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(54) Title: TRIAZOLE COMPOUNDS AND METHODS OF MAKING AND USING THE SAME

(57) Abstract: The present invention provides triazole macrocyclic compounds useful as therapeutic agents. More particularly, these compounds are useful as anti-infective, antiproliferative, anti-inflammatory, and prokinetic agents.

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TRIAZOLE COMPOUNDS AND METHODS OF MAKING AND USING THE SAME

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
5 relates to a family of triazole macrocyclic compounds that are useful as such 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
10 with the use of such therapeutic agents. However, such beliefs have been shaken because 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 staphylococci,
15 penicillin-resistant streptococci, and vancomycin-resistant enterococci have developed. These resistant bacteria can cause serious and even fatal results for patients infected with such resistant bacteria. Bacteria that are resistant to macrolide antibiotics have emerged. 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
20 *Staphylococcus aureus*," *J. Clin. Invest.*, vol. 111, no. 9, pp. 1265-1273 (2003); and Gold, H.S. and Moellering, R.C., Jr., "Antimicrobial-Drug Resistance," *N. Engl. J. Med.*, vol. 335, pp. 1445-53 (1996).

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

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, linezolid, which is sold under the
30 trade name Zyvox[®]. See, R.C. Moellering, Jr., "Linezolid: The First Oxazolidinone

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Antimicrobial," *Annals of Internal Medicine*, vol. 138, no. 2, pp. 135-142 (2003).

Linezolid was approved for use as an anti-bacterial agent active against Gram-positive organisms. However, linezolid-resistant strains of organisms are already being reported. See, Tsiodras *et al.*, *Lancet*, vol. 358, p. 207 (2001); Gonzales *et al.*, *Lancet*, vol 357, p.

5 1179 (2001); Zurenko *et al.*, *Proceedings Of The 39th Annual Interscience Conference On Antibacterial Agents And Chemotherapy (ICAAC)*, San Francisco, CA, USA (September 26-29, 1999).

Another class of antibiotics is the macrolides, so named for their characteristic 14-
to 16-membered ring. The macrolides also often have one or more 6-membered sugar-
10 derived rings attached to the main macrolide ring. The first macrolide antibiotic to be developed was erythromycin, which was isolated from a soil sample from the Philippines in 1952. Even though erythromycin has been one of the most widely prescribed antibiotics, its disadvantages are relatively low bioavailability, gastrointestinal side effects, and a limited spectrum of activity. Another macrolide is the compound, azithromycin,
15 which is an azolide derivative of erythromycin incorporating a methyl-substituted nitrogen in the macrolide ring. Azithromycin is sold under the trade name Zithromax[®]. A more recently introduced macrolide is telithromycin, which is sold under the trade name Ketek[®]. Telithromycin is a semisynthetic macrolide in which a hydroxyl group of the macrolide ring has been oxidized to a ketone group. See Yong-Ji Wu, Highlights of Semi-synthetic
20 Developments from Erythromycin A, *Current Pharm. Design*, vol. 6, pp. 181-223 (2000), and Yong-Ji Wu and Wei-uo Su, Recent Developments on Ketolides and Macrolides, *Curr. Med. Chem.*, vol. 8, no. 14, pp. 1727-1758 (2001).

In the search for new therapeutic agents, researchers have tried combining or linking various portions of antibiotic molecules to create multifunctional or hybrid
25 compounds. Other researches have tried making macrolide derivatives by adding further substituents to the large macrolide ring or associated sugar rings. However, this approach for making macrolide derivatives has also met with limited success.

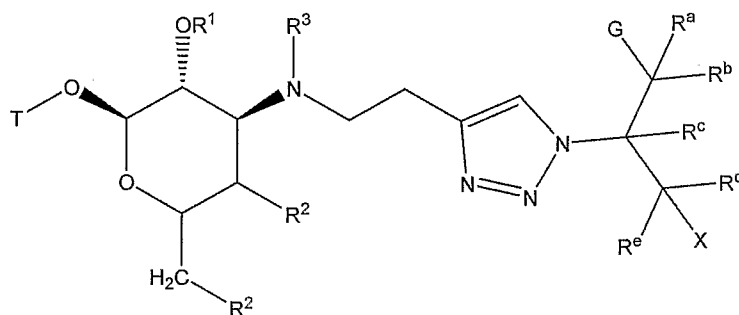
Notwithstanding the foregoing, there is an ongoing need for new anti-infective and anti-proliferative agents. Furthermore, because many anti-infective and anti-proliferative
30 agents have utility as anti-inflammatory agents and prokinetic agents, there is also an ongoing need for new compounds useful as anti-inflammatory and prokinetic agents. The present invention provides compounds that meet these needs.

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SUMMARY OF THE INVENTION

The invention provides compounds useful as anti-infective agents and/or anti-proliferative agents, for example, anti-biotic agents, anti-microbial agents, anti-bacterial agents, anti-fungal agents, anti-parasitic agents, anti-viral agents, and chemotherapeutic agents. The present invention also provides compounds useful as anti-inflammatory agents, and/or prokinetic (gastrointestinal modulatory) agents. The present invention also provides pharmaceutically acceptable salts, esters, *N*-oxides, or prodrugs of these compounds.

The present invention provides compounds having the structure:



or a stereoisomer, pharmaceutically acceptable salt, ester, *N*-oxide, or prodrug thereof. In the formula, variables G, T, X, R¹, R², R³, Rᵃ, Rᵇ, Rᶜ, Rᵈ and Rᵉ can be selected from the respective groups of chemical moieties later defined in the detailed description.

In addition, the invention provides methods of synthesizing the foregoing compounds. Following synthesis, a therapeutically effective amount of one or more of the compounds can be formulated with a pharmaceutically acceptable carrier for administration to a mammal, particularly humans, for use as an anti-cancer, anti-biotic, anti-microbial, anti-bacterial, anti-fungal, anti-parasitic or anti-viral agent, or to treat a proliferative disease, an inflammatory disease or a gastrointestinal motility disorder, or to suppress disease states or conditions caused or mediated by nonsense or missense mutations. Accordingly, the compounds or the formulations can 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 can be more fully understood by reference to the following detailed description and claims.

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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 can be used without limitation, for example, as anti-cancer, anti-microbial, anti-bacterial, anti-fungal, anti-
5 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
10 constipation. Further, the compounds can be used to treat or prevent a disease state in a mammal caused or mediated by a nonsense or missense mutation.

The compounds described herein can have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom can be isolated in optically active or racemic forms. It is well known in the art how to prepare optically
15 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 can be isolated as a mixture of isomers or as
20 separate isomeric forms. All chiral, diastereomeric, racemic, and geometric isomeric forms of a structure are intended, unless 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
25 invention.

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
30 stable compound. When a substituent is keto (i.e., =O), then 2 hydrogens on the atom are

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replaced. 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
5 different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and C-14.

When any variable (e.g., R²) 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 one
10 or more R² moieties, then the group can optionally be substituted with one, two, three, four, five, or more R² moieties, and R² at each occurrence is selected independently from the definition of R². Also, combinations of substituents and/or variables are permissible, but only if such combinations result in stable compounds.

A chemical structure showing a dotted line representation for a chemical bond
15 indicates that the bond is optionally present. For example, a dotted line drawn next to a solid single bond indicates that the bond can be either a single bond or a double bond.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent can be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the
20 compound of a given formula, then such substituent can 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.

In cases wherein there are nitrogens in the compounds of the present invention, these can be converted to N-oxides by treatment with an oxidizing agent (e.g., MCPBA
25 and/or hydrogen peroxides) to afford other compounds of the present invention. Thus, all shown and claimed nitrogens are considered to cover both the shown nitrogen and its N-oxide (N→O) derivative.

As used herein, the term "anomeric carbon" means the acetal carbon of a glycoside.

As used herein, the term "glycoside" is a cyclic acetal.

30 As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. C₁₋₆ alkyl is intended to include C₁, C₂, C₃, C₄, C₅, and C₆ alkyl groups. C₁₋₈ alkyl is intended

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to include C₁, C₂, C₃, C₄, C₅, C₆, C₇, and C₈ 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, n-hexyl, n-heptyl, and n-octyl.

As used herein, "alkenyl" is intended to include hydrocarbon chains of either
5 straight or branched configuration and one or more unsaturated carbon-carbon bonds that can occur in any stable point along the chain, such as ethenyl and propenyl. C₂₋₆ alkenyl is intended to include C₂, C₃, C₄, C₅, and C₆ alkenyl groups. C₂₋₈ alkenyl is intended to include C₂, C₃, C₄, C₅, C₆, C₇, and C₈ alkenyl groups.

As used herein, "alkynyl" is intended to include hydrocarbon chains of either
10 straight or branched configuration and one or more triple carbon-carbon bonds that can occur in any stable point along the chain, such as ethynyl and propynyl. C₂₋₆ alkynyl is intended to include C₂, C₃, C₄, C₅, and C₆ alkynyl groups. C₂₋₈ alkynyl is intended to include C₂, C₃, C₄, C₅, C₆, C₇, and C₈ alkynyl groups.

Furthermore, "alkyl", "alkenyl", and "alkynyl" are intended to include moieties
15 which are diradicals, i.e., having two points of attachment, an example of which in the present invention is when D is selected from these chemical groups. A nonlimiting example of such an alkyl moiety that is a diradical is -CH₂CH₂-, i.e., a C₂ alkyl group that is covalently bonded via each terminal carbon atom to the remainder of the molecule.

As used herein, the terms used to describe various carbon-containing moieties,
20 including, for example, "alkyl," "alkenyl," "alkynyl," "phenyl," and any variations thereof, are intended to include univalent, bivalent, or multivalent species. For example, "C₁₋₆ alkyl-R³" is intended to represent a univalent C₁₋₆ alkyl group substituted with a R³ group, and "O-C₁₋₆ alkyl-R³" is intended to represent a bivalent C₁₋₆ alkyl group, i.e., an "alkylene" group, substituted with an oxygen atom and a R³ group.

As used herein, "cycloalkyl" is intended to include saturated ring groups, such as
25 cyclopropyl, cyclobutyl, or cyclopentyl. C₃₋₈ cycloalkyl is intended to include C₃, C₄, C₅, C₆, C₇, and C₈ cycloalkyl groups.

As used herein, "halo" or "halogen" refers to fluoro, chloro, bromo, and iodo
substituents.

"Counterion" is used to represent a small, negatively charged species such as
30 chloride, bromide, hydroxide, acetate, and sulfate.

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As used herein, "haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example $-C_vF_w$ where $v = 1$ to 3 and $w = 1$ to $(2v+1)$). Examples of haloalkyl include, but are not limited to, trifluoromethyl,

5 trichloromethyl, pentafluoroethyl, and pentachloroethyl.

As used herein, "alkoxy" refers to an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. C_{1-6} alkoxy, is intended to include C_1 , C_2 , C_3 , C_4 , C_5 , and C_6 alkoxy groups. C_{1-8} alkoxy, is intended to include C_1 , C_2 , C_3 , C_4 , C_5 , C_6 , C_7 , and C_8 alkoxy groups. Examples of alkoxy include,

10 but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, n-pentoxo, s-pentoxo, n-heptoxo, and n-octoxo.

As used herein, "alkylthio" refers to an alkyl group as defined above with the indicated number of carbon atoms attached through an sulfur bridge. C_{1-6} alkylthio, is intended to include C_1 , C_2 , C_3 , C_4 , C_5 , and C_6 alkylthio groups. C_{1-8} alkylthio, is

15 intended to include C_1 , C_2 , C_3 , C_4 , C_5 , C_6 , C_7 , and C_8 alkylthio groups.

As used herein, "carbocycle" or "carbocyclic ring" is intended to mean, unless otherwise specified, any stable 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12-membered monocyclic, bicyclic or tricyclic ring, any of which can be saturated, unsaturated (including partially and fully unsaturated), or aromatic, recognizing that rings with certain numbers of

20 members cannot be bicyclic or tricyclic, e.g., a 3-membered ring can only be a monocyclic ring. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cycloheptenyl, cycloheptyl, cycloheptenyl, adamantyl, cyclooctyl, cyclooctenyl, cyclooctadienyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane, [2.2.2]bicyclooctane,

25 fluorenyl, phenyl, naphthyl, indanyl, adamantyl, and tetrahydronaphthyl. As shown above, bridged rings are also included in the definition of carbocycle (e.g., [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

30 recited for the ring can also be present on the bridge. Fused (e.g., naphthyl and tetrahydronaphthyl) and spiro rings are also included.

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As used herein, the term "heterocycle" means, unless otherwise stated, a stable 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12-membered monocyclic, bicyclic or tricyclic ring (recognizing that rings with certain numbers of members cannot be bicyclic or tricyclic, e.g., a 3-membered ring can only be a monocyclic ring), which is saturated, unsaturated (including partially and fully unsaturated), or aromatic, and consists of 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 nitrogen, oxygen, and sulfur, and including any bicyclic or tricyclic group in which any of the above-defined heterocyclic rings is fused to a second ring (e.g., a benzene ring). The nitrogen and sulfur heteroatoms can 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 can be substituted or unsubstituted (i.e., N or NR wherein R is H or another substituent, as defined). The heterocyclic ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. The heterocyclic rings described herein can be substituted on carbon or on a nitrogen atom if the resulting compound is stable. A nitrogen in the heterocycle can optionally be quaternized. 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 can 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, 7, 8, 9, 10, 11, or 12-membered monocyclic or bicyclic aromatic ring (recognizing that rings with certain numbers of members cannot be a bicyclic aromatic, e.g., a 5-membered ring can only be a monocyclic aromatic 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 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 can be (e.g., quinoline). The second ring can also be fused or

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bridged as defined above for heterocycles. The nitrogen atom can be substituted or unsubstituted (i.e., N or NR wherein R is H or another substituent, as defined). The nitrogen and sulfur heteroatoms can optionally be oxidized (i.e., N→O and S(O)_p, where p = 1 or 2). In certain compounds, the total number of S and O atoms in the aromatic
5 heterocycle is not more than 1.

Examples of heterocycles include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzoxazoliny, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazoliny, carbazolyl, 4*aH*-carbazolyl, carbolinyl, chromanyl,
10 chromenyl, cinnoliny, decahydroquinoliny, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazoliny, imidazolyl, 1*H*-indazolyl, indolenyl, indoliny, indoliziny, indolyl, 3*H*-indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindoliny, isoindolyl, isoquinoliny, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholiny, naphthyridiny,
15 octahydroisoquinoliny, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidiny, oxazolyl, oxindolyl, pyrimidinyl, phenanthridiny, phenanthroliny, phenaziny, phenothiaziny, phenoxathiny, phenoxaziny, phthalaziny, piperaziny, piperidiny, piperidonyl, 4-piperidonyl, piperonyl, pteridiny, puriny, pyranyl, pyraziny, pyrazolidiny, pyrazoliny, pyrazolyl, pyridaziny,
20 pyridooxazole, pyridoimidazole, pyridothiazole, pyridiny, pyridyl, pyrimidinyl, pyrrolidinyl, pyrroliny, 2*H*-pyrrolyl, pyrrolyl, quinazoliny, quinoliny, 4*H*-quinoliziny, quinoxaliny, quinuclidiny, tetrahydrofuranyl, tetrahydroisoquinoliny, tetrahydroquinoliny, tetrazolyl, 6*H*-1,2,5-thiadiaziny, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl,
25 thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triaziny, 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, 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
30 animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

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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, hydroiodide, hydroxymaleic, hydroxynaphthoic, isethionic, lactic, lactobionic, lauryl sulfonic, maleic, malic, mandelic, methane sulfonic, napsylic, nitric, oxalic, pamoic, pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicylic, stearic, subacetic, succinic, sulfamic, sulfanilic, sulfuric, tannic, tartaric, and toluene sulfonic.

The pharmaceutically acceptable salts of the present invention can be synthesized from the 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, Easton, PA, USA, p. 1445 (1990).

Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (e.g., solubility, bioavailability, manufacturing, etc.) the compounds of the present invention can 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

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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, it cleaves to form a free
5 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,
10 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.,
15 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 "therapeutically effective amount" refers to a compound, or a combination of compounds, of the present invention present in or on a recipient in an
20 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. The combination of compounds is preferably a synergistic combination. Synergy, as described, for example, by Chou and Talalay, *Adv. Enzyme Regul.* vol. 22, pp. 27-55 (1984), occurs when the effect of the compounds when administered in combination is
25 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.

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

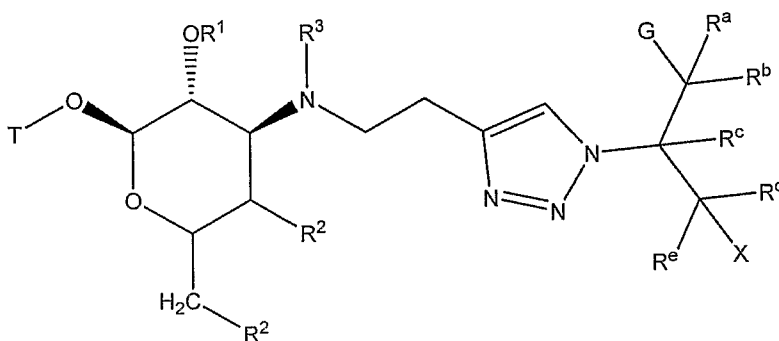
Throughout the description, where compositions are described as having, including, or comprising specific components, or where processes are described as having,

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including, or comprising specific process steps, it is contemplated that compositions of the present invention also consist essentially of, or consist of, the recited components, and that the processes of the present invention 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 can be conducted simultaneously.

2. Compounds of the Invention

In one aspect, the invention relates to a compound having the structure:



or a pharmaceutically acceptable salt, ester, *N*-oxide, or prodrug thereof, wherein

T is a 14- or 15-membered macrolide connected via a macrocyclic ring carbon atom;

X is selected from (a) H, (b) halogen, (c) a C₁₋₆ alkyl group, (d) a C₂₋₆ alkenyl group, (e) a C₂₋₆ alkynyl group, (f) -OH, (g) -OR⁵, (h) -NR⁴R⁴, (i) -C(O)R⁵, (j) -C(O)OR⁵, (k) -C(O)-NR⁴R⁴, (l) -C(S)R⁵, (m) -C(S)OR⁵, (n) -C(O)SR⁵, (o) -C(S)-NR⁴R⁴, (p) -N₃, (q) -CN, (r) -CF₃, (s) -CF₂H, (t) -CFH₂, (u) -SH, (v) -SR⁵, (w) -S(O)_pOH, (x) -S(O)_pOR⁵, (y) -S(O)_pNR⁴R⁴, (z) -S(O)_pC₁₋₆alkyl, (aa) -S(O)_paryl, (bb) a C₃₋₇ saturated, unsaturated, or aromatic carbocycle, and (cc) a 3-7 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur;

R^a and R^b independently are selected from: (a) H, (b) a C₁₋₆ alkyl group, (c) a C₂₋₆ alkenyl group, (d) a C₂₋₆ alkynyl group, (e) -OH, (f) -OR⁵, (g) -NR⁴R⁴, (h) -C(O)R⁵, (i) -C(O)OR⁵, (j) -C(O)-NR⁴R⁴, (k) -C(S)R⁵, (l) -C(S)OR⁵, (m) -C(O)SR⁵, (n) -C(S)-NR⁴R⁴, and (m) halogen, or alternatively R^a and R^b are taken together with the carbon to which they are attached to form (a) -C(O)-, (b) -C(S)-, (c) -C=NR⁴, (d) -C=NOR⁵;

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R^c is selected from: (a) H, (b) a C_{1-6} alkyl group, (c) a C_{2-6} alkenyl group, (d) a C_{2-6} alkynyl group, (e) $-OH$, (f) $-OR^5$, (g) $-NR^4R^4$, (f) $-C(O)R^5$, (g) $-C(O)OR^5$, (h) $-C(O)-NR^4R^4$, (i) $-C(S)R^5$, (j) $-C(S)OR^5$, (k) $-C(O)SR^5$, (l) $-C(S)-NR^4R^4$, and (m) halogen;

R^d and R^e independently are selected from: (a) H, (b) a C_{1-6} alkyl group, (c) a C_{2-6} alkenyl group, (d) a C_{2-6} alkynyl group, (e) $-OH$, (f) $-OR^5$, (g) $-NR^4R^4$, (f) $-C(O)R^5$, (g) $-C(O)OR^5$, (h) $-C(O)-NR^4R^4$, (i) $-C(S)R^5$, (j) $-C(S)OR^5$, (k) $-C(O)SR^5$, (l) $-C(S)-NR^4R^4$, and (m) halogen, or alternatively R^d and R^e are taken together with the carbon to which they are attached to form (a) $-C(O)-$, (b) $-C(S)-$, (c) $-C=NR^4$, or (d) $-C=NR^5$;

R^1 and R^3 independently are selected from: (a) H, (b) a C_{1-6} alkyl group, (c) a C_{2-6} alkenyl group, (d) a C_{2-6} alkynyl group, (e) $-C(O)R^5$, (f) $-C(O)OR^5$, (g) $-C(O)-NR^4R^4$, (h) $-C(S)R^5$, (i) $-C(S)OR^5$, (j) $-C(O)SR^5$, and (k) $-C(S)-NR^4R^4$;

R^2 is hydrogen or $-OR^{12}$;

G is selected from: (a) $-B'$ and (b) $-B'-Z-B''$, wherein each B' and B'' is independently selected from (aa) an aryl group, (bb) a heteroaryl group, (cc) a biaryl group, (dd) a fused bicyclic or tricyclic saturated, unsaturated or aromatic ring system optionally containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur, (ee) a 3-10 membered saturated or unsaturated heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur, and (ff) a 3-10 membered saturated, or unsaturated carbocycle, wherein each (aa)-(ff) optionally is substituted with one or more R^{11} or R^{11a} groups;

Z is selected from (aa) a single bond, (bb) a C_{1-6} alkyl group, (cc) a C_{2-6} alkenyl group, (dd) a C_{2-6} alkynyl group, (ee) $-C(O)-$, (ff) $-C(O)O-$, (gg) $-C(O)NR^4-$, (hh) $-C(=NR^4)-$, (ii) $-C(=NR^4)O-$, (jj) $-C(=NR^4)NR^4-$, (kk) $-S(O)_p-$, (ll) $-OC(O)-$, (mm) $-C(S)-$, (nn) $-C(S)NR^4-$, (oo) $-C(NR^4)S-$, (pp) $-C(O)S-$, (qq) $-O-$, (rr) $-NR^4-$, (ss) $-NR^4C(O)-$, (tt) $-OC(NR^4)-$, (uu) $-NC(NR^4)-$, (vv) $-C(S)O-$, (ww) $-SC(O)-$, (xx) $-OC(S)-$ and (yy) $-S(O)_p-$;

R^4 , at each occurrence, independently is selected from: (a) H, (b) a C_{1-6} alkyl group, (c) a C_{2-6} alkenyl group, (d) a C_{2-6} alkynyl group, (e) a C_{6-10} saturated, unsaturated, or aromatic carbocycle, (f) a 3-12 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from 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) $-C(O)-$

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C₆₋₁₀ saturated, unsaturated, or aromatic carbocycle, (k) -C(O)-3-12 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur, (l) -C(O)O-C₁₋₆ alkyl, (m) -C(O)O-C₂₋₆ alkenyl, (n) -C(O)O-C₂₋₆ alkynyl, (o) -C(O)O-C₆₋₁₀ saturated, unsaturated, or aromatic carbocycle, (p) -C(O)O-3-12 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur, and q) -C(O)NR⁶R⁶,
 5 wherein any of (b)-(p) optionally is substituted with one or more R⁵ groups,

alternatively, NR⁴R⁴ forms a 3-7 membered saturated, unsaturated or aromatic ring including the nitrogen atom to which the R⁴ groups are bonded, wherein said ring is
 10 optionally substituted at a position other than the nitrogen atom to which the R⁴ groups are bonded, with one or more moieties selected from O, S(O)_p, N, and NR⁸;

R⁵ is selected from: (a) R⁷, (b) a C₁₋₈ alkyl group, (c) a C₂₋₈ alkenyl group, (d) a C₂₋₈ alkynyl group, (e) a C₃₋₁₂ saturated, unsaturated, or aromatic carbocycle, and (f) a 3-12 membered saturated, unsaturated, or aromatic heterocycle containing one or more
 15 heteroatoms selected from nitrogen, oxygen, and sulfur, or two R⁵ groups, when present on the same carbon atom can be taken together with the carbon atom to which they are attached to form a spiro 3-6 membered carbocyclic ring or heterocyclic ring containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur; wherein any of (b)-(f) immediately above optionally is substituted with one or more R⁷ groups;

20 R⁶, at each occurrence, independently is selected from: (a) H, (b) a C₁₋₆ alkyl group, (c) a C₂₋₆ alkenyl group, (d) a C₂₋₆ alkynyl group, (e) a C₃₋₁₀ saturated, unsaturated, or aromatic carbocycle, and (f) a 3-10 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur, wherein any of (b)-(f) optionally is substituted with one or more moieties selected
 25 from: (aa) a carbonyl group, (bb) a formyl group, (cc) F, (dd) Cl, (ee) Br, (ff) I, (gg) CN, (hh) NO₂, (ii) -OR⁸, (jj) -S(O)_pR⁸, (kk) -C(O)R⁸, (ll) -C(O)OR⁸, (mm) -OC(O)R⁸, (nn) -C(O)NR⁸R⁸, (oo) -OC(O)NR⁸R⁸, (pp) -C(=NR⁸)R⁸, (qq) -C(R⁸)(R⁸)OR⁸, (rr) -C(R⁸)₂OC(O)R⁸, (ss) -C(R⁸)(OR⁸)(CH₂)_tNR⁸R⁸, (tt) -NR⁸R⁸, (uu) -NR⁸OR⁸, (vv) -NR⁸C(O)R⁸, (ww) -NR⁸C(O)OR⁸, (xx) -NR⁸C(O)NR⁸R⁸, (yy) -NR⁸S(O)_rR⁸, (zz) -C(OR⁸)(OR⁸)R⁸, (ab) -C(R⁸)₂NR⁸R⁸, (ac) =NR⁸, (ad) -C(S)NR⁸R⁸, (ae) -NR⁸C(S)R⁸, (af) -OC(S)NR⁸R⁸, (ag) -NR⁸C(S)OR⁸, (ah) -NR⁸C(S)NR⁸R⁸, (ai) -SC(O)R⁸, (aj) a C₁₋₈ alkyl group, (ak) a C₂₋₈ alkenyl group, (al) a C₂₋₈ alkynyl group, (am) a C₁₋₈ alkoxy group, (an) a

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C₁₋₈ alkylthio group, (ao) a C₁₋₈ acyl group, (ap) -CF₃, (aq) -SCF₃, (ar) a C₃₋₁₀ saturated, unsaturated, or aromatic carbocycle, and (as) a 3-10 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur, alternatively, NR⁶R⁶ forms a 3-10 membered saturated, unsaturated or aromatic ring including the nitrogen atom to which the R⁶ groups are attached wherein said ring is optionally substituted at a position other than the nitrogen atom to which the R⁶ groups are bonded, with one or more moieties selected from O, S(O)_p, N, and NR⁸; alternatively, CR⁶R⁶ forms a carbonyl group;

R⁷, at each occurrence, is selected from: (a) H, (b) =O, (c) F, (d) Cl, (e) Br, (f) I, (g) -CF₃, (h) -CN, (i) -N₃, (j) -NO₂, (k) -NR⁶(CR⁶R⁶)_tR⁹, (l) -OR⁹, (m) -S(O)_pC(R⁶R⁶)_tR⁹, (n) -C(O)(CR⁶R⁶)_tR⁹, (o) -OC(O)(CR⁶R⁶)_tR⁹, (p) -SC(O)(CR⁶R⁶)_tR⁹, (q) -C(O)O(CR⁶R⁶)_tR⁹, (r) -NR⁶C(O)(CR⁶R⁶)_tR⁹, (s) -C(O)NR⁶(CR⁶R⁶)_tR⁹, (t) -C(=NR⁶)(CR⁶R⁶)_tR⁹, (u) -C(=NNR⁶R⁶)(CR⁶R⁶)_tR⁹, (v) -C(=NNR⁶C(O)R⁶)(CR⁶R⁶)_tR⁹, (w) -C(=NOR⁹)(CR⁶R⁶)_tR⁹, (x) -NR⁶C(O)O(CR⁶R⁶)_tR⁹, (y) -OC(O)NR⁶(CR⁶R⁶)_tR⁹, (z) -NR⁶C(O)NR⁶(CR⁶R⁶)_tR⁹, (aa) -NR⁶S(O)_p(CR⁶R⁶)_tR⁹, (bb) -S(O)_pNR⁶(CR⁶R⁶)_tR⁹, (cc) -NR⁶S(O)_pNR⁶(CR⁶R⁶)_tR⁹, (dd) -NR⁶R⁶, (ee) -NR⁶(CR⁶R⁶), (ff) -OH, (gg) -NR⁶R⁶, (hh) -OCH₃, (ii) -S(O)_pR⁶, (jj) -NC(O)R⁶, (kk) a C₁₋₆ alkyl group, (ll) a C₂₋₆ alkenyl group, (mm) a C₂₋₆ alkynyl group, (nn) -C₃₋₁₀ saturated, unsaturated, or aromatic carbocycle, and (oo) 3-10 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur, wherein any of (kk)-(oo) optionally is substituted with one or more R⁹ groups; alternatively, two R⁷ groups can form -O(CH₂)_uO-;

R⁸ is selected from: (a) R⁵, (b) H, (c) a C₁₋₆ alkyl group, (d) a C₂₋₆ alkenyl group, (e) a C₂₋₆ alkynyl group, (f) a C₃₋₁₀ saturated, unsaturated, or aromatic carbocycle, (g) a 3-10 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur, (h) -C(O)-C₁₋₆ alkyl, (i) -C(O)-C₁₋₆ alkenyl, (j) -C(O)-C₁₋₆ alkynyl, (k) -C(O)-C₃₋₁₀ saturated, unsaturated, or aromatic carbocycle, and (l) -C(O)-3-10 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur, wherein any of (c)-(k) optionally is substituted with one or more moieties selected from: (aa) H, (bb) F, (cc) Cl, (dd) Br, (ee) I, (ff) CN, (gg) NO₂, (hh) OH, (ii) NH₂, (jj) NH(C₁₋₆ alkyl),

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(kk) $N(C_{1-6} \text{ alkyl})_2$, (ll) a C_{1-6} alkoxy group, (mm) an aryl group, (nn) a substituted aryl group, (oo) a heteroaryl group, (pp) a substituted heteroaryl group, and qq) a C_{1-6} alkyl group optionally substituted with one or more moieties selected from an aryl group, a substituted aryl group, a heteroaryl group, a substituted heteroaryl group, F, Cl, Br, I, CN, NO₂, CF₃, SCF₃, and OH;

R^9 , at each occurrence, independently is selected from: (a) R^{10} , (b) a C_{1-6} alkyl group, (c) a C_{2-6} alkenyl group, (d) a C_{2-6} alkynyl group, (e) a C_{3-10} saturated, unsaturated, or aromatic carbocycle, and (f) a 3-10 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur, wherein any of (b)–(f) optionally is substituted with one or more R^{10} groups;

R^{10} , at each occurrence, independently is selected from: (a) H, (b) =O, (c) F, (d) Cl, (e) Br, (f) I, (g) –CF₃, (h) –CN, (i) –NO₂, (j) –NR⁶R⁶, (k) –OR⁶, (l) –S(O)_pR⁶, (m) –C(O)R⁶, (n) –C(O)OR⁶, (o) –OC(O)R⁶, (p) NR⁶C(O)R⁶, (q) –C(O)NR⁶R⁶, (r) –C(=NR⁶)R⁶, (s) –NR⁶C(O)NR⁶R⁶, (t) –NR⁶S(O)_pR⁶, (u) –S(O)_pNR⁶R⁶, (v) –NR⁶S(O)_pNR⁶R⁶, (w) a C_{1-6} alkyl group, (x) a C_{2-6} alkenyl group, (y) a C_{2-6} alkynyl group, (z) a C_{3-10} saturated, unsaturated, or aromatic carbocycle, and (aa) a 3-10 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur, wherein any of (w)–(aa) optionally is substituted with one or more moieties selected from R^6 , F, Cl, Br, I, CN, NO₂, –OR⁶, –NH₂, –NH(C_{1-6} alkyl), –N(C_{1-6} alkyl)₂, a C_{1-6} alkoxy group, a C_{1-6} alkylthio group, and a C_{1-6} acyl group;

R^{11} and R^{11a} each occurrence, independently is selected from: (a) a carbonyl group, (b) a formyl group, (c) F, (d) Cl, (e) Br, (f) I, (g) CN, (h) NO₂, (i) OR⁸, (j) –S(O)_pR⁸, (k) –C(O)R⁸, (l) –C(O)OR⁸, (m) –OC(O)R⁸, (n) –C(O)NR⁸R⁸, (o) –OC(O)NR⁸R⁸, (p) –C(=NR⁸)R⁸, (q) –C(R⁸)(R⁸)OR⁸, (r) –C(R⁸)₂OC(O)R⁸, (s) –C(R⁸)(OR⁸)(CH₂)_rNR⁸R⁸, (t) –NR⁸R⁸, (u) –NR⁸OR⁸, (v) –NR⁸C(O)R⁸, (w) –NR⁸C(O)OR⁸, (x) –NR⁸C(O)NR⁸R⁸, (y) –NR⁸S(O)_pR⁸, (z) –C(OR⁸)(OR⁸)R⁸, (aa) –C(R⁸)₂NR⁸R⁸, (bb) =NR⁸, (cc) –C(S)NR⁸R⁸, (dd) –NR⁸C(S)R⁸, (ee) –OC(S)NR⁸R⁸, (ff) –NR⁸C(S)OR⁸, (gg) –NR⁸C(S)NR⁸R⁸, (hh) –SC(O)R⁸, (ii) a C_{1-8} alkyl group, (jj) a C_{2-8} alkenyl group, (kk) a C_{2-8} alkynyl group, (ll) a C_{1-8} alkoxy group, (mm) a C_{1-8} alkylthio group, (nn) a C_{1-8} acyl group, (oo) a C_{3-10} saturated, unsaturated, or aromatic carbocycle, and (pp) a 3-10 membered

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saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur, wherein (ii)-(kk) optionally are substituted with one or more R^5 groups;

R^{12} is selected from: (a) H, (b) a C_{1-6} alkyl group, (c) a C_{2-6} alkenyl group, (d) a C_{2-6} alkynyl group, (e) $-C(O)R^5$, (f) $-C(O)OR^5$, (g) $-C(O)-NR^4R^4$, (h) $-C(S)R^5$, (i) $-C(S)OR^5$, (j) $-C(O)SR^5$, (k) $-C(S)-NR^4R^4$, (l) a C_{3-10} saturated, unsaturated, or aromatic carbocycle, or (m) a 3-10 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur, (n) a $-(C_{1-6} \text{ alkyl})-C_{3-10}$ saturated, unsaturated, or aromatic carbocycle, or (o) a $-(C_{1-6} \text{ alkyl})-3-10$ membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur, wherein (a)-(d) and (l)-(o) optionally are substituted with one or more R^5 groups;

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

r at each occurrence is 0, 1, or 2;

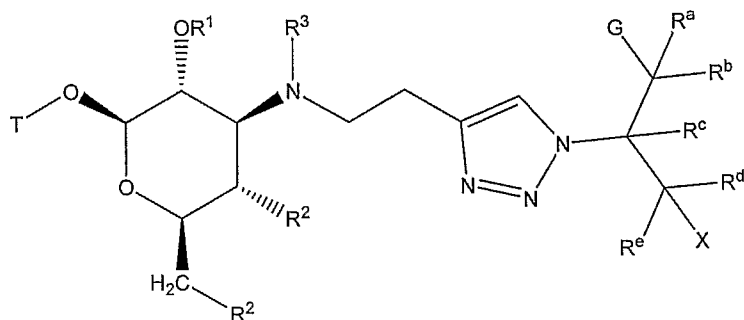
t at each occurrence is 0, 1, or 2;

and u at each occurrence is 1, 2, 3, or 4.

In the present invention, the macrolide, "T" is defined to include various 14- and 15-membered ring systems, which can contain one or more heteroatoms. Also, as defined herein, the macrolide, "T" is connected via a macrocyclic ring carbon atom", which means that the connection or bond is made to a carbon atom on the 14- or 15-membered ring of the macrolide moiety. The macrolide can include further substituents, including ring substituents. For example, the substituent designated as R^{103} can in certain embodiments be a sugar moiety, e.g. a cladinose sugar, or the substituents such as R^{104} and R^{105} are taken together in certain embodiments to form a bridged bicyclic ring system with the macrolide ring, or the substituents R^{105} and R^{106} are taken together in certain embodiments to form a fused bicyclic ring system with the macrolide ring, or the substituents or components M, R^{105} , and R^{106} are taken together to form a fused tricyclic ring system with the macrolide ring, etc. It is also recognized in the present invention that "T" is depicted as being connected to a 6-membered ring, for example in certain embodiments a desosamine sugar ring.

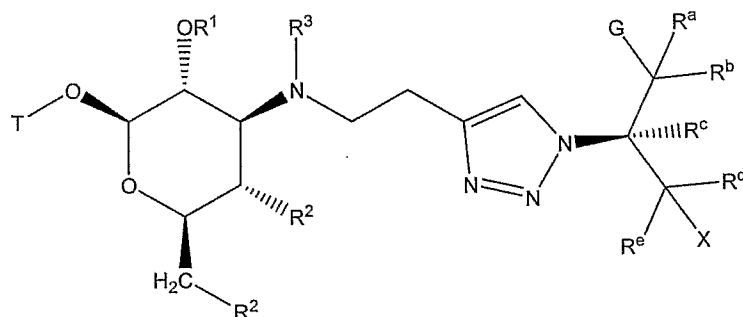
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In one embodiment, a compound of the invention is:



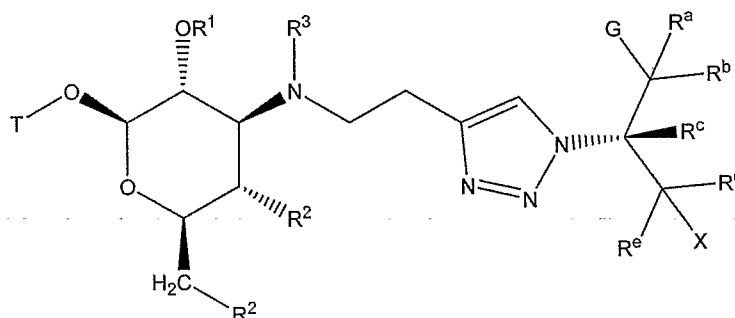
or a pharmaceutically acceptable salt, ester, *N*-oxide, or prodrug thereof.

In another embodiment, a compound of the invention is:



or a pharmaceutically acceptable salt, ester, *N*-oxide, or prodrug thereof.

For example, a compound of the invention is



or a pharmaceutically acceptable salt, ester, *N*-oxide, or prodrug thereof.

- 10 In another embodiment, X is (a) H, (b) Cl, (c) Br, (d) F, (e) -OH, (f) -CN, (g) -CF₃, (h) -CF₂H, (i) -CFH₂, (j) -O(C₁₋₆ alkyl), (k) -N₃, (l) -COOH, (m) -COO(C₁₋₆alkyl), (n) -NH₂, (o) -NH(C₁₋₆alkyl), (p) -N(C₁₋₆alkyl)₂, (q) -C(O)NH₂, (r) -C(O)NH(C₁₋₆alkyl), (s) -C(O)N(C₁₋₆alkyl)₂, (t) -NHC(O)H, (u) -NHC(O)(C₁₋₆alkyl), (v) -N(C₁₋₆alkyl)C(O)H,

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or (w) $-N(C_{1-6}alkyl)C(O)N(C_{1-6}alkyl)$. For example, in one embodiment, X is F or OH. For example, X is F. In another embodiment, X is -OH.

In another embodiment, R^d and R^e are selected from (a) Cl, (b) Br, (c) F, (d) H and (e) $C_{1-6}alkyl$. For example, in one embodiment, R^d and R^e are H.

5 In another embodiment, R^c is selected from (a) H, (b) Cl, (c) Br, (d) F, (e) $C_{1-6}alkyl$, (f) $-CF_3$, (g) $-CF_2H$, and (h) $-CFH_2$. For example, in one embodiment, R^c is H.

In another embodiment, R^a and R^b are selected from (a) H, (b) Cl, (b) Br, (d) F, (g) -OH, (h) $-O(C_{1-6}alkyl)$, (i) $-N_3$, (j) $-COOH$, (k) $-COO(C_{1-6}alkyl)$, (l) $-CN$, (m) $-NH_2$, (n) $-NH(C_{1-6}alkyl)$, (o) $-N(C_{1-6}alkyl)_2$, (p) $-C(O)NH_2$, (q) $-C(O)NH(C_{1-6}alkyl)$, (r) $-C(O)N(C_{1-6}alkyl)_2$, (s) $-NHC(O)H$, (t) $-NHC(O)(C_{1-6}alkyl)$, (u) $-N(C_{1-6}alkyl)C(O)H$, (v) $-N(C_{1-6}alkyl)C(O)N(C_{1-6}alkyl)$, or alternatively R^a and R^b are taken together with the carbon to which they are attached to form (aa) $-CO$ or (bb) $-CS$. For example, in one embodiment, R^a and R^b are selected from H, F, and -OH.

15 In one embodiment, R^a is H and R^b is F. In another embodiment, R^a is H and R^b is -OH.

In one embodiment, R^a and R^b are taken together with the carbon to which they are attached to form $-CO$.

In one embodiment, R^1 is H.

In one embodiment, R^2 is H.

20 In one embodiment, R^3 is $C_{1-6}alkyl$. For example, in one embodiment, R^3 is methyl.

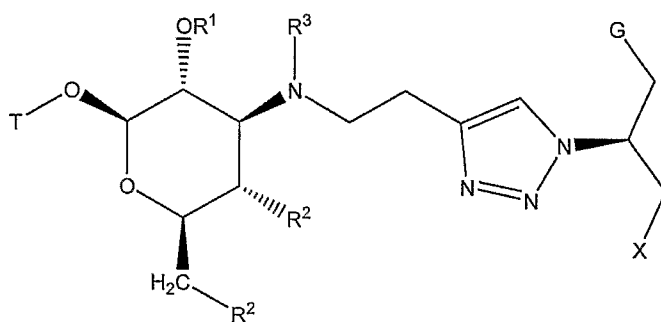
In one embodiment, G is B'. For example, in one embodiment, B' is selected from: (a) an aryl group, (b) a heteroaryl group, (c) a biaryl group, and (d) a fused bicyclic or tricyclic unsaturated or aromatic ring system optionally containing one or more carbonyl groups and one or more heteroatoms selected from nitrogen, oxygen, and sulfur, wherein each (a)-(d) optionally is substituted with one or more R^{11} groups.

25 In another embodiment, G is $-B'-Z-B''$. For example, B' and B'' are independently selected from: (a) an aryl group, (b) a heteroaryl group, (c) a biaryl group, and (d) a fused bicyclic or tricyclic unsaturated or aromatic ring system optionally containing one or more carbonyl groups and one or more heteroatoms selected from nitrogen, oxygen, and sulfur, wherein each (a)-(d) optionally is substituted with one or more R^{11} groups, and Z is

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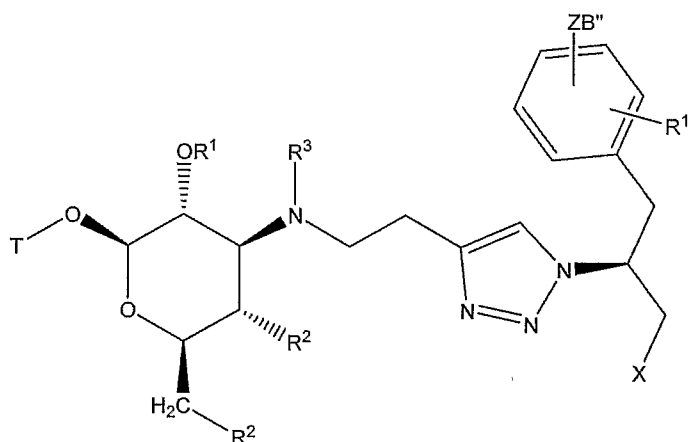
selected from Z is selected from (aa) a single bond, (bb) $-O-$, (cc) $-NR^4-$, (dd) $-C(O)-$, (ee) $-C(S)-$, (ff) $-S(O)_p-$, and (gg) a C_{1-6} alkyl.

In one embodiment, the invention relates to a compound having the structure:



5 or a pharmaceutically acceptable salt, ester, *N*-oxide, or prodrug thereof.

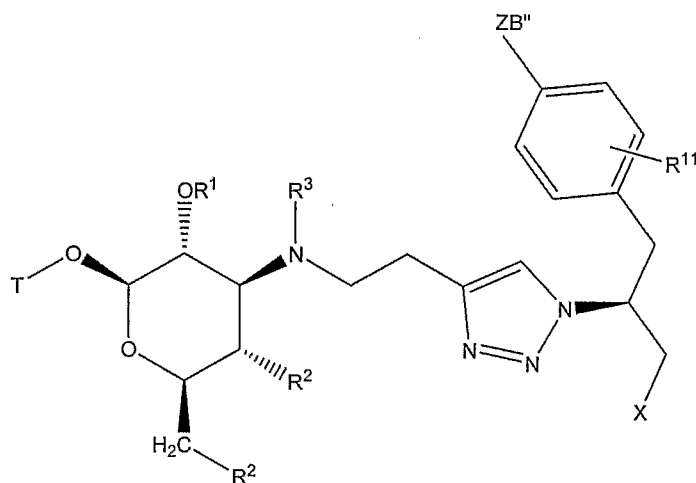
In one embodiment, a compound of the invention is



or a pharmaceutically acceptable salt, ester, *N*-oxide, or prodrug thereof.

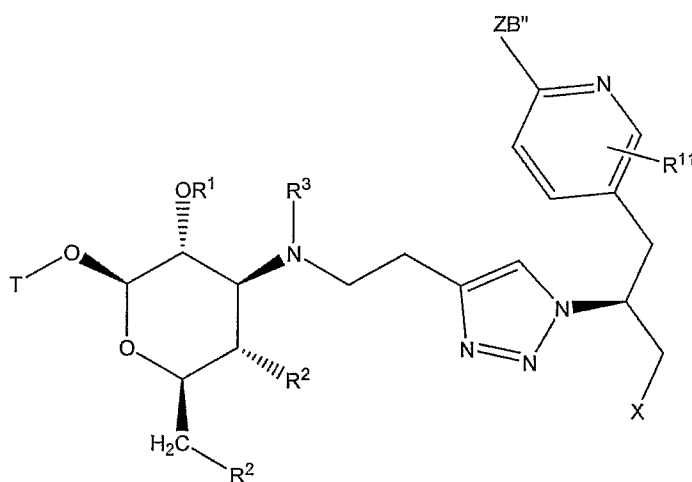
In one embodiment, a compound of the invention is

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or a pharmaceutically acceptable salt, ester, *N*-oxide, or prodrug thereof.

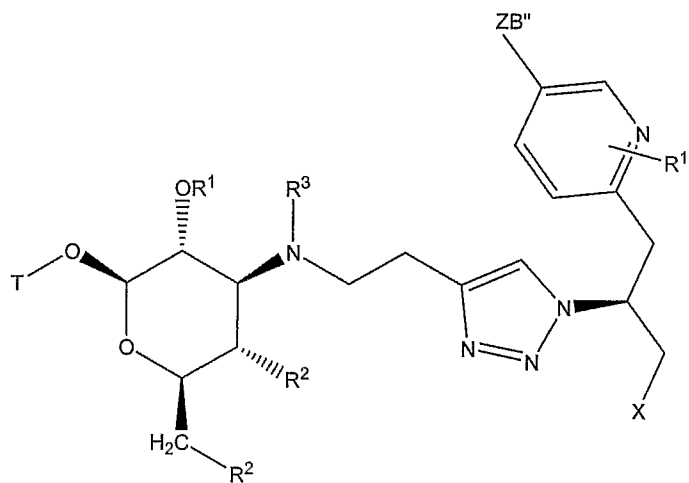
In one embodiment, a compound of the invention is:



5 or a pharmaceutically acceptable salt, ester, *N*-oxide, or prodrug thereof.

In one embodiment, a compound of the invention is:

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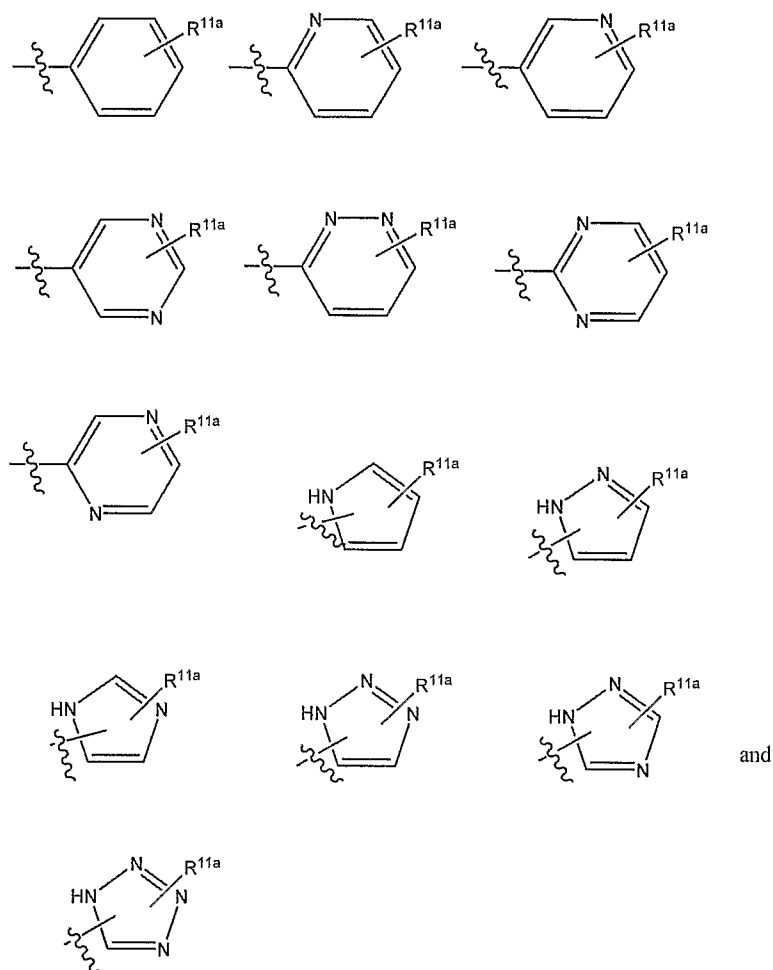
or a pharmaceutically acceptable salt, ester, *N*-oxide, or prodrug thereof.

In one embodiment, in compounds of the invention, X is selected from F and OH. For example, X is F. Further, in certain compounds of the invention, X is OH.

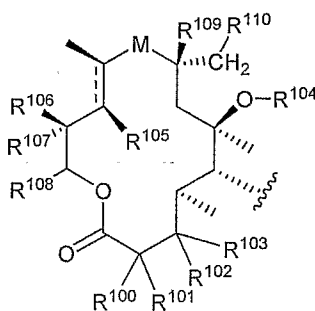
- 5 In one embodiment, R¹¹ is selected from H and F. For example, R¹¹ is H. Further, in certain compounds of the invention, R¹¹ is F.

