PURINE DERIVATIVES AND THEIR USE AS ANTI-COAGULANTS

Field of the Invention

The present invention is directed to purine derivatives and their pharmaceutically acceptable salts, which inhibit the enzyme, factor Xa, thereby being useful as anti-coagulants. It also relates to pharmaceutical compositions containing the derivatives or their pharmaceutically acceptable salts, and methods of their use.

BACKGROUND OF THE INVENTION

Factor Xa is a member of the trypsin-like serine protease class of enzymes. A one-to-one binding of factors Xa and Va with calcium ions and phospholipid forms the prothrombinase complex which converts prothrombin to thrombin. Thrombin, in turn, converts fibrinogen to fibrin which polymerizes to form insoluble fibrin.

In the coagulation cascade, the prothrombinase complex is the convergent point of the intrinsic (surface activated) and extrinsic (vessel injury-tissue factor) pathways (*Biochemistry* (1991), Vol. 30, p. 10363; and *Cell* (1988), Vol. 53, pp. 505-518). The model of the coagulation cascade has been refined further with the discovery of the mode of action of tissue factor pathway inhibitor (TFPI) (*Seminars in Hematology* (1992), Vol. 29, pp. 159-161). TFPI is a circulating multi-domain serine protease inhibitor with three Kunitz-like domains which competes with factor Va for free factor Xa. Once formed, the binary complex of factor Xa and TFPI becomes a potent inhibitor of the factor VIIa and tissue factor complex.

Factor Xa can be activated by two distinct complexes, by tissue factor-VIIa complex on the "Xa burst" pathway and by the factor IXa-VIIIA complex (TENase) of the "sustained Xa" pathway in the coagulation cascade. After vessel injury, the "Xa burst" pathway is activated via tissue factor (TF). Up regulation of the coagulation cascade occurs via increased factor Xa production via the "sustained Xa" pathway. Down regulation of the coagulation cascade occurs with the formation of the factor Xa-TFPI complex, which not only removes factor Xa but also inhibits further factor formation via the "Xa burst" pathway. Therefore, the coagulation cascade is naturally regulated by factor Xa.

The primary advantage of inhibiting factor Xa over thrombin in order to prevent coagulation is the focal role of factor Xa versus the multiple functions of thrombin. Thrombin not only catalyzes the conversion of fibrinogen to fibrin, factor VIII to VIIIA, factor V to Va, and factor XI to XIa, but also activates platelets, is a monocyte chemotactic factor, and mitogen for lymphocytes and smooth muscle cells. Thrombin activates protein C, the *in vivo* anti-coagulant inactivator of factors Va and VIIIa, when bound to thrombomodulin. In circulation, thrombin is rapidly inactivated by antithrombin III (ATIII) and heparin cofactor II (HCII) in a reaction which is catalyzed by heparin or other proteoglycan-associated glycosaminoglycans, whereas thrombin in

tissues is inactivated by the protease, nexin. Thrombin carries out its multiple cellular activation functions through a unique "tethered ligand" thrombin receptor (*Cell* (1991), Vol. 64, p. 1057), which requires the same anionic binding site and active site used in fibrinogen binding and cleavage and by thrombomodulin binding and protein C activation. Thus, a diverse group of *in vivo* molecular targets compete to bind thrombin and the subsequent proteolytic events will have very different physiological consequences depending upon which cell type and which receptor, modulator, substrate or inhibitor binds thrombin.

Published data with the proteins antistasin and tick anti-coagulant peptide (TAP) demonstrate that factor Xa inhibitors are efficacious anti-coagulants (*Thrombosis and Haemostasis* (1992), Vol. 67, pp. 371-376; and *Science* (1990), Vol. 248, pp. 593-596).

The active site of factor Xa can be blocked by either a mechanism-based or a tight binding inhibitor (a tight binding inhibitor differs from a mechanism-based inhibitor by the lack of a covalent link between the enzyme and the inhibitor). Two types of mechanism-based inhibitors are known, reversible and irreversible, which are distinguished by ease of hydrolysis of the enzyme-inhibitor link (*Thrombosis Res* (1992), Vol. 67, pp. 221-231; and *Trends Pharmacol. Sci.* (1987), Vol. 8, pp. 303-307). A series of guanidino compounds are examples of tight-binding inhibitors (*Thrombosis Res.* (1980), Vol. 19, pp. 339-349). Arylsulfonyl-arginine-piperidine-carboxylic acid derivatives have also been shown to be tight-binding inhibitors of thrombin (*Biochem.* (1984), Vol. 23, pp. 85-90), as well as a series of arylamidine-containing compounds, including 3-amidinophenylaryl derivatives (*Thrombosis Res.* (1983), Vol. 29, pp. 635-642) and bis(amidino)benzyl cycloketones (*Thrombosis Res.* (1980), Vol. 17, pp. 545-548). However, these compounds demonstrate poor selectivity for factor Xa.

Related Disclosures

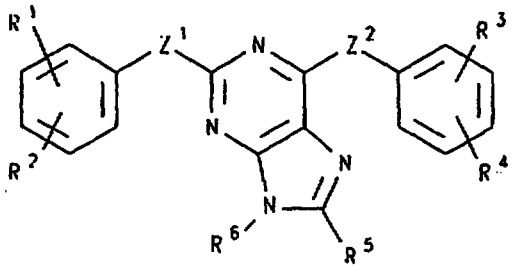
European Published Patent Application 0 540 051 (Nagahara *et al.*) describes aromatic amidine derivatives which are stated to be capable of showing a strong anticoagulant effect through reversible inhibition of factor Xa.

The synthesis of α,α'-bis(amidinobenzylidene)cycloalkanones and α,α'-bis(amidino-benzyl)cycloalkanones is described in *Pharmazie* (1977), Vol. 32, No. 3, pp. 141-145. These compounds are disclosed as being serine protease inhibitors.

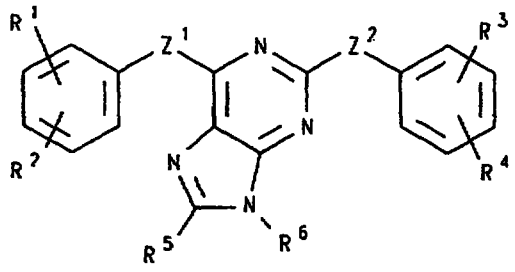
SUMMARY OF THE INVENTION

This invention is directed to compounds or their pharmaceutically acceptable salts which inhibit human factor Xa and are therefore useful as pharmacological agents for the treatment of disease-states characterized by thrombotic activity.

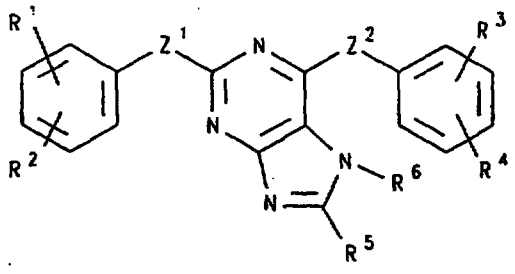
Accordingly, in one aspect, this invention provides compounds selected from the group consisting of the following formulae:



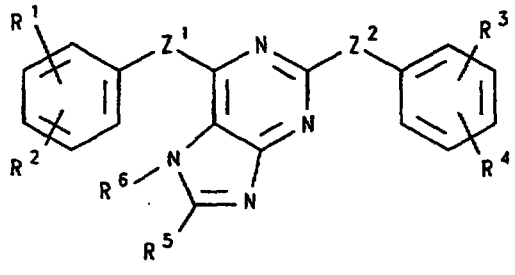
(I)



(II)



(III)



(IV)

wherein:

Z^1 and Z^2 are independently -O-, -N(R^{10})- or -OCH_2-;

R^1 and R^4 are each independently hydrogen, halo, alkyl, -OR^{10}, -C(O)OR^{10}, -C(O)N(R^{10})R^{11}, -N(R^{10})R^{11}, -N(R^{10})C(O)R^{10}, or -N(H)S(O)$_2R^{13}$;

R^2 is -C(NH)NH_2, -C(NH)N(H)OR^{10}, -C(NH)N(H)C(O)OR^{13}, -C(NH)N(H)C(O)R^{10}, -C(NH)N(H)S(O)$_2R^{13}$, or -C(NH)N(H)C(O)N(H)R^{10};

R^3 is halo, alkyl, haloalkyl, haloalkoxy, ureido, cyano, guanidino, -OR^{10}, -C(NH)NH_2, -C(NH)N(H)OR^{10}, -C(O)N(R^{10})R^{11}, -R^{12}-C(O)N(R^{10})R^{11}, -CH(OH)C(O)N(R^{10})R^{11}, -N(R^{10})R^{11}, -R^{12}-N(R^{10})R^{11}, -C(O)OR^{10}, -R^{12}-C(O)OR^{10}, -N(R^{10})C(O)R^{10}, (1,2)-tetrahydropyrimidinyl (optionally substituted by alkyl), (1,2)-imidazolyl (optionally substituted by alkyl), or (1,2)-imidazolinyl (optionally substituted by alkyl);

R^5 is hydrogen, halo, alkyl, cycloalkyl, haloakyl, aryl, aralkyl, alkylthio, hydroxy, mercapto,

alkoxy, or $-N(R^{10})R^{11}$;

R^6 is $-(C(R^7)(R^8))_n-R^9$ (where n is 1 to 4), hydrogen, alkyl, aryl (optionally substituted by halo, alkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, alkyl, aryl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl);

each R^7 is independently hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, cycloalkyl, cycloalkylalkyl, $-C(O)OR^{10}$, $-R^{12}-C(O)OR^{10}$, $-R^{12}-C(O)N(R^{10})R^{11}$, $-C(O)-R^{12}-N(R^{10})R^{11}$, $-R^{12}-C(O)R^{10}$, $-R^{12}-C(O)N(R^{10})N(R^{10})R^{11}$, $-R^{12}-C(R^{10})(OR^{10})-R^{12}-N(R^{10})(R^{11})$, $-C(R^{10})(OR^{10})C(O)OR^{11}$, $-R^{12}-C(R^{10})(C(O)OR^{10})_2$, $-C(R^{10})(N(R^{10})R^{11})C(O)OR^{10}$, $-R^{12}-C(R^{10})(N(R^{10})R^{11})C(O)OR^{10}$, $-C(R^{10})(OR^{10})R^{11}$, $-R^{12}-N(R^{10})R^{11}$, $-R^{12}-N(R^{10})C(O)OR^{13}$, $-R^{12}-N(R^{10})C(O)R^{11}$, $-R^{12}-N(R^{10})C(NR^{10})R^{13}$, $-R^{12}-N(R^{10})S(O)_2R^{13}$, $-R^{12}-N(R^{10})C(O)N(R^{10})R^{11}$, $-R^{12}-N(R^{10})C(NR^{10})N(R^{10})R^{11}$, $-R^{12}-N(R^{10})C(NR^{10})N(R^{10})N(R^{10})R^{11}$, $-R^{12}-N(R^{10})-R^{12}-C(R^{10})(N(R^{10})R^{11})C(O)OR^{10}$, $-R^{12}-N(R^{10})S(O)R^{11}$, $-R^{12}OR^{10}$, $-R^{12}-ON(R^{10})C(NR^{10})N(R^{10})R^{11}$, $-R^{12}-OS(O)_2OR^{10}$, $-R^{12}-P(O)(OR^{10})R^{11}$, $-R^{12}-OP(O)(OR^{10})_2$, $-R^{12}-P(O)(OR^{10})_2$, $-R^{12}-SR^{10}$, $-R^{12}-S-R^{12}-C(O)OR^{10}$, $-R^{12}-S-R^{12}-N(R^{10})R^{11}$, $-R^{12}-S-R^{12}-C(R^{10})(N(R^{10})R^{11})C(O)OR^{10}$, $-R^{12}-S-R^{12}-N(R^{10})C(O)OR^{10}$, $-R^{12}-S-R^{12}-N(R^{10})C(O)R^{10}$, $-R^{12}-S-S-R^{12}-C(R^{10})(N(R^{10})R^{11})C(O)OR^{10}$, $-R^{12}-SC(O)N(R^{10})R^{11}$, $-R^{12}-SC(S)N(R^{10})R^{11}$, $-R^{12}-S(O)R^{10}$, $-R^{12}-S(O)_2R^{13}$, $-R^{12}-S(O)OR^{10}$, $-R^{12}-S(O)_2OR^{10}$, $-R^{12}-S(O)_2N(R^{10})R^{11}$, $-R^{12}-S(O)(NR^{10})R^{11}$,

or each R^7 is aryl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, haloalkoxy, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})R^{11}$, $-C(O)OR^{10}$, $-C(O)N(R^{10})R^{11}$, $-S(O)_2OR^{10}$ and $-OP(O)(OR^{10})_2$),

or each R^7 is aralkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, haloalkoxy, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})R^{11}$, $-C(O)OR^{10}$, $-C(O)N(R^{10})R^{11}$, $-S(O)_2OR^{10}$ and $-OP(O)(OR^{10})_2$),

or each R^7 is heterocyclyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, haloalkoxy, aralkyl, $-OR^{10}$, $-C(O)OR^{10}$, $-N(R^{10})R^{11}$, $-C(O)N(R^{10})R^{11}$, $-S(O)_2OR^{10}$ and $-OP(O)(OR^{10})_2$),

or each R^7 is heterocyclylalkyl (where the heterocyclyl radical is optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, haloalkoxy, aralkyl, $-OR^{10}$, $-SR^{10}$, $-C(O)OR^{10}$, $-N(R^{10})R^{11}$, $-C(O)N(R^{10})R^{11}$), $-S(O)_2OR^{10}$ and $-OP(O)(OR^{10})_2$),

or each R^7 is adamantyl (optionally substituted by alkyl, halo, haloalkyl, haloalkoxy, $-OR^{10}$, $-SR^{10}$, $-C(O)OR^{10}$, $-N(R^{10})R^{11}$, $-C(O)N(R^{10})R^{11}$, $-S(O)_2OR^{10}$ and $-OP(O)(OR^{10})_2$),

or each R^7 is adamantylalkyl (where the adamantyl radical is optionally substituted by alkyl, halo, haloalkyl, haloalkoxy, $-OR^{10}$, $-SR^{10}$, $-C(O)OR^{10}$, $-N(R^{10})R^{11}$, $-C(O)N(R^{10})R^{11}$, $-S(O)_2OR^{10}$ and $-OP(O)(OR^{10})_2$);

each R^8 is independently hydrogen, alkyl, cycloalkyl, or aryl;

R^9 is $-C(O)OR^{10}$ or $-C(O)N(R^{10})R^{11}$;

each R^{10} and R^{11} is independently hydrogen, alkyl, aryl (optionally substituted by halo, alkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, alkyl, aryl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl);

R^{12} is a straight or branched alkylene chain; and

R^{13} is alkyl, aryl (optionally substituted by halo, alkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, alkyl, aryl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl);

as a single stereoisomer or a mixture thereof; or a pharmaceutically acceptable salt thereof.

In another aspect, this invention provides compositions useful in treating a human having a disease-state characterized by thrombotic activity, which composition comprises a therapeutically effective amount of a compound of the invention as described above, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In another aspect, this invention provides a method of treating a human having a disease-state characterized by thrombotic activity, which method comprises administering to a human in need thereof a therapeutically effective amount of a compound of the invention as described above.

In another aspect, this invention provides a method of treating a human having a disease-state alleviated by the inhibition of factor Xa, which method comprises administering to a human in need thereof a therapeutically effective amount of a compound of the invention as described above.

In another aspect, this invention provides a method of inhibiting human factor Xa *in vitro* or *in vivo* by the administration of a compound of the invention.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated:

"Alkyl" refers to a straight or branched chain monovalent or divalent radical consisting solely of carbon and hydrogen, containing no unsaturation and having from one to six carbon atoms, *e.g.*, methyl, ethyl, *n*-propyl, 1-methylethyl (*iso*-propyl), *n*-butyl, *n*-pentyl, 1,1-dimethylethyl (*t*-butyl), and the like.

"Alkenyl" refers to a straight or branched chain monovalent or divalent radical consisting solely of carbon and hydrogen, containing at least one double bond and having from one to six carbon atoms, *e.g.*, ethenyl, prop-1-enyl, but-1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like.

"Alkynyl" refers to a straight or branched chain monovalent or divalent radical consisting solely of carbon and hydrogen, containing at least one triple bond and having from one to six carbon atoms, *e.g.*, ethynyl, prop-1-ynyl, but-1-ynyl, pent-1-ynyl, pent-3-ynyl, and the like.

"Alkoxy" refers to a radical of the formula $-OR_a$ where R_a is alkyl as defined above, *e.g.*, methoxy, ethoxy, *n*-propoxy, 1-methylethoxy (*iso*-propoxy), *n*-butoxy, *n*-pentoxy, 1,1-dimethylethoxy (*t*-butoxy), and the like.

"Alkoxycarbonyl" refers to a radical of the formula $-C(O)OR_a$ where R_a is alkyl as defined above, *e.g.*, methoxycarbonyl, ethoxycarbonyl, *n*-propoxycarbonyl, *iso*-propoxycarbonyl, *t*-butoxycarbonyl, and the like.

"Alkylene" refers to straight or branched chain divalent radical consisting solely of carbonyl and hydrogen, containing no unsaturation and having from one to six carbon atoms, *e.g.*, methylene, ethylene, propylene, *n*-butylene, and the like.

"Alkylthio" refers to a radical of the formula $-SR_a$ where R_a is alkyl as defined above, *e.g.*, methylthio, ethylthio, *n*-propylthio, *t*-butylthio, and the like.

"Amidino" refers to the radical $-C(NH)-NH_2$.

"Aminocarbonyl" refers to the radical $-C(O)NH_2$.

"Aryl" refers to a phenyl or naphthyl radical.

"Aralkyl" refers to a radical of the formula $-R_aR_b$ where R_a is alkyl as defined above and R_b is aryl as defined above, *e.g.*, benzyl.

"Aralkoxy" refers to a radical of the formula $-OR_c$ where R_c is aralkyl as defined above, *e.g.*, benzyloxy, and the like.

"Cycloalkyl" refers to a stable 3- to 7-membered monocyclic cyclic radical which is saturated, and which consist solely of carbon and hydrogen atoms, *e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like.

"Cycloalkylalkyl" refers to a alkyl radical, as defined above, substituted by a cycloalkyl radical, as defined above, *e.g.*, (cyclobutyl)methyl, 2-(cyclopentyl)ethyl, 3-(cyclohexyl)propyl, and the like.

"Dialkylamino" refers to a radical of the formula $-NR_aR_a$ where each R_a is independently an alkyl radical as defined above, *e.g.*, dimethylamino, methylethylamino, diethylamino, dipropylamino, ethylpropylamino, and the like.

"Dialkylaminocarbonyl" refers to a radical of the formula $-C(O)NR_aR_a$ where each R_a is independently an alkyl radical as defined above, *e.g.*, dimethylaminocarbonyl, methylethylaminocarbonyl, diethylaminocarbonyl, dipropylaminocarbonyl, ethylpropylaminocarbonyl, and the like.

"Halo" refers to bromo, iodo, chloro or fluoro.

"Haloalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, trifluoromethyl, difluoromethyl, trichloromethyl, 2-trifluoroethyl, 3-bromo-2-fluoropropyl, 1-bromomethyl-2-bromoethyl, and the like.

"Haloalkenyl" refers to an alkenyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, 2-difluoroethenyl, 3-bromo-2-fluoroprop-1-enyl, and the like.

"Haloalkoxy" refers to a radical of the formula $-OR_f$ where R_f is haloalkyl as defined above, *e.g.*, trifluoromethoxy, difluoromethoxy, trichloromethoxy, 2-trifluoroethoxy, 1-fluoromethyl-2-fluoroethoxy, 3-bromo-2-fluoropropoxy, 1-bromomethyl-2-bromoethoxy, and the like.

"Heterocyclyl" refers to a stable 3- to 10-membered monocyclic or bicyclic radical which is either saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and wherein the nitrogen, carbon or sulfur atoms may be optionally oxidized, and the nitrogen atom may be optionally quaternized. The heterocyclyl radical may be attached to the main structure at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic radicals include, but are not limited to, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, triazolyl, indanyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, octahydroindolyl, octahydroisoindolyl, quinolyl, isoquinolyl, decahydroisoquinolyl, benzimidazolyl, thiadiazolyl, benzopyranyl, benzothiazolyl, benzoxazolyl, furyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, and oxadiazolyl. Preferred heterocyclyl radicals in this invention are indolyl, imidazolyl, thiazolyl, isoxazolyl, triazolyl, pyridinyl, thienyl, benzothienyl, furyl, and 3,4-dihydro-2,3-dioxo-1(2H)-pyrimidinyl.

"Heterocyclylalkyl" refers to a radical of the formula $-R_aR_g$ where R_a is an alkyl radical as defined above and R_g is a heterocyclyl radical as defined above, *e.g.*, indolinylmethyl or imidazolylmethyl, and the like.

"(1,2)-Imidazolyl" refers to an imidazolyl radical attached at either the 1- or 2-position.

"(1,2)-Imidazolinyl" refers to a 4,5-dihydroimidazolyl radical attached at either the 1- or

the 2-position.

"Monoalkylamino" refers to a radical of the formula -NHR_a where R_a is an alkyl radical as defined above, *e.g.*, methylamino, ethylamino, propylamino, and the like.

"Monoalkylaminocarbonyl" refers to a radical of the formula -$C(O)NHR_a$ where R_a is an alkyl radical as defined above, *e.g.*, methylaminocarbonyl, ethylaminocarbonyl, propylaminocarbonyl, and the like.

"(1,2)-Tetrahydropyrimidinyl" refers to a tetrahydropyrimidinyl attached at either the 1- or 2-position.

"Adamantylalkyl" refers to a radical of the formula -R_aR_h where R_a is an alkyl radical as defined above, and R_h is an adamantyl radical, *e.g.*, adamantylmethyl, 2-adamantylethyl, and the like.

"Optional" or "optionally" means that the subsequently described event of circumstances may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted aryl" means that the aryl radical may or may not be substituted and that the description includes both substituted aryl radicals and aryl radicals having no substitution.

"Pharmaceutically acceptable salt" includes both acid and base addition salts.

"Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, *p*-toluenesulfonic acid, salicylic acid, and the like.

"Pharmaceutically acceptable base addition salt" refers to those salts which retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. Salts derived from inorganic bases include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Preferred inorganic salts are the ammonium, sodium, potassium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, trimethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, *N*-ethylpiperidine, polyamine resins

and the like. Particularly preferred organic bases are isopropylamine, diethylamine, ethanolamine, trimethamine, dicyclohexylamine, choline and caffeine.

"Therapeutically effective amount" refers to that amount of a compound of the invention which, when administered to a human in need thereof, is sufficient to effect treatment, as defined below, for disease-states characterized by thrombotic activity. The amount of a compound of the invention which constitutes a "therapeutically effective amount" will vary depending on the compound, the disease-state and its severity, and the age of the human to be treated, but can be determined routinely by one of ordinary skill in the art having regard to his own knowledge and to this disclosure.

"Treating" or "treatment" as used herein cover the treatment of a disease-state in a human, which disease-state is characterized by thrombotic activity; and include:

(i) preventing the disease-state from occurring in a human, in particular, when such human is predisposed to the disease-state but has not yet been diagnosed as having it;

(ii) inhibiting the disease-state, i.e., arresting its development; or

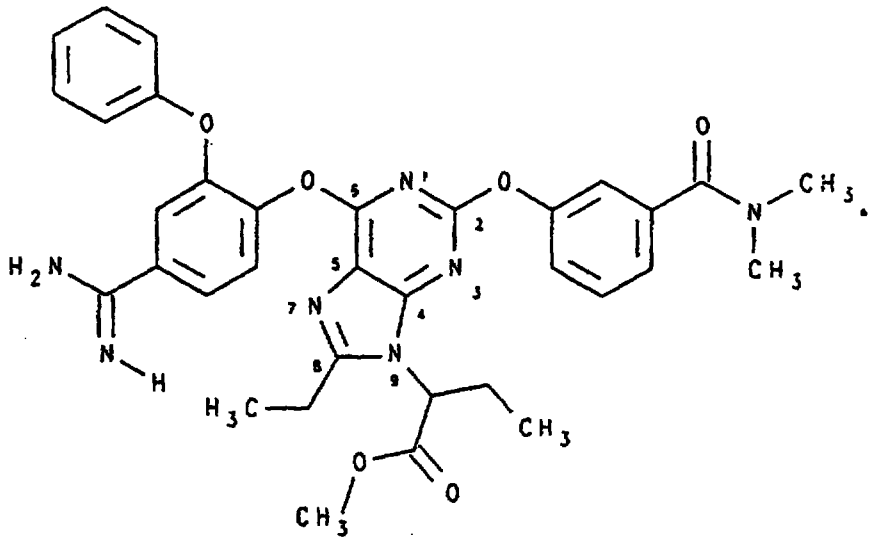
(iii) relieving the disease-state, i.e., causing regression of the disease-state.

The yield of each of the reactions described herein is expressed as a percentage of the theoretical yield.

The compounds of the invention, or their pharmaceutically acceptable salts, may have asymmetric carbon atoms in their structure. The compounds of the invention and their pharmaceutically acceptable salts may therefore exist as single stereoisomers, racemates, and as mixtures of enantiomers and diastereomers. All such single stereoisomers, racemates and mixtures thereof are intended to be within the scope of this invention.

It is noted that when R^1 is the same substituent at R^3, R^2 is the same substituent as R^4, and Z^1 and Z^2 are the same, compounds of formula (I) are the same as compounds of formula (II) and compounds of formula (III) are the same as compounds of formula (IV).

The nomenclature used herein is a modified form of the I.U.P.A.C. system wherein the compounds of the invention are named as derivatives of purine. For example, a compound of the invention selected from formula (II), wherein Z^1 and Z^2 are both -O-; R^1 is $-OR^{10}$ where R^{10} is phenyl; R^2 is $-C(NH)NH_2$; R^3 is $-C(O)N(R^{10})R^{11}$ where R^{10} and R^{11} are both methyl; R^4 is hydrogen; R^5 is ethyl; and R^6 is $-(C(R^7)(R^8))_n-R^9$ where n is 1, R^7 is hydrogen, R^8 is ethyl, and R^9 is $-C(O)OR^{10}$ where R^{10} is methyl, *i.e.* a compound of the following formula:



is named herein as 2-(3-dimethylaminocarbonylphenoxy)-6-(2-phenoxy-4-amidinophenoxy)-9-(1-methoxycarbonylpropyl)-8-ethylpurine.

