BIARYL HETEROCYCLIC COMPOUNDS AND METHODS OF MAKING AND USING THE SAME

RELATED APPLICATIONS

This application claims the benefit of and priority to U.S. Patent Application Nos. 60/475,430, filed June 3, 2003; 60/475,453, filed June 3, 2003; 60/490,855, filed July 29, 2003; 60/529,731, filed December 15, 2003; and 60/531,584, filed December 19, 2003, the enclosures of which are incorporated by reference herein.

FIELD OF THE INVENTION

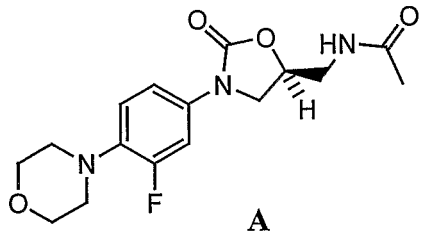
The present invention relates generally to the field of anti-infective, anti-proliferative, anti-inflammatory, and prokinetic agents. More particularly, the invention relates to a family of biaryl heterocyclic compounds, comprising both a biaryl moiety and at least one heterocyclic moiety, that are useful as therapeutic agents.

BACKGROUND

Since the discovery of penicillin in the 1920s and streptomycin in the 1940s, many new compounds have been discovered or specifically designed for use as antibiotic agents. It was once believed that infectious diseases could be completely controlled or eradicated with the use of such therapeutic agents. However, such beliefs have been shaken by the fact that strains of cells or microorganisms resistant to currently effective therapeutic agents continue to evolve. In fact, virtually every antibiotic agent developed for clinical use has ultimately encountered problems with the emergence of resistant bacteria. For example, resistant strains of Gram-positive bacteria such as methicillin-resistant staphylocci, penicillin-resistant streptococci, and vancomycin-resistant enterococci have developed, which can cause serious and even fatal results for patients infected with such resistant bacteria. Bacteria that are resistant to macrolide antibiotics, i.e., antibiotics based on a 14- to 16-membered lactone ring, have developed. Also, resistant strains of Gram-negative bacteria such as *H. influenzae* and *M. catarrhalis* have been identified. *See, e.g.*, F.D. Lowry, "Antimicrobial Resistance: The Example of *Staphylococcus aureus*," *J. Clin. Invest.*, **2003**, *111*(9), 1265-1273; and Gold, H.S. and Moellering, R.C., Jr., "Antimicrobial-Drug Resistance," *N. Engl. J. Med.*, **1996**, *335*, 1445-53.

The problem of resistance is not limited to the area of anti-infective agents, because resistance has also been encountered with anti-proliferative agents used in cancer chemotherapy. Therefore, there exists a need for new anti-infective and anti-proliferative agents that are both effective against resistant bacteria and resistant strains of cancer cells.

In the antibiotic area, despite the problem of increasing antibiotic resistance, no new major classes of antibiotics have been developed for clinical use since the approval in the United States in 2000 of the oxazolidinone ring-containing antibiotic, N-[[(5S)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl acetamide, which is known as linezolid and is sold under the tradename Zyvox® (*see* compound A). *See,* R.C. Moellering, Jr., "Linezolid: The First Oxazolidinone Antimicrobial," *Annals of Internal Medicine*, **2003**, *138*(2), 135-142.



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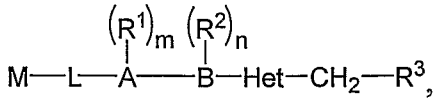
Linezolid was approved for use as an anti-bacterial agent active against Gram-positive organisms. Unfortunately, linezolid-resistant strains of organisms are already being reported. *See,* Tsiodras *et al.*, *Lancet*, **2001**, *358*, 207; Gonzales *et al.*, *Lancet*, **2001**, *357*, 1179; Zurenko *et al.*, *Proceedings Of The 39th Annual Interscience Conference On Antibacterial Agents And Chemotherapy (ICAAC)*; San Francisco, CA, USA, (September 26-29, 1999). Because linezolid is both a clinically effective and commercially significant anti-microbial agent, investigators have been working to develop other effective linezolid derivatives.

Notwithstanding the foregoing, there is an ongoing need for new anti-infective and anti-proliferative agents. Furthermore, because many anti-infective and anti-proliferative agents have utility as anti-inflammatory agents and prokinetic agents, there is also an ongoing need for new compounds useful as anti-inflammatory and prokinetic agents.

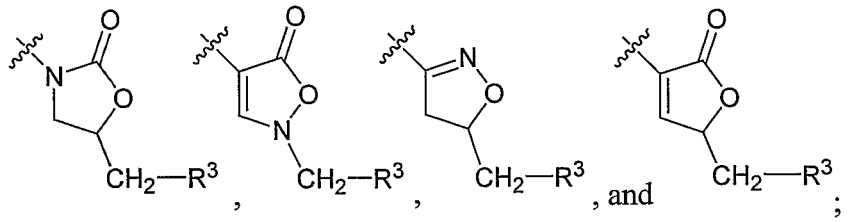
SUMMARY OF THE INVENTION

The invention provides a family of compounds useful as anti-infective agents and/or anti-proliferative agents, for example, chemotherapeutic agents, anti-microbial agents, anti-bacterial agents, anti-fungal agents, anti-parasitic agents, anti-viral agents, anti-inflammatory

agents, and/or prokinetic (gastrointestinal modulatory) agents. The compounds have the formula:

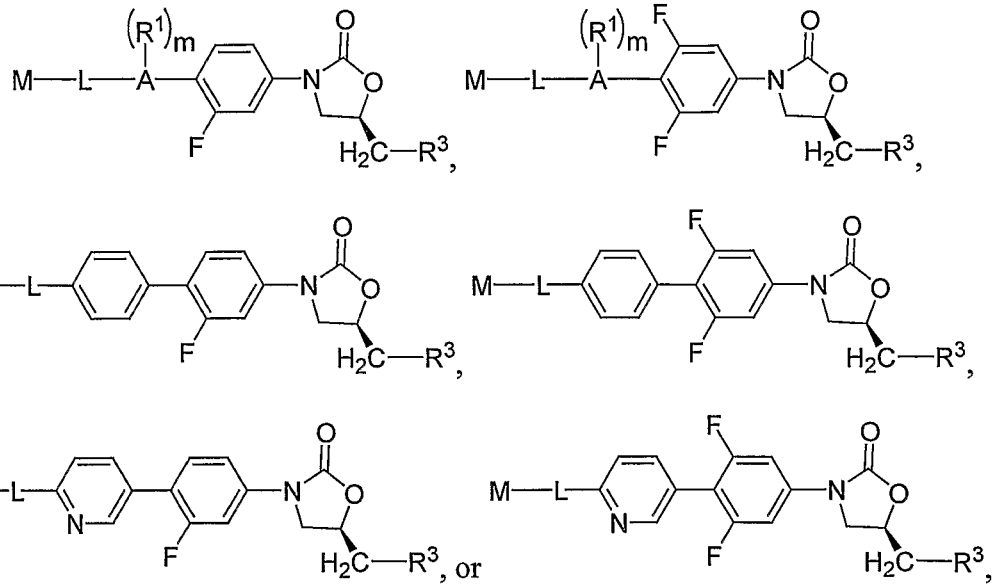


or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein Het-CH_2-R^3 is selected from the group consisting of:



A and B independently are selected from the group consisting of phenyl, pyridyl, pyrazinyl, pyrimidinyl, and pyridazinyl; M-L is selected from the group consisting of M-X, M-L^1, M-L^1-X, M-X-L^2, M-L^1-X-L^2, M-X-L^1-X-L^2, M-L^1-X-L^2-X, M-X-X-, M-L^1-X-X-, M-X-X-L^2, and M-L^1-X-X-L^2; M is an optionally substituted saturated, unsaturated, or aromatic C_{3-14} carbocycle, or an optionally substituted saturated, unsaturated, or aromatic 3-14 membered heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur; and the variables L^1, L^2,M, R^1, R^2, R^3, X, m, and n are selected from the respective groups of chemical moieties or integers later defined in the detailed description.

Particular embodiments of compounds of the invention include those having the formula:



wherein the variables A, L, M, R^1, R^3, and m are selected from the respective groups of chemical moieties or integers later defined in the detailed description.

In addition, the invention provides methods of synthesizing the foregoing compounds. Following synthesis, an effective amount of one or more of the compounds may be formulated with a pharmaceutically acceptable carrier for administration to a mammal for use as an anti-cancer, anti-microbial, anti-biotic, anti-fungal, anti-parasitic or anti-viral agent, or to treat a proliferative disease, an inflammatory disease or a gastrointestinal motility disorder. The compounds or formulations may be administered, for example, via oral, parenteral, or topical routes, to provide an effective amount of the compound to the mammal.

The foregoing and other aspects and embodiments of the invention may be more fully understood by reference to the following detailed description and claims.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a family of compounds that can be used as anti-proliferative agents and/or anti-infective agents. The compounds may be used without limitation, for example, as anti-cancer, anti-microbial, anti-bacterial, anti-fungal, anti-parasitic and/or anti-viral agents. Further, the present invention provides a family of compounds that can be used without limitation as anti-inflammatory agents, for example, for use in treating chronic inflammatory airway diseases, and/or as prokinetic agents, for example, for use in treating gastrointestinal motility disorders such as gastroesophageal reflux disease, gastroparesis (diabetic and post surgical), irritable bowel syndrome, and constipation.

1. Definitions

The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced. Keto substituents are not present on aromatic moieties. Ring double bonds, as used herein, are double bonds that are formed between two adjacent ring atoms (e.g., C=C, C=N, or N=N).

The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium, and isotopes of carbon include C-13 and C-14.

The compounds described herein may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic, and geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated. All processes used to prepare compounds of the present invention and intermediates made therein are considered to be part of the present invention. All tautomers of shown or described compounds are also considered to be part of the present invention.

When any variable (e.g., R^1) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R^1 moieties, then the group may optionally be substituted with up to two R^1 moieties and R^1 at each occurrence is selected independently from the definition of R^1. Also, combinations of substituents and/or variables are permissible, but only if such combinations result in stable compounds.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom in the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible, but only if such combinations result in stable compounds.

Compounds of the present invention that contain nitrogens can be converted to N-oxides by treatment with an oxidizing agent (e.g., MCPBA and/or hydrogen peroxides) to afford other compounds of the present invention. Thus, all shown and claimed nitrogen-containing compounds are considered, when allowed by valency and structure, to include both the compound as shown and its N-oxide derivative (which can be designated as $N\rightarrow O$ or $N^+\text{-}O^-$). Furthermore, in other instances, the nitrogens in the compounds of the present invention can be converted to N-hydroxy or N-alkoxy compounds. For example, N-hydroxy compounds can

be prepared by oxidation of the parent amine by an oxidizing agent such as MCPBA. All shown and claimed nitrogen-containing compounds are also considered, when allowed by valency and structure, to cover both the compound as shown and its N-hydroxy (i.e., N-OH) and N-alkoxy (i.e., N-OR, wherein R is substituted or unsubstituted C_{1-6} alkyl, alkenyl, alkynyl, C_{3-14} carbocycle, or 3-14-membered heterocycle) derivatives.

When an atom or chemical moiety is followed by a subscripted numeric range (e.g., C_{1-6}), the invention is meant to encompass each number within the range as well as all intermediate ranges. For example, "C_{1-6} alkyl" is meant to include alkyl groups with 1, 2, 3, 4, 5, 6, 1-6, 1-5, 1-4, 1-3, 1-2, 2-6, 2-5, 2-4, 2-3, 3-6, 3-5, 3-4, 4-6, 4-5, and 5-6 carbons.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, C_{1-6} alkyl is intended to include C_1, C_2, C_3, C_4, C_5, and C_6 alkyl groups. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl, and n-hexyl.

As used herein, "alkenyl" is intended to include hydrocarbon chains of either straight or branched configuration having one or more carbon-carbon double bonds occurring at any stable point along the chain. For example, C_{2-6} alkenyl is intended to include C_2, C_3, C_4, C_5, and C_6 alkenyl groups. Examples of alkenyl include, but are not limited to, ethenyl and propenyl.

As used herein, "alkynyl" is intended to include hydrocarbon chains of either straight or branched configuration having one or more carbon-carbon triple bonds occurring at any stable point along the chain. For example, C_{2-6} alkynyl is intended to include C_2, C_3, C_4, C_5, and C_6 alkynyl groups. Examples of alkynyl include, but are not limited to, ethynyl and propynyl.

As used herein, "halo" or "halogen" refers to fluoro, chloro, bromo, and iodo. "Counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, and sulfate.

As used herein, "carbocycle" or "carbocyclic ring" is intended to mean any stable monocyclic, bicyclic, or tricyclic ring having the specified number of carbons, any of which may be saturated, unsaturated, or aromatic. For example a C_{3-14} carbocycle is intended to mean a mono-, bi-, or tricyclic ring having 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 carbon atoms. Examples of carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cycloheptenyl, cycloheptyl, cycloheptenyl, adamantyl,

cyclooctyl, cyclooctenyl, cyclooctadienyl, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, and tetrahydronaphthyl. Bridged rings are also included in the definition of carbocycle, including, for example, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane, and [2.2.2]bicyclooctane. A bridged ring occurs when one or more carbon atoms link two non-adjacent carbon atoms. Preferred bridges are one or two carbon atoms. It is noted that a bridge always converts a monocyclic ring into a tricyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge. Fused (e.g., naphthyl and tetrahydronaphthyl) and spiro rings are also included.

As used herein, the term "heterocycle" or "heterocyclic" is intended to mean any stable monocyclic, bicyclic, or tricyclic ring which is saturated, unsaturated, or aromatic and comprises carbon atoms and one or more ring heteroatoms, e.g., 1 or 1-2 or 1-3 or 1-4 or 1-5 or 1-6 heteroatoms, independently selected from the group consisting of nitrogen, oxygen, and sulfur. A bicyclic or tricyclic heterocycle may have one or more heteroatoms located in one ring, or the heteroatoms may be located in more than one ring. The nitrogen and sulfur heteroatoms may optionally be oxidized (i.e., $N \rightarrow O$ and $S(O)_p$, where $p = 1$ or 2). When a nitrogen atom is included in the ring it is either N or NH, depending on whether or not it is attached to a double bond in the ring (i.e., a hydrogen is present if needed to maintain the tri-valency of the nitrogen atom). The nitrogen atom may be substituted or unsubstituted (i.e., N or NR wherein R is H or another substituent, as defined). The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. A nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. Bridged rings are also included in the definition of heterocycle. A bridged ring occurs when one or more atoms (i.e., C, O, N, or S) link two non-adjacent carbon or nitrogen atoms. Preferred bridges include, but are not limited to, one carbon atom, two carbon atoms, one nitrogen atom, two nitrogen atoms, and a carbon-nitrogen group. It is noted that a bridge always converts a monocyclic ring into a tricyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge. Spiro and fused rings are also included.

As used herein, the term "aromatic heterocycle" or "heteroaryl" is intended to mean a stable 5, 6, or 7-membered monocyclic or bicyclic aromatic heterocyclic ring or 7, 8, 9, 10, 11,

or 12-membered bicyclic aromatic heterocyclic ring which consists of carbon atoms and one or more heteroatoms, e.g., 1 or 1-2 or 1-3 or 1-4 or 1-5 or 1-6 heteroatoms, independently selected from the group consisting of nitrogen, oxygen, and sulfur. In the case of bicyclic heterocyclic aromatic rings, only one of the two rings needs to be aromatic (e.g., 2,3-dihydroindole), though both may be (e.g., quinoline). The second ring can also be fused or bridged as defined above for heterocycles. The nitrogen atom may be substituted or unsubstituted (i.e., N or NR wherein R is H or another substituent, as defined). The nitrogen and sulfur heteroatoms may optionally be oxidized (i.e., N→O and $S(O)_p$, where p = 1 or 2). It is to be noted that total number of S and O atoms in the aromatic heterocycle is not more than 1.

Examples of heterocycles include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzoxazolinyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4a*H*-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1*H*-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxindolyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6*H*-1,2,5-thiadiazinyl, 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.

As used herein, the phrase "pharmaceutically acceptable" refers to those compounds, materials, compositions, carriers, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals

without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines, alkali or organic salts of acidic residues such as carboxylic acids, and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include, but are not limited to, those derived from inorganic and organic acids selected from 2-acetoxybenzoic, 2-hydroxyethane sulfonic, acetic, ascorbic, benzene sulfonic, benzoic, bicarbonic, carbonic, citric, edetic, ethane disulfonic, ethane sulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, glycollyarsanilic, hexylresorcinic, hydrabamic, hydrobromic, hydrochloric, hydroiodic, hydroxymaleic, hydroxynaphthoic, isethionic, lactic, lactobionic, lauryl sulfonic, maleic, malic, mandelic, methane sulfonic, napsylic, nitric, oxalic, pamoic, pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicyclic, stearic, subacetic, succinic, sulfamic, sulfanilic, sulfuric, tannic, tartaric, and toluene sulfonic.

The pharmaceutically acceptable salts of the present invention can be synthesized from a parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 18th ed. (Mack Publishing Company, 1990).

Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (e.g., solubility, bioavailability, manufacturing, etc.) the compounds of the present invention may be delivered in prodrug form. Thus, the present invention is intended to cover prodrugs of the presently claimed compounds, methods of delivering the same and compositions containing the same. "Prodrugs" are intended to include any covalently bonded carriers that release an active parent drug of the present invention *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs the present invention are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in

routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds of the present invention wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug of the present invention is administered to a mammalian subject, cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate, and benzoate derivatives of alcohol and amine functional groups in the compounds of the present invention.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

As used herein, "treating" or "treatment" means the treatment of a disease-state in a mammal, particularly in a human, and include: (a) preventing the disease-state from occurring in a mammal, in particular, when such mammal is predisposed to the disease-state but has not yet been diagnosed as having it; (b) inhibiting the disease-state, i.e., arresting its development; and/or (c) relieving the disease-state, i.e., causing regression of the disease state.

As used herein, "mammal" refers to human and non-human patients.

As used herein, the term "effective amount" refers to an amount of a compound, or a combination of compounds, of the present invention effective when administered alone or in combination as an anti-proliferative and/or anti-infective agent. The combination of compounds is preferably a synergistic combination. Synergy, as described, for example, by Chou and Talalay, *Adv. Enzyme Regul.* **1984**, *22*:27-55, occurs when the effect of the compounds when administered in combination is greater than the additive effect of the compounds when administered alone as a single agent. In general, a synergistic effect is most clearly demonstrated at sub-optimal concentrations of the compounds. Synergy can be in terms of lower cytotoxicity, increased anti-proliferative and/or anti-infective effect, or some other beneficial effect of the combination compared with the individual components.

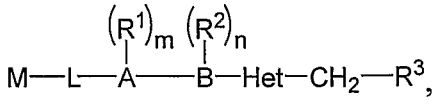
All percentages and ratios used herein, unless otherwise indicated, are by weight.

Throughout the description, where compositions are described as having, including, or comprising specific components, it is contemplated that compositions also consist essentially of, or consist of, the recited components. Similarly, where processes are described as having, including, or comprising specific process steps, the processes also consist essentially of, or consist of, the recited processing steps. Further, it should be understood that the order of steps

or order for performing certain actions are immaterial so long as the invention remains operable. Moreover, two or more steps or actions may be conducted simultaneously.

2. Compounds of the Invention

In one aspect, the invention provides compounds having the formula:



or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein:

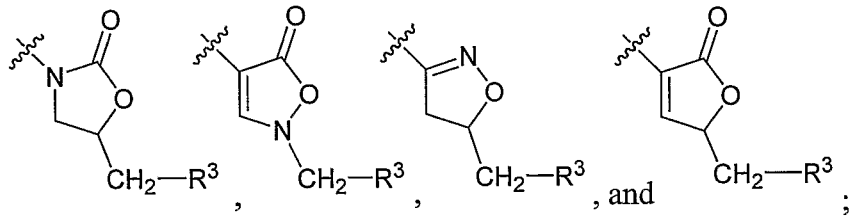
A is selected from the group consisting of:

phenyl, pyridyl, pyrazinyl, pyrimidinyl, and pyridazinyl;

B is selected from the group consisting of:

phenyl, pyridyl, pyrazinyl, pyrimidinyl, and pyridazinyl;

Het-CH_2-R^3 is selected from the group consisting of:



M is selected from the group consisting of:

a) saturated, unsaturated, or aromatic C_{3-14} carbocycle, and b) saturated, unsaturated, or aromatic 3-14 membered heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,

wherein a) or b) optionally is substituted with one or more R^5 groups;

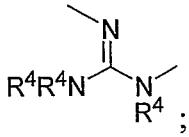
M-L is selected from the group consisting of:

a) M-X, b) M-L^1, c) M-L^1-X, d) M-X-L^2, e) M-L^1-X-L^2, f) M-X-L^1-X-L^2, g) M-L^1-X-L^2-X, h) M-X-X-, i) M-L^1-X-X-, j) M-X-X-L^2, and k) M-L^1-X-X-L^2, wherein

X, at each occurrence, independently is selected from the group consisting of:

a) -O-, b) -NR^4-, c) –N(O)-, d) –N(OR^4)-, e) -$S(O)_p$-, f) -SO_2NR^4-, g) -NR^4SO_2-, h) -NR^4-N=, i) =N-NR^4-, j) -O-N=, k) =N-O-, l) -N=, m) =N-, n) -NR^4-NR^4-, o) -$NR^4C(O)O$-, p) -$OC(O)NR^4$-, q) -$NR^4C(O)NR^4$- r) -$NR^4C(NR^4)NR^4$-, and

s)



;

L^1 is selected from the group consisting of:

a) C_{1-6} alkyl, b) C_{2-6} alkenyl, and c) C_{2-6} alkynyl,

wherein any of a) – c) optionally is substituted with one or more R^5 groups; and

L^2 is selected from the group consisting of:

a) C_{1-6} alkyl, b) C_{2-6} alkenyl, and c) C_{2-6} alkynyl,

wherein any of a) – c) optionally is substituted with one or more R^5 groups;

R^1, at each occurrence, independently is selected from the group consisting of:

a) F, b) Cl, c) Br, d) I, e) $-CF_3$, f) $-OR^4$, g) -CN, h) $-NO_2$, i) $-NR^4R^4$, j) $-C(O)R^4$, k) $-C(O)OR^4$, l) $-OC(O)R^4$, m) $-C(O)NR^4R^4$, n) $-NR^4C(O)R^4$, o) $-OC(O)NR^4R^4$, p) $-NR^4C(O)OR^4$, q) $-NR^4C(O)NR^4R^4$, r) $-C(S)R^4$, s) $-C(S)OR^4$, t) $-OC(S)R^4$, u) $-C(S)NR^4R^4$, v) $-NR^4C(S)R^4$, w) $-OC(S)NR^4R^4$, x) $-NR^4C(S)OR^4$, y) $-NR^4C(S)NR^4R^4$, z) $-NR^4C(NR^4)NR^4R^4$, aa) $-S(O)_pR^4$, bb) $-SO_2NR^4R^4$, and cc) R^4;

R^2, at each occurrence, independently is selected from the group consisting of:

a) F, b) Cl, c) Br, d) I, e) $-CF_3$, f) $-OR^4$, g) -CN, h) $-NO_2$, i) $-NR^4R^4$, j) $-C(O)R^4$, k) $-C(O)OR^4$, l) $-OC(O)R^4$, m) $-C(O)NR^4R^4$, n) $-NR^4C(O)R^4$, o) $-OC(O)NR^4R^4$, p) $-NR^4C(O)OR^4$, q) $-NR^4C(O)NR^4R^4$, r) $-C(S)R^4$, s) $-C(S)OR^4$, t) $-OC(S)R^4$, u) $-C(S)NR^4R^4$, v) $-NR^4C(S)R^4$, w) $-OC(S)NR^4R^4$, x) $-NR^4C(S)OR^4$, y) $-NR^4C(S)NR^4R^4$, z) $-NR^4C(NR^4)NR^4R^4$, aa) $-S(O)_pR^4$, bb) $-SO_2NR^4R^4$, and cc) R^4;

R^3 is selected from the group consisting of:

a) $-OR^4$, b) $-NR^4R^4$, c) $-C(O)R^4$, d) $-C(O)OR^4$, e) $-OC(O)R^4$, f) $-C(O)NR^4R^4$, g) $-NR^4C(O)R^4$, h) $-OC(O)NR^4R^4$, i) $-NR^4C(O)OR^4$, j) $-NR^4C(O)NR^4R^4$, k) $-C(S)R^4$, l) $-C(S)OR^4$, m) $-OC(S)R^4$, n) $-C(S)NR^4R^4$, o) $-NR^4C(S)R^4$, p) $-OC(S)NR^4R^4$, q) $-NR^4C(S)OR^4$, r) $-NR^4C(S)NR^4R^4$, s) $-NR^4C(NR^4)NR^4R^4$, t) $-S(O)_pR^4$, u) $-SO_2NR^4R^4$, and v) R^4;

R^4, at each occurrence, independently is selected from the group consisting of:

a) H, b) C_{1-6} alkyl, c) C_{2-6} alkenyl, d) C_{2-6} alkynyl, e) C_{3-14} saturated, unsaturated, or aromatic carbocycle, f) 3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, g) -C(O)-C_{1-6} alkyl, h) -C(O)-C_{2-6} alkenyl, i) –C(O)-C_{2-6} alkynyl, j) -C(O)-C_{3-14} saturated, unsaturated, or aromatic carbocycle, k) -C(O)-3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, l) -C(O)O-C_{1-6} alkyl, m) -C(O)O-C_{2-6} alkenyl, n) –C(O)O-C_{2-6} alkynyl, o) -C(O)O-C_{3-14} saturated, unsaturated, or aromatic carbocycle, and p) -C(O)O-3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,

wherein any of b) – p) optionally is substituted with one or more R^5 groups;

R^5, at each occurrence, is independently selected from the group consisting of:

a) F, b) Cl, c) Br, d) I, e) =O, f) =S, g) =NR^6, h) =NOR^6, i) =N-NR^6R^6, j) -CF_3, k) –OR^6, l) -CN, m) -NO_2, n) –NR^6R^6, o) -C(O)R^6, p) -C(O)OR^6, q) -OC(O)R^6, r) -C(O)NR^6R^6, s) –NR^6C(O)R^6, t) -OC(O)NR^6R^6, u) -NR^6C(O)OR^6, v) -NR^6C(O)NR^6R^6, w) -C(S)R^6, x) -C(S)OR^6, y) -OC(S)R^6, z) -C(S)NR^6R^6, aa) -NR^6C(S)R^6, bb) -OC(S)NR^6R^6, cc) -NR^6C(S)OR^6, dd) –NR^6C(S)NR^6R^6, ee) –NR^6C(NR^6)NR^6R^6, ff) -S(O)$_p$$R^6$, gg) -$SO_2NR^6R^6$, and hh) R^6;

R^6, at each occurrence, independently is selected from the group consisting of:

a) H, b) C_{1-6} alkyl, c) C_{2-6} alkenyl, d) C_{2-6} alkynyl, e) C_{3-14} saturated, unsaturated, or aromatic carbocycle, f) 3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, g) -C(O)-C_{1-6} alkyl, h) -C(O)-C_{2-6} alkenyl, i) –C(O)-C_{2-6} alkynyl, j) -C(O)-C_{3-14} saturated, unsaturated, or aromatic carbocycle, k) -C(O)-3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, l) -C(O)O-C_{1-6} alkyl, m) -C(O)O-C_{2-6} alkenyl, n) –C(O)O-C_{2-6} alkynyl, o) -C(O)O-C_{3-14} saturated,

unsaturated, or aromatic carbocycle, and p) -C(O)O-3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,

wherein any of b) – p) optionally is substituted with one or more R^7 groups;

R^7, at each occurrence, independently is selected from the group consisting of:

a) F, b) Cl, c) Br, d) I, e) =O, f) =S, g) $=NR^8$, h) $=NOR^8$, i) $=N\text{-}NR^8R^8$, j) $-CF_3$, k) $-OR^8$, l) -CN, m) $-NO_2$, n) $-NR^8R^8$, o) $-C(O)R^8$, p) $-C(O)OR^8$, q) $-OC(O)R^8$, r) $-C(O)NR^8R^8$, s) $-NR^8C(O)R^8$, t) $-OC(O)NR^8R^8$, u) $-NR^8C(O)OR^8$, v) $-NR^8C(O)NR^8R^8$, w) $-C(S)R^8$, x) $-C(S)OR^8$, y) $-OC(S)R^8$, z) $-C(S)NR^8R^8$, aa) $-NR^8C(S)R^8$, bb) $-OC(S)NR^8R^8$, cc) $-NR^8C(S)OR^8$, dd) $-NR^8C(S)NR^8R^8$, ee) $-NR^8C(NR^8)NR^8R^8$, ff) $-S(O)_pR^8$, gg) $-SO_2NR^8R^8$, hh) C_{1-6} alkyl, ii) C_{2-6} alkenyl, jj) C_{2-6} alkynyl, kk) C_{3-14} saturated, unsaturated, or aromatic carbocycle, and ll) 3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,

wherein any of hh) – ll) optionally is substituted with one or more moieties selected from the group consisting of R^8, F, Cl, Br, I, $-CF_3$, $-OR^8$, $-SR^8$, -CN, $-NO_2$, $-NR^8R^8$, $-C(O)R^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-C(O)NR^8R^8$, $-NR^8C(O)R^8$, $-OC(O)NR^8R^8$, $-NR^8C(O)OR^8$, $-NR^8C(O)NR^8R^8$, $-C(S)R^8$, $-C(S)OR^8$, $-OC(S)R^8$, $-C(S)NR^8R^8$, $-NR^8C(S)R^8$, $-OC(S)NR^8R^8$, $-NR^8C(S)OR^8$, $-NR^8C(S)NR^8R^8$, $-NR^8C(NR^8)NR^8R^8$, $-SO_2NR^8R^8$, and-$S(O)_pR^8$;

R^8, at each occurrence, independently is selected from the group consisting of:

a) H, b) C_{1-6} alkyl, c) C_{2-6} alkenyl, d) C_{2-6} alkynyl, e) C_{3-14} saturated, unsaturated, or aromatic carbocycle, f) 3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, g) $-C(O)\text{-}C_{1-6}$ alkyl, h) $-C(O)\text{-}C_{2-6}$ alkenyl, i) $-C(O)\text{-}C_{2-6}$ alkynyl, j) $-C(O)\text{-}C_{3-14}$ saturated, unsaturated, or aromatic carbocycle, k) -C(O)-3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, l) $-C(O)O\text{-}C_{1-6}$ alkyl,

m) -C(O)O-C_{2-6} alkenyl, n) –C(O)O-C_{2-6} alkynyl, o) -C(O)O-C_{3-14} saturated, unsaturated, or aromatic carbocycle, and p) -C(O)O-3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,

wherein any of b) – p) optionally is substituted with one or more moieties selected from the group consisting of F, Cl, Br, I, -CF_3, -OH, -OCH_3, -SH, -SCH_3, -CN, -NO_2, –NH_2, -$NHCH_3$, -$N(CH_3)_2$, -$C(O)CH_3$, -$C(O)OCH_3$, -$C(O)NH_2$, –$NHC(O)CH_3$, -SO_2NH_2, -SO_2NHCH_3, -$SO_2N(CH_3)_2$, and-$S(O)_pCH_3$;

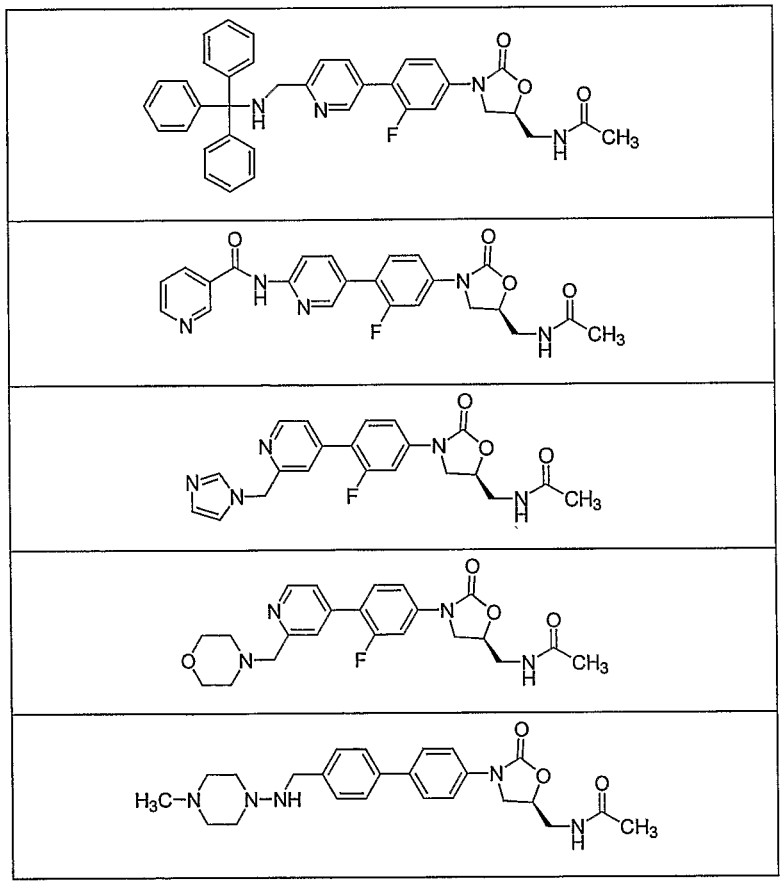
m is 0, 1, 2, 3, or 4;

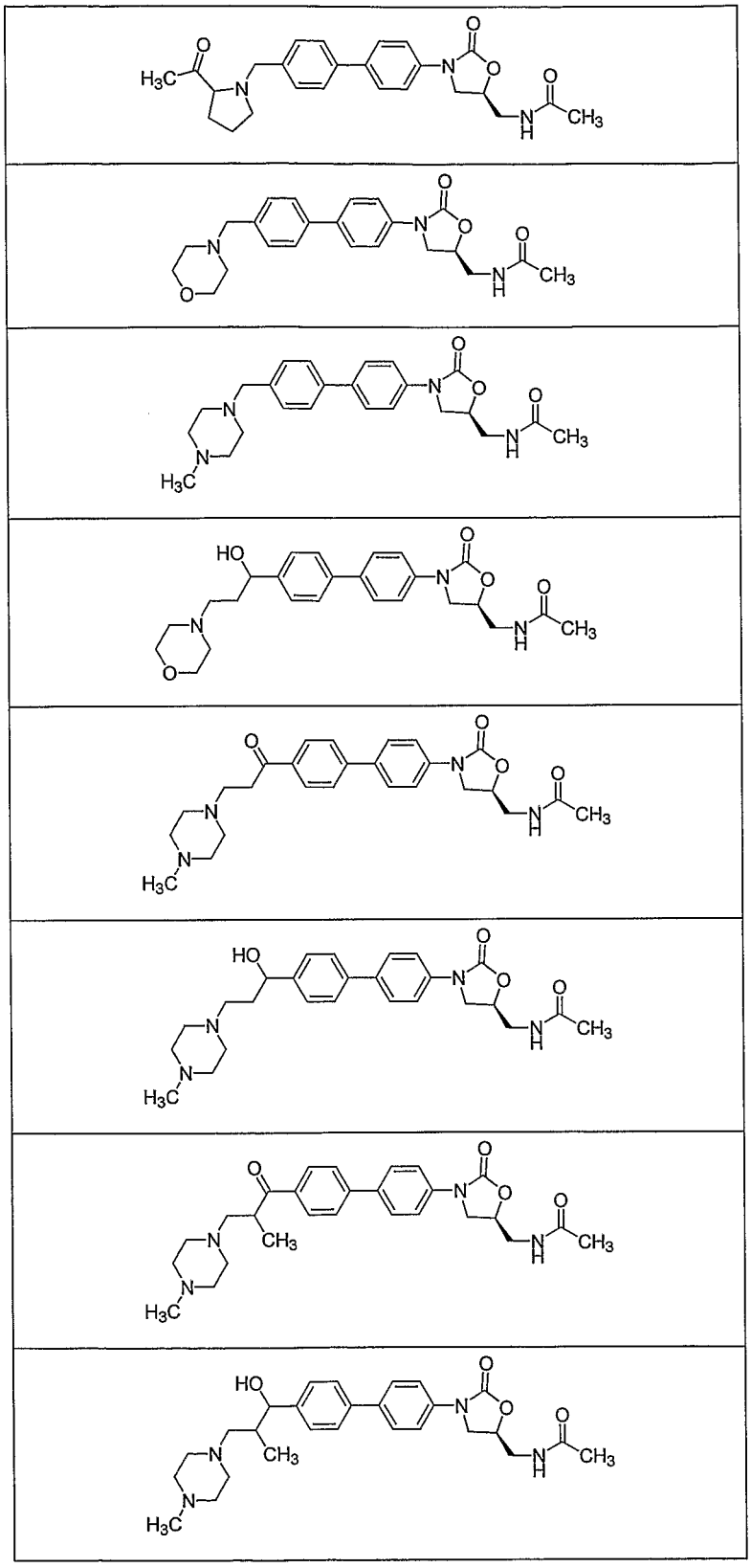
n is 0, 1, 2, 3, or 4; and

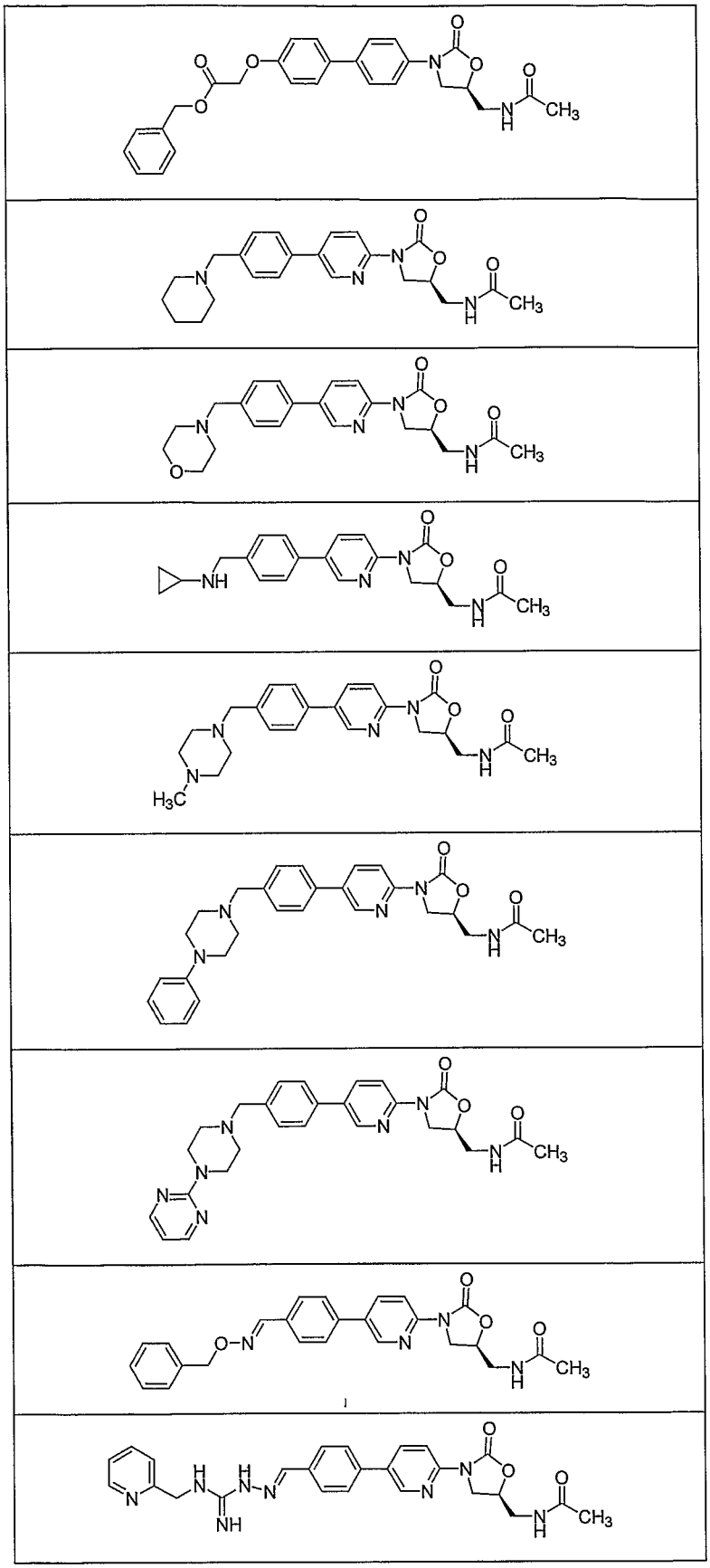
p, at each occurrence, independently is 0, 1, or 2,

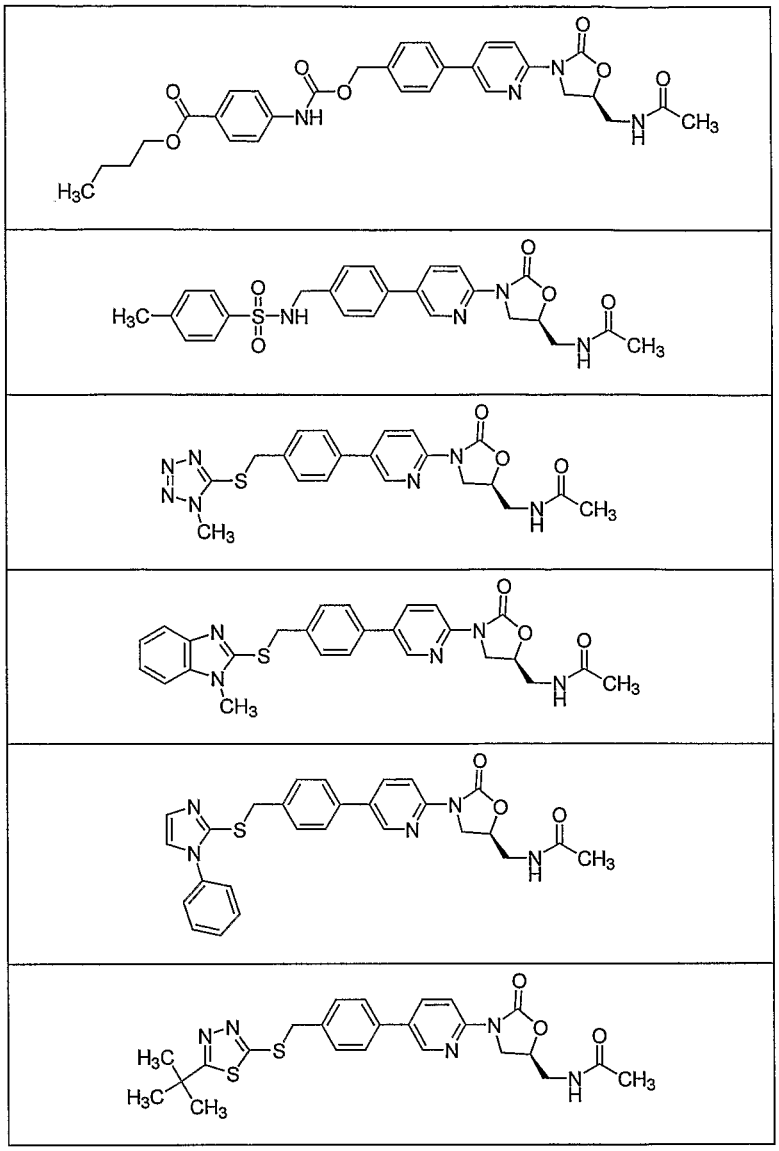
and wherein the compound does not have the formula corresponding to any of the structures listed in Table 1.

Table 1

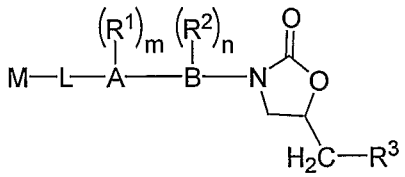






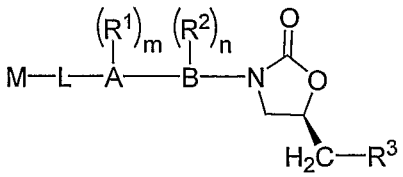


Particular embodiments of the invention include compounds having the formula:



or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein A, B, L, M, R^1, R^2, R^3, m, and n are defined above.

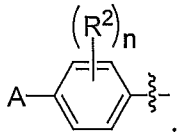
Other embodiments include compounds having the formula:



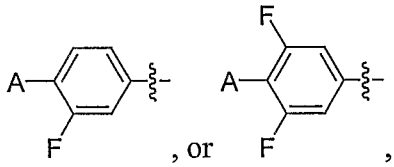
or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein A, B, L, M, R^1, R^2, R^3, m, and n are defined as described above.

Particular compounds include those where A is selected from the group consisting of phenyl and pyridyl; B is selected from the group consisting of phenyl and pyridyl; m is 0, 1, or 2; and n is 0, 1, or 2.

In some embodiments, A-B is:

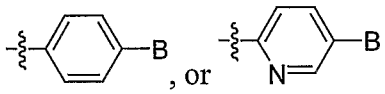


wherein A, R^2, and n are defined as described above. In particular embodiments, A-B is:



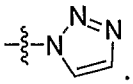
wherein A is defined as described above.

In various embodiments, A-B is:

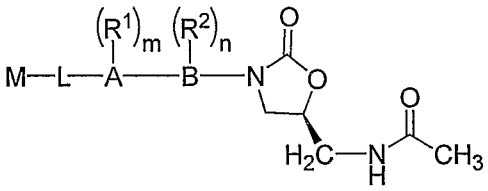


wherein B is defined as described in above.

In some embodiments, R^3 is $-NHC(O)R^4$. Particular compounds according to these embodiments include those where R^4 is $-CH_3$. In other embodiments, R^3 is:

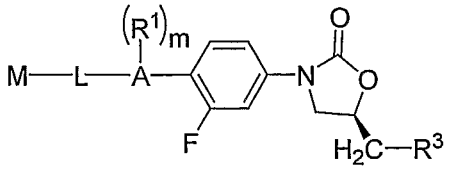


Particular embodiments of the invention include compounds having the formula:



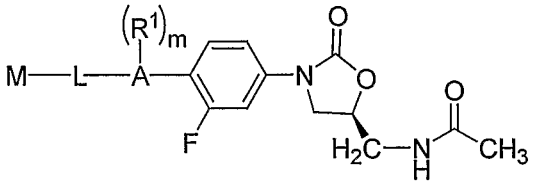
or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein A, B, L, M, R^1, R^2, m, and n are defined as described above.

Other embodiments of the invention include compounds having the formula:



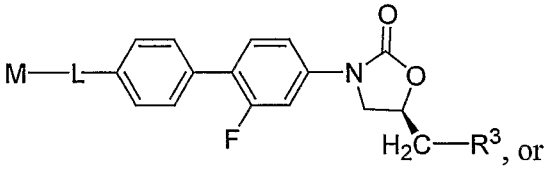
or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein A, L, M, R^1, R^3, and m are defined as described above.

Still other embodiments of the invention include compounds having the formula:

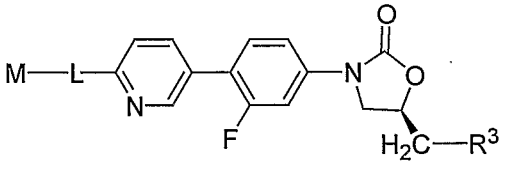


or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein A, L, M, R^1, and m are defined as described above.

Some embodiments of the invention include compounds having the formula:

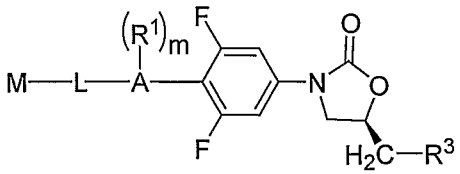


, or



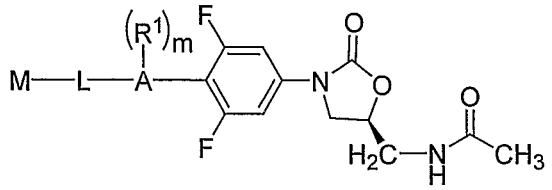
or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein L, M, and R^3 are defined as described above. Particular compounds according to these embodiments include those wherein R^3 is $-NHC(O)CH_3$.

Other embodiments of the invention include compounds having the formula:



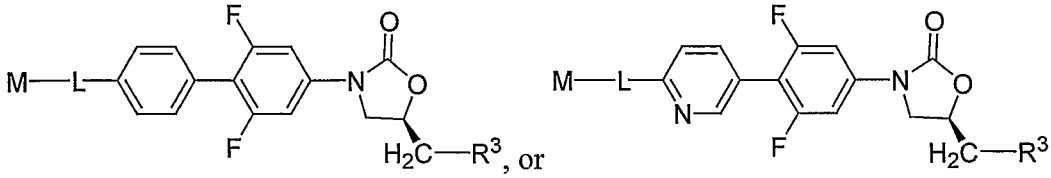
or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein A, L, M, R^1, R^3, and m are defined as described above.

Still other embodiments of the invention include compounds having the formula:



or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein A, L, M, R^1, and m are defined as described above.

Some embodiments of the invention include compounds having the formula:

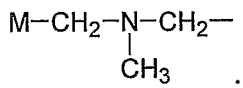


or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein L, M, and R^3 are defined as described above. Particular compounds according to these embodiments include those wherein R^3 is $-NHC(O)CH_3$.

In some embodiments, M-L is M-L^1, and L^1 is C_{1-6} alkyl. In particular embodiments, M-L^1 is M–CH_2-.

In other embodiments, M-L is M-L^1-X-L^2, and X is -NR^4-. In particular compounds according to these embodiments, X is –NH-, –N(O)-, or –N(OR^4)-, where R^4 is H or C_{1-6} alkyl. Other compounds include those where X is

In certain compounds according to these embodiments, L^1 is C_{1-6} alkyl, and L^2 is C_{1-6} alkyl. In some embodiments, L^1 is $–CH_2$- and L^2 is -CH_2-. Particular examples of compounds according to these embodiments include those where M-L is M-CH_2-NH-CH_2- or



In still other embodiments, M-L is M-S-L^1-NR^4- L^2, wherein L^1 is C_{1-6} alkyl, and L^2 is C_{1-6} alkyl. In particular compounds according to these embodiments, M-L is M-S-CH_2CH_2-NH-CH_2-.

In particular embodiments, M is selected from the group consisting of:

a) phenyl, b) pyridyl, c) pyrazinyl, d) pyrimidinyl, e) pyridazinyl, f) oxiranyl, g) aziridinyl, h) furanyl, i) thiophenyl, j) pyrrolyl, k) oxazolyl, l) isoxazolyl,

m) imidazolyl, n) pyrazolyl, o) isothiazolyl, p) thiazolyl, q) triazolyl, r) tetrazolyl, s) indolyl, t) purinyl, u) benzofuranyl, v) benzoxazolyl, w) benzisoxazolyl, x) quinolinyl, y) isoquinolinyl, z) quinoxalinyl, aa) quinazolinyl, bb) cinnolinyl, cc) cyclopropyl, dd) cyclobutyl, ee) cyclopentyl, ff) cyclohexyl, gg) cycloheptyl, hh) oxetanyl, ii) tetrahydrofuranyl, jj) tetrahydropyranyl, kk) azetidinyl, ll) pyrrolidinyl, mm) piperidinyl, nn) thietanyl, oo) tetrahydrothiophenyl, pp) tetrahydrothiopyranyl, qq) piperazinyl, rr) quinuclidinyl, ss) 1-azabicyclo[2.2.1]hyeptanyl, tt) morpholinyl, uu) thiomorpholinyl, vv) thiooxomorpholinyl, ww) thiodioxomorpholinyl, and xx) benzothiophenyl

wherein any of a) – xx) optionally is substituted with one or more R^5 groups. In particular embodiments, M is 4-isoxazolyl, [1,2,3]triazol-1-yl, 3H-[1,2,3]triazol-4-yl, 1H-tetrazol-5-yl, piperidin-1-yl, or pyrolidin-1-yl.

In preferred embodiments, A is phenyl, substituted phenyl, pyridyl, or substituted pyridyl. Under certain circumstances, when A is pyridin-4-yl substituted with M-L at the 2 position, M-L is not (imidazol-1-yl)methyl or (morpholin-4-yl)methyl.

In preferred embodiments, B is phenyl or substituted phenyl. More preferably, B is substituted phenyl. Preferred substituents include halogens, and in particular, fluorine. Under certain circumstances, when B is unsubstituted phenyl, M-L is selected from the group consisting of M-X, M-L^1-X, M-L^1-X-L^2, M-X-L^1-X-L^2, M-X-X-, M-L^1-X-X-, M-X-X-L^2, and M-L^1-X-X-L^2. Under certain circumstances, when B is pyridin-2-yl substituted with A at the 5 position, M-L is selected from the group consisting of M-X, M-L^1-X, M-L^1-X-L^2, M-L^1-X-L^2-X, M-X-X-, M-X-X-L^2, and M-L^1-X-X-L^2.

In another aspect, the invention provides a pharmaceutical composition comprising an effective amount of one or more of the foregoing compounds and a pharmaceutically acceptable carrier. Suitable formulating agents are described in detail in section 5 hereinbelow.

One or more of the foregoing compounds may also be incorporated into a medical device. For example, a medical device, such as a medical stent, can contain or be coated with one or more of the compounds of the invention.

In another aspect, the invention provides a method for treating a microbial infection, a fungal infection, a viral infection, a parasitic disease, a proliferative disease, an inflammatory disease, or a gastrointestinal motility disorder in a mammal. The method involves

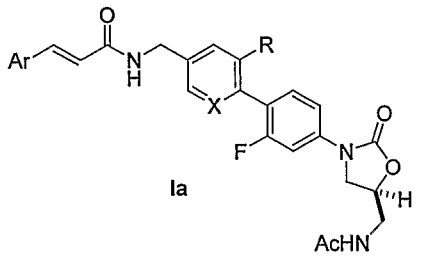
administering an effective amount of one or more compounds or pharmaceutical compositions of the invention, for example, via oral, parenteral or topical routes.

The invention provides a method of treating a disorder in a mammal comprising the step of administering to the mammal an effective amount of one or more compounds of the invention thereby to ameliorate a symptom of a particular disorder. Such a disorder can be selected from the group consisting of a skin infection, nosocomial pneumonia, post-viral pneumonia, an abdominal infection, a urinary tract infection, bacteremia, septicemia, endocarditis, an atrio-ventricular shunt infection, a vascular access infection, meningitis, surgical prophylaxis, a peritoneal infection, a bone infection, a joint infection, a methicillin-resistant *Staphylococcus aureus* infection, a vancomycin-resistant *Enterococci* infection, a linezolid-resistant organism infection, and tuberculosis.

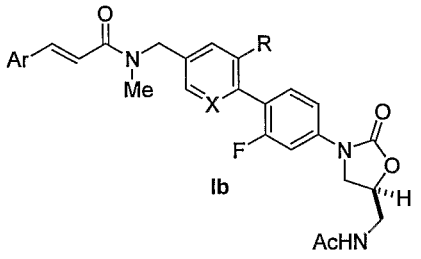
3. Synthesis of the Compounds of the Invention

The invention provides methods and intermediates for making compounds of the present invention. The following schemes depict some exemplary chemistries available for synthesizing the compounds of the invention. It will be appreciated, however, that the desired compounds may be synthesized using other alternative chemistries known in the art.

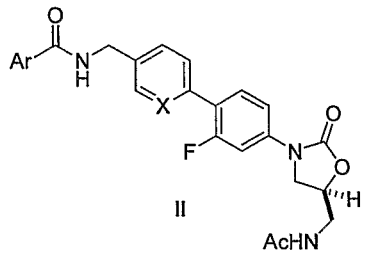
The following examples illustrate some of the compounds of the present invention. Compounds of general structures Ia through IVb (wherein X is CH or N) can be synthesized by the chemistries exemplified below in the following schemes.



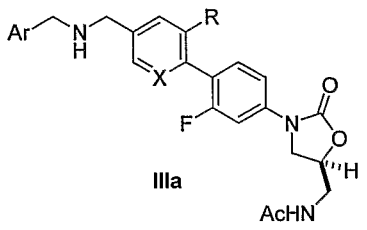
Ia



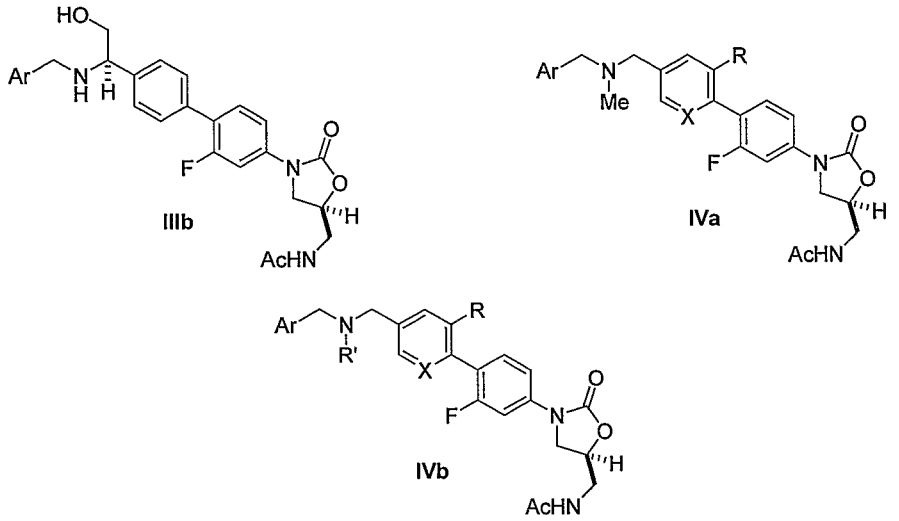
Ib



II

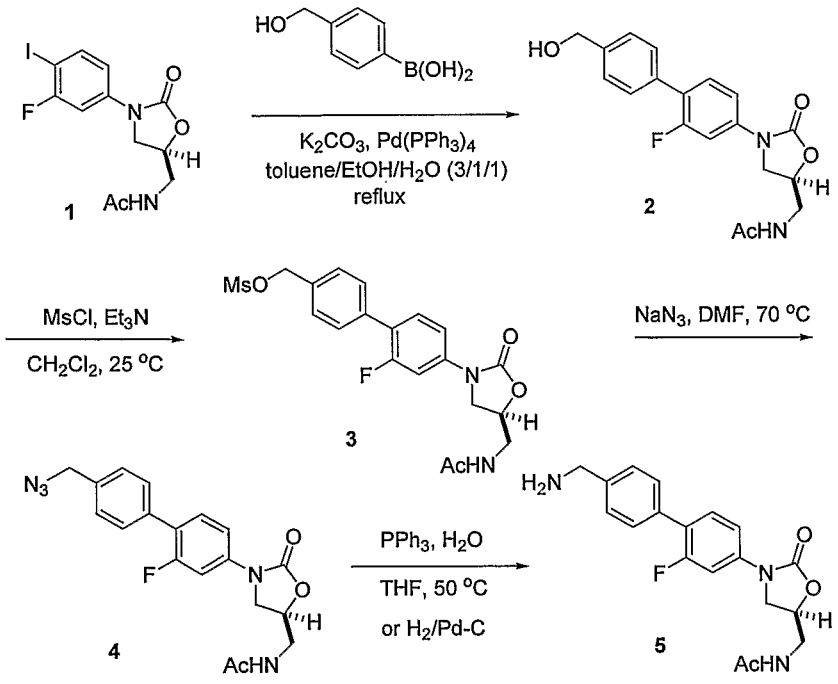


IIIa



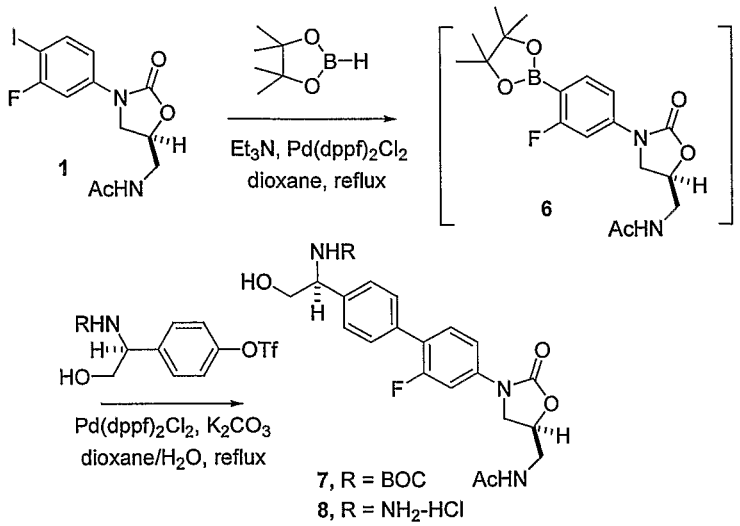
Scheme A exemplifies the synthesis of biaryl amine intermediate **5**, which is useful in producing certain compounds of the present invention. Known iodoaryl oxazolidinone intermediate **1** (*see* U.S. Patent Nos. 5,523,403 and 5,565,571) is coupled to a substituted aryl boronic acid (the Suzuki reaction) to produce biaryl alcohol **2**. Other coupling reactions (for example, the Stille reaction) using alternate coupling intermediates easily obtained or synthesized by those skilled in the art could also be employed to synthesize target biaryl intermediates similar to **2**. These alternate coupling reactions are within the scope of the present invention. Alcohol **2** is then converted to amine **5** by chemistry well known to those skilled in the art.

Scheme A



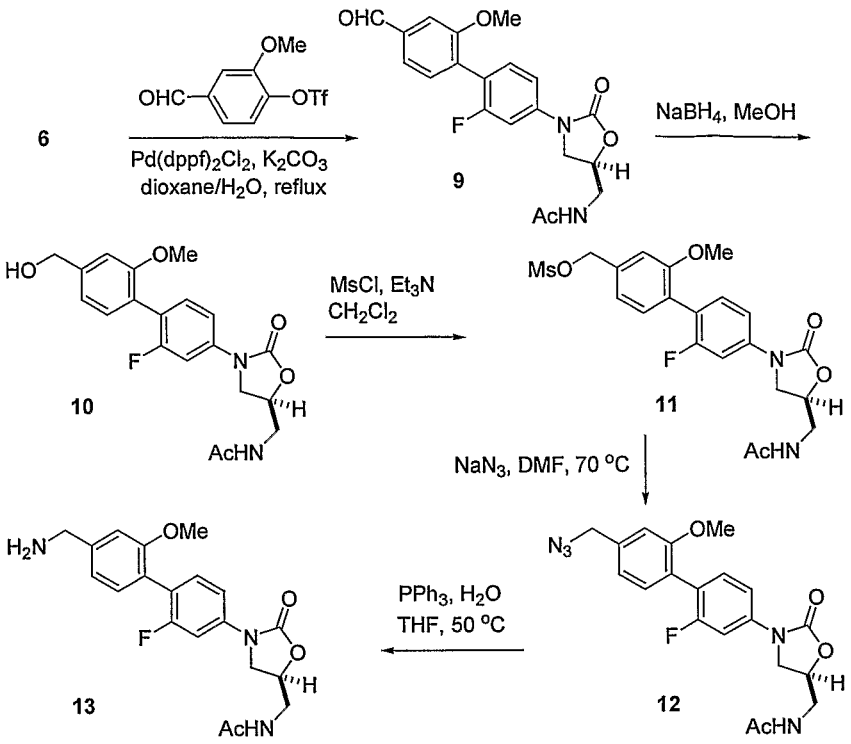
Scheme B illustrates the synthesis of intermediates **7** and **8** of the present invention using Suzuki coupling chemistry between boronic acids and aryl triflates. Boronic ester **6** is treated with an appropriate aryl triflate to yield the BOC-protected biaryl **7**. The BOC group of **7** is removed to provide amine **8**, an intermediate useful in the synthesis of certain compounds of the present invention.

Scheme B



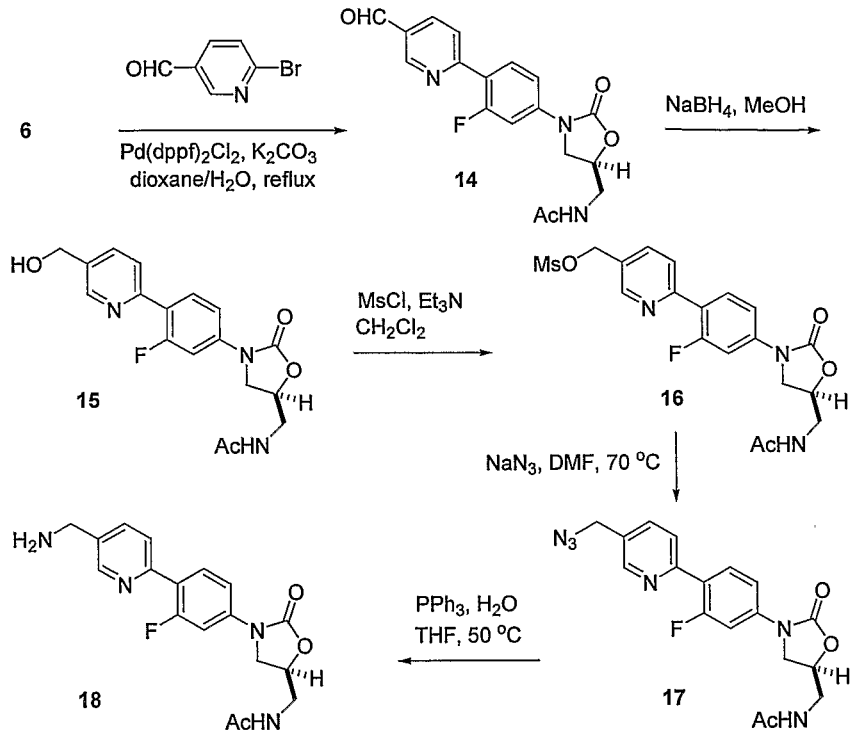
Scheme C depicts the synthesis of intermediates **9-13**, which are useful in producing certain methoxy-substituted biaryl derivatives of the present invention. Suzuki coupling of boronic ester **6** produces biaryl aldehyde **9**, which can be reduced to alcohol **10**. Mesylation of **10** yields **11** that can be converted to azide **12**. Reduction of azide **12** yields amine **13**.

Scheme C



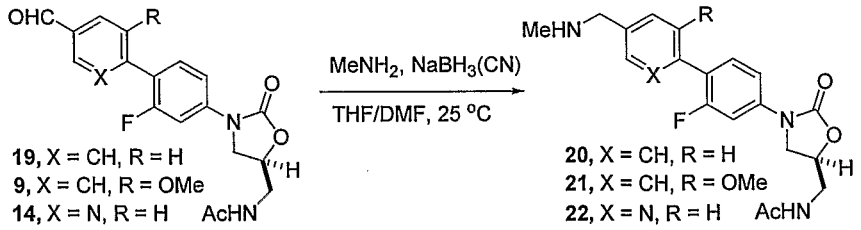
Scheme D depicts the synthesis of pyridyl intermediates, which are useful for the synthesis of compounds of the present invention, via similar chemistry to that shown in Scheme C. Coupling of boronic ester **6** to a halopyridine aldehyde produces biaryl aldehyde **14**. Aldehyde **14** serves as the precursor to intermediates **15-18** via chemistry described above.

Scheme D



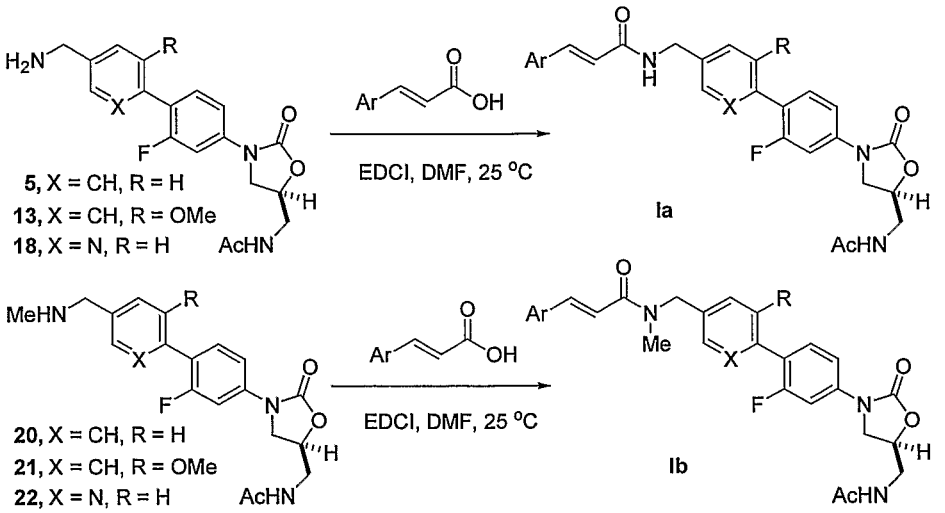
Biaryl aldehyde **19** (Scheme E) can be synthesized from a Suzuki coupling of iodide **1** and 4-formylphenylboronic acid. Scheme E illustrates how intermediate aldehydes of type **19**, **9**, and **14** can be converted via reductive amination chemistry to other amines, such as amines **20-22**, which are useful as intermediates for the synthesis of certain compounds of the invention.

Scheme E



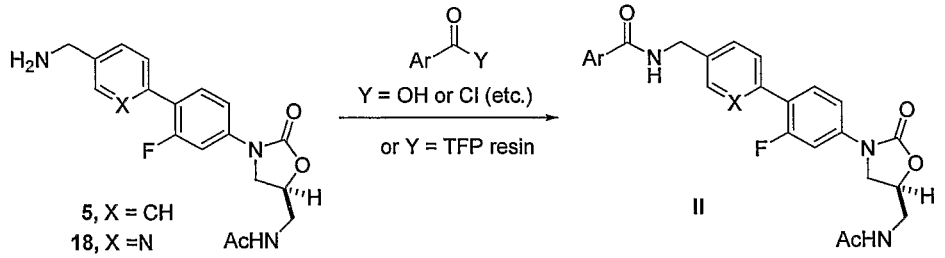
Scheme F depicts the general synthesis of compounds of type Ia and Ib from amines of type **5**, **13**, **18**, and **20-22**. Compounds of type Ia and Ib are synthesized via acylation of amines **5**, **13** and **18** and **20-22** with the appropriate acids using, for example, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) as the coupling agent. Compounds **4001-4007** were specifically synthesized from amine **5** and the appropriate carboxylic acids.

Scheme F



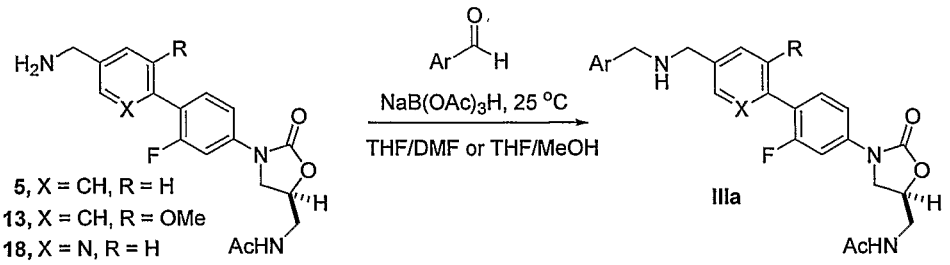
Scheme G highlights the synthesis of compounds of general structure II from amines of type **5** and **18**. The amine can be acylated with carboxylic acids using EDCI (or other commonly employed peptide coupling reagents known in the art) to afford amides II. Acid chlorides can be purchased or synthesized and allowed to react with amines **5** and **18**, in the presence of bases such as triethylamine, to also produce amides II. Alternatively, carboxylic acids can be pre-loaded onto a solid polymeric support, such as a tetrafluorophenol containing resin (TFP resin), and reacted with amines to yield amide products of general structure II (such as compounds **4008-4015**).

Scheme G



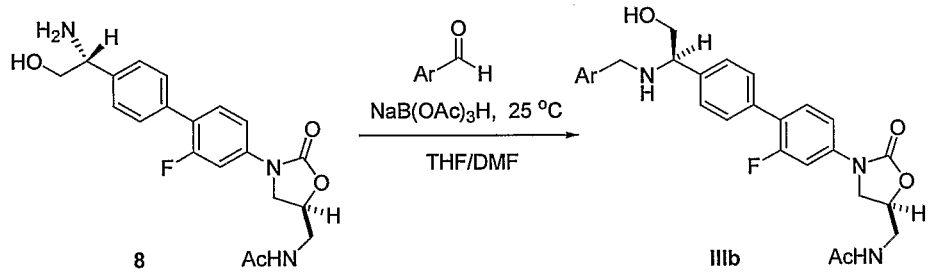
Scheme H illustrates the synthesis of compounds of general structure IIIa from amines of type **5**, **13**, and **18** using reductive amination chemistry. For example, biaryl amine compounds **4016-4028** are synthesized in this manner.

Scheme H



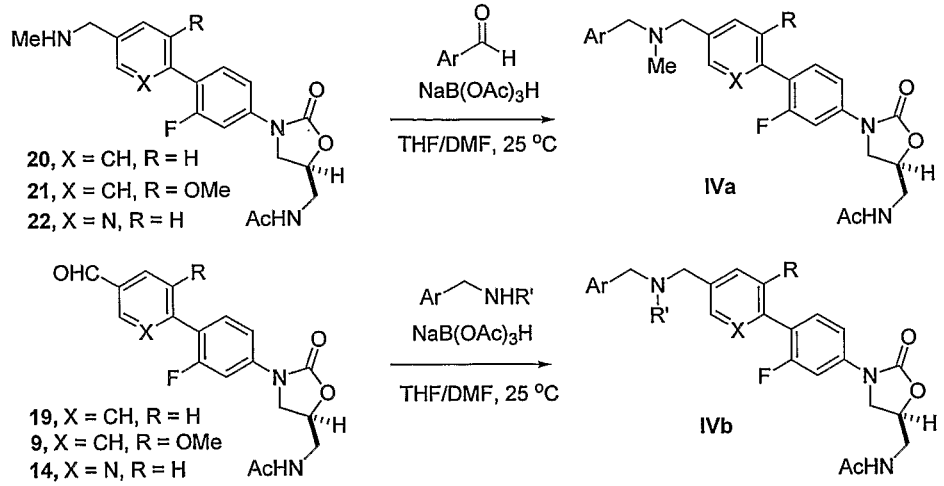
Scheme I depicts the synthesis of general structure IIIb of the present invention from amine intermediate **8**. For example, compounds **4029-4031** are synthesized using this reductive amination chemistry.

Scheme I



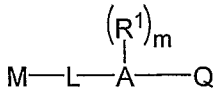
Scheme J shows the synthesis of compounds of general structure IVa and IVb. Amines **20**, **21**, and **22** can be converted to tertiary amines IVa, such as compounds **4032-4034** and **4036**, using standard reductive amination chemistry employed earlier for other derivatives. This reductive amination chemistry can be employed on biaryl aldehyde intermediates such as **19**, **9**, and **14** to yield optionally substituted amines of general structure IVb, illustrated by compound **4037**.

Scheme J

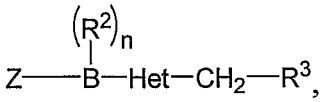


It should be noted that, when X is N, any of the synthetic routes described above may be used to produce compounds having any regioisomer of pyridine (e.g., pyridin-2-yl or pyridin-3-yl).

In addition, the invention provides alternative approaches for synthesizing compounds of the invention. In one approach, the method includes the step of combining a compound of formula (I):



with a compound of formula (II):



in a solvent in the presence of a base and a palladium catalyst, wherein

Q is a boronate having the formula $-BY_2$, wherein

Y, at each occurrence, independently is selected from the group consisting of:

a) –OH, and b) –O-C_{1-4} alkyl,

alternatively, two Y groups taken together are selected from the group consisting of:

a) -$OC(R^4)(R^4)C(R^4)(R^4)O$-, and b) -$OC(R^4)(R^4)CH_2C(R^4)(R^4)O$-,

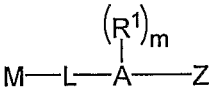
alternatively, two Y groups taken together with the boron to which they are bound comprise a BF_3 alkali metal salt;

Z is selected from the group consisting of:

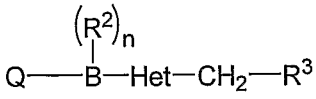
a) I, b) Br, c) Cl, and d) R^4OSO_3-; and

A, B, Het, L, M, R^1, R^2, R^3, R^4, m, and n are defined as described above.

In another approach, the method includes the step of combining a compound of formula (III):

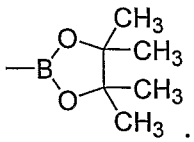


with a compound of formula (IV):



in a solvent in the presence of a base and a palladium catalyst, wherein A, B, Het, L, M, R^1, R^2, R^3, R^4, Q, Z, m, and n are defined as described above.

In either approach, Z can be I. Furthermore, Q can be $-BF_2 \cdot KF$ or



In some embodiments, the base is selected from the group consisting of an alkali metal hydroxide, an alkali metal carbonate, an alkali metal fluoride, a trialkyl amine, and mixtures thereof. Examples of suitable bases include potassium carbonate, sodium carbonate, potassium fluoride, triethylamine, diisopropylethylamine, and mixtures thereof. In particular embodiments, the ratio of equivalents of base to equivalents of compound (I) or compound (III) is about 3:1.

In some embodiments, the palladium catalyst is a ligand coordinated palladium (0) catalyst, such as a tetrakis(trialkylphosphine) palladium (0) or a tetrakis(triarylphosphine) palladium (0) catalyst. An example of a suitable palladium catalyst is tetrakis(triphenylphosphine) palladium (0). In particular embodiments, the ratio of the equivalents of tetrakis(triphenylphosphine) palladium (0) to the equivalents of compound (I) or compound (III) is about 1:20.

In some embodiments, the solvent comprises an aqueous solvent. In other embodiments, the solvent comprises a mixture of water and an organic solvent, wherein the organic solvent is selected from the group consisting of methanol, ethanol, propanol, isopropanol, butanol, isobutanol, secondary butanol, tertiary butanol, benzene, toluene, tetrahydrofuran, dimethylformamide, 1,2-diethyl ether, dimethoxyethane, diisopropyl ether, methyltertiarybutyl ether, methoxymethyl ether, 2-methoxyethyl ether, 1,4-dioxane, 1,3-dioxolane, and mixtures thereof. In a particular embodiment, the solvent is a mixture of water, toluene, and ethanol in a ratio, for example, of about 1:3:1 by volume.

In some embodiments, the method is carried out at a temperature between about 20 °C and about 100 °C. In other embodiments, the process is carried out at the reflux temperature of the solvent.

4. Characterization of Compounds of the Invention

Compounds designed, selected and/or optimized by methods described above, once produced, may be characterized using a variety of assays known to those skilled in the art to determine whether the compounds have biological activity. For example, the molecules may be characterized by conventional assays, including but not limited to those assays described below, to determine whether they have a predicted activity, binding activity and/or binding specificity.

Furthermore, high-throughput screening may be used to speed up analysis using such assays. As a result, it may be possible to rapidly screen the molecules described herein for activity, for example, as anti-cancer, anti-bacterial, anti-fungal, anti-parasitic or anti-viral agents. Also, it may be possible to assay how the compounds interact with a ribosome or ribosomal subunit and/or are effective as modulators (for example, inhibitors) of protein synthesis using techniques known in the art. General methodologies for performing high-throughput screening are described, for example, in Devlin, *High Throughput Screening*, (Marcel Dekker, 1998); and U.S. Patent No. 5,763,263. High-throughput assays can use one or more different assay techniques including, but not limited to, those described below.

(1) *Surface Binding Studies*. A variety of binding assays may be useful in screening new molecules for their binding activity. One approach includes surface plasmon resonance (SPR) that can be used to evaluate the binding properties of molecules of interest with respect to a ribosome, ribosomal subunit or a fragment thereof.

SPR methodologies measure the interaction between two or more macromolecules in real-time through the generation of a quantum-mechanical surface plasmon. One device, (BIAcore Biosensor RTM from Pharmacia Biosensor, Piscatawy, N.J.) provides a focused beam of polychromatic light to the interface between a gold film (provided as a disposable biosensor "chip") and a buffer compartment that can be regulated by the user. A 100 nm thick "hydrogel" composed of carboxylated dextran that provides a matrix for the covalent immobilization of analytes of interest is attached to the gold film. When the focused light interacts with the free electron cloud of the gold film, plasmon resonance is enhanced. The resulting reflected light is spectrally depleted in wavelengths that optimally evolved the resonance. By separating the reflected polychromatic light into its component wavelengths (by means of a prism), and determining the frequencies that are depleted, the BIAcore establishes an optical interface which accurately reports the behavior of the generated surface plasmon

resonance. When designed as above, the plasmon resonance (and thus the depletion spectrum) is sensitive to mass in the evanescent field (which corresponds roughly to the thickness of the hydrogel). If one component of an interacting pair is immobilized to the hydrogel, and the interacting partner is provided through the buffer compartment, the interaction between the two components can be measured in real time based on the accumulation of mass in the evanescent field and its corresponding effects of the plasmon resonance as measured by the depletion spectrum. This system permits rapid and sensitive real-time measurement of the molecular interactions without the need to label either component.

(2) *Fluorescence Polarization.* Fluorescence polarization (FP) is a measurement technique that can readily be applied to protein-protein, protein-ligand, or RNA-ligand interactions in order to derive IC_{50}s and Kds of the association reaction between two molecules. In this technique one of the molecules of interest is conjugated with a fluorophore. This is generally the smaller molecule in the system (in this case, the compound of interest). The sample mixture, containing both the ligand-probe conjugate and the ribosome, ribosomal subunit or fragment thereof, is excited with vertically polarized light. Light is absorbed by the probe fluorophores, and re-emitted a short time later. The degree of polarization of the emitted light is measured. Polarization of the emitted light is dependent on several factors, but most importantly on viscosity of the solution and on the apparent molecular weight of the fluorophore. With proper controls, changes in the degree of polarization of the emitted light depends only on changes in the apparent molecular weight of the fluorophore, which in-turn depends on whether the probe-ligand conjugate is free in solution, or is bound to a receptor. Binding assays based on FP have a number of important advantages, including the measurement of IC_{50}s and Kds under true homogenous equilibrium conditions, speed of analysis and amenity to automation, and ability to screen in cloudy suspensions and colored solutions.

(3) *Protein Synthesis.* It is contemplated that, in addition to characterization by the foregoing biochemical assays, the compound of interest may also be characterized as a modulator (for example, an inhibitor of protein synthesis) of the functional activity of the ribosome or ribosomal subunit.

Furthermore, more specific protein synthesis inhibition assays may be performed by administering the compound to a whole organism, tissue, organ, organelle, cell, a cellular or subcellular extract, or a purified ribosome preparation and observing its pharmacological and

inhibitory properties by determining, for example, its inhibition constant (IC_{50}) for inhibiting protein synthesis. Incorporation of ^{3}H leucine or ^{35}S methionine, or similar experiments can be performed to investigate protein synthesis activity. A change in the amount or the rate of protein synthesis in the cell in the presence of a molecule of interest indicates that the molecule is a modulator of protein synthesis. A decrease in the rate or the amount of protein synthesis indicates that the molecule is a inhibitor of protein synthesis.

Furthermore, the compounds may be assayed for anti-proliferative or anti-infective properties on a cellular level. For example, where the target organism is a microorganism, the activity of compounds of interest may be assayed by growing the microorganisms of interest in media either containing or lacking the compound. Growth inhibition may be indicative that the molecule may be acting as a protein synthesis inhibitor. More specifically, the activity of the compounds of interest against bacterial pathogens may be demonstrated by the ability of the compound to inhibit growth of defined strains of human pathogens. For this purpose, a panel of bacterial strains can be assembled to include a variety of target pathogenic species, some containing resistance mechanisms that have been characterized. Use of such a panel of organisms permits the determination of structure-activity relationships not only in regards to potency and spectrum, but also with a view to obviating resistance mechanisms. The assays may be performed in microtiter trays according to conventional methodologies as published by The National Committee for Clinical Laboratory Standards (NCCLS) guidelines (NCCLS. M7-A5-Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard-Fifth Edition. NCCLS Document M100-S12/M7 (ISBN 1-56238-394-9)).

5. Formulation and Administration

The compounds of the invention may be useful in the prevention or treatment of a variety of human or other animal disorders, including for example, bacterial infection, fungal infections, viral infections, parasitic diseases, and cancer. It is contemplated that, once identified, the active molecules of the invention may be incorporated into any suitable carrier prior to use. The dose of active molecule, mode of administration and use of suitable carrier will depend upon the intended recipient and target organism. The formulations, both for veterinary and for human medical use, of compounds according to the present invention typically include such compounds in association with a pharmaceutically acceptable carrier.

The carrier(s) should be "acceptable" in the sense of being compatible with the other ingredients of the formulations and not deleterious to the recipient. Pharmaceutically acceptable carriers, in this regard, are intended to include any and all solvents, dispersion media, coatings, anti-bacterial and anti-fungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds (identified or designed according to the invention and/or known in the art) also can be incorporated into the compositions. The formulations may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy/microbiology. In general, some formulations are prepared by bringing the compound into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation.

