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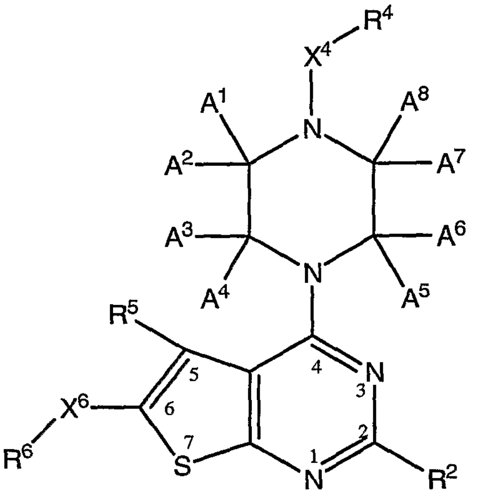
(54) Title: 4-PIPERAZINNYLTHIENO [2,3-D] PYRIMIDINE COMPOUNDS AS PLATELET AGGREGATION INHIBITORS



(I)

(57) Abstract: Compounds and pharmaceutically acceptable salts of the compounds are disclosed, wherein the compounds have the structure of Formula (I), wherein A^1, A^2, A^3, A^4, A^5, A^6, A^7, A^8, X^4, X^6, R^2, R^4, R^5, and R^6 are as defined in the detailed description of the invention. Corresponding pharmaceutical compositions, methods of treatment, methods of synthesis, and intermediates are also disclosed.

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4-PIPERAZINNYLTHIENO[2,3-D]PYRIMIDINE COMPOUNDS AS PLATELET AGGREGATION INHIBITORS

CROSS REFERENCE TO OTHER APPLICATIONS

This application claims priority to U.S. Provisional application number 60/665,316, filed March 25, 2005.

FIELD OF THE INVENTION

The present invention comprises a novel class of thieno[2,3-*d*]pyrimidine compounds having the structure of Formula I (including tautomers and salts of those compounds) and pharmaceutical compositions comprising a compound of Formula I. The present invention also comprises methods of treating a subject by administering a therapeutically effective amount of a compound of Formula I to the subject. In general, these compounds, in whole or in part, inhibit ADP-mediated platelet aggregation. The present invention further comprises methods for making the compounds of Formula I and corresponding intermediates.

BACKGROUND OF THE INVENTION

Thrombosis is a pathological process in which a platelet aggregate and/or a fibrin clot occludes a blood vessel. Arterial thrombosis may result in ischemic necrosis of the tissue supplied by the artery. Venous thrombosis may cause edema and inflammation in the tissue drained by the vein. Compounds that inhibit platelet function can be administered to a patient to decrease the risk of occlusive arterial events in patients suffering from or susceptible to atherosclerotic cardiovascular, cerebrovascular and peripheral arterial diseases. Commercially available drugs that inhibit platelet function typically fall within one of three classes of drugs that antagonize different molecular targets: (1) cycloxygenase inhibitors, such as aspirin (*see* Awtry, E.H. et al., *Circulation*, 2000, Vol. 101, pg. 1206); (2) glycoprotein IIb-IIIa antagonists, such as tirofiban (*see* Scarborough, R.M. et al., *Journal of Medicinal Chemistry,* 2000, Vol. 43, pg. 3453); and (3) P2Y12 receptor antagonists (also known as ADP receptor antagonists), such as the thienopyridine compounds ticlopidine and clopidogrel (*see* Quinn, M.J. et al., *Circulation*, 1999, Vol.100, pg.1667.

There are several disadvantages associated with use of the P2Y12 receptor antagonists ticlopidine and clopidogrel. First, although both compounds selectively inhibit platelet aggregation by blocking the P2Y12 receptor, such inhibition is irreversible and increases the bleeding risk to the patient. Second, both ticlopidine and clopidogrel each have a relatively slow onset of action. Both compounds apparently are prodrugs that first must be metabolized by the liver into the corresponding active metabolites. Third, a number of patients are resistant to treatment with clopidogrel. Such resistance may result, in whole or in part, from drug-drug interactions between clopidogrel and other drugs commonly administered to atherosclerotic patients. Fourth, both ticlopidine and clopidogrel have been associated with side-effects such as thrombocytopenia in some patients (*see* Bennett, C.L. et al., *New England Journal of Medicine*, 2000, Vol. 342, pg. 1773).

Other compounds have been reported in the literature as useful for the treatment of cardiovascular events such as thrombosis:

US2003/0153566 A1 (published August 14, 2003)describes a class of piperazine compounds as ADP receptor antagonists.

WIPO Int'l Publ. No. WO99/05144 A1 (published February 4, 1999) describes a class of triazolo[4,5-d]pyrimidine compounds as P2T antagonists.

WIPO Int'l Publ. No. WO99/36425 A1 (published July 22, 1999) describes a class of tricyclic compounds as ADP receptor antagonists.

WIPO Int'l Publ. No. WO01/57037 A1 (published August 9, 2001) describes a class of compounds including sulfonylureas as ADP receptor antagonists.

US 5,057,517 (granted October 15, 1991) describes a class of heteroaromatic compounds including 6-piperazinopurines as antidiabetic agents.

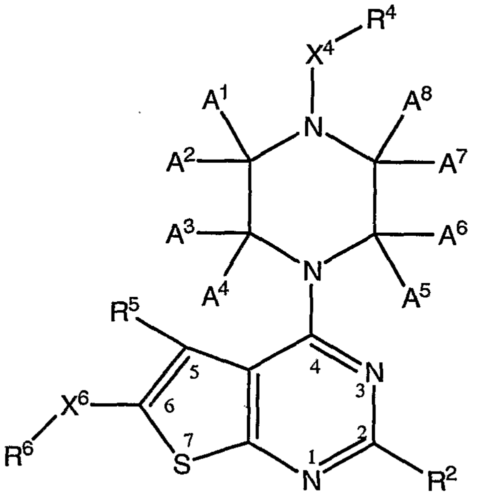
US 4,459,296 (granted July 10, 1984) describes a class of N-(benzimidazolyl, indolyl, purinyl or benzotriazolyl)-piperazine compounds as antihypertensive agents.

Humphries et al. describe several purine compounds as selective ADP receptor antagonists in an animal thrombosis model. *Trends in Pharmacological Sciences*, 1995, Vol. 16, pg. 179. These compounds are further described in Ingall, A.H et al., *Journal of Medicinal Chemistry*, 1999, Vol. 42, pg. 213.

Accordingly, a need still exists for new drug therapies for the treatment of subjects suffering from or susceptible to a platelet aggregation mediated condition. In particular, a need still exists for new P2Y12 antagonists having one or more improved properties (such as safety profile, efficacy, or physical properties) relative to currently available P2Y12 antagonists.

SUMMARY OF THE INVENTION

In one embodiment, the invention comprises a class of compounds (including the pharmaceutically acceptable salts of the compounds) having the structure of Formula I:



Formula I

wherein A^1, A^2, A^3, A^4, A^5, A^6, A^7, A^8, X^4, X^6, R^2, R^4, R^5, and R^6 are as defined in the detailed description of the invention.

In another embodiment, the invention comprises a pharmaceutical composition comprising a compound having the structure of Formula I.

In another embodiment, the invention comprises methods of treating a condition in a subject by administering to a subject a therapeutically effective amount of a compound having the structure of Formula I. The conditions that can be treated in accordance with the present invention include, but are not limited to, atherosclerotic cardiovascular diseases, cerebrovascular diseases and peripheral arterial diseases. Other conditions that can be treated in accordance with the present invention include hypertension and angiogenesis.

In another embodiment, the invention comprises methods for inhibiting platelet aggregation in a subject by administering to the subject a compound having a structure of Formula I.

In another embodiment, the invention comprises methods of making compounds having the structure of Formula I.

In another embodiment, the invention comprises intermediates useful in the synthesis of compounds having the structure of Formula I.

DETAILED DESCRIPTION OF THE INVENTION

This detailed description of embodiments is intended only to acquaint others skilled in the art with Applicants' inventions, its principles, and its practical application so that others skilled in the art may adapt and apply the inventions in their numerous forms, as they may be best suited to the requirements of a particular use. These inventions, therefore, are not limited to the embodiments described in this specification, and may be variously modified.

A. Abbreviations and Definitions

TABLE A - Abbreviations

1-HOAT	1-hydroxy-7-azabenzotriazole
1-HOBt	1-hydroxybenzotriazole hydrate
ADP	Adenosine diphosphate (the natural ligand of P2Y12)
AMP	Adenosine monophospate
ASA	Acetylsalicylic acid
ATP	Adenosine triphosphate
Bn	Benzyl group
Boc	*tert*-butoxycarbonyl
BOP-Cl	bis(2-oxo-3-oxazolidinyl)phosphinic chloride
Br	Broad
BSA	Bovine serum albumin
Cbz	benzyloxycarbonyl
CD_3OD	Deuterated methanol
$CDCl_3$	Deuterated chloroform
CDI	1,1'-carbonyldiimidazole
D	Doublet
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DCM	dichloromethane

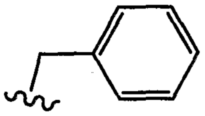
Dd	Doublet of doublets
DEPC	diethyl cyanophosphonate
DIEA	diisopropylethylamine
DMF	N,N-dimethylformamide
DMSO	dimethyl sulphoxide
DPBS	Dulbecco's Phosphate Buffered Saline
EBSS	Earle's Balanced Salt Solution
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EDTA	ethylenediaminetetraacetic acid
EGTA	ethyleneglycol-*bis*(β-aminoethyl)-N,N,N',N'-tetraacetic Acid
ESI	Electrospray Ionization for mass spectrometry
Et_3N	triethylamine
EtOAc	ethyl acetate
EtOH	ethanol
FBS	Fetal bovine serum
Fmoc	Fluorene methyloxycarbonyl
HATU	O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HBTU	O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate
HCl	Hydrochloric acid
HEK	Human embryonic kidney
HEPES	4-(2-hydroxyethyl)-1-Piperazineethane sulfonic acid
HRMS	High Resolution Mass Spectroscopy (electrospray ionization positive scan)
K_3PO_4	Potassium phosphate
LCMS	Liquid Chromatography – Mass Spectroscopy
LRMS	Low Resolution Mass Spectroscopy (electrospray or thermospray ionization positive scan)
LRMS (ES^-)	Low Resolution Mass Spectroscopy (electrospray ionization negative scan)
m	Multiplet
m/z	Mass spectrum peak
MEM	Minimum essential medium
MeOH	methanol
MHz	Megahertz
MS	Mass spectroscopy
NaH	Sodium hydride
NMM	N-methylmorpholine
NMP	1-methyl-2-pyrrolidinone
NMR	Nuclear Magnetic Resonance
PG	Protecting group. Exemplary protecting groups include Boc, Cbz, Fmoc and benzyl
Pg.	Page
PPP	Platelet poor plasma
PRP	Platelet rich plasma
q	Quartet
Rpm	Revolutions per minute
s	Singlet
t	Triplet
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	Thin layer chromatography
Vol.	Volume
δ	Chemical shift

The term "alkyl" refers to a linear or branched-chain saturated hydrocarbyl substituent (i.e., a substituent containing only carbon and hydrogen) containing in one embodiment, from about one to about twenty carbon atoms; in another embodiment from about one to about twelve carbon atoms; in another embodiment, from about one to about ten carbon atoms; in another embodiment, from about one to about six carbon atoms; and in another embodiment, from about one to about four carbon atoms. Examples of such substituents include methyl, ethyl, propyl (including n-propyl and isopropyl), butyl (including n-butyl, isobutyl, sec-butyl and tert-butyl), pentyl, iso-amyl, hexyl and the like.

The term "alkenyl" refers to a linear or branched-chain hydrocarbyl substituent containing one or more double bonds and from about two to about twenty carbon atoms; in another embodiment, from about two to about twelve carbon atoms; in another embodiment, from about two to about six carbon atoms; and in another embodiment, from about two to about four carbon atoms. Examples of alkenyl include ethenyl (also known as vinyl), allyl, propenyl (including 1-propenyl and 2-propenyl) and butenyl (including 1-butenyl, 2-butenyl and 3-butenyl). The term "alkenyl" embraces substituents having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations.

The term "alkynyl" refers to linear or branched-chain hydrocarbyl substituents containing one or more triple bonds and from about two to about twenty carbon atoms; in another embodiment, from about two to about twelve carbon atoms; in another embodiment, from about two to about six carbon atoms; and in another embodiment, from about two to about four carbon atoms. Examples of alkynyl substituents include ethynyl, propynyl (including 1-propynyl and 2-propynyl) and butynyl (including 1-butynyl, 2-butynyl and 3-butynyl).

The term "benzyl" refers to methyl radical substituted with phenyl, *i.e.*, the following structure: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The term "carbocyclyl" refers to a saturated cyclic (*i.e.*, "cycloalkyl"), partially saturated cyclic (*i.e.*, "cycloalkenyl"), or completely unsaturated (*i.e.*, "aryl") hydrocarbyl substituent containing from 3 to 14 carbon ring atoms ("ring atoms" are the atoms bound together to form the ring or rings of a cyclic substituent). A carbocyclyl may be a single ring, which typically contains from 3 to 6 ring atoms. Examples of such single-ring carbocyclyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, and phenyl. A carbocyclyl alternatively may be 2 or 3 rings fused together, such as naphthalenyl, tetrahydronaphthalenyl (also known as "tetralinyl"), indenyl, isoindenyl, indanyl, bicyclodecanyl, anthracenyl, phenanthrene, benzonaphthenyl (also known as "phenalenyl"), fluorenyl, and decalinyl.

The term "cycloalkyl" refers to a saturated carbocyclic substituent having three to about fourteen carbon atoms. In another embodiment, a cycloalkyl substituent has three to about eight carbon atoms. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term “cycloalkylalkyl” refers to alkyl substituted with cycloalkyl. Examples of cycloalkylalkyl include cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, and cyclohexylmethyl.

The term “cycloalkenyl” refers to a partially unsaturated carbocyclyl substituent. Examples of cycloalkenyl include cyclobutenyl, cyclopentenyl, and cyclohexenyl.

The term "aryl" refers to a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" refers to aromatic substituents such as phenyl, naphthyl and anthracenyl.

The term “arylalkyl” refers to alkyl substituted with aryl.

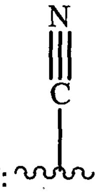
In some instances, the number of carbon atoms in a hydrocarbyl substituent (*e.g.*, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, etc.) is indicated by the prefix “C_x-C_y-,” wherein x is the minimum and y is the maximum number of carbon atoms in the substituent. Thus, for example, “C_1-C_6-alkyl” refers to an alkyl substituent containing from 1 to 6 carbon atoms. Illustrating further, C_3-C_6-cycloalkyl refers to saturated carbocyclyl containing from 3 to 6 carbon ring atoms.

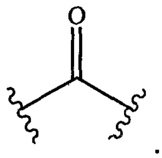
The term “hydrogen” refers to hydrogen substituent, and may be depicted as -H.

The term “hydroxy” refers to –OH. When used in combination with another term(s), the prefix “hydroxy” indicates that the substituent to which the prefix is attached is substituted with one or more hydroxy substituents. Compounds bearing a carbon to which one or more hydroxy substituents include, for example, alcohols, enols and phenol.

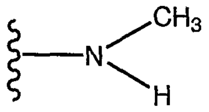
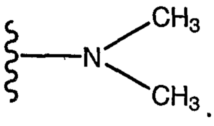
The term “hydroxyalkyl” refers to an alkyl that is substituted with at least one hydroxy substituent. Examples of hydroxyalkyl include hydroxymethyl, hydroxyethyl, hydroxypropyl and hydroxybutyl.

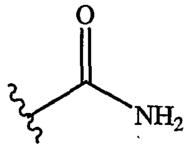
The term “nitro” means -NO_2.

The term “cyano” (also referred to as “nitrile”) -CN, which also may be depicted: .

The term “carbonyl” refers to -C(O)-, which also may be depicted as: .

The term “amino” refers to -NH_2.

The term “alkylamino” refers to an amino group, wherein at least one alkyl chain is bonded to the amino nitrogen in place of a hydrogen atom. Examples of alkylamino substituents include monoalkylamino such as methylamino (exemplified by the formula –$NH(CH_3)$), which may also be depicted:  and dialkylamino such as dimethylamino, (exemplified by the formula –$N((CH_3)_2)$, which may also be depicted: .

The term “aminocarbonyl” refers to -C(O)-NH_2, which also may be depicted as: .

The term “halogen” refers to fluorine (which may be depicted as -F), chlorine (which may be depicted as -Cl), bromine (which may be depicted as -Br), or iodine (which may be depicted as -I). In one embodiment, the halogen is chlorine. In another embodiment, the halogen is a fluorine.

The prefix “halo” indicates that the substituent to which the prefix is attached is substituted with one or more independently selected halogen substituents. For example, haloalkyl refers to an alkyl that is substituted with at least one halogen substituent. Where there is more than one hydrogen replaced with halogens, the halogens may be the identical or different. Examples of haloalkyls include chloromethyl, dichloromethyl, difluorochloromethyl, dichlorofluoromethyl, trichloromethyl, 1-bromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, difluoroethyl, pentafluoroethyl, difluoropropyl, dichloropropyl, and heptafluoropropyl. Illustrating further, “haloalkoxy” refers to an alkoxy that is substituted with at least one halogen substituent. Examples of haloalkoxy substituents include chloromethoxy, 1-bromoethoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy (also known as “perfluoromethyloxy”), and 2,2,2-trifluoroethoxy. It should be recognized that if a substituent is substituted by more than one halogen substituent, those halogen substituents may be identical or different (unless otherwise stated).

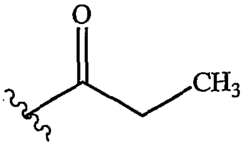
The prefix “perhalo” indicates that each hydrogen substituent on the substituent to which the prefix is attached is replaced with an independently selected halogen substituent. If all the halogen substituents are identical, the prefix may identify the halogen substituent. Thus, for example, the term “perfluoro” means that every hydrogen substituent on the substituent to which the prefix is attached is replaced with a fluorine substituent. To illustrate, the term “perfluoroalkyl” refers to an alkyl substituent wherein a fluorine substituent is in the place of each hydrogen substituent. Examples of perfluoroalkyl substituents include trifluoromethyl (-CF_3), perfluorobutyl, perfluoroisopropyl, perfluorododecyl, and perfluorodecyl. To illustrate further, the term “perfluoroalkoxy” refers to an alkoxy substituent wherein each hydrogen substituent is replaced with a fluorine substituent. Examples of perfluoroalkoxy substituents include trifluoromethoxy (-O-CF_3), perfluorobutoxy, perfluoroisopropoxy, perfluorododecoxy, and perfluorodecoxy.

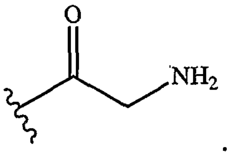
The term “oxo” refers to =O.

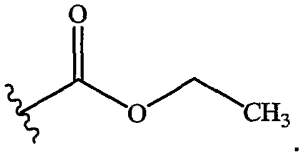
The term “oxy” refers to an ether substituent, and may be depicted as -O-.

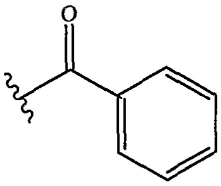
The term “alkoxy” refers to an alkyl linked to an oxygen, which may also be represented as –O-R, wherein the R represents the alkyl group. Examples of alkoxy include methoxy, ethoxy, propoxy and butoxy.

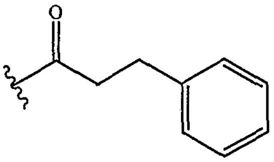
The term “alkylthio” refers to -S-alkyl. For example, “methylthio” is -S-CH_3. Other examples of alkylthio include ethylthio, propylthio, butylthio, and hexylthio.

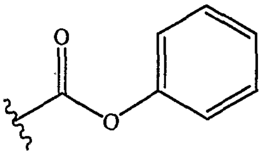
The term "alkylcarbonyl" refers to -C(O)-alkyl. For example, "ethylcarbonyl" may be depicted as:  . Examples of other alkylcarbonyl include methylcarbonyl, propylcarbonyl, butylcarbonyl, pentylcarbonyl, and hexylcarbonyl.

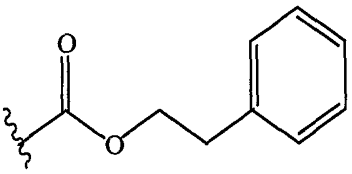
The term "aminoalkylcarbonyl" refers to -C(O)-alkyl-NH_2. For example, "aminomethylcarbonyl" may be depicted as:  .

The term "alkoxycarbonyl" refers to -C(O)-O-alkyl. For example, "ethoxycarbonyl" may be depicted as:  . Examples of other alkoxycarbonyl include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, pentoxycarbonyl, and hexyloxycarbonyl. In another embodiment, where the carbon atom of the carbonyl is attached to a carbon atom of a second alkyl, the resulting functional group is an ester.

The term "carbocyclylcarbonyl" refers to -C(O)-carbocyclyl. For example, "phenylcarbonyl" may be depicted as:  . Similarly, the term "heterocyclylcarbonyl," alone or in combination with another term(s), refers to -C(O)-heterocyclyl.

The term "carbocyclylalkylcarbonyl" refers to -C(O)-alkyl-carbocyclyl. For example, "phenylethylcarbonyl" may be depicted as:  . Similarly, the term "heterocyclylalkylcarbonyl," alone or in combination with another term(s), means -C(O)-alkyl-heterocyclyl.

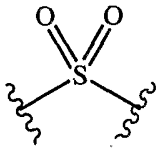
The term "carbocyclyloxycarbonyl," refers to -C(O)-O-carbocyclyl. For example, "phenyloxycarbonyl" may be depicted as:  .

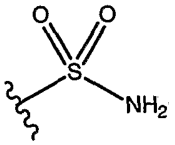
The term “carbocyclylalkoxycarbonyl” refers to -C(O)-O-alkyl-carbocyclyl. For example, “phenylethoxycarbonyl” may be depicted as:  .

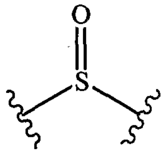
The terms “thio” and “thia” refer to a divalent sulfur atom and such a substituent may be depicted as -S-. For example, a thioether is represented as “alkyl-thio-alkyl” or, alternatively, alkyl-S-alkyl.

The term “thiol” refers to a sulfhydryl substituent, and may be depicted as -SH.

The term “thione” refers to =S.

The term “sulfonyl” refers to $-S(O)_2-$, which also may be depicted as:  . Thus, for example, “alkyl-sulfonyl-alkyl” refers to alkyl-$S(O)_2$-alkyl. Examples of alkylsulfonyl include methylsulfonyl, ethylsulfonyl, and propylsulfonyl.

The term “aminosulfonyl” refers to $-S(O)_2-NH_2$, which also may be depicted as:  .

The terms “sulfinyl” and “sulfoxido” refer to -S(O)-, which also may be depicted as:  . Thus, for example, “alkylsulfinylalkyl” or “alkylsulfoxidoalkyl” refers to alkyl-S(O)-alkyl. Exemplary alkylsulfinyl groups include methylsulfinyl, ethylsulfinyl, butylsulfinyl, and hexylsulfinyl.

The term “heterocyclyl” refers to a saturated, partially saturated, or completely unsaturated ring structure containing a total of 3 to 14 ring atoms. At least one of the ring atoms is a heteroatom (*i.e.,* oxygen, nitrogen, or sulfur), with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen, and sulfur.

A heterocyclyl may be a single ring, which typically contains from 3 to 7 ring atoms, more typically from 3 to 6 ring atoms, and even more typically 5 to 6 ring atoms. Examples of single-ring heterocyclyls include furanyl, dihydrofurnayl, tetradydrofurnayl, thiophenyl (also known as “thiofuranyl”), dihydrothiophenyl, tetrahydrothiophenyl, pyrrolyl, isopyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, isoimidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, dithiolyl, oxathiolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, thiodiazolyl, oxathiazolyl, oxadiazolyl (including oxadiazolyl, 1,2,4-oxadiazolyl (also known as “azoximyl”), 1,2,5-oxadiazolyl (also known as “furazanyl”), or 1,3,4-oxadiazolyl), oxatriazolyl (including 1,2,3,4-oxatriazolyl or 1,2,3,5-oxatriazolyl), dioxazolyl (including 1,2,3-dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, or

1,3,4-dioxazolyl), oxathiazolyl, oxathiolyl, oxathiolanyl, pyranyl (including 1,2-pyranyl or 1,4-pyranyl), dihydropyranyl, pyridinyl (also known as "azinyl"), piperidinyl, diazinyl (including pyridazinyl (also known as "1,2-diazinyl"), pyrimidinyl (also known as "1,3-diazinyl" or "pyrimidyl"), or pyrazinyl (also known as "1,4-diazinyl")), piperazinyl, triazinyl (including s-triazinyl (also known as "1,3,5-triazinyl"), as-triazinyl (also known 1,2,4-triazinyl), and v-triazinyl (also known as "1,2,3-triazinyl")), oxazinyl (including 1,2,3-oxazinyl, 1,3,2-oxazinyl, 1,3,6-oxazinyl (also known as "pentoxazolyl"), 1,2,6-oxazinyl, or 1,4-oxazinyl), isoxazinyl (including o-isoxazinyl or p-isoxazinyl), oxazolidinyl, isoxazolidinyl, oxathiazinyl (including 1,2,5-oxathiazinyl or 1,2,6-oxathiazinyl), oxadiazinyl (including 1,4,2-oxadiazinyl or 1,3,5,2-oxadiazinyl), morpholinyl, azepinyl, oxepinyl, thiepinyl, and diazepinyl.

A heterocyclyl alternatively may comprise 2 or 3 rings fused together, wherein at least one such ring contains a heteroatom as a ring atom (*e.g.*, nitrogen, oxygen, or sulfur). Examples of 2-fused-ring heterocyclyls include, indolizinyl, pyrindinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, naphthyridinyl, pyridopyridinyl (including pyrido[3,4-b]-pyridinyl, pyrido[3,2-b]-pyridinyl, or pyrido[4,3-b]-pyridinyl), and pteridinyl, indolyl, isoindolyl, indoleninyl, isoindazolyl, benzazinyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl, benzopyranyl, benzothiopyranyl, benzoxazolyl, indoxazinyl, anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl, benzisoxazinyl, and tetrahydroisoquinolinyl.

Other examples of fused-ring heterocyclyls include benzo-fused heterocyclyls, such as indolyl, isoindolyl (also known as "isobenzazolyl" or "pseudoisoindolyl"), indoleninyl (also known as "pseudoindolyl"), isoindazolyl (also known as "benzpyrazolyl"), benzazinyl (including quinolinyl (also known as "1-benzazinyl") or isoquinolinyl (also known as "2-benzazinyl")), phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl (including cinnolinyl (also known as "1,2-benzodiazinyl") or quinazolinyl (also known as "1,3-benzodiazinyl")), benzopyranyl (including "chromanyl" or "isochromanyl"), benzothiopyranyl (also known as "thiochromanyl"), benzoxazolyl, indoxazinyl (also known as "benzisoxazolyl"), anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl (also known as "coumaronyl"), isobenzofuranyl, benzothienyl (also known as "benzothiophenyl," "thionaphthenyl," or "benzothiofuranyl"), isobenzothienyl (also known as "isobenzothiophenyl," "isothionaphthenyl," or "isobenzothiofuranyl"), benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl (including 1,3,2-benzoxazinyl , 1,4,2-benzoxazinyl , 2,3,1-benzoxazinyl , or 3,1,4-benzoxazinyl), benzisoxazinyl (including 1,2-benzisoxazinyl or 1,4-benzisoxazinyl), tetrahydroisoquinolinyl , carbazolyl, xanthenyl, and acridinyl.

The term "heteroaryl" refers to an aromatic heterocyclyl containing from 5 to 14 ring atoms. A heteroaryl may be a single ring or 2 or 3 fused rings. Examples of heteroaryl substituents include 6-membered ring substituents such as pyridyl, pyrazyl, pyrimidinyl, and pyridazinyl; 5-membered ring substituents such as triazolyl, imidazyl, furanyl, thiophenyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, 1,2,3-, 1,2,4-, 1,2,5-, or 1,3,4-oxadiazolyl and isothiazolyl; 6/5-membered fused ring substituents such as benzothiofuranyl, isobenzothiofuranyl, benzisoxazolyl, benzoxazolyl, purinyl, and anthranilyl; and 6/6-membered fused rings such as quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, and 1,4-benzoxazinyl.

The term "heterocyclylalkyl" refers to alkyl substituted with a heterocyclyl.

The term "heterocycloalkyl" refers to a fully saturated heterocyclyl.

A substituent is "substitutable" if it comprises at least one carbon, sulfur, oxygen or nitrogen atom that is bonded to one or more hydrogen atoms. Thus, for example, hydrogen, halogen, and cyano do not fall within this definition.

If a substituent is described as being "substituted," a non-hydrogen substituent is in the place of a hydrogen substituent on a carbon or nitrogen of the substituent. Thus, for example, a substituted alkyl substituent is an alkyl substituent wherein at least one non-hydrogen substituent is in the place of a hydrogen substituent on the alkyl substituent. To illustrate, monofluoroalkyl is alkyl substituted with a fluoro substituent, and difluoroalkyl is alkyl substituted with two fluoro substituents. It should be recognized that if there are more than one substitutions on a substituent, each non-hydrogen substituent may be identical or different (unless otherwise stated).

If a substituent is described as being "optionally substituted," the substituent may be either (1) not substituted, or (2) substituted. If a carbon of a substituent is described as being optionally substituted with one or more of a list of substituents, one or more of the hydrogens on the carbon (to the extent there are any) may separately and/or together be replaced with an independently selected optional substituent. If a nitrogen of a substituent is described as being optionally substituted with one or more of a list of substituents, one or more of the hydrogens on the nitrogen (to the extent there are any) may each be replaced with an independently selected optional substituent.

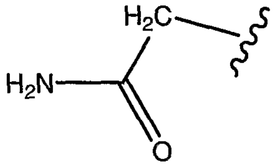
One exemplary substituent may be depicted as –NR'R," wherein R' and R" together with the nitrogen atom to which they are attached, may form a heterocyclic ring. The heterocyclic ring formed from R' and R" together with the nitrogen atom to which they are attached may be partially or fully saturated. In one embodiment, the heterocyclic ring consists of 3 to 7 atoms. In another embodiment, the heterocyclic ring is selected from the group consisting of pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, isoxazolyl, pyridyl and thiazolyl.

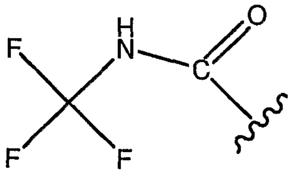
This specification uses the terms "substituent," "radical," and "group" interchangeably.

If a group of substituents are collectively described as being optionally substituted by one or more of a list of substituents, the group may include: (1) unsubstitutable substituents, (2) substitutable substituents that are not substituted by the optional substituents, and/or (3) substitutable substituents that are substituted by one or more of the optional substituents.

If a substituent is described as being optionally substituted with up to a particular number of non-hydrogen substituents, that substituent may be either (1) not substituted; or (2) substituted by up to that particular number of non-hydrogen substituents or by up to the maximum number of substitutable positions on the substituent, whichever is less. Thus, for example, if a substituent is described as a heteroaryl optionally substituted with up to 3 non-hydrogen substituents, then any heteroaryl with less than 3 substitutable positions would be optionally substituted by up to only as many non-hydrogen substituents as the heteroaryl has substitutable positions. To illustrate, tetrazolyl (which has only one substitutable position) would be optionally substituted with up to one non-hydrogen substituent. To illustrate further, if an amino nitrogen is described as being optionally substituted with up to 2 non-hydrogen substituents, then the nitrogen will be optionally substituted with up to 2 non-hydrogen substituents if the amino nitrogen is a primary nitrogen, whereas the amino nitrogen will be optionally substituted with up to only 1 non-hydrogen substituent if the amino nitrogen is a secondary nitrogen.

A prefix attached to a multi-moiety substituent only applies to the first moiety. To illustrate, the term "alkylcycloalkyl" contains two moieties: alkyl and cycloalkyl. Thus, the C_1-C_6- prefix on C_1-C_6-alkylcycloalkyl means that the alkyl moiety of the alkylcycloalkyl contains from 1 to 6 carbon atoms; the C_1-C_6- prefix does not describe the cycloalkyl moiety. To illustrate further, the prefix "halo" on haloalkoxyalkyl indicates that *only* the alkoxy moiety of the alkoxyalkyl substituent is substituted with one or more halogen substituents. If halogen substitution may *alternatively or additionally* occur on the alkyl moiety, the substituent would instead be described as "halogen-substituted alkoxyalkyl" rather than "haloalkoxyalkyl." And finally, if the halogen substitution may *only* occur on the alkyl moiety, the substituent would instead be described as "alkoxyhaloalkyl."

When a substituent is comprised of multiple moieties, unless otherwise indicated, it is the intention for the final moiety to serve as the point of attachment to the remainder of the molecule. For example, in a substituent A-B-C, moiety C is attached to the remainder of the molecule. In a substituent A-B-C-D, moiety D is attached to the remainder of the molecule. Similarly, in a substituent aminocarbonylmethyl, the methyl moiety is attached to the remainder of the molecule, where the substituent may also be be depicted as 

. In a substituent trifluoromethylaminocarbonyl, the carbonyl moiety is attached to the remainder of the molecule, where the substituent may also be depicted as 

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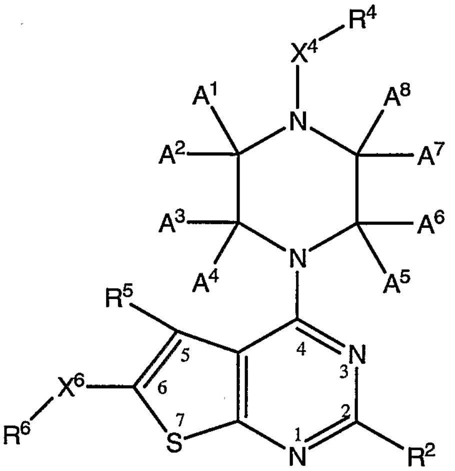
If substituents are described as being "independently selected" from a group, each substituent is selected independent of the other. Each substituent therefore may be identical to or different from the other substituent(s).

B. Compounds

The present invention comprises, in part, a novel class of thieno[2,3-*d*]pyrimidine compounds. These compounds are useful as inhibitors of platelet mediated aggregation.

The present invention is directed, in part, to a class of compounds and pharmaceutically acceptable salts of the compounds or tautomers are disclosed, wherein the compounds have the structure of Formula I:



Formula I

wherein:

A^1, A^2, A^3, A^4, A^5, A^6, A^7 and A^8 are independently selected from the group consisting of hydrogen, alkyl, and haloalkyl;

R^2 is selected from the group consisting of $-S(O)R^{2a}$, $-S(O)_2R^{2a}$, $-S(O)_2NR^{2a}R^{2b}$, $-SC(O)R^{2a}$, and $-SR^{2j}$; wherein:

R^{2a} and R^{2b} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl; wherein the R^{2a} and R^{2b} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl substituents may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, cyano, oxo, =S, nitro, $-R^{2d}$, $-C(O)R^{2d}$, $-C(S)R^{2d}$, $-C(O)OR^{2d}$, $-C(S)OR^{2d}$, $-C(O)SR^{2d}$, $-C(O)NR^{2d}R^{2e}$, $-C(S)NR^{2d}R^{2e}$, $-OR^{2d}$, $-OC(O)R^{2d}$, $-OC(S)R^{2d}$, $-OC(O)OR^{2d}$, $-OC(O)NR^{2d}R^{2e}$, $-OC(S)NR^{2d}R^{2e}$, $-NR^{2d}R^{2e}$, $-NR^{2d}C(O)R^{2e}$, $-NR^{2d}C(S)R^{2e}$, $-NR^{2d}C(O)OR^{2e}$, $-NR^{2d}C(S)OR^{2e}$, $-NR^{2d}S(O)_nR^{2e}$, $-NR^{2d}C(O)NR^{2e}R^{2f}$, $-S(O)_nR^{2d}$, $-S(O)_nNR^{2d}R^{2e}$, and $-SC(O)R^{2d}$;

n is 0, 1 or 2;

R^{2d}, R^{2e} and R^{2f} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl;

wherein the R^{2d}, R^{2e} and R^{2f} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl substituents may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, cyano, oxo, =S, nitro, $-R^{2g}$, $-C(O)R^{2g}$, $-C(S)R^{2g}$, $-C(O)OR^{2g}$, $-C(S)OR^{2g}$, $-C(O)SR^{2g}$, $-C(O)NR^{2g}R^{2h}$, $-C(S)NR^{2g}R^{2h}$, $-OR^{2g}$, $-OC(O)R^{2g}$, $-OC(S)R^{2g}$, $-OC(O)OR^{2g}$, $-OC(O)NR^{2g}R^{2h}$, $-OC(S)NR^{2g}R^{2h}$, $-NR^{2g}R^{2h}$, $-NR^{2g}C(O)R^{2h}$, $-NR^{2g}C(S)R^{2h}$, $-NR^{2g}C(O)OR^{2h}$, $-NR^{2g}C(S)OR^{2h}$, $-NR^{2g}S(O)_pR^{2h}$, $-NR^{2g}C(O)NR^{2h}R^{2i}$, $-S(O)_pR^{2g}$, $-S(O)_pNR^{2g}R^{2h}$, and $-SC(O)R^{2g}$;

p is 0, 1 or 2;

R^{2g}, R^{2h} and R^{2i} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl;

wherein the R^{2g}, R^{2h} and R^{2i} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl substituents may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxy, cyano, oxo, =S, nitro, alkyl, haloalkyl, hydroxyalkyl, carboxy, and alkoxy;

R^{2j} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl; wherein:

(a) the R^{2j} C_7-C_{20} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl substituent may be optionally substituted with one or more substituents independently selected from the group consisting of halogen and -R^{2m}; and

(b) the R^{2j} C_1-C_6 alkyl substituent is substituted with at least one substituent independently selected from the group consisting of chloro, bromo, iodo, and -R^{2m};

R^{2m} is selected from the group consisting of cyano, nitro, -NH_2, oxo, =S, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, -C(O)R^{2n}, -C(S)R^{2n}, -C(O)OR^{2n}, -C(S)OR^{2n}, -C(O)SR^{2n}, -C(O)N$R^{2n}R^{2o}$, -C(S)N$R^{2n}R^{2o}$, –OR^{2n}, -OC(O)R^{2n}, -OC(S)R^{2n}, -OC(O)OR^{2n}, -OC(O)N$R^{2n}R^{2o}$, -OC(S)N$R^{2n}R^{2o}$, -N$R^{2n}R^{2o}$, -NR^{2n}C(O)R^{2o}, -NR^{2n}C(S)R^{2o}, -NR^{2n}C(O)OR^{2o}, -NR^{2n}C(S)OR^{2o}, -NR^{2n}S$(O)_q R^{2o}$, -NR^{2n}C(O)N$R^{2o}R^{2p}$, -S$(O)_q R^{2n}$, -S$(O)_q$N$R^{2n}R^{2o}$, and -SC(O)R^{2n};

q is 0, 1 or 2;

R^{2n}, R^{2o} and R^{2p} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl;

wherein the R^{2m}, R^{2n}, R^{2o} and R^{2p} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl substituents may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, cyano, nitro, oxo, =S, -R^{2q}, -C(O)R^{2q}, -C(S)R^{2q}, -C(O)OR^{2q}, -C(S)OR^{2q}, -C(O)SR^{2q}, -C(O)N$R^{2q}R^{2r}$, -C(S)N$R^{2q}R^{2r}$, –OR^{2q}, -OC(O)R^{2r}, -OC(S)R^{2q},-OC(O)OR^{2q},-OC(O)N$R^{2q}R^{2r}$, -OC(S)N$R^{2q}R^{2r}$, -N$R^{2q}R^{2r}$, -NR^{2q}C(O)R^{2r}, -NR^{2q}C(S)R^{2r}, -NR^{2q}C(O)OR^{2r}, -NR^{2q}C(S)OR^{2r}, -NR^{2q}S$(O)_r R^{2r}$, -NR^{2q}C(O)N$R^{2r}R^{2s}$, -S$(O)_r R^{2q}$, -S$(O)_r$N$R^{2q}R^{2r}$, and -SC(O)R^{2q};

r is 0, 1 or 2;

R^{2q}, R^{2r} and R^{2s} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl; wherein the R^{2q}, R^{2r} and R^{2s} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl substituents may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxy, cyano, oxo, =S, -SH, nitro, alkyl, haloalkyl, hydroxyalkyl, carboxy, and alkoxy;

X^4 is selected from the group consisting of –C(O)-, -C(S)-, -S(O)- and –$S(O)_2$-;

R^4 is selected from the group consisting of -R^{4j}, -OR^{4j}, and -N$R^{4j}R^{4k}$;

wherein R^{4j} and R^{4k} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, cycloalkylalkyl, arylalkyl, heterocyclylalkyl, arylcycloalkyl, heterocyclylcycloalkyl, cycloalkylaryl, cycloalkylheterocyclyl, arylaryl, heterocyclylheterocyclyl, arylheterocyclyl, heterocyclylaryl, cycloalkoxyalkyl, heterocyclyloxyalkyl, aryloxyaryl, heterocyclyloxyheterocyclyl, aryloxyheterocyclyl, heterocyclyloxyaryl, arylcarbonylaryl, heterocyclylcarbonylheterocyclyl, aryloxyalkyl, arylcarbonylheterocyclyl, heterocyclylcarbonylaryl, arylcarbonylaminoalkyl, heterocyclylcarbonylaminoalkyl, arylcarbonylaminoalkyl, and heterocyclylcarbonylaminoalkyl;

wherein the R^{4j} and R^{4k} substituents may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyalkyl, oxo, =S, nitro, cyano, $-R^{4l}$, $-OR^{4l}$, $-C(O)R^{4l}$, $-C(O)OR^{4l}$, $-C(O)NR^{4l}R^{4m}$, $-OC(O)R^{4l}$, $-ONR^{4l}R^{4m}$, $-NR^{4l}R^{4m}$, $-NR^{4l}C(O)R^{4m}$, $-NR^{4l}S(O)_2R^{4m}$, $-S(O)_bR^{4l}$, $-SC(O)R^{4l}$ and $-SC(O)NR^{4l}R^{4m}$;

b is 0, 1 or 2;

R^{4l} and R^{4m} are independently selected from the group consisting of hydrogen, alkyl, haloalkyl, alkenyl, cycloalkyl, aryl and heterocyclyl;

wherein the R^{4l} and R^{4m} alkyl, haloalkyl, alkenyl, cycloalkyl, aryl and heterocyclyl substituents may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxy, cyano, oxo, =S, nitro, -SH, amino, alkyl, haloalkyl, hydroxyalkyl, carboxy, alkoxy, alkoxycarbonyl and alkylamino;

R^5 is selected from the group consisting of hydrogen, halogen, alkyl, haloalkyl, alkoxy and haloalkoxy;

X^6 represents a bond or is -C(O)-; wherein:

(a) when X^6 is –C(O)-, R^6 is selected from the group consisting of $-R^{6a}$ and $-OR^{6a}$;

(b) when X^6 represents a bond, R^6 is selected from the group consisting of halogen, cyano, $-R^{6a}$ and $-OR^{6a}$;

R^{6a} is selected from the group consisting of hydrogen, alkyl, cycloalkyl and aryl; and wherein the R^{6a} alkyl, cycloalkyl and aryl substituent may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxy, oxo, =S, cyano, alkyl, haloalkyl, hydroxyalkyl, cycloalkyl, carboxy, aryl and heterocyclyl.

In one embodiment of the compounds of Formula (I), A^1, A^2, A^3, A^4, A^5, A^6, A^7 and A^8 are each hydrogen. In another embodiment, A^1, A^2, A^4, A^5, A^6, A^7 and A^8 are each hydrogen and A^3 is methyl. In still another embodiment, A^2, A^3, A^4, A^5, A^6, A^7 and A^8 are each hydrogen and A^1 is methyl.

In another embodiment of the compounds of Formula (I), R^5 is selected from the group consisting of hydrogen, halogen, and alkyl, wherein the R^5 alkyl substituent may be optionally substituted as above. In still another embodiment, R^5 is selected from the group consisting of hydrogen, halogen and methyl. In still another embodiment, R^5 is hydrogen.

In another embodiment of the compounds of Formula (I), R^6 is selected from the group consisting of halogen, $-R^{6a}$ and $-OR^{6a}$, wherein R^{6a} is defined as provided in other embodiments herein. In one embodiment, R^6 is halogen. In another embodiment, R^6 is fluorine. In another embodiment, R^6 is chlorine. In another embodiment, R^6 is bromine. In another embodiment, R^6 is cyano.

In still another embodiment, X^6 represents a bond and R^6 is $-R^{6a}$, wherein R^{6a} is defined as provided in other embodiments herein. In still another embodiment, X^6 is -C(O)- and R^6 is $-OR^{6a}$, wherein R^{6a} is defined as provided in claim 1. In still another embodiment, R^6 is selected from the group consisting of $-R^{6a}$ and $-OR^{6a}$, and R^{6a} is selected from the group consisting of hydrogen, alkyl and aryl, wherein the R^{6a} alkyl and aryl substituents may be optionally substituted as provided in other embodiments herein. In still another embodiment, X^6 represents a bond, R^6 is $-R^{6a}$; and R^{6a} is hydrogen and alkyl, wherein the R^{6a} alkyl substituent may be optionally substituted as provided in other embodiments herein.

In still another embodiment, X^6 represents a bond, R^6 is $-R^{6a}$; and R^{6a} is hydrogen.

In still another embodiment, X^6 represents a bond, R^6 is $-R^{6a}$; and R^{6a} is selected from the group consisting of methyl, ethyl, propyl, butyl, pentyl, hexyl and phenyl. In still another embodiment, X^6 represents a bond, R^6 is $-R^{6a}$; and R^{6a} is selected from the group consisting of methyl, ethyl, propyl, butyl, pentyl, and hexyl. In still another embodiment, X^6 represents a bond, R^6 is $-R^{6a}$; and R^{6a} is selected from the group consisting of methyl, ethyl, propyl, butyl, and pentyl. In another embodiment, X^6 represents a bond, R^6 is $-R^{6a}$; and R^{6a} is unsubstituted alkyl.

In still another embodiment, X^6 represents a bond, R^6 is $-R^{6a}$; and R^{6a} is selected from the group consisting of methyl, ethyl, propyl, butyl, pentyl and hexyl, wherein said R^{6a} substituent is substituted with one or more halogen substituents. In still another embodiment, X^6 represents a bond, R^6 is $-R^{6a}$; and R^{6a} is selected from the group consisting of methyl, ethyl, propyl, butyl, pentyl and hexyl, wherein said R^{6a} substituent is substituted with one or more fluorine substituents. In another embodiment, X^6 represents a bond, R^6 is $-R^{6a}$; and R^{6a} is selected from the group consisting of methyl, ethyl, propyl, butyl, pentyl and hexyl, wherein said R^{6a} substituent is substituted with one or more chlorine substituents. In another embodiment, X^6 represents a bond, R^6 is $-R^{6a}$; and R^{6a} is selected from the group consisting of methyl, ethyl, propyl, butyl, pentyl and hexyl, wherein said R^{6a} substituent is substituted with one or more bromine substituents.

In another embodiment of the compounds of Formula (I), X^4 is –C(O)-.

In another embodiment of the compounds of Formula (I), R^4 is selected from the group consisting of -R^{4j}, -OR^{4j}, and -N$R^{4j}R^{4k}$; wherein R^{4j} and R^{4k} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, cycloalkylalkyl, arylalkyl, heterocyclylalkyl, arylcycloalkyl, heterocyclylcycloalkyl, cycloalkylaryl, cycloalkylheterocyclyl, arylaryl, heterocyclylheterocyclyl, arylheterocyclyl, heterocyclylaryl, cycloalkoxyalkyl, heterocyclyloxyalkyl, aryloxyaryl, heterocyclyloxyheterocyclyl, aryloxyheterocyclyl, heterocyclyloxyaryl, arylcarbonylaryl, heterocyclylcarbonylheterocyclyl, aryloxyalkyl, arylcarbonylheterocyclyl, heterocyclylcarbonylaryl, arylcarbonylaminoalkyl, heterocyclylcarbonylaminoalkyl, arylcarbonylaminoalkyl, and heterocyclylcarbonylaminoalkyl; and, wherein the R^{4j} and R^{4k} substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (I), R^4 is -R^{4j}; wherein R^{4j} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, cycloalkylalkyl, arylalkyl, heterocyclylalkyl, arylcycloalkyl, heterocyclylcycloalkyl, cycloalkylaryl, cycloalkylheterocyclyl, arylaryl, heterocyclylheterocyclyl, arylheterocyclyl, heterocyclylaryl, cycloalkoxyalkyl, heterocyclyloxyalkyl, aryloxyaryl, heterocyclyloxyheterocyclyl, aryloxyheterocyclyl, heterocyclyloxyaryl, arylcarbonylaryl, heterocyclylcarbonylheterocyclyl, aryloxyalkyl, arylcarbonylheterocyclyl, heterocyclylcarbonylaryl, arylcarbonylaminoalkyl, heterocyclylcarbonylaminoalkyl, arylcarbonylaminoalkyl, and heterocyclylcarbonylaminoalkyl; and, wherein the R^{4j} substituent may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyalkyl, oxo, =S, nitro, cyano, -R^{4l}, -OR^{4l}, -C(O)R^{4l}, -C(O)OR^{4l}, -C(O)N$R^{4l}R^{4m}$, -OC(O)R^{4l}, -ON$R^{4l}R^{4m}$, -N$R^{4l}R^{4m}$, -NR^{4l}C(O)R^{4m}, -NR^{4l}S(O)$_2R^{4m}$, -S(O)$_b R^{4l}$, -SC(O)R^{4l} and -SC(O)N$R^{4l}R^{4m}$; wherein b is 0, 1 or 2 and R^{4l} and R^{4m} are independently selected from the group consisting of hydrogen, alkyl, haloalkyl, alkenyl, cycloalkyl, aryl and heterocyclyl wherein the R^{4l} and R^{4m} alkyl, haloalkyl, alkenyl, cycloalkyl, aryl and heterocyclyl substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (I), R^4 is -OR^{4j}; wherein R^{4j} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, cycloalkylalkyl, arylalkyl, heterocyclylalkyl, arylcycloalkyl, heterocyclylcycloalkyl, cycloalkylaryl, cycloalkylheterocyclyl, arylaryl, heterocyclylheterocyclyl, arylheterocyclyl, heterocyclylaryl, cycloalkoxyalkyl, heterocyclyloxyalkyl, aryloxyaryl, heterocyclyloxyheterocyclyl, aryloxyheterocyclyl, heterocyclyloxyaryl, arylcarbonylaryl, heterocyclylcarbonylheterocyclyl, aryloxyalkyl, arylcarbonylheterocyclyl, heterocyclylcarbonylaryl, arylcarbonylaminoalkyl, heterocyclylcarbonylaminoalkyl, arylcarbonylaminoalkyl, and heterocyclylcarbonylaminoalkyl; and, wherein the R^{4j} substituent may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyalkyl, oxo, =S, nitro, cyano, $-R^{4l}$, $-OR^{4l}$, $-C(O)R^{4l}$, $-C(O)OR^{4l}$, $-C(O)NR^{4l}R^{4m}$, $-OC(O)R^{4l}$, $-ONR^{4l}R^{4m}$, $-NR^{4l}R^{4m}$, $-NR^{4l}C(O)R^{4m}$, $-NR^{4l}S(O)_2R^{4m}$, $-S(O)_bR^{4l}$, $-SC(O)R^{4l}$ and $-SC(O)NR^{4l}R^{4m}$; wherein b is 0, 1 or 2 and R^{4l} and R^{4m} are independently selected from the group consisting of hydrogen, alkyl, haloalkyl, alkenyl, cycloalkyl, aryl and heterocyclyl wherein the R^{4l} and R^{4m} alkyl, haloalkyl, alkenyl, cycloalkyl, aryl and heterocyclyl substituents may be optionally substituted as provided in other embodiments herein.

