)合钯(0)以及 0.078mL (0.90 mmol)吗啉在 20mL CH_2Cl_2 中的溶液 1 小时。TLC 显示还存在一些原料，因此再加入 50mg 钯催化剂。搅拌 45 分钟后，浓缩反应混合物，层析(10:1 CH_2Cl_2:7N NH_3/MeOH)残留物，得黄色固体产物。

^{1}H NMR ($CDCl_3$): δ 1.57 (9H, s), 1.64 (9H, s), 2.88 (4H, m), 7.23 (1H, dd, J_1= 8.7 Hz, J_2= 1.2 Hz), 7.77 (1H, s), 8.16 (1H, d, J = 8.7 Hz), 8.25 (1H, s). MS (EI) m/z 402 M$^+$.

参考实施例 7b

4-(1-[叔丁氧羰基甲基]-2-氧代-2H-吡啶-5-基)苯甲酸

采用和参考实施例 7a 所用基本相同的方法制备，只是其中使用 4-(1-[叔丁氧羰基甲基]-2-氧代-2H-吡啶-5-基)苯甲酸烯丙酯（参考实施例 85d）作为底物。MS （离子喷雾） m/z 330 $(M+H)^+$,

参考实施例 8

1-叔丁氧羰基-3-(叔丁氧羰基脒基)-5-(2-[烯丙氧羰基氨基]乙基)吲哚

在 40℃，搅拌 0.346g (0.999 mmol) 3-脒基-5-(2-[烯丙氧羰基氨基]乙基)吲哚(参考实施例 9)、0.655g (3.00 mmol)二碳酸二叔丁酯和 0.49mL (3.5 mmol)三乙胺在 40mL 1:1 CH_2Cl_2:THF 中的溶液 7 小时，然后室温搅拌过夜，再于 40℃搅拌 4 小时，接着进行浓缩。层析(2:1 己烷:乙酸乙酯)所得残留物，从而以 36％的收率得到白色固体产物。

^{1}H NMR ($CDCl_3$): δ 1.56 (9H, s), 1.66 (9H, s), 2.95 (2H, t, J = 6.5 Hz), 3.56 (2H, m), 4.51 (2H, d, J = 5.4 Hz), 5.21 (2H, m), 5.85 (1H, m), 7.21 (1H, d, J = 8.3 Hz), 7.76 (1H, s), 8.15 (1H, d, J = 8.3 Hz), 8.40 (1H, s).

MS （离子喷雾） m/z 487 $(M+H)^+$.

参考实施例 9

3-脒基-5-(2-[烯丙氧基羰基氨基]乙基)吲哚

向 0.392g (1.11 mmol) 1-烯丙氧基羰基-3-氰基-5-(2-[烯丙氧基羰基氨基]乙基)吲哚（参考实施例 10）在 10mL 9:1 吡啶: 三乙胺中的溶液内通硫化氢气流 15 分钟。封闭反应物，搅拌 36 小时，然后通过蒸馏除去溶剂。将残留物溶于 10mL 丙酮，加入 1.82mL 碘甲烷。在反应器上配置冷凝管，然后加热至 60℃持续 1 小时。浓缩反应物，加入 10mL MeOH 和 0.940g (12.2 mmol)。60℃搅拌此混合物 4 小时，然后室温搅拌过夜，接着浓缩并加以层析(5:1 CH_2Cl_2:MeOH)，从而得

到乙酸盐形式产物，产率 90%。

^{1}H NMR (CD_3OD): δ 1.98 (3H, s), 2.94 (2H, t, J = 7.2 Hz), 3.41 (2H, t, J = 7.2 Hz), 4.49 (2H, d, J = 4.9 Hz), 5.19 (2H, m), 5.87 (1H, m), 7.20 (1H, d, J = 8.3 Hz), 7.50 (1H, d, J = 8.3 Hz), 7.73 (1H, s), 8.14 (1H, s).

MS （离子喷雾） m/z 287 $(M+H)^+$.

该化合物也可以使用和上文所述基本相同的方法而由 3－氰基－5－（2-[烯丙氧基羰基氨基]乙基）吲哚（参考实施例 23）直接制备。

参考实施例 10

1-烯丙氧基羰基-3-氰基-5-(2-[烯丙氧基羰基氨基]乙基)吲哚

搅拌 1.89g (8.95 mmol) 3-氰基-5-(2-叠氮基乙基)-吲哚(参考实施例 3)和 2.58g (9.85 mmol)三苯膦在 40mL THF 中的溶液过夜，产生白色沉淀物。向其中加入 0.32mL 水，继续搅拌过夜。然后加入 4.75g (44.8 mmol)碳酸氢钠和 15mL 水，接着再加入 2.1mL (20 mmol) 氯甲酸烯丙酯。搅拌过夜后，加入另一份 2mL 氯甲酸烯丙酯，随后再搅拌过夜。用乙酸乙酯稀释反应混合物，然后用蒸馏水洗涤。浓缩有机层，并层析(顺序用 3:1 和 1:1 的己烷: 乙酸乙酯洗脱)所得残留物，从而获得白色固体产物，产率 61.7%。

^{1}H NMR ($CDCl_3$): δ 2.96 (2H, t, J = 7.0 Hz), 3.50 (2H, m), 4.56 (2H, d, J = 5.4 Hz), 4.97 (2H, d, J = 5.9 Hz), 5.25 (2H, m), 5.46 (2H, m), 5.91 (1H, m), 6.06 (1H, m), 7.31 (1H, d, J = 8.6 Hz), 7.54 (1H, s), 8.14 (1H, d, J = 8.6 Hz), 8.15 (1H, s).

MS (EI) m/z 353 M^+, 268 $(M-CO_2$烯丙基$)^+$.

参考实施例 11a

4-[吡啶-4-基]-苯甲酸

向 4-[吡啶-4-基]-苯甲醛(大约 2.8g, 15 mmol) (参考实施例 12a)的叔丁醇(100mL)溶液内顺序加入 2-甲基-丁-2-烯(15mL)和包含 $NaClO_2$ (14.7g, 工业级)和 $NaH_2PO_4.H_2O$ (14.7g, 105 mmol)的在水

(100mL)中形成的溶液。搅拌该混合物 20 分钟，然后滤出沉淀固体物。固体物用水洗涤，然后搁置一旁。分离母液的有机相，随后用盐水洗涤，硫酸镁干燥并浓缩，从而得到一固体物。将该固体物与过滤得到的固体物合并，经真空干燥后得 2.34g 标题化合物。

^{1}H NMR (DMSO) d 7.77 (d, J = 6Hz, 2H), 7.93 (d, J = 8Hz, 2H), 8.06 (d, J = 8Hz, 2H), 8.70 (d, J = 6Hz, 2H). MS (EI) m/z 199 $(M)^+$.

参考实施例 11b

采用和参考实施例 11a 所用基本相同的方法，只是其中使用参考实施例 12b 的产物，从而制得 4-[吡啶-3-基]-苯甲酸。

^{1}H NMR (DMSO) d 7.52 (dd, J = 8, 5Hz, 1H), 7.87 (d, J = 8Hz, 2H), 8.06 (d, J = 8Hz, 2H), 8.15 (dd, J = 8, 2Hz, 1H), 8.62 (dd, J = 5, 2Hz, 1H), 8.96 (s, 1H), 13.05 (bs, 1H). MS (EI) m/z 199 $(M)^+$.

参考实施例 11c

采用和参考实施例 11a 所用基本相同的方法，只是其中使用参考实施例 12c 的产物，从而制得 4-[嘧啶-5-基]-苯甲酸。

^{1}H NMR (DMSO) d 7.95 (d, J = 8Hz, 2H), 8.10 (d, J = 8Hz, 2H), 9.23 (s, 2H), 9.25 (s, 1H), MS (EI) m/z 200 $(M)^+$.

参考实施例 11d

采用和参考实施例 11a 所用基本相同的方法，只是其中使用参考实施例 12d 的产物，从而制得 4-[哒嗪-3-基]-苯甲酸。

^{1}H NMR (DMSO) d 7.85 (dd, J = 8, 4Hz. 1H), 8.1 (d, J = 8Hz, 2H), 8.29 (d, J = 8Hz, 2H), 8.31 (d, J = 8Hz, 1H), 9.26 (d, J = 4Hz, 1H). MS (EI) m/z 200 $(M)^+$.

参考实施例 11e

采用和参考实施例 11a 所用基本相同的方法，只是其中使用参考实施例 12e 的产物，从而制得 4-[哒嗪-4-基]-苯甲酸。

^{1}H NMR (DMSO) d 8.10 (m, 5H), 9.33 (d, J = 4Hz, 1H), 9.67 (bs, 1H). MS (EI) m/z 200 $(M)^+$.

参考实施例 11f

采用和参考实施例 11a 所用基本相同的方法，只是其中使用参考实施例 12f 的产物，从而制得 4-(6-甲氧基-哒嗪-3-基)-苯甲酸。 ^{1}H NMR (DMSO) δ 4.10 (s, 3H), 7.36 (d, J = 9Hz, 1H), 8.08 (d, J = 8Hz, 2H), 8.20 (d, J = 8Hz, 2H), 8.26 (d, J = 9Hz, 1H), 13.00 (bs, 1H). MS (EI) m/z 230 (M^+).

参考实施例 11g

采用和参考实施例 11a 所用基本相同的方法，只是其中使用参考实施例 12g 的产物，从而制得 4-[2-氯-嘧啶-4-基]-苯甲酸。

^{1}H NMR (DMSO)

δ 8.09 (d, J = 8Hz, 2H), 8.21 (d, J = 5Hz, 1H), 8.30 (d, J = 8Hz, 2H), 8.88 (d, J = 5Hz, 1H).

MS (EI) m/z 234/236 (M^+, Cl 图案).

参考实施例 11h

采用和参考实施例 11a 所用基本相同的方法，只是其中使用参考实施例 97a 的产物，从而制得 4-[2-氧代-嘧啶-4-基]-苯甲酸。

^{1}H NMR (DMSO) δ

7.77 (d, J = 8Hz, 2H), 7.97 (d, J = 8Hz, 1H), 8.70 (bs, 2H). MS (EI) m/z 216 $(M)^+$.

参考实施例 11i

采用和参考实施例 11a 所用基本相同的方法，只是其中使用参考实施例 97b 的产物，从而制得联苯-3,4′-二羧酸 3-甲基酯。 ^{1}H NMR (DMSO) δ 3.90 (s, 3H), 7.69 (t, J = 8Hz, 2H), 7.86 (d, J = 8Hz, 2H), 8.0-8.11 (m, 4H), 8.25 (s, 1H). MS (EI) m/z 256 $(M)^+$.

参考实施例 11j

采用和参考实施例 11a 所用基本相同的方法，只是其中使用参考

实施例 97c 的产物，从而制得联苯-2,4′-二羧酸 2-甲基酯。

^{1}H NMR ($CDCl_3$) δ 3.68 (s, 3H), 7.47-7.51 (m, 5H), 8.19 (d, J = 8Hz, 1H). MS (EI) m/z 256 $(M)^+$.

参考实施例 12a

4-[吡啶-4-基]-苯甲醛

向草酰氯的二氯甲烷冷溶液(15mL, 1M, -78℃)内滴加入 DMSO (3mL)。搅拌所得溶液 5 分钟，然后滴加入 4-[吡啶-4-基]-苄醇(2.80g, 15 mmol) (参考实施例 13a)在 CH_2Cl_2/DMSO (27mL, 3:1 CH_2Cl_2/DMSO)中的溶液。搅拌所得混合物 5 分钟，然后一次性加入 15mL(108 mmol)三乙胺。移去冷却浴，继续搅拌 15 分钟。然后用乙酸乙酯稀释反应混合物，用水及盐水顺序洗涤，硫酸镁干燥并浓缩。所得橙色固体粗产物无需进一步纯化而直接使用。

参考实施例 12b

采用和参考实施例 12a 所用基本相同的方法，只是其中使用参考实施例 13b 的产物，从而制得 4-[吡啶-3-基]-苯甲醛。

参考实施例 12c

采用和参考实施例 12a 所用基本相同的方法，只是其中使用参考实施例 13c 的产物，从而制得 4-[嘧啶-5-基]-苯甲醛。

参考实施例 12d

采用和参考实施例 12a 所用基本相同的方法，只是其中使用参考实施例 14a 的产物，从而制得 4-[哒嗪-3-基]-苯甲醛。

参考实施例 12e

采用和参考实施例 12a 所用基本相同的方法，只是其中使用参考实施例 14b 的产物，从而制得 4-[哒嗪-4-基]-苯甲醛。

参考实施例 12f

采用和参考实施例 12a 所用基本相同的方法，只是其中使用参考实施例 13d 的产物，从而制得 4-(6-甲氧基-哒嗪-3-基)-苯甲醛。

^{1}H NMR

($CDCl_3$) δ 4.22 (s, 3H), 7.10 (d, J = 9Hz, 1H), 7.86 (d, J = 9Hz, 1H), 8.02 (d, J = 8Hz, 2H), 8.20 (d, J = 8Hz, 2H), 10.10 (s, 1H). MS (EI) m/z 214 (M^+).

参考实施例 12g

采用和参考实施例 12a 所用基本相同的方法，只是其中使用参考实施例 14c 的产物，从而制得 4-[2-(2-氯)-嘧啶-4-基]-苯甲醛。

^{1}H NMR

(DMSO) δ 8.10 (d, J = 8Hz, 2H), 8.29 (d, J = 5Hz, 1H), 8.41 (d, J = 8Hz, 2H), 8.94 (d, J = 5Hz, 1H), 10.13 (s, 1H).

MS (EI) m/z 218/220 (M^+, Cl 图案).

参考实施例 13a

4-[吡啶-4-基]-苄醇

向 4-溴-苄基-(叔丁基二甲基甲硅烷基)-醚(5.46g, 18 mmol) (参考实施例 16)的 THF(40mL)冷(-78℃)溶液内滴加入 n-BuLi (8.8 mL, 2.5M 己烷溶液)。加毕后，搅拌所得溶液 10 分钟，然后加入 $ZnCl_2$ (40mL, 0.5M THF 溶液)。移去冷却浴，继续搅拌 10 分钟。向此溶液内顺序加入 4-溴-吡啶* (大约 2.2mL, 22mmol)的己烷(25mL)溶液和 $(Ph_3P)_4Pd$ (900mg, 0.77 mmol)。加热所得混合物至 60℃，并在这一温度下搅拌 1 小时。然后冷却混合物至室温，加乙醚稀释，顺序用 5%氢氧化铵水溶液和盐水洗涤，硫酸镁干燥并浓缩。残留物溶于 THF(30mL)，用 $n\text{-}Bu_4NF$ (25mL, 1M THF 溶液)处理。搅拌所得溶液 25 分钟，然后加乙酸乙酯稀释，用水和盐水洗涤，硫酸镁干燥并浓缩。残留物进而用乙醚研制，过滤，并将固体物在真空下干燥，从而得到 2.8g 褐色固体产物。

*4-溴-吡啶按下所述由其盐酸盐制备：将所述盐溶于 1M NaOH 冷溶液内(过量 5%)，然后用冷己烷提取。己烷提取物用硫酸镁干燥后直接使用，无需进一步处理。

参考实施例 13b

采用和参考实施例 13a 所用基本相同的方法，只是其中使用 3-溴吡啶，从而制得 4-[吡啶-3-基]-苄醇。

^{1}H NMR (DMSO) d 4.55 (d, J = 6 Hz, 2H), 5.25 (t, J = 6Hz, 1H), 7.44 (d, J = 8Hz, 2H), 7.48 (dd, J = 8, 5Hz, 1H), 7.68 (d, J = 8Hz, 2H), 8.07 (dt, J = 8, 2Hz, 1H), 8.56 (dd, J = 5, 2Hz, 1H), 8.88 (d, J = 2Hz, 1H). MS (EI) m/z 185 $(M)^+$.

参考实施例 13c

采用和参考实施例 13a 所用基本相同的方法，只是其中使用 5-溴嘧啶，从而制得 4-[嘧啶-5-基]-苄醇。 ^{1}H NMR ($CDCl_3$) d 2.61 (bs, 1H), 4.80 (d, J = 7Hz, 2H), 7.55 (m, 4H), 8.88 (s, 2H), 9.20 (s, 1H). MS (EI) m/z 186 $(M)^+$.

参考实施例 13d

采用和参考实施例 13a 所用基本相同的方法，只是其中使用参考实施例 41b 的产物，从而制得 4-(6-甲氧基-哒嗪-3-基)-苄醇。^{1}H NMR ($CDCl_3$) δ 1.85 (bt, 1H), 4.19 (s, 3H), 4.78 (d, J = 5Hz, 2H), 7.06 (d, J = 9Hz, 1H), 7.50 (d, J = 8Hz, 2H), 7.78 (d, J = 9Hz, 1H), 8.01 (d, J = 8Hz, 2H). MS (EI) m/z 216 (M^+).

参考实施例 14a

4-[哒嗪-3-基]-苄醇

向 4-[哒嗪-3-基]-苄基-(叔丁基二甲基甲硅烷基)醚(2.71g, 9 mmol) (参考实施例 15,极性较低的产物)的溶液中加入氟化四正丁基铵的 THF 溶液(12mL, 1M)。搅拌所得溶液 15 分钟，然后用乙酸乙酯稀释。该溶液依次用水和盐水洗涤。水洗涤物再用 10%甲醇/二氯甲烷反

提取。用硫酸镁干燥合并的有机提取物，然后浓缩。残留物进而通过快速色谱纯化（以乙酸乙酯洗脱），得 1.50g 白色固体标题化合物。^{1}H NMR ($CDCl_3$) d 2.28 (t, J = 5Hz, 1H), 4.79 (d, J = 5Hz, 2H), 7.50 (m, 3H), 7.85 (dd, J = 8, 1 Hz, 1H), 8.05 (d, J = 8 Hz, 2H), 9.13 (dd, J = 5, 1Hz, 1) MS (EI) m/z 186 $(M)^+$.

参考实施例 14b

采用和参考实施例 14a 所用基本相同的方法，只是其中使用参考实施例 15 中的极性较高的产物，从而制得 4-[哒嗪-4-基]-苄醇。^{1}H NMR ($CDCl_3$) d 2.20 (t, J = 6Hz, 1H), 4.79 (d, J = 6 Hz, 2H), 7.53 (d, J = 8Hz, 2H), 7.63 (m, 3H), 9.18 (d, J = 4Hz, 1H), 9.42 (bs, 1H). MS (EI) m/z 186 $(M)^+$.

参考实施例 14c

采用和参考实施例 14a 所用基本相同的方法，只是其中使用参考实施例 84 的产物，从而制得 4-[2-(2-氯)-嘧啶-4-基]-苄醇。^{1}H NMR (DMSO) d 4.57 (d, J = 5Hz, 2H), 5.34 (t, J = 5Hz, 1H), 7.49 (d, J = 8Hz, 2H), 8.14 (m, 3H), 8.79 (d, J = 5Hz, 1H),

MS (EI) m/z 220/222 (M^+, Cl 图案)

参考实施例 15

4-[哒嗪-3-基]-苄基-(叔丁基二甲基甲硅烷基)醚和 4-[哒嗪-4-基]-苄基-(叔丁基二甲基甲硅烷基)醚

向 4-溴苄基(叔丁基二甲基甲硅烷基)醚(9.03g, 30 mmol)（参考实施例 16)的 THF (60mL)冷(-78℃)溶液内滴加入 n-BuLi (12.6mL, 2.5M 己烷溶液)。搅拌所得溶液 5 分钟，然后一次性加入 2.25mL (31 mmol)哒嗪。搅拌该溶液 20 分钟，随后加入盐酸水溶液(30mL, 1M)。加乙醚稀释反应混合物，用盐水洗涤，硫酸镁干燥后浓缩。将残留物溶于丙酮(45mL)，并将该溶液加到 $KMnO_4$ 的丙酮溶液内(9.3g, 60 mmol, 溶在大约 200mL 丙酮中)。一旦加毕后，搅拌棕色混合物 5 分钟，尔后通过硅藻土过滤。浓缩母液，残留物进而通过快速色谱纯化（以 50%

乙酸乙酯/己烷洗脱），得 2.71g 4-[哒嗪-3-基]-苄基-(叔丁基二甲基甲硅烷基)醚:

^{1}H NMR ($CDCl_3$) d 0.12 (s, 6H), 0.99 (s, 9H), 4.83 (s, 2H), 7.50 (d, J = 8Hz, 2H), 7.53 (dd, J = 8, 5 Hz, 1H), 7.85 (dd, J = 8, 1Hz, 1H), 8.06 (d, J = 8Hz, 2H), 9.14 (dd, J = 5, 1Hz, 1H). MS (EI) m/z 301 $(M+H)^+$

和 2.0g 4-[哒嗪-4-基]-苄基-(叔丁基二甲基甲硅烷基)醚:

^{1}H NMR ($CDCl_3$) d 0.11 (s, 6H), 0.96 (s, 9H), 4.80 (s, 2H), 7.47 (d, J = 8Hz, 2H), 7.63 (m, 3H), 9.20 (d, J = 4Hz, 1H), 9.45 (bs, 1H). MS (EI) m/z 301 $(M+H)^+$.

参考实施例 16

4-溴苄基-(叔丁基二甲基甲硅烷基)-醚

向 4-溴-苄醇(3.74g, 20 mmol)的乙醚(80mL)冷(0℃)溶液内顺序加入 2,6-二甲基吡啶(2.6mL, 22 mmol)和叔丁基二甲基甲硅烷基三氟甲磺酸酯(5.05mL, 22 mmol)。搅拌所得混合物 40 分钟，然后加乙醚稀释，用水及盐水顺序洗涤，硫酸镁干燥并浓缩。残留物通过快速色谱纯化（以 5%乙醚/己烷洗脱），得 6.0g 油状标题化合物。

^{1}H NMR ($CDCl_3$) d 0.09 (s, 6H), 0.93 (s, 9H), 4.68 (s, 2H), 7.18 (d, J = 8Hz, 2H), 7.44 (d, J = 8Hz, 2H). MS (EI) m/z 300 $(M)^+$.

参考实施例 17a

4-[吡啶-N-氧化物-4-基]-苯甲酸

搅拌 0.940g 4-[吡啶-N-氧化物-4-基]-苯甲酸甲酯（参考实施例 18）(4.10mmol)与 6mL 1N NaOH 和 20mL 1:1 THF:CH_3OH。18 小时后再加入 3mL NaOH 溶液。再经过 24 小时后用 1N HCl 加以酸化。过滤收集产生的白色固体物。水洗，风干。该产物直接使用无需进一步纯化。MS(EI) m/z 215 (M^+), 171 $(M-CO_2)^+$.

参考实施例 17b

采用和参考实施例 17a 所用基本相同的方法，只是其中使用 4-(2-

甲氧基-嘧啶-4-基)苯甲酸甲酯(参考实施例 19b)，从而制得 4-(2-甲氧基-嘧啶-4-基)-苯甲酸。

^{1}H NMR (DMSO) d 3.99 (s, 3H), 7.78 (d, J = 5Hz, 1H), 8.06 (d, J = 8Hz, 2H), 8.27 (d, J = 8Hz, 2H), 8.70 (d, J = 5Hz, 1H). MS (EI) m/z 230 (M+).

参考实施例 17c

采用和参考实施例 17a 所用基本相同的方法，只是其中使用 4-(1-[2-二甲氨基乙基]-6-氧代-1,6-二氢吡啶-3-基)苯甲酸乙酯(参考实施例 85a)，从而制得 4-(1-[2-二甲氨基乙基]-6-氧代-1,6-二氢吡啶-3-基)-苯甲酸。通过 HPLC 纯化，分离得到其 TFA 盐。

^{1}H NMR (D_2O): δ 2.86 (6H, s), 3.47 (2H, m), 4.34 (2H, m), 6.62 (1H, d, J = 8.6 Hz), 7.50 (2H, d, J = 8.4 Hz), 7.82-7.91 (4H, m).

MS (离子喷雾) m/z 287 $(M+H)^+$.

参考实施例 17d

采用与制备参考实施例 17a 所用基本相同的方法，只是其中使用 4-(1-氨基甲酰基甲基-6-氧代-1,6-二氢吡啶-3-基)苯甲酸乙酯(参考实施例 1av)，从而制得 4-(1-氨基甲酰基甲基-6-氧代-1,6-二氢吡啶-3-基)-苯甲酸。MS (离子喷雾) m/z 273 $(M+H)^+$.

参考实施例 17e

采用与制备参考实施例 17a 所用基本相同的方法，只是其中使用 4-(6-[2-二甲氨基乙氧基]-吡啶-3-基)苯甲酸乙酯(参考实施例 85a)，从而制得 4-(6-[2-二甲氨基乙氧基]-吡啶-3-基)-苯甲酸。通过 HPLC 纯化，分离得到其 TFA 盐。

^{1}H NMR (D_2O): δ 2.84 (6H, s), 3.48 (2H, m), 4.44 (2H, m), 6.81 (1H, d, J = 8.6 Hz), 7.50 (2H, d, J = 8.2 Hz), 7.85 (2H, d, J = 8.2 Hz), 7.88 (1H, m), 8.18 (1H, s).

MS (离子喷雾) m/z 287 $(M+H)^+$.

参考实施例 17f

采用与制备参考实施例 17a 所用基本相同的方法，只是其中使用 4-(2-氧代-六氢-嘧啶-5-基)苯甲酸甲酯作为底物(参考实施例 95)，从而制得 4-(2-氧代-六氢-嘧啶-5-基)-苯甲酸。

^{1}H NMR (DMSO) δ 3.15 (m, 1H), 3.4 (m, 4H), 6.33 (bs, 2H), 7.45 (d, J = 8Hz, 2H), 7.90 (d, J = 8Hz, 2H).

参考实施例 17g

采用与制备参考实施例 17a 所用基本相同的方法，只是其中使用 4-(1,3-二甲基-2-氧代-六氢-嘧啶-5-基)苯甲酸甲酯作为底物(参考实施例 98)，从而制得 4-(1,3-二甲基-2-氧代-六氢-嘧啶-5-基)-苯甲酸。 MS (离子喷雾) m/z 249 $(M+H)^+$.

参考实施例 17h

采用与制备参考实施例 17a 所用基本相同的方法，只是其中使用联苯-3,4′-二羧酸 4′-{[2-(3-氯基-1H-吲哚-5-基)-乙基]-酰胺}3-甲基酯作为底物(参考实施例 1aac)，从而制得联苯-3,4′-二羧酸 4′-{[2-(3-氯基-1H-吲哚-5-基)-乙基]-酰胺}. MS (Cl) m/z 410 $(M+H)^+$.

参考实施例 17i

采用与制备参考实施例 17a 所用基本相同的方法，只是其中使用联苯-2,4′-二羧酸 4′-{[2-(3-氯基-1H-吲哚-5-基)-乙基]-酰胺}2-甲基酯作为底物(参考实施例 1aad)，从而制得联苯-2,4′-二羧酸 4′-{[2-(3-氯基-1H-吲哚-5-基)-乙基]-酰胺}. MS (离子喷雾) m/z 410 $(M+H)^+$.

参考实施例 17j

采用与制备参考实施例 17a 所用基本相同的方法，只是其中使用

4-[2-(乙酰氨基-甲基)-吡啶-4-基]-苯甲酸甲酯作为底物(参考实施例 102b)，从而制得 4-[2-(乙酰氨基-甲基)-吡啶-4-基]-苯甲酸。MS (离子喷雾) m/z 271 $(M+H)^+$.

参考实施例 17k

采用与制备参考实施例 17a 所用基本相同的方法，只是其中使用 4-[[4-(4-甲氧羰基-苯基)-吡啶-2-基甲基]-氨基甲酰基]-哌啶-1-羧酸叔丁酯作为底物(参考实施例 102a)，从而制得 4-[[4-(4-羧基-苯基)-吡啶-2-基甲基]-氨基甲酰基]-哌啶-1-羧酸叔丁酯。MS (离子喷雾) m/z 440 $(M+H)^+$.

参考实施例 17l

采用与制备参考实施例 17a 所用基本相同的方法，只是其中使用 4-[1-(3-二甲氨基丙基)-6-氧代-1,6-二氢吡啶-3-基]-苯甲酸乙酯(参考实施例 85c)作为底物，从而制得 4-[1-(3-二甲氨基丙基)-6-氧代-1,6-二氢吡啶-3-基]-苯甲酸。MS (离子喷雾) m/z 301 $(M+H)^+$.

参考实施例 17m

采用与制备参考实施例 17a 所用基本相同的方法，只是其中使用 4-[6-(3-二甲氨基丙氧基)-吡啶-3-基]-苯甲酸乙酯(参考实施例 85c)作为底物，从而制得 4-[6-(3-二甲氨基丙氧基)-吡啶-3-基]-苯甲酸。MS (离子喷雾) m/z 301 $(M+H)^+$.

