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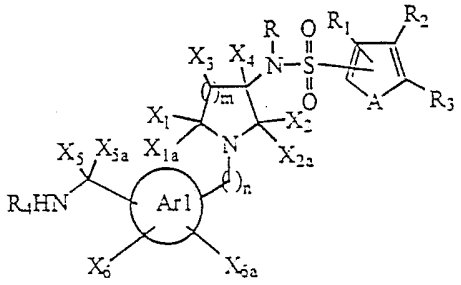
(54) Title: Substituted Sulfonic Acid N-[(Aminoiminomethyl)Phenylalkyl]-Azaheterocyclamide Compounds

(57) Abstract: The compounds of formula (I) exhibit useful pharmacological activity and accordingly are incorporated into pharmaceutical compositions and used in the treatment of patients suffering from certain medical disorders. More specifically, they are inhibitors of the activity of Factor Xa. The present invention is directed to compounds of formula (I), compositions containing compounds of formula (I), and their use, which are for treating a patient suffering from, or subject to, physiological condition which can be ameliorated by the administration of an inhibitor of the activity of Factor Xa.



formula I

(56) Documents Cited: CA V.119, NO.3, P.861, C.1, ABSTR.28019N (MACK)

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SUBSTITUTED SULFONIC ACID N-[(AMINOIMINOMETHYL)PHENYLALKYL]-AZAHETEROCYCLAMIDE COMPOUNDS

This application is a continuation-in-part application of copending United States Patent Application Serial No. 08/761,414, filed December 6, 1996, which in turn is a continuation-in-part application of PCT US96/09816, filed June 7, 1996, which designates the United States, which in turn is a continuation-in-part application of United States Patent Application Serial No. 08/481,024, filed June 7, 1995, now United States Patent No. 5,612,353, issued March 18, 1997. This application is also a continuation-in-part of copending United States Patent Application Serial No. not assigned, filed November 21,1997, which in turn is a continuation application of PCT US96/09816, filed June 7, 1996

Field of the Invention

The compounds of formula I exhibit useful pharmacological activity and accordingly are incorporated into pharmaceutical compositions and used in the treatment of patients suffering from certain medical disorders. More specifically, they are Factor Xa inhibitors. The present invention is directed to compounds of formula I, compositions containing compounds of formula I, and their use, which are for treating a patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of Factor Xa.

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

Anticoagulant therapy is indicated for the treatment and prophylaxis of a variety of thrombotic conditions of both the venous and arterial vasculature. In the arterial system, abnormal thrombus formation is primarily associated with arteries of the coronary, cerebral and peripheral vasculature. The diseases associated with thrombotic occlusion of these vessels principally include acute myocardial infarction (AMI), unstable angina, thromboembolism, acute vessel closure associated with thrombolytic therapy and percutaneous transluminal coronary angioplasty (PTCA),

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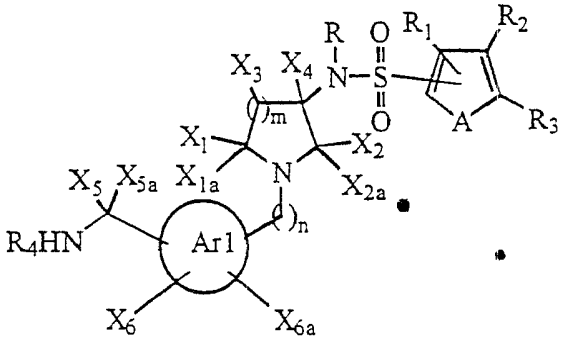
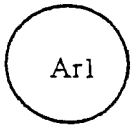
transient ischemic attacks, stroke, intermittent claudication and bypass grafting of the coronary (CABG) or peripheral arteries. Chronic anticoagulant therapy may also be beneficial in preventing the vessel luminal narrowing (restenosis) that often occurs following PTCA and CABG, and in the maintenance of vascular access patency in long-term hemodialysis patients. With respect to the venous vasculature, pathologic thrombus formation frequently occurs in the veins of the lower extremities following abdominal, knee and hip surgery (deep vein thrombosis, DVT). DVT further predisposes the patient to a higher risk of pulmonary thromboembolism. A systemic, disseminated intravascular coagulopathy (DIC) commonly occurs in both vascular systems during septic shock, certain viral infections and cancer. This condition is characterized by a rapid consumption of coagulation factors and their plasma inhibitors resulting in the formation of life-threatening clots throughout the microvasculature of several organ systems. The indications discussed above include some, but not all, of the possible clinical situations where anticoagulant therapy is warranted. Those experienced in this field are well aware of the circumstances requiring either acute or chronic prophylactic anticoagulant therapy.

