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(54) BENZAMIDES AND RELATED INHIBITORS OF FACTOR XA

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(57) **ABSTRACT**

Novel benzamide compounds including their pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives having activity against mammalian factor Xa are described. Compositions containing such compounds are also described. The compounds and compositions are useful in vitro or in vivo for preventing or treating coagulation disorders.

BENZAMIDES AND RELATED INHIBITORS OF FACTOR XA

FIELD OF THE INVENTION

[0001] This invention relates to novel compounds which are potent and highly selective inhibitors of isolated factor Xa or when assembled in the prothrombinase complex. These compounds show selectivity for factor Xa versus other proteases of the coagulation (e.g. thrombin, fVIIa, fIXa) or the fibrinolytic cascades (e.g. plasminogen activators, plasmin). In another aspect, the present invention relates to novel monoamidino-containing compounds, their pharmaceutically acceptable salts, and pharmaceutically acceptable compositions thereof which are useful as potent and specific inhibitors of blood coagulation in mammals. In yet another aspect, the invention relates to methods for using these inhibitors as therapeutic agents for disease states in mammals characterized by coagulation disorders.

BACKGROUND OF THE INVENTION

[0002] Hemostasis, the control of bleeding, occurs by surgical means, or by the physiological properties of vasoconstriction and coagulation. This invention is particularly concerned with blood coagulation and ways in which it assists in maintaining the integrity of mammalian circulation after injury, inflammation, disease, congenital defect, dysfunction or other disruption. Although platelets and blood coagulation are both involved in thrombus formation, certain components of the coagulation cascade are primarily responsible for the amplification or acceleration of the processes involved in platelet aggregation and fibrin deposition.

[0003] Thrombin is a key enzyme in the coagulation cascade as well as in hemostasis. Thrombin plays a central role in thrombosis through its ability to catalyze the conversion of fibrinogen into fibrin and through its potent platelet activation activity. Direct or indirect inhibition of thrombin activity has been the focus of a variety of recent anticoagulant strategies as reviewed by Claeson, G., "Synthetic Peptides and Peptidomimetics as Substrates and Inhibitors of Thrombin and Other Proteases in the Blood Coagulation System", Blood Coag. Fibrinol. 5, 411-436 (1994). Several classes of anticoagulants currently used in the clinic directly or indirectly affect thrombin (i.e. heparins, low-molecular weight heparins, heparin-like compounds and coumarins).

[0004] A prothrombinase complex, including Factor Xa (a serine protease, the activated form of its Factor X precursor and a member of the calcium ion binding, gamma carboxyglutamyl (Gla)-containing, vitamin K dependent, blood coagulation glycoprotein family), converts the zymogen prothrombin into the active procoagulant thrombin. Unlike thrombin, which acts on a variety of protein substrates as well as at a specific receptor, factor Xa appears to have a single physiologic substrate, namely prothrombin. Since one molecule of factor Xa may be able to generate up to 138 molecules of thrombin (Elodi et al., *Thromb. Res.* 15, 617-619 (1979)), direct inhibition of factor Xa as a way of indirectly inhibiting the formation of thrombin may be an efficient anticoagulant strategy. Therefore, it has been suggested that compounds which selectively inhibit factor Xa may be useful as in vitro diagnostic agents, or for therapeutic administration in certain thrombotic disorders, see e.g., WO 94/13693.

[0005] Polypeptides derived from hematophagous organisms have been reported which are highly potent and specific inhibitors of factor Xa. U.S. Pat. No. 4,588,587 describes anticoagulant activity in the saliva of the Mexican leech, *Haementeria officinalis*. A principal component of this saliva was shown to be the polypeptide factor Xa inhibitor, antistasin (ATS), by Nutt, E. et al., "The Amino Acid Sequence of Antistasin, a Potent Inhibitor of Factor Xa Reveals a Repeated Internal Structure", J. Biol. Chem., 263, 10162-10167 (1988). Another potent and highly specific inhibitor of Factor Xa, called tick anticoagulant peptide (TAP), has been isolated from the whole body extract of the soft tick *Ornithidoros moubata,* as reported by Waxman, L., et al., "Tick Anticoagulant Peptide (TAP) is a Novel Inhibitor of Blood Coagulation Factor Xa" Science, 248, 593-596 (1990).

[0006] Factor Xa inhibitory compounds which are not large polypeptide-type inhibitors have also been reported including: Tidwell, R. R. et al., "Strategies for Anticoagulation With Synthetic Protease Inhibitors. Xa Inhibitors Versus Thrombin Inhibitors", Thromb. Res., 19, 339-349 (1980); Turner, A. D. et al., "p-Amidino Esters as Irreversible Inhibitors of Factor IXa and Xa and Thrombin", Biochemistry, 25, 4929-4935 (1986); Hitomi, Y. et al., "Inhibitory Effect of New Synthetic Protease Inhibitor (FUT-175) on the Coagulation System", Haemostasis, 15, 164-168 (1985); Sturzebecher, J. et al., "Synthetic Inhibitors of Bovine Factor Xa and Thrombin. Comparison of Their Anticoagulant Efficiency", Thromb. Res., 54, 245-252 (1989); Kam, C. M. et al., "Mechanism Based Isocoumarin Inhibitors for Trypsin and Blood Coagulation Serine Proteases: New Anticoagulants", Biochemistry, 27, 2547-2557 (1988); Hauptmann, J. et al., "*Comparison* of the Anticoagulant and Antithrombotic Effects of Synthetic Thrombin and Factor Xa Inhibitors", Thromb. Haemost., 63, 220-223 (1990); and the like.

[0007] Others have reported Factor Xa inhibitors which are small molecule organic compounds, such as nitrogen containing heterocyclic compounds which have amidino substituent groups, wherein two functional groups of the compounds can bind to Factor Xa at two of its active sites. For example, WO 98/28269 describes pyrazole compounds having a terminal C(=NH)—NH_2 group; WO 97/21437 describes benzimidazole compounds substituted by a basic radical which are connected to a naththyl group via a straight or branched chain alkylene,—C(=O) or —$S(=O)_2$ bridging group; WO 99/10316 describes compounds having a 4-phenyl-N-alkylamidino-piperidine and 4-phenoxy-N-alkylamidino-piperidine group connected to a 3-amidinophenyl group via a carboxamidealkyleneamino bridge; and EP 798295 describes compounds having a 4-phenoxy-N-alkylamidino-piperidine group connected to an amidinonaphthyl group via a substituted or unsubstituted sulfonamide or carboxamide bridging group.

[0008] There exists a need for effective therapeutic agents for the regulation of hemostasis, and for the prevention and treatment of thrombus formation and other pathological processes in the vasculature induced by thrombin such as restenosis and inflammation. In particular, there continues to be a need for compounds which selectively inhibit factor Xa or its precursors. Compounds that have different combinations of bridging groups and functional groups than compounds previously discovered are needed, particularly com-

pounds which selectively or preferentially bind to Factor Xa. Compounds with a higher degree of binding to Factor Xa than to thrombin are desired, especially those compounds having good bioavailability and/or solubility.

SUMMARY OF THE INVENTION

[0009] As discussed above, a number of non-peptide, specific, factor Xa inhibitors have been described either in the scientific or patent literature (Zhu and Scarborough, Ann. Rep. Med. Chem. 35: 83-102 (2000)). Most of these compounds rely on the interaction of P1 and P4 elements of the inhibitor compounds with the S1 and S4 sub-sites on the factor Xa enzyme. In general, it has been described that P1 elements utilize a highly charged benzamidine functionality in order to interact with the S1 pocket of the factor Xa enzyme. Furthermore, substitution on the benzamidine nitrogens either by alkylation or cyclization (cyclic amidines) of these previously described inhibitors is detrimental to their interaction with the enzyme at the S1 pocket. In the present application, a novel series of inhibitors of factor Xa which do not utilize a S1-interacting benzamidine but utilize a neutral P1 species are described. In addition the compounds also utilize a substituted benzamidine or a cyclic amidine as a P4 element which can each interact with the S4 sub-site of factor Xa enzyme. Surprisingly, the inhibitors of this invention with modified amidine elements are not only of high potency in vitro, but also have excellent pharmacological and pharmaceutical properties in vivo. These are results that would not have been predicted for such structures.

[0010] Accordingly, the present invention relates to novel compounds which inhibit factor Xa, their pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives, and pharmaceutically acceptable compositions thereof which have particular biological properties and are useful as potent and specific inhibitors of blood coagulation in mammals. In another aspect, the invention relates to methods of using these inhibitors as diagnostic reagents or as therapeutic agents for disease states in mammals characterized by undesired thrombosis or which have coagulation disorders, such as in the treatment or prevention of any thrombotically mediated acute coronary or cerebrovascular syndrome, any thrombotic syndrome occurring in the venous system, any coagulopathy, and any thrombotic complications associated with extracorporeal circulation or instrumentation, and for the inhibition of coagulation in biological samples.

[0011] In certain embodiments, this invention relates to novel compounds which are potent and highly selective inhibitors of isolated factor Xa when assembled in the prothrombinase complex. These compounds show selectivity for factor Xa versus other proteases of the coagulation cascade (e.g. thrombin, etc.) or the fibrinolytic cascade, and are useful as diagnostic reagents as well as antithrombotic agents.

[0012] In one embodiment, the present invention relates to a compound according to the formula (I):

A-Q-D-E-G-J-X (I)

[0013] where:

[0014] A is selected from:

[0015] (a) C_1-C_6-alkyl;

[0016] (b) C_3-C_8-cycloalkyl;

[0017] (c) —$N(R^1,R^2)$, $N(R^1,R^2)$—$C(=NR^3)$—, $N(R^1,R^2)$—$C(=NR^3)$—$N(R^4)$—, R^1—$C(=NR^3)$—, R^1—$C(=NR^3)$—$N(R^4)$—;

[0018] (d) phenyl, which is independently substituted with 0-2 R substitutuents;

[0019] (e) naphthyl, which is independently substituted with 0-2 R substitutuents; and

[0020] (f) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R substitutuents;

[0021] R is selected from:

[0022] H, halo, —CN, —CO_2R^1, —C(=O)—$N(R^1, R^2)$, —$(CH_2)_m$—CO_2R^1, —$(CH_2)_m$—C(=O)—$N(R^1, R^2)$, —NO_2, —$SO_2N(R^1, R^2)$, —SO_2R^1, —$(CH_2)_mNR^1R^2$, —$(CH_2)_m$—$C(=NR^3)$—R^1, —$(CH_2)_m$—$C(=NR^3)$—$N(R^1,R^2)$, —$(CH_2)_m$—$N(R^4)$—$C(=NR^3)$—$N(R^1,R^2)$, —$(CH_2)_mNR^1$— group appended to a 3 to 6 membered heterocyclic ring containing from 1-4 heteroatoms selected from N, O and S, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —CF_3, —OR^2, and a 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic system may be independently replaced with a member selected from the group consisting of halo, —C_1-C_4-alkyl, —C_{1-4}alkyl-CN, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl and —NO_2;

[0023] m is an integer of 0-2;

[0024] R^1, R^2, R^3 and R^4 are independently selected from the group consisting of:

[0025] H, —OR^5, —$N(—R^5, —R^6)$, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —C_{0-4}alkylphenyl and —C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8} cycloalkyl, —CO_{0-4}alkylC_{3-8}cycloalkyl, —CN, and —NO_2; or

[0026] R^1 and R^2, or R^2 and R^3 taken together can form a 3-8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C_1-C_4-alkyl, —CN —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl and —NO_2;

[0027] R^5 and R^6 are independently selected from the group consisting of:

[0028] H, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —C_{0-4}alkylphenyl and —C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —CN, and —NO_2; or

[0029] R^5 and R^6 taken together can form a 3-8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, —C_1-C_4-alkyl, —CN —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl and —NO_2;

[0030] Q is a member selected from the group consisting of:

[0031] a direct link, —CH_2—, —C(═O)—, —O—, —N(R^7)—, —N(R^7)CH_2—, —CH_2N(R^7)—, —C(═NR^7)—, —C(═O)—N(R^7)—, —N(R^7)—C(═O)—, —S—, —SO—, —SO_2—, —SO_2—N(R^7)— and —N(R^7)—SO_2—;

[0032] R^7 is selected from:

[0033] H, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —C_{0-4}alkylphenyl and —C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —CN, and —NO_2;

[0034] D is a direct link or is a member selected from the group consisting of:

[0035] (a) phenyl, which is independently substituted with 0-2 R^{1a} substitutuents;

[0036] (b) naphthyl, which is independently substituted with 0-2 R^{1a} substitutuents; and

[0037] (c) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be subsituted from 0-2 R^{1a} substitutuents;

[0038] R^{1a} is selected from:

[0039] halo, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —CN, —NO_2, —$(CH_2)_n$N$R^{2a}R^{3a}$, —$(CH_2)_n$$CO_2R^{2a}$, —$(CH_2)_nCONR^{2a}R^{3a}$, —$SO_2NR^{2a}R^{3a}$, —$SO_2R^{2a}$, —$CF_3$, —$OR^{2a}$, and a 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the aromatic heterocyclic system may be independently replaced with a member selected from the group consisting of halo, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —CN and —NO_2,

[0040] R^{2a} and R^{3a} are independently selected from the group consisting of:

[0041] H, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —C_{0-4}alkylphenyl and —C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —CN and —NO_2;

[0042] n is an integer of 0-2;

[0043] E is a direct link or a member selected from the group consisting of:

[0044] —C_{1-2}-alkyl-, —O—, —S—, —SO—, —SO_2—, —C_{0-1}-alkyl-C(═O), —C_{0-1}-alkyl-C(═O)—N(—R^8)— C_{0-1}-alkyl-, —C_{0-1}-alkyl-N(—R^8)—C(═O)—C_{0-1}-alkyl-, —N(—R^8)—C(═O)—N(—R^8)— and —C_{0-1}-alkyl-N(—R^8)—;

[0045] R^8 is a member selected from the group consisting of:

[0046] H; —C_{1-4}-alkyl; —C_{0-4}-alkylaryl; —C_{0-4}-alkyl-heteroaryl; —C_{1-4}-alkyl-C(═O)—OH, —C_{1-4} -alkyl-C(═O)—O—C_{1-4}-alkyl, and —C_{1-4}-alkyl-C(═O)—N(—R^{2b}, —R^{3b});

[0047] R^{2b} and R^{3b} are each a member independently selected from the group consisting of:

[0048] H, —C_{1-4}-alkyl, —C_{0-4}-alkyl-aryl; —C_{0-4}-alkyl-heterocyclic group, and R^{2b} and R^{3b} together with the N atom to which they are attached can form a 5-8 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S, wherein the heterocyclic ring may be substituted with 0-2 R^{1c} groups;

[0049] R^{1c} is a member selected from the group consisting of:

[0050] Halo; —C_{1-4}-alkyl; —CN, —NO_2; —C(═O)—N(—R^{2c}, R^{3c}); —C(═O)—OR^{2c}; —$(CH_2)_q$—N(—R^{2c},—R^{3c});—SO_2—N(—R^{2c}, —R^{3c}); —SO_2R^{2c}; —CF_3 and —$(CH_2)_q$—OR^{2c};

[0051] R^{2c} and R^{3c} are each independently a member selected from the group consisting of:

[0052] H; —C_{1-4}-alkyl and —C_{1-4}-alkyl-aryl;

[0053] q is an integer of 0-2;

[0054] G is a member selected from the group consisting of:

[0055] (a) C_2-alkenyl or C_{3-8}-cycloalkenyl, wherein the alkenyl and cycloalkenyl attachment points are the alkenyl carbon atoms and wherein the —C_2-alkenyl or —C_{3-8}-cycloalkenyl are substituted with 0-4 R^{1d} groups;

[0056] (b) a phenylene group wherein the ring carbon atoms of the phenylene group are substituted with 0-4 R^{1d} groups;

[0057] (c) a 3-8 membered a saturated, partially unsaturated or aromatic monocyclic- heterocyclic ring system containing 1-4 heteroatoms selected from N, O and S, wherein 0-2 ring atoms of the heterocyclic ring may be substituted with 0-4 R^{1d} groups; and,

[0058] (d) an 8-10 membered fused heterocyclic bicyclic ring system, containing 1-4 heteroatoms selected from N, O and S, wherein 0-2 ring atoms of the fused bicyclic ring, system may be substituted with 0-4 R^{1d} groups;

[0059] R^{1d} is a member selected from the group consisting of:

[0060] H, halo; C_{1-6}-alkyl, carbocylic aryl, —CN; $—NO_2$; $—(CH_2)_{0-6}—NR^{2d}R^{3d}$; $—SO_2NR^{2d}R^{3d}$; $—SO_2R^{2d}$; $—CF_3$; $—(CH_2)_{0-6}—OR^{2d}$; —OH, $—OC_{1-6}$alkyl, ,—O—$(CH_2)_{1-6}OR^{2d}$; —O—$(CH_2)_{1-6}$—C(═O)—O—R^{2d}; —O—$(CH_2)_{1-6}$—C(═O)—N(R^{2d}, R^{3d}); —N(R^{5a})—$(CH_2)_{1-6}$—OR^{2d}; —N(R^{5a})—$(CH_2)_{1-6}$—N(R^{2d},R^{3d}); —C(═O)—N(R^{2d},R^{3d}); —N(R^{5a})—$(CH_2)_{1-6}$—C(═O)—N(R^{2d},R^{3d}); —N(—$(CH_2)_{1-6}$—OR^{2d})$_2$; —N(R^{5a})—$(CH_2)_{1-6}$—OR^{2d}; —N(R^{5a})—C(═O)—R^{2d}; —N(R^{5a})—SO_2—R^{2d}; —$(CH_2)_{0-6}$—C(═O)—O—R^{2d}; —$(CH_2)_{0-6}$—C(═O)—N(R^{2d},R^{3d}); —$(CH_2)_{0-6}$—C(═NR) —N(R^{3d},R^{4d}); —$(CH_2)_{0-6}$—N(R^{5a})C(═NR^{2d})—N(R^{3d},R^{4c}); a —$(CH_2)_{0-6}$—N(R^{3d})C_{5-6} membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S, and a —$(CH_2)_{0-6}$-5-6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

[0061] R^{5a}, R^{2d}, R^{3d} and R^{4d} are each independently a member selected from the group consisting of:

[0062] H, C_{1-6}-alkyl and C_{1-6}-alkylaryl, —CN; $—NO_2$; carbocylic aryl, —CN; $—NO_2$; or

[0063] R^{2d} and R^{3d} taken together with the N atoms they are independently attached form a 5-7 membered saturated, partially unsaturated or aromatic heterocyclic ring; or

[0064] R^{3d} and R^{4d} taken together with the N atom to which they are attached form a 5-8 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

[0065] J is a direct link or is a member selected from the group consisting of:

[0066] —N(—R^9)—C(═O)—; —C(═O)—N(—R^9)—; —O—; —S—; —SO—; $—SO_2—$; $—CH_2—$; —N(—R^9)—; and —N(—R^9)—SO_2—;

[0067] R^9 is a member selected from the group consisting of:

[0068] H; —C_{1-4}-alkyl; —C_{0-4}-alkyl-carbocyclic aryl; —$(CH_2)_{0-4}$-5-6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S; —$(CH_2)_{1-6}$—C(═O)—O—C_{1-4}-alkyl; and —$(CH_2)_{1-6}$—C(═O)—N(R^{6a},R^{6b});

[0069] R^{6a} and R^{6b} are each a member independently selected from the group consisting of:

[0070] H and —C_{1-6}-alkyl;

[0071] X is a member selected from the group consisting of:

[0072] (a) phenyl substituted with 0-3 R^{1e} groups;

[0073] (b) naphthyl substituted with 0-3 R^{1e} groups and

[0074] (c) a 6-membered aromatic heterocyclic ring system containing 1-3 N atoms and having 0-3 ring atoms substituted with 0-3 R^{1e} groups; and

[0075] (d) an 8-10 membered fused aromatic heterocyclic bicyclic ring system containing 1-4 heteroatoms selected from N, O and S and 0-3 ring atoms of the fused heterocyclic bicyclic ring system are substituted with 0-3 R^{1e} groups;

[0076] R^{1e} is a member independently selected from the group consisting of:

[0077] Halo; CF_3; —C_{1-4}-alkyl; carbocyclic aryl; —C_{0-2}-alkyl-CN; —O—R^{2e}; —C_{0-2}-alkyl-C(═O)—O—R^{2e}; —C_{0-2}-alkyl-C(═O)—N(R^{2e}, R^{3e}); —C_{0-2}-alkyl-NO_2; —C_{0-2}-alkyl-N(R^{2e}, R^{3c}); —C_{0-2}-alkyl-SO_2—N(R^{2e}, R^{3e}); —C_{0-2}-alkyl-SO_2—R^{2e}; trihaloalkyl; —O—C_{0-2}-alkyl-O—R^{2e}; —C_{0-2}-alkyl-O—R^{2e}; —O—C_{1-4}-alkyl-C(═O)—N(R^{2e}, R^{3e}); —O—C_{1-4}-alkyl-C(═O)—O—R^{2e}; —C_{0-2}-alkyl-N(R^{2e})—C(═O)—R^{3e}; —C_{0-2}-alkyl-N(—R^{2e})—SO_2—R^{3e}; —CH_2—N(R^{2e})—C(═O)—R^{3e}; —CH_2—N(R^{2e})—SO_2—R^{3e}; —$(CH_2)_{0-6}$—N$R^{2e}R^{3e}$; —C(═O)—N(R^{2e},R^{3e}); —N(—$(CH_2)_{1-6}$—OR^{2e})$_2$; —N(R^{10})—$(CH_2)_{1-6}$—OR^{2e}; —N(R^{10})—C(═O)—R^{2e}; —N(R^{10})—SO_2—R^{2e}; —C(═N(R^{10}))—N(R^{2e},R^{3e}); and a —$(CH_2)_{0-6}$-5-6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

[0078] R^{10}, R^{2e} and R^{3e} are each independently a member selected from the group consisting of:

[0079] H; —C_{1-4}-alkyl; —CO_{0-2}-alkyl-O-R^{1g}; —C_{0-2} -alkyl-N(—R^{1g},—R^{2g});—C_{1-4}-alkyl-carbocyclic aryl; —C_{1-4}-alkyl-heterocyclic; and R^{10} and R^{2e}, or R^{2e} and R^{3e} together with the N atom to which they are attached can form 5-8 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S which can be substituted with 0-2 R^{1g} groups;

[0080] R^{1g} and R^{2g} are indepedently a member selected from the group of:

[0081] H; halo; —C_{1-4}-alkyl, a carbocyclic aryl group; a saturated, partially unsaturated or aromatic heterocyclic group; —CN; —C(═O)—N(R^{3g})R^{4g}; —C(═O)—OR^{3g}; $—NO_2$; —$(CH_2)_p$—N$R^{3g}R^{4g}$; —$SO_2NR^{3g}R^{4g}$; —SO_2R^{3g}; $—CF_3$; and —$(CH_2)_p$OR^{3g};

[0082] p is an integer of 0-2;

[0083] R^{3g} and R^{4g} are each independently selected from the group consisting of:

[0084] H; C_{1-4}-alkyl and —C_{0-4}-alkyl-carbocyclic aryl;

[0085] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0086] In certain aspects of this invention, compounds are provided which are useful as diagnostic reagents. In another aspect, the present invention includes pharmaceutical compositions comprising a pharmaceutically effective amount of the compounds of this invention and a pharmaceutically acceptable carrier. In yet another aspect, the present invention includes methods comprising using the above compounds and pharmaceutical compositions for preventing or treating disease states characterized by undesired thrombosis or disorders of the blood coagulation process in mammals, or for preventing coagulation in stored blood products and samples. Optionally, the methods of this invention comprise administering the pharmaceutical composition in combination with an additional therapeutic agent such as an antithrombotic and/or a thrombolytic agent and/or an anticoagulant.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0087] In accordance with the present invention and as used herein, the following terms are defined with the following meanings, unless explicitly stated otherwise.

[0088] The term "alkenyl" refers to a trivalent straight chain or branched chain unsaturated aliphatic radical. The term "alkinyl" (or "alkynyl") refers to a straight or branched chain aliphatic radical that includes at least two carbons joined by a triple bond. If no number of carbons is specified alkenyl and alkinyl each refer to radicals having from 2-12 carbon atoms.

[0089] The term "alkyl" refers to saturated aliphatic groups including straight-chain, branched-chain and cyclic groups having the number of carbon atoms specified, or if no number is specified, having up to 12 carbon atoms. The term "cycloalkyl" as used herein refers to a mono-, bi-, or tricyclic aliphatic ring having 3 to 14 carbon atoms and preferably 3 to 7 carbon atoms.

[0090] As used herein, the terms "carbocyclic ring structure" and "C_{3-16} carbocyclic mono, bicyclic or tricyclic ring structure" or the like are each intended to mean stable ring structures having only carbon atoms as ring atoms wherein the ring structure is a substituted or unsubstituted member selected from the group consisting of: a stable monocyclic ring which is aromatic ring ("aryl") having six ring atoms; a stable monocyclic non-aromatic ring having from 3 to 7 ring atoms in the ring; a stable bicyclic ring structure having a total of from 7 to 12 ring atoms in the two rings wherein the bicyclic ring structure is selected from the group consisting of ring structures in which both of the rings are aromatic, ring structures in which one of the rings is aromatic and ring structures in which both of the rings are non-aromatic; and a stable tricyclic ring structure having a total of from 10 to 16 atoms in the three rings wherein the tricyclic ring structure is selected from the group consisting of: ring structures in which three of the rings are aromatic, ring structures in which two of the rings are aromatic and ring structures in which three of the rings are non-aromatic. In each case, the non-aromatic rings when present in the monocyclic, bicyclic or tricyclic ring structure may independently be saturated, partially saturated or fully saturated. Examples of such carbocyclic ring structures include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctane, [4.3.0] bicyclononane, [4.4.0]bicyclodecane (decalin), 2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl (tetralin). Moreover, the ring structures described herein may be attached to one or more indicated pendant groups via any carbon atom which results in a stable structure. The term "substituted" as used in conjunction with carbocyclic ring structures means that hydrogen atoms attached to the ring carbon atoms of ring structures described herein may be substituted by one or more of the substituents indicated for that structure if such substitution(s) would result in a stable compound.

[0091] The term "aryl" which is included with the term "carbocyclic ring structure" refers to an unsubstituted or substituted aromatic ring, substituted with one, two or three substituents selected from loweralkoxy, loweralkyl, loweralkylamino, hydroxy, halogen, cyano, hydroxyl, mercapto, nitro, thioalkoxy, carboxaldehyde, carboxyl, carboalkoxy and carboxamide, including but not limited to carbocyclic aryl, heterocyclic aryl, and biaryl groups and the like, all of which may be optionally substituted. Preferred aryl groups include phenyl, halophenyl, loweralkylphenyl, napthyl, biphenyl, phenanthrenyl and naphthacenyl.

[0092] The term "arylalkyl" which is included with the term "carbocyclic aryl" refers to one, two, or three aryl groups having the number of carbon atoms designated, appended to an alkyl group having the number of carbon atoms designated. Suitable arylalkyl groups include, but are not limited to, benzyl, picolyl, naphthylmethyl, phenethyl, benzyhydryl, trityl, and the like, all of which may be optionally substituted.

[0093] As used herein, the term "heterocyclic ring" or "heterocyclic ring system" is intended to mean a substituted or unsubstituted member selected from the group consisting of stable monocyclic ring having from 5-7 members in the ring itself and having from 1 to 4 hetero ring atoms selected from the group consisting of N, O and S; a stable bicyclic ring structure having a total of from 7 to 12 atoms in the two rings wherein at least one of the two rings has from 1 to 4 hetero atoms selected from N, O and S, including bicyclic ring structures wherein any of the described stable monocyclic heterocyclic rings is fused to a hexane or benzene ring; and a stable tricyclic heterocyclic ring structure having a total of from 10 to 16 atoms in the three rings wherein at least one of the three rings has from 1 to 4 hetero atoms selected from the group consisting of N, O and S. Any nitrogen and sulfur atoms present in a heterocyclic ring of such a heterocyclic ring structure may be oxidized. Unless indicated otherwise the terms "heterocyclic ring" or "heterocyclic ring system" include aromatic rings, as well as non-aromatic rings which can be saturated, partially saturated or fully saturated non-aromatic rings. Also, unless

indicated otherwise the term "heterocyclic ring system" includes ring structures wherein all of the rings contain at least one hetero atom as well as structures having less than all of the rings in the ring structure containing at least one hetero atom, for example bicyclic ring structures wherein one ring is a benzene ring and one of the rings has one or more hetero atoms are included within the term "heterocyclic ring systems" as well as bicyclic ring structures wherein each of the two rings has at least one hetero atom. Moreover, the ring structures described herein may be attached to one or more indicated pendant groups via any hetero atom or carbon atom which results in a stable structure. Further, the term "substituted" means that one or more of the hydrogen atoms on the ring carbon atom(s) or nitrogen atom(s) of the each of the rings in the ring structures described herein may be replaced by one or more of the indicated substituents if such replacement(s) would result in a stable compound. Nitrogen atoms in a ring structure may be quaternized, but such compounds are specifically indicated or are included within the term "a pharmaceutically acceptable salt" for a particular compound. When the total number of O and S atoms in a single heterocyclic ring is greater than 1, it is preferred that such atoms not be adjacent to one another. Preferably, there are no more that 1 O or S ring atoms in the same ring of a given heterocyclic ring structure.

[**0094**] Examples of monocylic and bicyclic heterocylic ring systems, in alphabetical order, are acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl. benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalinyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1, 5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl (benzimidazolyl), isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyroazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pryidooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6H-1,2,5-thiadazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl. Preferred heterocyclic ring structures include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrrolidinyl, imidazolyl, indolyl, benzimidazolyl, 1H-indazolyl, oxazolinyl, or isatinoyl. Also included are fused ring and spiro compounds containing, for example, the above heterocylic ring structures.

[**0095**] As used herein the term "aromatic heterocyclic ring system" has essentially the same definition as for the monocyclic and bicyclic ring systems except that at least one ring of the ring system is an aromatic heterocyclic ring or the bicyclic ring has an aromatic or non-aromatic heterocyclic ring fused to an aromatic carbocyclic ring structure.

[**0096**] The terms "halo" or "halogen" as used herein refer to Cl, Br, F or I substituents. The term "haloalkyl", and the like, refer to an aliphatic carbon radicals having at least one hydrogen atom replaced by a Cl, Br, F or I atom, including mixtures of different halo atoms. Trihaloalkyl includes trifluoromethyl and the like as preferred radicals, for example.

[**0097**] The term "methylene" refers to —CH_2—.

[**0098**] The term "pharmaceutically acceptable salts" includes salts of compounds derived from the combination of a compound and an organic or inorganic acid. These compounds are useful in both free base and salt form. In practice, the use of the salt form amounts to use of the base form; both acid and base addition salts are within the scope of the present invention.

[**0099**] "Pharmaceutically acceptable acid addition salt" refers to salts retaining the biological effectiveness and properties of the free bases and which are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicyclic acid and the like.

[**0100**] "Pharmaceutically acceptable base addition salts" include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Particularly preferred are the ammonium, potassium, sodium, calcium and magnesium salts. Salts derived from pharmaceutically acceptable organic nontoxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-diethylaminoethanol, trimethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperizine, piperidine, N-ethylpiperidine, polyamine resins and the like. Particularly preferred organic nontoxic bases are isopropylamine, diethylamine, ethanolamine, trimethamine, dicyclohexylamine, choline, and caffeine.

[**0101**] "Biological property" for the purposes herein means an in vivo effector or antigenic function or activity that is directly or indirectly performed by a compound of this invention that are often shown by in vitro assays. Effector functions include receptor or ligand binding, any enzyme activity or enzyme modulatory activity, any carrier binding activity, any hormonal activity, any activity in promoting or inhibiting adhesion of cells to an extracellular matrix or cell surface molecules, or any structural role. Antigenic functions include possession of an epitope or antigenic site that is capable of reacting with antibodies raised against it.

[**0102**] In the compounds of this invention, carbon atoms bonded to four non-identical substituents are asymmetric. Accordingly, the compounds may exist as diastereoisomers,

enantiomers or mixtures thereof. The syntheses described herein may employ racemates, enantiomers or diastereomers as starting materials or intermediates. Diastereomeric products resulting from such syntheses may be separated by chromatographic or crystallization methods, or by other methods known in the art. Likewise, enantiomeric product mixtures may be separated using the same techniques or by other methods known in the art. Each of the asymmetric carbon atoms, when present in the compounds of this invention, may be in one of two configurations (R or S) and both are within the scope of the present invention.

Preferred Embodiments

[0103] The invention provides a compound according to the formula (I):

A-Q-D-E-G-J-X (I)

[0104] where:

[0105] A is selected from:

[0106] (a) C_1-C_6-alkyl;

[0107] (b) C_3-C_8-cycloalkyl;

[0108] (c) —N(R^1,R^2), N(R^1,R^2)—C(=NR^3)—, N(R^1,R^2)—C(=NR^3)—N(R^4)—, R^1—C(=NR^3)—, R^1—C(=NR^3)—N(R^4)—;

[0109] (d) phenyl, which is independently substituted with 0-2 R substitutuents;

[0110] (e) naphthyl, which is independently substituted with 0-2 R substitutuents; and

[0111] (f) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R substitutuents;

[0112] R is selected from:

[0113] H, halo, —CN, —CO_2R^1, —C(=O)—N(R^1, R^2), —$(CH_2)_m$—CO_2R^1, —$(CH_2)_m$—C(=O)—N(R^1, R^2), —NO_2, —$SO_2N(R^1, R^2)$, —SO_2R^1, —$(CH_2)_mNR^1R^2$, —$(CH_2)_m$—C(=NR^3)—R^1, —$(CH_2)_m$—C(=NR^3)—N(R^1, R^2), —$(CH_2)_m$—N(R^4)—C(=NR^3)—N(R^1, R^2), —$(CH_2)_mNR^1$—C_{3-6}heterocyclics, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, —CF_3, —OR^2, and a 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic system may be independently replaced with a member selected from the group consisting of halo, C_1-C_4-alkyl, CN—C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl and —NO_2;

[0114] m is an integer of 0-2;

[0115] R^1, R^2, R^3 and R^4 are independently selected from the group consisting of:

[0116] H, —OR^5, —N(—R^5, —R^6), —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —C_{0-4}alkylphenyl and —C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —CN, and —NO_2; or

[0117] R^1 and R^2, or R^2 and R^3 taken together can form a 3-8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C_1-C_4-alkyl, —CN —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl and —NO_2;

[0118] R^5 and R^6 are independently selected from the group consisting of:

[0119] H, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —C_{0-4}alkylphenyl and —C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —CN, and —NO_2; or

[0120] R^5 and R^6 taken together can form a 3-8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C_1-C_4-alkyl, —CN —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl and —NO_2;

[0121] Q is a member selected from the group consisting of:

[0122] a direct link, —CH_2—, —C(=O)—, —O—, —N(R^7)—, —N(R^7)CH_2—, —CH_2N(R^7)—, —C(=NR^7)—, —C(=O)—N(R^7)—, —N(R^7)—C(=O)—, —S—, —SO—, —SO_2—, —SO_2—N(R^7)— and —N(R^7)—SO_2—;

[0123] R^7 is selected from:

[0124] H, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{1-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —C_{0-4}alkylphenyl and —C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —CN, and —NO_2;

[0125] D is a direct link or is a member selected from the group consisting of:

[0126] (a) phenyl, which is independently substituted with 0-2 R^{1a} substitutuents;

[0127] (b) naphthyl, which is independently substituted with 0-2 R^{1a} substitutuents; and

[0128] (c) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be subsituted from 0-2 R^{1a} substitutuents;

[0129] R^{1a} is selected from:

[0130] halo, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —CN, —NO_2, —$(CH_2)_nNR^{2a}R^{3a}$, —$(CH_2)_nCO_2R^{2a}$, —$(CH_2)_nCONR^{2a}R^{3a}$, —$SO_2NR^{2a}R^{3a}$, —SO_2R^{2a}, —CF_3, —OR^{2a}, and a 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the aromatic heterocyclic system may be independently replaced with a member selected from the group consisting of halo, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —CN and —NO_2;

[0131] R^{2a} and R^{3a} are independently selected from the group consisting of:

[0132] H, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —C_{0-4}alkylphenyl and —C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —CN and —NO_2;

[0133] n is an integer of 0-2;

[0134] E is a direct link or a member selected from the group consisting of:

[0135] —C_{1-2}-alkyl-, —O—, —S—, —SO—, —SO_2—, —C_{0-1}-alkyl-C(=O)—, —C_{0-1}-alkyl-C(=O)—N(—R^8)—C_{0-1}-alkyl-, —C_{0-1}-alkyl-N(—R^8)—C(=O)—C_{0-1}-alkyl-, —N(—R^8)—C(=O)—N(—R^8)— and —C_{0-1}-alkyl-N(—R^8)—;

[0136] R^8 is a member selected from the group consisting of:

[0137] H; —C_{1-4}-alkyl; —C_{0-4}-alkylaryl; —C_{0-4}-alkyl-heteroaryl; —C_{1-4}-alkyl-C(=O)—OH, —C_{1-4} -alkyl-C(=O)—O—C_{1-4}-alkyl, and —C_{1-4}-alkyl-C(=O)—N(—R^{2b}, —R^3b);

[0138] R^{2b} and R^{3b} are each a member independently selected from the group consisting of:

[0139] H, —C_{1-4}-alkyl, —C_{0-4}-alkyl-aryl; —C_{0-4}-alkyl-heterocyclic group, and R^{2b} and R^{3b} together with the N atom to which they are attached can form a 5-8 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S, wherein the heterocyclic ring may be substituted with 0-2 R^{1c} groups;

[0140] R^{1c} is a member selected from the group consisting of:

[0141] Halo; —C_{1-4}-alkyl; —CN, —NO_2; —C(=O)—N(—R^{2c}, —R^{3c}); —C(=O)—OR^{2c};

[0142] —$(CH_2)_q$—N(—R^{2c}, —R^{3c}); —SO_2—N(—R^{2c}, —R^{3c}); —SO_2R^{2c}; —CF_3 and —$(CH_2)_q$—OR^{2c};

[0143] R^{2c} and R^{3c} are each independently a member selected from the group consisting of:

[0144] H; —C_{1-4}-alkyl and —C_{1-4}-alkyl-aryl;

[0145] q is an integer of 0-2;

[0146] G is a member selected from the group consisting of:

[0147] (a) C_2-alkenyl or C_{3-8}-cycloalkenyl, wherein the alkenyl and cycloalkenyl attachment points are the alkenyl carbon atoms and wherein C_2-alkenyl or C_{3-8}-cycloalkenyl are substituted with 0-4 R^{1d} groups;

[0148] (b) a phenylene group wherein the ring carbon atoms of the phenylene group are substituted with 0-4 R^{1d} groups;

[0149] (c) a 3-8 membered a saturated, partially unsaturated or aromatic monocyclic- heterocyclic ring system containing 1-4 heteroatoms selected from N, O and S, wherein 0-4 ring atoms of the heterocyclic ring may be substituted with 0-4 R^{1d} groups; and,

[0150] (d) an 8-10 membered fused heterocyclic bicyclic ring system, containing 1-4 heteroatoms selected from N, O and S, wherein 0-4 ring atoms of the fused bicyclic ring system may be substituted with 0-4 R^{1d} groups;

[0151] R^{1d} is a member selected from the group consisting of:

[0152] H, halo; C_{1-6}-alkyl, carbocylic aryl, —CN; —NO_2; —$(CH_2)_{0-6}$—$NR^{2d}R^{3d}$; —$SO_2NR^{2d}R^{3d}$; —SO_2R^{2d}; —CF_3; —$(CH_2)_{0-6}$—OR^{2d}; —OH, —OC_{1-6}alkyl , —O—$(CH_2)_{1-6}OR^{2d}$; —O—$(CH_2)_{1-6}$—C(=O)—O—R^{2d}; —O—$(CH_2)_{1-6}$—C(=O)—N(R^{2d},R^{3d}); —N(R^{5a})—$(CH_2)_{1-6}$—OR^{2d}; —N(R^{5a})—$(CH_2)_{1-6}$—N(R^{2d},R^{3d});—C(=O)—N(R^{2d},R^{3d}); —N(R^{5a})—$(CH_2)_{1-6}$—C(=O)—N(R^{2d},R^{3d}); —N(—$(CH_2)_{1-6}$—OR^{2d})$_2$; —N(R^{5a})—$(CH_2)_{1-6}$—OR^{2d}; —N(R^{5a})—C(=O)R^{2d}; —N(R^{5a})—SO_2—R^{2d}; —$(CH_2)_{0-6}$—C(=O)—O—R^{2d}; —$(CH_2)_{0-6}$—C(=O)—N(R^{2d},R^{3d}); —$(CH_2)_{0-6}$—C(=NR^{2d})—N(R^{3d},R^{4d}); —$(CH_2)_{0-6}$—N(R^{5a})C(=NR^{2d})—N(R^{3d},R^{4d}); and —$(CH_2)_{0-6}$—N(—R^{3d})— group attached directly by its nitrogen atom to a carbon atom of a 5 to 6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S, and a —$(CH_2)_{0-6}$— group attached to a 5-6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

[0153] R^{5a}, R^{2d}, R^{3d} and R^{4d} are each independently a member selected from the group consisting of:

[0154] H, C_{1-6}-alkyl and C_{1-6}-alkylaryl, —CN; —NO_2; carbocylic aryl, —CN; —NO_2; or

[0155] R^{2d} and R^{3d} taken together with the N atoms ther are independently attached form a 5-7 membered saturated, partially unsaturated or aromatic heterocyclic ring; or

[0156] R^{3d} and R^{4d} taken together with the N atom to which they are attached form a 5-8 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

[0157] J is a direct link or is a member selected from the group consisting of:

[0158] —N(—R^9)—C(=O)—; —C(=O)—N(—R^9)—; —O—; —S—; —SO—; —SO_2—; —CH_2—; —N(—R^9)—; and —N(—R^9)—SO_2—;

[0159] R^9 is a member selected from the group consisting of:

[0160] H; —C_{1-4}-alkyl; —C_{0-4}-alkyl-carbocyclic aryl; —$(CH_2)_{0-4}$-5-6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S; —$(CH_2)_{1-6}$—C(=O)—O—C_{1-4}-alkyl; and —$(CH_2)_{1-6}$—C(=O)—N(R^{6a},R^{6b});

[0161] R^{6a} and R^{6b} are each a member independently selected from the group consisting of:

[0162] H and —C_{1-6}-alkyl;

[0163] X is a member selected from the group consisting of:

[0164] (a) phenyl substituted with 0-3 R^{1e} groups;

[0165] (b) naphthyl substituted with 0-3 R^{1e} groups;

[0166] (c) a 6-membered aromatic heterocyclic ring system containing 1-3 N atoms and having 0-3 ring atoms substituted with 0-3 R^{1e} groups; and

[0167] (d) an 8-10 membered fused aromatic heterocyclic bicyclic ring system containing 1-4 heteroatoms selected from N, O and S and 0-3 ring atoms of the fused heterocyclic bicyclic ring system are substituted with 0-3 R^{1e} groups;

[0168] R^{1e} is a member independently selected from the group consisting of:

[0169] Halo; CF_3; —C_{1-4}-alkyl; carbocyclic aryl; —C_{0-2}-alkyl-CN; —O—R^{2e}; —C_{0-2}-alkyl-C(=O)—O—R^{2e}; —C_{0-2}-alkyl-C(=O)—N(R^{2e}, R^{3e}); —C_{0-2}-alkyl-NO_2: —C_{0-2}-alkyl-N(R^{2e}, R^{3e}); —C_{0-2}-alkyl-SO_2—N(R^{2e}, R^{3e}); —C_{0-2}-alkyl-SO_2—R^{2e}; trihaloalkyl; —O—C_{0-2}-alkyl-O—R^{2e}; —C_{0-2}-alkyl-O—R^{2e}; —O—C_{1-4}-alkyl-C(=O)—N(R^{2e}, R^{3e}); —O—C_{1-4}-alkyl-C(=O)—O—R^{2e}; —C_{0-2}-alkyl-N(R^{2e})—C(=O)—R^{3e}; —C_{0-2}alkyl-N(—R^{2e})—SO_2—R^{3e}; —CH_2—N(R^{2e})—C(=O)—R^{3e};—CH_2—N(R^{2e})—SO_2—R^{3e}; —$(CH_2)_{0-6}$—N$R^{2e}R^{3e}$; —C(=O)—N(R^{2e},R^{3e}); —N(—$(CH_2)_{1-6}$-$OR^{2e})_2$; —N(R^{10})—$(CH_2)_{1-6}$—OR^{2e};—N(R^{10})—C(=O)—R^{2e}; —N(R^{10})—SO_2—R^{2e}; —C(=N(R^{10}))—N(R^{2e},R^{3e}); and a —$(CH_2)_{0-6}$-5-6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

[0170] R^{10}, R^{2e}, and R^{3e} are each independently a member selected from the group consisting of:

[0171] H; —C_{1-4}-alkyl; —C_{0-2}-alkyl-O—R^{1g}; —C_{0-2} -alkyl-N(—R^{1g}, —R^{2g});—C_{1-4}-alkyl-carbocyclic aryl; —C_{1-4}-alkyl-heterocyclic; and R^{10} and R^{2e}, or R^{2e} and R^{3e} together with the N atom to which they are attached can form 5-8 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S which can be substituted with 0-2 R^{1g} groups;

[0172] R^{1g} and R^{2g} are indepedently a member selected from the group of:

[0173] H; halo; —C_{1-4}-alkyl, a carbocyclic aryl group ; a saturated, partially unsaturated or aromatic heterocyclic group; —CN; —C(=O)—N(R^{3g})R^{4g}; —C(=O)—OR^{3g}; —NO_2; —$(CH_2)_p$—N$R^{3g}R^{4g}$; —$SO_2N R^{3g}R^{4g}$; —SO_2R^{3g}; —CF_3; and —$(CH_2)_p OR^{3g}$;

[0174] p is an integer of 0-2; and

[0175] R^{3g} and R^{4g} are each independently selected from the group consisting of:

[0176] H; C_{1-4}-alkyl and —C_{0-4}-alkyl-carbocyclic aryl;

[0177] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0178] A preferred embodiment of formula I are compounds of formula (Ia):

A-Q-D-E-G-J-X (Ia)

[0179] where:

[0180] A is selected from:

[0181] (a) C_1-C_6-alkyl;

[0182] (b) C_3-C_8-cycloalkyl;

[0183] (c) —N(R^1,R^2), N(R^1,R^2)—C(=NR^3)—, N(R^1,R^2)—C(=NR^3)—N(R^4)—, R^1—C(=NR^3)—, R^1—C(=NR^3)—N(R^4)—;

[0184] (d) phenyl, which is independently substituted with 0-2 R substitutuents;

[0185] (e) naphthyl, which is independently substituted with 0-2 R substitutuents; and

[0186] (f) monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R substitutuents;

[0187] R is selected from:

[0188] H, halo, —CN, —CO_2R^1, —C(=O)—N(R^1, R^2), —$(CH_2)_m$—CO_2R^1, —$(CH_2)_m$—C(=O)—N(R^1, R^2), —NO_2, —$SO_2N(R^1, R^2)$, —SO_2R^1, —$(CH_2)_m NR^1R^2$, —$(CH_2)_m$—C(=NR^3)—R^1, —$(CH_2)_m$—C(=NR^3)—N(R^1,R^2), —$(CH_2)_m$—N(R^4)—C(=NR^3)—N(R^1,R^2), —$(CH_2)_m NR^1$— group attached to a 3-6 membered heterocylic ring having from 1 to 3 heteroatoms selected from the group consisting of N, O and S, —C_{1-4}alkyl, —C_{2-6}

alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —CF_3, —OR^2, and a 5-6 membered heterocyclic aromatic or partially saturated system, including imidazoline, containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic system may be independently replaced with a member selected from the group consisting of halo, -methyl, —C_2-C_4-alkyl, —CN, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl and —NO_2;

[0189] m is an integer of 0-2;

[0190] R^1, R^2, R^3 and R^4 are independently selected from the group consisting of:

[0191] H, —OR^5, —N(—R^5, —R^6), —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —C_{0-4}alkylphenyl and —C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8} cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —CN, and —NO_2; or

[0192] R^1 and R^2, or R^2 and R^3 taken together can form a 3-8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C_1-C_4-alkyl, —CN —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl and —NO_2;

[0193] R^5 and R^6 are independently selected from the group consisting of:

[0194] H, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —C_{0-4}alkylphenyl and —C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —CN, and —NO_2; or

[0195] R^5 and R^6 taken together can form a 3-8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C_1-C_4-alkyl, —CN —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl and —NO_2;

[0196] Q is a member selected from the group consisting of:

[0197] a direct link, —CH_2—, —C(=O)—, —O—, —NH—, —NMe—, —$NHCH_2$—, —$NMeCH_2$—, —CH_2NH—, —C(=NH)—, —C(=O)—NH—, —NH—C(=O)—, —CH_2NMe—, —C(=NMe)—;

[0198] D is a direct link or is a member selected from the group consisting of:

[0199] (a) phenyl, which is independently substituted with 0-2 R^{1a} substitutuents;

[0200] (b) naphthyl, which is independently substituted with 0-2 R^{1a} substitutuents; and

[0201] a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be subsituted from 0-2 R^{1a} substitutuents;

[0202] R^{1a} is selected from:

[0203] halo, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —CN, —NO_2, —$(CH_2)_nNR^{2a}R^{3a}$, —$(CH_2)_nCO_2R^{2a}$, —$(CH_2)_nCONR^{2a}R^{3a}$, —$SO_2NR^{2a}R^{3a}$, —SO_2R^{2a}, —CF_3, —OR^{2a}, and a 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the aromatic heterocyclic system may be independently replaced with a member selected from the group consisting of halo, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —CN and —NO_2,

[0204] R^{2a} and R^{3a} are independently selected from the group consisting of:

[0205] H, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —C_{0-4} alkylphenyl and —C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4} alkylC_{3-8}cycloalkyl, —CN and —NO_2;

[0206] n is an integer of 0-2;

[0207] E is a member selected from the group consisting of:

[0208] a direct link, —O—, —NH—, —CH_2NH—, —$NHCH_2$—, —NMe—, —NH—C(=O)—NH—, —C(=O)—NH—, —NH—C(=O)—;

[0209] G is a member selected from the group consisting of:

[0210] (a) a C_2-alkenyl group or a C_{3-8}-cycloalkenyl group, wherein the alkenyl group and cycloalkenyl group attachment points are the alkenyl carbon atoms and wherein the C_2-alkenyl group or C_{3-8}-cycloalkenyl group is substituted with 0-4 R^{1d} groups;

[0211] (b) a phenylene group wherein the ring carbon atoms of the phenylene group are substituted with 0-4 R^{1d} groups;

[0212] (c) a 3-8 membered a saturated, partially unsaturated or aromatic monocyclic- heterocyclic ring system containing 1-4 heteroatoms selected from N, O and S, wherein 0-4 ring atoms of the heterocyclic ring may be substituted with 0-4 R^{1d} groups; and,

[0213] (d) an 8-10 membered fused heterocyclic bicyclic ring system, containing 1-4 heteroatoms selected from N, O and S, wherein 0-4 ring atoms of the fused bicyclic ring system may be substituted with 0-4 R^{1d} groups;

[0214] R^{1d} is a member selected from the group consisting of:

[0215] H, halo; C_{1-6}-alkyl, carbocylic aryl, —CN; —NO_2; —$(CH_2)_{0-6}$—$NR^{2d}R^{3d}$; —$SO_2NR^{2d}R^{3d}$; —SO_2R^{2d}; —CF_3; —$(CH_2)_{0-6}$—OR^{2d}; —OH, —OC_{1-6}alkyl, —O—$(CH_2)_{1-6}OR^{2d}$; —O—$(CH_2)_{1-6}$—C(═O)—O—R^{2d}; —O—$(CH_2)_{1-6}$—C(═O)—$N(R^{2d},R^{3d})$; —$N(R^{5a})$—$(CH_2)_{1-6}$—OR^{2d}; —$N(R^{5a})$—$(CH_2)_{1-6}$—$N(R^{2d},R^{3d})$; —C(═O)—$N(R^{2d},R^{3d})$; —$N(R^{5a})$—$(CH_2)_{1-6}$—C(═O)—$N(R^{2d},R^{3d})$; —N(—$(CH_2)_{1-6}$—$OR^{2d})_2$; —$N(R^{5a})$—$(CH_2)_{1-6}OR^{2d}$; —$N(R^{5a})$—C(═O)—R^{2d}; —$N(R^{5a})$—SO_2—R^{2d}; —$(CH_2)_{0-6}$—C(═O)—O—R^{2d}; —$(CH_2)_{0-6}$—C(═O)—$N(R^{2d},R^{3d})$; —$(CH_2)_{0-6}$—C(═NR^{2d})—$N(R^{3d},R^{4d})$; —$(CH_2)_{0-6}$—$N(R^{5a})$C(═NR^{2d})—$N(R^{3d},R^{4d})$; and a —$(CH_2)_{0-6}$—$N(R^{3d})$ group wich is attached via the nitrogen atom to a carbon atom of a 5 to 6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S, and a —$(CH_2)_{0-6}$- group attached to a 5-6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

[0216] R^{5a}, R^{2d}, R^{3d} and R^{4d} are each independently a member selected from the group consisting of:

[0217] H, C_{1-6}-alkyl and C_{1-6}-alkylaryl, —CN; —NO_2; carbocylic aryl, —CN; —NO_2; or

[0218] R^{2d} and R^{3d} taken together with the N atoms ther are independently attached form a 5-7 membered saturated, partially unsaturated or aromatic heterocyclic ring; or

[0219] R^{3d} and R^{4d} taken together with the N atom to which they are attached form a 5-8 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

[0220] J is a member selected from the group consisting of:

[0221] a direct link, —O—, —NH—, —NMe—, —C(═O)—NH—, —NH—C(═O)—;

[0222] X is a member selected from the group consisting of:

[0223] (a) phenyl substituted with 0-3 R^{1e} groups;

[0224] (b) naphthyl substituted with 0-3 R^{1e} groups and

[0225] (c) a 6-membered aromatic heterocyclic ring system containing 1-3 N atoms and having 0-3 ring atoms substituted with 0-3 R^{1e} groups; and

[0226] (d) an 8-10 membered fused aromatic heterocyclic bicyclic ring system containing 1-4 heteroatoms selected from N, O and S and 0-3 ring atoms of the fused heterocyclic bicyclic ring system are substituted with 0-3 R^{1e} groups;

[0227] R^{1e} is a member independently selected from the group consisting of:

[0228] Halo; CF_3; —C_{1-4}-alkyl; carbocyclic aryl; —CO_{0-2}-alkyl-CN; —O—R^{2e}; —CO_{0-2}-alkyl-C(═O)—O—R^{2e}; —C_{0-2}-alkyl-C(═O)—$N(R^{2e},R^{3e})$; —C_{0-2}-alkyl-NO_2; —C_{0-2}-alkyl-$N(R^{2e},R^{3e})$; —C_{0-2}-alkyl-SO_2—$N(R^{2e},R^{3e})$; —C_{0-2}-alkyl-SO_2—R^{2e}; trihaloalkyl; —O—C_{0-2}-alkyl-O—R^{2e}; —C_{0-2}-alkyl-O—R^{2e}; —O—C_{1-4}-alkyl-C(═O)—$N(R^{2e},R^{3e})$; —O—C_{1-4}-alkyl-C(═O)—O—R^{2e}; —C_{0-2}-alkyl-$N(R^{2e})$—C(═O)—R^{3e}; —C_{0-2}-alkyl-N(—R^{2e})—SO_2—R^{3e}; —CH_2—$N(R^{2e})$—C(═O)—R^{3e};—CH_2—$N(R^{2e})$—SO_2—R^{3e}; —$(CH_2)_{0-6}$—$NR^{2e}R^{3e}$; —C(═O)—$N(R^{2e},R^{3e})$; —N(—$(CH_2)_{1-6}$—$OR^{2e})_2$; —$N(R^{10})$—$(CH_2)_{1-6}$-OR^{2e}; —$N(R^{10})$—C(═O)—R^{2e}; —$N(R^{10})$—SO_2—R^{2e}; —C(═$N(R^{10})$)—$N(R^{2e},R^{3e})$; and a —$(CH_2)_{0-6}$-5-6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

[0229] R^{10}, R^{2e} and R^{3e} are each independently a member selected from the group consisting of:

[0230] H; —C_{1-4}-alkyl; —C_{0-2}-alkyl-O—R^{1g}; —C_{0-2} -alkyl-N(—R^{1g}, —R^{2g});—C_{1-4}-alkyl-carbocyclic aryl; —C_{1-4}-alkyl-heterocyclic; and R^{10} and R^{2e}, or R^{2e} and R^{3e} together with the N atom to which they are attached can form 5-8 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S which can be substituted with 0-2 R groups;

[0231] R^{1g} and R^{2g} are indepedently a member selected from the group of:

[0232] H; halo; —C_{1-4}-alkyl, a carbocyclic aryl group; a saturated, partially unsaturated or aromatic heterocyclic group. —CN; —C(═O)—$N(R^{3g},R^{4g})$; —C(═O)—OR^{3g}; —NO_2; —$(CH_2)_p$—$NR^{3g}R^{4g}$; —$SO_2NR^{3g}R^{4g}$; —SO_2R^{3g}, —CF_3; and —$(CH_2)_pOR^{3g}$;

[0233] p is an integer of 0-2; and

[0234] R^{3g} and R^{4g} are each independently selected from the group consisting of:

[0235] H; C_{1-4}-alkyl and —C_{0-4}-alkyl-carbocyclic aryl;

[0236] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0237] Another preferred embodiment of formula I are compounds of formula (Ib):

A-Q-D-E-G-J-X (Ib)

[0238] where:

[0239] A is selected from:

[0240] (a) C_1-C_6-alkyl;

[0241] (b) C_3-C_8-cycloalkyl;

[0242] (c) —$N(R^1,R^2)$, $N(R^1,R^2)$—$C(=NR^3)$—, $N(R^1,R^2)$—$C(=NR^3)$—$N(R^4)$—, R^1—$C(=NR^3)$—, R^1—$C(=NR^3)$—$N(R^4)$—;

[0243] (d) phenyl, which is independently substituted with 0-2 R substitutuents;

[0244] (e) naphthyl, which is independently substituted with 0-2 R substitutuents;

[0245] (f) a monocyclic or fused bicyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R substitutuents;

[0246] R is selected from:

[0247] H, halo, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6} alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —CF_3, —CN, —$(CH_2)_m$—CO_2R^1, —$(CH_2)_m$—$C(=O)$—$N(R^1, R^2)$, —$(CH_2)_m$—$C(=S)$—$N(R^1, R^2)$, —NO_2, —$(CH_2)_m$—$SO_2N(R^1, R^2)$, —$(CH_2)_m$—SO_2R^1, —$(CH_2)_m$$NR^1R^2$, $(CH_2)_mOR^1$, —$(CH_2)_m$—$C(=NR^3)$—R^1, —$(CH_2)_m$—$C(=NR^3)$—$N(R^1,R^2)$, $(CH_2)_m$—$N(R^4)$—$C(=NR^3)$—$N(R^1,R^2)$, and a 3-8 membered cyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C_1-C_4-alkyl, —CN —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8} cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl and —NO_2;

[0248] m is an integer of 0-2;

[0249] R^1, R^2, R^3 and R^4 are independently selected from the group consisting of:

[0250] H, —$(CH_2)_{0-4}OR^5$, —$(CH_2)_{0-4}$—CO_2R^5, —$(CH_2)_{0-4}N(—R^5, —R^6)$, —$C_{1-4}$alkyl, —$C_{2-6}$alkenyl, —$C_{2-6}$alkynyl, —$C_{3-8}$cycloalkyl, —$C_{0-4}$ alkylC_{3-8}cycloalkyl, —C_{0-4}alkylaryl and —C_{0-4} alkylheteroaryl, and a 3-8 membered cyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C_1-C_4-alkyl, —CN —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl and —NO_2; or

[0251] R^1 and R^2, or R^2 and R^3 taken together can form a 3-8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1-4 heteroatoms selected from N, O and S, where the hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C_1-C_4-alkyl, —CN, —CO_2R^5, —OH —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8} cycloalkyl and —NO_2;

[0252] R^5 and R^6 are independently selected from the group consisting of:

[0253] H, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —C_{0-4}alkylaryl and —C_{0-4}alkylheteroaryl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8} cycloalkyl, —CN, and —NO_2; or

[0254] R^5 and R^6 taken together can form a 3-8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with I to 2 rings being in the ring system and contain from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, —C_1-C_4-alkyl, —CN —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8} cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl and —NO_2;

[0255] Q is a member selected from the group consisting of:

[0256] a direct link, —CH_2—, —$C(=O)$—, —O—, —$N(R^7)$—, —$N(R^7)CH_2$—, —$CH_2N(R^7)$—, —$C(=NR^7)$—, —$C(=O)$—$N(R^7)$—, —$N(R^7)$—$C(=O)$—, —S—, —SO—, SO_2—, —SO_2—$N(R^7)$— and —$N(R^7)$—SO_2—; preferably, Q is a member selected from the group consisting of: a direct link, —CH_2—, —$C(=O)$—, —O—, —NH—, —NMe—, —$NHCH_2$—, —$NMeCH_2$—, —CH_2NH—, —$C(=NH)$—, —$C(=O)$—NH—, —NH—$C(=O)$—, —CH_2NMe—, —$C(=NMe)$—;

[0257] R^7 is selected from:

[0258] H; —C_{1-4}-alkyl; —C_{0-4}-alkylaryl; —C_{0-4}-alkyl-heteroaryl; —C_{1-4}-alkyl-O—C_{1-4}-alkyl, —C_{1-4} -alkyl-N(—C_{1-4}-alkyl, —C_{1-4}-alkyl); —C_{1-4} -alkyl-$C(=O)$—O—C_{1-4}-alkyl, and —C_{1-4}-alkyl-$C(=O)$—N(—C_{1-4}-alkyl, —C_{1-4}-alkyl);

[0259] D is a direct link or is a member selected from the group consisting of:

[0260] (a) phenyl, which is independently substituted with 0-2 R^{1a} substitutuents;

[0261] (b) naphthyl, which is independently substituted with 0-2 R^{1a} substitutuents; and

[0262] (c) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be subsituted from 0-2 R^{1a} substitutuents;

[0263] R^{1a} is selected from:

[0264] halo, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl,

—CN, —NO_2, —$(CH_2)_nOR^{2a}$, —$(CH_2)_nNR^{2a}R^{3a}$, —$(CH_2)_nCO_2R^{2a}$, —$(CH_2)_nCONR^{2a}R^{3a}$, —$SO_2NR^{2a}R^{3a}$, —SO_2R^{2a}, —CF_3, and a 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the aromatic heterocyclic system may be independently replaced with a member selected from the group consisting of halo, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —CN and —NO_2.

[0265] R^{2a} and R^{3a} are independently selected from the group consisting of:

[0266] H, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —C_{0-4}alkylaryl and —C_{0-4}alkylheteroaryl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —CN and —NO_2;

[0267] n is an integer of 0-2;

[0268] E is a direct link or a member selected from the group consisting of:

[0269] —C_{1-2}-alkyl-, —S—, —SO—, —SO_2—, —O—C_{0-1}-alkyl-, —C_{0-1}-alkyl-O—, —C_{0-1}-alkyl-N(—R^8)—, —N(—R^8)—C_{0-1}-alkyl-, —C_{0-1}-alkyl-C(=O)—N(—R^8)—C_{0-1}-alkyl, —C_{0-1}-alkyl-N(—R^8)—C(=O)—C_{0-1}-alkyl-, and -C_{0-1}-alkyl-N(—R^8)—C(=O)—N(—R^8)—C_{0-1}-alkyl-; preferably, E is a member selected from the group consisting of: a direct link, —O—, —NH—, —CH_2NH—, —$NHCH_2$—, —CH_2O—, —OCH_2—, —NMe—, —NH—C(=O)—NH—, —CH_2—NH—C(=O)—NH—,—C(=O)—NH—, —NH—C(=O)—, —C(=O)—NMe—, —NMe—C(=O)—;

[0270] R^8 is a member selected from the group consisting of:

[0271] H; —C_{1-4}-alkyl; —C_{0-4}-alkylaryl; —C_{0-4}-alkyl-heteroaryl; —C_{1-4}-alkyl-OR^{2b}, —C_{1-4}-alkyl-N(—R^{2b}, —R^{3b}); —C_{1-4}-alkyl-C(=O)—OR^{2b}; —C_{1-4}-alkyl-C(=O)—N(—R^{2b}, —R^{3b}); —C_{0-4}-alkyl-C(=O)—R^{2b}; and —C_{0-4}-alkyl-SO_2—R^{2b};

[0272] R^{2b} and R^{3b} are each a member independently selected from the group consisting of:

[0273] H, —C_{1-4}-alkyl, —C_{1-4}-alkyl-CO_2—C_{0-4}-alkyl, —C_{0-4}-alkyl-aryl; —C_{0-4}-alkyl-heterocyclic group, and R^{2b} and R^{3b} together with the N atom to which they are attached can form a 5-8 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S, wherein the heterocyclic ring may be substituted with 0-2 R^{1c} groups;

[0274] R^{1c} is a member selected from the group consisting of:

[0275] Halo; —C_{1-4}-alkyl; —CN, —NO_2; —C(=O)—N(—R^{2c}, —R^{3c}); —C(=O)—OR^{2c};

[0276] —$(CH_2)_q$—N(—R^{2c}, R^{3c}); —SO_2—N(—R^{2c}, —R^{3c}); —SO_2R^{2c}; —CF_3 and —$(CH_2)_q$—OR^{2c};

[0277] R^{2c} and R^{3c} are each independently a member selected from the group consisting of:

[0278] H; —C_{1-4}-alkyl and —C_{1-4}-alkyl-aryl;

[0279] q is an integer of 0-2;

[0280] G is a member selected from the group consisting of:

[0281] (a) C_2-alkenyl or C_{3-8}-cycloalkenyl, wherein the alkenyl and cycloalkenyl attachment points are the alkenyl carbon atoms and wherein the —C_2-alkenyl or —C_{3-8}-cycloalkenyl are substituted with 0-4 R^{1d} groups;

[0282] (b) a phenylene group wherein the ring carbon atoms of the phenylene group are substituted with 0-4 R^{1d} groups;

[0283] (c) a 3-8 membered a saturated, partially unsaturated or aromatic monocyclic ring system containing 1-4 heteroatoms selected from N, O and S, wherein 0-2 ring atoms of the heterocyclic ring may be substituted with 0-4 R^{1d} groups; and,

[0284] (d) an 8-10 membered fused cyclic system, containing 0-4 heteroatoms selected from N, O and S, wherein 0-2 ring atoms of the fused bicyclic ring system may be substituted with 0-4 R^{1d} groups;

[0285] R^{1d} a member selected from the group consisting of:

[0286] H, halo; —CF_3; —OCF_3, —OCF_2H, —$OCFH_2$, —OCH_2CF_3, —OCF_2CF_3, C_{1-6}-alkyl, carbocylic aryl, —CN; —NO_2; —$(CH_2)_{0-6}$—$NR^{2d}R^{3d}$; —$(CH_2)_{0-6}$—OR^{2d}; —OH, —OC_{1-6}alkyl, —O—$(CH_2)_{1-6}OR^{2d}$; —O—$(CH_2)_{1-6}$—$NR^{2d}R^{3d}$; —$N(R^{5a})$—$(CH_2)_{1-6}$—OR^{2d}; —$N(R^{5a})$—$(CH_2)_{1-6}$—$N(R^{2d},R^{3d})$; —$(CH_2)_{0-6}$—C(=O)—O—R^{2d}; —$(CH_2)_{0-6}$—C(=O)—$N(R^{2d},R^{3d})$; —O—$(CH_2)_{1-6}$—C(=O)—O—R^{2d}; —O—$(CH_2)_{1-6}$—C(=O)—$N(R^{2d},R^{3d})$; —$N(R^{5a})$—$(CH_2)_{1-6}$—C(=O)—O—R^{2d}; —$N(R^{5a})$—$(CH_2)_{1-6}$—C(=O)—$N(R^{2d},R^{3d})$; —N(—$(CH_2)_{1-6}$—OR^{2d})$_2$; —N(—$(CH_2)_{1-6}$—$N(R^{2d},R^{3d})$)$_2$; —$(CH_2)_{0-6}$—$SO_2NR^{2d}R^{3d}$; —$(CH_2)_{0-6}$—SO_2R^{2d}; —$(CH_2)_{0-6}$—$N(R^{5a})$—C(=O)—R^{2d}; —$(CH_2)_{0-6}$—$N(R^{5a})$—SO_2—R^{2d}, —$(CH_2)_{0-6}$—C(=NR^{2d})—$N(R^{3d},R^{4d})$; —$(CH_2)_{0-6}$—$N(R^{5a})$C(=NR^{2d})—$N(R^{3d},R^{4d})$; —$(CH_2)_{0-6}$—$N(R^{5a})$C(=NR^{2d})—R^{4d}; —O—$(CH_2)_{1-6}$—$SO_2NR^{2d}R^{3d}$; —O—$(CH_2)_{1-6}$—SO_2R^{2d}; —O—$(CH_2)_{1-6}$—$N(R^{5a})$—C(=O)—R^{2d}; —O—$(CH_2)_{1-6}$—$N(R^{5a})$—SO_2—R^{2d}, —O—$(CH_2)_{1-6}$—C(=NR^{2d})—$N(R^{3d},R^{4d})$; —O—$(CH_2)_{1-6}$—$N(R^{5a})$C(=NR^{2d})—$N(R^{3d}.R^{4d})$;—O—$(CH_2)_{1-6}$—$N(R^{5a})$C(=NR^{2d})—R^{4d}; —$N(R^{5d})$—$(CH_2)_{1-6}$—$SO_2NR^{2d}R^{3d}$; —$N(R^{5d})$—$(CH_2)_{1-6}$—SO_2R^{2d}; —$N(R^{5d})$—$(CH_2)_{1-6}$—$N(R^{5a})$—C(=O)—R^{2d}; —$N(R^{5d})$—$(CH_2)_{1-6}$—$N(R^{5a})$—SO_2—R^{2d}, —$N(R^{5d})$—$(CH_2)_{1-6}$—C(=NR^{2d})—$N(R^{3d},R^{4d})$; —$N(R^{5d})$—$(CH_2)_{1-6}$—$N(R^{5a})$C(=NR^{2d})—$N(R^{3d},R^{4d})$; —$N(R^{5d})$—$(CH_2)_{1-6}$—$N(R^{5a})$C(=NR^{2d})—R^{4d}; and a 3-8 membered cyclic system containing from 1-4

heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C_1-C_4-alkyl, —CN —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl and —NO_2;

[0287] R^{5a}, R^{2d}, R^{3d}, R^{4d} and R^{5d} are each independently a member selected from the group consisting of:

[0288] H, C_{1-6}-alkyl and C_{1-6}-alkylaryl, —CN; —NO_2; or

[0289] R^{2d} and R^{3d}, or R^{3d} and R^{4d} taken together with the N atoms they are independently attached form a 3-8 membered saturated, partially unsaturated or aromatic heterocyclic ring;

[0290] J is a direct link or is a member selected from the group consisting of:

[0291] —N(—R^9)—C(=O)—; —C(=O)—N(—R^9)—; —O—; —S—; —SO—; —SO2N(R9)—CH_2—; —N(—R^9)—; and —N(—R^9)—SO_2—; preferably, J is a member selected from the group consisting of: a direct link, —O—, —SO2—, —SO2NH—, —NH—, —NMe—, —C(=O)—NH—, —NH—C(=O)—;

[0292] R^9 is a member selected from the group consisting of:

[0293] H; —C_{1-4}-alkyl; —C_{0-4}-alkylaryl; —C_{0-4}-alkyl-heteroaryl; —C_{1-4}-alkyl-OR^{6a}, —C_{1-4}-alkyl-N(—R^{6a}, —R^{6b}); —C_{1-4}-alkyl-C(=O)—OR^{6a}, and —C_{1-4}-alkyl-C(=O)—N(—R^{6a}, —R^{6b};

[0294] R^{6a} and R^{6b} are each a member independently selected from the group consisting of:

[0295] H and —C_{1-6}-alkyl;

[0296] X is a member selected from the group consisting of:

[0297] (a) phenyl substituted with 0-3 R^{1e} groups;

[0298] (b) naphthyl substituted with 0-3 R^{1e} groups and

[0299] (c) a 6-membered aromatic heterocyclic ring system containing 1-3 N atoms and having 0-3 ring atoms substituted with 0-3 R^{1e} groups; and

[0300] (d) an 8-10 membered fused bicyclic ring system containing 1-4 heteroatoms selected from N, O and S and 0-3 ring atoms of the fused heterocyclic bicyclic ring system are substituted with 0-3 R^{1e} groups;

[0301] R^{1e} is a member independently selected from the group consisting of:

[0302] Halo; CF_3; —C_{1-4}-alkyl; carbocyclic aryl; —C_{0-2}-alkyl-CN; —O—R^{2e}; —C_{0-2}-alkyl-C(=O)—O—R^{2e}; —C_{0-2}- alkyl-C(=O)—N(R^{2e}, R^{3e}); —C_{0-2}-alkyl-NO_2; —C_{0-2}-alkyl-N(R^{2e}, R^{3e}); —C_{0-2}-alkyl-SO_2—N(R^{2e}, R^{3e}); —C_{0-2}-alkyl-SO_2—R^{2e}; trihaloalkyl; —O—C_{0-2}-alkyl-O—R^{2e}; —C_{0-2}-alkyl-O—R^{2e}; —O—C_{1-4}-alkyl-C(=O)—N(R^{2e}, R^{3e}); —O—C_{1-4}-alkyl-C(=O)—O—R^{2e}; —C_{0-2}-alkyl-N(R^{2e})—C(=O)—R^{3e}; —C_{0-2}-alkyl-N(—R^{2e})—SO_2—R^{3e}; —CH_2—N(R^{2e})—C(=O)—R^{3e};—CH_2—N(R^{2e})—SO_2—R^{3e}; —$(CH_2)_{0-6}$—$NR^{2e}R^{3e}$; —C(=O)—N(R^{2e},R^{3e}); —N(—$(CH_2)_{1-6}$—OR^{2e})$_2$; —N(R^{10})—$(CH_2)_{1-6}$—OR^{2e}; —N(R^{10})—C(=O)—R^{2e}; —N(R^{10})—SO_2—R^{2e}; —C(=N(R^{10}))—N(R^{2e},R^{3e}); and a —$(CH_2)_{0-6}$-5-6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

[0303] R^{10}, R^{2e} and R^{3e} are each independently a member selected from the group consisting of:

[0304] H; —C_{1-4}-alkyl; —C_{0-2}-alkyl-O—R^{1g}; —C_{0-2}-alkyl-N(—R^{1g}, —R^{2g});—C_{1-4}-alkyl-carbocyclic aryl; —C_{1-4}-alkyl-heterocyclic; and R^{10} and R^{2e} or R^{2e} and R^{3e} together with the N atom to which they are attached can form 5-8 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S which can be substituted with 0-2 R^{1g} groups;

[0305] R^{1g} and R^{2g} are indepedently a member selected from the group of:

[0306] H; halo; —C_{1-4}-alkyl, a carbocyclic aryl group; a saturated, partially unsaturated or aromatic heterocyclic group; —CN; —C(=O)—N(R^{3g})R^{4g}; —C(=O)—OR^{3g}; —NO_2; —$(CH_2)_p$—$NR^{3g}R^{4g}$; —$SO_2NR^{3g}R^{4g}$; —SO_2R^{3g}; —CF_3; and —$(CH_2)_pOR^{3g}$;

[0307] p is an integer of 0-2;

[0308] R^{3g} and R^{4g} are each independently selected from the group consisting of:

[0309] H; C_{1-4}-alkyl and —C_{0-4}-alkyl-carbocyclic aryl;

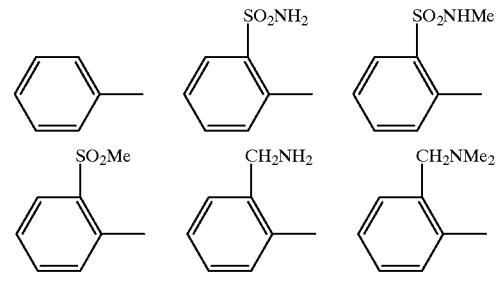
[0310] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0311] Another preferred embodiment of formula I are compounds of formula (Ic):

A-Q-D-E-G-J-X (Ic)

[0312] where:

[0313] A is a member selected from the group consisting of:



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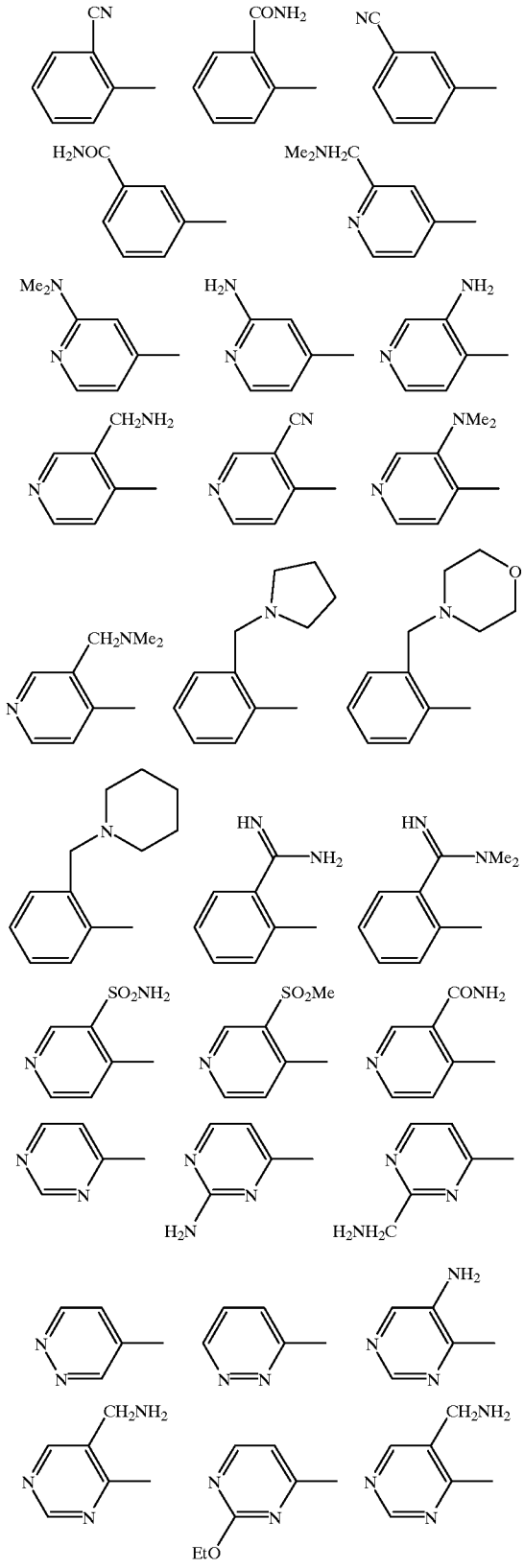

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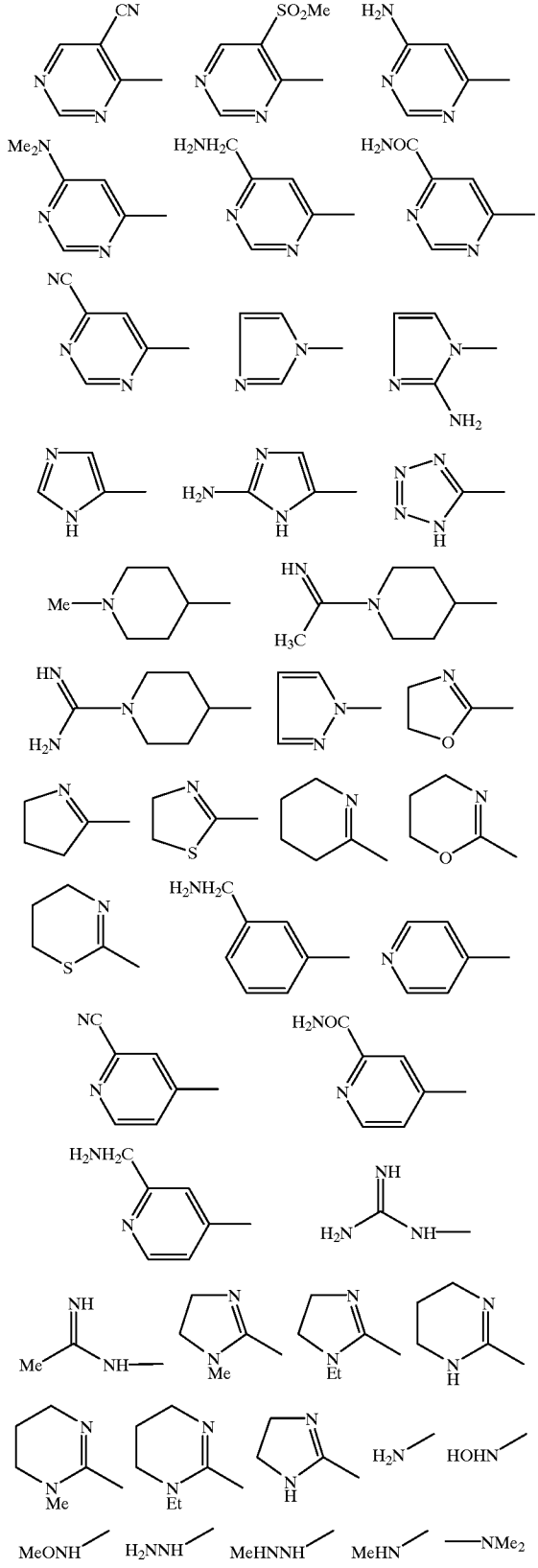

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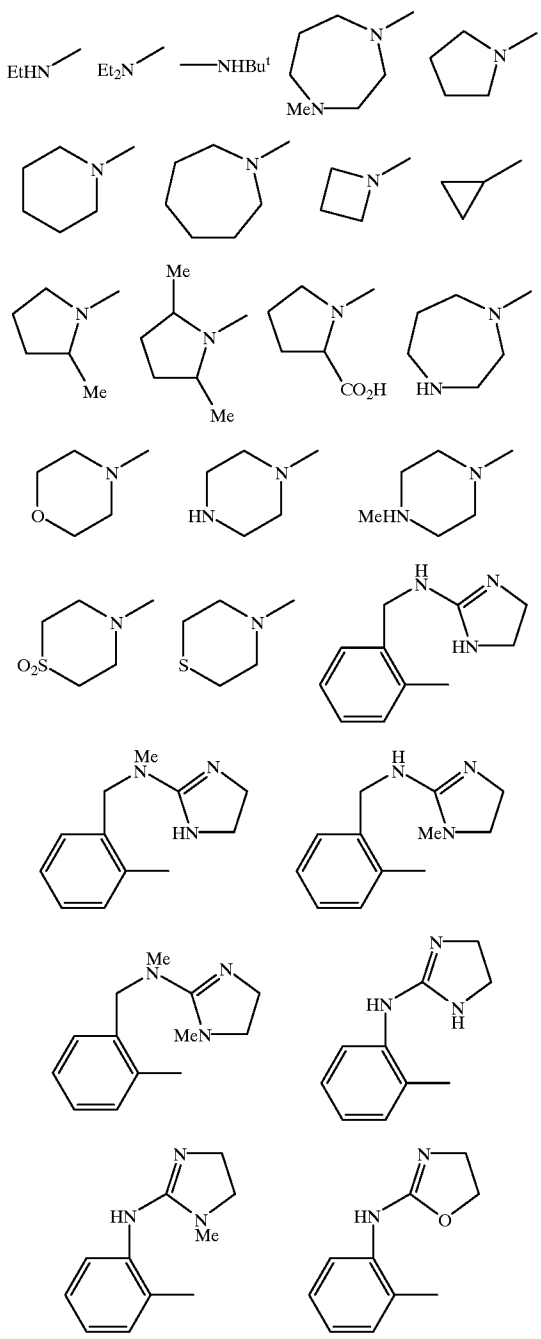
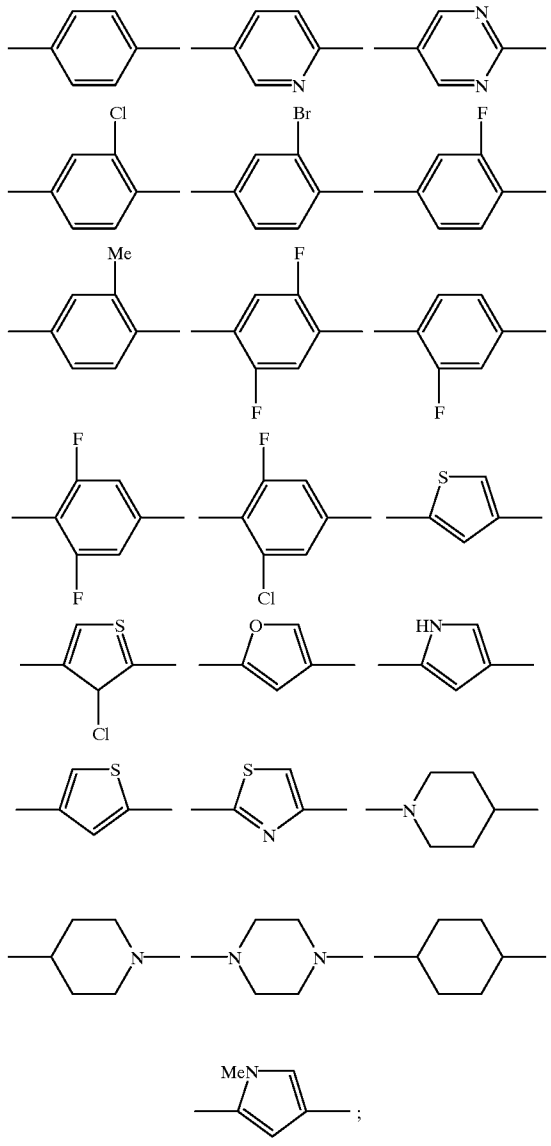


[0314] Q is a member selected from the group consisting of:

[0315] a direct link, —C(═O)—, —NH—, —NMe—, —NHCH$_2$—, —NMeCH$_2$—, —C(═NH)—, —C(═NMe)—;

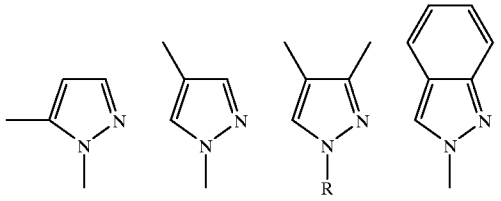
[0316] D is a direct link or is a member selected from the group consisting of:



[0317] E is a member selected from the group consisting of:

[0318] a direct link, —CH$_2$NH—, —C(═O)—NH—, —NH—C(═O)—;

[0319] G is a member selected from the group consisting of:



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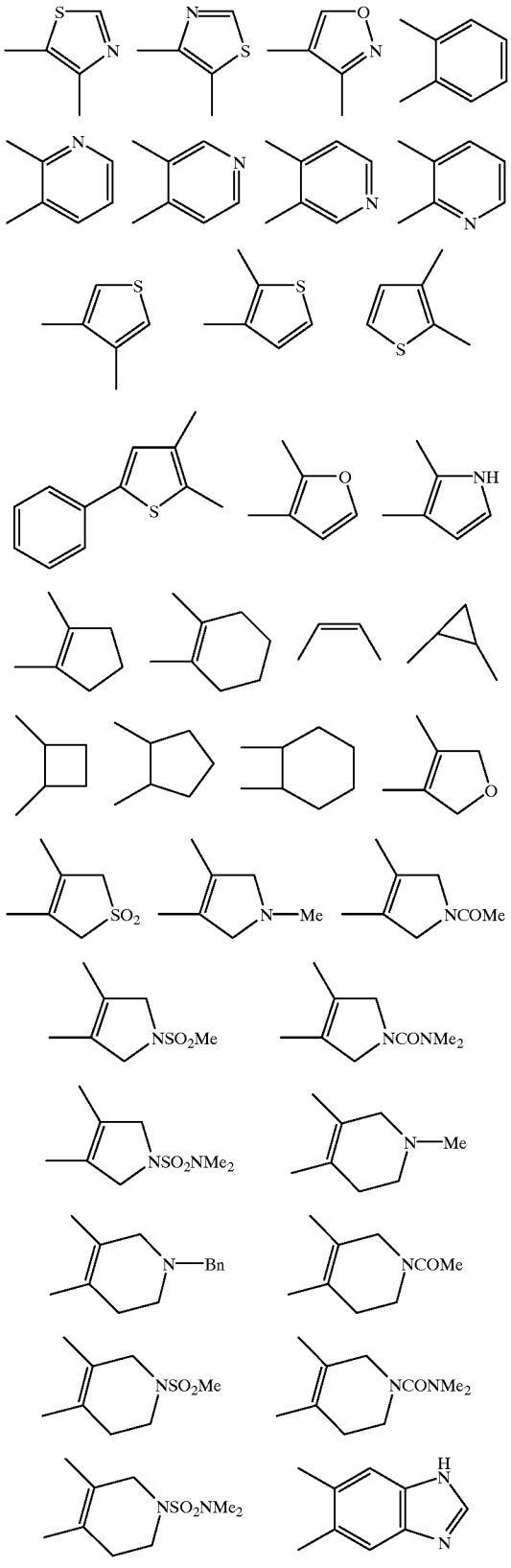

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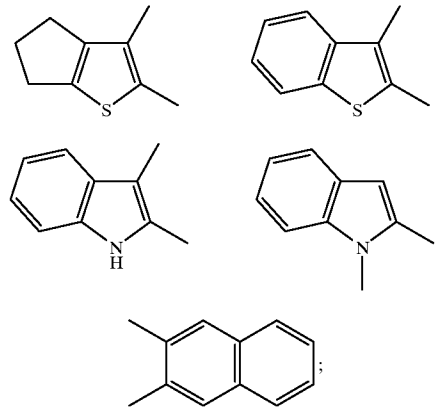
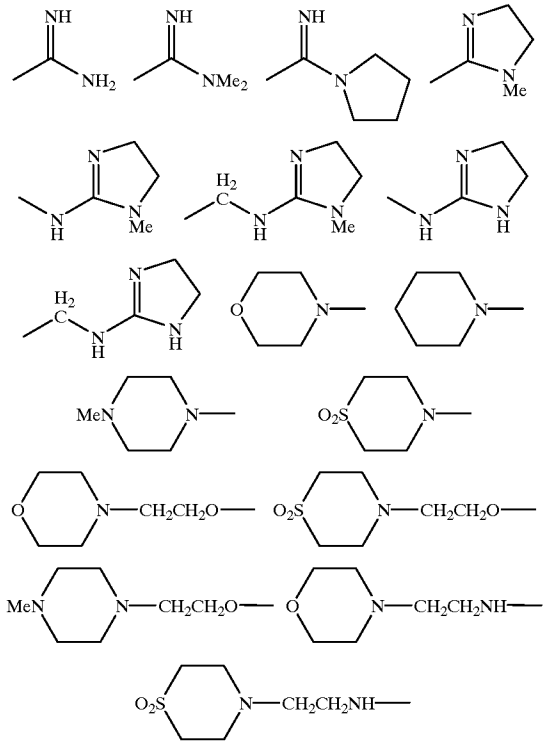


[0320] G is substituted by 0-4 R^{1d} groups and each R^{1d} group is independently selected from the group consisting of:

[0321] H, —CH_3, —CF_3, —Cl, —F, —Br, —NH_2, —NMe_2, —OH, —OMe, —$NHSO_2Me$, —NO_2, —CN, —C(═O)—OMe, —CO_2H, —$CONH_2$. —SO_2NH_2, —SO_2CH_3, —NHC(═O)Me, —C(═O)N(—Me)$_2$, —CH_2NH_2, —CH_2N(—Me)$_2$, —CH_2OH, —OCH_2CO_2H, —OCH_2C(═O)—OMe, —OCH_2C(═O)—NH_2 and —OCH_2C(═O)N(—Me)$_2$,



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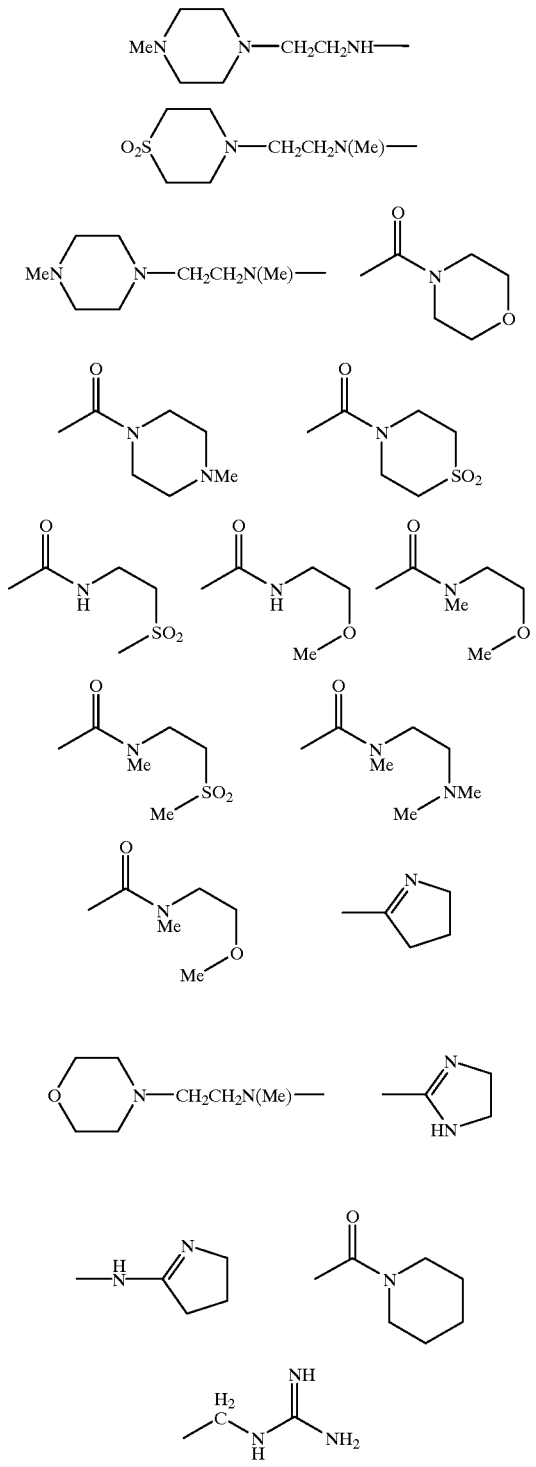
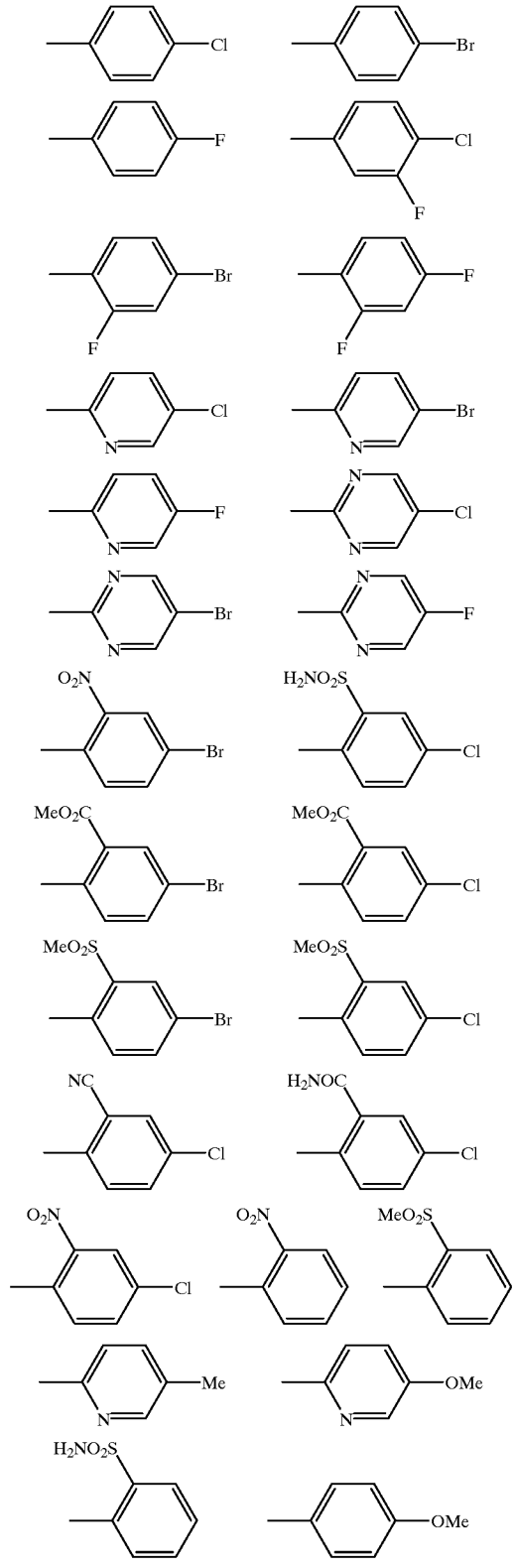


[0322] J is a member selected from the group consisting of:

[0323] a direct link, —O—, —NH—, —C(═O)—NH— and —NH—C(═O)—;

[0324] X is a member selected from the group consisting of:



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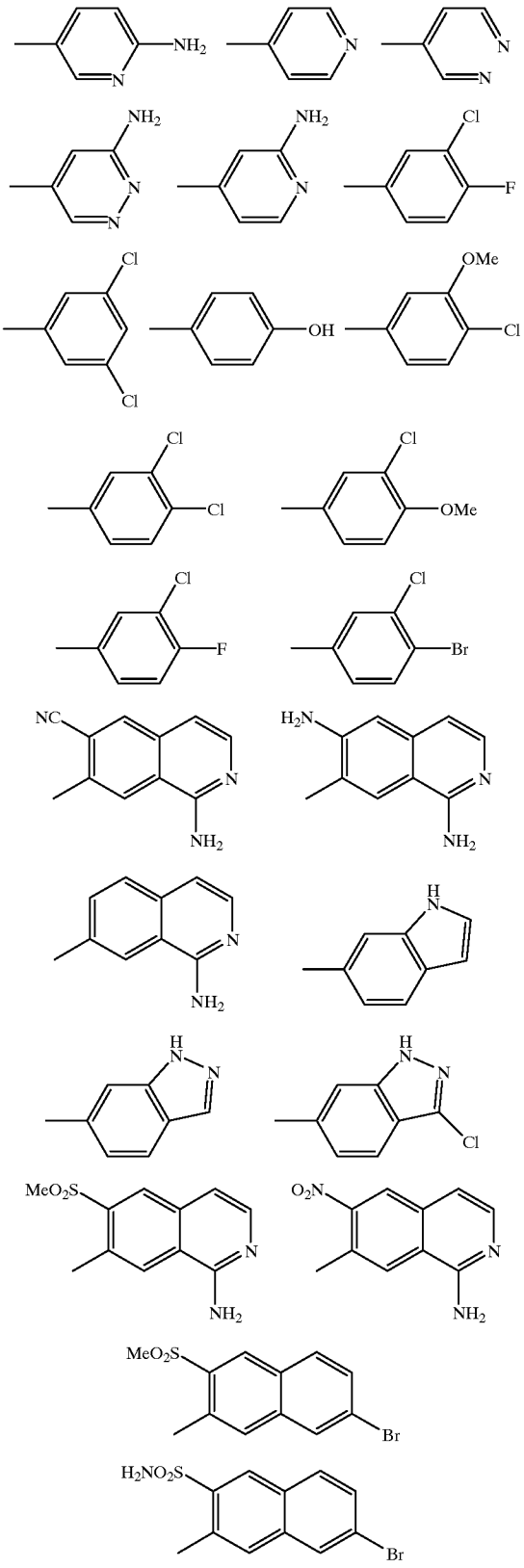

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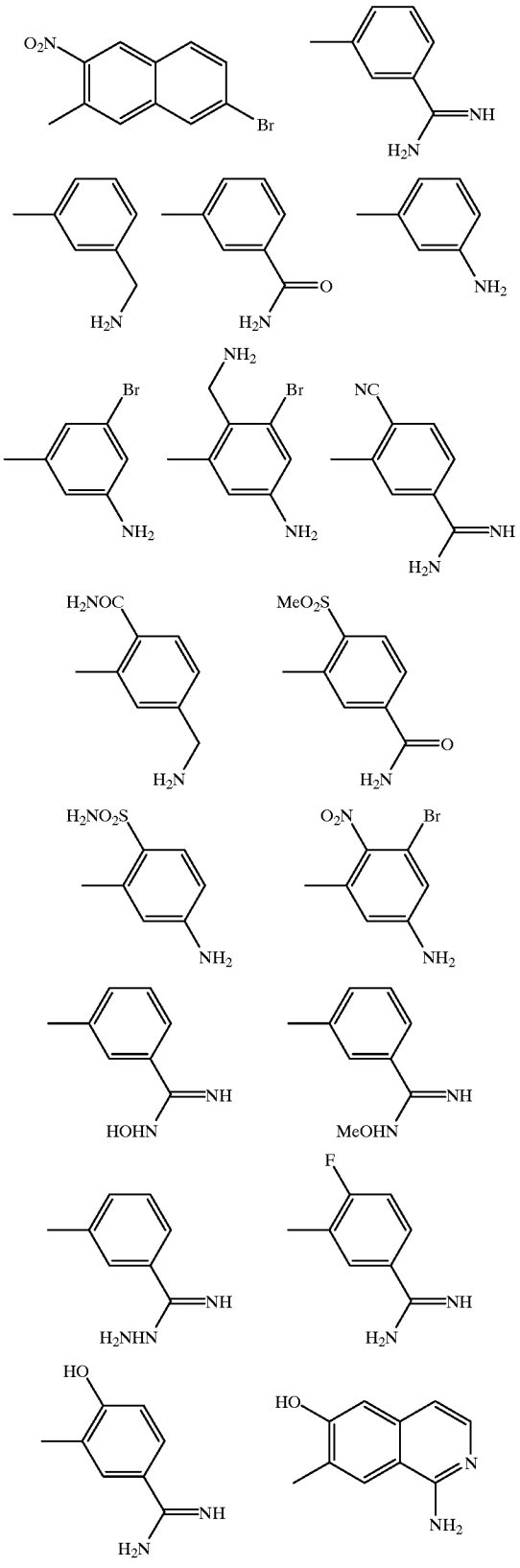

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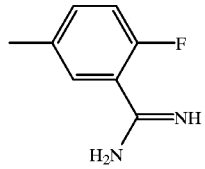
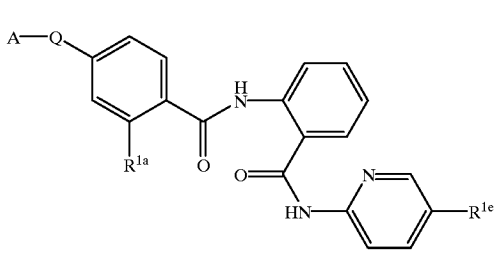


[0325] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0326] Still another preferred embodiment of the invention are compounds of the following formula (II):



(II)

[0327] where:

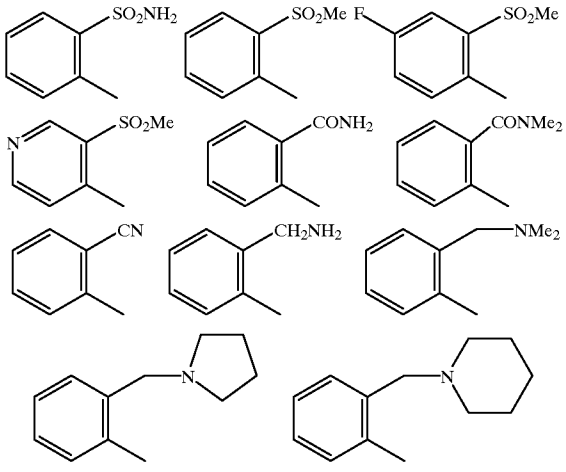
[0328] R^{1a} is a member selected from the group consisting of:

[0329] H, —F, —Cl and —Br;

[0330] R^{1e} is a member selected from the group consisting of:

[0331] H, —F, —Cl, —Br, —OMe, —OH, —Me, —CF, and —CH_2NH_2; and

[0332] A-Q is a member selected from the group consisting of:



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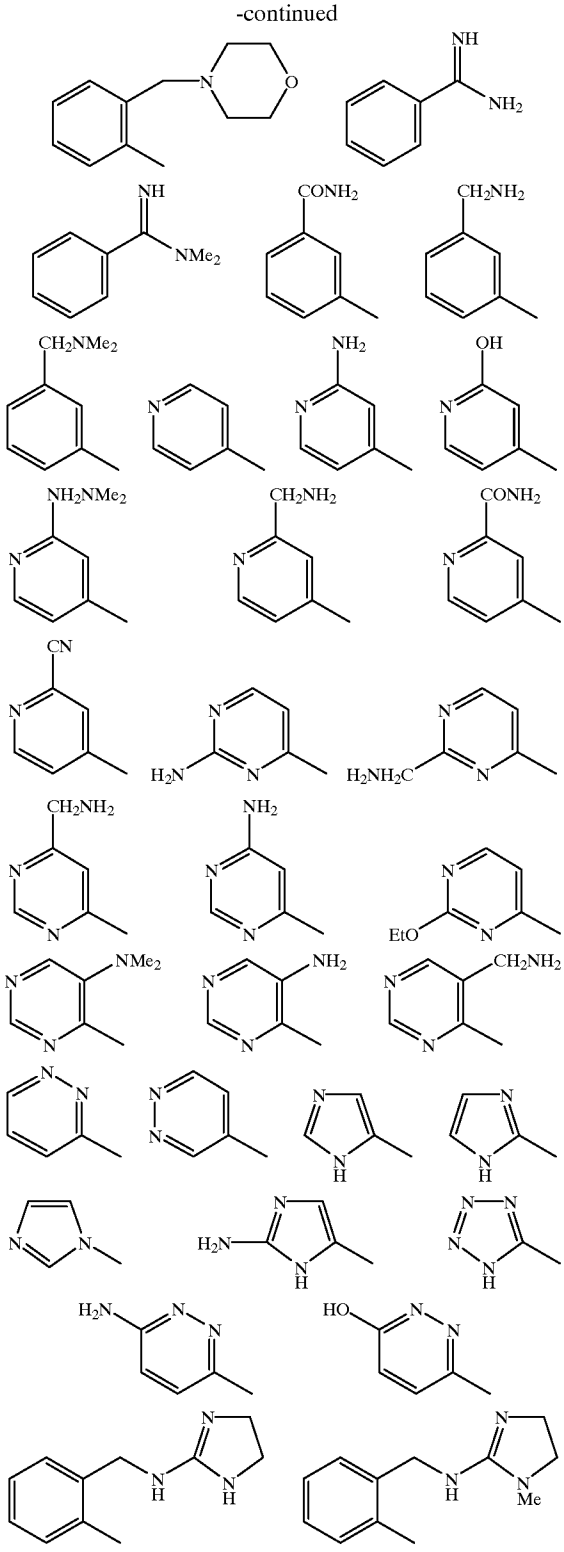
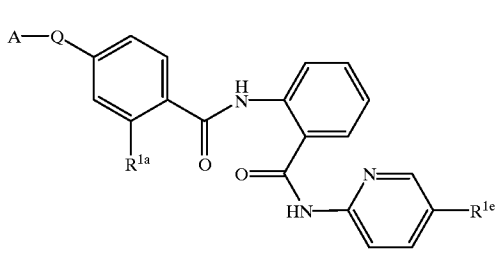


[0333] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0334] Still another preferred embodiment the invention are compounds of formula (III):



(III)

[0335] where:

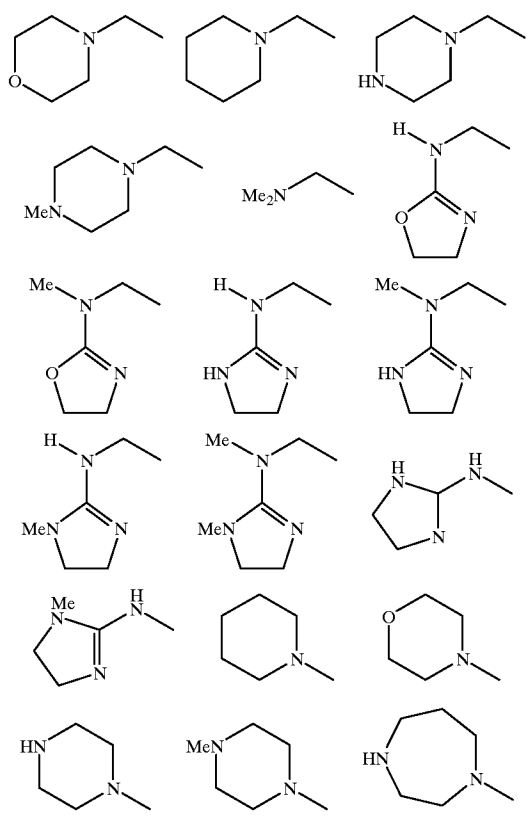
[0336] R^{1a} is a member selected from the group consisting of:

[0337] H, —F, —Cl and —Br;

[0338] R^{1e} is a member selected from the group consisting of:

[0339] H, —F, —Cl, —Br, —OMe, —OH, —Me, —CF_3 and —CH_2NH_2; and

[0340] A-Q is a member selected from the group consisting of:



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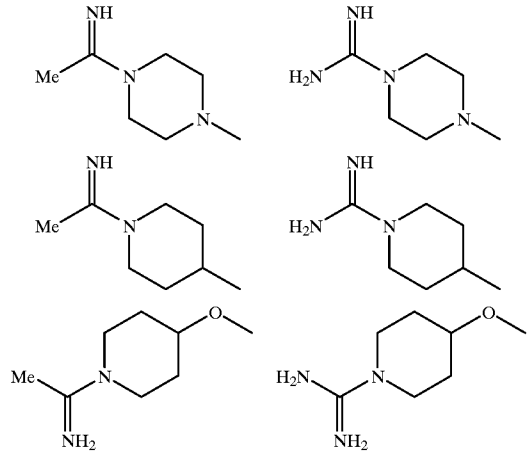
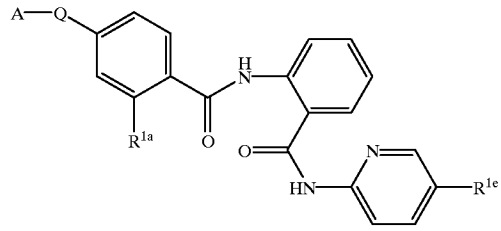


[0341] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0342] Another further preferred embodiment of the invention are compounds according to the formula (IV):



(IV)

[0343] where:

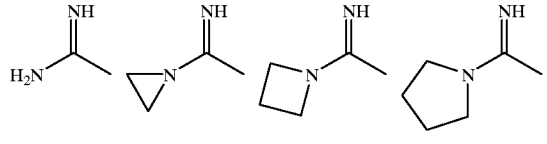
[0344] R^{1a} is a member selected from the group consisting of:

[0345] H, —F, —Cl and —Br;

[0346] R^{1e} is a member selected from the group consisting of:

[0347] H, —F, —Cl, —Br, —OMe, —OH, —Me, —CF_3 and —CH_2NH_2;

[0348] A-Q is a member selected from the group consisting of:



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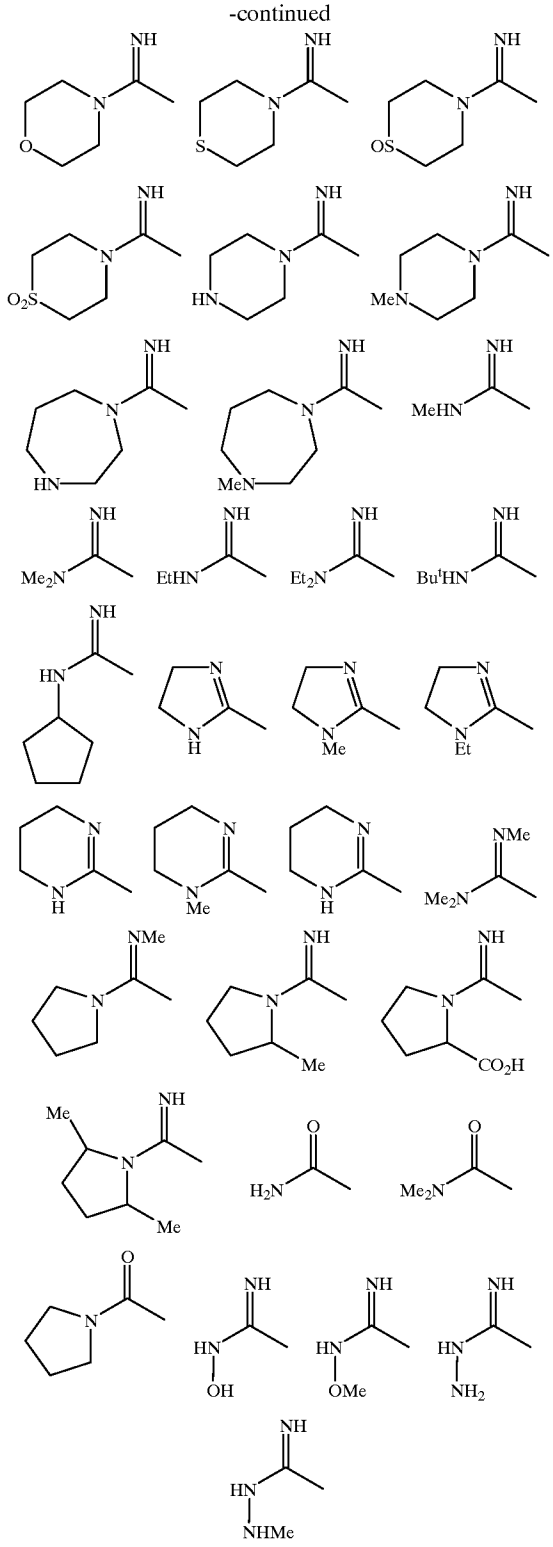
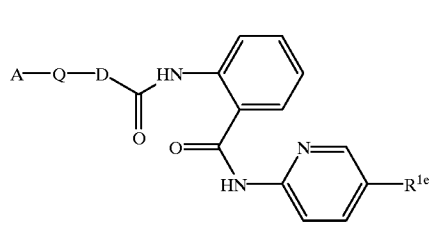


[0349] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0350] Still another preferred embodiment of the invention are compounds of formula (V):



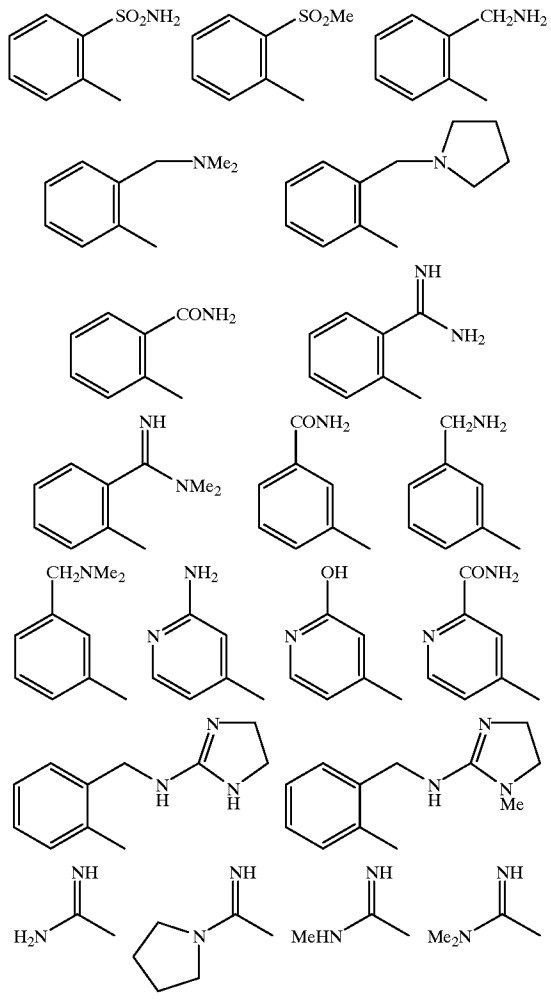
(V)

[0351] where:

[0352] R^{1e} is a member selected from the group consisting of:

[0353] H, —F, —Cl, —Br, —OMe, —OH, —Me, $—CF_3$ and $—CH_2NH_2$;

[0354] A-Q is a member selected from the group consisting of:



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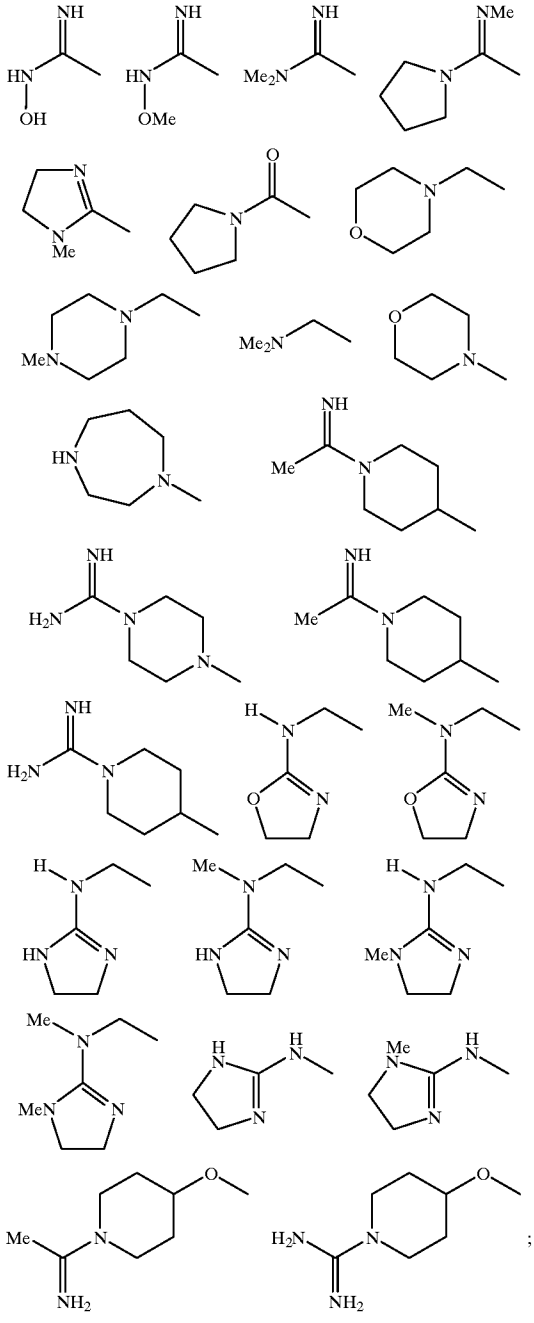
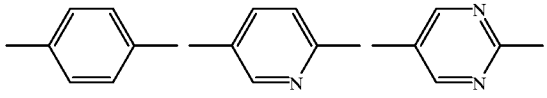


;

[0355] ;and

[0356] D is a member selected from the group consisting of:



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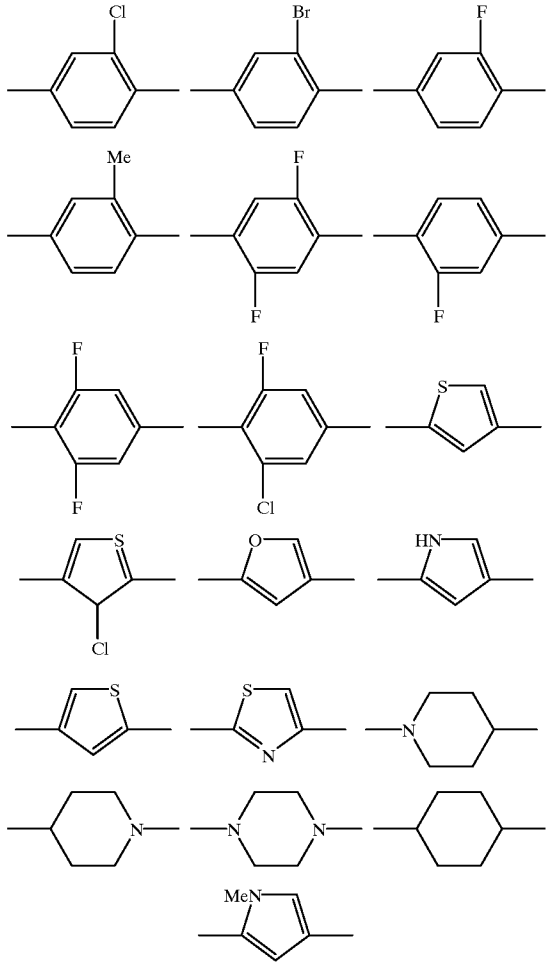
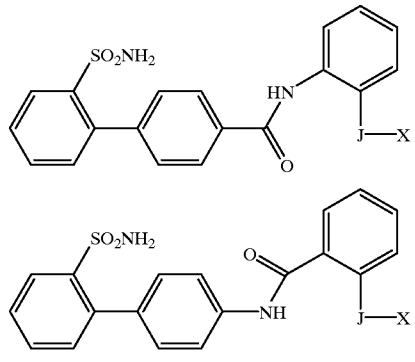


[0357] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0358] In another preferred embodiment, the present invention provides a compound according to the formula:

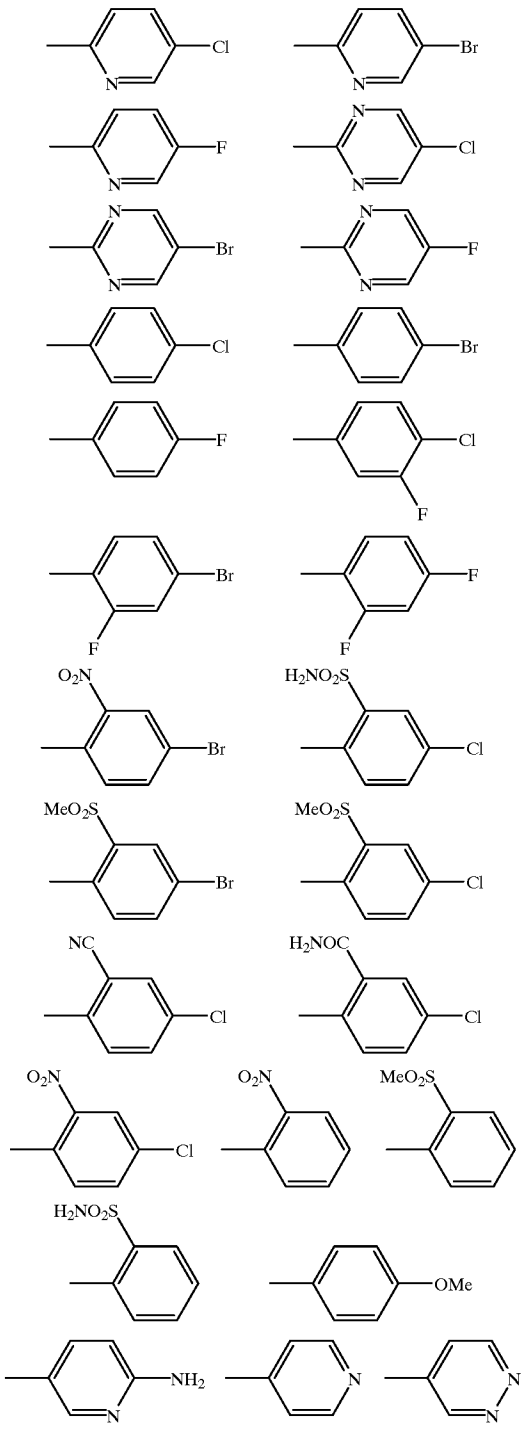


[0359] where:

[0360] J is a member selected from the group consisting of:

[0361] —NHC(═O)—, —C(═O)NH—;

[0362] X is a member selected from the group consisting of:



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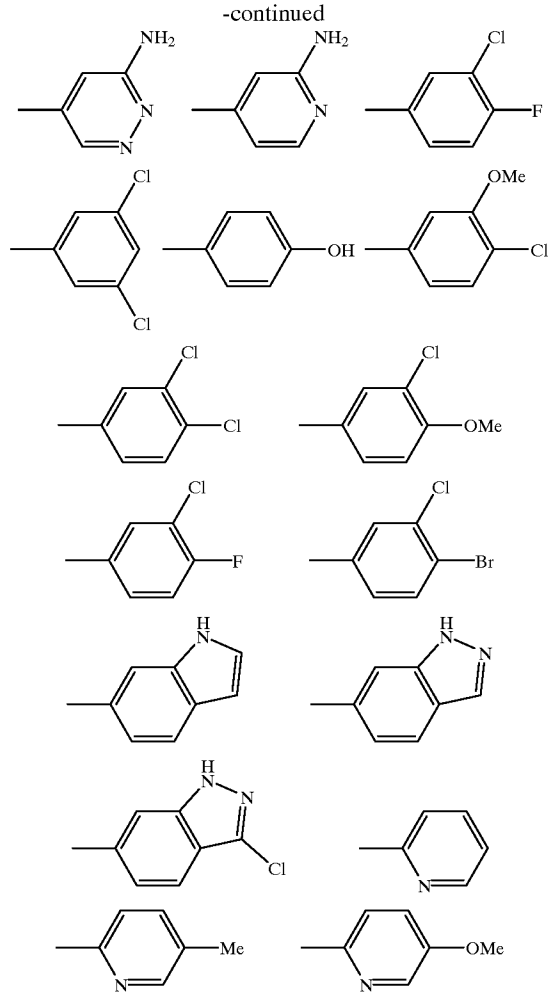
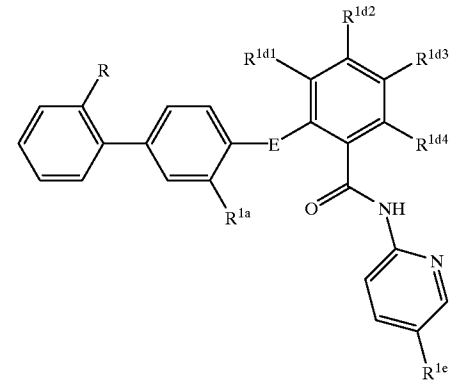


[0363] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0364] In another embodiment the present invention provides a compound according to the formula:



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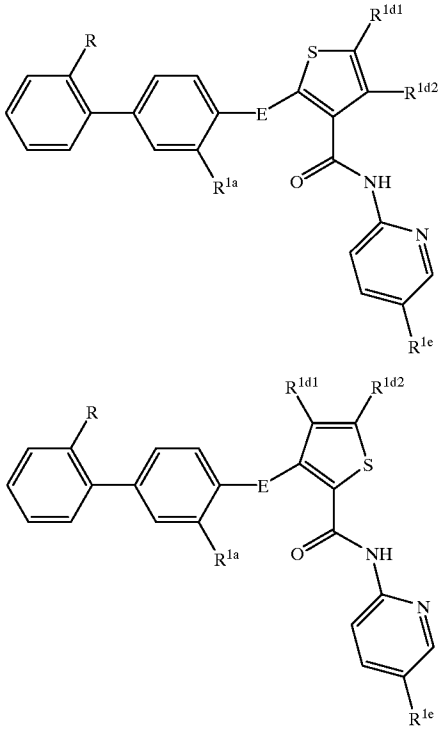

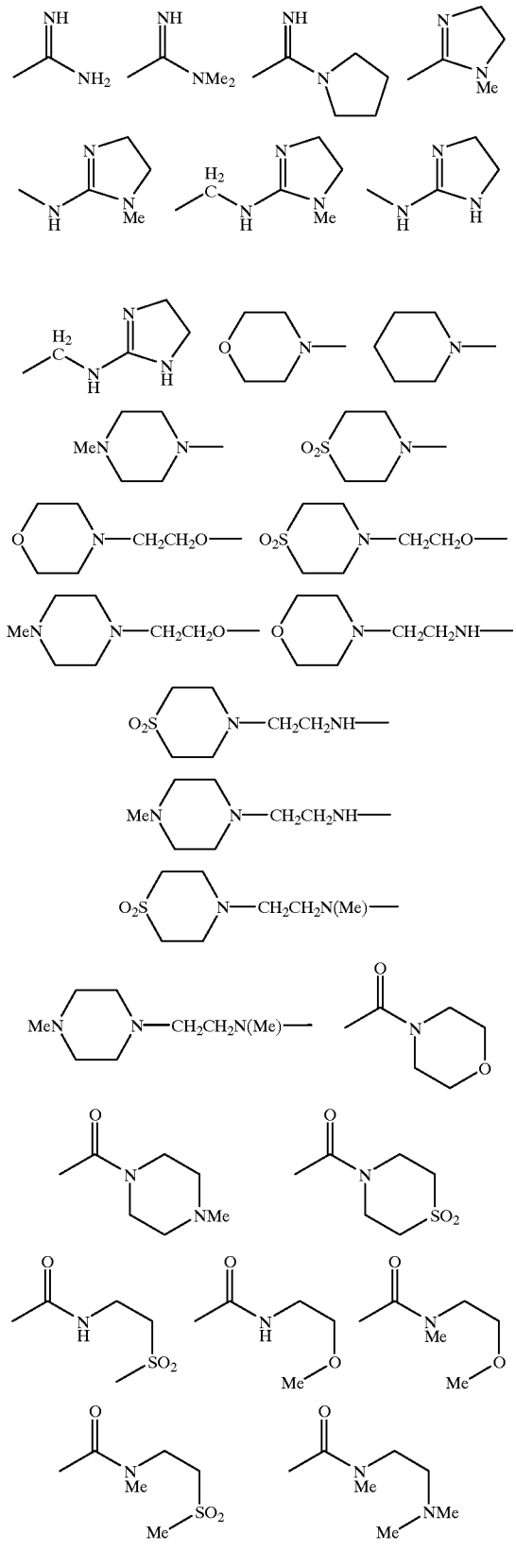

[0365] wherein:

[0366] R is a member selected from the group of:

[0367] —SO_2—NH_2 and —SO_2Me;

[0368] R^{1a} is a member selected from the group of:

[0369] H, —F, —Cl and Br;

[0370] E is a member selected from the group consisting of:

[0371] —NHC(═O)— and —C(═O)NH—;

[0372] R^{1d1}, R^{1d2}, and R^{1d4} are independently a member selected from the group of:

[0373] H, —F, —Cl, —Br, —Me, —NO_2, —OH, —OMe, —NH_2, —NHAc, —$NHSO_2$Me, —CH_2OH and —CH_2NH_2,

[0374] R^{1d3} is a member selected from the group of:

[0375] H, —CH_3, —CF_3, —Cl, —F, —Br, —NH_2, —N(—Me)$_2$, —OH, —OMe, —$NHSO_2$Me, —NO_2, —CN, —C(═O)—OMe, —CO_2H, —C(═O)—NH_2, —SO_2NH_2, —SO_2CH_3, —NHC(═O)—Me, —C(═O)—N(—Me)$_2$, —CH_2NH_2, —CH_2—N(—Me)$_2$, —CH_2OH, —OCH_2CO_2H, —OCH_2C(═O)—OMe, —OCH_2C(═O)—NH_2, and —OCH_2C(═O)—N(—Me)$_2$.

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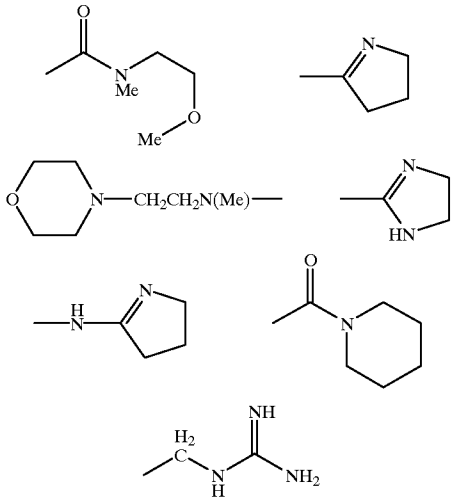
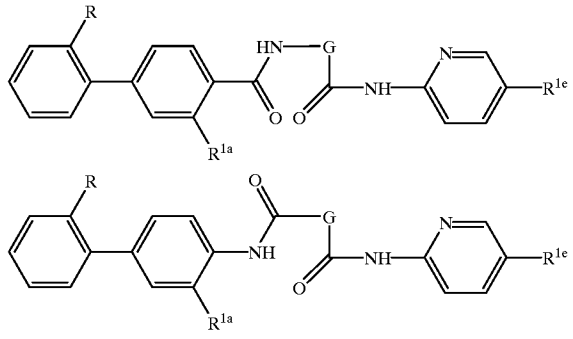


[0376] R^{1e} is a member selected from the group of:

[0377] F, —Cl, —Br, —OH, —Me and —OMe,

[0378] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0379] In another further preferred embodiment, the present invention provides a compound according to the formula:



[0380] wherein:

[0381] R is a member selected from the group consisting of:

[0382] —SO_2NH_2, —SO_2Me;

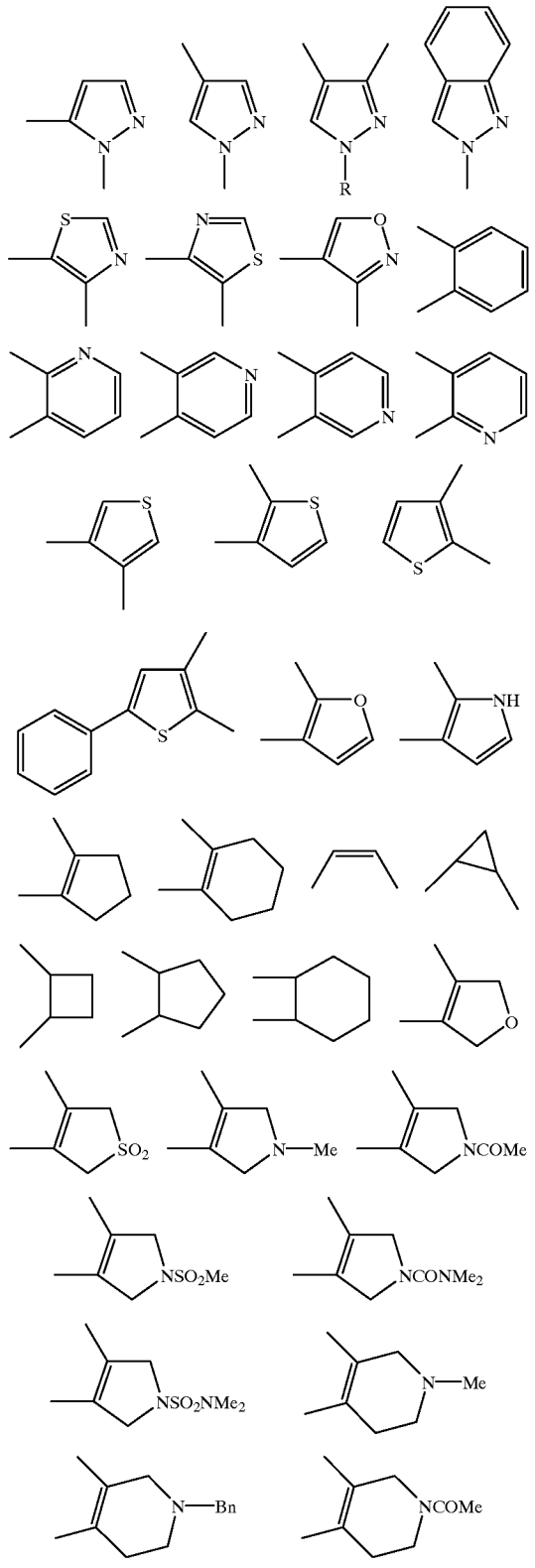
[0383] R^{1a} is a member selected from the group consisting of:

[0384] H, —F, —Cl and Br;

[0385] R^{1e} is a member selected from the group consisting of:

[0386] H, —F, —Cl, —Br, —OMe, —OH, —Me, —CF_3 and —CH_2NH_2; and

[0387] G is a member selected from the group consisting of:



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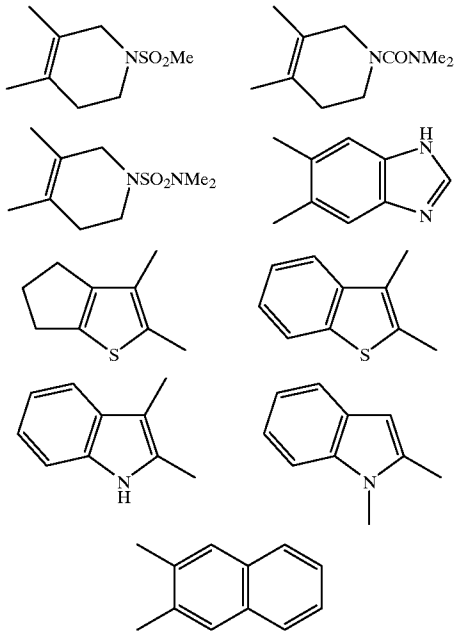
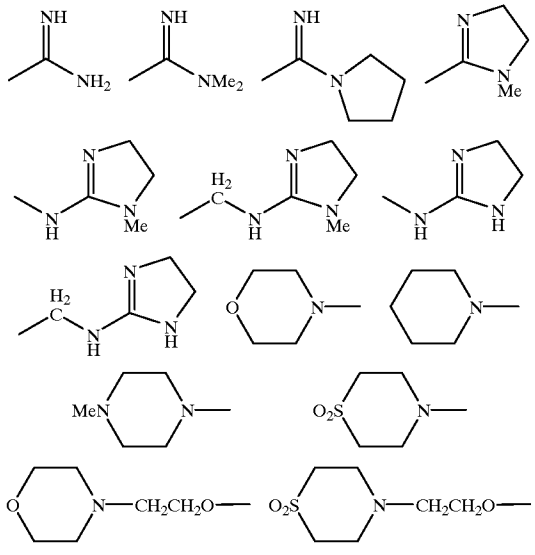


[0388] wherein each G group may be substituted by 0-4 R^{1d} groups and each such R^{1d} group is independently selected from the group consisting of:

[0389] H, —CH_3, —CF_3, —Cl, —F, —Br, —NH_2, —N(—Me)$_2$, —OH, —OMe, —$NHSO_2Me$, —NO_2, —CN, —C(=O)—OMe, —CO_2H, —C(=O)—NH_2, —SO_2NH_2, —SO_2CH_3, —NH—C(=O)—Me, —C(=O)—N(—Me)$_2$, —CH_2NH_2, —CH_2—N(—Me)$_2$, —CH_2OH, —OCH_2CO_2H, —OCH_2CO_2Me, —OCH_2C(=O)—NH_2, —OCH_2C(=O)—N(—Me)$_2$,



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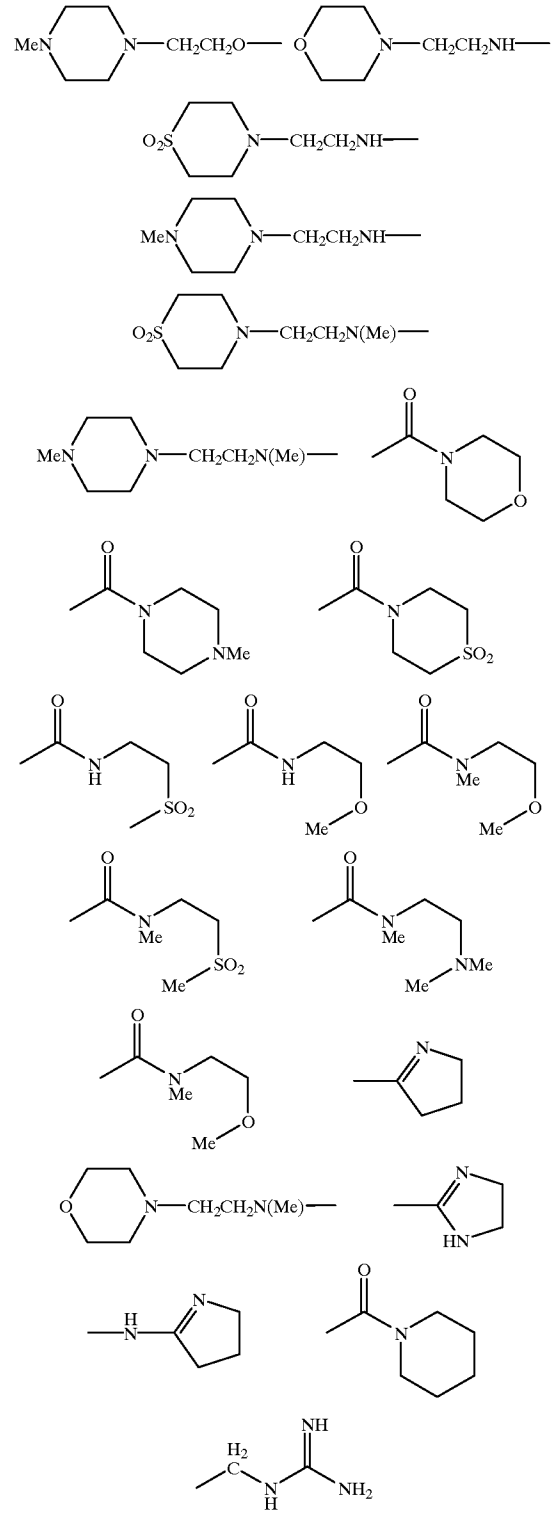
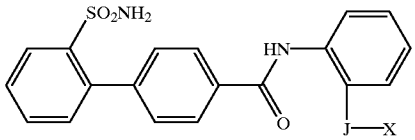
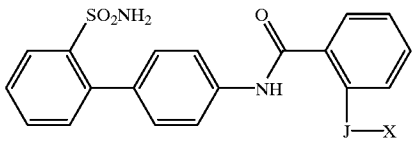


[0390] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

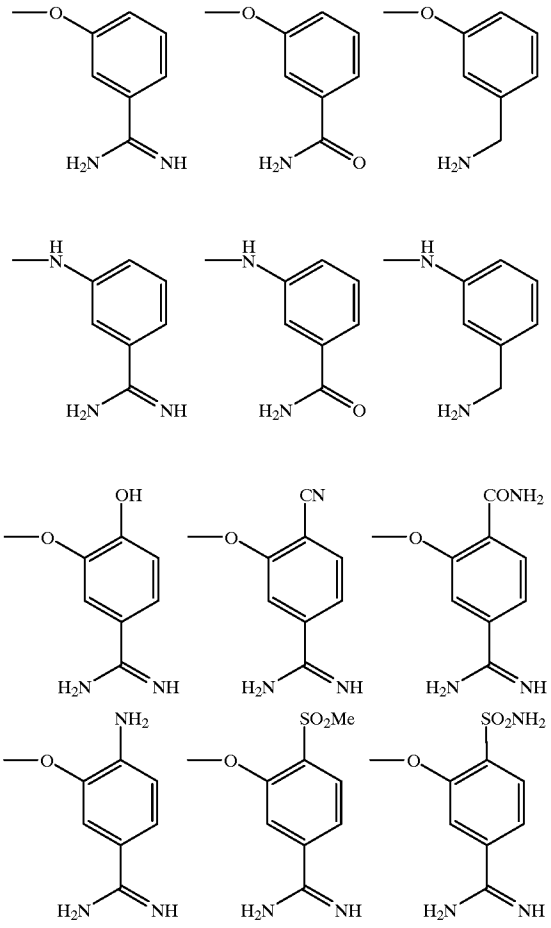
[0391] In another further preferred embodiment the present invention provides a compound according to the formula:





[0392] wherein:

[0393] J-X are collectively a member selected from the group consisting of:



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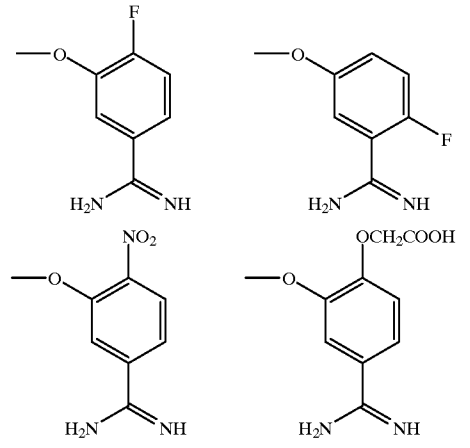
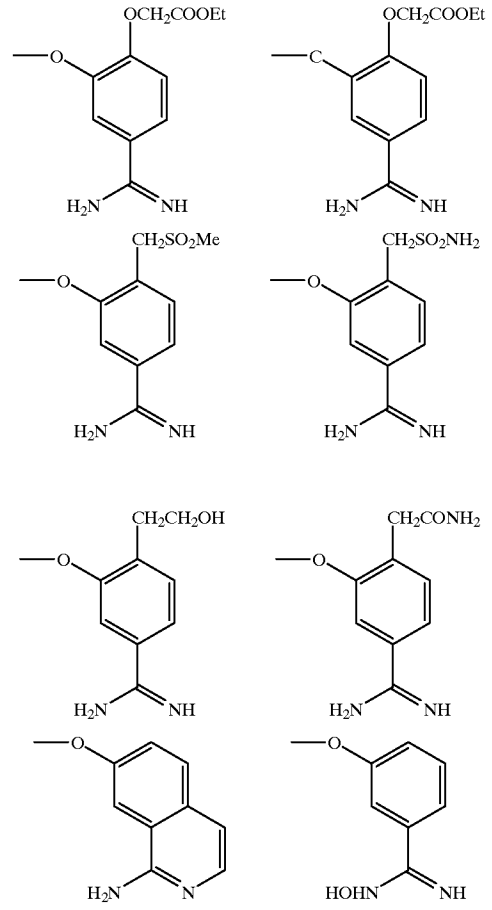
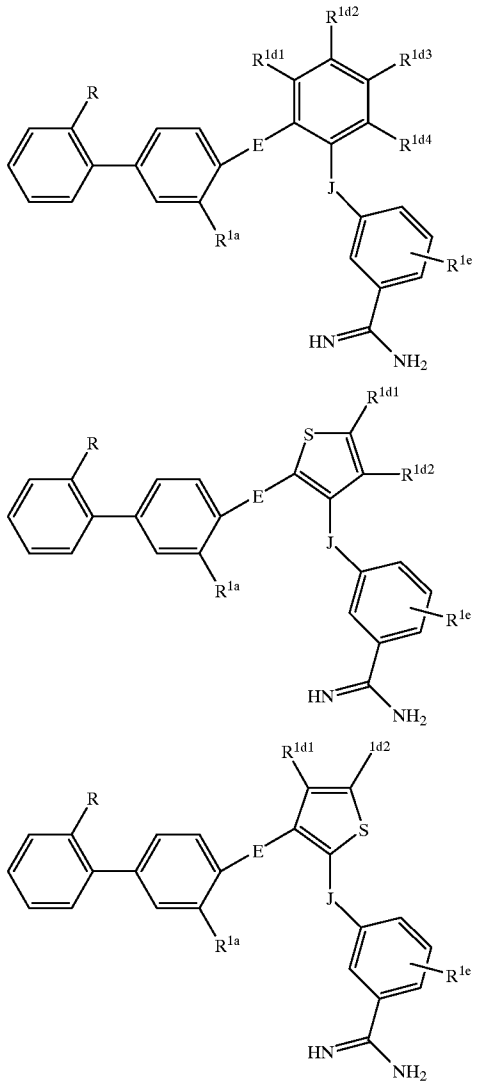




[0394] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0395] In another further preferred embodiment the present invention provides a compound according to the formula:



[0396] wherein:

[0397] R is a member selected from the group of:

[0398] —SO_2NH_2, and —SO_2Me;

[0399] R^{1a} is a member selected from the group of:

[0400] H, —F, —Cl and Br;

[0401] E is a member selected from the group consisting of:

[0402] —NHC(═O)— and —C(═O)NH—;

[0403] J is a member selected from the group consisting of:

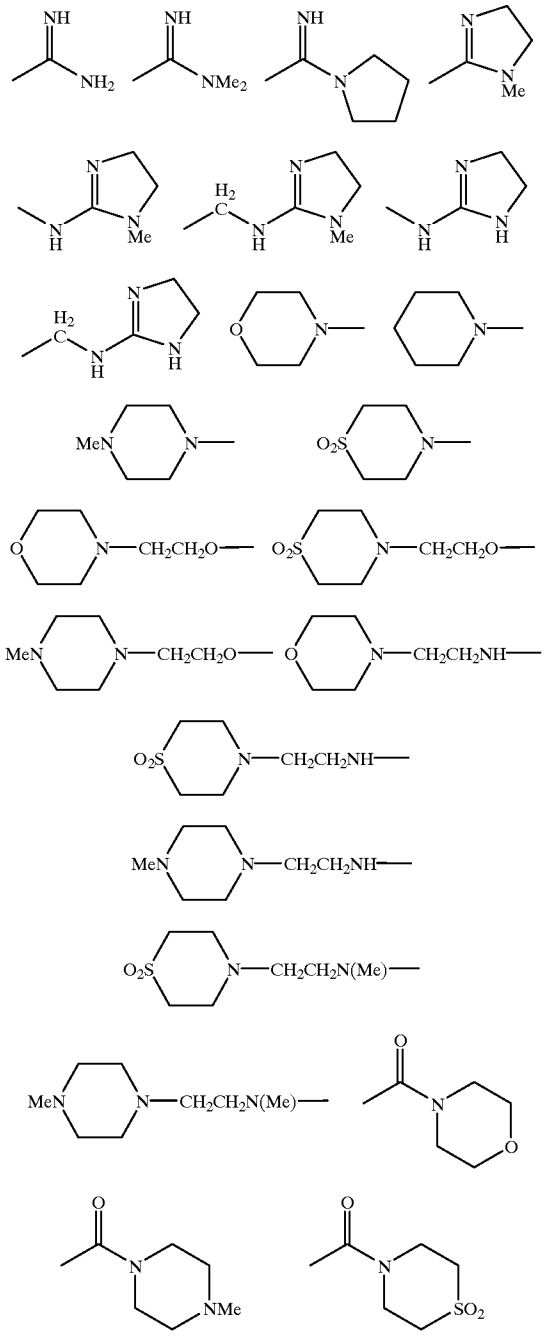
[0404] —NHC(═O)— and —C(═O)NH—, O;

[0405] R^{1d1}, R^{1d2}, and R^{1d4} are independently a member selected from the group of:

[0406] H, —F, —Cl, —Br, —Me, —NO_2, —OH, —OMe, —NH_2, —NHAc, —$NHSO_2Me$, —CH_2OH, —CH_2NH_2,

[0407] R^{1d3} is a member selected from the group of:

[0408] H, —CH_3, —CF_3, —Cl, —F, —Br, —NH_2, —N(—Me)$_2$, —OH, —OMe, —$NHSO_2Me$, —NO_2, —CN, —CO_2Me, —CO_2H, —C(═O)—NH_2, —SO_2NH_2, —SO_2CH_3, —NHC(═O)—Me, —C(═O)—N(—Me)$_2$, —CH_2NH_2, —CH_2—N(—Me)$_2$, —CH_2OH, —OCH_2CO_2H, —OCH_2C(═O)—OMe, —OCH_2C(═O)—NH_2, —OCH_2C(═O)—N(—Me)$_2$,



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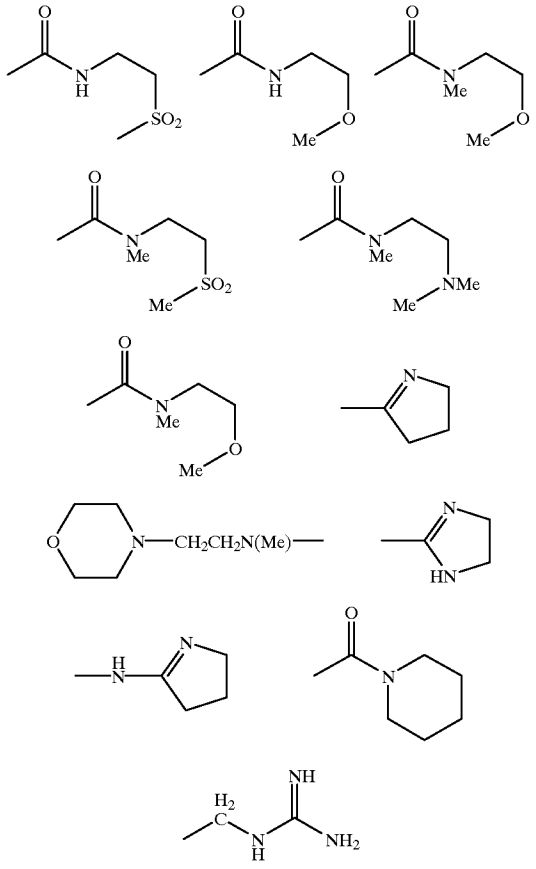

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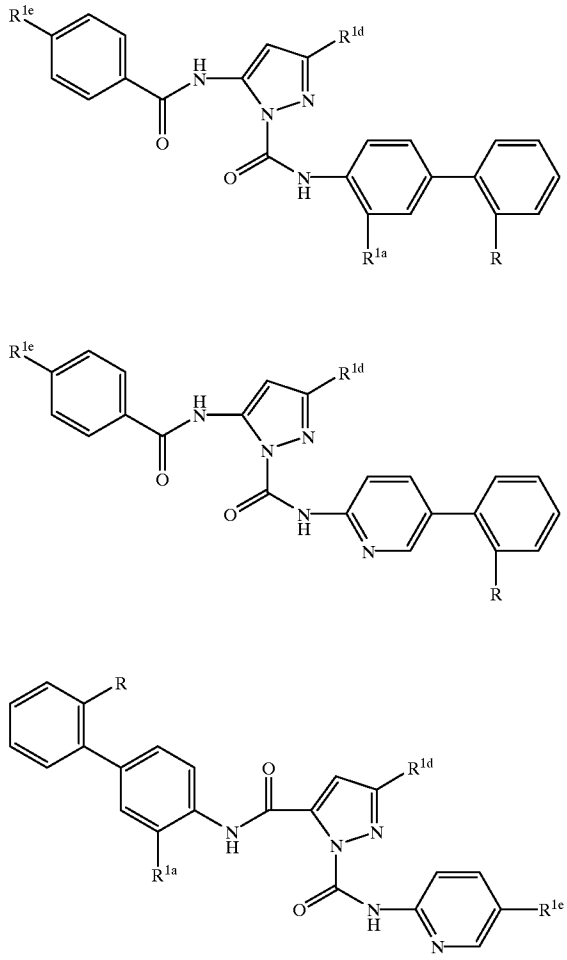
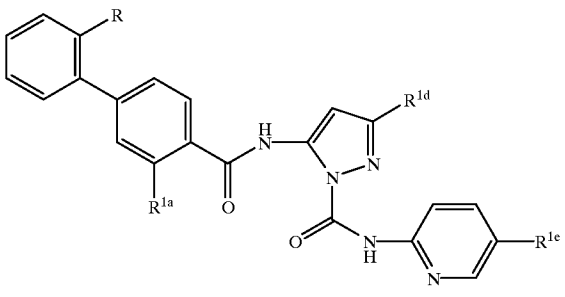


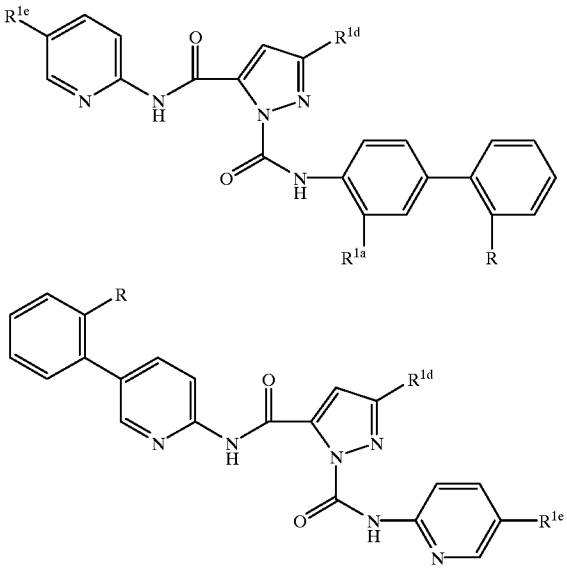
[0409] R^{1e} is a member selected from the group of:

[0410] F, —Cl, —Br, —OH, —Me and —OMe;

[0411] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0412] In another preferred embodiment, the present invention provides a compound of the following formulae, which illustrate the compounds having preferred substituents for G, particularly when G is a pyrazole ring structure.





