MIXED DISULFIDE CONJUGATES OF THIENOPYRIDINE COMPOUNDS AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application claims priority to U.S. Provisional Patent Application No. 62/155,231, filed April 30, 2015, hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

This invention is in the field of medicinal chemistry. In particular, the invention relates to mixed disulfide conjugates of thienopyridine compounds, and their use as therapeutics for the treatment, amelioration, and prevention of cardiovascular diseases.

INTRODUCTION

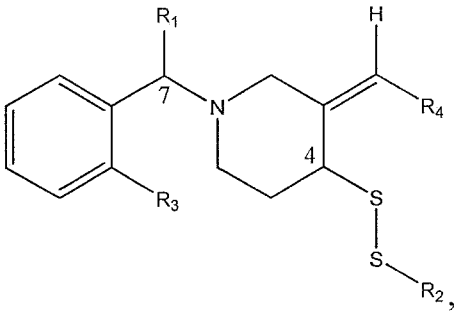
Thienopyridinyl compounds are widely used as antiplatelet agents to prevent heart attack and stroke. In this category, clopidogrel (Plavix), ticlopidine (Ticlid) and prasugrel (Effient) are three commonly used prodrugs. These agents require polymorphic cytochrome (P450) mediated oxidative bioactivation. Such oxidative bioactivation results in slow on-set of therapeutic effect and several adverse effects including neutropenia and thrombotic thrombocytopenic purpura.

Improved antiplatelet agents not requiring polymorphic cytochrome (P450) mediated oxidative bioactivation are needed.

SUMMARY

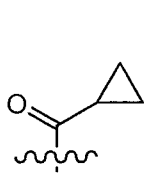
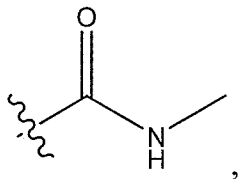
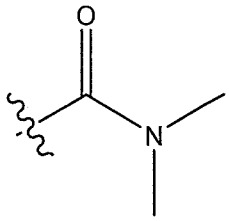
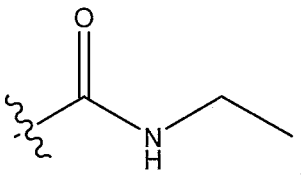
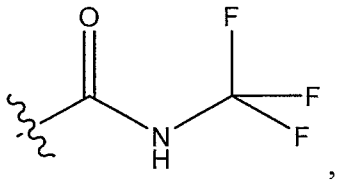
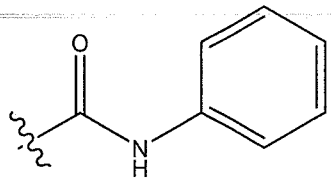
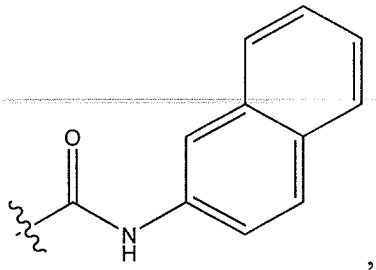
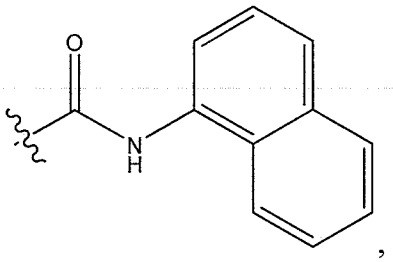
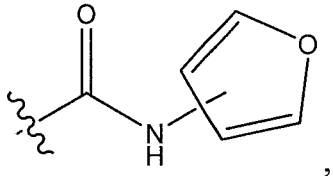
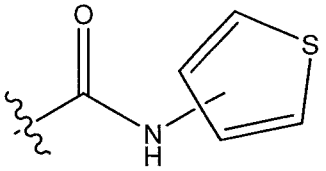
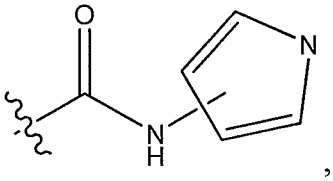
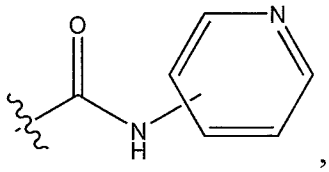
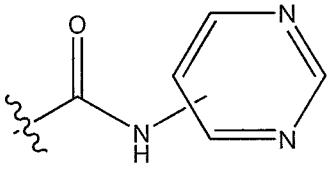
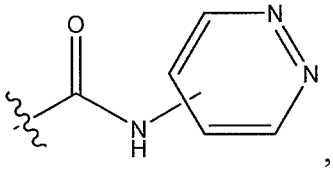
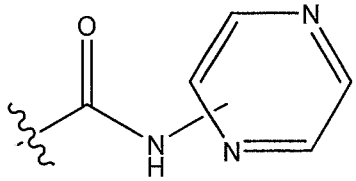
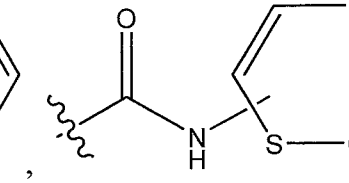
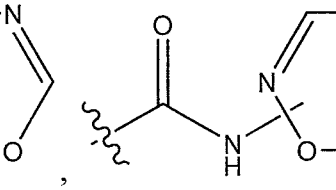
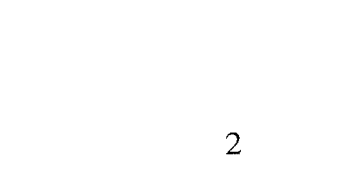
Clopidogrel (Plavix), ticlopidine (Ticlid) and prasugrel (Effient) belong to a class of thienopyridinyl compounds widely used as antiplatelet agents to prevent heart attack and stroke. However, several serious drawbacks have been associated with these drugs including lack of response, toxicity and excessive bleeding. These drawbacks are closely related to the fact that they are all prodrugs that require oxidative bioactivation by polymorphic cytochromes P450 enzymes (P450s).

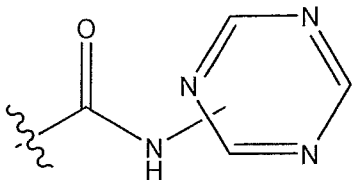
In one aspect, the present invention refers to a compound having Formula I:



, or a pharmaceutically acceptable salt thereof;

wherein independently each of R_1, R_2, R_3 and R_4 are

R_1 is selected from the group consisting of -CO-OCH_3,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , ,  , ,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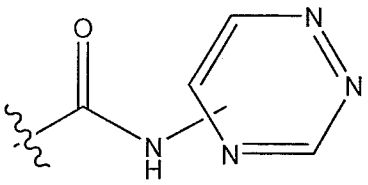
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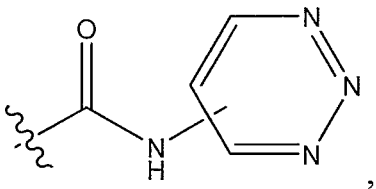
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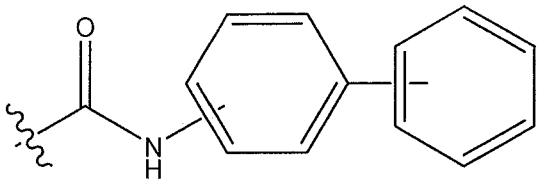
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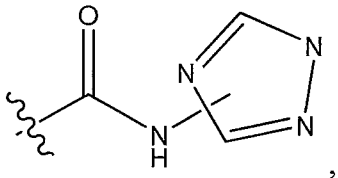
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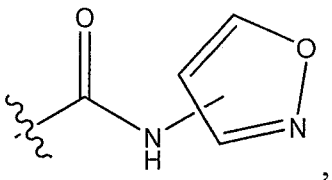
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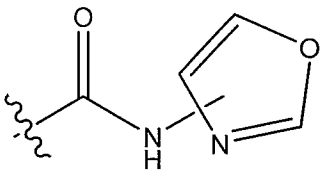
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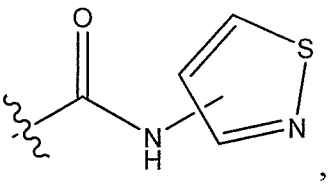
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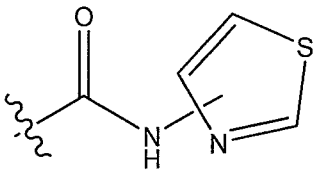
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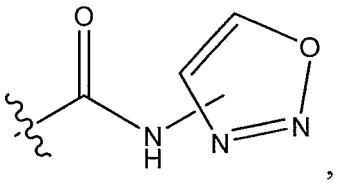
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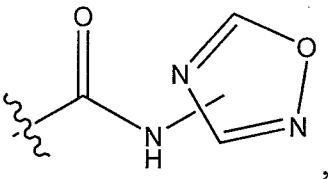
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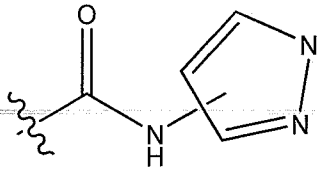
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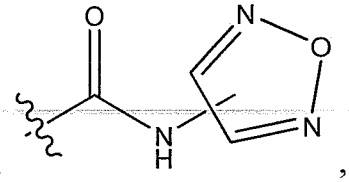
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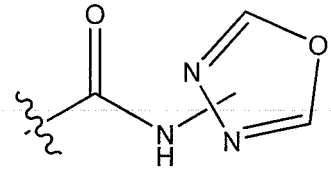
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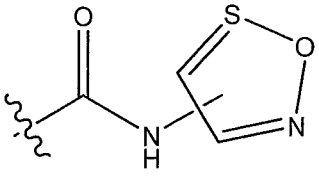
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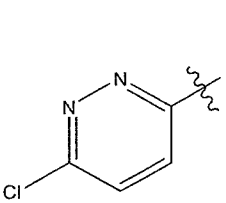
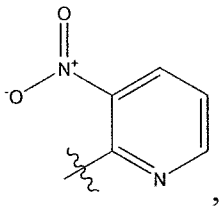
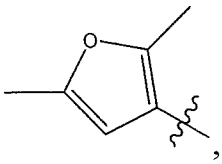
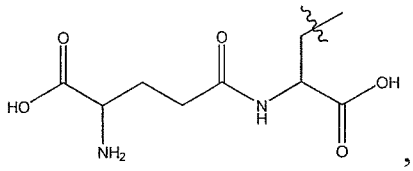
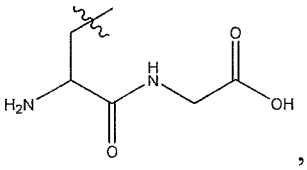
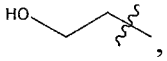
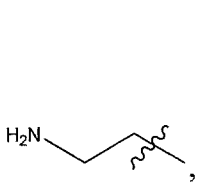
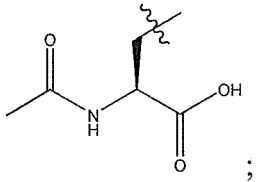
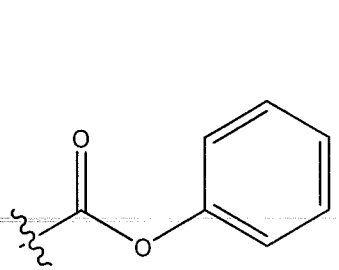
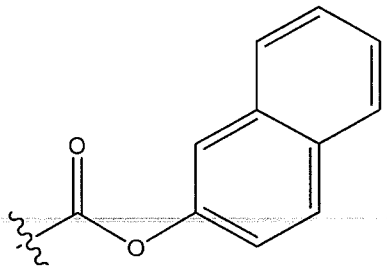
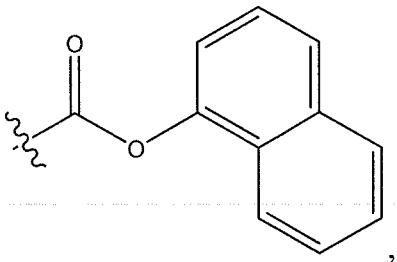
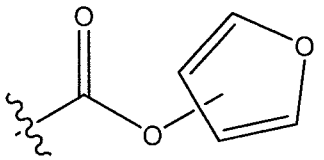
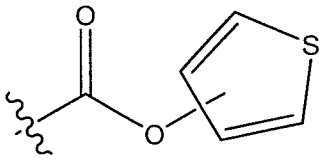
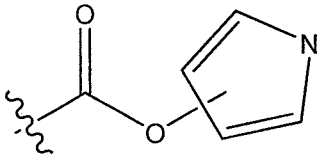
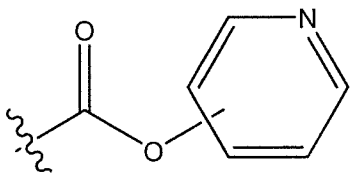
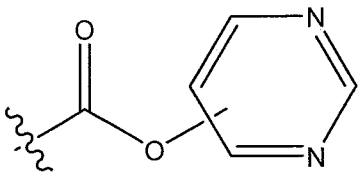
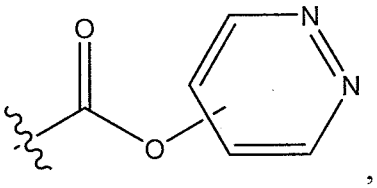
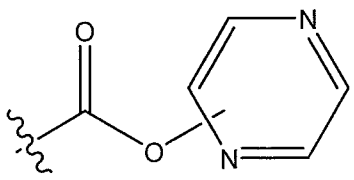
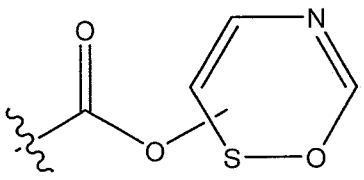
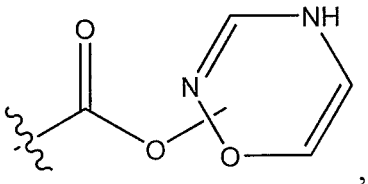
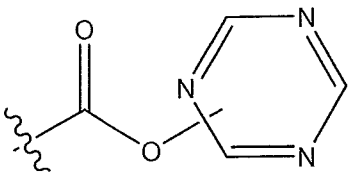
R_2 is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ;

R_3 is selected from the group consisting of Cl, Br, I, F, CN, NO_2, CF_3, H, and OCH_3; and