参考实施例 17n

采用与制备参考实施例 17a 所用基本相同的方法，只是其中使用 4-{1-[(2-二甲氨基乙基氨基甲酰基)甲基]-6-氧代-1,6-二氢吡啶-3-基}-苯甲酸乙酯(参考实施例 1aar)作为底物，从而制得 4-{1-[(2-二甲氨基乙基氨基甲酰基)甲基]-6-氧代-1,6-二氢吡啶-3-基}-苯甲酸。MS (离子喷雾) m/z 344 $(M+H)^+$.

参考实施例 17o

采用与制备参考实施例 17a 所用基本相同的方法，只是其中使用 4-(1-甲基-哌啶-4-基氧基)-苯甲酸甲酯(参考实施例 114d)作为底物，从而制得 4-(1-甲基-哌啶-4-基氧基)-苯甲酸。

参考实施例 17p

采用与制备参考实施例 17a 所用基本相同的方法，只是其中使用 4-(1-甲磺酰基-哌啶-4-基)-苯甲酸甲酯(参考实施例 126)作为底物，并且通过反相 HPLC 加以纯化，从而制得 4-(1-甲磺酰基-哌啶-4-基)-苯甲酸。

^{1}H NMR (DMSO): d 7.88 (d, 2H), 7.40 (d, 2H), 3.68 (d, 2H), 2.91 (s, 3H), 2.70-2.85 (m, 3H), 1.84-1.93 (m, 2H), 1.68 (dq, 2H).

参考实施例 18

4-[吡啶-N-氧化物-4-基]-苯甲酸甲酯

向 4-[吡啶-4-基]-苯甲酸甲酯(2.1g, 10 mmol)（参考实施例 19a）的二氯甲烷(41mL)冷(0℃)溶液内加入 m-CPBA (3.4g, 50-60%工业级, 10 mmol)。搅拌所得溶液 1 小时，然后加入另一份 m-CPBA (1.7g, 5 mmol)。搅拌此溶液 1 小时（温度介于 5-10℃之间），随后将反应混合物直接倒入硅胶柱上。以 10% MeoH/40% EtOAc/50% CH_2Cl_2 洗脱，得 2.0g 褐色固体标题化合物。

^{1}H NMR (CD_3OD) d 3.94 (s, 3H), 7.90 (m, 4H), 8.14 (d, J = 8.5 Hz, 2H), 8.39 (d, J = 7Hz, 2H). MS (EI) m/z 230 $(M)^+$.

参考实施例 19a

4-[吡啶-4-基]-苯甲酸甲酯

向 4-[吡啶-4-基]-苯甲酸(2.0g, 10 mmol)（参考实施例 11a）的甲醇(30mL)内加入浓硫酸(4mL)。温热所得溶液至 60℃，并在此温度

下搅拌 2.5 小时。然后冷却反应混合物至室温，倒入冰中。用 10M NaOH 溶液调节所得溶液的 pH 至 7。产物然后提取到乙酸乙酯内。该溶液用盐水洗涤，硫酸镁干燥并浓缩，从而得到 2.1g 白色固体标题化合物。

^{1}H NMR ($CDCl_3$) d 3.94 (s, 3H), 7.50 (d, J = 5Hz, 2H), 7.69 (d, J = 8Hz, 2H), 8.13 (d, J = 5Hz, 2H) 8.68 (d, J = 5Hz, 2H). MS (EI) m/z 213 $(M)^+$.

参考实施例 19b

采用与制备参考实施例 19a 所用基本相同的方法，只是其中使用 4-(2-氯-嘧啶-4-基)-苯甲酸(参考实施例 11g)，从而制得 4-(2-甲氧基-嘧啶-4-基)-苯甲酸甲酯。

^{1}H NMR ($CDCl_3$) 3.93 (s, 3H), 4.09 (s, 3H), 7.39 (d, J = 5Hz, 1H), 8.13 (d, J = 8Hz, 2H), 8.16 (d, J = 8Hz, 2H), 8.59 (d, J = 5Hz, 1H). MS (EI) m/z 244 (M+).

参考实施例 19c

4-(2-氧代-嘧啶-5-基)-苯甲酸甲酯

采用与制备参考实施例 19a 所用基本相同的方法，只是其中使用 4-(2-氧代-嘧啶-5-基)-苯甲酸(参考实施例 1h)作为底物。

^{1}H NMR (CD_3OD) 3.28 (m, 1H), 3.47 (d, J = 7Hz, 4H), 3.90 (s, 3H), 7.44 (d, J = 8Hz, 2H), 7.90 (d, J = 8Hz, 2H).

参考实施例 20

[3-(4-呋喃-2-基-苯基)-3-甲基-丁基]-氨基甲酸叔丁酯

向 2-[4-(3-叠氮基-1,1-二甲基-丙基)-苯基]-呋喃(1.06g, 4.2 mmol) (参考实施例 21)的 THF (14mL)溶液内加入三苯膦(1.21g, 4.6 mmol)，搅拌所得溶液 5 小时，然后加入水(151μl, 8.4 mmol)，搅拌 3 小时。向溶液中加入二碳酸二叔丁酯(3.7g, 16.8 mmol)，搅拌 16 小时，然后浓缩。残留物通过快速色谱纯化(以 15%乙酸乙酯/己烷洗脱)，得 1.17g 无色油状标题化合物。 ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 6H), 1.39 (s, 9H), 1.83 (m, 2H), 2.92 (m, 2H), 4.27 (bs, 1H), 6.46 (m, 1H), 6.61 (d, J = 3Hz, 1H), 7.34 (d, J = 9Hz, 2H), 7.45 (d, J = 2Hz, 1H), 7.60 (d, J = 9Hz, 2H).

MS（离子喷雾）m/z 330 $(M+H)^+$.

参考实施例 21

2-[4-(3-叠氮基-1,1-二甲基-丙基)-苯基]-呋喃

向 3-（4-呋喃-2-基-苯基）-3-甲基-丁-1-醇(1.2g, 5.2 mmol)（参考实施例 22)的二氯甲烷(17mL)冰冷(0℃)溶液内加入三乙胺(0.86mL, 6.2 mmol)、对-甲苯磺酰氯(1.18g, 6.2 mmol)和 4-二甲氨基吡啶(305mg, 2.5 mmol)。温热所得溶液至 20℃，搅拌 1.5 小时。然后加乙酸乙酯稀释，用水和盐水洗涤，硫酸镁干燥并浓缩。将残留物溶于 DMF (17mL)，加入叠氮化钠(845mg, 13 mmol)，加热混合物至 60℃，搅拌 3 小时。冷却混合物至 20℃，然后加乙酸乙酯稀释，用水和盐水洗涤，硫酸镁干燥并浓缩。残留物进而通过快速色谱纯化（以 10%乙酸乙酯/己烷洗脱），得 1.06g 无色油状标题化合物。

^{1}H NMR ($CDCl_3$) δ 1.36 (s, 6H), 1.95 (t, J = 8Hz, 2H), 3.03 (t, J = 8Hz, 2H), 6.46 (m, 1H), 6.62 (m, 1H), 7.34 (d, J = 8Hz, 2H), 7.46 (d, J = 2Hz, 1H), 7.62 (d, J = 8Hz, 2H).

MS（离子喷雾）m/z 256 $(M+H)^+$.

参考实施例 22

3-(4-呋喃-2-基-苯基)-3-甲基-丁-1-醇

向 2-[4-(1,1-二甲基-烯丙基)-苯基]-呋喃(424mg, 2 mmol)（参考实施例 51)的 THF (4mL)冰冷(0℃)溶液内滴加入(1M)硼烷-THF 复合物(2.2mL, 2.2 mmol)，搅拌所得混合物 1 小时。向此混合物中加入 10% NaOH (1.5mL)和 30wt% H_2O_2 (1.5mL)，搅拌 1 小时，同时温热至 20℃。混合物用乙醚稀释，接着用水和盐水洗涤，硫酸镁干燥并浓缩。残留物进而通过快速色谱纯化（以 25%乙酸乙酯/己烷洗脱），得 341mg 标题化合物。

^{1}H NMR ($CDCl_3$) δ 1.34 (s, 6H), 1.40 (m, 1H), 1.94 (t, J = 8Hz, 2H), 3.48 (t, J = 8Hz, 2H), 6.45 (m, 1H), 6.60 (m, 1H), 7.35 (d, J = 8Hz, 2H), 7.44 (bs, 1H), 6.61 (d, J = 8Hz, 2H). MS (EI) m/z 230 (M+).

参考实施例 23

3-氰基-5-(2-[烯丙氧基-羰基-氨基]-乙基)吲哚

向 5-(2-氨基-乙基)-3-氰基-吲哚(参考实施例 2) (925mg, 5 mmol)在 CH_2Cl_2/THF (20mL, 1/1)中的悬浮液内加入 N,N-二异丙基乙胺(869mL, 5 mmol), 接着再加入碳酸烯丙基-1-苯并三唑基酯(1.096g, 5 mmol)。搅拌所得混合物 25 分钟, 然后浓缩。残留物进而通过快速色谱纯化(以 7% MeOH/CH_2Cl_2 洗脱), 得 1.27g 白色固体产物。

^{1}H NMR ($CDCl_3$) d 2.92 (t, J = 7Hz, 2H), 3.50 (q, J = 7Hz, 2H), 4.53 (d, J = 5Hz, 2H), 4.79 (bs, 1H), 5.18 (d, J = 10 Hz, 1H), 5.26 (d, J = 17Hz, 1H), 5.87 (m, 1H), 7.10 (dd, J = 8,1 Hz, 1H), 7.34 (d, J = 8Hz, 1H), 7.54 (s, 1H), 7.67 (d, J = 1Hz, 1H), 9.08 (bs, 1H). MS (EI) m/z 269 (M+).

参考实施例 24a

6-吗啉-4-基-烟酸

120℃搅拌 2.00g (12.7 mmol) 6-氯烟酸与 1.1mL (12.7 mmol) 吗啉的混合物 6 小时。冷却之后, 快速层析反应混合物(依次用 5:1 和 3:1 的二氯甲烷: 大约 7N NH_3/MeOH 洗脱), 得 0.419g 褐色固体产物。其中混有两种起始原料。该产物直接使用无需进一步纯化。MS (离子喷雾) m/z 209 $(M+H)^+$.

参考实施例 24b

4-(5-2[-{3-氰基吲哚-5-基}乙基氨基甲酰基]吡啶-2-基)哌嗪-1-羧酸乙酯

采用和参考实施例 24a 所用基本相同的方法进行制备, 只是其中使用 N-(2-[3-氰基吲哚-5-基]乙基)-6-氯烟酰胺(参考实施例 1e)。

^{1}H NMR (5:1 $CDCl_3$: CD_3OD): δ 1.30 (3H, t, J = 7.1 Hz), 3.04 (2H, t, J = 7.2 Hz), 3.58-3.73 (10H, m), 4.17 (2H, q, J = 7.1 Hz), 6.68 (1H, d, J= 9.0 Hz), 7.20 (1H, d, J = 8.3 Hz), 7.43 (1H, d, J = 8.3 Hz), 7.58 (1H, s), 7.91 (1H, d, J = 9.0 Hz), 7.98 (1H, s), 8.50 (1H, d, J = 2.4 Hz).

MS (离子喷雾) m/z 447 $(M+H)^+$.

参考实施例 24c

6-(2-羟基乙基氨基)烟酸

采用和参考实施例 24a 所用基本相同的方法进行制备，只是其中使用 2-氨基-乙醇。 ^{1}H NMR (CD_3OD): δ 3.47 (2H, m), 3.72 (2H, m), 6.53 (1H, d, J = 9.3 Hz), 7.92 (1H, d, J = 9.3 Hz), 8.58 (1H, s).

MS （离子喷雾） m/z 183 $(M+H)^+$.

参考实施例 25a

2-(4-(羧基)-苯基)-2-甲基-丙酰胺

向 2-(4-(呋喃-2-基)苯基)-2-甲基丙酰胺(参考实施例 26) (124mg, 0.5 mmol)在 $CH_3CN/CCl_4/H_2O$ (7mL, 2/2/3)中的溶液内顺序加入 $NaIO_4$ (420mg, 2 mmol)和 $RuCl_3(H_2O)$ (3mg)。剧烈搅拌所得混合物 1.5 小时，然后加乙酸乙酯稀释，用水和盐水洗涤，硫酸镁干燥并浓缩，从而得到 100mg 橙色固体标题化合物。

^{1}H NMR (CD_3OD) d 1.58 (s, 6H), 7.50 (d, J = 8Hz, 2H), 7.98 (d, J = 8Hz, 2H). MS (EI) m/z 208 (M+H).

应用与上所述述基本相同的方法，只是其中使用指定的呋喃衍生物，制备参考实施例 25b。

N-(2-甲氧基-乙基)-2-(4-(羧基)-苯基)-2-甲基-丙酰胺. 使用参考实施例 27 的产物。

^{1}H NMR (CD_3OD) d 1.58 (s, 6H), 3.29 (s, 3H), 3.36 (m, 4H), 6.24 (bs, 1H), 7.45 (m, 2H), 8.05 (m, 2H). MS (EI) m/z 266 (M+).

参考实施例 25c

4-(2-[N-叔丁氧羰基-氨基]-1,1-二甲基-乙基)-苯甲酸. 使用参考实施例 29 的产物。

^{1}H NMR ($CDCl_3$) d 1.30 (s, 6H), 1.38 (s, 9H), 3.26 (bs, 1H), 3.33 (d, J = 6Hz, 2H), 7.44 (d, J = 8Hz, 2H), 8.05 (d, J = 8Hz, 2H).

参考实施例 25d

4-(3-叔丁氧羰基氨基-1,1-二甲基-丙基)-苯甲酸. 使用参考实施例 20 的产物。

^{1}H NMR (DMSO) δ 1.25 (s, 6H), 1.36 (s, 9H), 1.75 (m, 2H), 2.65 (m, 2H), 6.66 (bt, 1H), 7.47 (d, J = 8Hz, 2H), 7.88 (d, J = 8Hz, 2H), 12.79 (bs, 1H). MS (EI) m/z 308 $(M+H)^+$.

参考实施例 26

2-(4-(呋喃-2-基)-苯基)-2-甲基-丙酰胺

向 2-(4-呋喃-2-基)-苯基)-2-甲基丙酸(参考实施例 28) (115mg, 0.5 mmol)的二氯甲烷(3mL)溶液内顺序加入 DMF (10mL)和草酰氯(0.3mL, 2M 二氯甲烷溶液)。搅拌所得溶液 2.5 小时, 然后浓缩。残留物溶于氨的甲醇溶液(7N), 搅拌 14.5 小时, 然后浓缩得到 124mg 褐色固体标题化合物。

^{1}H NMR ($CDCl_3$) d 1.58 (s, 6H), 5.2 (bs, 1H), 5.3 (bs, 1H), 6.45 (dd, J = 3, 1Hz, 1H), 6.63 (m, 1H), 7.39 (m, 2H), 7.45 (bs, 1H), 7.65 (m, 2H). MS (EI), m/z 229 (M+).

参考实施例 27

N-(2-甲氧基-乙基)-2-(4-(呋喃-2-基)-苯基)-2-甲基-丙酰胺

向 2-(4-(呋喃-2-基)-苯基)-2-甲基-丙酸(参考实施例 28) (344mg, 1.5 mmol)的二氯甲烷(4mL)溶液内顺序加入 TBTU (528mg, 1.65 mmol)和二异丙基乙胺(280mL, 1.6 mmol)。搅拌所得混合物 2 小时, 然后再加入另一份 DIEA (280mL)和 2-甲氧基-乙胺(225mL, 2.6 mmol)。搅拌所得溶液 90 分钟, 然后浓缩。残留物进而通过快速色谱纯化(以 10% CH_2Cl_2/50%乙酸乙酯/己烷洗脱), 得 380mg 白色固体产物。

^{1}H NMR (CD_3OD) d 1.58 (s, 6H), 3.24 (s, 3H), 3.36 (m, 4H), 5.58 (bs, 1H), 6.47 (dd, J = 3, 2Hz, 1H), 6.65 (d, J = 3Hz, 1H), 7.41 (m, 2H), 7.49 (d, J = 2Hz, 1H), 7.65 (m, 2H). MS (EI) m/z 287 (M+).

参考实施例 28

2-(4-(呋喃-2-基)-苯基)-2-甲基-丙酸

向 2-(4-(呋喃-2-基)-苯基)-2-甲基-丙酸甲酯(2.0g, 8.2 mmol)(参考实施例 30a)在 MeOH/THF (20mL, 1/1)中的溶液内加入 NaOH (2mL, 6M)。搅拌所得溶液 1 小时，然后加热到 65℃，并在此温度下搅拌 2 小时。随后冷却反应混合物，用盐酸(2M)酸化(至 pH 1)。加乙醚稀释所得混合物，用水和盐水洗涤，硫酸镁干燥并浓缩，从而得到 1.78g 标题化合物固体。

^{1}H NMR ($CDCl_3$) d 1.61 (s, 6H), 6.45 (dd, J = 3, 2 Hz, 1H), 6.62 (d, J = 3 Hz, 1H), 7.42 (m, 2H), 7.45 (d, J = 2 Hz, 1H), 7.64 (m, 2H). MS (EI) m/z 230 (M+)

参考实施例 29

2-[4-(2-[N-叔丁氧羰基-氨基]-1,1-二甲基-乙基)-苯基]-呋喃

向氢化铝锂(152mg, 4 mmol)的 THF (6mL)冰冷(0℃)溶液内加入 2-(4-(呋喃-2-基)-苯基)-2-甲基丙腈(422mg, 2 mmol) (参考实施例 30b)。加毕后，移去冷却浴，继续搅拌 3.5 小时。冷却所得混合物至 0℃，然后依次加入水(150mL)、NaOH (150mL, 5M)和水(300mL)。用乙醚稀释所得浆液，尔后通过硅藻土过滤。浓缩滤液，进而将残留物溶于 THF (5mL)。向此溶液中加入二碳酸二叔丁酯(480mg, 2.2 mmol)。搅拌所得溶液 1 小时，然后浓缩，残留物进而通过快速色谱纯化(以 10%乙酸乙酯/己烷洗脱)，得 524mg 油状产物。

^{1}H NMR ($CDCl_3$) d 1.31 (s, 6H), 1.39 (s, 9H), 3.31 (bd, J = 6Hz, 2H), 6.45 (dd, J = 2, 1Hz, 1H), 6.61 (d, J = 2Hz, 1H), 7.35 (d, J = 8Hz, 2H), 7.44 (d, J = 1Hz, 1H), 7.62 (d, J = 8Hz, 2H).

MS (离子喷雾) m/z 316 $(M+H)^+$.

参考实施例 30a

2-(4-(呋喃-2-基)-苯基)-2-甲基-丙酸甲酯

向呋喃(5.7mL, 78mmol)的 TMEDA/THF (81.4mL, 14/86)冰冷(0℃)溶液中加入 n-buLi (15mL, 2.5M 己烷溶液)。移去冷却浴，搅拌所得溶液 45 分钟，然后加入 $ZnCl_2$ 的 THF 溶液(40mL, 0.5M)。向此溶液内再加入 $(Ph_3P)_4Pd$ (1.0g, 0.86 mmol)和 2-(4-溴-苯基)-2-甲基丙酸甲酯(4.5g, 17.5 mmol) (参考实施例 31a)。温热所得溶液到 60℃，搅拌 3 小时。然后冷却反应混合物，加乙醚稀释，再依次用盐酸(2M)和盐水洗涤，硫酸镁干燥并浓缩。残留物进而通过快速色谱纯化(以 5%乙醚/己烷洗脱)，得 3.84g 标题化合物固体。 ^{1}H NMR ($CDCl_3$) d 1.60 (s, 6H), 3.67 (s, 3H), 6.45 (m, 1H), 6.63 (d, J = 3Hz, 1H), 7.35 (m, 2H), 7.46 (m, 1H), 7.65 (m, 2H). MS (EI) m/z 245 $(M+H)^+$.

参考实施例 30b

2,2-二甲基-(4-[呋喃-2-基]-苯基)-乙腈. 应用和参考实施例 30a 基本相同的方法，只是其中使用 2-(4-溴-苯基)-2-甲基-丙腈(参考实施例 31b)。 ^{1}H NMR ($CDCl_3$) d 1.74 (s, 6H), 6.47 (dd, J = 2, 1Hz, 1H), 6.66 (d, J = 2Hz, 1H), 7.47 (m, 3H), 7.68 (m, 2H),. MS (EI) m/z 211 $(M)^+$.

参考实施例 31a

2-(4-溴-苯基)-2-甲基-丙酸甲酯

向 4-溴苯基-乙酸甲酯(9.1g, 40 mmol) (参考实施例 32)的 THF (80mL)冷(-20℃)溶液内加入碘甲烷(5.6mL, 90mmol)，接着再加入 KOt-Bu 的 THF 溶液(88mL, 1M)。搅拌所得混合物 1 小时，然后加乙醚稀释，依次用水和盐水洗涤，硫酸镁干燥并浓缩，得 9.8g 油状标题化合物。

^{1}H NMR ($CDCl_3$) d 1.55 (s, 6H), 3.63 (s, 3H), 7.2 (m, 2H), 7.43 (m, 2H).

参考实施例 31b

2-(4-溴-苯基)-2-甲基-丙腈. 应用和参考实施例 31a 基本相同的方法，只是其中使用(4-溴-苯基)-乙腈。

^{1}H NMR ($CDCl_3$) d 1.70 (s, 6H), 7.34 (d, J = 8Hz, 2H), 7.50 (d, J = 8Hz, 2H).

MS (EI) m/z 223, 225 Br 图案$(M)^+$.

参考实施例 32

4-溴-苯基-乙酸甲酯

向 4-溴-苯基-乙酸(8.6g, 40 mmol)的 DMF (80mL)溶液中顺序加入碳酸钾(6.16g, 44 mmol)和碘甲烷(2.8mL, 45 mmol)。搅拌所得混合物 2.5 小时，然后加乙醚稀释，再用水和盐水洗涤，硫酸镁干燥并浓缩，从而得到 9.1g 油状标题化合物。该产物无需进一步纯化可直接使用。

^{1}H NMR ($CDCl_3$) d 3.58 (s, 2H), 3.69 (s, 3H), 7.13 (d, J = 8Hz, 2H), 7.43 (d, J = 8Hz, 2H).

MS (EI) m/z 228/230 (M+) Br 图案.

参考实施例 33a

2-甲基-4-(2-甲氧基-吡啶-5-基)-苯甲酸

向 2-甲基-4-(2-甲氧基吡啶-5-基)-苯甲酸甲酯(600mg, 2.6 mmol)(参考实施例 34a)的 THF/MeOH (8mL, 1/1)溶液中加入 NaOH (3mL, 1M)。搅拌所得混合物 12 小时，然后用盐酸(2M)酸化(达到 pH 5)。混合物用乙醚稀释，然后再用盐水洗涤，硫酸镁干燥并浓缩。残留固体进而用乙醚/己烷(1/20)研制。所得产物(500mg)无需进一步纯化可直接使用。

^{1}H NMR ($CDCl_3$) d 2.71 (s, 3H), 3.98 (s, 3H), 6.82 (d, J = 8Hz, 1H), 7.41 (m, 2H), 7.81 (dd, J = 8, 2Hz, 1H), 8.13 (d, J = 8 Hz, 1H), 8.43 (d, J = 2 Hz, 1H). MS (EI) m/z 243 (M+).

应用与上面参考实施例 33a 所述基本相同的方法，使用指定酯制备下列化合物。

参考实施例 33b

4-(3,4-二甲氧基苯基)苯甲酸. 使用 4-(3,4-二甲氧基苯基)苯甲酸乙酯（参考实施例 34b）。

参考实施例 33c

4-(6-甲氧基-吡啶-3-基)-苯甲酸. 使用 4-(6-甲氧基-吡啶-3-基)-苯甲酸乙酯(参考实施例 34c).

^{1}H NMR (DMSO) δ 3.92 (s, 3H), 6.95 (d, J = 9Hz, 1H), 7.80 (d, J = 8Hz, 2H), 8.02 (d, J = 8Hz, 2H), 8.10 (dd, J = 9, 2Hz, 1H), 8.58 (d, J = 2Hz, 1H)MS (EI) m/z 229 (M+).

参考实施例 33d

3-氯-4-(6-甲氧基-吡啶-3-基)-苯甲酸. 使用 3-氯-4-(6-甲氧基-吡啶-3-基)-苯甲酸甲酯(参考实施例 38)。

^{1}H NMR (DMSO) δ 3.92 (s,3H), 6.96 (d, J = 9 Hz, 1H), 7.60 (d, J = 8Hz, 1H), 7.88 (dd, J = 9, 2Hz, 1H), 7.96 (d, J = 8Hz, 1H), 8.04 (s, 1H), 8.29 (d, J = 2Hz, 1H). MS (EI) m/z 263/265 (M+, Cl).

参考实施例 33e

4-(2-[叔丁氧羰基氨基-甲基]-吡啶-4-基)-苯甲酸. 使用参考实施例 56 的产物。

^{1}H NMR (DMSO) δ 1.39 (s, 9H), 4.31 (d, J = 6Hz, 2H), 7.47 (bt, J = 6Hz, 1H), 7.65 (m, 2H), 7.86 (d, J = 8Hz, 2H), 8.07 (d, J = 8Hz, 2H), 8.60 (d, J = 5Hz, 1H).

MS （离子喷雾） m/z 329 (M+H).

参考实施例 33f

4-(2-氨基甲酰基-吡啶-4-基)-苯甲酸. 使用参考实施例 58 的产物。

^{1}H NMR (DMSO) δ 7.74 (bs, 1H), 7.97 (m, 3H), 8.05 (d, J = 8Hz, 2H), 8.20 (bs, 1H), 8.34 (bs, 1H), 8.73 (d, J = 5Hz, 1H). MS (EI) m/z 242 M+.

参考实施例 33g

4-(2-[N, N-二甲基氨基-甲基]-吡啶-4-基)-苯甲酸. 使用参考实施例 59 的产物，并通过反相 HPLC 纯化(0.1% TFA/乙腈/水梯度液)。

^{1}H NMR (DMSO) δ 2.81 (s, 6H), 4.51 (s, 2H), 7.85 (d, J = 5Hz, 1H), 7.93 (s, 1H), 7.94 (d, J = 8Hz, 2H), 8.08 (d, J = 8Hz, 2H), 8.75 (d, J = 5Hz, 1H).

MS (离子喷雾) m/z 257 (M+H).

参考实施例 34a

2-甲基-4-(2-甲氧基-吡啶-5-基)-苯甲酸甲酯

向 2-甲氧基-5-溴-吡啶(1.88g, 10 mmol)的 THF (25mL)冷(-78℃)溶液中滴加入 n-BuLi (4.4mL, 2.5M 己烷溶液)。一旦加毕之后随即搅拌所得溶液 10 分钟，然后再加入 $ZnCl_2$ (21mL, 0.5M THF 溶液)。移去冷却浴，继续搅拌 15 分钟。向此溶液内加入由 4-溴-2-甲基-苯甲酸甲酯(2.25g, 9.8 mmol)和 $(Ph_3P)_4Pd$ (0.56g, 0.48 mmol)在 THF (5mL)中形成的溶液。温热所得溶液到 60℃，在该温度下搅拌 2 小时。冷却反应混合物，然后用乙酸乙酯稀释，接着用氯化铵溶液(饱和)和盐水洗涤，硫酸镁干燥并浓缩。残留物进而通过快速色谱纯化(以 10%乙酸乙酯/己烷洗脱)，得 626mg 油状标题化合物。

^{1}H NMR ($CDCl_3$) d 2.68 (s, 3H), 3.93 (s, 3H), 3.98 (s, 3H), 6.82 (d, J = 9Hz, 1H), 7.39 (m, 2H), 7.81 (d, J = 9Hz, 1H), 8.00 (d, J = 9 Hz, 1H), 8.40 (d, J = 2 Hz, 1H). MS (EI) m/z 257 (M+).

采用与上面参考实施例 34a 所述基本相同的方法，只是其中使用市售 4-溴苯甲酸乙酯和 3,4-二甲氧基-苯基溴(替代 5-溴-2-甲氧基-吡啶)，从而制备:

参考实施例 34b

4-(3,4-二甲氧基苯基)苯甲酸乙酯.

^{1}H NMR($CDCl_3$) δ 1.43 (3H, m), 3.92 (3H, m), 3.98 (3H, m), 6.95 (1H, m), 7.23 (1H, s), 7.20 (1H, m), 7.61 (2H, m), 8.12 (2H, m).