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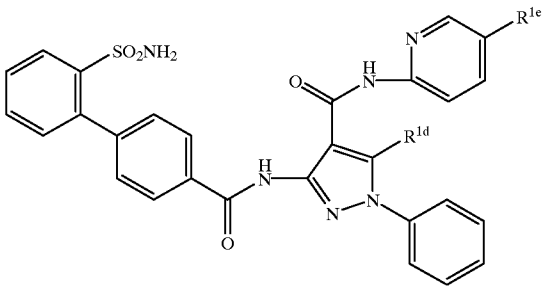

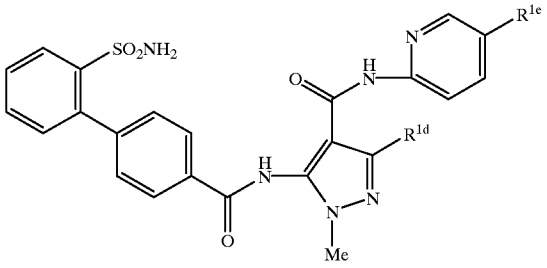

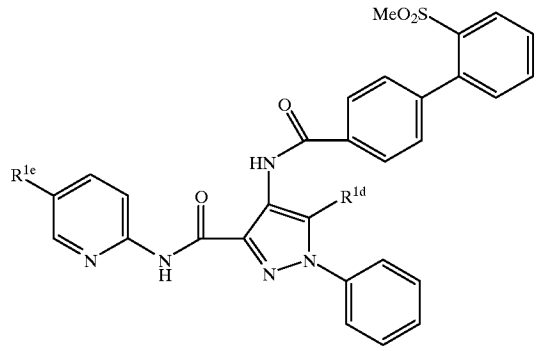

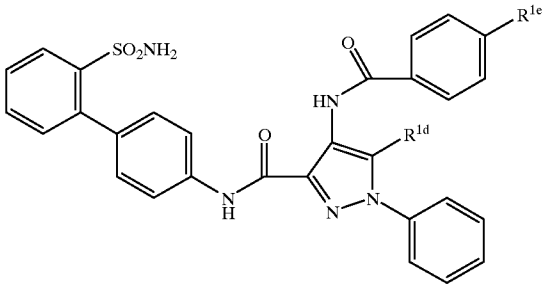

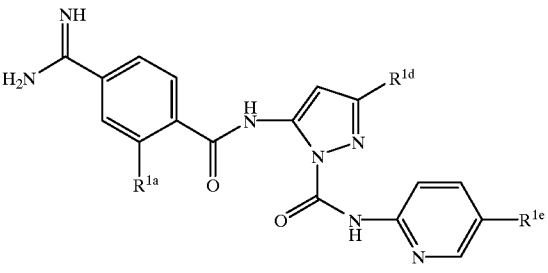

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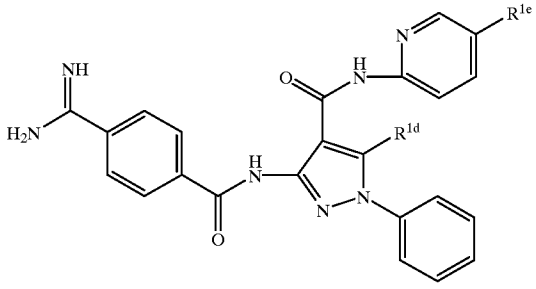


[0413] wherein:

[0414] R is a member selected from the group of:

[0415] —SO_2—NH_2, and —SO_2Me;

[0416] R^{1a} is a member selected from the group of:

[0417] H, —F, —Cl and Br;

[0418] R^{1d} is a member selected from the group consisting of:

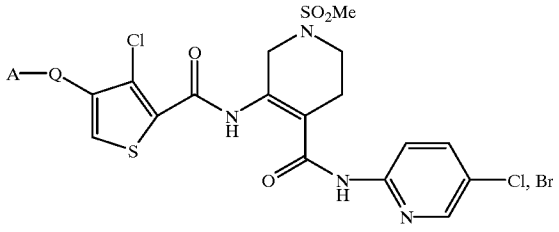
[0419] —H, —CH_3, —CF_3, —CN, —SO_2NH_2 and —SO_2CH_3; and

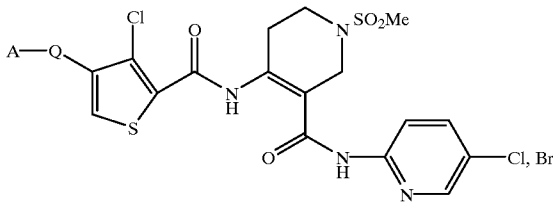
[0420] R^{1e} is a member selected from the group of:

[0421] —Cl and —Br;

[0422] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

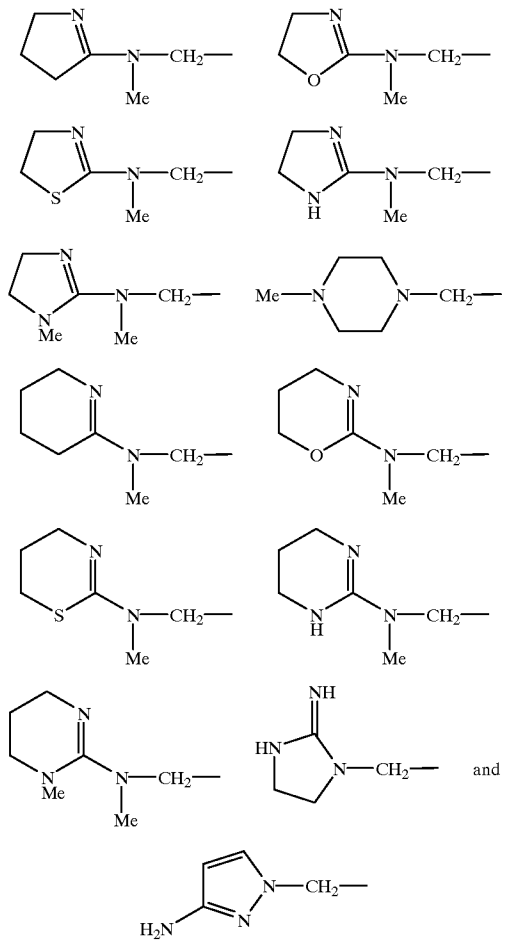
[0423] In another preferred embodiment, the present invention provides a compound of the following formulae, which illustrate the compounds having preferred substituents for A-Q taken collectively when the remainder of the compound structure has the one of the following two formulae:





[0424] wherein:

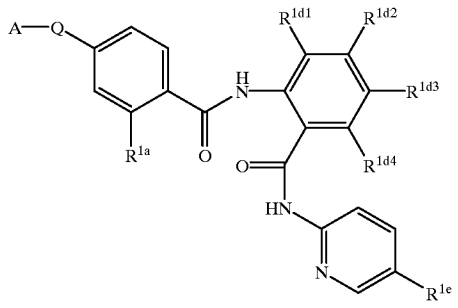
[0425] A-Q taken together are a member selected from the group consisting of:



and

[0426] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0427] In another preferred embodiment the present invention provides a compound according to the formula:



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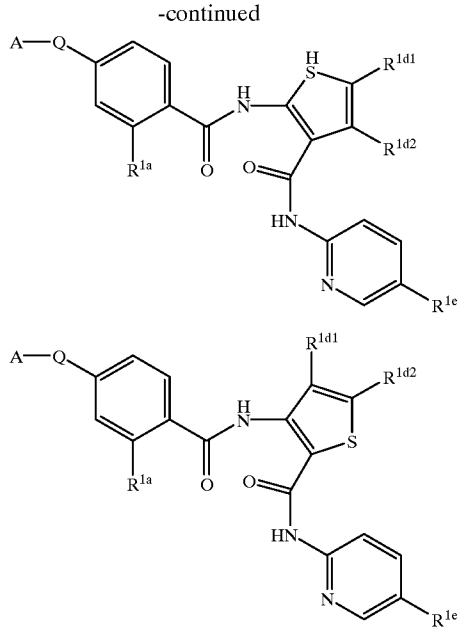
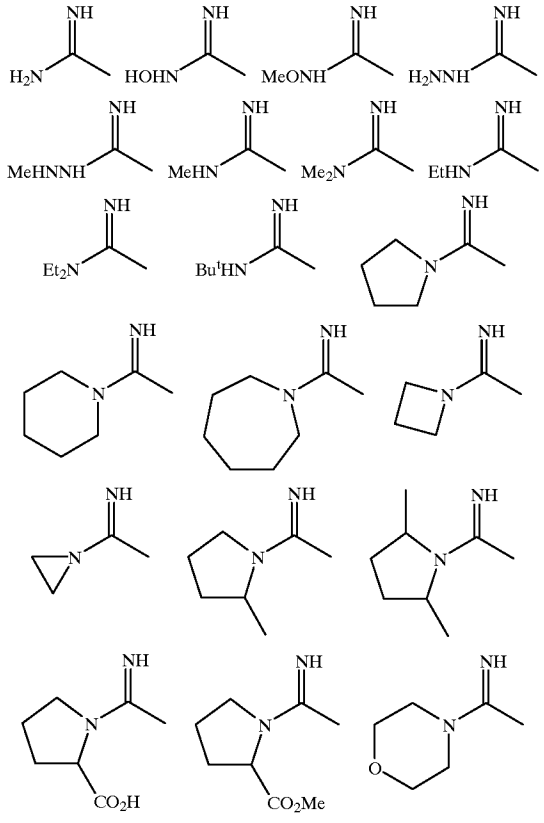


[0428] wherein:

[0429] A-Q is a member selected from the group of:



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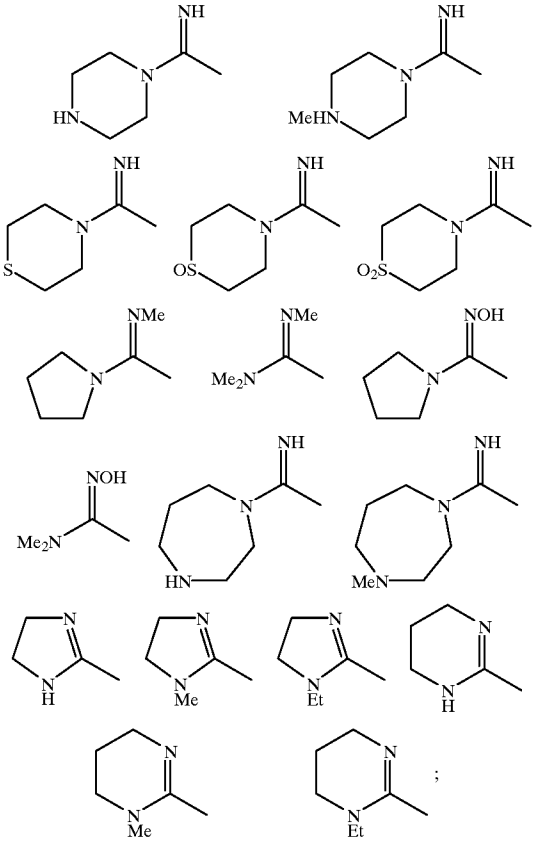


[0430] where A-Q may optionally be further substituted with at least one Z' group, where each Z' group is independently a C_1-C_6 alkyl, preferably a C_1-C_3 alkyl group, most preferably a methyl group and where each Z' group may optionally be substituted with a hydroxyl, carboxylic acid or carboxylic acid C_1-C_6 ester group, preferably a hydroxyl, carboxylic acid or carboxylic acid C_1-C_3 ester group, and most preferably, a hydroxyl, carboxylic acid or carboxylic acid methyl ester;

[0431] R^{1a} is a member selected from the group of:

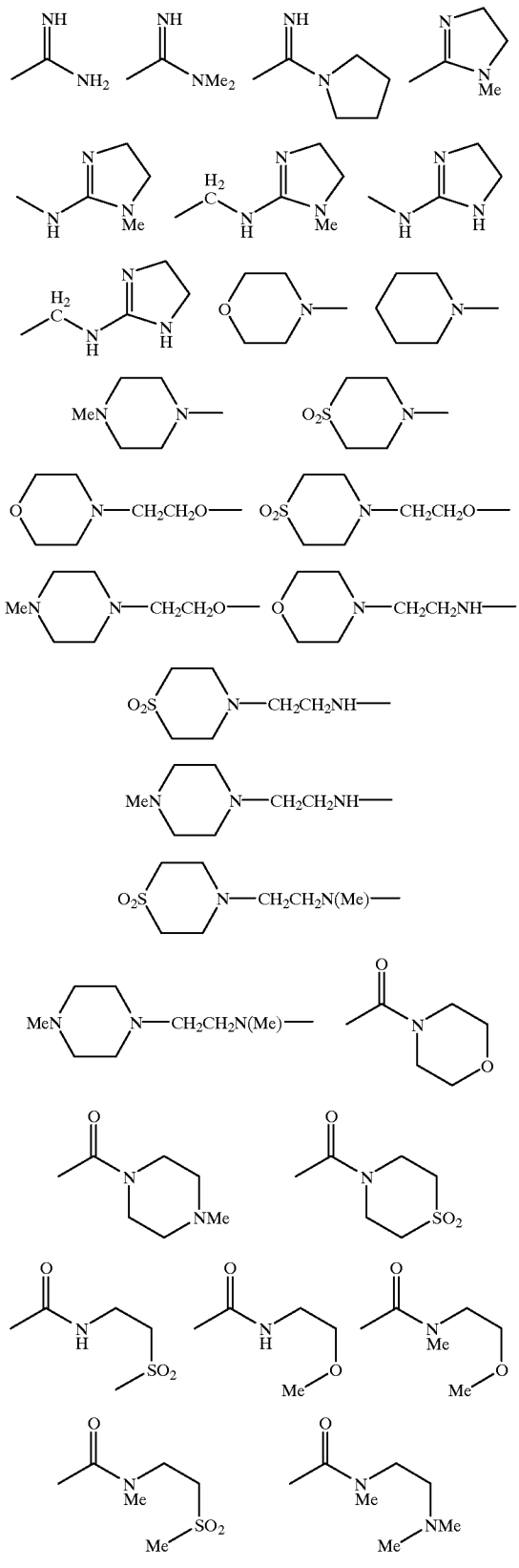
[0432] H, —F, —Cl and Br;

[0433] R^{1d1}, R^{1d2}, and R^{1d4} are independently a member selected from the group of:

[0434] H, —F, —Cl, —Br, —Me, —NO_2, —OH, —OMe, —NH_2, —NHAc, —$NHSO_2Me$, —CH_2OH, —CH_2NH_2

[0435] R^{1d3} is a member selected from the group of:

[0436] H, —CH_3, —CF_3, —Cl, —F, —Br, —NH_2, —N(—Me)$_2$, —OH, —OMe, —$NHSO_2Me$, —NO_2, —CN, —C(=O)—OMe, —CO_2H, —C(=O)—NH_2, —SO_2NH_2, —SO_2CH_3, —NHC(=O)—Me, —C(=O)—N(Me)$_2$, —CH_2NH_2, —CH_2—N(—Me)$_2$, —CH_2OH, —OCH_2CO_2H, —OCH_2C(=O)—OMe, —OCH_2C(=O)—NH_2, —OCH_2C(=O)—N(—Me)$_2$,



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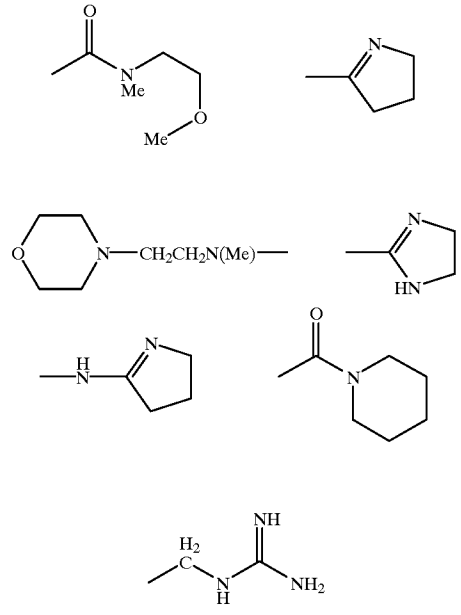
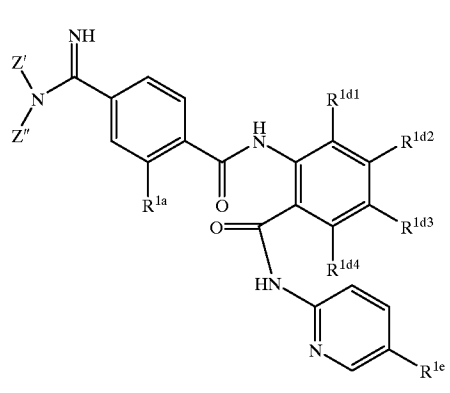


[0437] R^{1e} is a member selected from the group of:

[0438] F, —Cl, —Br, —OH, —Me and —OMe;

[0439] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0440] In another embodiment, the invention provides a compound of formula VI:



(VI)

[0441] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0442] In formula VI:

[0443] Z' and Z" are each independently a C_1-C_6 alkyl, preferably a C_1-C_3 alkyl group, most preferably a methyl group; where Z' and Z" may be optionally substituted with a hydroxyl, carboxylic acid or carboxylic acid C_1-C_6 ester group, preferably a hydroxyl, carboxylic acid or carboxylic acid C_1-C_3 ester group, and most preferably, a hydroxyl, carboxylic acid or carboxylic acid methyl ester;

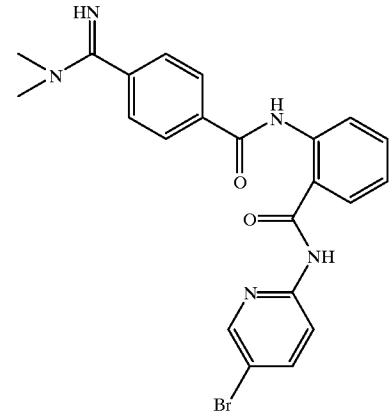
[0444] R^{1a} is a member selected from the group of H, —F, —Cl and Br;

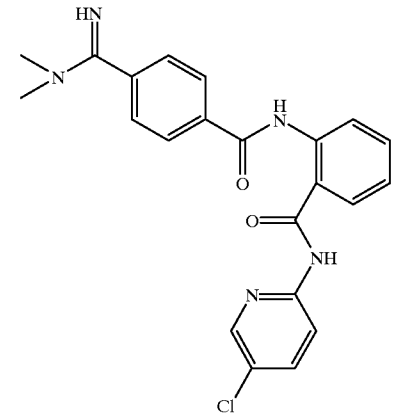
[0445] R^{1d2} and R^{1d4} are each H;

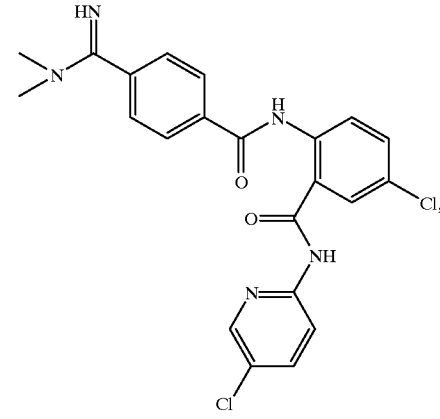
[0446] R^{1d1} and R^{1d3} are each independently a member selected from the group of H, —Cl, —F, —Br, —OH and —OMe; and

[0447] R^{1e} is a member selected from the group of —F, —Cl, —Br, —OH, —Me and —OMe.

[0448] Examples of suitable compounds of formula VI, as described above, include, but are not limited to:







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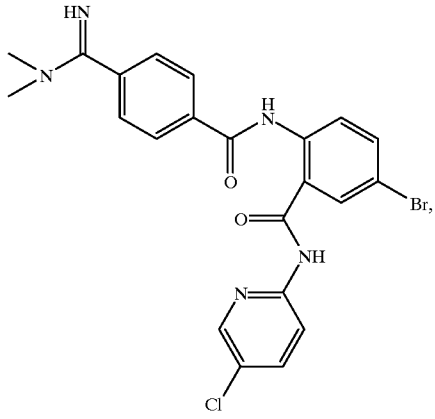

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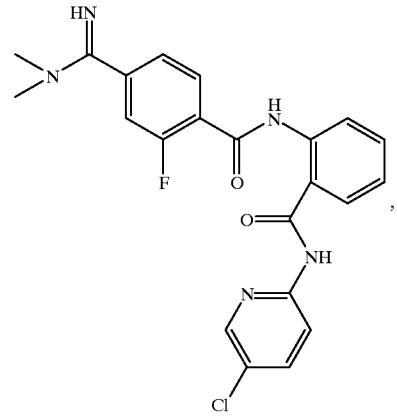

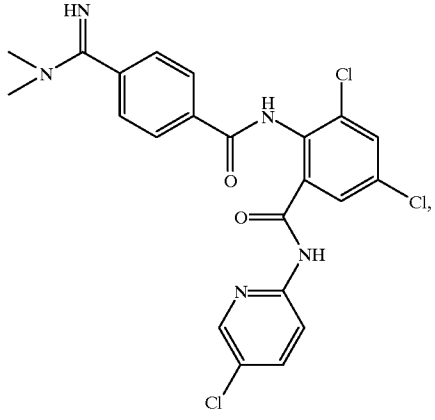

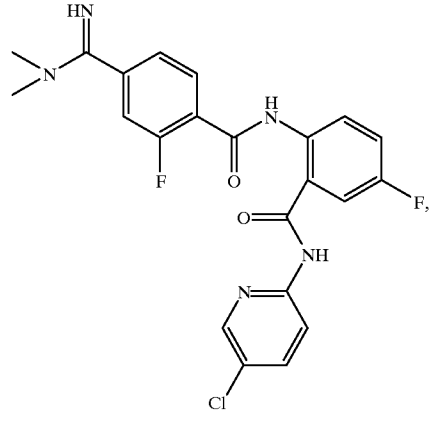

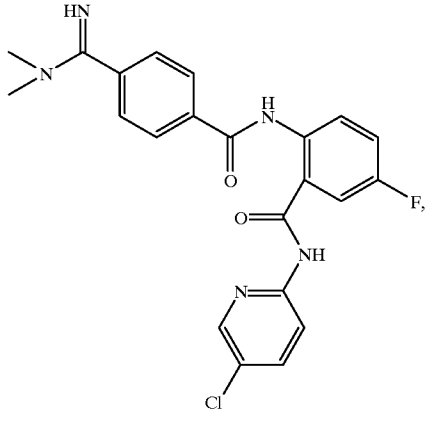

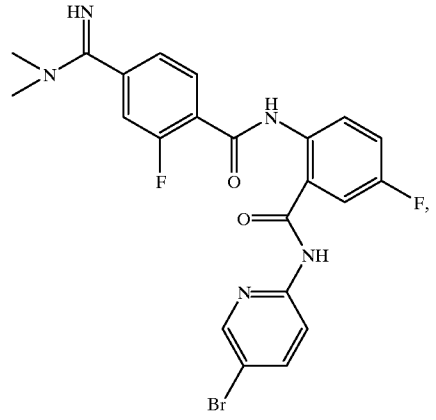

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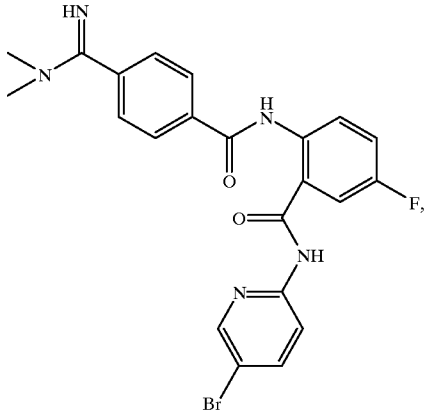

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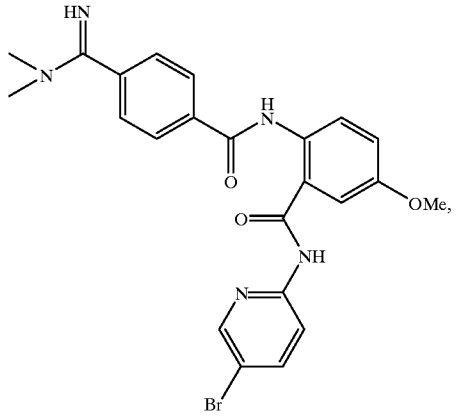

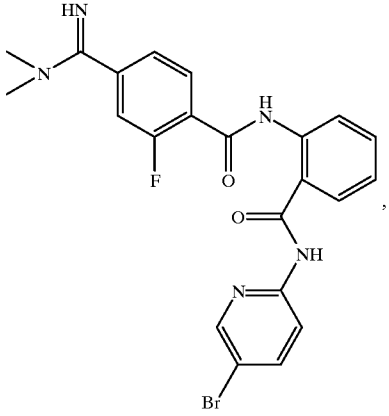

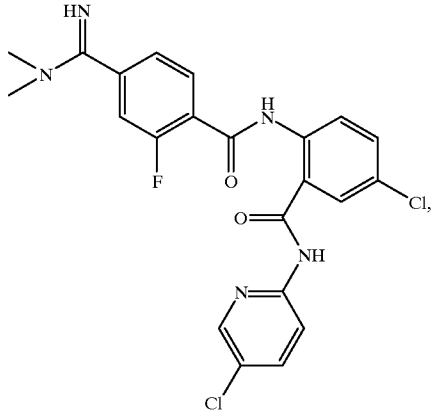

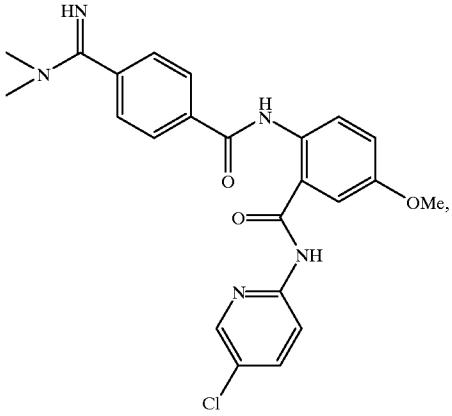

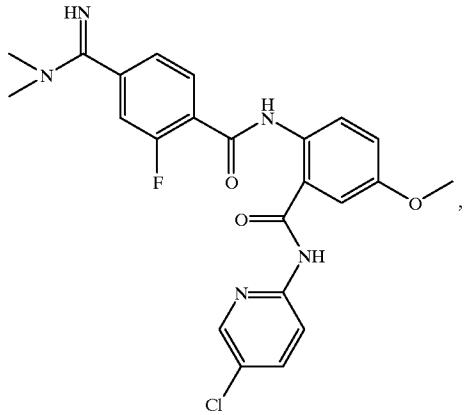

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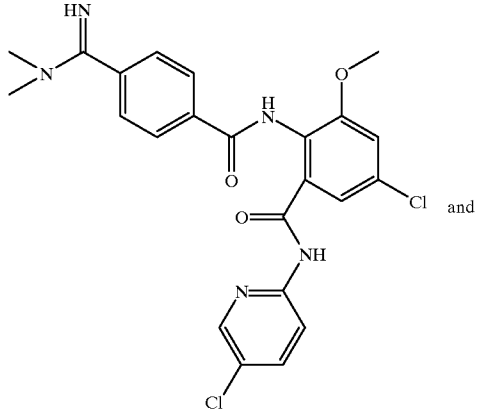

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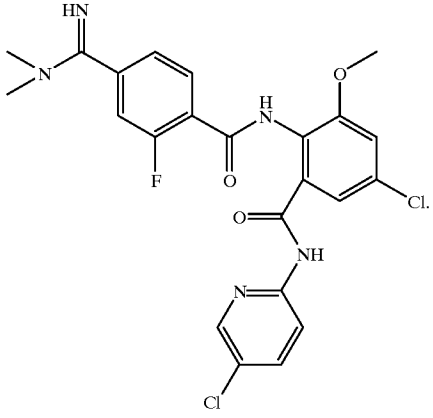
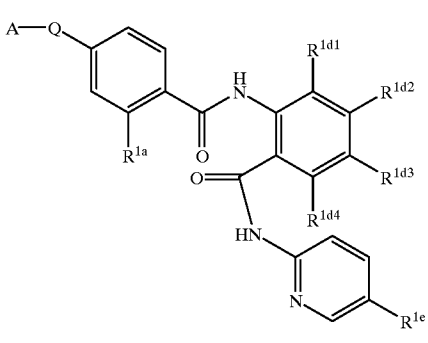


[0449] In another embodiment, the invention further provides a compound of formula VII:

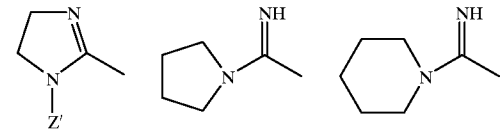


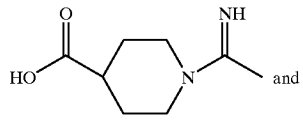
(VII)

[0450] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0451] In formula VII:

[0452] A-Q is a member selected from the group of:





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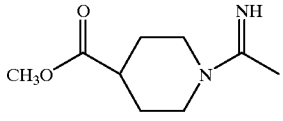


[0453] where Z' is as described above;

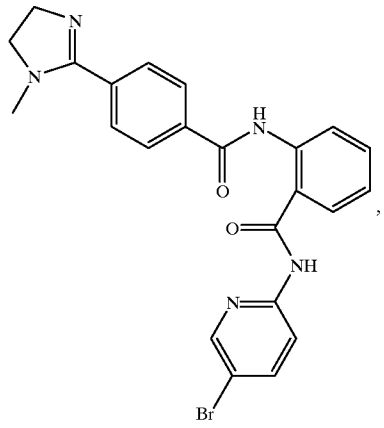
[0454] R^{1a} is a member selected from the group of H, —F, —Cl and Br;

[0455] R^{1d2} and R^{1d4} are each H;

[0456] R^{1d1} is R^{1d3} are each independently a member selected from the group of H, —Cl, —F, —Br, —OH and —OMe;

[0457] R^{1e} is a member selected from the group of —F, —Cl, —Br, —OH, —Me and —OMe.

[0458] Examples of suitable compounds of formula VII, as described above, include, but are not limited to:



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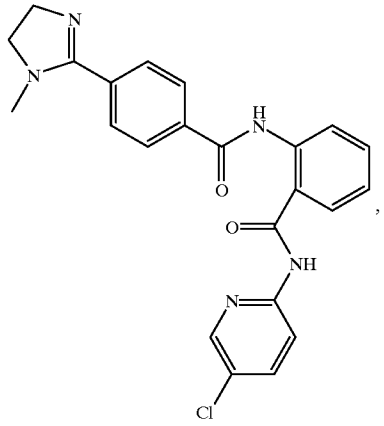

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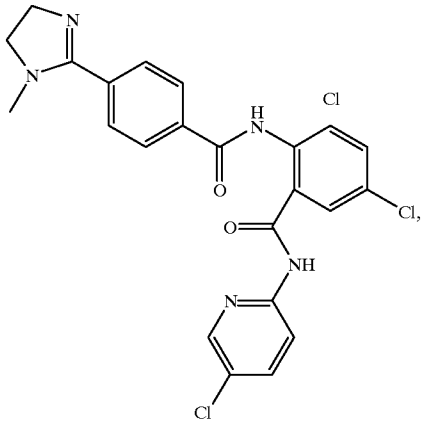

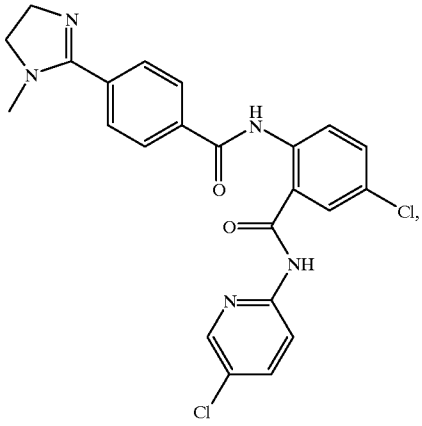

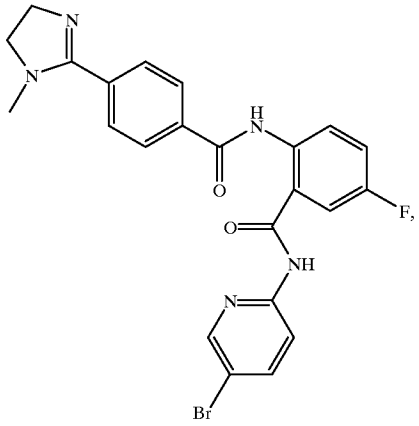

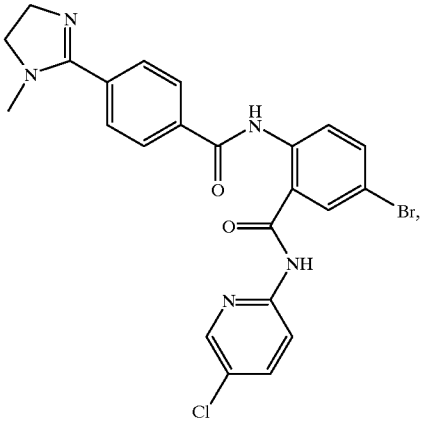

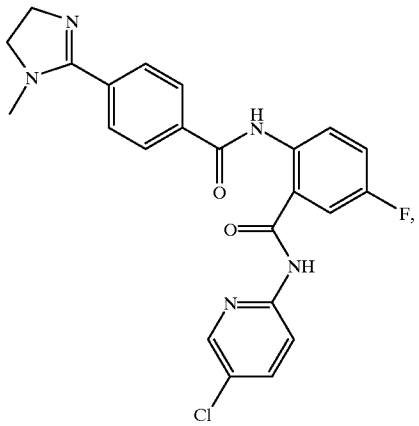

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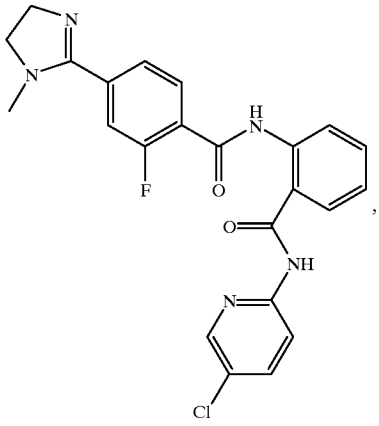

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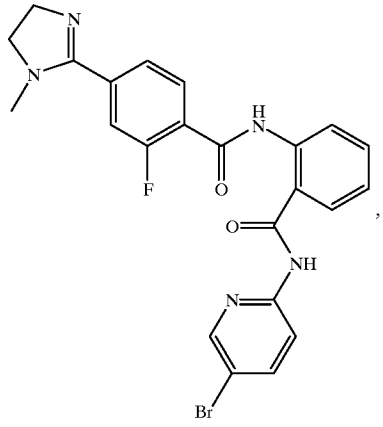

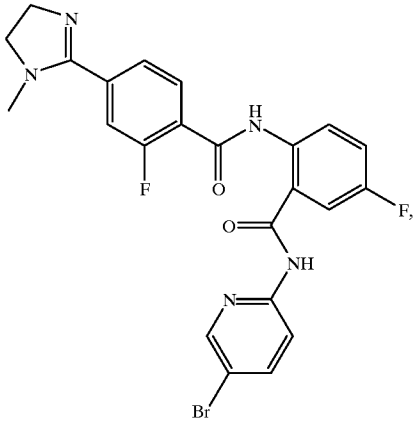

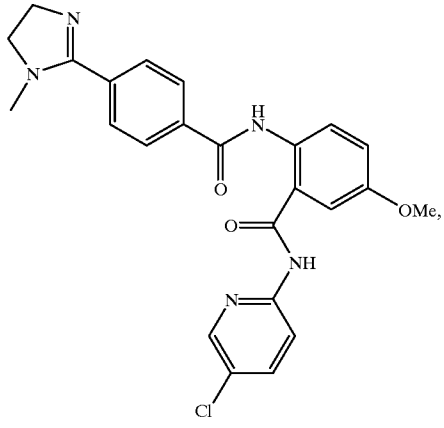

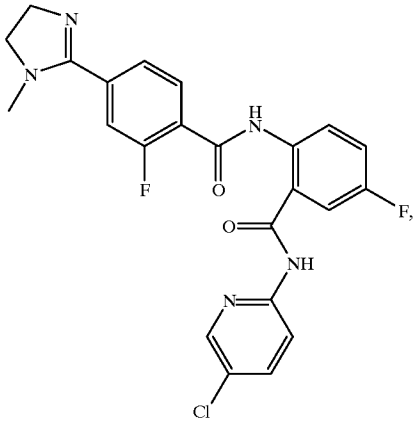

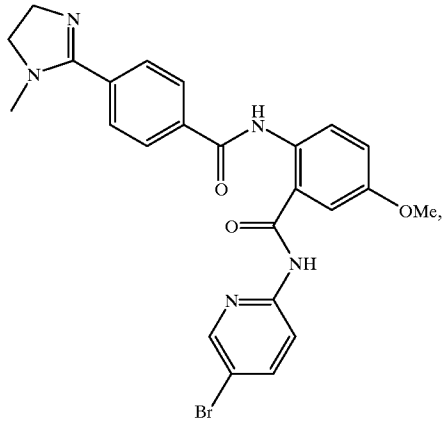

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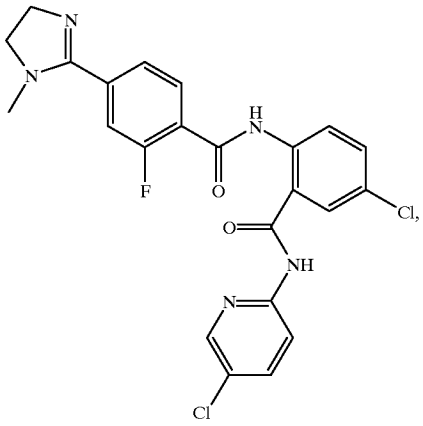

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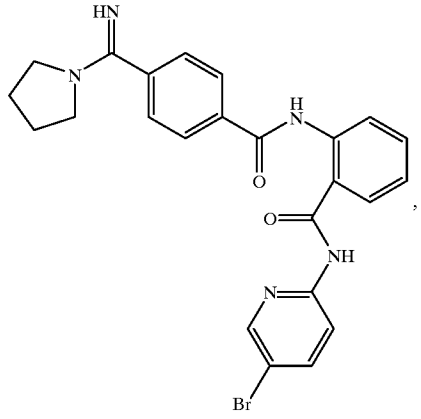

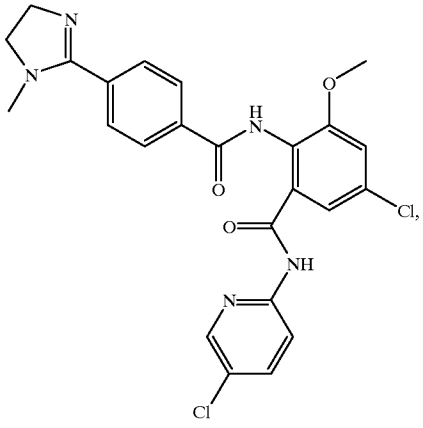

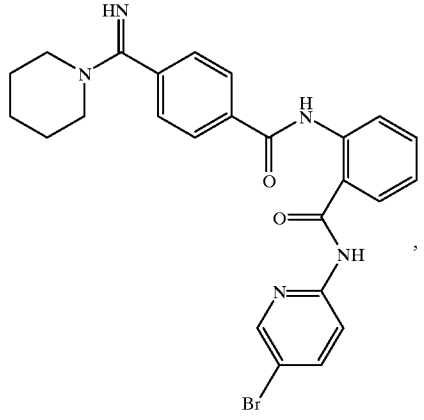

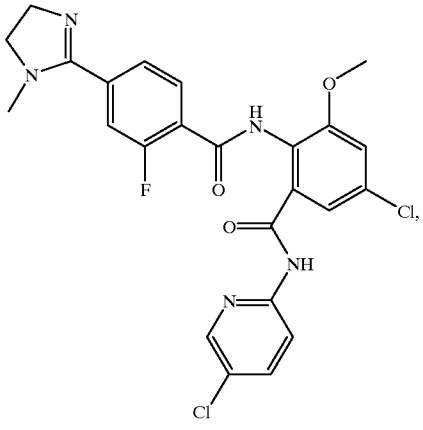

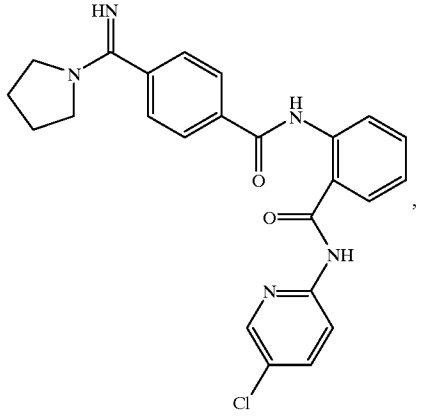

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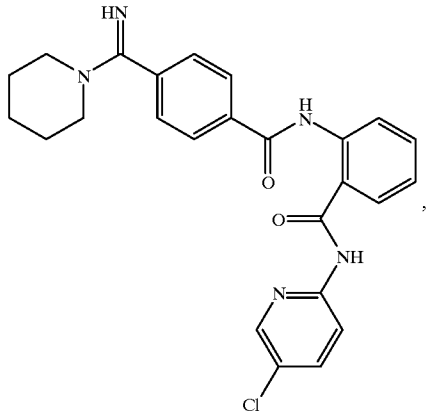

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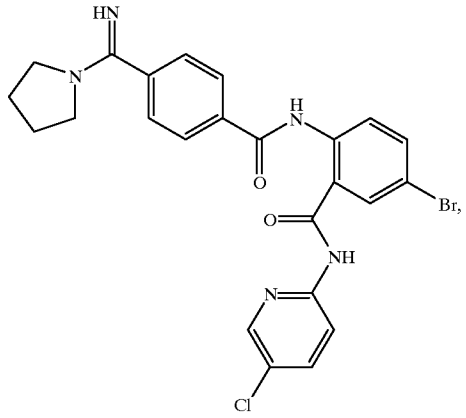

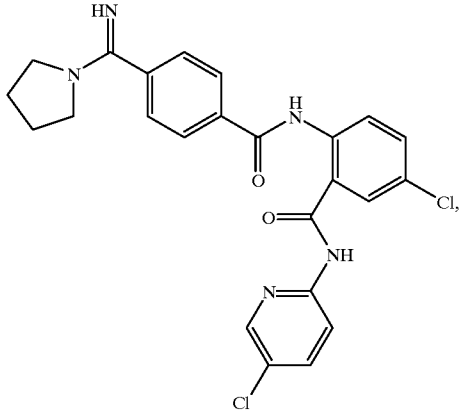

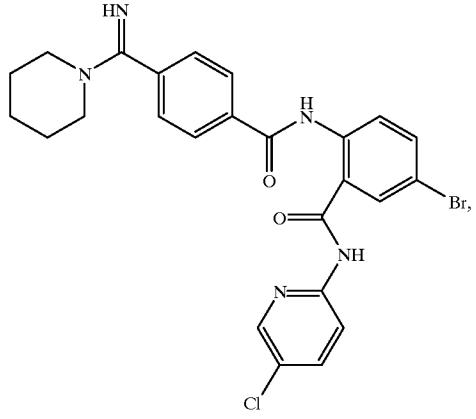

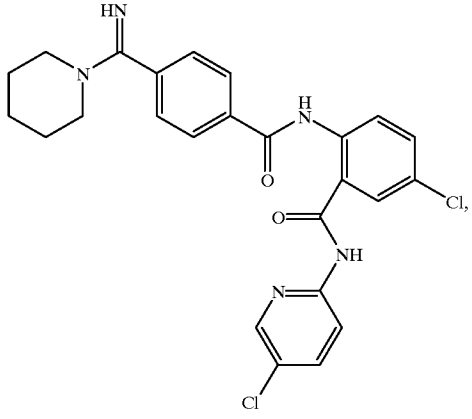

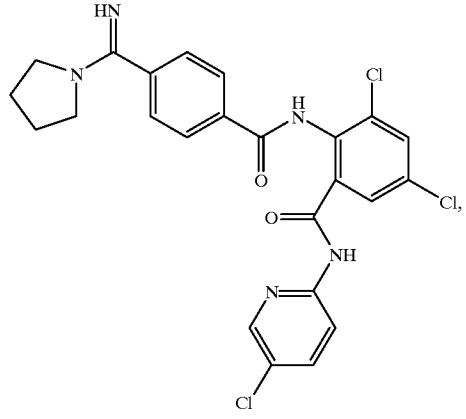

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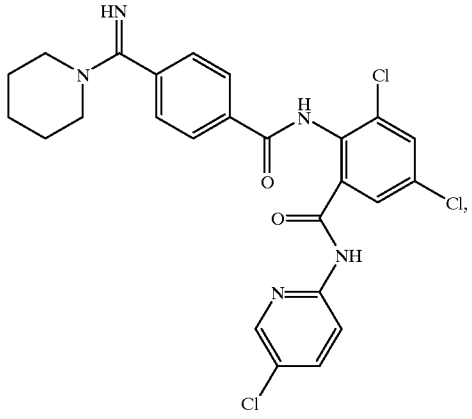

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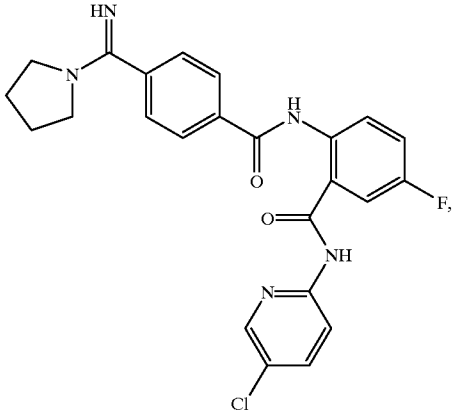

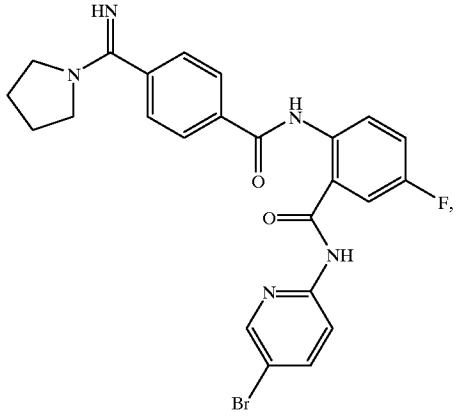

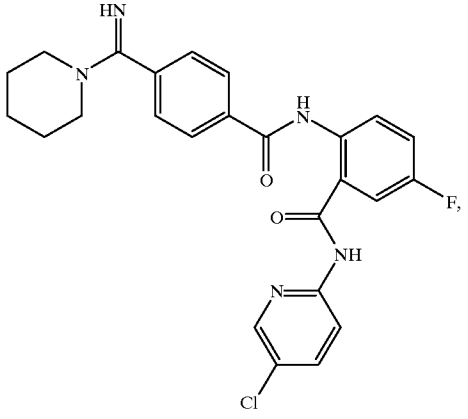

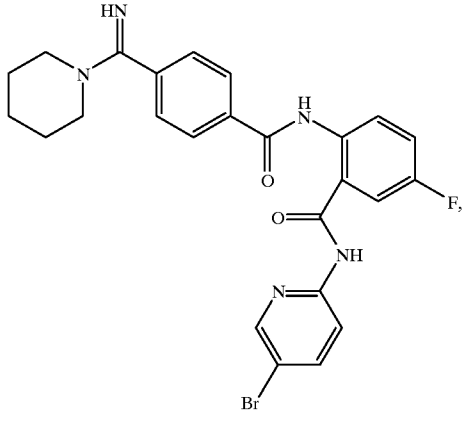

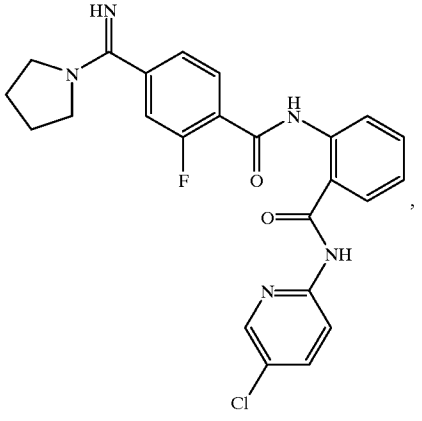

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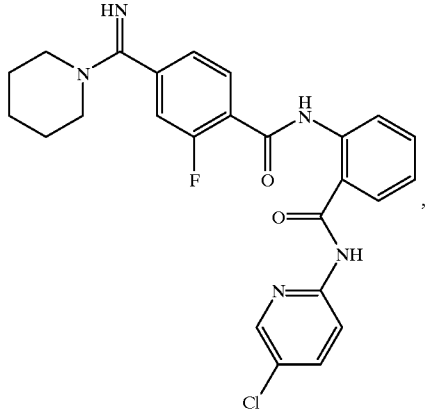

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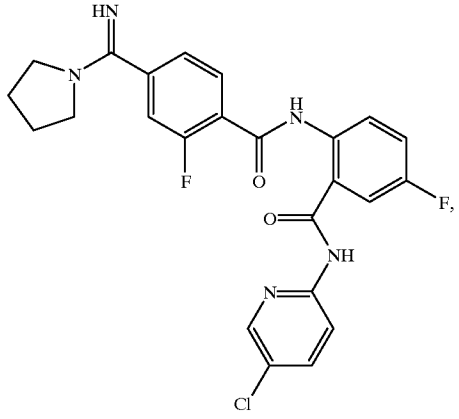

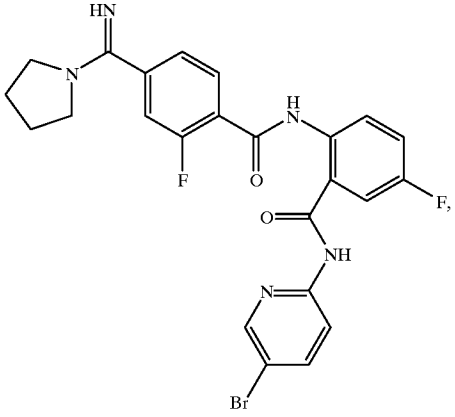

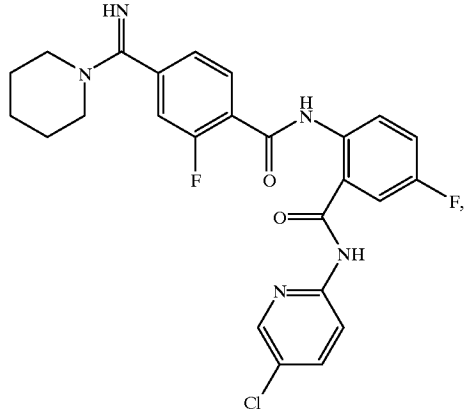

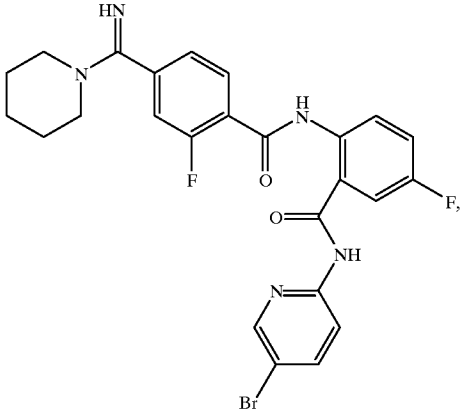

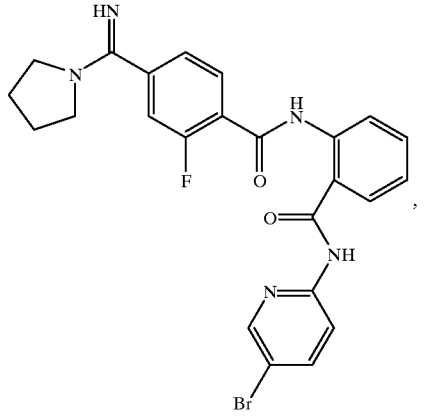

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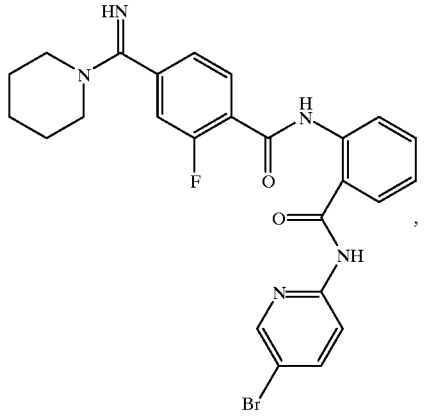

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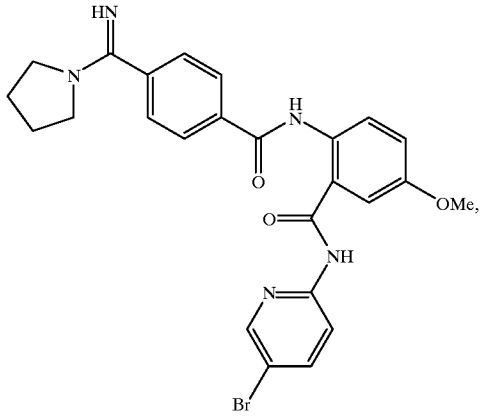

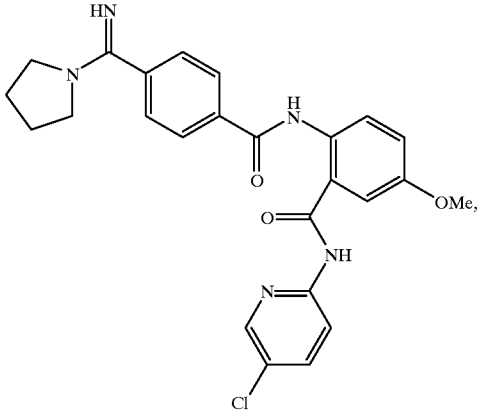

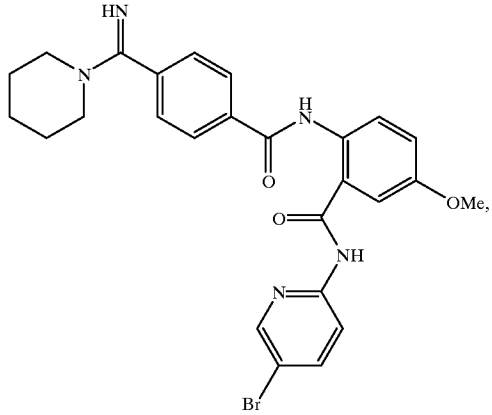

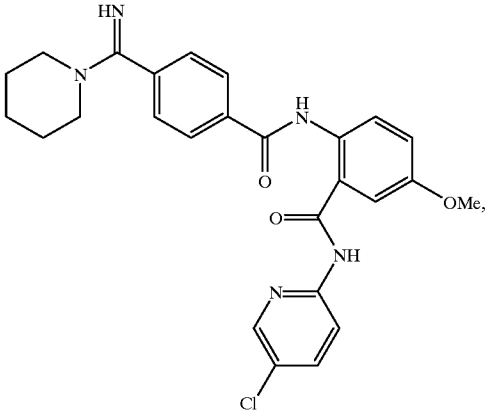

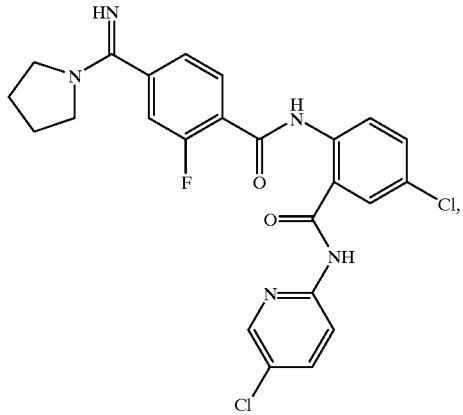

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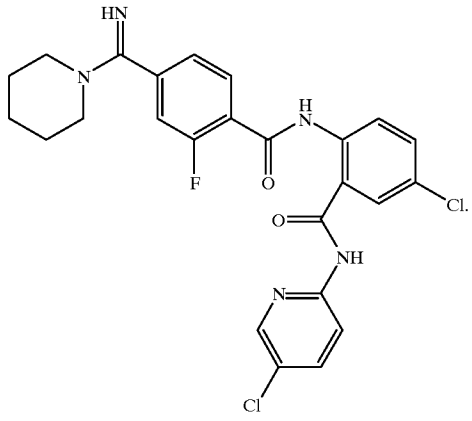

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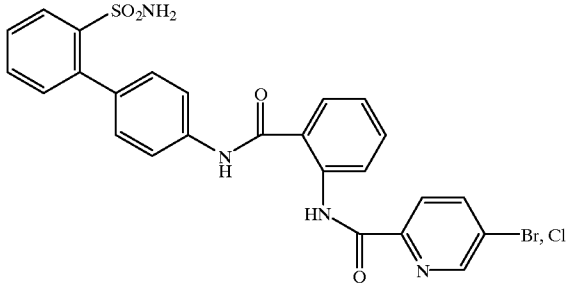
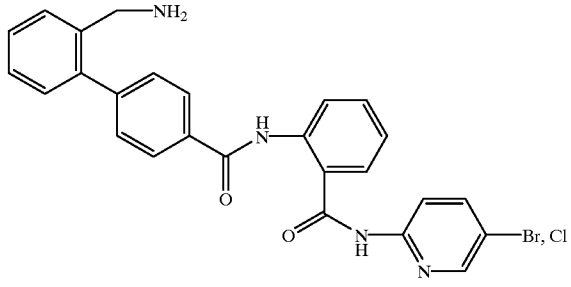
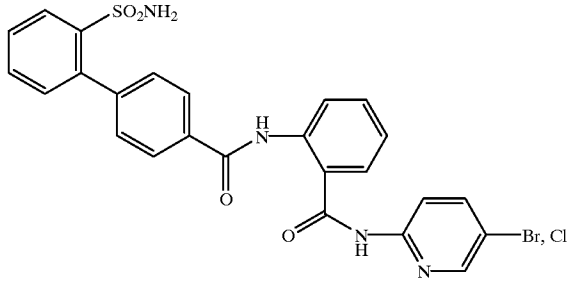
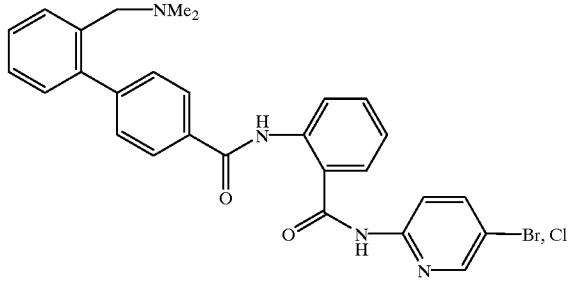
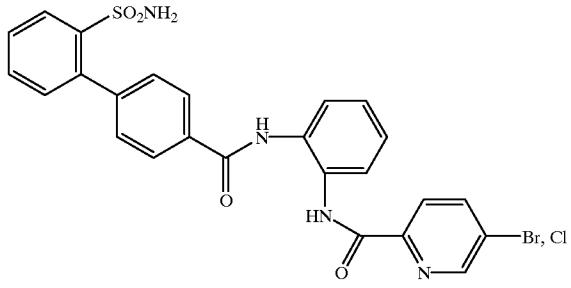


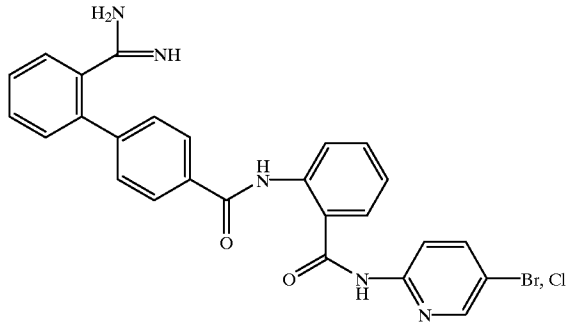


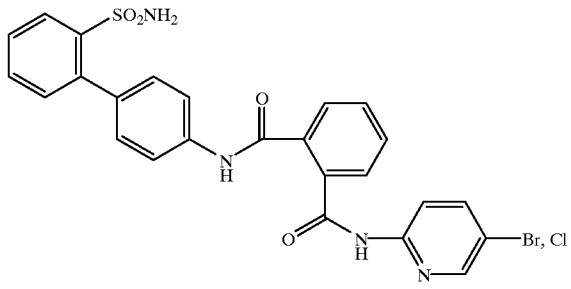
[0459] In another further preferred embodiment the present invention provides the following compounds:

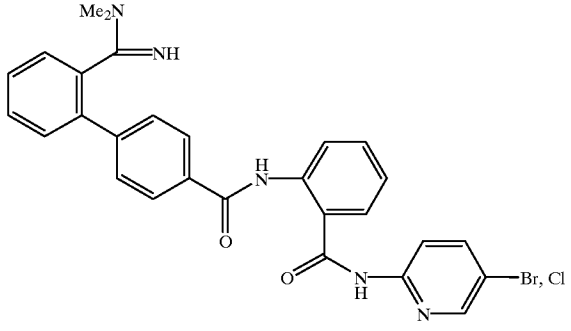












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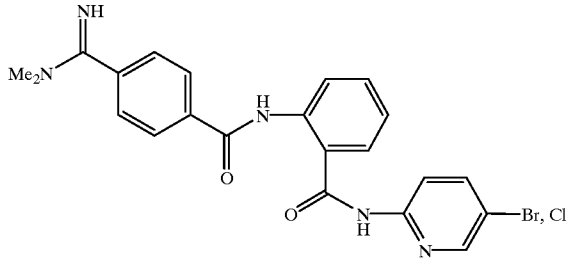

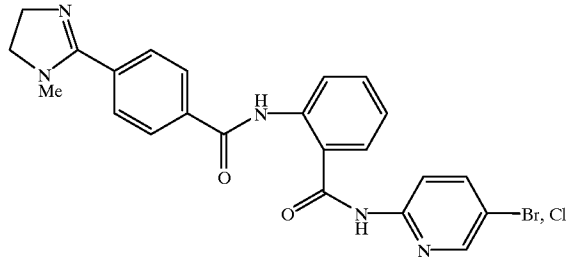

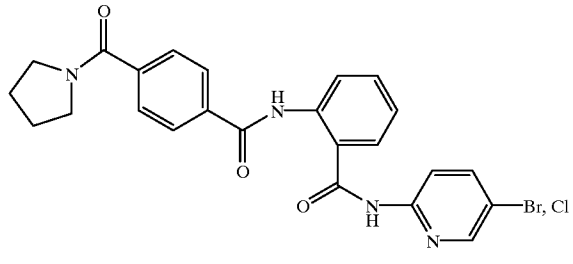

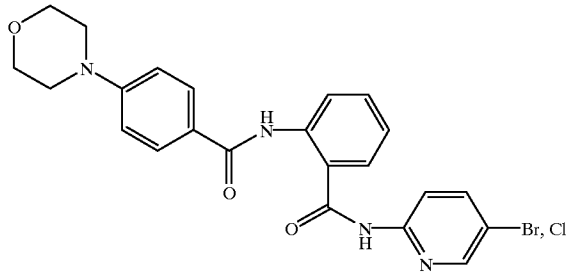

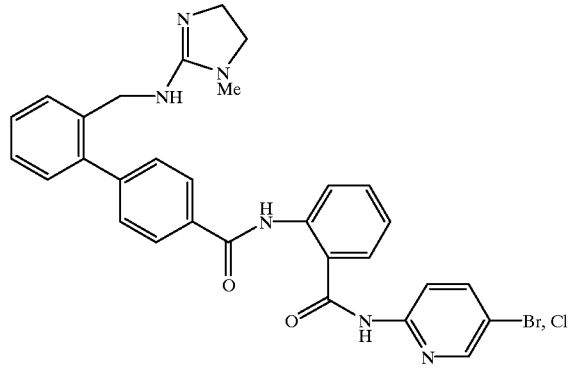

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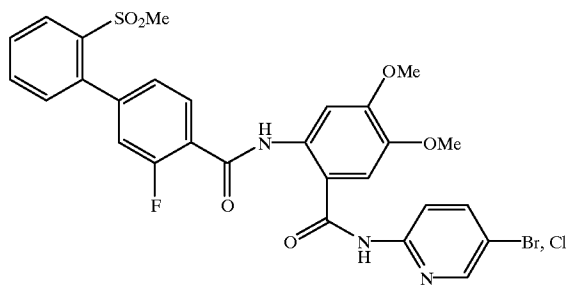

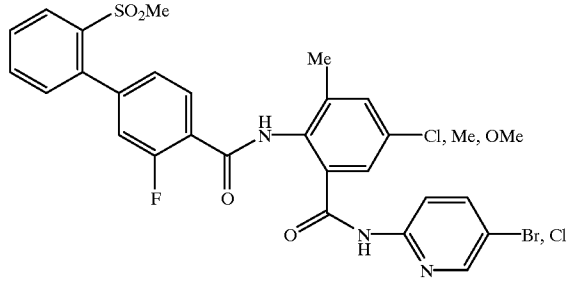

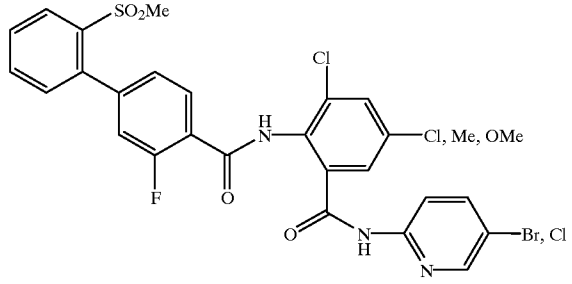

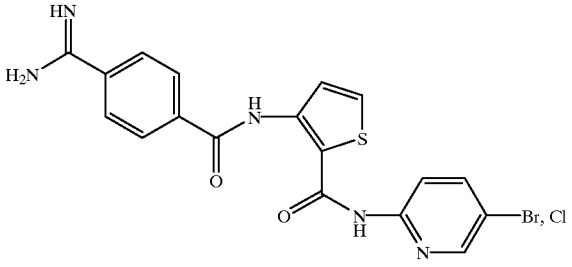

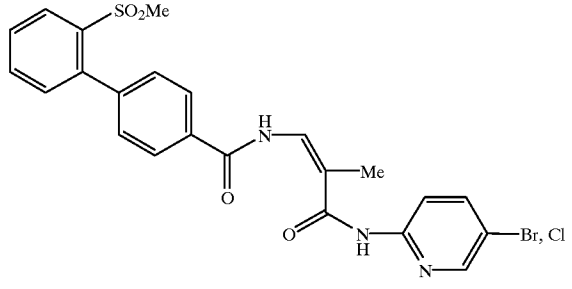

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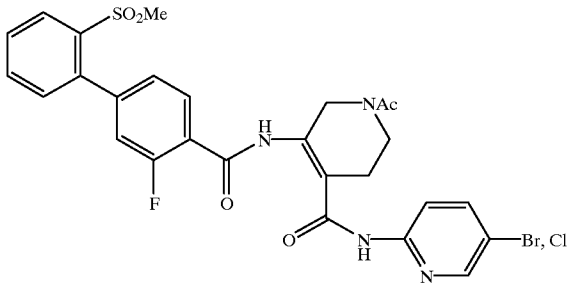
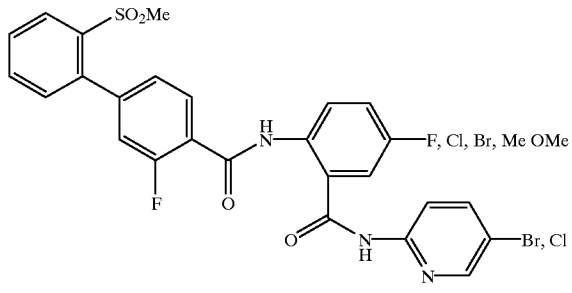
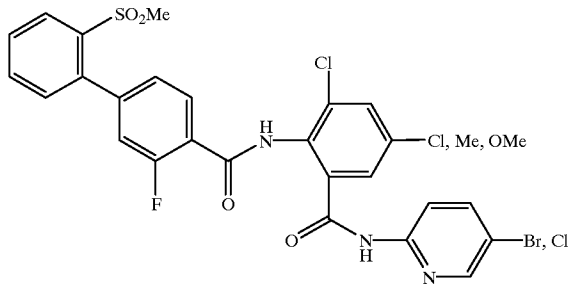
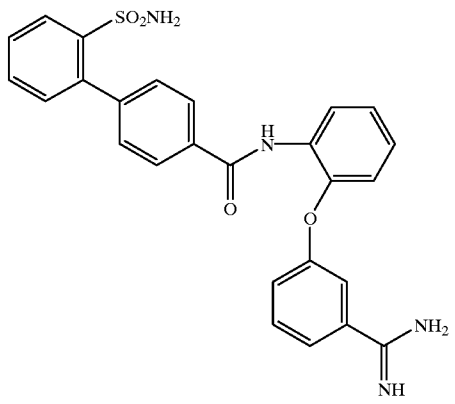






[**0460**] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[**0461**] In another further preferred embodiment the present invention provides the following compounds:



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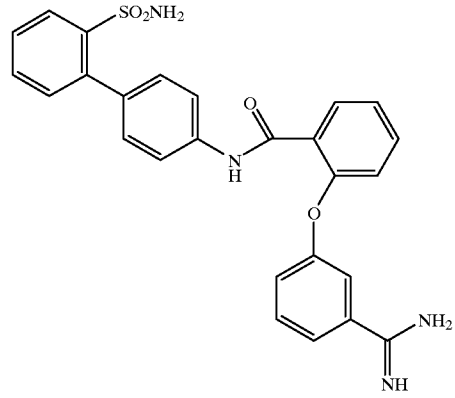

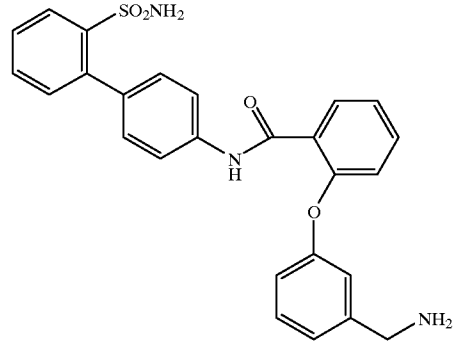

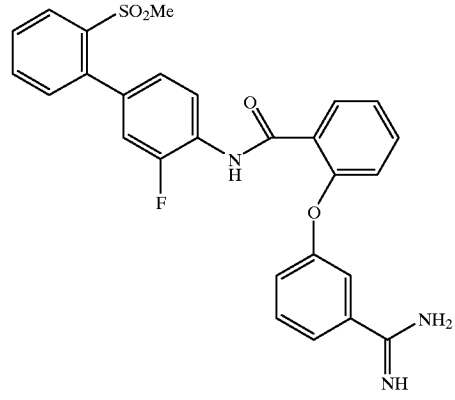

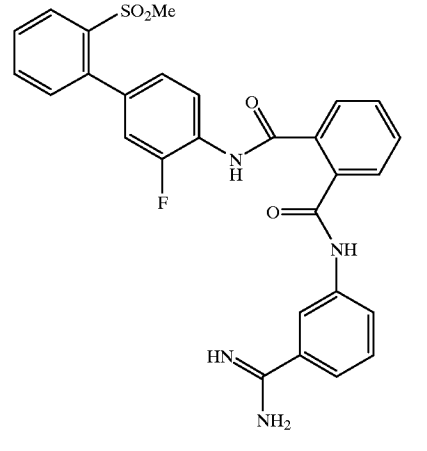

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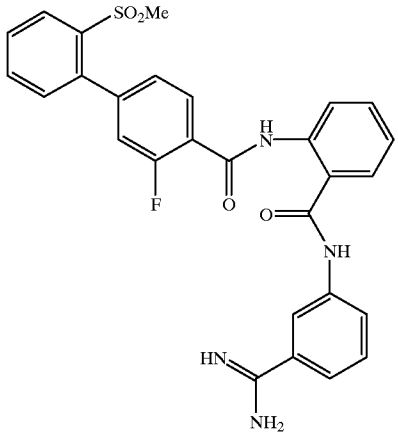

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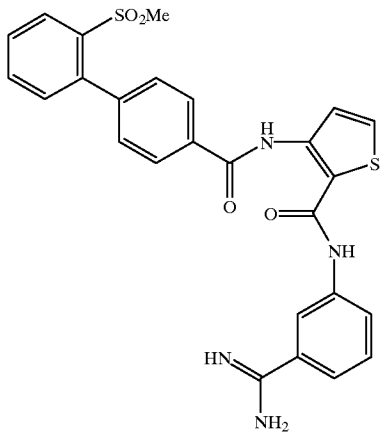

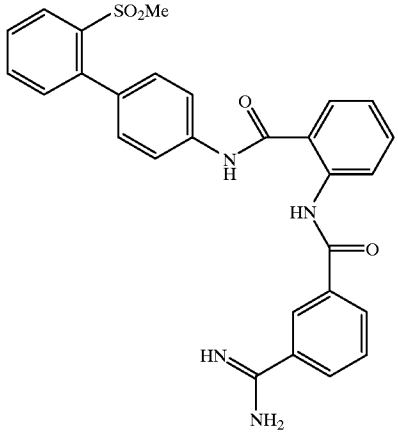

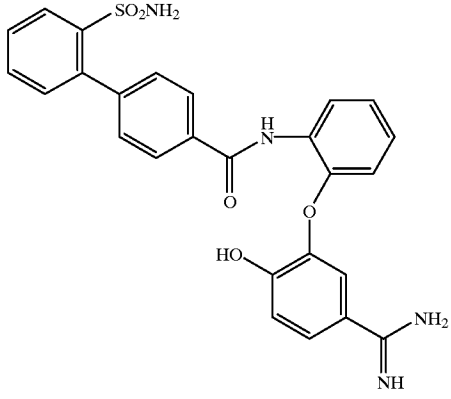

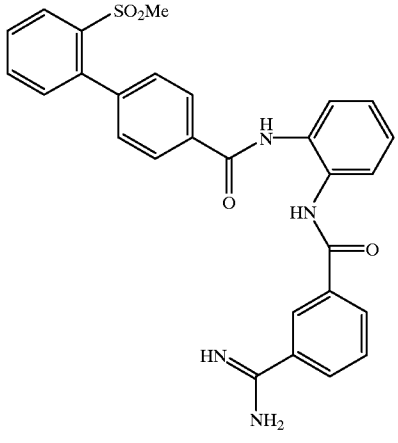

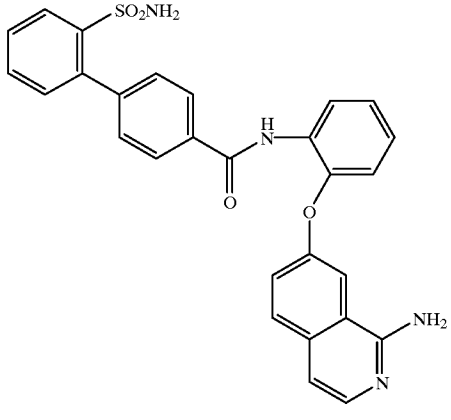

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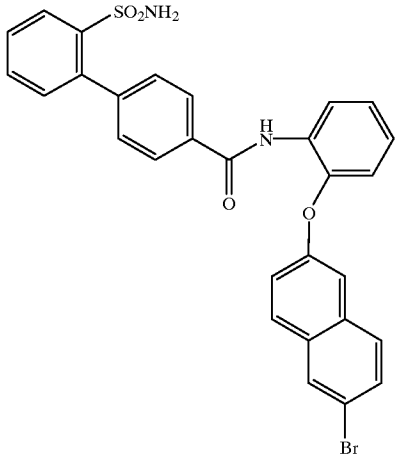

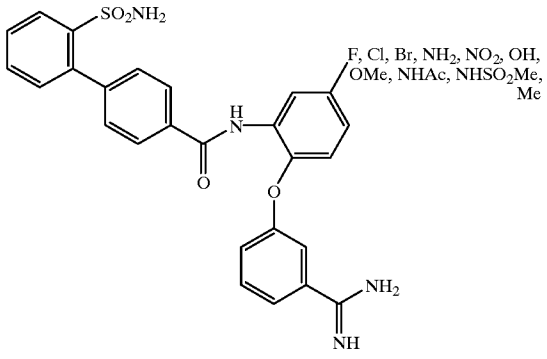

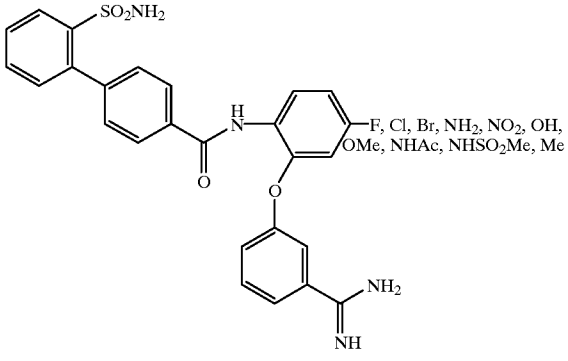

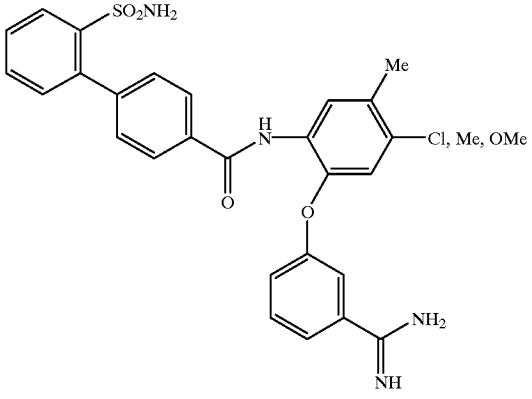

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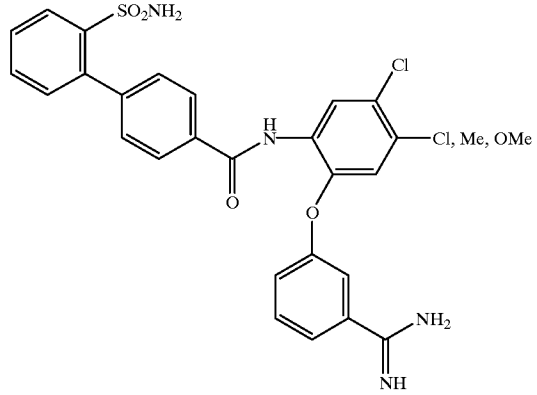
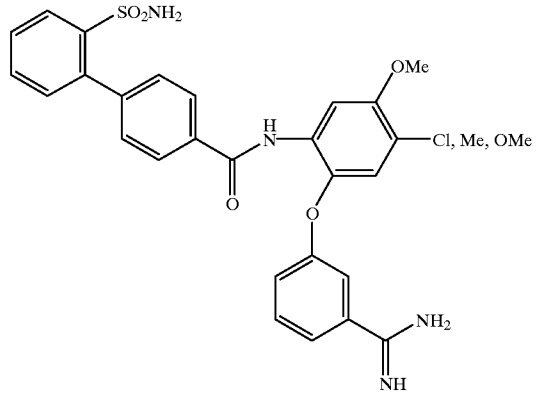
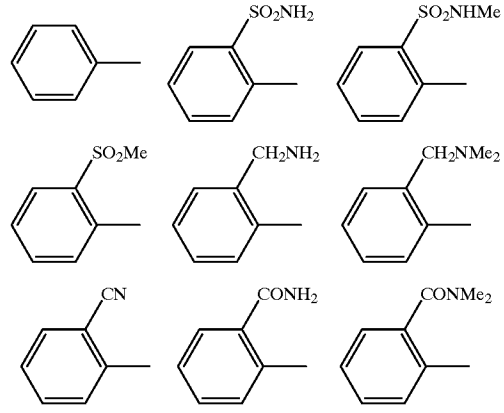




[0462] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0463] The invention also provides compounds of formula Ib, as set forth above, wherein:

[0464] A is a member selected from the group consisting of:



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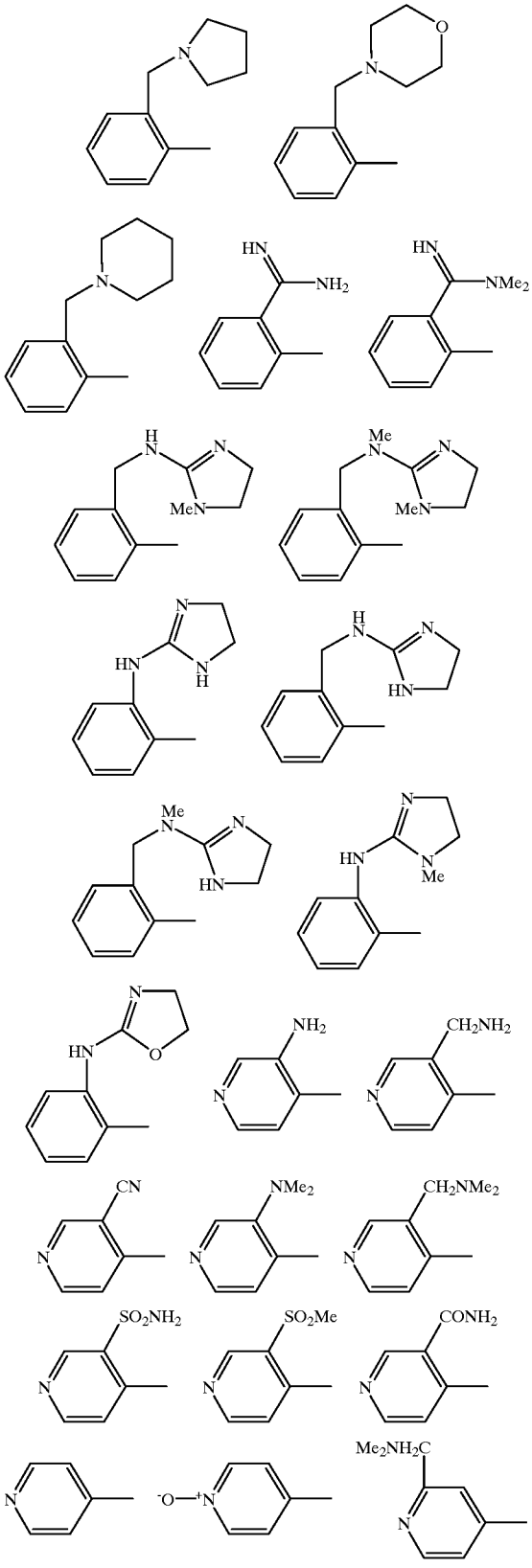

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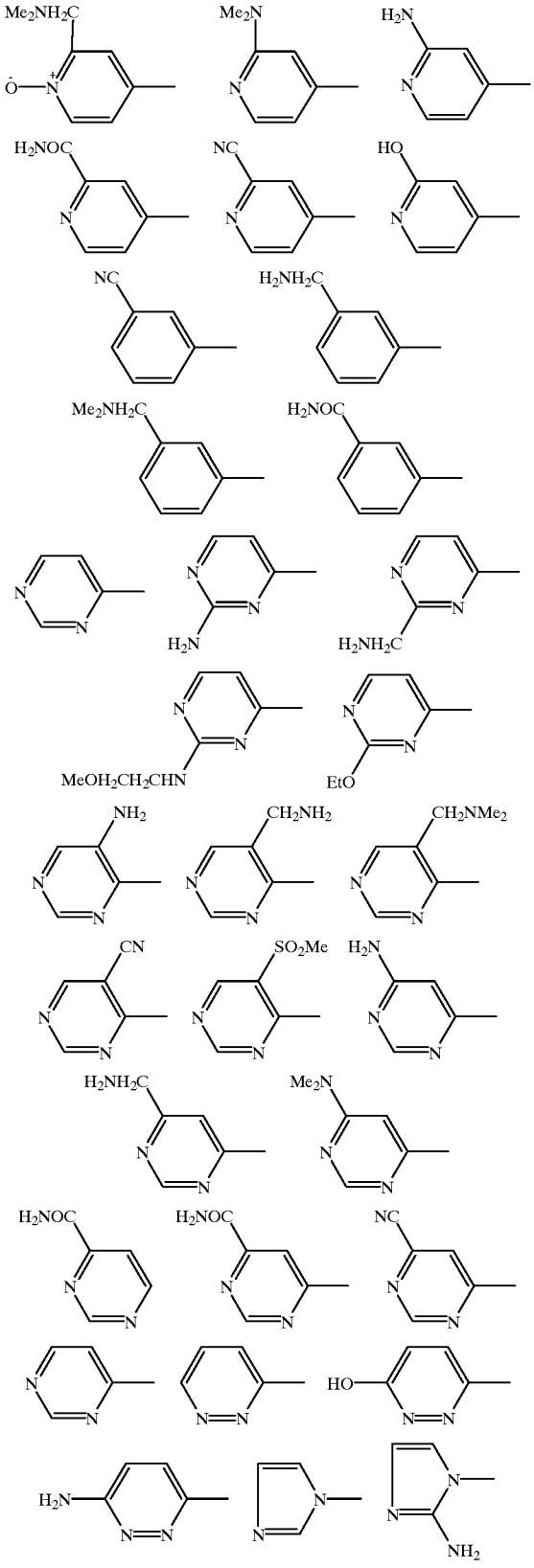

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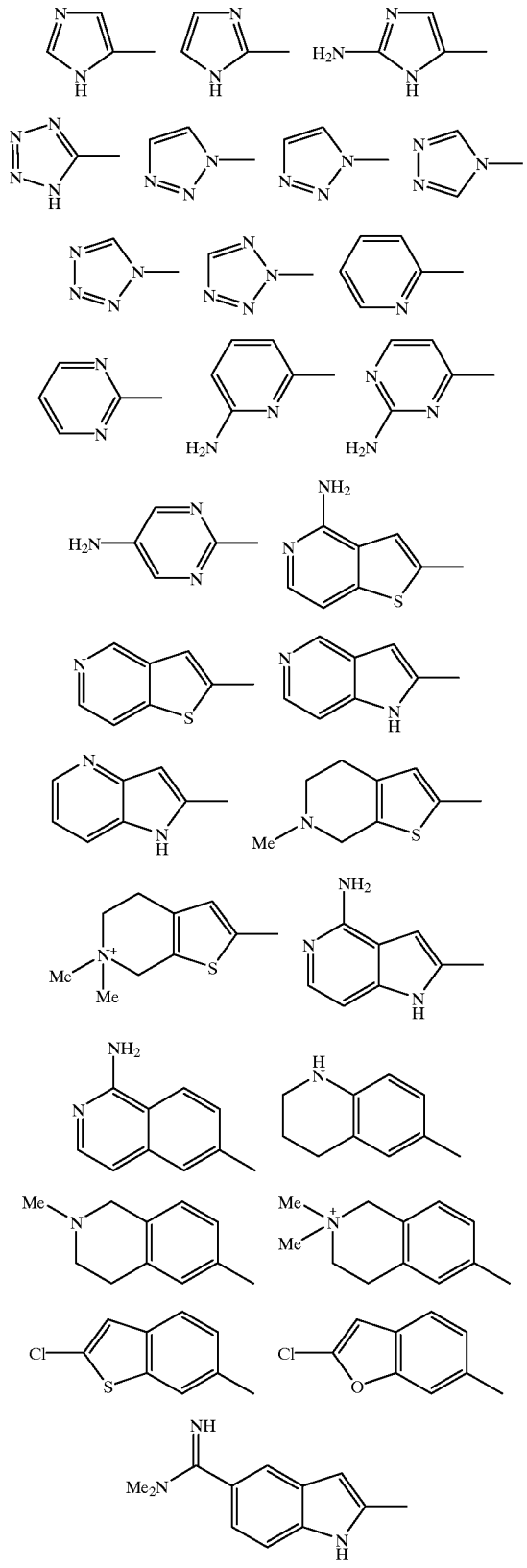

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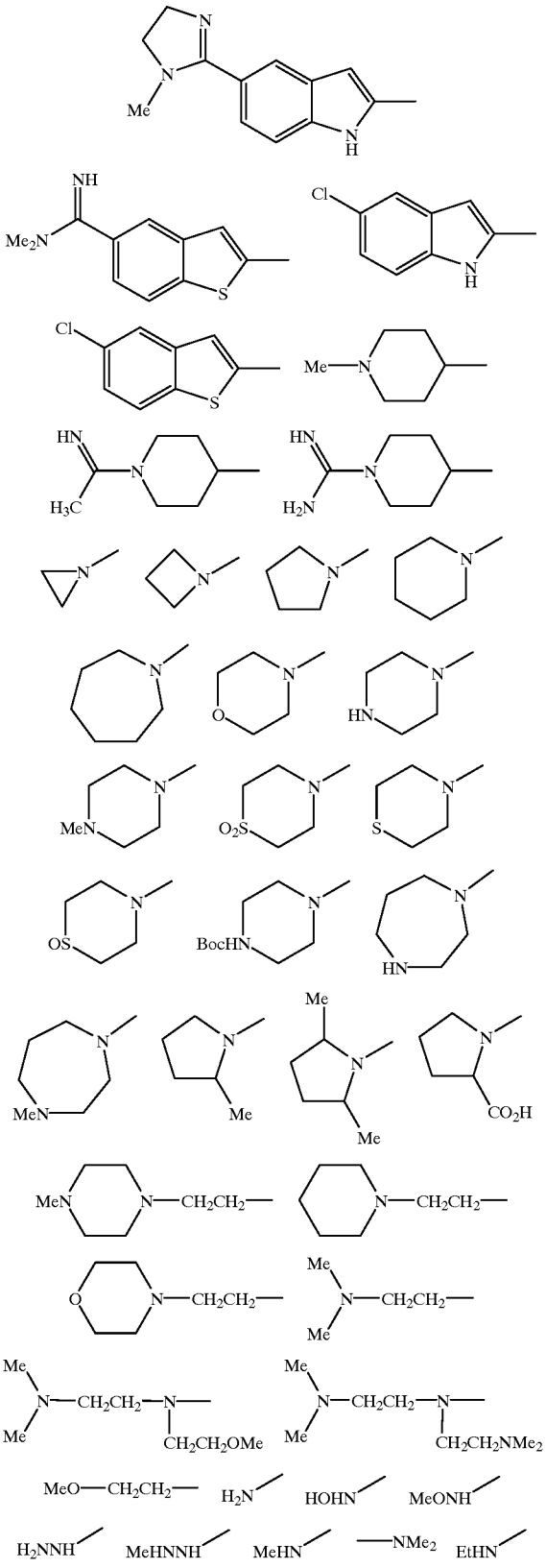

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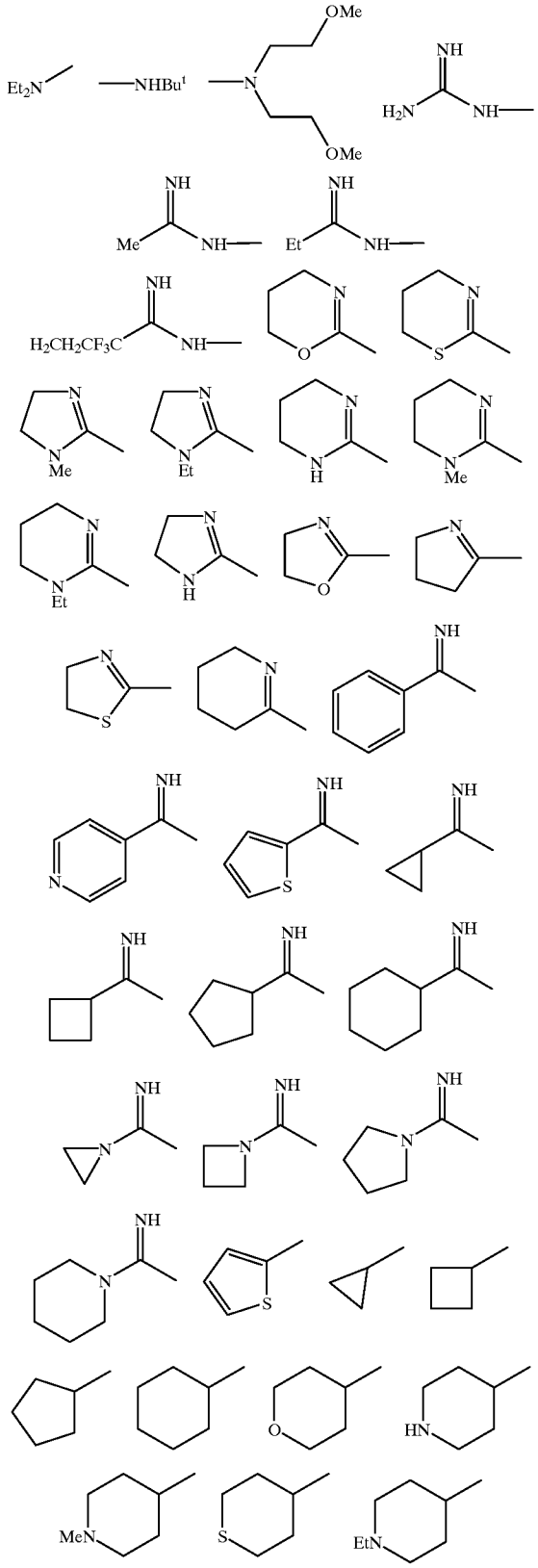

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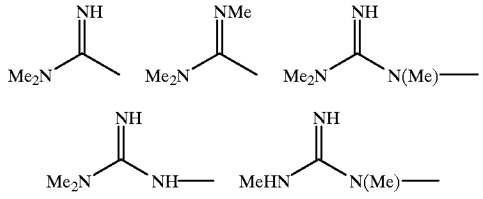
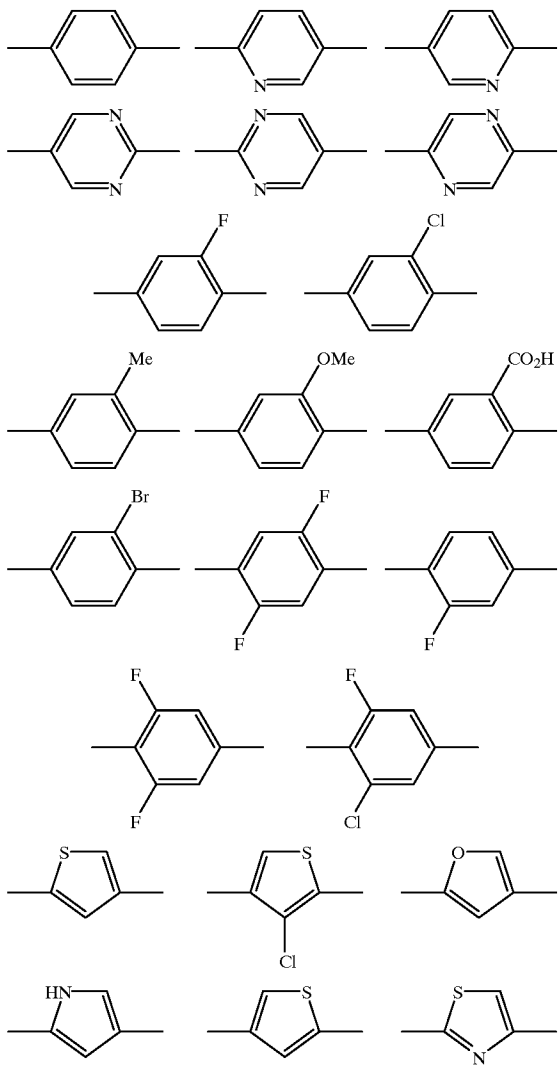


[0465] Q is a member selected from the group consisting of:

[0466] a direct link, —CH_2—, —C(═O)—, —NH—, —N(Me)—, —$NHCH_2$—, —N(Me)CH_2—, —C(═NH)—, —C(═NMe)—;

[0467] D is a direct link or is a member selected from the group consisting of:



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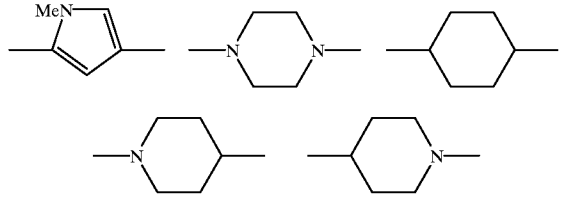
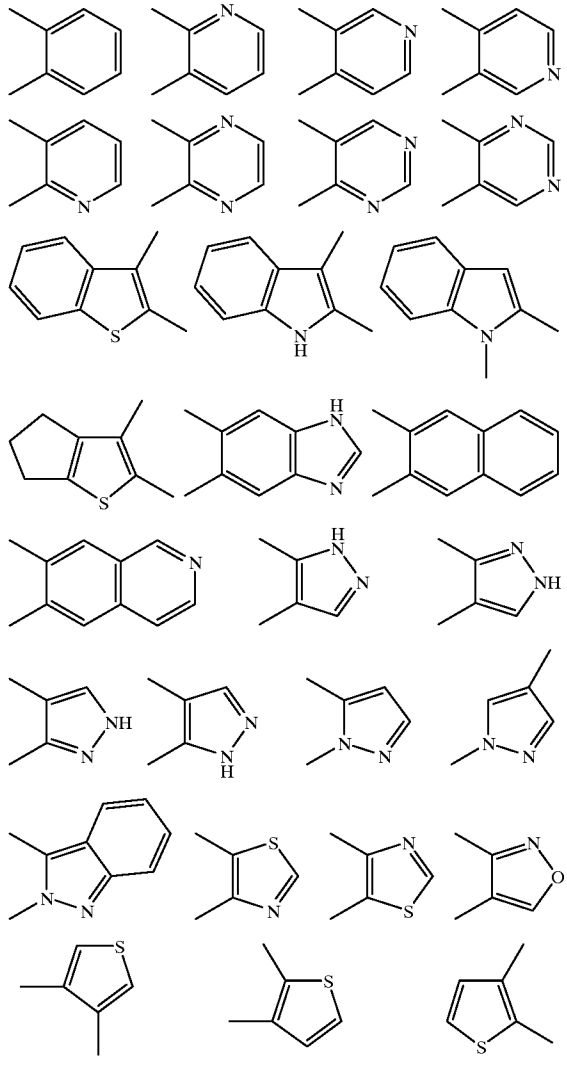


[0468] E is a member selected from the group consisting of:

[0469] a direct link, —CH_2NH—, —$NHCH_2$—, —CH_2O—, —OCH_2—, —CH_2NH—, —CONH—, —NHCO—, —CONMe—, —NMeCO—;

[0470] G is a member selected from the group consisting of:



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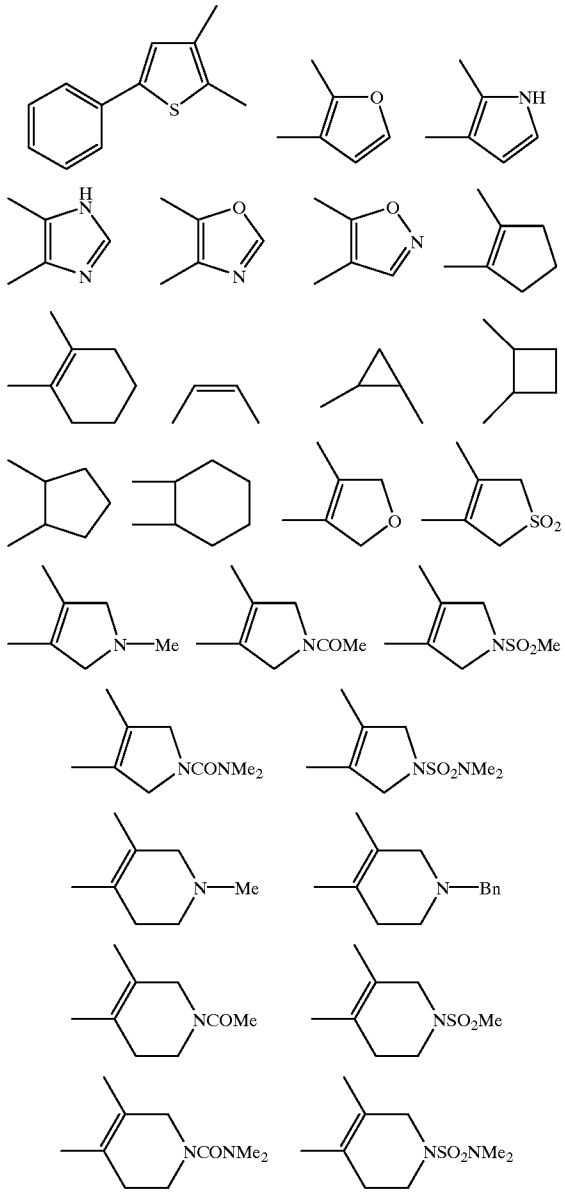
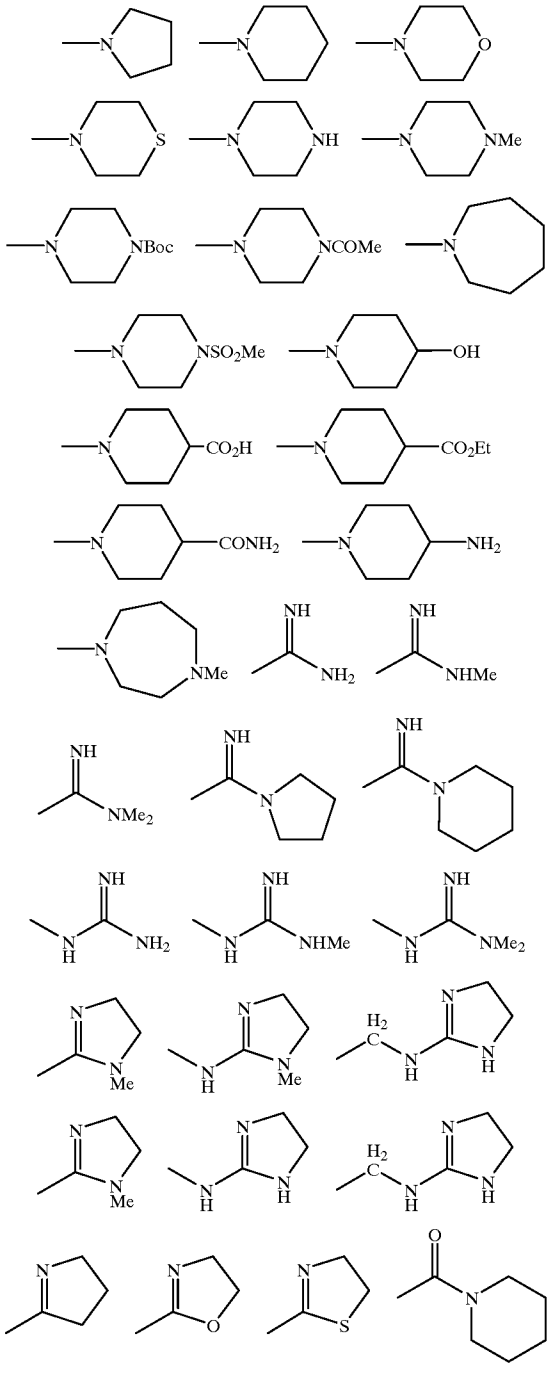


[0471] G is substituted by 0-4 R^{1d} groups and each R^{1d} group is independently selected from the group consisting of:

[0472] H, —Me, —F, —Cl, —Br, aryl, heteroaryl, —NH_2, —NMe_2, —NHMe, —$NHSO_2Me$, —NHCOMe, —CH_3, —CF_3, —OH, —OCH_3, —SCH_3, —OCF_3, —OCH_2F, —$OCHF_2$, —OCH_2CF_3, —OCF_2CF_3, —NO_2, —CN, —CO_2H, —CO_2Me, —CO_2Et, —$CONH_2$, —CONHMe, —$CONMe_2$, —SO_2NH_2, —SO_2CH_3, —SO_2NMe_2, —CH_2OH, —CH_2NH_2, —CH_2NHMe, —CH_2NMe_2, —OCH_2CO_2H, —OCH_2CO_2Me, —OCH_2CO_2Et, —OCH_2CONH_2, —OCH_2CONMe_2, —$OCH_2CONHMe$, —OCH_2CH_2OMe, —OCH_2CH_2OEt, —$OCH_2CH_2NH_2$, —OCH_2CH_2NHMe, —$OCH_2CH_2NMe_2$, —$NHCH_2CH_2OMe$, —SCH_2CH_2OMe,

—$SO_2CH_2CH_2OMe$, —$OCH_2CH_2SO_2Me$, —$NHCH_2CH_2NHMe$, —$NHCH_2CH_2NMe_2$, —$N(CH_2CH_2OH)_2$, —$N(CH_2CH_2OMe)_2$, —$NHCH_2CO_2H$, —$NHCH_2CO_2Et$, —$NHCH_2CO_2Et$, —$NHCH_2CONH_2$, —$NHCH_2CONMe_2$, —$NHCH_2CONHMe$, —$N(CH_3)CH_2CO_2H$, —$N(CH_3)CH_2CO_2Et$, —(NMe)CH2COOH, —N(Me)CH2CONH2, —N(Me)CH2CH2NMe2, —N(Me)CH2CH2OMe, —NHCH2CH2OMe,



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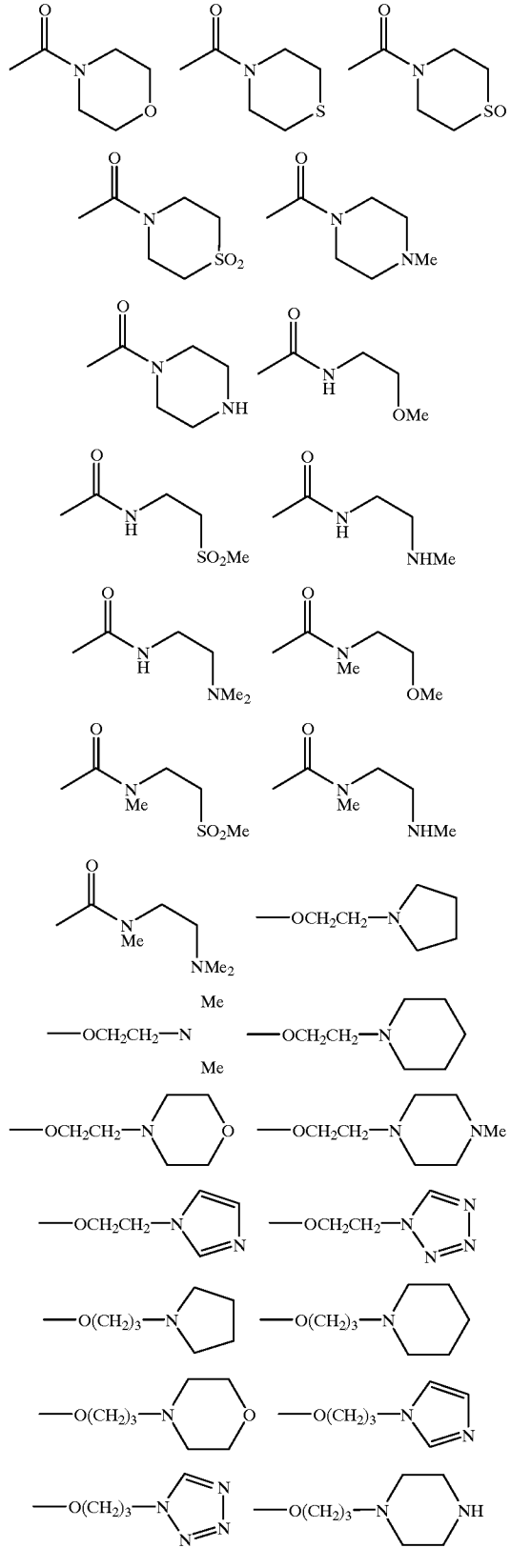

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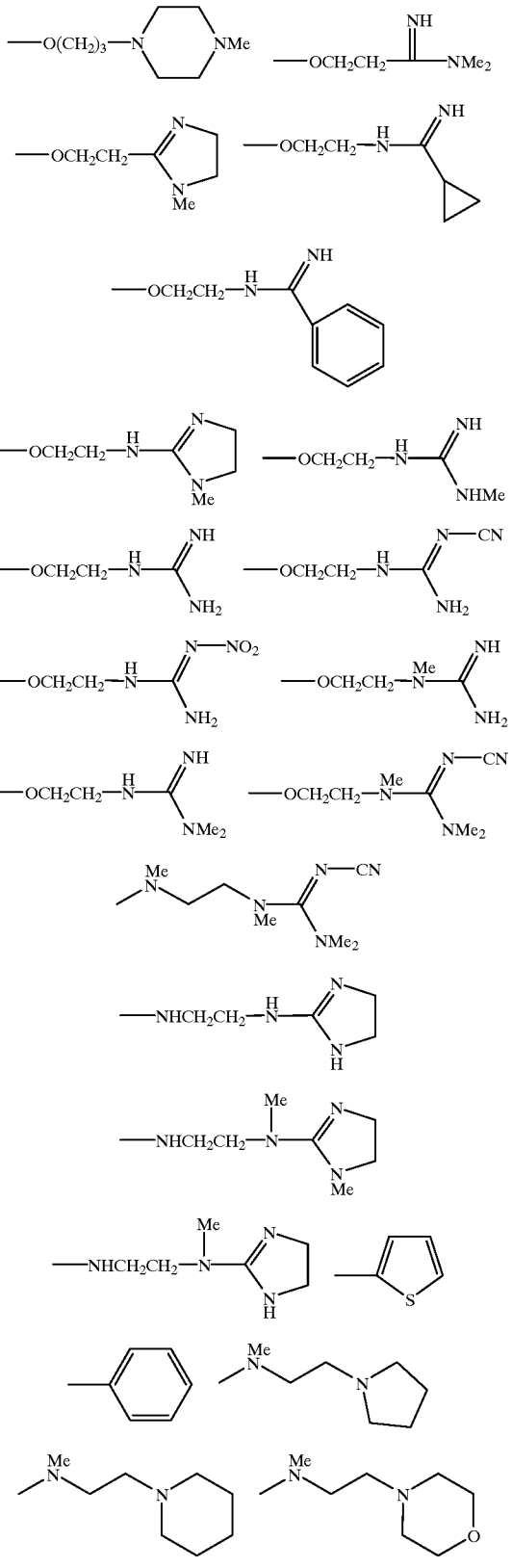

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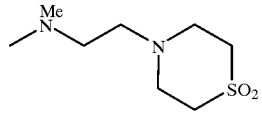
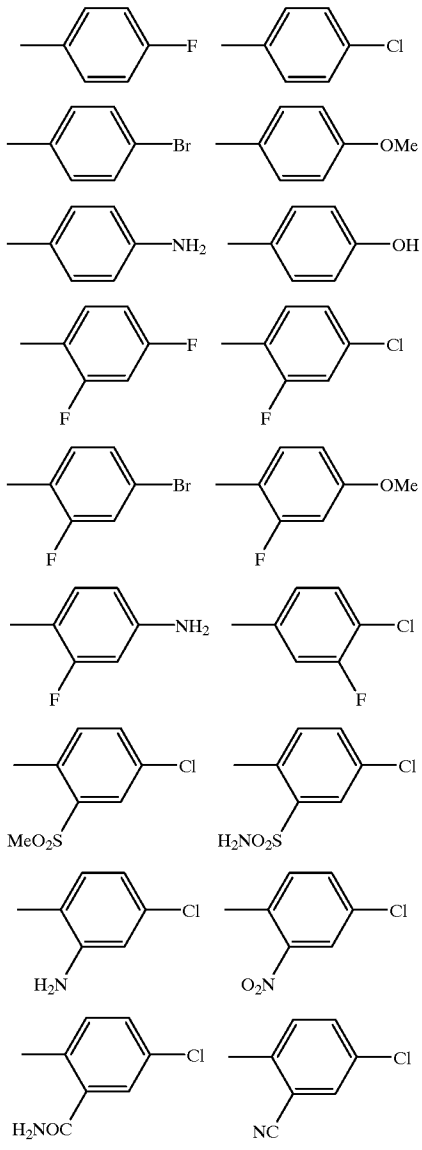


[0473] J is a member selected from the group consisting of:

[0474] a direct link, —SO2—, —CO—, —O—, —NH—, —C(═O)—NH— and —NH—C(═O)—;

[0475] X is a member selected from the group consisting of:



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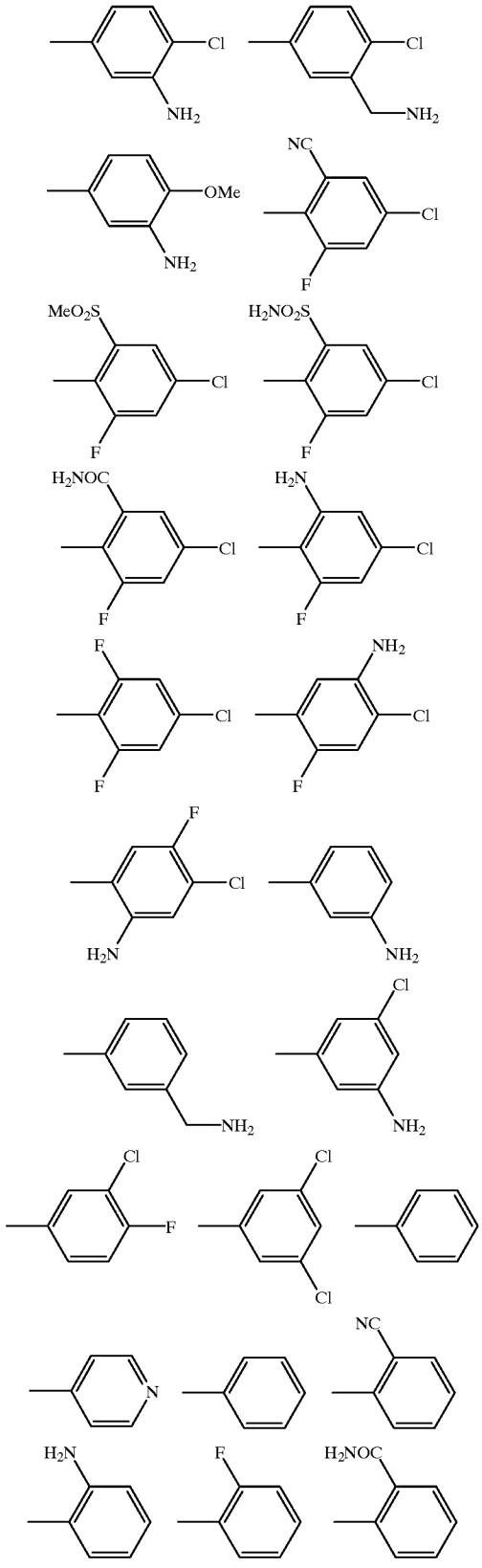

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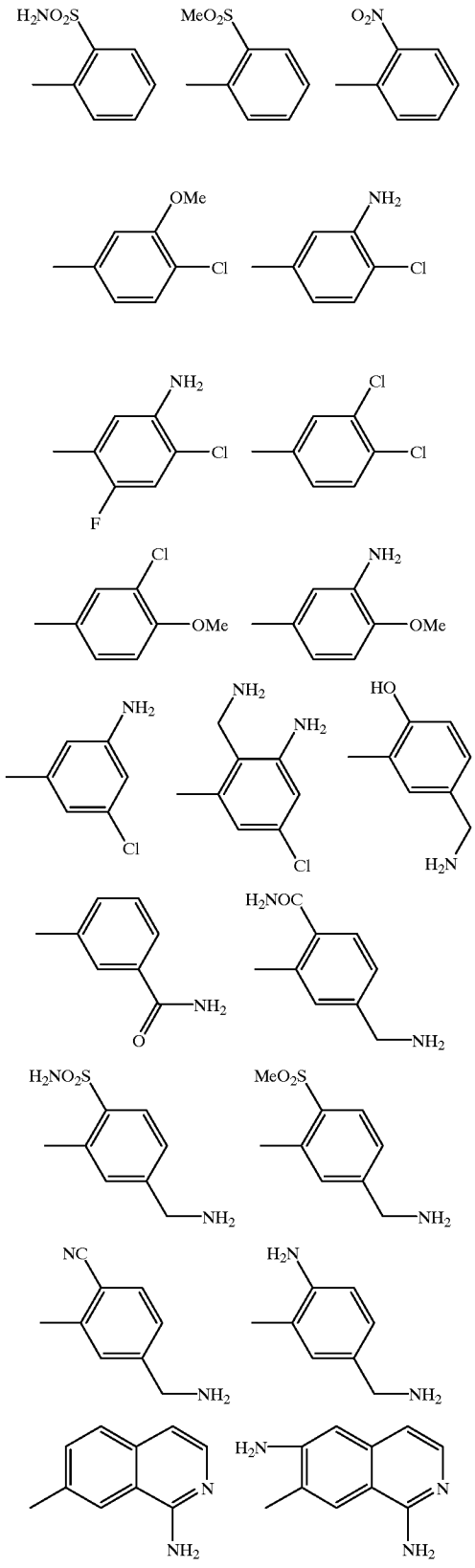

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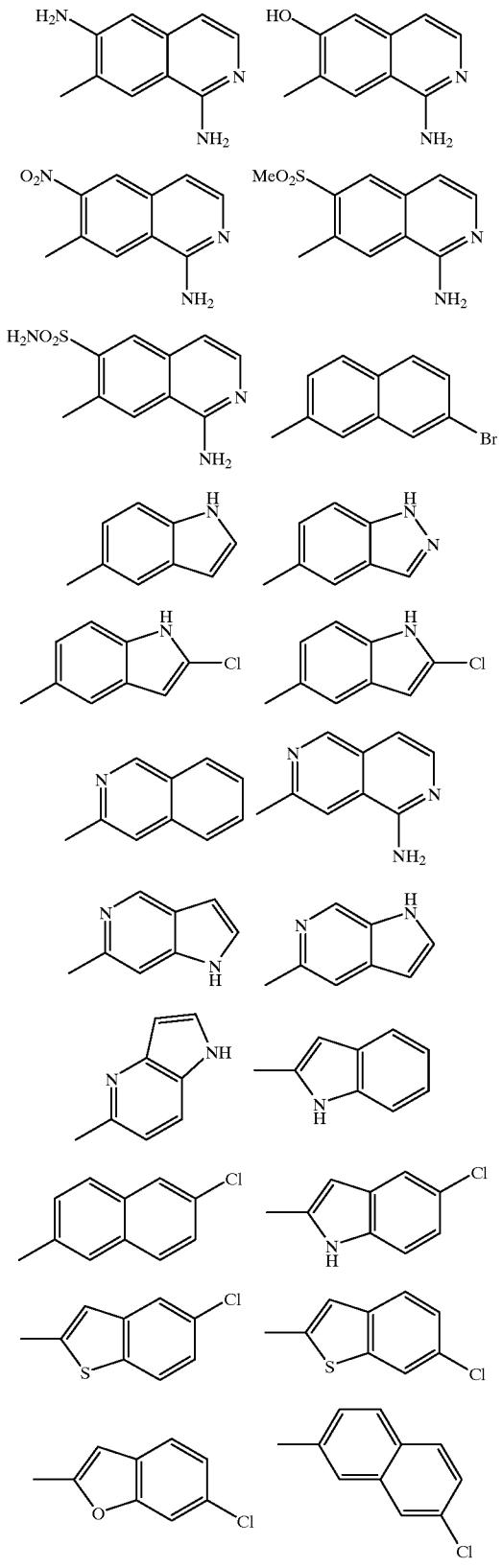

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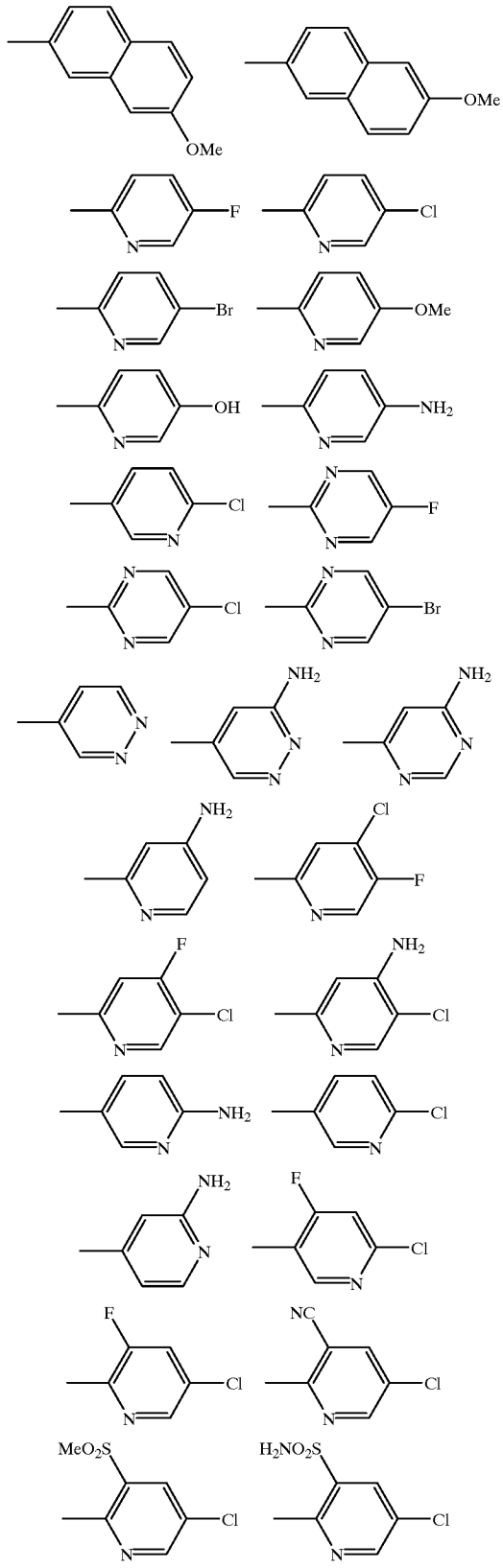

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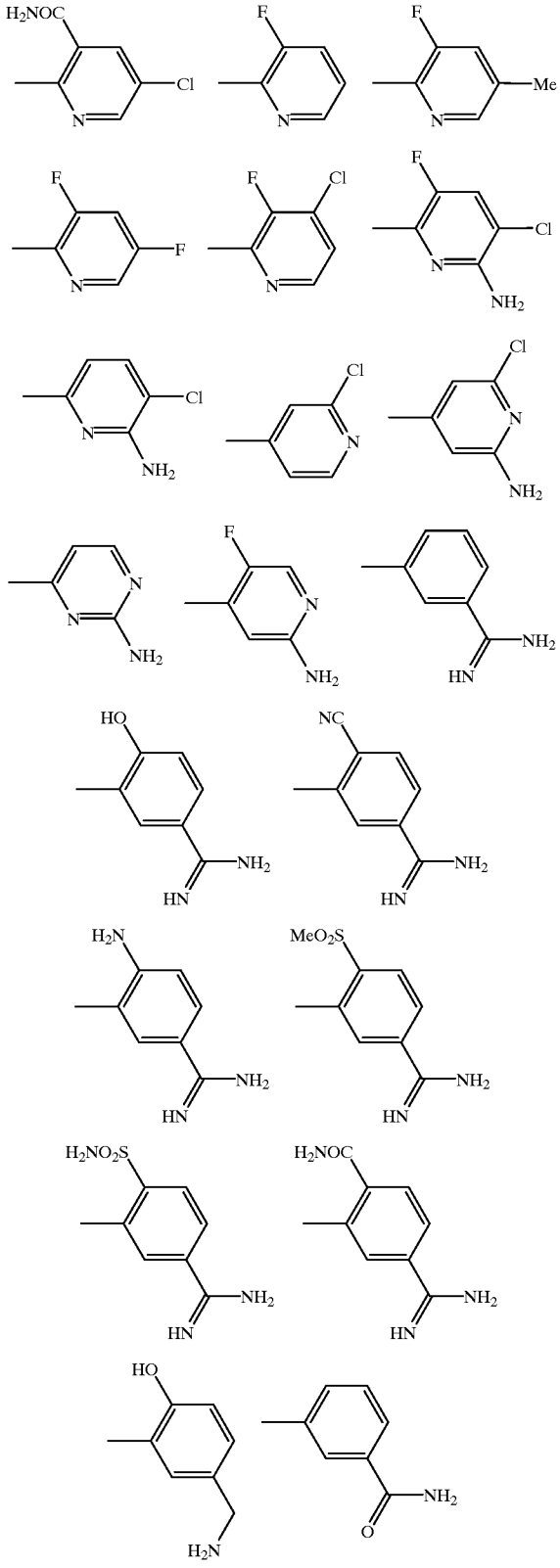

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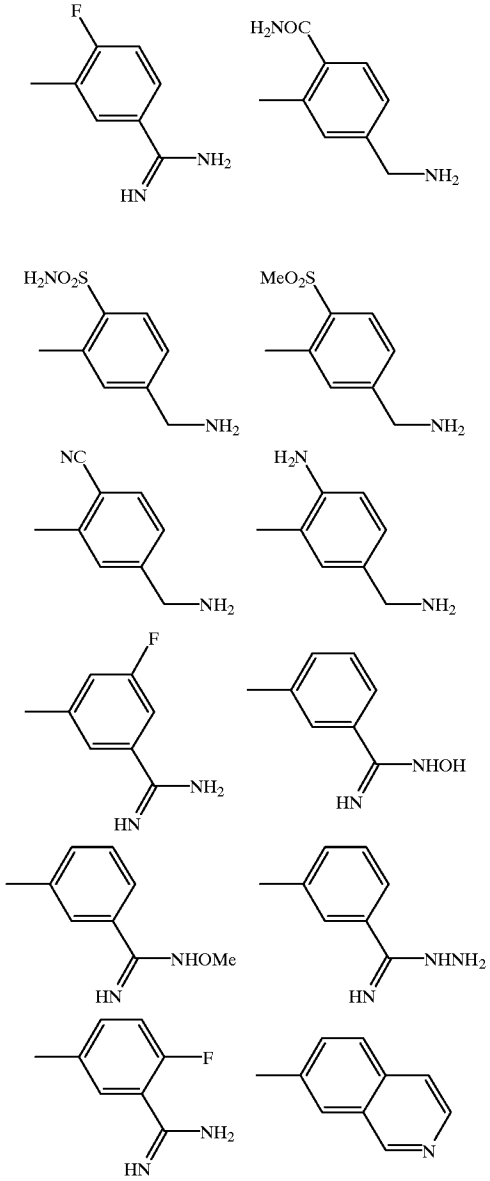
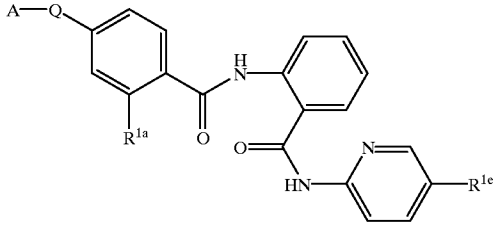


[0476] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0477] The invention provides compound of formula Ib, as described above, having the following structure:



[0478] where:

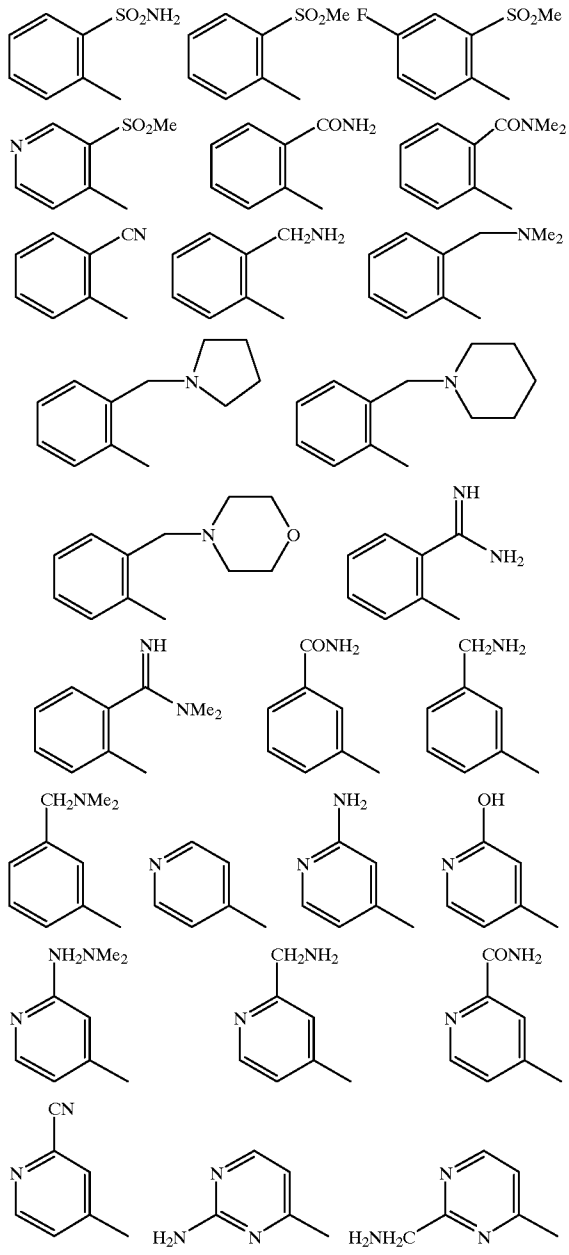
[0479] R^{1a} is a member selected from the group consisting of:

[0480] H, —F, —Cl and —Br;

[0481] R^{1e} is a member selected from the group consisting of:

[0482] H, —F, —Cl, —Br, —OMe, —OH, —Me, —CF_3 and —CH_2NH_2; and

[0483] A-Q is a member selected from the group consisting of:



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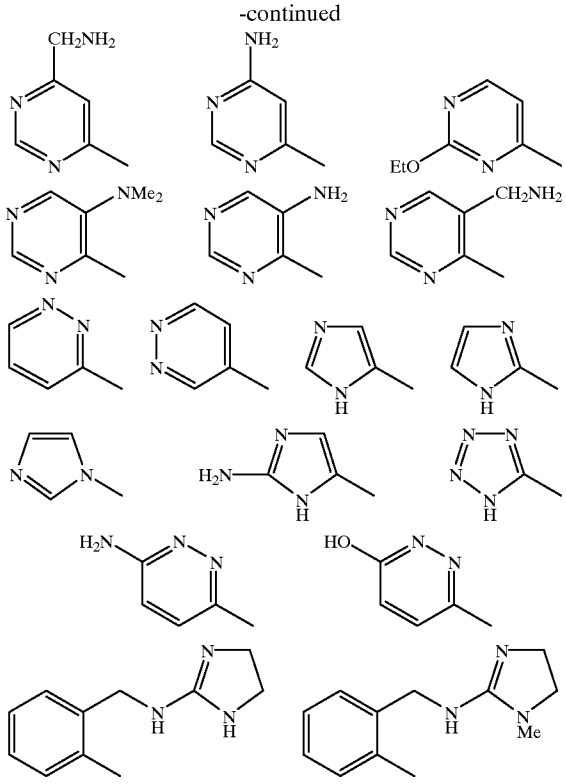
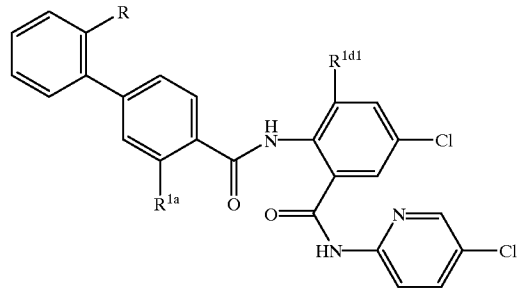


[0484] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0485] The invention provides compound of formula Ib, having the following structure:



[0486] wherein:

[0487] R is a member selected from the group consisting of:

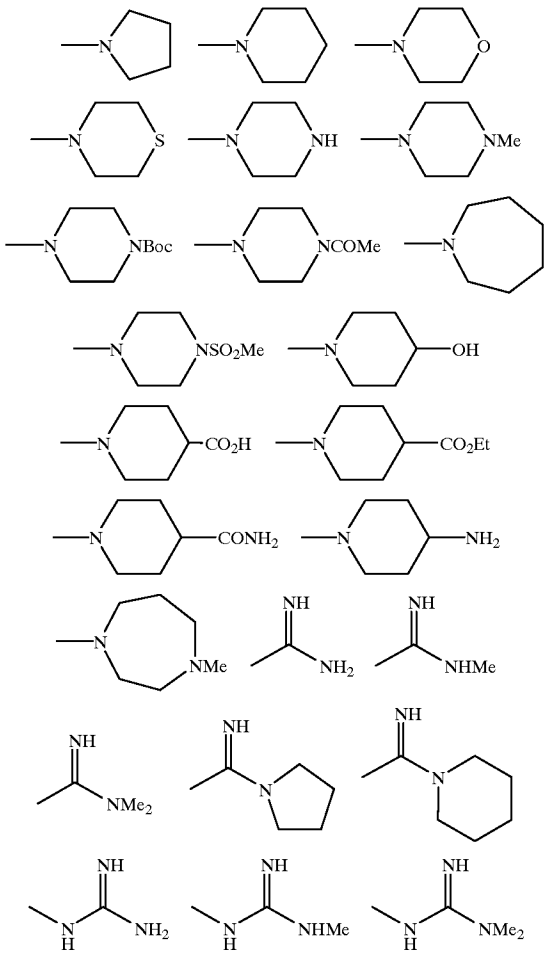
[0488] —SO_2Me, —SO_2NH_2, —CH_2NH_2, —$CH_2N(CH_3)_2$;

[0489] R^{1a} is a member selected from the group consisting of:

[0490] H, —F;-

[0491] R^{1d1} is a member selected from the group consisting of:

[0492] H, —Me, —F, —Cl, —Br, aryl, heteroaryl, —NH_2, —NMe_2, —NHMe, —$NHSO_2Me$, —NHCOMe, —CH_3, —CF_3, —OH, —OCH_3, —SCH_3, —OCF_3, —OCH_2F, —$OCHF_2$, —OCH_2CF_3, —OCF_2CF_3, —NO_2, —CN, —CO_2H, —CO_2Me, —CO_2Et, —$CONH_2$, —CONHMe, —$CONMe_2$, —SO_2NH_2, —SO_2CH_3, —SO_2NMe_2, —CH_2OH, —CH_2NH_2, —CH_2NHMe, —CH_2NMe_2, —OCH_2CO_2H, —OCH_2CO_2Me, —OCH_2CO_2Et, —OCH_2CONH_2, —OCH_2CONMe_2, —$OCH_2CONHMe$, —OCH_2CH_2OMe, —OCH_2CH_2OEt, —$OCH_2CH_2NH_2$, —OCH_2CH_2NHMe, —$OCH_2CH_2NMe_2$, —$NHCH_2CH_2OMe$, —SCH_2CH_2OMe, —$SO_2CH_2CH_2OMe$, —$OCH_2CH_2SO_2Me$, —$NHCH_2CH_2NHMe$, —$NHCH_2CH_2NMe_2$, —$N(CH_2CH_2OH)_2$, —$N(CH_2CH_2OMe)_2$, —$NHCH_2CO_2H$, —$NHCH_2CO_2Et$, —$NHCH_2CO_2Et$, —$NHCH_2CONH_2$, —$NHCH_2CONMe_2$, —$NHCH_2CONHMe$, —$N(CH_3)CH_2CO_2H$, —$N(CH_3)CH_2CO_2Et$, —(NMe)CH2COOH, —N(Me)CH2CONH2, —N(Me)CH2CH2NMe2, —N(Me)CH2CH2OMe, —NHCH2CH2OMe,



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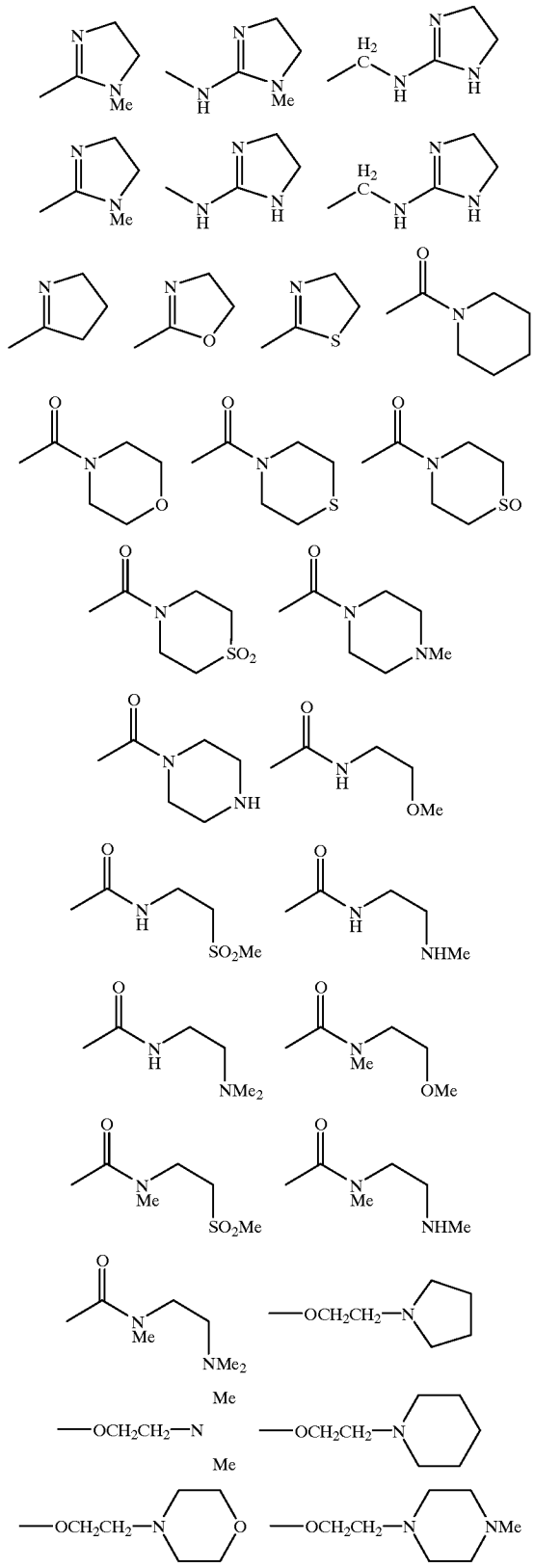

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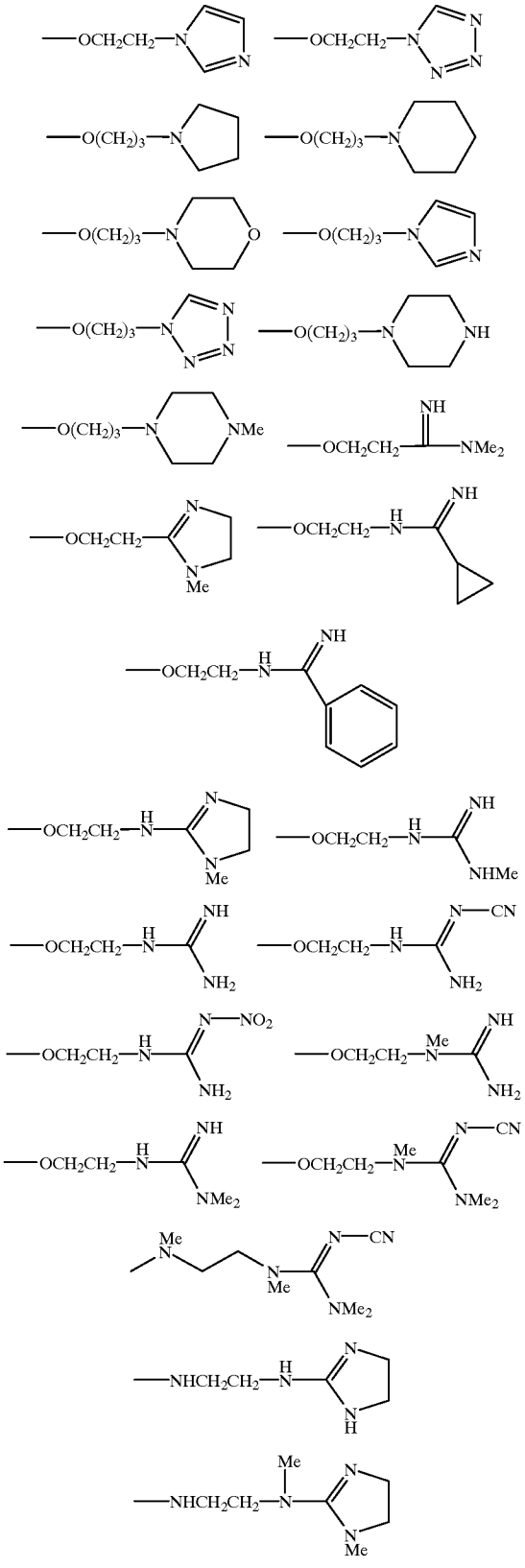

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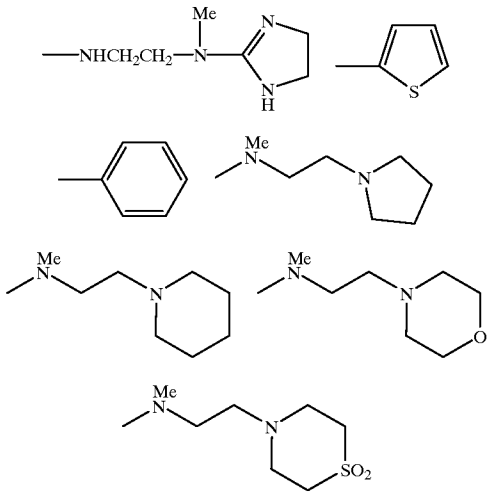
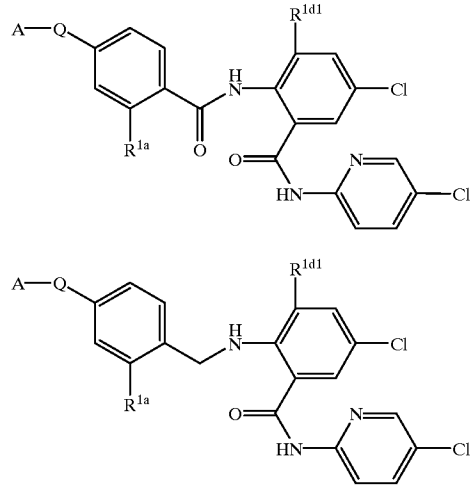