Utility and Administration

A. Utility

The compounds of the invention are inhibitors of factor Xa and therefore useful in disease-states characterized by thrombotic activity based on factor Xa's role in the coagulation cascade (see Background of the Invention above). A primary indication for the compounds is prophylaxis for long term risk following myocardial infarction. Additional indications are prophylaxis of deep vein thrombosis (DVT) following orthopedic surgery or prophylaxis of selected patients following a transient ischemic attack. The compounds of the invention may also be useful for indications in which coumarin is currently used, such as for DVT or other types of surgical intervention such as coronary artery bypass graft and percutaneous transluminal coronary angioplasty. The compounds are also useful for the treatment of thrombotic complications associated with acute promyelocytic leukemia, diabetes, multiple myelomas, disseminated intravascular coagulation associated with septic shock, purpura fulminanas associated infection, adult respiratory distress syndrome, unstable angina, and thrombotic complications associated with aortic valve or vascular prosthesis. The compounds are also useful for prophylaxis for thrombotic diseases, in particular in patients who have a high risk of developing such disease.

In addition, the compounds of the invention are useful as *in vitro* diagnostic reagents for selectively inhibiting factor Xa without inhibiting other components of the coagulation cascade.

B. Testing

The primary bioassays used to demonstrate the inhibitory effect of the compounds of the

invention on factor Xa are simple chromogenic assays involving only serine protease, the compound of the invention to be tested, substrate and buffer (see, *e.g.*, *Thrombosis Res.* (1979), Vol. 16, pp. 245-254). For example, four tissue human serine proteases can be used in the primary bioassay, free factor Xa, prothrombinase, thrombin (IIa) and tissue plasminogen activator (tPA). The assay for TPA has been successfully used before to demonstrate undesired side effects in the inhibition of the fibrinolytic process (see, *e.g.*, *J. Med. Chem.* (1993), Vol. 36, pp. 314-319). Another bioassay useful in demonstrating the utility of the compounds of the invention in inhibiting factor Xa demonstrates the potency of the compounds against free factor Xa in citrated plasma. For example, the anticoagulant efficacy of the compounds of the invention will be tested using either the prothrombin time (PT), or activated partial thromboplastin time (aPTT) while selectivity of the compounds is checked with the thrombin clotting time (TCT) assay. Correlation of the K_i in the primary enzyme assay with the K_i for free factor Xa in citrated plasma will screen against compounds which interact with or are inactivated by other plasma components. Correlation of the K_i with the extension of the PT is a necessary *in vitro* demonstration that potency in the free factor Xa inhibition assay translates into potency in a clinical coagulation assay. In addition, extension of the PT in citrated plasma can be used to measure duration of action in subsequent pharmacodynamic studies.

For further information on assays to demonstrate the activity of the compounds of the invention, see R. Lottenberg *et al.*, *Methods in Enzymology* (1981), Vol. 80, pp. 341-361, and H. Ohno *et al.*, *Thrombosis Research* (1980), Vol. 19, pp. 579-588.

C. General Administration

Administration of the compounds of the invention, or their pharmaceutically acceptable salts, in pure form or in an appropriate pharmaceutical composition, can be carried out via any of the accepted modes of administration or agents for serving similar utilities. Thus, administration can be, for example, orally, nasally, parenterally, topically, transdermally, or rectally, in the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as for example, tablets, suppositories, pills, soft elastic and hard gelatin capsules, powders, solutions, suspensions, or aerosols, or the like, preferably in unit dosage forms suitable for simple administration of precise dosages. The compositions will include a conventional pharmaceutical carrier or excipient and a compound of the invention as the/an active agent, and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, *etc.*

Generally, depending on the intended mode of administration, the pharmaceutically acceptable compositions will contain about 1% to about 99% by weight of a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, and 99% to 1% by weight of a suitable pharmaceutical excipient. Preferably, the composition will be about 5% to 75% by weight of a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, with the rest being

suitable pharmaceutical excipients.

The preferred route of administration is oral, using a convenient daily dosage regimen which can be adjusted according to the degree of severity of the disease-state to be treated. For such oral administration, a pharmaceutically acceptable composition containing a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, is formed by the incorporation of any of the normally employed excipients, such as, for example, pharmaceutical grades of mannitol, lactose, starch, pregelatinized starch, magnesium stearate, sodium saccharine, talcum, cellulose ether derivatives, glucose, gelatin, sucrose, citrate, propyl gallate, and the like. Such compositions take the form of solutions, suspensions, tablets, pills, capsules, powders, sustained release formulations and the like.

Preferably such compositions will take the form of capsule, caplet or tablet and therefore will also contain a diluent such as lactose, sucrose, dicalcium phosphate, and the like; a disintegrant such as croscarmellose sodium or derivatives thereof; a lubricant such as magnesium stearate and the like; and a binder such as a starch, gum acacia, polyvinylpyrrolidone, gelatin, cellulose ether derivatives, and the like.

The compounds of the invention, or their pharmaceutically acceptable salts, may also be formulated into a suppository using, for example, about 0.5% to about 50% active ingredient disposed in a carrier that slowly dissolves within the body, *e.g.*, polyoxyethylene glycols and polyethylene glycols (PEG), *e.g.*, PEG 1000 (96%) and PEG 4000 (4%).

Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, *etc.*, a compound(s) of the invention (about 0.5% to about 20%), or a pharmaceutically acceptable salt thereof, and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol and the like, to thereby form a solution or suspension.

If desired, a pharmaceutical composition of the invention may also contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents, antioxidants, and the like, such as, for example, citric acid, sorbitan monolaurate, triethanolamine oleate, butylated hydroxytoluene, *etc.*

Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see *Remington's Pharmaceutical Sciences*, 18th Ed., (Mack Publishing Company, Easton, Pennsylvania, 1990). The composition to be administered will, in any event, contain a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, for treatment of a disease-state alleviated by the inhibition of factor Xa in accordance with the teachings of this invention.

The compounds of the invention, or their pharmaceutically acceptable salts, are administered in a therapeutically effective amount which will vary depending upon a variety of factors including the activity of the specific compound employed, the metabolic stability and

length of action of the compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular disease-states, and the host undergoing therapy. Generally, a therapeutically effective daily dose is from about 0.14 mg to about 14.3 mg/kg of body weight per day of a compound of the invention, or a pharmaceutically acceptable salt thereof; preferably, from about 0.7 mg to about 10 mg/kg of body weight per day; and most preferably, from about 1.4 mg to about 7.2 mg/kg of body weight per day. For example, for administration to a 70 kg person, the dosage range would be from about 10 mg to about 1.0 gram per day of a compound of the invention, or a pharmaceutically acceptable salt thereof, preferably from about 50 mg to about 700 mg per day, and most preferably from about 100 mg to about 500 mg per day.

Preferred Embodiments

Of the compounds of the invention as set forth above in the Summary of the Invention, a preferred group are those compounds wherein Z^1 and Z^2 are independently -O- or -OCH_2-; R^1 and R^4 are each independently hydrogen, halo or -OR^{10}; R^2 is -$C(NH)NH_2$, -$C(NH)N(H)S(O)_2R^{13}$, or -$C(NH)N(H)C(O)N(H)R^{10}$; R^3 is ureido, guanidino, -$C(O)N(R^{10})R^{11}$, -$N(R^{10})R^{11}$, -$C(O)OR^{10}$, -$N(R^{10})C(O)R^{10}$, (1,2)-tetrahydropyrimidinyl (optionally substituted by alkyl), (1,2)-imidazolyl (optionally substituted by alkyl), or (1,2)-imidazolinyl (optionally substituted by alkyl); R^5 is hydrogen, halo, alkyl, haloalkyl, aryl, or aralkyl; R^6 is alkyl, aryl, aralkyl, or -$(C(R^7)(R^8))_n$-R^9 (where n is 1); R^7 is alkyl, -R^{12}-$C(O)OR^{10}$, -R^{12}-$C(O)N(R^{10})R^{11}$, -R^{12}-$C(R^{10})(C(O)OR^{10})_2$, -R^{12}-$N(R^{10})R^{11}$, -R^{12}-$N(R^{10})C(NR^{10})R^{13}$, -$R^{12}$-$N(R^{10})C(O)N(R^{10})R^{11}$, -$R^{12}$-$N(R^{10})C(NR^{10})N(R^{10})R^{11}$, -$R^{12}OR^{10}$, -$R^{12}$-$OP(O)(OR^{10})_2$, -$R^{12}$-$SR^{10}$, -$R^{12}$-$S(O)_2R^{13}$; or R^7 is aralkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, haloalkoxy, -OR^{10}, -SR^{10}, -$N(R^{10})R^{11}$, -$C(O)OR^{10}$, -$C(O)N(R^{10})R^{11}$, -$S(O)_2OR^{10}$ and -$OP(O)(OR^{10})_2$); or R^7 is heterocyclylalkyl (where the heterocyclyl radical is optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, haloalkoxy, aralkyl, -OR^{10}, -SR^{10}, -$C(O)OR^{10}$, -$N(R^{10})R^{11}$, -$C(O)N(R^{10})R^{11}$, -$S(O)_2OR^{10}$ and -$OP(O)(OR^{10})_2$); R^8 is independently hydrogen or alkyl; R^9 is -$C(O)OR^{10}$ or -$C(O)N(R^{10})R^{11}$; each R^{10} and R^{11} is independently hydrogen, alkyl, aryl (optionally substituted by halo, alkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, alkyl, aryl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl); R^{12} is a straight or branched alkylene chain; and R^{13} is alkyl, aryl (optionally substituted by halo, alkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, alkyl, aryl, hydroxy, alkoxy,

aralkyl, amino, dialkylamino, monoalkylamino, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl).

Of this group of compounds, a preferred subgroup of compounds is that subgroup wherein Z^1 and Z^2 are each -O-; R^1 is hydrogen or $-OR^{10}$; R^2 is $-C(NH)NH_2$; R^3 is $-C(O)N(R^{10})R^{11}$, (1,2)-tetrahydropyrimidinyl (optionally substituted by alkyl), (1,2)-imidazolyl (optionally substituted by alkyl), or (1,2)-imidazolinyl (optionally substituted by alkyl); R^4 is hydrogen; R^5 is alkyl or aralkyl; R^6 is alkyl, aralkyl or $-C(R^7)(R^8)-R^9$; R^7 is alkyl, $-R^{12}-C(O)OR^{10}$, $-R^{12}-C(O)N(R^{10})R^{11}$, $-R^{12}-C(R^{10})(C(O)OR^{10})_2$, $-R^{12}-N(R^{10})R^{11}$, $-R^{12}-N(R^{10})C(NR^{10})R^{13}$, $-R^{12}-N(R^{10})C(O)N(R^{10})R^{11}$, $-R^{12}-N(R^{10})C(NR^{10})N(R^{10})R^{11}$, $-R^{12}OR^{10}$, $-R^{12}-OP(O)(OR^{10})_2$, $-R^{12}-SR^{10}$, $-R^{12}-S(O)_2R^{13}$; or R^7 is aralkyl (optionally substituted by one or more substituents selected from the group consisting of halo, haloalkyl, hydroxy and $-OP(O)(OR^{10})_2$); or R^7 is imidazolylalkyl or indolylalkyl; R^8 is hydrogen or alkyl; R^9 is $-C(O)OR^{10}$ or $-C(O)N(R^{10})R^{11}$; each R^{10} and R^{11} is independently hydrogen or alkyl; R^{12} is a s traight or branched alkylene chain; and R^{13} is alkyl or aryl.

Of this subgroup of compounds, a preferred class of compounds is that class wherein Z^1 and Z^2 are each -O-; R^1 is hydrogen; R^2 is $-C(NH)NH_2$; R^3 is $-C(O)N(R^{10})R^{11}$, (1,2)-tetrahydropyrimidinyl (optionally substituted by alkyl), (1,2)-imidazolyl (optionally substituted by alkyl), or (1,2)-imidazolinyl (optionally substituted by alkyl); R^4 is hydrogen; R^5 is alkyl; R^6 is aralkyl or $-C(R^7)(R^8)-R^9$; R^7 is alkyl, $-R^{12}-C(O)OR^{10}$, $-R^{12}-C(O)N(R^{10})R^{11}$, $-R^{12}-C(R^{10})(C(O)OR^{10})_2$, $-R^{12}-N(R^{10})R^{11}$, $-R^{12}-N(R^{10})C(NR^{10})R^{13}$, $-R^{12}-N(R^{10})C(O)N(R^{10})R^{11}$, $-R^{12}-N(R^{10})C(NR^{10})N(R^{10})R^{11}$, $-R^{12}OR^{10}$, $-R^{12}-OP(O)(OR^{10})_2$, $-R^{12}-SR^{10}$, $-R^{12}-S(O)_2R^{13}$; or R^7 is aralkyl (optionally substituted by one or more substituents selected from the group consisting of halo, haloalkyl, hydroxy and $-OP(O)(OR^{10})_2$); or R^7 is imidazolylalkyl or indolylalkyl; R^8 is hydrogen or alkyl; R^9 is $-C(O)OR^{10}$ or $-C(O)N(R^{10})R^{11}$; each R^{10} and R^{11} is independently hydrogen or alkyl; R^{12} is a straight or branched alkylene chain; and R^{13} is alkyl or aryl.

Of this class of compounds, a preferred subclass of compounds is that subclass wherein R^3 is $-C(O)N(R^{10})R^{11}$, (1,2)-imidazolyl (optionally substituted by alkyl) or (1,2)-imidazolinyl (optionally substituted by alkyl); R^4 is hydrogen; R^5 is alkyl; R^6 is aralkyl or $-C(R^7)(R^8)-R^9$; R^7 is alkyl, $-R^{12}-C(O)OR^{10}$, $-R^{12}-C(O)N(R^{10})R^{11}$, $-R^{12}-C(R^{10})(C(O)OR^{10})_2$, $-R^{12}-N(R^{10})R^{11}$, $-R^{12}-N(R^{10})C(NR^{10})R^{13}$, $-R^{12}-N(R^{10})C(O)N(R^{10})R^{11}$, $-R^{12}-N(R^{10})C(NR^{10})N(R^{10})R^{11}$, $-R^{12}OR^{10}$, $-R^{12}-OP(O)(OR^{10})_2$, $-R^{12}-SR^{10}$, $-R^{12}-S(O)_2R^{13}$; R^8 is hydrogen; R^9 is $-C(O)OR^{10}$; each R^{10} and R^{11} is independently hydrogen or alkyl; R^{12} is a straight or branched alkylene chain; and R^{13} is alkyl or aryl.

Preferred compounds of this subclass are those compounds wherein R^3 is $-C(O)N(R^{10})R^{11}$; R^4 is hydrogen; R^5 is methyl or ethyl; R^6 is benzyl; and R^{10} and R^{11} are independently hydrogen or methyl.

More preferred compounds of this subclass are those compounds from formula (I) or formula (II) wherein R^3 is $-C(O)N(R^{10})R^{11}$ where R^{10} and R^{11} are both methyl, R^4 is hydrogen, R^5

is methyl, and R^6 is benzyl, namely, 2-(2-hydroxy-5-cyanophenoxy)-6-(3-dimethylaminocarbonyl)phenoxy-8-methyl-9-benzylpurine, and 6-(2-hydroxy-5-cyanophenoxy)-2-(3-dimethylaminocarbonyl)phenoxy-8-methyl-9-benzylpurine.

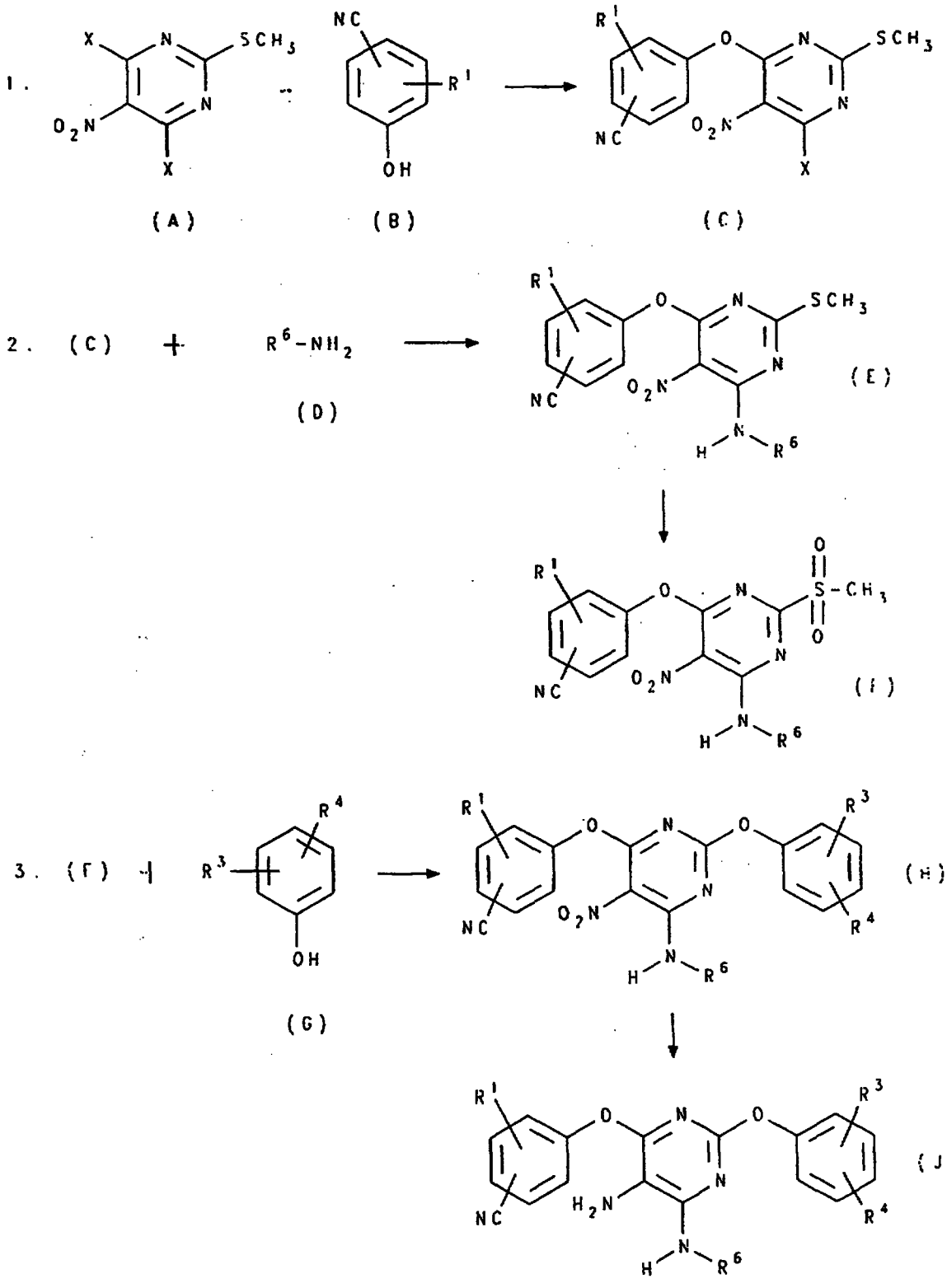
Preparation of Compounds of The Invention

As a matter of convenience, the following description of the preparation of the compounds of the invention is directed to the preparation of compounds of formula (I) and (II). It is understood, however, that similar synthetic processes may be used to prepare the compounds of formula (III) and (IV). It is also understood that in the following description, combinations of substituents and/or variables (*e.g.*, R^7 and R^8) in the depicted compounds are permissible only if such combinations result in stable compounds.

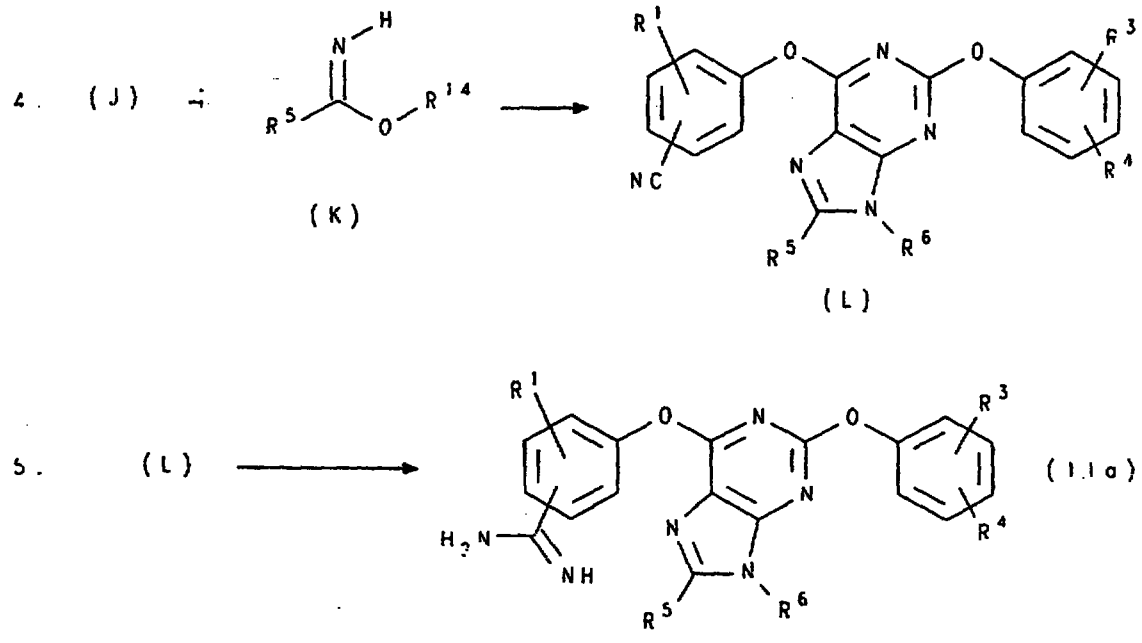
A. Preparation of Compounds of Formula (IIa)

Compounds of formula (IIa) are compounds of formula (II) where Z^1 and Z^2 are both -O- and R^2 is $-C(NH)NH_2$. These compounds may be prepared as illustrated in the following Reaction Scheme 1 wherein: R^1 and R^4 are each independently hydrogen, halo, alkyl, $-OR^{10}$, $-C(O)OR^{10}$, $-C(O)N(R^{10})R^{11}$, $-N(R^{10})R^{11}$, $-N(R^{10})C(O)R^{10}$, or $-N(H)S(O)_2R^{13}$; R^3 is halo, alkyl, haloalkyl, haloalkoxy, ureido, cyano, guanidino, $-OR^{10}$, $-C(NH)NH_2$, $-C(NH)N(H)OR^{10}$, $-C(O)N(R^{10})R^{11}$, $-R^{12}$-$C(O)N(R^{10})R^{11}$, $-CH(OH)C(O)N(R^{10})R^{11}$, $-N(R^{10})R^{11}$, $-R^{12}$-$N(R^{10})R^{11}$, $-C(O)OR^{10}$, $-R^{12}$-$C(O)OR^{10}$, $-N(R^{10})C(O)R^{10}$, (1,2)-tetrahydropyrimidinyl (optionally substituted by alkyl), (1,2)-imidazolyl (optionally substituted by alkyl), or (1,2)-imidazolinyl (optionally substituted by alkyl); R^5 is hydrogen, alkyl, cycloalkyl, haloalkyl, aryl, or aralkyl; R^6 is hydrogen, alkyl, aryl (optionally substituted by halo, alkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, alkyl, aryl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl); each R^{10} and R^{11} is independently hydrogen, alkyl, aryl (optionally substituted by halo, alkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, alkyl, aryl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl); R^{12} is a straight or branched alkylene chain; and R^{13} is alkyl, aryl (optionally substituted by halo, alkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, alkyl, aryl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl); and R^{14} is alkyl:

REACTION SCHEME 1



REACTION SCHEME 1 continued



Compounds of formula (A), formula (B), formula (D), formula (G) and formula (K) are commercially available, for example, from Aldrich Chemical Co., or Sigma Chemical Co., or ICN Biomedicals, or may be prepared according to methods known to those skilled in the art.

In general, compounds of formula (IIa) were prepared by first treating a compound of formula (A) in an aprotic solvent, such as acetonitrile, at temperatures between about -10°C and 10°C, preferably at 0°C, with an equimolar amount of a compound of formula (B) in the presence of a base, for example, cesium carbonate. The reaction mixture was allowed to stir at ambient temperature for 12 to 20 hours, preferably about 16 hours. The compound of formula (C) was then isolated from the reaction mixture by standard isolation techniques, such as extraction, *in vacuo* removal of solvent and flash chromatography.

The compound of formula (C) in an aprotic solvent, preferably acetonitrile, at temperatures between about -10°C and 10°C, preferably at 0°C, in the presence of a base, preferably cesium carbonate, was treated with an equimolar amount of a compound of formula (D). The resulting reaction mixture was heated to about 50°C for about 3 to 6 hours, preferably for about 4 hours. The compound of formula (E) was isolated from the reaction mixture by standard techniques, such as filtration, *in vacuo* removal of solvents and flash chromatography.

The compound of formula (E) in a protic solvent, such as methanol, at temperatures from about -10°C to about 10°C, preferably at 0°C, was then treated with a strong oxidizing agent, such as potassium metabisulfite ($KHSO_5$) in water. The resulting reaction mixture was allowed to stir at ambient temperature for about 12 to 16 hours, preferably for about 15 hours. The mixture

was concentrated and extracted with an aprotic solvent, such as methylene chloride, to afford the corresponding sulfonyl compound of formula (F). The compound of formula (F) was dissolved in an aprotic solvent, preferably acetonitrile, at temperatures from about -10°C to about 10°C, preferably at about 0°C, in the presence of a base, preferably cesium carbonate. A compound of formula (G) was then added to the solution and the resulting reaction mixture was stirred at ambient temperatures for about 12 to about 16 hours, preferably for about 16 hours. The compound of formula (H) was then isolated from the reaction mixture by standard isolation techniques, such as *in vacuo* removal of solvent and flash chromatography.

The compound of formula (H) was reduced under standard reducing conditions, such as Zn/HCl. The resulting amino compound of formula (J) was isolated from the reaction mixture through standard techniques, such as neutralization with a weak base, for example, $NaHCO_3$, followed by extraction with an organic solvent such as ethyl acetate and *in vacuo* removal of solvent. The compound of formula (J) was treated with an imidate of the formula (K) in a polar solvent, such as in a mixture of tetrahydrofuran (THF) and ethanol, at temperatures from about 60°C to about 75°C, preferably at about 70°C, for about 2 to 4 hours, preferably for about 3 hours. The compound was then heated under vacuum from about 150°C to about 200°C, preferably at about 170°C, for about 1 to 3 hours, preferably for about 2 hours. The reaction mixture was then concentrated to afford an oil, which was further purified by standard purification techniques (filtration, extraction and *in vacuo* removal of solvent) to afford the purine of formula (L).