A pharmaceutical composition of the invention should be formulated to be compatible with its intended route of administration. Examples of routes of administration include oral or parenteral, for example, intravenous, intradermal, inhalation, transdermal (topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide.

Useful solutions for oral or parenteral administration can be prepared by any of the methods well known in the pharmaceutical art, described, for example, in *Remington's Pharmaceutical Sciences*, 18th ed. (Mack Publishing Company, 1990). Formulations for parenteral administration can also include glycocholate for buccal administration, methoxysalicylate for rectal administration, or citric acid for vaginal administration. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic. Suppositories for rectal administration also can be prepared by mixing

the drug with a non-irritating excipient such as cocoa butter, other glycerides, or other compositions which are solid at room temperature and liquid at body temperatures. Formulations also can include, for example, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, and hydrogenated naphthalenes. Formulations for direct administration can include glycerol and other compositions of high viscosity. Other potentially useful parenteral carriers for these drugs include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, and liposomes. Formulations for inhalation administration can contain as excipients, for example, lactose, or can be aqueous solutions containing, for example, polyoxyethylene-9-lauryl ether, glycocholate and deoxycholate, or oily solutions for administration in the form of nasal drops, or as a gel to be applied intranasally. Retention enemas also can be used for rectal delivery.

Formulations of the present invention suitable for oral administration may be in the form of: discrete units such as capsules, gelatin capsules, sachets, tablets, troches, or lozenges, each containing a predetermined amount of the drug; a powder or granular composition; a solution or a suspension in an aqueous liquid or non-aqueous liquid; or an oil-in-water emulsion or a water-in-oil emulsion. The drug may also be administered in the form of a bolus, electuary or paste. A tablet may be made by compressing or molding the drug optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the drug in a free-flowing form such as a powder or granules, optionally mixed by a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding, in a suitable machine, a mixture of the powdered drug and suitable carrier moistened with an inert liquid diluent.

Oral compositions generally include an inert diluent or an edible carrier. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients. Oral compositions prepared using a fluid carrier for use as a mouthwash include the compound in the fluid carrier and are applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose; a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent

such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor ELTM (BASF, Parsippany, NJ) or phosphate buffered saline (PBS). It should be stable under the conditions of manufacture and storage and should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyetheylene glycol), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filter sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation include vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Formulations suitable for intra-articular administration may be in the form of a sterile aqueous preparation of the drug that may be in microcrystalline form, for example, in the form of an aqueous microcrystalline suspension. Liposomal formulations or biodegradable polymer systems may also be used to present the drug for both intra-articular and ophthalmic administration.

Formulations suitable for topical administration, including eye treatment, include liquid or semi-liquid preparations such as liniments, lotions, gels, applicants, oil-in-water or water-in-

oil emulsions such as creams, ointments or pastes; or solutions or suspensions such as drops. Formulations for topical administration to the skin surface can be prepared by dispersing the drug with a dermatologically acceptable carrier such as a lotion, cream, ointment or soap. Particularly useful are carriers capable of forming a film or layer over the skin to localize application and inhibit removal. For topical administration to internal tissue surfaces, the agent can be dispersed in a liquid tissue adhesive or other substance known to enhance adsorption to a tissue surface. For example, hydroxypropylcellulose or fibrinogen/thrombin solutions can be used to advantage. Alternatively, tissue-coating solutions, such as pectin-containing formulations can be used.

For inhalation treatments, inhalation of powder (self-propelling or spray formulations) dispensed with a spray can, a nebulizer, or an atomizer can be used. Such formulations can be in the form of a fine powder for pulmonary administration from a powder inhalation device or self-propelling powder-dispensing formulations. In the case of self-propelling solution and spray formulations, the effect may be achieved either by choice of a valve having the desired spray characteristics (*i.e.,* being capable of producing a spray having the desired particle size) or by incorporating the active ingredient as a suspended powder in controlled particle size. For administration by inhalation, the compounds also can be delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable propellant, *e.g.,* a gas such as carbon dioxide, or a nebulizer.

Systemic administration also can be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants generally are known in the art, and include, for example, for transmucosal administration, detergents and bile salts. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds typically are formulated into ointments, salves, gels, or creams as generally known in the art.

The active compounds may be prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. Liposomal suspensions can also be used as

pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811.

Oral or parenteral compositions can be formulated in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals. Furthermore, administration can be by periodic injections of a bolus, or can be made more continuous by intravenous, intramuscular or intraperitoneal administration from an external reservoir (*e.g.*, an intravenous bag).

Where adhesion to a tissue surface is desired the composition can include the drug dispersed in a fibrinogen-thrombin composition or other bioadhesive. The compound then can be painted, sprayed or otherwise applied to the desired tissue surface. Alternatively, the drugs can be formulated for parenteral or oral administration to humans or other mammals, for example, in effective amounts, *e.g.*, amounts that provide appropriate concentrations of the drug to target tissue for a time sufficient to induce the desired effect.

Where the active compound is to be used as part of a transplant procedure, it can be provided to the living tissue or organ to be transplanted prior to removal of tissue or organ from the donor. The compound can be provided to the donor host. Alternatively or, in addition, once removed from the donor, the organ or living tissue can be placed in a preservation solution containing the active compound. In all cases, the active compound can be administered directly to the desired tissue, as by injection to the tissue, or it can be provided systemically, either by oral or parenteral administration, using any of the methods and formulations described herein and/or known in the art. Where the drug comprises part of a tissue or organ preservation solution, any commercially available preservation solution can be used to advantage. For example, useful solutions known in the art include Collins solution, Wisconsin solution, Belzer solution, Eurocollins solution and lactated Ringer's solution.

Active compound as identified or designed by the methods described herein can be administered to individuals to treat disorders (prophylactically or therapeutically). In

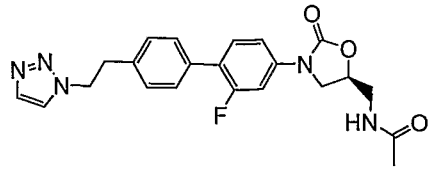
conjunction with such treatment, pharmacogenomics (*i.e.*, the study of the relationship between an individual's genotype and that individual's response to a foreign compound or drug) may be considered. Differences in metabolism of therapeutics can lead to severe toxicity or therapeutic failure by altering the relation between dose and blood concentration of the pharmacologically active drug. Thus, a physician or clinician may consider applying knowledge obtained in relevant pharmacogenomics studies in determining whether to administer a drug as well as tailoring the dosage and/or therapeutic regimen of treatment with the drug.

In therapeutic use for treating, or combating, bacterial infections in mammals, the compounds or pharmaceutical compositions thereof will be administered orally, parenterally and/or topically at a dosage to obtain and maintain a concentration, that is, an amount, or blood-level or tissue level of active component in the animal undergoing treatment which will be anti-microbially effective. The term "effective amount" is understood to mean that the compound of the invention is present in or on the recipient in an amount sufficient to elicit biological activity, for example, anti-microbial activity, anti-fungal activity, anti-viral activity, anti-parasitic activity, and/or anti-proliferative activity. Generally, an effective amount of dosage of active component will be in the range of from about 0.1 to about 100, more preferably from about 1.0 to about 50 mg/kg of body weight/day. The amount administered will also likely depend on such variables as the type and extent of disease or indication to be treated, the overall health status of the particular patient, the relative biological efficacy of the compound delivered, the formulation of the drug, the presence and types of excipients in the formulation, and the route of administration. Also, it is to be understood that the initial dosage administered may be increased beyond the above upper level in order to rapidly achieve the desired blood-level or tissue level, or the initial dosage may be smaller than the optimum and the daily dosage may be progressively increased during the course of treatment depending on the particular situation. If desired, the daily dose may also be divided into multiple doses for administration, for example, two to four times per day.

6. Examples

Exemplary compounds synthesized in accordance with the invention are listed in Table 2.

Table 2

Compound Number	Structure
1001	
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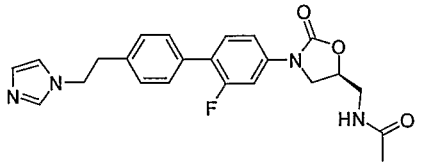
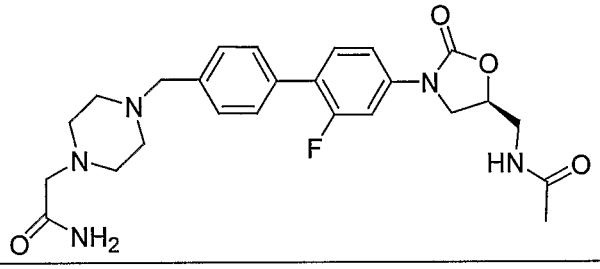
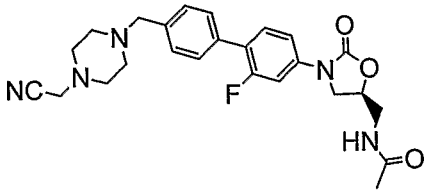
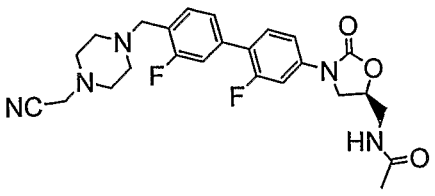
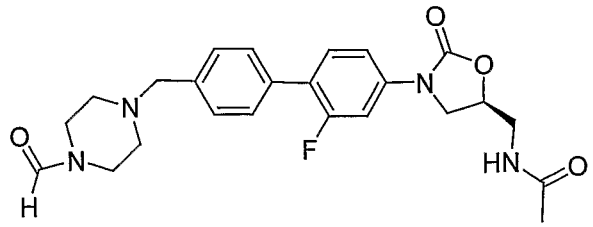
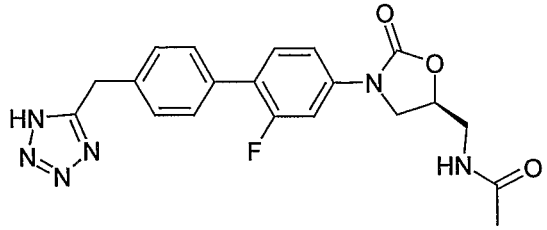
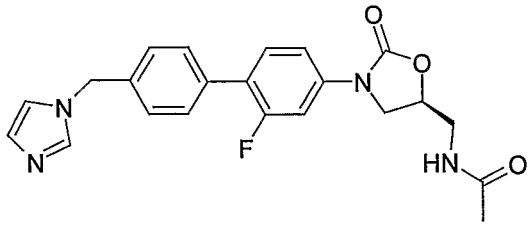
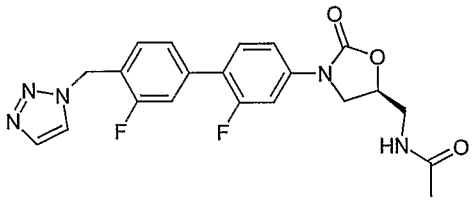
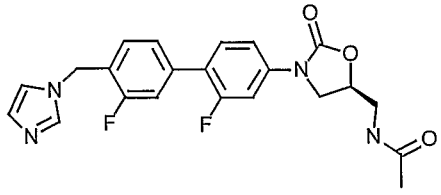
1002	
	N-{3-[2-Fluoro-4'-(2-imidazol-1-yl-ethyl)-biphenyl-4-yl]-2-oxo-oxazolidin-5-(S)-ylmethyl}-acetamide
1003	
	2-(4-{4'-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-piperazin-1-yl)-acetamide
1004	
	N-{3-[4'-(4-Cyanomethyl-piperazin-1-ylmethyl)-2-fluoro-biphenyl-4-yl]-2-oxo-oxazolidin-5-(S)-ylmethyl}-acetamide
1005	
	N-{3-[4'-(4-Cyanomethyl-piperazin-1-ylmethyl)-2,3'-difluoro-biphenyl-4-yl]-2-oxo-oxazolidin-5-(S)-ylmethyl}-acetamide

1006	
	N-{3-[2-Fluoro-4'-(4-formyl-piperazin-1-ylmethyl)-biphenyl-4-yl]-2-oxo-oxazolidin-5-(S)-ylmethyl}-acetamide
1007	
	N-{3-[2-Fluoro-4'-(1H-tetrazol-5-(S)-ylmethyl)-biphenyl-4-yl]-2-oxo-oxazolidin-5-(S)-ylmethyl}-acetamide
1008	
	N-[3-(2-Fluoro-4'-imidazol-1-ylmethyl-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
1009	
	N-[3-(2,3'-Difluoro-4'-[1,2,3]triazol-1-ylmethyl-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
1010	
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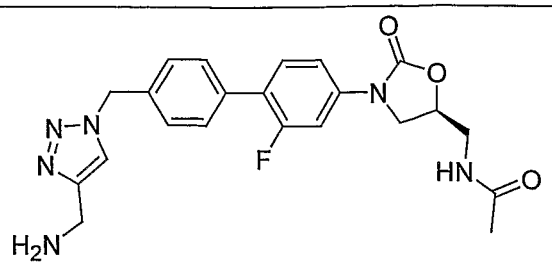
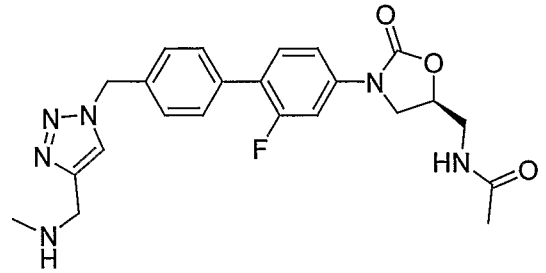
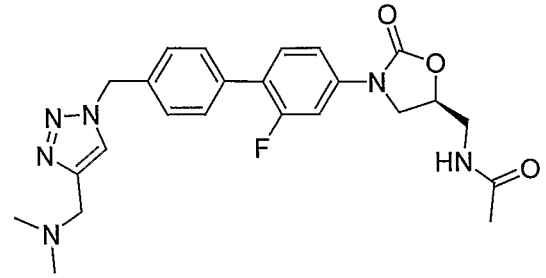
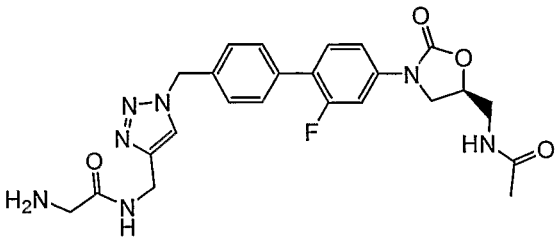
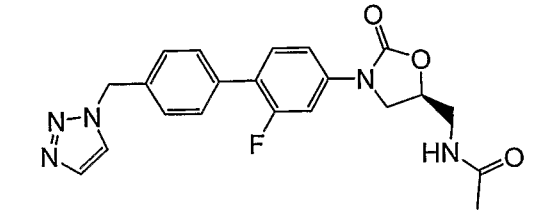
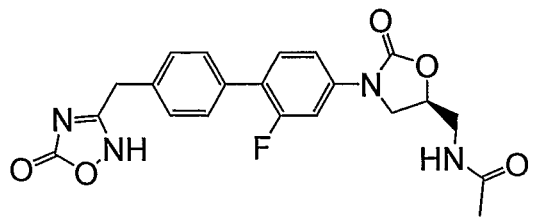
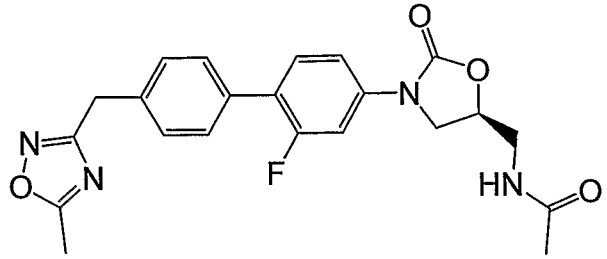
1011	
	N-{3-[4'-(4-Aminomethyl-[1,2,3]triazol-1-ylmethyl)-2-fluoro-biphenyl-4-yl]-2-oxo-oxazolidin-5-(S)-ylmethyl}-acetamide
1012	
	N-{3-[2-Fluoro-4'-(4-methylaminomethyl-[1,2,3]triazol-1-ylmethyl)-biphenyl-4-yl]-2-oxo-oxazolidin-5-(S)-ylmethyl}-acetamide
1013	
	N-{3-[4'-(4-Dimethylaminomethyl-[1,2,3]triazol-1-ylmethyl)-2-fluoro-biphenyl-4-yl]-2-oxo-oxazolidin-5-(S)-ylmethyl}-acetamide
1014	
	N-(1-{4'-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-1H-[1,2,3]triazol-4-ylmethyl)-2-amino-acetamide
1015	
	N-[3-(2-Fluoro-4'-[1,2,3]triazol-1-ylmethyl-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide

1016	
	N-{3-[2-Fluoro-4'-(5-(S)-oxo-2,5-(S)-dihydro-[1,2,4]oxadiazol-3-ylmethyl)-biphenyl-4-yl]-2-oxo-oxazolidin-5-(S)-ylmethyl}-acetamide
1017	
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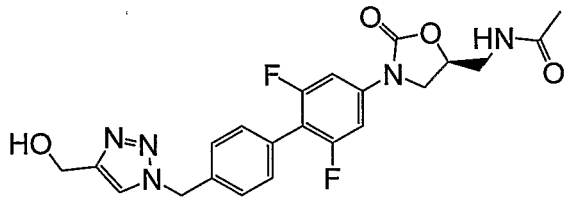
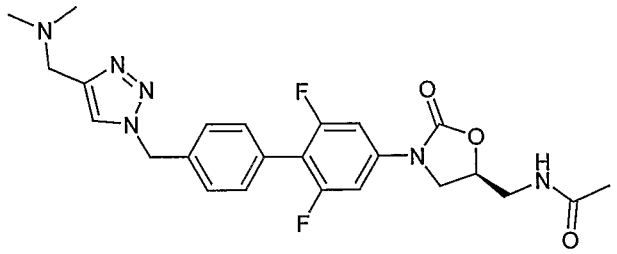
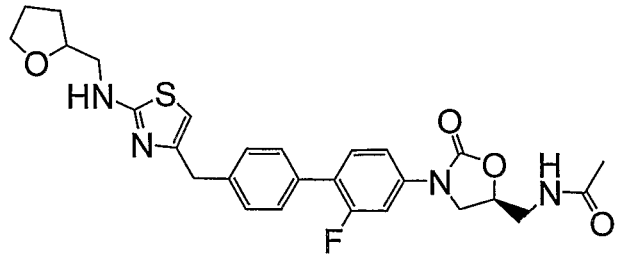
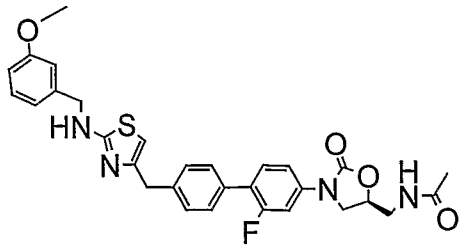
1018	
	N-{3-[2,6-Difluoro-4'-(4-hydroxymethyl-[1,2,3]triazol-1-ylmethyl)-biphenyl-4-yl]-2-oxo-oxazolidin-5-(S)-ylmethyl}-acetamide
1019	
	N-{3-[4'-(4-Dimethylaminomethyl-[1,2,3]triazol-1-ylmethyl)-2,6-difluoro-biphenyl-4-yl]-2-oxo-oxazolidin-5-(S)-ylmethyl}-acetamide
1020	
	N-[3-(2-Fluoro-4'-{2-[(tetrahydro-furan-2-ylmethyl)-amino]-thiazol-4-ylmethyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide

1021	
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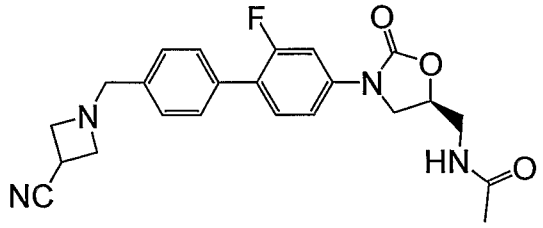
1022	
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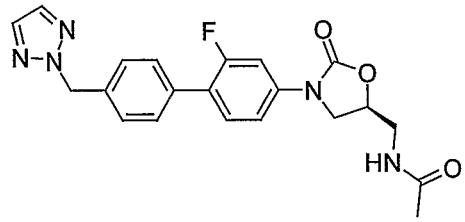
1023	
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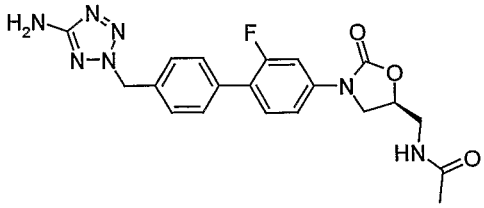
1024	
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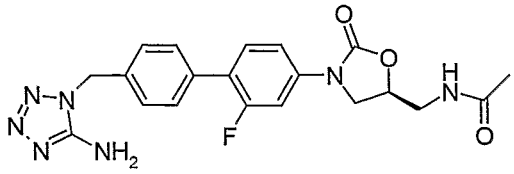
1025	
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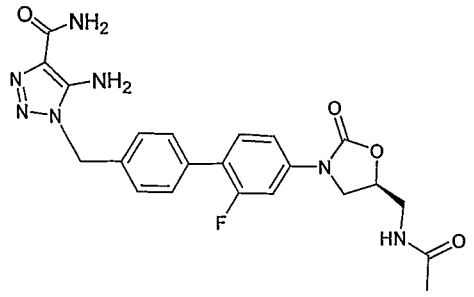
1026	
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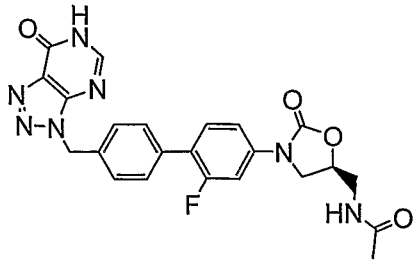
1027	
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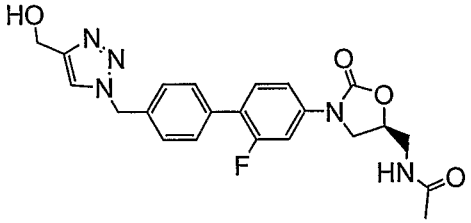
1028	
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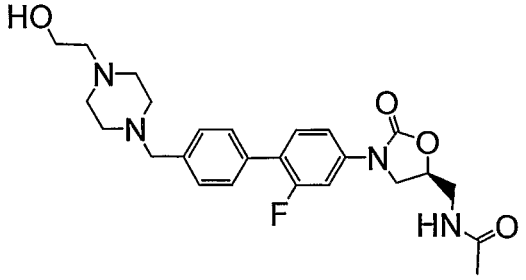
1029	
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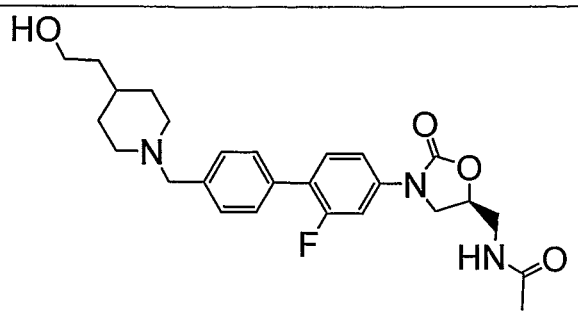
1030	
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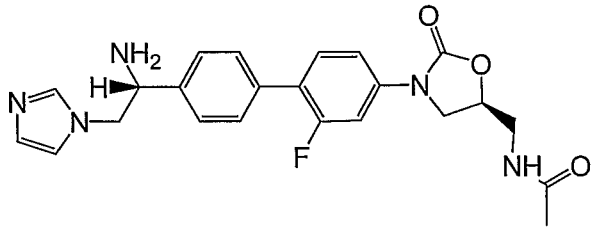
1031	
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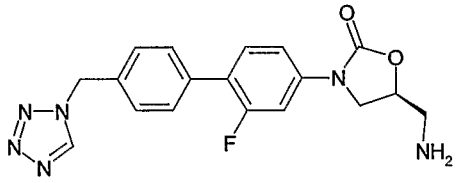
1032	
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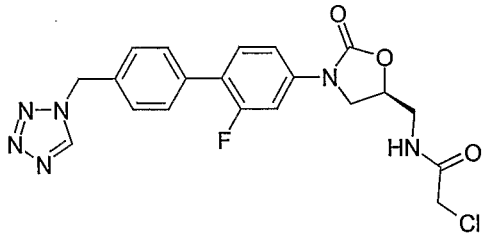
1033	
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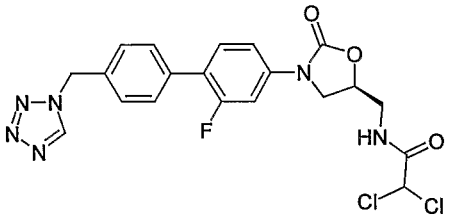
1034	
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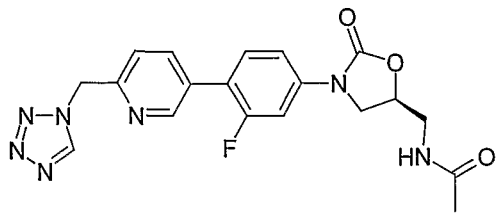
1035	
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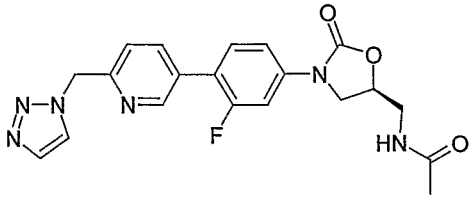
1036	
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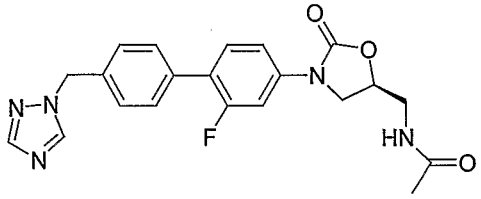
1037	
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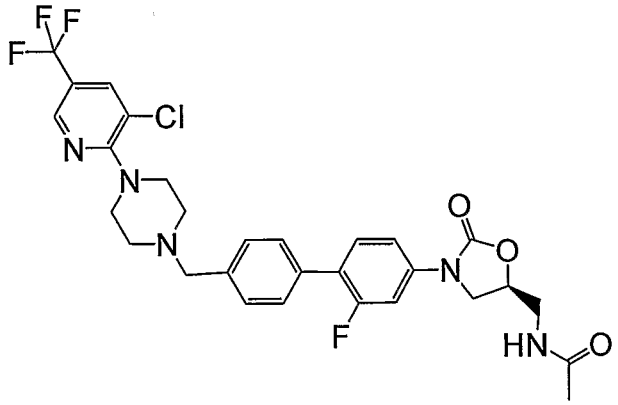
1038	
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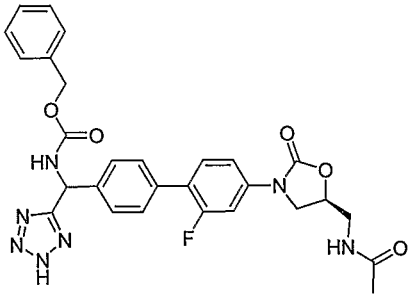
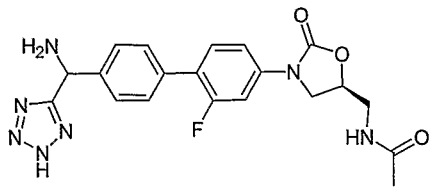
1039	

	[{4'-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-yl}-(2H-tetrazol-5-(R/S)-yl)-methyl]-carbamic acid benzyl ester
1040	
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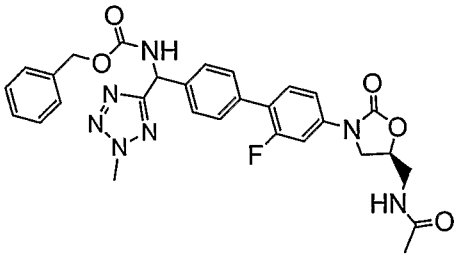
1041	
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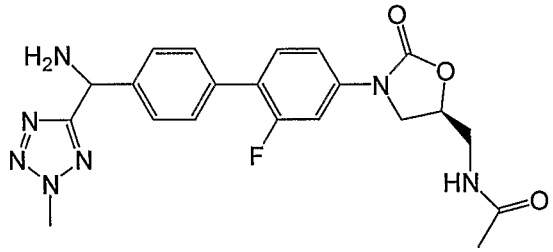
1042	
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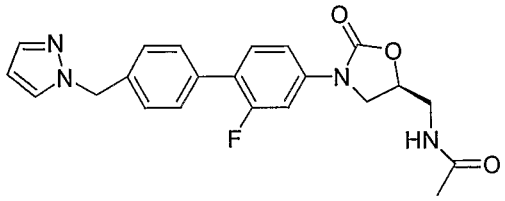
1043	
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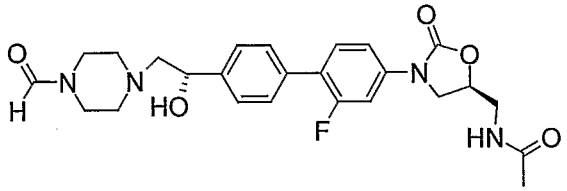
1044	
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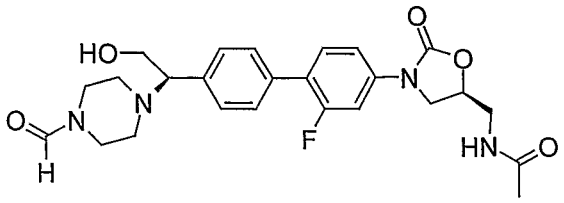
1045	
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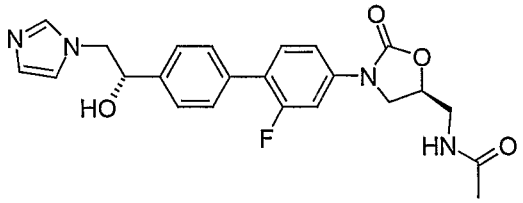
1046	
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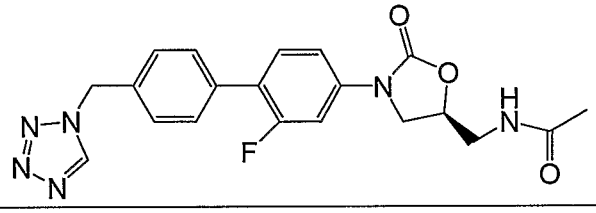
1047	
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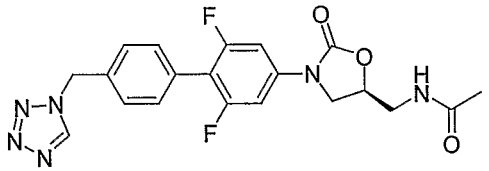
1048	
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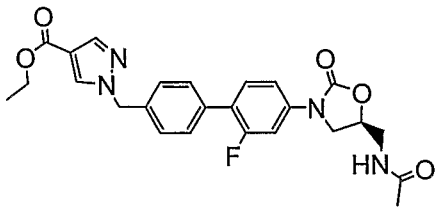
1049	
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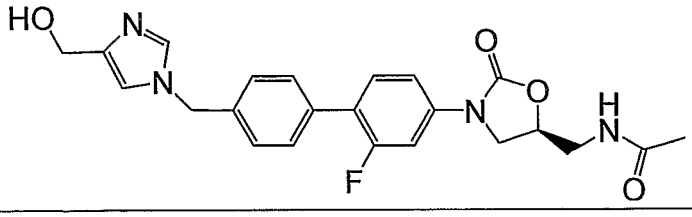
1050	

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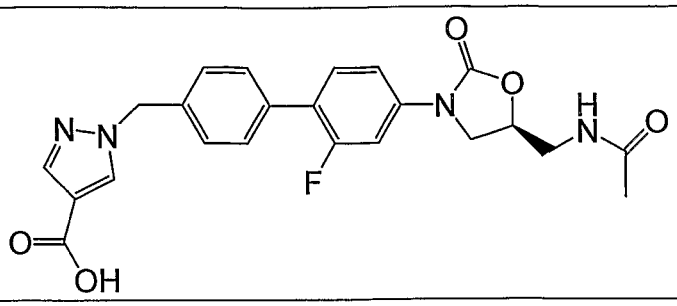
1051	
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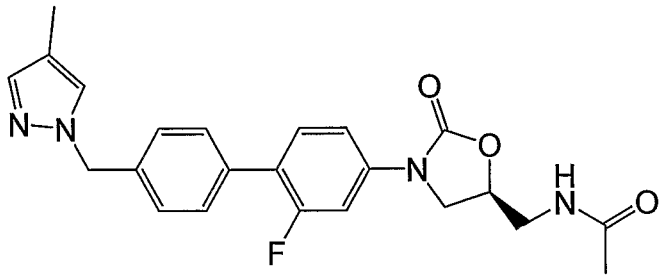
1052	
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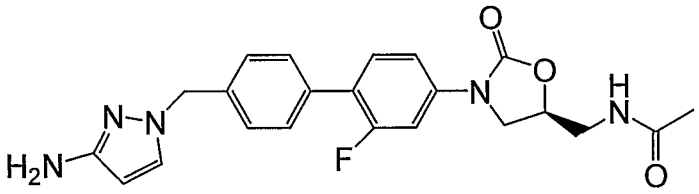
1053	
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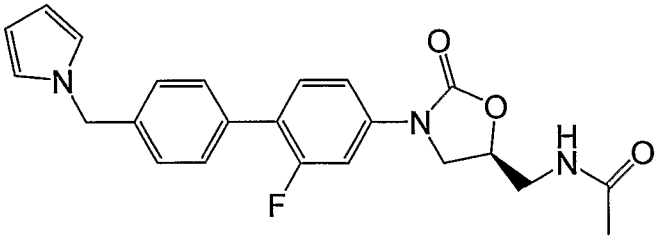
1054	
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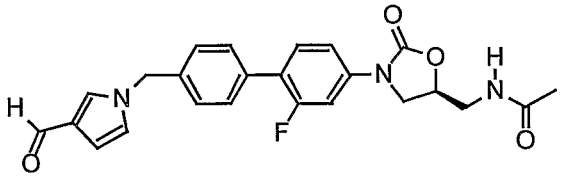
1055	
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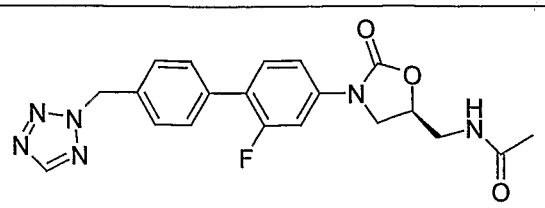
1056	
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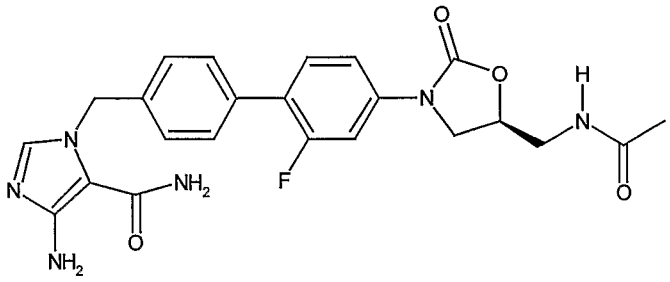
1057	
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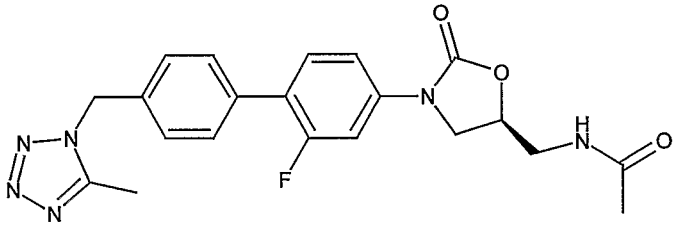
1058	
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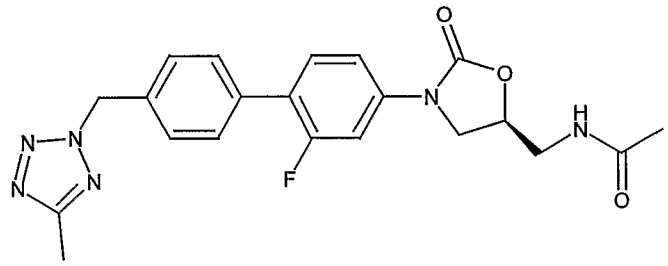
1059	
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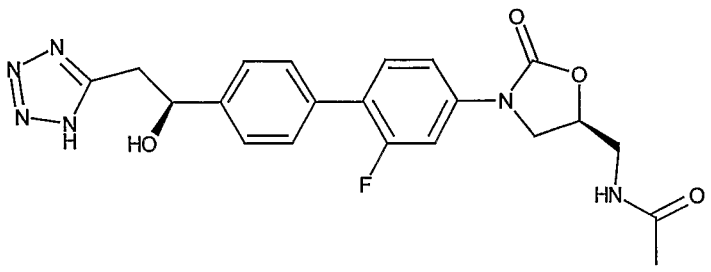
1060	

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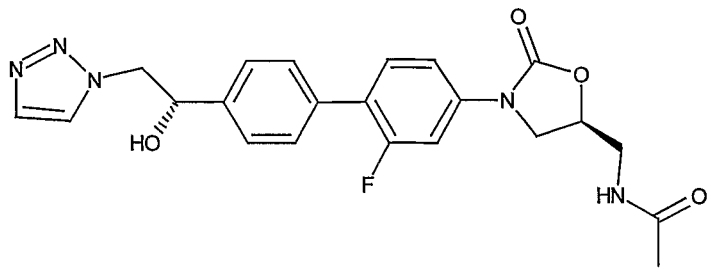
1061	
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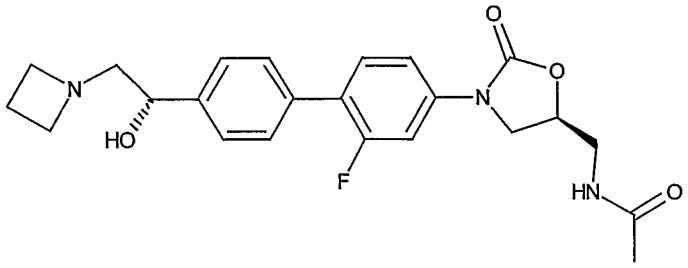
1062	
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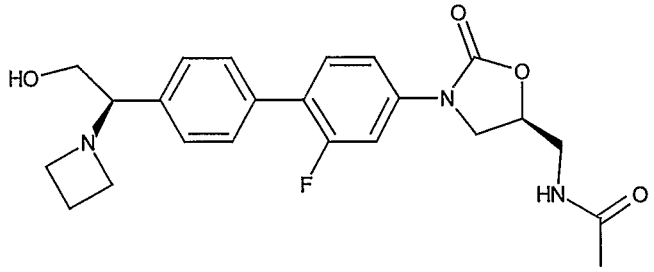
1063	
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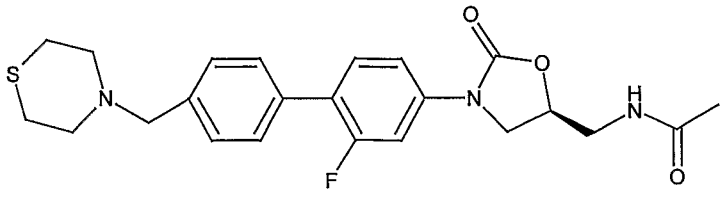
1064	
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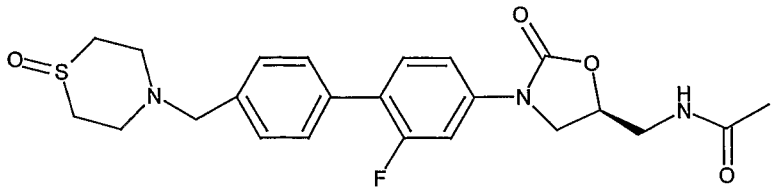
1065	
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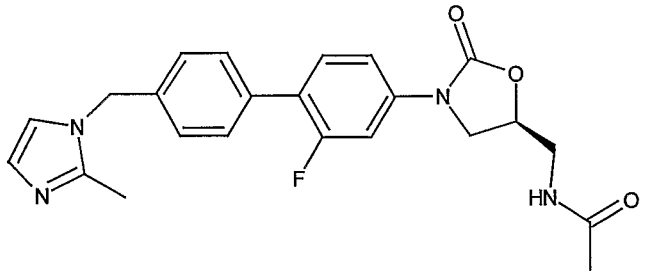
1066	
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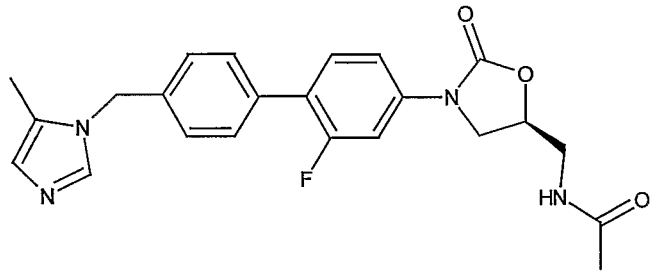
1067	
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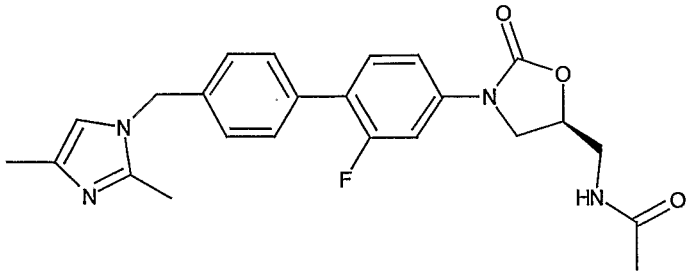
1068	
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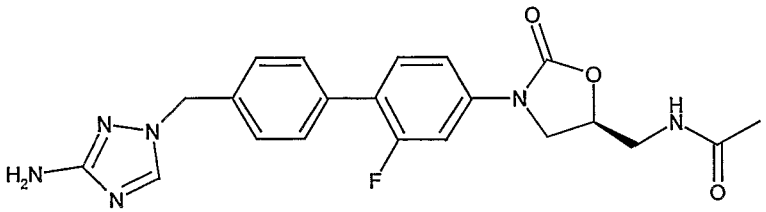
1069	

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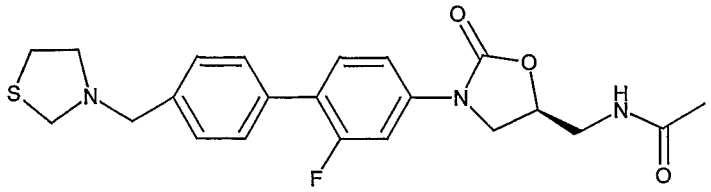
1070	
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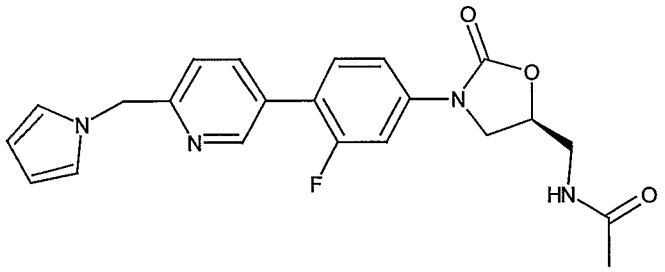
1071	
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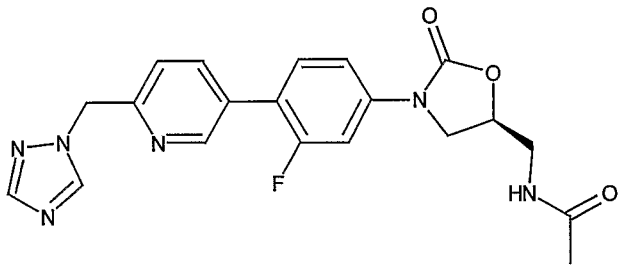
1072	
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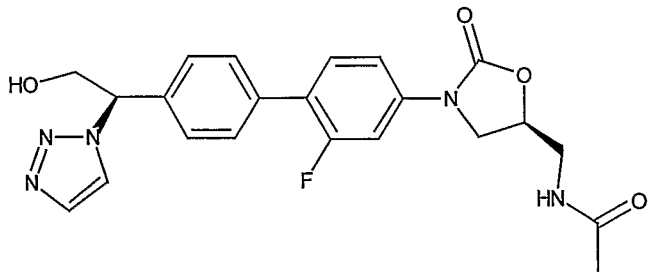
1073	
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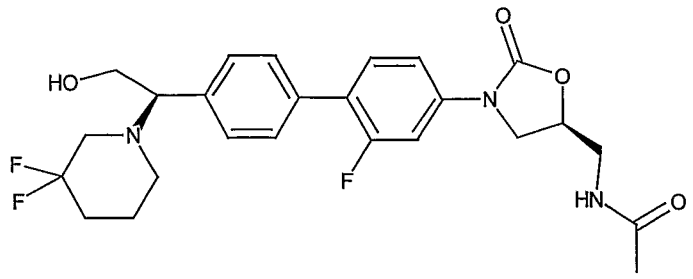
1074	
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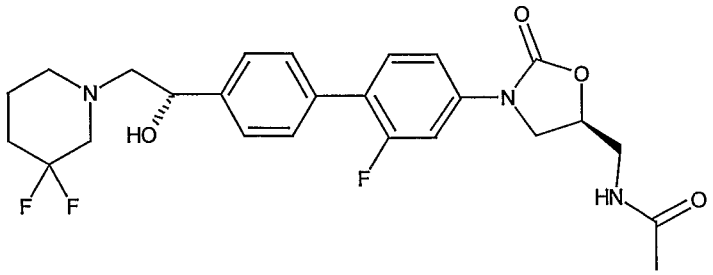
1075	
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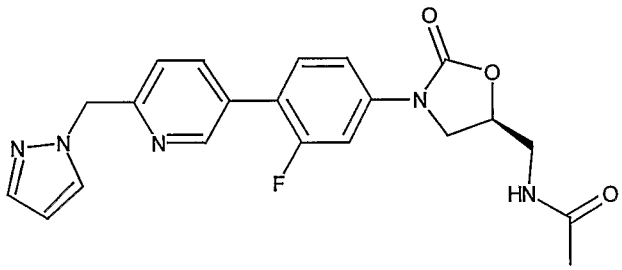
1076	
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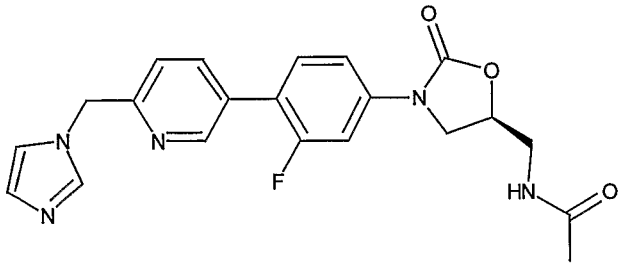
1077	
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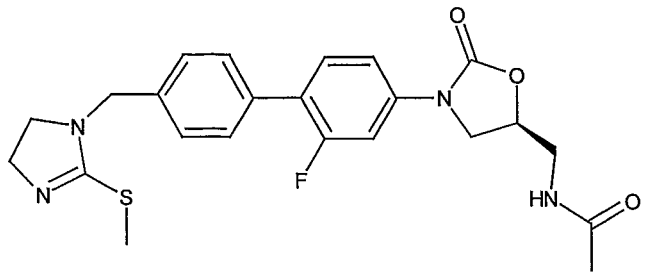
1078	
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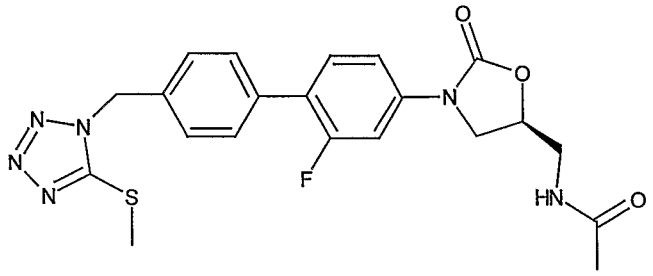
1079	
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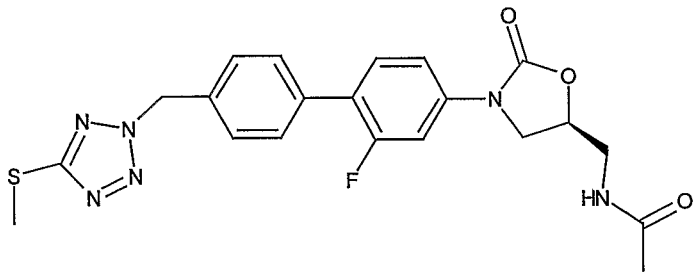
1080	
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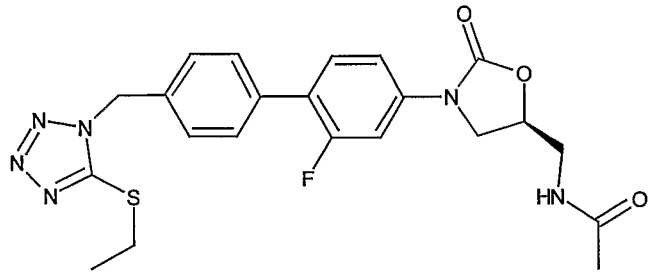
1081	
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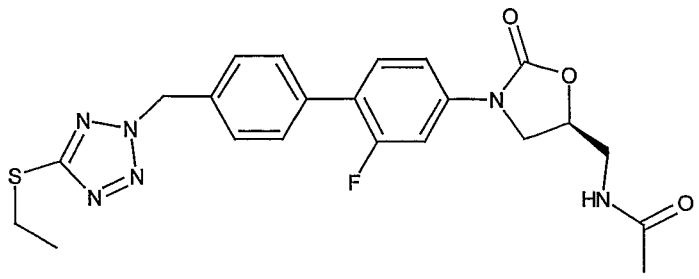
1082	
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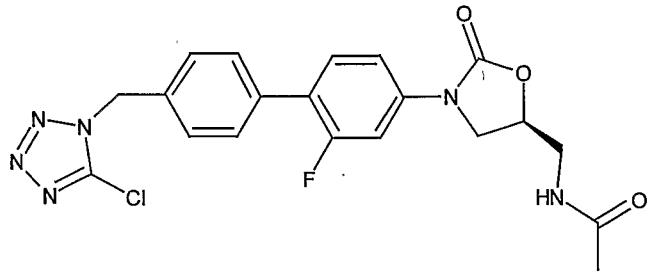
1083	
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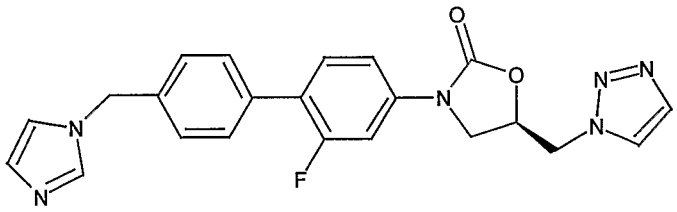
1084	
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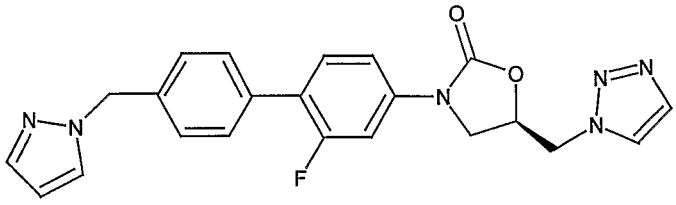
1085	
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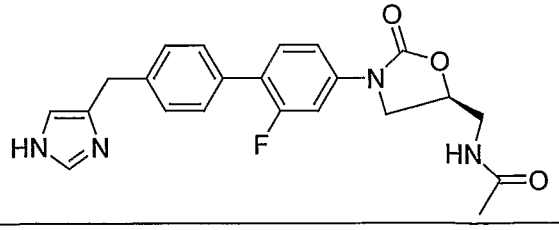
1086	
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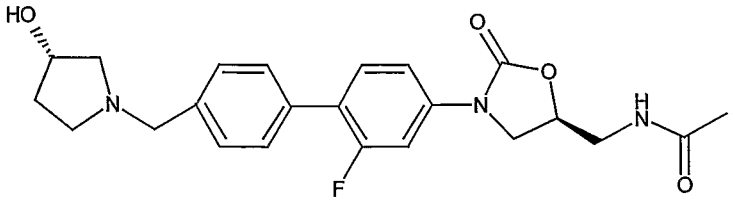
1087	
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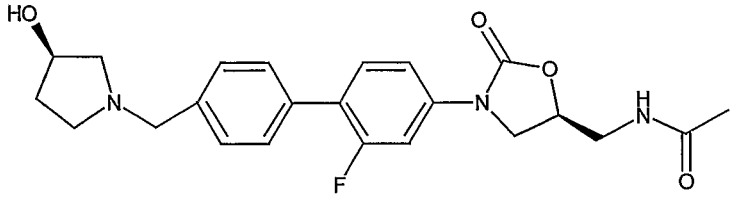
1088	
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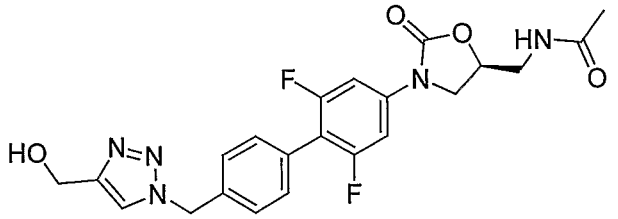
1089	
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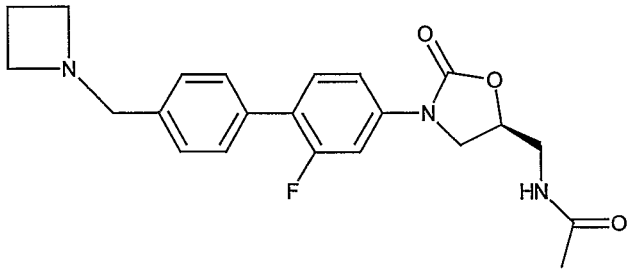
1090	
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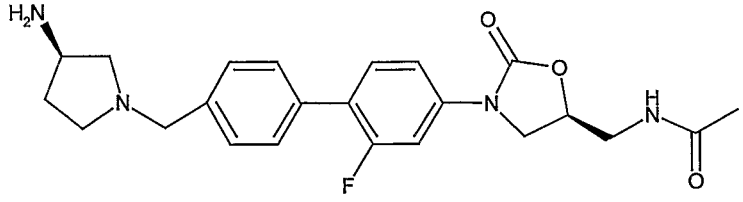
1091	
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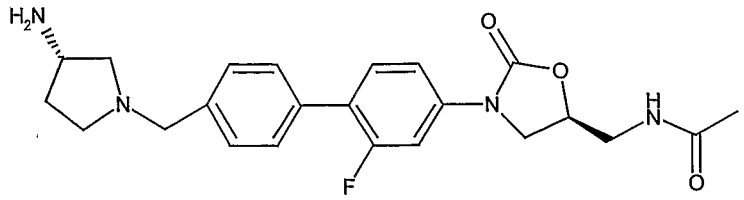
1092	
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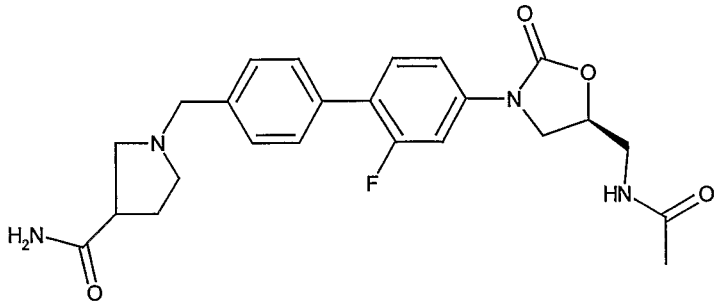
1093	
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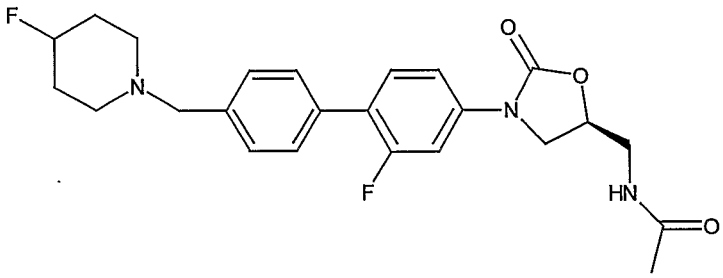
1094	
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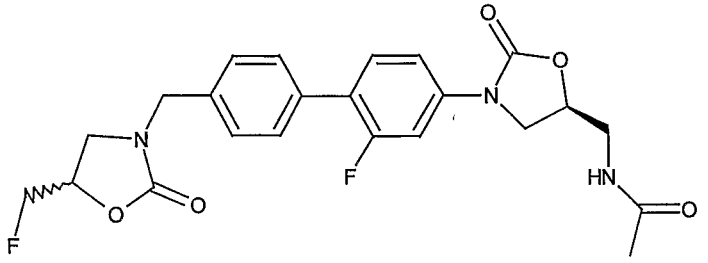
1095	
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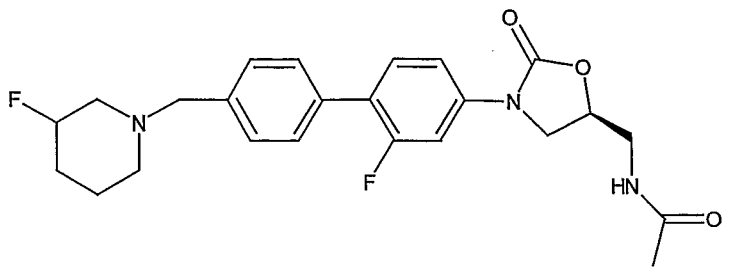
1096	
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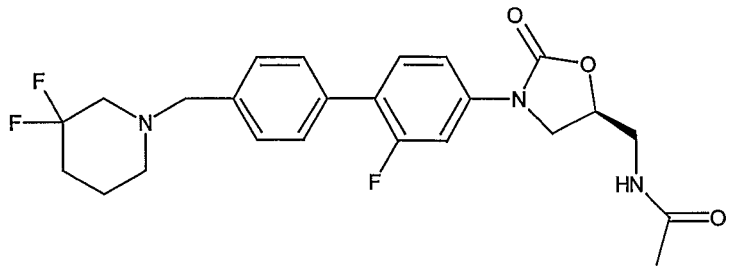
1097	
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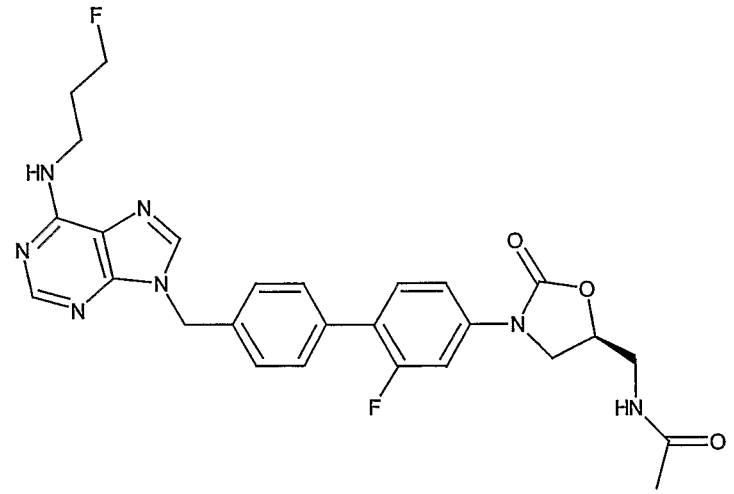
1098	
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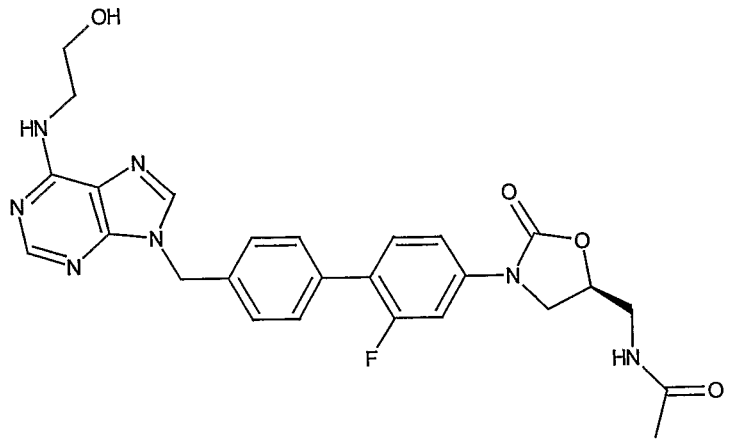
1099	
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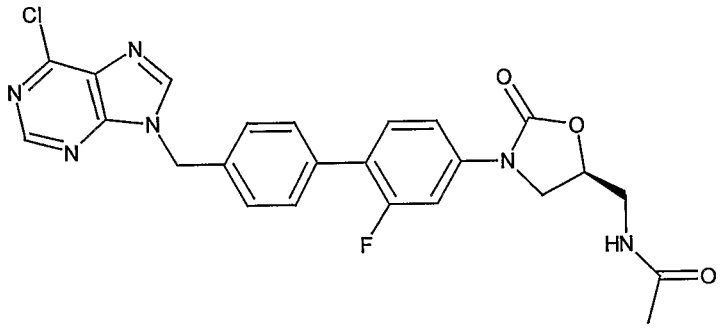
1100	
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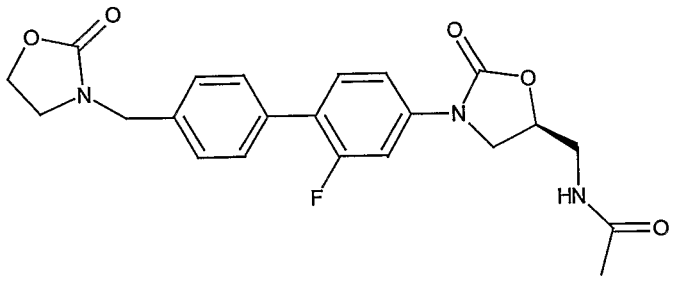
1101	
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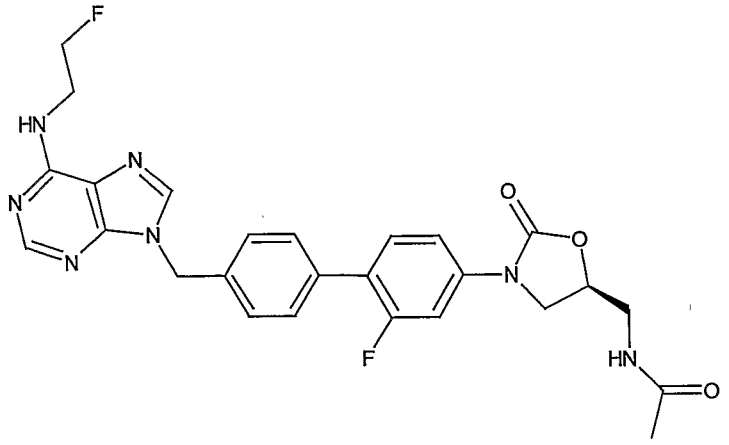
1102	
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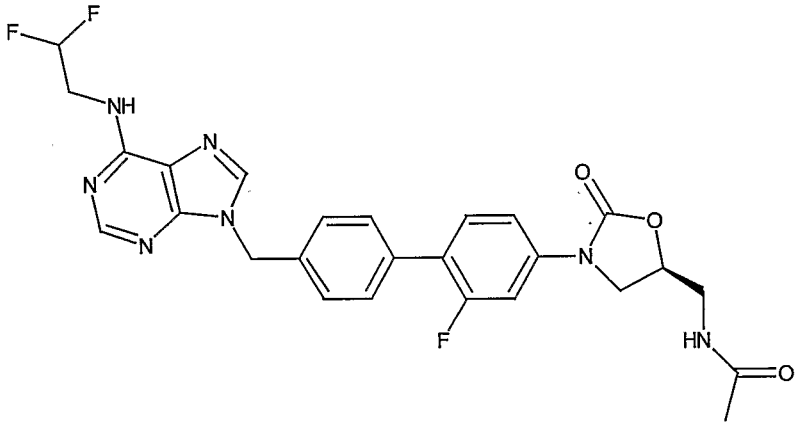
1103	
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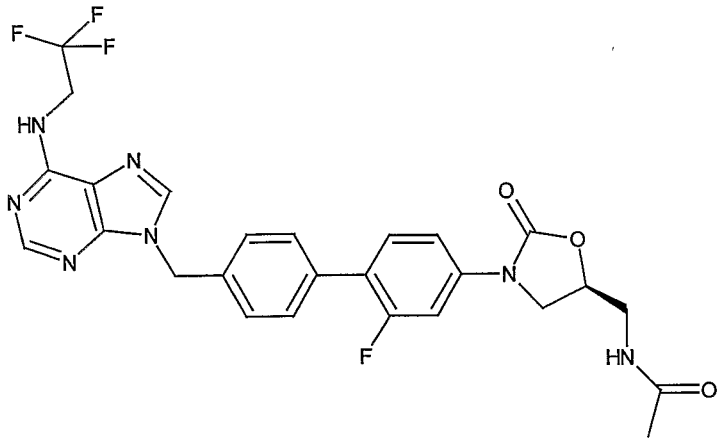
1104	
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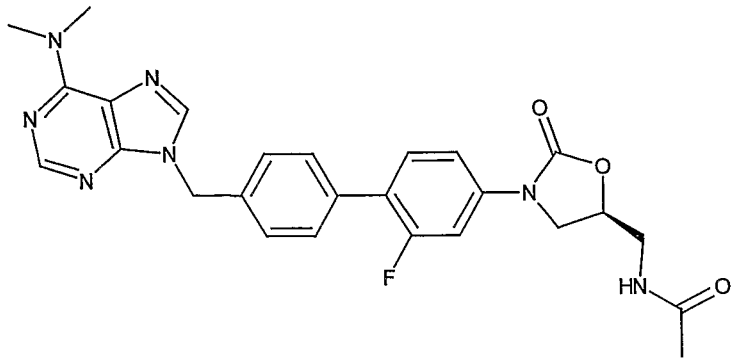
1105	
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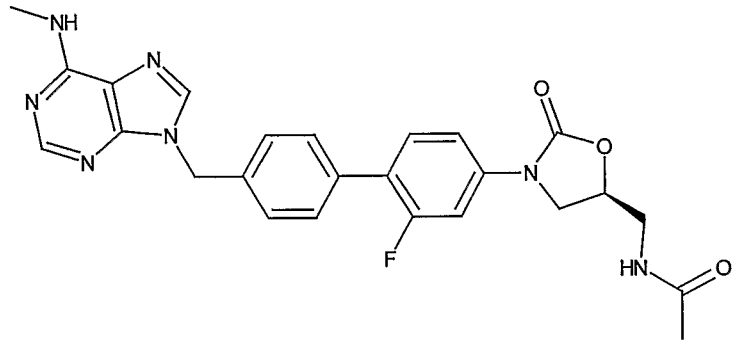
1106	
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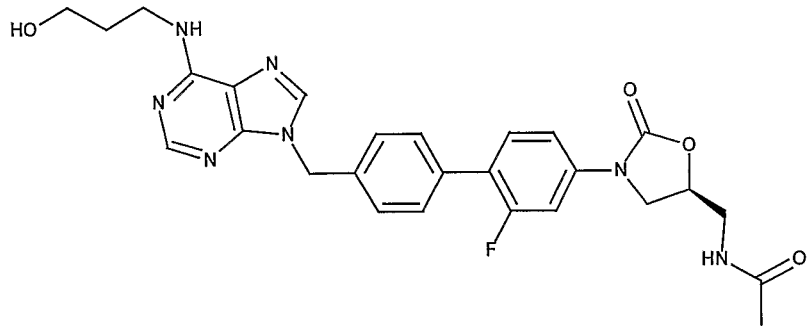
1107	
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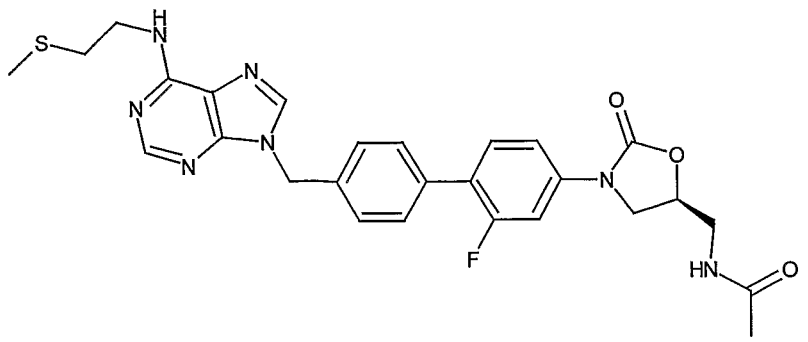
1108	
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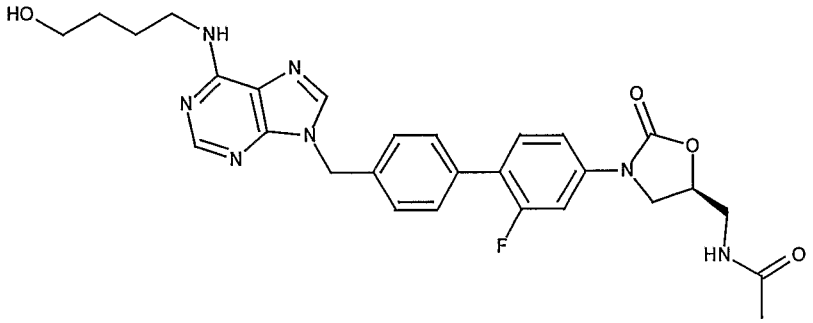
1109	
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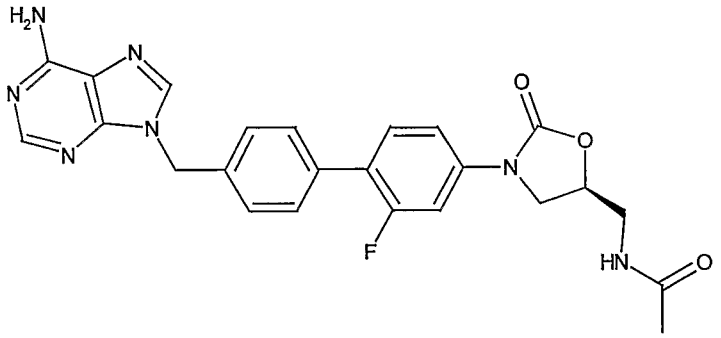
1110	
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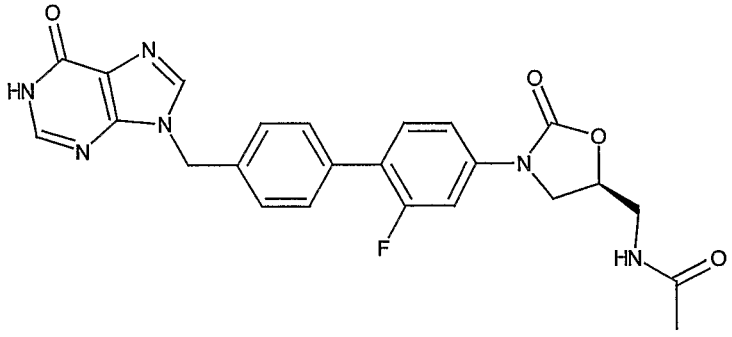
1111	

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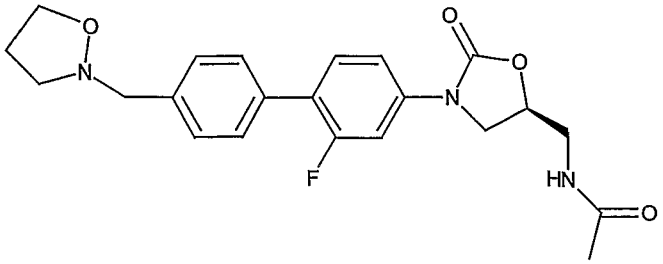
1112	
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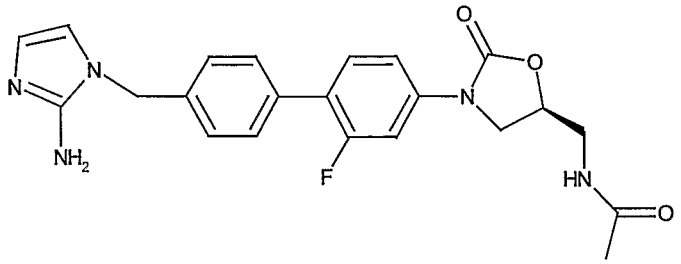
1113	
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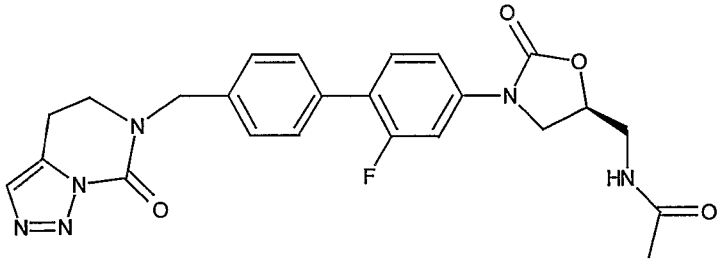
1114	
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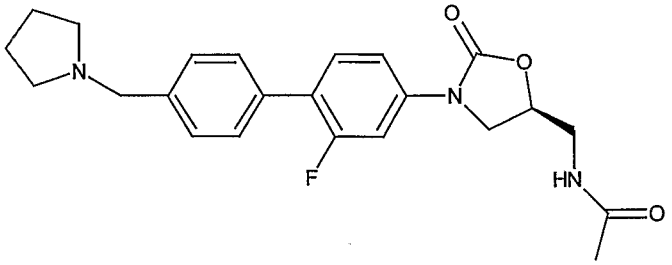
1115	
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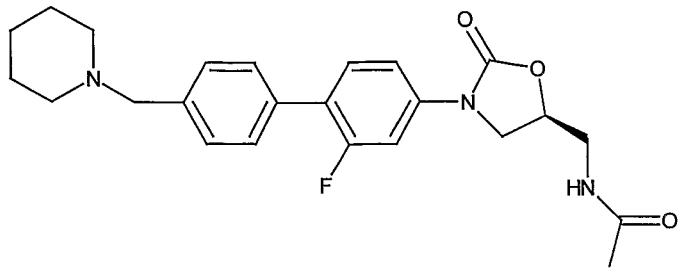
1116	
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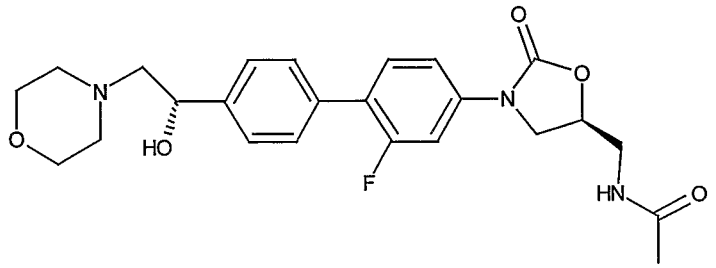
1117	
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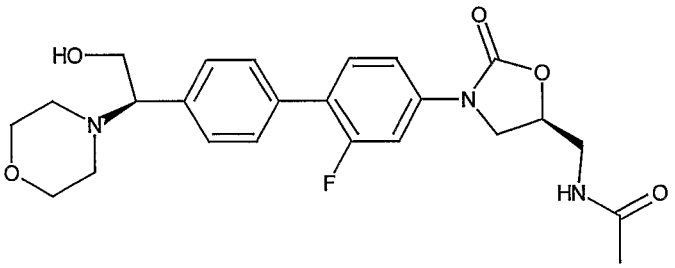
1118	
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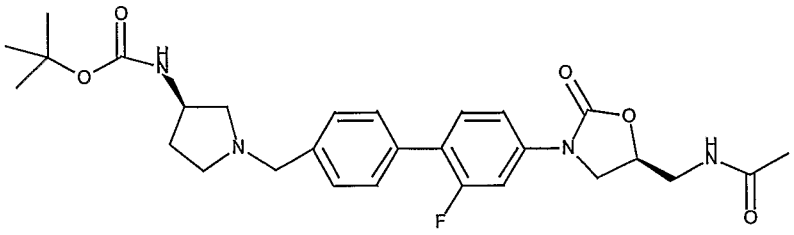
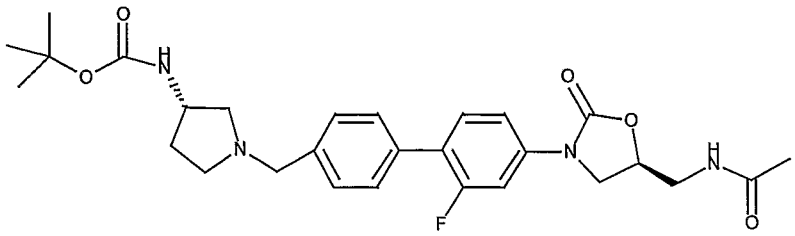
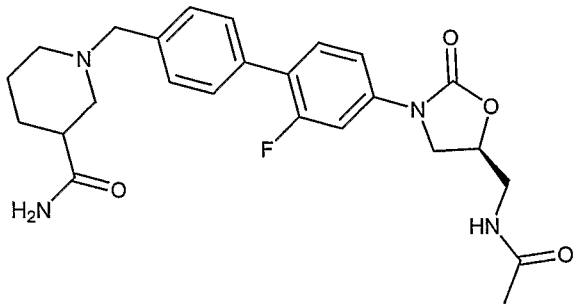
1119	
	(1-{4'-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-pyrrolidin-3-(R)-yl)-carbamic acid tert-butyl ester

1120	
	(1-{4'-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-pyrrolidin-3-(S)-yl)-carbamic acid tert-butyl ester
1121	
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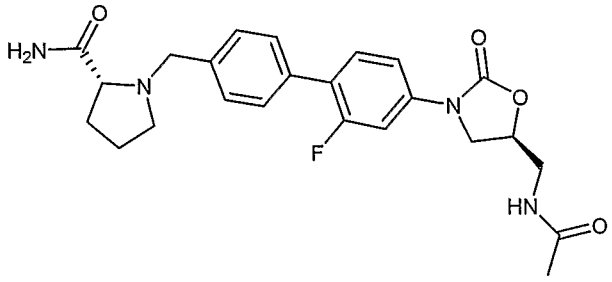
1122	
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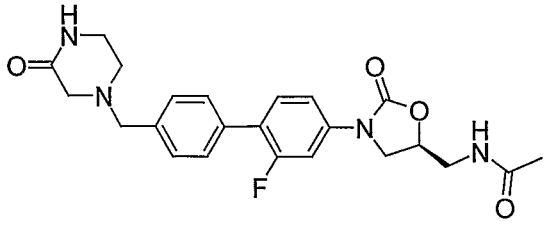
1123	
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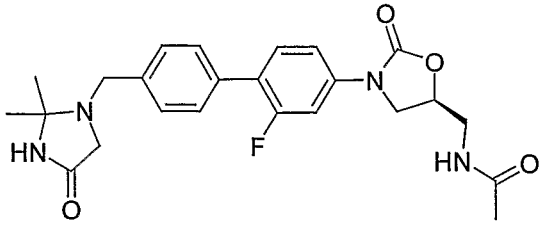
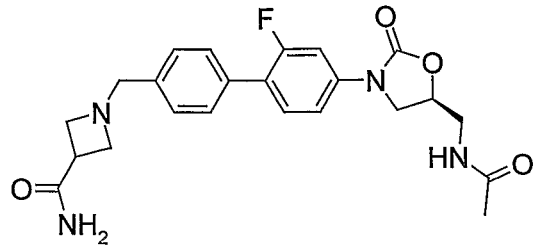
1124	
	N-{3-[4'-(2,2-Dimethyl-4-oxo-imidazolidin-1-ylmethyl)-2-fluoro-biphenyl-4-yl]-2-oxo-oxazolidin-5-(S)-ylmethyl}-acetamide

1125	
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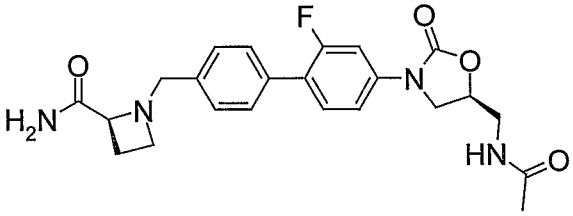
1126	
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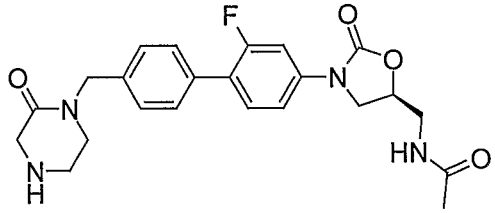
1127	
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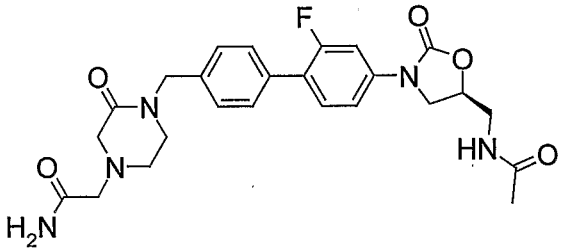
1128	
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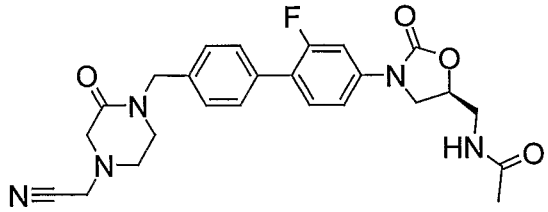
1129	
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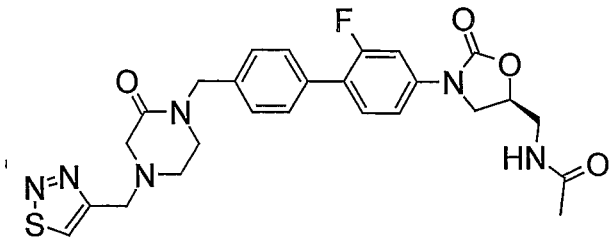
1130	
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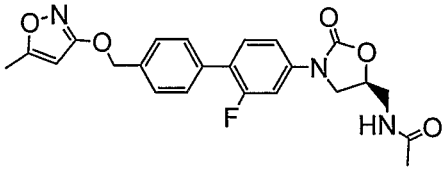
2001	
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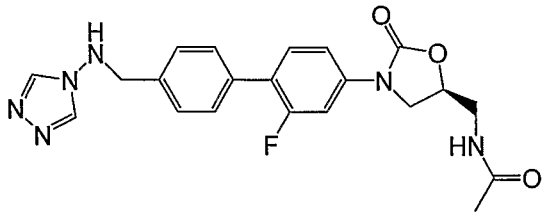
2002	
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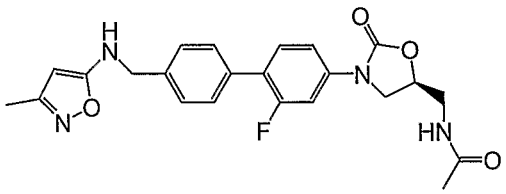
2003	
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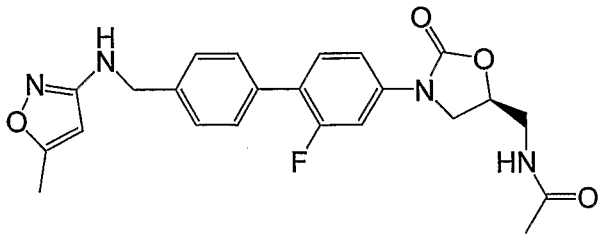
2004	
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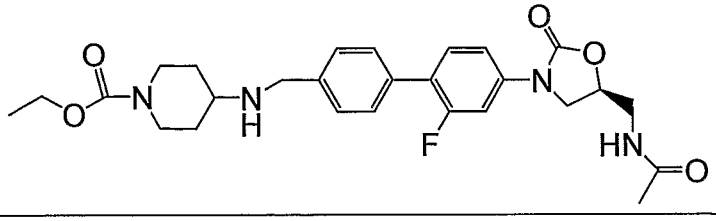
2005	