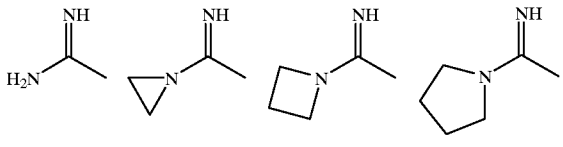
[0493] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0494] The invention provides compound of formula Ib, as described above, having the following structure:



[0495] wherein:

[0496] A-Q is a member selected from the group consisting of:



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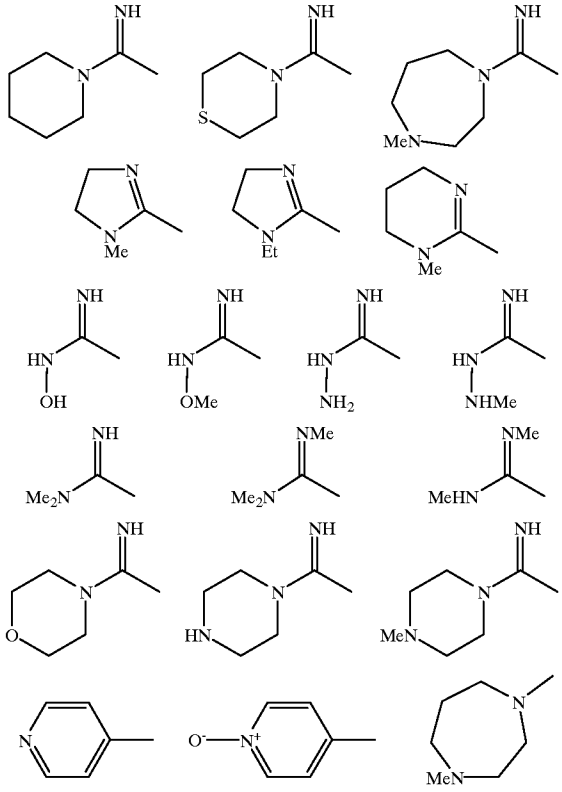
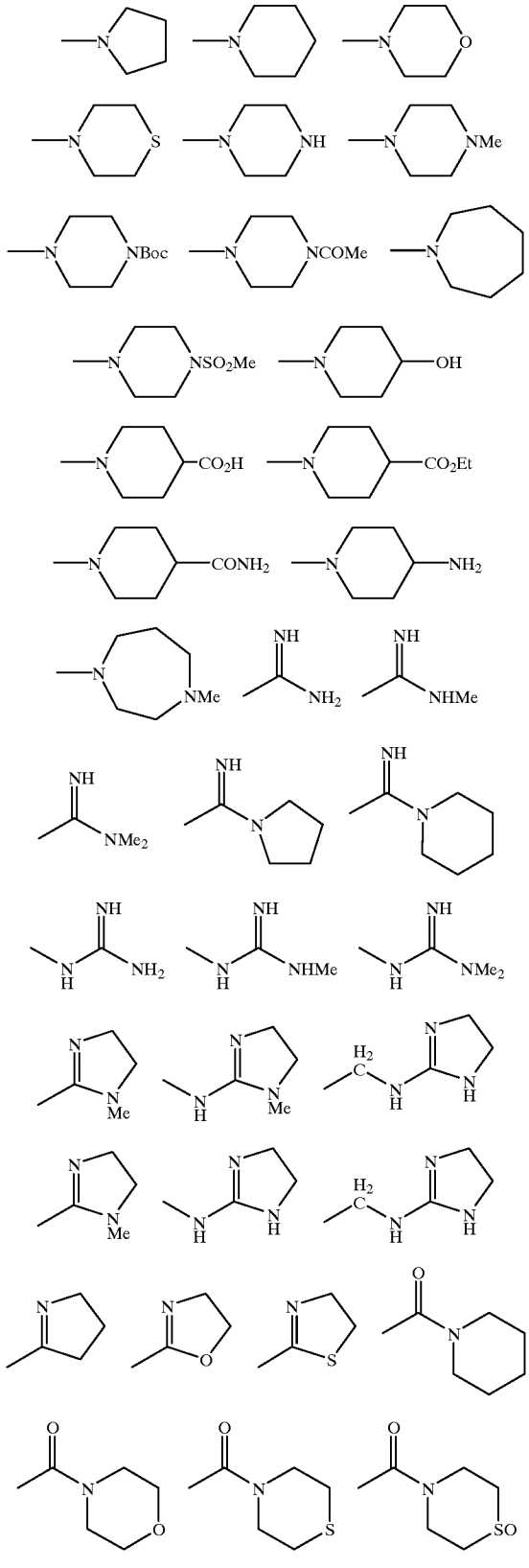


[0497] R^{1a} is a member selected from the group consisting of:

[0498] H, —F;

[0499] R^{1d1} is a member selected from the group consisting of:

[0500] H, —Me, —F, —Cl, —Br, aryl, heteroaryl, NH_2, —NMe_2, —NHMe, —$NHSO_2Me$, —NHCOMe, —CH_3, —CF_3, —OH, —OCH_3, —SCH_3, —OCF_3, —OCH_2F, —$OCHF_2$, —OCH_2CF_3, —OCF_2CF_3, —NO_2, —CN, —CO_2H, —CO_2Me, —CO_2Et, —$CONH_2$, —CONHMe, —$CONMe_2$, —SO_2NH_2, —SO_2CH_3, —SO_2NMe_2, —CH_2OH, —CH_2NH_2, —CH_2NHMe, —CH_2NMe_2, —OCH_2CO_2H, —OCH_2CO_2Me, —OCH_2Et, —OCH_2CONH_2, —OCH_2CONMe_2, —$OCH_2CONHMe$, —OCH_2CH_2OMe, —OCH_2CH_2OEt, —$OCH_2CH_2NH_2$, —OCH_2CH_2NHMe, —$OCH_2CH_2NMe_2$, —$NHCH_2CH_2OMe$, —SCH_2CH_2OMe, —$SO_2CH_2CH_2OMe$, —$OCH_2CH_2SO_2Me$, —$NHCH_2CH_2NHMe$, —$NHCH_2CH_2NMe_2$, —$N(CH_2CH_2OH)_2$, —$N(CH_2CH_2OMe)_2$, —$NHCH_2CO_2H$, —$NHCH_2CO_2Et$, —$NHCH_2CO_2Et$, —$NHCH_2CONH_2$, —$NHCH_2CONMe_2$, —$NHCH_2CONHMe$, —$N(CH_3)CH_2CO_2H$, —$N(CH_3)CH_2CO_2Et$, —(NMe)CH2COOH, —N(Me)CH2CONH2, —N(Me)CH2CH2NMe2, —N(Me)CH2CH2OMe, —NHCH2CH2OMe,



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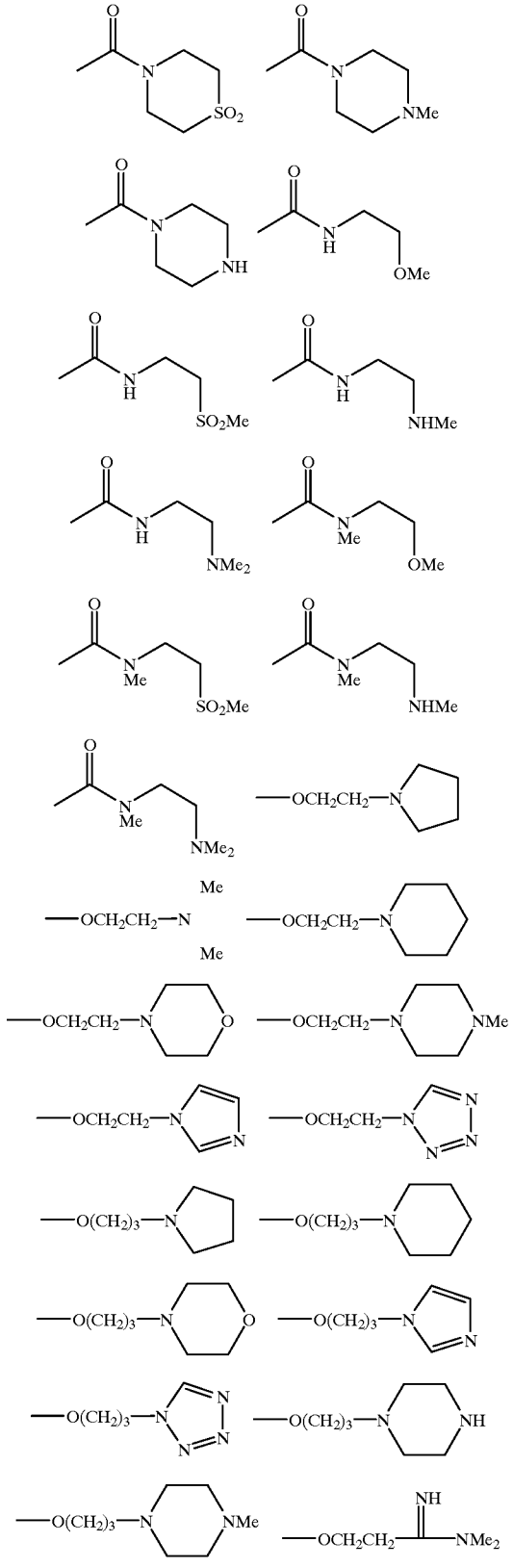

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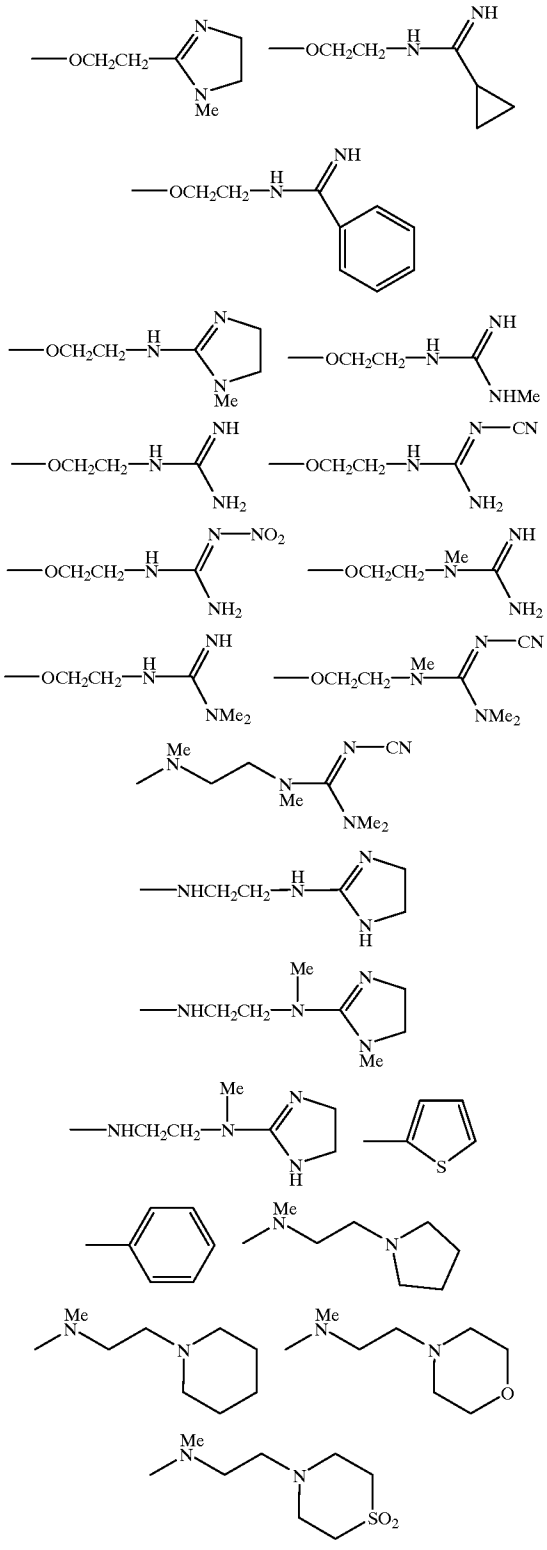
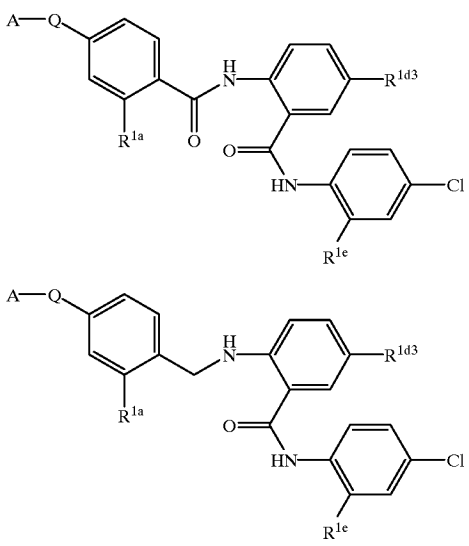


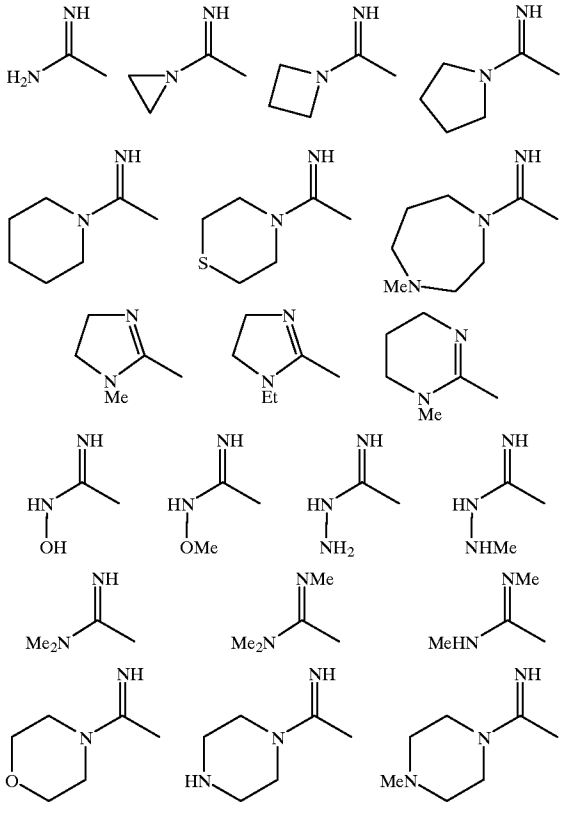
[0501] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0502] The invention provides compound of formula Ib, as described above, having the following structure:



[0503] wherein:

[0504] A-Q is a member selected from the group consisting of:



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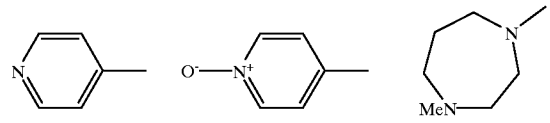


[0505] R^{1a} is a member selected from the group consisting of:

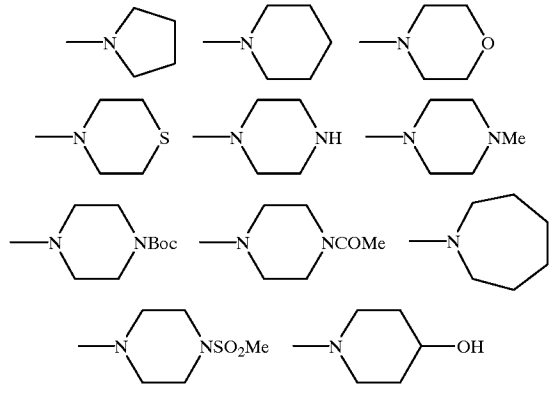
[0506] H, —F;

[0507] R^{1e} is a member selected from the group consisting of:

[0508] H, —F, —SO_2Me, —SO_2NH_2, —CN, —$CONH_2$, —CH_2NH_2, —CH_2NMe_2;

[0509] R^{1d3} is a member selected from the group consisting of:

[0510] H, —Me, —F, —Cl, —Br, aryl, heteroaryl, —NH_2, —NMe_2, —NHMe, —$NHSO_2Me$, —NHCOMe, —CH_3, —CF_3, —OH, —OCH_3, —SCH_3, —OCF_3, —OCH_2F, —$OCHF_2$, —OCH_2CF_3, —OCF_2CF_3, —NO_2, —CN, —CO_2H, —CO_2Me, —CO_2Et, —$CONH_2$, —CONHMe, —$CONMe_2$, —SO_2NH_2, —SO_2CH_3, —SO_2NMe_2, —CH_2OH, —CH_2NH_2, —CH_2NHMe, —CH_2NMe_2, —OCH_2CO_2H, —OCH_2CO_2Me, —OCH_2CO_2Et, —OCH_2CONH_2, —OCH_2CONMe_2, —$OCH_2CONHMe$, —OCH_2CH_2OMe, —OCH_2CH_2OEt, —$OCH_2CH_2NH_2$, —OCH_2CH_2NHMe, —$OCH_2CH_2NMe_2$, —$NHCH_2CH_2OMe$, —SCH_2CH_2OMe, —$SO_2CH_2CH_2OMe$, —$OCH_2CH_2SO_2Me$, —$NHCH_2CH_2NHMe$, —$NHCH_2CH_2NMe_2$, —$N(CH_2CH_2OH)_2$, —$N(CH_2CH_2OMe)_2$, —$NHCH_2CO_2H$, —$NHCH_2CO_2Et$, —$NHCH_2CO_2Et$, —$NHCH_2CONH_2$, —$NHCH_2CONMe_2$, —$NHCH_2CONHMe$, —$N(CH_3)CH_2CO_2H$, —$N(CH_3)CH_2CO_2Et$, —(NMe)CH2COOH, —N(Me)CH2CONH2, —N(Me)CH2CH2NMe2, —N(Me)CH2CH2OMe, —NHCH2CH2OMe,



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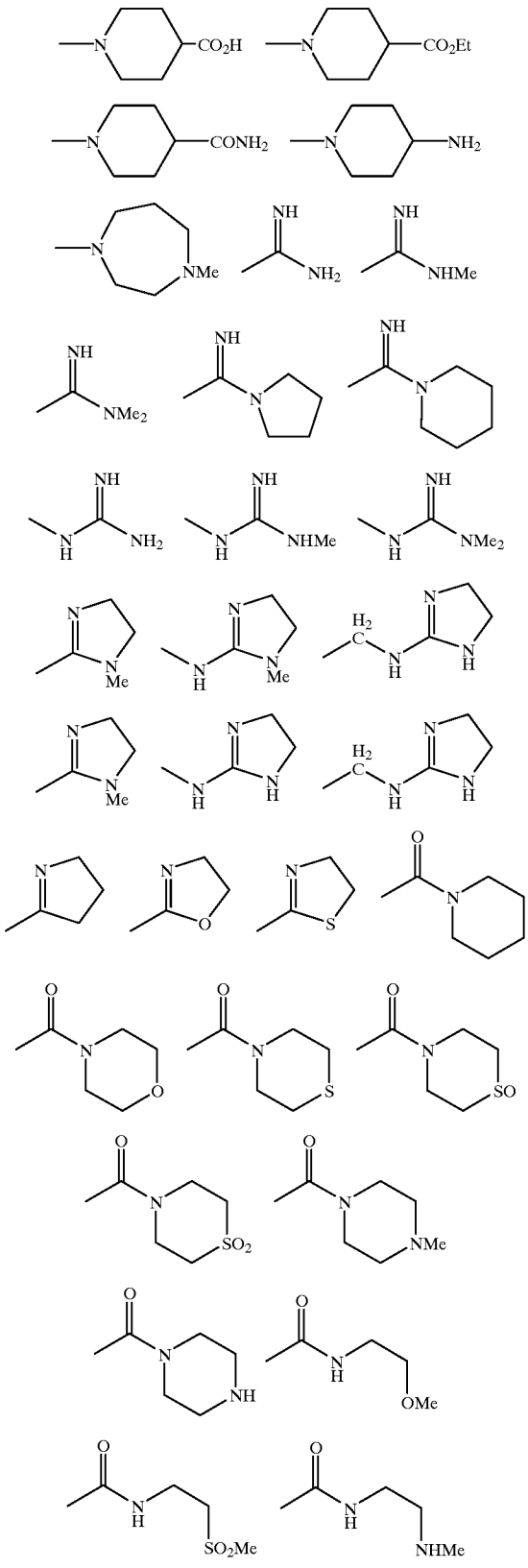

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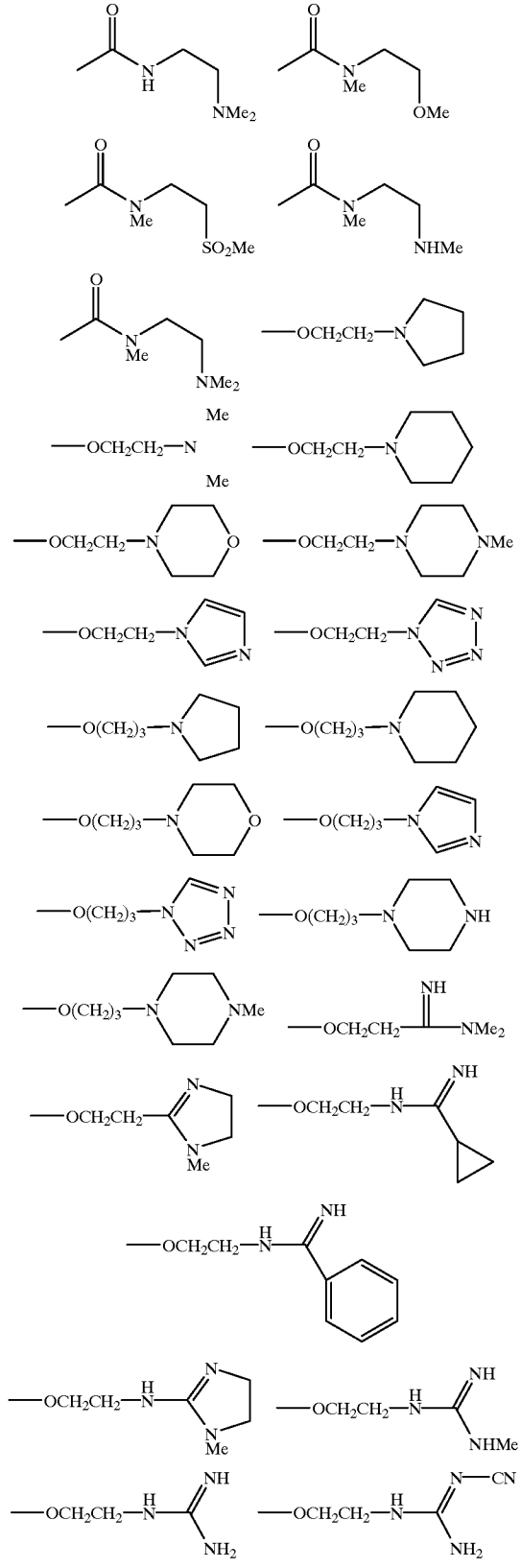

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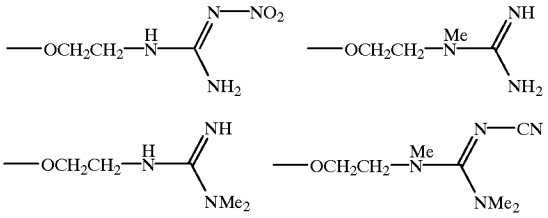
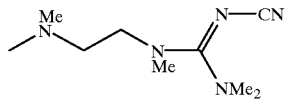
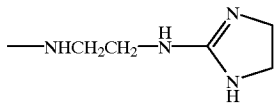
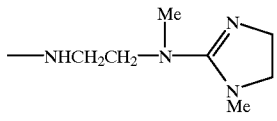
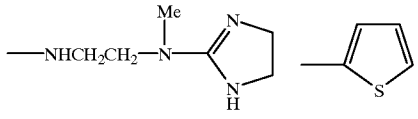
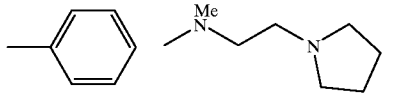


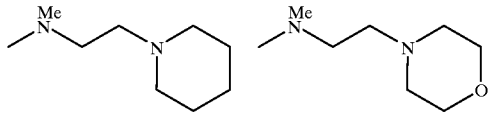


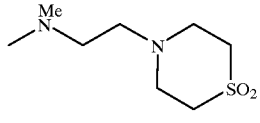






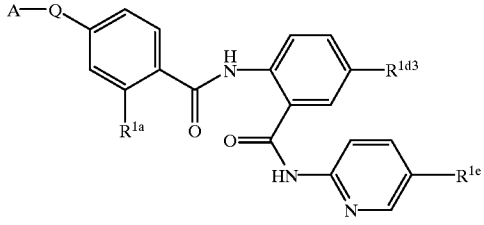






[0511] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0512] The invention provides compound of formula Ib, as described above, having the following structure:



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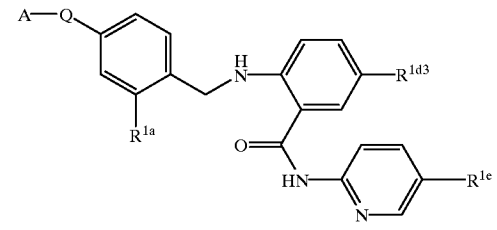
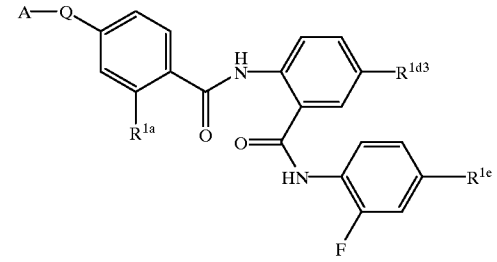
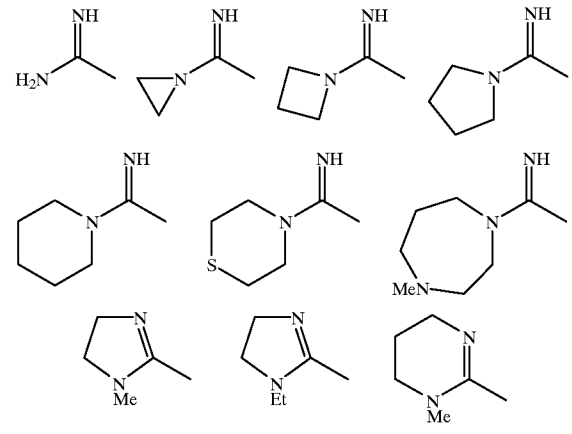
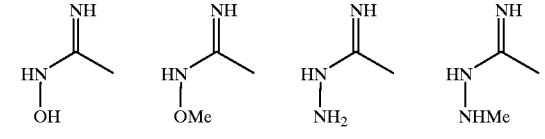


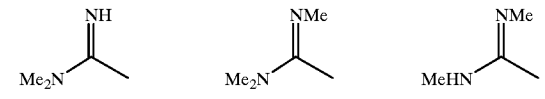


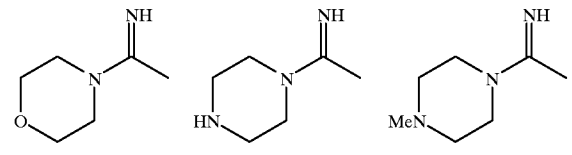
[0513] wherein:

[0514] A-Q is a member selected from the group consisting of:









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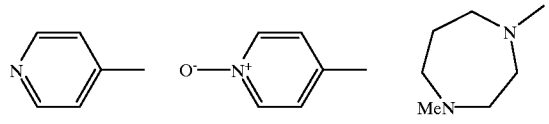


[0515] R^{1a} is a member selected from the group consisting of:

[0516] H, —F;

[0517] R^{1e} is a member selected from the group consisting of:

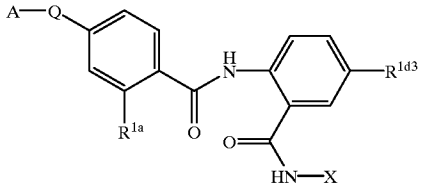
[0518] —Cl, —Br;

[0519] R^{1d3} is a member selected from the group consisting of:

[0520] H, F, Cl, Br, —OCH_3, —OCF_3, —OCH_2F, —$OCHF_2$, —OCH_2CF_3, —OCF_2CF_3;

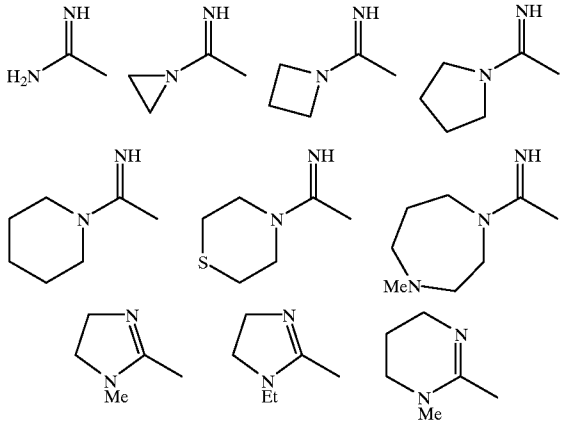
[0521] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0522] The invention provides compound of formula Ib, as described above, having the following structure:



[0523] wherein:

[0524] A-Q is a member selected from the group consisting of:



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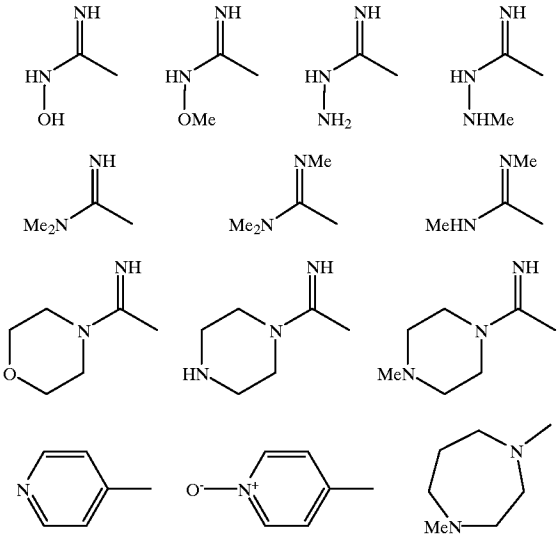


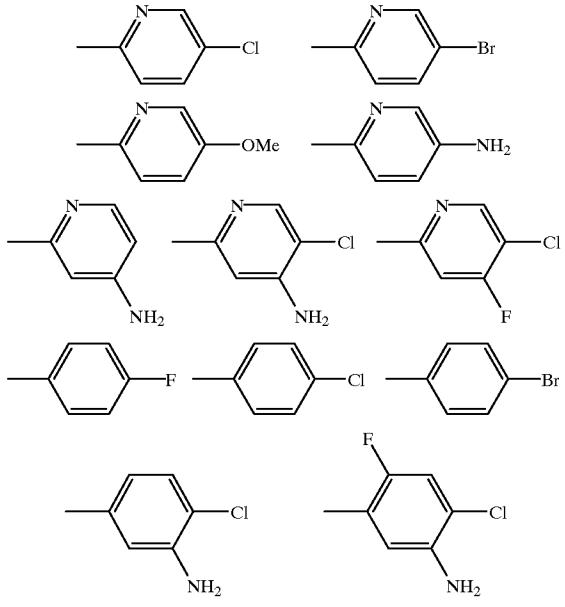
[0525] R^{1a} is a member selected from the group consisting of:

[0526] H, —F;

[0527] R^{1d3} is a member selected from the group consisting of:

[0528] H, —F, —Cl, —Br, —OCH_3, —OCF_3, —OCH_2F, —$OCHF_2$, —OCH_2CF_3, —OCF_2CF_3, —$NHSO_2Me$, —NHAc, —SO_2Me, —SO_2NH_2;

[0529] X is a member selected from the group consisting of:



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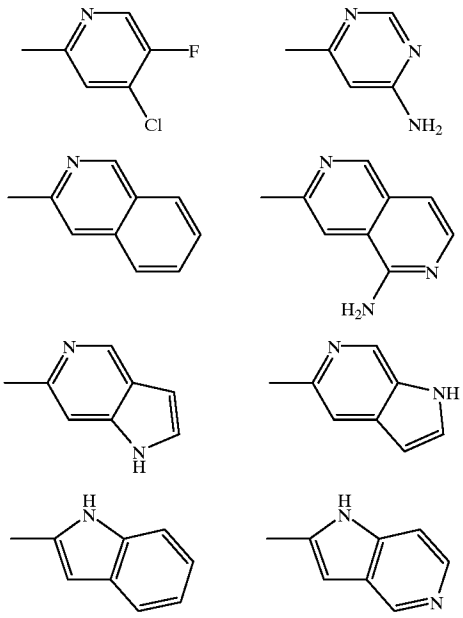
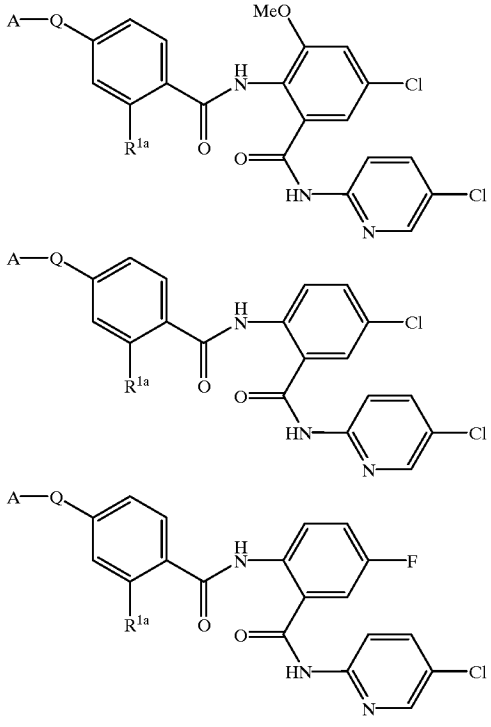


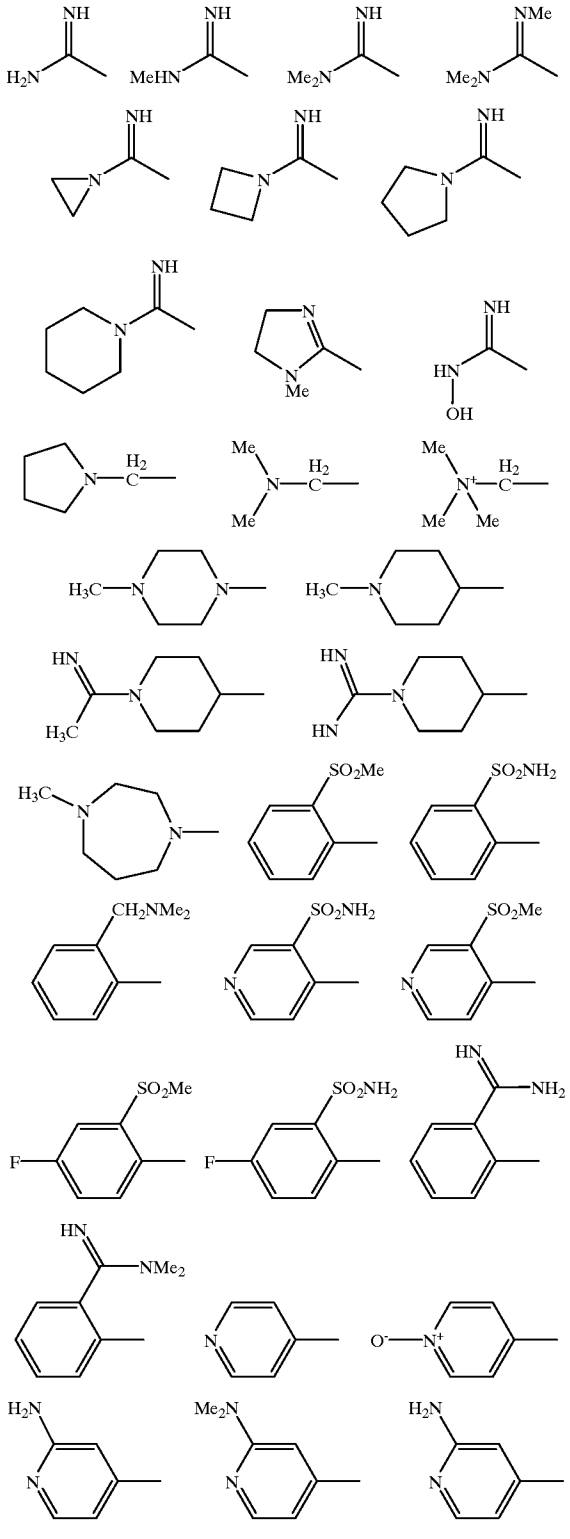
[0530] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0531] The invention provides compound of formula Ib, as described above, having the following structure:



[0532] wherein:

[0533] A-Q is a member selected from the group consisting of:



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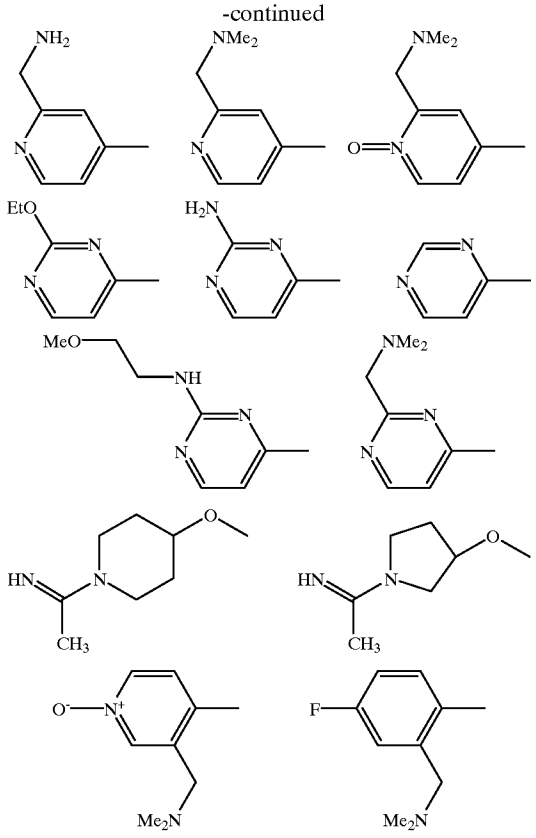
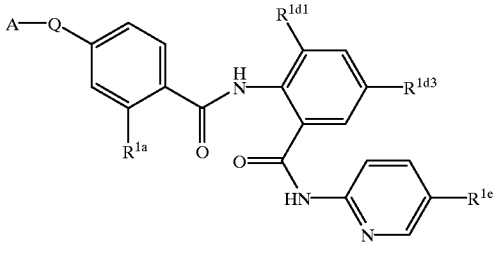


[0534] R^{1a} is a member selected from the group consisting of:

[0535] H, —F;

[0536] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0537] The invention provides compound of formula Ib, as described above, having the following structure:



[0538] wherein:

[0539] R^{1a} is a member selected from the group consisting of:

[0540] H, —F;

[0541] R^{1d1} is a member selected from the group consisting of:

[0542] H, —OMe;

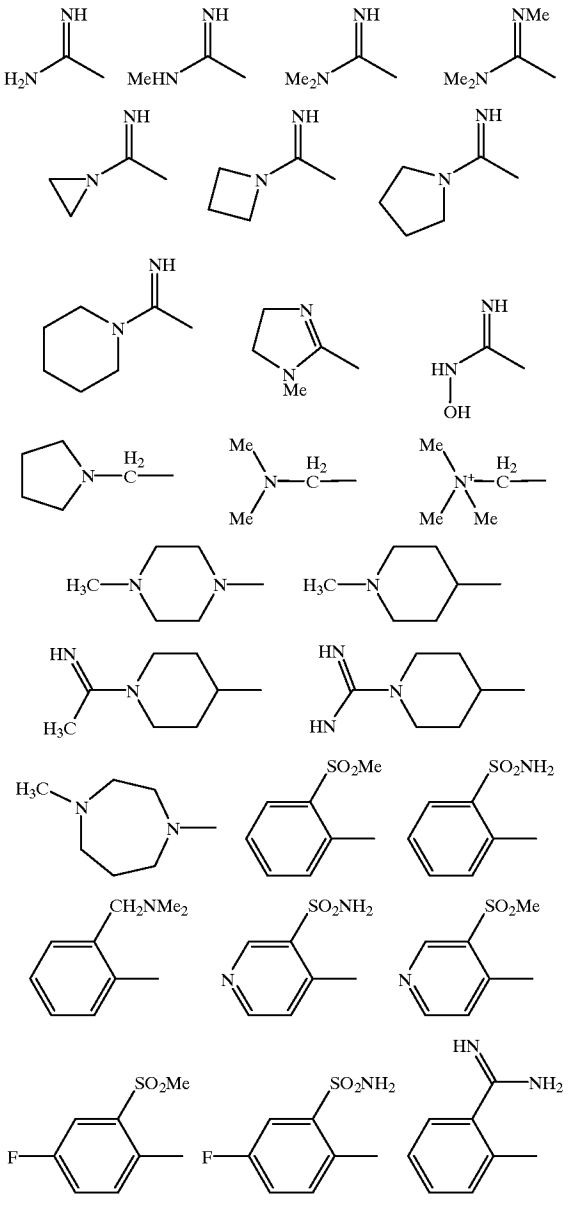
[0543] R^{1d3} is a member selected from the group consisting of:

[0544] H, —F, —Cl, —Br, —OMe, —OCF_3;

[0545] R^{1e} is a member selected from the group consisting of:

[0546] H, —F, —Cl, —Br;

[0547] A-Q is a member selected from the group consisting of:



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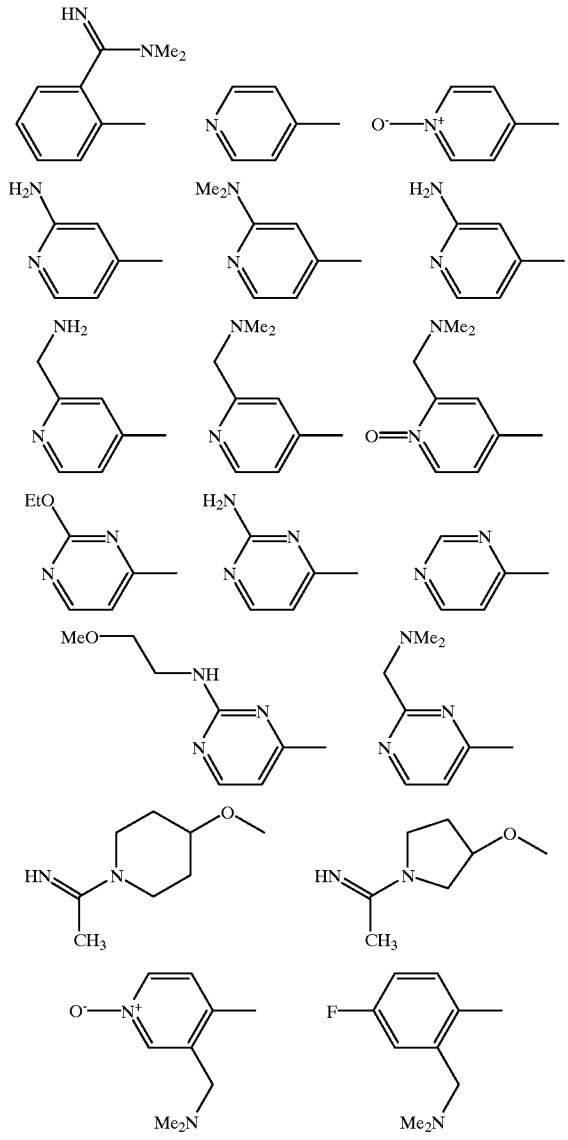
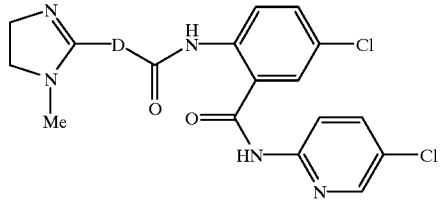


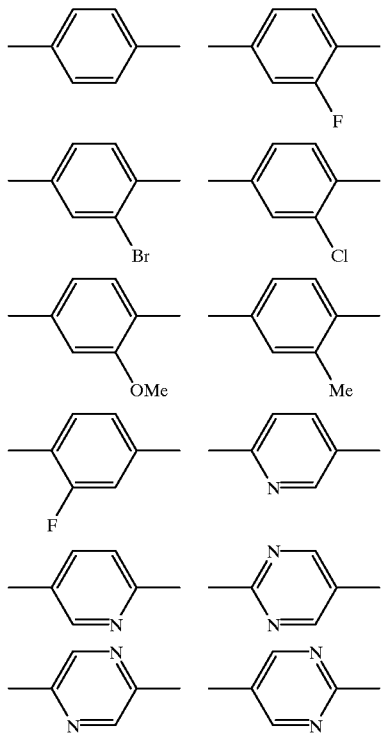
[0548] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0549] The invention provides compound of formula Ib, as described above, having the following structure:



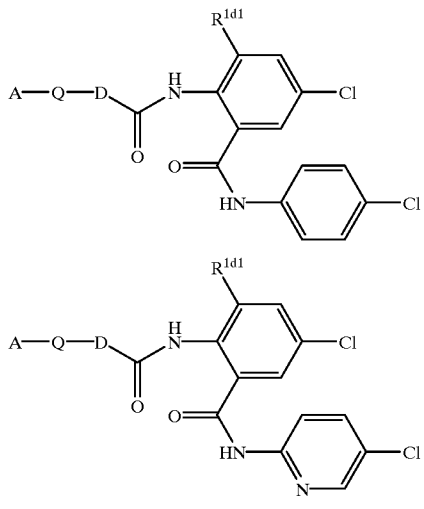
[0550] wherein:

[0551] D is a member selected from the group consisting of:



[0552] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

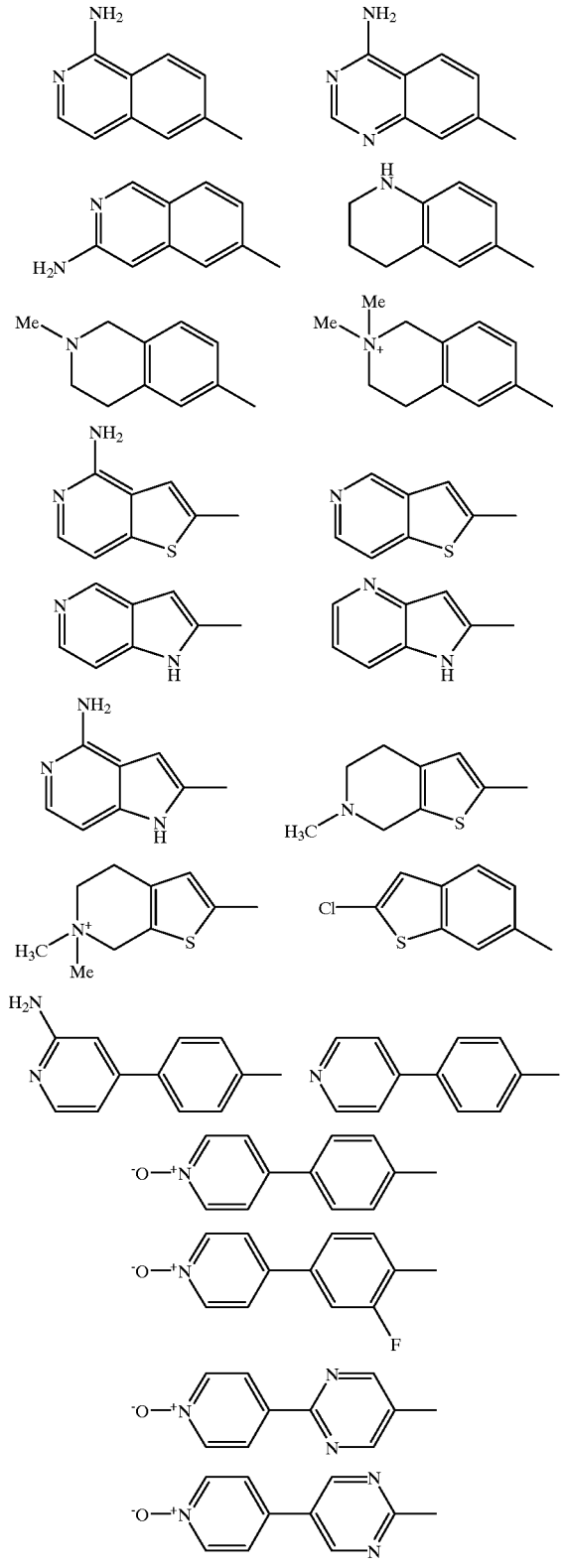
[0553] The invention provides compound of formula Ib, as described above, having the following structure:



[0554] wherein:

[0555] R^{1d1} is H or —OMe;

[0556] A-Q-D is a member selected from the group consisting of:



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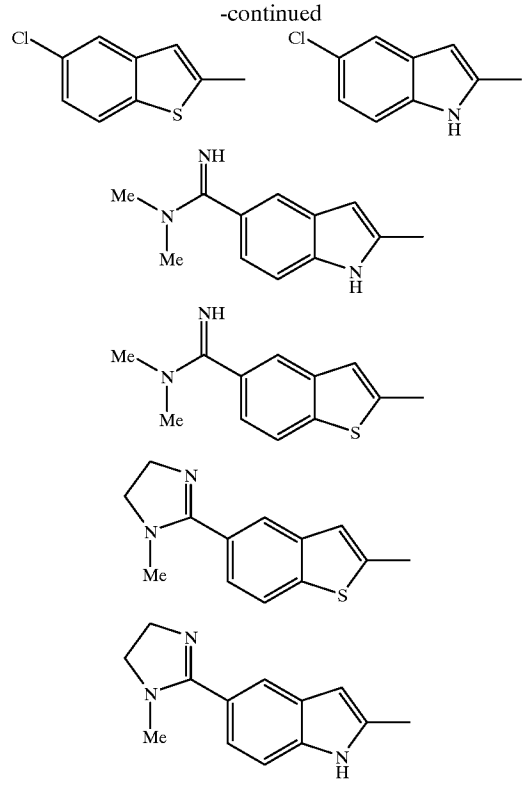
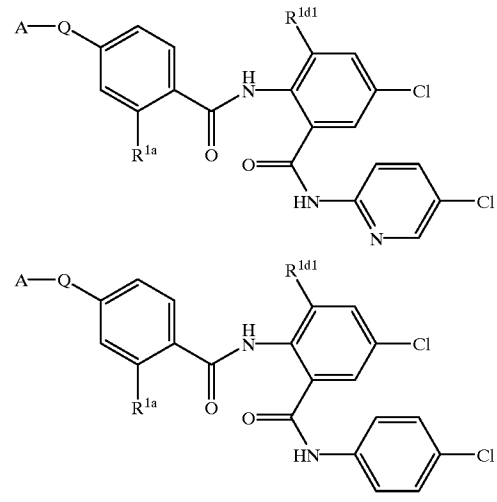


[0557] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0558] The invention provides compound of formula Ib, as described above, having the following structure:

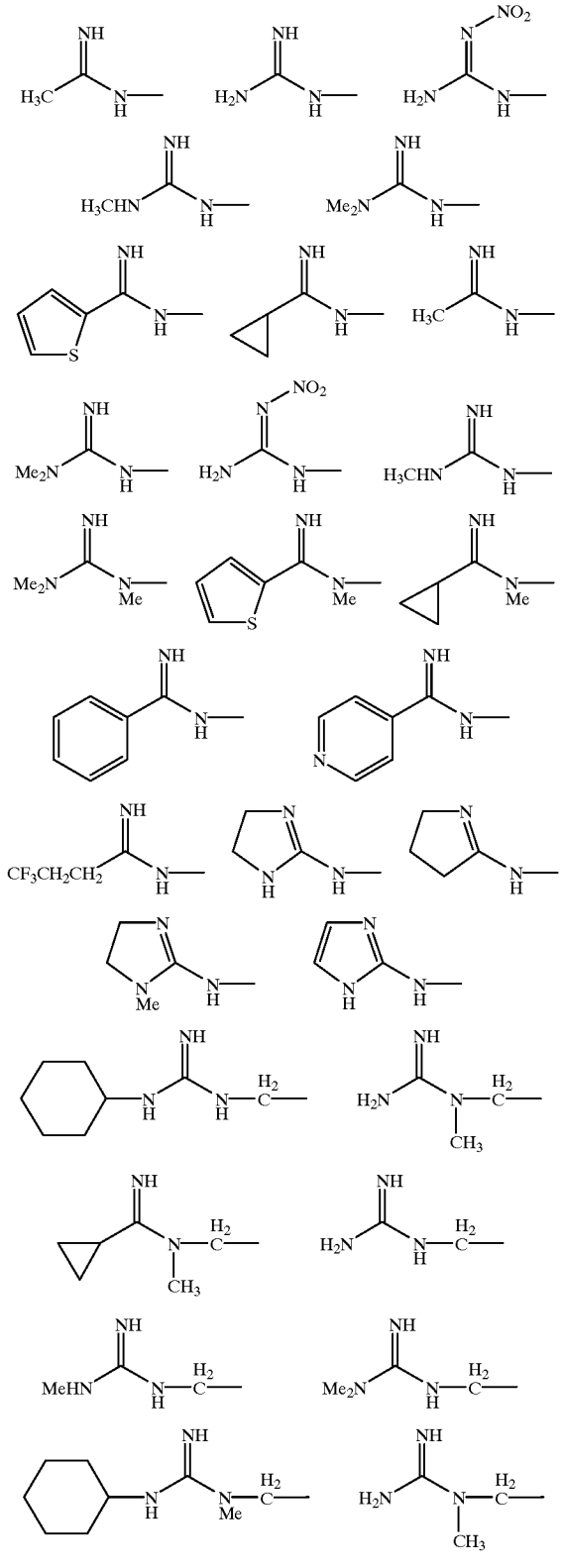


[0559] wherein:

[0560] R^{1a} is H or F;

[0561] R^{1d1} is H or —OMe;

[0562] A-Q is a member selected from the group consisting of:



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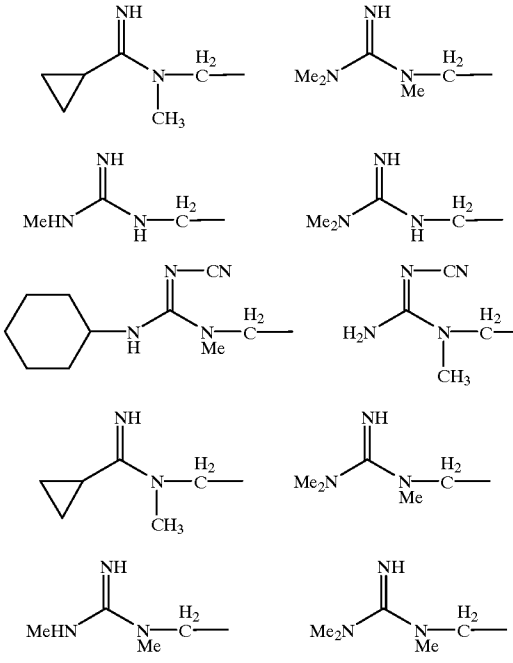
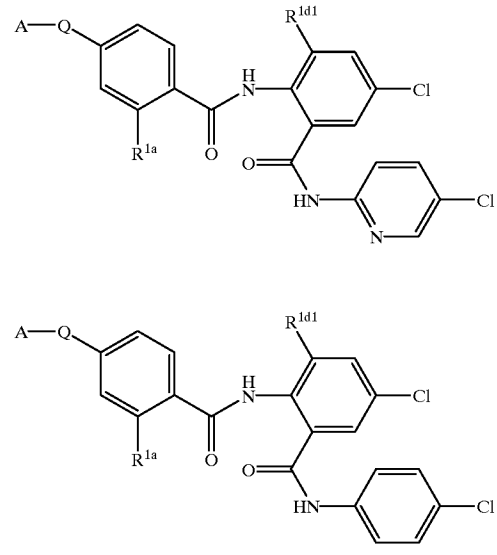


[0563] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0564] The invention provides compound of formula Ib, as described above, having the following structure:

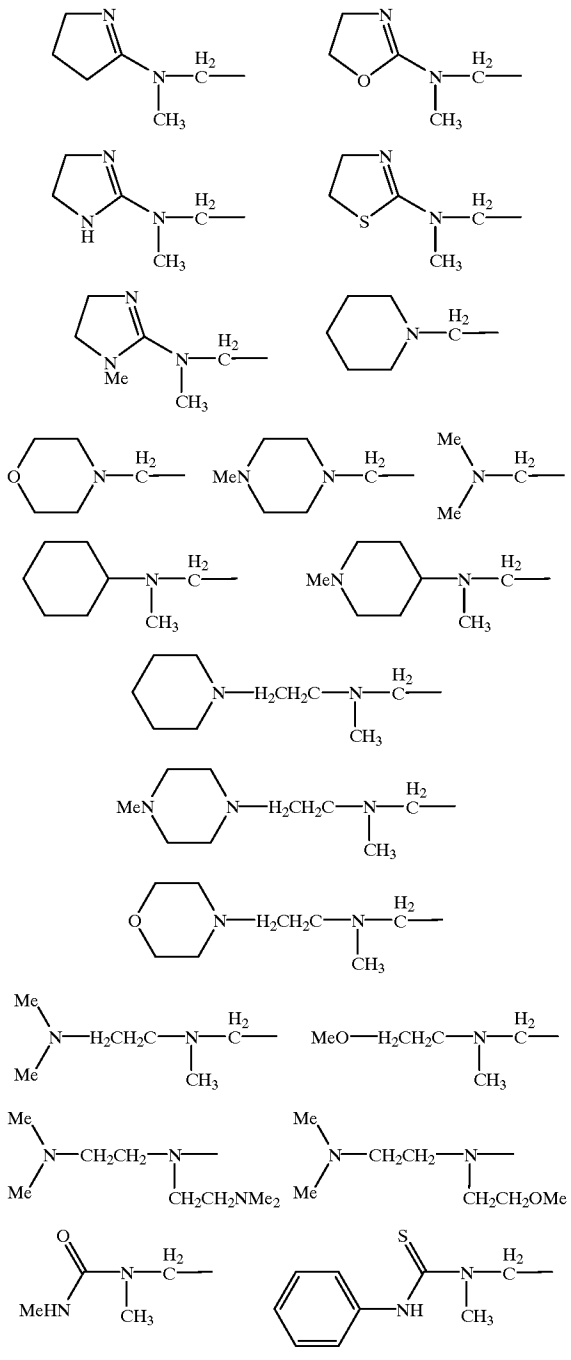


[0565] wherein:

[0566] R^{1a} is H or F;

[0567] R^{1d1} is H or —OMe;-

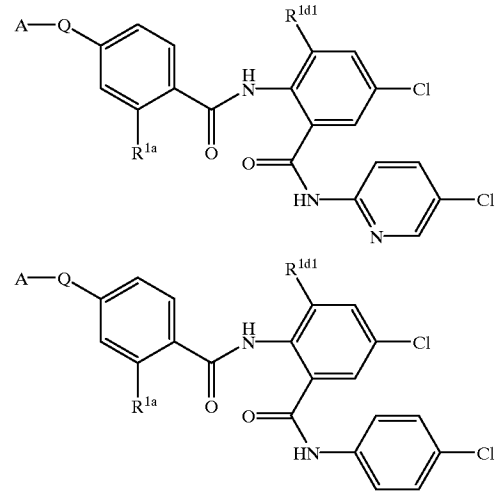
[0568] A-Q is a member selected from the group consisting of:



[0569] ;and

[0570] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0571] The invention provides compound of formula Ib, as described above, having the following structure:

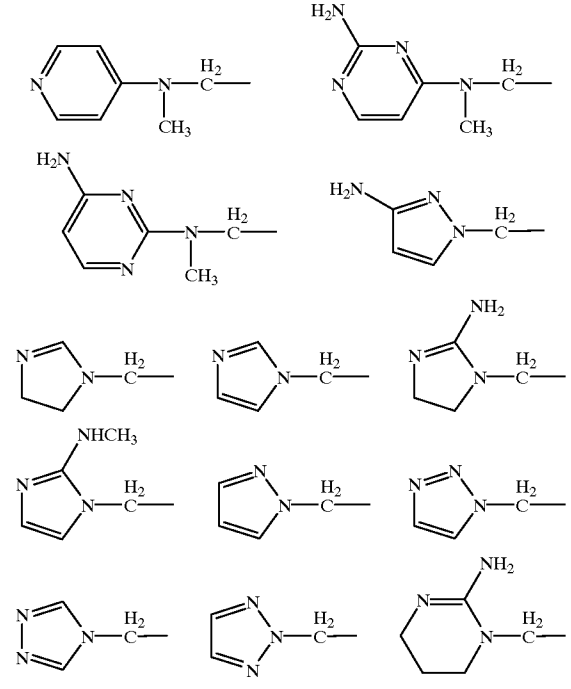


[0572] wherein:

[0573] R^{1a} is H or F;

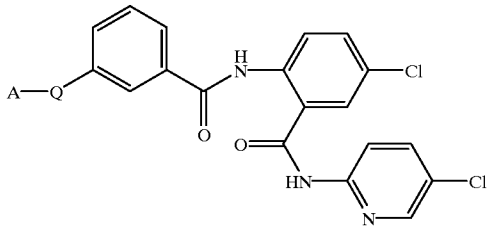
[0574] R^{1d1} is H or —OMe; and

[0575] A-Q is a member selected from the group consisting of:



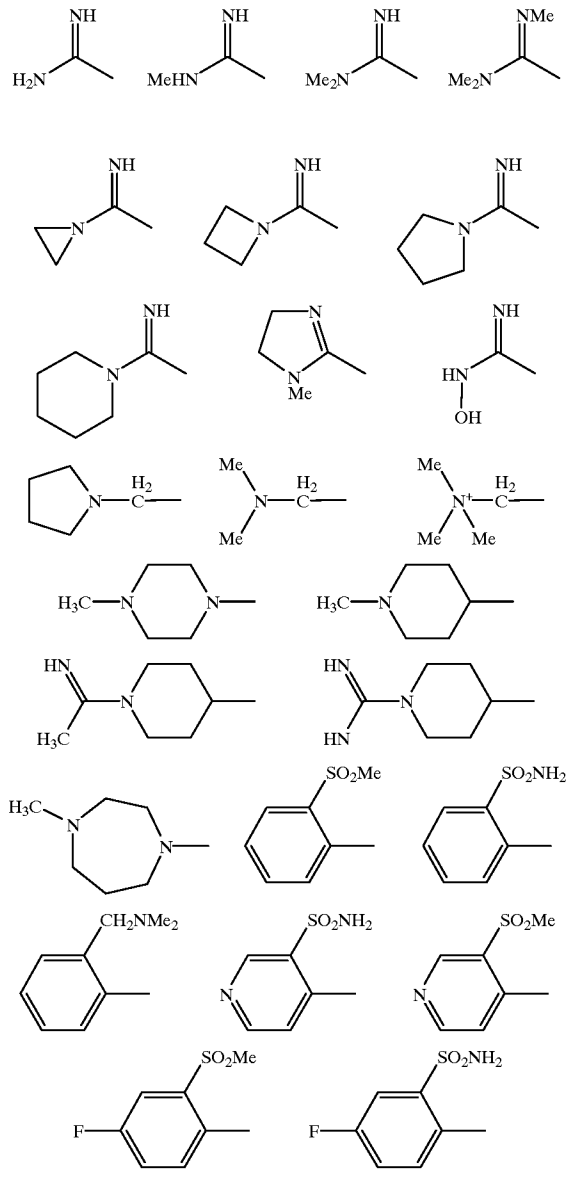
[0576] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0577] The invention provides compound of formula Ib, as described above, having the following structure:



[0578] wherein:

[0579] A-Q is a member selected from the group consisting of:



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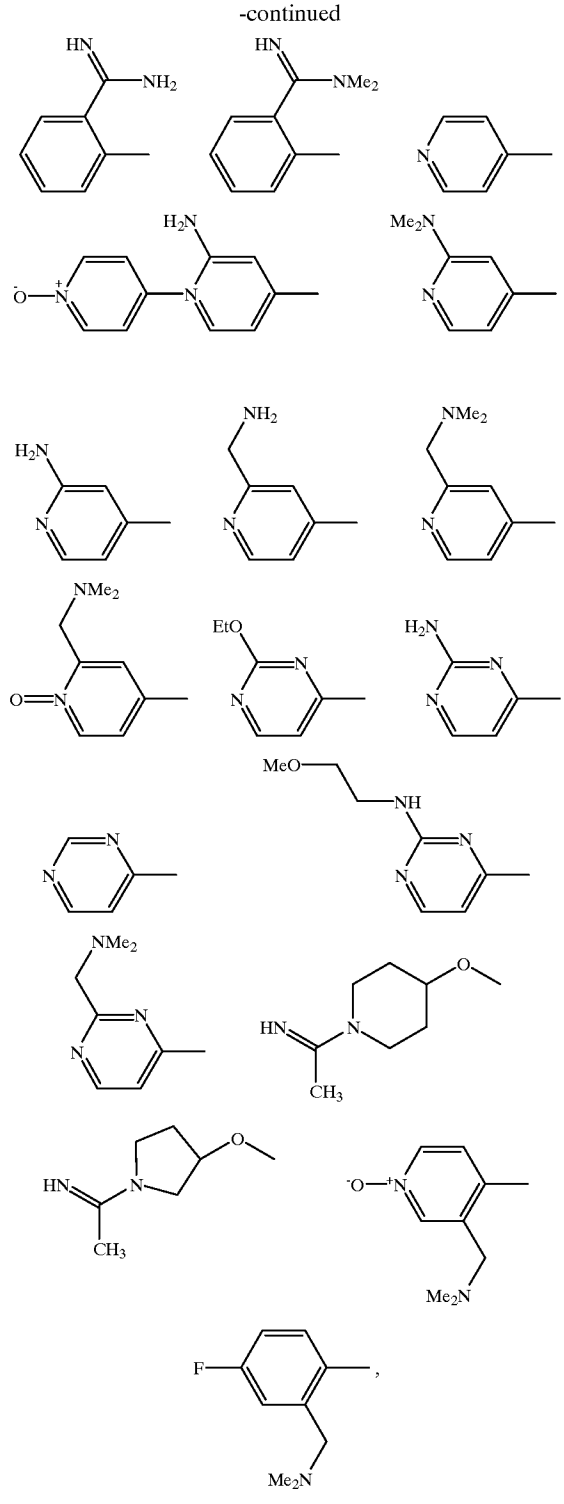
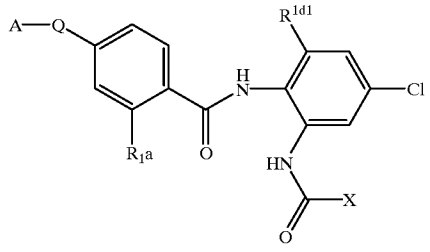


[0580] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0581] The invention provides compound of formula Ib, as described above, having the following structure:

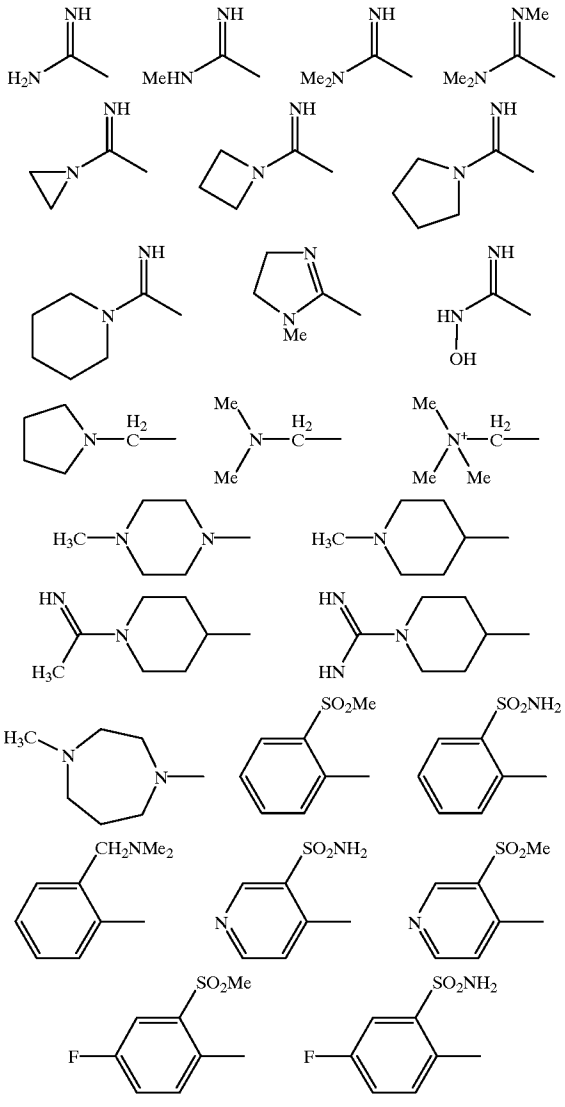


[0582] wherein:

[0583] R^{1a} is H or F;

[0584] R^{1d1} is H or —OMe;

[0585] A-Q is a member selected from the group consisting of:



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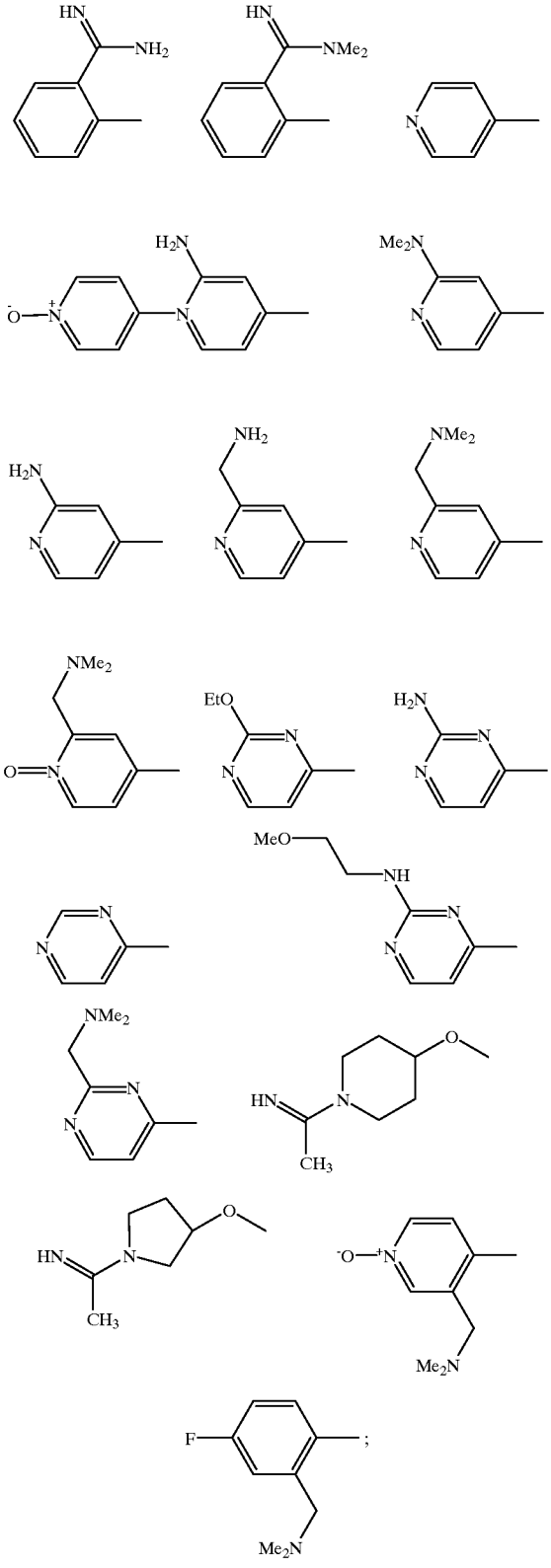
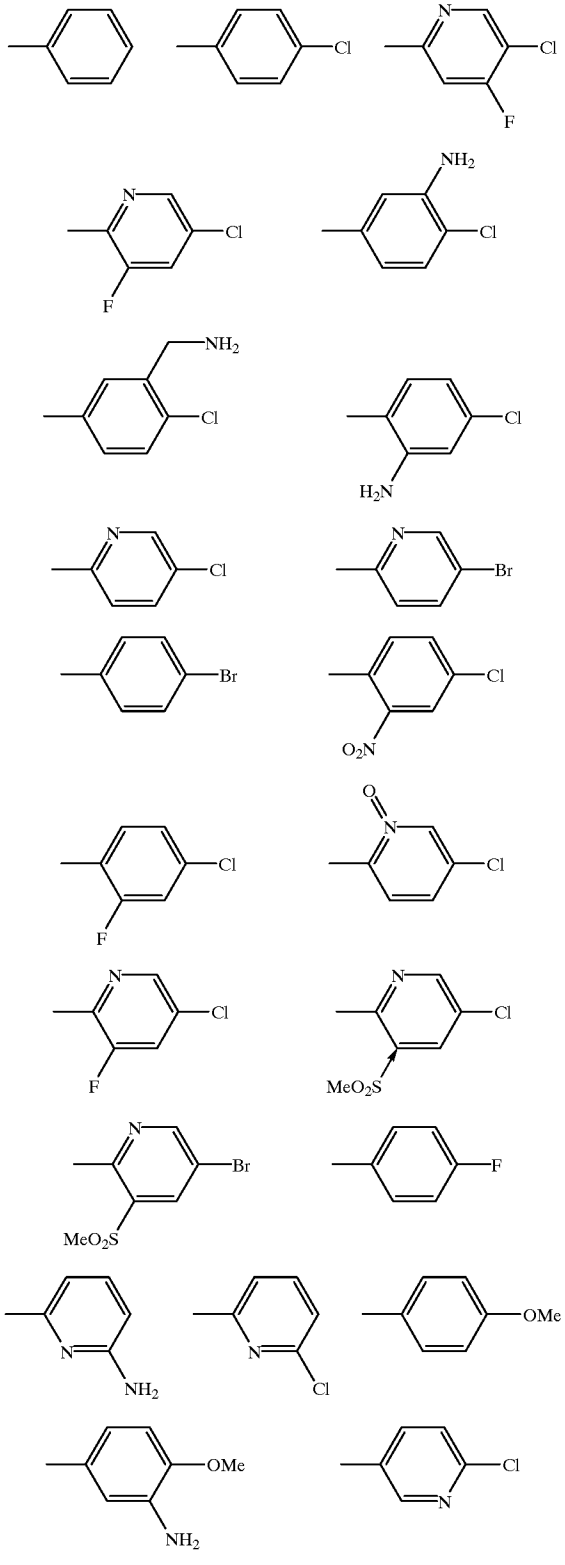


[0586] and X is a member selected from the group consisting of:



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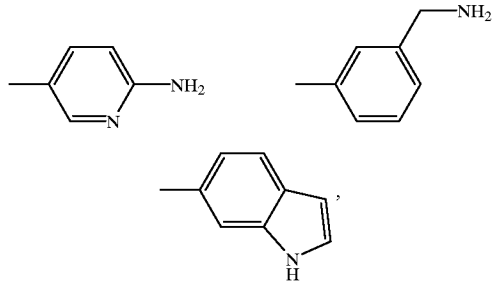
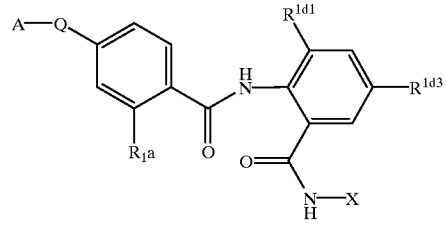


[0587] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

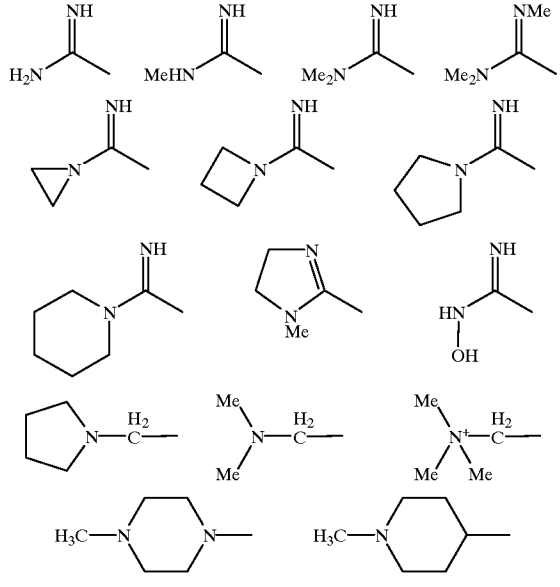
[0588] The invention provides compound of formula Ib, as describe above, having the following structure:



[0589] wherein:

[0590] R^{1a} is H or F;

[0591] A-Q is a member selected from the group consisting of:



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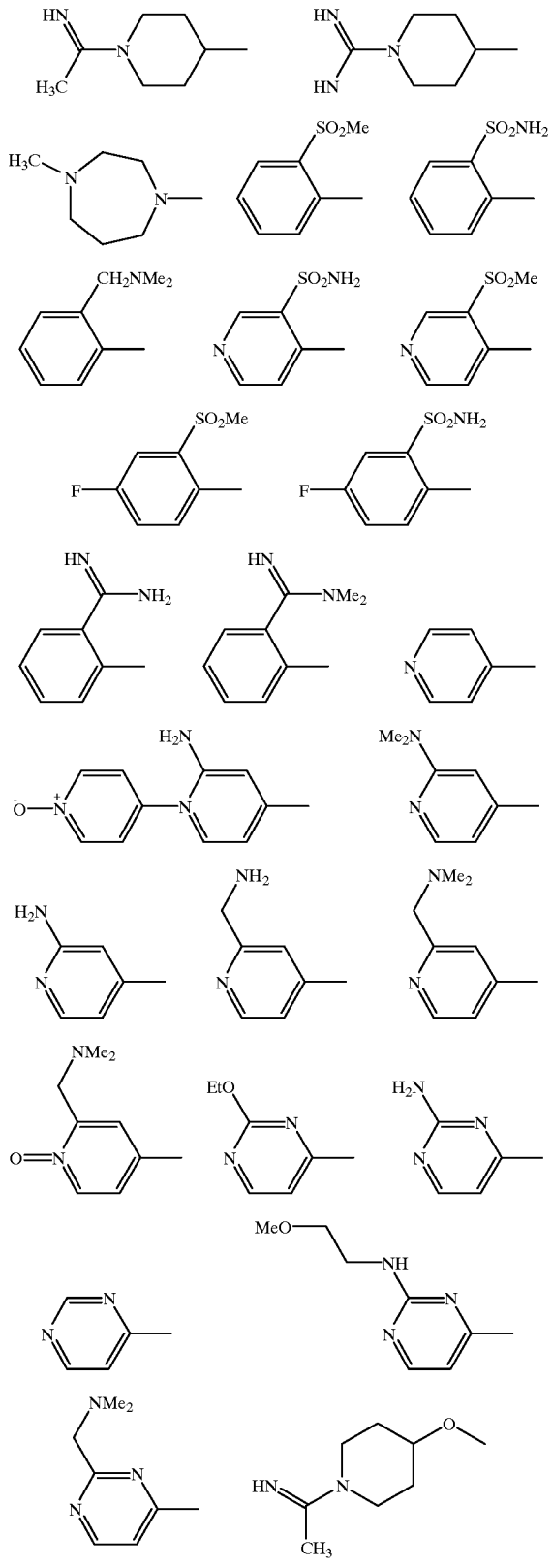

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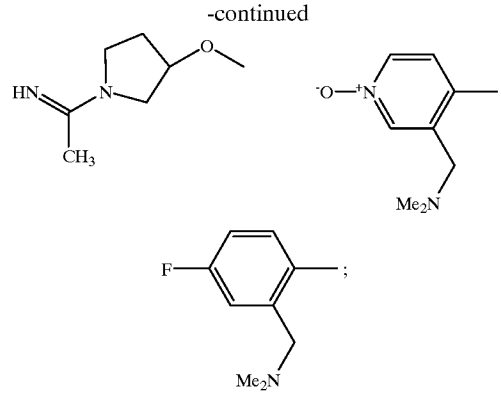
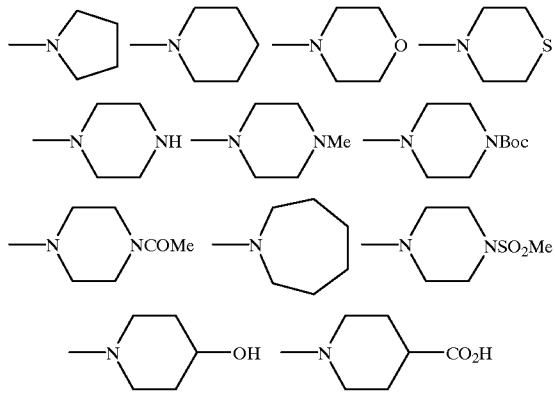


[0592] R^{1d1} is a member selected from the group consisting of:

[0593] H, —F, —Cl, —Br, aryl, heteroaryl, —NH_2, —NMe_2, —NHMe, —$NHSO_2Me$, —NHCOMe, —CH_3, —CF_3, —OH, —OCH_3, —SCH_3, —OCF_3, —OCH_2F, —$OCHF_2$, —OCH_3CF_3, —OCF_2CF_3, —NO_2, —CN, —CO_2H, —CO_2Me, —CO_2Et, —$CONH_2$, —CONHMe, —$CONMe_2$, —SO_2NH_2, —SO_2CH_3, —SO_2NMe_2, —CH_2OH, —CH_2NH_2, —CH_2NHMe, —CH_2NMe_2, —OCH_2CO_2H, —OCH_2CO_2Me, —OCH_2CO_2Et, —OCH_3CONH_2, —OCH_2CONMe_2, —$OCH_2CONHMe$, —OCH_2CH_2OMe, —OCH_2CH_2OEt, —$OCH_2CH_2NH_2$, —OCH_2CH_2NHMe, —$OCH_2CH_2NMe_2$, —$NHCH_2CH_2OMe$, —SCH_2CH_2OMe, —$SO_2CH_2CH_2OMe$, —$OCH_3CH_2SO_2Me$, —$NHCH_2CH_2NHMe$, —$NHCH_2CH_2NMe_2$, —$N(CH_2CH_2OH)_2$, —$N(CH_2CH_2OMe)_2$, —$NHCH_2CO_2H$, —$NHCH_2CO_2Et$, —$NHCH_2CO_2Et$, —$NHCH_2CONH_2$, —$NHCH_2CONMe_2$, —$NHCH_3CONHMe$, —$N(CH_3)CH_2CO_2H$, —$N(CH_3)CH_2CO_2Et$, —(NMe)CH2COOH, —N(Me)CH2CONH2, —N(Me)CH2CH2NMe2, —N(Me)CH2CH2OMe, —NHCH2CH2OMe,



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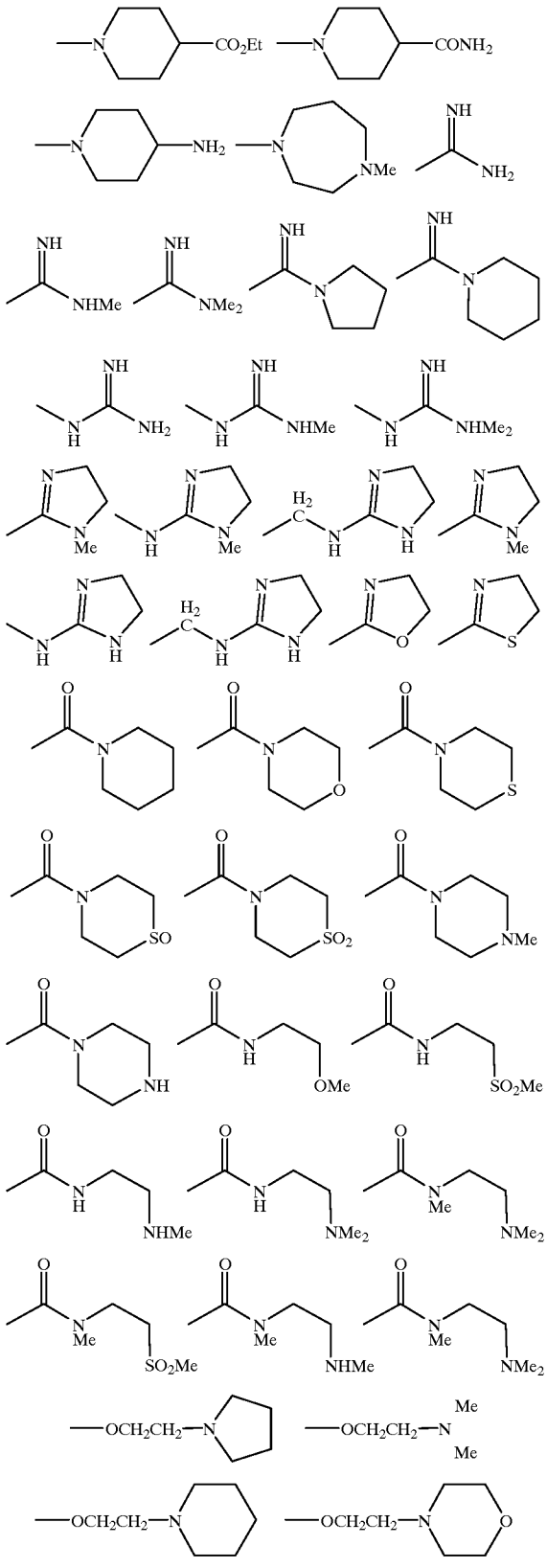

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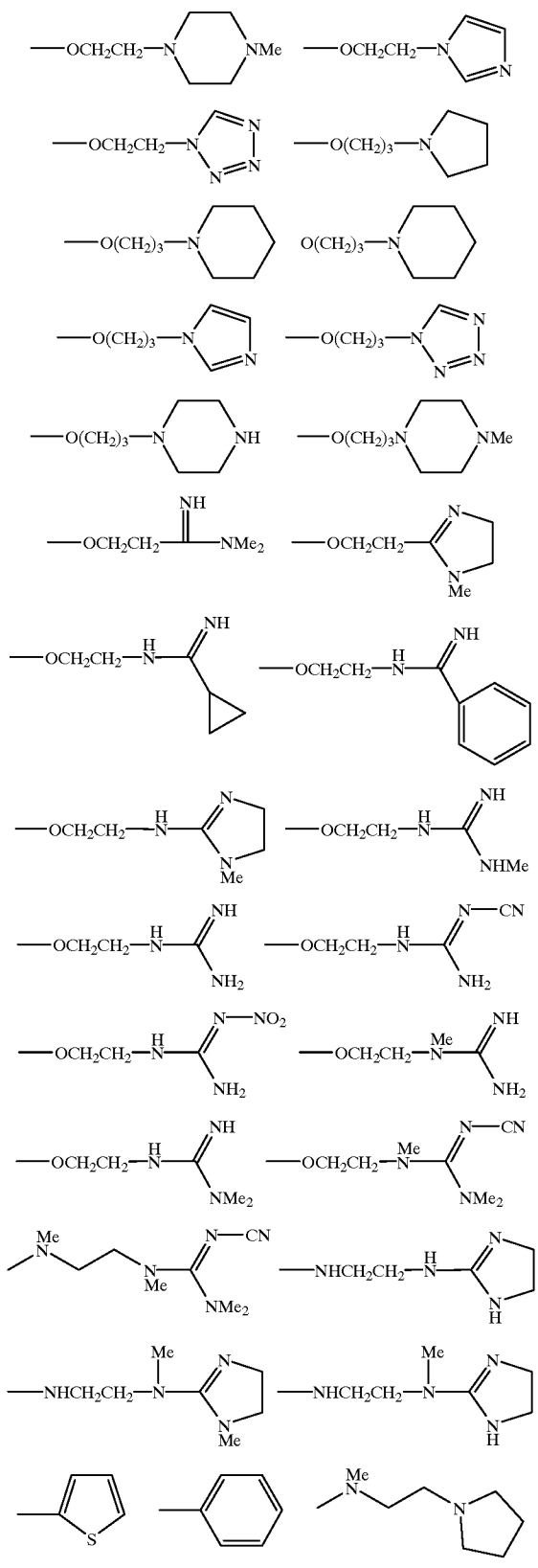

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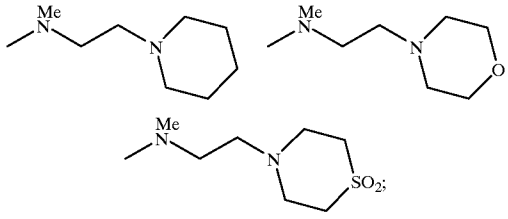
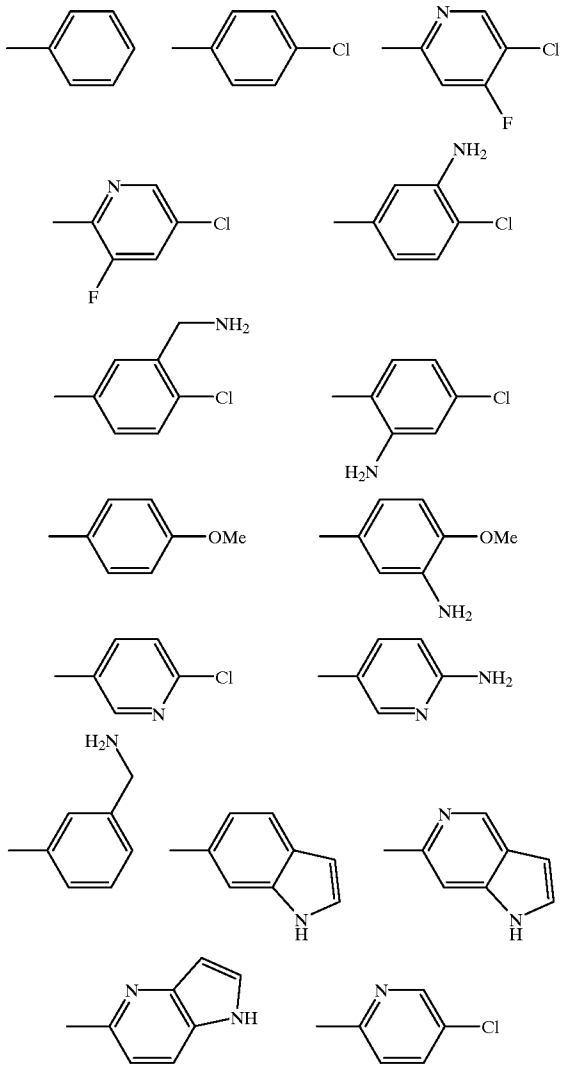


[0594] R^{1d3} is a member selected from the group consisting of:

[0595] H, —F, —Cl, —Br, —OCH_3, —OCF_3, —OCH_2F, —$OCHF_2$, —OCH_2CF_3, —OCF_2CF_3; and

[0596] X is a member selected from the group consisting of:



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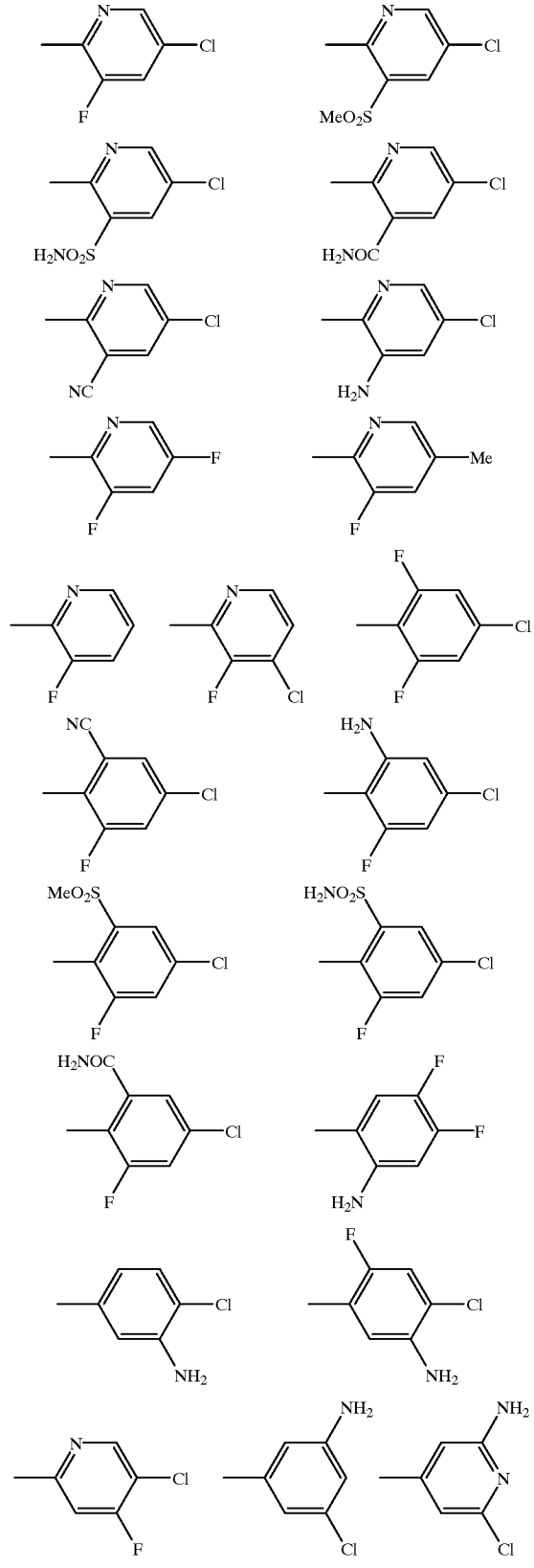

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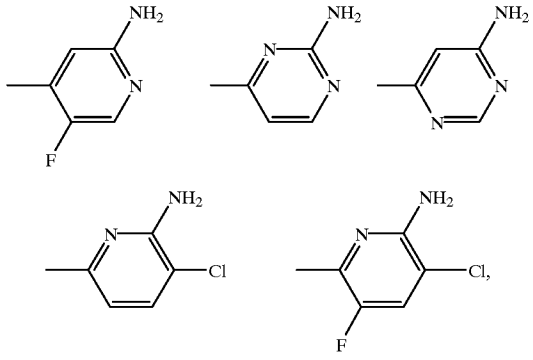
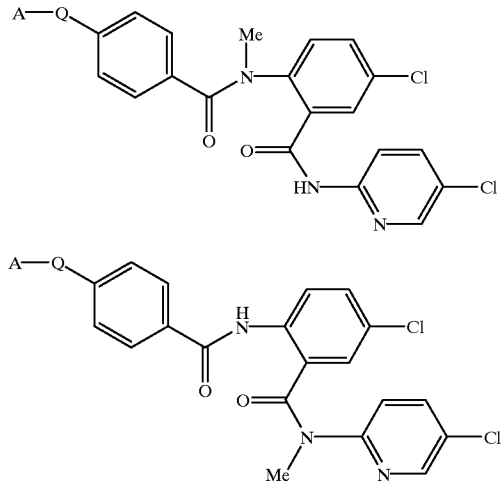


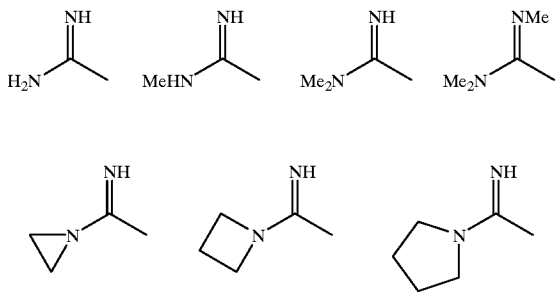
[0597] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug, derivatives thereof.

[0598] The invention provides compound of formula Ib, as described above, having the following structure:



[0599] wherein:

[0600] A-Q is a member selected from the group consisting of:



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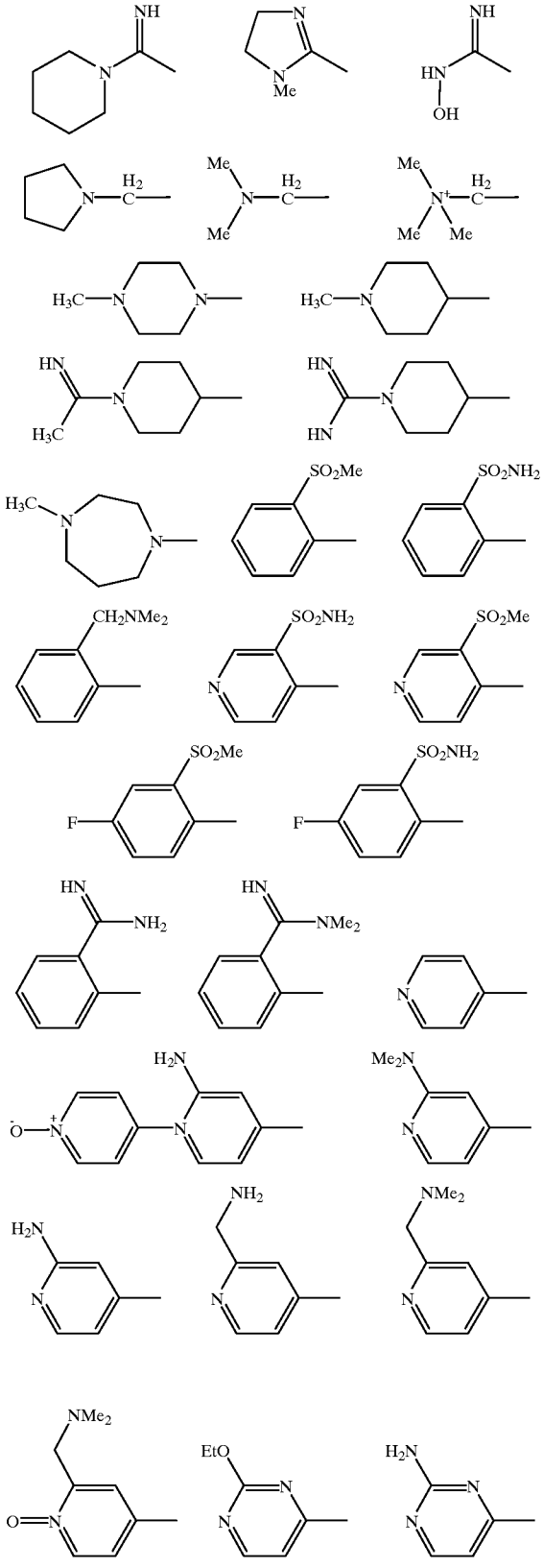

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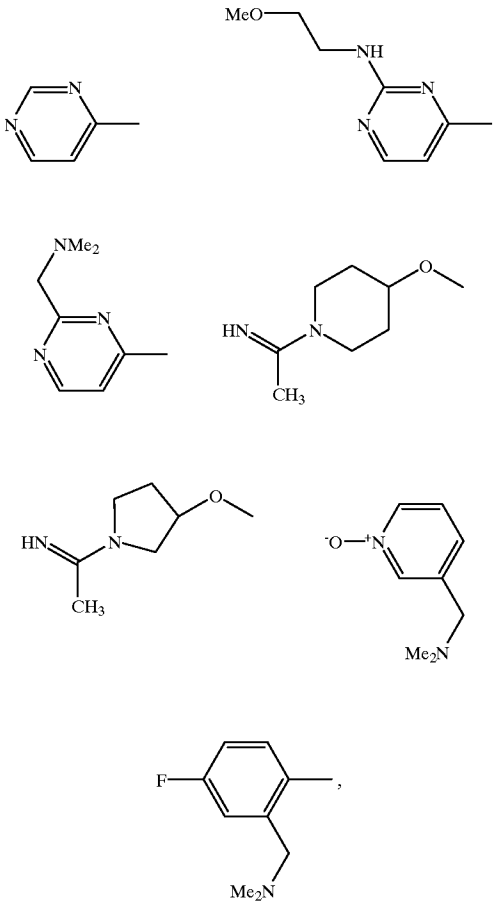

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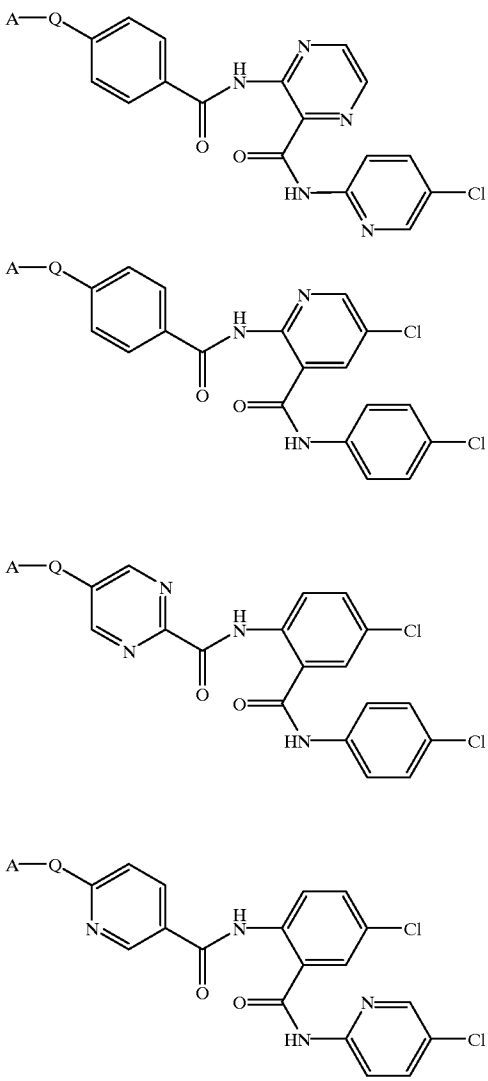
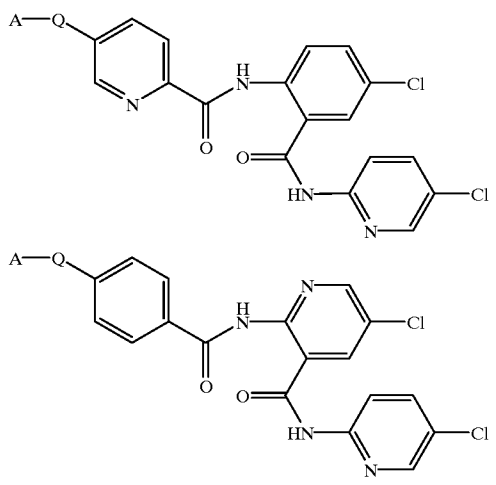
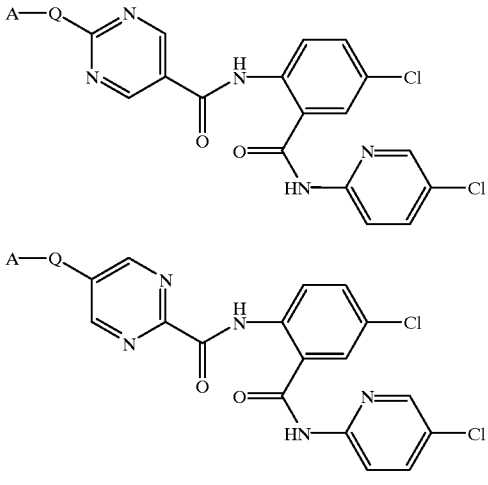


[0601] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0602] The invention provides compound of formula Ib, as described above, having the following structure:





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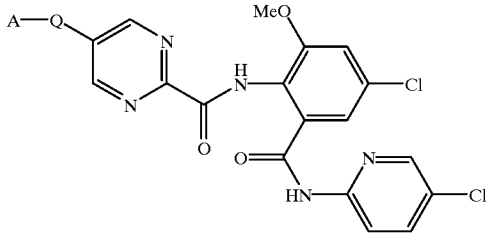
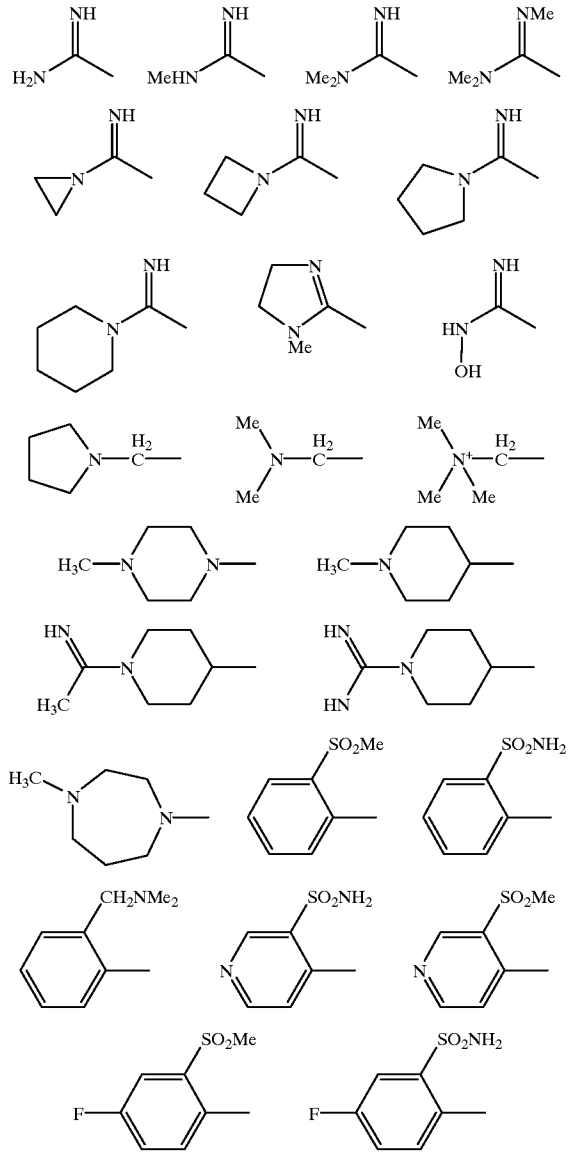


[0603] wherein:

[0604] A-Q is a member selected from the group consisting of:



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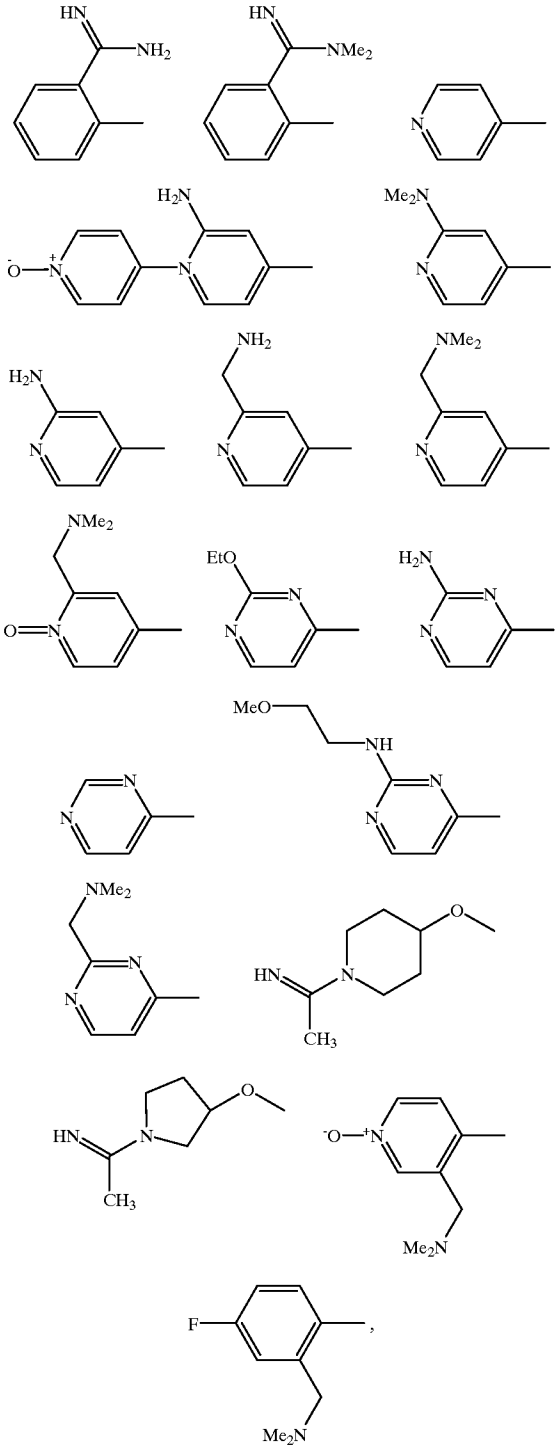
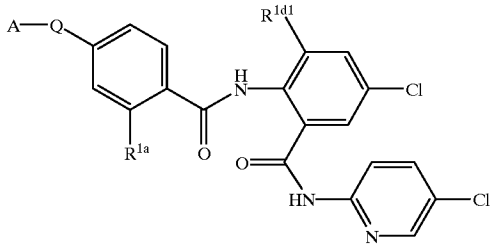


[0605] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

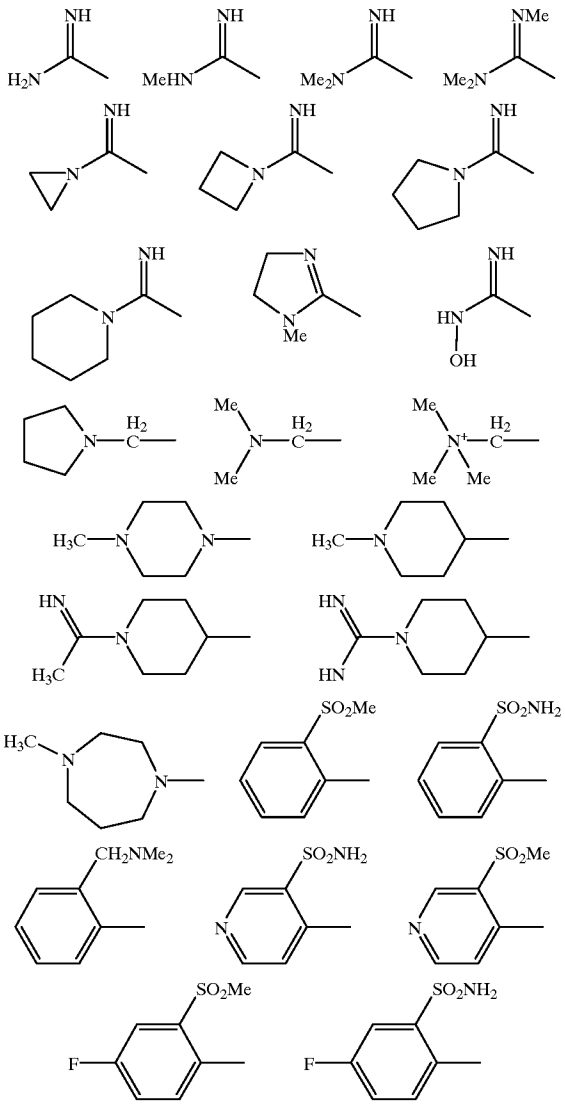
[0606] The invention provides compound of formula Ib, as described above, having the following structure:



[0607] wherein:

[0608] R^{1a} is H or F;

[0609] A-Q is a member selected from the group consisting of:



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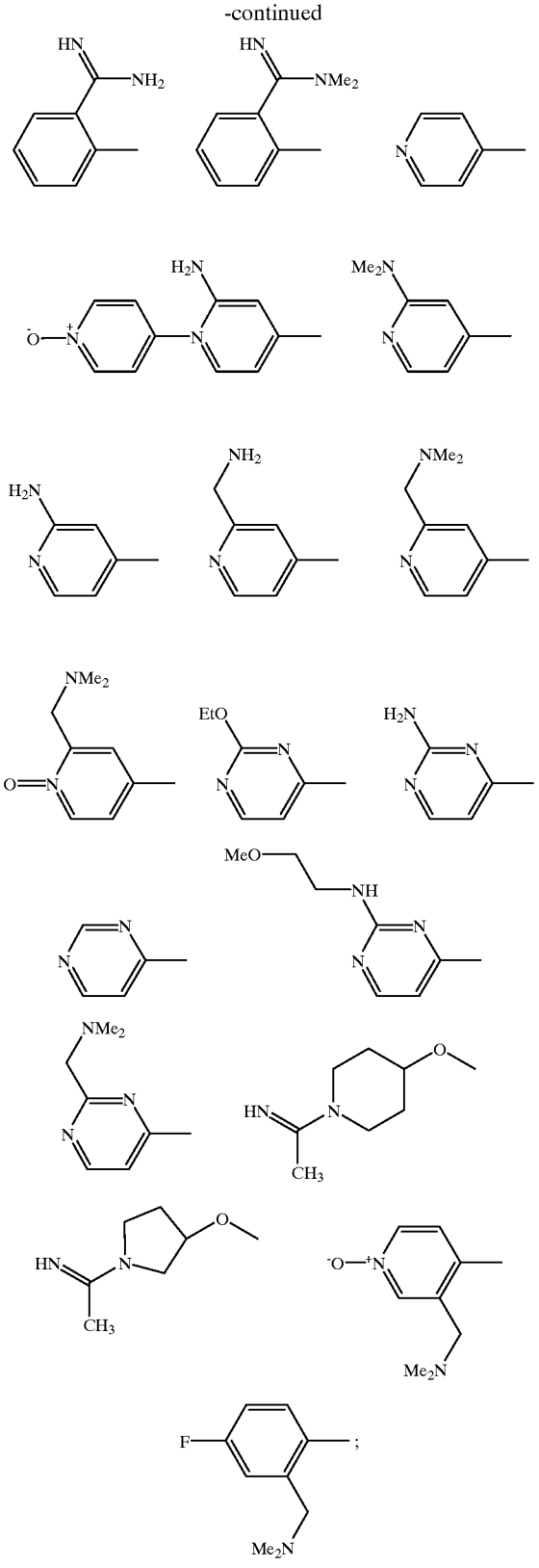
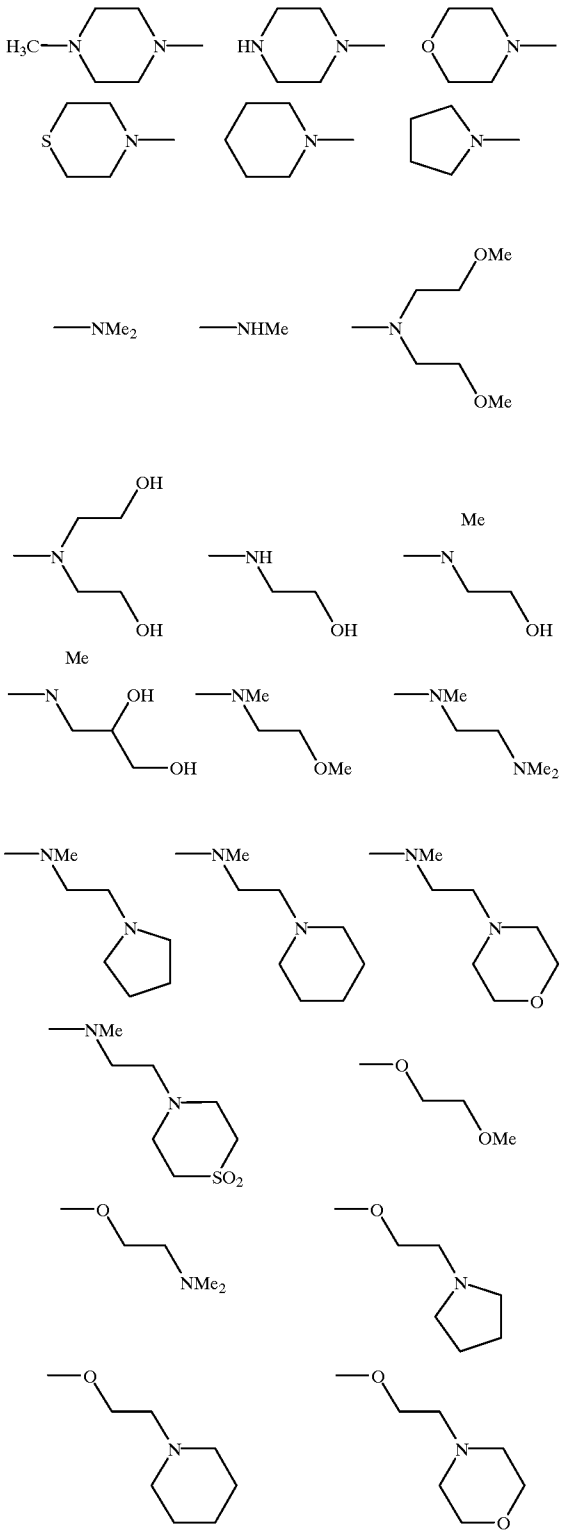


[0610] R^{1d1} is a member selected from the group consisting of:

[0611] H, OMe, Cl, F, OCF_3,



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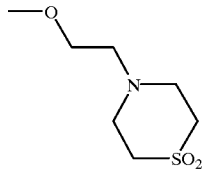
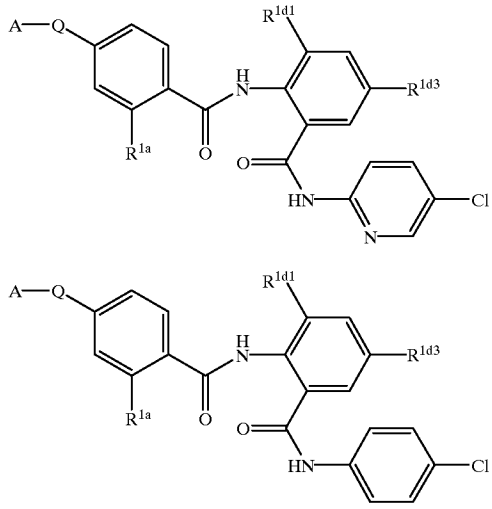


[0612] —N(Me)COOEt, —N(Me)CH2OOH,

[0613] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

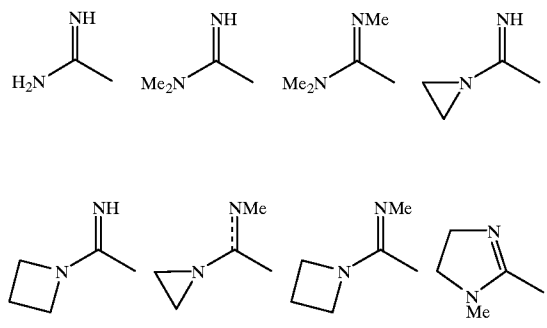
[0614] The invention provides compound of formula Ib, as described above, having the following structure:



[0615] wherein:

[0616] R^{1a} is H or F;

[0617] A-Q is a member selected from the group consisting of:



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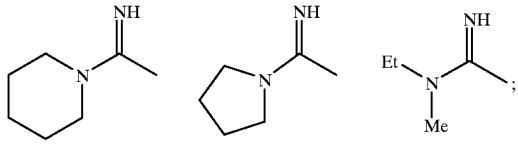


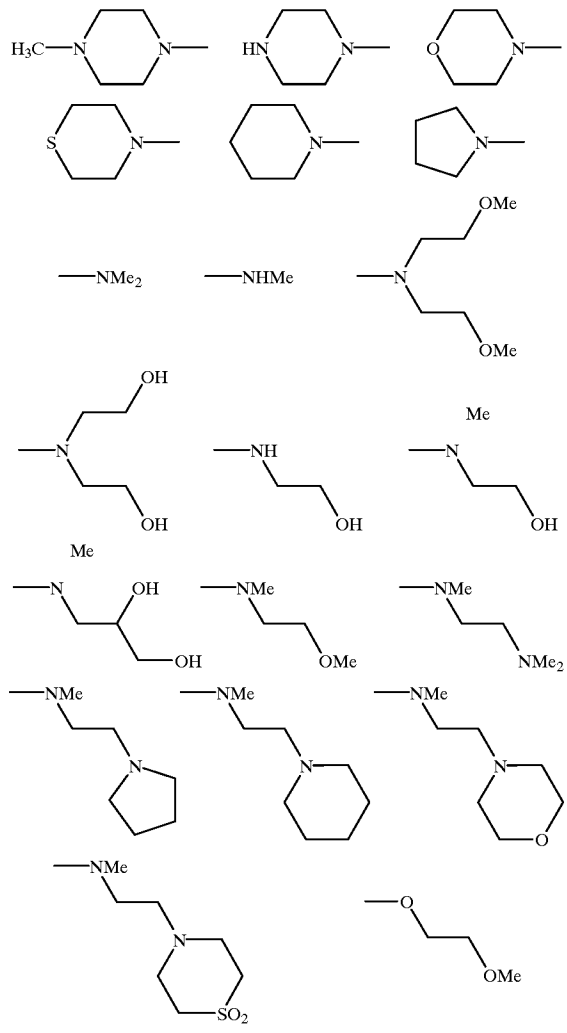
[0618] R^{1d1} is a member selected from the group consisting of:

[0619] H, —F, —Cl, —Br, —OMe, —OCF_3, —OH, —NMe_2, —OCH_2CO_2Et, —OCH_2CO_2H;

[0620] R^{1d3} is a member selected from the group consisting of:

[0621] H, —F, —Cl, —Br, —OMe, —OCF_3, —OH, —NMe, —OCH_2CO_2Et, —OCH_2CO_2H.

[0622] —OCF_2H, —$OCFH_2$, —OCF_2CF_3, —OCH_2CH_3,



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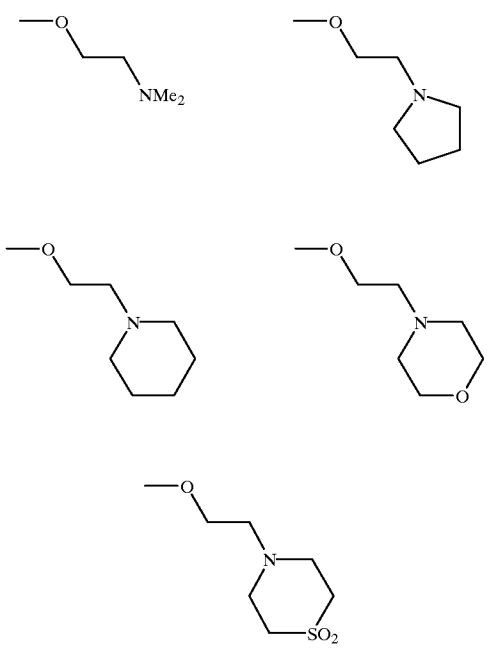
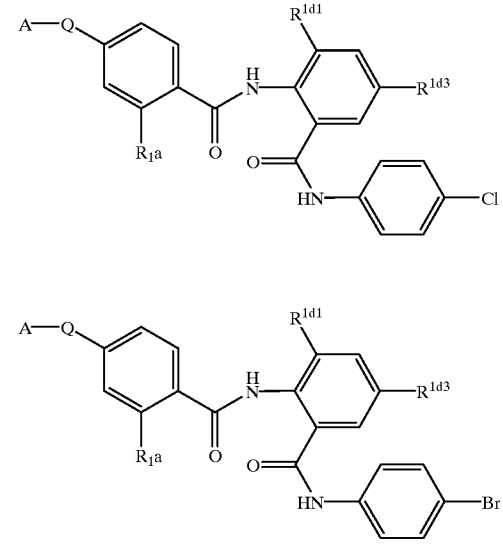


[0623] —N(Me)COOEt, —N(Me)CH2OOH

[0624] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

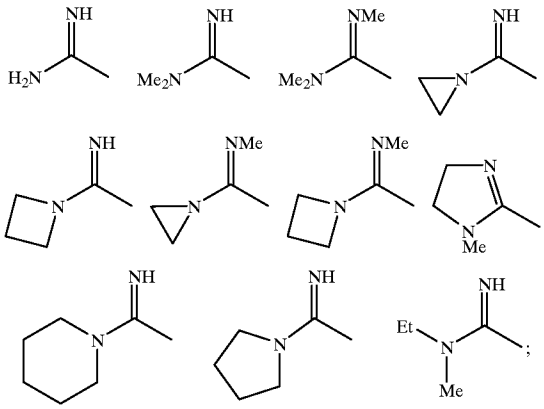
[0625] The invention provides compound of formula Ib, as described above, having the following structure:



[0626] wherein:

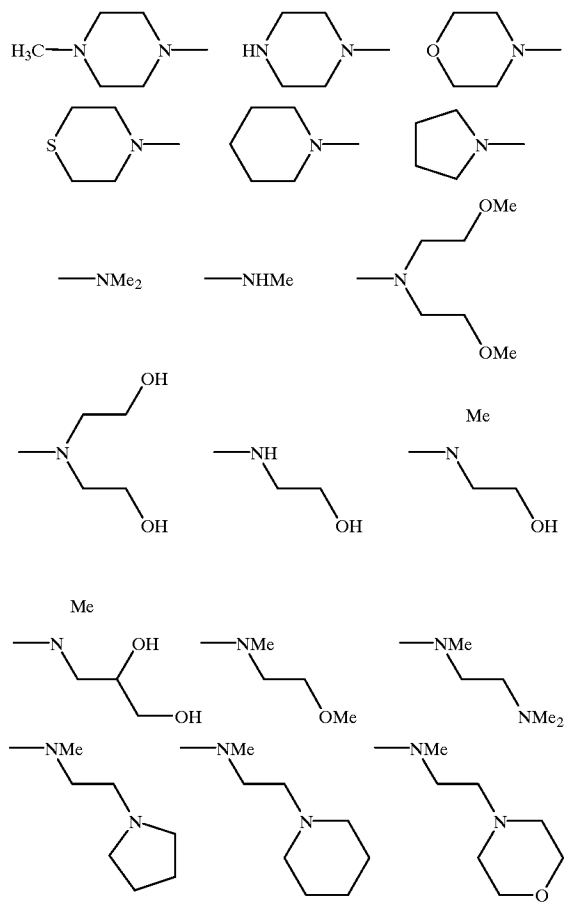
[0627] R^{1a} is H or F;

[0628] A-Q is a member selected from the group consisting of:



[0629] R^{1d1} is a member selected from the group consisting of:

[0630] H, —F, —Cl, —Br, —OMe, —OCF_3, —OH, —NMe_2, —OCH_2CO_2Et, —OCH_2CO_2H



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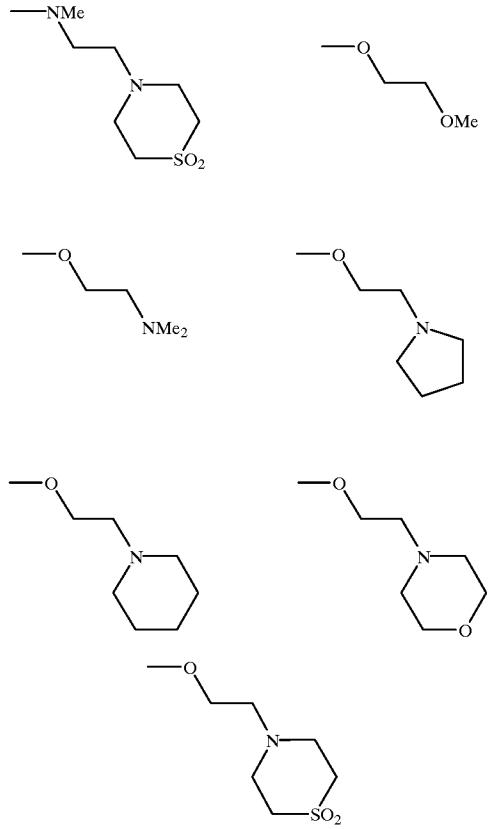


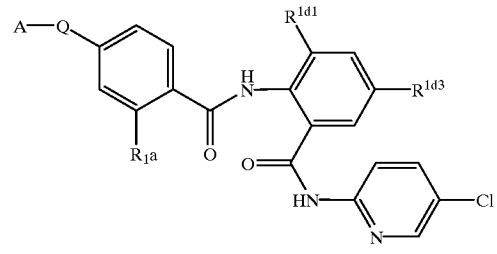
[0631] —N(Me)COOEt, —N(Me)CH2OOH

[0632] R^{1d3} is a member selected from the group consisting of:

[0633] H, —F, —Cl, —Br, —OMe, —OCF_3, —OH, —NMe_2, —OCH_2CO_2Et, —OCH_2CO_2H, —OCF_2H, —$OCFH_2$, —OCF_2CF_3, —OCH_2CH_3.