R_4 is selected from the group consisting of $-COOCH_3$, $-COOCH_2CH_3$, $COOCF_3$,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  .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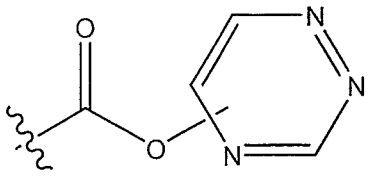
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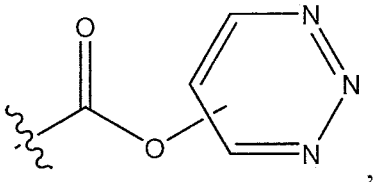
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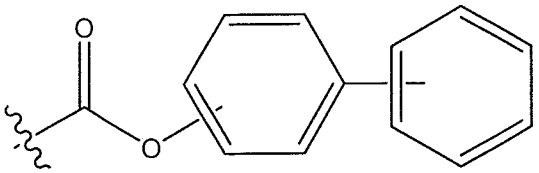
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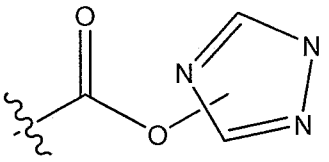
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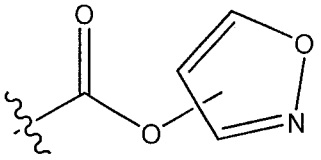
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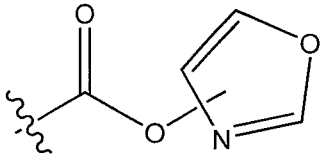
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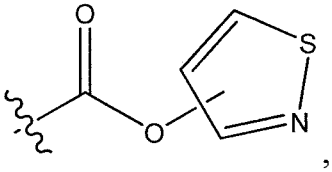
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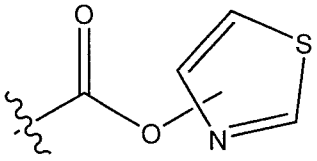
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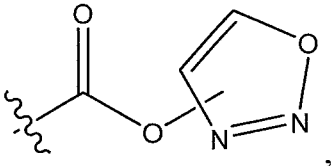
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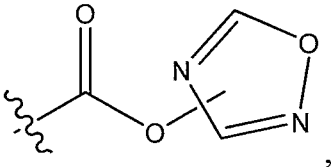
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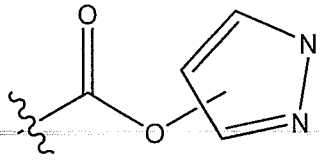
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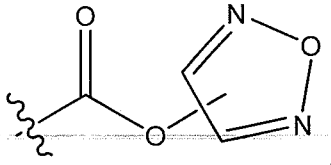
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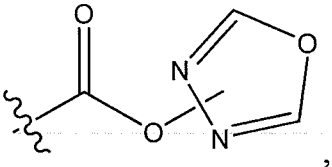
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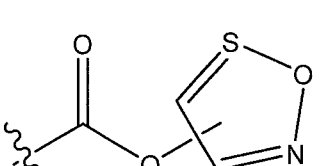
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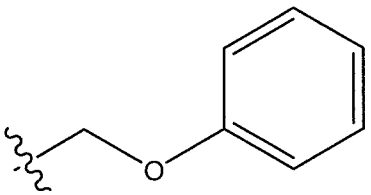
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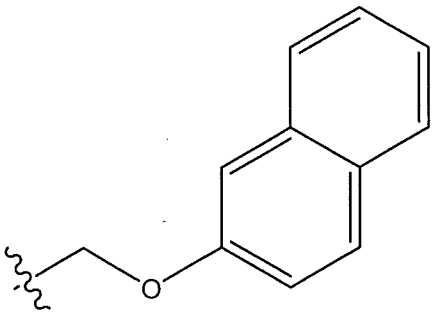
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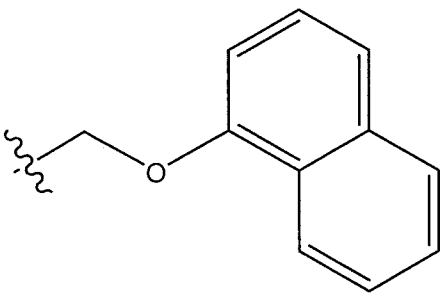
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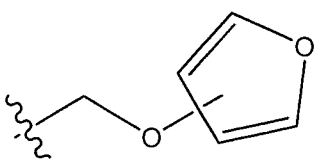
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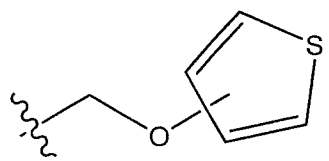
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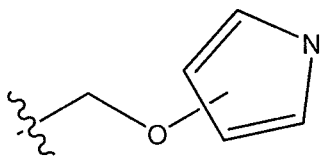
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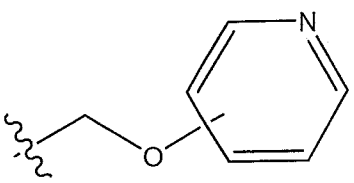
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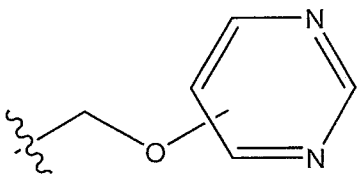
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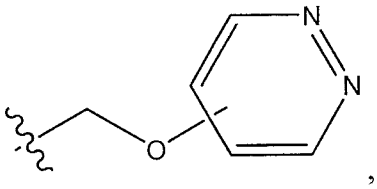
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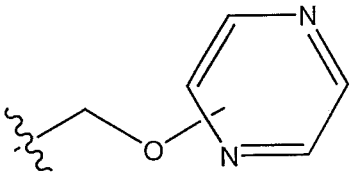
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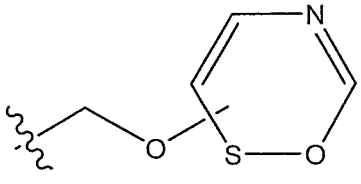
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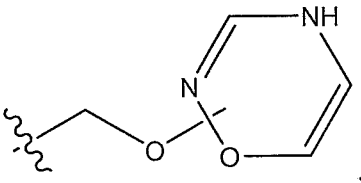
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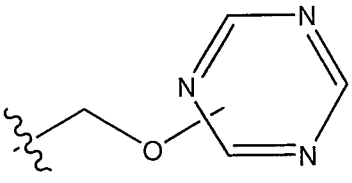
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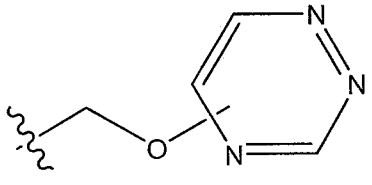
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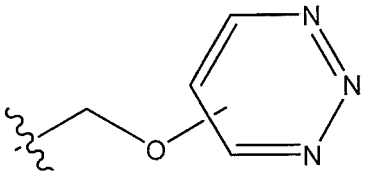
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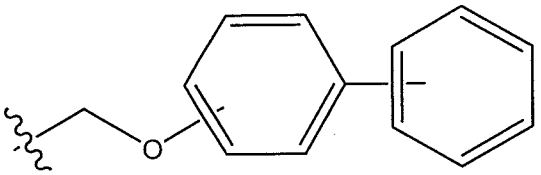
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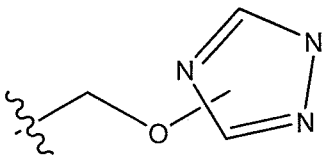
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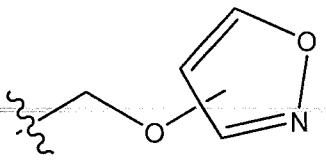
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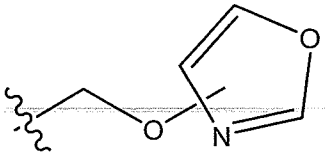
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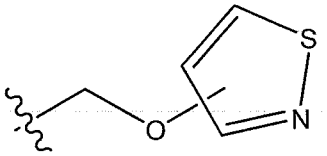
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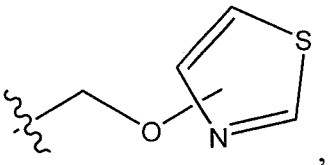
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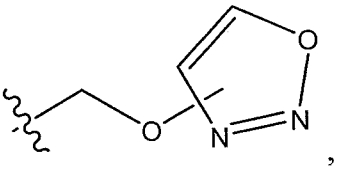
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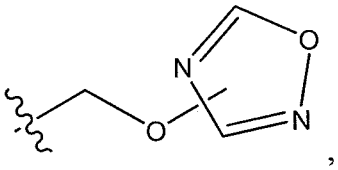
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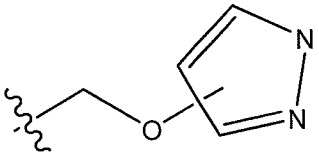
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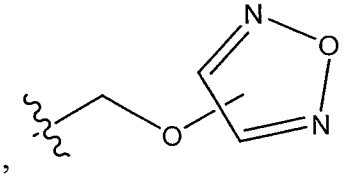
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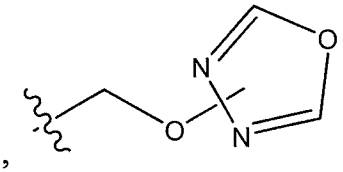
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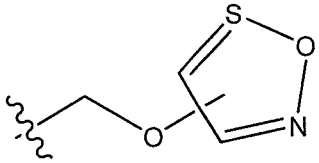
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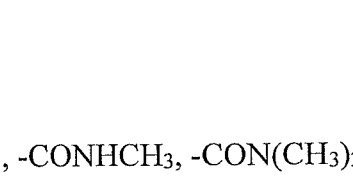
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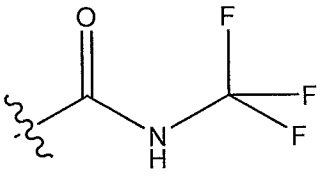
-CONHCH$_2$CH$_3$, -CONHCF$_3$, -CON(CH$_3$)$_2$, 
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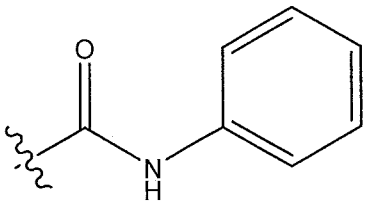
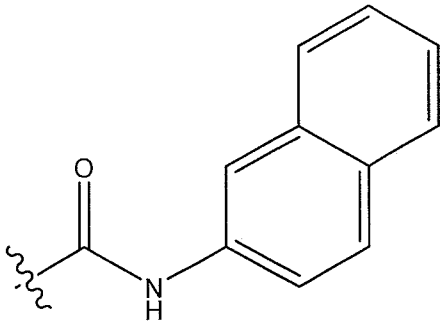
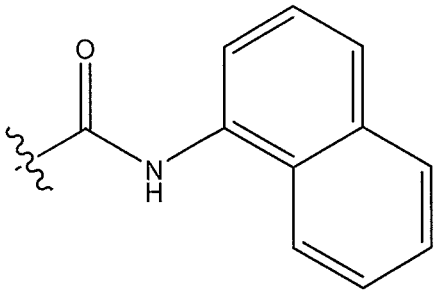
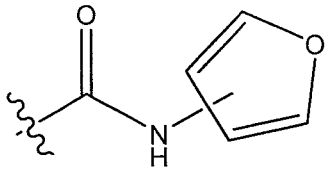
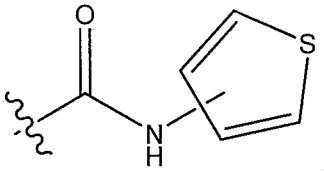
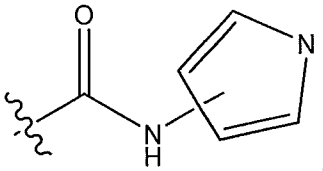
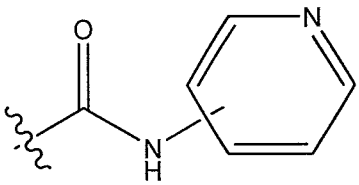
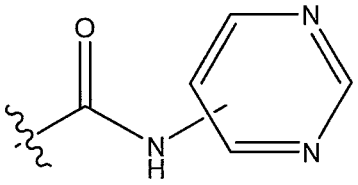
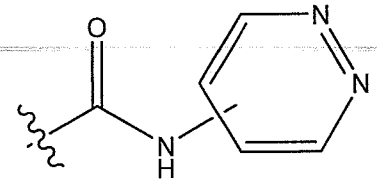
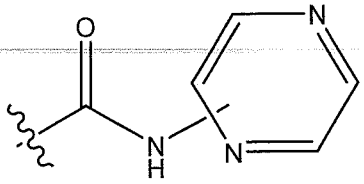
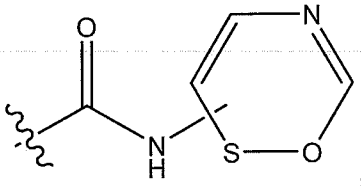
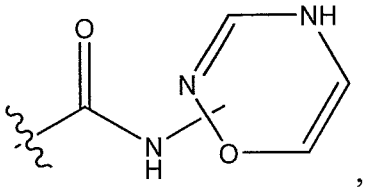
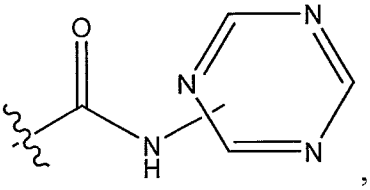
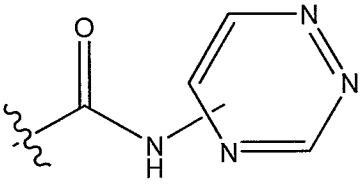
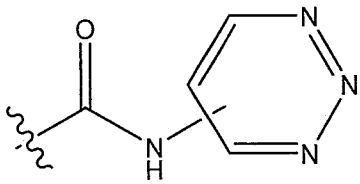
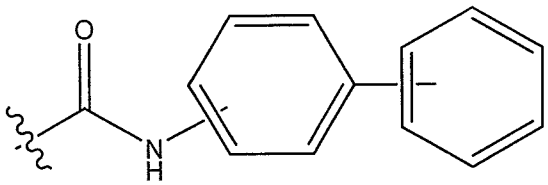
 ,  ,

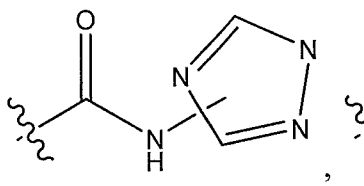
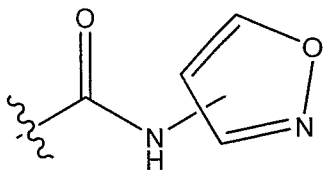
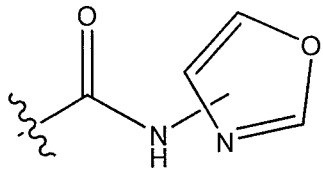
 ,  ,  ,

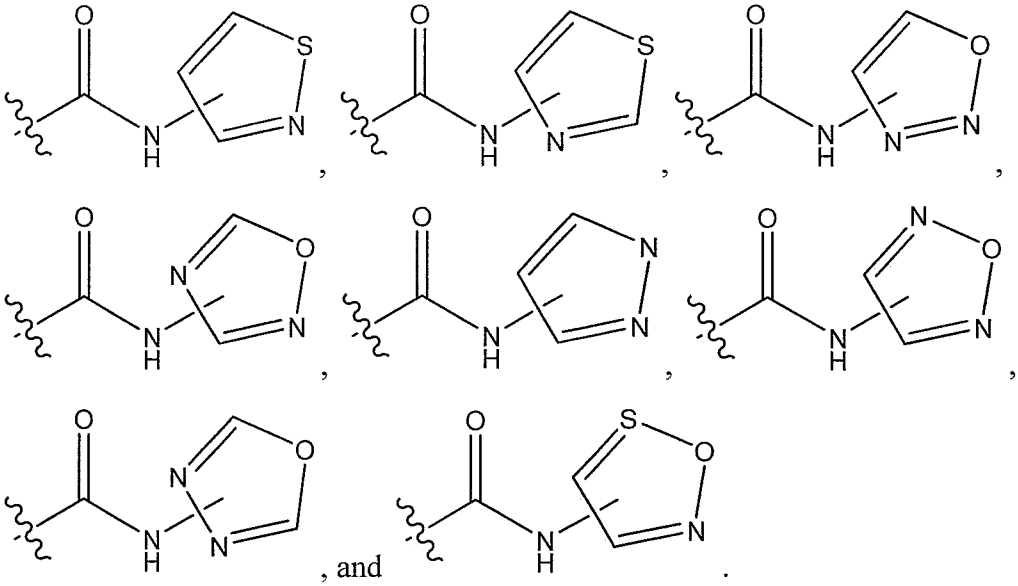
 ,  ,  ,

 ,  ,  ,

 ,  ,  ,

 ,  ,

 ,  ,  ,


, and .