In one embodiment, -ZB'' is selected from:

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In another embodiment, T is:



or an *N*-oxide, pharmaceutically acceptable salt, ester or prodrug thereof,

5

wherein: M is selected from:

- (a) $-C(O)-$, (b) $-CH(OR^{114})-$, (c) $-NR^{114}CH_2-$, (d) $-CH_2NR^{114}-$, (e) $-CH(NR^{114}R^{114})-$, (f) $-C(=NNR^{114}R^{114})-$, (g) $-NR^{114}C(O)-$, (h) $-C(O)NR^{114}-$, (i) $-C(=NR^{114})-$, (j) $-CR^{115}R^{115}-$, and (k) $-C(=NOR^{127})-$;

R^{100} is selected from H and C_{1-6} alkyl;

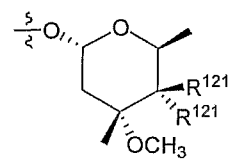
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R^{101} is selected from: (a) H, (b) Cl, (c) F, (d) Br, (e) I, (f) $-NR^{114}R^{114}$, (g) $-NR^{114}C(O)R^{114}$, (h) $-OR^{114}$, (i) $-OC(O)R^{114}$, (j) $-OC(O)OR^{114}$, (k) $-OC(O)NR^{114}R^{114}$, (l) $-O-C_{1-6}$ alkyl, (m) $-OC(O)-C_{1-6}$ alkyl, (n) $-OC(O)O-C_{1-6}$ alkyl, (o) $-OC(O)NR^{114}-C_{1-6}$ alkyl, (p) C_{1-6} alkyl, (q) C_{1-6} alkenyl, and (r) C_{1-6} alkynyl, wherein any of (l) – (r) optionally is substituted with one or more

R^{115} groups;

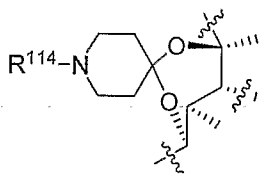
R^{102} is H;

R^{103} is selected from: (a) H, (b) $-OR^{114}$, (c) $-O-C_{1-6}$ alkyl- R^{115} , (d) $-OC((O)R^{114})$, (e) $-OC(O)-C_{1-6}$ alkyl- R^{115} , (f) $-OC(O)OR^{114}$, (g) $-OC(O)O-C_{1-6}$ alkyl- R^{115} , (h) –



$OC(O)NR^{114}R^{114}$, (i) $-OC(O)NR^{114}-C_{1-6}$ alkyl- R^{115} , and (j) alternatively, R^{102} and R^{103} taken together form a carbonyl group; or, alternatively, R^{101} and R^{103} taken together are a single bond between the respective carbons to which these two groups are attached thereby creating a double bond between the carbons to which R^{100} and R^{102} are attached; or, alternatively, R^{101} and R^{103} taken together are an epoxide moiety;

R^{104} is selected from: (a) H, (b) R^{114} , (c) $-C(O)R^{114}$, (d) $-C(O)OR^{114}$, (e) $-C(O)NR^{114}R^{114}$, (f) $-C_{1-6}$ alkyl- $K-R^{114}$, (g) $-C_{2-6}$ alkenyl- $K-R^{114}$, and (h) $-C_{2-6}$ alkynyl- $K-R^{114}$; alternatively R^{103} and R^{104} , taken together with the atoms to which they are bonded, form:

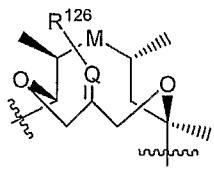


K is selected from: (a) $-C(O)-$, (b) $-C(O)O-$, (c) $-C(O)NR^{114}-$, (d) $-C(=NR^{114})-$, (e) $-C(=NR^{114})O-$, (f) $-C(=NR^{114})NR^{114}-$, (g) $-OC(O)-$, (h) $-OC(O)O-$, (i) $-OC(O)NR^{114}-$, (j) $-NR^{114}C(O)-$, (k) $-NR^{114}C(O)O-$, (l) $-NR^{114}C(O)NR^{114}-$, (m) $-NR^{114}C(=NR^{114})NR^{114}-$, and (o) $-S(O)_p-$;

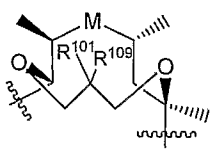
R^{105} is selected from: (a) R^{114} , (b) $-OR^{114}$, (c) $-NR^{114}R^{114}$, (d) $-O-C_{1-6}$ alkyl- R^{115} , (e) $-C(O)-R^{114}$, (f) $-C(O)-C_{1-6}$ alkyl- R^{115} , (g) $-OC(O)-R^{114}$, (h) $-OC(O)-C_{1-6}$ alkyl- R^{115} , (i) $-OC(O)O-R^{114}$, (j) $-OC(O)O-C_{1-6}$ alkyl- R^{115} , (k) $-OC(O)NR^{114}R^{114}$, (l) –

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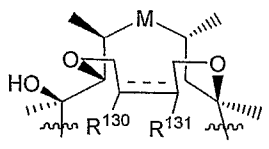
OC(O)NR¹¹⁴-C₁₋₆ alkyl-R¹¹⁵, (m) -C(O)-C₂₋₆ alkenyl-R¹¹⁵, and (n) -C(O)-C₂₋₆ alkynyl-R¹¹⁵; or, alternatively, R¹⁰⁴ and R¹⁰⁵, taken together with the atoms to which they are bonded, form:



5 wherein Q is CH or N, and R¹²⁶ is -OR¹¹⁴, -NR¹¹⁴ or R¹¹⁴; or, alternatively, R¹⁰⁴ and R¹⁰⁵, taken together with the atoms to which they are bonded, form:



wherein R¹⁰¹ is as defined above; or, alternately, R¹⁰¹ and R¹⁰⁹ can be taken together form a carbonyl group; or, alternately, R¹⁰¹ and R¹⁰⁹ can be taken together to form the group -O(CR¹¹⁶R¹¹⁶)_nO-; or, alternatively, R¹⁰⁴ and R¹⁰⁵, taken together with the atoms to which they are bonded, form:

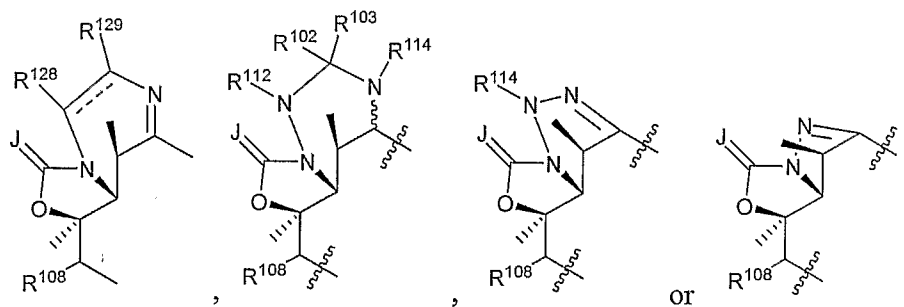


wherein R¹³⁰ is -OH, =C(O), or R¹¹⁴, R¹³¹ is -OH, =C(O), or R¹¹⁴, or, alternately, R¹³⁰ and R¹³¹ together with the carbons to which they are attached form a 3-7 membered saturated, unsaturated or aromatic carbocyclic or heterocyclic ring which can optionally be substituted with one or more R¹¹⁴ groups;

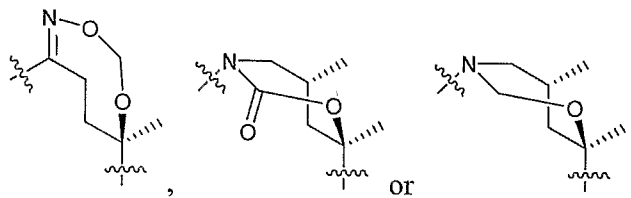
R¹⁰⁶ is selected from: (a) -OR¹¹⁴, (b) -C₁₋₆ alkoxy-R¹¹⁵, (c) -C(O)R¹¹⁴, (d) -OC(O)R¹¹⁴, (e) -OC(O)OR¹¹⁴, (f) -OC(O)NR¹¹⁴R¹¹⁴, and (g) -NR¹¹⁴R¹¹⁴; or, alternatively, R¹⁰⁵ and R¹⁰⁶ taken together with the atoms to which they are attached form a 5-membered ring by attachment to each other through a chemical moiety selected from: (a) -OC(R¹¹⁵)₂O-, (b) -OC(O)O-, (c) -OC(O)NR¹¹⁴-, (d) -NR¹¹⁴C(O)O-, (e) -OC(O)NOR¹¹⁴-, (f) -NOR¹¹⁴-C(O)O-, (g) -OC(O)NNR¹¹⁴R¹¹⁴-, (h) -NNR¹¹⁴R¹¹⁴-C(O)O-, (i) -OC(O)C(R¹¹⁵)₂-, (j) -C(R¹¹⁵)₂C(O)O-, (k) -OC(S)O-, (l) -OC((S)NR¹¹⁴-, (m) -NR¹¹⁴C(S)O-, (n) -OC(S)NOR¹¹⁴-, (o) -NOR¹¹⁴-C(S)O-, (p) -OC(S)NNR¹¹⁴R¹¹⁴-, (q) -NNR¹¹⁴R¹¹⁴-C(S)O-, (r) -OC(S)C(R¹¹⁵)₂-, and (s) -C(R¹¹⁵)₂C(S)O-; or,

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alternatively, M, R¹⁰⁵, and R¹⁰⁶ taken together with the atoms to which they are attached form:



wherein J is selected from O, S and NR¹¹⁴; or, alternatively, M and R¹⁰⁴ taken together with the atoms to which they are attached form:



R¹⁰⁷ is selected from (a) H, (b) -C₁₋₄ alkyl, (c) -C₂₋₄ alkenyl, which can be further substituted with C₁₋₁₂ alkyl or one or more halogens, (d) -C₂₋₄ alkynyl, which can be further substituted with C₁₋₁₂ alkyl or one or more halogens, (e) aryl or heteroaryl, which can be further substituted with C₁₋₁₂ alkyl or one or more halogens, (f) -C(O)H, (g) -COOH, (h) -CN, (i) -COOR¹¹⁴, (j) -C(O)NR¹¹⁴R¹¹⁴, (k) -C(O)R¹¹⁴, and (l) -C(O)SR¹¹⁴, wherein (b) is further substituted with one or more substituents selected from (aa) -OR¹¹⁴, (bb) halogen, (cc) -SR¹¹⁴, (dd) C₁₋₁₂ alkyl, which can be further substituted with halogen, hydroxyl, C₁₋₆ alkoxy, or amino, (ee) -OR¹¹⁴, (ff) -SR¹¹⁴, (gg) -NR¹¹⁴R¹¹⁴, (hh) -CN, (ii) NO₂, (jj) -NC(O)R¹¹⁴, (kk) -COOR¹¹⁴, (ll) -N₃, (mm) =N-O-R¹¹⁴, (nn) =NR¹¹⁴, (oo) =N-NR¹¹⁴R¹¹⁴, (pp) =N-NH-C(O)R¹¹⁴, and (qq) =N-NH-C(O)NR¹¹⁴R¹¹⁴; or, alternatively R¹⁰⁶ and R¹⁰⁷ are taken together with the atom to which they are attached to form an epoxide, a carbonyl, an olefin, or a substituted olefin, or a C₃-C₇ carbocyclic, carbonate, or carbamate, wherein the nitrogen of said carbamate can be further substituted with a C₁-C₆ alkyl;

R¹⁰⁸ is selected from: (a) C₁₋₆ alkyl, (b) C₂₋₆ alkenyl, and (c) C₂₋₆ alkynyl, wherein any of (a)-(c) optionally is substituted with one or more R¹¹⁴ groups;

R¹¹¹ is selected from H and -C(O)R¹¹⁴;

R¹¹² is selected from H, OH, and OR¹¹⁴;

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R^{113} is selected from: (a) H, (b) R^{114} , (c) $-C_{1-6}$ alkyl- $K-R^{114}$, (d) $-C_{2-6}$ alkenyl- $K-R^{114}$, and (e) $-C_{2-6}$ alkynyl- $K-R^{114}$, wherein any of (c)-(e) optionally is substituted with one or more R^{115} groups;

R^{114} , at each occurrence, independently is selected from: (a) H, (b) C_{1-6} alkyl, (c) C_{2-6} alkenyl, (d) C_{2-6} alkynyl, (e) C_{6-10} saturated, unsaturated, or aromatic carbocycle, (f) 3-12 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from 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) $-C(O)-C_{6-10}$ saturated, unsaturated, or aromatic carbocycle, (k) $-C(O)-3-12$ membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from 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) $-C(O)O-C_{6-10}$ saturated, unsaturated, or aromatic carbocycle, (p) $-C(O)O-3-12$ membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur, and (q) $-C(O)NR^{116}R^{116}$, wherein any of (b)-(p) optionally is substituted with one or more R^{115} groups, wherein one or more non-terminal carbon moieties of any of (b)-(d) optionally is replaced with oxygen, $S(O)_p$, or $-NR^{116}$, or, alternatively, $NR^{114}R^{114}$ forms a 3-7 membered saturated, unsaturated or aromatic ring including the nitrogen atom to which the R^{114} groups are bonded and optionally one or more moieties selected from O, $S(O)_p$, N, and NR^{118} ;

R^{115} is selected from: (a) R^{117} , (b) C_{1-8} alkyl, (c) C_{2-8} alkenyl, (d) C_{2-8} alkynyl, (e) C_{3-12} saturated, unsaturated, or aromatic carbocycle, (f) 3-12 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur, wherein any of (b)-(f) optionally is substituted with one or more R^{117} groups;

R^{116} , at each occurrence, independently is selected from: (a) H, (b) C_{1-6} alkyl, (c) C_{2-6} alkenyl, (d) C_{2-6} alkynyl, (e) C_{3-10} saturated, unsaturated, or aromatic carbocycle, and (f) 3-10 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur, wherein one or more non-terminal carbon moieties of any of (b)-(d) optionally is replaced with oxygen, $S(O)_p$, or $-NR^{114}$, wherein any of (b)-(f) optionally is substituted with one or more moieties selected from: (aa) carbonyl, (bb) formyl, (cc) F, (dd) Cl, (ee) Br, (ff) I, (gg) CN, (hh) N_3 , (ii) NO_2 , (jj) OR^{118} , (kk) $-S(O)_pR^{118}$, (ll) $-C(O)R^{118}$, (mm) $-C(O)OR^{118}$, (nn) $-OC(O)R^{118}$, (oo) $-$

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- $C(O)NR^{118}R^{118}$, (pp) $-OC(O)NR^{118}R^{118}$, (qq) $-C(=NR^{118})R^{118}$, (rr) $-C(R^{118})(R^{118})OR^{118}$,
 (ss) $-C(R^{118})_2OC(O)R^{118}$, (tt) $-C(R^{118})(OR^{118})(CH_2)_rNR^{118}R^{118}$, (uu) $-NR^{118}R^{118}$; (vv) $-$
 $NR^{118}OR^{118}$, (ww) $-NR^{118}C(O)R^{118}$, (xx) $-NR^{118}C(O)OR^{118}$, (yy) $-NR^{118}C(O)NR^{118}R^{118}$,
 (zz) $-NR^{118}S(O)_rR^{118}$, (ab) $-C(OR^{118})(OR^{118})R^{118}$, (ac) $-C(R^{118})_2NR^{118}R^{118}$, (ad) $=NR^{118}$,
 5 (ae) $-C(S)NR^{118}R^{118}$, (af) $-NR^{118}C(S)R^{118}$, (ag) $-OC(S)NR^{118}R^{118}$, (ah) $-NR^{118}C(S)OR^{118}$,
 (ai) $-NR^{118}C(S)NR^{118}R^{118}$, (aj) $-SC(O)R^{118}$, (ak) C_{1-8} alkyl, (al) C_{2-8} alkenyl, (am)
 C_{2-8} alkynyl, (an) C_{1-8} alkoxy, (ao) C_{1-8} alkylthio, (ap) C_{1-8} acyl, (aq) saturated,
 unsaturated, or aromatic C_{3-10} carbocycle, and (ar) saturated, unsaturated, or aromatic 3-10
 membered heterocycle containing one or more heteroatoms selected from nitrogen,
 10 oxygen, and sulfur, or, alternatively, $NR^{116}R^{116}$ forms a 3-10 membered saturated,
 unsaturated or aromatic ring including the nitrogen atom to which the R^{116} groups are
 attached and optionally one or more moieties selected from O, $S(O)_p$, N, and NR^{118} ; or,
 alternatively, $CR^{116}R^{116}$ forms a carbonyl group;
- R^{117} , at each occurrence, is selected from: (a) H, (b) =O, (c) F, (d) Cl, (e) Br, (f) I,
 15 (g) $(CR^{116}R^{116})_rCF_3$, (h) $(CR^{116}R^{116})_rCN$, (i) $(CR^{116}R^{116})_rNO_2$,
 (j) $(CR^{116}R^{116})_rNR^{116}(CR^{116}R^{116})_tR^{119}$, (k) $(CR^{116}R^{116})_rOR^{119}$,
 (l) $(CR^{116}R^{116})_rS(O)_p(CR^{116}R^{116})_tR^{119}$, (m) $(CR^{116}R^{116})_rC(O)(CR^{116}R^{116})_tR^{119}$,
 (n) $(CR^{116}R^{116})_rOC(O)(CR^{116}R^{116})_tR^{119}$, (o) $(CR^{116}R^{116})_rSC(O)(CR^{116}R^{116})_tR^{119}$,
 (p) $(CR^{116}R^{116})_rC(O)O(CR^{116}R^{116})_tR^{119}$, (q) $(CR^{116}R^{116})_rNR^{116}C(O)(CR^{116}R^{116})_tR^{119}$,
 20 (r) $(CR^{116}R^{116})_rC(O)NR^{116}(CR^{116}R^{116})_tR^{119}$, (s) $(CR^{116}R^{116})_rC(=NR^{116})(CR^{116}R^{116})_tR^{119}$,
 (t) $(CR^{116}R^{116})_rC(=NNR^{116}R^{116})(CR^{116}R^{116})_tR^{119}$, (u) $(CR^{116}R^{116})_rC(=NNR^{116}C(O)R^{116})($
 $CR^{116}R^{116})_tR^{119}$, (v) $(CR^{116}R^{116})_rC(=NOR^{119})(CR^{116}R^{116})_tR^{119}$,
 (w) $(CR^{116}R^{116})_rNR^{116}C(O)O(CR^{116}R^{116})_tR^{119}$,
 (x) $(CR^{116}R^{116})_rOC(O)NR^{116}(CR^{116}R^{116})_tR^{119}$,
 25 (y) $(CR^{116}R^{116})_rNR^{116}C(O)NR^{116}(CR^{116}R^{116})_tR^{119}$,
 (z) $(CR^{116}R^{116})_rNR^{116}S(O)_p(CR^{116}R^{116})_tR^{119}$, (aa) $(CR^{116}R^{116})_rS(O)_pNR^{116}(CR^{116}R^{116})_tR^{119}$,
 (bb) $(CR^{116}R^{116})_rNR^{116}S(O)_pNR^{116}(CR^{116}R^{116})_tR^{119}$, (cc) $(CR^{116}R^{116})_rNR^{116}R^{116}$,
 (dd) C_{1-6} alkyl, (ee) C_{2-6} alkenyl, (ff) C_{2-6} alkynyl, (gg) $(CR^{116}R^{116})_r-C_{3-10}$ saturated,
 unsaturated, or aromatic carbocycle, and (hh) $(CR^{116}R^{116})_r-3-10$ membered saturated,
 30 unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from
 nitrogen, oxygen, and sulfur, wherein any of (dd)–(hh) optionally is substituted with one
 or more R^{119} groups; or, alternatively, two R^{117} groups can form $-O(CH_2)_uO-$;

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R^{118} is selected from: (a) H, (b) C_{1-6} alkyl, (c) C_{2-6} alkenyl, (d) C_{2-6} alkynyl, (e) C_{3-10} saturated, unsaturated, or aromatic carbocycle, (f) 3-10 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur, (g) $-C(O)-C_{1-6}$ alkyl, (h) $-C(O)-C_{1-6}$ alkenyl, (i) $-C(O)-C_{1-6}$ alkynyl, (j) $-C(O)-C_{3-10}$ saturated, unsaturated, or aromatic carbocycle, and (k) $-C(O)-3-10$ membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur, wherein any of (b)–(j) optionally is substituted with one or more moieties selected from : (aa) H, (bb) F, (cc) Cl, (dd) Br, (ee) I, (ff) CN, (gg) NO_2 , (hh) OH, (ii) NH_2 , (jj) $NH(C_{1-6} \text{ alkyl})$, (kk) $N(C_{1-6} \text{ alkyl})_2$, (ll) C_{1-6} alkoxy, (mm) aryl, (nn) substituted aryl, (oo) heteroaryl, (pp) substituted heteroaryl, and (qq) C_{1-6} alkyl, optionally substituted with one or more moieties selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, F, Cl, Br, I, CN, NO_2 , and OH;

R^{119} , at each occurrence, independently is selected from: (a) R^{120} , (b) C_{1-6} alkyl, (c) C_{2-6} alkenyl, (d) C_{2-6} alkynyl, (e) C_{3-10} saturated, unsaturated, or aromatic carbocycle, and (f) 3-10 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur, wherein any of (b)–(f) optionally is substituted with one or more R^{119} groups;

R^{120} , at each occurrence, independently is selected from: (a) H, (b) =O, (c) F, (d) Cl, (e) Br, (f) I, (g) $(CR^{116}R^{116})_rCF_3$, (h) $(CR^{116}R^{116})_rCN$, (i) $(CR^{116}R^{116})_rNO_2$, (j) $(CR^{116}R^{116})_rNR^{116}R^{116}$, (k) $(CR^{116}R^{116})_rOR^{116}$, (l) $(CR^{116}R^{116})_rS(O)_pR^{116}$, (m) $(CR^{116}R^{116})_rC(O)R^{116}$, (n) $(CR^{116}R^{116})_rC(O)OR^{116}$, (o) $(CR^{116}R^{116})_rOC(O)R^{116}$, (p) $(CR^{116}R^{116})_rNR^{116}C(O)R^{116}$, (q) $(CR^{116}R^{116})_rC(O)NR^{116}R^{116}$, (r) $(CR^{116}R^{116})_rC(=NR^{116})R^{116}$, (s) $(CR^{116}R^{116})_rNR^{116}C(O)NR^{116}R^{116}$, (t) $(CR^{116}R^{116})_rNR^{116}S(O)_pR^{116}$, (u) $(CR^{116}R^{116})_rS(O)_pNR^{116}R^{116}$, (v) $(CR^{116}R^{116})_rNR^{116}S(O)_pNR^{116}R^{116}$, (w) C_{1-6} alkyl, (x) C_{2-6} alkenyl, (y) C_{2-6} alkynyl, (z) $(CR^{116}R^{116})_r-C_{3-10}$ saturated, unsaturated, or aromatic carbocycle, and (aa) $(CR^{116}R^{116})_r-3-10$ membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur, wherein any of (w)–(aa) optionally is substituted with one or more moieties selected from R^{116} , F, Cl, Br, I, CN, NO_2 , $-OR^{116}$, $-NH_2$, $-NH(C_{1-6} \text{ alkyl})$, $-N(C_{1-6} \text{ alkyl})_2$, C_{1-6} alkoxy, C_{1-6} alkylthio, and C_{1-6} acyl;

R^{121} , at each occurrence, independently is selected from: (a) H, (b) $-OR^{118}$, (c) $-O-C_{1-6}$ alkyl- $OC(O)R^{118}$, (d) $-O-C_{1-6}$ alkyl- $OC(O)OR^{118}$, (e) $-O-C_{1-6}$ alkyl- $OC(O)NR^{118}R^{118}$, (f) $-O-C_{1-6}$ alkyl- $C(O)NR^{118}R^{118}$, (g) $-O-C_{1-6}$ alkyl- $NR^{118}C(O)R^{118}$, (h) $-O-C_{1-6}$ alkyl- $NR^{118}C(O)OR^{118}$, (i) $-O-C_{1-6}$ alkyl- $NR^{118}C(O)NR^{118}R^{118}$, (j) $-O-C_{1-6}$ alkyl- $NR^{118}C(=N(H)NR^{118}R^{118})$, (k) $-O-C_{1-6}$ alkyl- $S(O)_pR^{118}$, (l) $-O-C_{2-6}$ alkenyl- $OC(O)R^{118}$, (m) $-O-C_{2-6}$ alkenyl- $OC(O)OR^{118}$, (n) $-O-C_{2-6}$ alkenyl- $OC(O)NR^{118}R^{118}$, (o) $-O-C_{2-6}$ alkenyl- $C(O)NR^{118}R^{118}$, (p) $-O-C_{2-6}$ alkenyl- $NR^{118}C(O)R^{118}$, (q) $-O-C_{2-6}$ alkenyl- $NR^{118}C(O)OR^{118}$, (r) $-O-C_{2-6}$ alkenyl- $NR^{118}C(O)NR^{118}R^{118}$, (s) $-O-C_{2-6}$ alkenyl- $NR^{118}C(=N(H)NR^{118}R^{118})$, (t) $-O-C_{2-6}$ alkenyl- $S(O)_pR^{118}$, (u) $-O-C_{2-6}$ alkynyl- $OC(O)R^{118}$, (v) $-O-C_{2-6}$ alkynyl- $OC(O)OR^{118}$, (w) $-O-C_{2-6}$ alkynyl- $OC(O)NR^{118}R^{118}$, (x) $-O-C_{2-6}$ alkynyl- $C(O)NR^{118}R^{118}$, (y) $-O-C_{2-6}$ alkynyl- $NR^{118}C(O)R^{118}$, (z) $-O-C_{2-6}$ alkynyl- $NR^{118}C(O)OR^{118}$, (aa) $-O-C_{2-6}$ alkynyl- $NR^{118}C(O)NR^{118}R^{118}$, (bb) $-O-C_{2-6}$ alkynyl- $NR^{118}C(=N(H)NR^{118}R^{118})$, (cc) $-O-C_{2-6}$ alkynyl- $S(O)_pR^{118}$, and (dd) $-NR^{118}R^{118}$; or, alternatively, two R^{121} groups taken together form $=O$, $=NOR^{118}$, or $=NNR^{118}R^{118}$;

R^{122} is R^{115} ;

R^{123} is selected from: (a) R^{116} , (b) F, (c) Cl, (d) Br, (e) I, (f) CN, (g) NO_2 , and (h) $-OR^{114}$;

alternatively, R^{122} and R^{123} taken together are $-O(CH_2)_uO-$;

R^{124} , at each occurrence, independently is selected from: (a) H, (b) F, (c) Cl, (d) Br, (e) I, (f) CN, (g) $-OR^{114}$, (h) $-NO_2$, (i) $-NR^{114}R^{114}$, (j) C_{1-6} alkyl, (k) C_{1-6} acyl, and (l) C_{1-6} alkoxy;

R^{125} is selected from: (a) C_{1-6} alkyl, (b) C_{2-6} alkenyl, (c) C_{2-6} alkynyl, (d) C_{1-6} acyl, (e) C_{1-6} alkoxy, (f) C_{1-6} alkylthio, (g) saturated, unsaturated, or aromatic C_{5-10} carbocycle, (h) saturated, unsaturated, or aromatic 5-10 membered heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur, (i) $-O-C_{1-6}$ alkyl-saturated, unsaturated, or aromatic 5-10 membered heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur, (j) $-NR^{114}-C_{1-6}$ alkyl-saturated, unsaturated, or aromatic 5-10 membered heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur, (k) saturated, unsaturated, or aromatic 10-membered bicyclic ring system optionally containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur, (l) saturated, unsaturated, or aromatic 13-membered tricyclic ring

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system optionally containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur, (m) $-OR^{114}$, (n) $-NR^{114}R^{114}$, (o) $-S(O)_pR^{114}$, and (p) $-R^{124}$, wherein any of (a)-(l) optionally is substituted with one or more R^{115} groups; or, alternatively, R^{125} and one R^{124} group, taken together with the atoms to which they are bonded, form a 5-7 membered saturated or unsaturated carbocycle, optionally substituted with one or more R^{115} groups; or a 5-7 membered saturated or unsaturated heterocycle containing one or more atoms selected from nitrogen, oxygen, and sulfur, and optionally substituted with one or more R^{115} groups;

R^{126} at each occurrence, independently is selected from: (a) hydrogen, (b) an electron-withdrawing group, (c) aryl, (d) substituted aryl, (e) heteroaryl, (f) substituted heteroaryl, and (g) C_{1-6} alkyl, optionally substituted with one or more R^{115} groups; or, alternatively, any R^{126} and any R^{123} , taken together with the atoms to which they are bonded, form a 5-7 membered saturated or unsaturated carbocycle, optionally substituted with one or more R^{115} groups; or a 5-7 membered saturated or unsaturated heterocycle containing one or more atoms selected from nitrogen, oxygen, and sulfur, and optionally substituted with one or more R^{115} groups;

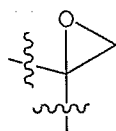
R^{109} is H or F;

R^{127} is R^{114} , a monosaccharide or disaccharide (including amino sugars and halo sugar(s), $-(CH_2)_n-(O-CH_2CH_2-)_m-O(CH_2)_pCH_3$ or $-(CH_2)_n-(O-CH_2CH_2-)_m-OH$;

R^{128} is R^{114}

R^{129} is R^{114}

R^{110} is R^{114} , or, alternatively, R^{109} and R^{110} taken together with the carbons to which they are attached form:



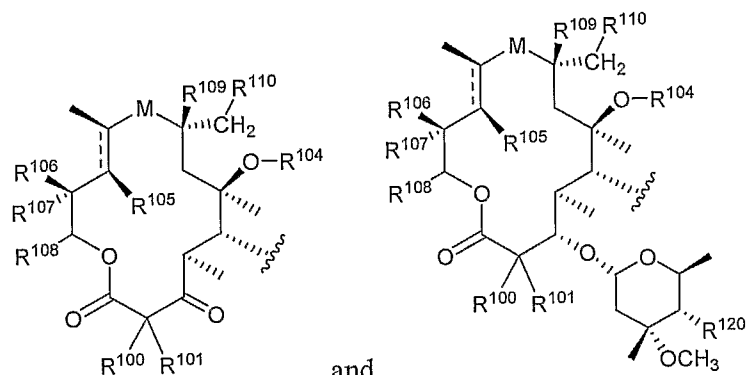
, or alternately, R^{128} and R^{129} together with the carbons to which they are attached form a 3-6 membered saturated, unsaturated or aromatic carbocyclic or heterocyclic ring which can optionally be substituted with one or more R^{114} groups;

m, at each occurrence is 0, 1, 2, 3, 4, or 5;

n, at each occurrence is 1, 2, or 3.

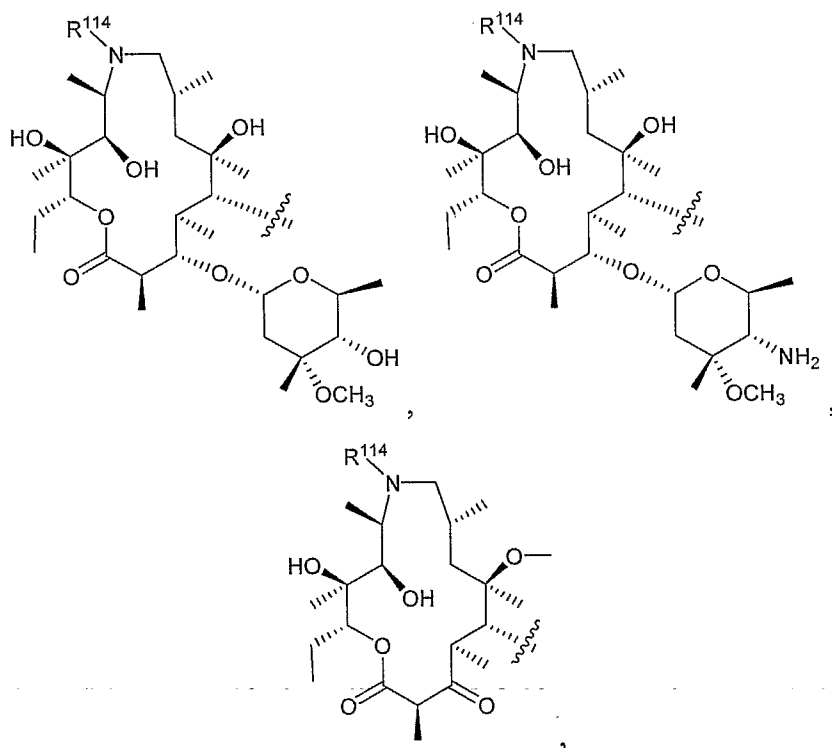
In some embodiments, in compounds of the invention, T is a macrolide selected from:

- 32 -

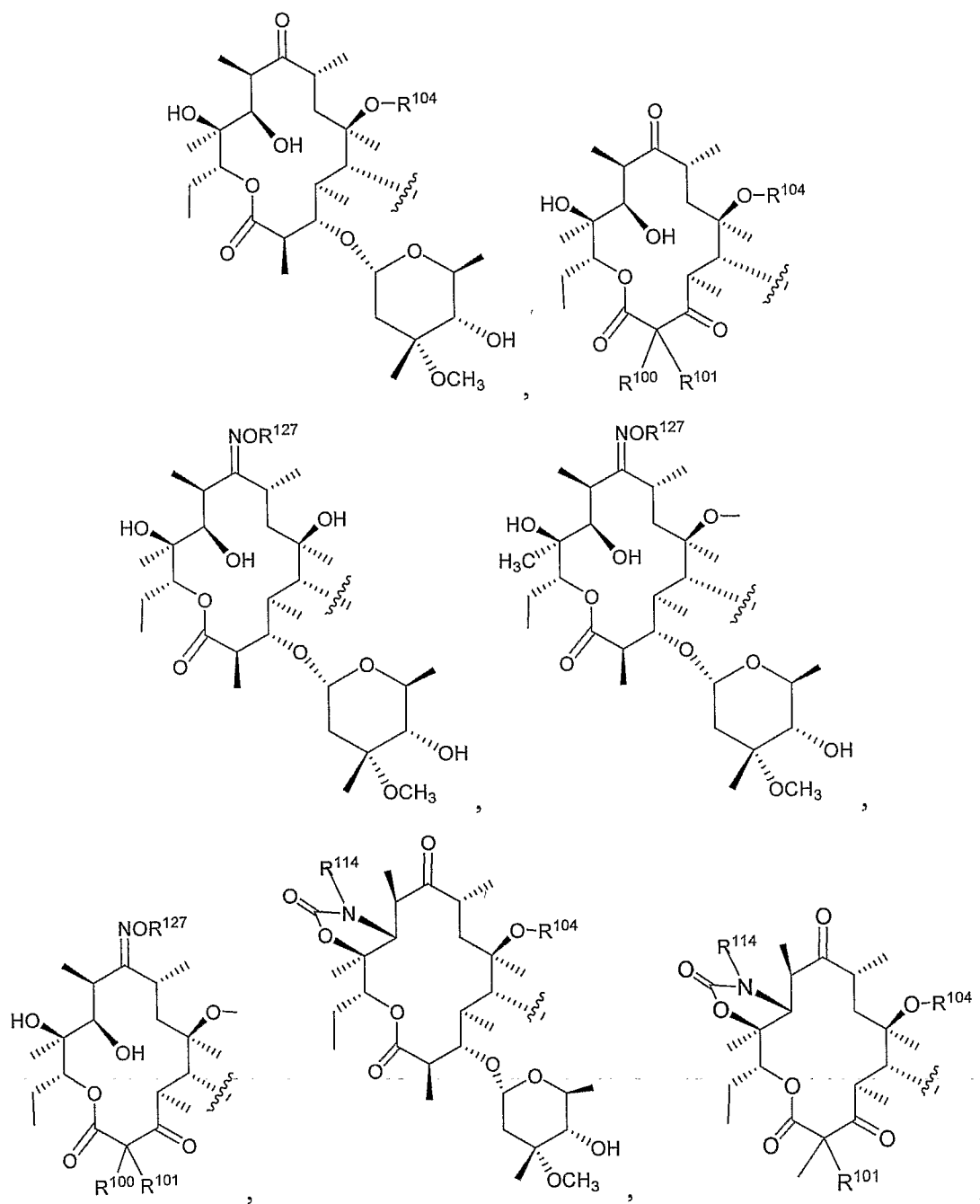


and
and an *N*-oxide pharmaceutically acceptable salt, ester, or prodrug thereof.

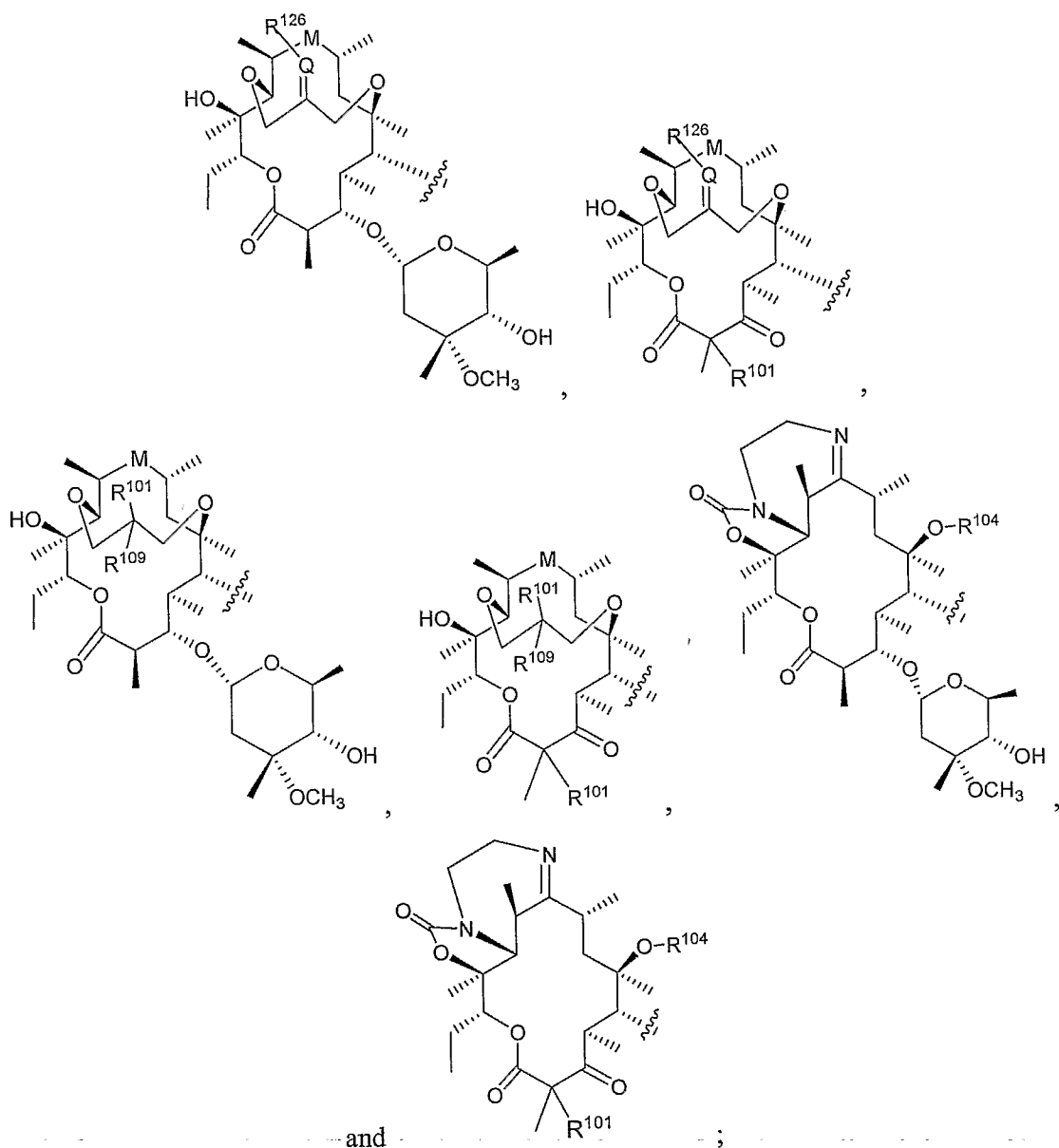
In some embodiments, T is a macrolide selected from:



- 33 -



- 34 -

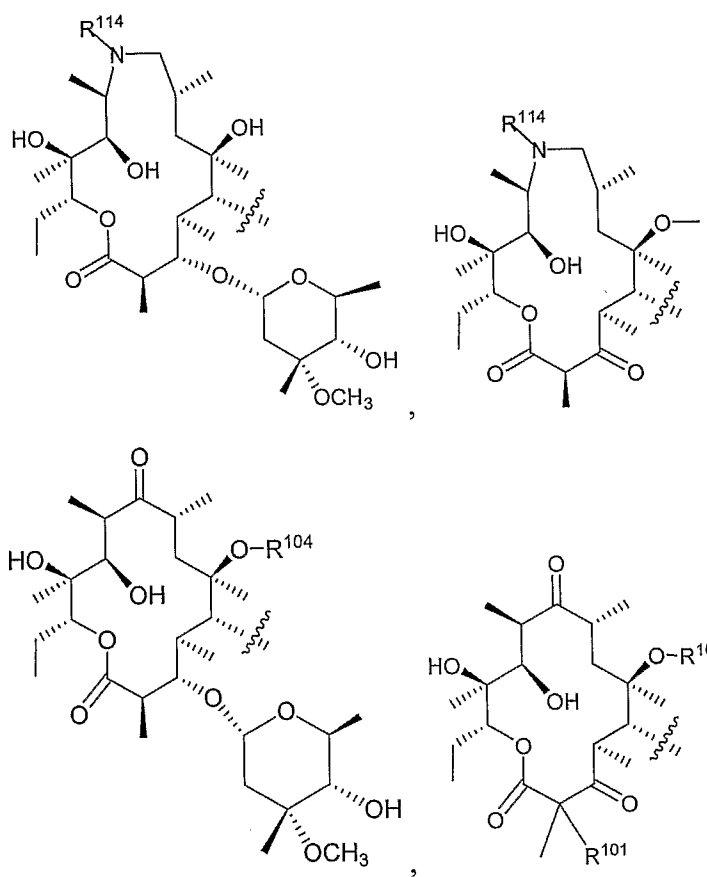


and an *N*-oxide pharmaceutically acceptable salt, ester, or prodrug thereof.

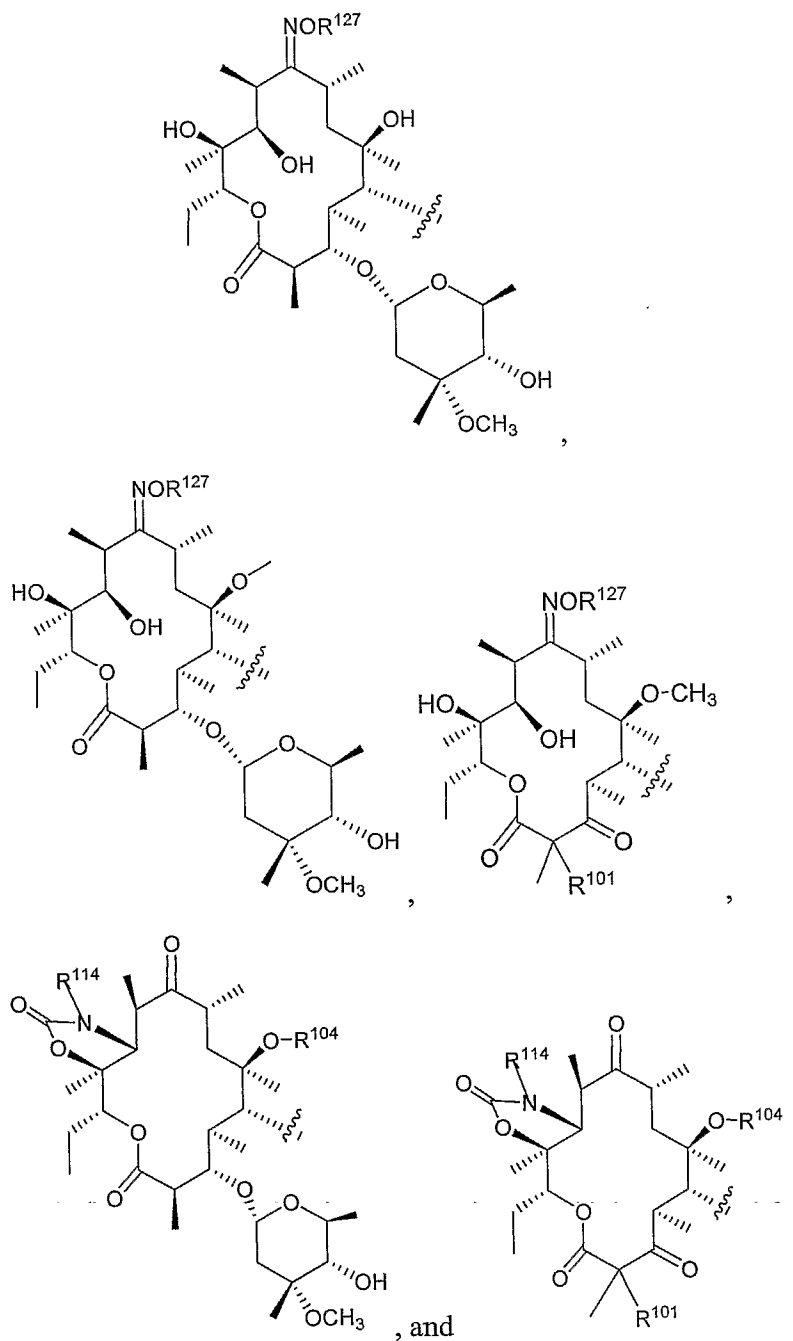
5

In some embodiments, T is a macrolide selected from:

- 35 -



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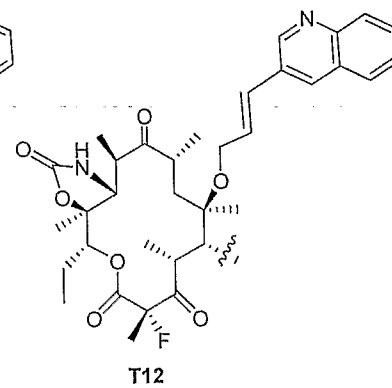
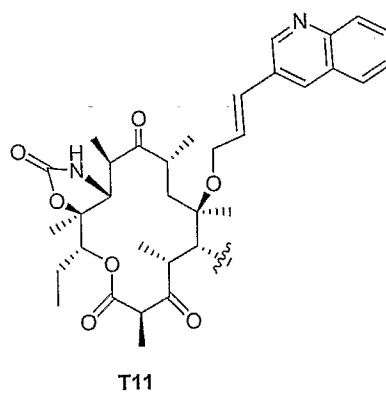
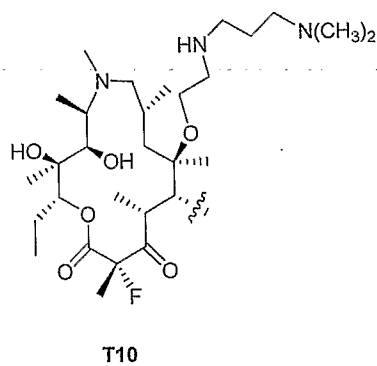
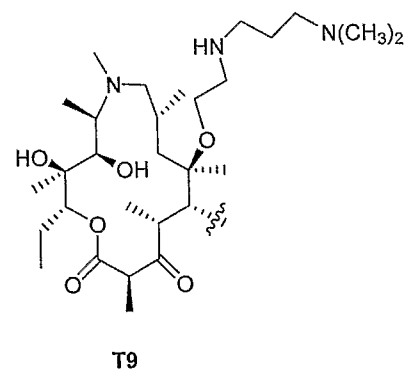
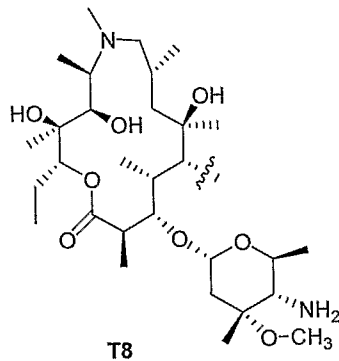
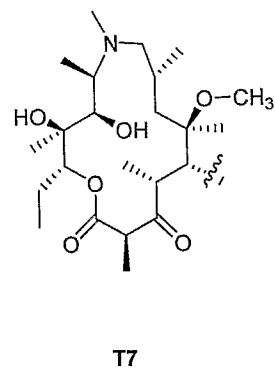
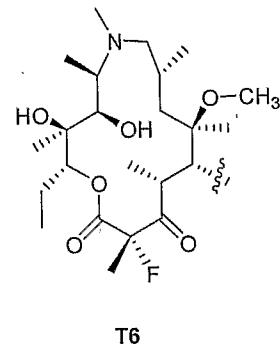
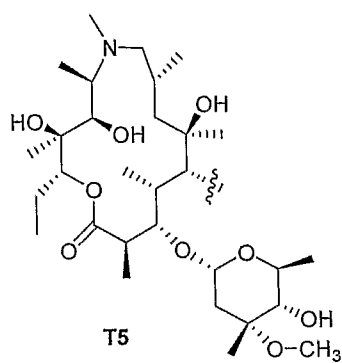
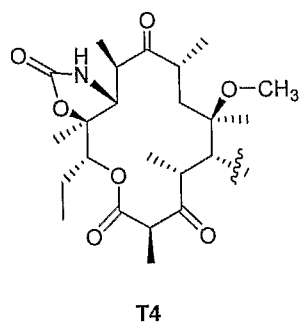
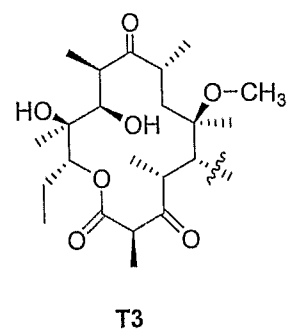
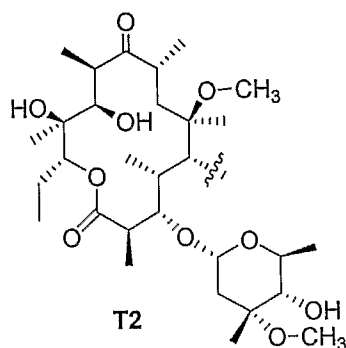
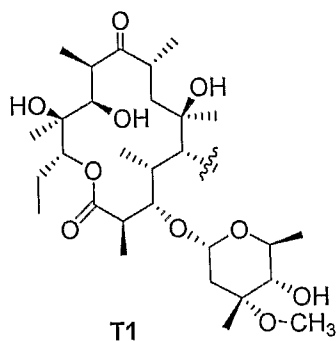


and an *N*-oxide pharmaceutically acceptable salt, ester, or prodrug thereof.