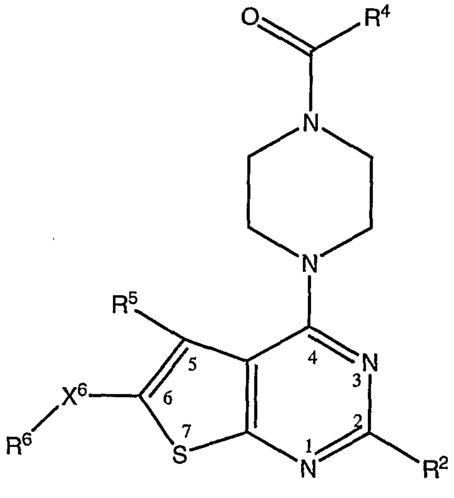
In another embodiment of the compounds of Formula (I), R^4 is $-NR^{4j}R^{4k}$; wherein R^{4j} and R^{4k} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, cycloalkylalkyl, arylalkyl, heterocyclylalkyl, arylcycloalkyl, heterocyclylcycloalkyl, cycloalkylaryl, cycloalkylheterocyclyl, arylaryl, heterocyclylheterocyclyl, arylheterocyclyl, heterocyclylaryl, cycloalkoxyalkyl, heterocyclyloxyalkyl, aryloxyaryl, heterocyclyloxyheterocyclyl, aryloxyheterocyclyl, heterocyclyloxyaryl, arylcarbonylaryl, heterocyclylcarbonylheterocyclyl, aryloxyalkyl, arylcarbonylheterocyclyl, heterocyclylcarbonylaryl, arylcarbonylaminoalkyl, heterocyclylcarbonylaminoalkyl, arylcarbonylaminoalkyl, and heterocyclylcarbonylaminoalkyl; and, wherein the R^{4j} and R^{4k} substituents may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyalkyl, oxo, =S, nitro, cyano, $-R^{4l}$, $-OR^{4l}$, $-C(O)R^{4l}$, $-C(O)OR^{4l}$, $-C(O)NR^{4l}R^{4m}$, $-OC(O)R^{4l}$, $-ONR^{4l}R^{4m}$, $-NR^{4l}R^{4m}$, $-NR^{4l}C(O)R^{4m}$, $-NR^{4l}S(O)_2R^{4m}$, $-S(O)_bR^{4l}$, $-SC(O)R^{4l}$ and $-SC(O)NR^{4l}R^{4m}$; wherein b is 0, 1 or 2 and R^{4l} and R^{4m} are independently selected from the group consisting of hydrogen, alkyl, haloalkyl, alkenyl, cycloalkyl, aryl and heterocyclyl wherein the R^{4l} and R^{4m} alkyl, haloalkyl, alkenyl, cycloalkyl, aryl and heterocyclyl substituents may be optionally substituted as provided in other embodiments herein. In another embodiment, R^{4k} is hydrogen and R^{4j} is as provided above.

In another embodiment of the compounds of Formula (I), R^4 is $-R^{4j}$; and R^{4j} is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl, wherein the R^{4j} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl substituents may be optionally substituted as provided in other embodiments herein. In another embodiment, R^4 is $-R^{4j}$; and R^{4j} is selected from the group consisting of phenyl, oxadiazolyl, thiazolyl, pyridinyl, cyclopropyl, cyclobutyl, methyl, ethyl and fluorenyl; wherein the R^{4l} substituents may be optionally substituted as provided in other embodiments herein. In still another embodiment, R^4 is $-OR^{4j}$; and R^{4j} is selected from the group consisting of methyl and ethyl, wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein. In still another embodiment, R^4 is $-NR^{4j}R^{4j}$; and R^{4j} is methyl and R^{4l} is hydrogen, wherein the R^{4a} methyl may be optionally substituted as provided in other embodiments herein.

In still another embodiment of the compounds of Formula (I), R^4 is $-R^{4j}$; and R^{4l} is selected from the group consisting of methyl, ethyl, propyl, butyl, pentyl and hexyl, wherein said R^{4a} substituent is substituted with one or more halogen substituents. In still another embodiment, R^4 is $-R^{4j}$; and R^{4j} is selected from the group consisting of methyl, ethyl, propyl, butyl, pentyl and hexyl, wherein said R^{4j} substituent is substituted with one or more fluorine substituents. In another embodiment, R^4 is $-R^{4j}$; and R^{4j} is selected from the group consisting of methyl, ethyl, propyl, butyl, pentyl and hexyl, wherein said R^{4j} substituent is substituted with one or more chlorine substituents. In another embodiment, R^4 is $-R^{4j}$; and R^{4j} is selected from the group consisting of methyl, ethyl, propyl, butyl, pentyl and hexyl, wherein said R^{4a} substituent is substituted with one or more bromine substituents.

In another embodiment of the compounds of Formula (I), R^2 is $-S(O)R^{2a}$, wherein R^{2a} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl and may be optionally substituted as provided in other embodiments herein. In still another embodiment, R^2 is $-S(O)_2R^{2a}$, wherein R^{2a} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl and may be optionally substituted as provided in other embodiments herein. In still another embodiment, R^2 is $-S(O)_2NR^{2a}R^{2b}$, wherein R^{2a} and R^{2b} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl and each may be optionally substituted as provided in other embodiments herein. In still another embodiment, R^2 is $-SC(O)R^{2a}$, wherein R^{2a} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl and may be optionally substituted as provided in other embodiments herein. In still another embodiment, R^2 is $-SR^{2j}$, wherein R^{2j} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl and may be optionally substituted as provided in other embodiments herein.

Another class of compounds of specific interest includes compounds, and pharmaceutically acceptable salts of the compounds, wherein the compounds have the structure of Formula II:



Formula II

wherein:

R^2 is selected from the group consisting of $-S(O)R^{2a}$, $-S(O)_2R^{2a}$, $-S(O)_2NR^{2a}R^{2b}$, $-SC(O)R^{2a}$, and $-SR^{2j}$; wherein:

R^{2a} and R^{2b} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl;

wherein the R^{2a} and R^{2b} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl substituents may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, cyano, oxo, =S, nitro, $-R^{2d}$, $-C(O)R^{2d}$, $-C(S)R^{2d}$, $-C(O)OR^{2d}$, $-C(S)OR^{2d}$, $-C(O)SR^{2d}$,

$-C(O)NR^{2d}R^{2e}$, $-C(S)NR^{2d}R^{2e}$, $-OR^{2d}$, $-OC(O)R^{2d}$, $-OC(S)R^{2d}$, $-OC(O)OR^{2d}$, $-OC(O)NR^{2d}R^{2e}$, $-OC(S)NR^{2d}R^{2e}$, $-NR^{2d}R^{2e}$, $-NR^{2d}C(O)R^{2e}$, $-NR^{2d}C(S)R^{2e}$, $-NR^{2d}C(O)OR^{2e}$, $-NR^{2d}C(S)OR^{2e}$, $-NR^{2d}S(O)_nR^{2e}$, $-NR^{2d}C(O)NR^{2e}R^{2f}$, $-S(O)_nR^{2d}$, $-S(O)_nNR^{2d}R^{2e}$, and $-SC(O)R^{2d}$;

n is 0, 1 or 2;

R^{2d}, R^{2e} and R^{2f} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl;

wherein the R^{2d}, R^{2e} and R^{2f} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl substituents may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, cyano, oxo, =S, nitro, $-R^{2g}$, $-C(O)R^{2g}$, $-C(S)R^{2g}$, $-C(O)OR^{2g}$, $-C(S)OR^{2g}$, $-C(O)SR^{2g}$, $-C(O)NR^{2g}R^{2h}$, $-C(S)NR^{2g}R^{2h}$, $-OR^{2g}$, $-OC(O)R^{2g}$, $-OC(S)R^{2g}$, $-OC(O)OR^{2g}$, $-OC(O)NR^{2g}R^{2h}$,

$-OC(S)NR^{2g}R^{2h}$, $-NR^{2g}R^{2h}$, $-NR^{2g}C(O)R^{2h}$, $-NR^{2g}C(S)R^{2h}$, $-NR^{2g}C(O)OR^{2h}$, $-NR^{2g}C(S)OR^{2h}$, $-NR^{2g}S(O)_pR^{2h}$, $-NR^{2g}C(O)NR^{2h}R^{2i}$, $-S(O)_pR^{2g}$, $-S(O)_pNR^{2g}R^{2h}$, and $-SC(O)R^{2g}$;

p is 0, 1 or 2;

R^{2g}, R^{2h} and R^{2i} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl;

wherein the R^{2g}, R^{2h} and R^{2i} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl substituents may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxy, cyano, oxo, =S, nitro, alkyl, haloalkyl, hydroxyalkyl, carboxy, and alkoxy;

R^{2j} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl; wherein:

(a) the R^{2j} C_7-C_{20} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl substituent may be optionally substituted with one or more substituents independently selected from the group consisting of halogen and $-R^{2m}$; and

(b) the R^{2j} C_1-C_6 alkyl substituent is substituted with at least one substituent independently selected from the group consisting of chloro, bromo, iodo, and $-R^{2m}$;

R^{2m} is selected from the group consisting of cyano, nitro, $-NH_2$, oxo, =S, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, $-C(O)R^{2n}$, $-C(S)R^{2n}$, $-C(O)OR^{2n}$, $-C(S)OR^{2n}$, $-C(O)SR^{2n}$, $-C(O)NR^{2n}R^{2o}$,

$-C(S)NR^{2n}R^{2o}$, $-OR^{2n}$, $-OC(O)R^{2n}$, $-OC(S)R^{2n}$, $-OC(O)OR^{2n}$, $-OC(O)NR^{2n}R^{2o}$, $-OC(S)NR^{2n}R^{2o}$, $-NR^{2n}R^{2o}$,

$-NR^{2n}C(O)R^{2o}$, $-NR^{2n}C(S)R^{2o}$, $-NR^{2n}C(O)OR^{2o}$, $-NR^{2n}C(S)OR^{2o}$, $-NR^{2n}S(O)_qR^{2o}$, $-NR^{2n}C(O)NR^{2o}R^{2p}$,
$-S(O)_qR^{2n}$, $-S(O)_qNR^{2n}R^{2o}$, and $-SC(O)R^{2n}$;

q is 0, 1 or 2;

R^{2n}, R^{2o} and R^{2p} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl;

wherein the R^{2m}, R^{2n}, R^{2o} and R^{2p} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl substituents may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, cyano, nitro, oxo, =S, $-R^{2q}$, $-C(O)R^{2q}$, $-C(S)R^{2q}$, $-C(O)OR^{2q}$, $-C(S)OR^{2q}$, $-C(O)SR^{2q}$, $-C(O)NR^{2q}R^{2r}$, $-C(S)NR^{2q}R^{2r}$, $-OR^{2q}$, $-OC(O)R^{2r}$, $-OC(S)R^{2q}$, $-OC(O)OR^{2q}$, $-OC(O)NR^{2q}R^{2r}$, $-OC(S)NR^{2q}R^{2r}$,
$-NR^{2q}R^{2r}$, $-NR^{2q}C(O)R^{2r}$, $-NR^{2q}C(S)R^{2r}$, $-NR^{2q}C(O)OR^{2r}$, $-NR^{2q}C(S)OR^{2r}$, $-NR^{2q}S(O)_rR^{2r}$, $-NR^{2q}C(O)NR^{2r}R^{2s}$, $-S(O)_rR^{2q}$, $-S(O)_rNR^{2q}R^{2r}$, and $-SC(O)R^{2q}$;

r is 0, 1 or 2;

R^{2q}, R^{2r} and R^{2s} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl; wherein the R^{2q}, R^{2r} and R^{2s} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl substituents may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxy, cyano, oxo, =S, -SH, nitro, alkyl, haloalkyl, hydroxyalkyl, carboxy, and alkoxy;

R^4 is selected from the group consisting of $-R^{4j}$, $-OR^{4j}$, and $-NR^{4j}R^{4k}$;

wherein R^{4j} and R^{4k} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, cycloalkylalkyl, arylalkyl, arylalkenyl, heterocyclylalkyl, arylcycloalkyl, heterocyclylcycloalkyl, cycloalkylaryl, cycloalkylheterocyclyl, arylaryl, heterocyclylheterocyclyl, arylheterocyclyl, heterocyclylaryl, cycloalkoxyalkyl, heterocyclyloxyalkyl, aryloxyaryl, heterocyclyloxyheterocyclyl, aryloxyheterocyclyl, heterocyclyloxyaryl, arylcarbonylaryl, heterocyclylcarbonylheterocyclyl, aryloxyalkyl, arylcarbonylheterocyclyl, heterocyclylcarbonylaryl, arylcarbonylaminoalkyl, heterocyclylcarbonylaminoalkyl, arylcarbonylaminoalkyl, alkoxyaryl, alkoxyalkyl, heterocyclylcarbonylaminoalkyl, haloalkoxyaryl, alkoxycarbonylalkyl, alkoxycarbonylaryl, alkoxyheterocyclyl;

wherein the R^{4j} and R^{4k} substituents may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyalkyl, oxo, =S, nitro, cyano, $-R^{4l}$, $-OR^{4l}$, $-C(O)R^{4l}$, $-C(O)OR^{4l}$, $-C(O)NR^{4l}R^{4m}$, $-OC(O)R^{4l}$, $-ONR^{4l}R^{4m}$, $-NR^{4l}R^{4m}$, $-NR^{4l}C(O)R^{4m}$,
$-NR^{4l}S(O)_2R^{4m}$, $-S(O)_bR^{4l}$, $-SC(O)R^{4l}$ and $-SC(O)NR^{4l}R^{4m}$;

b is 0, 1 or 2;

R^{4l} and R^{4m} are independently selected from the group consisting of hydrogen, alkyl, haloalkyl, alkenyl, cycloalkyl, aryl and heterocyclyl;

wherein the R^{4l} and R^{4m} alkyl, haloalkyl, alkenyl, cycloalkyl, aryl and heterocyclyl substituents may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxy, cyano, oxo, =S, nitro, -SH, amino, alkyl, haloalkyl, hydroxyalkyl, carboxy, alkoxy, alkoxycarbonyl and alkylamino;

R^5 is selected from the group consisting of hydrogen, halogen, alkyl, haloalkyl, alkoxy and haloalkoxy;

X^6 represents a bond or is -C(O)-; wherein:

(a) when X^6 is –C(O)-, R^6 is selected from the group consisting of -R^{6a} and -OR^{6a};

(b) when X^6 represents a bond, R^6 is selected from the group consisting of halogen, cyano, -R^{6a} and -OR^{6a};

R^{6a} is selected from the group consisting of hydrogen, alkyl, cycloalkyl and aryl; and wherein the R^{6a} alkyl, cycloalkyl and aryl substituent may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, oxo, =S, cyano, alkyl, haloalkyl, hydroxyalkyl, cycloalkyl, aryl and heterocyclyl.

In another embodiment of the compounds of Formula (II), R^5 is selected from the group consisting of hydrogen, halogen, alkyl, and alkoxy, wherein the R^5 alkyl and alkoxy substituents may be optionally substituted as provided in other embodiments herein. In another embodiment, R^5 is selected from the group consisting of hydrogen, halogen, and alkyl, wherein the R^5 alkyl substituent may be optionally substituted as above. In still another embodiment, R^5 is selected from the group consisting of hydrogen, halogen and methyl. In still another embodiment, R^5 is hydrogen.

In another embodiment of the compounds of Formula (II), R^6 is selected from the group consisting of halogen, –R^{6a} and –OR^{6a}, wherein R^{6a} is defined as provided in other embodiments herein. In one embodiment, R^6 is halogen. In another embodiment, R^6 is fluorine. In another embodiment, R^6 is chlorine. In another embodiment, R^6 is bromine. In another embodiment, R^6 is cyano.

In still another embodiment of Formula (II), X^6 represents a bond and R^6 is –R^{6a}, wherein R^{6a} is defined as provided in other embodiments herein. In still another embodiment, X^6 is –C(O)- and R^6 is –OR^{6a}, wherein R^{6a} is defined as provided in claim 1. In still another embodiment, R^6 is selected from the group consisting of –R^{6a} and –OR^{6a}, and R^{6a} is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl and heterocyclyl, wherein the R^{6a} alkyl, cycloalkyl, aryl and heterocyclyl substituents may be optionally substituted as provided in other embodiments herein. In still another embodiment, R^6 is selected from the group consisting of –R^{6a} and –OR^{6a}, and R^{6a} is selected from the group consisting of hydrogen, alkyl and aryl, wherein the R^{6a} alkyl and aryl substituents may be optionally substituted as provided in other embodiments herein. In still another embodiment, X^6 represents a bond, R^6 is –R^{6a}; and R^{6a} is hydrogen and alkyl, wherein the R^{6a} alkyl substituent may be optionally substituted as provided in other embodiments herein.

In still another embodiment of Formula (II), X^6 represents a bond, R^6 is $-R^{6a}$; and R^{6a} is hydrogen.

In still another embodiment of Formula (II), X^6 represents a bond, R^6 is $-R^{6a}$; and R^{6a} is selected from the group consisting of methyl, ethyl, propyl, butyl, pentyl, hexyl and phenyl. In still another embodiment, X^6 represents a bond, R^6 is $-R^{6a}$; and R^{6a} is selected from the group consisting of methyl, ethyl, propyl, butyl, pentyl, and hexyl. In still another embodiment, X^6 represents a bond, R^6 is $-R^{6a}$; and R^{6a} is selected from the group consisting of methyl, ethyl, propyl, butyl, and pentyl. In another embodiment, X^6 represents a bond, R^6 is $-R^{6a}$; and R^{6a} is unsubstituted alkyl.

In still another embodiment of Formula (II), X^6 represents a bond, R^6 is $-R^{6a}$; and R^{6a} is selected from the group consisting of methyl, ethyl, propyl, butyl, pentyl and hexyl, wherein said R^{6a} substituent is substituted with one or more halogen substituents. In still another embodiment, X^6 represents a bond, R^6 is $-R^{6a}$; and R^{6a} is selected from the group consisting of methyl, ethyl, propyl, butyl, pentyl and hexyl, wherein said R^{6a} substituent is substituted with one or more fluorine substituents. In another embodiment, X^6 represents a bond, R^6 is $-R^{6a}$; and R^{6a} is selected from the group consisting of methyl, ethyl, propyl, butyl, pentyl and hexyl, wherein said R^{6a} substituent is substituted with one or more chlorine substituents. In another embodiment, X^6 represents a bond, R^6 is $-R^{6a}$; and R^{6a} is selected from the group consisting of methyl, ethyl, propyl, butyl, pentyl and hexyl, wherein said R^{6a} substituent is substituted with one or more bromine substituents.

In another embodiment of the compounds of Formula (II), R^4 is selected from the group consisting of $-R^{4j}$, $-OR^{4j}$, and $-NR^{4j}R^{4k}$; and R^{4j} and R^{4k} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl, wherein the R^{4j} and R^{4k} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl substituents may be optionally substituted as provided in other embodiments herein. In another embodiment, R^4 is selected from the group consisting of $-R^{4j}$, $-OR^{4j}$, and $-NR^{4j}R^{4k}$; R^{4j} is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, and heterocyclyl, wherein the R^{4j} alkyl, cycloalkyl, aryl, and heterocyclyl substituents may be optionally substituted as provided in other embodiments herein; and R^{4k} is selected from the group consisting of hydrogen and alkyl, wherein the R^{4k} alkyl substituent may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is selected from the group consisting of $-R^{4j}$, $-OR^{4j}$, and $-NR^{4j}R^{4k}$; and R^{4j} and R^{4k} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, cycloalkylalkyl, arylalkyl, heterocyclylalkyl, arylcycloalkyl, heterocyclylcycloalkyl, cycloalkylaryl, cycloalkylheterocyclyl, arylaryl, heterocyclylheterocyclyl, arylheterocyclyl, heterocyclylaryl, cycloalkoxyalkyl, heterocyclyloxyalkyl, aryloxyaryl, heterocyclyloxyheterocyclyl, aryloxyheterocyclyl, heterocyclyloxyaryl, arylcarbonylaryl, heterocyclylcarbonylheterocyclyl, aryloxyalkyl, arylcarbonylheterocyclyl, heterocyclylcarbonylaryl, arylcarbonylaminoalkyl, heterocyclylcarbonylaminoalkyl, arylcarbonylaminoalkyl, and heterocyclylcarbonylaminoalkyl; wherein the R^{4j} and R^{4k} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, cycloalkylalkyl, arylalkyl, heterocyclylalkyl, arylcycloalkyl, heterocyclylcycloalkyl, cycloalkylaryl, cycloalkylheterocyclyl, arylaryl, heterocyclylheterocyclyl, arylheterocyclyl, heterocyclylaryl, cycloalkoxyalkyl, heterocyclyloxyalkyl, aryloxyaryl, heterocyclyloxyheterocyclyl, aryloxyheterocyclyl, heterocyclyloxyaryl, arylcarbonylaryl, heterocyclylcarbonylheterocyclyl, aryloxyalkyl, arylcarbonylheterocyclyl, heterocyclylcarbonylaryl, arylcarbonylaminoalkyl, heterocyclylcarbonylaminoalkyl, arylcarbonylaminoalkyl, and heterocyclylcarbonylaminoalkyl substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is selected from the group consisting of $-R^{4j}$, $-OR^{4j}$, and $-NR^{4j}R^{4k}$; and R^{4j} and R^{4k} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, cycloalkylalkyl, arylalkyl, heterocyclylalkyl, arylcycloalkyl, heterocyclylcycloalkyl, cycloalkylaryl, cycloalkylheterocyclyl, arylaryl, heterocyclylheterocyclyl, arylheterocyclyl, heterocyclylaryl, cycloalkoxyalkyl, heterocyclyloxyalkyl, aryloxyaryl, heterocyclyloxyheterocyclyl, aryloxyheterocyclyl, heterocyclyloxyaryl, arylcarbonylaryl, heterocyclylcarbonylheterocyclyl, aryloxyalkyl, arylcarbonylheterocyclyl, heterocyclylcarbonylaryl, arylcarbonylaminoalkyl, heterocyclylcarbonylaminoalkyl, arylcarbonylaminoalkyl, and heterocyclylcarbonylaminoalkyl; wherein the R^{4j} and R^{4k} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, cycloalkylalkyl, arylalkyl, heterocyclylalkyl, arylcycloalkyl, heterocyclylcycloalkyl, cycloalkylaryl, cycloalkylheterocyclyl, arylaryl, heterocyclylheterocyclyl, arylheterocyclyl, heterocyclylaryl, cycloalkoxyalkyl, heterocyclyloxyalkyl, aryloxyaryl, heterocyclyloxyheterocyclyl, aryloxyheterocyclyl, heterocyclyloxyaryl, arylcarbonylaryl, heterocyclylcarbonylheterocyclyl, aryloxyalkyl, arylcarbonylheterocyclyl, heterocyclylcarbonylaryl, arylcarbonylaminoalkyl, heterocyclylcarbonylaminoalkyl, arylcarbonylaminoalkyl, and heterocyclylcarbonylaminoalkyl substituents may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyalkyl, oxo, =S, nitro, cyano, $-R^{4l}$, $-OR^{4l}$, $-C(O)R^{4l}$, $-C(O)OR^{4l}$, $-C(O)NR^{4l}R^{4m}$, $-OC(O)R^{4l}$, $-ONR^{4l}R^{4m}$, $-NR^{4l}R^{4m}$, $-NR^{4l}C(O)R^{4m}$, $-NR^{4l}S(O)_2R^{4m}$, $-SR^{4l}$, $-S(O)R^{4l}$, $-S(O)_2R^{4l}$, $-SC(O)R^{4l}$ and $-SC(O)NR^{4l}R^{4m}$; wherien R^{4l} and R^{4m} are independently selected from the group consisting of hydrogen, alkyl, haloalkyl, alkenyl, cycloalkyl, aryl and heterocyclyl; and wherein the R^{4l} and R^{4m} alkyl, haloalkyl, alkenyl, cycloalkyl, aryl and heterocyclyl substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is $-NR^{4j}R^{4k}$; wherein R^{4j} and R^{4k} are independently selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, phenyl, phenylphenyl, phenylmethyl, phenylethyl, phenylpropyl, and phenylbutyl; and wherein the R^{4j} and R^{4k} methyl, ethyl, propyl, butyl, phenyl, phenylphenyl, phenylmethyl, phenylethyl, phenylpropyl, and phenylbutyl may be optionally substituted as provided in claim 2.

In another embodiment of the compounds of Formula (II), R^4 is $-NR^{4j}R^{4k}$; wherein R^{4j} and R^{4k} are independently selected from the group consisting of hydrogen, phenylmethyl and phenylphenyl; and wherein the R^{4j} and R^{4k} phenylmethyl and phenylphenyl may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is $-R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of alkyl, aryl, heterocyclyl, arylaryl, arylalkyl, heterocyclylalkyl, arylcycloalkyl, cycloalkylaryl, arylheterocyclyl, aryloxyaryl, heterocyclyloxyaryl, arylcarbonylaryl, and arylcarbonylaminoalkyl; and wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is $-R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of $(C_1\text{-}C_6)$-alkyl, $(C_3\text{-}C_{10})$-aryl, $(C_3\text{-}C_{14})$-heterocyclyl, $(C_3\text{-}C_{10})$-aryl -$(C_1\text{-}C_6)$-alkyl, $(C_3\text{-}C_{14})$-heterocyclyl-$(C_1\text{-}C_6)$-alkyl, $(C_3\text{-}C_{10})$-aryl-$(C_3\text{-}C_6)$-cycloalkyl, $(C_3\text{-}C_6)$-cycloalkyl-$(C_3\text{-}C_{10})$-aryl, $(C_3\text{-}C_{10})$-aryl-$(C_3\text{-}C_{14})$-heterocyclyl, $(C_3\text{-}C_{10})$-aryl-O-$(C_3\text{-}C_{10})$-aryl, $(C_3\text{-}C_{10})$-aryl-$(C_3\text{-}C_{10})$-aryl, $(C_3\text{-}C_{14})$-heterocyclyl-O-$(C_3\text{-}C_{10})$-aryl, $(C_3\text{-}C_{10})$-aryl-C(O)-$(C_3\text{-}C_{10})$-aryl, $(C_3\text{-}C_{10})$-aryl-O-$(C_1\text{-}C_6)$-alkyl, and $(C_3\text{-}C_{10})$-aryl-C(O)-amino-$(C_1\text{-}C_6)$-alkyl; wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is $-R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of methyl, ethyl, propyl, butyl, ethenyl, propenyl, butenyl, propynyl, butynyl, pentynyl, hexynyl, phenyl, naphthyl, anthracenyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, tetrahydrofuranyl, furanyl, dioxolanyl, imidazolidinyl, imidazolynyl, imidazolyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiophenyl, thiazolyl, thiadiazolyl, triazolyl, piperidinyl, pyridinyl, piperazinyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, morpholinyl, dioxanyl, tetrahydro-2H-pyranyl, 2H-pyranyl, 4H-pyranyl, thiomorpholinyl, indolyl, dihydrobenzofuranyl, quinolinyl and fluorenyl; and wherein the R^{4j} substituents may be may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is $-R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of phenylphenyl, phenylnaphthyl, phenylanthracenyl, naphthylphenyl, naphthylnaphthyl, naphthylanthracenyl, anthracenylphenyl, anthracenylnaphthyl and anthracenylanthracenyl; and wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is $-R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of phenylmethyl, phenylethyl, phenylpropyl, phenylbutyl, naphthylmethyl, naphthylethyl, naphthylpropyl, naphthylbutyl, anthracenylmethyl, anthracenylethyl, anthracenylpropyl, anthracenylbutyl, phenylcyclopropyl, phenylcyclobutyl, phenylcyclopentyl, phenylcyclohexyl, naphthylcyclopropyl, naphthylcyclobutyl, naphthylcyclopentyl, naphthylcyclohexyl, anthracenylcyclopropyl, anthracenylcyclobutyl, anthracenylcyclopentyl, anthracenylcyclohexyl, cyclopropylphenyl, cyclopropylnaphthyl, cyclopropylanthracenyl, cyclobutylphenyl, cyclobutylnaphthyl, cyclobutylanthracenyl, cyclopentylphenyl, cyclopentylnaphthyl, cyclopentylanthracenyl, cyclohexylphenyl, cyclohexylnaphthyl, cyclohexylanthracenyl, phenylphenylmethyl, phenylphenylethyl, phenylphenylpropyl, phenylphenylbutyl, diphenylmethyl, diphenylethyl, diphenylpropyl and diphenylbutyl; and wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is $-R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of phenyloxymethyl, phenyloxyethyl, phenyloxypropyl, phenyloxybutyl, naphthyloxymethyl, naphthyloxyethyl, naphthyloxypropyl, naphthyloxybutyl, anthracenyloxymethyl, anthracenyloxyethyl, anthracenyloxypropyl, anthracenyloxybutyl, methoxyphenyl, ethoxyphenyl, propoxyphenyl, butoxyphenyl, methoxynaphthyl, ethoxynaphthyl, propoxynaphthyl, butoxynaphthyl, phenyloxyphenyl, phenyloxynaphthyl, phenyloxyanthracenyl, naphthyloxyphenyl, naphthyloxynaphthyl, naphthyloxyanthracenyl, anthracenyloxyphenyl, anthracenyloxynaphthyl and anthracenyloxyanthracenyl; wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is $-R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of phenylcarbonylphenyl, phenylcarbonylnaphthyl, phenylcarbonylanthracenyl, naphthylcarbonylphenyl, naphthylcarbonylnaphthyl, naphthylcarbonylanthracenyl, anthracenylcarbonylphenyl, anthracenylcarbonylnaphthyl, anthracenylcarbonylanthracenyl, phenylcarbonylaminomethyl, phenylcarbonylaminoethyl, phenylcarbonylaminopropyl, phenylcarbonylaminobutyl, naphthylcarbonylaminomethyl, naphthylcarbonylaminoethyl, naphthylcarbonylaminopropyl, naphthylcarbonylaaminobutyl, anthracenylcarbonylaminomethyl, anthracenylcarbonylaminoethyl, anthracenylcarbonylaminopropyl and anthracenylcarbonylaminobutyl; and wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is $-R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of pyrrolidinylmethyl, pyrrolidinylethyl, pyrrolidinylpropyl, pyrrolidinylbutyl, pyrrolinylmethyl, pyrrolinylethyl, pyrrolinylpropyl, pyrrolinylbutyl, pyrrolylmethyl, pyrrolylethyl, pyrrolylpropyl, pyrrolylbutyl, tetrahydrofuranylmethyl, tetrahydrofuranylethyl, tetrahydrofuranylpropyl, tetrahydrofuranylbutyl, furanylmethyl, furanylethyl, furanylpropyl, furanylbutyl, dioxolanylmethyl, dioxolanylethyl, dioxolanylpropyl, dioxolanylbutyl, imidazolidinylmethyl, imidazolidinylethyl, imidazolidinylpropyl, imidazolidinylbutyl, imidazolynylmethyl, imidazolynylethyl, imidazolynylpropyl, imidazolynylbutyl, imidazolylmethyl, imidazolylethyl, imidazolylpropyl, imidazolylbutyl, pyrazolidinylmethyl, pyrazolidinylethyl, pyrazolidinylpropyl, pyrazolidinylbutyl, pyrazolinylmethyl, pyrazolinylethyl, pyrazolinylpropyl, pyrazolinylbutyl, pyrazolylmethyl, pyrazolylethyl, pyrazolylpropyl, pyrazolylbutyl, oxazolylmethyl, oxazolylethyl, oxazolylpropyl, oxazolylbutyl, isoxazolylmethyl, isoxazolylethyl, isoxazolylpropyl, isoxazolylbutyl, oxadiazolylmethyl, oxadiazolylethyl, oxadiazolylpropyl, oxadiazolylbutyl, thiophenylmethyl, thiophenylethyl, thiophenylpropyl, thiophenylbutyl, thiazolylmethyl, thiazolylethyl, thiazolylpropyl, thiazolylbutyl, thiadiazolylmethyl, thiadiazolylethyl, thiadiazolylpropyl, thiadiazolylbutyl, triazolylmethyl, triazolylethyl, triazolylpropyl, triazolylbutyl, piperidinylmethyl, piperidinylethyl, piperidinylpropyl, piperidinylbutyl, pyridinylmethyl, pyridinylethyl, pyridinylpropyl, pyridinylbutyl, piperazinylmethyl, piperazinylethyl, piperazinylpropyl, piperazinylbutyl, pyrazinylmethyl, pyrazinylethyl, pyrazinylpropyl, pyrazinylbutyl, pyrimidinylmethyl, pyrimidinylethyl, pyrimidinylpropyl, pyrimidinylbutyl, pyridazinylmethyl, pyridazinylethyl, pyridazinylpropyl, pyridazinylbutyl, triazinylmethyl, triazinylethyl, triazinylpropyl, triazinylbutyl, morpholinylmethyl, morpholinylethyl, morpholinylpropyl, morpholinylbutyl, dioxanylmethyl, dioxanylethyl, dioxanylpropyl, dioxanylbutyl, tetrahydro-2H-pyranylmethyl, tetrahydro-2H-pyranylethyl, tetrahydro-2H-pyranylpropyl, tetrahydro-2H-pyranylbutyl, 2H-pyranylmethyl, 2H-pyranylethyl, 2H-pyranylpropyl, 2H-pyranylbutyl, 4H-pyranylmethyl, 4H-pyranylethyl, 4H-pyranylpropyl, 4H-pyranylbutyl, thiomorpholinylmethyl, thiomorpholinylethyl, thiomorpholinylpropyl, thiomorpholinylbutyl, quinolinylmethyl, quinolinylethyl, quinolinylpropyl, quinolinylbutyl, fluorenylmethyl, fluorenylethyl, fluorenylpropyl and fluorenylbutyl; and wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is $-R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of phenylpyrrolidinyl, naphthylpyrrolidinyl, anthracenylpyrrolidinyl, phenylpyrrolinyl, naphthylpyrrolinyl, anthracenylpyrrolinyl, phenylpyrrolyl, naphthylpyrrolyl, anthracenylpyrrolyl, phenyltetrahydrofuranyl, naphthyltetrahydrofuranyl, anthracenyltetrahydrofuranyl, phenylfuranyl, naphthylfuranyl, anthracenylfuranyl, phenyldioxolanyl, naphthyldioxolanyl, anthracenyldioxolanyl, phenylimidazolidinyl, naphthylimidazolidinyl, anthracenylimidazolidinyl, phenylimidazolynyl, naphthylimidazolynyl, anthracenylimidazolynyl, phenylimidazolyl, naphthylimidazolyl, anthracenylimidazolyl, phenylpyrazolidinyl, naphthylpyrazolidinyl, anthracenylpyrazolidinyl, phenylpyrazolinyl, naphthylpyrazolinyl, anthracenylpyrazolinyl, phenylpyrazolyl, naphthylpyrazolyl, anthracenylpyrazolyl, phenyloxazolyl, naphthyloxazolyl, anthracenyloxazolyl, phenylisoxazolyl, naphthylisoxazolyl, anthracenylisoxazolyl, phenyl-oxadiazolyl, naphthyl-oxadiazolyl, anthracenyl-oxadiazolyl, phenylthiophenyl, naphthylthiophenyl, anthracenylthiophenyl, phenylthiazolyl, naphthylthiazolyl, anthracenylthiazolyl, phenylthiadiazolyl, naphthylthiadiazolyl, anthracenylthiadiazolyl, phenyltriazolyl, naphthyltriazolyl, anthracenyltriazolyl, phenylpiperidinyl, naphthylpiperidinyl, anthracenylpiperidinyl, phenylpyridinyl, naphthylpyridinyl, anthracenylpyridinyl, phenylpiperazinyl, naphthylpiperazinyl, anthracenylpiperazinyl, phenylpyrazinyl, naphthylpyrazinyl, anthracenylpyrazinyl, phenylpyrimidinyl, naphthylpyrimidinyl, anthracenylpyrimidinyl, phenylpyridazinyl, naphthylpyridazinyl, anthracenylpyridazinyl, phenyltriazinyl, naphthyltriazinyl, anthracenyltriazinyl, phenylmorpholinyl, naphthylmorpholinyl, anthracenylmorpholinyl, phenyldioxanyl, naphthyldioxanyl, anthracenyldioxanyl, phenyltetrahydro-2H-pyranyl, naphthyltetrahydro-2H-pyranyl, anthracenyltetrahydro-2H-pyranyl, phenyl-2H-pyranyl, naphthyl-2H-pyranyl, anthracenyl-2H-pyranyl, phenyl-4H-pyranyl, naphthyl-4H-pyranyl, anthracenyl-4H-pyranyl, phenylthiomorpholinyl, naphthylthiomorpholinyl, anthracenylthiomorpholinyl, phenylquinolinyl, naphthylquinolinyl, anthracenylquinolinyl, phenylfluorenyl, naphthylfluorenyl and anthracenylfluorenyl; and wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is $-R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of pyrrolidinyloxyphenyl, pyrrolidinyloxynaphthyl, pyrrolidinyloxyanthracenyl, pyrrolinyloxyphenyl, pyrrolinyloxynaphthyl, pyrrolinyloxyanthracenyl, pyrrolyloxyphenyl, pyrrolyloxynaphthyl, pyrrolyloxyanthracenyl, tetrahydrofuranyloxyphenyl, tetrahydrofuranyloxynaphthyl, tetrahydrofuranyloxyanthracenyl, furanyloxyphenyl, furanyloxynaphthyl, furanyloxyanthracenyl, dioxolanyloxyphenyl, dioxolanyloxynaphthyl, dioxolanyloxyanthracenyl, imidazolidinyloxyphenyl, imidazolidinyloxynaphthyl,imidazolidinyloxyanthracenyl, imidazolynyloxyphenyl, imidazolynyloxynaphthyl, imidazolynyloxyanthracenyl, imidazolyloxyphenyl, imidazolyloxynaphthyl, imidazolyloxyanthracenyl, pyrazolidinyloxyphenyl, pyrazolidinyloxynaphthyl, pyrazolidinyloxyanthracenyl, pyrazolinyloxyphenyl, pyrazolinyloxynaphthyl, pyrazolinyloxyanthracenyl, pyrazolyloxyphenyl, pyrazolyloxynaphthyl, pyrazolyloxyanthracenyl, oxazolyloxyphenyl, oxazolyloxynaphthyl, oxazolyloxyanthracenyl, isoxazolyloxyphenyl, isoxazolyloxynaphthyl, isoxazolyloxyanthracenyl, oxadiazolyloxyphenyl, oxadiazolyloxynaphthyl, oxadiazolyloxyanthracenyl, thiophenyloxyphenyl, thiophenyloxynaphthyl, thiophenyloxyanthracenyl, thiazolyloxyphenyl, thiazolyloxynaphthyl, thiazolyloxyanthracenyl, thiadiazolyloxyphenyl, thiadiazolyloxynaphthyl, thiadiazolyloxyanthracenyl, triazolyloxyphenyl, triazolyloxynaphthyl, triazolyloxyanthracenyl, piperidinyloxyphenyl, piperidinyloxynaphthyl, piperidinyloxyanthracenyl, pyridinyloxyphenyl, pyridinyloxynaphthyl, pyridinyloxyanthracenyl, piperazinyloxyphenyl, piperazinyloxynaphthyl, piperazinyloxyanthracenyl, pyrazinyloxyphenyl, pyrazinyloxynaphthyl, pyrazinyloxyanthracenyl, pyrimidinyloxyphenyl, pyrimidinyloxynaphthyl, pyrimidinyloxyanthracenyl, pyridazinyloxyphenyl, pyridazinyloxynaphthyl, pyridazinyloxyanthracenyl, triazinyloxyphenyl, triazinyloxynaphthyl, triazinyloxyanthracenyl, morpholinyloxyphenyl, morpholinyloxynaphthyl, morpholinyloxyanthracenyl, dioxanyloxyphenyl, dioxanyloxynaphthyl, dioxanyloxyanthracenyl, tetrahydro-2H-pyranyloxyphenyl, tetrahydro-2Hpyranyloxynaphthyl, tetrahydro-2H-pyranyloxyanthracenyl, 2H-pyranyloxy phenyl, 2H-pyranyloxy naphthyl, 2H-pyranyloxy anthracenyl, 4H-pyranyloxyphenyl, 4H-pyranyloxynaphthyl, 4H-pyranyloxyanthracenyl, thiomorpholinyloxyphenyl, thiomorpholinyloxynaphthyl, thiomorpholinyloxyanthracenyl, quinolinyloxyphenyl, quinolinyloxynaphthyl, quinolinyloxyanthracenyl, fluorenyloxyphenyl, fluorenyloxynaphthyl and fluorenyloxyanthracenyl; and wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is $-R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of pyrrolidinylphenyl, pyrrolidinylnaphthyl, pyrrolidinylanthracenyl, pyrrolinylphenyl, pyrrolinylnaphthyl, pyrrolinylanthracenyl, pyrrolylphenyl, pyrrolylnaphthyl, pyrrolylanthracenyl, tetrahydrofuranylphenyl, tetrahydrofuranylnaphthyl, tetrahydrofuranylanthracenyl, furanylphenyl, furanylnaphthyl, furanylanthracenyl, dioxolanylphenyl, dioxolanylnaphthyl, dioxolanylanthracenyl, imidazolidinylphenyl, imidazolidinylnaphthyl, imidazolidinylanthracenyl, imidazolynylphenyl, imidazolynylnaphthyl, imidazolynylanthracenyl, imidazolylphenyl, imidazolylnaphthyl, imidazolylanthracenyl, pyrazolidinylphenyl, pyrazolidinylnaphthyl, pyrazolidinylanthracenyl, pyrazolinylphenyl, pyrazolinylnaphthyl, pyrazolinylanthracenyl, pyrazolylphenyl, pyrazolylnaphthyl, pyrazolylanthracenyl, oxazolylphenyl, oxazolylnaphthyl, oxazolylanthracenyl, isoxazolylphenyl, isoxazolylnaphthyl, isoxazolylanthracenyl, oxadiazolylphenyl, oxadiazolylnaphthyl, oxadiazolylanthracenyl, thiophenylphenyl, thiophenylnaphthyl, thiophenylanthracenyl, thiazolylphenyl, thiazolylnaphthyl, thiazolylanthracenyl, thiadiazolylphenyl, thiadiazolylnaphthyl, thiadiazolylanthracenyl, triazolylphenyl, triazolylnaphthyl, triazolylanthracenyl, piperidinylphenyl, piperidinylnaphthyl, piperidinylanthracenyl, pyridinylphenyl, pyridinylnaphthyl, pyridinylanthracenyl, piperazinylphenyl, piperazinylnaphthyl, piperazinylanthracenyl, pyrazinylphenyl, pyrazinylnaphthyl, pyrazinylanthracenyl, pyrimidinylphenyl, pyrimidinylnaphthyl, pyrimidinylanthracenyl, pyridazinylphenyl, pyridazinylnaphthyl, pyridazinylanthracenyl, triazinylphenyl, triazinylnaphthyl, triazinylanthracenyl, morpholinylphenyl, morpholinylnaphthyl, morpholinylanthracenyl, dioxanylphenyl, dioxanylnaphthyl, dioxanylanthracenyl, tetrahydro-2H-pyranylphenyl, tetrahydro-2H-pyranylnaphthyl, tetrahydro-2H-pyranylanthracenyl, 2H-pyranyl phenyl, 2H-pyranyl naphthyl, 2H-pyranyl anthracenyl, 4H-pyranylphenyl, 4H-pyranylnaphthyl, 4H-pyranylanthracenyl, thiomorpholinylphenyl, thiomorpholinylnaphthyl, thiomorpholinylanthracenyl, quinolinylphenyl, quinolinylnaphthyl, quinolinylanthracenyl, fluorenylphenyl, fluorenylnaphthyl and fluorenylanthracenyl; and wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is $-R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclopropylethyl, cyclopropylpropyl, cyclopropylbutyl, cyclobutylmethyl, cyclobutylethyl, cyclobutylpropyl, cyclobutylbutyl, cyclopentylmethyl, cyclopentylethyl, cyclopentylpropyl, cyclopentylbutyl, cyclohexylmethyl, cyclohexylethyl, cyclohexylpropyl and cyclohexylbutyl; and wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is $-R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of methylphenyl, methylnapthalenyl, methylanthracenyl, ethylphenyl, ethylnapthalenyl, ethylanthracenyl, propylphenyl, propylnapthalenyl, propylanthracenyl, butylphenyl, butylnapthalenyl, butylanthracenyl, methoxyphenyl, ethoxyphenyl, propoxyphenyl, butoxyphenyl, methoxynapthalenyl, ethoxynapthalenyl, propoxynapthalenyl, butoxynapthalenyl, methoxyanthracenyl, ethoxyanthracenyl, propoxyanthracenyl and butoxynanthracenyl; and wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is $-R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of methoxyphenylpyrrolidinyl, methoxyphenylpyrrolinyl, methoxyphenylpyrrolyl, methoxyphenyltetrahydrofuranyl, methoxyphenylfuranyl, methoxyphenyldioxolanyl, methoxyphenylimidazolidinyl, methoxyphenylimidazolynyl, methoxyphenylimidazolyl, methoxyphenylpyrazolidinyl, methoxyphenylpyrazolinyl, methoxyphenylpyrazolyl, methoxyphenyloxazolyl, methoxyphenylisoxazolyl, methoxyphenyloxadiazolyl, methoxyphenyloxadiazolyl, methoxyphenylthiophenyl, methoxyphenylthiazolyl, methoxyphenylthiadiazolyl, methoxyphenyltriazolyl, methoxyphenylisothiazolyl, methoxyphenylpiperidinyl, methoxyphenylpyridinyl, methoxyphenylpiperazinyl, methoxyphenylpyrazinyl, methoxyphenylpyrimidinyl, methoxyphenylpyridazinyl, methoxyphenyltriazinyl, methoxyphenylmorpholinyl, methoxyphenyldioxanyl, methoxyphenyltetrahydro-2H-pyranyl, methoxyphenyl2H-pyranyl, methoxyphenyl4H-pyranyl, methoxyphenylthiomorpholinyl, methoxyphenylindolyl, methoxyphenyldihydrobenzofuranyl, methoxyphenyldihydrobenzodioxinyl, methoxyphenylquinolinyl and methoxyphenylfluorenyl; and wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is $-R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of ethoxyphenylpyrrolidinyl, ethoxyphenylpyrrolinyl, ethoxyphenylpyrrolyl, ethoxyphenyltetrahydrofuranyl, ethoxyphenylfuranyl, ethoxyphenyldioxolanyl, ethoxyphenylimidazolidinyl, ethoxyphenylimidazolynyl, ethoxyphenylimidazolyl, ethoxyphenylpyrazolidinyl, ethoxyphenylpyrazolinyl, ethoxyphenylpyrazolyl, ethoxyphenyloxazolyl, ethoxyphenylisoxazolyl, ethoxyphenyloxadiazolyl, ethoxyphenyloxadiazolyl, ethoxyphenylthiophenyl, ethoxyphenylthiazolyl, ethoxyphenylthiadiazolyl, ethoxyphenyltriazolyl, ethoxyphenylisothiazolyl, ethoxyphenylpiperidinyl, ethoxyphenylpyridinyl, ethoxyphenylpiperazinyl, ethoxyphenylpyrazinyl, ethoxyphenylpyrimidinyl, ethoxyphenylpyridazinyl, ethoxyphenyltriazinyl, ethoxyphenylmorpholinyl, ethoxyphenyldioxanyl, ethoxyphenyltetrahydro-2H-pyranyl, ethoxyphenyl2H-pyranyl, ethoxyphenyl4H-pyranyl, ethoxyphenylthiomorpholinyl, ethoxyphenylindolyl, ethoxyphenyldihydrobenzofuranyl, ethoxyphenyldihydrobenzodioxinyl, ethoxyphenylquinolinyl and ethoxyphenylfluorenyl; and wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is $-R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of propoxyphenylpyrrolidinyl, propoxyphenylpyrrolinyl, propoxyphenylpyrrolyl, propoxyphenyltetrahydrofuranyl, propoxyphenylfuranyl, propoxyphenyldioxolanyl, propoxyphenylimidazolidinyl, propoxyphenylimidazolynyl, propoxyphenylimidazolyl, propoxyphenylpyrazolidinyl, propoxyphenylpyrazolinyl, propoxyphenylpyrazolyl, propoxyphenyloxazolyl, propoxyphenylisoxazolyl, propoxyphenyloxadiazolyl, propoxyphenyloxadiazolyl, propoxyphenylthiophenyl, propoxyphenylthiazolyl, propoxyphenylthiadiazolyl, propoxyphenyltriazolyl, propoxyphenylisothiazolyl, propoxyphenylpiperidinyl, propoxyphenylpyridinyl, propoxyphenylpiperazinyl, propoxyphenylpyrazinyl, propoxyphenylpyrimidinyl, propoxyphenylpyridazinyl, propoxyphenyltriazinyl, propoxyphenylmorpholinyl, propoxyphenyldioxanyl, propoxyphenyltetrahydro-2H-pyranyl, propoxyphenyl2H-pyranyl, propoxyphenyl4H-pyranyl, propoxyphenylthiomorpholinyl, propoxyphenylindolyl, propoxyphenyldihydrobenzofuranyl, propoxyphenyldihydrobenzodioxinyl, propoxyphenylquinolinyl and propoxyphenylfluorenyl; and wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is $-R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of butoxyphenylpyrrolidinyl, butoxyphenylpyrrolinyl, butoxyphenylpyrrolyl, butoxyphenyltetrahydrofuranyl, butoxyphenylfuranyl, butoxyphenyldioxolanyl, butoxyphenylimidazolidinyl, butoxyphenylimidazolynyl, butoxyphenylimidazolyl, butoxyphenylpyrazolidinyl, butoxyphenylpyrazolinyl, butoxyphenylpyrazolyl, butoxyphenyloxazolyl, butoxyphenylisoxazolyl, butoxyphenyloxadiazolyl, butoxyphenyloxadiazolyl, butoxyphenylthiophenyl, butoxyphenylthiazolyl, butoxyphenylthiadiazolyl, butoxyphenyltriazolyl, butoxyphenylisothiazolyl, butoxyphenylpiperidinyl, butoxyphenylpyridinyl, butoxyphenylpiperazinyl, butoxyphenylpyrazinyl, butoxyphenylpyrimidinyl, butoxyphenylpyridazinyl, butoxyphenyltriazinyl, butoxyphenylmorpholinyl, butoxyphenyldioxanyl, butoxyphenyltetrahydro-2H-pyranyl, butoxyphenyl2H-pyranyl, butoxyphenyl4H-pyranyl, butoxyphenylthiomorpholinyl, butoxyphenylindolyl, butoxyphenyldihydrobenzofuranyl, butoxyphenyldihydrobenzodioxinyl, butoxyphenylquinolinyl and butoxyphenylfluorenyl; and wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is $-R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of methoxynapthalenylpyrrolidinyl, methoxynapthalenylpyrrolinyl, methoxynapthalenylpyrrolyl, methoxynapthalenyltetrahydrofuranyl, methoxynapthalenylfuranyl, methoxynapthalenyldioxolanyl, methoxynapthalenylimidazolidinyl, methoxynapthalenylimidazolynyl, methoxynapthalenylimidazolyl, methoxynapthalenylpyrazolidinyl, methoxynapthalenylpyrazolinyl, methoxynapthalenylpyrazolyl, methoxynapthalenyloxazolyl, methoxynapthalenylisoxazolyl, methoxynapthalenyloxadiazolyl, methoxynapthalenyloxadiazolyl, methoxynapthalenylthiophenyl, methoxynapthalenylthiazolyl, methoxynapthalenylthiadiazolyl, methoxynapthalenyltriazolyl, methoxynapthalenylisothiazolyl, methoxynapthalenylpiperidinyl, methoxynapthalenylpyridinyl, methoxynapthalenylpiperazinyl, methoxynapthalenylpyrazinyl, methoxynapthalenylpyrimidinyl, methoxynapthalenylpyridazinyl, methoxynapthalenyltriazinyl, methoxynapthalenylmorpholinyl, methoxynapthalenyldioxanyl, methoxynapthalenyltetrahydro-2H-pyranyl, methoxynapthalenyl2H-pyranyl, methoxynapthalenyl4H-pyranyl, methoxynapthalenylthiomorpholinyl, methoxynapthalenylindolyl, methoxynapthalenyldihydrobenzofuranyl, methoxynapthalenyldihydrobenzodioxinyl, methoxynapthalenylquinolinyl and methoxynapthalenylfluorenyl; and wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is $-R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of ethoxynapthalenylpyrrolidinyl, ethoxynapthalenylpyrrolinyl, ethoxynapthalenylpyrrolyl, ethoxynapthalenyltetrahydrofuranyl, ethoxynapthalenylfuranyl, ethoxynapthalenyldioxolanyl, ethoxynapthalenylimidazolidinyl, ethoxynapthalenylimidazolynyl, ethoxynapthalenylimidazolyl, ethoxynapthalenylpyrazolidinyl, ethoxynapthalenylpyrazolinyl, ethoxynapthalenylpyrazolyl, ethoxynapthalenyloxazolyl, ethoxynapthalenylisoxazolyl, ethoxynapthalenyloxadiazolyl, ethoxynapthalenyloxadiazolyl, ethoxynapthalenylthiophenyl, ethoxynapthalenylthiazolyl, ethoxynapthalenylthiadiazolyl, ethoxynapthalenyltriazolyl, ethoxynapthalenylisothiazolyl, ethoxynapthalenylpiperidinyl, ethoxynapthalenylpyridinyl, ethoxynapthalenylpiperazinyl, ethoxynapthalenylpyrazinyl, ethoxynapthalenylpyrimidinyl, ethoxynapthalenylpyridazinyl, ethoxynapthalenyltriazinyl, ethoxynapthalenylmorpholinyl, ethoxynapthalenyldioxanyl, ethoxynapthalenyltetrahydro-2H-pyranyl, ethoxynapthalenyl2H-pyranyl, ethoxynapthalenyl4H-pyranyl, ethoxynapthalenylthiomorpholinyl, ethoxynapthalenylindolyl, ethoxynapthalenyldihydrobenzofuranyl, ethoxynapthalenyldihydrobenzodioxinyl, ethoxynapthalenylquinolinyl and ethoxynapthalenylfluorenyl; and wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is $-R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of propoxynapthalenylpyrrolidinyl, propoxynapthalenylpyrrolinyl, propoxynapthalenylpyrrolyl, propoxynapthalenyltetrahydrofuranyl, propoxynapthalenylfuranyl, propoxynapthalenyldioxolanyl, propoxynapthalenylimidazolidinyl, propoxynapthalenylimidazolynyl, propoxynapthalenylimidazolyl, propoxynapthalenylpyrazolidinyl, propoxynapthalenylpyrazolinyl, propoxynapthalenylpyrazolyl, propoxynapthalenyloxazolyl, propoxynapthalenylisoxazolyl, propoxynapthalenyloxadiazolyl, propoxynapthalenyloxadiazolyl, propoxynapthalenylthiophenyl, propoxynapthalenylthiazolyl, propoxynapthalenylthiadiazolyl, propoxynapthalenyltriazolyl, propoxynapthalenylisothiazolyl, propoxynapthalenylpiperidinyl, propoxynapthalenylpyridinyl, propoxynapthalenylpiperazinyl, propoxynapthalenylpyrazinyl, propoxynapthalenylpyrimidinyl, propoxynapthalenylpyridazinyl, propoxynapthalenyltriazinyl, propoxynapthalenylmorpholinyl, propoxynapthalenyldioxanyl, propoxynapthalenyltetrahydro-2H-pyranyl, propoxynapthalenyl2H-pyranyl, propoxynapthalenyl4H-pyranyl, propoxynapthalenylthiomorpholinyl, propoxynapthalenylindolyl, propoxynapthalenyldihydrobenzofuranyl, propoxynapthalenyldihydrobenzodioxinyl, propoxynapthalenylquinolinyl and propoxynapthalenylfluorenyl; and wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is $-R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of butoxynapthalenylpyrrolidinyl, butoxynapthalenylpyrrolinyl, butoxynapthalenylpyrrolyl, butoxynapthalenyltetrahydrofuranyl, butoxynapthalenylfuranyl, butoxynapthalenyldioxolanyl, butoxynapthalenylimidazolidinyl, butoxynapthalenylimidazolynyl, butoxynapthalenylimidazolyl, butoxynapthalenylpyrazolidinyl, butoxynapthalenylpyrazolinyl, butoxynapthalenylpyrazolyl, butoxynapthalenyloxazolyl, butoxynapthalenylisoxazolyl, butoxynapthalenyloxadiazolyl, butoxynapthalenyloxadiazolyl, butoxynapthalenylthiophenyl, butoxynapthalenylthiazolyl, butoxynapthalenylthiadiazolyl, butoxynapthalenyltriazolyl, butoxynapthalenylisothiazolyl, butoxynapthalenylpiperidinyl, butoxynapthalenylpyridinyl, butoxynapthalenylpiperazinyl, butoxynapthalenylpyrazinyl, butoxynapthalenylpyrimidinyl, butoxynapthalenylpyridazinyl, butoxynapthalenyltriazinyl, butoxynapthalenylmorpholinyl, butoxynapthalenyldioxanyl, butoxynapthalenyltetrahydro-2H-pyranyl, butoxynapthalenyl2H-pyranyl, butoxynapthalenyl4H-pyranyl, butoxynapthalenylthiomorpholinyl, butoxynapthalenylindolyl, butoxynapthalenyldihydrobenzofuranyl, butoxynapthalenyldihydrobenzodioxinyl, butoxynapthalenylquinolinyl and butoxynapthalenylfluorenyl; and wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is $-R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of methoxycarbonylmethyl, ethoxycarbonylmethyl, propoxycarbonylmethyl, butoxycarbonylmethyl, methoxycarbonylethyl, ethoxycarbonylethyl, propoxycarbonylethyl, butoxycarbonylethyl, methoxycarbonylpropyl, ethoxycarbonylpropyl, propoxycarbonylpropyl, butoxycarbonylpropyl, methoxycarbonylbutyl, ethoxycarbonylbutyl, propoxycarbonylbutyl and butoxycarbonylbutyl; and wherein the R^{4j} substituents may be optionally substituted as provided in claim 2.