采用与参考实施例 34a 所述基本相同的方法，只是其中使用 4-溴苯甲酸乙酯，从而制得:

参考实施例 34c

4-(6-甲氧基吡啶-3-基)苯甲酸乙酯

^{1}H NMR($CDCl_3$) δ 1.41 (3H, t, J= 7.24 Hz), 3.99 (3H, s), 4.40 (2H, q, J= 7.24 Hz), 8.63 (1H, d, J= 8.63 Hz), 7.60 (2H, d, J= 8.36 Hz), 7.83 (1H, dd, J_1= 8.63 Hz, J_2= 2.58 Hz), 8.12 (2H, d, J= 8.36 Hz), 8.43 (1H, d, J= 2.58 Hz). MS(EI) m/z 257 M^+.

参考实施例 35a

4-(1,2,4)噻二唑-5-基苯甲酸

加热 0.500g (2.17 mmol) 5-(对-三氟甲基苯基)-(1,2,4)噻二唑在 5mL 浓硫酸(Fisher)中的混合物至 150℃持续 5 小时，然后倒入冰水内。过滤收集黄色沉淀物，水洗，干燥后得 0.439g 硫酸盐产物，白色固体，79.3%收率。该产物无需进一步纯化而直接使用。MS (EI) m/z 206M^+.

参考实施例 35b

采用基本相同的方法，只是以 4-(3H-味唑-4-基)三氟甲基苯(参考实施例 37)为原料，从而制得 4-(3H-味唑-4-基)-苯甲酸。该产物经进一步纯化后使用。MS (EI) m/z 188 (M^+).

参考实施例 36a

N-[2-(3-氯基-1H-吲哚-5-基)-乙基]-2-甲基-4-(6-氧代-1,6-二氢-吡啶-5-基)-苯甲酰胺

加热 N-[2-(3-氯基-1H-吲哚-5-基)-乙基]-4-(2-甲氧基-吡啶

-5-基)-2-甲基-苯甲酰胺(146mg, 0.35 mmol) (参考实施例 1n)和盐酸吡啶(3g)的混合物至 160℃, 并在此温度下搅拌 3 分钟。然后冷却所得液体, 与水混合。过滤产生的沉淀固体物, 水洗(3x), 尔后真空干燥, 得 133mg 标题化合物固体。该产物无需进一步纯化而直接使用。MS(离子喷雾) m/z 397 (M+H).

采用基本相同的方法, 只是其中使用指定的甲氧基-吡啶衍生物, 从而制得:

参考实施例 36b

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-(6-氧代-1,6-二氢-吡啶-5-基)-苯甲酰胺. 使用参考实施例 1p 的产物。MS(离子喷雾) m/z 383 (M+H).

参考实施例 36c

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-3-氯-4-(6-氧代-1,6-二氢-吡啶-3-基)-苯甲酰胺. 使用参考实施例 1u 的产物。

^{1}H NMR (DMSO) δ 2.97 (bt, 2H), 3.53 (m, 2H), 6.42 (d, J = 9Hz, 1H), 7.17 (d, J = 9Hz, 1H), 7.54 (m, 4H), 7.82 (d, J = 8Hz, 1H), 7.95 (m, 2H), 8.20 (m, 1H), 8.73 (bt, 1H), 8.88 (m, 1H), 12.15 (bs, 1H).

MS(离子喷雾) m/z 417/419 $(M+H)^+$, Cl.

参考实施例 36d

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-(6-氧代-1,6-二氢-哒嗪-3-基)-苯甲酰胺. 使用参考实施例 1ak 的产物。

^{1}H NMR (DMSO) δ 2.98 (t, J = 7Hz, 2H), 3.55 (m, 2H), 7.02 (d, J = 10Hz, 1H), 7.18 (d, J = 7Hz, 1H), 7.48 (m, 2H), 7.94 (m, 4H), 8.10 (d, J = 10Hz, 1H), 8.20 (d, J = 3Hz, 1H), 8.66 (bt, 1H), 12.11 (s, 1H), 13.29 (s, 1H).

MS(离子喷雾) m/z 384 $(M+H)^+$.

参考实施例 36e

4-(6-氧代-1,6-二氢-哒嗪-3-基)-苯甲酸甲酯. 使用参考实施例 63 的产物。

^{1}H NMR (DMSO) δ 3.88 (s, 3H), 7.04 (d, J = 10Hz, 1H), 8.02 (d, J = 8Hz, 2H), 8.06 (d, J = 8Hz, 2H), 8.12 (d, J = 10Hz, 1H), 13.37 (bs, 1H). MS (EI) m/z 230 (M^+).

参考实施例 36f

4-(6-氧代-1,6-二氢-吡啶-3-基)-苯甲酸乙酯. 使用参考实施例 34c 的产物。

^{1}H NMR (5:1 $CDCl_3$:CD_3OD): δ 1.41 (3H, t, J= 7 Hz), 4.40 (2H, q, J = 7 Hz), 6.70 (1H, d, J = 10 Hz), 7.52 (2H, d, J = 8 Hz), 7.63 (1H, d, J = 3 Hz), 7.83 (1H, dd, J = 3 Hz, 10 Hz), 8.09 (2H, d, J = 8 Hz).

参考实施例 37

4-(3H-咪唑-4-基)-三氟甲基苯

向冷却到 0℃的 5g (24 mmol) 4-(三氟甲基)苯甲酰氯的 100mL THF 溶液内滴加入 72mm 重氮甲烷的 200mL 乙醚溶液。0℃反应 18 小时后，加乙酸分解过量的重氮甲烷，然后浓缩所得溶液。向所余残留物中加入 100mL THF 和 40mL 1M HCl 的乙醚溶液。1 小时后，浓缩反应物，随后在 25mL MeOH 中温热，并将该温热溶液逐滴加到 8.6g (47 mmol) 乙酸铜(II) (Aldrich)在 5mL 37%甲醛水溶液和 100mL 28%氢氧化铵中的溶液内。加热反应物至 100℃持续 30 分钟，尔后冷却过夜。慢慢滗析出棕色沉淀上方的溶液，水洗沉淀物，进而溶于 150mL 1:1 EtOH:水。向该溶液内鼓入硫化氢，得到褐色固体；搅拌溶液 2 小时并浓缩。将残留物悬浮于乙醇/水溶液，通过 Celite 过滤，经 HPLC 纯化后得 2.1g 产物，产率 43%. MS (EI) m/z 212 (M^+).

参考实施例 38

3-氯-4-(6-甲氧基-吡啶-3-基)-苯甲酸甲酯

10 分钟内，向 2-甲氧基-5-溴吡啶(1.13g, 6 mmol, 参考实

施例 41a)在 THF (12mL)中的冷溶液(-78℃)内加入(2.5M)正丁基锂(2.4mL, 6 mmol),搅拌所得溶液 15 分钟。然后向此溶液内滴加入(0.5M)氯化锌(12mL, 6 mmol),并在搅拌下温热该芳基溴化锌溶液至 0℃。在另一烧瓶内,向双(二亚苄基丙酮)合钯(288mg, 0.5 mmol)和 1,1'-双(二苯膦基)二茂铁(276mg, 0.5 mmol)在 THF(2 mL)中的冷溶液(0℃)内加入 3-氯-4-三氟甲磺酰氧基苯甲酸甲酯(1.59g, 5 mmol)(参考实施例 39)的 THF (2mL)溶液,接着加入上述芳基溴化锌溶液。加热所得溶液至 65℃,搅拌 2.5 小时,尔后冷却至 20℃,加乙醚稀释、用饱和氯化铵溶液和盐水洗涤,硫酸镁干燥并浓缩。残留物通过快速色谱纯化(洗脱剂: 25%乙醚/己烷),得 428mg 黄色结晶固体标题化合物。

^{1}H NMR($CDCl_3$) δ 3.95 (s, 3H), 4.00 (s, 3H), 6.84 (d, J = 9Hz, 1H), 7.40 (d, J = 8Hz, 1H), 7.72 (dd, J = 9, 2Hz, 1H), 7.98 (dd, J = 8, 2Hz, 1H), 8.15 (s, 1H), 8.25 (d, J = 2Hz, 1H). MS (EI) m/z 277 (M+).

参考实施例 39

3-氯-4-三氟甲磺酰氧基-苯甲酸甲酯

向(60%)氢化钠(1.1g, 27.5 mmol)的 THF(60mL)冷却混合物(-5℃)中滴加入 3-氯-4-羟基苯甲酸甲酯(4.66g, 25 mmol) (参考实施例 40)的 THF (10mL)溶液, 0℃搅拌混合物 30 分钟。向该混合物内加入 N-苯基三氟甲磺酰胺(13.4g, 37.5 mmol)和 1,3-二甲基-3,4,5,6-四氢-2(1H)-嘧啶酮(20mL)在 THF(10mL)中的溶液。温热所得混合物至 20℃并搅拌 1 小时,加乙醚稀释,用水和盐水洗涤,硫酸镁干燥并浓缩。残留物通过快速色谱纯化(以 10%乙醚/己烷洗脱),得 6.86g 无色油状标题化合物。

^{1}H NMR($CDCl_3$) δ 3.96 (s, 3H), 7.44 (d, J = 9Hz, 1H), 8.02 (dd, J = 9, 2Hz, 1H), 8.21 (d, J = 2Hz, 1H). MS (EI) m/z 318/320 (M+, Cl).

参考实施例 40

3-氯-4-羟基-苯甲酸甲酯

向 3－氯－4－羟基－苯甲酸半水合物(9.08g, 50 mmol)的甲醇(150mL)溶液内缓慢加入（浓）硫酸(22.5mL)。加热所形成的溶液至55℃，搅拌2小时，然后冷却到20℃。将溶液倒入冰中，用乙醚提取。有机物用盐水洗涤、硫酸镁干燥并浓缩。残留物进而通过快速色谱纯化（以30%乙酸乙酯/己烷洗脱），得9.5g白色结晶固体标题化合物。

^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3H), 7.06 (d, J = 9Hz, 1H), 7.88 (dd, J = 9, 2Hz, 1H), 8.05 (d, J = 2Hz, 1H). MS (EI) m/z 186/188 (M+, Cl).

参考实施例 41a

2-甲氧基-5-溴吡啶

向 2, 5－二溴吡啶(20g, 84 mmol)的 DMSO (84mL)溶液内加入(25wt%)甲醇钠(21.2mL, 93 mmol)。加热所得溶液至 80℃，搅拌 45分钟，然后冷却到20℃，加乙醚稀释，用水及盐水洗涤、硫酸镁干燥并浓缩。残留物进而通过快速色谱纯化（以 10%乙醚/己烷洗脱），得14.6g无色油状标题化合物。

^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3H), 6.66 (d, J = 9Hz, 1H), 7.63 (dd, J = 9, 3Hz, 1H), 8.20 (d, J = 3Hz, 1H). MS (EI) m/z 187/189 (M+, Br).

参考实施例 41b

采用与制备参考实施例 41a 所用基本相同的方法，使用参考实施例 60 的产物，从而制得 3－溴－6－甲氧基哒嗪。

^{1}H NMR ($CDCl_3$) δ 4.11 (s, 3H), 6.87 (d, J = 9Hz, 1H), 7.48 (d, J = 9Hz, 1H). MS (ion spray) m/z 189/191 $(M+H)^+$, Br.

参考实施例 42a

4-(7H-吡咯并[2,3-d]嘧啶-6-基)-苯甲酸

向 4-(7H-吡咯并[2,3-d]嘧啶-6-基)-苯甲酸甲酯(0.601g, 2.4 mmol)（参考实施例 43a)的 1:1 THF-甲醇(10mL)溶液中加入 NaOH (10N)(2.4 mL, 24 mmol)和 0.5ml H_2O。搅拌所得溶液 1 小时，然后冷却至

0-5℃，用 2N HCl 调节 pH 为 3。滤出沉淀的固体物，用少量水洗涤，高真空下干燥，得 0.355g 黄色固体标题化合物。

^{1}H NMR (DMSO) δ 7.59 (s, 1H), 8.10 (d, J = 8Hz, 2H), 8.20 (d, J = 8Hz, 2H), 9.22 (s, 1H), 9.50 (bs, 1H), 14.10 (bs, 1H). MS (EI) m/z 239 (M+).

采用与参考实施例 42a 基本相同的方法，只是使用指定的酯，从而制得:

参考实施例 42b

4-(1H-吡咯并[3,2-c]吡啶-2-基)-苯甲酸（使用参考实施例 43b 的产物）。

^{1}H NMR (DMSO) δ 7.63 (s, 1H), 7.99 (d, J = 6Hz, 1H), 8.16 (m, 4H), 8.46 (d, J = 6Hz,1H), 9.34 (s, 1H), 13.67 (bs, 1H). MS (EI) m/z 238 (M+).

参考实施例 42c

4-呋喃并[3,2-c]吡啶-2-基-苯甲酸（使用参考实施例 43c 的产物）。

^{1}H NMR (DMSO) δ 7.89 (s, 1H), 8.05 (d, J = 7Hz, 1H), 8.12 (m, 4H), 8.68 (bd, 1H), 9.24 (bs, 1H), 13.20 (bs, 1H). MS (EI) m/z 239 (M+).

参考实施例 43a

4-(7H-吡咯并[2,3-d]嘧啶-6-基)-苯甲酸甲酯

向(5-碘-嘧啶-4-基)氨基甲酸叔丁酯(1.46g, 4.55 mmol)（参考实施例 44a)的 DMF(15mL)溶液内加入 4-乙炔基-苯甲酸甲酯(0.721g, 4.5 mmol)（参考实施例 46)、铜碘化物 99.999% (21mg, 0.112 mmol)、双（三苯膦）氯化钯(II) (158mg, 0.225 mmol)和 1,8-二氮杂二环[5.4.0]-十一碳-7-烯(1.5mL, 10 mmol)。加热所得溶液至 100℃，搅拌 1 小时，然后冷却至 20℃。加乙酸乙酯稀释所得溶液，进而用水和盐水洗涤、硫酸镁干燥并浓缩。残留物通过快速色谱纯化（以 50%乙酸乙酯，5%甲醇/己烷洗脱)，得 601mg 黄色结晶固体标题化合物。

^{1}H NMR (DMSO) δ 3.89 (s, 3H), 7.24 (s, 1H), 8.06 (d, J = 8Hz, 2H), 8.14 (d, J = 8Hz, 2H), 8.81 (bs, 1H), 9.05 (bs, 1H), 12.79 (bs, 1H).

MS(离子喷雾) m/z 254 $(M+H)^+$.

采用与参考实施例 43a 基本相同的方法，只是使用指定的芳基碘，从而制得:

参考实施例 43b

4-(1H-吡咯并[3,2-c]吡啶-2-基)-苯甲酸甲酯（使用参考实施例 49 的产物）。

^{1}H NMR ($CDCl_3$) δ 1.34 (s, 9H), 3.96 (s, 3H), 6.69 (s, 1H), 7.51 (d, J = 8Hz, 2H), 8.08 (d, J = 8Hz, 1H), 8.11 (d, J = 7Hz, 2H), 8.51 (d, J = 6Hz, 1H), 8.90 (s, 1H). MS (EI) m/z 352 (M+).

参考实施例 43c

4-呋喃并[3,2-c]吡啶-2-基-苯甲酸甲酯（使用参考实施例 50 的产物）。

^{1}H NMR ($CDCl_3$) δ 3.96 (s, 3H), 7.20 (s, 1H), 7.49 (d, J = 5Hz, 1H), 7.94 (d, J = 8Hz, 2H), 8.14 (d, J = 8Hz, 2H), 8.53 (d, J = 5Hz, 1H), 8.97 (s, 1H). MS (EI) m/z 253 (M+).

参考实施例 44a

(5-碘-嘧啶-4-基)氨基甲酸叔丁酯

向 5-碘-嘧啶-4-基胺(3.52g, 15.9 mmol)（参考实施例 45)在 THF (100mL)中的混合物加入吡啶(1.4mL, 17.5 mmol)和二碳酸二叔丁酯(3.82g, 17.5 mmol)。加热所得混合物至 50-55℃，搅拌 2.5 小时，然后冷却至室温、浓缩。残留物进而通过快速色谱纯化（以 20%乙酸乙酯、5%甲醇/己烷洗脱)，得 1.46g 浅黄色固体标题化合物。^{1}H NMR (DMSO) δ 1.48 (s, 9H), 8.87 (s, 1H), 9.01 (s, 1H), 9.60 (bs, 1H). MS (EI) m/z 321 (M+).

参考实施例 44b

采用与参考实施例 44a 基本相同的方法，只是使用 4-氨基-吡啶，从而制得吡啶-4-基-氨基甲酸叔丁酯。

^{1}H NMR ($CDCl_3$) δ 1.52 (s, 9H), 6.82 (bs, 1H), 7.30 (d, J = 7Hz, 2H), 8.43 (d, J = 7Hz, 2H).

参考实施例 45

5-碘-嘧啶-4-基胺

(基于 Brown, D. J.; J. S. C. I., 69, 1950 年 12 月, 353-356 页). 向 4-氨基嘧啶(2.8g, 29.4 mmol)的乙酸(30mL)溶液内加入 ICl (3.03mL, 60.4 mmol). 加热溶液至 100℃, 搅拌 3 小时, 然后倒入水(140mL)中。混合物用亚硫酸氢钠脱色, 随后冷却至 0-5℃, 用 NaOH(s)调节 pH 至 6-7。滤出沉淀产物, 用少量水洗涤, 然后高真空干燥, 得 3.52g 白色固体标题化合物。

^{1}H NMR (DMSO) δ 7.09 (bs, 2H), 8.30 (s, 1H), 8.45 (s, 1H). MS (EI) m/z 221 $(M+H)^+$.

参考实施例 46

4-乙炔基-苯甲酸甲酯

向 4-三甲基甲硅烷基乙炔基-苯甲酸甲酯(4.65g, 20 mmol) (参考实施例 47)的 THF (40mL)溶液内加入(1M)氟化四丁基铵(30mL, 30 mmol)和乙酸(1.9mL, 33 mmol)。搅拌所得溶液 25 分钟, 加乙酸乙酯稀释, 用水和盐水洗涤, 然后硫酸镁干燥并浓缩。残留物进而通过快速色谱纯化(以含 10%乙醚、10%二氯甲烷的己烷洗脱), 得 2.56g 浅黄色固体标题化合物。

^{1}H NMR ($CDCl_3$) δ 3.23 (s, 1H), 3.92 (s, 3H), 7.55 (d, J = 8Hz, 2H), 8.00 (d, J = 8Hz, 2H). MS (EI) m/z 160 (M+).

参考实施例 47

4-三甲基甲硅烷基乙炔基-苯甲酸甲酯

向（三甲基甲硅烷基）乙炔(4.2mL, 30 mmol)的 THF (25mL)冷溶液(-78℃)内滴加入(2.5M)正丁基锂(11.6mL, 29 mmol)，搅拌 30 分钟，接着缓慢加入(0.5M)氯化锌(58mL, 29 mmol)。温热所得溶液至 20℃，然后加入 4-碘-苯甲酸甲酯(5.24g, 20 mmol)（参考实施例 48)和四（三苯膦）合钯(0)（1.16g, 1 mmol)在 THF(10mL)中的溶液。加热所得混合物至 55℃，搅拌 2 小时，然后冷却到 20℃。加乙酸乙酯稀释反应混合物，用饱和氯化铵溶液、水和盐水洗涤，硫酸镁干燥并浓缩，得 4.65g 标题化合物。

^{1}H NMR ($CDCl_3$) δ 0.26 (s, 2H), 3.91 (s, 3H), 7.52 (d, J = 8Hz, 2H), 7.97 (d, J = 8Hz, 2H). MS (EI) m/z 232 (M+).

参考实施例 48

4-碘-苯甲酸甲酯

向 4-碘苯甲酸(9.92g, 40 mmol)的 DMF(80mL)溶液内加入碳酸钾(5.8g, 42 mmol)和碘甲烷(2.6mL, 42 mmol)。搅拌所得混合物 17 小时，加乙酸乙酯稀释，然后用水和盐水洗涤、硫酸镁干燥并浓缩。固体粗品用乙酸乙酯/己烷重结晶，得 8.74g 标题化合物。^{1}H NMR ($CDCl_3$) δ 3.91 (s, 3H), 7.74 (d, J = 8Hz, 2H), 7.80 (d, J = 8Hz, 2H). MS (EI) m/z 262 (M+).

参考实施例 49

(3-碘-吡啶-4-基)-氨基甲酸叔丁酯

向吡啶-4-基氨基甲酸叔丁酯(14.8g, 76.3 mmol)（参考实施例 44b)的 THF (300mL)溶液内加入 N, N, N′, N′-四甲基乙二胺(34.5mL, 230 mmol)，冷却所得溶液至-78℃。向此溶液内缓慢加入(2.5M)正丁基锂(91.5mL, 230 mmol)，升温反应混合物至-20℃，搅拌所得混合物 1.5 小时。冷却混合物至-78℃，加入碘(29.04g, 114 mmol)的 THF (60ml)溶液，然后搅拌 10 分钟。再温热混合物至 20℃，搅拌 30 分钟，然后

加乙酸乙酯稀释，用水、饱和硫代硫酸钠溶液和盐水洗涤，硫酸镁干燥并浓缩。残留物进而通过快速色谱纯化(以20%乙酸乙酯/己烷洗脱)，得17.7g浅黄色结晶固体标题化合物。

^{1}H NMR ($CDCl_3$) δ 1.54 (s, 9H), 7.03 (bs, 1H), 8.10 (d, J = 6Hz, 1H), 8.34 (d, J = 6Hz, 1H), 8.74 (s,1H). MS (EI) m/z 320 (M+).

参考实施例 50

3-碘-吡啶-4-酚

向 4-羟基吡啶(12g, 126 mmol)的水(30mL)溶液内加入碳酸钠(11.32g, 107 mmol)，加热所得混合物至回流(100℃)，接着滴加入碘化钾(19.8g, 119 mmol)和碘(18g, 71 mmol)的水(50mL)溶液。所得热溶液用 2N HCl 溶液调节至 pH 6，趁热通过烧结玻璃漏斗过滤。冷却滤液，过滤收集沉淀产物。加热滤液至回流状态，重复上述步骤。粗产物在 0.3M HCl 溶液中加热至回流，通过烧结玻璃漏斗过滤。保持滤液为近回流状态，同时用 1N NaOH 溶液调节 pH 至 6，然后冷却到 5℃，收集沉淀物并在高真空下干燥，得 8g 黄色固体标题化合物。

^{1}H NMR (DMSO) δ 6.16 (d, J = 7Hz, 1H), 7.70 (d, J = 7Hz, 1H), 8.27 (s, 1H), 11.70 (bs, 1H). MS (EI) m/z 221 (M+.).

参考实施例 51

2-[4-(1,1-二甲基-烯丙基)-苯基]-呋喃

向溴化甲基三苯基磷鎓(18.8g, 52.6 mmol)的 THF (60mL)冷浆液(0℃)中滴加入(1M)双(四甲基甲硅烷基)氨化钠(52.6mL, 52.6 mmol)，搅拌所得混合物 30 分钟。向此混合物内加入 2-(4-呋喃-2-基-苯基)-2-甲基-丙醛(5.64g, 26.3 mmol) (参考实施例 52)的 THF (25mL)溶液，进而搅拌所得混合物 45 分钟。加乙醚稀释上述混合物，用水和盐水洗涤，经硫酸镁干燥后浓缩。残留物通过快速色谱纯化(以10%乙酸乙酯/己烷洗脱)，得 6.2g 黄色油状标题化合物。

^{1}H NMR ($CDCl_3$) δ 1.41 (s, 6H), 5.03 (s,

1H), 5.08 (d, J = 7Hz, 1H), 6.03 (m, 1H), 6.45 (m, 1H), 6.60 (d, J = 3Hz, 1H), 7.36 (d, J = 8Hz, 2H), 7.44 (s, 1H), 7.60 (d, J = 8Hz, 2H). MS (EI) m/z 212 (M+).

参考实施例 52

2-(4-呋喃-2-基-苯基)-2-甲基-丙醛

向 2-(4-呋喃-2-基-苯基)-2-甲基-丙-1-醇(6.56g, 30 mmol)(参考实施例 53)的 CH_2Cl_2 (200mL)溶液内加入 Dess-Martin periodinane (22.5g, 53 mmol), 搅拌所得混合物 45 分钟, 然后浓缩。残留物进而通过快速色谱纯化(以 10%乙酸乙酯/己烷洗脱), 得 5.64g 标题化合物。

^{1}H NMR ($CDCl_3$) δ 1.48 (s, 6H), 6.47 (m, 1H), 6.66 (d, J = 3Hz, 1H), 7.30 (d, J = 8Hz, 2H), 7.46 (s, 1H), 7.68 (d, J = 8Hz, 2H), 9.50 (s, 1H). MS (EI) m/z 214 (M+).

参考实施例 53

2-(4-呋喃-2-基-苯基)-2-甲基-丙-1-醇

向(1M)氢化铝锂(13.3mL, 13.3 mmol)的 THF (27mL)冷溶液(0℃)内加入 2-(4-呋喃-2-基-苯基)-2-丙酸甲酯(3.1g, 12.7 mmol) (参考实施例 30a)的 THF (11mL)溶液。搅拌所得溶液 15 分钟, 然后缓慢加入水(0.5mL)、15% NaOH (0.5mL)和水(1.5mL)。加乙醚稀释所得浆液, 通过硅藻土垫过滤, 进而浓缩滤液, 从而获得 2.7g 白色结晶固体标题化合物。

^{1}H NMR ($CDCl_3$) δ 1.34 (s, 6H), 3.62 (m, 3H), 6.46 (m, 1H), 6.62 (d, J = 3Hz, 1H), 7.40 (d, J = 8Hz, 2H), 7.46 (bs, 1H), 7.64 (d, J = 8Hz, 2H). MS (EI) m/z 216 (M+).

参考实施例 54

振摇 TFP 树脂(美国专利申请号 60/090,558) (1g, 0.83 mmol/g)和 4-叔丁基-苯甲酸(295mg, 1.66 mmol)在 DMF(10mL)中的悬浮液 10 分钟, 然后加入 DMAP (20mg, 0.16 mmol)/DMF (1mL)。进而向此混合物内再加入 1, 3-二异丙基碳二亚胺(200mL, 1.6 mmol)。振摇所形成的悬浮液 2.5 小时, 然后过滤, 固体物用各自大约 10mL 的

CH_2Cl_2、DMF、THF、CH_2Cl_2顺序洗涤。真空干燥所得酰化树脂。该产物无需进一步加工而直接使用。

采用与上所述基本相同的方法可以活化各种不同的羧酸。这类羧酸的代表性实例包括:

4-(4-氨基甲酰基-苯基)-苯甲酸

4-(4-甲氧基-苯基)-苯甲酸

5-甲氧基-吲哚-2-基-羧酸

6-氯-苯并噻吩-2-基羧酸

4-(4-苄氧基-苯基)-苯甲酸

4-氯-苯甲酸

4-(甲磺酰基)-苯甲酸

4-(氨基磺酰基)-苯甲酸

参考实施例 55

N-(2-[3-氰基-1-甲基吲哚-5-基]乙基)-4-(6-甲氧基吡啶-3-基)苯甲酰胺

向 0.0328g (0.820 mmol)氢化钠(60%矿物油悬浮物)在 2mL DMF 中的冷(0℃)溶液内加入 0.250g (0.631 mmol) N-(2-[3-氰基-吲哚-5-基]乙基)-4-(6-甲氧基吡啶-3-基)苯甲酰胺(参考实施例 1p)的 5mL DMF 溶液。10 分钟后再加入 0.043mL (0.69 mmol)碘甲烷，移去冷却浴。3 小时后，加水终止反应，浓缩，快速层析(2:2:1 CH_2Cl_2: EtOAc:己烷)所剩残留物，得 0.167g 白色固体产物，产率 65%。

^{1}H NMR ($CDCl_3$) δ 3.09 (2H, t, J = 7 Hz), 3.80 (2H, m), 3.86 (3H, s), 3.99 (3H, s), 6.17 (1H, m, br), 6.83 (1H, d, J = 8 Hz), 7.29 (1H, s), 7.37 (1H, d, J = 8 Hz), 7.55-7.58 (3H, m), 7.64 (1H, s), 7.76-7.82 (3H, m), 8.40 (1H, d, J = 2 Hz).

MS(离子喷雾) m/z 411 $(M+H)^+$.