The compound of formula (L) was dissolved in an alkanol, preferably ethanol, at 0°C, and the resulting solution was then saturated with a mineral acid gas, preferably hydrochloric acid. The reaction mixture was sealed and allowed to warm to ambient temperature over a period of time from about 12 hours to 16 hours. The reaction mixture was concentrated and a polar solvent, such as ether was added to the concentrated mixture. The resulting precipitate was dissolved in an alkanol, preferably ethanol and the resulting solution was cooled to about 0°C and then treated with anhydrous ammonia (gas) for about 5 to 20 minutes. The reaction mixture was then sealed and heated at temperatures from between ambient temperature and 100°C, preferably at about 60°C for about 2 to 6 hours, preferably for about 2 hours. The reaction mixture was cooled and the solvents were evaporated. A compound of formula (IIa) was isolated from the reaction mixture by standard isolation techniques, such as filtration, evaporation of the solvents, and purification by preparative HPLC.

Alternatively, instead of treating the resulting solution above with anhydrous ammonia, the resulting solution may be treated with a compound of the formula NH_2OR^{10} to afford the compound of formula (II) wherein R^2 is $-C(NH)N(H)OR^{10}$.

Compounds of formula (IIa) wherein R^3 is $-C(NH)NH_2$ or $-C(NH)N(H)OR^{10}$ are produced from the corresponding cyano compounds in a similar manner as that described above for

compounds of formula (L).

In addition, compounds of formula (IIa) wherein R^1, R^3, R^4 or R^6 contains a $-C(O)N(R^{10})R^{11}$ group or a $-C(O)OR^{10}$ group (where each R^{10} and R^{11} is independently alkyl, optionally substituted aryl or optionally substituted aralkyl) may be hydrolyzed under acidic conditions to prepare compounds of the invention where R^1, R^3, R^4 or R^6 contains a carboxy group.

In addition, compounds of formula (IIa) wherein R^1, R^3, R^4 or R^6 contains a $-C(O)OR^{10}$ group where R^{10} is hydrogen, alkyl, optionally substituted aryl or optionally substituted aralkyl may be amidated under standard amidation conditions to form the corresponding compounds of formula (IIa) where R^1, R^3, R^4 or R^6 contains a $-C(O)N(R^{10})R^{11}$ group where R^{10} and R^{11} are independently hydrogen, alkyl, optionally substituted aryl or optionally substituted aralkyl.

In addition, compounds of formula (IIa) where R^1, R^3, R^4 or R^6 group contains an amino group can be treated with the appropriate alkylating agents to afford the corresponding compounds of formula (IIa) where R^1, R^3, R^4 or R^6 contains $-N(R^{10})R^{11}$ or $-N(R^{10})C(O)R^{11}$ where each R^{10} and R^{11} is independently hydrogen, alkyl, optionally substituted aryl or optionally substituted aralkyl.

Compounds of formula (IIa) may be further treated with the appropriate acid halide, preferably acid chloride, or with the appropriate acid anhydride or an equivalent, to yield compounds of the invention wherein R^2 is $-C(NH)N(H)C(O)R^{10}$ where R^{10} is hydrogen, alkyl, optionally substituted aryl or optionally substituted aralkyl. Alternatively, compounds of formula (IIa) may further be treated with carbamoyl chlorides or their equivalents to yield compounds of the invention where R^2 is $-C(NH)N(H)C(O)OR^{13}$ where R^{13} is described above in the Summary of the Invention.

Alternatively, compounds of formula (IIa) may be further treated with compounds of the formula R^{13}-$S(O)_2$-imidazole, where R^{13} is as described in the Summary of the Invention, in a polar solvent, such as methylene chloride, at ambient temperature to afford compounds of the invention where R^2 is $-C(NH)N(H)S(O)_2R^{13}$.

Alternatively, compounds of formula (IIa) may be further treated with an appropriately *N*-R^{10}-substituted phenylcarbamate in a polar solvent, preferably methylene chloride, at ambient temperature, for about 6 to 24 hours, preferably for about 12 hours, to afford compounds of the invention where R^2 is $-C(NH)N(H)C(O)N(H)R^{10}$.

In addition, compounds of formula (IIa) wherein R^6 is hydrogen may be treated in a manner similar to the method described in Dusert, P., *Eur. J. Med. Chem.* (1980), Vol. 15, No. 3, p. 199, to produce compounds of formula (IIa) wherein R^6 is $-(C(R^7)(R^8))_n-R^9$. For example, a compound of formula (IIa) wherein R^6 is hydrogen can be first treated with a strong base, such as *sodium hydride*, in an aprotic solvent, such as DMF, followed by treatment with an equimolar amount of a compound of formula $X(C(R^7)(R^8))_n-R^9$ where X is bromo or chloro and n, R^7, R^8 and

R^9 are as described above in the Summary of the Invention. The resulting reaction mixture can then be stirred for 2 to 6 hours, preferably for about 4 hours, at ambient temperature to about 80°C. The compound of formula (IIa) wherein R^6 is $-(C(R^7)(R^8))_n-R^9$ can then isolated from the reaction mixture by standard isolation techniques.

Alternatively, compounds of formula (IIa) wherein R^5 is hydrogen can be treated in a manner similar to the method described in Stevenson, T.M., *J. Org. Chem.* (1984), Vol. 49, No. 12, p. 2158, to produce compounds of formula (IIa) wherein R^5 is halo. For example, a compound of formula (IIa) where R^5 is hydrogen can be treated with a mild electrophilic halogenating agent, such as *N*-bromosuccinimide or *N*-chlorosuccinimide, in carbon tetrachloride to produce a compound of formula (IIa) wherein R^5 is chloro or bromo.

In addition, compounds of formula (J) can be treated with *N,N*-carbonyldiimidazole or *N,N*-thiocarbonyldiimidazole under the appropriate reaction conditions to form compounds of formula (L) where R^5 is hydroxy (as the carbonyl tautomer) or mercapto. The compound so formed can be treated in the same manner described above to produce a compound of formula (IIa) wherein R^5 is hydroxy or mercapto.

In addition, compounds of formula (J) can be treated with a thioisocyanate of the formula $R^{10}NCS$ where R^{10} is as described above in the Summary of the Invention by the method described in Omar, A., *et al.*, *Synthesis* (1977), p. 864; Ram, S., *Org. Prep. Proced. Int.* (1985), Vol. 17, No. 3, p. 215; or Janssens, F., *J. Med. Chem.* (1985), Vol. 28, No. 12, p. 1925; to produce a compound of formula (L) where R^5 is $-N(H)R^{10}$. This compound can then be treated with a standard alkylating agent, such as an alkyl halide of the formula $R^{11}X$ or acid halide of the formula $R^{11}C(O)X$ where X is halo and R^{11} is as described above in the Summary of the Invention, to produce a compound of formula (L) where R^5 is $-NR^{10}R^{11}$ and wherein the nitrogen in the 5-position is likewise alkylated.

The compound of formula (IIa) where R^5 is mercapto can be further treated with an alkyl halide, such as methyl bromide, in a dipolar solvent, such as dimethylsulfoxide and in the presence of a mild base, such as potassium carbonate, to afford a compound of formula (IIa) where R^5 is alkylthio.

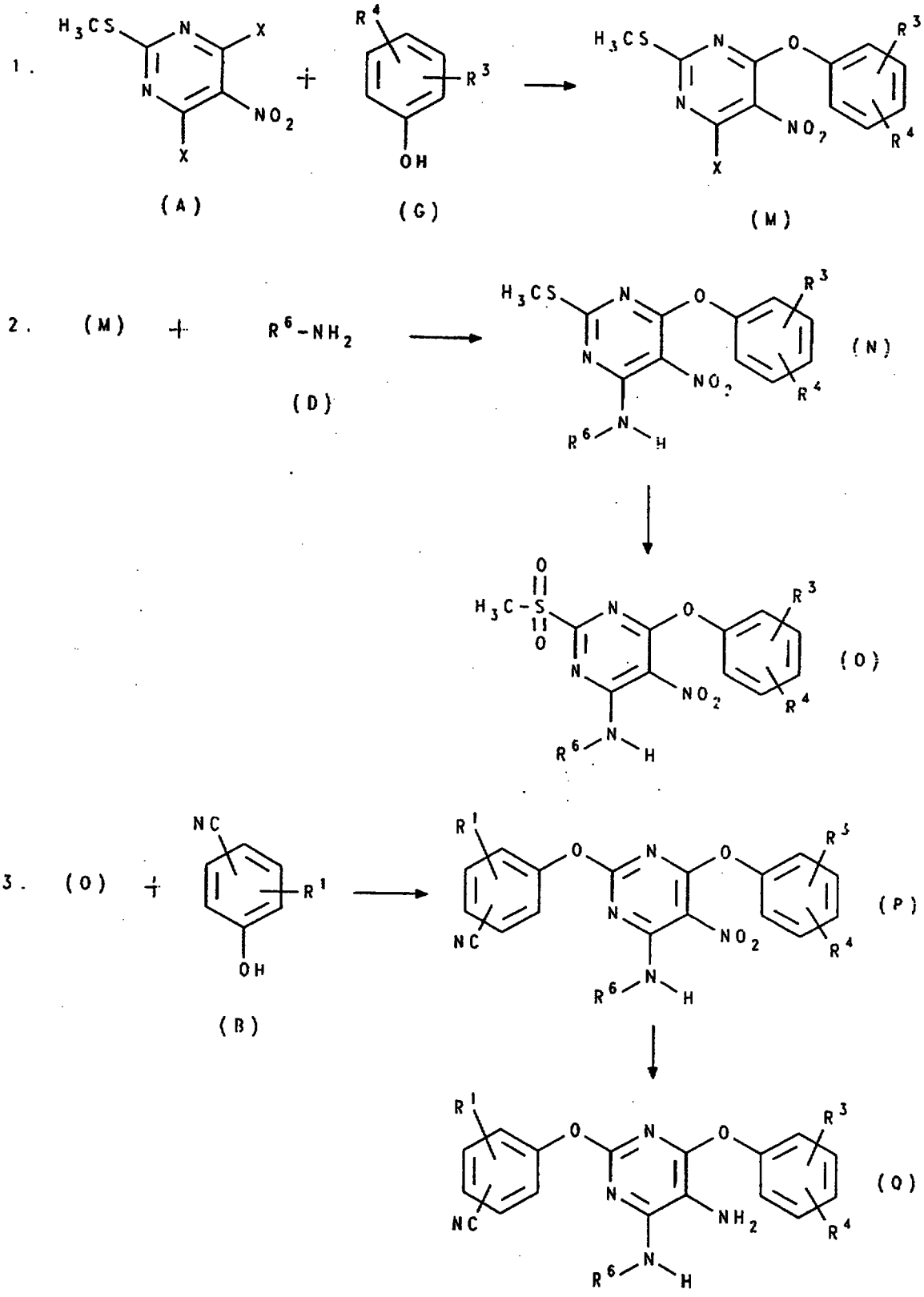
Similarly, the compound of formula (IIa) where R^5 is hydroxy can be further treated with an alkyl halide in the presence of a strong base, such as sodium hydride and in an aprotic solvent, such as DMF, to afford a compound of formula (IIa) where R^5 is alkoxy.

B. Preparation of Compounds of Formula (Ia)

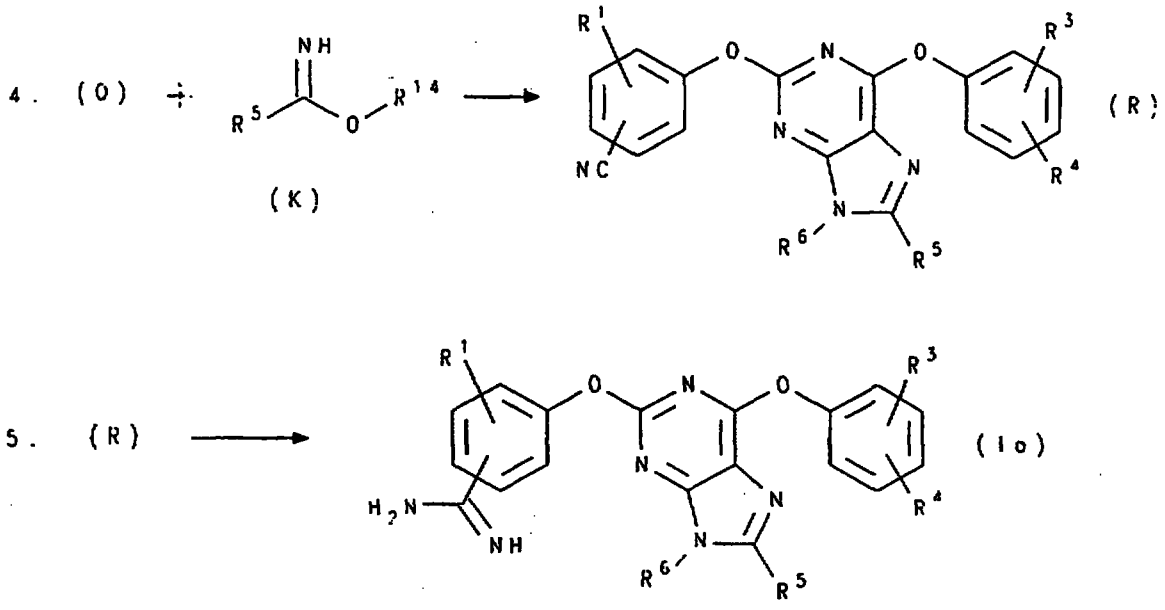
Compounds of formula (Ia) are compounds of formula (I) wherein Z^1 and Z^2 are -O- and R^2 is $-C(NH)NH_2$. These compounds may be prepared as illustrated in the following Reaction Scheme 2 wherein X is halo; R^1 and R^4 are each independently hydrogen, halo, alkyl, $-OR^{10}$, $-C(O)OR^{10}$, $-C(O)N(R^{10})R^{11}$, $-N(R^{10})R^{11}$, $-N(R^{10})C(O)R^{10}$, or $-N(H)S(O)_2R^{13}$; R^3 is halo, alkyl,

haloalkyl, haloalkoxy, ureido, guanidino, $-OR^{10}$, $-C(NH)NH_2$, $-C(NH)N(H)OR^{10}$, $-C(O)N(R^{10})R^{11}$, $-R^{12}-C(O)N(R^{10})R^{11}$, $-CH(OH)C(O)N(R^{10})R^{11}$, $-N(R^{10})R^{11}$, $-R^{12}-N(R^{10})R^{11}$, $-C(O)OR^{10}$, $-R^{12}-C(O)OR^{10}$, $-N(R^{10})C(O)R^{10}$, (1,2)-tetrahydropyrimidinyl (optionally substituted by alkyl), (1,2)-imidazolyl (optionally substituted by alkyl), or (1,2)-imidazolinyl (optionally substituted by alkyl); R^5 is hydrogen, alkyl, cycloalkyl, haloalkyl, aryl, or aralkyl; R^6 is alkyl, aryl (optionally substituted by halo, alkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, cyano, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl) or aralkyl (optionally substituted by halo, alkyl, aryl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, cyano, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl); each R^{10} and R^{11} is independently hydrogen, alkyl, aryl (optionally substituted by halo, alkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, cyano, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, alkyl, aryl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, cyano, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl); R^{12} is a straight or branched alkylene chain; and R^{13} is alkyl, aryl (optionally substituted by halo, alkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, cyano, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, alkyl, aryl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, cyano, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl); and R^{14} is alkyl:

REACTION SCHEME 2



REACTION SCHEME 2 continued



In general, compounds of formula (Ia) are prepared by first treating a compound of formula (A) with a compound of formula (G) in a manner similar to that described above for the preparation of compounds of formula (H) from compounds of formulae (F) and (G) to afford a compound of formula (M). The compound of formula (M) is then treated with a compound of formula (D) in a manner similar to that described above for the compound of formula (C) to afford a compound of formula (N). The compound of formula (N) is then oxidized to the corresponding compound of formula (O) in a manner similar to that described above for the compounds of formula (E). The compound of formula (O) is treated with a compound of formula (B) in a manner similar to that described above for the compound of formula (A) to afford a compound of formula (P), which is then reduced to the corresponding compound of formula (Q) in a manner similar as that described above for compounds of formula (H). The compound of formula (Q) is then treated with an alkyl imidate of formula (K) similar to the manner described above for the compound of formula (J) to afford a compound of formula (R), which is converted to the corresponding amidine derivative of formula (Ia) in the manner similar to that described above for the compound of formula (L).

In addition, all the various substituent conversions described above for the compounds of formula (IIa) apply to the compounds of formula (Ia) to afford additional compounds of the invention not depicted in the foregoing Reaction Scheme.

In addition, similar reactions may be performed on similar starting materials and intermediates to produce the corresponding compounds of formula (III) and compounds of formula (IV).

In addition, all compounds of the invention that exist in free base form or free acid form may be converted to their pharmaceutically acceptable salts by treatment with the appropriate inorganic or organic acid, or by the appropriate inorganic or organic base. Salts of the compounds of the invention can also be converted to the free base form or to the free acid form or to another salt by methods known to those of ordinary skill in the chemical arts.

* * * * *

The following specific preparations and examples are provided as a guide to assist in the practice of the invention, and are not intended as a limitation on the scope of the invention.

PREPARATION 1

Compounds of formula (C) and formula (P)

A. To 4,6-dichloro-5-nitro-2-methylthiopyrimidine (5.0 g, 20.8 mmol) in 200 mL acetonitrile at 0°C was added cesium carbonate (8.82 g, 27.1 mmol) followed by the addition of 3-hydroxy-4-benzyloxybenzonitrile (4.69 g, 20.8 mmol), and the resulting reaction mixture was stirred for 16 hours. The volatiles were evaporated and the residue chromatographed on silica gel (hexane/ethyl acetate, 2:1) to afford 5.0 g of 2-methylthio-4-chloro-5-nitro-6-(2-benzyloxy-5-cyanophenoxy)pyrimidine, a compound of formula (C).

B. In a similar manner, the following compounds of formula (C) are made:

2-methylthio-4-chloro-5-nitro-6-(2-methoxy-5-cyanophenoxy)pyrimidine;

2-methylthio-4-chloro-5-nitro-6-(2-ethoxy-5-cyanophenoxy)pyrimidine;

2-methylthio-4-chloro-5-nitro-6-(3-methoxy-5-cyanophenoxy)pyrimidine;

2-methylthio-4-chloro-5-nitro-6-(3-ethoxy-5-cyanophenoxy)pyrimidine;

2-methylthio-4-chloro-5-nitro-6-(2-phenoxy-5-cyanophenoxy)pyrimidine;

2-methylthio-4-chloro-5-nitro-6-(3-phenoxy-5-cyanophenoxy)pyrimidine;

2-methylthio-4-chloro-5-nitro-6-(2-chloro-5-cyanophenoxy)pyrimidine;

2-methylthio-4-chloro-5-nitro-6-(3-bromo-5-cyanophenoxy)pyrimidine;

2-methylthio-4-chloro-5-nitro-6-(2-methyl-5-cyanophenoxy)pyrimidine;

2-methylthio-4-chloro-5-nitro-6-(3-methyl-4-cyanophenoxy)pyrimidine;

2-methylthio-4-chloro-5-nitro-6-(2-nitro-5-cyanophenoxy)pyrimidine;

2-methylthio-4-chloro-5-nitro-6-(3-nitro-4-cyanophenoxy)pyrimidine;

2-methylthio-4-chloro-5-nitro-6-(2-carboxy-5-cyanophenoxy)pyrimidine;

2-methylthio-4-chloro-5-nitro-6-(3-carboxy-4-cyanophenoxy)pyrimidine;

2-methylthio-4-chloro-5-nitro-6-(2-*t*-butoxycarbonyl-5-cyanophenoxy)pyrimidine;

2-methylthio-4-chloro-5-nitro-6-(3-*t*-butoxycarbonyl-4-cyanophenoxy)pyrimidine;

2-methylthio-4-chloro-5-nitro-6-(2-aminocarbonyl-5-cyanophenoxy)pyrimidine;

2-methylthio-4-chloro-5-nitro-6-(3-aminocarbonyl-4-cyanophenoxy)pyrimidine;

2-methylthio-4-chloro-5-nitro-6-(2-dimethylamino-5-cyanophenoxy)pyrimidine;

2-methylthio-4-chloro-5-nitro-6-(3-dimethylamino-4-cyanophenoxy)pyrimidine;
2-methylthio-4-chloro-5-nitro-6-(2-dimethylamino-5-cyanophenoxy)pyrimidine; and
2-methylthio-4-chloro-5-nitro-6-(3-dimethylamino-4-cyanophenoxy)pyrimidine.

C. In a similar manner, 2-methylsulfonyl-4-benzylamino-5-nitro-6-(3-dimethylaminocarbonylphenoxy)pyrimidine was treated with 3-hydroxy-4-benzyloxybenzonitrile in the presence of cesium carbonate to afford 2-(2-benzyloxy-5-cyanophenoxy)-4-benzylamino-5-nitro-6-(3-dimethylaminocarbonylphenoxy)pyrimidine, a compound of formula (P).

D. In a similar manner, the following compounds of formula (P) are made:
2-(2-benzyloxy-5-cyanophenoxy)-4-benzylamino-5-nitro-6-(3-dimethylaminocarbonyl-phenoxy)pyrimidine;
2-(2-methoxy-5-cyanophenoxy)-4-benzylamino-5-nitro-6-(3-dimethylaminocarbonyl-phenoxy)pyrimidine;
2-(2-ethoxy-5-cyanophenoxy)-4-benzylamino-5-nitro-6-(3-dimethylaminocarbonyl-phenoxy)pyrimidine;
2-(2-phenoxy-5-cyanophenoxy)-4-benzylamino-5-nitro-6-(3-dimethylaminocarbonyl-phenoxy)pyrimidine;
2-(2-chloro-5-cyanophenoxy)-4-benzylamino-5-nitro-6-(3-dimethylaminocarbonyl-phenoxy)pyrimidine;
2-(2-methyl-5-cyanophenoxy)-4-benzylamino-5-nitro-6-(3-dimethylaminocarbonyl-phenoxy)pyrimidine;
2-(2-*t*-butyl-5-cyanophenoxy)-4-benzylamino-5-nitro-6-(3-dimethylaminocarbonyl-phenoxy)pyrimidine;
2-(2-nitro-5-cyanophenoxy)-4-benzylamino-5-nitro-6-(3-dimethylaminocarbonyl-phenoxy)pyrimidine;
2-(2-carboxy-5-cyanophenoxy)-4-benzylamino-5-nitro-6-(3-dimethylaminocarbonyl-phenoxy)pyrimidine;
2-(2-benzyloxycarbonyl-5-cyanophenoxy)-4-benzylamino-5-nitro-6-(3-dimethylaminocarbonyl-phenoxy)pyrimidine;
2-(2-diethylaminocarbonyl-5-cyanophenoxy)-4-benzylamino-5-nitro-6-(3-dimethylaminocarbonyl-phenoxy)pyrimidine;
2-(2-amino-5-cyanophenoxy)-4-benzylamino-5-nitro-6-(3-dimethylaminocarbonyl-phenoxy)pyrimidine;
2-(2-benzyloxy-5-cyanophenoxy)-4-benzylamino-5-nitro-6-(3-(1-methylimidazolin-2-yl)-phenoxy)pyrimidine;
2-(2-methoxy-5-cyanophenoxy)-4-benzylamino-5-nitro-6-(3-(2-(*t*-butoxycarbonyl)ethyl)-phenoxy)pyrimidine;
2-(2-ethoxy-5-cyanophenoxy)-4-benzylamino-5-nitro-6-(3-*t*-butoxycarbonyl-

phenoxy)pyrimidine;

2-(2-phenoxy-5-cyanophenoxy)-4-benzylamino-5-nitro-6-(3-carboxyphenoxy)pyrimidine;

2-(2-chloro-5-cyanophenoxy)-4-benzylamino-5-nitro-6-(3-(2-aminoethyl)phenoxy)pyrimidine;

2-(2-methyl-5-cyanophenoxy)-4-benzylamino-5-nitro-6-(3-(benzyloxy)phenoxy)pyrimidine;

2-(2-*t*-butyl-5-cyanophenoxy)-4-benzylamino-5-nitro-6-(3-ethoxyphenoxy)pyrimidine;

2-(2-nitro-5-cyanophenoxy)-4-benzylamino-5-nitro-6-(3-guanidinophenoxy)pyrimidine;

2-(2-carboxy-5-cyanophenoxy)-4-benzylamino-5-nitro-6-(3-ureidophenoxy)pyrimidine;

2-(2-benzyloxycarbonyl-5-cyanophenoxy)-4-benzylamino-5-nitro-6-(3-aminophenoxy)pyrimidine;

2-(2-diethylaminocarbonyl-5-cyanophenoxy)-4-benzylamino-5-nitro-6-(3-nitro-

phenoxy)pyrimidine; and

2-(2-amino-5-cyanophenoxy)-4-benzylamino-5-nitro-6-(3-trifluoromethoxyphenoxy)pyrimidine.

PREPARATION 2

Compounds of formula (E) and formula (N)

A. To 6-(2-benzyloxy-5-cyanophenoxy)-4-chloro-5-nitro-2-methylthiopyrimidine (2.5 g, 5.83 mmol) in 50 mL acetonitrile at 0°C was added cesium carbonate (2.47 g, 7.58 mmol) followed by benzylamine (0.64 mL) and the reaction mixture was heated at 50°C for 4 hours. The reaction was filtered, the filtrate evaporated and the residue chromatographed on silica gel (ethyl acetate:hexane) to afford 1.82 g (65%) of 6-(2-benzyloxy-5-cyanophenoxy)-4-(benzyl)amino-5-nitro-2-methylthiopyrimidine, a compound of formula (E).