In another embodiment of the compounds of Formula (II), R^4 is $–R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of methoxycarbonylphenyl, ethoxycarbonylphenyl, propoxycarbonylphenyl, butoxycarbonylphenyl, methoxycarbonylnapthalenyl, ethoxycarbonylnapthalenyl, propoxycarbonylnapthalenyl, butoxycarbonylnapthalenyl, methoxycarbonylanthracenyl, ethoxycarbonylanthracenyl, propoxycarbonylanthracenyl and butoxycarbonylanthracenyl; and wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is $–R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of methylaminophenyl, ethylaminophenyl, propylaminophenyl, butylaminophenyl, dimethylaminophenyl, diethylaminophenyl, dipropylaminophenyl, dibutylaminophenyl, methylethylaminophenyl, methylpropylaminophenyl, methylbutylaminophenyl, ethylpropylaminophenyl, ethylbutylaminophenyl, propylbutylaminophenyl, methylaminonapthalenyl, ethylaminonapthalenyl, propylaminonapthalenyl, butylaminonapthalenyl, dimethylaminonapthalenyl, diethylaminonapthalenyl, dipropylaminonapthalenyl, dibutylaminonapthalenyl, methylethylaminonapthalenyl, methylpropylaminonapthalenyl, methylbutylaminonapthalenyl, ethylpropylaminonapthalenyl, ethylbutylaminonapthalenyl and propylbutylaminonapthalenyl; and wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is $–R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of methylaminopyrrolidinyl, ethylaminopyrrolidinyl, propylaminopyrrolidinyl, butylaminopyrrolidinyl, dimethylaminopyrrolidinyl, diethylaminopyrrolidinyl, dipropylaminopyrrolidinyl, dibutylaminopyrrolidinyl, methylethylaminopyrrolidinyl, methylpropylaminopyrrolidinyl, methylbutylaminopyrrolidinyl, ethylpropylaminopyrrolidinyl, ethylbutylaminopyrrolidinyl, propylbutylaminopyrrolidinyl, methylaminopyrrolinyl, ethylaminopyrrolinyl, propylaminopyrrolinyl, butylaminopyrrolinyl, dimethylaminopyrrolinyl, diethylaminopyrrolinyl, dipropylaminopyrrolinyl, dibutylaminopyrrolinyl, methylethylaminopyrrolinyl, methylpropylaminopyrrolinyl, methylbutylaminopyrrolinyl, ethylpropylaminopyrrolinyl, ethylbutylaminopyrrolinyl and propylbutylaminopyrrolinyl; and wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is $–R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of methylaminopyrrolyl, ethylaminopyrrolyl, propylaminopyrrolyl, butylaminopyrrolyl, dimethylaminopyrrolyl, diethylaminopyrrolyl, dipropylaminopyrrolyl, dibutylaminopyrrolyl, methylethylaminopyrrolyl, methylpropylaminopyrrolyl, methylbutylaminopyrrolyl, ethylpropylaminopyrrolyl, ethylbutylaminopyrrolyl, propylbutylaminopyrrolyl, methylaminotetrahydrofuranyl, ethylaminotetrahydrofuranyl, propylaminotetrahydrofuranyl, butylaminotetrahydrofuranyl, dimethylaminotetrahydrofuranyl, diethylaminotetrahydrofuranyl, dipropylaminotetrahydrofuranyl, dibutylaminotetrahydrofuranyl, methylethylaminotetrahydrofuranyl, methylpropylaminotetrahydrofuranyl, methylbutylaminotetrahydrofuranyl, ethylpropylaminotetrahydrofuranyl, ethylbutylaminotetrahydrofuranyl and propylbutylaminotetrahydrofuranyl; and wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is $-R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of methylaminofuranyl, ethylaminofuranyl, propylaminofuranyl, butylaminofuranyl, dimethylaminofuranyl, diethylaminofuranyl, dipropylaminofuranyl, dibutylaminofuranyl, methylethylaminofuranyl, methylpropylaminofuranyl, methylbutylaminofuranyl, ethylpropylaminofuranyl, ethylbutylaminofuranyl, propylbutylaminofuranyl, methylaminodioxolanyl, ethylaminodioxolanyl, propylaminodioxolanyl, butylaminodioxolanyl, dimethylaminodioxolanyl, diethylaminodioxolanyl, dipropylaminodioxolanyl, dibutylaminodioxolanyl, methylethylaminodioxolanyl, methylpropylaminodioxolanyl, methylbutylaminodioxolanyl, ethylpropylaminodioxolanyl, ethylbutylaminodioxolanyl and propylbutylaminodioxolanyl; and wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is $-R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of methylaminoimidazolidinyl, ethylaminoimidazolidinyl, propylaminoimidazolidinyl, butylaminoimidazolidinyl, dimethylaminoimidazolidinyl, diethylaminoimidazolidinyl, dipropylaminoimidazolidinyl, dibutylaminoimidazolidinyl, methylethylaminoimidazolidinyl, methylpropylaminoimidazolidinyl, methylbutylaminoimidazolidinyl, ethylpropylaminoimidazolidinyl, ethylbutylaminoimidazolidinyl, propylbutylaminoimidazolidinyl, methylaminoimidazolynyl, ethylaminoimidazolynyl, propylaminoimidazolynyl, butylaminoimidazolynyl, dimethylaminoimidazolynyl, diethylaminoimidazolynyl, dipropylaminoimidazolynyl, dibutylaminoimidazolynyl, methylethylaminoimidazolynyl, methylpropylaminoimidazolynyl, methylbutylaminoimidazolynyl, ethylpropylaminoimidazolynyl, ethylbutylaminoimidazolynyl and propylbutylaminoimidazolynyl; and wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is $-R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of methylaminoimidazolyl, ethylaminoimidazolyl, propylaminoimidazolyl, butylaminoimidazolyl, dimethylaminoimidazolyl, diethylaminoimidazolyl, dipropylaminoimidazolyl, dibutylaminoimidazolyl, methylethylaminoimidazolyl, methylpropylaminoimidazolyl, methylbutylaminoimidazolyl, ethylpropylaminoimidazolyl, ethylbutylaminoimidazolyl, propylbutylaminoimidazolyl, methylaminopyrazolidinyl, ethylaminopyrazolidinyl, propylaminopyrazolidinyl, butylaminopyrazolidinyl, dimethylaminopyrazolidinyl, diethylaminopyrazolidinyl, dipropylaminopyrazolidinyl, dibutylaminopyrazolidinyl, methylethylaminopyrazolidinyl, methylpropylaminopyrazolidinyl, methylbutylaminopyrazolidinyl, ethylpropylaminopyrazolidinyl, ethylbutylaminopyrazolidinyl and propylbutylaminopyrazolidinyl; and wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is $-R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of methylaminopyrazolinyl, ethylaminopyrazolinyl, propylaminopyrazolinyl, butylaminopyrazolinyl, dimethylaminopyrazolinyl, diethylaminopyrazolinyl, dipropylaminopyrazolinyl, dibutylaminopyrazolinyl, methylethylaminopyrazolinyl, methylpropylaminopyrazolinyl, methylbutylaminopyrazolinyl, ethylpropylaminopyrazolinyl, ethylbutylaminopyrazolinyl, propylbutylaminopyrazolinyl, methylaminopyrazolyl, ethylaminopyrazolyl, propylaminopyrazolyl, butylaminopyrazolyl, dimethylaminopyrazolyl, diethylaminopyrazolyl, dipropylaminopyrazolyl, dibutylaminopyrazolyl, methylethylaminopyrazolyl, methylpropylaminopyrazolyl, methylbutylaminopyrazolyl, ethylpropylaminopyrazolyl, ethylbutylaminopyrazolyl and propylbutylaminopyrazolyl; and wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is $-R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of methylaminooxazolyl, ethylaminooxazolyl, propylaminooxazolyl, butylaminooxazolyl, dimethylaminooxazolyl, diethylaminooxazolyl, dipropylaminooxazolyl, dibutylaminooxazolyl, methylethylaminooxazolyl, methylpropylaminooxazolyl, methylbutylaminooxazolyl, ethylpropylaminooxazolyl, ethylbutylaminooxazolyl, propylbutylaminooxazolyl, methylaminoisoxazolyl, ethylaminoisoxazolyl, propylaminoisoxazolyl, butylaminoisoxazolyl, dimethylaminoisoxazolyl, diethylaminoisoxazolyl, dipropylaminoisoxazolyl, dibutylaminoisoxazolyl, methylethylaminoisoxazolyl, methylpropylaminoisoxazolyl, methylbutylaminoisoxazolyl, ethylpropylaminoisoxazolyl, ethylbutylaminoisoxazolyl and propylbutylaminoisoxazolyl; and wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is $-R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of methylaminooxadiazolyl, ethylaminooxadiazolyl, propylaminooxadiazolyl, butylaminooxadiazolyl, dimethylaminooxadiazolyl, diethylaminooxadiazolyl, dipropylaminooxadiazolyl, dibutylaminooxadiazolyl, methylethylaminooxadiazolyl, methylpropylaminooxadiazolyl, methylbutylaminooxadiazolyl, ethylpropylaminooxadiazolyl, ethylbutylaminooxadiazolyl, propylbutylaminooxadiazolyl, methylaminothiophenyl, ethylaminothiophenyl, propylaminothiophenyl, butylaminothiophenyl, dimethylaminothiophenyl, diethylaminothiophenyl, dipropylaminothiophenyl, dibutylaminothiophenyl, methylethylaminothiophenyl, methylpropylaminothiophenyl, methylbutylaminothiophenyl, ethylpropylaminothiophenyl, ethylbutylaminothiophenyl and propylbutylaminothiophenyl; and wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is $-R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of methylaminothiazolyl, ethylaminothiazolyl, propylaminothiazolyl, butylaminothiazolyl, dimethylaminothiazolyl, diethylaminothiazolyl, dipropylaminothiazolyl, dibutylaminothiazolyl, methylethylaminothiazolyl, methylpropylaminothiazolyl, methylbutylaminothiazolyl, ethylpropylaminothiazolyl, ethylbutylaminothiazolyl, propylbutylaminothiazolyl, methylaminothiadiazolyl, ethylaminothiadiazolyl, propylaminothiadiazolyl, butylaminothiadiazolyl, dimethylaminothiadiazolyl, diethylaminothiadiazolyl, dipropylaminothiadiazolyl, dibutylaminothiadiazolyl, methylethylaminothiadiazolyl, methylpropylaminothiadiazolyl, methylbutylaminothiadiazolyl, ethylpropylaminothiadiazolyl, ethylbutylaminothiadiazolyl and propylbutylaminothiadiazolyl; and wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is $-R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of methylaminotriazolyl, ethylaminotriazolyl, propylaminotriazolyl, butylaminotriazolyl, dimethylaminotriazolyl, diethylaminotriazolyl, dipropylaminotriazolyl, dibutylaminotriazolyl, methylethylaminotriazolyl, methylpropylaminotriazolyl, methylbutylaminotriazolyl, ethylpropylaminotriazolyl, ethylbutylaminotriazolyl, propylbutylaminotriazolyl, methylaminopiperidinyl, ethylaminopiperidinyl, propylaminopiperidinyl, butylaminopiperidinyl, dimethylaminopiperidinyl, diethylaminopiperidinyl, dipropylaminopiperidinyl, dibutylaminopiperidinyl, methylethylaminopiperidinyl, methylpropylaminopiperidinyl, methylbutylaminopiperidinyl, ethylpropylaminopiperidinyl, ethylbutylaminopiperidinyl and propylbutylaminopiperidinyl; and wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is $-R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of methylaminopyridinyl, ethylaminopyridinyl, propylaminopyridinyl, butylaminopyridinyl, dimethylaminopyridinyl, diethylaminopyridinyl, dipropylaminopyridinyl, dibutylaminopyridinyl, methylethylaminopyridinyl, methylpropylaminopyridinyl, methylbutylaminopyridinyl, ethylpropylaminopyridinyl, ethylbutylaminopyridinyl, propylbutylaminopyridinyl, methylaminopiperazinyl, ethylaminopiperazinyl, propylaminopiperazinyl, butylaminopiperazinyl, dimethylaminopiperazinyl, diethylaminopiperazinyl, dipropylaminopiperazinyl, dibutylaminopiperazinyl, methylethylaminopiperazinyl, methylpropylaminopiperazinyl, methylbutylaminopiperazinyl, ethylpropylaminopiperazinyl, ethylbutylaminopiperazinyl and propylbutylaminopiperazinyl; and wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is $-R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of methylaminopyrazinyl, ethylaminopyrazinyl, propylaminopyrazinyl, butylaminopyrazinyl, dimethylaminopyrazinyl, diethylaminopyrazinyl, dipropylaminopyrazinyl, dibutylaminopyrazinyl, methylethylaminopyrazinyl, methylpropylaminopyrazinyl, methylbutylaminopyrazinyl, ethylpropylaminopyrazinyl, ethylbutylaminopyrazinyl, propylbutylaminopyrazinyl, methylaminopyrimidinyl, ethylaminopyrimidinyl, propylaminopyrimidinyl, butylaminopyrimidinyl, dimethylaminopyrimidinyl, diethylaminopyrimidinyl, dipropylaminopyrimidinyl, dibutylaminopyrimidinyl, methylethylaminopyrimidinyl, methylpropylaminopyrimidinyl, methylbutylaminopyrimidinyl, ethylpropylaminopyrimidinyl, ethylbutylaminopyrimidinyl and propylbutylaminopyrimidinyl; and wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is $-R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of methylaminopyridazinyl, ethylaminopyridazinyl, propylaminopyridazinyl, butylaminopyridazinyl, dimethylaminopyridazinyl, diethylaminopyridazinyl, dipropylaminopyridazinyl, dibutylaminopyridazinyl, methylethylaminopyridazinyl, methylpropylaminopyridazinyl, methylbutylaminopyridazinyl, ethylpropylaminopyridazinyl, ethylbutylaminopyridazinyl, propylbutylaminopyridazinyl, methylaminotriazinyl, ethylaminotriazinyl, propylaminotriazinyl, butylaminotriazinyl, dimethylaminotriazinyl, diethylaminotriazinyl, dipropylaminotriazinyl, dibutylaminotriazinyl, methylethylaminotriazinyl, methylpropylaminotriazinyl, methylbutylaminotriazinyl, ethylpropylaminotriazinyl, ethylbutylaminotriazinyl and propylbutylaminotriazinyl; and wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is $-R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of methylaminomorpholinyl, ethylaminomorpholinyl, propylaminomorpholinyl, butylaminomorpholinyl, dimethylaminomorpholinyl, diethylaminomorpholinyl, dipropylaminomorpholinyl, dibutylaminomorpholinyl, methylethylaminomorpholinyl, methylpropylaminomorpholinyl, methylbutylaminomorpholinyl, ethylpropylaminomorpholinyl, ethylbutylaminomorpholinyl, propylbutylaminomorpholinyl, methylaminodioxanyl, ethylaminodioxanyl, propylaminodioxanyl, butylaminodioxanyl, dimethylaminodioxanyl, diethylaminodioxanyl, dipropylaminodioxanyl, dibutylaminodioxanyl, methylethylaminodioxanyl, methylpropylaminodioxanyl, methylbutylaminodioxanyl, ethylpropylaminodioxanyl, ethylbutylaminodioxanyl and propylbutylaminodioxanyl; and wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is $-R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of methylaminotetrahydro-2H-pyranyl, ethylaminotetrahydro-

2H-pyranyl, propylaminotetrahydro-2H-pyranyl, butylaminotetrahydro-2H-pyranyl, dimethylaminotetrahydro-2H-pyranyl, diethylaminotetrahydro-2H-pyranyl, dipropylaminotetrahydro-2H-pyranyl, dibutylaminotetrahydro-2H-pyranyl, methylethylaminotetrahydro-2H-pyranyl, methylpropylaminotetrahydro-2H-pyranyl, methylbutylaminotetrahydro-2H-pyranyl, ethylpropylaminotetrahydro-2H-pyranyl, ethylbutylaminotetrahydro-2H-pyranyl, propylbutylaminotetrahydro-2H-pyranyl, methylamino2H-pyranyl, ethylamino2H-pyranyl, propylamino2H-pyranyl, butylamino2H-pyranyl, dimethylamino2H-pyranyl, diethylamino2H-pyranyl, dipropylamino2H-pyranyl, dibutylamino2H-pyranyl, methylethylamino2H-pyranyl, methylpropylamino2H-pyranyl, methylbutylamino2H-pyranyl, ethylpropylamino2H-pyranyl, ethylbutylamino2H-pyranyl and propylbutylamino2H-pyranyl; and wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is $-R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of methylamino4H-pyranyl, ethylamino4H-pyranyl, propylamino4H-pyranyl, butylamino4H-pyranyl, dimethylamino4H-pyranyl, diethylamino4H-pyranyl, dipropylamino4H-pyranyl, dibutylamino4H-pyranyl, methylethylamino4H-pyranyl, methylpropylamino4H-pyranyl, methylbutylamino4H-pyranyl, ethylpropylamino4H-pyranyl, ethylbutylamino4H-pyranyl, propylbutylamino4H-pyranyl, methylaminothiomorpholinyl, ethylaminothiomorpholinyl, propylaminothiomorpholinyl, butylaminothiomorpholinyl, dimethylaminothiomorpholinyl, diethylaminothiomorpholinyl, dipropylaminothiomorpholinyl, dibutylaminothiomorpholinyl, methylethylaminothiomorpholinyl, methylpropylaminothiomorpholinyl, methylbutylaminothiomorpholinyl, ethylpropylaminothiomorpholinyl, ethylbutylaminothiomorpholinyl and propylbutylaminothiomorpholinyl; and wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is $-R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of methylaminoindolyl, ethylaminoindolyl, propylaminoindolyl, butylaminoindolyl, dimethylaminoindolyl, diethylaminoindolyl, dipropylaminoindolyl, dibutylaminoindolyl, methylethylaminoindolyl, methylpropylaminoindolyl, methylbutylaminoindolyl, ethylpropylaminoindolyl, ethylbutylaminoindolyl, propylbutylaminoindolyl, methylaminodihydrobenzofuranyl, ethylaminodihydrobenzofuranyl, propylaminodihydrobenzofuranyl, butylaminodihydrobenzofuranyl, dimethylaminodihydrobenzofuranyl, diethylaminodihydrobenzofuranyl, dipropylaminodihydrobenzofuranyl, dibutylaminodihydrobenzofuranyl, methylethylaminodihydrobenzofuranyl, methylpropylaminodihydrobenzofuranyl, methylbutylaminodihydrobenzofuranyl, ethylpropylaminodihydrobenzofuranyl, ethylbutylaminodihydrobenzofuranyl and propylbutylaminodihydrobenzofuranyl; and wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^4 is $-R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of methylaminodihydrobenzodioxinyl, ethylaminodihydrobenzodioxinyl, propylaminodihydrobenzodioxinyl, butylaminodihydrobenzodioxinyl, dimethylaminodihydrobenzodioxinyl, diethylaminodihydrobenzodioxinyl, dipropylaminodihydrobenzodioxinyl, dibutylaminodihydrobenzodioxinyl, methylethylaminodihydrobenzodioxinyl, methylpropylaminodihydrobenzodioxinyl, methylbutylaminodihydrobenzodioxinyl, ethylpropylaminodihydrobenzodioxinyl, ethylbutylaminodihydrobenzodioxinyl, propylbutylaminodihydrobenzodioxinyl, methylaminoquinolinyl, ethylaminoquinolinyl, propylaminoquinolinyl, butylaminoquinolinyl, dimethylaminoquinolinyl, diethylaminoquinolinyl, dipropylaminoquinolinyl, dibutylaminoquinolinyl, methylethylaminoquinolinyl, methylpropylaminoquinolinyl, methylbutylaminoquinolinyl, ethylpropylaminoquinolinyl, ethylbutylaminoquinolinyl and propylbutylaminoquinolinyl; and wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

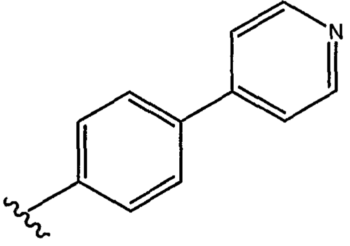
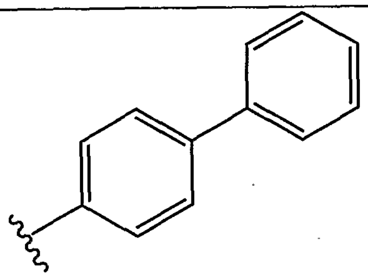
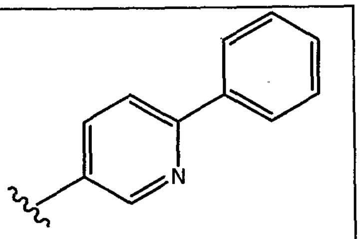
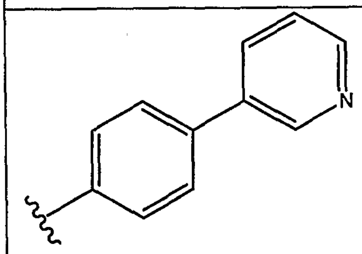
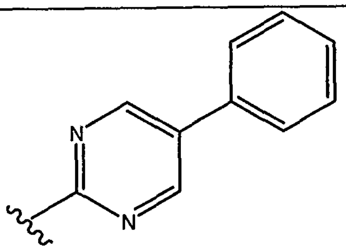
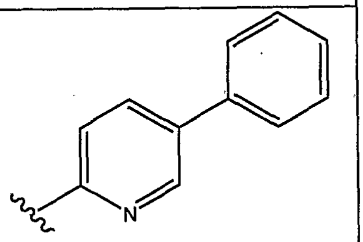
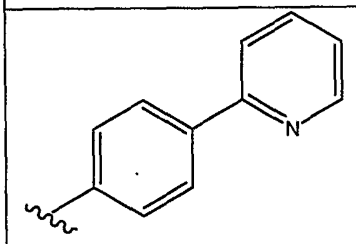
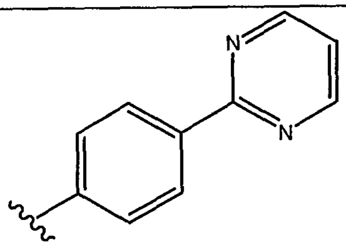
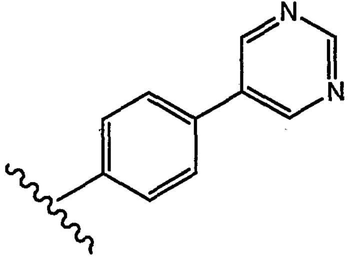
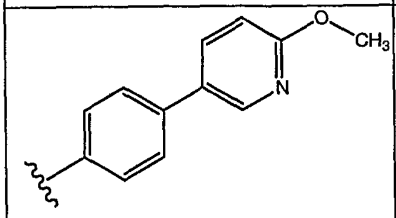
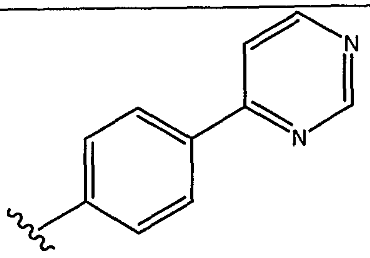
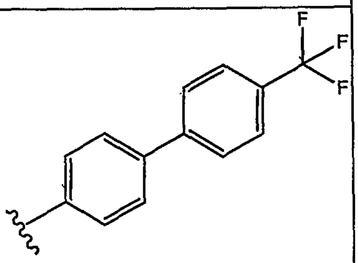
In another embodiment of the compounds of Formula (II), R^4 is $-R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of methylaminofluorenyl, ethylaminofluorenyl, propylaminofluorenyl, butylaminofluorenyl, dimethylaminofluorenyl, diethylaminofluorenyl,. dipropylaminofluorenyl, dibutylaminofluorenyl, methylethylaminofluorenyl, methylpropylaminofluorenyl, methylbutylaminofluorenyl, ethylpropylaminofluorenyl, ethylbutylaminofluorenyl and propylbutylaminofluorenyl; and wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

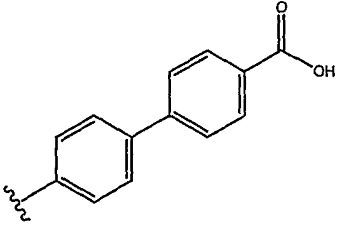
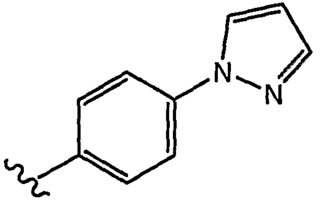
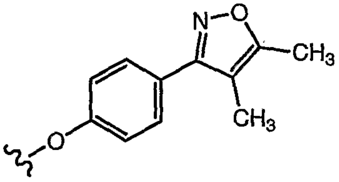
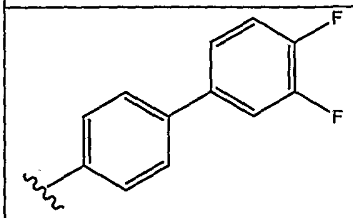
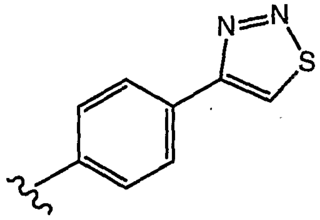
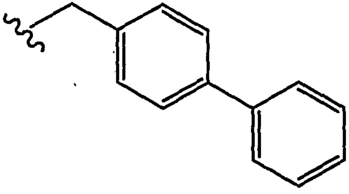
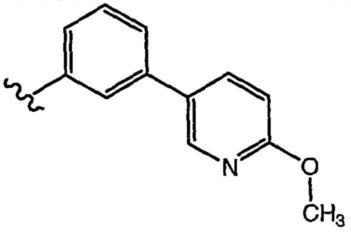
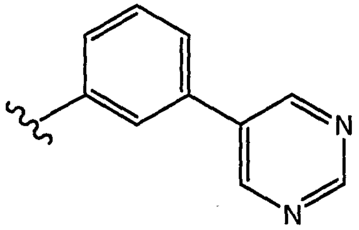
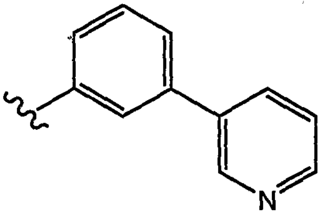
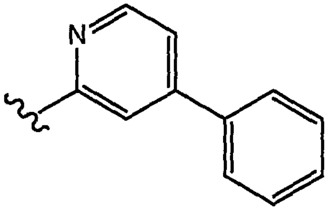
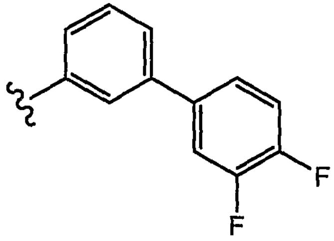
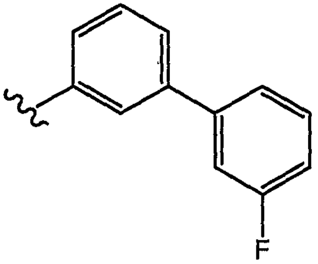
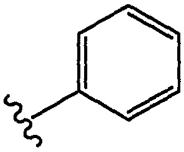
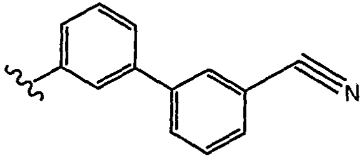
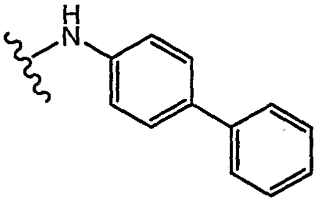
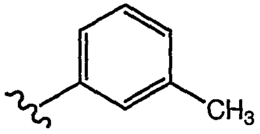
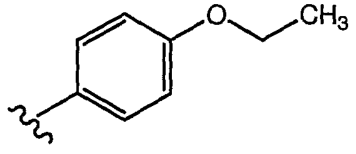
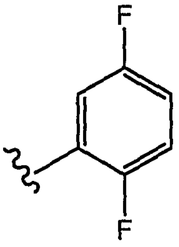
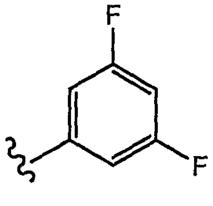
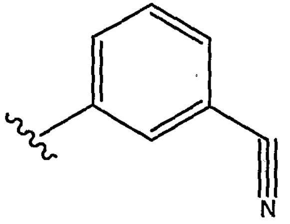
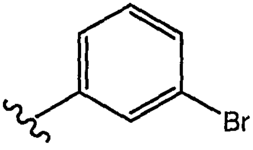
In another embodiment of the compounds of Formula (II), R^4 is $-R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of aminocarbonylphenyl, aminocarbonylnapthalenyl and aminocarbonylanthracenyl; and wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

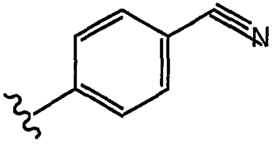
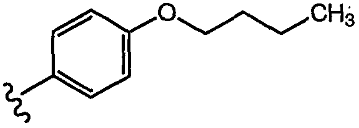
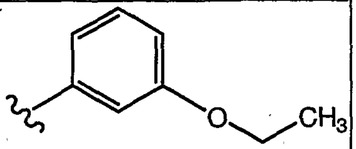
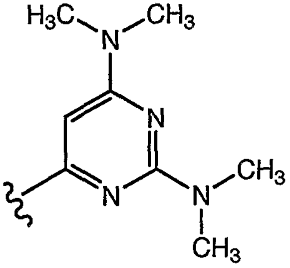
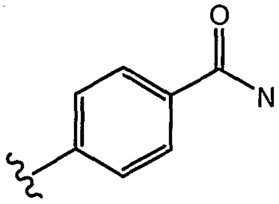
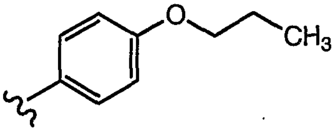
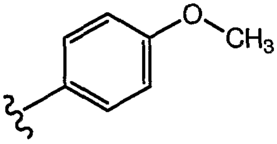
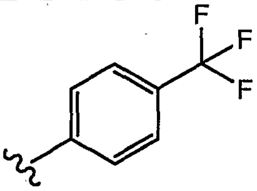
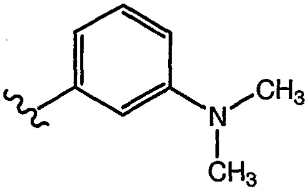
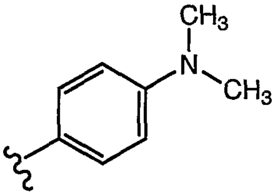
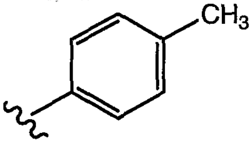
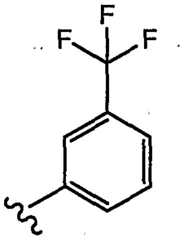
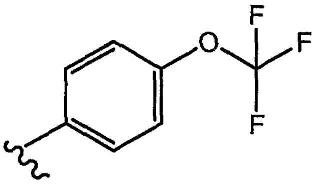
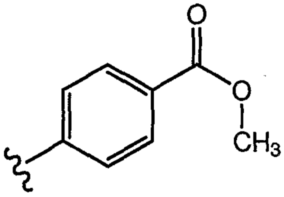
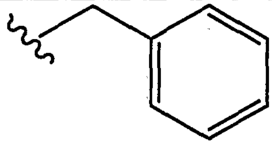
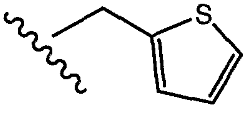
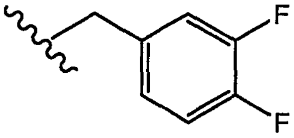
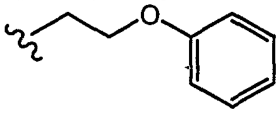
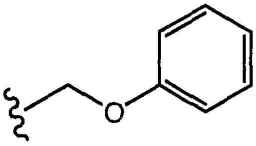
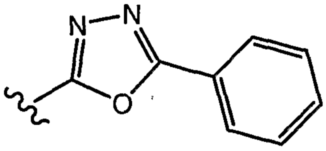
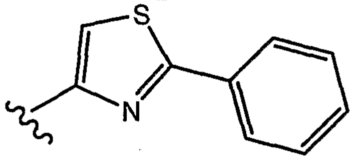
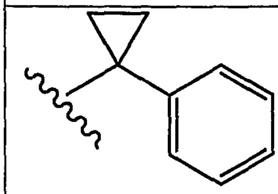
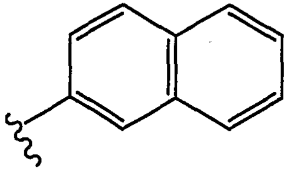
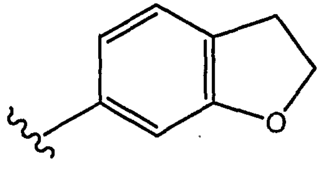
In another embodiment of the compounds of Formula (II), R^4 is $-R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of phenylmethyl, phenylphenyl, phenylisothiazolyl, phenyloxadiazolyl, pentynyl, hexynyl, pyrazolylphenyl, propoxyphenyl, thiadiazolylphenyl, benzofuranyl, butoxyphenyl,dihydrobenzodioxinyl, bis(dimethylamino)pyridinyl, ethoxyphenyl, dihydrobenzofuranyl, butynyl, napthalenyl, phenylthiazolyl, indolyl, methylphenyl, phenyl, methoxycarbonylpropyl, methoxycarbonylbutyl, methoxycarbonylphenyl, methoxyethyl, methoxycarbonylmethyl, methoxycarbonylethyl, cyclopentylethyl, dimethylaminophenyl, phenylethenyl, methoxyphenyl, methylmethoxyphenyl, methoxyphenylisoxazolyl, aminocarbonylphenyl and pentyl; and wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

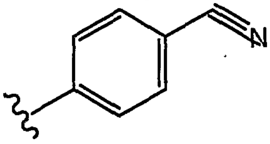
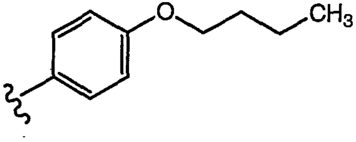
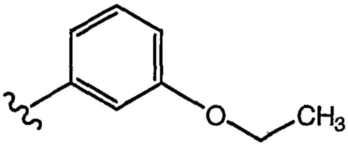
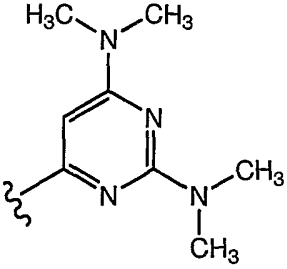
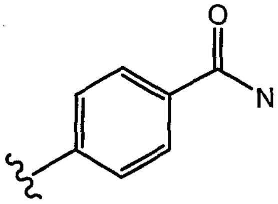
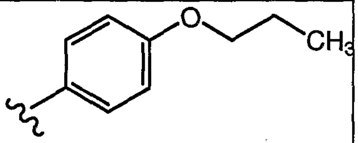
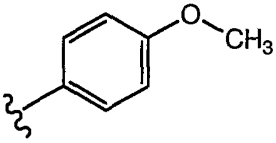
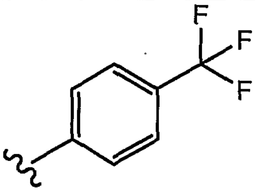
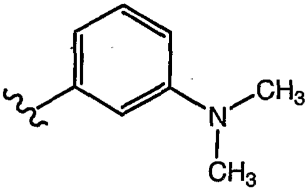
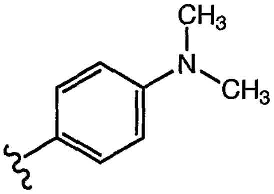
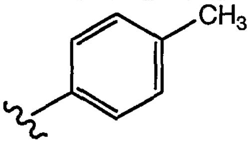
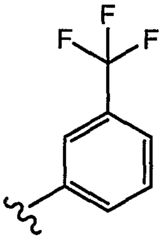
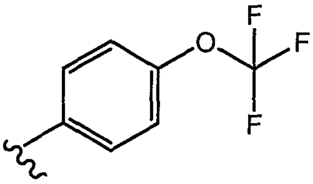
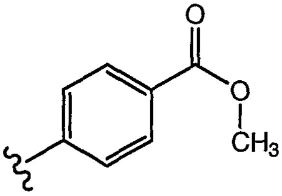
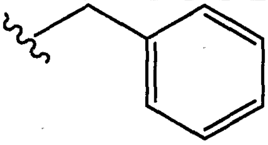
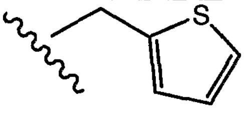
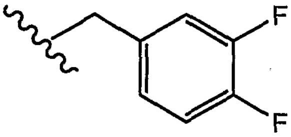
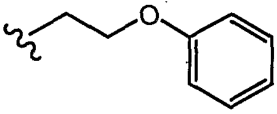
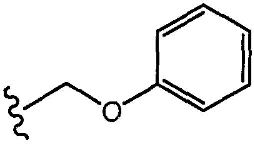
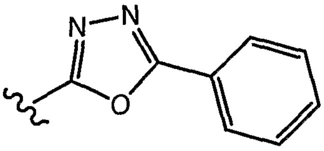
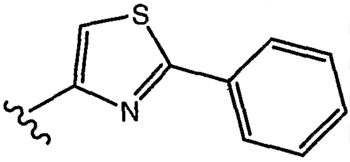
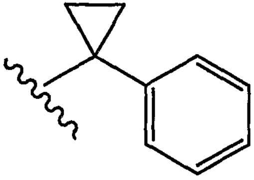
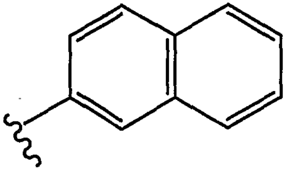
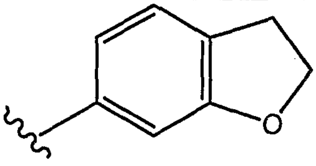
In another embodiment of the compounds of Formula (II), R^4 is $-R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of butyl, phenyl, fluorenyl, phenylphenyl, phenylmethyl, phenylethyl, phenylphenylmethyl, diphenylethyl, phenyloxymethyl, phenyloxyethyl, phenyloxyphenyl, naphthyloxymethyl, phenylcyclopropyl, phenylcarbonylphenyl, phenylcarbonylaminoethyl, thiophenylmethyl, phenyl-oxadiazolyl, thiazolylphenyl, phenylthiazolyl, phenylpyridinyl, phenylpyrimidinyl, pyridinylphenyl and pyrimidinylphenyl; and wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein.

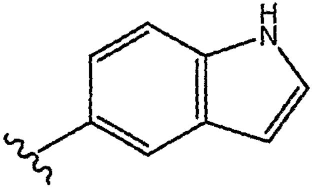
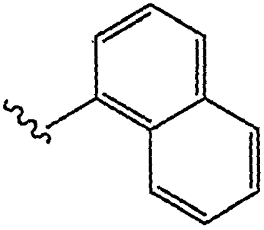
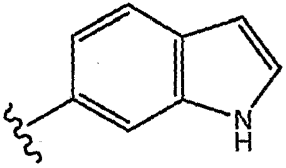
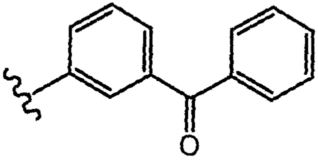
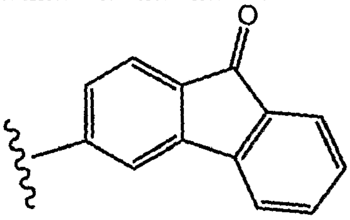
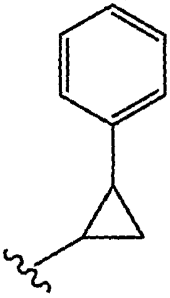
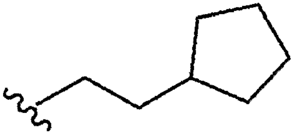
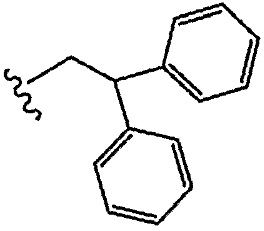
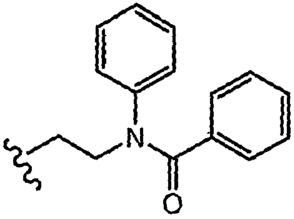
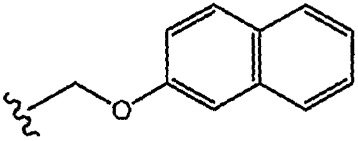
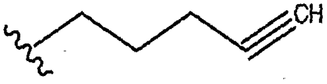
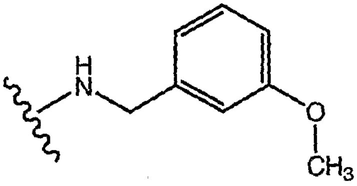
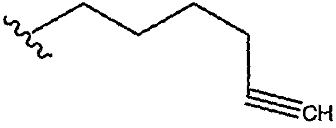
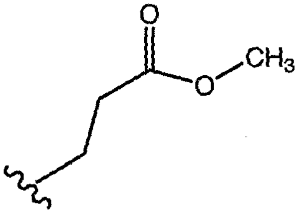
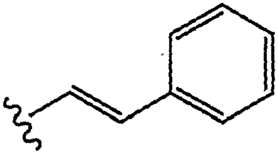
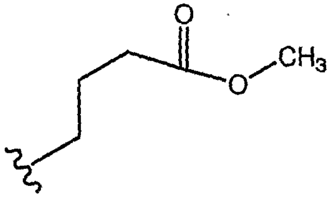
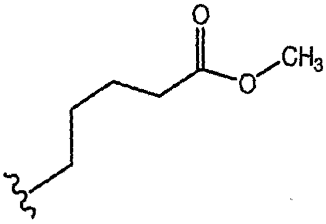
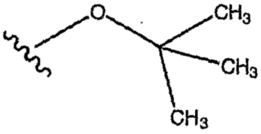
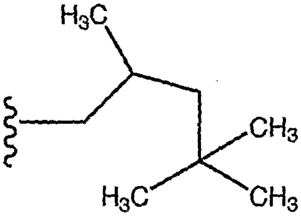
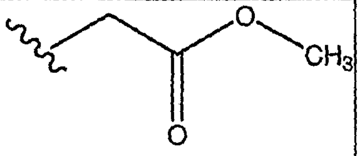
In another embodiment of the compounds of Formula (II), R^4 is selected from the group consisting of $-R^{4j}$, $-OR^{4j}$ and $-NR^{4j}R^{4k}$; wherein R^{4j} and R^{4k} are independently selected from the group consisting of:

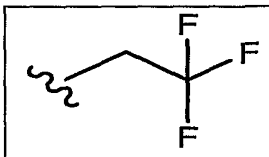
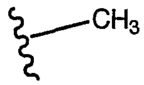
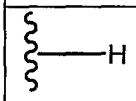
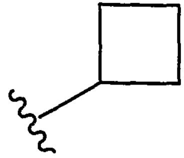
		
		
		
		

N	O CH3	O CH3
H3C N CH3 N N N CH3 CH3	O N	O CH3
O CH3	F F F	CH3 N CH3
CH3 N CH3	CH3	F F F
O F F F	O O CH3	
S	F F	O
O	N N O	S N
		O

		
	and	

wherein the R^{4j} and R^{4k} substituents may be optionally substituted as provided in other embodiments herein.