参考实施例 56

4-(2-[叔丁氧羰基氨基-甲基]-吡啶-4-基)-苯甲酸甲酯

向 4-(2-氰基吡啶-4-基)苯甲酸甲酯(1.15g, 4.8 mmol) (参考实施例 57)的 THF (20mL)溶液内顺序加入钯-碳(200mg, 10%重量 Pd)和二碳酸二叔丁酯(1.12g, 5.1 mmol)。所得混合物在氢气氛下搅拌 16 小时。然后用氮气净化，加乙酸乙酯稀释，并通过硅藻土过滤。减压浓缩滤液，残留物进而通过快速色谱纯化(以 50%乙酸乙酯/己烷洗脱)，得 534mg 油状标题化合物(32%)。

^{1}H NMR ($CDCl_3$) δ 1.47 (s, 9H), 3.96 (s, 3H), 4.51 (d, J = 6Hz, 2H), 7.41 (dd, J = 5, 1.4Hz, 1H), 7.50 (bs, 1H), 7.71 (d, J = 8Hz, 2H), 8.16 (d, J = 8Hz, 2H), 8.61 (d, J = 5Hz, 1H).

MS (离子喷雾) m/z 343 (M+H).

参考实施例 57

4-(2-氰基-吡啶-4-基)-苯甲酸甲酯

向 4-(吡啶-N-氧化物-4-基)苯甲酸甲酯(1.15g, 5 mmol) (参考实施例 18)的二氯甲烷(10mL)溶液内顺序加入 TMSCN (736mL, 5.5mmol)和 N,N-二乙基氨基甲酰氯(742mL, 5.8mmol)。搅拌所得溶液 116 小时，然后加入碳酸钾水溶液(10mL, 10%)。加乙酸乙酯稀释反应混合物，进而用盐水洗涤、硫酸镁干燥并浓缩，从而获得 1.15g 褐色固体标题化合物。该产物无需进一步纯化而直接使用。

^{1}H NMR ($CDCl_3$) δ 3.86 (s, 3H), 8.05 (m, 2H), 8.08 (m, 2H), 8.12 (dd, J = 5, 2Hz, 1H), 8.49 (bs, 1H), 8.82 (d, J = 5Hz, 1H). MS (EI) m/z 238 M+.

参考实施例 58

4-(2-氨基甲酰基-吡啶-4-基)-苯甲酸甲酯

室温搅拌 4-(2-氰基-吡啶-4-基)苯甲酸甲酯(400mg, 1.68 mmol) (参考实施例 57)在 80%硫酸(3mL)中的溶液 12 小时。将所得溶液倒在冰上，混合物用碳酸氢钠饱和溶液调节至 pH 8，然后以乙酸乙酯提取，经盐水洗涤、硫酸镁干燥后浓缩。残留物进而通过快速色谱纯化(以 40%乙酸乙酯/氯仿洗脱)，得 340mg 标题化合物。

^{1}H NMR ($CDCl_3$) δ 3.94 (s, 3H), 5.72 (bs, 1H), 7.67 (dd, J = 5, 1Hz, 1H), 7.75 (d, J = 8Hz, 2H), 7.9 (bs, 1H), 8.15 (d, J = 8Hz, 2H), 8.46 (bs, 1H), 8.63 (d, J = 5Hz, 1H). MS (EI) m/z 256.

参考实施例 59

4-(2-[N, N-二甲基氨基-甲基]-吡啶-4-基)-苯甲酸甲酯

向 4-(2-[叔丁氧羰基氨基-甲基]-吡啶-4-基)-苯甲酸甲酯(参考实施例 56) (520mg, 1.5 mmol)的二氯甲烷(5mL)溶液内加入 TFA (1.5mL)和 2 滴水(大约 100mL)。搅拌所得溶液 90 分钟，然后减压浓缩。残留物进而溶于 THF (4mL)，然后顺序加入 $NaBH_4$ (22mg, 6mmol)和多聚甲醛(360mg, 12 mmol)。再向该混合物内滴加入 TFA (4mL)。搅拌所得混合物 6 小时，尔后浓缩。残留物用 NaOH (1M)和饱和 $NaHCO_3$ 水溶液调节至 pH 8。然后将混合物用乙酸乙酯、乙酸乙酯-甲醇(9/1)提取。盐水洗涤合并的有机提取物，经硫酸镁干燥后浓缩。残留物进而通过快速色谱纯化(以 10%甲醇/CH_2Cl_2 洗脱)，得 329mg 标题化合物。

^{1}H NMR (CD_3OD) δ 3.00 (s, 6H), 3.94 (s, 3H), 4.56 (s, 2H), 7.74 (d, J = 5 Hz, 1H), 7.83 (s, 1H), 7.88 (d, J = 8Hz, 2H), 8.17 (d, J = 8Hz, 2H), 8.76 (d, J = 5Hz, 1H).

MS (离子喷雾) m/z 271 (M+H).

参考实施例 60

3, 6-二溴哒嗪

向三溴化磷(15.7mL, 165mmol)的冷溶液(0℃)内滴加入溴(8.5mL, 165 mmol)。将所生成的固体物放置 10 分钟，然后迅速用刮刀充分混合。向固体 PBr_5 中加入 3, 6-二羟基哒嗪(16.8g, 150mmol)，充分混合固体物，然后在烧瓶上配置冷凝管和干燥管。加热混合物至 100℃保持 3 小时，然后冷却至 20℃。将固体物少量多批转移到已冷却(-5℃)的 2N NH_4OH 溶液(200mL)内。过滤收集固体物，用冷(-5℃) 1N NaOH (120mL)洗涤，然后再水洗至中性 pH。将固体溶于乙醚，硫酸镁干燥，浓缩并在高真空下干燥，从而得 25.8g 浅黄色固体标题化合物。

^{1}H NMR (DMSO) δ 8.01 (s, 2H). MS (EI) m/z 236/238/240 (M^+), Br_2.

参考实施例 61a

4-[1-(2-二甲氨基-乙基)-6-氧代-1,6-二氢-哒嗪-3-基]-苯甲酸

向 4-[1-(2-二甲氨基-乙基)-6-氧代-1,6-二氢-哒嗪-3-基]-苯甲酸甲酯(542mg, 1.8 mmol, 参考实施例 62a)在 1:1 THF/甲醇(6mL)中的溶液内加入 10N NaOH (1.8mL, 18 mmol), 接着加入水(0.5mL)。搅拌所得溶液 1.5 小时, 然后冷却至 0-5℃, 用 2N HCl 调节至 pH 6, 再加以浓缩。残留物通过反相 HPLC 纯化(以 15%-40%乙腈(0.1% TFA)/H_2O (0.1%TFA)洗脱 20 分钟), 得 487mg 标题化合物。

^{1}H NMR (DMSO) δ 2.89 (s, 6H), 3.59 (m, 2H), 4.52 (bt, 2H), 7.14 (d, J = 10Hz, 1H), 8.04 (s, 4H), 8.16 (d, J = 10Hz, 1H), 9.63 (bs, 1H).

MS (离子喷雾) m/z 288 $(M+H)^+$.

实施例 61b

采用与制备参考实施例 61a 所用基本相同的方法, 但使用参考实施例 62b 的产物, 从而制得 4-[1-(3-二甲氨基-丙基)-6-氧代-1,6-二氢-哒嗪-3-基]-苯甲酸。

^{1}H NMR (DMSO) δ 2.17 (m, 2H), 2.78 (s, 3H), 2.79 (s, 3H), 3.16 (m, 2H), 4.24 (bt, 2H), 7.14 (d, J = 10Hz, 1H), 8.05 (s, 4H), 8.16 (d, J = 10Hz, 1H), 9.61 (bs, 1H). MS (EI) m/z 302 $(M+H)^+$.

参考实施例 62a

4-[1-(2-二甲氨基-乙基)-6-氧代-1,6-二氢-哒嗪-3-基]-苯甲酸甲酯

向 DMSO (3.5mL)中加入 60%NaH 矿物油悬浮物(84mg, 2.1 mmol), 搅拌所得混合物 5 分钟。然后向此溶液内加入 4-(6-氧代-1,6-二氢-哒嗪-3-基)-苯甲酸甲酯(460mg, 2mmol, 参考实施例 36e),

搅拌混合物 10 分钟（直至均相）。在另一含有 DMSO (3.5mL) 的烧瓶内加入 60% NaH (101mg, 2.5 mmol)，搅拌 5 分钟。向这一溶液内再加入 2-二甲氨基乙基氯盐酸盐(346mg, 2.4 mmol)，并搅拌 5 分钟。然后将此溶液转移到上述反应溶液内，加热到 50℃，搅拌 2 小时。随后冷却至 20℃，用 NH_4Cl 饱和溶液(2mL)处理，接着浓缩。残留物通过短程快速色谱纯化（以 10%甲醇/二氯甲烷洗脱），得 542mg 标题化合物。

^{1}H NMR (CD_3OD) δ 2.35 (s, 6H), 2.88 (t, J = 7Hz, 2H), 3.93 (s, 3H), 4.42 (t, J = 7Hz, 2H), 7.08 (d, J = 10Hz, 1H), 8.06 (m, 5H). MS (EI) m/z 302 $(M+H)^+$.

参考实施例 62b

采用和制备参考实施例 61a 所用基本相同的方法，但只是使用 3-（二甲氨基）-丙基氯盐酸盐，从而制得 4-[1-(3-二甲氨基-丙基)-6-氧代-1,6-二氢-哒嗪-3-基]-苯甲酸甲酯。

^{1}H NMR (CD_3OD) δ 2.07 (m, 2H), 2.25 (s, 6H), 2.45 (bt, 2H), 3.92 (s, 3H), 4.29 (bt, 2H), 7.07 (d, J = 10Hz, 1H), 8.04 (m, 5H).

MS（离子喷雾）m/z 316 $(M+H)^+$.

参考实施例 63

4-(6-甲氧基-哒嗪-3-基)-苯甲酸甲酯

向 4-(6-甲氧基-哒嗪-3-基)苯甲酸(5.02g, 21.8 mmol)（参考实施例 11f)的甲醇(75mL)溶液中缓慢加入浓硫酸(3.75mL)。加热所得溶液到 50℃，搅拌 1 小时。然后浓缩溶液到 1/3 体积，冷却至 0-5℃，用 $NaHCO_3$ 饱和溶液调节 pH 为 6，进而提取到乙酸乙酯内。盐水洗涤有机层，经硫酸镁干燥后浓缩。残留物随后通过快速色谱纯化（以 20%乙酸乙酯/二氯甲烷洗脱），得 4.26g 白色结晶固体标题化合物。

^{1}H NMR (DMSO) δ 3.90 (s, 3H), 4.10 (s, 3H), 7.38 (d, J = 9Hz, 1H), 8.10 (d, J = 9Hz, 2H), 8.25 (m, 3H). MS (EI) m/z 244 (M^+).

参考实施例 64a

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-(6-氧代-哌啶-3-基)-苯甲酰胺

将 4-（6-氧代-哌啶-3-基）苯甲酸(190mg, 0.87 mmol, 参考实施例 65)和 5-（2-氨基-乙基）-1H-吲哚-3-甲腈(161mg, 0.87 mmol, 参考实施例 2)溶于无水 DMF (3mL)。向这一溶液内加入二异丙基乙胺(330μl, 1.9 mmol)，接着再加入 HBTU (330mg, 0.87 mmol)，然后室温搅拌过夜(16 小时)。产物通过反相层析反应混合物粗品进行分离(Dynamax C-18 60A (5 x 30 cm), 50ml/min, λ@ 220nm, 10-70%B/15 分钟, A: 0.1% TFA/水, B: 0.1%TFA/乙腈)。

^{1}H NMR (300 MHz, DMSO) δ 1.94 (m, 2H), 2.26 (m, 2H), 2.92 (t, J = 7.1, 2H), 3.19 (m, 1H), 3.48 (m, 2H), 3.46 (m, 2H), 7.13 (d, J = 8.4, 1H), 7.15 (d, J = 1.4, 2H), 7.36 (d, J = 8.3, 2H), 7.43 (d, J = 8.5, 1H), 7.46 (s, 1H), 7.55 (d, J = 2.5, 1H), 7.73 (d, J = 8.3, 2H), 8.17 (d, J = 3.0, 1H), 8.47 (t, J = 5.5, 1H).

MS (离子喷雾) m/z 387 $(M+H)^+$.

参考实施例 64b

采用和制备参考实施例 64a 所用基本相同的方法，只是使用参考实施例 68 的产物，从而制得 N-Boc-3-氰基-5-{2-[4-(6-氧代-1,6-二氢-吡啶-3-基)-苯甲酰基氨基]-丙基}-吲哚。

^{1}H NMR (300 MHz, $CDCl_3$) d 8.11 (d, J = 8.7 Hz, 1H), 8.09 (s, 1H), 7.79 (dd, J = 9.4, 2.4 Hz, 1H), 7.76 (d, J = 8.1 Hz, 2H), 7.65 (d, J = 2.4 Hz, 1H), 7.56 (s, 1H), 7.47 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.6 Hz, 1H), 6.71 (d, J = 9.4 Hz, 1H), 6.02 (d, J = 8.1 Hz, 1H), 4.57-4.47 (m, 1H), 3.13-2.96 (m, 2H), 1.68 (s, 9H), 1.27 (d, J = 6.7 Hz, 3H);

MS (离子喷雾) m/z 497 $(M+H^+)$.

参考实施例 64c

采用和制备参考实施例 64a 所用基本相同的方法，只是使用参考实施例 75 的产物，从而制得 4-{4-[2-(3-氰基-1H-吲哚-5-基)乙基氨基甲酰基]-苯基}-3,6-二氢-2H-吡啶-1-羧酸叔丁酯。

^{1}H NMR (300 MHz, $CDCl_3$) d 8.92 (bs, 1H), 7.72-7.64 (m, 4H), 7.42-7.38 (m, 3H), 7.21 (d, J = 6.9 Hz, 1H), 6.17 (bt, 1H), 6.09 (bs, 1H), 4.10-4.06 (m, 2H), 3.78 (dd, J = 12.9, 6.7 Hz, 2H), 3.64 (t, J = 5.7 Hz, 2H), 3.07 (t, J = 6.8 Hz, 2H), 2.55-2.47 (m, 2H), 1.49 (s, 9H);

MS （离子喷雾） m/z 471 $(M+H^+)$.

参考实施例 64d

采用和制备参考实施例 64a 所用基本相同的方法，只是其中使用参考实施例 81 的产物，从而制得(3-{4-[2-(3-氰基-1H-吲哚-5-基)乙基氨基甲酰基]苯基}-丙-2-炔基)氨基甲酸叔丁酯。

^{1}H NMR (300 MHz, CD_3OD) d 11.62 (bs, 1H), 8.56 (bs, 1H), 7.90 (d, 1H), 7.71 (m, 2H), 7.55 (s, 1H), 7.50-7.40 (m, 3H), 7.21 (d, 1H), 4.08 (s, 2H), 3.63 (m, 2H), 3.05 (t, 2H).

参考实施例 65

4-(6-氧代-哌啶-3-基)-苯甲酸

将 4-(6-氧代-哌啶-3-基)-苯甲酸乙酯(320mg, 1.30 mmol, 参考实施例 66)溶于 MeOH (8mL)。向这一溶液中加入 1N NaOH (1.43mL, 1.43mmol)，室温搅拌所得溶液 1 小时。再加入另一份 1N NaOH (2mL)，室温搅拌混合物过夜(16 小时)。然后加 1N HCl 直至 pH 达到 2-3。过滤所形成的沉淀物，水洗，然后置于真空烘箱内干燥过夜，得细小白色结晶（针状）标题化合物(250mg, 88%)。^{1}H NMR

(300 MHz, DMSO) δ 1.94 (m, 2H), 2.23 (m, 2H), 3.06 (m, 1H), 3.23 (m, 2H), 7.42 (d, J = 8.3, 2H), 7.57 (bs, 1H), 7.87 (d, J = 8.1, 2H);

MS （离子喷雾） m/z 220 $(M+H)^+$.

参考实施例 66

4-(6-氧代-哌啶-3-基)-苯甲酸乙酯

将 4-（6-氧代-1，6-二氢-吡啶-3-基）-苯甲酸乙酯(450mg, 1.8 mmol) (参考实施例 36f)溶于 HOAc (15mL)，并通过 N_2/

真空变换脱气溶液数次。加入 50mg PtO_2，混合物在置于 H_2 氛围中之前再脱气数次。室温搅拌混合物 9 小时，然后通过 N_2/真空变换再脱气数次，随后通过硅藻土塞过滤。塞子用 HOAc 充分洗涤，然后浓缩滤液。残留物首先通过硅胶层析(3% MeOH/CH_2Cl_2)层析，继而再通过反相 HPLC 层析，从而获得 330mg 白色固体标题化合物(72%)。

^{1}H NMR ($CDCl_3$) δ 1.39 (t, J = 7 Hz, 3H), 2.12 (m, 2H), 2.56 (m, 2H), 3.13 (m, 1H), 3.41 (dd, J = 11.3, 11.3, 1H), 3.53 (m, 1H), 4.37 (q, J = 7, 2H), 6.78 (bs, 1H), 7.16 (d, J = 8 Hz, 2H), 8.01 (d, J = 8 Hz, 2H).

MS (离子喷雾) m/z 248 $(M+H)^+$.

参考实施例 67a

4-(1-羧基甲基-6-氧代-1,6-二氢吡啶-3-基)苯甲酸乙酯

向 4-(1-叔丁氧羰基甲基-6-氧代-1,6-二氢吡啶-3-基)苯甲酸乙酯[1.03g, 2.88 mmol, 参考实施例 85b]在二氯甲烷[10ml]和水[0.125ml]中的溶液内加入三氟乙酸[2.5ml]。18 小时后真空除去溶剂，并用二氯甲烷研制所得固体，从而得到 0.815g 白色固体产物，产率 93.9%。

^{1}H NMR (1:1 CD_3OD: $CDCl_3$): δ 1.43 (3H, t, J= 7 Hz), 4.40 (2H, q, J = 7 Hz), 4.81 (2H, s), 6.73 (1H, d, J = 9 Hz), 7.60 (2H, d, J = 8 Hz), 7.60 (1H, s), 7.88 (1H, d, J = 9.0 Hz), 8.09 (2H, d, J = 8 Hz).

MS (离子喷雾) m/z 302 $(M+H)^+$.

参考实施例 67b

采用和制备实施例 67a 所用基本相同的方法，只是其中使用参考实施例 64c 的产物，从而制得 N-[2-(3-氰基-1H-吲哚-5-基)乙基]-4-(1,2,3,6-四氢吡啶-4-基)苯甲酰胺。

^{1}H NMR (300 MHz, DMSO-d_6) d 12.11 (bs, 1H), 8.84 (bs, 2H), 8.57 (t, 1H), 8.19 (d, J = 2.9 Hz, 1H), 7.82 (d, J = 8.3 Hz, 2H), 7.55 (d, J = 8.3 Hz, 2H), 7.47 (s, 1H), 7.46 (d, J = 8.9 Hz, 1H), 7.16 (d, J = 8.9 Hz, 1H), 6.31 (bs, 1H), 3.77 (bm, 2H), 3.55-3.47 (m, 2H), 3.36-3.29 (m, 2H), 2.94 (t, 2H), 2.69 (bm, 2H);

MS（离子喷雾）m/z 371 $(M+H)^+$.

参考实施例 67c

3-氰基-5-{2-[4-(6-氧代-1,6-二氢-吡啶-3-基)-苯甲酰氨基]-丙基}-吲哚

采用和制备实施例 67a 所用基本相同的方法，只是其中使用参考实施例 64b 的产物，从而制得标题化合物。

^{1}H NMR (300 MHz, DMSO-d_6) d 12.07 (bs, 1H), 8.30 (d, J = 8.0 Hz, 1H), 8.17 (s, 1H), 7.88 (d, J = 9.5 Hz, 1H), 7.83-7.80 (m, 3H), 7.62 (d, J = 8.4 Hz, 2H), 7.50 (s, 1H), 7.42 (d, J = 8.3 Hz, 1H), 7.17 (d, J = 8.5 Hz, 1H), 6.43 (d, J = 9.6 Hz, 1H), 4.26-4.17 (m, 1H), 3.02-2.82 (m, 2H), 1.16 (d, J = 6.6 Hz, 3H);

MS（离子喷雾）m/z 397 $(M+H^+)$.

参考实施例 68

N-Boc-5-(2-氨基丙基)-吲哚-3-甲腈

向 N-Boc-5-(2-叠氮基丙基)-吲哚-3-甲腈(0.33g, 0.97 mmol, 参考实施例 69)在四氢呋喃(5mL)和一滴水中的溶液内加入三苯膦(1.1g, 4.2 mmol)。搅拌反应混合物 3 天，然后浓缩并通过柱色谱纯化(硅胶，3%-5% MeOH/CH_2Cl_2)，从而得 0.12g N-Boc-5-(2-氨基丙基)-吲哚-3-甲腈.

^{1}H NMR (300 MHz, DMSO-d_6) d 8.62 (s, 1H), 8.04 (d, J = 8.6 Hz, 1H), 7.51 (s, 1H), 7.34 (d, J = 8.7 Hz, 1H), 3.13-3.05 (m, 1H), 2.69 (d, J = 6.6 Hz, 2H), 1.64 (s, 9H), 0.97 (d, J = 6.2 Hz, 3H);

MS（离子喷雾）m/z 300 $(M+H^+)$.

参考实施例 69

N-Boc-5-(2-叠氮基丙基)-吲哚-3-甲腈

将 N-Boc-5-(2-羟基丙基)-吲哚-3-甲腈(480mg, 1.6 mmol, 参考实施例 70)溶于 THF (10mL)，冷却到 0℃。加入三苯膦(0.5g, 2 mmol)、偶氮二羧酸二乙酯(0.3mL, 2mmol)和二苯基磷酰叠氮(0.41mL, 2

mmol)，搅拌反应物 14 小时。再加入另一份(2 mmol)上述各种试剂，继续搅拌反应物 6 小时。将所得混合物分配到乙酸乙酯和碳酸氢钠饱和溶液之间。分离有机层，干燥(硫酸镁)、浓缩并通过柱色谱纯化(硅胶，20% EtOAc/石油醚 - EtOAc)，得 0.33g N-Boc-5-(2-叠氮基丙基)-吲哚-3-甲腈。

^{1}H NMR (300 MHz, $CDCl_3$) d 8.11 (d, J = 8.2 Hz, 1H), 8.10 (s, 1H), 7.54 (d, J = 1.0 Hz, 1H), 7.29 (dd, J = 8.7, 1.6 Hz, 1H), 3.81-3.70 (m, 1H), 2.97-2.83 (m, 2H), 1.69 (s, 9H), 1.29 (d, J = 6.5 Hz, 3H).

参考实施例 70

N-Boc-5-(2-羟基丙基)-吲哚-3-甲腈

冷却 N-Boc-5-(2-氧代丙基)-吲哚-3-甲腈(0.48g，1.6 mmol，参考实施例 71)在 THF (15mL)和乙醇(15mL)中的溶液到 0℃，15 分钟内分两批加入硼氢化钠(95mg，2.5 mmol)。另搅拌 15 分钟后，将反应混合物分配到乙酸乙酯(150mL)与饱和氯化铵水溶液(50mL)之内。干燥(硫酸镁)有机层，浓缩得到半纯样品 N-Boc-5-(2-羟基丙基)-吲哚-3-甲腈，该产物无需进一步纯化直接使用。

^{1}H NMR (300 MHz, $CDCl_3$) d 8.10 (d, J = 8.1 Hz, 1H), 8.09 (s, 1H), 7.56 (s, 1H), 7.30 (dd, J = 8.7, 1.3 Hz, 1H), 4.16-4.04 (m, 1H), 3.7 (bs, 1H), 2.95-2.79 (m, 2H), 1.67 (s, 9H), 1.26 (d, J = 6.4 Hz, 3H); MS (EI) m/z 300 (M^+).

参考实施例 71

N-Boc-5-(2-氧代丙基)-吲哚-3-甲腈

脱气包含 N-Boc-5-溴吲哚-3-甲腈(1.08g，3.36 mmol，参考实施例 72)、三丁基氟化锡(2.1g，6.7 mmol)、双(三-邻甲苯基膦)二氯化钯(66mg，0.13 mmol)、2-三甲基甲硅烷氧基-丙烯(1.1mL，6.7 mmol)和甲苯(25mL)的混合物，然后在 80℃浴中加热 3 小时。再加入另一份钯催化剂(70mg)、2-三甲基甲硅烷氧基-丙烯(0.7mL)和三丁基氟化锡(2.0g)，另加热反应物 1 小时。冷却反应物，加入乙醚(25mL)和 1N NaOH (25mL)，接着剧烈搅拌 10 分钟。分出乙醚层，干燥(硫酸镁)、浓缩并通过柱色谱纯化(硅胶，CH_2Cl_2)，得 0.48g N-Boc-5-(2-

氧代丙基)-吲哚-3-甲腈。

^{1}H NMR (300 MHz, DMSO-d_6) d 8.64 (s, 1H), 8.06 (d, J = 8.6 Hz, 1H), 7.54 (s, 1H), 7.30 (d, J = 8.6 Hz, 1H), 3.94 (s, 2H), 2.16 (s, 3H), 1.65 (s, 9H).); MS (EI) m/z 299 ($M+H^+$).

参考实施例 72

N-Boc-5-溴吲哚-3-甲腈

向 CH_2Cl_2 (20mL)和丙酮(5mL)的混合物中加入 5-溴吲哚-3-甲腈(1.23g, 5.5 mmol, 参考实施例 73)和二碳酸二叔丁酯(1.21g, 5.5 mmol)。加入 N,N-二甲氨基吡啶(24mg, 0.2 mmol), 搅拌反应物 1 小时。过滤所形成的沉淀物, 得 0.63g N-Boc-5-溴吲哚-3-甲腈白色固体。浓缩滤液得 1.1g 半纯净产物。过滤得到的产物具有下列分析数据:

^{1}H NMR (300 MHz, DMSO-d_6) d 8.73 (s, 1H), 8.07 (d, J = 8.9 Hz, 1H), 7.90 (s, 1H), 7.66 (d, J = 8.9 Hz, 1H), 1.64 (s, 9H).

参考实施例 73

5-溴吲哚-3-甲腈

向 5-溴吲哚-3-甲醛(14.7g, 66 mmol, 参考实施例 74)与甲醇(100mL)的混合物中加入盐酸羟胺(4.5g, 66mmol)。1 小时后加入甲苯(80mL)和 THF (30mL), 浓缩反应物。另加入 80mL 甲苯, 再次共沸反应物。将混合物溶于甲苯(200mL), 加入亚硫酰氯(12mL, 165mmol), 产生轻微放热。将反应物置于 70℃浴中, 加热 45 分钟。然后冷却反应物, 与 CH_2Cl_2 与 THF 的混合物一起共沸。将反应混合物粗品溶于甲醇和二氯甲烷, 吸附到硅胶上, 再用二氯甲烷提取, 从而得 11.4g 5-溴吲哚-3-甲腈。用甲苯重结晶得分析纯样品:(浅红色针状晶体), m.p. 189 - 191.

^{1}H NMR (300 MHz, DMSO-d_6) d 12.38 (bs, 1H), 8.30 (d, J = 3.0 Hz, 1H), 7.79 (d, J = 1.5 Hz, 1H), 7.52 (d, J = 8.6 Hz, 1H), 7.40 (dd, J = 8.6, 1.6 Hz, 1H); MS (EI) m/z 220 (M^+,Br).

参考实施例 74

5-溴吲哚-3-甲醛

在水浴冷却下，10 分钟内向二甲基甲酰胺(15mL)中缓慢加入磷酰氯(10.5mL，112 mmol)。15 分钟内向此溶液内加入 5 - 溴吲哚(15g，93 mmol)的二甲基甲酰胺(15mL)溶液，产生轻微放热。5 分钟后，将反应物置于 80℃浴中加热 10 分钟。稍微冷却反应物，然后加入水(15mL)，产生剧烈放热。反应物在 90℃的热，浴中加热 1.5 小时。冷却反应物，然后极缓慢地加到 0.4N NaOH (500mL)中，生成棕色沉淀物，进而过滤，再溶于 EtOAc，干燥（硫酸镁）并浓缩，得浅红色固体。放置过夜后，滤液又沉淀出另一批产物，收集并与第一批产物合并，得到半纯净醛(15.3g)，该产物无需进一步纯化直接使用。

^{1}H NMR (300 MHz, DMSO-d_6) d 12.30 (bs, 1H), 9.92 (s, 1H), 8.34 (d, J = 3.0 Hz, 1H), 8.21 (s, 1H), 7.49 (d, J = 8.6 Hz, 1H), 7.38 (dd, J = 8.7, 1.8 Hz, 1H).