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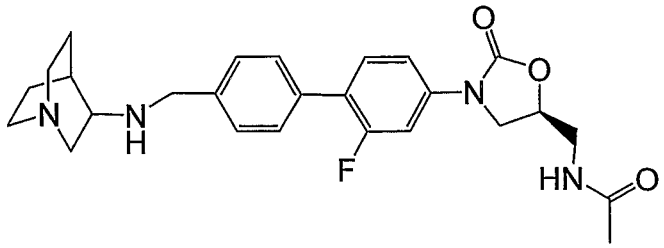
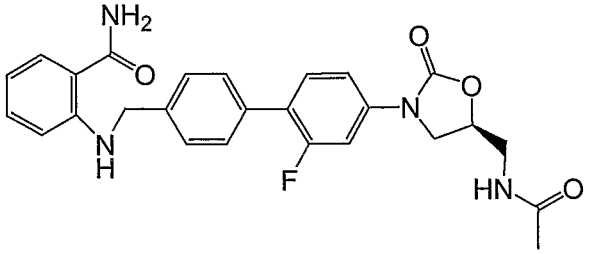
2006	
	N-(3-{4'-[(1-Aza-bicyclo[2.2.2]oct-3-ylamino)-methyl]-2-fluoro-biphenyl-4-yl}-2-oxo-oxazolidin-5-(S)-ylmethyl)-acetamide
2007	
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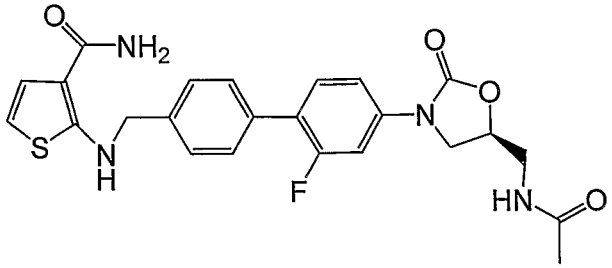
2008	
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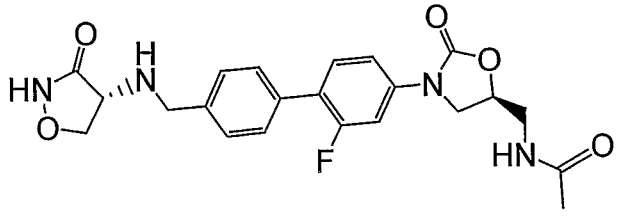
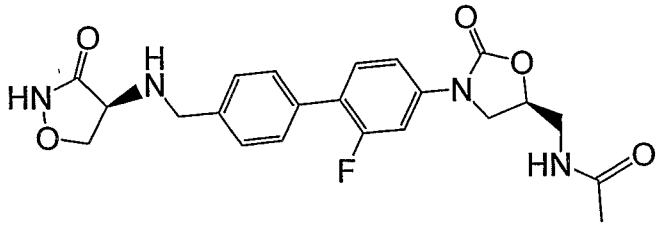
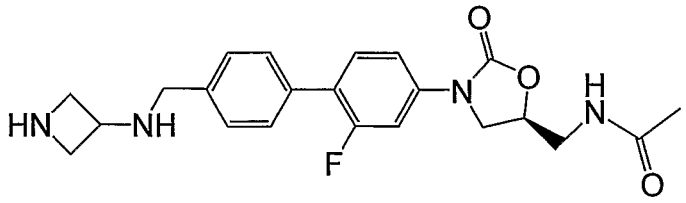
2009	
	N-(3-{2-Fluoro-4'-[(3-oxo-isoxazolidin-4-(R)-ylamino)-methyl]-biphenyl-4-yl}-2-oxo-oxazolidin-5-(S)-ylmethyl)-acetamide
2010	
	N-(3-{2-Fluoro-4'-[(3-oxo-isoxazolidin-4-(S)-ylamino)-methyl]-biphenyl-4-yl}-2-oxo-oxazolidin-5-(S)-ylmethyl)-acetamide

2011	
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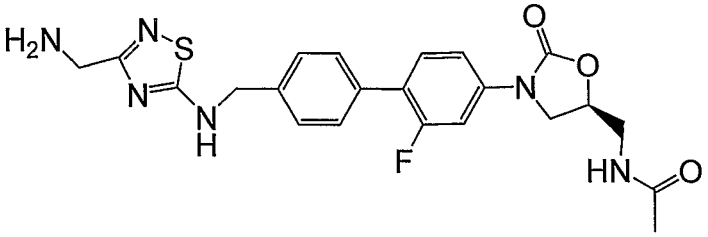
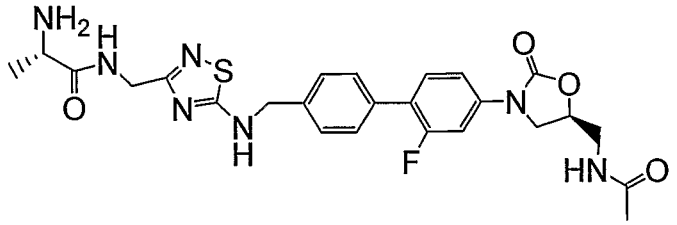
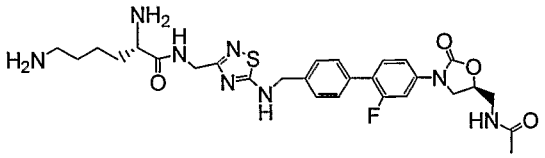
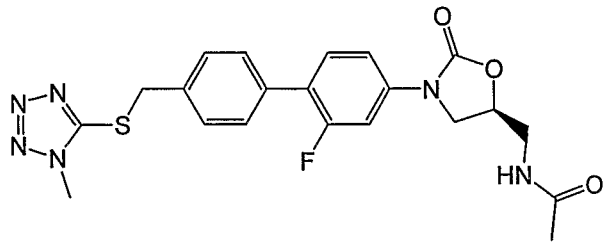
2012	
	N-(3-{4'-[(3-Aminomethyl-[1,2,4]thiadiazol-5-ylamino)-methyl]-2-fluoro-biphenyl-4-yl}-2-oxo-oxazolidin-5-(S)-ylmethyl)-acetamide
2013	
	N-[5-({4'-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-amino)-[1,2,4]thiadiazol-3-ylmethyl]-2-(S)-amino-propionamide
2014	
	2,6-Diamino-hexanoic acid [5-({4'-[5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-amino)-[1,2,4]thiadiazol-3-ylmethyl]-amide
2015	
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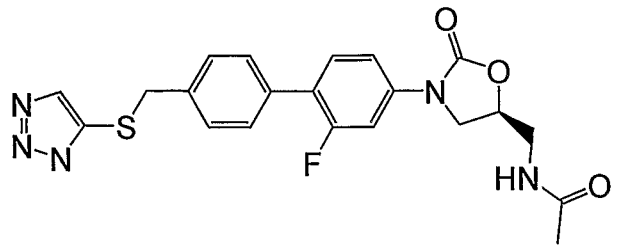
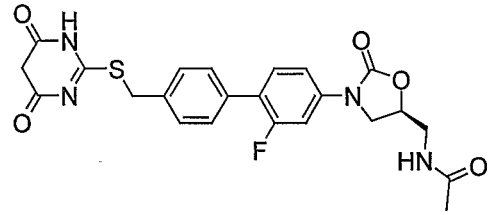
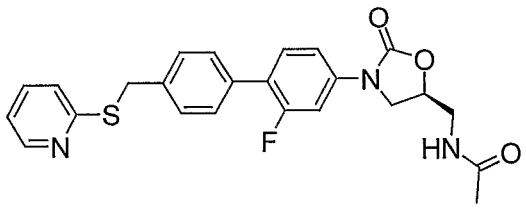
2016	
	N-{3-[2-Fluoro-4'-(3H-[1,2,3]triazol-4-ylsulfanylmethyl)-biphenyl-4-yl]-2-oxo-oxazolidin-5-(S)-ylmethyl}-acetamide
2017	
	N-{3-[4'-(4,6-Dioxo-1,4,5,6-tetrahydro-pyrimidin-2-ylsulfanylmethyl)-2-fluoro-biphenyl-4-yl]-2-oxo-oxazolidin-5-(S)-ylmethyl}-acetamide
2018	
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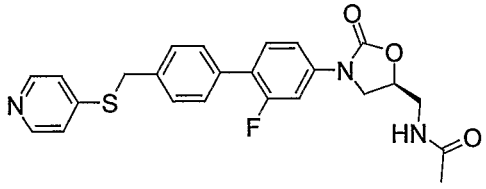
2019	
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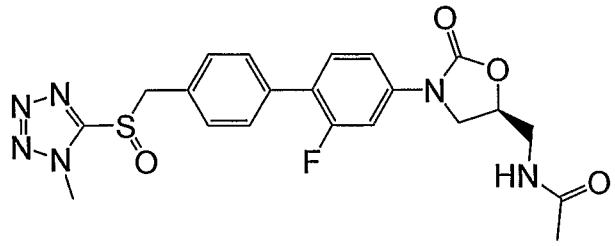
2020	
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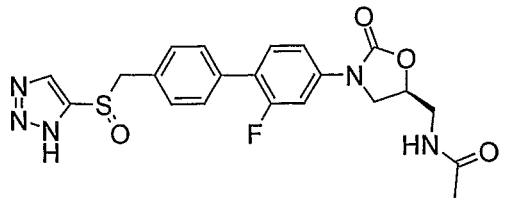
2021	
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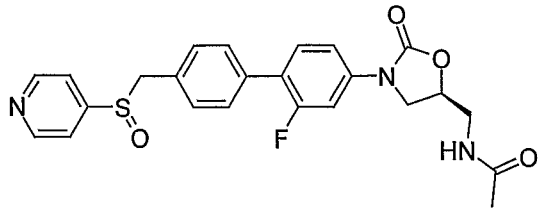
2022	
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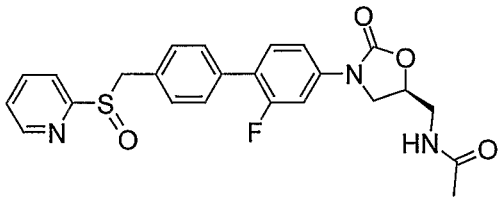
2023	
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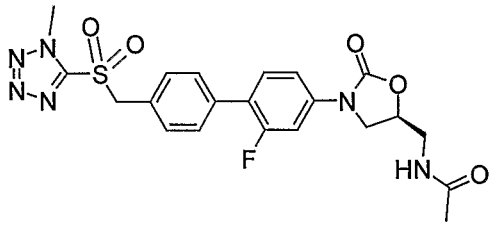
2024	
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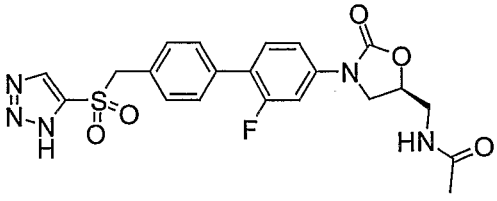
2025	
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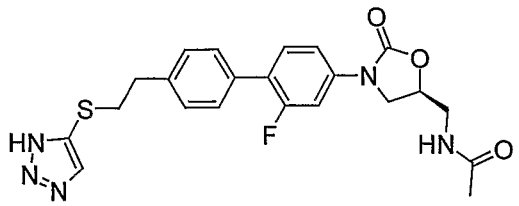
2026	
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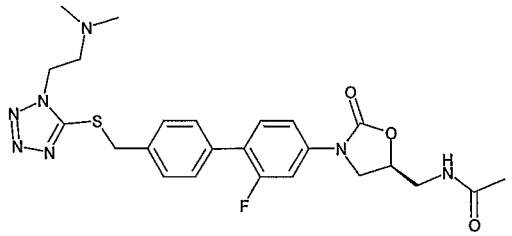
2027	
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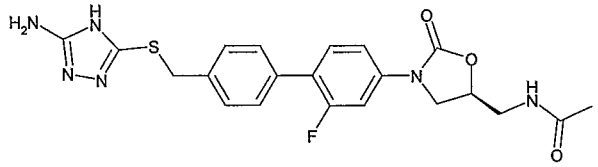
2028	
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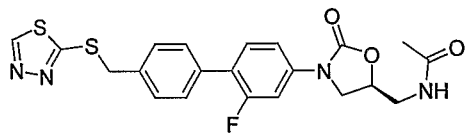
2029	
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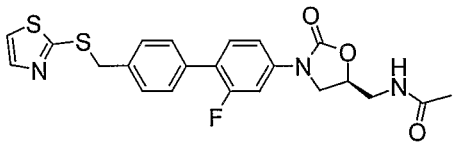
2030	
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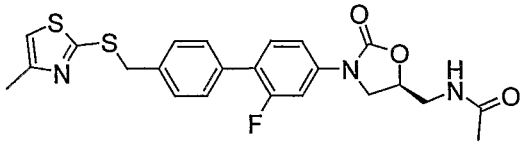
2031	
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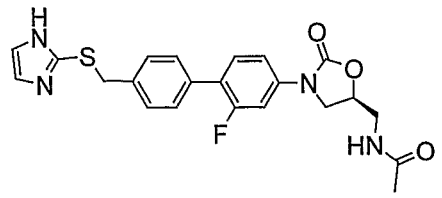
2032	
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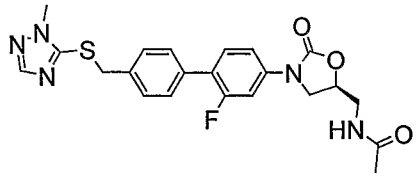
2033	
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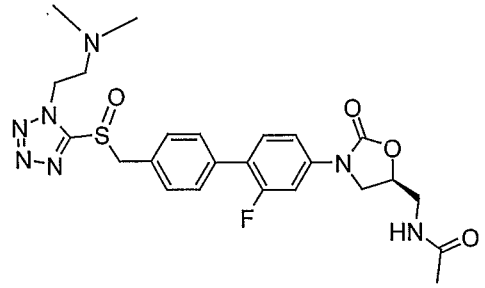
2034	
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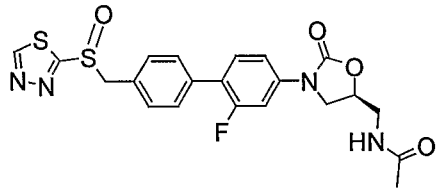
2035	
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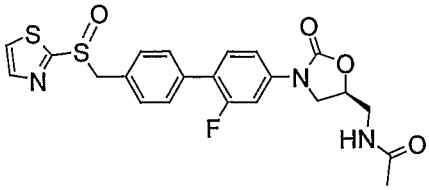
2036	
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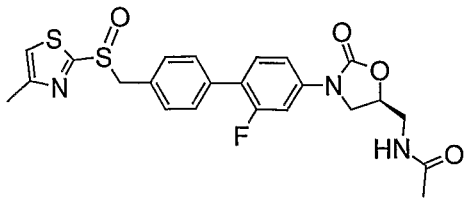
2037	
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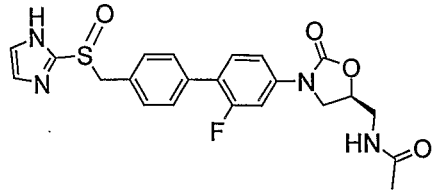
2038	
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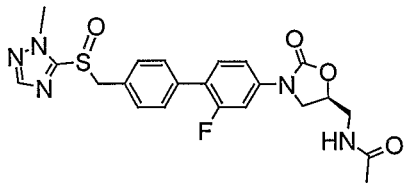
2039	
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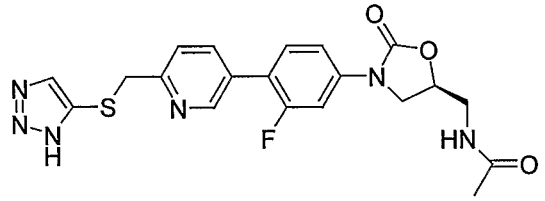
2040	
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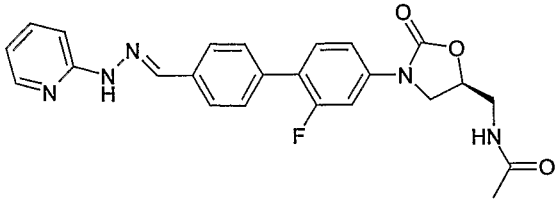
2041	
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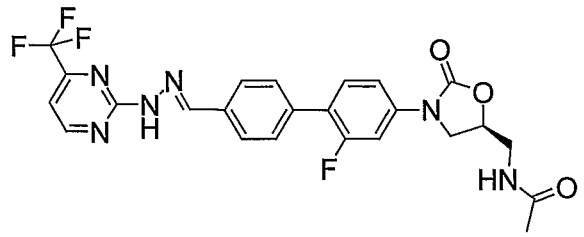
2042	
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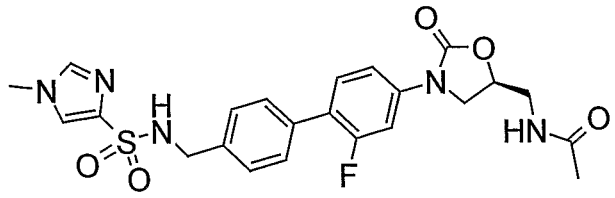
2043	
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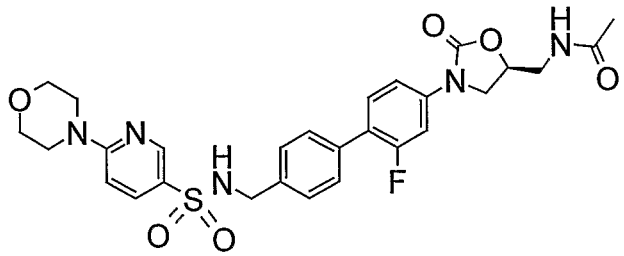
2044	
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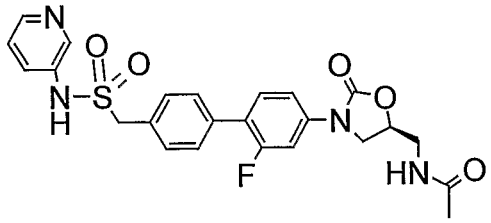
2045	
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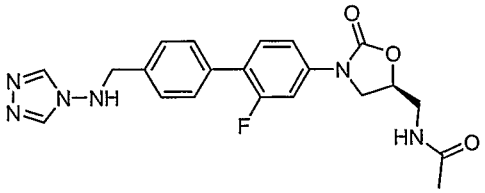
2046	
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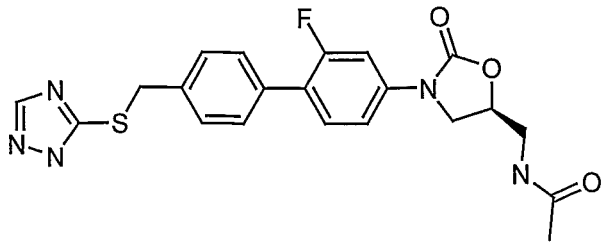
2047	
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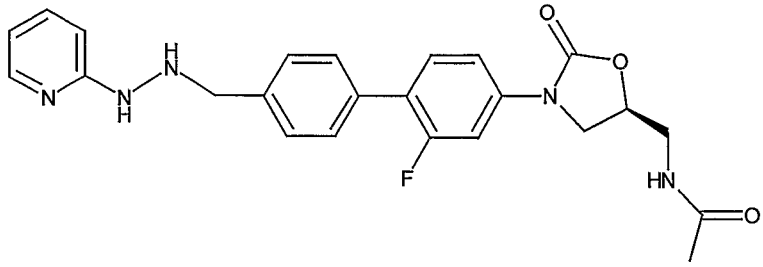
2048	
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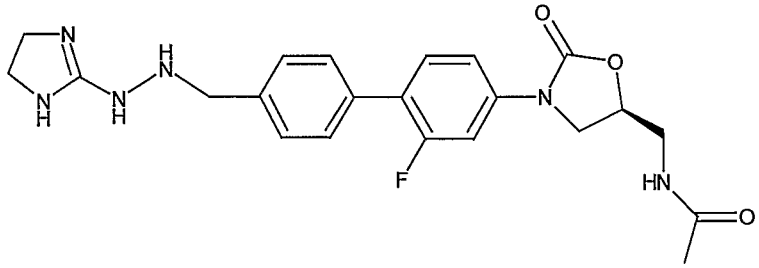
2049	
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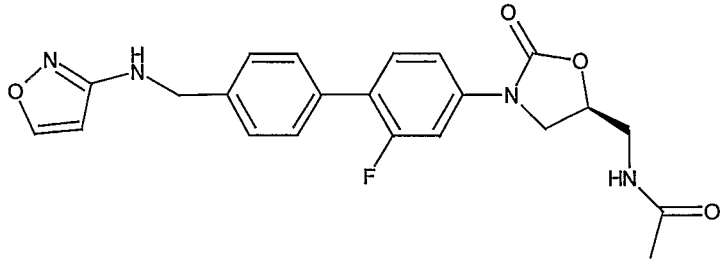
2050	
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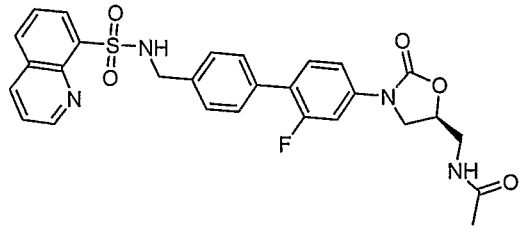
2051	

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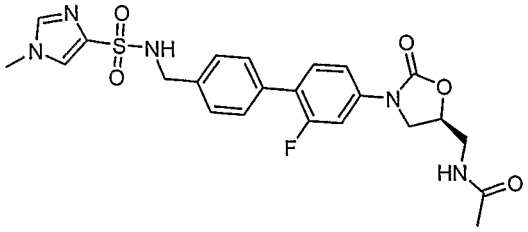
2052	
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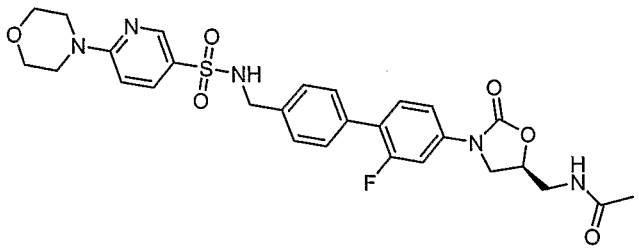
2053	
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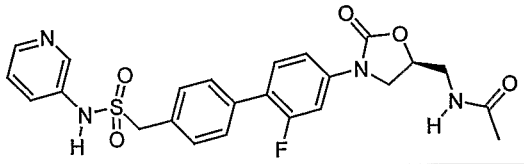
2054	
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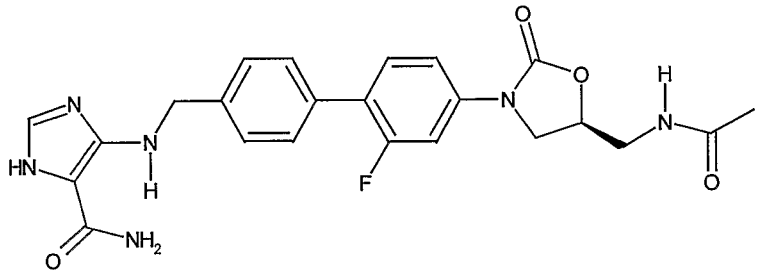
2055	
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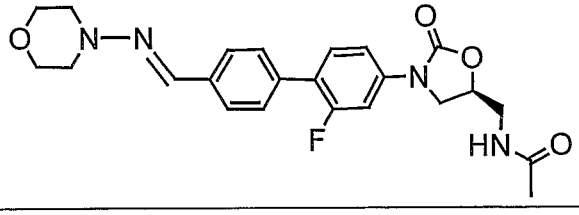
2056	
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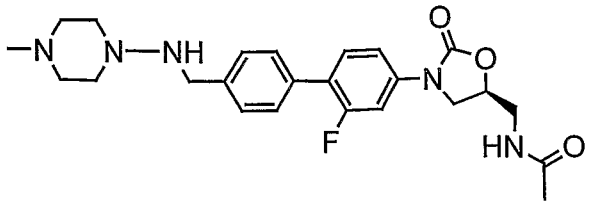
2057	
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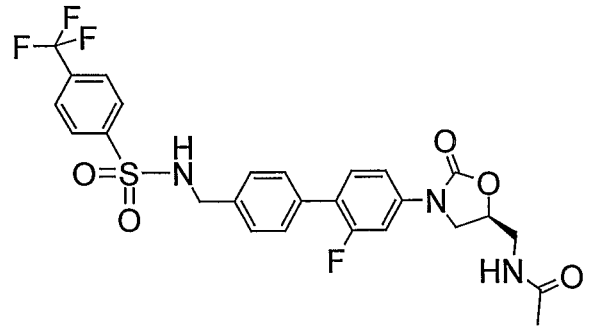
2058	
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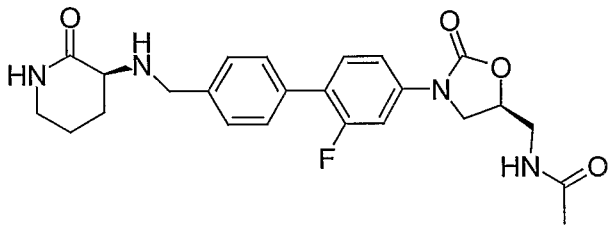
2059	
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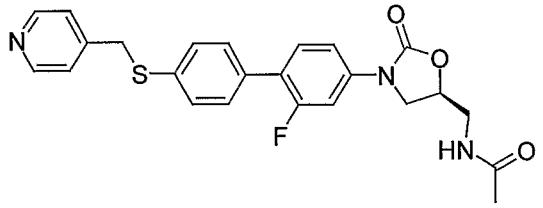
3001	
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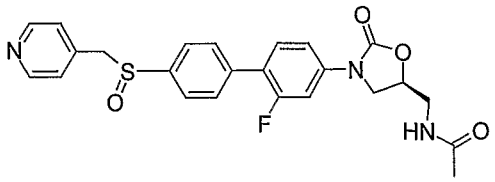
3002	
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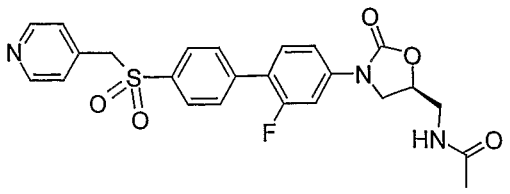
3003	
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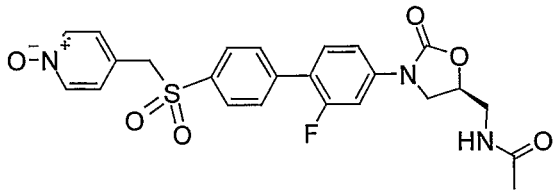
3004	
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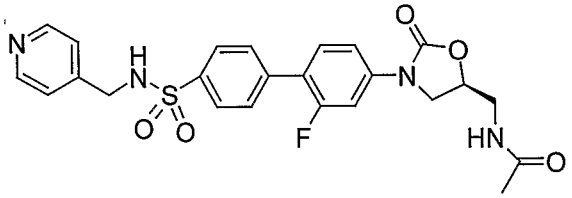
3005	
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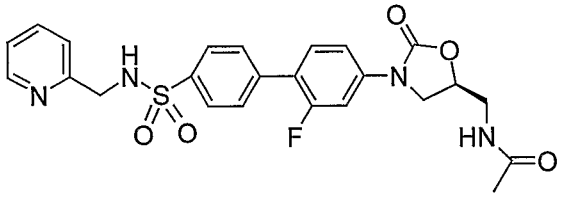
3006	
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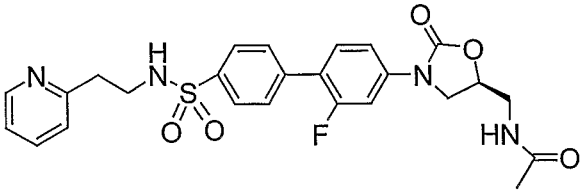
3007	
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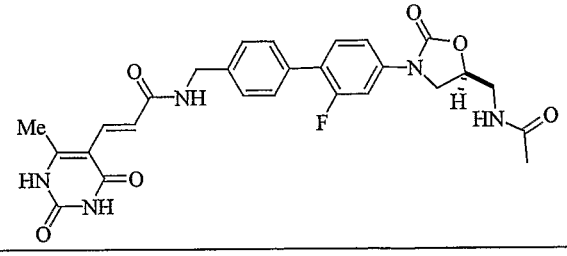
4001	

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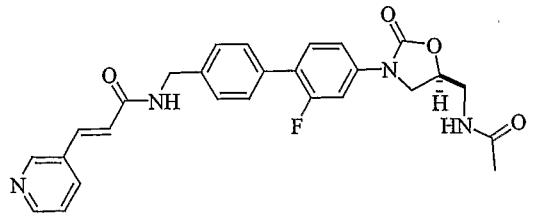
4002	
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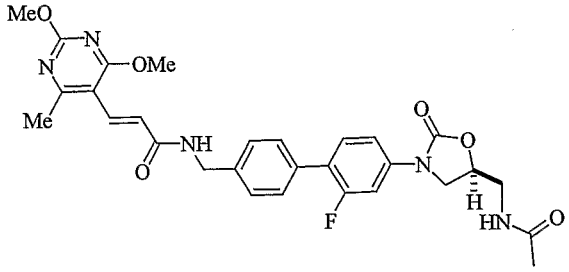
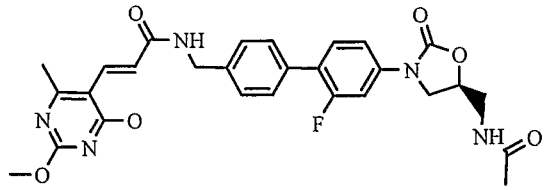
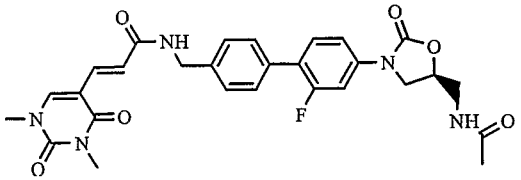
4003	
	N-{4'-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-3-(2,4-dimethoxy-6-methyl-pyrimidin-5-yl)-acrylamide
4004	
	N-{4'-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-3-(4-hydroxy-2-methoxy-6-methyl-pyrimidin-5-yl)-acrylamide
4005	
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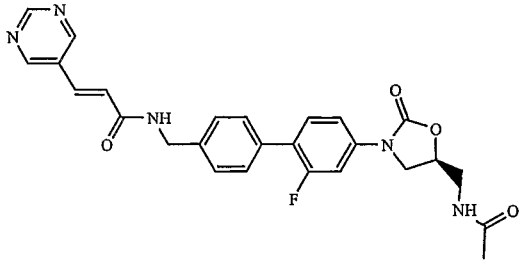
4006	

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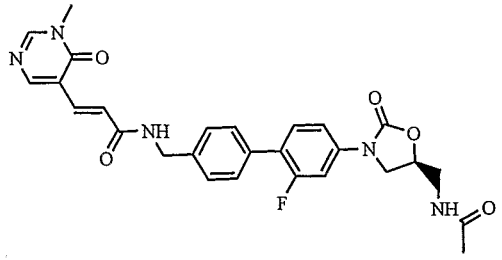
4007	
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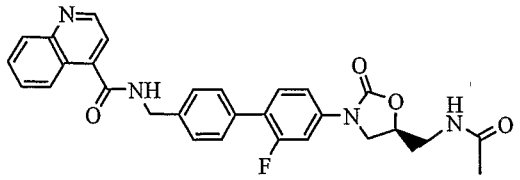
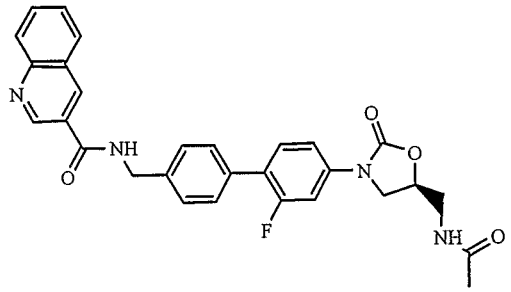
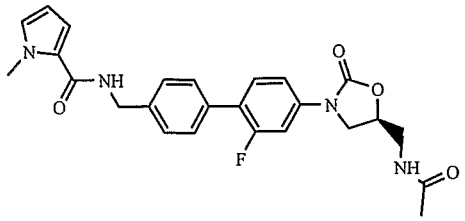
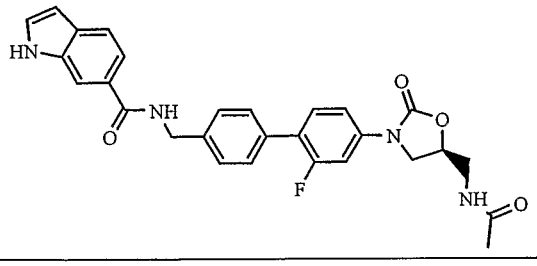
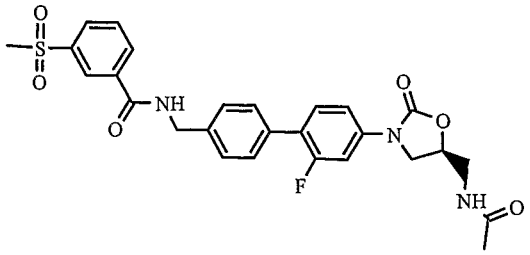
4008	
	Quinoline-4-carboxylic acid {4'-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-amide
4009	
	Quinoline-3-carboxylic acid {4'-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-amide
4010	
	1-Methyl-1H-pyrrole-2-carboxylic acid {4'-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-amide
4011	

	1H-Indole-6-carboxylic acid {4'-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-amide
4012	
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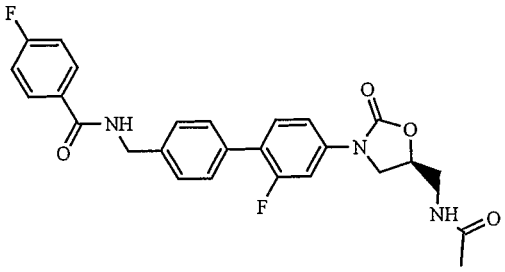
4013	
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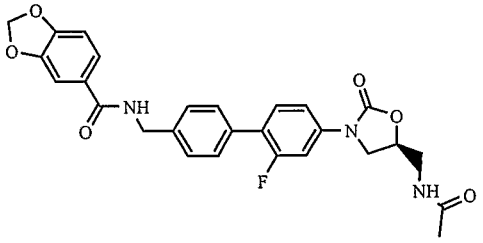
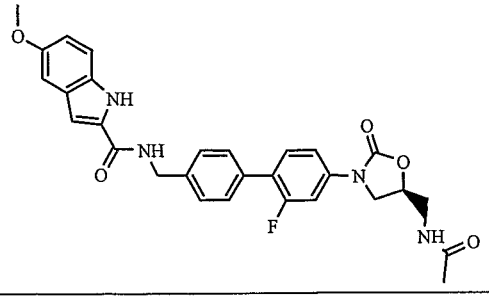
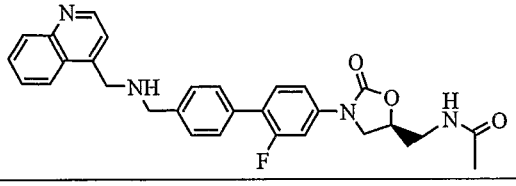
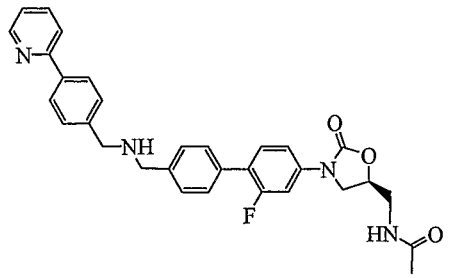
4014	
	Benzo[1,3]dioxole-5-carboxylic acid {4'-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-amide
4015	
	5-Methoxy-1H-indole-2-carboxylic acid {4'-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-amide
4016	

	N-[3-(2-Fluoro-4'-{[(quinolin-4-ylmethyl)-amino]-methyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
4017	
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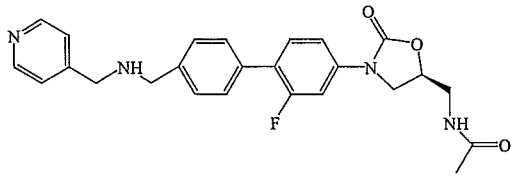
4018	
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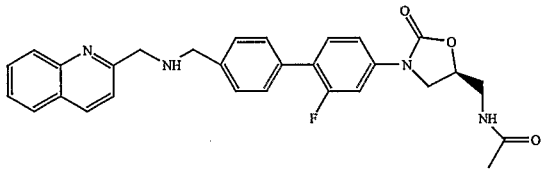
4019	
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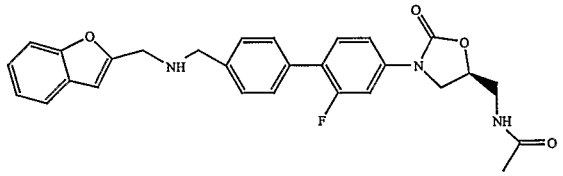
4020	
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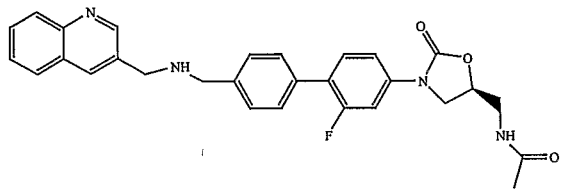
4021	
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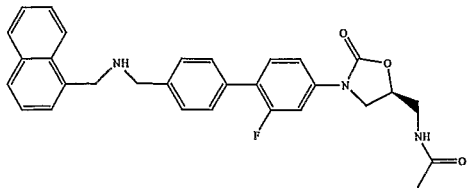
4022	
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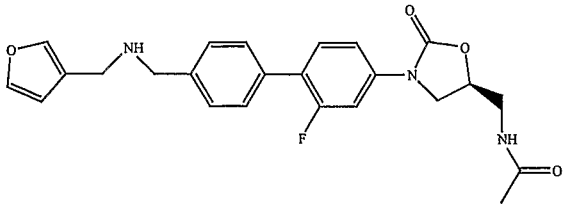
4023	
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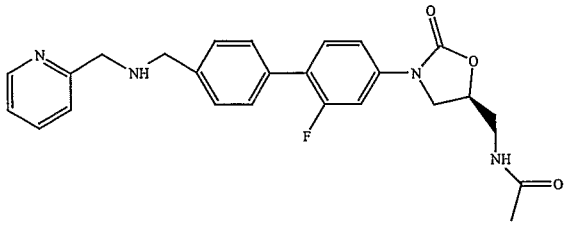
4024	
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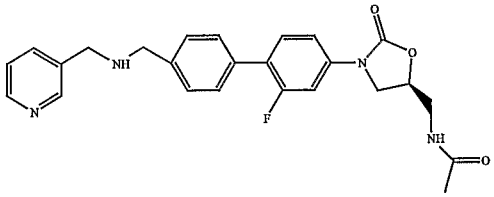
4025	
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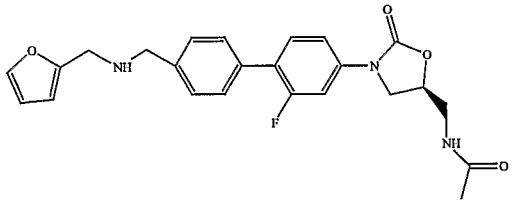
4026	
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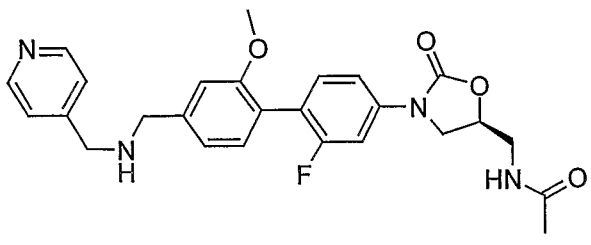
4027	

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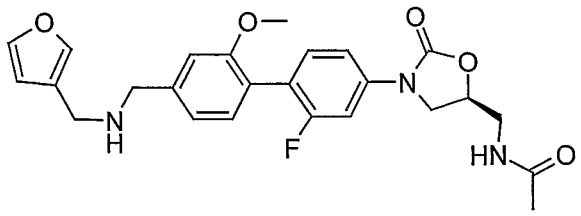
4028	
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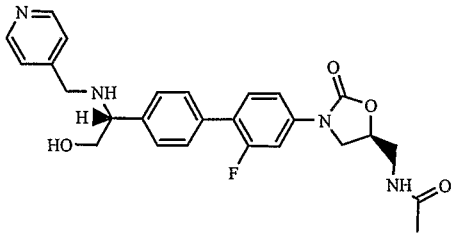
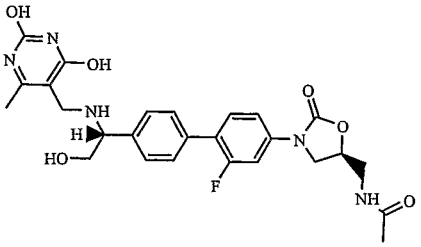
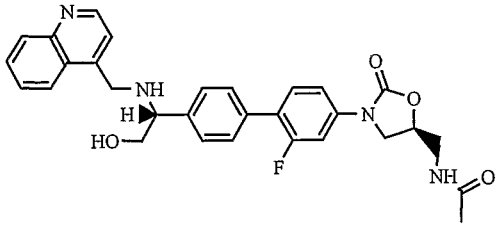
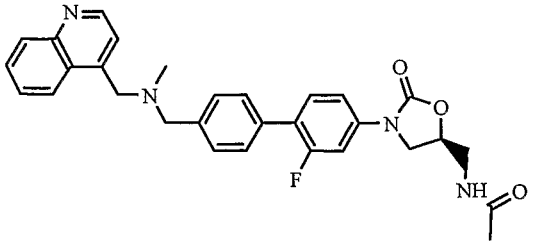
4029	
	N-[3-(2-Fluoro-4'-{2-hydroxy-1-(R)-[(pyridin-4-ylmethyl)-amino]-ethyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
4030	
	N-[3-(4'-{1-(R)-[(2,4-Dihydroxy-6-methyl-pyrimidin-5-ylmethyl)-amino]-2-hydroxy-ethyl}-2-fluoro-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
4031	
	N-[3-(2-Fluoro-4'-{2-hydroxy-1-(R)-[(quinolin-4-ylmethyl)-amino]-ethyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
4032	

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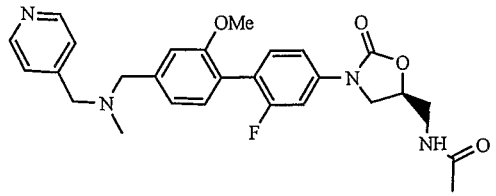
4033	
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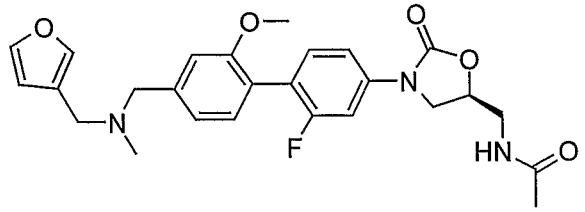
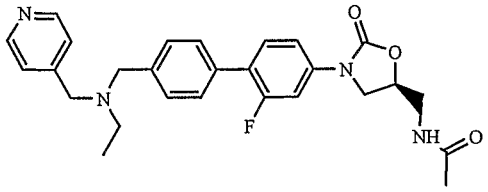
4034	
	N-(3-{2-Fluoro-4'-[(furan-3-ylmethyl-methyl-amino)-methyl]-2'-methoxy-biphenyl-4-yl}-2-oxo-oxazolidin-5-(S)-ylmethyl)-acetamide
4035	
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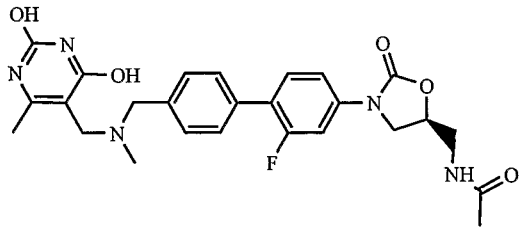
4036	
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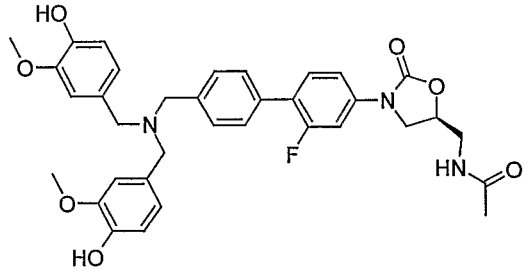
4037	
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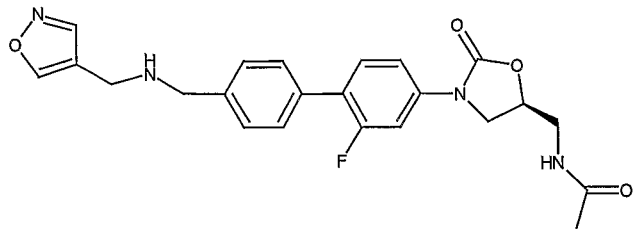
4038	
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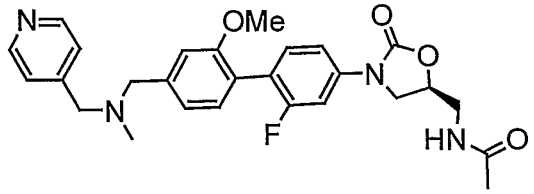
4039	
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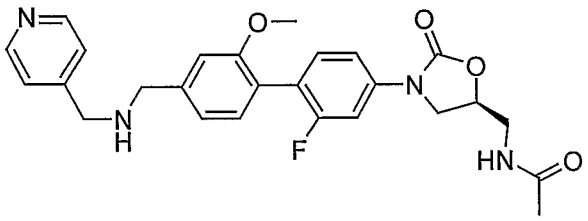
4040	
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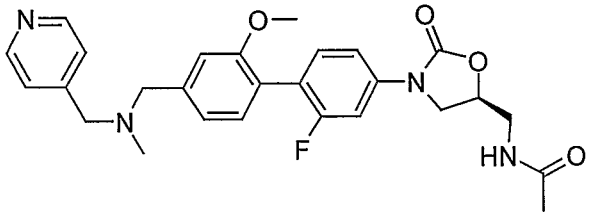
4041	
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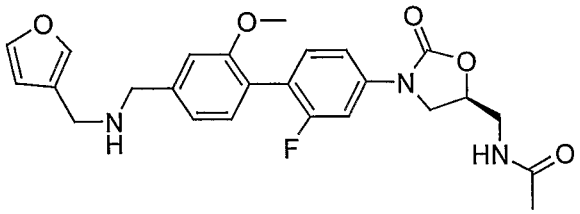
4042	
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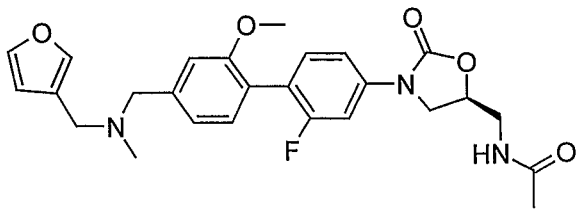
4043	
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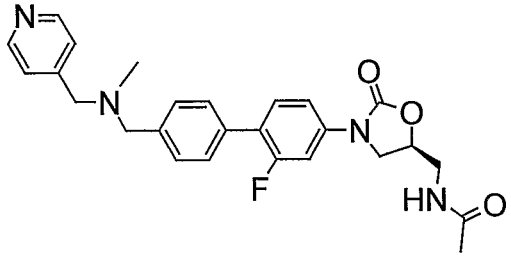
4044	
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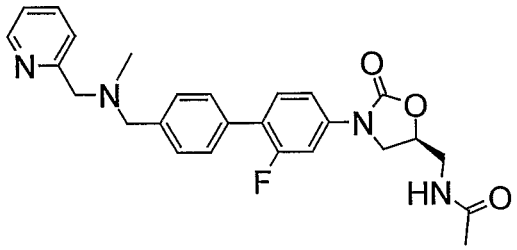
4045	
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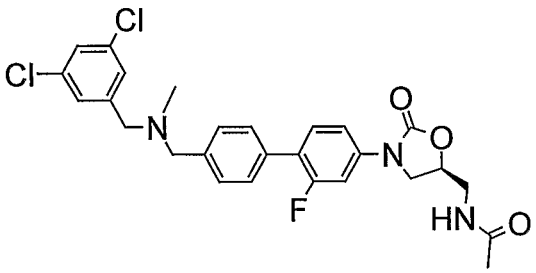
4046	
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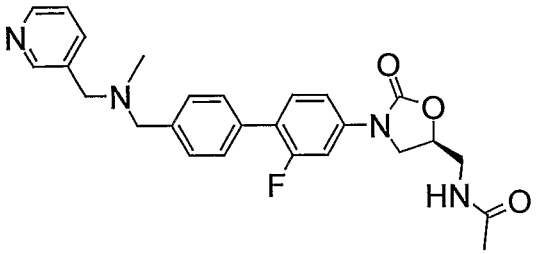
4047	

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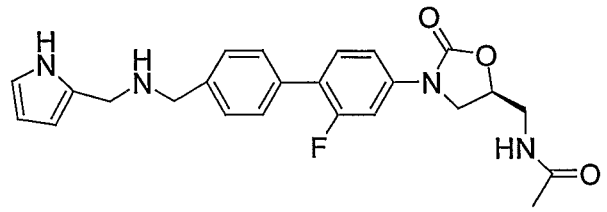
4048	
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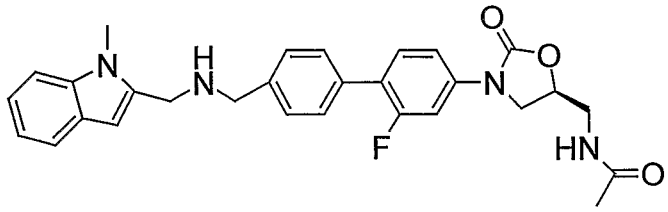
4049	
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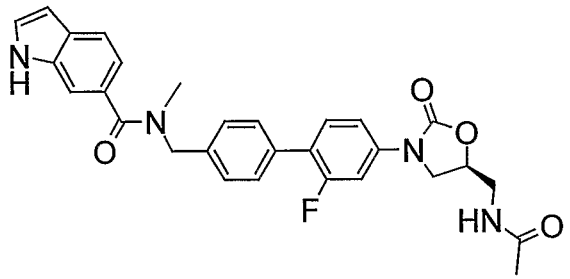
4050	
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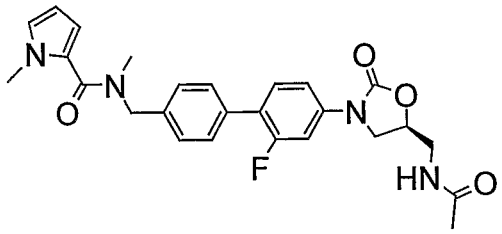
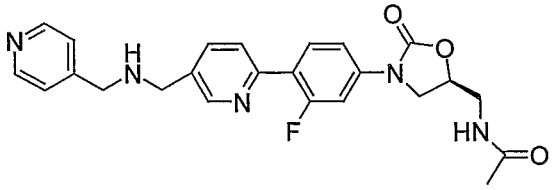
4051	
	1-Methyl-1H-pyrrole-2-carboxylic acid {4'-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-methyl-amide
4052	

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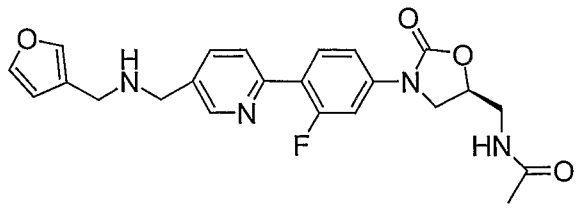
4053	
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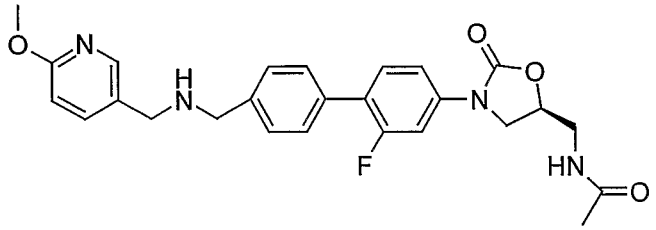
4054	
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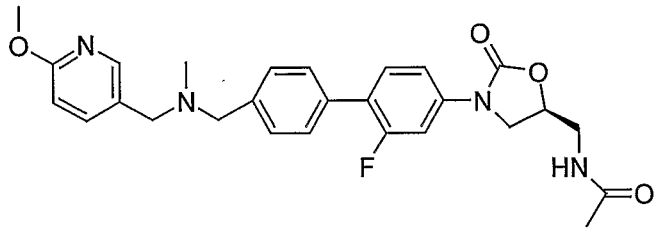
4055	
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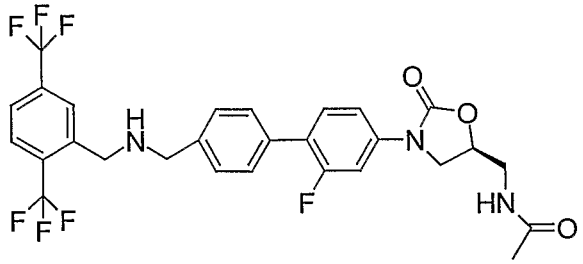
4056	
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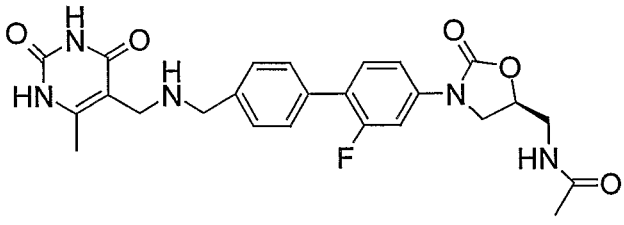
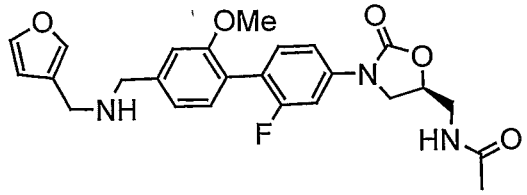
4057	

	N-[3-(2-Fluoro-4'-{[(6-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-ylmethyl)-amino]-methyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
4058	
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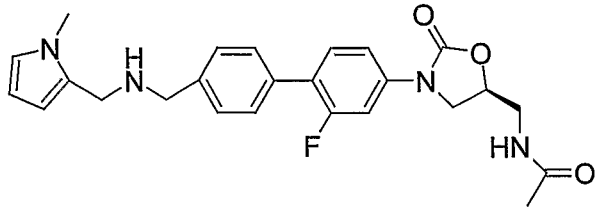
4059	
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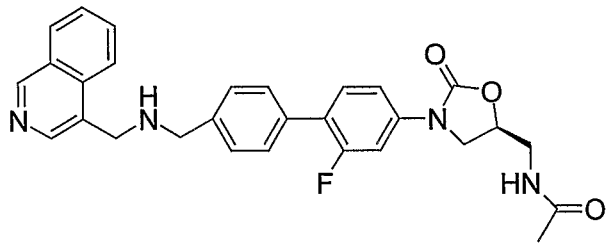
4060	
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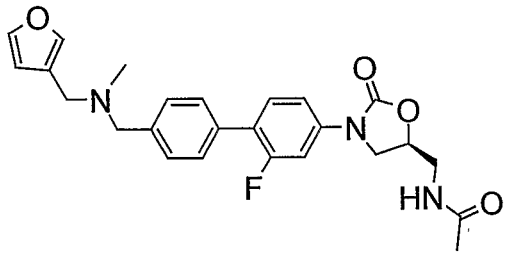
4061	
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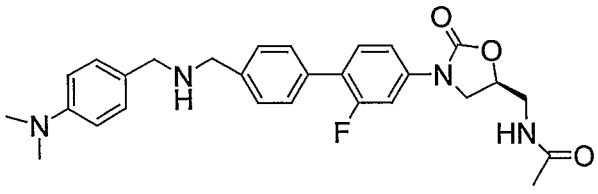
4062	
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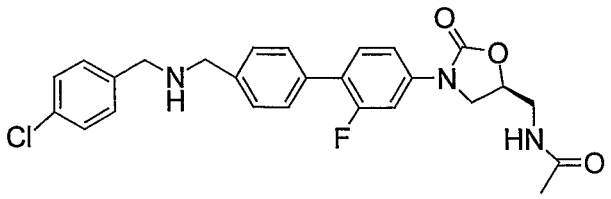
4063	
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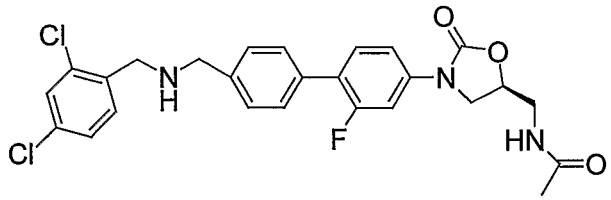
4064	
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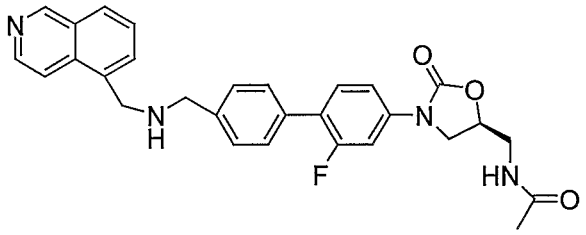
4065	
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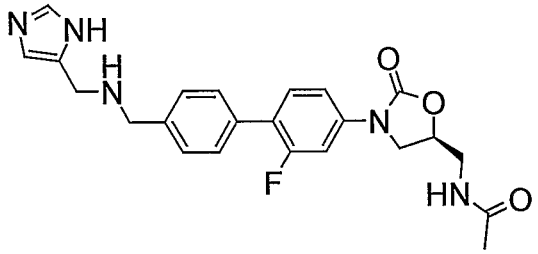
4066	
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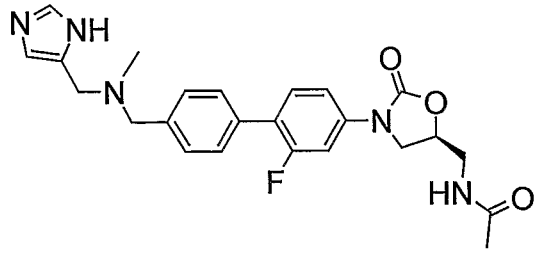
4067	
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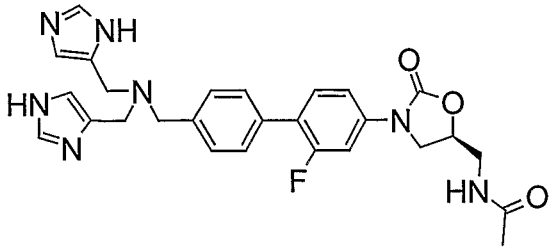
4068	
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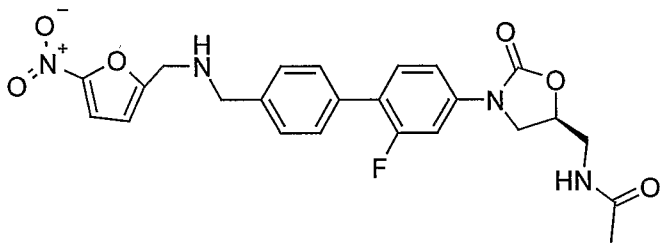
4069	
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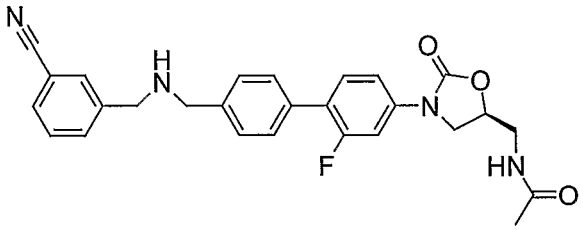
4070	
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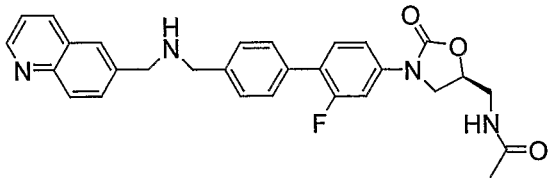
4071	
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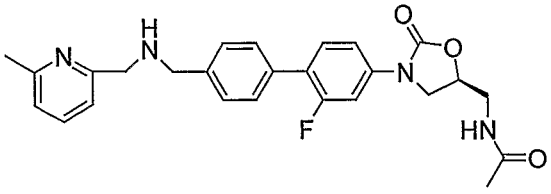
4072	
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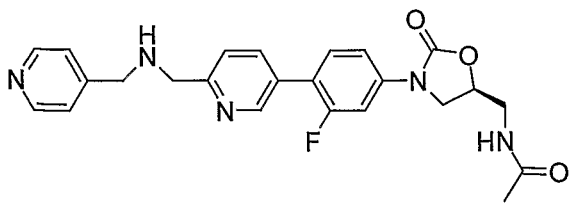
4073	
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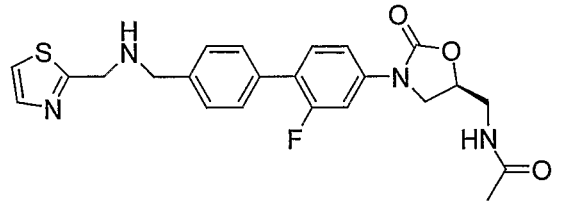
4074	
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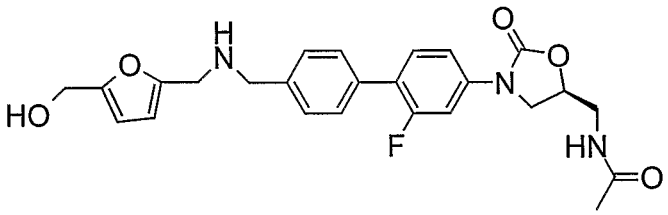
4075	
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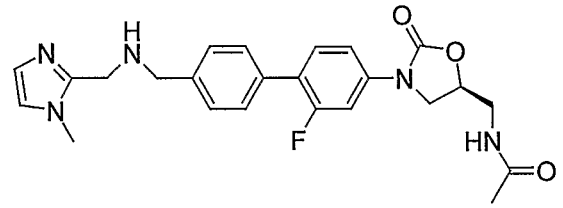
4076	
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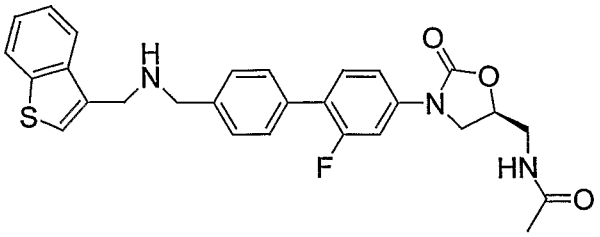
4077	
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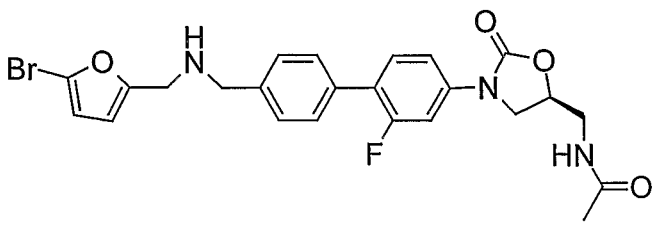
4078	
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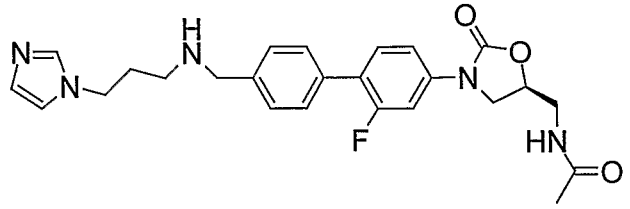
4079	
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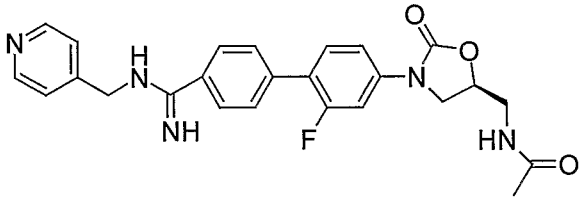
4080	
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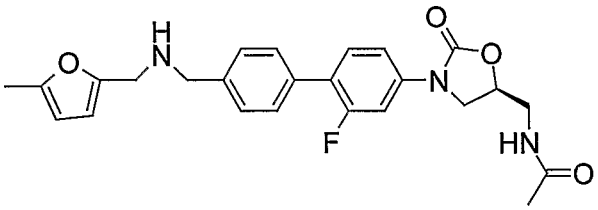
4081	
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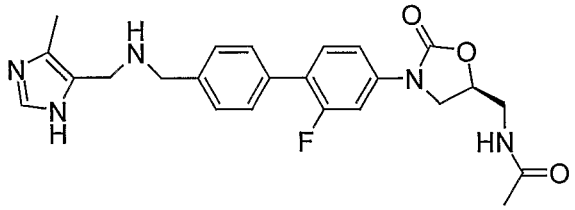
4082	
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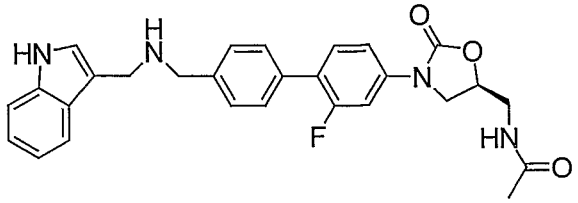
4083	
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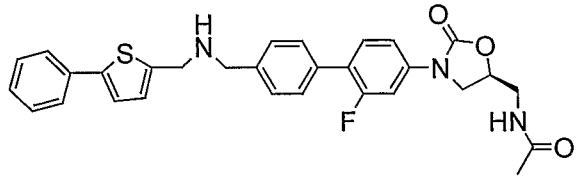
4084	
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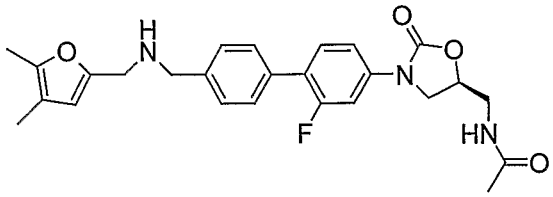
4085	
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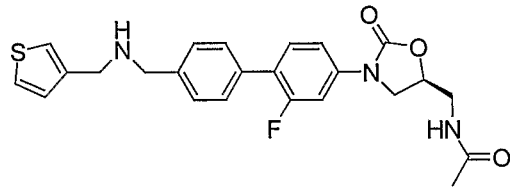
4086	
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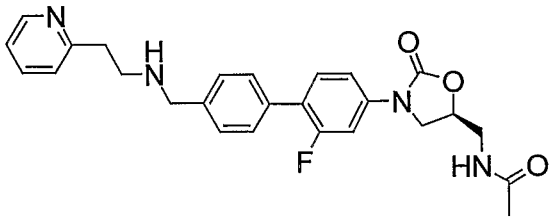
4087	
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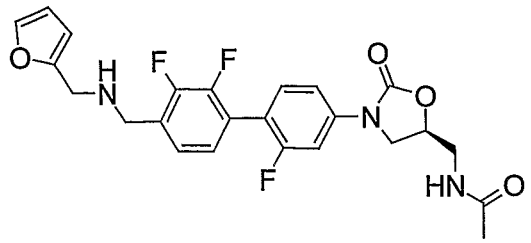
4088	
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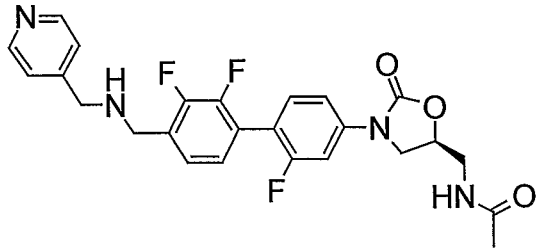
4089	
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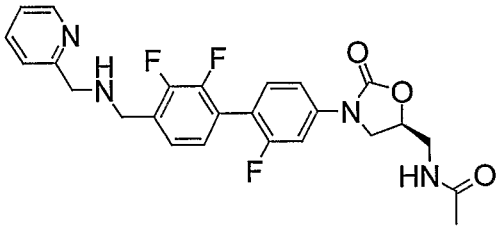
4090	
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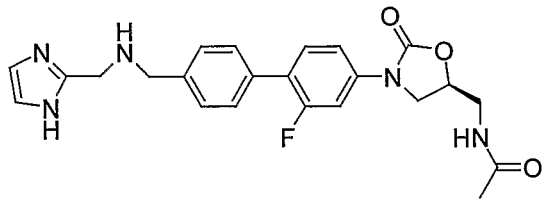
4091	
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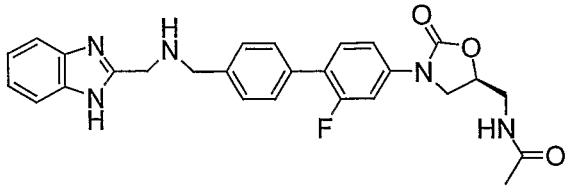
4092	
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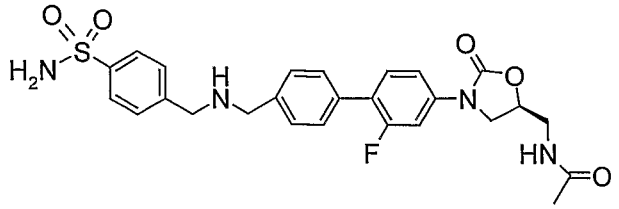
4093	
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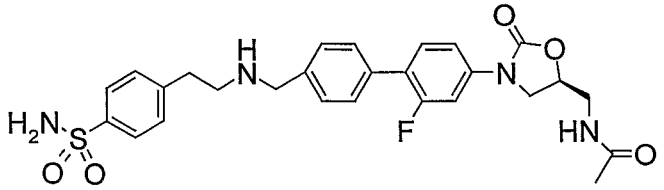
4094	
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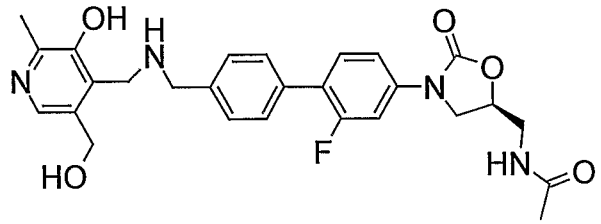
4095	
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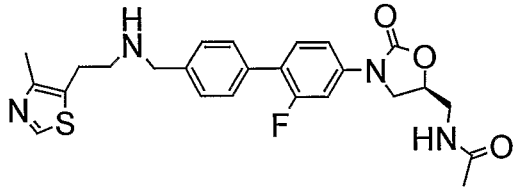
4096	
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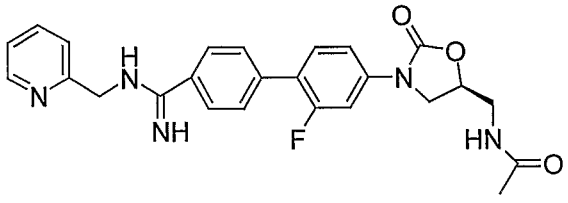
4097	
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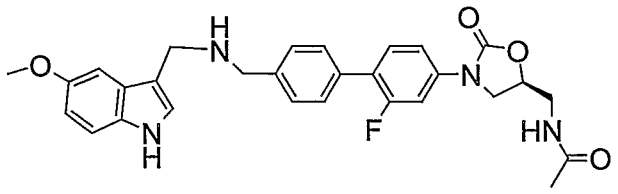
4098	
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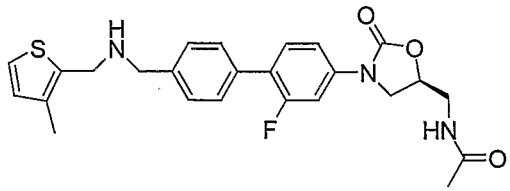
4099	
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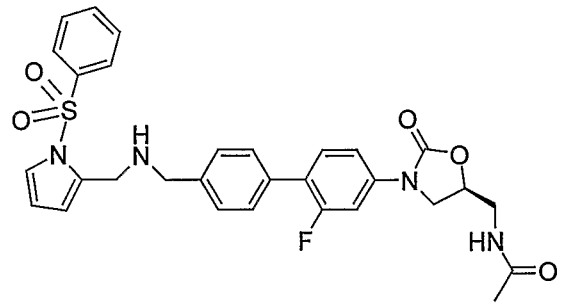
4100	
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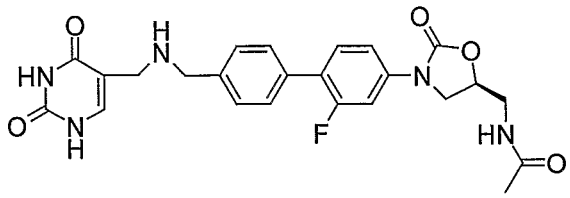
4101	
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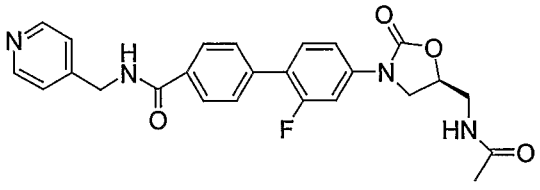
4102	
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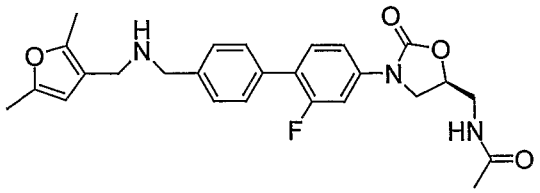
4103	
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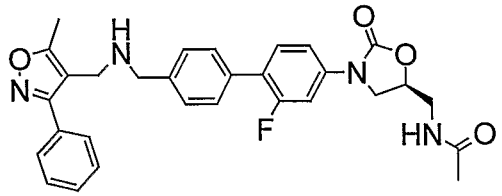
4104	
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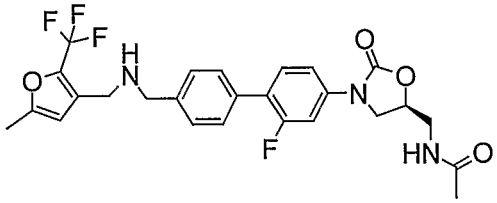
4105	
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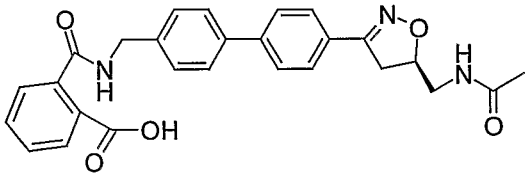
4106	
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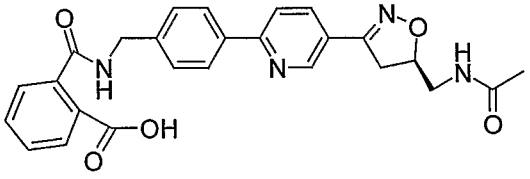
4107	
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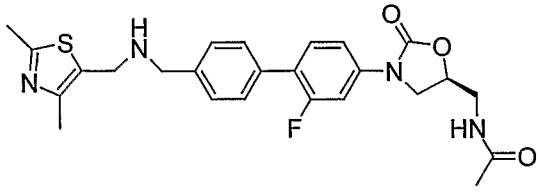
4108	

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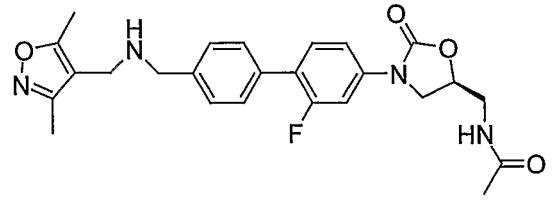
4109	
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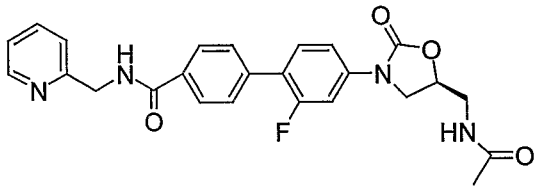
4110	
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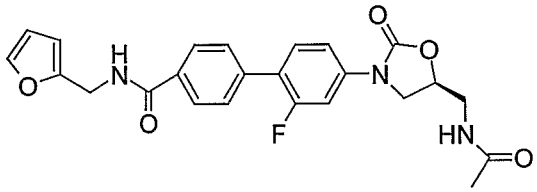
4111	
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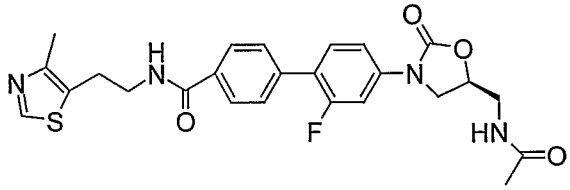
4112	
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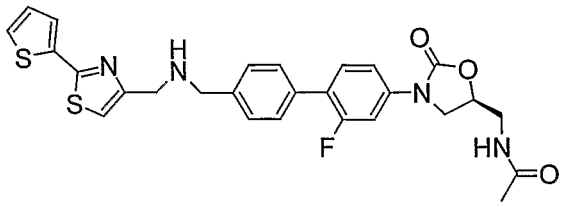
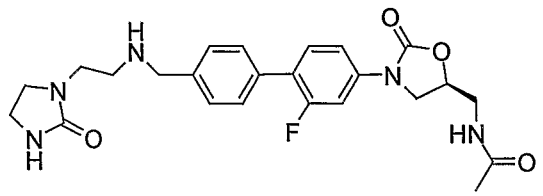
4113	
	N-[3-(2-Fluoro-4'-{[(2-thiophen-2-yl-thiazol-4-ylmethyl)-amino]-methyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide

4114	
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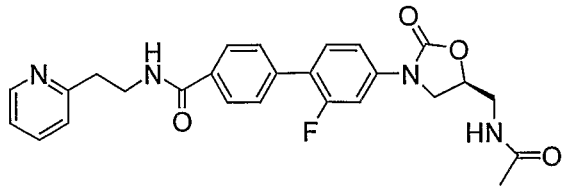
4115	
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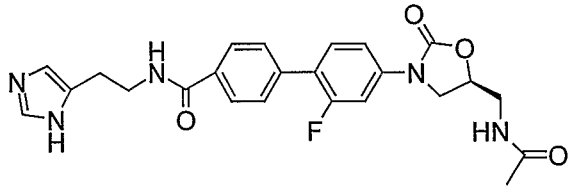
4116	
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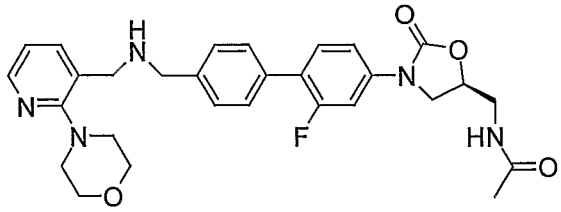
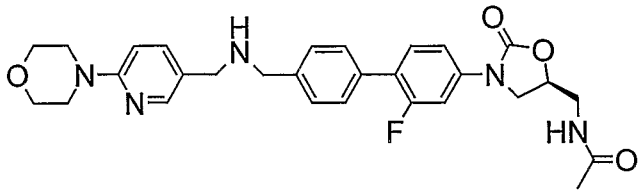
4117	
	N-[3-(2-Fluoro-4'-{[(2-morpholin-4-yl-pyridin-3-ylmethyl)-amino]-methyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
4118	
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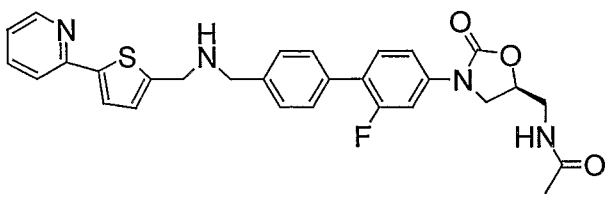
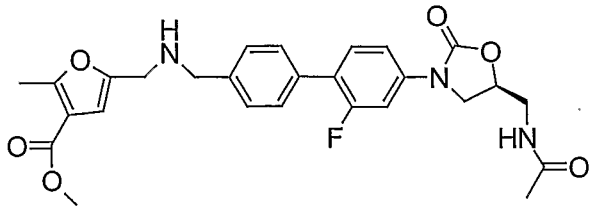
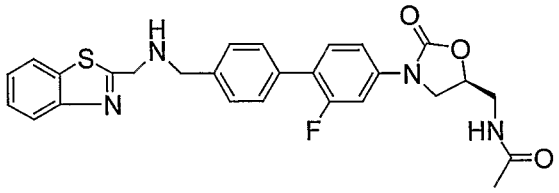
4119	

	N-[3-(2-Fluoro-4'-{[(5-pyridin-2-yl-thiophen-2-ylmethyl)-amino]-methyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
4120	
	5-[({4'-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-amino)-methyl]-2-methyl-furan-3-carboxylic acid methyl ester
4121	
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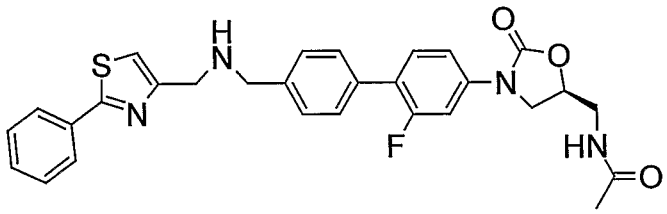
4122	
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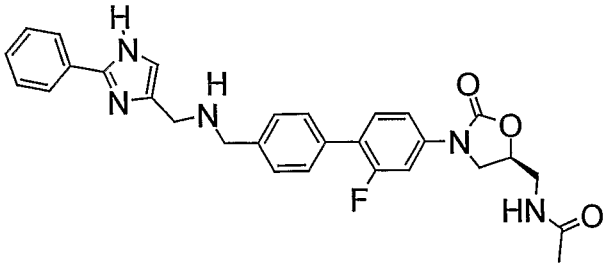
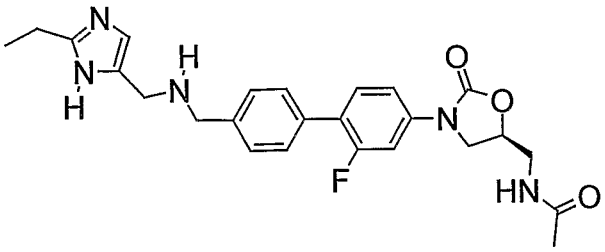
4123	
	N-[3-(2-Fluoro-4'-{[(2-phenyl-1H-imidazol-4-ylmethyl)-amino]-methyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
4124	

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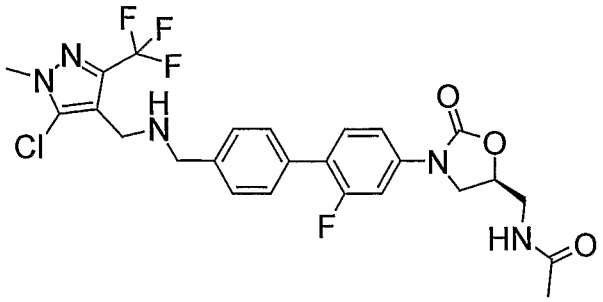
4125	
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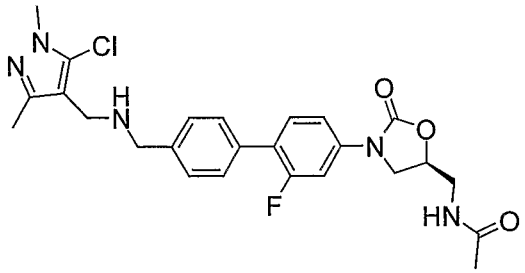
4126	
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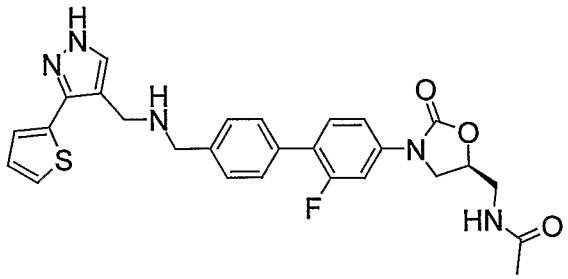
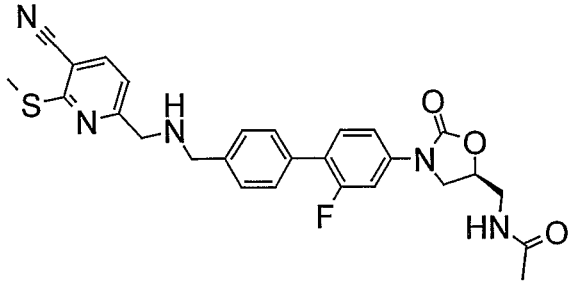
4127	
	N-[3-(2-Fluoro-4'-{[(3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-amino]-methyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
4128	