SUMMARY OF THE INVENTION

This invention is directed to the pharmaceutical use of a compound of formula I below for treating a patient suffering from a physiological disorder capable of being modulated by inhibiting the activity of Factor Xa, where formula I is as follows:



formula I



is phenyl or monocyclic heteroaryl;

R is hydrogen, optionally substituted alkyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, $R_6O(CH_2)_x$-, $R_6O_2C(CH_2)_x$-, $Y^1Y^2NC(O)(CH_2)_x$-, or $Y^1Y^2N(CH_2)_x$-;

R_1 is hydrogen, alkyl, hydroxy, alkoxy, Y^1Y^2N-, halogen, $-CO_2R_6$, $-C(O)NY^1Y^2$,

$-(CH_2)_xOR_6$, $-(CH_2)_xNY^1Y^2$, or -CN;

R_2 and R_3 are independently selected from hydrogen, hydroxy, alkoxy, Y^1Y^2N-, halogen, $-CO_2R_6$, $-C(O)NY^1Y^2$, $-(CH_2)_xOR_6$, $-(CH_2)_xNY^1Y^2$, -CN, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aralkyl, optionally substituted heteroaralkyl, optionally substituted aralkenyl or optionally substituted heteroaralkenyl, or R_2 and R_3 taken together with the carbon atoms through which they are linked form an optionally substituted 5 to 7 membered fused cycloalkyl, optionally substituted 5 to 7 membered fused heterocyclyl ring or an optionally substituted 6 membered fused aryl, or an optionally substituted 5 to 7 membered fused heteroaryl ring;

R_4 is hydrogen or optionally substituted lower alkyl, optionally substituted aralkyl or optionally substituted heteroaralkyl;

X_1 and X_{1a} are independently selected from hydrogen, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl or optionally substituted heteroaralkyl, or X_1 and X_{1a} taken together form oxo;

X_2 and X_{2a} are hydrogen, or taken together form oxo;

X_3 is hydrogen, hydroxy, optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aralkyl or optionally substituted heteroaralkyl, or X_3 and one of X_1 and X_{1a} taken together with the carbon atoms through which X_3 and one of X_1 and X_{1a} are linked form a 4 to 7 membered cycloalkyl or heterocyclyl ring;

X_4 is hydrogen, optionally substituted alkyl or an optionally substituted aralkyl;

X_5 and X_{5a} are hydrogen or taken together are $=NR_5$;

R_5 is hydrogen, R_6O_2C-, R_6O-, cyano, R_6CO-, optionally substituted lower alkyl, nitro or Y^1Y^2N-;

Y^1 and Y^2 are independently hydrogen, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl or optionally substituted heteroaralkyl, or Y^1 and Y^2 taken together with the N through which Y^1 and Y^2 are linked form a 4 to 7 membered heterocyclyl;

X_6 and X_{6a} are independently hydrogen, R_7R_8N-, R_9O-, R_7R_8NCO-, $R_7R_8NSO_2$-, $R_7R_8NSO_2N$ -, $R_7R_8SO_2O$-, R_9CO-, $-CO_2R_6$, $-C(O)NY^1Y^2$, $-(CH_2)_xCO_2R_6$, $-(CH_2)_xC(O)NY^1Y^2$, $-(CH_2)_xOR_6$, $-(CH_2)_xNY^1Y^2$, halo, cyano or nitro;

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R_6 is hydrogen, optionally substituted alkyl, optionally substituted aralkyl or optionally substituted heteroaralkyl;

R_7 and R_8 are independently hydrogen or optionally substituted lower alkyl, or one of R_7 and R_8 is hydrogen and the other of R_7 and R_8 is $R_{10}(O)CCH_2$- or lower acyl;

R_9 is hydrogen, optionally substituted lower alkyl, optionally substituted lower acyl or $R_{10}(O)CCH_2$-;

R_{10} is hydrogen, optionally substituted lower alkyl, optionally substituted alkoxy or hydroxy;

A is S or -CH=CH-;

m is 0, 1, 2 or 3;

n is 0, 1, 2 or 3; and

x is 1, 2, 3, 4, or 5, or

a pharmaceutically acceptable salt thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

DETAILED DESCRIPTION OF THE INVENTION

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

Definitions

"Patient" includes both human and other mammals.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched having about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups have 1 to about 12 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkyl chain. "Lower alkyl" means about 1 to about 4 carbon atoms in the chain which may be straight or branched. The alkyl may be substituted with one or more "alkyl group substituents" which may be the same or different, and include halo, cycloalkyl, hydroxy, alkoxy, amino, acylamino, aroylamino, carboxy, alkoxycarbonyl, aralkyloxycarbonyl,

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heteroaralkyloxycarbonyl or Y^1Y^2NCO-, wherein Y^1 and Y^2 are independently hydrogen, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl or optionally substituted heteroaralkyl, or Y^1 and Y^2 taken together with the N through which Y^1 and Y^2 are linked form a 4 to 7 membered heterocyclyl. Exemplary alkyl groups include methyl, trifluoromethyl, cyclopropylmethyl, cyclopentylmethyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *t*-butyl, *n*-pentyl, 3-pentyl, methoxyethyl, carboxymethyl, methoxycarbonylethyl, benzyloxycarbonylmethyl, pyridylmethyloxycarbonylmethyl.