[0634] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0635] The invention provides compound of formula Ib, as described above, having the following structure:



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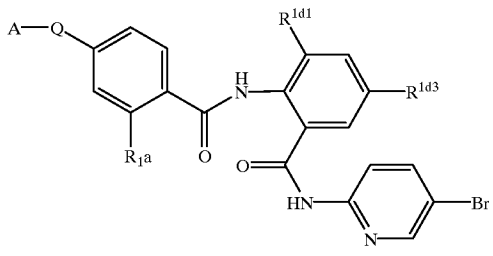
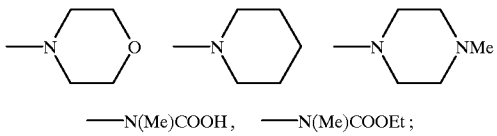


[0636] wherein:

[0637] R^{1a} is H or F;

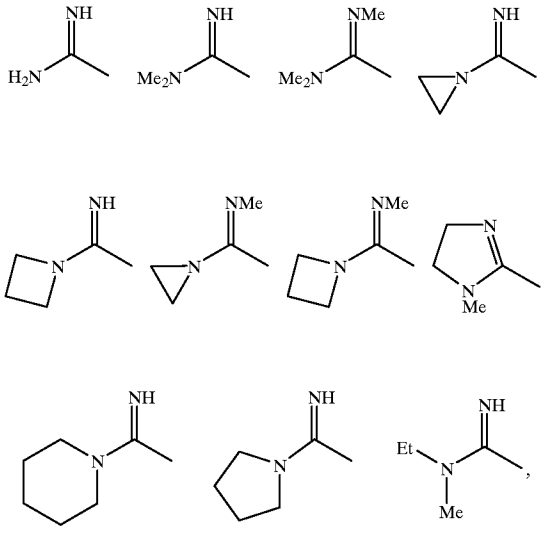
[0638] R^{1d1} is selected from H, —OMe, —NMe_2,



—N(Me)COOH, —N(Me)COOEt;

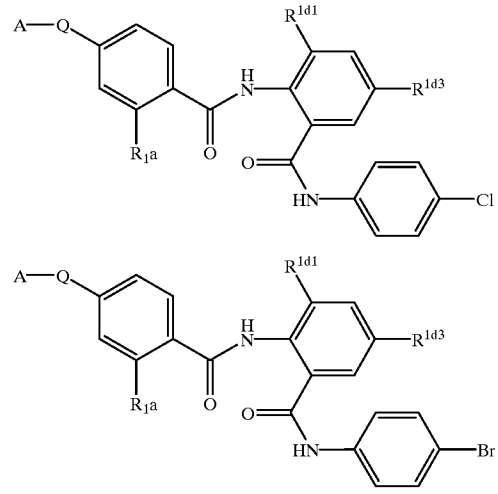
[0639] R^{1d3} is Cl or Br;

[0640] A-Q is a member selected from the group consisting of:



[0641] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

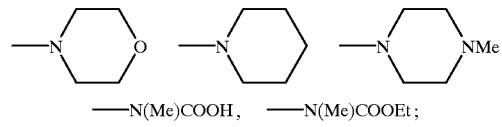
[0642] The invention provides compound of formula Ib, as described above, having the following structure:



[0643] wherein:

[0644] R^{1a} is H or F;

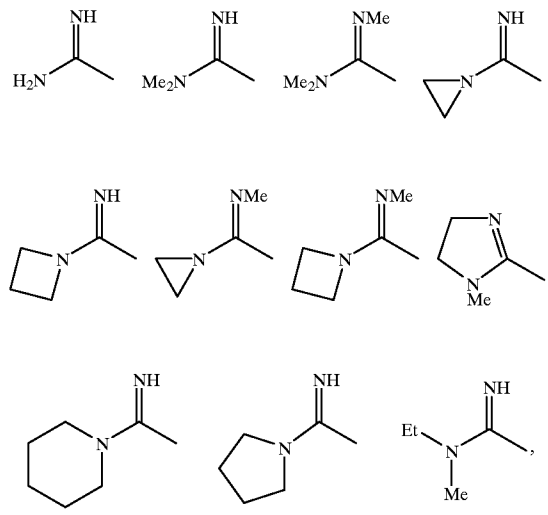
[0645] R^{1d1} is selected from H, —OMe, —NMe_2,



—N(Me)COOH, —N(Me)COOEt;

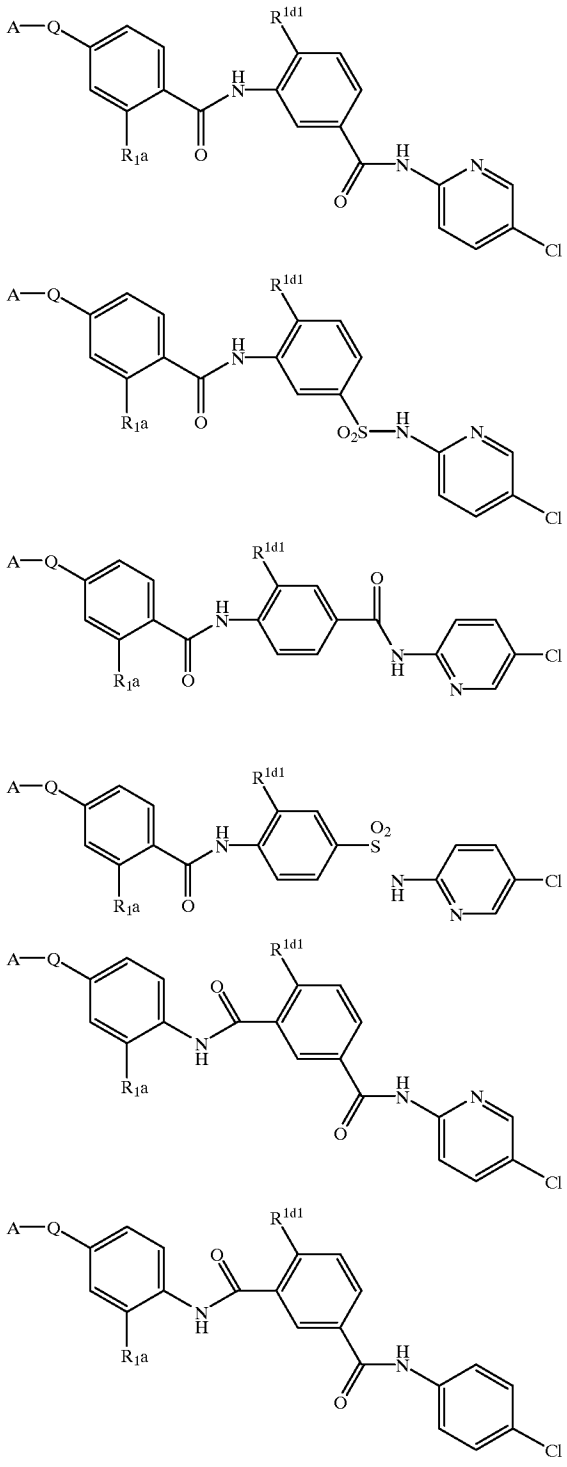
[0646] R^{1d3} is Cl or Br;

[0647] A-Q is a member selected from the group consisting of:



[0648] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

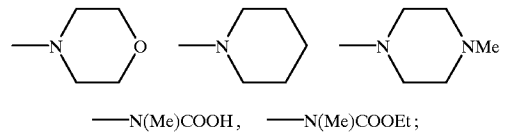
[0649] The invention provides compound of formula Ib, as described above, having the following structure:



[0650] wherein:

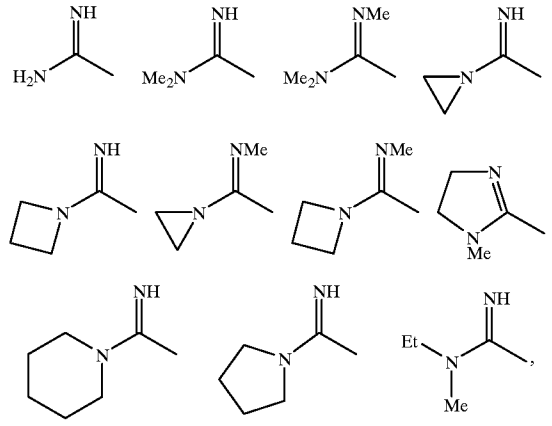
[0651] R^{1a} is H or F;

[0652] R^{1d1} is selected from H, —OMe, —NMe_2,



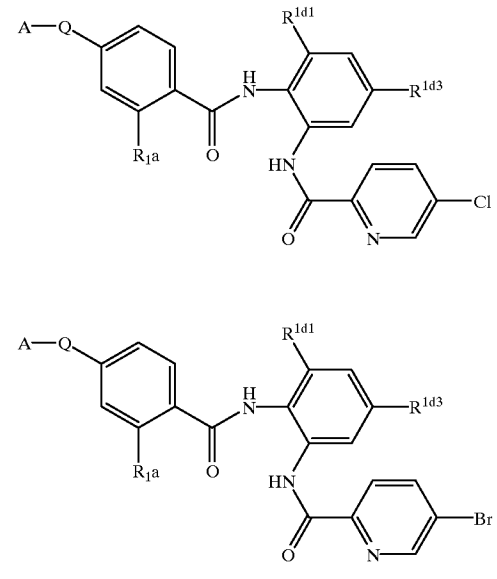
—N(Me)COOH, —N(Me)COOEt;

[0653] A-Q is a member selected from the group consisting of:



[0654] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0655] The invention provides compound of formula Ib, as described above, having the following structure:



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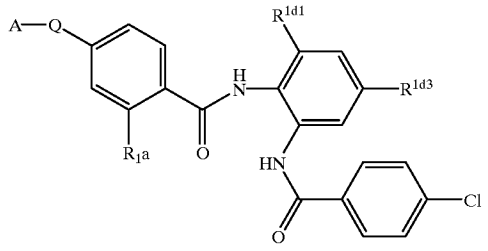
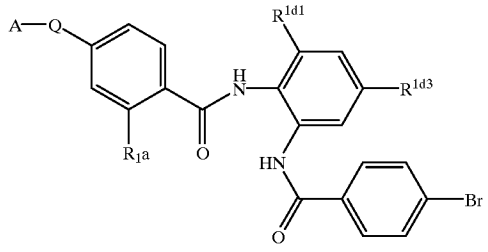
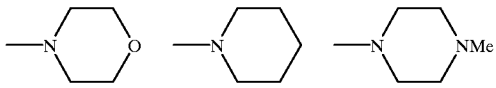




[0656] wherein:

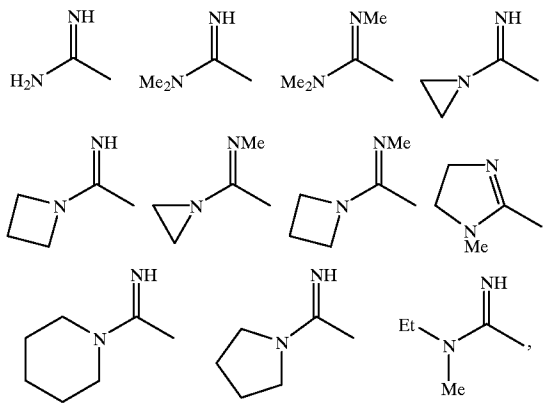
[0657] R^{1a} is H or F;

[0658] R^{1d1} is selected from H, —OMe, —NMe_2,



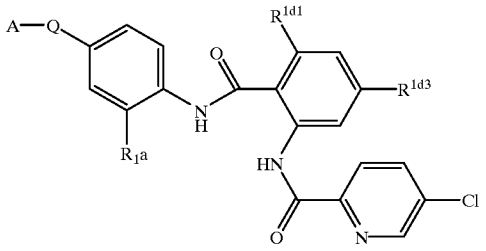
—N(Me)COOH, —N(Me)COOEt;

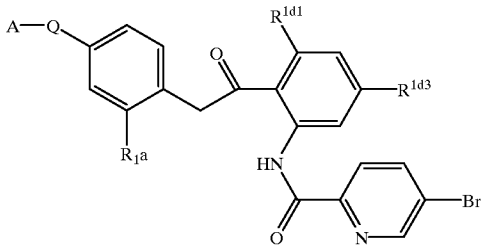
[0659] A-Q is a member selected from the group consisting of:

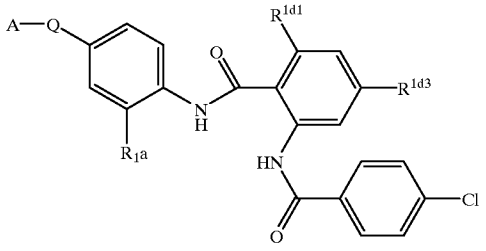


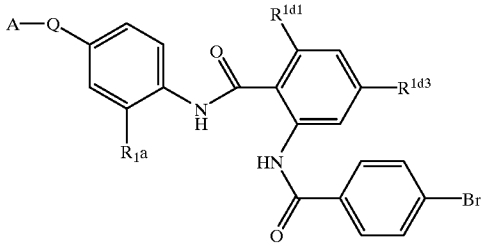
[0660] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0661] The invention provides a compound of formula Ib, as described above, having the following structure:





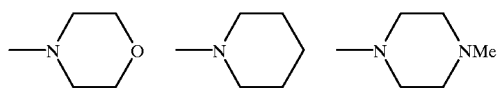




[0662] wherein:

[0663] R^{1a} is H or F;

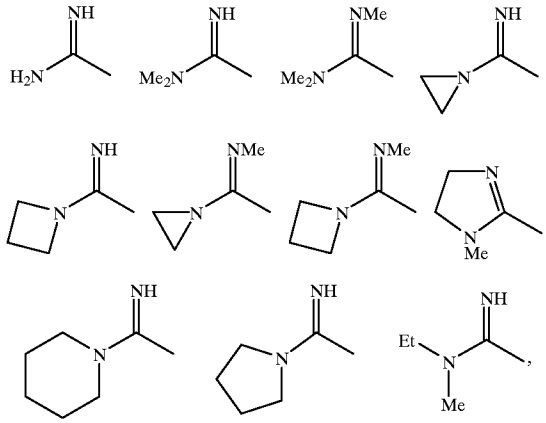
[0664] R^{1d1} is selected from H, —OMe, —NMe_2,



—N(Me)COOH, —N(Me)COOEt;

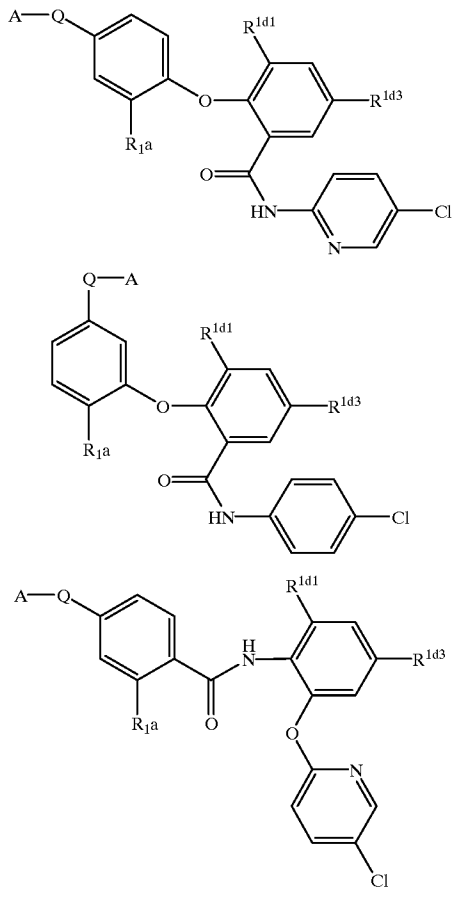
and R^{1d3} is —Cl or —Br;

[0665] A-Q is a member selected from the group consisting of:



[0666] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0667] The invention provides compound of formula Ib, as described above, having the following structure:



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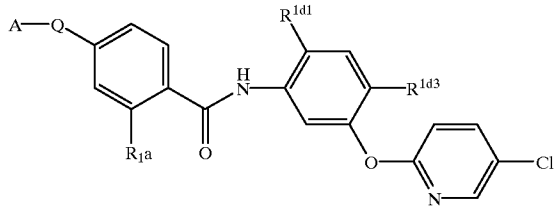
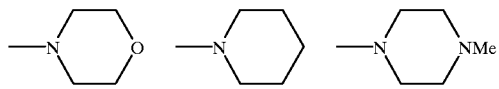


[0668] wherein:

[0669] R^{1a} is H or F;

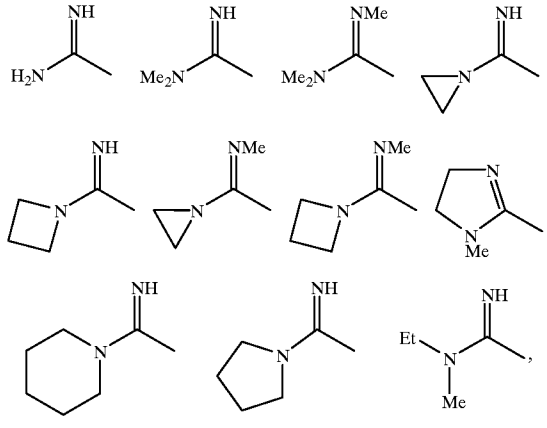
[0670] R^{1d1} is selected from H, —OMe, —NMe_2,



—N(Me)COOH, —N(Me)COOEt;

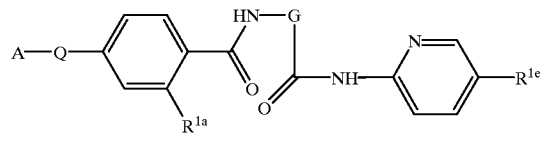
and R^{1d3} is —Cl or —Br;

[0671] A-Q is a member selected from the group consisting of:



[0672] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0673] The invention provides compound of formula Ib, as described above, having the following structure:



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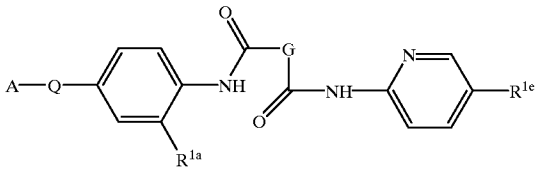
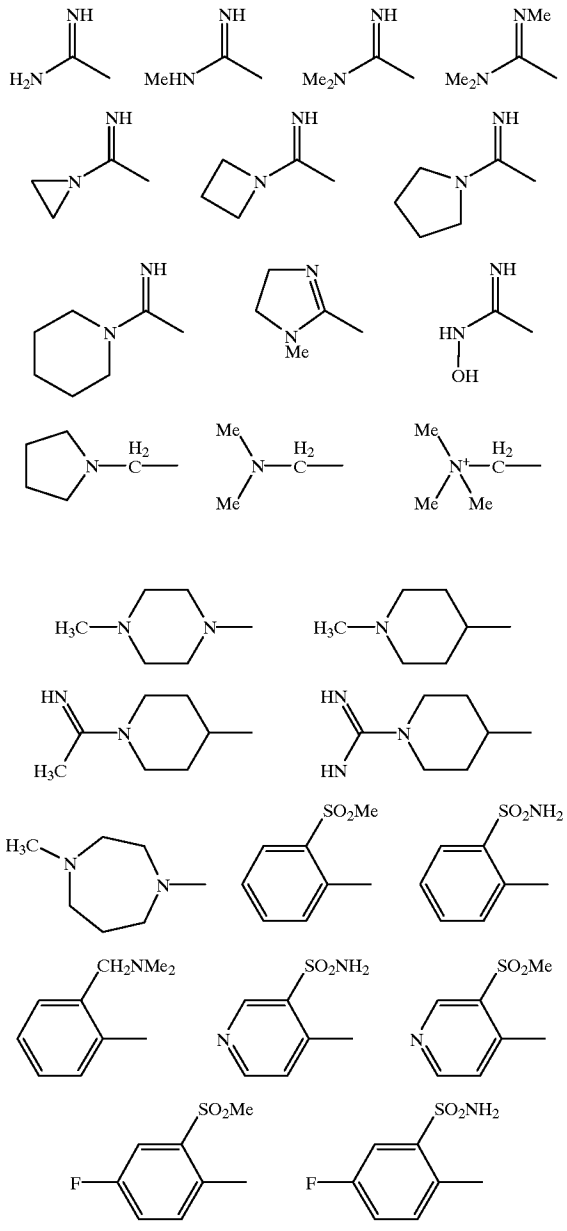


[0674] wherein:

[0675] A-Q is a member selected from the group consisting of:



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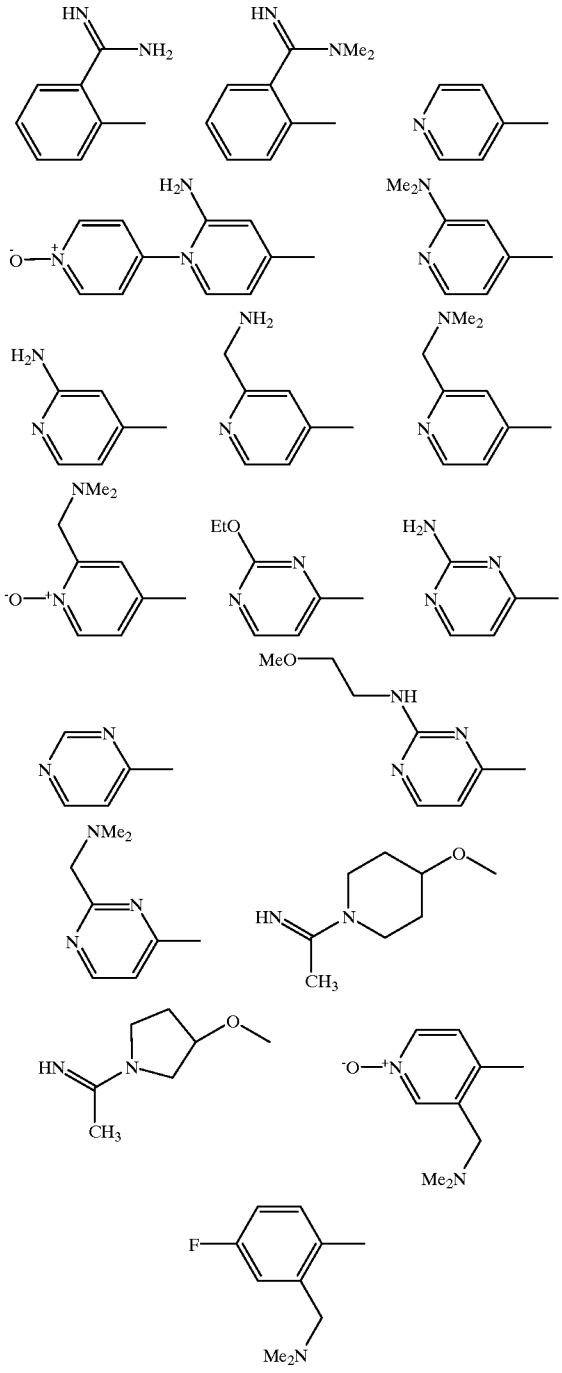


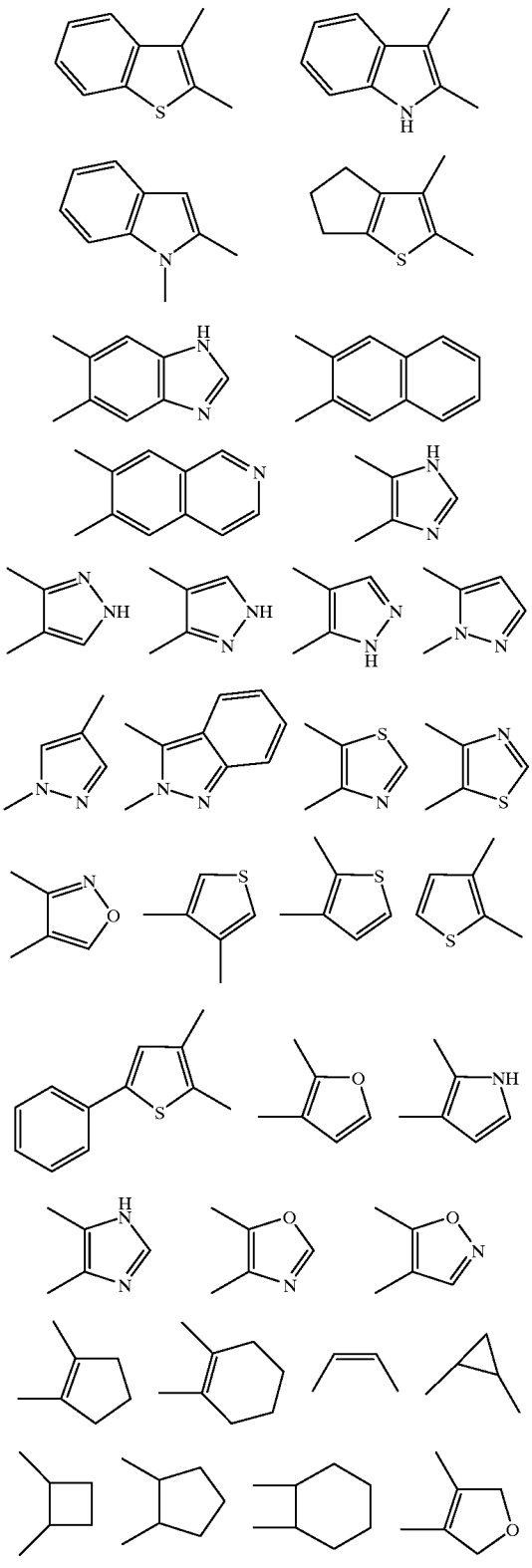
[0676] R^{1a} is a member selected from the group consisting of:

[0677] H, —F, —Cl and Br;

[0678] R^{1e} is a member selected from the group consisting of:

[0679] H, —F, —Cl, —Br, —OMe, —OH, —Me, —CF_3 and —CH_2NH_2; and

[0680] G is a member selected from the group consisting of:



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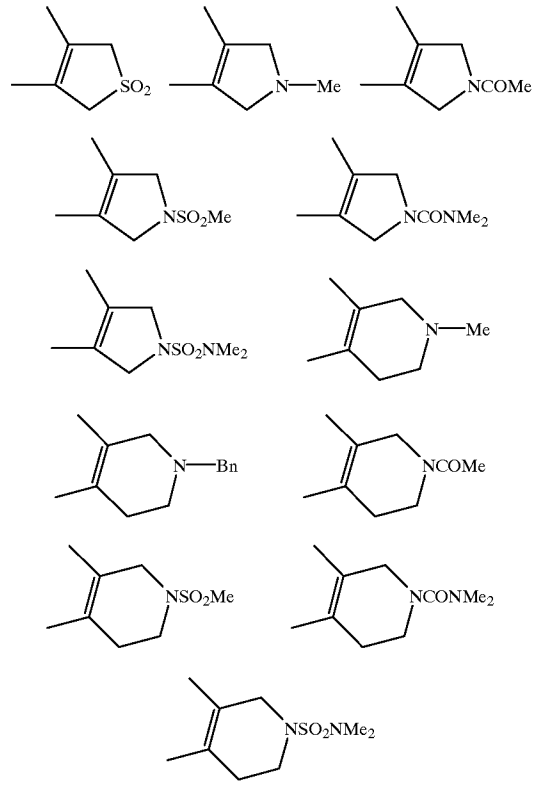
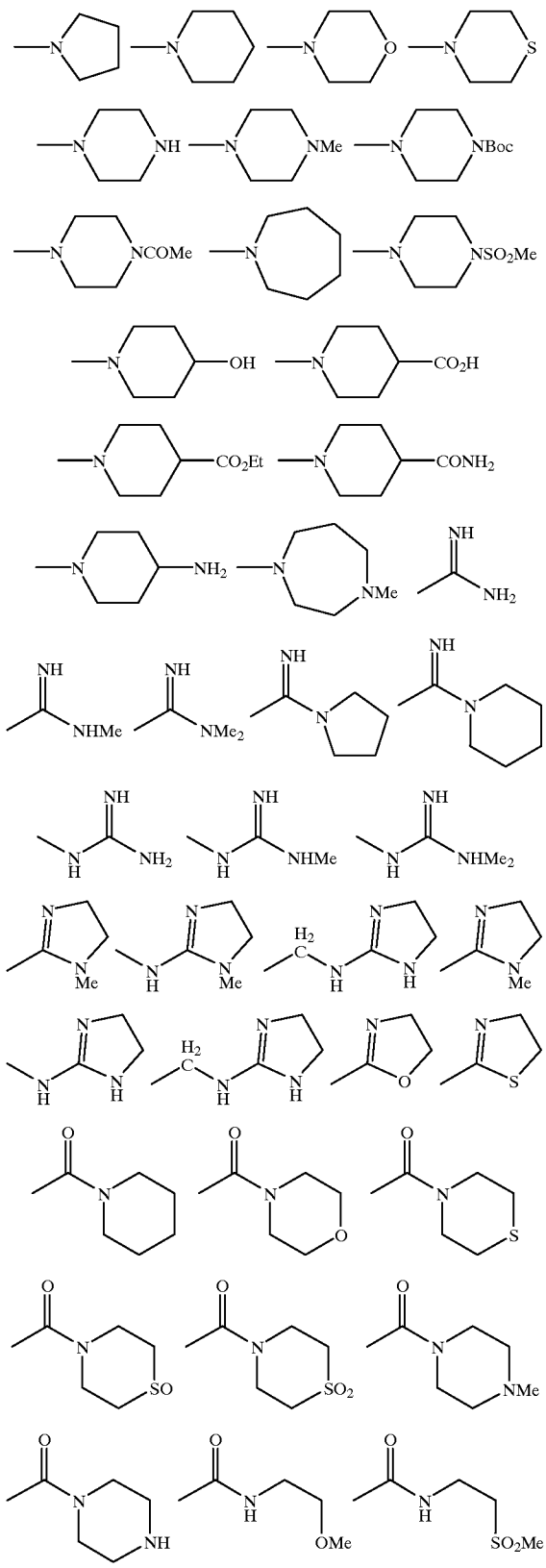


[0681] wherein each G group is substituted by 0-4 R^{1d} groups and each such R^{1d} group is independently selected from the group consisting of:

[0682] H, —Me, —F, —Cl, —Br aryl, heteroaryl, —NH_2, —NMe_2, —NHMe, —$NHSO_2Me$, —NHCOMe, —CH_3, —CF_3, —OH, —OCH_3, —SCH_3, —OCF_3, —OCH_2F, —$OCHF_2$, —OCH_2CF_3, —OCF_2CF_3, —NO_2, —CN, —CO_2H, —CO_2Me, —CO_2Et, —$CONH_2$, —CONHMe, —$CONMe_2$, —SO_2NH_2, —SO_2CH_3, —SO_2NMe_2, —CH_2OH, —CH_2NH_2, —CH_2NHMe, —CH_2NMe_2, —OCH_2CO_2H, —OCH_2CO_2Me, —OCH_2CO_2Et, —OCH_2CONH_2, —OCH_2CONMe_2, —$OCH_2CONHMe$, —OCH_2CH_2OMe, —OCH_2CH_2OEt, —$OCH_2CH_2NH_2$, —OCH_2CH_2NHMe, —$OCH_2CH_2NMe_2$, —$NHCH_2CH_2OMe$ —SCH_2CH_2OMe, —$SO_2CH_2CH_2OMe$, —$OCH_2CH_2SO_2Me$, —$NHCH_2CH_2NHMe$, —$NHCH_2CH_2NMe_2$, —$N(CH_2CH_2OH)_2$, —$N(CH_2CH_2OMe)_2$, —$NHCH_2CO_2H$, —$NHCH_2CO_2Et$, —$NHCH_2CO_2Et$, —$NHCH_2CONH_2$, —$NHCH_2CONMe_2$, —$NHCH_2CONHMe$, —$N(CH_3)CH_2CO_2H$, —$N(CH_3)CH_2CO_2Et$, —(NMe)CH2COOH, —N(Me)CH2CONH2, —N(Me)CH2CH2NMe2, —N(Me)CH2CH2OMe, —NHCH2CH2OMe,



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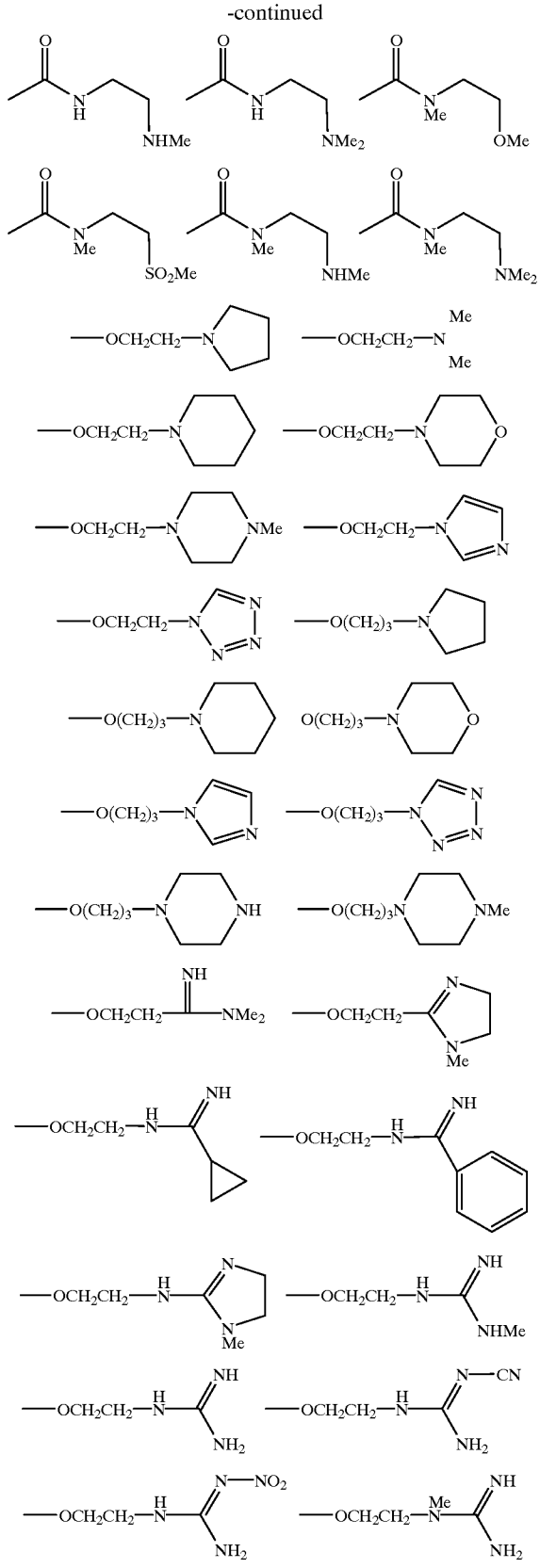

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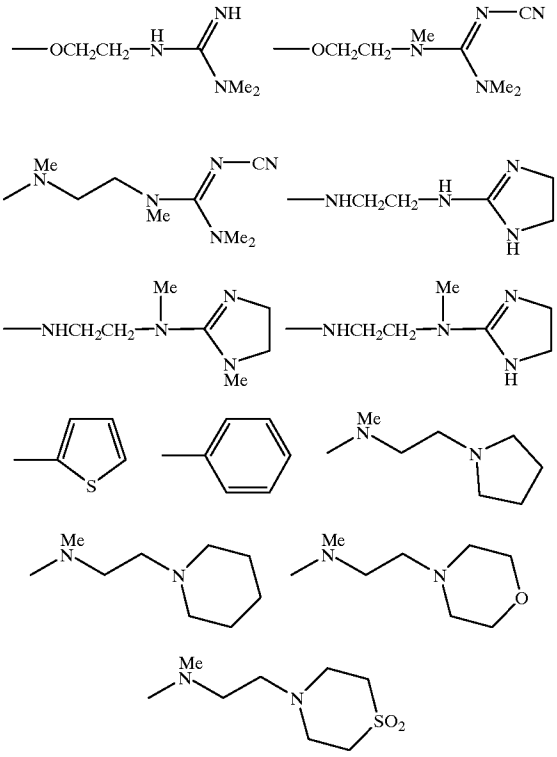
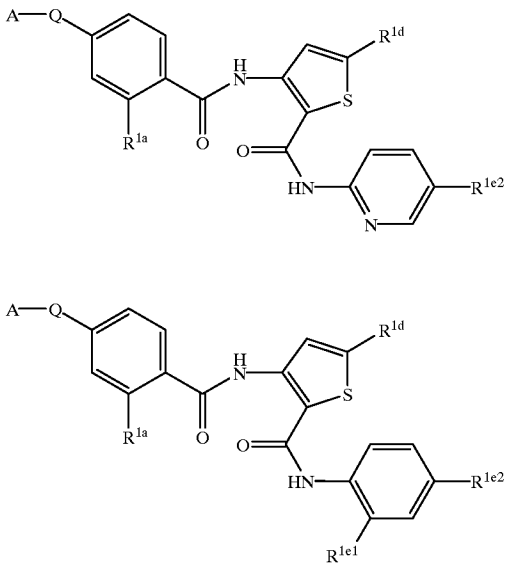


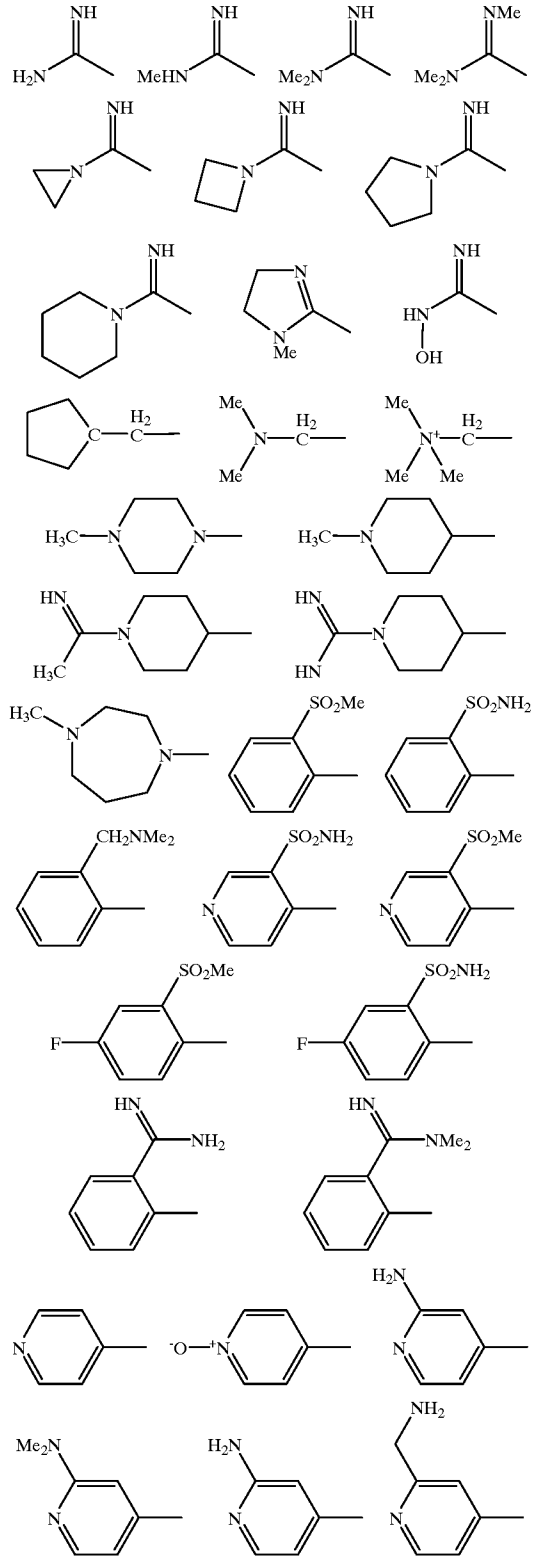
[0683] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0684] The invention provides compound of formula Ib, as described above, having the following structure:



[0685] wherein:

[0686] A-Q is a member selected from the group of:



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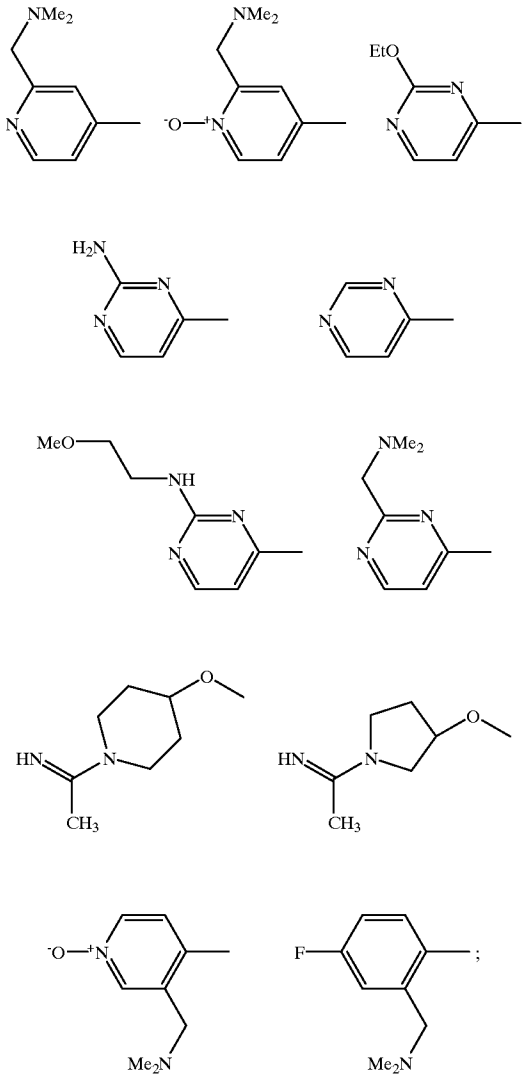


[0687] R^{1a} is a member selected from the group of:

[0688] H, —F, —Cl, —Br;

[0689] R^{1d} is a member selected from the group of:

[0690] H, —F, —Cl, —Br, —OMe;

[0691] R^{1e1} is a member selected from the group of:

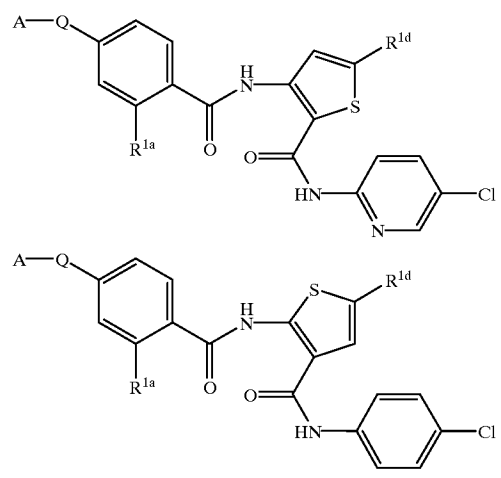
[0692] H, —F, —Cl, —Br, —NH_2, —CH_2NH_2, —OMe, —OH, —CN, —SO_2Me, —SO_2NH_2; and

[0693] R^{1e2} is a member selected from the group of:

[0694] H, —F, —Cl, —Br, —NH_2,

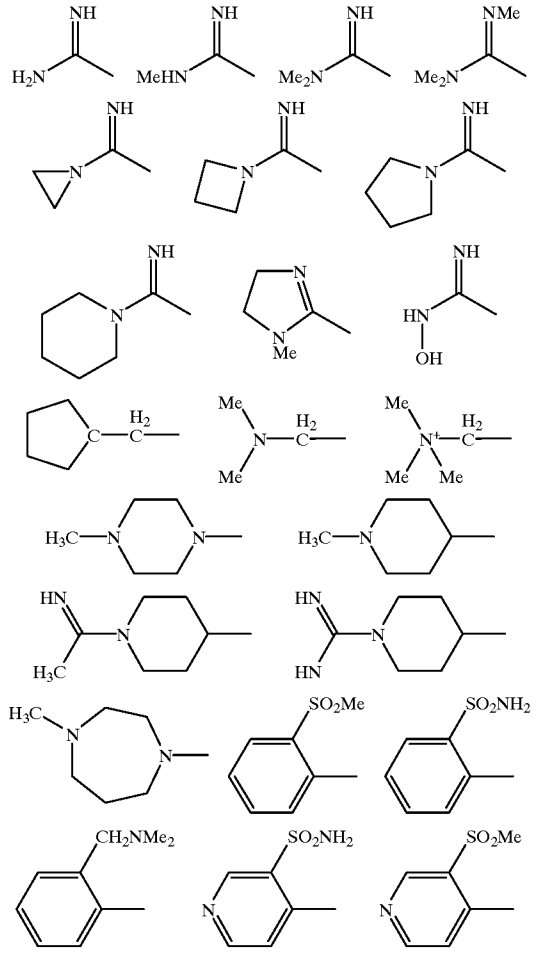
[0695] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0696] The invention provides compound of formula Ib, as described above, having the following structure:



[0697] wherein:

[0698] A-Q is a member selected from the group of:



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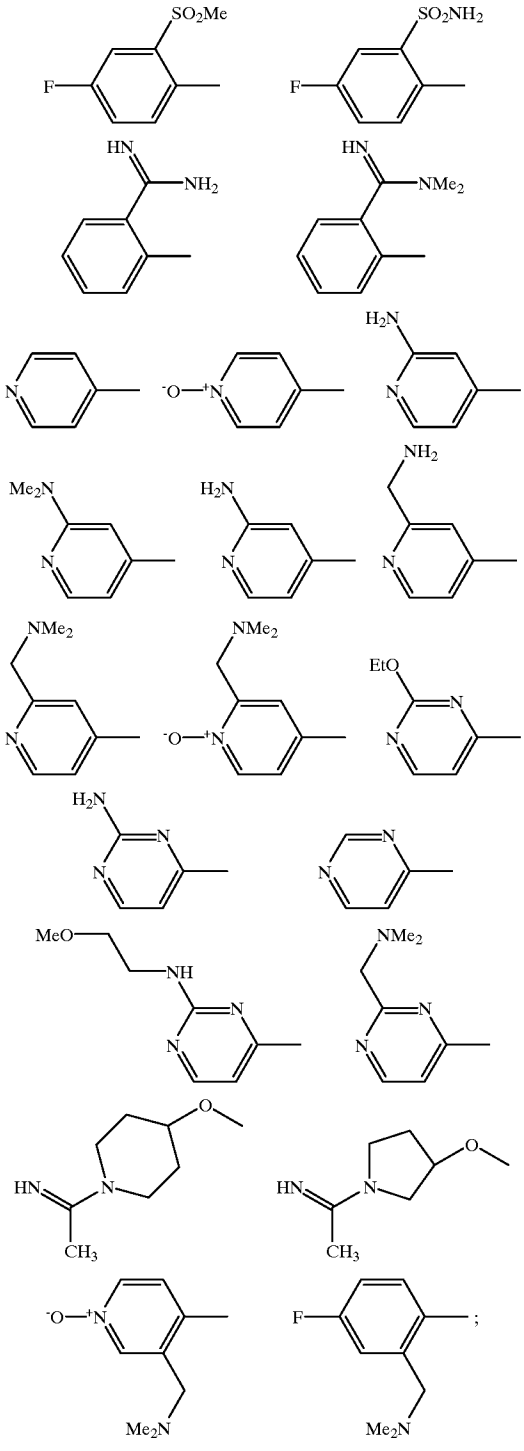


[0699] R^{1a} is a member selected from the group of:

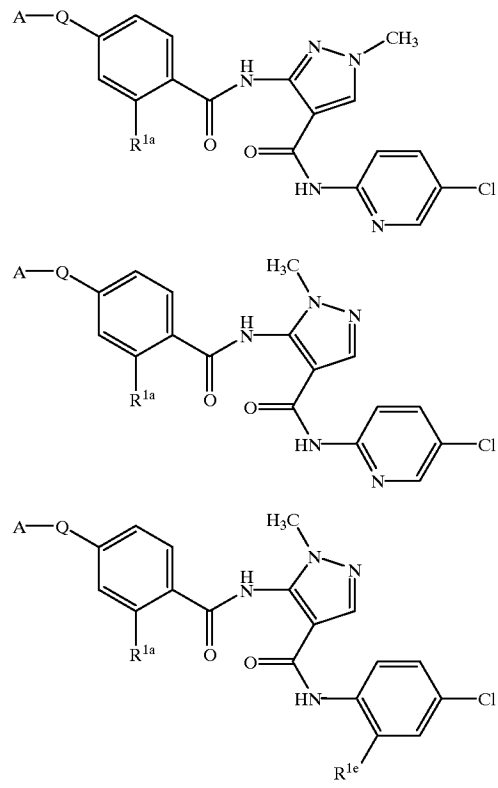
[0700] H, —F, —Cl and Br; and

[0701] R^{1d} is a member selected from the group of:

[0702] H, —F, —Cl, —Br, —OMe,

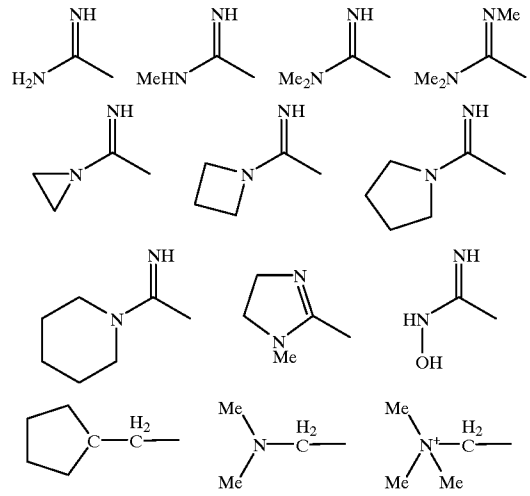
[0703] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0704] The invention provides compound of formula Ib, as described above, having the following structure:



[0705] wherein:

[0706] A-Q is a member selected from the group of:



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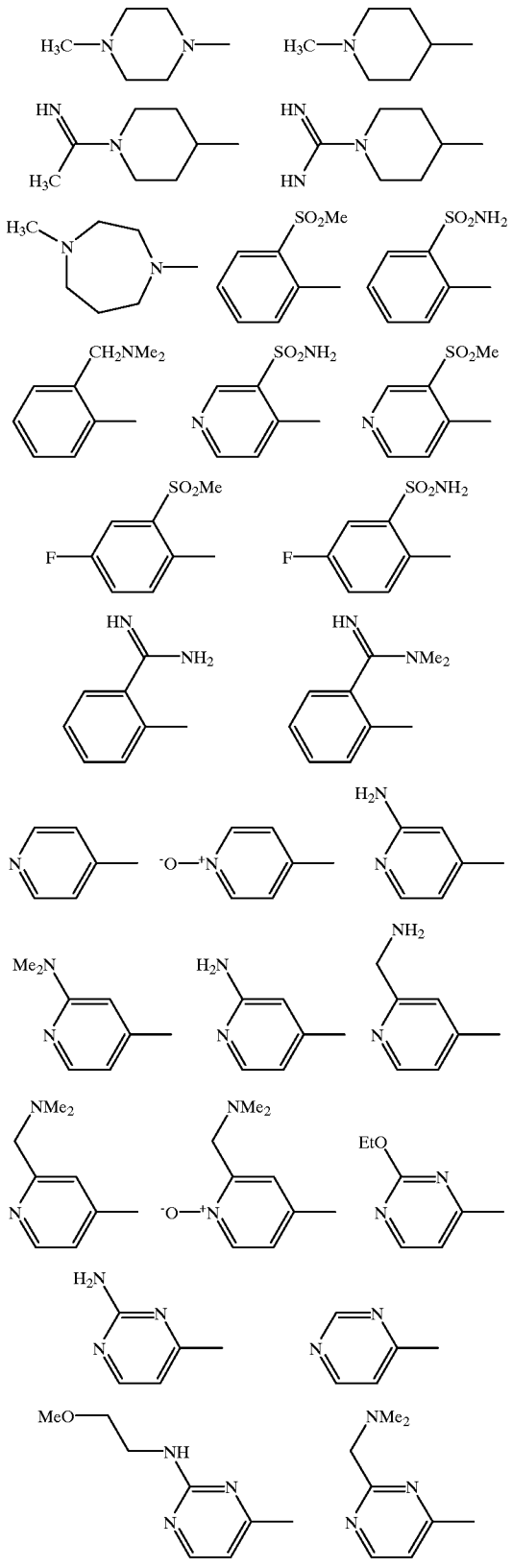

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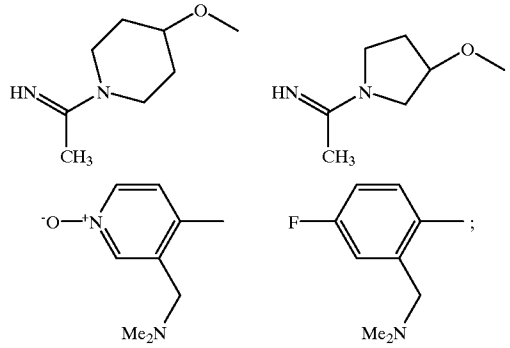


[0707] R^{1a} is a member selected from the group of:

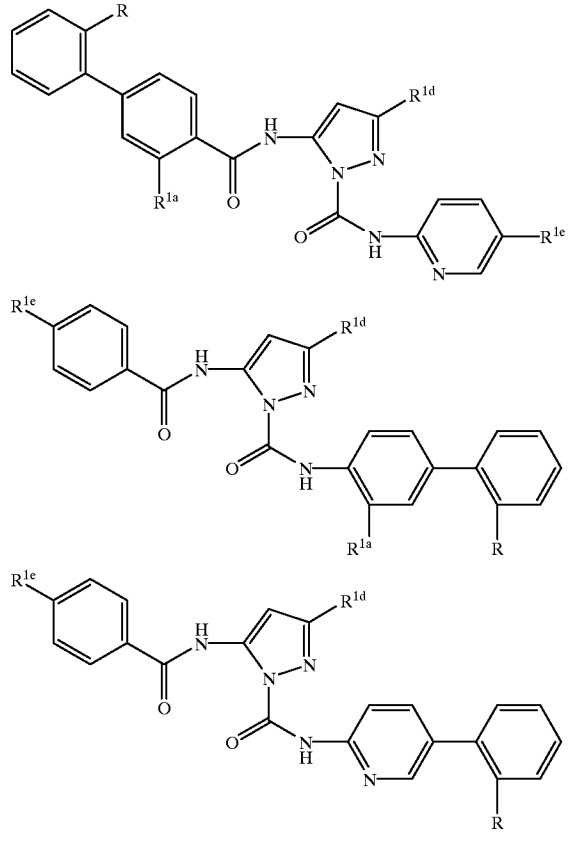
[0708] H, —F, —Cl and Br, and

[0709] R^{1e} is a member selected from the group of:

[0710] H, —F, —Cl, —Br, —NH_2, —CH_2NH_2, —OMe, —OH, —CN, —SO_2Me, —SO_2NH_2.

[0711] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0712] The invention provides compound of formula Ib, as described above, having the following structure:



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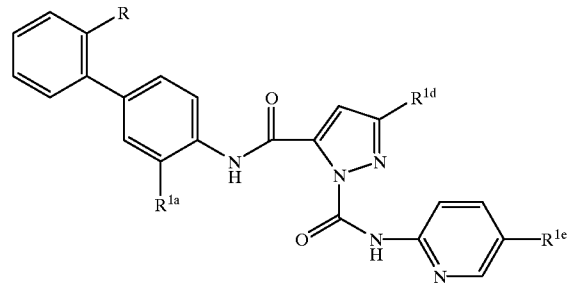

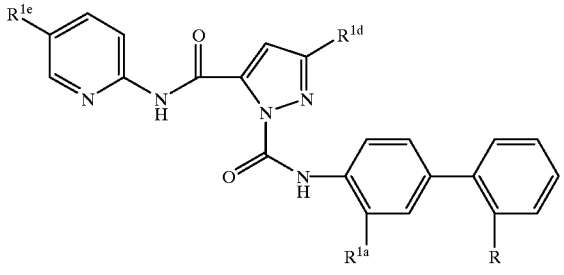

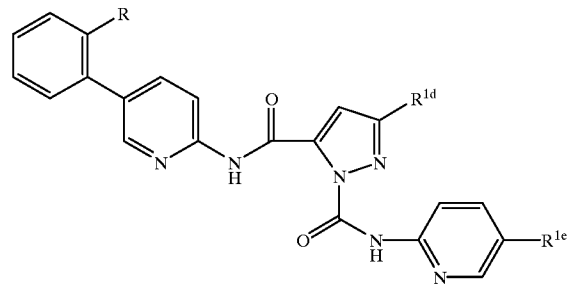

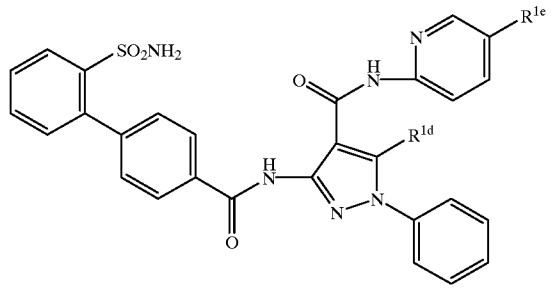

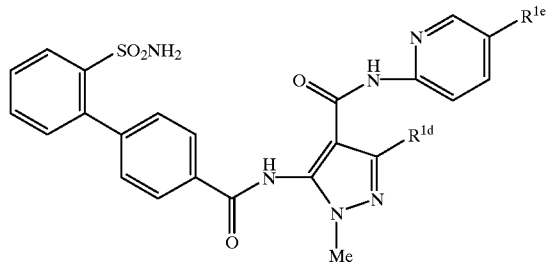

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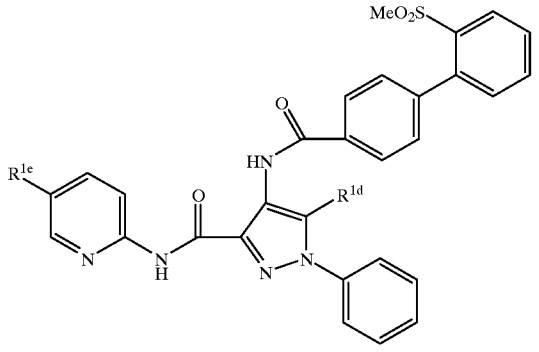
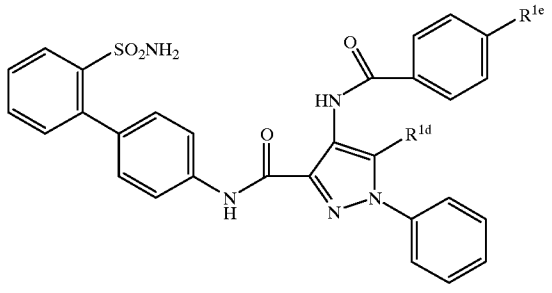
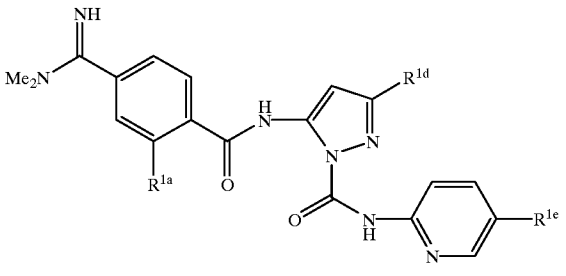
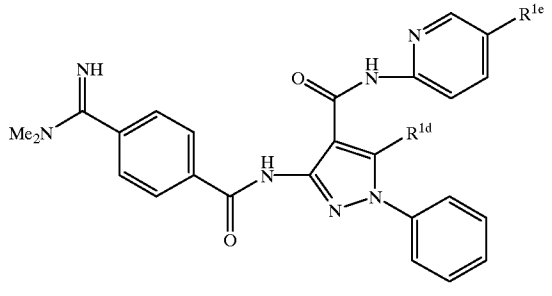








[0713] wherein:

[0714] R is a member selected from the group of:

[0715] —SO_2NH_2, —SO_2Me, —CH_2NMe_2;

[0716] R^{1a} is a member selected from the group of:

[0717] H, —F, —Cl, —Br;

[0718] R^{1d} is a member selected from the group of:

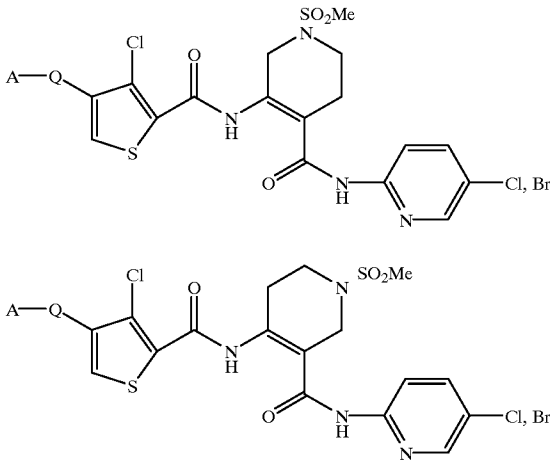
[0719] H, —F, —Cl, —Br, —CN, CF_3, —CH_3, —SO_2NH_2, —SO_2Me; and

[0720] R is a member selected from the group of:

[0721] —Cl, —Br,

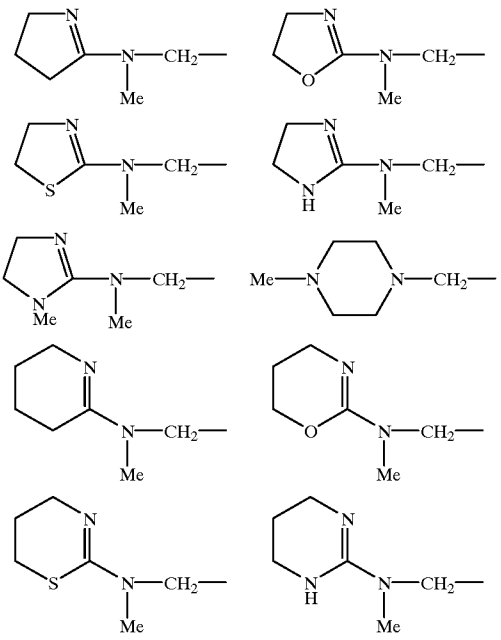
[0722] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0723] The invention provides compound of formula Ib, as described above, having the following structure:



[0724] wherein:

[0725] A-Q taken together are a member selected from the group consisting of:



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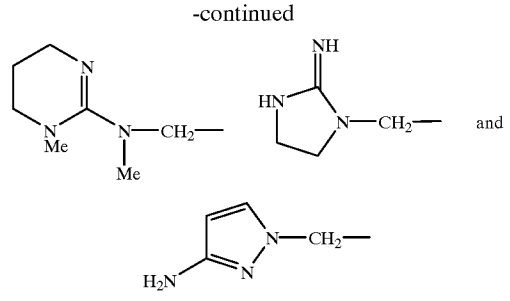
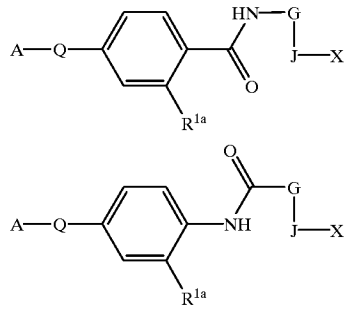


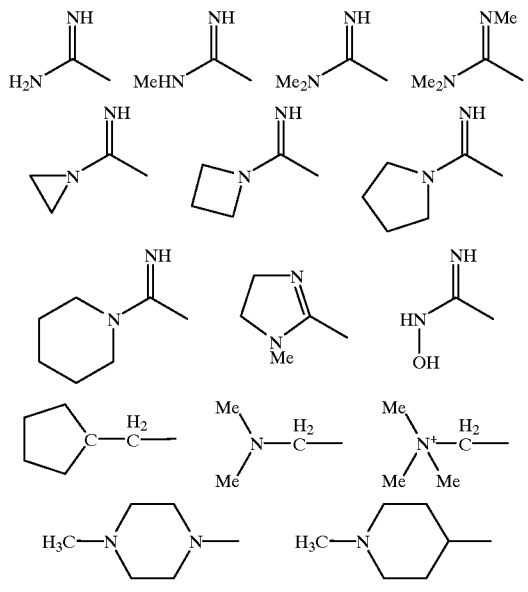
[0726] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0727] The invention provides compound of formula Ib, as described above, having the following structure:



[0728] wherein:

[0729] A-Q is a member selected from the group consisting of:



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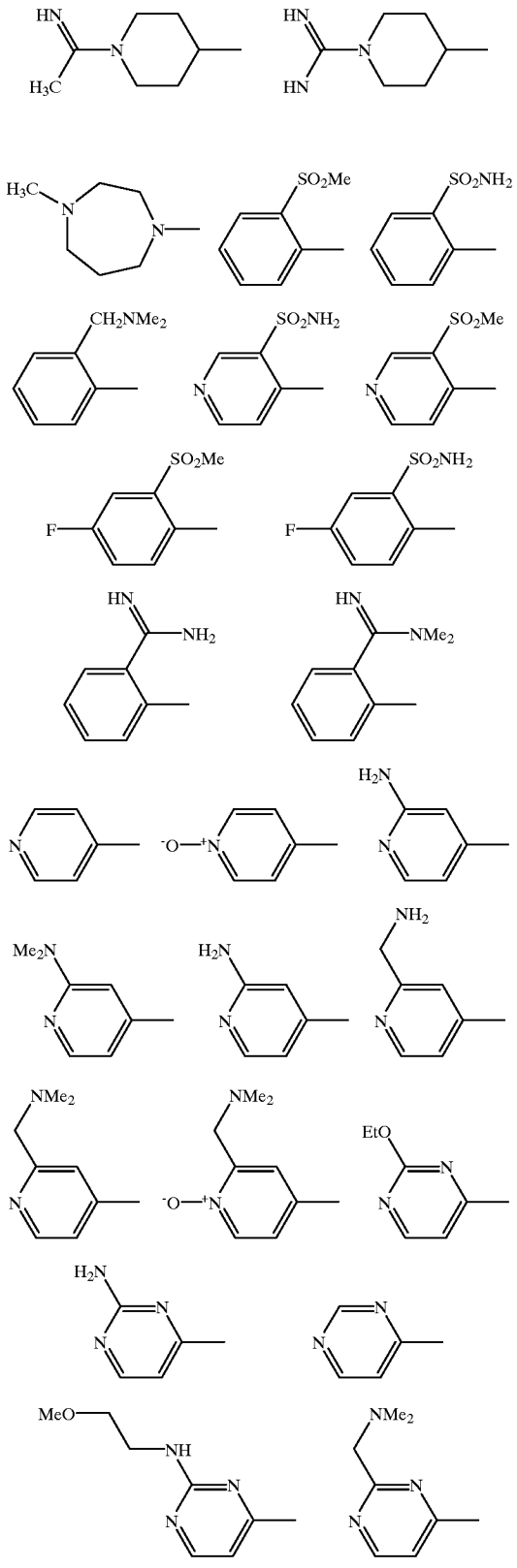

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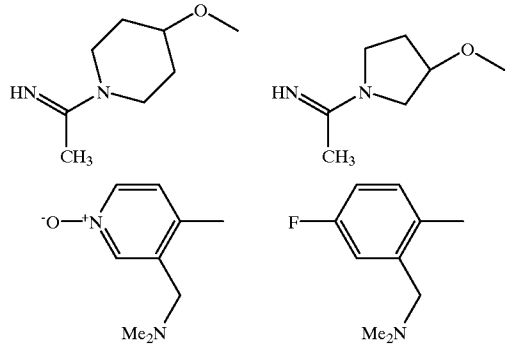
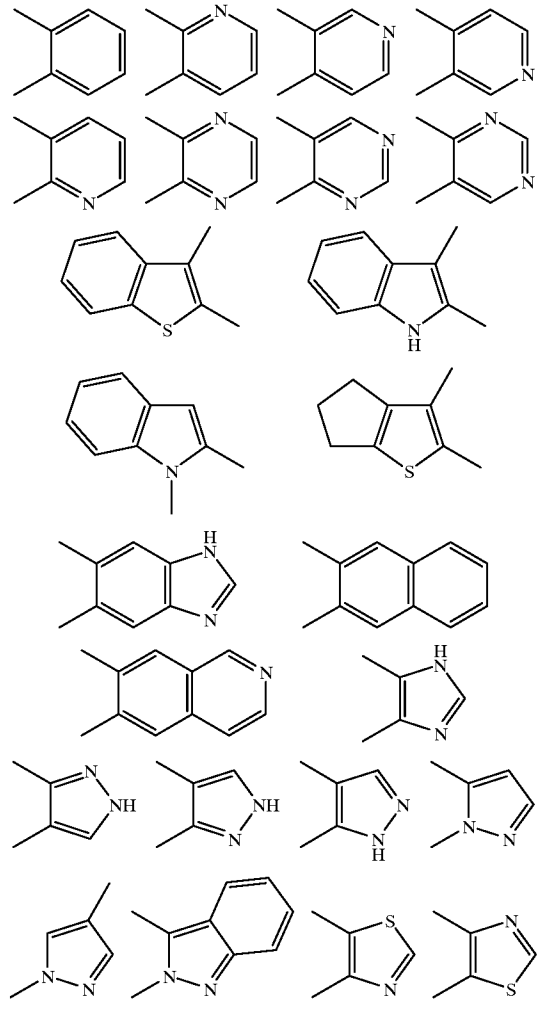


[0730] R^{1a} is a member selected from the group consisting of:

[0731] H, —F, —Cl and Br;

[0732] G is a member selected from the group consisting of:



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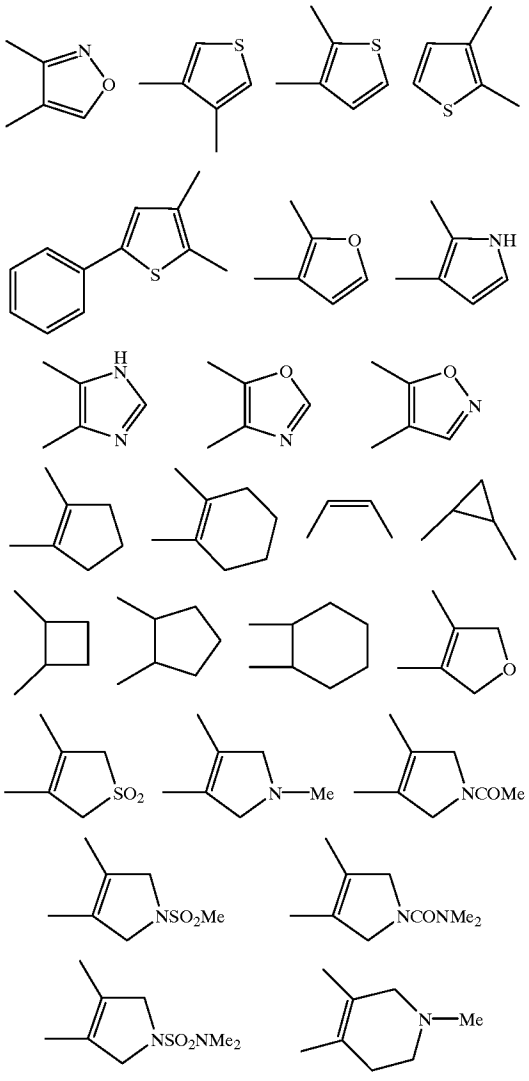
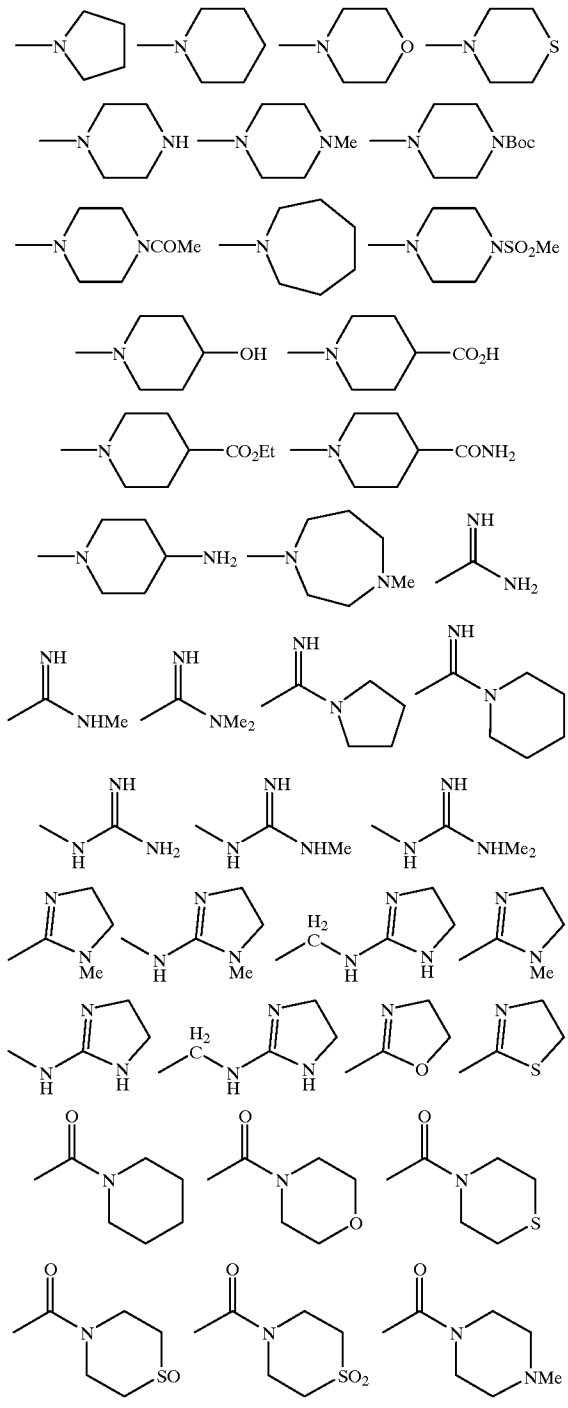


[0733] wherein each G group is substituted by 0-4 R^{1d} groups and each such R^{1d} group is independently selected from the group consisting of:

[0734] H, —Me, —F, —Cl, —Br, aryl, heteroaryl, —NH_2, —NMe_2, —NHMe, —$NHSO_2Me$, —NHCOMe, —CH_3, —CF_3, —OH, —OCH_3, —SCH_3, —OCF_3, —OCH_2F, —$OCHF_2$, —OCH_2CF_3, —OCF_2CF_3, —NO_2, —CN, —CO_2H, —CO_2Me, —CO_2Et, —$CONH_2$, —CONHMe, —$CONMe_2$, —SO_2NH_2, —SO_2CH_3, —SO_2NMe_2, —CH_2OH, —CH_2NH_2, —CH_2NHMe, —CH_2NMe_2, —OCH_2CO_2H, —OCH_2CO_2Me, —OCH_2CO_2Et, —OCH_2CONH_2, —OCH_2CONMe_2, —$OCH_2CONHMe$, —OCH_2CH_2OMe, —OCH_2CH_2OEt, —$OCH_2CH_2NH_2$, —OCH_2CH_2NHMe, —$OCH_2CH_2NMe_2$, —$NHCH_2CH_2OMe$, —SCH_2CH_2OMe, —$SO_2CH_2CH_2OMe$, —$OCH_2CH_2SO_2Me$, —$NHCH_2CH_2NHMe$, —$NHCH_2CH_2NMe_2$, —$N(CH_2CH_2OH)_2$, —$N(CH_2CH_2OMe)_2$, —$NHCH_2CO_2H$, —$NHCH_2CO_2Et$, —$NHCH_2CO_2Et$, —$NHCH_2CONH_2$, —$NHCH_2CONMe_2$, —$NHCH_2CONHMe$, —$N(CH_3)CH_2CO_2H$, —$N(CH_3)CH_2CO_2Et$, —(NMe)CH2COOH, —N(Me)CH2CONH2, —N(Me)CH2CH2NMe2, —N(Me)CH2CH2OMe, —NHCH2CH2OMe,



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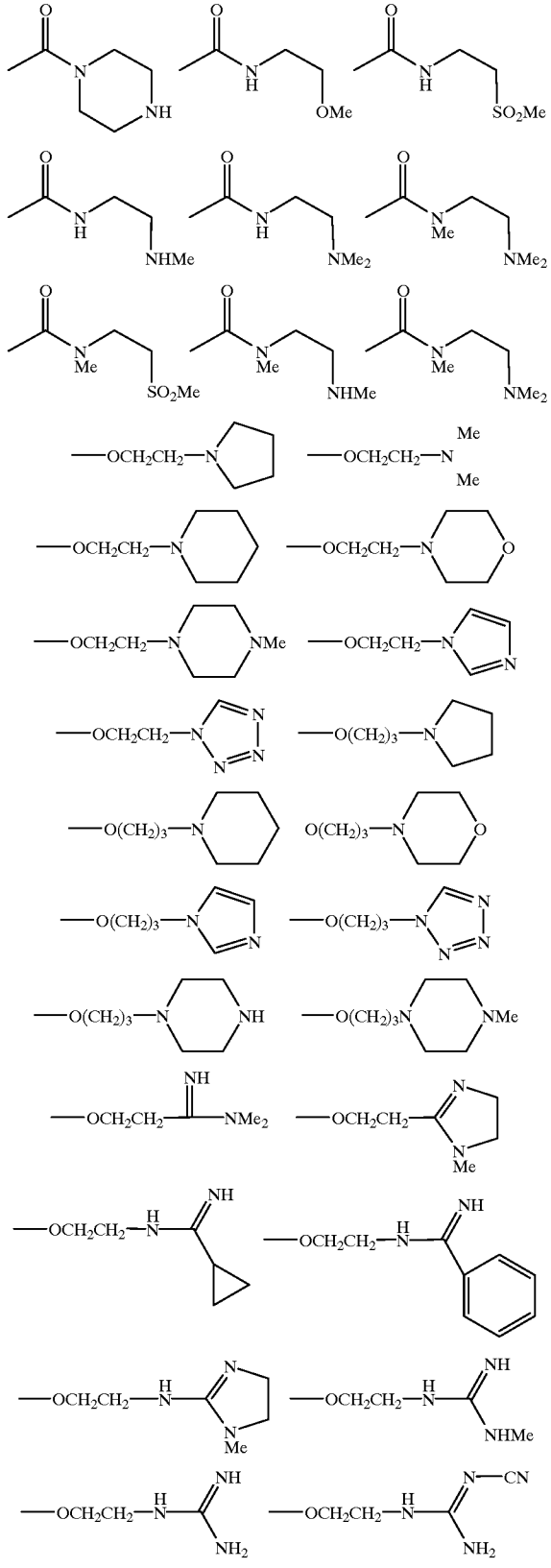

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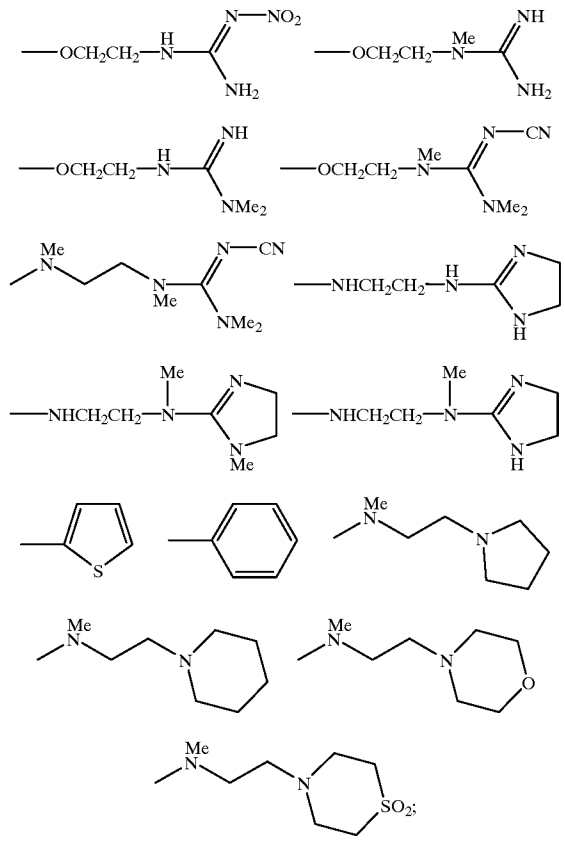
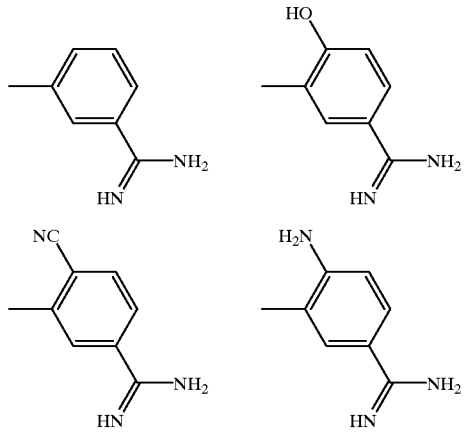


[0735] J is a member selected from the group consisting of:

[0736] —CONH—, —NHCO—, —O—, —NH—, —NMe—, —CONMe—, —NMeCO—; and

[0737] X is a member selected from the group consisting of:



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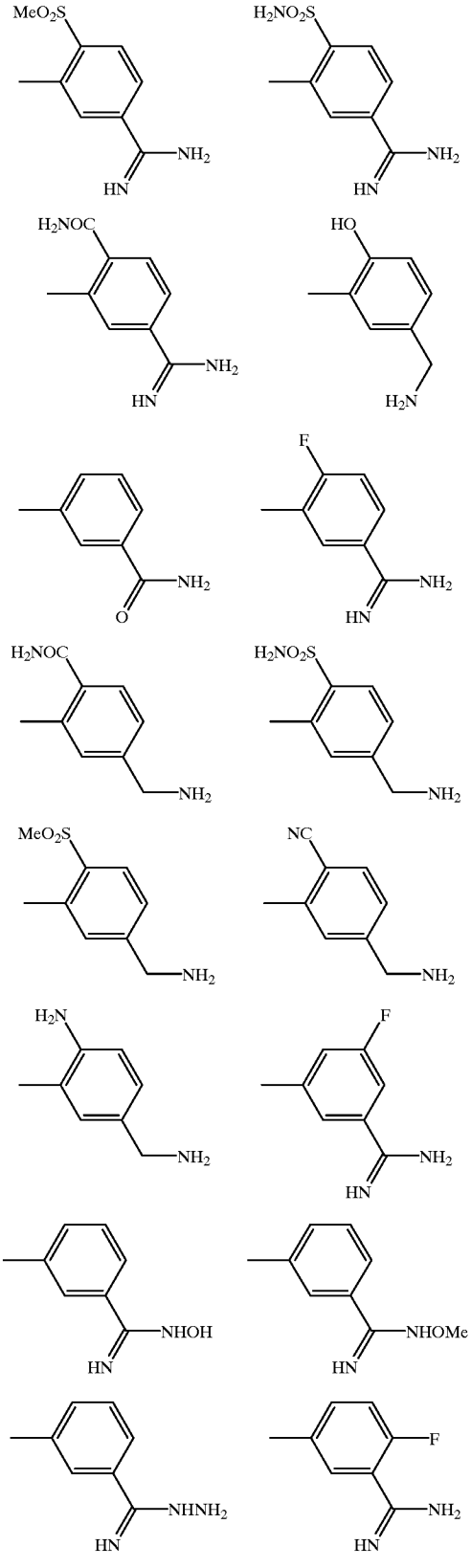

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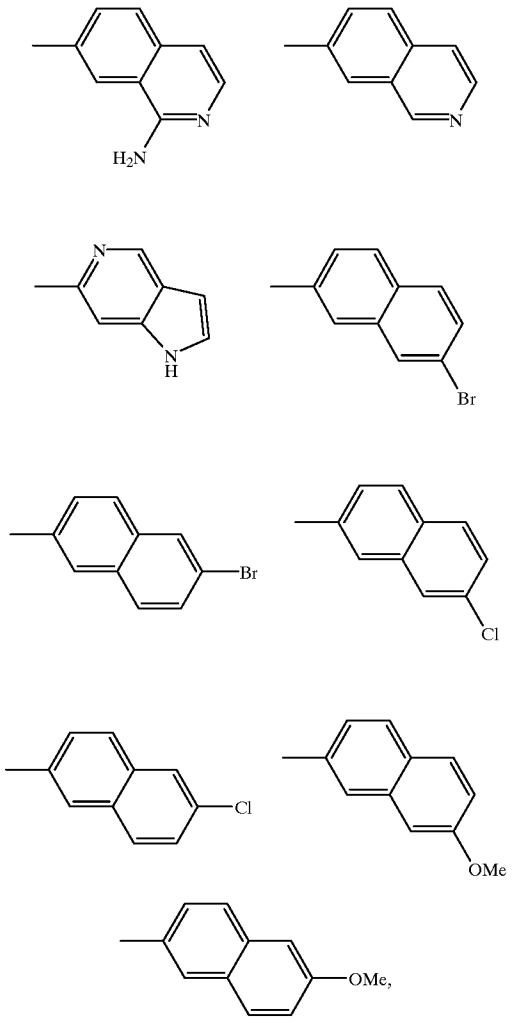
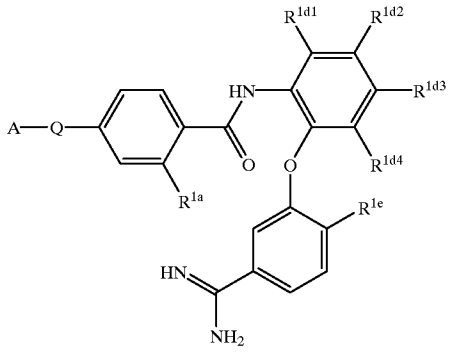


[0738] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0739] The invention provides compound of formula Ib, as described above, having the following structure:



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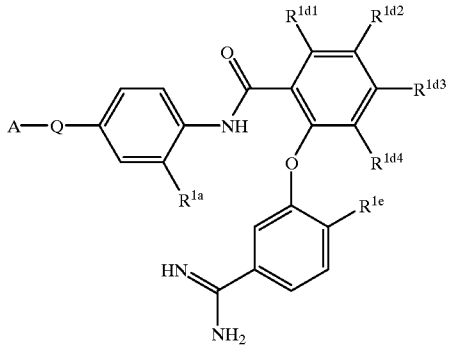
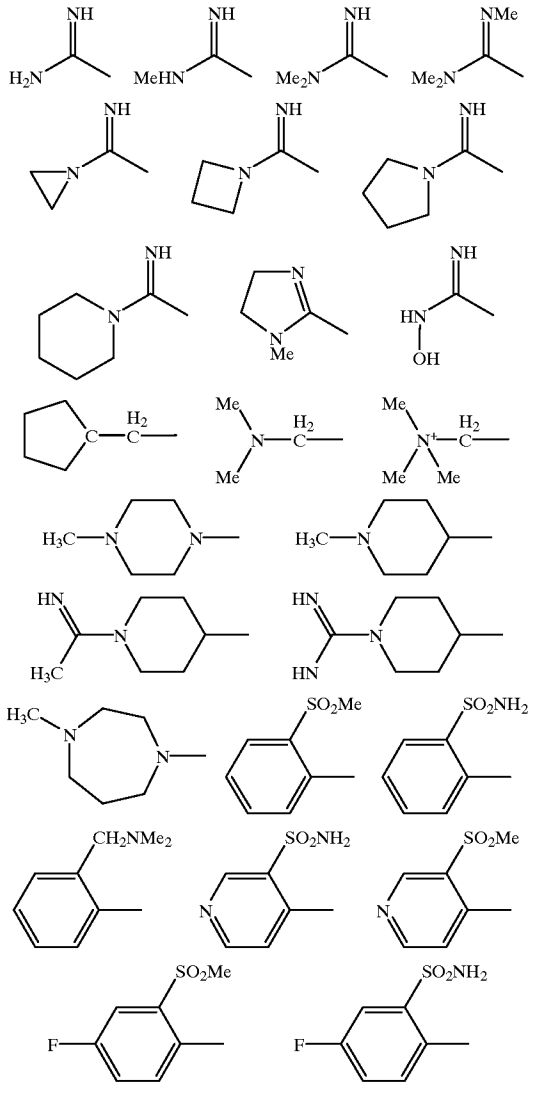


[0740] wherein:

[0741] A-Q is a member selected from the group of:



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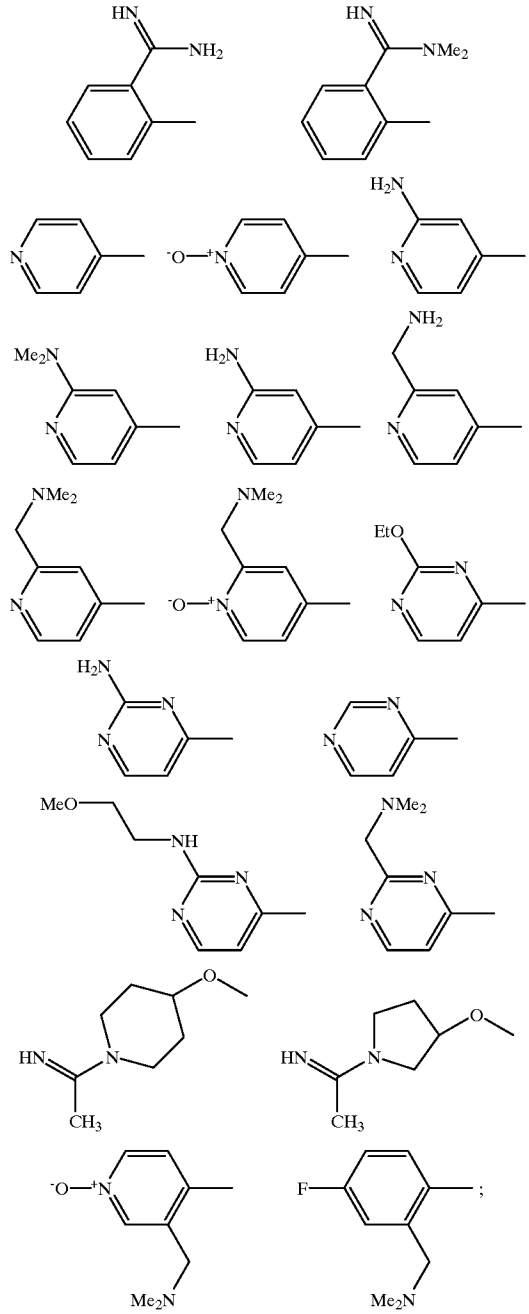
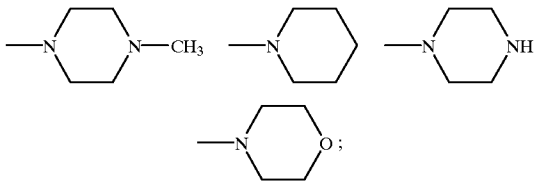


[0742] R^{1a} is a member selected from the group of:

[0743] H, —F, —Cl, —Br;

[0744] R^{1d1}, R^{1d2}, R^{1d3} and R^{1d4} is independently a member selected from the group of:

[0745] H, —F, —Cl, —Br, —NO_2, —NH_2, —NHMe, —NMe_2, —NHAc, —$NHSO_2Me$, —SO_2Me, —CO_2H, —CO_2Me, —OH, —OMe, —N(Me)CO2H, —N(Me)CO2Et and



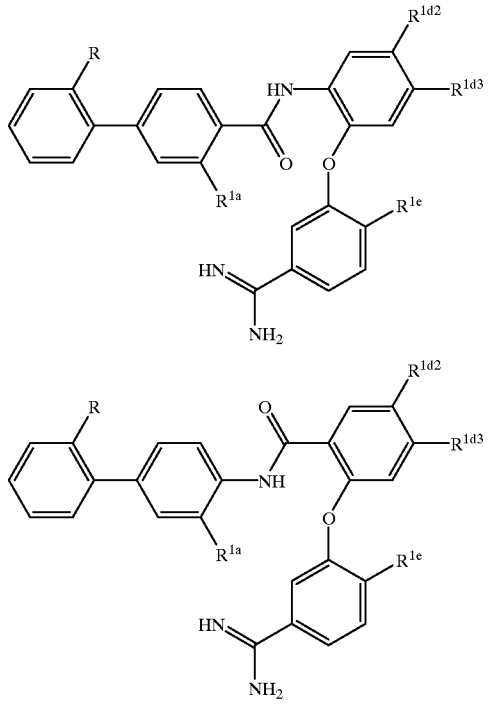
and

[0746] R^{1e} is a member selected from the group of:

[0747] H, —OH,

[0748] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0749] The invention provides compound of formula Ib, as described above, having the following structure:



[0750] R is a member selected from the group of:

[0751] —SO_2Me, —SO_2NH_2, —CH_2NH_2, —$CH_2N(CH_3)_2$;

[0752] R^{1a} is a member selected from the group of:

[0753] H, —F;

[0754] R^{1d2} and R^{1d3} is independently a member selected from the group of:

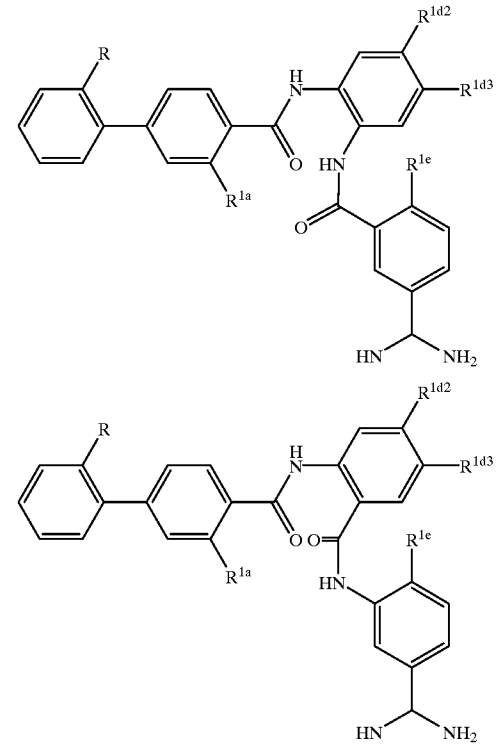
[0755] H, —F, —Cl, —Br, —NO_2, —NH_2, —NHMe, —NMe_2, —NHAc, —$NHSO_2Me$, —SO_2Me, —CO_2H, —CO_2Me, —OH, —OMe; and

[0756] R^{1e} is a member selected from the group of:

[0757] H,—OH,

[0758] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0759] The invention provides compound of formula Ib, as described above, having the following structure:



[0760] wherein:

[0761] R is a member selected from the group of:

[0762] —SO_2Me, —SO_2NH_2, —CH_2NH_2, —$CH_2N(CH_3)_2$;

[0763] R^{1a} is a member selected from the group of:

[0764] H, —F;

[0765] R^{1d2} and R^{1d3} is independently a member selected from the group of:

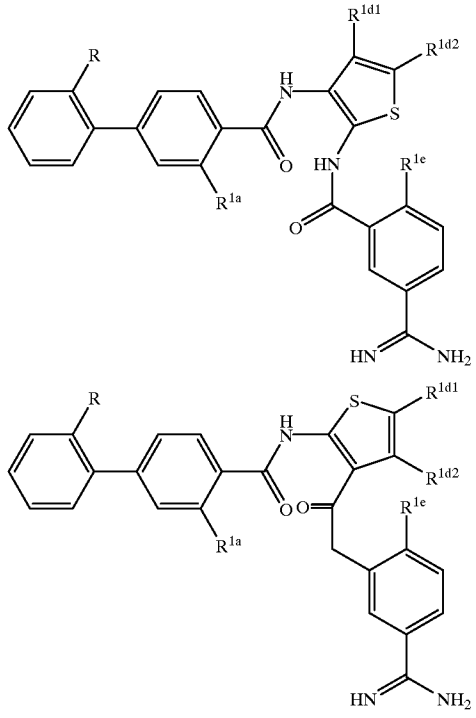
[0766] H, —F, —Cl, —Br, —NO_2, —NH_2, —NHMe, —NMe_2, —NHAc, —$NHSO_2Me$, —SO_2Me, —CO_2H, —CO_2Me, —OH, —OMe; and

[0767] R^{1e} is a member selected from the group of:

[0768] H, —OH,

[0769] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0770] The invention provides compound of formula Ib, as described above, having the following structure:



[0771] R is a member selected from the group of:

[0772] —SO_2Me, —SO_2NH_2, —CH_2NH_2, —$CH_2N(CH_3)_2$;

[0773] R^{1a} is a member selected from the group of:

[0774] H, —F;

[0775] R^{1d1} and R^{1d2} is independently a member selected from the group of:

[0776] H, —F, —Cl, —Br, —OMe; and

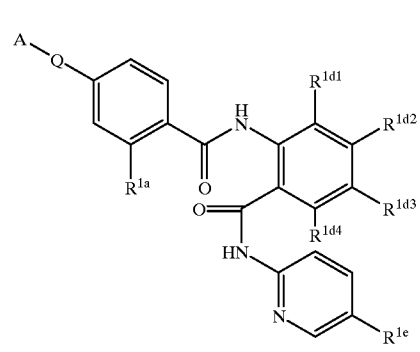
[0777] R^{1e} is a member selected from the group of:

[0778] H, —OH,

[0779] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0780] The following preferred embodiments of the present invention illustrate compounds wherein the central aromatic ring structure is divalent phenylene, however divalent 6 membered heteroaromatic rings having from 1 to 3 nitrogen atoms may be substituted for the bivalent phenylene structure. Further the terminal aromatic ring substituted which is substituted by a R^{1e} group as illustrated below in the preferred embodiments is either a phenyl or a 2-pyridyl group, however other 6 membered heteroaromatic rings having from 1 to 3 nitrogen atoms can be substituted for either the phenyl or 2-pyridyl. Moreover, 2 to 3 additional R^{1e} groups other than hydrogen may each be independently substituted for a hydrogen atom attached to a ring carbon on the terminal rings illustrated or substituted for the illustrated terminal ring structure.

[0781] A preferred embodiment of the invention provides a compound of formula VIII:



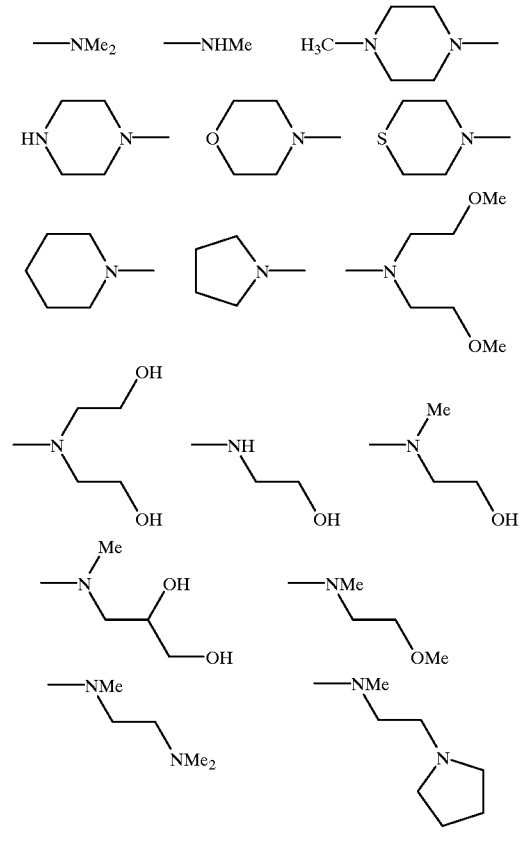
(VIII)

[0782] wherein:

[0783] R^{1a} is a member selected from the group of H, —F, —Cl and Br;

[0784] R^{1d2} and R^{1d4} are each H or F;

[0785] R^{1d1} and R^{1d3} are each independently a member selected from the group of H, —Cl, —F, —Br, —OH, —OMe, —OCF_3, $OCHF_2$, OCH_2F, —NH_2, —NMe_2, —OCH_2COOEt, —OCH_2COOH, —$N(Me)CH_2COOH$, —N(Me)COOEt, and,



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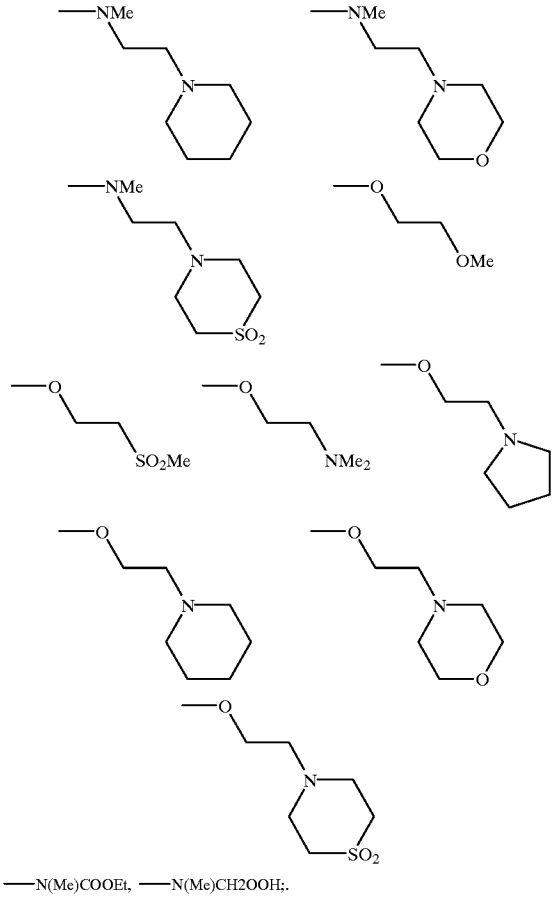
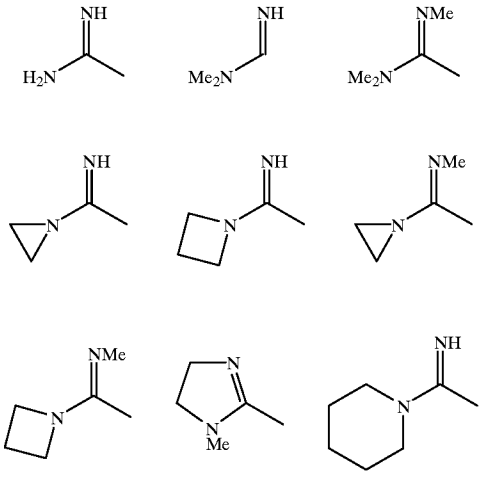


[0786] R^{1e} is a member selected from the group of —F, —Cl, —Br, —OH, —Me and —OMe;

[0787] A-Q is a member selected from the group consisting of:



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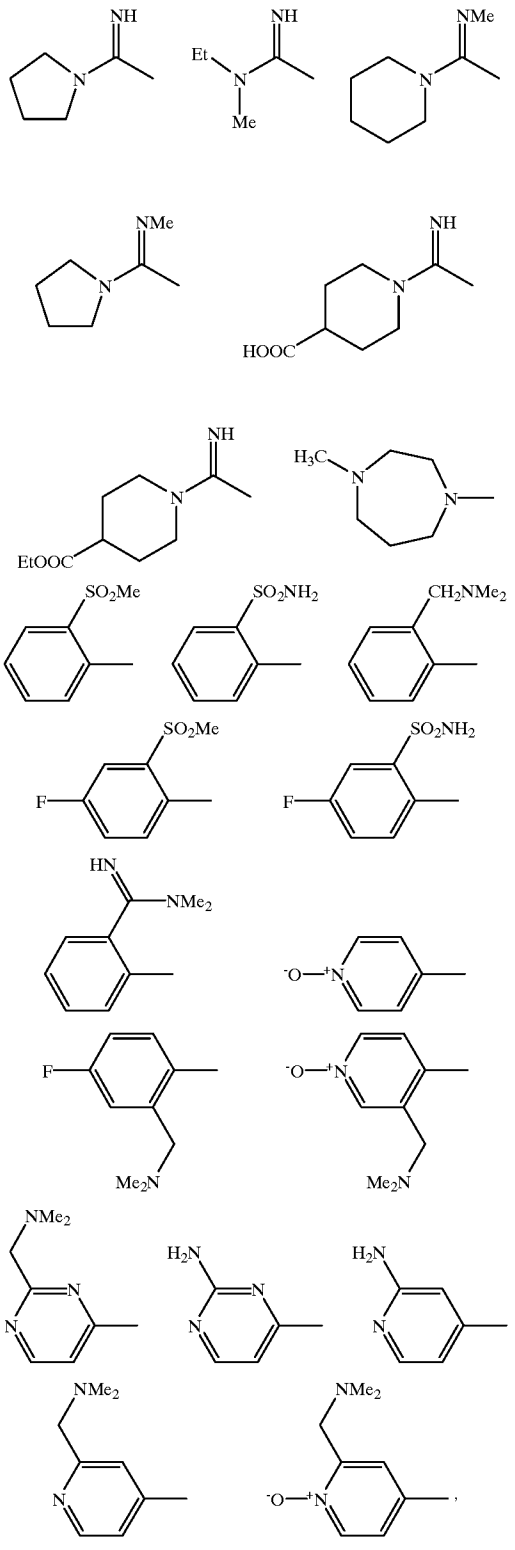
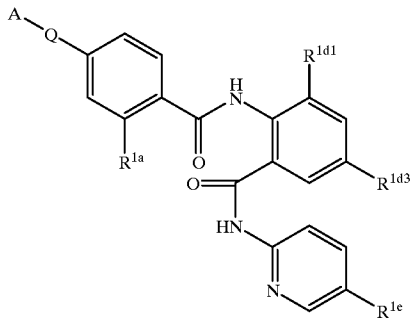


[0788] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

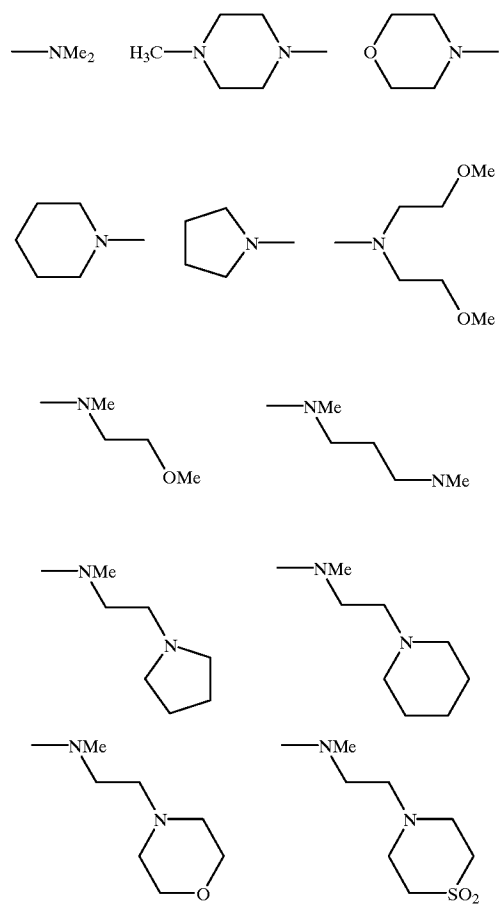
[0789] Another preferred embodiment provides a compound of formula VIII having the following structure:



[0790] wherein:

[0791] R^{1a} is a member selected from the group of H, or —F;

[0792] R^{1d1} is each independently a member selected from the group of H, —Cl, —OMe, —NMe_2, —OCH_2COOEt, —OCH_2COOH, —N(Me)CH_2COOH, —N(Me)COOEt,



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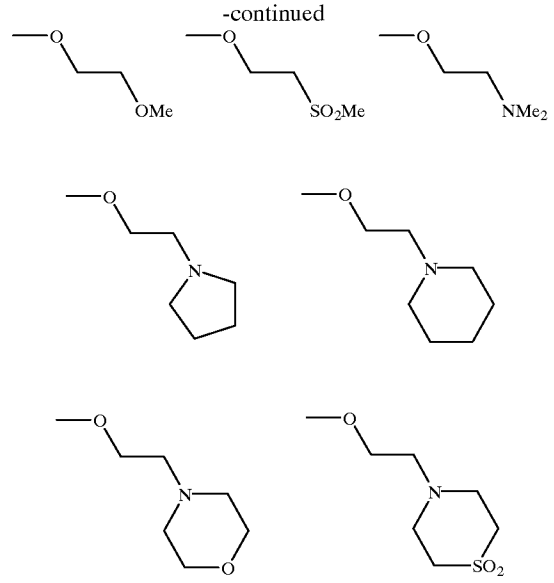
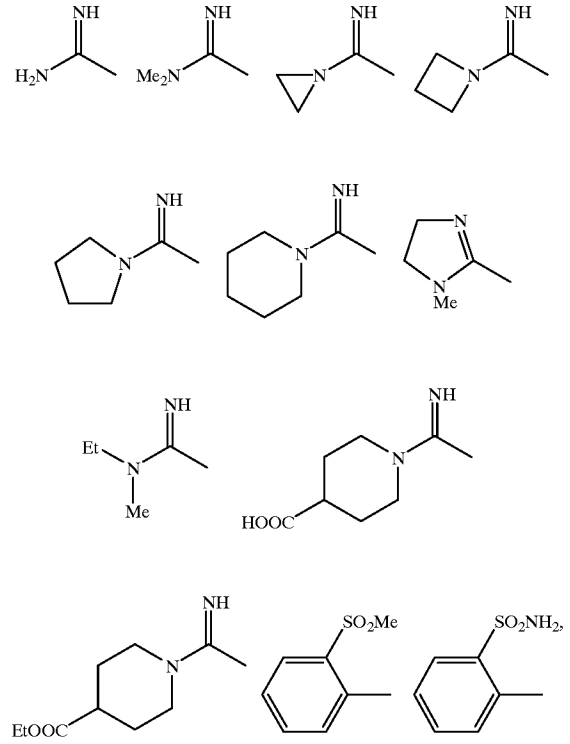


[0793] R^{1d3} are independently a member selected from the group of H, —Cl, —Br, —F, and —OMe;

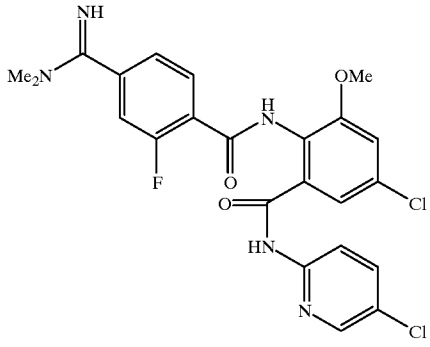
[0794] R^{1e} is a member selected from the group of —Cl, and —Br;

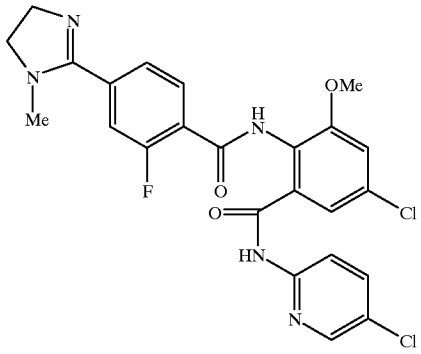
[0795] A-Q is a member selected from the group consisting of:

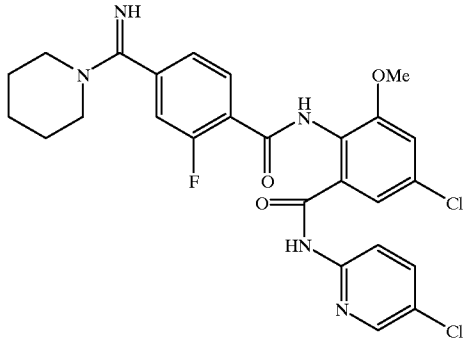


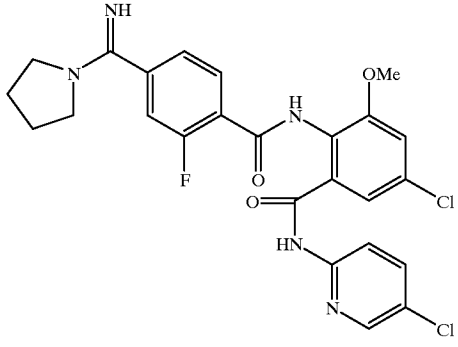
[0796] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0797] Another preferred embodiment according to the present invention provides an individual compound, which is a member selected from the following strictures:









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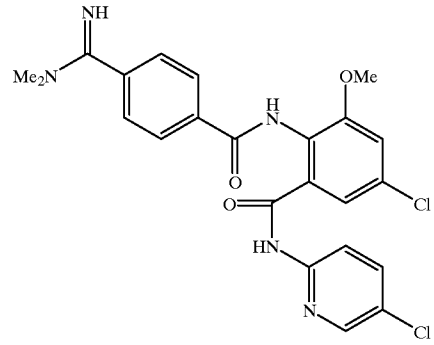

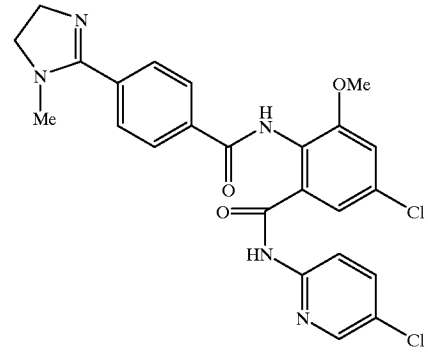

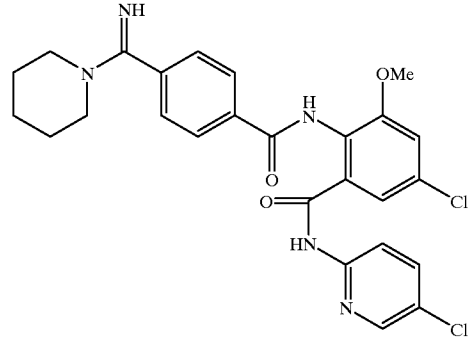

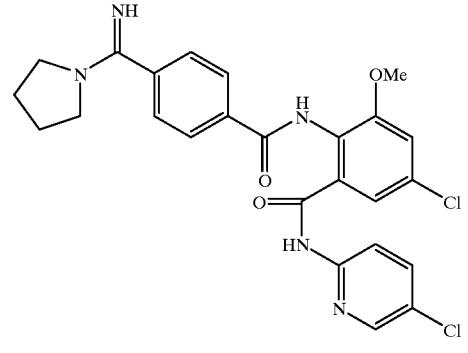

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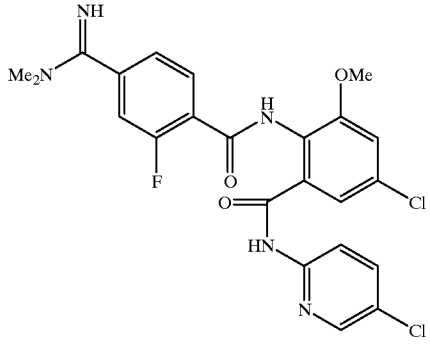

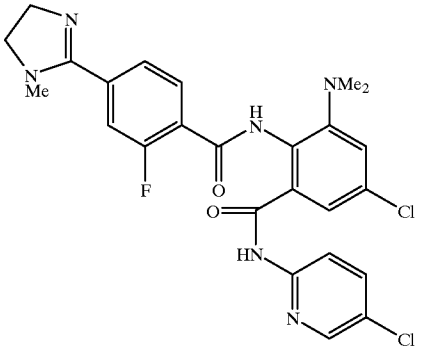

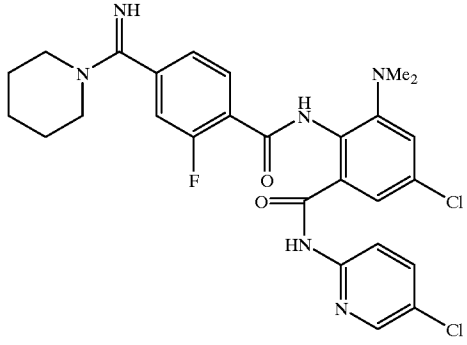

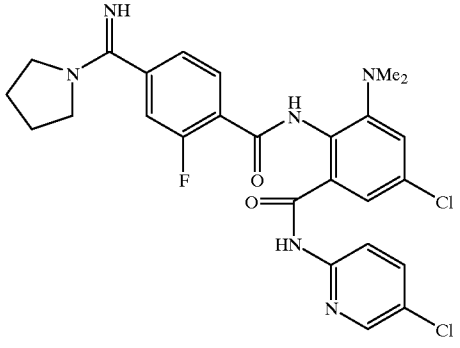

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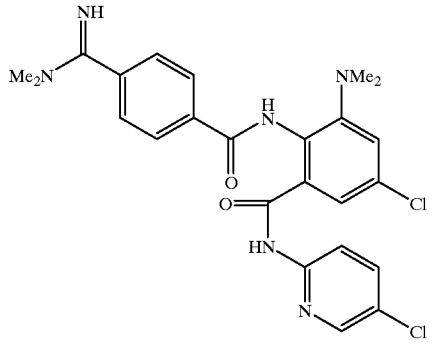

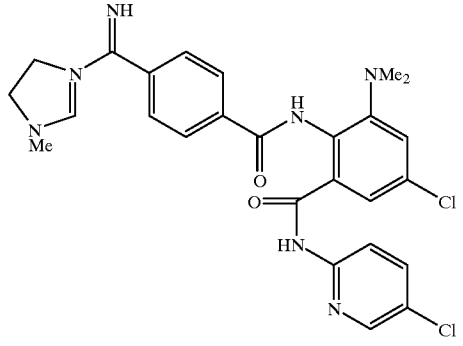

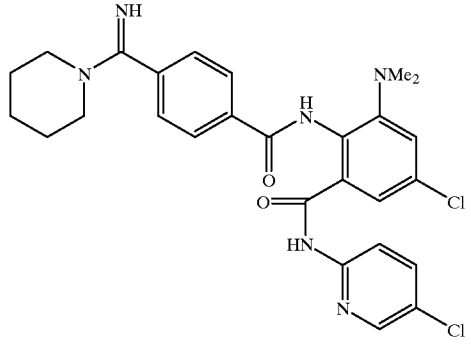

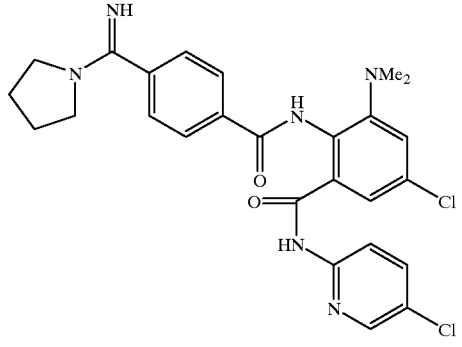

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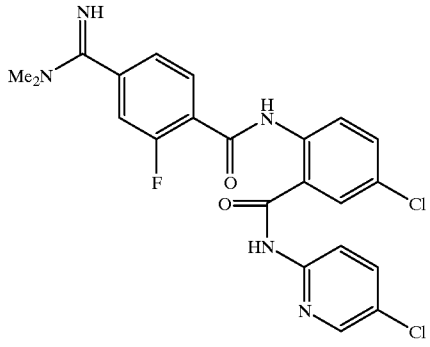

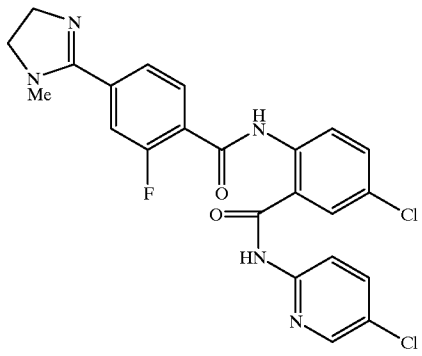

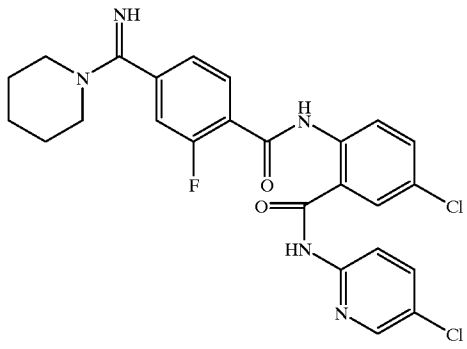

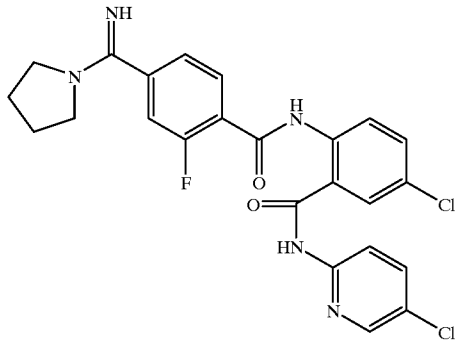

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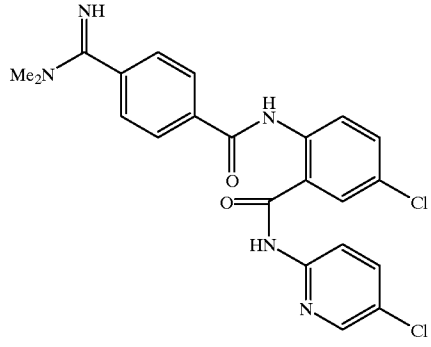

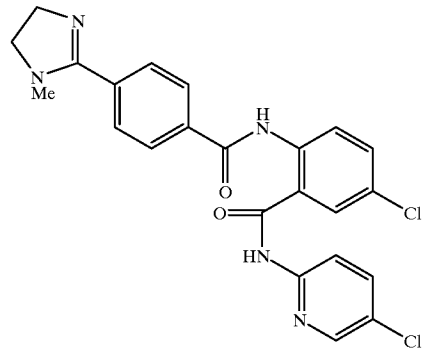

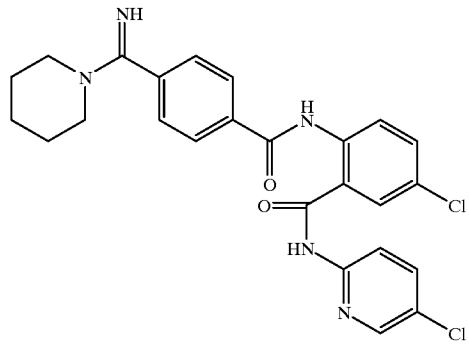

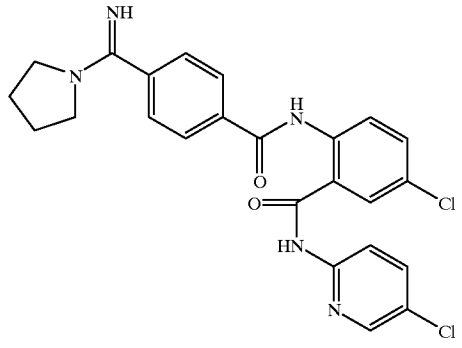

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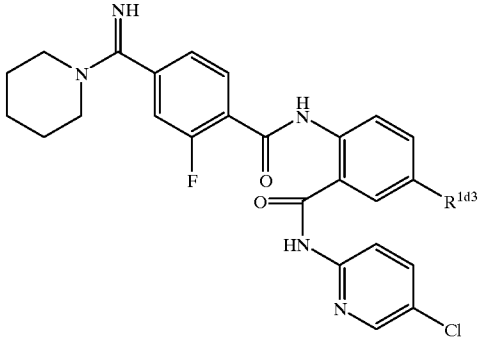

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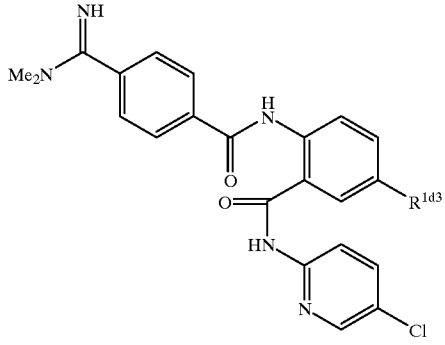
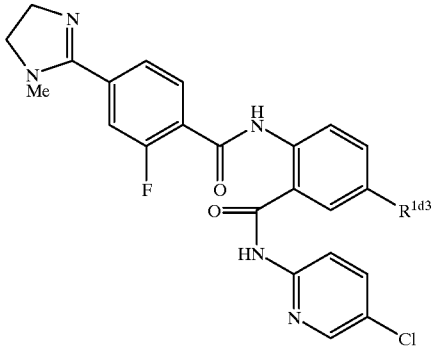
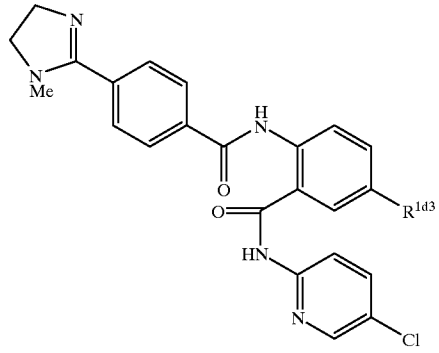
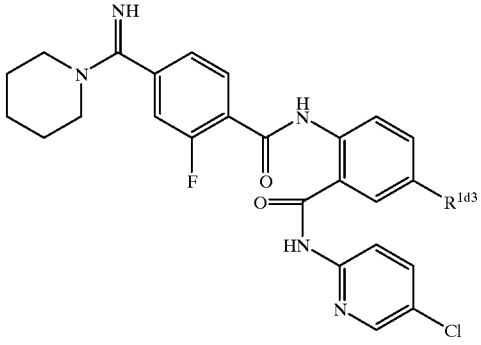
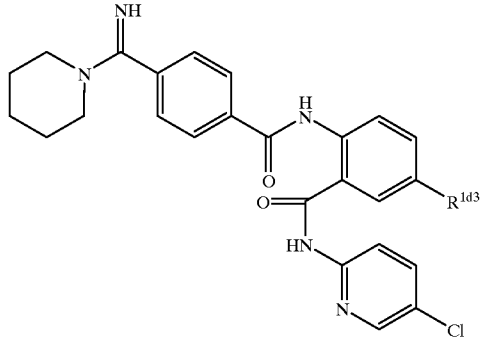
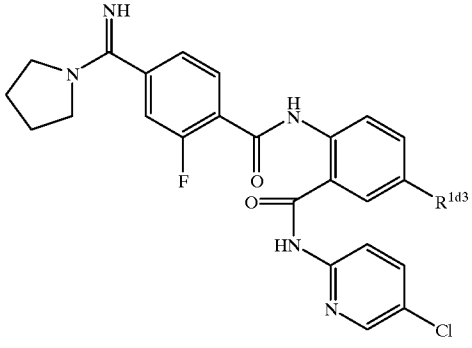


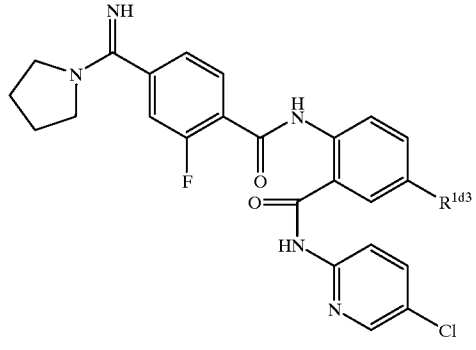












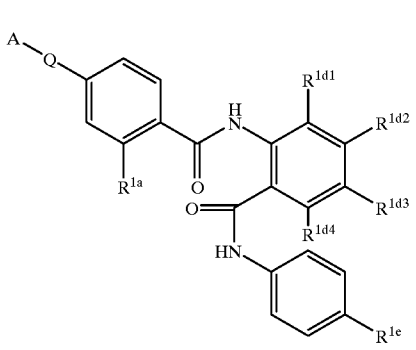
[0798] wherein

[0799] R^{1d3} is a member selected from the group consisting of:

[0800] H, —F, —Cl, —Br, —OMe, —OCF_3, —OCF_2H, and —OCF_2H;

[0801] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0802] A still further embodiment of the present invention provides a compound according to the formula IX, as follow:



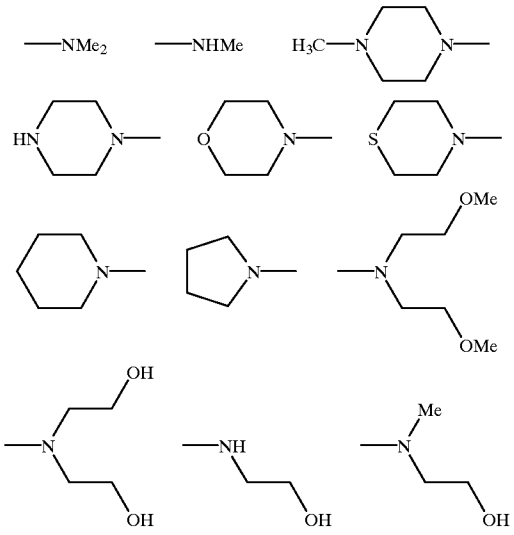
(IX′)

[0803] wherein:

[0804] R^{1a} is a member selected from the group of H, —F, —Cl and Br,

[0805] R^{1d2} and R^{1d4} are each H or F;

[0806] R^{1d1} and R^{1d3} are each independently a member selected from the group of H, —Cl, —F, —Br, —OH, —OMe, —OCF_3, $OCHF_2$, OCH_2F, —NH_2, —NMe_2, —OCH_2COOEt, —OCH_2COOH, —N(Me)CH_2COOH, —N(Me)COOEt,



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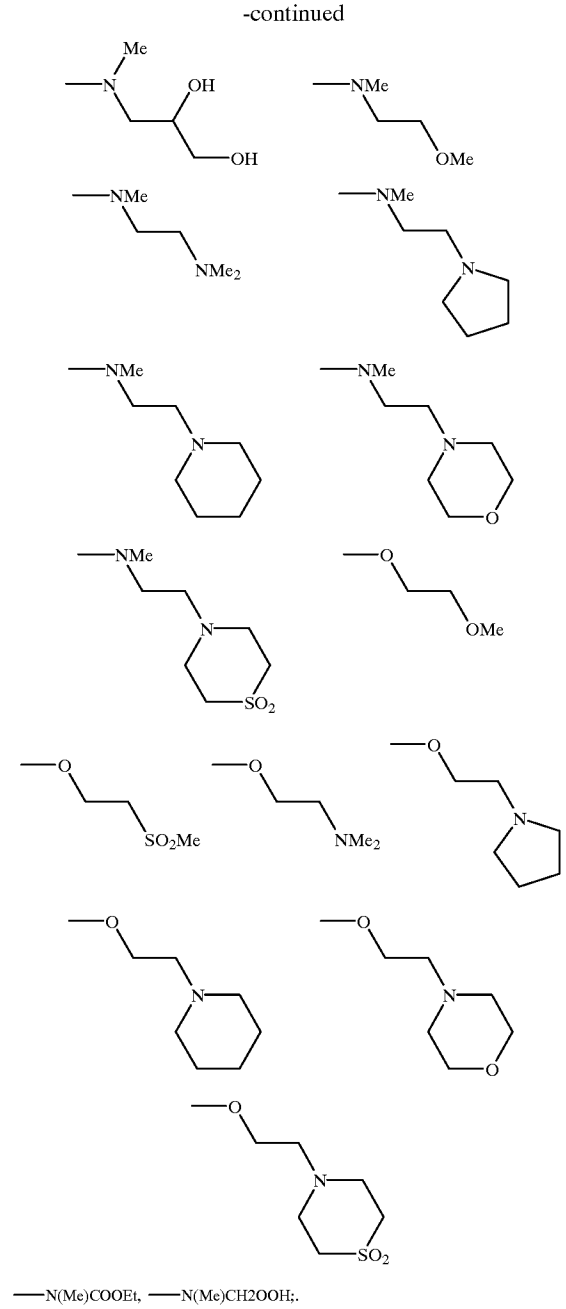
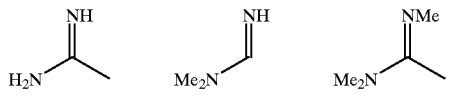


—N(Me)COOEt, —N(Me)CH2OOH;.

[0807] R^{1e} is a member selected from the group of —F, —Cl, —Br, —OH, —Me and —OMe;

[0808] A-Q is a member selected from the group consisting of:



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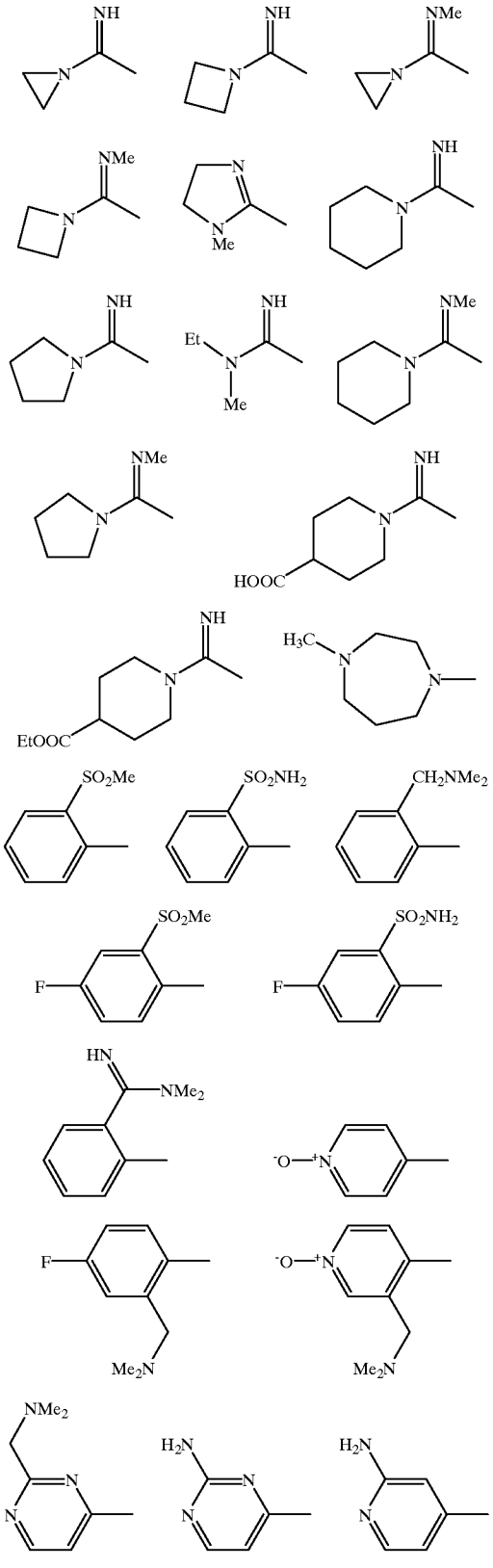

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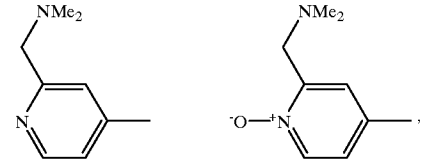
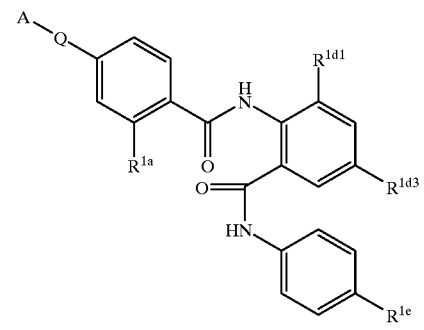


[0809] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

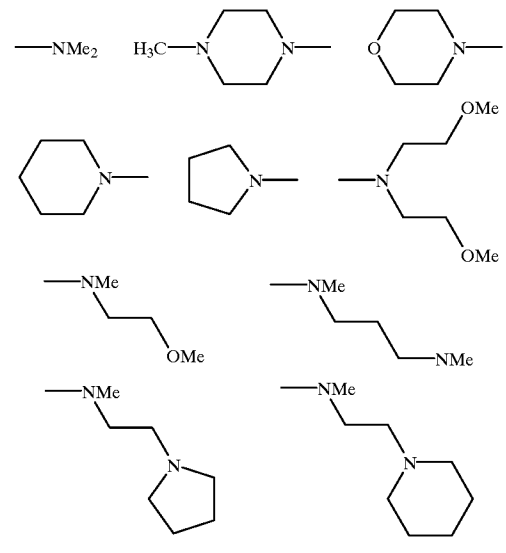
[0810] A particularly preferred embodiment of the present invention provides such compounds having the following formula:



[0811] wherein:

[0812] R^{1a} is a member selected from the group of H, or —F

[0813] R^{1d1} is each independently a member selected from the group of H, —Cl, —OMe, —NMe_2, —OCH_2COOEt, —OCH_2COOH, —N(Me)CH_2COOH, —N(Me)COOEt, and,



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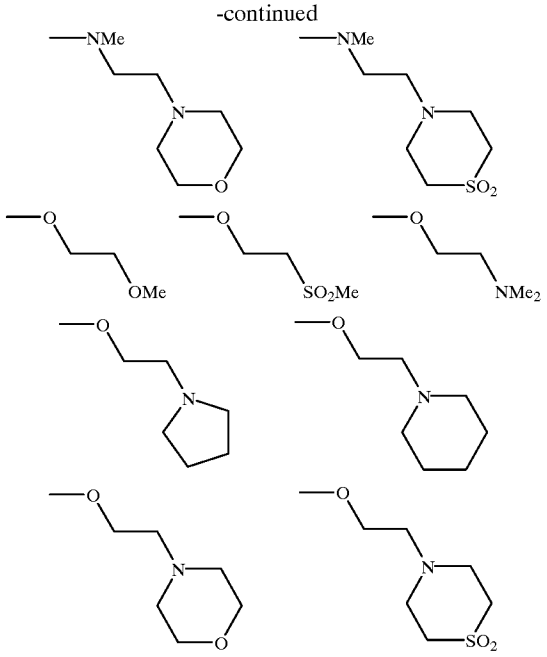
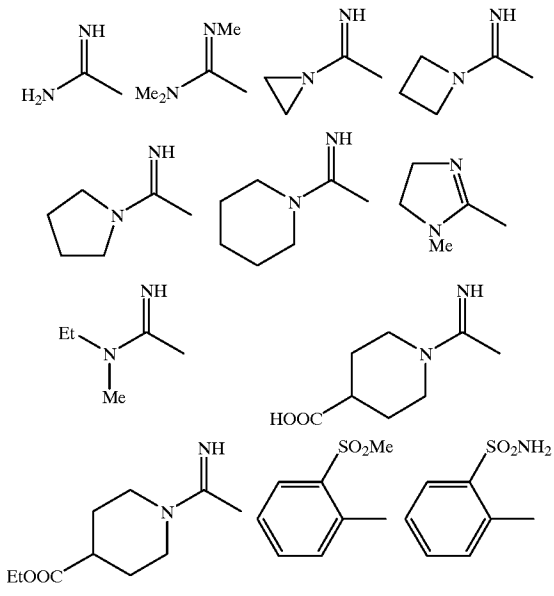


[0814] R^{1d3} are independently a member selected from the group of H, —Cl, —Br, —F, and —OMe,

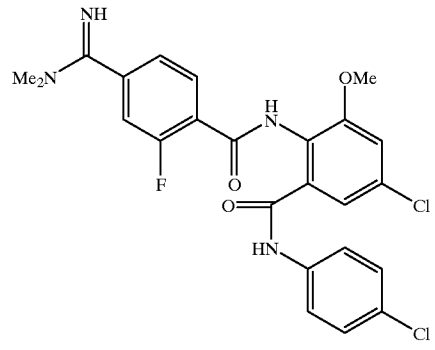
[0815] R^{1e} is a member selected from the group of —Cl, and —Br,

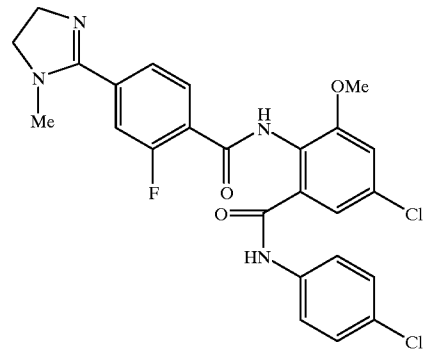
[0816] A-Q is a member selected from the group consisting of:

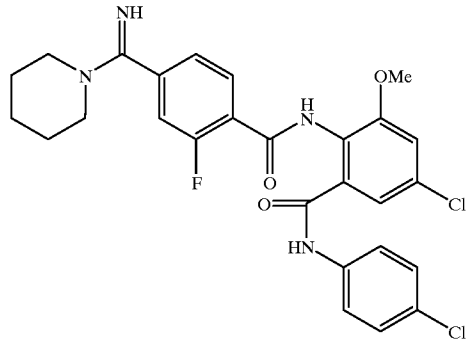


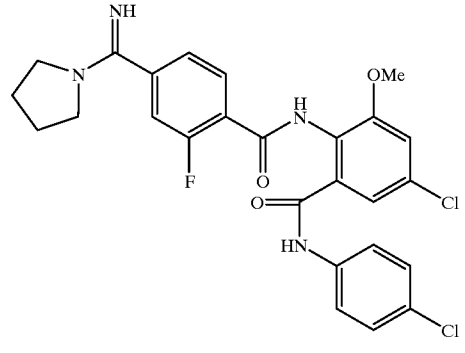
[0817] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0818] A still further embodiment of the present invention provides an individual compound which is a member selected from the following structures:









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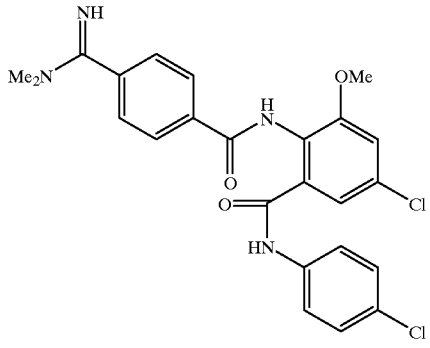

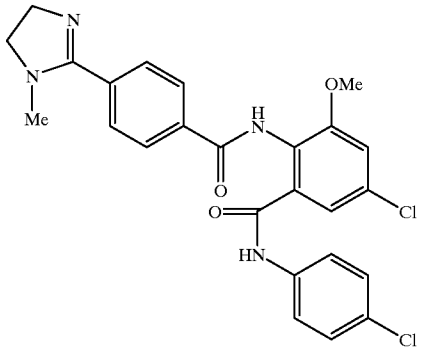

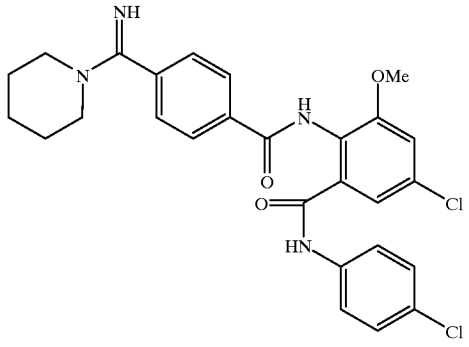

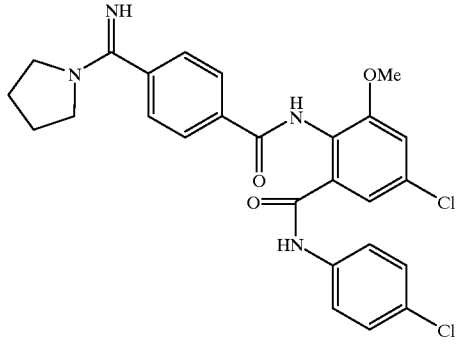

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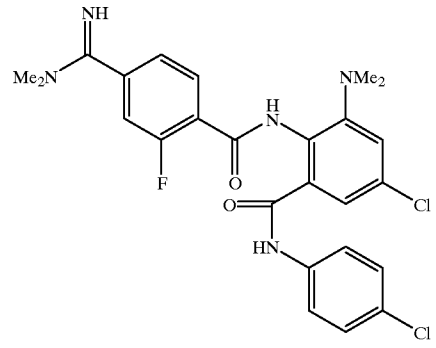

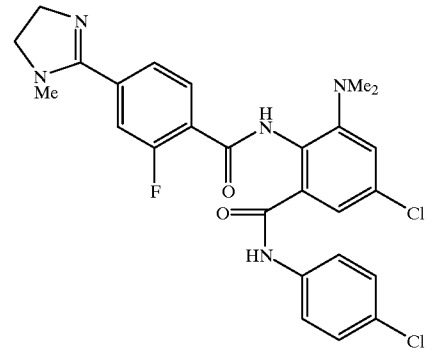

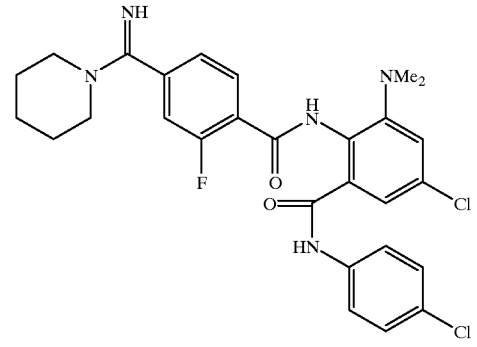

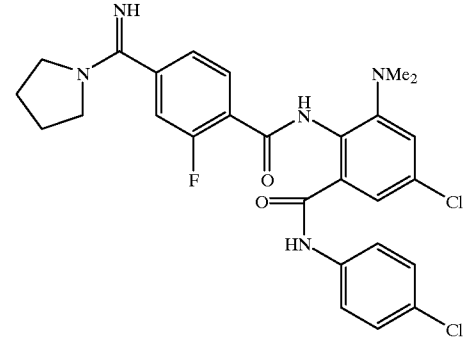

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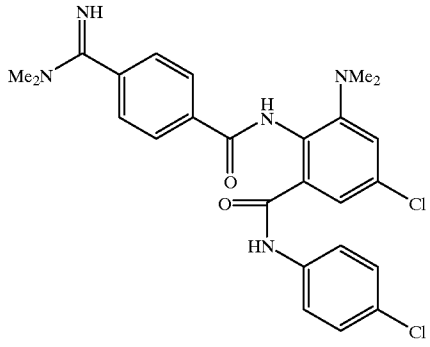

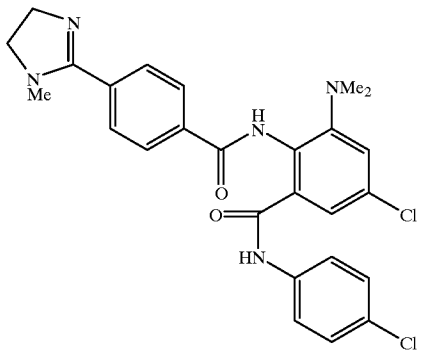

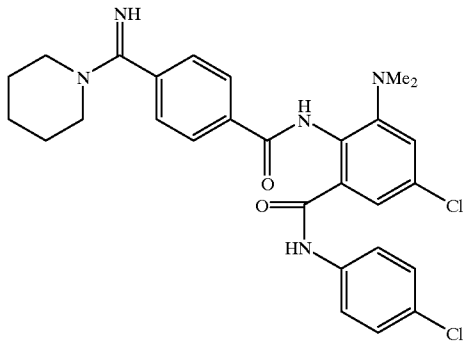

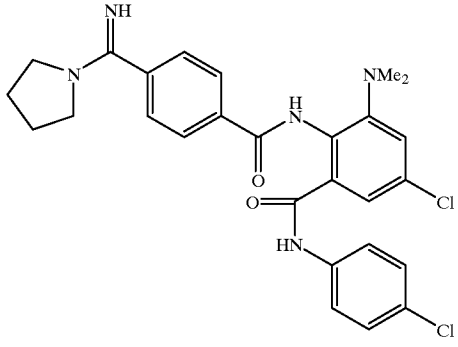

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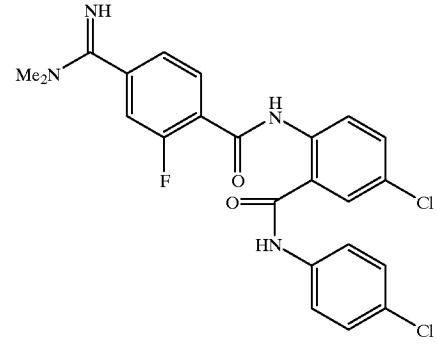

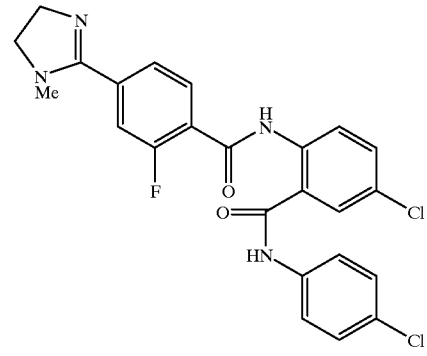

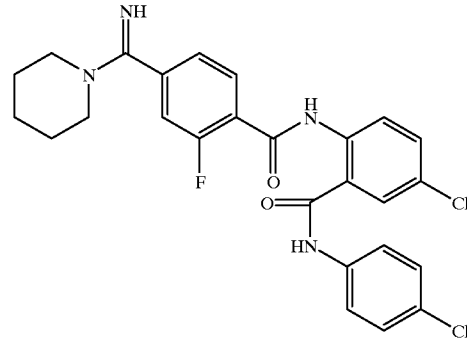

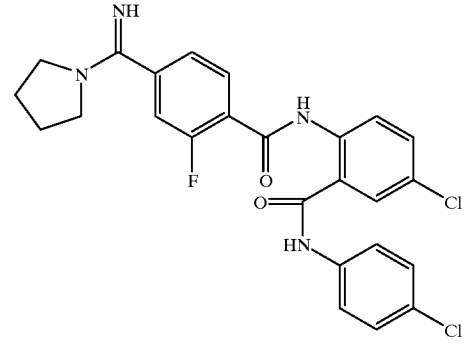

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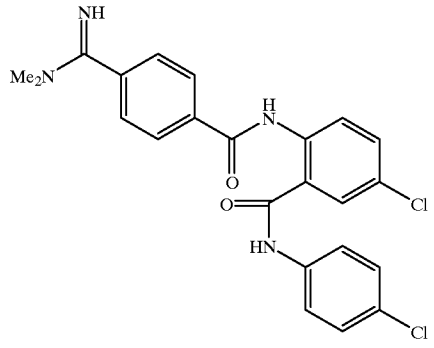

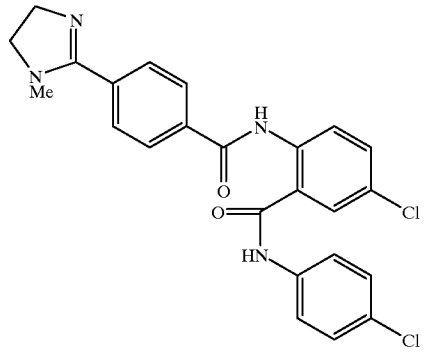

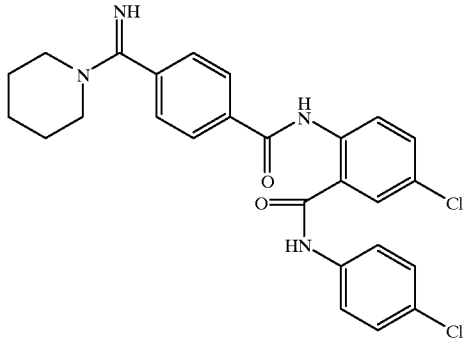

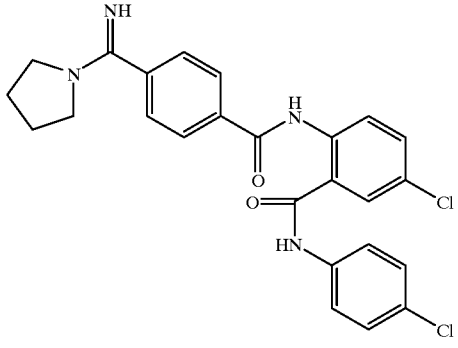

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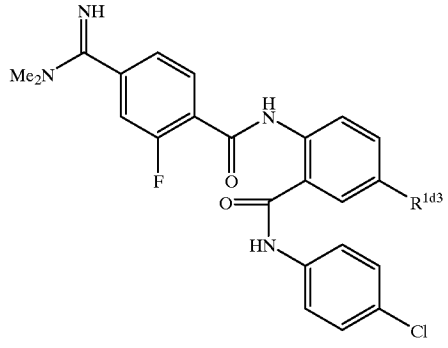

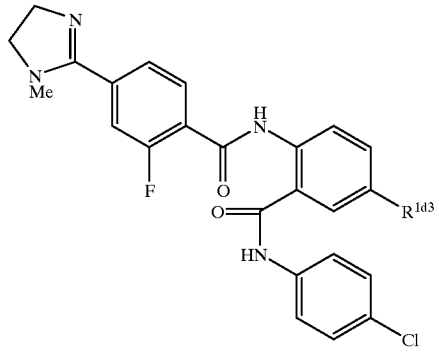

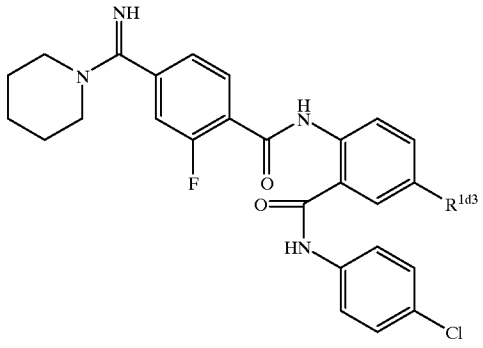

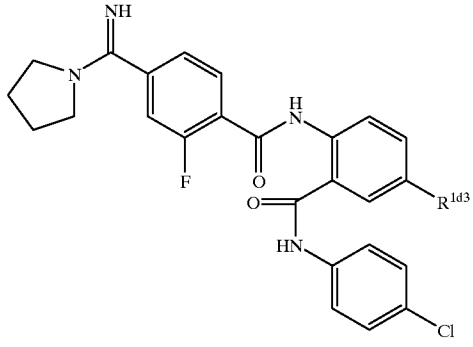

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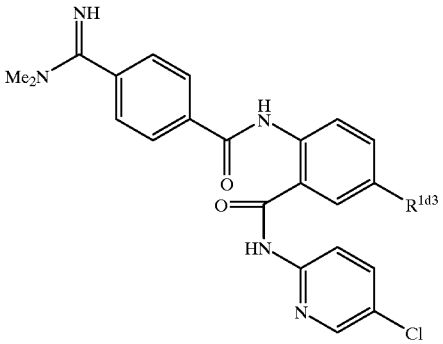
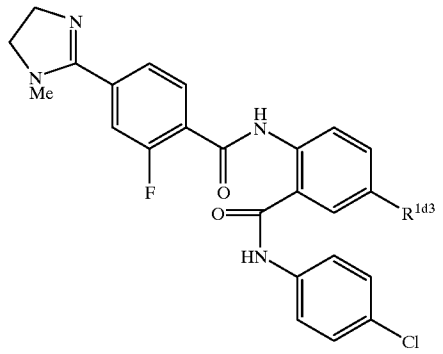
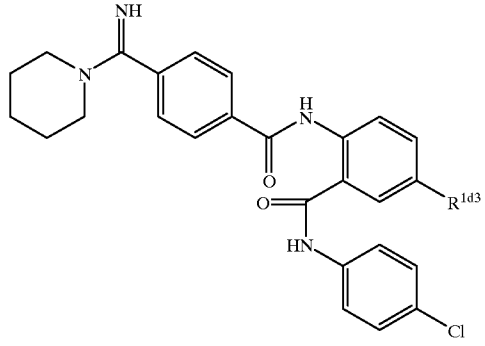
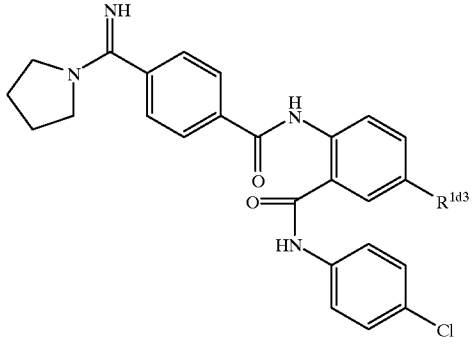








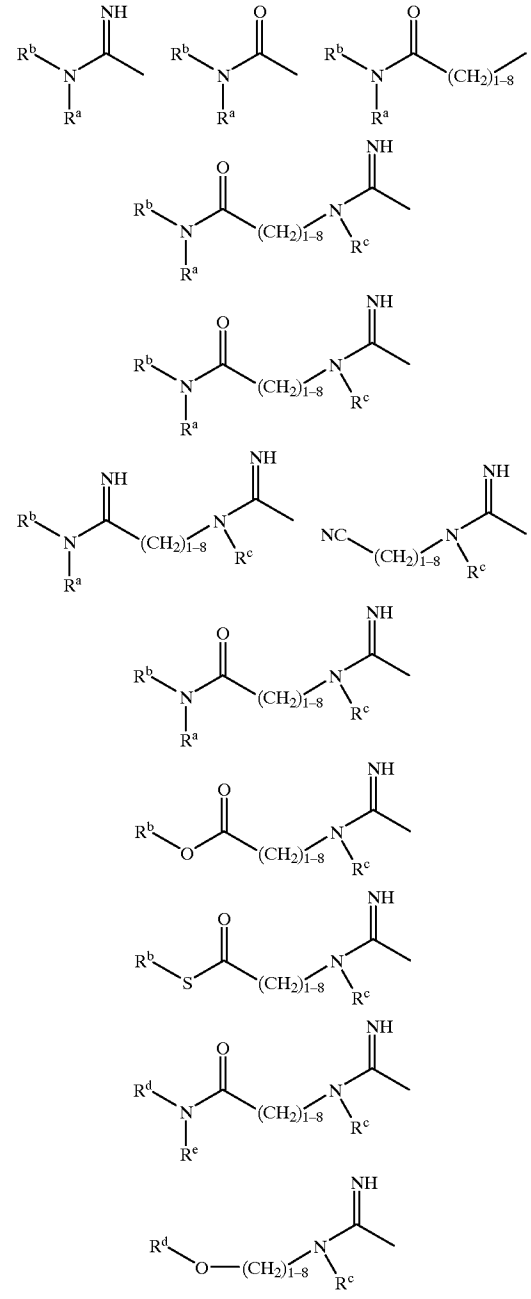
[0819] wherein

[0820] R^{1d3} is a member selected from the group consisting of:

[0821] H, —F, —Cl, —Br, —OMe, —OCF_3, —OCF_2H, and —OCF_2H,

[0822] and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0823] Another preferred embodiment of the present invention provides compounds according to the invention as illustrated herein, wherein the A-Q- substituent is an amidinosubstituent, the amine portion of which is a cyclized amine heterocyclic ring, preferably a saturated cyclized amine heterocyclic ring, and the cyclized amine ring is substituted by 1-3 members. Examples of such A-Q substituents include but are not limited to:



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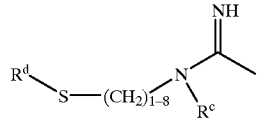


[0824] wherein each of R^a, R^b, R^c, R^d and R^e is independently a member selected from the group consisting of C_1-C_8 alkyl, C_2-C_8 alkenyl, C_1-C_8 acyl and C_1-C_8 acyl C_1-C_8 alkyl ester, and the Ra and Rb groups together with the nitrogen atom to which they are both attached may be cyclized to form a C_3-C_8 heterocylic ring having from 1 to 4 additional hetero ring atoms selected from O, N and S, and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0825] Another preferred embodiment is an embodiment wherein the amidino groups illustrated above as substituents for the cyclized amine heterocyclic ring are instead form an acyclic amidino A-Q group and and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

[0826] Such compounds are formed by reacting the appropriate acyclic amine or cycliczed amine with an amidino group or with a thioimino group wherein the remainder of the structures D-E-G-J-X are defined as in formula I or as in a preferred D-E-G-J-X structure illustrated in a preferred embodiment herein. Other ways to produce such compound structures will be apparent to an ordinary praticitioner in this field upon consideration of the description herein and the illustrated preferred embodiments.

[0827] This invention also encompasses all pharmaceutically acceptable isomers. salts, hydrates, solvates, and prodrug derivatives of the preferred compounds. In addition, the preferred compounds can exist in various isomeric and tautomeric forms, and all such forms are meant to be included in the invention, along with pharmaceutically acceptable salts, hydrates, solvates, and prodrug derivatives of such isomers and tautomers.

[0828] The compounds of this invention may be isolated as the free acid or base or converted to salts of various inorganic and organic acids and bases. Such salts are within the scope of this invention. Non-toxic and physiologically compatible salts are particularly useful although other less desirable salts may have use in the processes of isolation and purification.

[0829] A number of methods are useful for the preparation of the salts described above and are known to those skilled in the art. For example, the free acid or free base form of a compound of one of the formulas above can be reacted with one or more molar equivalents of the desired acid or base in a solvent or solvent mixture in which the salt is insoluble, or in a solvent like water after which the solvent is removed by evaporation, distillation or freeze drying. Alternatively, the free acid or base form of the product may be passed over an ion exchange resin to form the desired salt or one salt form of the product may be converted to another using the same general process.

Prodrug Derivatives of Compounds

[0830] This invention also encompasses prodrug derivatives of the compounds contained herein. The term "prodrug" refers to a pharmacologically inactive derivative of a parent drug molecule that requires biotransformation, either spontaneous or enzymatic, within the organism to release the active drug. Prodrugs are variations or derivatives of the compounds of this invention which have groups cleavable under metabolic conditions. Prodrugs become the compounds of the invention which are pharmaceutically active in vivo, when they undergo solvolysis under physiological conditions or undergo enzymatic degradation. Prodrug compounds of this invention may be called single, double, triple etc., depending on the number of biotransformation steps required to release the active drug within the organism, and indicating the number of functionalities present in a precursor-type form. Prodrug forms often offer advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (see, 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, Calif., 1992). Prodrugs commonly known in the art include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acids with a suitable alcohol, or amides prepared by reaction of the parent acid compound with an amine, or basic groups reacted to form an acylated base derivative. Moreover, the prodrug derivatives of this invention may be combined with other features herein taught to enhance bioavailability.

[0831] As mentioned above, the compounds of this invention find utility as therapeutic agents for disease states in mammals which have disorders of coagulation such as in the treatment or prevention of unstable angina, refractory angina, myocardial infarction, transient ischemic attacks, thrombotic stroke, embolic stroke, disseminated intravascular coagulation including the treatment of septic shock, deep venous thrombosis in the prevention of pulmonary embolism or the treatment of reocclusion or restenosis of reperfused coronary arteries. Further, these compounds are useful for the treatment or prophylaxis of those diseases which involve the production and/or action of factor Xa/prothrombinase complex. This includes a number of thrombotic and prothrombotic states in which the coagulation cascade is activated which include but are not limited to, deep venous thrombosis, pulmonary embolism, myocardial infarction, stroke, thromboembolic complications of surgery and peripheral arterial occlusion.

[0832] Accordingly, a method for preventing or treating a condition in a mammal characterized by undesired thrombosis comprises administering to the mammal a therapeutically effective amount of a compound of this invention. In addition to the disease states noted above, other diseases

treatable or preventable by the administration of compounds of this invention include, without limitation, occlusive coronary thrombus formation resulting from either thrombolytic therapy or percutaneous transluminal coronary angioplasty, thrombus formation in the venous vasculature, disseminated intravascular coagulopathy, a condition wherein there is rapid consumption of coagulation factors and systemic coagulation which results in the formation of life-threatening thrombi occurring throughout the microvasculature leading to widespread organ failure, hemorrhagic stroke, renal dialysis, blood oxygenation, and cardiac catheterization.

[0833] The compounds of the invention also find utility in a method for inhibiting the coagulation biological samples, which comprises the administration of a compound of the invention.

[0834] The compounds of the present invention may also be used in combination with other therapeutic or diagnostic agents. In certain preferred embodiments, the compounds of this invention may be coadministered along with other compounds typically prescribed for these conditions according to generally accepted medical practice such as anticoagulant agents, thrombolytic agents, or other antithrombotics, including platelet aggregation inhibitors, tissue plasminogen activators, urokinase, prourokinase, streptokinase, heparin, aspirin, or warfarin. The compounds of the present invention may act in a synergistic fashion to prevent reocclusion following a successful thrombolytic therapy and/or reduce the time to reperfusion. These compounds may also allow for reduced doses of the thrombolytic agents to be used and therefore minimize potential hemorrhagic side-effects. The compounds of this invention can be utilized in vivo, ordinarily in mammals such as primates, (e.g. humans), sheep, horses, cattle, pigs, dogs, cats, rats and mice, or in vitro.

[0835] The biological properties of the compounds of the present invention can be readily characterized by methods that are well known in the art, for example by the in vitro protease activity assays and in vivo studies to evaluate antithrombotic efficacy, and effects on hemostasis and hematological parameters, such as are illustrated in the examples.

[0836] Diagnostic applications of the compounds of this invention will typically utilize formulations in the form of solutions or suspensions. In the management of thrombotic disorders the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for oral administration, suppositories, sterile solutions or suspensions or injectable administration, and the like, or incorporated into shaped articles. Subjects in need of treatment (typically mammalian) using the compounds of this invention can be administered dosages that will provide optimal efficacy. The dose and method of administration will vary from subject to subject and be dependent upon such factors as the type of mammal being treated, its sex, weight, diet, concurrent medication, overall clinical condition, the particular compounds employed, the specific use for which these compounds are employed, and other factors which those skilled in the medical arts will recognize.

[0837] Formulations of the compounds of this invention are prepared for storage or administration by mixing the compound having a desired degree of purity with physiologically acceptable carriers, excipients, stabilizers etc., and may be provided in sustained release or timed release formulations. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical field, and are described, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Co., (A. R. Gennaro edit. 1985). Such materials are nontoxic to the recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, acetate and other organic acid salts, antioxidants such as ascorbic acid, low molecular weight (less than about ten residues) peptides such as polyarginine, proteins, such as serum albumin, gelatin, or immunoglobulins, hydrophilic polymers such as polyvinylpyrrolidinone, amino acids such as glycine, glutamic acid, aspartic acid, or arginine, monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, mannose or dextrins, chelating agents such as EDTA, sugar alcohols such as mannitol or sorbitol, counterions such as sodium and/or nonionic surfactants such as Tween, Pluronics or polyethyleneglycol.

[0838] Dosage formulations of the compounds of this invention to be used for therapeutic administration must be sterile. Sterility is readily accomplished by filtration through sterile membranes such as 0.2 micron membranes, or by other conventional methods. Formulations typically will be stored in lyophilized form or as an aqueous solution. The pH of the preparations of this invention typically will be 3-11, more preferably 5-9 and most preferably 7-8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of cyclic polypeptide salts. While the preferred route of administration is by injection, other methods of administration are also anticipated such as orally, intravenously (bolus and/or infusion), subcutaneously, intramuscularly, colonically, rectally, nasally, transdermally or intraperitoneally, employing a variety of dosage forms such as suppositories, implanted pellets or small cylinders, aerosols, oral dosage formulations and topical formulations such as ointments, drops and dermal patches. The compounds of this invention are desirably incorporated into shaped articles such as implants which may employ inert materials such as biodegradable polymers or synthetic silicones, for example, Silastic, silicone rubber or other polymers commercially available.

[0839] The compounds of the invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of lipids, such as cholesterol, stearylamine or phosphatidylcholines.

[0840] The compounds of this invention may also be delivered by the use of antibodies, antibody fragments, growth factors, hormones, or other targeting moieties, to which the compound molecules are coupled. The compounds of this invention may also be coupled with suitable

polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidinone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxyethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, compounds of the invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels. Polymers and semipermeable polymer matrices may be formed into shaped articles, such as valves, stents, tubing, prostheses and the like.

[0841] Therapeutic compound liquid formulations generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by hypodermic injection needle.

[0842] Therapeutically effective dosages may be determined by either in vitro or in vivo methods. For each particular compound of the present invention, individual determinations may be made to determine the optimal dosage required. The range of therapeutically effective dosages will be influenced by the route of administration, the therapeutic objectives and the condition of the patient. For injection by hypodermic needle, it maybe assumed the dosage is delivered into the body's fluids. For other routes of administration, the absorption efficiency must be individually determined for each compound by methods well known in pharmacology. Accordingly, it may be necessary for the therapist to titer the dosage and modify the route of administration as required to obtain the optimal therapeutic effect. The determination of effective dosage levels, that is, the dosage levels necessary to achieve the desired result, will be readily determined by one skilled in the art. Typically, applications of compound are commenced at lower dosage levels, with dosage levels being increased until the desired effect is achieved.

[0843] The compounds of the invention can be administered orally or parenterally in an effective amount within the dosage range of about 0.1 to 100 mg/kg, preferably about 0.5 to 50 mg/kg and more preferably about 1 to 20 mg/kg on a regimen in a single or 2 to 4 divided daily doses and/or continuous infusion.

[0844] Typically, about 5 to 500 mg of a compound or mixture of compounds of this invention, as the free acid or base form or as a pharmaceutically acceptable salt, is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, dye, flavor etc., as called for by accepted pharmaceutical practice. The amount of active ingredient in these compositions is such that a suitable dosage in the range indicated is obtained.

[0845] Typical adjuvants which may be incorporated into tablets, capsules and the like are binders such as acacia, corn starch or gelatin, and excipients such as microcrystalline cellulose, disintegrating agents like corn starch or alginic acid, lubricants such as magnesium stearate, sweetening agents such as sucrose or lactose, or flavoring agents. When a dosage form is a capsule, in addition to the above materials it may also contain liquid carriers such as water, saline, or a fatty oil. Other materials of various types may be used as coatings or as modifiers of the physical form of the dosage unit. Sterile compositions for injection can be formulated according to conventional pharmaceutical practice. For example, dissolution or suspension of the active compound in a vehicle such as an oil or a synthetic fatty vehicle like ethyl oleate, or into a liposome may be desired. Buffers, preservatives, antioxidants and the like can be incorporated according to accepted pharmaceutical practice.

Preparation of Compounds

[0846] The compounds of the present invention may be synthesized by either solid or liquid phase methods described and referenced in standard textbooks, or by a combination of both methods. These methods are well known in the art. See, Bodanszky, "The Principles of Peptide Synthesis", Hafner, et al., Eds., Springer-Verlag, Berlin, 1984.

[0847] Starting materials used in any of these methods are commercially available from chemical vendors such as Aldrich, Sigma, Nova Biochemicals, Bachem Biosciences, and the like, or may be readily synthesized by known procedures.

[0848] Reactions are carried out in standard laboratory glassware and reaction vessels under reaction conditions of standard temperature and pressure, except where otherwise indicated.

[0849] During the synthesis of these compounds, the functional groups of the amino acid derivatives used in these methods are protected by blocking groups to prevent cross reaction during the coupling procedure. Examples of suitable blocking groups and their use are described in "The Peptides: Analysis, Synthesis, Biology", Academic Press, Vol. 3 (Gross, et al., Eds., 1981) and Vol. 9 (1987), the disclosures of which are incorporated herein by reference.

[0850] Compounds according to the invention can be synthesized utilizing procedures well known in the art. The reaction products are isolated and purified by conventional methods, typically by solvent extraction into a compatible solvent. The products may be further purified by column chromatography or other appropriate methods.

Compositions and Formulations

[0851] The compounds of this invention may be isolated as the free acid or base or converted to salts of various inorganic and organic acids and bases. Such salts are within the scope of this invention. Non-toxic and physiologically compatible salts are particularly useful although other less desirable salts may have use in the processes of isolation and purification.