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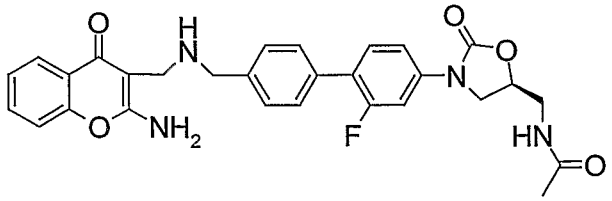
4129	
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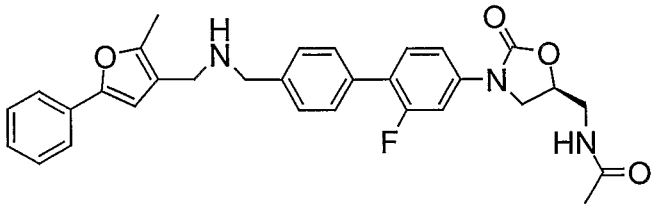
4130	
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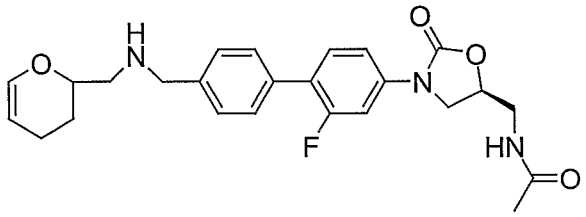
4131	
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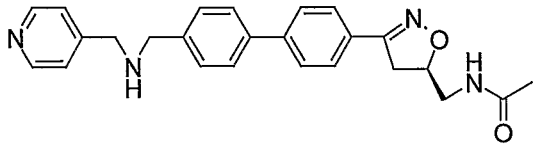
4132	
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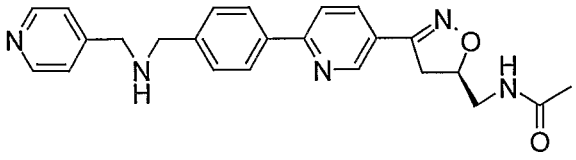
4133	
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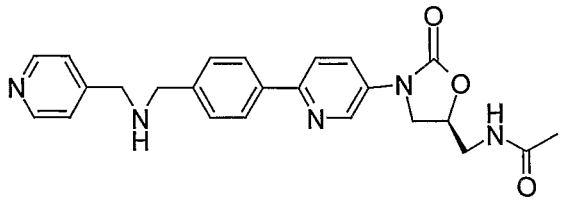
4134	
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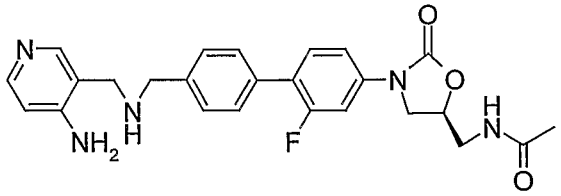
4135	
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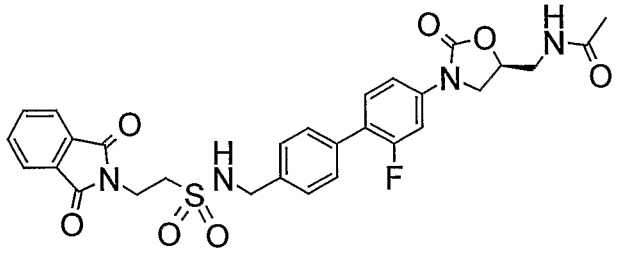
4136	
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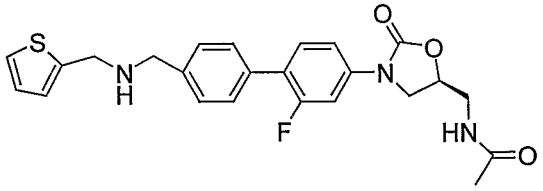
4137	
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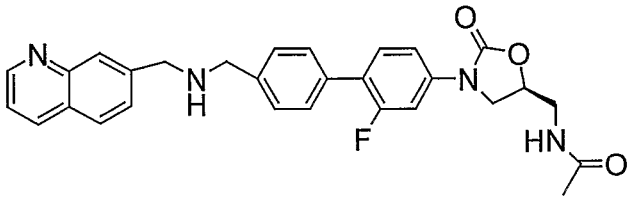
4138	
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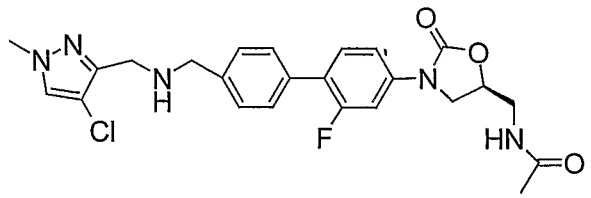
4139	
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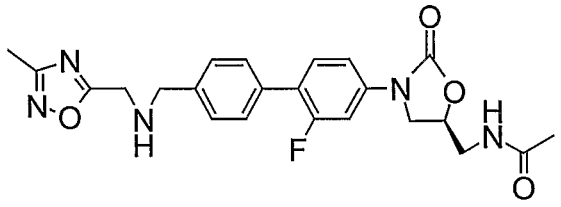
4140	
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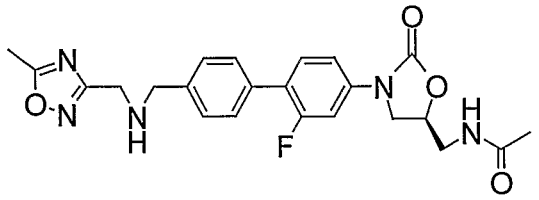
4141	
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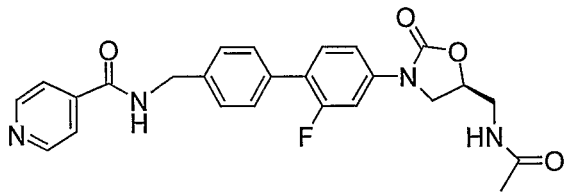
4142	
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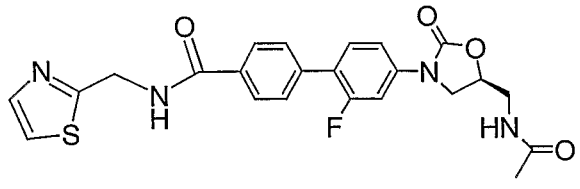
4143	
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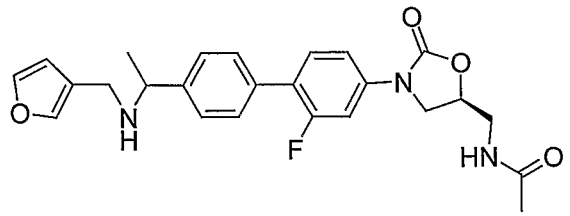
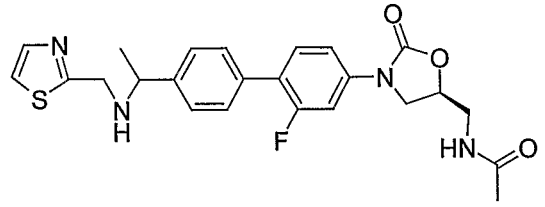
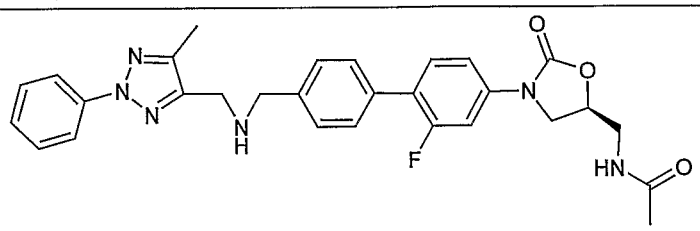
4144	
	N-[3-(2-Fluoro-4'-{1-(R/S)-[(furan-3-ylmethyl)-amino]-ethyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
4145	
	N-[3-(2-Fluoro-4'-{1-(R/S)-[(thiazol-2-ylmethyl)-amino]-ethyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
4146	
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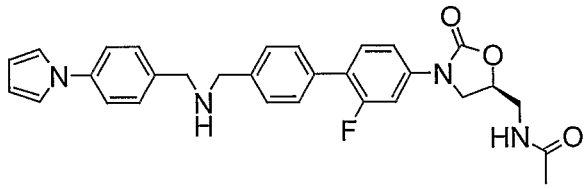
4147	
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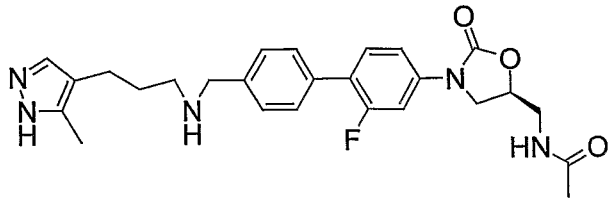
4148	
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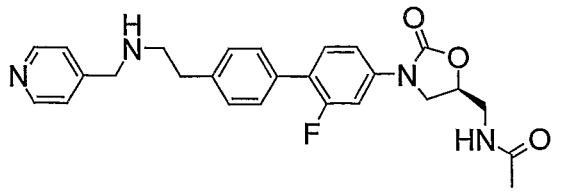
4149	
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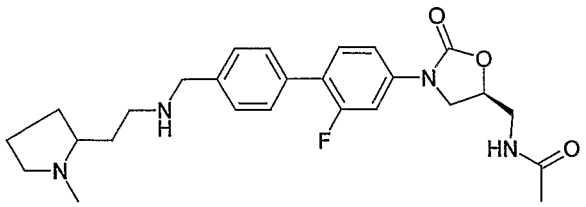
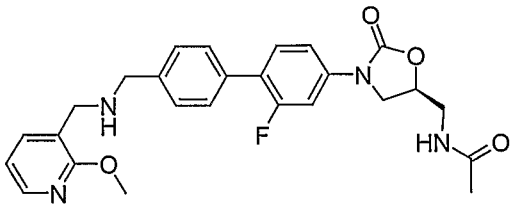
4150	
	N-[3-(2-Fluoro-4'-{[2-(R/S)-(1-methyl-pyrrolidin-2-yl)-ethylamino]-methyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
4151	
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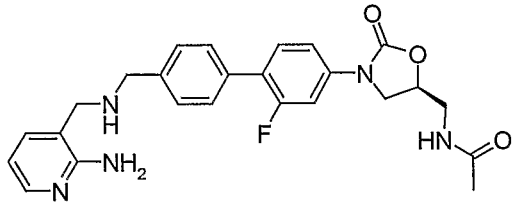
4152	
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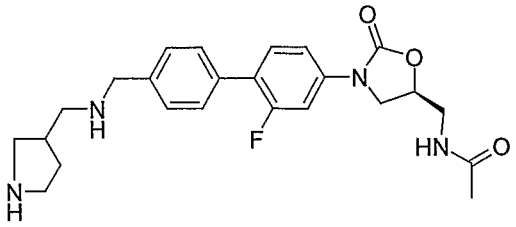
4153	
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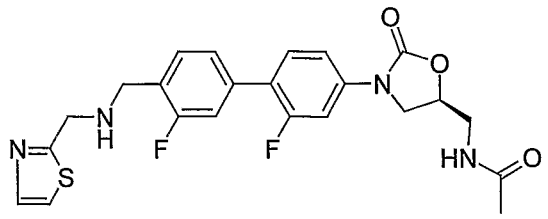
4154	
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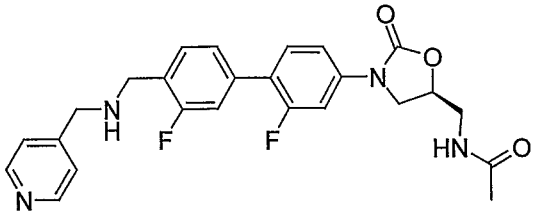
4155	
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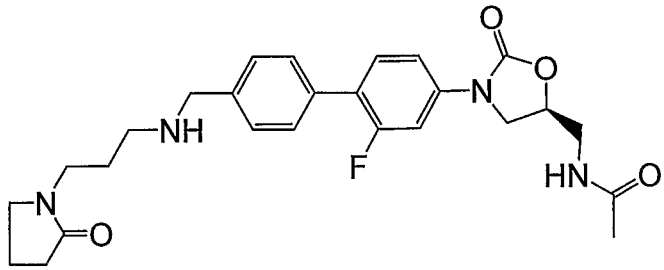
4156	
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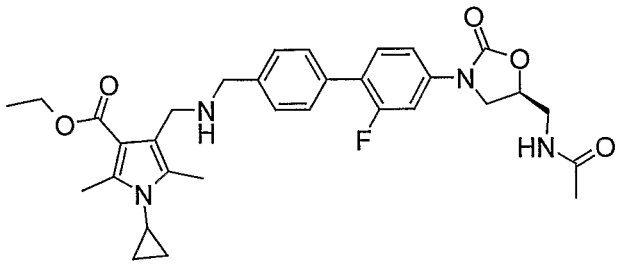
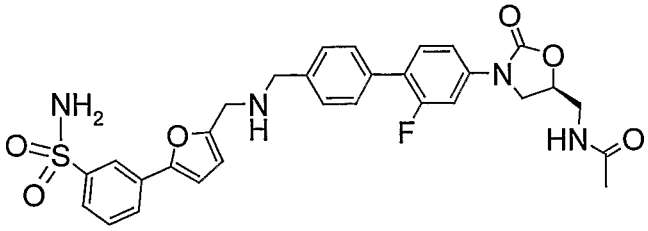
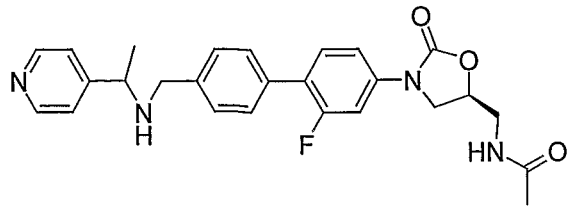
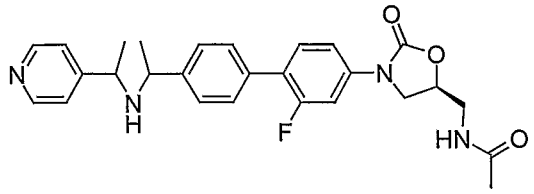
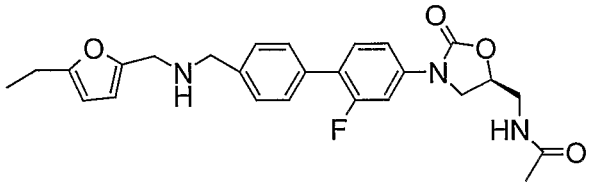
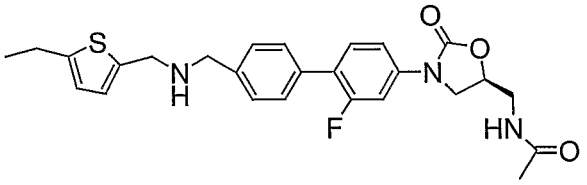
4157	
	4-[({4'-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-amino)-methyl]-1-cyclopropyl-2,5-dimethyl-1H-pyrrole-3-carboxylic acid ethyl ester
4158	

	N-{3-[2-Fluoro-4'-({[5-(3-sulfamoyl-phenyl)-furan-2-ylmethyl]-amino}-methyl)-biphenyl-4-yl]-2-oxo-oxazolidin-5-(S)-ylmethyl}-acetamide
4159	
	N-(3-{2-Fluoro-4'-[(1-pyridin-4-(R/S)-yl-ethylamino)-methyl]-biphenyl-4-yl}-2-oxo-oxazolidin-5-(S)-ylmethyl)-acetamide
4160	
	N-(3-{2-Fluoro-4'-[1-(R/S)-(1-pyridin-4-(R/S)-yl-ethylamino)-ethyl]-biphenyl-4-yl}-2-oxo-oxazolidin-5-(S)-ylmethyl)-acetamide
4161	
	N-[3-(4'-{[(5-Ethyl-furan-2-ylmethyl)-amino]-methyl}-2-fluoro-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
4162	
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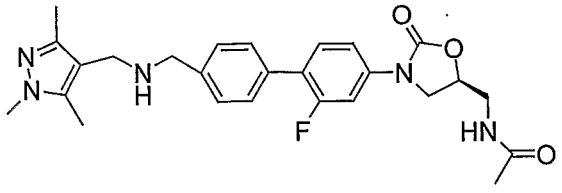
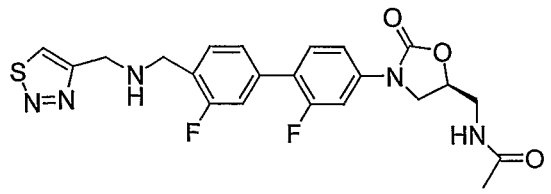
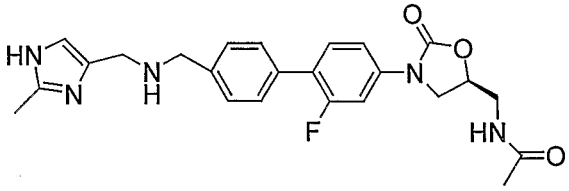
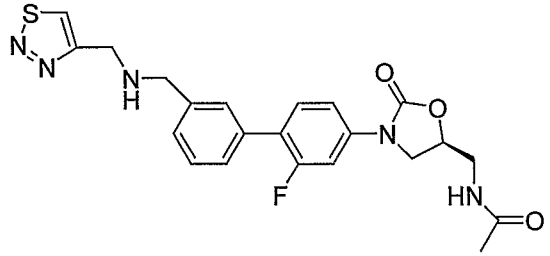
4163	
	N-[3-(2-Fluoro-4'-{[(1,3,5-trimethyl-1H-pyrazol-4-ylmethyl)-amino]-methyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide

4164	
	N-[3-(2,3'-Difluoro-4'-{[([1,2,3]thiadiazol-4-ylmethyl)-amino]-methyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
4165	
	N-[3-(2-Fluoro-4'-{[(2-methyl-1H-imidazol-4-ylmethyl)-amino]-methyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
4166	
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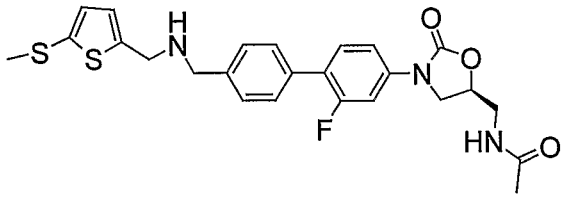
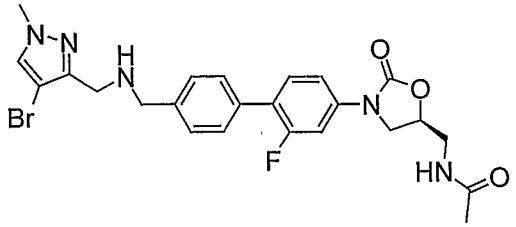
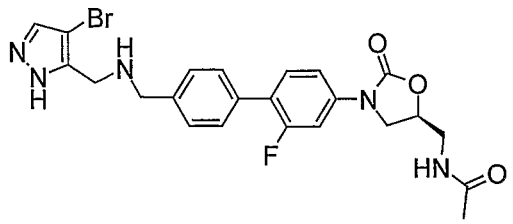
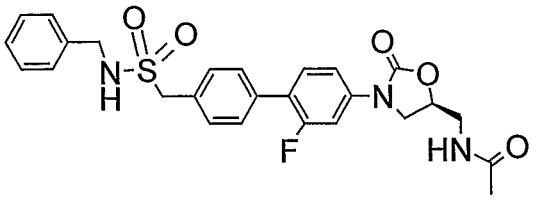
4167	
	N-[3-(2-Fluoro-4'-{[(5-methylsulfanyl-thiophen-2-ylmethyl)-amino]-methyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
4168	
	N-[3-(4'-{[(4-Bromo-1-methyl-1H-pyrazol-3-ylmethyl)-amino]-methyl}-2-fluoro-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide

4169	
	N-[3-(4'-{[(4-Bromo-2H-pyrazol-3-ylmethyl)-amino]-methyl}-2-fluoro-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
4170	
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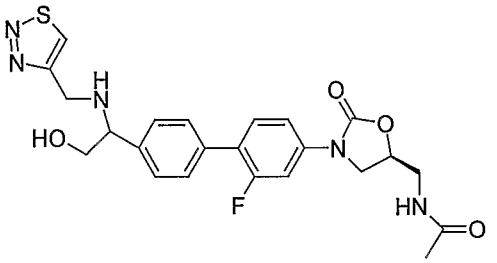
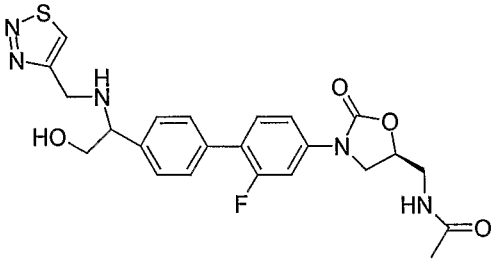
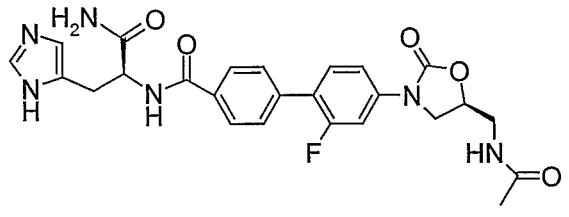
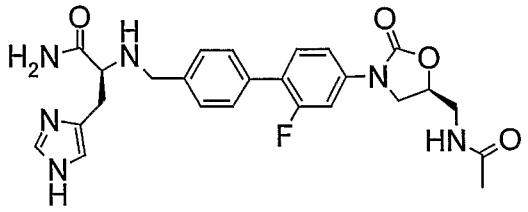
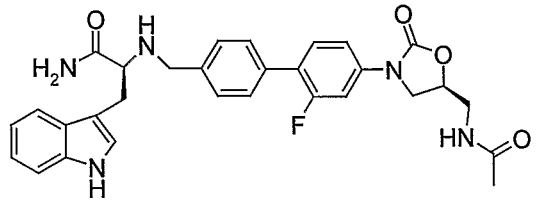
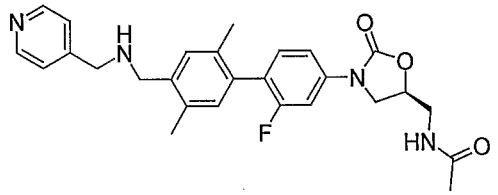
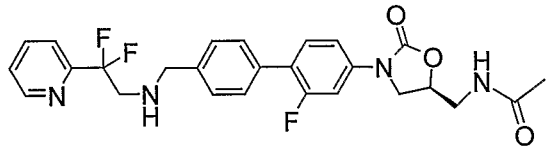
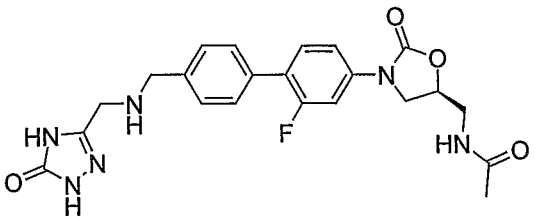
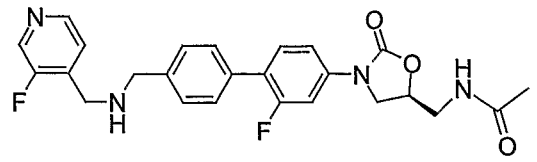
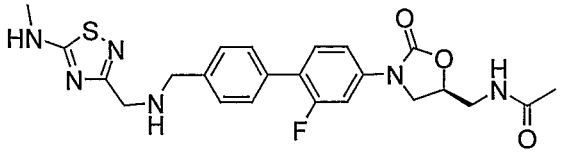
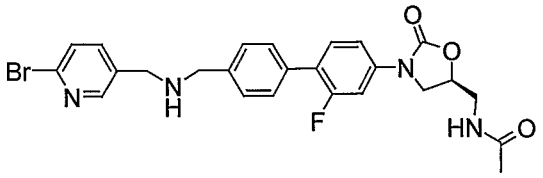
4171	
	N-[3-(2-Fluoro-4'-{2-hydroxy-1-[([1,2,3]thiadiazol-4-(R/S)-ylmethyl)-amino]-ethyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
4172	
	N-[3-(2-Fluoro-4'-{2-hydroxy-1-[([1,2,3]thiadiazol-4-(R/S)-ylmethyl)-amino]-ethyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
4173	

	4'-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-carboxylic acid [1-carbamoyl-2-(S)-(3H-imidazol-4-yl)-ethyl]-amide
4174	
	2-({4'-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-amino)-3-(S)-(1H-imidazol-4-yl)-propionamide
4175	
	2-({4'-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-amino)-3-(S)-(1H-indol-3-yl)-propionamide
4176	
	N-[3-(2-Fluoro-2',5'-dimethyl-4'-{[(pyridin-4-ylmethyl)-amino]-methyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
4177	
	N-(3-{4'-[(2,2-Difluoro-2-pyridin-2-yl-ethylamino)-methyl]-2-fluoro-biphenyl-4-yl}-2-oxo-oxazolidin-5-(S)-ylmethyl)-acetamide
4178	
	N-[3-(2-Fluoro-4'-{[(5-(S)-oxo-4,5-dihydro-1H-[1,2,4]triazol-3-ylmethyl)-amino]-methyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide

4179	
	N-[3-(2-Fluoro-4'-{[(3-fluoro-pyridin-4-ylmethyl)-amino]-methyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
4180	
	N-[3-(2-Fluoro-4'-{[(5-methylamino-[1,2,4]thiadiazol-3-ylmethyl)-amino]-methyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
4181	
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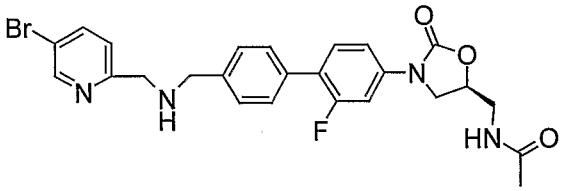
4182	
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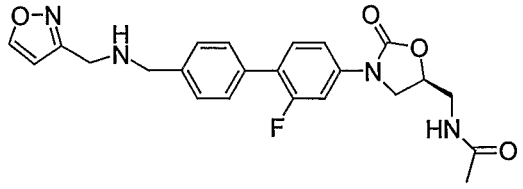
4183	
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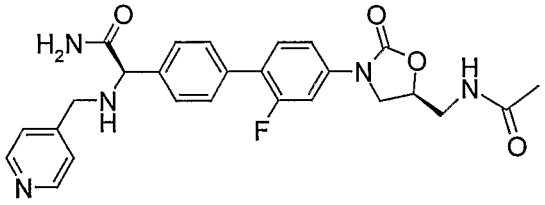
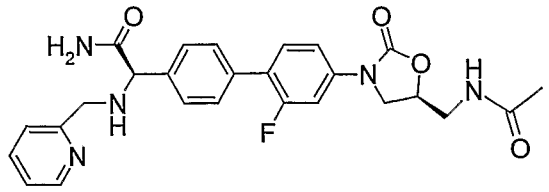
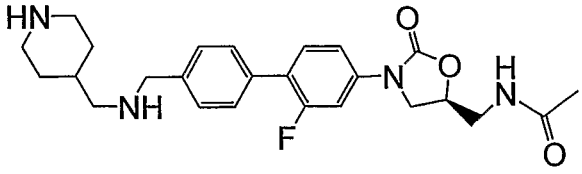
4184	
	2-{4'-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-yl}-2-(R)-[(pyridin-4-ylmethyl)-amino]-acetamide

4185	
	2-{4'-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-yl}-2-(R)-[(pyridin-2-ylmethyl)-amino]-acetamide
4186	
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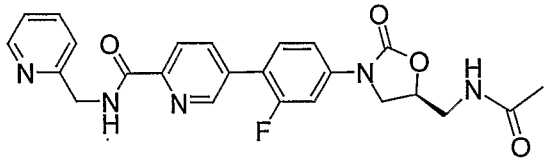
4187	
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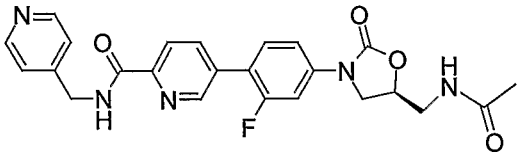
4188	
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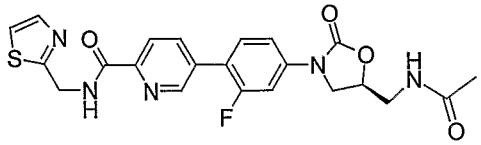
4189	
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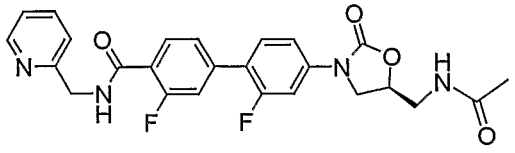
4190	
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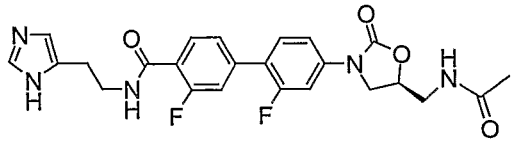
4191	

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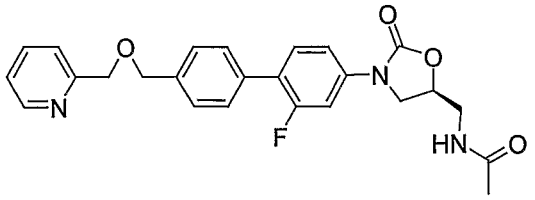
4192	
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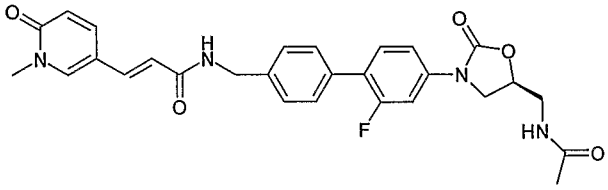
4193	
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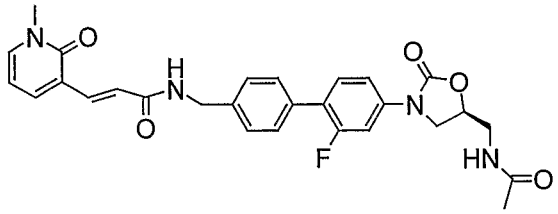
4194	
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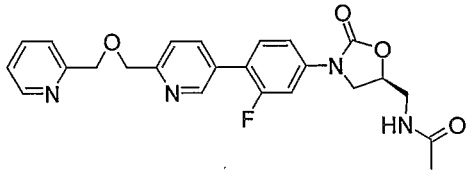
4195	
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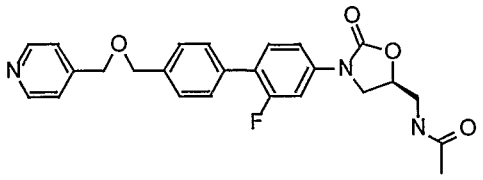
4196	
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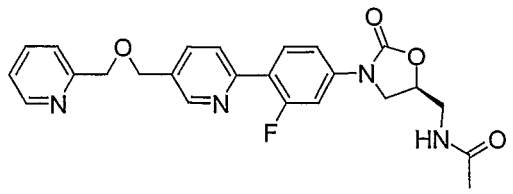
4197	
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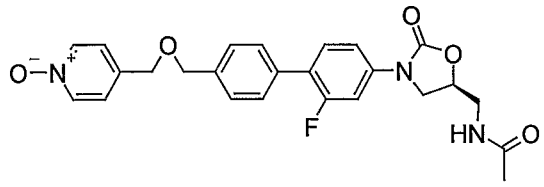
4198	
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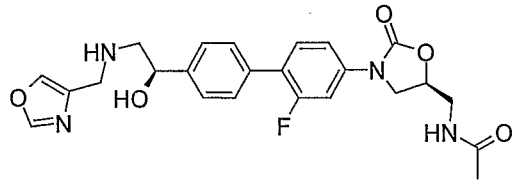
4199	
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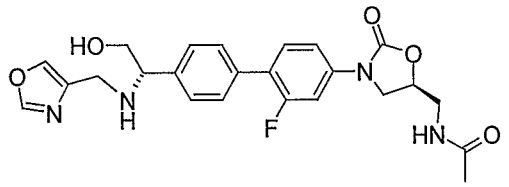
4200	
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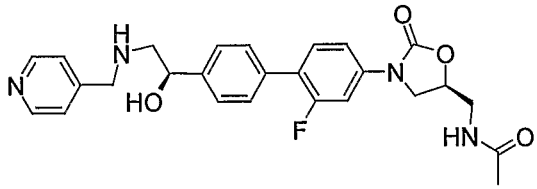
4201	
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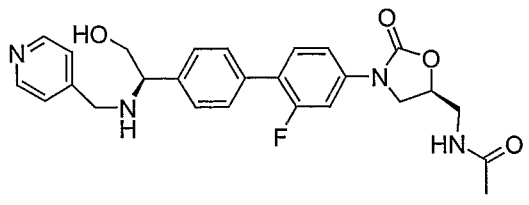
4202	

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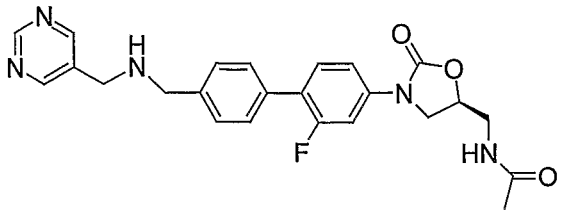
4203	
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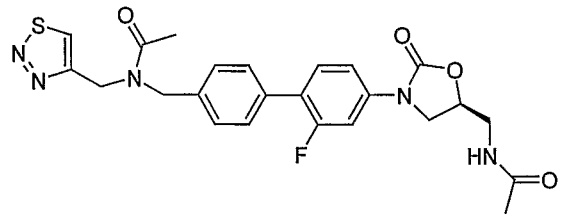
4204	
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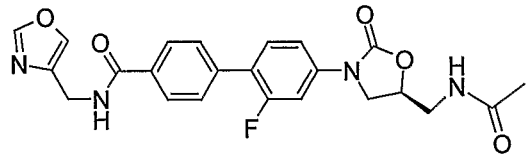
4205	
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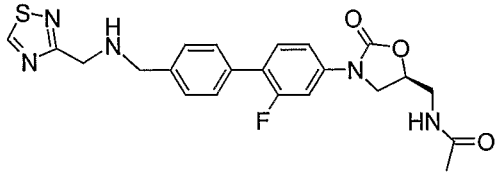
4206	
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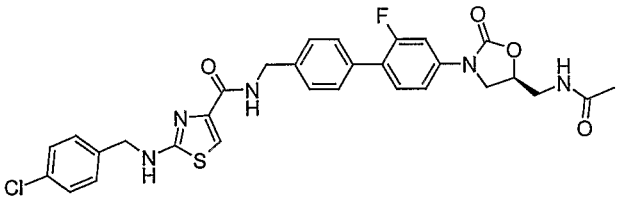
4207	
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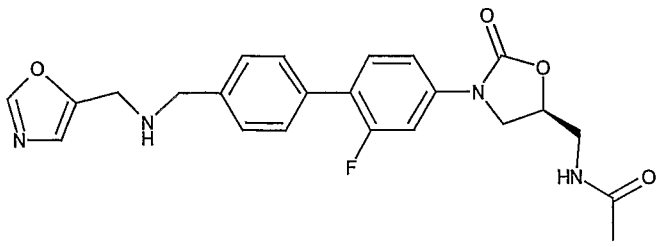
4208	
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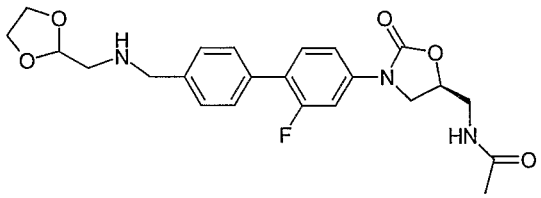
4209	
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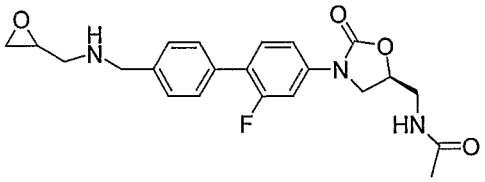
4210	
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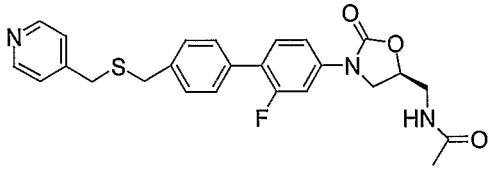
4211	
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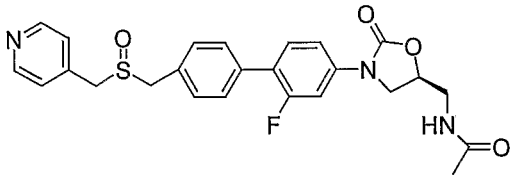
4212	
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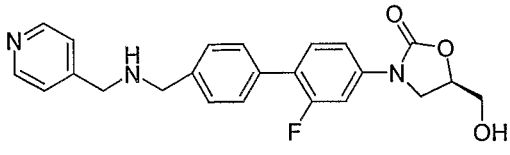
4213	
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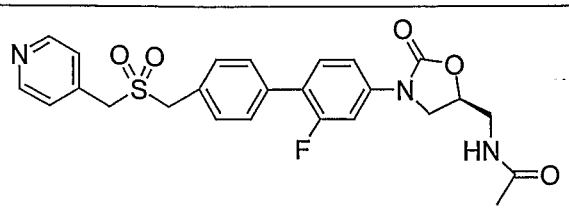
4214	
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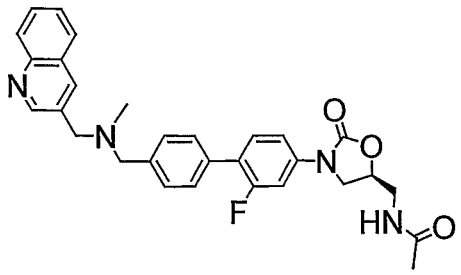
4215	
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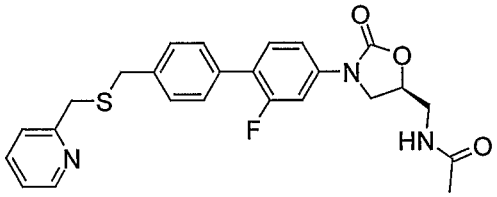
4216	
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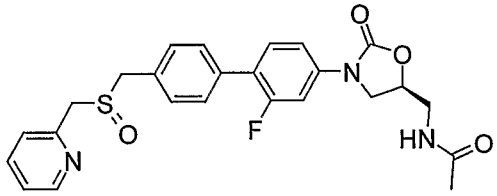
4217	
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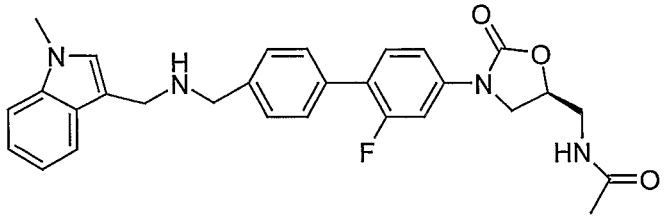
4218	
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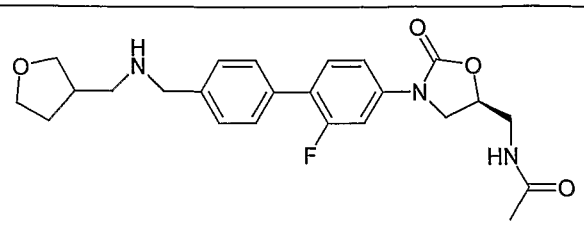
4219	
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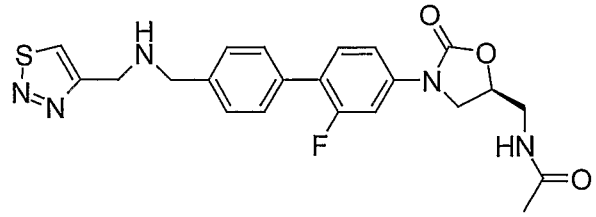
4220	
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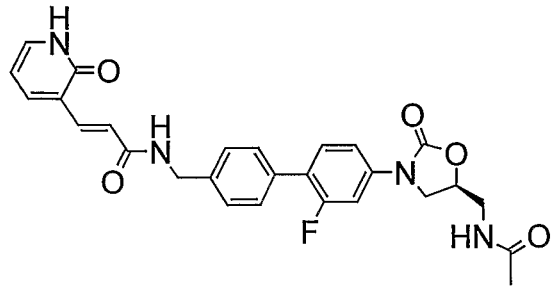
4221	
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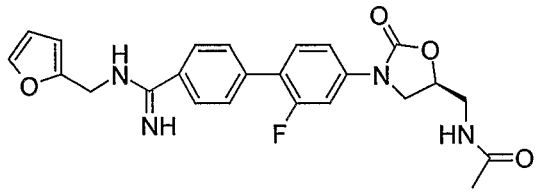
4222	
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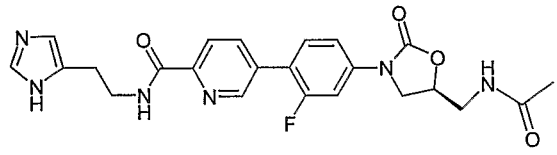
4223	
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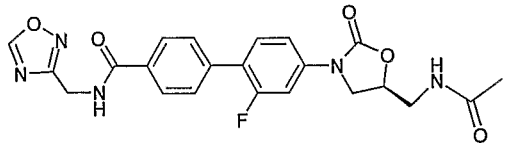
4224	

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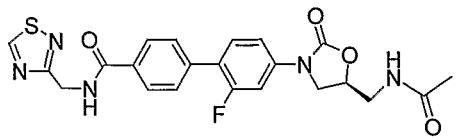
4225	
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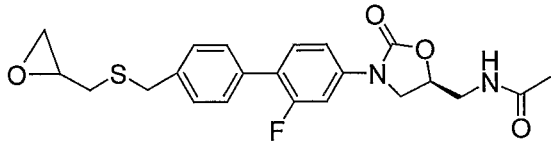
4226	
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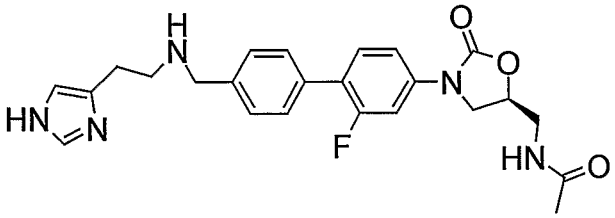
4227	
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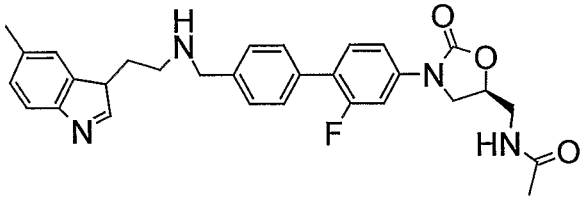
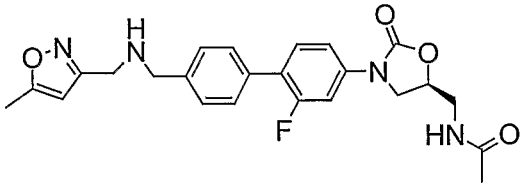
4228	
	N-[3-(2-Fluoro-4'-{[2-(5-methyl-3H-indol-3-yl)-ethylamino]-methyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
4229	
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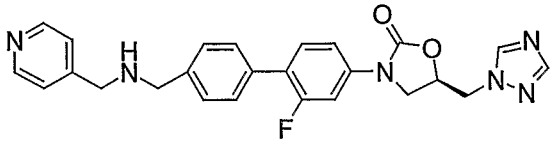
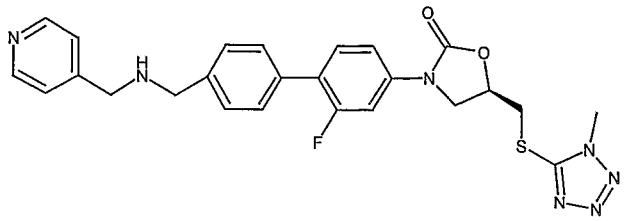
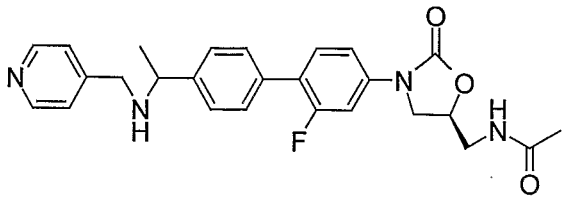
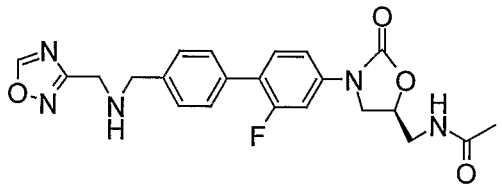
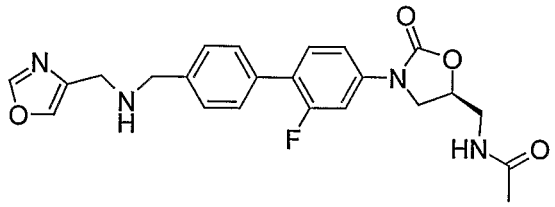
4230	

	3-(2-Fluoro-4'-{[(pyridin-4-ylmethyl)-amino]-methyl}-biphenyl-4-yl)-5-(R)-[1,2,4]triazol-1-ylmethyl-oxazolidin-2-one
4231	
	3-(2-Fluoro-4'-{[(pyridin-4-ylmethyl)-amino]-methyl}-biphenyl-4-yl)-5-(R)-(1-methyl-1H-tetrazol-5-ylsulfanylmethyl)-oxazolidin-2-one
4232	
	N-[3-(2-Fluoro-4'-{1-(R/S)-[(pyridin-4-ylmethyl)-amino]-ethyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
4233	
	N-[3-(2-Fluoro-4'-{[([1,2,4]oxadiazol-3-ylmethyl)-amino]-methyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
4234	
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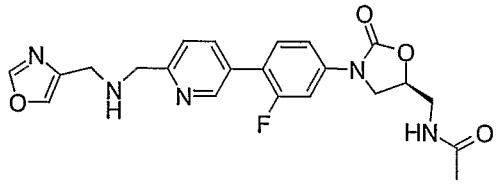
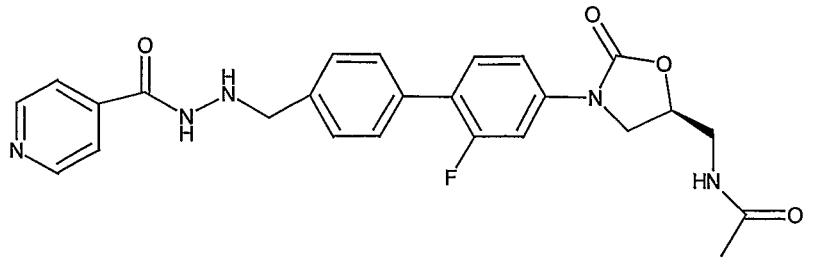
4235	
	N-{3-[3-Fluoro-4-(6-{[(oxazol-4-ylmethyl)-amino]-methyl}-pyridin-3-yl)-phenyl]-2-oxo-oxazolidin-5-(S)-ylmethyl}-acetamide

4236	
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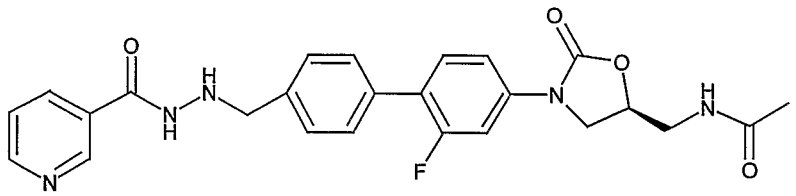
4237	
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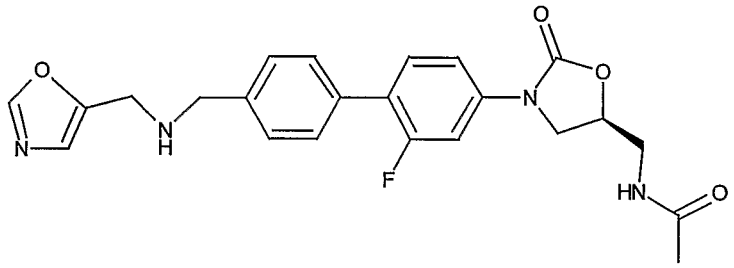
4238	
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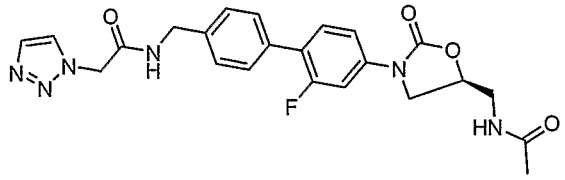
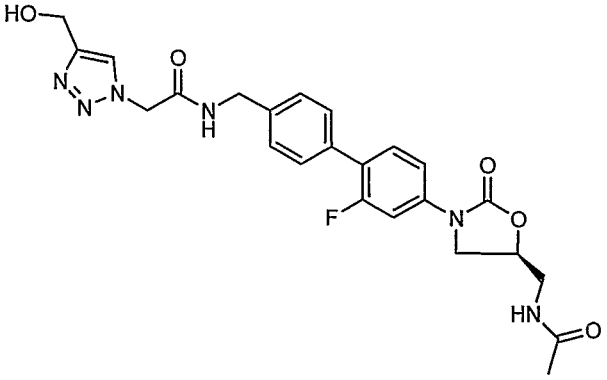
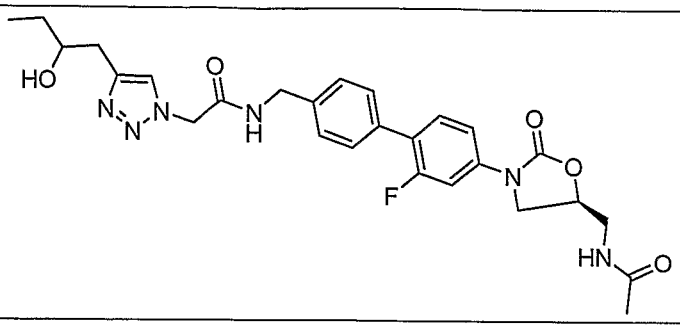
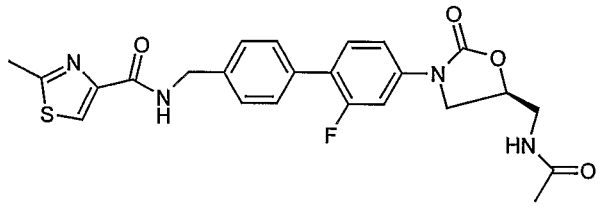
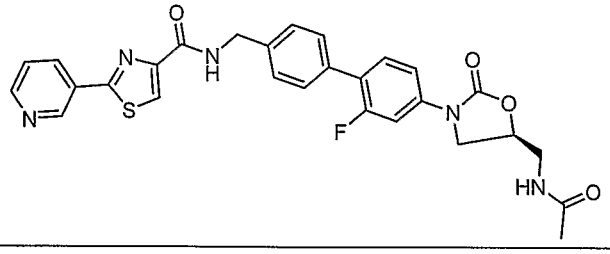
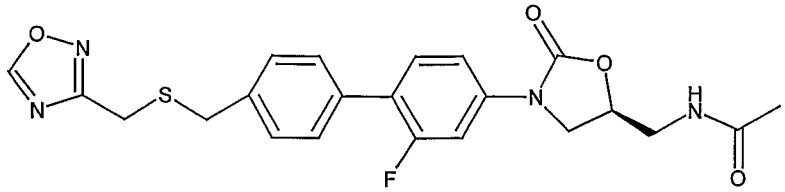
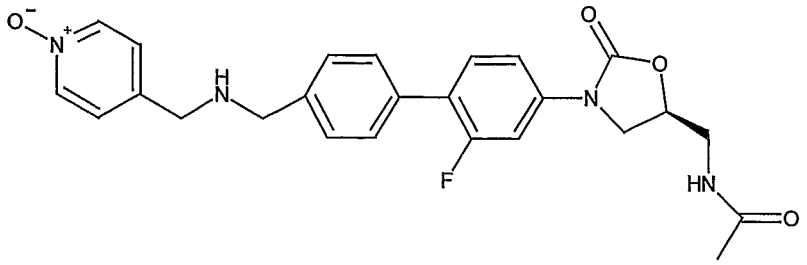
4239	
	N-{4'-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-2-[1,2,3]triazol-1-yl-acetamide
4240	

	N-{4'-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-2-(4-hydroxymethyl-[1,2,3]triazol-1-yl)-acetamide
4241	
	N-{4'-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-2-[4-(2-hydroxy-butyl)-[1,2,3]triazol-1-yl]-acetamide
4242	
	2-Methyl-thiazole-4-carboxylic acid {4'-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-amide
4243	
	2-Methyl-thiazole-4-carboxylic acid {4'-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-amide
4244	
	N-{3-[2-Fluoro-4'-([1,2,4]oxadiazol-3-ylmethylsulfanylmethyl)-biphenyl-4-yl]-2-oxo-oxazolidin-5-(S)-ylmethyl}-acetamide

4245	
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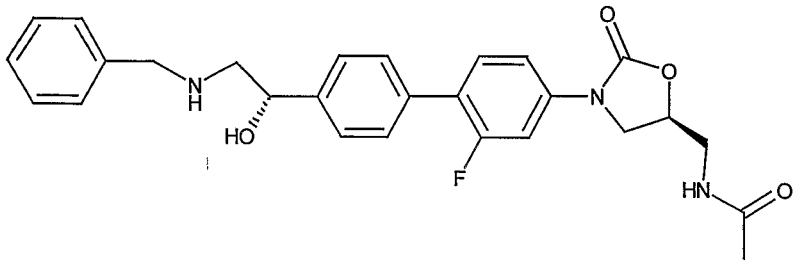
4246	
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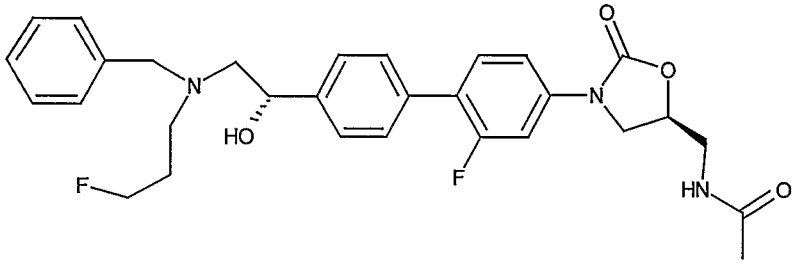
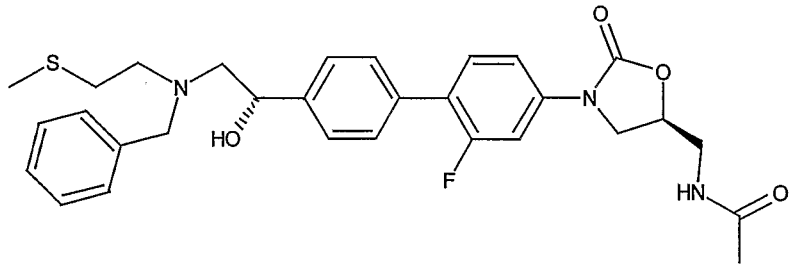
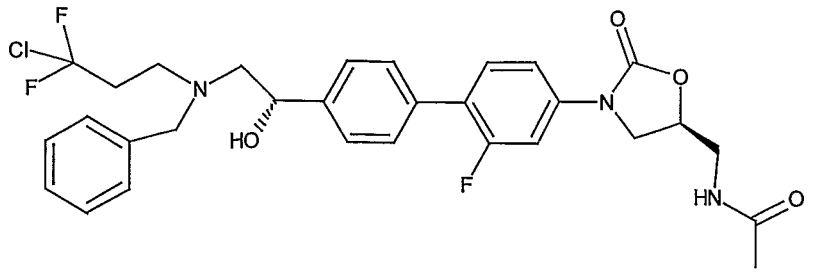
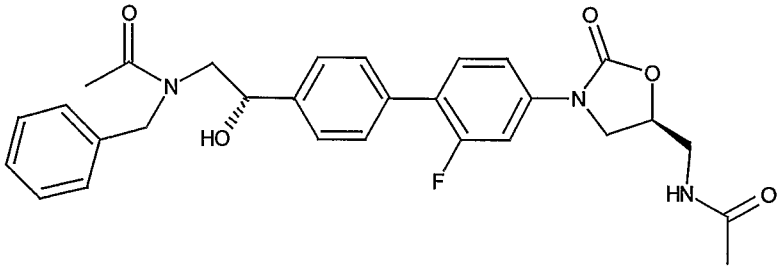
4247	
	N-[3-(4'-{2-[Benzyl-(3-fluoro-propyl)-amino]-1-(S)-hydroxy-ethyl}-2-fluoro-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
4248	
	N-[3-(4'-{2-[Benzyl-(2-methylsulfanyl-ethyl)-amino]-1-(S)-hydroxy-ethyl}-2-fluoro-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide

4249	
	N-[3-(4'-{2-[Benzyl-(3-chloro-3,3-difluoro-propyl)-amino]-1-(S)-hydroxy-ethyl}-2-fluoro-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
4250	
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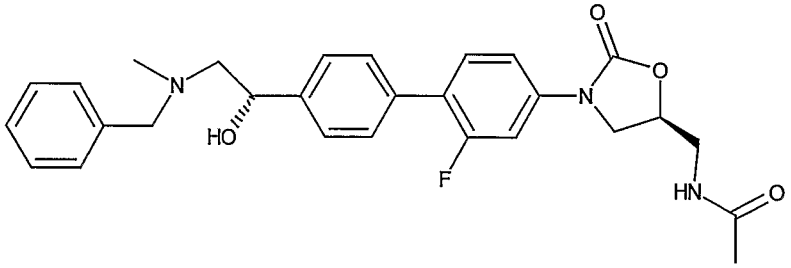
4251	
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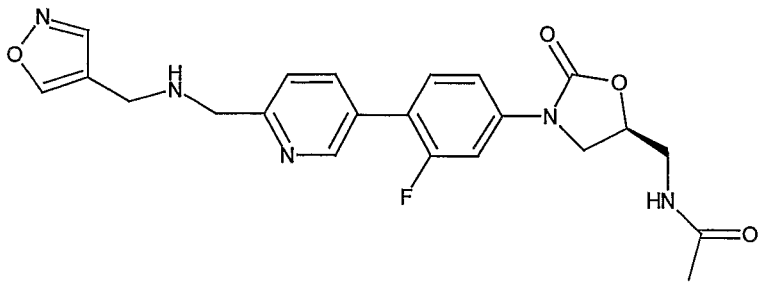
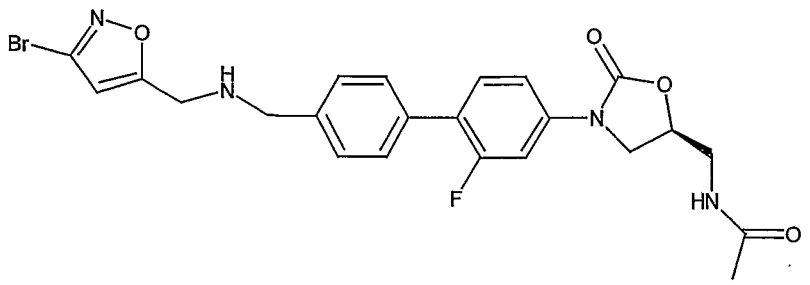
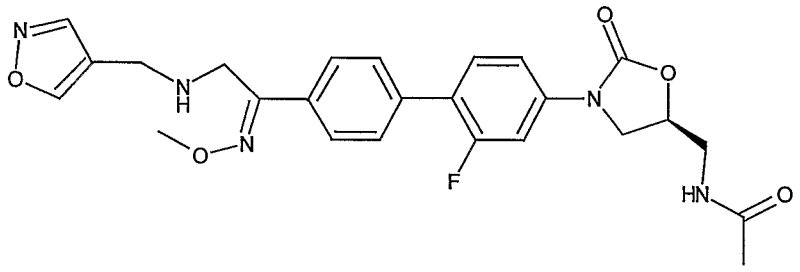
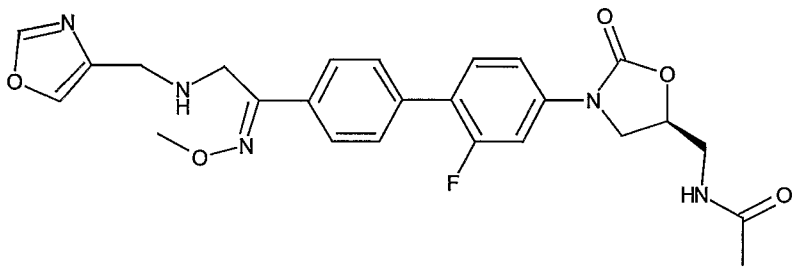
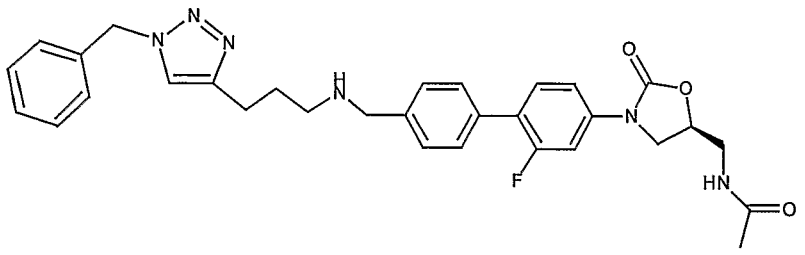
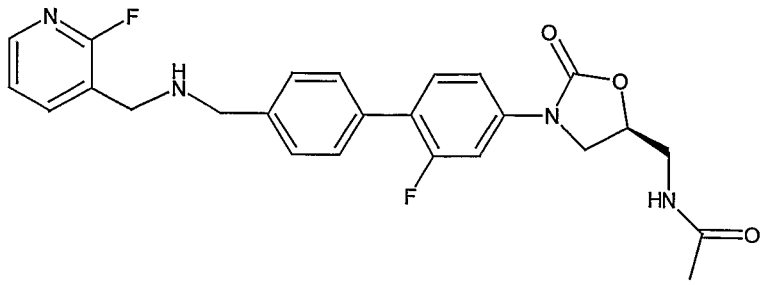
4252	
	N-{3-[3-Fluoro-4-(6-{[(isoxazol-4-ylmethyl)-amino]-methyl}-pyridin-3-yl)-phenyl]-2-oxo-oxazolidin-5-(S)-ylmethyl}-acetamide

4253	
	N-[3-(4'-{[(3-Bromo-isoxazol-5-ylmethyl)-amino]-methyl}-2-fluoro-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
4254	
	N-[3-(2-Fluoro-4'-{2-[(isoxazol-4-ylmethyl)-amino]-1-methoxyimino-ethyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
4255	
	N-[3-(2-Fluoro-4'-{1-methoxyimino-2-[(oxazol-4-ylmethyl)-amino]-ethyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
4256	
	N-[3-(4'-{[3-(1-Benzyl-1H-[1,2,3]triazol-4-yl)-propylamino]-methyl}-2-fluoro-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide

4257	
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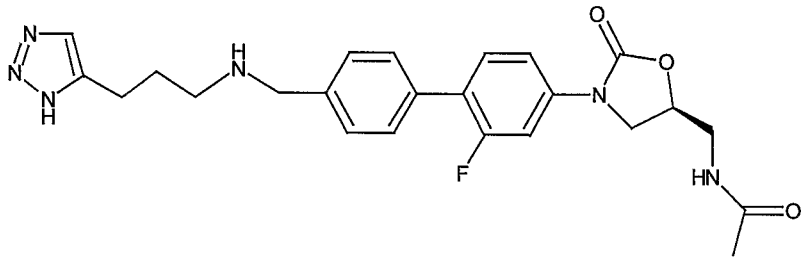
4258	
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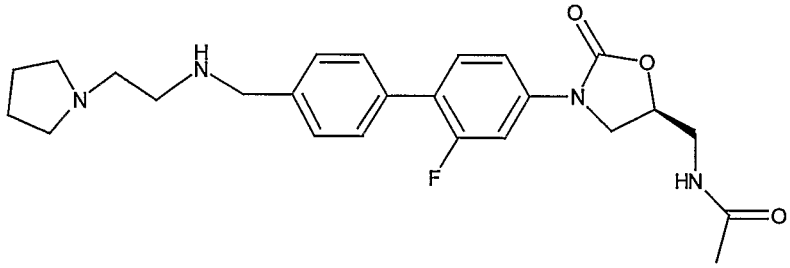
4259	
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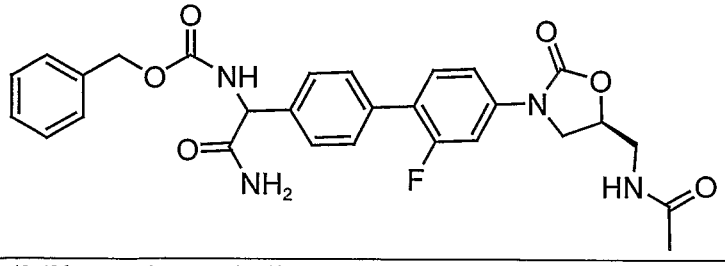
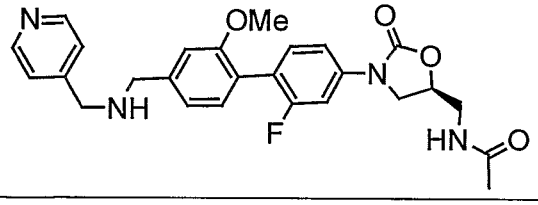
4260	
	N-[3-(3-Fluoro-4-morpholin-4-yl-phenyl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-3-(5-pyrimidin-2-yl-pyridin-2-yl)-propionamide
4261	

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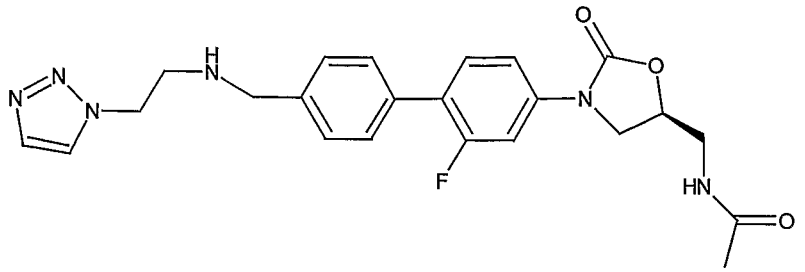
4262	
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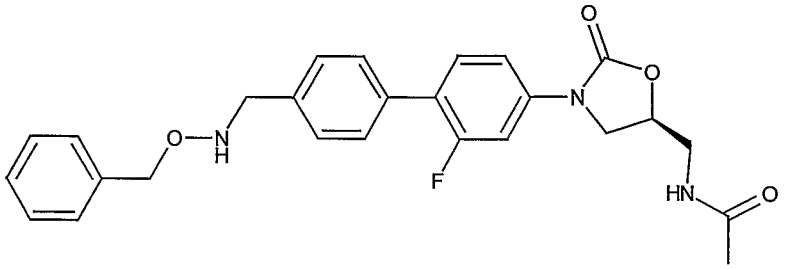
4263	
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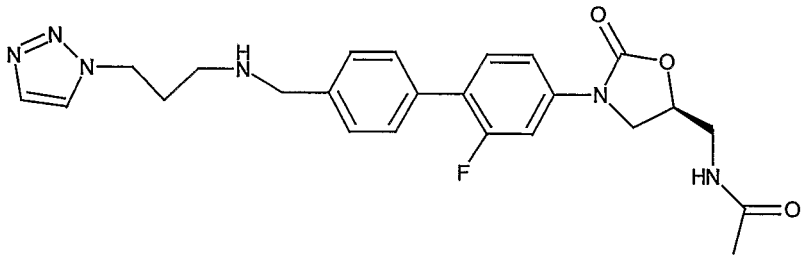
4264	
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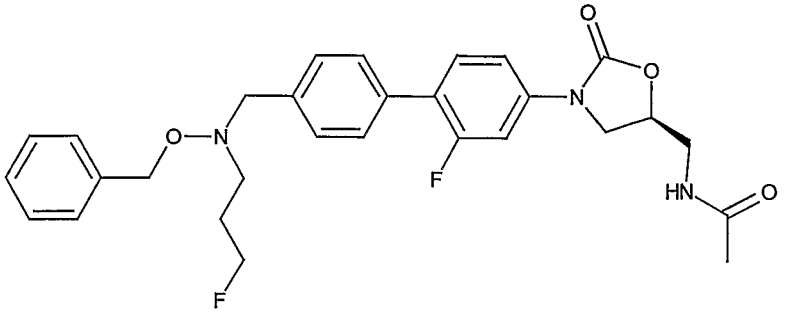
4265	
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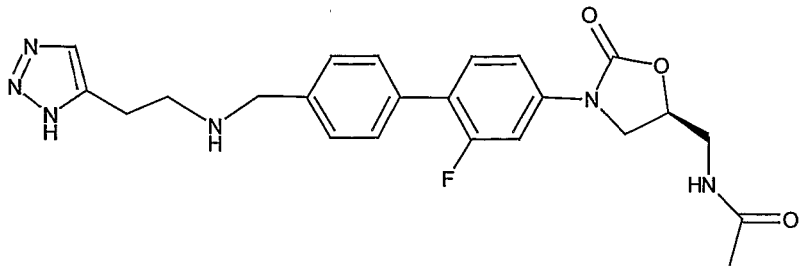
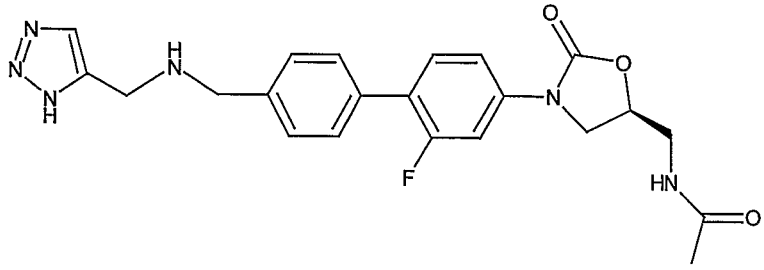
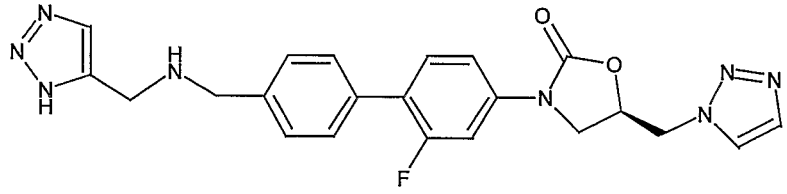
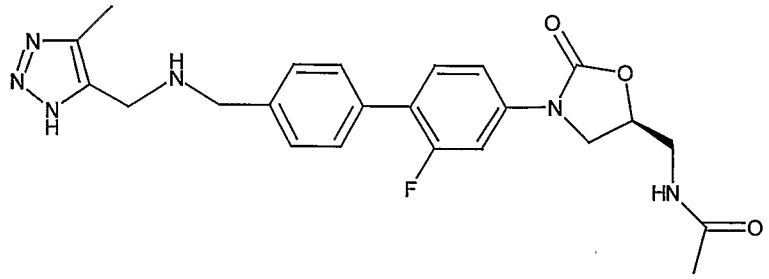
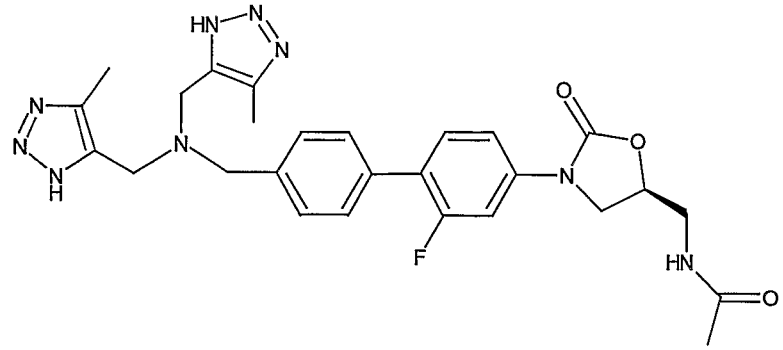
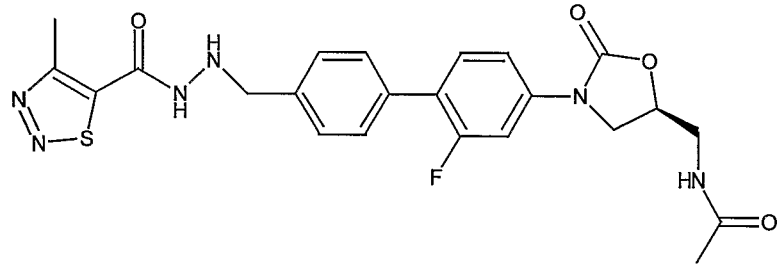
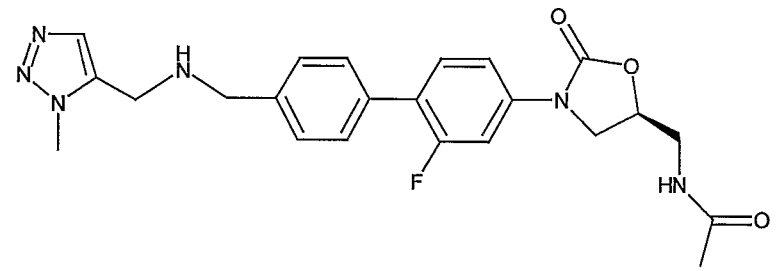
4266	
	N-[3-(2-Fluoro-4'-{[2-(3H-[1,2,3]triazol-4-yl)-ethylamino]-methyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
4267	
	N-[3-(2-Fluoro-4'-{[(3H-[1,2,3]triazol-4-ylmethyl)-amino]-methyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
4268	
	3-(2-Fluoro-4'-{[(3H-[1,2,3]triazol-4-ylmethyl)-amino]-methyl}-biphenyl-4-yl)-5-(R)-[1,2,3]triazol-1-ylmethyl-oxazolidin-2-one
4269	
	N-[3-(2-Fluoro-4'-{[(5-methyl-3H-[1,2,3]triazol-4-ylmethyl)-amino]-methyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide

4270	
	N-[3-(4'-{[Bis-(5-methyl-3H-[1,2,3]triazol-4-ylmethyl)-amino]-methyl}-2-fluoro-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
4271	
	N-(3-{2-Fluoro-4'-[N'-(4-methyl-[1,2,3]thiadiazole-carbonyl)-hydrazinomethyl]-biphenyl-4-yl}-2-oxo-oxazolidin-5-(S)-ylmethyl)-acetamide
4272	
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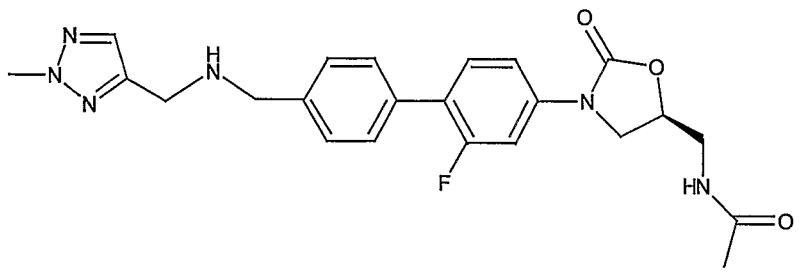
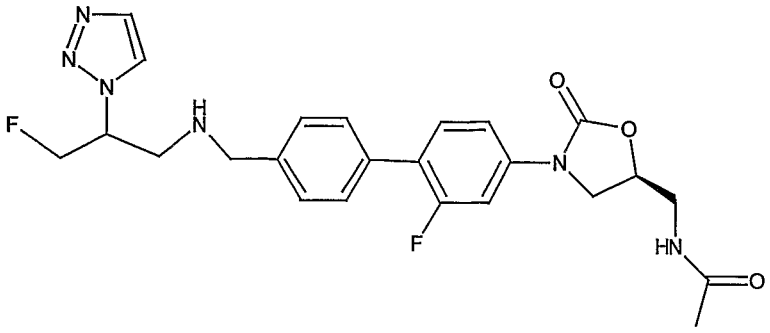
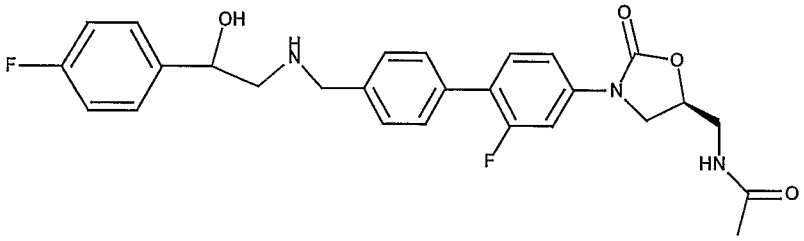
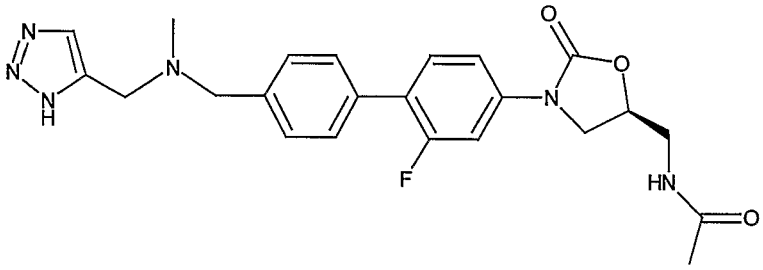
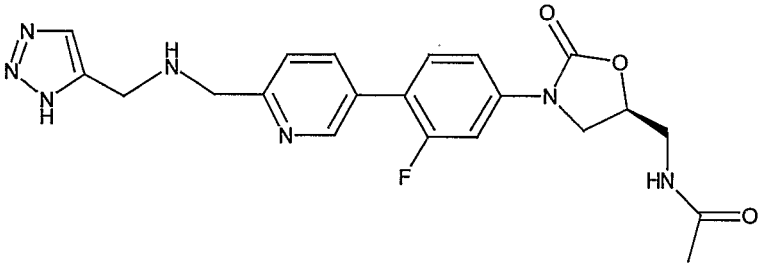
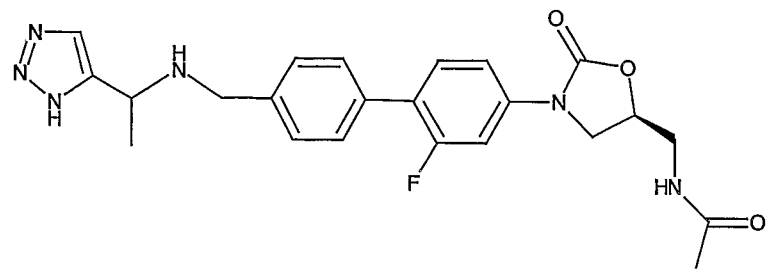
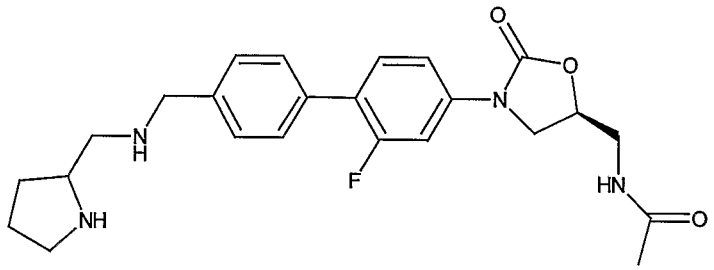
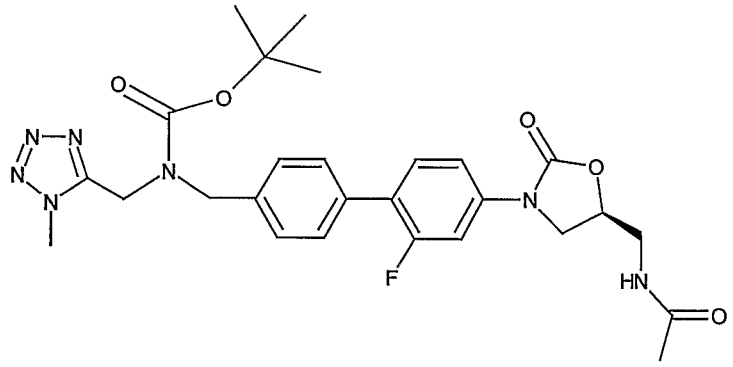
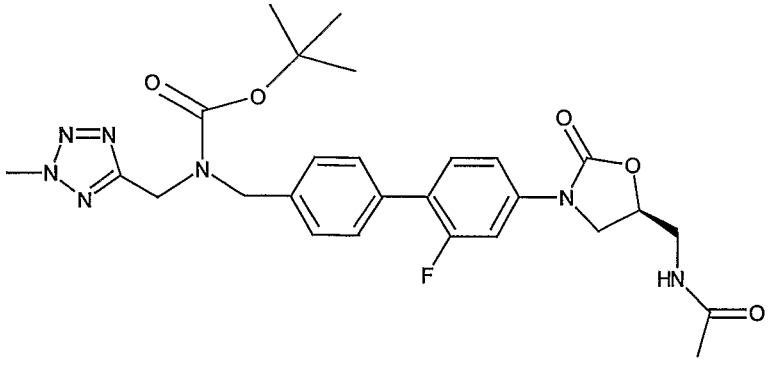
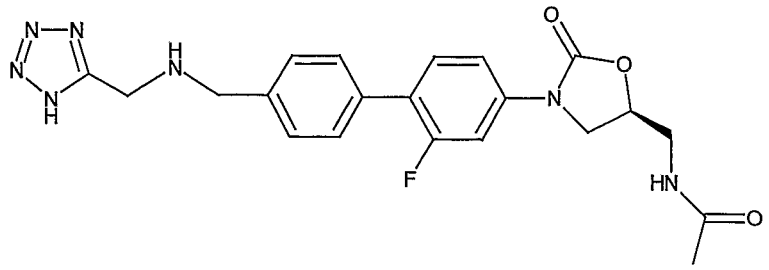
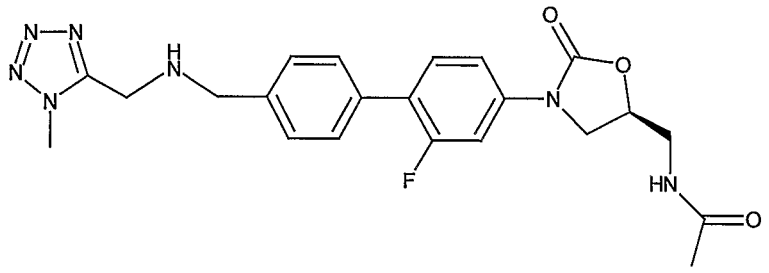
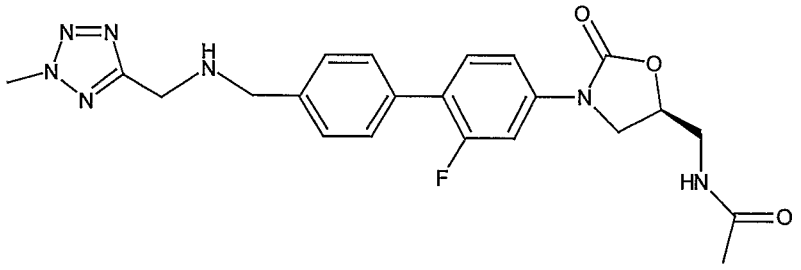
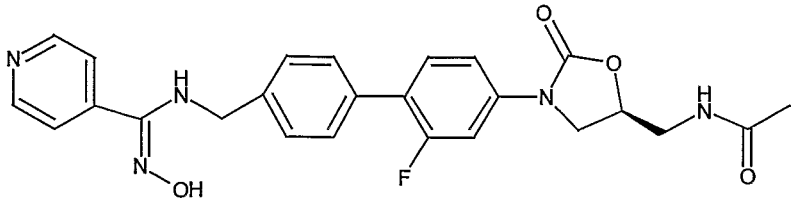
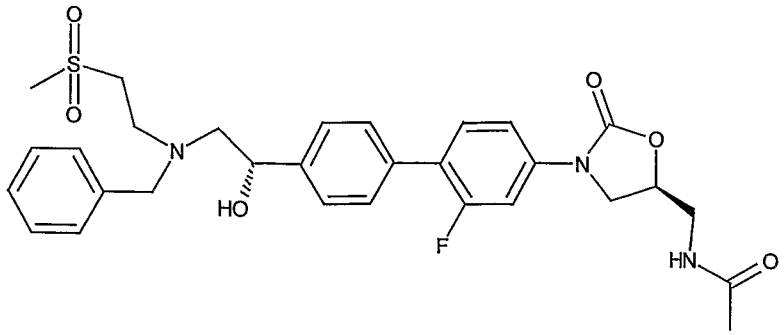
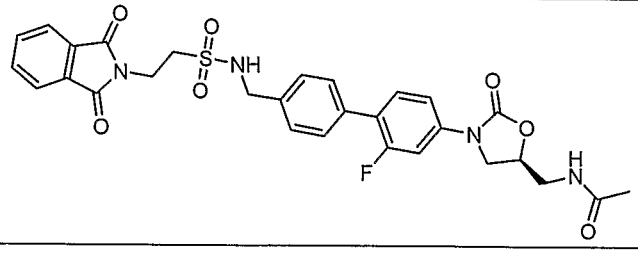
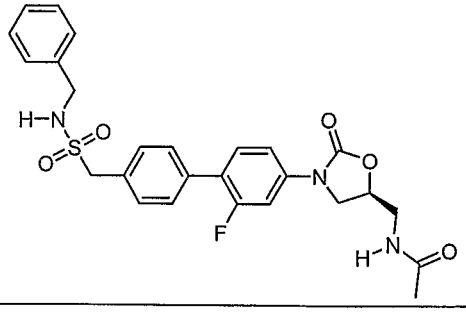
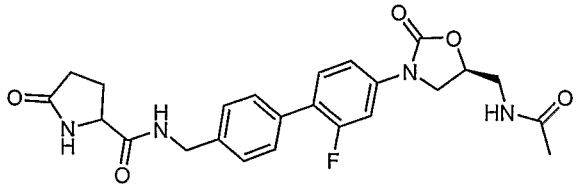
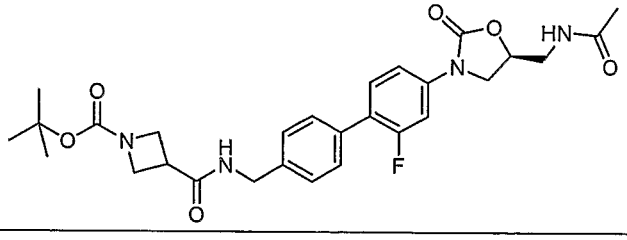
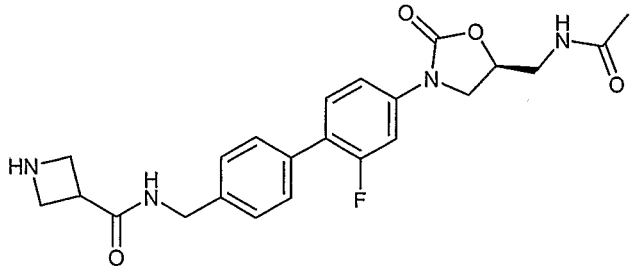
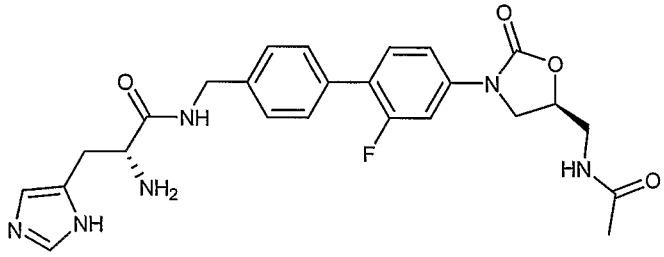
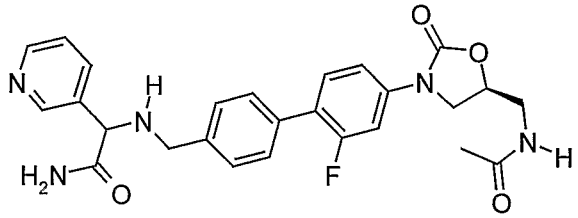
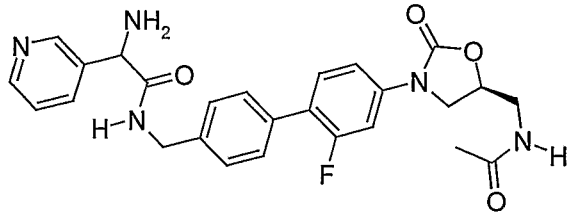
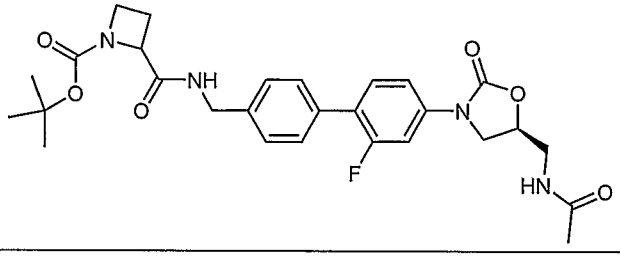
4273	
	N-[3-(2-Fluoro-4'-{[(2-methyl-2H-[1,2,3]triazol-4-ylmethyl)-amino]-methyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide

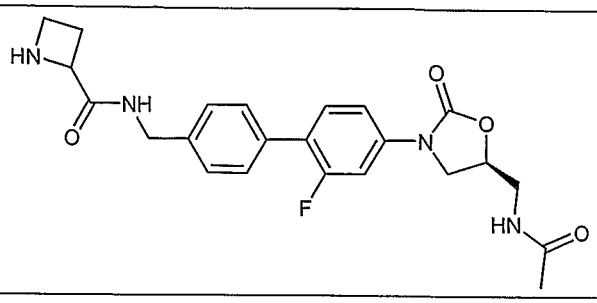
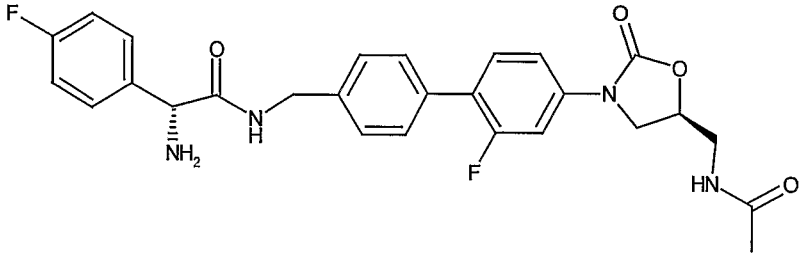
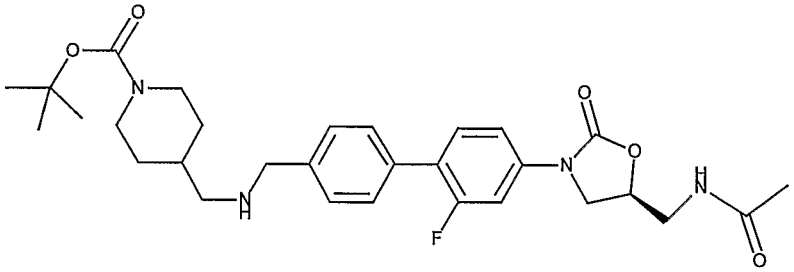
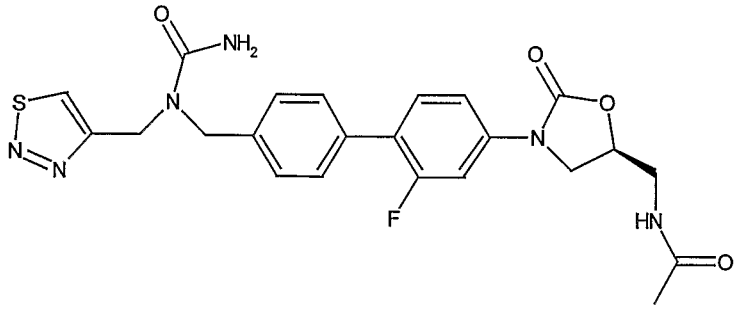
4274	
	N-(3-{2-Fluoro-4'-[(3-fluoro-2-[1,2,3]triazol-1-yl-propylamino)-methyl]-biphenyl-4-yl}-2-oxo-oxazolidin-5-(S)-ylmethyl)-acetamide
4275	
	N-[3-(2-Fluoro-4'-{[2-(4-fluoro-phenyl)-2-(R/S)-hydroxy-ethylamino]-methyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
4276	
	N-[3-(2-Fluoro-4'-{[methyl-(3H-[1,2,3]triazol-4-ylmethyl)-amino]-methyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
4277	
	N-{3-[3-Fluoro-4-(6-{[(3H-[1,2,3]triazol-4-ylmethyl)-amino]-methyl}-pyridin-3-yl)-phenyl]-2-oxo-oxazolidin-5-(S)-ylmethyl}-acetamide

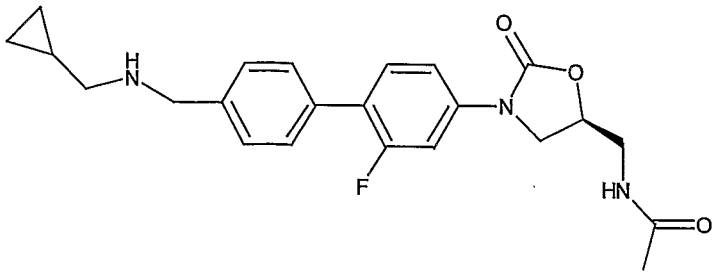
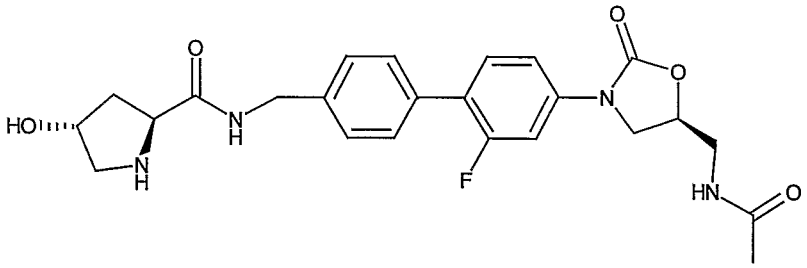
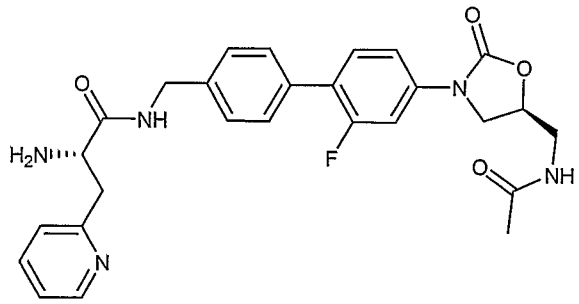
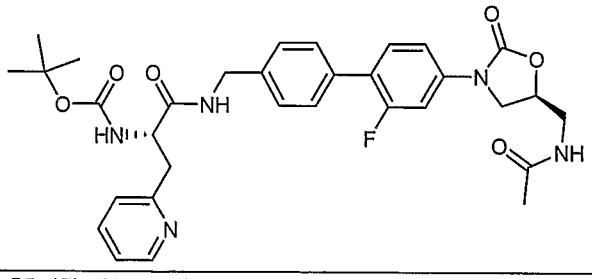
4278	
	N-[3-(2-Fluoro-4'-{[1-(R/S)-(3H-[1,2,3]triazol-4-yl)-ethylamino]-methyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
4279	
	N-[3-(2-Fluoro-4'-{[(pyrrolidin-2-(R/S)-ylmethyl)-amino]-methyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
4280	
	{4'-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro biphenyl-4-ylmethyl}-(1-methyl-1H-tetrazol-5-ylmethyl)-carbamic acid tert-butyl ester
4281	

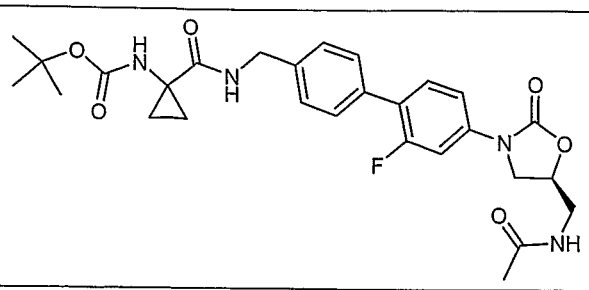
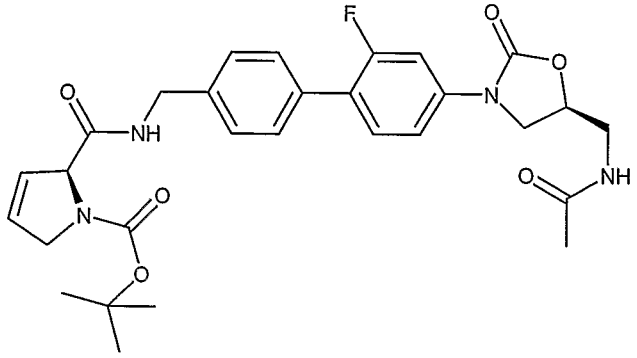
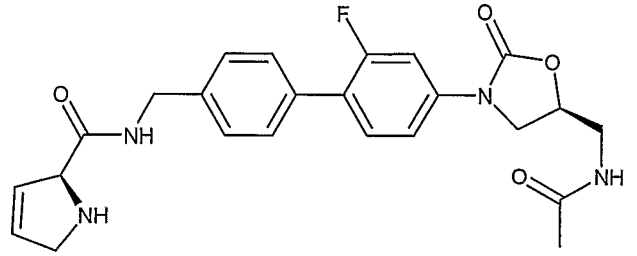
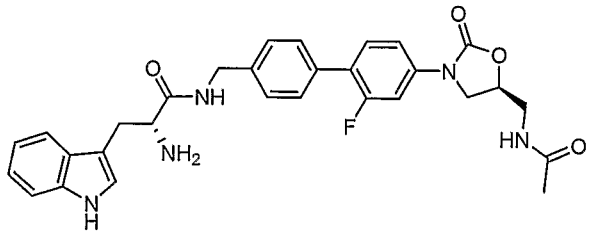
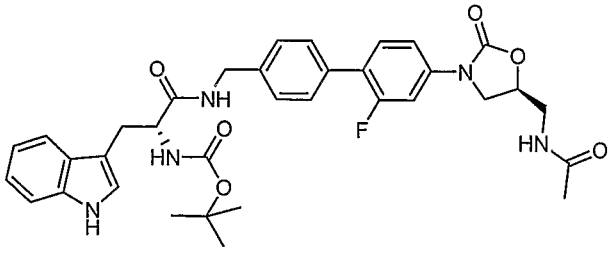
	{4'-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-(2-methyl-2H-tetrazol-5-ylmethyl)-carbamic acid tert-butyl ester
4282	
	N-[3-(2-Fluoro-4'-{[(1H-tetrazol-5-ylmethyl)-amino]-methyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
4283	
	N-[3-(2-Fluoro-4'-{[(1-methyl-1H-tetrazol-5-ylmethyl)-amino]-methyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
4284	
	N-[3-(2-Fluoro-4'-{[(2-methyl-2H-tetrazol-5-ylmethyl)-amino]-methyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
4285	
	N-[3-(2-Fluoro-4'-{[(N-hydroxy-pyridine-4-carboximidoyl)-amino]-methyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide

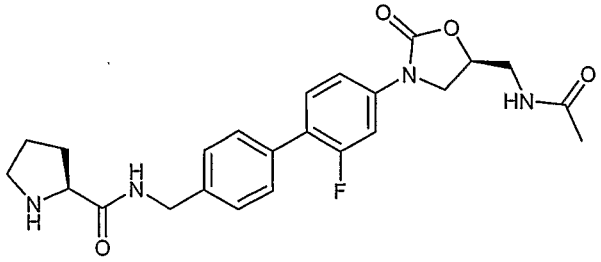
4286	
	N-[3-(4'-{2-[Benzyl-(2-methanesulfonyl-ethyl)-amino]-1-(S)-hydroxy-ethyl}-2-fluoro-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
4287	
	N-[3-(4'-{[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-ethanesulfonylamino]-methyl}-2-fluoro-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
4288	
	N-{3-[4'-(Benzylsulfamoyl-methyl)-2-fluoro-biphenyl-4-yl]-2-oxo-oxazolidin-5-(S)-ylmethyl}-acetamide
4289	
	5-Oxo-pyrrolidine-2-carboxylic acid {4'-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-amide
4290	

	3-({4'-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-carbamoyl)-azetidine-1-carboxylic acid tert-butyl ester
4291	
	Azetidine-3-carboxylic acid {4'-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-amide
4292	
	N-{4'-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-2-(R)-amino-3-(3H-imidazol-4-yl)-propionamide
4293	
	2-({4'-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-amino)-2-pyridin-3-yl-acetamide
4294	
	N-{4'-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-2-amino-2-pyridin-3-yl-acetamide
4295	

	2-({4'-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-carbamoyl)-azetidine-1-carboxylic acid tert-butyl ester
4296	
	Azetidine-2-carboxylic acid {4'-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-amide
4297	
	N-{4'-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-2-(R)-amino-2-(4-fluoro-phenyl)-acetamide
4298	
	4-[({4'-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-amino)-methyl]-piperidine-1-carboxylic acid tert-butylester
4299	
	N-{3-[2-Fluoro-4'-(1-[1,2,3]thiadiazol-4-ylmethyl-ureidomethyl)-biphenyl-4-yl]-2-oxo-oxazolidin-5-(S)-ylmethyl}-acetamide

4300	
	N-(3-{4'-[(Cyclopropylmethyl-amino)-methyl]-2-fluoro-biphenyl-4-yl}-2-oxo-oxazolidin-5-(S)-ylmethyl)-acetamide
4301	
	4-(R)-Hydroxy-pyrrolidine-2-(S)-carboxylicacid {4'-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-amide
4302	
	N-{4'-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-2-(S)-amino-3-pyridin-2-yl-propionamide
4303	
	[1-(S)-({4'-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-carbamoyl)-2-pyridin-2-yl-ethyl]-carbamic acid tert-butyl ester

4304	
	[1-({4'-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-carbamoyl)-cyclopropyl]-carbamic acid tert-butyl ester
4305	
	2-({4'-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-carbamoyl)-2,5-dihydro-pyrrole-1-(S)-carboxylic acid tert-butylester
4306	
	2,5-Dihydro-1H-pyrrole-2-(S)-carboxylic acid {4'-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-amide
4307	
	N-{4'-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-2-(R)-amino-3-(1H-indol-3-yl)-propionamide
4308	

	[1-(R)-({4'-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-carbamoyl)-2-(1H-indol-3-yl)-ethyl]-carbamic acid tert-butyl ester
4309	
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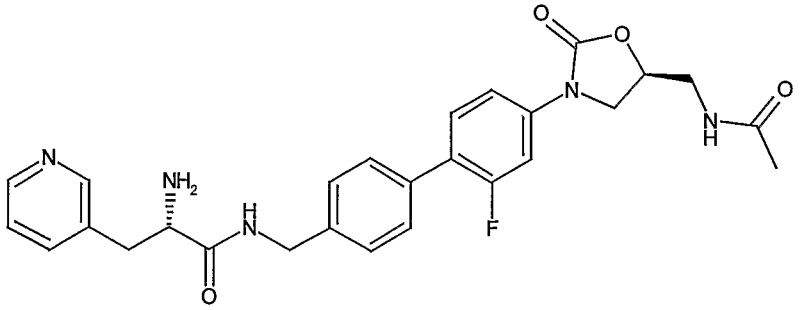
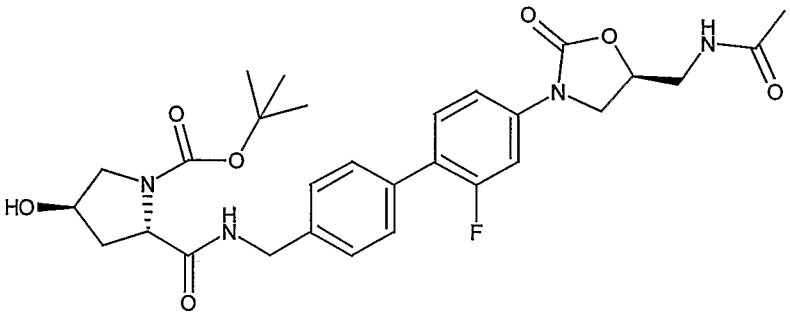
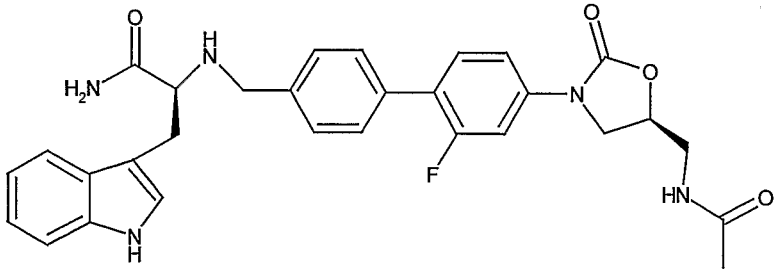
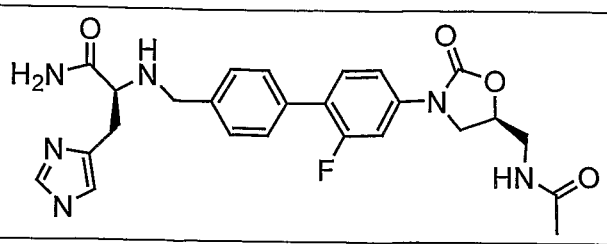
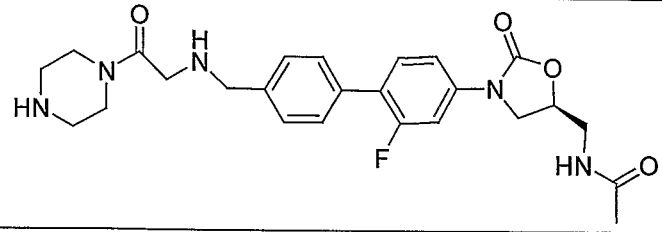
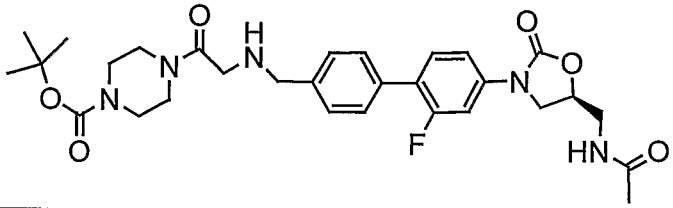
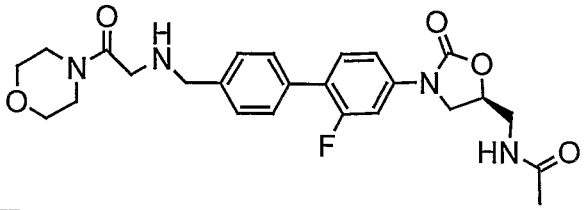
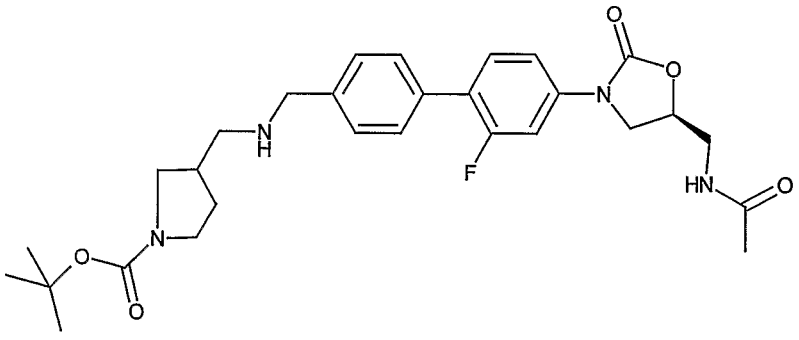
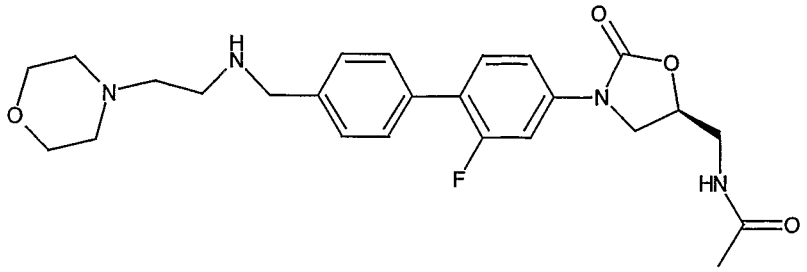
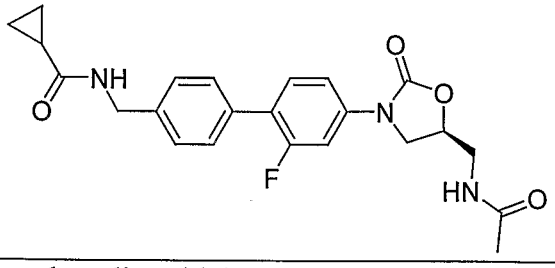
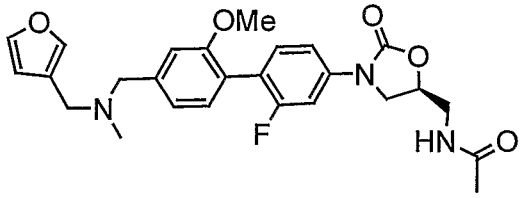
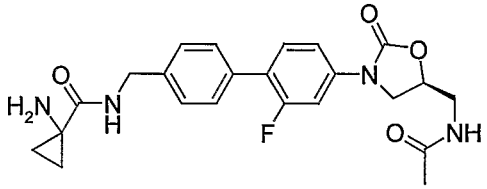
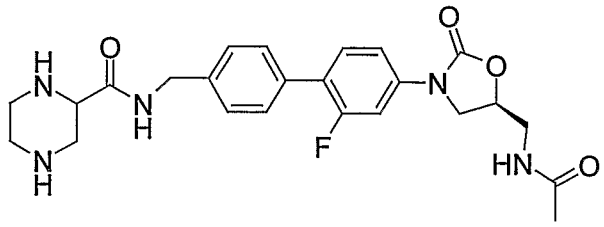
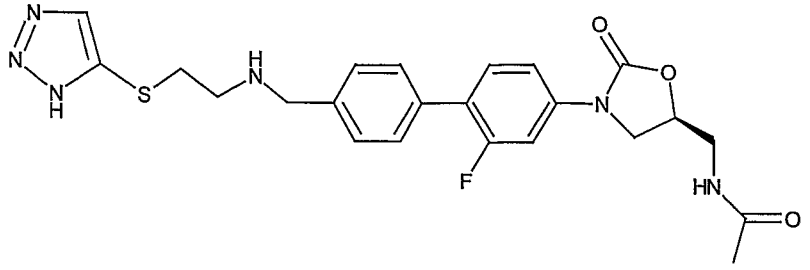
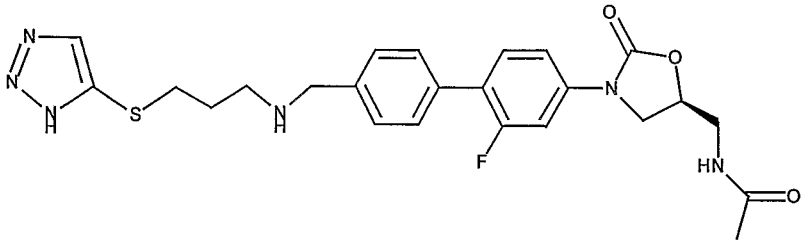
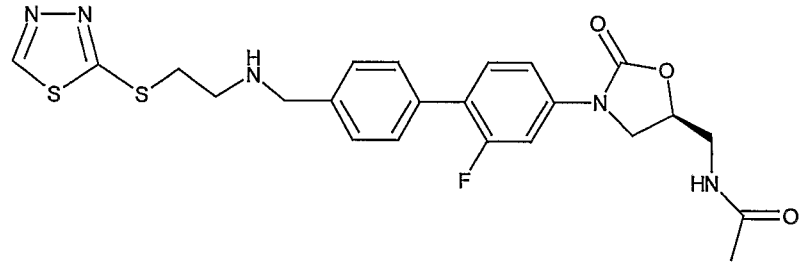
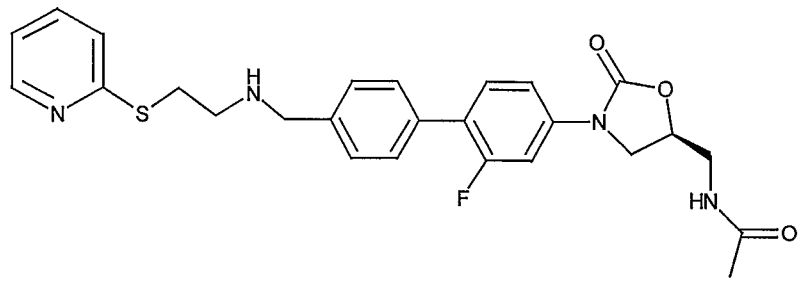
4310	
	N-{4'-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-2-(R)-amino-3-pyridin-3-yl-propionamide
4311	
	2-({4'-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-carbamoyl)-4-(R)-hydroxy-pyrrolidine-1-(S)-carboxylic acid tert-butyl ester
4312	
	2-({4'-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-amino)-3-(S)-(1H-indol-3-yl)-propionamide

4313	
	2-({4'-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-amino)-3-(1H-imidazol-4-yl)-propionamide
4314	
	N-(3-{2-Fluoro-4'-[(2-oxo-2-piperazin-1-yl-ethylamino)-methyl]-biphenyl-4-yl}-2-oxo-oxazolidin-5-(S)-ylmethyl)-acetamide
4315	
	4-[2-({4'-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-amino)-acetyl]-piperazine-1-carboxylic acid tert-butyl ester
4316	
	N-(3-{2-Fluoro-4'-[(2-morpholin-4-yl-2-oxo-ethylamino)-methyl]-biphenyl-4-yl}-2-oxo-oxazolidin-5-(S)-ylmethyl)-acetamide
4317	
	3-[({4'-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-amino)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester

4318	
	N-(3-{2-Fluoro-4'-[(2-morpholin-4-yl-ethylamino)-methyl]-biphenyl-4-yl}-2-oxo-oxazolidin-5-(S)-ylmethyl)-acetamide
4319	
	Cyclopropanecarboxylic acid {4'-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-amide
4320	
	N-(3-{2-Fluoro-4'-[(furan-3-ylmethyl-methyl-amino)-methyl]-2'-methoxy-biphenyl-4-yl}-2-oxo-oxazolidin-5-(S)-ylmethyl)-acetamide
4321	
	1-Amino-cyclopropanecarboxylic acid {4'-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-amide
4322	
	Piperazine-2-(R/S)-carboxylic acid {4'-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-amide

5001	
	N-[3-(2-Fluoro-4'-{[2-(3H-[1,2,3]triazol-4-ylsulfanyl)-ethylamino]-methyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
5002	
	N-[3-(2-Fluoro-4'-{[3-(3H-[1,2,3]triazol-4-ylsulfanyl)-propylamino]-methyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
5003	
	N-[3-(2-Fluoro-4'-{[2-([1,3,4]thiadiazol-2-ylsulfanyl)-ethylamino]-methyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
5004	
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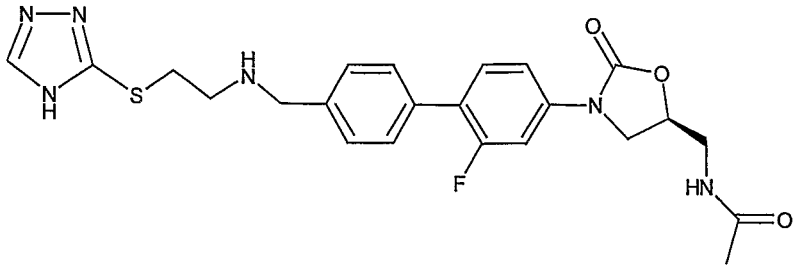
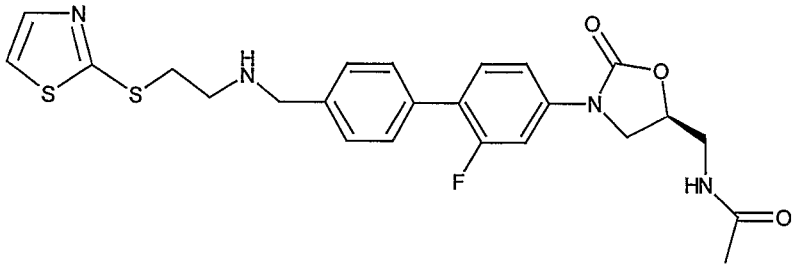
5005	
	N-[3-(2-Fluoro-4'-{[2-(4H-[1,2,4]triazol-3-ylsulfanyl)-ethylamino]-methyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
5006	
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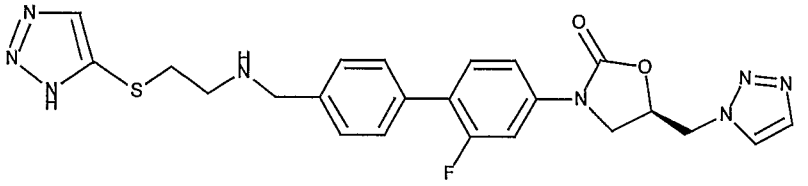
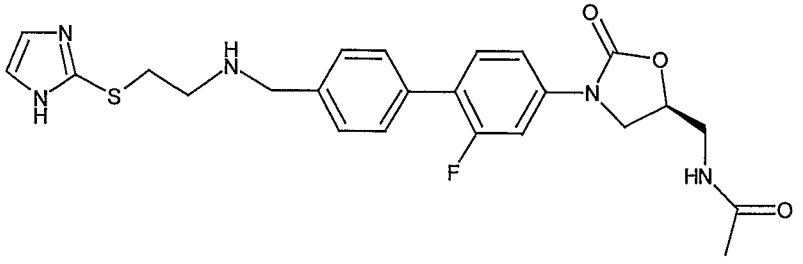
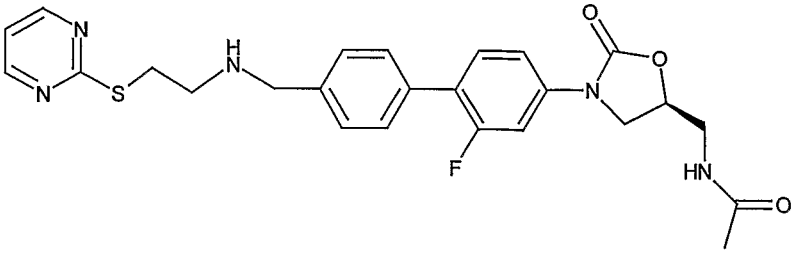
5007	
	3-(2-Fluoro-4'-{[2-(3H-[1,2,3]triazol-4-ylsulfanyl)-ethylamino]-methyl}-biphenyl-4-yl)-5-(R)-[1,2,3]triazol-1-ylmethyl-oxazolidin-2-one
5008	
	N-[3-(2-Fluoro-4'-{[2-(1H-imidazol-2-ylsulfanyl)-ethylamino]-methyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
5009	

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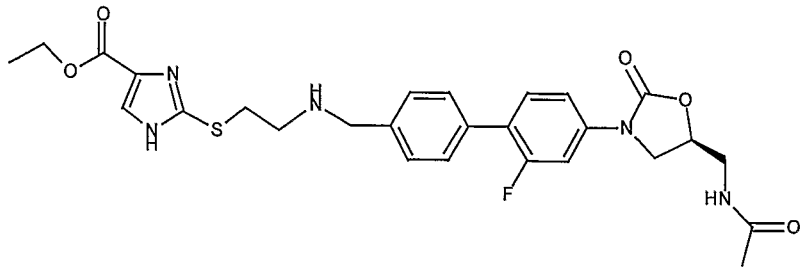
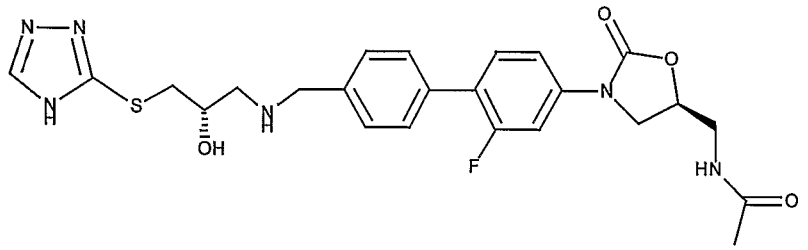
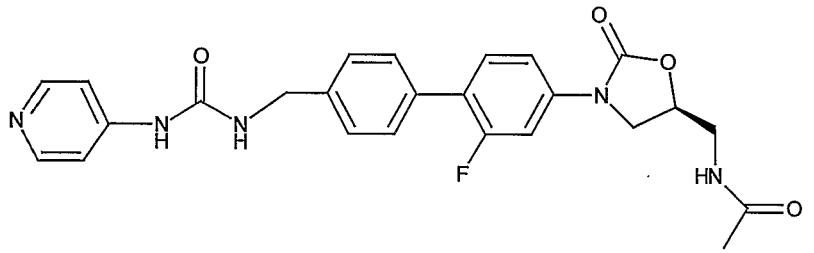
5010	
	2-[2-({4'-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-amino)-ethylsulfanyl]-1H-imidazole-4-carboxylic acid ethyl ester
5011	
	N-[3-(2-Fluoro-4'-{[2-(S)-(hydroxy-3-(4H-[1,2,4]triazol-3-ylsulfanyl)-propylamino]-methyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
5012	
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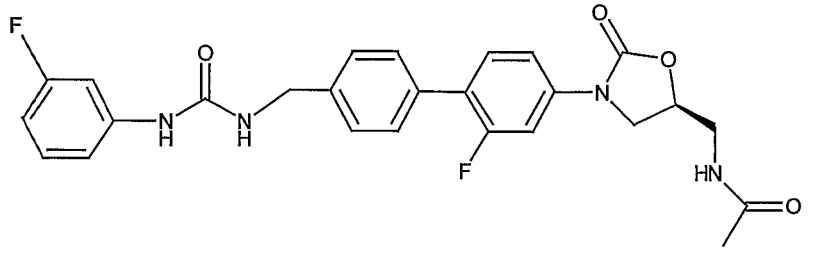
5013	
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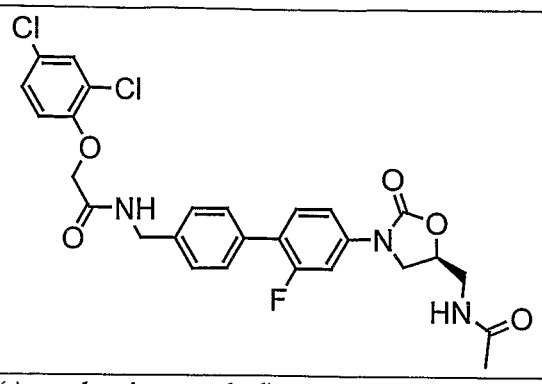
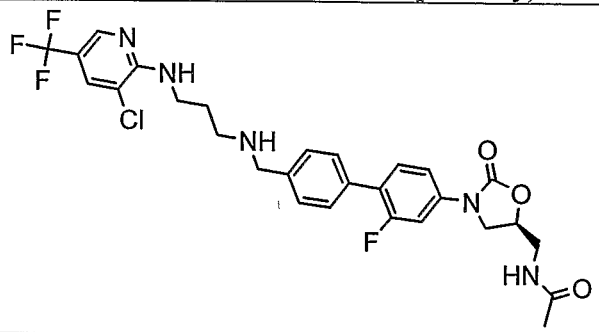
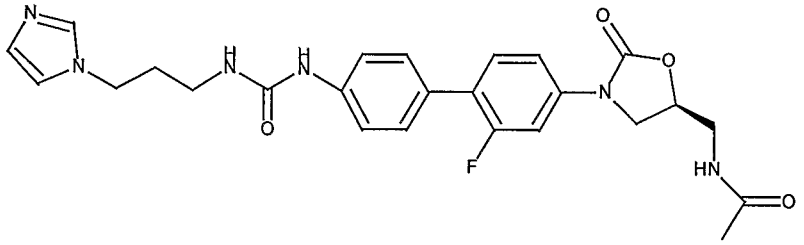
5014	
	N-{4'-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl}-2-(2,4-dichloro-phenoxy)-acetamide
5015	
	N-[3-(4'-{[3-(3-Chloro-5-trifluoromethyl-pyridin-2-ylamino)-propylamino]-methyl}-2-fluoro-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide
6001	
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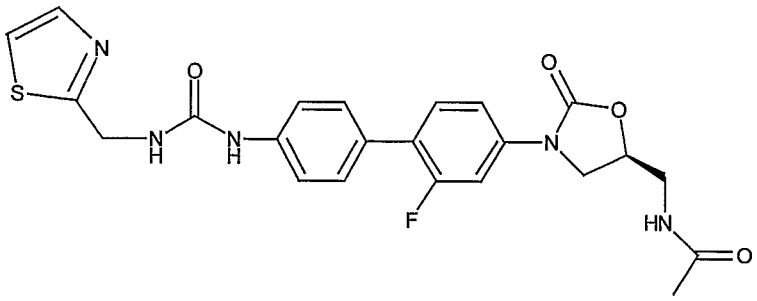
6002	
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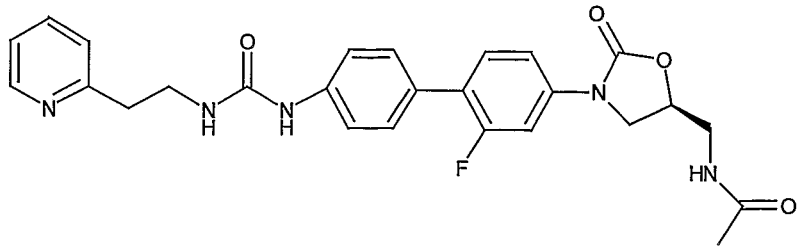
6003	
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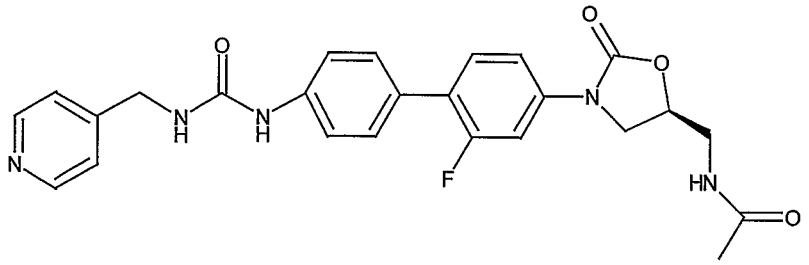
6004	
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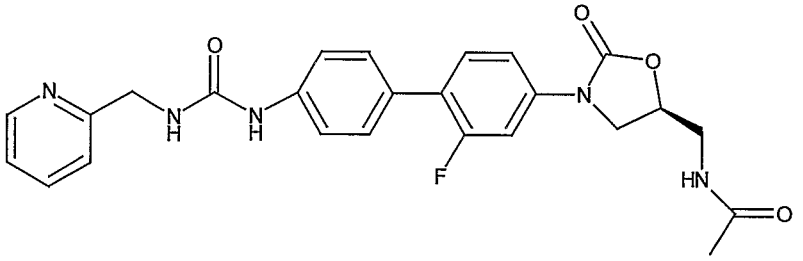
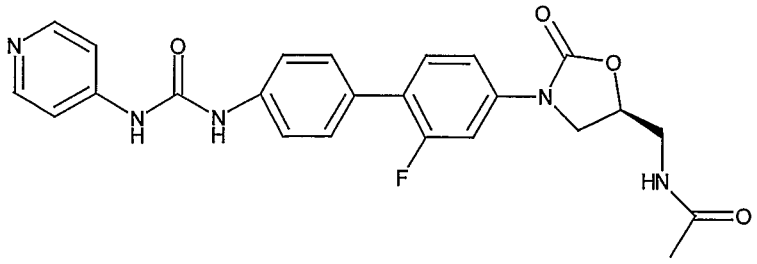
6005	
	N-{3-[2-Fluoro-4'-(3-pyridin-2-ylmethyl-ureido)-biphenyl-4-yl]-2-oxo-oxazolidin-5-(S)-ylmethyl}-acetamide
6006	
	N-{3-[2-Fluoro-4'-(3-pyridin-4-yl-ureido)-biphenyl-4-yl]-2-oxo-oxazolidin-5-(S)-ylmethyl}-acetamide

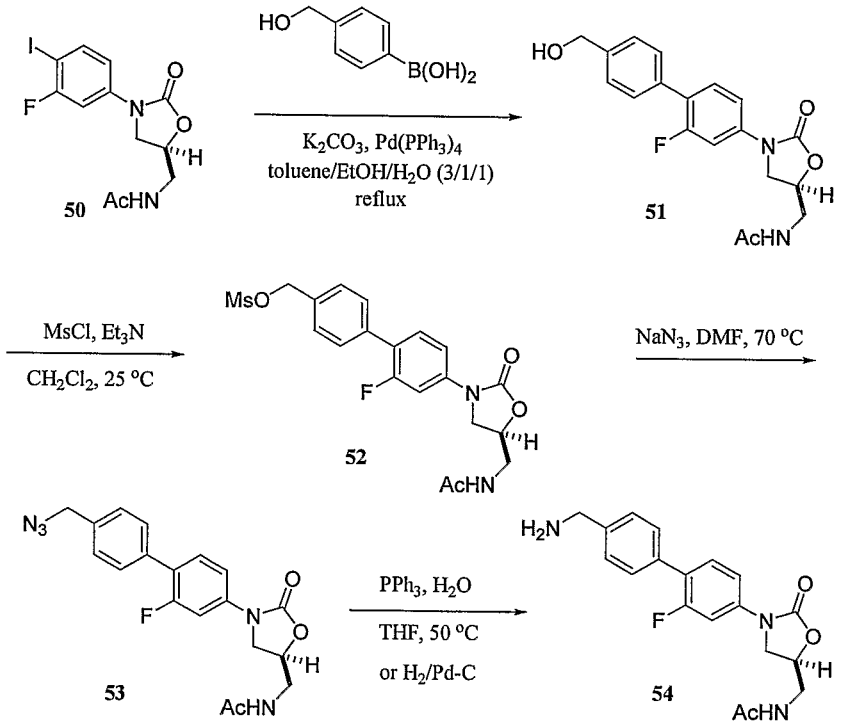
Nuclear magnetic resonance (NMR) spectra were obtained on a Bruker Avance 300 or Avance 500 spectrometer, or in some cases a GE-Nicolet 300 spectrometer. Common reaction solvents were either high performance liquid chromatography (HPLC) grade or American Chemical Society (ACS) grade, and anhydrous as obtained from the manufacturer unless

otherwise noted. "Chromatography" or "purified by silica gel" refers to flash column chromatography using silica gel (EM Merck, Silica Gel 60, 230-400 mesh) unless otherwise noted.

Example 1 – Synthesis of Biaryl Precursors

Scheme 1 depicts the synthesis of various biaryl intermediates useful in producing compounds of the present invention. Known iodoaryl oxazolidinone intermediate **50** (*see* U.S. Patent Nos. 5,523,403 and 5,565,571) is coupled to a substituted aryl boronic acid (the Suzuki reaction) to produce biaryl alcohol **51**. Mesylate **52**, azide **53**, and amine **54** are then synthesized using chemistry well known to those skilled in the art.

Scheme 1



Synthesis of alcohol 51

A suspension of *N*-[3-(3-fluoro-4-iodo-phenyl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide **50** (14.0 g, 37 mmol) in toluene (120 mL) was treated with 4-(hydroxymethyl) phenylboronic acid (7.87 g, 51.8 mmol, 1.4 equiv), potassium carbonate (K_2CO_3, 15.32 g, 111 mmol, 3.0 equiv), ethanol (EtOH, 40 mL), and H_2O (40 mL) at 25 °C, and the resulting mixture was degassed three times under a steady stream of argon at 25 °C. Tetrakis(triphenylphosphine)palladium ($Pd(PPh_3)_4$, 2.14 g, 1.85 mmol, 0.05 equiv) was subsequently added to the reaction mixture, and the resulting reaction mixture was degassed

three times again before being warmed to gentle reflux for 6 h. When thin layer chromatography (TLC) and HPLC showed the coupling reaction was complete, the reaction mixture was cooled to room temperature before being treated with H_2O (240 mL). The resulting mixture was then stirred at room temperature for 10 min before being cooled to 0-5 °C for 1 h. The solid precipitates were collected by filtration, washed with H_2O (2 x 100 mL) and 20% ethyl acetate (EtOAc)/hexane (2 X 50 mL), and dried *in vacuo*. The crude desired *N*-[3-(2-Fluoro-4'-hydroxymethyl-biphenyl-4-yl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide **51** (12.50 g, 94% yield) was obtained as off-white solids. This material was found to be essentially pure by HPLC and ^{1}H NMR and was directly used in the subsequent reaction without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.76 (s, 3H, COCH_3), 3.35 (t, 2H, J = 5.4 Hz), 3.69 (dd, 1H, J = 6.4, 9.2 Hz), 4.08 (t, 1H, J = 9.1 Hz), 4.46 (d, 2H, J = 5.7 Hz, CH_2OH), 4.68 (m, 1H), 5.16 (t, 1H, J = 5.7 Hz, O*H*), 7.25 – 7.52 (m, 7H, aromatic-*H*), 8.18 (t, 1H, J = 5.8 Hz, N*H*COCH$_3$). LCMS (ESI) *m/e* 359 $(M + H)^+$.

Synthesis of mesylate 52

A suspension of **51** (12.49 g, 34.90 mmol) in methylene chloride (CH_2Cl_2, 150 mL) was treated with triethylamine (Et_3N, 7.07 g, 9.7 mL, 70 mmol, 2.0 equiv) at 25 °C, and the resulting mixture was cooled to 0–5 °C before being treated dropwise with methanesulfonyl chloride (4.80 g, 3.24 mL, 41.9 mmol, 1.2 equiv) at 0–5 °C. The resulting reaction mixture was subsequently stirred at 0–5 °C for 2 h. When TLC and HPLC showed the reaction was complete, the reaction mixture was treated with H_2O (100 mL) at 0-5 °C. The mixture was then concentrated *in vacuo* to remove most of the CH_2Cl_2, and the resulting slurry was treated with H_2O (150 mL). The mixture was stirred at room temperature for 10 min before being cooled to 0–5 °C for 30 min. The solid precipitates were collected by filtration, washed with H_2O (2 x 100 mL) and 20% EtOAc/hexane (2 X 50 mL), and dried *in vacuo*. The crude desired methanesulfonic acid 4'-[5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-ylmethyl ester **52** (11.84 g, 78% yield) was obtained as off-white solids, which by TLC and HPLC was found to be essentially pure and was directly used in the subsequent reaction without further purification. LCMS (ESI) *m/e* 437 $(M + H)^+$.

Synthesis of azide 53

A solution of **52** (9.27 g, 21.26 mmol) in anhydrous *N,N*-dimethylformamide (DMF, 50 mL) was treated with sodium azide (NaN_3, 5.53 g, 85.04 mmol, 4.0 equiv) at 25 °C, and the resulting reaction mixture was warmed to 70–80 °C for 4 h. When TLC and HPLC showed the

reaction was complete, the reaction mixture was cooled to room temperature before being treated with H_2O (150 mL). The resulting mixture was stirred at room temperature for 10 min before being cooled to 0–5 °C for 1 h. The solid precipitates were collected by filtration, washed with H_2O (2 x 100 mL) and 20% EtOAc/hexane (2 X 50 mL), and dried *in vacuo*. The crude desired *N*-[3-(4'-azidomethyl-2-fluoro-biphenyl-4-yl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide **53** (7.16 g, 88% yield) was obtained as off-white solids. The material was found to be essentially pure by TLC and HPLC and was directly used in the subsequent reaction without further purification. LCMS (ESI) *m/e* 384 $(M + H)^+$.

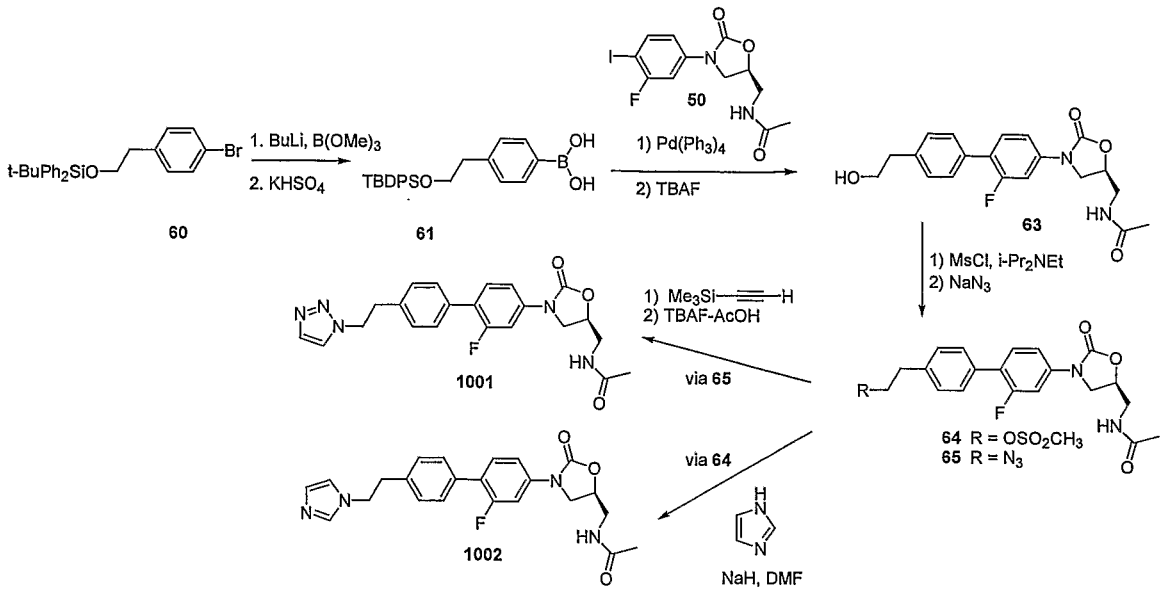
Synthesis of amine 54

A solution of **53** (7.16 g, 18.69 mmol) in tetrahydrofuran (THF) (100 mL) was treated with triphenylphosphine (PPh_3, 5.88 g, 22.43 mmol, 1.2 equiv) and H_2O (3.6 g, 3.6 mL, 0.2 mmol, 11.0 equiv) at 25 °C, and the resulting reaction mixture was warmed to 50-55 °C for 12 h. When TLC and HPLC showed the reduction reaction was complete, the reaction mixture was cooled to room temperature before the solvents were removed *in vacuo*. The residue was directly purified by flash column chromatography (0–15% MeOH-CH_2Cl_2 gradient elution) to afford the desired *N*-[3-(4'-Aminomethyl-2-fluoro-biphenyl-4-yl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide **54** (5.82 g, 87% yield) as off-white crystals, which were of sufficient purity to be directly used in subsequent reactions. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.85 (s, 3H, COCH_3), 3.04 (br. s, 2H, NH_2), 3.44 (t, 2H, J = 5.4 Hz), 3.78 (m, 3H), 4.18 (t, 1H, J = 9.1 Hz), 4.77 (m, 1H), 7.25 – 7.60 (m, 7H, aromatic-*H*), 8.20 (t, 1H, J = 5.8 Hz, N*H*COCH$_3$). LCMS (ESI) *m/e* 359 $(M + 2H)^{2+}$.

Example 2 - Synthesis of Triazole 1001 and Imidazole 1002

Scheme 2 illustrates the synthesis of triazole **1001** and imidazole **1002**. Aryl bromide **60** was converted to boronic acid **61** which was used in a Suzuki coupling with aryl iodide **50** to afford alcohol **63** after desilylation. The alcohol was converted to mesylate **64** and then to azide **65**. The cycloaddition of azide **65** with trimethylsilylacetylene followed by desilylation afforded triazole **1001**. Alkylation of mesylate **64** with imidazole yielded compound **1002**.

Scheme 2



Synthesis of bromide 60

To a solution of 4-bromophenethyl alcohol (5.60 g, 27.9 mmol), imidazole (3.80 g, 55.7 mmol) and a catalytic amount of 4-dimethylaminopyridine (DMAP) in DMF (55 mL) was added *t*-butyldiphenylchlorosilane (TBDPSCl, 7.20 mL, 27.9 mmol) at 0 °C and the mixture was stirred at ambient temperature for 72 h. The reaction was quenched with ice cold water (50 mL) and extracted with ether (4 x 50 mL). The combined etheral layer was washed with water (4 x 100 mL), dried over anhydrous sodium sulfate (Na_2SO_4), concentrated and purified by flash chromatography (2% ethyl acetate in hexanes) to yield 10.6 g of **60**.

Synthesis of boronic acid 61

To a solution of **60** (10.5 g, 24.0 mmol) in THF (50 mL) was added *n*-butyl lithium (*n*-BuLi, 2.5M in hexane, 11.5 mL, 28.8 mmol) at -78 °C and the mixture was stirred for 1 h before the addition of trimethyl borate (3.54 mL, 31.2 mmol). The solution was then stirred overnight at ambient temperature and quenched with 1M potassium hydrogen sulfate ($KHSO_4$, 25 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 50 mL), washed with brine (3 x 100 mL), dried (anhydrous Na_2SO_4), concentrated and purified by flash chromatography (25% ethyl acetate in hexanes) to yield 5 g of boronic acid **61** as mixture of acid and cyclic anhydrides.

Synthesis of alcohol 63

To a mixture of boronic acid **61** (4.7 g, 11.7 mmol), known oxazolidinone **50** (4.00 g, 10.6 mmol; *see* U.S. Patent Nos. 5,523,403 and 5,565,571), potassium carbonate (K_2CO_3, 4.40

g, 31.8 mmol) and $Pd(PPh_3)_4$ (0.613 g, 5 mol%) was added toluene (90 mL), ethanol (30 mL) and H_2O (30 mL). The reaction mixture was refluxed overnight under argon atmosphere, concentrated and redissolved in CH_2Cl_2 (100 mL). The organic phase was washed with brine solution (2 x 100 mL), dried (anhydrous Na_2SO_4), concentrated and used for the next step without further purification. To a solution of this crude material in THF (70 mL) was added tetrabutylammonium fluoride (TBAF, 20 mL, 20 mmol) and the mixture was stirred overnight at ambient temperature. The reaction mixture was concentrated and washed with water (4 x 100 mL) to yield 3.5 g of **63**. LCMS (ESI) *m/z* 373 (M+H).

Synthesis of mesylate 64 and azide 65

To a solution of **63** (1.0 g, 2.7 mmol) in CH_2Cl_2 (15 mL), DMF (4 mL) and *N,N*-diisopropylethylamine (Hunig's base, 0.75 mL, 4.05 mmol) was added methanesulfonyl chloride (0.32 mL, 2.7 mmol) at 0 °C. After 2 h the reaction mixture was poured into CH_2Cl_2 (150 mL) and the organic layer was washed with water (3 x 100 mL), dried, concentrated to afford **64** as a solid. The crude solid **64** thus obtained was heated with NaN_3 (0.35 g, 5.4 mmol) at 90 °C overnight. The reaction mixture was poured into ethyl acetate (100 mL). The ethyl acetate layer was washed with water (3 x 50 mL), dried and concentrated to yield 1.1 g of pure azide **65**. LCMS (ESI) *m/z* 398 (M+H).

Synthesis of triazole 1001

A solution of azide **65** (100 mg, 0.252 mmol) and trimethylsilylacetylene (0.072 mL, 0.504 mmol) in DMF (3 mL) was heated at 90°C until the azide was consumed. The reaction mixture was concentrated and treated with TBAF (1 mL, 1 mmol) and acetic acid (0.028 mL, 0.504 mmol) in THF (3 mL). The solution was stirred for 72 h and concentrated. The crude product was purified by flash chromatography using 4% methanol (MeOH) in CH_2Cl_2 to yield 85 mg of **1001**. LCMS (ESI) *m/z* 424 (M+H).

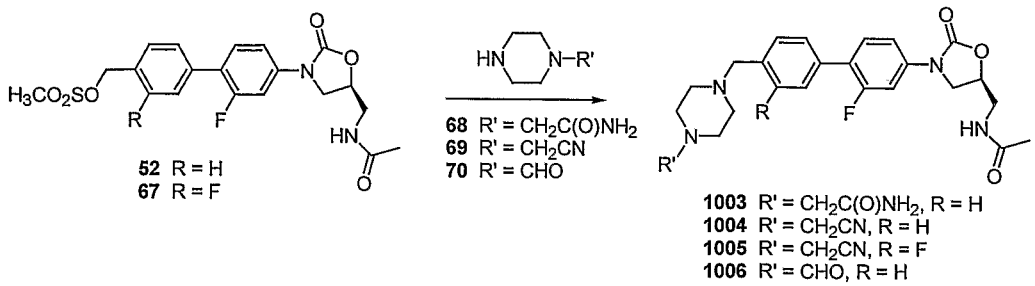
Synthesis of imidazole 1002

To a solution of imidazole (70 mg, 1.0 mmol) in DMF (5 mL) was added sodium hydride (NaH, 60%, 41 mg, 1 mmol) at 0 °C and the mixture was stirred for 30 minutes before the addition of mesylate **64** (114 mg, 0.250 mmol). The resulting solution was heated to 80 °C for 3h, concentrated and purified by flash chromatography (5% MeOH in CH_2Cl_2). After trituration with ether, the residue afforded 40 mg of **1002**. LCMS (ESI) *m/z* 423 (M+H).

Example 3 - Synthesis of Piperazines 1003-1006

Scheme 3 illustrates the synthesis of compounds **1003-1006**. Mesylate **52** served as alkylating agent for piperazine intermediates **68**, **69** and **70** to afford compounds **1003**, **1004** and **1006** respectively. Mesylate **67** was employed to alkylate piperazine intermediate **69** to provide compound **1005**.

Scheme 3



Synthesis of mesylate 67

Mesylate **67** was synthesized by coupling iodide **50** and 4-formyl-3-fluorophenylboronic acid following the procedure described above for the synthesis of *N*-[3-(2-fluoro-4'-hydroxymethyl-biphenyl-4-yl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide (see Example 1). The biaryl aldehyde obtained (1.0 g, 2.67 mmol) was suspended in 40 mL methanol and the mixture was cooled to 0°C. Sodium borohydride (0.112 g, 2.943 mmol) was added, and the mixture was stirred for 50 min. Water was added (20 mL), and after stirring another 20 min the mixture was partitioned between methylene chloride and brine. The aqueous phase was extracted twice with methylene chloride. The aqueous phase was acidified to pH 7, then extracted twice with methylene chloride. The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated. The crude material was azeotroped with toluene to afford the expected alcohol (900 mg).

The above alcohol (900 mg) was dissolved in methylene chloride (20 mL), DMF (13 mL) and Hunig's base (1.23 mL) and the mixture was cooled to 0°C. Methanesulfonyl chloride (557 uL, 7.20 mmol) was added and the mixture was stirred for 1.5 h at 0°C. LCMS indicated a mixture of desired mesylate and some of the corresponding benzyl chloride. The mixture was stirred for another 30 min and then concentrated. The residue was treated with 400 mL water, and the precipitate was filtered and washed with water. Drying under vacuum overnight yielded 750 mg crude mesylate **67** (as a mixture with some of the corresponding chloride).

Synthesis of piperazine 68

A solution of *tert*–butyl-1-piperazine carboxylate (1 g, 5.4 mmol), bromoacetamide (820 mg, 5.94 mmol) and Hunig's base (1.2 mL, 7.2 mmol) in a mixture of CH_2Cl_2 (10 mL) and MeOH (10 mL) was heated to reflux for 4 h. The reaction mixture was concentrated and the crude product thus obtained was purified by flash chromatography (19 :1 :0.01 CH_2Cl_2/MeOH/ NH_4OH) to yield 1.3 g of pure BOC-protected piperazinyl acetamide. To a solution of the acetamide (250 mg, 1 mmol) in CH_2Cl_2 (10 mL) was added trifluoroacetic acid (TFA, 5 mL) at 0°C and the mixture was stirred at that temperature for 2 h. The reaction mixture was concentrated to yield **68** which was used for subsequent reactions without further purification.

Synthesis of piperazine 69

A solution of *tert* –butyl-1-piperazine carboxylate (1 g, 5.4 mmol), bromoacetonitrile (0.5 mL, 5.94 mmol) and Hunig's base (1.2 mL, 7.2 mmol) in a mixture of CH_2Cl_2 (10 mL) and MeOH (10 mL) was stirred at ambient temperature for 4 h. The reaction mixture was concentrated and the crude product thus obtained was purified by flash chromatography (19:1:0.01 CH_2Cl_2/MeOH/NH_4OH) to yield 1.3 g of pure BOC-protected piperazinyl acetonitrile. To a solution of the piperazinyl acetonitrile (300 mg, 1.3 mmol) in CH_2Cl_2 (10 mL) was added TFA (5 mL) at 0°C and the mixture was stirred at that temperature for 2 h. The reaction mixture was concentrated to yield **69** which was used for subsequent reactions without further purification.

Synthesis of compound 1003

A solution of mesylate of **52** (138 mg, 0.320 mmol) and **68** (~1 mmol) in Hunig's base (2 mL) and DMF (8 mL) was heated to 90°C for 2 h. Then the solution was concentrated and purified by flash chromatography over silica gel (20:1:0.01 CH_2Cl_2/MeOH/NH_4OH) to yield **1003**. LCMS (ESI) *m/z* 484 $(M + H)^+$.

Synthesis of compound 1004

Compound **1004** was synthesized from mesylate **52** and piperazine intermediate **69** in the same manner as described above for the synthesis of compound **1003**. LCMS (ESI) *m/z* 466 $(M + H)^+$.

Synthesis of compound 1005

Compound **1005** was synthesized from mesylate **67** and piperazine intermediate **69** in the same manner as described above for the synthesis of compound **1003**. LCMS (ESI) *m/z* 484 $(M + H)^+$.

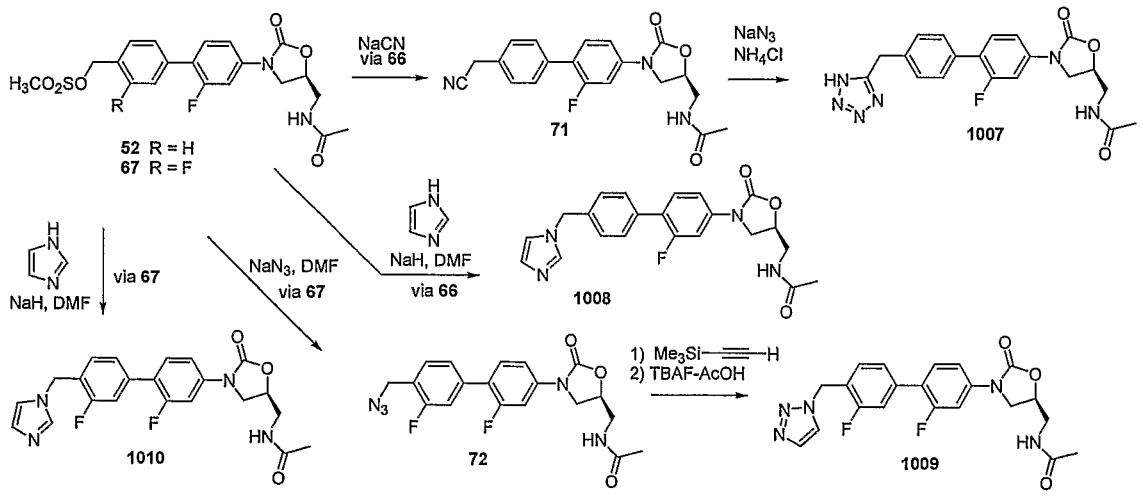
Synthesis of compound 1006

Compound **1006** was synthesized from mesylate **52** and available piperazine intermediate **70** in the same manner as described above for the synthesis of compound **1003**. LCMS (ESI) *m/z* 455 $(M + H)^+$.

Example 4 - Synthesis of Compounds 1007-1010

Scheme 4 illustrates the synthesis of compounds **1007-1010**. Mesylate **52** was converted to nitrile **71**, which was subsequently transformed to tetrazole **1007**. Mesylate **52** served as alkylating agent for the anion derived from imidazole to afford imidazole derivative **1008**. Mesylate **67** was converted to azide **72**, which was then subsequently converted to triazole **1009**. Mesylate **67** served as alkylating agent for the anion derived from imidazole to afford imidazole derivative **1010**.

Scheme 4



Synthesis of tetrazole 1007

To a solution of mesylate **52** (2.0 g, 4.6 mmol) in DMF (30 mL) was added sodium cyanide (NaCN, 0.45 g, 9.2 mmol) and the mixture was heated to 70°C for 3 h. The reaction mixture was cooled to ambient temperature and poured into water (800 mL). The solid thus

obtained was filtered and passed through a small bed of silica gel (CH_2Cl_2: MeOH = 12:1) to yield 1.8 g of nitrile **71**. LCMS (ESI) *m/z* 368 $(M + H)^+$.

A mixture of **71** (100 mg, 0.272 mmol), NaN_3 (40 mg, 0.598 mmol) and ammonium chloride (NH_4Cl, 32 mg, 0.598 mmol) in DMF (2 mL) was heated to 90°C for 3 days. The reaction mixture was concentrated and purified by flash chromatography (10% MeOH in CH_2Cl_2) to yield 35.6 mg of tetrazole **1007**. LCMS (ESI) *m/z* 411 $(M + H)^+$.

Synthesis of imidazole 1008

To a solution of imidazole (37.4 mg, 0.550 mmol) in DMF (5 mL) was added NaH (60%, 20 mg, 0.50 mmol) at 0°C and the mixture was stirred for 30 minutes before the addition of mesylate **52** (200 mg, 0.459 mmol). The resulting solution was heated to 60°C for 2 h and poured into water (75 mL). The aqueous suspension was extracted with 10% MeOH in CH_2Cl_2 (3 x 75 mL) and the combined organic layer was washed with saturated NH_4Cl solution (2 x 100 mL). The organic layer was dried (anhydrous Na_2SO_4), concentrated and triturated with ether to yield 170 mg of imidazole **1008**. LCMS (ESI) *m/z* 409 $(M + H)^+$.

Synthesis of azide 72

Crude mesylate **67** (100 mg, 0.224 mmol; as a mixture with some corresponding benzyl chloride) was dissolved in DMF (10 mL) and sodium azide (114.6 mg, 1.762 mmol) was added. The mixture was stirred at room temperature for 14 h, and then partitioned between ethyl acetate and water. The organic phase was washed with water, dried over Na_2SO_4, and concentrated to provide azide **72** as a solid (190 mg).

Synthesis of triazole 1009

Compound **1009** was synthesized from azide **72** and trimethylsilylacetylene in the same manner as described above for the synthesis of triazole **1001**. LCMS (ESI) *m/z* 428 $(M + H)^+$.

Synthesis of imidazole 1010

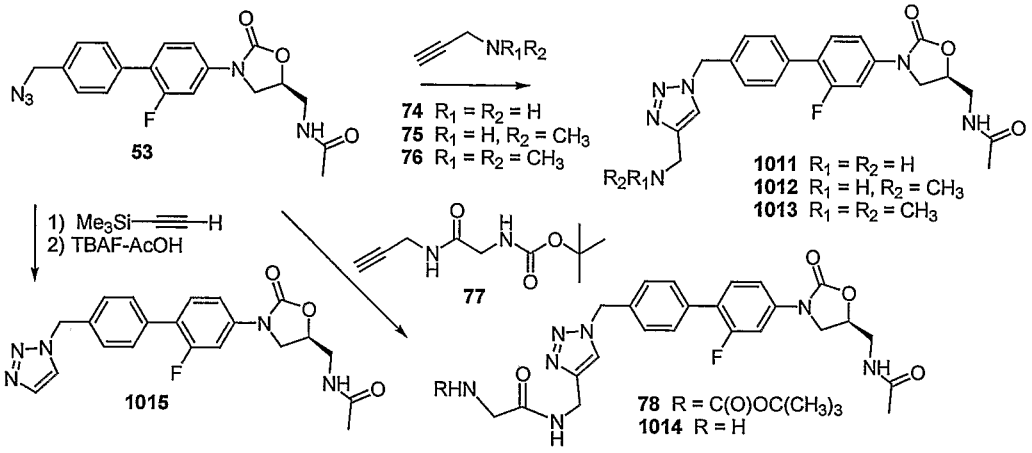
Compound **1010** was synthesized from mesylate **67** and imidazole in the same manner as described above for the synthesis of imidazole derivative **1008**. LCMS (ESI) *m/z* 427 $(M + H)^+$.

Example 5 - Synthesis of Compounds 1011-1015

Scheme 5 illustrates the synthesis of compounds **1011-1015**. The cycloaddition of azide **53** with alkynes **74-76** afforded triazoles **1011-1013** respectively. The cycloaddition of

azide **53** with alkyne **77** gave BOC-protected intermediate **78** which was subsequently cleaved to provide derivative **1014**. The cycloaddition of azide **53** with trimethylsilylacetylene, followed by desilylation, yielded triazole **1015**.

Scheme 5



Synthesis of triazole 1011

A solution of azide **53** (0.10 g, 0.26 mmol) in propargyl amine **74** (0.50 mL) was treated with copper iodide (0.05 g, 0.26 mmol) and was stirred at 23 °C for 0.5 h. The reaction mixture was diluted with CH_2Cl_2 and MeOH and purified by flash chromatography and preparative TLC to afford **1011** as a brown solid (0.027 g; 24%). LCMS (ESI) *m/z* 439 $(M + H)^+$.

Synthesis of triazole 1012

A solution of azide **53** (0.10 g, 0.26 mmol) in N-methylpropargyl amine **75** (0.50 mL) was treated with copper iodide (5.00 mg, 0.026 mmol) and stirred at 23 °C for 12 h. The solvent was removed *in vacuo*, and the crude product was purified by preparative TLC to afford **1012** as a brown solid (0.038 g; 32%). LCMS (ESI) *m/z* 453 $(M + H)^+$.

Synthesis of triazole 1013

A solution of azide **53** (0.10 g, 0.26 mmol) in N, N-dimethylpropargyl amine **76** (0.056 mL, 0.520 mmol) was treated with copper iodide (5.00 mg, 0.026 mmol) and stirred at 23 °C for 12 h. The solvent was removed *in vacuo*, and the crude product was purified by flash chromatography to afford **1013** as a yellow film (0.073 g; 60%). LCMS (ESI) *m/z* 467 $(M + H)^+$.

Synthesis of alkyne 77

A solution of propargyl amine **74** (0.34 mL, 5.0 mmol) in methylene chloride (25 mL) was treated with BOC-glycine (0.96 g, 5.5 mmol) and EDCI (1.1 g, 5.5 mmol) and stirred at 23 °C for 0.5 h. The reaction mixture was diluted with CH_2Cl_2, washed with 1.0 M HCl (aqueous), washed with saturated aqueous sodium bicarbonate ($NaHCO_3$), dried over Na_2SO_4, and the solvent evaporated *in vacuo* to afford alkyne **77** (0.51g; 48%).

Synthesis of triazole 1014

A solution of azide **53** (0.15 g, 0.39 mmol) in THF (2 mL) was treated with alkyne **77** (0.17 g, 0.78 mmol) and copper iodide (7.00 mg, 0.039 mmol) and stirred at 23 °C for 16 h. The solvent was removed *in vacuo*, and the crude product was purified by flash chromatography to afford **78** as a white powder (0.16 g; 68%). LCMS (ESI) *m/z* 618 $(M + Na)^+$.

A solution of **78** (0.15 g, 0.25 mmol) was treated with HCl (1.3 mL of 4.0 M solution in dioxane) and was stirred at 23 °C for 2 h. The solvent was removed *in vacuo*, and the residue twice redissolved in methylene chloride and evaporated to afford **1014** as a white film (0.14 g, 100%). LCMS (ESI) *m/z* 496 $(M + H)^+$.

Synthesis of triazole 1015

A solution of azide **53** (0.75 mg, 2.0 mmol) in DMF (10 mL) was treated with trimethylacetylene (2.3 mL, 20 mmol) and was stirred at 90 °C for 12 h. The reaction mixture was cooled to 23 °C and the solvent was removed *in vacuo* to afford the expected silyl-substituted triazole as a brown foam (0.24 mg; 25%). LCMS (ESI) *m/z* 482 $(M + H)^+$.

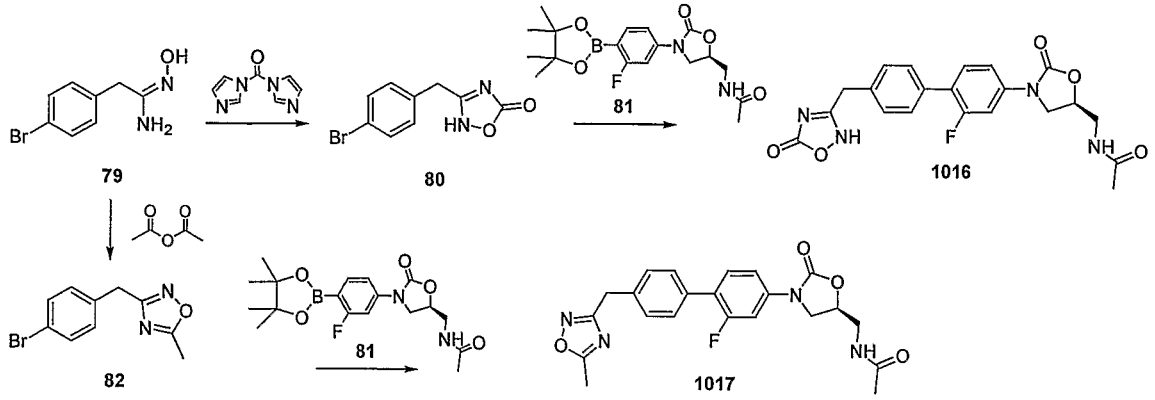
A solution of the above silyl-substituted triazole (0.050 g, 0.10 mmol) in THF (0.20 mL) was treated with acetic acid (6 μL, 0.10 mmol) and tetrabutylammonium fluoride (0.21 mL of 1.0 M solution in THF) and was stirred at 23 °C for 16 h. The reaction mixture was diluted with CH_2Cl_2, washed with water, dried (Na_2SO_4), and the solvent removed *in vacuo*. The crude product was purified to afford **1015** as a white powder (0.020 g; 47%). LCMS (ESI) *m/z* 432 $(M + Na)^+$.

Example 6 - Synthesis of Compounds 1016-1017

Scheme 6 illustrates the synthesis of compounds **1016-1017**. Hydroxyamidine **79** was converted to bromide **80** which was subsequently coupled to boronate **81** to afford compound

1016. Hydroxyamidine **79** was transformed to oxadiazole **82**, which was coupled to boronate **81** to afford compound **1017**.

Scheme 6



Synthesis of hydroxyamidine 79

A solution of 4-bromophenylacetonitrile (10 g, 54 mmol) in methanol (100 mL) was treated with sodium bicarbonate (2.2 g, 57 mmol) and hydroxylamine hydrochloride (4.0 g, 57 mmol) and refluxed for 1.5 h. Additional sodium bicarbonate (0.21 g, 5.4 mmol) and hydroxylamine hydrochloride (0.38 g, 5.4 mmol) were added, and the reaction mixture was refluxed for 12 h. The reaction mixture was cooled to 23 °C and the solvent removed *in vacuo* to afford hydroxyamidine **79** as a blue powder (4.0 g; 34%).

Synthesis of bromide 80

A solution of hydroxyamidine **79** (0.20 g, 0.91 mmol) in 1,4-dioxane (1 mL) was treated with 1,1'-carbonyldiimidazole (0.18 g, 1.1 mmol) and diazabicycloundecene (DBU, 0.15 mL, 0.97 mmol) and stirred at 105 °C for 1 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The water layer was treated with 1.0 M HCl (aqueous) until the pH was 2, and then extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, and the solvent removed *in vacuo* to afford bromide **80** as a yellow powder (0.11 g; 49%).

Synthesis of boronate 81

A suspension of *N*-[3-(3-fluoro-4-iodo-phenyl)-2-oxo-oxazolidin-5-ylmethyl]acetamide **62** (20.0 g, 52.8 mmol) in anhydrous 1,4-dioxane (130 mL) was treated with 4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (10.2 g, 11.6 mL, 80.0 mmol) and triethylamine (16.0 g, 22.4 mL, 158.4 mmol) at room temperature, and the resulting reaction mixture was degassed three times under

a steady stream of argon before being treated with dichloro[1,1'-bis(diphenylphosphino)ferrocene] palladium (II) ($Pd(dppf)_2Cl_2$, 1.32 g, 1.6 mmol, 0.03 equiv) at room temperature. The reaction mixture was then degassed three times again under a steady stream of argon before being heated to reflux for 7 h. When TLC and LCMS showed that the reaction was complete, the reaction mixture was cooled down to room temperature before being treated with water (100 mL) and ethyl acetate (100 mL). The two layers were separated, and the aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with water (2 x 50 mL) and saturated aqueous NaCl solution (50 mL), dried over magnesium sulfate ($MgSO_4$), and concentrated *in vacuo*. The residual brown oil was further dried *in vacuo* to afford the crude desired *N*-{3-[3-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}acetamide **81** (18.8 g, 20.0 g theoretical, 94%) as a brown solid which was of sufficient purity to be used in subsequent reactions.

Synthesis of compound 1016

A solution of boronate ester **81** (0.085 g, 0.220 mmol), bromide **80** (0.055 g, 0.220 mmol), and potassium carbonate (0.12 g, 0.90 mmol) in dioxane (1.4 mL), ethanol (0.46 mL) and water (0.46 mL) was degassed and treated with $Pd(dppf)Cl_2$ (6.0 mg, 6.7 μmol), degassed again, and heated at 80 °C for 1.5 h. The reaction mixture was diluted with CH_2Cl_2 and water, and the precipitate in the water layer was recovered by vacuum filtration to afford **1016** as a grey powder (0.034 g; 36%). LCMS (ESI) *m/z* 427 $(M + H)^+$.

Synthesis of bromide 82

A solution of hydroxyamidine **79** (0.25 g, 1.1 mmol) in pyridine (5 mL) was cooled to 0 °C and treated with a solution of acetic anhydride (0.11 mL, 1.1 mmol) in pyridine (5 mL) and then stirred at 120 °C for 1.5 h. The reaction mixture was diluted with ethyl acetate, washed with 1.0 M HCl (aqueous), washed with saturated aqueous sodium bicarbonate, dried over Na_2SO_4, and the solvent evaporated *in vacuo*. The crude product was purified by flash chromatography to afford bromide **82** as a clear film (0.10 g; 36%).

Synthesis of compound 1017

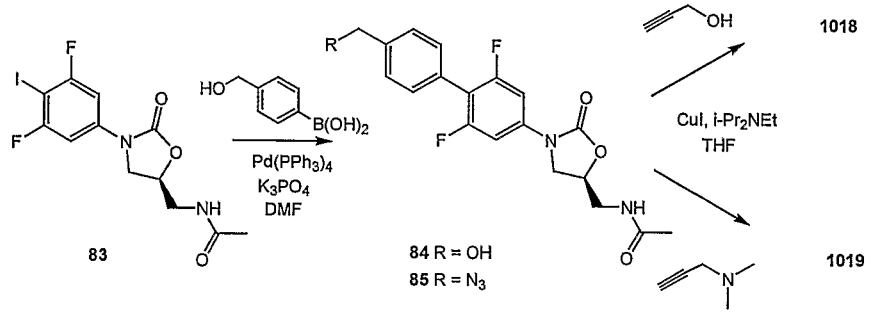
A solution of boronate ester **81** (0.15 g, 0.40 mmol), bromide **82** (0.10 g, 0.40 mmol), and potassium carbonate (0.22 g, 1.6 mmol) in dioxane (2.5 mL), ethanol (0.83 mL) and water (0.83 mL) was degassed and treated with $Pd(dppf)Cl_2$ (10.0 mg, 0.012 mmol), degassed again,

and stirred at 80 °C for 2 h. The reaction mixture was diluted with CH_2Cl_2 and washed with water. The water layer was extracted with 2 x CH_2Cl_2, dried over Na_2SO_4, and the solvent evaporated *in vacuo*. The crude product was purified by flash chromatography and preparative TLC to afford **1017** as a white powder (0.054 g; 32%). LCMS (ESI) *m/z* 425 $(M + H)^+$.

Example 7 - Synthesis of Compounds 1018-1019

Scheme 7 illustrates the synthesis of compounds **1018-1019**. Known aryl iodide **83** was coupled to 4-hydroxymethylboronic acid to afford biaryl alcohol **84**. Alcohol **84** was converted to azide **85**, which was used in alkyne cycloaddition reactions to afford triazoles **1018** and **1019**.

Scheme 7



Synthesis of azide 85

Known aryl iodide **83** (Gravestock, M.B., International Patent Application WO9910342) (1.00 g, 2.52 mmol) was dissolved in 6 mL DMF. 4-Hydroxymethyl-phenylboronic acid (0.461 g, 3.03 mmol) was added, followed by potassium phosphate (K_3PO_4, 0.804 g, 3.79 mmol) and $Pd(PPh_3)_4$ (0.292 g, 0.253 mmol). The mixture was degassed by evacuating the air from the flask, and refilling with argon (3 times), and then heated to 100°C for 4 hours. The mixture was allowed to cool and was then partitioned between ethyl acetate and water. The aqueous phase was extracted with ethyl acetate, and the combined organic phase was washed with brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica using a gradient mixture of methanol/methylene chloride (1% to 8%) to afford alcohol **84** (0.315 g, 0.838 mmol; 33%) as an ivory solid. An analytical sample was obtained by recrystallizing the material from methanol/methylene chloride/pentane. LCMS (ESI) *m/z* 377.