B. In a similar manner, compounds of formula (E) are made:

2-methylthio-4-(benzyl)amino-5-nitro-6-(2-methoxy-5-cyanophenoxy)pyrimidine;

2-methylthio-4-(benzyl)amino-5-nitro-6-(2-ethoxy-5-cyanophenoxy)pyrimidine;

2-methylthio-4-(benzyl)amino-5-nitro-6-(3-methoxy-5-cyanophenoxy)pyrimidine;

2-methylthio-4-(benzyl)amino-5-nitro-6-(3-ethoxy-5-cyanophenoxy)pyrimidine;

2-methylthio-4-(benzyl)amino-5-nitro-6-(2-phenoxy-5-cyanophenoxy)pyrimidine;

2-methylthio-4-(benzyl)amino-5-nitro-6-(3-phenoxy-5-cyanophenoxy)pyrimidine;

2-methylthio-4-(benzyl)amino-5-nitro-6-(2-chloro-5-cyanophenoxy)pyrimidine;

2-methylthio-4-(benzyl)amino-5-nitro-6-(3-bromo-5-cyanophenoxy)pyrimidine;

2-methylthio-4-(benzyl)amino-5-nitro-6-(2-methyl-5-cyanophenoxy)pyrimidine;

2-methylthio-4-(benzyl)amino-5-nitro-6-(2-methyl-5-cyanophenoxy)pyrimidine;

2-methylthio-4-(benzyl)amino-5-nitro-6-(3-methyl-4-cyanophenoxy)pyrimidine;

2-methylthio-4-(benzyl)amino-5-nitro-6-(2-nitro-5-cyanophenoxy)pyrimidine;

2-methylthio-4-(benzyl)amino-5-nitro-6-(3-nitro-4-cyanophenoxy)pyrimidine;

2-methylthio-4-(benzyl)amino-5-nitro-6-(2-carboxy-5-cyanophenoxy)pyrimidine;

2-methylthio-4-(benzyl)amino-5-nitro-6-(3-carboxy-4-cyanophenoxy)pyrimidine;

2-methylthio-4-(benzyl)amino-5-nitro-6-(2-*t*-butoxycarbonyl-5-cyanophenoxy)pyrimidine;

2-methylthio-4-(benzyl)amino-5-nitro-6-(3-*t*-butoxycarbonyl-4-cyanophenoxy)pyrimidine;
2-methylthio-4-(benzyl)amino-5-nitro-6-(2-aminocarbonyl-5-cyanophenoxy)pyrimidine;
2-methylthio-4-(benzyl)amino-5-nitro-6-(3-aminocarbonyl-4-cyanophenoxy)pyrimidine;
2-methylthio-4-(benzyl)amino-5-nitro-6-(2-dimethylamino-5-cyanophenoxy)pyrimidine;
2-methylthio-4-(benzyl)amino-5-nitro-6-(3-dimethylamino-4-cyanophenoxy)pyrimidine;
2-methylthio-4-(benzyl)amino-5-nitro-6-(2-dimethylamino-5-cyanophenoxy)pyrimidine;
2-methylthio-4-(benzyl)amino-5-nitro-6-(3-dimethylamino-4-cyanophenoxy)pyrimidine;
2-methylthio-4-amino-5-nitro-6-(2-methoxy-5-cyanophenoxy)pyrimidine;
2-methylthio-4-amino-5-nitro-6-(2-ethoxy-5-cyanophenoxy)pyrimidine;
2-methylthio-4-amino-5-nitro-6-(3-methoxy-5-cyanophenoxy)pyrimidine;
2-methylthio-4-amino-5-nitro-6-(3-ethoxy-5-cyanophenoxy)pyrimidine;
2-methylthio-4-amino-5-nitro-6-(2-phenoxy-5-cyanophenoxy)pyrimidine;
2-methylthio-4-amino-5-nitro-6-(3-phenoxy-5-cyanophenoxy)pyrimidine;
2-methylthio-4-amino-5-nitro-6-(2-chloro-5-cyanophenoxy)pyrimidine;
2-methylthio-4-amino-5-nitro-6-(3-bromo-5-cyanophenoxy)pyrimidine;
2-methylthio-4-amino-5-nitro-6-(2-methyl-5-cyanophenoxy)pyrimidine;
2-methylthio-4-amino-5-nitro-6-(2-methyl-5-cyanophenoxy)pyrimidine;
2-methylthio-4-amino-5-nitro-6-(3-methyl-4-cyanophenoxy)pyrimidine;
2-methylthio-4-amino-5-nitro-6-(2-nitro-5-cyanophenoxy)pyrimidine;
2-methylthio-4-amino-5-nitro-6-(3-nitro-4-cyanophenoxy)pyrimidine;
2-methylthio-4-amino-5-nitro-6-(2-carboxy-5-cyanophenoxy)pyrimidine;
2-methylthio-4-amino-5-nitro-6-(3-carboxy-4-cyanophenoxy)pyrimidine;
2-methylthio-4-amino-5-nitro-6-(2-*t*-butoxycarbonyl-5-cyanophenoxy)pyrimidine;
2-methylthio-4-amino-5-nitro-6-(3-*t*-butoxycarbonyl-4-cyanophenoxy)pyrimidine;
2-methylthio-4-amino-5-nitro-6-(2-aminocarbonyl-5-cyanophenoxy)pyrimidine;
2-methylthio-4-amino-5-nitro-6-(3-aminocarbonyl-4-cyanophenoxy)pyrimidine;
2-methylthio-4-amino-5-nitro-6-(2-dimethylamino-5-cyanophenoxy)pyrimidine;
2-methylthio-4-amino-5-nitro-6-(3-dimethylamino-4-cyanophenoxy)pyrimidine;
2-methylthio-4-amino-5-nitro-6-(2-dimethylamino-5-cyanophenoxy)pyrimidine; and
2-methylthio-4-amino-5-nitro-6-(3-dimethylamino-4-cyanophenoxy)pyrimidine.

C. In a similar manner, to 2-methylthio-4-chloro-5-nitro-6-(3-dimethylaminocarbonylphenoxy)pyrimidine (3.19 g, 8.65 mmol), a compound of formula (M), in 90 mL acetonitrile at 0°C was added cesium carbonate (3.66 g, 11.2 mmol), followed by the addition of benzylamine (0.95 mL, 8.65 mmol). The reaction mixture was heated at 75°C for 4 hours. The reaction mixture was filtered, the filtrate evaporated and the residue chromatographed on silica gel (ethyl acetate:methanol, 10:1) to afford 1.76 g (48%) of 2-methylthio-4-(benzyl)amino-5-nitro-6-(3-dimethylaminocarbonylphenoxy)pyrimidine, a compound

of formula (N).

D. In a similar manner, the following compounds of formula (N) are made:

2-methylthio-4-benzylamino-5-nitro-6-[3-(2-(dimethylaminocarbonyl)ethyl)phenoxy)pyrimidine;

2-methylthio-4-benzylamino-5-nitro-6-(3-(2-(dimethylaminocarbonyl)ethyl)-5-methoxyphenoxy)pyrimidine;

2-methylthio-4-benzylamino-5-nitro-6-(3-(2-(dimethylaminocarbonyl)ethyl)-5-chlorophenoxy)pyrimidine;

2-methylthio-4-benzylamino-5-nitro-6-(3-chloro-5-methoxyphenoxy)pyrimidine;

2-methylthio-4-benzylamino-5-nitro-6-(3-trifluoromethyl-5-(dimethylaminocarbonyl)-phenoxypyrimidine;

2-methylthio-4-benzylamino-5-nitro-6-(3-guanidinophenoxy)pyrimidine;

2-methylthio-4-benzylamino-5-nitro-6-(3-ureidophenoxy)pyrimidine;

2-methylthio-4-benzylamino-5-nitro-6-(3-nitrophenoxy)pyrimidine;

2-methylthio-4-benzylamino-5-nitro-6-(3-guanidino-5-methylphenoxy)pyrimidine;

2-methylthio-4-benzylamino-5-nitro-6-(3-ureido-5-methylphenoxy)pyrimidine; and

2-methylthio-4-benzylamino-5-nitro-6-(3-nitro-5-aminophenoxy)pyrimidine.

PREPARATION 3

Compounds of formula (F) and (O)

A. To 2-methylthio-4-benzylamino-5-nitro-6-(2-benzyloxy-5-cyanophenoxy)pyrimidine (1.82 g, 3.76 mmol) in 40 mL MeOH and 40 mL dioxane at 0°C was added potassium metabisulfite ($KHSO_5$) (3.59 g, 11.3 mmol) in 40 mL water. The suspension was allowed to warm to ambient temperature and stirred for 15 hours. The reaction was concentrated to 25 mL and extracted with methylene chloride (200 mL). The organic layer was dried (Na_2SO_4), evaporated and chromatographed on silica gel (2:1, hexane/ethyl acetate) to afford 0.26 g of 2-methylsulfonyl-4-benzylamino-5-nitro-6-(2-benzyloxy-5-cyanophenoxy)pyrimidine, a compound of formula (F), as a white solid.

B. In a similar manner, the following compounds of formula (F) are made:

2-methylsulfonyl-4-(benzyl)amino-5-nitro-6-(2-methoxy-5-cyanophenoxy)pyrimidine;

2-methylsulfonyl-4-(benzyl)amino-5-nitro-6-(2-ethoxy-5-cyanophenoxy)pyrimidine;

2-methylsulfonyl-4-(benzyl)amino-5-nitro-6-(3-methoxy-5-cyanophenoxy)pyrimidine;

2-methylsulfonyl-4-(benzyl)amino-5-nitro-6-(3-ethoxy-5-cyanophenoxy)pyrimidine;

2-methylsulfonyl-4-(benzyl)amino-5-nitro-6-(2-phenoxy-5-cyanophenoxy)pyrimidine;

2-methylsulfonyl-4-(benzyl)amino-5-nitro-6-(3-phenoxy-5-cyanophenoxy)pyrimidine;

2-methylsulfonyl-4-(benzyl)amino-5-nitro-6-(2-chloro-5-cyanophenoxy)pyrimidine;

2-methylsulfonyl-4-(benzyl)amino-5-nitro-6-(3-bromo-5-cyanophenoxy)pyrimidine;

2-methylsulfonyl-4-(benzyl)amino-5-nitro-6-(2-methyl-5-cyanophenoxy)pyrimidine;

2-methylsulfonyl-4-(benzyl)amino-5-nitro-6-(2-methyl-5-cyanophenoxy)pyrimidine;
2-methylsulfonyl-4-(benzyl)amino-5-nitro-6-(3-methyl-4-cyanophenoxy)pyrimidine;
2-methylsulfonyl-4-(benzyl)amino-5-nitro-6-(2-nitro-5-cyanophenoxy)pyrimidine;
2-methylsulfonyl-4-(benzyl)amino-5-nitro-6-(3-nitro-4-cyanophenoxy)pyrimidine;
2-methylsulfonyl-4-(benzyl)amino-5-nitro-6-(2-carboxy-5-cyanophenoxy)pyrimidine;
2-methylsulfonyl-4-(benzyl)amino-5-nitro-6-(3-carboxy-4-cyanophenoxy)pyrimidine;
2-methylsulfonyl-4-(benzyl)amino-5-nitro-6-(2-*t*-butoxycarbonyl-5-cyanophenoxy)pyrimidine;
2-methylsulfonyl-4-(benzyl)amino-5-nitro-6-(3-*t*-butoxycarbonyl-4-cyanophenoxy)pyrimidine;
2-methylsulfonyl-4-(benzyl)amino-5-nitro-6-(2-aminocarbonyl-5-cyanophenoxy)pyrimidine;
2-methylsulfonyl-4-(benzyl)amino-5-nitro-6-(3-aminocarbonyl-4-cyanophenoxy)pyrimidine;
2-methylsulfonyl-4-(benzyl)amino-5-nitro-6-(2-dimethylamino-5-cyanophenoxy)pyrimidine;
2-methylsulfonyl-4-(benzyl)amino-5-nitro-6-(3-dimethylamino-4-cyanophenoxy)pyrimidine;
2-methylsulfonyl-4-(benzyl)amino-5-nitro-6-(2-dimethylamino-5-cyanophenoxy)pyrimidine;
2-methylsulfonyl-4-(benzyl)amino-5-nitro-6-(3-dimethylamino-4-cyanophenoxy)pyrimidine;
2-methylsulfonyl-4-amino-5-nitro-6-(2-methoxy-5-cyanophenoxy)pyrimidine;
2-methylsulfonyl-4-amino-5-nitro-6-(2-ethoxy-5-cyanophenoxy)pyrimidine;
2-methylsulfonyl-4-amino-5-nitro-6-(3-methoxy-5-cyanophenoxy)pyrimidine;
2-methylsulfonyl-4-amino-5-nitro-6-(3-ethoxy-5-cyanophenoxy)pyrimidine;
2-methylsulfonyl-4-amino-5-nitro-6-(2-phenoxy-5-cyanophenoxy)pyrimidine;
2-methylsulfonyl-4-amino-5-nitro-6-(3-phenoxy-5-cyanophenoxy)pyrimidine;
2-methylsulfonyl-4-amino-5-nitro-6-(2-chloro-5-cyanophenoxy)pyrimidine;
2-methylsulfonyl-4-amino-5-nitro-6-(3-bromo-5-cyanophenoxy)pyrimidine;
2-methylsulfonyl-4-amino-5-nitro-6-(2-methyl-5-cyanophenoxy)pyrimidine;
2-methylsulfonyl-4-amino-5-nitro-6-(2-methyl-5-cyanophenoxy)pyrimidine;
2-methylsulfonyl-4-amino-5-nitro-6-(3-methyl-4-cyanophenoxy)pyrimidine;
2-methylsulfonyl-4-amino-5-nitro-6-(2-nitro-5-cyanophenoxy)pyrimidine;
2-methylsulfonyl-4-amino-5-nitro-6-(3-nitro-4-cyanophenoxy)pyrimidine;
2-methylsulfonyl-4-amino-5-nitro-6-(2-carboxy-5-cyanophenoxy)pyrimidine;
2-methylsulfonyl-4-amino-5-nitro-6-(3-carboxy-4-cyanophenoxy)pyrimidine;
2-methylsulfonyl-4-amino-5-nitro-6-(2-*t*-butoxycarbonyl-5-cyanophenoxy)pyrimidine;
2-methylsulfonyl-4-amino-5-nitro-6-(3-*t*-butoxycarbonyl-4-cyanophenoxy)pyrimidine;
2-methylsulfonyl-4-amino-5-nitro-6-(2-aminocarbonyl-5-cyanophenoxy)pyrimidine;
2-methylsulfonyl-4-amino-5-nitro-6-(3-aminocarbonyl-4-cyanophenoxy)pyrimidine;
2-methylsulfonyl-4-amino-5-nitro-6-(2-dimethylamino-5-cyanophenoxy)pyrimidine;
2-methylsulfonyl-4-amino-5-nitro-6-(3-dimethylamino-4-cyanophenoxy)pyrimidine;
2-methylsulfonyl-4-amino-5-nitro-6-(2-dimethylamino-5-cyanophenoxy)pyrimidine; and
2-methylsulfonyl-4-amino-5-nitro-6-(3-dimethylamino-4-cyanophenoxy)pyrimidine.

C. In a similar manner, 2-methylthio-4-benzylamino-5-nitro-6-(3-dimethylaminocarbonylphenoxy)pyrimidine, a compound of formula (N), was oxidized to afford 2-methylsulfonyl-4-benzylamino-5-nitro-6-(3-dimethylaminocarbonylphenoxy)pyrimidine, a compound of formula (O).

D. In a similar manner, the following compounds of formula (O) are prepared:
2-methylsulfonyl-4-benzylamino-5-nitro-6-(3-(2-(dimethylaminocarbonyl)ethyl)phenoxy)pyrimidine;
2-methylsulfonyl-4-benzylamino-5-nitro-6-(3-(2-(dimethylaminocarbonyl)ethyl)-5-methoxyphenoxy)pyrimidine;
2-methylsulfonyl-4-benzylamino-5-nitro-6-(3-(2-(dimethylaminocarbonyl)ethyl)-5-chlorophenoxy)pyrimidine;
2-methylsulfonyl-4-benzylamino-5-nitro-6-(3-chloro-5-methoxyphenoxy)pyrimidine;
2-methylsulfonyl-4-benzylamino-5-nitro-6-(3-trifluoromethyl-5-(dimethylaminocarbonyl)-phenoxypyrimidine;
2-methylsulfonyl-4-benzylamino-5-nitro-6-(3-guanidinophenoxy)pyrimidine;
2-methylsulfonyl-4-benzylamino-5-nitro-6-(3-ureidophenoxy)pyrimidine;
2-methylsulfonyl-4-benzylamino-5-nitro-6-(3-nitrophenoxy)pyrimidine;
2-methylsulfonyl-4-benzylamino-5-nitro-6-(3-guanidino-5-methylphenoxy)pyrimidine;
2-methylsulfonyl-4-benzylamino-5-nitro-6-(3-ureido-5-methylphenoxy)pyrimidine; and
2-methylsulfonyl-4-benzylamino-5-nitro-6-(3-nitro-5-aminophenoxy)pyrimidine.

PREPARATION 4

Compounds of formula (H) and (M)

A. To 2-methylsulfonyl-4-benzylamino-5-nitro-6-(2-benzyloxy-5-cyanophenoxy)pyrimidine, a compound of formula (F) (0.69 g, 1.38 mmol) in 15 mL acetonitrile at 0°C was added cesium carbonate (0.58 g, 1.80 mmol) followed by the addition of 3-(dimethylaminocarbony)phenol (0.20 g, 1.24 mmol) and the reaction stirred for 16 hours. The volatiles were evaporated and the residue chromatographed on silica gel (CH_2Cl_2/ethyl acetate, 7:2) to afford 0.29 g of 2-(3-dimethyl-aminocarbonylphenoxy)-4-benzylamino-5-nitro-6-(2-benzyloxy-5-cyanophenoxy)pyrimidine, a compound of formula (H).

B. In a similar manner, the following compounds of formula (H) are made:
2-(3-methylphenoxy)-4-(benzyl)amino-5-nitro-6-(2-methoxy-5-cyanophenoxy)pyrimidine;
2-(3-chloro-5-methoxyphenoxy)-4-(benzyl)amino-5-nitro-6-(2-ethoxy-5-cyanophenoxy)pyrimidine;
2-(4-trifluoromethylphenoxy)-4-(benzyl)amino-5-nitro-6-(3-methoxy-5-cyanophenoxy)pyrimidine;
2-(3,5-dinitrophenoxy)-4-(benzyl)amino-5-nitro-6-(3-ethoxy-5-cyanophenoxy)pyrimidine;
2-(3-guanidino-5-methylphenoxy)-4-(benzyl)amino-5-nitro-6-(2-phenoxy-5-cyanophenoxy)pyrimidine;
2-(3-ureidophenoxy)-4-(benzyl)amino-5-nitro-6-(3-phenoxy-5-cyanophenoxy)pyrimidine;

2-(3-(2-chloroethyl)-5-methylphenoxy)-4-(benzyl)amino-5-nitro-6-(2-chloro-5-cyanophenoxy)pyrimidine;

2-(3-dimethylaminocarbonylphenoxy)-4-(benzyl)amino-5-nitro-6-(3-bromo-5-cyanophenoxy)pyrimidine;

2-(4-ethoxycarbonylphenoxy)-4-(benzyl)amino-5-nitro-6-(2-methyl-5-cyanophenoxy)pyrimidine;

2-(3-(1-methylimidazol-2-yl)phenoxy)-4-(benzyl)amino-5-nitro-6-(2-methyl-5-cyanophenoxy)pyrimidine;

2-(3-dimethylaminophenoxy)-4-(benzyl)amino-5-nitro-6-(3-methyl-4-cyanophenoxy)pyrimidine;

2-(3-(1-methylimidazolin-2-yl)phenoxy-4-(benzyl)amino-5-nitro-6-(2-nitro-5-cyanophenoxy)pyrimidine;

2-(3-*t*-butoxycarbonylphenoxy)-4-(benzyl)amino-5-nitro-6-(3-nitro-4-cyanophenoxy)pyrimidine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(benzyl)amino-5-nitro-6-(2-carboxy-5-cyanophenoxy)pyrimidine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(benzyl)amino-5-nitro-6-(3-carboxy-4-cyanophenoxy)pyrimidine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(benzyl)amino-5-nitro-6-(2-*t*-butoxycarbonyl-5-cyanophenoxy)pyrimidine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(benzyl)amino-5-nitro-6-(3-*t*-butoxycarbonyl-4-cyanophenoxy)pyrimidine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(benzyl)amino-5-nitro-6-(2-aminocarbonyl-5-cyanophenoxy)pyrimidine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(benzyl)amino-5-nitro-6-(3-aminocarbonyl-4-cyanophenoxy)pyrimidine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(benzyl)amino-5-nitro-6-(2-dimethylamino-5-cyanophenoxy)pyrimidine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(benzyl)amino-5-nitro-6-(3-dimethylamino-4-cyanophenoxy)pyrimidine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(benzyl)amino-5-nitro-6-(2-dimethylamino-5-cyanophenoxy)pyrimidine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(benzyl)amino-5-nitro-6-(3-dimethylamino-4-cyanophenoxy)pyrimidine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-4-amino-5-nitro-6-(2-methoxy-5-cyanophenoxy)pyrimidine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-4-amino-5-nitro-6-(2-ethoxy-5-cyanophenoxy)pyrimidine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-4-amino-5-nitro-6-(3-methoxy-5-cyanophenoxy)pyrimidine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-4-amino-5-nitro-6-(3-ethoxy-5-cyanophenoxy)pyrimidine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-4-amino-5-nitro-6-(2-phenoxy-5-cyanophenoxy)pyrimidine;

2-(3-dimethylaminocarbonylphenoxy)-4-amino-5-nitro-6-(3-phenoxy-5-cyanophenoxy)pyrimidine;

2-(3-dimethylaminocarbonylphenoxy)-4-amino-5-nitro-6-(2-chloro-5-cyanophenoxy)pyrimidine;
2-(3-dimethylaminocarbonylphenoxy)-4-amino-5-nitro-6-(3-bromo-5-cyanophenoxy)pyrimidine;
2-(3-dimethylaminocarbonylphenoxy)-4-amino-5-nitro-6-(2-methyl-5-cyanophenoxy)pyrimidine;
2-(3-dimethylaminocarbonylphenoxy)-4-amino-5-nitro-6-(2-methyl-5-cyanophenoxy)pyrimidine;
2-(3-dimethylaminocarbonylphenoxy)-4-amino-5-nitro-6-(3-methyl-4-cyanophenoxy)pyrimidine;
2-(3-dimethylaminocarbonylphenoxy)-4-amino-5-nitro-6-(2-nitro-5-cyanophenoxy)pyrimidine;
2-(3-dimethylaminocarbonylphenoxy)-4-amino-5-nitro-6-(3-nitro-4-cyanophenoxy)pyrimidine;
2-(3-guanidinophenoxy)-4-amino-5-nitro-6-(2-carboxy-5-cyanophenoxy)pyrimidine;
2-(3-guanidinophenoxy)-4-amino-5-nitro-6-(3-carboxy-4-cyanophenoxy)pyrimidine;
2-(3-guanidinophenoxy)-4-amino-5-nitro-6-(2-*t*-butoxycarbonyl-5-cyanophenoxy)pyrimidine;
2-(3-guanidinophenoxy)-4-amino-5-nitro-6-(3-*t*-butoxycarbonyl-4-cyanophenoxy)pyrimidine;
2-(3-guanidinophenoxy)-4-amino-5-nitro-6-(2-aminocarbonyl-5-cyanophenoxy)pyrimidine;
2-(3-guanidinophenoxy)-4-amino-5-nitro-6-(3-aminocarbonyl-4-cyanophenoxy)pyrimidine;
2-(3-guanidinophenoxy)-4-amino-5-nitro-6-(2-dimethylamino-5-cyanophenoxy)pyrimidine;
2-(3-guanidinophenoxy)-4-amino-5-nitro-6-(3-dimethylamino-4-cyanophenoxy)pyrimidine;
2-(3-guanidinophenoxy)-4-amino-5-nitro-6-(2-dimethylamino-5-cyanophenoxy)pyrimidine; and
2-(3-guanidinophenoxy)-4-amino-5-nitro-6-(3-dimethylamino-4-cyanophenoxy)pyrimidine.

C. In a similar manner, 2-methylthio-5-nitro-4,6-dichloropyrimidine was treated with 3-(dimethylaminocarbonyl)phenol in the presence of cesium carbonate to afford 2-methylthio-5-nitro-4-chloro-6-(3-dimethylaminocarbonylphenoxy)pyrimidine, a compound of formula (M).

D. In a similar manner, the following compounds of formula (M) are prepared:
2-methylthio-4-chloro-5-nitro-6-(3-(2-(dimethylaminocarbonyl)ethyl)phenoxy)pyrimidine;
2-methylthio-4-chloro-5-nitro-6-(3-(2-(dimethylaminocarbonyl)ethyl)-5-methoxyphenoxy)pyrimidine;
2-methylthio-4-chloro-5-nitro-6-(3-(2-(dimethylaminocarbonyl)ethyl)-5-chlorophenoxy)pyrimidine;
2-methylthio-4-chloro-5-nitro-6-(3-chloro-5-methoxyphenoxy)pyrimidine;
2-methylthio-4-chloro-5-nitro-6-(3-trifluoromethyl-5-(dimethylaminocarbonyl)phenoxypyrimidine;
2-methylthio-4-chloro-5-nitro-6-(3-guanidinophenoxy)pyrimidine;
2-methylthio-4-chloro-5-nitro-6-(3-ureidophenoxy)pyrimidine;
2-methylthio-4-chloro-5-nitro-6-(3-nitrophenoxy)pyrimidine;
2-methylthio-4-chloro-5-nitro-6-(3-guanidino-5-methylphenoxy)pyrimidine;
2-methylthio-4-chloro-5-nitro-6-(3-ureido-5-methylphenoxy)pyrimidine; and
2-methylthio-4-chloro-5-nitro-6-(3-nitro-5-aminophenoxy)pyrimidine.

PREPARATION 5

Compounds of formula (J) and formula (Q)

A. 2-(3-Dimethylaminocarbonylphenoxy)-4-benzylamino-5-nitro-6-(2-benzyloxy-5-cyanophenoxy)pyrimidine, a compound of formula (H) (0.29 g, 0.47 mmol) and 0.1 g granular zinc were mixed with 10 mL THF and 1.0 mL 10% aqueous HCl. The reaction was heated at 80°C for 90 minutes. The volatiles were evaporated. Saturated aqueous $NaHCO_3$ was added and the solution extracted with ethyl acetate (300 ml). The organic layer was dried (Na_2SO_4) and evaporated to afford 0.27 g of 2-(3-dimethylaminocarbonylphenoxy)-4-benzylamino-5-amino-6-(2-benzyloxy-5-cyanophenoxy)pyrimidine, a compound of formula (J).