参考实施例 75

4-(4-羧基苯基)-3,6-二氢-2H-吡啶-1-羧酸叔丁酯

向 1,2,3,6-四氢-4-[(三氟甲基)磺酰氧基]吡啶-1-羧酸叔丁酯(2.63g，7.9 mmol，参考实施例 76)的二甲氧基乙烷(21mL)溶液内加入 4-羧基苯硼酸(1.44g，8.7 mmol)、2M 碳酸钠水溶液(17.4mL)和氯化锂(0.99g，24 mmol)。脱气混合物，然后加入四(三苯膦)钯(450mg，0.4 mmol)，再次脱气反应物，尔后加热回流 6 小时。过滤反应物，固体用 EtOAc 洗涤。有机相用 0.5N HCl 洗涤，干燥($MgSO_4$)，浓缩并通过柱色谱纯化（硅胶，3% MeOH/CH_2Cl_2/0.1% HOAc)，得半纯净产物。将该产物用乙醚和少量二氯甲烷研制，得 0.27g 白色固体标题化合物：m.p. 200-209 (分解).

^{1}H NMR (300 MHz, $CDCl_3$) d 8.07 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 6.20 (bs, 1H), 4.15-4.00 (m, 2H), 3.66 (t, J = 5.6 Hz, 2H), 2.60-2.52 (m, 2H), 1.50 (s, 9H);

MS (离子喷雾) m/z 304 ($M+H^+$).

参考实施例 76

1,2,3,6-四氢-4-[(三氟甲基)磺酰氧基]吡啶-1-羧酸叔丁酯

按照 Wustrow 和 Wise 的方法(《合成》Synthesis 1991, 993)。冷却二异丙胺(4.2g, 29 mmol)的 THF (9mL)溶液至-78℃, 并在-78℃下加入正丁基锂溶液(11.2mL, 2.5M 己烷溶液), 温热反应物到 0℃, 然后再冷却至-78℃。滴加入 4-氧代哌啶-1-羧酸叔丁酯(5.4g, 27 mmol)的 THF (15mL)溶液(历时 5 分钟)。另搅拌 25 分钟后, 加入 N-苯基三氟甲烷磺酰亚胺(10g, 28 mmol)的 THF (25mL)溶液, 室温搅拌反应物 2 小时。浓缩反应物, 溶于二氯甲烷, 倒在氧化铝干垫(350g)上。产物用 10% EtOAc/石油醚(1L)洗脱, 浓缩得 8g 低熔点固体标题化合物。

^{1}H NMR (300 MHz, $CDCl_3$) d 5.77 (bs, 1H), 4.06-4.04 (m, 2H), 3.63 (t, J = 5.7 Hz, 2H), 2.46-2.40 (m, 2H), 1.48 (s, 9H).

参考实施例 77

5-[2-[4-(3-叔丁氧羰基氨基丙-1-炔基)-苯甲酰基氨基]乙基}-3-甲脒基-吲哚-1-羧酸叔丁酯

将 5-[2-[4-(3-叔丁氧羰基氨基丙-1-炔基)-苯甲酰基氨基]乙基}-3-硫代氨基甲酰基-吲哚-1-羧酸叔丁酯(73mg, 0.13 mmol, 参考实施例 78)溶于丙酮(75mL), 加入甲基碘(5mL)。加热该混合物至回流状态。15 分钟后, 真空除去溶剂, 得一黄色残留物。MS (离子喷雾) m/z 591 $(M+H)^+$. 残留物(80mg, 0.13 mmol)溶于 MeOH (15mL), 加入乙酸铵(0.5g), 加热回流此混合物 20 分钟。真空除去溶剂, 残留物进而分配到二氯甲烷和水之内。水层用二氯甲烷提取, 水洗合并的有机层, 硫酸镁干燥并真空浓缩。粗产物通过反相 HPLC 纯化, 以 30-70%洗脱 15 分钟, 得 22mg。MS (离子喷雾) m/z 560 $(M+H)^+$.

参考实施例 78

5-[2-[4-(3-叔丁氧基羰基氨基丙-1-炔基)-苯甲酰基氨基]乙基}-3-

硫代氨基甲酰基-吲哚-1-羧酸叔丁酯

将 5-[2-[4-(3-叔丁氧基羰基氨基丙-1-炔基)-苯甲酰基氨基]乙基}-3-氰基-吲哚-1-羧酸叔丁酯(80mg, 0.15 mmol, 参考实施例 79)溶于吡啶(20mL), 加入三乙胺(2mL)。向反应物中通硫化氢 5 分钟。然后室温放置反应物过夜。真空除去溶剂, 将残留物溶于二氯甲烷, 水洗并用硫酸镁干燥。真空除去溶剂得 80mg 残留物, 该产物无需进一步纯化直接使用。 ^{1}H NMR (300 MHz, $CDCl_3$) d 8.61 (t, J =3.0 Hz, 2H), 8.24 (s, 1H), 8.12-8.06 (m, 2H), 7.71-7.59 (m, 2H), 7.39-7.20 (m, 3H), 6.41 (bs, 1H), 4.89 (bs, 1H), 4.14 (d, J = 5.1 Hz, 2H), 3.78 (q, J = 6.4 Hz, 2H), 3.05 (t, J = 6.6 Hz, 2H), 1.66 (s, 9H), 1.46 (s, 9H).

参考实施例 79

5-{2-[4-(3-叔丁氧基羰基氨基丙-1-炔基)-苯甲酰基氨基]乙基}-3-氰基-吲哚-1-羧酸叔丁酯

向(3-{4-[2-(3-氰基-1H-吲哚-5-基)乙基氨基甲酰基]苯基}-丙-2-炔基)氨基甲酸叔丁酯(95mg, 0.22mmol, 参考实施例 64d)的丙酮(5mL)悬浮液内加入二碳酸二叔丁酯(47mg, 0.22mmol)和 DMAP (0.9mg, 8 mmol)。然后加入吡啶(1mL), 室温搅拌混合物过夜。真空除去溶剂, 将残留物溶于二氯甲烷, 用水洗涤, 然后以硫酸镁干燥, 并真空除去溶剂, 从而得 88mg 固体残余物(75%产率).

^{1}H NMR: (300 MHz, $CDCl_3$) d 8.63 (bs, 1H), 8.11 (d, J = 9.7 Hz, 1H), 7.72-7.57 (m, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.34-7.27 (m, 2H), 6.25 (bs, 1H), 4.84 (bs, 1H), 4.15 (d, J = 5.2 Hz, 2H), 3.76 (q, J = 6.6 Hz, 2H), 3.07 (t, J = 6.9 Hz, 2H), 1.69 (s, 9H), 1.47 (s, 9H).

参考实施例 80

4-(3-叔丁氧羰基氨基丙-1-炔基)苯甲酸

将 4-(3-叔丁氧羰基氨基丙-1-炔基)苯甲酸甲酯(1.09g, 38 mmol, 参考实施例 81)溶于 MeOH (15mL), 向该溶液内加入 NaOH (0.15g, 38 mmol)的水(5mL)溶液。加热此混合物至回流。5 小时后, 真空除去溶剂, 向残留物中加入二氯甲烷和 1N HCl。有机层用 1N HCl、水和盐水洗涤, 然后再用硫酸镁干燥。真空除去溶剂后得白色固体(0.60g,

57%产率).

^{1}H NMR (300 MHz, CD_3OD) d 7.86 (d, 2H), 7.39 (d, 2H), 3.98 (s, 2H), 1.38 (s, 9H).

参考实施例 81

4-(3-叔丁氧基羰基氨基丙-1-炔基)苯甲酸甲酯

将 4-碘苯甲酸甲酯(1.5g, 5.7 mmol)和丙-2-炔基氨基甲酸叔丁酯(0.89g, 5.7 mmol, 参考实施例 82)溶于哌啶(12mL), 用氮气净化该溶液。加入碘化亚铜(I)(22mg, 0.11mmol)和双(三苯膦)二氯化钯(40mg, 0.057 mmol), 在室温下搅拌此混合物。2 小时后, 真空除去溶剂, 残留物加到二氯甲烷中, 用 1N HCl、水和盐水洗涤, 然后硫酸镁干燥。真空除去溶剂, 残留物进而通过快速色谱纯化, 以 20%乙酸乙酯/己烷洗脱, 得白色固体标题化合物(1.1g, 67%产率).

^{1}H NMR (300 MHz, $CDCl_3$) d 7.98 (d, 2H), 7.48 (d, 2H), 4.79 (bs, 1H), 4.17 (d, 2H), 3.91 (s, 3H), 1.48 (s, 9H).

参考实施例 82

丙-2-炔基氨基甲酸叔丁酯

将炔丙胺(10g, 0.18 mol)溶于二氯甲烷(40mL), 用冰浴冷却。然后在 20 分钟加入二碳酸二叔丁酯(40g, 0.18 mol)的二氯甲烷(60mL)溶液。移去冷却浴, 温热反应物至室温, 搅拌过夜。真空除去溶剂, 所得残留物无需进一步纯化可直接使用。

^{1}H NMR (300 MHz, $CDCl_3$) d 4.75 (bs, 1H), 3.90 (d, 2H), 2.21 (t, 1H), 1.45 (s, 9H).

参考实施例 83

4-[2-(2-二甲氨基-乙基氨基)-嘧啶-4-基]-苯甲酸

向 4-[2-氯-嘧啶-4-基]-苯甲酸(234mg, 1mmol, 参考实施例 11g)的 DMSO (2mL)溶液内加入 2-(N, N-二甲氨基)乙胺(291mL, 2 mmol)。

加热所得溶液至85℃，在该温度下搅拌3.5小时，然后冷却并浓缩。残留物进而通过反相HPLC纯化，得296mg标题化合物，为其TFA盐形式。

^{1}H NMR (CD_3OD) d 2.97 (s, 6H), 3.45 (t, J = 6Hz, 2H), 3.88 (t, J = 6Hz, 2H), 7.31 (d, J = 5Hz, 1H), 8.13 (d, J = 8Hz, 2H), 8.20 (d, J = 8Hz, 2H), 8.44 (d, J = 5Hz, 1H).

MS（离子喷雾）m/z 286 (M+).

参考实施例84

4-[2-(2-氯)-嘧啶-4-基]-苄基(叔丁基二甲基甲硅烷基)醚

向4-溴-苄基叔丁基二甲基甲硅烷基醚(3.0g, 10 mmol, 参考实施例16)在THF (30mL)中的冷溶液(-78℃)内滴加入n-buLi (4.08mL, 2.5M 己烷溶液)。搅拌所得溶液10分钟，然后一次性加入1.14g (10mmol) 2-氯-嘧啶的THF (30mL)溶液。温热该溶液至-30℃，搅拌20分钟，尔后加入乙酸(600mL, 10mmol)和H_2O (100mL, 5.5 mmol)在THF (5mL)中形成的溶液。温热所得混合物到0℃，然后加入DDQ (2.27g, 10mmol)的THF (10mL)溶液。移去冷却浴，继续搅拌10分钟。再向该混合物内加入NaOH (10mL, 1M)，然后将混合物分配到乙醚和水之内。醚部分用盐水洗涤、硫酸镁干燥、活性炭脱色、经硅藻土过滤后浓缩滤液。残留物进而通过快速色谱纯化（以20%乙酸乙酯/己烷洗脱），得1.68g油状标题化合物，放置后析出结晶。 ^{1}H NMR ($CDCl_3$) d 0.04 (s, 6H), 0.84 (s, 9H), 4.70 (s, 2H), 7.45 (d, J = 8Hz, 2H), 7.53 (d, J = 5Hz, 1H), 7.96 (d, J = 8Hz, 2H), 8.50 (d, J = 5Hz, 1H).

MS（离子喷雾）m/z 335 (M+H, Cl 图形).

参考实施例85a

4-(1-[2-二甲氨基乙基]-6-氧代-1,6-二氢吡啶-3-基)苯甲酸乙酯和4-(6-[2-二甲氨基乙氧基]吡啶-3-基)苯甲酸乙酯

向4-(6-氧代-1,6-二氢吡啶-3-基)苯甲酸乙酯[0.500g, 2.06 mmol, 参考实施例 36f]在 THF:DMF [30mL 5:1]中的冷(0℃)浆液内加入60%氢化钠[0.247g, 6.18 mmol]。10分钟后加入碘化钾[2 mg]和2-二甲氨基乙基氯盐酸盐[Aldrich, 0.386g, 2.68 mmol], 并加热到50℃。20小时后, 缓慢加水[5ml]终止反应, 接着用二氯甲烷提取。合并有机提取物, 浓缩, 然后在HPLC上纯化(40-60% AcCN/水(含0.1% TFA)), 得4-(1-[2-二甲氨基乙基]-6-氧代-1,6-二氢吡啶-3-基)苯甲酸乙酯[0.337g, 38.2%产率](TFA 盐形式)和 4-(6-[2-二甲氨基乙氧基]吡啶-3-基)苯甲酸乙酯[0.110g, 12.5%收率] (TFA 盐形式)。

4-(1-[2-二甲氨基乙基]-6-氧代-1,6-二氢吡啶-3-基)苯甲酸乙酯:

^{1}H NMR (CD_3OD): δ 1.40 (3H, t, J = 7.8 Hz), 3.03 (6H, s), 3.62 (2H, t, J = 5.9 Hz), 4.38 (2H, q, J = 7.8 Hz), 4.49 (2H, t, J = 5.9 Hz), 6.72 (1H, d, J = 9.2 Hz), 7.68 (2H, d, J = 8.8 Hz), 7.98 (1H, dd, J = 9.2 Hz, 3.0 Hz), 8.07 (2H, d, J = 8.8 Hz), 8.13 (1H, d, J = 3.0 Hz).

MS(离子喷雾) m/z 315 $(M+H)^+$.

4-(6-[2-二甲氨基乙氧基]吡啶-3-基)苯甲酸乙酯:

^{1}H NMR (CD_3OD): δ 1.41 (3H, t, J = 8.1 Hz), 3.02 (6H, s), 3.64 (2H, t, J = 6.1 Hz), 4.39 (2H, q, J = 8.1 Hz), 4.74 (2H, t, J = 6.1 Hz), 7.01 (1H, d, J = 9.4 Hz), 7.73 (2H, d, J = 8.8 Hz), 8.07 (1H, dd, J = 9.4 Hz, 2.5 Hz), 8.10 (2H, d, J = 8.8 Hz), 8.51 (1H, d, J = 2.5 Hz).

MS(离子喷雾) m/z 315 $(M+H)^+$.

参考实施例 85b

采用和制备参考实施例 85a 所用基本相同的条件, 只是其中使用溴乙酸叔丁酯作为烷基化剂, 从而制得 4-(1-叔丁氧羰基甲基-6-氧代-1,6-二氢吡啶-3-基)苯甲酸乙酯。

^{1}H NMR ($CDCl_3$): δ 1.41 (3H, t, J = 7.3 Hz), 1.50 (9H, s), 4.40 (2H, q, J = 7.3 Hz), 4.64 (2H, s), 6.70 (1H, d, J = 9.5 Hz), 7.48 (2H, d, J = 8.2 Hz), 7.50 (1H, s), 7.68 (1H, d, J = 9.5 Hz), 8.08 (2H, d, J = 8.2 Hz).

MS(离子喷雾) m/z 358 $(M+H)^+$; 302 $(M-tBu)^+$.

参考实施例 85c

采用和制备 85a 所用基本相同的条件，只是其中使用 3-二甲氨基丙基氯盐酸盐作为烷基化剂，从而制得 4-[1-(3-二甲氨基丙基)-6-氧代-1,6-二氢吡啶-3-基]苯甲酸乙酯，MS(离子喷雾) m/z 329 $(M+H)^+$；以及 4-[6-(3-二甲氨基丙氧基)吡啶-3-基]苯甲酸乙酯，MS(离子喷雾) m/z 329 $(M+H)^+$.

参考实施例 85d

采用和制备参考实施例 85a 所用基本相同的条件，只是其中使用 4-(2-氧代-2H-吡啶-5-基)苯甲酸烯丙酯(参考实施例 104)和溴乙酸叔丁酯作为底物，从而制得 4-(1-[叔丁氧羰基甲基]-2-氧代-2H-吡啶-5-基)苯甲酸烯丙酯. MS(离子喷雾) m/z 370 $(M+H)^+$.

参考实施例 86a

4-(3-氨基-[1,2,4]三嗪-6-基)苯甲酸和 4-(3-氨基-[1,2,4]三嗪-5-基)苯甲酸

向 4-(3-氨基-[1,2,4]三嗪-5-基)苯甲酸乙酯与 4-(3-氨基-[1,2,4]三嗪-6-基)苯甲酸乙酯的 2:1 混合物(0.80g, 3.3 mmol, 参考实施例 87a)在 MeOH (50mL)和 THF (100mL)中的溶液内加入氢氧化钠水溶液(1N, 8.2mL, 8.2 mmol)。室温搅拌 18 小时后，用 2N HCl 酸化反应混合物至 pH 4-5，然后部分蒸发。收集产生的沉淀物，水洗并在真空下干燥，得到含~10% 4-(3-氨基-[1,2,4]三嗪-5-基)苯甲酸的 4-(3-氨基-[1,2,4]三嗪-6-基)苯甲酸；产量 0.23g (32%)：^{1}H NMR (DMSO-d_6) d 8.10 (2H, d, J=7.3Hz), 8.27 (2H, d, 7.3 Hz), 9.26 (1H, s)；MS, m/z (异构体混合物，离子喷雾) 235 $[(M+18)+H]^+$, 217 $(M+H)^+$. 进一步蒸发母液，过滤沉淀出的固体物得 4-(3-氨基-[1,2,4]三嗪-5-基)苯甲酸。产量 0.40g (56%)：^{1}H NMR (DMSO-d_6) d 7.8-8.2 (4H, m), 8.95 (1H, s).

参考实施例 86b

4-(3-氧代-2,3-二氢-[1,2,4]三嗪-6-基)苯甲酸

采用实施例 86a 的方法，只是用 4-(3-氧代-2,3-二氢-[1,2,4]三嗪-6-基)-苯甲酸乙酯(参考实施例 87b)替换 4-(3-氨基-[1,2,4]三嗪-5-基)苯甲酸乙酯与 4-(3-氨基-[1,2,4]三嗪-6-基)苯甲酸乙酯的混合物，从而制得标题化合物： ^{1}H NMR (DMSO-d_6) d 3.90 [(0.2H, d, J=4.9 Hz), (水合物)], 7.72 (0.80H, s), 8.05 (3.2H, s), 8.11 [(0.4H, d, J=7.7 Hz), (水合物)], 8.32 [(0.4H, d, J=7.7 Hz), (水合物)], 8.77 [(0.2H, s), (水合物)]。

参考实施例 86c

4-(5-氧代-4,5-二氢-[1,2,4]噁二唑-3-基)-苯甲酸

采用实施例 86a 的方法，只是其中使用参考实施例 89 的产物，从而制得标题化合物： ^{1}H NMR (DMSO-d_6) d 7.93 (2H, d, J=7.3 Hz), 8.12 (2H, d, J=7.3 Hz).

参考实施例 87a

4-(3-氨基-[1,2,4]三嗪-5-基)苯甲酸乙酯和 4-(3-氨基-[1,2,4]三嗪-6-基)苯甲酸乙酯

采用下述改进的 Loev, B.和 Goodman, M.M.的方法(《四面体通信》Tetrahedron Lett., 1968, 789)，只是其中使用 4-乙氧羰基苯基乙二醛水合物替代乙二醛水合物，相应地得到大约 2:1 的 4-(3-氨基-[1,2,4]三嗪-5-基)苯甲酸乙酯与 4-(3-氨基-[1,2,4]三嗪-6-基)苯甲酸乙酯的混合物：

向氨基胍盐酸盐(1g, 4.7 mol)的水溶液中加入固体碳酸氢钠(0.79g, 9.4 mmol)。然后将所得溶液加到 4-乙氧羰基苯基乙二醛水合物(1g, 4.7mmol, 参考实施例 88)溶液中。室温搅拌反应混合物 72 小时，收集沉淀物，水洗并风干。粗产物通过硅胶垫过滤，以 4% CH_2Cl_2/MeOH

洗脱。收集只含产物的馏分，减压除去溶剂。残留物用乙醚研制，得2:1标题化合物的混合物(^{1}H NMR)，系白色固体物；产量0.80g (70%)。

^{1}H NMR (DMSO-d_6) d 1.35 (3H, t), 4.35 (1.34H, q), 4.37 (0.66H, q), 7.38 (0.33H, s), 7.56 (0.67H, s), 8.08 (1.34H, d), 8.13 (0.67H, d), 8.18 (1.34H, d), 8.32 (0.67H, d), 8.89 (0.67, s), 9.28 (0.33H, s); MS, m/z (EI) 244 (M^+).

按照Lalezari等人方法(《杂环化学杂志》J. Het. Chem. 1969, 403)，使用取代的4-乙酰基苯甲酸乙酯替代利于鉴定相应的区域异构体结构的苯乙酮，从而也可以制得区域化学纯的4-(3-氨基-[1,2,4]三嗪-5-基)苯甲酸乙酯.

^{1}H NMR (DMSO-d_6) d 1.35 (3H, t, J = 7.1 Hz), 4.35 (2H, q, J =7.1 Hz), 7.56 (1H, s), 8.08 (2H, d, J =7.5 Hz), 8.18 (2H, d, J = 7.5 Hz), 8.89 (1H, s);

MS, m/z (离子喷雾) 263 $[(M+18)+H]^+$, 245 $(M+H)^+$.

参考实施例87b

4-(3-氧代-2,3-二氢-[1,2,4]三嗪-6-基)-苯甲酸乙酯

采用参考实施例87a的方法，只是其中使用氨基脲盐酸盐替代氨基胍盐酸盐，从而制得标题化合物。

^{1}H NMR (DMSO-d_6) d 1.33 (3H, t, J = 4.6 Hz), 4.38 (2H, q, J = 4.6 Hz), 7.74 (1H, s), 8.10 (4H, s), 11.12 (1H, s); MS, m/z (EI) 264 $[(M+18)+H]^+$, 246 $(M + H)^+$.

参考实施例88

4-乙氧基羰基苯基乙二醛水合物

应用下述改良的苯基乙二醛制备方法[《有机合成制备》Org. Syn. preparation(第2卷, 509)]，使用4-乙酰基苯甲酸乙酯替代苯乙酮，制备标题化合物:

向4-乙酰基苯甲酸乙酯(5g, 0.026 mol)在二噁烷(30mL)和水(1mL)中的溶液内加入二氧化硒(2.8g, 0.026 mol)。加热回流反应混合物18小时，冷却到室温，通过硅藻土垫过滤除去沉淀出的硒。减压

浓缩滤液，残留物通过硅胶垫真空过滤，依次用 33%和 50%己烷/乙酸乙酯洗脱，得色谱醇黄色油状标题化合物；产量 4.8g (87%)。取部分样品进一步通过用乙醚研制进行纯化，从而得白色固体。

^{1}H NMR (DMSO-d_6) d 1.32 (3H, t, J = 6.3 Hz), 4.35 (2H, q, J = 6.3 Hz), 5.67 (1H, t, J = 5.9 Hz), 6.88 (2H, d, J = 5.9 Hz), 8.08 (2H, d, J = 7.1 Hz), 8.17 (2H, d, J = 7.1 Hz).

参考实施例 89

4-(5-氧代-4,5-二氢-[1,2,4]噁二唑-3-基)-苯甲酸甲酯

室温下，向 4-（甲氧羰基）苯甲醛偕胺肟(0.38g, 2 mmol, 参考实施例 90)的吡啶(10mL)溶液内加入氯甲酸乙酯(0.23mL, 0.26g, 2mmol)。加热回流反应混合物 5 小时，然后蒸发溶剂。残留物倒入水中，部分蒸发至有沉淀出现为止。收集固体物，水洗、风干，进而再在真空下干燥，从而得白色固体标题化合物；产量 0.25g (57%)。

^{1}H NMR ($CDCl_3$ / DMSO-d_6) d 3.95 (3H, s), 7.73 (2H, d, J = 8.0 Hz), 8.13 (2H, d, J = 8.0 Hz); MS, m/z(EI) 220 (M^+).

参考实施例 90

4-(甲氧基羰基)苯甲醛偕胺肟

0℃下向 4-（甲氧基羰基）苯甲醛肟(2.7g, 0.015 mol, 参考实施例 91)的 $CHCl_3$溶液内通入氯气。反应混合物变绿，接着有沉淀生成。继续通气至反应混合物变为均相，此时停止通气并密封容器。室温再搅拌 1/2 小时后，向反应混合物内通入氮气以除去过量的氯。蒸发溶剂，残留物再溶于 EtOH (100mL)，加入 NH_3/MeOH (7M, 11mL, 110 mmol)。室温搅拌 1 小时后，蒸发溶剂，残留物通过硅胶垫真空过滤，以 4% MeOH/CH_2Cl_2洗脱。合并只含产物的馏分，进而浓缩。残留物再用乙醚研制，从而得白色固体标题化合物；产量 0.69g (24%)。

^{1}H NMR ($CDCl_3$ / DMSO-d_6) 3.92 (3H, s), 5.24 (2H,s), 7.77 (2H, d, J = 9.1 Hz), 8.02 (2H, d, J = 9.1 Hz), 9.68 (1H, s);

MS, m/z(离子喷雾) 195 $(M+H)^+$.

参考实施例 91

4-(甲氧基羰基)苯甲醛肟

向盐酸羟胺(3.3g, 0.048 mol)的 EtOH (100mL)溶液内加入乙醇钠(2.9g, 0.43 mol)。过滤混合物除去沉淀出的 NaCl, 在室温下加入 4-(甲氧基羰基)苯甲醛。在此温度下搅拌 18 小时后, 蒸发溶剂, 残留物进而用水研制, 风干后得白色固体标题化合物; 产量 5.3g (99%): MS (EI) m/z 180 $(M+H)^+$.

参考实施例 92a

4-[2-(吗啉-4-基-乙基氨基)-嘧啶-4-基]-苯甲酸

向 4-[2-氯-嘧啶-4-基]-苯甲酸(234mg, 1 mmol, 参考实施例 11g)的 DMF (或 DMSO) (3mL)溶液内加入 2-(吗啉-4-基)乙胺(275μL, 2.1 mmol)。温热所得混合物至 80℃, 搅拌 4 小时、然后在氮气流下浓缩反应混合物, 残留物进而通过反相 HPLC 纯化, 得 166mg 标题化合物。

^{1}H NMR (DMSO-d_6) 3.18 (m, 2H), 3.40 (m, 2H), 3.50-3.80 (m, 6H), 3.97 (m, 2H) 7.33 (d, J = 5Hz, 1H), 7.53 (bt, 1H), 8.07 (d, J = 8Hz, 2H), 8.25 (d, J = 8Hz, 2H), 8.49 (d, J = 5Hz, 1H), 9.70 (bs, 1H).

MS (EI) m/z 329 $(M+H)^+$.

下列化合物采用与参考实施例 92a 所用基本相同的方法制备, 只是其中使用指定胺替代 2-(吗啉-4-基)-乙胺。

参考实施例 92b

4-[2-(3-二甲氨基-丙基氨基)-嘧啶-4-基]-苯甲酸。使用 3-二甲氨基-丙胺。

^{1}H NMR (CD_3OD) 2.1 (m, 2H), 2.88 (s, 6H), 3.28 (t, J = 7Hz, 2H), 3.65 (bm, 2H), 7.33 (d, J = 5Hz, 1H), 8.15 (d, J = 8Hz, 2H), 8.24 (d, J = 8Hz, 2H), 8.40 (d, J = 5Hz, 1H).

MS （离子喷雾） m/z 301 $(M+H)^+$.

参考实施例 92c

4-[2-(2-二甲氨基-乙基-甲基氨基)-嘧啶-4-基]-苯甲酸。使用 2-(二甲氨基-乙基)-甲胺。

^{1}H NMR (CD_3OD) 3.0 (s, 6H), 3.31 (s, 3H), 3.50 (t, J = 7Hz, 2H), 4.15 (t, J = 7Hz, 2H), 7.28 (d, J = 5Hz, 1H), 8.14 (d, J = 8Hz, 2H), 8.22 (d, J = 8Hz, 2H), 8.49 (d, J = 5Hz, 1H).

MS （离子喷雾） m/z 301 $(M+H)^+$.