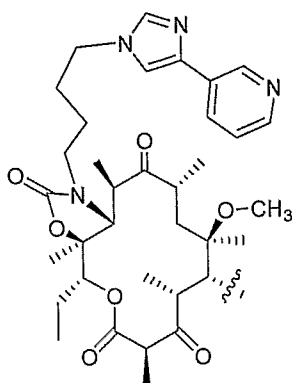
5

In some embodiments, T is a macrolide selected from T1 through T33:

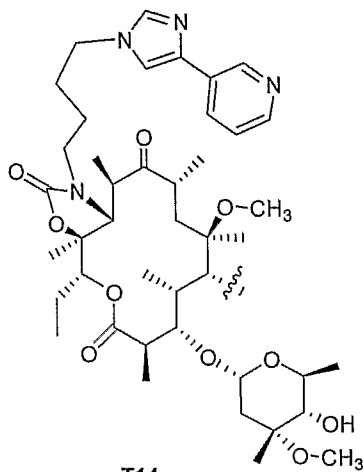
- 37 -



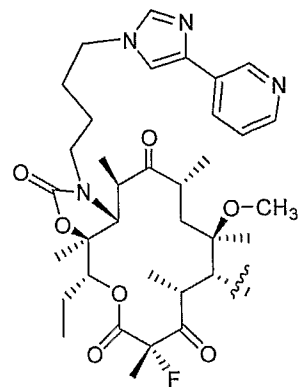
- 38 -



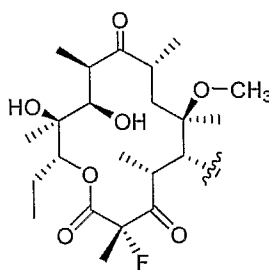
T13



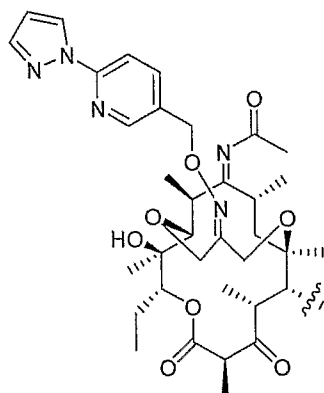
T14



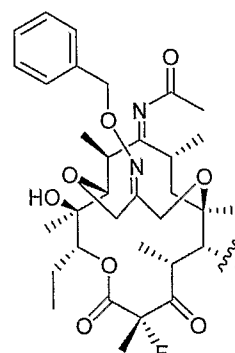
T15



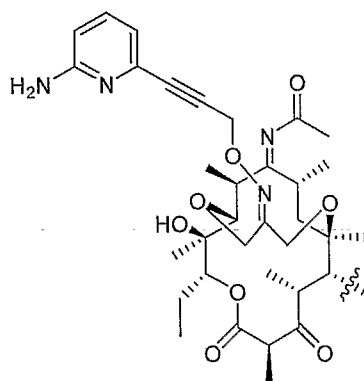
T16



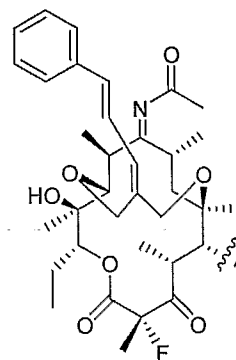
T17



T18

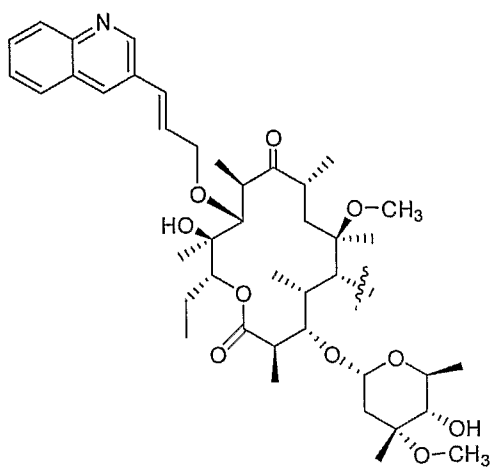


T19

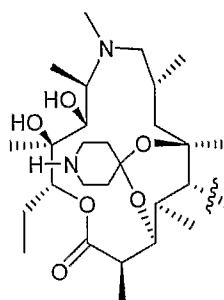


T20

- 39 -

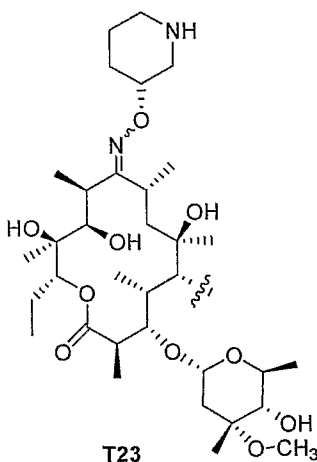


T21

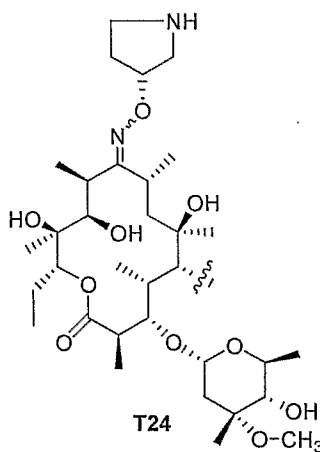


T22

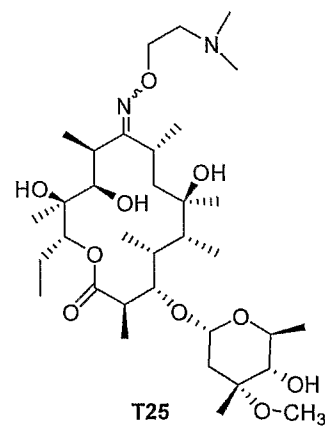
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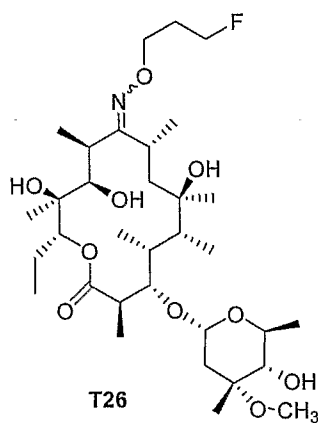
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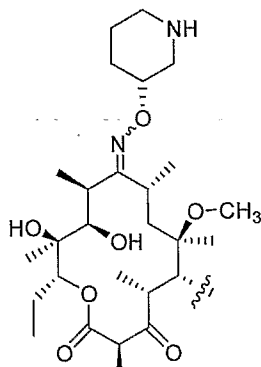
T24



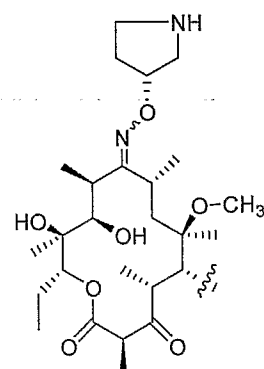
T25



T26

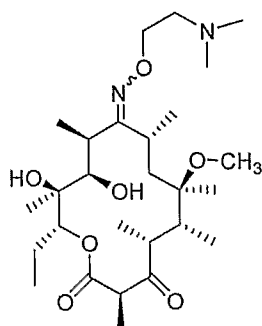


T27

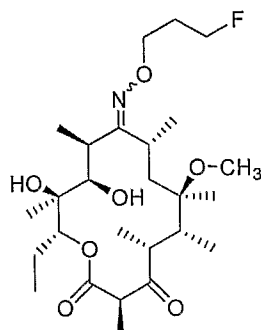


T28

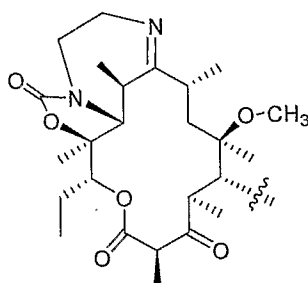
- 40 -



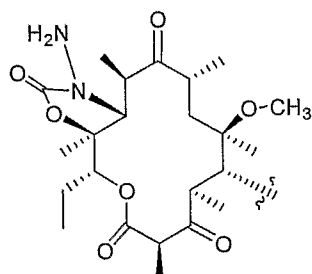
T29



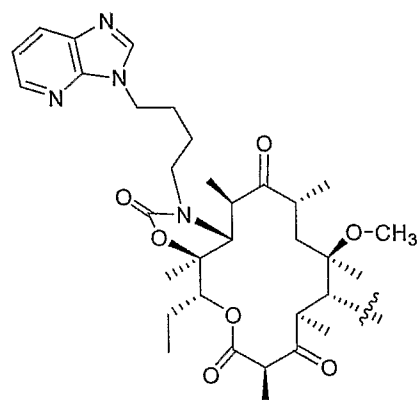
T30



T31



T32



T33

5 As is seen from the foregoing, the macrolide component of the compounds of the present invention can comprise a wide range of structures. Examples of such macrolide components and their syntheses are provided in the following documents, all of which are incorporated by reference in their entirety: PCT application No. WO 2005/118610, published December 15, 2005, to Rib-X Pharmaceuticals, Inc.; PCT application No. WO 10 2005/085266, published September 15, 2005, to Rib-X Pharmaceuticals, Inc.; PCT application No. WO 2005/049632, published June 2, 2005, to Rib-X Pharmaceuticals, Inc.; PCT application No. WO 2005/042554, published May 12, 2005, to Rib-X Pharmaceuticals, Inc.; PCT application No. WO 2004/078770, published September 16, 2004, to Rib-X Pharmaceuticals, Inc.; PCT application No. WO 2004/029066, published 15 April 8, 2004, to Rib-X Pharmaceuticals, Inc.; U.S. Patent No.; U.S. Patent No. 6,992,069, to Gu et al., issued January 31, 2006; U.S. Patent No. 6,953,782, to Phan et al., issued October 11, 2005; U.S. Patent No. 6,939,861, to Ashley et al., issued September 6, 2005; U.S. Patent No., 6,927,057, to Khosla et al., issued August 9, 2005; U.S. Patent No.

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6,794,366, to Chu et al., issued September 21, 2004; U.S. Patent No. 6,762,168, to Chu, issued July 13, 2004; U.S. Patent No. 6,756,359, to Chu et al, issued June 29, 2004; U.S. Patent No. 6,750,205, to Ashley et al, issued June 15, 2004; U.S. Patent No. 6,740,642, to Angehrn et al., issued May 25, 2004; U.S. Patent No. 6,727,352, to Cheng et al., issued April 27, 2004; U.S. Patent Application Publication No. US 2006/0154881, to Or et al., published July 13, 2006; U.S. Patent Application Publication No. US 2006/0142215, to Tang et al., published June 29, 2006; U.S. Patent Application Publication No. US 2006/0142214, to Or et al, published June 29, 2006; U.S. Patent Application Publication No. US 2006/0122128, to Or et al., published June 8, 2006; U.S Patent Application Publication No. US 2006/0069048, to Or et al. published March 30, 2006; U.S. Patent Application Publication No. US 2005/0272672, to Li et al., published December 8, 2005; U.S. Patent Application Publication No US 2005/0009764, to Burger et al, published January 13, 2005; PCT application No. WO 2006/067589, to Pfizer Products Inc., published June 29, 2006; PCT application No. WO 2004/096823, to Chiron Corporation, published November 11, 2004; PCT application No. WO 2004/096822, to Chiron Corporation, published November 11, 2004; PCT application No. WO 2004/080391, to Optimer Pharmaceuticals, Inc., published September 23, 2004; PCT application No. WO 2004/078771, to Taisho Pharmaceutical Co., Ltd., published September 16, 2004; PCT application no. WO 03/061671, to Kosan Biosciences, Inc. published July 31, 2003; and European Patent Document EP 1 256 587 B1, to the Kitasato Institute, granted March 29, 2006.

In another aspect, the invention relates to a compound having the structure corresponding to any one of the structures listed in Tables 1 or Table 1A, or a pharmaceutically acceptable salt, ester, *N*-oxide, or prodrug thereof.

In another aspect, the invention relates to a pharmaceutical composition comprising a compound of the invention and a pharmaceutically acceptable carrier.

In another aspect, the invention relates to a method for treating or preventing a disease state in a mammal comprising administering to a mammal in need thereof an effective amount of a compound of the invention.

In another aspect, the invention relates to a method of treating a microbial infection in a mammal comprising administering to the mammal an effective amount of a compound of the invention.

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In another aspect, the invention relates to a method of treating a fungal infection in a mammal comprising administering to the mammal an effective amount of a compound of the invention.

5 In another aspect, the invention relates to a method of treating a parasitic disease in a mammal comprising administering to the mammal an effective amount of a compound of the invention.

In another aspect, the invention relates to a method of treating a proliferative disease in a mammal comprising administering to the mammal an effective amount of a compound of the invention.

10 In another aspect, the invention relates to a method of treating a viral infection in a mammal comprising administering to the mammal an effective amount of a compound of the invention.

In another aspect, the invention relates to a method of treating an inflammatory disease in a mammal comprising administering to the mammal an effective amount of a compound of the invention.

15 In another aspect, the invention relates to a method of treating a gastrointestinal motility disorder in a mammal comprising administering to the mammal an effective amount of a compound of the invention.

In another aspect, the invention relates to a method of treating or preventing a disease state in a mammal caused or mediated by a nonsense or missense mutation comprising administering to a mammal in need thereof an effective amount of a compound of the invention to suppress expression of the nonsense or missense mutation.

In another aspect, the invention relates to a method of treating a disease or disorder by administering a compound of the invention orally, parentally, or topically.

25 In another aspect, the invention relates to a method of synthesizing a compound of the invention.

In another aspect, the invention relates to a medical device containing a compound of the invention. For example, the medical device is a stent.

30 **3. Synthesis of the Compounds of the Invention**

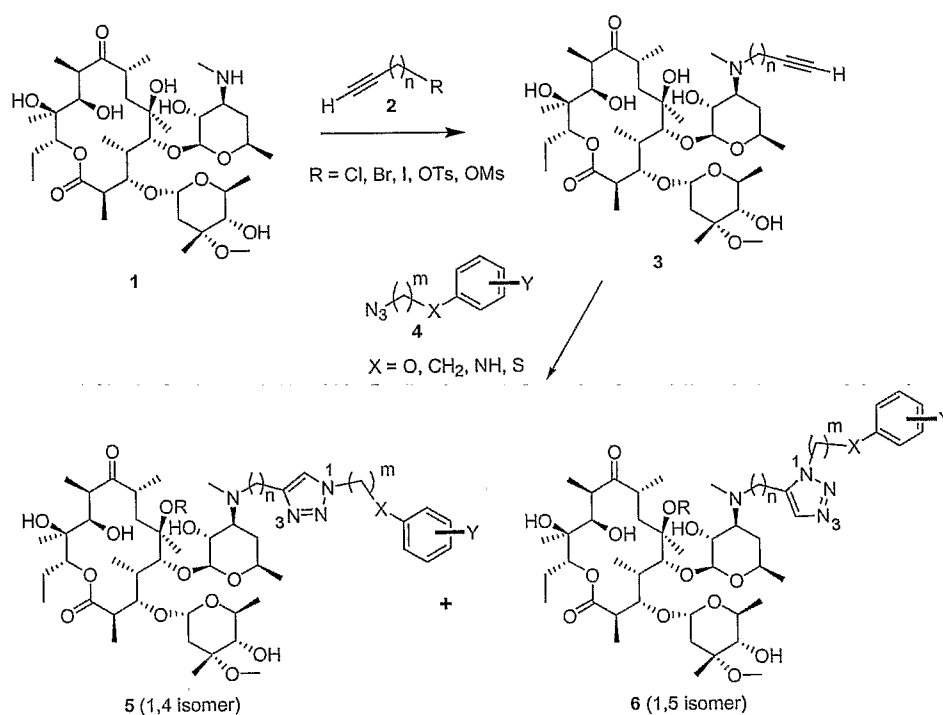
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The invention provides methods for making the compounds of the invention. The following schemes depict exemplary chemistries available for synthesizing the compounds of the invention.

Scheme 1 illustrates the synthesis of triazole compounds of type 5 and 6.

- 5 Erythromycin can be N-demethylated as described in the art (U.S. Patent No. 3,725,385; Flynn *et al.* (1954) J. Am. Chem. Soc. 76: 3121; Ku *et al.* (1997) Bioorg. Med. Chem. Lett. 7: 1203; Stenmark *et al.* (2000) J. Org. Chem. 65: 3875) to afford secondary amine 1. Alkylation of 1 with electrophiles of type 2 yields alkynes of type 3 containing an alkyl chain of appropriate length, generally between one and about four carbon atoms between the nitrogen atom and the alkyne group. Cycloaddition of azides of type 4 with alkynes 3 generates two regioisomeric triazole products. The reaction can be thermally catalyzed, or a number of catalysts could be added to facilitate the reaction (such as, but not limited to, copper (I) iodide: see, Tornøe, C.W. *et al.* (2002) J. Org. Chem. 67: 3057). The major isomer (for steric reasons) is the “anti” isomer 5, a 1,4 disubstituted triazole. The minor component is the “syn” isomer 6, a 1,5 disubstituted triazole.
- 15 component is the “syn” isomer 6, a 1,5 disubstituted triazole.

Scheme 1



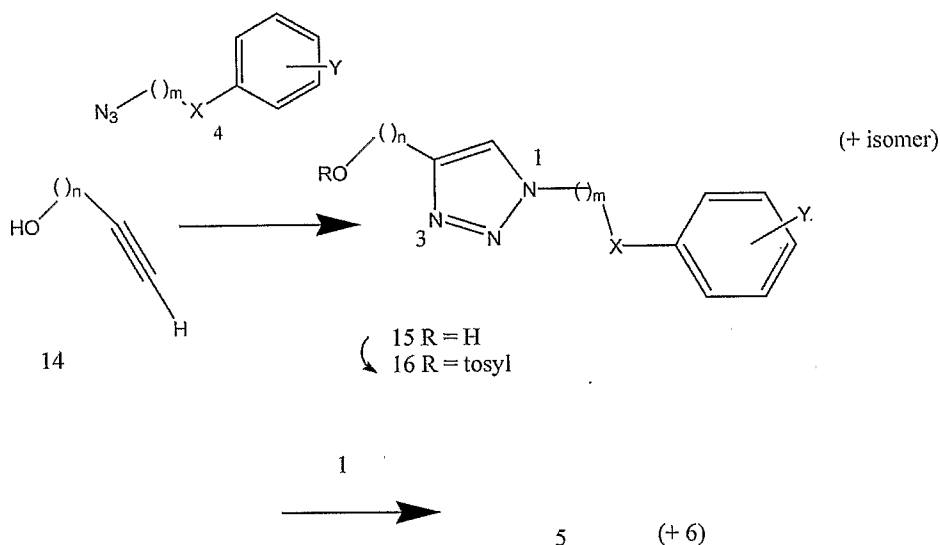
- It is to be understood that other macrolide compounds such as, but not limited to, azithromycin and clarithromycin, could be N-demethylated and serve as starting materials for the chemistry exemplified in Scheme 1. Target compounds derived from such
- 20 for the chemistry exemplified in Scheme 1. Target compounds derived from such

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alternate macrolide precursors are to be considered within the scope of the present invention.

An alternate approach to derivatives of type **5** and **6** is illustrated by Scheme 2. Acetylenic alcohols of type **14** can be treated with azides **4** to yield intermediate alcohol **15** (along with a minor amount of the regioisomeric triazole). Tosylation of **15** will provide tosylates **16** which can serve as alkylating agents for macrolide amines of type **1** to afford targets **5** (and its isomer **6**). It will be appreciated that other sulfonate derivatives or halides could be formed from intermediate alcohol **15**, and these would be useful as electrophiles for the alkylation of macrolide amines such as **1** to afford compounds of the invention.

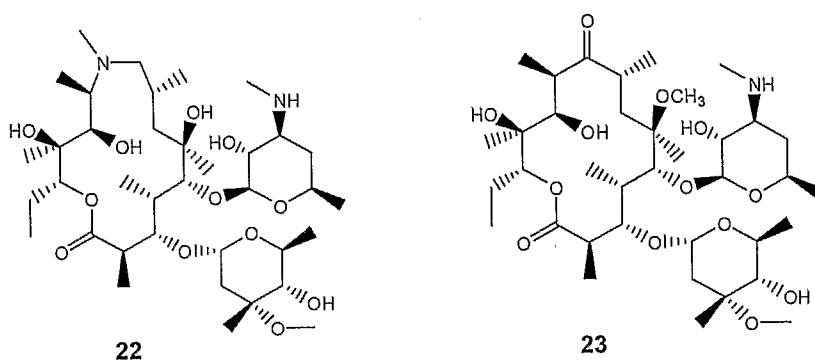
Scheme 2



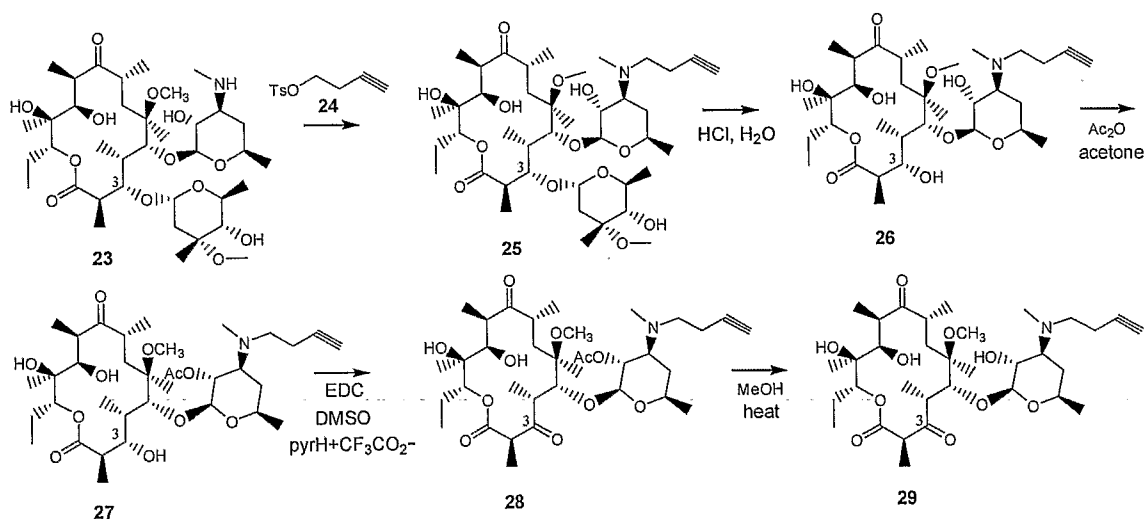
Other starting materials for the synthesis of compounds of the present invention are readily synthesizable. For example, des-methyl macrolide amines **22** and **23** can be prepared from azithromycin and clarithromycin respectively, using the same procedure for the synthesis of **1** from erythromycin. Ketolide derivatives (C-3 keto compounds synthesized from macrolides) of the present invention can be prepared by chemistry such as that shown in Scheme 3. Clarithromycin-derived amine **23** is alkylated with tosylate **24** to afford alkyne **25**. The cladinose sugar at C-3 is hydrolyzed to afford the C-3 hydroxy intermediate **26**, which is then selectively acetylated on the hydroxyl of the aminosaccharide group to yield **27**. Oxidation of **27** yields C-3 keto derivative **28** which is then deacylated to provide alkyne **29**. Alkyne **29** can be exposed to the chemistry of

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Scheme 1 above to deliver triazole and isoxazole compounds of the present invention that have C-3 keto clarithromycin-derived structures. It will be understood that alkylation of **23** with electrophiles of type 7, and then exposure of the product nitriles to the chemistry shown in Scheme 3, will yield tetrazoles that have C-3 keto clarithromycin-derived structures. Additionally, C-3 keto azithromycin and erythromycin intermediates could be prepared from **1** and **22** using the chemistry of Scheme 3, and subsequently serve as starting materials for compounds of the present invention.



Scheme 3



10

4. Characterization of Compounds of the Invention

Compounds designed, selected and/or optimized by methods described above, once produced, can 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 can be characterized by conventional assays, including but not limited to those assays .

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described below, to determine whether they have a predicted activity, binding activity and/or binding specificity.

Furthermore, high-throughput screening can be used to speed up analysis using such assays. As a result, it can be possible to rapidly screen the molecules described
5 herein for activity, for example, as anti-cancer, anti-bacterial, anti-fungal, anti-parasitic or anti-viral agents. Also, it can 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 (1998) High
10 Throughput Screening, Marcel Dekker; 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 can be useful in screening new molecules for their binding activity. One approach includes surface
15 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, Piscataway, N.J.) provides a
20 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
25 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
30 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

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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
5 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 K_d s of the association reaction between two molecules. In this technique one of the molecules of interest is conjugated with a
10 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
15 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
20 on FP have a number of important advantages, including the measurement of IC_{50} s and K_d s 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 can also be characterized as a
25 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 can 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
30 pharmacological and inhibitory properties by determining, for example, its inhibition constant (IC_{50}) for inhibiting protein synthesis. Incorporation of ^3H leucine or ^{35}S methionine, or similar experiments can be performed to investigate protein synthesis

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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.

5 Furthermore, the compounds can 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 can be assayed by growing the microorganisms of interest in media either containing or lacking the compound. Growth inhibition can be indicative that the molecule can be acting as a protein synthesis inhibitor. More
10 specifically, the activity of the compounds of interest against bacterial pathogens can 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
15 structure-activity relationships not only in regards to potency and spectrum, but also with a view to obviating resistance mechanisms. The assays can 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
20 Standard-Fifth Edition. NCCLS Document M100-S12/M7 (ISBN 1-56238-394-9)).

5. **Formulation and Administration**

The compounds of the invention can be useful in the prevention or treatment of a variety of human or other animal, including mammalian and non mammalian, disorders, including for example, bacterial infection, fungal infections, viral infections, parasitic
25 diseases, and cancer. It is contemplated that, once identified, the active molecules of the invention can 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
30 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.

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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 can conveniently be presented in dosage unit form and can 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, (Gennaro, A., ed.), Mack Pub., (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,

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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-
5 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
10 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 can 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
15 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 can also be administered in the form of a bolus, electuary or paste. A tablet can be made by compressing or moulding the drug optionally with one or more accessory ingredients. Compressed tablets can be prepared by compressing, in a suitable machine, the drug in a free-flowing form such as a
20 powder or granules, optionally mixed by a binder, lubricant, inert diluent, surface active or dispersing agent. Moulded tablets can be made by moulding, 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
25 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
30 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

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

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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
5 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
10 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
15 powder inhalation device or self-propelling powder-dispensing formulations. In the case of self-propelling solution and spray formulations, the effect can 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
20 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
25 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.

30 The active compounds can 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,

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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. Patent 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 therapeutically 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

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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.

5 The compounds of the present invention can be administered directly to a tissue locus by applying the compound to a medical device that is placed in contact with the tissue. An example of a medical device is a stent, which contains or is coated with one or more of the compounds of the present invention.

 For example, an active compound can be applied to a stent at the site of vascular
10 injury. Stents can be prepared by any of the methods well known in the pharmaceutical art. See, e.g., Fattori, R. and Piva, T., "Drug Eluting Stents in Vascular Intervention," Lancet, 2003, 361, 247-249; Morice, M. C., "A New Era in the Treatment of Coronary Disease?" European Heart Journal, 2003, 24, 209-211; and Toutouzas, K. et al.,
15 "Sirolimus-Eluting Stents: A Review of Experimental and Clinical Findings," Z. Kardiol., 2002, 91(3), 49-57. The stent can be fabricated from stainless steel or another bio-compatible metal, or it can be made of a bio-compatible polymer. The active compound can be linked to the stent surface, embedded and released from polymer materials coated on the stent, or surrounded by and released through a carrier which coats or spans the stent. The stent can be used to administer single or multiple active compounds to tissues
20 adjacent to the stent.

 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
25 between an individual's genotype and that individual's response to a foreign compound or drug) can 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 can consider applying knowledge obtained in relevant pharmacogenomics studies in determining whether to administer a drug as well as tailoring the dosage and/or therapeutic
30 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,

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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. 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 can be increased beyond the above upper level in order to rapidly achieve the desired blood-level or tissue level, or the initial dosage can be smaller than the optimum and the daily dosage can be progressively increased during the course of treatment depending on the particular situation. If desired, the daily dose can also be divided into multiple doses for administration, for example, two to four times per day.

Various disease states or conditions in humans and other mammals are found to be caused by or mediated by nonsense or missense mutations. These mutations cause or mediate the disease state or condition by adversely affecting, for example, protein synthesis, folding, trafficking and/or function. Examples of disease states or conditions in which an appreciable percentage of the disease or condition is believed to result from nonsense or missense mutations include hemophilia (factor VIII gene), neurofibromatosis (NF1 and NF2 genes), retinitis pigmentosa (human USH2A gene), bullous skin diseases like Epidermolysis bullosa pruriginosa (COL7A1 gene), cystic fibrosis (cystic fibrosis transmembrane regulator gene), breast and ovarian cancer (BRCA1 and BRCA2 genes), Duchenne muscular dystrophy (dystrophin gene), colon cancer (mismatch repair genes, predominantly in MLH1 and MSH2), and lysosomal storage disorders such as Neimann-Pick disease (acid sphingomyelinase gene). See Sanders CR, Myers JK. Disease-related misassembly of membrane proteins. *Annu Rev Biophys Biomol Struct.* 2004;33:25-51; National Center for Biotechnology Information (U.S.) Genes and disease Bethesda, MD : NCBI, NLM ID: 101138560; and Raskó, István; Downes, C S Genes in medicine : molecular biology and human genetic disorders 1st ed. London ; New York : Chapman & Hall, 1995. NLM ID: 9502404. The compounds of the present invention can be used to

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treat or prevent a disease state in a mammal caused or mediated by such nonsense or missense mutations by administering to a mammal in need thereof an effective amount of the present invention to suppress the nonsense or missense mutation involved in the disease state.

5 6. Examples

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
10 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.

Some of the abbreviations used in the following experimental details of the synthesis of the examples are defined below:

15 hr = hour(s); min = minute(s); mol = mole(s); mmol = millimole(s); M = molar; μ M = micromolar; g = gram(s); μ g = microgram(s); rt = room temperature; L = liter(s); mL = milliliter(s); Et₂O = diethyl ether; THF = tetrahydrofuran; DMSO = dimethyl sulfoxide; EtOAc = ethyl acetate; Et₃N = triethylamine; *i*-Pr₂NEt = diisopropylethylamine; CH₂Cl₂ = methylene chloride; CHCl₃ = chloroform; CDCl₃ =
20 deuterated chloroform; CCl₄ = carbon tetrachloride; MeOH = methanol; CD₃OD = deuterated methanol; EtOH = ethanol; DMF = dimethylformamide; BOC = *t*-butoxycarbonyl; CBZ = benzyloxycarbonyl; TBS = *t*-butyldimethylsilyl; TBSCl = *t*-butyldimethylsilyl chloride; TFA = trifluoroacetic acid; DBU = diazabicycloundecene; TBDPSCl = *t*-butyldiphenylchlorosilane; Hunig's Base = *N,N*-diisopropylethylamine;
25 DMAP = 4-dimethylaminopyridine; CuI = copper (I) iodide; MsCl = methanesulfonyl chloride; NaN₃ = sodium azide; Na₂SO₄ = sodium sulfate; NaHCO₃ = sodium bicarbonate; NaOH = sodium hydroxide; MgSO₄ = magnesium sulfate; K₂CO₃ = potassium carbonate; KOH = potassium hydroxide; NH₄OH = ammonium hydroxide; NH₄Cl = ammonium chloride; SiO₂ = silica; Pd-C = palladium on carbon; Pd(dppf)Cl₂
30 = dichloro[1,1'-bis(diphenylphosphino)ferrocene] palladium (II).

Exemplary compounds synthesized in accordance with the invention are listed in Table 1. A bolded or dashed bond is shown to indicate a particular stereochemistry at a

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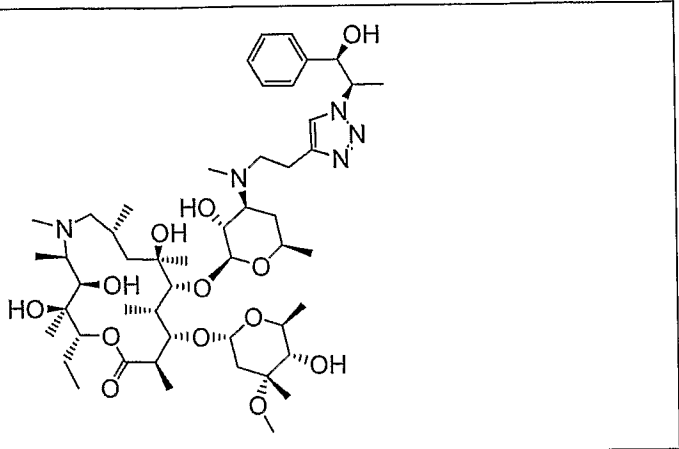
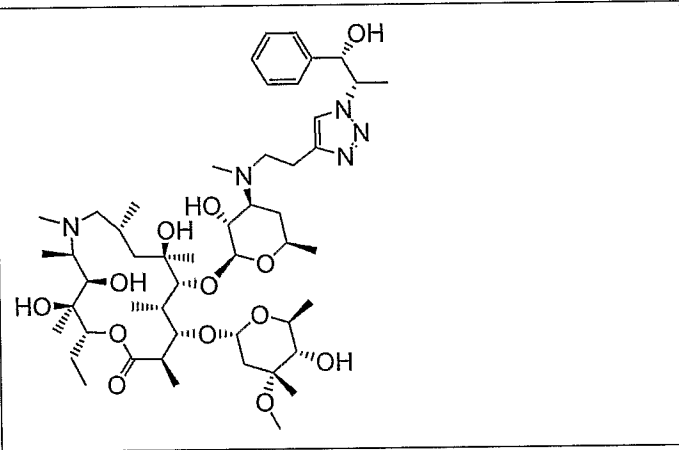
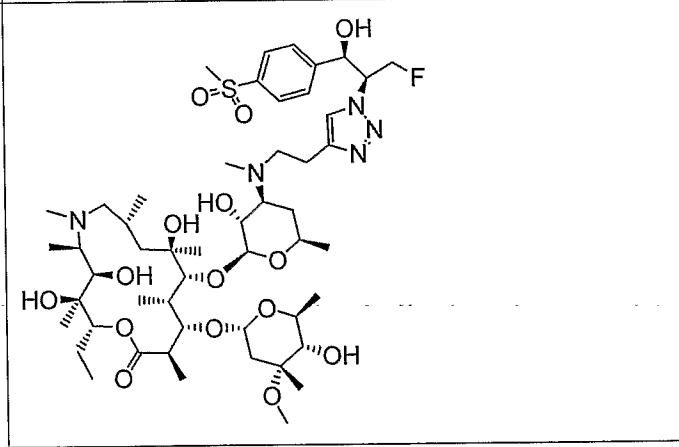
chiral center, whereas a wavy bond indicates that the substituent can be in either orientation or that the compound is a mixture thereof. It should also be known that in the interest of space, the chemical structures have been condensed, for example the methyl and ethyl group substituents are designated with just a carbon backbone representation, and the unsaturated bonds in the triazole rings might not always be visible.

Other exemplary compounds synthesized in accordance with the invention are listed in Table 1A.

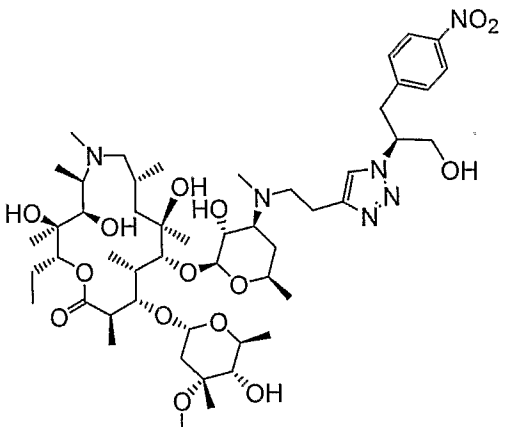
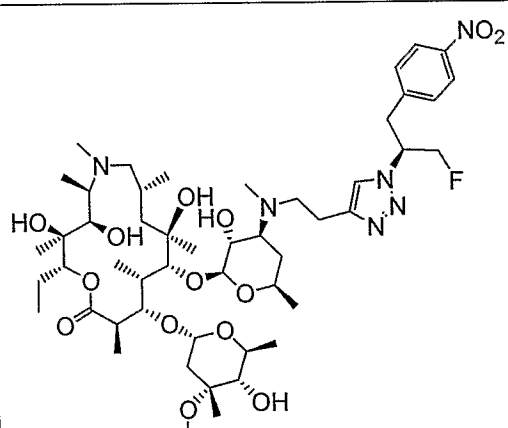
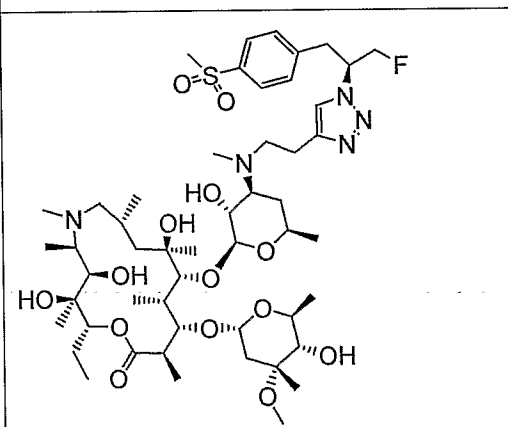
The compounds of the present invention can be prepared, formulated, and delivered as salts, esters, and prodrugs. For convenience, the compounds are generally shown without indicating a particular salt, ester, or prodrug form.

Table 1		
Compound No.		Structure
101		
102		

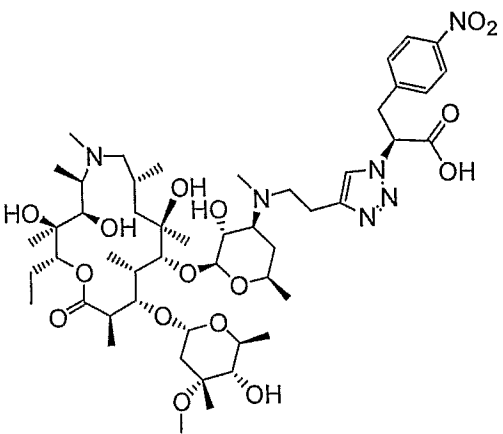
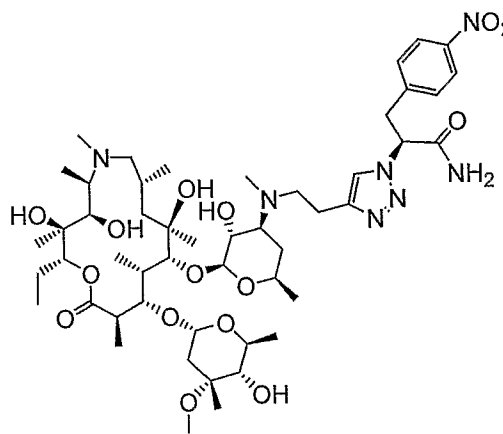
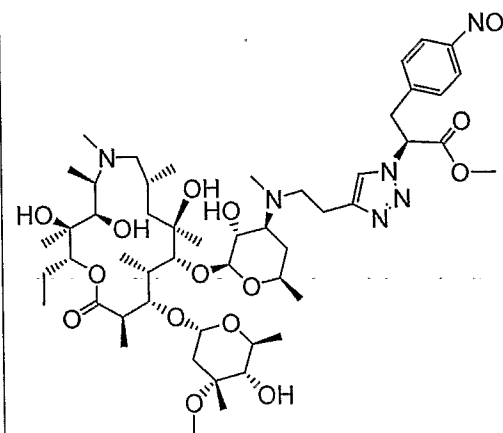
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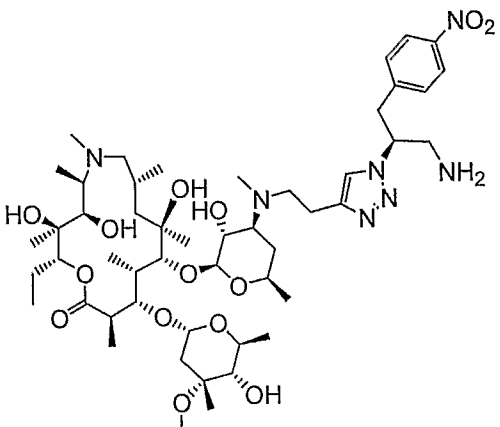
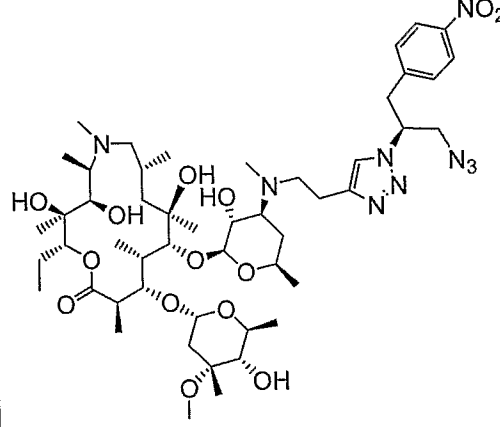
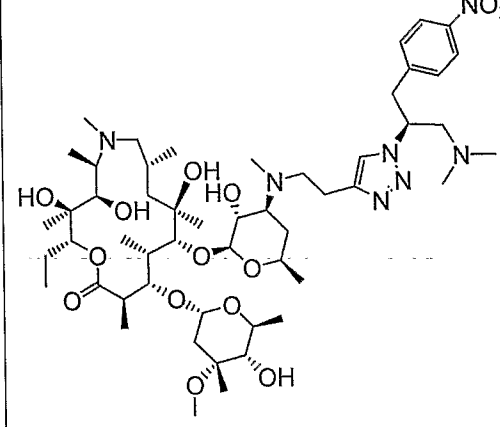
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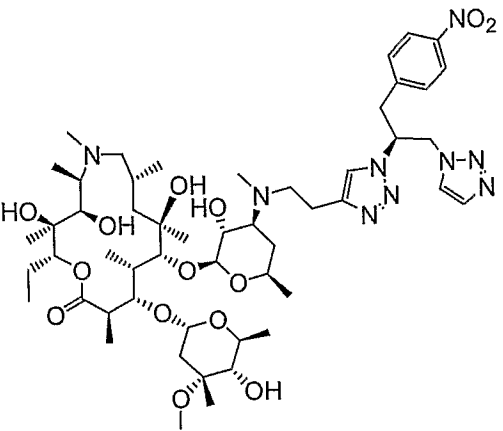
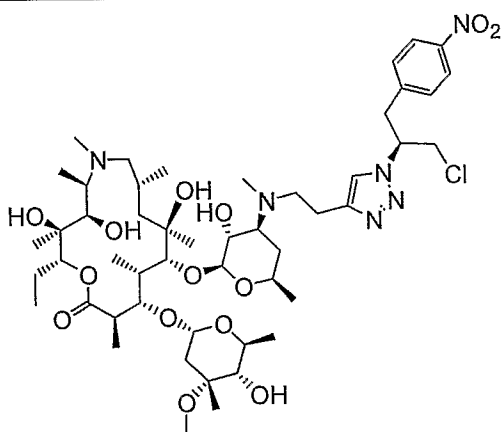
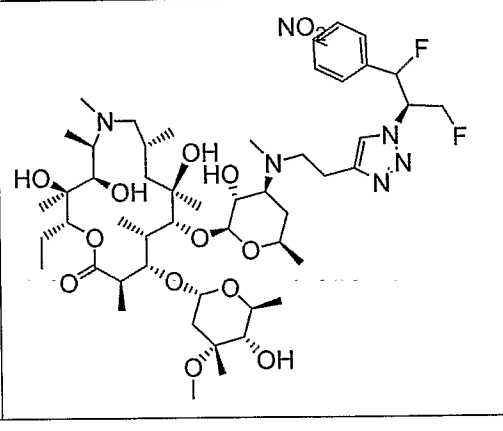
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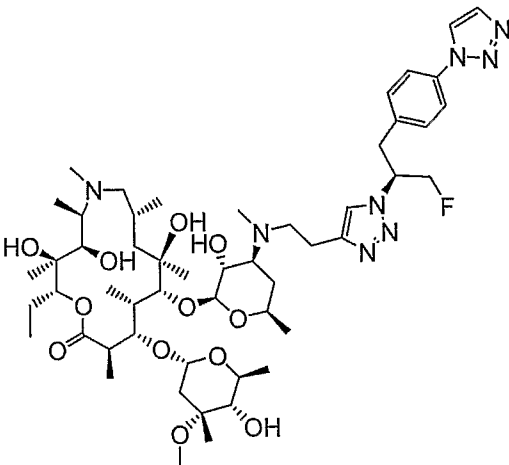
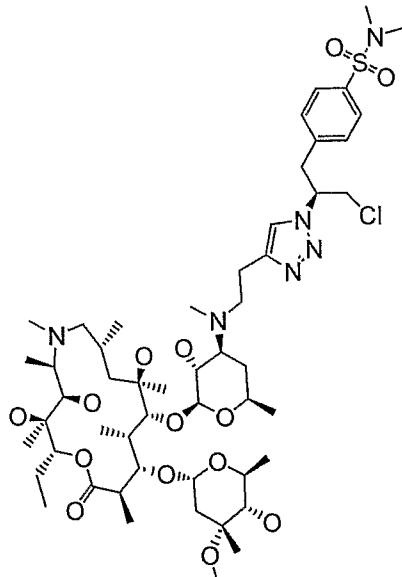
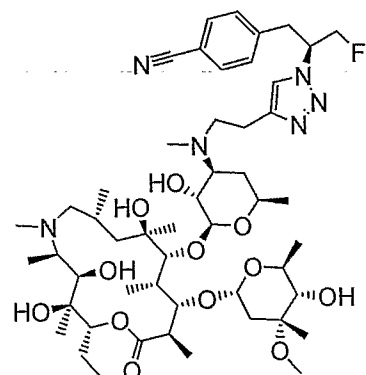
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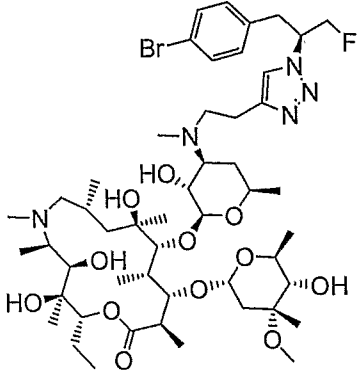
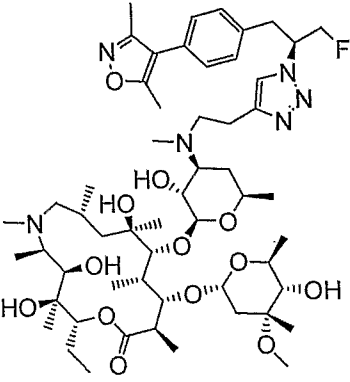
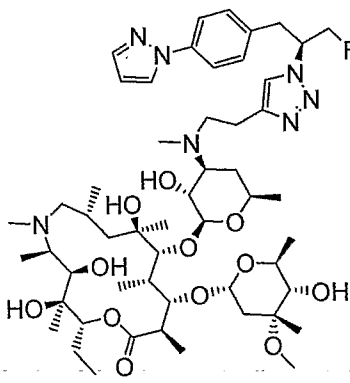
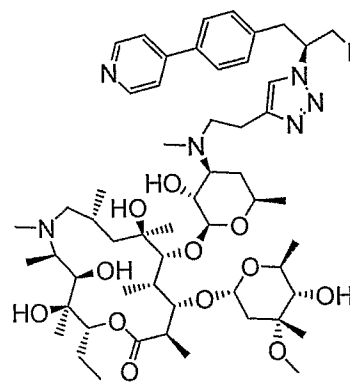
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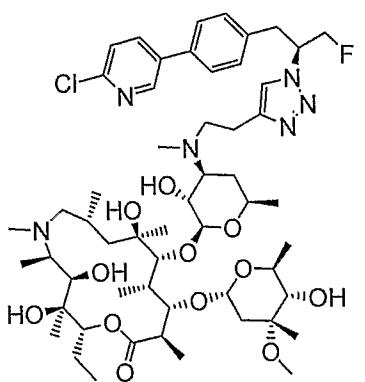
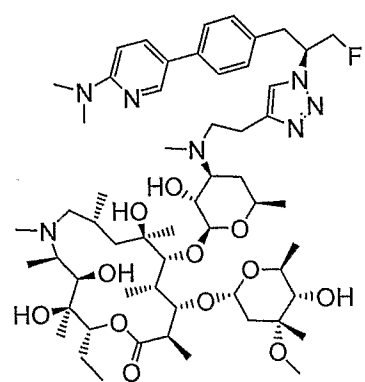
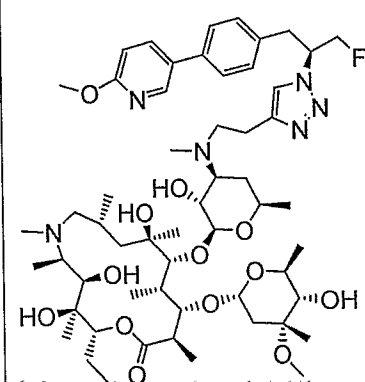
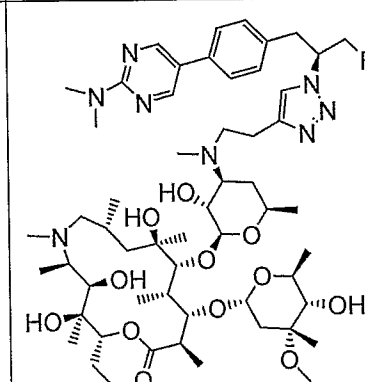
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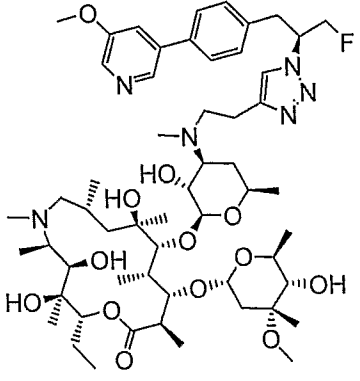
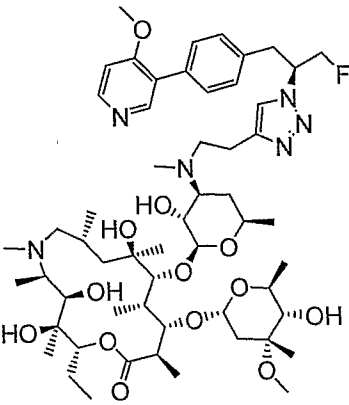
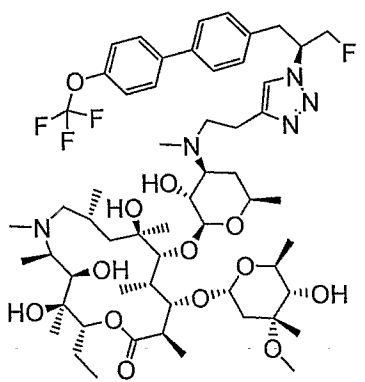
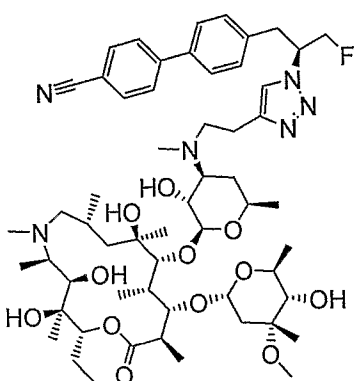
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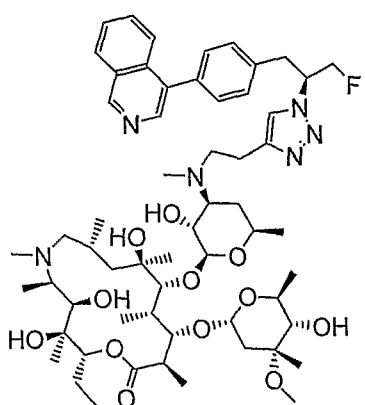
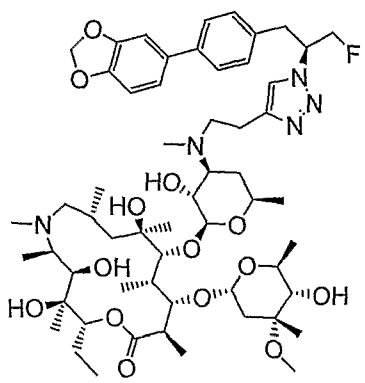
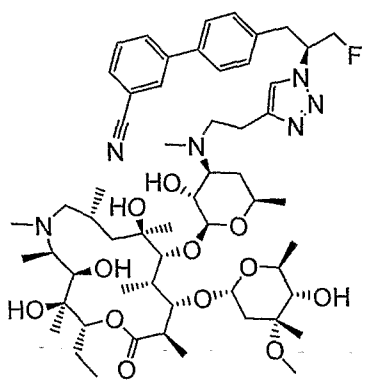
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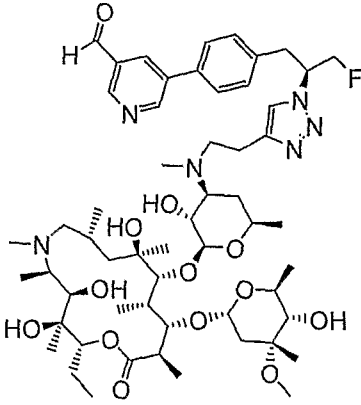
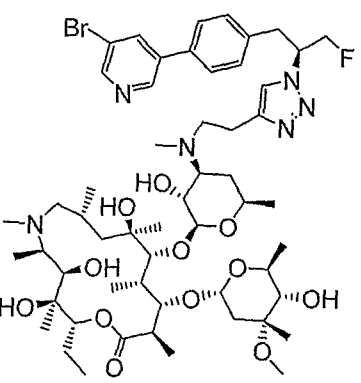
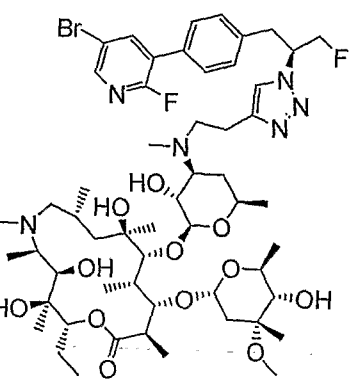
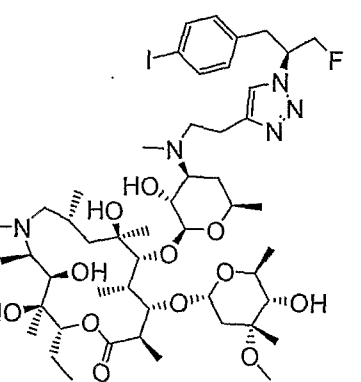
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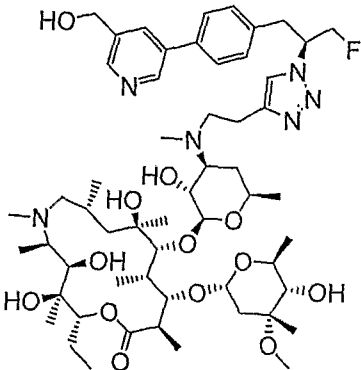
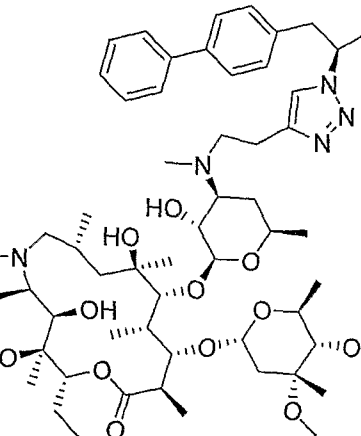
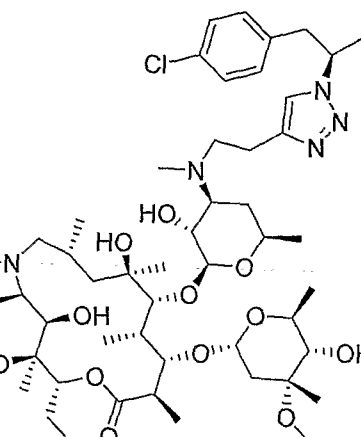
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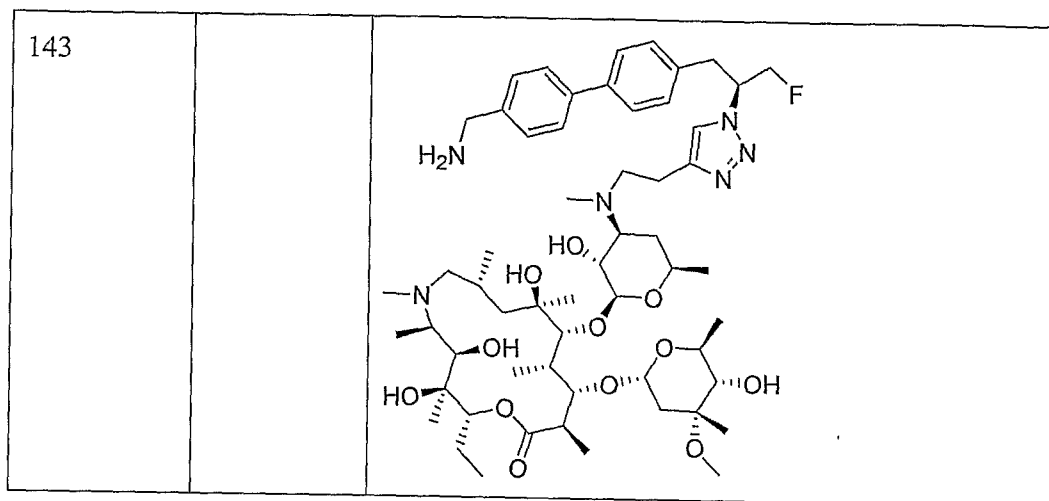
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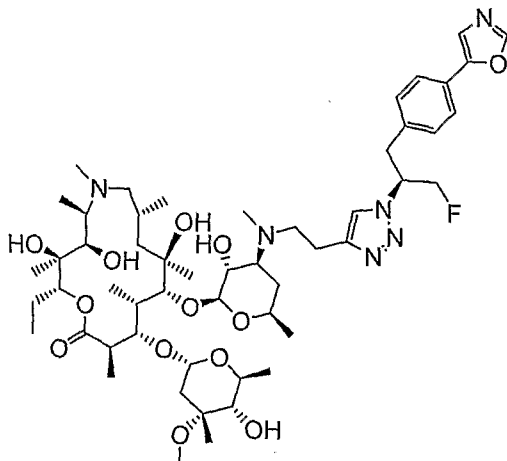
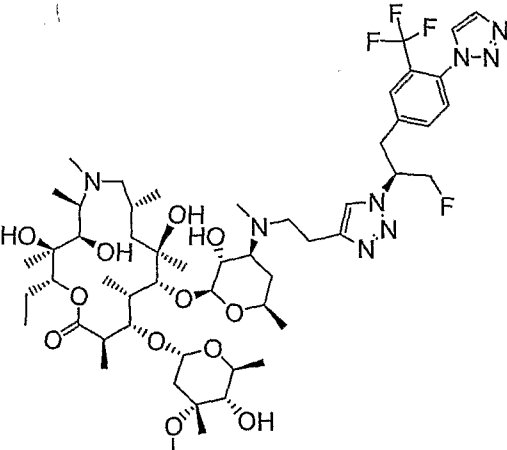
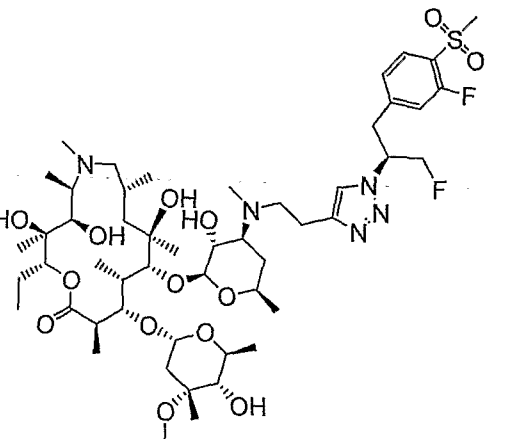
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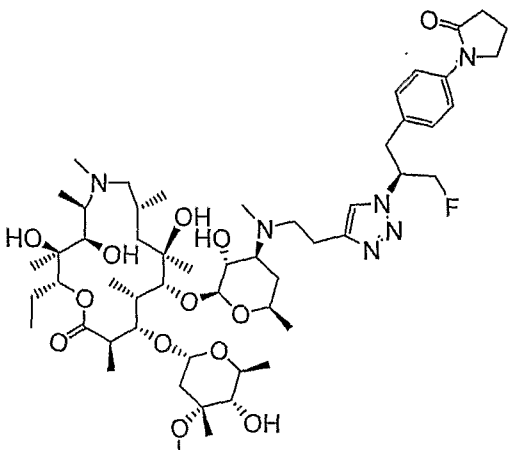
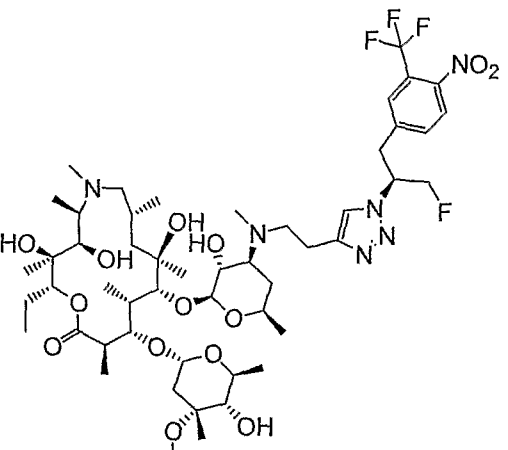
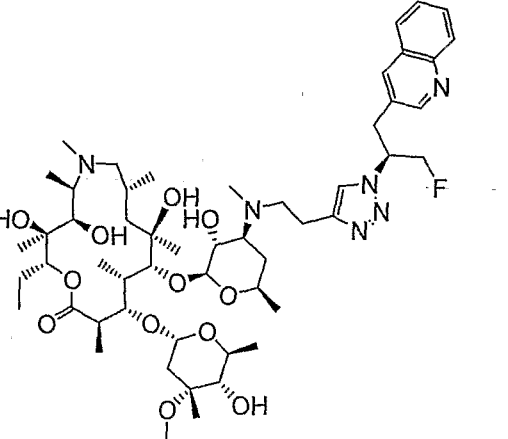
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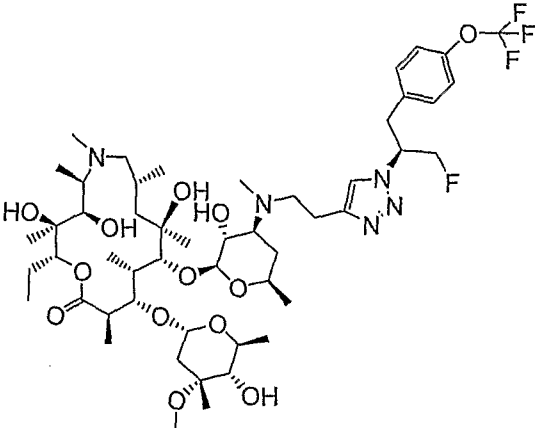
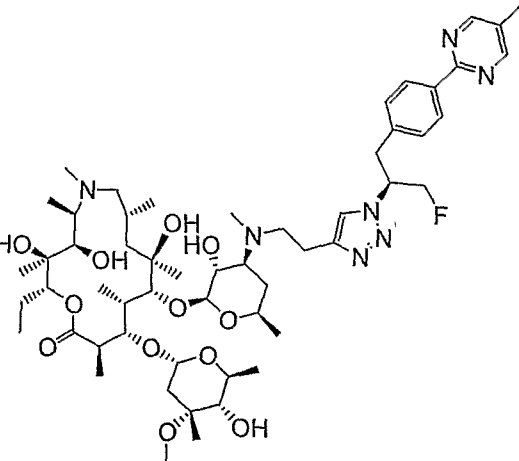
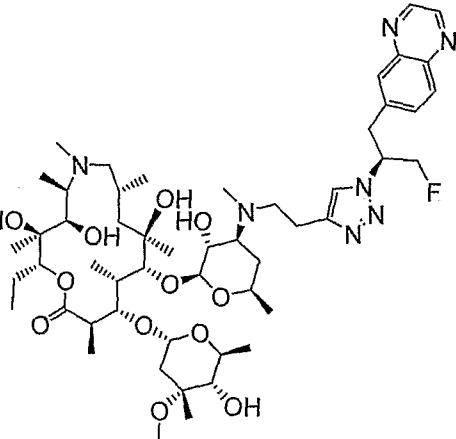
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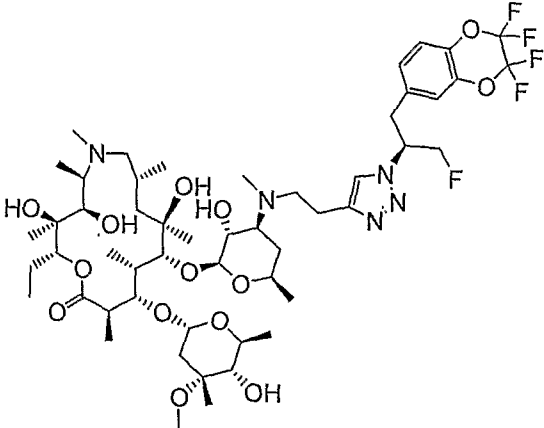
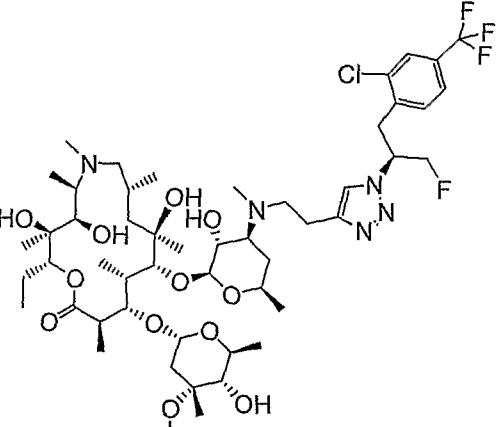
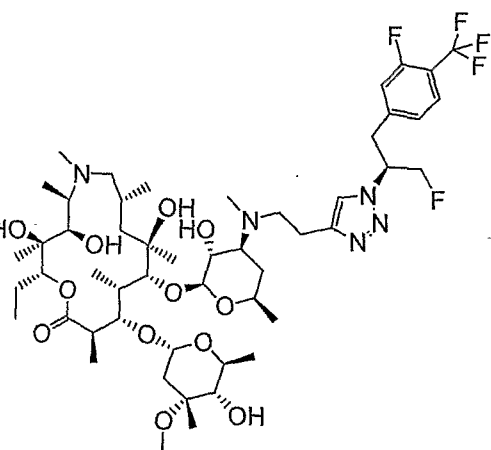