B. In a similar manner, the following compounds of formula (J) are made:

2-(3-methylphenoxy)-4-(benzyl)amino-5-amino-6-(2-methoxy-5-cyanophenoxy)pyrimidine;

2-(3-chloro-5-methoxyphenoxy)-4-(benzyl)amino-5-amino-6-(2-ethoxy-5-cyanophenoxy)pyrimidine;

2-(4-trifluoromethylphenoxy)-4-(benzyl)amino-5-amino-6-(3-methoxy-5-cyanophenoxy)pyrimidine;

2-(3,5-diaminophenoxy)-4-(benzyl)amino-5-amino-6-(3-ethoxy-5-cyanophenoxy)pyrimidine;

2-(3-guanidino-5-methylphenoxy)-4-(benzyl)amino-5-amino-6-(2-phenoxy-5-cyanophenoxy)pyrimidine;

2-(3-ureidophenoxy)-4-(benzyl)amino-5-amino-6-(3-phenoxy-5-cyanophenoxy)pyrimidine;

2-(3-(2-chloroethyl)-5-methylphenoxy)-4-(benzyl)amino-5-amino-6-(2-chloro-5-cyanophenoxy)pyrimidine;

2-(3-dimethylaminocarbonylphenoxy)-4-(benzyl)amino-5-amino-6-(3-bromo-5-cyanophenoxy)pyrimidine;

2-(4-ethoxycarbonylphenoxy)-4-(benzyl)amino-5-amino-6-(2-methyl-5-cyanophenoxy)pyrimidine;

2-(3-(1-methylimidazol-2-yl)phenoxy)-4-(benzyl)amino-5-amino-6-(2-methyl-5-cyanophenoxy)pyrimidine;

2-(3-dimethylaminophenoxy)-4-(benzyl)amino-5-amino-6-(3-methyl-4-cyanophenoxy)pyrimidine;

2-(3-(1-methylimidazolin-2-yl)phenoxy-4-(benzyl)amino-5-amino-6-(2-amino-5-cyanophenoxy)pyrimidine;

2-(3-*t*-butoxycarbonylphenoxy)-4-(benzyl)amino-5-amino-6-(3-amino-4-cyanophenoxy)pyrimidine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(benzyl)amino-5-amino-6-(2-carboxy-5-cyanophenoxy)pyrimidine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(benzyl)amino-5-amino-6-(3-carboxy-4-cyanophenoxy)pyrimidine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(benzyl)amino-5-amino-6-(2-*t*-butoxycarbonyl-5-cyanophenoxy)pyrimidine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(benzyl)amino-5-amino-6-(3-*t*-butoxycarbonyl-4-cyanophenoxy)pyrimidine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(benzyl)amino-5-amino-6-(2-aminocarbonyl-

5-cyanophenoxy)pyrimidine;
2-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(benzyl)amino-5-amino-6-(3-aminocarbonyl-4-cyanophenoxy)pyrimidine;
2-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(benzyl)amino-5-amino-6-(2-dimethylamino-5-cyanophenoxy)pyrimidine;
2-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(benzyl)amino-5-amino-6-(3-dimethylamino-4-cyanophenoxy)pyrimidine;
2-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(benzyl)amino-5-amino-6-(2-dimethylamino-5-cyanophenoxy)pyrimidine;
2-(3-(1-methylimidazolin-2-yl)phenoxy)-4-(benzyl)amino-5-amino-6-(3-dimethylamino-4-cyanophenoxy)pyrimidine;
2-(3-(1-methylimidazolin-2-yl)phenoxy)-4,5-diamino-6-(2-methoxy-5-cyanophenoxy)pyrimidine;
2-(3-(1-methylimidazolin-2-yl)phenoxy)-4,5-diamino-6-(2-ethoxy-5-cyanophenoxy)pyrimidine;
2-(3-(1-methylimidazolin-2-yl)phenoxy)-4,5-diamino-6-(3-methoxy-5-cyanophenoxy)pyrimidine;
2-(3-(1-methylimidazolin-2-yl)phenoxy)-4,5-diamino-6-(3-ethoxy-5-cyanophenoxy)pyrimidine;
2-(3-(1-methylimidazolin-2-yl)phenoxy)-4,5-diamino-6-(2-phenoxy-5-cyanophenoxy)pyrimidine;
2-(3-dimethylaminocarbonylphenoxy)-4,5-diamino-6-(3-phenoxy-5-cyanophenoxy)pyrimidine;
2-(3-dimethylaminocarbonylphenoxy)-4,5-diamino-6-(2-chloro-5-cyanophenoxy)pyrimidine;
2-(3-dimethylaminocarbonylphenoxy)-4,5-diamino-6-(3-bromo-5-cyanophenoxy)pyrimidine;
2-(3-dimethylaminocarbonylphenoxy)-4,5-diamino-6-(2-methyl-5-cyanophenoxy)pyrimidine;
2-(3-dimethylaminocarbonylphenoxy)-4,5-diamino-6-(2-methyl-5-cyanophenoxy)pyrimidine;
2-(3-dimethylaminocarbonylphenoxy)-4,5-diamino-6-(3-methyl-4-cyanophenoxy)pyrimidine;
2-(3-dimethylaminocarbonylphenoxy)-4,5-diamino-6-(2-amino-5-cyanophenoxy)pyrimidine;
2-(3-dimethylaminocarbonylphenoxy)-4,5-diamino-6-(3-amino-4-cyanophenoxy)pyrimidine;
2-(3-guanidinophenoxy)-4,5-diamino-6-(2-carboxy-5-cyanophenoxy)pyrimidine;
2-(3-guanidinophenoxy)-4,5-diamino-6-(3-carboxy-4-cyanophenoxy)pyrimidine;
2-(3-guanidinophenoxy)-4,5-diamino-6-(2-*t*-butoxycarbonyl-5-cyanophenoxy)pyrimidine;
2-(3-guanidinophenoxy)-4,5-diamino-6-(3-*t*-butoxycarbonyl-4-cyanophenoxy)pyrimidine;
2-(3-guanidinophenoxy)-4,5-diamino-6-(2-aminocarbonyl-5-cyanophenoxy)pyrimidine;
2-(3-guanidinophenoxy)-4,5-diamino-6-(3-aminocarbonyl-4-cyanophenoxy)pyrimidine;
2-(3-guanidinophenoxy)-4,5-diamino-6-(2-dimethylamino-5-cyanophenoxy)pyrimidine;
2-(3-guanidinophenoxy)-4,5-diamino-6-(3-dimethylamino-4-cyanophenoxy)pyrimidine;
2-(3-guanidinophenoxy)-4,5-diamino-6-(2-dimethylamino-5-cyanophenoxy)pyrimidine; and
2-(3-guanidinophenoxy)-4,5-diamino-6-(3-dimethylamino-4-cyanophenoxy)pyrimidine.

C. In a similar manner, 2-(2-benzyloxy-5-cyanophenoxy)-4-benzylamino-5-nitro-6-(3-dimethylaminocarbonyl)phenoxypyrimidine (1.2 g, 1.95 mmol), a compound of formula (P), was reduced to afford 1.30 g of 2-(2-benzyloxy-5-cyanophenoxy)-4-benzylamino-5-amino-6-(3-

dimethylaminocarbonyl)phenoxypyrimidine, a compound of formula (Q).

D. In a similar manner, the following compounds of formula (Q) are made:

2-(2-benzyloxy-5-cyanophenoxy)-4-(benzyl)amino-5-amino-6-(3-dimethylaminocarbonyl-phenoxy)pyrimidine;

2-(2-methoxy-5-cyanophenoxy)-4-(benzyl)amino-5-amino-6-(3-dimethylaminocarbonyl-phenoxy)pyrimidine;

2-(2-ethoxy-5-cyanophenoxy)-4-(benzyl)amino-5-amino-6-(3-dimethylaminocarbonyl-phenoxy)pyrimidine;

2-(2-phenoxy-5-cyanophenoxy)-4-(benzyl)amino-5-amino-6-(3-dimethylaminocarbonyl-phenoxy)pyrimidine;

2-(2-chloro-5-cyanophenoxy)-4-(benzyl)amino-5-amino-6-(3-dimethylaminocarbonyl-phenoxy)pyrimidine;

2-(2-methyl-5-cyanophenoxy)-4-(benzyl)amino-5-amino-6-(3-dimethylaminocarbonyl-phenoxy)pyrimidine;

2-(2-*t*-butyl-5-cyanophenoxy)-4-(benzyl)amino-5-amino-6-(3-dimethylaminocarbonyl-phenoxy)pyrimidine;

2-(2-amino-5-cyanophenoxy)-4-(benzyl)amino-5-amino-6-(3-dimethylaminocarbonyl-phenoxy)pyrimidine;

2-(2-carboxy-5-cyanophenoxy)-4-(benzyl)amino-5-amino-6-(3-dimethylaminocarbonyl-phenoxy)pyrimidine;

2-(2-benzyloxycarbonyl-5-cyanophenoxy)-4-(benzyl)amino-5-amino-6-(3-dimethylaminocarbonyl-phenoxy)pyrimidine;

2-(2-diethylaminocarbonyl-5-cyanophenoxy)-4-(benzyl)amino-5-amino-6-(3-dimethylaminocarbonyl-phenoxy)pyrimidine;

2-(2-amino-5-cyanophenoxy)-4-(benzyl)amino-5-amino-6-(3-dimethylaminocarbonyl-phenoxy)pyrimidine;

2-(2-benzyloxy-5-cyanophenoxy)-4-(benzyl)amino-5-amino-6-(3-(1-methylimidazolin-2-yl)-phenoxy)pyrimidine;

2-(2-methoxy-5-cyanophenoxy)-4-(benzyl)amino-5-amino-6-(3-(2-(*t*-butoxycarbonyl)ethyl)-phenoxy)pyrimidine;

2-(2-ethoxy-5-cyanophenoxy)-4-(benzyl)amino-5-amino-6-(3-*t*-butoxycarbonyl-phenoxy)pyrimidine;

2-(2-phenoxy-5-cyanophenoxy)-4-(benzyl)amino-5-amino-6-(3-carboxy-phenoxy)pyrimidine;

2-(2-chloro-5-cyanophenoxy)-4-(benzyl)amino-5-amino-6-(3-(2-aminoethyl)-phenoxy)pyrimidine;

2-(2-methyl-5-cyanophenoxy)-4-(benzyl)amino-5-amino-6-(3-(benzyloxy)-

phenoxy)pyrimidine;

2-(2-*t*-butyl-5-cyanophenoxy)-4-(benzyl)amino-5-amino-6-(3-ethoxyphenoxy)pyrimidine;

2-(2-amino-5-cyanophenoxy)-4-(benzyl)amino-5-amino-6-(3-guanidinophenoxy)pyrimidine;

2-(2-carboxy-5-cyanophenoxy)-4-(benzyl)amino-5-amino-6-(3-ureidophenoxy)pyrimidine;

2-(2-benzyloxycarbonyl-5-cyanophenoxy)-4-(benzyl)amino-5-amino-6-(3-amino-phenoxy)pyrimidine;

2-(2-diethylaminocarbonyl-5-cyanophenoxy)-4-(benzyl)amino-5-amino-6-(3-amino-phenoxy)pyrimidine; and

2-(2-amino-5-cyanophenoxy)-4-(benzyl)amino-5-amino-6-(3-trifluoromethoxy-phenoxy)pyrimidine.

PREPARATION 6

Compounds of formula (L) and (R)

A. 2-(3-Dimethylaminocarbonylphenoxy)-4-(benzyl)amino-5-amino-6-(2-benzyloxy-5-cyanophenoxy)pyrimidine, a compound of formula (J), (0.26 g, 0.44 mmol), was treated with ethyl imidate hydrochloride (0.17 g, 1.3 mmol) in THF/ethanol at 80°C for 6 hours and then concentrated to an oil. The residue was heated in a sand bath under vacuum at 170°C for 2.0 hours, cooled and filtered through a pad of silica, eluting with 5% methanol in methylene chloride. Evaporation of the volatiles afforded 0.20 g of 2-(3-dimethylaminocarbonylphenoxy)-6-(2-benzyloxy-5-cyanophenoxy)-8-methyl-9-benzylpurine, a compound of formula (L).

B. In a similar manner, the following compounds of formula (L) are made:

2-(3-methylphenoxy)-6-(2-methoxy-5-cyanophenoxy)-8-methyl-9-benzylpurine;

2-(3-chloro-5-methoxyphenoxy)-6-(2-ethoxy-5-cyanophenoxy)-8-methyl-9-benzylpurine;

2-(4-trifluoromethylphenoxy)-6-(3-methoxy-5-cyanophenoxy)-8-methyl-9-benzylpurine;

2-(3,5-diaminophenoxy)-6-(3-ethoxy-5-cyanophenoxy)-8-methyl-9-benzylpurine;

2-(3-guanidino-5-methylphenoxy)-6-(2-phenoxy-5-cyanophenoxy)-8-methyl-9-benzylpurine;

2-(3-ureidophenoxy)-6-(3-phenoxy-5-cyanophenoxy)-8-methyl-9-benzylpurine;

2-(3-(2-chloroethyl)-5-methylphenoxy)-6-(2-chloro-5-cyanophenoxy)-8-methyl-9-benzylpurine;

2-(3-dimethylaminocarbonylphenoxy)-6-(3-bromo-5-cyanophenoxy)-8-methyl-9-benzylpurine;

2-(4-ethoxycarbonylphenoxy)-6-(2-methyl-5-cyanophenoxy)-8-methyl-9-benzylpurine;

2-(3-(1-methylimidazol-2-yl)phenoxy)-6-(2-methyl-5-cyanophenoxy)-8-methyl-9-benzylpurine;

2-(3-dimethylaminophenoxy)-6-(3-methyl-4-cyanophenoxy)-8-methyl-9-benzylpurine;

2-(3-(1-methylimidazolin-2-yl)phenoxy-6-(2-amino-5-cyanophenoxy)-8-methyl-9-benzylpurine;

2-(3-*t*-butoxycarbonylphenoxy)-6-(3-amino-4-cyanophenoxy)-8-methyl-9-benzylpurine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(2-carboxy-5-cyanophenoxy)-8-methyl-9-benzylpurine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(3-carboxy-4-cyanophenoxy)-8-methyl-9-benzylpurine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(2-*t*-butoxycarbonyl-

5-cyanophenoxy)-8-methyl-9-benzylpurine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(3-*t*-butoxycarbonyl-4-cyanophenoxy)-8-methyl-9-benzylpurine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(2-aminocarbonyl-5-cyanophenoxy)-8-methyl-9-benzylpurine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(3-aminocarbonyl-4-cyanophenoxy)-8-methyl-9-benzylpurine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(2-dimethylamino-5-cyanophenoxy)-8-methyl-9-benzylpurine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(3-dimethylamino-4-cyanophenoxy)-8-methyl-9-benzylpurine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(2-dimethylamino-5-cyanophenoxy)-8-methyl-9-benzylpurine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(3-dimethylamino-4-cyanophenoxy)-8-methyl-9-benzylpurine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(2-methoxy-5-cyanophenoxy)-8-methylpurine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(2-ethoxy-5-cyanophenoxy)-8-methylpurine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(3-methoxy-5-cyanophenoxy)-8-methylpurine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(3-ethoxy-5-cyanophenoxy)-8-methylpurine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(2-phenoxy-5-cyanophenoxy)-8-methylpurine;

2-(3-dimethylaminocarbonylphenoxy)-6-(3-phenoxy-5-cyanophenoxy)-8-methylpurine;

2-(3-dimethylaminocarbonylphenoxy)-6-(2-chloro-5-cyanophenoxy)-8-methylpurine;

2-(3-dimethylaminocarbonylphenoxy)-6-(3-bromo-5-cyanophenoxy)-8-methylpurine;

2-(3-dimethylaminocarbonylphenoxy)-6-(2-methyl-5-cyanophenoxy)-8-methylpurine;

2-(3-dimethylaminocarbonylphenoxy)-6-(2-methyl-5-cyanophenoxy)-8-methylpurine;

2-(3-dimethylaminocarbonylphenoxy)-6-(3-methyl-4-cyanophenoxy)-8-methylpurine;

2-(3-dimethylaminocarbonylphenoxy)-6-(2-amino-5-cyanophenoxy)-8-methylpurine;

2-(3-dimethylaminocarbonylphenoxy)-6-(3-amino-4-cyanophenoxy)-8-methylpurine;

2-(3-guanidinophenoxy)-6-(2-carboxy-5-cyanophenoxy)-8-methylpurine;

2-(3-guanidinophenoxy)-6-(3-carboxy-4-cyanophenoxy)-8-methylpurine;

2-(3-guanidinophenoxy)-6-(2-*t*-butoxycarbonyl-5-cyanophenoxy)-8-methylpurine;

2-(3-guanidinophenoxy)-6-(3-*t*-butoxycarbonyl-4-cyanophenoxy)-8-methylpurine;

2-(3-guanidinophenoxy)-6-(2-aminocarbonyl-5-cyanophenoxy)-8-methylpurine;

2-(3-guanidinophenoxy)-6-(3-aminocarbonyl-4-cyanophenoxy)-8-methylpurine;

2-(3-guanidinophenoxy)-6-(2-dimethylamino-5-cyanophenoxy)-8-methylpurine;

2-(3-*guanidino*phenoxy)-6-(3-dimethylamino-4-cyanophenoxy)-8-methylpurine;

2-(3-guanidinophenoxy)-6-(2-dimethylamino-5-cyanophenoxy)-8-methylpurine;

2-(3-guanidinophenoxy)-6-(3-dimethylamino-4-cyanophenoxy)-8-methylpurine;
2-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(2-methoxy-5-cyanophenoxy)-8-ethylpurine;
2-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(2-ethoxy-5-cyanophenoxy)-8-ethylpurine;
2-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(3-methoxy-5-cyanophenoxy)-8-ethylpurine;
2-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(3-ethoxy-5-cyanophenoxy)-8-ethylpurine;
2-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(2-phenoxy-5-cyanophenoxy)-8-ethylpurine;
2-(3-dimethylaminocarbonylphenoxy)-6-(3-phenoxy-5-cyanophenoxy)-8-ethylpurine;
2-(3-dimethylaminocarbonylphenoxy)-6-(2-chloro-5-cyanophenoxy)-8-benzylpurine;
2-(3-dimethylaminocarbonylphenoxy)-6-(3-bromo-5-cyanophenoxy)-8-benzylpurine;
2-(3-dimethylaminocarbonylphenoxy)-6-(2-methyl-5-cyanophenoxy)-8-benzylpurine;
2-(3-dimethylaminocarbonylphenoxy)-6-(2-methyl-5-cyanophenoxy)-8-phenylpurine;
2-(3-dimethylaminocarbonylphenoxy)-6-(3-methyl-4-cyanophenoxy)-8-phenylpurine;
2-(3-dimethylaminocarbonylphenoxy)-6-(2-amino-5-cyanophenoxy)-8-phenylpurine;
2-(3-dimethylaminocarbonylphenoxy)-6-(3-amino-4-cyanophenoxy)-8-phenylpurine;
2-(3-guanidinophenoxy)-6-(2-carboxy-5-cyanophenoxy)-8-*t*-butylpurine;
2-(3-guanidinophenoxy)-6-(3-carboxy-4-cyanophenoxy)-8-*t*-butylpurine;
2-(3-guanidinophenoxy)-6-(2-*t*-butoxycarbonyl-5-cyanophenoxy)-*t*-butylpurine;
2-(3-guanidinophenoxy)-6-(3-*t*-butoxycarbonyl-4-cyanophenoxy)-8-trifluoromethylpurine;
2-(3-guanidinophenoxy)-6-(2-aminocarbonyl-5-cyanophenoxy)-8-trifluoromethylpurine;
2-(3-guanidinophenoxy)-6-(3-aminocarbonyl-4-cyanophenoxy)-8-ethylpurine;
2-(3-guanidinophenoxy)-6-(2-dimethylamino-5-cyanophenoxy)-8-ethylpurine.

C. In a similar manner, treatment of 2-(2-benzyloxy-5-cyanophenoxy)-4-(benzyl)amino-5-amino-6-(3-dimethylaminocarbonyl)phenoxypyrimidine (1.14 g, 1.94 mmol) with ethyl imidate hydrochloride (0.31 g, 2.53 mmol) yielded 0.65 g of 2-(2-benzyloxy-5-cyanophenoxy)-6-(3-dimethylaminocarbonyl)phenoxy-8-methyl-9-benzylpurine, a compound of formula (R).

D. In a similar manner, the following compounds of formula (R) are made:
2-(2-benzyloxy-5-cyanophenoxy)-6-(3-dimethylaminocarbonylphenoxy-8-methyl-9-benzylpurine;
2-(2-methoxy-5-cyanophenoxy)-6-(3-dimethylaminocarbonylphenoxy-8-methyl-9-benzylpurine;
2-(2-ethoxy-5-cyanophenoxy)-6-(3-dimethylaminocarbonylphenoxy-8-methyl-9-benzylpurine;
2-(2-phenoxy-5-cyanophenoxy)-6-(3-dimethylaminocarbonylphenoxy-8-methyl-9-benzylpurine;
2-(2-chloro-5-cyanophenoxy)-6-(3-dimethylaminocarbonylphenoxy-8-methyl-9-benzylpurine;
2-(2-methyl-5-cyanophenoxy)-6-(3-dimethylaminocarbonylphenoxy-8-methyl-9-benzylpurine;
2-(2-*t*-butyl-5-cyanophenoxy)-6-(3-dimethylaminocarbonylphenoxy-8-methyl-9-benzylpurine;
2-(2-amino-5-cyanophenoxy)-6-(3-dimethylaminocarbonylphenoxy-8-methyl-9-benzylpurine;
2-(2-carboxy-5-cyanophenoxy)-6-(3-dimethylaminocarbonylphenoxy-8-methyl-9-benzylpurine;
2-(2-benzyloxycarbonyl-5-cyanophenoxy)-6-(3-dimethylaminocarbonyl-

phenoxy-8-methyl-9-benzylpurine;

2-(2-diethylaminocarbonyl-5-cyanophenoxy)-6-(3-dimethylaminocarbonyl-phenoxy-8-methyl-9-benzylpurine;

2-(2-amino-5-cyanophenoxy)-6-(3-dimethylaminocarbonylphenoxy-8-methyl-9-benzylpurine;

2-(2-benzyloxy-5-cyanophenoxy)-6-(3-(1-methylimidazolin-2-yl)phenoxy-8-methyl-9-benzylpurine;

2-(2-methoxy-5-cyanophenoxy)-6-(3-(2-(*t*-butoxycarbonyl)ethyl)phenoxy-8-methyl-9-benzylpurine;

2-(2-ethoxy-5-cyanophenoxy)-6-(3-*t*-butoxycarbonylphenoxy-8-methyl-9-benzylpurine;

2-(2-phenoxy-5-cyanophenoxy)-6-(3-carboxyphenoxy-8-methyl-9-benzylpurine;

2-(2-chloro-5-cyanophenoxy)-6-(3-(2-aminoethyl)phenoxy-8-methyl-9-benzylpurine;

2-(2-methyl-5-cyanophenoxy)-6-(3-(benzyloxy)phenoxy-8-methyl-9-benzylpurine;

2-(2-*t*-butyl-5-cyanophenoxy)-6-(3-ethoxyphenoxy-8-methyl-9-benzylpurine;

2-(2-amino-5-cyanophenoxy)-6-(3-guanidinophenoxy-8-methyl-9-benzylpurine;

2-(2-carboxy-5-cyanophenoxy)-6-(3-ureidophenoxy-8-methyl-9-benzylpurine;

2-(2-benzyloxycarbonyl-5-cyanophenoxy)-6-(3-aminophenoxy-8-methyl-9-benzylpurine;

2-(2-diethylaminocarbonyl-5-cyanophenoxy)-6-(3-aminophenoxy-8-methyl-9-benzylpurine;

2-(2-amino-5-cyanophenoxy)-6-(3-trifluoromethoxyphenoxy-8-methyl-9-benzylpurine;

2-(2-benzyloxy-5-cyanophenoxy)-6-(3-dimethylaminocarbonylphenoxy-8-methylpurine;

2-(2-methoxy-5-cyanophenoxy)-6-(3-dimethylaminocarbonylphenoxy-8-methylpurine;

2-(2-ethoxy-5-cyanophenoxy)-6-(3-dimethylaminocarbonylphenoxy-8-methylpurine;

2-(2-phenoxy-5-cyanophenoxy)-6-(3-dimethylaminocarbonylphenoxy-8-methylpurine;

2-(2-chloro-5-cyanophenoxy)-6-(3-dimethylaminocarbonylphenoxy-8-methylpurine;

2-(2-methyl-5-cyanophenoxy)-6-(3-dimethylaminocarbonylphenoxy-8-methylpurine;

2-(2-*t*-butyl-5-cyanophenoxy)-6-(3-dimethylaminocarbonylphenoxy-8-methylpurine;

2-(2-amino-5-cyanophenoxy)-6-(3-dimethylaminocarbonylphenoxy-8-methylpurine;

2-(2-carboxy-5-cyanophenoxy)-6-(3-dimethylaminocarbonylphenoxy-8-methylpurine;

2-(2-benzyloxycarbonyl-5-cyanophenoxy)-6-(3-dimethylaminocarbonyl-phenoxy-8-methylpurine;

2-(2-diethylaminocarbonyl-5-cyanophenoxy)-6-(3-dimethylaminocarbonyl-phenoxy-8-methylpurine;

2-(2-amino-5-cyanophenoxy)-6-(3-dimethylaminocarbonylphenoxy-8-methylpurine;

2-(2-benzyloxy-5-cyanophenoxy)-6-(3-(1-methylimidazolin-2-yl)phenoxy-8-methylpurine;

2-(2-methoxy-5-cyanophenoxy)-6-(3-(2-(*t*-butoxycarbonyl)ethyl)phenoxy-8-methylpurine;

2-(2-ethoxy-5-cyanophenoxy)-6-(3-*t*-butoxycarbonylphenoxy-8-methylpurine;

2-(2-phenoxy-5-cyanophenoxy)-6-(3-carboxyphenoxy-8-methylpurine;

2-(2-chloro-5-cyanophenoxy)-6-(3-(2-aminoethyl)phenoxy-8-methylpurine;

2-(2-methyl-5-cyanophenoxy)-6-(3-(benzyloxy)phenoxy-8-methylpurine;

2-(2-*t*-butyl-5-cyanophenoxy)-6-(3-ethoxyphenoxy-8-methylpurine;

2-(2-amino-5-cyanophenoxy)-6-(3-guanidinophenoxy-8-methylpurine;
2-(2-carboxy-5-cyanophenoxy)-6-(3-ureidophenoxy-8-methylpurine;
2-(2-benzyloxycarbonyl-5-cyanophenoxy)-6-(3-aminophenoxy-8-methylpurine;
2-(2-diethylaminocarbonyl-5-cyanophenoxy)-6-(3-aminophenoxy-8-methylpurine;
2-(2-amino-5-cyanophenoxy)-6-(3-trifluoromethoxyphenoxy-8-ethylpurine;
2-(2-methyl-5-cyanophenoxy)-6-(3-dimethylaminocarbonylphenoxy-8-ethylpurine;
2-(2-*t*-butyl-5-cyanophenoxy)-6-(3-dimethylaminocarbonylphenoxy-8-ethylpurine;
2-(2-amino-5-cyanophenoxy)-6-(3-dimethylaminocarbonylphenoxy-8-ethylpurine;
2-(2-carboxy-5-cyanophenoxy)-6-(3-dimethylaminocarbonylphenoxy-8-ethylpurine;
2-(2-benzyloxycarbonyl-5-cyanophenoxy)-6-(3-dimethylaminocarbonyl-phenoxy-8-ethylpurine;
2-(2-diethylaminocarbonyl-5-cyanophenoxy)-6-(3-dimethylaminocarbonyl-phenoxy-8-ethylpurine;
2-(2-amino-5-cyanophenoxy)-6-(3-dimethylaminocarbonylphenoxy-8-ethyl-9-ethylpurine;
2-(2-benzyloxy-5-cyanophenoxy)-6-(3-(1-methylimidazolin-2-yl)phenoxy-8-ethyl-9-ethylpurine;
2-(2-methoxy-5-cyanophenoxy)-6-(3-(2-(*t*-butoxycarbonyl)ethyl)phenoxy-8-ethyl-9-ethylpurine;
2-(2-ethoxy-5-cyanophenoxy)-6-(3-*t*-butoxycarbonylphenoxy-8-ethyl-9-ethylpurine;
2-(2-phenoxy-5-cyanophenoxy)-6-(3-carboxyphenoxy-8-ethyl-9-ethylpurine;
2-(2-chloro-5-cyanophenoxy)-6-(3-(2-aminoethyl)phenoxy-8-ethyl-9-ethylpurine;
2-(2-methyl-5-cyanophenoxy)-6-(3-(benzyloxy)phenoxy-8-ethyl-9-ethylpurine;
2-(2-*t*-butyl-5-cyanophenoxy)-6-(3-ethoxyphenoxy-8-ethyl-9-ethylpurine;
2-(2-amino-5-cyanophenoxy)-6-(3-guanidinophenoxy-8-ethyl-9-ethylpurine;
2-(2-carboxy-5-cyanophenoxy)-6-(3-ureidophenoxy-8-ethyl-9-ethylpurine;
2-(2-benzyloxycarbonyl-5-cyanophenoxy)-6-(3-aminophenoxy-8-ethyl-9-ethylpurine;
2-(2-diethylaminocarbonyl-5-cyanophenoxy)-6-(3-aminophenoxy-8-ethyl-9-ethylpurine; and
2-(2-amino-5-cyanophenoxy)-6-(3-trifluoromethoxyphenoxy-8-ethyl-9-ethylpurine.