[0852] A number of methods are useful for the preparation of the salts described above and are known to those skilled

in the art. For example, reaction of the free acid or free base form of a compound of the structures recited above with one or more molar equivalents of the desired acid or base in a solvent or solvent mixture in which the salt is insoluble, or in a solvent like water after which the solvent is removed by evaporation, distillation or freeze drying. Alternatively, the free acid or base form of the product may be passed over an ion exchange resin to form the desired salt or one salt form of the product may be converted to another using the same general process.

[0853] Diagnostic applications of the compounds of this invention will typically utilize formulations such as solution or suspension. In the management of thrombotic disorders the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for oral administration, suppositories, sterile solutions or suspensions or injectable administration, and the like, or incorporated into shaped articles. Subjects in need of treatment (typically mammalian) using the compounds of this invention can be administered dosages that will provide optimal efficacy. The dose and method of administration will vary from subject to subject and be dependent upon such factors as the type of mammal being treated, its sex, weight, diet, concurrent medication, overall clinical condition, the particular compounds employed, the specific use for which these compounds are employed, and other factors which those skilled in the medical arts will recognize.

[0854] Formulations of the compounds of this invention are prepared for storage or administration by mixing the compound having a desired degree of purity with physiologically acceptable carriers, excipients, stabilizers etc., and may be provided in sustained release or timed release formulations. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical field, and are described, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Co., (A. R. Gennaro edit. 1985). Such materials are nontoxic to the recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, acetate and other organic acid salts, antioxidants such as ascorbic acid, low molecular weight (less than about ten residues) peptides such as polyarginine, proteins, such as serum albumin, gelatin, or immunoglobulins, hydrophilic polymers such as polyvinalpyrrolidinone, amino acids such as glycine, glutamic acid, aspartic acid, or arginine, monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, mannose or dextrins, chelating agents such as EDTA, sugar alcohols such as mannitol or sorbitol, counterions such as sodium and/or nonionic surfactants such as Tween, Pluronics or polyethyleneglycol.

[0855] Dosage formulations of the compounds of this invention to be used for therapeutic administration must be sterile. Sterility is readily accomplished by filtration through sterile membranes such as 0.2 micron membranes, or by other conventional methods. Formulations typically will be stored in lyophilized form or as an aqueous solution. The pH of the preparations of this invention typically will be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of cyclic polypeptide salts. While the preferred route of administration is by injection, other methods of administration are also anticipated such as intravenously (bolus and/or infusion), subcutaneously, intramuscularly, colonically, rectally, nasally or intraperitoneally, employing a variety of dosage forms such as suppositories, implanted pellets or small cylinders, aerosols, oral dosage formulations and topical formulations such as ointments, drops and dermal patches. The compounds of this invention are desirably incorporated into shaped articles such as implants which may employ inert materials such as biodegradable polymers or synthetic silicones, for example, Silastic, silicone rubber or other polymers commercially available.

[0856] The compounds of this invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of lipids, such as cholesterol, stearylamine or phosphatidylcholines.

[0857] The compounds of this invention may also be delivered by the use of antibodies, antibody fragments, growth factors, hormones, or other targeting moieties, to which the compound molecules are coupled. The compounds of this invention may also be coupled with suitable polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxyethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the factor Xa inhibitors of this invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels. Polymers and semipermeable polymer matrices may be formed into shaped articles, such as valves, stents, tubing, prostheses and the like.

[0858] Therapeutic compound liquid formulations generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by hypodermic injection needle.

[0859] Therapeutically effective dosages may be determined by either in vitro or in vivo methods. For each particular compound of the present invention, individual determinations may be made to determine the optimal dosage required. The range of therapeutically effective dosages will naturally be influenced by the route of administration, the therapeutic objectives, and the condition of the patient. For injection by hypodermic needle, it may be assumed the dosage is delivered into the body's fluids. For other routes of administration, the absorption efficiency must be individually determined for each inhibitor by methods well known in pharmacology. Accordingly, it may be necessary for the therapist to titer the dosage and modify the route of administration as required to obtain the optimal therapeutic effect. The determination of effective dosage levels, that is, the dosage levels necessary to achieve the desired result, will be within the ambit of one skilled in the art. Typically, applications of compound are commenced at

lower dosage levels, with dosage levels being increased until the desired effect is achieved.

[0860] A typical dosage might range from about 0.001 mg/kg to about 1000 mg/kg, preferably from about 0.01 mg/kg to about 100 mg/kg, and more preferably from about 0.10 mg/kg to about 20 mg/kg. Advantageously, the compounds of this invention may be administered several times daily, and other dosage regimens may also be useful.

[0861] Typically, about 0.5 to 500 mg of a compound or mixture of compounds of this invention, as the free acid or base form or as a pharmaceutically acceptable salt, is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, dye, flavor etc., as called for by accepted pharmaceutical practice. The amount of active ingredient in these compositions is such that a suitable dosage in the range indicated is obtained.

[0862] Typical adjuvants which may be incorporated into tablets, capsules and the like are a binder such as acacia, corn starch or gelatin, and excipient such as microcrystalline cellulose, a disintegrating agent like corn starch or alginic acid, a lubricant such as magnesium stearate, a sweetening agent such as sucrose or lactose, or a flavoring agent. When a dosage form is a capsule, in addition to the above materials it may also contain a liquid carrier such as water, saline, a fatty oil. Other materials of various types may be used as coatings or as modifiers of the physical form of the dosage unit. Sterile compositions for injection can be formulated according to conventional pharmaceutical practice. For example, dissolution or suspension of the active compound in a vehicle such as an oil or a synthetic fatty vehicle like ethyl oleate, or into a liposome may be desired. Buffers, preservatives. antioxidants and the like can be incorporated according to accepted pharmaceutical practice.

[0863] In practicing the methods of this invention, the compounds of this invention may be used alone or in combination, or in combination with other therapeutic or diagnostic agents. In certain preferred embodiments, the compounds of this inventions may be coadministered along with other compounds typically prescribed for these conditions according to generally accepted medical practice, such as anticoagulant agents, thrombolytic agents, or other antithrombotics, including platelet aggregation inhibitors, tissue plasminogen activators, urokinase, prourokinase, streptokinase, heparin, aspirin, or warfarin. The compounds of this invention can be utilized in vivo, ordinarily in mammals such as primates, such as humans, sheep, horses, cattle, pigs, dogs, cats, rats and mice, or in vitro.

[0864] The preferred compounds of the present invention are characterized by their ability to inhibit thrombus formation with acceptable effects on classical measures of coagulation parameters, platelets and platelet function, and acceptable levels of bleeding complications associated with their use. Conditions characterized by undesired thrombosis would include those involving the arterial and venous vasculature.

[0865] With respect to the coronary arterial vasculature, abnormal thrombus formation characterizes the rupture of an established atherosclerotic plaque which is the major cause of acute myocardial infarction and unstable angina, as well as also characterizing the occlusive coronary thrombus formation resulting from either thrombolytic therapy or percutaneous transluminal coronary angioplasty (PTCA).

[0866] With respect to the venous vasculature, abnormal thrombus formation characterizes the condition observed in patients undergoing major surgery in the lower extremities or the abdominal area who often suffer from thrombus formation in the venous vasculature resulting in reduced blood flow to the affected extremity and a predisposition to pulmonary embolism. Abnormal thrombus formation further characterizes disseminated intravascular coagulopathy commonly occurs within both vascular systems during septic shock, certain viral infections and cancer, a condition wherein there is rapid consumption of coagulation factors and systemic coagulation which results in the formation of life-threatening thrombi occurring throughout the microvasculature leading to widespread organ failure.

[0867] The compounds of this present invention, selected and used as disclosed herein, are believed to be useful for preventing or treating a condition characterized by undesired thrombosis, such as (a) the treatment or prevention of any thrombotically mediated acute coronary syndrome including myocardial infarction, unstable angina, refractory angina, occlusive coronary thrombus occurring post-thrombolytic therapy or post-coronary angioplasty, (b) the treatment or prevention of any thrombotically mediated cerebrovascular syndrome including embolic stroke, thrombotic stroke or transient ischemic attacks, (c) the treatment or prevention of any thrombotic syndrome occurring in the venous system including deep venous thrombosis or pulmonary embolus occurring either spontaneously or in the setting of malignancy, surgery or trauma, (d) the treatment or prevention of any coagulopathy including disseminated intravascular coagulation (including the setting of septic shock or other infection, surgery, pregnancy, trauma or malignancy and whether associated with multi-organ failure or not), thrombotic thrombocytopenic purpura, thromboangiitis obliterans, or thrombotic disease associated with heparin induced thrombocytopenia, (e) the treatment or prevention of thrombotic complications associated with extracorporeal circulation (e.g. renal dialysis, cardiopulmonary bypass or other oxygenation procedure, plasmapheresis), (f) the treatment or prevention of thrombotic complications associated with instrumentation (e.g. cardiac or other intravascular catheterization, intra-aortic balloon pump, coronary stent or cardiac valve), and (g) those involved with the fitting of prosthetic devices.

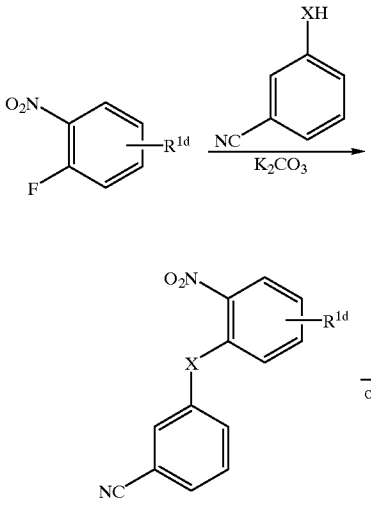
[0868] Anticoagulant therapy is also useful to prevent coagulation of stored whole blood and to prevent coagulation in other biological samples for testing or storage. Thus the compounds of this invention can be added to or contacted with any medium containing or suspected to contain factor Xa and in which it is desired that blood coagulation be inhibited, e.g., when contacting the mammal's blood with material such as vascular grafts, stents, orthopedic prostheses, cardiac stents, valves and prostheses, extra corporeal circulation systems and the like.

[0869] Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the following illustrative examples, make and utilize the compounds of the present invention and practice the claimed methods.

EXAMPLES

[0870] Examples of Chemical Production Process General Reaction Schemes

Scheme 1



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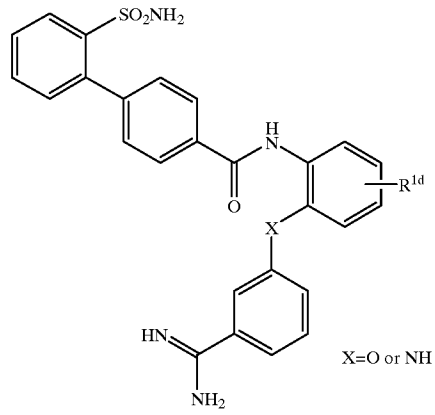
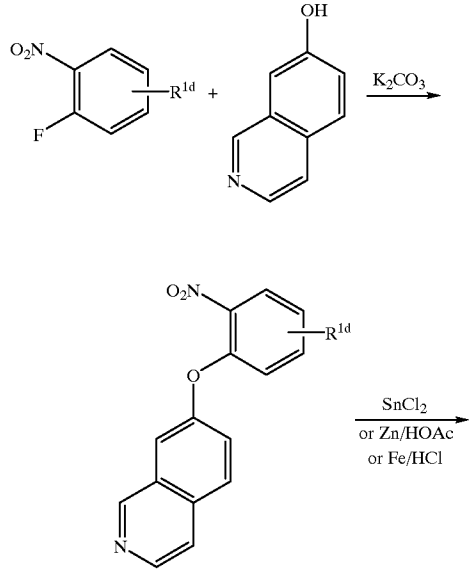
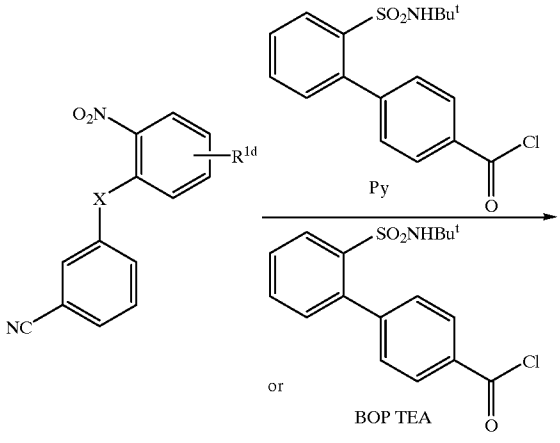
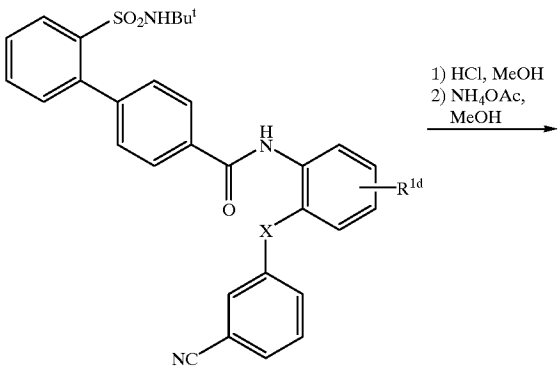
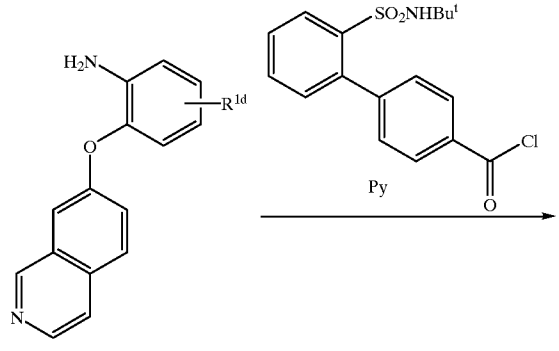


Scheme 2









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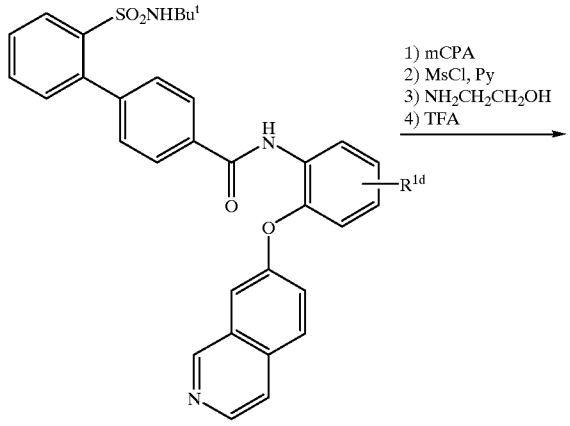

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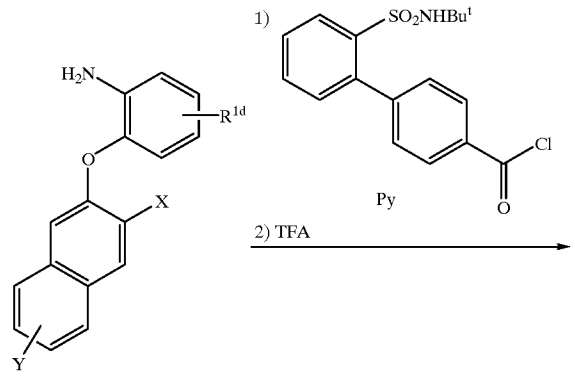

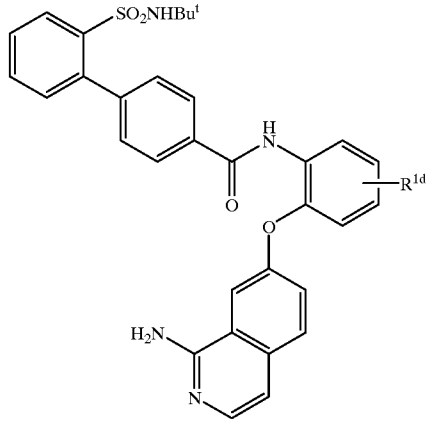

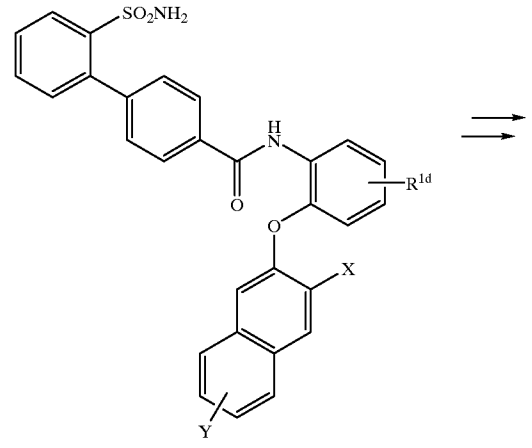

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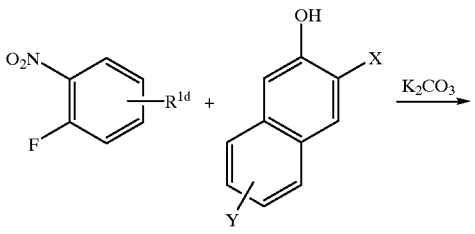
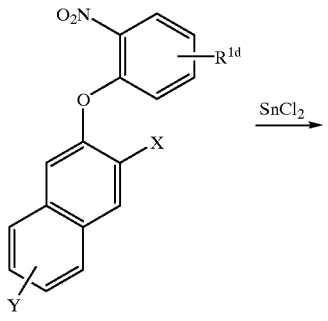
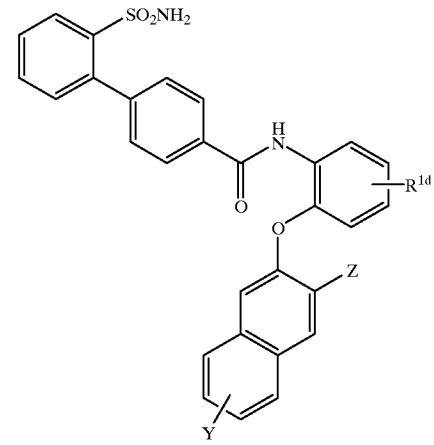
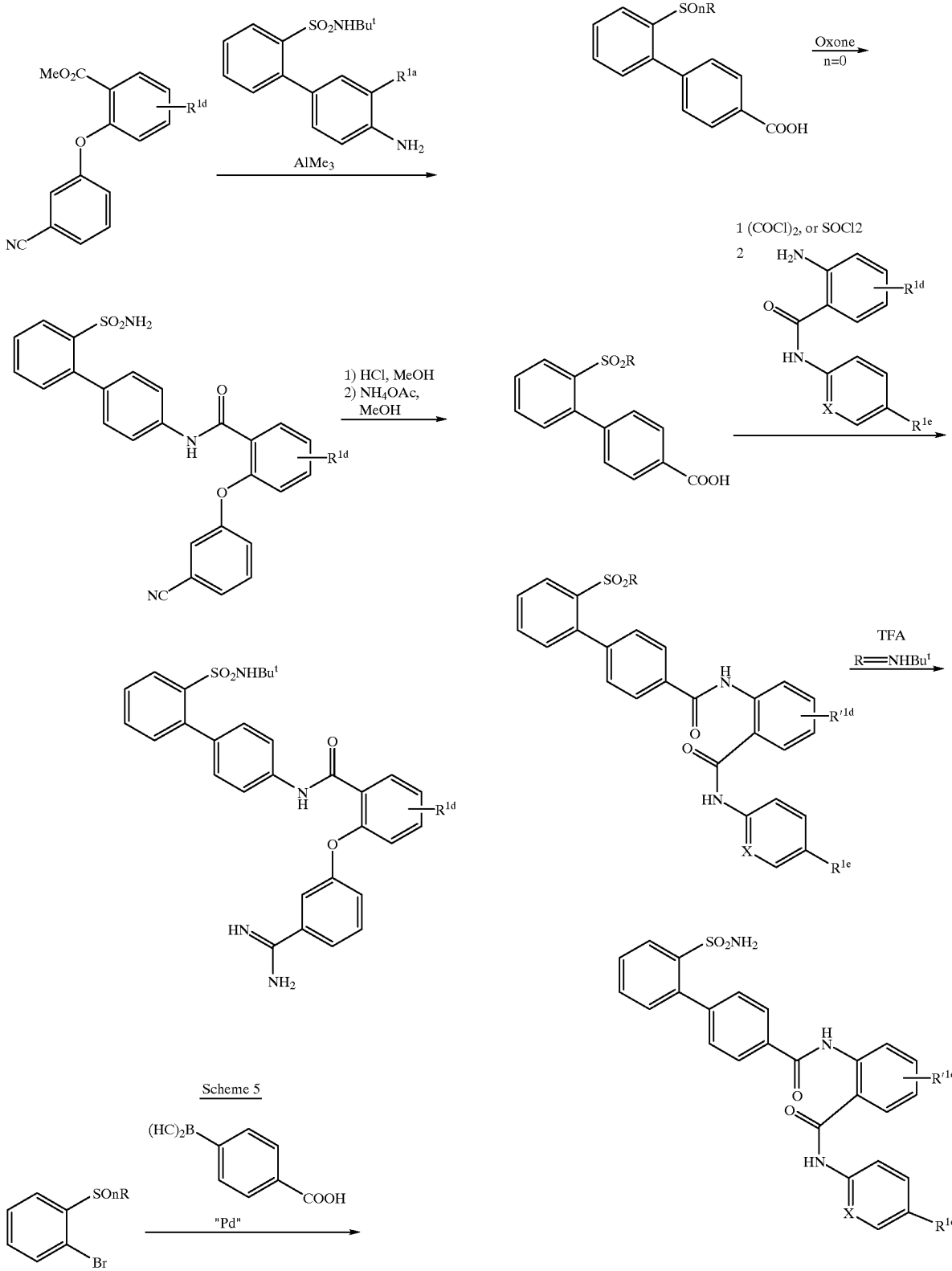


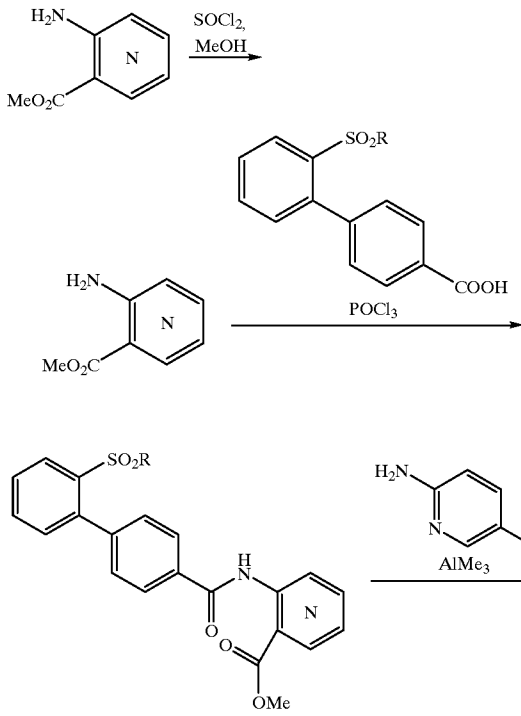




Scheme 4


MeO2C
R1d
O
NC
SO2NHBut
R1a
NH2
AlMe3
SO2NH2
1) HCl, MeOH
2) NH4OAc,
MeOH
N
H
SO2NHBut
HN
NH2
SOnR
Br
(HC)2B
COOH
"Pd"
-continued
SOnR
Oxone
n=0
COOH
1 (COCl)2, or SOCl2
2
H2N
HN
X
R1e
SO2R
TFA
R=NHBut
R'1d

Scheme 6



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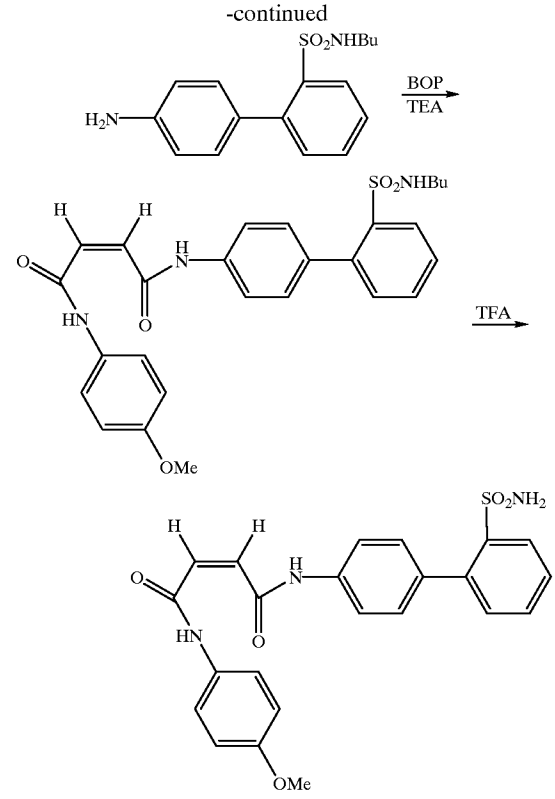

Scheme 7

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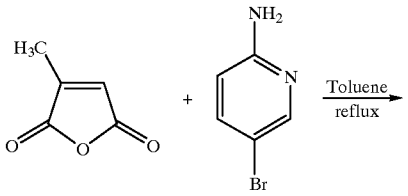
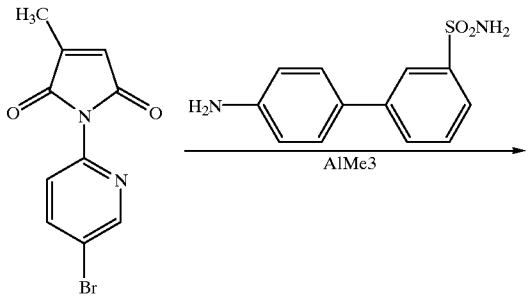
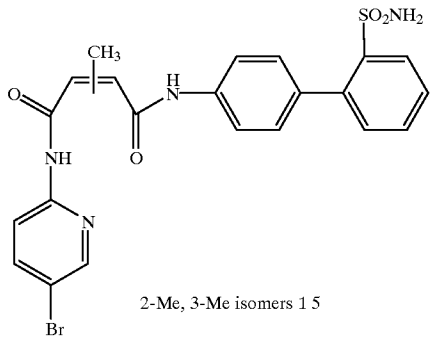
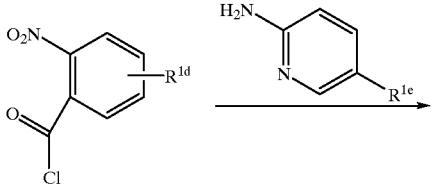


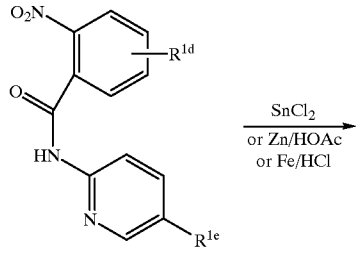




2-Me, 3-Me isomers 1 5

Scheme 8





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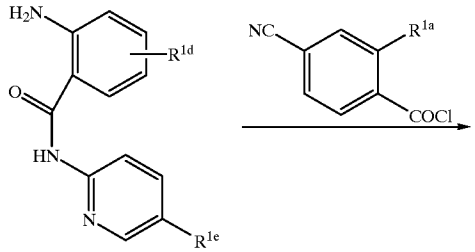

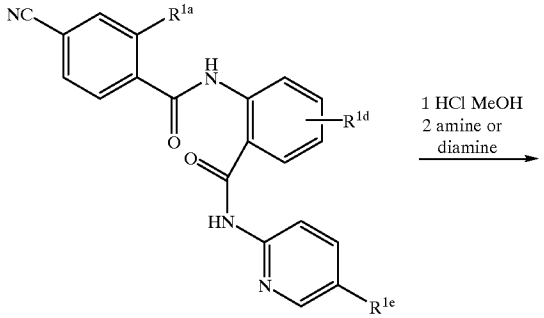

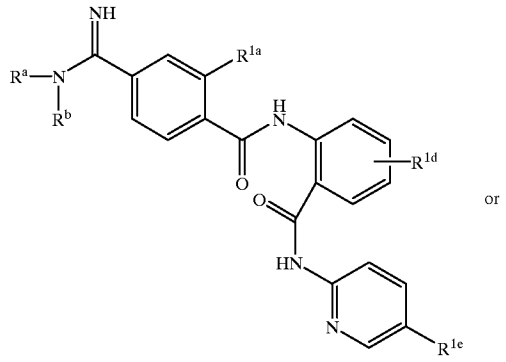

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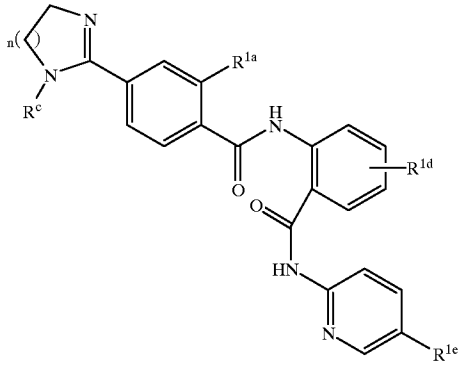

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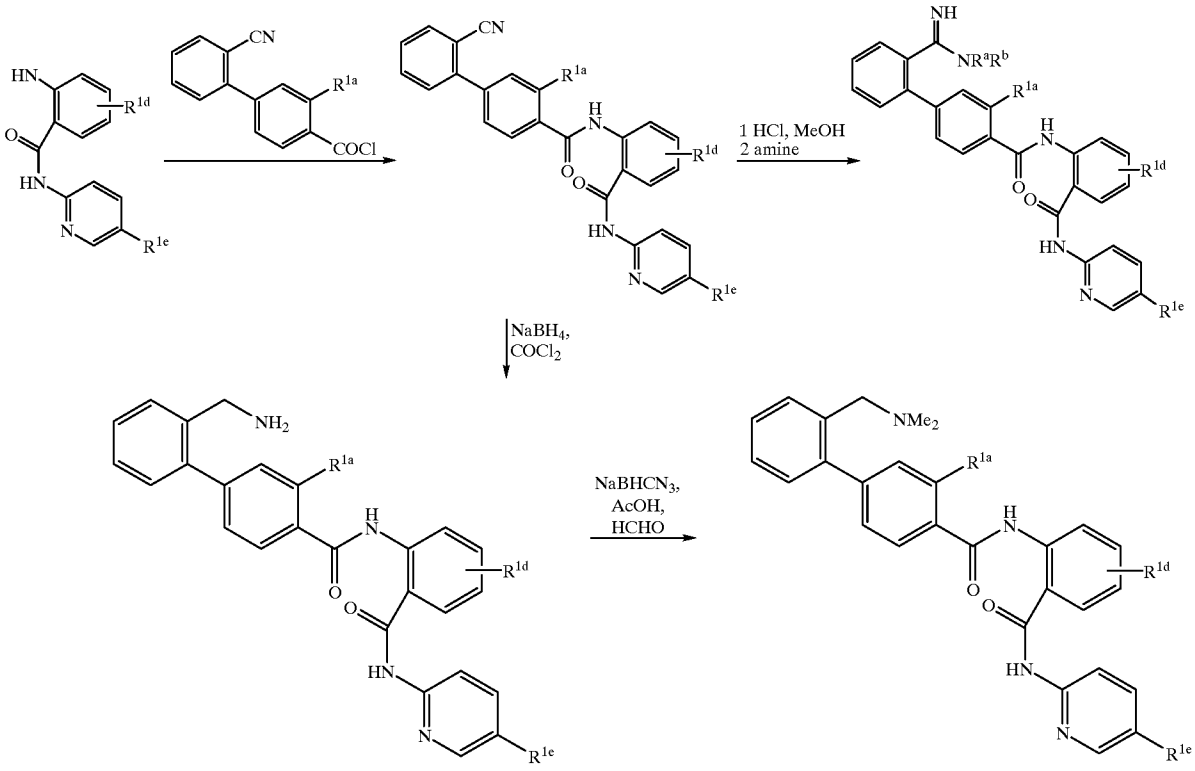

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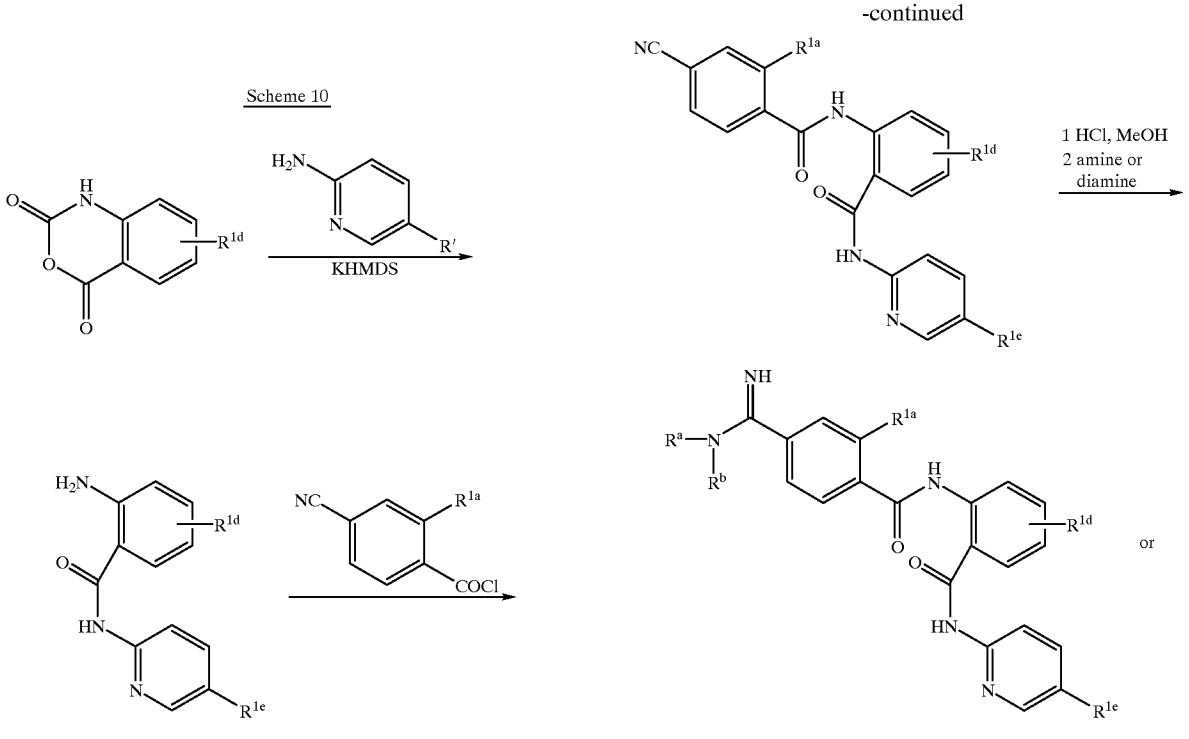
Scheme 10



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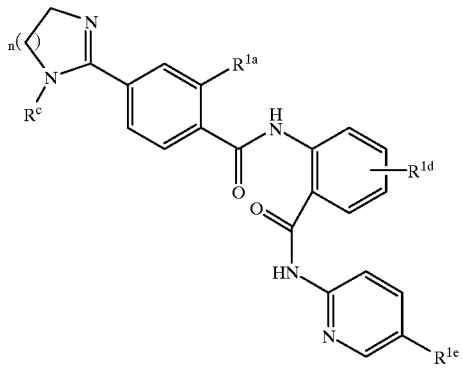

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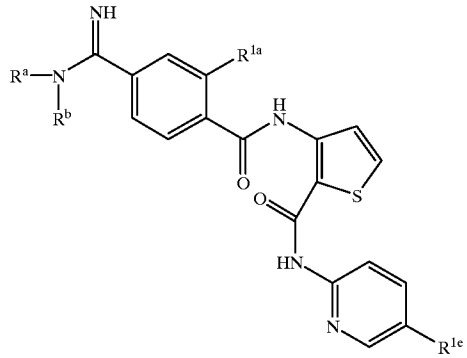

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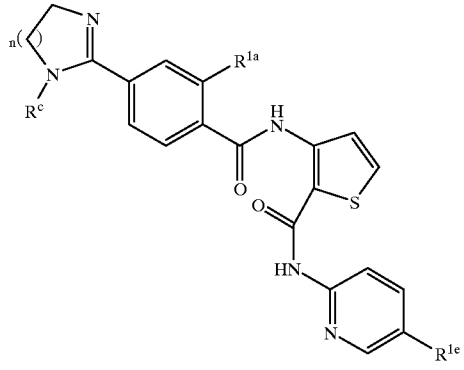
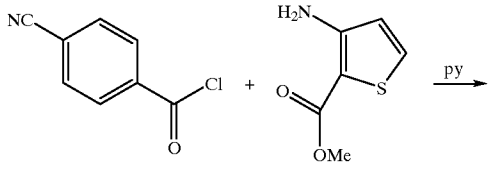
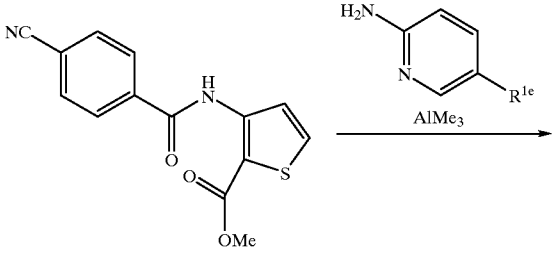


Scheme 11





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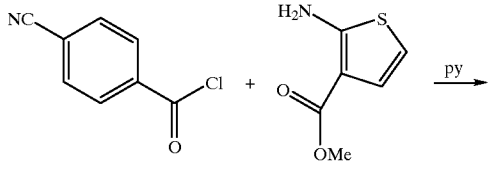

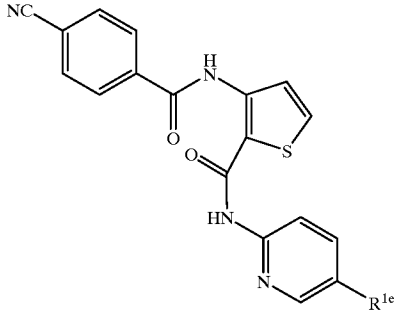

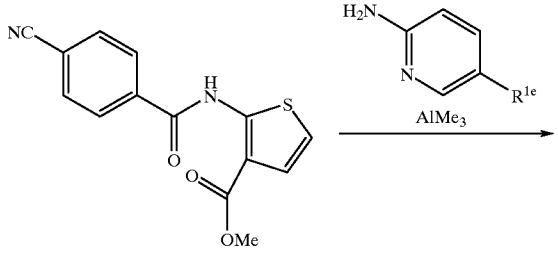

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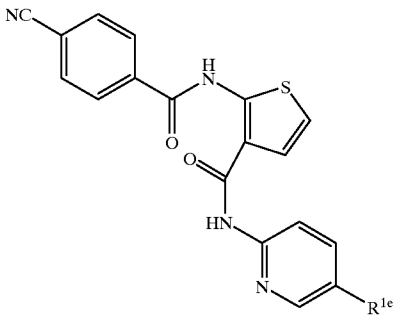
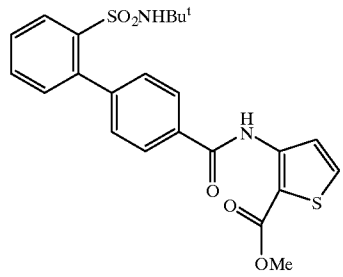


1. HCl, MeOH
2. amine or diamine



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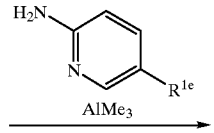
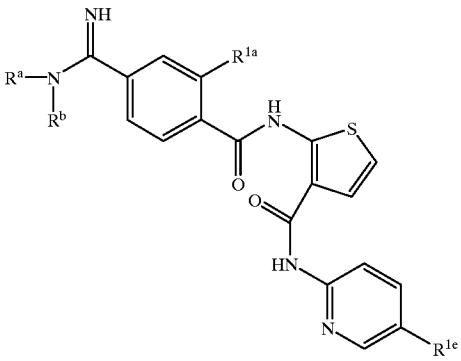
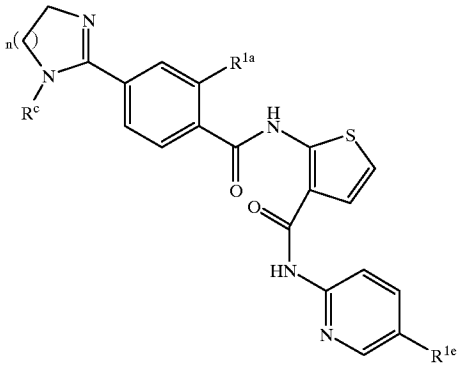
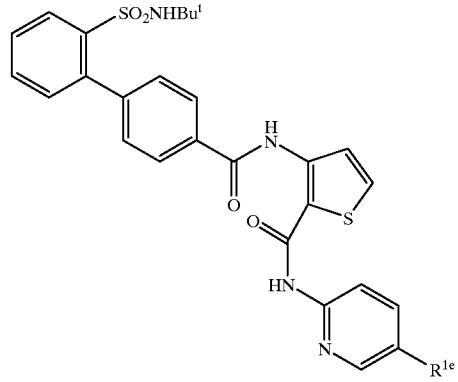


AlMe3

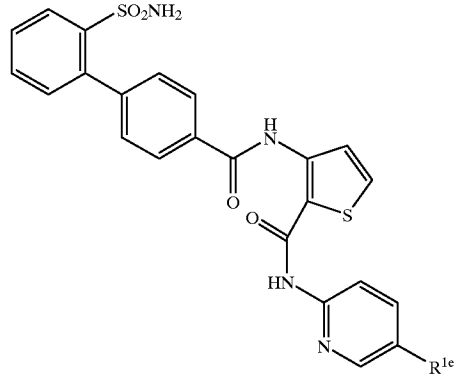


or

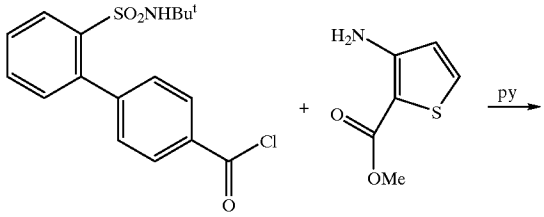




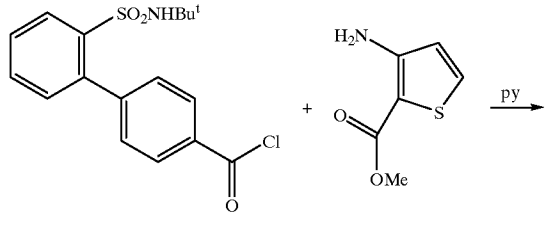
TFA



Scheme 13



Scheme 14



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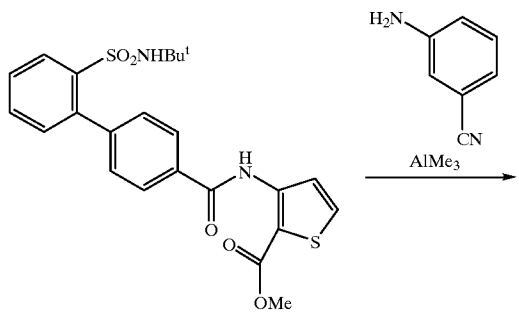

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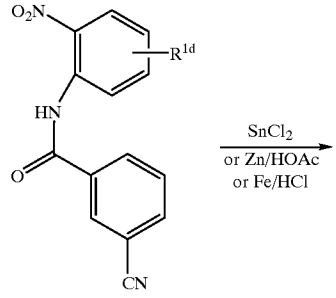
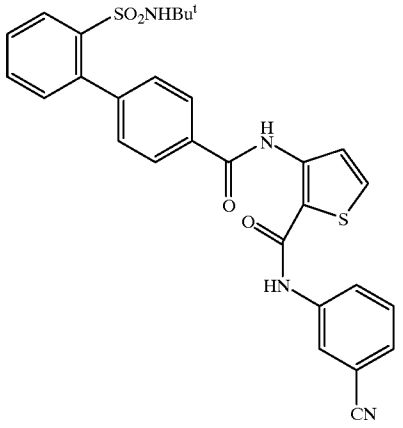
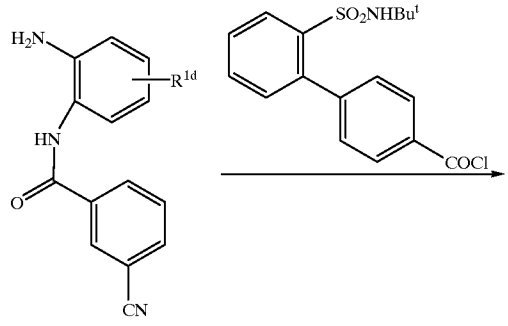
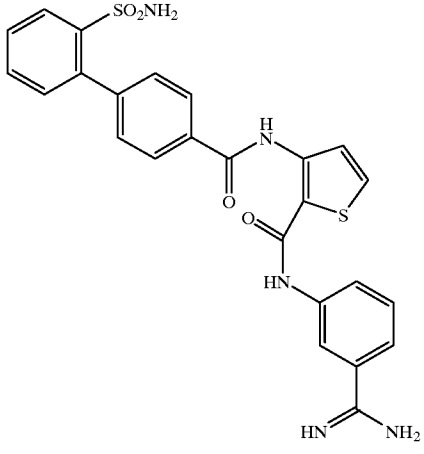
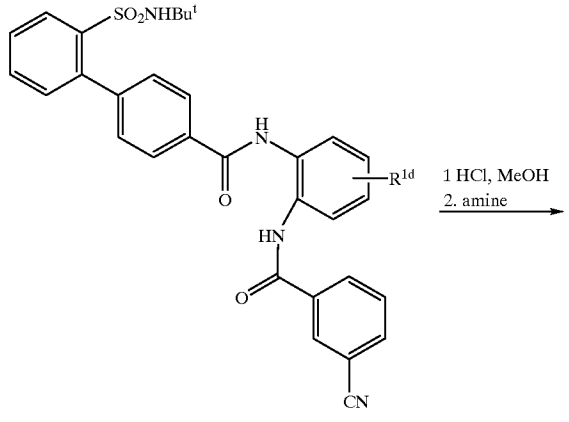
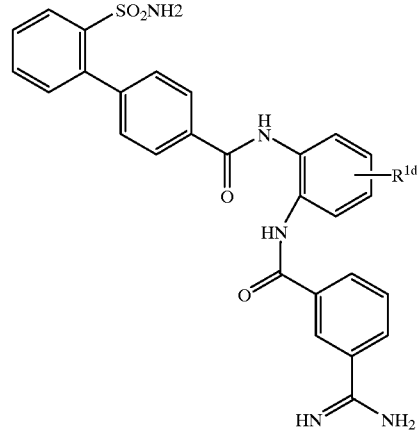




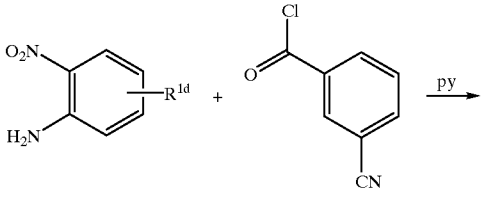






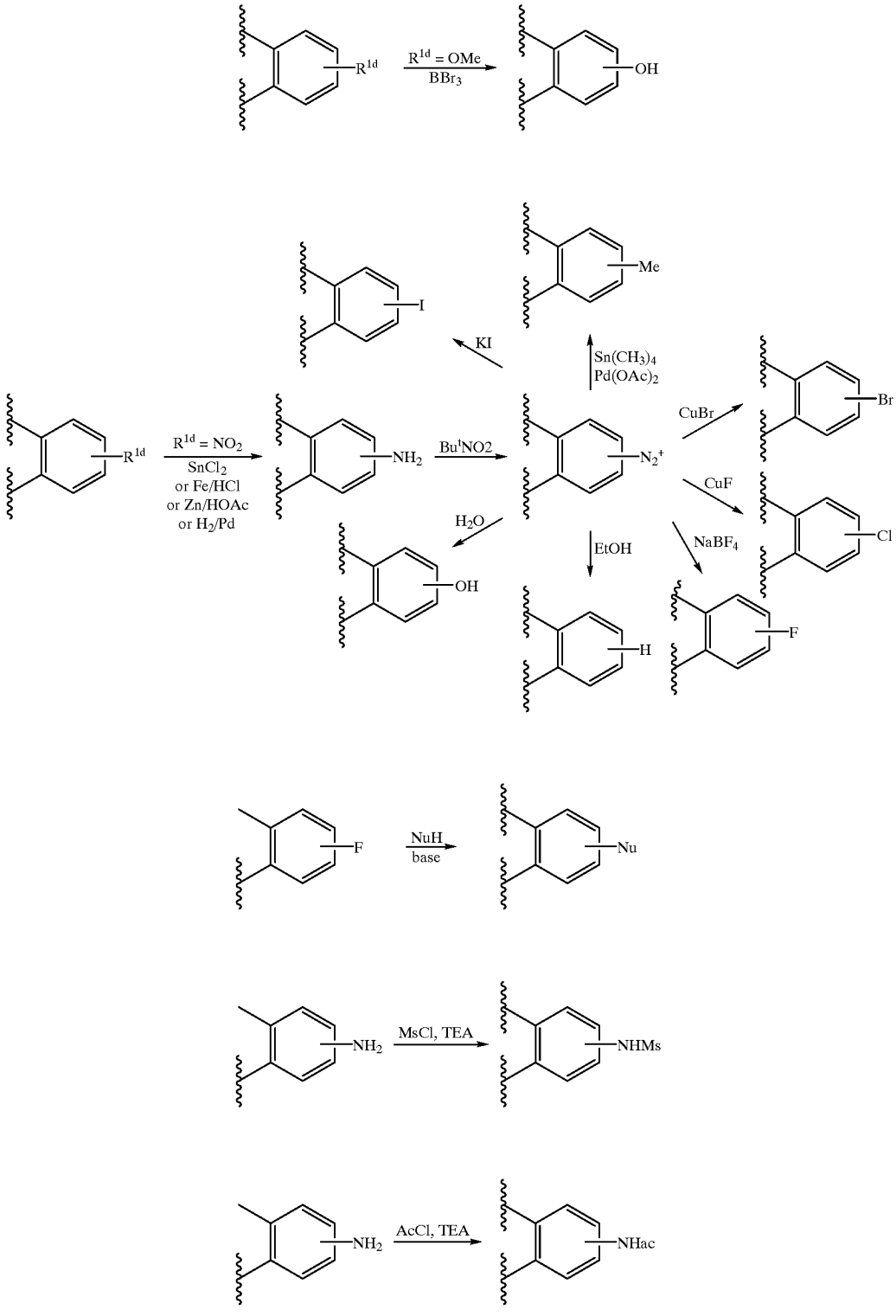


Scheme 15



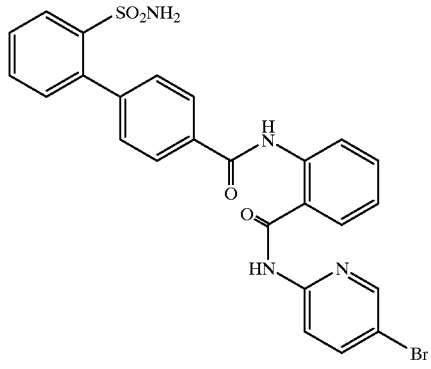
Scheme 16

Transformations of R^{1d}



Example 1

[0871] N-(5-bromo-2-pyridinyl)-(2-4- [(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenylcarboxamide.



[0872] Step 1: A solution of 2-nitrobenzoyl chloride (3.70 g, 20 mmol, 1.0 equiv), 2-amino-5-bromopyridine (3.50 g, 1.0 equiv), pyridine (10 mL) in 25 mL of methylene chloride was stirred overnight. The volatile was evaporated, flash chromatography on silica gel gave N-(5-bromo-2-pyridinyl)-(2-nitro)phenylcarboxamide (5.02 g, 77%).

[0873] MS found for $C_{12}H_9BrN_3O_3$ $(M+H)^+$: 322.

[0874] Step 2: A solution of N-(5-bromo-2-pyridinyl)-(2-nitro)phenylcarboxamide (1.0 g, 3.1 mmol, 1.0 equiv) in 30 mL of EtOAc was treated with $SnCl_22H_2O$ (2.80 g, 4 equiv) at reflux for 4 h. The volatile was evaporated and the residue was redissolved in EtOAc, washed with saturated aqueous $NaHCO_3$ and 1N NaOH. The organic layer was dried over $MgSO_4$, filtered and evaporated to N-(5-bromo-2-pyridinyl)-(2-amino)phenylcarboxamide (0.89 g, 98%).

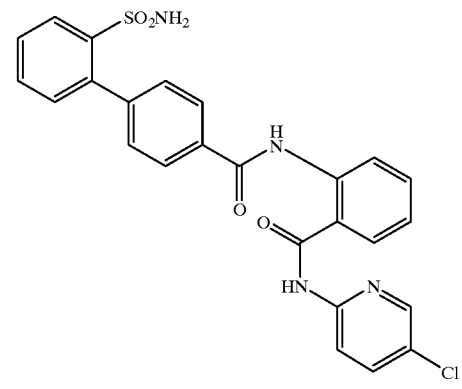
[0875] MS found for $C_{12}H_{11}BrN_3O$ $(M+H)^+$: 292.

[0876] Step 3: A mixture of N-(5-bromo-2-pyridinyl)-(2-amino)phenylcarboxamide (292 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoyl chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN gave N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenylcarboxamide (470 mg, 85%).

[0877] MS found for $C_{25}H_{20}BrN_4O_4S$ $(M+H)^+$: 551.

Example 2

[0878] N-(5-chloro-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenylcarboxamide.

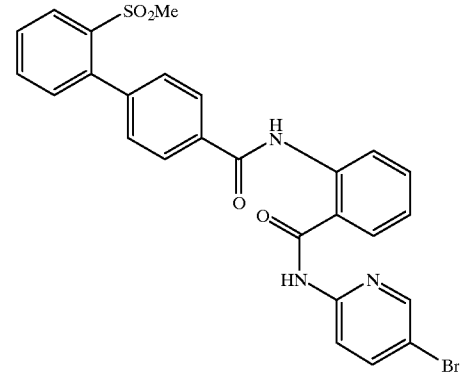


[0879] A mixture of N-(5-chloro-2-pyridinyl)-(2-amino)phenylcarboxamide (247 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoyl chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 ml, of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN gave N-(5-chloro-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenylcarboxamide (370 mg, 73%).

[0880] MS found for $C_{25}H_{20}ClN_4O_4S$ $(M+H)^+$: 507.

Example 3

[0881] N-(5-bromo-2-pyridinyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide.



[0882] Step 1: To a mixture of 2-bromothioanisole (4.8 g, 23.6 mmol), 4-carboxybenzeneboronic acid (3.92 g, 23.6 mmol) and 2M K_2CO_3 (35.5 mmol, 71 mmol) in dioxane (20 ml) was added dichlorobis(triphenylphosphine)palladium (II) (415 mg, 0.6 mmol) under Ar. It was refluxed for 2 hrs. After the removal of the solvent, the residue was neutralized by 1N HCl and extracted with dichloromethane. The organic

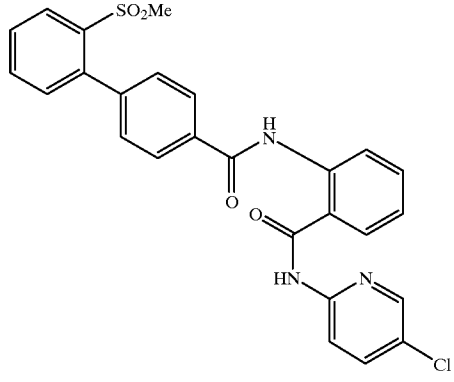
layer was dried over $MgSO_4$ and concentrated in vacuo to give 4-[(2-methylthio)phenyl]benzoic acid (5.9 g, 100%). ES-MS $(M+H)^+$=245.

[0883] Step 2: To a solution of 4-[(2-methylthio)phenyl] benzoic acid (3.43 g, 14 mmol) in H_2O (10 ml) and acetone (20 ml) was added oxone monopersulfate (34.6 g, 56 mmol). The mixture was stirred at r.t. overnight. After the removal of the solvent, the residue was extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to give 2.16 g (63%) 4-[(2-methylsulfonyl)phenyl] benzoic acid. ES-MS $(M+H)^+$=277.

[0884] Step 3: To a solution of 4-[(2-methylsulfonyl)phenyl]benzoic acid (552 mg, 2 mmol) in dichloromethane (5 ml) was added oxalyl chloride (350 ul, 4 mmol) and 2 drops of DMF. The mixture was stirred at r.t. for 2 hrs. After the removal of the solvent in vacuo, the residue was dissolved in dichloromethane (5 ml), N-(5-bromo-2-pyridinyl)-(2-amino)phenylcarboxamide (700 mg, 2.4 mmol), pyridine (486 ul, 6 mmol) and catalytic amount of DMAP were added. The mixture was stirred at r.t. overnight. After the removal of the solvent, the residue was purified by flash column (30% ethyl acetate/hexane) and then preparative HPLC to get 414 mg (38%) of N-(5-bromo-2-pyridinyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide. ES-MS M^+=550, $(M+2)^+$=552.

Example 4

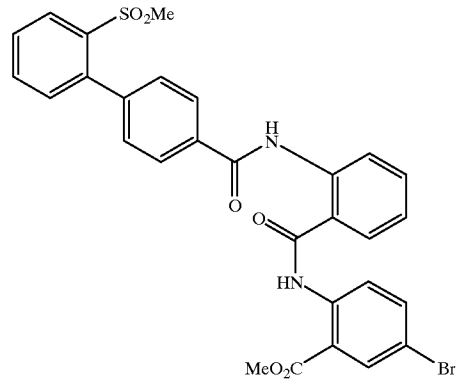
[0885] N-(5-chloro-2-pyridinyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide.



[0886] To a solution of 4-[(2-methylsulfonyl)phenyl]benzoic acid (280 mg, 1 mmol) in dichloromethane (5 ml) was added oxalyl chloride (175 ul, 2 mmol) and 2 drops of DMF. The mixture was stirred at r.t. for 2 hrs. After the removal of the solvent in vacuo, the residue was dissolved in dichloromethane (5 ml), N-(5-chloro-2-pyridinyl)-(2-amino)phenylcarboxamide (297 mg, 1.2 mmol), pyridine (243 ul, 3 mmol) and catalytic amount of DMAP were added. The mixture was stirred at r.t. overnight. After the removal of the solvent, the residue was purified by flash column (30% ethyl acetate/hexane) and then preparative HPLC to get 95 mg (20%) of N-(5-chloro-2-pyridinyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide. ES-MS M+=505.5, (M+2)+=507.5.

Example 5

[0887] N-(4-bromo-2-methoxycarbonyphenyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide.

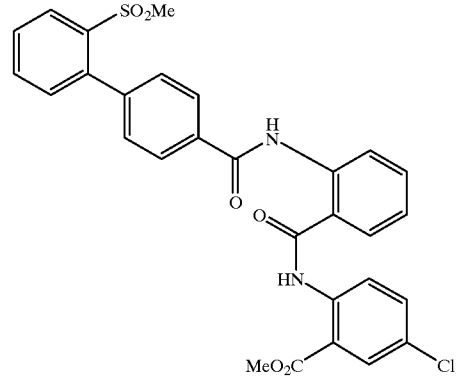


[0888] A sample of 4-[(2-methylsulfonyl)phenyl]benzoic acid (280 mg, 1 mmol, 1 equiv) was refluxed with 2 mL of thionyl chloride for 2 h and evaporated. The residue was dissolved in 5 mL of dichloromethane, N-(4-bromo-2-methoxycarbonyphenyl)-(2-amino)phenylcarboxamide (348 mg, 1 equiv), pyridine (3 mL) were added. The mixture was stirred at r.t. overnight. After the removal of the solvent, the residue was purified by flash column to give 480 mg (79%) of N-(4-bromo-2-methoxycarbonyphenyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide.

[0889] MS found for $C_{29}H_{24}BrN_2O_6S$ $(M+H)^+$: 607.

Example 6

[0890] N-(4-chloro-2-methoxycarbonyphenyl)-(2-(4- [(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide.

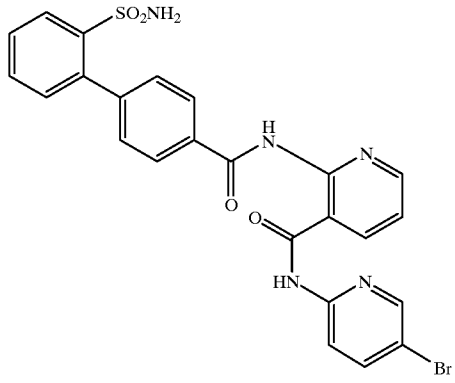


[0891] A sample of 4-[(2-methylsulfonyl)phenyl]benzoic acid (280 mg, 1 mmol, 1 equiv) was refluxed with 2 mL of thionyl chloride for 2 h and evaporated. The residue was dissolved in 5 mL of dichloromethane, N-(4-chloro-2-methoxycarbonyphenyl)-(2-amino)phenylcarboxamide (304 mg,1 equiv), pyridine (3 mL) were added. The mixture was stirred at r.t. overnight. After the removal of the solvent, the residue was purified by flash column to give 479 mg (85%) of N-(4-chloro-2-methoxycarbonyphenyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide.

[0892] MS found for $C_{29}H_{24}ClN_2O_6S$ $(M+H)^+$: 563.

Example 7

[0893] N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pyridinyl-3-carboxamide.



[0894] Step 1: A solution of 2-aminopyridine-3-carboxylic acid (138 mg, 1 mmol) in 10 mL of methanol was treated with thionyl chloride in portions until complete reaction. The solvent was evaporated and the residue was dissolved in 10 mL of pyridine. To the solution were added 4-[(2-t-butylaminosulfonyl)phenyl]benzoic acid and $POCl_3$. The resulting mixture was stirred at rt overnight, quenched by slow addition of water, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and flash chromatographied to give methyl 2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonyl)aminopyridine-3-carboxylate (243 mg, 52%).

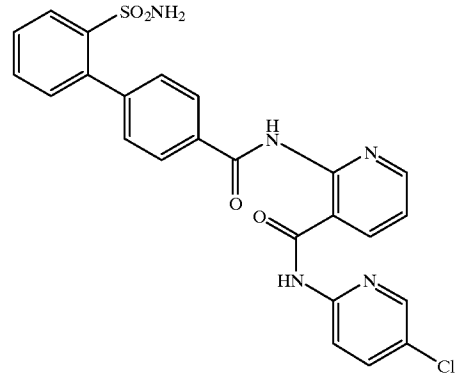
[0895] MS found for $C_{24}H_{26}N_3O_5S$ $(M+H)^+$: 468.

[0896] Step 2: To A solution of 2-amino-5-bromopridine (45 mg, 4.0 equiv) in 5 mL of methylene chloride treated with $AlMe_3$ (2M in hexane, 0.65 mL, 20 equiv) for 30 min was added methyl 2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonyl)aminopyridine-3-carboxylate (30 mg, 0.064 mmol, 1 equiv). The mixture was stirred at rt overnight, quenched with saturated aqueous potassium sodium tartrate. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN gave N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pyridinyl-3-carboxamide (17 mg, 48%).

[0897] MS found for $C_{24}H_{19}BrN_5O_4S$ $(M+H)^+$: 552.

Example 8

[0898] N-(5-chloro-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pyridinyl-3-carboxamide.

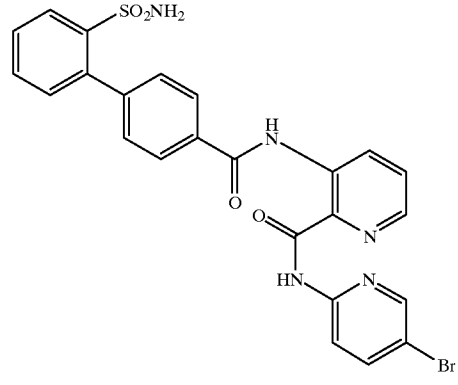


[0899] To A solution of 2-amino-5-chloropridine (32 mg, 4.0 equiv) in 5 mL of methylene chloride treated with $AlMe_3$ (2M in hexane, 0.65 mL, 20 equiv) for 30 min was added methyl 2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonyl)aminopyridine-3-carboxylate (30 mg, 0.064 mmol, 1 equiv). The mixture was stirred at rt overnight, quenched with saturated aqueous potassium sodium tartrate. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN gave N-(5-chloro-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pyridinyl-3-carboxamide (21 mg, 66%).

[0900] MS found for $C_{24}H_{19}ClN_5O_4S$ $(M+H)^+$: 508.

Example 9

[0901] N-(5-bromo-2-pyridinyl)-(3-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pyridinyl-2-carboxamide.

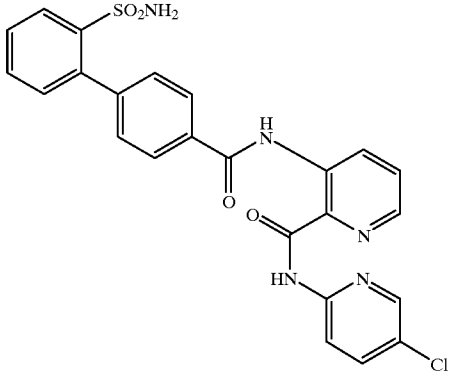


[0902] To A solution of 2-amino-5-bromopridine (69.2 mg, 4.0 equiv) in 5 mL of methylene chloride treated with $AlMe_3$ (2M in hexane, 1 mL, 20 equiv) for 30 min was added 3-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonyl)aminopyridine-2-carboxylate (46.7 mg, 1 equiv). The mixture was stirred at rt overnight, quenched with saturated aqueous potassium sodium tartrate. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN gave N-(5-bromo-2-pyridinyl)-(3-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pyridinyl-2-carboxamide (29 mg, 53%).

[0903] MS found for $C_{24}H_{19}BrN_5O_4S$ $(M+H)^+$: 552.

Example 10

[0904] N-(5-chloro-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pyridinyl-3-carboxamide.



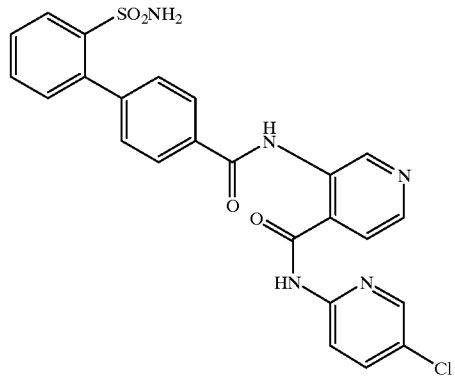
[0905] To A solution of 2-amino-5-chloropridine (51.2 mg, 4.0 equiv) in 5 mL of methylene chloride treated with $AlMe_3$ (2M in hexane, 1 mL, 20 equiv) for 30 min was added 3-(4- [(2-t-butylaminosulfonyl)phenyl]phenylcarbonyl)aminopyridine-2-carboxylate (46.7 mg, 0.1 mmol, 1 equiv). The mixture was stirred at rt overnight, quenched with saturated aqueous potassium sodium tartrate. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN gave N-(5-chloro-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pyridinyl-3-carboxamide (33 mg, 64%).

[0906] MS found for $C_{24}H_{19}ClN_5O_4S$ $(M+H)^+$: 508.

Examples 11-14

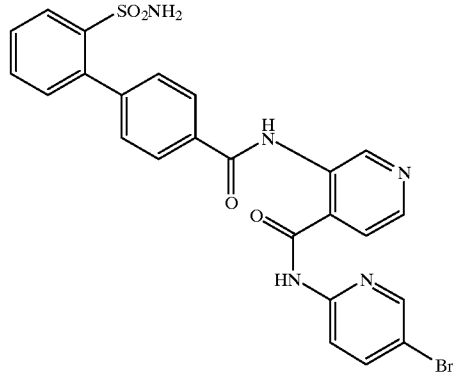
[0907] The following compounds were prepared using the procedure described previously:

Example 11



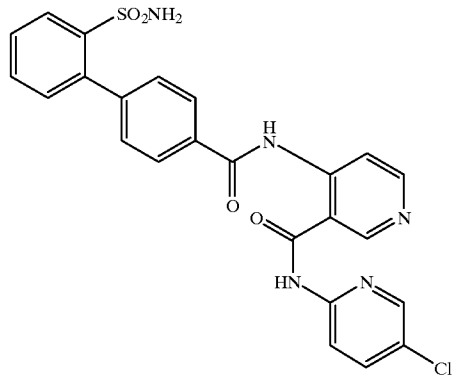
MS (M + H): 508

Example 12



MS (M + H): 552

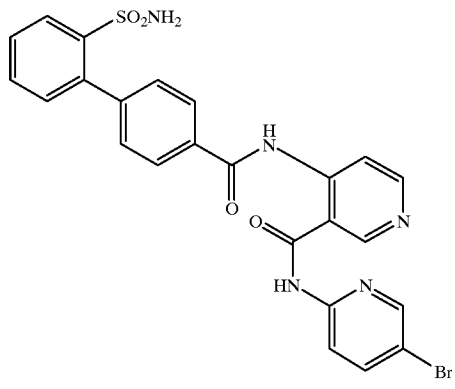
Example 13



MS (M + H): 508

-continued

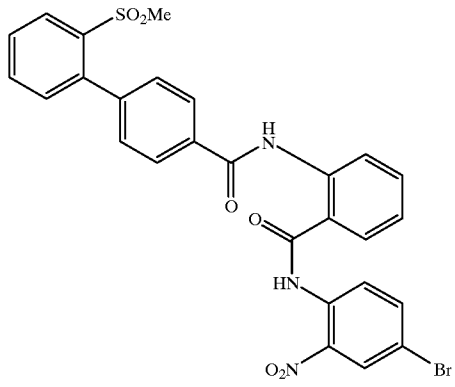
Example 14



MS (M + H): 552

Example 15

[0908] N-(4-bromo-2-nitrophenyl)-(2-(4- [(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide.



[0909] Step 1: A mixture of methyl 2-aminobenzoate (150 mg, 1 mmol, 1.0 equiv), 4-[(2-methylsulfonyl)phenyl]benzoic chloride (294 mg, 1 equiv). pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave methyl 2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)aminobenzoate (250 mg, 54%).

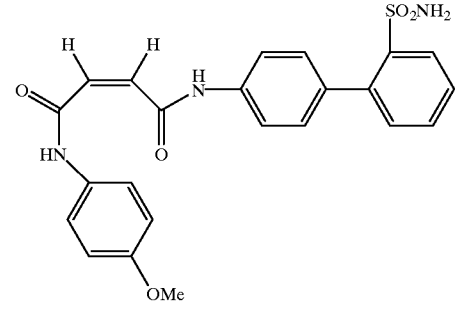
[0910] MS found for $C_{25}H_{27}N_2O_5S$ $(M+H)^+$: 467.

[0911] Step 2: To a solution of 4-bromo-2-ntroaniline (43.4 mg, 0.2 mmol, 2.0 equiv) in 5 mL of methylene chloride treated with $AlMe_3$ (2M in hexane. 0.3 mL, 6 equiv) for 30 min was added methyl 2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)aminobenzoate (46.6 mg, 1 equiv). The mixture was stirred at rt overnight, quenched with saturated aqueous potassium sodium tartrate. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave N-(4-bromo-2-nitrophenyl)-(2-(4-[(2-(ethylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide (5 mg, 9%).

[0912] MS found for $C_{27}H_{21}BrN_3O_6S$ $(M+H)^+$: 594.

Example 16

[0913] N-(4-methoxyphenyl)-N'-(4-[(2-aminosulfonyl)phenyl]phenyl)-maleamic amide



[0914] A. Preparation of N-(4-methoxyphenyl)-N'-(4-[(2-tert-butylaminosulfonyl)phenyl]phenyl)-maleamic amide.

[0915] To a solution of commercially available N-(4-methoxyphenyl)maleamic acid (100 mg, 0.452 mmol), triethylamine (0.126 mL, 0.906 mmol) and 4-(2-tert-butylaminosulfonylphenyl)aniline (138 mg, 0.454 mmol) in anhydrous DMF (5 mL), BOP (260 mg, 0.588 mmol) was added. The mixture was stirred at room temperature overnight. Water and EtOAc were added. The organic phase was separated, washed with H2O, then with 5% NaHCO3, dried over Na2SO4, concentrated in vacuo. The residue was purified by HPLC using a gradient of 20% CH3CN in H2O (containing 0.1% TFA) to 100% CH3CN over 80 min. Fractions containing the desired product were pooled, and lyophilized to give a powder (70 mg, yield: 31 %). MS 508 (M+H).

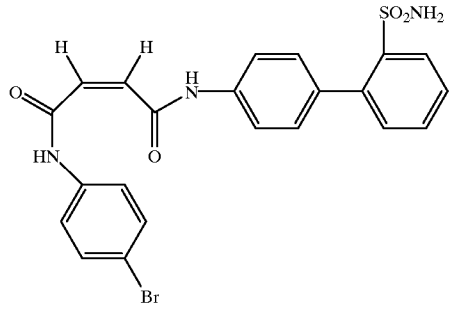
[0916] B. Preparation of N-(4-methoxyphenyl)-N'-(4-[(2-aminosulfonyl)phenyl]phenyl)-maleamic amide.

[0917] The compound N-(4-methoxyphenyl)-N'-(4-[(2-tert-butylaminosulfonyl)phenyl]phenyl)-maleamic amide (40 mg, 79 mol) was dissolved in TFA (3 mL). It was allowed to stand at room temperature overnight. TFA was removed in vacuo. The residue was purified by HPLC using a gradient of 5% CH3CN in H2O (containing 0.1% TFA) to 95% CH3CN over 60 min. Fractions containing the desired product were pooled, and lyophilized to give a powder (18 mg, yield: 51%). MS 452 (M+H) and 474 (M+Na).

[0918] ^1H NMR (CDCl3) δ 11.40 (br.s., 1H), 10.28 (br.s, 1H), 8.12 (d, 1H, J=8 Hz), 7.72 (d, 2H, J=8 Hz), 7.60 - 7.20 (m, 9H), 6.86 (AB type, 2H), 6.45 (br.s, 2H), 3.79 (s, 3H).

Example 17

[0919] N-(4-bromophenyl)-N'-(4-[(2-aminosulfonyl)phenyl]phenyl)-maleamic amide.



[0920] A. Preparation of N-(4-[(2-tert-butylaminosulfonyl)phenyl]phenyl)maleamic methyl ester.

[0921] To a solution of commercially available maleic acid monomethyl ester (277 mg, 2.13 mmol), 4-(2-tert-butylaminosulfonylphenyl)aniline (648 mg, 2.13 mmol) and triethylamine (0.593 mL, 4.26 mmol) in CH2Cl2 (20 mL), BOP (1.13 g, 2.55 mmol) was added. The mixture was stirred at room temperature overnight. More maleic acid monomethyl ester (50 mg, 0.385 mmol) was added. It was stirred for 3 hours. The CH2Cl2 solution was then washed with sat. NaHCO3, 1N HCl and sat. NaCl. The solution was dried over Na2SO4, concentrated in vacuo. The residue was purified by a silica gel column using a gradient of 10-40% EtOAc in hexane as solvents, to give the titled compound (360 mg, yield: 41%). MS 361 (M+H–^{t}Bu) and 439 (M+Na).

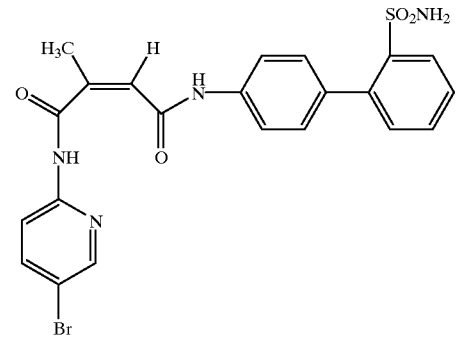
[0922] B. Preparation of N-(4-bromophenyl)-N'-(4-[(2-aminosulfonyl)phenyl]phenyl)-maleamic amide.

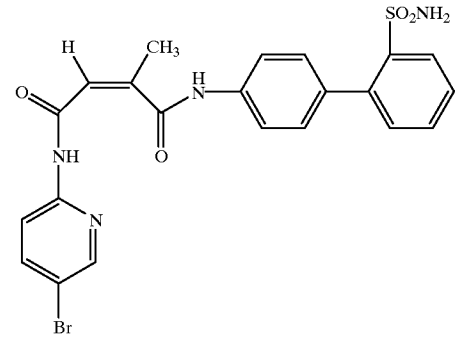
[0923] To a solution of 4-bromoaniline (93 mg, 0.543 mmol) in CH2Cl2 (5 mL) at room temperature, trimethylaluminum (0.82 mL, 2.0 M in hexane, 1.64 mmol) was added dropwise. After the solution was stirred for 30 min at room temperature compound N-(4-[(2-tert-butylaminosulfonyl)phenyl]phenyl)maleamic methyl ester (113 mg, 0.272 mmol) was added. The mixture was stirred at room temperature for 2 days. The solution was neutralized with 1N HCl to pH 2-3. Water and CH2Cl2 were added, and organic phase was separated, dried over Na2SO4, concentrated in vacuo. The residue was dissolved in TFA (4 mL). It was allowed to stand at room temperature overnight. TFA was removed in vacuo. The residue was purified by HPLC using a gradient of 5% CH3CN in H2O (containing 0.1% TFA) to 95% CH3CN over 60 min. Fractions containing the desired product were pooled, and lyophilized to give a powder (8 mg, yield: 6%). MS 500 and 502 (M+H), 522 and 524 (M+Na).

[0924] ^{1}H NMR (CD3OD) δ 8.09 (d, 1H, J=8 Hz), 7.68 (d, 2H, J=8 Hz), 7.64 - 7.28 (m, 9H), 6.45 (AB type, 2H).

Examples 18 and 19

[0925] Preparation of N^1-(5-bromopyridin-2-yl)-N^4-(4-[(2-aminosulfonyl)phenyl]phenyl)-2-methylmaleamic amide and N^1-(5-bromopyridin-2-yl)-N^4-(4-[(2-aminosulfonyl)phenyl]phenyl)-3-methylmaleamic amide.





[0926] A. Preparation of N-(5-bromopyridin-2-yl)-methylmaleimide.

[0927] A mixture of citraconic anhydride (1.00 mL, 11.1 mmol) and 2-amino-5-bromopyridine (1.93 g, 11.2 mmol) in toluene (60 mL) was heated to reflux overnight. The solution was cooled down, filtered. The filtrate was concentrated in vacuo to give a solid (2.10 g, yield: 71%). MS 267 and 269 (M+H).

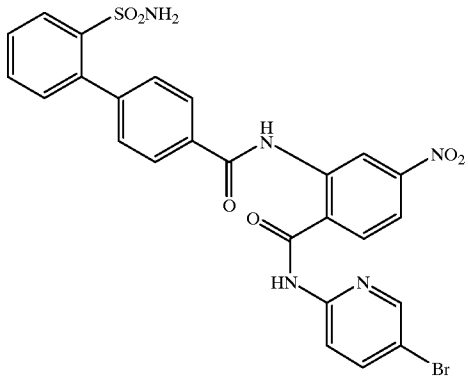
[0928] B. Preparation of N^t-(5-bromopyridin-2-yl)-N^4-(4-[(2-aminosulfonyl)phenyl]phenyl)-2-methylmaleamic amide and N^1-(5-bromopyridin-2-yl)-N^4-(4-[(2-aminosulfonyl)phenyl]phenyl)-3-methylmaleamic amide.

[0929] To the solution of 4-(2-aminosulfonylphenyl)aniline (0.170 g, 0.685 mmol) in CH2Cl2 (10 mL) at room temperature, trimethylaluminum (2.0 M in hexane, 2.00 mL, 4.00 mmol) was added dropwise, during which time, white gel-like precipitates came out the solution. It was stirred for 30 min. A solution of N-(5-bromopyridin-2-yl)-methylmaleimide (0.122 g, 0.457 mmol) in CH2Cl2 (5 mL) was added. It was stirred for 1 hour, during which time the precipitates started to dissolve, and the solution became clear. It was stirred for another 2 hours. 1N HCl was added to neutralize the solution to pH 2-3, which resulted in

precipitation. The precipitates were collected by filtration, dried on vacuum. The precipitates (75 mg, yield: 32%) were a mixture of 2-methyl and 3-methylmaleamic amide isomers in a ratio of 1:5. MS 515 and 517 (M+H), 537 and539 (M+Na).

Example 20

[0930] N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-4-nitrophenylcarboxamide.



[0931] Step 1: A solution of 2-amino-4-nitrobenzoic acid (182 mg, 1 mmol, 1 equiv) in 10 mL of methanol was treated with thionyl chloride in portions until complete reaction. The solvent was evaporated and the residue was dissolved in 10 mL of pyridine. To the solution were added 4-[(2-t-butylaminosulfonyl)phenyl]benzoic acid (330 mg, 1 equiv) and $POCl_3$ (0.93 mL, 10 equiv). The resulting mixture was stirred at rt overnight, quenched by slow addition of water, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and flash chromatographied to give methyl 2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonyl)amino-4-nitrobenzoate (430 mg, 84%).

[0932] MS found for $C_{25}H_{26}N_3O_7S$ $(M+H)^+$: 512.

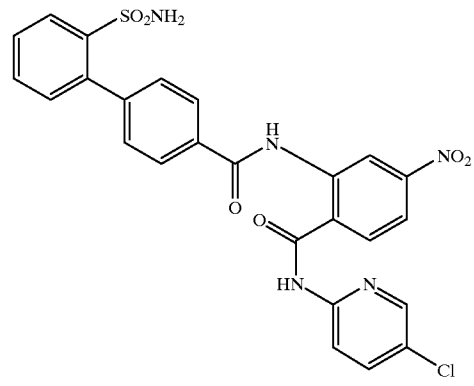
[0933] Step 2: To A solution of 2-amino-5-bromopridine (135 mg, 4.0 equiv) in 5 mL of methylene chloride treated with $AlMe_3$ (2M in hexane, 1 mL, 10 equiv) for 30 min was added methyl 2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonyl)amino-4-nitrobenzoate (100 mg, 0.2 mmol, 1 equiv). The mixture was stirred at rt overnight, quenched with saturated aqueous potassium sodium tartrate. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN gave N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-4-nitrophenylcarboxamide (42 mg, 36%).

[0934] MS found for $C_{25}H_{19}BrN_5O_6S$ $(M+H)^+$: 596.

Examples 21-23

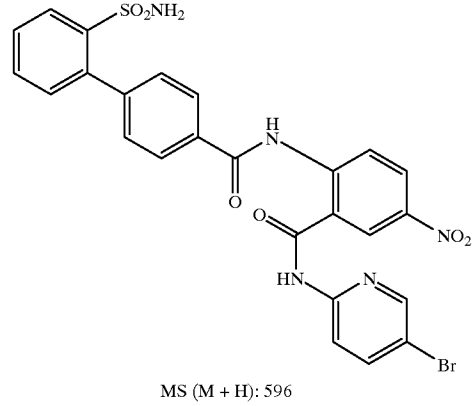
[0935] The following compounds were prepared according to the procedure described previously:

Example 21



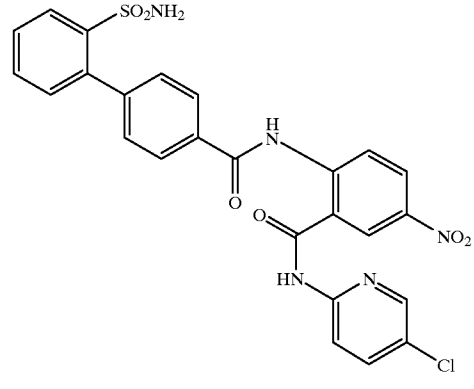
MS (M + H): 552

Example 22



MS (M + H): 596

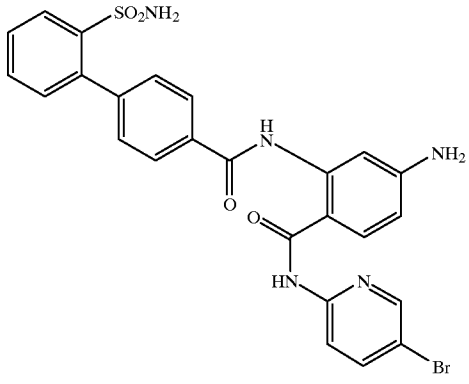
Example 23



MS (M + H): 552

Example 24

[0936] N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-4-aminophenylcarboxamide.

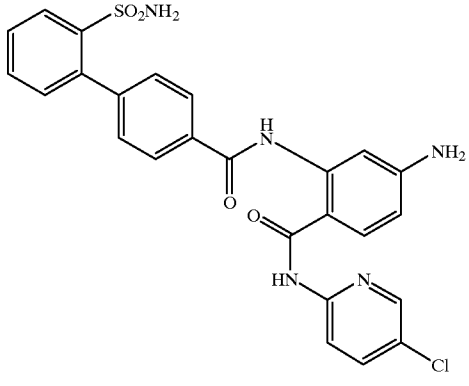


[0937] A solution of N-(5-bromo-2-pyridinyl)-(2-(4-[(2-t-butylsulfonyl)phenyl]phenylcarbonyl) amino)-4-nitrophenylcarboxamide (65 mg, 0.1 mmol, 1 equiv) in 10 mL of EtOAc was treated with $SnCl_2 2H_2O$ (90 mg, 4 equiv) at reflux for 4 h. The volatile was evaporated and the residue was redissolved in EtOAc, washed with saturated aqueous $NaHCO_3$ and 1N NaOH. The organic layer was dried over $MgSO_4$, filtered and evaporated to give N-(5-bromo-2-pyridinyl)-(2-(4-[(2-t-butylsulfonyl)phenyl]phenylcarbonyl) amino)-4-aminophenyl carboxamide, which was refluxed with 2 mL of TFA for 1 h. After removal of TFA by rotavap, the residue was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl] phenylcarbonyl)amino)-4-aminophenylcarboxamide (47 mg, 84%).

[0938] MS found for $C_{25}H_{21}BrN_5O_4S$ $(M+H)^+$: 566.

Example 25

[0939] N-(5-chloro-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-4-aminophenylcarboxamide.

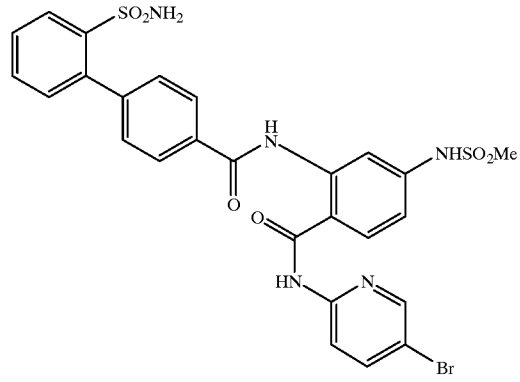


[0940] This compound was prepared according to the procedure described in example 50.

[0941] MS found for $C_{25}H_{21}ClN_5O_4S$ $(M+H)^+$: 522.

Example 26

[0942] N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-4-methylsulfonylaminophenylcarboxamide.

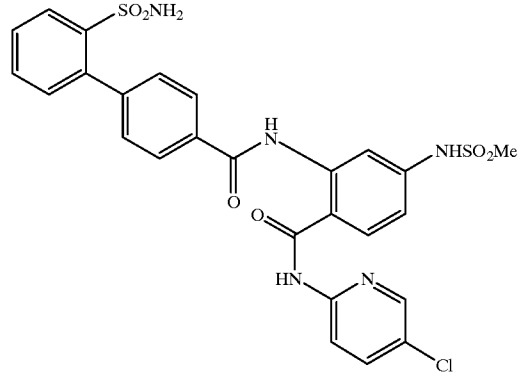


[0943] A solution of N-(5-bromo-2-pyridinyl)-(2-(4-[(2-t-butylsulfonyl)phenyl]phenylcarbonyl) amino)-4-aminophenyl carboxamide (62 mg, 0.1 mmol, 1 equiv) in 3 mL of CH_2Cl_2 was treated with MsCl (23 mg, 2 equiv) and TEA (0.5 mL) at rt for 4 h. The mixture was washed with water and dried over $MgSO_4$, filtered and evaporated. The residue was refluxed with 2 mL of TFA for 1 h. After removal of TFA by rotavap, the residue was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl] phenylcarbonyl)amino)-4-methylsulfonylaminophenylcarboxamide (33 mg, 52%).

[0944] MS found for $C_{26}H_{23}BrN_5O_6S2$ $(M+H)^+$: 644.

Example 27

[0945] N-(5-chloro-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-4-methylsulfonylaminophenylcarboxamide.

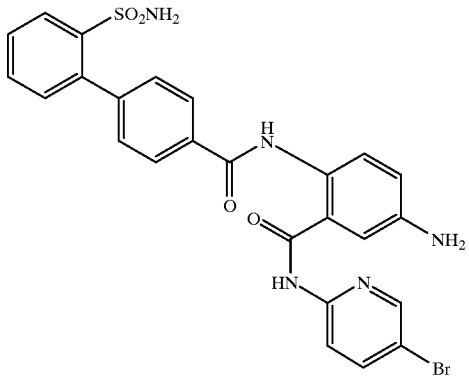


[0946] This compound was prepared according to the procedure described in example 53.

[0947] MS found for $C_{26}H_{23}ClN_5O_6S_2$ $(M+H)^+$: 600.

Example 28

[0948] N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-5-aminophenylcarboxamide.

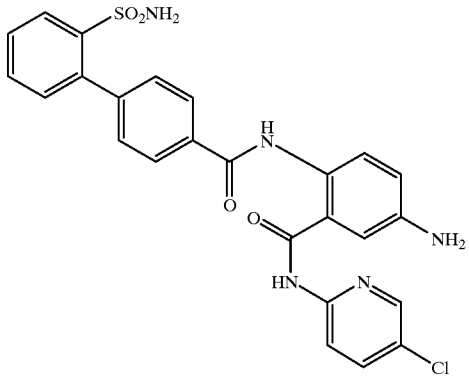


[0949] This compound was prepared according to the procedure described in example 50.

[0950] MS found for $C_{25}H_{21}BrN_5O_4S$ $(M+H)^+$: 566

Example 29

[0951] N-(5-chloro-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-5-aminophenylcarboxamide.

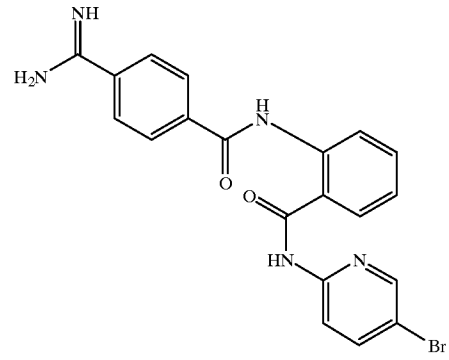


[0952] This compound was prepared according to the procedure described in example 50.

[0953] MS found for $C_{25}H_{21}ClN_5O_4S$ $(M+H)^{30}$: 522.

Example 30

[0954] N-(5-bromo-2-pyridinyl)-(2-(4-amidinophenylcarbonyl)amino)-phenylcarboxamide.



[0955] Step 1: A mixture of N-(5-bromo-2-pyridinyl)-(2-amino)phenylcarboxamide (292 mg, 1 mmol, 1.0 equiv), 4-cyano benzoyl chloride (165 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered, evaporated to give N-(5-bromo-2-pyridinyl)-(2-(4-cyanophenylcarbonyl)amino)-phenylcarboxamide (349 mg, 70%).

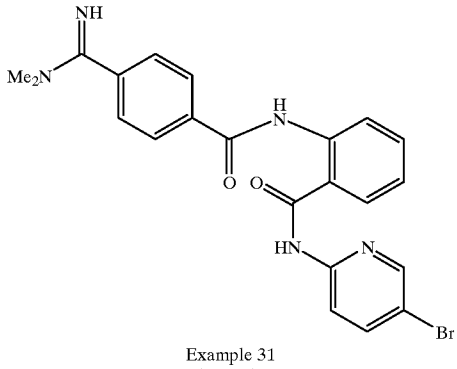
[0956] MS found for $C_{20}H_{14}BrN_4O_2$ $(M+H)^+$: 421.

[0957] Step 2: A stream of HCl(g) was bubbled through a 0° C. solution of N-(5-bromo-2-pyridinyl)-(2-(4-cyanophenylcarbonyl)amino)-phenylcarboxamide (49 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (40 mg) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give N-(5-bromo-2-pyridinyl)-(2-(4-amidinophenylcarbonyl)amino)-phenylcarboxamide (31 mg, 70%).

[0958] MS found for $C_{20}H_{17}BrN_5O_2$ $(M+H)^+$: 438.

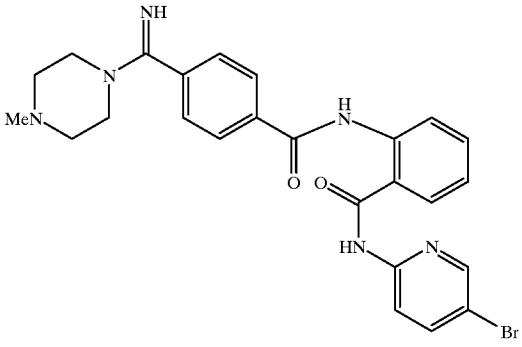
Examples 31-60

[0959] The following compounds were prepared according to the procedure described previously

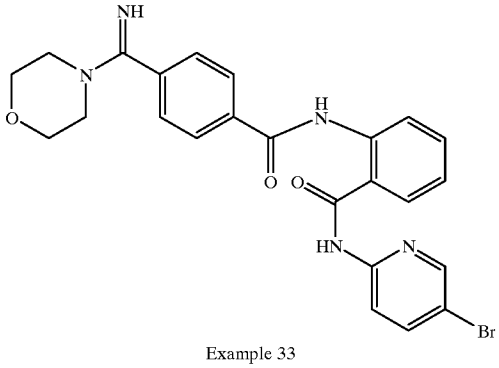


Example 31
MS (M + H): 466

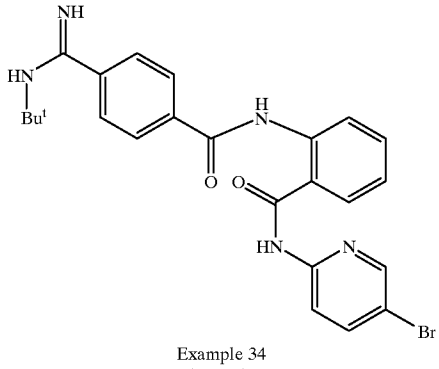
-continued



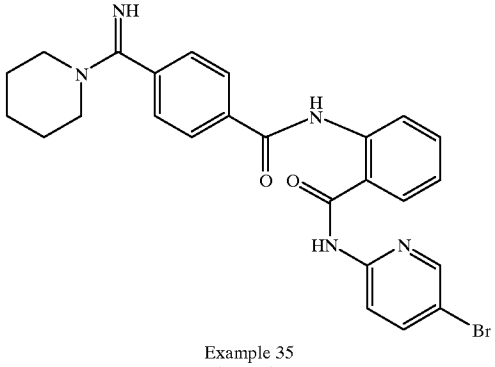
Example 32
MS (M + H): 521



Example 33
MS (M + H): 508

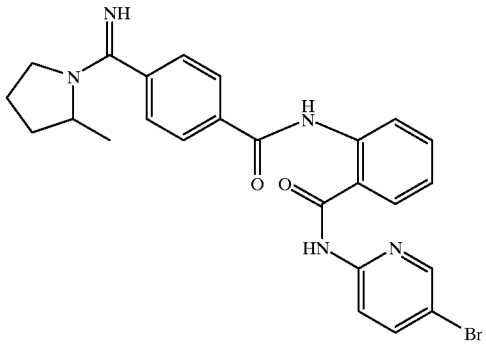


Example 34
MS (M + H): 494

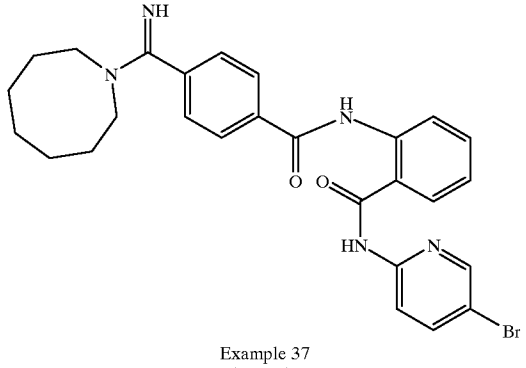


Example 35
MS (M + H): 506

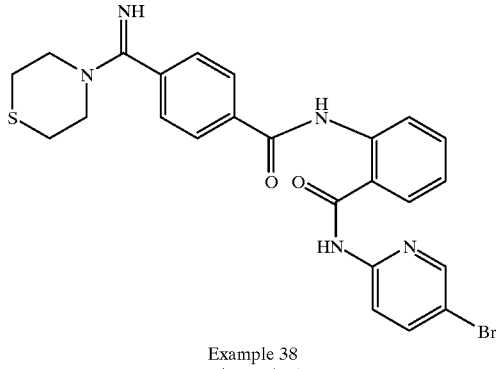
-continued



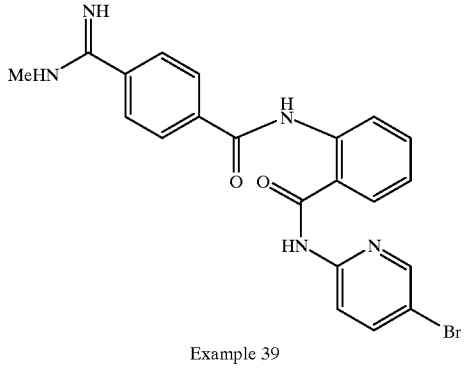
Example 36
MS (M + H): 506



Example 37
MS (M + H): 520

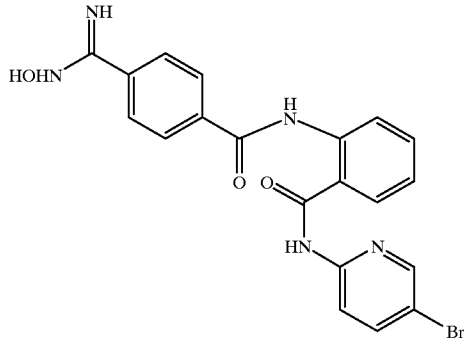


Example 38
MS (M + H): 524

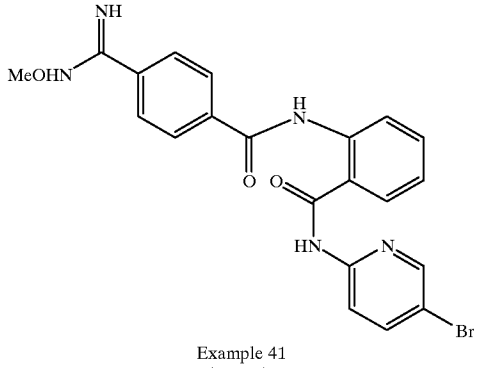


Example 39
MS (M + H): 452

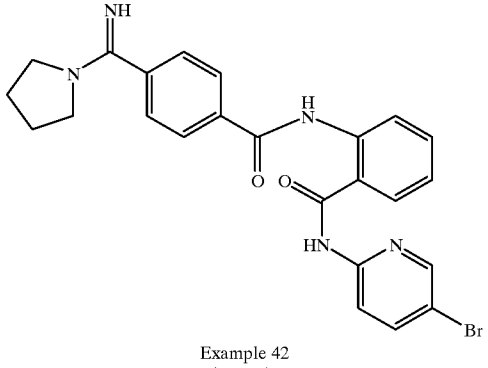
-continued



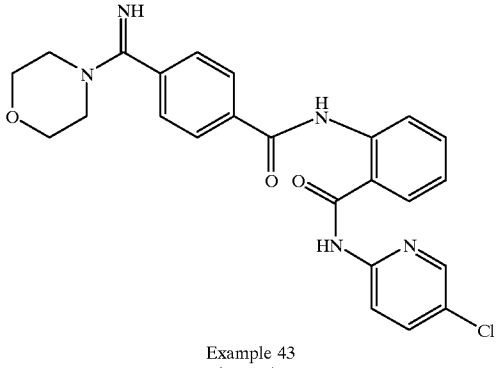
Example 40
MS (M + H): 454



Example 41
MS (M + H): 468

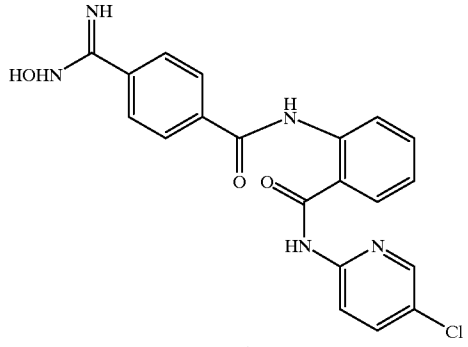


Example 42
MS (M + H): 492

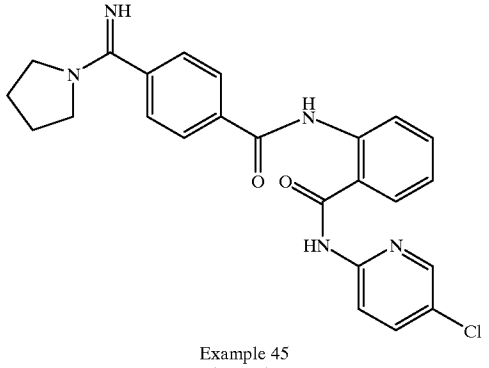


Example 43
MS (M + H): 464

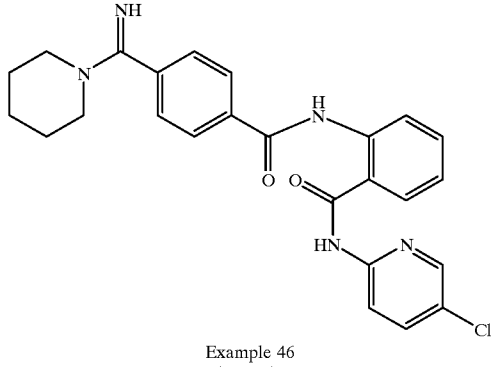
-continued



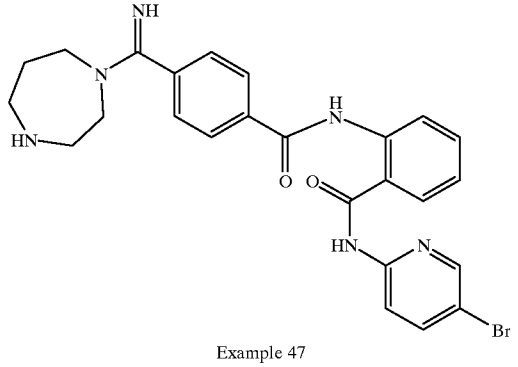
Example 44
MS (M + H): 410



Example 45
MS (M + H): 448

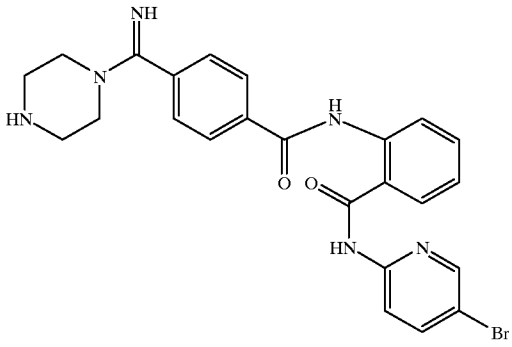


Example 46
MS (M + H): 462

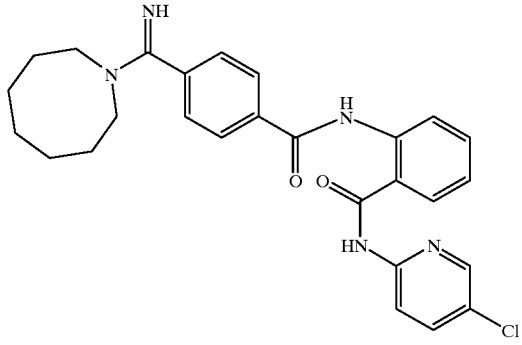


Example 47
MS (M + H): 521

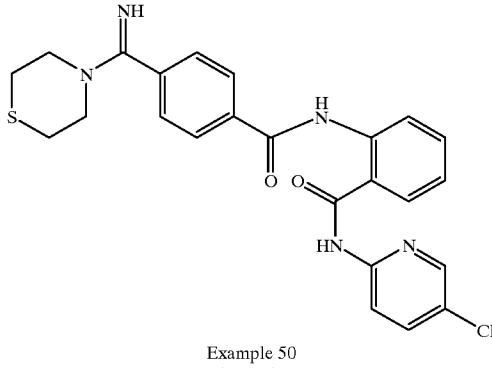
-continued



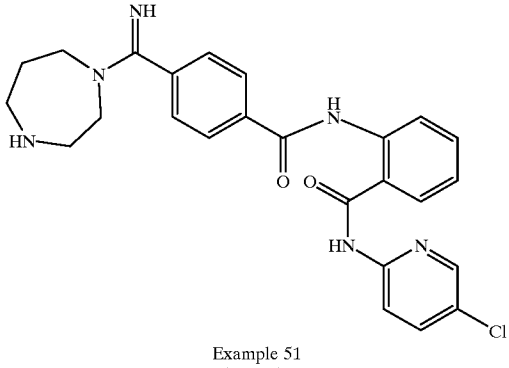
Example 48
MS (M + H): 507



Example 49
MS (M + H): 476

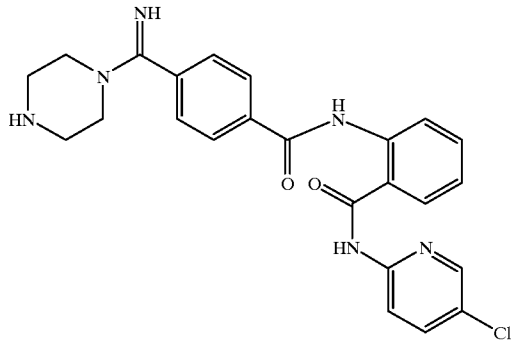


Example 50
MS (M + H): 480

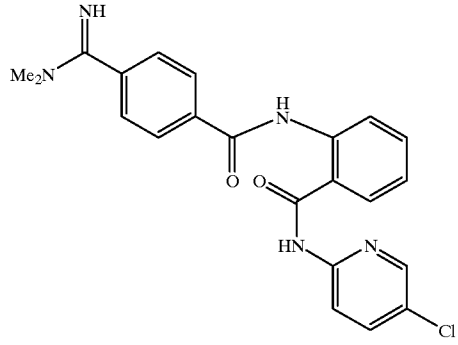


Example 51
MS (M + H): 477

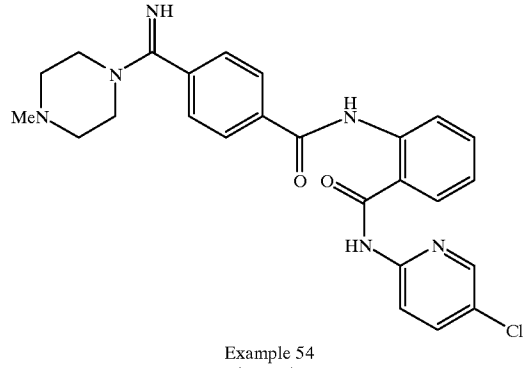
-continued



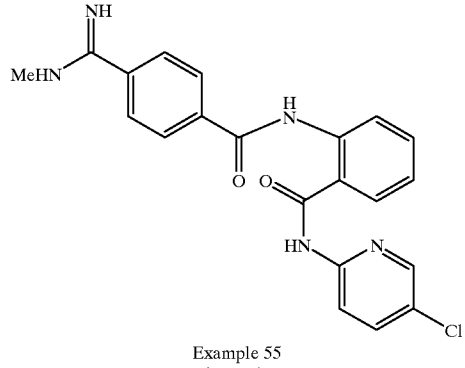
Example 52
MS (M + H): 463



Example 53
MS (M + H): 422

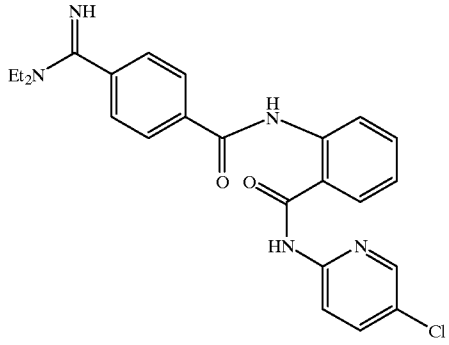


Example 54
MS (M + H): 477

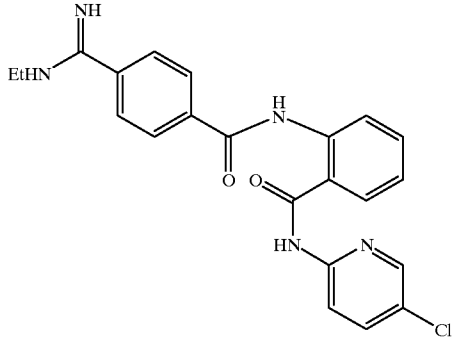


Example 55
MS (M + H): 408

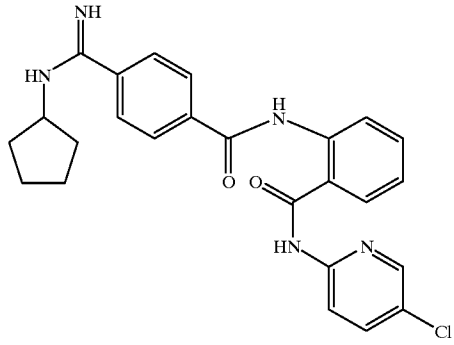
-continued



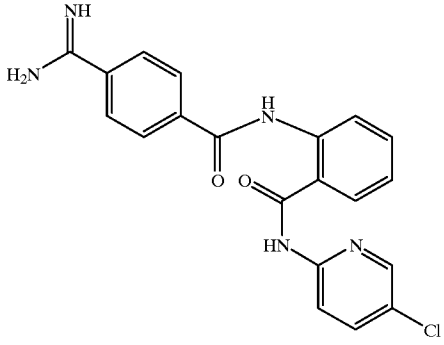
Example 56
MS (M + H): 22



Example 57
MS (M + H): 450

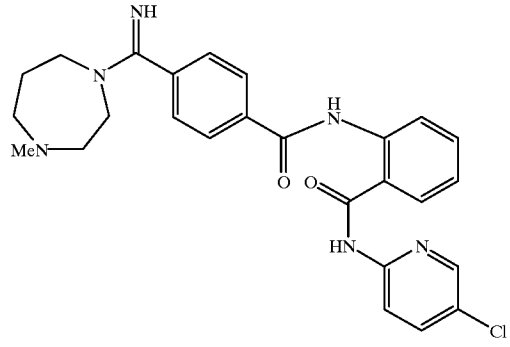


Example 58
MS (M + H): 462



Example 59
MS (M + H): 394

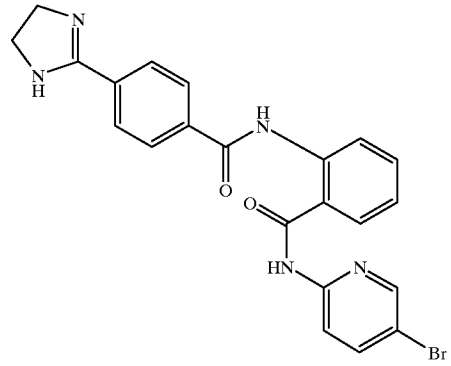
-continued



Example 60
MS (M + H): 491

Example 61

[0960] N-(5-bromo-2-pyridinyl)-(2-(4-(2-imidazolinyl)phenylcarbonyl)amino)-phenylcarboxamide.

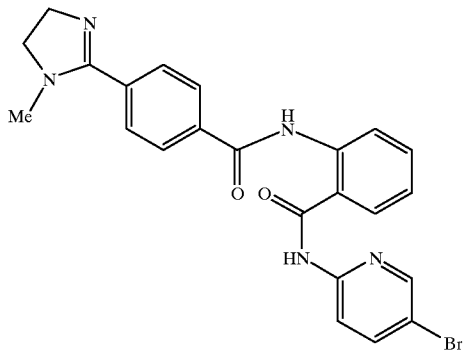


[0961] A stream of HCl(g) was bubbled through a 0° C. solution of N-(5-bromo-2-pyridinyl)-(2-(4-cyanophenylcarbonyl)amino)-phenylcarboxamide (49 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ethylene diamine (40 mg) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give N-(5-bromo-2-pyridinyl)-(2-(4-(2-imidazolinyl)phenylcarbonyl)amino)-phenylcarboxamide (41 mg, 89%).

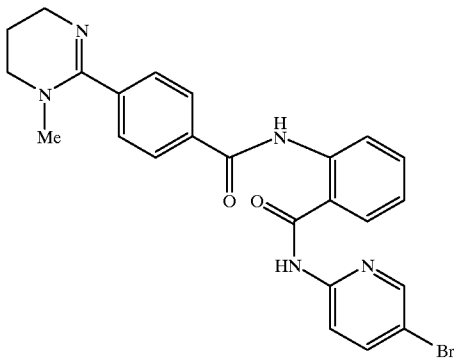
[0962] MS found for $C_{22}H_{19}BrN_5O_2$ $(M+H)^+$: 464.

Examples 62-70

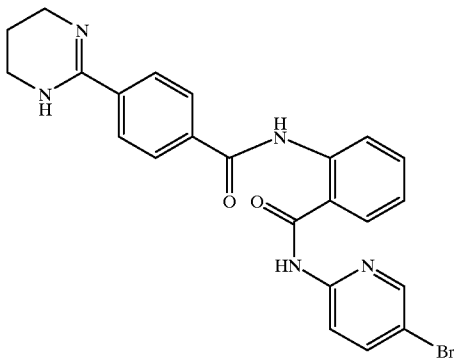
[0963] The following compounds were prepared according to the procedure previously described



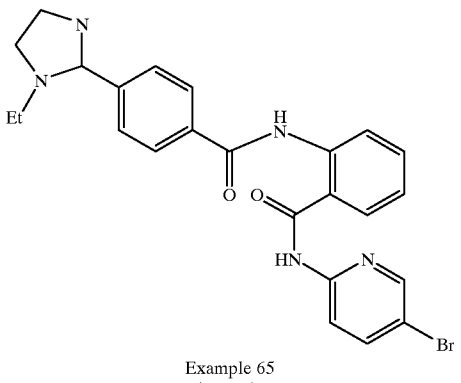
Example 62
MS (M + H): 478



Example 63
MS (M + H): 492

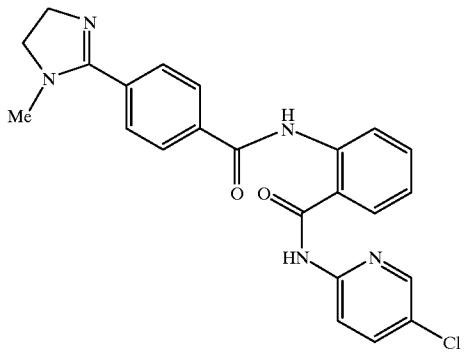


Example 64
MS (M + H): 478

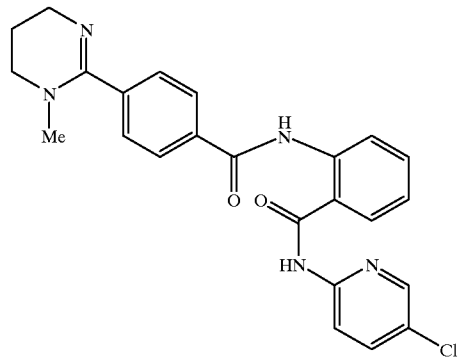


Example 65
MS (M + H): 492

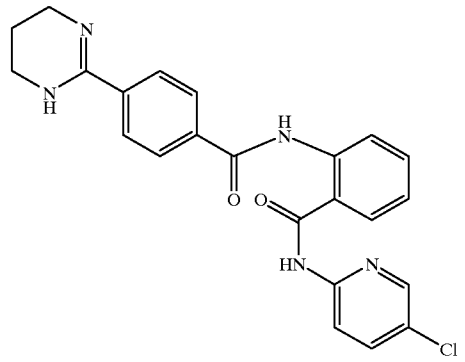
-continued



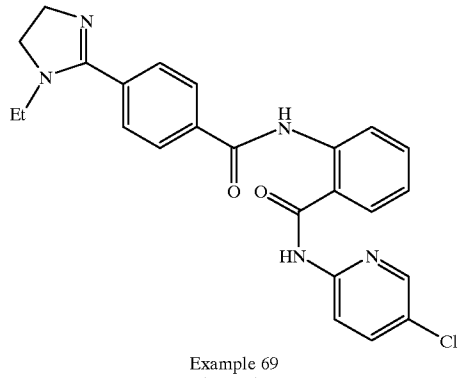
Example 66
MS (M + H): 434



Example 67
MS (M + H): 448

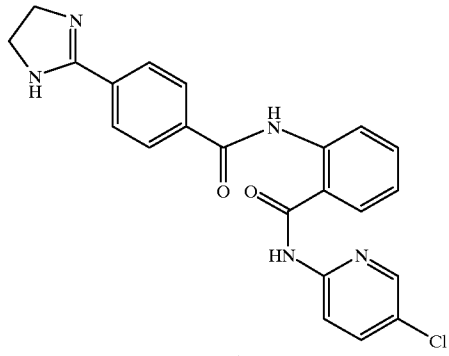


Example 68
MS (M + H): 434



Example 69
MS (M + H): 448

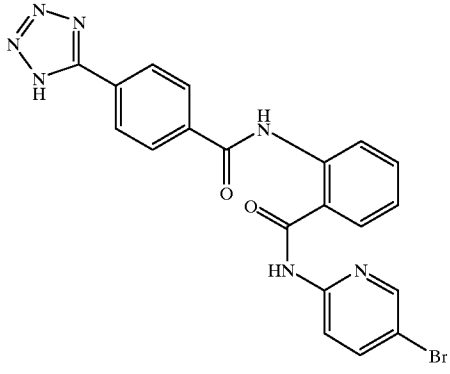
-continued



Example 70
MS (M + H): 420

Example 71

[0964] N-(5-bromo-2-pyridinyl)-(2-(4-(5-tetrazolyl)phenylcarbonyl)amino)-phenylcarboxamide.

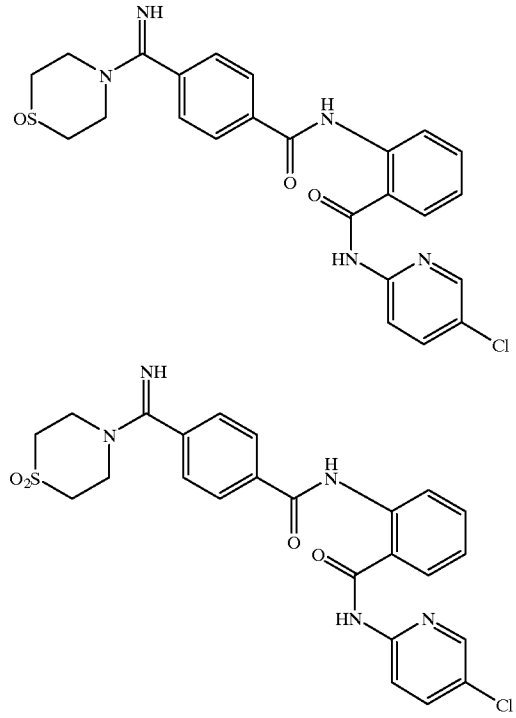


[0965] A mixture of N-(5-bromo-2-pyridinyl)-(2-(4-cyanophenylcarbonyl)amino)-phenylcarboxamide (49 mg, 0.1 mmol) and sodium azide (67 mg, 10 equiv) in 5 mL of DMF was heated at 100° C. for 24 h. The reaction mixture was diluted with EtOAc, washed with water, dried, filtered and evaporated. The residue was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give N-(5-bromo-2-pyridinyl)-(2-(4-(5-tetrazolyl)phenylcarbonyl)amino)-phenylcarboxamide (33 mg, 65%).

[0966] MS found for $C_{20}H_{15}BrN_7O_2$ $(M+H)^+$: 464.

Example 72 and Example 73

[0967] N-(5-bromo-2-pyridinyl)-(2-(4 [-[1,1-doxo(1,4-thiazaperhydroin-4-yl))iminimethylphenylcarbonyl)amino)-phenylcarboxamide and N-(5-bromo-2-pyridinyl)-(2-(4-[1-oxo(1,4-thiazaperhydroin-4-yl))iminimethylphenylcarbonyl)amino)-phenylcarboxamide.



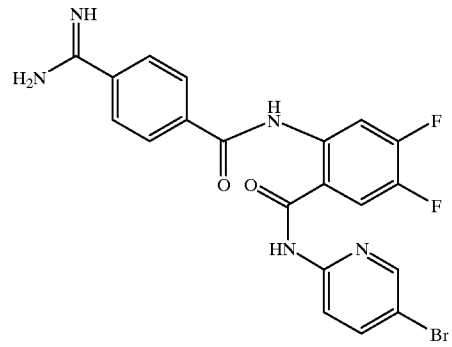
[0968] A mixture of N-(5-bromo-2-pyridinyl)-(2-(4-(1,4-thiazaperhydroin-4-yl)iminimethy]phenylcarbonyl)amino)-phenylcarboxamide (48 mg, 0.1 mmol) and and 3 mL of 30% hydrogen doxide was stirred at rt for 12 h. The reaction was quenched with solid $Na_2S_2O_3$. Purification by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN gave N-(5-bromo-2-pyridinyl)-(2-(4[-[1,1-doxo(1,4-thiazaperhydroin-4-yl))iminimethy]phenylcarbonyl)amino)-phenylcarboxamide (15 mg, 31%)

[0969] MS found for $C_{24}H_{23}ClN_5O_4S$ $(M+H)^+$: 512 and N-(5-bromo-2-pyridinyl)-(2-(4-[1 -oxo(1 ,4-thiazaperhydroin-4-yl))iminimethy]phenylcarbonyl)amino)-phenylcarboxamide (20 mg, 41%).

[0970] MS found for $C_{24}H_{23}ClN_5O_3S$ $(M+H)^+$: 496.

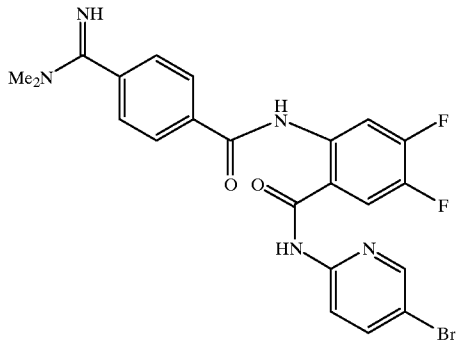
Examples 74-79

[0971] The following compounds were prepared according to the procedure previously described

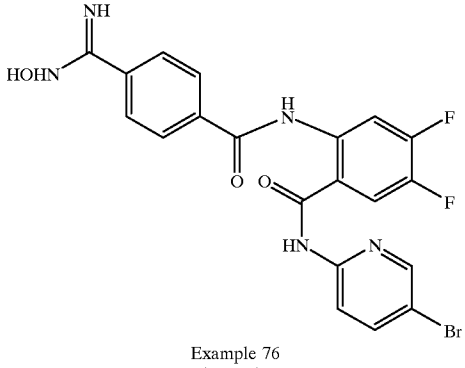


Example 74
MS (M + H): 474

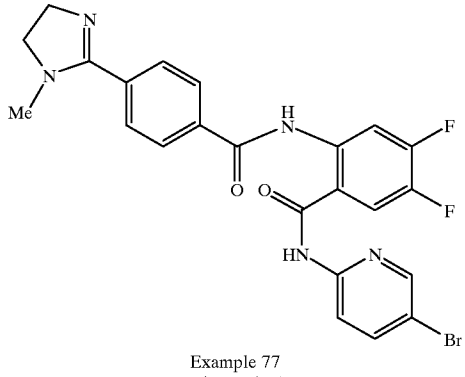
-continued



Example 75
MS (M + H): 502

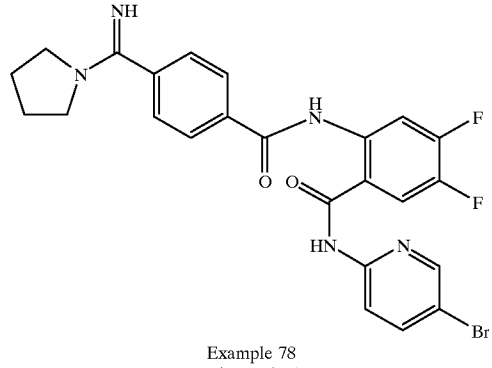


Example 76
MS (M + H): 490

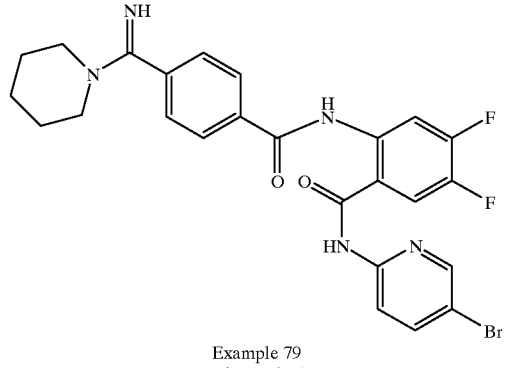


Example 77
MS (M + H): 514

-continued



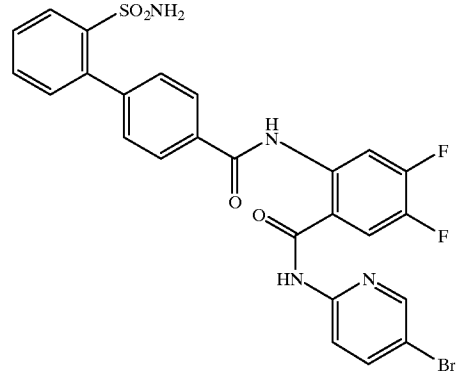
Example 78
MS (M + H): 528



Example 79
MS (M + H): 542

Example 80

[0972] N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)-4,5-difluorophenylcarboxamide.

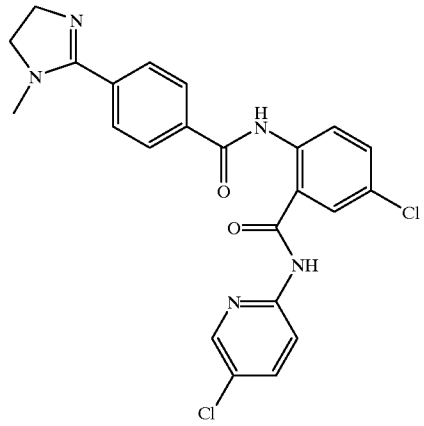


[0973] This compound was prepared according to the procedure previously described.

[0974] MS found for $C_{25}H_{18}BrF_2N_4O_4S$ $(M+H)^+$: 587.

Example 81

[0975]



[0976] Step 1: To a solution of 2-amino-5-chloropyridine (328 mg, 2.55 mmol) in tetrahydrofuran (5 ml) was 0.5M potassium bis(trimethylsilyl)amide in toluene (10 ml, 5.05 mmol) dropwise at −78° C. After stirred for additional 0.5 hr at −78° C., the mixture was added 5-chloroisatoic anhydride (0.5 g, 2.55 mmol) at −78° C. The mixture was warmed up to r.t gradually and stirred overnight. After quenched by saturated ammonium chloride solution, the mixture was extracted by ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated to give (2-amino-5-chlorophenyl)-N-(5-chloro(2-pyridyl))carboxamide (0.71 g. 100%).

[0977] MS found for C12H9Cl2N3O M^+=282, $(M+2)^+$= 284.

[0978] Step 2: To a solution of the compound of (2-amino-5-chlorophenyl)-N-(5-chloro(2-pyridyl))carboxamide (0.71 g, 2.52 mmol) in dichloromethane (10 ml) was added 3-cyanobenzoly chloride (417 mg, 2.52 mmol) and pyridine (0.611 ml, 7.55 mmol). The mixture was stirred at r.t. overnight. The precipitate was filtered and washed with dichloromethane to give N-{4-chloro-2-[N-(5 -chloro(2-pyridyl))carbamoyl]phenyl (4-cyanophenyl)carboxamide as a solid (683 mg, 66%).

[0979] MS found for C20H12Cl2N4O2 M^+=411, $(M+2)^+$=413.

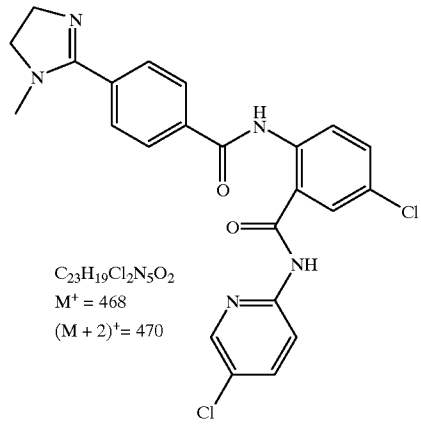
[0980] Step 3: To a solution of the compound of N-{4-chloro-2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}(4-cyanophenyl)carboxamide (683 mg, 1.66 mmol) in anhydrous pyridine (10 ml) and triethyl amine (1 ml) was saturated with hydrogen sulfide gas at 0° C. The mixture was stirred at r.t. overnight. After the evaporated the solvent, the residue was dissolved in anhydrous acetone (5 ml) and iodomethane (1 ml, 16.6 mmol) was added. The mixture was stirred under reflux condition for 2 hrs. After the evaporation of solvent, the residue was dissolved in anhydrous methanol (5 ml) and added a solution of N-methylethylenediamine (0.732 ml, 8.3 mmol) and acetic acid (1.5 ml) in anhydrous methanol (5 ml).The mixture was stirred under reflux condition for 2 hrs. After the evaporation of solvent, the crude residue was purified by RP-HPLC to give N-{4-chloro-2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}[4-(1-methyl(2-imidazolin-2-yl))phenyl]carboxamide as a white powder.

[0981] MS found for C23H19Cl2N5O2 M^+=468 $(M+2)^+$= 470.

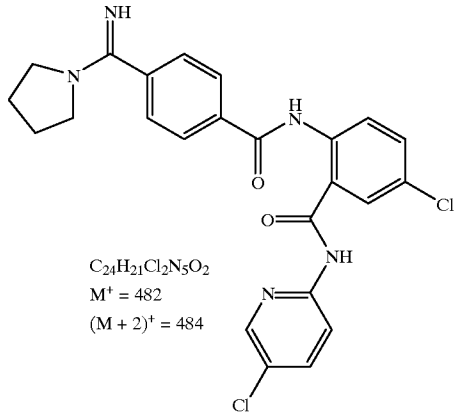
Examples 82-106

[0982] The following compounds were prepared according to the procedure previously described

Example 82



Example 83



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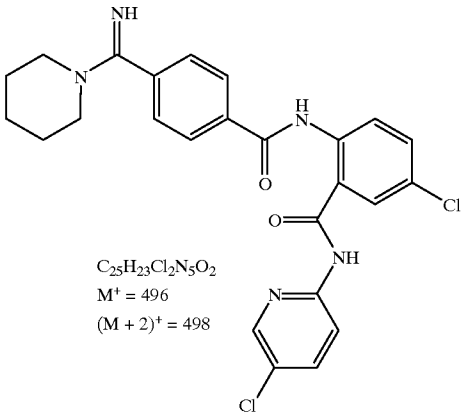
Example 84

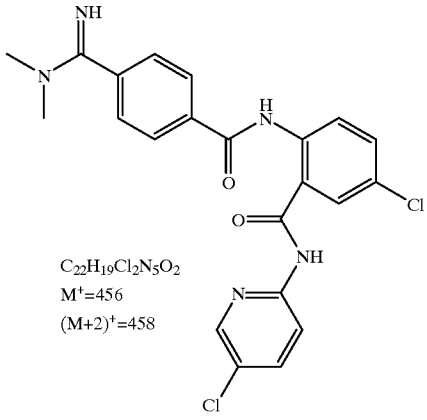


$C_{25}H_{23}Cl_2N_5O_2$

$M^+ = 496$

$(M + 2)^+ = 498$

Example 85

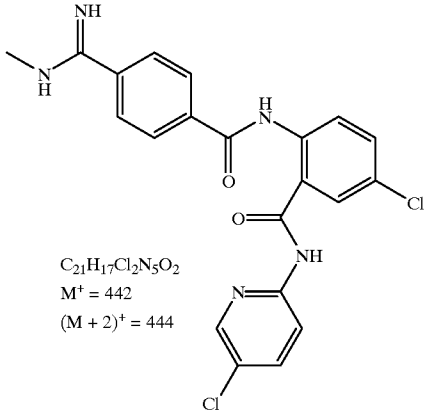


$C_{22}H_{19}Cl_2N_5O_2$

$M^+=456$

$(M+2)^+=458$

Example 86



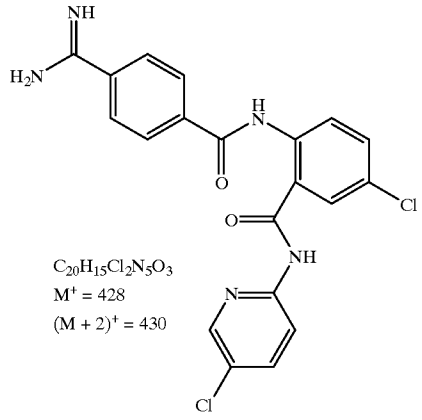
$C_{21}H_{17}Cl_2N_5O_2$

$M^+ = 442$

$(M + 2)^+ = 444$

-continued

Example 87

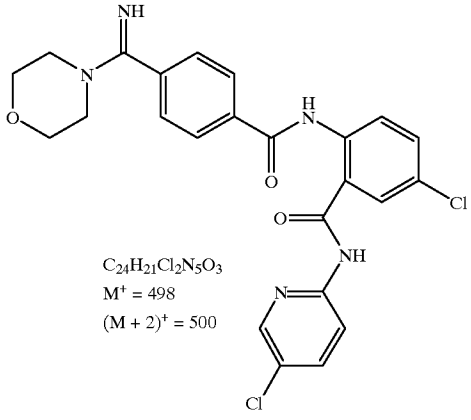


$C_{20}H_{15}Cl_2N_5O_3$

$M^+ = 428$

$(M + 2)^+ = 430$

Example 88

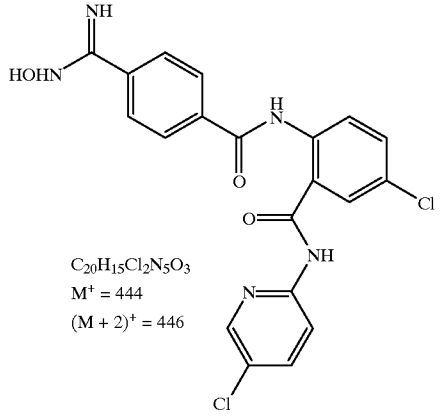


$C_{24}H_{21}Cl_2N_5O_3$

$M^+ = 498$

$(M + 2)^+ = 500$

Example 89



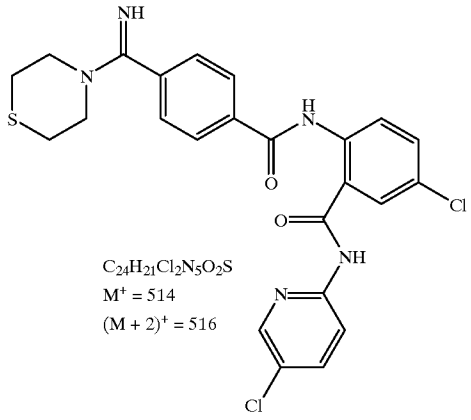
$C_{20}H_{15}Cl_2N_5O_3$

$M^+ = 444$

$(M + 2)^+ = 446$

-continued

Example 90

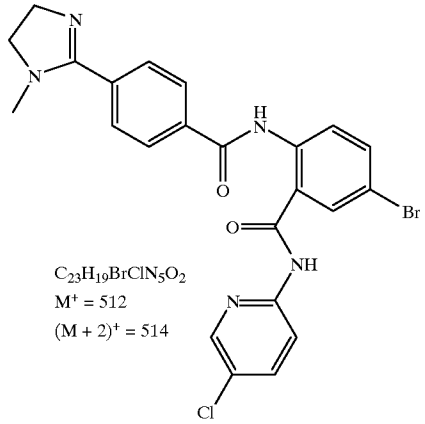


$C_{24}H_{21}Cl_2N_5O_2S$

$M^+ = 514$

$(M + 2)^+ = 516$

Example 91

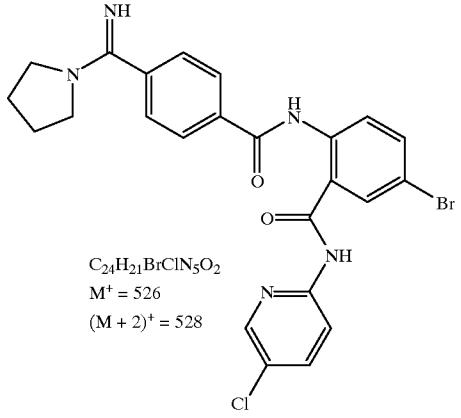


$C_{23}H_{19}BrClN_5O_2$

$M^+ = 512$

$(M + 2)^+ = 514$

Example 92



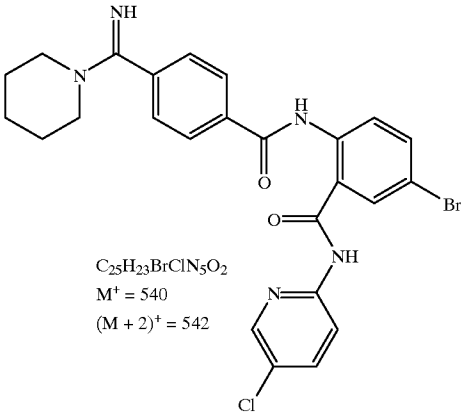
$C_{24}H_{21}BrClN_5O_2$

$M^+ = 526$

$(M + 2)^+ = 528$

-continued

Example 93

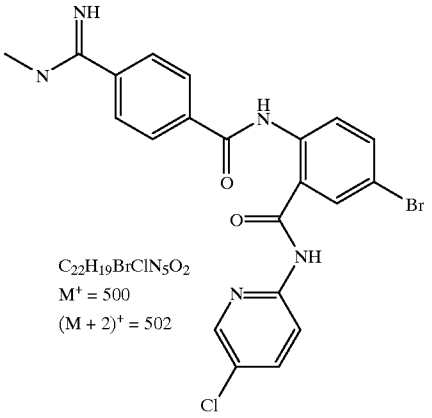


$C_{25}H_{23}BrClN_5O_2$

$M^+ = 540$

$(M + 2)^+ = 542$

Example 94

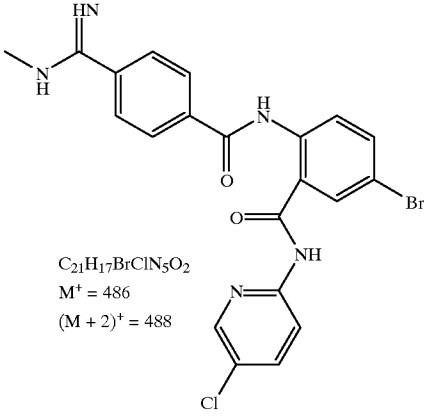


$C_{22}H_{19}BrClN_5O_2$

$M^+ = 500$

$(M + 2)^+ = 502$

Example 95



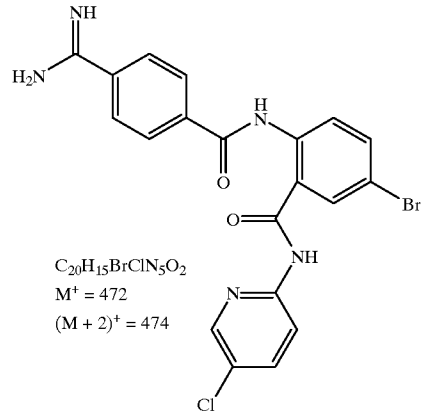
$C_{21}H_{17}BrClN_5O_2$

$M^+ = 486$

$(M + 2)^+ = 488$

-continued

Example 96

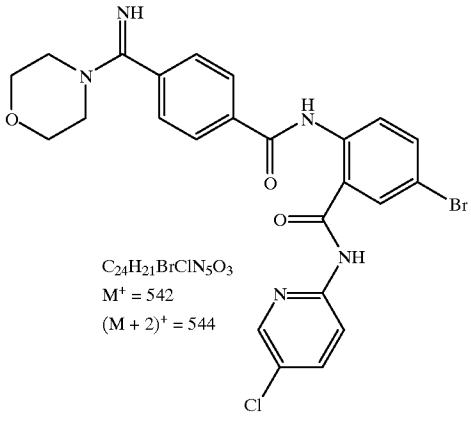


$C_{20}H_{15}BrClN_5O_2$

$M^+ = 472$

$(M + 2)^+ = 474$

Example 97

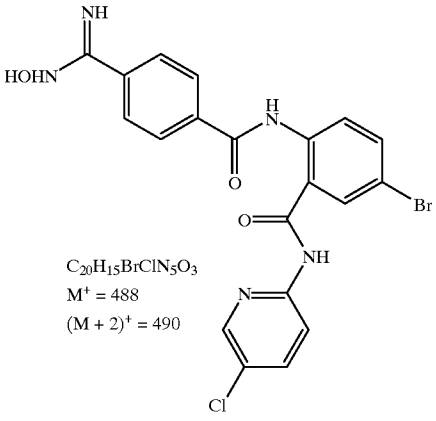


$C_{24}H_{21}BrClN_5O_3$

$M^+ = 542$

$(M + 2)^+ = 544$

Example 98



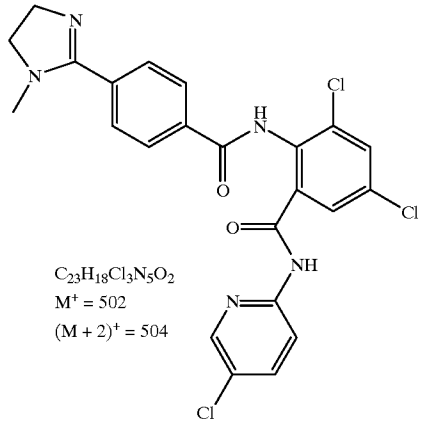
$C_{20}H_{15}BrClN_5O_3$

$M^+ = 488$

$(M + 2)^+ = 490$

-continued

Example 99

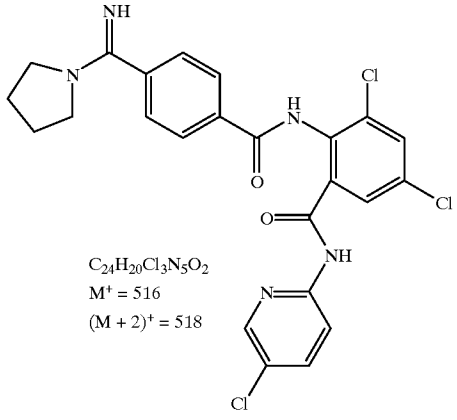


$C_{23}H_{18}Cl_3N_5O_2$

$M^+ = 502$

$(M + 2)^+ = 504$

Example 100

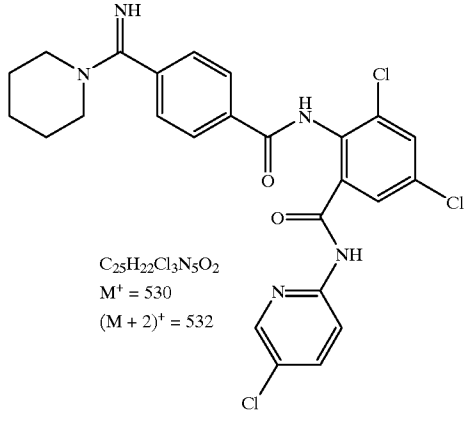


$C_{24}H_{20}Cl_3N_5O_2$

$M^+ = 516$

$(M + 2)^+ = 518$

Example 101



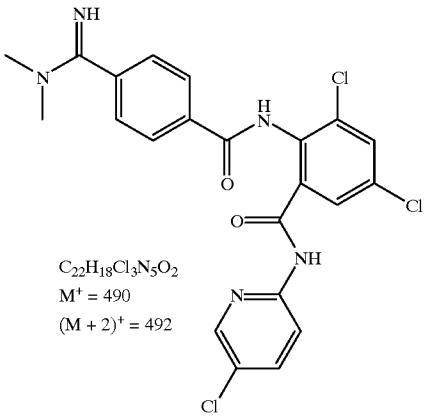
$C_{25}H_{22}Cl_3N_5O_2$

$M^+ = 530$

$(M + 2)^+ = 532$

-continued

Example 102

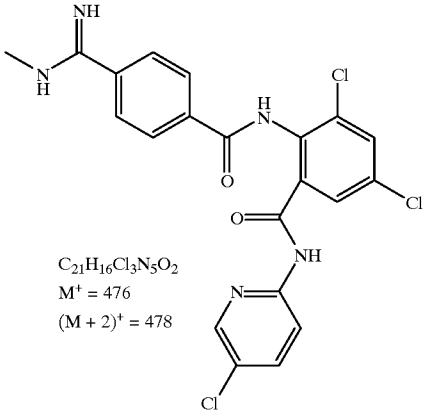


$C_{22}H_{18}Cl_3N_5O_2$

$M^+ = 490$

$(M + 2)^+ = 492$

Example 103

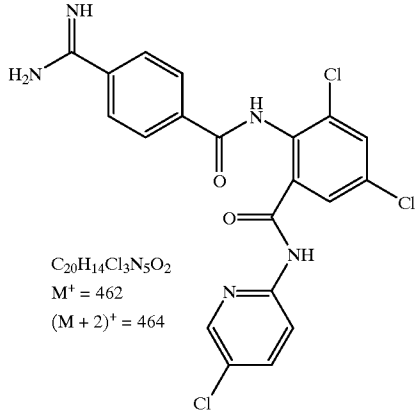


$C_{21}H_{16}Cl_3N_5O_2$

$M^+ = 476$

$(M + 2)^+ = 478$

Example 104



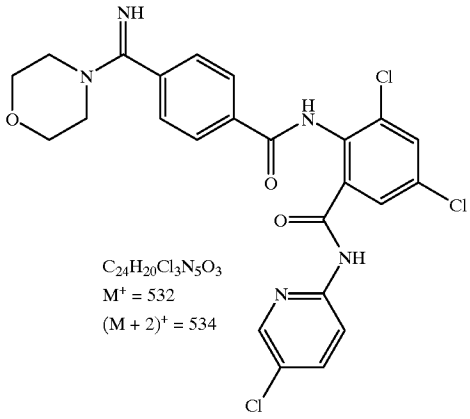
$C_{20}H_{14}Cl_3N_5O_2$

$M^+ = 462$

$(M + 2)^+ = 464$

-continued

Example 105

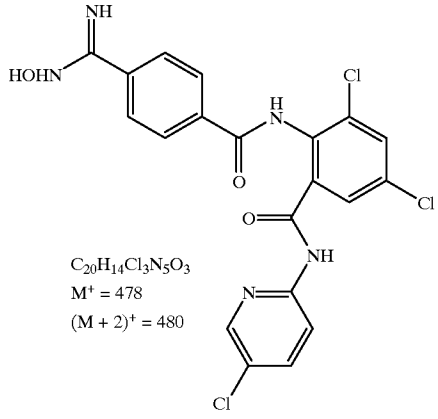


$C_{24}H_{20}Cl_3N_5O_3$

$M^+ = 532$

$(M + 2)^+ = 534$

Example 106

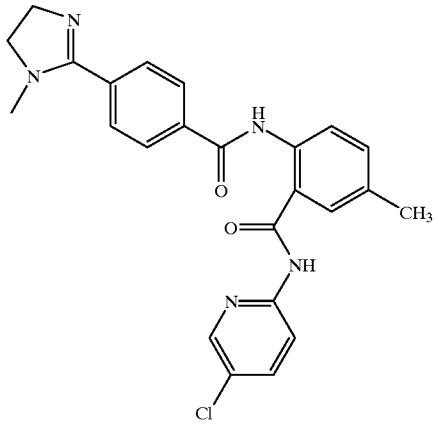


$C_{20}H_{14}Cl_3N_5O_3$

$M^+ = 478$

$(M + 2)^+ = 480$

Example 107



[0983] Step 1: To a solution of 5-methyl-2-nitrobenzoic acid (1 g, 5.52 mmol) in dichloromethane (5 ml) was added oxalyl chloride (0.964 ml , 11.04 mmol) and a few drops of dimethylformamide. The mixture was stirred at r.t. for 2 hrs. After the evaporation of the solvent, the residue was dissolved in dichloromethane (5 ml). 2-amino-5-chloropyridine (852 mg, 6.62 mmol) and pyridine (1.34 ml , 16.56 mmol) were added to the solution. The mixture was stirred at r.t. overnight. After the evaporation of the solvent, the crude residue was purified by silica gel column chromatography using solvent system 25% ethyl acetate in hexane as eluent to give N-(5-chloro(2-pyridyl))(5-methyl-2-nitrophenyl)carboxamide as a solid (1.48 g, 92%).

[0984] MS found for C13H10ClN3O3 $M^{+=291,}$ $(M+2)^+$= 293.