Alcohol **84** (0.889 g, 2.36 mmol) was suspended in 0.3 mL methylene chloride and 0.3 mL DMF. Triethylamine (0.66 mL, 4.74 mmol) was added, and the mixture was cooled to

0°C. Methanesulfonyl chloride (0.260 mL, 3.36 mmol) was added dropwise, and the mixture was stirred for 25 minutes. The mixture was then partitioned with ethyl acetate and water, and the organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was dissolved in 3 mL DMF, and sodium azide (0.384 g, 5.91 mmol) was added. The mixture was heated to 70°C for 4 hours. The reaction mixture was partitioned with ethyl acetate and water, and the organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica using a gradient mixture of methanol/methylene chloride (1% to 4%) to afford azide **85** (0.480 g, 1.20 mmol; 51%) as a tan solid. LCMS (ESI) *m/z* 402.

Synthesis of triazole 1018

Azide **85** (0.084 g, 0.209 mmol) was dissolved in 0.7 mL THF and propargyl alcohol (25 μL, 0.400 mmol) was added, followed by Hunig's base (73 μL, 0.400 mmol) and copper(I) iodide (0.040 g, 0.210 mmol). The mixture was allowed to stir overnight at room temperature, and then was placed in a -20°C freezer for 2 days. The mixture was then partitioned with ethyl acetate and water, and the aqueous layer was extracted with ethyl acetate and then 2%methanol/methylene chloride. The combined organic layer was washed with brine, dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica using a gradient mixture of methanol/methylene chloride (1% to 8%) to afford triazole **1018** (0.060 g, 0.131 mmol; 63%) as an ivory solid. LCMS (ESI) *m/z* 458.

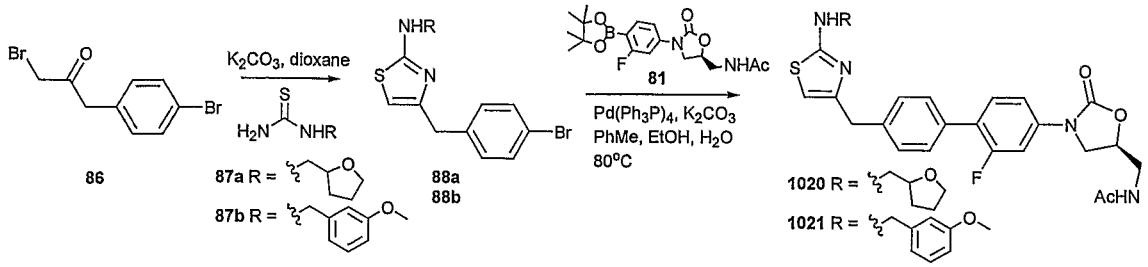
Synthesis of triazole 1019

Azide **85** (0.135 g, 0.337 mmol) was dissolved in 1.5 mL THF and dimethyl-prop-2-ynyl-amine (72 μL, 0.674 mmol) was added, followed by *i*-Pr_2NEt (117 μL, 0.674 mmol) and copper(I)iodide (0.064 g, 0.337 mmol). The mixture was allowed to stir overnight at room temperature (the solvents evaporated overnight with positive pressure from argon gas). The residue was suspended in ethyl acetate and methylene chloride and filtered through celite. The pad of celite was washed with ethyl acetate and methylene chloride, and the combined organic washes were evaporated. The residue was chromatographed on silica using a gradient mixture of methanol/methylene chloride (0% to 14%) and the product obtained was triturated with methylene chloride and pentane. The tan solid was collected to afford triazole **1019** (0.072 g, 0.149 mmol; 44%). LCMS (ESI) *m/z* 485.

Example 8 - Synthesis of Compounds 1020-1021

Scheme 8 illustrates the synthesis of compounds **1020-1021**. Bromoketone **86** was subjected to alkylation with thioureas **87a** and **87b** to afford thiazoles **88a** and **88b** respectively. Coupling of **88a** and **88b** with boronate **81** yielded thiazoles **1020** and **1021**.

Scheme 8



Synthesis of thiazole 88a

Bromoketone **86** (0.29 g, 1.0 mmol) was dissolved in dioxane (10 mL). Thiourea **87a** (0.19 g, 1.2 mmol) and potassium carbonate (0.28 g, 2 mmol) were added sequentially and the resulting slurry stirred at 50°C for 4 h. The mixture was cooled to room temperature, diluted with 100 mL CH_2Cl_2, and washed with sat. aq. $NaHCO_3$, and brine. The aqueous washes were back-extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts were dried over K_2CO_3, filtered and concentrated *in vacuo* to afford **88a** as a yellow solid (0.32 g) which was used without further purification. LCMS (ESI) *m/z* 353 $(M + H)^+$.

Synthesis of thiazole 1020

The crude aryl bromide **88a** obtained above (0.20 g, 0.56 mmol), boronate ester **81** (0.25 g, 0.66 mmol), and K_2CO_3 (0.14 g, 1.0 mmol) were combined with a 1:1:1 mixture of toluene, ethanol and water (2 mL each). The slurry was degassed by alternately applying high vacuum to the reaction mixture and flushing with dry argon. The reaction vessel was then sealed and heated in an 80°C oil bath for 14 h. The reaction mixture was cooled to room temperature, diluted with 100 mL 9:1 CH_2Cl_2/MeOH, and washed with water and brine (50 mL each). The aqueous washes were back-extracted once with 50 mL 9:1 CH_2Cl_2/MeOH. The combined organic extracts were dried on K_2CO_3, filtered, and concentrated *in vacuo* to afford 0.48 g of a brown solid which was purified by silica gel chromatography (25mm x 6" column eluted with 7:3 acetone/hexane) to yield **1020** as an off-white solid (0.17 g, 0.32 mmol). LCMS (ESI) *m/z* 525 $(M + H)^+$.

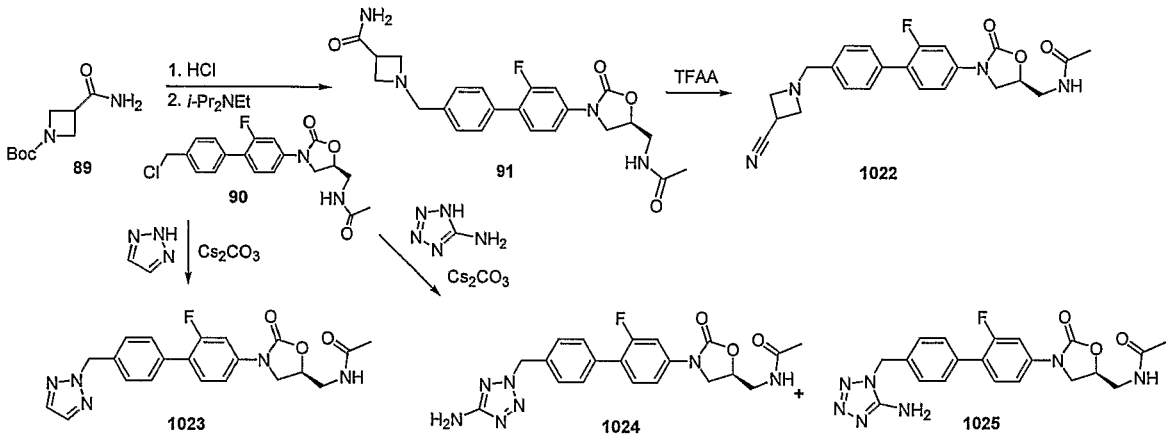
Synthesis of thiazole 1021

Compound **21** was synthesized according to the procedure described above for **1020**, using thiourea **88b** in place of **88a**. The reaction yielded **1021** as a white solid (0.12 g, 0.21 mmol). LCMS (ESI) *m/z* 561 $(M + H)^+$.

Example 9 - Synthesis of Compounds 1022-1025

Scheme 9 illustrates the synthesis of compounds **1022-1025**. Azetidine **89** was deprotected and alkylated with chloride **90** to afford amide **91**. The amide of **91** was dehydrated with trifluoroacetic anhydride to produce nitrile **1022**. The alkylation of 1,2,3-triazole with benzyl chloride **90** gave triazole **1023**. Similarly, the alkylation of 5-aminotetrazole with benzyl chloride **90** yielded a mixture of tetrazole **1024** and tetrazole **1025**.

Scheme 9



Synthesis of chloride 90

N-[3-(2-fluoro-4'-hydroxymethyl-biphenyl-4-yl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide **51** (3.0 g, 8.4 mmol) 51 was dissolved in CH_2Cl_2 (20 mL) and Hunig's base (2 mL). Methanesulfonyl chloride (1.4 mL, 12.6 mmol) was added dropwise and the resulting solution stirred at room temperature for 4 h. The mixture was poured into 100 mL sat. aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated to give 3.9 g of an oily yellow solid. The crude material was purified by silica gel chromatography to give chloride **90** as an off-white solid (2.7 g, 7.2 mmol). LCMS (ESI) *m/z* 377 $(M + H)^+$, 418 $(M + CH_3CN + H)^+$, 440 $(M + CH_3CN + Na)^+$.

Synthesis of amide 91

A solution of **89** (*J. Med. Chem.* **1993**, *36*, 801) (33 mg, 0.17 mmol) in CH_2Cl_2 (1.0 mL) was treated with 4.0 M HCl–dioxane (0.2 mL) and stirred at 23°C for 2 h. The reaction mixture was evaporated and the residue dissolved in DMF (1.0 mL) and treated with benzyl chloride **90** (63 mg, 0.17 mmol) and Hunig's base (0.17 mL, 1.0 mmol) and stirred at 60°C for 2 h. The reaction mixture was cooled to 23°C, diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (4 × 25 mL), dried (Na_2SO_4) and evaporated. The crude residue was purified by preparative TLC (1% NH_4OH–10% MeOH–89% CH_2Cl_2) to afford **91** (36 mg; 50%) as a tan powder. LCMS (ESI) *m/z* 441.1 $(M + H)^+$.

Synthesis of nitrile 1022

A solution of **91** (26 mg, 0.06 mmol) in CH_2Cl_2 (1.0 mL) was treated with pyridine (0.02 mL, 0.2 mmol) and trifluoroacetic anhydride (0.035 mL, 0.21 mmol) and stirred at 0°C for 1 h. The reaction mixture was directly purified by preparative TLC (1% NH_4OH–10% MeOH–89% CH_2Cl_2) to afford **1022** (6.0 mg; 24%) as a tan powder. LCMS (ESI) *m/z* 423.1 $(M + H)^+$.

Synthesis of triazole 1023

A solution of **90** (0.19 g, 0.50 mmol) in DMF (2.0 mL) was treated with 1,2,3-triazole (0.058 mL, 1.0 mmol) and cesium carbonate (Cs_2CO_3, 0.33 g, 1.0 mmol) and stirred at 23°C for 16 h. The reaction mixture was diluted with H_2O (100 mL) and the resulting precipitate was isolated by filtration and purified by preparative TLC (10% MeOH-45% CH_2Cl_2-45% EtOAc) to afford **1023** (39 mg; 19%) as a white powder. LCMS (ESI) *m/z* 473.2 $(M + CH_3CN + Na)^+$.

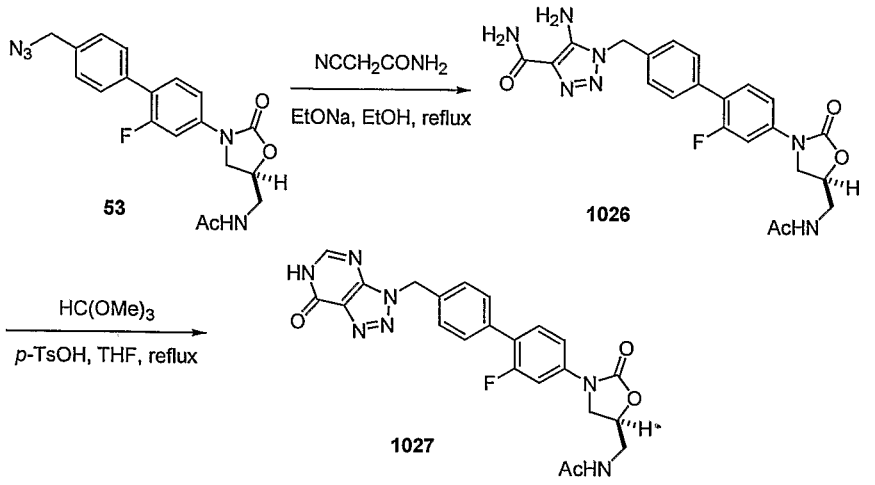
Synthesis of tetrazoles 1024 and 1025

A solution of **90** (0.19 g, 0.50 mmol) in DMF (2.0 mL) was treated with 5-aminotetrazole (87 mg, 1.0 mmol) and Cs_2CO_3 (0.33 g, 1.0 mmol) and stirred at 23°C for 12 h. The reaction mixture was diluted with H_2O (100 mL) and the resulting precipitate was isolated by filtration and suspended in 50 mL of a 1:1 mixture of CH_2Cl_2 and MeOH. The insoluble material (55 mg; 26%) was isolated by filtration and assigned the structure of **1024**. LCMS (ESI) *m/z* 426.1 $(M + H)^+$. The soluble material was isolated by evaporation and purified by preparative TLC (1%NH_4OH–10% MeOH–89% CH_2Cl_2) to afford a white powder assigned the structure of **1025** (39 mg; 19%). LCMS (ESI) *m/z* 489.2 $(M + CH_3CN + Na)^+$.

Example 10 - Synthesis of Compounds 1026 and 1027

Scheme 10 illustrates the synthesis of compounds **1026** and **1027**. Azide **53** was converted to triazole **1026**, which was then subsequently cyclized to compound **1027**.

Scheme 10



Synthesis of triazole 1026

A solution of azide **53** (383 mg, 1.0 mmol) in ethanol (4.0 mL) was treated with cyanoacetamide (101 mg, 1.2 mmol) and a solution of sodium ethoxide (21% wt solution in ethanol, 648 mg, 0.75 mL) at room temperature under N_2. The resulting reaction mixture was stirred for 10 min at room temperature before being warmed up to reflux for 2 h. When TLC showed that the reaction was complete, the reaction mixture was cooled down to room temperature before being treated with H_2O (10 mL). The white precipitate was then collected by filtration, washed with H_2O (2 x 10 mL), and dried *in vacuo* to afford the desired triazole **1026** (312 mg; 67%) as an off-white powder, which was of sufficient purity to be used directly in subsequent reactions. LCMS (ESI) *m/z* 468 $(M + H)^+$.

Synthesis of compound 1027

A suspension of **1026** (165 mg, 0.353 mmol) in anhydrous THF (5 mL) was treated with *p*-toluenesulfonic acid monohydrate (34.2 mg, 0.18 mmol) and trimethyl orthoformate (374 mg, 0.386 mL, 3.53 mmol) at 25°C under N_2, and the resulting mixture was warmed up to reflux for 2 h. The solvents were removed *in vacuo*, and the residue was directly purified by column chromatography (5–10% $MeOH/CH_2Cl_2$ gradient elution) to afford the desired compound **1027** (42 mg; 25%) as a white powder. LCMS (ESI) *m/z* 478 $(M + H)^+$.

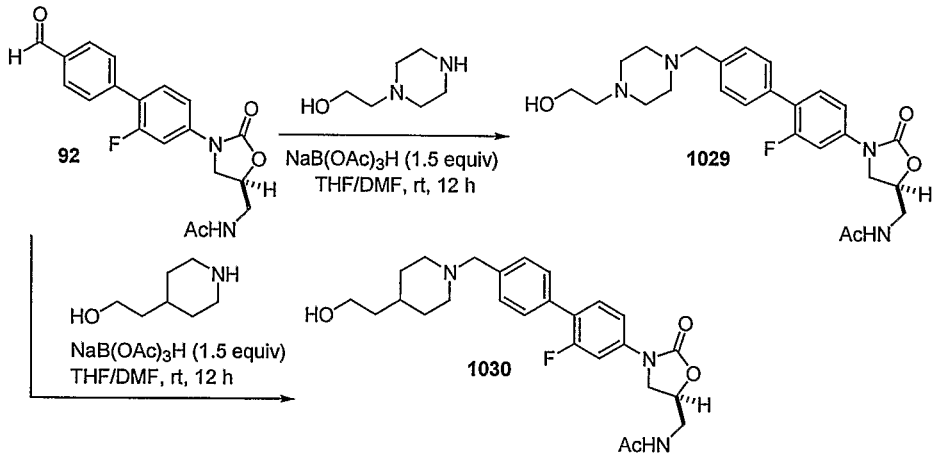
Example 11 - Synthesis of Triazole 1028

A suspension of azide **53** (124 mg, 0.324 mmol) in anhydrous 1,4-dioxane (5.0 mL) was treated with propargyl alcohol (182 mg, 0.19 mL, 3.24 mmol) at 25°C, and the resulting reaction mixture was warmed up to reflux for 12 h. When TLC and LCMS showed the reaction was complete, the reaction mixture was concentrated *in vacuo*, and the residue was directly purified by column chromatography (0–5% MeOH/CH_2Cl_2 gradient elution) to afford triazole **1028** (93.9 mg; 66%) as a pale-yellow solid. LCMS (ESI) *m/z* 440 $(M + H)^+$.

Example 12 - Synthesis of Piperazine 1029 and Piperidine 1030

Scheme 11 illustrates the reductive amination chemistry used to synthesize **1029** and **1030**.

Scheme 11



Synthesis of piperazine 1029

A solution of aldehyde **92** (made from iodide **50** and 4-formylboronic acid in the same fashion as *N*-[3-(2-fluoro-4'-hydroxymethyl-biphenyl-4-yl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide in Example 1) (180 mg, 0.5 mmol) and 2-piperidin-4-yl-ethanol (65 mg, 0.065 mL, 0.5 mmol) in anhydrous THF (4.0 mL) and anhydrous DMF (1.0 mL) was treated with sodium triacetoxyborohydride (160 mg, 0.75 mmol) at 25°C, and the resulting mixture was stirred at 25°C for 12 h. When TLC and LCMS showed the reductive amination reaction was complete, the reaction mixture was concentrated *in vacuo*. The residue was directly purified by flash column chromatography (0–5% MeOH-CH_2Cl_2 gradient elution) to afford piperazine **1029** (306 mg; 65%) as a colorless oil, which solidified upon standing at room temperature *in vacuo*. LCMS (ESI) *m/z* 471 $(M + H)^+$.

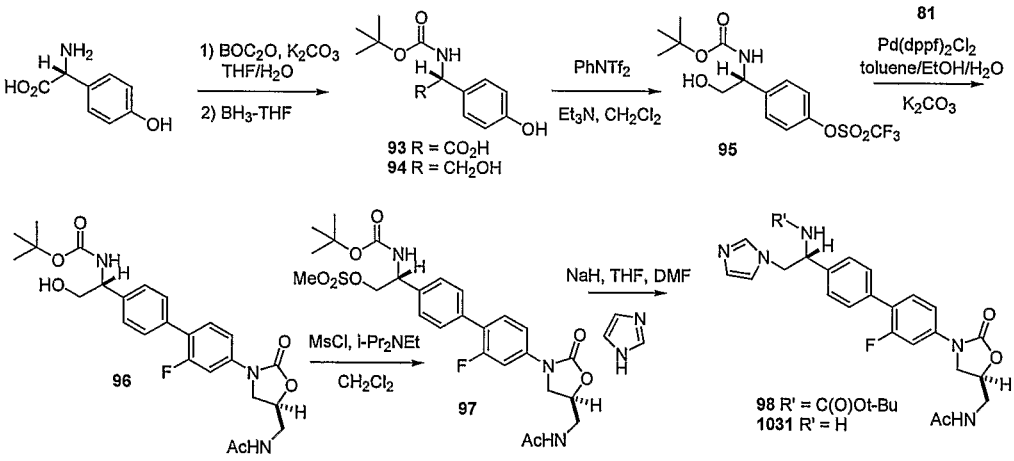
Synthesis of piperidine 1030

A solution of aldehyde **92** (356 mg, 1.0 mmol) and 2-piperazin-1-yl-ethanol (130 mg, 0.123 mL, 1.0 mmol) in anhydrous THF (8.0 mL) and anhydrous DMF (1.6 mL) was treated with sodium triacetoxyborohydride ($NaB(OAc)_3H$, 318 mg, 1.5 mmol) at 25°C, and the resulting mixture was stirred at 25°C for 12 h. When TLC and LCMS showed the reductive amination reaction was complete, the reaction mixture was concentrated *in vacuo*. The residue was directly purified by flash column chromatography (0–5% MeOH-CH_2Cl_2 gradient elution) to afford piperidine **1030** (169 mg; 72%) as a colorless oil, which solidified upon standing at room temperature *in vacuo*. LCMS (ESI) *m/z* 470 $(M + H)^+$.

Example 13 - Synthesis of Imidazole 1031

Scheme 12 depicts the synthesis of tetrazole derivative **1031**. D-*p*-Hydroxyphenyl-glycine was converted to triflate **95**, which was subsequently coupled to boronate **81** to afford alcohol **96**. Mesylation of **96**, followed by displacement with the anion of imidazole and deprotection of the BOC group yielded imidazole derivative **1031**.

Scheme 12



Synthesis of triflate 95

A solution of D-*p*-hydroxyphenylglycine (23.8 g, 142.3 mmol) and potassium carbonate (39.3 g, 284.6 mmol) in THF (200 mL) and H_2O (200 mL) was treated with di-*tert*-butyl dicarbonate (BOC_2O, 34.14 g, 156.6 mmol) at 25°C, and the resulting reaction mixture was stirred at 25°C for 2 h. When TLC and LCMS showed that the reaction was complete, the reaction mixture was treated with ethyl acetate (200 mL) and H_2O (200 mL). The two layers were separated, and the aqueous solution was extracted with ethyl acetate (200 mL), and the

combined organic extracts were discarded. The aqueous layer was then acidified with a 2 N HCl aqueous solution to pH 4 before being extracted with ethyl acetate (2 x 200 mL). The combined organic extracts were then washed with water (2 x 100 mL) and saturated aqueous NaCl solution (100 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residual white solids were further dried *in vacuo* to afford the crude desired acid **93** (36.5 g; 96%), which was of suitable purity for use in subsequent reactions.

A solution of acid **93** (4.005 g, 15 mmol) in anhydrous THF (20 mL) was treated dropwise with a 1 M solution of BH_3-THF in THF (30 mL, 30 mmol) at 0–5°C, and the resulting reaction mixture was stirred at 0– 5°C for an additional 2 h. When TLC and LCMS showed that the reduction reaction was complete, the reaction mixture was treated with water (50 mL) and ethyl acetate (50 mL). The mixture was then stirred at 25°C for 30 min before being separated, and the aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were then washed with water (2 x 20 mL) and saturated aqueous NaCl solution (20 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was then directly purified by flash column chromatography (0-5% MeOH-CH_2Cl_2 gradient elution) to afford desired alcohol **94** (2.50 g; 66%) as a white powder which was of suitable purity for use in subsequent reactions.

A suspension alcohol **94** (670 mg, 2.65 mmol) in CH_2Cl_2 (10 mL) was treated with *N*-phenyltrifluoromethane sulfonamide (947 mg, 2.65 mmol) and triethylamine (535.3 mg, 0.74 mL, 5.3 mmol) at 25°C, and the resulting reaction mixture was stirred at 25°C for an additional 2 h. When TLC and LCMS showed that the reaction was complete, the reaction mixture was quenched with water (10 mL) and CH_2Cl_2 (20 mL). The two layers were then separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were then washed with water (2 x 10 mL) and saturated aqueous NaCl solution (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was then directly purified by flash column chromatography (0-5% MeOH-CH_2Cl_2 gradient elution) to afford triflate **95** (945 mg; 93%) as a white powder which was of suitable purity for use in subsequent reactions.

Synthesis of alcohol 96

A solution of boronate **81** (2.162 g, 5.72 mmol) and triflate **95** (1.70 g, 4.4 mmol) in toluene (24 mL) was treated with solid potassium carbonate (1.82 g, 13.2 mmol), ethanol (8.0 mL) and H_2O (8.0 mL) at room temperature, and the resulting reaction mixture was degassed three times under a steady stream of argon before being treated with $Pd(dppf)_2Cl_2$ (184 mg,

0.22 mmol) at room temperature. The reaction mixture was then degassed three times again under a steady stream of argon before being warmed up to reflux for 2 h. When TLC and LCMS showed that the reaction was complete, the reaction mixture was cooled down to room temperature before being treated with water (20 mL) and ethyl acetate (20 mL). The two layers were separated, and the aqueous layer was extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were washed with water (2 x 20 mL) and saturated aqueous NaCl solution (20 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was then purified by flash column chromatography (0-5% MeOH-CH_2Cl_2 gradient elution) to afford (1-{4'-[5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2'-fluoro-biphenyl-4-yl}-2-hydroxyethyl)carbamic acid *tert*-butyl ester **96** (1.543 g; 72%) as yellow oil, which solidified upon standing at room temperature *in vacuo*.

Synthesis of mesylate 97

A suspension of alcohol **96** (694 mg, 1.43 mmol) in anhydrous CH_2Cl_2 (10 mL) was treated with diisopropylethylamine (388 mg, 0.522 mL, 2.85 mmol) and methanesulfonyl chloride (196 mg, 0.132 mL, 1.71 mmol) at 0–5°C, and the resulting reaction mixture was stirred at 0–5°C for an additional 2 h. When TLC and LCMS showed that the reaction was complete, the reaction mixture was quenched with water (10 mL). The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were washed with water (2 x 10 mL) and saturated aqueous NaCl solution (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was then purified by flash column chromatography (0-5% MeOH-CH_2Cl_2 gradient elution) to afford mesylate **97** (647 mg; 80%) as a pale-yellow solid, which was of suitable purity for use in subsequent reactions.

Synthesis of imidazole 98

A solution of imidazole (41 mg, 0.6 mmol) in anhydrous THF (3 mL) was treated with NaH (60% oil dispersion, 29 mg, 0.72 mmol) at 0°C, and the resulting mixture was stirred at 0-5°C for 30 min before a solution of mesylate **97** (170 mg, 0.3 mmol) in anhydrous DMF (3.0 mL) was added. The resulting reaction mixture was then stirred at 0–5°C for 30 min before being gradually warmed up to room temperature for 12 h. When TLC and LCMS showed that the reaction was complete, the solvents were removed *in vacuo*, and the residue was directly purified by flash column chromatography (0-5% MeOH-CH_2Cl_2 gradient elution) to afford imidazole **98** (46 mg; 29%) as a yellow solid.

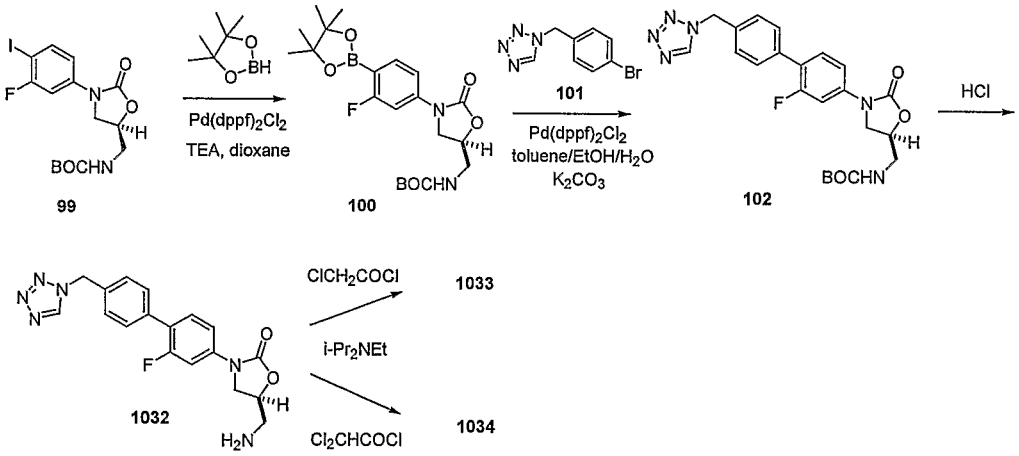
Synthesis of imidazole 1031

A solution of imidazole **98** (23 mg, 0.043 mmol) in MeOH (1.0 mL) was treated with a solution of 4 N HCl in 1,4-dioxane (3.0 mL), and the resulting reaction mixture was stirred at room temperature for 30 min. When TLC and LCMS showed that the reaction was complete, the solvents were removed *in vacuo*, and the desired *N*-{3-[4'-(1-amino-2-imidazol-1-yl-ethyl)-2-fluoro-biphenyl-4-yl]-2-oxo-oxazolidin-5-ylmethyl}acetamide hydrochloride **1031** (18.8 mg; 100%) was obtained as a yellow solid. LCMS (ESI) *m/z* 438 $(M + H)^+$.

Example 14 - Synthesis of tetrazoles 1032-1034

Scheme 13 depicts the synthesis of tetrazole derivatives **1032-1034**. Iodide **99** was converted to boronate **100** which served as the coupling partner for bromide **101** to afford tetrazole **102**. Deprotection of **102** afforded tetrazole amine **1032**, which was subsequently acylated to afford tetrazole **1033** and **1034**.

Scheme 13



Synthesis of iodide 99

A solution of known 5-aminomethyl-3-(3-fluoro-4-iodo-phenyl)-oxazolidin-2-one (2.02 g, 6.0 mmol; *see* U.S. Patent Nos. 5,523,403 and 5,565,571) and potassium carbonate (1.66 g, 12.0 mmol) in THF (20 mL) and H_2O (20 mL) was treated with BOC_2O (1.334 g, 6.12 mmol) at 25°C, and the resulting reaction mixture was stirred at 25°C for 2 h. When TLC and LCMS showed the reaction was complete, the reaction mixture was treated with ethyl acetate (20 mL) and H_2O (20 mL). The two layers were separated, and the aqueous solution was extracted with ethyl acetate (20 mL), and the combined organic extracts were then washed with water (2 x 10 mL) and saturated aqueous NaCl solution (10 mL), dried over $MgSO_4$, and concentrated *in*

vacuo. The residual white solids were further dried *in vacuo* to afford the crude, desired iodide **99** (2.40 g; 92%), which was of suitable purity for use in subsequent reactions.

Synthesis of boronate 100

A solution of iodide **99** (1.11 g, 2.55 mmol) in 1,4-dioxane (25 mL) was treated with 4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (489 mg, 0.56 mL, 3.82 mmol) and triethylamine (772 mg, 1.07 mL, 7.65 mmol) at room temperature, and the resulting reaction mixture was degassed three times under a steady stream of argon before being treated with $Pd(dppf)_2Cl_2$ (107 mg, 0.13 mmol) at room temperature. The reaction mixture was then degassed three times again under a steady stream of argon before being warmed up to reflux for 6 h. When TLC and LCMS showed that the reaction was complete, the reaction mixture was cooled down to room temperature before being treated with water (20 mL) and ethyl acetate (20 mL). The two layers were separated, and the aqueous layer was extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were washed with water (2 x 20 mL) and saturated aqueous NaCl solution (20 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residual brown oil was then purified by flash column chromatography (10-30% EtOAc-hexanes gradient elution) to afford boronate **100** (646 mg; 58%) as a brown oil, which solidified upon standing at room temperature *in vacuo* and was of suitable purity for use in subsequent reactions.

Synthesis of bromide 101

A solution of 4-bromobenzylamine hydrochloride (2.22 g, 10.0 mmol) in acetic acid (30 mL) was treated with triethyl orthoformate (2.964 g, 3.29 mL, 20.0 mmol) and sodium azide (2.30 g, 20.0 mmol) at room temperature, and the resulting reaction mixture was subsequently stirred at reflux for 12 h. When TLC and LCMS showed that the reaction was complete, the reaction mixture was cooled down to room temperature, and the cooled reaction mixture was poured into ice-water (100 mL). The precipitate was then collected by filtration, washed with water (2 x 20 mL), and dried *in vacuo* to afford crude bromide **101** (460 mg; 19%) as a white solid, which was of suitable purity for use in subsequent reactions.

Synthesis of tetrazole 102

A solution of boronate **100** (658 mg, 1.5 mmol) and bromide **101** (300 mg, 1.25 mmol) in toluene (9.0 mL) was treated with solid potassium carbonate (621 mg, 4.5 mmol), ethanol (3.0 mL) and H_2O (3.0 mL) at room temperature, and the resulting reaction mixture was degassed three times under a steady stream of argon before being treated with $Pd(dppf)_2Cl_2$

(52.3 mg, 0.063 mmol) at room temperature. The reaction mixture was then degassed three times again under a steady stream of argon before being warmed up to reflux for 3 h. When TLC and LCMS showed that the reaction was complete, the reaction mixture was cooled down to room temperature before being treated with water (10 mL) and ethyl acetate (20 mL). The two layers were separated, and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic extracts were washed with water (2 x 5 mL) and saturated aqueous NaCl solution (5 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was then purified by flash column chromatography (0-5% MeOH-CH_2Cl_2 gradient elution) to afford tetrazole **102** (357 mg; 61%) as a yellow oil, which solidified upon standing at room temperature *in vacuo*.

Synthesis of tetrazole 1032

A solution of tetrazole **102** (350 mg, 0.748 mmol) in EtOAc (5.0 mL) was treated with a solution of 4 N HCl in 1,4-dioxane (5.0 mL), and the resulting reaction mixture was stirred at room temperature for 30 min. When TLC and LCMS showed that the reaction was complete, the solvents were removed *in vacuo*, and the residue was treated with an aqueous sodium bicarbonate solution (10 mL) and EtOAc (15 mL). The mixture was stirred at room temperature for 30 min before the two layers were separated. The aqueous layer was extracted with EtOAc (10 mL), and the combined organic extracts were washed with H_2O (10 mL) and saturated aqueous NaCl solution (10 mL), dried over $MgSO_4$, and concentrated *in vacuo* to afford tetrazole amine **1032** (266 mg; 97%) as a pale-yellow solid. LCMS (ESI) *m/z* 369 $(M + H)^+$.

Synthesis of tetrazole 1033

A suspension of tetrazole amine **1032** (74 mg, 0.2 mmol) in anhydrous CH_2Cl_2 (5.0 mL) was treated with diisopropylethylamine (52 mg, 0.07 mL, 0.4 mmol) and chloroacetyl chloride (34 mg, 0.024 mL, 0.3 mmol) at 0–5°C, and the resulting reaction mixture was stirred at 0-5°C for 2 h. When TLC and LCMS showed the reaction was complete, the reaction mixture was concentrated *in vacuo*. The residue was directly purified by flash column chromatography (0-5% MeOH-CH_2Cl_2 gradient elution) to afford tetrazole **1033** (43 mg; 48% yield) as a white solid. LCMS (ESI) *m/z* 445 $(M + H)^+$.

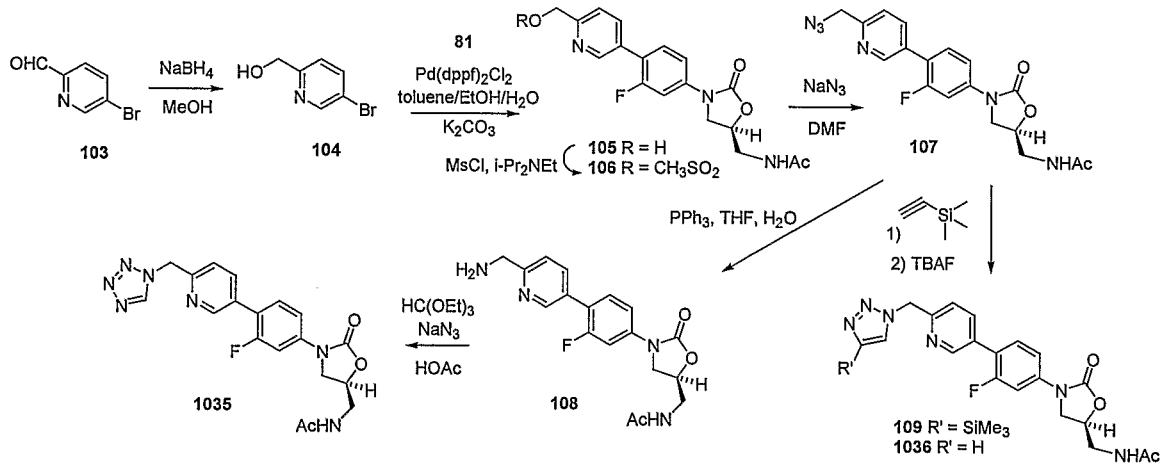
Synthesis of tetrazole 1034

A suspension of tetrazole amine **1032** (74 mg, 0.2 mmol) in anhydrous CH_2Cl_2 (5.0 mL) was treated with diisopropylethylamine (52 mg, 0.07 mL, 0.4 mmol) and dichloroacetyl chloride (44 mg, 0.029 mL, 0.3 mmol) at 0–5°C, and the resulting reaction mixture was stirred at 0-5°C for 2 h. When TLC and LCMS showed the reaction was complete, the reaction mixture was concentrated *in vacuo*. The residue was directly purified by flash column chromatography (0-5% MeOH-CH_2Cl_2 gradient elution) to afford tetrazole **1034** (41 mg; 43% yield) as a white solid. LCMS (ESI) *m/z* 479 $(M + H)^+$.

Example 15 - Synthesis of compounds 1035 and 1036

Scheme 14 depicts the synthesis of tetrazole derivatives **1035** and **1036**. Aldehyde **103** was reduced to **104** which was coupled to boronate **81** to yield alcohol **105**. Mesylation of **105**, followed by displacement with sodium azide, yielded azide **107**. Reduction of **107** to amine **108** was followed by conversion to tetrazole **1035**. Cycloaddition of azide **107** with trimethylsilylacetylene, followed by desilylation, afforded triazole **1036**.

Scheme 14



Synthesis of aldehyde 103

A solution of 2,5-dibromopyridine (25 g, 105.5 mmol) in toluene (1.24 L) was cooled down to –78°C before being treated dropwise with a 2.5 M solution of *n*-BuLi in hexane (50.6 mL, 126.6 mmol) at –78°C under N_2. The resulting reaction mixture was stirred at –78°C for 1 h before being treated with anhydrous DMF (11.6 g, 12.2 mL, 158.0 mmol) at –78°C. The reaction mixture was stirred at –78°C for an additional 1 h before being gradually warmed up to room temperature for 6 h. When TLC and LCMS showed that the reaction was complete, the

reaction mixture was quenched with water (200 mL). The two layers were separated, and the aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were then washed with H_2O (2 x 200 mL), and saturated aqueous NaCl solution (100 mL), and dried over $MgSO_4$. The solvents were then removed *in vacuo*, and the residual pale-yellow oil was purified by flash column chromatography (0–15% EtOAc-hexane gradient elution) to afford aldehyde 103 (10.2 g; 52%) as a pale-yellow solid.

Synthesis of bromide 104

A solution aldehyde **103** (4.91 g, 26.4 mmol) in methanol (120 mL) was treated with sodium borohydride (1.18 g, 31.7 mmol) at 0–5°C, and the resulting reaction mixture was stirred at 0–5°C for an additional 1 h. When TLC and LCMS showed that the reaction was complete, the reaction mixture was quenched with water (20 mL). The solvents were then removed *in vacuo*, and the residue was directly purified by flash column chromatography (5–25% EtOAc-hexane gradient elution) to afford bromide **104** (4.23 g; 85%) as a white solid.

Synthesis of alcohol 105

A solution of boronate **81** (11.05 g, 29.2 mmol) and bromide **104** (4.227 g, 22.5 mmol) in toluene (150 mL) was treated with solid potassium carbonate (9.315 g, 67.5 mmol), ethanol (50 mL) and H_2O (50 mL) at room temperature, and the resulting reaction mixture was degassed three times under a steady stream of argon before being treated with $Pd(dppf)_2Cl_2$ (564 mg, 0.675) at room temperature. The reaction mixture was then degassed three times again under a steady stream of argon before being warmed up to reflux for 1 h. When LCMS showed that the reaction was complete, the reaction mixture was cooled down to room temperature before being treated with water (200 mL) and ethyl acetate (100 mL). The two layers were separated, and the aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with water (2 x 50 mL) and saturated aqueous NaCl solution (50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was then purified by flash column chromatography (0-5% MeOH-CH_2Cl_2 gradient elution) to afford alcohol **105** (6.16 g; 76%) as a grey solid.

Synthesis of azide 107

A suspension of alcohol **105** (2.15 g, 6.0 mmol) in CH_2Cl_2 (25 mL) was treated with diisopropylethylamine (1.551 g, 2.10 mL, 12.0 mmol) and methanesulfonyl chloride (756 mg, 0.511 mL, 6.6 mmol) at 0–5°C, and the resulting reaction mixture was stirred at 0-5°C for an

additional 2 h. When TLC and LCMS showed that the reaction was complete, the reaction mixture was treated with water (20 mL) and CH_2Cl_2 (40 mL). The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic extracts were washed with water (20 mL) and saturated aqueous NaCl solution (20 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was then purified by flash column chromatography (0-5% MeOH-CH_2Cl_2 gradient elution) to afford mesylate **106** (2.47 g; 94%) as a yellow solid.

A solution of mesylate **106** (874 mg, 2.0 mmol) in DMF (8.0 mL) was treated with sodium azide (260 mg, 4.0 mmol) at room temperature, and the resulting reaction mixture was warmed up to 40-45°C for 3 h. When TLC and LCMS showed that the reaction was complete, the reaction mixture was treated with water (20 mL), and the precipitate was collected by filtration, washed with water (2 x 10 mL), and dried *in vacuo* to afford crude azide **107** (699 mg; 91%) as a grey solid, which was of suitable purity for use in subsequent reactions.

Synthesis of amine 108

A suspension of azide **107** (2.611 g, 6.8 mmol) in THF (25 mL) was treated with water (0.13 mL, 68 mmol) and triphenylphosphine (PPh_3, 2.14 g, 8.2 mmol) at room temperature, and the resulting reaction mixture was subsequently stirred at room temperature for 12 h. When TLC and LCMS showed that the reaction was complete, the solvents were removed *in vacuo*, and the residue was directly purified by flash column chromatography (0-15% MeOH-CH_2Cl_2 gradient elution) to afford amine **108** (2.233 g; 92%) as a yellow solid.

Synthesis of tetrazole 1035

A solution of amine **108** (90 mg, 0.25 mmol) in acetic acid (3.0 mL) was treated with triethyl orthoformate (0.1 mL) and sodium azide (40 mg) at room temperature, and the resulting reaction was subsequently stirred at reflux for 4 h. When TLC and LCMS showed that the reaction was complete, the reaction mixture was cooled down to room temperature and concentrated *in vacuo*. The residue was then directly purified by flash column chromatography (0-5% MeOH-CH_2Cl_2 gradient elution) to afford tetrazole **1035** (43 mg; 36%) as a white solid. LCMS (ESI) *m/z* 412 $(M + H)^+$.

Synthesis of triazole 1036

A solution of azide **107** (142 mg, 0.37 mmol) in DMF (5 mL) was treated with thimethylsilyl acetylene (0.5 mL) at room temperature, and the resulting reaction mixture was

subsequently stirred at 70–80°C for 12 h. When TLC and LCMS showed that the reaction was complete, the reaction mixture was cooled down to room temperature before being concentrated *in vacuo*. The residue was then directly purified by flash column chromatography (0-5% MeOH-CH_2Cl_2 gradient elution) to afford triazole **109** (152 mg; 85%) as a pale-yellow oil, which was directly used in the subsequent reaction.

A solution of triazole **109** (152 mg, 0.315 mmol) in THF (10 mL) was treated with a 1N solution of tetrabutylammonium fluoride in THF (2.0 mL) at 0–5°C, and the resulting reaction mixture was stirred at 0–5°C for 1 h before being gradually warmed up to room temperature for 10 h. When TLC and LCMS showed that the reaction was complete, the reaction mixture was cooled down to room temperature before being concentrated *in vacuo*. The residue was then directly purified by flash column chromatography (0-5% MeOH-CH_2Cl_2 gradient elution) to afford triazole **1036** (67 mg; 52%) as a pale-yellow oil, which solidified upon standing at room temperature *in vacuo*. LCMS (ESI) *m/z* 411 $(M + H)^+$.

Example 16 - Synthesis of Triazole 1037

A solution of mesylate **52** (436 mg, 1.0 mmol) in anhydrous DMF (5 mL) was treated with 1,2,4-triazole sodium salt (182 mg, 2.0 mmol) at 0–5°C, and the resulting reaction mixture was stirred at 0–5°C for 1 h before being gradually warmed up to room temperature for 10 h. When TLC and LCMS showed that the reaction was complete, the reaction mixture was concentrated *in vacuo*. The residue was then directly purified by flash column chromatography (0-5% MeOH-CH_2Cl_2 gradient elution) to afford triazole **1037** (388 mg; 95%) as a white solid. LCMS (ESI) *m/z* 410 $(M + H)^+$.

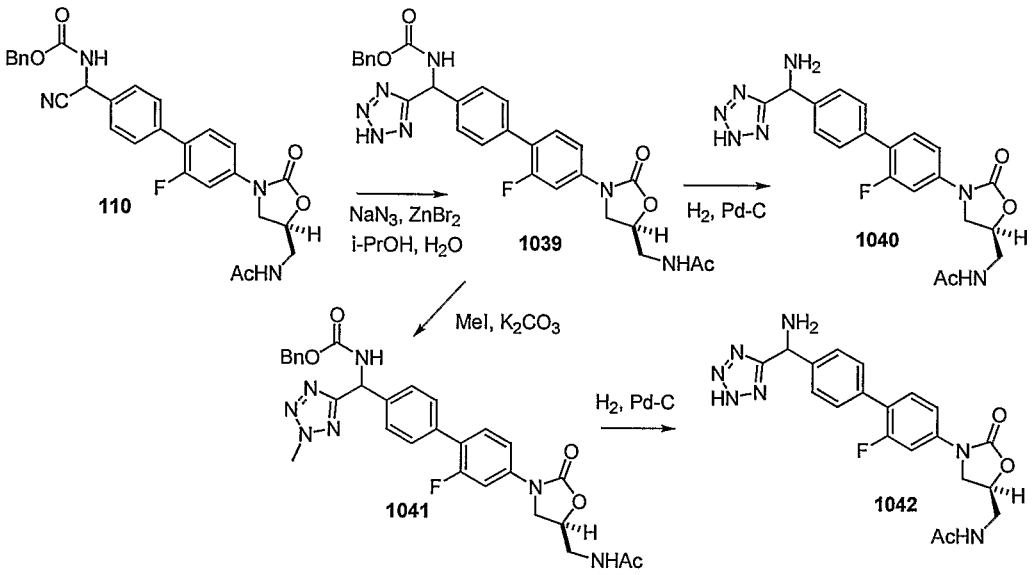
Example 17 - Synthesis of Piperazine 1038

A suspension of the aldehyde **92** (142 mg, 0.4 mmol) in MeOH (4.0 mL) and THF (1.0 mL) was treated with 1-(3-chloro-5-trifluoromethyl-pyridin-2-yl)piperazine (106 mg, 0.4 mmol) and sodium triacetoxyborohydride (160 mg, 0.8 mmol) at 25°C, and the resulting reaction mixture was stirred at 25°C for 6 h. When TLC and LCMS showed the reductive amination reaction was complete, the reaction mixture was concentrated *in vacuo*. The residue was directly purified by flash column chromatography (0–5% MeOH-CH_2Cl_2 gradient elution) to afford piperazine **1038** (38 mg; 16% yield) as a colorless oil, which solidified upon standing at room temperature *in vacuo*. LCMS (ESI) *m/z* 607 $(M + H)^+$.

Example 18 – Synthesis of Tetrazoles 1039-1042

Scheme 15 shows the synthesis of compounds **1039-1042**. Nitrile **110** is converted to tetrazole **1039**, which was deprotected to afford tetrazole **1040**. Tetrazole **1039** is methylated to afford **1041**, which was subsequently deprotected to yield **1042**.

Scheme 15



Synthesis of nitrile 110

A suspension of aldehyde **92** (1.884 g, 5.3 mmol) in MeOH (25 mL) was treated with a solution of NaCN (312 mg, 6.4 mmol) in H_2O (10 mL) and a solution of ammonium chloride (340 mg, 6.4 mmol) in H_2O (15 mL) at 25°C, and the resulting mixture was stirred at 25°C for 30 min before being warmed up to 50°C for 1 h. When TLC and LCMS showed that the reaction was complete, the reaction mixture was cooled down to room temperature before being treated with H_2O (25 mL) at 25°C, and the resulting mixture was cooled down to 0–5 °C for 1 h. The solid precipitates were collected by filtration, washed with H_2O (2 x 20 mL) and 20% EtOAc/hexane (2 X 20 mL), and dried *in vacuo*. The crude desired *N*-{3-[4'-(amino-cyano-methyl)-2-fluoro-biphenyl-4-yl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (1.801 g; 89% yield) was obtained as off-white solids, which by HPLC and ^1H NMR was of sufficient purity to be used in subsequent reactions. LCMS (ESI) *m/z* 383 $(M + H)^+$.

A solution of *N*-{3-[4'-(amino-cyano-methyl)-2-fluoro-biphenyl-4-yl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide obtained above (1.70 g, 4.45 mmol) in THF (40 mL) and H_2O (40 mL) was treated with benzyl chloroformate (940 mg, 5.34 mmol) and potassium carbonate (1.23 g, 8.9 mmol) at 25°C, and the resulting reaction mixture was stirred at 25°C for

2 h. When TLC and LCMS showed the reaction was complete, the reaction mixture was quenched with H_2O (20 mL) and EtOAc (50 mL). The two layers were separated, and the aqueous layer was extracted with EtOAc (50 mL). The combined organic extracts were washed with water (2 x 20 mL), and saturated aqueous NaCl solution (20 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was then purified by column chromatography (0–5% MeOH-CH_2Cl_2 gradient elution) to afford the desired nitrile **110** (2.20 g; 96%) as a colorless oil, which solidified upon standing at room temperature *in vacuo*. This material by ^1H NMR was found to be a mixture of two diastereomers. LCMS (ESI) *m/z* 517 $(M + H)^+$.

Synthesis of tetrazole 1039

A solution of 0.130 g (2.52 mmol) of nitrile **110**, 0.033 g (5.04 mmol) of NaN_3, and 0.028 g (1.26 mmol) of zinc bromide ($ZnBr_2$) in 9 ml of isopropanol/H_2O (1:2) was allowed to stir at reflux for 24 h. Once the reaction mixture cooled down, it was diluted with 1 N HCl, extracted with MeOH/CH_2Cl_2 (1:3) (40 ml x 3), and the combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated to give 0.050 g of tetrazole **1039** as a mixture of tautomers. LCMS (ESI) *m/z* 560 $(M + H)^+$.

Synthesis of tetrazole 1040

A solution of 0.030 g of **1039** and 0.020 g of palladium on carbon (Pd/C) (10%) in 6 ml of (1:1 H_2O/THF) was allowed to stir at 25°C under H_2 atmosphere (balloon) for 16 h. The reaction mixture was filtered through celite, and washed with MeOH/CH_2Cl_2. The filtrate was concentrated, washed with small amount of EtOAc, then dried via vacuum to give 0.010 g of tetrazole **1040**. LCMS (ESI) *m/z* 426 $(M + H)^+$.

Synthesis of methyl tetrazole 1041

A solution of 0.218 g (0.39 mmol) of **1039**, 0.080 g (0.58 mmol) of K_2CO_3, and 0.061 g (0.43 mmol) of methyl iodide (MeI) in 5 ml of DMF was allowed to stir at 25°C for 16 h. The reaction solvent was removed by vacuum. The residue was dissolved in a mixture of MeOH/CH_2Cl_2 (1:1), filtered through a pipette column, and the filtrate was concentrated to give the crude product **1041** in the amount of about 0.220 g. A small amount was purified through preparative HPLC. LCMS (ESI) *m/z* 574 $(M + H)^+$.

Synthesis of methyl tetrazole 1042

A solution of 0.220 g of **1041** and 0.020 g of Pd (10% on carbon) in 3 ml of DMF was allowed to stir at 25°C under H_2 atmosphere (balloon) for 24 h. The solvents were removed by

rotary evaporation, the residue was then dissolved in a mixture of MeOH/CH_2Cl_2, and filtered through celite. The filtrate was concentrated and further purified by preparative HPLC to give 0.052 g of methyl tetrazole **1042**. LCMS (ESI) *m/z* 440 $(M + H)^+$.

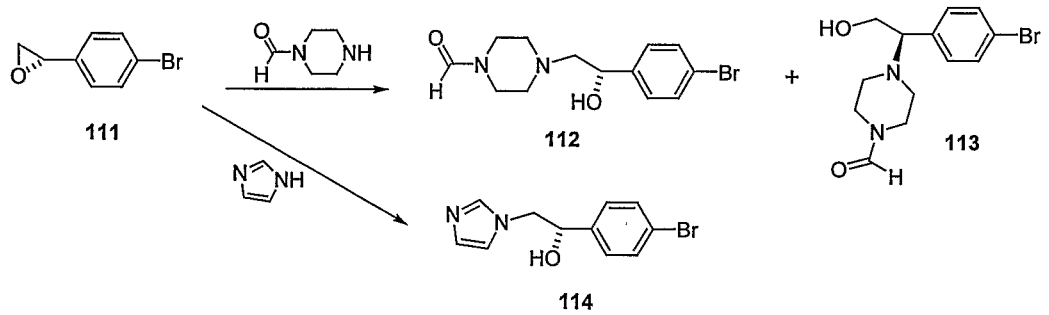
Example 19 – Synthesis of Pyrazole 1043

To a suspension of 0.048 g (2.0 mmol) of NaH and 0.125 g (1.83 mmol) of pyrazole in 8 ml of DMF at 0°C was added 0.400 g (0.92 mmol) of mesylate **52**. Then, the reaction mixture was warmed up to 25°C, and was allowed to stir for 3 h. The DMF was removed and the residue was purified by preparative TLC to give 0.360 g of pyrazole **1043** (96% yield). LCMS (ESI) *m/z* 409 $(M + H)^+$.

Example 20 – Synthesis of Compounds 1044-1046

Scheme 16 depicts the synthesis of aryl bromides **112-114** required for the synthesis of compounds **1044-1046**. Epoxide **111** was treated with 1-formyl piperazine to afford a mixture of **112** and **113**. Epoxide ring-opening of **111** with imidazole afforded **114**. These bromides were coupled with boronate **81** to deliver the target compounds **1044-1046**.

Scheme 16



Synthesis of epoxide 111

To a solution of 4-bromostyrene (5.00 g, 26.8 mmol) in CH_2Cl_2 (130 mL) was added 4-methylmorpholine *N*-oxide (NMO, 12.90 g, 107.1 mmol, anhydrous) and Jacobsen catalyst ((1S, 2S)-(+)-[1,2-(cyclohexanodiamino-N,N'-bis(3,5-di-t-butyl-salicylidene)] manganese(III) chloride, 850 mg, 1.34 mmol). The solution was cooled to -78°C, then *m*-chloroperbenzoic acid (*m*-CPBA, 7.40 g, 42.8 mmol) was added in four portions every 10 min. The mixture was stirred at -78°C for 2 h. The reaction was quenched by addition of sodium thiosulfate ($Na_2S_2O_3$) solution (10.0 g in 30 mL water), then the cooling bath was removed, and water (70 mL), 1N sodium hydroxide (NaOH, 60 mL) was added. The aqueous phase was extracted with

CH_2Cl_2 (30 mL x 3), dried with Na_2SO_4, and evaporated. The residue was purified by flash chromatography (4:100 Et_2O/Hexane) to yield 5.20 g epoxide **111** (98% yield).

General procedure for the synthesis of bromides 112-114 from epoxide 111

To a suspension of epoxide **111** (1mmol, 1eq) in acetonitrile (3.0 mL) at room temperature was added lithium perchlorate ($LiClO_4$, 1.05 mmol, 1.05 eq). After the formation of a clear solution, the amine (1.5 mmol, 1.5 eq) was added. The mixture was stirred at room temperature or at 60°C. The solvent was removed under vacuum and the residue was purified by flash chromatography.

Conditions for 112 and 113: room temperature, 16 h, flash chromatography (3:100 MeOH/CH_2Cl_2). Yield of **112**: 132 mg; Yield of **113**: 42 mg.

Conditions for 114: 60°C, 4 h, flash chromatography (3:100 MeOH/CH_2Cl_2). Yield of **114**: 103 mg.

General procedure for the synthesis of compounds 1044-1046 from bromides 112-114

A suspension of bromide intermediate (1 eq), boronate **81** (1 eq), $PdCl_2(dppf)_2$ (0.05 eq), and K_2CO_3 (4 eq) in a mixture of dioxane/EtOH/H_2O (ratio of 3:1:1) was degassed by a stream of argon. The mixture was stirred at 75°C to 85°C for 3 to 15 h. The solvent was removed by vacuum and the residue was purified by flash chromatography to afford the product.

Conditions for 1044: 80°C, 3.5 h, flash chromatography (4:100 MeOH/CH_2Cl_2); Yield 150 mg. LCMS (ESI) *m/z* 485 $(M + H)^+$.

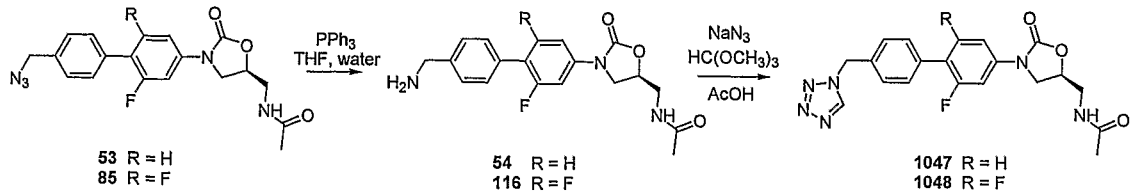
Conditions for 1045: 80°C, 3.5 h, flash chromatography (5:100 MeOH/CH_2Cl_2); Yield 52 mg. LCMS (ESI) *m/z* 485 $(M + H)^+$.

Conditions for 1046: 80°C, 2.5 h, flash chromatography (10:100 MeOH/CH_2Cl_2); Yield 155 mg. LCMS (ESI) *m/z* 439 $(M + H)^+$.

Example 21 – Synthesis of Compounds 1047 and 1048

Scheme 17 depicts the synthesis of tetrazoles **1047** and **1048**. Azides **53** and **85** were reduced to amines **115** and **116** respectively. These amines were then converted to triazoles **1047** and **1048** by treatment with sodium azide and trimethylorthoformate in hot acetic acid.

Scheme 17



Synthesis of amine 54

Amine **54** was prepared from azide **53** according to the method described in Example 1.

Synthesis of amine 116

Azide **85** (1.10 g, 2.74 mmol) was dissolved in 17 mL THF and 0.6 mL water. Triphenylphosphine (1.30 g, 4.96 mmol) was added, and the mixture was heated to reflux for 4 h. The mixture was allowed to stir overnight at room temperature, and was partitioned between ethyl acetate and 20 mL 2N aqueous HCl. The organic layer was extracted with 20 mL 2N aqueous HCl, and then the aqueous layer was basified with 85 mL 1N aqueous NaOH. The cloudy aqueous phase was extracted with ethyl acetate (2 x), and 5% methanol/methylene chloride (2 x). The combined organic extracts were dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica gel using a gradient elution of methylene chloride then methanol/methylene chloride (up to 10% methanol) to afford amine **116** (0.587 g, 1.57 mmol; 57%) as a tan solid. LCMS (ESI) *m/z* 376 $(M + H)^+$.

Synthesis of tetrazole 1047

A solution of amine **54** (0.20 g, 0.56 mmol) in acetic acid (5 mL) was treated with sodium azide (0.05 g, 0.84 mmol) followed by triethylorthoformate (0.15 mL, 0.90mmol). The reaction mixture was heated to reflux for 4 h. The mixture was cooled and added to ice water (10 mL). After standing at room temperature for 48 h, the precipitated product was collected by filtration and washed with cold CH_3OH to yield tetrazole **1047** (101mg; 50%) as a white solid. LCMS (ESI) *m/z* 474 $(M + H)^+$.

Synthesis of tetrazole 1048

Tetrazole **1048** was made from amine **116** using the same procedure for the synthesis of **1047**. LCMS (ESI) *m/z* 429.

Example 22 – Synthesis of Compounds 1049-1054

Synthesis of 1049

A solution of mesylate **52** (0.10 g, 0.24 mmol) in dimethyl sulfoxide (DMSO, 2.0 mL) was treated with ethyl 4-pyrazole carboxylate (0.03 g, 0.24 mmol), K_2CO_3 (0.06 g, 0.46 mmol) and the mixture was heated to 90°C for 16 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (100 mL), and washed with brine (2 x 50 mL). The organic phase was dried and evaporated. The residue was purified by preparative thin layer chromatography (using 95% CH_2Cl_2, 5% MeOH as eluant) to provide **1049**. LCMS (ESI) *m/z* 481 $(M + H)^+$.

Synthesis of 1050

This compound was made from mesylate **52** and 4-(hydroxymethyl)imidazole using the same procedure described for the synthesis of **1049**. LCMS (ESI) *m/z* 439 $(M + H)^+$.

Synthesis of 1051

This compound was made from mesylate **52** and 4-pyrazolecarboxylic acid using the same procedure described for the synthesis of **1049**. LCMS (ESI) *m/z* 453 $(M + H)^+$.

Synthesis of 1052

This compound was made from mesylate **52** and 4-methylpyrazole using the same procedure described for the synthesis of **1049**. LCMS (ESI) *m/z* 423 $(M + H)^+$.

Synthesis of 1053

This compound was made from mesylate **52** and 3-aminopyrazole using the same procedure for the synthesis of **1049**. LCMS (ESI) *m/z* 424 $(M + H)^+$.

Synthesis of 1054

This compound was made from mesylate **52** and pyrrole using the same procedure for the synthesis of **1049**. LCMS (ESI) *m/z* 408 $(M + H)^+$.

Example 23 – Synthesis of Aldehyde 1055

A solution of amine **54** (0.20 g, 0.56 mmol) in acetic acid (5 mL) was treated with 2,5-dimethoxy-3-tetrahydrofurancarboxaldehyde (0.12 g, 0.78 mmol). The reaction mixture was heated to reflux for 2 h. The mixture was cooled and the solvent removed under high vacuum.

The residue was purified by preparative thin layer chromatography (using 95% CH_2Cl_2, 5% MeOH as eluant) to provide **1055**. LCMS (ESI) *m/z* 436 $(M + H)^+$.

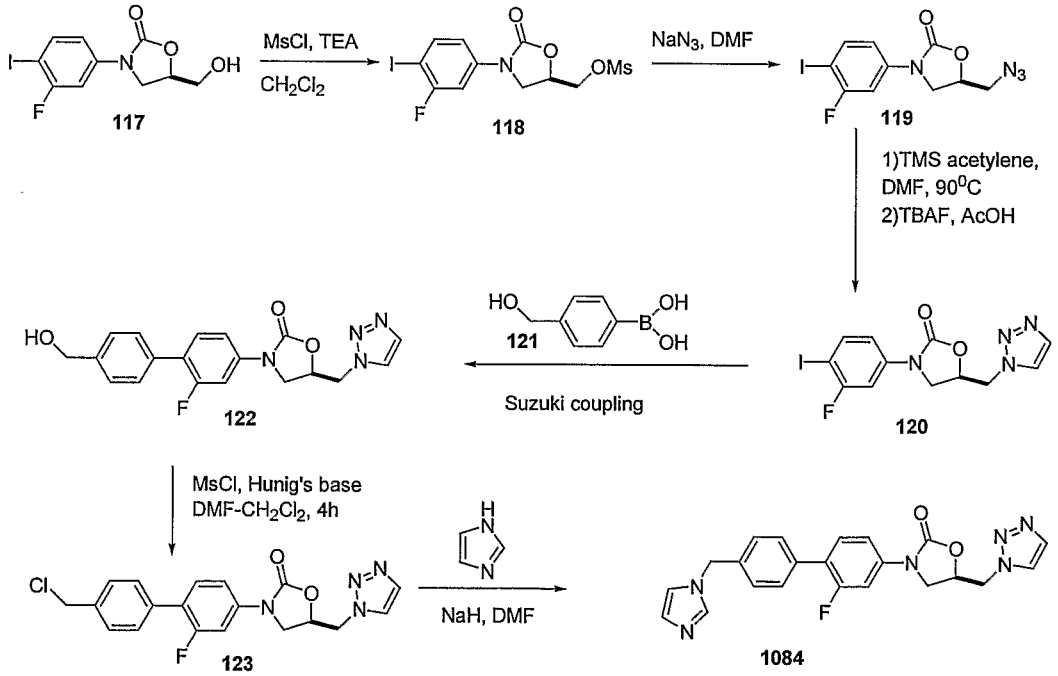
Example 24 – Synthesis of Tetrazole 1056

A solution of mesylate **52** (0.50 g, 1.14 mmol) in acetonitrile (CH_3CN, 5 mL) was treated with tetrazole (12 mL, 5.73 mmol), and triethylamine (0.8 mL, 5.73 mmol), and the mixture was heated to reflux for 18 h. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (100 mL), and washed with brine (2 x 50 mL). The organic phase was dried and evaporated. The residue was purified by preparative thin layer chromatography (using 95% CH_2Cl_2, 5% MeOH as eluant) to provide **1056**. LCMS (ESI) *m/z* 411.

Example 25 - Synthesis of Imidazole 1084

Scheme 18 depicts the synthesis of imidazole **1084**.

Scheme 18



Synthesis of iodide 120

To a suspension of alcohol **117** (5 g, 14.84 mmol) in CH_2Cl_2 (80 mL) was added triethyl amine (2.5 mL, 17.8 mmol) and methanesulphonyl acid chloride (1.4 mL, 17.8 mmol) at 0 °C and stirred the clear solution for 1 h at the same temperature. The reaction mixture was poured into brine solution (100 mL) and extracted with CH_2Cl_2 (2 x 50 mL). The combined

organic layer was washed with brine solution (3 x 100 mL), dried over anhydrous Na_2SO_4, and concentrated to yield mesylate **118**. To this was added NaN_3 (2 g, 29.7 mmol) and DMF (50 mL) and the mixture was heated to 80 °C overnight. The solution was poured into a mixture of ethyl acetate (150 mL) and water (100 mL). The organic layer was separated and the aqueous portion was extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with brine (1 x 150 mL), dried over anhydrous Na_2SO_4, and concentrated to yield 5.4 g of azide **119**.

A solution of aizde **119** (5.4 g, 14.84 mmol) and trimethylsilyl acetylene (10.48 mL, 74.2 mmol) in DMF (20 mL) was heated to 90 °C for 12 h. The reaction mixture was concentrated and treated with TBAF (60 mL, 1M in THF) and acetic acid (2 mL, 29.7 mmol) and stirred at ambient temperature for 12 h. The solution was concentrated and poured into a mixture of saturated NH_4Cl (50 mL), ethyl acetate (150 mL) and brine solution (50 mL). The organic layer was separated and the aqueous portion was extracted with ethyl acetate (3 x 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated and the solid thus obtained was washed with water (5 x 200 mL) to yield 5.7 g of tetrazole derivative **120**. LCMS (ESI) m/e 389 ($M+H^+$).

Synthesis of alcohol 122

To a mixture of tetrazole **120** (5.7 g, 14.84 mmol), boronic acid **121** (2.9 g, 19.29 mmol), K_2CO_3 (6.0 g, 44.52 mmol) and $Pd(PPh_3)_4$ (857 mg, 5 mol %) was added toluene (120 mL), ethyl alcohol (40 mL) and water (40 mL). The reaction mixteure was degassed, flushed with argon, and refluxed for 4 h. The solvent was concentrated under reduced pressure and the residue thus obtained was poured into water (2000 mL). The pale yellow solid was filtered, and dried at 40 °C under vacuum to yield 4.76 g of alcohol **122**. LCMS (ESI) m/e 369 ($M+H^+$).

Synthesis of chloride 123

To a solution of alcohol **122** (4.6 g, 12.5 mmol) and Hunig's base (6.4 mL, 38.75 mmol) in DMF (40 mL) and CH_2Cl_2 (30 mL) was added methanesulphonyl chloride (2.9 mL, 37.5 mmol) at 0 °C, and the resulting solution was stirred at ambient temperature for 3 h. The solution was concentrated to remove the CH_2Cl_2 and poured into water (1000 mL). The pale yellow solid was filtered and successively washed with water (5 x 200 mL), 10% ethyl acetate in hexanes (5 x 100 mL) and 50% ether in hexanes (5 x 100 mL). The resulting solid was dried at 40 °C under vacuum to yield 4.5 g of chloride **123**. LCMS (ESI) m/e 387 ($M+H^+$).

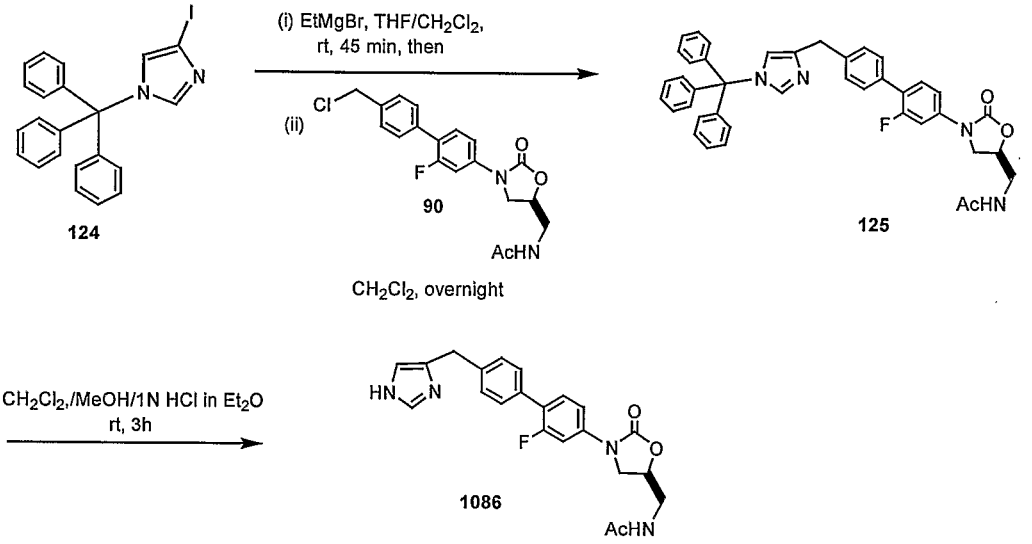
Synthesis of 1084

To a solution of imidazole (31 mg, 0.224 mmol) in DMF (3 mL) was added NaH (17 mg, 0.448 mmol) at 0 °C, and the solution was stirred for 20 min at 0 °C. Chloride **123** was added and the reaction was stirred at ambient temperature for 90 min. The reaction mixture was concentrated and purified by flash chromatography over silica gel (96:4 CH_2Cl_2/MeOH) to yield 65 mg of **1084**. LCMS (ESI) m/e 419 ($M+H^+$).

Example 26 - Synthesis of Imidazole 1086

Scheme 19 depicts the synthesis of imidazole **1086**.

Scheme 19



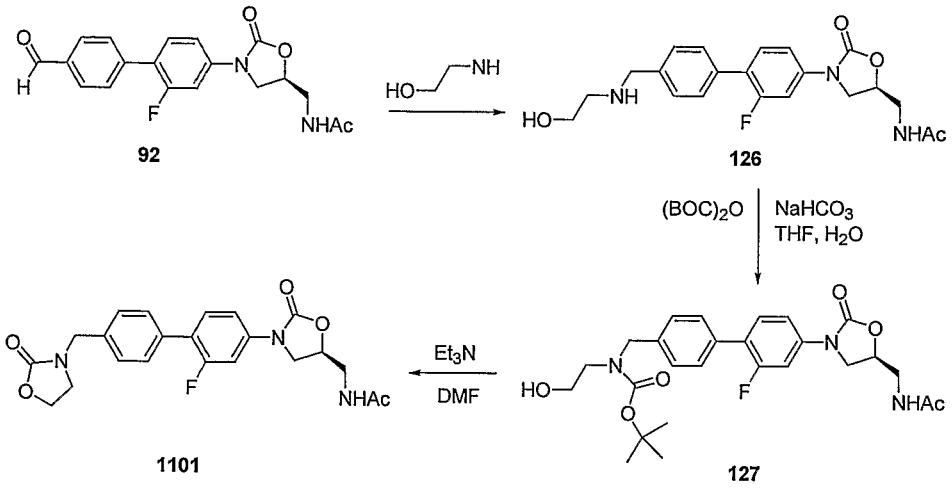
To a solution of imidazole **124** (0.25g, 0.56 mmol) in dry CH_2Cl_2 (3 mL) was added 1M ethyl magnesium bromide (EtMgBr) in THF (0.62 mL, 0.62 mmol) at room temperature. After stirring for 45 min, oxazolidinone **90** (0.233g, 0.62 mmol) was added to the mixture and stirring continued overnight. The reaction was quenched with aqueous NH_4Cl (20 mL), extracted with CH_2Cl_2 (25 mL) and dried over Na_2SO_4. The solvent was evaporated to yield **125** as a solid residue. The crude was dissolved in 10 % MeOH in CH_2Cl_2 (10 mL), and 1N HCl in diethyl ether (2 mL, 2 mmol) was added, followed by stirring for 3h. The solvent was evaporated and the residue was partitioned between dilute NH_4OH (30 mL) and CH_2Cl_2 (30 mL). The layers were separated, the aqueous layer was back extracted with CH_2Cl_2 (2 X 30 mL), and the combined organic layer was dried over Na_2SO_4. The solvent was evaporated and the crude product was purified on silica gel column, eluting with 1- 8 % MeOH in CH_2Cl_2 to

yield imidazole **1086** as a thick oil which precipitated to white solid in diethyl ether (0.051g, 22 %). LCMS (ESI) m/e 409.0 $(M + H)^+$.

Example 27 - Synthesis of Compound 1101

Scheme 20 depicts the synthesis of compound **1101**.

Scheme 20



Synthesis of alcohol 126

To a stirred solution of 0.050 g (0.14 mmol) of aldehyde **92** and 0.010 g (0.17 mmol) of aminoethanol in 5 ml of DMF was added 0.059 g (0.28 mmol) of $NaB(OAc)_3H$. The reaction mixture was stirred for 2 h. DMF was removed *in vacuo*, and the residue was purified by preparative TLC to give 0.055 g of alcohol **126**. MS (M+1): 438.

Synthesis of alcohol 127

A solution of 0.050 g (0.11 mmol) of **126**, 0.030 g (0.14 mmol) of $(BOC)_2O$, 0.038 g (0.46 mmol) of $NaHCO_3$ in 10 ml of THF:H_2O (4:1) was stirred at 25 °C for 6 h. The reaction mixture was diluted with water (30 ml) and extracted with CH_2Cl_2 (50 ml x 3). The combined organic layers were washed with brine (40 ml), dried over $MgSO_4$, and concentrated to give 0.040 g of alcohol **127**. MS (M+1): 501.

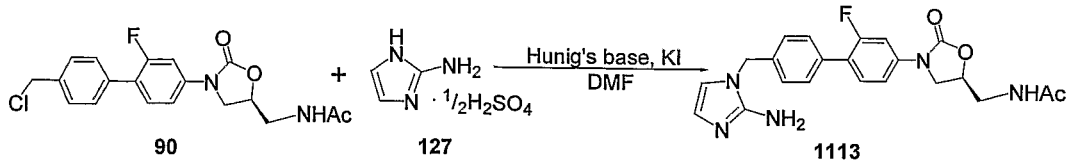
Synthesis of compound 1101

A solution of 0.126 g (0.25 mmol) of alcohol **127** and 0.11 ml (0.75 mmol) of Et_3N in 5ml of DMF was heated to 60 °C for 24 h. The reaction mixture was cooled and the solvent was removed *in vacuo*. The residue was purified via preparative TLC to yield 0.033 g of compound **1101**. MS (M+1): 428.

Example 28 - Synthesis of Imidazole 1113

Scheme 21 depicts the synthesis of imidazole **1113**.

Scheme 21



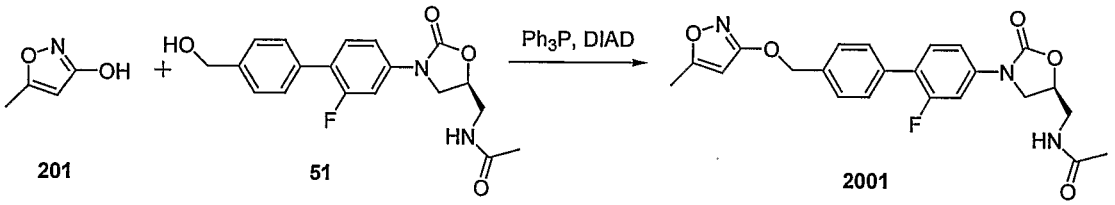
90 127 1113

A mixture of chloride **90** (113 mg, 0.3 mmol), 2-aminoimidazole sulfate **127** (119 mg, 0.9 mmol), N,N-diisopropylethylamine (0.26 mL, 1.5 mmol) and KI (17 mg, 0.1 mmol) in DMF (5 mL) was stirred at room temperature for 12 h. The reaction was concentrated *in vacuo*, and the crude product was purified by preparative thin layer chromatography (10:1:0.1 CH_2Cl_2: MeOH:$NH_3 \cdot H_2O$) to afford 90 mg of **1113** in a yield of 71%. MS (ESI): 424.0 (100%, $(M+H)^+$).

Example 29 – Synthesis of Isoxazole 2001

Scheme 22 depicts the reaction leading to isoxazole **2001**. Hydroxyisoxazole **201** was coupled to alcohol **51** using the Mitsunobu reaction to yield isoxazole **2001**.

Scheme 22



201 51 2001

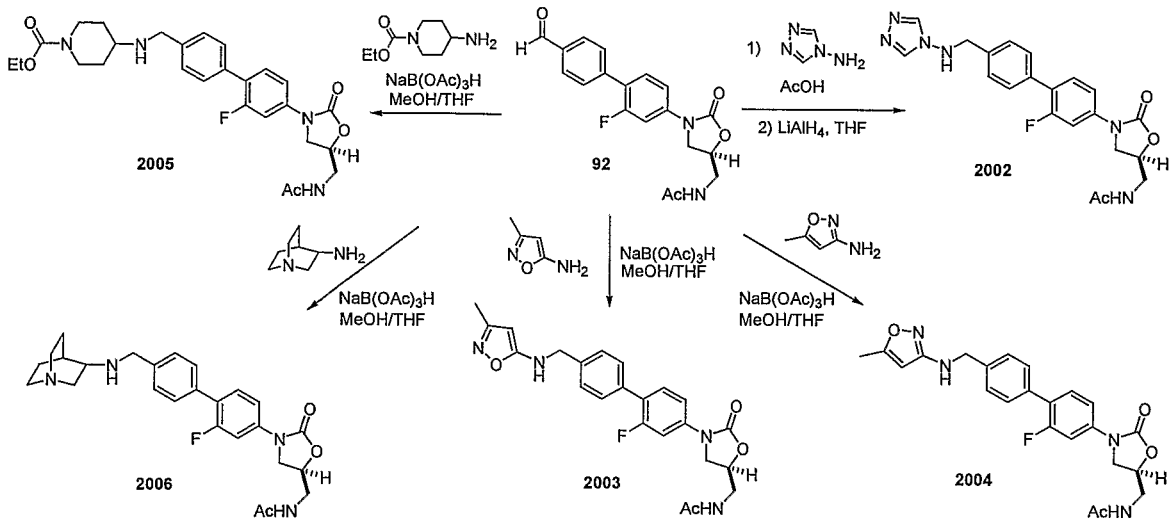
Synthesis of isoxazole 2001

The known isoxazole **201** was synthesized from methyl tetrolate as reported in literature (Iwai, I. *et al. Chem. Pharm. Bull.* **1966**, *14*, 1277-1286). To a suspension of isoxazole **201** (33 mg, 0.279 mmol), alcohol **51** (100 mg, 0.335 mmol) and triphenyl phosphine (95 mg, 0.363 mmol) was added diisopropyl azodicarboxylate (DIAD, 0.072 mL, 0.363 mmol) at -20°C. The reaction mixture was warmed to ambient temperature and stirred for 3 h. The solution was concentrated and purified by flash chromatography (4% MeOH in 1:1 CH_2Cl_2/EtOAc) to yield 64 mg of **2001**. LCMS (ESI) *m/z* 440 $(M + H)^+$.

Example 30 – Synthesis of Compounds 2002-2006

Scheme 23 illustrates the reductive amination chemistry leading to compounds **2002-2006**. Aldehyde **92** is treated with various amines in the presence of a reducing agent to yield the desired targets.

Scheme 23



Synthesis of triazole 2002

A suspension of the aldehyde **92** (178 mg, 0.5 mmol) in THF (4.0 mL) was treated with [1,2,4]triazol-4-ylamine (84 mg, 1.0 mmol) and acetic acid (0.02 mL) at room temperature, and the resulting reaction mixture was stirred at room temperature for 1 h before lithium aluminumhydride (38 mg, 1.0 mmol) was added at room temperature. The resulting reaction mixture was stirred at room temperature for an additional 1 h. When TLC and LCMS showed the reaction was complete, the reaction mixture was concentrated *in vacuo*, and the residue was directly purified by column chromatography (0–5% MeOH/CH_2Cl_2 gradient elution) to afford the desired triazole **2002** (40 mg; 19%) as a yellow solid. LCMS (ESI) *m/z* 425 $(M + H)^+$.

Synthesis of isoxazole 2003

A suspension of aldehyde **92** (107 mg, 0.3 mmol) in MeOH (4.0 mL) and THF (1.0 mL) was treated with 3-methyl-isoxazol-5-ylamine (59 mg, 0.6 mmol) and sodium triacetoxyborohydride (127 mg, 0.6 mmol) at 25°C, and the resulting reaction mixture was stirred at 25°C for 6 h. When TLC and LCMS showed the reductive amination reaction was complete, the reaction mixture was concentrated *in vacuo*. The residue was directly purified by flash column chromatography (0–5% MeOH-CH_2Cl_2 gradient elution) to afford the desired

isoxazole **2003** (12 mg; 9% yield) as a colorless oil, which solidified upon standing at room temperature *in vacuo*. LCMS (ESI) *m/z* 439 $(M + H)^+$.

Synthesis of isoxazole 2004

A solution of aldehyde **92** (107 mg, 0.3 mmol) in MeOH (3.0 mL) and THF (3.0 mL) was treated with 5-methyl-isoxazol-3-ylamine (59 mg, 0.6 mmol) and sodium triacetoxyborohydride (127 mg, 0.6 mmol) at 25°C, and the resulting reaction mixture was stirred at 25°C for 6 h. When TLC and LCMS showed the reductive amination reaction was complete, the reaction mixture was concentrated *in vacuo*. The residue was directly purified by flash column chromatography (0–5% MeOH-CH_2Cl_2 gradient elution) to afford isoxazole **2004** (41 mg; 31%) as a colorless oil, which solidified upon standing at room temperature *in vacuo*. LCMS (ESI) *m/z* 439 $(M + H)^+$.

Synthesis of carbamate 2005

A suspension of aldehyde **92** (142 mg, 0.4 mmol) in MeOH (4.0 mL) and THF (1.0 mL) was treated with 4-amino-piperidine-1-carboxylic acid ethyl ester (69 mg, 0.4 mmol) and sodium triacetoxyborohydride (160 mg, 0.8 mmol) at 25°C, and the resulting reaction mixture was stirred at 25°C for 6 h. When TLC and LCMS showed the reductive amination reaction was complete, the reaction mixture was concentrated *in vacuo*. The residue was directly purified by flash column chromatography (0–5% MeOH-CH_2Cl_2 gradient elution) to afford carbamate **2005** (98 mg; 48% yield) as a colorless oil, which solidified upon standing at room temperature *in vacuo*. LCMS (ESI) *m/z* 513 $(M + H)^+$.

Synthesis of bicyclic diamine 2006

A suspension of aldehyde **92** (142 mg, 0.4 mmol) in MeOH (4.0 mL) and THF (1.0 mL) was treated with 1-aza-bicyclo[2.2.2]oct-3-ylamine (80 mg, 0.4 mmol) and sodium triacetoxyborohydride (160 mg, 0.8 mmol) at 25°C, and the resulting reaction mixture was stirred at 25°C for 6 h. When TLC and LCMS showed the reductive amination reaction was complete, the reaction mixture was concentrated *in vacuo*. The residue was directly purified by flash column chromatography (0–5% MeOH-CH_2Cl_2 gradient elution) to afford diamine **2006** (71 mg; 38% yield) as a colorless oil, which solidified upon standing at room temperature *in vacuo*. LCMS (ESI) *m/z* 467 $(M + H)^+$.

Example 31 – Synthesis of Compounds 2007 and 2008

Synthesis of amide 2007

To a solution of anthranilamide (74 mg, 0.532 mmol) and mesylate **52** (100 mg, 0.229 mmol) in DMF (2.0 mL) was added Hunig's base (185 μL, 1.06 mmol). The mixture was stirred at 80°C for 16 h, then the mixture was concentrated by vacuum. The residue was directly isolated by reverse-phase preparative HPLC, to give 112 mg of **2007** as a white powder in 88% yield. LCMS (ESI) *m/z* 477 $(M + H)^+$.