"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system of about 3 to about 10 carbon atoms. Exemplary monocyclic cycloalkyl rings include cyclopentyl, cyclohexyl and cycloheptyl. The cycloalkyl group is optionally partially unsaturated or optionally substituted with one or more cycloalkyl group substituents which may be the same or different, where "cycloalkyl group substituent" includes hydrogen, alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, acylamino, aroylamino, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, fused cycloalkyl, fused heterocyclyl, arylazo, heteroarylazo, Y^1Y^2N-, Y^1Y^2NCO- or $Y^1Y^2NSO_2$-, wherein Y^1 and Y^2 are independently hydrogen, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl or optionally substituted heteroaralkyl, or Y^1 and Y^2 taken together with the N through which Y^1 and Y^2 are linked form a 4 to 7 membered heterocyclyl. The aryl group substituents are as defined herein. Exemplary multicyclic cycloalkyl rings include 1-decalin, norbornyl, adamant-(1- or 2-)yl.

"Heterocyclyl" means a non-aromatic monocyclic or multicyclic ring system of about 3 to about 10 ring atoms. Preferred rings include about 5 to about 6 ring atoms wherein one of the ring atoms is oxygen, nitrogen or sulfur. The heterocyclyl is optionally partially unsaturated or optionally substituted with one or more heterocyclyl group substituents which may be the same or different, where " heterocyclyl group substituent" includes hydrogen, alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, acylamino, aroylamino, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, fused cycloalkyl, fused heterocyclyl, arylazo, heteroarylazo, Y^1Y^2N-, Y^1Y^2NCO- or $Y^1Y^2NSO_2$-, wherein Y^1 and Y^2 are independently hydrogen, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl or optionally substituted heteroaralkyl, or Y^1 and Y^2 taken together with the N through which Y^1 and Y^2 are linked form a 4 to 7 membered heterocyclyl. The heterocyclyl group substituents are as defined herein. Exemplary monocyclic rings include pyrrolidyl, piperidyl, tetrahydrofuranyl, tetrahydrothienyl and

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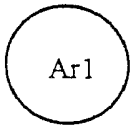
tetrahydrothiopyranyl. The thio or nitrogen moiety of the heterocyclyl may also be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide.

"Aryl" means a 6 to 10 membered aromatic monocyclic or multicyclic hydrocarbon ring system. Exemplary aryl include phenyl or naphthyl, or phenyl substituted or naphthyl substituted with one or more aryl group substituents which may be the same or different, where "aryl group substituent" includes hydrogen, alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, acylamino, aroylamino, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, fused cycloalkyl, fused heterocyclyl, arylazo, heteroarylazo, Y^1Y^2N-, Y^1Y^2NCO- or $Y^1Y^2NSO_2$-, wherein Y^1 and Y^2 are independently hydrogen, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl or optionally substituted heteroaralkyl, or Y^1 and Y^2 taken together with the N through which Y^1 and Y^2 are linked form a 4 to 7 membered heterocyclyl. The aryl group substituents are as defined herein. Preferred aryl groups are optionally substituted phenyl or optionally substituted naphthyl. Preferred aryl group substituents include hydrogen, alkyl, hydroxy, acyl, aryl aroyl, aryloxy, halo, nitro, alkoxy, cyano, alkoxycarbonyl, acylamino, alkylthio, Y^1Y^2N-, Y^1Y^2NCO- or $Y^1Y^2NSO_2$-, where Y^1 and Y^2 are independently optionally substituted alkyl, aryl, aralkyl or heteroaralkyl; preferred phenyl group substituents are hydroxy, halogen, alkyl, amino.

"Heteroaryl" means about a 5- to about a 10- membered aromatic monocyclic or multicyclic hydrocarbon ring system in which one or more of the carbon atoms in the ring system is/are element(s) other than carbon, for example nitrogen, oxygen or sulfur. The "heteroaryl" may also be substituted by one or more of the above-mentioned "aryl group substituents". Exemplary heteroaryl groups include substituted pyrazinyl, furanyl, thienyl, pyridyl, pyrimidinyl, isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl and isoquinolinyl.

Where 

is a monocylic heteroaryl, then preferred heteroaryls include thienyl or pyridyl.

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

"Heteroaralkyl" means a heteroaryl-alkyl- group in which the heteroaryl and alkyl are as previously described. Preferred heteroaralkyls contain a lower alkyl moiety. Exemplary heteroaralkyl groups may contain thienylmethyl, pyridylmethyl, imidazolylmethyl and pyrazinylmethyl.