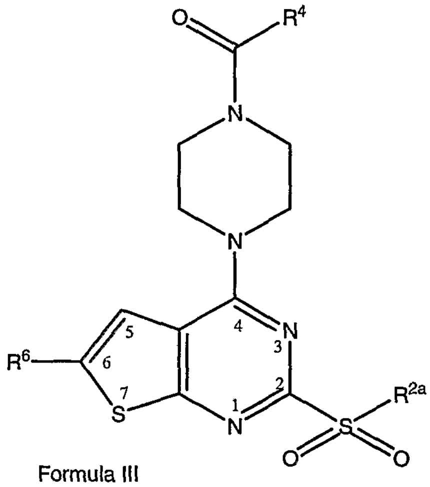
In another embodiment of the compounds of Formula (II), the R^{4j} and R^{4k} substituents each may be optionally substituted with one or more substituents independently selected from the group consisting of oxo, cyano, chloro, bromo, fluoro, methyl, ethyl, propyl, butyl, phenyl, methoxy, trifluoromethyl, trifluoromethoxy, ethoxy, propoxy, butoxy, dimethylamino, carboxy, $-C(O)OCH_3$ and $-C(O)NH_2$.

In another embodiment of the compounds of Formula (II), R^2 is selected from the group consisting of $-S(O)_2R^{2a}$ and $-SR^{2j}$; R^4 is $-R^{4j}$; wherein R^{4j} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl, wherein the R^{4j} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl substituents may be optionally substituted as provided in claim 2; R^5 is selected from the group consisting of hydrogen, halogen, alkyl, and $-OR^{5a}$, wherein the R^5 alkyl substituent may be optionally substituted as provided in claim 1, and R^{5a} is defined as provided in claim 2; and R^6 is selected from the group consisting of halogen, cyano, $-R^{6a}$ and $-OR^{6a}$, wherein R^{6a} is defined as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^2 is selected from the group consisting of $-S(O)_2R^{2a}$ and $-SR^{2j}$; R^4 is $-R^{4j}$ and wherein R^{4j} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl, wherein the R^{4j} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl substituents may be optionally substituted as provided in other embodiments herein; R^5 is selected from the group consisting of hydrogen, halogen, and alkyl; R^6 is selected from the group consisting of $-R^{6a}$ and $-OR^{6a}$; and R^{6a} is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl and heterocyclyl, wherein the R^{6a} alkyl, cycloalkyl, aryl and heterocyclyl substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (II), R^2 is selected from the group consisting of $-S(O)_2R^{2a}$ and $-SR^{2j}$; R^4 is $-R^{4j}$ and wherein R^{4j} is selected from the group consisting of methyl, phenyl, isothiazolyl, oxadiazolyl, pentynyl, hexynyl, furanyl, dihydrobenzodioxine, pyridinyl, dihydrobenzofuranyl, butynyl, napthalenyl, thiazolyl, indolyl, propyl, butyl, ethyl, ethenyl, isoxazolyl and pentanyl; wherein the R^{4j} substituents may be optionally substituted as provided in other embodiments herein; R^5 is hydrogen; X^6 represents a bond; R^6 is $-R^{6a}$; and R^{6a} is alkyl, wherein the R^{6a} alkyl substituent may be optionally substituted as provided in other embodiments herein.

Another class of compounds of specific interest includes compounds, and pharmaceutically acceptable salts of the compounds, wherein the compounds have the structure of Formula III:



Formula III

wherein:

R^{2a} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl;

wherein the R^{2a} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl substituents may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, cyano, oxo, =S, nitro, $-R^{2d}$, $-C(O)R^{2d}$, $-C(S)R^{2d}$, $-C(O)OR^{2d}$, $-C(S)OR^{2d}$, $-C(O)SR^{2d}$,

$-C(O)NR^{2d}R^{2e}$, $-C(S)NR^{2d}R^{2e}$, $-OR^{2d}$, $-OC(O)R^{2d}$, $-OC(S)R^{2d}$, $-OC(O)OR^{2d}$, $-OC(O)NR^{2d}R^{2e}$, $-OC(S)NR^{2d}R^{2e}$, $-NR^{2d}R^{2e}$, $-NR^{2d}C(O)R^{2e}$, $-NR^{2d}C(S)R^{2e}$, $-NR^{2d}C(O)OR^{2e}$, $-NR^{2d}C(S)OR^{2e}$, $-NR^{2d}S(O)_nR^{2e}$, $-NR^{2d}C(O)NR^{2e}R^{2f}$, $-S(O)_nR^{2d}$, $-S(O)_nNR^{2d}R^{2e}$, and $-SC(O)R^{2d}$;

n is 0, 1 or 2;

R^{2d}, R^{2e} and R^{2f} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl;

wherein the R^{2d}, R^{2e} and R^{2f} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl substituents may be optionally substituted as provided in other embodiments herein;

R^4 is $-R^{4j}$; wherein R^{4j} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl, wherein the R^{4j} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl substituents may be optionally substituted as provided in other embodiments herein;

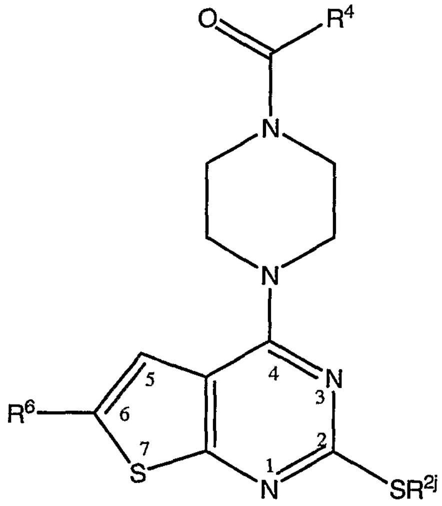
R^5 is selected from the group consisting of hydrogen, halogen, alkyl, and $-OR^{5a}$, wherein the R^5 alkyl substituent may be optionally substituted as provided in claim 1, and R^{5a} is defined as provided in claim 2; and R^6 is selected from the group consisting of $-R^{6a}$ and $-OR^{6a}$, wherein R^{6a} is defined as provided in other embodiments herein.

In another embodiment of the compounds of Formula (III), R^{2a} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl; wherein the R^{2a} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl substituents may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, cyano, oxo, =S, nitro, $-R^{2d}$, $-C(O)R^{2d}$, $-C(S)R^{2d}$, $-C(O)OR^{2d}$, $-C(S)OR^{2d}$, $-C(O)SR^{2d}$, $-C(O)NR^{2d}R^{2e}$, $-C(S)NR^{2d}R^{2e}$, , $-OR^{2d}$, $-OC(O)R^{2d}$, $-OC(S)R^{2d}$, $-OC(O)OR^{2d}$, $-OC(O)NR^{2d}R^{2e}$, $-OC(S)NR^{2d}R^{2e}$, $-NR^{2d}R^{2e}$, $-NR^{2d}C(O)R^{2e}$, $-NR^{2d}C(S)R^{2e}$, $-NR^{2d}C(O)OR^{2e}$, $-NR^{2d}C(S)OR^{2e}$, $-NR^{2d}S(O)_nR^{2e}$, $-NR^{2d}C(O)NR^{2e}R^{2f}$, $-S(O)_nR^{2d}$, $-S(O)_nNR^{2d}R^{2e}$, and $-SC(O)R^{2d}$; n is 0, 1 or 2; R^{2d}, R^{2e} and R^{2f} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl; wherein the R^{2d}, R^{2e} and R^{2f} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (III), R^{2a} is alkyl; wherein the R^{2a} alkyl substituent may be optionally substituted with $-C(O)OR^{2d}$; R^{2d} is alkyl; and wherein the R^{2d} alkyl substituent may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (III), R^{2a} is methyl; wherein the R^{2a} methyl substituent may be optionally substituted with $-C(O)OR^{2d}$; and R^{2d} is methyl. In another embodiment of the compounds of Formula (II), R^{2a} is methoxycarbonylmethyl.

Another class of compounds of specific interest includes compounds, and pharmaceutically acceptable salts of the compounds, wherein the compounds have the structure of Formula IV:



Formula IV

wherein:

R^{2j} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl; wherein:

(a) the R^{2j} C_7-C_{20} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl substituent may be optionally substituted with one or more substituents independently selected from the group consisting of halogen and -R^{2m}; and

(b) the R^{2j} C_1-C_6 alkyl substituent is substituted with at least one substituent independently selected from the group consisting of chloro, bromo, iodo, and -R^{2m};

R^{2m} is selected from the group consisting of cyano, nitro, -NH_2, oxo, =S, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, -C(O)R^{2n}, -C(S)R^{2n}, -C(O)OR^{2n}, -C(S)OR^{2n}, -C(O)SR^{2n}, -C(O)N$R^{2n}R^{2o}$,

-C(S)N$R^{2n}R^{2o}$, -C(O)ON$R^{2n}R^{2o}$, -C(O)OC(O)R^{2n}, -C(O)SC(O)R^{2n}, –OR^{2n}, -OC(O)R^{2n}, -OC(S)R^{2n}, -OC(O)OR^{2n}, -OC(O)N$R^{2n}R^{2o}$, -OC(S)N$R^{2n}R^{2o}$, -N$R^{2n}R^{2o}$, -NR^{2n}C(O)R^{2o}, -NR^{2n}C(S)R^{2o}, -NR^{2n}C(O)OR^{2o},

-NR^{2n}C(S)OR^{2o}, -NR^{2n}S(O)$_q$$R^{2o}$, -N$R^{2n}$C(O)N$R^{2o}R^{2p}$, -S(O)$_q$$R^{2n}$, -S(O)$_qNR^{2n}R^{2o}$, and -SC(O)$R^{2n}$;

q is 0, 1 or 2;

R^{2n}, R^{2o} and R^{2p} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl;

wherein the R^{2m}, R^{2n}, R^{2o} and R^{2p} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl substituents may be optionally substituted as provided in other embodiments herein.

R^4 is –R^{4j}; wherein R^{4j} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl, wherein the R^{4j} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl substituents may be optionally substituted as provided in other embodiments herein; and R^6 is selected from the group consisting of –R^{6a} and –OR^{6a}, wherein R^{6a} is defined as provided in other embodiments herein.

In another embodiment of the compounds of Formula (IV, R^{2j} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl; wherein: (a) the R^{2j} alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl substituent may be optionally substituted with one or more substituents independently selected from the group consisting of halogen and -R^{2m}; and (b) the R^{2j} C_1-C_6 alkyl substituent is substituted with at least one substituent independently selected from the group consisting of chloro, bromo, iodo, and -R^{2m}; R^{2m} is selected from the group consisting of cyano, nitro, -NH_2, oxo, =S, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, -C(O)R^{2n}, -C(S)R^{2n}, -C(O)OR^{2n}, -C(S)OR^{2n}, -C(O)SR^{2n}, -C(O)N$R^{2n}R^{2o}$, -C(S)N$R^{2n}R^{2o}$, -C(O)ON$R^{2n}R^{2o}$, -C(O)OC(O)R^{2n}, -C(O)SC(O)R^{2n}, –OR^{2n}, -OC(O)R^{2n}, -OC(S)R^{2n}, -OC(O)OR^{2n}, -OC(O)N$R^{2n}R^{2o}$, -OC(S)N$R^{2n}R^{2o}$, -N$R^{2n}R^{2o}$, -NR^{2n}C(O)R^{2o}, -NR^{2n}C(S)R^{2o}, -NR^{2n}C(O)OR^{2o}, -NR^{2n}C(S)OR^{2o}, -NR^{2n}S(O)$_q$$R^{2o}$, -N$R^{2n}$C(O)N$R^{2o}R^{2p}$, -S(O)$_q$$R^{2n}$, -S(O)$_qNR^{2n}R^{2o}$, and -SC(O)$R^{2n}$; q is 0, 1 or 2; R^{2n}, R^{2o} and R^{2p} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl; wherein the R^{2m}, R^{2n}, R^{2o} and R^{2p} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (III), R^{2j} is selected from the group consisting of C_1-C_6 alkyl and alkenyl; wherein: (a) the R^{2j} alkenyl substituent may be optionally substituted with one or more substituents independently selected from the group consisting of halogen and -R^{2m}; and (b) the R^{2j} C_1-C_6 alkyl substituent is substituted with at least one substituent independently selected from the group consisting of chloro, bromo, iodo, and -R^{2m}; R^{2m} is selected from the group consisting of cyano, nitro, -NH_2, oxo, =S, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, -C(O)R^{2n}, -C(S)R^{2n}, -C(O)OR^{2n}, -C(S)OR^{2n}, -C(O)SR^{2n}, -C(O)N$R^{2n}R^{2o}$, -C(S)N$R^{2n}R^{2o}$, -C(O)ON$R^{2n}R^{2o}$, -C(O)OC(O)R^{2n}, -C(O)SC(O)R^{2n}, –OR^{2n}, -OC(O)R^{2n}, -OC(S)R^{2n}, -OC(O)OR^{2n}, -OC(O)N$R^{2n}R^{2o}$, -OC(S)N$R^{2n}R^{2o}$, -N$R^{2n}R^{2o}$, -NR^{2n}C(O)R^{2o}, -NR^{2n}C(S)R^{2o}, -NR^{2n}C(O)OR^{2o}, -NR^{2n}C(S)OR^{2o}, -NR^{2n}S$(O)_q$$R^{2o}$, -N$R^{2n}$C(O)N$R^{2o}R^{2p}$, -S$(O)_q$$R^{2n}$, -S$(O)_qNR^{2n}R^{2o}$, and -SC(O)$R^{2n}$; q is 0, 1 or 2; R^{2n}, R^{2o} and R^{2p} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl; wherein the R^{2m}, R^{2n}, R^{2o} and R^{2p} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (III), R^{2j} is selected from the group consisting of C_1-C_6 alkyl and alkenyl; wherein: (a) the R^{2j} alkenyl substituent may be optionally substituted with one or more substituents independently selected from the group consisting of halogen and -R^{2m}; and (b)the R^{2j} C_1-C_6 alkyl substituent is substituted with at least one substituent -R^{2m}; R^{2m} is selected from the group consisting of aryl, heterocyclyl, -C(O)R^{2n}, -C(O)OR^{2n}, -C(O)N$R^{2n}R^{2o}$, –OR^{2n} and -N$R^{2n}R^{2o}$; R^{2n} and R^{2o} are independently selected from the group consisting of hydrogen, alkyl and aryl; wherein the R^{2m}, R^{2n} and R^{2o} alkyl, aryl and heterocyclyl substituents may be optionally substituted as provided in other embodiments herein.

In another embodiment of the compounds of Formula (III), R^{2j} is selected from the group consisting of C_1-C_6 alkyl and alkenyl; wherein: (a) the R^{2j} alkenyl substituent may be optionally substituted with one or more substituents independently selected from the group consisting of halogen and -R^{2m}; and (b) the R^{2j} C_1-C_6 alkyl substituent is substituted with at least one substituent -R^{2m}; R^{2m} is selected from the group consisting of aryl, heterocyclyl, -C(O)R^{2n}, -C(O)OR^{2n}, -C(O)N$R^{2n}R^{2o}$, –OR^{2n} and -N$R^{2n}R^{2o}$; R^{2n} and R^{2o} are independently selected from the group consisting of hydrogen, alkyl and aryl; wherein the R^{2j} substituents may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxy, amino, cyano, oxo, =S, -SH, nitro, alkyl, haloalkyl, hydroxyalkyl, carboxy, alkoxy and alkoxycarbonyl.

In another embodiment of the compounds of Formula (III), R^{2j} is selected from the group consisting of alkyl and alkenyl; wherein: (a) the R^{2j} alkenyl substituent may be optionally substituted with one or more substituents independently selected from the group consisting of halogen and -R^{2m}; and (b) the R^{2j} C_1-C_6 alkyl substituent is substituted with at least one substituent -R^{2m}; R^{2m} is selected from the group consisting of aryl, heterocyclyl, -C(O)R^{2n}, -

C(O)OR^{2n}, -C(O)NR^{2n}R^{2o}, –OR^{2n} and -NR^{2n}R^{2o}; R^{2n} and R^{2o} are independently selected from the group consisting of hydrogen, alkyl and aryl; wherein the R^{2m}, R^{2n} and R^{2o} alkyl, aryl and heterocyclyl substituents may be optionally substituted with one or more substituents independently selected from the group consisting of hydroxy, amino, alkyl and carboxy.

In another embodiment of the compounds of Formula (III), R^{2j} is selected from the group consisting of alkenyl, hydroxyalkyl, arylalkyl, heterocyclylalkyl, carboxyalkyl, alkylaminoalkyl, alkylcarbonylalkyl, alkylaminocarbonylalkyl, aminocarbonylalkyl, alkoxycarbonylalkyl, alkoxyalkylcarbonylalkyl, arylaminocarbonylalkyl and carboxyalkylaminocarbonylalkyl; wherein the R^{2j} substituents may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxy, amino, cyano, oxo, =S, -SH, nitro, alkyl, haloalkyl, hydroxyalkyl, carboxy, alkoxy and alkoxycarbonyl.

In another embodiment of the compounds of Formula (III), R^{2j} is selected from the group consisting of carboxymethylaminocarbonylethyl, carboxymethylaminocarbonylmethyl, methoxycarbonylmethyl, hydroxypropyl, hydroxyethyl, methylcarbonylethyl, methylcarbonylmethyl, aminocarbonylmethyl, carboxymethylaminocarbonylethyl, carboxymethylaminocarbonylmethyl, methoxycarbonylethyl, methoxycarbonylethyl, phenylaminocarbonylmethyl, ethylaminocarbonylmethyl, hydroxypropyl, hydroxybutyl, carboxymethyl, pyridinylethyl, propenyl, methylaminoethyl, napthalenylaminocarbonylmethyl, phenylmethyl and furanylmethyl; wherein the R^{2j} substituents may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxy, amino, cyano, oxo, =S, -SH, nitro, alkyl, haloalkyl, hydroxyalkyl, carboxy, alkoxy and alkoxycarbonyl.

In another embodiment of the compounds of Formula (III), R^{2j} is selected from the group consisting of carboxymethylaminocarbonylethyl, carboxymethylaminocarbonylmethyl, methoxycarbonylmethyl, hydroxypropyl, hydroxyethyl, methylcarbonylethyl, methylcarbonylmethyl, aminocarbonylmethyl, carboxymethylaminocarbonylethyl, carboxymethylaminocarbonylmethyl, methoxycarbonylethyl, methoxycarbonylethyl, phenylaminocarbonylmethyl, ethylaminocarbonylmethyl, hydroxypropyl, hydroxybutyl, carboxymethyl, pyridinylethyl, propenyl, methylaminoethyl, napthalenylaminocarbonylmethyl, phenylmethyl and furanylmethyl; and wherein the R^{2j} substituents may be optionally substituted with one or more substituents independently selected from the group consisting of hydroxy, amino, alkyl and carboxy.

In another embodiment of the compounds of Formula (III), R^{2j} is selected from the group consisting of alkenyl, hydroxyalkyl, arylalkyl, heterocyclylalkyl, carboxyalkyl, alkylaminoalkyl, alkylcarbonylalkyl, alkylaminocarbonylalkyl, aminocarbonylalkyl, alkoxycarbonylalkyl, alkoxyalkylcarbonylalkyl, arylaminocarbonylalkyl and carboxyalkylaminocarbonylalkyl; wherein the R^{2j} substituents may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxy, amino, cyano, oxo, =S, -SH, nitro, alkyl, haloalkyl, hydroxyalkyl, carboxy, alkoxy and alkoxycarbonyl;R^4 is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heterocyclyl, arylalkyl, arylalkenyl, arylaryl, arylheterocyclyl, heterocyclylalkyl, heterocyclylaryl, cycloalkylalkyl, haloaryl, haloalkylaryl, haloalkoxyaryl, cyanoaryl, alkoxyalkyl, alkoxyaryl, alkoxyarylheterocyclyl, alkoxycarbonylalkyl, alkoxycarbonylaryl, alkylaminoaryl, alkylaminoheterocyclyl and aminocarbonylaryl; wherein the R^4 substituents may be optionally substituted with one or more substituents independently selected from the group consisting of hydroxy, oxo, cyano, chloro, bromo, fluoro, methyl, ethyl, propyl, butyl, phenyl, methoxy, trifluoromethyl, trifluoromethoxy, ethoxy, propoxy, butoxy, dimethylamino, carboxy, $-C(O)OCH_3$ and $-C(O)NH_2$; and R^6 is alkyl.

In another embodiment of the compounds of Formula (III), R^{2j} is hydroxyalkyl; wherein the R^{2j} hydroxyalkyl may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxy, amino, cyano, alkyl, haloalkyl, hydroxyalkyl, carboxy, alkoxy and alkoxycarbonyl; R^4 is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heterocyclyl, arylalkyl, arylalkenyl, arylaryl, arylheterocyclyl, heterocyclylalkyl, heterocyclylaryl, cycloalkylalkyl, haloaryl, haloalkylaryl, haloalkoxyaryl, cyanoaryl, alkoxyalkyl, alkoxyaryl, alkoxyarylheterocyclyl, alkoxycarbonylalkyl, alkoxycarbonylaryl, alkylaminoaryl, alkylaminoheterocyclyl and aminocarbonylaryl; wherein the R^4 substituents may be optionally substituted with one or more substituents independently selected from the group consisting of hydroxy, oxo, cyano, chloro, bromo, fluoro, methyl, ethyl, propyl, butyl, phenyl, methoxy, trifluoromethyl, trifluoromethoxy, ethoxy, propoxy, butoxy, dimethylamino, carboxy, $-C(O)OCH_3$ and $-C(O)NH_2$; and R^6 is alkyl.

In another embodiment of the compounds of Formula (III), R^{2j} is alkoxycarbonylalkyl; wherein the R^{2j} alkoxycarbonylalkyl may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxy, amino, cyano, alkyl, haloalkyl, hydroxyalkyl, carboxy, alkoxy and alkoxycarbonyl; R^4 is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heterocyclyl, arylalkyl, arylalkenyl, arylaryl, arylheterocyclyl, heterocyclylalkyl, heterocyclylaryl, cycloalkylalkyl, haloaryl, haloalkylaryl, haloalkoxyaryl, cyanoaryl, alkoxyalkyl, alkoxyaryl, alkoxyarylheterocyclyl, alkoxycarbonylalkyl, alkoxycarbonylaryl, alkylaminoaryl, alkylaminoheterocyclyl and aminocarbonylaryl;

wherein the R^4 substituents may be optionally substituted with one or more substituents independently selected from the group consisting of hydroxy, oxo, cyano, chloro, bromo, fluoro, methyl, ethyl, propyl, butyl, phenyl, methoxy, trifluoromethyl, trifluoromethoxy, ethoxy, propoxy, butoxy, dimethylamino, carboxy, $-C(O)OCH_3$ and $-C(O)NH_2$; and R^6 is alkyl.

In another embodiment of the compounds of Formula (III), R^{2j} is selected from the group consisting of carboxymethylaminocarbonylethyl, carboxymethylaminocarbonylmethyl,

methoxycarbonylmethyl, hydroxypropyl, hydroxyethyl, methylcarbonylethyl, methylcarbonylmethyl, aminocarbonylmethyl, carboxymethylaminocarbonylethyl, carboxymethylaminocarbonylmethyl, methoxycarbonylethyl, methoxycarbonylethyl, methoxycarbonylethyl, phenylaminocarbonylmethyl, ethylaminocarbonylmethyl, hydroxypropyl, hydroxybutyl, carboxymethyl, pyridinylethyl, propenyl, methylaminoethyl, napthalenylaminocarbonylmethyl, phenylmethyl and furanylmethyl; wherein the R^{2j} substituents may be optionally substituted with one or more substituents independently selected from the group consisting of hydroxy, amino, alkyl and carboxy; R^{4j} is selected from the group consisting of phenylmethyl, phenylphenyl, phenylisothiazolyl, phenyloxadiazolyl, pentynyl, hexynyl, pyrazolylphenyl, propoxyphenyl, thiadiazolylphenyl, benzofuranyl, butoxyphenyl,dihydrobenzodioxinyl, bis(dimethylamino)pyridinyl, ethoxyphenyl, dihydrobenzofuranyl, butynyl, napthalenyl, phenylthiazolyl, indolyl, methylphenyl, phenyl, methoxycarbonylpropyl, methoxycarbonylbutyl, methoxycarbonylphenyl, methoxyethyl, methoxycarbonylmethyl, methoxycarbonylethyl, cyclopentylethyl, dimethylaminophenyl, phenylethenyl, methoxyphenyl, methylmethoxyphenyl, methoxyphenylisoxazolyl, aminocarbonylphenyl and pentyl;wherein the R^4 substituents may be optionally substituted with one or more substituents independently selected from the group consisting of hydroxy, oxo, cyano, chloro,
bromo, fluoro, methyl, ethyl, propyl, butyl, phenyl, methoxy, trifluoromethyl, trifluoromethoxy, ethoxy, propoxy, butoxy, dimethylamino, carboxy, $-C(O)OCH_3$ and $-C(O)NH_2$; and R^6 is selected from the group consisting of methyl, ethyl, propyl and butyl.

In another embodiment of the compounds of Formula (III), R^{2j} is selected from the group consisting of carboxymethylaminocarbonylethyl, carboxymethylaminocarbonylmethyl, methoxycarbonylmethyl, hydroxypropyl, hydroxyethyl, methylcarbonylethyl, methylcarbonylmethyl, aminocarbonylmethyl, carboxymethylaminocarbonylethyl, carboxymethylaminocarbonylmethyl, methoxycarbonylethyl, methoxycarbonylethyl, phenylaminocarbonylmethyl, ethylaminocarbonylmethyl, hydroxypropyl, hydroxybutyl, carboxymethyl, pyridinylethyl, propenyl, methylaminoethyl, napthalenylaminocarbonylmethyl, phenylmethyl and furanylmethyl; wherein the R^{2j} substituents may be optionally substituted with one or more substituents independently selected from the group consisting of hydroxy, amino, alkyl and carboxy; R^{4j} is selected from the group consisting of phenylmethyl, phenylphenyl, phenylisothiazolyl, phenyloxadiazolyl, pentynyl, hexynyl, pyrazolylphenyl, propoxyphenyl, thiadiazolylphenyl, benzofuranyl, butoxyphenyl,dihydrobenzodioxinyl, bis(dimethylamino)pyridinyl, ethoxyphenyl, dihydrobenzofuranyl, butynyl, napthalenyl, phenylthiazolyl, indolyl, methylphenyl, phenyl, methoxycarbonylpropyl, methoxycarbonylbutyl, methoxycarbonylphenyl, methoxyethyl, methoxycarbonylmethyl, methoxycarbonylethyl, cyclopentylethyl, dimethylaminophenyl, phenylethenyl, methoxyphenyl, methylmethoxyphenyl, methoxyphenylisoxazolyl, aminocarbonylphenyl and pentyl; wherein the R^4 substituents may be optionally substituted with one or more substituents independently selected from the group consisting of hydroxy, oxo, cyano, chloro, bromo, fluoro, methyl, ethyl, propyl, butyl, phenyl, methoxy, trifluoromethyl, trifluoromethoxy, ethoxy, propoxy, butoxy, dimethylamino, carboxy, -C(O)OCH$_3$ and –C(O)NH$_2$; and R^6 is ethyl.

Another embodiment of the compounds of Formula (I) is selected from group consisting of:
methyl ({6-ethyl-4-[4-(phenylacetyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)acetate;
Methyl ({6-ethyl-4-[4-(phenylacetyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}sulfonyl)acetate;
2-({6-Ethyl-4-[4-(phenylacetyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)-N-2-naphthylacetamide;
2-(Allylthio)-6-ethyl-4-[4-(phenylacetyl)piperazin-1-yl]thieno[2,3-d]pyrimidine;
N-[2-({6-Ethyl-4-[4-(phenylacetyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)propanoyl]glycine;
3-({6-Ethyl-4-[4-(phenylacetyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)propane-1,2-diol;
2-({6-Ethyl-4-[4-(phenylacetyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)-N-methylacetamide;
3-({6-Ethyl-4-[4-(phenylacetyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)butan-2-one;
N-[2-({6-Ethyl-4-[4-(phenylacetyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)ethyl]acetamide;
Methyl S-{6-ethyl-4-[4-(phenylacetyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}-L-cysteinate;
1-({6-Ethyl-4-[4-(phenylacetyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)propan-2-ol;
Methyl ({4-[4-(1,1'-biphenyl-4-ylcarbonyl)piperazin-1-yl]-6-ethylthieno[2,3-d]pyrimidin-2-yl}thio)acetate;
2-({6-Ethyl-4-[4-(phenylacetyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)-N-phenylacetamide;
2-({6-Ethyl-4-[4-(phenylacetyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)acetamide;
2-({6-Ethyl-4-[4-(phenylacetyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)propanoic acid;
6-Ethyl-4-[4-(phenylacetyl)piperazin-1-yl]-2-[(2-pyridin-4-ylethyl)thio]thieno[2,3-d]pyrimidine;
N-[2-({4-[4-(1,1'-Biphenyl-4-ylcarbonyl)piperazin-1-yl]-6-ethylthieno[2,3-d]pyrimidin-2-yl}thio)ethyl]acetamide ;
3-({4-[4-(1,1'-Biphenyl-4-ylcarbonyl)piperazin-1-yl]-6-ethylthieno[2,3-d]pyrimidin-2-yl}thio)propane-1,2-diol;
3-({4-[4-(1,1'-Biphenyl-4-ylcarbonyl)piperazin-1-yl]-6-ethylthieno[2,3-d]pyrimidin-2-yl}thio)butan-2-one;
N-[2-({4-[4-(1,1'-Biphenyl-4-ylcarbonyl)piperazin-1-yl]-6-ethylthieno[2,3-d]pyrimidin-2-yl}thio)propanoyl]glycine;
2-({4-[4-(1,1'-Biphenyl-4-ylcarbonyl)piperazin-1-yl]-6-ethylthieno[2,3-d]pyrimidin-2-yl}thio)acetamide;
2-({4-[4-(1,1'-Biphenyl-4-ylcarbonyl)piperazin-1-yl]-6-ethylthieno[2,3-d]pyrimidin-2-yl}thio)ethanol;
Methyl {[6-ethyl-4-(4-hex-5-ynoylpiperazin-1-yl)thieno[2,3-d]pyrimidin-2-yl]thio}acetate;
Methyl {[6-ethyl-4-(4-hept-6-ynoylpiperazin-1-yl)thieno[2,3-d]pyrimidin-2-yl]thio}acetate;
Methyl {[6-ethyl-4-(4-pent-4-ynoylpiperazin-1-yl)thieno[2,3-d]pyrimidin-2-yl]thio}acetate;
Methyl ({4-[4-(2,3-dihydro-1,4-benzodioxin-2-ylcarbonyl)piperazin-1-yl]-6-ethylthieno[2,3-d]pyrimidin-2-yl}thio)acetate;

Methyl ({6-ethyl-4-[4-(3,5,5-trimethylhexanoyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)acetate;

Methyl ({4-[4-(3-cyclopentylpropanoyl)piperazin-1-yl]-6-ethylthieno[2,3-d]pyrimidin-2-yl}thio)acetate;

Methyl 5-(4-{6-ethyl-2-[(2-methoxy-2-oxoethyl)thio]thieno[2,3-d]pyrimidin-4-yl}piperazin-1-yl)-5-oxopentanoate;

Methyl 4-(4-{6-ethyl-2-[(2-methoxy-2-oxoethyl)thio]thieno[2,3-d]pyrimidin-4-yl}piperazin-1-yl)-4-oxobutanoate;

Methyl 6-(4-{6-ethyl-2-[(2-methoxy-2-oxoethyl)thio]thieno[2,3-d]pyrimidin-4-yl}piperazin-1-yl)-6-oxohexanoate;

Methyl 3-(4-{6-ethyl-2-[(2-methoxy-2-oxoethyl)thio]thieno[2,3-d]pyrimidin-4-yl}piperazin-1-yl)-3-oxopropanoate;

Methyl ({6-ethyl-4-[4-(4-methylbenzoyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)acetate;

Methyl [(6-ethyl-4-{4-[4-(trifluoromethyl)benzoyl]piperazin-1-yl}thieno[2,3-d]pyrimidin-2-yl)thio]acetate;

Methyl [(6-ethyl-4-{4-[(2E)-3-phenylprop-2-enoyl]piperazin-1-yl}thieno[2,3-d]pyrimidin-2-yl)thio]acetate;

Methyl [(6-ethyl-4-{4-[4-(1H-pyrazol-1-yl)benzoyl]piperazin-1-yl}thieno[2,3-d]pyrimidin-2-yl)thio]acetate;

Methyl [(6-ethyl-4-{4-[4-(trifluoromethoxy)benzoyl]piperazin-1-yl}thieno[2,3-d]pyrimidin-2-yl)thio]acetate;

Methyl ({6-ethyl-4-[4-(1-naphthoyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)acetate;

Methyl ({4-[4-(3,5-difluorobenzoyl)piperazin-1-yl]-6-ethylthieno[2,3-d]pyrimidin-2-yl}thio)acetate;

Methyl ({4-[4-(4-cyanobenzoyl)piperazin-1-yl]-6-ethylthieno[2,3-d]pyrimidin-2-yl}thio)acetate;

Methyl ({4-[4-(2,5-difluorobenzoyl)piperazin-1-yl]-6-ethylthieno[2,3-d]pyrimidin-2-yl}thio)acetate;

Methyl [(4-{4-[4-(dimethylamino)benzoyl]piperazin-1-yl}-6-ethylthieno[2,3-d]pyrimidin-2-yl)thio]acetate;

Methyl ({6-ethyl-4-[4-(2-naphthoyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)acetate;

Methyl {[4-(4-benzoylpiperazin-1-yl)-6-ethylthieno[2,3-d]pyrimidin-2-yl]thio}acetate;

Methyl ({4-[4-(4-ethoxybenzoyl)piperazin-1-yl]-6-ethylthieno[2,3-d]pyrimidin-2-yl}thio)acetate;

Methyl ({6-ethyl-4-[4-(3-methoxypropanoyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)acetate;

Methyl ({6-ethyl-4-[4-(4-methoxybenzoyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)acetate;

Methyl [(6-ethyl-4-{4-[3-(trifluoromethyl)benzoyl]piperazin-1-yl}thieno[2,3-d]pyrimidin-2-yl)thio]acetate;

Methyl ({6-ethyl-4-[4-(3-methylbenzoyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)acetate;

Methyl ({6-ethyl-4-[4-(1H-indol-5-ylcarbonyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)acetate;

Methyl ({6-ethyl-4-[4-(1H-indol-6-ylcarbonyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)acetate;

Methyl ({4-[4-(3-cyanobenzoyl)piperazin-1-yl]-6-ethylthieno[2,3-d]pyrimidin-2-yl}thio)acetate;

Methyl ({4-[4-(1-benzofuran-6-ylcarbonyl)piperazin-1-yl]-6-ethylthieno[2,3-d]pyrimidin-2-yl}thio)acetate ;

Methyl [(6-ethyl-4-{4-[4-(1,2,3-thiadiazol-4-yl)benzoyl]piperazin-1-yl}thieno[2,3-d]pyrimidin-2-yl)thio]acetate;

Methyl ({4-[4-(2,3-dihydro-1-benzofuran-6-ylcarbonyl)piperazin-1-yl]-6-ethylthieno[2,3-d]pyrimidin-2-yl}thio)acetate;

Methyl {[6-ethyl-4-(4-{[3-(4-methoxyphenyl)-5-methylisoxazol-4-yl]carbonyl}piperazin-1-yl)thieno[2,3-d]pyrimidin-2-yl]thio}acetate;

Methyl [(6-ethyl-4-{4-[(2-phenyl-1,3-thiazol-4-yl)carbonyl]piperazin-1-yl}thieno[2,3-d]pyrimidin-2-yl)thio]acetate;

Methyl [(6-ethyl-4-{4-[(5-phenyl-1,3,4-oxadiazol-2-yl)carbonyl]piperazin-1-yl}thieno[2,3-d]pyrimidin-2-yl)thio]acetate;

Methyl ({6-ethyl-4-[4-(4-propoxybenzoyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)acetate;

Methyl {[4-(4-{[2,6-bis(dimethylamino)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-6-ethylthieno[2,3-d]pyrimidin-2-yl]thio}acetate;

Methyl ({4-[4-(4-butoxybenzoyl)piperazin-1-yl]-6-ethylthieno[2,3-d]pyrimidin-2-yl}thio)acetate;

Methyl [(4-{4-[3-(dimethylamino)benzoyl]piperazin-1-yl}-6-ethylthieno[2,3-d]pyrimidin-2-yl)thio]acetate ;

Methyl ({6-ethyl-4-[4-(3-methoxybenzoyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)acetate;

Methyl ({4-[4-(3-ethoxybenzoyl)piperazin-1-yl]-6-ethylthieno[2,3-d]pyrimidin-2-yl}thio)acetate;

Methyl ({6-ethyl-4-[4-(quinoxalin-6-ylcarbonyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)acetate;

Methyl ({4-[4-(1,1'-biphenyl-3-ylcarbonyl)piperazin-1-yl]-6-ethylthieno[2,3-d]pyrimidin-2-yl}thio)acetate;

Methyl [(4-{4-[4-(aminocarbonyl)benzoyl]piperazin-1-yl}-6-ethylthieno[2,3-d]pyrimidin-2-yl)thio]acetate;

Methyl 4-[(4-{6-ethyl-2-[(2-methoxy-2-oxoethyl)thio]thieno[2,3-d]pyrimidin-4-yl}piperazin-1-yl)carbonyl]benzoate;

Methyl [(6-ethyl-4-{4-[(2-pyridin-3-yl-1,3-thiazol-4-yl)carbonyl]piperazin-1-yl}thieno[2,3-d]pyrimidin-2-yl)thio]acetate;

methyl 3-({6-ethyl-4-[4-(phenylacetyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)propanoate;

({6-ethyl-4-[4-(phenylacetyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)acetic acid;

4-({6-ethyl-4-[4-(phenylacetyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)butan-1-ol;

2-(benzylthio)-6-ethyl-4-[4-(phenylacetyl)piperazin-1-yl]thieno[2,3-d]pyrimidine;

6-ethyl-2-[(2-furylmethyl)thio]-4-[4-(phenylacetyl)piperazin-1-yl]thieno[2,3-d]pyrimidine;

2-({6-ethyl-4-[4-(phenylacetyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)ethanol; and

N-[2-({6-ethyl-4-[4-(phenylacetyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)ethyl]-N,N-dimethylamine.

C. Isomers

When an asymmetric center is present in a compound of Formulae (I) through (IV) the compound may exist in the form of optical isomers (enantiomers). In one embodiment, the present invention comprises enantiomers and mixtures, including racemic mixtures of the compounds of Formulae (I) through (IV). In another embodiment, for compounds of Formulae (I) through (IV) that contain more than one asymmetric center, the present invention comprises diastereomeric forms (individual diastereomers and mixtures thereof) of compounds. When a compound of Formulae (I) through (IV) contains an alkenyl group or moiety, geometric isomers may arise.

D. Tautomeric Forms

The present invention comprises the tautomeric forms of compounds of Formulae (I) through (IV). Where structural isomers are interconvertible *via* a low energy barrier, tautomeric isomerism ('tautomerism') can occur. This can take the form of proton tautomerism in compounds of formula I containing, for example, an imino, keto, or oxime group, or so-called valence tautomerism in compounds which contain an aromatic moiety. It follows that a single compound may exhibit more than one type of isomerism. The various ratios of the tautomers in solid and liquid form is dependent on the various substituents on the molecule as well as the particular crystallization technique used to isolate a compound.

E. Salts

The compounds of this invention may be used in the form of salts derived from inorganic or organic acids. Depending on the particular compound, a salt of the compound may be advantageous due to one or more of the salt's physical properties, such as enhanced pharmaceutical stability in differing temperatures and humidities, or a desirable solubility in water or oil. In some instances, a salt of a compound also may be used as an aid in the isolation, purification, and/or resolution of the compound.

Where a salt is intended to be administered to a patient (as opposed to, for example, being used in an *in vitro* context), an exemplary saly is pharmaceutically acceptable. The term "pharmaceutically acceptable salt" refers to a salt prepared by combining a compound of Formulae (I) – (IV) with an acid whose anion, or a base whose cation, is generally considered suitable for human consumption. Pharmaceutically acceptable salts are particularly useful as products of the methods of the present invention because of their greater aqueous solubility relative to the parent compound. For use in medicine, the salts of the compounds of this invention are non-toxic "pharmaceutically acceptable salts." Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid. Suitable pharmaceutically acceptable acid addition salts of the compounds of the present invention when possible include those derived from inorganic acids, such as hydrochloric, hydrobromic, hydrofluoric, boric, fluoroboric, phosphoric, metaphosphoric, nitric, carbonic, sulfonic, and sulfuric acids, and organic acids such as acetic, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic, isothionic, lactic, lactobionic, maleic, malic, methanesulfonic, trifluoromethanesulfonic, succinic, toluenesulfonic, tartaric, and trifluoroacetic acids. Suitable organic acids generally include, for example, aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclylic, carboxylic, and sulfonic classes of organic acids.

Specific examples of suitable organic acids include acetate, trifluoroacetate, formate, propionate, succinate, glycolate, gluconate, digluconate, lactate, malate, tartaric acid, citrate, ascorbate, glucuronate, maleate, fumarate, pyruvate, aspartate, glutamate, benzoate, anthranilic acid, mesylate, stearate, salicylate, p-hydroxybenzoate, phenylacetate, mandelate, embonate (pamoate), methanesulfonate, ethanesulfonate, benzenesulfonate, pantothenate, toluenesulfonate, 2-hydroxyethanesulfonate, sufanilate, cyclohexylaminosulfonate, algenic acid, β-hydroxybutyric acid, galactarate, galacturonate, adipate, alginate, butyrate, camphorate, camphorsulfonate, cyclopentanepropionate, dodecylsulfate, glycoheptanoate, glycerophosphate, heptanoate, hexanoate, nicotinate, 2-naphthalesulfonate, oxalate, palmoate, pectinate, 3-phenylpropionate, picrate, pivalate, thiocyanate, tosylate, and undecanoate.

In another embodiment, examples of suitable addition salts formed include the acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsyate, citrate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihidrogen phosphate, saccharate, stearate, succinate, tartrate, tosylate and trifluoroacetate salts. In another embodiment, representative salts include benzenesulfonate, hydrobromide and hydrochloride.

Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g., sodium or potassium salts; alkaline earth metal salts, e.g., calcium or magnesium salts; and salts formed with suitable organic ligands, e.g., quaternary ammonium salts. In another embodiment, base salts are formed from bases which form non-toxic salts, including aluminum, arginine, benzathine, choline, diethylamine, diolamine, glycine, lysine, meglumine, olamine, tromethamine and zinc salts.

Organic salts may be made from secondary, tertiary or quaternary amine salts, such as tromethamine, diethylamine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), and procaine. Basic nitrogen-containing groups may be quaternized with agents such as lower alkyl (C_1-C_6) halides *(e.g.,* methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides), dialkyl sulfates *(e.g.,* dimethyl, diethyl, dibuytl, and diamyl sulfates), long chain halides *(e.g.,* decyl, lauryl, myristyl, and stearyl chlorides, bromides, and iodides), arylalkyl halides *(e.g.,* benzyl and phenethyl bromides), and others.

In one embodiment, hemisalts of acids and bases may also be formed, for example, hemisulphate and hemicalcium salts.

The compounds of the invention may exist in both unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention and a stoichiometric amount of one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water. Included within the scope of the invention are complexes such as clathrates, drug-host inclusion complexes wherein, in contrast to the aforementioned solvates, the drug and host are present in stoichiometric or non-stoichiometric amounts. Also included are complexes of the drug containing two or more organic and/or inorganic components which may be in stoichiometric or non-stoichiometric amounts. The resulting complexes may be ionised, partially ionised, or non-ionised. For a review of such complexes, see J Pharm Sci, 64 (8), 1269-1288, by Haleblian (August 1975).

F. Prodrugs

Also within the scope of the present invention are so-called "prodrugs" of the compounds of Formulae (I) through (IV). Thus, certain derivatives of compounds of any of Formulae (I) through (IV) which may have little or no pharmacological activity themselves can, when administered into or onto the body, be converted into compounds of any of Formulae (I) through (IV) having the desired activity, for example, by hydrolytic cleavage. Such derivatives are referred to as "prodrugs." Further information on the use of prodrugs may be found in "Pro-drugs as Novel Delivery Systems, Vol. 14, ACS Symposium Series (T Higuchi and W Stella) and "Bioreversible Carriers in Drug Design," Pergamon Press, 1987 (ed. E B Roche, American Pharmaceutical Association). Prodrugs in accordance with the invention can, for example, be produced by replacing appropriate functionalities present in the compounds of any of Formulae (I) through (IV) with certain moieties known to those skilled in the art as "pro-moieties" as described, for example, in "Design of Prodrugs" by H Bundgaard (Elseview, 1985).

G. Methods of Treatment

The present invention further comprises methods for treating a condition in a subject having or susceptible to having such a condition, by administering to the subject a therapeutically-effective amount of one or more compounds of Formulae (I) through (IV) as described above. In one embodiment, the treatment is preventative treatment. In another embodiment, the treatment is palliative treatment. In another embodiment, the treatment is restorative treatment.

1. Conditions

The conditions that can be treated in accordance with the present invention include platelet aggregation mediated conditions such as atherosclerotic cardiovascular conditions, cerebrovascular conditions and peripheral arterial conditions, particularly those related to thrombosis. In another embodiment, platelet aggregation mediation conditions may be treated. In still another embodiment, the compounds of the present invention can be used to treat platelet dependent thrombosis or a platelet dependent thrombosis-related condition.

In one embodiment, the compounds of the invention can be used to treat acute coronary syndrome. Acute coronary syndrome includes, but is not limited to, angina (such as unstable angina) and myocardial infarction (such as non-ST-segment elevation myocardial infarction, non-Q-wave myocardial infarction and Q-wave myocardial infarction).

In another embodiment, the compounds of the present invention can be used to treat stroke (such as thrombotic stroke, ischemic stroke, embolic stroke and transient ischemic attack).

In another embodiment, the compounds of the present invention can be used to treat a subject who has suffered from at least one event selected from the group consisting of myocardial infarction and stroke. In another embodiment, the compounds of the present invention can be used to treat atherosclerotic events selected from the group consisting of myocardial infarction, transient ischemic attack, stroke, and vascular death.

In another embodiment, the compounds of the present invention can be used to treat thrombotic and restenotic complications or treat reocclusion following invasive procedures including, but not limited to, angioplasty, percutaneous coronary intervention, carotid endarterectomy, coronary arterial bypass graft ("CABG") surgery, vascular graft surgery, stent placements, lower limb arterial graft, prosthetic heart valve placement, hemodialysis and insertion of endovascular devices and prostheses.

In another embodiment, the compounds of the present invention can be used to treat platelet dependent thrombosis or a platelet dependent thrombosis-related condition that is selected from the group consisting of acute coronary syndrome; unstable angina; non Q-wave myocardial infarction; non-ST segment elevation myocardial infarction; acute myocardial infarction; deep vein thrombosis; pulmonary embolism; ischemic necrosis of tissue; atrial fibrillation; thrombotic stroke; embolic stroke; recent myocardial infarction; peripheral arterial disease; peripheral vascular disease; refractory ischemia; preeclampsia, eclampsia; acute ischemic stroke; disseminated intravascular coagulation; and thrombotic cytopenic purpura.

In another embodiment, the compounds of the present invention can be used to treat thrombotic or restenotic complications or reocclusion. In still another embodiment the thrombotic or restenotic complications or reocclusion are selected from the group consisting of angioplasty, percutaneous coronary intervention, carotid endarterectomy, post-coronary arterial bypass graft surgery, vascular graft surgery, stent placements, lower limb arterial graft, atrial fibrillation, prosthetic heart valve placement, hemodialysis and insertion of endovascular devices and prostheses.

In another embodiment, the compounds of the present invention can be used to reduce the risk in a subject of experiencing vascular events. In still another embodiment, the vascular events are selected from the group consisting of myocardial infarction, stable angina, coronary artery disease, ischemic stroke, transient ischemic attack and peripheral arterial disease.

In another embodiment, the compounds of the present invention can be used to treat hypertension.

In another embodiment, the compounds of the present invention can be used to treat angiogenesis.

2. Administration and Dosing

Typically, a compound described in this specification is administered in an amount effective to inhibit ADP mediated platelet aggregation. The compounds of the present invention are administered by any suitable route in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. Therapeutically effective doses of the compounds required to prevent or arrest the progress of or to treat the medical condition are readily ascertained by one of ordinary skill in the art using preclinical and clinical approaches familiar to the medicinal arts.

The compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth.

In another embodiment, the compounds of the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

In another embodiment, the compounds of the invention may also be administered topically to the skin or mucosa, that is, dermally or transdermally. In another embodiment, the compounds of the invention can also be administered intranasally or by inhalation. In another embodiment, the compounds of the invention may be administered rectally or vaginally. In another embodiment, the compounds of the invention may also be administered directly to the eye or ear.

The dosage regimen for the compounds and/or compositions containing the compounds is based on a variety of factors, including the type, age, weight, sex and medical condition of the patient; the severity of the condition; the route of administration; and the activity of the particular compound employed. Thus the dosage regimen may vary widely. Dosage levels of the order from about 0.01 mg to about 100 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions. In one embodiment, the total daily dose of a compound of Formulae (I) through (IV) (administered in single or divided doses) is typically from about 0.01 to about 100 mg/kg. In another embodiment, total daily dose of the compound of Formulae (I) through (IV) is from about 0.1 to about 50 mg/kg, and in another embodiment, from about 0.5 to about 30 mg/kg (*i.e.*, mg compound of Formulae (I) through (IV) per kg body weight). In one embodiment, dosing is from 0.01 to 10 mg/kg/day. In another embodiment, dosing is from 0.1 to 1.0 mg/kg/day. Dosage unit compositions may contain such amounts or submultiples thereof to make up the daily dose. In many instances, the administration of the compound will be repeated a plurality of times in a day (typically no greater than 4 times). Multiple doses per day typically may be used to increase the total daily dose, if desired.

For oral administration, the compositions may be provided in the form of tablets containing 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 75.0, 100, 125, 150, 175, 200, 250 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. A medicament typically contains from about 0.01 mg to about 500 mg of the active ingredient, or in another embodiment, from about 1mg to about 100 mg of active ingredient. Intravenously, doses may range from about 0.1 to about 10 mg/kg/minute during a constant rate infusion.

Suitable subjects to be treated according to the present invention include mammalian subjects. Mammals according to the present invention include, but are not limited to, canine, feline, bovine, caprine, equine, ovine, porcine, rodents, lagomorphs, primates, and the like, and encompass mammals *in utero*. In one embodiment, humans are suitable subjects. Human subjects may be of either gender and at any stage of development.

H. Use in the Preparation of a Medicament

In one embodiment, the present invention comprises methods for the preparation of a pharmaceutical composition (or "medicament) comprising the compounds of Formulae (I) through (IV) in combination with one or more pharmaceutically-acceptable carriers and/or other active ingredients for use in treating a platelet aggregation mediated condition.

In another embodiment, the invention comprises the use of one or more compounds of Formulae (I) through (IV) in the preparation of a medicament for the treatment of acute coronary syndrome.

In another embodiment, the invention comprises the use of one or more compounds of Formulae (I) through (IV) in the preparation of a medicament for the reduction of atherosclerotic events.

In another embodiment, the invention comprises the use of one or more compounds of Formulae (I) through (IV) in the preparation of a medicament for the treatment of thrombosis.

In another embodiment, the invention comprises the use of one or more compounds of Formulae (I) through (IV) in the preparation of a medicament to be co-administered before, during or after revascularization procedures, including, but not limited to, lower limb arterial graft, carotid endarterectomy, coronary artery bypass surgery, atrial fibrillation, prosthetic heart valve placement, hemodialysis and placement of mechanical devices.