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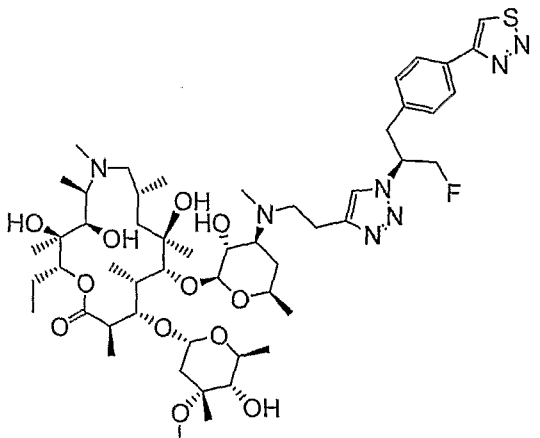
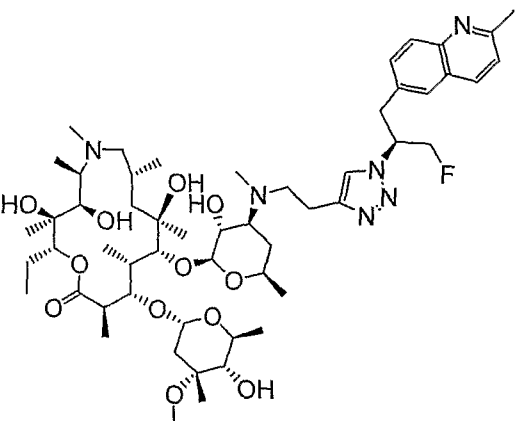
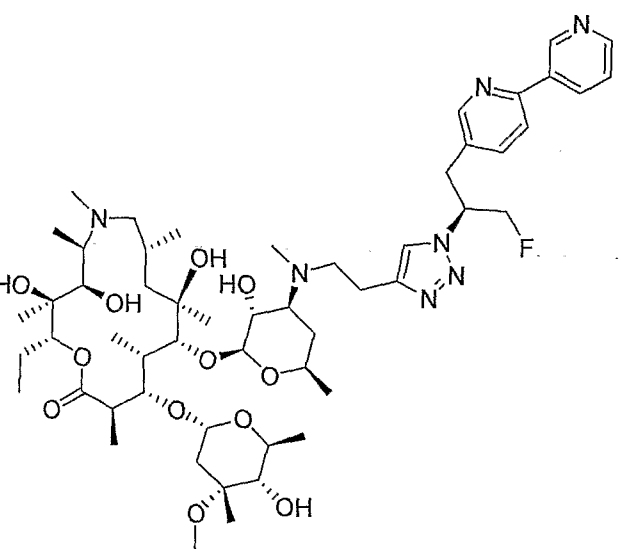
144		 Chemical structure 144: A complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a side chain containing a triazole ring, a fluorine atom, and a 4-isoxazol-5-yl group.
145		 Chemical structure 145: A complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a side chain containing a triazole ring, a fluorine atom, and a 2,2-difluoro-5-(1H-1,2,4-triazol-1-yl)phenyl group.
146		 Chemical structure 146: A complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a side chain containing a triazole ring, a fluorine atom, and a 2-fluoro-4-(sulfonyl)phenyl group.

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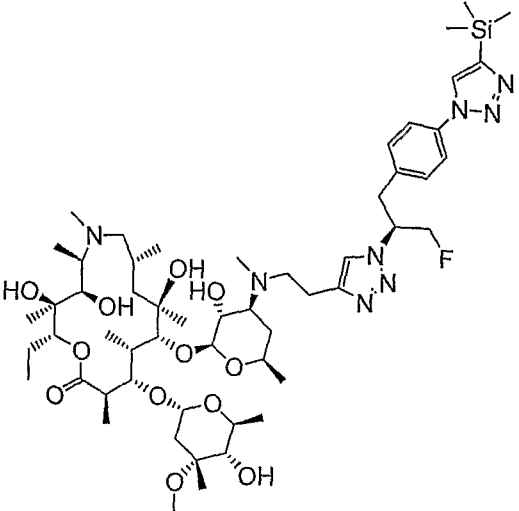
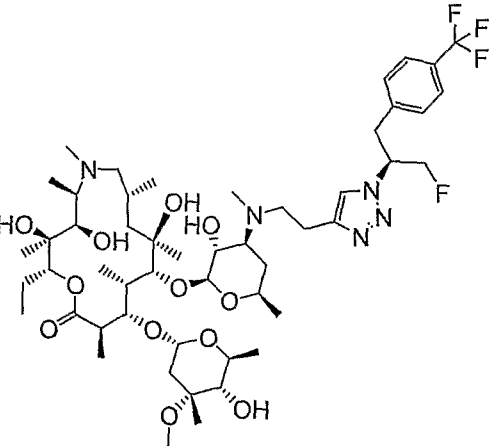
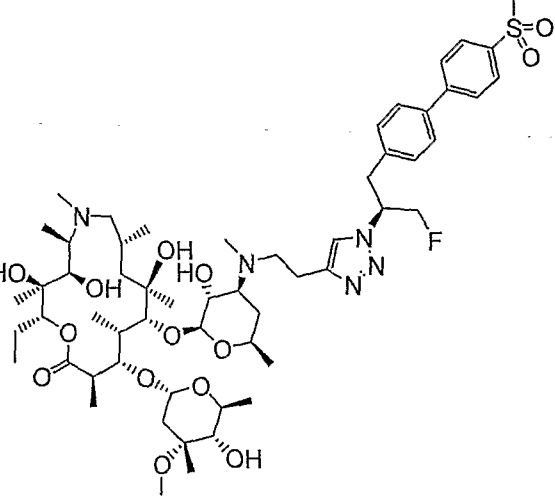
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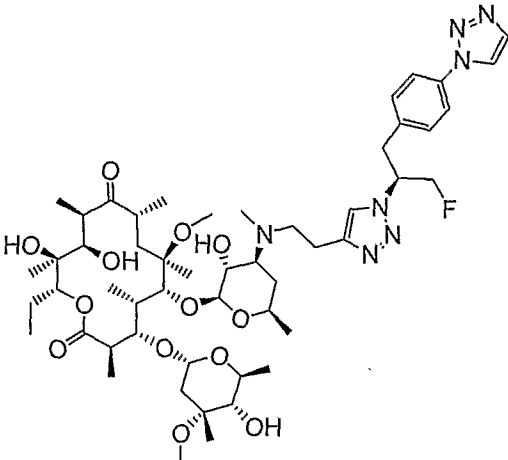
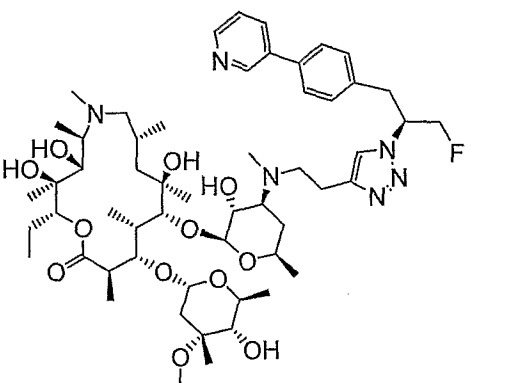
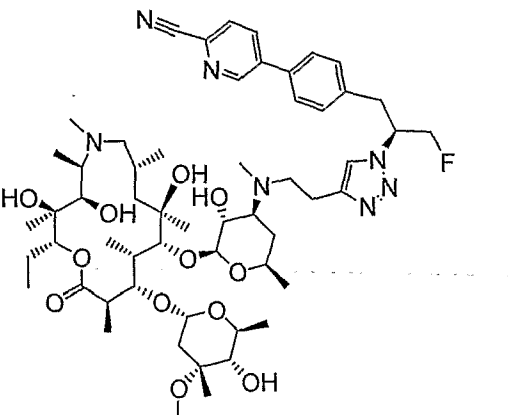
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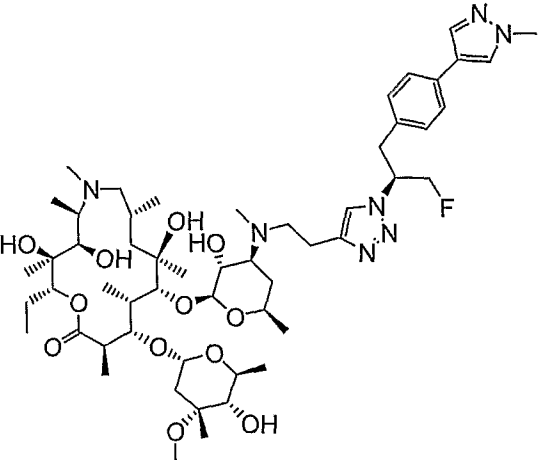
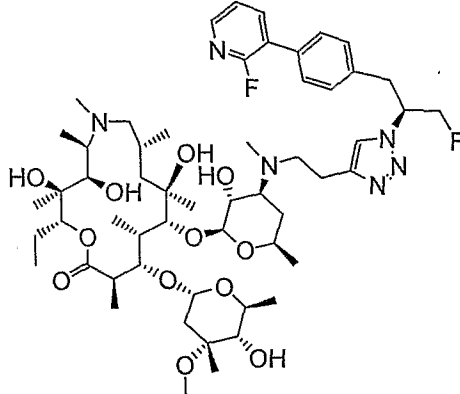
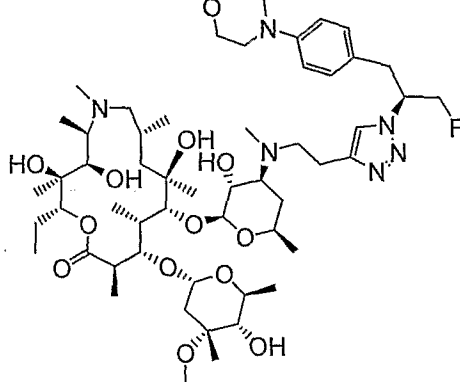
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159		 Chemical structure 159: A complex molecule featuring a central core with multiple hydroxyl groups and a side chain containing a 1,2,3-triazole ring, a fluorine atom, and a 4-(trimethylsilyl)phenyl group.
160		 Chemical structure 160: A complex molecule featuring a central core with multiple hydroxyl groups and a side chain containing a 1,2,3-triazole ring, a fluorine atom, and a 4-(trifluoromethyl)phenyl group.
161		 Chemical structure 161: A complex molecule featuring a central core with multiple hydroxyl groups and a side chain containing a 1,2,3-triazole ring, a fluorine atom, and a 4-(sulfonyl)phenyl group.

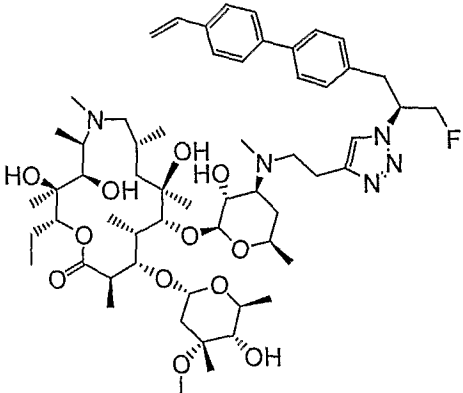
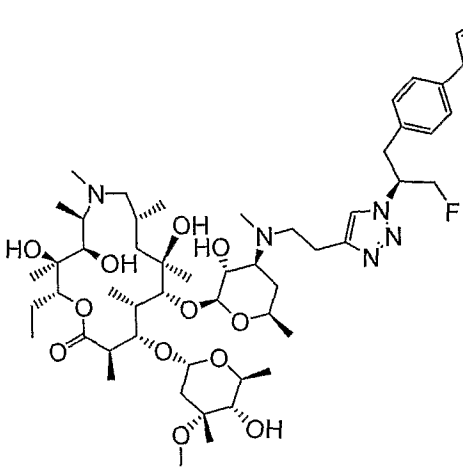
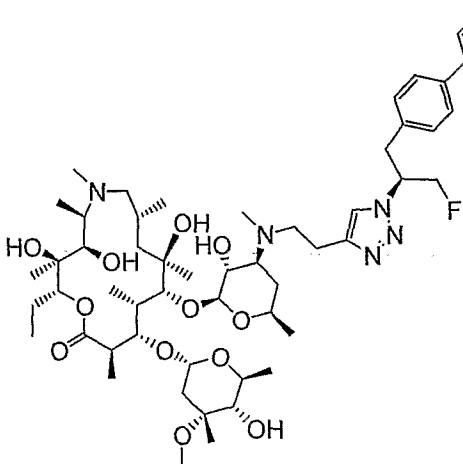
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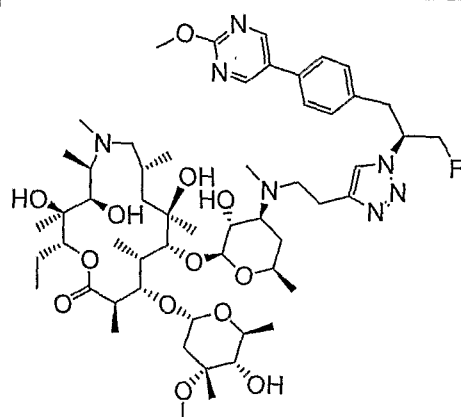
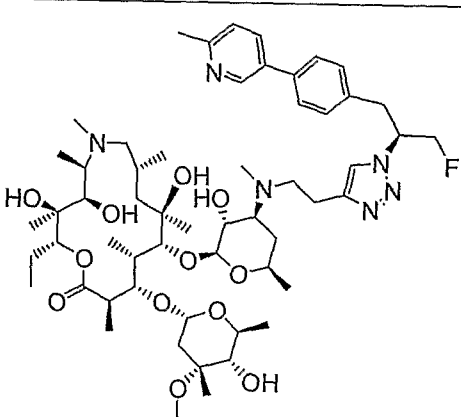
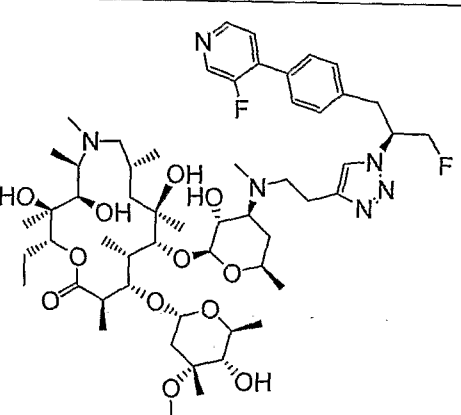
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165		 Chemical structure of compound 165: A complex molecule featuring a central core with multiple hydroxyl groups and a fluorinated side chain. The side chain includes a triazole ring system connected to a phenyl ring, which is further substituted with a pyrazole ring.
166		 Chemical structure of compound 166: A complex molecule featuring a central core with multiple hydroxyl groups and a fluorinated side chain. The side chain includes a triazole ring system connected to a phenyl ring, which is further substituted with a pyridine ring.
167		 Chemical structure of compound 167: A complex molecule featuring a central core with multiple hydroxyl groups and a fluorinated side chain. The side chain includes a triazole ring system connected to a phenyl ring, which is further substituted with a morpholine ring.

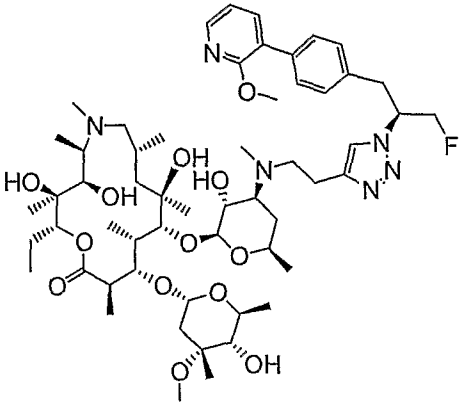
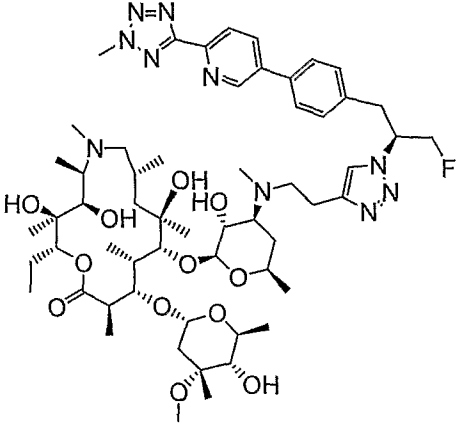
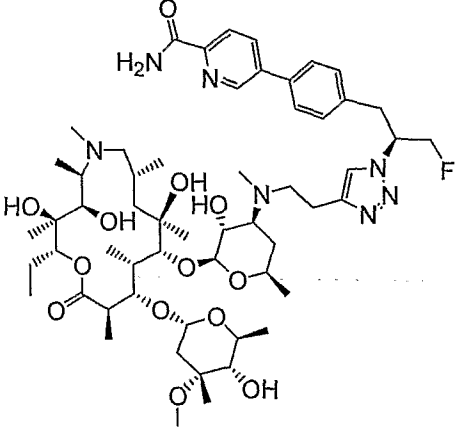
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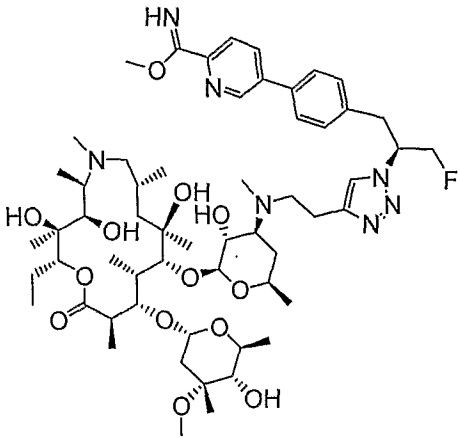
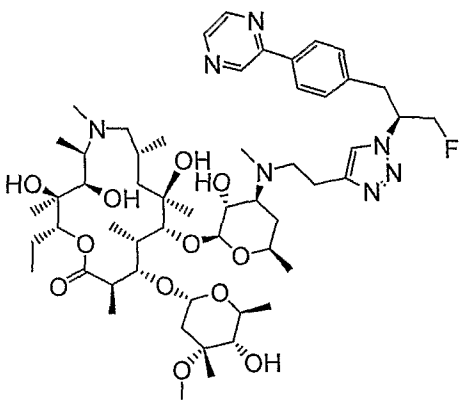
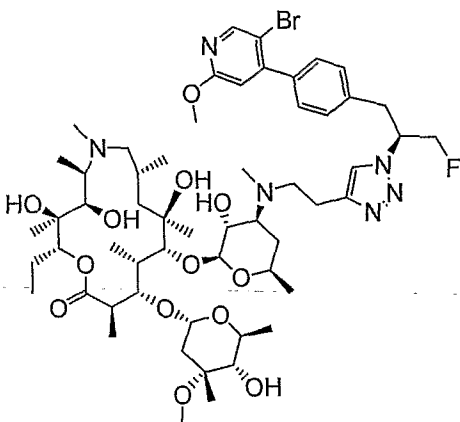
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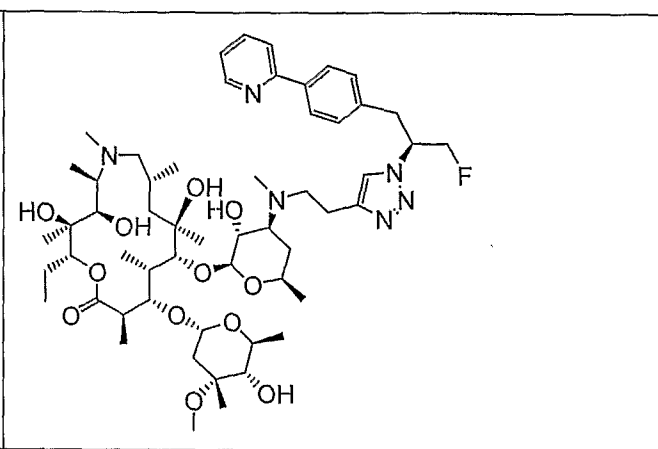
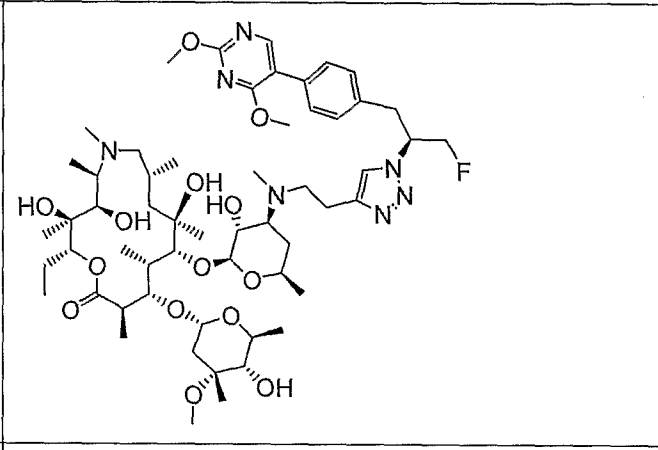
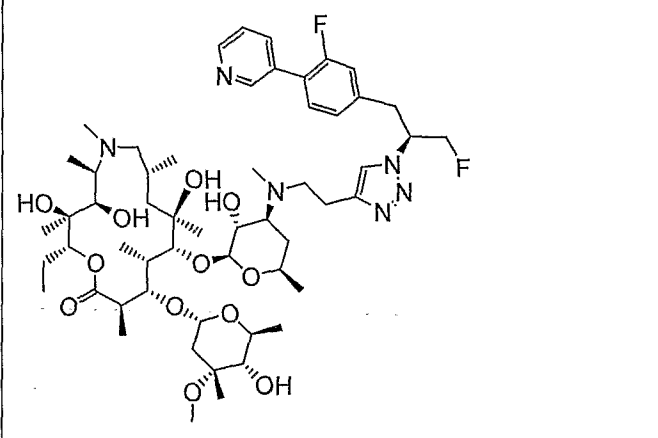
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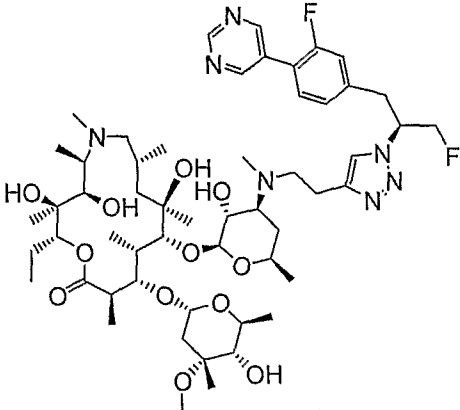
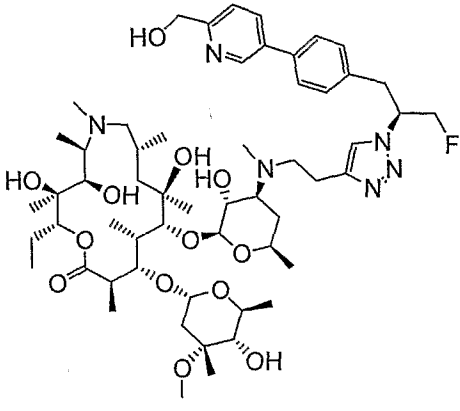
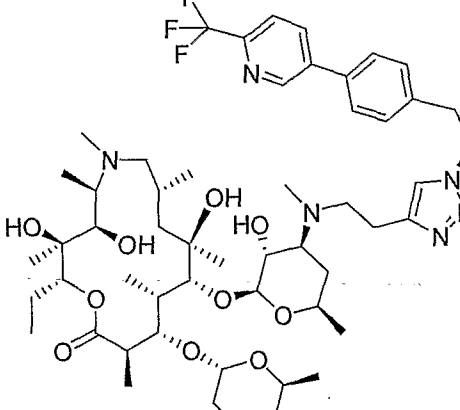
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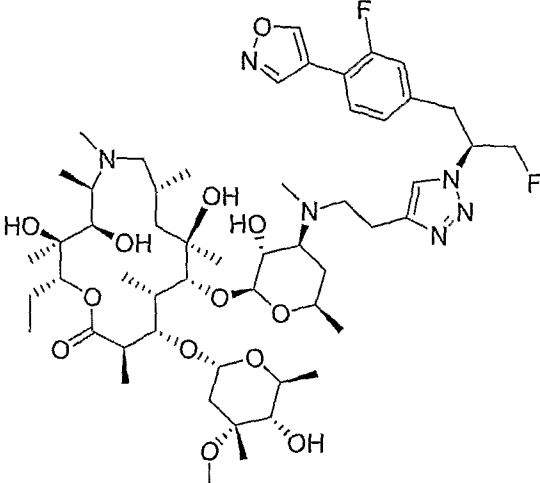
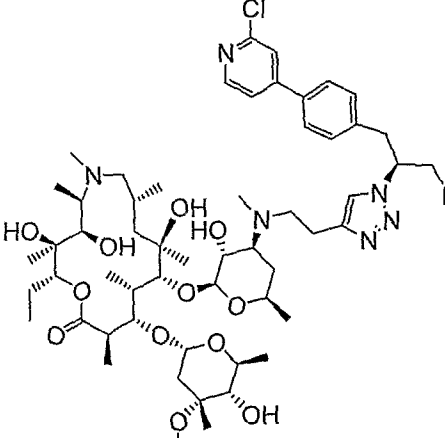
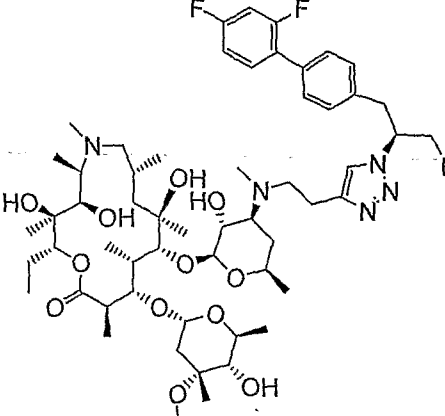
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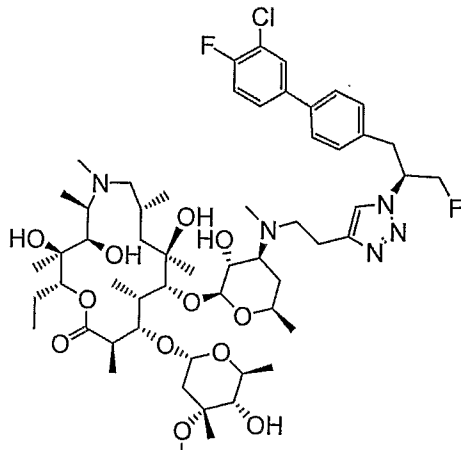
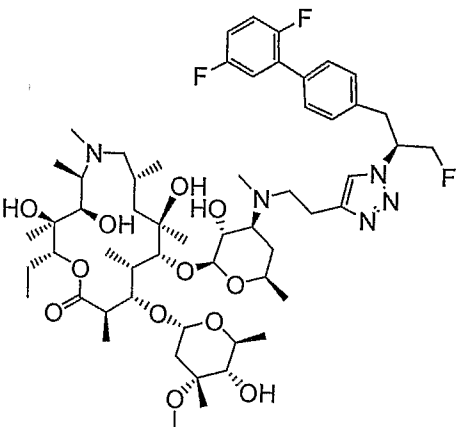
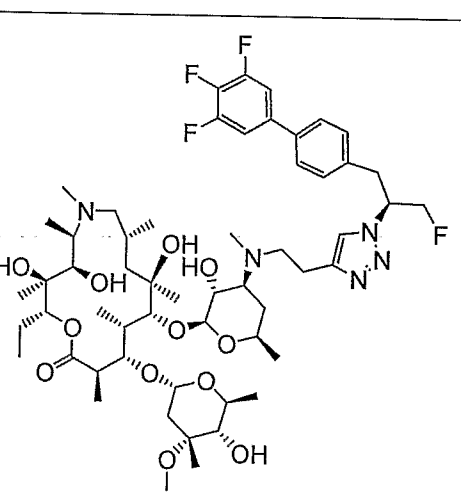
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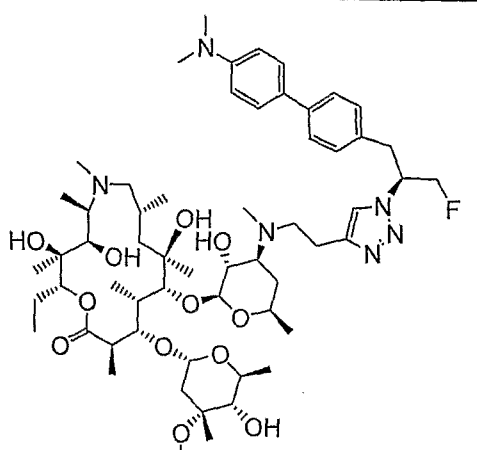
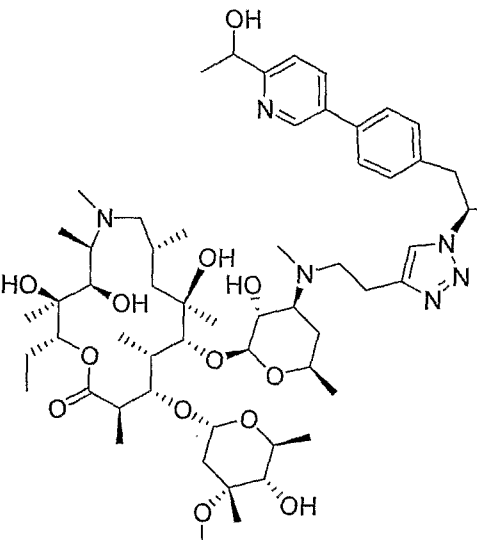
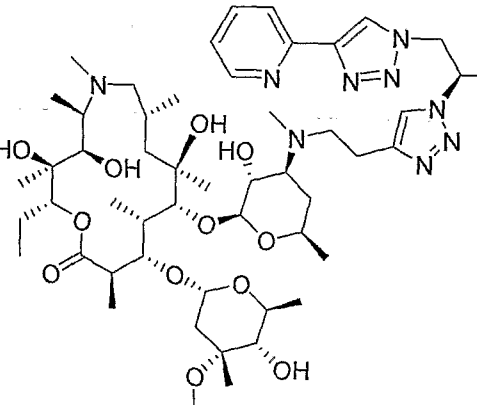
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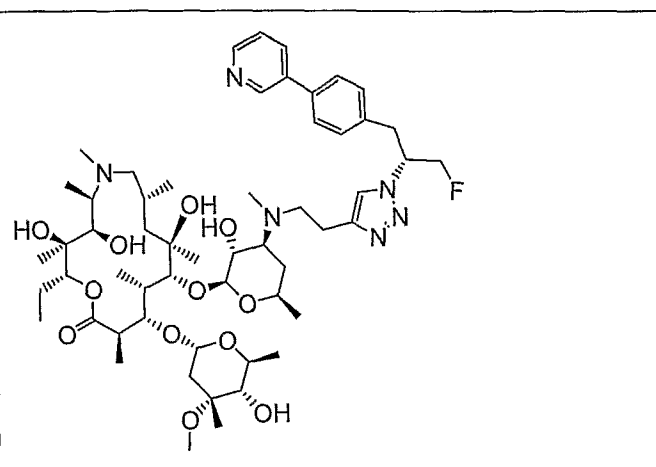
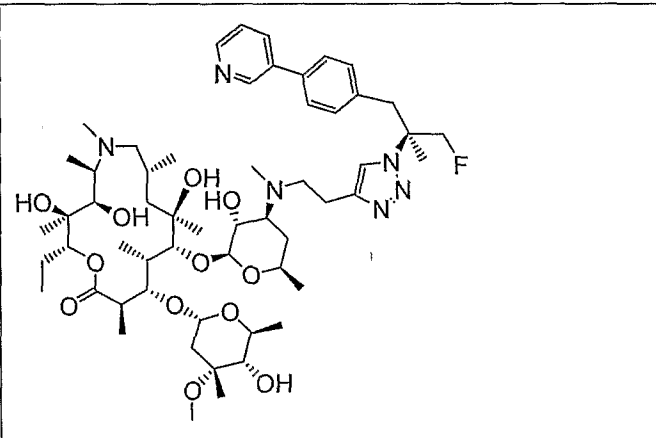
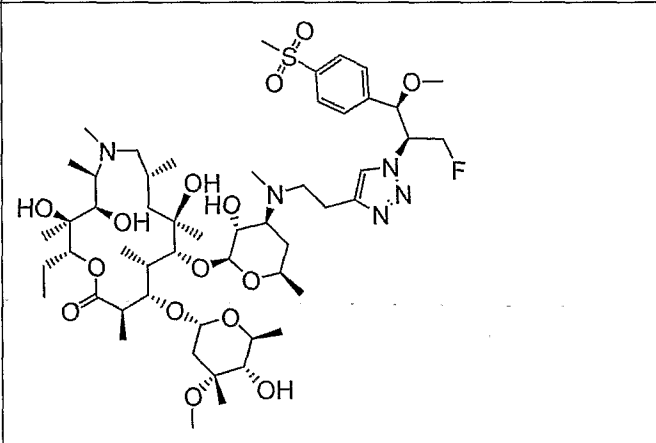
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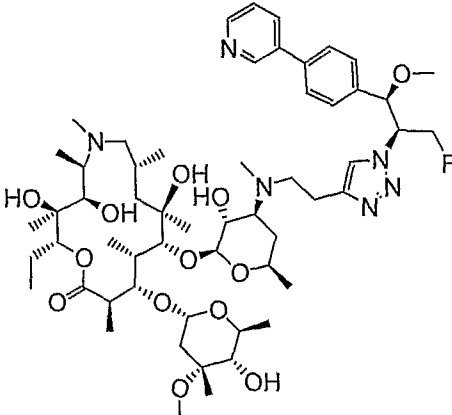
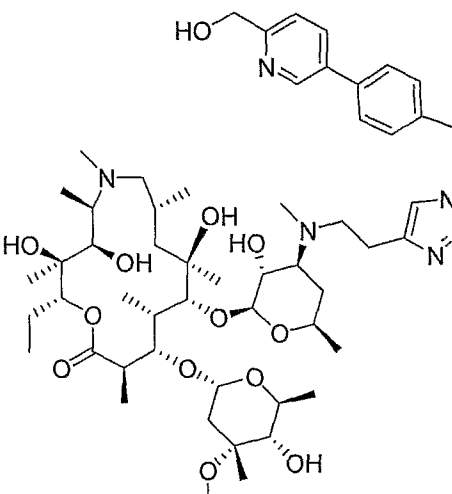
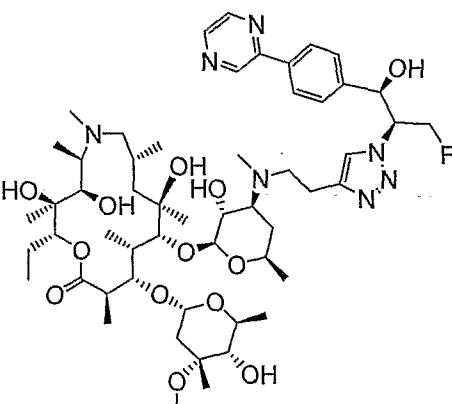
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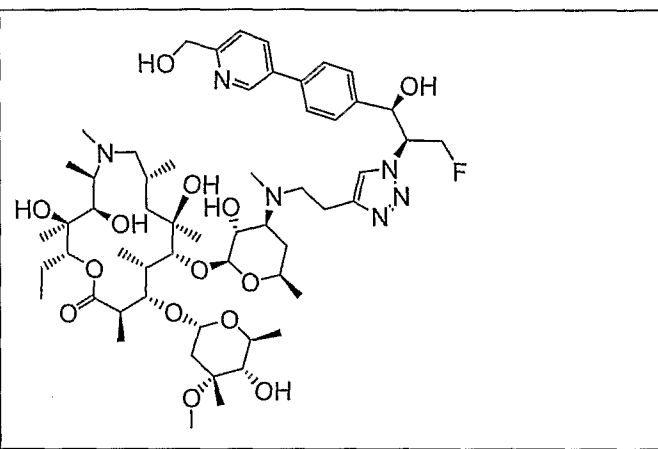
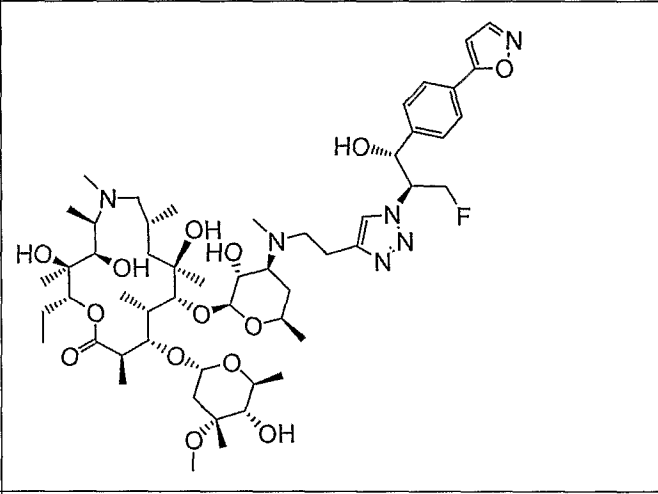
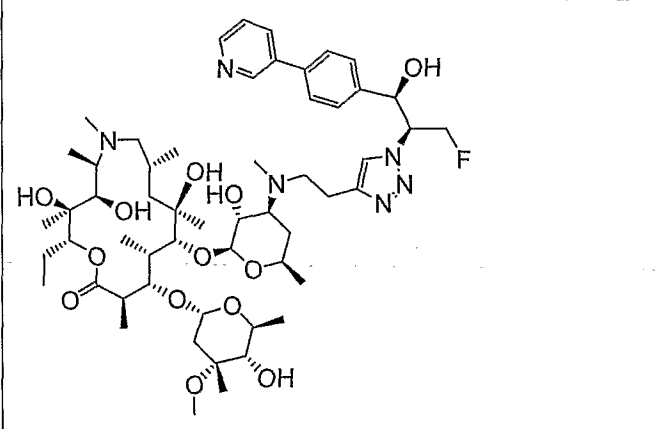
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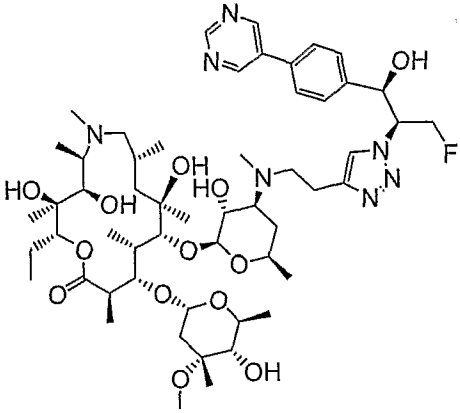
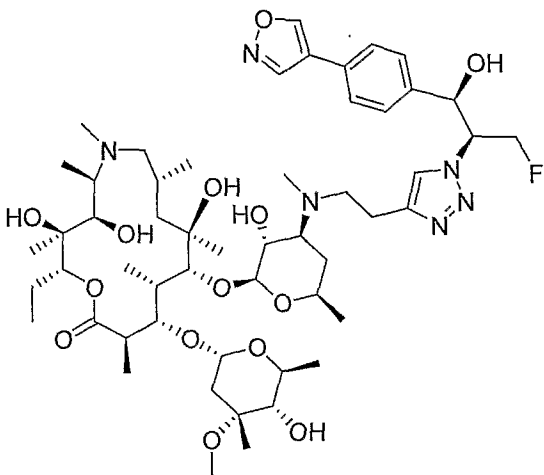
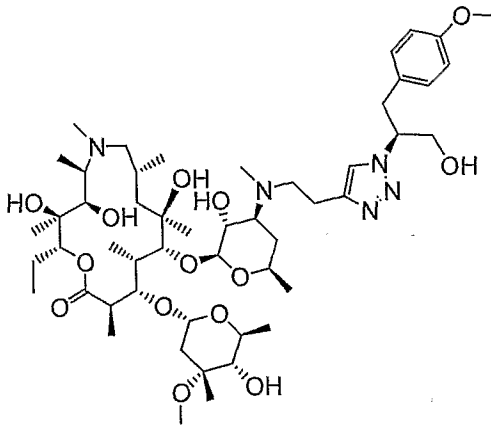
195		 Chemical structure of compound 195, a complex molecule featuring a central core with multiple hydroxyl groups and a side chain containing a pyridine ring, a benzene ring, and a fluorinated alkyl group.
196		 Chemical structure of compound 196, a complex molecule featuring a central core with multiple hydroxyl groups and a side chain containing a pyridine ring, a benzene ring, and a fluorinated alkyl group.
197		 Chemical structure of compound 197, a complex molecule featuring a central core with multiple hydroxyl groups and a side chain containing a pyridine ring, a benzene ring, and a fluorinated alkyl group.