参考实施例 92d

2-[(4-{4-[2-(3-氰基-1H-吲哚-5-基)-乙基氨基甲酰基]-苯基}-嘧啶-2-基)-甲基-氨基]-乙烷磺酸。使用 2-甲基氨基-乙磺酸和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺（参考实施例 1az）作为底物。

参考实施例 92e

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-{2-[甲基-2(S),3(R),4(R),5(R),6-五羟基-己基)-氨基]嘧啶-4-基}-苯甲酰胺。采用 N-甲基-(2(S),3(R),4(R),5(R),6-五羟基-己基)-胺和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺（参考实施例 1az）作为底物。

参考实施例 92f

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-{2-[甲基-2(S),3(R),4(S),5(R),6-五羟基-己基)-氨基]嘧啶-4-基}-苯甲酰

胺。采用 N-甲基-(2(S),3(R),4(S),5(R),6-五羟基-己基)-胺和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺（参考实施例 1az）作为底物。

参考实施例 92g

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-(2-羟基-1-羟甲基-乙基氨基）嘧啶-4-基]-苯甲酰胺。采用 2-羟基-1-羟甲基-乙基胺和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺（参考实施例 1az）作为底物。MS（离子喷雾）m/z 457 $(M+H)^+$.

参考实施例 92h

2-[(4-{4-[2-(3-氰基-1H-吲哚-5-基)-乙基氨基甲酰基]-苯基}-嘧啶-2-基)-甲基-氨基]-乙烷磺酸。采用 2-(N-甲基-氨基)-乙烷磺酸和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺（参考实施例 1az）作为底物。

参考实施例 92i

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-(3-咪唑-1-基-丙基氨基)嘧啶-4-基]-苯甲酰胺。采用 3-咪唑-1-基-丙胺和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺（参考实施例 1az）作为底物。

参考实施例 92j

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-{2-[(2-二乙氨基-乙基)-甲基-氨基]嘧啶-4-基}-苯甲酰胺。使用 2-(二乙基氨基)-乙基-甲基-胺和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺（参考实施例 1az）作为底物。

参考实施例 92k

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-(2-二异丙基氨基-乙基氨基)嘧啶-4-基]-苯甲酰胺。使用 2-(二异丙基氨基)-乙胺和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺（参考实施例 1az）作为底物。

参考实施例 921

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-(2-二丁氨基-乙基氨基)嘧啶-4-基]-苯甲酰胺。使用 2-(二丁氨基)-乙胺和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺（参考实施例 1az）作为底物。

参考实施例 92m

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-(3-吗啉-4-基-丙基氨基)嘧啶-4-基]-苯甲酰胺。使用 3-(吗啉-4-基)-丙胺和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺（参考实施例 1az）作为底物。

参考实施例 92n

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-(3-二乙氨基-丙基氨基)嘧啶-4-基]-苯甲酰胺。使用 3-(二乙基氨基)-丙胺和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺（参考实施例 1az）作为底物。

参考实施例 92p

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-(3-哌啶-1-基-丙基氨基)嘧啶-4-基]-苯甲酰胺。使用 3-(哌啶-1-基)-丙胺和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺（参考实施例 1az）作为底物。

参考实施例 92q

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-(2-{[2-(乙基-甲基-氨基)-乙基]-甲基-氨基}-嘧啶-4-基)-苯甲酰胺。使用[2-(乙基-甲基-氨基)-乙基]-甲基-胺和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺（参考实施例 1az）作为底物。

参考实施例 92r

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-(5-二甲氨基-戊基氨基)嘧啶-4-基]-苯甲酰胺。使用 5-二甲氨基-戊胺（参考实施例 93a）和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺（参考实施例 1az）作为底物。MS（离子喷雾）m/z 496 $(M+H)^+$.

参考实施例 92s

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-(5-吗啉-4-基-戊基氨基)嘧啶-4-基]-苯甲酰胺。使用 5-(吗啉-4-基)-戊胺(参考实施例 93b)和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺（参考实施例 1az）作为底物。MS（离子喷雾）m/z 538 $(M+H)^+$.

参考实施例 92t

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-(5-哌啶-1-基-戊基氨基)嘧啶-4-基]-苯甲酰胺。使用 5-(哌啶-1-基)-戊胺(参考实施例 93c)和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺（参考实施例 1az）作为底物。MS（离子喷雾）m/z 536 $(M+H)^+$.

参考实施例 92u

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-(5-吡咯烷-1-基-戊基氨基)嘧啶-4-基]-苯甲酰胺。使用 5-(吡咯烷-1-基)-戊胺(参考实施例 93d)和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺（参考实施例 1az）作为底物。MS（离子喷雾）m/z 522 $(M+H)^+$.

参考实施例 92v

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-(4-甲基哌嗪-1-基)嘧啶-4-基]-苯甲酰胺。使用 N-甲基-哌嗪和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺（参考实施例 1az）作为底物。MS（离子喷雾）m/z 466 $(M+H)^+$.

参考实施例 92w

4-[(4-{4-[2-(3-氰基-1H-吲哚-5-基)乙基氨基甲酰基]苯基}嘧啶-2-基)-甲基氨基]-丁酸。使用 4-(甲基氨基)-丁酸和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺（参考实施例 1az）作为底物。MS（离子喷雾）m/z 483 $(M+H)^+$.

参考实施例 92x

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-(2,2,2-三氟乙氧基)嘧啶-4-基]-苯甲酰胺。使用三氟乙醇和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺（参考实施例 1az）作为底物。MS（离子喷雾）m/z 466 $(M+H)^+$.

参考实施例 92y

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-(2-吡咯烷-1-基嘧啶-4-基)-苯甲酰胺。使用吡咯烷和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺（参考实施例 1az）作为底物。MS（离子喷雾）m/z 437 $(M+H)^+$.

参考实施例 92z

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-(2-羟甲基吡咯烷-1-基)嘧啶-4-基]-苯甲酰胺。使用 2-(羟甲基)-吡咯烷和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺（参考实施例 1az）作为底物。MS（离子喷雾）m/z 467 $(M+H)^+$.

参考实施例 92aa

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-(氨基甲酰基甲基-N-甲基氨基)嘧啶-4-基]-苯甲酰胺。使用 N-甲基甘氨酰胺和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺（参考实施例 1az）作为底物。MS（离子喷雾）m/z 454 $(M+H)^+$.

参考实施例 92ab

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-(6-吡咯烷-1-基-己基氨基)嘧啶-4-基]-苯甲酰胺。使用 6-吡咯烷-1-基己胺(参考实施例 93e)和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺（参考实施例 1az）作为底物。MS（离子喷雾）m/z 536 $(M+H)^+$.

参考实施例 92ac

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-(6-哌啶-1-基-己基氨基)嘧啶-4-基]-苯甲酰胺。使用 6-哌啶-1-基己胺(参考实施例 93f)和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺（参考实施例 1az）作为底物。MS（离子喷雾）m/z 550 $(M+H)^+$.

参考实施例 92ad

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-(4-哌啶-1-基-丁基氨基)嘧啶-4-基]-苯甲酰胺。使用 4-哌啶-1-基丁胺(参考实施例 93g)和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺（参考实施例 1az）作为底物。MS（离子喷雾）m/z 522 $(M+H)^+$.

参考实施例 92ae

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-(4-二乙氨基丁基氨基)嘧啶-4-基]-苯甲酰胺。使用 4-二乙基氨基丁胺(参考实施例 93h)和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺（参考实施例 1az）作为底物。MS（离子喷雾）m/z 510 $(M+H)^+$.

参考实施例 92af

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-(6-吗啉-4-基-己基氨基)嘧啶-4-基]-苯甲酰胺。使用 6-吗啉-4-基己胺(参考实施例 93i)和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺(参考实施例 1az)作为底物。MS (离子喷雾) m/z 552 $(M+H)^+$.

参考实施例 92ag

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-(6-二甲氨基己基氨基)嘧啶-4-基]-苯甲酰胺。使用 6-(二甲氨基)-己胺和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺(参考实施例 1az)作为底物。MS (离子喷雾) m/z 510 $(M+H)^+$.

参考实施例 92ah

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-(4-二甲氨基丁基氨基)嘧啶-4-基]-苯甲酰胺。采用 4-(二甲氨基)-丁胺和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺(参考实施例 1az)作为底物。MS (离子喷雾) m/z 482 $(M+H)^+$.

参考实施例 92ai

4-[2-(二环[2.2.1]庚-2-基氨基)嘧啶-4-基]-N-[2-(3-氰基-1H-吲哚-5-基)-乙基]苯甲酰胺。使用二环[2.2.1]庚-2-基胺和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺(参考实施例 1az)作为底物。MS (离子喷雾) m/z 477 $(M+H)^+$.

参考实施例 92aj

1-(4-{4-[2-(3-氰基-1H-吲哚-5-基)乙基氨基甲酰基]苯基}嘧啶-2-基)吡咯烷-2-羧酰胺。使用吡咯烷-2-羧酰胺和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺(参考实施例 1az)作为底物。MS (离子喷雾) m/z 480 $(M+H)^+$.

参考实施例 92ak

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-{2-[(2-羟基-乙基)-N-甲基氨基]嘧啶-4-基}-苯甲酰胺。使用(2-羟基-乙基)-N-甲基胺和N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺（参考实施例 1az）作为底物。MS（离子喷雾）m/z 441 $(M+H)^+$.

参考实施例 92al

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-(2-吗啉-4-基-嘧啶-4-基)-苯甲酰胺。使用吗啉和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺（参考实施例 1az）作为底物。

^{1}H NMR (DMSO) δ 2.98 (bt, 2H, J = 7Hz); 3.56 (m, 2H); 3.70 (bs, 4H); 3.79 (bs, 4H); 7.18 (d, 1H, J = 9Hz); 7.32 (d, 1H, J = 5Hz); 7.49 (m, 2H); 7.94 (d, 2H, J = 8Hz); 8.22 (m, 3H); 8.50 (d, 1H, J = 5Hz); 8.74 (bt, 1H); 12.20 (bs, 1H).

MS（离子喷雾）m/z 453 $(M+H)^+$.

参考实施例 92am

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-(环丙基甲基-氨基)嘧啶-4-基]-苯甲酰胺。使用环丙基甲基-胺和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺（参考实施例 1az）作为底物。

^{1}H NMR (DMSO) δ 0.26 (m, 2H); 0.44 (m, 2H); 3.00 (bt, 2H, J = 7Hz); 3.25 (bs, 2H); 3.56 (m, 2H); 7.20 (m, 2H); 7.36 (bt, 1H); 7.50 (m, 2H); 7.94 (d, 2H, J = 8Hz); 8.29 (m, 3H); 8.38 (d, 1H, J = 5Hz); 8.69 (bt, 1H); 12.15 (bs, 1H).

MS（离子喷雾）m/z 437 $(M+H)^+$.

参考实施例 92an

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-[(2-甲氧基-乙基)-甲基-氨基]-嘧啶-4-基]-苯甲酰胺。使用(2-甲氧基-乙基)-甲基-胺和N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺（参考实施例 1az）作为底物。

^{1}H NMR (DMSO) δ 2.98 (t, 2H, J = 7Hz); 3.22 (s, 3H); 3.28 (s, 3H); 3.58 (m, 4H); 3.85 (m, 2H); 7.21 (m, 2H); 7.50 (m,2H); 7.93 (d, 2H, J = 9Hz); 8.20 (m, 3H); 8.45 (d, 1H, J = 5Hz); 8.69 (bt, 1H); 12.13 (bs, 1H).

MS （离子喷雾） m/z 455 $(M+H)^+$.

参考实施例 92ap

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-(3-羟基-丙基氨基)-嘧啶-4-基]-苯甲酰胺。使用 3-羟基-丙胺和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺（参考实施例 1az）作为底物。

^{1}H NMR (DMSO) δ 1.73 (t, 2H, J = 7Hz); 2.98 (t, 2H, J = 7Hz); 3.40 (m, 2H); 4.48 (bs, 1H); 7.20 (m, 3H); 7.48 (m, 2H); 7.92 (d, 2H, J = 8Hz); 8.18 (m, 3H); 8.37 (bd, 1H, J = 5Hz); 8.68 (bt, 1H); 12.12 (bs, 1H).

MS （离子喷雾） m/z 441 $(M+H)^+$.

参考实施例 92aq

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-(2-羟基-乙基)-丙基-氨基]-嘧啶-4-基]-苯甲酰胺。使用(2-羟基-乙基)-丙基-胺和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺（参考实施例 1az）作为底物。

^{1}H NMR (DMSO) δ .90 (t, 3H, J = 7Hz); 1.63 (bd, 2H); 2.98 (t, 2H, J = 7Hz); 3.63 (m, 8H); 4.73 (t, 1H, J = 5Hz); 7.19 (m, 2H); 7.48 (m, 2H); 7.92 (d, 2H, J = 8Hz); 8.19 (m, 3H); 8.43 (d, 1H, J = 5Hz); 8.67 (bt, 1H); 12.11 (bs, 1H).

MS （离子喷雾） m/z 469 $(M+H)^+$.

参考实施例 92ar

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-(2-哌啶-1-基-嘧啶-4-基)-苯甲酰胺。采用哌啶和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺（参考实施例 1az）作为底物。

^{1}H NMR (DMSO) δ 1.6 (m, 6H); 2.98 (m, 2H); 3.55 (m, 2H); 3.84 (m, 4H); 7.19 (m, 2H); 7.49 (m, 2H); 7.93 (d, 2H, J = 8Hz); 8.20 (m, 3H); 8.44 (d, 1H, J = 5Hz); 8.69 (bt, 1H); 12.14 (bs, 1H).

MS （离子喷雾） m/z 451 $(M+H)^+$.

参考实施例 92as

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-(乙基-甲基-氨基)-嘧啶-4-基]-苯甲酰胺。使用乙基甲基胺和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺（参考实施例 1az）作为底物。

^{1}H NMR (DMSO) δ 1.15 (t, 3H, J = 7Hz); 2.99 (bt, 2H); 3.17 (s, 3H); 3.56 (m, 2H); 3.73 (m, 2H); 7.20 (m, 2H); 7.50 (m, 2H); 7.94 (d, 2H, J = 7Hz); 8.20 (m, 3H); 8.44 (d, 1H, J = 5Hz); 8.69 (bs, 1H); 12.14 (bs, 1H).

MS （离子喷雾） m/z 425 $(M+H)^+$.

参考实施例 92at

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-(4-羟基-哌啶-1-基)-嘧啶-4-基]-苯甲酰胺。使用 4-羟基哌啶和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺（参考实施例 1az）作为底物。

^{1}H NMR (DMSO) δ 1.36 (m, 2H); 1.82 (m, 2H); 2.98 (t, 2H, J = 7Hz); 3.34 (m, 2H); 3.55 (m, 2H); 3.76 (bs, 1H); 4.39 (bd, 2H); 4.75 (bs, 1H); 7.20 (m, 2H); 7.48 (m, 2H); 7.92 (d, 2H, J = 9Hz); 8.20 (m, 3H); 8.45 (d, 1H, J = 5Hz); 8.67 (bt, 1H); 12.12 (bs, 1H).

MS （离子喷雾） m/z 467 $(M+H)^+$.

参考实施例 92au

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-(2,3-二羟基-丙基氨基)-嘧啶-4-基]-苯甲酰胺。使用 2,3-二羟基-丙胺和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺（参考实施例 1az）作为底物。MS （离子喷雾） m/z 457 $(M+H)^+$.

参考实施例 92av

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-[(2,3-二羟基-丙基)-甲基-氨基]-嘧啶-4-基]-苯甲酰胺。使用 2,3-二羟基-丙基-甲基-胺和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺（参考实施例 1az）作为底物。MS （离子喷雾） m/z 471 $(M+H)^+$.

参考实施例 92aw

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-((s)-2-甲氧基甲基-吡咯烷-1-基)-嘧啶-4-基]-苯甲酰胺。使用(s)-2-甲氧基甲基-吡咯烷和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺（参考实施例 1az）作为底物。MS （离子喷雾） m/z 481 $(M+H)^+$.

参考实施例 92ax

4-[4-[4-[2-(3-氰基-1H-吲哚-5-基)-乙基氨基甲酰基]-苯基]-嘧啶-2-基]-哌嗪-1-羧酸叔丁酯。使用哌嗪-1-羧酸叔丁酯和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺（参考实施例 1az）作为底物。 ^{1}H NMR (DMSO) δ 1.44 (s, 9H); 2.98 (t, 2H, J = 7Hz); 3.45 (bs, 4H); 3.56 (m, 2H); 3.83 (bs, 4H); 7.18 (d, 1H, J = 8Hz); 7.31 (d, 1H, J = 5Hz); 7.48 (d, 1H, J = 8Hz); 7.51 (s, 1H); 7.94 (d, 2H, J = 8Hz); 8.22 (m, 3H); 8.49 (d, 1H, J = 5Hz); 8.70 (bt, 1H); 12.12 (bs, 1H).

MS （离子喷雾） m/z 552 $(M+H)^+$.

参考实施例 92ay

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-[2-(2-氧代-咪唑烷-1-基)-乙基氨基]-嘧啶-4-基]-苯甲酰胺。使用 2-(2-氧代-咪唑烷-1-基)-乙胺和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺（参考实施例 1az）作为底物。 ^{1}H NMR (DMSO) δ 2.96 (bt, 2H); 3.24 (m, 4H); 3.47 (m, 6H); 6.26 (s, 1H); 7.18 (m, 2H); 7.27 (bt, 1H, J = 5Hz); 7.48 (m, 2H); 7.91 (d, 2H, J = 9Hz); 8.19 (m, 3H); 8.36 (bd, 1H); 8.67 (t, 1H, J = 5Hz); 12.10 (bs, 1H).

MS （离子喷雾） m/z 495 $(M+H)^+$.

参考实施例 92az

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-(3-甲氧基-丙基氨基)-嘧啶-4-基]-苯甲酰胺。使用 3-甲氧基-丙胺和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺（参考实施例 1az）作为底物。

^{1}H NMR (DMSO) δ 1.81 (m, 2H); 2.98 (m, 2H); 3.24 (s, 3H); 3.41 (m, 4H); 3.56 (m, 2H); 7.19 (m, 2H); 7.28 (bs, 1H); 7.50 (m, 2H); 7.92 (m, 2H); 8.18 (m, 3H); 8.38 (bs, 1H); 8.68 (bs, 1H); 12.13 (bs, 1H).

MS （离子喷雾） m/z 455 $(M+H)^+$.

参考实施例 92aaa

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-(2-羟基-乙基氨基)-嘧啶-4-基]-苯甲酰胺。使用 2-羟基-乙胺和 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯-嘧啶-4-基]-苯甲酰胺（参考实施例 1az）作为底物。^{1}H NMR (DMSO) δ 2.98 (t, 2H, J = 7Hz); 3.44 (bs, 2H); 3.55 (m, 4H); 4.70 (t, 1H, J = 6Hz); 7.17 (m, 3H); 7.48 (m, 2H); 7.92 (d, 2H, J = 9Hz); 8.18 (m, 3H); 8.38 (d, 1H, J = 5Hz); 8.68 (bt, 1H); 12.12 (bs, 1H).

MS （离子喷雾） m/z 427 $(M+H)^+$.

参考实施例 92aab

4-(2-二甲氨基-嘧啶-4-基)-苯甲酸。使用二甲胺和 4-[2-氯-嘧啶-4-基]-苯甲酸作为底物。MS （离子喷雾） m/z 244 $(M+H)^+$.

参考实施例 93a

5-二甲氨基-戊胺

向氢化铝锂的冷溶液(8ml, 0.5M 乙醚溶液, 0℃)内缓慢加入 5-（二甲氨基）-戊腈(126mg, 1 mmol, 参考实施例 94a)的乙醚(1mL)溶液。加毕后，移去冷却浴，继续搅拌 2 小时。然后冷却反应混合物到 0℃，依次滴加水(160mL)、氢氧化钠溶液(160mL, 5M)、水(160mL)处理反应物。通过硅藻土过滤所得混合物，减压浓缩滤液得油状物，该产物无需进一步纯化可直接使用。

下列化合物采用与参考实施例 93a 所用基本相同的方法制备，只是其中使用指定的腈替换 5-(二甲氨基)-戊腈。

参考实施例 93b

5-(吗啉-4-基)-戊胺。使用 5-(吗啉-4-基)-戊腈(参考实施例 94b)作为底物。

参考实施例 93c

5-(哌啶-1-基)-戊胺。使用 5-(哌啶-1-基)-戊腈（参考实施例 94c）作为底物。

参考实施例 93d

5-(吡咯烷-1-基)-戊胺。使用 5-(吡咯烷-1-基)-戊腈（参考实施例 94d）作为底物。

参考实施例 93e

6-吡咯烷-1-基-己胺。使用 6-吡咯烷-1-基己腈（参考实施例 94e）作为底物。MS （离子喷雾） m/z 171 $(M+H)^+$.

参考实施例 93f

6-哌啶-1-基己胺。使用 6-哌啶-1-基己腈（参考实施例 94f）作为底物。MS （离子喷雾） m/z 185 $(M+H)^+$.

参考实施例 93g

4-哌啶-1-基-丁胺。使用 4-哌啶-1-基丁腈（参考实施例 94g）作为底物。MS （离子喷雾） m/z 157 $(M+H)^+$.

参考实施例 93h

4-(二乙基氨基)-丁胺。使用 4-(二乙基氨基)-丁腈（参考实施例 94h）作为底物。MS （离子喷雾） m/z 145 $(M+H)^+$.

参考实施例 93i

6-吗啉-4-基己胺。使用 6-吗啉-4-基己腈（参考实施例 94i）作为底物。MS（离子喷雾）m/z 187 $(M+H)^+$.

参考实施例 94a

5-(二甲基氨基)-戊腈

搅拌二甲胺(4mL, 40%水溶液)与 5-溴戊腈(2.3mL, 20 mmol)的混合物 24 小时。加氢氧化钠溶液(10mL, 5M)稀释所得反应混合物，然后用乙醚提取。乙醚提取物以 K_2CO_3 干燥，减压浓缩后得一油状物(1.5g)，该产物无需进一步纯化而直接使用。

下列化合物采用与参考实施例 94a 所用基本相同的方法制备，只是其中使用指定胺(2 eq.)/苯(4mL)替代二甲胺/水。

参考实施例 94b

5-(吗啉-4-基)-戊腈。采用吗啉作为底物，得 3.5g 油状物。

参考实施例 94c

5-(哌啶-1-基)-戊腈。采用哌啶作为底物，得 3.29g 油状物。

参考实施例 94d

5-(吡咯烷-1-基)-戊腈。采用吡咯烷作为底物，得 3.32g 油状物。

参考实施例 94e

6-吡咯烷子基-己腈。采用吡咯烷和 6-氯-己腈作为底物。MS（离子喷雾）m/z 167 $(M+H)^+$.

参考实施例 94f

6-哌啶-1-基己腈。采用哌啶和 6-氯-己腈作为底物。MS（离子喷雾）m/z 181 $(M+H)^+$.

参考实施例 94g

4-哌啶-1-基丁腈。采用哌啶和 4-氯丁腈作为底物。MS（离子喷雾）m/z 153 $(M+H)^+$.

参考实施例 94h

4-(二乙基氨基)-丁腈。采用二乙胺和 6-氯-丁腈作为底物。MS（离子喷雾）m/z 141 $(M+H)^+$.

参考实施例 94i

6-吗啉-4-基己腈。采用吗啉和 6-氯-己腈作为底物。MS（离子喷雾）m/z 183 $(M+H)^+$.

参考实施例 95

4-(2-氧代-六氢-嘧啶-5-基)-苯甲酸甲酯

向 4-(2-氧代-嘧啶-5-基)-苯甲酸甲酯(761mg, 3.3 mmol, 参考实施例 19c)在 DMF (20mL)和甲醇(5mL)中的溶液内加入 Pd-C (250mg, 10% w/w)。在氢气气氛中搅拌所得混合物 3 小时。用氮气净化该混合物，然后通过硅藻土过滤。浓缩滤液，残留物进而通过快速色谱纯化（以 5%甲醇/二氯甲烷洗脱），得白色固体标题化合物(421mg)。 ^1H NMR (CD_3OD) 3.28 (m, 1H), 3.47 (d, J = 7Hz, 4H), 3.90 (s, 3H), 7.44 (d, J = 8Hz, 2H), 7.90 (d, J = 8Hz, 2H).

参考实施例 96

4-(2-氧代-嘧啶-5-基)-苯甲醛

向 4-(2-[叔丁基二苯基甲硅烷氧基]-嘧啶-5-基)-苯甲醛缩二甲醇(2.28g, 4.7 mmol, 参考实施例 97a)的 THF (10mL)溶液内加入盐酸(10mL, 2M)。搅拌所得混合物 1 小时。减压浓缩该混合物至其原始体积的一半。滤出固体，然后用水和乙醚洗涤，得白色固体标题化合物(1.1g)。

^{1}H NMR (DMSO) δ 7.88 (d, J = 8Hz, 2H), 7.95 (d, J = 8Hz, 2H), 8.79 (s, 2H), 9.99 (s, 1H).

参考实施例 97a

4-(2-[叔丁基二苯基甲硅烷氧基]-嘧啶-5-基)-苯甲醛缩二甲醇

向 4-溴-苯甲醛缩二甲醇(2.31g, 10 mmol)的 THF (30mL)冷(-78℃)溶液内滴加入正丁基锂(4.4mL, 2.5M 己烷溶液)。加毕后搅拌反应混合物 5 分钟，然后加入 $ZnCl_2$溶液(20mL, 0.5M THF 溶液)。移去冷却浴，继续搅拌 5 分钟，尔后加入包含 5-溴-(2-[叔丁基二苯基甲硅烷氧基]-嘧啶(4.13g, 10 mmol)和$(Ph_3P)_4Pd$ (1.1g, 1 mmol)的 THF (20mL)溶液。温热此混合物到 60℃，并在此温度下搅拌 2 小时。冷却所得溶液到室温，加乙醚稀释，顺序用 5%氨水溶液、水和盐水洗涤，硫酸镁干燥并浓缩。残留物进而通过快速色谱纯化(以含 10%乙酸乙酯、10%二氯甲烷的己烷溶液洗脱)，得 2.28g 油状标题化合物。

^{1}H NMR ($CDCl_3$) δ 1.18 (s, 9H), 3.35 (s, 6H), 5.44 (s, 1H), 7.38 (m, 6H), 7.44 (d, J = 8Hz, 2H), 7.53 (d, J = 8Hz, 2H), 7.8 (m, 4H), 8.59 (s, 2H).

参考实施例 97b

4-(3-甲氧羰基-苯基)-苯甲醛

采用和参考实施例 97a 所用基本相同的方法，只是其中使用 3-溴-苯甲酸甲酯替代 5-溴-(2-[叔丁基二苯基甲硅烷氧基]-嘧啶作为底物，并使用下述改进的后处理步骤：冷却到室温后，加乙酸乙酯稀释反应混合物，然后依次用盐酸(2M)和盐水洗涤，硫酸镁干燥并浓缩。残留物通过快速色谱纯化(以含 20%乙酸乙酯/5%二氯甲烷的己烷洗脱)，得黄色固体标题化合物。MS (EI) m/z 240 $(M)^+$.

参考实施例 97c

4-(2-甲氧基羰基-苯基)-苯甲醛. 采用和参考实施例 97b 所用基本相同的方法，只是其中用 2-碘苯甲酸甲酯作为底物替换 3-溴-苯甲酸甲

酯。MS (EI) m/z 240 $(M)^+$.

参考实施例 98

4-(1,3-二甲基-2-氧代-六氢-嘧啶-5-基)-苯甲酸甲酯

向氢化钠分散物(60%/矿物油) (88mg, 2.2 mmol)的 THF (3mL)冷悬浮液(0℃)内加入包含 4-(2-氧代-六氢-嘧啶-5-基)-苯甲酸甲酯(236mg, 1 mmol, 参考实施例 95)和甲基碘(300μL, 5 mmol)以及 DMF (4mL)的溶液。搅拌所得混合物 16 小时, 然后加水终止反应, 用乙酸乙酯稀释, 接着用水和盐水洗涤, 硫酸镁干燥并浓缩, 从而得到褐色固体标题化合物(255mg)。^{1}H NMR ($CDCl_3$) δ 2.98 (s, 6H), 3.37-3.53 (m, 5H), 3.93 (s, 3H), 7.32 (d, J = 8Hz, 2H), 8.01 (d, J = 8Hz, 2H).

MS (离子喷雾) m/z 263 $(M+H)^+$.

参考实施例 99a

联苯-3,4'-二羧酸 4'-{[2-(3-氰基-1H-吲哚-5-基)-乙基]-酰胺}3-[(2-甲氧基-乙基)-酰胺]

向联苯-3,4'-二羧酸 4'-{[2-(3-氰基-1H-吲哚-5-基)-乙基]-酰胺} (102mg, 0.25 mmol, 参考实施例 17h)在二氯甲烷/DMF (3:1, 1mL 总体积)中的溶液内加入 TBTU (88mg, 0.27 mmol)和二异丙基乙胺(48mL, 0.28 mmol)。搅拌所得溶液 2 分钟, 然后加入另一份二异丙基乙胺(48mL)和 2-甲氧基-乙胺(44mL)。搅拌该溶液 35 分钟, 然后减压浓缩。将残留物悬浮于二氯甲烷, 过滤。固体物用二氯甲烷/甲醇(3:1)洗涤, 尔后真空干燥, 得 121mg 标题化合物。MS (离子喷雾) m/z 467 $(M+H)^+$.