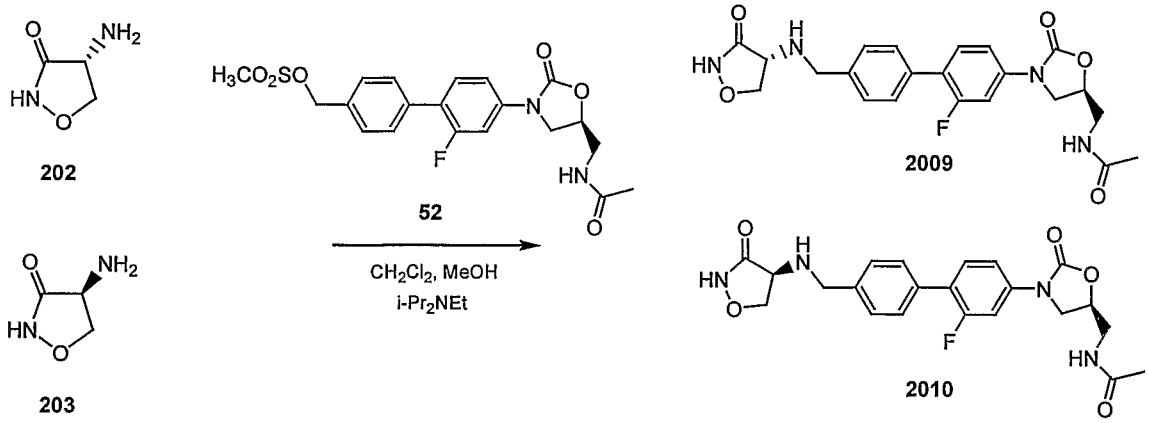
Synthesis of amide 2008

To a solution of 3-aminothiophene-2-carboxamide (67 mg, 0.459 mmol) and mesylate **52** (100 mg, 0.229 mmol) in DMF (2.0 mL) was added Hunig's base (160 μL, 0.916 mmol). The mixture was stirred at 80°C for 16 h, then the mixture was concentrated under vacuum. The residue was directly isolated by flash chromatography on silica gel (5:100 MeOH/CH_2Cl_2 as eluant), to afford 51 mg of **2008** as a white powder in 46% yield. LCMS (ESI) *m/z* 482 $(M + Na)^+$.

Example 32 – Synthesis of Compounds 2009 and 2010

Scheme 24 depicts the synthesis of **2009** and **2010** from D- and L-cycloserine respectively via alkylation with mesylate **52**.

Scheme 24



Synthesis of cycloserine derivative 2009

A mixture of D-cycloserine **202** (0.22 g, 2.04 mmol) and mesylate **52** (0.30 g, 0.68 mmol) in anhydrous CH_2Cl_2 (5 mL), MeOH (5 mL) and Hunig's base (2 mL) was heated to reflux for 3 h. The solvent was evaporated and the crude was purified on silica gel column,

eluting with CH_2Cl_2/MeOH 20:1 then with CH_2Cl_2/MeOH/NH_4OH 20:1:0.04 to 16:1:0.04 to give a white solid. The isolated solid was titurated with Et_2O/CH_3CN 1:1 (15 mL) and the suspension filtered to give analytically pure **2009** as a white solid (0.072 g, 24%). LCMS (ESI) *m/z* 443 $(M + H)^+$.

Synthesis of cycloserine derivative 2010

Compound **2010** was synthesized from L-cycloserine **203** and mesylate **52** as described above for the synthesis of **2009**. LCMS (ESI) *m/z* 443 $(M + H)^+$.

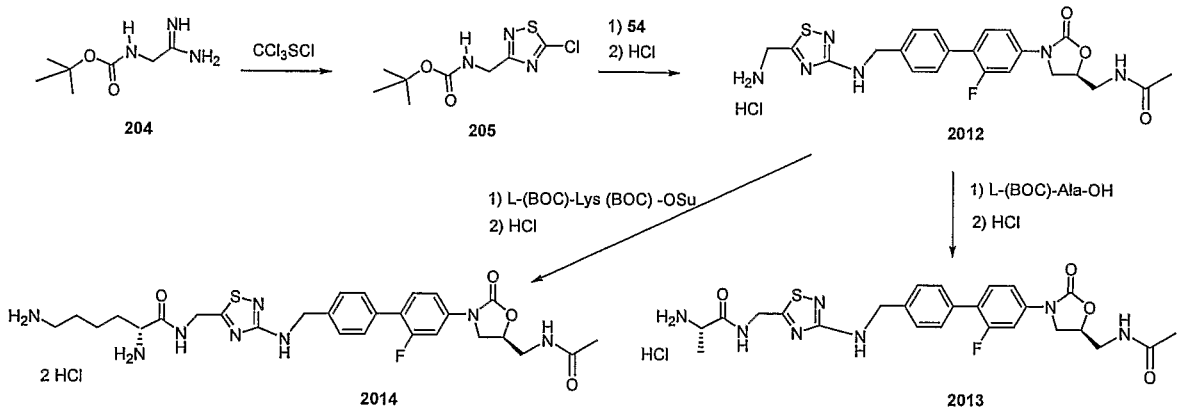
Example 33 – Synthesis of Azetidine 2011

A mixture of aldehyde **92** (100 mg, 0.28 mmol) and tert-butyl 3-amino-azetidine-1-carboxylate (58 mg, 0.34 mmol) in THF (2 mL) and DMF (0.5 mL) was stirred at room temperature for 1 h. Sodium triacetoxyborohydride (120 mg, 0.56 mmol) was added. After stirring at room temperature for 2 h, the reaction was concentrated, and the residue was dissolved in CH_2Cl_2, washed with water, and dried over $MgSO_4$. The CH_2Cl_2 solution was treated with trifluoroacetic acid (0.5 mL) at room temperature. After stirring for 1 h, the mixture was concentrated and purified by preparative thin layer chromatography (10:1:0.05 CH_2Cl_2/MeOH/$NH_3.H_2O$) to afford 45 mg of **2011** in a yield of 39%. LCMS (ESI) *m/z* 413.1 $(M + H)^+$.

Example 34 – Synthesis of Thiadiazoles 2012-2013

As Scheme 25 illustrates, thiadiazole **2012** was synthesized from chlorothiadiazole **205** by substitution with amine **54** followed by BOC deprotection. Acylation of **2012** with aminoacid fragments afforded thiadiazoles **2013** and **2014**.

Scheme 25



Synthesis of chlorothiadiazole 205

To a solution of BOC-aminoacetoamidine **204** (3.11 g, 18 mmol) in CH_2Cl_2 (60 mL) was added 3M NaOH (12.6 mL, 37.7 mmol) at -10°C. Under strong stirring, half of a solution of trichloromethanesulfenyl chloride (Cl_3CSCl, 1.96 mL, 18 mmol) in CH_2Cl_2 (30 mL) was slowly added. Then an additional 3M NaOH (12.6 mL, 37.7 mmol) was added, followed by the remaining Cl_3CSCl solution. The mixture was stirred at -10°C for 30 min and then at 0°C for 15 min before being diluted with ice-water (50 mL) and extracted with in CH_2Cl_2 (2 x 80 mL). The combined organic layer was washed with brine (1 x 20 mL), dried over Na_2SO_4 and the solvent was evaporated. The crude residue was purified on silica gel eluting with hexanes/ethyl acetate 6:1, yielding **205** as a yellow oil (2.9 g; 65%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.12 (s 1H), 4.42-4.40 (m, 2H), 1.29 (s, 9H).

Synthesis of thiadiazole 2012

To a solution of the amine **54** (1.0 g, 2.8 mmol) in MeOH (15 mL) and DMF (3 mL) was added chlorothiadiazole **205** (800 mg, 3.1 mmol) and Hunig's base (1 mL, 5.6 mmol). The mixture was stirred at 50°C overnight and then poured into 5% Na_2CO_3/ice (20 mL) and extracted with 9:1 CH_2Cl_2-isopropanol (2 x 100 mL). The combined organic layer was dried over Na_2SO_4 and the solvent evaporated. The crude residue was purified on silica gel eluting with 10:1 ethyl acetate/CH_2Cl followed by 95:5 ethyl acetate/MeOH, yielding white crystals, which were dissolved in 4M HCl in dioxane (20 mL). The mixture was stirred at room temperature for 2 h. The suspension was filtered and washed with ether (2 x 10 mL), and dried at high vacuum, yielding **2012** (830 mg; 93%). LCMS (ESI) *m/z* 471 $(M + H)^+$.

Synthesis of thiadiazole 2013

To a solution of thiadiazole **2012** (150 mg, 0.30 mmol) in CH_2Cl_2 (4 mL) and DMF (3 mL) was added Hunig's base (0.16 mL, 0.90 mmol), (L)-BOC-Ala-OH (67 mg, 0.36 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI, 79 mg, 0.42 mmol). The mixture was stirred overnight at room temperature, then additional amounts of (L)-BOC-Ala-OH (34 mg, 0.18 mmol), EDCI (40 mg, 0.21 mmol) and Hunig's base (0.08 mL, 0.44 mmol) were added. The mixture was stirred at room temperature overnight, poured into 1N HCl-ice (20 mL), and extracted with CH_2Cl_2-isopropanol 95:5 (2 x 50 mL). The combined organic layer was washed with water (15 mL), 5% sodium carbonate (Na_2CO_3, 15 mL), water (15 mL), brine (15 mL), and then dried over Na_2SO_4 and the solvent evaporated. The crude

residue was purified on silica gel eluting with ethyl acetate/ MeOH 95:5. The residue was dissolved in 4M HCl in dioxane (7 mL). The mixture was stirred at room temperature for 2 h and then evaporated. The residue was diluted with ether (3 mL), filtered, and the solid washed with ether (2 x 5 mL), then dried at high vacuum, yielding **2013** (122 mg; 91%). LCMS (ESI) *m/z* 542 $(M + H)^+$.

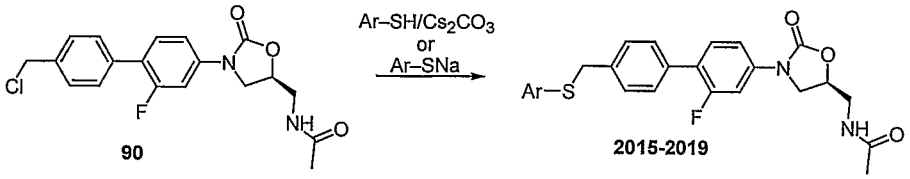
Synthesis of thiadiazole 2014

To a solution of of thiadiazole **2012** (150 mg, 0.30 mmol) in CH_2Cl_2 (3 mL) and DMF (3 mL) was added Hunig's base (0.08 mL, 0.45 mmol) and (L)-BOC-Lys (BOC)-OSu (157 mg, 0.36 mmol). The mixture was stirred overnight at room temperature, poured into 5% Na_2CO_3-ice (20 mL), extracted with CH_2Cl_2-isopropanol 95:5 (3 x 50 mL), dried over Na_2SO_4 and the solvent evaporated. The crude residue was purified on silica gel eluting with ethyl acetate followed by 5:1 ethyl acetate / MeOH. The BOC-protected material obtained was dissolved in 4M HCl in dioxane (6 mL) and MeOH (2 mL), stirred at room temperature for 3 h and then evaporated. The residue was diluted with ether (6 mL), filtered, washed with ether (2x 5 mL) and dried at high vacuum, yielding **2014** (100 mg; 50%). LCMS (ESI) *m/z* 599 $(M + H)^+$.

Example 35 – Synthesis of Compounds 2015-2019

As Scheme 26 illustrates, benzyl chloride **90** served as alkylating agent for thiolates or thiols to afford compounds **2015-2019**.

Scheme 26



Synthesis of tetrazole 2015

A solution of chloride **90** (0.15 g, 0.40 mmol) in DMF (2 mL) was treated with 5-mercapto-4-methyltetrazole, sodium salt, dihydrate (0.14 g, 0.80 mmol) and stirred at 23°C for 0.5 h. The reaction mixture was diluted with water and the precipitate was recovered by vacuum filtration to afford tetrazole **2015** as a white powder (63%). LCMS (ESI) *m/z* 456 $(M + H)^+$.

Synthesis of triazole 2016

Tetrazole **2016** was prepared with chloride **90** (0.30 g, 0.80 mmol) and 4-mercapto-1,2,3-triazole, sodium salt, (0.20 g, 1.6 mmol) according to the procedure above used to synthesize tetrazole **2015** to afford **2016** as a yellow powder (0.29 g, 0.66 mmol, 82%). LCMS (ESI) *m/z* 442 $(M + Na)^+$.

Synthesis of compound 2017

Compound **2017** was prepared with chloride **90** (0.20 g, 0.53 mmol) and 2-thiobarbituric acid, sodium salt, (0.18 g, 1.1 mmol) according to the procedure above used to synthesize tetrazole **2015** to afford **2017** as a white powder (0.078 g, 0.16 mmol; 30%). LCMS (ESI) *m/z* 507 $(M + Na)^+$.

Synthesis of mercaptopyridine 2018

A solution of chloride **90** (0.20 g, 0.53 mmol) in DMF (2.7 mL) was treated with cesium carbonate (0.21 g, 0.64 mmol) and 2-mercaptopyridine (0.071 g, 0.64 mmol) and was stirred at 23°C for 0.5 h. The reaction mixture was diluted with water and the precipitate was recovered by vacuum filtration to afford **2018** as a yellow powder (91%). LCMS (ESI) *m/z* 452 $(M + H)^+$.

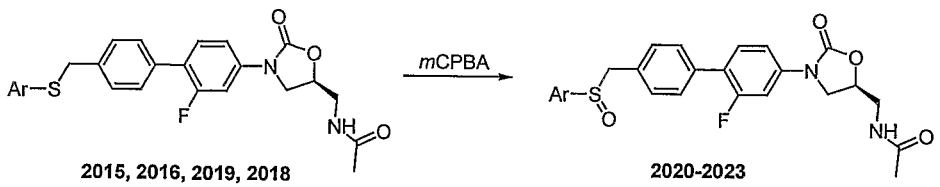
Synthesis of mercaptopyridine 2019

Mercaptopyridine **2019** was prepared with chloride **90** (0.20 g, 0.53 mmol), cesium carbonate (0.21 g, 0.64 mmol), and 4-mercaptopyridine (0.071 g, 0.64 mmol) according to the procedure above used to synthesize **2018** to afford a yellow powder (0.078 g, 0.16 mmol; 30%). LCMS (ESI) *m/z* 452 $(M + H)^+$.

Example 36 – Synthesis of Sulfoxides 2020-2023

As Scheme 27 illustrates, sulfides **2015**, **2016**, **2019**, and **2018** were oxidized under controlled conditions to afford sulfoxides **2020-2023** respectively.

Scheme 27



Synthesis of sulfoxide 2020

A solution of **2015** (0.020 g, 0.044 mmol) in chloroform (0.44 mL) and methanol (0.050 mL) was treated with 3-chloroperoxybenzoic acid (77%, 0.010 g, 0.044 mmol) and stirred at 23°C for 12 h. The reaction mixture was diluted with methylene chloride, washed with saturated aqueous sodium bicarbonate, dried over Na_2SO_4, and the solvent removed *in vacuo*. The crude product was purified with preparative TLC (1:4.5:4.5 MeOH/ethyl acetate/CH_2Cl_2) to afford **2020** as a white powder (3.6 mg, 0.008 mmol; 19%). LCMS (ESI) *m/z* 495 $(M + Na)^+$.

Synthesis of sulfoxide 2021

Sulfoxide **2021** was prepared from sulfide **2016** (0.030 g, 0.068 mmol) and 3-chloroperoxybenzoic acid (77%, 0.015 g, 0.068 mmol) according to the procedure described above for the synthesis of sulfoxide **2020** to afford a white powder (0.021 g, 0.046 mmol; 68%). LCMS (ESI) *m/z* 480 $(M + Na)^+$.

Synthesis of sulfoxide 2022

Sulfoxide **2022** was prepared from sulfide **2019** (0.080 g, 0.18 mmol) and 3-chloroperoxybenzoic acid (77%, 0.040 g, 0.18 mmol) according to the procedure described above for the synthesis of sulfoxide **2020** to afford a white powder (0.021 g, 0.094 mmol; 52%). LCMS (ESI) *m/z* 468 $(M + H)^+$.

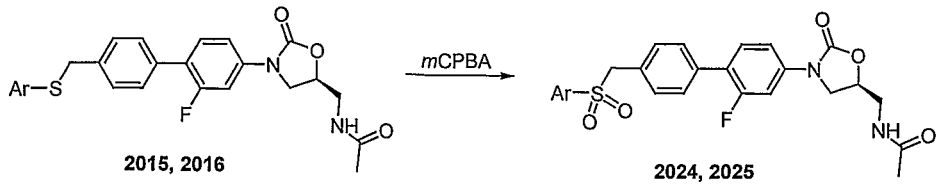
Synthesis of sulfoxide 2023

Sulfoxide **2023** was prepared from sulfide **2018** (0.10 g, 0.22 mmol) and 3-chloroperoxybenzoic acid (77%, 0.050 g, 0.22 mmol) according to the procedure described above for the synthesis of sulfoxide **2020** to afford a white powder (0.068 g, 0.15 mmol; 66%). LCMS (ESI) *m/z* 466.

Example 37 – Synthesis of Sulfones 2024 and 2025

As Scheme 28 illustrates, sulfides **2015** and **2016** were oxidized with excess 3-chloroperoxybenzoic acid to afford sulfones **2024** and **2025**.

Scheme 28



2015, 2016 2024, 2025

Synthesis of sulfone 2024

A solution of sulfide **2015** (0.020 g, 0.044 mmol) in chloroform (0.44 mL) and methanol (0.050 mL) was treated with 3-chloroperoxybenzoic acid (77%, 0.030 g, 0.13 mmol) and stirred at 23°C for 1 h and then heated to 50°C for 12 h. The reaction mixture was cooled to 23°C, diluted with methylene chloride, washed with saturated aqueous sodium bicarbonate, dried (Na_2SO_4), and the solvent removed *in vacuo*. The crude product was purified by preparative TLC (5% MeOH in CH_2Cl_2) to afford sulfone **2024** as a white powder (3.6 mg; 17%). LCMS (ESI) *m/z* 489 $(M + H)^+$.

Synthesis of sulfone 2025

A solution of sulfide **2016** (0.050 g, 0.11 mmol) in chloroform (1.1 mL) and methanol (0.1 mL) was treated with 3-chloroperoxybenzoic acid (77%, 0.076 g, 0.34 mmol) and stirred at 23°C for 2 h. The precipitate was recovered through vacuum filtration to yield sulfone **2025** as a white solid (0.020 g; 37%). LCMS (ESI) *m/z* 474 $(M + H)^+$.

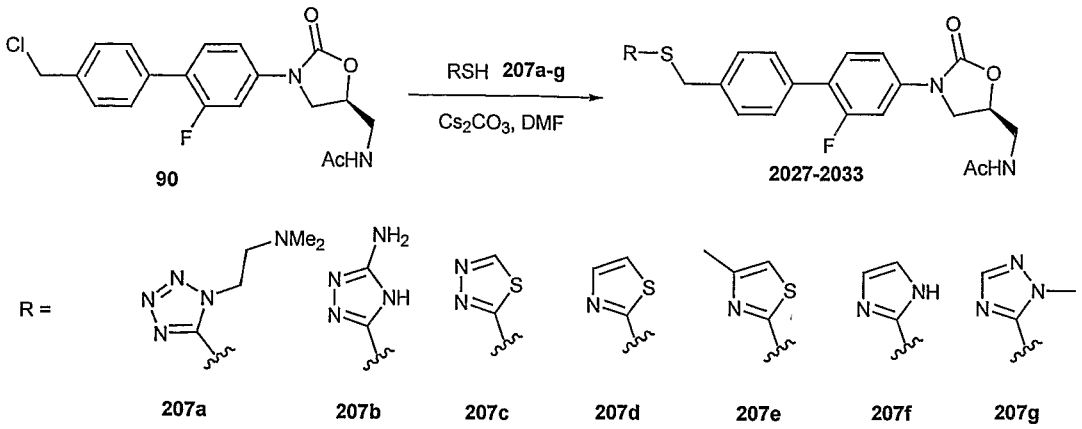
Example 38 – Synthesis of Mercaptotriazole 2026

A solution of mesylate **64** (0.012 g, 0.027 mmol) in DMF (0.14 mL) was treated with 4-mercapto-1,2,3-triazole, sodium salt (7 mg, 0.054 mmol) and was stirred at 45°C for 2 h. The solvent was removed *in vacuo* and the crude product was purified by preparative TLC (5% MeOH in CH_2Cl_2) to afford mercaptotriazole **2026** as a white solid (3.1 mg; 24%). LCMS (ESI) *m/z* 456 $(M + H)^+$.

Example 39 – Synthesis of Compounds 2027-2033

As Scheme 29 illustrates, benzyl chloride **90** was used to alkylate thiols **207a-g** to provide compounds **2027-2033** respectively.

Scheme 29



Synthesis of tetrazole 2027

Benzyl chloride **90** (0.20 g, 0.53 mmol) was dissolved in DMF (5 mL). Thiol **207a** (62 mg, 0.53 mmol) and cesium carbonate (0.20 g, 0.64 mmol) were added sequentially and the resulting slurry stirred at room temperature for 4 h. The mixture was poured into 70 mL H_2O and stirred for 1 h. The solids were filtered, rinsed with ether and dried under vacuum to afford tetrazole **2027** as a brown solid (187 mg, 0.36 mmol). LCMS (ESI) *m/z* 514 $(M + H)^+$.

Synthesis of triazole 2028

Triazole **2028** was synthesized by the process described for **2027** above using thiol **207b** in place of **207a** to yield 138 mg of triazole **2028** as a yellow solid (0.30 mmol). LCMS (ESI) *m/z* 457 $(M + H)^+$.

Synthesis of thiadiazole 2029

Thiadiazole **2029** was synthesized by the process described for **2027** above using thiol **207c** in place of **207a** to yield 147 mg of thiadiazole **2029** as a white solid (0.32 mmol). LCMS (ESI) *m/z* 481 $(M + Na)^+$, 522 $(M + Na + CH_3CN)^+$.

Synthesis of thiazole 2030

Thiazole **2030** was synthesized by the process described for **2027** above using thiol **207d** in place of **207a** to yield 129 mg of thiazole **2030** as a white solid (0.28 mmol). LCMS (ESI) *m/z* 458 $(M + H)^+$, 521 $(M + Na + CH_3CN)^+$.

Synthesis of thiazole 2031

Thiazole **2031** was synthesized by the process described for **2027** above using thiol **207e** in place of **207a** to yield 155 mg of thiazole **2031** as an off-white solid (0.33 mmol). LCMS (ESI) *m/z* 472 $(M + H)^+$.

Synthesis of imidazole 2032

Imidazole **2032** was synthesized by the process described for **2027** above using thiol **207f** in place of **207a** to yield 91 mg of imidazole **2032** as a white solid (0.21 mmol). LCMS (ESI) *m/z* 441 $(M + H)^+$.

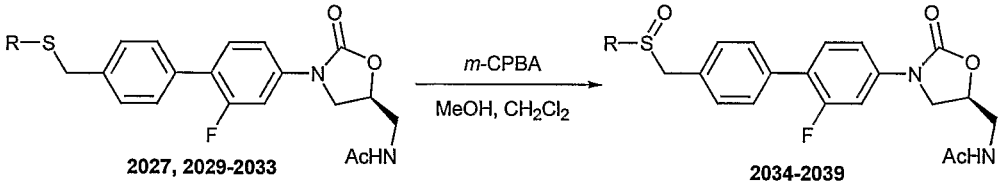
Synthesis of triazole 2033

Triazole **2033** was synthesized by the process described for **2027** above using thiol **207g** in place of **207a** to yield 91 mg of triazole **2033** as a white solid (0.21 mmol). LCMS (ESI) *m/z* 456 $(M + H)^+$, 478 $(M + Na)^+$, 519 $(M + Na + CH_3CN)^+$.

Example 40 – Synthesis of Compounds 2034-2039

As Scheme 30 illustrates, compounds **2027** and **2029-2033** were oxidized to afford sulfoxides **2034-2039** respectively.

Scheme 30



Synthesis of sulfoxide 2034

Tetrazole **2027** (80 mg, 0.16 mmol) was dissolved in 3:1 CH_2Cl_2/MeOH (3 mL). *m*-CPBA was added (75% pure; 39 mg, 0.17 mmol) and the mixture was stirred at room temperature for 6 h. The reaction mixture was poured into 50 mL ether and stirred for 1 h. The solids were filtered and dried *in vacuo* to give sulfoxide **2034** as an off-white solid (55 mg, 0.10 mmol). LCMS (ESI) *m/z* 530 $(M + H)^+$.

Synthesis of sulfoxide 2035

Sulfoxide **2035** was synthesized by the process described above for **2034** starting with thiadiazole **2029** in place of tetrazole **2027** to yield 39 mg of **2035** as a white solid (0.08 mmol). LCMS (ESI) *m/z* 497 $(M + Na)^+$, 538 $(M + Na + CH_3CN)^+$.

Synthesis of sulfoxide 2036

Sulfoxide **2036** was synthesized by the process described above for **2034** starting with thiazole **2030** in place of tetrazole **2027** to yield 48 mg of **2036** as an off-white solid (0.10 mmol). LCMS (ESI) *m/z* 496 $(M + Na)^+$, 537 $(M + Na + CH_3CN)^+$.

Synthesis of sulfoxide 2037

Sulfoxide **2037** was synthesized by the process described above for **2034** starting with thiazole **2031** in place of tetrazole **2027** to yield 44 mg of **2037** as an off-white solid (0.09 mmol). LCMS (ESI) *m/z* 488 $(M + H)^+$, 510 $(M + Na)^+$, 551 $(M + Na + CH_3CN)^+$.

Synthesis of sulfoxide 2038

Sulfoxide **2038** was synthesized by the process described above for **2034** starting with imidazole **2032** in place of tetrazole **2027** to yield 51 mg of **2038** as a white solid (0.11 mmol). LCMS (ESI) *m/z* 457 $(M + H)^+$.

Synthesis of sulfoxide 2039

Sulfoxide **2039** was synthesized by the process described above for **2034** starting with triazole **2033** in place of tetrazole **2027** to yield 48 mg of **2039** as a white solid (0.10 mmol). LCMS (ESI) *m/z* 472 $(M + H)^+$ 494 $(M + Na)^+$, 535 $(M + Na + CH_3CN)^+$.

Example 41 – Synthesis of Compound 2040

A solution of mesylate **106** (43.7 mg, 1.0 mmol) in anhydrous DMF (4.0 mL) was treated with 1*H*-5-mercapto-1,2,3-triazole sodium salt (24.6 mg, 2.0 mmol) at room temperature, and the resulting reaction mixture was stirred at room temperature overnight. When TLC and LCMS showed that the reaction was complete, the reaction mixture was concentrated *in vacuo*, and the residue was directly purified by flash column chromatography (0–5% MeOH-CH_2Cl_2 gradient elution) to afford mercaptotriazole **2040** (29.0 mg; 66%) as a pale-yellow solid. LCMS (ESI) *m/z* 443 $(M + H)^+$.

Example 42 – Synthesis of Compounds 2043 and 2044

Synthesis of compound 2043

A solution of amine **54** (0.070 g, 0.20 mmol) in DMF (1.0 mL) was treated with triethylamine (0.055 mL, 0.40 mmol) and 1-methyl-1H-imidazole-4-sulfonyl chloride (0.039 mg, 0.22 mmol) and stirred at 23 °C for 30 minutes. The solvent was removed *in vacuo*, and

the crude product was purified by flash chromatography (4.5:4.5:1 methylene chloride/ethyl acetate/methanol) to afford compound **2043** (0.054 g, 0.11 mmol, 55%). MS (ESI): 502 $(M+H)^+$.

Synthesis of Compound 2044

A solution of amine **54** (0.070 g, 0.20 mmol) in DMF (1.0 mL) was treated with triethylamine (0.055 mL, 0.40 mmol) and 6-morpholin-4-yl-pyridine-3-sulfonyl chloride (0.057 g, 0.22 mmol) and stirred at 23 °C for 30 minutes. The solvent was removed *in vacuo*, and the crude product was purified by flash chromatography (0-10% methanol in 1:1 ethyl acetate/ methylene chloride) to afford compound **2044** (0.052 g, 0.09 mmol, 45%). MS (ESI): 584 $(M+H)^+$.

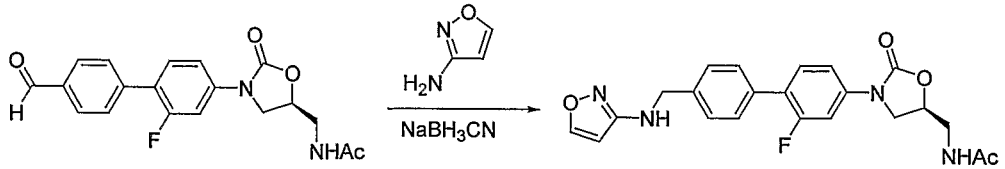
Example 43 – Synthesis of Compound 2047

A solution of chloride **90** (0.19 g, 0.50 mmol) in DMF (5 mL) was treated with 3-mercapto-1,2,4-triazole (0.20 g, 1.0 mmol) and Cs_2CO_3 (0.33 g, 1.0 mmol), and stirred at 23 °C for 1 h. The reaction mixture was diluted with H_2O (45 mL), and the resulting precipitate filtered, washed with H_2O and dried under vacuum to afford compound **2047** (0.139 g, 0.315 mmol, 63%) as a white powder. MS (ESI): 442 $(M+H)^+$.

Example 44 – Synthesis of Compound 2050

Scheme 31 depicts the synthesis of compound **2050**.

Scheme 31

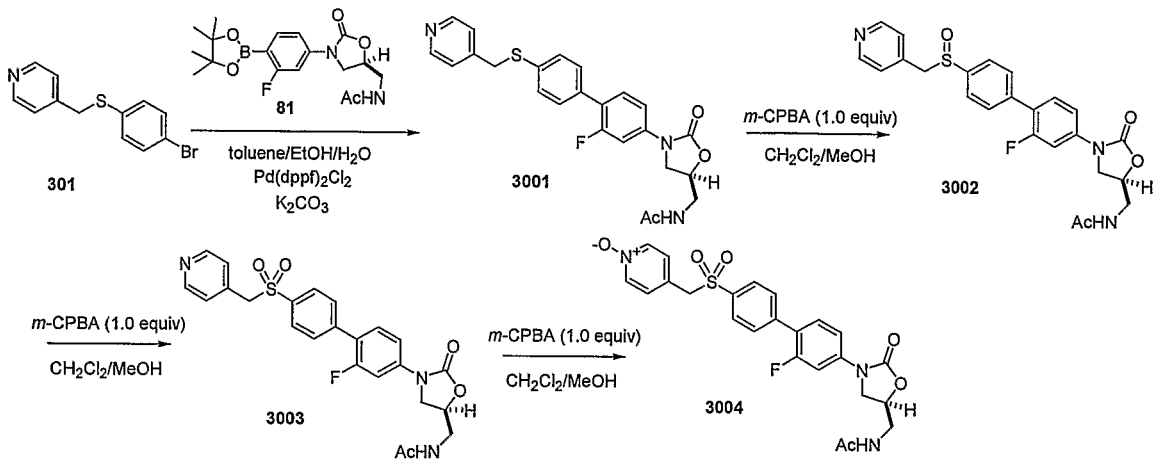


To a solution of 0.050 g (0.15 mmol) of aldehyde **92** and 0.026 g (0.30 mmol) of aminoisoxazole in 2 ml of TFA at 25 °C was added 0.018 g (0.30 mmol) of sodium cyanoborohydride ($NaBH_3CN$). The reaction mixture was stirred at 25 °C for 4 h. The TFA was removed, and the residue was purified by preparative TLC to give 0.040 g of compound **2050**. MS (M+1): 425.

Example 45 – Synthesis of Compounds 3001-3004

As Scheme 32 illustrates, bromide **301** was coupled to boronate **81** to yield pyridyl derivative **3001**. Successive oxidations provided sulfoxide **3002**, sulfone **3003**, and the pyridyl *N*-oxide **3004**.

Scheme 32



Synthesis of bromide 301

A suspension of 4-bromomethylpyridine hydrochloride (1.59 g, 6.3 mmol) in THF (10 mL) was treated dropwise with a solution of potassium carbonate (3.33 g, 24.0 mmol) in H_2O (6 mL) at 0–5°C, and the resulting mixture was stirred at 0–5°C for 10 min before being treated dropwise with a solution of 4-bromo-benzenethiol (1.14 g, 6.0 mmol) in THF (5.0 mL) at 0–5°C under N_2. The resulting reaction mixture was subsequently stirred at 0–5°C for an additional 20 min. When TLC and LCMS showed that the reaction was complete, the reaction mixture was treated with water (15 mL) and ethyl acetate (25 mL). The two layers were separated, and the aqueous layer was extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were washed with water (2 x 15 mL) and saturated aqueous NaCl solution (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography (5–25% EtOAc-hexane gradient elution) to afford the desired 4-(4-bromo-phenylsulfanylmethyl) pyridine **301** (1.374 g; 82%) as a pale-yellow solid, which was directly used in subsequent reactions.

Synthesis of compound 3001

A solution of boronate **81** (200 mg, 0.53 mmol) and bromide **301** (150 mg, 0.53 mmol) in toluene (9 mL) was treated with solid potassium carbonate (220 mg, 1.6 mmol), ethanol (3.0

mL) and H_2O (3.0 mL) at room temperature, and the resulting reaction mixture was degassed three times under a steady stream of argon before being treated with $Pd(dppf)_2Cl_2$ (16 mg, 0.013 mmol) at room temperature. The reaction mixture was then degassed three times again under a steady stream of argon before being warmed up to reflux for 2 h. When LCMS showed that the reaction was complete, the reaction mixture was cooled down to room temperature before being treated with water (10 mL) and ethyl acetate (20 mL). The two layers were separated, and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic extracts were washed with water (2 x 10 mL) and saturated aqueous NaCl solution (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was then purified by flash column chromatography (0-5% MeOH-CH_2Cl_2 gradient elution) to afford compound **3001** (177 mg; 74%) as a yellow oil, which solidified upon standing at room temperature *in vacuo*. LCMS (ESI) *m/z* 452 $(M + H)^+$.

Synthesis of sulfoxide 3002

A solution of compound **3001** (58 mg, 0.13 mmol) in CH_2Cl_2 (2.0 mL) and MeOH (0.5 mL) was treated with *m*-CPBA (22 mg, 0.13 mmol) at room temperature, and the resulting reaction mixture was stirred at room temperature for 2 h. The solvents were removed, and the residue was directly purified by flash column chromatography (0–5% MeOH-CH_2Cl_2 gradient elution) to afford sulfoxide **3002** (43 mg; 71%) as a colorless oil, which solidified upon standing at room temperature *in vacuo*. LCMS (ESI) *m/z* 468 $(M + H)^+$.

Synthesis of sulfone 3003

A solution of sulfoxide 2002 (22 mg, 0.047 mmol) in CH_2Cl_2 (2.0 mL) and MeOH (0.5 mL) was treated with *m*-CPBA (9.0 mg, 0.047 mmol) at room temperature, and the resulting reaction mixture was stirred at room temperature for 2 h. The solvents were removed, and the residue was directly purified by flash column chromatography (0–5% MeOH-CH_2Cl_2 gradient elution) to afford sulfone **3003** (16 mg; 71%) as a colorless oil, which solidified upon standing at room temperature *in vacuo*. LCMS (ESI) *m/z* 484 $(M + H)^+$.

Synthesis of pyridyl *N*-oxide 3004

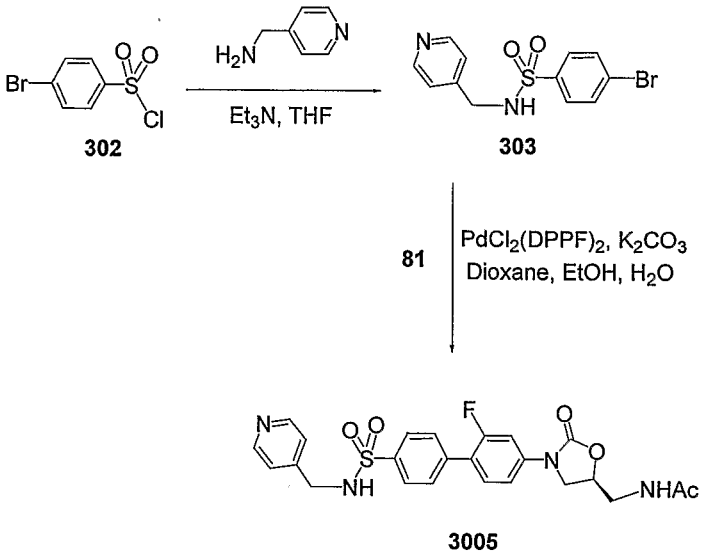
A solution of sulfone **3003** (16 mg, 0.033 mmol) in CH_2Cl_2 (1.0 mL) and MeOH (0.5 mL) was treated with *m*-CPBA (6.0 mg, 0.033 mmol) at room temperature, and the resulting reaction mixture was stirred at room temperature for 2 h. The solvents were removed, and the residue was directly purified by flash column chromatography (0–5% MeOH-CH_2Cl_2 gradient

elution) to afford the pyridyl *N*-oxide **3004** (11 mg; 67% yield) as colorless oil, which solidified upon standing at room temperature *in vacuo*. LCMS (ESI) *m/z* 500 $(M + H)^+$.

Example 46 – Synthesis of Compound 3005

Scheme 33 illustrates the synthesis of compound **3005**.

Scheme 33



Synthesis of bromide 303

4-bromobenzenesulfonyl chloride **302** (2.56 g, 10 mmol) was added to a solution of 4-aminomethylpyridine (1.08 g, 10 mmol) and triethylamine (2 mL, 14.3 mmol) in THF (20 mL) at 0 °C. After stirring at same temperature for 1 h, 50 mL of cool water was added. A white solid was collected by filtration, washing with EtOAc and dried in vaccum to give 3.10 g of bromide **303** in a yield of 95%.

Synthesis of compound 3005

Bromide **303** (327 mg, 1 mmol), boronate **81** (378 mg, 1 mmol), $Pd(dppf)_2Cl_2$ (40 mg, 0.05 mmol) and K_2CO_3 (414 mg, 3 mmol) were dissolved 8 mL of a mixture of dioxane:EtOH: H_2O (3:1:1) under argon atmosphere. After heating at 100°C for 12 hours, the reaction was added to 20 mL of cool water. The organic solvent was removed *in vacuo* and the crude product was collected by filtration. The crude product was treated with active charcoal and recrystallized in a mixed solvent system (1:2:2 MeOH:CH_2Cl_2:acetone) to give 155 mg of **3005** in a yield of 31%. MS (ESI): 499.1 (100%, $(M+H)^+$).

Example 47 - Synthesis of Amide 4008

A solution of amine **54** (36 mg, 0.1 mmol) in DMF was treated with quinoline-4-carboxylic acid (26 mg, 0.15 mmol, 1.5 equiv) at 25 °C under N_2, and the resulting mixture was treated with EDCI (28.5 mg, 0.15 mmol, 1.5 equiv) at 25 °C under N_2. The reaction mixture was subsequently stirred at 25 °C for 12 h. When TLC and HPLC showed the coupling reaction was complete, the reaction mixture was concentrated *in vacuo*. The residue was then directly purified by flash column chromatography (0–7% MeOH-CH_2Cl_2 gradient elution) to afford the desired amide **4008** (36.4 mg, 71% yield) as an off-white powder. LCMS (ESI) *m/e* 513 (M^+ + H).

Example 48 – General Synthesis of Carboxylic Acid-Loaded Tfp Resins and Synthesis of Amide 4011

A suspension of polymeric 4-hydroxy-2,3,5,6-tetrafluorophenol (TFP, *J. Comb. Chem.* **2000**, *2*, 691) amide resin (1.00 g, 1.27 mmol) in DMF (10 mL) was shaken for 10 minutes in a 70 mL polypropylene cartridge and then treated with indole-6-carboxylic acid (1.02 g, 6.35 mmol), 3-hydroxybenzotriazole (18 mg, 0.13 mmol), and diisopropylcarbodiimide (1.2 mL, 7.6 mmol). The reaction mixture was shaken for 18 h at 23 °C, and then the resin was washed with DMF (10 x 50 mL), THF (10 x 50 mL), and methylene chloride (10 x 50 mL) and dried *in vacuo*.

A suspension of the above TFP ester (35 mg) in 1 mL of DMF was treated with amine **54** (10 mg, 0.027 mmol) and shaken for 18 h in a 10 mL polypropylene cartridge. The filtrate was collected and dried to give amide **4011** (11 mg, 0.022 mmol, 81%) as a yellow solid. ^{1}HNMR (300 MHz, 10:1 $CDCl_3$: CD_3OD): δ 7.89 (s, 1H), 7.75-7.71 (m, 1H), 7.55-7.52 (m, 1H), 7.46-7.30 (m, 6H), 7.16 (dd, J = 8, 2 Hz, 1H), 6.45-6.44 (m, 1H), 4.70-4.68 (m, 1H), 4.60-4.59 (m, 2H), 4.03-3.97 (m, 1H), 3.73-3.71 (m, 4H), 3.58-3.42 (m, 2H), 3.27-3.25 (m, 1H), 1.90 (s, 3H). LCMS (ESI) *m/e* 501.0 $(M+H)^+$.

Example 49 – Synthesis of Amides 4010 and 4012-4105

Synthesis of Amide 4010

Amide **4010** was prepared from the TFP ester of *N*-methylpyrrole-2-carboxylic acid (477 mg, 3.81 mmol), which was prepared according to the general method of Example 48. The TFP ester was reacted with amine **54** using the acylation procedure of Example 48 to synthesize amide **4011**. The desired amide **4010** was obtained as a solid (10 mg, 0.022 mmol,

81%). ^{1}HNMR (300 MHz, 10:1 $CDCl_3$: CD_3OD): δ 7.71-7.56 (m, 6H), 7.33 (dd, J = 9, 2 Hz, 1H), 6.93-6.92 (m, 1H), 6.77 (dd, J = 4, 2 Hz, 1H), 6.55 (dd, J = 12, 6 Hz, 2H), 6.27 (dd, J = 4, 3 Hz, 1H), 4.77-4.69 (m, 1H), 4.54-4.52 (m, 2H), 4.02-3.96 (m, 1H), 3.90 (s, 3H), 3.73 (dd, J = 9, 7 Hz, 1H), 3.62-3.58 (m, 2H), 1.96 (s, 3H). LCMS (ESI) *m/e* 465.0 $(M+H)^+$.

Synthesis of Amide 4012

Amide **4012** was prepared from the TFP ester of 3-methylsulfonylbenzoic acid (1.27 g, 6.35 mmol), which was prepared according to the general method of Example 48. The TFP ester was reacted with amine **54** using the acylation procedure of Example 48 to synthesize amide **4011**. The desired amide **4012** was obtained as a solid (13 mg, 0.024 mmol, 89%). ^{1}HNMR (300 MHz, 10:1 $CDCl_3$: CD_3OD): δ 8.31-8.30 (m, 1H), 8.14-8.11 (m, 1H), 8.00-7.97 (m, 1H), 7.64-7.58 (m, 2H), 7.45-7.29 (m, 6H), 7.12 (dd, J = 9, 2 Hz, 1H), 4.73-4.71 (m, 1H), 4.59-4.58 (m, 2H), 4.05-3.99 (m, 1H), 3.73 (dd, J = 9, 7 Hz, 1H), 3.61-3.44 (m, 6H), 3.30-3.27 (m, 1H), 3.03 (s, 3H). LCMS (ESI) *m/e* 540.1 $(M+H)^+$.

Synthesis of Amide 4013

Amide **4013** was prepared from the TFP ester of 4-fluorobenzoic acid (890 mg, 6.35 mmol), which was prepared according to the general method of Example 48. The TFP ester was reacted with amine **54** using the acylation procedure of Example 48 to synthesize amide **4011**. The desired amide **4013** was obtained as a solid (12 mg, 0.025 mmol, 93%). LCMS (ESI) *m/e* 480.0 $(M+H)^+$.

Synthesis of Amide 4014

Amide **4014** was prepared from the TFP ester of piperonylic acid (1.05 g, 6.35 mmol), which was prepared according to the general method of Example 48. The TFP ester was reacted with amine **54** using the acylation procedure of Example 48 to synthesize amide **4011**. The desired amide **4014** was obtained as a solid (13 mg, 0.026 mmol, 96%). ^{1}HNMR (300 MHz, $CDCl_3$): δ 7.72-7.70 (m, 1H), 7.54-7.28 (m, 8H), 7.24-7.23 (m, 1H), 7.17 (dd, J = 9, 2 Hz, 1H), 5.93 (s, 2H), 4.65-4.79 (m, 1H), 4.54-4.52 (m, 2H), 4.05-3.99 (m, 1H), 3.72 (dd, J = 9, 7 Hz, 1H), 3.55-3.48 (m, 2H), 3.28-3.26 (m, 2H), 1.92 (s, 3H). LCMS (ESI) *m/e* 506.0 $(M+H)^+$.

Synthesis of Amide 4015

Amide **4015** was prepared from the TFP ester of 5-methoxyindole-2-carboxylic acid (486 mg, 2.54 mmol), which was prepared according to the general method of Example 48.

The TFP ester was reacted with amine **54** using the acylation procedure of Example 48 to synthesize amide **4011**. The desired amide **4015** was obtained as a solid (10 mg, 0.019 mmol, 70%). ^{1}HNMR (300 MHz, 10:1 $CDCl_3$: CD_3OD): δ 7.87-7.79 (m, 1H), 7.48-7.14 (m, 7H), 6.94 (s, 1H), 6.89-6.81 (m, 2H), 4.67-4.61 (m, 1H), 4.54-4.52 (m, 2H), 4.02-3.93 (m, 2H), 3.71-3.61 (s, 3H), 1.89 (s, 3H). LCMS (ESI) *m/e* 531.1 $(M+H)^+$.

Example 50 - Synthesis of Amine 4016

A solution of amine **54** (36 mg, 0.1 mmol) in a mixture of THF and DMF (3:1, v/v) was treated with quinoline-4-carboxaldehyde (16 mg, 0.1 mmol, 1.0 equiv) at 25 °C under argon, and the resulting reaction mixture was stirred at 25 °C for 30 min before being treated with sodium triacetoxyborohydride ($NaB(OAc)_3H$, 33 mg, 0.15 mmol, 1.5 equiv) at 25 °C. The reaction mixture was subsequently stirred at 25 °C for 6 h. When TLC and HPLC showed the reductive amination reaction was complete, the reaction mixture was concentrated *in vacuo*. The residue was then directly purified by flash column chromatography (0–7% MeOH-CH_2Cl_2 gradient elution) to produce the desired *N*-[3-(2-fluoro-4'-{[(quinolin-4-ylmethyl)-amino]-methyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide **4016** (32.9 mg, 66% yield) as pale-yellow oil, which solidified upon standing at room temperature *in vacuo*. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.85 (s, 3H, $COCH_3$), 3.44 (t, 2H, J = 5.4 Hz), 3.79 (dd, 1H, J = 6.4, 9.2 Hz), 3.88 (s, 2H), 4.17 (t, 1H, J = 9.1 Hz), 4.30 (s, 2H), 4.77 (m, 1H), 7.41 (dd, 1H, J = 2.0, 8.0 Hz), 7.51–7.63 (m, 8H, aromatic-*H*), 7.74 (t, 1H, J = 8.0 Hz), 8.04 (d, 1H, J = 8.0 Hz), 8.18 (d, 1H, J = 8.0 Hz), 8.27 (t, 1H, J = 5.8 Hz, $NHCOCH_3$), 8.87 (d, 1H, J = 8.0 Hz). LCMS (ESI) *m/e* 499 $(M + H)^+$.

Example 51 - Synthesis of Amines 4018-4026

Synthesis of Amine 4018

To a solution of 0.032 g (0.089 mmol) of amine **54** in 3 mL of MeOH/THF (2:1, with 1% acetic acid) were added 0.009 g (0.080 mmol) of 4-pyridylcarboxaldehyde and 0.027 g (0.12 mmol) of sodium triacetoxyborohydride at room temperature. The reaction mixture was allowed to stir at 25 °C until the aldehyde was consumed based on TLC analysis. The solvents of the reaction were removed via rotary evaporation and the residue was then purified on a preparative TLC plate to give 7.0 mg of **4018**. ^{1}H NMR (300 MHz, CD_3OD): δ 8.57 (s, 1 H), 8.48 (d, J = 4.2 Hz, 1 H), 7.91-7.33 (a series of multiplet peaks, 9 H), 2.05 (s, 3 H). LCMS (ESI) *m/e* 449 $(M+H)^+$.

Synthesis of Amine 4019

To a solution of 0.080 g (0.22 mmol) of amine **54** in 3 mL of MeOH/THF (2:1, with 1% acetic acid) were added 0.032 g (0.20 mmol) of 2-quinolinecarboxaldehyde and 0.094 g (0.44 mmol) of sodium triacetoxyborohydride at room temperature. The reaction mixture was allowed to stir at 25 °C until the aldehyde was consumed based on TLC analysis. The solvents of the reaction were removed via rotary evaporation, and the residue was then purified on a preparative TLC plate to give 44 mg of **4019**. ^{1}H NMR (300 MHz, CD_3OD + $CDCl_3$): δ 8.32 (d, J = 5.4 Hz, 1 H), 8.06 (d, J = 5.4 Hz, 1 H), 7.94 (d, J = 6 Hz, 1 H), 7.79-7.36 (a series of multiplet peaks, 10 H), 4.83 (m, 1 H), 3.97 (s, 1 H), 2.05 (s, 3 H). LCMS (ESI) *m/e* 499 $(M+H)^+$.

Synthesis of 4020

To a solution of 0.080 g (0.22 mmol) of amine **54** in 3 mL of MeOH/THF (2:1, with 1% acetic acid) was added 0.030 g (0.20 mmol) of 2-benzofurancarboxaldehyde and 0.094 g (0.44 mmol) of sodium triacetoxyborohydride at room temperature. The reaction mixture was allowed to stir at 25 °C until the aldehyde was consumed based on TLC analysis. The solvents of the reaction were removed via rotary evaporation, and the residue was then purified on a preparative TLC plate to give 49 mg of **4020**. ^{1}H NMR (300 MHz, CD_3OD + $CDCl_3$): δ 7.44-7.01 (a series of multiplet peaks, 11 H), 6.62 (s, 1 H), 3.92 (s, 2 H), 3.82 (s, 2 H), 3.75-3.60 (m, 1 H). LCMS (ESI) *m/e* 488 $(M+H)^+$.

Synthesis of Amine 4021

To a solution of 0.080 g (0.22 mmol) of amine **54** in 3 mL of MeOH/THF (2:1, with 1% acetic acid) were added 0.032 g (0.20 mmol) of 3-quinolinecarboxaldehyde and 0.094 g (0.44 mmol) of sodium triacetoxyborohydride at room temperature. The reaction mixture was allowed to stir at 25 °C until the aldehyde was consumed based on TLC analysis. The solvents of the reaction was removed via rotary evaporation, and the residue was then purified on a preparative TLC plate to give 49 mg of **4021**. ^{1}H NMR (300 MHz, CD_3OD + $CDCl_3$): δ 8.89 (s, 1 H), 8.33 (s, 1 H), 8.03 (d, J = 5.4 Hz, 1 H), 7.95 (d, J = 5.4 Hz, 1 H), 7.80 ~ 7.34 (a series of multiple peaks, 9 H), 1.98 (s, 3 H). LCMS (ESI) *m/e* 499 $(M+H)^+$.

Synthesis of Amine 4022

To a solution of 0.100 g (0.28 mmol) of amine **54** in 3 mL of MeOH/THF (2:1, with 1% acetic acid) were added 0.042 g (0.27 mmol) of 1-naphthaldehyde and 0.119 g (0.56 mmol) of

sodium triacetoxyborohydride at room temperature. The reaction mixture was allowed to stir at 25 °C until the aldehyde was consumed based on TLC analysis. The solvents of the reaction were removed via rotary evaporation, and the residue was then purified on a preparative TLC plate to give 49 mg of **4022**. ^{1}H NMR (300 MHz, CD_3OD + $CDCl_3$): δ 7.98 ~ 7.24 (a series of multiple peaks, 14 H), 2.00 (s, 3 H). LCMS (ESI) *m/e* 498 $(M+H)^+$.

Synthesis of Amine 4023

To a solution of 0.100 g (0.28 mmol) of amine **54** in 3 mL of MeOH/THF (2:1, with 1% acetic acid) were added 0.024 g (0.25 mmol) of 3-furaldehyde and 0.119 g (0.56 mmol) of sodium triacetoxyborohydride at room temperature. The reaction mixture was allowed to stir at 25 °C until the aldehyde was consumed based on TLC analysis. The solvents of the reaction were removed via rotary evaporation, and the residue was then purified on a preparative TLC plate to give 32 mg of 4023. ^{1}H NMR (300 MHz, CD_3OD + $CDCl_3$): δ 7.50 ~ 7.22 (a series of multiple peaks, 9 H), 6.39 (s, 1 H), 1.90 (s, 3 H). LCMS (ESI) *m/e* 438 $(M+H)^+$.

Synthesis of Amine 4024

To a solution of 0.100 g (0.28 mmol) of amine **54** in 3 mL of MeOH/THF (2:1, with 1% acetic acid) were added 0.027 g (0.25 mmol) of 2-pyridylcarboxaldehyde and 0.089 g (0.42 mmol) of sodium triacetoxyborohydride at room temperature. The reaction mixture was allowed to stir at 25 °C until the aldehyde was consumed based on TLC analysis. The solvents of the reaction was removed via rotary evaporation, and the residue was then purified on a preparative TLC plate to give 30.0 mg of **4024**. ^{1}H NMR (300 MHz, CD_3OD): δ 8.39 (s, 1 H), 8.30 (d, J = 2.1 Hz, 1 H), 7.70 ~ 7.21 (a series of multiplet peaks, 9 H), 1.86 (s, 3 H). LCMS (ESI) *m/e* 449 $(M+H)^+$.

Synthesis of Amine 4025

To a solution of 0.100 g (0.28 mmol) of amine **54** in 3 mL of MeOH/THF (2:1, with 1% acetic acid) were added 0.027 g (0.25 mmol) of 3-pyridylcarboxaldehyde and 0.089 g (0.42 mmol) of sodium triacetoxyborohydride at room temperature. The reaction mixture was allowed to stir at 25 °C until the aldehyde was consumed based on TLC analysis. The solvents of the reaction were removed via rotary evaporation, and the residue was then purified on a preparative TLC plate to give 30.0 mg of **4025**. ^{1}H NMR (300 MHz, CD_3OD): δ 8.57 (s, 1 H), 8.48 (d, J = 4.2 Hz, 1 H), 7.91 ~ 7.33 (a series of multiplet peaks, 9 H), 2.05 (s, 3 H). LCMS (ESI) *m/e* 449 $(M+H)^+$.

Synthesis of Amine 4026

To a solution of 0.100 g (0.28 mmol) of amine **54** in 3 mL of MeOH/THF (2:1, with 1% acetic acid) were added 0.024 g (0.25 mmol) of 2-furaldehyde and 0.089 g (0.42 mmol) of sodium triacetoxyborohydride at room temperature. The reaction mixture was allowed to stir at 25 °C until the aldehyde was consumed based on TLC analysis. The solvents of the reaction were removed via rotary evaporation, and the residue was then purified on a preparative TLC plate to give 26.6 mg of **4026**. ^{1}H NMR (300 MHz, CD_3OD): δ 7.52 ~ 7.26 (a series of multiplet peaks, 10 H), 1.87 (s, 3 H). LCMS (ESI) *m/e* 438 $(M+H)^+$.

Example 52 - Synthesis of Amine 4038

Method A

A solution of 8.00 g (115.9 mmol) of isoxazole and 31.30 g (139.1 mmol) of *N*-iodosuccinimide in 60 ml of trifluoroacetic acid was heated to 50°C for 6 h. The reaction mixture was cooled and evaporated at 0°C to remove the majority of trifluoroacetic acid. The residue was then dissolved in 200 ml of diethyl ether, washed sequentially with saturated $NaHCO_3$ (40 ml x 4), 10% sodium thiosulfate (40 ml x 2), and brine (40 ml), dried over $MgSO_4$, filtered and concentrated to give 16.50 g of the desired 4-iodoisoxazole product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.44 (s, 1 H), 8.29 (s, 1 H).

To a solution of 6.80 g (34.8 mmol) of 4-iodoisoxazole in 200 ml of THF at -100°C was added dropwise 22.9 ml (36.6 mmol) of *n*-BuLi (1.6 M in hexanes). The reaction mixture was allowed to stir for 30 min. Ethyl formate (3.08 ml, 38.4 mmol) was added to the mixture, and the mixture was stirred further for 30 min at -100 °C. Hydrochloric acid (36.60 ml of 1 *N* HCl in ether) was added at -100 °C, and the reaction mixture was allowed to warm gradually to 25°C. The mixture was diluted with ether (200 ml), washed sequentially with saturated $NaHCO_3$ (100 ml) and brine (100 ml), dried over $MgSO_4$, filtered and concentrated (at 0°C) to give ~ 2.00 g of the desired isoxazole-4-carbaldehyde (based on estimation from ^{1}H NMR; contaminated with residual EtOH) of suitable purity for use in subsequent reactions. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.01 (s, 1 H), 9.05 (s, 1 H), 8.68 (s, 1 H).

A solution of 4.00 g (11.2 mmol) of amine **54**, 1.03 g (10.6 mmol) of isoxazole-4-carbaldehyde, and 4.750 g (22.4 mmol) of $NaB(OAc)_3H$ in 30 ml of DMF with 1.0 ml of acetic acid was stirred at 25°C for 4 h. The reaction solvents were removed by rotary evaporation. The residue was purified by silica gel column chromatography using 5% MeOH in CH_2Cl_2 as

eluent to give 1.57 g of amine **4038** plus 1.58 g of the imine intermediate. LCMS (ESI) *m/e* 439 $(M+H)^+$.

Method B

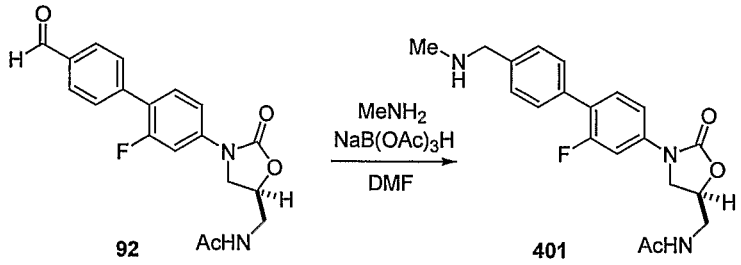
A solution of 1.00 g (5.05 mmol) of isoxazol-4-ylmethyl-carbamic acid tert-butyl ester in 10 ml of 4.0 N HCl in dioxane was stirred at 25°C for 6 h. The reaction mixture was then diluted with 30 ml of diethyl ether and filtered. The solid was washed with diethyl ether and dried to give 0.65 g of *C*-isoxazol-4-yl-methylamine hydrochloride salt of suitable purity for use in subsequent reactions. ^{1}H NMR (300 MHz, DMSO): δ 9.02 (s, 1 H), 8.68 (s, 1 H), 3.94 (q, J = 6, 1 H).

A solution of aldehyde **92** (0.150 g, 0.42 mmol), *C*-isoxazol-4-yl-methylamine hydrochloride salt (0.068 g, 0.51 mmol) obtained above, and $NaB(OAc)_3H$ (0.268 g, 1.26 mmol) in 5 ml of DMF was stirred at 25°C for 2 h. The reaction solvent was removed by rotary evaporation, and the residue was purified by preparative thin-layer chromatography to give 0.160 g of amine **4038**. LCMS (ESI) *m/e* 439 $(M+H)^+$.

Example 53 - Synthesis of Amine 4215

Scheme 34 depicts the synthesis of amine **401** used in the synthesis of compound **4215**.

Scheme 34



Synthesis of amine 401

A solution of aldehyde **92** (3.56 g, 10.0 mmol) in anhydrous DMF (20 mL) was treated with a 2 N solution of methylamine in THF (25 mL, 50.0 mmol) and sodium triacetoxyborohydride (3.20 g, 15.0 mmol) at room temperature, and the resulting reaction mixture was stirred at room temperature for 6 h. When TLC and LCMS showed that the reaction was complete, the reaction mixture was quenched with H_2O (40 mL), and the resulting mixture was stirred at room temperature for 30 min. The solid precipitate was then collected by filtration, washed with H_2O (2 x 50 mL), and dried *in vacuo*. This crude material was

subsequently purified by flash column chromatography (5–15 % MeOH-CH_2Cl_2 gradient elution) to afford amine **401** (2.26 g; 61%) as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.03 (s, 3H, $COCH_3$), 2.46 (s, 3H, NMe), 3.62 (t, 2H, J = 5.4 Hz), 3.86 (s, 2H, Ar-CH_2)), 3.96 (dd, 1H, J = 6.4, 9.2 Hz), 4.35 (t, 1H, J = 9.2 Hz), 4.90 – 4.99 (m, 1H), 7.58 – 7.80 (m, 7H, aromatic-*H*), 8.45 (t, 1H, J = 5.8 Hz, N*H*$COCH_3$); LCMS (ESI) *m/z* 372 $(M + H)^+$.

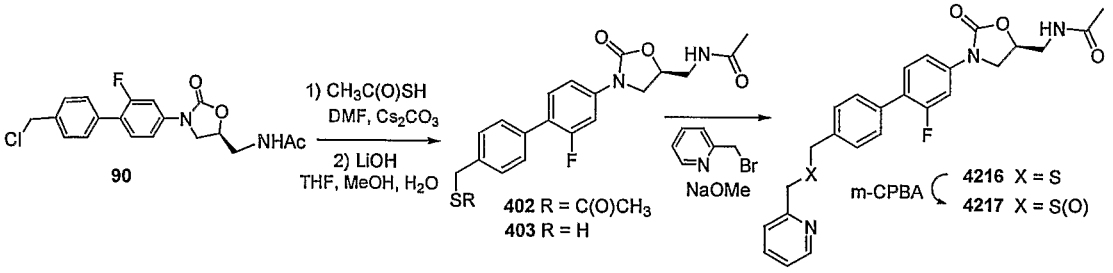
Synthesis of amine 4215

A solution of amine **401** (0.070 g, 0.19 mmol) in methanol (2 mL) and acetic acid (0.020 mL) was treated with quinoline-3-carboxaldehyde (0.033 g, 0.21 mmol) and sodium triacetoxyborohydride (0.080 g, 0.38 mmol) and stirred at 23°C for 2 h. Additional sodium triacetoxyborohydride (0.080 g, 0.38 mmol) and acetic acid (0.020 mL) were added, and the reaction mixture was stirred for 16 h. The solvent was removed *in vacuo*, and the residue was dissolved in THF (3 mL) and acetic acid (0.020 mL) and treated with quinoline-3-carboxaldehyde (0.015 g, 0.095 mmol) and sodium triacetoxyborohydride (0.080 g, 0.38 mmol) and stirred for 9 h. Additional sodium triacetoxyborohydride (0.080 g, 0.38 mmol) was added, and the reaction mixture was stirred for 60 h. The reaction mixture was diluted with methylene chloride (30 mL) and washed with saturated aqueous sodium bicarbonate (25 mL). Drying over Na_2SO_4 and evaporation of solvent yielded crude product, which was purified by flash chromatography (18:1:0.1 methylene chloride:methanol:ammonium hydroxide, 5-10% methanol in 1:1 methylene chloride:ethyl acetate) to afford amine **4215** as a solid (0.030 g, 0.059 mmol; 31%). LCMS (ESI) *m/z* 513 $(M + H)^+$.

Example 54 - Synthesis of Sulfide 4216 and Sulfoxide 4217

Scheme 35 depicts the synthesis of compounds **4216** and **4217**. Benzyl chloride **90** is displaced with thiolacetic acid to afford thioacetate **402**. Hydrolysis of **402** afforded thiol **403** which was alkylated with 2-bromomethyl pyridine to yield sulfide **4216**. Oxidation of **4216** then provided sulfoxide **4217**.

Scheme 35



Synthesis of chloride 90

Alcohol **51** (3.0 g, 8.4 mmol) was dissolved in CH_2Cl_2 (20 mL) and Hunig's base (2 mL). Methanesulfonyl chloride (1.4 mL, 12.6 mmol) was added dropwise and the resulting solution stirred at rt for 4 h. The mixture was poured into 100 mL sat. aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated to give 3.9 g of an oily yellow solid. The crude material was purified by silica gel chromatography to give chloride **90** as an off-white solid (2.7 g, 7.2 mmol). LCMS (ESI) *m/z* 377 $(M + H)^+$, 418 $(M + CH_3CN + H)^+$, 440 $(M + CH_3CN + Na)^+$.

Synthesis of thioester 402

Under an argon atmosphere, thiolacetic acid (1.55 mL, 21.7 mmol) was added to a mixture of chloride **90** (4.08 g, 10.8 mmol) and Cs_2CO_3 (3.52 g, 10.8 mmol) in DMF (25 mL). The reaction was stirred at room temperature for 2 hours. Then 50 mL of water was added. The off-white product **402** (4.3 g) was collected by filtration in a yield of 96%. LCMS (ESI) *m/z* 417 $(M + H)^+$.

Synthesis of thiol 403

LiOH (360 mg, 15 mmol) was added to a solution of **402** (4.3 g, 10.3 mmol) in a mixture of THF (50 mL), MeOH (50 mL) and water (20 mL). After stirring for 30 minutes at room temperature under argon atmosphere, the insoluble solid was removed by filtration. The filtrate was diluted with water (50 mL), concentrated to remove organic solvents, then neutralized with 10% HCl. The off-white product **403** (3.5 g) was collected by filtration in a yield of 91%. LCMS (ESI) *m/z* 375 $(M + H)^+$.

Synthesis of sulfide 4216

A solution of sulfide **403** (0.20 g, 0.54 mmol) in tetrahydrofuran (1.3 mL), methanol (1.3 mL), and dimethylformamide (1.3 mL) was treated with sodium methoxide (25% in methanol, 0.24 mL, 1.1 mmol) and 2-(bromomethyl)pyridine and stirred at 23°C for 0.5 h. The reaction mixture was diluted with methylene chloride (25 mL), washed with water (25 mL), and the water layer was extracted with methylene chloride (25 mL). The combined organic fractions were dried over Na_2SO_4, and evaporated *in vacuo* to yield crude product, which was purified by preparative thin-layer chromatography (5% methanol/methylene chloride) to afford **4216** as a white powder (0.12 g, 0.26 mmol; 48%). LCMS (ESI) *m/z* 466 $(M + H)^+$.

Synthesis of sulfoxide 4217

A solution of **4216** (0.11 g, 0.23 mmol) in methylene chloride (2.3 mL) was treated with 3-chloroperoxybenzoic acid (0.051 g, 0.23 mmol) and stirred at 23°C for 15 minutes. The solvent was evaporated *in vacuo* and the crude product was purified by flash chromatography (5% methanol/methylene chloride) to afford **4217** as a white powder (0.093 g, 0.19 mmol; 83 %). LCMS (ESI) *m/z* 482 $(M + H)^+$.

Example 55 – Synthesis of Compounds 4218-4220

Synthesis of amine 4218

A solution of amine **54** (0.600 g, 1.68 mmol), 1-methyl-indole-3-carboxaldehyde (0.254 g, 1.60 mmol), and $NaB(OAc)_3H$ (0.712 g, 3.36 mmol) in 30 ml of MeOH with a few drops of acetic acid was stirred at 25°C for 24 h. The reaction solvents were removed by rotary evaporation. The residue was purified by preparative TLC plate to give 0.070 g of amine **4218**. LCMS (ESI) *m/z* 501 $(M + H)^+$.

Synthesis of amine 4219

A solution of amine **54** (0.060 g (0.17 mmol), tetrahydrofuran-3-carboxaldehyde (0.016 g, 0.16 mmol), and $NaB(OAc)_3H$ (0.071 g, 0.34 mmol) in 5 ml of MeOH with a few drops of acetic acid was stirred at 25°C for 6 h. The reaction solvents were removed by rotary evaporation. The residue was purified by preparative TLC plate to give 0.057 g of amine **4219**. LCMS (ESI) *m/z* 442 $(M + H)^+$.

Synthesis of amine 4220

A solution of amine **54** (0.500 g, 1.40 mmol), 1,2,3-thiadiazole-4-carboxaldehyde (0.152 g, 1.33 mmol), and $NaB(OAc)_3H$ (0.594 g, 2.80 mmol) in 8 ml of DMF with a few drops of acetic acid was stirred at 25°C for 2 h. The reaction solvents were removed by rotary evaporation. The residue was purified by preparative TLC to give 0.484 g of amine **4220**. LCMS (ESI) *m/z* 492 $(M + H)^+$.

Example 56 – Synthesis of Compound 4221

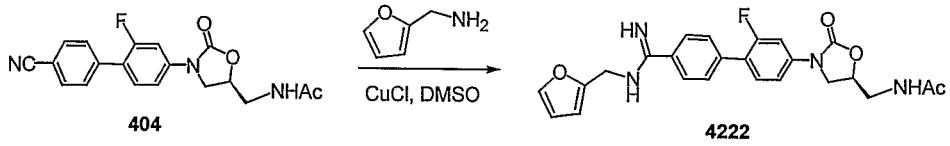
A solution of amine **54** (79.0 mg, 0.22 mmol) in anhydrous DMF (3 mL) was treated with 3-(2-oxo-1,2-dihydro-pyridin-3-yl)-acrylic acid (36.3 mg, 0.22 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (62.7 mg, 0.33 mmol) at room temperature, and the resulting reaction mixture was stirred at 25°C for 12 h. When TLC and

LCMS showed that the reaction was complete, the reaction mixture was concentrated *in vacuo*. The residue was directly purified by flash column chromatography (0–7% MeOH-CH_2Cl_2 gradient elution) to afford amide **4221** (45.5 mg; 41%) as a white solid. LCMS (ESI) *m/z* 505 $(M + H)^+$.

Example 57 – Synthesis of Amidine 4222

Scheme 36 illustrates the synthesis of amidine **4222**. Nitrile **404** and furfurylamine were heated together in the presence of copper chloride to yield amidine **4222**.

Scheme 36



Synthesis of nitrile 404

This compound was made from 4-cyanophenylboronic acid and iodide **50** as described above for the synthesis of alcohol **51**.

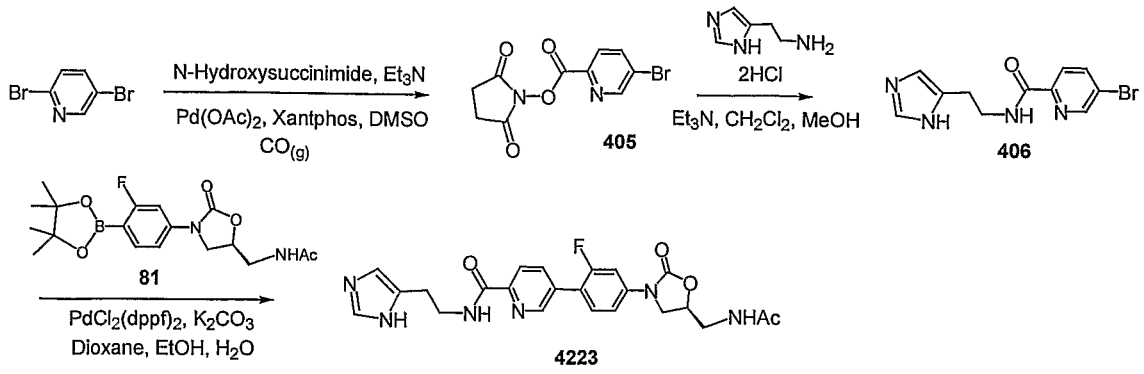
Synthesis of amidine 4222

Under an argon atmosphere, a mixture of nitrile **404** (98 mg, 0.28 mmol), furfurylamine (27 mg, 0.28 mmol) and copper (I) chloride (CuCl, 28 mg, 0.28 mmol) in DMSO (2 mL) was heated at 80°C for 48 h. The reaction was diluted with CH_2Cl_2, washed with saturated Na_2CO_3 and dried under vaccum. The crude product was purified by chromatography (5:1:0.05 CH_2Cl_2/ MeOH/$NH_3.H_2O$) to afford **4222** (14 mg; 11%). LCMS (ESI) *m/z* 451 $(M + H)^+$.

Example 58 – Synthesis of Amide 4223

Scheme 37 illustrates the synthesis of amide **4223**. 2,5-Dibromopyridine is converted to activated pyridyl ester **405** which is then treated with histamine to provide amide **406**. The Suzuki coupling of **406** and boronate **81** gave the final target amide **4223**.

Scheme 37



Synthesis of ester 405

Under an argon atmosphere, triethylamine (0.31 mL, 2.25 mmol) was added to a mixture of 2,5-dibromopyridine (355 mg, 1.5 mmol), palladium acetate (16.8 mg. 0.075 mmol), Xantphos (4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, 43.4 mg, 0.075 mmol) and *N*-hydroxysuccinimide (241.5 mg, 2.1 mmol) in DMSO (2 mL). The solution was purged with carbon monoxide for 15 min and stirred under a carbon monoxide balloon at 80°C for 16 h. The reaction mixture was then cooled to room temperature, diluted with 20 mL of ethyl acetate and washed with saturated sodium bicarbonate solution and water. The organic phase was dried over sodium sulfate and evaporated to give crude product. Chromatography on silica gel using hexane:acetone (3:1) provided ester **405** (75 mg; 17%). ^{1}HNMR (300 MHz, $CDCl_3$) δ 8.85 (m, 1H), 8.06 (m, 2H), 2.90 (s, 4H) .

Synthesis of amide 406

A mixture of active ester **405** (350 mg, 1.17 mmol), histamine dihydrochloride (216 mg, 1.17 mmol) and Et_3N (0.33 mL, 2.34 mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature for 1 h. The reaction was washed with brine and dried under vaccum. The crude product was purified by chromatography (15:1:0.05 CH_2Cl_2/MeOH/$NH_3.H_2O$) to afford **406** (280 mg; 81%). LCMS (ESI) *m/z* 295 $(M + H)^+$.

Synthesis of amide 4223

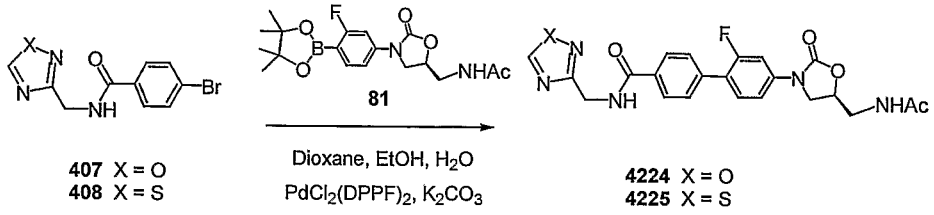
Under an argon atmosphere, a mixture of **406** (230 mg, 0.78 mmol), boronate **81** (295 mg, 0.78 mmol), $Pd(dppf)_2Cl_2$ (19 mg, 0.023 mmol) and K_2CO_3 (323 mg, 2.34 mmol) in 5 mL of a mixture of dioxane/EtOH/H_2O (3:1:1) was heated at 100°C for 12 h. The reaction was concentrated and the residue was dissolved in MeOH (2 mL) and CH_2Cl_2 (10 mL). Inorganic salts were removed by filtration. The filtrate was concentrated and purified by chromatography

(15:1:0.05 CH_2Cl_2/MeOH/$NH_3.H_2O$) to afford amide **4223** (106 mg; 29%). LCMS (ESI) *m/z* 467 $(M + H)^+$.

Example 59 – Synthesis of Amides 4224 and 4225

Scheme 38 illustrates the synthesis of amides **4224** and **4225**. Aryl bromides **407** and **408** were coupled to boronate **81** to afford **4224** and **4225** respectively.

Scheme 38



Synthesis of amide 4224

A mixture of 4-bromobenzoyl chloride (110 mg, 0.5 mmol), 1,2,4-oxadiazol-3-yl-methylamine hydrochloride (68 mg, 0.5 mmol), DMF (1 drop) and Et_3N (0.33 mL, 2.34 mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature for 4 h. The reaction was washed with brine and dried under vaccum to afford crude amide **407**. The amide **407** obtained was added to a mixture of boronate **81** (189 mg, 0.5 mmol), $Pd(dppf)_2Cl_2$ (20 mg, 0.025 mmol) and K_2CO_3 (207 mg, 1.5 mmol) in 5 mL of dioxane/EtOH/H_2O (3:1:1) under an argon atmosphere. After being heated at 100°C for 12 h, the reaction was diluted with water and MeOH, and then filtered through celite. The filtrate was concentrated to remove organic solvent. The crude product was collected by filtration and further purified by chromatography (25:1:0.05 CH_2Cl_2/MeOH/$NH_3.H_2O$) to afford **4224** (45 mg; 32%). LCMS (ESI) *m/z* 452 $(M - H)^+$.

Synthesis of amide 4225

A mixture of 4-bromobenzoyl chloride (29 mg, 0.132 mmol), 1,2,4-thiadiazol-3-yl-methylamine hydrochloride (20 mg, 0.132 mmol), DMF (1 drop) and Et_3N (27 mg, 0.264 mmol) in THF (4 mL) was stirred at room temperature for 2 h. The reaction was concentrated, dissolved in CH_2Cl_2, washed with brine and dried under vaccum to afford crude amide **408**. The resultant amide **408** obtained above was added to a mixture of boronate **81** (50 mg, 0.132 mmol), $Pd(dppf)_2Cl_2$ (6 mg, 0.0066 mmol) and K_2CO_3 (55 mg, 0.396 mmol) in 2 mL of dioxane/EtOH/ H_2O (3:1:1) under an argon atmosphere. After being heated at 100°C for 12 h, the reaction was concentrated, dissolved in EtOAc, washed with brine and dried under vaccum. The crude product was purified by chromatography on silica gel (25:1:0.05

CH_2Cl_2/MeOH/$NH_3.H_2O$) to afford amide **4225** (30 mg; 48%). LCMS (ESI) *m/z* 470 $(M + H)^+$.

Example 60 – Synthesis of Sulfide 4226

Under an argon atmosphere, sodium methoxide (NaOMe, 25% by wt. in MeOH, 95 mg, 0.44 mmol) was added to a solution of thiol **403** (75 mg, 0.2 mmol) and epibromohydrin (30 mg, 0.22 mmol) in MeOH (3 mL) and THF (3 mL). After stirring at room temperature for 2 h, the reaction was concentrated. The residue was dissolved CH_2Cl_2, washed with brine, dried over $MgSO_4$ and concentrated under vaccum. The crude product was purified by chromatography on silica gel (25:1:0.05 CH_2Cl_2/MeOH/$NH_3.H_2O$) to afford sulfide **4226** (55 mg; 61% as a mix of diastereomers). LCMS (ESI) *m/z* 453 $(M + Na)^+$.

Example 61 – Synthesis of Amines 4227-4229

Synthesis of amine 4227

A suspension of aldehyde **92** (107 mg, 0.3 mmol) in anhydrous THF (2 mL) and anhydrous methanol (MeOH, 2 mL) was treated with 2-(1*H*-imidazol-4-yl)-ethylamine (110.0 mg, 0.6) and sodium triacetoxyborohydride (127 mg, 0.6 mmol) at room temperature, and the resulting reaction mixture was stirred at room temperature for 6 h. When TLC and LCMS showed that the reaction was complete, the reaction mixture was concentrated *in vacuo*. This residue was directly purified by flash column chromatography (0–10% MeOH-CH_2Cl_2 gradient elution) to afford amine **4227** (24 mg, 135.3 mg; 18%) as an off-white solid. LCMS (ESI) *m/z* 452 $(M + H)^+$.

Synthesis of amine 4228

A suspension of aldehyde **92** (107 mg, 0.3 mmol) in anhydrous THF (2 mL) and anhydrous methanol (MeOH, 2 mL) was treated with 2-(5-methyl-1*H*-indol-3-yl)-ethylamine hydrochloride (126.0 mg, 0.6 mmol) and sodium triacetoxyborohydride (127 mg, 0.6 mmol) at room temperature, and the resulting reaction mixture was stirred at room temperature for 12 h. When TLC and LCMS showed that the reaction was complete, the reaction mixture was concentrated *in vacuo*. This residue was directly purified by flash column chromatography (0–10% MeOH-CH_2Cl_2 gradient elution) to afford amine **4228** (32 mg; 21%) as off-white solids. LCMS (ESI) *m/z* 515 $(M + H)^+$.

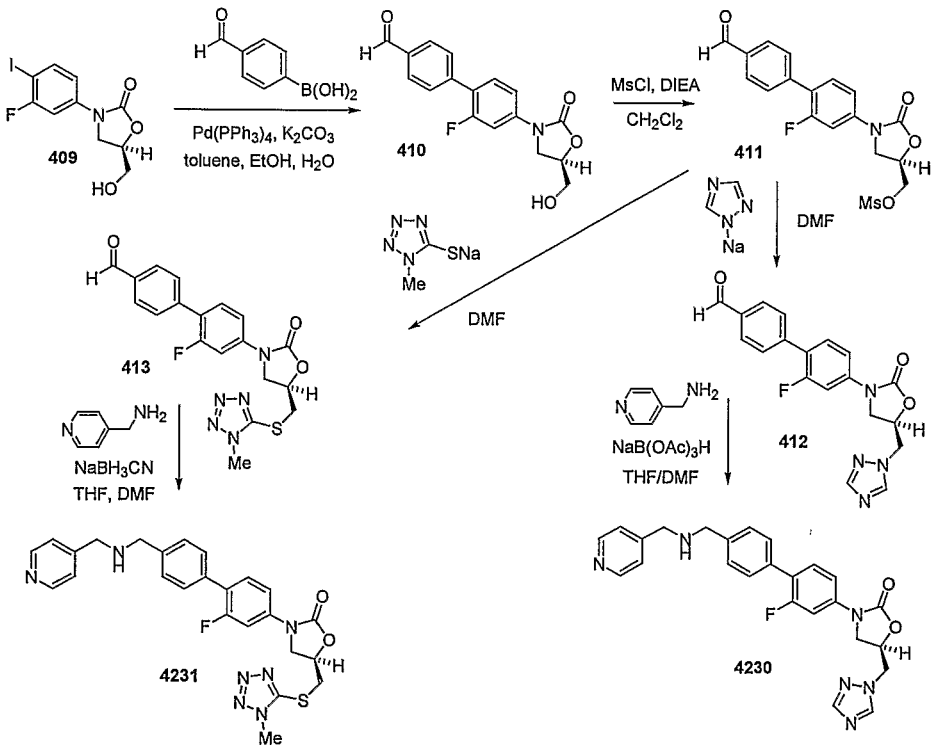
Synthesis of amine 4229

A suspension of aldehyde **92** (107 mg, 0.3 mmol) in anhydrous THF (2 mL) and anhydrous methanol (2 mL) was treated with (5-methyl-isoxazol-3-yl)-methylamine (67.0 mg, 0.6 mmol) and sodium triacetoxyborohydride (127 mg, 0.6 mmol) at room temperature, and the resulting reaction mixture was stirred at room temperature for 12 h. When TLC and LCMS showed that the reaction was complete, the reaction mixture was concentrated *in vacuo*. This residue was directly purified by flash column chromatography (0–5% MeOH-CH_2Cl_2 gradient elution) to afford amine **4229** (34 mg; 25%) as an off-white solid. LCMS (ESI) *m/z* 453 $(M + H)^+$.

Example 62 – Synthesis of Amines 4230 and 4231

Scheme 39 shows the synthesis of amines **4230** and **4231**. Known alcohol **409** (*see* U.S. Patent Nos. 5,523,403 and 5,565,571) is coupled to 4-formylphenylboronic acid to afford alcohol **410** which is then converted to mesylate **411**. Alkylation of mesylate **411** with the appropriate nucleophiles affords biaryl aldehydes **412** and **413** which are transformed to amines **4230** and **4231** respectively by reductive amination chemistry.

Scheme 39



Synthesis of alcohol 410

A suspension of alcohol **409** (5.07 g, 15.0 mmol) in toluene (30 mL) was treated with 4-formylphenylboronic acid (3.15 g, 21.0 mmol), K_2CO_3 (6.22 g, 45.0 mmol), EtOH (10 mL), and H_2O (10 mL) at 25°C, and the resulting mixture was degassed three times under a steady stream of argon at 25°C. $Pd(dppf)_2Cl_2$ (370 mg, 0.45 mmol) was subsequently added to the reaction mixture, and the resulting reaction mixture was degassed three times again before being warmed to gentle reflux for 2 h. When TLC and LCMS showed the coupling reaction was complete, the reaction mixture was cooled to room temperature before being treated with H_2O (100 mL). The resulting mixture was then stirred at room temperature for 10 min before being cooled to 0–5°C for 1 h. The solid precipitate was collected by filtration, washed with H_2O (2 x 40 mL) and 20% EtOAc/hexane (2 X 40 mL), and dried *in vacuo*. The crude alcohol **410** (4.62 g; 98%) was obtained as a brown solid, which by HPLC and ^1H NMR was found to be of suitable purity to be used in subsequent reactions. LCMS (ESI) *m/z* 316 $(M + H)^+$.