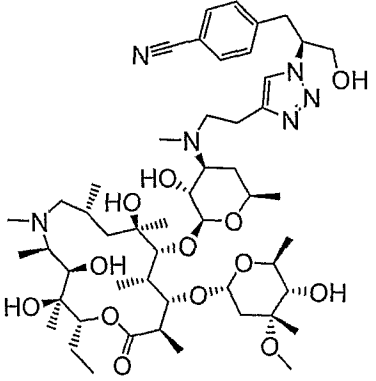
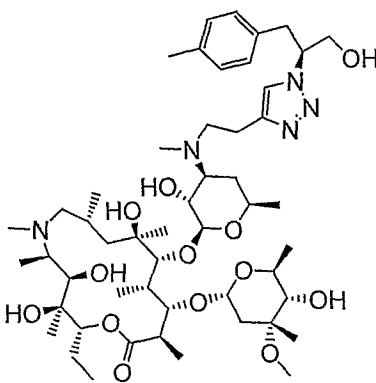
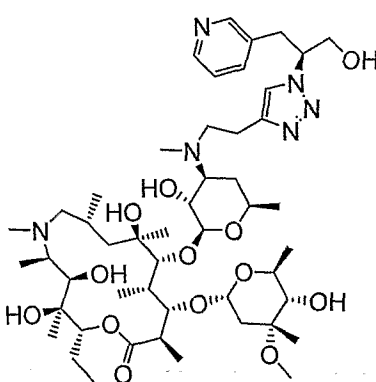
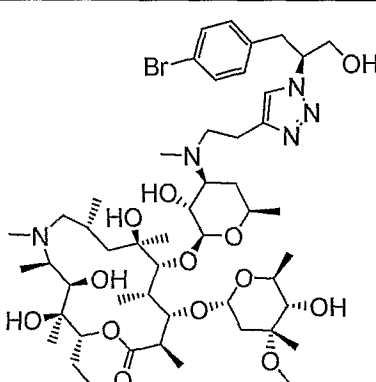
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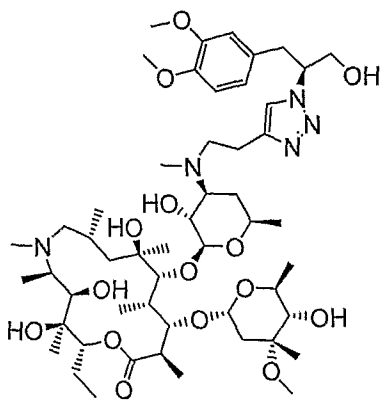
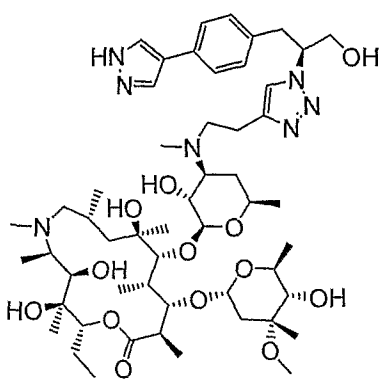
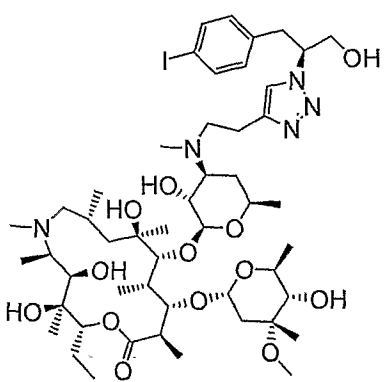
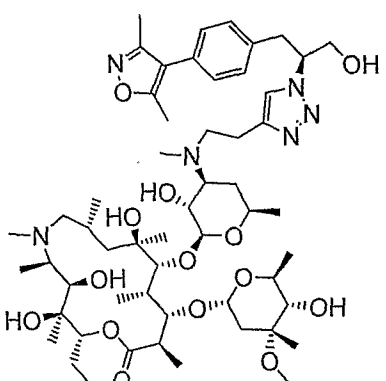
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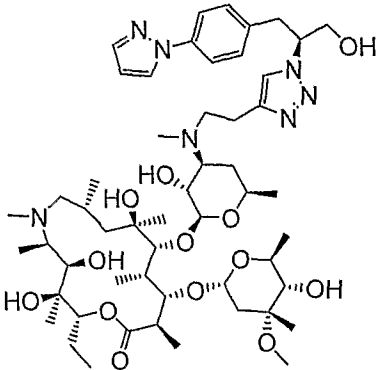
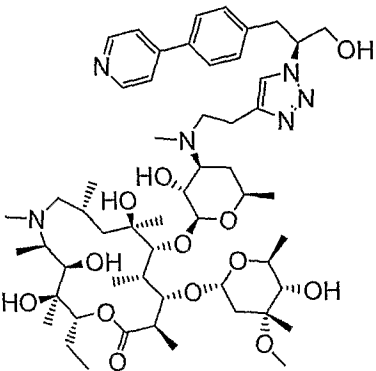
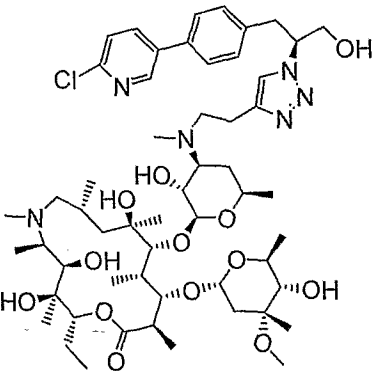
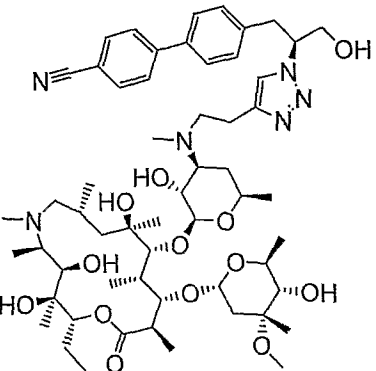
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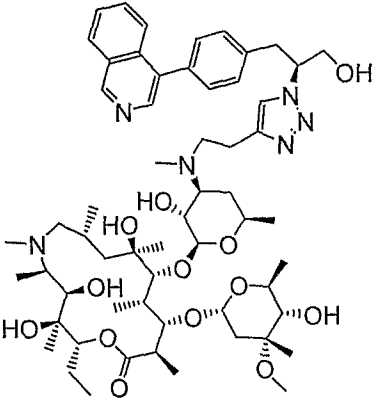
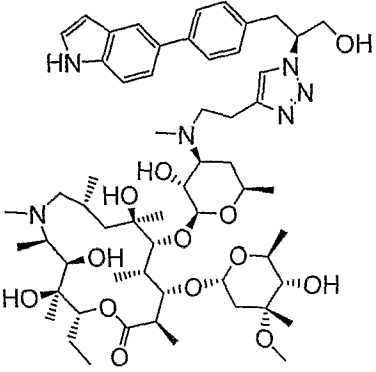
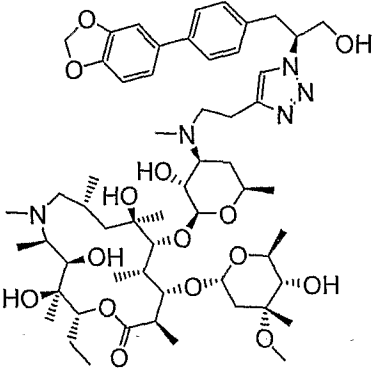
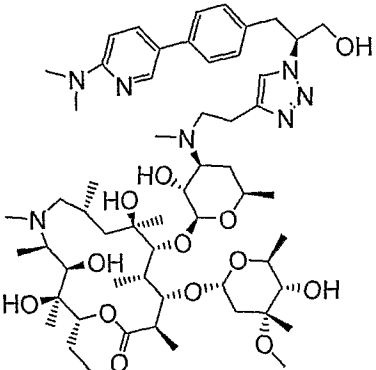
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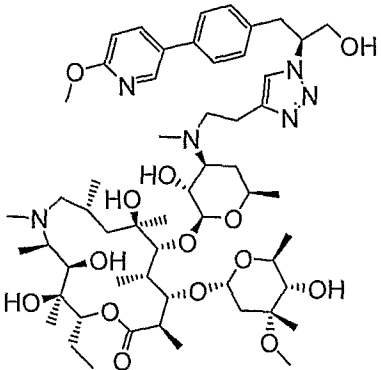
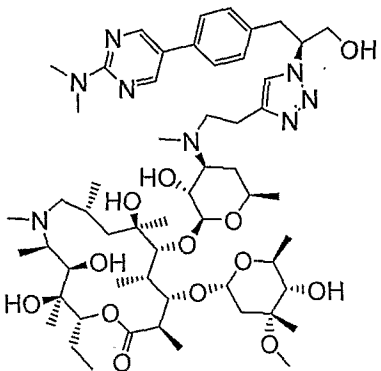
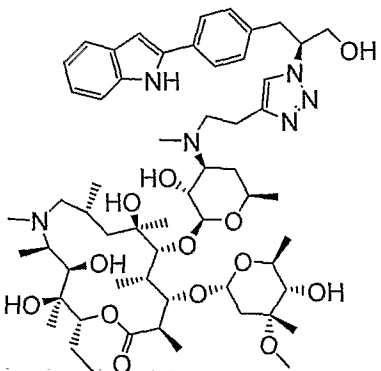
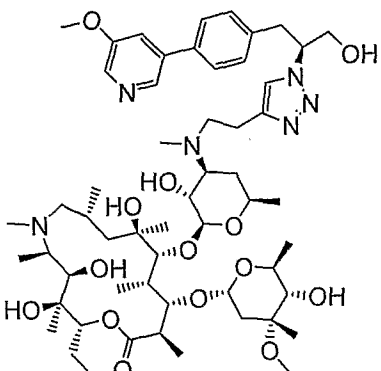
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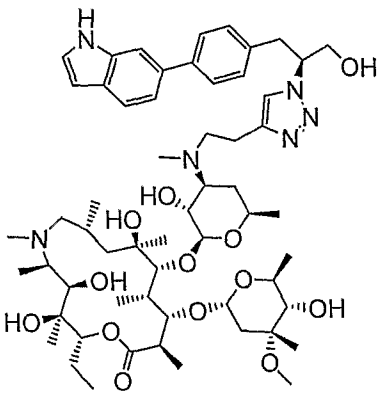
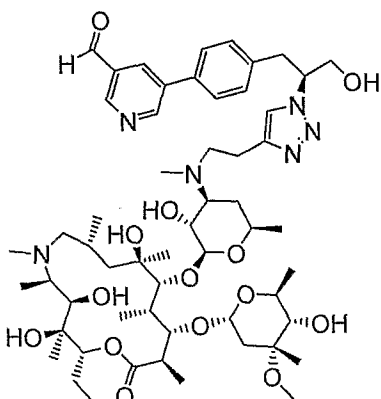
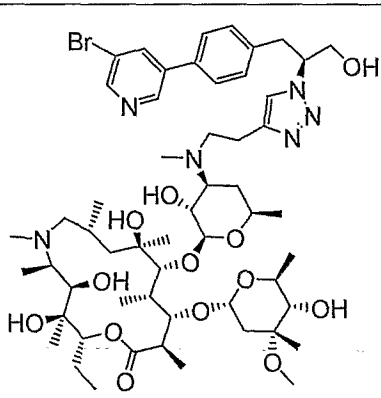
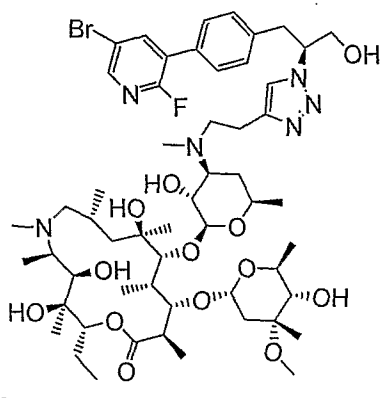
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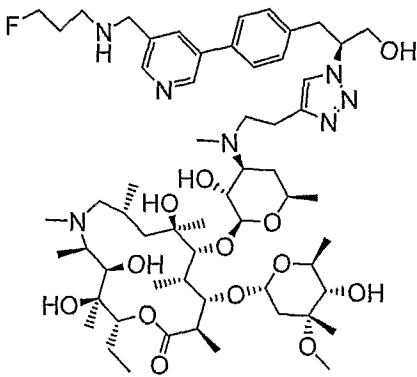
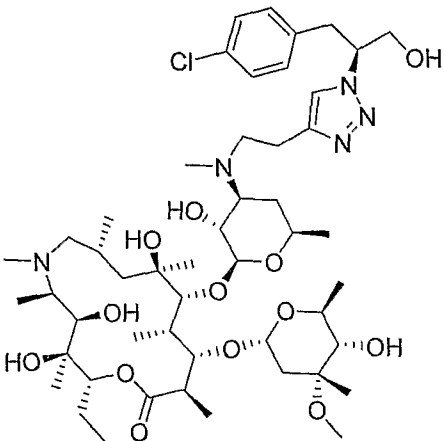
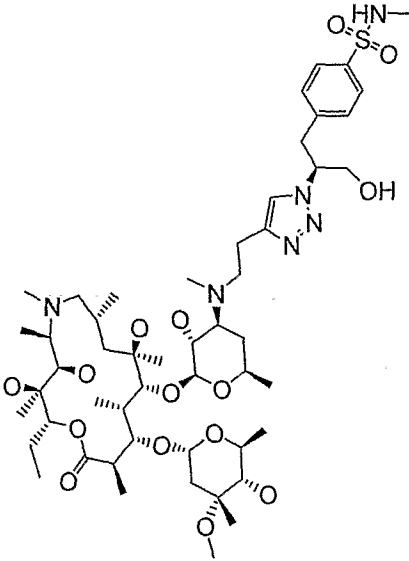
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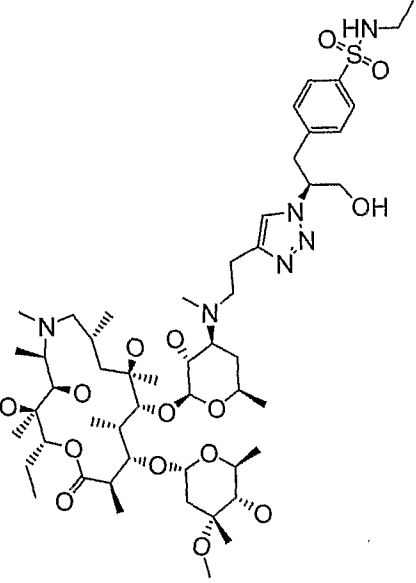
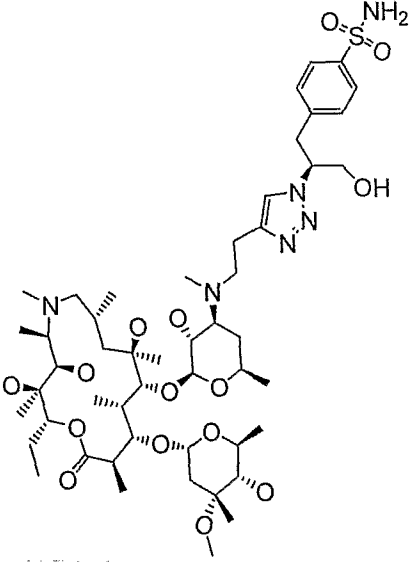
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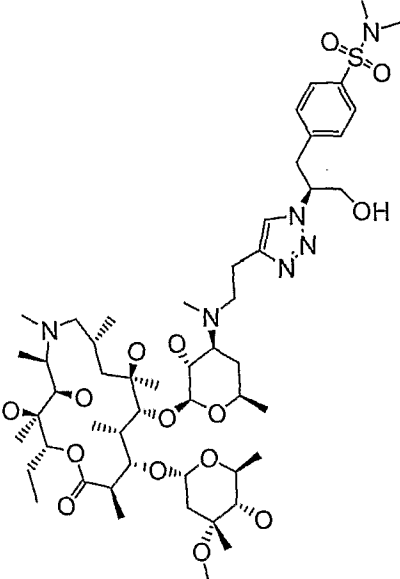
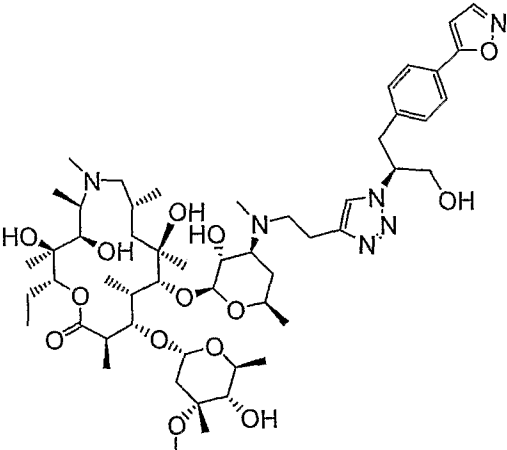
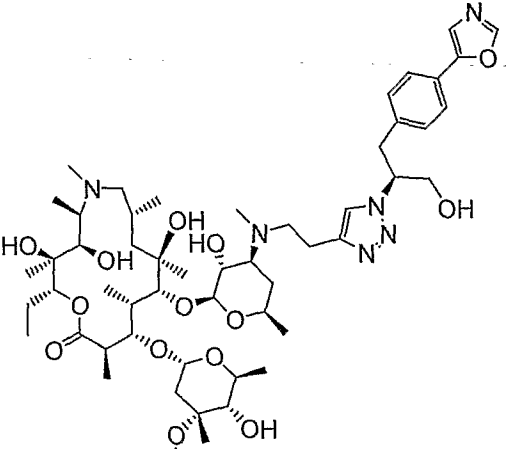
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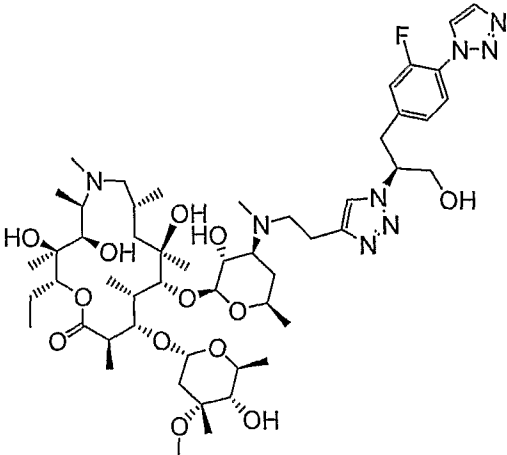
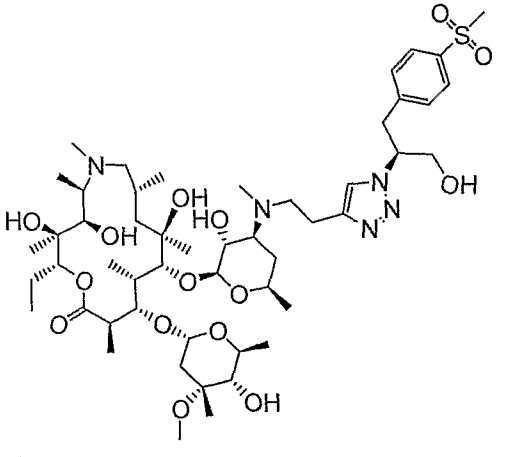
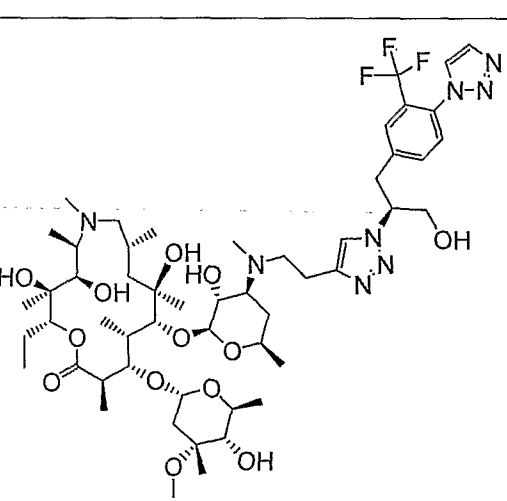
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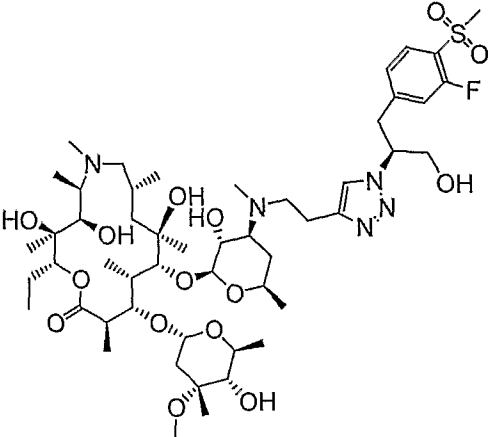
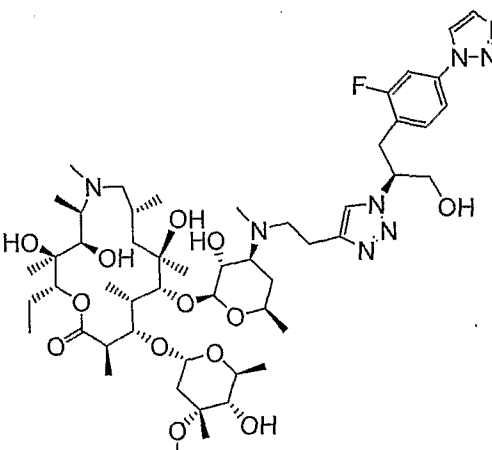
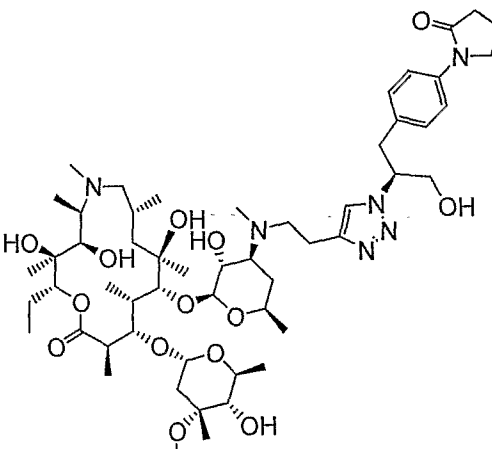
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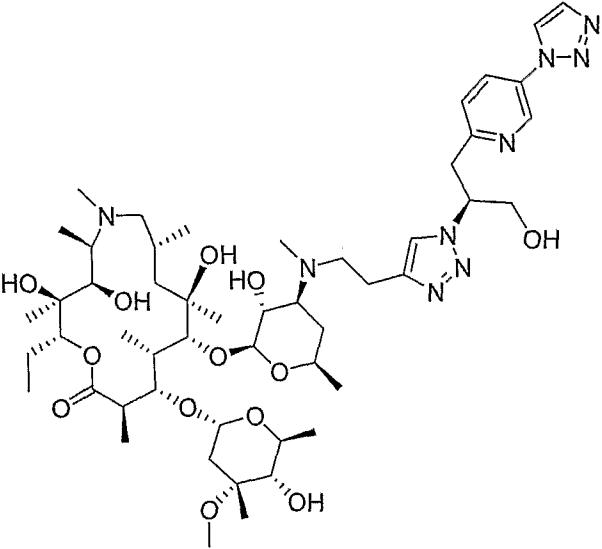
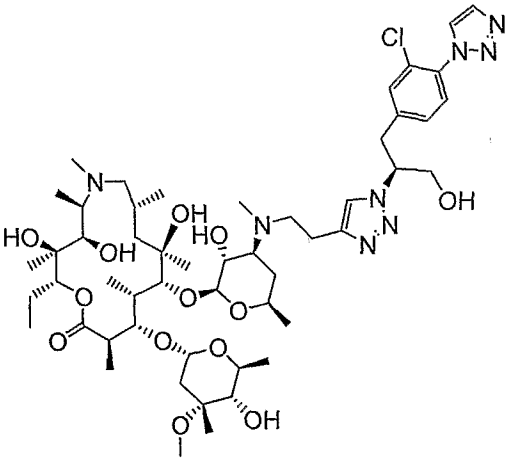
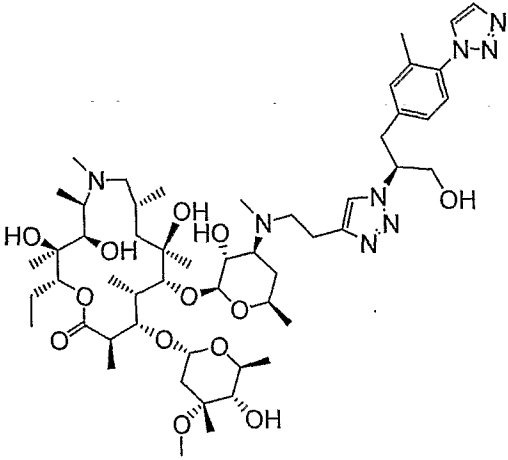
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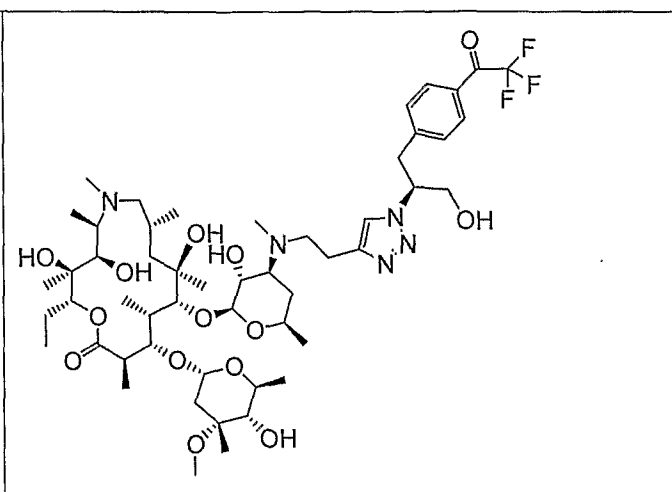
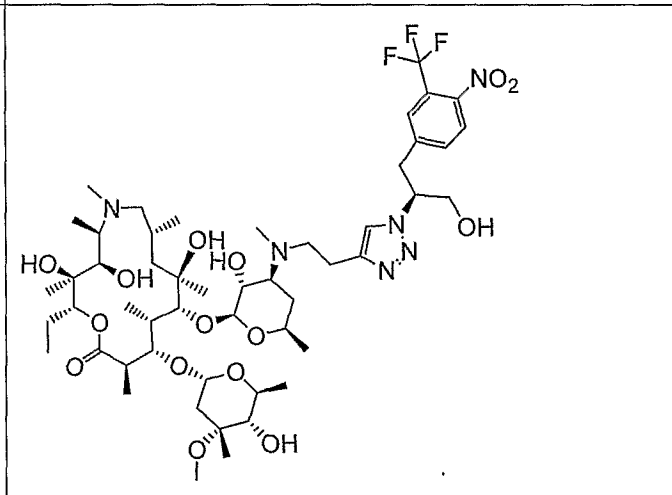
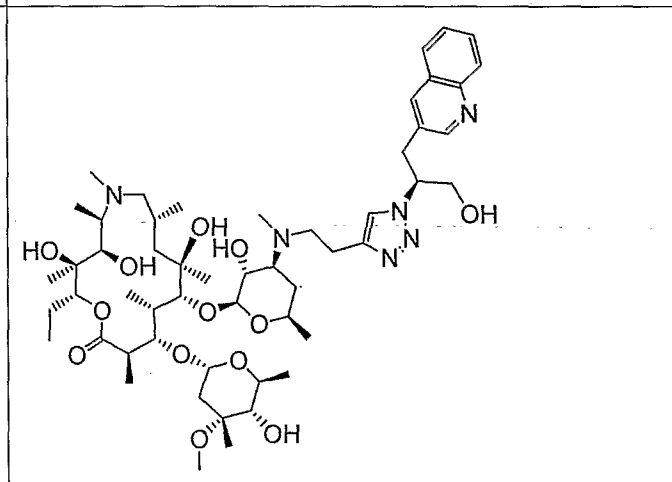
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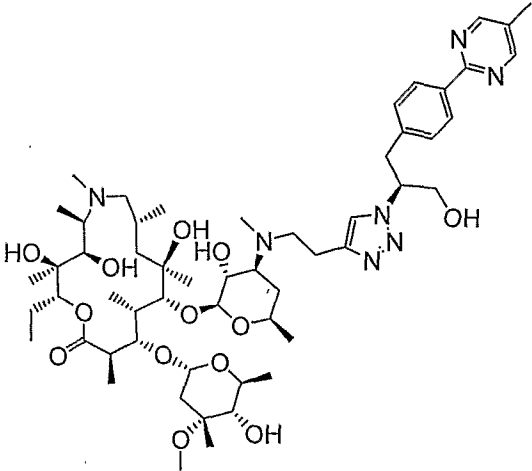
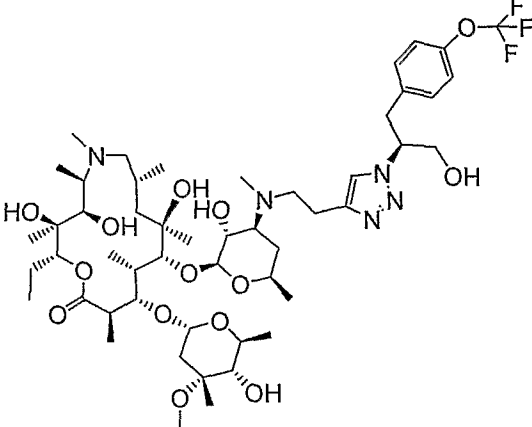
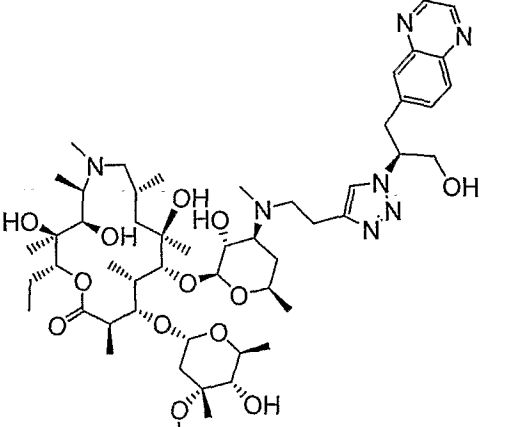
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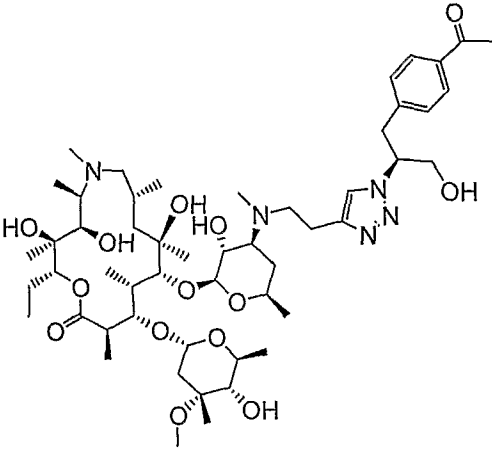
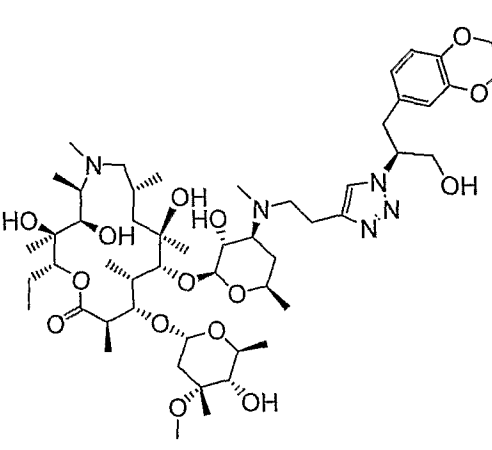
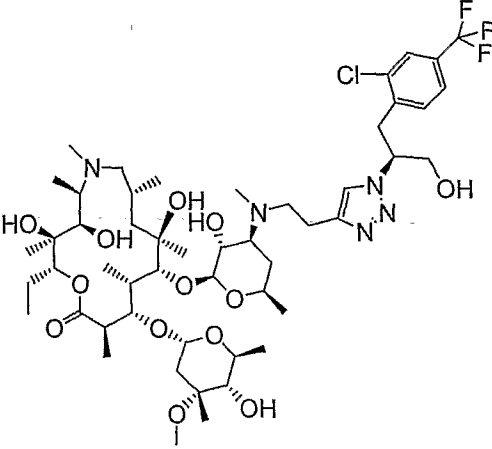
245		 Chemical structure 245: A complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a side chain containing a pyridine ring substituted with a 1,2,3-triazole group.
246		 Chemical structure 246: A complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a side chain containing a pyridine ring substituted with a 1,2,3-triazole group and a chlorine atom.
247		 Chemical structure 247: A complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a side chain containing a pyridine ring substituted with a 1,2,3-triazole group.

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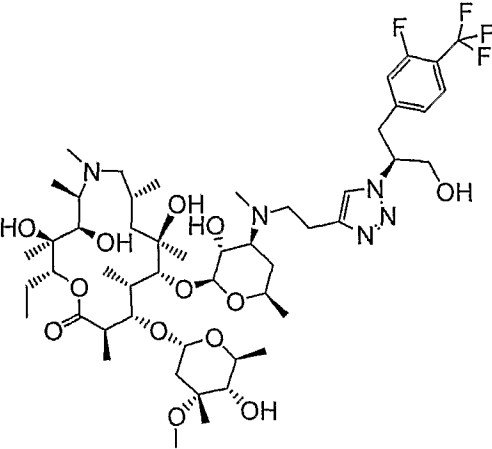
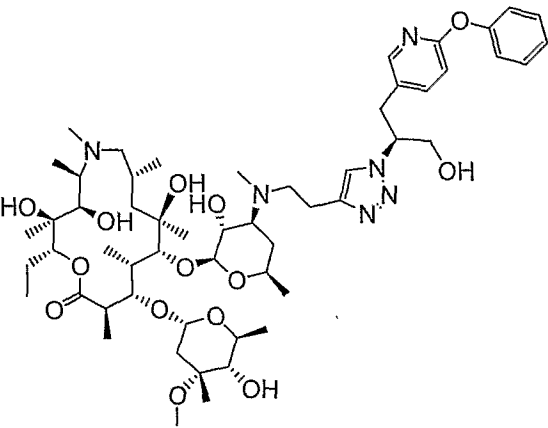
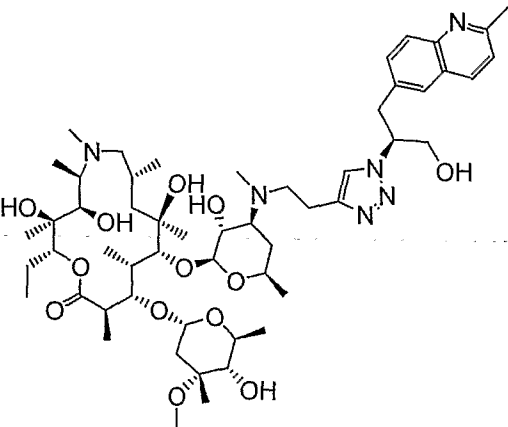
248		 Chemical structure of compound 248: A complex molecule featuring a central core with multiple hydroxyl groups and a trifluoromethyl group. The structure includes a benzene ring substituted with a trifluoromethyl group and a side chain containing a triazole ring and a hydroxyl group.
249		 Chemical structure of compound 249: A complex molecule featuring a central core with multiple hydroxyl groups and a trifluoromethyl group. The structure includes a benzene ring substituted with a trifluoromethyl group and a side chain containing a triazole ring and a hydroxyl group.
250		 Chemical structure of compound 250: A complex molecule featuring a central core with multiple hydroxyl groups and a trifluoromethyl group. The structure includes a benzene ring substituted with a trifluoromethyl group and a side chain containing a triazole ring and a hydroxyl group.

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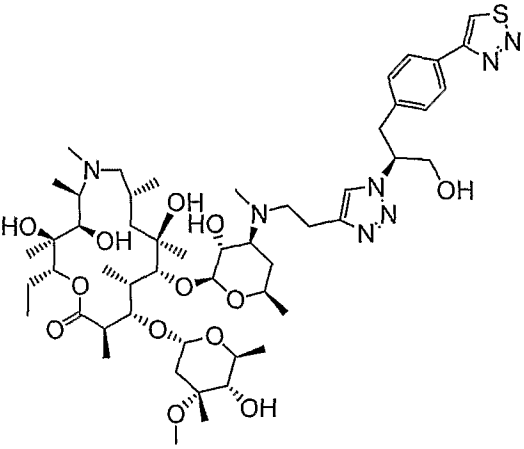
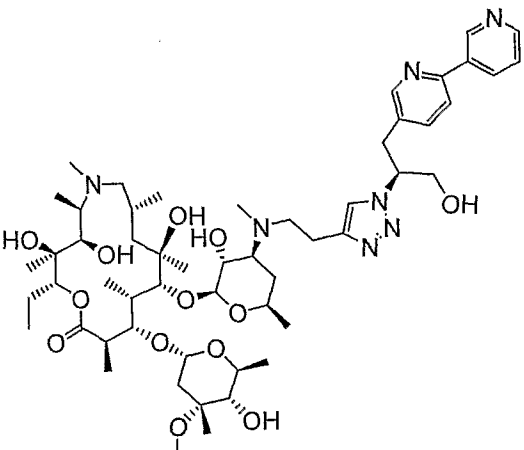
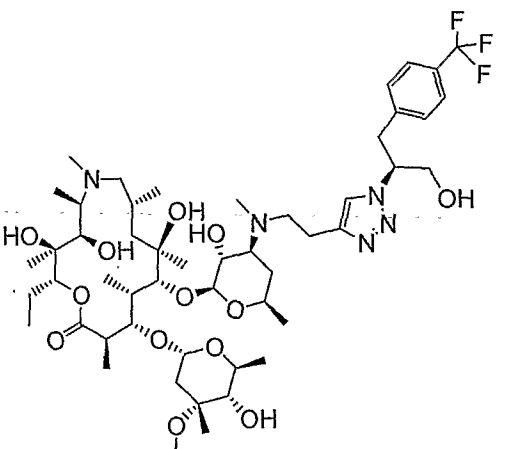
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254		 Chemical structure 254: A complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a side chain containing a triazole ring and a 4-acetylphenyl group.
255		 Chemical structure 255: A complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a side chain containing a triazole ring and a 2,2,2-trifluoro-1,3-dioxol-5-yl group.
256		 Chemical structure 256: A complex molecule featuring a central bicyclic core with multiple hydroxyl groups and a side chain containing a triazole ring and a 4-chloro-2,2,2-trifluorophenyl group.

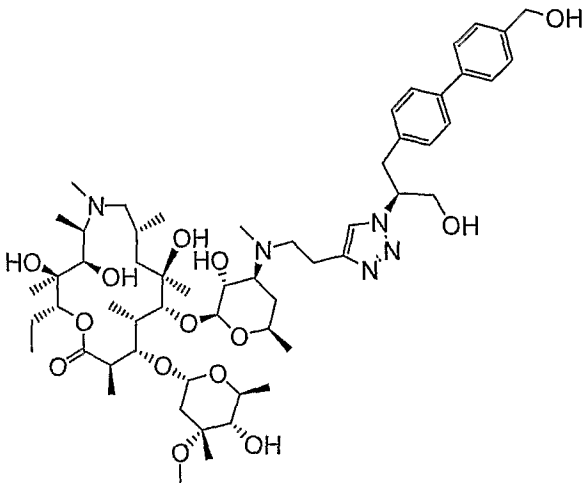
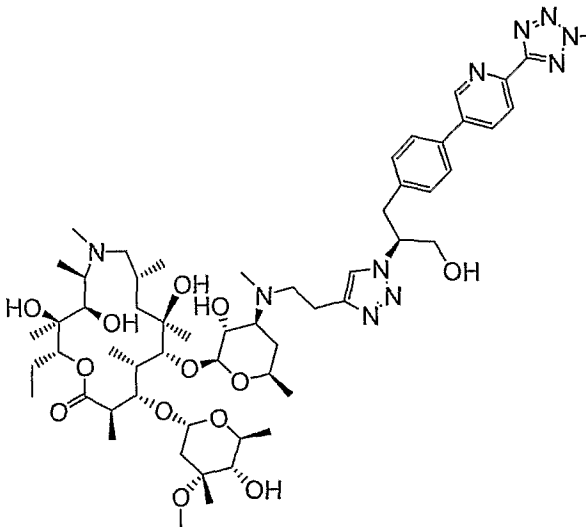
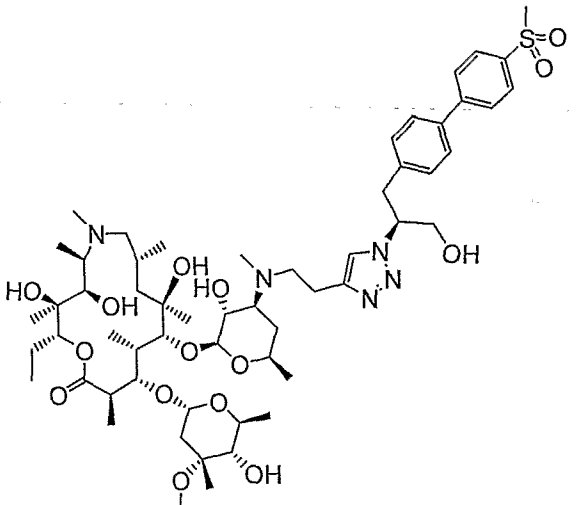
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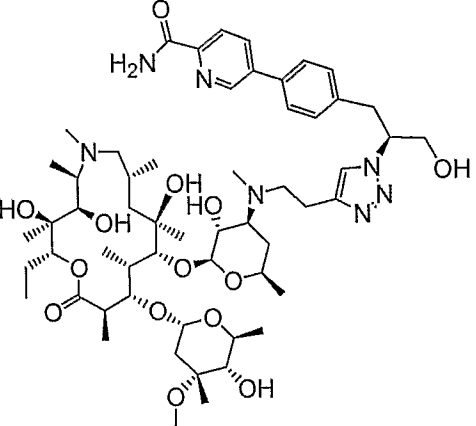
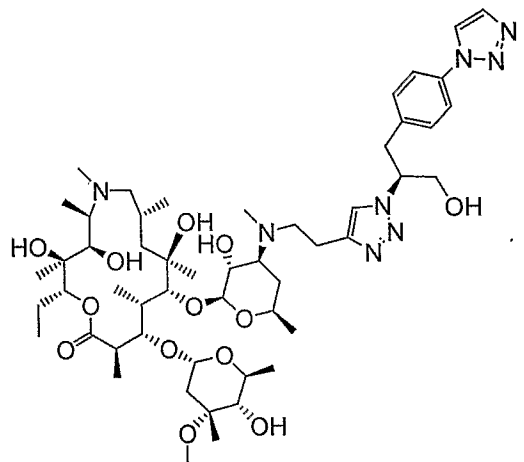
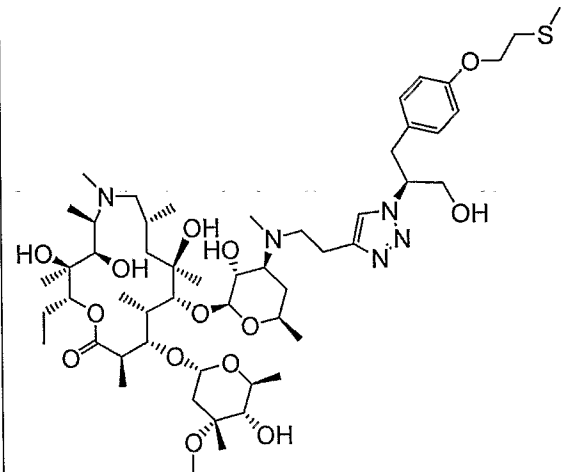
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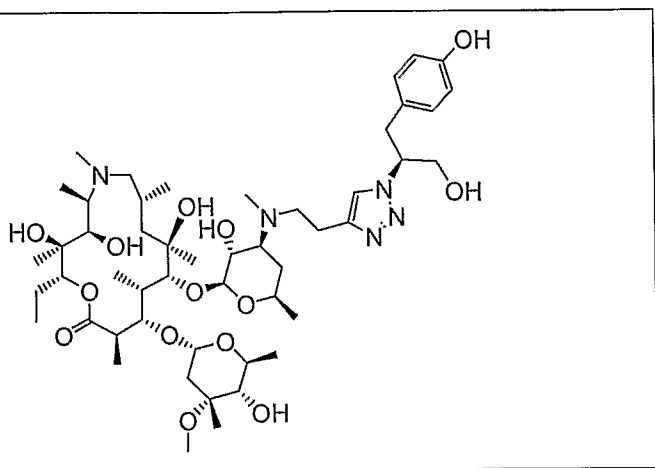
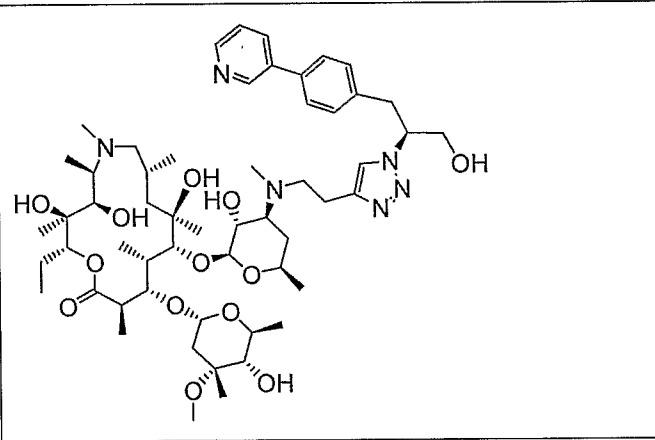
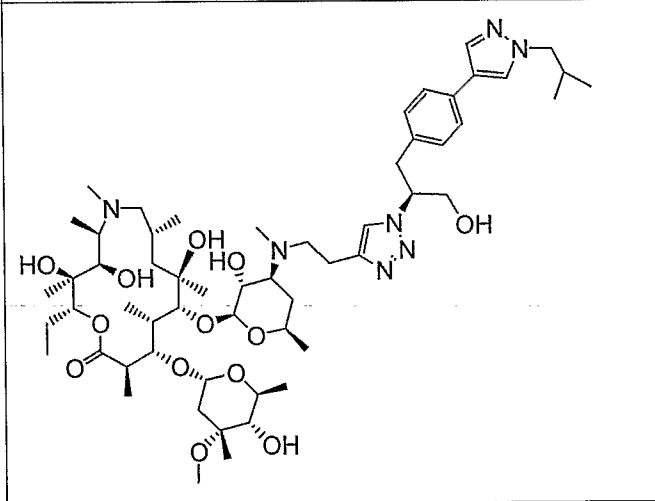
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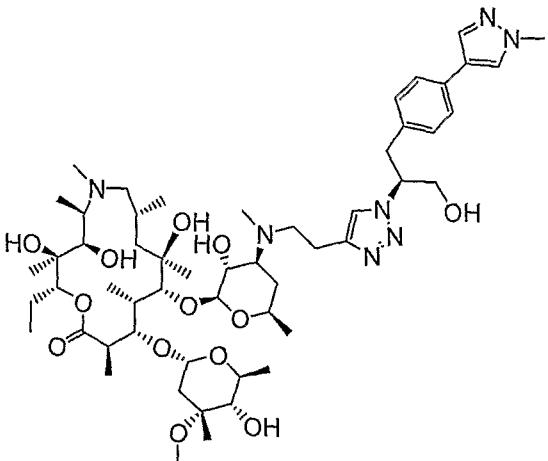
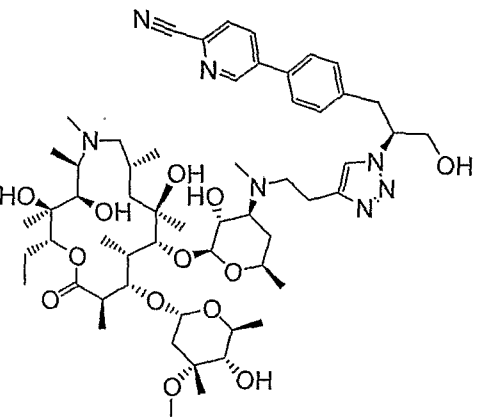
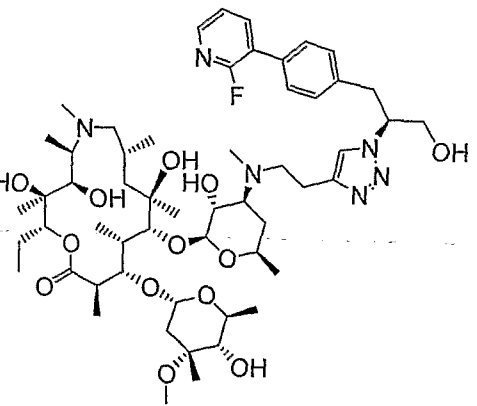
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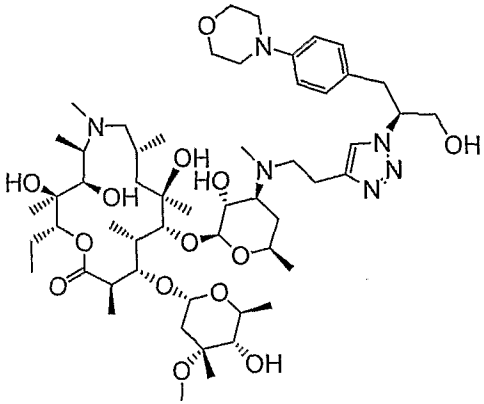
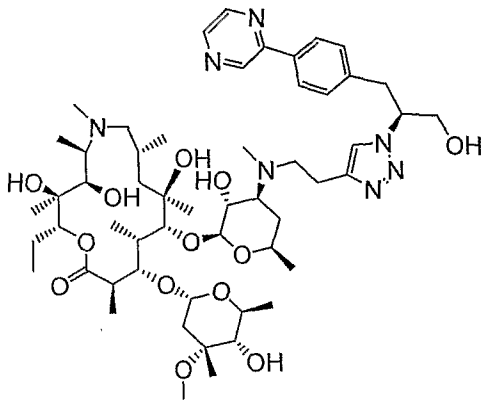
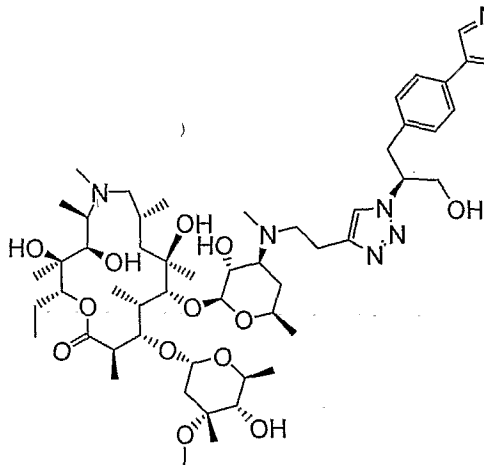
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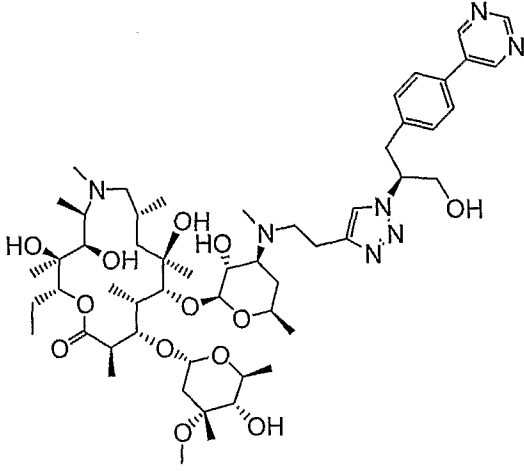
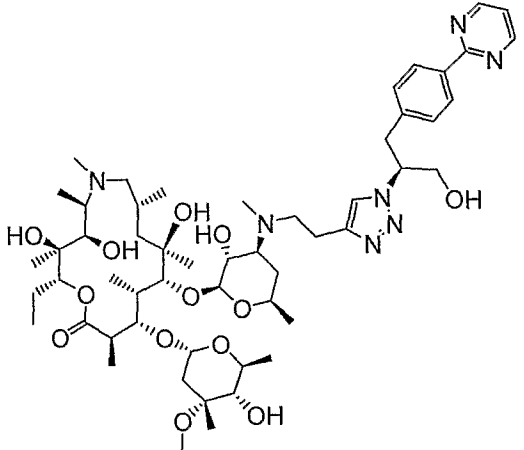
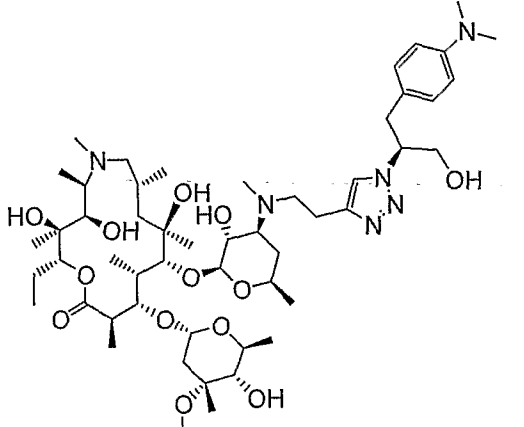
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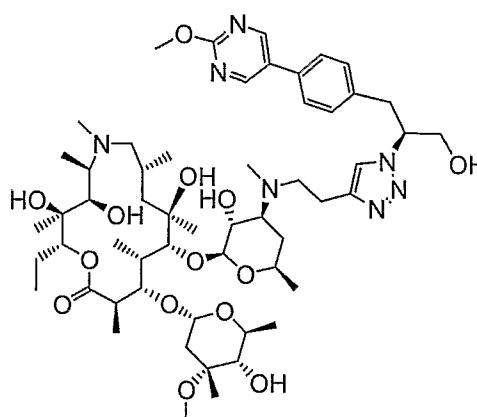
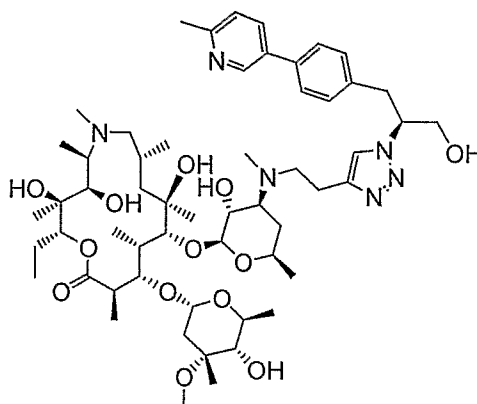
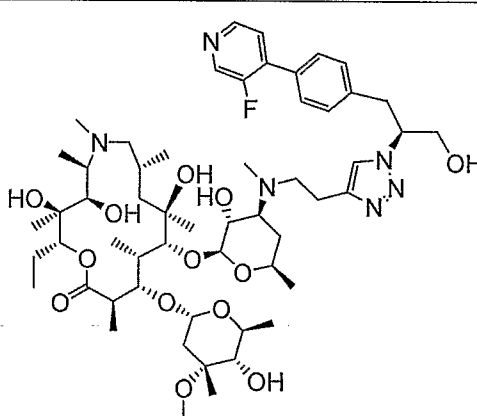
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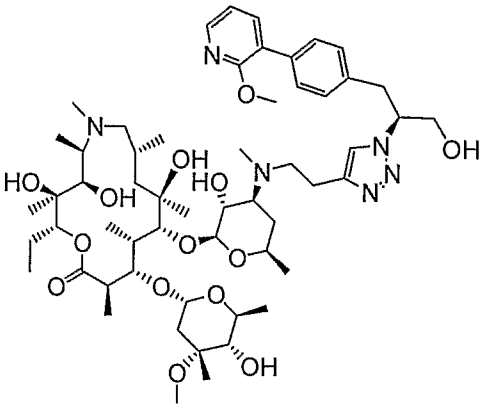
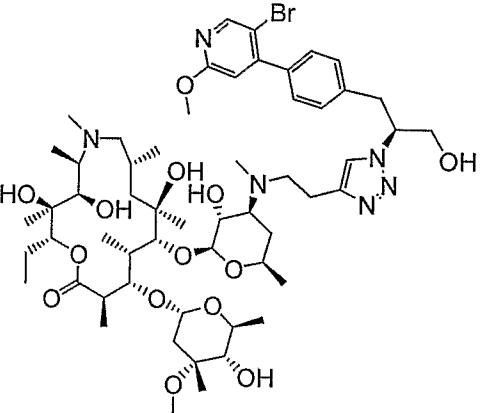
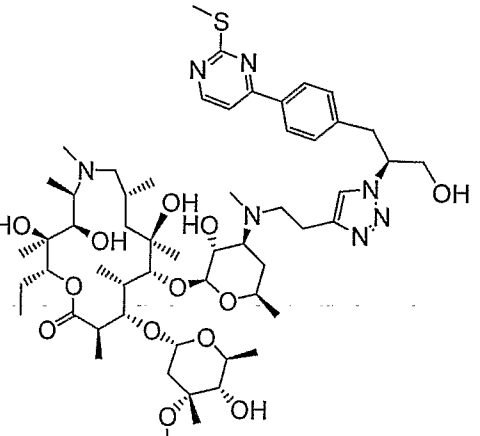
- 114 -