I. Pharmaceutical Compositions

For the treatment of the conditions referred to above, the compounds of Formulae (I) through (IV) can be administered as compound *per se*. Alternatively, pharmaceutically acceptable salts are suitable for medical applications because of their greater aqueous solubility relative to the parent compound.

In another embodiment, the present invention comprises pharmaceutical compositions. Such pharmaceutical compositions comprise compounds of Formulae (I) through (IV) presented with a pharmaceutically-acceptable carrier. The carrier can be a solid, a liquid, or both, and may be formulated with the compound as a unit-dose composition, for example, a tablet, which can contain from 0.05% to 95% by weight of the active compounds. Compounds of Formulae (I) through (IV) may be coupled with suitable polymers as targetable drug carriers. Other pharmacologically active substances can also be present.

The active compounds of the present invention may be administered by any suitable route, wherein exemplary active compounds are in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The active compounds and compositions, for example, may be administered orally, rectally, parenterally, or topically.

Oral administration of a solid dose form may be, for example, presented in discrete units, such as hard or soft capsules, pills, cachets, lozenges, or tablets, each containing a predetermined amount of at least one compound of the present invention. In another embodiment, the oral administration may be in a powder or granule form. In another embodiment, the oral dose form is sub-lingual, such as, for example, a lozenge. In such solid dosage forms, the compounds of Formulae (I) through (IV) are ordinarily combined with one or more adjuvants. Such capsules or tablets may contain a controlled-release formulation. In the case of capsules, tablets, and pills, the dosage forms also may comprise buffering agentsor may be prepared with enteric coatings.

In another embodiment, oral administration may be in a liquid dose form. Liquid dosage forms for oral administration include, for example, pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art (*e.g.,* water). Such compositions also may comprise adjuvants, such as wetting, emulsifying, suspending, flavoring *(e.g.,* sweetening), and/or perfuming agents.

In another embodiment, the present invention comprises a parenteral dose form. "Parenteral administration" includes, for example, subcutaneous injections, intravenous injections, intraperitoneally, intramuscular injections, intrasternal injections, and infusion. Injectable preparations *(e.g.,* sterile injectable aqueous or oleaginous suspensions) may be formulated according to the known art using suitable dispersing, wetting agents, and/or suspending agents.

In another embodiment, the present invention comprises a topical dose form. "Topical administration" includes, for example, transdermal administration, such as via transdermal patches or iontophoresis devices, intraocular administration, or intranasal or inhalation administration. Compositions for topical administration also include, for example, topical gels, sprays, ointments, and creams. A topical formulation may include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. When the compounds of this invention are administered by a transdermal device, administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibres, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated - see, for example, J Pharm Sci, 88 (10), 955-958, by Finnin and Morgan (October 1999).

In another embodiment, the compounds of the present invention may be administered in combination with treatment of restenosis resulting from angioplasty, including, without limitation, such therapies as inserting a stent at the site of angioplasty. The stent itself comprises the compound of the present invention and is used as a carrier to effect local delivery of the compound to the target vessel. The compound is coated on, adsorbed on, affixed to or present on the surface of the stent or is otherwise present in or on the matrix of the stent, either alone or in combination with other active drugs and pharmaceutically acceptable carriers, adjuvants, binding agents and the like.

One exemplary stent comprises a compound of the invention in the form of an extended release composition that provides for release of the compound over an extended period of time. Another exemplary stent comprises a hydrogel containing entrapped the compound, wherein the hydrogel is attached directly onto a stent or attached to a polymer coated stent. This hydrogel, containing entrapped the compound of this invention, can be used as a topcoat on a stent to provide a fast release, bolus-like localized administration of the entrapped compound. Under the hydrogel/therapeutic agent topcoating, other biodegradable polymer coatings (e.g., poly ester-amide with covalently conjugated or matrixed drugs) can be positioned to create a sustained release local drug/biologic delivery system. This hydrogel system is exemplified in U.S. Patent No. 6,716,445 (granted April 6, 2004).

Formulations suitable for topical administration to the eye include, for example, eye drops wherein the compound of this invention is dissolved or suspended in suitable carrier. A typical formulation suitable for ocular or aural administration may be in the form of drops of a micronised suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and aural administration include ointments, biodegradable (*e.g.* absorbable gel sponges, collagen) and non-biodegradable (*e.g.* silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. A polymer such as crossed-linked polyacrylic acid, polyvinylalcohol, hyaluronic acid, a cellulosic polymer, for example, hydroxypropylmethylcellulose, hydroxyethylcellulose, or methyl cellulose, or a heteropolysaccharide polymer, for example, gelan gum, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis.

For intranasal administration or administration by inhalation, the active compounds of the invention are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant. Formulations suitable for intranasal administration are typically administered in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler or as an aerosol spray from a pressurised container, pump, spray, atomiser (for example, an atomiser using electrohydrodynamics to produce a fine mist), or nebuliser, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.

In another embodiment, the present invention comprises a rectal dose form. Such rectal dose form may be in the form of, for example, a suppository. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate.

Other carrier materials and modes of administration known in the pharmaceutical art may also be used. Pharmaceutical compositions of the invention may be prepared by any of the well-known techniques of pharmacy, such as effective formulation and administration procedures. The above considerations in regard to effective formulations and administration procedures are well known in the art and are described in standard textbooks. Formulation of drugs is discussed in, for example, Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania, 1975; Liberman, et al., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Kibbe, et al., Eds., Handbook of Pharmaceutical Excipients (3rd Ed.), American Pharmaceutical Association, Washington, 1999.

J. Co-administration

The compounds of the present invention can be used, alone or in combination with other therapeutic agents, in the treatment of various conditions or disease states. The compound(s) of the present invention and other therapeutic agent(s) may be may be administered simultaneously (either in the same dosage form or in separate dosage forms) or sequentially.

The administration of two or more compounds "in combination" means that the two compounds are administered closely enough in time that the presence of one alters the biological effects of the other. The two or more compounds may be administered simultaneously, concurrently or sequentially. Additionally, simultaneous administration may be carried out by mixing the compounds prior to administration or by administering the compounds at the same point in time but at different anatomic sites or using different routes of administration.

The phrases "concurrent administration," "co-administration," "simultaneous administration," and "administered simultaneously" mean that the compounds are administered in combination.

In one embodiment, compounds of Formulae (I) through (IV) may be co-administered with an oral antiplatelet agent, including, but not limited to, aspirin, dipyridamole, cilostazol and anegrilide hydrochloride. In still another embodiment, compounds of Formulae (I) through (IV) may be co-administered with aspirin.

In another embodiment, compounds of Formulae (I) through (IV) may be co-administered with a glycoprotein IIb/IIIa inhibitor, including, but not limited to, abciximab, eptifibatide and tirofiban. In still another embodiment, compounds of Formulae (I) through (IV) may be co-administered with eptifibatide.

In another embodiment, compounds of Formulae (I) through (IV) may be co-administered with a heparin or heparinoid, including, but not limited to, heparin sodium, enoxaparin sodium, dalteparin sodium, ardeparin sodium, nadroparin calcium, reviparin sodium, tinzaparin sodium and fondaparinux sodium.

In another embodiment, compounds of Formulae (I) through (IV) may be co-administered with a direct thrombin inhibitor, including, but not limited to, danaparoid, hirudin, bivalirudin and lepirudin.

In another embodiment, compounds of Formulae (I) through (IV) may be co-administered with an anti-coagulant including, but not limited to, warfarin, warfarin sodium, 4-hydroxycoumarin, dicoumarol, phenprocoumon, anisindione, acenocoumerol and phenindione. In still another embodiment, compounds of Formulae (I) through (IV) may be co-administered with warfarin sodium.

In another embodiment, compounds of Formulae (I) through (IV) may be co-administered with an oral factor Xa inhibitor including, but not limited to, ximelagatran, melagatran, dabigatran etexilate and argatroban. In still another embodiment, compounds of Formulae (I) through (IV) may be co-administered with ximelagatran.

In another embodiment, compounds of Formulae (I) through (IV) may be co-administered with a fibrinolytic including, but not limited to, streptokinase, urokinase, tissue plasminogen activator, tenecteplase, reteplase, alteplase and aminocaproic acid.

In another embodiment, compounds of Formulae (I) through (IV) may be co-administered with an investigational compound useful in treating platelet aggregation including, but not limited to, BAY 59-7939, YM-60828, M-55532, M-55190, JTV-803 and DX-9065a.

K. Kits

The present invention further comprises kits that are suitable for use in performing the methods of treatment or prevention described above. In one embodiment, the kit contains a first dosage form comprising one or more of the compounds of the present invention and a container for the dosage, in quantities sufficient to carry out the methods of the present invention.

In another embodiment, the kit of the present invention comprises one or more compounds of Formulae (I) through (IV) and an oral antiplatelet agent, including, but not limited to, aspirin, dipyridamole, cilostazol and anegrilide hydrochloride. In still another embodiment, the kit of the present invention comprises one or more compounds of Formulae (I) through (IV) and aspirin.

In another embodiment, the kit of the present invention comprises one or more compounds of Formulae (I) through (IV) and a glycoprotein IIb/IIIa inhibitor, including, but not limited to, abciximab, eptifibatide and tirofiban. In still another embodiment, the kit of the present invention comprises one or more compounds of Formulae (I) through (IV) and eptifibatide.

In another embodiment, the kit of the present invention comprises one or more compounds of Formulae (I) through (IV) and a heparin or heparinoid, including, but not limited to, heparin sodium, enoxaparin sodium, dalteparin sodium, ardeparin sodium, nadroparin calcium, reviparin sodium, tinzaparin sodium and fondaparinux sodium.

In another embodiment, the kit of the present invention comprises one or more compounds of Formulae (I) through (IV) and a direct thrombin inhibitor, including, but not limited to, danaparoid, hirudin, bivalirudin and lepirudin.

In another embodiment, the kit of the present invention comprises one or more compounds of Formulae (I) through (IV) and an anti-coagulant including, but not limited to, warfarin, warfarin sodium, 4-hydroxycoumarin, dicoumarol, phenprocoumon, anisindione, acenocoumerol and phenindione. In still another embodiment, the kit of the present invention comprises one or more compounds of Formulae (I) through (IV) and warfarin sodium.

In another embodiment, the kit of the present invention comprises one or more compounds of Formulae (I) through (IV) and an oral factor Xa inhibitor including, but not limited to, ximelagatran, melagatran, dabigatran etexilate and argatroban. In still another embodiment, the kit of the present invention comprises one or more compounds of Formulae (I) through (IV) and ximelagatran.

In another embodiment, the kit of the present invention comprises one or more compounds of Formulae (I) through (IV) and a fibrinolytic including, but not limited to, streptokinase, urokinase, tissue plasminogen activator, tenecteplase, reteplase, alteplase and aminocaproic acid.

In another embodiment, the kit of the present invention comprises one or more compounds of Formulae (I) through (IV) and an investigational compound useful in treating platelet aggregation including, but not limited to, BAY 59-7939, YM-60828, M-55532, M-55190, JTV-803 and DX-9065a.

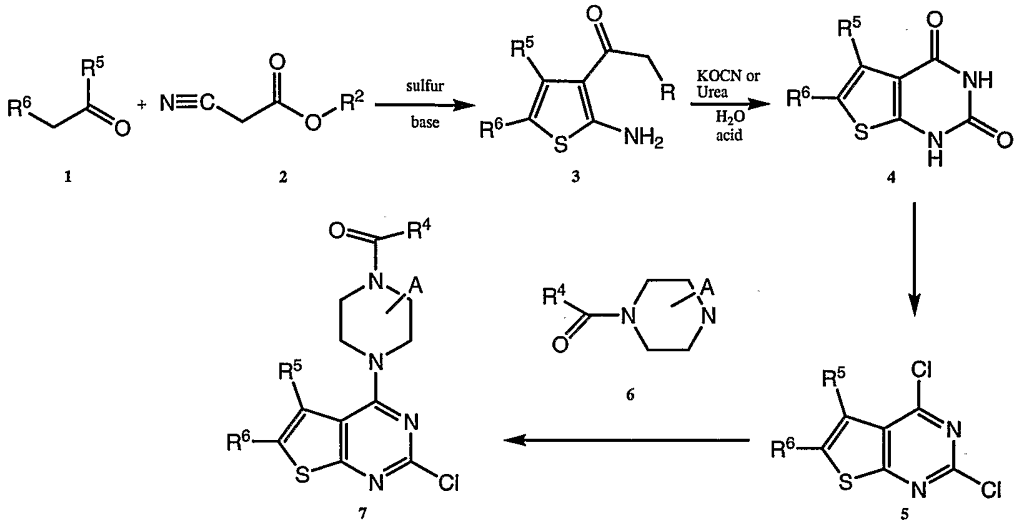
L. Intermediates

In another embodiment, the invention relates to the novel intermediates of Examples 30 and 33 useful for preparing the thieno[2,3-*d*]pyrimidine compounds of Formulas (I)-(IV).

M. General Synthetic Schemes

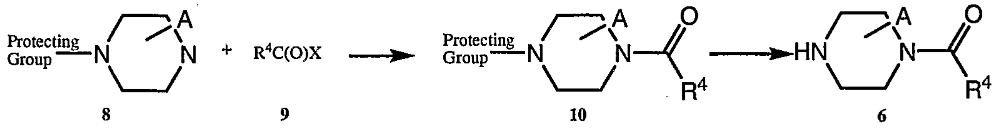
The starting materials used herein are commercially available or may prepared by routine methods known in the art (such as those methods disclosed in standard reference books such as the COMPENDIUM OF ORGANIC SYNTHETIC METHODS, Vol. I-VI (published by Wiley-Interscience)). The compounds of the present invention may be prepared using the methods illustrated in the general synthetic schemes and experimental procedures detailed below. The general synthetic schemes are presented for purposes of illustration and are not intended to be limiting.

Scheme A



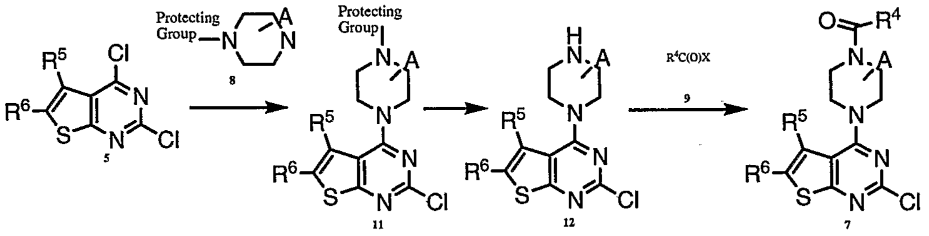
Scheme A. Thienopyrimidines may be prepared by various methods. One method for the preparation of thienopyrimidine 7 is depicted in Scheme A. Commercially available aldehyde/ketone 1 and esters 2 are combined in the presence of sulfur to give thiophene 3 using the general method of Tinney et al. (J. Med. Chem. (1981) 24, 878-882). Thiophene 3 is then treated with potassium cyanate or urea in the presence of water and an acid such as acetic acid to give dione 4. Dione 4 is then treated with a chloride source such as phosphorous oxychloride, thionyl chloride, or phosphorous pentachloride with or without the presence of a tertiary amine or concentrated HCl and with or without added inert solvent such as dimethylformamide at temperatures ranging from 75 °C to 175 °C, optionally with an excess of phosphorous oxychloride in a sealed vessel at 130-175 °C, to give dichloropyrimidine 5. Dichloropyrimidine 5 is then treated with piperazine 6 (see Scheme B) in the presence of a base such as trialkylamine, pyridine, potassium carbonate, sodium carbonate, cesium carbonate, and other bases well known to those versed in the art and in the presence of a solvent such as THF, acetonitrile, dichloromethane, dialkyl ether, toluene, DMF, N-methyl pyrrolidinone and the like at temperatures ranging from room temperature to the reflux temperature of the solvent to give thienopyrimidine 7.

Scheme B



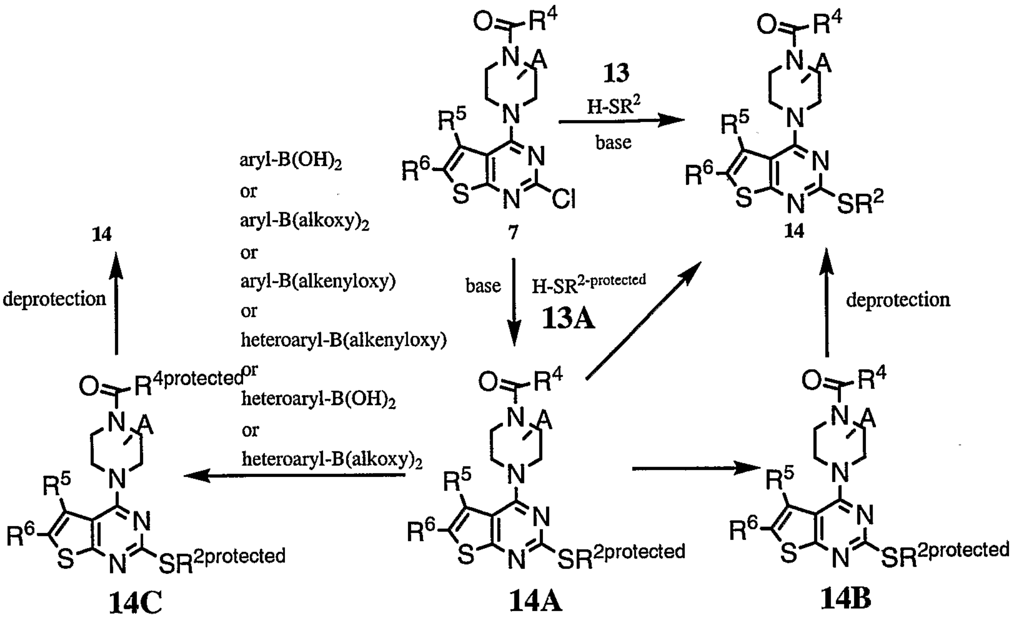
Scheme B. Scheme B depicts the preparation of intermediate 6. Protected piperazine 8 is commercially available or can be prepared by (1) attaching a suitable protecting group including, but not limited to, Boc, Cbz, Fmoc and benzyl, to one of the nitrogen ring atoms of the piperazine and (2) reacting with alkylOCOCl or $(alkylOCO)_2O$). Protected piperazine 8 is then acylated using acyl reagent 9, where acyl reagent 9 is used in its acid form (X = OH) in the presence of a coupling agent. Suitable coupling agents include, but are not limited to, DCC, EDC, DEPC, HATU, HBTU and CDI. In an alternative preparation of intermediate 6, acyl reagent 9 is used in the form of an acid halide ($X = Cl, Br, F$) or anhydride ($X = O(COR_4)$)in the presence of a base, including, but not limited to, a trialkylamine, pyridine, or an alkaline earth metal carbonate and in the presence of inert solvents such as THF, dichloromethane, acetonitrile, toluene, dialkyl ether, DMF, N-methylpyrrolidinone, dimethylacetamide and the like at temperatures ranging between ice/water temperature to the reflux temperature of the solvent, to give bisamide 10. Bisamide 10 is converted to piperazine 6 using methods well know to those versed in the art, many of which are discussed by Greene and Wuts in Protective Groups in Organic Synthesis, Third Ed., Wiley-Interscience, pp. 502-550. When the protecting group of bisamide 10 is a benzyl group, then removal of the benzyl group to give intermediate 6 is accomplished using standard methods known in the art (e.g., those discussed by Greene and Wuts in Protective Groups in Organic Synthesis, Third Ed., Wiley-Interscience, pp. 502-550).

Scheme C



Scheme C. The order of addition of various functionalities to the thienopyrimidine can be changed to take advantage of commercially available materials or in order to avoid reactivities at other parts of the molecule. An alternative method for the preparation of thienopyrmidine 7 using an order of addition differing from that of Scheme A is shown in Scheme C. Dichloropyrimidine 5 (Scheme A) is aminated with 8 (Scheme B) in inert solvents at temperatures ranging from room temperature to the boiling point of the solvent to give pyrimidine 11. The amination may be done using excess 8 or in the presence of a base, including but not limited to, a trialkylamine, pyridine, or an alkaline earth metal carbonate. Removal of the protecting group to give pyrimidine-piperazine 12 is achieved using standard deprotection method, such as those discussed by Greene and Wuts in Protective Groups in Organic Synthesis, Third Ed., Wiley-Interscience, pp. 502-550. Thienopyrimidine 7 is obtained upon combining acyl reagent 9 ($X = OH$) with pyrimidine-piperazine 11 using coupling reagents, many of which are well known to those versed in the art and include but are not limited to DCC, EDC, DEPC, HATU, HBTU and CDI. Alternatively, 9 is used in the form of an acid halide $X = Cl, Br, F$) or anhydride ($X = O(COR_4)$) in the presence of a base, exemplary bases including, but not limited to, a trialkylamine, pyridine, or an alkaline earth metal carbonate and in the presence of inert solvents including, but not limited to, THF, dichloromethane, acetonitrile, toluene, dialkyl ether, DMF, N-methylpyrrolidinone and the like at temperatures ranging between ice/water temperature to the reflux temperature of the solvent.

Scheme D



Scheme D. Elaboration of thienopyrimidine 7 to substituted thienopyrimidine 14 is accomplished by treating thienopyrimidine 7 with H-SR^2 (13), and where H-SR^2 is commercially available or may be prepared by methods well-known to those versed in the art.

Reagent 13 is combined with thienopyrimidine 7 in the presence of a base and an inert solvent to give substituted thienopyrimidine 14. Reagent 13 may be used in a one- to ten-fold excess, wherein an exemplary base is a trialkylamine base, exemplary solvents include, but are not limited to, N-methyl pyrrolidinone and butanol, and the temperature is between room temperature and 160 °C. The chemist may choose to omit added base and instead use excess H-SR$_7$ as the base. To reduce undesired reactions, reagent 13 can be protected first (i.e. R^2 is in a protected form) namely reagent 13A, to give substituted thienopyrimidine 14A, wherein the protecting group may be removed at a later stage to give substituted thienopyrimidine 14. Reagent 13A is commercially available or may be prepared by methods known in the art. For example, when R$_7$ is desired to be an alkyl diol, the diol of H-SR^2 may be protected using methods known in the art. Methods for the synthesis and removal diol protecting groups are discussed by Greene and Wuts in "Protective Groups in Organic Synthesis," Third Ed., Wiley-Interscience, pp. 201-245. Alternatively, R^2 in 14A may be an alkyl aldehyde or alkyl ketone in its protected form. Many protected aldehydes and ketones 13A are commercially available. Conventional procedures for the synthesis and removal of aldehyde and ketone protecting groups are known in the art (e.g. the procedures discussed by Greene and Wuts in "Protective Groups in Organic Synthesis," Third Ed., Wiley-Interscience, pp. 201-245.) After removal of the aldehyde or ketone protecting group to give substituted thienopyrimidine 14B, the aldehyde or ketone may be further manipulated. For example, treatment of an aldehyde with an oxidizing agent such as 3-chloroperoxbenzoic acid and the like gives substituted thienopyrimidine 14 where R^2 contains a carboxylic acid. Treatment of an aldehyde or ketone with an amine in the presence of a reducing agent such as sodium cyanoborohydride, sodium triacetoxyborohydride, tri(trifluoroacetoxy)borohydride, or hydrogen gas and a metal catalyst give substituted thienopyrimidine 14 where R^2 contains an amino group.

When R_4 is phenyl or heteroaryl substituted with Br, I, Cl, and O-triflate, then additional manipulations of R^4 may be carried out using standard methods known in the art. For example, aryl- or heteroaryl-boronic acids or esters, many of which are commercially available, may be reacted, in the presence of a metal catalyst, with substituted thienopyrimidine 14A to give biaryl substituted thienopyrimidine 14C. Thus, treatment with an aryl or heteroaryl boronic acid or heteroaryl or aryl boronic acid ester such as [(aryl or heteroaryl)-$B(OH)_2$] or [(aryl or heteroaryl)-$B(OR^a)(OR^b)$ (where R^a and R^b are each C_1-C_6 alkyl, or when taken together, R^a and R^b are C_2-C_{12} alkylene)] in the presence of a metal catalyst with or without a base in an inert solvent yields biaryl substituted thienopyrimidine 14C. Metal catalysts in these transformations include, but are not limited to, salts or phosphine complexes of Cu, Pd, or Ni (for example, $Cu(OAc)_2$, $PdCl_2(PPh_3)_2$, $NiCl_2(PPh_3)_2$). Bases may include, but are not limited to, alkaline earth metal carbonates, alkaline earth metal bicarbonates, alkaline earth metal hydroxides, alkali metal carbonates, alkali metal bicarbonates, alkali metal hydroxides, alkali metal hydrides, alkali metal alkoxides, alkaline earth metal hydrides, alkali metal dialkylamides, alkali metal bis(trialkylsilyl)amides, trialkyl amines or aromatic amines.

In one embodiment, the alkali metal hydride is sodium hydride. In another embodiment, the alkali metal alkoxide is sodium methoxide. In another embodiment, the alkali metal alkoxide is sodium ethoxide. In another embodiment, the alkali metal dialkylamide is lithium diisopropylamide. In another embodiment, the alkali metal bis(trialkylsilyl)amide is sodium bis(trimethylsilyl)amide. In another embodiment, the trialkyl amine is diisopropylethylamine. In another embodiment, the trialkylamine is triethylamine. In another embodiment, the aromatic amine is pyridine.

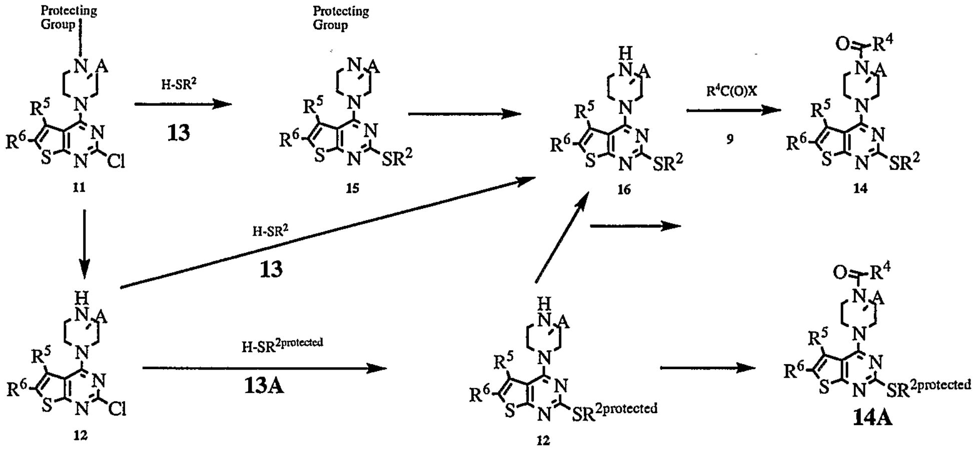
Inert solvents may include, but are not limited to, acetonitrile, dialkyl ethers, cyclic ethers, N,N-dialkylacetamides (dimethylacetamide), N,N-dialkylformamides, dialkylsulfoxides, aromatic hydrocarbons or haloalkanes.

In one embodiment, the dialkyl ether is diethyl ether. In another embodiment, the cyclic ether is tetrahydrofuran. In another embodiment, the cyclic ether is 1,4-dioxane. In another embodiment the N,N-dialkylacetamide is dimethylacetamide. In another embodiment, the N,N-dialkylformamide is dimethylformamide. In another embodiment, the dialkylsulfoxide is dimethylsulfoxide. In another embodiment, the aromatic hydrocarbon is benzene. In another embodiment, the aromatic hydrocarbon is toluene. In another embodiment, the haloalkane is methylene chloride.

Exemplary reaction temperatures range from room temperature up to the boiling point of the solvent employed. Non-commercially available boronic acids or boronic acid esters may be obtained from the corresponding optionally substituted aryl halide as described in *Tetrahedron*, 50, 979-988 (1994). Alternatively, as described in *Tetrahedron*, 50, 979-988 (1994), one may convert the R^4 substituent to the corresponding boronic acid or boronic acid ester $(OH)_2B$- or

$(OR^a)(OR^b)B$- and obtain the same products set forth above by treating with a suitable aryl or heteroaryl halide or triflate. The protecting group on R'^2 of 14C is then removed using conditions discussed above to give 14.

Scheme E



Scheme E. The order of addition of various functionalities of the thienopyrimidine can be changed in the preparation of substituted thienopyrimidine 14 in order to take advantage of commercially available materials or in order to avoid reactivities at other parts of the molecule. Another method for the preparation of substituted thienopyrimidine 14 is shown in Scheme E, where piperazinyl pyrimidine 11 is combined with reagent 13 where H-SR_7 is commercially available or may be prepared by methods well-known to those versed in the art, to give di-substituted thienopyrimidine 15. Reagent 13 is combined with piperazinyl pyrimidine 11 in the presence of a base and an inert solvent to give di-substituted thienopyrimidine 15. Reagent 13 may be used in a one- to ten-fold excess, an exemplary base is a trialkylamine base, exemplary solvents include, but are not limited to, N-methylpyrrolidinone or butanol, and the temperature is between room temperature and 160 °C. The chemist may choose to omit added base and instead use excess HYR_7 (13) as the base. Disubstituted thienopyrmidine 15 is then combined with a reagent suitable for the removal of the protecting group to give amine 16. Suitable means for removal of the the protecting group depends on the nature of the group. For example, to remove the protecting group, BOC, one may dissolve disubstituted thienopyrimidine in a trifluoroacetic acid/dichloromethane mixture. A second exemplary method is the addition of hydrogen chloride gas dissolved in an alcohol or ether such as methanol or dioxane. When complete, the solvents are removed under reduced pressure to give the corresponding amine as the corresponding salt, i.e. trifluoroacetic acid or hydrogen chloride salt. However, if desired, the amine can be purified further by means well known to those skilled in the art, such as for example, recrystallization. Further, if the non-salt form is desired that also can be obtained by means known to those skilled in the art, such as for example, preparing the free base amine via treatment of the salt with mild basic conditions.

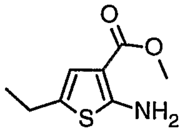
Additional deprotection conditions and deprotection conditions for other protecting groups can be found in T.W. Green and P.G.M. Wuts in "Protective Groups in Organic Chemistry," John Wiley and Sons, 1999, pp. 502-550. Thienopyrimidine 14 is obtained upon combining acyl reagent 9 (X = OH) with amine 16 using coupling reagents, which include but are not limited to DCC, EDC, DEPC, HATU, HBTU, CDI, or 9 is used in the form of an acid halide (X = Cl, Br, F) or anhydride (X = O(COR$_4$)) in the presence of a base, including, but not limited to, a trialkylamine, pyridine, or an alkaline earth metal carbonate and in the presence of inert solvents such as THF, dichloromethane, acetonitrile, toluene, dialkyl ether, DMF, N-methylpyrrolidinone and the like at temperatures ranging between ice/water temperature to the reflux temperature of the solvent. Depending upon the nature of the various substituents, it may be desirable to change the order of addition of the substituents. For example, the protecting group of 11 may be removed to give 12 as described in Scheme C. Pyrimidine piperazine 12 may then be reacted with 13 in the same manner as described for the conversion of 7 to 14 in Scheme D to give 16. Alternatively, pyrimidine piperazine 12 may be reacted with a protected form of 13, namely 13A, to give 17. Addition of R^{4}COX (9) to 17 gives 14A, which then may be further manipulated as described for Scheme D. Alternatively, amine 17 may be converted to 16 by methods described for the conversion of 14A to 14 in Scheme D.

N. Working Examples

The following illustrate the synthesis of various compounds of the present invention. Additional compounds within the scope of this invention may be prepared using the methods illustrated in these Examples, either alone or in combination with techniques generally known in the art.

EXAMPLE 1

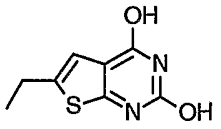
Methyl 2-amino-5-ethylthiophene-3-carboxylate



To a mixture of sulfur (6.4 g) in DMF (25 mL) was added methyl cyanoacetate (19.8 g) and triethylamine (15 mL,) under nitrogen. The mixture was stirred for 10 minutes at which time butyraldehyde (18 mL) was added drop-wise at a sufficient rate to maintain a temperature of 50 °C. The mixture was then stirred at room temperature for 20 hours. The mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed three times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using ethyl acetate-hexanes (10/90) to give a solid. The solid was slurried in hexanes, collected, and dried to give 25.74 g of the desired product as an off-white solid: MS (ESI+) for C8 H11 N1 O2 S$_1$ *m/z* 186.0598 (M+H)$^+$. ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.22 (t, 3 H), 2.6 (q, 2 H), 3.79 (s, 3 H), 5.79 (s, 2 H), 6.62 (s, 1 H).

EXAMPLE 2

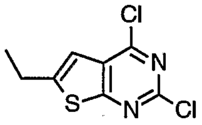
6-Ethyl-4a, 7a-dihydrothieno[2,3-d] pyrimidine-2, 4-diol



To a mixture of methyl 2-amino-5-ethylthiophene-3-carboxylate (EXA 1; 25.2 g) in glacial acetic acid (450 mL) and water (45 mL) was added drop-wise a solution of potassium cyanate (30.9 g) in water (150 mL). The mixture exothermed to 33°C and some gas was evolved. A white precipitate formed during addition. The mixture was stirred at room temperature for 20 hours. Ice water (300 mL) was added to the mixture and the solids were collected by filtration and washed with water (200 mL). The solids were transferred to a round-bottomed flask to which was added 6% aq. sodium hydroxide (500 mL). The mixture was refluxed for 2 h, then cooled to room temperature. The temperature was further lowered to 5 °C in an ice-water bath. The pH was adjusted to ~6 with concentrated hydrochloric acid. The resulting solids were collected, washed with water, and dried under reduced pressure to give 16.39 g of the title compound as an off-white solid. The material was subsequently azeotroped using THF/toluene to remove any residual water: MS (ESI+) for C8 H8 N2 O2 S_1 *m/z* 197.0 $(M+H)^+$; ^1H NMR 400 MHz, DMSO-*d_6*) δ 1.24 (t, 3 H), 2.74 (q, 2 H), 6.85 (s, 1 H), 11.1 (s, 1 H), 11.8 (s, 1 H).

EXAMPLE 3

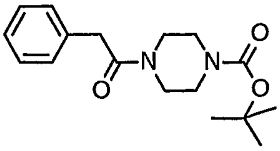
2,4-Dichloro-6-ethylthieno[2,3-d]pyrimidine



6-Ethyl-4a,7a-dihydrothieno[2,3-d]pyrimidine-2,4-diol (EXA 2; 4.0 g,) was placed into a glass pressure vessel with phosphorus oxychloride (35 mL). The mixture was heated to 150 °C for 1.5 hours. The mixture was cooled to room temperature and concentrated under reduced pressure. Residual phosphorus oxychloride was azeotroped twice with toluene (50 mL) under reduced pressure. The residue was partitioned between saturated sodium bicarbonate and dichloromethane. The resulting layers were separated and decolorizing carbon (1 g) was added to the organic layer. The organic layer was filtered through anhydrous magnesium sulfate and the filtrate was concentrated to dryness under reduced pressure to give 3.96 g of the title compound: MS (ESI+) for C8 H6 Cl2 N2 S_1 *m/z* 233.0 $(M+H)^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 1.4 (t, 3 H), 3.0 (q, 2 H), 7.1 (s, 1 H).

EXAMPLE 4

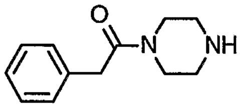
Tert-butyl 4-(phenylacetyl)piperazine-1-carboxylate



To a mixture of Boc-piperazine (4.2 g) in dry THF (30 mL) in a round bottomed flask in an ice-water bath was added triethylamine (3.14 mL). Phenyl acetyl chloride (2.9 mL) was added drop-wise such that the temperature remained below 15 °C. Once addition was complete, the mixture was removed from the ice bath and allowed to stir at room temperature for 2 hours. The solvents were removed under reduced pressure and the residue partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed with brine. The organic layer was then dried over anhydrous magnesium sulfate and concentrated. Hexanes were added and the resulting solids were collected via filtration to give 6.24 g of the title compound: MS (ESI+) for C17 H24 N2 O_3 *m/z* 327.0 $(M+H+Na)^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9 H), 3.2 (m, 2 H), 3.4 (m, 4 H), 3.6 (m, 2 H), 7.25 (m, 3 H), 7.33 (m, 2 H).

EXAMPLE 5

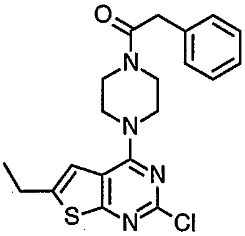
1-(Phenylacetyl)piperazine



To a mixture of tert-butyl 4-(phenylacetyl)piperazine-1-carboxylate (EXA 4; 6.0 g) in dichloromethane (5 mL) was added trifluoroacetic acid (5.0 mL). The mixture was stirred at room temperature for 8 hours. The solvents were removed under reduced pressure and the residue partitioned between saturated sodium bicarbonate and dichloromethane. The layers were separated and the aqueous layer extracted with dichloromethane. The combined dichloromethane extracts were dried using anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using methanol-dichloromethane (8/92) with 0.1% ammonium hydroxide to give 2.01 g of the title compound: ^1H NMR (300 MHz, $CDCl_3$) δ 1.75 (s, 1 H), 2.66 (t, 2 H), 2.8 (t, 2 H), 3.4 (t, 2 H), 3.6 (t, 2 H), 3.7 (s, 2 H), 7.2 (m, 3 H), 7.3 (m, 2 H).

EXAMPLE 6

2-Chloro-6-ethyl-4-[4-(phenylacetyl)piperazin-1-yl]thieno[2,3-d]pyrimidine

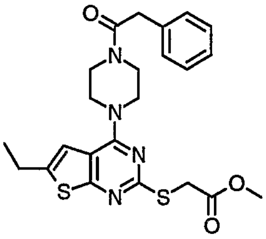


To a mixture of 2,4-dichloro-6-ethylthieno[2,3-d]pyrimidine (EXA 3; 1.53 g) in dry THF (60 mL) was added diisopropylethylamine (4.6 mL) and 1-(phenylacetyl)piperazine (EXA 5; 1.35g). The mixture was stirred at room temperature for 2.5 h, at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using methanol-dichloromethane (2/98) to give 2.28 g of the title compound: MS (ESI+) for C20 H21 Cl1 N4 O1 S_1 *m/z* 401.0 $(M+H)^+$; ^1H NMR (300 MHz, $CDCl_3$)

δ 1.35 (t, 3 H), 2.85 (q, 2 H), 3.63 (m, 2 H), 3.74 (m, 2 H), 3.80 (s, 2 H), 3.85 (m, 2 H), 3.89 (m, 2 H), 6.9 (s, 1 H), 7.27 (m, 3 H), 7.34 (m, 2 H).

EXAMPLE 7

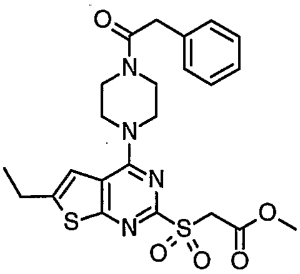
methyl ({6-ethyl-4-[4-(phenylacetyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)acetate



To methyl thiolglycolate (0.0198 g), the pyrimidine of Example 6 (0.075 g), and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) (0.0615 mL) in an 8 mL capacity glass screw-cap vial was added DMF (0.2 mL). The mixture was placed on a shaker plate and the disappearance of the pyrimidine of Example 6 was monitored by TLC. Additional methyl thiolglycolate and DBU (and DMF if solids formed) were added over several days until the reaction was judged complete by TLC. Ethyl acetate was added to the reaction mixture, which was then extracted with water and aqueous ammonium chloride. The ethyl acetate layer was then taken to dryness and the residue was chromatographed on silica gel using ethyl acetate-hexane (1/1) as eluent to give 0.057 g of the title compound. MS [m+H] 471.14; ^{1}H NMR ($CDCl_3$) δ 1.32 (t, 3H), 2.84 (q, 2H), 3.55 (m, 2H), 3.65 (m, 2H), 3.70 (s, 3H), 3.78 (s, 2H), 3.80 (m, 4H), 3.89 (s, 2H), 6.81 (s, 1H), 7.27 (m, 3H), 7.33 (m, 2H).

EXAMPLE 8

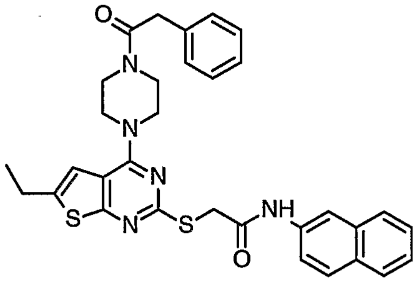
Methyl ({6-ethyl-4-[4-(phenylacetyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}sulfonyl)acetate



To a mixture of the acetate salt of Example 7 (0.1134 g) in dichloromethane (9.0 mL) was added m-chloroperoxybenzoic acid (0.112 g). The mixture was stirred at room temperature for 20 hours, then partitioned between water and dichloromethane. The layers were separated and the organic layer washed three times with saturated sodium bicarbonate, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel (100 mL) using 2% methanol in dichloromethane to give 0.0723 g (60%) of the title compound: MS (ESI+) for C23 H26 N4 O5 S_2 *m/z* 503.07 $(M+H)^+$; ^{1}H NMR ($CDCl_3$) δ 1.38 (t, 3 H), 2.97 (q, 2 H), 3.66 (m, 2 H), 3.73 (s, 3 H), 3.8 (s, 2 H), 3.83 (m, 4 H), 3.95 (m, 2 H), 4.53 (s, 2 H), 7.02 (s, 1 H), 7.28 (m, 3 H), 7.35 (m, 2 H).

EXAMPLE 9

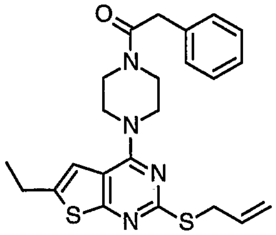
2-({6-Ethyl-4-[4-(phenylacetyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)-N-2-naphthylacetamide



The pyrimidine of Example 6 (0.15 g), DMF (3.0 mL), 1,8-diazobicyclo[5.4.0]undec-7-ene (0.24 mL), and thionalide (0.244 g) were placed in a 2 dram screw cap vial and placed in a Lab-Line MAX Q2000 orbital shaker for 24 hours. The mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed three times with brine, dried over anhydrous magnesium sulfate and concentrated to dryness. The residue was recrystallized using ethyl acetate/hexanes to give 0.064 g (30%) of the title compound: MS (ESI+) for C32 H31 N5 O2 S_2 *m/z* 582.21 $(M+H)^+$; ^{1}H NMR ($CDCl_3$) δ 1.38 (t, 3 H), 2.91 (q, 2 H), 3.55 (m, 2 H), 3.72 (s, 2 H), 3.75 (m, 4 H), 3.97 (m, 2 H), 3.91 (s, 2 H), 6.88 (s, 1 H), 7.22 (m, 3 H), 7.35 (m, 2 H), 7.4 (m, 3 H), 7.71 (m, 3 H), 8.20 (s, 1 H), 9.64 (s, 1 H).

EXAMPLE 10

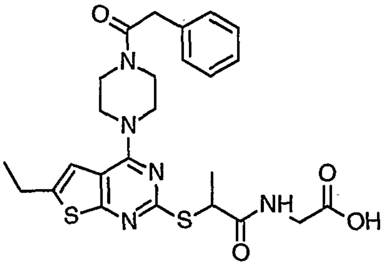
2-(Allylthio)-6-ethyl-4-[4-(phenylacetyl)piperazin-1-yl]thieno[2,3-d]pyrimidine



The pyrimidine of Example 6 (0.15 g), DMF (3.0 mL), 1,8-diazobicyclo[5.4.0]undec-7-ene (0.24 mL), and allyl mercaptan (0.089 mL) were placed in a 2 dram screw cap vial and placed in a Lab-Line MAX Q2000 orbital shaker for 24 hours. The mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed three times with brine, dried over anhydrous magnesium sulfate and concentrated to dryness. The residue was chromatographed on silica gel (100 mL) using 35% dichloromethane in hexanes to give 0.115 g (70%) of the title compound: MS (ESI+) for C23 H26 N4 O1 S_2 *m/z* 439.21 $(M+H)^+$; ^{1}H NMR ($CDCl_3$) δ 1.33 (t, 3 H), 2.86 (q, 2 H), 3.63 (m, 2 H), 3.69 (m, 2 H), 3.81 (m, 7 H), 5.07 (d, 1 H), 5.19 (d, 1 H), 6.0 (m, 1 H), 6.82 (s, 1 H), 7.27 (m, 3 H), 7.34 (m, 2 H).

EXAMPLE 11

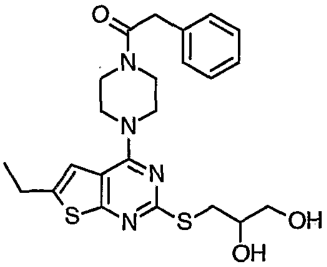
N-[2-({6-Ethyl-4-[4-(phenylacetyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)propanoyl]glycine



The pyrimidine of Example 6 (0.15 g), DMF (3.0 mL), 1,8-diazobicyclo[5.4.0]undec-7-ene (0.24 mL), and N-(2-mercaptopropionyl) glycine (0.183 g) were placed in a 2 dram screw cap vial and placed in a Lab-Line MAX Q2000 orbital shaker for 24 hours. The mixture was partitioned between 1N HCl and ethyl acetate. The layers were separated and the organic layer washed three times with 1N HCl, dried over anhydrous magnesium sulfate and concentrated to dryness. The residue was chromatographed on silica gel (100 mL) using 12% methanol in dichloromethane with 0.2% glacial acetic acid to give 0.0394 g (20%) of the title compound: MS (ESI+) for C25 H29 N5 O4 S_2 *m/z* 528.14 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.34 (t, 3 H), 1.57 (d, 2 H), 2.83 (q, 2 H), 3.62 (m, 2 H), 3.72 (m, 2 H), 3.74-3.84 (m, 6 H), 3.9-4.1 (m, 2 H), 4.4 (m, 1 H), 6.85 (s, 1 H), 7.26 (m, 3 H), 7.31 (m, 2 H), 7.85 (m, 1 H).

EXAMPLE 12

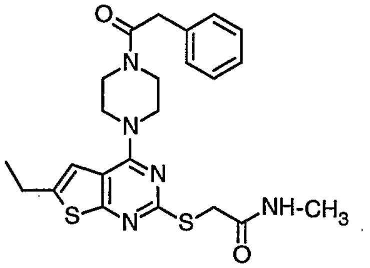
3-({6-Ethyl-4-[4-(phenylacetyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)propane-1,2-diol



The pyrimidine of Example 6 (0.15 g), DMF (3.0 mL), 1,8-diazobicyclo[5.4.0]undec-7-ene (0.24 mL), and 3-mercapto-1,2-propanediol (0.097 mL) were placed in a 2 dram screw cap vial and placed in a Lab-Line MAX Q2000 orbital shaker for 24 hours. The mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed three times with brine, dried over anhydrous magnesium sulfate and concentrated to dryness. The residue was chromatographed on silica gel (100 mL) using 85% dichloromethane, 10% hexanes, and 5% methanol to give 0.0642 g (36%) of the title compound: MS (ESI+) for C23 H28 N4 O3 S_2 *m/z* 473.16 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.34 (t, 3 H), 2.87 (q, 2 H), 3.34 (d, 2 H), 3.62 (m, 2 H), 3.67 (m, 2 H), 3.69 (m, 2 H), 3.74 (s, 2 H), 3.79 (m, 2 H), 3.98 (m, 2 H), 6.85 (s, 1 H), 7.28 (m, 3 H), 7.35 (m, 2 H).

EXAMPLE 13

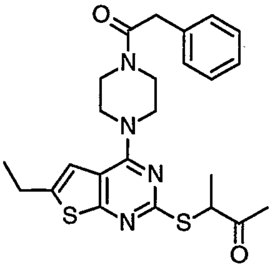
2-({6-Ethyl-4-[4-(phenylacetyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)-N-methylacetamide



The pyrimidine of Example 6 (0.15 g), DMF (3.0 mL), 1,8-diazobicyclo[5.4.0]undec-7-ene (0.24 mL), and N-methyl-mercaptoacetamide (0.099 mL) were placed in a 2 dram screw cap vial and placed in a Lab-Line MAX Q2000 orbital shaker for 24 hours. The mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed three times with brine, dried over anhydrous magnesium sulfate and concentrated to dryness. The residue was recrystallized using ethyl acetate/hexanes to give 0.142 g (81%) of the title compound: MS (ESI+) for C23 H26 N5 O2 S_2 *m/z* 470.20 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.32 (t, 3 H), 2.76 (m, 3 H), 2.88 (q, 2 H), 3.62 (m, 2 H), 3.74 (m, 2 H), 3.78 (m, 4 H), 3.84 (m, 2 H), 4.12 (m, 1 H), 6.86 (s, 1 H), 6.97 (s, 1 H), 7.29 (m, 3 H), 7.34 (m, 2 H);

EXAMPLE 14

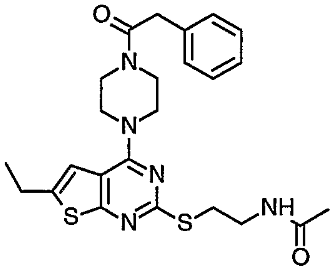
3-({6-Ethyl-4-[4-(phenylacetyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)butan-2-one



The pyrimidine of Example 6 (0.15 g), DMF (3.0 mL), 1,8-diazobicyclo[5.4.0]undec-7-ene (0.24 mL), and 3-mercapto-2-butanone (0.115 mL) were placed in a 2 dram screw cap vial and placed in a Lab-Line MAX Q2000 orbital shaker for 24 hours. The mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed three times with brine, dried over anhydrous magnesium sulfate and concentrated to dryness. The residue was recrystallized using ethyl acetate/hexanes to give 0.1237 g (70%) of the title compound: MS (ESI+) for C24 H28 N4 O2 S_1 *m/z* 469.19 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.31, 1.52, 2.86, 3.63, 3.66, 3.80, 4.33, 6.83, 7.13, 7.26, 7.32, 7.34, 7.37; ^1H NMR ($CDCl_3$) δ 1.31 (t, 3 H), 1.52 (d, 3 H), 2.3 (s, 3 H), 2.86 (q, 2 H), 3.63 (m, 2\ H), 3.66 (m, 2 H), 3.66 (m, 6 H), 4.33 (m, 1 H), 6.83 (s, 1 H), 7.13 (m, 3 H), 7.34 (m, 2 H).

EXAMPLE 15

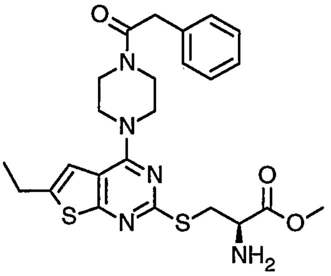
N-[2-({6-Ethyl-4-[4-(phenylacetyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)ethyl]acetamide



The pyrimidine of Example 6 (0.15 g), DMF (3.0 mL), 1,8-diazobicyclo[5.4.0]undec-7-ene (0.24 mL), and N-acetylcyteamine (0.119 mL) were placed in 2 dram screw cap vial and placed in a Lab-Line MAX Q2000 orbital shaker for 24 hours. The mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed three times with brine, dried over anhydrous magnesium sulfate and concentrated to dryness. The residue was chromatographed on silica gel (100 mL) using 85% dichloromethane, 10% hexanes, and 5% methanol to give 0.124 g (68%) of the title compound: MS (ESI+) for C24 H29 N5 O2 S_2 *m/z* 484.18 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.32 (t, 3 H), 1.94 (s, 3 H), 2.88 (q, 2 H), 3.33 (m, 2 H), 3.62 (m, 4 H), 3.76-3.87 (m, 8 H), 6.86 (s, 1 H), 7.26 (m, 3 H), 7.34 (m, 2 H).