参考实施例 99b

3'-(吗啉-4-羰基)-联苯-4-羧酸[2-(3-氰基-1H-吲哚-5-基)-乙基]-

酰胺. 采用和参考实施例 99a 所用基本相同的方法，只是其中使用吗啉作为底物替代 2-甲氧基-乙胺。MS （离子喷雾） m/z 479 $(M+H)^+$.

参考实施例 99c

联苯-3,4′-二羧酸 4′-{[2-(3-氰基-1H-吲哚-5-基)-乙基]-酰胺} 3-[(2-吗啉-4-基-乙基)-酰胺]. 采用和参考实施例 99a 所用基本相同的方法，只是其中使用 2-(吗啉-4-基)-乙胺作为底物替代 2-甲氧基-乙胺。MS （离子喷雾） m/z 522 $(M+H)^+$.

参考实施例 99d

联苯-2,4′-二羧酸 4′-{[2-(3-氰基-1H-吲哚-5-基)-乙基]-酰胺} 2-[(3-二乙基氨基-丙基)-酰胺]. 采用和参考实施例 99a 所用基本相同的方法，只是其中使用 3-(二乙基氨基)-丙胺和联苯-2,4′-二羧酸 4′-{[2-(3-氰基-1H-吲哚-5-基)-乙基]-酰胺} （参考实施例 17i）作为底物。MS （离子喷雾） m/z 522 $(M+H)^+$.

参考实施例 99e

联苯-2,4′-二羧酸 4′-{[2-(3-氰基-1H-吲哚-5-基)-乙基]-酰胺} 2-[(3-吗啉-4-基-丙基)-酰胺]. 采用和参考实施例 99a 所用基本相同的方法，只是其中使用 3-(吗啉-4-基)-丙胺和联苯-2,4′-二羧酸 4′-{[2-(3-氰基-1H-吲哚-5-基)-乙基]-酰胺} （参考实施例 17i）作为底物。MS （离子喷雾） m/z 536 $(M+H)^+$.

参考实施例 99f

联苯-2,4′-二羧酸 4′-{[2-(3-氰基-1H-吲哚-5-基)-乙基]-酰胺} 2-[(3-哌啶-1-基-丙基)-酰胺]. 采用和参考实施例 99a 所用基本相同的方法，只是其中使用 3-(哌啶-1-基)-丙胺和联苯-2,4′-二羧酸 4′-{[2-(3-氰基-1H-吲哚-5-基)-乙基]-酰胺} （参考实施例 17i）作为底物。MS （离子喷雾） m/z 534 $(M+H)^+$.

参考实施例 99g

联苯-2,4′-二羧酸 4′-{[2-(3-氰基-1H-吲哚-5-基)-乙基]-酰胺} 2-[(4-二甲氨基-丁基)-酰胺]. 采用和参考实施例 99a 所用基本相同的方法，只是其中使用 4-(二甲基氨基)-丁胺和联苯-2,4′-二羧酸 4′-{[2-(3-氰基-1H-吲哚-5-基)-乙基]-酰胺} (参考实施例 17i)作为底物。MS (离子喷雾) m/z 508 $(M+H)^+$.

参考实施例 99h

联苯-2,4′-二羧酸 4′-{[2-(3-氰基-1H-吲哚-5-基)-乙基]-酰胺} 2-[(2,3-二羟基-丙基)-甲基-酰胺]. 采用和参考实施例 99a 所用基本相同的方法，只是其中使用(2,3-二羟基-丙基)-甲基-胺和联苯-2,4′-二羧酸 4′-{[2-(3-氰基-1H-吲哚-5-基)-乙基]-酰胺} (参考实施例 17i)作为底物。MS (离子喷雾) m/z 497 $(M+H)^+$.

参考实施例 99i

联苯-2,4′-二羧酸 4′-{[2-(3-氰基-1H-吲哚-5-基)-乙基]-酰胺} 2-[(2,3-二羟基-丙基)-酰胺]. 采用和参考实施例 99a 所用基本相同的方法，只是其中使用 2,3-二羟基-丙胺和联苯-2,4′-二羧酸 4′-{[2-(3-氰基-1H-吲哚-5-基)-乙基]-酰胺} (参考实施例 17i)作为底物。MS (离子喷雾) m/z 497 $(M+H)^+$.

参考实施例 100a

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-(2-甲氧基乙氧基)-嘧啶-4-基]苯甲酰胺

向 2-甲氧基乙醇(0.118mL, 1.50 mmol)的 DMSO (5mL)溶液内加入氢化钠(Aldrich, 60%分散物, 0.0720g, 1.80 mmol)，接着搅拌至无氢气逸出为止(~15 分钟)。取 1 毫升这种醇盐储备溶液加到 N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-氯嘧啶-4-基]苯甲酰胺(0.147g, 0.249 mmol, 参考实施例 1az)中，随后加热(60℃)。2 小

时后再加入 0.5mL 这种醇盐储备溶液。再过 2 小时后，加水(40mL)终止反应，过滤收集所产生的沉淀物。沉淀物用水和 CH_2Cl_2 洗涤，经高真空干燥后得白色固体产物。MS（离子喷雾） m/z 422 $(M+H)^+$.

下列化合物采用和参考实施例 100a 所用基本相同的方法制备，只是其中使用指定醇代替 2-甲氧基乙醇。

参考实施例 100b

N-[(2-(3-氰基-1H-吲哚-5-基)乙基]-4-[2-(1-氨基甲酰基乙氧基)嘧啶-4-基]苯甲酰胺. 使用 2-羟基-丙酰胺作为底物。MS（离子喷雾） m/z 455 $(M+H)^+$.

参考实施例 100c

N-[(2-(3-氰基-1H-吲哚-5-基)乙基]-4-[2-(6-二甲氨基己氧基)嘧啶-4-基]苯甲酰胺. 使用 6-二甲氨基己醇作为底物。MS（离子喷雾） m/z 511 $(M+H)^+$.

参考实施例 100d

N-[(2-(3-氰基-1H-吲哚-5-基)乙基]-4-[2-(2-氧代哌啶-3-基氧基)嘧啶-4-基]苯甲酰胺. 使用 2-羟基-戊内酰胺作为底物。MS（离子喷雾） m/z 481 $(M+H)^+$.

参考实施例 100e

N-[(2-(3-氰基-1H-吲哚-5-基)乙基]-4-[2-(2-吡咯烷-1-基-乙氧基)嘧啶-4-基]苯甲酰胺. 使用 2-(吡咯烷-1-基)-乙醇作为底物。MS（离子喷雾） m/z 481 $(M+H)^+$.

参考实施例 100f

N-[2-(3-氰基-1H-吲哚-5-基)乙基]-4-[2-(2-二甲氨基乙氧基)嘧啶

-4-基]苯甲酰胺. 使用 2-(二甲氨基)-乙醇作为底物。MS (离子喷雾) m/z 455 $(M+H)^+$.

参考实施例 101a

4-(3-[2-二甲氨基乙氧基]苯基)苯甲酸

真空下，搅拌 3-(2-二甲氨基乙氧基)苯基碘(0.495g, 1.70 mmol)、4-羧基苯硼酸(Lancaster, 0.282g, 1.70 mmol)、和碳酸钠(0.360g, 3.40 mmol)在 1:1 H_2O: AcCN (20mL)中的溶液 5 分钟，接着加入四(三苯膦)钯(0) (0.170g)。90℃加热反应混合物 3 小时，并通过 Celite 滤除催化剂。稍加浓缩滤液以除去 AcCN，所得水溶液以 2N HCl 酸化，进而通过 HPLC 纯化，得 0.462g 标题化合物，系其 TFA 盐形式。MS (离子喷雾) m/z 286 $(M+H)^+$.

下列化合物采用与参考实施例 101a 所用基本相同的方法制备，只是其中使用指定的芳基卤替代 3-(2-二甲氨基乙氧基)苯基碘。

参考实施例 101b

4-(1-氧化吡啶-2-基)苯甲酸. 使用 2-溴-吡啶-N-氧化物。MS (离子喷雾) m/z 216 $(M+H)^+$.

参考实施例 101c

4-(2-[2-二甲氨基乙氧基]苯基)苯甲酸. 使用 2-(2-二甲氨基乙氧基]苯基碘作为底物。MS (离子喷雾) m/z 286 $(M+H)^+$.

参考实施例 101d

4-(2-[3-二甲氨基丙氧基]苯基)苯甲酸. 使用 2-[3-二甲氨基丙氧基]苯基碘作为底物。MS (离子喷雾) m/z 300 $(M+H)^+$.

参考实施例 101e

4-(3-[3-二甲氨基丙氧基]苯基)苯甲酸. 使用 3-[3-二甲氨基丙氧基]苯基碘作为底物。MS (离子喷雾) m/z 300 $(M+H)^+$.

参考实施例 101f

4-(1-氧化吡啶-3-基)苯甲酸. 使用 3-溴-吡啶-N-氧化物作为底物。

参考实施例 102a

4-[[4-(4-甲氧基羰基-苯基)-吡啶-2-基甲基]-氨基甲酰基]-哌啶-1-羧酸叔丁酯

向哌啶-1,4-二羧酸一叔丁酯(275mg, 1.2 mmol)的二氯甲烷(2ml)溶液内加入二异丙基乙胺(0.23ml, 1.32 mmol)。搅拌所得溶液 5 分钟,然后加入 TBTU (337mg, 1.26 mmol), 搅拌 20 分钟。向反应混合物内加入 4-(2-氨基甲基-吡啶-4-基)-苯甲酸甲酯三氟乙酸盐(356mg, 1 mmol, 参考实施例 103a)和二异丙基乙胺(0.192ml, 1.1 mmol)在 CH_2Cl_2 (2 ml)中的溶液。搅拌反应混合物 45 分钟, 然后减压浓缩。残留物通过快速色谱纯化(以 40%乙酸乙酯/10%甲醇/己烷洗脱), 得 455mg 白色泡沫体产物。MS (离子喷雾) m/z 454 $(M+H)^+$.

参考实施例 102b

采用与制备参考实施例 102 所用基本相同的方法, 只是其中使用乙酸作为底物替代哌啶-1,4-二羧酸一叔丁酯, 从而制得 4-[2-(乙酰氨基-甲基)-吡啶-4-基]-苯甲酸甲酯。MS (离子喷雾) m/z 285 $(M+H)^+$.

参考实施例 103a

4-(2-氨基甲基-吡啶-4-基)-苯甲酸甲酯三氟乙酸盐

向 4-[2-(叔丁氧羰基氨基-甲基)-吡啶-4-基]-苯甲酸甲酯(1.96g, 5.72 mmol, 参考实施例 56)的二氯甲烷(19ml)溶液中加入 TFA (6ml)。搅拌反应溶液 3 小时, 然后减压浓缩。残留物用乙醚研制纯化。过滤收集固体物, 用乙醚洗涤, 经真空干燥后得 1.68g 产物。

MS (EI) m/z 243 $(M+H)^+$.

参考实施例 103b

4-(1-[羧甲基]-6-氧代-1,6-二氢吡啶-3-基)苯甲酸乙酯

采用与制备参考实施例 103a 所用基本相同的方法进行制备,但其中使用 4-{1-[(叔丁氧羰基)甲基]-6-氧代-1,6-二氢吡啶-3-基}苯甲酸乙酯(参考实施例 85b). MS (离子喷雾) m/z 302 $(M+H)^+$.

参考实施例 104

4-(2-氧代-2H-吡啶-5-基)苯甲酸烯丙酯

向 4-(2-氧代-2H-吡啶-5-基)苯甲酸乙酯(1.24g, 5.10 mmol, 参考实施例 36f)的烯丙醇(50mL)溶液内加入异丙醇钛(IV)。加热所得混合物至 70℃反应 7 小时, 然后再加入异丙醇钛(IV) (3mL)。18 小时后,停止加热,加入 1N HCl 溶液(50mL),接着用二氯甲烷(200mL)提取。分离有机层, 浓缩得到标题化合物, 产率定量。MS (离子喷雾) m/z 256 $(M+H)^+$.

参考实施例 105

4-[2-氨基-1,1-二甲基-乙基]-N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-苯甲酰胺

向 (2-[4-[2-(3-氰基-1H-吲哚-5-基)-乙基氨基甲酰基]-苯基]-2-甲基-丙基)-氨基甲酸叔丁酯(1.16g, 2.5 mmol) (采用参考实施例 1w 的方法制备)的二氯甲烷(8ml)溶液内加入 TFA (1.6ml), 搅拌反应物 2 小时。加水 50μl, 然后减压浓缩反应物。残留物进而通过快速色谱纯化(以 10% 7M NH_3 的甲醇溶液/CH_2Cl_2 洗脱), 得 808mg 产物。MS (离子喷雾) m/z 361 $(M+H)^+$.

参考实施例 106

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-(2-甲磺酰氨基-1,1-二甲基

-乙基)-苯甲酰胺

向 4-[2-氨基-1,1-二甲基-乙基]-N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-苯甲酰胺(97mg, 0.27 mmol) (参考实施例 105)的二氯甲烷(1ml)溶液内加入吡啶(24μL, 0.30 mmol)和甲磺酰氯(23μL, 0.30 mmol)。搅拌反应物 5 分钟，然后减压浓缩。残留物进而通过快速色谱纯化（以 8% 7M NH_3的甲醇溶液/CH_2Cl_2洗脱)，得 95mg 产物。MS (离子喷雾) m/z 439 $(M+H)^+$.

参考实施例 107a

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-(1,1-二甲基-2-脲基-乙基)-苯甲酰胺

向 4-[2-氨基-1,1-二甲基-乙基]-N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-苯甲酰胺(90mg, 0.25 mmol) (参考实施例 105)的 1,4-二噁烷(1ml)溶液内加入异氰酸三甲基甲硅烷基酯(68μL, 0.50 mmol)。搅拌所得混合物 16 小时。真空过滤收集沉淀出的固体物，用少量二氯甲烷洗涤，高真空干燥后得 99mg 产物。MS (离子喷雾) m/z 404 $(M+H)^+$.

参考实施例 107b

N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-4-[2-(3-乙基-脲基)-1,1-二甲基-乙基]-苯甲酰胺. 采用与参考实施例 107a 所用基本相同的方法制备，只是其中使用异氰酸乙酯作为底物。MS (离子喷雾) m/z 432 $(M+H)^+$.

参考实施例 107c

4-(1-氨基甲酰基-哌啶-4-基)-苯甲酸. 采用与参考实施例 107a 所用基本相同的方法制备，只是其中使用 4-(哌啶-4-基)-苯甲酸（参考实施例 109）作为底物。

参考实施例 108

4-(2-二甲氨基-3,4,5,6-四氢-嘧啶-4-基)-苯甲酸

向4-(2-二甲氨基嘧啶-4-基)苯甲酸(275mg, 1.13 mmol, 参考实施例92aab)的水(13ml)溶液内加入浓盐酸(212 μL, 2.54mmol), 接着加入10%钯-碳(366mg)。在氢气氛下搅拌所得混合物2.5小时。通过硅藻土垫过滤混合物以除去催化剂, 用二氯甲烷洗涤。减压浓缩滤液, 得260mg盐酸盐产物。MS (离子喷雾) m/z 248 $(M+H)^+$.

参考实施例109

4-(哌啶-4-基)-苯甲酸

向悬浮在20% AcOH/MeOH (20ml)的4-吡啶苯甲酸钠盐(500mg, 2.25 mmol)中加入PtO_2 (250mg), 在搅动(Parr)下于50psi氢化该混合物4小时。所得溶液通过硅藻土过滤, 用甲醇(3 x 5 ml)洗涤, 与己烷(4x)一起蒸发以共沸除去乙酸。粗产物的TLC ($EtOH/H_2O/NH_4OH$ 10:1:1)表明已无起始物质, 但显示存在两个极性点。蒸发己烷后, 白色固体物(596mg粗品, 仍含有残留量HOAc)在真空下干燥过夜, 并且不需进一步纯化而直接用于后续步骤。MS m/z $[M+H]^+$.

参考实施例110

4-(1-乙酰基-哌啶-4-基)-苯甲酸的制备. 向4-哌啶-4-基)-苯甲酸(102mg, 0.5 mmol, 参考实施例109)的吡啶(2mL)溶液内加入乙酐(255mg, 2.5 mmol), 室温搅拌反应物过夜。真空浓缩反应物, 残留吡啶通过与二氯甲烷/甲醇1:1共沸部分除去。粗产物然后用二氯甲烷洗涤, 浅去溶剂得到白色固体残余物(61mg, 49%) 4-(1-乙酰基-哌啶-4-基)-苯甲酸。

^1H NMR (CD_3OD): δ 7.89 (d, 2H); 7.27 (d, 2H); 4.65 (d, 1H); 4.03 (d, 1H); 3.21 (dt, 2H); 2.68-2.88 (m, 2H); 1.93 (s, 3H); 1.85-2.04 (m, 2H); 1.50-1.75 (m, 3H). MS m/z 248 (M+H)+.

参考实施例111

4-(1-甲基-哌啶-4-基)-苯甲酸

向低聚甲醛(180mg, 6 mmol)在 MeOH (10mL)和 $NaCNBH_3$ (120mg, 1.94 mmol)中的溶液内加入 4-哌啶-4-基-苯甲酸(110mg, 0.54 mmol, 参考实施例 109)。室温搅拌反应物 4 天, 此时 HPLC 显示已无起始物存在。用浓盐酸酸化溶液至 pH 2, 蒸发, 再溶于水(20mL), 并用乙醚(3 x 20mL)提取。然后用片状 KOH 调节溶液的 pH 到 12, 用二氯甲烷(3 x 20 mL)提取, 最后再用乙酸调节至 pH 5。冻干混合物, 固体物用 MeOH (3 x 15 mL)提取。蒸发合并的甲醇提取物, 进而层析残留物(反相 HPLC, C18 柱 10-100% CH_3CN/水), 经冻干后得 72mg 所需产物(61%)。

^1H NMR (CD_3OD): δ 7.98 (d, 2H), 7.38 (d, 2H), 3.60 (m, 2H), 3.18 (t, 2H), 2.94 (s, 3H), 2.85 - 2.95 (m, 2H), 2.08 - 2.18 (m, 2H), 1.90 - 2.02 (m, 2H).

MS (离子喷雾) m/z 220 $(M+H)^+$. > 98%纯度(分析 HPLC).

参考实施例 112

4-(1-氧代-1-甲基-哌啶-4-基)-苯甲酸

将溶在 $CHCl_3$ (3mL)中的 4-(1-甲基-哌啶-4-基)-苯甲酸 (47mg, 0.21 mmol, 参考实施例 111)加到 mCPBA (60mg)中。3 小时后, HPLC 显示只有一个非起始物质的峰(9 min)。蒸发溶剂, 粗产物通过反相-HPLC (C-18 柱, 10-100% CH_3CN/水)部分纯化, 得到固体产物 4-(1-氧代-1-甲基-哌啶-4-基)-苯甲酸(28mg, 56%)。 ^1H NMR (CD_3OD): δ 7.98 (d, 2H), 7.42 (d, 2H), 3.72-3.88 (m, 4H), 3.58 (s, 3H), 2.91-3.02 (m, 2H), 2.28-2.42 (m, 2H), 2.01-2.07 (m, 2H)

MS (离子喷雾) m/z 236 $(M+H)^+$. > 92%纯度(分析 HPLC).

参考实施例 113a

4-(4-二甲氨基-哌啶-1-基)-苯甲酸

将 280mg (1.22 mmol) 4-(4-二甲氨基-哌啶-1-基)-苄腈(参考实

施例 114a)溶于 2ml 乙酸，加入 4ml 6N HCl，搅拌回流该混合物 16 小时。冷却后，加入 20ml 水，用 DCM (3x)提取。水相的 pH 用片状 KOH 调节至 5，滤出沉淀的白色固体物，洗涤并加以干燥，从而得到 257mg 标题化合物(85%收率). ^{1}H NMR ($CDCl_3$): δ 7.88 (dd, 2H), 6.98 (dd, 2H), 4.09 (d, 2H), 3.42 (m, 1H), 3.29 (t, 2H), 2.90 (s, 6H), 2.89-2.96 (m, 2H), 2.18 (m, 2H), 1.80 (dq, 2H).

MS (离子喷雾) m/z 249 $(M+H)^+$. 90%纯度(分析 HPLC).

参考实施例 113b

4-(4-氨基-哌啶-1-基)-苯甲酸

采用和参考实施例 114a 所用基本相同的方法制备，只是其中使用 4-(4-氨基-哌啶-1-基)-苄腈(参考实施例 114b)作为底物。MS (离子喷雾) m/z 221 $(M+H)^+$.

参考实施例 113c

4-[4-(2-二甲氨基-乙基-氨基)-哌啶-1-基]-苯甲酸

采用和参考实施例 114a 所用基本相同的方法进行制备，只是其中使用 4-[4-(2-二甲氨基-乙基-氨基)-哌啶-1-基]-苄腈(参考实施例 114c)作为底物。MS (离子喷雾) m/z 292 $(M+H)^+$.

参考实施例 113d

4-(4-羟基-哌啶-1-基)-苯甲酸

采用和参考实施例 114a 所用基本相同的方法进行制备，只是其中使用 4-[4-(羟基)-哌啶-1-基]-苄腈(参考实施例 122)作为底物。MS (EI) m/z 221 $(M+H)^+$.

参考实施例 114a

4-(4-二甲氨基-哌啶-1-基)-苄腈

将 4-(4-氧代-哌啶-1-基)-苄腈(100mg, 0.5 mmol, 参考实施例 116)、二甲胺盐酸盐(408mg, 5 mmol)和 $NaCNBH_3$ (25mg, 0.4 mmol)的混合物溶于 MeOH (7 mL), 室温搅拌过夜。24 小时后, 加入另一份 $NaCNBH_3$ (24mg, 0.38 mmol), 室温搅拌所得混合物过夜。然后用浓盐酸调节混合物的 pH 至 2, 以乙醚(3x)提取。水相的 pH 值用片状 KOH 调节至 10, 用乙醚提取(3x)。后面合并的有机相以盐水洗涤, 硫酸钠干燥, 过滤并蒸发。粗产物无需进一步纯化直接用于下一步骤。

^{1}H NMR ($CDCl_3$): δ 7.44 (d, 2H), 6.83 (d, 2H), 3.86 (m, 2H), 2.86 (dt, 2H), 2.32-2.38 (m, 1H), 2.28 (s, 6H), 1.92 m(m, 2H), 1.54 (dq, 2H). MS (EI) m/z 229 (M+H)+.

参考实施例 114b

4-(4-氨基-哌啶-1-基)-苄腈. 采用和参考实施例 114a 所用基本相同的方法进行制备, 只是其中使用 NH_4OAc 作为底物替代二甲胺盐酸盐。

^{1}H NMR ($CDCl_3$): δ 7.45 (d, 2H), 6.84 (d, 2H), 3.80 (d, 3H), 2.92 (m, 2H), 1.92 (d, 2H), 1.28-1.46 (m, 2H).

MS (离子喷雾) m/z 202 $(M+H)^+$.

参考实施例 114c

4-[4-(2-二甲氨基-乙基-氨基)-哌啶-1-基]-苄腈. 采用和参考实施例 114a 使用基本相同的方法制备, 只是其中使用 N,N-二甲基乙二胺作为底物替代二甲胺盐酸盐。

^{1}H NMR ($CDCl_3$): d 7.45 (d, 2H), 6.84 (d, 2H), 3.27 (m, 1H), 2.94 (t, 2H), 2.73 (m, 2H), 2.39 (t, 2H), 2.21 (s, 6H), 1.94 (dd, 2H), 1.62 (brs, 2H), 1.43 (q, 2H).

MS (离子喷雾) m/z 273 $(M+H)^+$.

参考实施例 114d

4-(1-甲基-哌啶-4-基氧基)-苯甲酸甲酯. 采用和参考实施例 114a 使

用基本相同的方法制备，只是其中使用甲醛和 4-（哌啶-4-基氧基）苯甲酸甲酯（参考实施例 123）作为底物。

^{1}H NMR ($CDCl_3$): d 8.01 (d, 2H), 6.91 (d, 2H), 4.80 (s, 1H), 3.89 (s, 3H), 3.35 (brd, 2H), 3.13 (q, 2H), 2.80 (d, 3H), 2.65 (t, 2H), 2.18 (d, 2H).

MS （离子喷雾） m/z 250 $(M+H)^+$.

参考实施例 115

4-(4-[叔丁氧羰基氨基]-哌啶-1-基)-苯甲酸

向 4-(4-氨基哌啶-1-基)-苯甲酸(242mg, 1.1 mmol, 参考实施例 113b)溶在 5ml 二氯甲烷的溶液内加入 300mg 三乙胺和 305mg (1.4 mmol) Boc_2O。室温搅拌所得混合物 16 小时。蒸发溶剂，混合物通过硅胶色谱分离，以 DCM/MeOH (10%)洗脱，得 214mg 标题化合物。

^{1}H NMR (CD_3OD): δ 7.85 (d, 2H), 6.94 (d, 2H), 3.85 (m, 2H), 3.65 (m, 1H), 2.93 (m, 2H), 1.91 (m, 2H), 1.49 (s, 9H), 1.32-1.40 (m, 2H). MS (EI) m/z 320 (M+).

参考实施例 116

4-(4-氧代-哌啶-1-基)-苄腈

向溶在 THF (2mL)中的 4-(1,4-二氧杂-8-氮杂-螺[4,5-]癸-8-基)-苄腈(460mg, 1.88 mmol, 参考实施例 117)中加入 10% H_2SO_4 (4mL)，室温搅拌反应物 24 小时。TLC (40% EtOAc/己烷)显示仍存在少量起始物质，但主要为极性较高产物。加水稀释反应物，用二氯甲烷(3x)提取，再以氯化钠饱和水溶液洗涤，经硫酸钠干燥后过滤、蒸发。硅胶(20-40% EtOAc/己烷)层析粗产物，得标题化合物(315mg, 84%)。

^{1}H NMR ($CDCl_3$): δ 7.52 (d, 2H), 6.88 (d, 2H), 3.72 (t, 4H), 2.57 (t, 4H).

MS （离子喷雾） m/z 200 $(M+H)^+$.

参考实施例 117

4-(1,4-二氧杂-8-氮杂-螺[4,5]癸-8-基)-苄腈

回流 4-氟苄腈(2.49g, 20.57 mmol (14.73g, 103 mmol) 1,4-二氧杂-8-氮杂螺[4,5]癸烷和 K_2CO_3 (4.14g, 30 mmol)在二噁烷(40mL)中的混合物 65 小时。过滤反应物,蒸发溶剂。硅胶层析(10-30% EtOAc/己烷)得到所需烷基化产物 1,4-二氧杂-8-氮杂螺[4,5]癸烷(3.9g, 79%).

^{1}H NMR ($CDCl_3$): δ 7.47 (d, 2H), 6.86 (d, 2H), 3.98 (s, 4H), 3.48 (t, 4H), 1.78 (t, 4H).

MS (离子喷雾) m/z 245 $(M+H)^+$.

参考实施例 118

4-(1-氧化-吡啶-4-基氧基)-苯甲酸

将 246mg (1mol) 4-(1-氧化-吡啶-4-基氧基)-苯甲酸甲酯(参考实施例 119)溶于 6ml 乙醇, 加入 4ml 1N NaOH, 回流 3 小时。混合物用浓盐酸中和, 蒸发并经制备 HPLC 纯化。

^{1}H NMR ($CDCl_3$): d 8.51 (d, 1H); 7.86 (d, 2H); 7.33 (d, 2H); 6.80 (d, 2H).

MS (离子喷雾) m/z 232 $(M+H)^+$.

参考实施例 119

4-(1-氧化-吡啶-4-基氧基)-苯甲酸甲酯

将 304mg (2 mol) 4-羟基苯甲酸甲酯、280mg (2 mmol) 4-硝基吡啶氧化物(2 mol)和 420mg (3mol)碳酸钾溶于 5ml 无水 DMF, 110℃搅拌 2 小时。将冷却后的混合物倒入盐水中, 以 EtOAc (3x)提取、盐水洗涤、硫酸钠干燥并蒸发, 从而得到 246mg 标题化合物。

^{1}H NMR ($CDCl_3$): d 8.18 (d, 2H); 8.10 (d, 2H); 7.89 (d, 1H); 7.12 (d, 1H); 6.93 (d, 1H); 6.88 (d, 1H); 3.92 (s, 3H). MS (E1) m/z 245 (M+H)+.