278		 Chemical structure 278 is a complex molecule. It features a central core with multiple hydroxyl groups and a side chain containing a pyrazole ring, a phenyl ring, and a pyrimidine ring.
279		 Chemical structure 279 is a complex molecule. It features a central core with multiple hydroxyl groups and a side chain containing a pyrazole ring, a phenyl ring, and a pyrimidine ring.
280		 Chemical structure 280 is a complex molecule. It features a central core with multiple hydroxyl groups and a side chain containing a pyrazole ring, a phenyl ring, and a pyrimidine ring.

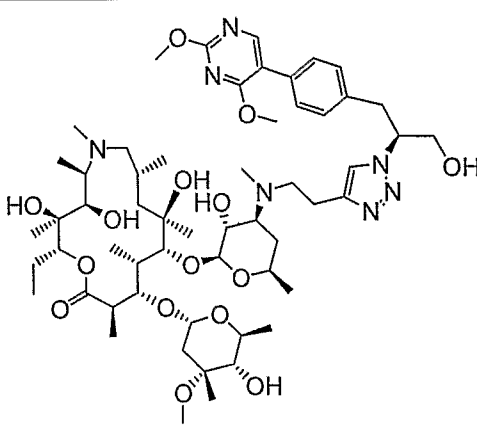
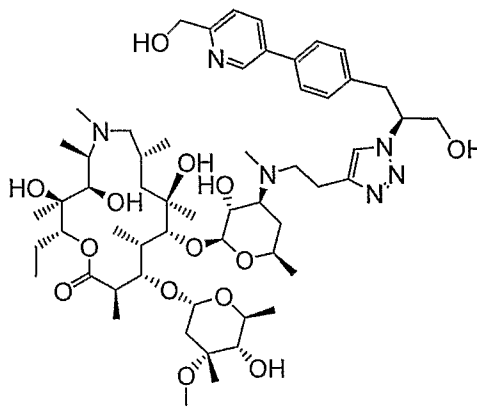
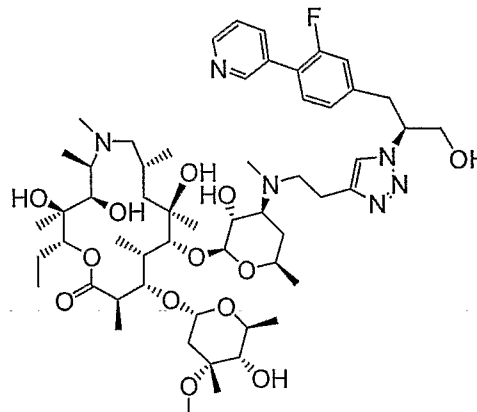
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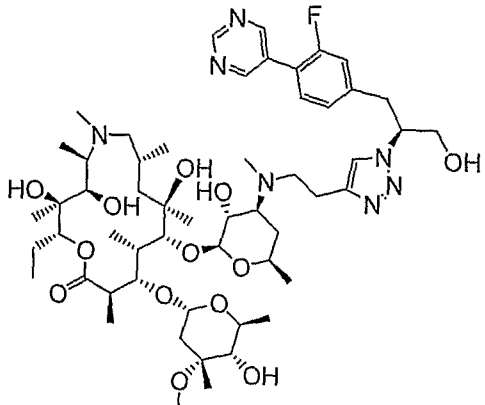
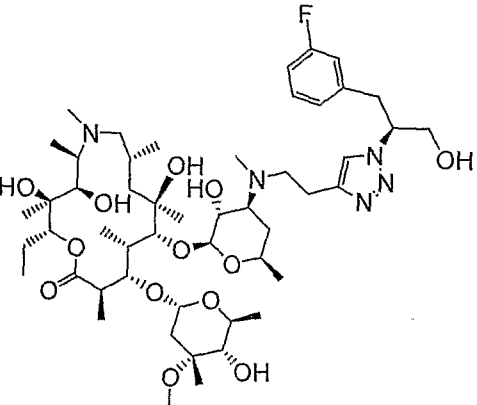
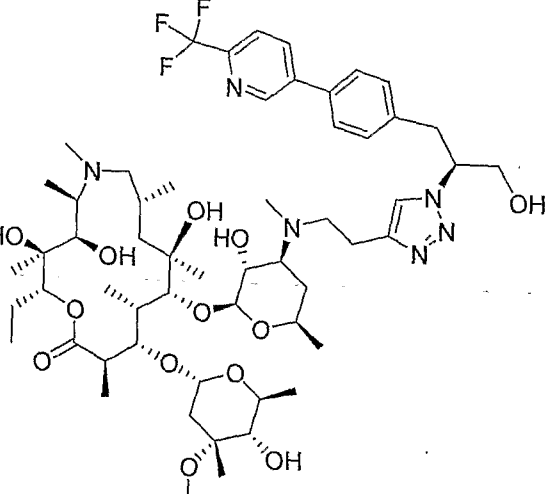
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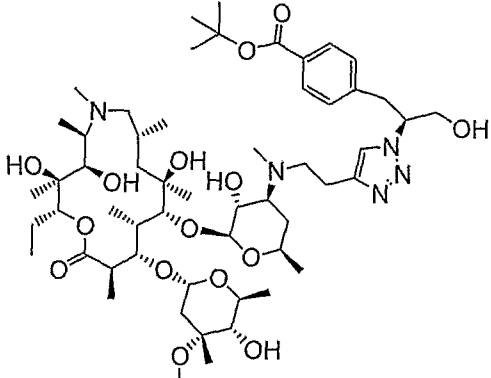
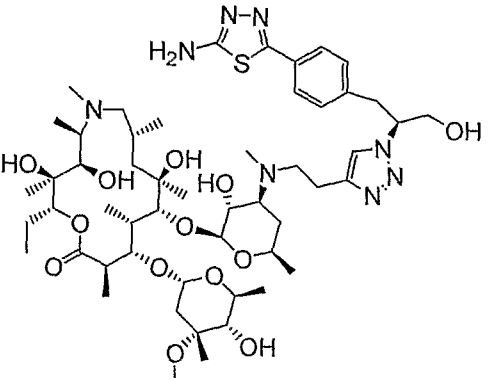
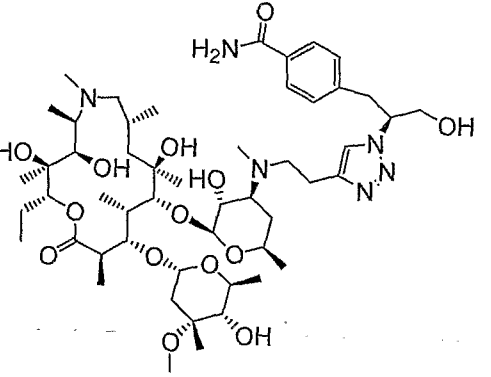
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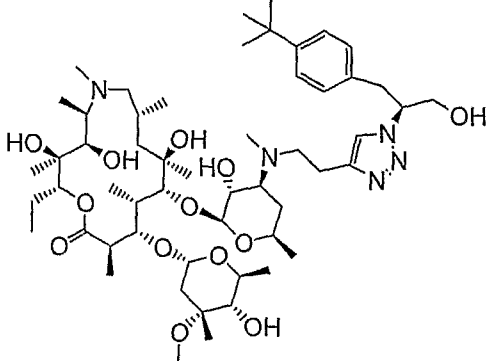
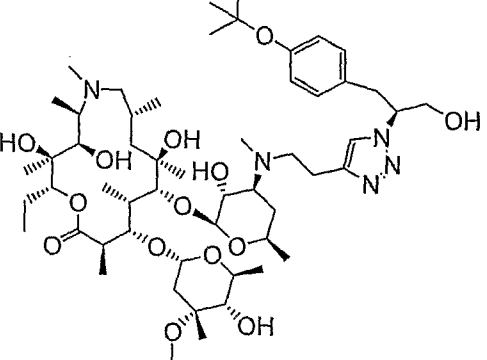
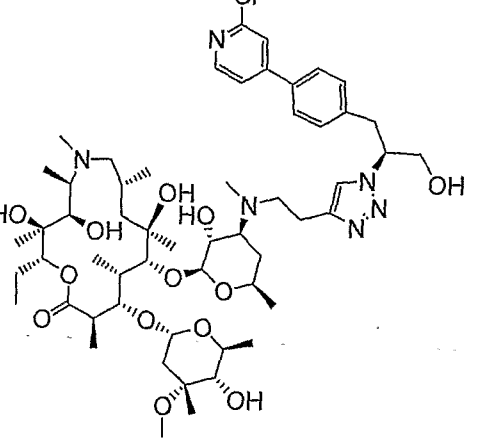
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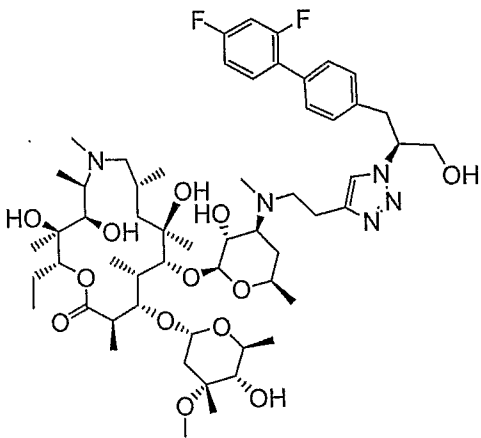
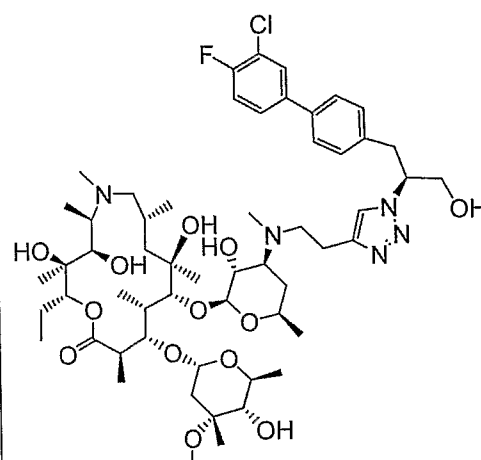
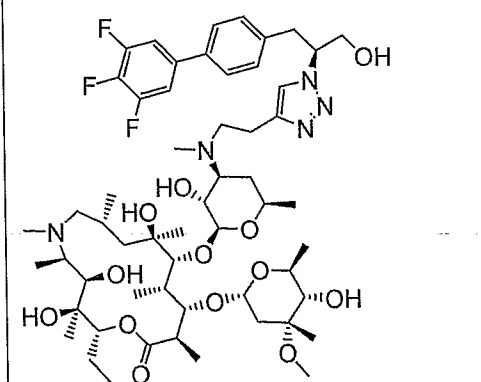
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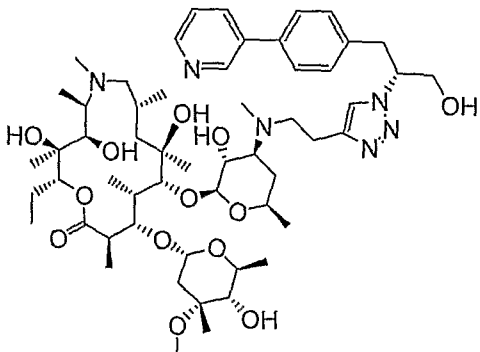
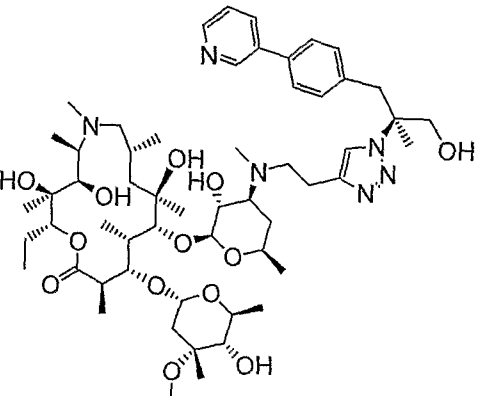
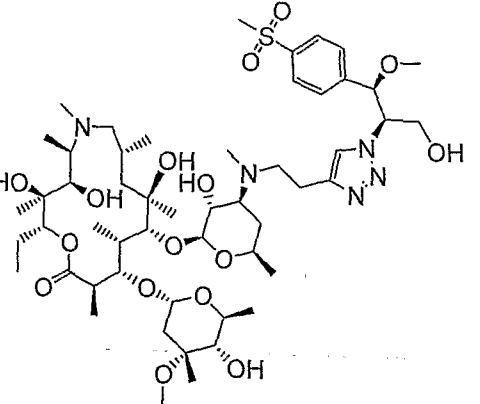
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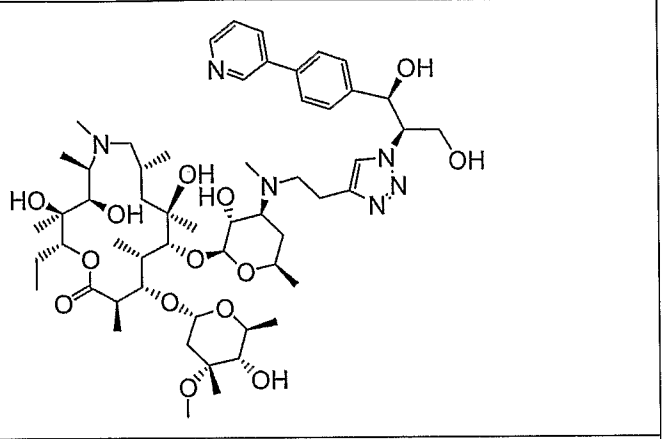
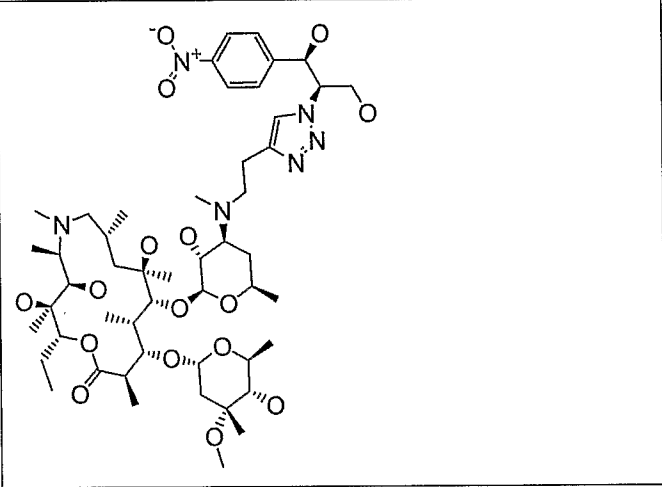
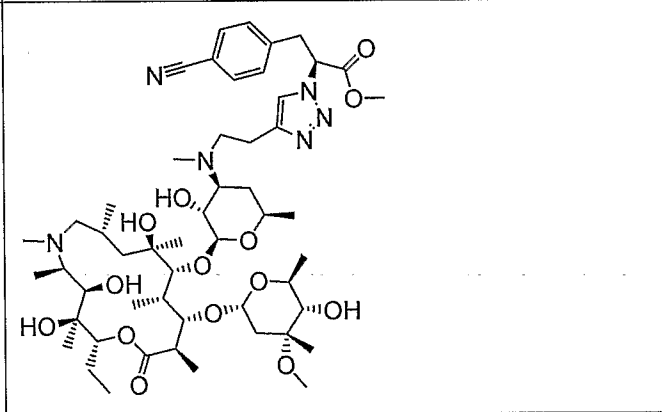
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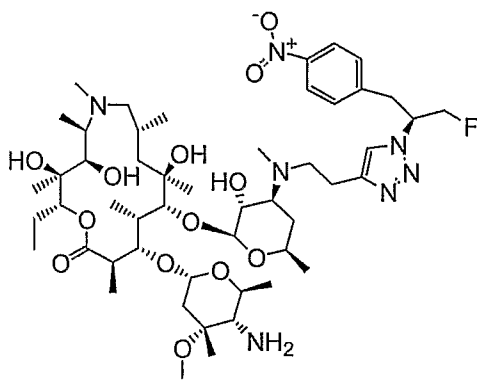
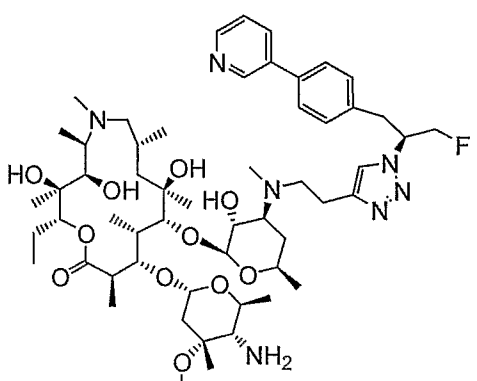
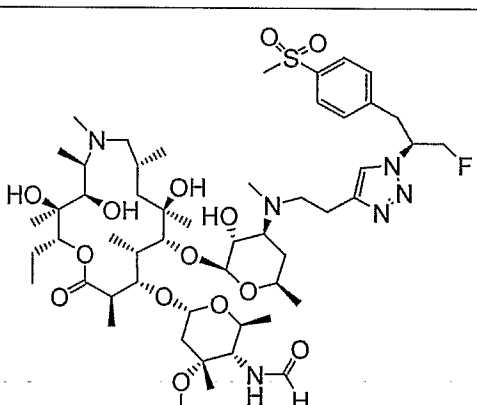
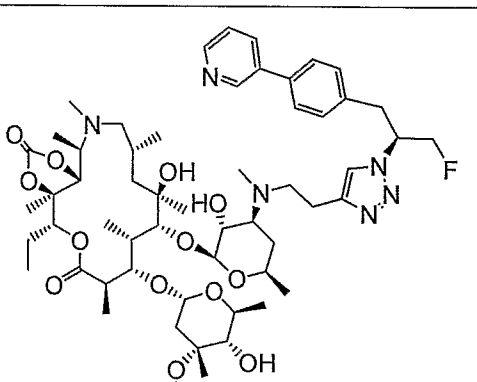
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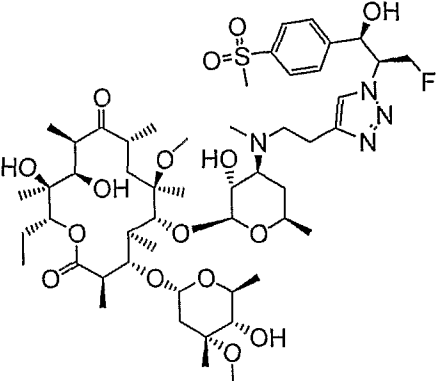
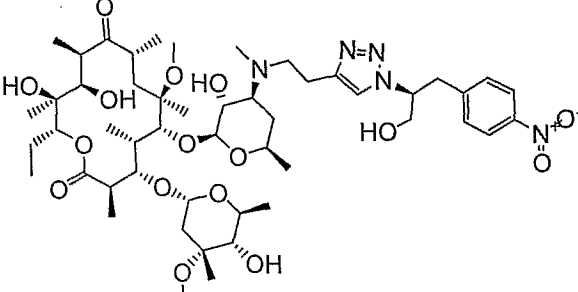
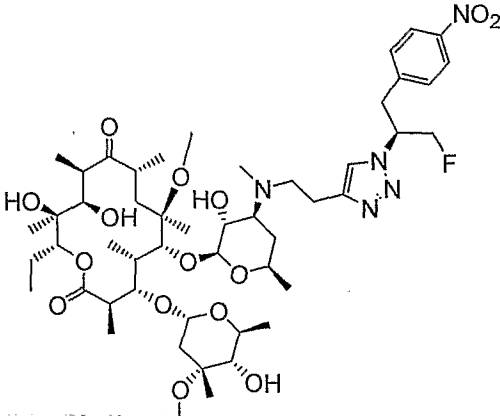
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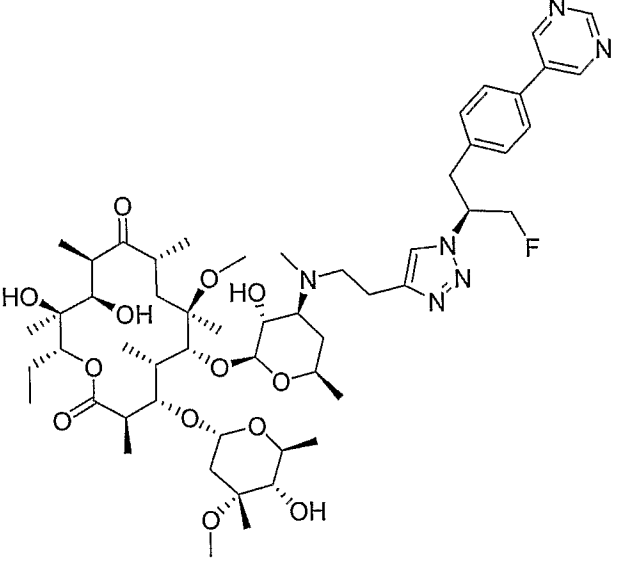
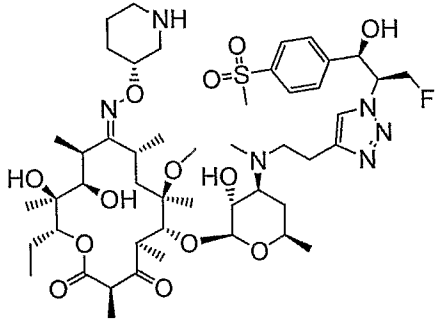
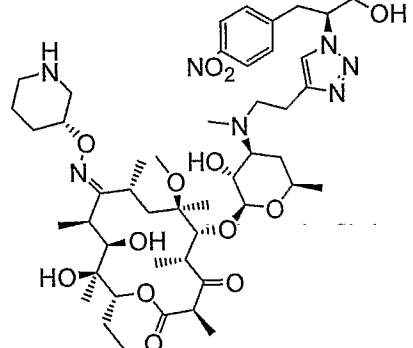
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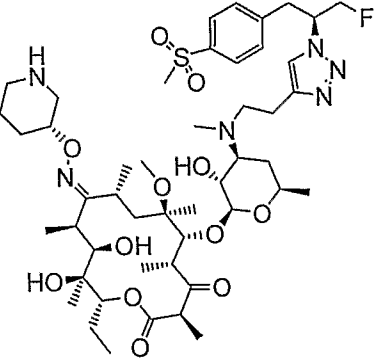
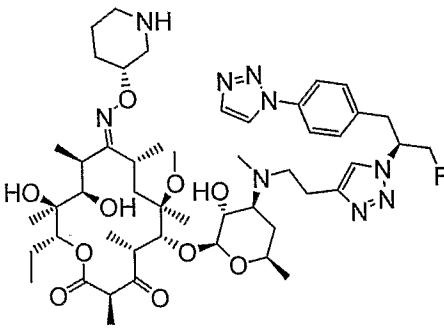
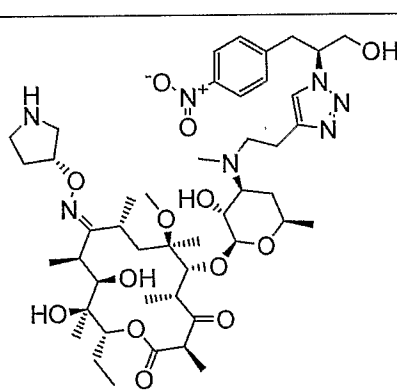
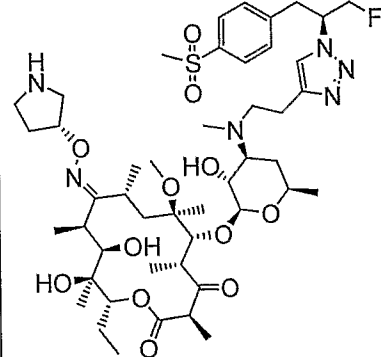
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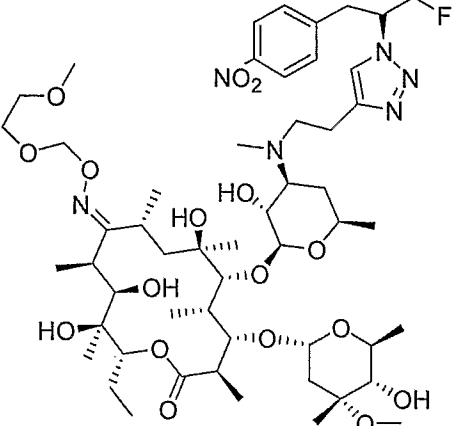
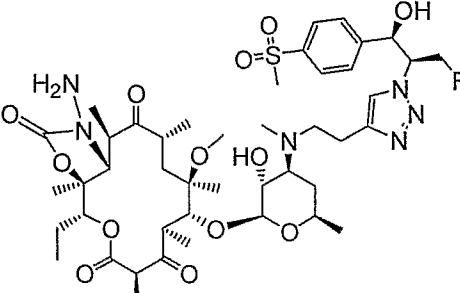
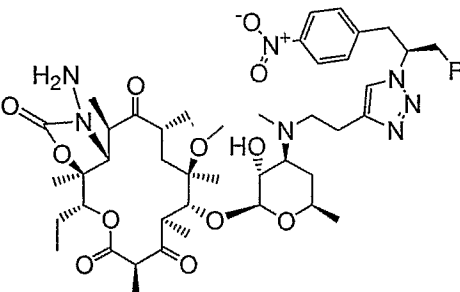
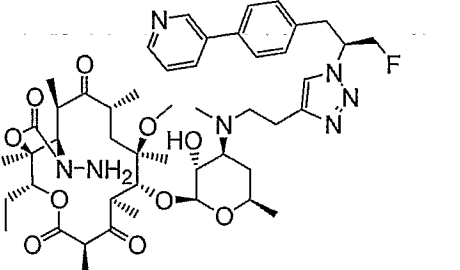
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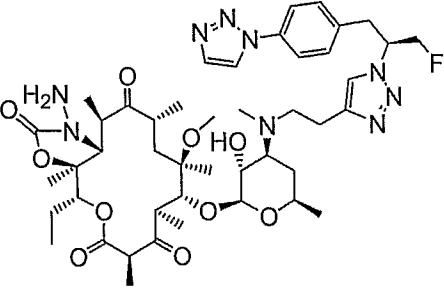
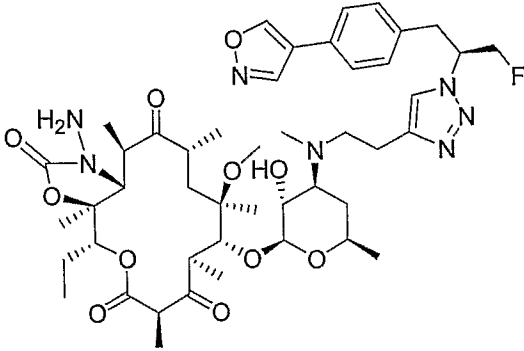
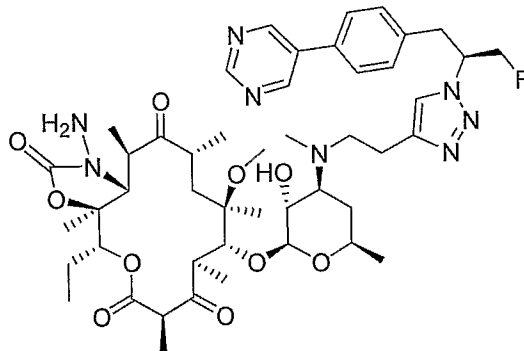
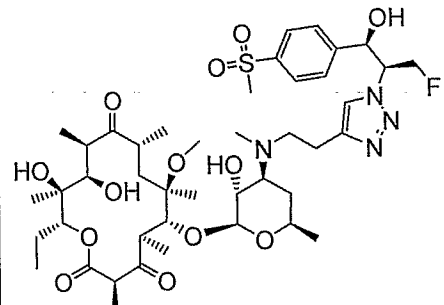
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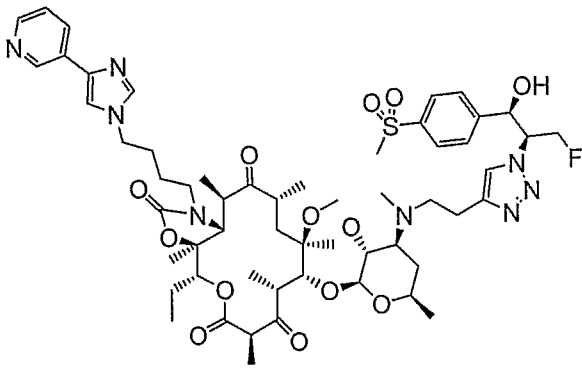
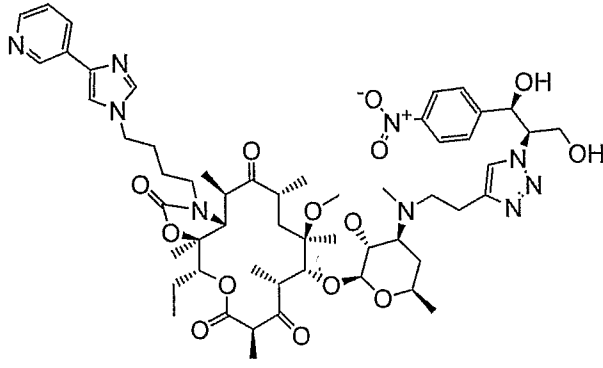
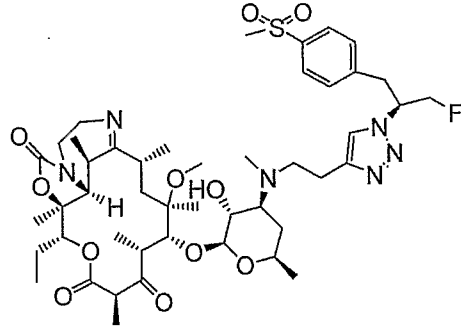
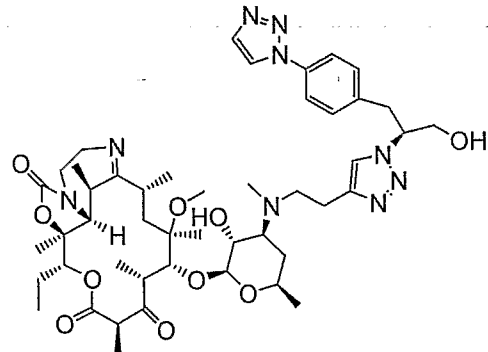
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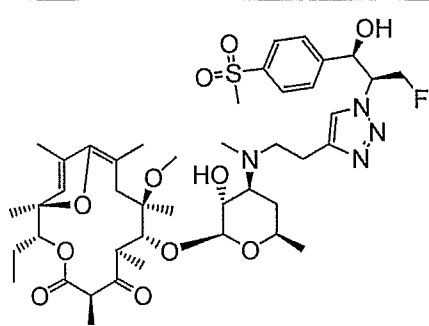
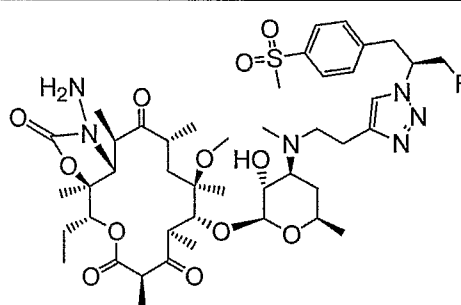
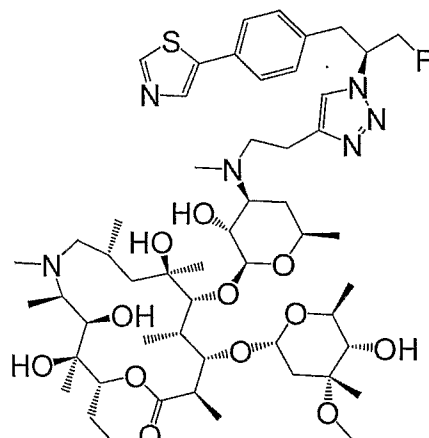
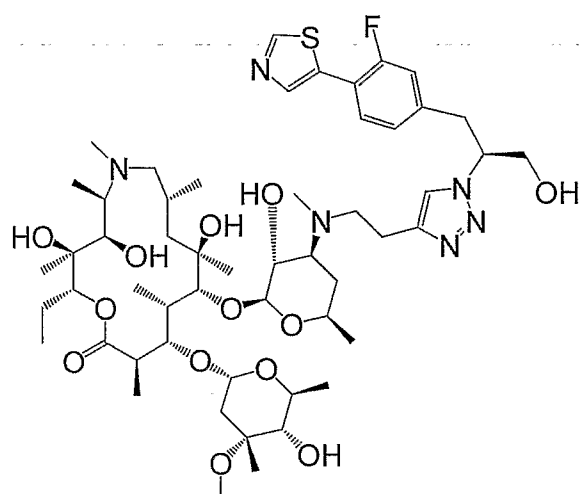
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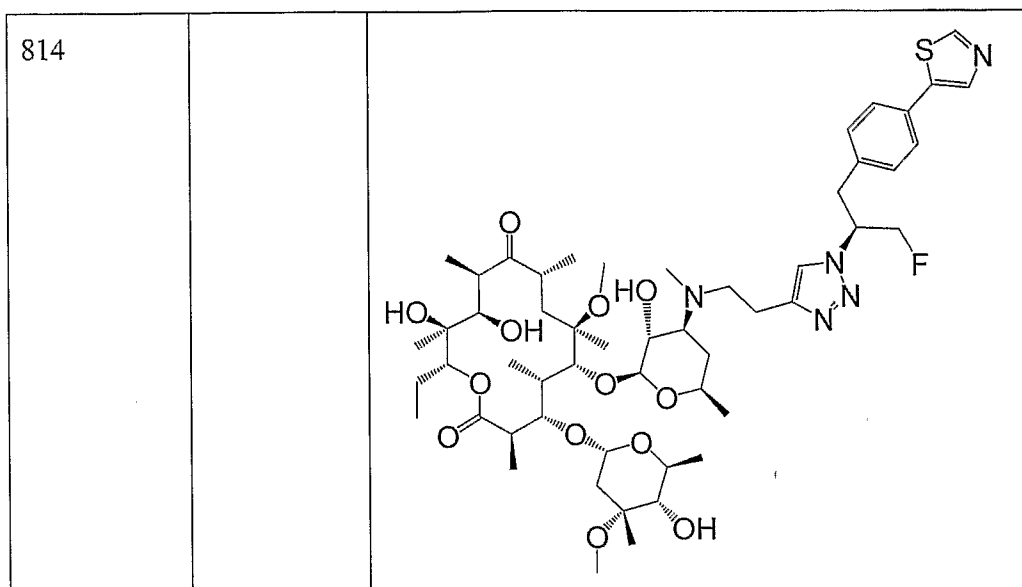
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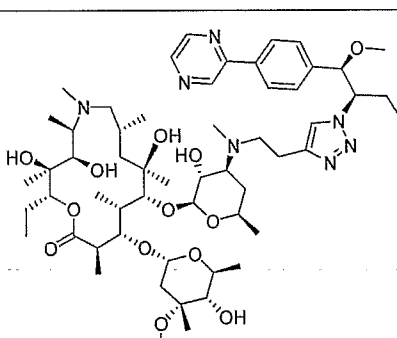
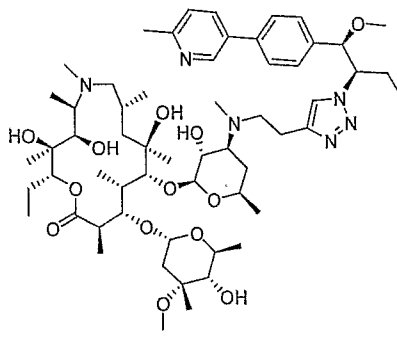
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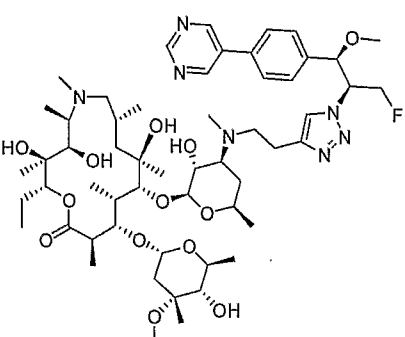
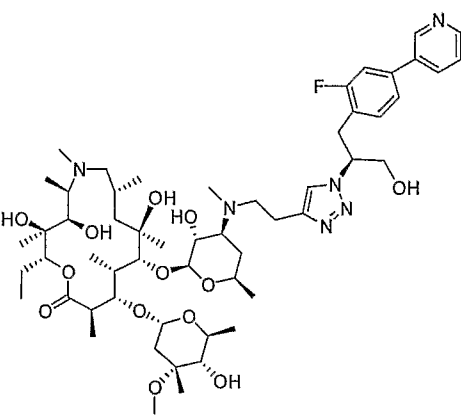
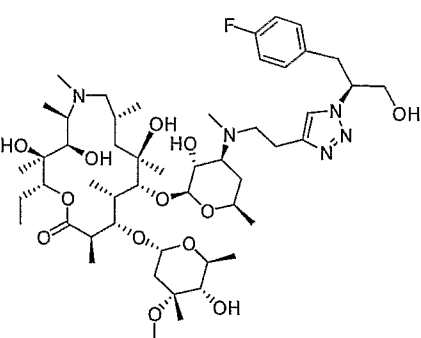
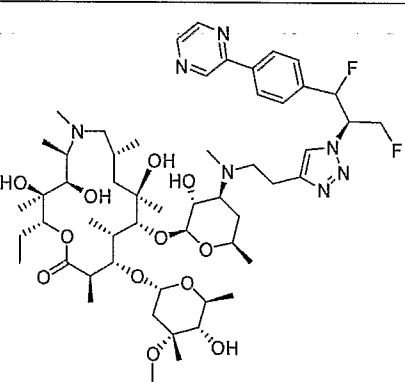


Other exemplary compounds synthesized in accordance with the invention are listed in Table 1A.

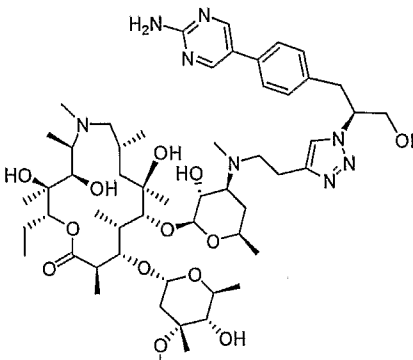
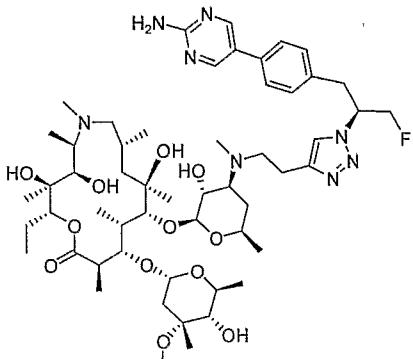
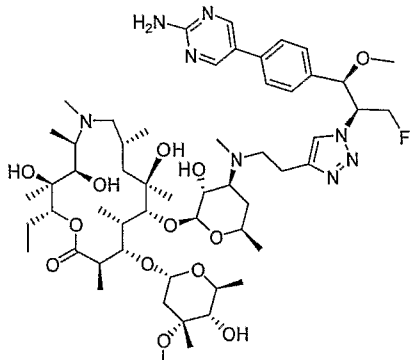
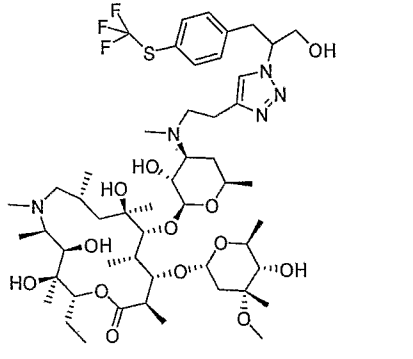
Table 1A

Compound No.	Structure
1000	 The chemical structure of compound 1000 is a complex molecule. It features a central core consisting of a fused bicyclic system, likely a pyranose derivative, with multiple hydroxyl groups and a carbonyl group. This core is substituted with a side chain that includes a triazole ring, a phenyl ring, and a thiazole ring. The thiazole ring is further substituted with a methyl group and a hydroxyl group. The phenyl ring is substituted with a methyl group and a hydroxyl group. The triazole ring is substituted with a methyl group and a hydroxyl group. The side chain also includes a fluorine atom and a methyl group.
1001	 The chemical structure of compound 1001 is a complex molecule. It features a central core consisting of a fused bicyclic system, likely a pyranose derivative, with multiple hydroxyl groups and a carbonyl group. This core is substituted with a side chain that includes a triazole ring, a phenyl ring, and a thiazole ring. The thiazole ring is further substituted with a methyl group and a hydroxyl group. The phenyl ring is substituted with a methyl group and a hydroxyl group. The triazole ring is substituted with a methyl group and a hydroxyl group. The side chain also includes a fluorine atom and a methyl group.