In another aspect, the present invention refers to pharmaceutical composition comprising an effective amount of the compound of the present invention, and a pharmaceutically acceptable carrier.

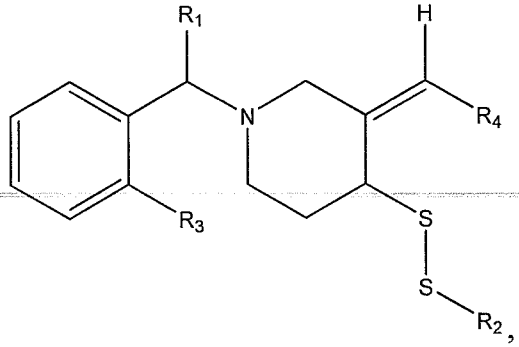
In another aspect, the present invention refers to use of the compound of the present invention in the manufacture of a medicament for treating a cardiovascular disease in a patient wherein the use comprises that a therapeutically effective amount of the compound of the present invention is to be administered to the patient, wherein said administration is selected from the group consisting of oral administration and intravenous administration, wherein said cardiovascular disease is selected from the group consisting of coronary artery disease, peripheral vascular disease, atherothrombosis, and cerebrovascular disease.

To overcome drawbacks associated with thienopyridine compounds (Clopidogrel (Plavix), ticlopidine (Ticlid) and prasugrel (Effient)), the present disclosure provides mixed disulfide conjugates of thienopyridine compounds. It is contemplated that such mixed disulfide conjugates of thienopyridine compounds of the present disclsoure are capable of producing active thienopyridine metabolites (e.g., active thienopyridine metabolites capable of antiplatelet activity) in the presence of endogenous glutathione (GSH) without the need for bioactivation by P450s. This approach not only bypasses the oxidative bioactivation process by P450s, but circumvents many of the drawbacks associated with thienopyridinyl drugs. For example, it is contemplated that the mixed disulfide conjugates of thienopyridine compounds of the present disclosure improve dosing consistency because production of the active metabolite from the conjugates is predictable. In addition, it is contemplated that use of the mixed disulfide conjugates of thienopyridine compounds of the present disclosure as antiplatelet agents reduce the toxicity as toxic reactive metabolites will not be produced by the thiol-exchange reaction. In addition, the therapeutic onset time for the mixed disulfide

conjugates of thienopyridine compounds of the present disclosure is shortened, which greatly benefits patients who experience acute cardiovascular events. For example, the standard regimen for thienopyridines requires continuously dosing patients for 3-5 days as only a small percentage of ingested thienopyridines are converted to the active metabolite. In contrast, it is contemplated that the mixed disulfide conjugates of thienopyridine compounds of the present disclosure will release the active metabolites with high yields in less than 5 min. In addition, it is contemplated that the mixed disulfide conjugates of thienopyridine compounds of the present disclosure will have superior stability over the active metabolites and therefore can be used to quantitatively generate the active metabolites for basic and clinical research in vitro.

Accordingly, in certain examples, the present disclosure provides mixed disulfide conjugates of thienopyridine compounds capable of overcoming such drawbacks associated with thienopyridinyl compounds widely used as antiplatelet agents (e.g., Clopidogrel (Plavix), ticlopidine (Ticlid) and prasugrel (Effient)).

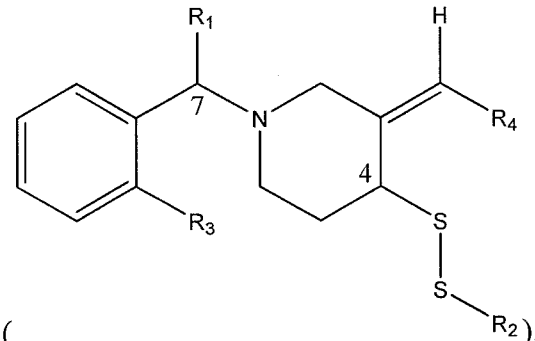
The present disclosure is not limited to particular mixed disulfide conjugates of thienopyridine compounds. In some examples, the mixed disulfide conjugates of thienopyridine compounds are described by Formula I:



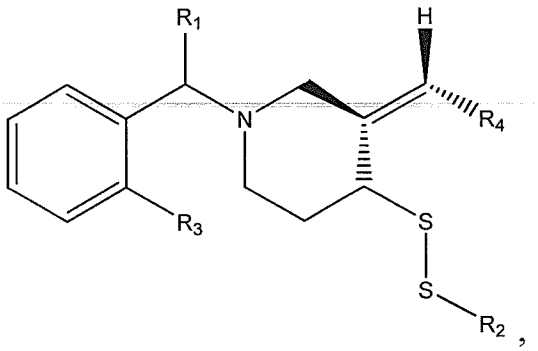
, including pharmaceutically acceptable salts, solvates, and/or prodrugs thereof, wherein R4 is selected from the group consisting of an ester moiety with an aliphatic and/or aromatic substituent, a ketone moiety with an aliphatic and/or aromatic substituent, and an amide moiety with an aliphatic and/or aromatic substituent.

Formula I is not limited to a particular chemical moiety R1, R2, R3, and R4. In some examples, R1, R2, R3, and R4 each independently include any chemical moiety that renders the resulting compound capable of producing active thienopyridine metabolites upon interaction with endogenous glutathione (GSH) (e.g., active thienopyridine metabolites capable of antiplatelet activity). In some examples R1, R2, R3, and R4 each independently include any chemical moiety that renders the resulting compound capable of producing active thienopyridine metabolites in the presence of endogenous glutathione (GSH) without the need for bioactivation by P450s. In some examples, R1, R2, R3, and R4 each independently include any chemical moiety that renders the resulting compound capable of treating, ameliorating, or preventing cardiovascular disorders (e.g., coronary artery disease, peripheral vascular disease, and cerebrovascular disease) in a patient, such as those that are responsive to antiplatelet agents (such as clopidogrel, ticlopidine, and prasugrel). In some examples, R1,

R2, R3, and R4 each independently include any chemical moiety that renders the resulting compound capable of inhibiting platelet aggregation by, for example, altering the function of platelet membranes by blocking ADP receptors (e.g., thereby preventing a conformational change of glycoprotein IIb/IIIa which allows platelet binding to fibrinogen). In some examples, R1, R2, R3, and R4 each independently include any chemical moiety that renders the resulting compound capable of reducing aggregation ("clumping") of platelets by irreversibly binding to $P2Y_{12}$ receptors.

Such mixed disulfide conjugates are not limited to particular steochemical configurations within Formula I (

). In some examples, the double bond connected with the R4 substituent is either in a Z or cis configuration. For example, in some examples, Formula I is represented by any of the following stereochemical configurations:



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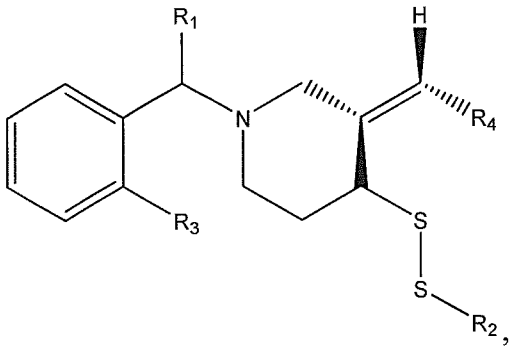

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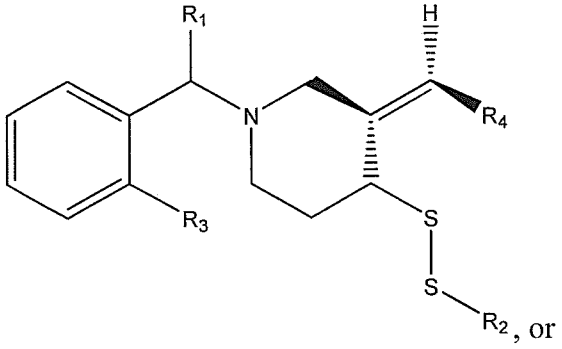

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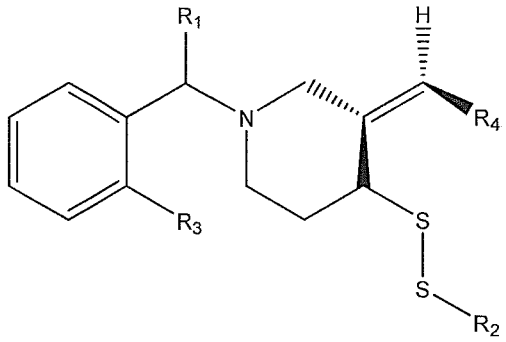
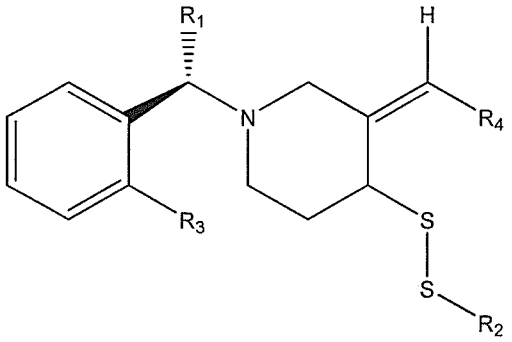
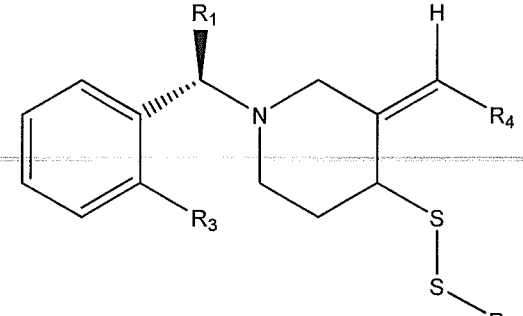


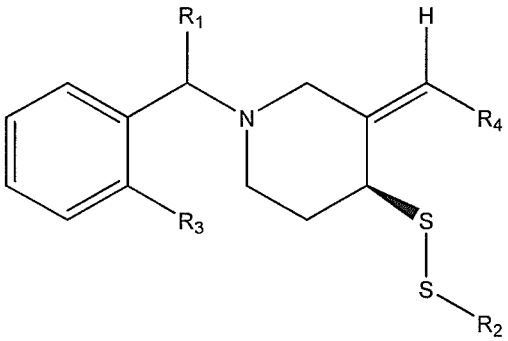
. In some examples, the C7 carbon is either in a racemic, R or S configuration. For example, in some examples, Formula I is represented by



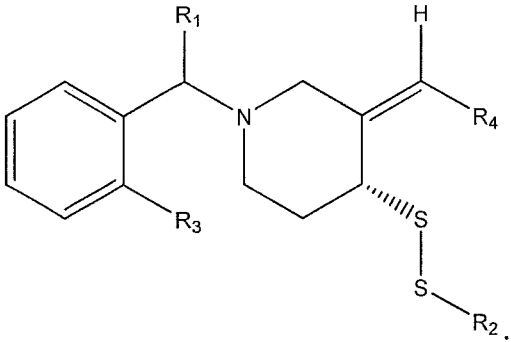
any of the following stereochemical configurations:



or . In some examples, the C7 carbon is either in a racemic, R or S configuration. For example, in some examples, Formula I is represented by

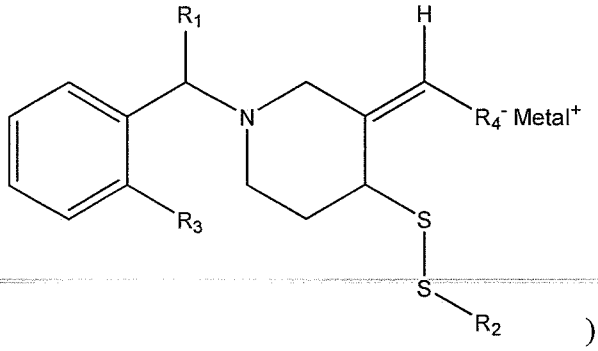


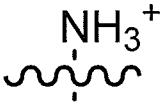
any of the following stereochemical configurations:



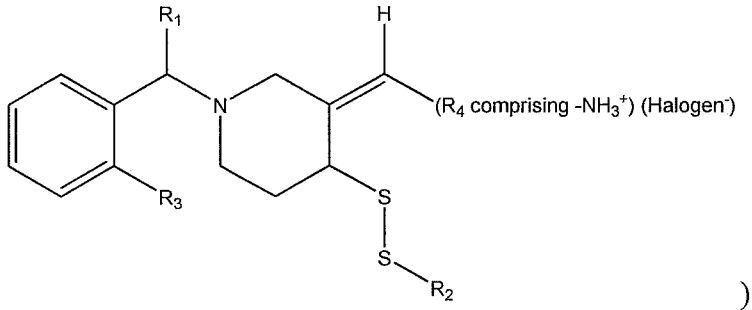
or . In some examples, the compound encompassed within Formula I contains one or more stereochemical configurations for the double bond connected to R4 (e.g., Z or cis configuration), the C7 carbon (e.g., racemic, R or S configuration), and the C4 carbon (e.g., racemic, R or S configuration).