EXAMPLE 1

Compounds of formula (I) and (II)

A. 6-(2-Benzyloxy-5-cyanophenoxy)-2-(3-dimethylaminocarbonyl)phenoxy-8-methyl-9-benzylpurine (0.2 g, 0.33 mmol) was dissolved in 5.0 mL ethanol in a pressure vessel at 0°C and saturated with HCl gas. The reaction was sealed and allowed to warm to ambient temperature over 16 hours. The reaction mixture was then concentrated to 20 mL and ether was added. The resulting precipitate was dissolved in 30 mL ethanol, cooled to 0°C and ammonia gas bubbled through the solution for 10 minutes. The reaction was sealed and heated at 60°C for 2 hours. The reaction mixture was allowed to cool, the tube opened with caution and the volatiles evaporated to afford 0.152 g of the crude product. Purification by preparative HPLC afforded

0.015 g of 6-(2-hydroxy-5-amidinophenoxy)-2-(3-dimethylaminocarbonyl)phenoxy-8-methyl-9-benzylpurine, a compound of formula (II) NMR (DMSO-d_6) 9.10 (brs, 2), 8.80 (brs, 2), 7.80 (d, 1), 7.70 (d, 1), 7.10-7.50 (m, 10), 5.40 (s, 2), 3.00 (brs, 6), 2.70 (s, 3).

B. In a similar manner, the following compounds of formula (II) are made:

2-(3-methylphenoxy)-6-(2-methoxy-5-amidinophenoxy)-8-methyl-9-benzylpurine;

2-(3-chloro-5-methoxyphenoxy)-6-(2-ethoxy-5-amidinophenoxy)-8-methyl-9-benzylpurine;

2-(4-trifluoromethylphenoxy)-6-(3-methoxy-5-amidinophenoxy)-8-methyl-9-benzylpurine;

2-(3,5-diaminophenoxy)-6-(3-ethoxy-5-amidinophenoxy)-8-methyl-9-benzylpurine;

2-(3-guanidino-5-methylphenoxy)-6-(2-phenoxy-5-amidinophenoxy)-8-methyl-9-benzylpurine;

2-(3-ureidophenoxy)-6-(3-phenoxy-5-amidinophenoxy)-8-methyl-9-benzylpurine;

2-(3-(2-chloroethyl)-5-methylphenoxy)-6-(2-chloro-5-amidinophenoxy)-8-methyl-9-benzylpurine;

2-(3-dimethylaminocarbonylphenoxy)-6-(3-bromo-5-amidinophenoxy)-8-methyl-9-benzylpurine;

2-(4-ethoxycarbonylphenoxy)-6-(2-methyl-5-amidinophenoxy)-8-methyl-9-benzylpurine;

2-(3-(1-methylimidazol-2-yl)phenoxyl-6-(2-methyl-5-amidinophenoxy)-8-methyl-9-benzylpurine,

2-(3-dimethylaminophenoxy)-6-(3-methyl-4-amidinophenoxy)-8-methyl-9-benzylpurine;

2-(3-(1-methylimidazolin-2-yl)phenoxy-6-(2-amino-5-amidinophenoxy)-8-methyl-9-benzylpurine;

2-(3-*t*-butoxycarbonylphenoxy)-6-(3-amino-4-amidinophenoxy)-8-methyl-9-benzylpurine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(2-carboxy-5-amidinophenoxy)-8-methyl-9-benzylpurine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(3-carboxy-4-amidinophenoxy)-8-methyl-9-benzylpurine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(2-*t*-butoxycarbonyl-5-amidinophenoxy)-8-methyl-9-benzylpurine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(3-*t*-butoxycarbonyl-4-amidinophenoxy)-8-methyl-9-benzylpurine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(2-aminocarbonyl-5-amidinophenoxy)-8-methyl-9-benzylpurine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(3-aminocarbonyl-4-amidinophenoxy)-8-methyl-9-benzylpurine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(2-dimethylamino-5-amidinophenoxy)-8-methyl-9-benzylpurine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(3-dimethylamino-4-amidinophenoxy)-8-methyl-9-benzylpurine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(2-dimethylamino-5-amidinophenoxy)-8-methyl-9-benzylpurine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(3-dimethylamino-4-amidinophenoxy)-8-methyl-9-benzylpurine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(2-methoxy-5-amidinophenoxy)-8-methylpurine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(2-ethoxy-5-amidinophenoxy)-8-methylpurine;

2-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(3-methoxy-5-amidinophenoxy)-8-methylpurine;
2-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(3-ethoxy-5-amidinophenoxy)-8-methylpurine;
2-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(2-phenoxy-5-amidinophenoxy)-8-methylpurine;
2-(3-dimethylaminocarbonylphenoxy)-6-(3-phenoxy-5-amidinophenoxy)-8-methylpurine;
2-(3-dimethylaminocarbonylphenoxy)-6-(2-chloro-5-amidinophenoxy)-8-methylpurine;
2-(3-dimethylaminocarbonylphenoxy)-6-(3-bromo-5-amidinophenoxy)-8-methylpurine;
2-(3-dimethylaminocarbonylphenoxy)-6-(2-methyl-5-amidinophenoxy)-8-methylpurine;
2-(3-dimethylaminocarbonylphenoxy)-6-(2-methyl-5-amidinophenoxy)-8-methylpurine;
2-(3-dimethylaminocarbonylphenoxy)-6-(3-methyl-4-amidinophenoxy)-8-methylpurine;
2-(3-dimethylaminocarbonylphenoxy)-6-(2-amino-5-amidinophenoxy)-8-methylpurine;
2-(3-dimethylaminocarbonylphenoxy)-6-(3-amino-4-amidinophenoxy)-8-methylpurine;
2-(3-guanidinophenoxy)-6-(2-carboxy-5-amidinophenoxy)-8-methylpurine;
2-(3-guanidinophenoxy)-6-(3-carboxy-4-amidinophenoxy)-8-methylpurine;
2-(3-guanidinophenoxy)-6-(2-*t*-butoxycarbonyl-5-amidinophenoxy)-8-methylpurine;
2-(3-guanidinophenoxy)-6-(3-*t*-butoxycarbonyl-4-amidinophenoxy)-8-methylpurine;
2-(3-guanidinophenoxy)-6-(2-aminocarbonyl-5-amidinophenoxy)-8-methylpurine;
2-(3-guanidinophenoxy)-6-(3-aminocarbonyl-4-amidinophenoxy)-8-methylpurine;
2-(3-guanidinophenoxy)-6-(2-dimethylamino-5-amidinophenoxy)-8-methylpurine;
2-(3-guanidinophenoxy)-6-(3-dimethylamino-4-amidinophenoxy)-8-methylpurine;
2-(3-guanidinophenoxy)-6-(2-dimethylamino-5-amidinophenoxy)-8-methylpurine;
2-(3-guanidinophenoxy)-6-(3-dimethylamino-4-amidinophenoxy)-8-methylpurine;
2-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(2-methoxy-5-amidinophenoxy)-8-ethylpurine;
2-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(2-ethoxy-5-amidinophenoxy)-8-ethylpurine;
2-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(3-methoxy-5-amidinophenoxy)-8-ethylpurine;
2-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(3-ethoxy-5-amidinophenoxy)-8-ethylpurine;
2-(3-(1-methylimidazolin-2-yl)phenoxy)-6-(2-phenoxy-5-amidinophenoxy)-8-ethylpurine;
2-(3-dimethylaminocarbonylphenoxy)-6-(3-phenoxy-5-amidinophenoxy)-8-ethylpurine;
2-(3-dimethylaminocarbonylphenoxy)-6-(2-chloro-5-amidinophenoxy)-8-benzylpurine;
2-(3-dimethylaminocarbonylphenoxy)-6-(3-bromo-5-amidinophenoxy)-8-benzylpurine;
2-(3-dimethylaminocarbonylphenoxy)-6-(2-methyl-5-amidinophenoxy)-8-benzylpurine;
2-(3-dimethylaminocarbonylphenoxy)-6-(2-methyl-5-amidinophenoxy)-8-phenylpurine;
2-(3-dimethylaminocarbonylphenoxy)-6-(3-methyl-4-amidinophenoxy)-8-phenylpurine;
2-(3-dimethylaminocarbonylphenoxy)-6-(2-amino-5-amidinophenoxy)-8-phenylpurine;
2-(3-dimethylaminocarbonylphenoxy)-6-(3-amino-4-amidinophenoxy)-8-phenylpurine;
2-(3-guanidinophenoxy)-6-(2-carboxy-5-amidinophenoxy)-8-*t*-butylpurine;
2-(3-guanidinophenoxy)-6-(3-carboxy-4-amidinophenoxy)-8-*t*-butylpurine;
2-(3-guanidinophenoxy)-6-(2-*t*-butoxycarbonyl-5-amidinophenoxy)-*t*-butylpurine;

2-(3-guanidinophenoxy)-6-(3-*t*-butoxycarbonyl-4-amidinophenoxy)-8-trifluoromethylpurine;
2-(3-guanidinophenoxy)-6-(2-aminocarbonyl-5-amidinophenoxy)-8-trifluoromethylpurine;
2-(3-guanidinophenoxy)-6-(3-aminocarbonyl-4-amidinophenoxy)-8-ethylpurine;
2-(3-guanidinophenoxy)-6-(2-dimethylamino-5-amidinophenoxy)-8-ethylpurine.

C. In a similar manner, 2-(2-benzyloxy-5-cyanophenoxy)-6-(3-dimethylaminocarbonyl)phenoxy-8-methyl-9-benzylpurine (0.65 g) was converted to 2-(2-hydroxy-5-amidinophenoxy)-6-(3-dimethylaminocarbonyl)phenoxy-8-methyl-9-benzylpurine (0.39 g), a compound of formula (I) NMR (DMSO-d_6) 9.10 (brs, 2), 8.80 (brs, 2), 7.70 (d, 1), 7.65 (d, 1), 7.50 (dd, 1), 7.25-7.40 (m, 8), 7.10 (d, 1), 5.40 (s, 2), 3.00 (s,3), 2.90 (s, 3), 2.70 (s, 3).

D. In a similar manner, the following compounds of formula (I) are made:
2-(2-hydroxy-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methyl-9-benzylpurine;
2-(2-methoxy-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methyl-9-benzylpurine;
2-(2-ethoxy-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methyl-9-benzylpurine;
2-(2-phenoxy-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methyl-9-benzylpurine;
2-(2-chloro-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methyl-9-benzylpurine;
2-(2-methyl-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methyl-9-benzylpurine;
2-(2-*t*-butyl-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methyl-9-benzylpurine;
2-(2-amino-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methyl-9-benzylpurine;
2-(2-carboxy-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methyl-9-benzylpurine;
2-(2-benzyloxycarbonyl-5-amidinophenoxy)-6-(3-dimethylaminocarbonyl-phenoxy)-8-methyl-9-benzylpurine;
2-(2-diethylaminocarbonyl-5-amidinophenoxy)-6-(3-dimethylaminocarbonyl-phenoxy)-8-methyl-9-benzylpurine;
2-(2-amino-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methyl-9-benzylpurine;
2-(2-hydroxy-5-amidinophenoxy)-6-(3-(1-methylimidazolin-2-yl)phenoxy)-8-methyl-9-benzylpurine;
2-(2-methoxy-5-amidinophenoxy)-6-(3-(2-(*t*-butoxycarbonyl)ethyl)phenoxy)-8-methyl-9-benzylpurine;
2-(2-ethoxy-5-amidinophenoxy)-6-(3-*t*-butoxycarbonylphenoxy)-8-methyl-9-benzylpurine;
2-(2-phenoxy-5-amidinophenoxy)-6-(3-carboxyphenoxy)-8-methyl-9-benzylpurine;
2-(2-chloro-5-amidinophenoxy)-6-(3-(2-aminoethyl)phenoxy)-8-methyl-9-benzylpurine;
2-(2-methyl-5-amidinophenoxy)-6-(3-hydroxyphenoxy)-8-methyl-9-benzylpurine;
2-(2-*t*-butyl-5-amidinophenoxy)-6-(3-ethoxyphenoxy)-8-methyl-9-benzylpurine;
2-(2-amino-5-amidinophenoxy)-6-(3-guanidinophenoxy)-8-methyl-9-benzylpurine;
2-(2-carboxy-5-amidinophenoxy)-6-(3-ureidophenoxy)-8-methyl-9-benzylpurine;
2-(2-benzyloxycarbonyl-5-amidinophenoxy)-6-(3-aminophenoxy)-8-methyl-9-benzylpurine;
2-(2-diethylaminocarbonyl-5-amidinophenoxy)-6-(3-aminophenoxy)-8-methyl-9-benzylpurine;
2-(2-amino-5-amidinophenoxy)-6-(3-trifluoromethoxyphenoxy)-8-methyl-9-benzylpurine;

2-(2-hydroxy-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methylpurine;
2-(2-methoxy-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methylpurine;
2-(2-ethoxy-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methylpurine;
2-(2-phenoxy-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methylpurine;
2-(2-chloro-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methylpurine;
2-(2-methyl-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methylpurine;
2-(2-*t*-butyl-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methylpurine;
2-(2-amino-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methylpurine;
2-(2-carboxy-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methylpurine;
2-(2-benzyloxycarbonyl-5-amidinophenoxy)-6-(3-dimethylaminocarbonyl-phenoxy)-8-methylpurine;
2-(2-diethylaminocarbonyl-5-amidinophenoxy)-6-(3-dimethylaminocarbonyl-phenoxy)-8-methylpurine;
2-(2-amino-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methylpurine;
2-(2-hydroxy-5-amidinophenoxy)-6-(3-(1-methylimidazolin-2-yl)phenoxy)-8-methylpurine;
2-(2-methoxy-5-amidinophenoxy)-6-(3-(2-(*t*-butoxycarbonyl)ethyl)phenoxy)-8-methylpurine;
2-(2-ethoxy-5-amidinophenoxy)-6-(3-*t*-butoxycarbonylphenoxy)-8-methylpurine;
2-(2-phenoxy-5-amidinophenoxy)-6-(3-carboxyphenoxy)-8-methylpurine;
2-(2-chloro-5-amidinophenoxy)-6-(3-(2-aminoethyl)phenoxy)-8-methylpurine;
2-(2-methyl-5-amidinophenoxy)-6-(3-hydroxyphenoxy)-8-methylpurine;
2-(2-*t*-butyl-5-amidinophenoxy)-6-(3-ethoxyphenoxy)-8-methylpurine;
2-(2-amino-5-amidinophenoxy)-6-(3-guanidinophenoxy)-8-methylpurine;
2-(2-carboxy-5-amidinophenoxy)-6-(3-ureidophenoxy)-8-methylpurine;
2-(2-benzyloxycarbonyl-5-amidinophenoxy)-6-(3-aminophenoxy)-8-methylpurine;
2-(2-diethylaminocarbonyl-5-amidinophenoxy)-6-(3-aminophenoxy)-8-methylpurine;
2-(2-amino-5-amidinophenoxy)-6-(3-trifluoromethoxyphenoxy)-8-ethylpurine;
2-(2-methyl-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-ethylpurine;
2-(2-*t*-butyl-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-ethylpurine;
2-(2-amino-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-ethylpurine;
2-(2-carboxy-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-ethylpurine;
2-(2-benzyloxycarbonyl-5-amidinophenoxy)-6-(3-dimethylaminocarbonyl-phenoxy)-8-ethylpurine;
2-(2-diethylaminocarbonyl-5-amidinophenoxy)-6-(3-dimethylaminocarbonyl-phenoxy)-8-ethylpurine;
2-(2-amino-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-ethyl-9-ethylpurine;
2-(2-hydroxy-5-amidinophenoxy)-6-(3-(1-methylimidazolin-2-yl)phenoxy)-8-ethyl-9-ethylpurine;
2-(2-methoxy-5-amidinophenoxy)-6-(3-(2-(*t*-butoxycarbonyl)ethyl)phenoxy)-8-ethyl-9-ethylpurine;

2-(2-ethoxy-5-amidinophenoxy)-6-(3-*t*-butoxycarbonylphenoxy)-8-ethyl-9-ethylpurine;
2-(2-phenoxy-5-amidinophenoxy)-6-(3-carboxyphenoxy)-8-ethyl-9-ethylpurine;
2-(2-chloro-5-amidinophenoxy)-6-(3-(2-aminoethyl)phenoxy)-8-ethyl-9-ethylpurine;
2-(2-methyl-5-amidinophenoxy)-6-(3-hydroxyphenoxy)-8-ethyl-9-ethylpurine;
2-(2-*t*-butyl-5-amidinophenoxy)-6-(3-ethoxyphenoxy)-8-ethyl-9-ethylpurine;
2-(2-amino-5-amidinophenoxy)-6-(3-guanidinophenoxy)-8-ethyl-9-ethylpurine;
2-(2-carboxy-5-amidinophenoxy)-6-(3-ureidophenoxy)-8-ethyl-9-ethylpurine;
2-(2-benzyloxycarbonyl-5-amidinophenoxy)-6-(3-aminophenoxy)-8-ethyl-9-ethylpurine;
2-(2-diethylaminocarbonyl-5-amidinophenoxy)-6-(3-aminophenoxy)-8-ethyl-9-ethylpurine; and
2-(2-amino-5-amidinophenoxy)-6-(3-trifluoromethoxyphenoxy)-8-ethyl-9-ethylpurine.

E. The compounds of formula (I) and formula (II) prepared above where R^5 is hydrogen may be further treated in a manner similar to the method described in Dusert, P., *Eur. J. Med. Chem.* (1980), Vol. 3, p. 199, to produce the following compounds:

2-(2-hydroxy-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methyl-9-(1-carboxyethyl)purine;
2-(2-hydroxy-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methyl-9-(1-ethoxycarbonylethyl)purine;
2-(2-hydroxy-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methyl-9-(1-aminocarbonylethyl)purine;
2-(2-methoxy-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methyl-9-(1-carboxy-2-methylpropyl)purine;
2-(2-methoxy-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methyl-9-(1-(ethoxycarbonyl)-2-methylpropyl)purine;
2-(2-methoxy-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methyl-9-(1-(aminocarbonyl)-2-methylpropyl)purine;
2-(2-ethoxy-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methyl-9-(1-carboxy-3-methylbutyl)purine;
2-(2-ethoxy-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methyl-9-(1-(ethoxycarbonyl)-3-methylbutyl)purine;
2-(2-ethoxy-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methyl-9-(1-(aminocarbonyl)-3-methylbutyl)purine;
2-(2-phenoxy-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methyl-9-(1-carboxy-2-methylbutyl)purine;
2-(2-phenoxy-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methyl-9-(1-(ethoxycarbonyl)-2-methylbutyl)purine;
2-(2-phenoxy-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methyl-9-(1-(aminocarbonyl)-2-methylbutyl)purine;

2-(2-chloro-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methyl-9-(1-carboxy-2-phenylethyl)purine;

2-(2-chloro-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methyl-9-(1-(ethoxycarbonyl)-2-phenylethyl)purine;

2-(2-chloro-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methyl-9-(1-(aminocarbonyl)-2-phenylethyl)purine;

2-(2-methyl-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methyl-9-(1-carboxy-2-(4-mercaptophenyl)ethyl)purine;

2-(2-methyl-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methyl-9-(1-(ethoxycarbonyl)-2-(4-mercaptophenyl)ethyl)purine;

2-(2-methyl-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methyl-9-(1-(aminocarbonyl)-2-(4-mercaptophenyl)ethyl)purine;

2-(2-*t*-butyl-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methyl-9-(1-carboxy-2-(indolin-3-yl)ethyl)purine;

2-(2-*t*-butyl-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methyl-9-(1-(ethoxycarbonyl)-2-(indolin-3-yl)ethyl)purine;

2-(2-*t*-butyl-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methyl-9-(1-(aminocarbonyl)-2-(indolin-3-yl)ethyl)purine;

2-(2-amino-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methyl-9-(1-carboxy-2-(imidazol-4-yl)ethyl)purine;

2-(2-amino-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methyl-9-(1-(ethoxycarbonyl)-2-(imidazol-4-yl)ethyl)purine;

2-(2-amino-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methyl-9-(1-(aminocarbonyl)-2-(imidazol-4-yl)ethyl)purine;

2-(2-carboxy-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methyl-9-(1-carboxy-2-hydroxyethyl)purine;

2-(2-carboxy-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methyl-9-(1-(ethoxycarbonyl)-2-hydroxyethyl)purine;

2-(2-carboxy-5-amidinophenoxy)-6-(3-dimethylaminocarbonylphenoxy)-8-methyl-9-(1-(aminocarbonyl)-2-hydroxyethyl)purine;

2-(2-benzyloxycarbonyl-5-amidinophenoxy)-6-(3-dimethylaminocarbonyl-phenoxy)-8-methyl-9-(1-carboxy-2-hydroxypropyl)purine;

2-(2-benzyloxycarbonyl-5-amidinophenoxy)-6-(3-dimethylaminocarbonyl-phenoxy)-8-methyl-9-(1-(ethoxycarbonyl)-2-hydroxypropyl)purine;

2-(2-benzyloxycarbonyl-5-amidinophenoxy)-6-(3-dimethylaminocarbonyl-phenoxy)-8-methyl-9-(1-(aminocarbonyl)-2-hydroxypropyl)purine;

2-(2-diethylaminocarbonyl-5-amidinophenoxy)-6-(3-dimethylaminocarbonyl-

phenoxy)-8-methyl-9-(1-carboxy-2-(aminocarbonyl)ethyl)purine;
2-(2-diethylaminocarbonyl-5-amidinophenoxy)-6-(3-dimethylaminocarbonyl-phenoxy)-8-methyl-9-(1-(ethoxycarbonyl)-2-(aminocarbonyl)ethyl)purine;
2-(2-diethylaminocarbonyl-5-amidinophenoxy)-6-(3-dimethylaminocarbonyl-phenoxy)-8-methyl-9-(1,2-di(aminocarbonyl)ethyl)purine;
2-(2-amino-5-amidinophenoxy)-6-(3-dimethylaminocarbonyl)phenoxy)-8-methyl-9-(1-carboxy-3-(aminocarbonyl)propyl)purine;
2-(2-amino-5-amidinophenoxy)-6-(3-dimethylaminocarbonyl)phenoxy)-8-methyl-9-(1-(ethoxycarbonyl)-3-(aminocarbonyl)propyl)purine;
2-(2-amino-5-amidinophenoxy)-6-(3-dimethylaminocarbonyl)phenoxy)-8-methyl-9-(1,3-di(aminocarbonyl)propyl)purine;
2-(2-hydroxy-5-amidinophenoxy)-6-(3-(1-methylimidazolin-2-yl)phenoxy)-8-methyl-9-(1,2-dicarboxyethyl)purine;
2-(2-hydroxy-5-amidinophenoxy)-6-(3-(1-methylimidazolin-2-yl)phenoxy)-8-methyl-9-(1,2-di(ethoxycarbonyl)ethyl)purine;
2-(2-methoxy-5-amidinophenoxy)-6-(3-(2-(*t*-butoxycarbonyl)ethyl)phenoxy)-8-methyl-9-(1,3-dicarboxypropyl)purine;
2-(2-methoxy-5-amidinophenoxy)-6-(3-(2-(*t*-butoxycarbonyl)ethyl)phenoxy)-8-methyl-9-(1,3-di(ethoxycarbonyl)propyl)purine;
2-(2-ethoxy-5-amidinophenoxy)-6-(3-*t*-butoxycarbonylphenoxy)-8-methyl-9-(1-carboxy-5-aminopentyl)purine;
2-(2-ethoxy-5-amidinophenoxy)-6-(3-*t*-butoxycarbonylphenoxy)-8-methyl-9-(1-(ethoxycarbonyl)-5-aminopentyl)purine;
2-(2-ethoxy-5-amidinophenoxy)-6-(3-*t*-butoxycarbonylphenoxy)-8-methyl-9-(1-(aminocarbonyl)-5-aminopentyl)purine;
2-(2-phenoxy-5-amidinophenoxy)-6-(3-carboxyphenoxy)-8-methyl-9-(1-carboxy-4-guanidinobutyl)purine;
2-(2-phenoxy-5-amidinophenoxy)-6-(3-carboxyphenoxy)-8-methyl-9-(1-(ethoxycarbonyl)-4-guanidinobutyl)purine; and
2-(2-phenoxy-5-amidinophenoxy)-6-(3-carboxyphenoxy)-8-methyl-9-(1-(aminocarbonyl)-4-guanidinobutyl)purine.

EXAMPLE 2

This example illustrates the preparation of representative pharmaceutical compositions for oral administration containing a compound of the invention, or a pharmaceutically acceptable salt *thereof*, *e.g.*, 2-(3-dimethylaminocarbonylphenoxy)-6-(2-hydroxy-4-amidinophenoxy)-9-(1-methoxycarbonyl-propyl)-8-methyl-9-benzylpurine:

A.	Ingredients	% wt./wt.
	Compound of the invention	20.0%
	Lactose	79.5%
	Magnesium stearate	0.5%

The above ingredients are mixed and dispensed into hard-shell gelatin capsules containing 100 mg each.