EXAMPLE 16

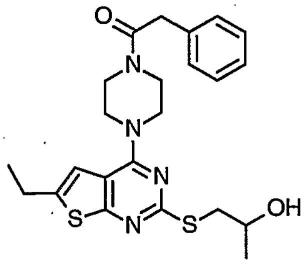
Methyl S-{6-ethyl-4-[4-(phenylacetyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}-L-cysteinate



The pyrimidine of Example 6 (0.15 g), DMF (3.0 mL), 1,8-diazobicyclo[5.4.0]undec-7-ene (0.3 mL), and L-cysteine methyl ester hydrochloride (0.192 g) were placed in a 2 dram screw cap vial and placed in a Lab-Line MAX Q2000 orbital shaker for 24 hours. The mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed three times with brine, dried over anhydrous magnesium sulfate and concentrated to dryness. The residue was chromatographed on silica gel (100 mL) using 85% dichloromethane, 10% hexanes, and 5% methanol to give 0.124 g (68%) of the title compound: MS (ESI+) for C24 H29 N5 O3 S_2 *m/z* 500.18 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.31 (t, 3 H), 2.88 (q, 2 H), 3.25 (m, 1 H), 3.61 (m, 2 H), 3.68 (m, 2 H), 3.72 (s, 2 H), 3.72-3.83 (m, 4 H), 4.02 (m, 1 H), 6.83 (s, 1 H), 7.28 (m, 3 H), 7.34 (m, 2 H).

EXAMPLE 17

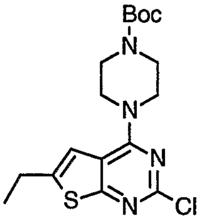
1-({6-Ethyl-4-[4-(phenylacetyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)propan-2-ol



The pyrimidine of Example 6 (0.15 g), DMF (3.0 mL), 1,8-diazobicyclo[5.4.0]undec-7-ene (0.24 mL), and 1-mercapto-2-propanol (0.098 g) were placed in a 2 dram screw cap vial and placed in a Lab-Line MAX Q2000 orbital shaker for 24 hours. The mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed three times with brine, dried over anhydrous magnesium sulfate and concentrated to dryness. The residue was chromatographed on silica gel (100 mL) using 85% dichloromethane, 10% hexanes, and 5% methanol to give 0.124 g (68%) of the title compound: MS (ESI+) for C23 H28 N4 O2 S_2 *m/z* 457.16 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.33 (t, 3 H), 2.88 (q, 2 H), 3.12 (m, 1 H), 3.34 (m, 1 H), 3.62 (m, 2 H), 3.7 (m, 2 H), 3.79 (s, 2 H), 3.83 (m, 4 H), 4.15 (m, 1 H), 6.83 (s, 1 H), 7.28 (m, 3 H), 7.34 (m, 2 H).

EXAMPLE 18

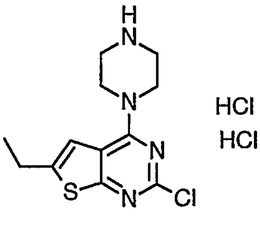
tert-Butyl 4-(2-chloro-6-ethylthieno[2,3-d]pyrimidin-4-yl)piperazine-1-carboxylate



To a mixture of the pyrimidine of Example 3 (10.38 g) in dry THF (60 mL) was added diisopropylethylamine (19.4 mL) and Boc-piperazine (9.9 g). The mixture was stirred at room temperature 6hoursat which time the solvents were removed under reduced pressure and the residue partitioned between brine and dichloromethane. The layers were separated and the organic layer washed with brine, dried over anhydrous magnesium sulfate and concentrated to dryness to give 15.35 g (90%) of the title compound: ^1H NMR ($CDCl_3$) δ 1.36 (t, 3 H), 1.49 (s, 9 H), 2.89 (q, 2 H), 3.62 (m, 4 H), 3.91 (m, 4 H), 6.95 (s, 1 H).

EXAMPLE 19

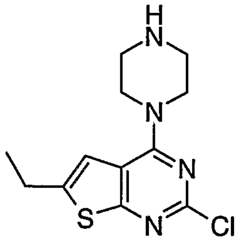
2-Chloro-6-ethyl-4-piperazin-1-ylthieno[2,3-d]pyrimidine dihydrochloride



HCl gas was bubbled through dry 1,4-dioxane (400 mL) for 15 minutes. Cooled to room temperature and added the carboxylate of Example 19(22.1 g) in dry 1,4-dioxane. Stirred at room temperature overnight. Removed solvents under reduced pressure and collected solids via filtration using dichloromethane to give 19.22 g (94%) of the title compound: ^{1}H NMR (DMSO-d_6) δ 1.28 (t, 3 H), 2.90 (q, 2 H), 3.23 (m, 4 H), 4.05 (m, 4 H), 7.39 (s, 1 H), 9.47 (s, 2 H).

EXAMPLE 20

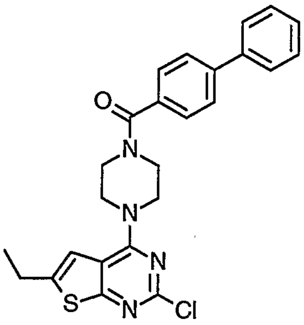
2-Chloro-6-ethyl-4-piperazin-1-ylthieno[2,3-d]pyrimidine



HCl gas was bubbled through a solution of the carboxylate of Example 18 (6.36 g) dissolved in methanol (100 mL) for 1 minute. The mixture was stirred at room temperature for 1 hour. The mixture was concentrated under reduced pressure. The residue was partitioned between saturated sodium bicarbonate and ethyl acetate. The layers were separated and the organic layer washed with brine, dried over anhydrous magnesium sulfate and concentrated to dryness to give 3.65 g (78%) of the title compound: ^{1}H NMR (CDCl$_3$) δ 1.34 (t, 3 H), 2.87 (q, 2 H), 3.05 (m, 4 H), 3.96 (m, 4 H), 6.93 (s, 1 H).

EXAMPLE 21

4-[4-(1,1'-Biphenyl-4-ylcarbonyl)piperazin-1-yl]-2-chloro-6-ethylthieno[2,3-d]pyrimidine

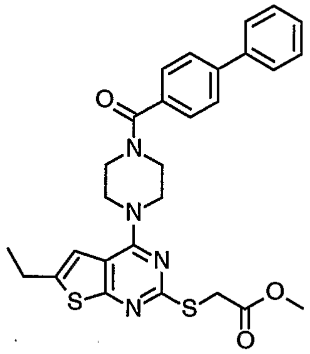


To a mixture of the dihydrochloride salt of Example 19(1.02 g) in DMF (5.0 mL) was added diisopropylethylamine (2.0 mL) and 4-biphenyl carbonyl chloride (0.63 g). The mixture was stirred at room temperature for 2 hours. The mixture was partitioned between ethyl acetate and water. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was dissolved in ethyl acetate, absorbed to silica gel and placed on top of a ½ inch silica gel plug in a 60mL sintered glass funnel. The silica was washed with dichloromethane to remove impurities. The silica gel plug was then washed with ethyl acetate. The ethyl acetate filtrates were concentrated to give 0.966

g (73%) of the title compound: MS (ESI+) for C25 H23 Cl1 N4 O1 S_1 *m/z* 465.14 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.36 (t, 3 H), 2.9 (q, 2 H), 3.98 (m, 8 H), 6.95 (s, 1 H), 7.37-7.68 (m, 9 H).

EXAMPLE 22

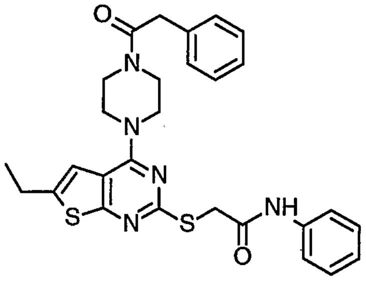
Methyl ({4-[4-(1,1'-biphenyl-4-ylcarbonyl)piperazin-1-yl]-6-ethylthieno[2,3-d]pyrimidin-2-yl}thio)acetate



To a mixture of the pyrimidine of Example 21 (0.15 g) in DMF (3.0 mL) was added 1,8-diazobicyclo[5.4.0]undec-7-ene (0.165 mL), and methyl thioglycolate (0.103 g). The mixture was stirred at room temperature for 20 hours. The mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel (100 mL) using 50% ethyl acetate in hexanes to give 0.118 g (68%) of the title compound: MS (ESI+) for C28 H28 N4 O3 S_2 *m/z* 533.18 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.34 (t, 3 H), 2.87 (q, 2 H), 3.6-40 (m, 13 H), 6.87 (s, 1 H), 7.40-7.68 (m, 9 H).

EXAMPLE 23

2-({6-Ethyl-4-[4-(phenylacetyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)-N-phenylacetamide

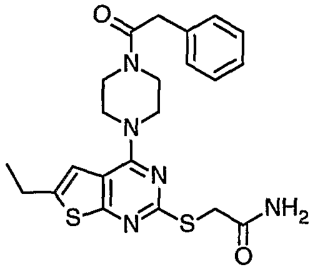


To a mixture of the pyrimidine of Example 6 (0.15 g) in DMF (3.0 mL) was added 1,8-diazobicyclo[5.4.0]undec-7-ene (0.27 mL), and 2-mercaptoacetanilide (0.2 g). The mixture was stirred at room temperature for 20 hours. The mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel (100 mL) using 50% ethyl acetate in hexanes to give 0.1149 g (58%) of the title compound: MS (ESI+) for C28 H29 N5 O2 S_2 *m/z* 532.21 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.36 (t, 3

H), 2.90 (q, 2 H), 3.56 (m, 2 H), 3.75 (m, 6 H), 3.86 (m, 4 H), 4.13 (m, 1 H), 6.88 (s, 1 H), 7.05 (m, 1 H), 7.3 (m, 6 H), 7.48 (d, 2 H), 9.4 (s, 1 H).

EXAMPLE 24

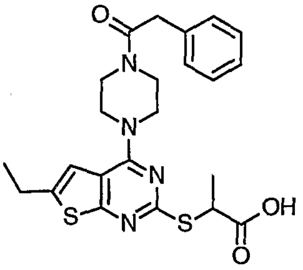
2-({6-Ethyl-4-[4-(phenylacetyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)acetamide



The pyrimidine of Example 6 (0.15 g), DMF (3.0 mL), 1,8-diazobicyclo[5.4.0]undec-7-ene (0.165 mL), and 2-mercaptoacetamide in methanolic ammonia (0.11 mL) were placed in a 2 dram screw cap vial and placed in a Lab-Line MAX Q2000 orbital shaker for 20 hours. The mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated to dryness to give 0.0914 g (54%) of the title compound: MS (ESI+) for C22 H25 N5 O2 S_2 *m/z* 456.19 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.34 (t, 3 H), 2.87 (q, 2 H), 3.62 (m, 2 H), 3.76-3.86 (m, 8 H), 5.33 (s, 1 H), 6.86 (s, 1 H), 6.90 (s, 1 H), 7.28 (m, 3 H), 7.34 (m, 2 H).

EXAMPLE 25

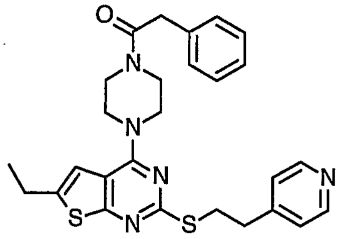
2-({6-Ethyl-4-[4-(phenylacetyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)propanoic acid



The pyrimidine of Example 6 (0.15 g), DMF (3.0 mL), 1,8-diazobicyclo[5.4.0]undec-7-ene (0.20 mL), and thiolactic acid (0.1 mL) were placed in a 2 dram screw cap vial and placed in a Lab-Line MAX Q2000 orbital shaker at 60 °C for 20 hours. The mixture was partitioned between 1N HCl and ethyl acetate. The layers were separated and the organic layer washed three times with 1N HCl, dried over anhydrous magnesium sulfate and concentrated to dryness. The residue was chromatographed on silica gel (100 mL) using 5% methanol in dichloromethane to give 0.0345 g (20%) of the title compound: MS (ESI+) for C23 H26 N4 O3 S_2 *m/z* 471.20 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.54 (t, 3 H), 2.23 (m, 1 H), 2.90 (q, 2 H), 3.55 (m, 1 H), 3.65 (m, 2 H), 3.76 (m, 2 H), 3.8 (s, 2 H), 3.85 (m, 2 H), 3.89 (m, 2 H), 6.88 (s, 1 H), 7.28 (m, 3 H), 7.35 (m, 2 H).

EXAMPLE 26

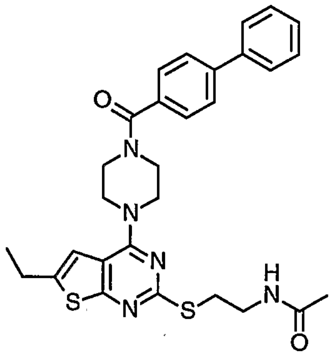
6-Ethyl-4-[4-(phenylacetyl)piperazin-1-yl]-2-[(2-pyridin-4-ylethyl)thio]thieno[2,3-d]pyrimidine



The pyrimidine of Example 6 (0.15 g), DMF (3.0 mL), 1,8-diazobicyclo[5.4.0]undec-7-ene (0.28 mL), and 4-pyridylethylmercaptan hydrochloride (0.196 g) were placed in a 2 dram screw cap vial and placed in a Lab-Line MAX Q2000 orbital shaker for 24 hours. The mixture was partitioned between water and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel (100 mL) using ethyl acetate as eluent to give 0.0387 g (20%) of the title compound: MS (ESI+) for C27 H29 N5 O1 S_2 *m/z* 504.27 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.35 (t, 3 H), 2.9 (q, 2 H), 3.1 (m, 2 H), 3.4 (m, 2 H), 3.62 (m, 2 H), 3.66 (m, 2 H), 3.8 (m, 6 H), 6.8 (s, 1 H), 7.28 (m, 3 H), 7.34 (m, 2 H), 8.5 (m, 1 H).

EXAMPLE 27

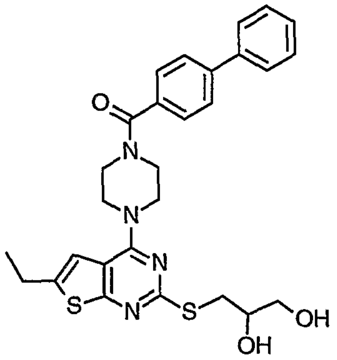
N-[2-({4-[4-(1,1'-Biphenyl-4-ylcarbonyl)piperazin-1-yl]-6-ethylthieno[2,3-d]pyrimidin-2-yl}thio)ethyl]acetamide



The pyrimidine of Example 21 (0.15 g), DMF (2.5 mL), 1,8-diazobicyclo[5.4.0]undec-7-ene (0.22 mL), and N-acetylcysteamine (0.103 mL) were placed in a 2 dram screw cap vial and placed in a Lab-Line MAX Q2000 orbital shaker for 20 hours. The mixture was partitioned between water and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated to dryness to give 0.155 g (88%) of the title compound: MS (ESI+) for C29 H31 N5 O2 S_2 *m/z* 546.18 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.34 (t, 3 H), 1.92 (s, 3 H), 2.85 (q, 2 H), 3.3 (m, 2 H), 3.61 (m, 2 H), 3.7-3.9 (m, 8 H), 654 (s, 1 H), 6.88 (s, 1 H), 7.38-7.66 (m, 9 H).

EXAMPLE 28

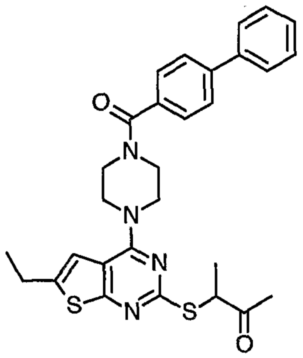
3-({4-[4-(1,1'-Biphenyl-4-ylcarbonyl)piperazin-1-yl]-6-ethylthieno[2,3-d]pyrimidin-2-yl}thio)propane-1,2-diol



The pyrimidine of Example 21 (0.15 g), DMF (2.5 mL), 1,8-diazobicyclo[5.4.0]undec-7-ene (0.22 mL), and 3-mercapto-1,2-propanediol (0.085 mL) were placed in a 2 dram screw cap vial and placed in a Lab-Line MAX Q2000 orbital shaker for 24 hours. The mixture was partitioned between water and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated to dryness to give 0.114g (66%) of the title compound: MS (ESI+) for C28 H30 N4 O3 S_2 *m/z* 535.20 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.34 (t, 3 H), 2.88 (q, 2 H), 3.35 (m, 2 H), 3.69-3.99 (m, 10 H), 6.89 (s, 1 H), 7.34-7.67 (m, 9 H).

EXAMPLE 29

3-({4-[4-(1,1'-Biphenyl-4-ylcarbonyl)piperazin-1-yl]-6-ethylthieno[2,3-d]pyrimidin-2-yl}thio)butan-2-one

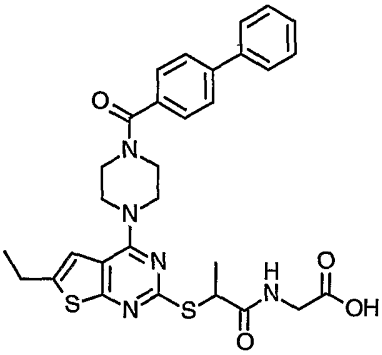


The pyrimidine of Example 21 (0.15 g), DMF (2.5 mL), 1,8-diazobicyclo[5.4.0]undec-7-ene (0.22 mL), and 3-mercapto-2-butanone (0.10 mL) were placed in a 2 dram screw cap vial and placed in a Lab-Line MAX Q2000 orbital shaker for 24 hours. The mixture was partitioned between water and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel (100 mL) using 40% ethyl acetate in hexanes as eluent to give 0.1036 g (60%) of the title compound: MS (ESI+) for C29 H30 N4 O2 S_2 *m/z* 531.17 $(M+H)^+$; ^1H

NMR ($CDCl_3$) δ 1.34 (t, 3 H), 1.46 (m, 5 H), 2.31 (s, 3 H), 2.88 (q, 2 H), 3.6-4.0 (m, 8 H), 4.33 (m, 1 H), 6.87 (s, 1 H), 7.37-7.67 (m, 9 H).

EXAMPLE 30

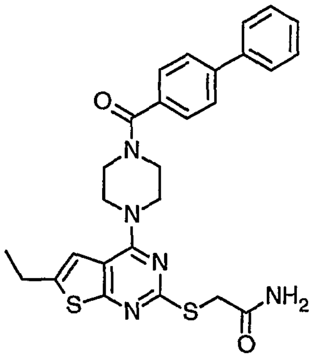
N-[2-({4-[4-(1,1'-Biphenyl-4-ylcarbonyl)piperazin-1-yl]-6-ethylthieno[2,3-d]pyrimidin-2-yl}thio)propanoyl]glycine



The pyrimidine of Example 21 (0.15 g), DMF (2.5 mL), 1,8-diazobicyclo[5.4.0]undec-7-ene (0.22 mL), and N-mercaptopropionyl glycine (0.159 mL) were placed in a 2 dram screw cap vial and placed in a Lab-Line MAX Q2000 orbital shaker for 24 hours. Added an additional (0.159 g) N-mercaptopropionyl glycine and 1,8-diazobicyclo[5.4.0]undec-7-ene (0.22 mL) and continued to shake for an additional 24 hours. The mixture was partitioned between 1N HCl and ethyl acetate. The layers were separated and the organic layer washed four times with 1N HCl, dried over anhydrous magnesium sulfate and concentrated to dryness to give 0.0956g (43%) of the title compound: ^{1}H NMR ($CDCl_3$) δ 1.32 (t, 3 H), 4.55 (m, 4 H), 2.88 (q, 2 H), 3.48 (m, 1 H), 3.6-4.1 (m, 8 H), 4.4 (m, 1 H), 6.9 (s, 1 H), 7.36-7.78 (m, 9 H), 7.8 (m, 1 H).

EXAMPLE 31

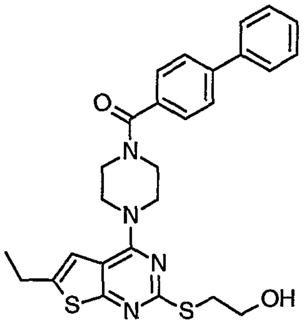
2-({4-[4-(1,1'-Biphenyl-4-ylcarbonyl)piperazin-1-yl]-6-ethylthieno[2,3-d]pyrimidin-2-yl}thio)acetamide



The pyrimidine of Example 21 (0.15 g), DMF (2.5 mL), 1,8-diazobicyclo[5.4.0]undec-7-ene (0.22 mL), and 2-mercaptoacetamide in methanolic ammonia (0.11 mL) were placed in a 2 dram screw cap vial and placed in a Lab-Line MAX Q2000 orbital shaker for 48 hours. The mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated to dryness to give 0.131g (78%) of the title compound: MS (ESI+) for C27 H27 N5 O2 S_2 *m/z* 518.19 $(M+H)^+$; ^{1}H NMR ($CDCl_3$) δ 1.34 (t, 3 H), 2.87 (q, 2 H), 3.6-4.05 (m, 10 H), 5.3 (s, 1 H), 6.9 (s, 2 H), 7.37-7.66 (m, 9 H).

EXAMPLE 32

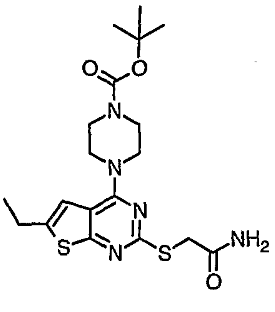
2-({4-[4-(1,1'-Biphenyl-4-ylcarbonyl)piperazin-1-yl]-6-ethylthieno[2,3-d]pyrimidin-2-yl}thio)ethanol



To a mixture of the pyrimidine of Example 21 (0.153 g) and 1,8-diazobicyclo[5.4.0]undec-7-ene (0.22 mL) in DMF (3.0 mL) was added 2-mercaptoethanol (0.069 mL). The mixture was stirred at room temperature for 20 hours at which time 2-mercaptoethanol (0.01 mL) was added every 2 hours for a period of 6 hours. The mixture was then partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed three times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel (100 mL) using 2% methanol in methylene chloride. The fractions containing product were concentrated and rechromatographed on silica gel (100 mL) using 60% ethyl acetate in hexanes to give 0.0344 g (21%) of the title compound: ^{1}H NMR ($CDCl_3$) δ 1.34 (t, 3 H), 2.87 (q, 2 H), 3.34 (m, 2 H), 3.65-3.95 (m, 10 H), 6.87 (s, 1 H), 7.37-7.67 (m, 9 H).

EXAMPLE 33

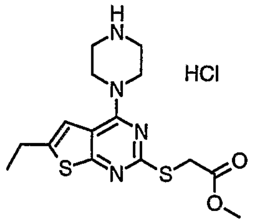
tert-Butyl 4-{2-[(2-amino-2-oxoethyl)thio]-6-ethylthieno[2,3-d]pyrimidin-4-yl}piperazine-1-carboxylate



To a mixture of the carboxylate of Example 23(4.0 g) in DMF (40 mL) was added 2-mercapto acetamide (10 g/100 mL) in methanolic ammonia (29 mL) and 1,8-diazobicyclo[5.4.0]undec-7-ene (4.68 g). The mixture was stirred at room temperature under nitrogen for 23 hours. The mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Hexanes were added to the residue and the solids filtered to give 4.5 g (100%) of the title compound: ^{1}H NMR ($CDCl_3$) δ 1.34 (t, 3 H), 1.48 (s, 9 H), 2.89 (q, 2 H), 3.59 (m, 4 H), 3.76 (s, 2 H), 3.87 (m, 4 H), 5.32 (s, 1 H), 6.94 (s, 1 H), 6.99 (s, 1 H).

EXAMPLE 34

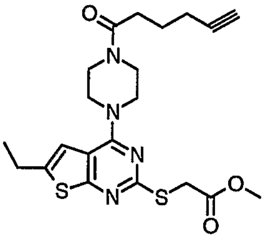
Methyl [(6-ethyl-4-piperazin-1-ylthieno[2,3-d]pyrimidin-2-yl)thio]acetate hydrochloride



The carboxylate of Example 36 (3.94 g) was dissolved in HCl saturated methanol (100 mL). The mixture was stirred at room temperature for 3 hours. The solvents were removed under reduced pressure and the residue dried under reduced pressure to give 3.46 g (99%) of the title compound: ^{1}H NMR (DMSO-d_6) δ 1.25 (t, 3 H), 2.86 (q, 2 H), 3.19 (m, 4 H), 3.63 (s, 3 H), 3.97 (m, 6 H), 7.26 (s, 1 H), 9.56 (s, 1 H).

EXAMPLE 35

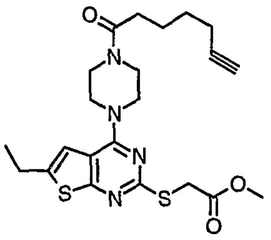
Methyl {[6-ethyl-4-(4-hex-5-ynoylpiperazin-1-yl)thieno[2,3-d]pyrimidin-2-yl]thio}acetate



To a mixture of hexynoic acid (0.042 mL) in N-methyl pyrrolidinone (2.5 mL) was added 1,1-carbonyldiimidazole (0.062 g). The mixture was placed in a 2 dram screw cap vial and placed in a Lab-Line MAX Q2000 orbital shaker for 1 hour at which time the hydrochloride salt of Example 34 (0.075 g) and diisopropylethylamine (0.05 g) were added. The mixture was placed back in the Lab-Line MAX Q2000 orbital shaker for 18 hours. The mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel (100 mL) using ethyl acetate as eluent to give 0.03 g (35%) of the title compound: ^{1}H NMR ($CDCl_3$) δ 1.33 (t, 3 H), 1.92 (q, 2 H), 1.99 (m, 1 H), 2.31 (m, 2 H), 2.51 (m, 2 H), 2.85 (m, 2 H), 3.66 (m, 2 H), 3.73 (s, 3 H), 3.73 (m, 2 H), 3.84 (m, 2 H), 3.91 (m, 4 H), 6.86 (s, 1 H).

EXAMPLE 36

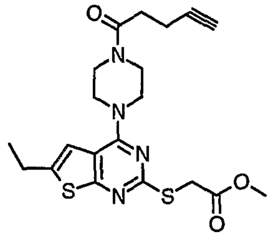
Methyl {[6-ethyl-4-(4-hept-6-ynoylpiperazin-1-yl)thieno[2,3-d]pyrimidin-2-yl]thio}acetate



To a mixture of heptynoic acid (0.048 mL) in N-methyl pyrrolidinone (2.5 mL) was added 1,1-carbonyldiimidazole (0.062 g). The mixture was placed in a 2 dram screw cap vial and placed in a Lab-Line MAX Q2000 orbital shaker for 1 hour at which time the hydrochloride salt of Example 34 (0.075 g) and diisopropylethylamine (0.05 g) were added. The mixture was placed back in the Lab-Line MAX Q2000 orbital shaker for 18 hours. The mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel (100 mL) using ethyl acetate as eluent to give 0.0283 g (32%) of the title compound: ^{1}H NMR (CDCl$_3$) δ 1.33 (t, 3 H), 1.56 (M, 2 H), 1.8 (M, 2 H), 1.96 (M, 1 H), 2.24 (M, 2 H), 2.4 (M, 2 H), 2.88 (Q, 2 H), 3.64 (M, 2 H), 3.73 (S, 3 H), 3.77 (M, 2 H), 3.83 (m, 4 H), 6.86 (s, 1 H).

EXAMPLE 37

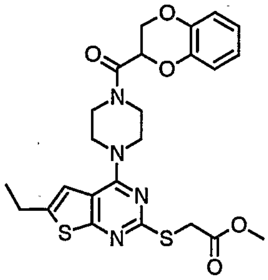
Methyl {[6-ethyl-4-(4-pent-4-ynoylpiperazin-1-yl)thieno[2,3-d]pyrimidin-2-yl]thio}acetate



To a mixture of pentynoic acid (0.038 g) in N-methyl pyrrolidinone (2.5 mL) was added 1,1-carbonyldiimidazole (0.062 g). The mixture was placed in a 2 dram screw cap vial and placed in a Lab-Line MAX Q2000 orbital shaker for 1 hour at which time the hydrochloride salt of Example 34 (0.075 g) and diisopropylethylamine (0.05 g) were added. The mixture was placed back in the Lab-Line MAX Q2000 orbital shaker for 18 hours. The mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel (100 mL) using ethyl acetate as eluent to give 0.0356 g (43%) of the title compound: ^{1}H NMR (CDCl$_3$) δ 1.33 (t, 3 H), 1.99 (m, 1 H), 2.58 (m, 4 H), 2.87 (q, 2 H), 3.66 (m, 2 H), 3.73 (s, 3 H), 3.80 (m, 2 H), 3.86 (m, 2 H), 3.91 (m, 4 H), 6.86 (s, 1 H).

EXAMPLE 38

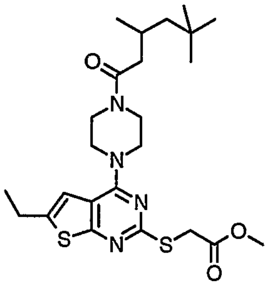
Methyl ({4-[4-(2,3-dihydro-1,4-benzodioxin-2-ylcarbonyl)piperazin-1-yl]-6-ethylthieno[2,3-d]pyrimidin-2-yl}thio)acetate



To a mixture of 1,4-benzodioxan-2-carboxylic acid (0.069 g) in N-methyl pyrrolidinone (2.5 mL) was added 1,1-carbonyldiimidazole (0.062 g). The mixture was placed in a 2 dram screw cap vial and placed in a Lab-Line MAX Q2000 orbital shaker for 1 hour at which time the hydrochloride salt of Example 34 (0.075 g) and diisopropylethylamine (0.05 g) were added. The mixture was placed back in the Lab-Line MAX Q2000 orbital shaker for 18 hours. The mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel (100 mL) using ethyl acetate as eluent to give 0.0429 g (43%) of the title compound: ^{1}H NMR ($CDCl_3$) δ 1.36 (t, 3 H), 2.88 (q, 2 H), 3.62-4.1 (m, 13 H), 4.2-4.88 (m, 4 H), 6.84-6.99 (m, 5 H).

EXAMPLE 39

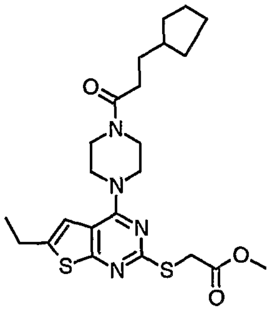
Methyl ({6-ethyl-4-[4-(3,5,5-trimethylhexanoyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)acetate



To a mixture of the hydrochloride salt of Example 34 (0.075 g) in DMF (2.5 mL) in a 2 dram screw cap vial was added diisopropylethylamine (0.104 g) and 3,5,5,-trimethyl hexanoyl chloride (0.045 mL). The mixture was placed in a Lab-Line MAX Q2000 orbital shaker for 20 hours at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using 65% ethyl acetate in hexanes as eluent to give 0.074 g (78%) of the title compound: MS (ESI+) for C24 H36 N4 O3 S_2 *m/z* 493.19 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 0.892 (s, 9 H), 1.02 (m, 3 H), 1.1-1.3 (m, 2 H), 1.35 (t, 3 H), 2.1 (m, 1 H), 2.2-2.5 (m, 2 H), 2.86 (q, 2 H), 3.66 (m, 2 H), 3.73 (s, 3 H), 3.77 (m, 2 H), 3.84 (m, 2 H), 3.89 (m, 2 H), 3.91 (s, 2 H), 6.86 (s, 1 H).

EXAMPLE 40

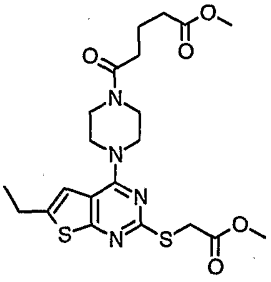
Methyl ({4-[4-(3-cyclopentylpropanoyl)piperazin-1-yl]-6-ethylthieno[2,3-d]pyrimidin-2-yl}thio)acetate



To a mixture of the hydrochloride salt of Example 34 (0.075 g) in DMF (2.5 mL) in a 2 dram screw cap vial was added diisopropylethylamine (0.104 g) and 3-cyclopentyl propionyl chloride (0.036 mL). The mixture was placed in a Lab-Line MAX Q2000 orbital shaker for 20 hours at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using 65% ethyl acetate in hexanes as eluent to give 0.0668 g (73%) of the title compound: MS (ESI+) for C23 H32 N4 O3 S_2 *m/z* 477.15 (M+H); ^{1}H NMR ($CDCl_3$) δ 1.13 (m, 3 H), 1.33 (t, 3 H), 1.5-1.7 (m, 8 H), 2.38 (m, 2 H), 2.86 (q, 2 H), 3.64 (m, 2 H), 3.73 (s, 3 H), 3.73 (m, 2 H), 3.78 (m, 2 H), 3.84 (m, 2 H), 3.91 (s, 2 H), 6.86 (s, 1 H).

EXAMPLE 41

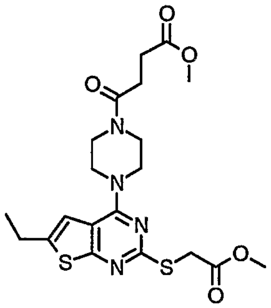
Methyl 5-(4-{6-ethyl-2-[(2-methoxy-2-oxoethyl)thio]thieno[2,3-d]pyrimidin-4-yl}piperazin-1-yl)-5-oxopentanoate



To a mixture of the hydrochloride salt of Example 34 (0.075 g in DMF (2.5 mL)) in a 2 dram screw cap vial was added diisopropylethylamine (0.104 g) and methyl-5-chloro-5-oxo valerate (0.033 mL). The mixture was placed in a Lab-Line MAX Q2000 orbital shaker for 20 hours at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using ethyl acetate as eluent to give 0.0497 g (54%) of the title compound: MS (ESI+) for C21 H28 N4 O5 S_2 *m/z* 481.16 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 1.33 (t, 3 Hz, H), 2.03 (m, 2 H), 2.44 (m, 4 H), 2.87 (q, 2 H), 3.6 (m, 2 H), 3.68 (s, 3 H), 3.73 (s, 3 H), 3.76 (m, 2 H), 3.85 (m, 2 H), 3.87 (m, 2 H), 3.91 (s, 2 H), 6.86 (s, 1 H).

EXAMPLE 42

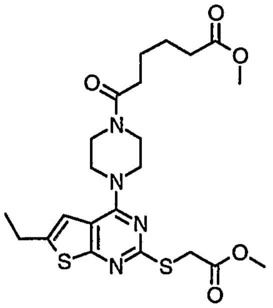
Methyl 4-(4-{6-ethyl-2-[(2-methoxy-2-oxoethyl)thio]thieno[2,3-d]pyrimidin-4-yl}piperazin-1-yl)-4-oxobutanoate



To a mixture of the hydrochloride salt of Example 34 (0.075 g) in DMF (2.5 mL) in a 2 dram screw cap vial was added diisopropylethylamine (0.104 g) and methyl-4-chloro oxobutyrate (0.029 mL). The mixture was placed in a Lab-Line MAX Q2000 orbital shaker for 20 h at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using ethyl acetate as eluent to give 0.0578 g (64%) of the title compound: MS (ESI+) for C20 H26 N4 O5 S_2 *m/z* 467.17 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 1.33 (t, 3 H), 2.69 (m, 4 H), 2.86 (q, 2 H), 3.69 (m, 2 H), 3.71 (s, 3 H), 3.71 (s, 3 H), 3.73 (m, 2 H), 3.77 (m, 2 H), 3.86 (m, 4 H), 6.86 (s, 1 H).

EXAMPLE 43

Methyl 6-(4-{6-ethyl-2-[(2-methoxy-2-oxoethyl)thio]thieno[2,3-d]pyrimidin-4-yl}piperazin-1-yl)-6-oxohexanoate

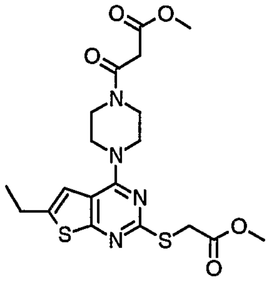


To a mixture of the hydrochloride salt of Example 34 (0.075 g) in DMF (2.5 mL) in a 2 dram screw cap vial was added diisopropylethylamine (0.104 g) and monomethyl adipoyl chloride (0.037 mL). The mixture was placed in a Lab-Line MAX Q2000 orbital shaker for 20 hours at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using ethyl acetate as eluent to give 0.0532 g (56%) of the title compound: MS (ESI+) for C22 H30 N4 O5 S_2 *m/z* 495.2

(M+H)$^+$. ^{1}H NMR (CDCl$_3$) δ 1.33 (t, 3 H), 1.7 (m, 4 H), 2.38 (m, 4 H), 2.86 (q, 2 H), 3.66 (m, 2 H), 3.67 (s, 3 H), 3.73 (s, 3 H), 3.76 (m, 2 H), 3.88 (m, 2 H), 3.91 (m, 4 H), 6.86 (s, 1 H)

EXAMPLE 44

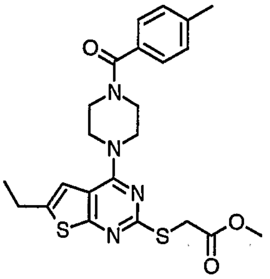
Methyl 3-(4-{6-ethyl-2-[(2-methoxy-2-oxoethyl)thio]thieno[2,3-d]pyrimidin-4-yl}piperazin-1-yl)-3-oxopropanoate



To a mixture of the hydrochloride salt of Example 34 (0.075 g) in DMF (2.5 mL) in a 2 dram screw cap vial was added diisopropylethylamine (0.104 g) and methyl malonyl chloride (0.025 mL). The mixture was placed in a Lab-Line MAX Q2000 orbital shaker for 20 hours at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using ethyl acetate as eluent to give 0.027 g (31%) of the title compound: MS (ESI+) for C19 H24 N4 O5 S$_2$ *m/z* 453.13 (M+H)$^+$. ^{1}H NMR (CDCl$_3$) δ 1.33 (t, 3 H), 2.86 (q, 2 H), 3.53 (s, 2 H), 3.62 (m, 2 H), 3.73 (s, 3 H), 3.77 (s, 3 H), 3.79 (m, 2 H), 3.81 (m, 2 H), 3.91 (m, 4 H), 6.85 (s, 1 H).

EXAMPLE 45

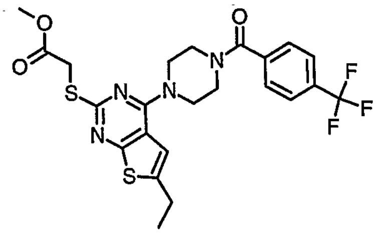
Methyl ({6-ethyl-4-[4-(4-methylbenzoyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)acetate



To a mixture of the hydrochloride salt of Example 34 (0.075 g) in DMF (2.5 mL) in a 2 dram screw cap vial was added diisopropylethylamine (0.104 g) and p-toluoyl chloride (0.031 mL). The mixture was placed in a Lab-Line MAX Q2000 orbital shaker for 20 hours at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using 65% ethyl acetate in hexanes as eluent to give 0.0511 g (56%) of the title compound: MS (ESI+) for C23 H26 N4 O3 S$_2$ *m/z* 471.14 (M+H)$^+$. ^{1}H NMR (CDCl$_3$) δ 1.33, 2.39, 2.85, 3.72, 3.90, 6.84, 7.24, 7.34.

EXAMPLE 46

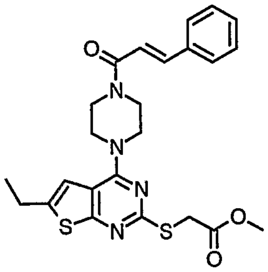
Methyl [(6-ethyl-4-{4-[4-(trifluoromethyl)benzoyl]piperazin-1-yl}thieno[2,3-d]pyrimidin-2-yl)thio]acetate



To a mixture of the hydrochloride salt of Example 34 (0.075 g) in DMF (2.5 mL) in a 2 dram screw cap vial was added diisopropylethylamine (0.104 g) and 4(trifluoromethyl) benzoyl chloride (0.035 mL). The mixture was placed in a Lab-Line MAX Q2000 orbital shaker for 20 hours at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using 65% ethyl acetate in hexanes as eluent to give 0.0632 g (62%) of the title compound: MS (ESI+) for C23 H23 F3 N4 O3 S_2 *m/z* 525.06 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 1.32 (t, 3 H), 2.86 (q, 2 H), 3.48 (m, 2 H), 3.72 (s, 3 H), 3.8-3.95 (m, 8 H), 6.84 (s, 1 H), 7.55 (d, 2 H), 7.71 (d, 2 H).

EXAMPLE 47

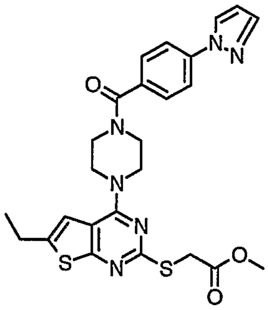
Methyl [(6-ethyl-4-{4-[(2E)-3-phenylprop-2-enoyl]piperazin-1-yl}thieno[2,3-d]pyrimidin-2-yl)thio]acetate



To a mixture of the hydrochloride salt of Example 34 (0.075 g) in DMF (2.5 mL) in a 2 dram screw cap vial was added diisopropylethylamine (0.104 g) and cinnamoyl chloride (0.039 g). The mixture was placed in a Lab-Line MAX Q2000 orbital shaker for 20 hours at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using 65% ethyl acetate in hexanes as eluent to give 0.0533 g (57%) of the title compound: MS (ESI+) for C24 H26 N4 O3 S_2 *m/z* 483.17 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 1.34 (t, 3 H), 2.87 (q, 2 H), 3.74 (s, 3 H), 3.84-3.95 (m, 10 H), 6.89 (m, 2 H), 7.38 (m, 3 H), 7.54 (m, 2 H), 7.77 (d, 1 H).

EXAMPLE 48

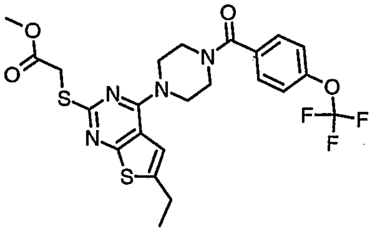
Methyl [(6-ethyl-4-{4-[4-(1H-pyrazol-1-yl)benzoyl]piperazin-1-yl}thieno[2,3-d]pyrimidin-2-yl)thio]acetate



To a mixture of the hydrochloride salt of Example 34 (0.075 g in DMF (2.5 mL)) in a 2 dram screw cap vial was added diisopropylethylamine (0.104 g) and 4-(1H-pyrazol-1yl) benzoyl chloride (0.049 g). The mixture was placed in a Lab-Line MAX Q2000 orbital shaker for 20 hours at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using ethyl acetate as eluent to give 0.0667 g (66%) of the title compound: MS (ESI+) for C25 H26 N6 O3 S_2 *m/z* 523.17 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.33 (t, 3 H), 2.88 (q, 2 H), 3.72 (s, 3 H), 3.9 (m, 10 H), 6.51 (m, 1 H), 6.85 (s, 1 H), 7.56 (d, 2 H), 7.78 (m, 3 H), 7.97 (m, 1 H).

EXAMPLE 49

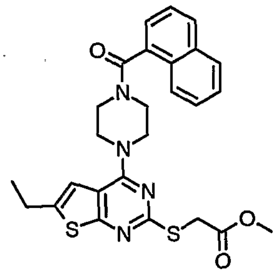
Methyl [(6-ethyl-4-{4-[4-(trifluoromethoxy)benzoyl]piperazin-1-yl}thieno[2,3-d]pyrimidin-2-yl)thio]acetate



To a mixture of the hydrochloride salt of Example 34 (0.075 g) in DMF (2.5 mL) in a 2 dram screw cap vial was added diisopropylethylamine (0.104 g) and 4-(trifluoromethoxy) benzoyl chloride (0.038 mL). The mixture was placed in a Lab-Line MAX Q2000 orbital shaker for 20 hours at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using 65% ethyl acetate in hexanes as eluent to give 0.067 g (64%) of the title compound: MS (ESI+) for C23 H23 F3 N4 O4 S_2 *m/z* 541.12 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.33 (t, 3 H), 2.86 (q, 2 H), 3.6 (m, 2 H), 3.72 (s, 3 H), 3.9 (m, 8 H), 6.84 (s, 1 H), 7.29 (d, 2 H), 7.51 (d, 2 H).

EXAMPLE 50

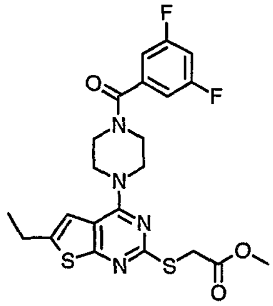
Methyl ({6-ethyl-4-[4-(1-naphthoyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)acetate



To a mixture of the hydrochloride salt of Example 34 (0.075 g) in DMF (2.5 mL) in a 2 dram screw cap vial was added diisopropylethylamine (0.104 g) and 1-naphthoyl chloride (0.035 mL). The mixture was placed in a Lab-Line MAX Q2000 orbital shaker for 20 hours at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using 65% ethyl acetate in hexanes as eluent to give 0.0735 g (75%) of the title compound: MS (ESI+) for C26 H26 N4 O3 S_2 m/z 507.17 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 1.31 (t, 3 H), 2.84 (q, 2 H), 3.34 (m, 2 H), 3.68 (m, 5 H), 3.88 (s, 2 H), 4.02 (m, 2 H), 4.14 (m, 4 H), 6.81 (s, 1 H), 7.4-7.6 (m, 4 H), 7.8-7.95 (m, 3 H).

EXAMPLE 51

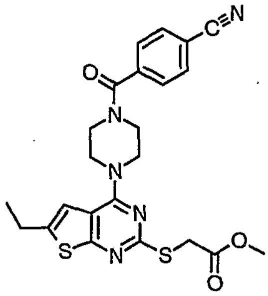
Methyl ({4-[4-(3,5-difluorobenzoyl)piperazin-1-yl]-6-ethylthieno[2,3-d]pyrimidin-2-yl}thio)acetate



To a mixture of the hydrochloride salt of Example 34 (0.075 g) in DMF (2.5 mL) in a 2 dram screw cap vial was added diisopropylethylamine (0.104 g) and 3,5-difluorobenzoyl chloride (0.042 g). The mixture was placed in a Lab-Line MAX Q2000 orbital shaker for 20 hours at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using 65% ethyl acetate in hexanes as eluent to give 0.063 g (66%) of the title compound: MS (ESI+) for C22 H22 F2 N4 O3 S_2 m/z 493.12 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 1.33 (t, 3 H), 2.86 (q, 2 H), 3.58 (m, 2 H), 3.72 (s, 3 H), 3.8-3.97 (m, 8 H), 6.84 (s, 1 H), 6.91 (m, 1 H), 6.98 (m, 2 H).

EXAMPLE 52

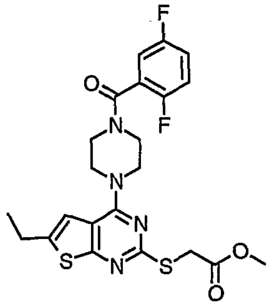
Methyl ({4-[4-(4-cyanobenzoyl)piperazin-1-yl]-6-ethylthieno[2,3-d]pyrimidin-2-yl}thio)acetate



To a mixture of the hydrochloride salt of Example 34 (0.075 g) in DMF (2.5 mL) in a 2 dram screw cap vial was added diisopropylethylamine (0.104 g) and 4-cyanobenzoyl chloride (0.039 g). The mixture was placed in a Lab-Line MAX Q2000 orbital shaker for 20 hours at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using 65% ethyl acetate in hexanes as eluent to give 0.0557 g (60%) of the title compound: MS (ESI+) for C23 H23 N5 O3 S_2 *m/z* 482.12 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 1.33 (t, 3 H), 2.86 (q, 2 H), 3.53 (m, 2 H), 3.72 (s, 3 H), 3.82 (m, 2 H), 3.9 (m, 6 H), 6.83 (s, 1 H), 7.55 (d, 2 H), 7.75 (d, 2 H).

EXAMPLE 53

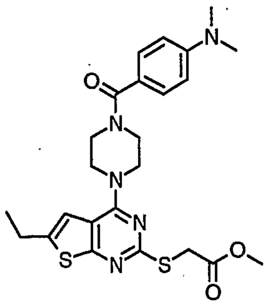
Methyl ({4-[4-(2,5-difluorobenzoyl)piperazin-1-yl]-6-ethylthieno[2,3-d]pyrimidin-2-yl}thio)acetate



To a mixture of the hydrochloride salt of Example 34 (0.075 g) in DMF (2.5 mL) in a 2 dram screw cap vial was added diisopropylethylamine (0.104 g) and 2,5-difluorobenzoyl chloride (0.03 mL). The mixture was placed in a Lab-Line MAX Q2000 orbital shaker for 20 hours at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using 65% ethyl acetate in hexanes as eluent to give 0.0789 g (83%) of the title compound: MS (ESI+) for C22 H22 F2 N4 O3 S_2 *m/z* 493.12 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 1.33 (t, 3 H), 2.85 (q, 2 H), 3.50 (m, 2 H), 3.75 (s, 3 H), 3.84 (m, 2 H), 3.9 (s, 2 H), 3.93 (m, 4 H), 6.84 (s, 1 H), 7.08-7.12 (m, 2 H), 7.82 (m, 1 H).

EXAMPLE 54

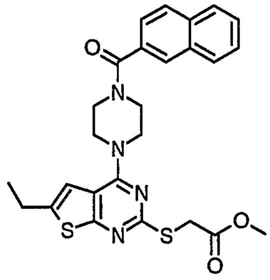
Methyl [(4-{4-[4-(dimethylamino)benzoyl]piperazin-1-yl}-6-ethylthieno[2,3-d]pyrimidin-2-yl)thio]acetate



To a mixture of the hydrochloride salt of Example 34 (0.075 g) in DMF (2.5 mL) in a 2 dram screw cap vial was added diisopropylethylamine (0.104 g) and 4-dimethlamino benzoyl chloride (0.044 g). The mixture was placed in a Lab-Line MAX Q2000 orbital shaker for 20 hours. 4-Dimethlamino benzoyl chloride (0.022 g) was added and the mixture shook an additional 24 hours at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using 65% ethyl acetate in hexanes as eluent to give 0.03 g (31%) of the title compound: MS (ESI+) for C24 H29 N5 O3 S_2 *m/z* 500.21 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 1.33 (t, 3 H), 2.85 (q, 2 H), 3.01 (s, 6 H), 3.72 (s, 3 H), 3.79 (m, 4 H), 3.88 (m, 4 H), 3.90 (s, 2 H), 6.69 (d, 2 H), 6.86 (s, 1 H), 7.40 (d, 2 H).