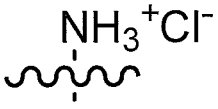
In some examples, the compound encompassed within Formula I is in a pharmaceutically acceptable salt form. For example, in some examples, the R4 substituent is engaged with an applicable metal to form a salt (e.g., Li, Na, K, etc) (e.g.,



). For example, in some examples, the R4 substituent has therein a Nitrogen moiety having a positive charge (e.g., 

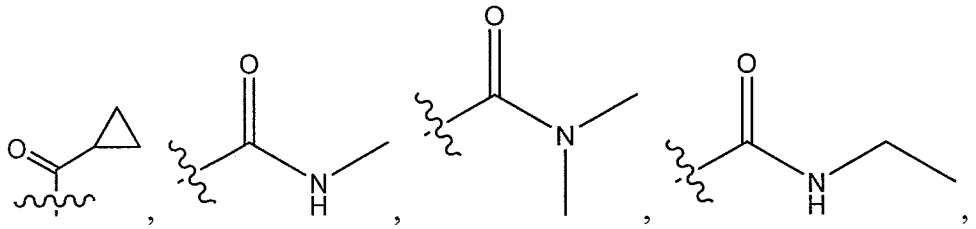
) which is engaged with a halogen (e.g., Cl^-, Br^-, Fl^-, etc) thereby generating an ammonium salt (e.g.,

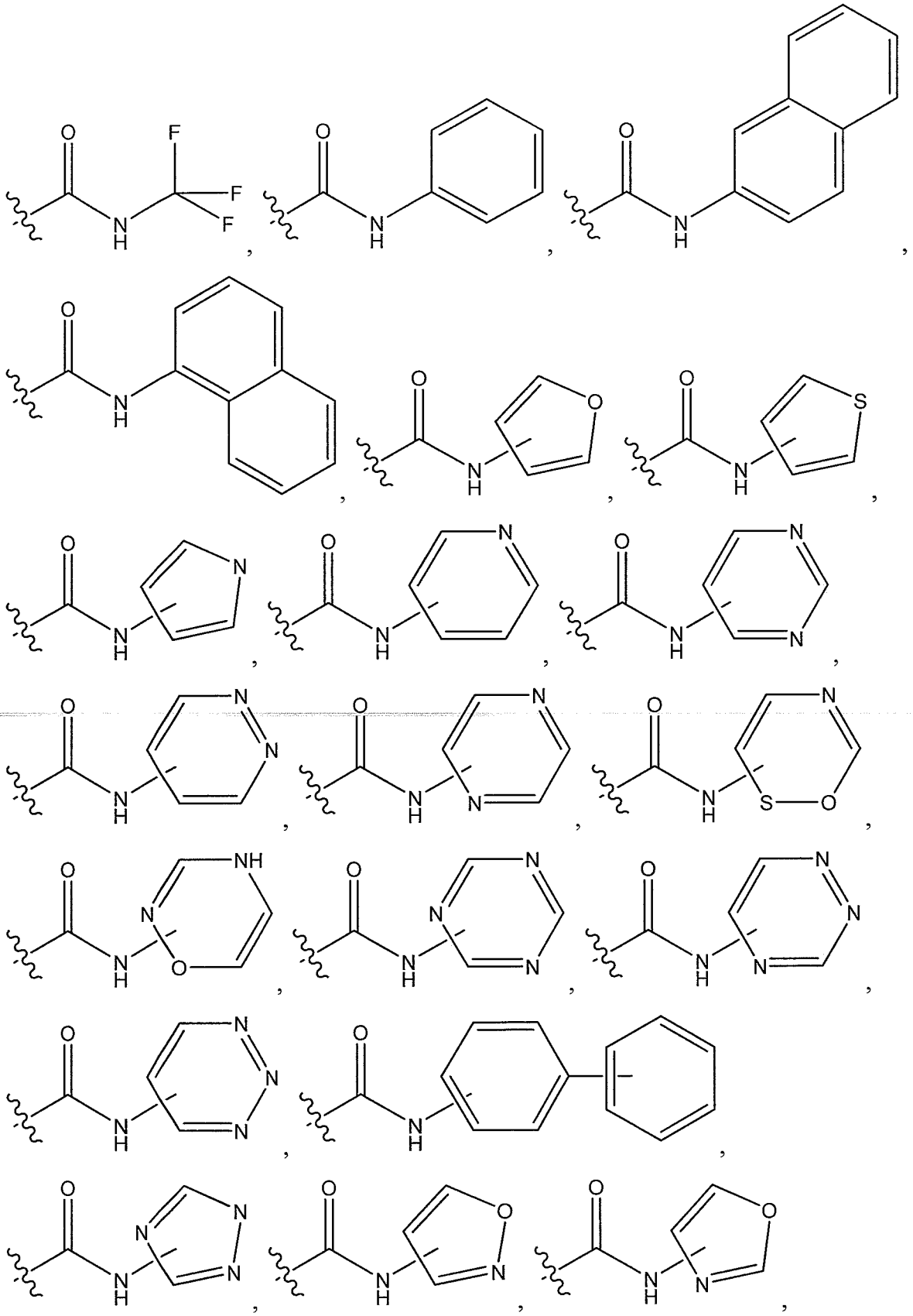


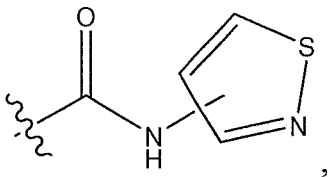


) (e.g.,).

n some example, R1 is selected from the group consisting of H, -CO-OCH3,



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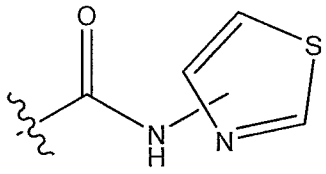
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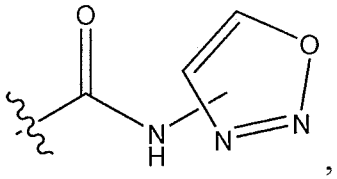
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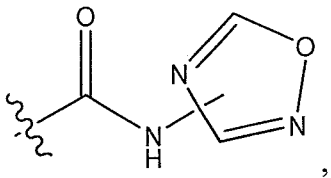
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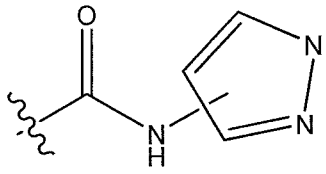
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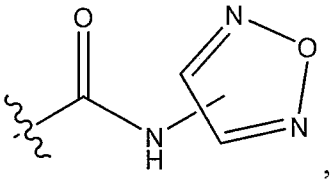
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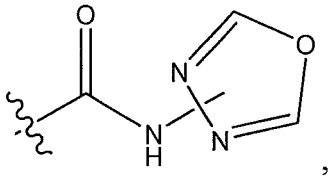
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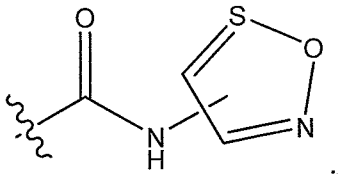
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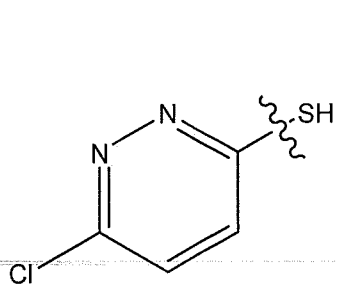
In some examples, R2 is selected from the group consisting of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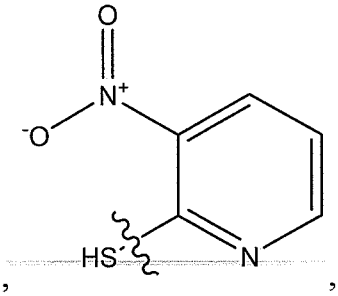
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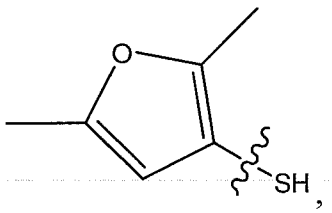
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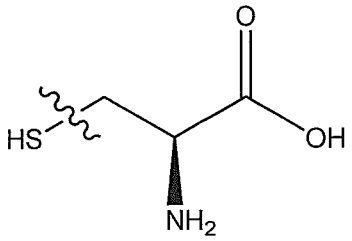
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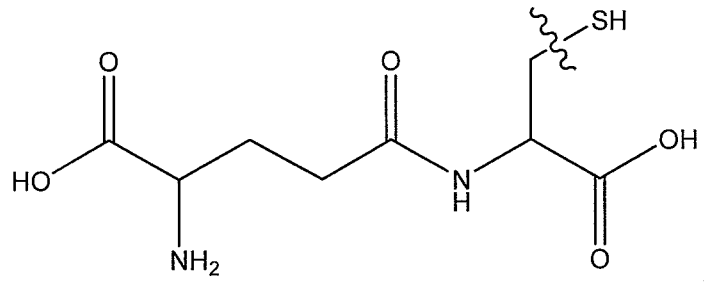
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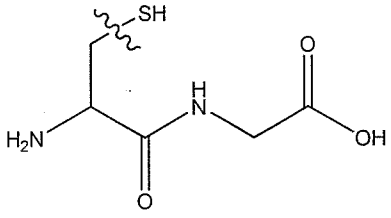
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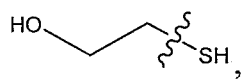
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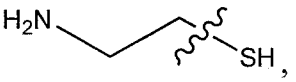
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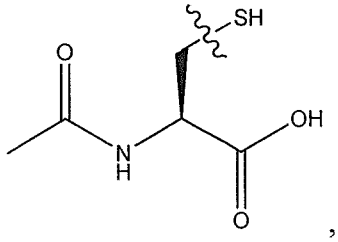
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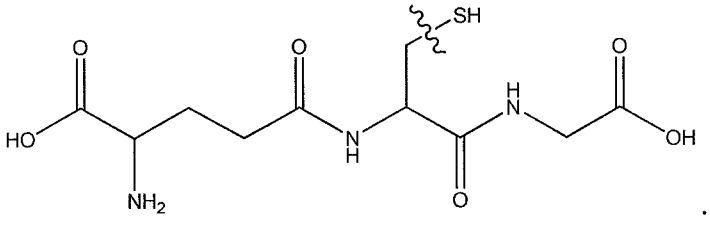
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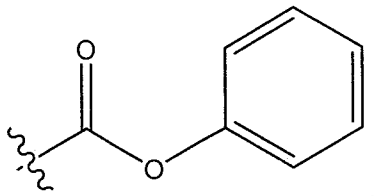
In some examples, R3 is an electron withdrawing group. In some examples, R3 is a halogen. In some examples, R3 is selected from Cl, Br, I, F, CN, NO_2, CF_3, H, OCH_3. In some examples, R3 is selected from a halogenated hydrocarbon group such as a trifluoromethyl group; a carboxyl group; an alkoxycarbonyl group such as a methoxycarbonyl group; an aryloxycarbonyl group such as a phenoxycarbonyl group; abn acyl group such as an acetyl group; an acyloxy groups such as an acetoxy group; a cyano group; an aryl group; a 1-alkenyl group; a nitro group; a sulfo group; an alkanesulfonyl group; an alkanesulfinyl group; and an alkoxysulfonyl group.

In some examples, R4 is any form of a salt.