B.	Ingredients	% wt./wt.
	Compound of the invention	20.0%
	Magnesium stearate	0.9%
	Starch	8.6%
	Lactose	79.6%
	PVP (polyvinylpyrrolidine)	0.9%

The above ingredients with the exception of the magnesium stearate are combined and granulated using water as a granulating liquid. The formulation is then dried, mixed with the magnesium stearate and formed into tablets with an appropriate tableting machine.

C.	Ingredients	
	Compound of the invention	0.1 g
	Propylene glycol	20.0 g
	Polyethylene glycol 400	20.0 g
	Polysorbate 80	1.0 g
	Water	q.s. 100 mL

The compound of the invention is dissolved in propylene glycol, polyethylene glycol 400 and polysorbate 80. A sufficient quantity of water is then added with stirring to provide 100 mL of the solution which is filtered and bottled.

D.	Ingredients	% wt./wt.
	Compound of the invention	20.0%
	Peanut Oil	78.0%
	Span 60	2.0%

The above ingredients are melted, mixed and filled into soft elastic capsules.

E.	Ingredients	% wt./wt.
	Compound of the invention	1.0%
	Methyl or carboxymethyl cellulose	2.0%
	0.9% saline	q.s. 100 mL

The compound of the invention is dissolved in the cellulose/saline solution, filtered and bottled for use.

EXAMPLE 3

This example illustrates the preparation of a representative pharmaceutical formulation for parenteral administration containing a compound of the invention, or a pharmaceutically acceptable salt thereof, *e.g.*, 2-(3-dimethylaminocarbonylphenoxy)-6-(2-phenoxy-4-amidinophenoxy)-9-(1-methoxycarbonylpropyl)-8-methylpurine:

Ingredients	
Compound of the invention	0.02 g
Propylene glycol	20.0 g
Polyethylene glycol 400	20.0 g
Polysorbate 80	1.0 g
0.9% Saline solution	q.s. 100 mL

The compound of the invention is dissolved in propylene glycol, polyethylene glycol 400 and polysorbate 80. A sufficient quantity of 0.9% saline solution is then added with stirring to provide 100 mL of the I.V. solution which is filtered through a 0.2 μ membrane filter and packaged under sterile conditions.

EXAMPLE 4

This example illustrates the preparation of a representative pharmaceutical composition in suppository form containing a compound of the invention, or a pharmaceutically acceptable salt thereof, *e.g.*, 2-(3-dimethylaminocarbonylphenoxy)-6-(2-phenoxy-4-amidinophenoxy)-9-(1-methoxycarbonylpropyl)-8-ethyl-9-benzylpurine:

Ingredients	% wt./wt.
Compound of the invention	1.0%
Polyethylene glycol 1000	74.5%
Polyethylene glycol 4000	24.5%

The ingredients are melted together and mixed on a steam bath, and poured into molds containing 2.5 g total weight.

EXAMPLE 5

This example illustrates the preparation of a representative pharmaceutical formulation for insufflation containing a compound of the invention, or a pharmaceutically acceptable salt thereof, *e.g.*, 2-(3-dimethylaminocarbonylphenoxy)-6-(2-phenoxy-4-amidinophenoxy)-9-(1-methoxycarbonylpropyl)-8-ethyl-9-benzylpurine:

Ingredients	% wt./wt.
Micronized compound of the invention	1.0%
Micronized lactose	99.0%

The ingredients are milled, mixed, and packaged in an insufflator equipped with a dosing pump.

EXAMPLE 6

This example illustrates the preparation of a representative pharmaceutical formulation in nebulized form containing a compound of the invention, or a pharmaceutically acceptable salt thereof, *e.g.*, 2-(3-dimethylaminocarbonylphenoxy)-6-(2-phenoxy-4-amidinophenoxy)-9-(1-methoxycarbonylpropyl)-8-ethylpurine:

Ingredients	% wt./wt.
Compound of the invention	0.005%
Water	89.995%
Ethanol	10.000%

The compound of the invention is dissolved in ethanol and blended with water. The formulation is then packaged in a nebulizer equipped with a dosing pump.

EXAMPLE 7

This example illustrates the preparation of a representative pharmaceutical formulation in aerosol form containing a compound of the invention, or a pharmaceutically acceptable salt thereof, *e.g.*, 2-(3-dimethylaminocarbonylphenoxy)-6-(2-phenoxy-4-amidinophenoxy)-9-(1-methoxycarbonylpropyl)-8-ethylpurine:

Ingredients	% wt./wt.
Compound of the invention	0.10%
Propellant 11/12	98.90%
Oleic acid	1.00%

The compound of the invention is dispersed in oleic acid and the propellants. The resulting mixture is then poured into an aerosol container fitted with a metering valve.

EXAMPLE 8

(*In vitro* assay for Factor Xa, Thrombin and Tissue Plasminogen Activator)

This assay demonstrates the activity of the compounds of the invention towards factor Xa, thrombin and tissue plasminogen activator. The activities were determined as an initial rate of cleavage of the peptide *p*-nitroanilide by the enzyme. The cleavage product, *p*-nitroaniline, absorbs at 405 nm with a molar extinction coefficient of 9920 $M^{-1}cm^{-1}$.

Reagents and Solutions:

Dimethyl sulfoxide (DMSO) (Baker analyzed grade).

Assay buffer:

50 mM TrisHCl, 150 mM NaCl, 2.5 mM $CaCl_2$, and 0.1% polyethylene glycol 6000, pH 7.5.

Enzymes (Enzyme Research Lab.):

1. Human factor Xa stock solution: 0.281 mg/mL in assay buffer, stored at -80°C (working solution (2X): 106 ng/mL or 2 nM in assay buffer, prepare prior to use).
2. Human thrombin stock solution: Stored at -80°C (working solution (2X): 1200 ng/mL or 40 nM in assay buffer, prepare prior to use).
3. Human tissue plasminogen activator (tPA) (Two chains, Sigma) stock solution: 1 mg/mL, stored at -80°C (working solution (2X): 1361 ng/mL in assay buffer, prepare prior to use).

Chromogenic substrates (Pharmacia Hepar Inc.):

1. S2222 (FXa assay) stock solution: 6 mM in dH_2O, store at 4°C (working solution (4X): 656 μM in assay buffer).
2. S2302 (Thrombin assay) stock solution: 10 mM in dH_2O, stored at 4°C (working solution (4X): 1200 μM in assay buffer).
3. S2288 (tPA assay) stock solution: 10 mM in dH_2O, stored at 4°C (working solution (4X): 1484 μM in assay buffer).

(All substrate working solutions were prepared on assay day 5.)

Standard inhibitor compound stock solution:

5 mM in DMSO, stored at -20°C.

Test compounds (compounds of the invention) stock solutions:

10 mM in DMSO, stored at -20°C.

Assay procedure:

Assays were performed in 96-well microtiter plates in a total volume of 200 μl. Assay components were in final concentration of 50 mM TrisHCl, 150 mM NaCl, 2.5 mM $CaCl_2$, 0.1% polyethylene glycol 6000, pH 7.5, in the absence or presence of the standard inhibitor or the test compounds and enzyme and substrate at following concentrations: (1) 1 nM factor Xa and 164 μM S2222; (2) 20 nM thrombin and 300 μM S2302; and (3) 10 nM tPA and 371 μM S2288. Concentrations of the standard inhibitor compound in the assay were from 5 μM to 0.021 μM in 1 to 3 dilution. Concentration of the test compounds in the assay typically were from 10 μM to 0.041 μM in 1 to 3 dilution. For potent test compounds, the concentrations used in the factor Xa assay were further diluted 100 fold (100 nM to 0.41 nM) or 1000 fold (10 nM to 0.041 nM). All substrate concentrations used are equal to their K_m values under the present assay conditions. Assays were performed at ambient temperature.

The first step in the assay was the preparation of 10 mM test compound stock solutions in DMSO (for potent test compounds, 10 mM stock solutions were further diluted to 0.1 or 0.01 mM for the factor Xa assay), followed by the preparation of test compound working solutions

(4X) by a serial dilutions of 10 mM stock solutions with Biomek 1000 (or Multiprobe 204) in 96 deep well plates as follows:

(a) Prepare a 40 μM working solution by diluting the 10 mM stock 1 to 250 in assay buffer in 2 steps: 1 to 100, and 1 to 2.5.

(b) Make another five serial dilutions (1:3) of the 40 μM solution (600 μl for each concentration). A total of six diluted test compound solutions were used in the assay. Standard inhibitor compound (5 mM stock) or DMSO (control) went through the same dilution steps as those described above for test compounds.

The next step in the assay was to dispense 50 μl of the test compound working solutions (4X) (from 40 uM to 0.164 uM) in duplicate to microtiter plates with Biomek or MP204. To this was added 100 μl of enzyme working solution (2X) with Biomek or MP204. The resulting solutions were incubated at ambient temperature for 10 minutes.

To the solutions was added 50 μl of substrate working solution (4X) with Biomek or MP204.

The enzyme kinetics were measured at 405 nm at 10 seconds intervals for five minutes in a THERMOmax plate reader at ambient temperature.

Calculation of K_i of the test compounds:

Enzyme rates were calculated as mOD/min based on the first two minutes readings. The IC_{50} values were determined by fitting the data to the log-logit equation (linear) or the Morrison equation (non-linear) with an EXCEL spread-sheet. Ki values were then obtained by dividing the IC_{50} by 2. Routinely, Ki(factor Xa) values less than 3 nM were calculated from the Morrison equation.

Compounds of the invention, when tested in this assay, demonstrated the selective ability to inhibit human factor Xa and human thrombin.

EXAMPLE 9

(*In vitro* assay for Human Prothrombinase)

This assay demonstrates the ability of the compounds of the invention to inhibit prothrombinase. Prothrombinase (PTase) catalyzes the activation of prothrombin to yield fragment 1.2 plus thrombin with meizothrombin as the intermediate. This assay is an end point assay. Activity of the prothrombinase is measured by activity of thrombin (one of the reaction products) or by the amount of thrombin formed/time based on a thrombin standard curve (nM vs mOD/min). For determination of IC_{50} (PTase) of the compounds of the invention, PTase activity was expressed by thrombin activity (mOD/min).

Materials:

Enzymes:

1. Human factor Va (Haematologic Technologies Inc., Cat# HCVA-0110) working solution: 1.0 mg/mL in 50% glycerol, 2 mM $CaCl_2$, stored at -20°C.
2. Human factor Xa (Enzyme Res. Lab. cat# HFXa1011) working solution: 0.281 mg/mL in assay buffer (without BSA), stored at -80°C.
3. Human prothrombin (FII) (Enzyme Res. Lab., Cat# HP1002) working solution: Diluted FII to 4.85 mg/mL in assay buffer (without BSA), stored at -80°C.

Phospholipid (PCPS) vesicles:

PCPS vesicles (80%PC, 20%PS) were prepared by modification of the method reported by Barenholz *et al., Biochemistry* (1977), Vol. 16, pp. 2806-2810.

Phosphatidyl serine (Avanti Polar Lipids, Inc., Cat#840032):

10 mg/mL in chloroform, purified from brain, stored -20°C under nitrogen or argon.

Phosphatidyl Choline (Avanti Polar Lipids, Inc., Cat# 850457):

50 mg/ml in chloroform, synthetic 16:0-18:1 Palmitoyl-Oleoyl, stored at -20°C under nitrogen or argon.

Spectrozyme-TH (American Diagnostica Inc., Cat# 238L, 50 μmoles, stored at room temperature) working solution: Dissolved 50 μmoles in 10 mL dH_2O.

BSA (Sigma Chem Co., Cat# A-7888, FractionV, RIA grade).

Assay buffer: 50 mM TrisHCl, pH 7.5, 150 mM NaCl, 2.5 mM $CaCl_2$, 0.1% PEG 6000 (BDH), 0.05% BSA (Sigma, Fr.V, RIA grade).

For one plate assay, prepare the following working solutions:

1. Prothrombinase complex:
   (a) 100 μM PCPS (27.5 μl of PCPS stock (4.36 mM) diluted to final 1200 μl with assay buffer.
   (b) 25 nM Human factor Va: 5.08 μl of Va stock(1 mg/mL) was diluted to final 1200 μl with assay buffer.
   (c) 5 pM Human factor Xa: Dilute Xa stock (0.281 mg/mL) 1:1,220,000 with assay buffer. Prepare at least 1200 μl.

   Combine equal volumes (1100 μl) of each component in the order of PCPS, Va and Xa. Let stand at ambient temperature for 5 to 10 minutes and use immediately or store in ice (bring to ambient temperature before use).
2. 6 μM Human prothrombin (FII): dilute 124 μL of FII stock (4.85 mg/mL) to final 1400 μL with assay buffer.
3. 20 mM EDTA/Assay buffer: 0.8 mL of 0.5 M EDTA (pH 8.5) plus 19.2 mL assay buffer.

4. 0.2 mM Spectrozyme-TH/EDTA buffer: 0.44 mL of SPTH stock (5 mM) plus 10.56 mL of 20 mM EDTA/assay buffer.

5. Test compounds (compounds of the invention):
Prepare a working solution (5X) from 10 mM stock (DMSO) and make a series of 1:3 dilution. Compounds were assayed at 6 concentrations in duplicate.

Assay conditions and procedure:

Prothrombinase reaction was performed in final 50 μL of mixture containing PTase (20 uM PCPS, 5 nM hFVa, and 1 pM hFXa), 1.2 uM human factor II and varied concentration of the test compounds (5 μM to 0.021 μM or lower concentration range). Reaction was started by addition of PTase and incubated for 6 minutes at room temperature. Reaction was stopped by addition of EDTA/buffer to final 10 mM. Activity of thrombin (product) was then measured in the presence of 0.1 mM of Spectrozyme-TH as substrate at 405 nm for 5 minutes (10 seconds intervals) at ambient temperature in a THERMOmax microplate reader. Reactions were performed in 96-well microtiter plates.

In the first step of the assay, 10 μl of diluted test compound (5X) or buffer was added to the plates in duplicate. Then 10 μl of prothrombin (hFII) (5X) was added to each well. Next 30 μl PTase was added to each well, mix for about 30 seconds. The plates were then incubated at ambient temperature for 6 minutes.

In the next step, 50 μl of 20 mM EDTA (in assay buffer) was added to each well to stop the reaction. The resulting solutions were then mixed for about 10 seconds. Then 100 μl of 0.2 mM spectrozyme was added to each well. The thrombin reaction rate was then measured at 405 nm for 5 minutes at 10 seconds intervals in a Molecular Devices microplate reader.

Calculations:

Thrombin reaction rate was expressed as mOD/min. using OD readings from the five minute reaction. IC_{50} values were calculated with the log-logit curve fit program.

The compounds of the invention demonstrated the ability to inhibit pro-thrombinase when tested in this assay.

EXAMPLE 10

(*In vivo* assay)

The following assay demonstrates the ability of the compounds to act as anti-coagulants.

Male rats (250-330 g) were anesthetized with sodium pentobarbital (90 mg/kg, i.p.) and prepared for surgery. The left carotid artery was cannulated for the measurement of blood pressure as well as for taking blood samples to monitor clotting variables (prothrombin time (PT) and activated partial thromboplastin time (aPTT)). The tail vein was cannulated for the purpose of

administering the test compounds (*i.e.*, the compounds of the invention and standards) and the thromboplastin infusion. The abdomen was opened via a mid-line incision and the abdominal vena cava was isolated for 2-3 cm distal to the renal vein. All venous branches in this 2-3 cm segment of the abdominal vena cava were ligated. Following all surgery, the animals were allowed to stabilize prior to beginning the experiment. Test compounds were administered as an intravenous bolus (t=0). Three minutes later (t=3), a 5-minute infusion of thromboplastin was begun. Two minutes into the infusion (t=5), the abdominal vena cava was ligated at both the proximal and distal ends. The vessel was left in place for 60 minutes, after which it was excised from the animal, slit open, the clot (if any) carefully removed, and weighed. Statistical analysis on the results was performed using a Wilcoxin-matched-pairs signed rank test.

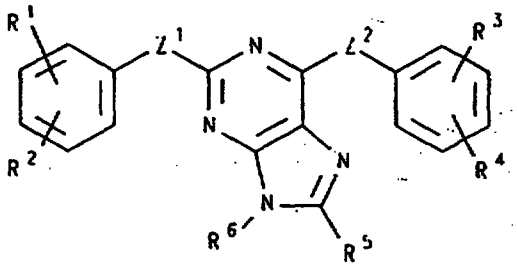
The compounds of the invention, when tested in this assay, demonstrated the ability to inhibit the clotting of blood.

* * * * *

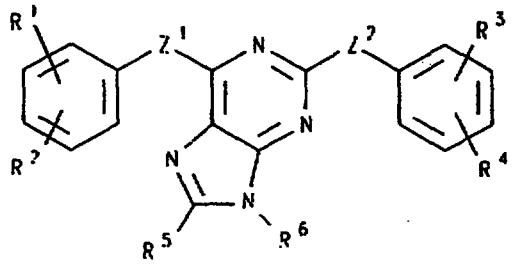
While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the invention. In addition, many modifications may be made and equivalents may be substituted without departing from the true spirit and scope of the invention. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective, spirit and scope of the present invention. All such modifications are intended to be within the scope of the claims appended hereto.

WHAT IS CLAIMED IS:

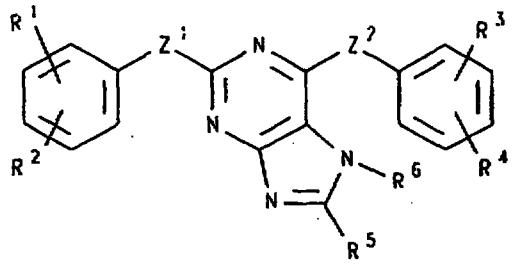
1. A compound selected from the group consisting of the following formulae:



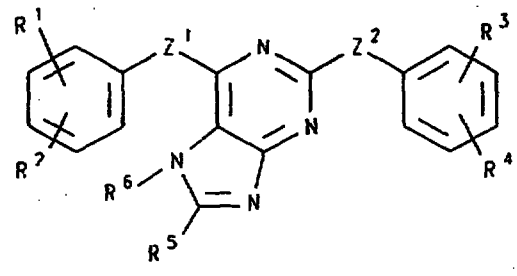
(I)



(II)



(III)



(IV)

wherein:

Z^1 and Z^2 are independently -O-, -N(R^{10})- or -OCH_2-;

R^1 and R^4 are each independently hydrogen, halo, alkyl, -OR^{10}, -C(O)OR^{10}, -C(O)N(R^{10})R^{11}, -N(R^{10})R^{11}, -N(R^{10})C(O)R^{10}, or -N(H)S(O)$_2R^{13}$;

R^2 is -C(NH)NH_2, -C(NH)N(H)OR^{10}, -C(NH)N(H)C(O)OR^{13}, -C(NH)N(H)C(O)R^{10}, -C(NH)N(H)S(O)$_2R^{13}$, or -C(NH)N(H)C(O)N(H)R^{10};

R^3 is halo, alkyl, haloalkyl, haloalkoxy, ureido, cyano, guanidino, -OR^{10}, -C(NH)NH_2, -C(NH)N(H)OR^{10}, -C(O)N(R^{10})R^{11}, -R^{12}-C(O)N(R^{10})R^{11}, -CH(OH)C(O)N(R^{10})R^{11}, -N(R^{10})R^{11}, -R^{12}-N(R^{10})R^{11}, -C(O)OR^{10}, -R^{12}-C(O)OR^{10}, -N(R^{10})C(O)R^{10}, (1,2)-tetrahydropyrimidinyl (optionally substituted by alkyl), (1,2)-imidazolyl (optionally

substituted by alkyl), or (1,2)-imidazolinyl (optionally substituted by alkyl);

R^5 is hydrogen, halo, alkyl, cycloalkyl, haloakyl, aryl, aralkyl, alkylthio, hydroxy, mercapto, alkoxy, or $-N(R^{10})R^{11}$;

R^6 is $-(C(R^7)(R^8))_n-R^9$ (where n is 1 to 4), hydrogen, alkyl, aryl (optionally substituted by halo, alkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, alkyl, aryl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl);

each R^7 is independently hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, cycloalkyl, cycloalkylalkyl, $-C(O)OR^{10}$, $-R^{12}-C(O)OR^{10}$, $-R^{12}-C(O)N(R^{10})R^{11}$, $-C(O)-R^{12}-N(R^{10})R^{11}$, $-R^{12}-C(O)R^{10}$, $-R^{12}-C(O)N(R^{10})N(R^{10})R^{11}$, $-R^{12}-C(R^{10})(OR^{10})-R^{12}-N(R^{10})(R^{11})$, $-C(R^{10})(OR^{10})C(O)OR^{11}$, $-R^{12}-C(R^{10})(C(O)OR^{10})_2$, $-C(R^{10})(N(R^{10})R^{11})C(O)OR^{10}$, $-R^{12}-C(R^{10})(N(R^{10})R^{11})C(O)OR^{10}$, $-C(R^{10})(OR^{10})R^{11}$, $-R^{12}-N(R^{10})R^{11}$, $-R^{12}-N(R^{10})C(O)OR^{13}$, $-R^{12}-N(R^{10})C(O)R^{11}$, $-R^{12}-N(R^{10})C(NR^{10})R^{13}$, $-R^{12}-N(R^{10})S(O)_2R^{13}$, $-R^{12}-N(R^{10})C(O)N(R^{10})R^{11}$, $-R^{12}-N(R^{10})C(NR^{10})N(R^{10})R^{11}$, $-R^{12}-N(R^{10})C(NR^{10})N(R^{10})N(R^{10})R^{11}$, $-R^{12}-N(R^{10})-R^{12}-C(R^{10})(N(R^{10})R^{11})C(O)OR^{10}$, $-R^{12}-N(R^{10})S(O)R^{11}$, $-R^{12}OR^{10}$, $-R^{12}-ON(R^{10})C(NR^{10})N(R^{10})R^{11}$, $-R^{12}-OS(O)_2OR^{10}$, $-R^{12}-P(O)(OR^{10})R^{11}$, $-R^{12}-OP(O)(OR^{10})_2$, $-R^{12}-P(O)(OR^{10})_2$, $-R^{12}-SR^{10}$, $-R^{12}-S-R^{12}-C(O)OR^{10}$, $-R^{12}-S-R^{12}-N(R^{10})R^{11}$, $-R^{12}-S-R^{12}-C(R^{10})(N(R^{10})R^{11})C(O)OR^{10}$, $-R^{12}-S-R^{12}-N(R^{10})C(O)OR^{10}$, $-R^{12}-S-R^{12}-N(R^{10})C(O)R^{10}$, $-R^{12}-S-S-R^{12}-C(R^{10})(N(R^{10})R^{11})C(O)OR^{10}$, $-R^{12}-SC(O)N(R^{10})R^{11}$, $-R^{12}-SC(S)N(R^{10})R^{11}$, $-R^{12}-S(O)R^{10}$, $-R^{12}-S(O)_2R^{13}$, $-R^{12}-S(O)OR^{10}$, $-R^{12}-S(O)_2OR^{10}$, $-R^{12}-S(O)_2N(R^{10})R^{11}$, $-R^{12}-S(O)(NR^{10})R^{11}$,

or each R^7 is aryl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, haloalkoxy, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})R^{11}$, $-C(O)OR^{10}$, $-C(O)N(R^{10})R^{11}$, $-S(O)_2OR^{10}$ and $-OP(O)(OR^{10})_2$),

or each R^7 is aralkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, haloalkoxy, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})R^{11}$, $-C(O)OR^{10}$, $-C(O)N(R^{10})R^{11}$, $-S(O)_2OR^{10}$ and $-OP(O)(OR^{10})_2$),

or each R^7 is heterocyclyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, haloalkoxy, aralkyl, $-OR^{10}$, $-C(O)OR^{10}$, $-N(R^{10})R^{11}$, $-C(O)N(R^{10})R^{11}$, $-S(O)_2OR^{10}$ and $-OP(O)(OR^{10})_2$),

or each R^7 is heterocyclylalkyl (where the heterocyclyl radical is optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, haloalkoxy, aralkyl, $-OR^{10}$, $-SR^{10}$, $-C(O)OR^{10}$, $-N(R^{10})R^{11}$, $-C(O)N(R^{10})R^{11}$), $-S(O)_2OR^{10}$ and $-OP(O)(OR^{10})_2$),

or each R^7 is adamantyl (optionally substituted by alkyl, halo, haloalkyl, haloalkoxy, $-OR^{10}$, $-SR^{10}$, $-C(O)OR^{10}$, $-N(R^{10})R^{11}$, $-C(O)N(R^{10})R^{11}$, $-S(O)_2OR^{10}$ and $-OP(O)(OR^{10})_2$),

or each R^7 is adamantylalkyl (where the adamantyl radical is optionally substituted by alkyl, halo, haloalkyl, haloalkoxy, $-OR^{10}$, $-SR^{10}$, $-C(O)OR^{10}$, $-N(R^{10})R^{11}$, $-C(O)N(R^{10})R^{11}$, $-S(O)_2OR^{10}$ and $-OP(O)(OR^{10})_2$);

each R^8 is independently hydrogen, alkyl, cycloalkyl, or aryl;

R^9 is $-C(O)OR^{10}$ or $-C(O)N(R^{10})R^{11}$;

each R^{10} and R^{11} is independently hydrogen, alkyl, aryl (optionally substituted by halo, alkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, alkyl, aryl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl);

R^{12} is a straight or branched alkylene chain; and

R^{13} is alkyl, aryl (optionally substituted by halo, alkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, alkyl, aryl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl);

as a single stereoisomer or a mixture thereof; or a pharmaceutically acceptable salt thereof.