参考实施例 120

4-[4-(2-二甲氨基-乙基-叔丁氧基羰基-氨基)-哌啶-1-基]-苯甲酸

将 140mg (0.48 mmol) 4-[4-(2-二甲氨基-乙基-氨基)-哌啶-1-基]-苯甲酸（参考实施例 113c）溶于 8ml THF，加入 655mg (3 mol) Boc_2O，室温搅拌 3 天。加水稀释混合物，接着用 DCM 提取(3x)；合并的提取物用盐水洗涤，经硫酸钠干燥后过滤并蒸发。所得固体物用 DCM/乙醚洗涤，干燥后得 114mg (61%)标题化合物。

^{1}H NMR ($CDCl_3$): d 7.84 (m, 2H), 6.79 (d, 1H), 3.95 (m, H), 3.70 (m, 4H), 3.18(m, 2H), 2.84 (s, 3H), 2.79 (s, 3H), 2.70 (t, 1H), 1.88 (m, 2H), 1.76 (m, 2H), 1.57 (s, 3H), 1.44 (s, 6H).

MS （离子喷雾） m/z 392 $(M+H)^+$.

参考实施例 121

4-(4-甲氧基-哌啶-1-基)-苯甲酸

将 170mg (0.77 mmol) 4-(4-羟基-哌啶-1-基)-苯甲酸（参考实施例 113d）溶于 3ml THF 与 3ml DMSO 内，加入 120mg (1.1 当量)甲基碘和 68mg (1.69 mmol) NaH，室温搅拌 16 小时。混合物倒入盐水内，用 DCM (3x)提取，然后将水相用 HCl 酸化至 pH 1，再用 DCM (3x)提取。盐水洗涤合并的有机提取物、硫酸钠干燥、过滤并蒸发。TLC (DCM/MeOH 10%)显示为起始物质(Rf ~ 0.5)与新产物(Rf ~ 0.6)的混合物。通过硅胶色谱分离这两种组分，以 DCM/MeOH (0-10%)为流动相，得 60mg 标题化合物。

^{1}H NMR ($CDCl_3$): d 7.95 (d, 2H), 6.87 (d, 2H), 3.68 (m, 2H), 3.63 (m, 1H), 3.38 (s, 3H), 3.14 (m, 2H), 1.98(m, 2H), 1.68 (m, 2H).

MS （离子喷雾） m/z 236 $(M+H)^+$.

参考实施例 122

4-(4-羟基-哌啶-1-基)-苄腈

240mg (1.2 mmol) 4-(4-氧代-哌啶-1-基)-苄腈(参考实施例 116)溶于 5ml 甲醇、加入 23mg (0.6 mmol) $NaBH_4$，室温搅拌 3 小时。加入数滴水后蒸发甲醇，然后再加入 20ml 水，用 DCM (3x)提取，硫酸钠干燥、过滤并蒸发，从而得到 230mg (95%收率)标题化合物。

^1H NMR ($CDCl_3$): d 7.47 (d, 2H), 6.85 (d, 2H), 3.93 (bs, H), 3.70 (m, 2H), 3.11 (m, 2H), 1.95 (m, 2H), 1.62 (m, 2H).

MS (离子喷雾) m/z 202 $(M+H)^+$.

参考实施例 123

4-(哌啶-4-基-氧基)-苯甲酸甲酯

将 266mg (0.79 mmol) 4-(N-BOC-哌啶-4-基-氧基)-苯甲酸甲酯(参考实施例 124)溶于 4ml DCM，加入 4ml TFA，室温搅拌 1 小时。蒸发混合物至干，进而通过制备 HPLC 纯化，以水/乙腈/0.1% TFA 为流动相，从而得到 217mg 标题化合物的 TFA 盐。

^1H NMR (CD_3OD): d 7.97 (d, 2H), 7.06 (d, 2H), 4.78-4.85 (m, 1H), 3.86 (s, 3H), 3.19-3.44 (m, 4H), 2.14-2.23 (m, 2H), 2.00-2.08 (m, 2H).

MS (离子喷雾) m/z 236 $(M+H)^+$.

参考实施例 124

4-(N-BOC-哌啶-4-基-氧基)-苯甲酸甲酯

0℃下，将 656mg (2.5 mmol)三苯膦和 304mg (2 mmol) 4-羟基苯甲酸甲酯溶于 3ml 无水 THF，5 分钟内滴加入 402mg (2 mmol) N-Boc-4-哌啶醇与 418mg (2.4 mmol)偶氮二羧酸二乙酯在 4ml 无水 THF 中的溶液。0℃搅拌混合物 2 小时，然后温热至室温，再搅拌 3 天。混合物通过硅胶色谱分离，以己烷/EtOAc (5-20%)梯度洗脱，从而得

266mg (40%收率)标题化合物。 ^{1}H NMR ($CDCl_3$): 7.96 (d, 2H), 6.90 (d, 2H), 4.52-4.56 (m, 1H), 3.87 (s, 3H), 3.65-3.72 (m, 2H), 3.31-3.39 (m, 2H), 1.83-1.97 (m, 2H), 1.70-1.82 (m, 2H), 1.45 (s, 9H). MS (EI) m/z 184.

参考实施例 125

4-(4-乙酰氨基-哌啶-1-基)-N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-苯甲酰胺

将 40mg (0.09 mmol) 4-(4-氨基-哌啶-1-基)-N-[2-(3-氰基-1H-吲哚-5-基)-乙基]-苯甲酰胺 (参考实施例 1aav)溶于 2ml 吡啶，加入 22mg (0.22 mmol)乙酐，室温搅拌 16 小时。蒸发反应混合物至干。MS (CI) 430 $(M+H)^+$.

参考实施例 126

4-(1-甲磺酰基-哌啶-4-基)-苯甲酸甲酯

将 87mg (0.40 mmol) 4-(哌啶-4-基)苯甲酸甲酯（参考实施例 127）溶于 3ml DCM，冷却到 0℃，加入 55mg (0.48 mmol)甲磺酰氯，搅拌 1 小时。混合物倒入水中，用 DCM(3x)提取，碳酸氢钠稀溶液洗涤、硫酸钠干燥、过滤并蒸发。粗产物通过硅胶色谱纯化，以己烷/EtOAc 为流动相，从而得到 81mg (61%收率)标题化合物。

^{1}H NMR ($CDCl_3$) : δ7.98 (d, 2H), 7.26 (d, 2H), 3.93 (m, 2H), 3.90 (s, 3H), 2.81 (s, 3H). 2.63-2.78 (m, 3H), 1.76-1.96 (m, 4H).

MS (离子喷雾) m/z 298 $(M+H)^+$.

参考实施例 127

4-(哌啶-4-基)苯甲酸甲酯

将 160mg (0.78 mmol) 4-(哌啶-4-基)苯甲酸（参考实施例 109）溶于 2ml MeOH，滴加入 0.5 ml 浓硫酸，回流混合物 2 小时。冷却后，加水稀释，用片状 KOH 调节 pH 至 12，然后用 DCM (3x)提取。水相通

过制备 HPLC 纯化，以 10-100%水/乙腈/0.1% TFA 梯度洗脱，得 87mg 标题化合物。MS（离子喷雾）m/z 220 $(M+H)^+$.

本文所述分子依靠它们抑制凝固级联中次末级酶(Xa 因子，而不是凝血酶)的能力能够抑制血液凝固，从而使得游离 Xa 因子和组装在凝血酶源酶复合物(Xa 因子、Va 因子、钙和磷脂)中的 Xa 因子得到抑制。通过在抑制剂与酶之间直接形成复合物而能实现对 Xa 因子的抑制，因此 Xa 因子的抑制不取决于血浆辅因子抗凝血酶 III。通过口服、连续静脉输注、药团输注或任何其它肠胃外途径施用本发明化合物能够有效地抑制 Xa 因子，从而防止 Xa 因子诱导凝血酶原形成凝血酶而达到所需的效果。

抗凝疗法用于治疗和预防各种静脉和动脉血管系统的血栓症状。在动脉系统中，异常血栓的形成最初与冠状、大脑和外周血管系统的动脉有关。与这些血管的血栓性闭合有关的疾病主要包括急性心肌梗塞(AMI)、不稳定性心绞痛、血栓栓塞、与溶栓治疗和经皮经管腔动脉血管成形术(PTCA)有关的急性血管闭合、暂短性缺血发作、中风、间歇性跛行和冠状或外周动脉旁路移植(CABG)。慢性抗凝疗法也有益于预防通常发生于 PTCA 和 CABG 之后的血管腔缩小(再狭窄)，并有益于维持长期血液透析患者的脉管通路开放。就静脉脉管系统而言，病理性血栓形成常发生于腹、膝和髋部外科手术之后的的较低肢端静脉(深静脉血栓形成，DVT)。DVT 进一步使患者易患高危肺血栓栓塞。全身、弥散性血管内凝血病(DIC)常发生于脓毒性休克、某些病毒感染和癌症期间的血管系统。这种病症的特征在于凝血因子的迅速消耗以及它们的血浆抑制剂导致在一些器官系统的整个微脉管系统中形成威胁生命的凝块。上述适应症包括一些(但不是所有)进行抗凝治疗的可能临床情况。本领域经验丰富人员能够十分清楚地确定需要急性或慢性预防性抗凝治疗的病情。

Xa 因子抑制剂除了用于抗凝疗法外，还可以用于治疗或预防其它凝血酶的生成在其中起病理作用的疾病。例如，已经有人提出，根据

凝血酶通过细胞表面凝血酶受体的特异性分裂和活化能够调节多种不同类型分化细胞、促细胞分离作用、多种细胞功能如细胞增殖，例如导致再狭窄或血管生成生成的血管异常增殖，释放 PDGF 和 DNA 合成酶的能力，它对诸如关节炎、癌、动脉粥样硬化和阿尔茨默氏病这类慢性和变性疾病的发病和死亡均产生影响。对 Xa 因子的抑制能有效地阻滞凝血酶的产生并因此抵消凝血酶对各种类型细胞的任何生理作用.

因此，本发明提供了抑制 Xa 因子的方法，其包括使 Xa 因子抑制有效量的式 I 化合物与含 Xa 因子的制品接触。本发明的进一步特征是提供抑制凝血酶产生的方法，其包括使 Xa 因子抑制有效量的式 I 化合物与含 Xa 因子的制品接触。

本发明的进一步特征是提供治疗患有或易患通过给药 Xa 因子抑制剂而能缓解的病症（例如上述病症）的人或动物体的方法，它包括将有效量的式(I)化合物或含有式(1)化合物的组合物给药于患者。"有效量"是指能有效抑制 Xa 因子并因此产生所需治疗效果的本发明化合物的用量。

本发明还包括在其范围内的药物制剂，该药物制剂含有至少一种与可药用载体或包衣层结合的式 I 化合物。

在实践中，本发明化合物一般可以通过胃肠外、静脉、皮下、肌内、结肠、经鼻、腹膜内、直肠或口服途径给药。

本发明产物可以以允许通过最适宜途径给药的形式存在。本发明还涉及药物组合物，这种药物组合物含有至少一种适合用于人类或兽类药物的本发明产物。这些组合物可按照常规方法用一种或多种药用助剂或赋形剂制备。助剂尤其包括稀释剂、无菌水介质和各种无毒有机溶剂。组合物可以以片剂、丸剂、颗粒剂、粉剂、水溶液或悬浮液、注射液、酏剂或糖浆剂的形式存在，而且为了获得可药用制剂，所述组合物可以含有一种或多种选自甜味剂、调味剂、着色剂和稳定剂的物质。

赋形剂的选择以及活性物质在赋形剂中的含量通常根据产物的溶解性及化学性质、具体的给药方式以及制药实践中要遵守的规定而定。

例如，赋形剂(如乳糖、柠檬酸钠、碳酸钙、磷酸二钙)和崩解剂(如淀粉、藻酸和某些复合硅酸盐)与润滑剂(如硬脂酸镁、十二烷基硫酸钠以及滑石)混合可用于制备片剂。为了制备胶囊，宜使用乳糖和高分子量聚乙二醇。当使用水悬浮液时，它们可还以含有乳化剂或利于悬浮的试剂。还可以使用稀释剂如蔗糖、乙醇、聚乙二醇、丙二醇、甘油和氯仿或它们的混合物。

对于胃肠外给药，使用本发明产物在植物油（例如芝麻油、花生油或橄榄油）中的的乳液、悬浮液或溶液，或水－有机溶液如水与丙二醇的溶液，可注射有机酯如油酸乙酯以及可药用盐的无菌水溶液。本发明产物的盐的溶液特别适用于肌内或皮下注射给药。水溶液（也包括盐在纯净蒸馏水中形成的溶液）可以用于静脉给药，条件是要适当地调节它们的 pH，用足够量的葡萄糖或氯化钠适当缓冲它们并赋予它们等渗性能，并且通过加热、辐照或微过滤对它们进行灭菌。

含有本发明化合物的适宜组合物可以通过常规方法制备，例如，可以将本发明化合物溶于或悬浮在供喷雾剂或悬浮液或溶液气雾剂用的适当载体中，或者可以将其吸附或吸收到供干粉吸入剂用的适当固体载体上。

直肠给药的固体组合物包括根据已知方法配制而成的栓剂，其中含有至少一种式 I 化合物。

本发明组合物中活性成分的百分比是可变的，但其比例应当是得到合适剂量所需的比例。显然，可以在大约同一时刻给药多个单位剂量形式，所用剂量由主治医师决定，并且取决于所需治疗效果、给药途径和治疗持续时间以及患者的症状。对成人而言，吸入给药的剂量通常为每天每千克体重大约 0.01-大约 100mg，优选大约 0.01—大约 10mg，而口服给药的剂量通常为每天每千克体重大约 0.01-大约 100mg,，优选 0.1-70mg，更优选 0.5-10mg，并且静脉给药的一般剂量为每天每千克体重大约 0.01－大约 50mg，优选 0.01-10mg。在每种具体情况下，剂量根据受治疗者的特定因素如年龄、体重、健康状态和其它能够影响医药产品效果的性质而定。

为了获得所需治疗效果，可以按照需要频繁地给药本发明产物。一些患者可能会对较高或较低剂量作出迅速反应并可以据此找到更弱的适当维持剂量。而对于其它患者，根据每一具体患者的生理需要，可能需要每天 1—4 剂量长期治疗。一般来讲，活性产物可以每天口服给药 1－4 次。但对于其它患者规定每天不多于一个或两个剂量将是必要的。

式（I）化合物可以单独使用，或者与其它诊断剂、心脏保护剂、直接(direct)凝血酶抑制剂、抗凝剂、抗血小板或溶纤剂联合使用。为了安全地完成干预操作或者防止血栓形成的有害作用，在干预操作之前、之中和之后通常用这些种类药剂并行处理患者。可以与式（I）化合物联合使用的药剂种类的一些实例选自：抗凝剂如 Xa 因子抑制剂，VIIa 因子抑制剂，华法令或肝素；合成五糖类；抗血小板剂如阿斯匹林，吡罗昔康或噻氯匹定；直接凝血酶抑制剂（如硼精氨酸衍生物，水蛭素或阿戈托班(Novastan®)）；纤维蛋白原受体拮抗剂；抑制素/纤维素(fibrates)；或溶纤剂(溶栓剂)如组织纤溶酶原激活物，阿尼链菌酶（anistreplase）(Eminase®)，尿激酶或链激酶；或它们的组合。

本文所用的术语“心脏保护剂”是指局部缺血期间用于保护心肌的药剂。这些心脏保护剂包括但不限于腺苷激动剂，β-阻滞剂和 Na/H 交换抑制剂。腺苷激动剂包括 Spada 等在美国专利 5,364,862 以及 Spada 等在美国专利 5,736,554 中公开的化合物，这两篇文献内容在此并入引作参考。腺苷激动剂的实例为 AMP 579 (Rhone-Poulenc Rorer)。Na/H 交换抑制剂的实例为 Cariporide (HOE 642)。

本文所用的术语“抗凝剂”是指能抑制血液凝固的药剂。这类药剂包括华法令(Coumadin®)和肝素。

本文所用的术语“抗血小板剂”是指例如能通过抑制血小板的聚集、粘连或颗粒状的分泌而抑制血小板功能的药剂。这类药剂包括各种已知的非甾类抗炎药(NSAIDS)，如包括其可药用盐或前药在内的阿斯匹林、布洛芬、萘普生、舒林酸、消炎痛、甲灭酸、哚昔康、双氯

灭痛、苯磺唑酮、和炎痛喜康(Feldane®)。其它适宜的抗血小板剂包括塞氯匹定(Ticlid)，血栓烷-2-受体拮抗剂和血栓烷-A2-合成酶抑制剂，以及它们的可药用盐或前药。

本文所用的短语“直接凝血酶抑制剂”(亦即 IIa 因子抑制剂)是指丝氨酸蛋白酶凝血酶的抑制剂。通过直接抑制凝血酶，能够抑制纤维蛋白原裂解成纤维蛋白，并且能够激活 XIIIa 因子、激活血小板和反馈凝血酶到凝固级联中产生更多的凝血酶。这类直接抑制剂包括硼精氨酸衍生物和硼肽类，水蛭素和阿戈托班(Novastan®)，并包括它们的可药用盐及前药。硼精氨酸衍生物和硼肽类包括硼酸的 N-乙酰基和肽衍生物，如赖氨酸、鸟氨酸、精氨酸、高精氨酸及其相应的异硫脲鎓类似物的 C-端α-氨基硼酸衍生物。本文所用的术语“水蛭素”包括水蛭素的适当衍生物或类似物，在这里它们统称作水蛭素，如二硫酸根合水蛭素。

本文所用的短语“溶纤剂(或溶栓剂或纤溶剂)”是指能溶解血凝块的药剂。这类药剂包括组织纤溶酶原激活物，阿尼链菌酶(Eminase®)，尿激酶或链激酶，并包括它们的可药用盐或前药。组织纤溶酶原激活物(tPA)可从 Genentech Inc.(South San Francisco, Calif.)购得。本文所用的术语“尿激酶”是指双链和单链尿激酶，后者在本文中也称作尿激酶原。

可给药本文所述化合物治疗各种动物如包括人在内的灵长类动物的血栓形成并发症。Xa 因子抑制剂不仅可用于具有血栓形成症状患者的抗凝治疗，而且还可用于需要抑制血液凝固的情形，如用于防止贮存全血凝聚和防止其它试验或贮存生物样品的凝聚。因此，可以将任何 Xa 因子活性抑制剂加到含有或怀疑含有 Xa 因子以及其中需要抑制血液凝聚的任何介质中或使其与这些介质接触。

本发明化合物可以与任何抗高血压药或者胆固醇或脂质调节剂联合使用，或者与治疗再狭窄、动脉粥样硬化或高血压时所用的药剂同时使用。一些可用于与本发明化合物联合给药治疗高血压的药剂实例包括下列种类化合物：β-阻滞剂，ACE 抑制剂，钙通道拮抗剂和α-受

体拮抗剂。一些可用于与本发明化合物联合给药治疗高胆固醇水平或脂质水平失调的药剂实例包括已知为 HMGCoA 还原酶抑制剂的化合物，fibrate 类化合物。

应当理解，本发明包括本发明化合物与一种或多种前述种类治疗剂的组合物。

根据文献和下文所述的其试验结果据信与人和其它哺乳动物的药理活性有关的试验，本发明范围内的化合物具有显著的药理活性。

酶试验:

通过使用纯化酶测定导致酶活性 50%丧失的抑制剂浓度(IC50)，评价本发明化合物作为 Xa 因子、凝血酶、胰蛋白酶、组织-纤溶酶原激活物(t-PA)、尿激酶-纤溶酶原激活物(u-PA)、纤溶酶和活化蛋白 C 抑制剂的能力。

所有酶试验均在 96-孔微量滴定板中于室温下进行，酶终浓度为 1nM。Xa 因子和凝血酶的浓度通过活性位点滴定法测定，所有其它酶的浓度均以生产厂商提供的蛋白质浓度为基础。将本发明化合物溶解在 DMSO 中，用它们各自的缓冲液稀释并在 1.25%DMSO 最高终浓度下测定。将稀释的化合物加到含有缓冲液和酶的各孔内，预平衡 5-30 分钟。通过加入底物启动酶反应，利用 Vmax 微量滴定板读数仪(Molecular Devices)在 405nm 处连续监测肽-对硝酰苯胺底物水解产生的颜色达 5 分钟。在这些条件下，在所有试验中使用低于 10%的底物。应用所测的初始速度计算使对照速度产生减少 50%时的抑制剂的量(IC50)。然后根据 Cheng-Prusoff 方程(IC50 = Ki [1+[S]/Km])计算表观 ki 值（假定为竞争抑制动力学)。

可以使用另一体外试验评价本发明化合物在正常人体血浆中的效力。活化局部凝血酶原激酶的凝血时间是基于血浆的凝血测定，它取决于 Xa 因子的原位产生、其组装到凝血酶原复合物中并相继产生凝血酶和最终得到作为试验终点的凝块的纤维蛋白形成过程。该试验在临床上广泛用于监测临床评价用的常用凝血药物肝素和直接抗凝血剂的

间接体内(ex vivo)效果。因此，该体外活性试验被认为是体内抗凝血活性的替代标志。

基于人血浆的凝聚试验:

在 MLA Electra 800 仪器上一式两份测定活化局部促凝血酶原激酶的凝聚时间。将 100μl 柠檬酸化的正常人混合血浆(George King Biomedical)加到含有 100μl 本发明化合物的 Tris/NaCl 缓冲液(pH7.5)的比色池中，并置于仪器内。温热 3 分钟后，仪器自动加入 100μl 活化 cephaloplastin 试剂(Actin, Dade)，接着加入 100μl 0.035M$CaCl_2$启动凝聚反应，用分光光度法测定凝块的形成，以秒为单位测量。化合物的效力以增加一倍无本发明化合物存在的情况下用人血浆测定的对照的形成凝块时间所需的浓度表示。

本发明化合物的体内抗凝血效力也可以用两种充分确认的急性血管血栓形成的动物试验模型评价。使用颈静脉血栓形成的兔模型和颈动脉血栓形成的大鼠模型说明这些化合物分别在人静脉血栓形成和动脉血栓形成的不同动物模型范例中抗血栓形成的活性。

兔静脉血栓形成模型的体内试验

这是一种早已确立的富纤维蛋白静脉血栓形成的模型，该模型已经文献证实并对包括肝素在内的各种抗凝药物敏感(在静脉血栓形成的试验中，阻断组织因子通道抑制剂(TFPI 1-161)的重组体的抗血栓形成效果 - 与低分子量肝素的效果对比，J. Holst, B. Lindblad, D. Bergqvist, O. Nordfang, P.B. Ostergaard, J.G.L. Petersen, G. Nielsen 和 U. Hedner. Thrombosis and Haemostasis, 71, 214-219 (1994)。使用该模型的目的是评价化合物防止损伤部位体内产生的静脉血栓(凝块)形成以及颈静脉中局部阻滞的能力。

用 35mg/kg 氯胺酮和 5mg/kg 甲苯噻嗪以 1mL/kg 体积量(i.m.)麻醉体重 1.5-2kg 雌雄不拘新西兰白兔。将套管插入右颈静脉滴注麻醉药(以大约 0.5mL/hr 的速率滴注氯胺酮/甲苯噻嗪 17/2.5mg/kg/hr)，

并给药试验物。将套管插入右颈动脉以记录动脉血压并收集血样，利用 GAYMAR T-PUMP 维持体温为 39℃。分离左外部颈静脉并沿暴露的 2—3cm 血管处扎住所有分支。将套管插入普通颈部双叉口上方的内颈静脉中并将套管尖端推进到普通颈静脉附近。用非创伤血管钳分离出 1cm 静脉片段，在末端钳下面用 18G 针头绕静脉打结形成相对狭窄，这样就在受伤处形成一个流量减少和局部淤滞的区域，在内颈静脉中通过套管用盐水漂洗分离片段 2－3 次。其后用 0.5mL 0.5％聚氧乙烯醚(W-1)充注分离片段 5 分钟。W-1 为能使片段的内皮细胞衬里破裂的去垢剂，因而提供了引发形成凝块的血栓形成表面。5 分钟后，从片段中除去 W－1，再次用盐水温和地漂洗分离片段 2－3 次。然后除去血管钳，使血液流经该血管部分。使凝决形成并生长 30 分钟后，在狭窄结下方切割下静脉，监测血流(血流不存在记录为完全闭合)。然后结扎整个分离的静脉片段，除去形成的凝决并称重(湿重)。使用试验物对最终凝块重量的作用作为初期终结点。另外维持动物 30 分钟以得到抗凝作用的最终药代动力学。在用 W－1 损伤血管前，给药 15 分钟，并在凝块形成和发展成熟的阶段继续给药。得到三份评价止血参数的血样(各 3mL)：一个为正好要使用 W-1 之前的血样，第二个为移去血管钳后 30 分钟的血样，第三个为试验结束的血样。抗血栓形成效力以与赋形剂处理对照组动物相比，用本发明化合物处理的动物中最终凝块重量的减少表示。

大鼠动脉血栓形成模型的体内试验

Xa 因子抑制剂对血小板富积动脉血栓形成的抗凝效力可以使用公认的大鼠颈动脉 $FeCl_2$-诱导血栓形成模型评价(与阿司匹林相比，血栓素受体桔抗剂在动脉和静脉血栓形成的大鼠模型中的优异活性，W.A. Schumacher, C.L. Heran, T.E. Steinbacher, S. Youssef 和 M. L. Ogletree, Journal of Cardiovascular Pharmacology, 22, 526-533 (199)；氯化铁诱导的大鼠动脉血栓形成模型，K.D. Kurtz, B.W. Main, 和 G.E. Sandusky. Thrombosis Research, 60, 269-280

(1990)；大鼠动脉血栓形成模型中的凝血酶抑制作用，R. J. Broersma, L. W. Kutcher 和 E. F. Heminger. Thrombosis Reserach 64, 405-412 (1991). 这种模型广泛用于评价包括肝素和直接凝血酶抑制剂在内的各种药剂的抗血栓形成能力。

用戊巴比妥钠(50mg/kg i.p.)麻醉体重 375－450g 的 Sprague Dawley 大鼠。一旦达到可接受的麻醉水平，切开颈部腹面并准备无菌手术。连接心电图电极，试验期间监测导联 II(lead II)。在右股静脉和动脉中分别插入 PE-50 管材套管用于给药本发明化合物和得到血样并监测血压。沿颈部腹面中线切开，暴露出气管，插入 PE-240 管材插管以确保气管开放。分离右颈动脉并沿血管方向放置两根 4—0 丝线以方便仪器测定。沿血管方向放置电磁流探针 (0.95-1 mm 流明)用以测定血流。在血管下方、探针末端放置 4x4 mm 石蜡膜条使其与周围的肌肉层隔离。进行基线流量测量后，将 2x5 mm 预先在 35% $FeCl_2$ 中饱和的滤纸条置于探针下游血管顶部 10 分钟，然后移去。$FeCl_2$ 扩散到动脉下侧片段上并产生导致急性血栓形成的去内皮化。在敷加 $FeCl_2$ 浸泡滤纸后，监测 60 分钟观察期间血压、动脉血流和心率的情况。在血管闭合(定义为达到零血流)之后或如果保持开放则在敷加滤纸后 60 分钟，结扎伤口近侧及远端的动脉，并切除血管。移出血栓，随即称重，记录研究的初期终点。

配备手术仪后，取对照血样(B1)。所有血样均采集于动脉导管，并与柠檬酸钠混合以防凝块。每次取血样后均用 0.5mL 0.9% 盐水冲洗导管。在施加 $FeCl_2$ 前 5 分钟静脉(i.v.)给药本发明化合物。记录施加 $FeCl_2$ 与颈动脉血流量达到零时之间的时间，作为闭合时间(TTO)，对于 60 分钟内不闭合的血管，将 TTO 指定为 60 分钟的值。施加 $FeCl_2$ 后 5 分钟，取第二份血样(B2)。$FeCl_2$ 暴露 10 分钟后，从血管上移去滤纸并监测剩余试验期间动物的情况。当达到零血流量时，吸取第三份血样(B3)，移出凝块并称重。在得到血样的同时对前肢脚趾垫进行模板出血时间的测定。对所有血样绘制活化局部凝血酶原激酶时间(APTT)与凝血酶原时间(PT)构成的凝固分布图。在某些情况下可以口

服本发明化合物。利用标准技术人工固定大鼠，化合物通过胃管饲法用 18 规格弯曲剂量针(5ml/kg 体积)给药。胃饲后 15 分钟，如前所述麻醉动物并给其配备仪器，然后按照上述方法进行试验。

本发明还可以用其它不背离本发明精神或其基本属性的特定形式具体化。