In some examples, R4 is selected from –COOCH3, -COOCH2CH3, COOCF3,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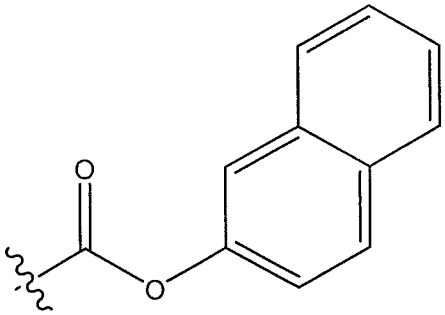
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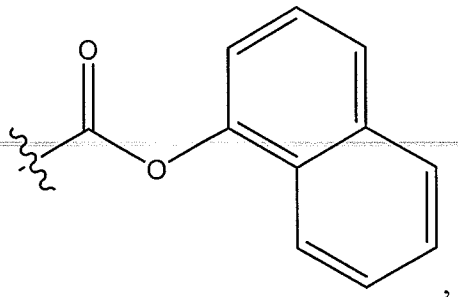
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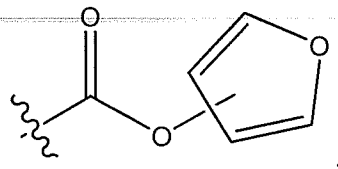
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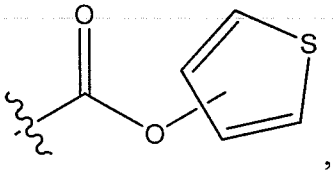
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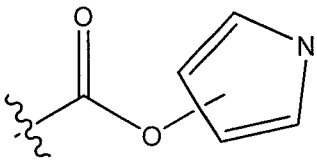
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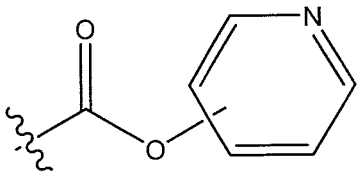
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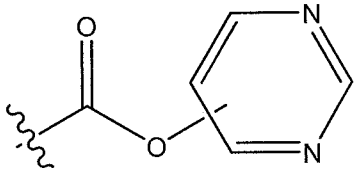
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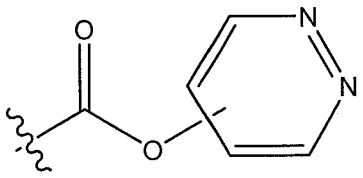
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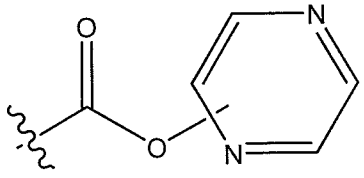
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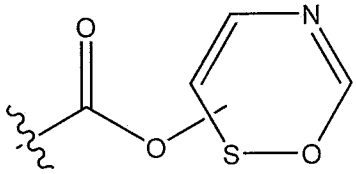
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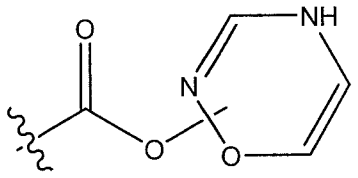
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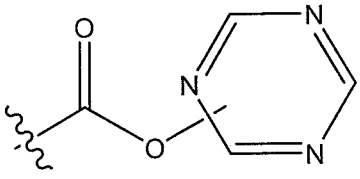
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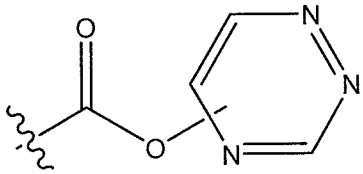
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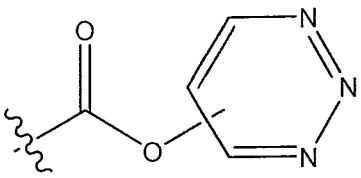
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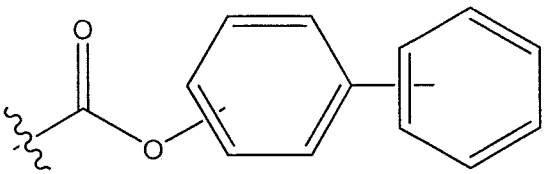
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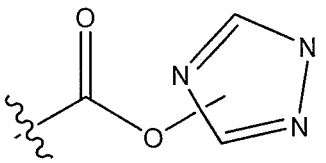
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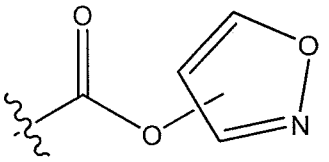
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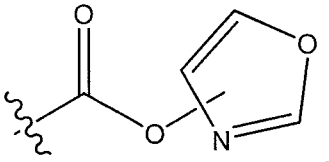
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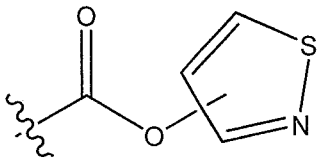
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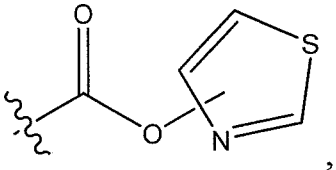
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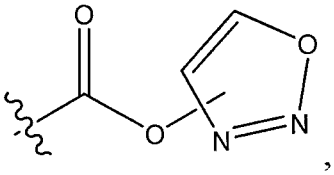
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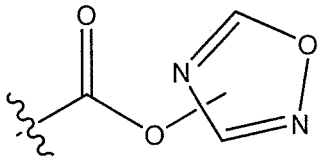
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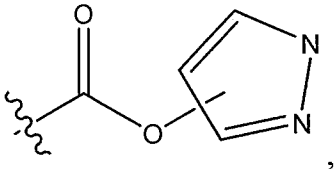
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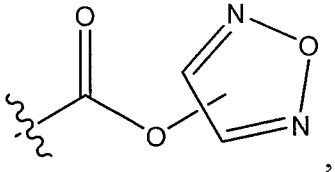
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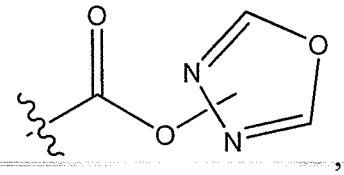
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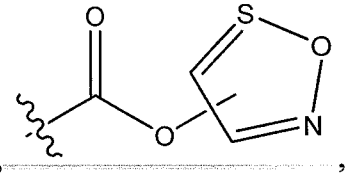
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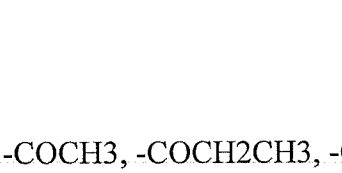
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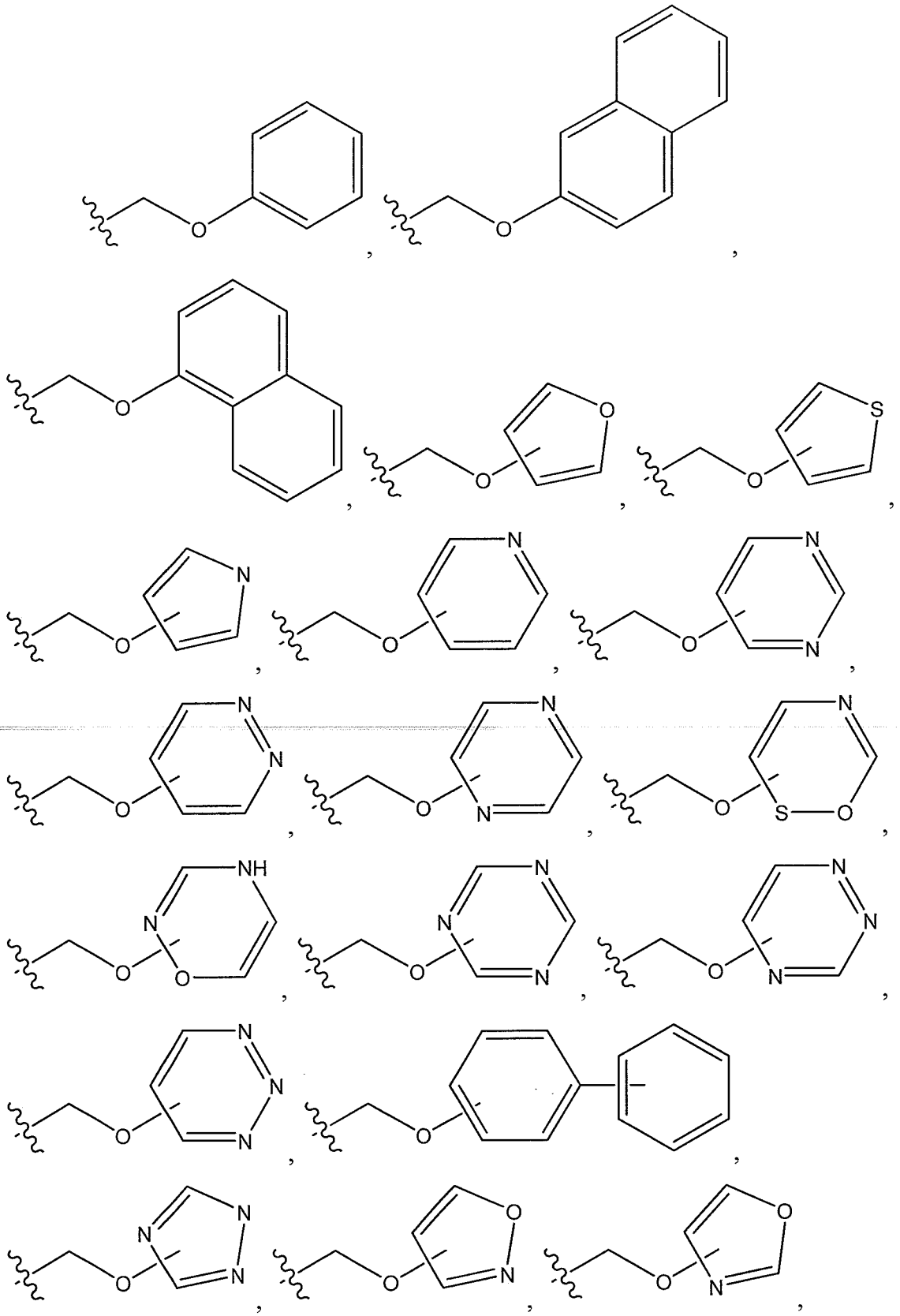
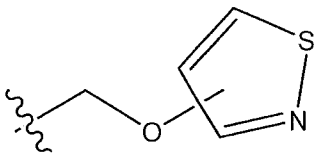
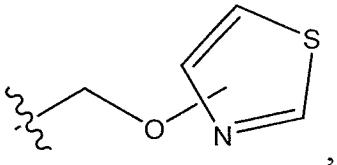
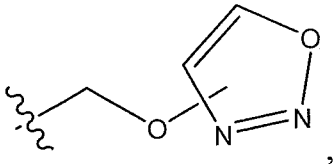
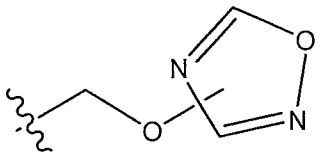
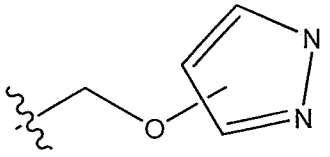
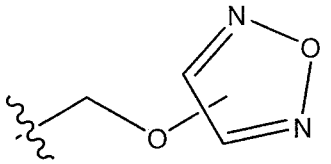
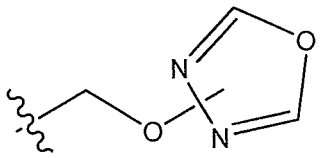
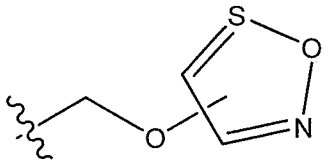
, -COCH3, -COCH2CH3, -COCF3,

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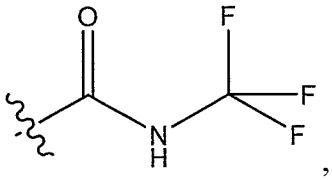
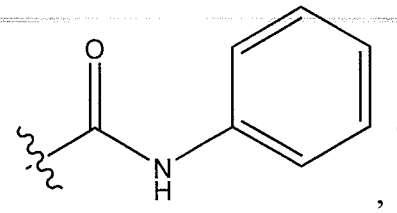
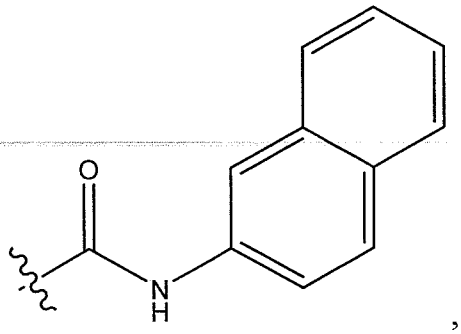
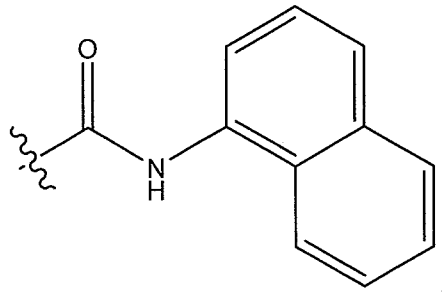
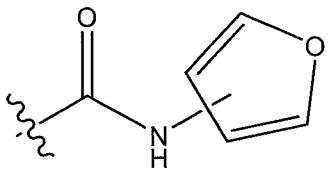
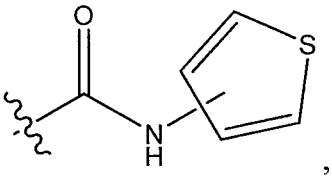
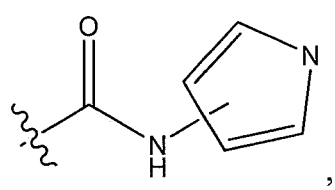
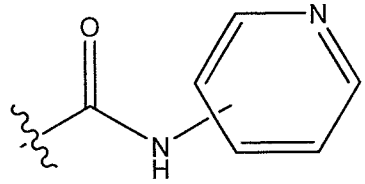
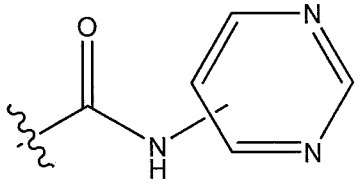
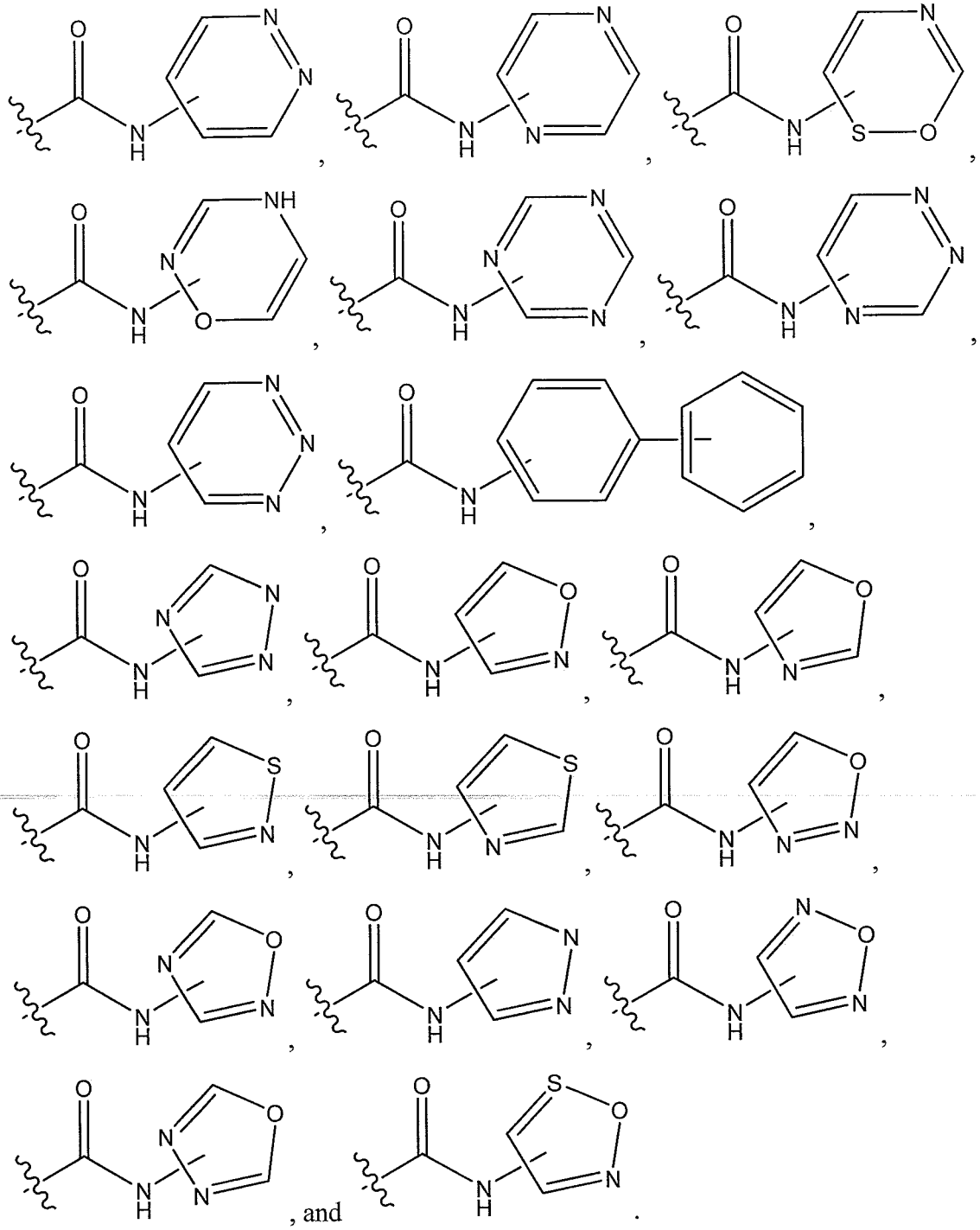
-CONHCH2CH3, -CONHCF3, -CON(CH3)2,












In some examples, the compounds encompassed within Formula I are stable in isolated form.

In some examples, the compounds are conjugated with a targeting moiety. For example, in some examples, the compounds are conjugated with an agent for targeting tumor cells. In some examples, the compounds are conjugated with antibodies that target tumor cells.

In certain examples, the present disclosure provides pharmaceutical compositions comprising a mixed disulfide conjugate of a thienopyridine compound and a pharmaceutically acceptable carrier.