"Aralkenyl" means an aryl-alkenyl- group in which the aryl and alkenyl are as previously described. Preferred aralkenyls contain a lower alkenyl moiety. An exemplary aralkenyl group is 2-phenethenyl.

"Heteroaralkenyl" means a heteroaryl-alkenyl- group in which the heteroaryl and alkenyl are as previously described. Preferred heteroaralkenyls contain a lower alkenyl moiety. Exemplary heteroaralkenyl groups may contain thienylethenyl, pyridylethenyl, imidazolylethenyl and pyrazinylethenyl.

"Hydroxyalkyl" means a HO-alkyl- group in which alkyl is as previously defined. Preferred hydroxyalkyls contain lower alkyl. Exemplary hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl.

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

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

"Heteroaroyl" means an means an heteroaryl-CO- group in which the heteroaryl group is as previously described. Exemplary groups include thiophenoyl and pyridinoyl.

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

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

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

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

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

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

"Y^1Y^2N-" means a substituted or unsubstituted amino group, wherein Y^1 and Y^2 are as previously described. Exemplary groups include amino (H_2N-), methylamino, dimethylamino, diethylamino, pyrrolidine, piperidine, benzylamino, or phenethylamino.

"Alkoxycarbonyl" means an alkyl-O-CO- group. Exemplary alkoxycarbonyl groups include methoxycarbonyl, ethoxycarbonyl, or t-butyloxycarbonyl.

"Aryloxycarbonyl" means an aryl-O-CO- group. Exemplary aryloxycarbonyl groups include phenoxycarbonyl and naphthoxycarbonyl.

"Aralkoxycarbonyl" means an aralkyl-O-CO- group. An exemplary aralkoxycarbonyl group is benzyloxycarbonyl.

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

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

"Acylamino" is an acyl-NH- group wherein acyl is as defined herein.

"Aroylamino" is an aroyl-NH- group wherein aroyl is as defined herein.

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

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

"Arylsulfonyl" means an aryl-SO_2- group.

"Arylsulfinyl" means an aryl-SO- group.

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

Preferred Embodiments

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

Another preferred compound aspect of the invention is the compound of formula I wherein n is 1, and m is 1.

Another preferred compound aspect of the invention is the compound of formula I wherein X_2 and X_{2a} taken together are oxo.

Another preferred compound aspect of the invention is the compound of formula I wherein X_1, X_{1a}, X_4 are hydrogen, and X_3 is hydrogen or alkyl.

Another preferred compound aspect of the invention is the compound formula I wherein X_5 and X_{5a} taken together are $=NR_5$ wherein R_5 is R_6O_2C-.

Another preferred compound aspect of the invention is the compound formula I wherein X_5 and X_{5a} taken together are $=NR_5$ wherein R_5 is -OH.

Another preferred compound aspect of the invention is the compound of formula I wherein X_5 and X_{5a} taken together are $=NR_5$ wherein R_5 is H.

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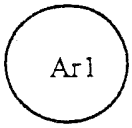
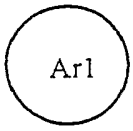
Another preferred compound aspect of the invention is the compound of formula I wherein  is phenyl and the carbon substituted with X_5, X_{5a} and R_4HN- is attached meta relative to the attachment of the -$(CH)_nN$- moiety to the phenyl.

Another preferred compound aspect of the invention is the compound of formula I wherein  is thienyl and the carbon substituted with X_5, X_{5a} and R_4HN- is attached in the 2 position relative to the sulfur of the thienyl and the attachment of the -$(CH)_nN$- moiety is to the 4 position of the thienyl.

Another preferred compound aspect of the invention is the compound of formula I wherein R is hydrogen, methyl, aralkyl, heteroaralkyl, HO_2CCH_2-, $H_2NC(O)CH_2$-, or $R_6HNC(O)CH_2$-.

Another preferred compound aspect of the invention is the compound of formula I wherein R_1 is hydrogen, alkyl, or halogen.

Another preferred compound aspect of the invention is the compound of formula I wherein R_2 and R_3 are independently hydrogen, halogen, alkyloxy, amino, aryl, or heteroaryl.

Another preferred compound aspect of the invention is the compound of formula I wherein R_2 and R_3 form an optionally substituted fused aryl or an optionally substituted fused heteroaryl ring wherein the substituent is halogen, alkyl, amino, hydroxy, or alkoxy.

Another preferred compound aspect of the invention is the compound of formula I wherein R_2 and R_3 form an optionally substituted fused cycloalkyl or an optionally substituted fused heterocyclyl in which the heteroatom is nitrogen wherein the substituent is hydrogen, Y^1Y^2N, or alkyl..

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