EXAMPLE 55

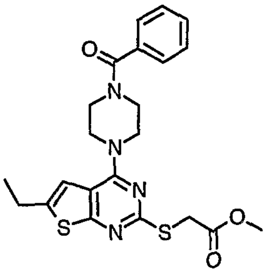
Methyl ({6-ethyl-4-[4-(2-naphthoyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)acetate



To a mixture of the hydrochloride salt of Example 34 (0.075 g in DMF (2.5 mL) in a 2 dram screw cap vial was added diisopropylethylamine (0.104 g) and 2-naphthoyl chloride (0.045 g). The mixture was placed in a Lab-Line MAX Q2000 orbital shaker for 20 hours at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using 65% ethyl acetate in hexanes as eluent to give 0.0572 g (58%) of the title compound: MS (ESI+) for C26 H26 N4 O3 S_2 *m/z* 507.13 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 1.32 (t, 3 H), 2.85 (q, 2 H), 3.71 (m, 5 H), 3.90 (m, 8 H), 6.85 (s, 1 H), 7.55 (m, 3 H), 7.87-7.95 (m, 4 H).

EXAMPLE 56

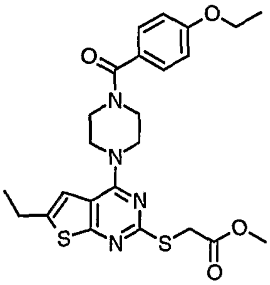
Methyl {[4-(4-benzoylpiperazin-1-yl)-6-ethylthieno[2,3-d]pyrimidin-2-yl]thio}acetate



To a mixture of the hydrochloride salt of Example 34 (0.075 g in N-methylpyrrolidinone (3.0 mL) in a 2 dram screw cap vial was added diisopropylethylamine (0.081 mL) and benzoyl chloride (0.027 mL). The mixture was placed in a Lab-Line MAX Q2000 orbital shaker for 20 hours at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using ethyl acetate as eluent to give 0.0606 g (69%) of the title compound: MS (ESI+) for C22 H24 N4 O3 S_2 *m/z* 457.16 (M+H); 1H NMR ($CDCl_3$) δ 1.34 (t, 3 H), 2.87 (q, 2 H), 3.61 (m, 2 H), 3.73 (s, 3 H), 3.8-3.97 (m, 8 H), 6.86 (s, 1 H), 7.45 (s, 5 H).

EXAMPLE 57

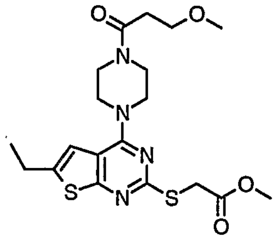
Methyl ({4-[4-(4-ethoxybenzoyl)piperazin-1-yl]-6-ethylthieno[2,3-d]pyrimidin-2-yl}thio)acetate



To a mixture of the hydrochloride salt of Example 34 (0.075 g) in N-methylpyrrolidinone (3.0 mL) in a 2 dram screw cap vial was added diisopropylethylamine (0.081 mL) and 4-ethoxybenzoyl chloride (0.043 g). The mixture was placed in a Lab-Line MAX Q2000 orbital shaker for 20 hours at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using ethyl acetate as eluent to give 0.0586 g (61%) of the title compound: MS (ESI+) for C24 H28 N4 O4 S_2 *m/z* 501.18 $(M+H)^+$. 1H NMR (CDCl3) δ 1.34 (t, 3 H), 1.45 (t, 3 H), 2.87 (q, 2 H), 3.73 (s, 3 H), 3.78 (m, 4 H), 3.88 (m, 4 H), 3.91 (s, 2 H), 4.08 (q, 2 H), 6.86 (s, 1 H), 6.93 (d, 2 H), 7.43 (d, 2 H).

EXAMPLE 58

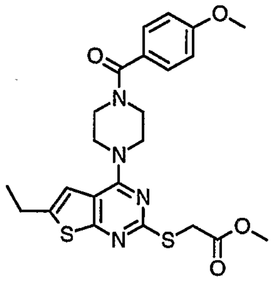
Methyl ({6-ethyl-4-[4-(3-methoxypropanoyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)acetate



To a mixture of the hydrochloride salt of Example 34 (0.075 g) in N-methylpyrrolidinone (3.0 mL) in a 2 dram screw cap vial was added diisopropylethylamine (0.081 mL) and 3-methoxypropionyl chloride (0.028 g). The mixture was placed in a Lab-Line MAX Q2000 orbital shaker for 20 hours at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using ethyl acetate as eluent to give 0.030 g (35%) of the title compound: MS (ESI+) for C19 H26 N4 O4 S_2 *m/z* 439.21 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.34 (t, 3 H), 2.65 (m, 2 H), 2.87 (q, 2 H), 3.38 (s, 3 H), 3.69-3.92 (m, 13 H), 6.87 (s, 1 H).

EXAMPLE 59

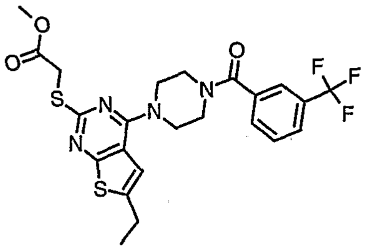
Methyl ({6-ethyl-4-[4-(4-methoxybenzoyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)acetate



To a mixture of the hydrochloride salt of Example 34 (0.075 g) in N-methylpyrrolidinone (3.0 mL) in a 2 dram screw cap vial was added diisopropylethylamine (0.081 mL) and 4-methoxybenzoyl chloride (0.040 g). The mixture was placed in a Lab-Line MAX Q2000 orbital shaker for 20 hours at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using ethyl acetate as eluent to give 0.0566 g (60%) of the title compound: MS (ESI+) for C23 H26 N4 O4 S_2 *m/z* 487.18 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.34 (t, 3 H), 2.88 (q, 2 H), 3.73 (s, 3 H), 3.78 (m, 4 H), 3.86 (s, 3 H), 3.88 (m, 2 H), 3.91 (s, 2 H), 6.86 (s, 1 H), 6.95 (d, 2 H), 7.44 (d, 2 H).

EXAMPLE 60

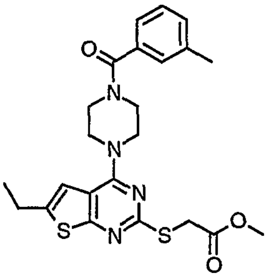
Methyl [(6-ethyl-4-{4-[3-(trifluoromethyl)benzoyl]piperazin-1-yl}thieno[2,3-d]pyrimidin-2-yl)thio]acetate



To a mixture of the hydrochloride salt of Example 34 (0.08 g) in DMF (2.5 mL) in a 2 dram screw cap vial was added diisopropylethylamine (0.058 g) and 3-trifluoromethyl benzyl chloride (0.044 g). The mixture was placed in a Lab-Line MAX Q2000 orbital shaker for 20 hours at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using ethyl acetate as eluent to give 0.0745 g (69%) of the title compound: MS (ESI+) for C23 H23 F3 N4 O3 S_2 *m/z* 525.18 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 1.33 (t, 3 H), 2.85 (q, 2 H), 3.59 (m, 2 H), 3.72 (s, 3 H), 3.8-3.98 (m, 8 H), 6.85 (s, 1 H), 7.56-7.65 (m, 2 H), 7.72 (m, 2 H).

EXAMPLE 61

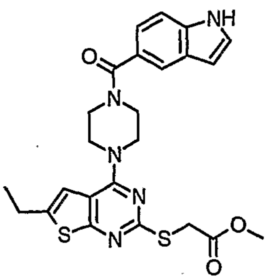
Methyl ({6-ethyl-4-[4-(3-methylbenzoyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)acetate



To a mixture of the hydrochloride salt of Example 34 (0.08 g) in DMF (2.5 mL) in a 2 dram screw cap vial was added diisopropylethylamine (0.058 g) and m-toluoyl chloride (0.033 g). The mixture was placed in a Lab-Line MAX Q2000 orbital shaker for 20 hours at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using 40% ethyl acetate in hexanes as eluent to give 0.0532 g (55%) of the title compound: MS (ESI+) for C23 H26 N4 O3 S_2 *m/z* 471.18 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 1.33, 2.39, 2.85, 3.60, 3.72, 3.90, 6.85, 7.20, 7.29. ^{1}H NMR ($CDCl_3$) δ 1.33 (t, *J* = 3 Hz, H), 2.39 (s, 3 H), 2.85 (q, 2 H), 3.6 (m, 2 H), 3.72 (s, 3 H), 3.8-3.98 (m, 8 H), 6.85 (s, 1 H), 7.20-7.33 (m, 4 H).

EXAMPLE 62

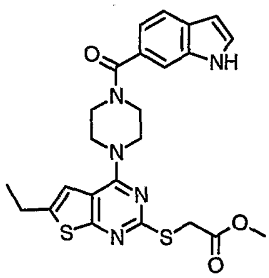
Methyl ({6-ethyl-4-[4-(1H-indol-5-ylcarbonyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)acetate



To a mixture of the hydrochloride salt of Example 34 (0.1 g) in DMF (3.0 mL) in a 2 dram screw cap vial was added diisopropylethylamine (0.135 g), indole-5-carboxylic acid (0.042 g), and HATU (0.099 g). The mixture was placed in a Lab-Line MAX Q2000 orbital shaker for 20 hours at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using 70% ethyl acetate in hexanes as eluent to give 0.0354 g (27%) of the title compound: MS (ESI+) for C24 H25 N5 O3 S_2 *m/z* 496.15 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 1.32 (t, 3 H), 2.85 (q, 2 H), 3.71 (s, 3 H), 3.78-3.97 (m, 10 H), 6.59 (s, 1 H), 6.85 (s, 1 H), 7.28 (m, 2 H), 7.3 (d, 1 H), 7.77 (s, 1 H), 8.53 (s, 1 H).

EXAMPLE 63

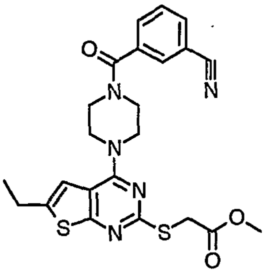
Methyl ({6-ethyl-4-[4-(1H-indol-6-ylcarbonyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)acetate



To a mixture of the hydrochloride salt of Example 34 (0.1 g) in DMF (3.0 mL) in a 2 dram screw cap vial was added diisopropylethylamine (0.135 g), indole-6-carboxylic acid (0.042 g), and HATU (0.099 g). The mixture was placed in a Lab-Line MAX Q2000 orbital shaker for 20 hours at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using 50% ethyl acetate in hexanes as eluent to give 0.043 g (33%) of the title compound: MS (ESI+) for C24 H25 N5 O3 S_2 *m/z* 496.15 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 1.32 (t, 3 H), 2.85 (q, 2 H), 3.6-4.0 (m, 13 H), 6.55 (s, 1 H), 6.84 (s, 1 H), 7.16 (d, 1 H), 7.27 (m, 2 H), 7.53 (s, 1 H), 7.64 (d, 1 H), 8.93 (s, 1 H).

EXAMPLE 64

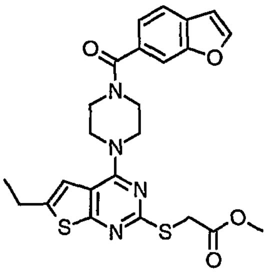
Methyl ({4-[4-(3-cyanobenzoyl)piperazin-1-yl]-6-ethylthieno[2,3-d]pyrimidin-2-yl}thio)acetate



To a mixture of the hydrochloride salt of Example 34 (0.1 g) in DMF (3.0 mL) in a 2 dram screw cap vial was added diisopropylethylamine (0.039 g), 3-cyanobenzioc acid (0.042 g), and CDI (0.049 g). The mixture was placed in a Lab-Line MAX Q2000 orbital shaker for 20 hours at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using ethyl acetate as eluent to give 0.0806 g (81%) of the title compound: ^{1}H NMR ($CDCl_3$) δ 1.34 (t, 3 H), 2.87 (q, 2 H), 3.73 (s, 3 H), 3.78 (m, 4 H), 3.91 (s, 2 H), 3.95 (m, 4 H), 6.84 (s, 1 H), 7.13 (s, 1 H), 7.24 (m, 2 H), 7.92 (s, 1 H).

EXAMPLE 65

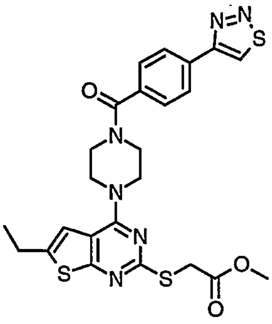
Methyl ({4-[4-(1-benzofuran-6-ylcarbonyl)piperazin-1-yl]-6-ethylthieno[2,3-d]pyrimidin-2-yl}thio)acetate



To a mixture of the hydrochloride salt of Example 34 (0.1 g) in DMF (2.5 mL) in a 2 dram screw cap vial was added diisopropylethylamine (0.15 mL) and 1-benzofuran-5-carbonyl chloride (0.054 g). The mixture was placed in a Lab-Line MAX Q2000 orbital shaker for 20 hours at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using ethyl acetate as eluent to give 0.0562 g (44%) of the title compound: MS (ESI+) for C24 H24 N4 O4 S_2 *m/z* 497.04 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 1.32 (t, 3 H), 2.85 (q, 2 H), 3.6-4.0 (m, 13 H), 6.83 (m, 2 H), 7.39 (d, 1 H), 7.55 (d, 1 H), 7.71 (d, 2 H).

EXAMPLE 66

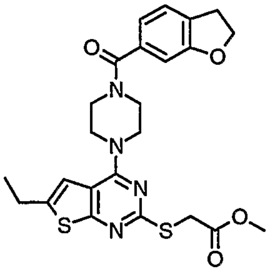
Methyl [(6-ethyl-4-{4-[4-(1,2,3-thiadiazol-4-yl)benzoyl]piperazin-1-yl}thieno[2,3-d]pyrimidin-2-yl)thio]acetate



To a mixture of the hydrochloride salt of Example 34 (0.1 g) in DMF (2.5 mL) in a 2 dram screw cap vial was added diisopropylethylamine (0.15 mL) and 4-(1,2,3-thiadiazol-4-yl) benzoyl chloride (0.067 g). The mixture was placed in a Lab-Line MAX Q2000 orbital shaker for 20 hours at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using ethyl acetate as eluent to give 0.0395 g (28%) of the title compound: MS (ESI+) for C24 H24 N6 O3 S_3 *m/z* 541.12 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.33 (t, 3 H), 2.85 (q, 2 H), 3.6-3.8 (m, 5 H), 3.8-4.0 (m, 8 H), 6.85 (s, 1 H), 7.6 (d, 2 H), 8.13 (d, 2 H), 8.73 (s, 1 H).

EXAMPLE 67

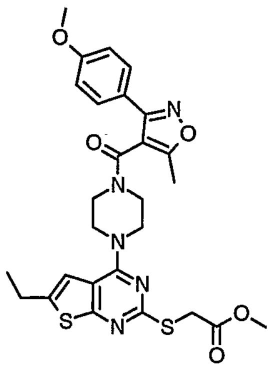
Methyl ({4-[4-(2,3-dihydro-1-benzofuran-6-ylcarbonyl)piperazin-1-yl]-6-ethylthieno[2,3-d]pyrimidin-2-yl}thio)acetate



To a mixture of the hydrochloride salt of Example 34 (0.1 g) in DMF (2.5 mL) in a 2 dram screw cap vial was added diisopropylethylamine (0.15 mL) and 2,3-(dihydro-1-benzofuran)-5-carbonyl chloride (0.055 g). The mixture was placed in a Lab-Line MAX Q2000 orbital shaker for 20 hours at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using ethyl acetate as eluent to give 0.055 g (43%) of the title compound: MS (ESI+) for C24 H26 N4 O4 S_2 *m/z* 499.17 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.32 (t, 3 H), 2.85 (q, 2 H), 3.24 (m, 2 H), 3.72 (s, 3 H), 3.77 (m, 4 H), 3.87 (m, 4 H), 3.90 (s, 2 H), 4.62 (m, 2 H), 6.79 (d, 1 H), 6.85 (s, 1 H), 7.21 (d, 1 H), 7.34 (s, 1 H).

EXAMPLE 68

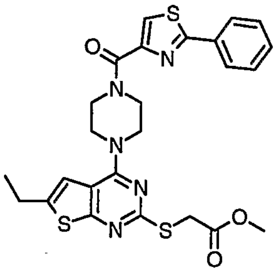
Methyl {[6-ethyl-4-(4-{[3-(4-methoxyphenyl)-5-methylisoxazol-4-yl]carbonyl}piperazin-1-yl)thieno[2,3-d]pyrimidin-2-yl]thio}acetate



To a mixture of the hydrochloride salt of Example 34 (0.105 g) in DMF (2.0 mL) in a 2 dram screw cap vial was added diisopropylethylamine (0.15 mL), 3-(4-methoxyphenyl)-5-methyl-4-isoxazole carboxylic acid (0.07 g), and HATU (0.15 g). The mixture was placed in a Lab-Line MAX Q2000 orbital shaker for 20 hours at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using ethyl acetate as eluent to give 0.0681 g (44%) of the title compound: MS (ESI+) for C27 H29 N5 O5 S_2 *m/z* 568.2 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.3 (t, 3 H), 2.5 (s, 3 H), 2.82 (q, 2 H), 3.22 (m, 2 H), 3.34 (m, 2 H), 3.68 (s, 3 H), 3.78-3.95 (m, 9 H), 6.72 (s, 1 H), 6.94 (d, 2 H), 7.58 (d, 2 H).

EXAMPLE 69

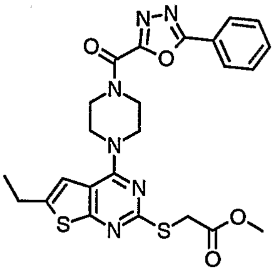
Methyl [(6-ethyl-4-{4-[(2-phenyl-1,3-thiazol-4-yl)carbonyl]piperazin-1-yl}thieno[2,3-d]pyrimidin-2-yl)thio]acetate



To a mixture of the hydrochloride salt of Example 34 (0.105 g) in DMF (2.0 mL) in a 2 dram screw cap vial was added diisopropylethylamine (0.15 mL), 2-(3-pyridyl)-1,3-thiazole-4-carboxylic acid (0.062 g), and HATU (0.15 g). The mixture was placed in a Lab-Line MAX Q2000 orbital shaker for 20 hours at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using ethyl acetate as eluent to give 0.06 g (41%) of the title compound: ^1H NMR ($CDCl_3$) δ 1.33 (t, 3 H), 2.86 (q, 2 H), 3.72 (s, 3 H), 3.91 (s, 2 H), 3.98 (m, 6 H), 4.23 (m, 2 H), 6.89 (s, 1 H), 7.46 (m, 3 H), 7.95 (m, 2 H), 8.01 (s, 1 H).

EXAMPLE 70

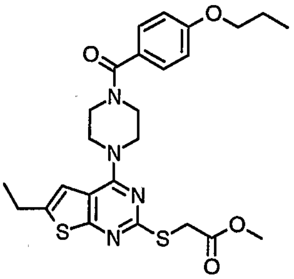
Methyl [(6-ethyl-4-{4-[(5-phenyl-1,3,4-oxadiazol-2-yl)carbonyl]piperazin-1-yl}thieno[2,3-d]pyrimidin-2-yl)thio]acetate



To a mixture of the hydrochloride salt of Example 34 (0.1 g) in DMF (10 mL), diisopropylethylamine (0.073 g) was added 5-phenyl-1,3,4-oxadiazole-2-carbonyl chloride (0.054 g) portion wise over 6 hours. The mixture was stirred overnight at room temperature at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using 40% ethyl acetate in hexanes as eluent to give 0.0261 g (19%) of the title compound: MS (ESI+) for C24 H24 N6 O4 S_2 *m/z* 525.12 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.34 (t, 3 H), 2.87 (q, 2 H), 3.74 (s, 3 H), 3.92 (s, 2 H), 4.0 (m, 6 H), 4.42 (m, 2 H), 6.88 (s, 1 H), 7.6-7.6 (m, 3 H), 8.15 (d, 2 H).

EXAMPLE 71

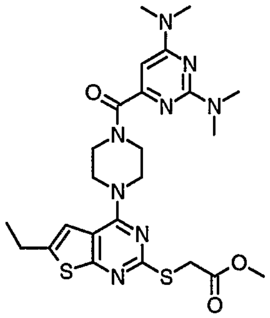
Methyl ({6-ethyl-4-[4-(4-propoxybenzoyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)acetate



To a mixture of the hydrochloride salt of Example 34 (0.10 g) in DMF (3.0 mL) in a 2 dram screw cap vial was added diisopropylethylamine (0.15 mL), 4-propoxy benzoic acid (0.048 g), and HATU (0.1 g). The mixture was placed in a Lab-Line MAX Q2000 orbital shaker for 20 hours at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using 1:1 ethyl acetate: hexanes as eluent to give 0.0733 g (55%) of the title compound: MS (ESI+) for C25 H30 N4 O4 S_2 *m/z* 515.17 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.05 (t, 3 H), 1.33 (t, 3 H), 1.83 (m, 2 H), 2.85 (q, 2 H), 3.72 (s, 3 H), 3.77 (m, 4 H), 3.88 (m, 4 H), 3.90 (s, 2 H), 3.95 (m, 2 H), 6.85 (s, 1 H), 6.91 (d, 2 H), 7.41 (d, 2 H).

EXAMPLE 72

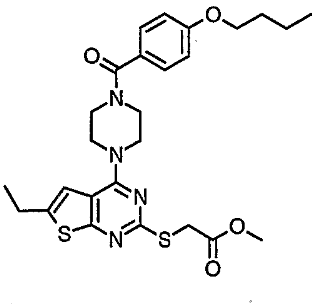
Methyl {[4-(4-{[2,6-bis(dimethylamino)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-6-ethylthieno[2,3-d]pyrimidin-2-yl]thio}acetate



To a mixture of the hydrochloride salt of Example 34 (0.10 g) in DMF (3.0 mL) in a 2 dram screw cap vial was added diisopropylethylamine (0.15 mL), 2,4-Bis(dimethylamino)pyrimidine-6-carboxylic acid (0.057 g), and HATU (0.1 g). The mixture was placed in a Lab-Line MAX Q2000 orbital shaker for 20 hours at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using 95:5 methylene chloride: methanol as eluent to give 0.0558 g (40%) of the title compound: MS (ESI+) for C24 H32 N8 O3 S_2 *m/z* 545.21 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 1.32 (t, 3 H), 2.85 (q, 2 H), 3.07 (s, 6 H), 3.13 (s, 6 H), 3.72 (s, 3 H), 3.8 (m, 2 H), 3.88 (m, 4 H), 3.90 (s, 2 H), 3.95 (m, 2 H), 6.07 (s, 1 H), 6.85 (s, 1 H).

EXAMPLE 73

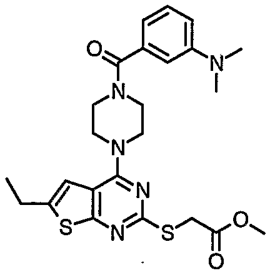
Methyl ({4-[4-(4-butoxybenzoyl)piperazin-1-yl]-6-ethylthieno[2,3-d]pyrimidin-2-yl}thio)acetate



To a mixture of the hydrochloride salt of Example 34 (0.10 g) in DMF (3.0 mL) in a 2 dram screw cap vial was added diisopropylethylamine (0.15 mL), 4-butoxy benzoic acid (0.052 g), and HATU (0.1 g). The mixture was placed in a Lab-Line MAX Q2000 orbital shaker for 20 hours at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using 1:1 ethyl acetate: hexanes as eluent to give 0.085 g (63%) of the title compound: MS (ESI+) for C26 H32 N4 O4 S_2 *m/z* 529.15 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 0.98 (t, 3 H), 1.33 (t, 3 H), 1.5 (m, 2 H), 1.77 (m, 2 H), 2.85 (q, 2 H), 3.72 (s, 3 H), 3.77 (m, 4 H), 3.88 (m, 4 H), 3.90 (s, 2 H), 4.0 (m, 2 H), 6.85 (s, 1 H), 6.92 (d, 2 H), 7.41 (d, 2 H).

EXAMPLE 74

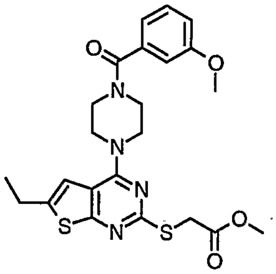
Methyl [(4-{4-[3-(dimethylamino)benzoyl]piperazin-1-yl}-6-ethylthieno[2,3-d]pyrimidin-2-yl)thio]acetate



To a mixture of the hydrochloride salt of Example 34 (0.10 g) in DMF (3.0 mL) in a 2 dram screw cap vial was added diisopropylethylamine (0.15 mL), 3-dimethylamino benzoic acid (0.045 g), and HATU (0.1 g). The mixture was placed in a Lab-Line MAX Q2000 orbital shaker for 20 hours at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using 95:5 methylene chloride: methanol as eluent to give 0.0602 g (47%) of the title compound: MS (ESI+) for C24 H29 N5 O3 S_2 *m/z* 500.21 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.32 (t, 3 H), 2.85 (q, 2 H), 2.98 (s, 6 H), 3.72 (m, 2 H), 3.81 (s, 3 H), 3.8 (m, 2 H), 3.88-4.0 (m, 6 H), 6.72 (m, 1 H), 6.78 (m, 2 H), 6.84 (s, 17.28 H).

EXAMPLE 75

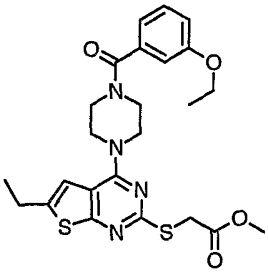
Methyl ({6-ethyl-4-[4-(3-methoxybenzoyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)acetate



To a mixture of the hydrochloride salt of Example 34 (0.10 g) in DMF (5.0 mL) in a 2 dram screw cap vial was added diisopropylethylamine (0.0698 g), m-anisic acid (0.04 g), and HATU (0.1 g). The mixture was placed in a Lab-Line MAX Q2000 orbital shaker for 20 hours at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using 60:40 ethyl acetate: hexanes as eluent to give 0.068 g (54%) of the title compound: ^1H NMR ($CDCl_3$) δ 1.33 (t, 3 H), 2.86 (q, 2 H), 3.61 (m, 2 H), 3.72 (s, 3 H), 3.8-3.95 (m, 11 H), 6.84 (s, 1 H), 6.97 (m, 3 H), 7.34 (m, 1 H).

EXAMPLE 76

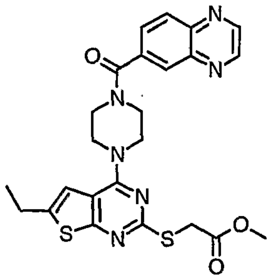
Methyl ({4-[4-(3-ethoxybenzoyl)piperazin-1-yl]-6-ethylthieno[2,3-d]pyrimidin-2-yl}thio)acetate



To a mixture of the hydrochloride salt of Example 34 (0.10 g) in DMF (3.0 mL) in a 2 dram screw cap vial was added diisopropylethylamine (0.078 g), 3-ethoxybenzoic acid (0.043 g), and HATU (0.1 g). The mixture was placed in a Lab-Line MAX Q2000 orbital shaker for 20 hours at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using 60:40 ethyl acetate: hexanes as eluent to give 0.0585 g (45%) of the title compound: MS (ESI+) for C24 H28 N4 O4 S_2 *m/z* 501.18 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 1.33 (t, 3 H), 1.42 (t, 3 H), 2.86 (q, 2 H), 3.61 (m, 2 H), 3.72 (s, 3 H), 3.8-4.0 (m, 8 H), 7.05 (q, 2 H), 6.84 (s, 1 H), 6.95 (m, 3 H), 7.32 (m, 1 H).

EXAMPLE 77

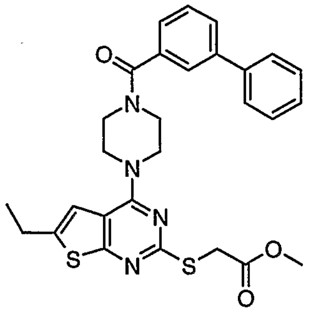
Methyl ({6-ethyl-4-[4-(quinoxalin-6-ylcarbonyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)acetate



To a mixture of the hydrochloride salt of Example 34 (0.10 g) in THF (14.0 mL) in a R. B. flask was added diisopropylethylamine (0.078 g), 6-quinoxaline carbonyl chloride (0.05 g). The mixture was stirred at room temperature for 20 hours at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using ethyl acetate as eluent to give 0.0599 g (46%) of the title compound: MS (ESI+) for C24 H24 N6 O3 S_2 *m/z* 509.18 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 1.32 (t, 3 H), 2.85 (q, 2 H), 3.71 (m, 5 H), 3.8-4.1 (m, 8 H), 6.85 (s, 1 H), 7.86 (d, 1 H), 8.18 (m, 2 H), 8.92 (s, 2 H).

EXAMPLE 78

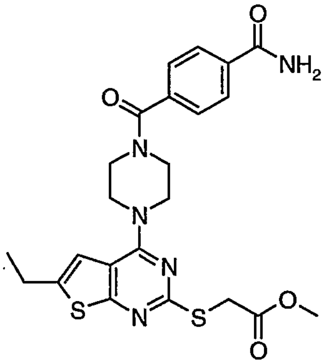
Methyl ({4-[4-(1,1'-biphenyl-3-ylcarbonyl)piperazin-1-yl]-6-ethylthieno[2,3-d]pyrimidin-2-yl}thio)acetate



To a mixture of the hydrochloride salt of Example 34 (0.10 g) in THF (4.0 mL) in a R. B. flask was added diisopropylethylamine (0.106 g), 3-biphenyl carboxylic acid (0.052 g), and HATU (0.099 g). The mixture was stirred at room temperature for 20 hours at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed three times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using 60:40 ethyl acetate: hexanes as eluent to give 0.0418 g (31%) of the title compound: ^{1}H NMR ($CDCl_3$) δ 1.32 (t, 3 H), 2.85 (q, 2 H), 3.65 (m, 2 H), 3.70 (s, 3 H), 3.8-4.0 (m, 8 H), 6.84 (s, 1 H), 7.35-7.49 (m, 5 H), 7.58 (d, 2 H), 7.68 (m, 2 H).

EXAMPLE 79

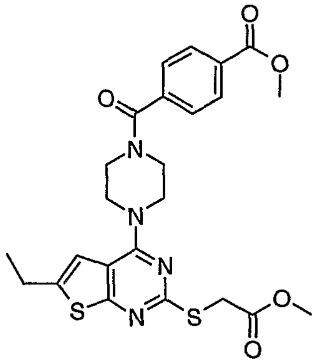
Methyl [(4-{4-[4-(aminocarbonyl)benzoyl]piperazin-1-yl}-6-ethylthieno[2,3-d]pyrimidin-2-yl)thio]acetate



To a mixture of the hydrochloride salt of Example 34 (0.182 g) in THF (15.0 mL) and NMP (5.0 mL) in a R. B. flask was added diisopropylethylamine (0.213 g), 4-(Aminocarbonyl)benzoic acid (0.078 g), and HATU (0.18 g). The mixture was stirred at room temperature for 20 hours at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed three times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using ethyl acetate as eluent to give 0.0748 g (32%) of the title compound: ^{1}H NMR ($CDCl_3$) δ 1.32 (t, 3 H), 2.85 (q, 2 H), 3.60 (m, 2 H), 3.72 (s, 3 H), 3.8-4.0 (m, 8 H), 7.52 (s, 1 H), 6.23 (s, 2 H), 7.59 (t, 1 H), 7.61 (d, 1 H), 7.90 (m, 2 H).

EXAMPLE 80

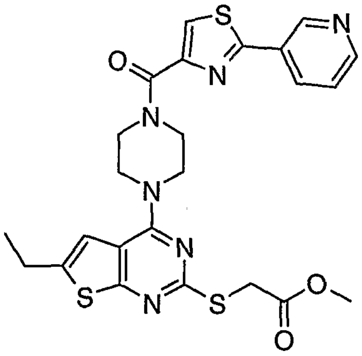
Methyl 4-[(4-{6-ethyl-2-[(2-methoxy-2-oxoethyl)thio]thieno[2,3-d]pyrimidin-4-yl}piperazin-1-yl)carbonyl]benzoate



To a mixture of the hydrochloride salt of Example 34 (0.075 g) in DMF (2.5 mL) in a 2 dram screw cap vial was added diisopropylethylamine (0.104 g) and teraphthalic acid monomethylester chloride (0.047 g). The mixture was placed in a Lab-Line MAX Q2000 orbital shaker for 48 hours at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using ethyl acetate as eluent to give 0.0103 g (10%) of the title compound: MS (ESI+) for C24 H26 N4 O5 S_2 *m/z* 515.17 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.33 (t, 3 H), 2.86 (q, 2 H), 3.55 (m, 2 H), 3.72 (s, 3 H), 3.8 (m, 2 H), 3.9-3.95 (m, 9 H), 6.8 (s, 1 H), 7.5 (d, 2 H), 8.11 (d, 2 H).

EXAMPLE 81

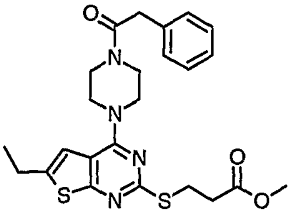
Methyl [(6-ethyl-4-{4-[(2-pyridin-3-yl-1,3-thiazol-4-yl)carbonyl]piperazin-1-yl}thieno[2,3-d]pyrimidin-2-yl)thio]acetate



To a mixture of the hydrochloride salt of Example 34 (0.105 g) in DMF (2.0 mL) in a 2 dram screw cap vial was added diisopropylethylamine (0.15 mL), 2-(3-pyridyl)-1,3-thiazole carboxylic acid (0.062 g), and HATU (0.15 g). The mixture was placed in a Lab-Line MAX Q2000 orbital shaker for 20 hours at which time the mixture was partitioned between brine and ethyl acetate. The layers were separated and the organic layer washed four times with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on silica gel using ethyl acetate as eluent and recrystallized from acetone to give 0.012 g (8%) of the title compound: MS (ESI+) for C24 H24 N6 O3 S_3 *m/z* 541.11 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 1.34 (t, 3 H), 2.87 (q, 2 H), 3.73 (s, 3 H), 3.92-3.98 (m, 8 H), 4.22 (m, 2 H), 6.9 (s, 1 H), 7.4 (m, 1 H), 8.09 (s, 1 H), 8.22 (m, 1 H), 8.7 (m, 1 H), 9.2 (m, 1 H).

EXAMPLE 82

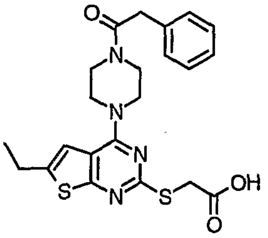
methyl 3-({6-ethyl-4-[4-(phenylacetyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)propanoate



To methyl 3-mercaptopropionate (0.0225 g), the pyrimidine of Example 6 (0.075 g), and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) (0.0615 mL) in an 8 mL capacity glass screw-cap vial was added DMF (0.2 mL). The mixture was placed on a shaker plate and the disappearance of the pyrimidine of Example 6 was monitored by TLC. Additional methyl 3-mercaptopropionate and DBU (and DMF if solids formed) were added over several days until the reaction was judged complete by TLC. Ethyl acetate was added to the reaction mixture, which was then extracted with water and aqueous ammonium chloride. The ethyl acetate layer was then taken to dryness and the residue was chromatographed on silica gel using ethyl acetate-hexane (1/1) as eluent to give 0.056 g of the title compound. MS [m+H] 485.19; ^{1}H NMR ($CDCl_3$) δ 1.32 (t, 3H), 2.82 (m, 4H), 3.36 (t, 2H) , 3.58-3.80 (m, 13H), 6.81 (s, 1H), 7.26 (m, 3H), 7.31 (m, 2H).

EXAMPLE 83

({6-ethyl-4-[4-(phenylacetyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)acetic acid

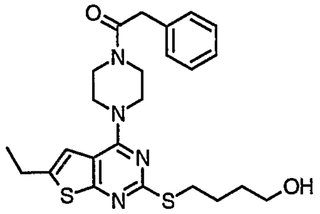


To mercaptoacetic acid sodium salt (0.0213 g), the pyrimidine of Example 6 (0.075 g), and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) (0.0615 mL) in an 8 mL capacity glass screw-cap vial was added DMF (0.2 mL). The mixture was placed on a shaker plate and the disappearance of the pyrimidine of Example 6 was monitored by TLC. Additional mercaptoacetic acid sodium salt and DBU (and DMF if solids formed) were added over several days until the reaction was judged complete by TLC. Water and concentrated HCl, to bring the pH to approximately 4 were then added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was then taken to dryness and the residue was chromatographed on silica gel using MeOH-dichloromethane (12/88) as eluent to give 0.0117 g of the title compound. MS [m+H] 457.16; ^{1}H NMR ($CDCl_3$) δ

1.30 (m, 3H), 2.84 (m, 2H), 3.58 (m, 2H), 3.75 (m, 8H), 3.90 (m, 2H), 6.82 (s, 1H), 7.25 (m, 3H), 7.35 (m, 2H).

EXAMPLE 84

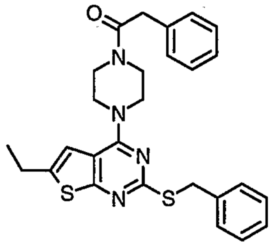
4-({6-ethyl-4-[4-(phenylacetyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)butan-1-ol



To 4-mercapto-1-butanol (0.0198 g), the pyrimidine of Example 6 (0.075 g), and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) (0.0615 mL) in an 8 mL capacity glass screw-cap vial was added DMF (0.2 mL). The mixture was placed on a shaker plate and the disappearance of the pyrimidine of Example 6 was monitored by TLC. Additional 4-mercapto-1-butanol and DBU (and DMF if solids formed) were added over several days until the reaction was judged complete by TLC. Ethyl acetate was added to the reaction mixture, which was then extracted with water and aqueous ammonium chloride. The ethyl acetate layer was then taken to dryness and the residue was chromatographed on silica gel using ethyl acetate-hexane (80/20) as eluent to give 0.080 g of the title compound. MS [m+H] 471.16. ^{1}H NMR ($CDCl_3$) δ 1.32 (t, 3H), 1.70 (m, 2H), 1.82 (m, 2H), 2.72 (t, 1H), 2.85 (q, 2H), 3.14 (m, 2H), 3.59 (m, 2H), 3.70 (m, 4H), 3.78, (s, 2H), 3.81 (s, 4H), 6.81 (s, 1H), 7.26 (m, 3H), 7.32 (m, 2H).

EXAMPLE 85

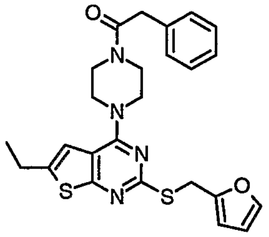
2-(benzylthio)-6-ethyl-4-[4-(phenylacetyl)piperazin-1-yl]thieno[2,3-d]pyrimidine



To benzyl mercaptan (0.0255 g), the pyrimidine of Example 6 (0.075 g), and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) (0.0615 mL) in an 8 mL capacity glass screw-cap vial was added DMF (0.2 mL). The mixture was placed on a shaker plate and the disappearance of the pyrimidine of Example 6 was monitored by TLC. Additional benzyl mercaptan and DBU (and DMF if solids formed) were added over several days until the reaction was judged complete by TLC. Isocyanate polymer (Aldrich 47368-5; 0.25 g) was added and the mixture was stirred for 2 hours at which time the polymer was removed by filtration and the filtrate was partitioned between ethyl acetate, water, and aqueous ammonium chloride. The layers were separated and, after standing overnight, the desired product began to crystallize out of the ethyl acetate solution. Hexane was added and after standing for additional time, the mother liquors were decanted and the remaining desired product was taken to dryness to give 0.90 g of the title compound. MS [m+H] 489.15 ^{1}H NMR (CDCl$_3$) δ 1.33 (t, 3H), 2.85 (q, 2H), 3.55 (m, 2H), 3.63 (m, 2H), 3.77 (s, 4H), 4.39 (s, 2H), 6.80 (s, 1H), 7.26 (m, 8H), 7.32 (m, 2H).

EXAMPLE 86

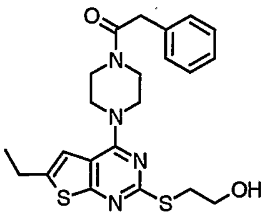
6-ethyl-2-[(2-furylmethyl)thio]-4-[4-(phenylacetyl)piperazin-1-yl]thieno[2,3-d]pyrimidine



To 2-furfural mercaptan (0.0213 g), the pyrimidine of Example 6 (0.075 g), and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) (0.0615 mL) in an 8 mL capacity glass screw-cap vial was added DMF (0.2 mL). The mixture was placed on a shaker plate and the disappearance of the pyrimidine of Example 6 was monitored by TLC. Additional 2-furfural mercaptan and DBU (and DMF if solids formed) were added over several days until the reaction was judged complete by TLC. Isocyanate polymer (Aldrich 47368-5; 0.25 g) was added and the mixture was stirred for 2 hours at which time the polymer was removed by filtration and the filtrate was partitioned between ethyl acetate, water, and aqueous ammonium chloride. The ethyl acetate layer was concentrated and the resulting material was chromatographed on silica gel using ethyl acetate-hexane (1/1) to give 0.067 g of the title compound. MS [m+H] 479.14; ^{1}H NMR (CDCl$_3$) δ 1.33 (t, 3H), 2.86 (q, 2H), 3.57 (m, 2H), 3.66 (m, 2H), 3.78 (s, 2H), 3.80 (m, 4H), 4.41 (s, 2H), 6.25 (m, 2H), 6.81 (s, 1H), 7.26 (m, 3H), 7.30 (m, 3H).

EXAMPLE 87

2-({6-ethyl-4-[4-(phenylacetyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)ethanol

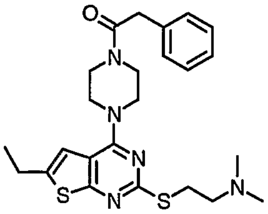


To 2-mercaptoethanol (0.0146 g), the pyrimidine of Example 6 (0.075 g), and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) (0.0615 mL) in an 8 mL capacity glass screw-cap vial was added DMF (0.2 mL). The mixture was placed on a shaker plate and the disappearance of the pyrimidine of Example 6 was monitored by TLC. Additional 2-mercaptoethanol and DBU (and DMF if solids formed) were added over several days until the reaction was judged complete by TLC. Ethyl acetate was added to the reaction mixture, which was then extracted with water and aqueous ammonium chloride. The ethyl acetate layer was then taken to dryness and the residue was chromatographed on silica gel using ethyl acetate-hexane (80/20) as eluent to give

0.076 g of the title compound. MS [m+H] 443.18. ^{1}H NMR ($CDCl_3$) δ 1.32 (t, 3H), 2.85 (q, 2H), 3.32 (m, 2H), 3.61 (m, 2H), 3.69 (m, 2H), 3.78 (s, 2H), 3.81 (br s, 4H), 3.95 (m, 2H), 6.81 (s, 1H), 7.26 (m 3H), 7.31 (m, 2H).

EXAMPLE 88

N-[2-({6-ethyl-4-[4-(phenylacetyl)piperazin-1-yl]thieno[2,3-d]pyrimidin-2-yl}thio)ethyl]-N,N-dimethylamine



To 2-(dimethylamino)ethanethiol (0.0265 g), the pyrimidine of Example 6 (0.075 g), and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) (0.089 mL) in an 8 mL capacity glass screw-cap vial was added DMF (0.2 mL). The mixture was placed on a shaker plate and the disappearance of the pyrimidine of Example 6 was monitored by TLC. Additional 2-(dimethylamino)ethanethiol and DBU (and DMF if solids formed) were added over several days until the reaction was judged complete by TLC. Water was then added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was then taken to dryness and the residue was chromatographed on silica gel using MeOH-dichloromethane-ammonium hydroxide (aqueous) (6/94/0.1) as eluent to give 0.046 g of the title compound. MS [m+H] 470.20; ^{1}H NMR ($CDCl_3$) δ 1.32 (t, 3H), 2.30 (s, 6H), 2.64 (m, 2H), 2.85 (q, 2H), 3.24 (m, 2H), 3.60 (m 2H), 3.67 (m, 2H), 3.78 (s, 2H), 3.80 (br s, 4H), 6.80 (s, 1H), 7.26 (m, 3H), 7.32 (m, 2H).

O. Biological Protocols

In vitro assays

1. Inhibition of [^{33}P]2MeS-ADP Binding to Washed Human Platelet Membranes.

The ability of a test compound to bind to the P2Y12 receptor was evaluated in a platelet membrane binding assay. In this competitive binding assay, the test compound competed against a radiolabelled agonist for binding to the P2Y12 receptor, which is found on the surface of platelets. Inhibition of binding of the labeled material was measured and correlated to the amount and potency of the test compound. Data from this assay are presented in Table F. Platelet rich plasma ("PRP") was obtained from the Interstate Blood bank, Memphis, Tennessee. Platelet rich plasma was prepared from blood units collected in ACD ((prepared by (1) combining: 2.5 g sodium citrate (Sigma S-4641); 1.5 g citric acid (Sigma C-0706); and, 2.0 g dextrose (Sigma G-7528); (2) bringing pH to 4.5; and (3) adding water to bring volume to 100 mL) and using the light spin protocol; this protocol involves centrifugation at room temperature for approximately 20 minutes at speeds up to 160xg. Platelet rich plasma is supplied in units of approximately 200 ml. Each unit is distributed into four 50 mL polypropylene conical tubes for centrifugation. Blood from each donor is maintained separately.

The 50 mL tubes were centrifuged for 15 minutes at 1100 rpm in Sorvall RT6000D (with H1000B rotor). Internal centrifuge temperature was maintained at approximately room temperature (22-24°C). This spin pelleted cellular components remaining from the PRP preparation.

The supernatant was decanted into fresh 50 mL tubes. To avoid carry over of cellular components following the room temperature centrifugation, approximately 5 mL of PRP was left in the tube and discarded. The tubes were capped and inverted 2-3 times and allowed to stand at room temperature for at least 15 minutes following inversion.

Optionally, a Coulter Counter may be used to count platelets from the resting samples during the resting phase. Normal human platelet counts are expected to range from 200,000 to 400,000 per µL of PRP supernatant.

The 50 mL tubes containing PRP supernatant were centrifuged for 15 minutes at 2300-2400 rpm to loosely pellet the platelets. The supernatant from this spin was decanted immediately into a clean cell culture bottle (Corning bottle) and saved in case further centrifugation was needed.

The pellet of each tube was resuspended in 2-4 mL of Wash buffer (pH 6.5) (1 L prepared new daily - 134 mM NaCl (Sigma S-5150); 3 mM KCl (Sigma P-9333); 1 mM $CaCl_2$ (JT Baker 1311-01); 2 mM $MgCl_2$ (Sigma M-2670); 5 mM glucose (EM 4074-2); 0.3 mM NaH_2PO_4 (Sigma S-9638)/12 mM $NaHCO_3$ (JT Baker 3506-01); 5 mM HEPES pH 7.4 (Gibco 12379-012); 0.35% BSA (Sigma A-7906); 330 mg Heparin (bovine lung, Sigma H-4898); and 30 mL of ACD) by repeated gentle aspiration using disposable polypropylene sample pipettes.

Wash buffer (pH 6.5) was added to each tube to bring the volume to approximately 40 mL. Each tube was incubated for at least 15 minutes at 37°C.

The tubes were then centrifuged again for 15 minutes at 2300-2400 rpm to loosely pellet the platelets. The supernatant was decanted and discarded. The pellet was resuspended in 2-4 mL of Assay buffer (pH 7.4) (1 L volume - 134 mM NaCl; 3 mM KCl; 1 mM $CaCl_2$; 2 mM $MgCl_2$; 5 mM glucose; 0.3 mM NaH_2PO_4/12 mM $NaHCO_3$; 5 mM HEPES pH 7.4; and 0.35% BSA) by repeated aspiration using disposable polypropylene sample pipettes. Tubes were combined and gently swirled to mix only when all pellets were successfully resuspended; pellets that did not resuspend or contained aggregates were not combined.

The pooled platelet preparation was counted using a Coulter Counter. The final concentration of platelets was brought to 1×10^6 per µL using Assay buffer pH 7.4. The platelets were rested for a minimum of 45 minutes at 37°C before use in the assay.

In one embodiment, the compounds were tested in 96-well microtiter filterplates (Millipore Multiscreen-FB opaque plates, #MAFBNOB50). These plates were used in the assay and pre-wet with 50 µL of Assay buffer pH 7.4 then filtered through completely with a Millipore plate vacuum. Next, 50 µL of platelet suspension was placed into 96-well filterplates. 5 µL of 2MeS-ADP (100 µM working stock concentration to give final concentration 5 µM in well) and 20 µL Assay buffer were added to background control wells. 25 µl Assay buffer were added to set of wells for total binding.

25 µL of 4X concentrated compound were added in duplicate to the 96-well filterplates. Next, 25 µL [^{33}P]2MeS-ADP (Perkin Elmer NEN custom synthesis, specific activity ~2100Ci/mmol) was

added to all wells. (1.6 nM working stock concentration to give 0.4 nM final concentration in well). The mixture was incubated for 60 minutes at room temperature and agitated with gentle shaking. The reaction was stopped by washing the 96-well filterplate three times with 100 µl/well of Cold Wash buffer (1 L volume - 134 mM NaCl; 10 mM Hepes pH 7.4, stored at 4°C) on a plate vacuum. The plate was disassembled and allowed to air dry overnight with the filter side up. The filter plates were snapped into adapter plates and 0.1 mL of Microscint 20 Scintillation Fluid (Perkin Elmer # 6013621) was added to each well. The top of the filterplate was sealed with plastic plate covers. The sealed filterplate was agitated for 30 minutes at room temperature. A Packard TopCount Microplate Scintillation Counter was used to measure counts. The binding of compound is expressed as a % binding decrease of the ADP samples after correcting for changes in unaggregated control samples.

2. Inhibition of Human Platelet Aggregation

The ability of a test compound to bind to the P2Y12 receptor was evaluated in a platelet aggregation assay. In this functional assay, the test compound competed against an agonist for binding to the P2Y12 receptor, which is found on the surface of platelets. Inhibition of platelet aggregation was measured using standard techniques. Data from this assay are presented in Table F.

As an alternative to the binding assay which measures a candidate compound's ability to bind to the P2Y12 receptor, an assay may be used that measures the effect of the candidate compound on cellular function. The candidate compound competes with ADP, a known agonist, for binding at P2Y12. ADP is sufficient to induce platelet aggregation; the presence of an effective candidate compound inhibits aggregation. The inhibition of platelet aggregation is measured using standard techniques.

Whole blood was collected by Pfizer medical personnel from volunteers (100 mL per volunteer) in 20 mL syringes containing 2 mL of buffered Citrate. In one embodiment, buffered Citrate is 0.105 M Citrate: 0.0840 M Na_3-citrate and 0.0210 M citric acid. In another embodiment, buffered Citrate is 0.109 M Citrate: 0.0945 M Na_3-citrate and 0.0175 M citric acid. The contents of the syringes were expelled into two 50 mL polypropylene conical tubes. Blood was combined only when collected from a single donor. The 50 mL tubes were centrifuged for 15 minutes at 1100 rpm in Sorvall RT6000D (with H1000B rotor). The internal centrifuges temperature was maintained between 22-24°C and was operating without using the centrifuge brake. This spin pelleted cellular components remaining from the PRP preparation. The PRP layer was collected from each tube and set aside. The supernatant was decanted into fresh 50 mL tubes. To avoid carry over of cellular components following the room temperature centrifugation, approximately 5 mL of PRP was left in the tube and discarded.