In certain examples, the present disclosure provides pharmaceutical compositions comprising mixed disulfide conjugates of thienopyridine compounds configured for intravenous (IV) administration. In some examples, such pharmaceutical compositions comprising mixed disulfide conjugates of thienopyridine compounds configured for intravenous (IV) administration are used in the treatment, amelioration and prevention of atherothrombosis. In some examples, such pharmaceutical compositions comprising mixed disulfide conjugates of thienopyridine compounds configured for intravenous (IV) administration are used for rapid inhibition of platelet aggregation. In some examples, such pharmaceutical compositions comprising mixed disulfide conjugates of thienopyridine compounds configured for intravenous (IV) administration are used during percutaneous coronary intervention procedures (e.g., coronoary angioplasty) for rapid inhibition of platelet aggregation.

In certain examples, the present disclosure provides methods of treating, ameliorating, or preventing a cardiovascular disease comprising administering to a patient a therapeutically effective amount of a mixed disulfide conjugate of a thienopyridine compound. In some examples, the administration is intravenous administration. In some examples, the cardiovascular disease is selected from the group consisting of coronary artery disease, peripheral vascular disease, and cerebrovascular disease. In some examples, the compound reduces aggregation of platelets (e.g., through irreversible binding to $P2Y_{12}$ receptors) (e.g., through blocking ADP receptors). In some examples, the compound is capable of producing active thienopyridine metabolites in the presence of endogenous glutathione without the need for bioactivation by P450s. In some examples, the methods further comprise co-administration of at least one agent selected from the group consisting of a HMG-CoA reductase inhibitor, an ACE Inhibitor, a Calcium Channel Blocker, a Platelet Aggregation Inhibitor, a Polyunsaturated Fatty Acid, Fibric Acid Derivative, a Bile Acid Sequestrant, an Antioxidant, and an Antianginal Agent.

In certain examples, the present disclosure provides methods of treating, ameliorating, or preventing aggregation of platelets onto blood vessels in a patient, comprising administering to the patient a therapeutically effective amount of a mixed disulfide conjugate of a thienopyridine compound. In some examples, the administration is intravenous

administration. In some examples, the patient has or is at risk for developing cardiovascular disease (e.g., coronary artery disease, peripheral vascular disease, and cerebrovascular disease). In some examples, the treating, ameliorating, or preventing the aggregation of the platelets occurs through irreversible binding to $P2Y_{12}$ receptors. In some examples, the treating, ameliorating, or preventing the aggregation of the platelets occurs through blocking ADP receptors. In some examples, the mixed disulfide conjugate of thienopyridine compound is capable of producing active thienopyridine metabolites in the presence of endogenous glutathione without the need for bioactivation by P450s.

DEFINITIONS

The term "thienopyridine compound" as used herein, refers to a class of ADP receptor/P2Y12 inhibitors used for their anti-platelet activity. Examples include, but are not limited to, clopidogrel (Plavix), ticlopidine (Ticlid), and Prasugrel (Effient).

The term "mixed disulfide conjugate of a thienopyridine compound" as used herein, refers to a modified thienopyridine compound capable of producing active thienopyridine metabolites upon interaction with endogenous glutathione (GSH).

The term "prodrug" as used herein, refers to a pharmacologically inactive derivative of a parent "drug" molecule that requires biotransformation (*e.g.*, either spontaneous or enzymatic) within the target physiological system to release, or to convert (*e.g.*, enzymatically, physiologically, mechanically, electromagnetically) the prodrug into the active drug. Prodrugs are designed to overcome problems associated with stability, water solubility, toxicity, lack of specificity, or limited bioavailability. Exemplary prodrugs comprise an active drug molecule itself and a chemical masking group (*e.g.*, a group that reversibly suppresses the activity of the drug). Some prodrugs are variations or derivatives of compounds that have groups cleavable under metabolic conditions. Prodrugs can be readily prepared from the parent compounds using methods known in the art, such as those described in A Textbook of Drug Design and Development, Krogsgaard-Larsen and H. Bundgaard (eds.), Gordon & Breach, 1991, particularly Chapter 5: "Design and Applications of Prodrugs"; Design of Prodrugs, H. Bundgaard (ed.), Elsevier, 1985; Prodrugs: Topical and Ocular Drug Delivery, K. B. Sloan (ed.), Marcel Dekker, 1998; Methods in Enzymology, K. Widder et al. (eds.), Vol. 42, Academic Press, 1985, particularly pp. 309-396; Burger's Medicinal Chemistry and Drug Discovery, 5th Ed., M. Wolff (ed.), John Wiley & Sons, 1995, particularly Vol. 1 and pp. 172-178 and pp. 949-982; Pro-Drugs as Novel Delivery Systems,

T. Higuchi and V. Stella (eds.), Am. Chem. Soc., 1975; and Bioreversible Carriers in Drug Design, E. B. Roche (ed.), Elsevier, 1987.

Exemplary prodrugs become pharmaceutically active *in vivo* or *in vitro* when they undergo solvolysis under physiological conditions or undergo enzymatic degradation or other biochemical transformation (*e.g.*, phosphorylation, hydrogenation, dehydrogenation, glycosylation). Prodrugs often offer advantages of water solubility, tissue compatibility, or delayed release in the mammalian organism. (*See e.g.*, Bundgard, Design of Prodrugs, *pp.* 7-9, 21-24, Elsevier, Amsterdam (1985); and Silverman, The Organic Chemistry of Drug Design and Drug Action, *pp.* 352-401, Academic Press, San Diego, CA (1992)). Common prodrugs include acid derivatives such as esters prepared by reaction of parent acids with a suitable alcohol (*e.g.*, a lower alkanol) or esters prepared by reaction of parent alcohol with a suitable carboxylic acid, (*e.g.*, an amino acid), amides prepared by reaction of the parent acid compound with an amine, basic groups reacted to form an acylated base derivative (*e.g.*, a lower alkylamide), or phosphorus-containing derivatives, *e.g.*, phosphate, phosphonate, and phosphoramidate esters, including cyclic phosphate, phosphonate, and phosphoramidate (see, e.g., US Patent Application Publication No. US 2007/0249564 A1).

The term "pharmaceutically acceptable salt" as used herein, refers to any salt (*e.g.*, obtained by reaction with an acid or a base) of a compound of the present disclosure that is physiologically tolerated in the target animal (*e.g.*, a mammal). Salts of the compounds of the present disclosure may be derived from inorganic or organic acids and bases. Examples of acids include, but are not limited to, hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, ethanesulfonic, formic, benzoic, malonic, sulfonic, naphthalene-2-sulfonic, benzenesulfonic acid, and the like. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the disclosure and their pharmaceutically acceptable acid addition salts.

Examples of bases include, but are not limited to, alkali metal (*e.g.*, sodium) hydroxides, alkaline earth metal (*e.g.*, magnesium) hydroxides, ammonia, and compounds of formula NW_4^+, wherein W is C_{1-4} alkyl, and the like.

Examples of salts include, but are not limited to: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate,

flucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, chloride, bromide, iodide, 2-hydroxyethanesulfonate, lactate, maleate, mesylate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, palmoate, pectinate, persulfate, phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, undecanoate, and the like. Other examples of salts include anions of the compounds of the present disclosure compounded with a suitable cation such as Na^+, NH_4^+, and NW_4^+ (wherein W is a C_{1-4} alkyl group), and the like. For therapeutic use, salts of the compounds of the present disclosure are contemplated as being pharmaceutically acceptable. However, salts of acids and bases that are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound.

The term "solvate" as used herein, refers to the physical association of a compound of the disclosure with one or more solvent molecules, whether organic or inorganic. This physical association often includes hydrogen bonding. In certain instances, the solvate is capable of isolation, for example, when one or more solvate molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolable solvates. Exemplary solvates include hydrates, ethanolates, and methanolates.

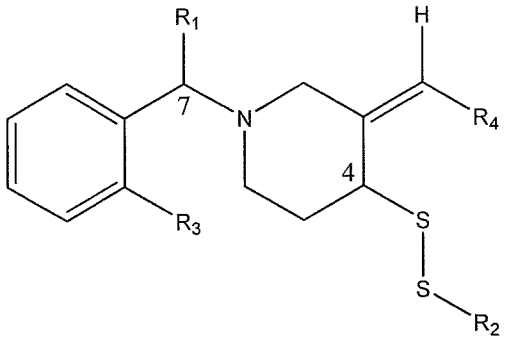
The term "therapeutically effective amount," as used herein, refers to that amount of the therapeutic agent sufficient to result in amelioration of one or more symptoms of a disorder, or prevent advancement of a disorder, or cause regression of the disorder. For example, with respect to the treatment and/or prevention of platelet aggregation onto a blood vessel, in one example, a therapeutically effective amount will refer to the amount of a therapeutic agent (e.g., a mixed disulfide conjugate of a thienopyridine compound) that decreases the reduces and/or prevents platelet aggregation by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

The term "pharmaceutically acceptable carrier" or "pharmaceutically acceptable vehicle" encompasses any of the standard pharmaceutical carriers, solvents, surfactants, or vehicles. Suitable pharmaceutically acceptable vehicles include aqueous vehicles and nonaqueous vehicles. Standard pharmaceutical carriers and their formulations are described in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA, 19th ed. 1995.

DETAILED DESCRIPTION OF THE INVENTION

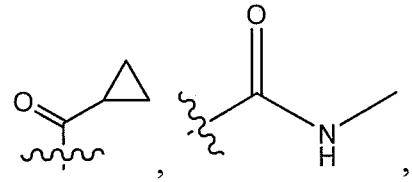
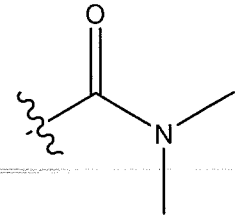
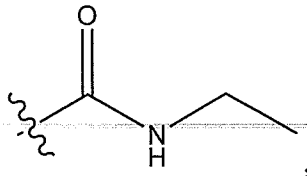
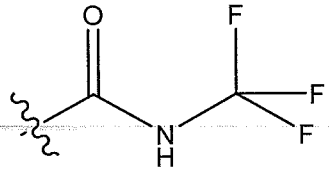
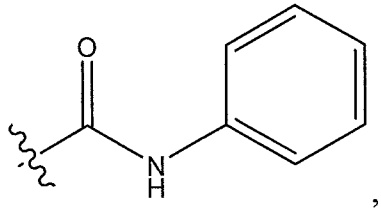
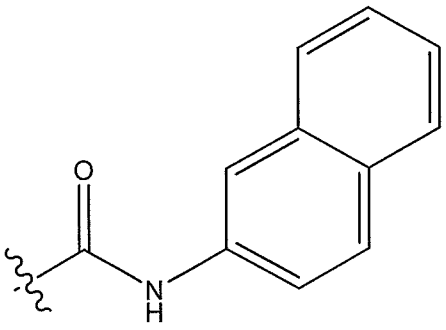
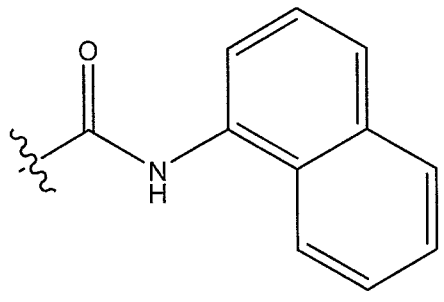
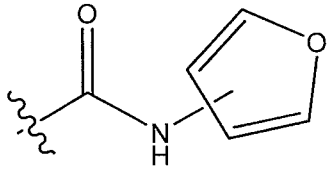
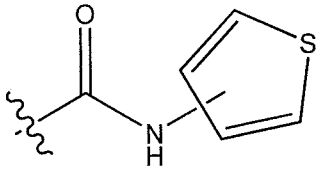
What Is Claimed Is:

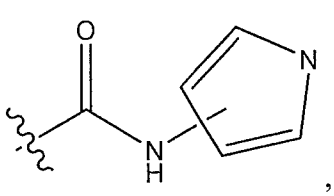
1. A compound having Formula I:



, or a pharmaceutically acceptable salt thereof;