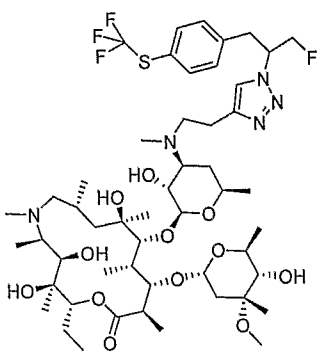
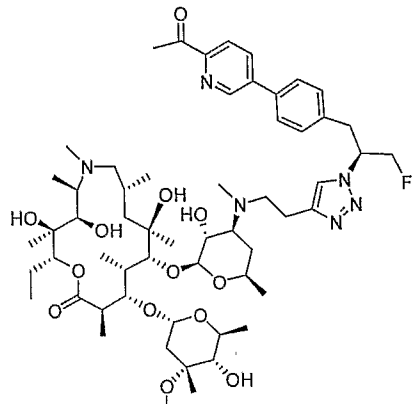
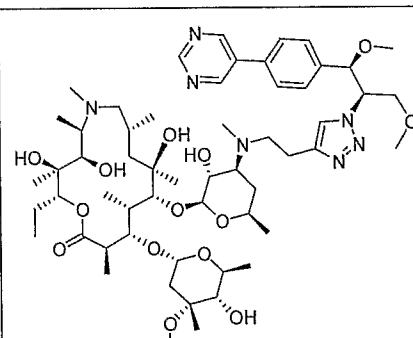
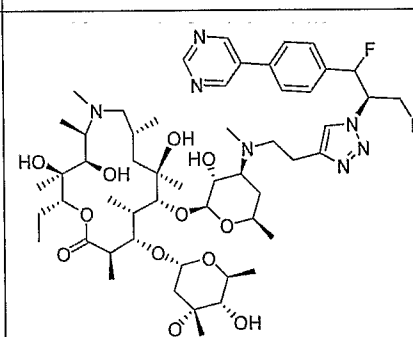
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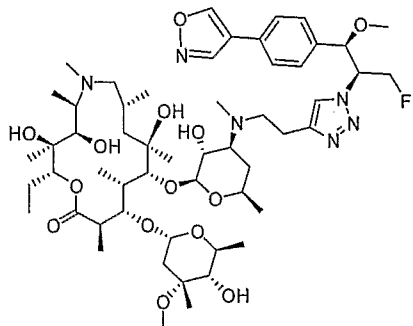
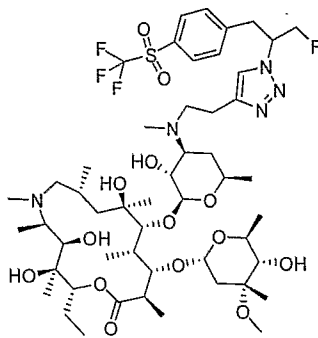
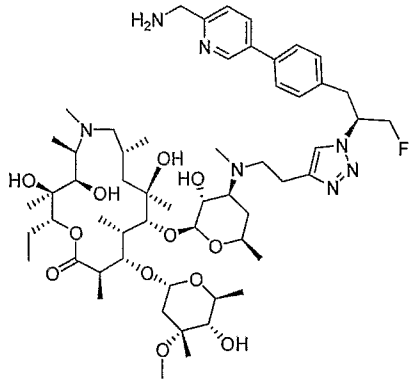
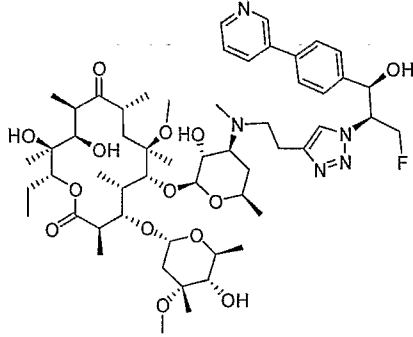
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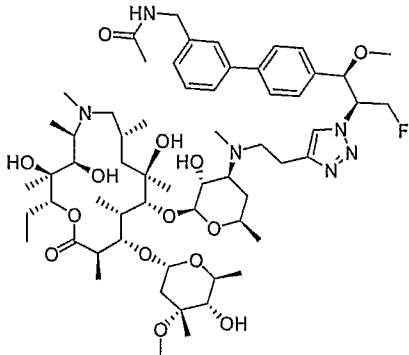
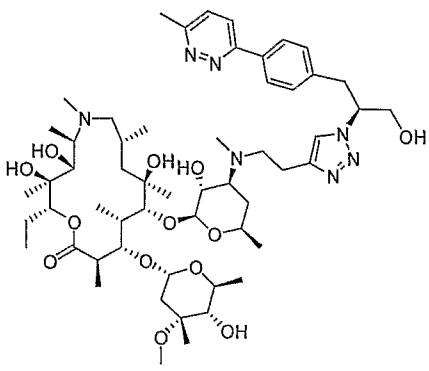
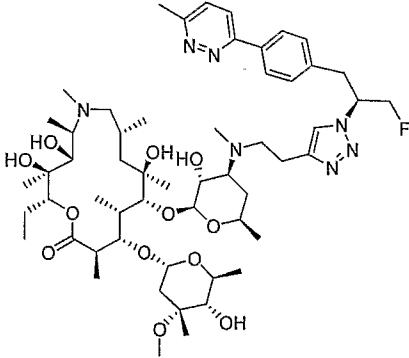
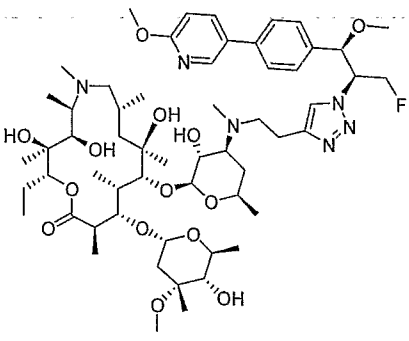
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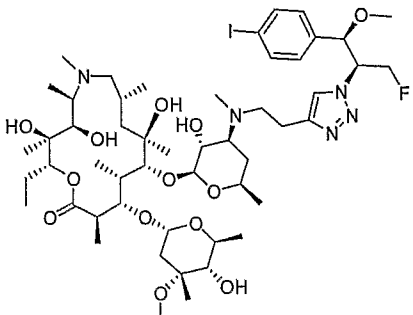
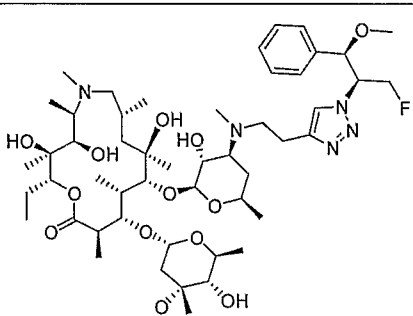
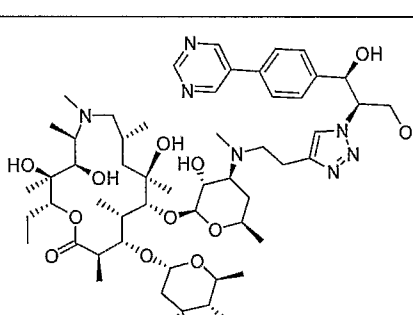
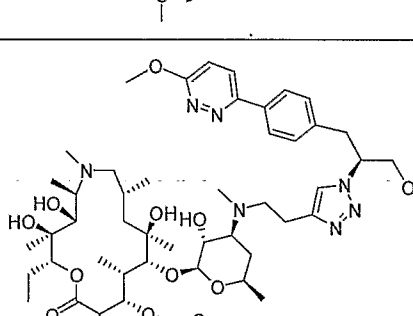
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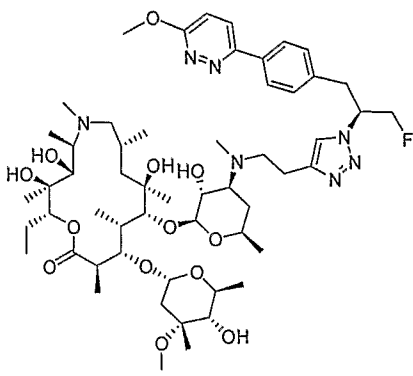
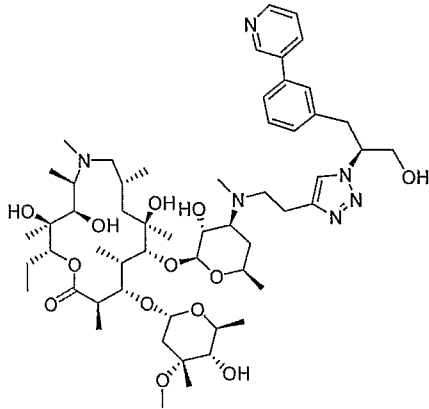
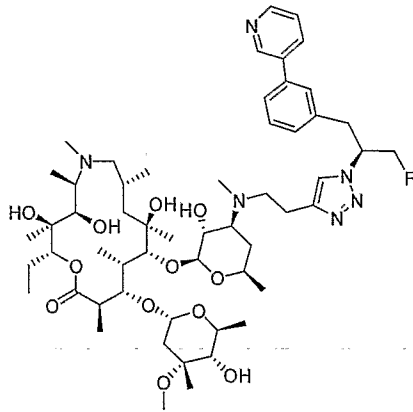
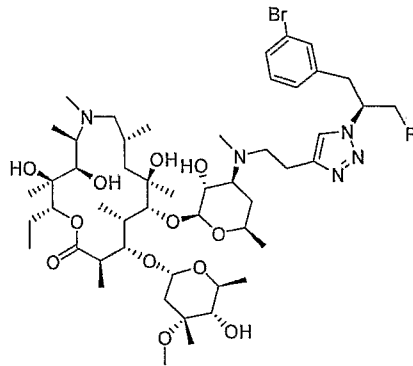
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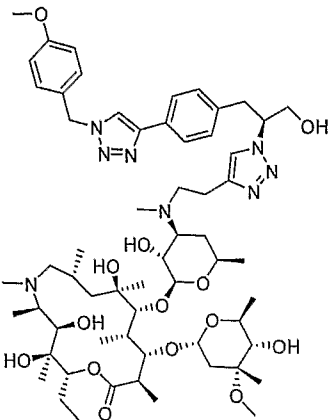
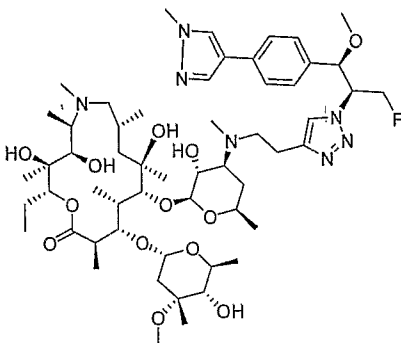
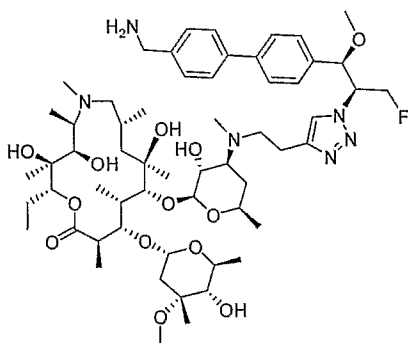
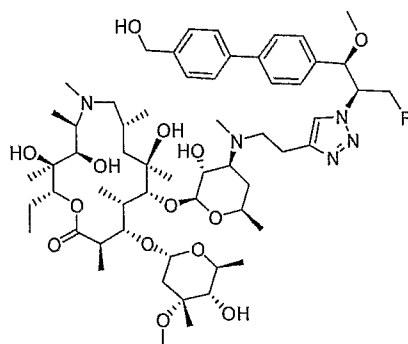
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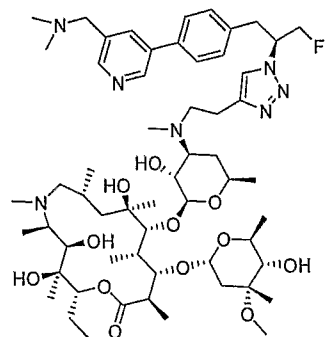
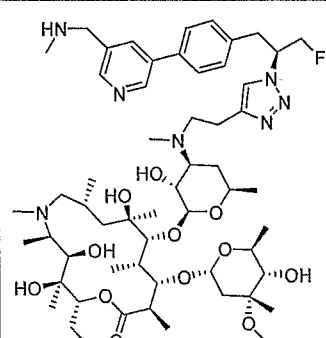
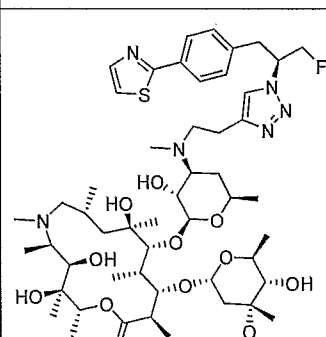
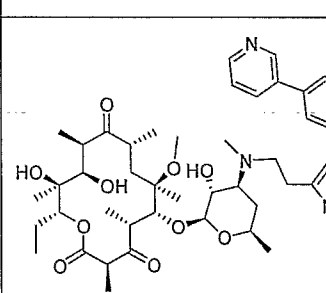
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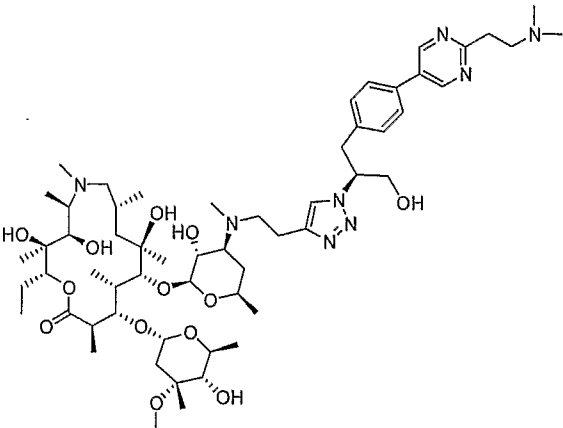
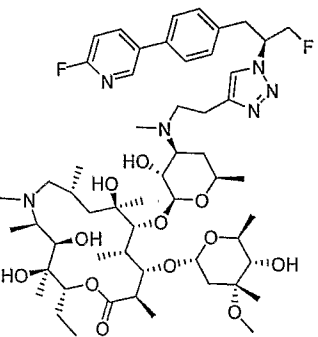
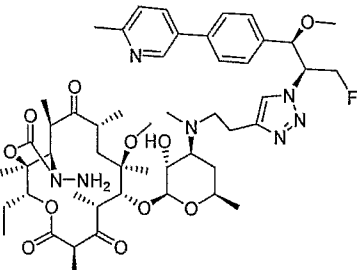
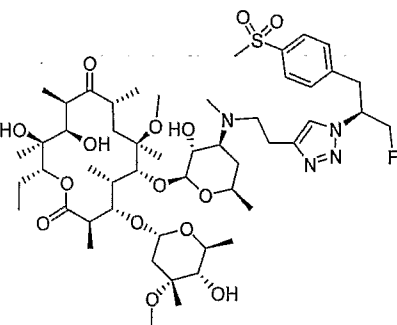
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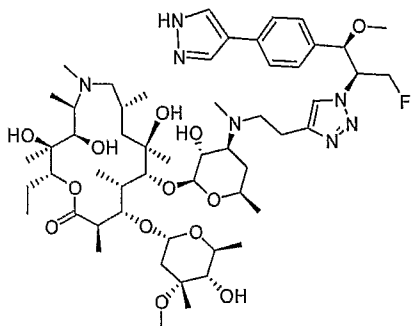
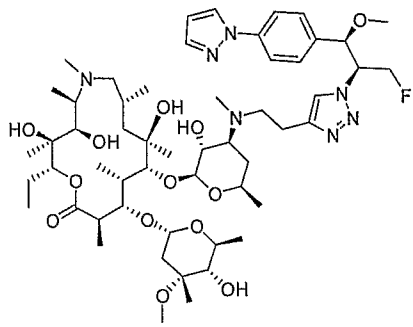
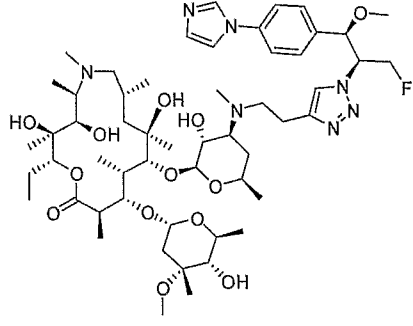
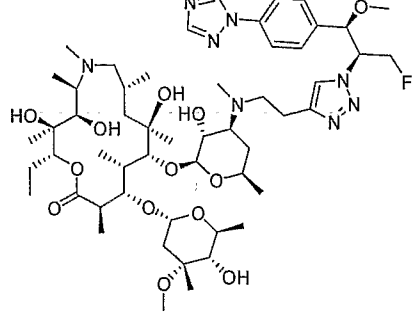
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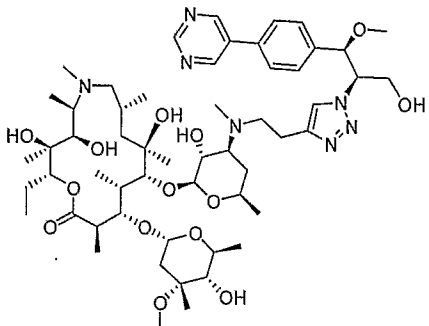
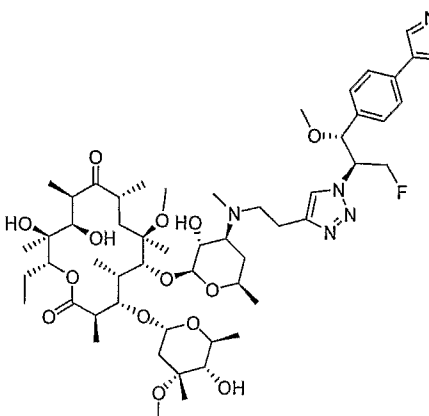
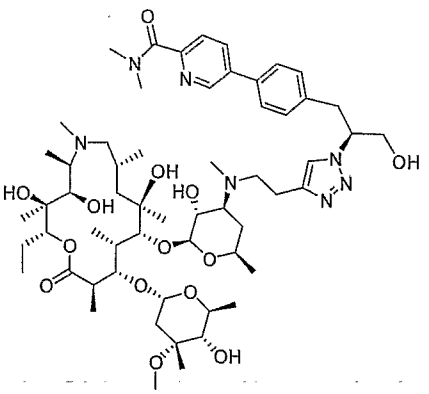
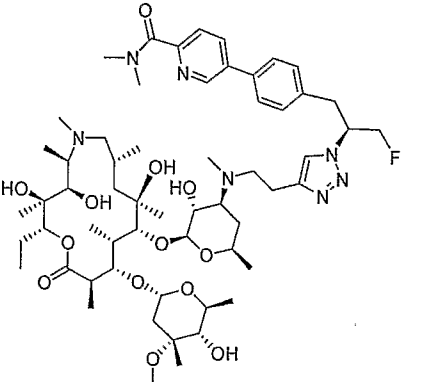
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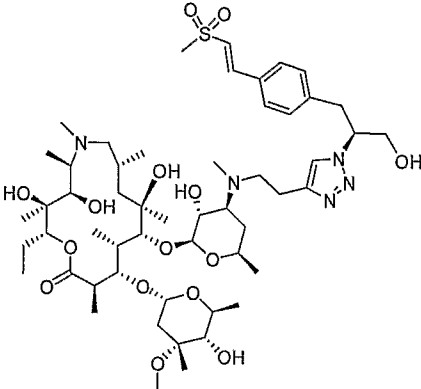
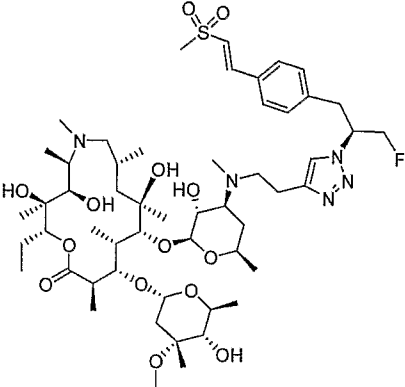
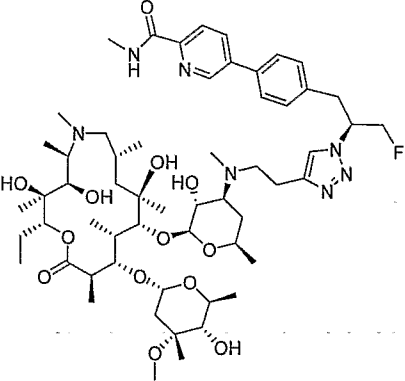
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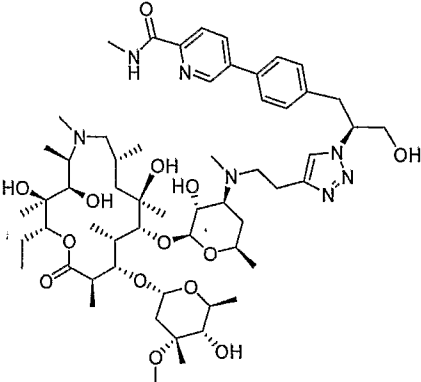
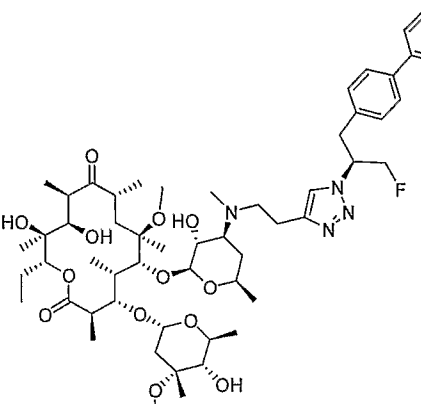
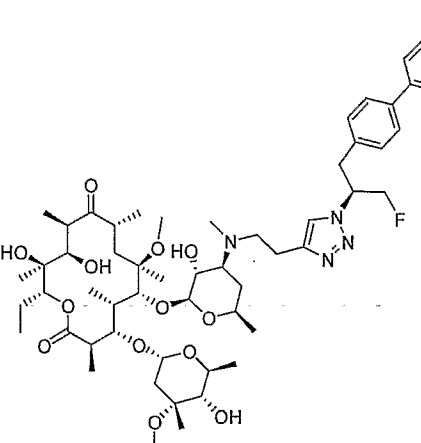
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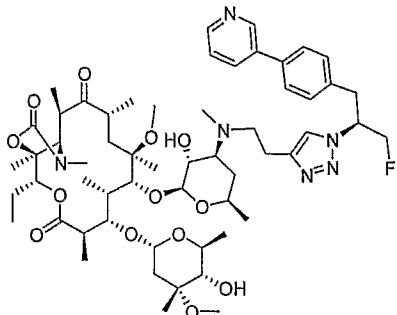
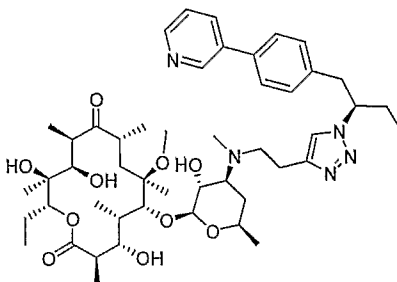
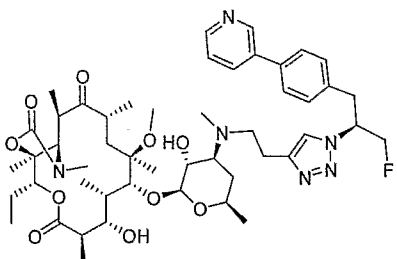
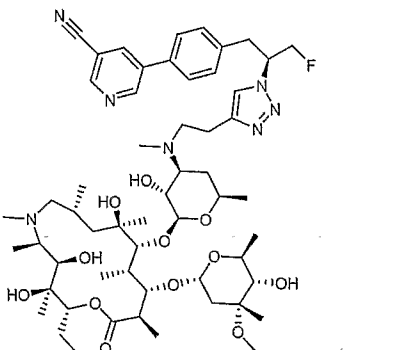
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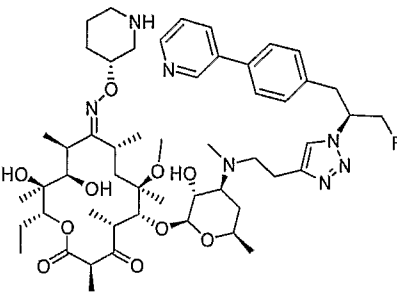
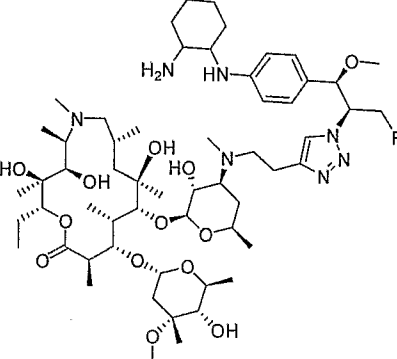
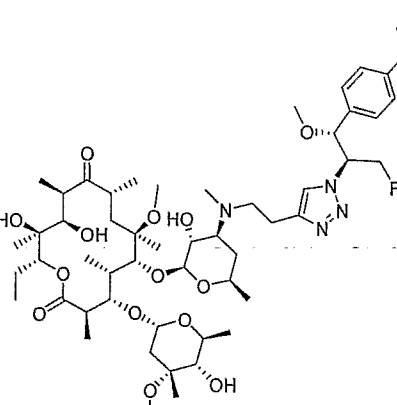
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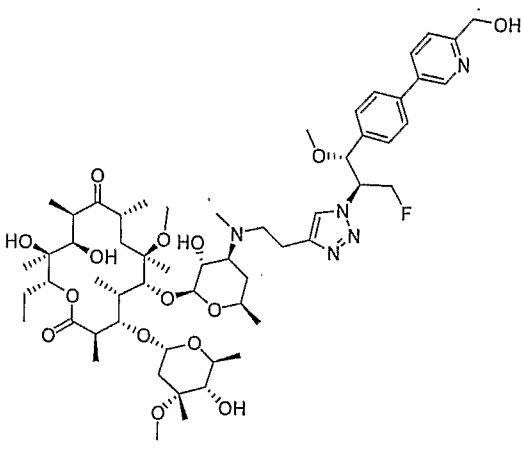
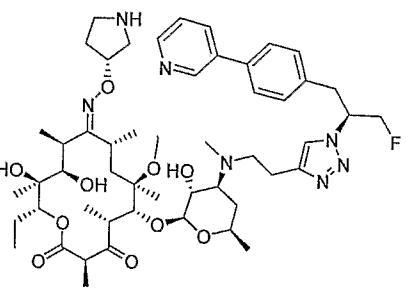
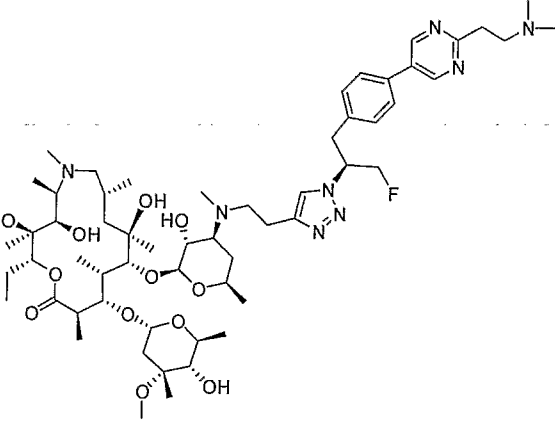
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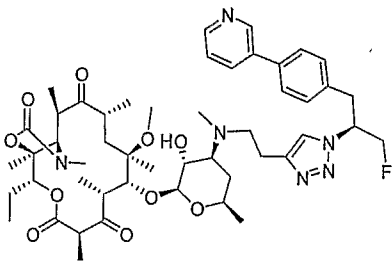
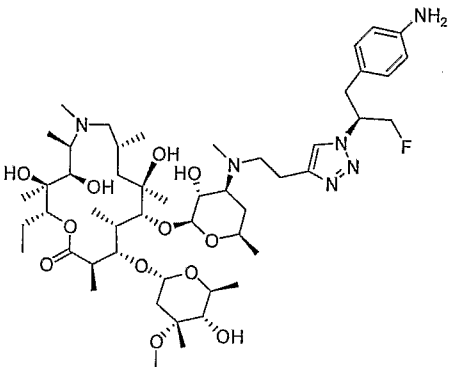
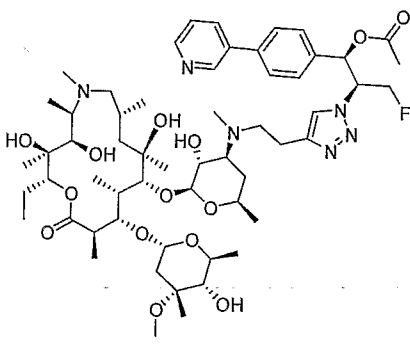
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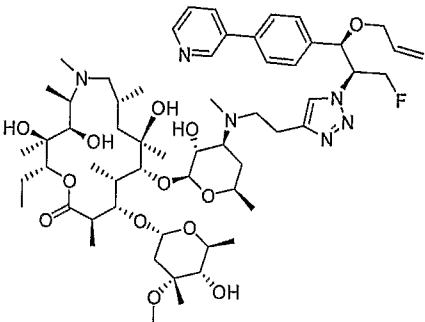
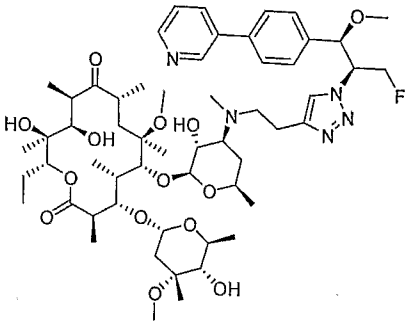
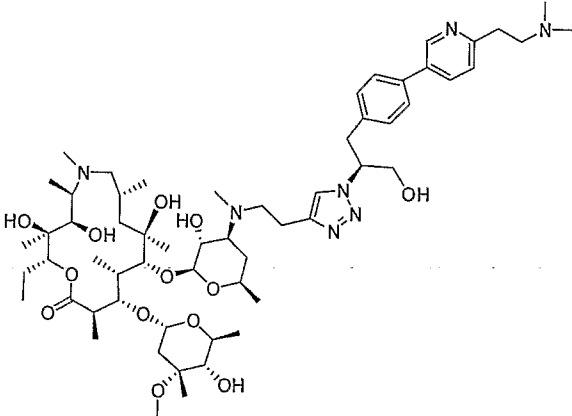
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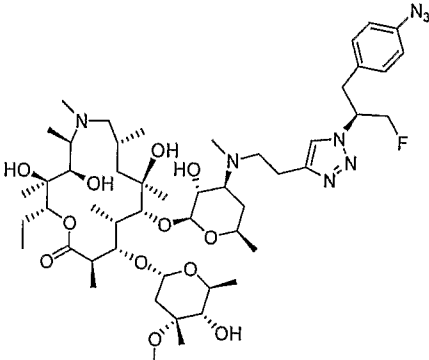
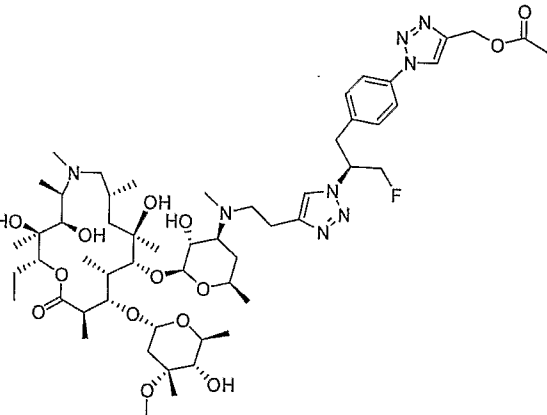
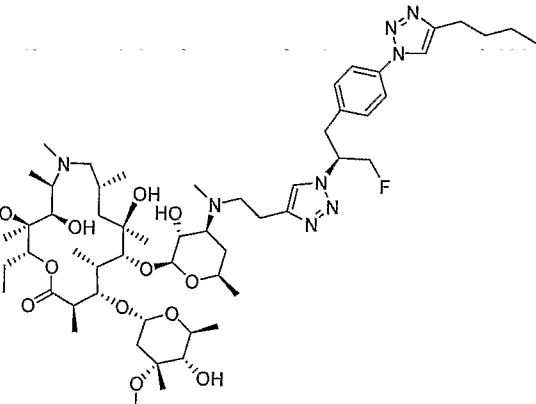
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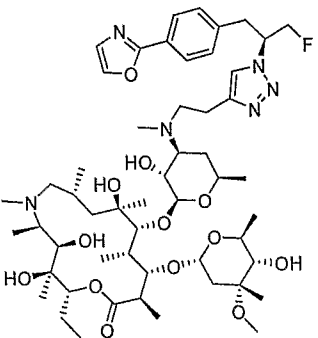
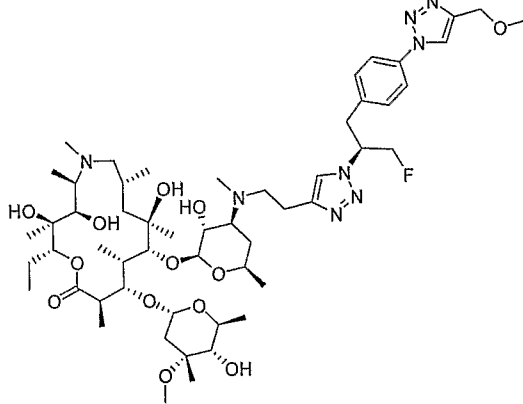
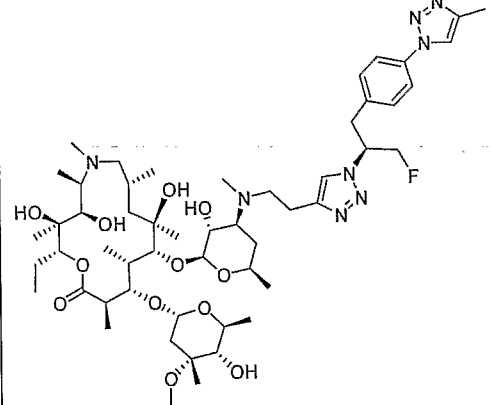
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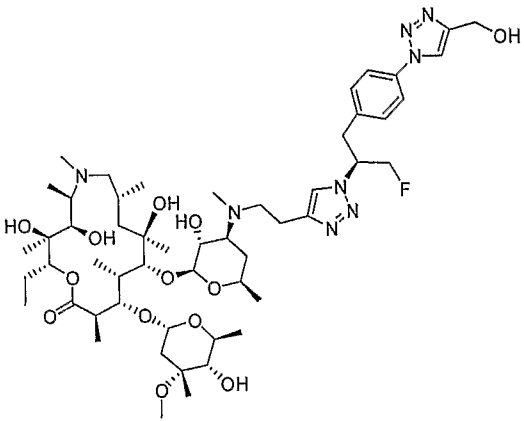
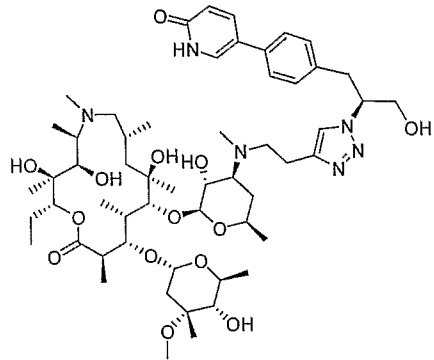
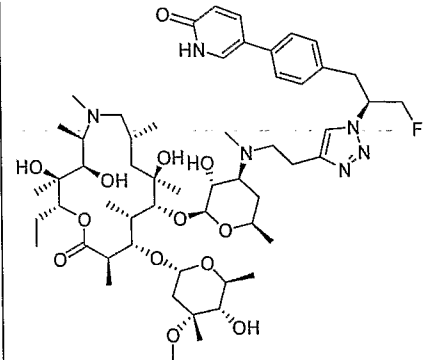
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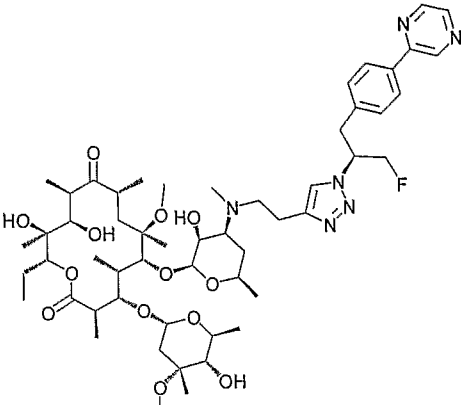
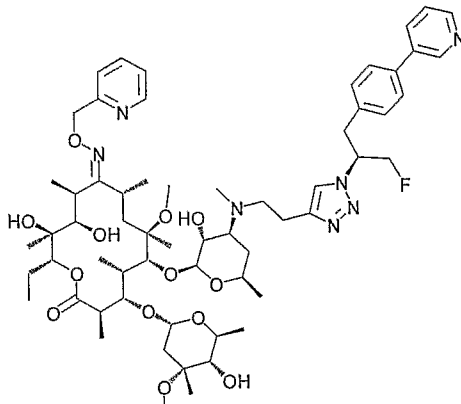
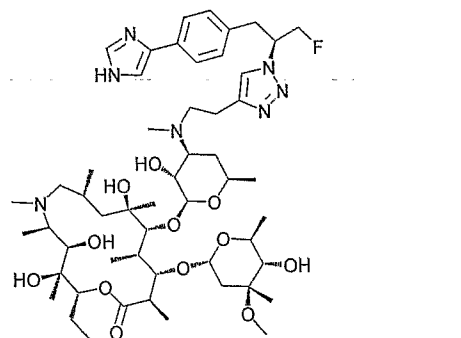
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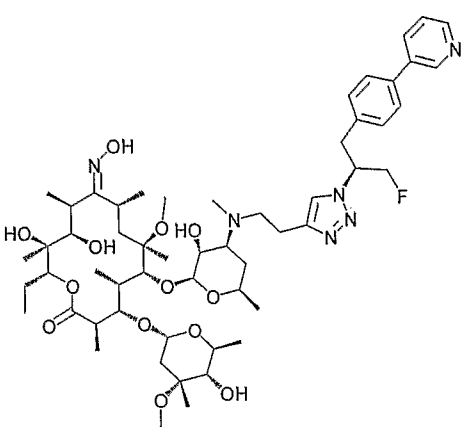
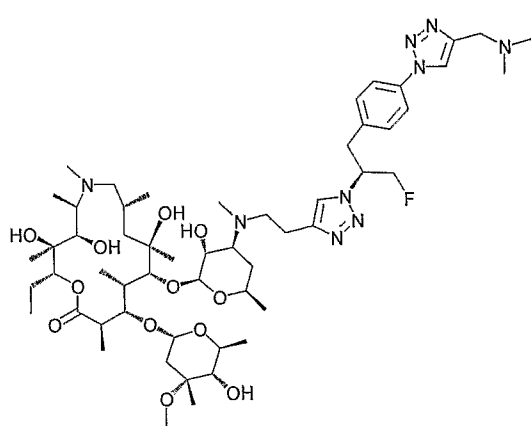
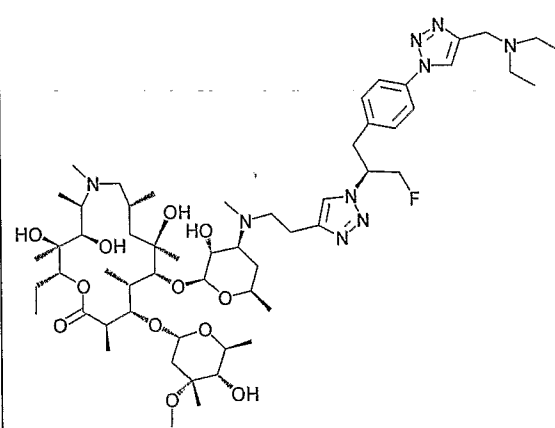
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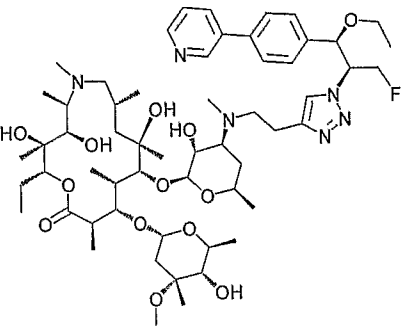
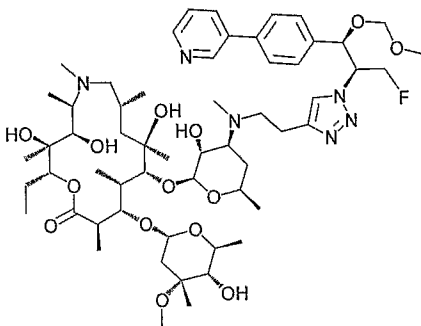
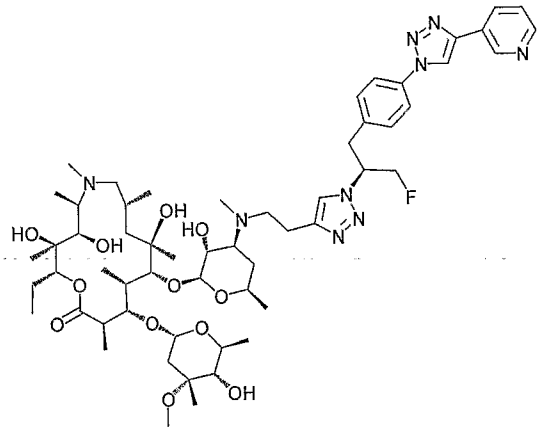
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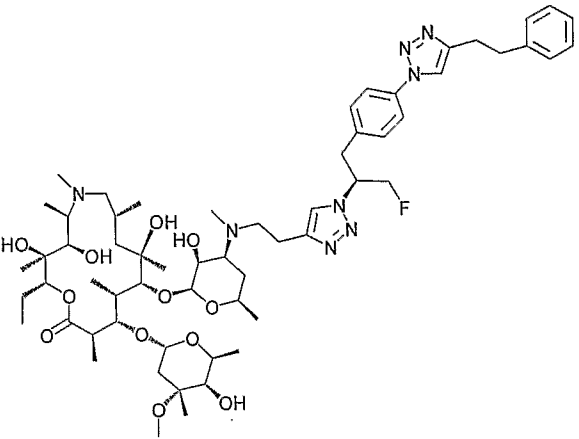
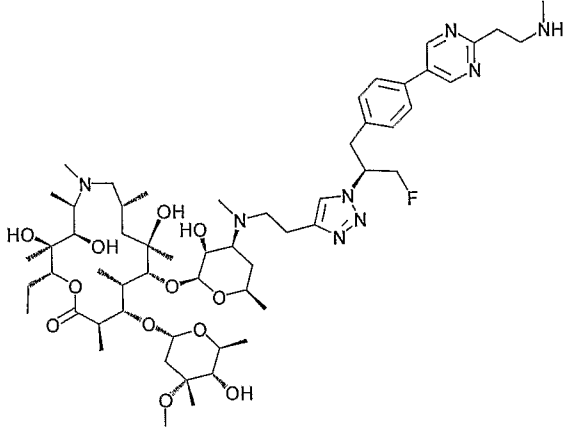
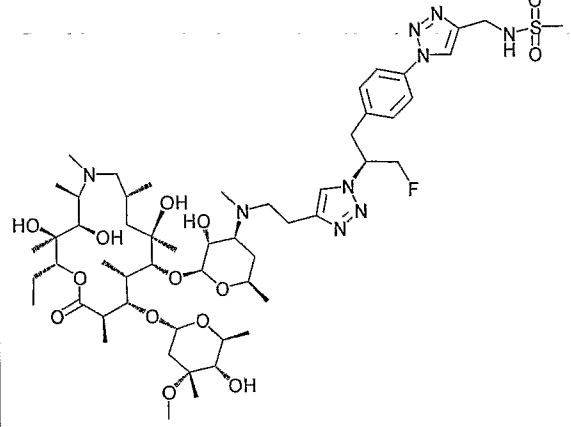
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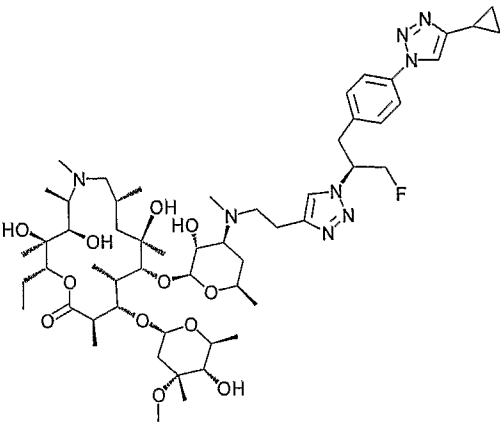
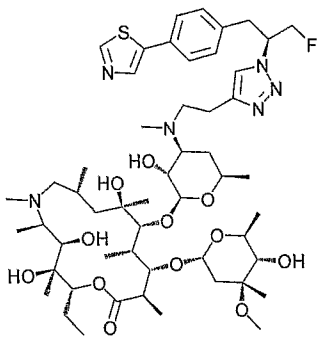
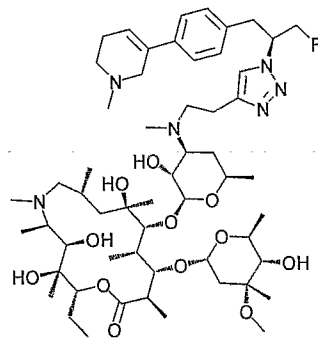
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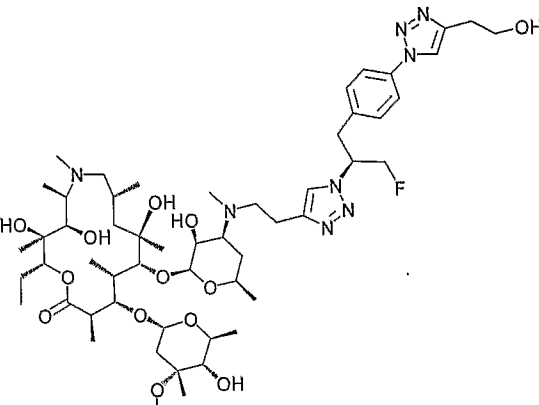
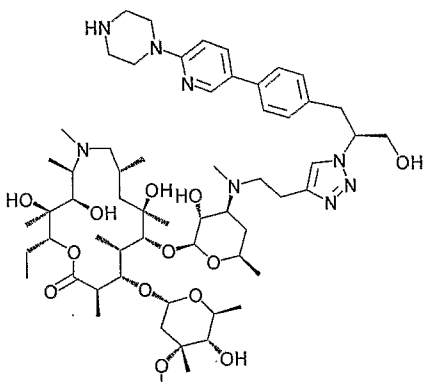
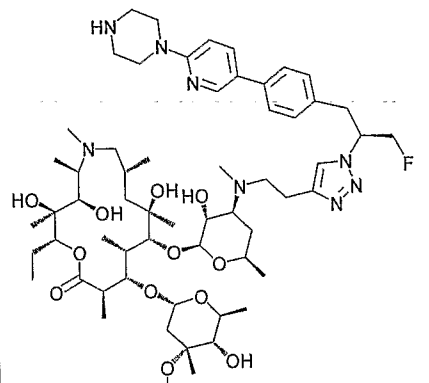
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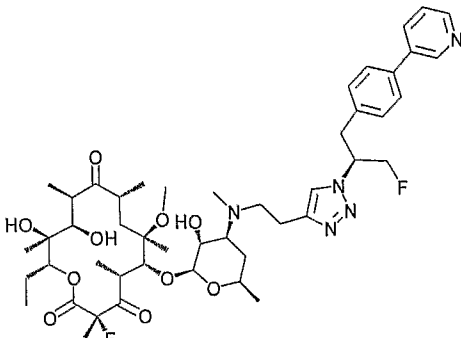
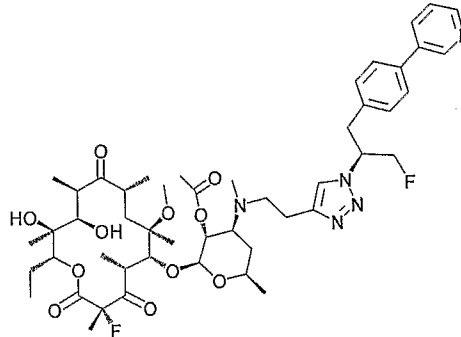
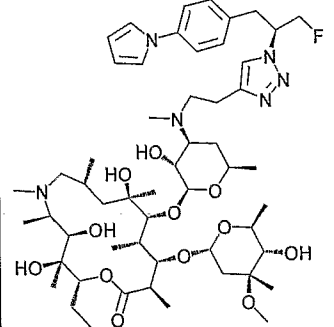
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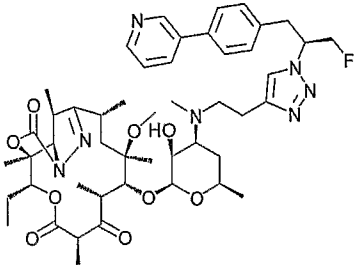
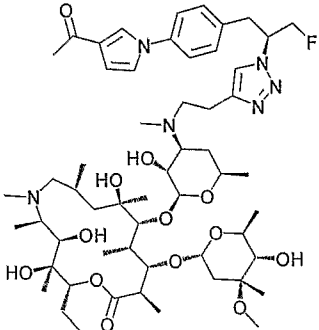
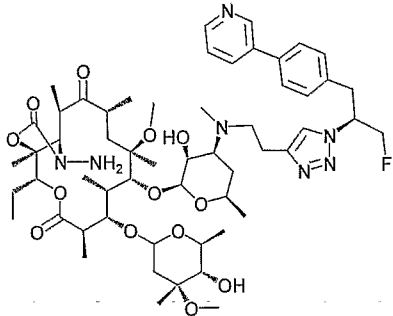
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1096		 Chemical structure of compound 1096: A complex molecule featuring a central core with multiple hydroxyl groups and a fluorine atom. The core is substituted with a side chain containing a 1,2,4-triazole ring, a phenyl ring, and a 1,3,4-oxadiazole ring, which is further substituted with a hydroxymethyl group.
1097		 Chemical structure of compound 1097: A complex molecule featuring a central core with multiple hydroxyl groups and a fluorine atom. The core is substituted with a side chain containing a 1,2,4-triazole ring, a phenyl ring, and a 1,3,4-oxadiazole ring, which is further substituted with a hydroxymethyl group.
1098		 Chemical structure of compound 1098: A complex molecule featuring a central core with multiple hydroxyl groups and a fluorine atom. The core is substituted with a side chain containing a 1,2,4-triazole ring, a phenyl ring, and a 1,3,4-oxadiazole ring, which is further substituted with a hydroxymethyl group.

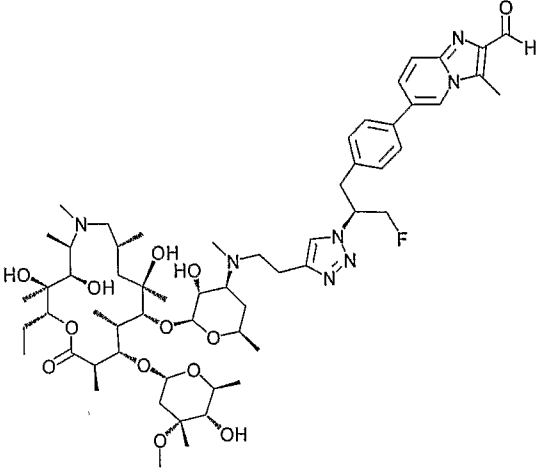
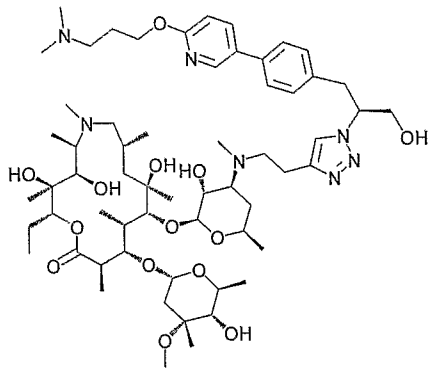
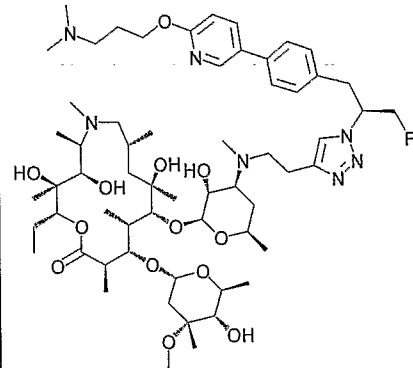
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1099		 Chemical structure of compound 1099: A complex molecule featuring a central core with multiple hydroxyl groups and a fluorine atom. It is substituted with a 1,2,3,4-tetrahydro-2H-pyran-2-yl group and a 1,2,3,4-tetrahydro-2H-pyran-2-yl group. The structure also includes a 1,2,3,4-tetrahydro-2H-pyran-2-yl group and a 1,2,3,4-tetrahydro-2H-pyran-2-yl group.
1100		 Chemical structure of compound 1100: A complex molecule featuring a central core with multiple hydroxyl groups and a fluorine atom. It is substituted with a 1,2,3,4-tetrahydro-2H-pyran-2-yl group and a 1,2,3,4-tetrahydro-2H-pyran-2-yl group. The structure also includes a 1,2,3,4-tetrahydro-2H-pyran-2-yl group and a 1,2,3,4-tetrahydro-2H-pyran-2-yl group.
1101		 Chemical structure of compound 1101: A complex molecule featuring a central core with multiple hydroxyl groups and a fluorine atom. It is substituted with a 1,2,3,4-tetrahydro-2H-pyran-2-yl group and a 1,2,3,4-tetrahydro-2H-pyran-2-yl group. The structure also includes a 1,2,3,4-tetrahydro-2H-pyran-2-yl group and a 1,2,3,4-tetrahydro-2H-pyran-2-yl group.