Synthesis of mesylate 411

A solution of the crude alcohol **410** (4.2 g, 13.3 mmol) in CH_2Cl_2 (50 mL) was treated with diisopropylethylamine (2.6 g, 3.5 mL, 20.0 mmol) at 25°C, and the resulting mixture was cooled to 0–5°C before being treated dropwise with methanesulfonyl chloride (1.83 g, 1.25 mL, 16.0 mmol) at 0–5°C. The resulting reaction mixture was subsequently stirred at 0–5°C for 2 h. When TLC and LCMS showed the reaction was complete, the reaction mixture was treated with H_2O (50 mL) at 0-5°C. The mixture was then concentrated *in vacuo* to remove most of the CH_2Cl_2, and the resulting slurry was treated with H_2O (50 mL). The mixture was stirred at room temperature for 10 min before being cooled to 0–5°C for 30 min. The solid precipitate was collected by filtration, washed with H_2O (2 x 40 mL) and 20% EtOAc/hexane (2 x 20 mL), and dried *in vacuo*. The crude mesylate **411** (4.60 g; 88%) was obtained as a brown solid, which by ^1H NMR and HPLC was found to be of suitable purity to be used in subsequent reactions. LCMS (ESI) *m/z* 394 $(M + H)^+$.

Synthesis of aldehyde 412

A solution of mesylate **411** (393 mg, 0.1 mmol) in anhydrous DMF (4 mL) was treated with 1*H*-1,2,4-triazole sodium salt (100 mg, 1.1 mmol) at room temperature, and the resulting reaction mixture was warmed to 40°C and stirred at 40°C for 4 h. When TLC and LCMS showed that the reaction was complete, the reaction mixture was concentrated *in vacuo*. This

residue was directly purified by flash column chromatography (0–5% MeOH-CH_2Cl_2 gradient elution) to afford aldehyde **412** (318.4 mg; 87%) as an off-white solid. LCMS (ESI) *m/z* 367 $(M + H)^+$.

Synthesis of amine 4230

A suspension of aldehyde **412** (90.0 mg, 0.25 mmol) in anhydrous THF (2 mL) and anhydrous DMF (2 mL) was treated with C-pyridin-4-yl-methylamine (29.0 mg, 0.27 mmol) and sodium triacetoxyborohydride (106.0 mg, 0.5 mmol) at room temperature, and the resulting reaction mixture was stirred at room temperature for 6 h. When TLC and LCMS showed that the reaction was complete, the reaction mixture was concentrated *in vacuo*. This residue was directly purified by flash column chromatography (0-5% MeOH-CH_2Cl_2 gradient elution) to afford amine **4230** (47.0 mg; 41%) as an off-white solid. LCMS (ESI) *m/z* 459 $(M + H)^+$.

Synthesis of aldehyde 413

A solution of 1-methyl-1*H*-tetrazole-5-thiol sodium salt (174.0 mg, 1.5 mmol) in anhydrous THF (5 mL) was treated with NaH (60% oil dispersion in mineral oil, 60.0 mg, 1.5 mmol) at 0–5°C, and the resulting reaction mixture was stirred at 0–5°C for 1 h. The mixture was then treated with mesylate **411** (393.0 mg, 1.0 mmol) and anhydrous DMF (5 mL) at 0–5°C, and the resulting reaction mixture was gradually warmed to room temperature before being warmed to 40°C for 4 h. When TLC and LCMS showed that the reaction was complete, the reaction mixture was concentrated *in vacuo*. This residue was directly purified by flash column chromatography (0–5% MeOH-CH_2Cl_2 gradient elution) to afford aldehyde **413** (272.6 mg; 66%) as an off-white solid. LCMS (ESI) *m/z* 414 $(M + H)^+$.

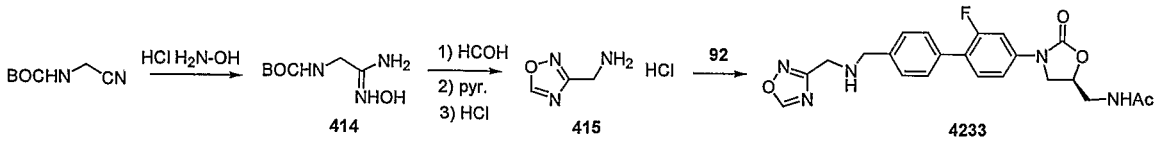
Synthesis of amine 4231

A suspension of aldehyde **413** (100.0 mg, 0.24 mmol) in anhydrous THF (2 mL) and anhydrous DMF (2 mL) was treated with C-pyridin-4-yl-methylamine (29.0 mg, 0.27 mmol) and sodiumborohydride (15.0 mg, 0.24 mmol) at room temperature, and the resulting reaction mixture was stirred at room temperature for 12 h. When TLC and LCMS showed that the reaction was complete, the reaction mixture was concentrated *in vacuo*. This residue was directly purified by flash column chromatography (0–5% MeOH-CH_2Cl_2 gradient elution) to afford amine **4231** (44.0 mg; 36%) as an off-white solid. LCMS (ESI) *m/z* 506 $(M + H)^+$.

Example 63 – Synthesis of Amine 4233

Scheme 40 shows the synthesis of isoxadiazole **4233**. BOC-Aminoacetonitrile was converted to hydroxyamidine **414** which was then cyclyzed to isoxadiazole **415**. Reductive amination of **415** with aldehyde **92** afforded amine **4233**.

Scheme 40



Synthesis of hydroxyamidine 414

To a solution of BOC-aminoacetonitrile (6.0 g, 38 mmol) in EtOH (60 mL) was added 50% aq. hydroxylamine (4.5 mL, 77 mmol) and the mixture was refluxed for 5 h. The solvents were evaporated and the residue redissolved in CH_2Cl_2 (100 mL), dried over Na_2SO_4 and again evaporated, yielding hydroxyamidine **414** (7 g; 96%). ^{1}H-NMR, (300 MHz, $CDCl_3$) δ 5.43-5.39 (m 1H), 5.12-5.03 (m, 3H), 3.75 (d, J = 5 Hz, 2H), 1.46 (s, 9H).

Synthesis of isoxadiazole 415

To a solution of **414** (2.8 g, 14.7 mmol) in CH_2Cl_2 (45 mL) was added Et_3N (4.1 mL, 29.5 mmol), formic acid (0.72 mL, 19.2 mmol), EDCI (4.24 g, 22 mmol), and DMAP (89 mg, 0.7 mmol). The mixture was stirred at room temperature for 3 h, evaporated to ca. 15 mL, diluted with ethyl acetate (50 mL), washed with 1M citric acid (20 mL), water (2 x 20 mL), brine (1 x 20 mL), dried over Na_2SO_4 and the solvent evaporated. The crude residue was dissolved in pyridine (11 mL) and stirred at 105°C for 4.5 h, poured into 1M citric acid-ice (100 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic layer was washed with water (2 x 15 mL), brine (1 x 15 mL), dried over Na_2SO_4 and the solvent evaporated. The residue was dissolved in 4M HCl in dioxane (7 mL). The mixture was stirred at room temperature for 2 h and then evaporated and diluted with ether (3 mL). The solution was filtered and the solid was washed with ether (2 x 5 mL) and dried under high vacuum to yield **415** (855 mg; 83%). ^{1}H-NMR, (300 MHz, d_6-DMSO) δ 9.6 (s, 1H), 8.77 (br s, 3H), 4.09 (m, 2H).

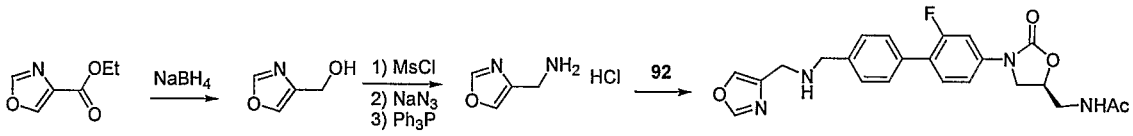
Synthesis of amine 4233

Amine **4233** was synthesized from **415** and aldehyde **92** using the same conditions described in Example 53 for the synthesis of amine **401** from aldehyde **92**. LCMS (ESI) *m/z* 441 $(M + H)^+$.

Example 64 – Synthesis of Amine 4234

Scheme 41 depicts the synthesis of amine **4234**. Known ester **416** (*Liebigs Annalen der Chemie* **1979**, 1370) was reduced to alcohol **417** which was manipulated to amine salt **418** via standard chemistry. Reductive amination of **418** with aldehyde **19** yielded amine **4234**.

Scheme 41



Synthesis of alcohol 417

To a solution of the oxazole **416** (500 mg, 4.4 mmol) in MeOH (20 mL) was added sodium borohydride ($NaBH_4$, 540 mg, 17.5 mmol). The mixture was stirred at room temperature for 2 h, then $NaBH_4$ (540 mg, 17.5 mmol) was added. After 1 h an additional amount of $NaBH_4$ (270 mg, 9.0 mmol) was added. After stirring for 2 h, the mixture was quenched with 5% Na_2CO_3 (2 mL) and evaporated. The crude residue was purified on silica gel eluting with ether, yielding **417** as a clear oil (300 mg; 86%). ^{1}H-NMR, (300 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.57 (s, 1H), 4.57 (s, 2 H).

Synthesis of amine hydrochloride 418

Alcohol **417** was converted to amine salt **418** following the procedure described above to make amine **54** from alcohol **51**. The crude material was taken up HCl in dioxane and then triturated with ether to isolate the salt as was described above for amine salt **415**.

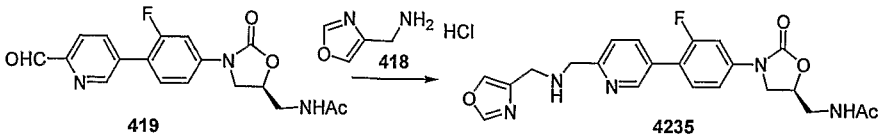
Synthesis of amine 4234

This amine was synthesized from **418** and aldehyde **92** using the same conditions described above for the synthesis of amine **401** from aldehyde **92**. LCMS (ESI) *m/z* 439 $(M + H)^+$.

Example 65 – Synthesis of Amine 4235

Scheme 42 depicts the synthesis of amine **4235** from aldehyde **419** and amine salt **418**.

Scheme 42



Synthesis of aldehyde 419

Aldehyde **419** was synthesized from 5-bromo-pyridine-2-carboxaldehyde and boronate ester **81** as described above for the synthesis of amide **4223**.

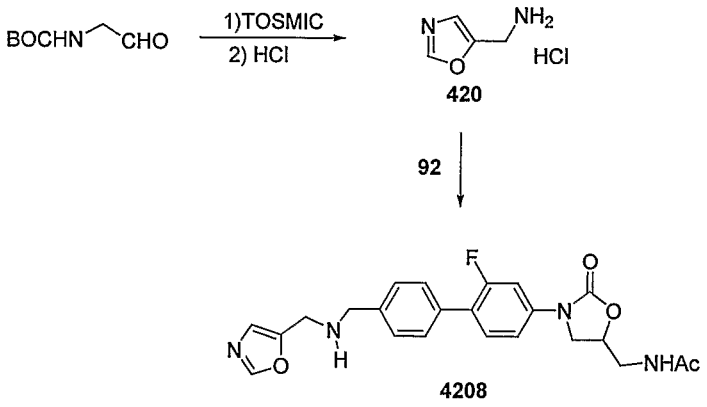
Synthesis of amine 4235

Amine **4235** was synthesized from aldehyde **419** and amine salt **418** using the same conditions described in Example 53 for the synthesis of amine **401** from aldehyde **92**. LCMS (ESI) *m/z* 440 $(M + H)^+$.

Example 66 – Synthesis of Compound 4208

Scheme 43 depicts the synthesis of compound **4208**.

Scheme 43



To a solution of *tert*-Butyl *N*-(2-oxoethyl)carbamate (4.0g, 25.1 mmol) in MeOH (80 mL) was added K_2CO_3 (10.4 g, 75.4 mmol) followed by tosylmethylisocyanide (TOSMIC, 4.91 g, 25.1 mmol). The suspension was refluxed for 1h and then evaporated. The residue was poured into ice-water (100 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with water (2x 20 mL), brine (1x 20 mL), dried over Na_2SO_4 and evaporated. The residue was purified on silica gel eluting with hexanes/ethyl acetate 1:1,

yielding a faint yellow oil which was directly dissolved in 4 M HCl in dioxane (15 mL), stirred for 45 min., and evaporated. The residue was crystallized with ether (10mL) and filtered, yielding amine **420** (1.50g, 42%). ^{1}H-NMR, (300 MHz, d-DMSO δ 8.73 (br.s 3H), 8.48 (s, 1H), 7.28 (s, 1H), 4.20-4.12 (m, 2H).

Compound **4208** was synthezised from amine **420** and aldehyde **92** using the same conditions described in Example 53 for the synthesis of amine **401** from aldehyde **92**. LCMS (ESI): 439.1 $(M + H)^+$.

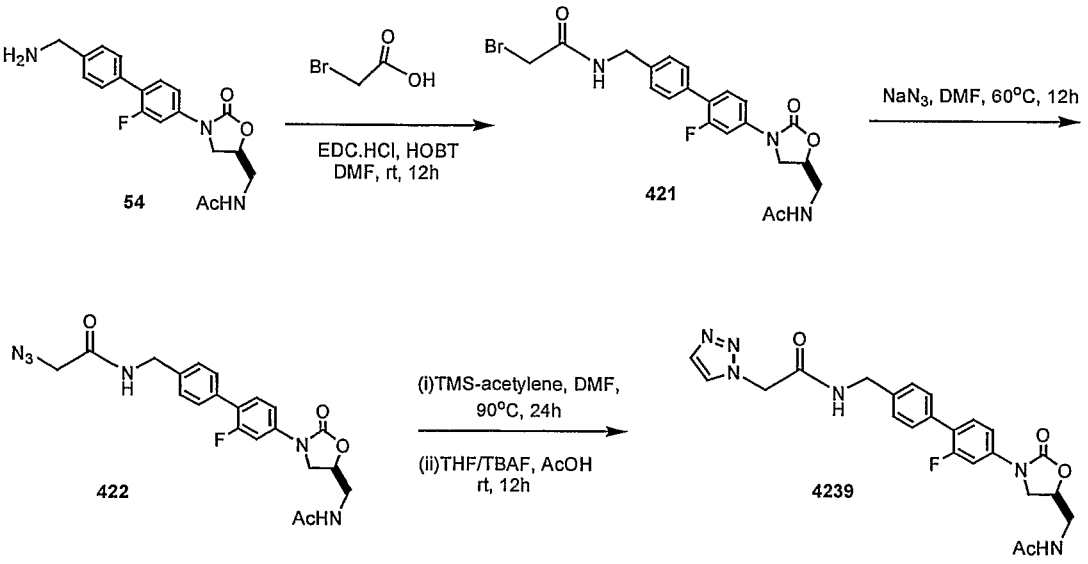
Example 67 – Synthesis of Compound 4136

A solution of amine **54** (0.070 g, 0.20 mmol) in DMF (1.0 ml) was treated with triethylamine (0.055 ml, 0.40 mmol) and 2-phthalimidoethanesulfonyl chloride (0.059 mg, 0.22 mmol) and stirred at 23 °C for 3.5 h. Additional 2-phthalimidoethanesulfonyl chloride (0.081 mg, 0.30 mmol) and triethylamine (0.087 ml, 0.63 mmol) were added, and the reaction mixture was stirred for 16 h. The reaction mixture was diluted with methylene chloride (20 ml), washed with 1 M hydrochloric acid (20 ml), and washed with saturated aqueous sodium bicarbonate (20 ml). Drying over Na_2SO_4 and evaporation of solvent yielded crude product, which was purified by flash chromatography (2.5-5% methanol in 1:1 methylene chloride/ethyl acetate) to afford compound **4136** (0.082 g, 0.14 mmol, 70%). MS (ESI): 617 $(M+Na)^+$.

Example 68 – Synthesis of Compound 4239

Scheme 44 depicts the synthesis of compound **4208**.

Scheme 44



Synthesis of azide 422

To a solution of bromoacetic acid (1.0g, 2.8 mmol) and 1-hydroxybenzotriazole hydrate (HOBT, 0.44g, 3.4 mmol) in DMF (15 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC.HCl, 0.66g, 3.4 mmol) and amine **54** (0.45g, 3.2 mmol) in a rapid succession. The resulting mixture was stirred at room temperature overnight. The solvent was evaporated and the crude product was suspended in water (about 40 mL). The suspension was filtered and the residue was washed with water, diethyl ether (about 50 mL) and dried *in vacuo* to give analytically pure compound **421** as white solid in quantitative yield.

Compound **421** was dissolved in DMF (10 mL) and NaN_3 (0.55g, 8.0 mmol) was added. The mixture was heated at 60 °C overnight and solvent evaporated off. The crude was suspended in water (about 40 mL), filtered, and the residue was washed with water, diethyl ether (about 50 mL) and dried *in vacuo* to give analytically pure azide **422** as white solid (0.97g, 69.3%). LCMS (ESI): 441 $(M + H)^+$.

Synthesis of triazole 4239

Azide **422** (0.25g, 0.57 mmol) and TMS-acetylene (0.28g, 2.84 mmol) were dissolved in DMF (5 mL) and the mixture was heated at 90°C for 24h under an argon atmosphere. The solvent was evaporated off, leaving a solid residue. The residue was suspended in water, filtered and dried *in vacuo*. To the solution of this residue in THF (5 mL) was added 1M TBAF in THF (1.14 mL) and acetic acid (0.04 mL, 0.57 mmol), and the mixture was stirred at room temperature overnight, after which time TLC showed a complete consumption of the starting material. The solvent was evaporated off and the crude was suspended in diethyl ether (about 40 mL). The suspension was filtered, and the residue was washed in succession with CH_2Cl_2 (about 50 mL), 10 % CH_3CN in diethyl ether (about 50 mL), diethyl ether (about 20 mL). The residue was air dried to give analytically pure triazole **4239** as white solid (0.238g, 89.6 %). LCMS (ESI): 467.1 $(M + H)^+$.

Example 69 – Synthesis of Compound 4252

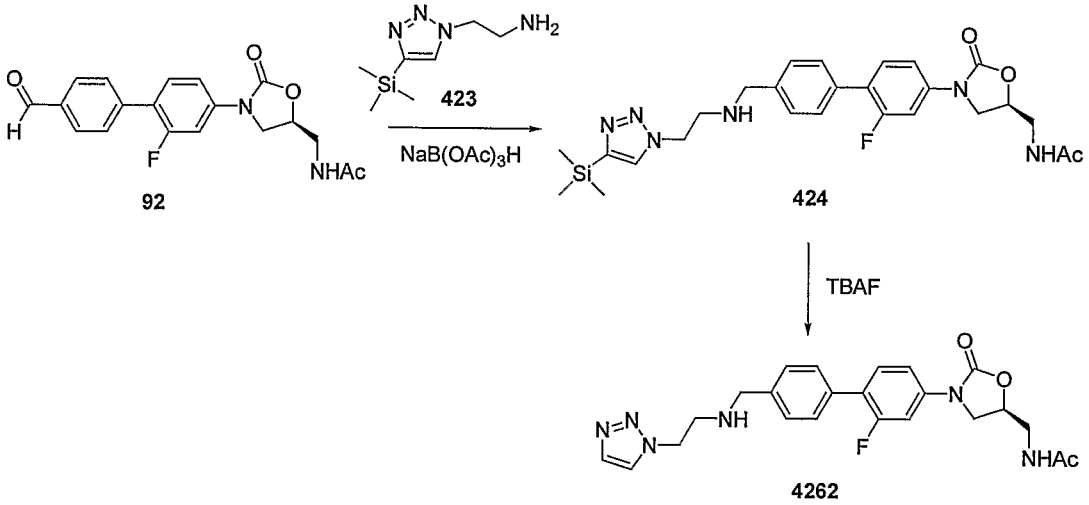
A solution of the methanesulfonic acid 5-{4-[5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-pyridin-2-ylmethyl ester **106** (220 mg, 0.5 mmol) in DMF (4.0 mL) was treated with C-isoxazol-4-yl-methylamine (68 mg, 0.5 mmol, 1.0 equiv) at room temperature, and the resulting reaction mixture was warmed to 60 °C and stirred for 6 hours. When TLC and MS showed the reaction to be complete, the reaction mixture was concentrated *in vacuo*,

and the residue was directly purified by column chromatography (0–5% MeOH/CH_2Cl_2 gradient elution) to afford the desired N-{3-[3-Fluoro-4-(6-{[(isoxazol-4-ylmethyl)-amino]-methyl}-pyridin-3-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide **4252** (22 mg, 10%) as off-white solids. LCMS (EI): 440 (M^+ + H).

Example 70 – Synthesis of Compound 4262

Scheme 45 depicts the synthesis of compound **4262**.

Scheme 45



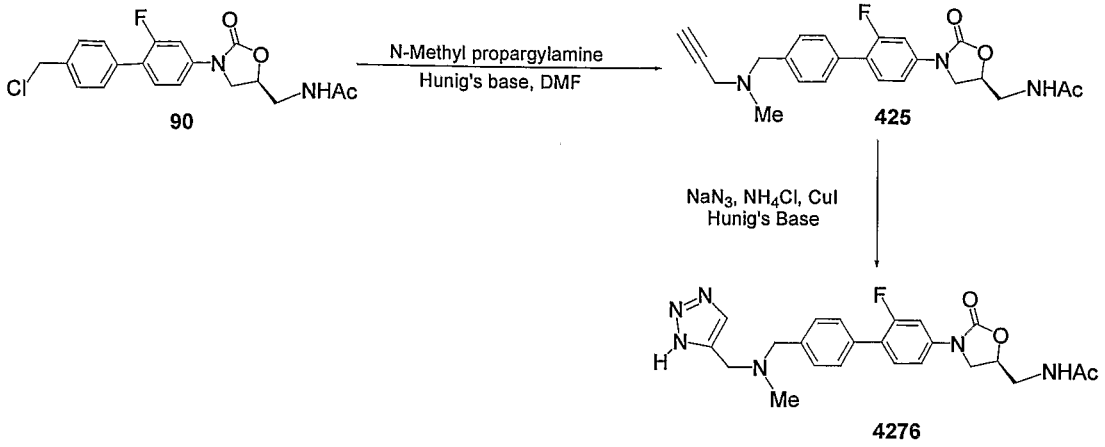
To a solution of 0.060 g (0.17 mmol) of aldehyde **92** and 0.056 g (0.25 mmol) of the HCl salt of amine **423** in 3 ml of DMF was added 0.071 g (0.34 mmol) of $NaB(OAc)_3H$. The reaction mixture was stirred at 25 °C for 2 h. The DMF was removed, and the residue was purified by preparative TLC to give 0.041 g of compound **424**. MS (M+1): 525.

To a solution of 0.012 g (0.023 mmol) of **424** and 0.03ml (0.027 mmol) of TBAF (1 M in THF) in 4 ml of CH_2Cl_2 was added a few drops of acetic acid, and the mixture was stirred at 0 °C for 4 h. The reaction solvents were removed by rotary evaporation, and the residue was purified by preparative TLC to give 0.008 g of compound **4262**. MS (M+1): 489.

Example 71 - Synthesis of Triazole 4276

Scheme 46 depicts the synthesis of triazole **4276**.

Scheme 46



Synthesis of Alkyne 425

To a solution of chloride **90** (2 g, 5.3 mmol) and Hunig's base (diisopropylethylamine, 1.7 mL, 10 mmol) in DMF (15 mL) was added a solution of N-methyl propargylamine (0.55g mg, 8.0 mmol) in DMF (1 mL). After stirring at room temperature for 16 h, the DMF was removed *in vacuo*. The crude product was purified by preparative thin layer chromatography (10:1:0.05 CH_2Cl_2/MeOH/$NH_3 \cdot H_2O$) to afford 2.05 g of alkyne **425** in a yield of 95%. MS (ESI): 410.1 (100%) $(M+Na)^+$.

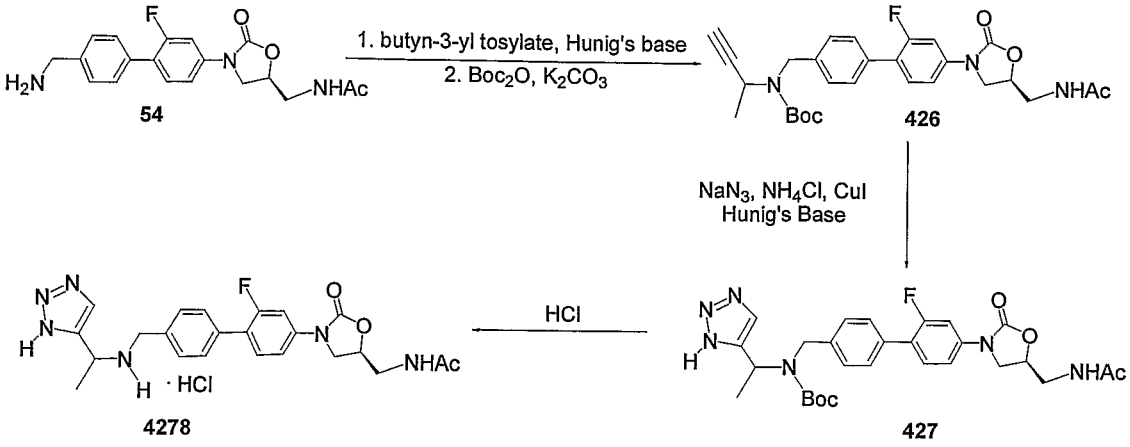
Synthesis of compound 4276

A mixture of alkyne **425** (1.8 g, 4.4 mmol), sodium azide (0.43 g, 6.6 mmol), ammonium chloride (0.35 g, 6.6 mmol), copper(I) iodide (84 mg, 0.44 mmol) and Hunig's base (3.5 mL, 20 mmol) in DMF (10 mL) was heated under argon atmosphere at 80 °C for 48 h. The DMF was removed *in vacuo*, and the residue was dissolved in MeOH (5 mL), CH_2Cl_2 (50 mL), conc. ammonium hydroxide (20 mL) and saturated ammonium chloride solution (20 mL). After stirring at room temperature for 2 h, the organic phase was separated, washed with saturated NH_4Cl solution and water, dried over $MgSO_4$, and concentrated. The crude product was purified by preparative thin layer chromatography (10:1:0.05 CH_2Cl_2/MeOH/$NH_3 \cdot H_2O$) to afford 1.75 mg of triazole **4276** in a yield of 88%. MS (ESI): 453.1 (100%) $(M+H)^+$, 475.2 $(M+Na)^+$.

Example 72 - Synthesis of Triazole 4278

Scheme 47 depicts the synthesis of triazole **4278**.

Scheme 47



Synthesis of alkyne 426

A mixture of amine **54** (422 mg, 1.18 mmol), butyn-3-yl tosylate (265 mg, 1.18 mmol), Hunig's base (diisopropylethylamine, 0.2 mL, 1.15 mmol) and potassium iodide (17 mg, 0.1 mmol) in DMF (5 mL) was heated at 70 °C 15 h. The DMF was removed *in vacuo*. The residue was dissolved in a mixed solvent of THF (10 mL) and water (2 mL), K_2CO_3 (276 mg, 2 mmol), and then di-tert-butyl dicarbonate (218 mg, 1 mmol) was added. The reaction was stirred at room temperature for 12 h, and the THF was removed *in vacuo*. 40 mL of EtOAc was added and the solution was washed with water, dried over $MgSO_4$ and concentrated. The crude product was purified by preparative thin layer chromatography (15:1:0.05 CH_2Cl_2/MeOH/$NH_3 \cdot H_2O$) to afford 210 mg of alkyne **426** in a yield of 22%. MS (ESI): 410.1, 532.1 $(M+Na)^+$, 573.1 (100%).

Synthesis of triazole 427

A mixture of alkyne **426** (150 mg, 0.29 mmol), sodium azide (29 mg, 0.44 mmol), ammonium chloride (24 mg, 0.44 mmol), copper(I) iodide (56 mg, 0.29 mmol) and Hunig's base (0.26 mL, 1.5 mmol) in DMF (3 mL) was heated under argon atmosphere at 80 °C for 24 h. The DMF was removed *in vacuo*, and the residue was dissolved in CH_2Cl_2 and conc. ammonium hydroxide solution. The organic phase was separated, washed with saturated NH_4Cl solution and water, dried over $MgSO_4$, and concentrated. The crude product was purified by preparative thin layer chromatography (15:1:0.05 CH_2Cl_2/MeOH/$NH_3 \cdot H_2O$) to afford 155 mg of triazole **427** in a yield of 95%. MS (ESI): 453.1 (100%), 575.1 $(M+Na)^+$.

Synthesis of compound 4278

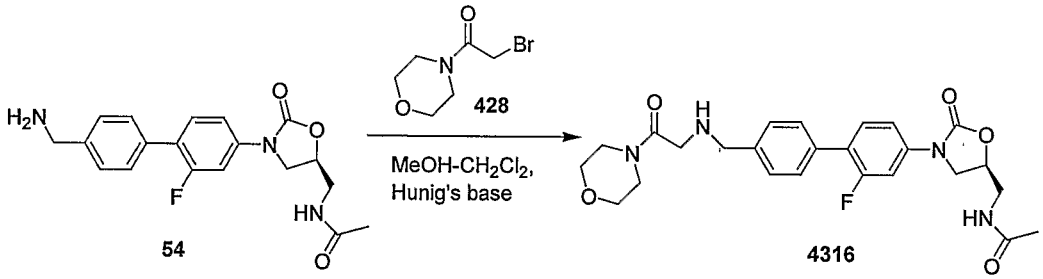
To a solution of triazole **427** (155 mg, 0.28 mmol) in CH_2Cl_2 (5 mL) and MeOH (1 mL) was added 2 mL of HCl solution (4.0 M in dioxane). After stirring at room temperature for 15 h, the reaction was concentrated and washed with EtOAc/MeOH to give 130 mg of compound **4278** in a yield of 95%. MS (ESI): 453.1.1(100%) $(M+H)^+$.

Example 73 – Synthesis of Compounds 4316 and 4314

Synthesis of morpholine 4316

Scheme 48 depicts the synthesis of morpholine **4316**.

Scheme 48

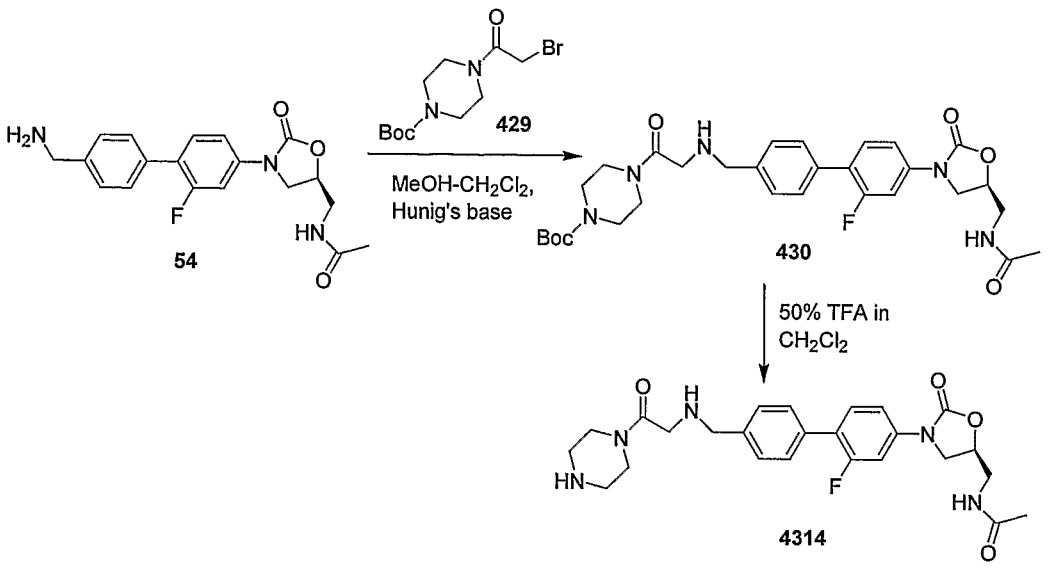


Known bromide **428** was synthesized from morpholine and bromoacetyl bromide as reported in the literature (Thompson, W. J. *et al. J. Med. Chem.* **1992**, *35*, 1685). To a solution of amine **54** (86 mg, 0.23 mmol) in a mixture of methyl alcohol (2 mL), methylene chloride (2 mL) and Hunig's base (2 mL) was added bromide **428** (32 mg, 0.23 mmol) at 0°C. The reaction mixture was warmed to room temperature and heated over an oil bath at 80°C for 18h. The solution was concentrated and purified by flash chromatography over silica gel (14:1:0.05 CH_2Cl_2/MeOH: NH_4OH) to yield 66 mg of compound **4316**. ^{1}HNMR (300 MHz, CD_3OD): δ 7.50-7.22 (m, 7H), 4.77-4.69 (m, 1H), 4.06 (t, J = 9 Hz, 1H), 3.77 (dd, J = 6, 3 Hz, 1H), 3.70 (s, 1H), 3.55-3.46 (m, 8H), 3.39-3.36 (m, 3H), 3.34-3.30 (m, 2H), 1.86 (s, 3H). LCMS (ESI) *m/e* 485 $(M+H)^+$.

Synthesis of piperazine 4314

Scheme 49 depicts the synthesis of piperazine **4314**.

Scheme 49

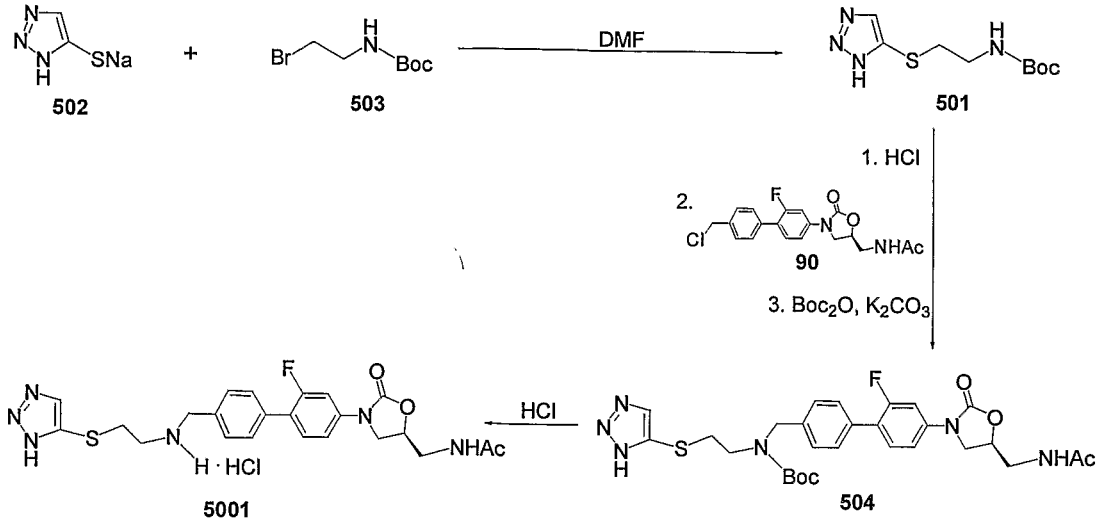


Bromide **429** was synthesized from tert-Butyl 1-piperazine carboxylate and bromoacetyl bromide following literature procedures (Thompson, W. J. *et al. J. Med. Chem.* **1992**, *35*, 1685). ^{1}HNMR (300 MHz, $CDCl_3$): δ 3.86 (s, 2H), 3.61-3.41 (m, 8H), 1.46 (s, 9H). Compound **430** was synthesized from amine **54** and bromide **429** using the same procedure as described for compound **4316**. LCMS (ESI) *m/e* 584 $(M+H)^+$. A solution of **430** (50 mg, 0.085 mmol) in CH_2Cl_2-CF_3COOH (1:1, 4 mL) was stirred at 0°C for 1h. The reaction mixture was concentrated and the crude product after purification (7:1:0.05 CH_2Cl_2/MeOH/NH_4OH) afforded 35 mg of compound **4314**. ^{1}HNMR (300 MHz, CD_3OD): δ 7.51-7.23 (m, 7H), 4.73-4.67 (m, 1H), 4.07 (t, J = 9 Hz, 1H), 3.75 (dd, J = 8, 3 Hz, 1H), 3.73 (s. 2H), 3.48-3.41 (m, 6H), 3.24 (s, 2H), 3.21-3.19 (m, 2H), 2.75-2.65 (m, 4H), 1.87 (s, 3H). LCMS (ESI) *m/e* 484 $(M+H)^+$.

Example 74 - Synthesis of Triazole 5001

Scheme 50 depicts the synthesis of triazole **5001**.

Scheme 50



Synthesis of triazole 501

A mixture of 1H-1,2,3-triazole-5-thiol sodium salt **502** (246 mg, 2 mmol) and 2-(Boc-amino)ethyl bromide **503** (448 mg, 2 mmol) in DMF (2 mL) was stirred at room temperature for 2 h. 50 mL of EtOAc was added and the solution was washed with water, dried over $MgSO_4$ and concentrated to afford 458 mg of triazole **501** as colorless oil in a yield of 94%. MS (ESI): 267.0 (100%) $(M+Na)^+$.

Synthesis of triazole 504

To a solution of triazole **501** (458 mg, 1.88 mmol) in CH_2Cl_2 (10 mL) and MeOH (2 mL) was added 4 mL of HCl solution (4.0 M in dioxane). After stirring at room temperature for 2 h, the reaction was concentrated to dryness. The residue was dissolved in DMF (7 mL) and then chloride **90** (377 mg, 1 mmol) and Hunig's base (diisopropylethylamine, 0.8 mL, 4.6 mmol) were added. The solution was heated at 70 °C for 3 h. The DMF was removed *in vacuo*, and the residue was dissolved in a mixed solvent of THF (10 mL) and water (2 mL). K_2CO_3 (414 mg, 3 mmol) and di-tert-butyl dicarbonate (545 mg, 2.5 mmol) were then added, and the reaction was stirred at room temperature for 12 h. The THF was removed *in vacuo,* 50 mL of EtOAc was added, and the solution was washed with water, dried over $MgSO_4$ and concentrated. The crude product was purified by preparative thin layer chromatography (15:1:0.1 CH_2Cl_2/MeOH/ $NH_3 \cdot H_2O$) to afford 192 mg of triazole **504** in a yield of 33%. MS (ESI): 485.1 (100%), 607.2 $(M+Na)^+$.

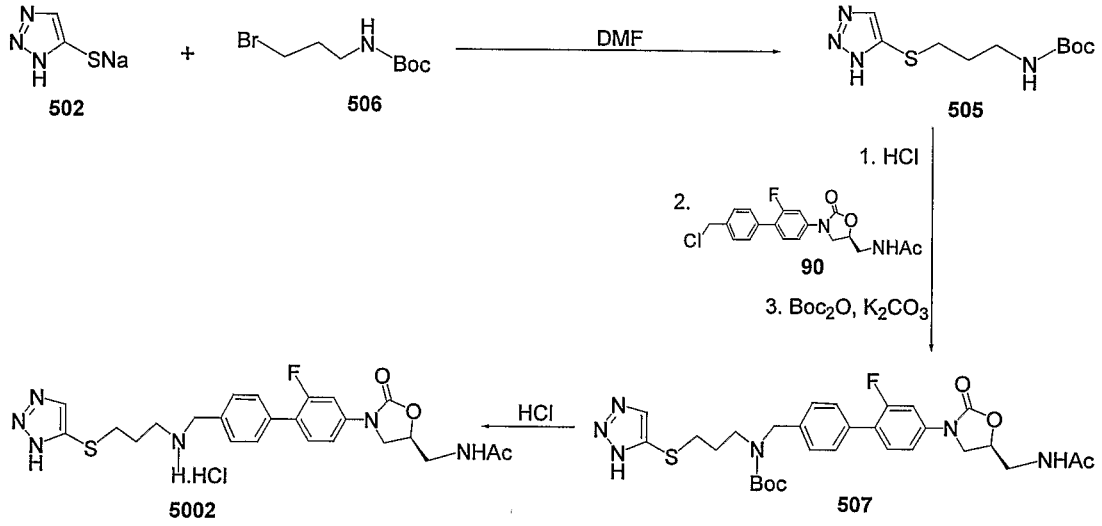
Synthesis of compound 5001

To a solution of triazole **504** (192 mg, 0.33 mmol) in CH_2Cl_2 (10 mL) and MeOH (2 mL) was added 4 mL of HCl solution (4.0 M in dioxane). After stirring at room temperature for 12 h, the reaction was concentrated and washed with EtOAc/MeOH to give 150 mg of triazole **5001** in a yield of 94%. MS (ESI): 485.1(100%) $(M+H)^+$, 507.2 $(M+Na)^+$.

Example 75 - Synthesis of Triazole 5002

Scheme 51 depicts the synthesis of triazole **5002**.

Scheme 51



Synthesis of triazole 505

A mixture of 1H-1,2,3-triazole-5-thiol sodium salt **502** (246 mg, 2 mmol) and 2-(BOC-amino)propyl bromide **506** (476 mg, 2 mmol) in DMF (2 mL) was stirred at room temperature for 1 h. 50 mL of EtOAc was added and the solution was washed with water, dried over $MgSO_4$ and concentrated to afford 508 mg of triazole **505** as colorless oil in a yield of 98%. MS (ESI): 281.1 (100%, $(M+Na)^+$).

Synthesis of triazole 507

To a solution of triazole **505** (365 mg, 1.36 mmol) in CH_2Cl_2 (10 mL) and MeOH (2 mL) was added 4 mL of HCl solution (4.0 M in dioxane). After stirring at room temperature for 2 h, the reaction was concentrated to dryness. The residue was dissolved in DMF (5 mL) and then chloride **90** (377 mg, 1 mmol) and Hunig's base (diisopropylethylamine, 0.52 mL, 3 mmol) were added. The solution was heated at 50 °C for 10 h. The DMF was removed *in*

vacuo and the residue was purified by preparative thin layer chromatography (10:1:0.1 CH_2Cl_2/MeOH/ $NH_3 \cdot H_2O$) to afford 230 mg of crude triazole **5002** (90% pure, MS (ESI): 499.1 (100%) $(M+H)^+$).

The free base of **5002** was dissolved in a mixed solvent of THF (10 mL) and water (2 mL), and K_2CO_3 (138 mg, 1 mmol) and di-tert-butyl dicarbonate (207 mg, 0.95 mmol) were then added. The reaction was stirred at room temperature for 12 h. The THF was removed *in vacuo*. 50 mL of EtOAc was added and the solution was washed with water, dried over $MgSO_4$ and concentrated. The crude product was purified by preparative thin layer chromatography (15:1:0.05 CH_2Cl_2/MeOH/$NH_3 \cdot H_2O$) to afford 220 mg of triazole **507** in a yield of 37%. MS (ESI): 499.3 (100%), 621.1 $(M+Na)^+$.

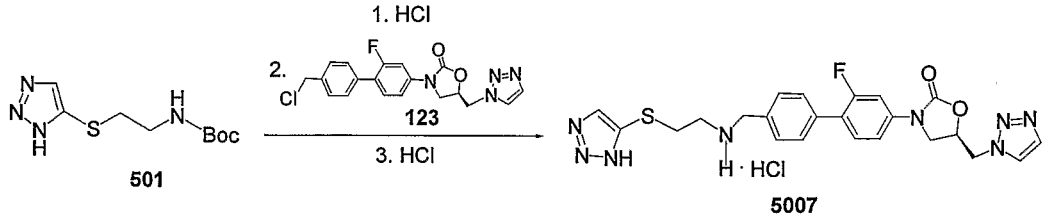
Synthesis of compound 5002

To a solution of **507** (98 mg, 0.16 mmol) in CH_2Cl_2 (5 mL) and MeOH (1 mL) was added 2 mL of HCl solution (4.0 M in dioxane). After stirring at room temperature for 12 h, the reaction was concentrated and washed with EtOAc/MeOH to give 78 mg of compound **5002** in a yield of 95%. MS (ESI): 499.1(100%, $(M+H)^+$).

Example 76 - Synthesis of Triazole 5007

Scheme 52 depicts the synthesis of triazole **5007**.

Scheme 52



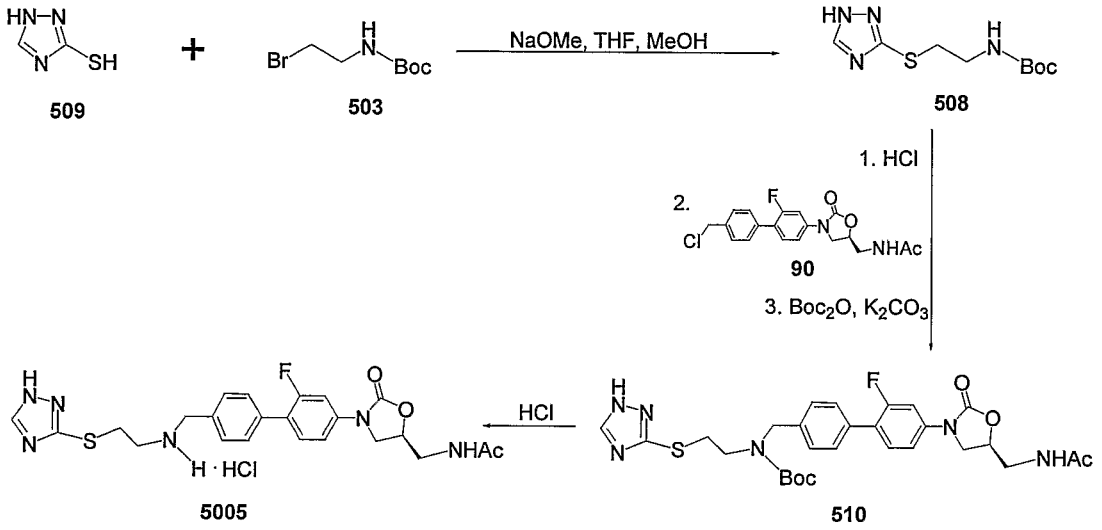
To a solution of triazole **501** (488 mg, 2 mmol) in CH_2Cl_2 (10 mL) and MeOH (2 mL) was added 4 mL of HCl solution (4.0 M in dioxane). After stirring at room temperature for 2 h, the reaction was concentrated to dryness. The residue was dissolved in DMF (5 mL) and then chloride **123** (541 mg, 1.4 mmol) and diisopropylethylamine (0.7 mL, 4 mmol) were added. The solution was heated at 50 °C for 18 h. The DMF was removed *in vacuo* and the residue was purified by preparative thin layer chromatography (10:1:0.15 CH_2Cl_2/MeOH/$NH_3 \cdot H_2O$) to afford 250 mg of compound **5007** in a yield of 36%. MS (ESI): 495.0 (100%) $(M+H)^+$.

The free base of compound **5007** was dissolved in CH_2Cl_2 (5 mL) and MeOH (5 mL). 2 mL of HCl solution (4.0 M in dioxane) was added at 0 °C. After stirring at room temperature for 1 h, the reaction was concentrated, washed with EtOAc/MeOH to give 260 mg of the HCl salt compound **5007** in a yield of 97%. MS (ESI): 495.1 (100%) $(M+H)^+$.

Example 77 - Synthesis of Triazole 5005

Scheme 53 depicts the synthesis of triazole **5005**.

Scheme 53



Synthesis of triazole 508

To a solution of 1H-1,2,4-triazole-3-thiol **509** (202 mg, 2 mmol) and 2-(BOC-amino)ethyl bromide **503** (448 mg, 2 mmol) in THF (5 mL) and MeOH (2 mL) was added a solution of NaOMe in MeOH (25% wt., 432 mg, 2 mmol). After stirring at room temperature for 2 h, 50 mL of EtOAc was added, and the solution was washed with water, dried over $MgSO_4$ and concentrated to afford 464 mg of triazole **508** as colorless oil in a yield of 95%. MS (ESI): 266.8 (100%) $(M+Na)^+$.

Synthesis of triazole 510

To a solution of triazole **508** (366 mg, 1.5 mmol) in CH_2Cl_2 (10 mL) and MeOH (2 mL) was added 4 mL of HCl solution (4.0 M in dioxane). After stirring at room temperature for 3 h, the reaction was concentrated to dryness. The residue was dissolved in DMF (5 mL) and then chloride **90** (377 mg, 1 mmol) and Hunig's base (diisopropylethylamine, 0.7 mL, 4 mmol) were added. The solution was heated at 50 °C for 12 h. The DMF was removed *in vacuo* and the residue was purified by preparative thin layer chromatography (10:1:0.15 CH_2Cl_2/MeOH/

$NH_3 \cdot H_2O$) to afford 250 mg of crude compound **5005** (85% pure, MS (ESI): 485.1 (100%) $(M+H)^+$)).

The crude **5005** was dissolved in a mixed solvent of THF (10 mL) and water (2 mL), and then K_2CO_3 (276 mg, 2 mmol) and di-tert-butyl dicarbonate (218 mg, 1 mmol) were added. The reaction was stirred at room temperature for 12 h. The THF was removed *in vacuo*. 50 mL of EtOAc was added and the solution was washed with water, dried over $MgSO_4$ and concentrated. The crude product was purified by preparative thin layer chromatography (15:1:0.1 CH_2Cl_2/MeOH/$NH_3 \cdot H_2O$) to afford 150 mg of **510** in a yield of 26%. MS (ESI): 485.1 (100%), 607.1 $(M+Na)^+$.

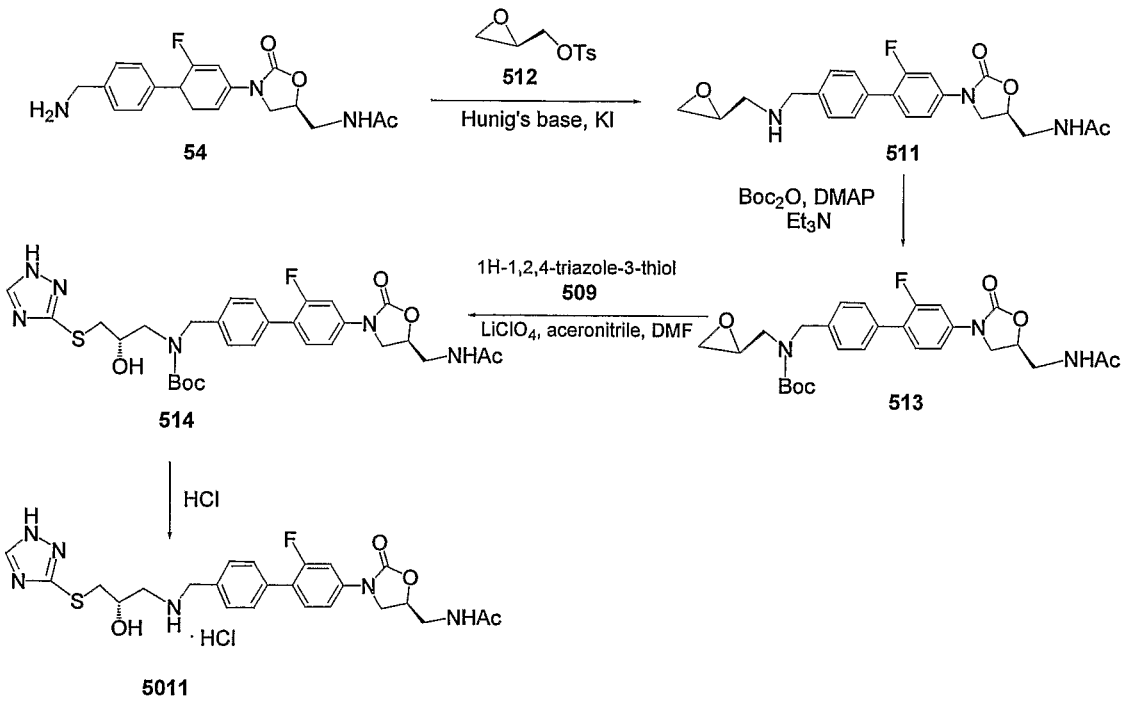
Synthesis of compound 5005

To a solution of triazole **510** (150 mg, 0.26 mmol) in CH_2Cl_2 (10 mL) and MeOH (2 mL) was added 2 mL of HCl solution (4.0 M in dioxane). After stirring at room temperature for 12 h, the reaction was concentrated and washed with EtOAc/MeOH to give 120 mg of compound **5005** in a yield of 89%. MS (ESI): 485.1 (100%, $(M+H)^+$), 507.0 $(M+Na)^+$.

Example 78 - Synthesis of 5011

Scheme 54 depicts the synthesis of triazole **5011**.

Scheme 54



Synthesis of compound 511

A mixture of amine **54** (714 mg, 2 mmol), 2R-(-)-glycidyl tosylate **512** (456 mg, 2 mmol), N,N-diisopropylethylamine (0.44 mL, 2.5 mmol) and potassium iodide (33 mg, 0.2 mmol) in DMF (5 mL) was heated at 70 °C for 1 h. The reaction was diluted with 50 mL of EtOAc. The solution was washed with water, dried over $MgSO_4$ and concentrated. The crude product was purified by preparative thin layer chromatography (10:1:0.1 CH_2Cl_2/MeOH/ $NH_3 \cdot H_2O$) to afford 350 mg of compound **511** in a yield of 42%. MS (ESI): 414.1 (100%), 436.0 $(M+Na)^+$.

Synthesis of compound 513

To a solution of compound **511** (160 mg, 0.39 mmol) in THF (10 mL) and DMF (1 mL) was added di-tert-butyl dicarbonate (138 mg, 0.63 mmol), triethylamine (0.2 mL, 1.4 mmol) and N,N-dimethylaminopyridine. The reaction was stirred at room temperature for 1 h, and THF was removed *in vacuo*. 40 mL of EtOAc was added and the solution was washed with water, dried over $MgSO_4$ and concentrated. The crude product was purified by preparative thin layer chromatography (15:1:0.1 CH_2Cl_2/MeOH/$NH_3 \cdot H_2O$) to afford 138 mg of compound **513** in a yield of 70%. MS (ESI): 514.1 (100%) $(M+H)^+$, 536.1 $(M+Na)^+$.

Synthesis of compound 514

To a solution of compound **513** (120 mg, 0.23 mmol) and $LiClO_4$ (27 mg, 0.25 mmol) in acetonitrile (2 mL) was added 1H-1,2,4-triazole-3-thiol **509** (24 mg, 0.23 mmol). The reaction was heated at 100 °C for 6 days and concentrated to dryness. The crude product was purified by preparative thin layer chromatography (15:1:0.1 CH_2Cl_2/MeOH/$NH_3 \cdot H_2O$) to afford 75 mg of compound **514** in a yield of 53%. MS (ESI): 515.1 (100%), 615.1 $(M+H)^+$.

Synthesis of compound 5011

To a solution of compound **514** (75 mg, 0.12 mmol) in CH_2Cl_2 (5 mL) and MeOH (1 mL) was added 1 mL of HCl solution (4.0 M in dioxane). After stirring at room temperature for 24 h, the reaction was concentrated and washed with EtOAc/MeOH to give 62 mg of **5011** in a yield of 94%. MS (ESI): 515.1 (100%) $(M+H)^+$.

INCORPORATION BY REFERENCE

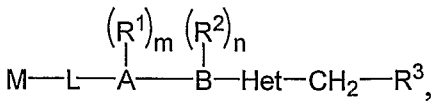
The entire disclosure of each of the patent documents and scientific articles referred to herein is incorporated by reference for all purposes.

EQUIVALENTS

The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting on the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

WHAT IS CLAIMED IS:

1. A compound having the formula:



or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein:

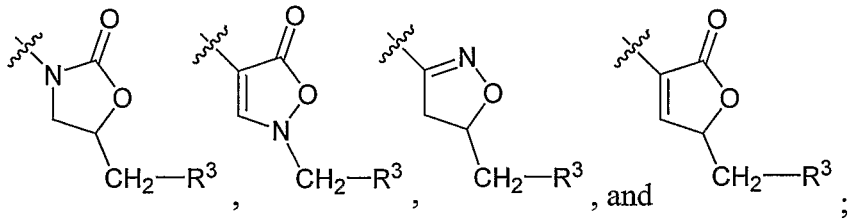
A is selected from the group consisting of:

phenyl, pyridyl, pyrazinyl, pyrimidinyl, and pyridazinyl;

B is selected from the group consisting of:

phenyl, pyridyl, pyrazinyl, pyrimidinyl, and pyridazinyl;

Het-CH_2-R^3 is selected from the group consisting of:



;

M is selected from the group consisting of:

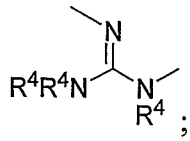
a) saturated, unsaturated, or aromatic C_{3-14} carbocycle, and b) saturated, unsaturated, or aromatic 3-14 membered heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, wherein a) or b) optionally is substituted with one or more R^5 groups;

M-L is selected from the group consisting of:

a) M-X, b) M-L^1, c) M-L^1-X, d) M-X-L^2, e) M-L^1-X-L^2, f) M-X-L^1-X-L^2, g) M-L^1-X-L^2-X, h) M-X-X-, i) M-L^1-X-X-, j) M-X-X-L^2, and k) M-L^1-X-X-L^2, wherein

X, at each occurrence, independently is selected from the group consisting of:

a) -O-, b) -NR^4-, c) –N(O)-, d) –N(OR^4)-, e) -$S(O)_p$-, f) -SO_2NR^4-, g) -NR^4SO_2-, h) -NR^4-N=, i) =N-NR^4-, j) -O-N=, k) =N-O-, l) -N=, m) =N-, n) -NR^4-NR^4-, o) -$NR^4C(O)O$-, p) -$OC(O)NR^4$-, q) -$NR^4C(O)NR^4$- r) -$NR^4C(NR^4)NR^4$-, and s)



;

L^1 is selected from the group consisting of:

a) C_{1-6} alkyl, b) C_{2-6} alkenyl, and c) C_{2-6} alkynyl,

wherein any of a) – c) optionally is substituted with one or more R^5 groups; and

L^2 is selected from the group consisting of:

a) C_{1-6} alkyl, b) C_{2-6} alkenyl, and c) C_{2-6} alkynyl,

wherein any of a) – c) optionally is substituted with one or more R^5 groups;

R^1, at each occurrence, independently is selected from the group consisting of:

a) F, b) Cl, c) Br, d) I, e) $-CF_3$, f) $-OR^4$, g) -CN, h) $-NO_2$, i) $-NR^4R^4$, j) $-C(O)R^4$, k) $-C(O)OR^4$, l) $-OC(O)R^4$, m) $-C(O)NR^4R^4$, n) $-NR^4C(O)R^4$, o) $-OC(O)NR^4R^4$, p) $-NR^4C(O)OR^4$, q) $-NR^4C(O)NR^4R^4$, r) $-C(S)R^4$, s) $-C(S)OR^4$, t) $-OC(S)R^4$, u) $-C(S)NR^4R^4$, v) $-NR^4C(S)R^4$, w) $-OC(S)NR^4R^4$, x) $-NR^4C(S)OR^4$, y) $-NR^4C(S)NR^4R^4$, z) $-NR^4C(NR^4)NR^4R^4$, aa) $-S(O)_pR^4$, bb) $-SO_2NR^4R^4$, and cc) R^4;

R^2, at each occurrence, independently is selected from the group consisting of:

a) F, b) Cl, c) Br, d) I, e) $-CF_3$, f) $-OR^4$, g) -CN, h) $-NO_2$, i) $-NR^4R^4$, j) $-C(O)R^4$, k) $-C(O)OR^4$, l) $-OC(O)R^4$, m) $-C(O)NR^4R^4$, n) $-NR^4C(O)R^4$, o) $-OC(O)NR^4R^4$, p) $-NR^4C(O)OR^4$, q) $-NR^4C(O)NR^4R^4$, r) $-C(S)R^4$, s) $-C(S)OR^4$, t) $-OC(S)R^4$, u) $-C(S)NR^4R^4$, v) $-NR^4C(S)R^4$, w) $-OC(S)NR^4R^4$, x) $-NR^4C(S)OR^4$, y) $-NR^4C(S)NR^4R^4$, z) $-NR^4C(NR^4)NR^4R^4$, aa) $-S(O)_pR^4$, bb) $-SO_2NR^4R^4$, and cc) R^4;

R^3 is selected from the group consisting of:

a) $-OR^4$, b) $-NR^4R^4$, c) $-C(O)R^4$, d) $-C(O)OR^4$, e) $-OC(O)R^4$, f) $-C(O)NR^4R^4$, g) $-NR^4C(O)R^4$, h) $-OC(O)NR^4R^4$, i) $-NR^4C(O)OR^4$, j) $-NR^4C(O)NR^4R^4$, k) $-C(S)R^4$, l) $-C(S)OR^4$, m) $-OC(S)R^4$, n) $-C(S)NR^4R^4$, o) $-NR^4C(S)R^4$, p) $-OC(S)NR^4R^4$, q) $-NR^4C(S)OR^4$, r) $-NR^4C(S)NR^4R^4$, s) $-NR^4C(NR^4)NR^4R^4$, t) $-S(O)_pR^4$, u) $-SO_2NR^4R^4$, and v) R^4;

R^4, at each occurrence, independently is selected from the group consisting of:

a) H, b) C_{1-6} alkyl, c) C_{2-6} alkenyl, d) C_{2-6} alkynyl, e) C_{3-14} saturated, unsaturated, or aromatic carbocycle, f) 3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, g) -C(O)-C_{1-6} alkyl, h) -C(O)-C_{2-6} alkenyl, i) –C(O)-C_{2-6} alkynyl, j) -C(O)-C_{3-14} saturated, unsaturated, or aromatic carbocycle, k) -C(O)-3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, l) -C(O)O-C_{1-6} alkyl, m) -C(O)O-C_{2-6} alkenyl, n) –C(O)O-C_{2-6} alkynyl, o) -C(O)O-C_{3-14} saturated, unsaturated, or aromatic carbocycle, and p) -C(O)O-3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,

wherein any of b) – p) optionally is substituted with one or more R^5 groups;

R^5, at each occurrence, is independently selected from the group consisting of:

a) F, b) Cl, c) Br, d) I, e) =O, f) =S, g) =NR^6, h) =NOR^6, i) =N-NR^6R^6, j) -CF_3, k) –OR^6, l) -CN, m) -NO_2, n) –NR^6R^6, o) -C(O)R^6, p) -C(O)OR^6, q) -OC(O)R^6, r) -C(O)NR^6R^6, s) –NR^6C(O)R^6, t) -OC(O)NR^6R^6, u) -NR^6C(O)OR^6, v) -NR^6C(O)NR^6R^6, w) -C(S)R^6, x) -C(S)OR^6, y) -OC(S)R^6, z) -C(S)NR^6R^6, aa) -NR^6C(S)R^6, bb) -OC(S)NR^6R^6, cc) -NR^6C(S)OR^6, dd) –NR^6C(S)NR^6R^6, ee) –NR^6C(NR^6)NR^6R^6, ff) -$S(O)_pR^6$, gg) -$SO_2NR^6R^6$, and hh) R^6;

R^6, at each occurrence, independently is selected from the group consisting of:

a) H, b) C_{1-6} alkyl, c) C_{2-6} alkenyl, d) C_{2-6} alkynyl, e) C_{3-14} saturated, unsaturated, or aromatic carbocycle, f) 3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, g) -C(O)-C_{1-6} alkyl, h) -C(O)-C_{2-6} alkenyl, i) –C(O)-C_{2-6} alkynyl, j) -C(O)-C_{3-14} saturated, unsaturated, or aromatic carbocycle, k) -C(O)-3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, l) -C(O)O-C_{1-6} alkyl, m) -C(O)O-C_{2-6} alkenyl, n) –C(O)O-C_{2-6} alkynyl, o) -C(O)O-C_{3-14} saturated,

unsaturated, or aromatic carbocycle, and p) -C(O)O-3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,

wherein any of b) – p) optionally is substituted with one or more R^7 groups;

R^7, at each occurrence, independently is selected from the group consisting of:

a) F, b) Cl, c) Br, d) I, e) =O, f) =S, g) $=NR^8$, h) $=NOR^8$, i) $=N\text{-}NR^8R^8$, j) $-CF_3$, k) $-OR^8$, l) -CN, m) $-NO_2$, n) $-NR^8R^8$, o) $-C(O)R^8$, p) $-C(O)OR^8$, q) $-OC(O)R^8$, r) $-C(O)NR^8R^8$, s) $-NR^8C(O)R^8$, t) $-OC(O)NR^8R^8$, u) $-NR^8C(O)OR^8$, v) $-NR^8C(O)NR^8R^8$, w) $-C(S)R^8$, x) $-C(S)OR^8$, y) $-OC(S)R^8$, z) $-C(S)NR^8R^8$, aa) $-NR^8C(S)R^8$, bb) $-OC(S)NR^8R^8$, cc) $-NR^8C(S)OR^8$, dd) $-NR^8C(S)NR^8R^8$, ee) $-NR^8C(NR^8)NR^8R^8$, ff) $-S(O)_pR^8$, gg) $-SO_2NR^8R^8$, hh) C_{1-6} alkyl, ii) C_{2-6} alkenyl, jj) C_{2-6} alkynyl, kk) C_{3-14} saturated, unsaturated, or aromatic carbocycle, and ll) 3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,

wherein any of hh) – ll) optionally is substituted with one or more moieties selected from the group consisting of R^8, F, Cl, Br, I, $-CF_3$, $-OR^8$, $-SR^8$, -CN, $-NO_2$, $-NR^8R^8$, $-C(O)R^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-C(O)NR^8R^8$, $-NR^8C(O)R^8$, $-OC(O)NR^8R^8$, $-NR^8C(O)OR^8$, $-NR^8C(O)NR^8R^8$, $-C(S)R^8$, $-C(S)OR^8$, $-OC(S)R^8$, $-C(S)NR^8R^8$, $-NR^8C(S)R^8$, $-OC(S)NR^8R^8$, $-NR^8C(S)OR^8$, $-NR^8C(S)NR^8R^8$, $-NR^8C(NR^8)NR^8R^8$, $-SO_2NR^8R^8$, and-$S(O)_pR^8$;

R^8, at each occurrence, independently is selected from the group consisting of:

a) H, b) C_{1-6} alkyl, c) C_{2-6} alkenyl, d) C_{2-6} alkynyl, e) C_{3-14} saturated, unsaturated, or aromatic carbocycle, f) 3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, g) $-C(O)\text{-}C_{1-6}$ alkyl, h) $-C(O)\text{-}C_{2-6}$ alkenyl, i) $-C(O)\text{-}C_{2-6}$ alkynyl, j) $-C(O)\text{-}C_{3-14}$ saturated, unsaturated, or aromatic carbocycle, k) -C(O)-3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, l) $-C(O)O\text{-}C_{1-6}$ alkyl,

m) -C(O)O-C_{2-6} alkenyl, n) –C(O)O-C_{2-6} alkynyl, o) -C(O)O-C_{3-14} saturated, unsaturated, or aromatic carbocycle, and p) -C(O)O-3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,

wherein any of b) – p) optionally is substituted with one or more moieties selected from the group consisting of F, Cl, Br, I, -CF_3, -OH, -OCH_3, -SH, -SCH_3, -CN, -NO_2, –NH_2, -$NHCH_3$, -$N(CH_3)_2$, -$C(O)CH_3$, -$C(O)OCH_3$, -$C(O)NH_2$, –$NHC(O)CH_3$, -SO_2NH_2, -SO_2NHCH_3, -$SO_2N(CH_3)_2$, and-$S(O)_pCH_3$;

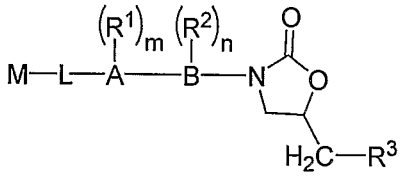
m, at each occurrence, independently is 0, 1, 2, 3, or 4;

n, at each occurrence, independently is 0, 1, 2, 3, or 4; and

p, at each occurrence, independently is 0, 1, or 2,

and wherein the compound does not have the formula corresponding to any of the structures listed in Table 1.

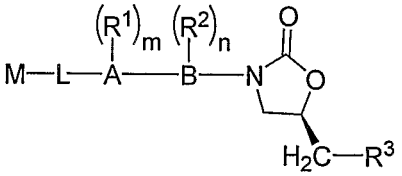
2. The compound according to claim 1, having the formula:



or a pharmaceutically acceptable salt, ester or prodrug thereof,

wherein A, B, L, M, R^1, R^2, R^3, m, and n are defined as described in claim 1.

3. The compound according to claim 1 or 2, having the formula:



or a pharmaceutically acceptable salt, ester or prodrug thereof,

wherein A, B, L, M, R^1, R^2, R^3, m, and n are defined as described in claim 1.

4. The compound according to any one of claims 1-3, wherein

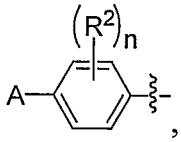
A is selected from the group consisting of phenyl and pyridyl;

B is selected from the group consisting of phenyl and pyridyl;

m is 0, 1, or 2; and

n is 0, 1, or 2.

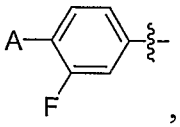
5. The compound according to any one of claims 1-4, wherein A-B is:



,

wherein A, R^2, and n are defined as described in claim 1.

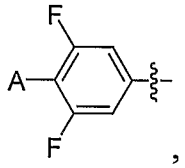
6. The compound according to claim 5, wherein A-B is:



,

wherein A is defined as described in claim 1.

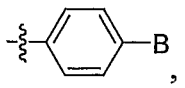
7. The compound according to claim 5, wherein A-B is:



,

wherein A is defined as described in claim 1.

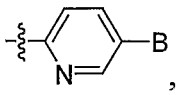
8. The compound according to any one of claims 1-7, wherein A-B is:



,

wherein B is defined as described in claim 1.

9. The compound according to any one of claims 1-7, wherein A-B is:



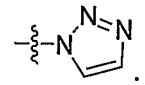
,

wherein B is defined as described in claim 1.

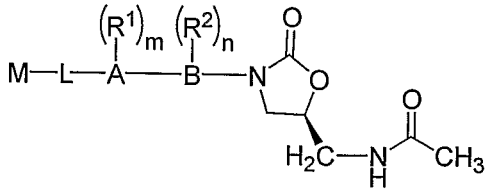
10. The compound according to any one of claims 1-9, wherein R^3 is $-NHC(O)R^4$.

11. The compound according to claim 10, wherein R^4 is $-CH_3$.

12. The compound according to any one of claims 1-9, wherein R^3 is:



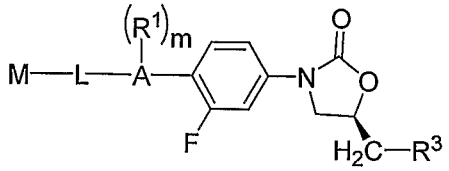
13. The compound according to claim 1 or 2, having the formula:



or a pharmaceutically acceptable salt, ester or prodrug thereof,

wherein A, B, L, M, R^1, R^2, m, and n are defined as described in claim 1.

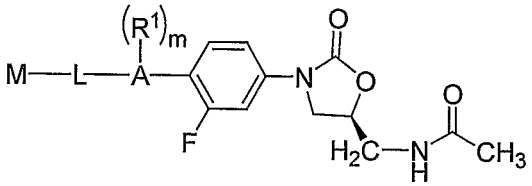
14. The compound according to claim 1 or 2, having the formula:



or a pharmaceutically acceptable salt, ester or prodrug thereof,

wherein A, L, M, R^1, R^3, and m are defined as described in claim 1.

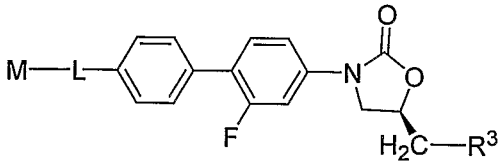
15. The compound according to claim 1 or 2, having the formula:



or a pharmaceutically acceptable salt, ester or prodrug thereof,

wherein A, L, M, R^1, and m are defined as described in claim 1.

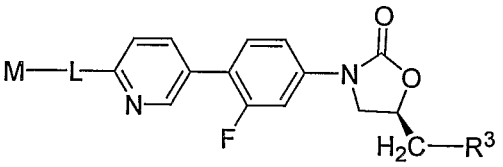
16. The compound according to claim 1 or 2, having the formula:



or a pharmaceutically acceptable salt, ester or prodrug thereof,

wherein L, M, and R^3 are defined as described in claim 1.

17. The compound according to claim 1 or 2, having the formula:

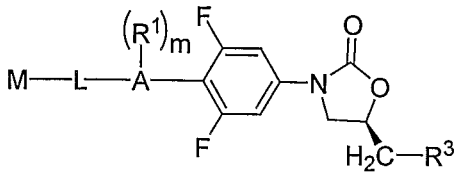


or a pharmaceutically acceptable salt, ester or prodrug thereof,

wherein L, M, and R^3 are defined as described in claim 1.

18. The compound according to claim 16 or 17, wherein R^3 is $-NHC(O)CH_3$.

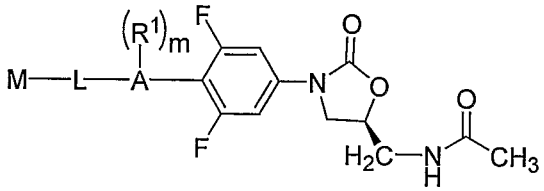
19. The compound according to claim 1 or 2, having the formula:



or a pharmaceutically acceptable salt, ester or prodrug thereof,

wherein A, L, M, R^1, R^3, and m are defined as described in claim 1.

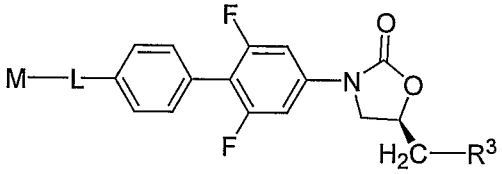
20. The compound according to claim 1 or 2, having the formula:



or a pharmaceutically acceptable salt, ester or prodrug thereof,

wherein A, L, M, R^1, and m are defined as described in claim 1.

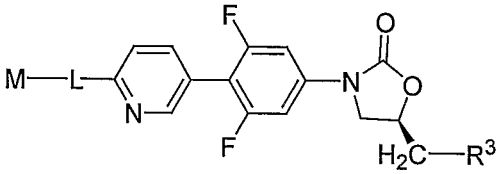
21. The compound according to claim 1 or 2, having the formula:



or a pharmaceutically acceptable salt, ester or prodrug thereof,

wherein L, M, and R^3 are defined as described in claim 1.

22. The compound according to claim 1 or 2, having the formula:



or a pharmaceutically acceptable salt, ester or prodrug thereof,

wherein L, M, and R^3 are defined as described in claim 1.

23. The compound according to claim 21 or 22, wherein R^3 is $-NHC(O)CH_3$.

24. The compound according to any one of claims 1-23, wherein

M-L is M-L^1, and

L^1 is C_{1-6} alkyl.

25. The compound according to claim 24, wherein M-L^1 is:

M–CH_2-.

26. The compound according to any one of claims 1-23, wherein

M-L is M-L^1-X-L^2, and

X is -NR^4-.

27. The compound according to claim 26, wherein X is –NH-.

28. The compound according to claim 26, wherein X is:

29. The compound according to claim 26, wherein X is –N(O)-.

30. The compound according to claim 26, wherein X is –N(OR^4)-.

31. The compound according to claim 30, wherein R^4 is H.

32. The compound according to claim 30, wherein R^4 is C_{1-6} alkyl.

33. The compound according to claim 26, wherein

L^1 is C_{1-6} alkyl, and

L^2 is C_{1-6} alkyl.

34. The compound according to claim 33, wherein

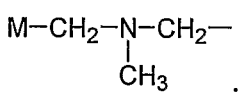
L^1 is –CH_2-, and

L^2 is -CH_2-.

35. The compound according to claim 26, wherein M-L is:

M-CH_2-NH-CH_2-.

36. The compound according to claim 26, wherein M-L is:



37. The compound according to any one of claims 1-23, wherein

M-L is M-S-L^1-NR^4- L^2,

L^1 is C_{1-6} alkyl, and

L^2 is C_{1-6} alkyl.

38. The compound according to claim 37, wherein M-L is:

M-S–CH_2CH_2-NH-CH_2-.

39. The compound according to any one of claims 1-38, wherein M is selected from the group consisting of:

a) phenyl, b) pyridyl, c) pyrazinyl, d) pyrimidinyl, e) pyridazinyl, f) oxiranyl, g) aziridinyl, h) furanyl, i) thiophenyl, j) pyrrolyl, k) oxazolyl, l) isoxazolyl, m) imidazolyl, n) pyrazolyl, o) isothiazolyl, p) thiazolyl, q) triazolyl, r) tetrazolyl, s) indolyl, t) purinyl, u) benzofuranyl, v) benzoxazolyl, w) benzisoxazolyl, x) quinolinyl, y) isoquinolinyl, z) quinoxalinyl, aa) quinazolinyl, bb) cinnolinyl, cc) cyclopropyl, dd) cyclobutyl, ee) cyclopentyl, ff) cyclohexyl, gg) cycloheptyl, hh) oxetanyl, ii) tetrahydrofuranyl, jj) tetrahydropyranyl, kk) azetidinyl, ll) pyrrolidinyl, mm) piperidinyl, nn) thietanyl, oo) tetrahydrothiophenyl, pp) tetrahydrothiopyranyl, qq) piperazinyl, rr) quinuclidinyl, ss) 1-azabicyclo[2.2.1]hyeptanyl, tt) morpholinyl, uu) thiomorpholinyl, vv) thiooxomorpholinyl, ww) thiodioxomorpholinyl, and xx) benzothiophenyl

wherein any of a) – xx) optionally is substituted with one or more R^5 groups.

40. The compound according to claim 39, wherein M is 4-isoxazolyl.

41. The compound according to claim 39, wherein M is [1,2,3]triazol-1-yl.

42. The compound according to claim 39, wherein M is 3H-[1,2,3]triazol-4-yl.

43. The compound according to claim 39, wherein M is 1H-tetrazol-5-yl.

44. The compound according to claim 39, wherein M is piperidin-1-yl.

45. The compound according to claim 39, wherein M is pyrolidin-1-yl.

46. A compound having the structure corresponding to any one of the structures listed in Table 2, or a pharmaceutically acceptable salt, ester, or prodrug thereof.

47. A pharmaceutical composition comprising one or more compounds according to any one of claims 1-46 and a pharmaceutically acceptable carrier.

48. A method of treating a microbial infection in a mammal comprising the step of administering to the mammal an effective amount of one or more compounds according to any one of claims 1-46.

49. A method of treating a fungal infection in a mammal comprising the step of administering to the mammal an effective amount of one or more compounds according to any one of claims 1-46.

50. A method of treating a parasitic disease in a mammal comprising the step of administering to the mammal an effective amount of one or more compounds according to any one of claims 1-46.

51. A method of treating a proliferative disease in a mammal comprising the step of administering to the mammal an effective amount of one or more compounds according to any one of claims 1-46.

52. A method of treating a viral infection in a mammal comprising the step of administering to the mammal an effective amount of one or more compounds according to any one of claims 1-46.

53. A method of treating an inflammatory disease in a mammal comprising the step of administering to the mammal an effective amount of one or more compounds according to any one of claims 1-46.

54. A method of treating a gastrointestinal motility disorder in a mammal comprising the step of administering to the mammal an effective amount of one or more compounds according to any one of claims 1-46.

55. A method of treating a disorder in a mammal comprising the step of administering to the mammal an effective amount of one or more compounds according to any one of claims 1-46 thereby to ameliorate a symptom of the disorder, wherein the disorder is selected from the group consisting of:

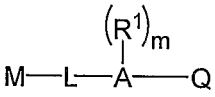
a skin infection, nosocomial pneumonia, post-viral pneumonia, an abdominal infection, a urinary tract infection, bacteremia, septicemia, endocarditis, an atrio-ventricular shunt infection, a vascular access infection, meningitis, surgical prophylaxis, a peritoneal infection, a bone infection, a joint infection, a methicillin-resistant *Staphylococcus aureus* infection, a vancomycin-resistant *Enterococci* infection, a linezolid-resistant organism infection, and tuberculosis.

56. The method according to any one of claims 48-55, wherein the compound is administered orally, parentally, or topically.

57. A medical device containing one or more compounds according to any one of claims 1-46.

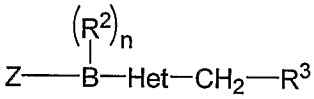
58. The medical device according to claim 57, wherein the device is a stent.

59. A process for preparing a compound according to claim 1, comprising the step of reacting a compound of formula (I):



(I)

with a compound of formula (II):



(II)

in a solvent in the presence of a base and a palladium catalyst, wherein

Q is a boronate having the formula $-BY_2$, wherein

Y, at each occurrence, independently is selected from the group consisting of:

a) –OH, and b) $-O-C_{1-4}$ alkyl,

alternatively, two Y groups taken together are selected from the group consisting of:

a) $-OC(R^4)(R^4)C(R^4)(R^4)O-$, and b) $-OC(R^4)(R^4)CH_2C(R^4)(R^4)O-$,

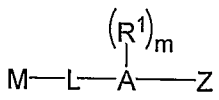
alternatively, two Y groups taken together with the boron to which they are bound comprise a BF_3 alkali metal salt;

Z is selected from the group consisting of:

a) I, b) Br, c) Cl, and d) R^4OSO_3-; and

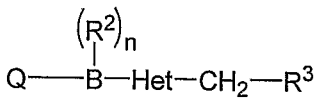
A, B, L, M, R^1, R^2, R^3, R^4, m, and n are defined as described in claim 1.

60. A process for preparing a compound according to claim 1, comprising the step of reacting a compound of formula (I):



(I)

with a compound of formula (II):



(II)

in a solvent in the presence of a base and a palladium catalyst, wherein

Q is a boronate having the formula $-BY_2$, wherein

Y, at each occurrence, independently is selected from the group consisting of:

a) –OH, and b) $-O-C_{1-4}$ alkyl,

alternatively, two Y groups taken together are selected from the group consisting of:

a) $-OC(R^4)(R^4)C(R^4)(R^4)O-$, and b) $-OC(R^4)(R^4)CH_2C(R^4)(R^4)O-$,

alternatively, two Y groups taken together with the boron to which they are bound comprise a BF_3 alkali metal salt;

Z is selected from the group consisting of:

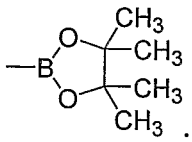
a) I, b) Br, c) Cl, and d) R^4OSO_3-; and

A, B, L, M, R^1, R^2, R^3, R^4, m, and n are defined as described in claim 1.

61. The process according to claim 59 or 60, wherein Z is I.

62. The process according to any one of claims 59-61, wherein Q is $-BF_2 \cdot KF$.

63. The process according to any one of claims 59-61, wherein Q is:



.

64. The process according to any one of claims 59-63, wherein the base is selected from the group consisting of an alkali metal hydroxide, an alkali metal carbonate, an alkali metal fluoride, a trialkyl amine, and mixtures thereof.

65. The process according to claim 64, wherein the base is selected from the group consisting of potassium carbonate, sodium carbonate, potassium fluoride, triethylamine, diisopropylethylamine, and mixtures thereof.

66. The process according to claim 64, wherein the ratio of equivalents of base to equivalents of compound (I) is about 3:1.

67. The process according to any one of claims 59-66, wherein the palladium catalyst is a ligand coordinated palladium (0) catalyst.

68. The process according to claim 67, wherein the palladium catalyst is a tetrakis(trialkylphosphine) palladium (0) or a tetrakis(triarylphosphine) palladium (0) catalyst.

69. The process according to claim 68, wherein the palladium catalyst is tetrakis(triphenylphosphine) palladium (0).

70. The process according to claim 67, wherein the ratio of the equivalents of palladium catalyst to the equivalents of compound (I) is about 1:20.

71. The process according to any one of claims 59-70, wherein the solvent comprises an aqueous solvent.

72. The process according to any one of claims 59-70, wherein the solvent comprises a mixture of water and an organic solvent, wherein the organic solvent is selected from the group consisting of:

methanol, ethanol, propanol, isopropanol, butanol, isobutanol, secondary butanol, tertiary butanol, benzene, toluene, tetrahydrofuran, dimethylformamide, 1,2-diethyl ether, dimethoxyethane, diisopropyl ether, methyltertiarybutyl ether, methoxymethyl ether, 2-methoxyethyl ether, 1,4-dioxane, 1,3-dioxolane, and mixtures thereof.

73. The process according to claim 72, wherein the solvent comprises a mixture of water, toluene, and ethanol.

74. The process according to claim 73 wherein the solvent comprises a mixture of water, toluene, and ethanol in a ratio of about 1:3:1 by volume.

75. The process according to any one of claims 59-74, wherein the process is carried out at a temperature between about 20 °C and about 100 °C.

76. The process according to any one of claims 59-74, wherein the process is carried out at the reflux temperature of the solvent.