2. The compound of Claim 1 wherein

Z^1 and Z^2 are independently -O- or $-OCH_2-$;

R^1 and R^4 are each independently hydrogen, halo or $-OR^{10}$;

R^2 is $-C(NH)NH_2$, $-C(NH)N(H)S(O)_2R^{13}$, or $-C(NH)N(H)C(O)N(H)R^{10}$;

R^3 is ureido, guanidino, $-C(O)N(R^{10})R^{11}$, $-N(R^{10})R^{11}$, $-C(O)OR^{10}$, $-N(R^{10})C(O)R^{10}$, (1,2)-tetrahydropyrimidinyl (optionally substituted by alkyl), (1,2)-imidazolyl (optionally substituted by alkyl), or (1,2)-imidazolinyl (optionally substituted by alkyl);

R^5 is hydrogen, halo, alkyl, haloalkyl, aryl, or aralkyl;

R^6 is alkyl, aryl, aralkyl, or $-(C(R^7)(R^8))_n-R^9$ (where n is 1);

R^7 is alkyl, $-R^{12}-C(O)OR^{10}$, $-R^{12}-C(O)N(R^{10})R^{11}$, $-R^{12}-C(R^{10})(C(O)OR^{10})_2$, $-R^{12}-N(R^{10})R^{11}$, $-R^{12}-N(R^{10})C(NR^{10})R^{13}$, $-R^{12}-N(R^{10})C(O)N(R^{10})R^{11}$, $-R^{12}-N(R^{10})C(NR^{10})N(R^{10})R^{11}$, $-R^{12}OR^{10}$, $-R^{12}-OP(O)(OR^{10})_2$, $-R^{12}-SR^{10}$, $-R^{12}-S(O)_2R^{13}$;

or R^7 is aralkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, haloalkoxy, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})R^{11}$, $-C(O)OR^{10}$, $-C(O)N(R^{10})R^{11}$, $-S(O)_2OR^{10}$ and $-OP(O)(OR^{10})_2$);

or R^7 is heterocyclylalkyl (where the heterocyclyl radical is optionally substituted

* C L M S *

by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, haloalkoxy, aralkyl, $-OR^{10}$, $-SR^{10}$, $-C(O)OR^{10}$, $-N(R^{10})R^{11}$, $-C(O)N(R^{10})R^{11}$), $-S(O)_2OR^{10}$ and $-OP(O)(OR^{10})_2$);

R^8 is independently hydrogen or alkyl;

R^9 is $-C(O)OR^{10}$ or $-C(O)N(R^{10})R^{11}$;

each R^{10} and R^{11} is independently hydrogen, alkyl, aryl (optionally substituted by halo, alkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, alkyl, aryl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl);

R^{12} is a straight or branched alkylene chain; and

R^{13} is alkyl, aryl (optionally substituted by halo, alkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, alkyl, aryl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl).

3. The compound of Claim 2 wherein

Z^1 and Z^2 are each -O-;

R^1 is hydrogen or $-OR^{10}$;

R^2 is $-C(NH)NH_2$;

R^3 is $-C(O)N(R^{10})R^{11}$, (1,2)-tetrahydropyrimidinyl (optionally substituted by alkyl), (1,2)-imidazolyl (optionally substituted by alkyl), or (1,2)-imidazolinyl (optionally substituted by alkyl);

R^4 is hydrogen;

R^5 is alkyl or aralkyl;

R^6 is alkyl, aralkyl or $-C(R^7)(R^8)-R^9$;

R^7 is alkyl, $-R^{12}-C(O)OR^{10}$, $-R^{12}-C(O)N(R^{10})R^{11}$, $-R^{12}-C(R^{10})(C(O)OR^{10})_2$, $-R^{12}-N(R^{10})R^{11}$, $-R^{12}-N(R^{10})C(NR^{10})R^{13}$, $-R^{12}-N(R^{10})C(O)N(R^{10})R^{11}$, $-R^{12}-N(R^{10})C(NR^{10})N(R^{10})R^{11}$, $-R^{12}OR^{10}$, $-R^{12}-OP(O)(OR^{10})_2$, $-R^{12}-SR^{10}$, $-R^{12}-S(O)_2R^{13}$;

or R^7 is aralkyl (optionally substituted by one or more substituents selected from the group consisting of halo, haloalkyl, hydroxy and $-OP(O)(OR^{10})_2$);

or R^7 is imidazolylalkyl or indolylalkyl;

R^8 is hydrogen or alkyl;

R^9 is $-C(O)OR^{10}$ or $-C(O)N(R^{10})R^{11}$;

each R^{10} and R^{11} is independently hydrogen or alkyl;

R^{12} is a straight or branched alkylene chain; and

R^{13} is alkyl or aryl.

4. The compound of Claim 3 wherein:

Z^1 and Z^2 are each -O-;

R^1 is hydrogen;

R^2 is $-C(NH)NH_2$;

R^3 is $-C(O)N(R^{10})R^{11}$, (1,2)-tetrahydropyrimidinyl (optionally substituted by alkyl), (1,2)-imidazolyl (optionally substituted by alkyl), or (1,2)-imidazolinyl (optionally substituted by alkyl);

R^4 is hydrogen;

R^5 is alkyl;

R^6 is aralkyl or $-C(R^7)(R^8)-R^9$;

R^7 is alkyl, $-R^{12}-C(O)OR^{10}$, $-R^{12}-C(O)N(R^{10})R^{11}$, $-R^{12}-C(R^{10})(C(O)OR^{10})_2$, $-R^{12}-N(R^{10})R^{11}$, $-R^{12}-N(R^{10})C(NR^{10})R^{13}$, $-R^{12}-N(R^{10})C(O)N(R^{10})R^{11}$, $-R^{12}-N(R^{10})C(NR^{10})N(R^{10})R^{11}$, $-R^{12}OR^{10}$, $-R^{12}-OP(O)(OR^{10})_2$, $-R^{12}-SR^{10}$, $-R^{12}-S(O)_2R^{13}$;

or R^7 is aralkyl (optionally substituted by one or more substituents selected from the group consisting of halo, haloalkyl, hydroxy and $-OP(O)(OR^{10})_2$);

or R^7 is imidazolylalkyl or indolylalkyl;

R^8 is hydrogen or alkyl;

R^9 is $-C(O)OR^{10}$ or $-C(O)N(R^{10})R^{11}$;

each R^{10} and R^{11} is independently hydrogen or alkyl;

R^{12} is a straight or branched alkylene chain; and

R^{13} is alkyl or aryl.

5. The compound of Claim 4 wherein:

R^3 is $-C(O)N(R^{10})R^{11}$, (1,2)-imidazolyl (optionally substituted by alkyl) or (1,2)-imidazolinyl (optionally substituted by alkyl);

R^4 is hydrogen;

R^5 is alkyl;

R^6 is aralkyl or $-C(R^7)(R^8)-R^9$;

R^7 is alkyl, $-R^{12}-C(O)OR^{10}$, $-R^{12}-C(O)N(R^{10})R^{11}$, $-R^{12}-C(R^{10})(C(O)OR^{10})_2$, $-R^{12}-N(R^{10})R^{11}$, $-R^{12}-N(R^{10})C(NR^{10})R^{13}$, $-R^{12}-N(R^{10})C(O)N(R^{10})R^{11}$, $-R^{12}-N(R^{10})C(NR^{10})N(R^{10})R^{11}$, $-R^{12}OR^{10}$, $-R^{12}-OP(O)(OR^{10})_2$, $-R^{12}-SR^{10}$, $-R^{12}-S(O)_2R^{13}$;

R^8 is hydrogen;

R^9 is $-C(O)OR^{10}$;

each R^{10} and R^{11} is independently hydrogen or alkyl;

R^{12} is a straight or branched alkylene chain; and

R^{13} is alkyl or aryl.

6. The compound of Claim 5 wherein:

R^3 is $-C(O)N(R^{10})R^{11}$;

R^4 is hydrogen;

R^5 is methyl or ethyl;

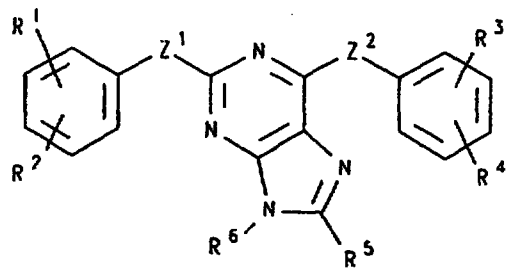
R^6 is benzyl; and

R^{10} and R^{11} are independently hydrogen or methyl.

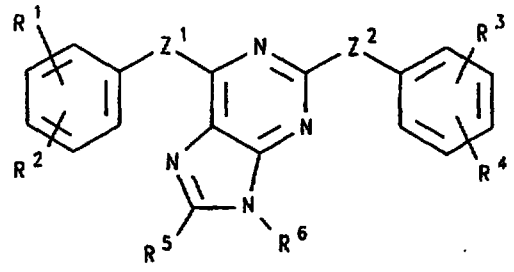
7. The compound of Claim 6 wherein the compound is a compound of formula (I) wherein R^3 is $-C(O)N(R^{10})R^{11}$ where R^{10} and R^{11} are both methyl, R^4 is hydrogen, R^5 is methyl, and R^6 is benzyl, namely, 2-(2-hydroxy-5-amidinophenoxy)-6-(3-dimethylaminocarbonyl)phenoxy)-8-methyl-9-benzylpurine.

8. The compound of Claim 6 wherein the compound is a compound of formula (II) wherein R^3 is $-C(O)N(R^{10})R^{11}$ where R^{10} and R^{11} are both methyl, R^4 is hydrogen, R^5 is methyl, and R^6 is benzyl, namely, 6-(2-hydroxy-5-amidinophenoxy)-2-(3-dimethylaminocarbonylphenoxy)-8-methyl-9-benzylpurine.

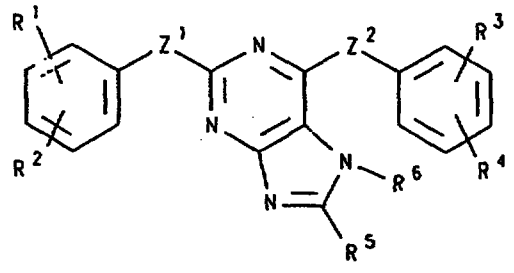
9. A pharmaceutical composition useful in treating a human having a disease-state characterized by thrombotic activity, which composition comprises a therapeutically effective amount of a compound selected from the group consisting of the following formulae:



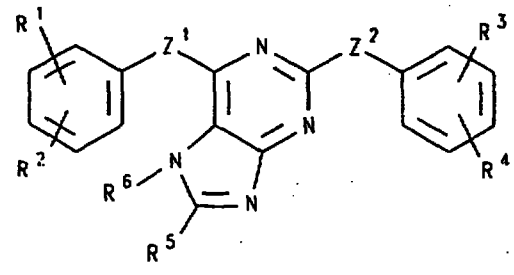
(I)



(II)



(III)



(IV)

wherein:

Z^1 and Z^2 are independently -O-, -N(R^{10})- or -OCH_2-;

R^1 and R^4 are each independently hydrogen, halo, alkyl, -OR^{10}, -C(O)OR^{10}, -C(O)N(R^{10})R^{11}, -N(R^{10})R^{11}, -N(R^{10})C(O)R^{10}, or -N(H)S(O)$_2R^{13}$;

R^2 is -C(NH)NH_2, -C(NH)N(H)OR^{10}, -C(NH)N(H)C(O)OR^{13}, -C(NH)N(H)C(O)R^{10}, -C(NH)N(H)S(O)$_2R^{13}$, or -C(NH)N(H)C(O)N(H)R^{10};

R^3 is halo, alkyl, haloalkyl, haloalkoxy, ureido, cyano, guanidino, -OR^{10}, -C(NH)NH_2, -C(NH)N(H)OR^{10}, -C(O)N(R^{10})R^{11}, -R^{12}-C(O)N(R^{10})R^{11}, -CH(OH)C(O)N(R^{10})R^{11}, -N(R^{10})R^{11}, -R^{12}-N(R^{10})R^{11}, -C(O)OR^{10}, -R^{12}-C(O)OR^{10}, -N(R^{10})C(O)R^{10}, (1,2)-tetrahydropyrimidinyl (optionally substituted by alkyl), (1,2)-imidazolyl (optionally substituted by alkyl), or (1,2)-imidazolinyl (optionally substituted by alkyl);

R^5 is hydrogen, halo, alkyl, cycloalkyl, haloakyl, aryl, aralkyl, alkylthio, hydroxy, mercapto,

alkoxy, or $-N(R^{10})R^{11}$;

R^6 is $-(C(R^7)(R^8))_n-R^9$ (where n is 1 to 4), hydrogen, alkyl, aryl (optionally substituted by halo, alkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, alkyl, aryl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl);

each R^7 is independently hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, cycloalkyl, cycloalkylalkyl, $-C(O)OR^{10}$, $-R^{12}-C(O)OR^{10}$, $-R^{12}-C(O)N(R^{10})R^{11}$, $-C(O)-R^{12}-N(R^{10})R^{11}$, $-R^{12}-C(O)R^{10}$, $-R^{12}-C(O)N(R^{10})N(R^{10})R^{11}$, $-R^{12}-C(R^{10})(OR^{10})-R^{12}-N(R^{10})(R^{11})$, $-C(R^{10})(OR^{10})C(O)OR^{11}$, $-R^{12}-C(R^{10})(C(O)OR^{10})_2$, $-C(R^{10})(N(R^{10})R^{11})C(O)OR^{10}$, $-R^{12}-C(R^{10})(N(R^{10})R^{11})C(O)OR^{10}$, $-C(R^{10})(OR^{10})R^{11}$, $-R^{12}-N(R^{10})R^{11}$, $-R^{12}-N(R^{10})C(O)OR^{13}$, $-R^{12}-N(R^{10})C(O)R^{11}$, $-R^{12}-N(R^{10})C(NR^{10})R^{13}$, $-R^{12}-N(R^{10})S(O)_2R^{13}$, $-R^{12}-N(R^{10})C(O)N(R^{10})R^{11}$, $-R^{12}-N(R^{10})C(NR^{10})N(R^{10})R^{11}$, $-R^{12}-N(R^{10})C(NR^{10})N(R^{10})N(R^{10})R^{11}$, $-R^{12}-N(R^{10})-R^{12}-C(R^{10})(N(R^{10})R^{11})C(O)OR^{10}$, $-R^{12}-N(R^{10})S(O)R^{11}$, $-R^{12}OR^{10}$, $-R^{12}-ON(R^{10})C(NR^{10})N(R^{10})R^{11}$, $-R^{12}-OS(O)_2OR^{10}$, $-R^{12}-P(O)(OR^{10})R^{11}$, $-R^{12}-OP(O)(OR^{10})_2$, $-R^{12}-P(O)(OR^{10})_2$, $-R^{12}-SR^{10}$, $-R^{12}-S-R^{12}-C(O)OR^{10}$, $-R^{12}-S-R^{12}-N(R^{10})R^{11}$, $-R^{12}-S-R^{12}-C(R^{10})(N(R^{10})R^{11})C(O)OR^{10}$, $-R^{12}-S-R^{12}-N(R^{10})C(O)OR^{10}$, $-R^{12}-S-R^{12}-N(R^{10})C(O)R^{10}$, $-R^{12}-S-S-R^{12}-C(R^{10})(N(R^{10})R^{11})C(O)OR^{10}$, $-R^{12}-SC(O)N(R^{10})R^{11}$, $-R^{12}-SC(S)N(R^{10})R^{11}$, $-R^{12}-S(O)R^{10}$, $-R^{12}-S(O)_2R^{13}$, $-R^{12}-S(O)OR^{10}$, $-R^{12}-S(O)_2OR^{10}$, $-R^{12}-S(O)_2N(R^{10})R^{11}$, $-R^{12}-S(O)(NR^{10})R^{11}$,

or each R^7 is aryl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, haloalkoxy, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})R^{11}$, $-C(O)OR^{10}$, $-C(O)N(R^{10})R^{11}$, $-S(O)_2OR^{10}$ and $-OP(O)(OR^{10})_2$),

or each R^7 is aralkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, haloalkoxy, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})R^{11}$, $-C(O)OR^{10}$, $-C(O)N(R^{10})R^{11}$, $-S(O)_2OR^{10}$ and $-OP(O)(OR^{10})_2$),

or each R^7 is heterocyclyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, haloalkoxy, aralkyl, $-OR^{10}$, $-C(O)OR^{10}$, $-N(R^{10})R^{11}$, $-C(O)N(R^{10})R^{11}$, $-S(O)_2OR^{10}$ and $-OP(O)(OR^{10})_2$),

or each R^7 is heterocyclylalkyl (where the heterocyclyl radical is optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, haloalkoxy, aralkyl, $-OR^{10}$, $-SR^{10}$, $-C(O)OR^{10}$, $-N(R^{10})R^{11}$, $-C(O)N(R^{10})R^{11}$), $-S(O)_2OR^{10}$ and $-OP(O)(OR^{10})_2$),

or each R^7 is adamantyl (optionally substituted by alkyl, halo, haloalkyl, haloalkoxy, $-OR^{10}$, $-SR^{10}$, $-C(O)OR^{10}$, $-N(R^{10})R^{11}$, $-C(O)N(R^{10})R^{11}$, $-S(O)_2OR^{10}$ and $-OP(O)(OR^{10})_2$),

* C L M S *

or each R^7 is adamantylalkyl (where the adamantyl radical is optionally substituted by alkyl, halo, haloalkyl, haloalkoxy, $-OR^{10}$, $-SR^{10}$, $-C(O)OR^{10}$, $-N(R^{10})R^{11}$, $-C(O)N(R^{10})R^{11}$, $-S(O)_2OR^{10}$ and $-OP(O)(OR^{10})_2$);

each R^8 is independently hydrogen, alkyl, cycloalkyl, or aryl;

R^9 is $-C(O)OR^{10}$ or $-C(O)N(R^{10})R^{11}$;

each R^{10} and R^{11} is independently hydrogen, alkyl, aryl (optionally substituted by halo, alkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, alkyl, aryl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl);

R^{12} is a straight or branched alkylene chain; and

R^{13} is alkyl, aryl (optionally substituted by halo, alkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, alkyl, aryl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl);

as a single stereoisomer or a mixture thereof; or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

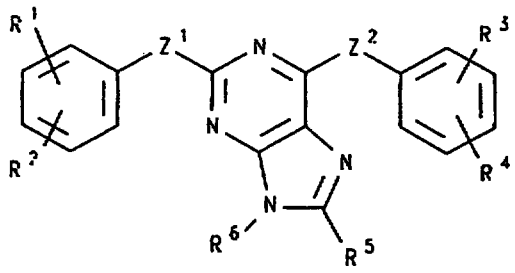
10. A method of treating a human having a disease-state characterized by thrombotic activity, which method comprises administering to a human in need thereof a therapeutically effective amount of a compound selected from the group consisting of the following formulae:

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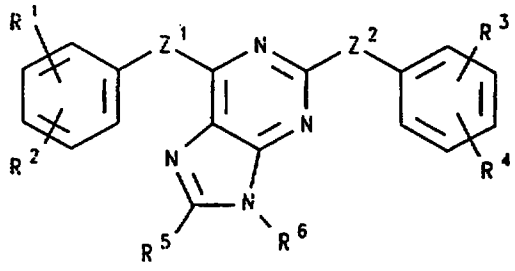
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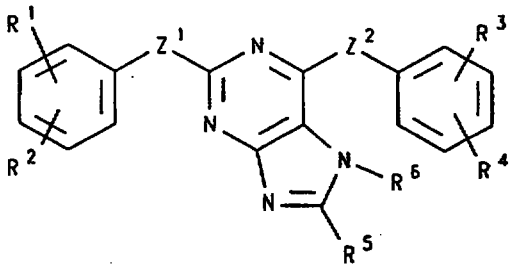
* C L M S *



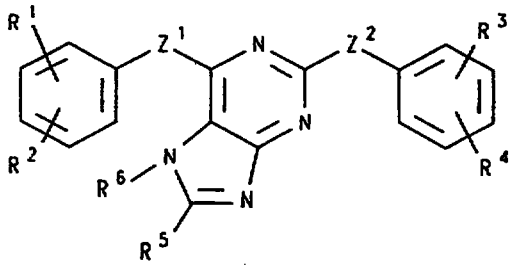
(I)



(II)



(III)



(IV)

wherein:

Z^1 and Z^2 are independently -O-, -N(R^{10})- or -OCH_2-;

R^1 and R^4 are each independently hydrogen, halo, alkyl, -OR^{10}, -C(O)OR^{10}, -C(O)N(R^{10})R^{11}, -N(R^{10})R^{11}, -N(R^{10})C(O)R^{10}, or -N(H)S(O)$_2R^{13}$;

R^2 is -C(NH)NH_2, -C(NH)N(H)OR^{10}, -C(NH)N(H)C(O)OR^{13}, -C(NH)N(H)C(O)R^{10}, -C(NH)N(H)S(O)$_2R^{13}$, or -C(NH)N(H)C(O)N(H)R^{10};

R^3 is halo, alkyl, haloalkyl, haloalkoxy, ureido, cyano, guanidino, -OR^{10}, -C(NH)NH_2, -C(NH)N(H)OR^{10}, -C(O)N(R^{10})R^{11}, -R^{12}-C(O)N(R^{10})R^{11}, -CH(OH)C(O)N(R^{10})R^{11}, -N(R^{10})R^{11}, -R^{12}-N(R^{10})R^{11}, -C(O)OR^{10}, -R^{12}-C(O)OR^{10}, -N(R^{10})C(O)R^{10}, (1,2)-tetrahydropyrimidinyl (optionally substituted by alkyl), (1,2)-imidazolyl (optionally substituted by alkyl), or (1,2)-imidazolinyl (optionally substituted by alkyl);

R^5 is hydrogen, halo, alkyl, cycloalkyl, haloakyl, aryl, aralkyl, alkylthio, hydroxy, mercapto,

alkoxy, or $-N(R^{10})R^{11}$;

R^6 is $-(C(R^7)(R^8))_n-R^9$ (where n is 1 to 4), hydrogen, alkyl, aryl (optionally substituted by halo, alkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, alkyl, aryl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl);

each R^7 is independently hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, cycloalkyl, cycloalkylalkyl, $-C(O)OR^{10}$, $-R^{12}-C(O)OR^{10}$, $-R^{12}-C(O)N(R^{10})R^{11}$, $-C(O)-R^{12}-N(R^{10})R^{11}$, $-R^{12}-C(O)R^{10}$, $-R^{12}-C(O)N(R^{10})N(R^{10})R^{11}$, $-R^{12}-C(R^{10})(OR^{10})-R^{12}-N(R^{10})(R^{11})$, $-C(R^{10})(OR^{10})C(O)OR^{11}$, $-R^{12}-C(R^{10})(C(O)OR^{10})_2$, $-C(R^{10})(N(R^{10})R^{11})C(O)OR^{10}$, $-R^{12}-C(R^{10})(N(R^{10})R^{11})C(O)OR^{10}$, $-C(R^{10})(OR^{10})R^{11}$, $-R^{12}-N(R^{10})R^{11}$, $-R^{12}-N(R^{10})C(O)OR^{13}$, $-R^{12}-N(R^{10})C(O)R^{11}$, $-R^{12}-N(R^{10})C(NR^{10})R^{13}$, $-R^{12}-N(R^{10})S(O)_2R^{13}$, $-R^{12}-N(R^{10})C(O)N(R^{10})R^{11}$, $-R^{12}-N(R^{10})C(NR^{10})N(R^{10})R^{11}$, $-R^{12}-N(R^{10})C(NR^{10})N(R^{10})N(R^{10})R^{11}$, $-R^{12}-N(R^{10})-R^{12}-C(R^{10})(N(R^{10})R^{11})C(O)OR^{10}$, $-R^{12}-N(R^{10})S(O)R^{11}$, $-R^{12}OR^{10}$, $-R^{12}-ON(R^{10})C(NR^{10})N(R^{10})R^{11}$, $-R^{12}-OS(O)_2OR^{10}$, $-R^{12}-P(O)(OR^{10})R^{11}$, $-R^{12}-OP(O)(OR^{10})_2$, $-R^{12}-P(O)(OR^{10})_2$, $-R^{12}-SR^{10}$, $-R^{12}-S-R^{12}-C(O)OR^{10}$, $-R^{12}-S-R^{12}-N(R^{10})R^{11}$, $-R^{12}-S-R^{12}-C(R^{10})(N(R^{10})R^{11})C(O)OR^{10}$, $-R^{12}-S-R^{12}-N(R^{10})C(O)OR^{10}$, $-R^{12}-S-R^{12}-N(R^{10})C(O)R^{10}$, $-R^{12}-S-S-R^{12}-C(R^{10})(N(R^{10})R^{11})C(O)OR^{10}$, $-R^{12}-SC(O)N(R^{10})R^{11}$, $-R^{12}-SC(S)N(R^{10})R^{11}$, $-R^{12}-S(O)R^{10}$, $-R^{12}-S(O)_2R^{13}$, $-R^{12}-S(O)OR^{10}$, $-R^{12}-S(O)_2OR^{10}$, $-R^{12}-S(O)_2N(R^{10})R^{11}$, $-R^{12}-S(O)(NR^{10})R^{11}$,

or each R^7 is aryl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, haloalkoxy, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})R^{11}$, $-C(O)OR^{10}$, $-C(O)N(R^{10})R^{11}$, $-S(O)_2OR^{10}$ and $-OP(O)(OR^{10})_2$),

or each R^7 is aralkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, haloalkoxy, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})R^{11}$, $-C(O)OR^{10}$, $-C(O)N(R^{10})R^{11}$, $-S(O)_2OR^{10}$ and $-OP(O)(OR^{10})_2$),

or each R^7 is heterocyclyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, haloalkoxy, aralkyl, $-OR^{10}$, $-C(O)OR^{10}$, $-N(R^{10})R^{11}$, $-C(O)N(R^{10})R^{11}$, $-S(O)_2OR^{10}$ and $-OP(O)(OR^{10})_2$),

or each R^7 is heterocyclylalkyl (where the heterocyclyl radical is optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, haloalkoxy, aralkyl, $-OR^{10}$, $-SR^{10}$, $-C(O)OR^{10}$, $-N(R^{10})R^{11}$, $-C(O)N(R^{10})R^{11}$), $-S(O)_2OR^{10}$ and $-OP(O)(OR^{10})_2$),

or each R^7 is adamantyl (optionally substituted by alkyl, halo, haloalkyl, haloalkoxy, $-OR^{10}$, $-SR^{10}$, $-C(O)OR^{10}$, $-N(R^{10})R^{11}$, $-C(O)N(R^{10})R^{11}$, $-S(O)_2OR^{10}$ and $-OP(O)(OR^{10})_2$),

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or each R^7 is adamantylalkyl (where the adamantyl radical is optionally substituted by alkyl, halo, haloalkyl, haloalkoxy, $-OR^{10}$, $-SR^{10}$, $-C(O)OR^{10}$, $-N(R^{10})R^{11}$, $-C(O)N(R^{10})R^{11}$, $-S(O)_2OR^{10}$ and $-OP(O)(OR^{10})_2$);

each R^8 is independently hydrogen, alkyl, cycloalkyl, or aryl;

R^9 is $-C(O)OR^{10}$ or $-C(O)N(R^{10})R^{11}$;

each R^{10} and R^{11} is independently hydrogen, alkyl, aryl (optionally substituted by halo, alkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, alkyl, aryl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl);

R^{12} is a straight or branched alkylene chain; and

R^{13} is alkyl, aryl (optionally substituted by halo, alkyl, hydroxy, alkoxy, aralkoxy, amino, dialkylamino, monoalkylamino, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl), or aralkyl (optionally substituted by halo, alkyl, aryl, hydroxy, alkoxy, aralkyl, amino, dialkylamino, monoalkylamino, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl, or dialkylaminocarbonyl);

as a single stereoisomer or a mixture thereof; or a pharmaceutically acceptable salt thereof.



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