[0985] Step 2: To a solution of the compound of N-(5-chloro(2-pyridyl))(5-methyl-2-nitrophenyl)carboxamide (1.48 g, 5.1 mmol) in methanol (10 ml) was added 5% Pt/C (1.48 g, 0.19 mmol). The mixture was applied hydrogen balloon at r.t.for 2 hrs. After the filtration by Celite, the filtrate was concentrated to give (2-aminophenyl)-N-(2-pyridyl)carboxamide, C, chloride, N (1.36 g, 100%).

[0986] MS found for C13H12ClN3O M^+=262, $(M+2)^+$= 264.

[0987] Step 3: To a solution of the compound of (2-aminophenyl)-N-(2-pyridyl)carboxamide, C, chloride, N (1.36 g, 5.2 mmol) in dichloromethane (10 ml) was added 3-cyanobenzoly chloride (860 mg, 5.2 mmol) and pyridine (1.26 ml, 15.6 mmol). The mixture was stirred at r.t. overnight. After the evaporation of the solvent, the crude residue was purified by silica gel column chromatography using solvent system 25% ethyl acetate in hexane as eluent to give N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]-4-methylphenyl}(4-cyanophenyl)carboxamide as a solid (830 mg, 41%).

[0988] MS found for C21H15ClN4O2 M^+=390, $(M+2)^+$= 392.

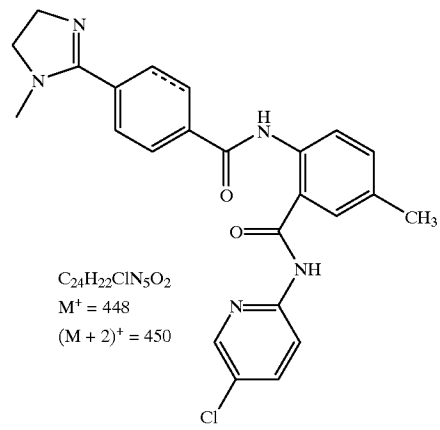
[0989] Step 4: To a lotion of the compound of N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]-4-methylphenyl}(4-cyanophenyl)carboxamide (830 mg, 2.1 mmol) in anhydrous methanol (5 ml) and ethyl acetate (10 ml) was saturated with hydrogen chloride gas at 0° C. The mixture was stirred at r.t. overnight. After the evaporated the solvent, the residue was dissolved in anhydrous methanol (5 ml) and N-methylethylenediamine (0.926 ml, 10.5 mmol) was added. The mixture was stirred under reflux condition for 2 hrs. After the evaporation of solvent, the crude residue was purified by RP-HPLC to give N- {2-[N-(5-chloro(2-pyridyl))carbamoyl]-4-methylphenyl}[4-(1 -methyl(2-imidazolin-2-yl))phenyl]carboxamide as a white powder.

[0990] MS found for C24H22ClN5O2 M^+=448, $(M+2)^+$= 450.

Examples 108-113

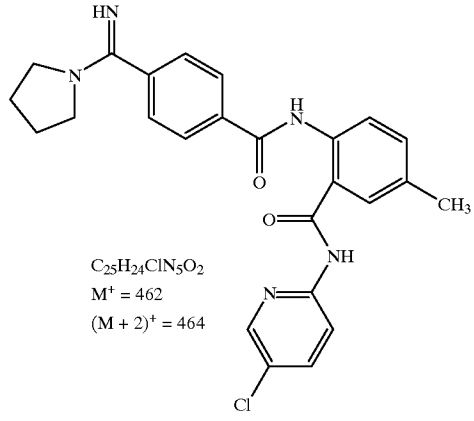
[0991] The following compounds were prepared according to the procedure previously described

Example 108



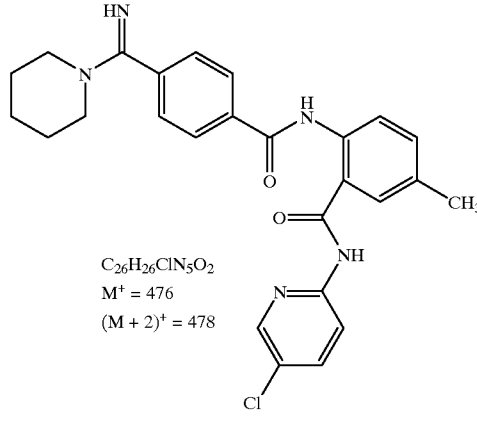
$C_{24}H_{22}ClN_5O_2$
M^+ = 448
$(M + 2)^+$ = 450

Example 109



$C_{25}H_{24}ClN_5O_2$
M^+ = 462
$(M + 2)^+$ = 464

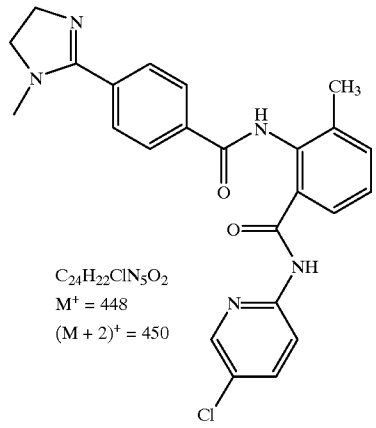
Example 110



$C_{26}H_{26}ClN_5O_2$
M^+ = 476
$(M + 2)^+$ = 478

-continued

Example 111

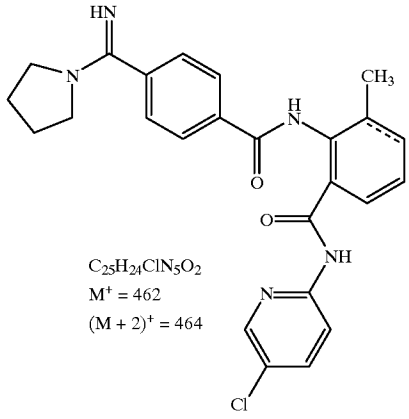


$C_{24}H_{22}ClN_5O_2$

$M^+ = 448$

$(M + 2)^+ = 450$

Example 112

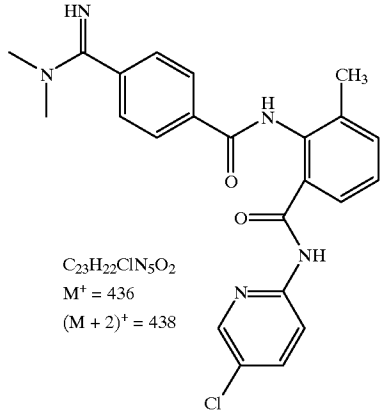


$C_{25}H_{24}ClN_5O_2$

$M^+ = 462$

$(M + 2)^+ = 464$

Example 113



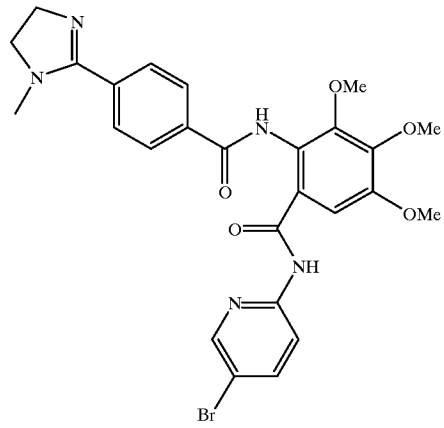
$C_{23}H_{22}ClN_5O_2$

$M^+ = 436$

$(M + 2)^+ = 438$

-continued

Example 114



[0992] Step 1: To a solution of 3,4,5-trimethoxy-2-nitrobenzoic acid (0.5 g, 1.95 mmol) in dichloromethane (5 ml) was added oxalyl chloride (0.34 ml, 3.9 mmol) and a few drops of dimethylformamide. The mixture was stirred at r.t. for 2 hrs. After the evaporation of the solvent, the residue was dissolved in dichloromethane (5 ml). 2-amino-5 -bromopyridine (0.81 g, 4.7 mmol) and pyridine (0.94 ml, 11.7 mmol) were added to the solution. The mixture was stirred at r.t. overnight. After the evaporation of the solvent, the crude residue was purified by silica gel column chromatography using solvent system 25% ethyl acetate in hexane as eluent to give N-(5-bromo(2-pyridyl))(3,4,5-trimethoxy-2-nitrophenyl)carboxamide as a solid (790 mg, 98%).

[0993] MS found for C15H14BrN3O6 M^+=412, $(M+2)^+$= 414.

[0994] Step 2: To a solution of the compound of N-(5-bromo(2-pyridyl))(3,4,5-trimethoxy-2-nitrophenyl)carboxamide (790 mg, 1.92 mmol) in ethyl acetate (5 ml) was added tin chloride (II) hydrate (1.73 g, 7.67 mmol). The mixture was stirred under reflux condition for 2 hrs. After filtered by Celite, the filtrate was added 1N sodium hydroxide solution and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated to give (2-amino-3,4,5-trimethoxyphenyl)-N-(5-bromo(2-pyridyl))carboxamide (570 mg, 77%).

[0995] MS found for C15H16BrN3O4 M^+=382, $(M+2)^+$= 384.

[0996] Step 3: To a solution of the compound of (2-amino-3,4,5-trimethoxyphenyl)-N-(5-bromo(2-pyridyl))carboxamide (570 mg, 1.49 mmol) in dichloromethane (5 ml) was added 3-cyanobenzoly chloride (247 mg, 1.49 mmol) and pyridine (0.362 ml, 4.48 mmol). The mixture was stirred at r.t. overnight. After the evaporation of the solvent, the crude residue was purified by silica gel column chromatography using solvent system 25% ethyl acetate in hexane as eluent

to give N-{6-[N-(5-bromo(2-pyridyl))carbamoyl]-2,3,4-trimethoxyphenyl}(4-cyanophenyl)carboxamide as a solid (680 mg, 69%).

[0997] MS found for C23H19BrN4O5 M^+=511, $(M+2)^+$= 513.

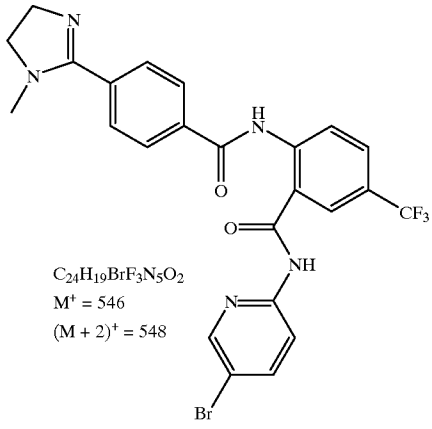
[0998] Step 4 To a lotion of the compound of N-{6-[N-(5-bromo(2-pyridyl))carbamoyl]-2,3,4-trimethoxyphenyl}(4-cyanophenyl)carboxamide (680 mg, 1.33 mmol) in anhydrous methanol (5 ml) and ethyl acetate (10 ml) was saturated with hydrogen chloride gas at 0° C. The mixture was stirred at r.t. overnight. After the evaporated the solvent, the residue was dissolved in anhydrous methanol (5 ml) and N-methylethylenediamine (0.586 ml, 6.65 mmol) was added. The mixture was stirred under reflux condition for 2 hrs. After the evaporation of solvent, the crude residue was purified by RP-HPLC to give N-{6-[N-(5-bromo(2-pyridyl))carbamoyl]-2,3,4-trimethoxyphenyl}[4-(1-methyl(2-imidazolin-2-yl))phenyl]carboxamide as a white powder (240 mg, 32%).

[0999] MS found for C26H26BrN5O5 M^+=568, $(M+2)^+$= 570.

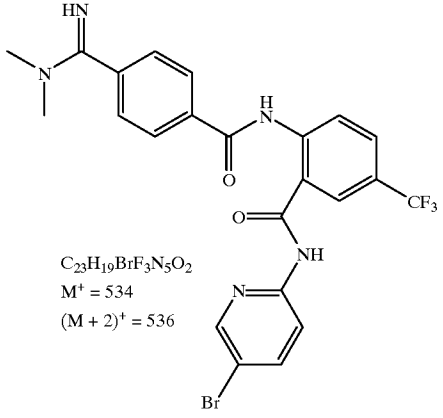
Examples 115-118

[1000] The following compounds were prepared according to the procedure previously described

Example 115

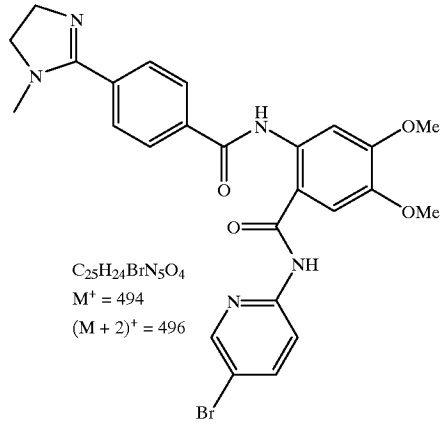


Example 116

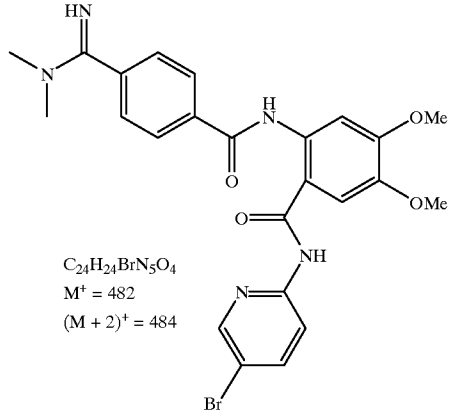


-continued

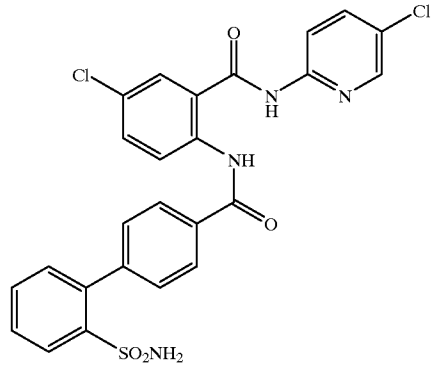
Example 117



Example 118



Example 119



[1001] Step 1: To a solution of 4-{2-{[(tert-butyl)amino}sulfonyl}phenyl}benzoic acid (167 mg, 0.5 mmol) in dichloromethane (5 ml) was added oxalyl chloride (0.09 ml, 1 mmol) and a few drops of dimethylformamide. The mixture was stirred at r.t. for 2 hrs. After the evaporation of the solvent, the residue was dissolved in dichloromethane (5 ml). The compound of (2-amino-5-chlorophenyl)-N-(5-

chloro(2-pyridyl))carboxamide (0.17 g, 0.6 mmol) and pyridine (0.122 ml, 1.5 mmol) were added to the solution. The mixture was stirred at r.t. overnight. The solvent was evaporated to give (2-{[4-(2-{[(tert-butyl)amino]sulfonyl}phenyl)phenyl]-carbonylamino}-5-chlorophenyl)-N-(5-chloro(2-pyridyl))carboxamide.

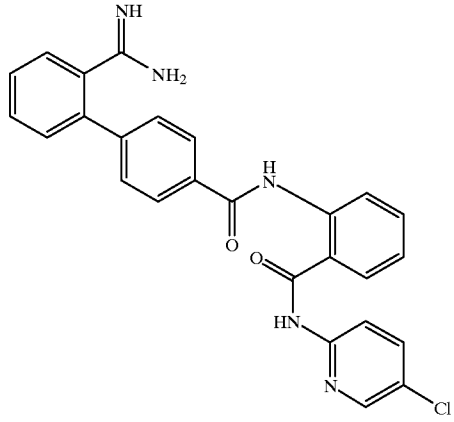
[1002] MS found for C29H26Cl2N4O4S M^+=597, $(M+2)^+$=599.

[1003] Step 2: The mixture of the compound of (2-{[4-(2-{[(tert-butyl)amino]sulfonyl}phenyl)phenyl]carbonylamino}-5-chlorophenyl)-N-(5-chloro(2-pyridyl))carboxamideexample 12 (0.5 mmol) in trifluoroacetic acid (5 ml) was stirred at r.t. for 5 hrs. After the evaporation of solvent, the crude residue was purified by RP-HPLC to give N-(5-chloro(2-pyridyl))(5-chloro-2-{[4-(2-sulfamoylphenyl)-phenyl]carbonylamino}phenyl)-carboxamide as a white powder (68 mg, 25%).

[1004] MS found for C25H18Cl2N4O4S M^+=541, $(M-2)^+$=543.

Example 120

[1005] 2-[4-(N-{2-[N-(5-chloro-2-pyridyl)carbamoyl]phenyl}carbamoyl)phenyl]-benzenecarboxamidine

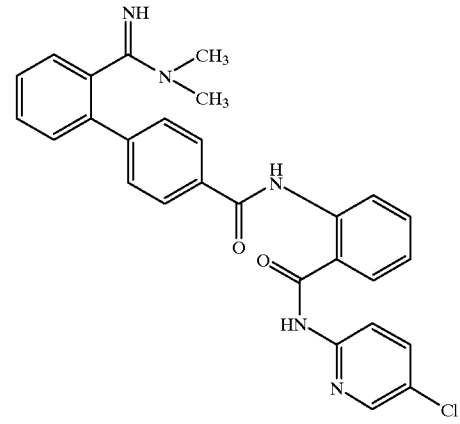


[1006] A stream of H_2S (g) was bubbled through a 0° C. solution of N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}[4-(2-cyanophenyl)phenyl]carboxamide (100 mg, 0.22 mmol, 1.0 equiv.) in 9 mL pyridine and 1 mL NEt_3 until saturation. The mixture was stirred at rt for 1 day and evaporated, The resulting residue was treated with MeI (94 mg, 0.663 mmol, 3.0 equiv.) in 10 mL acetone at reflux temperature for 1 hr and concentrated to dryness. The resulting residue was treated with a mixture of NH_4OAc (340 mg, 4.42 mmol, 20 equiv.) in 0.5 mL acetic acid and 2 mL methanol at 50° C. for 2 days. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.1% TFA in H_2O/CH_3CN to give 2-[4-(N-{2-[N-(5-chloro-2-pyridyl-)carbamoyl]phenyl}carbamoyl)phenyl]benzenecarboxamidine (15 mg, 15%).

[1007] MS found for $C_{26}H_{20}ClN_5O_2$ $(M+H)^+$: 470.

Example 121

[1008] (4-{2-[(dimethylamino)iminomethyl]phenyl}phenyl)-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}carboxamide

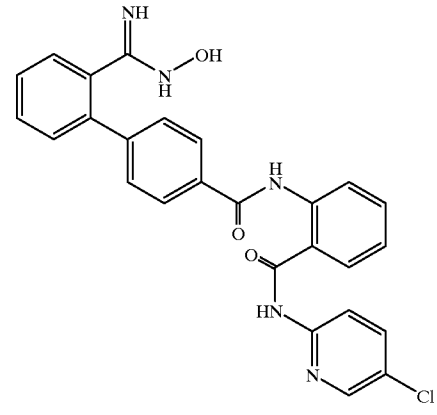


[1009] This compound was prepared according to the procedure previously described.

[1010] MS found for $C_{28}H_{24}ClN_5O_2$ $(M+H)^+$: 498.

Example 122

[1011] N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}{4-[2-((hydroxyamino)iminomethyl)-phenyl]phenyl}carboxamide

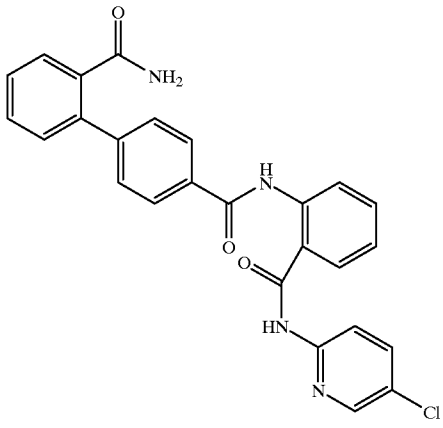


[1012] A mixture of N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}[4-(2-cyanophenyl)phenyl]carboxamide (14 mg, 0.03 mmol, 1.0 equiv.), hydroxyamine hydrochloride (6.25 mg, 0.09 mmol, 3.0 equiv.) and triethyl amine (0.03 mL, 0.3 mmol, 10.0 equiv.) in ethanol (3 mL) was stirred at rt for 6 days, concentrated and HPLC (C18 reversed phase) eluting with 0.1% TFA in H_2O/CH_3CN to give N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}{4-[2-((hydroxyamino)iminomethyl) phenyl]phenyl}carboxamide (4 mg, 27.5%).

[1013] MS found for $C_{26}H_{20}ClN_5O_3$ $(M+H)^+$: 486.

Example 123

[1014] 2-[4-(N-{2-[N-(5-chloro-2-pyridyl)carbamoyl] phenyl}carbamoyl)phenyl]benzamide

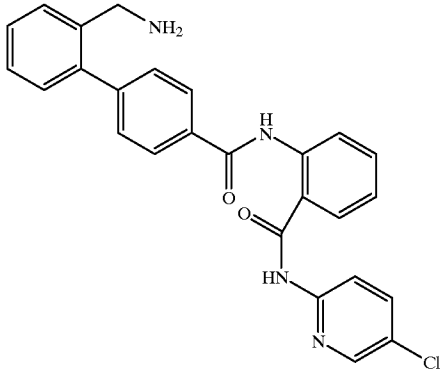


[1015] This compound was obtained as oneof the side product in Example 122.

[1016] MS found for $C_{26}H_{19}ClN_4O_3$ $(M+H)^+$: 471

Example 124

[1017] {4-[2-(aminomethyl)phenyl]phenyl}-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]-phenyl}carboxamide

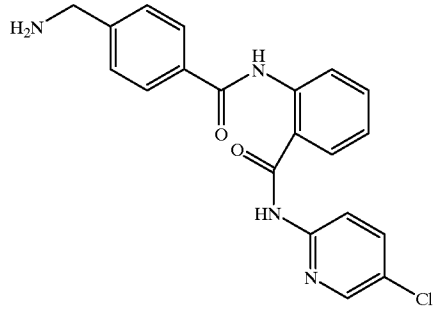


[1018] A mixture of N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}[4-(2-cyanophenyl)phenyl] carboxamide (200 mg, 0.442 mmol, 1.0 equiv.), cobalt chloride (86 mg, 0.664 mmol, 1.5 equiv.) and sodium borohydride (50 mg, 1.33 mmol, 3.0 equiv.) in DMF (15 mL) was stirred at 0° C. to rt for 3 days. The reaction was quenched with ice cubes, diluted with DCM (100 mL) and filtered through celite. The filtrate was washed with saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, evaporated and HPLC (C18 reversed phase) eluting with 0.1% TFA in H_2O/CH_3CN gave {4-[2-(aminomethyl)phenyl]phenyl}-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl] phenyl}carboxamide (87 mg, 43%).

[1019] MS found for $C_{26}H_{21}ClN_4O_2$ $(M+H)^+$: 457.

Example 125

[1020] [4-(aminomethyl)phenyl]-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}carboxamide

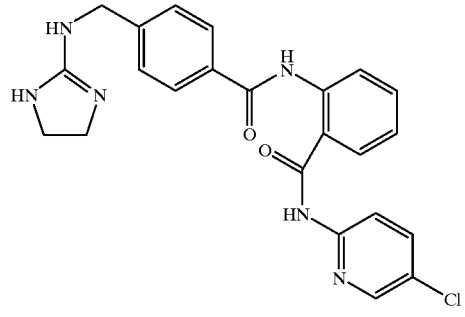


[1021] A mixture of N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}(4-cyanophenyl)carboxamide (1 g, 2.6 mmol, 1.0 equiv.), cobalt chloride (0.5 g, 3.85 mmol, 1.5 equiv.) and sodium borohydride (0.295 g, 7.8 mmol, 3.0 equiv.) in DMF (20 mL) was stirred at 0° C. to rt for 2.5 hr. The reaction was quenched with ice cubes, diluted with ethyl acetate (100 mL) and filtered through celite. The filtrate was washed with saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, evaporated and HPLC (C18 reversed phase) eluting with 0.1% TFA in H_2O/CH_3CN gave [4-(aminomethyl)phenyl]-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}carboxamide (320 mg, 30%).

[1022] MS found for $C_{20}H_{17}ClN_4O_2$ $(M+H)^+$: 381.

Example 126

[1023] N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}{4-[(2-imidazolin-2-ylamino)methyl]-phenyl}carboxamide

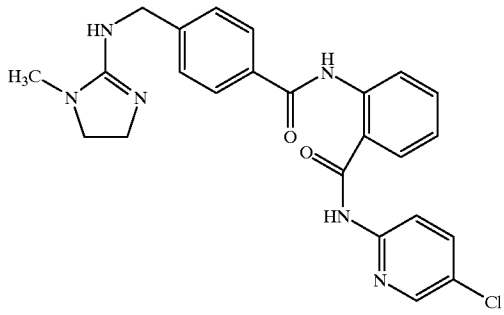


[1024] A mixture of [4-(aminomethyl)phenyl]-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}carboxamide (80 mg, 0.21 mmol), 2-methylthio-2-imidazoline hydriodide (77 mg, 0.315 mmol, 1.5 equiv.) and triethyl amine (0.5 mL) in 1 mL DMF was stirred at room temperature overnight, concentrated to dryness and HPLC (C18 reversed phase) eluting with 0.1% TFA in H_2O/CH_3CN gave N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}{4-[(2-imidazolin-2-ylamino)methyl]phenyl}carboxamide (13.5 mg, 15%).

[1025] MS found for $C_{23}H_{21}ClN_6O_2$ $(M+H)^+$: 449

Example 127

[1026] N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}(4-{[(1-methyl(2-imidazolin-2-yl))amino]methyl}phenyl)carboxamide



[1027] Step 1: To the boiling solution of 2-methylthio-2-imidazoline hydriodide (I g, 8.4 mmol) in methanol (10 mL) was added MeI (0.78 mL, 12.6 mmol, 1.5 equiv.) dropwise. The reaction mixture was stirred at reflux temperature for 1 hr, concentrated and crystallized with ether to give 1-methyl-2-methylthio-2-imidazoline (1.1 g, 100%).

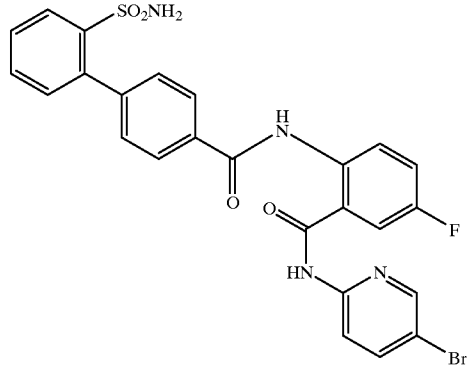
[1028] MS found for $C_5H_{10}N_2S$ $(M+H)^+$: 131.

[1029] Step 2: A mixture of [4-(aminomethyl)phenyl]-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl carboxamide (74 mg, 0.195 mmol), 1-methyl-2-methylthio-2-imidazoline (25 mg, 0.195 mmol), NEt3 (2 mL) and pyridine (5 mL) was stirred at 80° C. overnight, concentrated and HPLC (C18 reversed phase)eluting with 0.1% TFA in H2O/CH3CN gave N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}(4-{[(1-methyl(2-imidazolin-2-yl))amino]methyl}phenyl)carboxamide (52 mg, 65%).

[1030] MS found for $C_{24}H_{23}ClN_6O_2$ $(M+H)^+$: 463.

Example 128

[1031] N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)-5-fluorophenylcarboxamide.



[1032] Step 1: A solution of 5-fluoro-2-nitrobenzoic acid (10.0 g, 54 mmol, 1.0 equiv), 2-amino-5-bromopyridine (12.2 g, 1.3 equiv), in 80 mL of pyridine was treated with phosphorous oxychloride (25.3 g, 3.0 equiv) for 30 min. The volatile was evaporated and the residue was redissolved into EtOAc, washed with 1N HCl, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The organic layer was dried over Na_2SO_4, filtered, and evaporated. The volatile was evaporated, and the product was triturated with diethyl ether to give N-(5-bromo-2-pyridinyl)-(2-nitro)-5-fluorophenylcarboxamide (12.5 g, 68%).

[1033] MS found for $C_{12}H_7BrFN_3O_3$ $(M+H)^+$: 340, 342.

[1034] Step 2: A solution of N-(5-bromo-2-pyridinyl)-(2-nitro)-5-flurophenylcarboxamide (2.0 g, 5.88 mmol, 1.0 equiv) in 30 mL of EtOAc was treated with $SnCl_2$ $2H_2O$ (5.90 g, 4 equiv) at reflux for 4 h. The volatile was evaporated and the residue was redissolved in EtOAc, washed with saturated aqueous $NaHCO_3$ and 1N NaOH. The organic layer was dried over $MgSO_4$, filtered and evaporated to N-(5-bromo-2-pyridinyl)-(2-amino)-5-fluorophenylcarboxamide (1.79 g, 98%).

[1035] MS found for $C_{12}H_9BrFN_3O$ $(M+H)^+$: 310, 312.

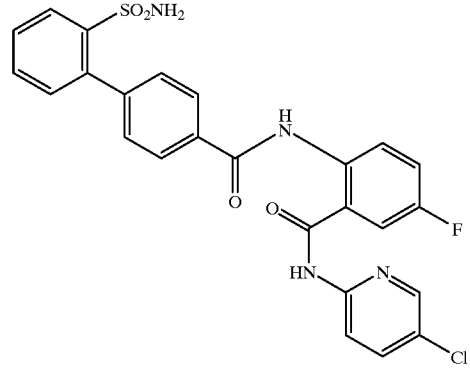
[1036] Step 3: A mixture of N-(5-bromo-2-pyridinyl)-(2-amino)-5-fluorophenylcarboxamide (0.310 g, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoyl chloride (0.430 g, 1.3 equiv), pyridine (2 mL) in 10 mL of dichloromethane was stirred at rt overnight The volatile was evaporated and the residue was redissolved into EtOAc, washed with 1N HCl, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The organic layer was dried over Na_2SO_4, filtered, and evaporated. The intermediate was reacted into 5 mL of trifluoroacetic acid at rt overnight. TFA was then evaporated and the product was triturated with diethyl ether, and then with chloroform to give N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)-5-fluorophenylcarboxamide (120 mg, 21%).

[1037] MS found for $C_{25}H_{18}BrFN_4O_4S$ $(M+H)^+$: 569, 571.

Example 129

[1038]

Example 129



[1039] This compound was prepared according to the procedure described in example 2 with the exception of

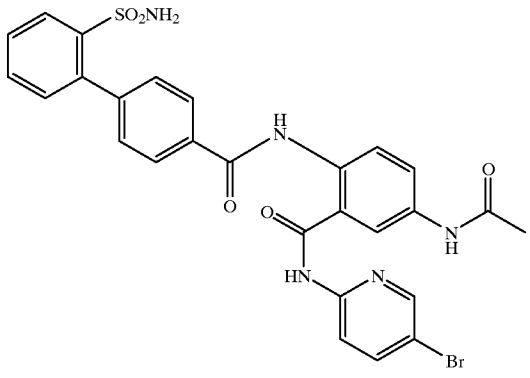
using zinc in acetic acid to reduce nitro-intermediate in step 2. The final product was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN.

[1040] MS found for $C_{25}H_{18}ClFN_4O_4S$ $(M+H)^+$: 525, 527.

Example 130

[1041]

Example 130

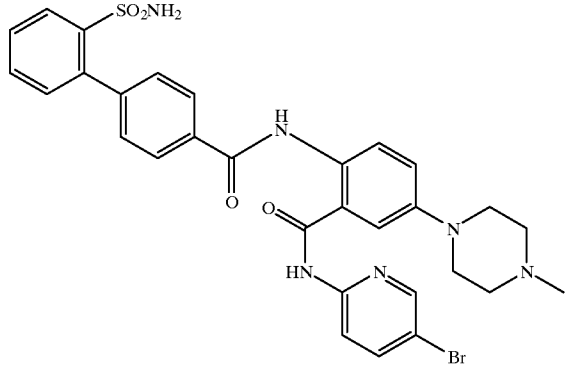


[1042] This compound was prepared according to the procedure described in example 2 with the exception of using 5-acetamido-2-nitrobenzoic acid as the starting material in step 1. The final product was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN

[1043] MS found for $C_{27}H_{22}BrN_5O_5S$ $(M+H)^+$: 608, 610.

Example 131

[1044]



[1045] This compound is prepared according to the procedure described in example 2 with the exception of the following step 1b performed on the nitro-intermediate from step 1. The final product was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN

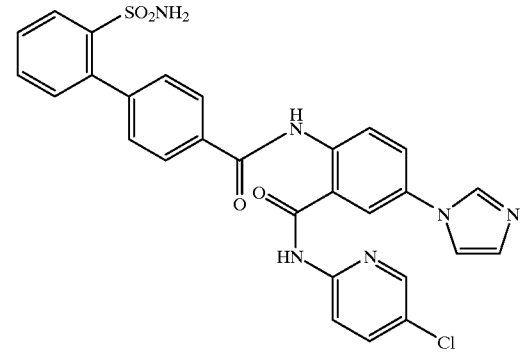
[1046] MS found for $C_{30}H_{29}BrN_6O_4S$ $(M+H)^+$: 649, 651.

[1047] Step 1b: A mixture of N-(5-bromo-2-pyridinyl)-(2-nitro)-5-fluorophenylcarboxamide (0.68 g, 2 mmol, 1.0 equiv), N-methylpiperazine (0.60 g, 3 equiv), and Cs_2CO_3 (1.30 g, 2 equiv) in 5 mL of dimethylformamide was stirred at 90° C. overnight. Ethyl acetate was added and washed with H_2O. The organic layer was dried over Na_2SO_4, filtered, evaporated, purified via flash chromatography on silica gel to give N-(5-bromo-2-pyridinyl)-(2-nitro)-5-(4-N-methylpiperazine)phenylcarboxamide (0.54 g, 65%).

[1048] MS found for $C_{17}H_{18}BrN_5O_3$ $(M+H)^+$: 419, 421.

Example 132

[1049]

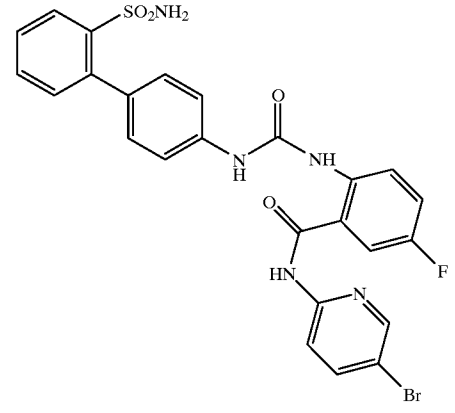


[1050] This compound was prepared according to the procedure described in example 5. The final product was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN

[1051] MS found for $C_{28}H_{21}ClN_6O_4S$ $(M+H)^+$: 573, 575.

Example 133

[1052] N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylaminocarbonylamino)-5-fluorophenylcarboxamide.



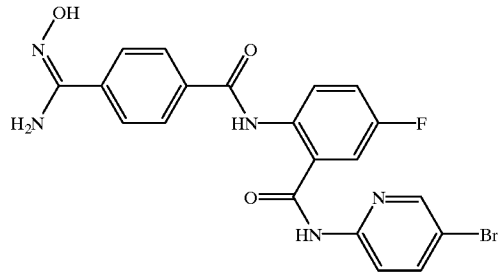
[1053] Step 3: A mixture of 4-[(2-t-butylaminosulfonyl)phenyl]phenylamine (0.180 g, 1.2 equiv), N,N'-disuccinimidyl carbonate (0.154 g, 1.2 equiv), 4-methylmorpho-

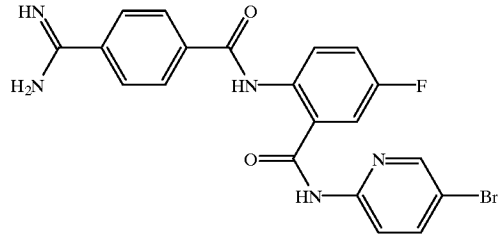
line (0.5 mL) in 10 mL of acetonitrile was stirred at rt for 30 min. N-(5-bromo-2-pyridinyl)-(2-amino)-5-fluorophenylcarboxamide (0.155 g, 0.5 mmol, 1.0 equiv) was added and the solution was stirred at rt for 3 hrs. The volatile was evaporated and the residue was redissolved into EtOAc, washed with 1N HCl, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The organic layer was dried over Na_2SO_4, filtered, and evaporated. The intermediate was reacted into 5 mL of trifluoroacetic acid at rt overnight. TFA was then evaporated and the product was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylaminocarbonylamino)-5-fluorophenylcarboxamide (0.053 g, 18%).

[1054] MS found for $C_{25}H_{19}BrFN_5O_4S$ $(M+H)^+$: 584, 586.

Examples 134-135

[1055] N-(5-bromo-2-pyridinyl)-(2-(4-amidinophenylcarbonyl)amino)5-fluorophenylcarboxamide.





[1056] Step 1: A mixture of N-(5-bromo-2-pyridinyl)-(2-amino)5-fluorophenylcarboxamide (1.24 g, 4 mmol, 1.0 equiv), 4-cyano benzoyl chloride (0.792 g, equiv), and pyridine (3 mL) in 15 mL of dichloromethane was stirred at rt overnight. The volatile was evaporated and the residue was redissolved into EtOAc, washed with 1N HCl, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The organic layer was dried over Na_2SO_4, filtered, and evaporated to give N-(5-bromo-2-pyridinyl)-(2-(4-cyanophenylcarbonyl)amino)5-fluorophenylcarboxamide (1.14 g, 65%).

[1057] MS found for $C_{20}H_{12}BrFN_4O_2$ $(M+H)^+$: 439, 441.

[1058] Step 2: A mixture of N-(5-bromo-2-pyridinyl)-(2-(4-cyanophenylcarbonyl)amino)5-fluorophenylcarboxamide (1.12 g, 2.56 mmol, 1.0 equiv), hydroxylamine-HCl (0.213 g, 1.2 equiv), and triethylamine (1 mL) in 15 mL of ethyl alcohol was stirred at 50° C. overnight. The volatile was evaporated and the residue was redissolved into EtOAc, washed with 1N HCl, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The organic layer was dried over Na_2SO_4, filtered, and evaporated to give N-(5-bromo-2-pyridinyl)-(2-hydroxyamidinophenylcarbonyl)amino)5-fluorophenylcarboxamide (compound Example 194) (0.84 g, 70%). One third of this material was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to yield 0.20 grams (71%).

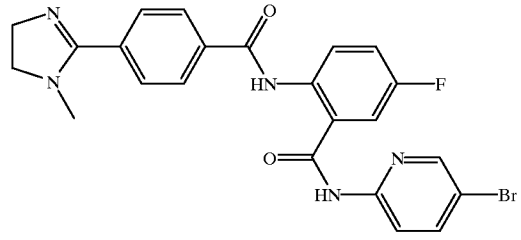
[1059] MS found for $C_{20}H_{15}BrFN_5O_3$ $(M+H)^+$: 472, 474.

[1060] Step 3: A mixture of N-(5-bromo-2-pyridinyl)-(2-(4-hydroxyamidinophenylcarbonyl)amino)5-fluorophenylcarboxamide (0.56 g, 1.19 mmol, 1.0 equiv) and zinc dust (0.39 g, 5.0 equiv), in 10 mL of acetic acid was stirred at rt for 45 min. The volatile was filtered and evaporated. The residue was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN give N-(5-bromo-2-pyridinyl)-(2 -(4-amidinophenylcarbonyl)amino)5-fluorophenylcarboxamide (compound Example 195) (0.24 g, 44%).

[1061] MS found for $C_{20}H_{15}BrFN_5O_2$ $(M+H)^+$: 456, 458.

Example 136

[1062] N-(5-bromo-2-pyridinyl)-(2-(4-(1-methyl-2-imadazolin-2-yl)phenylcarbonyl)amino)5-fluorophenylcarboxamide.



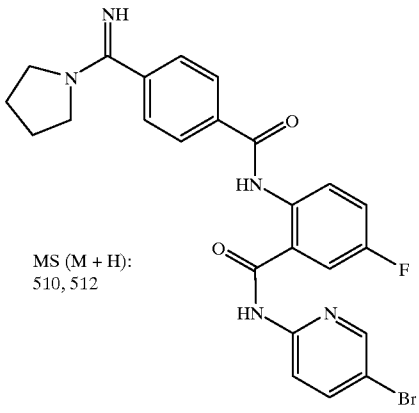
[1063] Step 1: A stream of HCl(g) was bubbled through a 0° C. solution of N-(5-bromo-2-pyridinyl)-(2-(4-cyanophenylcarbonyl)amino)5-fluorophenylcarboxamide (1.0 g, 2.3 mmol) in 30 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. One-fifth of the resulting residue was treated with (2-aminoethyl)methylamine (0.10 g) in 10 ml methanol at rt overnight. The solvent was removed at reduced pressure and the crude product was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give N-(5-bromo-2-pyridinyl)-(2-(4-(1 -methyl-2-imadazolin-2-yl)phenylcarbonyl) amino)5-fluorophenylcarboxamide (0.082 g, 37%).

[1064] MS found for $C_{23}H_{19}BrFN_5O_2$ $(M-H)^+$: 496, 498.

Examples 137-198

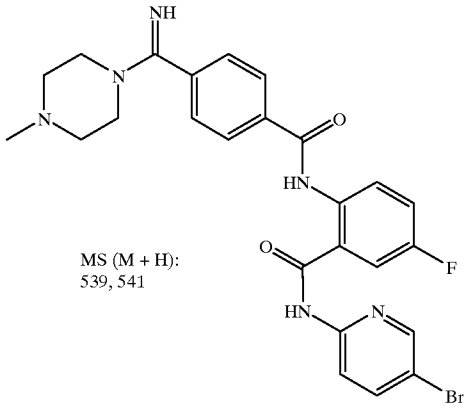
[1065] The following compounds were prepared generally according to the procedure described in Example 196.

Example 137



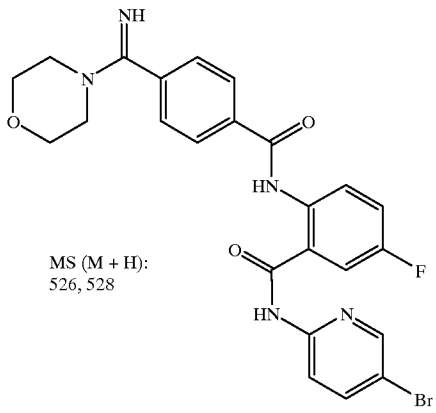
MS (M + H):
510, 512

Example 138



MS (M + H):
539, 541

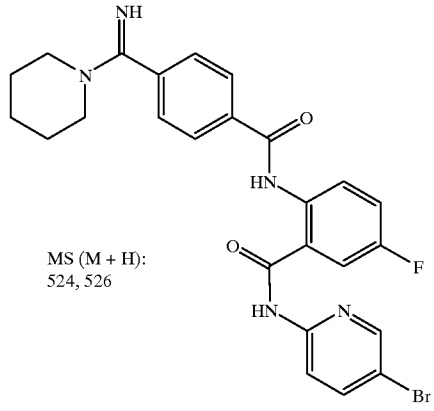
Example 139



MS (M + H):
526, 528

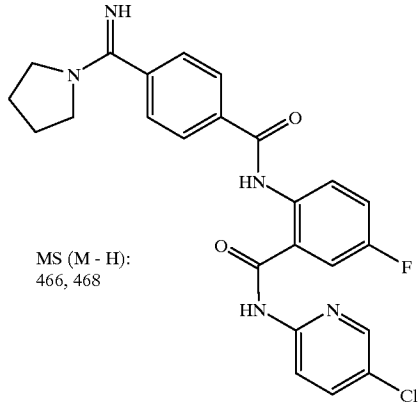
-continued

Example 140



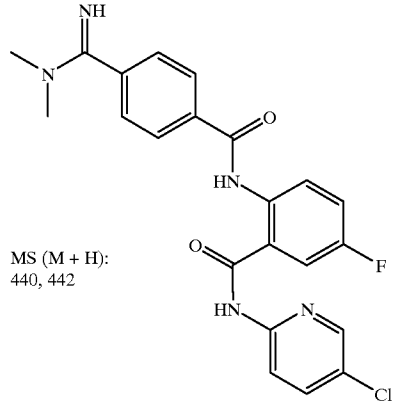
MS (M + H):
524, 526

Example 141



MS (M - H):
466, 468

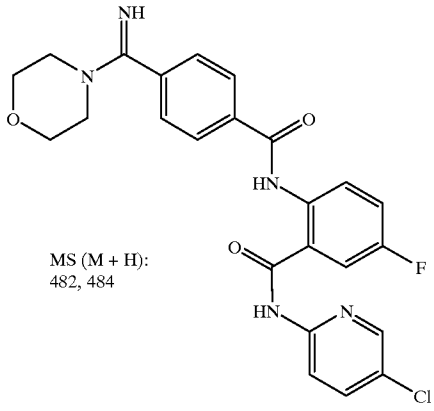
Example 142



MS (M + H):
440, 442

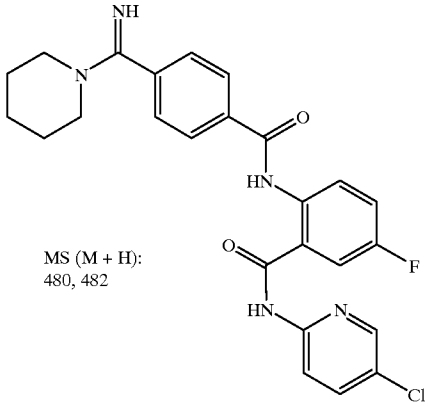
-continued

Example 143



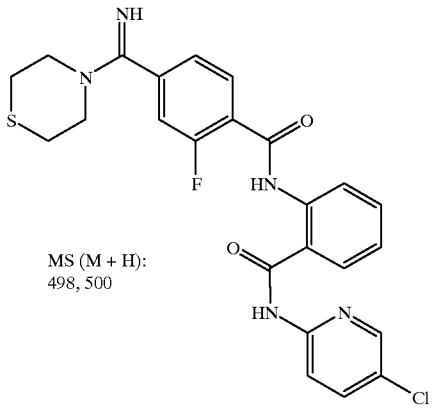
MS (M + H):
482, 484

Example 144



MS (M + H):
480, 482

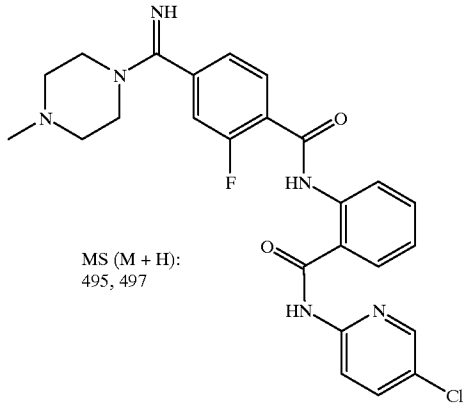
Example 145



MS (M + H):
498, 500

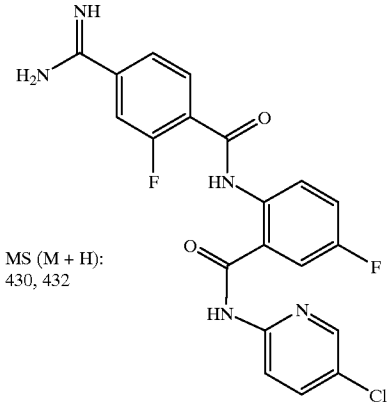
-continued

Example 146



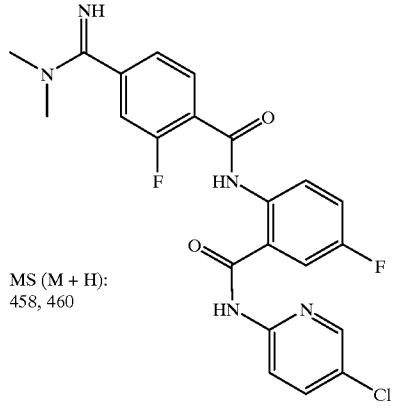
MS (M + H):
495, 497

Example 147



MS (M + H):
430, 432

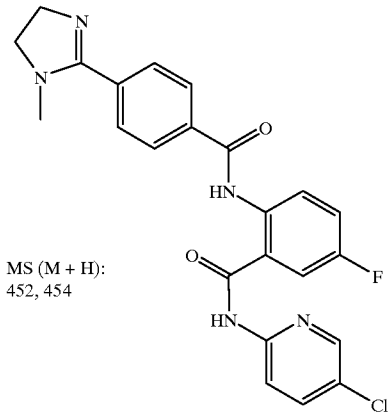
Example 148



MS (M + H):
458, 460

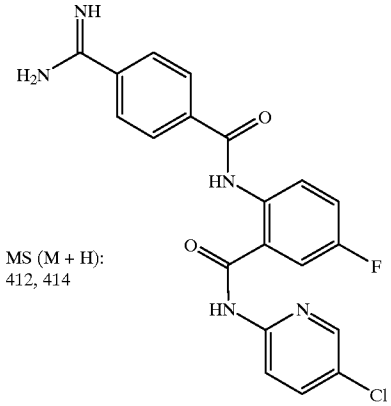
-continued

Example 149



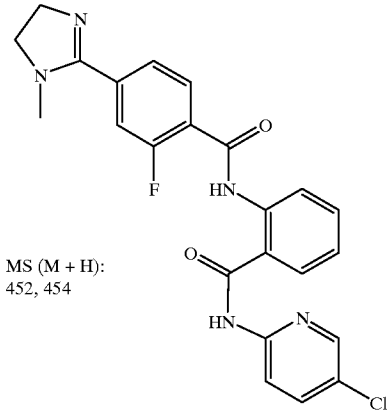
MS (M + H):
452, 454

Example 150



MS (M + H):
412, 414

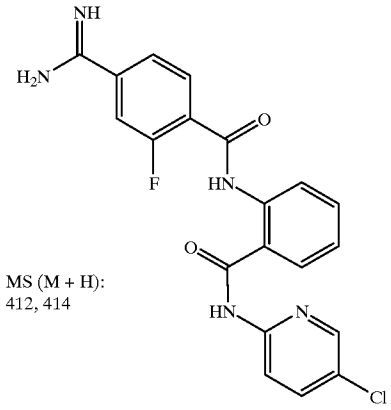
Example 151



MS (M + H):
452, 454

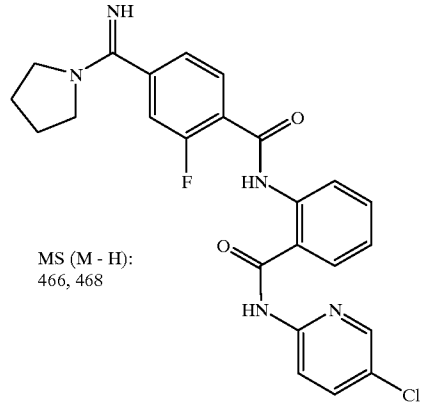
-continued

Example 152



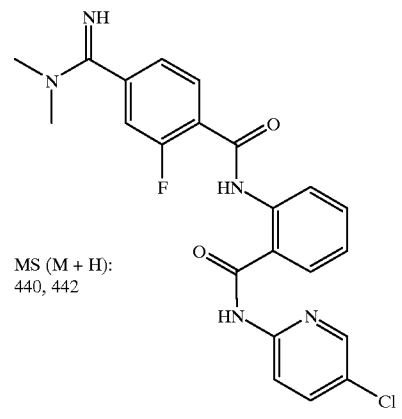
MS (M + H):
412, 414

Example 153



MS (M - H):
466, 468

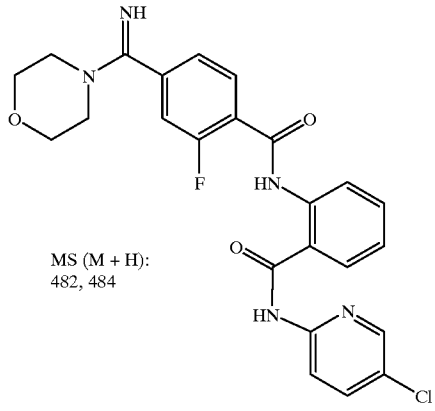
Example 154



MS (M + H):
440, 442

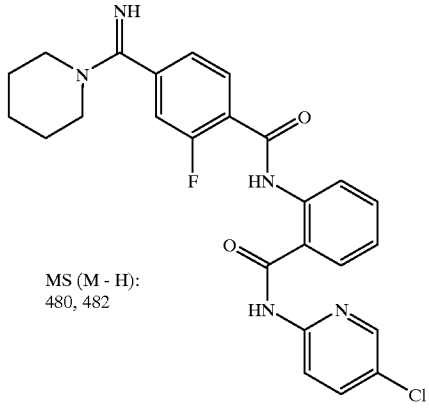
-continued

Example 155



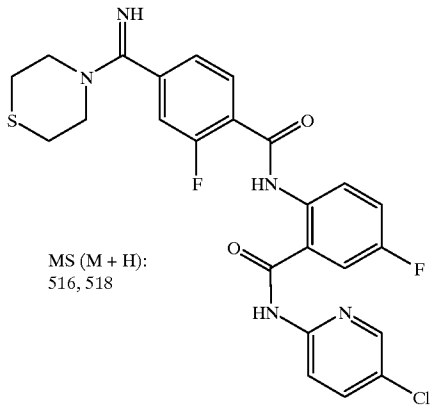
MS (M + H):
482, 484

Example 156



MS (M - H):
480, 482

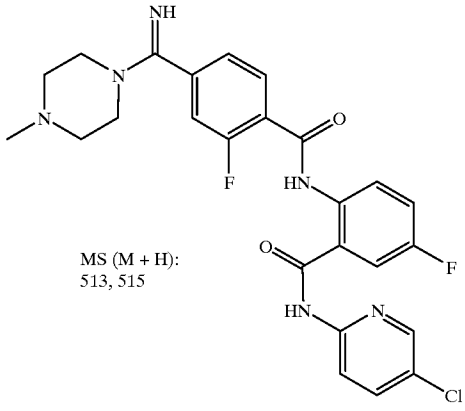
Example 157



MS (M + H):
516, 518

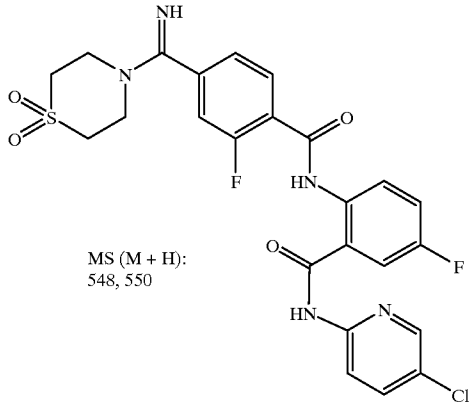
-continued

Example 158



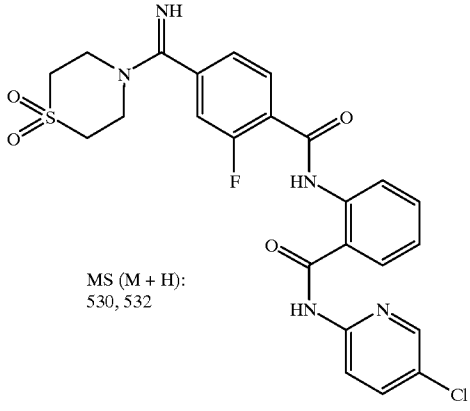
MS (M + H):
513, 515

Example 159



MS (M + H):
548, 550

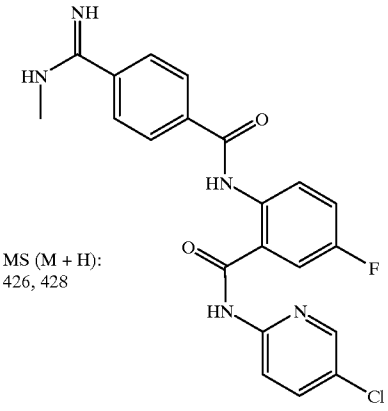
Example 160



MS (M + H):
530, 532

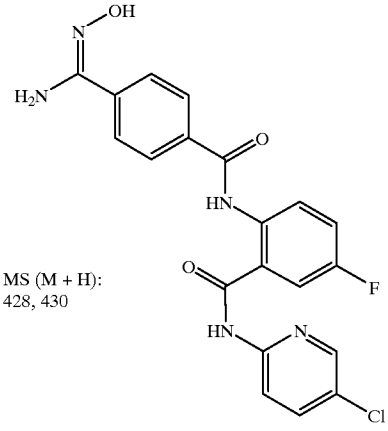
-continued

Example 161



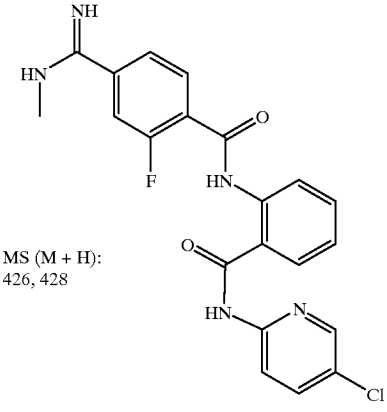
MS (M + H):
426, 428

Example 162



MS (M + H):
428, 430

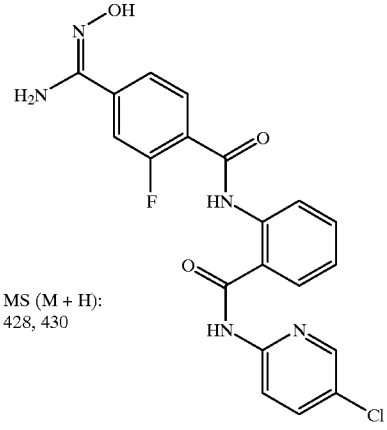
Example 163



MS (M + H):
426, 428

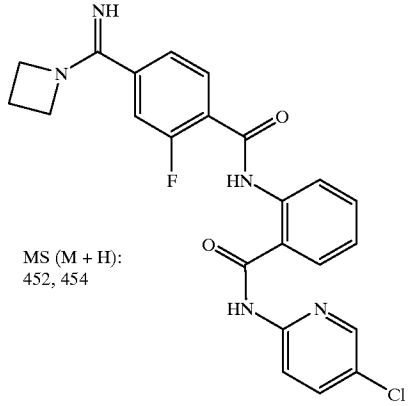
-continued

Example 164



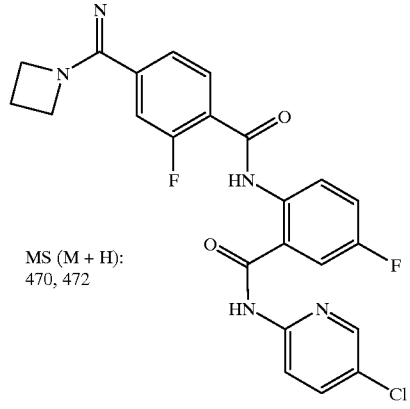
MS (M + H):
428, 430

Example 165



MS (M + H):
452, 454

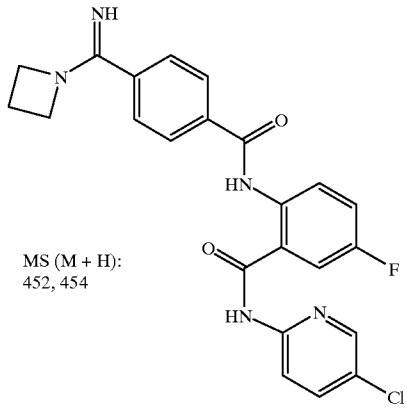
Example 166



MS (M + H):
470, 472

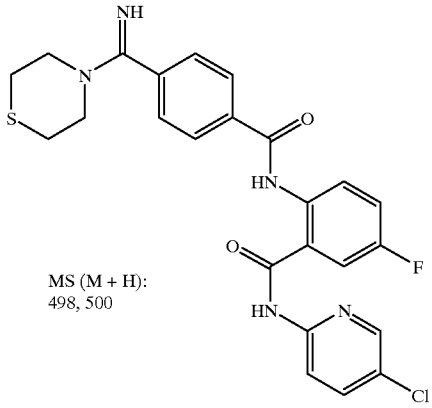
-continued

Example 167



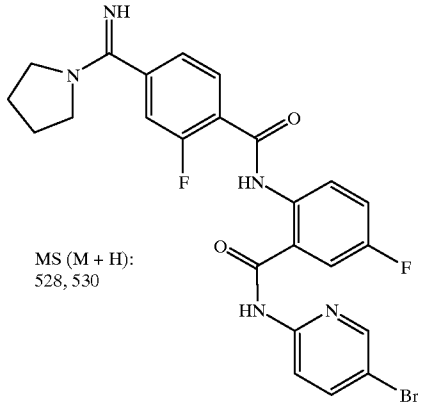
MS (M + H):
452, 454

Example 168



MS (M + H):
498, 500

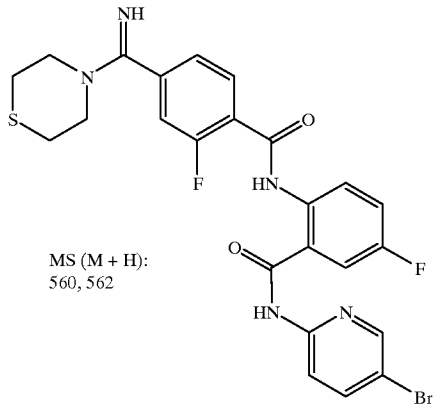
Example 169



MS (M + H):
528, 530

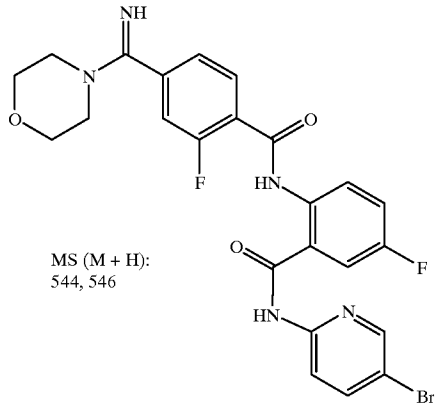
-continued

Example 170



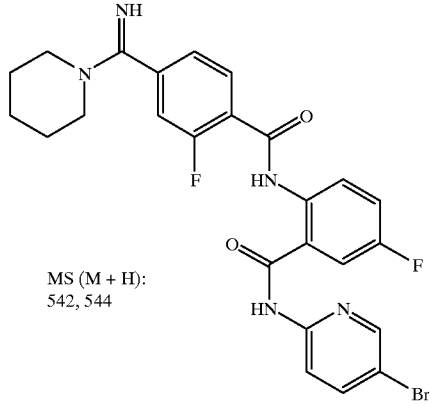
MS (M + H):
560, 562

Example 171



MS (M + H):
544, 546

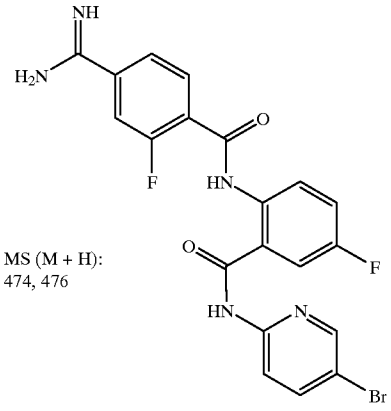
Example 172



MS (M + H):
542, 544

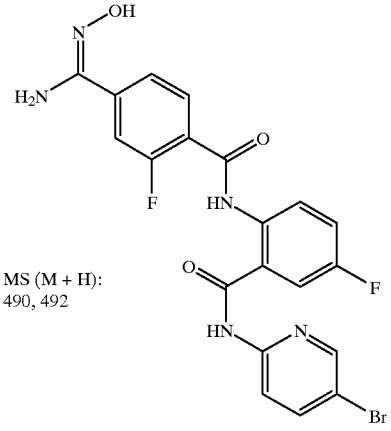
-continued

Example 173



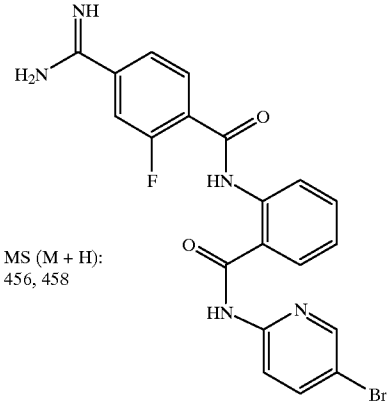
MS (M + H):
474, 476

Example 174



MS (M + H):
490, 492

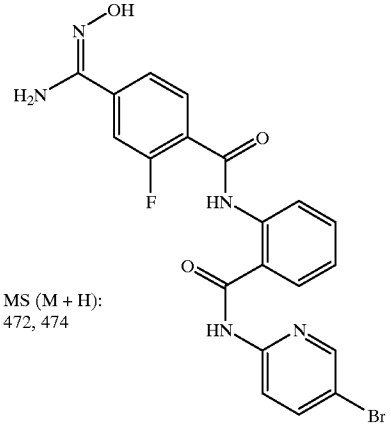
Example 175



MS (M + H):
456, 458

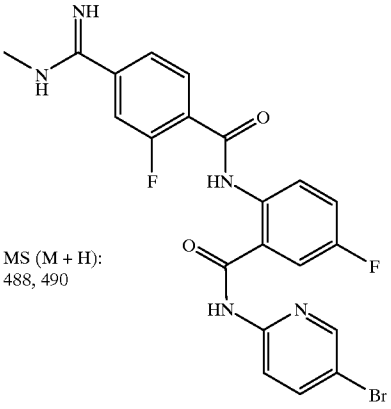
-continued

Example 176



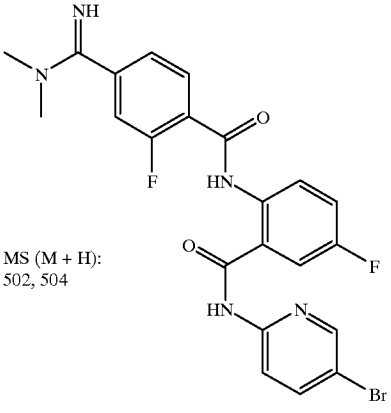
MS (M + H):
472, 474

Example 177



MS (M + H):
488, 490

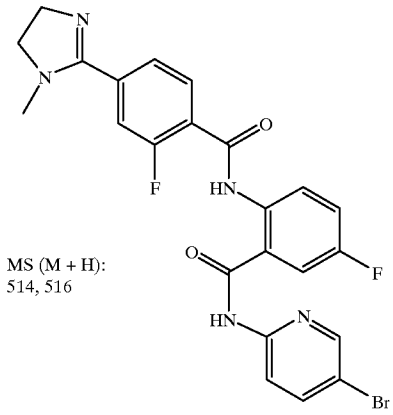
Example 178



MS (M + H):
502, 504

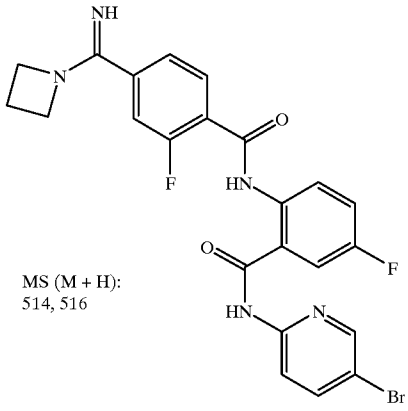
-continued

Example 179



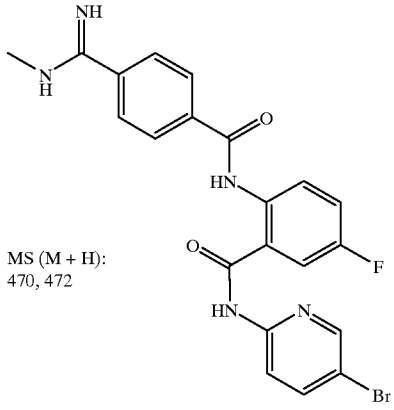
MS (M + H):
514, 516

Example 180



MS (M + H):
514, 516

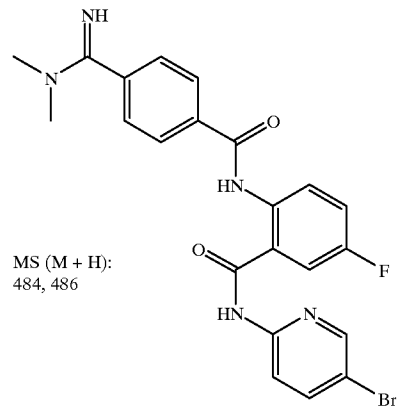
Example 181



MS (M + H):
470, 472

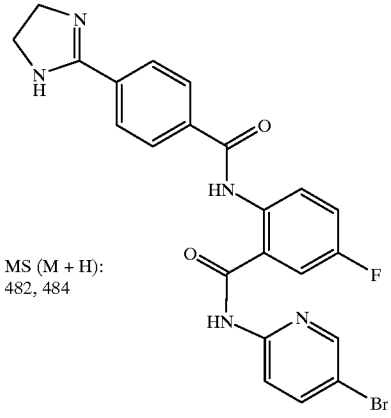
-continued

Example 182



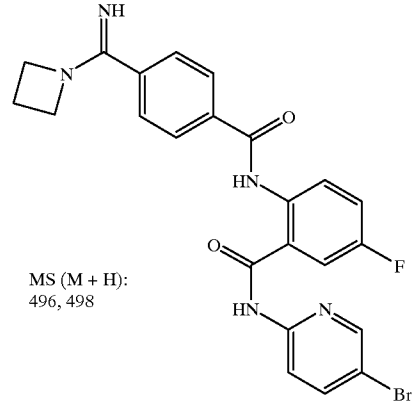
MS (M + H):
484, 486

Example 183



MS (M + H):
482, 484

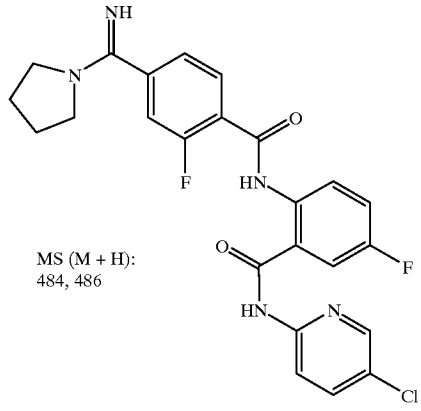
Example 184



MS (M + H):
496, 498

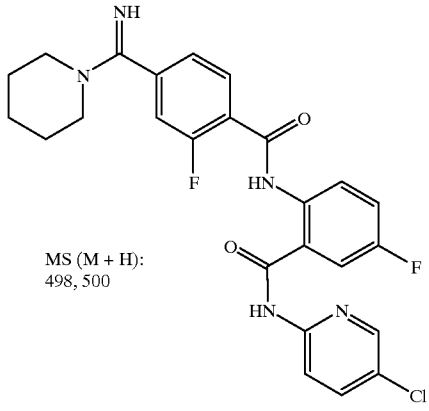
-continued

Example 185



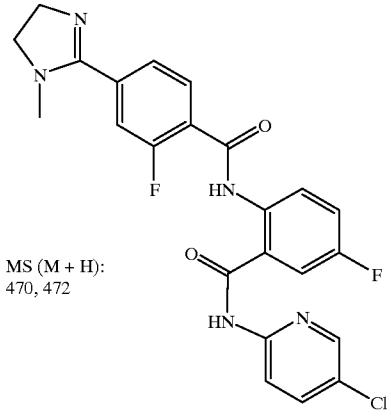
MS (M + H):
484, 486

Example 186



MS (M + H):
498, 500

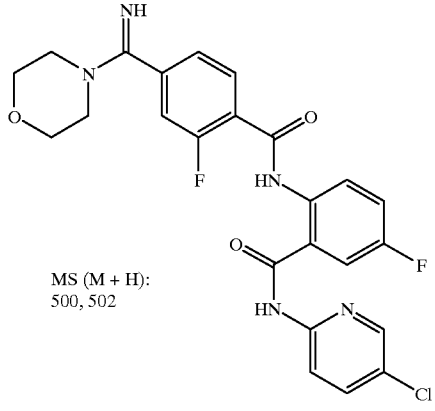
Example 187



MS (M + H):
470, 472

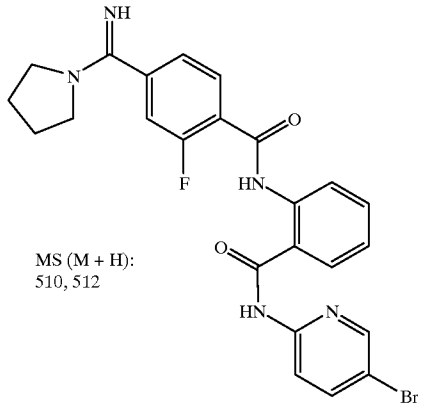
-continued

Example 188



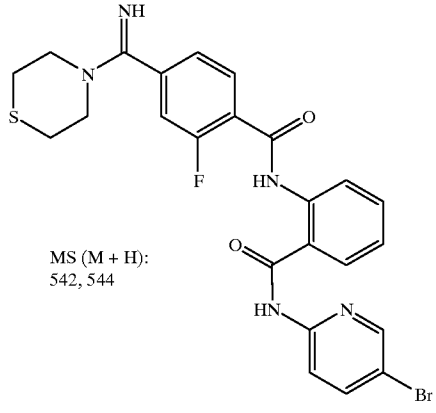
MS (M + H):
500, 502

Example 189



MS (M + H):
510, 512

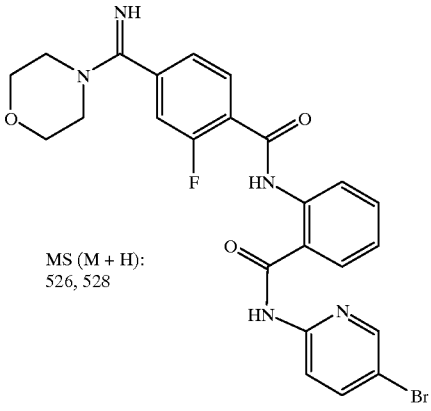
Example 190



MS (M + H):
542, 544

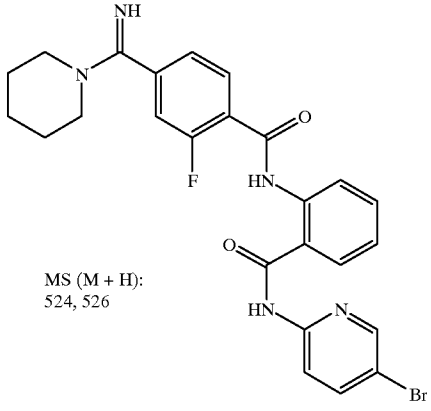
-continued

Example 191



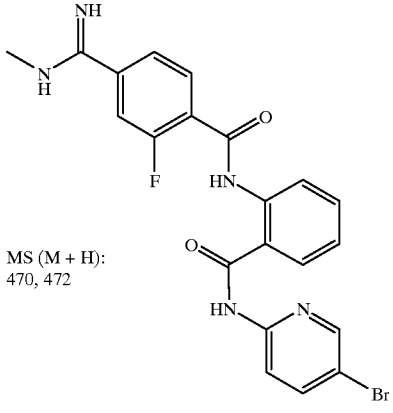
MS (M + H):
526, 528

Example 192



MS (M + H):
524, 526

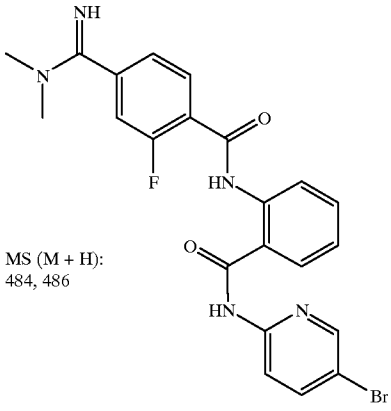
Example 193



MS (M + H):
470, 472

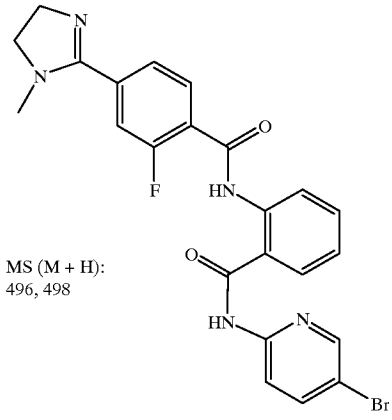
-continued

Example 194



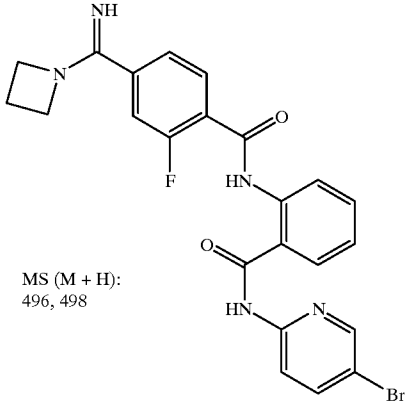
MS (M + H):
484, 486

Example 195



MS (M + H):
496, 498

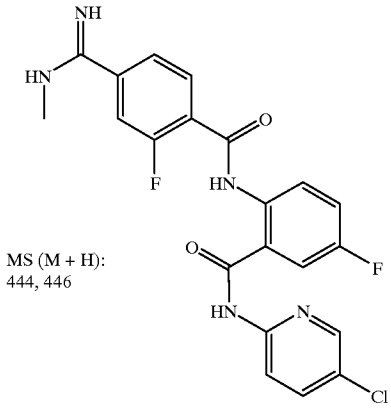
Example 196



MS (M + H):
496, 498

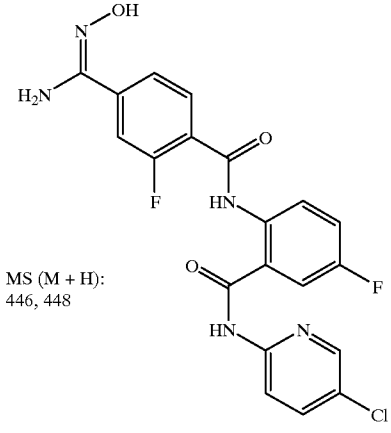
-continued

Example 197



MS (M + H): 444, 446

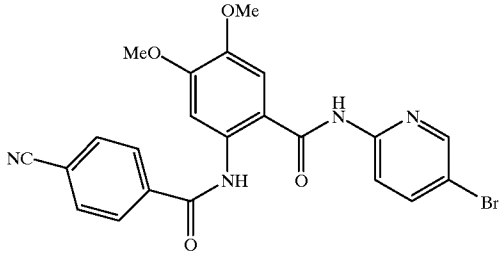
Example 198



MS (M + H): 446, 448

Example 199

[1066] N-{2-[N-(5-bromo(2pyridyl))carbamoyl]-4,5-dimethoxyphenyl}(4-cyanophenyl)carboxamide



[1067] To a solution of 4,5-dimethoxy-2-nitrobenzoic acid (2.2 gm, 10 mmol) and 2-amino-5-bromopyridine (2.4 gm, 14 mmol) in anhydrous pyridine (50 mL) at 0° C. was added $POCl_3$ (1.9 mL, 20 mmol). After stirring at room temperature for 30 min, the reaction was complete. The mixture was concentrated and diluted with EtOAc (200 mL). The organic solution was washed with brine, dried and evaporated to give intermediate compound 1 (3.0 gm, 80%).

[1068] MS found for $C_{14}H_{12}BrN_3O_5$ $(M+H)^+$: 382.00, 383.95.

[1069] A mixture of intermediate compound 1 (320 mg, 0.83 mmol) and $SnCl_2.2H_2O$ (900 mg, 4.0 mmol) in EtOAc (10 mL) was refluxed for 1 hour. Reduction completed. The solid was filtered through a celite bed. The filtrate was diluted with EtOAc (50 mL), and the red solution was washed with 1N aq. NaOH solution (×3) and brine, dried and evaporated to give intermediate compound 2 (230 mg, 78%).

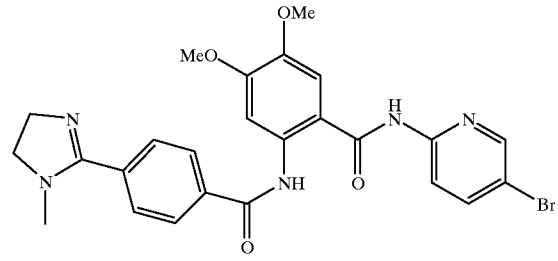
[1070] MS found for $C_{14}H_{14}BrN_3O_3$ $(M+H)^+$: 352.00, 354.05.

[1071] To a solution of intermediate compound 2 (200 mg, 0.57 mmol) in a mixture of pyridine (3 mL) and DCM (10 mL) was added 4-cyanobenzoyl chloride (140 mg, 0.85 mmol). Precipitate formed immediately and the reaction was complete. The solid was collected by filtration and washed with DCM. After drying in vacco, the titled compound was obtained as a yellow solid in 70% yield (190 mg).

[1072] MS found for $C_{22}H_{17}BrN_4O_4$ $(M+H)^+$: 481.00, 483.00.

Example 200

[1073] (4,5-dimethoxy-2-{[4-(1-methyl(2-imidazolin-2-yl))phenyl]carbonylamino}phenyl)-N-(5-bromo(2-pyridyl-))carboxamide

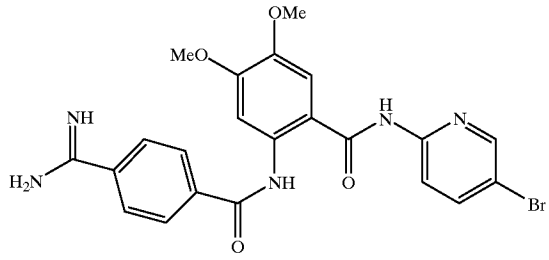


[1074] To a solution of compound obtained in Example 259 (100 mg, 0.20 mmol) in 10% Et_3N/pyridine (10 mL) at 0° C. was bubbled dry H_2S gas to saturation. The mixture was stirred at ambient temperatures overnight, and the conversion was complete. The solvent was removed to dryness, and the residue was suspended in anhydrous acetone (10 mL), followed by addition of MeI (1 mL). The reaction mixture was refluxed for 1 hour. The solvent was removed by rotary evaporation. To the residue was added anhydrous MeOH (10 mL) and N-methylethylenediamine (1 mL). The resulting mixture was refluxed for 1 hour, concentrated and subjected to RP-HPLC purification to give the title compound.

[1075] MS found for $C_{25}H_{24}BrN_5O_4$ $(M+H)^+$: 538.1, 540.1.

Example 201

[1076] 4-(N-{2-[N-(5-bromo(2-pyridyl))carbamoyl]-4,5-dimethoxyphenyl}carbamoyl)-benzenecarboxamidine

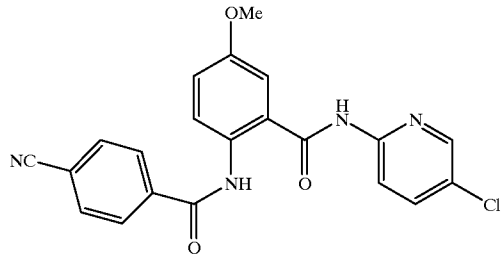


[1077] The title compound was obtained according to the procedure previously described.

[1078] MS found for $C_{22}H_{20}BrN_5O_4$ $(M+H)^+$: 498.1, 500.0.

Example 202

[1079] N-(5-chloro(2-pyridyl)){2-[(4-cyanophenyl)carbonylamino]-5-methoxyphenyl}-carboxamide

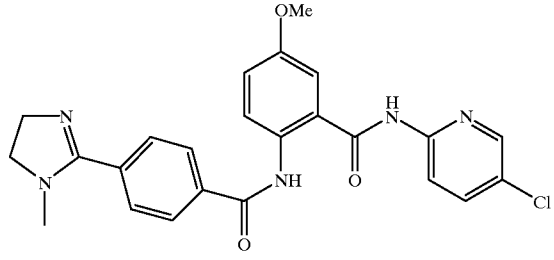


[1080] The title compound was obtained according to the procedure previously described.

[1081] MS found for $C_{21}H_{15}ClN_4O_3$ $(M+H)^+$: 407.0.

Example 203

[1082] N-(5-chloro(2-pyridyl))(5-methoxy-2-{[4-(1-methyl(2-imidazolin-2-yl))phenyl-carbonylamino}phenyl)carboxamide



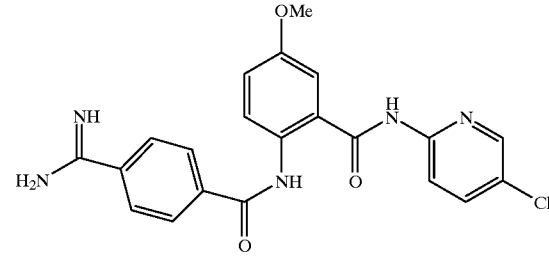
[1083] To the suspension of the compound Example 262 (100 mg) in a mixture of anhydrous MeOH (5mL) and EtOAc (5 mL) at 0° C. was bubbled anhydrous HCl gas to saturation. The mixture was stirred at ambient temperatures overnight. The conversion completed. The solvent was evaporated to dryness. The residue was dissolved in anhydrous MeOH (10 mL), followed by addition of N-methyl-ethylenediamine (1 mL).

[1084] The resulting mixture was refluxed for 1 hour, concentrated and subjected to RP-HPLC purification to give the title compound 263.

[1085] MS found for $C_{24}H_{22}ClN_5O_3$ $(M+H)^+$: 464.

Example 204

[1086] 4-(N- {2-[N-(5-chloro(2-pyridyl))carbamoyl]-4-methoxyphenyl} carbamoyl)benzene-carboxamidine

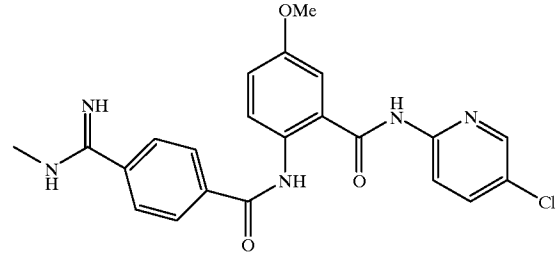


[1087] The title compound was obtained according to the procedure previously described.

[1088] MS found for $C_{21}H_{18}ClN_5O_3$ $(M+H)^+$: 424.

Example 205

[1089] N-(5-chloro(2-pyridyl))[2-({4-[imino(methylamino)methyl]phenyl}carbonylamino)-5-methoxyphenyl]carboxamide

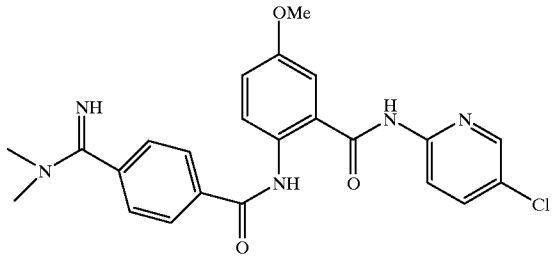


[1090] The title compound was obtained according to the procedure previously described.

[1091] MS found for $C_{22}H_{20}ClN_5O_3$ $(M+H)^+$: 438.

Example 206

[1092] [2-({4-[(dimethylamino)iminomethyl] phenyl}carbonylamino)-5-methoxyphenyl]-N-(5-chloro(2-pyridyl))carboxamide

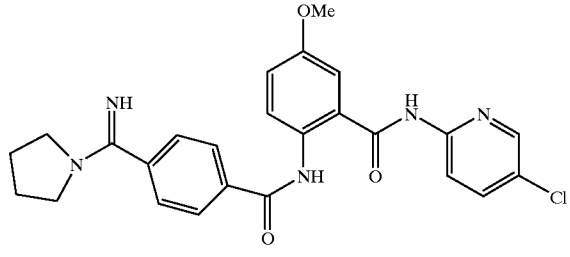


[1093] The title compound was obtained according to the procedure previously described.

[1094] MS found for $C_{23}H_{22}ClN_5O_3$ $(M+H)^+$: 452.

Example 207

[1095] N-(5-chloro(2-pyridyl))(2-{[4-(iminopyrrolidinylmethyl)phenyl]carbonylamino}-5-methoxyphenyl)carboxamide

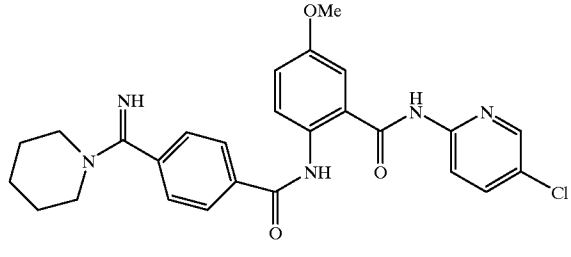


[1096] The title compound was obtained according to the procedure previously described.

[1097] MS found for $C_{25}H_{24}ClN_5O_3$ $(M+H)^+$: 478.

Example 208

[1098] N-(5-chloro(2-pyridyl))(2-{[4-(iminopiperidylmethyl)phenyl]carbonylamino}-5-methoxyphenyl)carboxamide

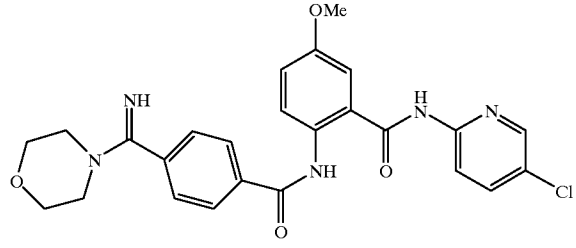


[1099] The title compound was obtained according to the procedure previously described.

[1100] MS found for $C_{26}H_{26}ClN_5O_3$ $(M+H)^+$: 492.

Example 209

[1101] N-(5-chloro(2-pyridyl))(2-{[4-(iminomorpholin-4-ylmethyl)phenyl]carbonylamin}-5-methoxyphenyl)carboxamide

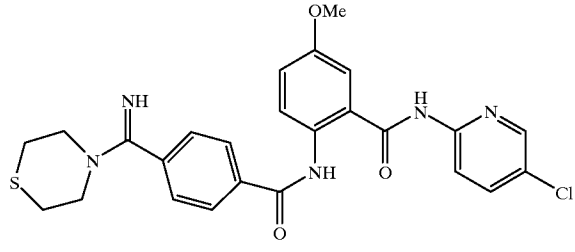


[1102] The title compound was obtained according to the procedure previously described.

[1103] MS found for $C_{25}H_{24}ClN_5O_4$ $(M+H)^+$: 494.1.

Example 210

[1104] N-(5-chloro(2-pyridyl))(2-{[4-(imino-1,4-thiazaperhydroin-4-ylmethyl)phenyl]carbonylamino}-5-methoxyphenyl)carboxamide

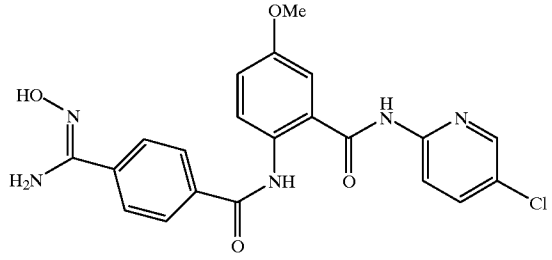


[1105] The title compound was obtained according to the procedure previously described.

[1106] MS found for $C_{25}H_{24}ClN_5O_3S$ $(M+H)^+$: 510.

Example 211

[1107] (2-{[4-(amino(hydroxyimino)methyl)phenyl]carbonylamino}-5-methoxyphenyl)-N-(5-chloro(2-pyridyl-))carboxamide

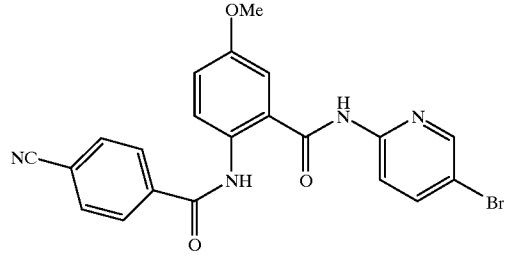


[1108] To a suspension of compound N-(5-chloro(2-pyridyl)) {2-[(4-cyanophenyl)carbonylamino]-5-methoxyphenyl carboxamide (150 mg) in EtOH (10 mL) was added hydroxyamine hydrochloride (80 mg) and Et_3N (200 μL). The mixture was stirred at 60° C. overnight and the reaction was complete. The solvent was evaporated and the crude material was purified by RP-HPLC to give the title compound.

[1109] MS found for $C_{21}H_{18}ClN_5O_4$ $(M+H)^+$: 440.1.

Example 212

[1110] N-(5-bromo(2-pyridyl))(2-[(4-cyanophenyl)carbonylamino]-5-methoxyphenyl}carboxamide

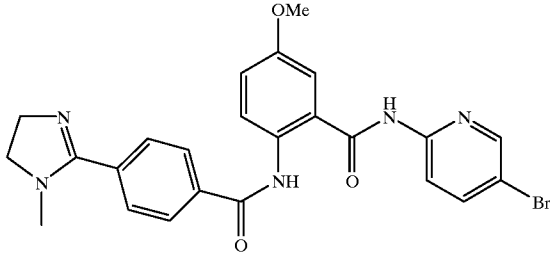


[1111] The title compound was obtained according to the procedure previously described.

[1112] MS found for $C_{21}H_{15}BrN_4O_3$ $(M+H)^+$: 451.00, 453.00.

Example 213

[1113] N-(5-bromo(2-pyridyl))(5-methoxy-2-{[4-(1-methyl(2-imidazolin-2-yl))phenyl] carbonylamino}phenyl)carboxamide

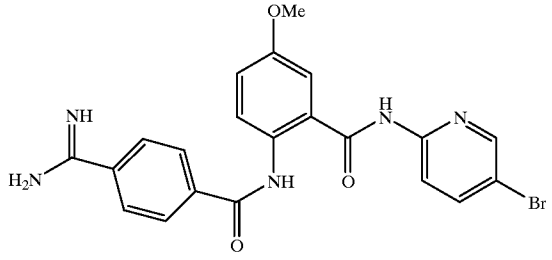


[1114] The title compound was obtained according to the procedure previously described.

[1115] MS found for $C_{24}H_{22}BrN_5O_3$ $(M+H)^-$: 508, 510.

Example 214

[1116] 4-(N-{2-[N-(5-bromo(2-pyridyl))carbamoyl]-4-methoxyphenyl}carbamoyl)benzenecarboxamidine

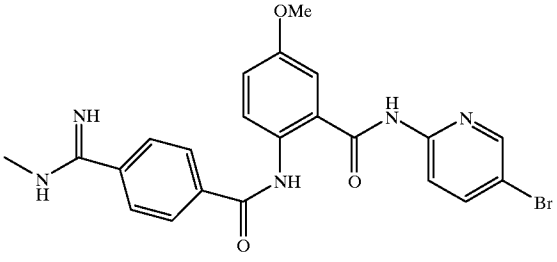


[1117] The title compound was obtained according to the procedure previously described.

[1118] MS found for $C_{21}H_{18}BrN_5O_3$ $(M+H)^+$: 468.05, 470.00.

Example 215

[1119] N-(5-bromo(2-pyridyl))[2-({4-[imino(methylamino)methyl]phenyl}carbonylamino)-5-methoxyphenyl]carboxamide

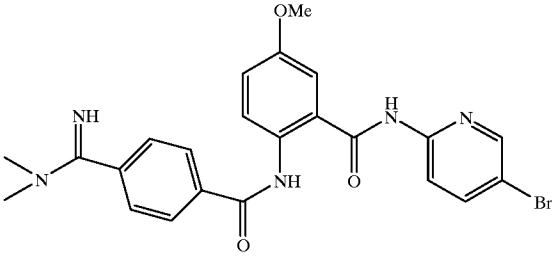


[1120] The title compound was obtained according to the procedure previously described.

[1121] MS found for $C_{22}H_{20}BrN_5O_3$ $(M+H)^+$: 482, 484.

Example 216

[1122] [2-({4-[(dimethylamino)iminomethyl] phenyl}carbonylamino)-5-methoxyphenyl]-N-(5-bromo(2-pyridyl))carboxamide

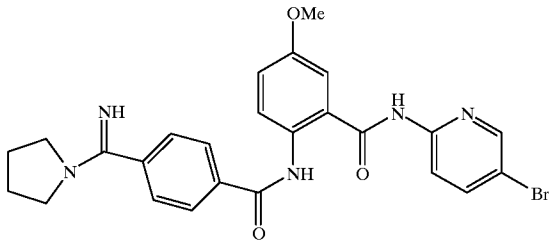


[1123] The title compound was obtained according to the procedure previously described.

[1124] MS found for $C_{23}H_{22}BrN_5O_3$ $(M+H)^+$: 496.1, 498.1.

Example 217

[1125] N-(5-chloro(2-pyridyl))(2-{[4-(iminopyrrolidinylmethyl)phenyl]carbonylamino}-5-methoxyphenyl)carboxamide

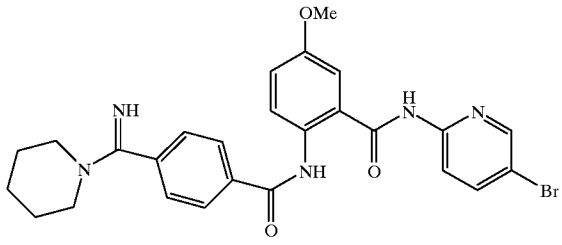


[1126] The title compound was obtained according to the procedure previously described.

[1127] MS found for $C_{25}H_{24}BrN_5O_3$ $(M+H)^+$: 522, 524.

Example 218

[1128] N-(N-(5-bromo(2-pyridyl))(2-{[4-(iminopiperidylmethyl)phenyl]carbonylamino}-5-methoxyphenyl-)carboxamide

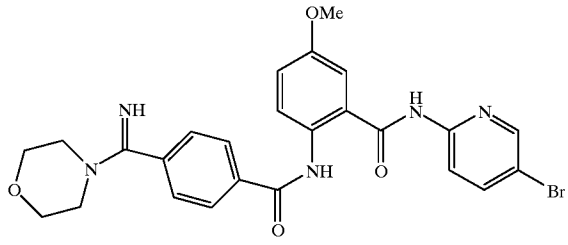


[1129] The title compound was obtained according to the procedure previously described.

[1130] MS found for $C_{26}H_{26}BrN_5O_3$ $(M+H)^+$: 536.1, 538.1.

Example 219

[1131] N-(5-bromo(2-pyridyl))(2-{[4-(iminomorpholin-4-ylmethyl)phenyl]carbonylamino}-5-methoxyphenyl)carboxamide

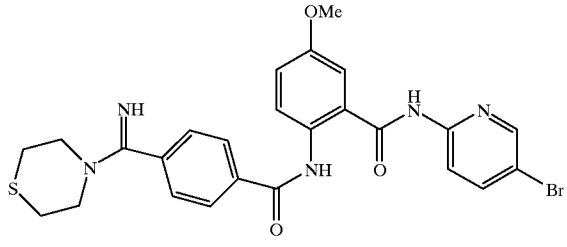


[1132] The title compound was obtained according to the procedure previously described.

[1133] MS found for $C_{25}H_{24}BrN_5O_4$ $(M+H)^+$: 538.1, 540.1.

Example 220

[1134] N-(5-bromo(2-pyridyl))(2-{[4-(imino-1,4-thiazaperhydroin-4-ylmethyl)phenyl]carbonylamino}-5-methoxyphenyl)carboxamide

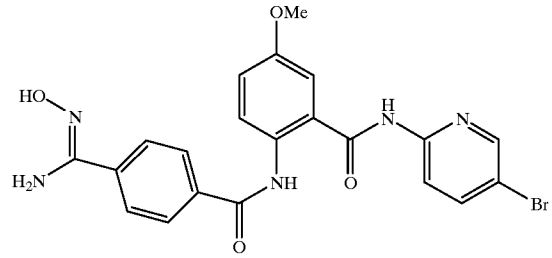


[1135] The title compound was obtained according to the procedure previously described.

[1136] MS found for $C_{25}H_{24}BrN_5O_3S$ $(M+H)^+$: 554.1, 556.05.

Example 221

[1137] (2-{[4-(amino(hydroxyimino)methyl)phenyl]carbonylamino}-5-methoxyphenyl)-N-(5-bromo(2-pyridyl)) carboxamide

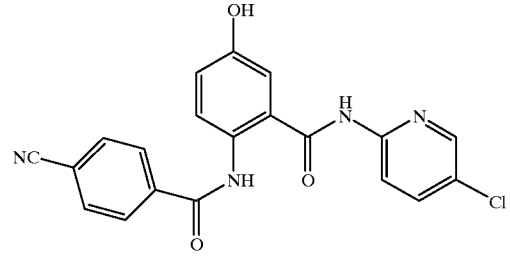


[1138] The title compound was obtained according to the procedure previously described.

[1139] MS found for $C_{21}H_{18}BrN_5O_4$ $(M+H)^+$: 484.1, 486.0.

Example 222

[1140] N-(5-chloro(2-pyridyl))(6-[(4-cyanophenyl)carbonylamino]-3-hydroxyphenyl}carboxamide

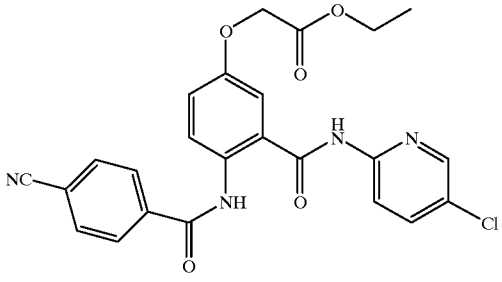


[1141] To a suspension of compound N-(5-chloro(2-pyridyl)) {2-[(4-cyanophenyl)-carbonylamino]-5-methoxyphenyl}carboxamide (500 mg, 1.2 mmol) in DCM (100 mL) at −78° C. was added BBr_3 (2 mL) The mixture was stirred at ambient temperatures for 72 hours. The solid was collected by filtration and was washed by DCM and water, dried under vacuum. The filtrate was concentrated and extracted with EtOAc. The organic extract was washed with brine, dried and evaporated. The resulting solid was combined with the solid obtained from filtration to give the title compound. Total yield is 90% (430 mg).

[1142] MS found for $C_{20}H_{13}ClN_4O_3$ $(M+H)^+$: 393.0.

Example 223

[1143] ethyl 2-{3-[N-(5-chloro(2-pyridyl))carbamoyl]-4-[(4-cyanophenyl)carbonylamino]-phenoxy}acetate

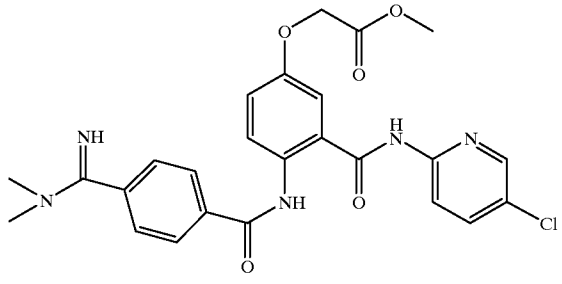


[1144] To a mixture of compound N-(5-chloro(2-pyridyl)) {6-[(4-cyanophenyl)-carbonylamino]-3-hydroxyphenyl}carboxamide (50 mg, 0.13 mmol) and Cs_2CO_3 (83 mg, 0.25 mmol) in DMF (1 mL) at room temperature was added ethyl bromoacetate (15 μL, 0.13 mmol). The mixture was stirred for 1 hour before diluted with EtOAc (20 mL) and water (10 mL). The organic layer was washed with brine dried and evaporated to give 70 mg of the crude compound, which was used without farther purification.

[1145] MS found for $C_{24}H_{19}ClN_4O_5$ $(M+H)^-$: 479.0.

Example 224

[1146] methyl 2-[4-({4-[(dimethylamino)iminomethyl] phenyl}carbonylamino)-3-[N-(5-chloro(2-pyridyl))carbamoyl]phenoxy]acetate

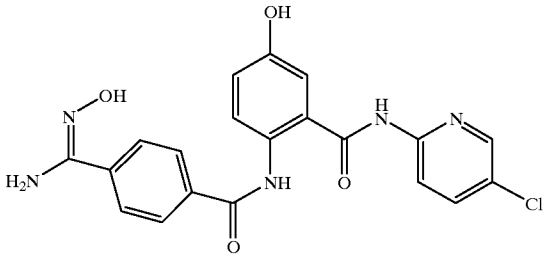


[1147] The title compound was obtained according to the procedure previously described.

[1148] MS found for $C_{25}H_{24}ClN_5O_5$ $(M+H)^+$: 510.1.

Example 225

[1149] (6-{[4-(amino(hydroxyimino)methyl)phenyl]carbonylamino}-3-hydroxyphenyl)-N-(5-chloro(2-pyridyl-))carboxamide

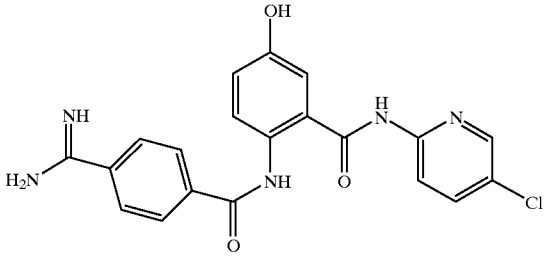


[1150] The title compound was obtained according to the procedure previously described.

[1151] MS found for $C_{20}H_{16}ClN_5O_4$ $(M+Na)^+$: 448.0.

Example 226

[1152] 4-(N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]-4-hydroxyphenyl}carbamoyl)-benzenecarboxamidine

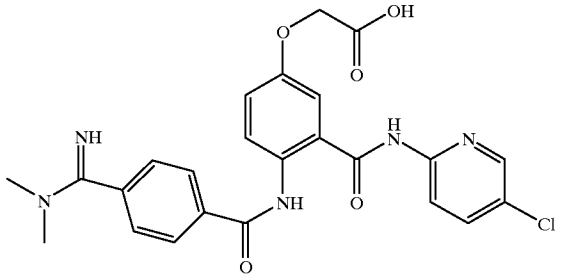


[1153] The title compound was obtained according to the procedure previously described.

[1154] MS found for $C_{20}H_{16}ClN_5O_3$ $(M+H)^+$: 410.1.

Example 227

[1155] 4-(N-{2-[N-(5-chloro(2-pyridyl))carbamoyl-4-hydroxyphenyl]carbamoyl)-benzenecarboxamidine

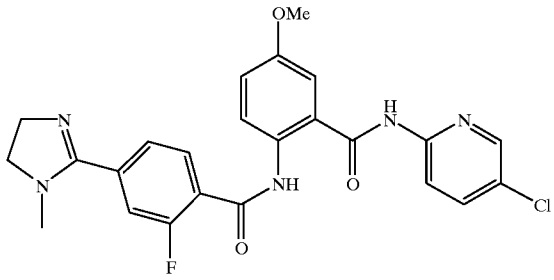


[1156] To a solution of Example 284 (10 mg) in MeOH (1 mL) was added 50 μL of 1N aq. LiOH solution. The mixture was stirred for 1 hour and purified by RP-HPLC to give the title compound.

[1157] MS found for $C_{24}H_{22}ClN_5O_5$ $(M+H)^+$: 496.

Example 228

[1158]



[1159] $C_{24}H_{21}ClFN_5O_3$

[1160] Exact Mass: 481.13

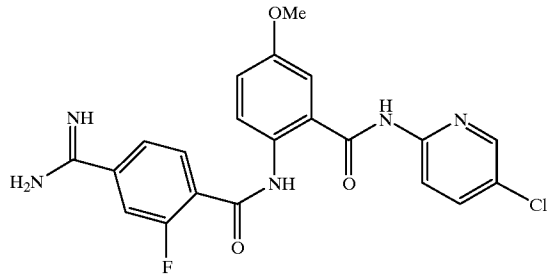
[1161] Mol. Wt.: 481.91

[1162] The title compound was synthesized according to the procedure described previously.

[1163] MS found for $C_{24}H_{21}ClFN_5O_3$: $(M+H)^+$: 482.1.

Example 229

[1164]



[1165] $C_{21}H_{17}ClFN_5O_3$

[1166] Exact Mass: 441.10

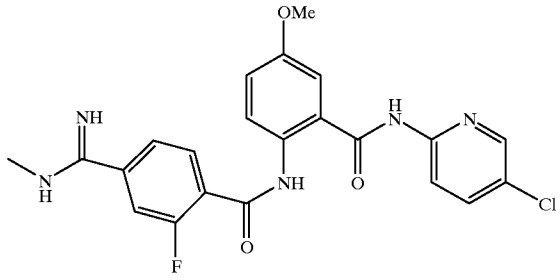
[1167] Mol. Wt.: 441.84

[1168] The title compound was synthesized according to the procedure described previously.

[1169] MS found for $C_{21}H_{17}ClFN_5O_3$: $(M+H)^+$: 442.1.

Example 230

[1170]



[1171] $C_{22}H_{19}ClFN_5O_3$

[1172] Exact Mass: 455.12

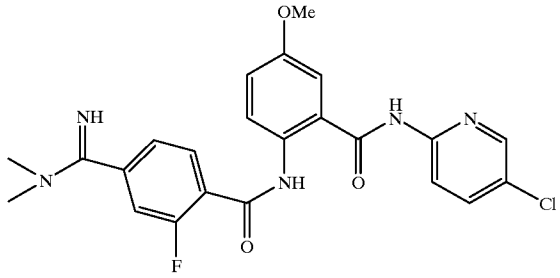
[1173] Mol. Wt.: 455.87

[1174] The title compound was synthesized according to the procedure described previously.

[1175] MS found for $C_{22}H_{19}ClFN_5O_3$: $(M+H)^+$: 456.1.

Example 231

[1176]



[1177] $C_{23}H_{21}ClFN_5O_3$

[1178] Exact Mass: 469.13

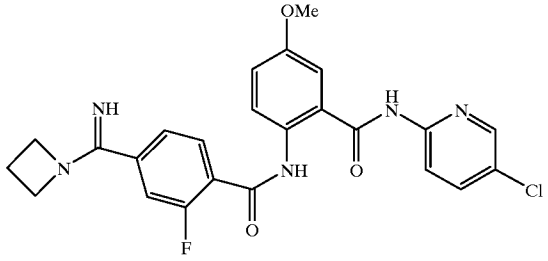
[1179] Mol. Wt.: 469.90

[1180] The title compound was synthesized according to the procedure described previously.

[1181] MS found for $C_{23}H_{21}ClFN_5O_3$: $(M+H)^+$: 470.1.

Example 232

[1182]



[1183] $C_{24}H_{21}ClFN_5O_3$

[1184] Exact Mass: 481.13

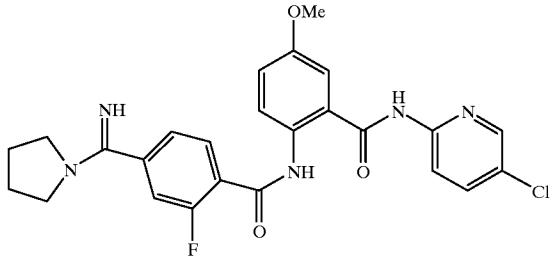
[1185] Mol. Wt.: 481 91

[1186] The title compound was synthesized according to the procedure described previously.

[1187] MS found for $C_{24}H_{21}ClFN_5O_3$: $(M+H)^+$: 482.1.

Example 233

[1188]



[1189] $C_{25}H_{23}ClFN_5O_3$

[1190] Exact Mass: 495.15

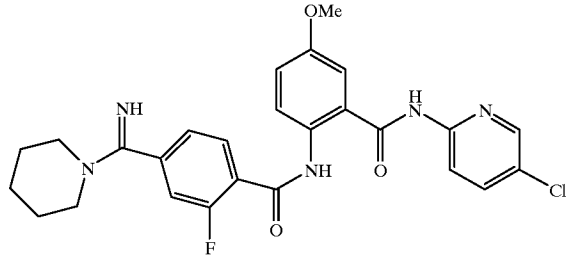
[1191] Mol. Wt.: 495.93

[1192] The title compound was synthesized according to the procedure described previously.

[1193] MS found for $C_{25}H_{23}ClFN_5O_3$: $(M+H)^+$: 496.1.

Example 234

[1194]



[1195] $C_{26}H_{25}ClFN_5O_3$

[1196] Exact Mass: 509.16

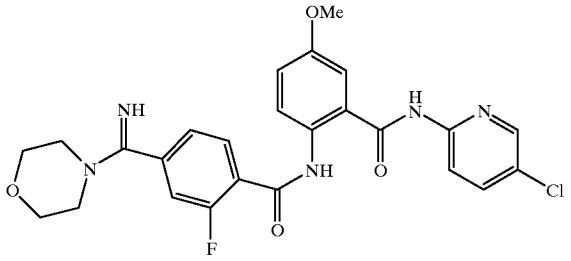
[1197] Mol. Wt.: 509 96

[1198] The title compound was synthesized according to the procedure described previously.

[1199] MS found for $C_{26}H_{25}ClFN_5O_3$: $(M+H)^+$: 510.2.

Example 235

[1200]



[1201] $C_{25}H_{23}ClFN_5O_4$

[1202] Exact Mass: 511.14

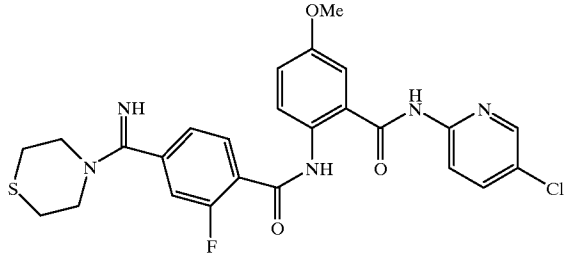
[1203] Mol. Wt.: 511.93

[1204] The title compound was synthesized according to the procedure described previously.

[1205] MS found for $C_{25}H_{23}ClFN_5O_4$: $(M+H)^+$: 512.2.

Example 236

[1206]



[1207] $C_{25}H_{23}ClFN_5O_3S$

[1208] Exact Mass: 527.12

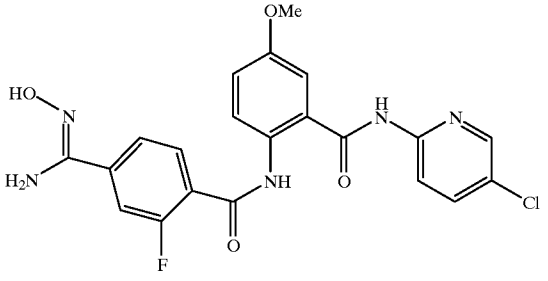
[1209] Mol. Wt.: 528 00

[1210] The title compound was synthesized according to the procedure described previously.

[1211] MS found for $C_{25}H_{23}ClFN_5O_3S$: $(M+H)^+$: 528.1.

Example 237

[1212]



[1213] $C_{21}H_{17}ClFN_5O_4$

[1214] Exact Mass: 457.10

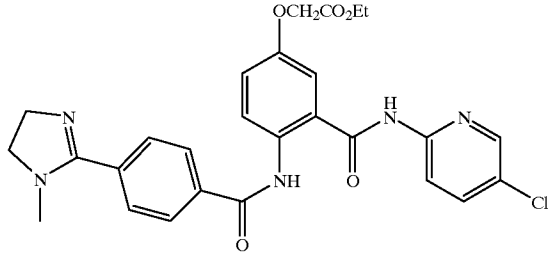
[1215] Mol. Wt.: 457 84

[1216] The title compound was synthesized according to the procedure described previously.

[1217] MS found for $C_{21}H_{17}ClFN_5O_4$: $(M+H)^+$: 458.1.

Example 238

[1218]



[1219] $C_{27}H_{26}ClN_5O_5$

[1220] Exact Mass: 535.16

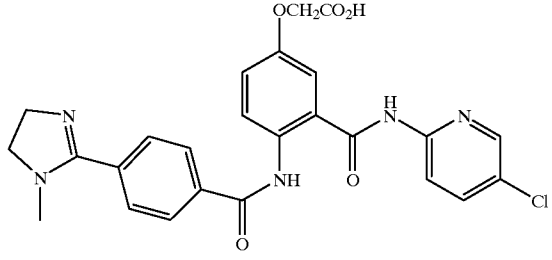
[1221] Mol. Wt.: 535.98

[1222] The title compound was synthesized according to the procedure described previously.

[1223] MS found for $C_{27}H_{26}ClN_5O_5$: $(M+H)^+$: 536.1.

Example 239

[1224]



[1225] $C_{25}H_{22}ClN_5O_5$

[1226] Exact Mass: 507.13

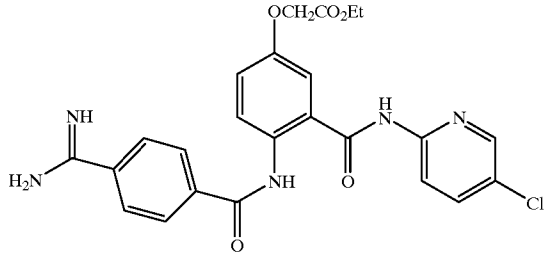
[1227] Mol. Wt.: 507.93

[1228] The title compound was synthesized according to the procedure described previously.

[1229] MS found for $C_{25}H_{22}ClN_5O_5$: $(M+H)^+$: 508.1.

Example 240

[1230]



[1231] $C_{24}H_{22}ClN_5O_5$

[1232] Exact Mass: 495.13

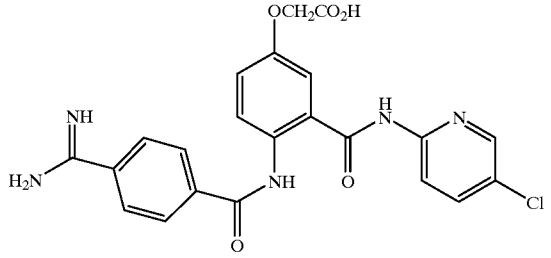
[1233] Mol. Wt.: 495.91

[1234] The title compound was synthesized according to the procedure described previously.

[1235] MS found for $C_{24}H_{22}ClN_5O_5$: $(M+H)^+$: 496.1.

Example 241

[1236]



[1237] $C_{22}H_{18}ClN_5O_5$

[1238] Exact Mass: 467.10

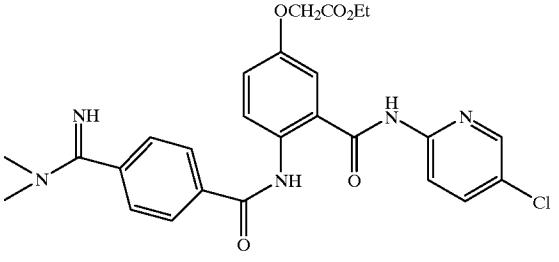
[1239] Mol. Wt.: 467.86

[1240] The title compound was synthesized according to the procedure described previously.

[1241] MS found for $C_{22}H_{18}ClN_5O_5$; $(M+H)^+$: 468.1.

Example 242

[1242]



[1243] $C_{26}H_{26}ClN_5O_5$

[1244] Exact Mass: 523.16

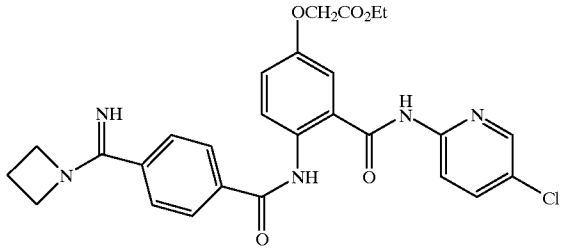
[1245] Mol. Wt.: 523.97

[1246] The title compound was synthesized according to the procedure described previously.

[1247] MS found for $C_{26}H_{26}ClN_5O_5$: $(M+H)^+$: 524.2.

Example 243

[1248]



[1249] $C_{27}H_{26}ClN_5O_5$

[1250] Exact Mass: 535.16

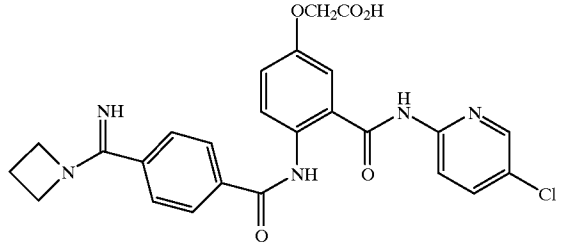
[1251] Mol. Wt.: 535.98

[1252] The title compound was synthesized according to the procedure described previously.

[1253] MS found for $C_{27}H_{26}ClN_5O_5$: $(M+H)^+$: 536.1.

Example 244

[1254]



[1255] $C_{25}H_{22}ClN_5O_5$

[1256] Exact Mass: 507.13

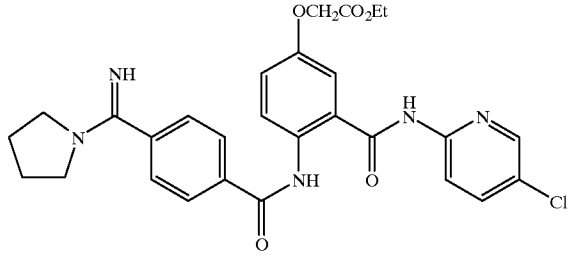
[1257] Mol. Wt.: 507.93

[1258] The title compound was synthesized according to the procedure described previously.

[1259] MS found for $C_{25}H_{22}ClN_5O_5$: $(M+H)^+$: 508.1.

Example 245

[1260]



[1261] $C_{28}H_{28}ClN_5O_5$

[1262] Exact Mass: 549.18

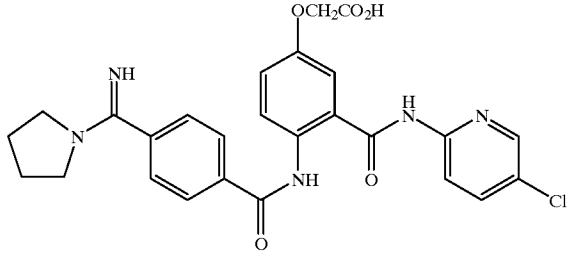
[1263] Mol. Wt.: 550.01

[1264] The title compound was synthesized according to the procedure described previously.

[1265] MS found for $C_{28}H_{28}ClN_5O_5$: $(M+H)^+$: 550.2.

Example 246

[1266]



[1267] $C_{26}H_{24}ClN_5O_5$

[1268] Exact Mass: 521.15

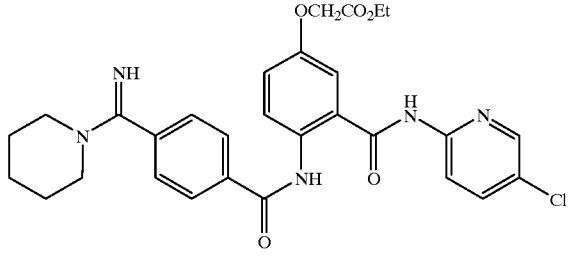
[1269] Mol. Wt.: 521.95

[1270] The title compound was synthesized according to the procedure described previously.

[1271] MS found for $C_{26}H_{24}ClN_5O_5$: $(M+H)^+$: 522.1.

Example 247

[1272]



[1273] $C_{29}H_{30}ClN_5O_5$

[1274] Exact Mass: 563.19

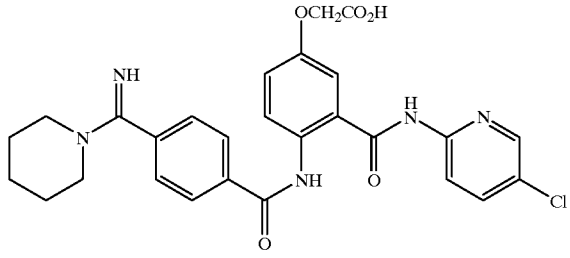
[1275] Mol. Wt.: 564.03

[1276] The title compound was synthesized according to the procedure described previously.

[1277] MS found for $C_{29}H_{30}ClN_5O_5$: $(M+H)^+$: 564.2.

Example 248

[1278]



[1279] $C_{27}H_{26}ClN_5O_5$

[1280] Exact Mass: 535.16

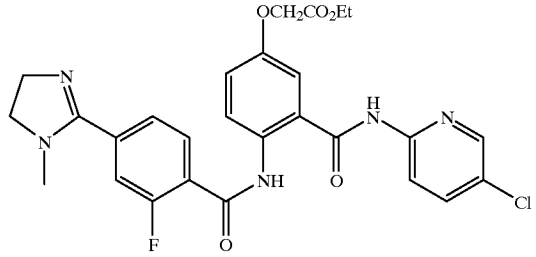
[1281] Mol. Wt.: 535.98

[1282] The title compound was synthesized according to the procedure described previously.

[1283] MS found for $C_{27}H_{26}ClN_5O_5$: $(M+H)^+$: 536.1.

Example 249

[1284]



[1285] $C_{27}H_{25}ClFN_5O_5$

[1286] Exact Mass: 553.15

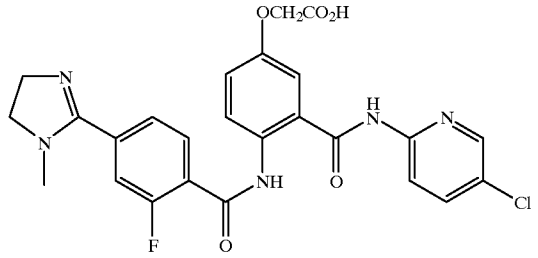
[1287] Mol. Wt.: 553.97

[1288] The title compound was synthesized according to the procedure described previously.

[1289] MS found for $C_{27}H_{25}ClFN_5O_5$: $(M+H)^+$. 554.2.

Example 250

[1290]



[1291] $C_{25}H_{21}ClFN_5O_5$

[1292] Exact Mass: 525.12

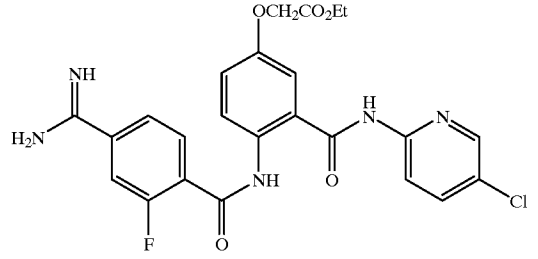
[1293] Mol. Wt.: 525.92

[1294] The title compound was synthesized according to the procedure described previously.

[1295] MS found for $C_{25}H_{21}ClFN_5O_5$: $(M+H)^+$: 526.1.

Example 251

[1296]



[1297] $C_{24}H_{21}ClFN_5O_5$

[1298] Exact Mass: 513.12

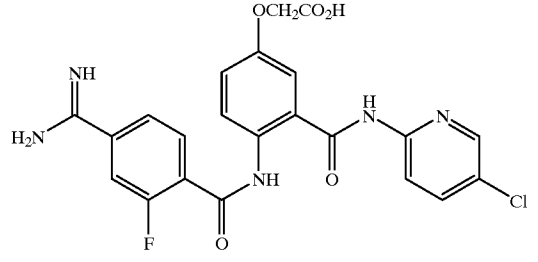
[1299] Mol. Wt.: 513.91

[1300] The title compound was synthesized according to the procedure described previously.

[1301] MS found for $C_{24}H_{21}ClFN_5O_5$: $(M+H)^+$: 514.1.

Example 252

[1302]



[1303] $C_{22}H_{17}ClFN_5O_5$

[1304] Exact Mass: 485.09

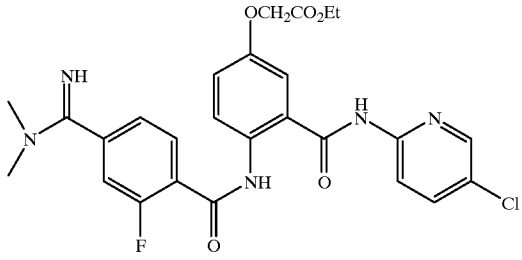
[1305] Mol. Wt.: 485.85

[1306] The title compound was synthesized according to the procedure described previously.

[1307] MS found for $C_{22}H_{17}ClFN_5O_5$: $(M+H)^+$: 486.

Example 253

[1308]



[1309] $C_{26}H_{25}ClFN_5O_5$

[1310] Exact Mass: 541.15

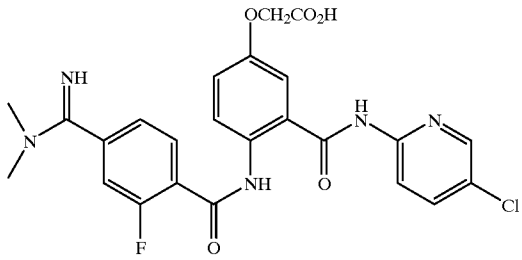
[1311] Mol. Wt.: 541.96

[1312] The title compound was synthesized according to the procedure described previously.

[1313] MS found for $C_{26}H_{25}ClFN_5O_5$: $(M+H)^+$: 542.1.

Example 254

[1314]



[1315] $C_{25}H_{21}ClFN_5O_5$

[1316] Exact Mass: 513,12

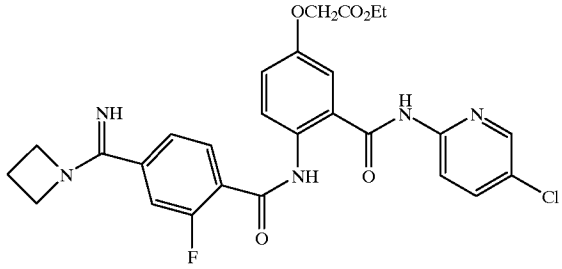
[1317] Mol. Wt.: 513.91

[1318] The title compound was synthesized according to the procedure described previously.

[1319] MS found for $C_{24}H_{21}ClFN_5O_5$: $(M+H)^+$: 514.1.

Example 255

[1320]



[1321] $C_{27}H_{25}ClFN_5O_5$

[1322] Exact Mass: 553.15

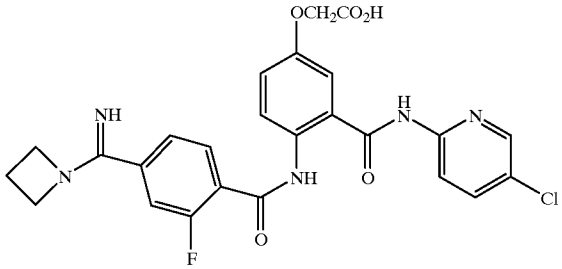
[1323] Mol. Wt.: 553.97

[1324] The title compound was synthesized according to the procedure described previously.

[1325] MS found for $C_{27}H_{25}ClFN_5O_5$: $(M+H)^+$: 554.1.

Example 256

[1326]



[1327] $C_{27}H_{21}ClFN_5O_5$

[1328] Exact Mass: 525 12

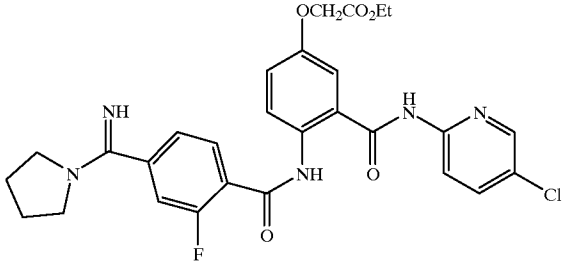
[1329] Mol. Wt.: 525.92

[1330] The title compound was synthesized according to the procedure described previously.

[1331] MS found for $C_{25}H_{21}ClFN_5O_5$: $(M+H)^+$: 526.1.

Example 257

[1332]



[1333] $C_{28}H_{27}ClFN_5O_5$

[1334] Exact Mass: 567.17

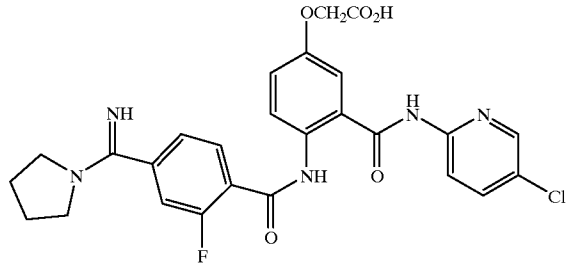
[1335] Mol. Wt.: 568.00

[1336] The title compound was synthesized according to the procedure described previously.

[1337] MS found for $C_{28}H_{27}ClFN_5O_5$: $(M+H)^+$: 568.1.

Example 258

[1338]



[1339] $C_{26}H_{23}ClFN_5O_5$

[1340] Exact Mass: 539.14

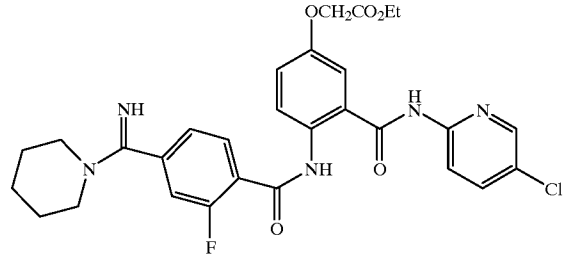
[1341] Mol. Wt.: 539.94

[1342] The title compound was synthesized according to the procedure described previously.

[1343] MS found for $C_{26}H_{23}ClFN_5O_5$: $(M+H)^+$: 540.1.

Example 259

[1344]



[1345] $C_{29}H_{29}ClFN_5O_5$

[1346] Exact Mass: 581.18

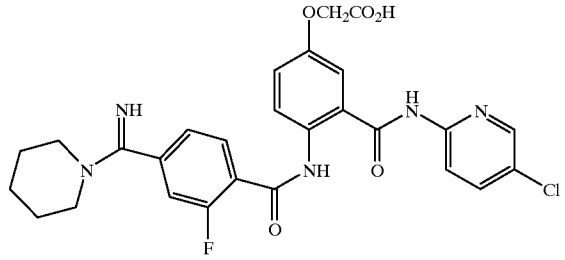
[1347] Mol. Wt.: 582.02

[1348] The title compound was synthesized according to the procedure described previously.

[1349] MS found for $C_{29}H_{29}ClFN_5O_5$: $(M+H)^+$: 582.2.

Example 260

[1350]



[1351] $C_{27}H_{25}ClFN_5O_5$

[1352] Exact Mass: 553.15

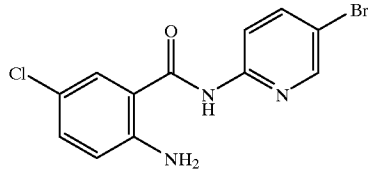
[1353] Mol. Wt.: 553.97

[1354] The title compound was synthesized according to the procedure described previously.

[1355] MS found for $C_{27}H_{25}ClN_5O_5$: $(M+H)^+$: 554.1.

Example 261

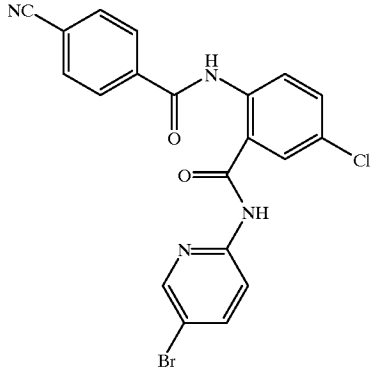
[1356] Step 1:



[1357] To a solution of 2-amino-5-bromopyridine (882 mg, 5.1 mmol) in tetrahydrofuran (5 ml) was added 0.5M potassium bis(trimethylsilyl)amide in toluene (20 ml, 10.1 mmol) dropwise at −78° C. After stirred for additional 0.5 hr at −78° C., the mixture was added 5-chloroisatoic anhydride (1 g, 5.1 mmol) at −78° C. The mixture was warmed up to r.t gradually and stirred overnight. After concentrated, the crude was washed with saturated ammonium chloride solution and extracted by ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated to give (2-amino-5-bromophenyl)-N-(5-chloro(2-pyridyl))carboxamide as yellow solid (1.54 g. 92%).

[1358] MS found for C12H9BrClN3O M^{30} =327, $(M+2)^+$=329.

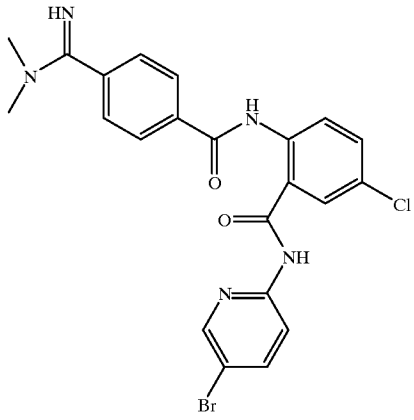
[1359] Step 2:



[1360] To a solution of the compound of (2-amino-5-bromophenyl)-N-(5-chloro(2-pyridyl))carboxamide (1.33 g, 4.07 mmol) in dichloromethane (10 ml) was added 4-cyanobenzoly chloride (808 mg, 4.88 mmol) and pyridine (1 ml, 12.21 mmol). The mixture was stirred at r.t. overnight. The precipitate was filtered and washed with a little amount of dichloromethane to give N-{4-chloro-2-[N-(5-bromo(2-pyridyl))carbamoyl]phenyl}(4-cyanophenyl)carboxamide as yellow solid (1.36 g, 73%).

[1361] MS found for C20H12BrClN4O2 M^+=455, $(M+2)^+$=457.

[1362] Step 3:

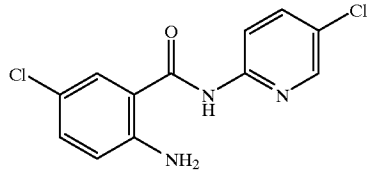


[1363] To a solution of the compound of N-{4-chloro-2-[N-(5-bromo(2-pyridyl))carbamoyl]phenyl}(4-cyanophenyl)carboxamide (1.36 g, 3 mmol) in anhydrous pyridine (20 ml) and triethyl amine (2 ml) was saturated with hydrogen sulfide gas at 0° C. The mixture was stirred at r.t. overnight. After concentrated, the residue was dissolved in anhydrous acetone (20 ml) and iodomethane (1.87 ml. 30 mmol) was added. The mixture was refluxed for 2 hrs. After concentrated, the residue was dissolved in anhydrous methanol (20 ml) and a solution of 2M dimethylamine (in THF) (15 ml, 30 mmol) and acetic acid (10 ml) in anhydrous methanol (5 ml) was added. The mixture was refluxed for 2 hrs. After concentrated, the crude residue was purified by RP-HPLC to give target as white solid (750 mg, 50%).

[1364] MS found C22H19BrClN5O2 M^{30} =500, $(M+2)^+$= 502.

Example 262

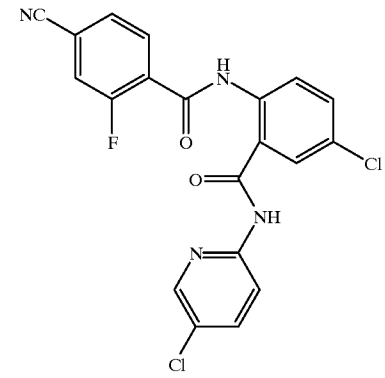
[1365] Step 1:



[1366] To a solution of 2-amino-5-chloropyridine (787 mg, 6.1 mmol) in tetrahydrofuran (5 ml) was added 0.5M potassium bis(trimethylsilyl)amide in toluene (20 ml, 10.1 mmol) dropwise at −78° C. After stirred for additional 0.5 hr at −78° C., the mixture was added 5-chloroisatoic anhydride (1 g, 5.1 mmol) at −78° C. The mixture was warmed up to r.t gradually and stirred overnight. After concentrated, the crude was washed with saturated ammonium chloride solution and extracted by ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated to give (2-amino-5-chlorophenyl)-N-(5-chloro(2-pyridyl))carboxamide as yellow solid (1.39 g. 99%).

[1367] MS found for C12H9Cl2N3O M^{30} =282, $(M+2)^+$= 284.

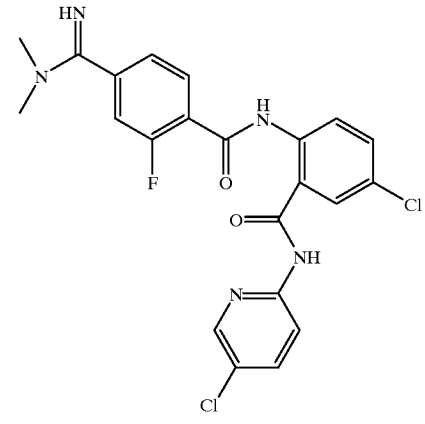
[1368] Step 2:



[1369] A solution of 2-fluoro-4-cyanobenzoic acid (1 g, 6.06 mmol) in thionyl chloride (5 ml) was refluxed for 2 hr. After concentration, the residue was dissolved in dichloromethane (5 ml). And a solution of the compound of (2-amino-5-chlorophenyl)-N-(5-chloro(2-pyridyl))carboxamide (1.2 g, 4.25 mmol) in dichloromethane (10 ml) and pyridine (1.47 ml, 18.18 mmol) were added. The mixture was stirred at r.t. overnight. The precipitate was filtered and washed with a little amount of dichloromethane to give N-{4-chloro-2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}(2-fluoro-4-cyanophenyl)carboxamide (2.03 g, 78%).

[1370] MS found for C20H11Cl2FN4O2 M^{30} =429, $(M+2)^+$=431.

[1371] Step 3:



[1372] To a solution of the compound of N-{4-chloro-2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl (2-fluoro-4-cy-

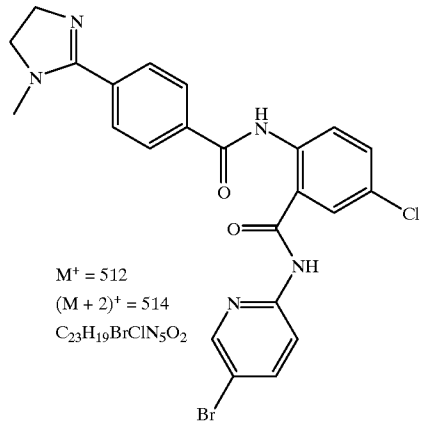
anophenyl)carboxamide (3 g, 7 mmol) in anhydrous pyridine (40 ml) and triethyl amine (4 ml) was saturated with hydrogen sulfide gas at 0° C. The mixture was stirred at r.t. overnight. After concentrated, the residue was dissolved in anhydrous acetone (60 ml) and iodomethane (4.36 ml, 70 mmol) was added. The mixture was refluxed for 2 hrs. After concentrated, the residue was dissolved in anhydrous methanol (50 ml) and a solution of 2M dimethylamine (in THF) (35 ml, 70 mmol) and acetic acid (30 ml) in anhydrous methanol (15 ml) was added. The mixture was refluxed for 2 hrs. After concentrated, the crude residue was purified by RP-HPLC to give target as white solid (1.7 g, 50%).

[1373] MS found C22H18Cl2FN5O2 M^{30} =474, $(M+2)^+$= 476.

Examples 263-280

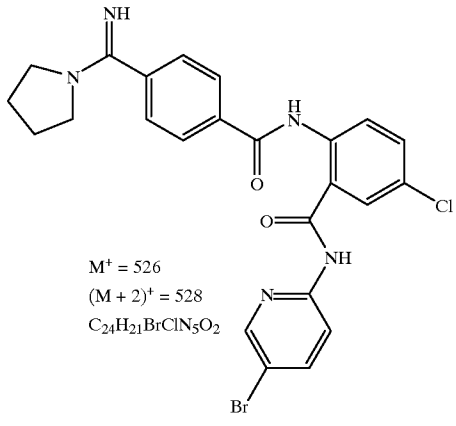
[1374] The following compounds were similarly prepared.