wherein independently each of R_1, R_2, R_3 and R_4 are

R_1 is selected from the group consisting of -CO-OCH_3,  , ,  ,  ,  ,  ,  ,  ,  ,  .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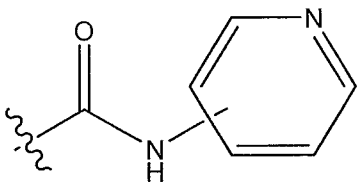
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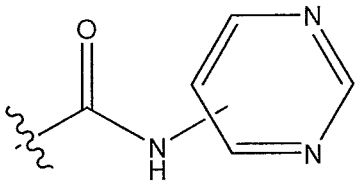
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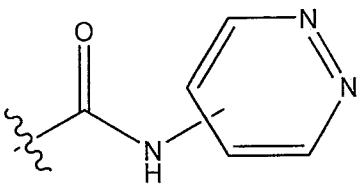
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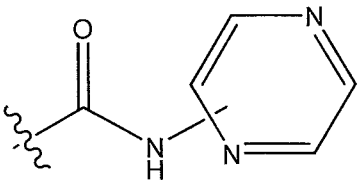
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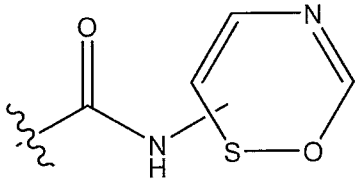
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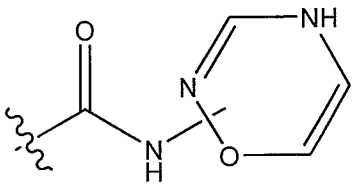
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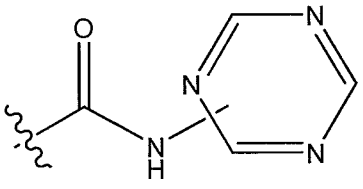
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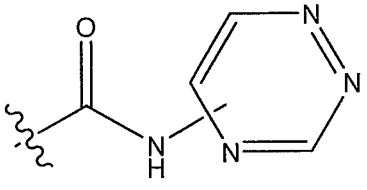
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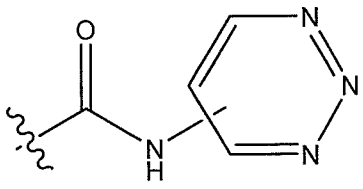
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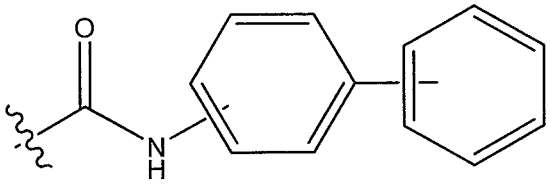
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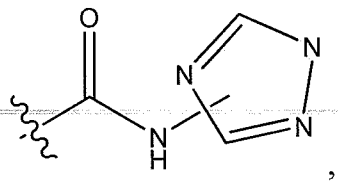
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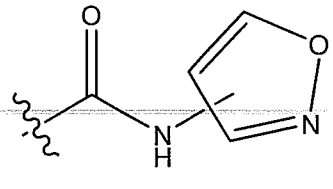
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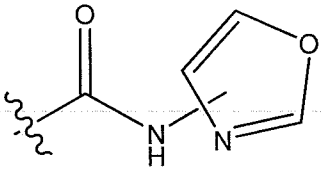
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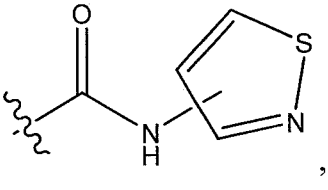
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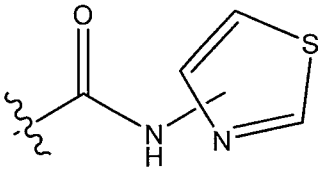
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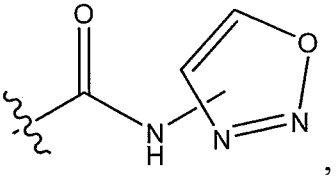
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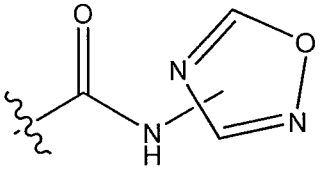
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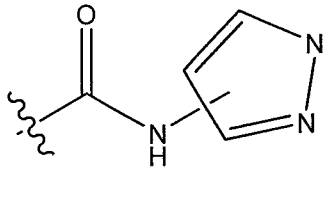
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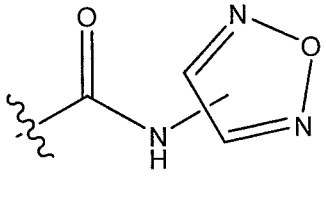
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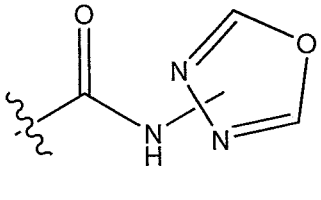
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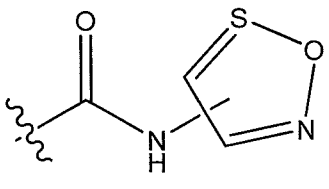
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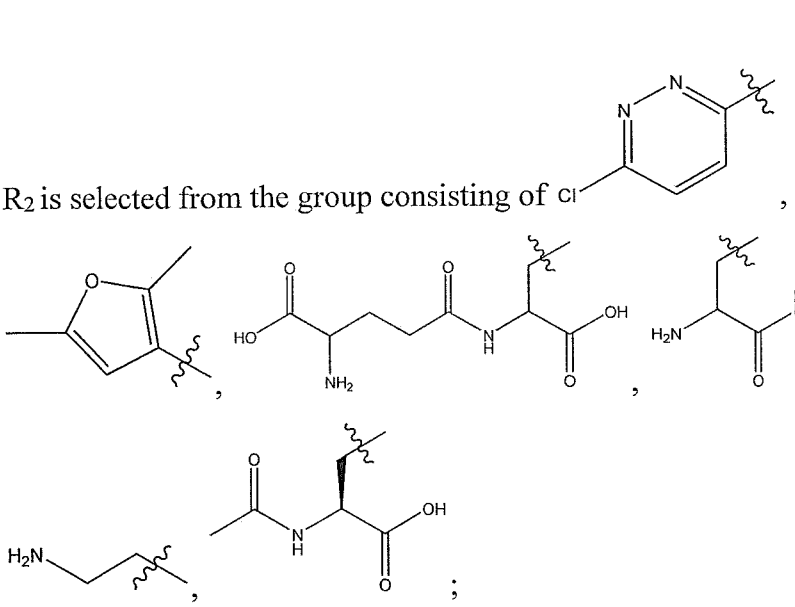
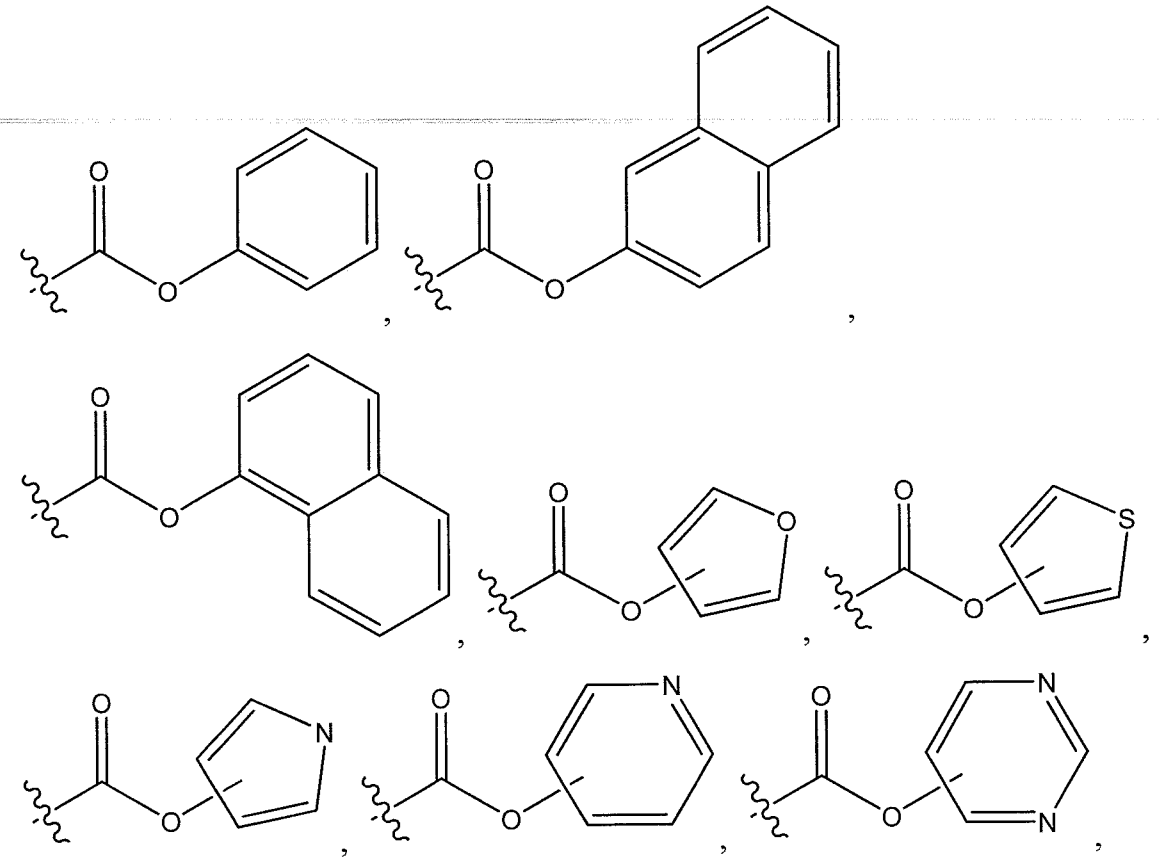
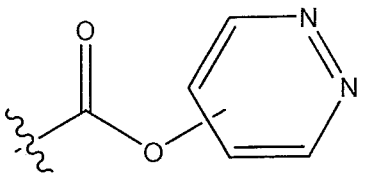
R_2 is selected from the group consisting of 

R_3 is selected from the group consisting of Cl, Br, I, F, CN, NO_2, CF_3, H, and OCH_3; and

R_4 is selected from the group consisting of $-COOCH_3$, $-COOCH_2CH_3$, $COOCF_3$,

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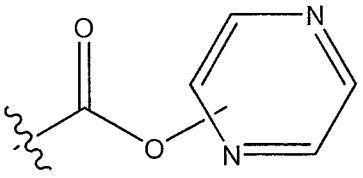
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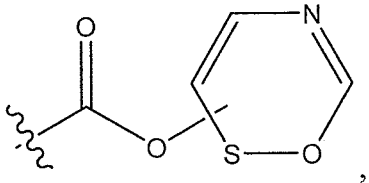
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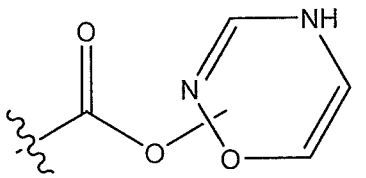
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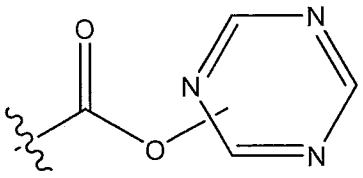
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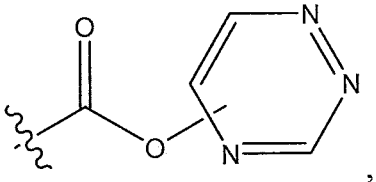
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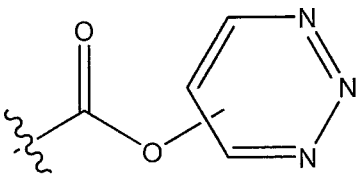
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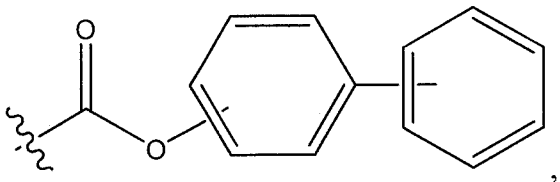
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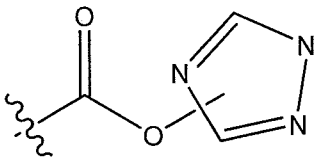
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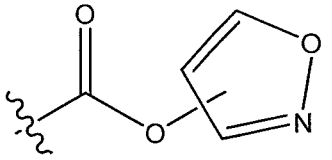
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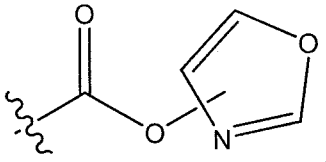
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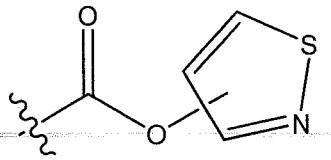
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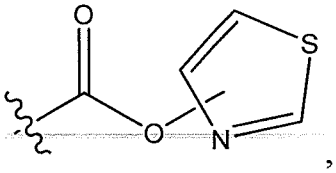
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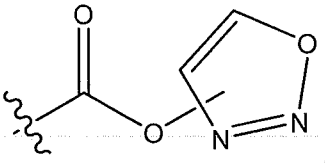
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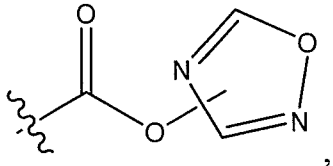
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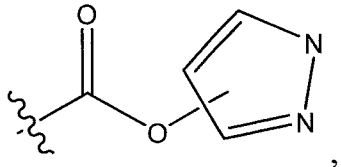
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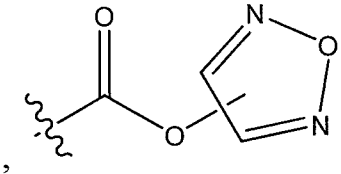
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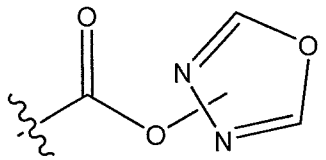
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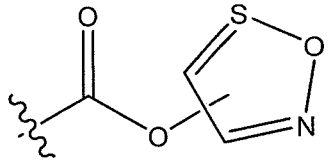
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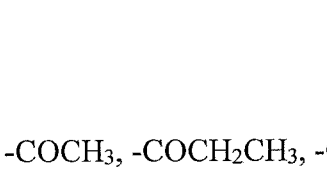
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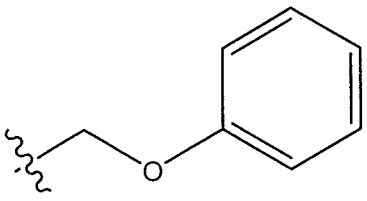
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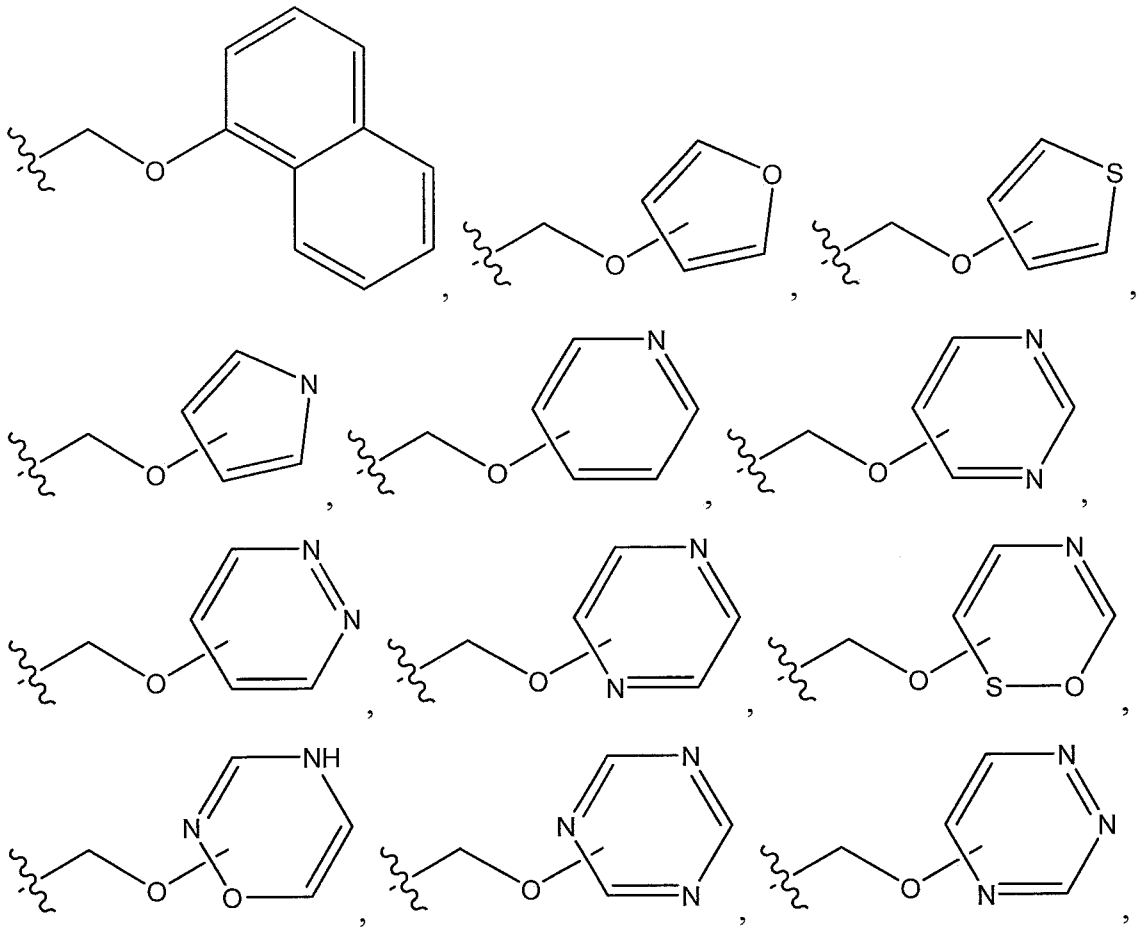