The 50 mL tubes were placed back into the centrifuge and spun for 15 minutes at 2800-3000 rpm (with the brake on). This pelleted out most particulate blood constituents remaining, leaving a layer of Platelet Poor Plasma ("PPP"). The PPP was collected and the platelet concentration determined using a Coulter Counter. The PRP layer, previously set aside, was diluted with PPP to a final concentration of approximately 330,000 platelets/µl with the PPP. The final preparation was split into multiple 50 mL conical tubes, each filled with only 25-30 mL of diluted PRP prep. In one embodiment, the tube was filled with $5\%CO_2/95\%O_2$ gas, to maintain the pH of the prep. Each tube was tightly capped and stored at room temperature.

The human platelet aggregation assay is performed is performed in 96-well plate using microtiter plate reader (SpectraMax Plus 384 with SoftMax Pro software from Molecular Devices). The instrument settings include: Absorbance at 626 nm and run time at 15 minutes with readings in 1-minute intervals and 45 seconds shaking between readings.

The reaction is incubated at 37^0C. First 18 µl of test compound at 10x final concentration in 5% DMSO is mixed with 144 µl fresh PRP for 30 seconds and incubated at 37°C for 5 minutes. Following that incubation period, 18 µl of 200 µM ADP is added to the reaction mix. This addition of ADP is sufficient to induce aggregation in the absence of an inhibitor. Results of the assay are expressed as % inhibition, and are calculated using absorbance values at 15 minutes.

3. Human P2Y12 Recombinant Cell Membrane Binding Assay with ^{33}P 2MeS-ADP.

The ability of a test compound to bind to the P2Y12 receptor was evaluated in a recombinant cell membrane binding assay. In this competitive binding assay, the test compound competed against a radiolabelled agonist for binding to the P2Y12 receptor, expressed on the cell membrane. Inhibition of binding of the labeled material was measured and correlated to the amount and potency of the test compound. Data from this assay are presented in Table F. This binding assay is a modification of the procedure in Takasaki, J. et. al, Mol. Pharmacol., 2001, Vol. 60, pg. 432.

HEK cells were transfected with the pDONR201P2Y12 vector and cultured in MEM with GlutaMAX I, Earle's salts, 25 mM HEPES (Gibco # 42360-032) containing 10% dialyzed FBS (Gibco # 26400-044), 100 µM nonessential amino acids (Gibco # 11140-050), 1 mM sodium pyruvate (Gibco # 11360-070), 0.05% geneticin (Gibco #10131-027), 3 µg/mL blasticidin (Fluka brand from Sigma # 15205), and 0.5 µg/mL puromycin (Sigma # P-8833).

Confluent cells were washed once with cold DPBS (Gibco # 14190-136). Fresh DPBS was added and the cells were scraped and centrifuged at 500 x g for 5 minutes at 4 °C. The cell pellets were resuspended in TEE buffer (25 mM Tris, 5 mM EDTA, 5 mM EGTA) containing 1 protease inhibitor cocktail tablet (Roche # 1 873 580) per 50 mL (called TEE + Complete) and can be flash frozen at this point.

In one embodiment, frozen cell pellets were used to prepare the membranes. In that embodiment, the frozen cell pellets were thawed on ice. In another embodiment, cell pellets may be used without flash freezing before moving on to the next step.

Cell pellets were resuspended in TEE buffer + Complete and homogenized in a glass dounce for 12 strokes. The cell suspension was centrifuged at 500 x g for 5 minutes at 4 °C. The supernatant was saved and centrifuged at 20,000 x g for 20 minutes at 4 °C. This supernatant was discarded and the cell pellet resuspended in TEE buffer + Complete and homogenized in a glass dounce for 12 strokes. This suspension was centrifuged at 20,000 x g for 20 minutes at 4

°C and the supernatant discarded. The pellet was resuspended in assay buffer (50 mM Tris, 100 mM NaCl, 1 mM EDTA) containing one protease inhibitor cocktail tablet per 50 mL, and can be flash frozen as 1 mL aliquots at this point.

Dry compounds were diluted as 10 mM DMSO stocks and tested in a seven-point, three-fold dilution series run in triplicate beginning at 10 µM, final concentration. A 1 mM DMSO intermediate stock was made in a dilution plate and from this the seven dilutions were made to 5X the final concentration in assay buffer containing 0.02% BSA.

To a polypropylene assay plate (Costar # 3365) the following were added: a) 30 µL of assay buffer containing one protease inhibitor cocktail tablet per 50 mL; b) 30 µL of 1 nM ^{33}P 2MeS-ADP made in assay buffer containing 0.02% BSA and 12.5 mg/mL ascorbic acid; 30 µL of cold 1.5 µM 2MeS-ADP for the positive control wells, or assay buffer containing 0.02% BSA and 12.5 mg/mL ascorbic acid for the negative control wells, or 5X drug dilution; and 60 µL of 1ug/well membranes.

The plates were incubated at room temperature for 1 hour. The reaction was stopped using a cell harvester to transfer the reaction mixture onto GF/B UniFilter plates (Perkin Elmer # 6005177), and washed three times with wash buffer (50 mM Tris), filtering between each wash. The filter plates were dried for approximately 20 minutes in an oven at 50 °C. Back seals were adhered to the filter plates and 25 uL of Microscint 20 scintillation fluid (Perkin Elmer # 6013621) were added. The filter plates were sealed, shaken for 30 minutes, and counted on a Top Count. Data were analyzed using a four-parameter curve fit with a fixed minimum and maximum experimentally defined as the average positive and negative controls on each plate, and with a hill slope equal to one.

4. Human P2Y12 Recombinant Cell Membrane Binding Assay With Human Serum Albumin, Alpha-1 Acid Glycoprotein and ^{33}P 2MeS-ADP

The ability of a test compound to bind to the P2Y12 receptor was evaluated in a recombinant cell membrane binding assay. In this competitive binding assay, the test compound competed against a radiolabelled agonist for binding to the P2Y12 receptor, expressed on the cell membrane. To simulate *in vivo* conditions, human protein is added to the assay mixture. Inhibition of binding of the labeled material was measured and correlated to the amount and potency of the test compound. Data from this assay are presented in Table F.

HEK cells were transfected with the pDONR201P2Y12 vector and cultured in MEM with GlutaMAX I, Earle's salts, 25 mM HEPES (Gibco # 42360-032) containing containing 10% dialyzed FBS (Gibco # 26400-044), 100 µM nonessential amino acids (Gibco # 11140-050), 1 mM sodium pyruvate (Gibco # 11360-070), 0.05% geneticin (Gibco #10131-027), 3 µg/mL blasticidin (Fluka brand from Sigma # 15205), and 0.5 µg/mL puromycin (Sigma # P-8833). Confluent cells were washed once with cold DPBS (Gibco # 14190-136). Fresh DPBS was added and the cells were scraped and centrifuged at 500 x g for 5 minutes at 4 °C. The cell pellets were resuspended in TEE buffer (25 mM Tris, 5 mM EDTA, 5 mM EGTA) containing 1 protease inhibitor cocktail tablet (Roche # 1 873 580) per 50 mL (called TEE + Complete) and can be flash frozen at this point.

In one embodiment, frozen cell pellets were used to prepare the membranes. In that embodiment, the frozen cell pellets were thawed on ice. In another embodiment, cell pellets may be used without flash freezing before moving on to the next step.

Cell pellets were resuspended in TEE buffer + Complete and homogenized in a glass dounce for 12 strokes. The cell suspension was centrifuged at 500 x g for 5 minutes at 4 °C. The supernatant was saved and centrifuged at 20,000 x g for 20 minutes at 4 °C. This supernatant was discarded and the cell pellet resuspended in TEE buffer + Complete and homogenized in a glass dounce for 12 strokes. This suspension was centrifuged at 20,000 x g for 20 minutes at 4 °C and the supernatant discarded. The pellet was resuspended in assay buffer (50 mM Tris, 100 mM NaCl, 1 mM EDTA) containing one protease inhibitor cocktail tablet per 50 mL, and can be flash frozen as 1 mL aliquots at this point.

Dry compounds were diluted as 10 mM DMSO stocks and tested in a seven-point, three-fold dilution series run in triplicate beginning at 10 μM, final concentration. A 1 mM DMSO intermediate stock was made in a dilution plate and from this the seven dilutions were made to 5X the final concentration in assay buffer containing 0.02% BSA.

To a polypropylene assay plate (Costar # 3365) the following were added: a) 30 μL of assay buffer containing one protease inhibitor cocktail tablet per 50 mL; b) 30 μL of 1 nM ^{33}P 2MeS-ADP made in assay buffer containing 0.02% BSA and 12.5 mg/mL ascorbic acid; c) 30 μL of cold 1.5 μM 2MeS-ADP for the positive control wells, or assay buffer containing 0.02% BSA and 12.5 mg/mL ascorbic acid for the negative control wells, or 5X drug dilution; and d) 60 μL of 1ug/well membranes containing 0.875% human serum albumin (Sigma # A-3782) and 0.0375% alpha-1 acid glycoprotein (Sigma # G-9885).

The plates were incubated at room temperature for 1 hour. The reaction was stopped using a cell harvester to transfer the reaction mixture onto GF/B UniFilter plates (Perkin Elmer # 6005177), and washed three times with wash buffer (50 mM Tris), filtering between each wash. The filter plates were dried for approximately 20 minutes in an oven at 50 °C. Back seals were adhered to the filter plates and 25 uL of Microscint 20 scintillation fluid (Perkin Elmer # 6013621) were added. The filter plates were sealed, shaken for 30 minutes, and counted on a Top Count Scintillation Counter.

Data are analyzed using a four-parameter curve fit with a fixed minimum and maximum, experimentally defined as the average positive and negative controls on each plate and with a Hill slope equal to one.

The table below presents the IC_{50}, K_i, and percent inhibition values for compounds tested in either washed human platelets membrane binding assay (assay #1 above) or recombinant cell membrane binding assay (Assay #3, above). Example number refers to the compound prepared as described in the example noted in the section Working Examples, above. The highest concentration of candidate compound tested is listed for each experimental run presented. Multiple data sets indicate multiple experimental runs completed for a given compound.

TABLE F - Data

Ex. #	[^{33}P]2MeS-ADP Binding to Washed Human Platelet Membranes (Assay 1)				[^{33}P]-2MeS-ADP Binding to Recombinant Human P2Y12 Membranes (Assay 3)			
	IC$_{50}$ (µM)	Ki (µM)	%Inhibition	[Highest] (µM)	IC$_{50}$ (µM)	Ki (µM)	%Inhibition	[Highest] (µM)
7	--	--	--	--	0.32 1.02 0.38 0.42	0.174 0.582 0.21 0.24	94.06 92.93 89.51 95.92	10 10 10 10
8	--	--	--	--	1.2 1.2	0.72 0.68	81.31 81.44	10 10
9	--	--	--	--	>10.0 9.3	>5.90 5.4	-37.97 33.16	10 10
10	--	--	--	--	0.99 0.55	0.57 0.33	82.32 79.53	10 10
11	--	--	--	--	0.33 0.23 0.27 0.328	0.19 0.13 0.16 0.189	90.54 92.50 88.81 81.00	10 10 10 1
12	--	--	--	--	0.34 0.37	0.2 0.21	83.44 92.83	10 10
13	--	--	--	--	0.28 0.53	0.16 0.31	88.22 88.77	10 10
14	--	--	--	--	0.29 0.33	0.16 0.2	89.94 83.72	10 10
15	--	--	--	--	0.3 0.3	0.17 0.17	86.95 92.26	10 10
16	--	--	--	--	0.27 0.36	0.15 0.21	88.73 87.82	10 10
17	--	--	--	--	0.5 0.53	0.29 0.31	90.56 87.05	10 10
21	--	--	--	--	0.022 0.01 0.02 0.043	0.012 0.01 0.012 0.025	91.88 95.84 98.24 95.00	1 10 10 1
22	--	--	--	--	0.043 0.051	0.025 0.028	92.67 90.70	10 10
23	--	--	--	--	>10.0 0.38	>5.70 0.21	64.64 75.04	10 10
24	--	--	--	--	0.19 0.24	0.11 0.13	83.08 92.16	10 10
25	--	--	--	--	0.2 0.27	0.11 0.15	88.60 94.08	10 10
26	--	--	--	--	0.8 0.8	0.46 0.43	88.68 88.94	10 10
27	--	--	--	--	0.1	0.058	96.48	10
28	--	--	--	--	0.038	0.022	94.31	10
29	--	--	--	--	0.16	0.091	82.19	10
31	--	--	--	--	0.031	0.018	99.67	10
32	--	--	--	--	0.052	0.029	93.16	10
35	--	--	--	--	>10.0	>6.70	-4.55	10
36	--	--	--	--	0.22	0.15	97.57	10
37	--	--	--	--	1.25	0.84	78.30	10
38	--	--	--	--	0.6	0.4	77.23	10
39	--	--	--	--	>10.0	>6.70	43.13	10

40	--	--	--	--	4.15	2.76	58.98	10
41	--	--	--	--	2.57	1.72	71.64	10
42	--	--	--	--	5.74	3.83	52.31	10
43	--	--	--	--	2.38	1.58	78.19	10
44	--	--	--	--	4.03	2.69	63.60	10
45	--	--	--	--	>10.0	>6.70	42.53	10
46	--	--	--	--	>10.0	>6.70	41.78	10
47	--	--	--	--	5.44	3.63	48.56	10
48	--	--	--	--	0.19	0.13	95.79	10
49	--	--	--	--	5.52	3.68	56.75	10
50	--	--	--	--	>10.0	>6.70	40.28	10
51	--	--	--	--	1.58	1.05	74.19	10
52	--	--	--	--	2.67	1.78	67.72	10
53	--	--	--	--	2.33	1.56	68.82	10
54	--	--	--	--	6.19 4.44	3.56 2.96	47.82 61.77	10 10
55	--	--	--	--	1.47	0.98	61.22	10
56	--	--	--	--	3.04	1.52	64.14	10
57	--	--	--	--	1.05	0.524	80.75	10
58	--	--	--	--	5.25	2.62	53.62	10
59	--	--	--	--	2.97	1.48	67.07	10
60	--	--	--	--	4.87	3.16	60.78	10
61	--	--	--	--	1.91	1.24	78.52	10
62	--	--	--	--	5.86	3.53	50.86	10
63	--	--	--	--	1.88	1.13	68.08	10
64	--	--	--	--	0.157 0.417 0.33	0.094 0.252 0.212	91.32 81.22 90.29	10 10 10
65	--	--	--	--	0.62	0.37	80.95	10
66	--	--	--	--	0.45	0.27	74.61	10
67	--	--	--	--	1.23	0.74	79.73	10
68	--	--	--	--	6.42	3.88	96.37	10
69	--	--	--	--	0.0878	0.053	56.75	10
70	--	--	--	--	0.144	0.089	82.07	10
71	--	--	--	--	0.289	0.179	89.32	10
72	--	--	--	--	0.681	0.423	88.65	10
73	--	--	--	--	0.371	0.23	82.02	10
74	--	--	--	--	5.74	3.69	59.05	10
75	--	--	--	--	3.5	2.25	70.45	10
76	--	--	--	--	1.17	0.73	75.94	10
77	--	--	--	--	4.85	2.81	63.41	10
78	--	--	--	--	0.035 0.02 0.069	0.02 0.01 0.04	92.59 87.73 94.00	10 10 1
79	--	--	--	--	8.7	5.05	47.66	10
80	--	--	--	--	3.78	2.45	59.97	10
81	--	--	--	--	1.72	1.07	76.68	10
82	--	--	--	--	0.39 1.17 0.22 0.27 0.4	0.212 0.667 0.12 0.15 0.23	92.65 86.00 93.95 94.10 89.55	10 10 10 10 10
83	--	--	--	--	0.23 0.94 0.43 0.47	0.127 0.54 0.24 0.27	92.01 90.75 91.85 86.17	10 10 10 10

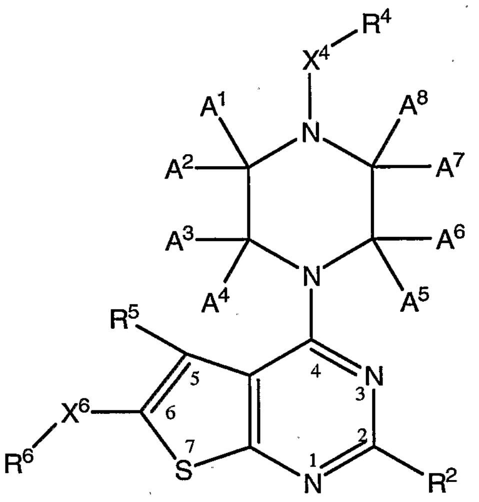
84	--	--	--	--	0.58	0.315	90.62	10
					1.44	0.825	71.83	10
					0.22	0.13	92.13	10
					0.27	0.15	94.46	10
					0.52	0.3	90.58	10
85	>10	--	39.5	10	--	--	--	--
86	7.93	7.51	52.9	10	--	--	--	--
87	--	--	--	--	0.57	031	88.82	10
					0.59	0.337	44.82	10
					0.2	0.11	95.43	10
					0.32	0.18	92.17	10
88	--	--	--	--	1.68	0.913	94.06	10
					1.48	0.848	80.30	10
					0.64	0.37	84.54	10
					0.37	0.21	89.14	10
					1.2	0.7	82.41	10

All mentioned documents are incorporated by reference as if here written. When introducing elements of the present invention or the exemplary embodiment(s) thereof, the articles “a,” “an,” “the” and “said” are intended to mean that there are one or more of the elements. The terms “comprising,” “including” and “having” are intended to be inclusive and mean that there may be additional elements other than the listed elements. Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations.

CLAIMS

What is claimed is:

1. A compound, or a pharmaceutically acceptable salt of the compound, wherein the compound has the structure of Formula I:



Formula I

wherein:

A^1, A^2, A^3, A^4, A^5, A^6, A^7 and A^8 are independently selected from the group consisting of hydrogen, alkyl, and haloalkyl;

R^2 is selected from the group consisting of $-S(O)R^{2a}$, $-S(O)_2R^{2a}$, $-S(O)_2NR^{2a}R^{2b}$, $-SC(O)R^{2a}$, and $-SR^{2j}$; wherein:

R^{2a} and R^{2b} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl; wherein the R^{2a} and R^{2b} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl substituents may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, cyano, oxo, =S, nitro, $-R^{2d}$, $-C(O)R^{2d}$, $-C(S)R^{2d}$, $-C(O)OR^{2d}$, $-C(S)OR^{2d}$, $-C(O)SR^{2d}$, $-C(O)NR^{2d}R^{2e}$, $-C(S)NR^{2d}R^{2e}$, $-OR^{2d}$, $-OC(O)R^{2d}$, $-OC(S)R^{2d}$, $-OC(O)OR^{2d}$, $-OC(O)NR^{2d}R^{2e}$, $-OC(S)NR^{2d}R^{2e}$, $-NR^{2d}R^{2e}$, $-NR^{2d}C(O)R^{2e}$, $-NR^{2d}C(S)R^{2e}$, $-NR^{2d}C(O)OR^{2e}$, $-NR^{2d}C(S)OR^{2e}$, $-NR^{2d}S(O)_nR^{2e}$, $-NR^{2d}C(O)NR^{2e}R^{2f}$, $-S(O)_nR^{2d}$, $-S(O)_nNR^{2d}R^{2e}$, and $-SC(O)R^{2d}$;

n is 0, 1 or 2;

R^{2d}, R^{2e} and R^{2f} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl;

wherein the R^{2d}, R^{2e} and R^{2f} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl substituents may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, cyano, oxo, =S, nitro, $-R^{2g}$, $-C(O)R^{2g}$, $-C(S)R^{2g}$, $-C(O)OR^{2g}$, $-C(S)OR^{2g}$, $-C(O)SR^{2g}$, $-C(O)NR^{2g}R^{2h}$, $-C(S)NR^{2g}R^{2h}$, $-OR^{2g}$, $-OC(O)R^{2g}$, $-OC(S)R^{2g}$, $-OC(O)OR^{2g}$, $-OC(O)NR^{2g}R^{2h}$,

-OC(S)NR^{2g}R^{2h}, -NR^{2g}R^{2h}, -NR^{2g}C(O)R^{2h}, -NR^{2g}C(S)R^{2h}, -NR^{2g}C(O)OR^{2h}, -NR^{2g}C(S)OR^{2h}, -NR^{2g}S(O)$_p$R^{2h}, -NR^{2g}C(O)NR^{2h}R^{2i}, -S(O)$_p$R^{2g}, -S(O)$_p$NR^{2g}R^{2h}, and -SC(O)R^{2g};

p is 0, 1 or 2;

R^{2g}, R^{2h} and R^{2i} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl;

wherein the R^{2g,} R^{2h} and R^{2i} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl substituents may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxy, cyano, oxo, =S, nitro, alkyl, haloalkyl, hydroxyalkyl, carboxy, and alkoxy;

R^{2j} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl; wherein:

(a) the R^{2j} C$_7$-C$_{20}$ alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl substituent may be optionally substituted with one or more substituents independently selected from the group consisting of halogen and -R^{2m}; and

(b) the R^{2j} C$_1$-C$_6$ alkyl substituent is substituted with at least one substituent independently selected from the group consisting of chloro, bromo, iodo, and -R^{2m};

R^{2m} is selected from the group consisting of cyano, nitro, -NH$_2$, oxo, =S, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, -C(O)R^{2n}, -C(S)R^{2n}, -C(O)OR^{2n}, -C(S)OR^{2n}, -C(O)SR^{2n}, -C(O)NR^{2n}R^{2o},

-C(S)NR^{2n}R^{2o}, –OR^{2n}, -OC(O)R^{2n}, -OC(S)R^{2n}, -OC(O)OR^{2n}, -OC(O)NR^{2n}R^{2o}, -OC(S)NR^{2n}R^{2o}, -NR^{2n}R^{2o},

-NR^{2n}C(O)R^{2o}, -NR^{2n}C(S)R^{2o}, -NR^{2n}C(O)OR^{2o}, -NR^{2n}C(S)OR^{2o}, -NR^{2n}S(O)$_q$R^{2o}, -NR^{2n}C(O)NR^{2o}R^{2p},

-S(O)$_q$R^{2n}, -S(O)$_q$NR^{2n}R^{2o}, and -SC(O)R^{2n};

q is 0, 1 or 2;

R^{2n}, R^{2o} and R^{2p} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl;

wherein the R^{2m}, R^{2n}, R^{2o} and R^{2p} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl substituents may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, cyano, nitro, oxo, =S, -R^{2q}, -C(O)R^{2q}, -C(S)R^{2q}, -C(O)OR^{2q}, -C(S)OR^{2q}, -C(O)SR^{2q}, -C(O)NR^{2q}R^{2r}, -C(S)NR^{2q}R^{2r}, –OR^{2q}, -OC(O)R^{2r}, -OC(S)R^{2q},-OC(O)OR^{2q},-OC(O)NR^{2q}R^{2r}, -OC(S)NR^{2q}R^{2r},

-NR^{2q}R^{2r}, -NR^{2q}C(O)R^{2r}, -NR^{2q}C(S)R^{2r}, -NR^{2q}C(O)OR^{2r}, -NR^{2q}C(S)OR^{2r}, -NR^{2q}S(O)$_r$R^{2r}, -NR^{2q}C(O)NR^{2r}R^{2s}, -S(O)$_r$R^{2q}, -S(O)$_r$NR^{2q}R^{2r}, and -SC(O)R^{2q};

r is 0, 1 or 2;

R^{2q}, R^{2r} and R^{2s} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl; wherein the R^{2q,} R^{2r} and R^{2s} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl substituents may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxy, cyano, oxo, =S, -SH, nitro, alkyl, haloalkyl, hydroxyalkyl, carboxy, and alkoxy;

X^4 is selected from the group consisting of –C(O)-, -C(S)-, -S(O)- and –$S(O)_2$-;

R^4 is selected from the group consisting of -R^{4j}, -OR^{4j}, and -$NR^{4j}R^{4k}$;

wherein R^{4j} and R^{4k} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, cycloalkylalkyl, arylalkyl, heterocyclylalkyl, arylcycloalkyl, heterocyclylcycloalkyl, cycloalkylaryl, cycloalkylheterocyclyl, arylaryl, heterocyclylheterocyclyl, arylheterocyclyl, heterocyclylaryl, cycloalkoxyalkyl, heterocyclyloxyalkyl, aryloxyaryl, heterocyclyloxyheterocyclyl, aryloxyheterocyclyl, heterocyclyloxyaryl, arylcarbonylaryl, heterocyclylcarbonylheterocyclyl, aryloxyalkyl, arylcarbonylheterocyclyl, heterocyclylcarbonylaryl, arylcarbonylaminoalkyl, heterocyclylcarbonylaminoalkyl, arylcarbonylaminoalkyl, and heterocyclylcarbonylaminoalkyl;

wherein the R^{4j} and R^{4k} substituents may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyalkyl, oxo, =S, nitro, cyano, -R^{4l}, -OR^{4l}, -$C(O)R^{4l}$, -$C(O)OR^{4l}$, -$C(O)NR^{4l}R^{4m}$, -$OC(O)R^{4l}$, -$ONR^{4l}R^{4m}$, -$NR^{4l}R^{4m}$, -$NR^{4l}C(O)R^{4m}$,
-$NR^{4l}S(O)_2R^{4m}$, -$S(O)_bR^{4l}$, -$SC(O)R^{4l}$ and -$SC(O)NR^{4l}R^{4m}$;

b is 0, 1 or 2;

R^{4l} and R^{4m} are independently selected from the group consisting of hydrogen, alkyl, haloalkyl, alkenyl, cycloalkyl, aryl and heterocyclyl;

wherein the R^{4l} and R^{4m} alkyl, haloalkyl, alkenyl, cycloalkyl, aryl and heterocyclyl substituents may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxy, cyano, oxo, =S, nitro, -SH, amino, alkyl, haloalkyl, hydroxyalkyl, carboxy, alkoxy, alkoxycarbonyl and alkylamino;

R^5 is selected from the group consisting of hydrogen, halogen, alkyl, haloalkyl, alkoxy and haloalkoxy;

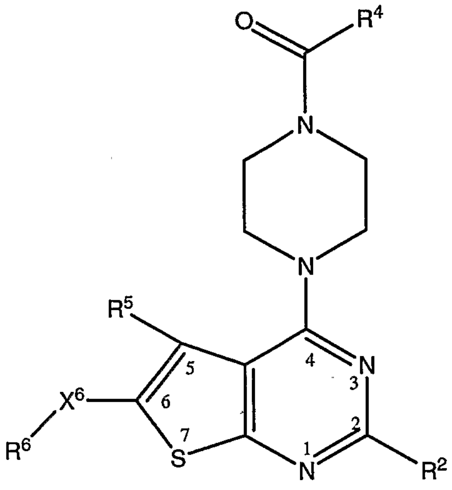
X^6 represents a bond or is -C(O)-; wherein:

(a) when X^6 is –C(O)-, R^6 is selected from the group consisting of -R^{6a} and -OR^{6a};

(b) when X^6 represents a bond, R^6 is selected from the group consisting of halogen, cyano, -R^{6a}
and -OR^{6a};

R^{6a} is selected from the group consisting of hydrogen, alkyl, cycloalkyl and aryl; and wherein the R^{6a} alkyl, cycloalkyl and aryl substituent may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxy, oxo, =S, cyano, alkyl, haloalkyl, hydroxyalkyl, cycloalkyl, carboxy, aryl and heterocyclyl.

2. A compound, or a pharmaceutically acceptable salt of the compound, wherein the compound has the structure of Formula I:



Formula II

wherein:

R^2 is selected from the group consisting of $-S(O)R^{2a}$, $-S(O)_2R^{2a}$, $-S(O)_2NR^{2a}R^{2b}$, $-SC(O)R^{2a}$, and

$-SR^{2j}$; wherein:

R^{2a} and R^{2b} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl;

wherein the R^{2a} and R^{2b} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl substituents may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, cyano, oxo, =S, nitro, $-R^{2d}$, $-C(O)R^{2d}$, $-C(S)R^{2d}$, $-C(O)OR^{2d}$, $-C(S)OR^{2d}$, $-C(O)SR^{2d}$,

$-C(O)NR^{2d}R^{2e}$, $-C(S)NR^{2d}R^{2e}$, $-OR^{2d}$, $-OC(O)R^{2d}$, $-OC(S)R^{2d}$, $-OC(O)OR^{2d}$, $-OC(O)NR^{2d}R^{2e}$, $-OC(S)NR^{2d}R^{2e}$, $-NR^{2d}R^{2e}$, $-NR^{2d}C(O)R^{2e}$, $-NR^{2d}C(S)R^{2e}$, $-NR^{2d}C(O)OR^{2e}$, $-NR^{2d}C(S)OR^{2e}$, $-NR^{2d}S(O)_nR^{2e}$, $-NR^{2d}C(O)NR^{2e}R^{2f}$, $-S(O)_nR^{2d}$, $-S(O)_nNR^{2d}R^{2e}$, and $-SC(O)R^{2d}$;

n is 0, 1 or 2;

R^{2d}, R^{2e} and R^{2f} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl;

wherein the R^{2d}, R^{2e} and R^{2f} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl substituents may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, cyano, oxo, =S, nitro, $-R^{2g}$, $-C(O)R^{2g}$, $-C(S)R^{2g}$, $-C(O)OR^{2g}$, $-C(S)OR^{2g}$, $-C(O)SR^{2g}$, $-C(O)NR^{2g}R^{2h}$, $-C(S)NR^{2g}R^{2h}$, $-OR^{2g}$, $-OC(O)R^{2g}$, $-OC(S)R^{2g}$, $-OC(O)OR^{2g}$, $-OC(O)NR^{2g}R^{2h}$,

$-OC(S)NR^{2g}R^{2h}$, $-NR^{2g}R^{2h}$, $-NR^{2g}C(O)R^{2h}$, $-NR^{2g}C(S)R^{2h}$, $-NR^{2g}C(O)OR^{2h}$, $-NR^{2g}C(S)OR^{2h}$, $-NR^{2g}S(O)_pR^{2h}$, $-NR^{2g}C(O)NR^{2h}R^{2i}$, $-S(O)_pR^{2g}$, $-S(O)_pNR^{2g}R^{2h}$, and $-SC(O)R^{2g}$;

p is 0, 1 or 2;

R^{2g}, R^{2h} and R^{2i} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl;

wherein the $R^{2g,}$ R^{2h} and R^{2i} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl substituents may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxy, cyano, oxo, =S, nitro, alkyl, haloalkyl, hydroxyalkyl, carboxy, and alkoxy;

R^{2j} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl; wherein:

(a) the R^{2j} C_7-C_{20} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl substituent may be optionally substituted with one or more substituents independently selected from the group consisting of halogen and $-R^{2m}$; and

(b) the R^{2j} C_1-C_6 alkyl substituent is substituted with at least one substituent independently selected from the group consisting of chloro, bromo, iodo, and $-R^{2m}$;

R^{2m} is selected from the group consisting of cyano, nitro, $-NH_2$, oxo, =S, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, $-C(O)R^{2n}$, $-C(S)R^{2n}$, $-C(O)OR^{2n}$, $-C(S)OR^{2n}$, $-C(O)SR^{2n}$, $-C(O)NR^{2n}R^{2o}$,
$-C(S)NR^{2n}R^{2o}$, $-OR^{2n}$, $-OC(O)R^{2n}$, $-OC(S)R^{2n}$, $-OC(O)OR^{2n}$, $-OC(O)NR^{2n}R^{2o}$, $-OC(S)NR^{2n}R^{2o}$, $-NR^{2n}R^{2o}$,
$-NR^{2n}C(O)R^{2o}$, $-NR^{2n}C(S)R^{2o}$, $-NR^{2n}C(O)OR^{2o}$, $-NR^{2n}C(S)OR^{2o}$, $-NR^{2n}S(O)_qR^{2o}$, $-NR^{2n}C(O)NR^{2o}R^{2p}$,
$-S(O)_qR^{2n}$, $-S(O)_qNR^{2n}R^{2o}$, and $-SC(O)R^{2n}$;

q is 0, 1 or 2;

R^{2n}, R^{2o} and R^{2p} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl;

wherein the R^{2m}, R^{2n}, R^{2o} and R^{2p} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl substituents may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, cyano, nitro, oxo, =S, $-R^{2q}$, $-C(O)R^{2q}$, $-C(S)R^{2q}$, $-C(O)OR^{2q}$, $-C(S)OR^{2q}$, $-C(O)SR^{2q}$, $-C(O)NR^{2q}R^{2r}$, $-C(S)NR^{2q}R^{2r}$, $-OR^{2q}$, $-OC(O)R^{2r}$, $-OC(S)R^{2q}$, $-OC(O)OR^{2q}$, $-OC(O)NR^{2q}R^{2r}$, $-OC(S)NR^{2q}R^{2r}$,
$-NR^{2q}R^{2r}$, $-NR^{2q}C(O)R^{2r}$, $-NR^{2q}C(S)R^{2r}$, $-NR^{2q}C(O)OR^{2r}$, $-NR^{2q}C(S)OR^{2r}$, $-NR^{2q}S(O)_rR^{2r}$, $-NR^{2q}C(O)NR^{2r}R^{2s}$, $-S(O)_rR^{2q}$, $-S(O)_rNR^{2q}R^{2r}$, and $-SC(O)R^{2q}$;

r is 0, 1 or 2;

R^{2q}, R^{2r} and R^{2s} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl; wherein the R^{2q}, R^{2r} and R^{2s} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl substituents may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxy, cyano, oxo, =S, -SH, nitro, alkyl, haloalkyl, hydroxyalkyl, carboxy, and alkoxy;

R^4 is selected from the group consisting of $-R^{4j}$, $-OR^{4j}$, and $-NR^{4j}R^{4k}$;

wherein R^{4j} and R^{4k} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, cycloalkylalkyl, arylalkyl, arylalkenyl, heterocyclylalkyl, arylcycloalkyl, heterocyclylcycloalkyl, cycloalkylaryl, cycloalkylheterocyclyl, arylaryl, heterocyclylheterocyclyl, arylheterocyclyl, heterocyclylaryl, cycloalkoxyalkyl, heterocyclyloxyalkyl, aryloxyaryl, heterocyclyloxyheterocyclyl, aryloxyheterocyclyl, heterocyclyloxyaryl, arylcarbonylaryl, heterocyclylcarbonylheterocyclyl, aryloxyalkyl, arylcarbonylheterocyclyl, heterocyclylcarbonylaryl, arylcarbonylaminoalkyl, heterocyclylcarbonylaminoalkyl, arylcarbonylaminoalkyl, alkoxyaryl, alkoxyalkyl, heterocyclylcarbonylaminoalkyl, haloalkoxyaryl, alkoxycarbonylalkyl, alkoxycarbonylaryl, alkoxyheterocyclyl;

wherein the R^{4j} and R^{4k} substituents may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyalkyl, oxo, =S, nitro, cyano, $-R^{4l}$, $-OR^{4l}$, $-C(O)R^{4l}$, $-C(O)OR^{4l}$, $-C(O)NR^{4l}R^{4m}$, $-OC(O)R^{4l}$, $-ONR^{4l}R^{4m}$, $-NR^{4l}R^{4m}$, $-NR^{4l}C(O)R^{4m}$, $-NR^{4l}S(O)_2R^{4m}$, $-S(O)_bR^{4l}$, $-SC(O)R^{4l}$ and $-SC(O)NR^{4l}R^{4m}$;

b is 0, 1 or 2;

R^{4l} and R^{4m} are independently selected from the group consisting of hydrogen, alkyl, haloalkyl, alkenyl, cycloalkyl, aryl and heterocyclyl;

wherein the R^{4l} and R^{4m} alkyl, haloalkyl, alkenyl, cycloalkyl, aryl and heterocyclyl substituents may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxy, cyano, oxo, =S, nitro, -SH, amino, alkyl, haloalkyl, hydroxyalkyl, carboxy, alkoxy, alkoxycarbonyl and alkylamino;

R^5 is selected from the group consisting of hydrogen, halogen, alkyl, haloalkyl, alkoxy and haloalkoxy;

X^6 represents a bond or is -C(O)-; wherein:

(a) when X^6 is –C(O)-, R^6 is selected from the group consisting of $-R^{6a}$ and $-OR^{6a}$;

(b) when X^6 represents a bond, R^6 is selected from the group consisting of halogen, cyano, $-R^{6a}$ and $-OR^{6a}$;

R^{6a} is selected from the group consisting of hydrogen, alkyl, cycloalkyl and aryl; and wherein the R^{6a} alkyl, cycloalkyl and aryl substituent may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, oxo, =S, cyano, alkyl, haloalkyl, hydroxyalkyl, cycloalkyl, aryl and heterocyclyl.

3. The compound of claim 2, wherein:

R^5 is hydrogen; X^6 represents a bond; R^6 is $–R^{6a}$, wherein R^{6a} is alkyl, wherein the R^{6a} alkyl substituent may be optionally substituted as provided in claim 2.

4. The compound of claim 3, wherein R^4 is $–NR^{4j}R^{4k}$; wherein

R^{4j} and R^{4k} are independently selected from the group consisting of hydrogen, alkyl and aryl, wherein the R^{4j} and R^{4k} alkyl and aryl may be optionally substituted as provided in claim 2.

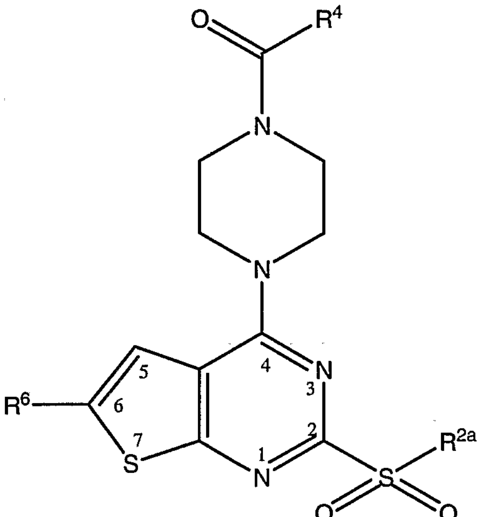
5. The compound of claim 3, wherein R^4 is $–NR^{4j}R^{4k}$;

wherein R^{4j} and R^{4k} are independently selected from the group consisting of hydrogen, phenylmethyl and phenylphenyl; and wherein the R^{4j} and R^{4k} phenylmethyl and phenylphenyl may be optionally substituted as provided in claim 2.

6. The compound of claim 3, wherein R^4 is $-R^{4j}$ or $-OR^{4j}$; wherein R^{4j} is selected from the group consisting of (C_1-C_6)-alkyl, (C_3-C_{10})-aryl, (C_3-C_{14})-heterocyclyl, (C_3-C_{10})-aryl -(C_1-C_6)-alkyl, (C_3-C_{14})-heterocyclyl-(C_1-C_6)-alkyl, (C_3-C_{10})-aryl-(C_3-C_6)-cycloalkyl, (C_3-C_6)-cycloalkyl-(C_3-C_{10})-aryl, (C_3-C_{10})-aryl-(C_3-C_{14})-heterocyclyl, (C_3-C_{10})-aryl-O-(C_3-C_{10})-aryl, (C_3-C_{10})-aryl-(C_3-C_{10})-aryl, (C_3-C_{14})-heterocyclyl-O-(C_3-C_{10})-aryl, (C_3-C_{10})-aryl-C(O)-(C_3-C_{10})-aryl, (C_3-C_{10})-aryl-O-(C_1-C_6)-alkyl, and (C_3-C_{10})-aryl-C(O)-amino-(C_1-C_6)-alkyl; wherein the R^{4j} substituents may be optionally substituted as provided in claim 2.

7. The compound of claim 3, wherein R^4 is $-R^{4j}$ or $-OR^{4j}$;
wherein R^{4j} is selected from the group consisting of butyl, phenyl, fluorenyl, phenylphenyl, phenylmethyl, phenylethyl, phenylphenylmethyl, diphenylethyl, phenyloxymethyl, phenyloxyethyl, phenyloxyphenyl, naphthyloxymethyl, phenylcyclopropyl, phenylcarbonylphenyl, phenylcarbonylaminoethyl, thiophenylmethyl, phenyl-oxadiazolyl, thiazolylphenyl, phenylthiazolyl, phenylpyridinyl, phenylpyrimidinyl, pyridinylphenyl and pyrimidinylphenyl; and wherein the R^{4j} substituents may be optionally substituted as provided in claim 2.

8. A compound, or a pharmaceutically acceptable salt of the compound, wherein the compound has the structure of Formula III:



Formula III

wherein:

R^{2a} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl;
wherein the R^{2a} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl substituents may be optionally substituted with one or more substituents independently selected from the

group consisting of halogen, cyano, oxo, =S, nitro, $-R^{2d}$, $-C(O)R^{2d}$, $-C(S)R^{2d}$, $-C(O)OR^{2d}$, $-C(S)OR^{2d}$, $-C(O)SR^{2d}$,

$-C(O)NR^{2d}R^{2e}$, $-C(S)NR^{2d}R^{2e}$, $-OR^{2d}$, $-OC(O)R^{2d}$, $-OC(S)R^{2d}$, $-OC(O)OR^{2d}$, $-OC(O)NR^{2d}R^{2e}$, $-OC(S)NR^{2d}R^{2e}$, $-NR^{2d}R^{2e}$, $-NR^{2d}C(O)R^{2e}$, $-NR^{2d}C(S)R^{2e}$, $-NR^{2d}C(O)OR^{2e}$, $-NR^{2d}C(S)OR^{2e}$, $-NR^{2d}S(O)_nR^{2e}$, $-NR^{2d}C(O)NR^{2e}R^{2f}$, $-S(O)_nR^{2d}$, $-S(O)_nNR^{2d}R^{2e}$, and $-SC(O)R^{2d}$;

n is 0, 1 or 2;

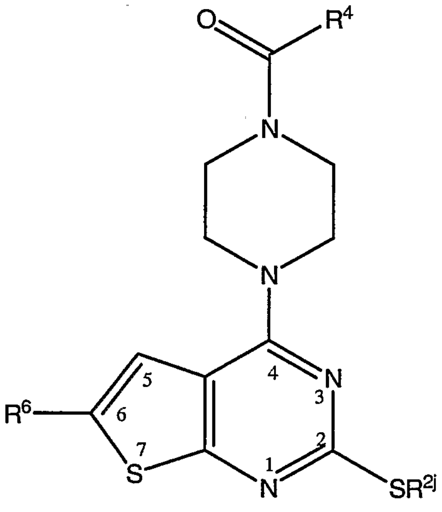
R^{2d}, R^{2e} and R^{2f} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl;

wherein the R^{2d}, R^{2e} and R^{2f} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl substituents may be optionally substituted as provided in claim 2;

R^4 is $-R^{4j}$; wherein R^{4j} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl, wherein the R^{4j} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl substituents may be optionally substituted as provided in claim 2;

R^5 is selected from the group consisting of hydrogen, halogen, alkyl, and $-OR^{5a}$, wherein the R^5 alkyl substituent may be optionally substituted as provided in claim 1, and R^{5a} is defined as provided in claim 2; and R^6 is selected from the group consisting of $-R^{6a}$ and $-OR^{6a}$, wherein R^{6a} is defined as provided in claim 2.

9. A compound, or a pharmaceutically acceptable salt of the compound, wherein the compound has the structure of Formula IV:



Formula IV

wherein:

R^{2j} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl; wherein:

(a) the R^{2j} C_7-C_{20} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl substituent may be optionally substituted with one or more substituents independently selected from the group consisting of halogen and $-R^{2m}$; and

(b) the R^{2j} C_1-C_6 alkyl substituent is substituted with at least one substituent independently selected from the group consisting of chloro, bromo, iodo, and -R^{2m};

R^{2m} is selected from the group consisting of cyano, nitro, -NH_2, oxo, =S, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, -C(O)R^{2n}, -C(S)R^{2n}, -C(O)OR^{2n}, -C(S)OR^{2n}, -C(O)SR^{2n}, -C(O)N$R^{2n}R^{2o}$,
-C(S)N$R^{2n}R^{2o}$, -C(O)ON$R^{2n}R^{2o}$, -C(O)OC(O)R^{2n}, -C(O)SC(O)R^{2n}, –OR^{2n}, -OC(O)R^{2n}, -OC(S)R^{2n}, -OC(O)OR^{2n}, -OC(O)N$R^{2n}R^{2o}$, -OC(S)N$R^{2n}R^{2o}$, -N$R^{2n}R^{2o}$, -NR^{2n}C(O)R^{2o}, -NR^{2n}C(S)R^{2o}, -NR^{2n}C(O)OR^{2o},
-NR^{2n}C(S)OR^{2o}, -NR^{2n}S$(O)_q$$R^{2o}$, -N$R^{2n}$C(O)N$R^{2o}R^{2p}$, -S$(O)_q$$R^{2n}$, -S$(O)_qNR^{2n}R^{2o}$, and -SC(O)$R^{2n}$;

q is 0, 1 or 2;

R^{2n}, R^{2o} and R^{2p} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl;

wherein the R^{2m}, R^{2n}, R^{2o} and R^{2p} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl substituents may be optionally substituted as provided in claim 1;

R^4 is –R^{4j}; wherein R^{4j} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl, wherein the R^{4j} alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl substituents may be optionally substituted as provided in claim 2; and R^6 is selected from the group consisting of –R^{6a} and –OR^{6a}, wherein R^{6a} is defined as provided in claim 2.

10. The compound of claim 9; wherein:

R^{2j} is selected from the group consisting of alkyl and alkenyl; wherein:

(a) the R^{2j} alkenyl substituent may be optionally substituted with one or more substituents independently selected from the group consisting of halogen and -R^{2m}; and

(b) the R^{2j} C_1-C_6 alkyl substituent is substituted with at least one substituent -R^{2m};

R^{2m} is selected from the group consisting of aryl, heterocyclyl, -C(O)R^{2n}, -C(O)OR^{2n}, -C(O)N$R^{2n}R^{2o}$, –OR^{2n} and -N$R^{2n}R^{2o}$;

R^{2n} and R^{2o} are independently selected from the group consisting of hydrogen, alkyl and aryl;

wherein the R^{2m}, R^{2n} and R^{2o} alkyl, aryl and heterocyclyl substituents may be optionally substituted with one or more substituents independently selected from the group consisting of hydroxy, amino, alkyl and carboxy.

11. The compound of claim 9; wherein:

R^{2j} is selected from the group consisting of alkenyl, hydroxyalkyl, arylalkyl, heterocyclylalkyl, carboxyalkyl, alkylaminoalkyl, alkylcarbonylalkyl, alkylaminocarbonylalkyl, aminocarbonylalkyl, alkoxycarbonylalkyl, alkoxyalkylcarbonylalkyl, arylaminocarbonylalkyl and carboxyalkylaminocarbonylalkyl;

wherein the R^{2j} substituents may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxy, amino, cyano, oxo, =S, -SH, nitro, alkyl, haloalkyl, hydroxyalkyl, carboxy, alkoxy and alkoxycarbonyl.

12. The compound of claim 9, wherein:

R^{2j} is hydroxyalkyl;

wherein the R^{2j} hydroxyalkyl may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxy, amino, cyano, alkyl, haloalkyl, hydroxyalkyl, carboxy, alkoxy and alkoxycarbonyl;

R^4 is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heterocyclyl, arylalkyl, arylalkenyl, arylaryl, arylheterocyclyl, heterocyclylalkyl, heterocyclylaryl, cycloalkylalkyl, haloaryl, haloalkylaryl, haloalkoxyaryl, cyanoaryl, alkoxyalkyl, alkoxyaryl, alkoxyarylheterocyclyl, alkoxycarbonylalkyl, alkoxycarbonylaryl, alkylaminoaryl, alkylaminoheterocyclyl and aminocarbonylaryl;

wherein the R^4 substituents may be optionally substituted with one or more substituents independently selected from the group consisting of hydroxy, oxo, cyano, chloro, bromo, fluoro, methyl, ethyl, propyl, butyl, phenyl, methoxy, trifluoromethyl, trifluoromethoxy, ethoxy, propoxy, butoxy, dimethylamino, carboxy, -C(O)OCH$_3$ and –C(O)NH$_2$; and R^6 is alkyl.

13. The compound of claim 9, wherein:

R^{2j} is selected from the group consisting of carboxymethylaminocarbonylethyl, carboxymethylaminocarbonylmethyl, methoxycarbonylmethyl, hydroxypropyl, hydroxyethyl, methylcarbonylethyl, methylcarbonylmethyl, aminocarbonylmethyl, carboxymethylaminocarbonylethyl, carboxymethylaminocarbonylmethyl, methoxycarbonylethyl, methoxycarbonylethyl, phenylaminocarbonylmethyl, ethylaminocarbonylmethyl, hydroxypropyl, hydroxybutyl, carboxymethyl, pyridinylethyl, propenyl, methylaminoethyl, napthalenylaminocarbonylmethyl, phenylmethyl and furanylmethyl;

wherein the R^{2j} substituents may be optionally substituted with one or more substituents independently selected from the group consisting of hydroxy, amino, alkyl and carboxy.

R^{4j} is selected from the group consisting of phenylmethyl, phenylphenyl, phenylisothiazolyl, phenyloxadiazolyl, pentynyl, hexynyl, pyrazolylphenyl, propoxyphenyl, thiadiazolylphenyl, benzofuranyl, butoxyphenyl,dihydrobenzodioxinyl, bis(dimethylamino)pyridinyl, ethoxyphenyl, dihydrobenzofuranyl, butynyl, napthalenyl, phenylthiazolyl, indolyl, methylphenyl, phenyl, methoxycarbonylpropyl, methoxycarbonylbutyl, methoxycarbonylphenyl, methoxyethyl, methoxycarbonylmethyl, methoxycarbonylethyl, cyclopentylethyl, dimethylaminophenyl, phenylethenyl, methoxyphenyl, methylmethoxyphenyl, methoxyphenylisoxazolyl, aminocarbonylphenyl and pentyl;

wherein the R^4 substituents may be optionally substituted with one or more substituents independently selected from the group consisting of hydroxy, oxo, cyano, chloro, bromo, fluoro, methyl, ethyl, propyl, butyl, phenyl, methoxy, trifluoromethyl, trifluoromethoxy, ethoxy, propoxy, butoxy, dimethylamino, carboxy, -C(O)OCH$_3$ and –C(O)NH$_2$; and R^6 is ethyl.

14. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1.

15. A method of treating a platelet dependent thrombosis or a platelet dependent thrombosis-related condition in a subject, comprising administering to the subject a therapeutically effective amount of a compound of claim 1.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2006/000687

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D495/04 A61K31/519 A61P7/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/022214 A2 (MILLENNIUM PHARMACEUTICALS, INC., USA) 20 March 2003 (2003-03-20) see claim 1 and pharmaceutical activity and e.g. examples 168 to 170	1-15
X	DE 22 00 764 A1 (THOMAE, DR. KARL, G.M.B.H.) 12 July 1973 (1973-07-12) see examples 7a	1,2,8

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search 7 July 2006	Date of mailing of the international search report 03/08/2006
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Traegler-Goeldel, M

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2006/000687

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03022214 A2	20-03-2003	AU 2002336462 A1	24-03-2003
DE 2200764 A1	12-07-1973	NONE	