Example 263



$M^+ = 512$
$(M + 2)^+ = 514$
$C_{23}H_{19}BrClN_5O_2$

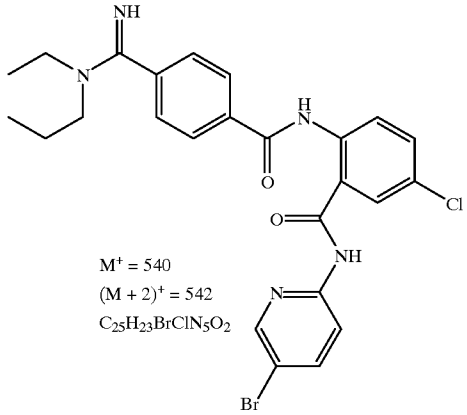
Example 264



$M^+ = 526$
$(M + 2)^+ = 528$
$C_{24}H_{21}BrClN_5O_2$

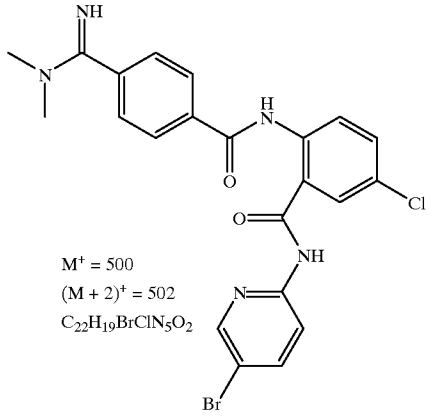
-continued

Example 265



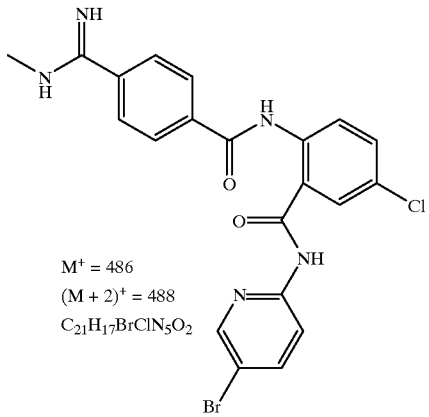
$M^+ = 540$
$(M + 2)^+ = 542$
$C_{25}H_{23}BrClN_5O_2$

Example 266



$M^+ = 500$
$(M + 2)^+ = 502$
$C_{22}H_{19}BrClN_5O_2$

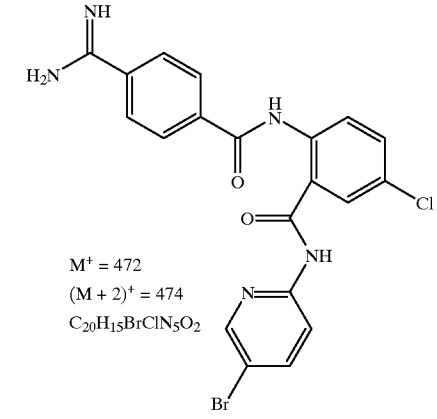
Example 267



$M^+ = 486$
$(M + 2)^+ = 488$
$C_{21}H_{17}BrClN_5O_2$

-continued

Example 268

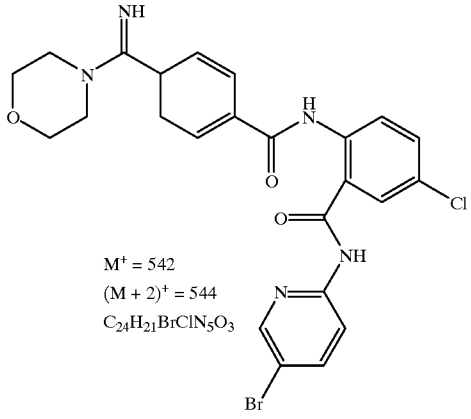


$M^+ = 472$

$(M + 2)^+ = 474$

$C_{20}H_{15}BrClN_5O_2$

Example 269

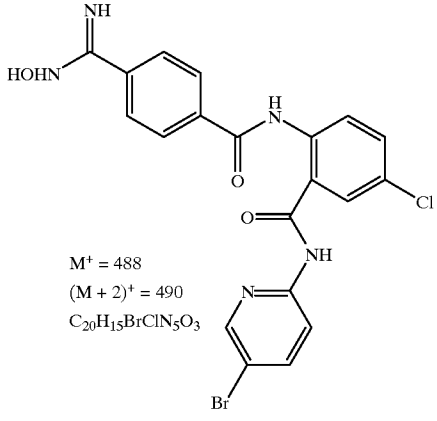


$M^+ = 542$

$(M + 2)^+ = 544$

$C_{24}H_{21}BrClN_5O_3$

Example 270



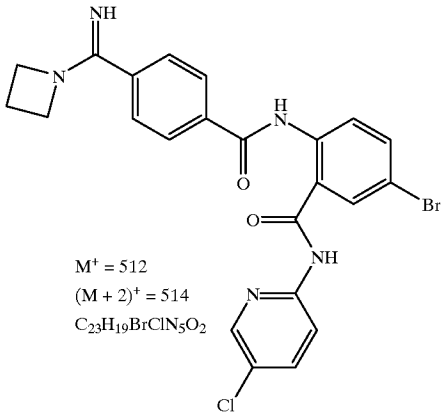
$M^+ = 488$

$(M + 2)^+ = 490$

$C_{20}H_{15}BrClN_5O_3$

-continued

Example 271

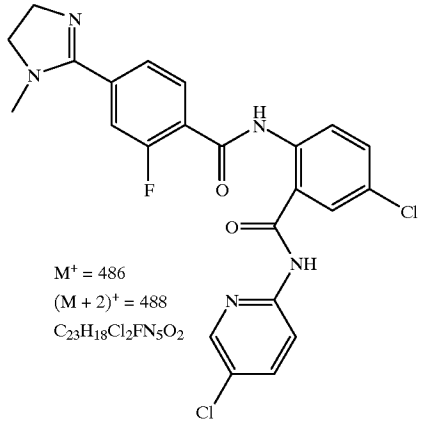


$M^+ = 512$

$(M + 2)^+ = 514$

$C_{23}H_{19}BrClN_5O_2$

Example 272

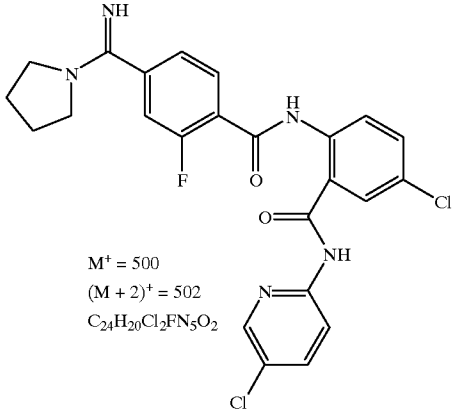


$M^+ = 486$

$(M + 2)^+ = 488$

$C_{23}H_{18}Cl_2FN_5O_2$

Example 273



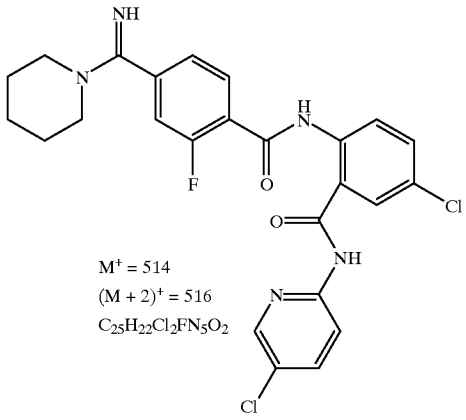
$M^+ = 500$

$(M + 2)^+ = 502$

$C_{24}H_{20}Cl_2FN_5O_2$

-continued

Example 274

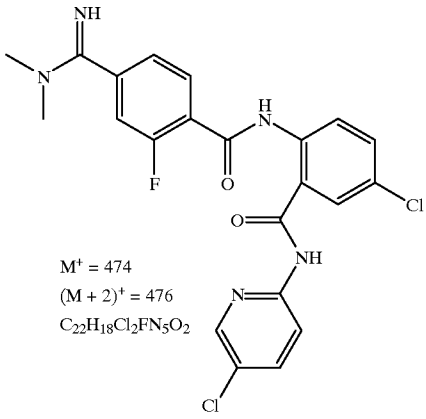


$M^+ = 514$

$(M + 2)^+ = 516$

$C_{25}H_{22}Cl_2FN_5O_2$

Example 275

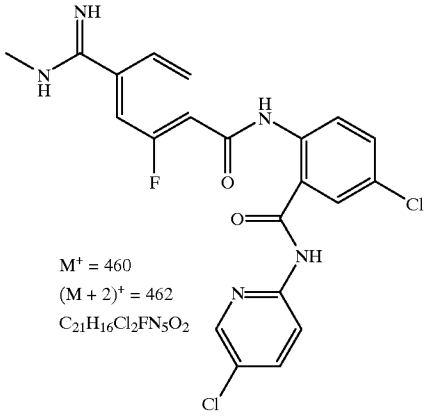


$M^+ = 474$

$(M + 2)^+ = 476$

$C_{22}H_{18}Cl_2FN_5O_2$

Example 276



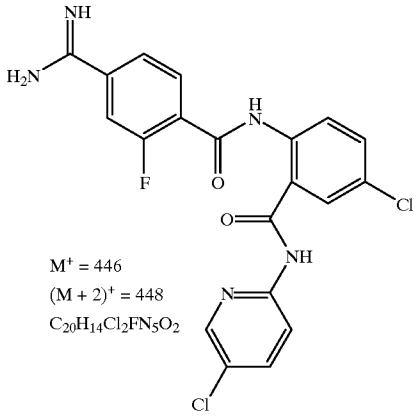
$M^+ = 460$

$(M + 2)^+ = 462$

$C_{21}H_{16}Cl_2FN_5O_2$

-continued

Example 277

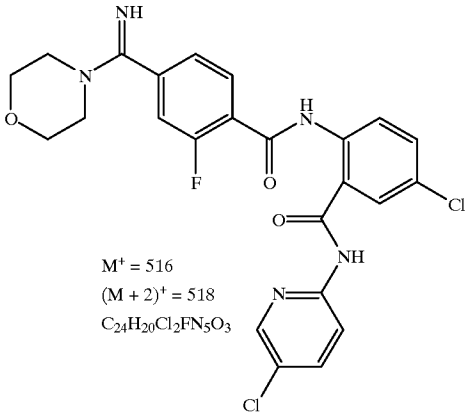


$M^+ = 446$

$(M + 2)^+ = 448$

$C_{20}H_{14}Cl_2FN_5O_2$

Example 278

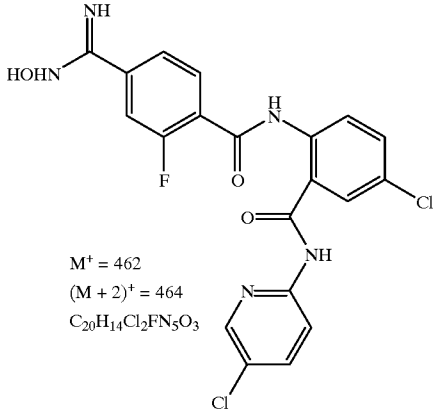


$M^+ = 516$

$(M + 2)^+ = 518$

$C_{24}H_{20}Cl_2FN_5O_3$

Example 279



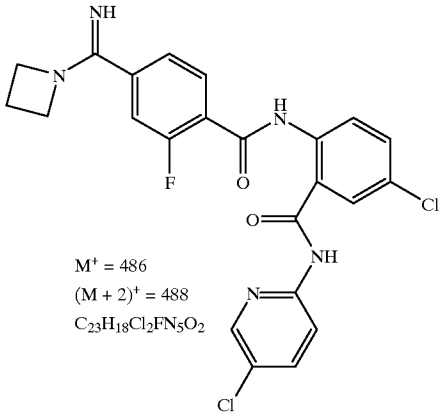
$M^+ = 462$

$(M + 2)^+ = 464$

$C_{20}H_{14}Cl_2FN_5O_3$

-continued

Example 280



$M^+ = 486$

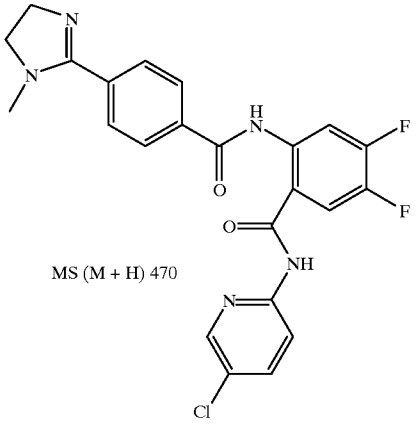
$(M + 2)^+ = 488$

$C_{23}H_{18}Cl_2FN_5O_2$

Examples 281-287

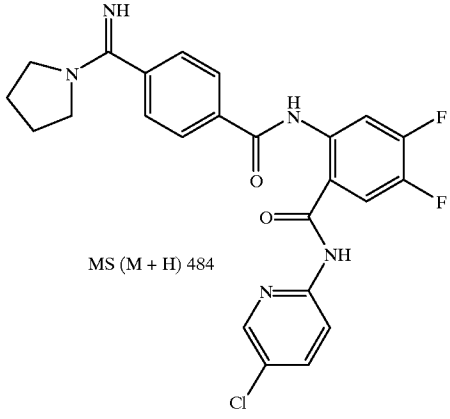
[1375] The following compounds were similarly prepared.

Example 281



MS (M + H) 470

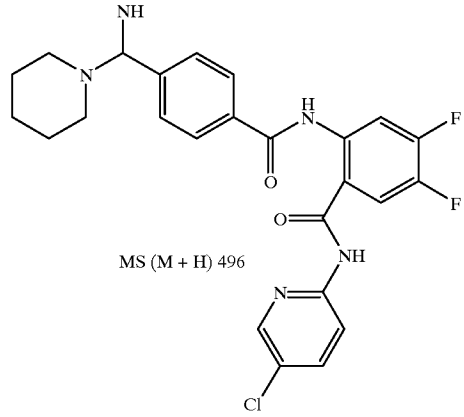
Example 282



MS (M + H) 484

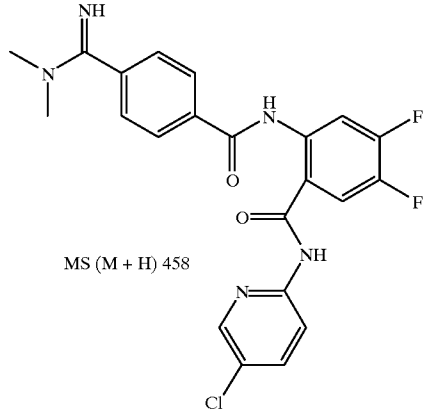
-continued

Example 283



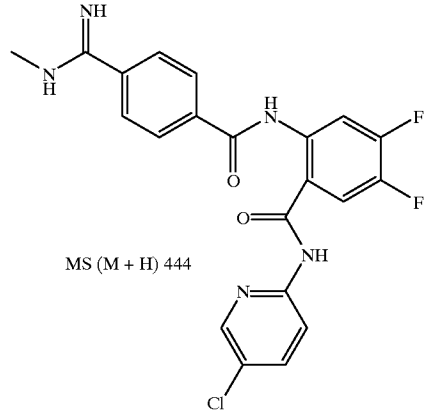
MS (M + H) 496

Example 284



MS (M + H) 458

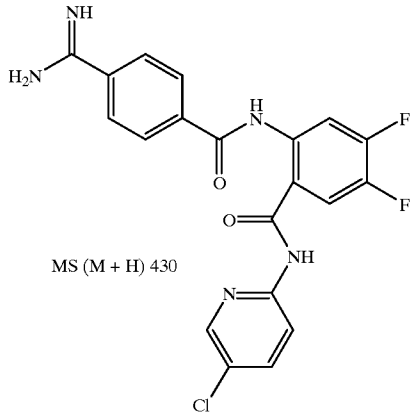
Example 285



MS (M + H) 444

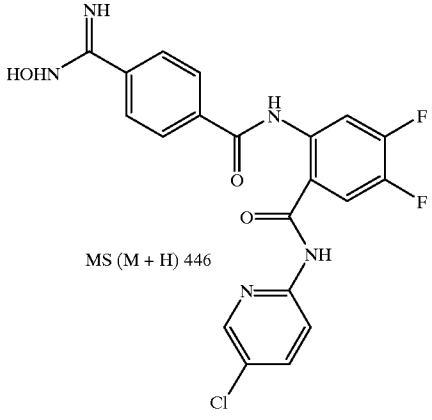
-continued

Example 286



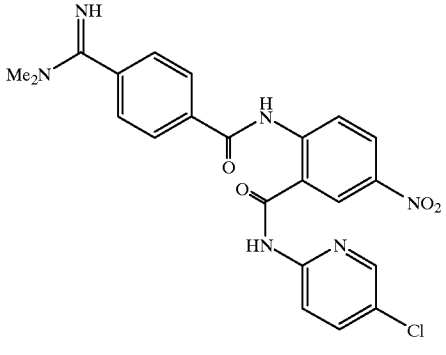
MS (M + H) 430

Example 287



MS (M + H) 446

Example 288



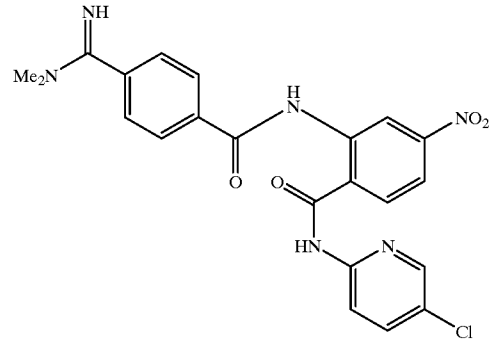
[1376] Step 1: A solution of methyl 2-amino-5-nitrobenzoate (1 equiv) and 4-cyanobenzoic acid (1 equiv) in pyridine was treated with $POCl_3$ (1.1 equiv) for 1 h. The resulting mixture was quenched by slow addition of water, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and flash chromatographied to give the desired product.

[1377] Step 2: A solution of 2-amino-5-bromopridine (45 mg, 4.0 equiv) in 5 mL of methylene chloride treated with $AlMe_3$ (2M in hexane, 0.65 mL, 20 equiv) for 30 min was added the compound obtained in step 1 (0.064 mmol, 1 equiv). The mixture was stirred at rt overnight, quenched with saturated aqueous potassium sodium tartrate. The organic layer was dried over $MgSO_4$, filtered, evaporated and purified by column chromatography to give the desired product.

[1378] Step 3: The product obtained in step 2 was subjected to standard Pinner conditions to give the title compound after HPLC (C18 reversed phase, eluting with 0.5% TFA in H_2O/CH_3CN). MS $(M+H)^+$: 467.

Example 289

[1379]

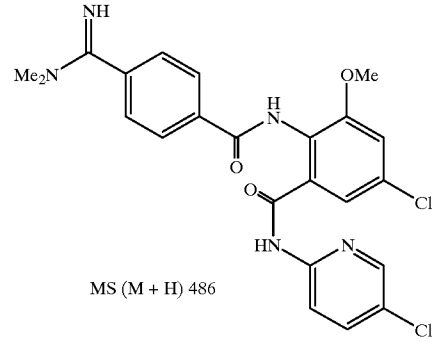


[1380] This compound was prepared according to the procedure previously described. MS $(M+H)^+$: 467.

Example 290-302

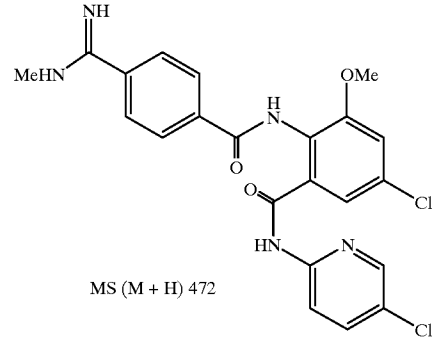
[1381] The following compounds were prepared according to the procedure previously described.

Example 290



MS (M + H) 486

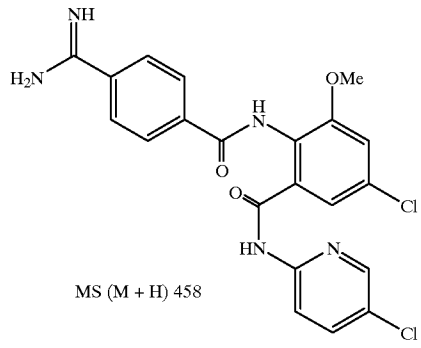
Example 291



MS (M + H) 472

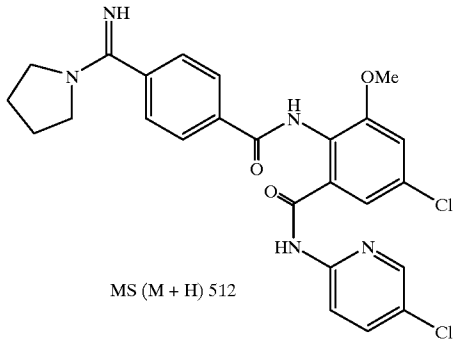
-continued

Example 292



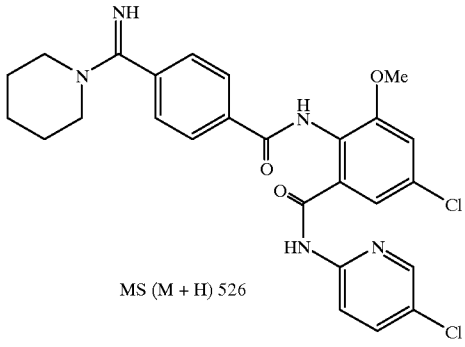
MS (M + H) 458

Example 293



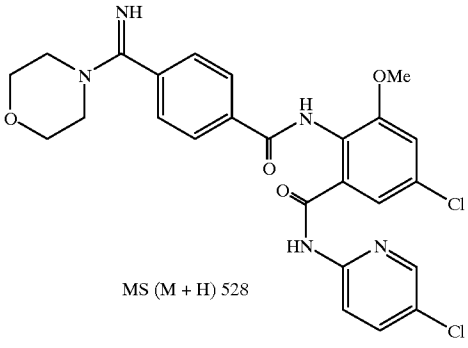
MS (M + H) 512

Example 294



MS (M + H) 526

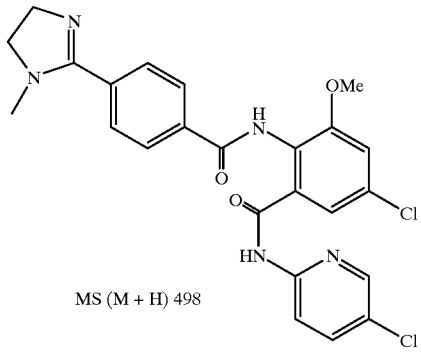
Example 295



MS (M + H) 528

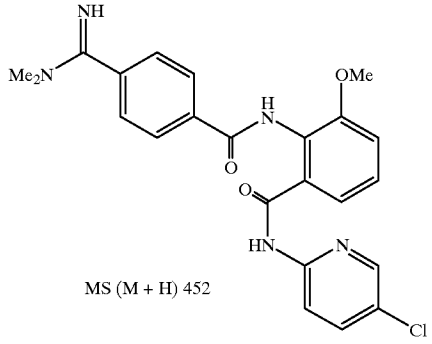
-continued

Example 296



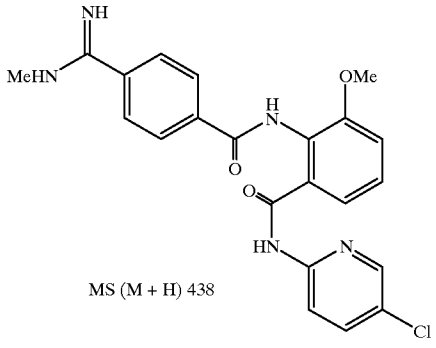
MS (M + H) 498

Example 297



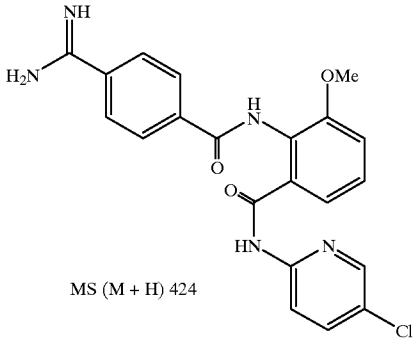
MS (M + H) 452

Example 298



MS (M + H) 438

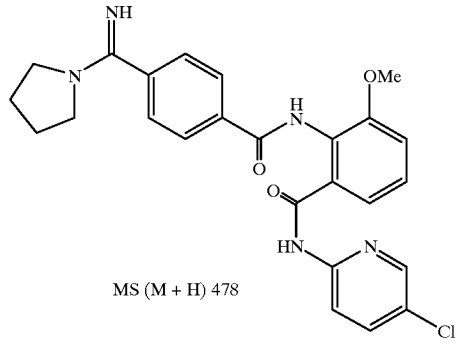
Example 299



MS (M + H) 424

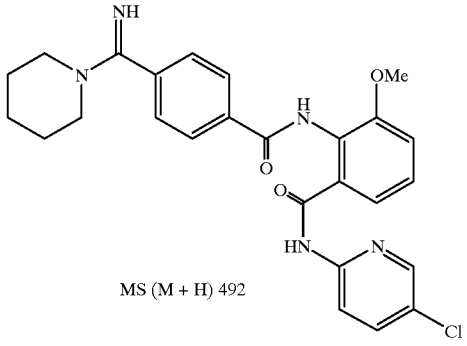
-continued

Example 300



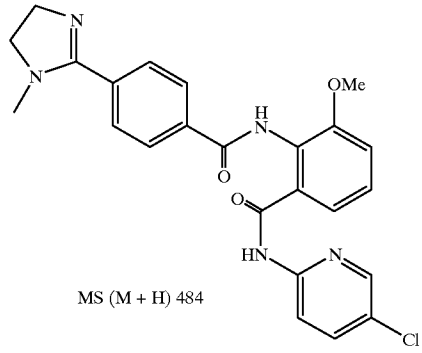
MS (M + H) 478

Example 301



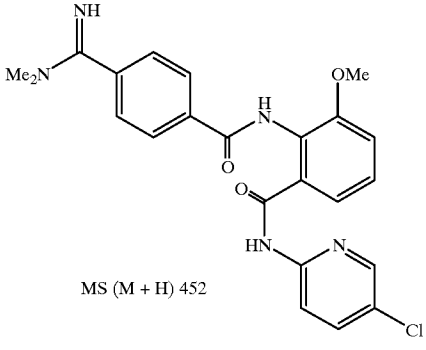
MS (M + H) 492

Example 302



MS (M + H) 484

Example 303



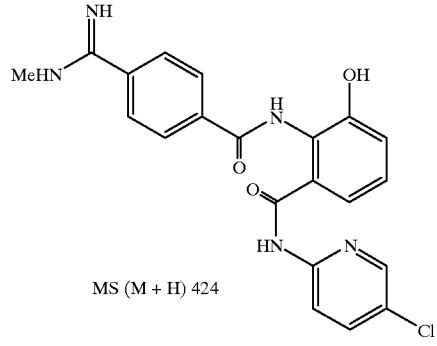
MS (M + H) 452

[1382] Example 297 (1 equiv) in CH_2Cl_2 was treated with BBr_3 (4 equiv) overnight, quenched with ice water. HPLC (C18 reversed phase, eluting with 0.5% TFA in H_2O/CH_3CN) gave the title compound. MS $(M+H)^+$: 438.

Example 304-308

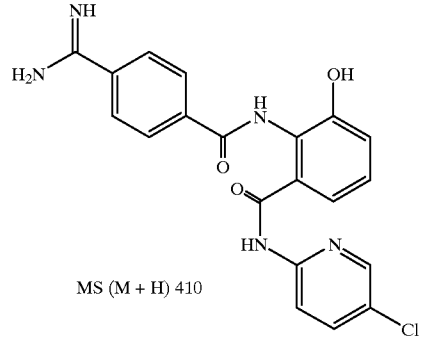
[1383] The following compounds were prepared according to the procedure previously described.

Example 304



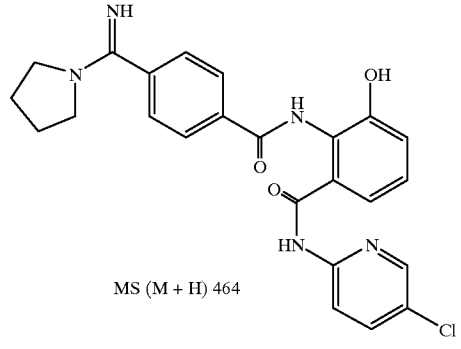
MS (M + H) 424

Example 305



MS (M + H) 410

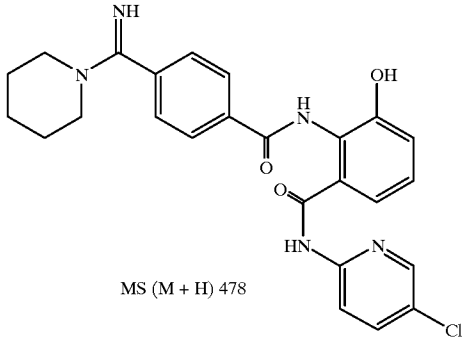
Example 306



MS (M + H) 464

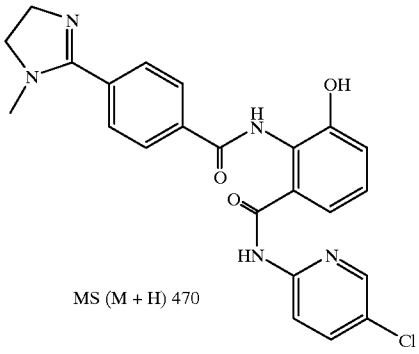
-continued

Example 307



MS (M + H) 478

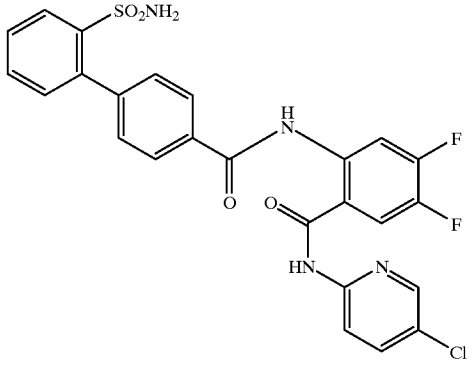
Example 308



MS (M + H) 470

Example 309

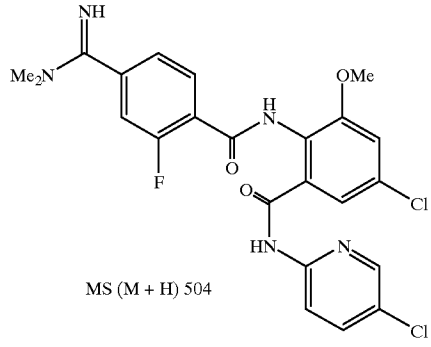
[1384] This compound was prepared according to the procedure previously described. MS $(M+H)^+$: 543.



Example 310-315

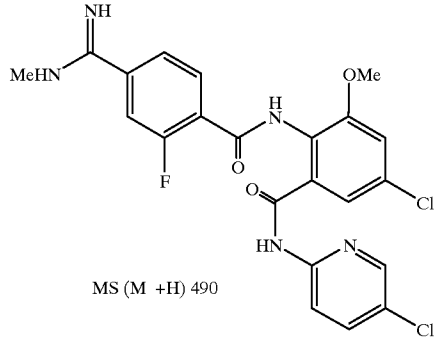
[1385] The following compounds were prepared according to the procedure previously described.

Example 310



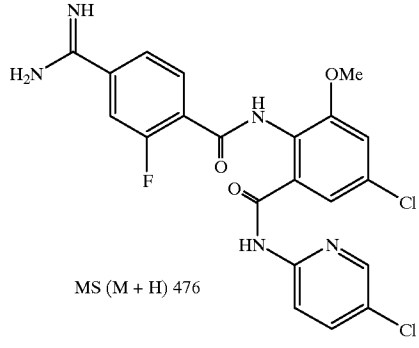
MS (M + H) 504

Example 311



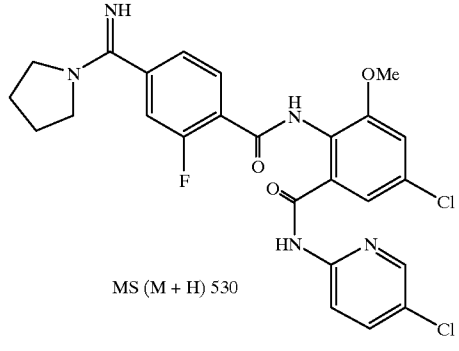
MS (M +H) 490

Example 312



MS (M + H) 476

Example 313



MS (M + H) 530

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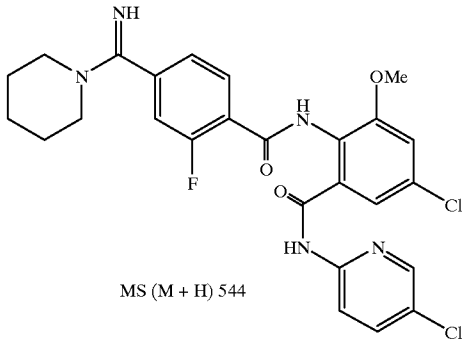
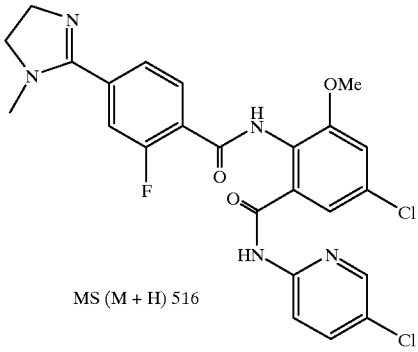
Example 314



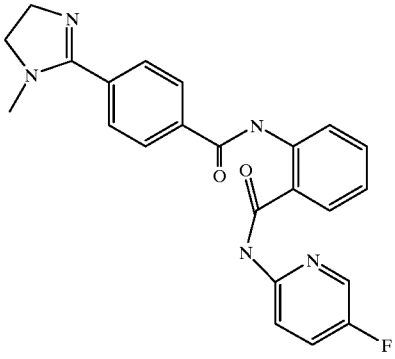
MS (M + H) 544

Example 315



MS (M + H) 516

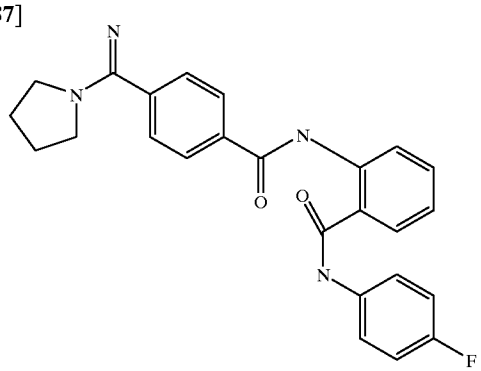
Example 316



[1386] The title compound was synthesized according to the procedure described previously. ES-MS 417(M+1).

Example 317

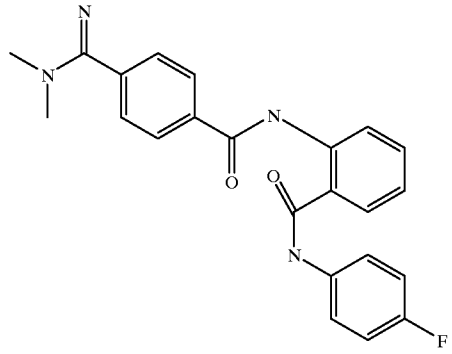
[1387]



[1388] The title compound was synthesized according to the procedure described previously. ES-MS 431(M+1).

Example 318

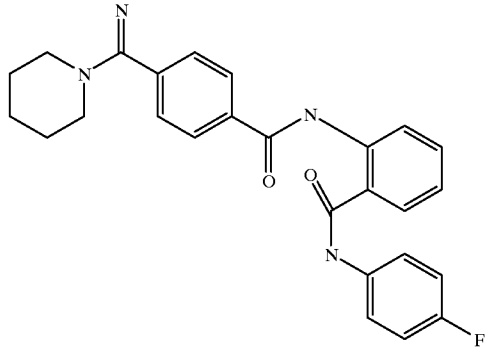
[1389]



[1390] The title compound was synthesized according to the procedure described previously. ES-MS 404(M+1).

Example 319

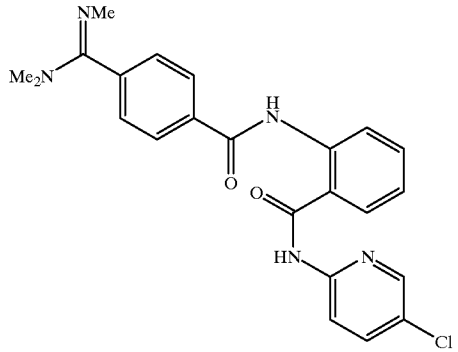
[1391]



[1392] The title compound was synthesized according to the procedure described previously. ES-MS 445(M+1).

Example 320

[1393]

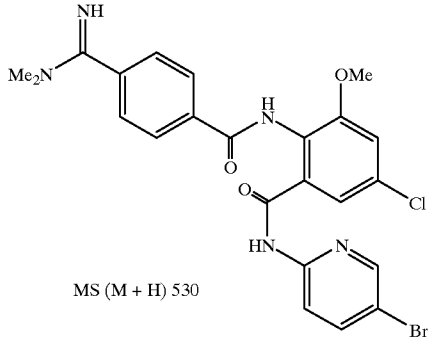


[1394] Example 53 (15 mg) was refluxed in pyridine in the presence of 0.1 mL of MeI overnight. The volatile was evaporated and the residue was purified by HPLC to give example 403. MS (M+H): 436.

Examples 321-322

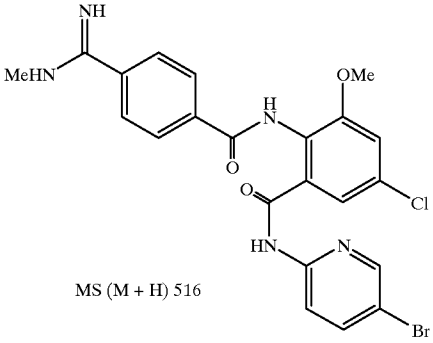
[1395] The following compounds were prepared according to the procedure previously described.

Example 321



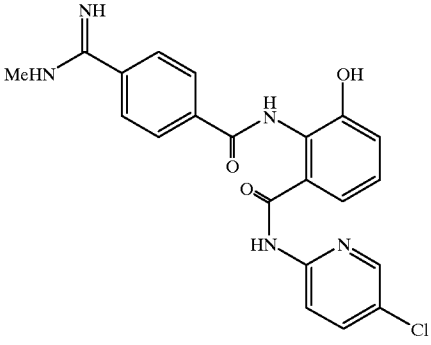
MS (M + H) 530

Example 322



MS (M + H) 516

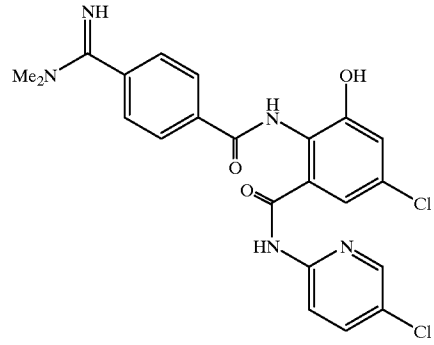
Example 323



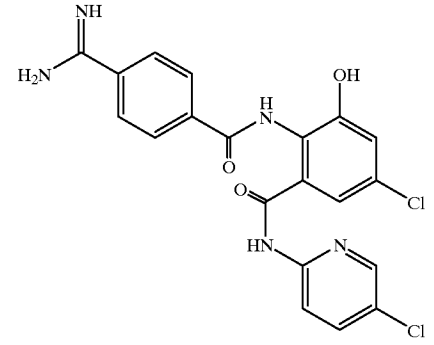
[1396] Compound 304 (20 mg) was dissolved in 10 mL of CH_2Cl_2 and was treated with 2 mL of BBr_3 (1N in CH_2Cl2) overnight. The reaction was quenched with water and reverse phase HPLC gave the desired product. ES-MS 424 (M+H).

Example 324-336

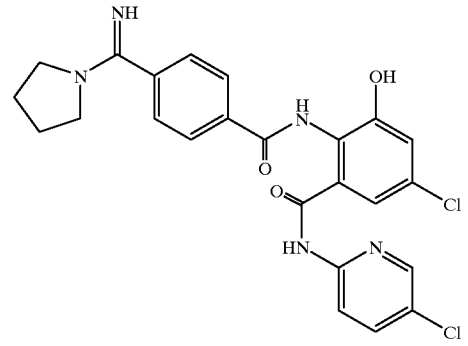
[1397] The following compounds were prepared according to the procedure previously described.



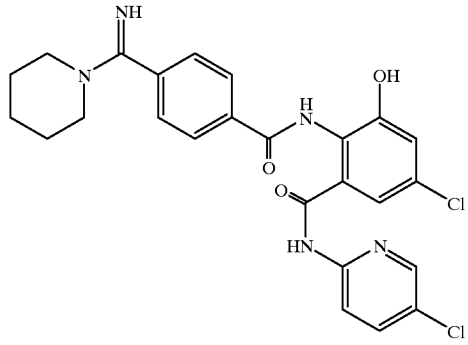
Example 324
MS (M + H) 472



Example 325
MS (M + H) 444

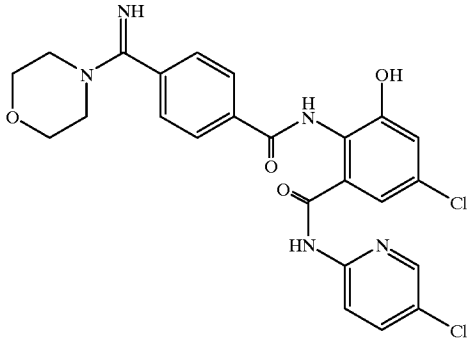


Example 326
MS (M + H) 498

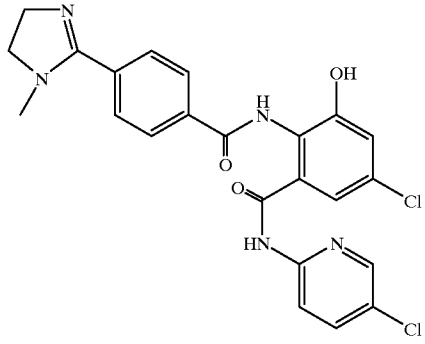


Example 327
MS (M + H) 512

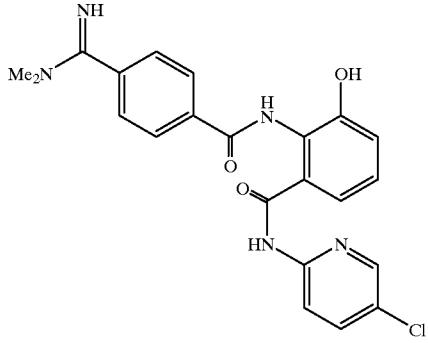
-continued



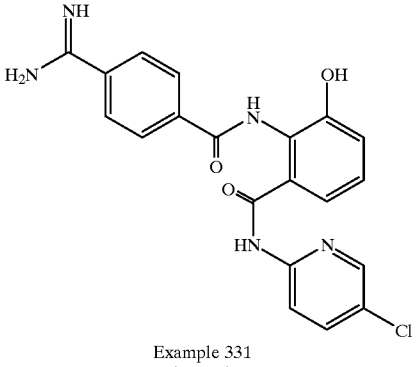
Example 328
MS (M + H) 514



Example 329
MS (M + H) 484

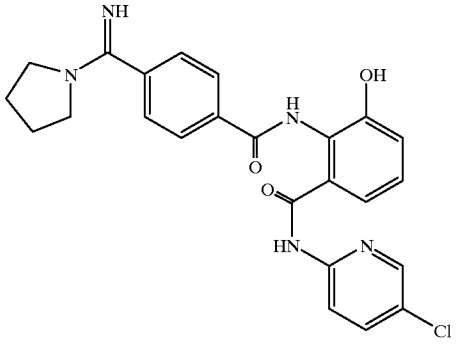


Example 330
MS (M + H) 438

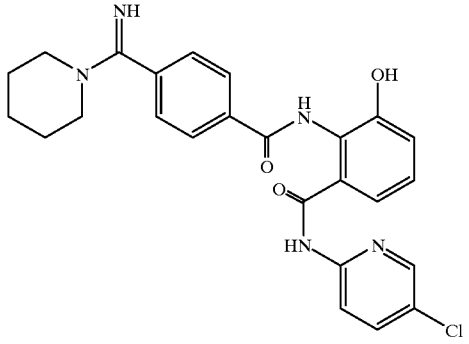


Example 331
MS (M + H) 410

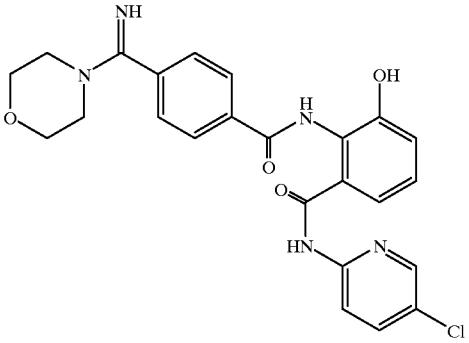
-continued



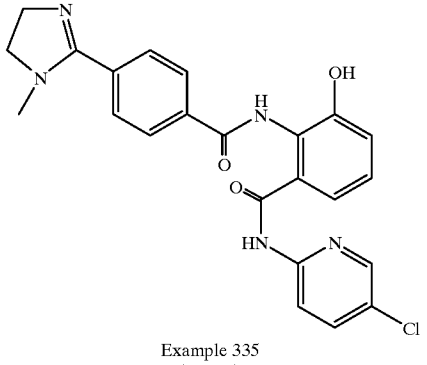
Example 332
MS (M + H) 464



Example 333
MS (M + H) 478

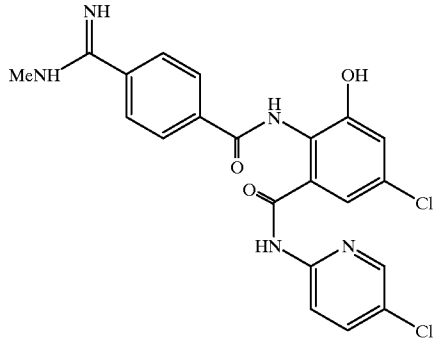


Example 334
MS (M + H) 480



Example 335
MS (M + H) 450

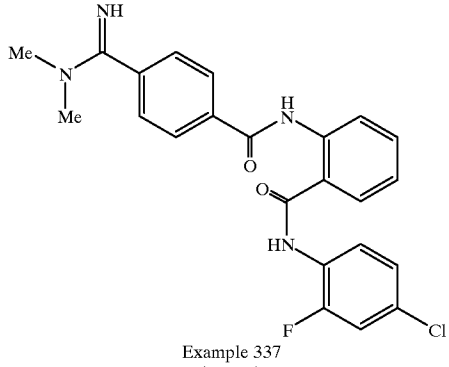
-continued



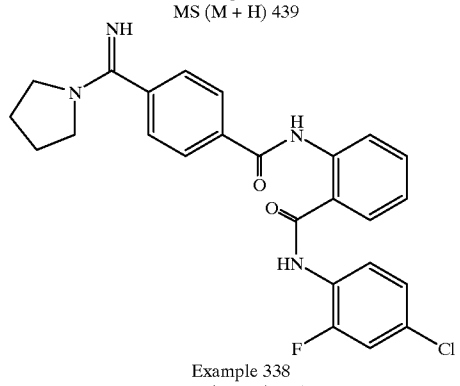
Example 336
MS (M + H) 458

Example 337-344

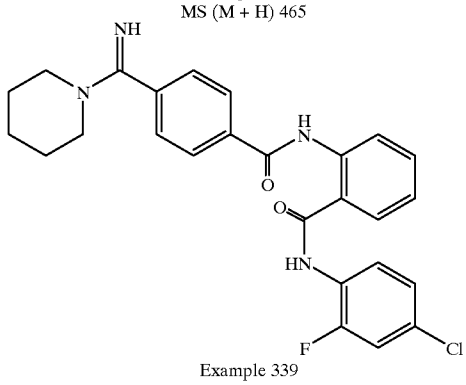
[1398] The following compounds were prepared according to the procedure previously described.



Example 337
MS (M + H) 439

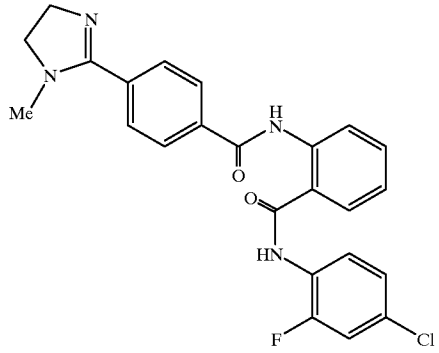


Example 338
MS (M + H) 465

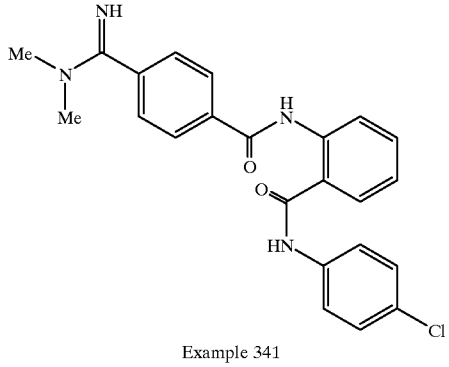


Example 339
MS (M + H) 479

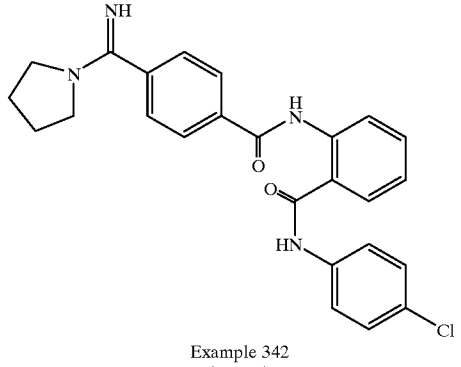
-continued



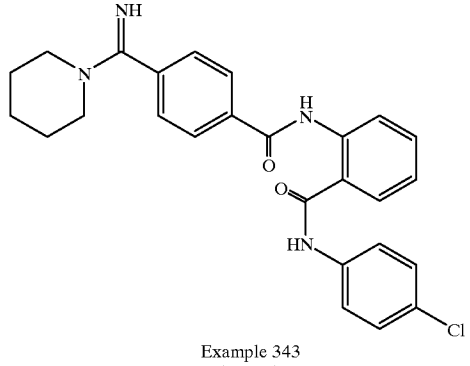
Example 340
MS (M + H) 451



Example 341
MS (M + H) 421

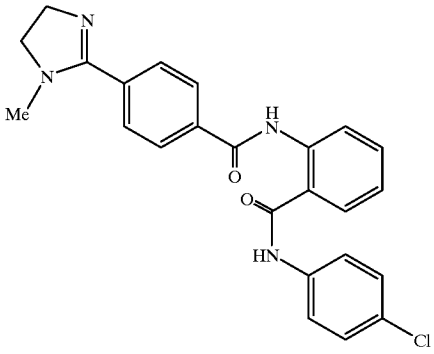


Example 342
MS (M + H) 447



Example 343
MS (M + H) 461

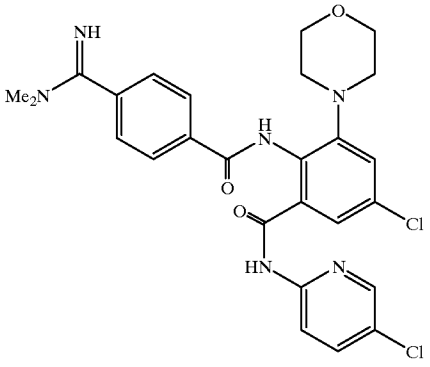
-continued



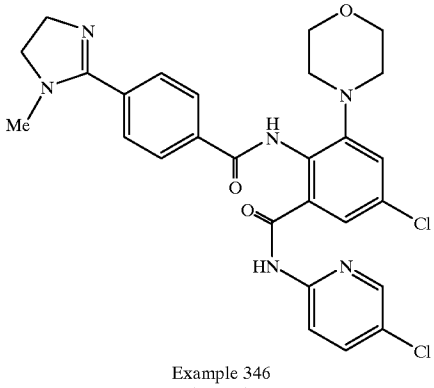
Example 344
MS (M + H) 433

Example 345-360

[1399] The following compounds were prepared according to the procedure previously described.

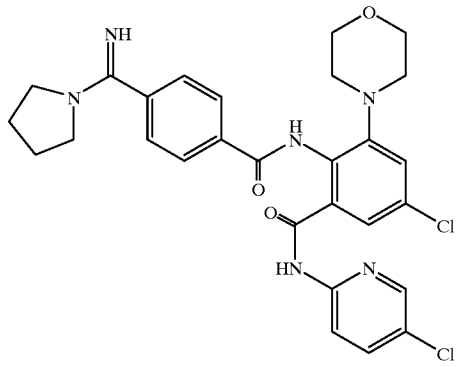


Example 345
MS (M + H) 541

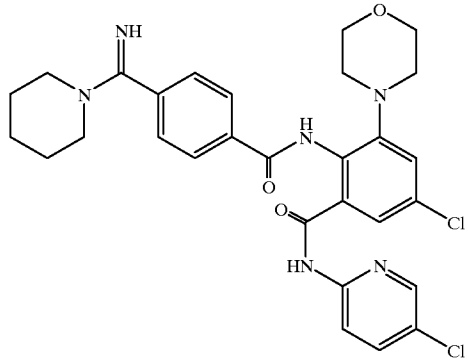


Example 346
MS (M + H) 553

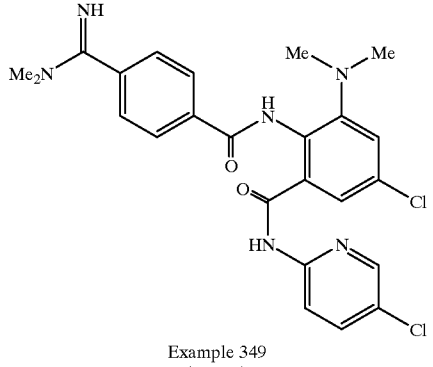
-continued



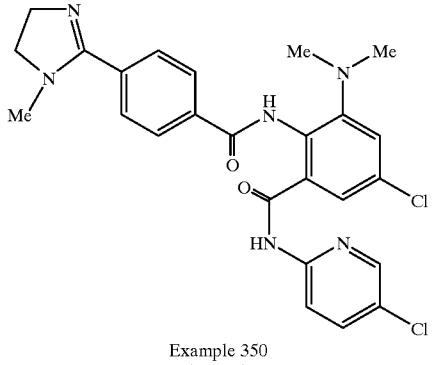
Example 347
MS (M + H) 567



Example 348
MS (M + H) 581

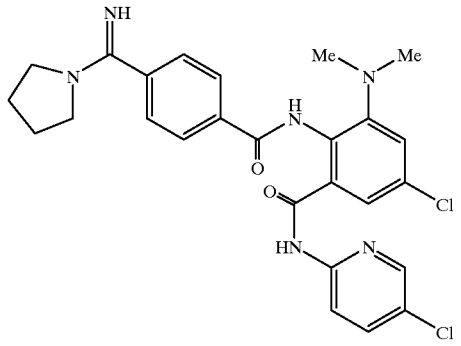


Example 349
MS (M + H) 499

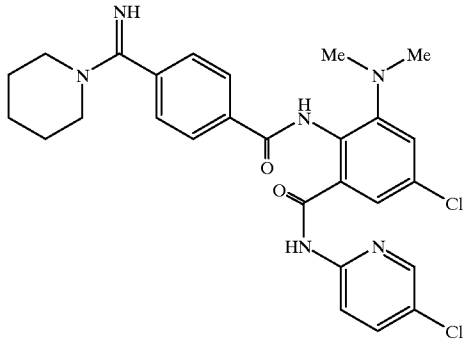


Example 350
MS (M + H) 511

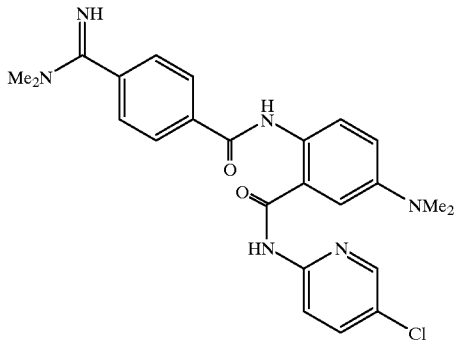
-continued



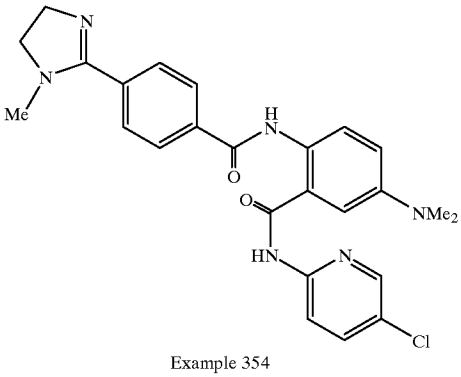
Example 351
MS (M + H) 525



Example 352
MS (M + H) 539

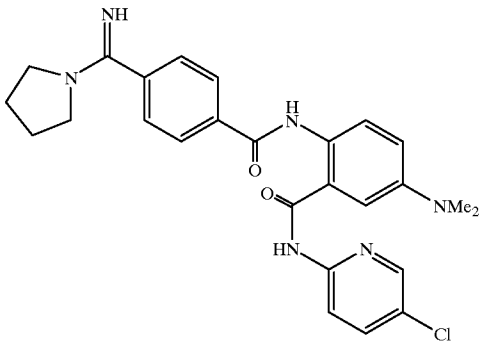


Example 353
MS (M + H) 499

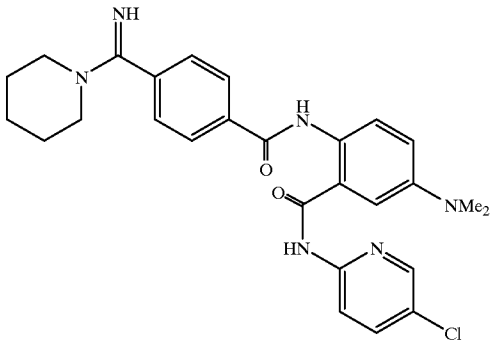


Example 354
MS (M + H) 511

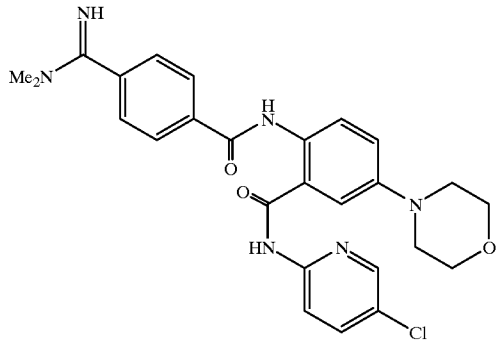
-continued



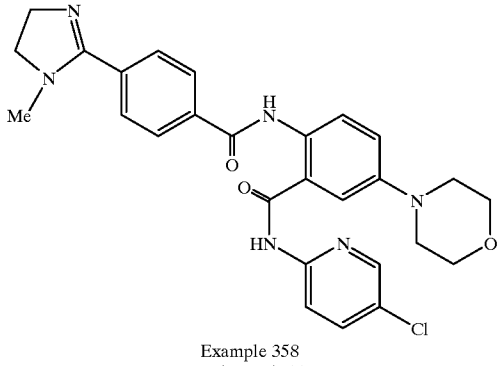
Example 355
MS (M + H) 525



Example 356
MS (M + H) 539

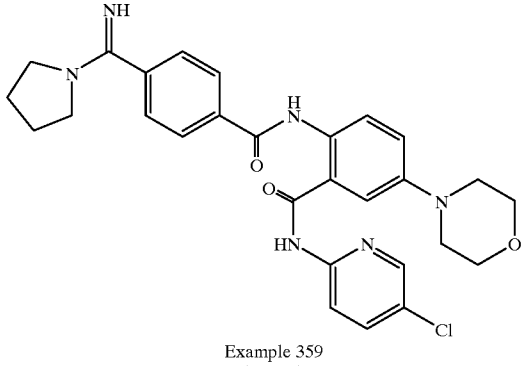


Example 357
MS (M + H) 541

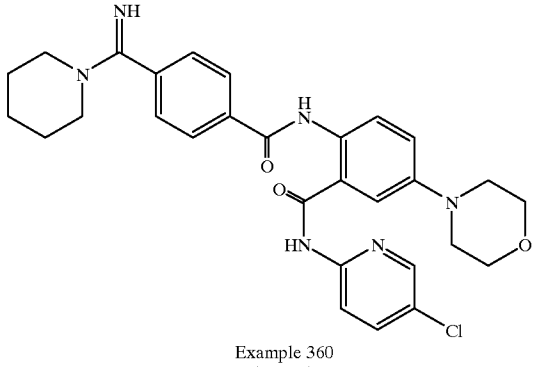


Example 358
MS (M + H) 553

-continued



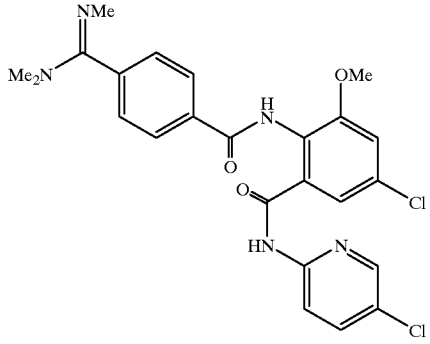
Example 359
MS (M + H) 567



Example 360
MS (M + H) 581

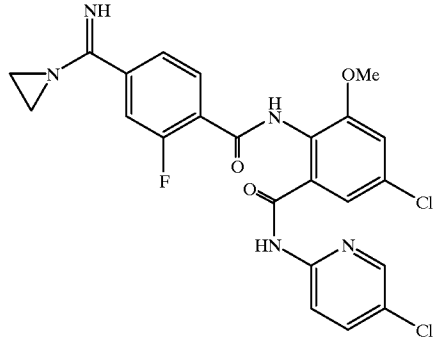
Example 361-390

[1400] The following compounds were prepared according to the procedure previously described.

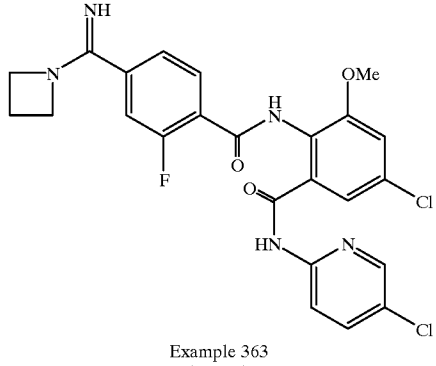


Example 361
MS (M + H) 500

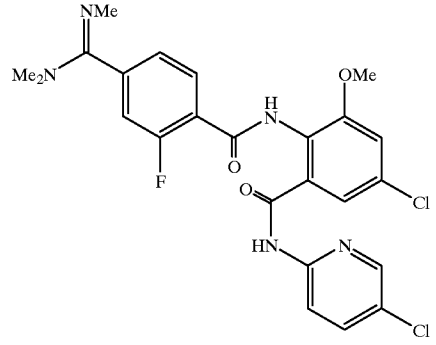
-continued



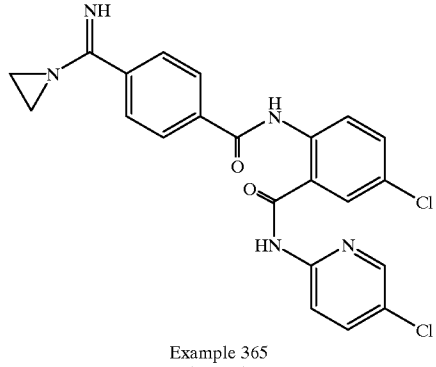
Example 362
MS (M + H) 502



Example 363
MS (M + H) 514

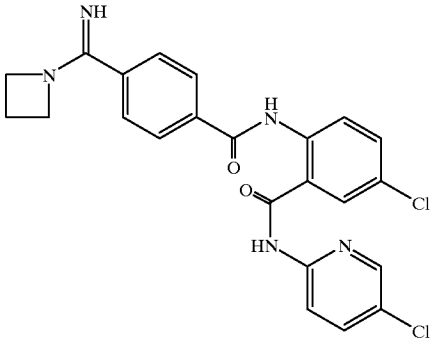


Example 364
MS (M + H) 512

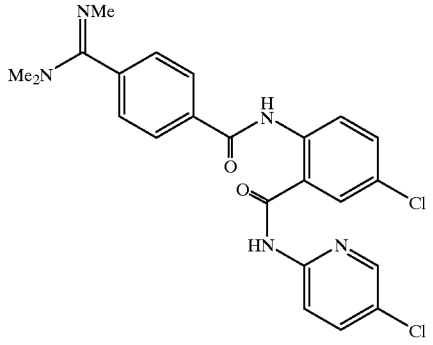


Example 365
MS (M + H) 454

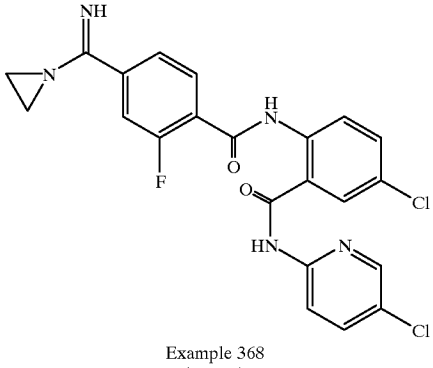
-continued



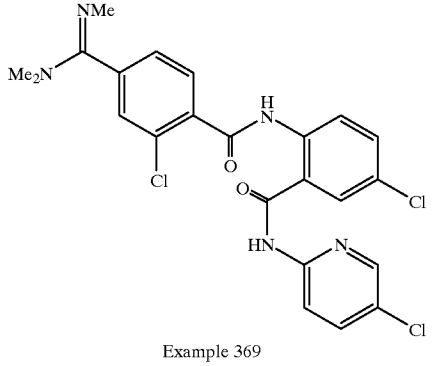
Example 366
MS (M + H) 468



Example 367
MS (M + H) 466

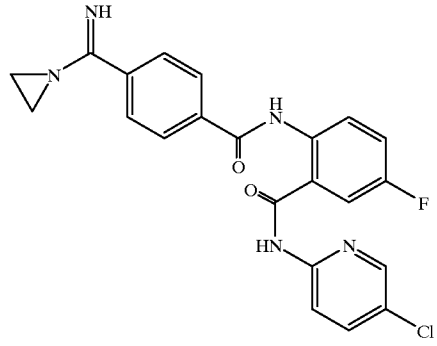


Example 368
MS (M + H) 472

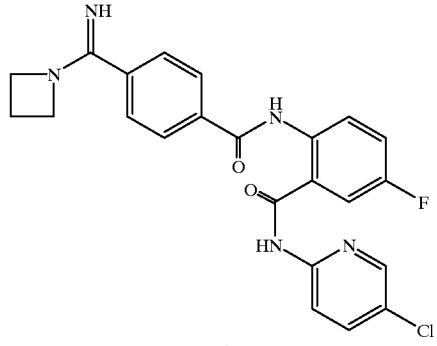


Example 369
MS (M + H) 504

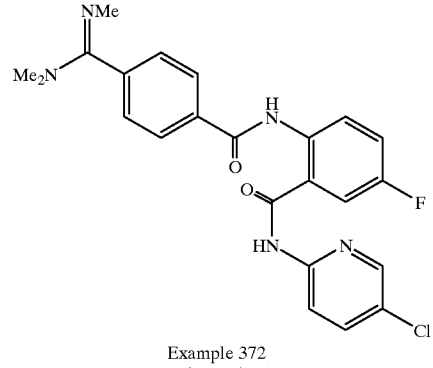
-continued



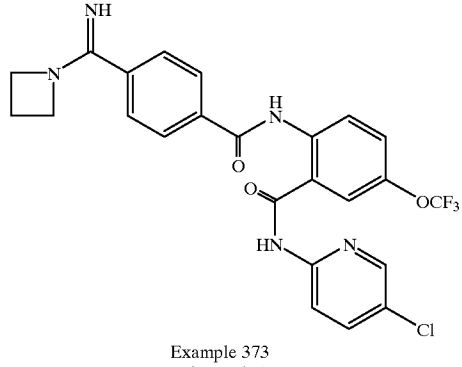
Example 370
MS (M + H) 438



Example 371
MS (M + H) 452

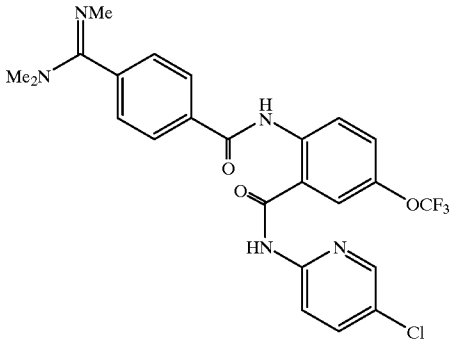


Example 372
MS (M + H) 450

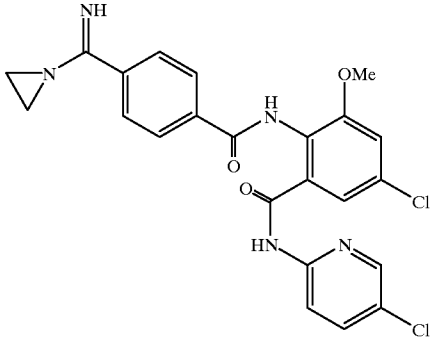


Example 373
MS (M + H) 518

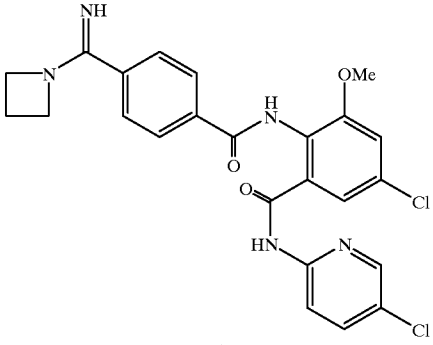
-continued



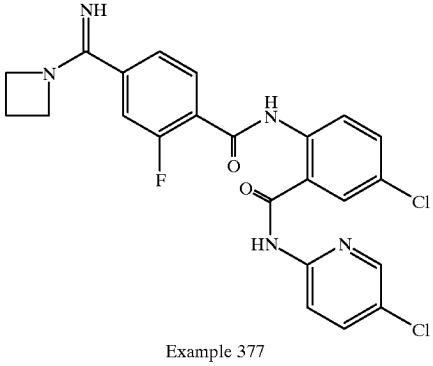
Example 374
MS (M + H) 516



Example 375
MS (M + H) 484

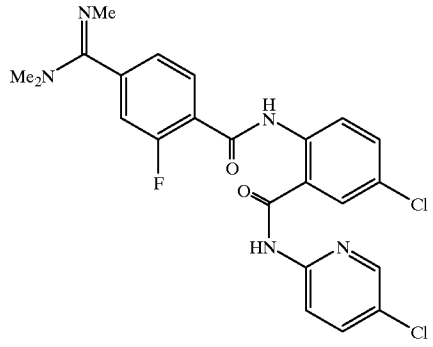


Example 376
MS (M + H) 498

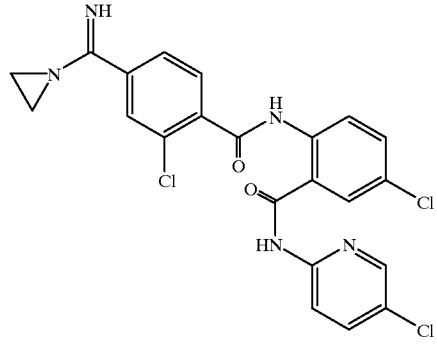


Example 377
MS (M + H) 486

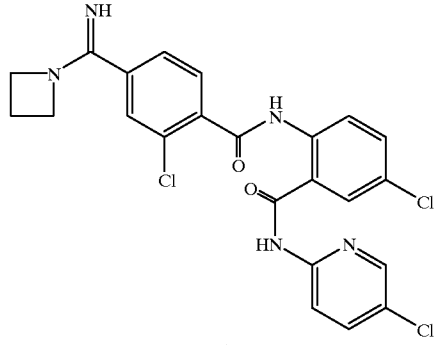
-continued



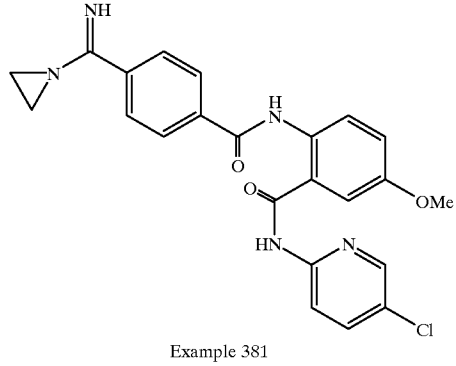
Example 378
MS (M + H) 484



Example 379
MS (M + H) 488

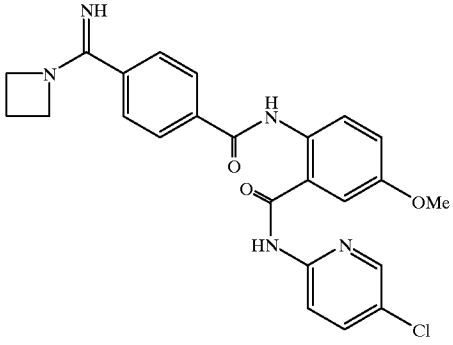


Example 380
MS (M + H) 502

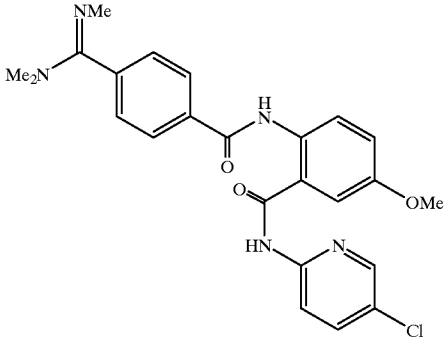


Example 381
MS (M + H) 450

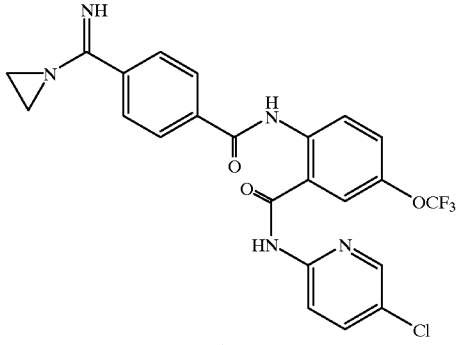
-continued



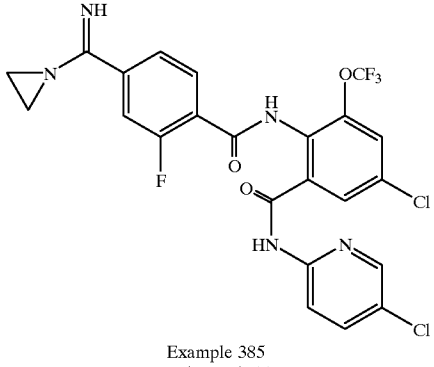
Example 382
MS (M + H) 464



Example 383
MS (M + H) 462

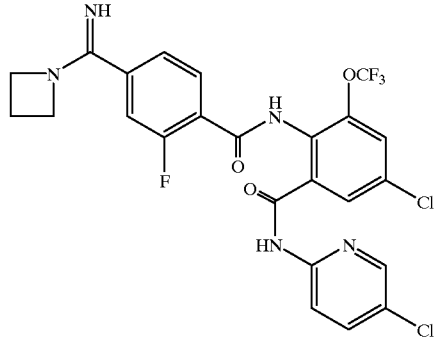


Example 384
MS (M + H) 504

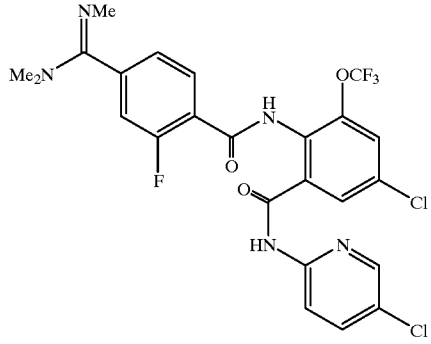


Example 385
MS (M + H) 556

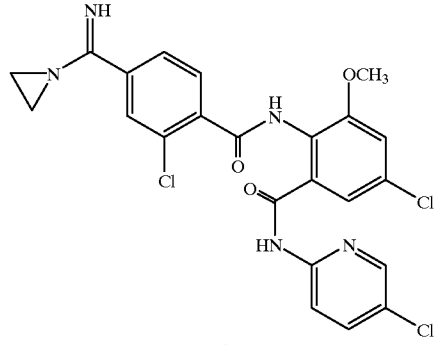
-continued



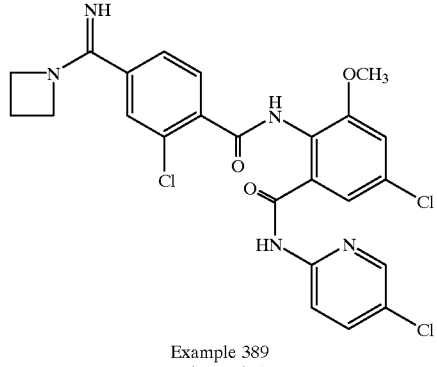
Example 386
MS (M + H) 568



Example 387
MS (M + H) 566

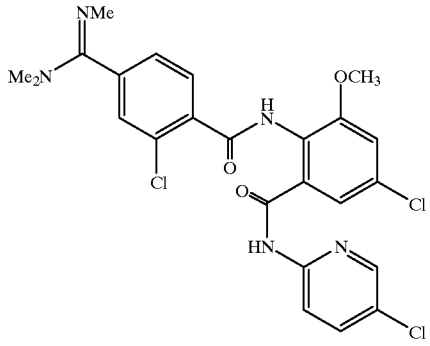


Example 388
MS (M + H) 518



Example 389
MS (M + H) 532

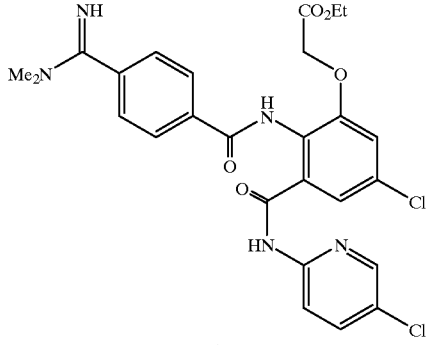
-continued



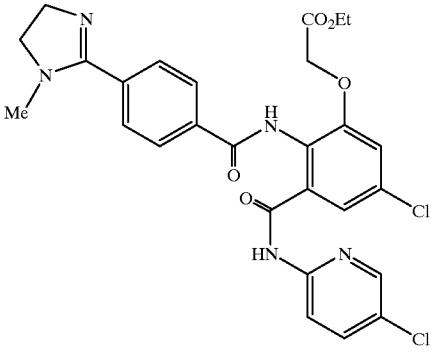
Example 390
MS (M + H) 530

Example 391-398

[1401] The following compounds were prepared according to the procedure previously described

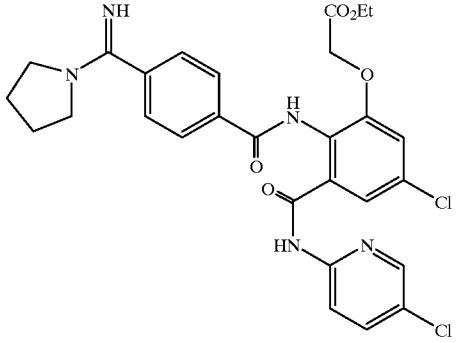


Example 391
MS (M + H) 558

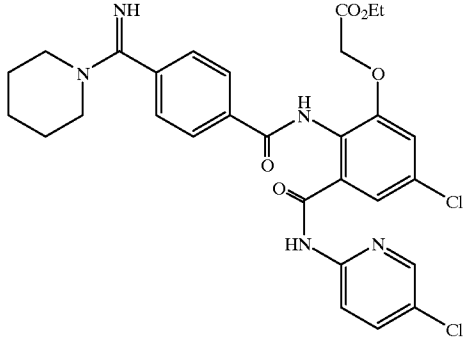


Example 392
MS (M + H) 570

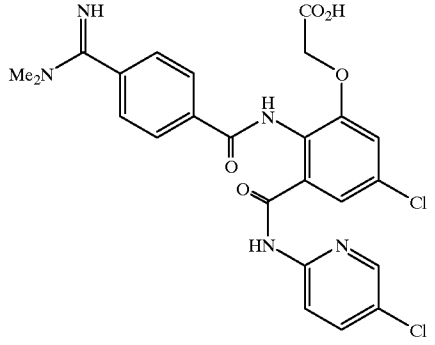
-continued



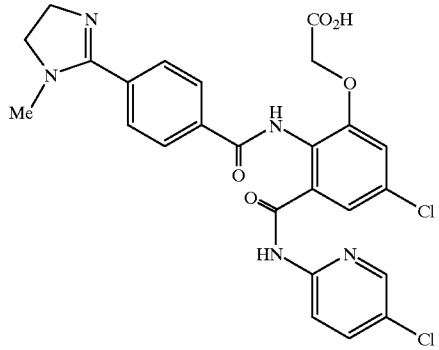
Example 393
MS (M + H) 584



Example 394
MS (M + H) 598

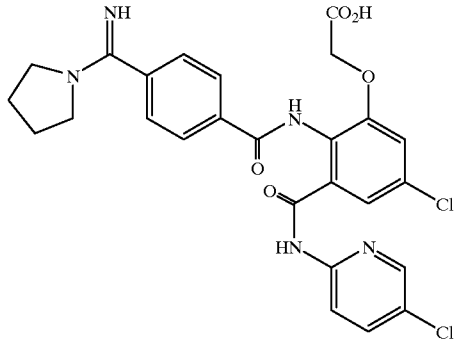


Example 395
MS (M + H) 530

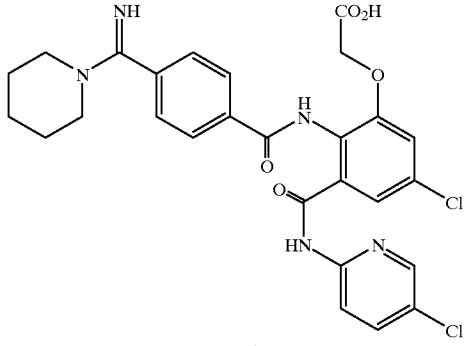


Example 396
MS (M + H) 542

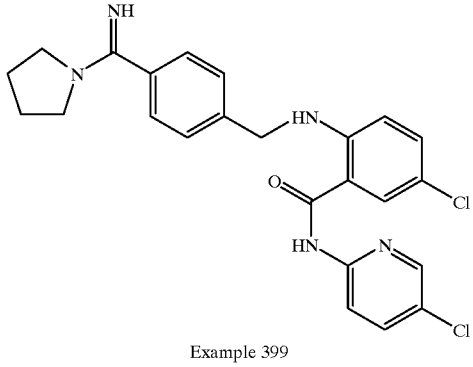
-continued



Example 397
MS (M + H) 556



Example 398
MS (M + H) 570



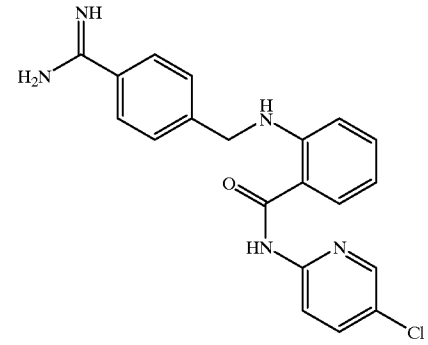
Example 399

[1402] Step 1: A mixture of 4-cyanobenzaldehyde (1 equiv), 4-chloro-2-(5-chloro-2-pyridinyl)amino-carbonyl aniline (1 equiv) and glacial acetic acid (10 equiv) in CH_2Cl_2 was stirred at rt for 30 min. $NaBH(OAc)_3$ (3 equiv) was added at once and the mixture was stirred overnight. The reaction was quenched with water and the organic layer was washed with brine and dried over Na_2SO_4. Column separation over silica gel gave the desired product.

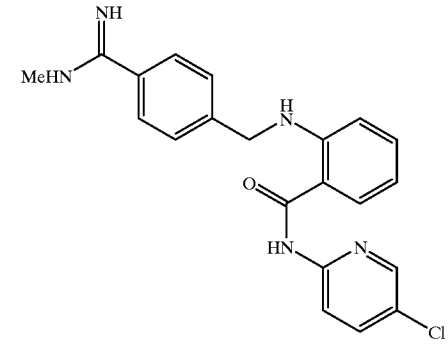
[1403] Step 2: A solution of the compound obtained in step 1 (15 mg) in anhydrous pyridine (10 mL) and triethyl amine (2 mL) was saturated with hydrogen sulfide gas at 0° C. The mixture was stirred at rt overnight. After concentration, the residue was dissolved in anhydrous acetone (10 mL) and iodomethane (1 mL) was added. The mixture was refluxed for 2 hrs. After concentration, the residue was dissolved in anhydrous methanol (5 mL) and a solution of pyrrolidine (0.5 mL) and acetic acid (0.5 mL) in anhydrous methanol (5 ml) was added. The mixture was refluxed for 15 min. After concentrated, the crude residue was purified by RP-HPLC to give target. MS (M+H) 468.

Examples 400-426

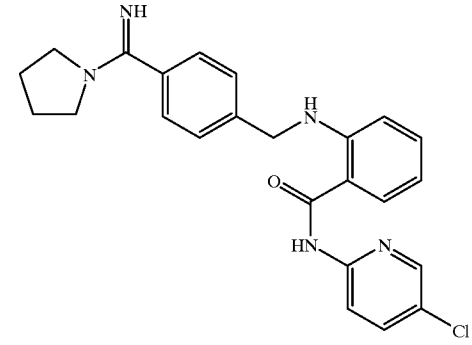
[1404] The following compounds were prepared according to the procedure previously described.



Example 400
MS (M + H) 414

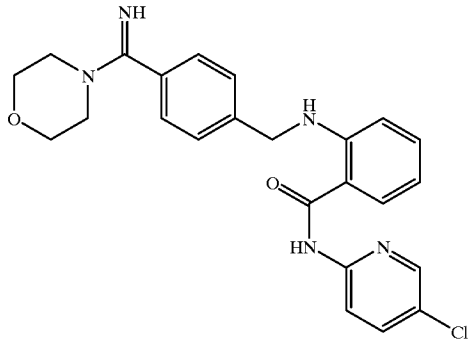


Example 401
MS (M + H) 428

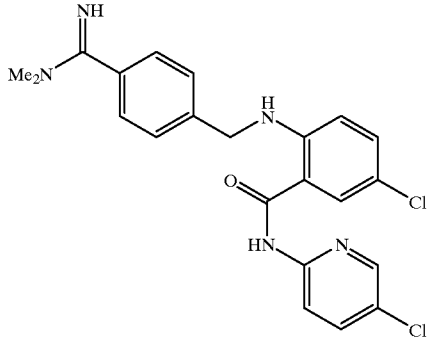


Example 402
MS (M + H) 468

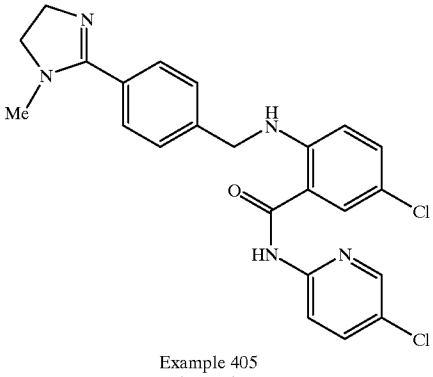
-continued



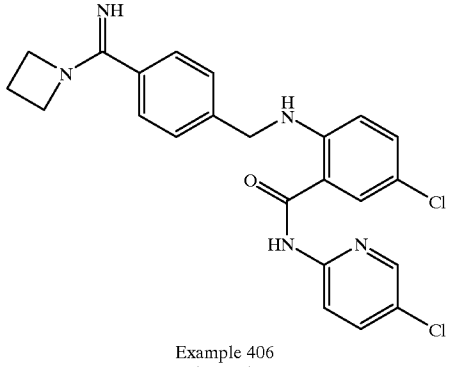
Example 403
MS (M + H) 484



Example 404
MS (M + H) 442

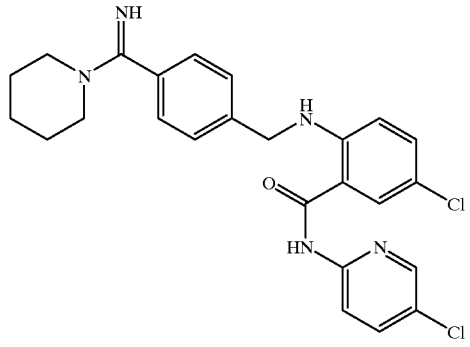


Example 405
MS (M + H) 428

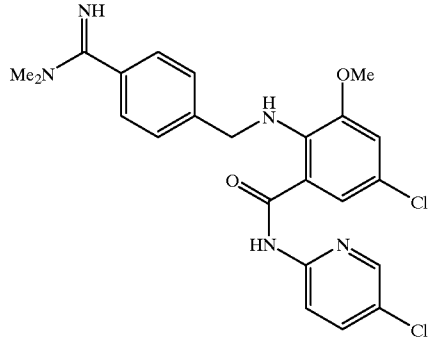


Example 406
MS (M + H) 468

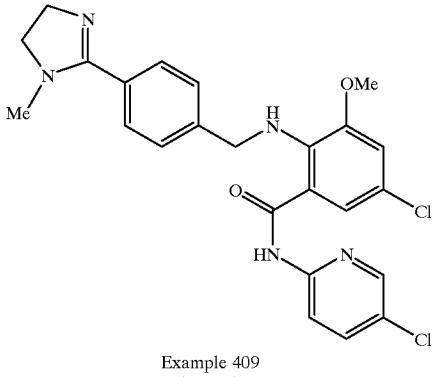
-continued



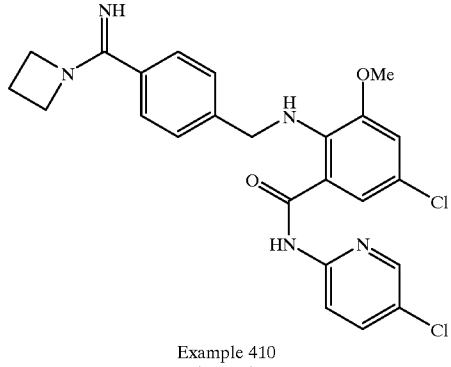
Example 407
MS (M + H) 484



Example 408
MS (M + H) 472

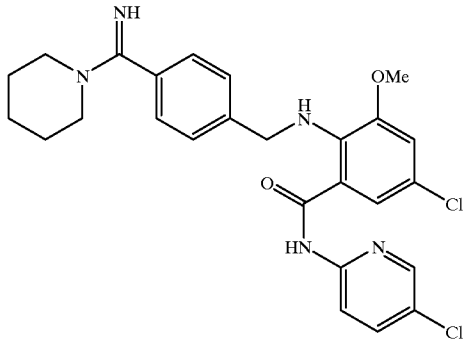


Example 409
MS (M + H) 484

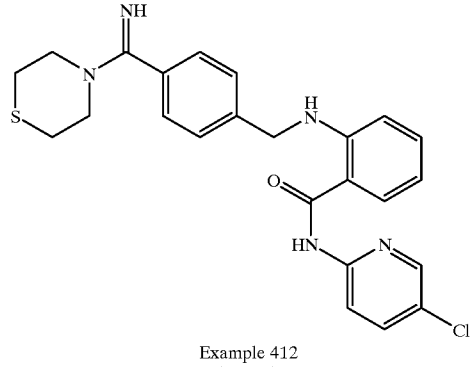


Example 410
MS (M + H) 484

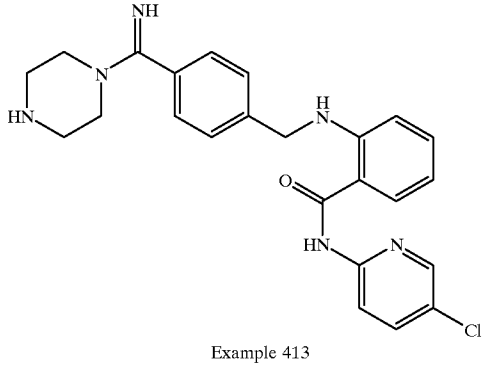
-continued



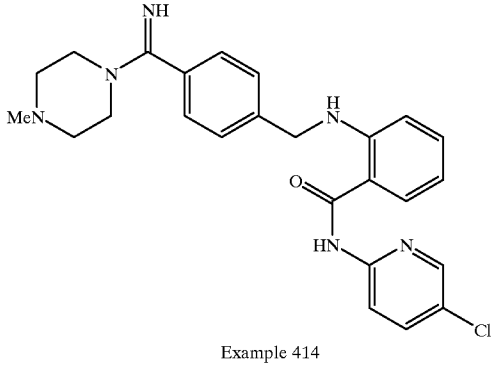
Example 411
MS (M + H) 512



Example 412
MS (M + H) 530

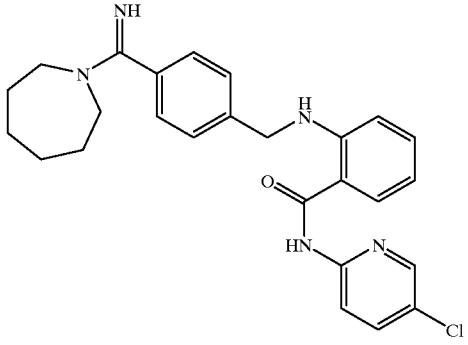


Example 413
MS (M + H) 513

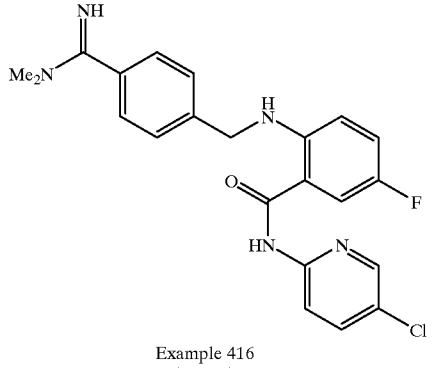


Example 414
MS (M + H) 527

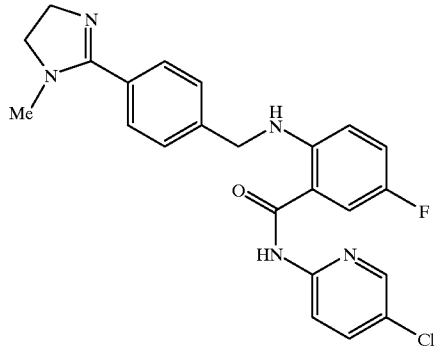
-continued



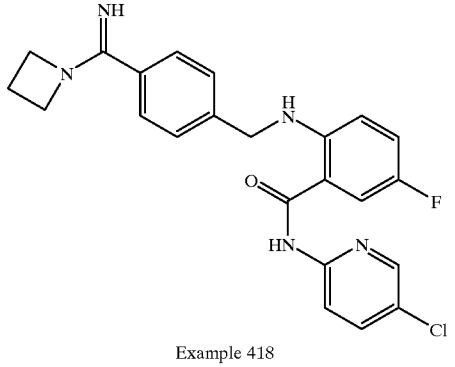
Example 415
MS (M + H) 526



Example 416
MS (M + H) 426

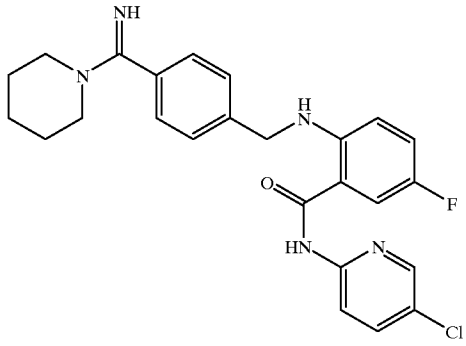


Example 417
MS (M + H) 438

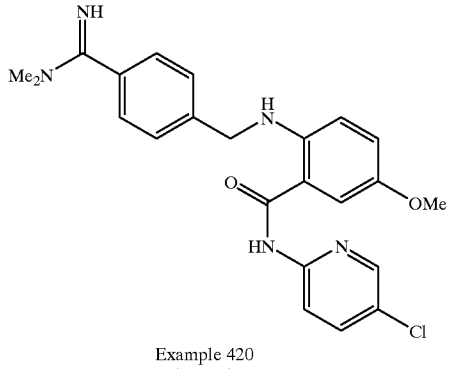


Example 418
MS (M + H) 438

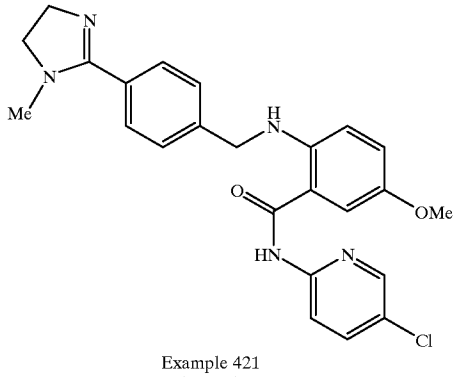
-continued



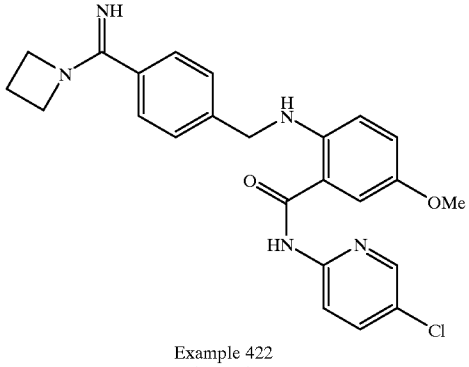
Example 419
MS (M + H) 466



Example 420
MS (M + H) 438

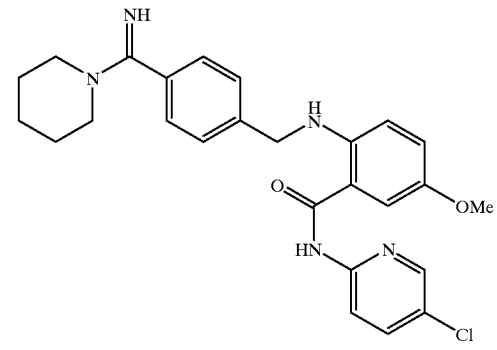


Example 421
MS (M + H) 450

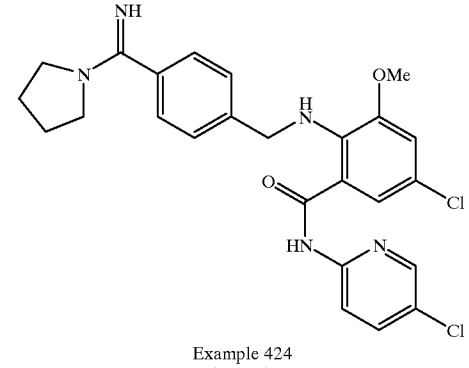


Example 422
MS (M + H) 450

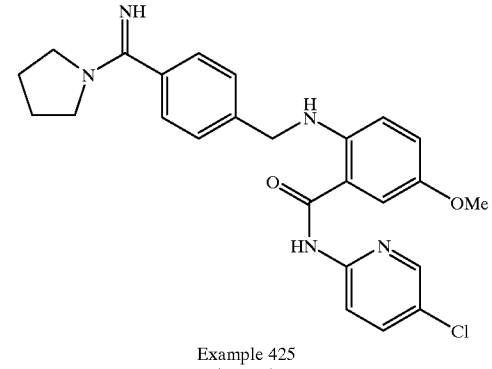
-continued



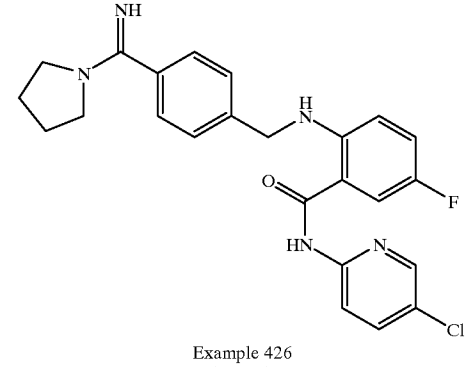
Example 423
MS (M + H) 478



Example 424
MS (M + H) 498

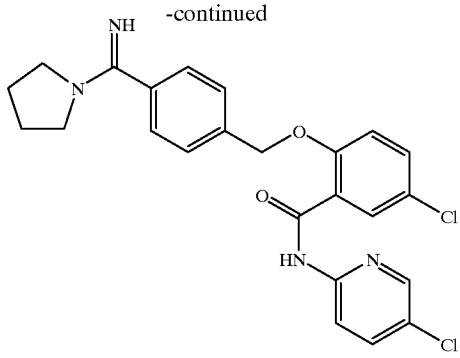


Example 425
MS (M + H) 464



Example 426
MS (M + H) 448

-continued



Example 427

[1405] Step 1: A mixture of 4-cyanobenzyl bromide (1 equiv), methyl 2-hydroxybenzoate (1 equiv) and cesium carbonate (10 equiv) in DMF was stirred at rt overnight. The mixture was then diluted with EtOAc, washed with water, dried over Na_2SO_4, filtered and evaporated to give the product.

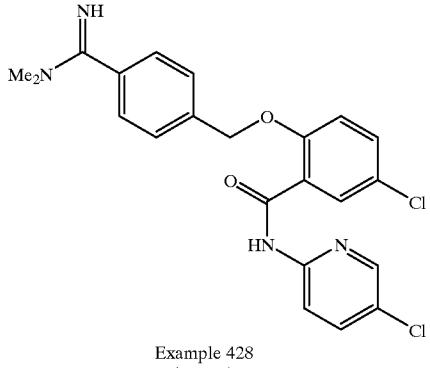
[1406] Step 2: A solution of the compound obtained in step 1 (1 equiv) in MeOH was treated with 1N LiOH (2.2 equiv) for 1 h. After removal of methanol and acidifying with 1N HCl to PH~1, the mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered and evaporated to give the product.

[1407] Step 3: A solution of the compound obtained in step 2 (1 equiv) in dichloromethane was treated with oxalyl chloride (3 equiv) and 2 drops of DMF at rt for 3 h. The volatile was evaporated and the residue was redissolved in methylenechloride. To the solution was added 2-amino-5-chloropyridine (1 equiv) and pyridine (5 equiv). The mixture was stirred at rt for 2 h, washed with water, dried over Na_2SO_4, filtered and evaporated to give the product.

[1408] Step 2: A solution of the compound obtained in step 3 (15 mg) in anhydrous pyridine (10 mL) and triethyl amine (2 mL) was saturated with hydrogen sulfide gas at 0° C. The mixture was stirred at rt overnight. After concentration, the residue was dissolved in anhydrous acetone (10 mL) and iodomethane (1 mL) was added. The mixture was refluxed for 2 hrs. After concentration, the residue was dissolved in anhydrous methanol (5 mL) and a solution of pyrrolidine (0.5 mL) and acetic acid (0.5 mL) in anhydrous methanol (5 ml) was added. The mixture was refluxed for 15 min. After concentrated, the crude residue was purified by RP-HPLC to give target. MS (M+H) 435.

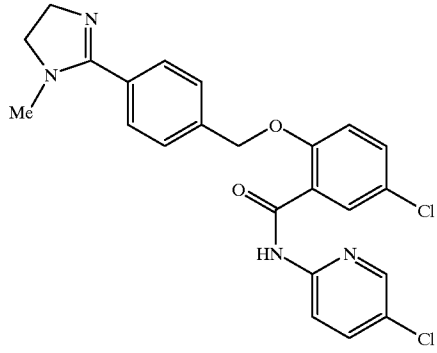
Examples 428-431

[1409] The following compounds were similarly prepared.

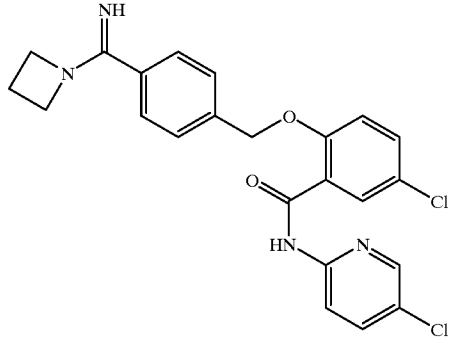


Example 428
MS (M + H) 409

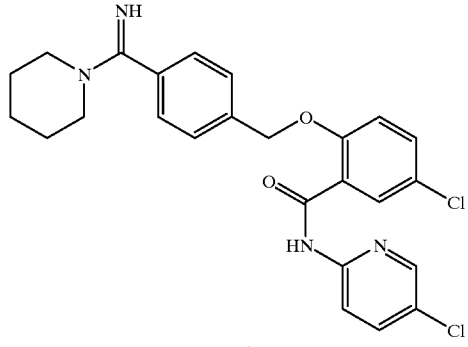
-continued



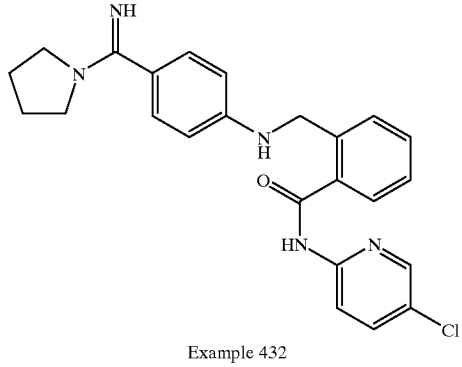
Example 429
MS (M + H) 421



Example 430
MS (M + H) 421



Example 431
MS (M + H) 449



Example 432

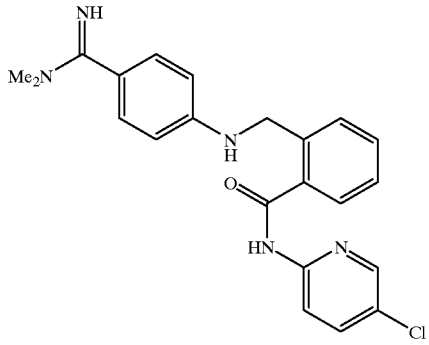
[1410] Step 1: A solution of 2-carboxybenzaldehyde (1 equiv) in dicloromethane was treated with oxalyl chloride (3 equiv) and 2 drops of DMF at rt for 3 h. The volatile was evaporated and the residue was redissolved in methylenechloride. To the solution was added 2-amino-5-chloropyridine (1 equiv) and pyridine (5 equiv). The mixture was stirred at rt for 2 h, washed with water, dried over Na_2SO_4, filtered and evaporated to give the product.

[1411] Step 2: A mixture of the compound obtained in step 1 (1 equiv), 4-cyanoaniline (1 equiv) and glacial acetic acid (10 equiv) in CH_2Cl_2 was stirred at rt for 30 min. $NaBH(OAc)_3$ (3 equiv) was added at once and the mixture was stirred overnight. The reaction was quenched with water and the organic layer was washed with brine and dried over Na_2SO_4. Column separation over silica gel gave the desired product.

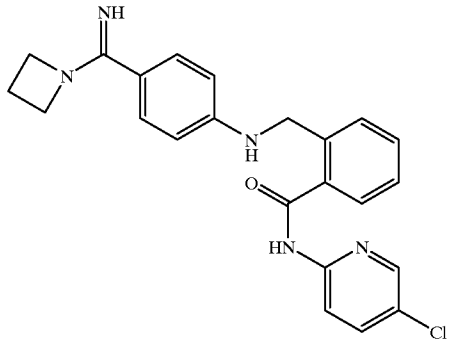
[1412] Step 3: A solution of the compound obtained in step 2 (15 mg) in anhydrous pyridine (10 mL) and triethyl amine (2 mL) was saturated with hydrogen sulfide gas at 0° C. The mixture was stirred at rt overnight. After concentration, the residue was dissolved in anhydrous acetone (10 mL) and iodomethane (1 mL) was added. The mixture was refluxed for 2 hrs. After concentration, the residue was dissolved in anhydrous methanol (5 mL) and a solution of pyrrolidine (0.5 mL) and acetic acid (0.5 mL) in anhydrous methanol (5 ml) was added. The mixture was refluxed for 15 min. After concentrated, the crude residue was purified by RP-HPLC to give target. MS (M−H) 434.

Examples 433-437

[1413] The following compounds were similarly prepared.

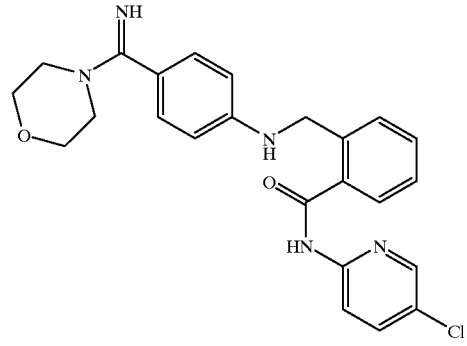


Example 433
MS (M + H) 408

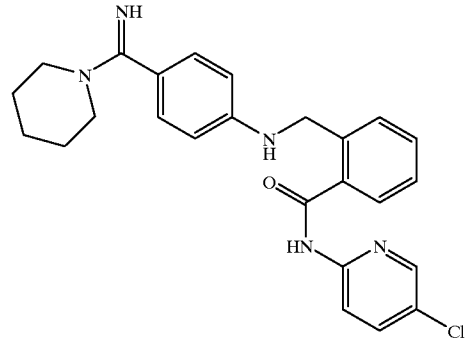


Example 434
MS (M + H) 420

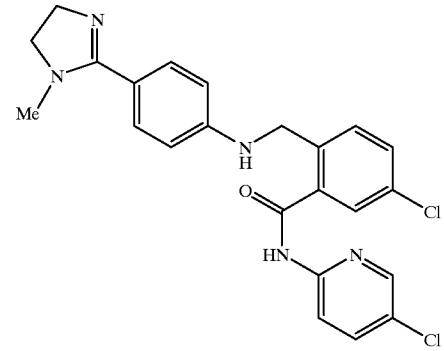
-continued



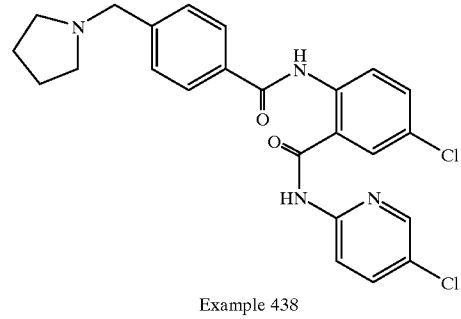
Example 435
MS (M + H) 450



Example 436
MS (M + H) 448



Example 437
MS (M + H) 420



Example 438

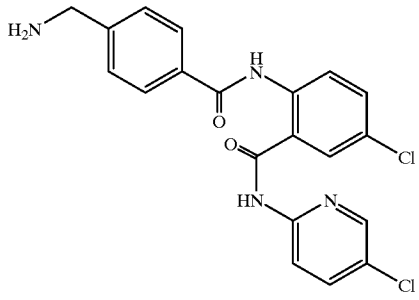
[1414] Step 1: A mixture of 4-chloromethylbemzoyl chloride (1 equiv), 4-chloro-2-(5-chloro-2-pyridinyl)amino-car-

bonyl aniline (1 equiv) and pyridine (5 equiv) in CH_2Cl_2 was stirred at reflux for 4 h. The reaction was cooled to rt and the organic layer was washed with brine and dried over Na_2SO_4. Column separation over silica gel gave the desired product (~20% yield).

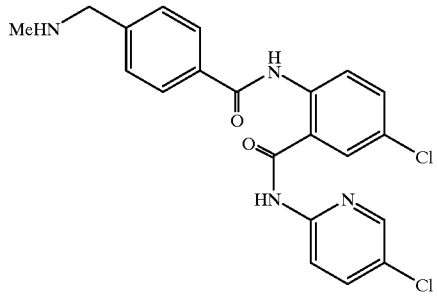
[1415] Step 2: A solution of the compound obtained in step 1 (15 mg) in DMF (1 mL) was treated with pyrrolidine (1 mL) at rt overnight. After removing the volatile, the crude residue was purified by RP-HPLC to give the target. MS (M+H) 469.

Example 439-458

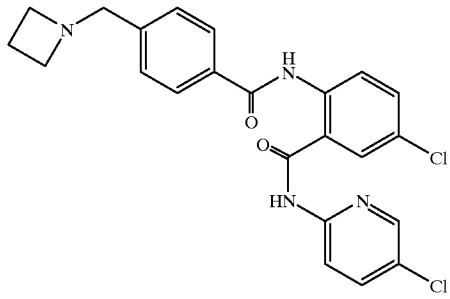
[1416] The following compounds were prepared according to the procedure previously described.



Example 439
MS (M + H) 415

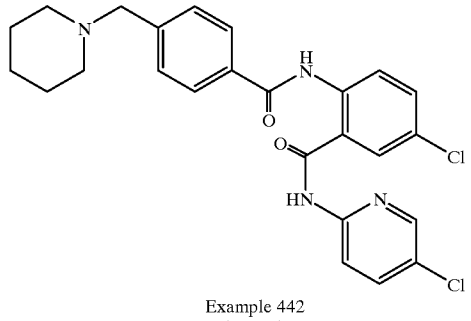


Example 440
MS (M + H) 429

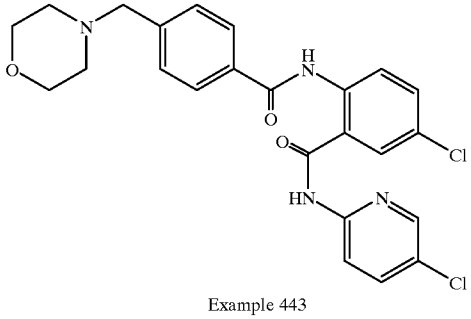


Example 441
MS (M + H) 455

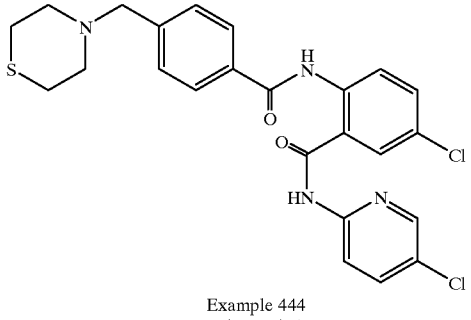
-continued



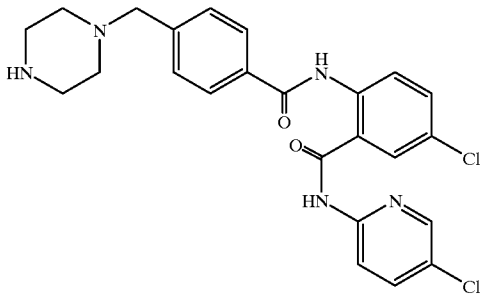
Example 442
MS (M + H) 483



Example 443
MS (M + H) 485

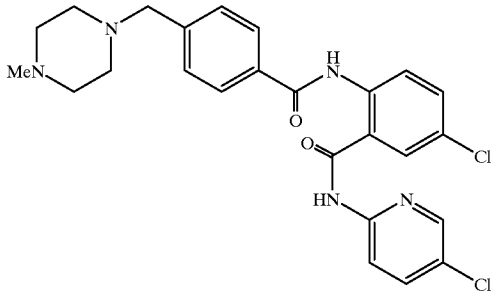


Example 444
MS (M + H) 501

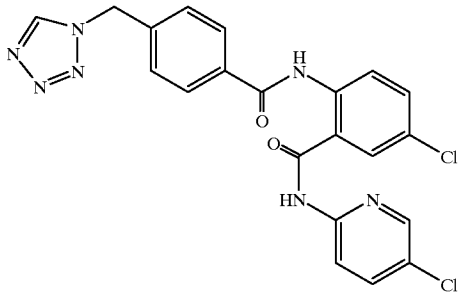


Example 445
MS (M + H) 484

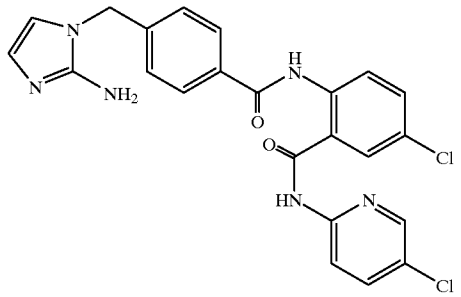
-continued



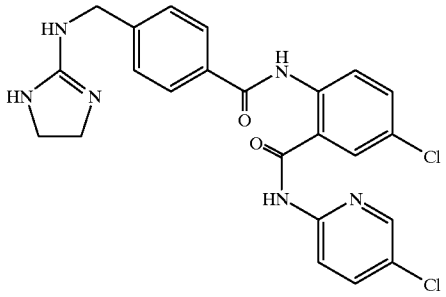
Example 446
MS (M + H) 498



Example 447
MS (M + H) 468

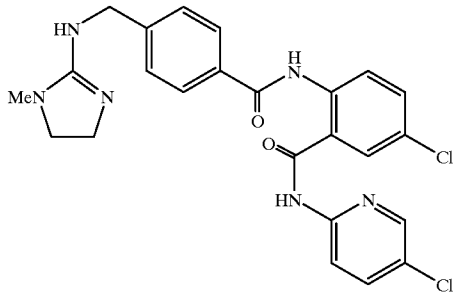


Example 448
MS (M + H) 481

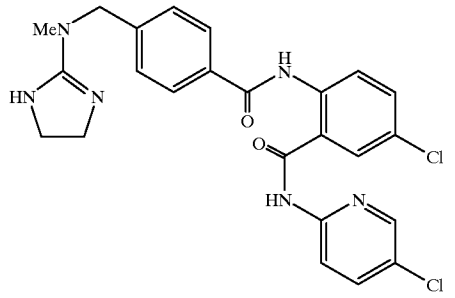


Example 449
MS (M + H) 483

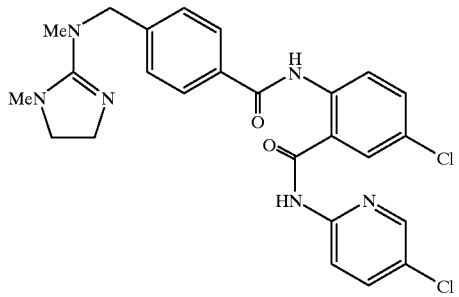
-continued



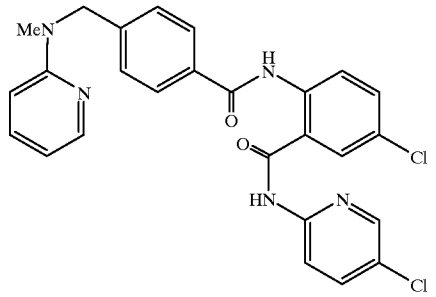
Example 450
MS (M + H) 497



Example 451
MS (M + H) 497

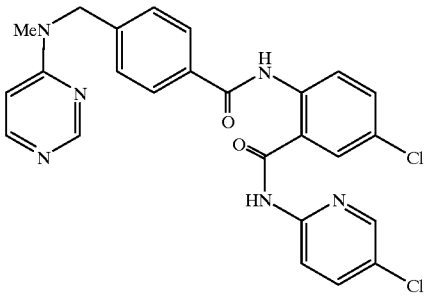


Example 452
MS (M + H) 511

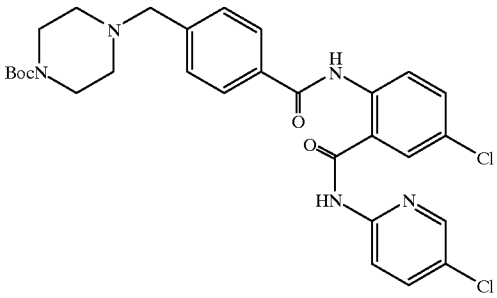


Example 453
MS (M + H) 506

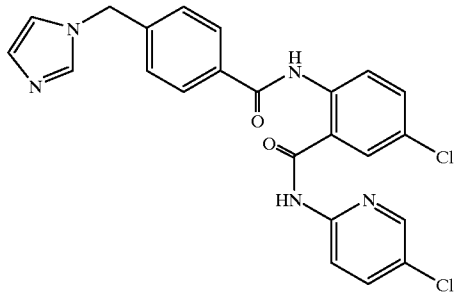
-continued



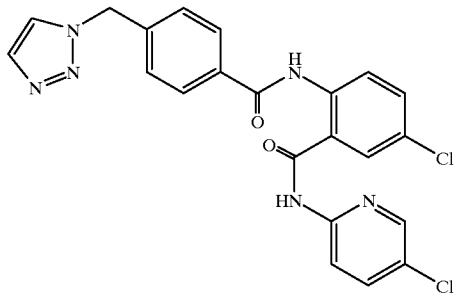
Example 454
MS (M + H) 507



Example 455
MS (M + H) 539

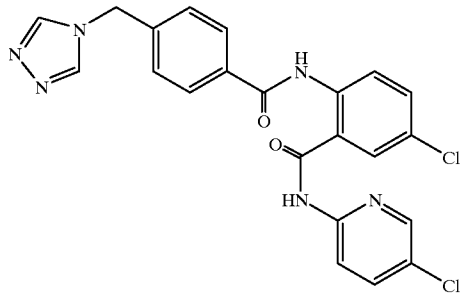


Example 456
MS (M + H) 466



Example 457
MS (M + H) 467

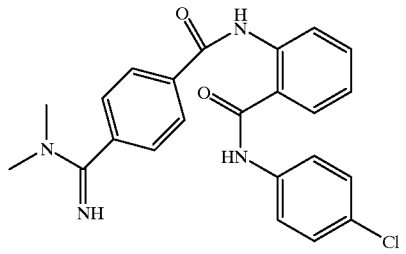
-continued



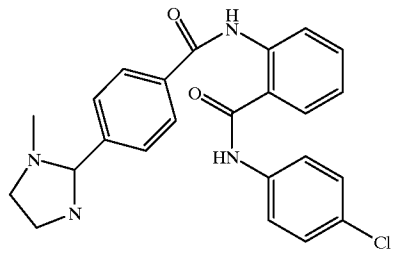
Example 458
MS (M + H) 467

Example 459-494

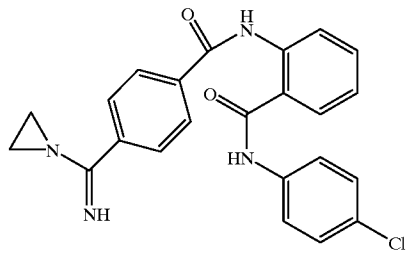
[1417] The following compounds were prepared according to the procedure previously described.



MS 421 (M + H)

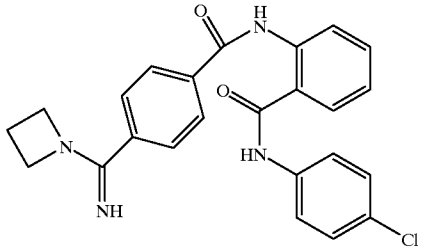


MS 433 (M + H)

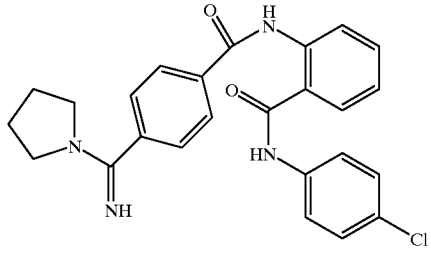


MS 419 (M + H)

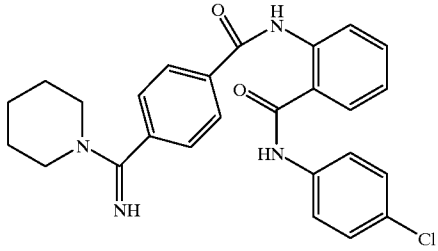
-continued



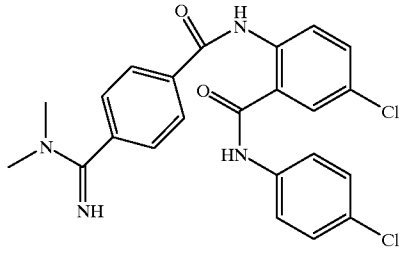
MS 433 (M + H)



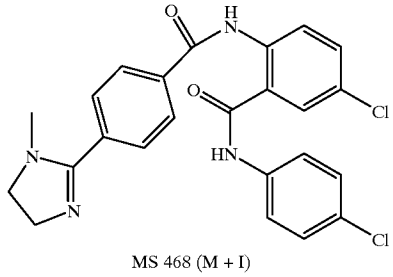
MS 447 (M + H)



MS 461 (M + H)

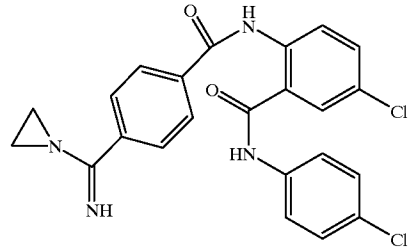


MS 456 (M + H)

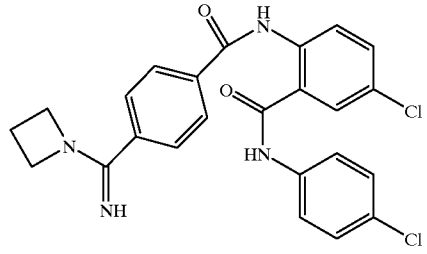


MS 468 (M + I)

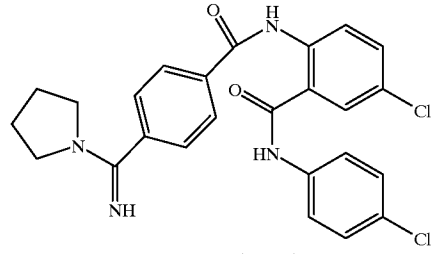
-continued



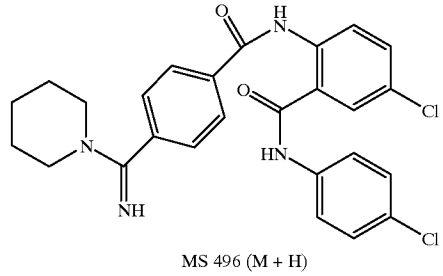
MS 454 (M + H)



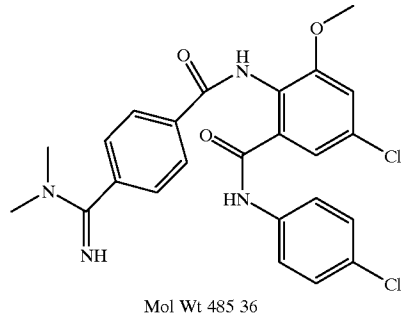
MS 468 (M + H)



MS 482 (M + H)

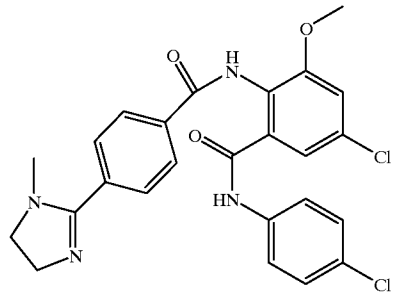


MS 496 (M + H)

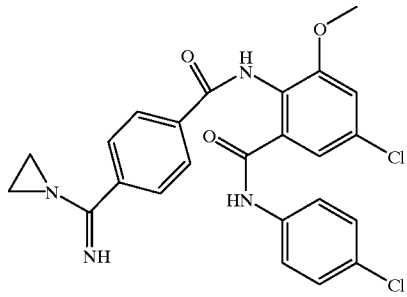


Mol Wt 485 36

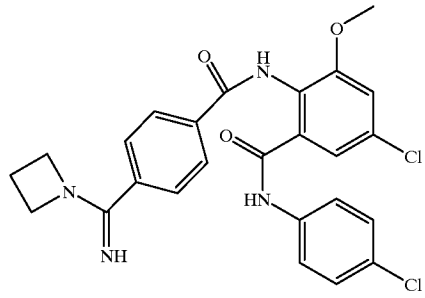
-continued



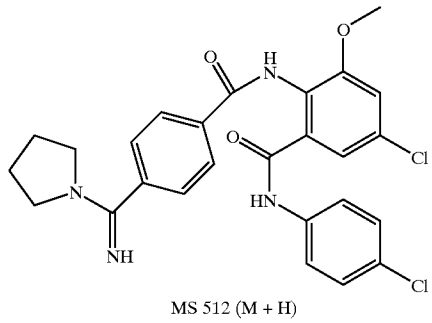
Mol Wt 497 37



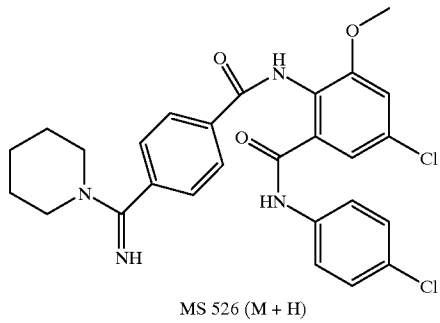
MS 484 (M + H)



MS 498 (M + H)

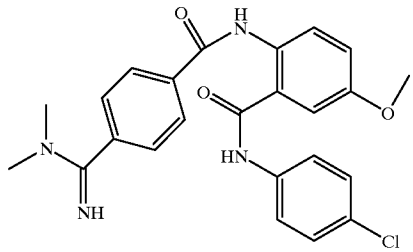


MS 512 (M + H)

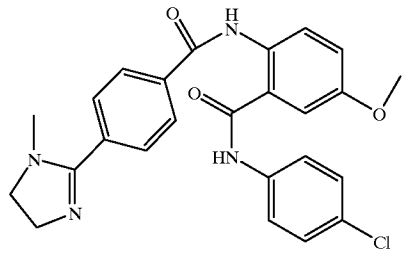


MS 526 (M + H)

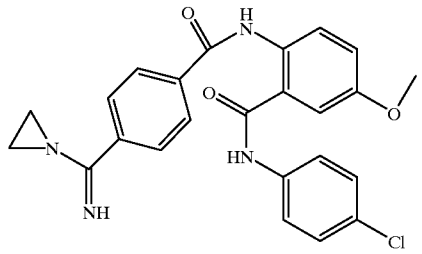
-continued



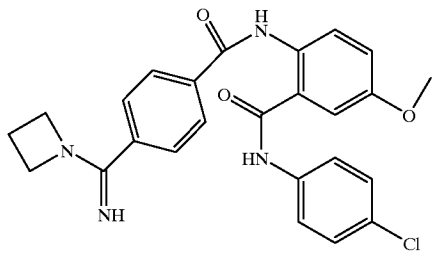
MS 451 (M + H)



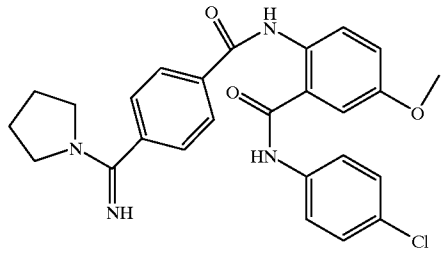
MS 463 (M + H)



MS 449 (M + H)

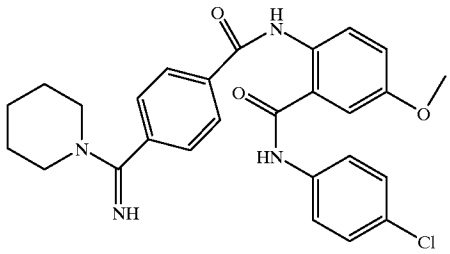


MS 463 (M + H)

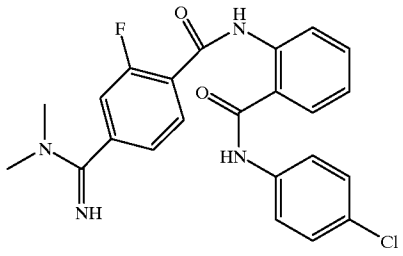


MS 477 (M + H)

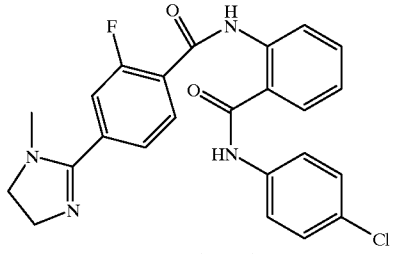
-continued



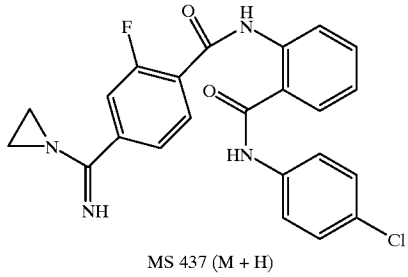
MS 491 (M + H)



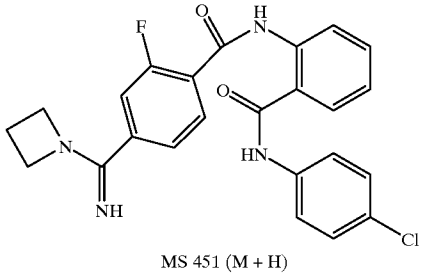
MS 439 (M + H)



MS 451 (M + H)

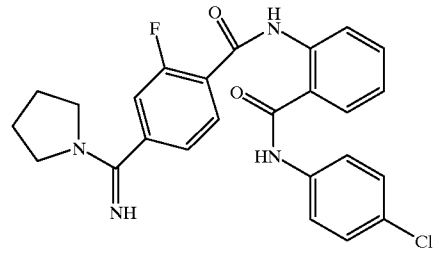


MS 437 (M + H)

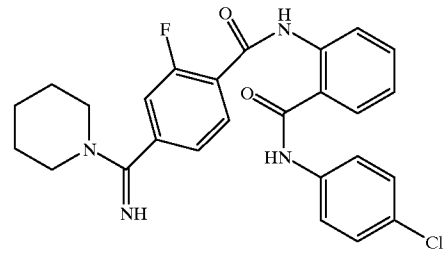


MS 451 (M + H)

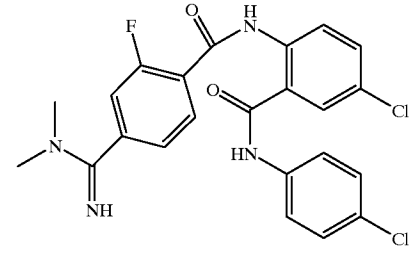
-continued



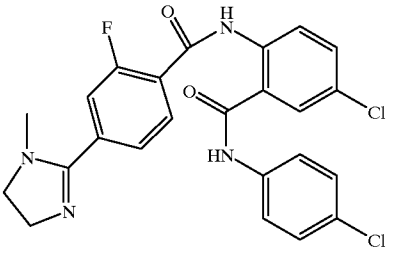
MS 465 (M + H)



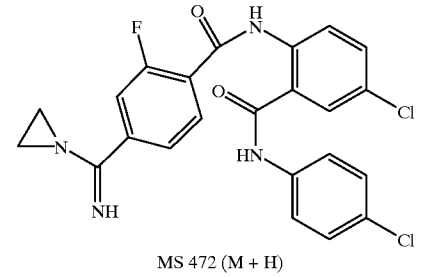
MS 479 (M + H)



MS 474 (M + H)



MS 486 (M + H)



MS 472 (M + H)

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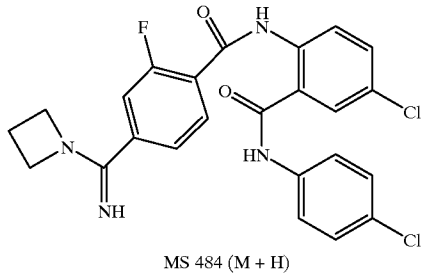
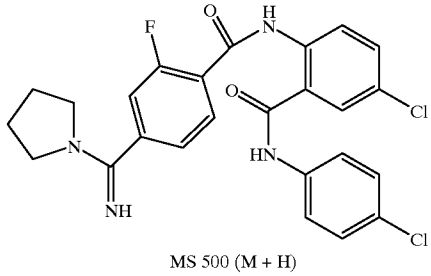
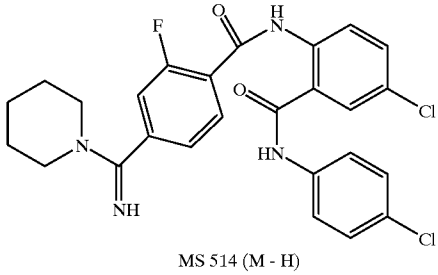


MS 484 (M + H)



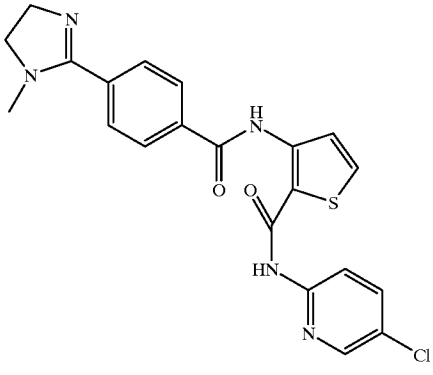
MS 500 (M + H)



MS 514 (M - H)

Example 495

[1418] N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}[4-(1-methyl(2-imidazolin-2-yl))phenyl]carboxamide



[1419] Preparation of methyl 3-[(4-cyanophenyl)carbonylamino]thiophene-2-carboxylate

[1420] A mixture of 4-cyanobenzoyl chloride (1.0500 g, 6.4 mmol), methyl 3-aminothiophenecarboxylate (1.0000 g, 6.4 mmol), and triethylamine (1 mL, 7.0 mmol) in dichloromethane was stirred at room temperature for 18 hours. The mixture was poured into a separatory funnel and washed by 1 N HCl. The organic layers were combined, dried over MgSO4, concentrated in vacuo, and chromatographed through a silica gel column to give the title compound 1.6588 g (91%). ES-MS 287 (M+1).

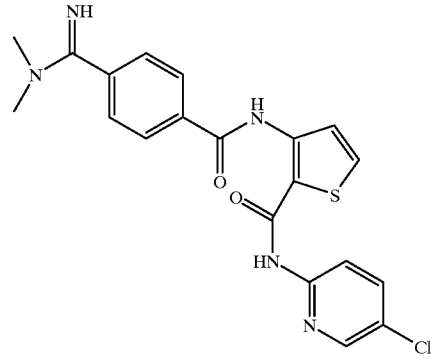
[1421] Preparation of N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}(4-cyanophenyl)carboxamide

[1422] A portion of 2-amino-5-chloropyridine (68.6 mg, 0.5 mmol) was treated with AlMe3 (0.8 mL, 1.6 mmol), followed by adding the product from step A (160 mg, 0.5 mmol). The mixture was stirred at room temperature for 18 hours. The excess of AlMe3 was killed by 1N HCl solution. The organic layers were combined, dried over MgSO4, concentrated in vacuo, and chromatographed through a silica gel column to give the title compound 0.1528 g (80%). ES-MS 383 (M+1).

[1423] A mixture of the product from step B (0.1528 g, 0.4 mmol) and EtOH saturated with HCl was stirred at room temperature for 18 hours. The solvent was removed by a rotovap. The crude oil was treated with 2 mL N-methylethylenediamine for 2 hours until the reaction was complete. Prep HPLC was used to purity the final product. It gave 0.1537 g (88%). ES-MS 440(M+1).

Example 496

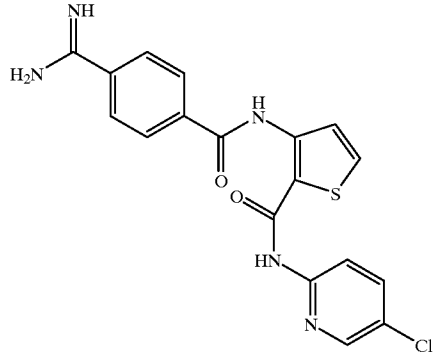
[1424] {4-[(dimethylamino)iminomethyl]phenyl}-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}carboxamide



[1425] The title compound was obtained according to the procedure previously described. ES-MS 428 (M+1).

Example 497

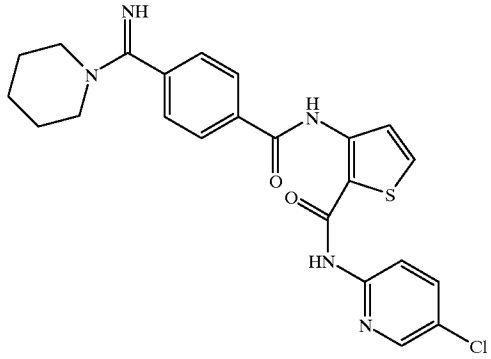
[1426] 4-(N-{2-[N-(5-chloro-2-pyridyl)carbamoyl]-3-thienyl}carbamoyl)benzenecarboxamidine



[1427] The title compound was obtained according to the procedure previously described. ES-MS 400(M+1).

Example 498

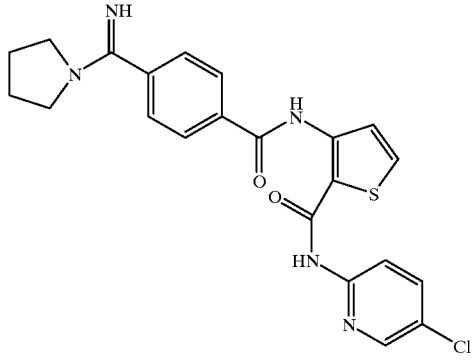
[1428] N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}[4-(iminopiperidylmethyl)-phenyl]carboxamide



[1429] The title compound was obtained according to the procedure previously described. ES-MS 468(M+1).

Example 499

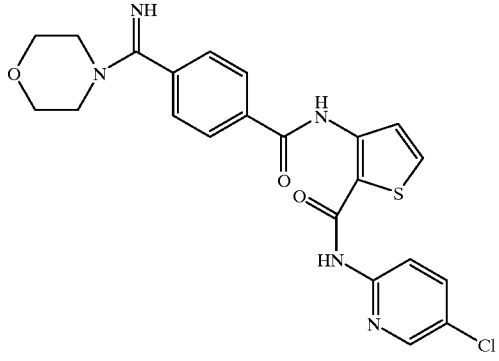
[1430] N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}[4-(iminopyrrolidinylmethyl)-phenyl]carboxamide



[1431] The title compound was obtained according to the procedure previously described. ES-MS 454(M+1).

Example 500

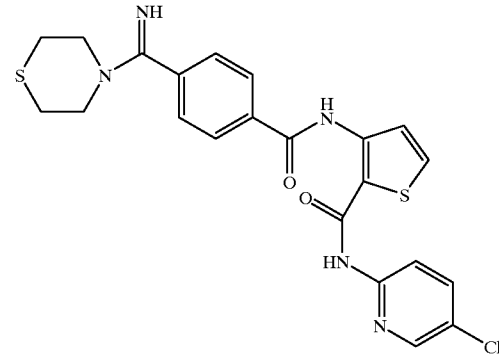
[1432] N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}[4-(iminomorpholin-4-ylmethyl)phenyl]carboxamide



[1433] The title compound was obtained according to the procedure previously described. ES-MS 470(M+1).

Example 501

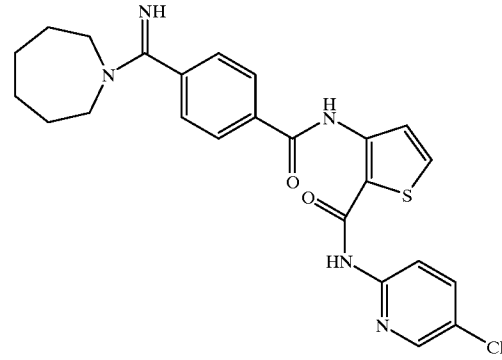
[1434] N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}[4-(imino-1,4-thiazaperhydroin-4-ylmethyl)phenyl] carboxamide



[1435] The title compound was obtained according to the procedure previously described. ES-MS 486(M+1).

Example 502

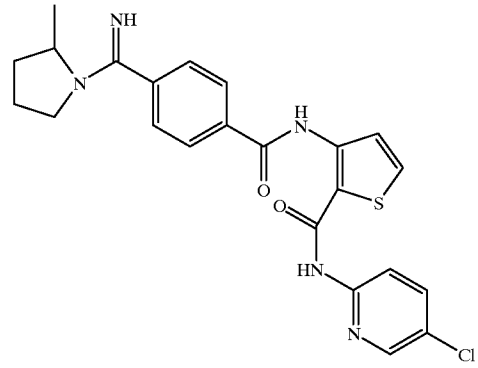
[1436] [4-(azaperhydroepinyliminomethyl)phenyl]-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}carboxamide



[1437] The title compound was obtained according to the procedure previously described. ES-MS 482(M+1).

Example 503

[1438]

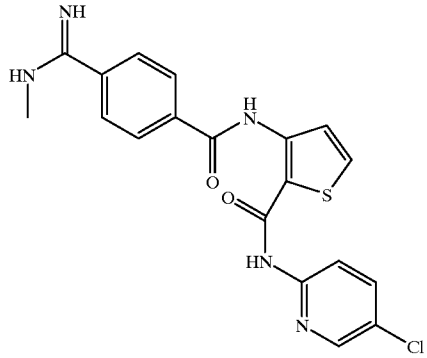


[1439] N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}{4-[imino(2-methylpyrrolidinyl)methyl]phenyl}carboxamide

[1440] The title compound was obtained according to the procedure previously described. ES-MS 468(M+1).

Example 504

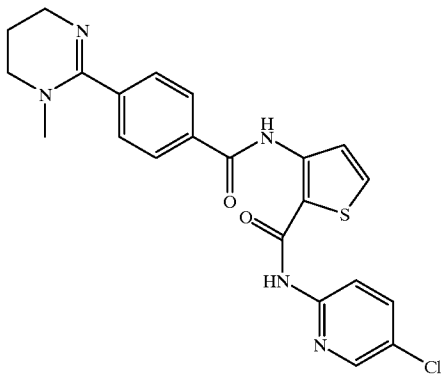
[1441] N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}{4-[imino(methylamino)methyl]-phenyl}carboxamide



[1442] The title compound was obtained according to the procedure previously described.

Example 505

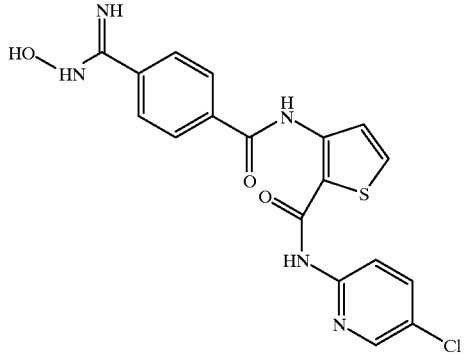
[1443] N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}[4-(3-methyl(3,4,5,6-tetrahydropyrimidin-2-yl))phenyl]carboxamide



[1444] The title compound was obtained according to the procedure previously described. ES-MS 414(M+1).

Example 506

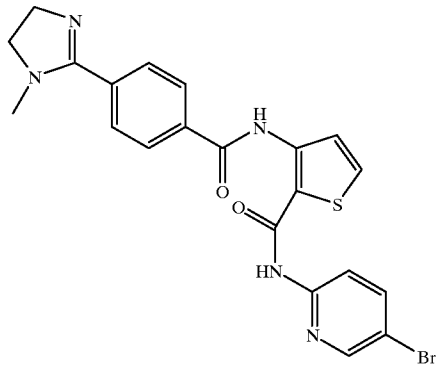
[1445] N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}[4-((hydroxyamino)iminomethyl)-phenyl]carboxamide



[1446] The title compound was obtained according to the procedure previously described. ES-MS 416(M+1).

Example 507

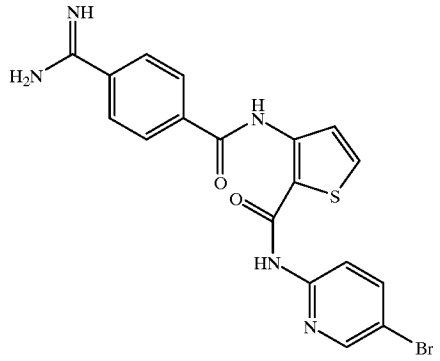
[1447] N-{2-[N-(5-bromo(2-pyridyl))carbamoyl](3-thienyl)}[4-(1-methyl(2-imidazolin-2-yl))phenyl]carboxamide



[1448] The title compound was obtained according to the procedure previously described. ES-MS 484(M+1).

Example 508

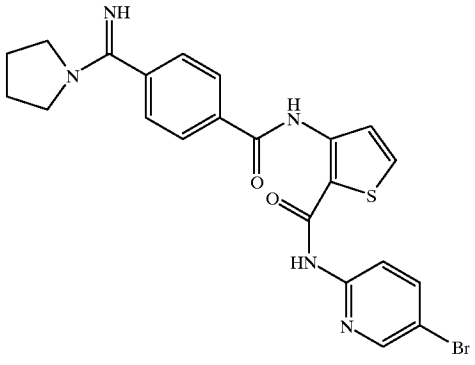
[1449] 4-(N-{2-[N-(5-bromo-2-pyridyl)carbamoyl]-3-thienyl}carbamoyl)benzenecarboxamidine



[1450] The title compound was obtained according to the procedure previously described. ES-MS 444(M+1).

Example 509

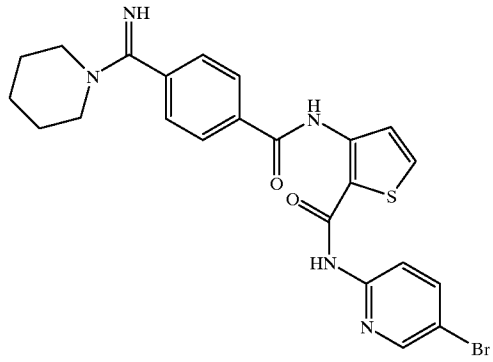
[1451] N-[2-[N-(5-bromo(2-pyridyl))carbamoyl](3-thienyl)}[4-(iminopyrrolidinylmethyl)phenyl]carboxamide



[1452] The title compound was obtained according to the procedure previously described. ES-MS 494(M+1).

Example 510

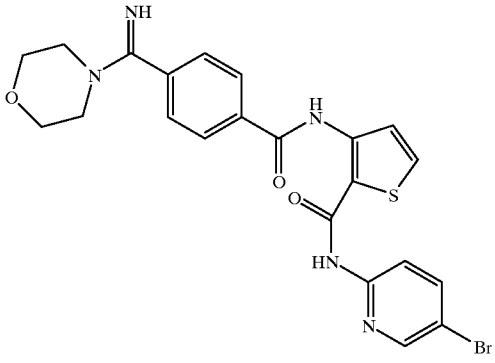
[1453] N-{2-[N-(5-bromo(2-pyridyl))carbamoyl](3-thienyl)}[4-(iminopiperidylmethyl)phenyl]carboxamide



[1454] The title compound was obtained according to the procedure previously described. ES-MS 512(M+1).

Example 511

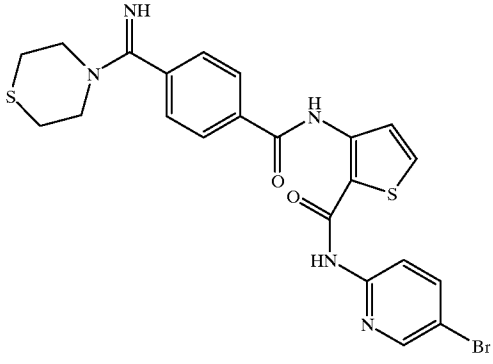
[1455] N-{2-[N-(5-bromo(2-pyridyl))carbamoyl](3-thienyl)}[4-(iminomorpholin-4-ylmethyl)phenyl]carboxamide



[1456] The title compound was obtained according to the procedure previously described. ES-MS 514(M+1).

Example 512

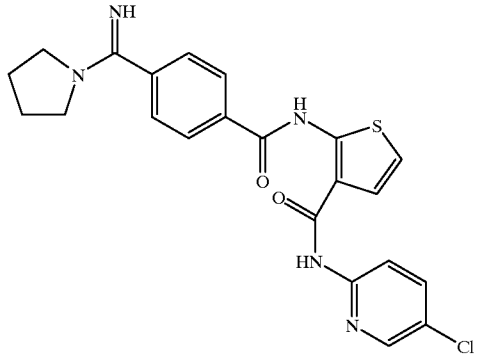
[1457] N-{2-[N-(5-bromo(2-pyridyl))carbamoyl](3-thienyl)}[4-(imino-1,4-thiazaperhydroin-4-ylmethyl)phenyl] carboxamide



[1458] The title compound was obtained according to the procedure previously described. ES-MS 530(M+1).

Example 513

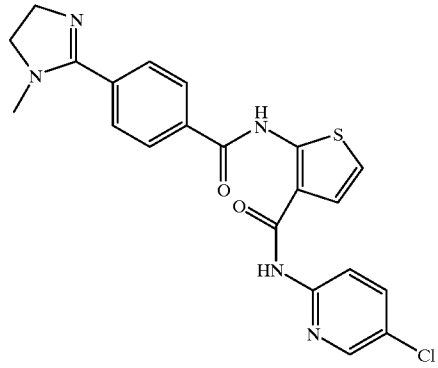
[1459] N-{3-[N-(5-chloro(2-pyridyl))carbamoyl](2-thienyl)}[4-(iminopyrrolidinylmethyl)phenyl]carboxamide



[1460] The title compound was obtained according to the procedure previously described. ES-MS 454(M+1).

Example 514

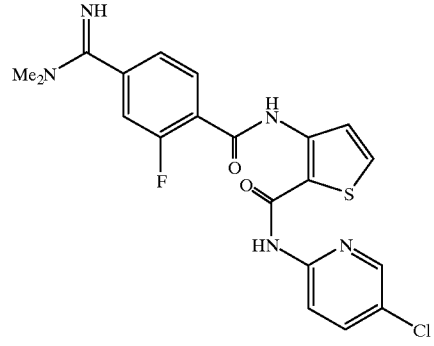
[1461] N-{3-[N-(5-chloro(2-pyridyl))carbamoyl](2-thienyl)}[4-(1-methyl(2-imidazolin-2-yl))phenyl]carboxamide



[1462] The title compound was obtained according to the procedure previously described. ES-MS 440(M+1.).

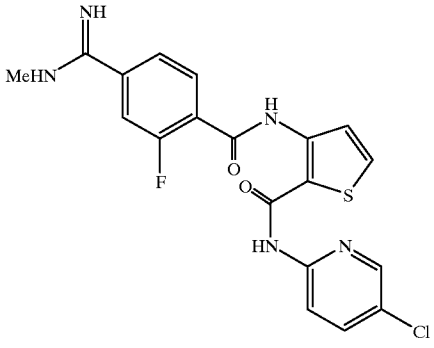
Examples 515-520

[1463] The following examples are prepared according to the procedure previously described.