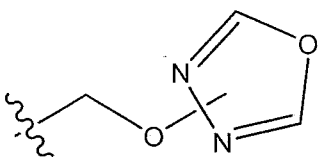
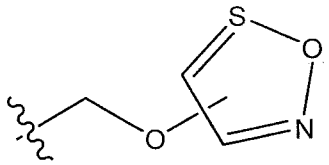
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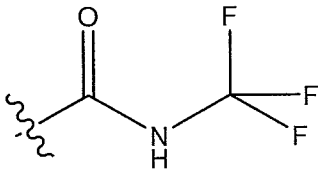
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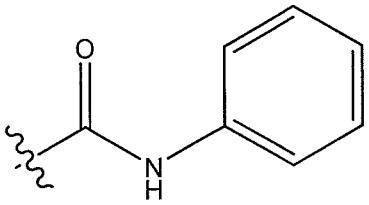
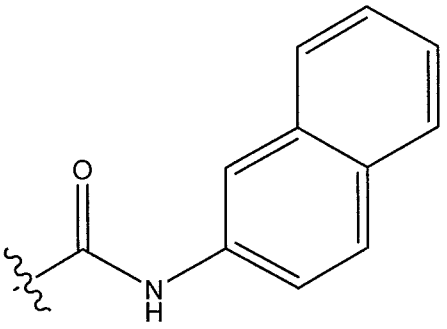
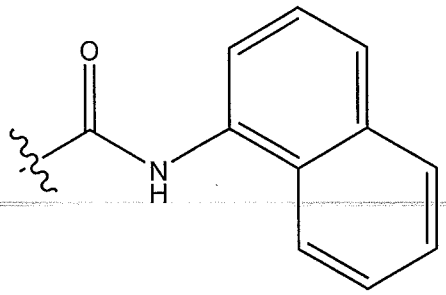
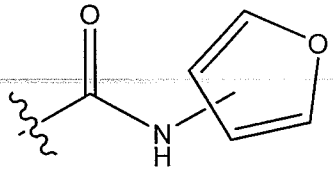
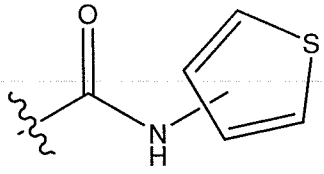
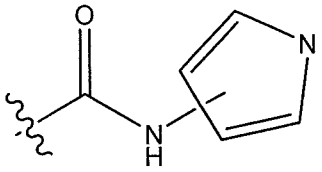
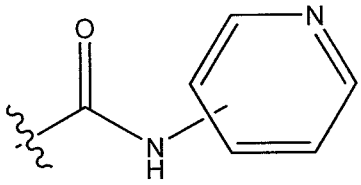
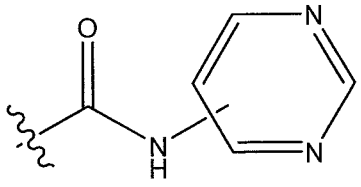
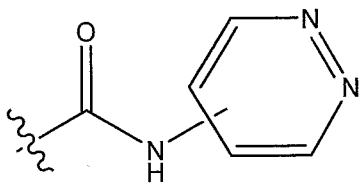
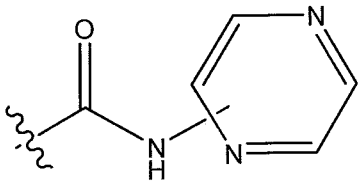
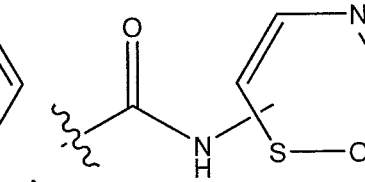
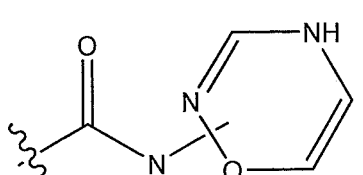
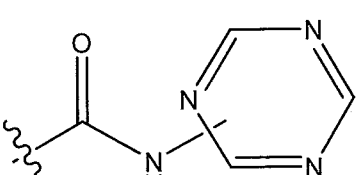
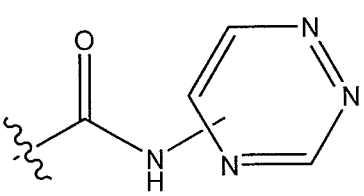

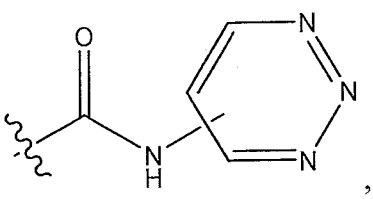
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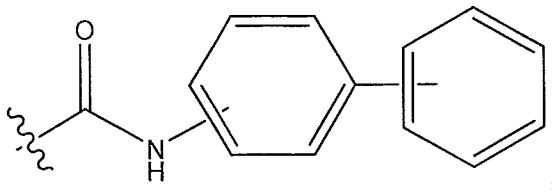
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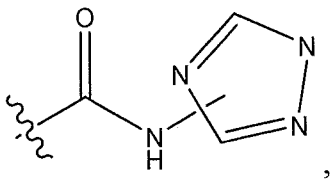
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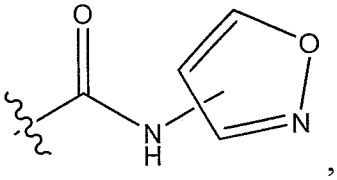
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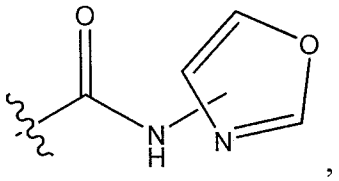
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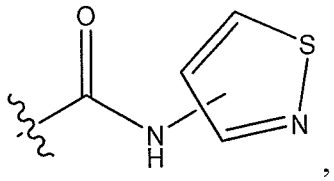
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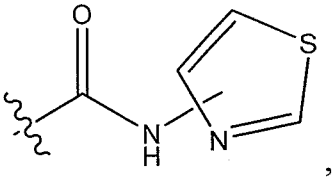
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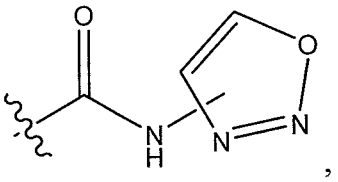
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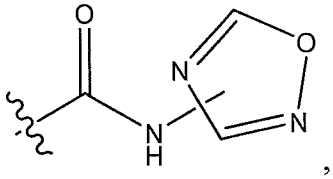
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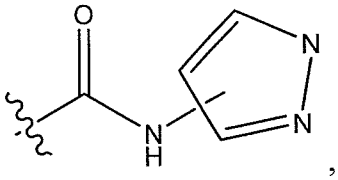
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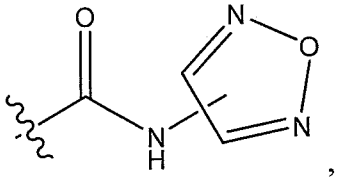
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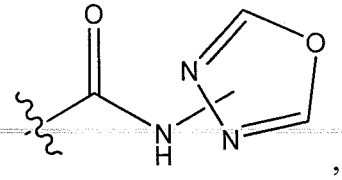
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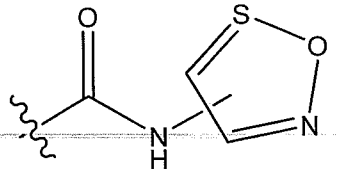
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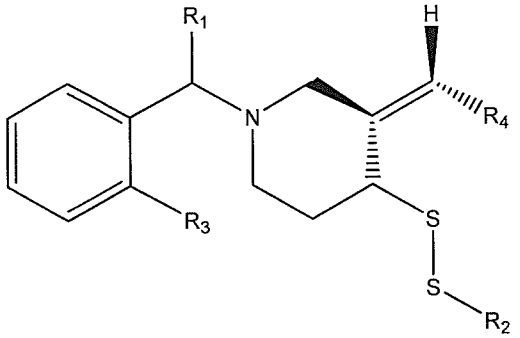
2. The compound of claim 1, wherein stereochemical configuration for Formula I is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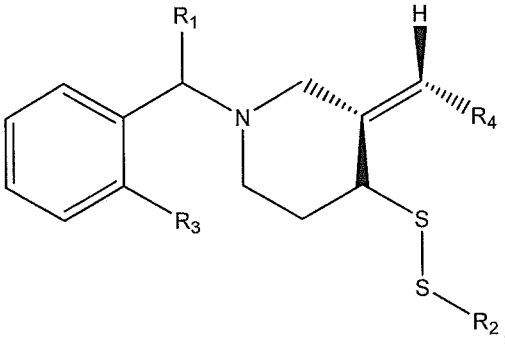
selected from the group consisting of: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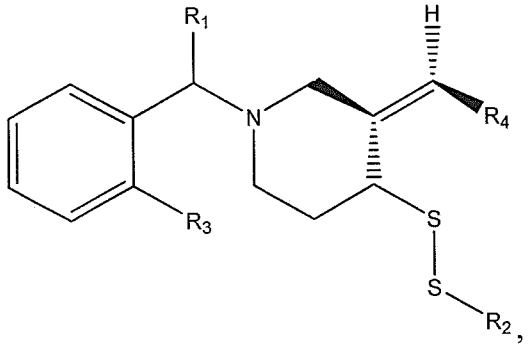
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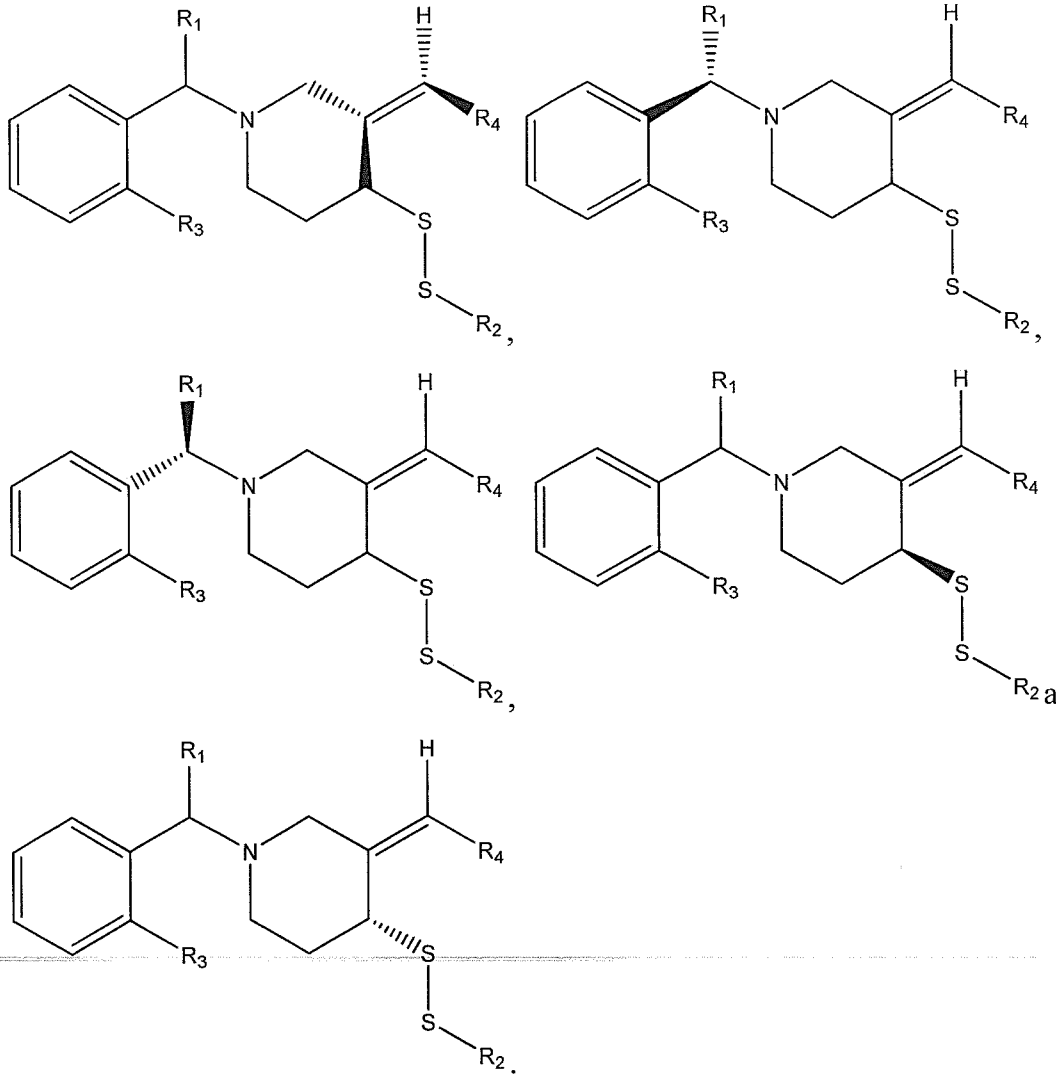

3. The compound of claim 1, wherein the R_4 substituent is engaged with an applicable metal to form a salt, wherein the applicable metal is selected from Na^+, K^+, and Li^+, or wherein the R_4 substituent is engaged with an applicable halogen to form an ammonium salt.

4. A pharmaceutical composition comprising an effective amount of the compound of claim 1, and a pharmaceutically acceptable carrier.

5. Use of the compound of claim 1 in the manufacture of a medicament for treating a cardiovascular disease in a patient wherein the use comprises that a therapeutically effective amount of the compound of claim 1 is to be administered to the patient, wherein said administration is selected from the group consisting of oral administration and intravenous administration, wherein said cardiovascular disease is selected from the group consisting of

coronary artery disease, peripheral vascular disease, atherothrombosis, and cerebrovascular disease.

6. The use of claim 5, further comprising co-administration of at least one agent selected from the group consisting of a HMG-CoA reductase inhibitor, an ACE inhibitor, a calcium channel blocker, a platelet aggregation inhibitor, a polyunsaturated fatty acid, fibric acid derivative, a bile acid sequestrant, an antioxidant, a thrombolytic agent, and an antianginal agent.

7. The pharmaceutical composition of claim 4, wherein said pharmaceutical composition is configured for intravenous administration.

8. The pharmaceutical composition of claim 7, wherein said pharmaceutical composition is to be intravenously administered to a patient during a percutaneous coronary intervention procedure.

9. The pharmaceutical composition of claim 8, wherein said percutaneous coronary intervention procedure is coronary angioplasty.