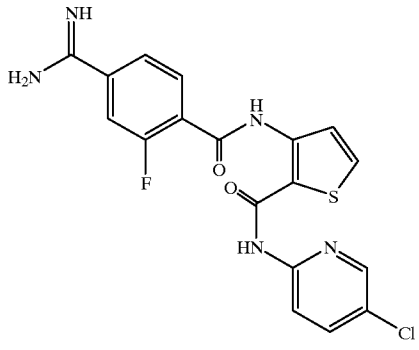


MS (M+H) 446

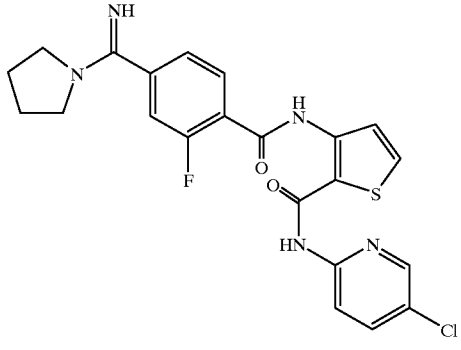
-continued



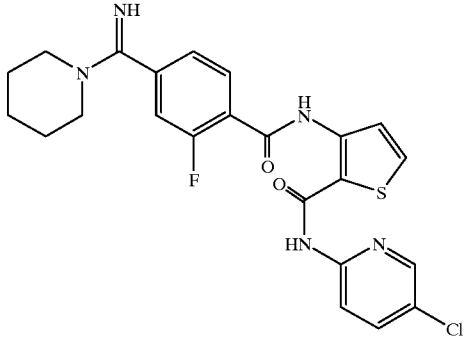
MS (M+H) 432



MS (M+H) 418

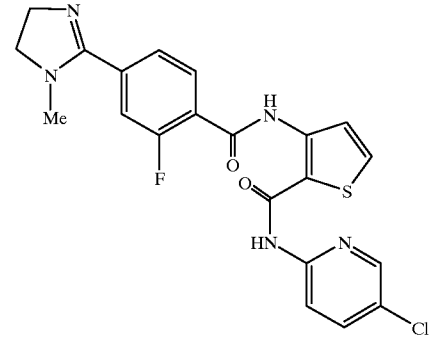


MS (M+H) 472



MS (M+H) 486

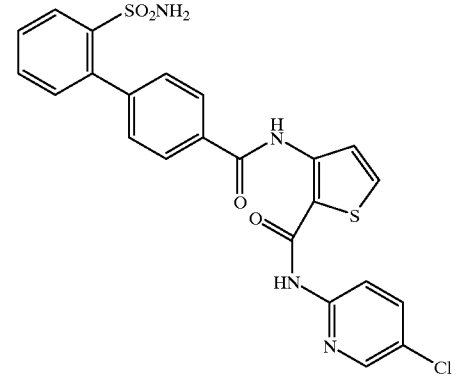
-continued



MS (M+H) 458

Example 521

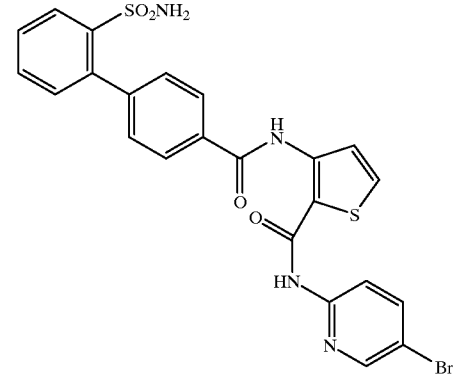
[**1464**] N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}[4-(2-sulfamoylphenyl)phenyl]carboxamide



[**1465**] A solution of 4-(2-{[(tert-butyl)amino]sulfonyl}phenyl)benzoyl chloride (1 equiv), 3-amino-2-(4-chloro-2-pyridinyl)aminocarbonyl thiophene (1 equiv), pyridine (5 equiv) in dichloromethane was stirred at rt overnight. The mixture was diluted with dichloromethane, washed with water, dried over Na2SO4, filtered and evaporated. The residue was refluxed with I mL of TFA for 2 h. After evaporation, reverse phase HPLC gave the title product. ES-MS 513(M+1).

Example 522

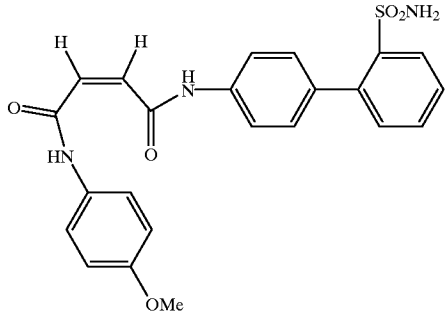
[**1466**] N-{2-[N-(5-bromo(2-pyridyl))carbamoyl](3-thienyl)}[4-(2-sulfamoylphenyl)phenyl]carboxamide



[1467] The title compound was obtained according to the procedure previously described. ES-MS 556(M+1).

Example 523

[1468] N-(4-methoxyphenyl)-N'-(4-[(2-aminosulfonyl)phenyl]phenyl)-maleamic amide



[1469] A. Preparation of N-(4-methoxyphenyl)-N'-(4-[(2-tert-butylaminosulfonyl)phenyl]phenyl)-maleamic amide.

[1470] To a solution of commercially available N-(4-methoxyphenyl)maleamic acid (100 mg, 0.452 mmol), triethylamine (0.126 mL, 0.906 mmol) and 4-(2-tert-butylaminosulfonylphenyl)aniline (138 mg, 0.454 mmol) in anhydrous DMF (5 mL), BOP (260 mg, 0.588 mmol) was added. The mixture was stirred at room temperature overnight. Water and EtOAc were added. The organic phase was separated, washed with H2O, then with 5% NaHCO3, dried over Na2SO4, concentrated in vacuo. The residue was purified by HPLC using a gradient of 20% CH3CN in H2O (containing 0.1% TFA) to 100% CH3CN over 80 min. Fractions containing the desired product were pooled, and lyophilized to give a powder (70 mg, yield: 31%). MS 508 (M+H).

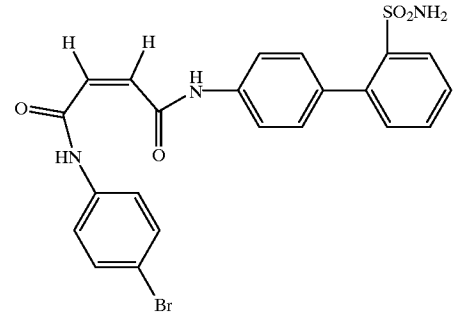
[1471] B. Preparation of N-(4-methoxyphenyl)-N'-(4-[(2-aminosulfonyl)phenyl]phenyl)-maleamic amide.

[1472] The compound N-(4-methoxyphenyl)-N'-(4-[(2-tert-butylaminosulfonyl)phenyl]phenyl)-maleamic amide (40 mg, 79 mol) was dissolved in TFA (3 mL). It was allowed to stand at room temperature overnight. TFA was removed in vacuo. The residue was purified by HPLC using a gradient of 5% CH3CN in H2O (containing 0.1% TFA) to 95% CH3CN over 60 min. Fractions containing the desired product were pooled, and lyophilized to give a powder (18 mg, yield: 51%). MS 452 (M+H) and 474 (M+Na).

[1473] ^{1}H NMR (CDCl3) δ 11.40 (br.s, 1H), 10.28 (br.s, 1H), 8.12 (d, 1H. J=8 Hz), 7.72 (d, 2H, J=8 Hz), 7.60 - 7.20 (m, 9H), 6.86 (AB type, 2H), 6.45 (br.s, 2H), 3.79 (s, 3H).

Example 524

[1474] N-(4-bromophenyl)-N'-(4-[(2-aminosulfonyl)phenyl]phenyl)-maleamic amide.



[1475] A. Preparation of N-(4-[(2-tert-butylaminosulfonyl)phenyl]phenyl)maleamic methyl ester.

[1476] To a solution of commercially available maleic acid monomethyl ester (277 mg, 2.13 mmol), 4-(2-tert-butylaminosulfonylphenyl)aniline (648 mg, 2.13 mmol) and triethylamine (0.593 mL, 4.26 mmol) in CH2Cl2 (20 mL), BOP (1.13 g, 2.55 mmol) was added. The mixture was stirred at room temperature overnight. More maleic acid monomethyl ester (50 mg, 0.385 mmol) was added. It was stirred for 3 hours. The CH2Cl2 solution was then washed with sat. NaHCO3, 1N HCl and sat. NaCl. The solution was dried over Na2SO4, concentrated in vacuo. The residue was purified by a silica gel column using a gradient of 10-40% EtOAc in hexane as solvents, to give the titled compound (360 mg, yield: 41%). MS 361 (M+H–^{t}Bu) and 439 (M+Na).

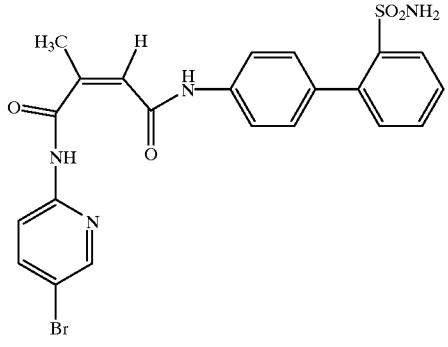
[1477] B. Preparation of N-(4-bromophenyl)-N'-(4-[(2-aminosulfonyl)phenyl]phenyl)-maleamic amide.

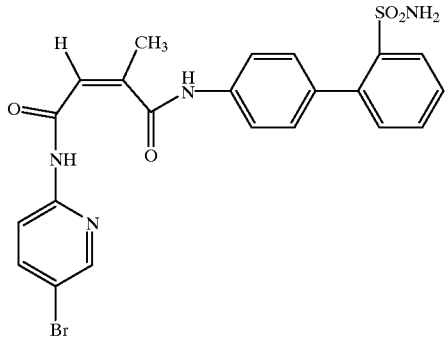
[1478] To a solution of 4-bromoaniline (93 mg, 0.543 mmol) in CH2Cl2 (5 mL) at room temperature, trimethylaluminum (0.82 mL, 2.0 M in hexane, 1.64 mmol) was added dropwise. After the solution was stirred for 30 min at room temperature, compound N-(4-[(2-tert-butylaminosulfonyl)phenyl]phenyl)maleamic methyl ester (113 mg, 0.272 mmol) was added. The mixture was stirred at room temperature for 2 days. The solution was neutralized with 1N HCl to pH 2-3. Water and CH2Cl2 were added, and organic phase was separated, dried over Na2SO4, concentrated in vacuo. The residue was dissolved in TFA (4 mL). It was allowed to stand at room temperature overnight. TFA was removed in vacuo. The residue was purified by HPLC using a gradient of 5% CH3CN in H20 (containing 0.1% TFA) to 95% CH3CN over 60 min. Fractions containing the desired product were pooled, and lyophilized to give a powder (8 mg, yield: 6%). MS 500 and 502 (M+H), 522 and 524 (M+Na).

[1479] ^{1}H NMR (CD3OD) δ 8.09 (d, 1H, J=8 Hz), 7.68 (d, 2H, J=8 Hz), 7.64-7.28 (m, 9H), 6.45 (AB type, 2H).

Examples 525 and 526

[1480] Preparation of N^1-(5-bromopyridin-2-yl)-N^4-(4-[(2-aminosulfonyl)phenyl]phenyl)-2-methylmaleamic amide and N^1-(5-bromopyridin-2-yl)-N^4-(4-[(2-aminosulfonyl)phenyl]phenyl)-3-methylmaleamic amide.





[1481] A. Preparation of N-(5-bromopyridin-2-yl)-methylmaleimide.

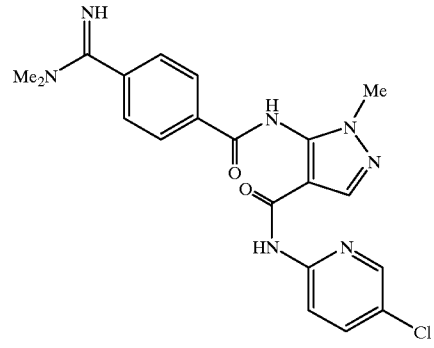
[1482] A mixture of citraconic anhydride (1.00 mL, 1.1 mmol) and 2-amino-5-bromopyridine (1.93 g, 11.2 mmol) in toluene (60 mL) was heated to reflux overnight. The solution was cooled down, filtered. The filtrate was concentrated in vacuo to give a solid (2.10 g, yield: 71%). MS 267 and 269 (M+H).

[1483] B. Preparation of N^1-(5-bromopyridin-2-yl)N^4-(4-[(2-aminosulfonyl)phenyl]phenyl)-2-methylmaleamic amide and N^1-(5-bromopyridin-2-yl)-N^4-(4-[(2-aminosulfonyl)phenyl]phenyl)-3-methylmaleamic amide.

[1484] To the solution of 4-(2-aminosulfonylphenyl)aniline (0.170 g, 0.685 mmol) in CH2Cl2 (10 mL) at room temperature, trimethylaluminum (2.0 M in hexane, 2.00 mL, 4.00 mmol) was added dropwise, during which time, white gel-like precipitates came out the solution. It was stirred for 30 min. A solution of N-(5-bromopyridin-2-yl)-methylmaleimide (0.122 g, 0.457 mmol) in CH2Cl2 (5 mL) was added. It was stirred for 1 hour, during which time the precipitates started to dissolve, and the solution became clear. It was stirred for another 2 hours. 1N HCl was added to neutralize the solution to pH 2-3, which resulted in precipitation. The precipitates were collected by filtration, dried on vacuum. The precipitates (75 mg, yield: 32%) were a mixture of 2-methyl and 3-methylmaleamic amide isomers in a ratio of 1:5. MS 515 and 517 (M+H), 537 and 539 (M+Na).

Example 527

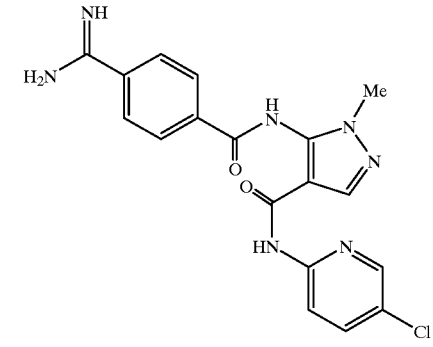
[1485]

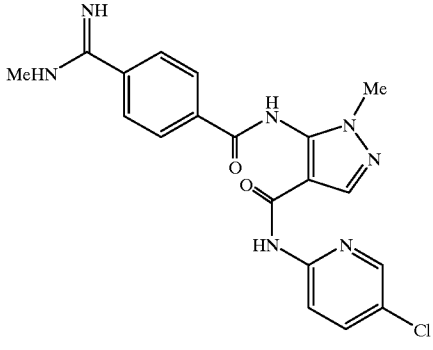


[1486] A solution of 3-amino-4-[(5-chloro-2-pyridinyl)aminocarbonyl]pyrazole (1 equiv) and 4-cyanobenzoic acid (1 equiv) in pyridine was treated with $POCl_3$ (1.1 equiv) for 30 min. The resulting mixture was quenched by slow addition of water, and extracted with CH_2Cl_2 and dried over $MgSO_4$. After evaporation, the residue was trituated with a small amount of CH_2Cl_2 and EtOAc. The solid on the glass wall was then subjected to standard Pinner conditions to give desired product. MS $(M+H)^+$: 426.

Examples 528-538

[1487] The following examples were prepared according to the procedure previously described.





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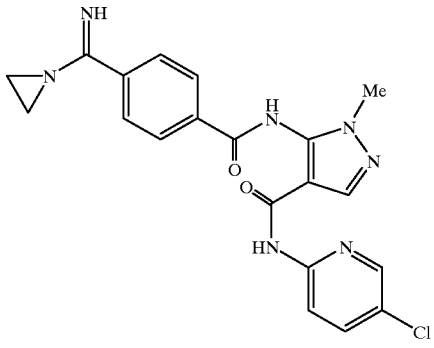

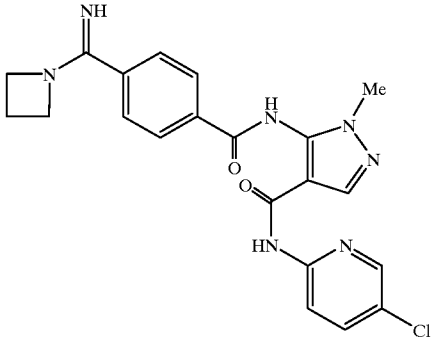

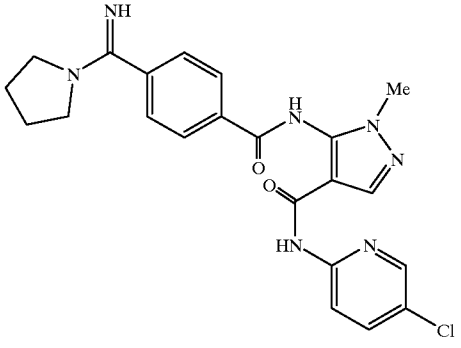

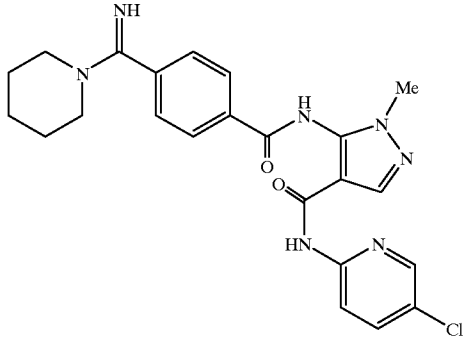

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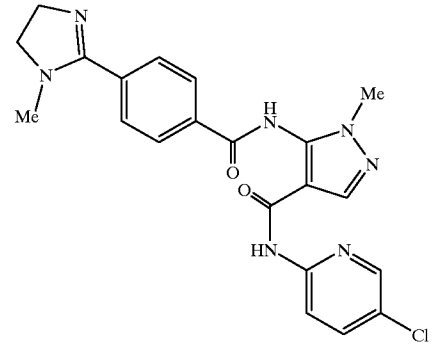

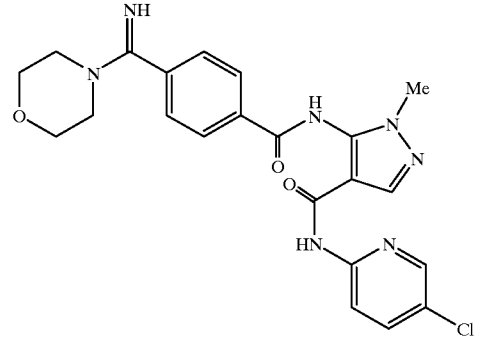

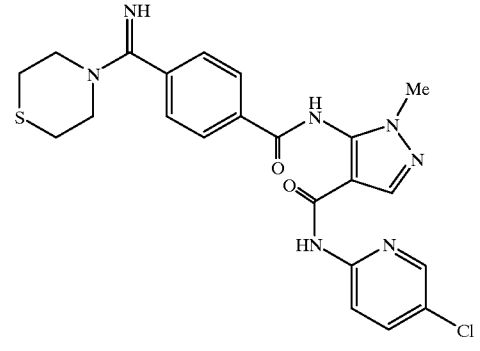

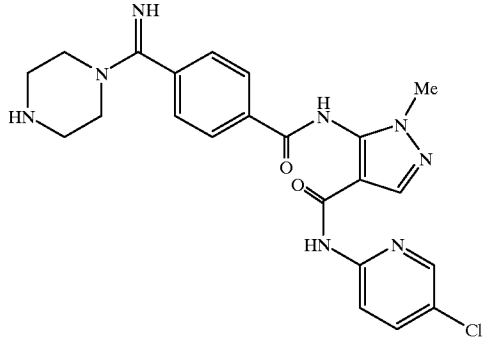

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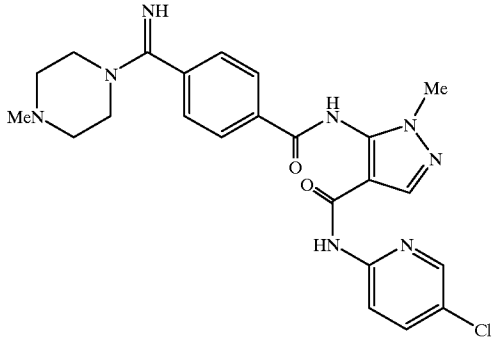
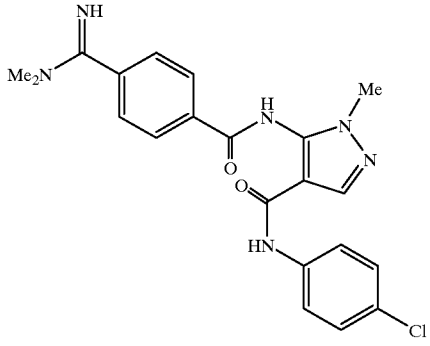


Example 539

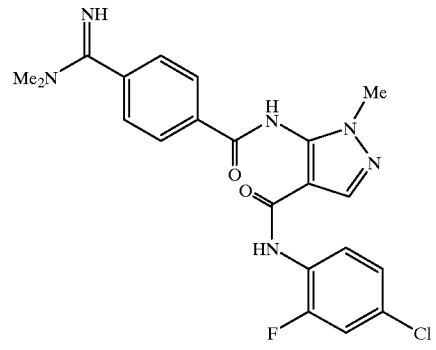


[1488] Step 1: A solution of 3-amino-4-ethoxycarbonyl-pyrazole (1 equiv) and 4-cyanobenzoic acid (1 equiv) in pyridine was treated with $POCl_3$ (1.1 equiv) for 1 h. The resulting mixture was quenched by slow addition of water, extracted with CH_2Cl_2, dried over $MgSO_4$, and purified by column chromatography to give the desired product.

[1489] Step 2: The compound obtained in step 1 (1 equiv) in DMF was treated with NaSMe (10 equiv) at 65° C. overnight. The resulting mixture was quenched by slow addition of water, and acidified with 1N HCl, extracted with EtOAc, and dried over $MgSO_4$. The acid was reflux in excess $SOCl_2$ for 2 h. The volatile was removed on rotovap, and the residue was redissolved in pyridine, refluxed overnight in the prsence of DMAP (1 equiv) and 4-chloroaniline (10 equiv). The resulting mixture was quenched by slow addition of water, and extracted with CH_2Cl_2 and dried over $MgSO_4$. After evaporation, the residue was trituated with a small amount of CH_2Cl_2 and EtOAc. The solid on the glass wall was then subjected to standard Pinner conditions to give desired product. MS $(M+H)^+$: 425.

Example 540

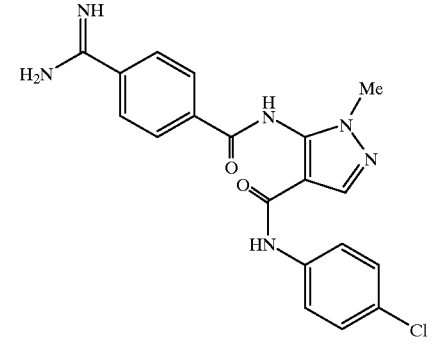
[1490]

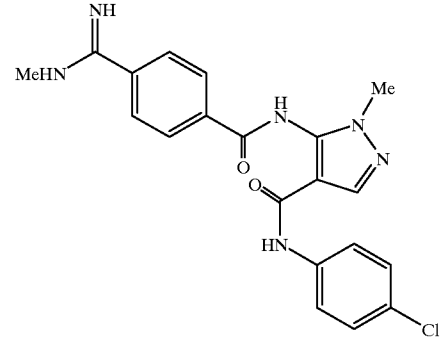


[1491] Similarly prepared as Example 350. MS $(M+H)^+$: 443.

Examples 541-551

[1492] The following examples were prepared according to the procedure previously described.





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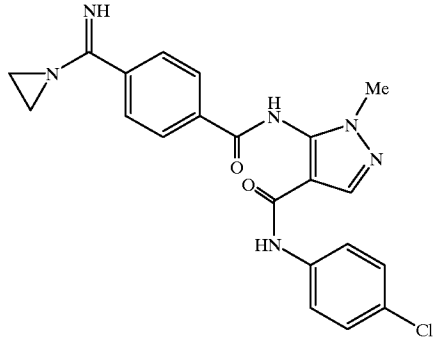

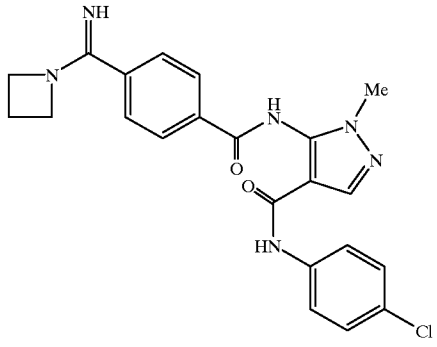

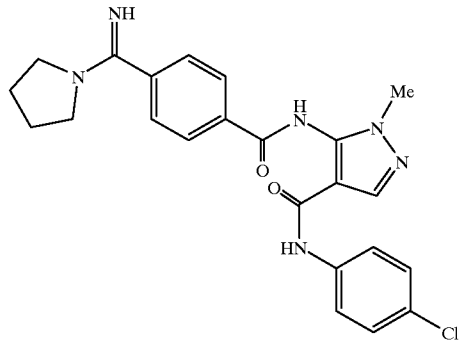

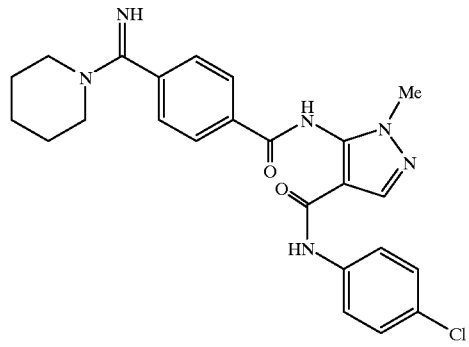

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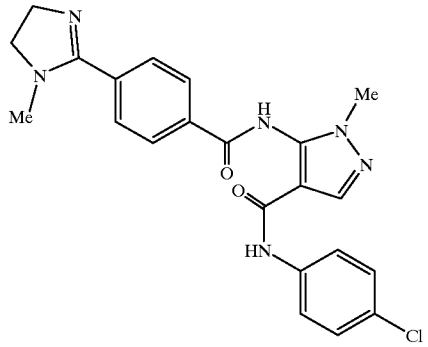

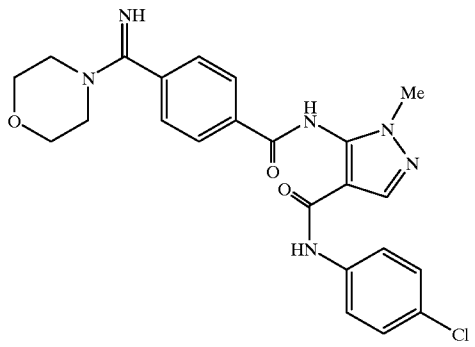

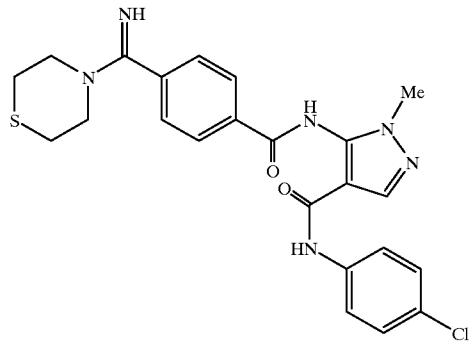

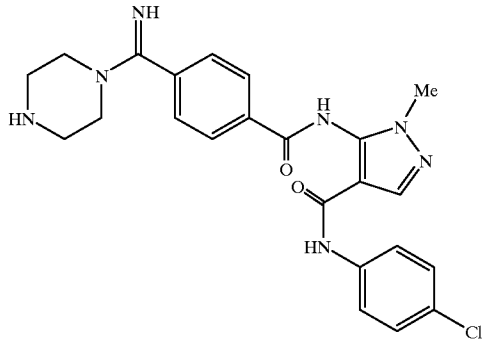

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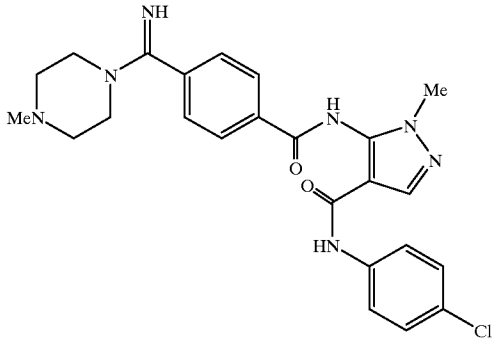
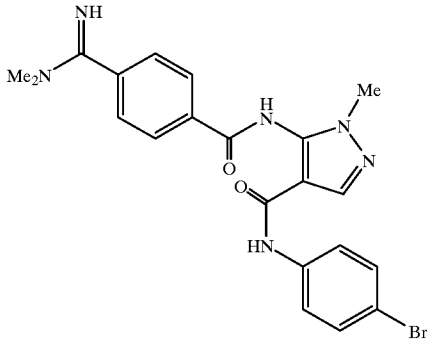
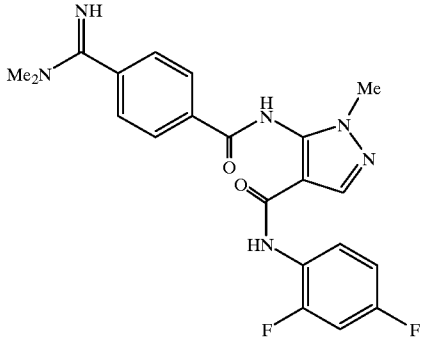
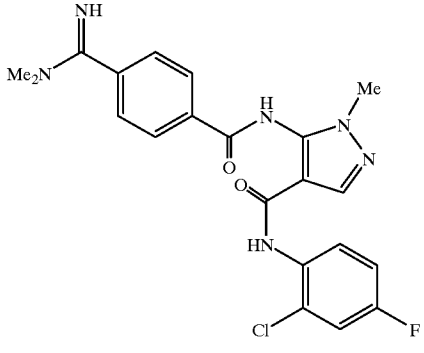


Examples 552-559

[1493] The following examples were prepared according to the procedure previously described.







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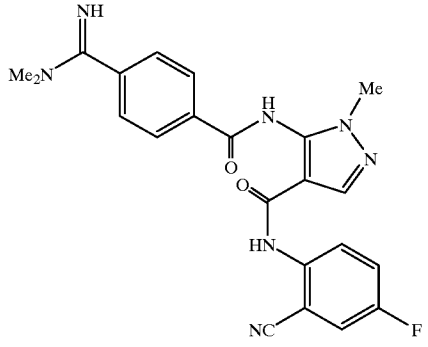

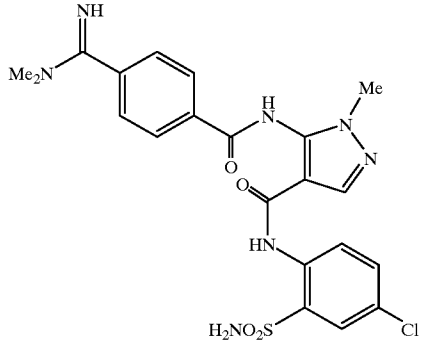

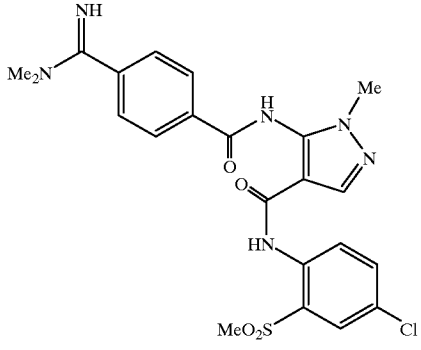

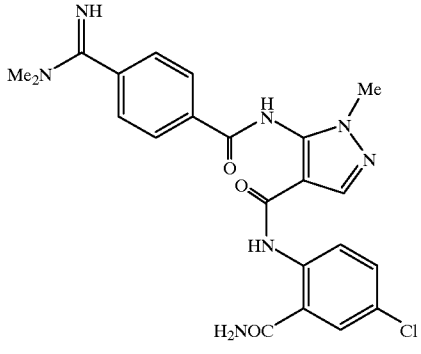

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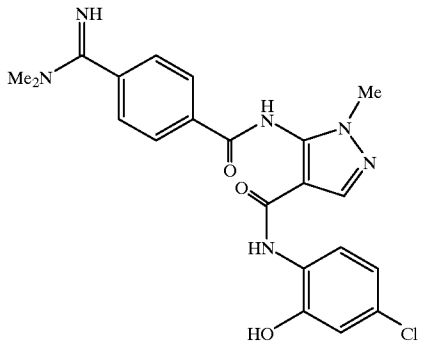
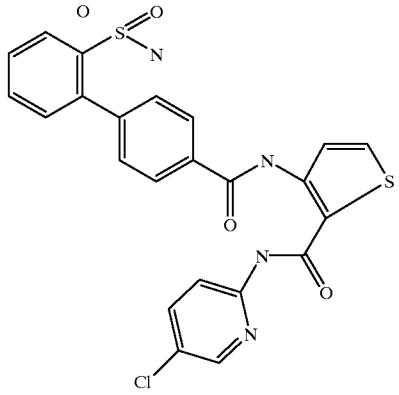


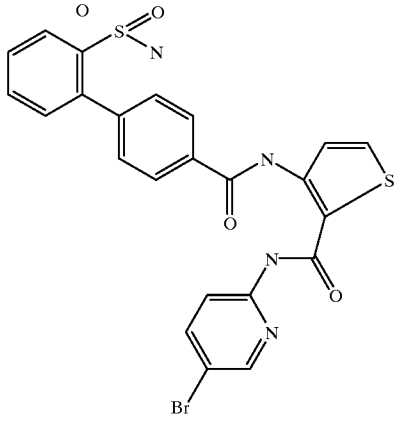
Example 560



[1494] The title compound was synthesized according to the procedure described previously. ES-MS 514(M+1).

Example 561

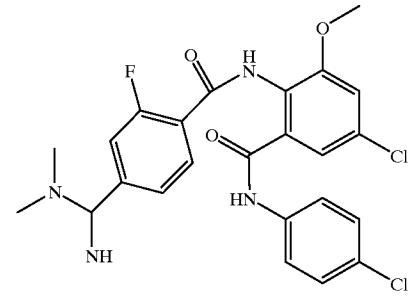
[1495]



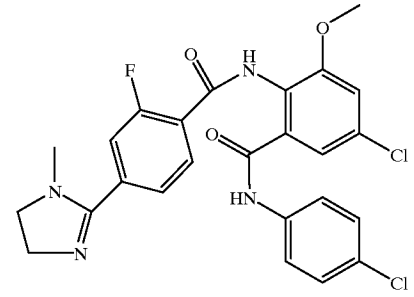
[1496] The title compound was synthesized according to the procedure described previously. ES-MS 558(M+1).

Example 562-585

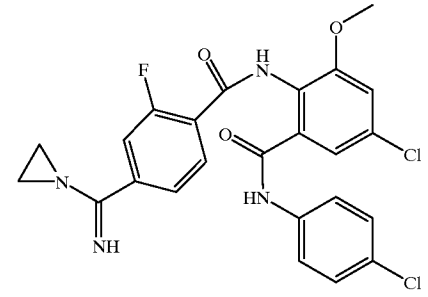
[1497] The following compounds were prepared according to the procedure previously described.



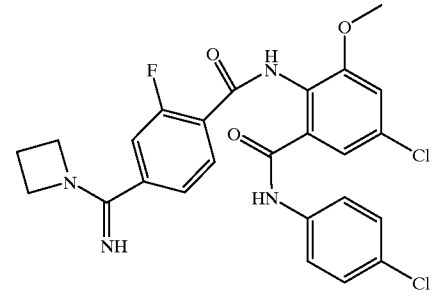
Mol Wt 503



Mol Wt 515



MS 502 (M+H)



MS 516 (M+H)

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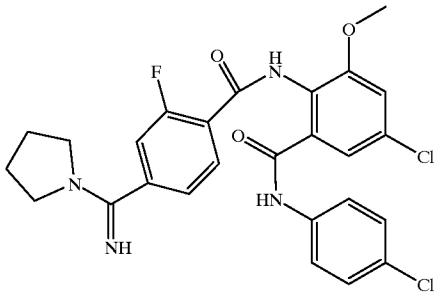
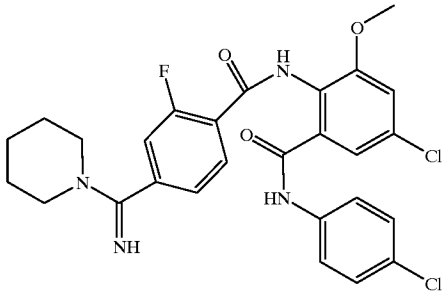
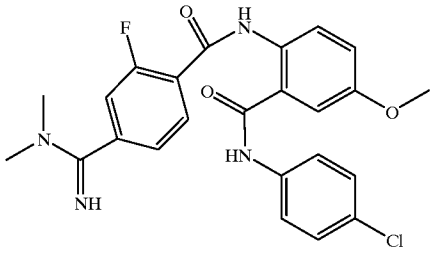


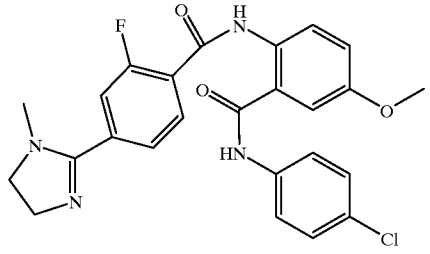
MS 530 (M+H)



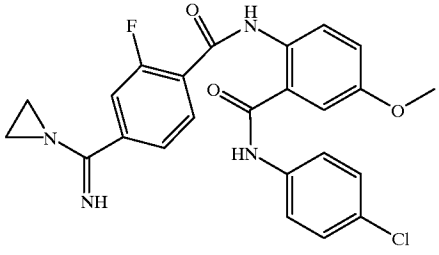
MS 544 (M+H)



MS 469 (M+H)



MS 481 (M+H)



MS 467 (M+H)

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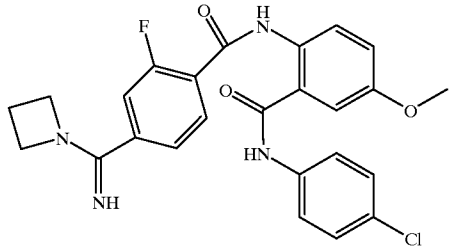
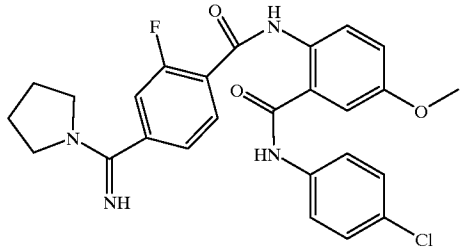
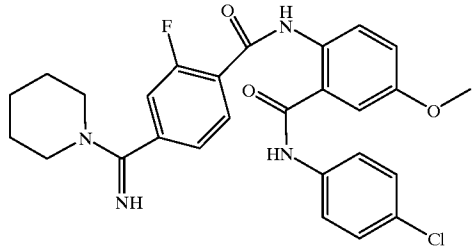


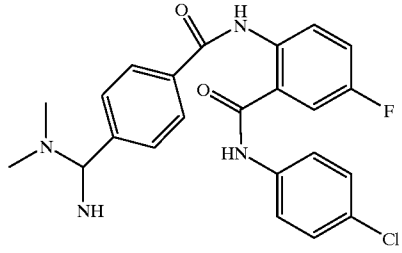
MS 481 (M+H)



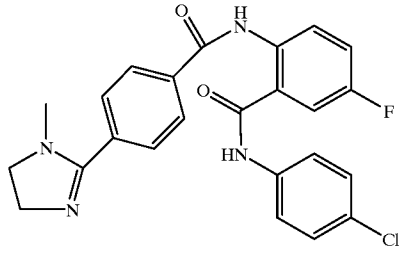
MS 495 (M+H)



MS 509 (M+H)



MS 409 (M+H)



MS 451 (M+H)

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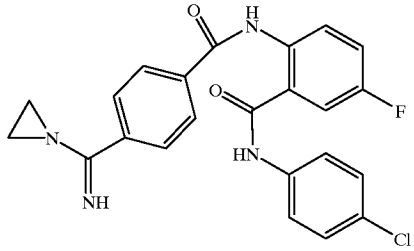
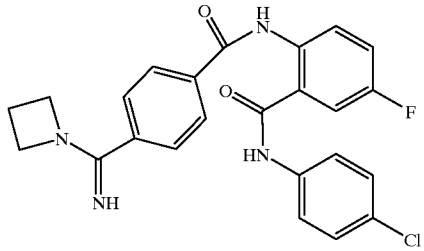
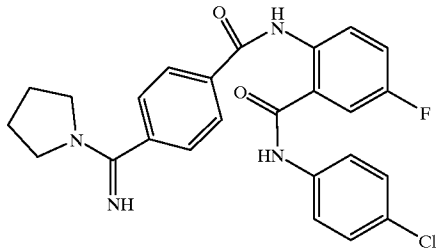


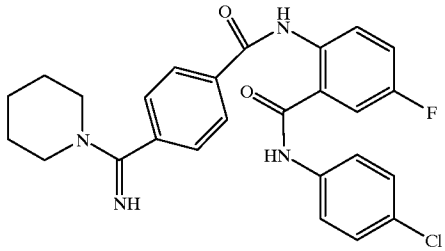
MS 437 (M+H)



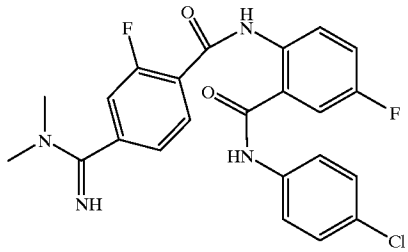
MS 451 (M+H)



MS 465 (M+H)



MS 479 (M+H)



MS 457 (M+H)

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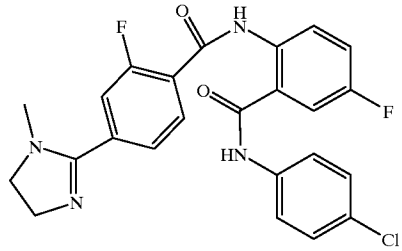
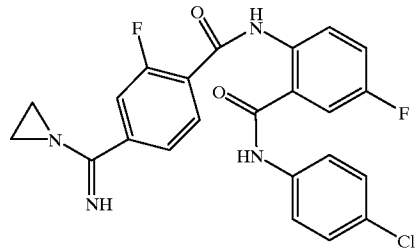
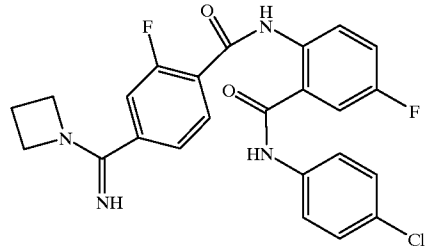


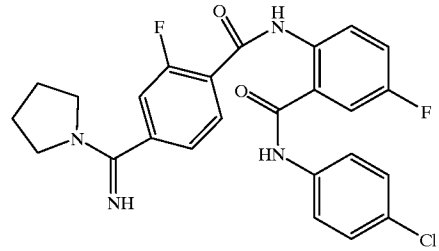
MS 469 (M+H)



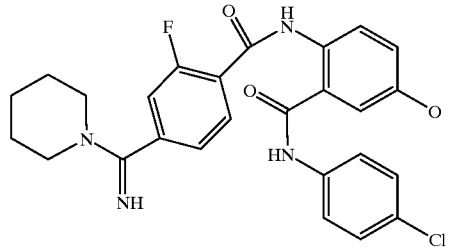
MS 455 (M+H)



MS 469 (M+H)



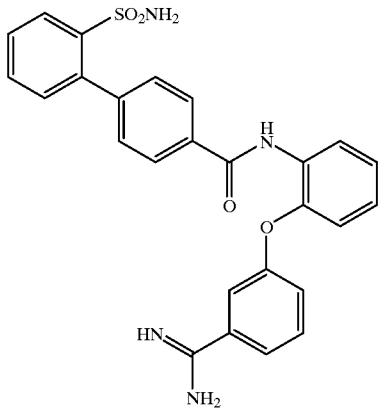
MS 483 (M+H)



MS 497 (M+H)

Example 586

[1498] 3-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino) phenoxy)benzamidine.



[1499] Step 1: To a solution of 2-fluoro nitrobenzene (1.41 g, 10 mmol, 1.0 equiv) and 3-hydroxybenzonitrile (1.19 g, 1.0 equiv) in 10 mL of DMF was added K_2CO_3 (2.76 g, 2 equiv). After stirring at 60° C. for 3 h, the mixture was diluted with EtOAc and washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated to give 3-(2-nitrophenoxy)benzonitrile (2.38 g, 99%).

[1500] MS found for $C_{13}H_9N_2O_3$ $(M+H)^+$: 241.

[1501] Step 2: A solution of 3-(2-nitrophenoxy)benzonitrile (1.21 g, 5 mmol, 1.0 equiv) in 30 mL of EtOH was treated with $SnCl_2$ $2H_2O$ (3.38 g, 3 equiv) at reflux for 4 h. The volatile was evaporated and the residue was redissolved in EtOAc, washed with saturated aqueous $NaHCO_3$ and 1N NaOH. The organic layer was dried over $MgSO_4$, filtered and evaporated to give 3-(2-aminophenoxy)benzonitrile (1.04 g, 99%).

[1502] MS found for $C_{13}H_{11}N_2O$ $(M+H)^+$: 211.

[1503] Step 3: A mixture of 3-(2-aminophenoxy)benzonitrile (210 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic acid (330 mg, 1 equiv), Bop reagent (880 mg, 2 equiv) and TEA (1.39 mL, 10 equiv) in 3 mL of DMF was stirred at rt overnight. The mixture was diluted with EtOAc, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl] benzoylamino)phenoxy)benzonitrile (300 mg, 57%).

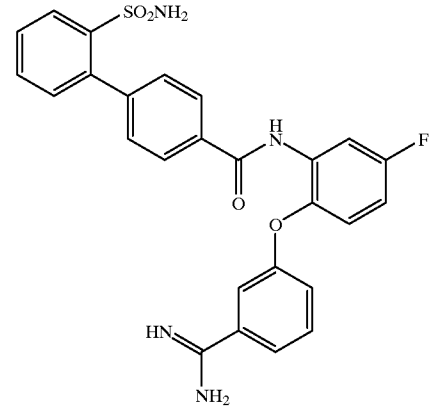
[1504] MS found for $C_{30}H_{28}N_3O_4S$ $(M+H)^-$: 526.

[1505] Step 4: A stream of HCl(g) was bubbled through a 0° C. solution of 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl] benzoylamino)phenoxy)benzonitrile (53 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (39 mg, 5 equiv) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 3-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino) phenoxy)benzamidine (40 mg, 83%).

[1506] MS found for $C_{26}H_{23}N_4O_4S$ $(M+H)^+$: 487.

Example 587

[1507] 3-(4-fluoro-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine.



[1508] Step 1: A mixture of 3-(2-amino-4-fluorophenoxy-)benzonitrile (230 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave 3-(4-fluoro-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzonitrile (495 mg, 91%).

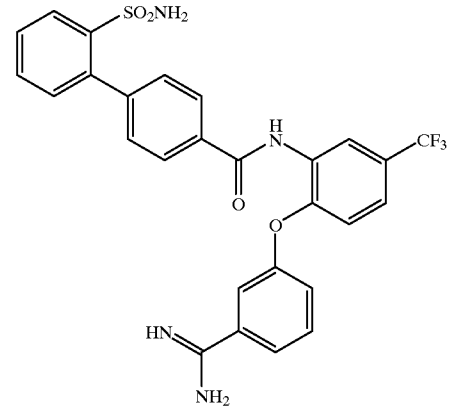
[1509] MS found for $C_{30}H_{27}FN_3O_4S$ $(M+H)^+$: 544.

[1510] Step 2: A stream of HCl(g) was bubbled through a 0° C. solution of 3-(4-fluoro-2-(4-[(2 -t- butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzonitrile (55 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (39 mg, 5 equiv) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 3-(4-fluoro-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine (39 mg, 77%).

[1511] MS found for $C_{26}H_{22}FN_4O_4S$ $(M+H)^+$: 505.

Example 588

[1512] 3-(4-trifluoromethyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine.



[1513] Step 1: A mixture of 3-(2-amino-4-trifluoromethylphenoxy)benzonitrile (280 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave 3-(4-trifluoromethyl-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzonitrile (529 mg, 89%).

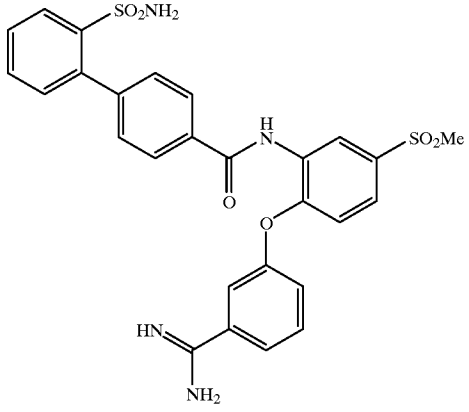
[1514] MS found for $C_{31}H_{27}F_3N_3O_4S$ $(M+H)^+$: 594.

[1515] Step 2: A stream of HCl(g) was bubbled through a 0° C. solution of 3-(4-trifluoromethyl-2-(4- [(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzonitrile (59 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (39 mg, 5 equiv) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 3-(4-trifluoromethyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine (35 mg, 63%).

[1516] MS found for $C_{27}H_{22}F_3N_4O_4S$ $(M+H)^+$: 555.

Example 589

[1517] 3-(4-methylsulfonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine.



[1518] Step 1: A mixture of 3-(2-amino-4-methylsulfonylphenoxy)benzonitrile (290 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave 3-(4-methylsulfonyl-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzonitrile (429 mg, 71%).

[1519] MS found for $C_{31}H_{30}N_3O_6S_2$ $(M+H)^+$: 604.

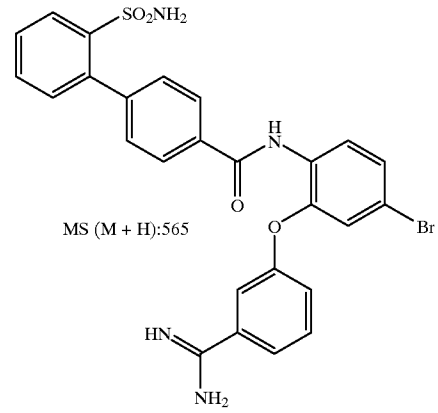
[1520] Step 2: A stream of HCl(g) was bubbled through a 0° C. solution of 3-(4-methylsulfonyl-2-(4- [(2-t-butylaminosulfonyl)phenyl] phenylcarbonylamino)phenoxy) benzonitrile (60 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (39 mg, 5 equiv) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 3-(4-methylsulfonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine (27 mg, 47%).

[1521] MS found for $C_{27}H_{25}N_4O_6S_2$ $(M+H)^+$: 565.

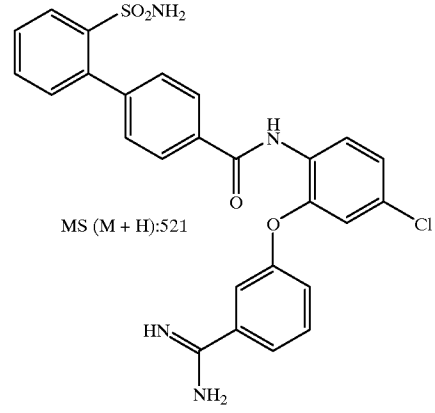
Examples 590-593

[1522] The following compounds were prepared using the procedure previously described.

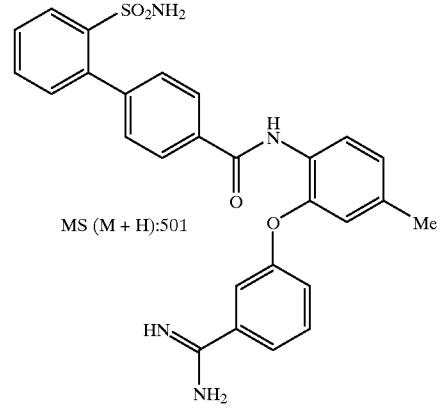
Example 590



Example 591

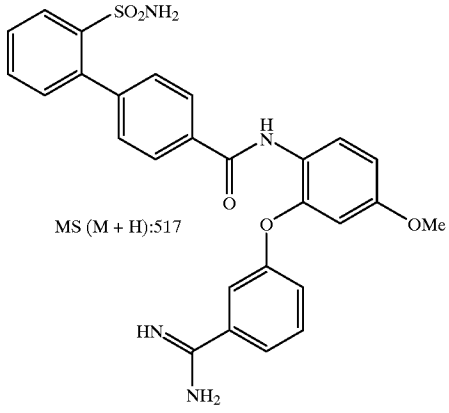


Example 592



-continued

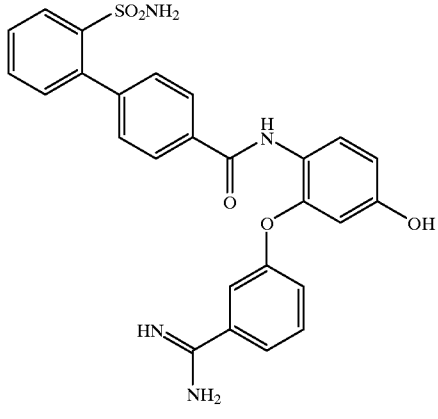
Example 593



MS (M + H):517

Example 594

[1523] 3-(5-hydroxy-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine.

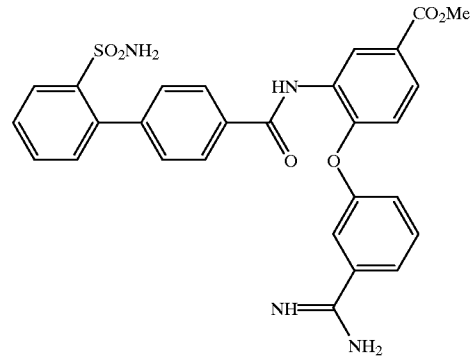


[1524] A solution of 3-(5-methoxy-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino) phenoxy) benzamidine (52 mg, 0.1 mmol, 1 equiv) in 5 mL of methylene chloride was treated with BBr_3 (1 M in dichloromethane, 0.5 mL, 5 equiv) overnight. The reaction was quenched with water carefully and after the volatile was evaporated, the aqueous residue was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 3-(5-hydroxy-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine. (41 mg, 82%).

[1525] MS found for $C_{26}H_{23}N_4O_6S$ $(M+H)^+$: 503.

Example 595

[1526] 3-(4-methoxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine.



[1527] Step 1: A mixture of 3-(2-amino-4-methoxycarbonylphenoxy)benzonitrile (270 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave 3 -(4-methoxycarbonyl-2-(4- [(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzonitrile (502 mg, 86%).

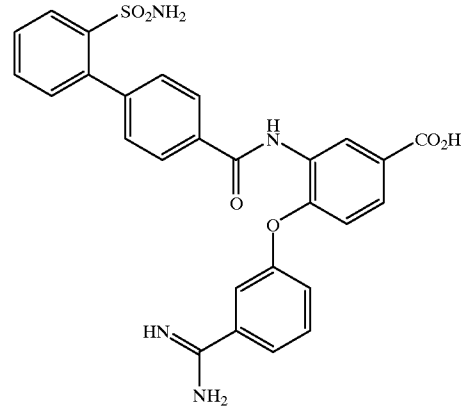
[1528] MS found for $C_{32}H_{30}N_3O_6S$ $(M+H)^+$: 584.

[1529] Step 2: A stream of HCl(g) was bubbled through a 0° C. solution of 3-(4-methoxycarbonyl-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzonitrile (58 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (39 mg, 5 equiv) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 3-(4-methoxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine (29.5 mg, 54%).

[1530] MS found for $C_{28}H_{25}N_4O_6S$ $(M+H)^+$: 545.

Example 596

[1531] 3-(4-hydroxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine.

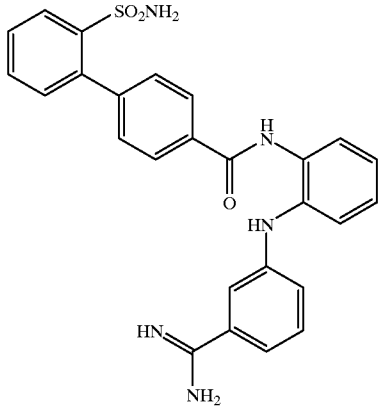


[1532] A solution of 3-(4-methoxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine (10.9 mg, 0.02 mmol, 1.0 equiv) in 5 mL of methanol was treated with 1N LiOH (2 mL) at rt for 2 h. Methanol was evaporated, the aqueous residue was subjected to HPLC with 0.5% TEA in H_2O/CH_3CN to give 3-(4-hydroxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine (8.9 mg, 84%).

[1533] MS found for $C_{27}H_{23}N_4O_6S$ $(M+H)^+$: 531.

Example 597

[1534] 3-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pheylamino) benzamidine.



[1535] Step 1: A mixture of 3-(2-amino-phenylamino)benzonitrile (196 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl] phenylcarbonylamino) phenylamino) benzonitrile (226 mg, 43%).

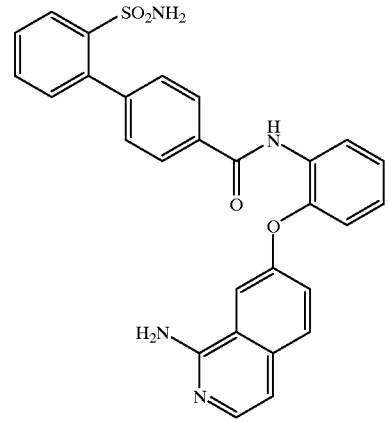
[1536] MS found for $C_{30}H_{29}N_4O_3S$ $(M+H)^+$: 525.

[1537] Step 2: A stream of HCl(g) was bubbled through a 0° C. solution of 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl] phenylcarbonylamino)pheylamino) benzonitrile (53 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (39 mg, 5 equiv) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 3-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pheylamino) benzamidine (27 mg, 55%).

[1538] MS found for $C_{26}H_{24}N_5O_3S$ $(M+H)^+$: 486.

Example 598

[1539] 7-(2-(4- [(2-aminosulfonyl)phenyl]benzoylamino)phenoxy)-1-aminoisoquinoline.



[1540] Step 1: A mixture of 7-(2-aminophenoxy)isoquinoline (237 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic acid (330 mg, 1 equiv), Bop reagent (880 mg, 2 equiv) and TEA (1.39 mL, 10 equiv) in 3 mL of DMF was stirred at rt overnight. The mixture was diluted with EtOAc, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave 7-(2-(4-[(2-t-butylaminosulfonyl)phenyl] benzoylamino)phenoxy) isoquinoline (469 mg, 85%).

[1541] MS found for $C_{32}H_{30}N_3O_4S$ $(M+H)^+$: 552.

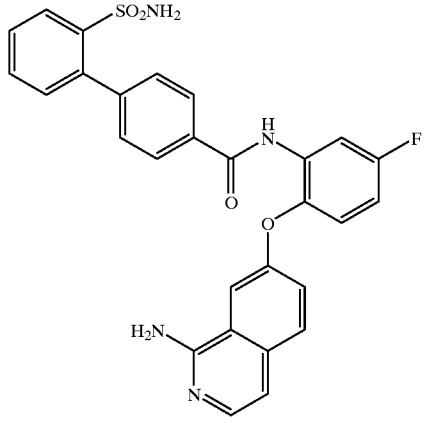
[1542] Step 2: A solution of 7-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)phenoxy) isoquinoline (110 mg, 0.2 mmol, 1 equiv) in 5 mL of acetone was treated with mCPBA (113 mg, 57%, 1.5 equiv) until HPLC showed complete reaction. Acetone was evaporated, the residue was partetioned between methylene chloride and saturated aqueous $NaHCO_3$. The organic layer was dried ove $MgSO_4$ and used in the next step directly.

[1543] Step 3: The compound obtained in step 2 in 5 mL of pyridine was treated with tosyl chloride (46 mg, 1.2 equiv) at rt overnight and pyridine was removed under reduced pressure. The residue was reacted with 5 mL of ethanolamine for 12 h. and partitioned between methylene chloride and water. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 3 mL of trifluoroacetic acid for 30 min. After removing TFA, the crude was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 7-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino)phenoxy)-1-aminoisoquinoline (43 mg, 42%).

[1544] MS found for $C_{28}H_{23}N_4O_4S$ $(M+H)^+$: 511.

Example 599

[1545] 7-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino)-4-fluorophenoxy)1-aminoisoquinoline.



[1546] Step 1: A mixture of 7-(2-amino-4-fluorophenoxy-)isoquinoline (255 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic acid (330 mg, 1 equiv), Bop reagent (880 mg, 2 equiv) and TEA (1.39 mL, 10 equiv) in 3 mL of DMF was stirred at rt overnight. The mixture was diluted with EtOAc, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave 7-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)-4-fluorophenoxy) isoquinoline (467 mg, 82%).

[1547] MS found for $C_{32}H_{29}FN_3O_4S$ $(M+H)^+$: 570.

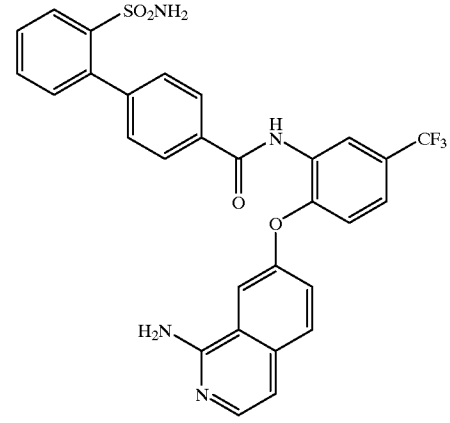
[1548] Step 2: A solution of 7-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)-4-fluorophenoxy) isoquinoline (114, 0.2 mmol, 1 equiv) in 5 mL of acetone was treated with mCPBA (113 mg, 57%, 1.5 equiv) until HPLC showed complete reaction. Acetone was evaporated, the residue was partetioned between methylene chloride and saturated aqueous $NaHCO_3$. The organic layer was dried ove $MgSO_4$ and used in the next step directly.

[1549] Step 3: The compound obtained in step 4 in 5 mL of pyridine was treated with tosyl chloride (46 mg, 1.2 equiv) at rt overnight and pyrine was removed under reduced pressure. The residue was reacted with 5 mL of ethanolamine for 12 h, and partitioned between methylene chloride and water. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 3 mL of trifluoroacetic acid for 30 min. After removing TFA, the crude was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 7-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino)-4-fluorophenoxy)1-aminoisoquinoline (77 mg, 50%).

[1550] MS found for $C_{28}H_{22}FN_4O_4S$ $(M+H)^+$: 529.

Example 600

[1551] 7-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino)-4-trifluoromethylphenoxy)1-aminoisoquinoline.



[1552] Step 1: A mixture of 7-(2-amino-4-trifluoromethylphenoxy)isoquinoline (305 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic acid (330 mg, 1 equiv), Bop reagent (880 mg, 2 equiv) and TEA (1.39 mL, 10 equiv) in 3 mL of DMF was stirred at rt overnight. The mixture was diluted with EtOAc, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave 7-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)-4-trifluoromethylphenoxy) isoquinoline (360 mg, 58%).

[1553] MS found for $C_{33}H_{29}F_3N_3O_4S$ $(M+H)^+$. 620.

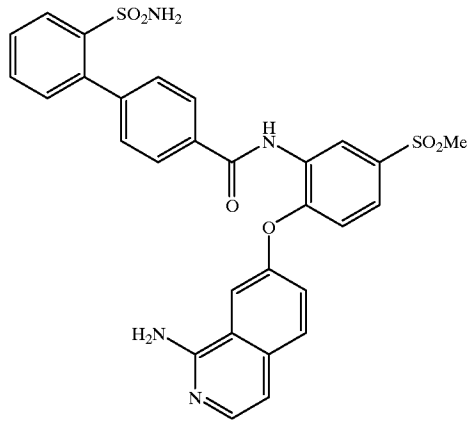
[1554] Step 2: A solution of 7-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)-4-trifluoromethylphenoxy) isoquinoline (124 mg, 0.2 mmol, 1 equiv) in 5 mL of acetone was treated with mCPBA (113 mg, 57%, 1.5 equiv) until HPLC showed complete reaction. Acetone was evaporated, the residue was partetioned between methylene chloride and saturated aqueous $NaHCO_3$. The organic layer was dried ove $MgSO_4$ and used in the next step directly.

[1555] Step 3: The compound obtained in step 4 in 5 mL of pyridine was treated with tosyl chloride (46 mg, 1.2 equiv) at rt overnight and pyrine was removed under reduced pressure. The residue was reacted with 5 mL of ethanolamine for 12 h, and partitioned between methylene chloride and water. The organic layer was dried ove $MgSO_4$, filtered, evaporated and refluxed in 3 mL of trifluoroacetic acid for 30 min. After removing TFA, the crude was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 7-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino)-4-trifluoromethylphenoxy)1-aminoisoquinoline (64 mg, 52%).

[1556] MS found for $C_{20}H_{22}F_3N_4O_4S$ $(M+H)^+$: 579.

Example 601

[1557] 7-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino)-4-methylsulfonylphenoxy)1-aminoisoquinoline.



[1558] Step 1: A mixture of 7-(2-amino-4-methylsulfonylphenoxy)isoquinoline (315 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic acid (330 mg, 1 equiv), Bop reagent (880 mg, 2 equiv) and TEA (1.39 mL, 10 equiv) in 3 mL of DMF was stirred at rt overnight. The mixture was diluted with EtOAc, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave 7-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)-4-methlsulfonylphenoxy) isoquinoline (460 mg, 73%).

[1559] MS found for $C_{33}H_{32}N_3O_6S_2$ $(M+H)^+$: 630.

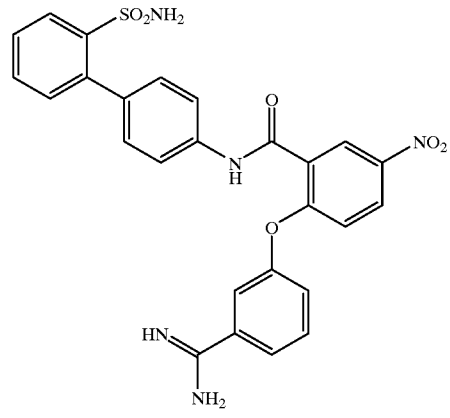
[1560] Step 2: A solution of 7-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)-4-methlsulfonylphenoxy) isoquinoline (126 mg, 0.2 mmol, 1 equiv) in 5 mL of acetone was treated with mCPBA (113 mg, 57%, 1.5 equiv) until HPLC showed complete reaction. Acetone was evaporated, the residue was partetioned between methylene chloride and saturated aqueous $NaHCO_3$. The organic layer was dried ove $MgSO_4$ and used in the next step directly.

[1561] Step 3: The compound obtained in step 4 in 5 mL of pyridine was treated with tosyl chloride (46 mg, 1.2 equiv) at rt overnight and pyrine was removed under reduced pressure. The residue was reacted with 5 mL of ethanolamine for 12 h, and partitioned between methylene chloride and water. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 3 mL of trifluoroacetic acid for 30 min. After removing TFA, the crude was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 7-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino)-4-methylsulfonylphenoxy)1-aminoisoquinoline (94 mg, 80%).

[1562] MS found for $C_{29}H_{25}N_4O_6S_2$ $(M+H)^+$: 589.

Example 602

[1563] 3-(2-(4-[(2-aminosulfonyl)phenyl]phenylaminocarbonyl-4-nitrophenoxy) benzamidine.



[1564] Step 1: A solution of 2-fluoro-5-nitrobenzoic acid (1.85 g, 10 mmol, 1.33 equiv) in thionyl chloride (5 mL) was refluxed for 2 h and evaporated. The residue was redissolved in 20 mL of methylene chloride and to the solution were added 4-[(2-t-butylaminosulfonyl)phenyl]aniline (2.0 g, 1.0 equiv) and 5 mL of pyridine. After stirring at rt overnight, the volatile was evaporated. Flash chromatography on silica gel 1-(4-[(2-t-butylaminosulfonyl)phenyl]phenylaminocarbonyl)-2-fluoro-5-nitrobenzene (2.9 g, 99%).

[1565] MS found for $C_{23}H_{23}FN_3O_5S$ $(M+H)^+$: 472.

[1566] Step 2: To a solution of 1-(4-[(2-t-butylaminosulfonyl)phenyl]phenylaminocarbonyl)-2-fluoro-5-nitrobenzene (1.18 g, 0.25 mmol, 1.0 equiv) and 3-hydroxybenzonitrile (298 mg, 1.0 equiv) in 10 mL of DMF was added K_2CO_3 (691 mg, 2 equiv). After stirring at 60° C. for 3 h, the mixture was diluted with EtOAc and washed with H_2O. The organic layer was dried over $MgSO_4$, filtered, evaporated and chromatographied to give 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylaminocarbonyl-4-nitrophenoxy) benzonitrile(950 g, 63%).

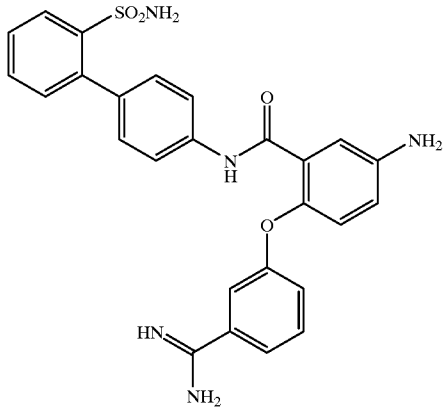
[1567] MS found for $C_{30}H_{27}N_4O_6S$ $(M+H)^+$: 571.

[1568] Step 3: A stream of HCl(g) was bubbled through a 0° C. solution of 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl] phenylaminocarbonyl-4-nitrophenoxy) benzonitrile (57 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (39 mg, 5 equiv) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to 3-(2-(4-[(2-aminosulfonyl)phenyl]phenylaminocarbonyl-4-nitrophenoxy) benzamidine (24 mg, 45%).

[1569] MS found for $C_{26}H_{22}N_5O_6S$ $(M+H)^+$: 532.

Example 603

[1570] 3-(2-(4-[(2-aminosulfonyl)phenyl]phenylaminocarbonyl-4-aminophenoxy) benzamidine.

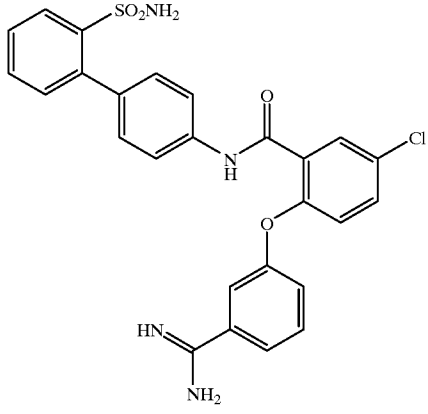


[1571] A mixure of 3-(2-(4-[(2-aminosulfonyl)phenyl] phenylaminocarbonyl-4-nitrophenoxy) benzamidine (53 mg, 0.1 mmol, 1 equiv), 5 mL of 1N HCl, 5 mg of Pd/C (10%) in 10 mL of methanol was stirred at rt under 1 atm H_2 atomosphere overnight. After filtration through a thin layer of Celite and removal of the volatile, the aqueous residue was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to 3-(2-(4-[(2-aminosulfonyl)phenyl]phenylaminocarbonyl-4-aminophenoxy) benzamidine (31 mg, 66%).

[1572] MS found for $C_{26}H_{24}N_5O_4S$ $(M+H)^+$: 502.

Example 604

[1573] 3-(2-(4-[(2-aminosulfonyl)phenyl]phenylaminocarbonyl-4-chlorophenoxy) benzamidine.



[1574] Step 1: A mixure of 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylaminocarbonyl-4-nitrophenoxy) benzonitrile (570 mg, 1 mmol, 1 equiv) and $SnCl_2.2H_2O$ (677 mg, 3 equiv) in 25 mL of EtOAc was refluxed for 2 h. The reaction was quenched with sat. $NaHCO_3$. The organic layer was separated and dried over $MgSO_4$, filtered and evaporated to give 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylaminocarbonyl-4-aminophenoxy) benzonitrile (45 mg, 83%).

[1575] MS found for $C_{30}H_{29}N_4O_4S$ $(M+H)^+$: 541.

[1576] Step 2: A mixure of t-$BuNO_2$ (21 mg, 0.1 mmol, 2 equiv), CuCl (20 mg, 2 equiv) in 5 mL of acetonitrile was refluxed for 10 min. To the solution was added 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylaminocarbonyl-4-aminophenoxy) benzonitrile (54 mg, 0.1 mmol, 1 equiv). The mixture was refluxed for 1 h and evaporated. Flash chromatography with 1:2 EtOAc/hexane to give [(2-t-butylaminosulfonyl)phenyl]phenylaminocarbonyl-4-chlorophenoxy) benzonitrile (43 mg, 77%)

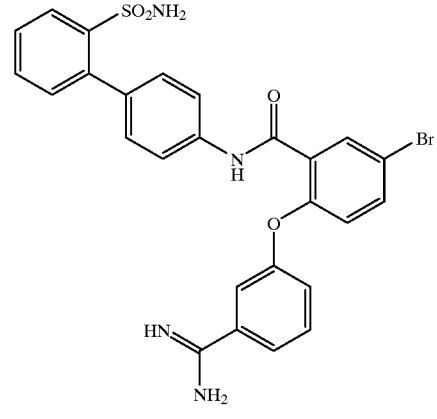
[1577] MS found for $C_{30}H_{27}ClN_3O_4S$ $(M+H)^+$: 561.

[1578] Step 3: A stream of HCl(g) was bubbled through a 0° C. solution of 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl] phenylaminocarbonyl-4-chlorophenoxy) benzonitrile (56 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (40 mg, 5 equiv) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to 3-(2-(4-[(2-aminosulfonyl)phenyl]phenylaminocarbonyl-4-chlorophenoxy) benzamidine (47 mg, 84%).

[1579] MS found for $C_{26}H_{22}ClN_4O_4S$ $(M+H)^+$: 521.

Example 605

[1580] 3-(2-(4-[(2-aminosulfonyl)phenyl]phenylaminocarbonyl-4-bromophenoxy) benzamidine.

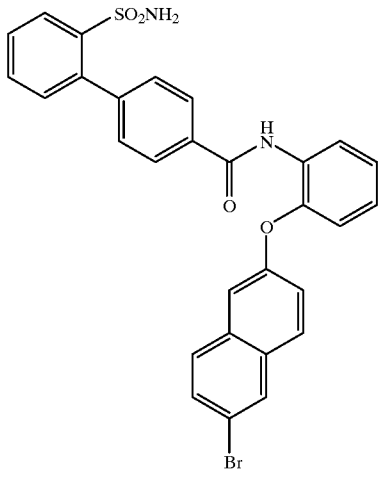


[1581] This compound was prepared according to the procedure described in example 19.

[1582] MS found for $C_{26}H_{22}BrN_4O_4S$ $(M+H)^{+}$: 565.

Example 606

[1583] 2-bromo-6-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy naphthalene.

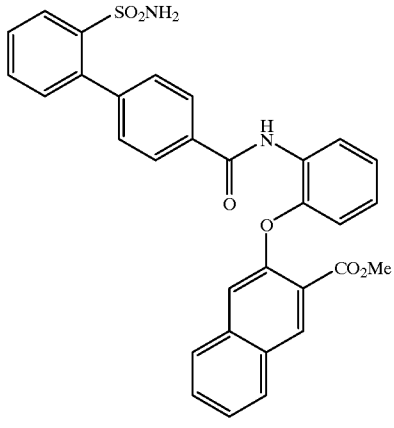


[1584] A mixture of 2-bromo-6-(2-aminophenoxy) naphthalene (314 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoyl chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN gave 2-bromo-6-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy naphthalene (378 mg, 66%).

[1585] MS found for $C_{29}H_{22}BrN_2O_4S$ $(M+H)^+$: 573.

Example 607

[1586] 3-methoxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy naphthalene.

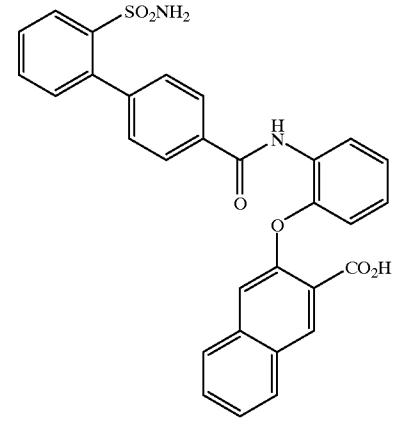


[1587] A mixture of 3-methoxycarbonyl-2-(2-aminophenoxy) (294 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoyl chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN gave 3-methoxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy naphthalene (420 mg, 76%).

[1588] MS found for $C_{31}H_{25}N_2O_6S$ $(M+H)^+$: 553.

Example 608

[1589] 3-hydroxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy naphthalene.

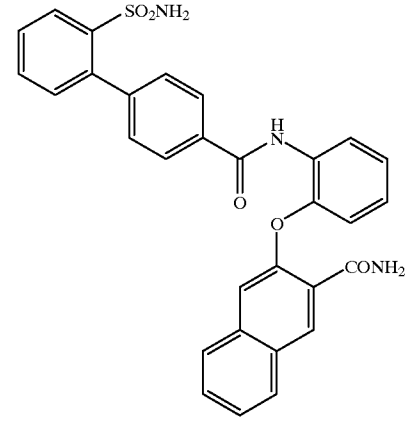


[1590] A solution of 3-methoxycarbonyl-2-(4-methylsulfonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) naphthalene (55 mg, 0.1 mmol, 1.0 equiv) in 5 mL of methanol was treated with 1N LiOH (2 mL) at rt for 2 h. Methanol was evaporated, the aqueous residue was subjected to HPLC with 0.5% TFA in H_2O/CH_3CN to give 3-hydroxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy naphthalene (47 mg, 88%).

[1591] MS found for $C_{30}H_{23}N_2O_6S$ $(M+H)^+$: 539.

Example 609

[1592] 3-aminocarbonyl-2-(4-[(2-aminosulfonyl)phenyl] phenylcarbonylamino)phenoxy naphthalene.



[1593] Step 1: A solution of 3-methoxycarbonyl-2-(4-methylsulfonyl-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) naphthalene (40 mg, 0.066 mmol) in 5 mL of methanol was treated with 1N LiOH (2 mL) at rt for 2 h. Methanol was evaporated, and acidified with 1N HCl until PH~1-2. The product (39 mg, 100%), 3-hydroxycarbonyl-2-(4-methylsulfonyl-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) naphthalene, was extracted with EtOAc, dried over $MgSO_4$, filtered and evaporated.

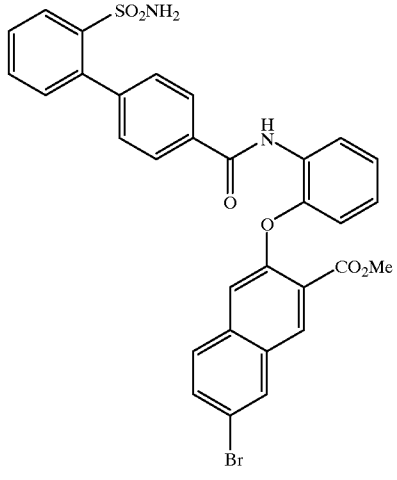
[1594] MS found for $C_{34}H_{31}N_2O_6S$ $(M+H)^+$: 595.

[1595] Step 2: A solution of 3-hydroxycarbonyl-2-(4-methylsulfonyl-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) naphthalene (39 mg, 0.066 mmol) was refluxed in 3 mL of thionyl chloride for 2 h and evaporated. The residue was then stirred in 5 mL of 2M ammonia in methanol overnight. The volatile was evaporated and the residue was refluxed in 2 mL of trifluoroacetic acid overnight to give the product 3-aminocarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy naphthalene (14 mg, 39%) after HPLC (C18 reversed phase, eluting with 0.5% TFA in H_2O/CH_3CN).

[1596] MS found for $C_{30}H_{24}N_3O_5S$ $(M+H)^+$: 538.

Example 610

[1597] 3-methoxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy-6-bromo naphthalene.

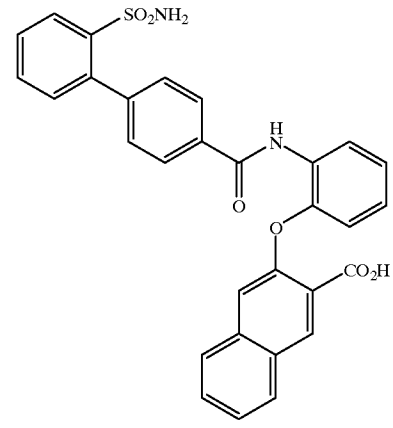


[1598] A mixture of 2-(2-aminophenoxy)-3-methoxycarbonyl-6-bromo naphthalene (372 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoyl chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN gave 3-methoxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy-6-bromo naphthalene (423 mg, 67%).

[1599] MS found for $C_{31}H_{24}BrN_2O_6S$ $(M+H)^+$: 631.

Example 611

[1600] 3-hydroxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy-6-bromo naphthalene.

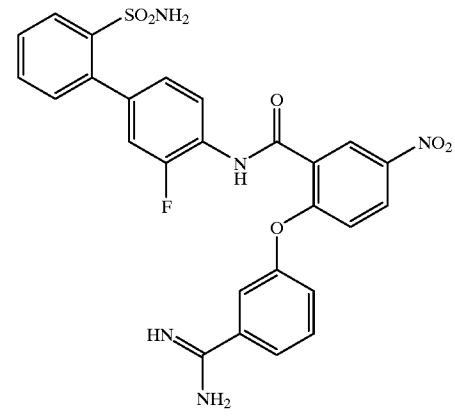


[1601] A solution of 3-methoxycarbonyl-2-(4-methylsulfonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy)-6-bromo naphthalene (63 mg, 0.1 mmol, 1.0 equiv) in 5 mL of methanol was treated with 1N LiOH (2 mL) at rt for 2 h. Methanol was evaporated, the aqueous residue was subjected to HPLC with 0.5% TFA in H_2O/CH_3CN to give 3-hydroxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy-6-bromo naphthalene (47 mg, 78%).

[1602] MS found for $C_{30}H_{22}BrN_2O6S$ $(M+H)^+$: 617.

Example 612

[1603] 3-(2-(4-[(2-aminosulfonyl)phenyl]-2-fluorophenylaminocarbonyl-4-aminophenoxy) benzamidine.

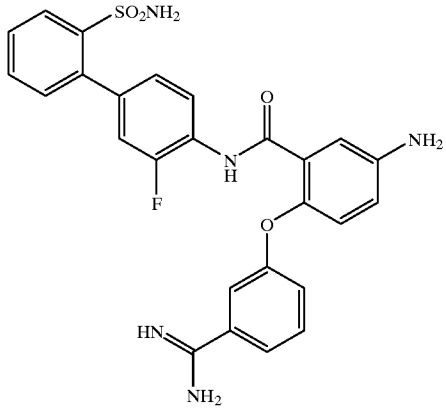


[1604] This compound was prepared according to the procedure described in example 17.

[1605] MS found for MS found for $C_{26}H_{21}FN_5O_6S$ $(M+H)^+$: 550.

Example 613

[1606] 3(2-(4-[(2-aminosulfonyl)phenyl]-2-fluorophenylaminocarbonyl-4-aminophenoxy) benzamidine.



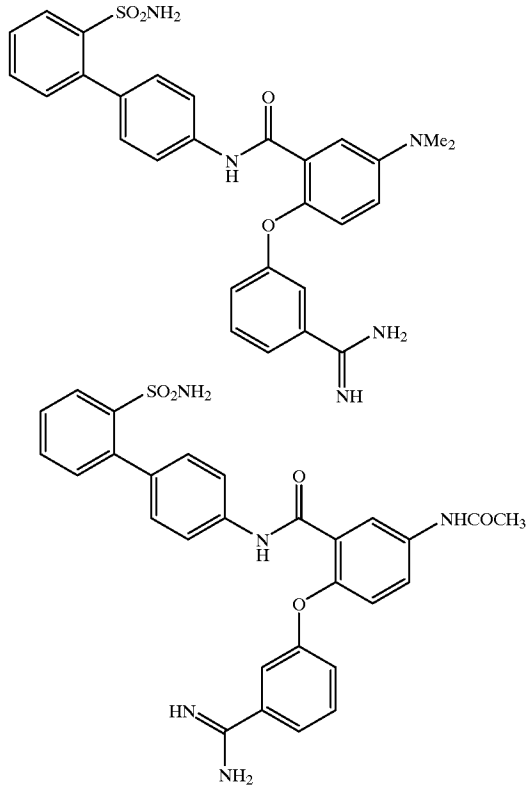
[1607] This compound was prepared according to the procedure described in example 18.

[1608] MS found for $C_{26}H_{23}FN_5O_4S$ $(M+H)^+$: 520.

Example 614

[1609] This compound was obtained as a side product in the preparation of example 18. MS $(M+H)^{30}$: 530.

Example 615



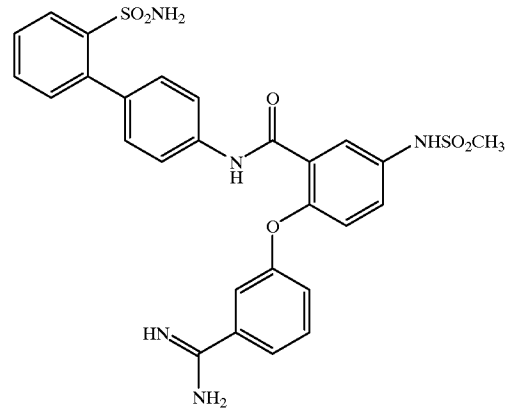
[1610] Step 1: A mixure of 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylaminocarbonyl-4-nitrophenoxy) benzonitrile (1 equiv) and $SnCl_2$ $2H_2O$ (3 equiv) in 15 mL of EtOAc was refluxed for 2 h. The mixture was diluted with EtOAc and washed with saturated aqueous NaHCO3. The organic layer was dried over Na2SO4, filtered and evaporated.

[1611] Step 2: The product obtained in step 1 (1 equiv) in 2 mL of pyridine was treated with AcCl (1 equiv) over night. The mixture was diluted with methylene chloride and washed with water. The organic layer was dried over Na_2SO_4, filtered and evaporated.

[1612] Step 3: A stream of HCl(g) was bubbled through a 0° C. solution of the product obtained in step 2 (1 equiv) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium (5 equiv) in 10 mL of methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to the title product. MS $(M+H)^+$: 544.

Example 616

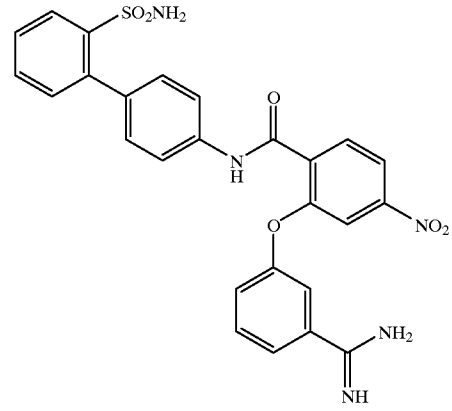
[1613]



[1614] This compound was similarly made as example 30. MS $(M+H)^+$: 580.

Examples 617-624

[1615] The following compounds were made according to the methods previously described.



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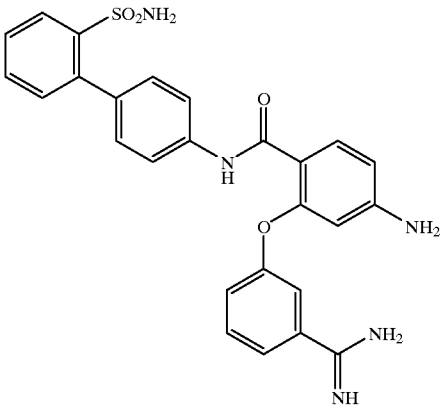

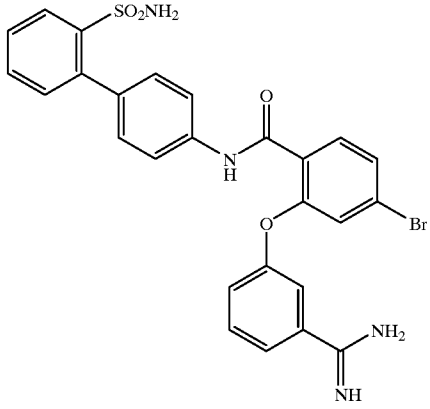

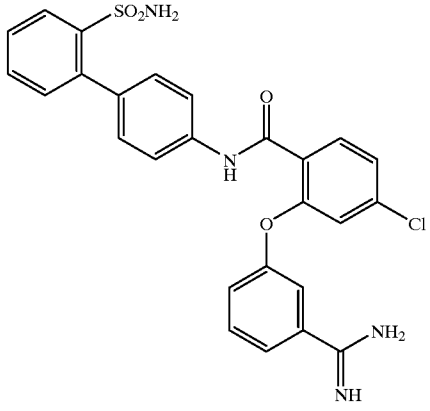

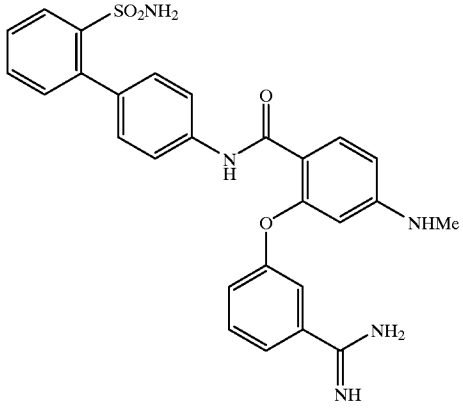

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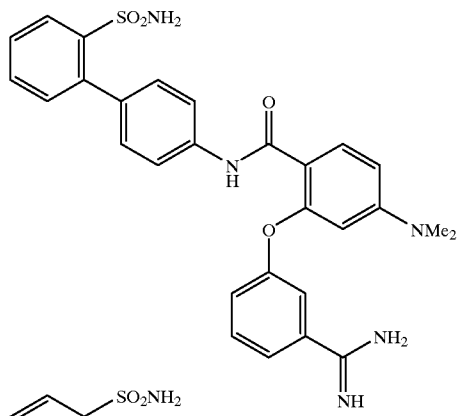
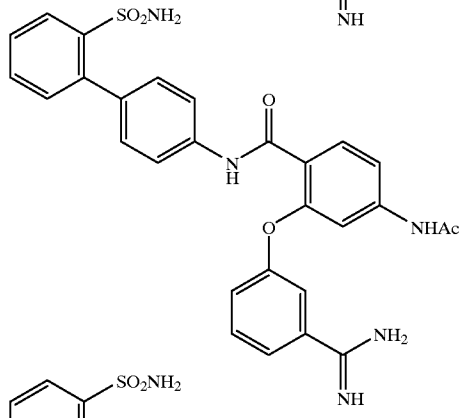
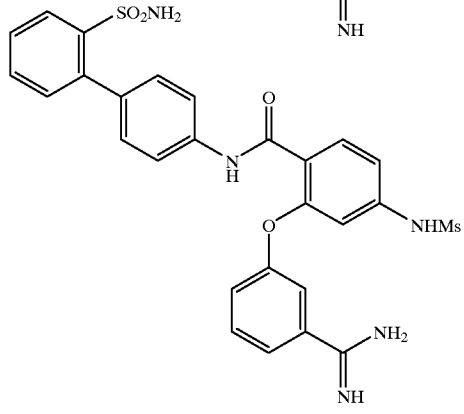
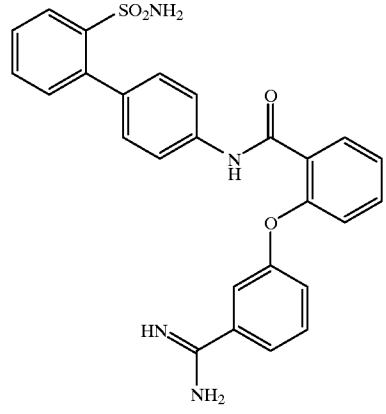






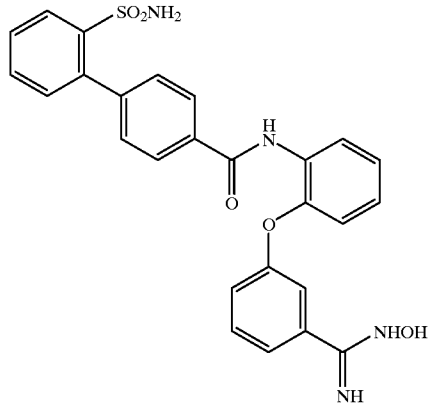
Example 625



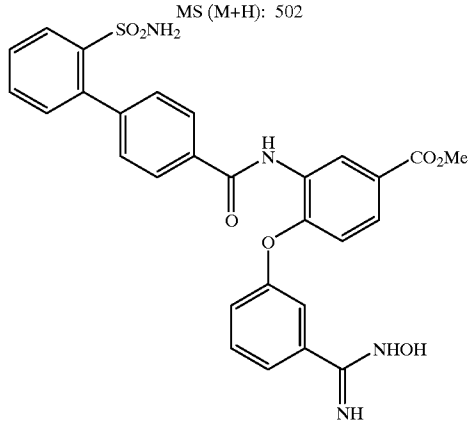
[1616] A mixure of compound 20 (1 equiv), 5 mL of 1N HCl, 5 mg of Pd/C (10%) in 10 mL of methanol was stirred at rt under 1 atm H_2 atomosphere overnight. After filtration through a thin layer of Celite and removal of the volatile, the aqueous residue was purified by HPLC (C18 reversed phase) eluting with 0.5°% TFA in H_2O/CH_3CN to give the title compound. MS $(M+H)^-$: 487.

Examples 626-631

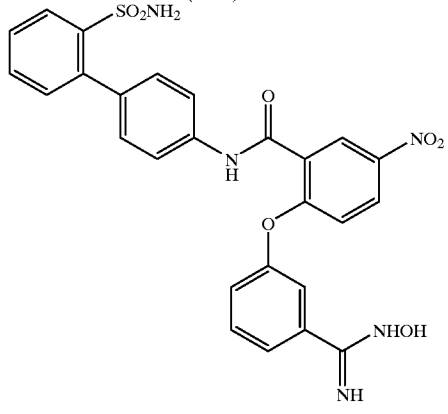
[1617] The following compounds were prepared according to the procedure described in the formation of amidines except that NH_2OH was used instead of NH_4OAc.



MS (M+H): 502

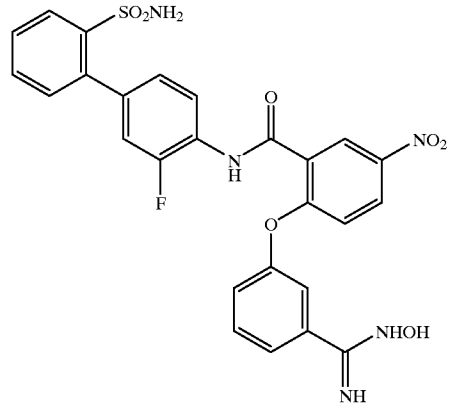


MS (M+H): 560

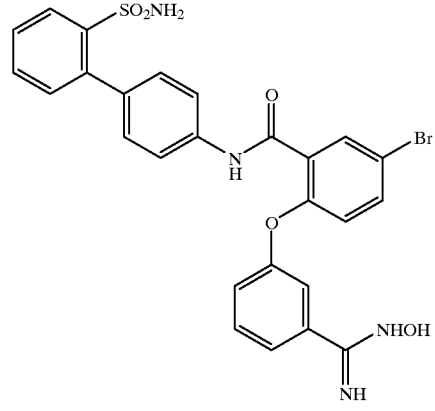


MS (M+H): 547

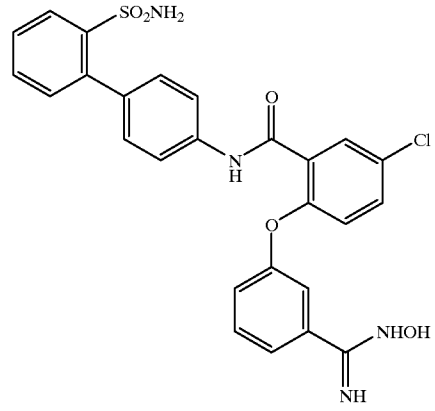
-continued



MS (M+H): 547



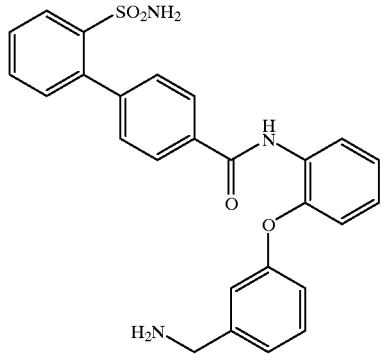
MS (M+H): 581



MS (M+H): 537

Example 632

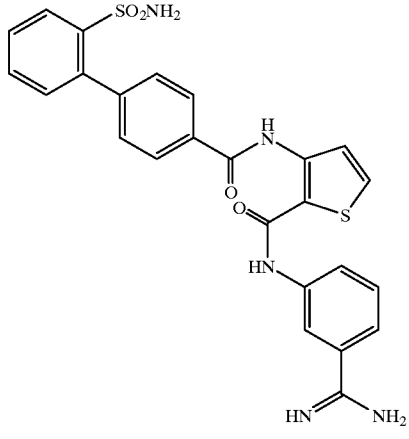
[1618] 3-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino) phenoxy)benzylamine.



[1619] A mixure of 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)phenoxy) benzonitrile (25 mg), 5 mL of 1N HCl, 5 mg of Pd/C (10%) in 10 mL of methanol was stirred at rt under 1 atm H_2 atomosphere overnight. After filtration through a thin layer of Celite and removal of the volatile, the aqueous residue was dried on vacuum pump and then refluxed with 1 mL of TFA for 2 h, evaporated and purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give the title compound. MS $(M+H)^+$: 500.

Example 633

[1620] 3-[(3-{[4-(2-sulfamoylphenyl)phenyl]carbonylamino}-2-thienyl)carbonylamino]benzenecarboxamidine

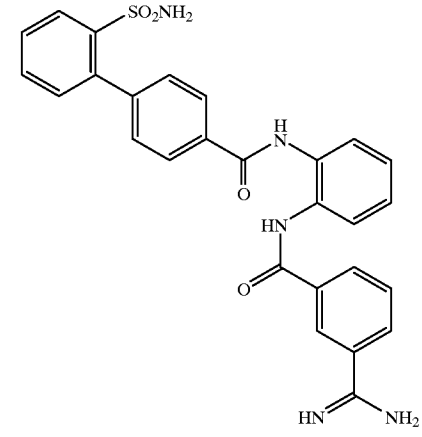


[1621] Step 1: A mixture of 3-amino-2-((3-cyanophenyl)aminocarbonyl)thiophene (1 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoyl chloride (1 equiv), pyridine (5 equiv) in 15 mL of dichloromethane was stirred at rt overnight. The mixture was diluted with methylene chloride, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated.

[1622] Step 2: A stream of HCl(g) was bubbled through a 0° C. solution of the compound obtained in step I in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (5 equiv) in 10 mL of methanol at reflux temperature for 2 h. The solvent was evaporated and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give the title compound. ES-MS 520 (M+1).

Example 634

[1623] 3-[(3-{[4-(2-sulfamoylphenyl)phenyl]carbonylamino}-2-thienyl)carbonylamino]benzenecarboxamidine



[1624] Step 1: A mixture of 2-nitroaniline, 3-cyanobenzoyl chloride (1 equiv), pyridine (5 equiv) in 15 mL of dichloromethane was stirred at rt overnight. The mixture was diluted with methylene chloride, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated.

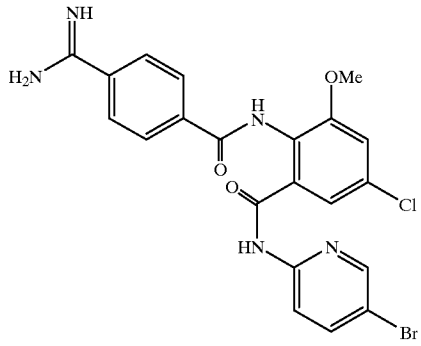
[1625] Step 2: A mixture of the compound obtained in step 1 (1 equiv) and $SnCl_2$ $2H_2O$ (3 equiv) in 15 mL of EtOAc was refluxed for 2 h. The mixture was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered and evaporated.

[1626] Step 3: A mixture of the compound obtained in step 2 (1 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoyl chloride (1 equiv), pyridine (5 equiv) in 15 mL of dichloromethane was stirred at rt overnight. The mixture was diluted with methylene chloride, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated.

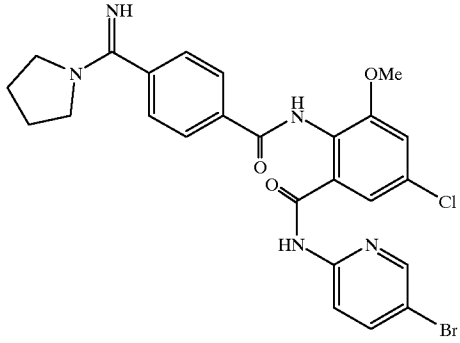
[1627] Step 4: A stream of HCl(g) was bubbled through a 0° C. solution of the compound obtained in step 1 in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (5 equiv) in 10 mL of methanol at reflux temperature for 2 h. The solvent was evaporated and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give the title compound. ES-MS 494 (M+1).

Example 635-640

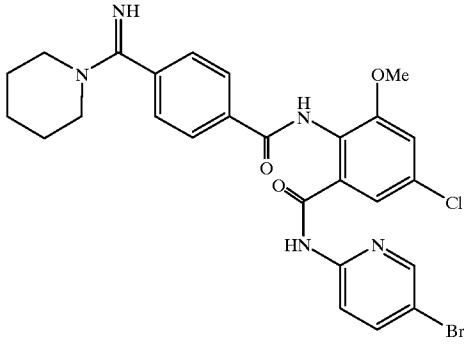
[1628] The following compounds were prepared according to the procedure previously described.



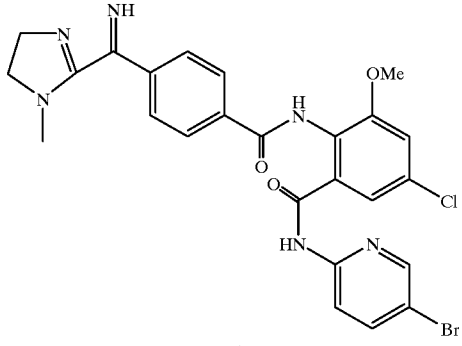
Example 635
MS (M+H) 502



Example 636
MS (M+H) 556

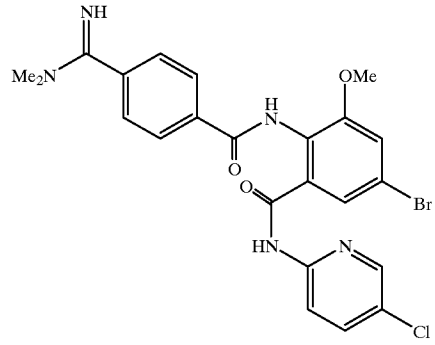


Example 637
MS (M+H) 570

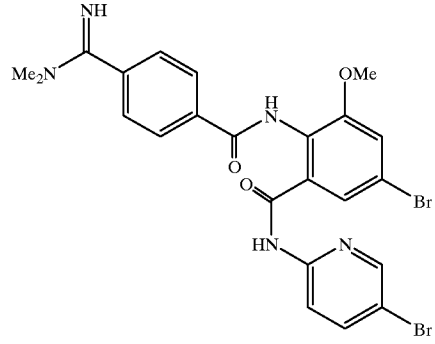


Example 638
MS (M+H) 542

-continued

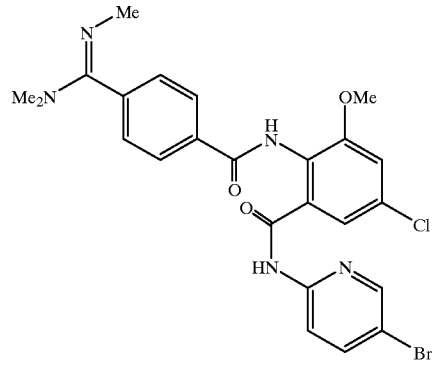


Example 639
MS (M+H) 530



Example 640
MS (M+H) 574

Example 641



[1629] This compound was obtained as a side product in the preparation of Example 322, described earlier, above. ES-MS 530 (M+H).

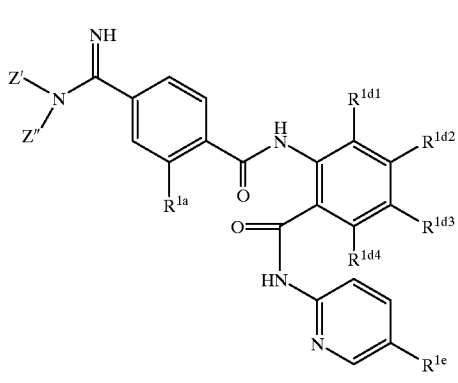
[1630] The above description and illustrative examples show numerous compounds within the formula A-Q-D-E-G-J-X which are potent factor Xa inhibitors. The description and illustrative examples also show the variety of combinations and substituents for each group A, Q, D, E, G, J and X which may be prepared according to the invention and be useful as factor Xa inhibitors. While, for example, compounds having the same A-Q structure but a variety of substituents or D-E-G and/or J-X structures and their substituents are described and shown, the description and illustrative examples are intended to show that compounds of the invention having a different A-Q structure can also have

various combinations of D-E-G- and/or J-X structures, even though such compounds may not be illustrated in the examples. In other words, each group within the A-Q-D-E-G-J-X, as each is defined above with their substituents, may be varied and combined to form sub-genuses and compounds of the invention. The description and illustrative examples show such combinations and are not intended to limit the sub-genuses or compounds within the A-Q-D-E-G-J-X genus of the invention.

[1631] Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the illustrative examples, make and utilize the compounds of the present invention and practice the claimed methods. It should be understood that the foregoing discussion and examples merely present a detailed description of certain preferred embodiments. It will be apparent to those of ordinary skill in the art that various modifications and equivalents can be made without departing from the spirit and scope of the invention. All the patents, journal articles and other documents discussed or cited above are herein incorporated by reference.

What is claimed:

1. A compound of formula VI:



(VI)

wherein:

Z' and Z" are each independently a C_1-C_6 alkyl which is optionally substituted with a hydroxyl, carboxylic acid or carboxylic acid ester group;

R^{1a} is a member selected from the group of H, —F, —Cl and Br;

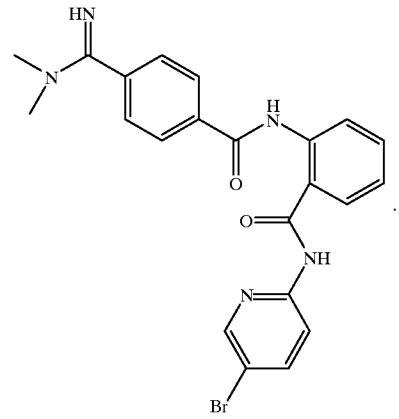
R^{1d2} and R^{1d4} are each H;

R^{1d1} and R^{1d3} are each independently a member selected from the group of H, —Cl, —F, —Br, —OH and —OMe;

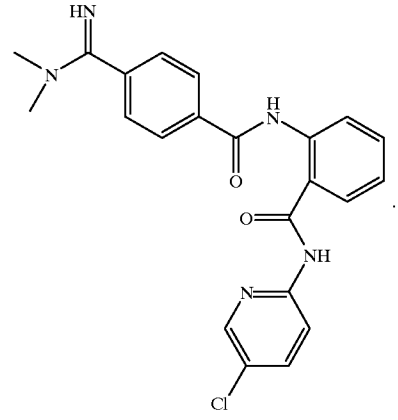
R^{1e} is a member selected from the group of —F, —Cl, —Br, —OH, —Me and —OMe, and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

2. A compound of claim 1 wherein Z' is —Me and Z" is —CH_2OH, —CH_2CO_2H, or -$CH_2CO_2CH_3$.

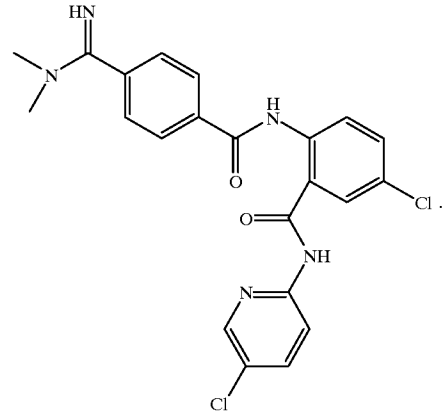
3. A compound of claim 1 having the following structure:



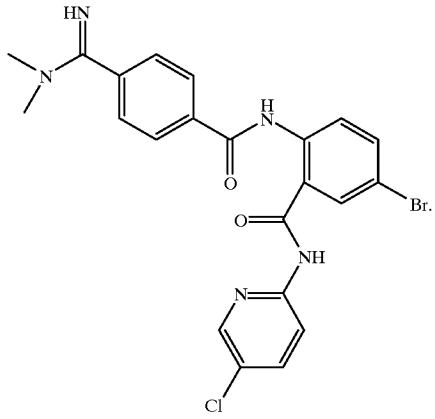
4. A compound of claim 1 having the following structure:



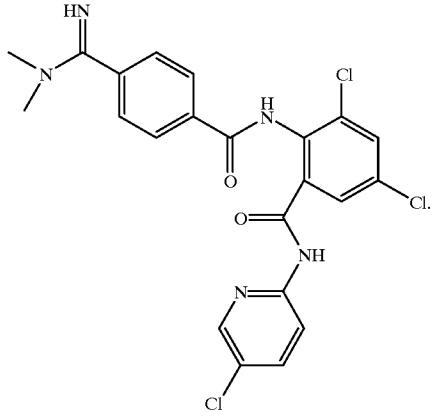
5. A compound of claim 1 having the folloiwng structure:



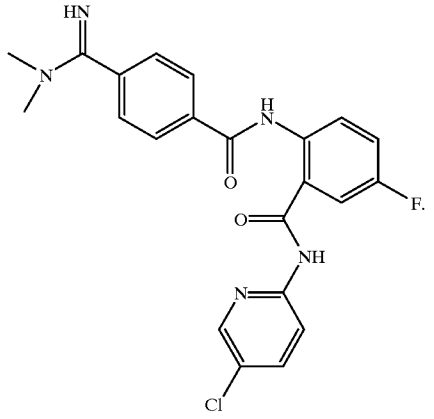
6. A compound of claim 1 having the following structure:



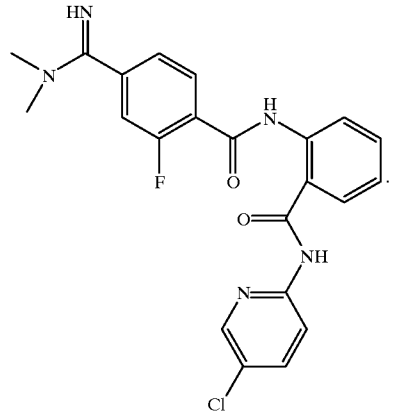
7. A compound of claim 1 having the following structure:



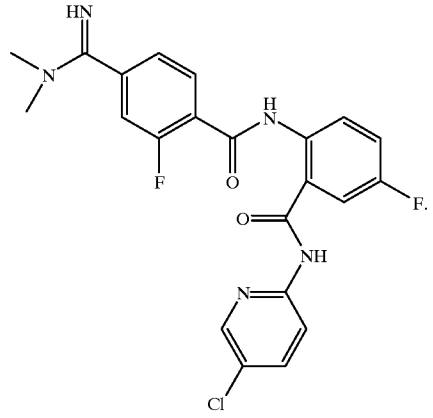
8. A compound of claim 1 having the following structure:



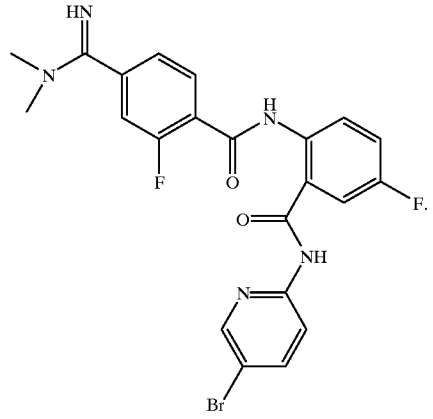
9. A compound of claim 1 having the following structure:



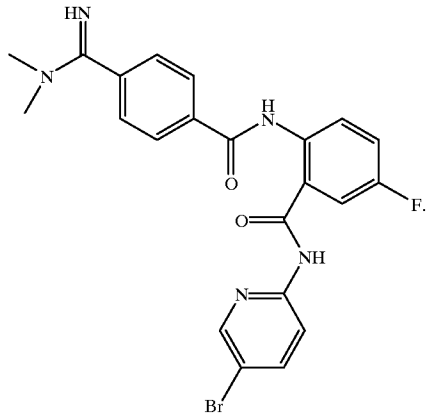
10. A compound of claim 1 having the following structure:



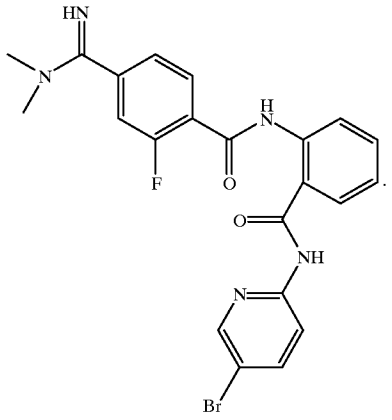
11. A compound of claim 1 having the following structure:



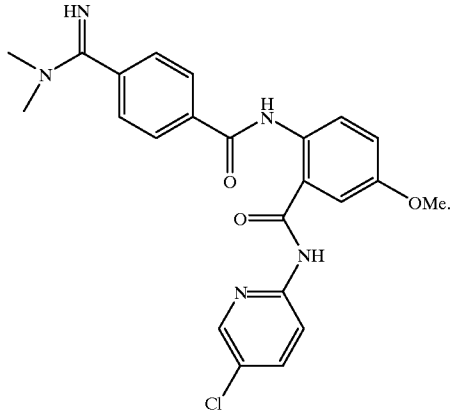
12. A compound of claim 1 having the following structure:



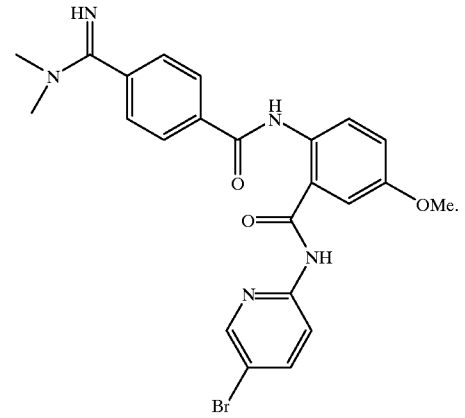
13. A compound of claim 1 having the following structure:



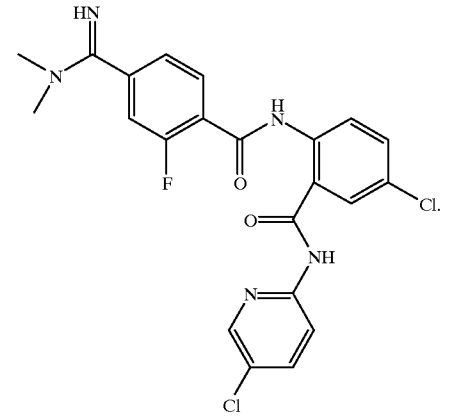
14. A compound of claim 1 having the following structure:



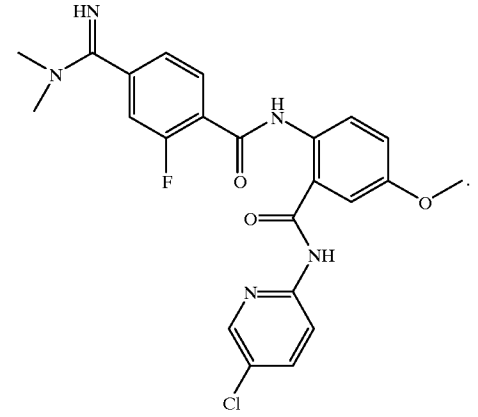
15. A compound of claim 1 having the following structure:



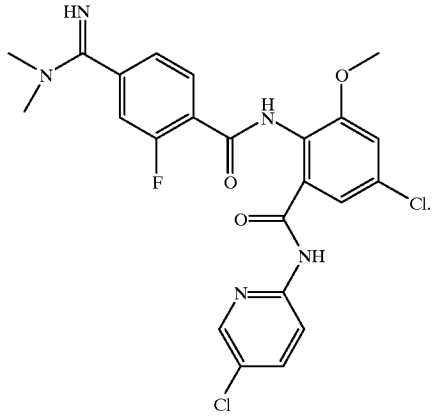
16. A compound of claim 1 having the following structure:



17. A compound of claim 1 having the following structure:



18. A compound of claim 1 having the following structure:



19. A pharmaceutical composition for preventing or treating a condition in a mammal characterized by undesired thrombosis comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of one of claims **1-18**.

20. A method for preventing or treating a condition in a mammal characterized by undesired thrombosis comprising administering to said mammal a therapeutically effective amount of a compound of one of claims **1-18**.

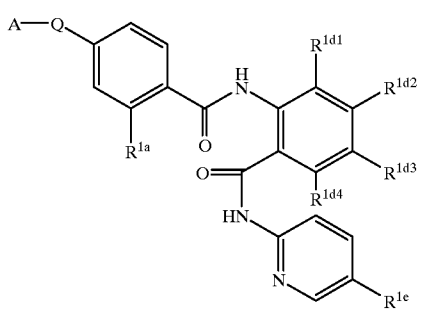
21. The method of claim 20, wherein the condition is selected from the group consisting of:

acute coronary syndrome, myocardial infarction, unstable angina, refractory angina, occlusive coronary thrombus occurring post-thrombolytic therapy or post-coronary angioplasty, a thrombotically mediated cerebrovascular syndrome, embolic stroke, thrombotic stroke, transient ischemic attacks, venous thrombosis, deep venous thrombosis, pulmonary embolus, coagulopathy, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, thromboangiitis obliterans, thrombotic disease associated with heparin-induced thrombocytopenia, thrombotic complications associated with extracorporeal circulation, thrombotic complications associated with instrumentation, and thrombotic complications associated with the fitting of prosthetic devices.

22. A method for inhibiting the coagulation of a biological sample comprising the step of administering a compound of one of claims **1-18**.

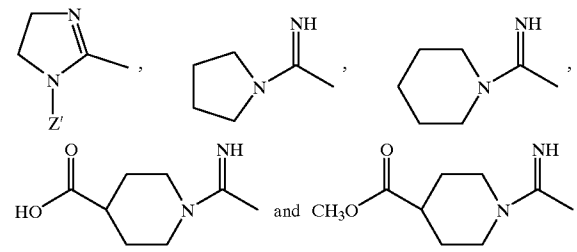
23. A compound formula VII:

(VII)



wherein:

A-Q is a member selected from the group of:



where Z' is a C_1-C_6 alkyl which is optionally substituted with a hydroxyl, carboxylic acid or carboxylic acid ester group;

R^{1a} is a member selected from the group of H, —F, —Cl and Br;

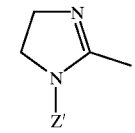
R^{1d2} and R^{1d4} are each H;

R^{1d1} and R^{1d3} are each independently a member selected from the group of H, —Cl, —F, —Br, —OH and —OMe;

R^{1e} is a member selected from the group of —F, —Cl, —Br, —OH, —Me and —OMe;

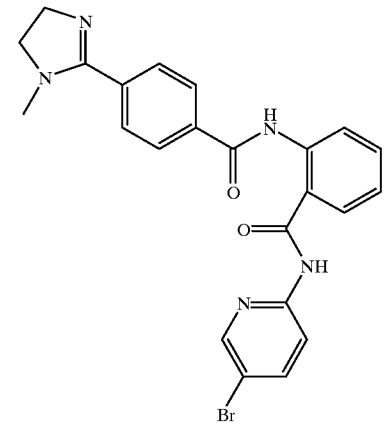
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

24. A compound of claim , wherein A-Q is:

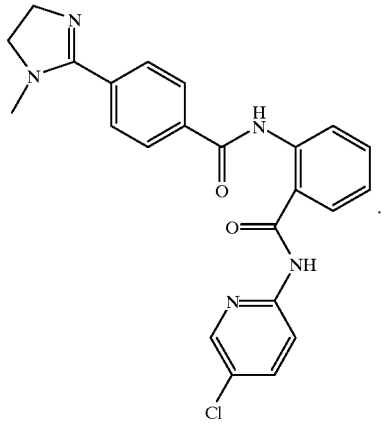


and Z' is —Me, —CH_2OH, —CH_2CO_2H, or —$CH_2CO_2CH_3$.

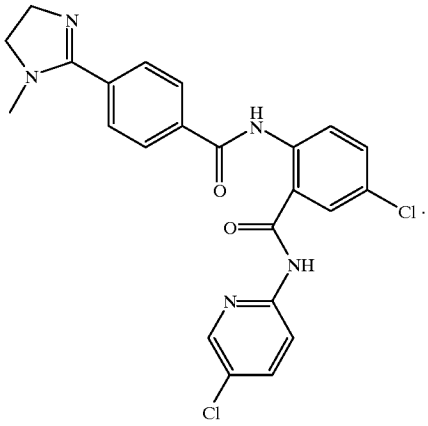
25. A compound of claim 24 having the following, structure:



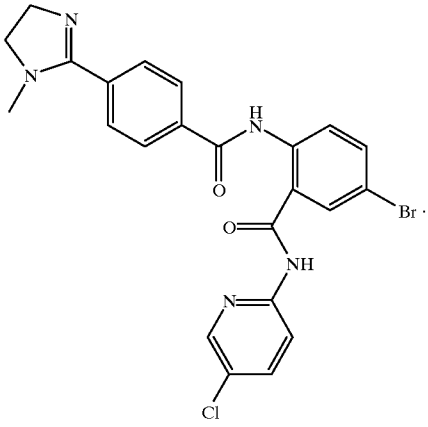
26. A compound of claim 24 having the following structure:



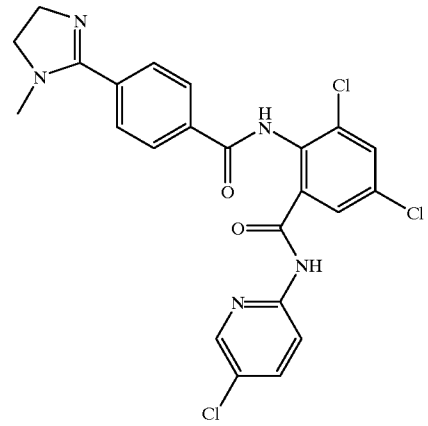
27. A compound of claim 24 having the following structure:



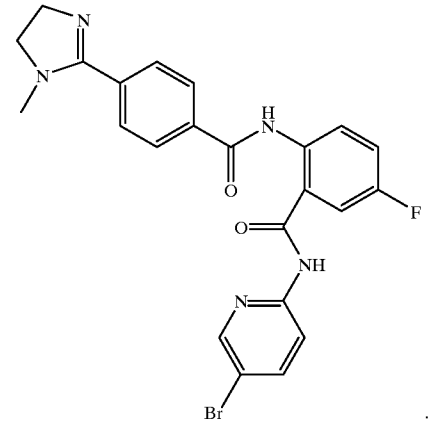
28. A compound of claim 24 having the following structure:



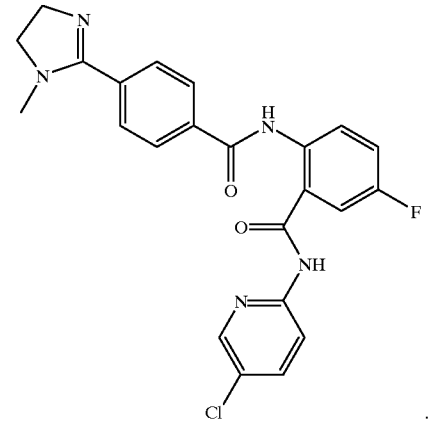
29. A compound of claim 24 having the following structure:



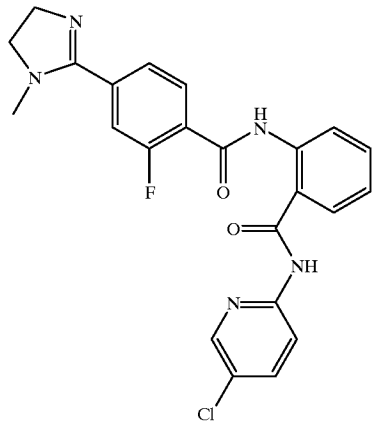
30. A compound of claim 24 having the following structure:



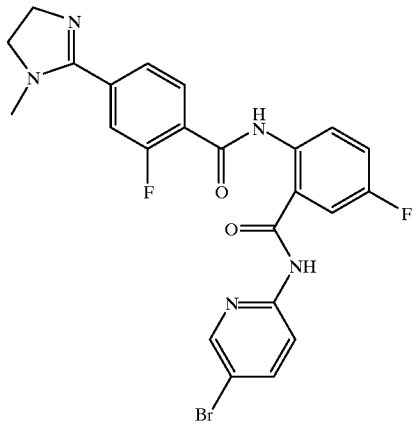
31. A compound of claim 24 having the following structure:



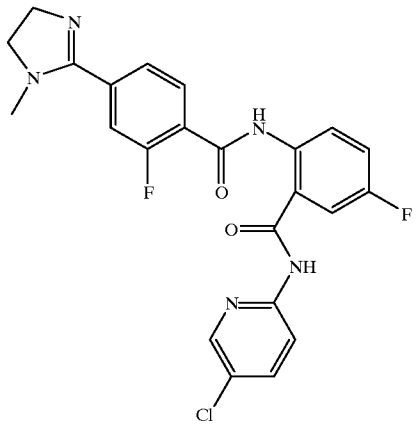
32. A compound of claim 24 having the following structure:



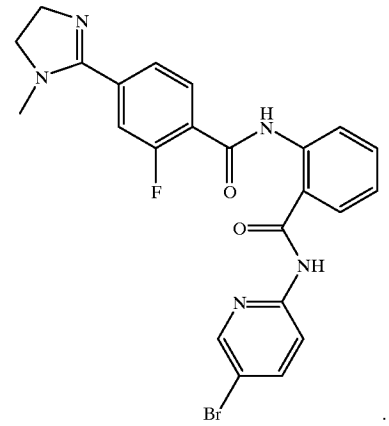
33. A compound of claim 24 having the following structure:



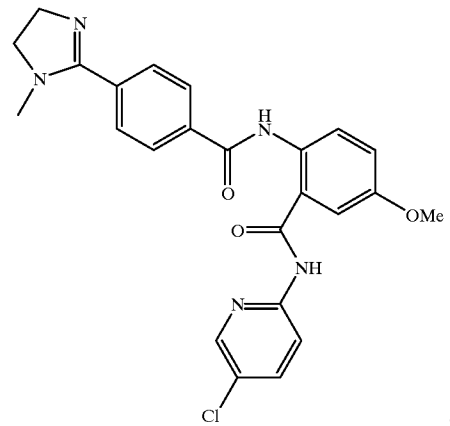
34. A compound of claim 24 having the following structure:



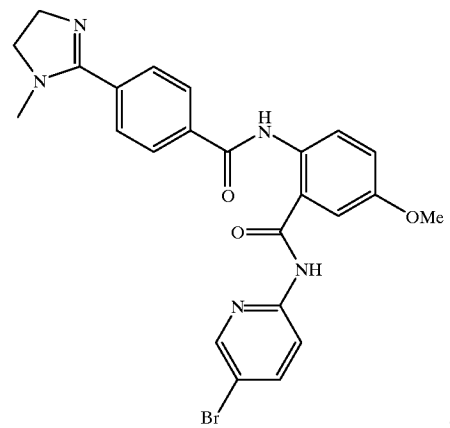
35. A compound of claim 24 having the following structure:



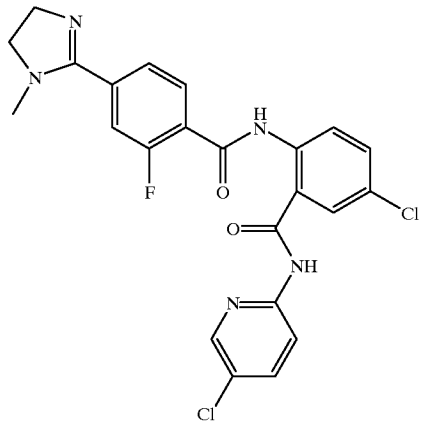
36. A compound of claim 24 having the following structure:



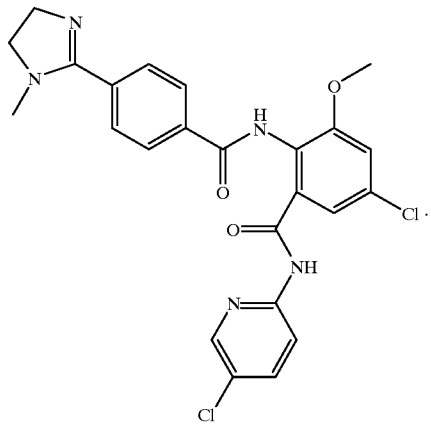
37. A compound of claim 24 having the following structure:



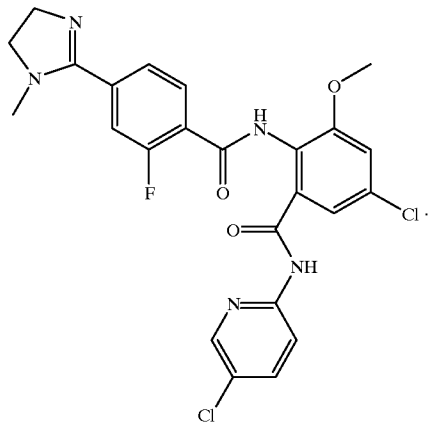
38. A compound of claim 24 having the following structure:



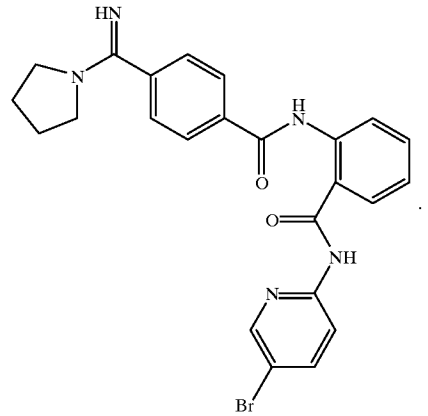
39. A compound of claim 24 having the following structure:



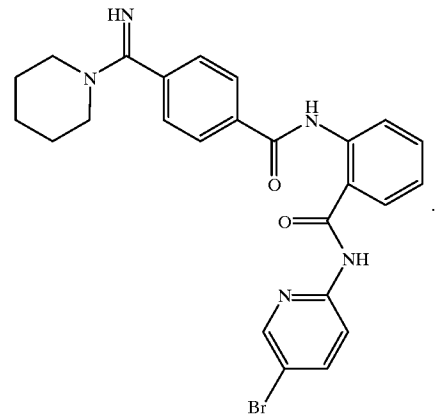
40. A compound of claim 24 having the following formula:



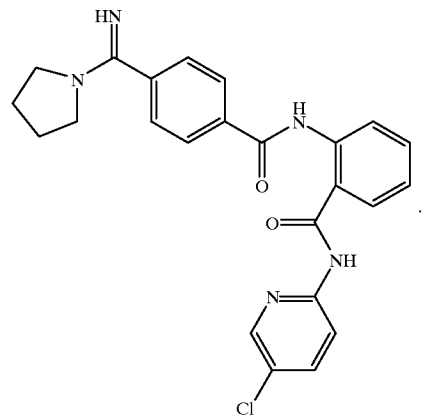
41. A compound of claim 23 having the following formula:



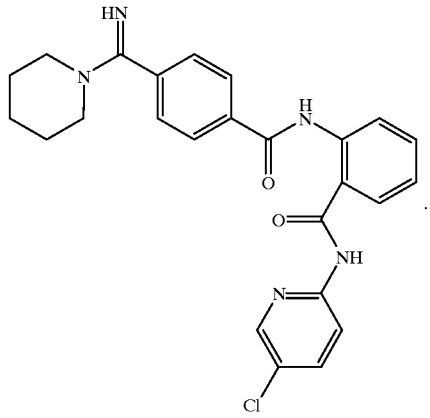
42. A compound of claim 23 having the following formula:



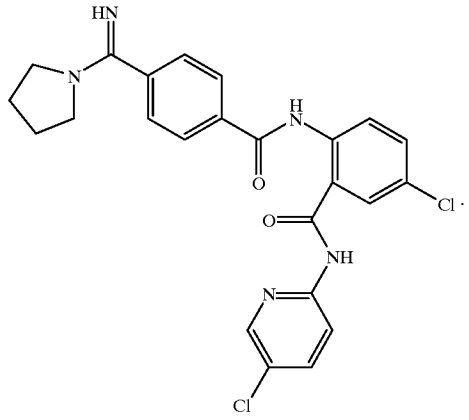
43. A compound of claim 23 having the following structure:



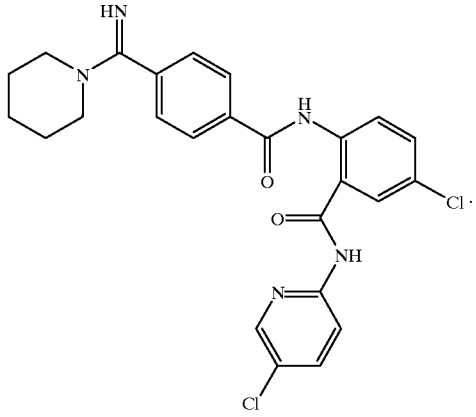
44. A compound of claim 23 having the following structure:



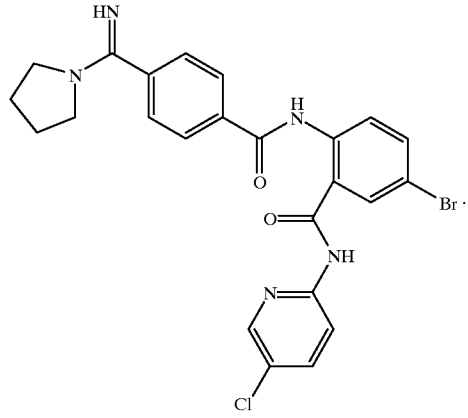
45. A compound of claim 23 having the following structure:



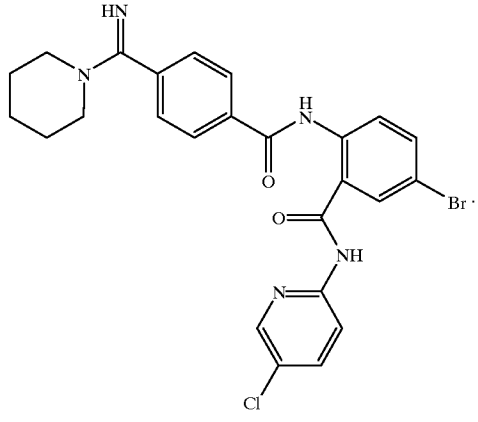
46. A compound of claim 23 having the following structure:



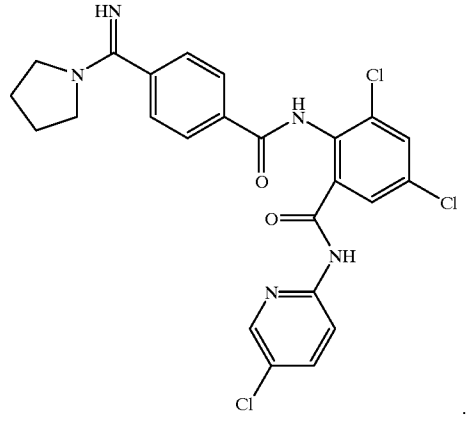
47. A compound of claim 23 having the following structure:



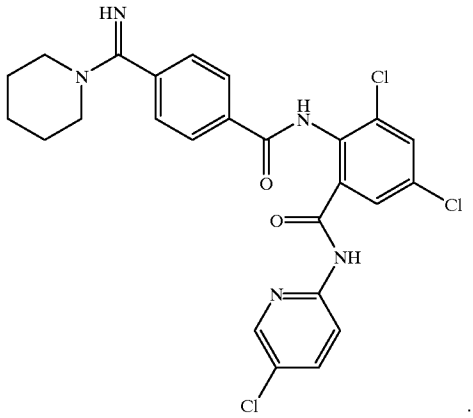
48. A compound of claim 23 having the following structure:



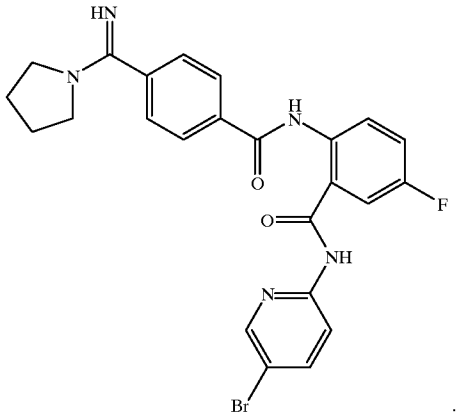
49. A compound of claim 23 having the following structure:



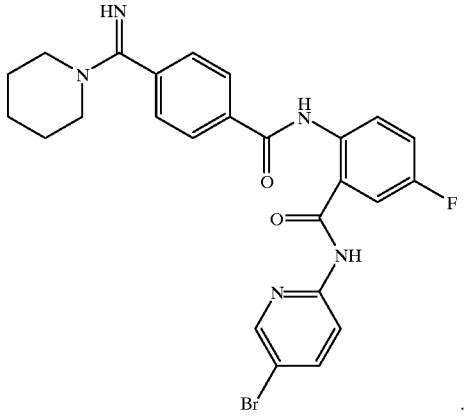
50. A compound of claim 23 having the following structure:



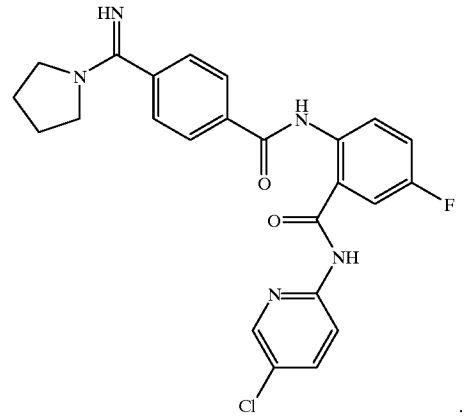
51. A compound of claim 23 having the following structure:



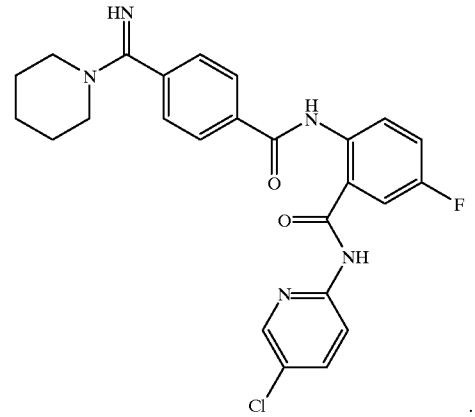
52. A compound of claim 23 having the following structure:



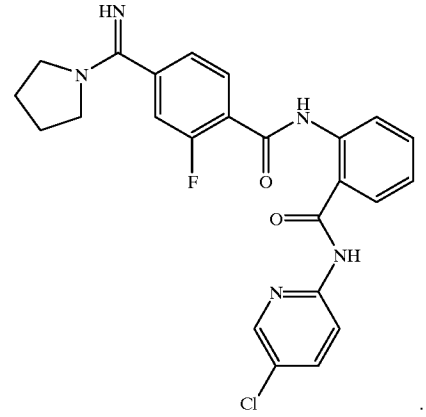
53. A compound of claim 23 having the following structure:



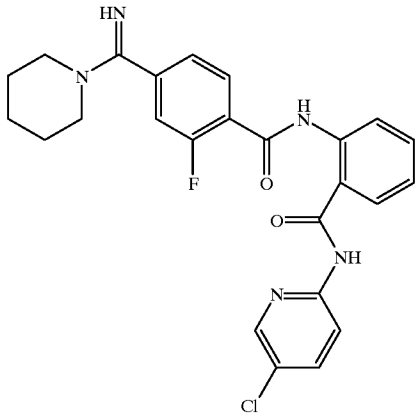
54. A compound of claim 23 having the following structure:



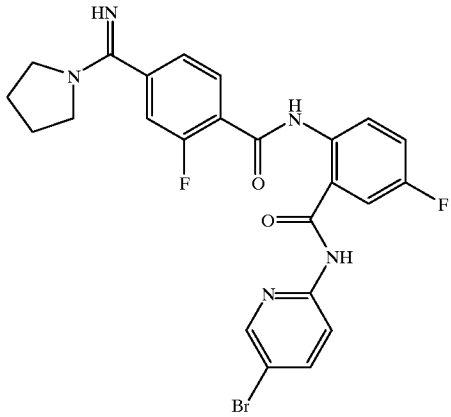
55. A compound of claim 23 having the following structure:



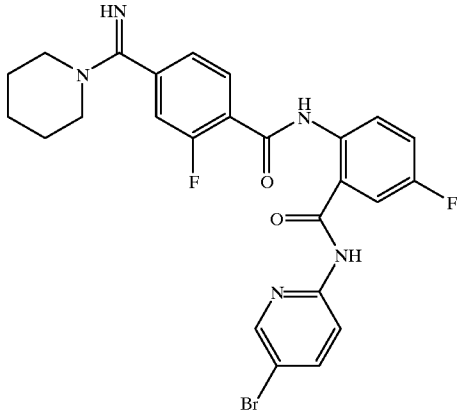
56. A compound of claim 23 having the following structure:



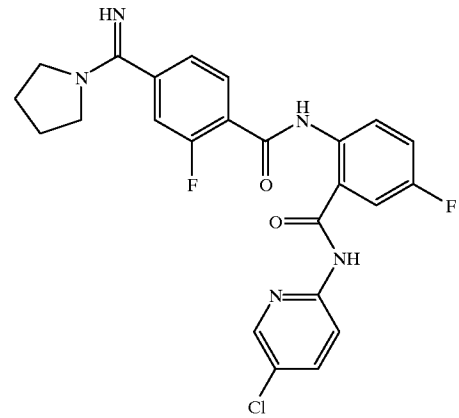
57. A compound of claim 23 having the following structure:



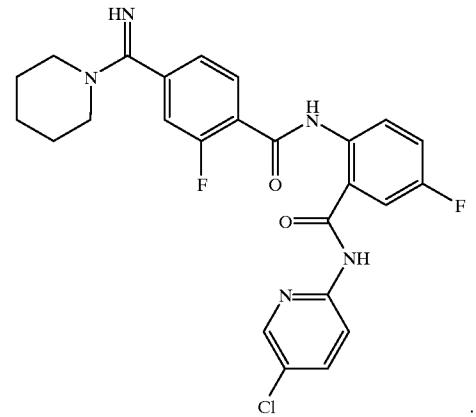
58. A compound of claim 23 having the following structure:



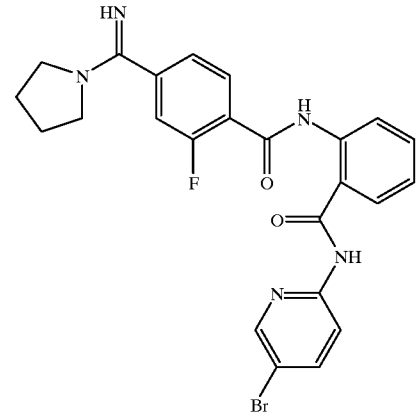
59. A compound of claim 23 having the following structure:



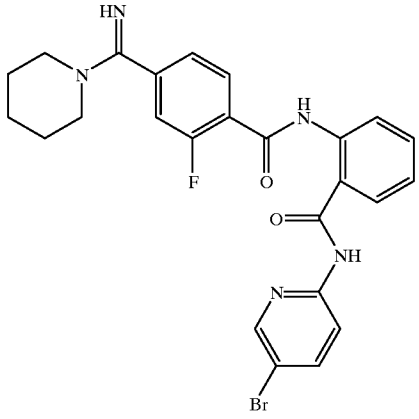
60. A compound of claim 23 having the following structure:



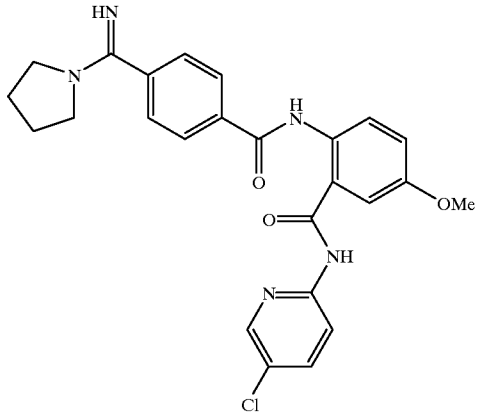
61. A compound of claim 23 having the following structure:



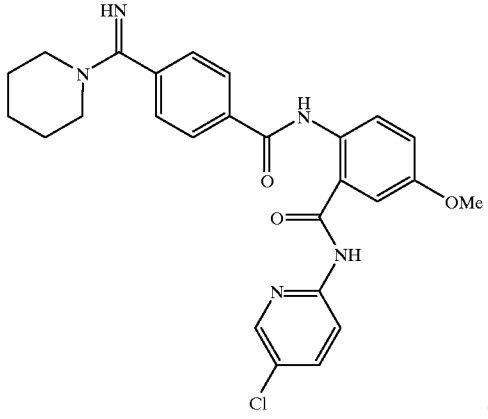
62. A compound of claim 23 having the following structure:



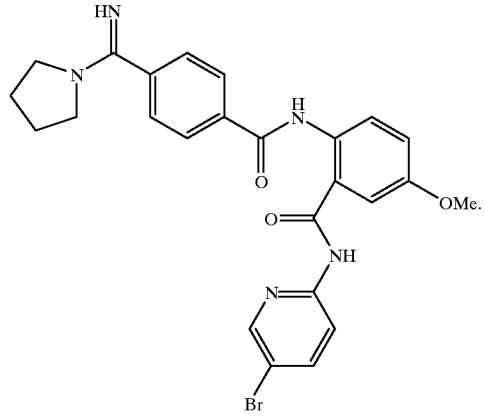
63. A compound of claim 23 having the following structure:



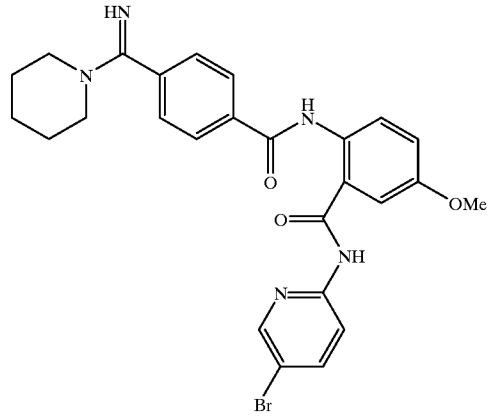
64. A compound of claim 23 having the following structure:



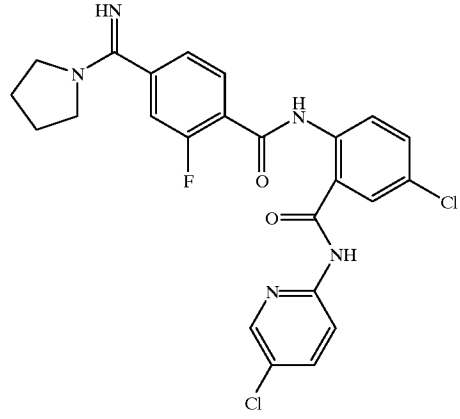
65. A compound of claim 23 having the following structure:



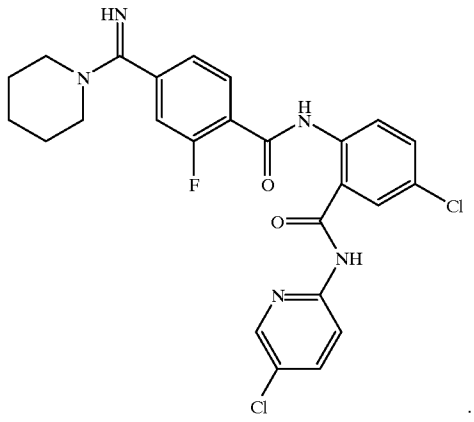
66. A compound of claim 23 having the following structure:



67. A compound of claim 23 having the following structure:



68. A compound of claim 23 having the following structure:



69. A pharmaceutical composition for preventing or treating a condition in a mammal characterized by undesired thrombosis comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of one of claims **23-68**.

70. A method for preventing or treating a condition in a mammal characterized by undesired thrombosis comprising administering to said mammal a therapeutically effective amount of a compound of one of claims **23-68**.

71. The method of claim 70, wherein the condition is selected from the group consisting of:

acute coronary syndrome, myocardial infarction, unstable angina, refractory angina, occlusive coronary thrombus occurring post-thrombolytic therapy or post-coronary angioplasty, a thrombotically mediated cerebrovascular syndrome, embolic stroke, thrombotic stroke, transient ischemic attacks, venous thrombosis, deep venous thrombosis, pulmonary embolus, coagulopathy, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, thromboangiitis obliterans, thrombotic disease associated with heparin-induced thrombocytopenia, thrombotic complications associated with extracorporeal circulation, thrombotic complications associated with instrumentation, and thrombotic complications associated with the fitting of prosthetic devices.

72. A method for inhibiting the coagulation of a biological sample comprising the step of administering a compound of one of claims **23-68**.

* * * * *