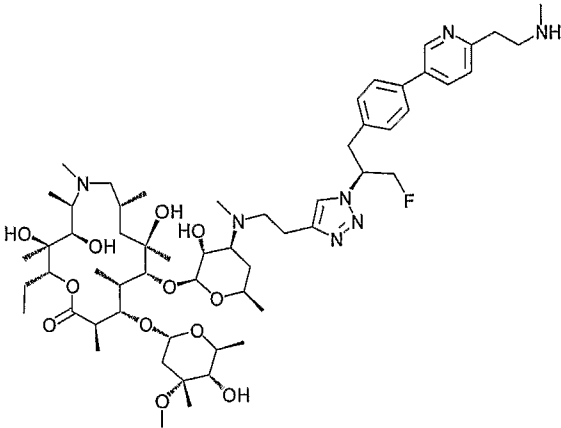
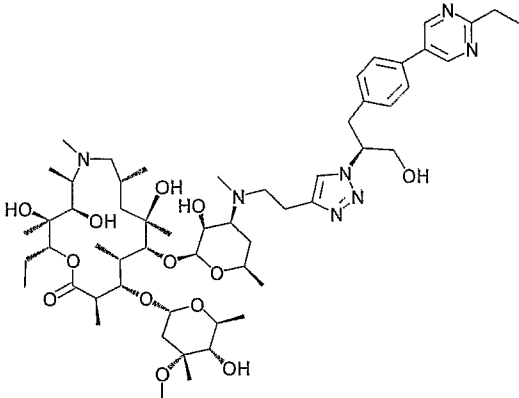
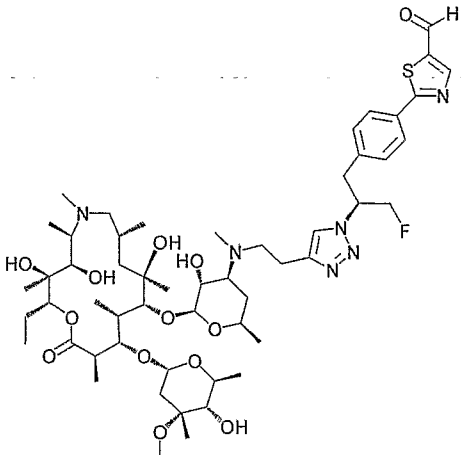
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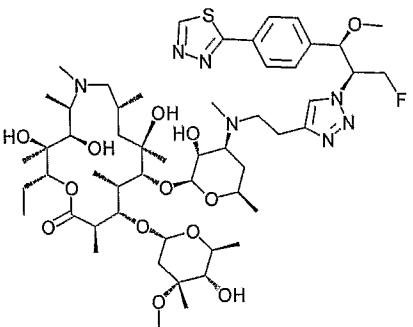
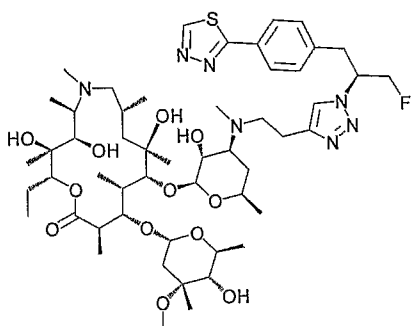
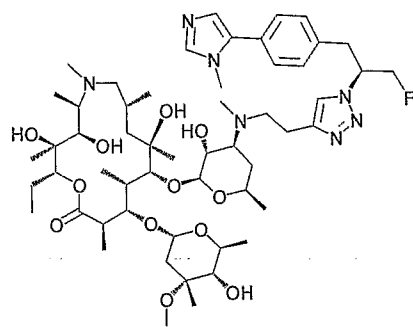
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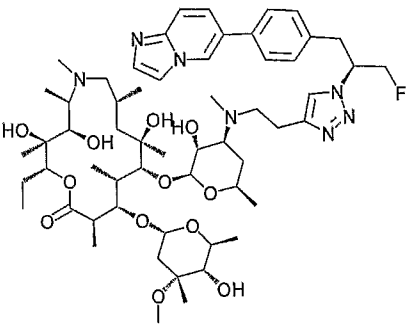
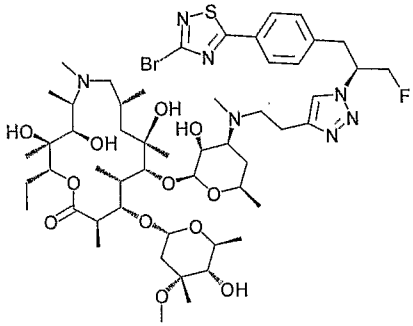
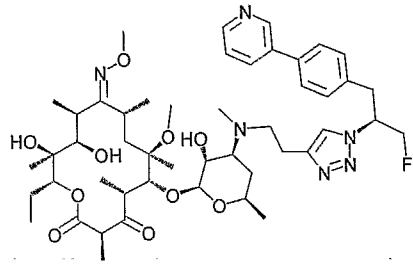
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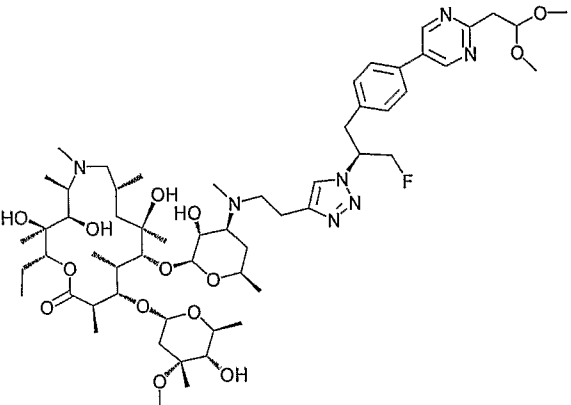
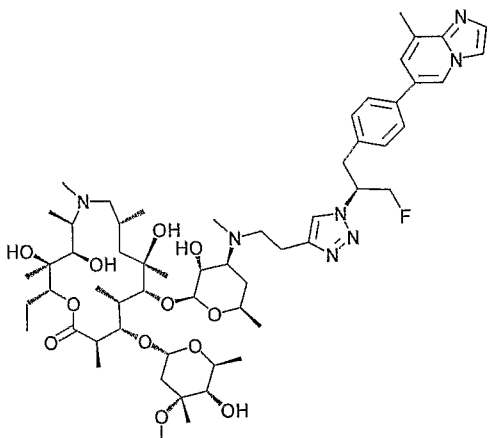
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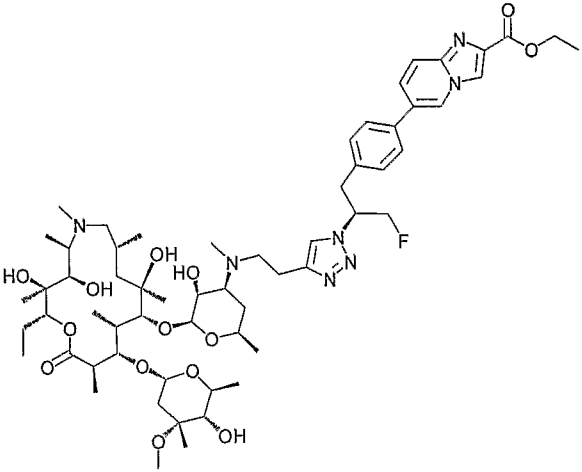
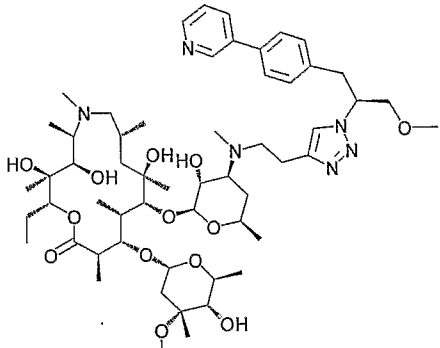
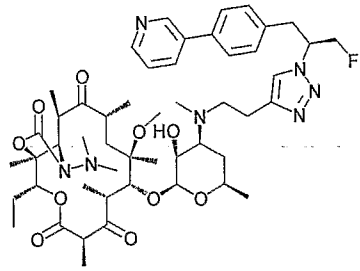
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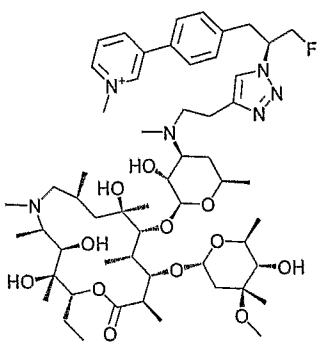
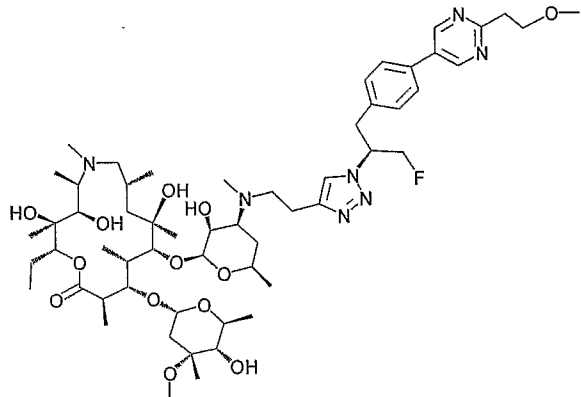
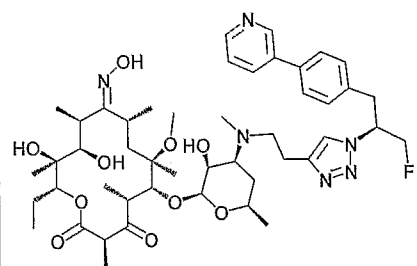
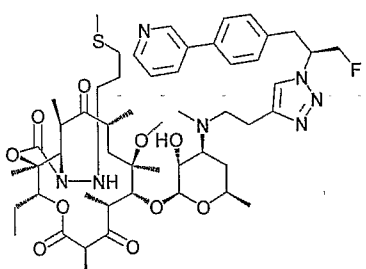
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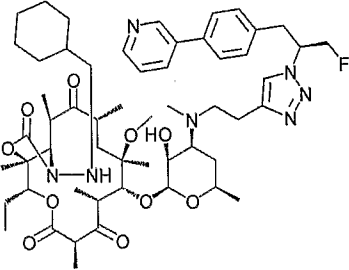
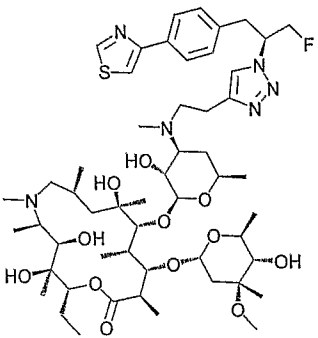
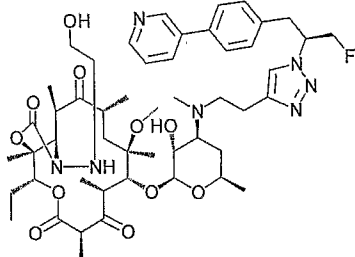
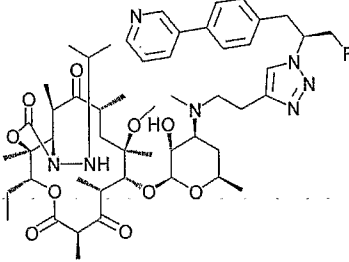
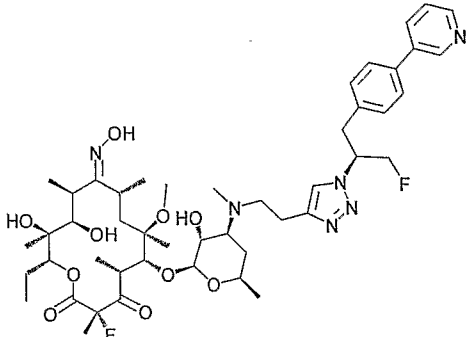
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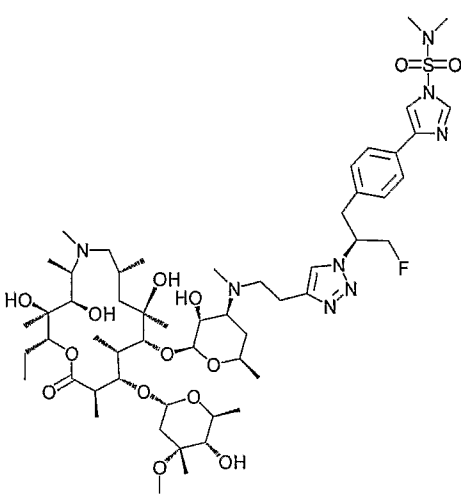
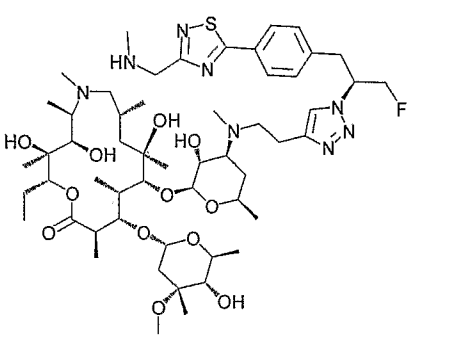
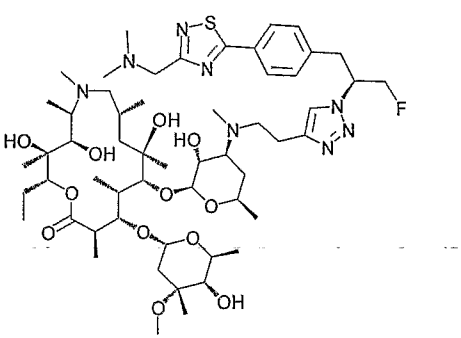
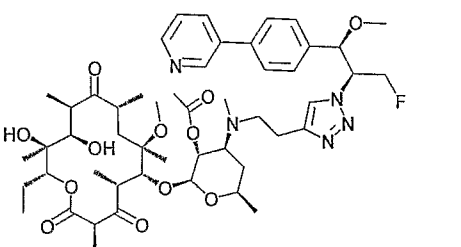
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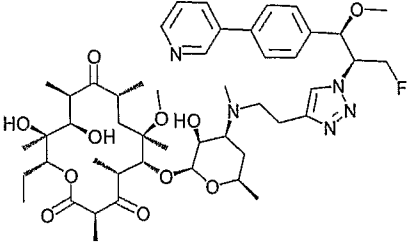
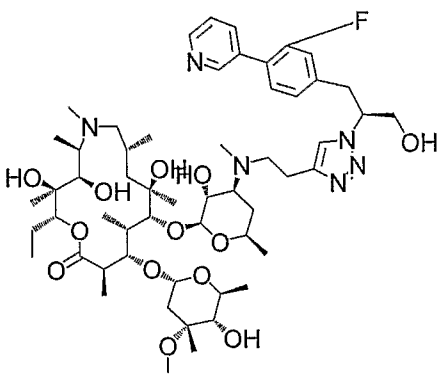
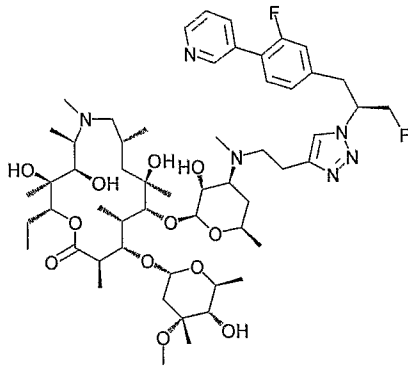
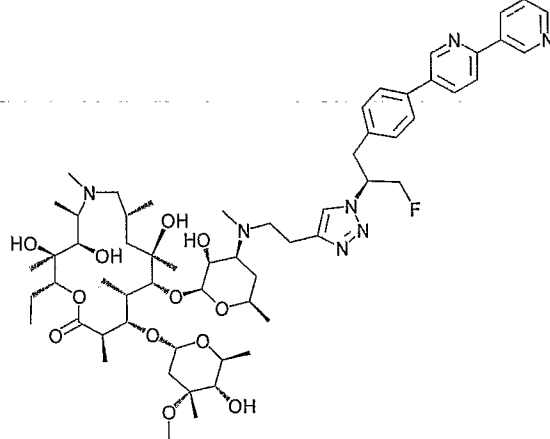
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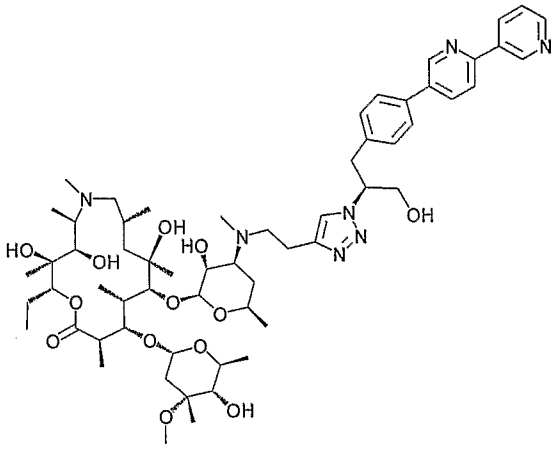
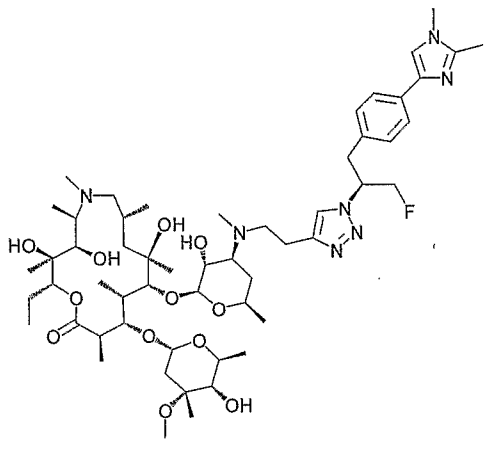
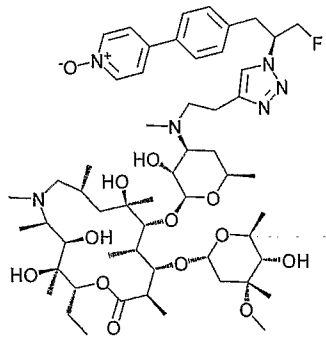
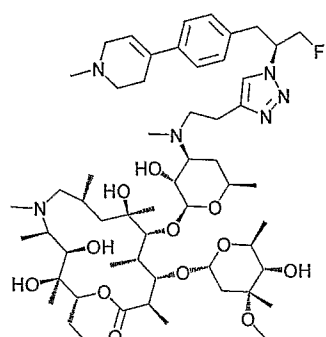
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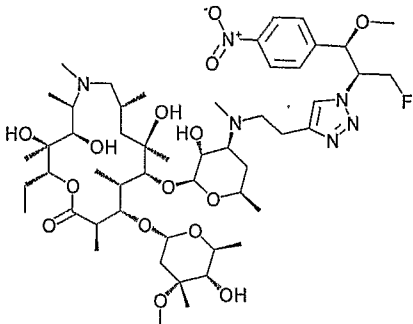
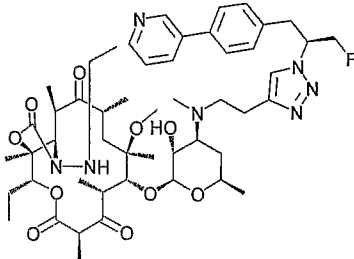
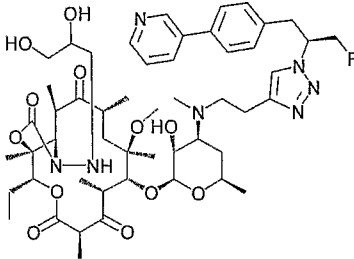
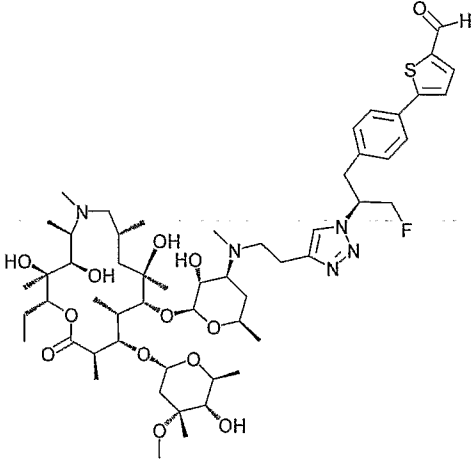
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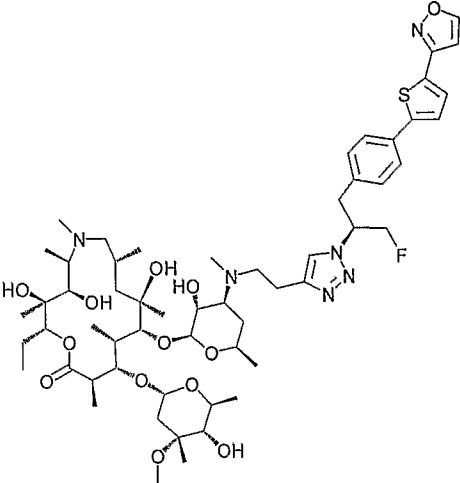
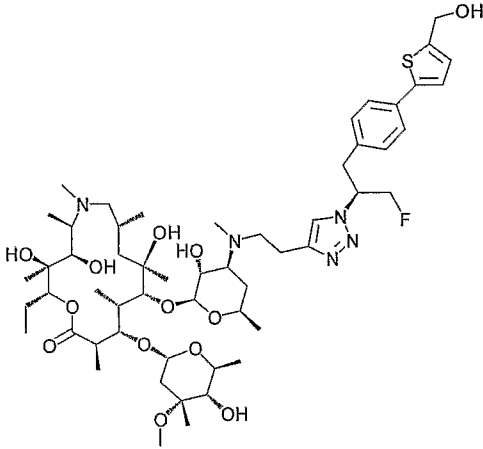
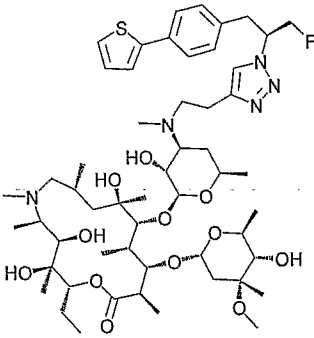
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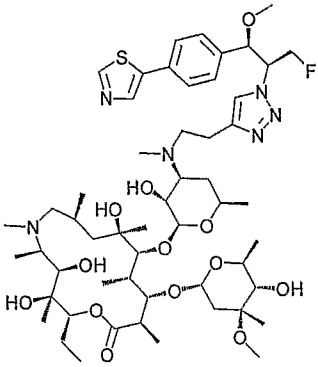
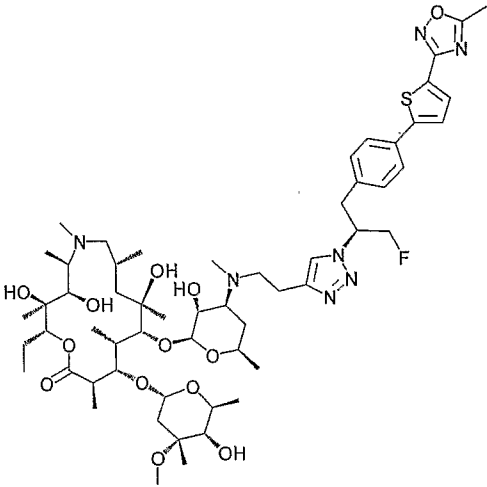
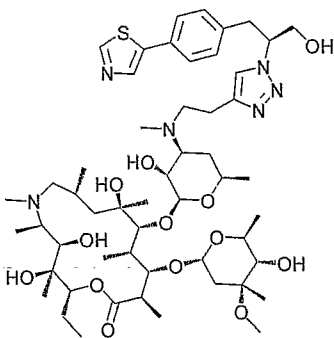
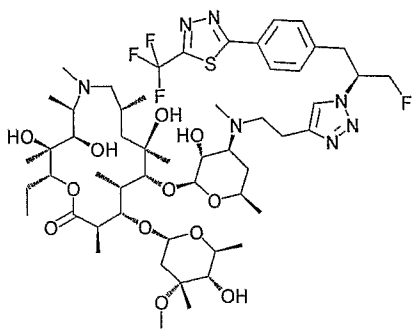
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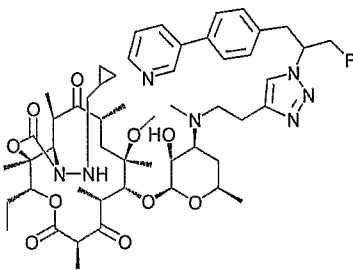
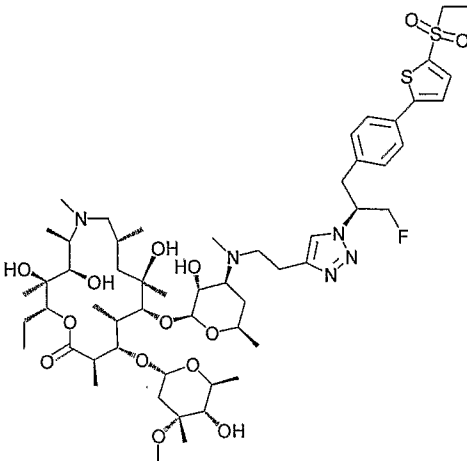
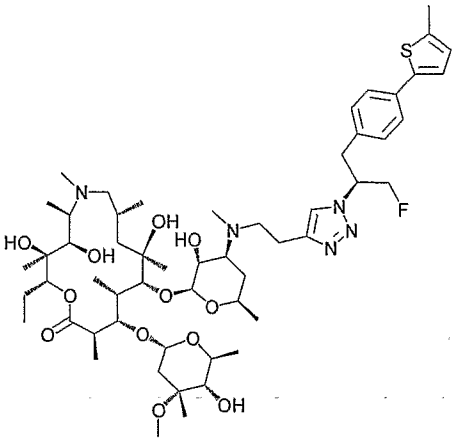
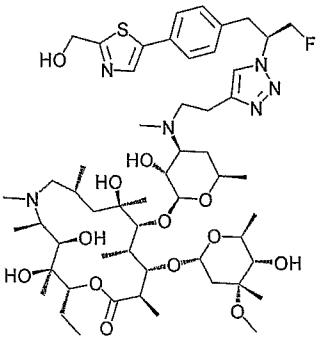
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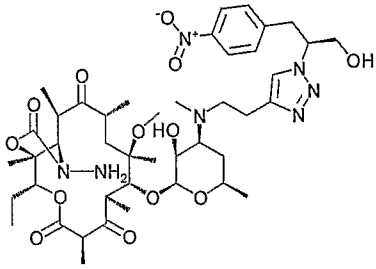
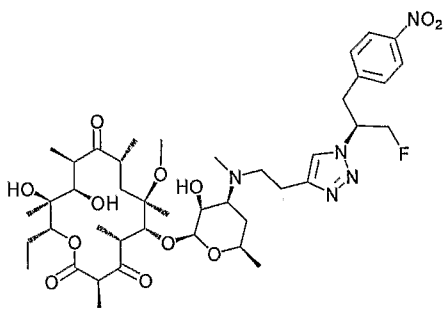
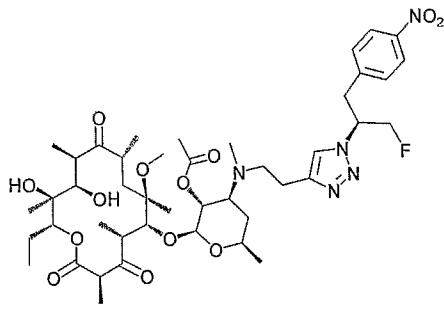
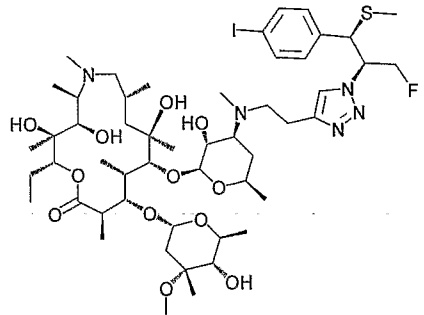
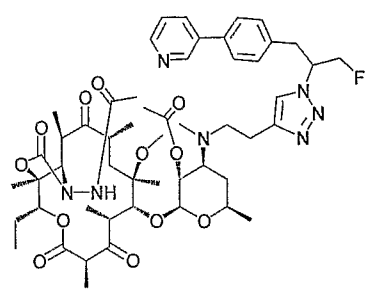
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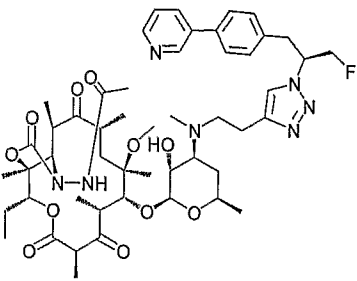
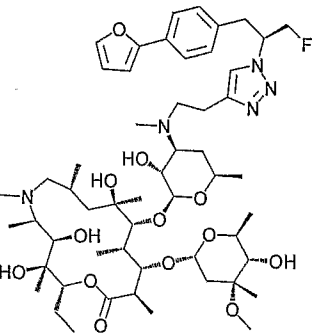
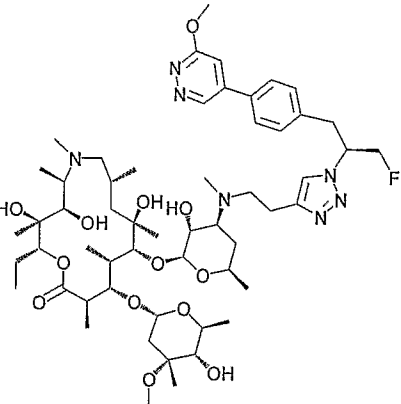
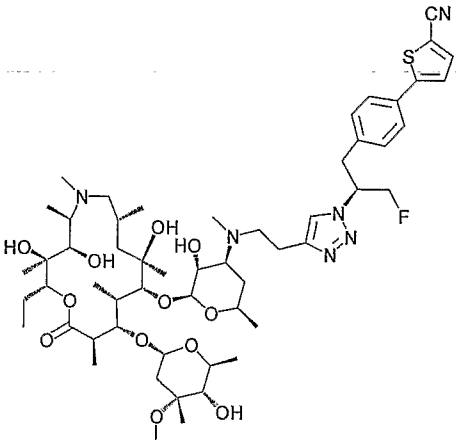
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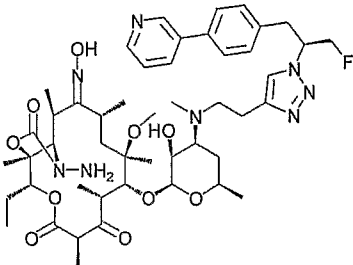
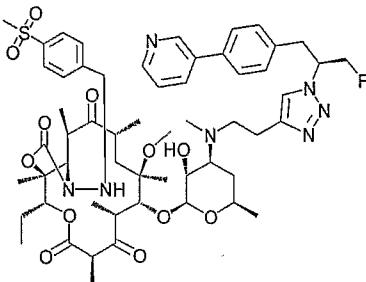
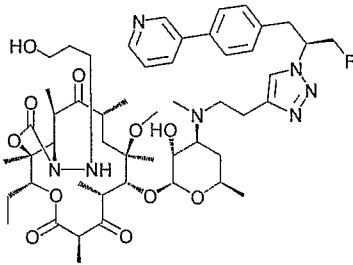
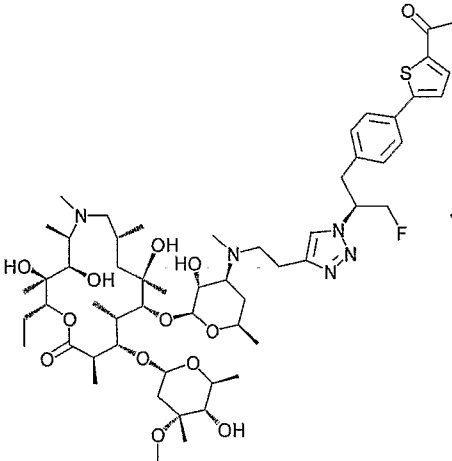
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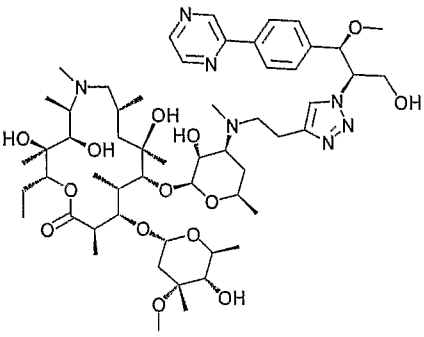
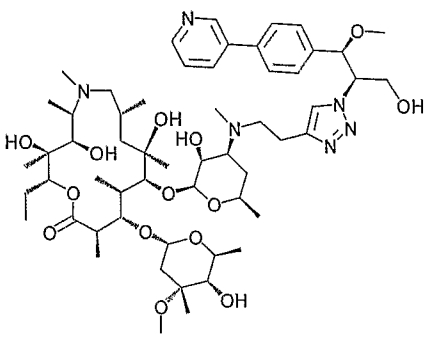
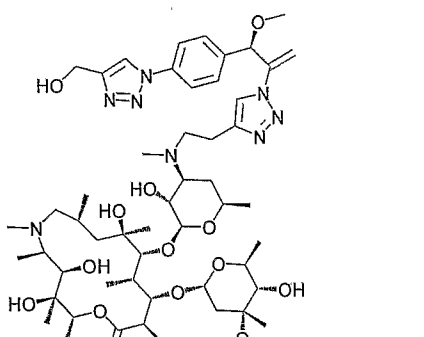
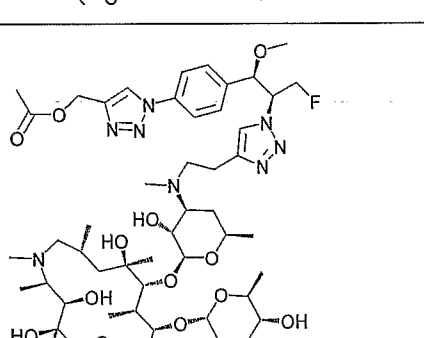
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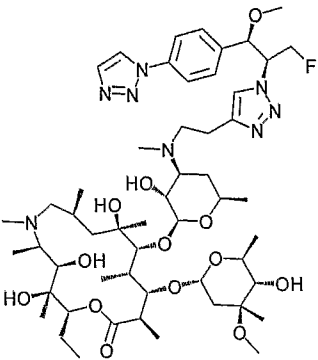
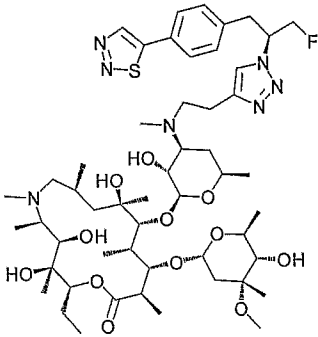
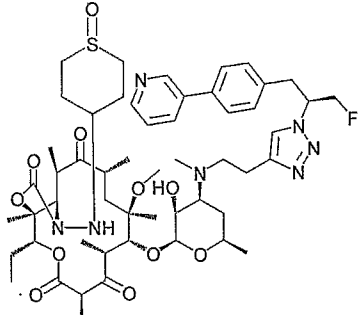
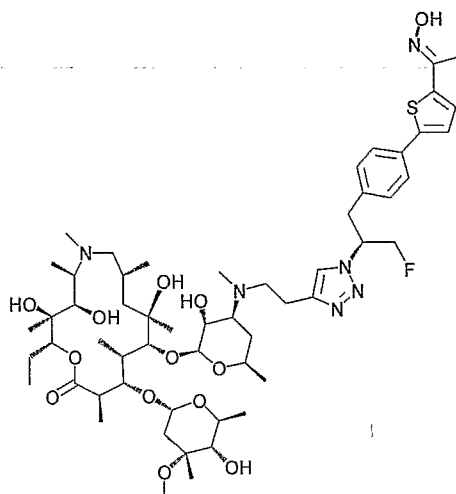
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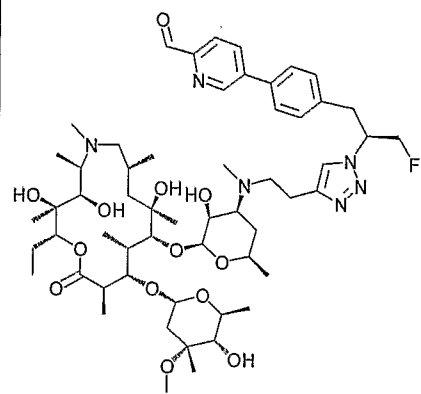
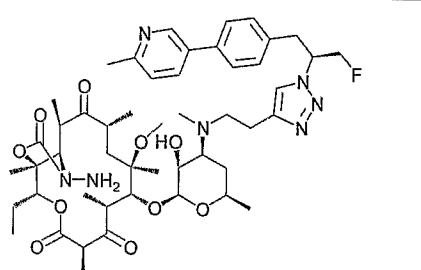
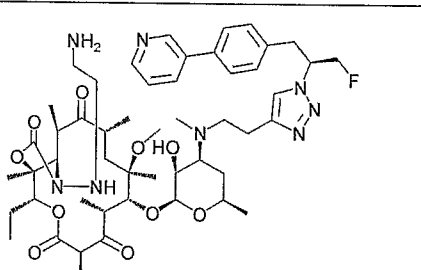
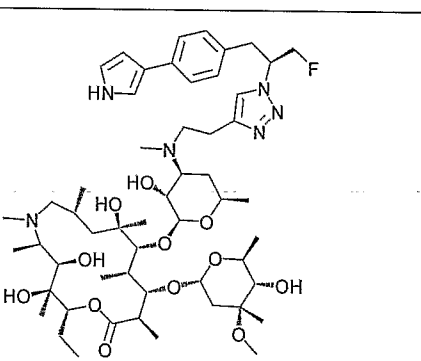
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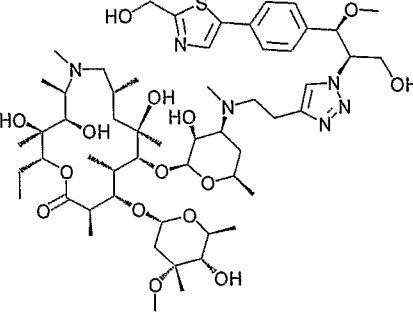
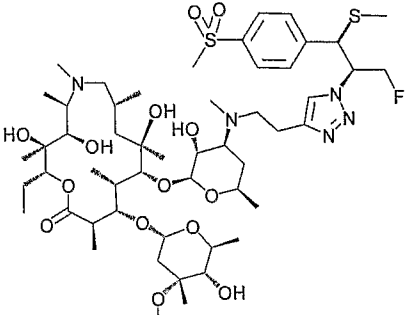
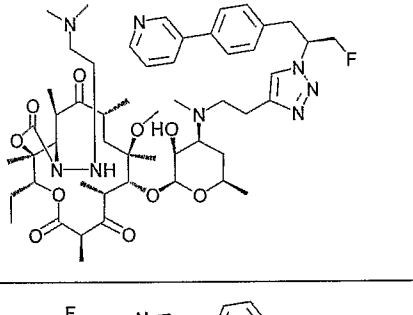
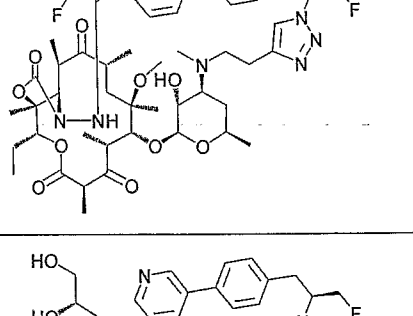
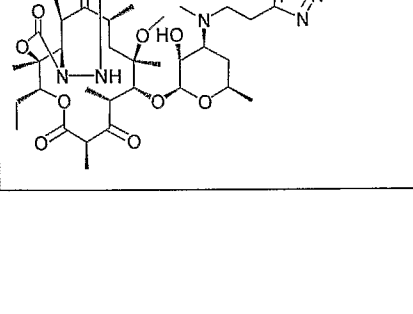
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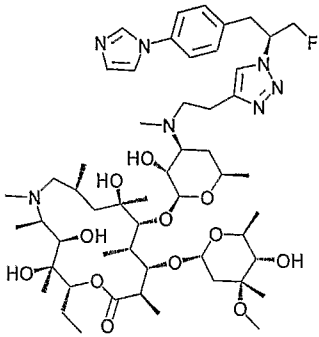
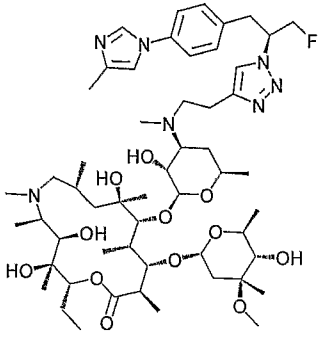
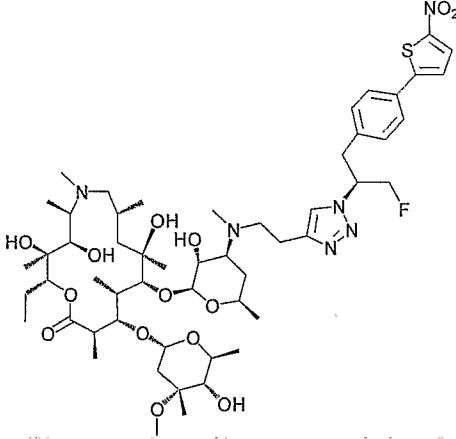
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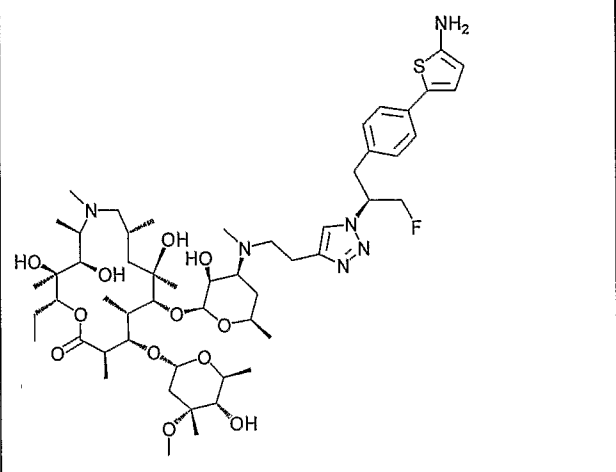
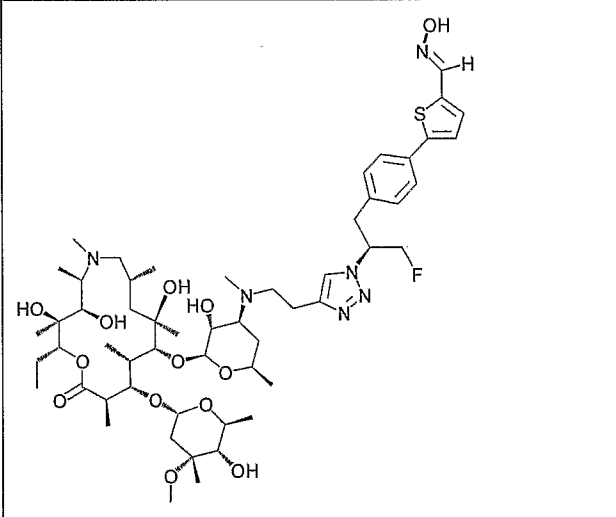
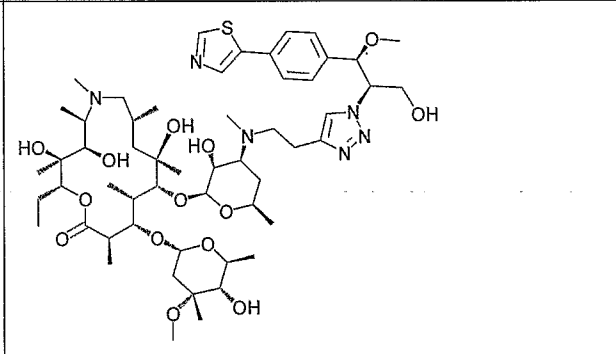
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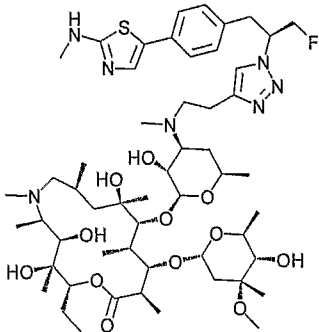
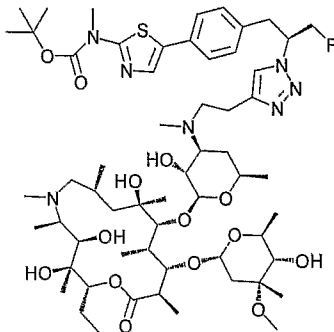
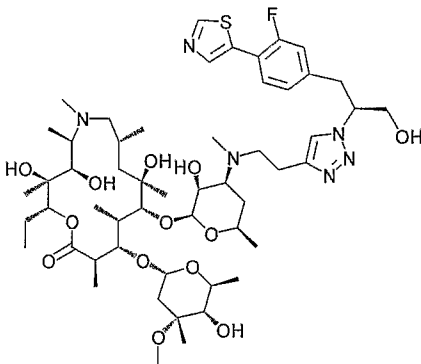
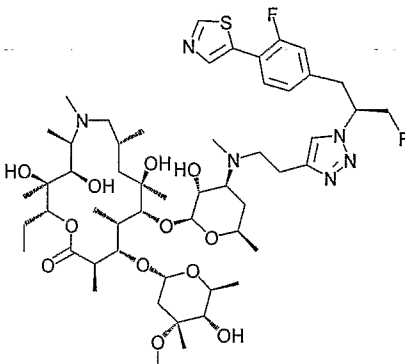
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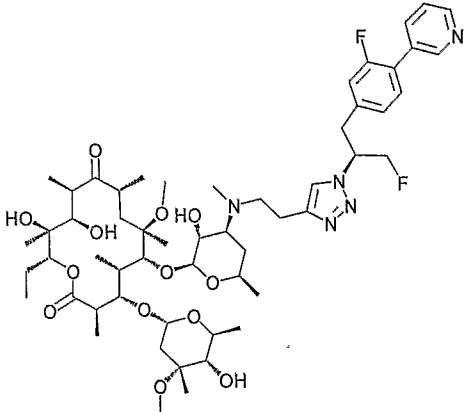
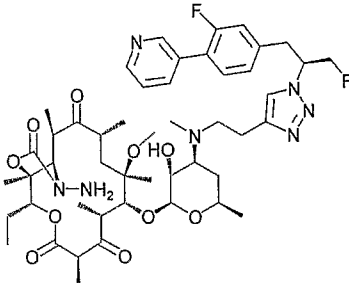
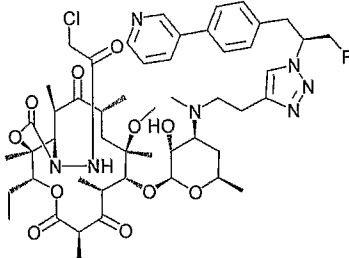
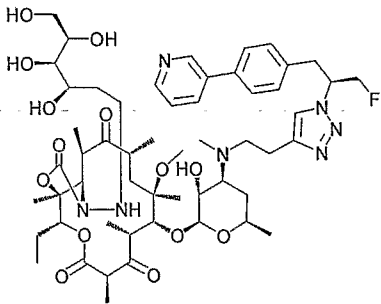
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1195		 Chemical structure of compound 1195: A complex molecule featuring a central core with multiple hydroxyl groups and a fluorine atom. The core is substituted with a 1,2,3-triazole ring, which is further substituted with a 4-(aminomethyl)phenyl group and a 4-(aminomethyl)thiophen-2-yl group.
1196		 Chemical structure of compound 1196: A complex molecule featuring a central core with multiple hydroxyl groups and a fluorine atom. The core is substituted with a 1,2,3-triazole ring, which is further substituted with a 4-(aminomethyl)phenyl group and a 4-(aminomethyl)thiophen-2-yl group.
1197		 Chemical structure of compound 1197: A complex molecule featuring a central core with multiple hydroxyl groups and a fluorine atom. The core is substituted with a 1,2,3-triazole ring, which is further substituted with a 4-(aminomethyl)phenyl group and a 4-(aminomethyl)thiophen-2-yl group.

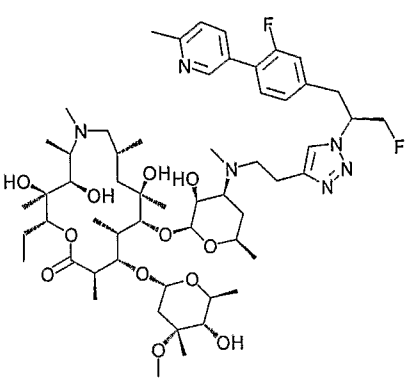
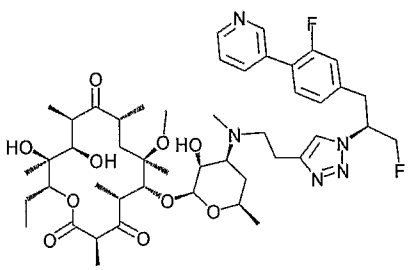
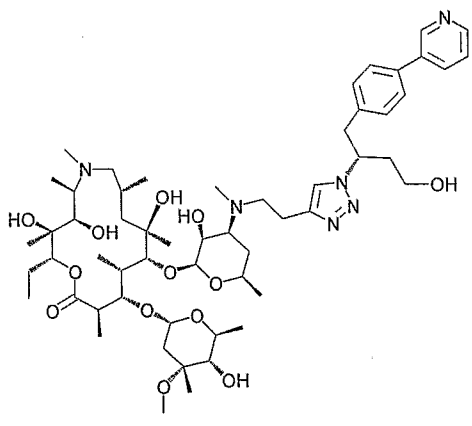
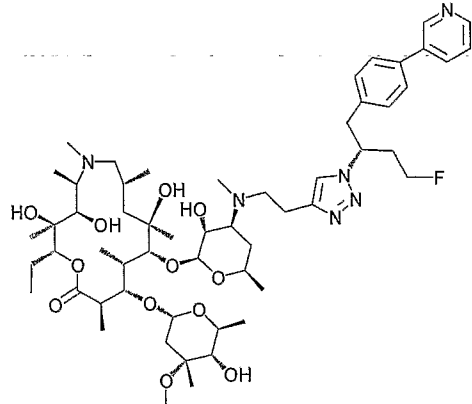
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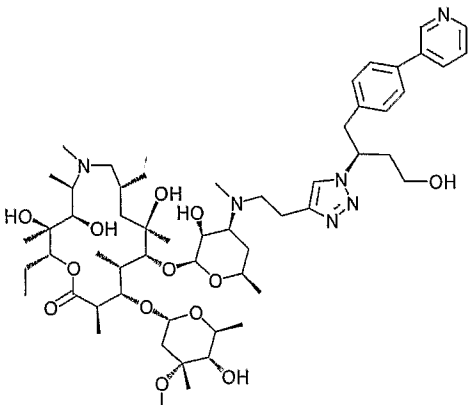
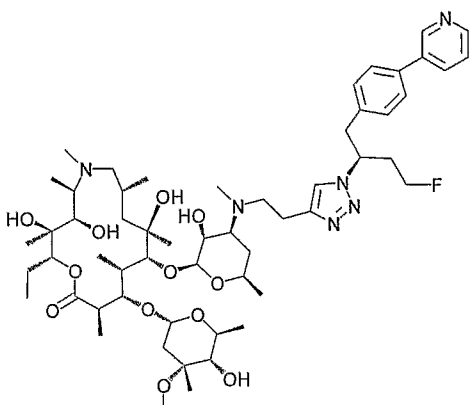
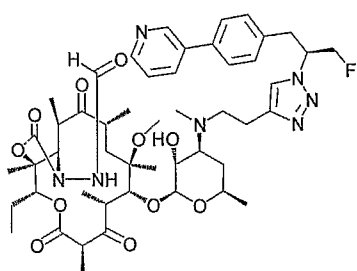
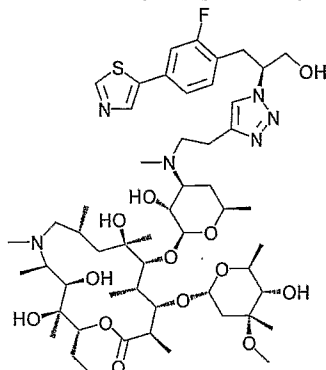
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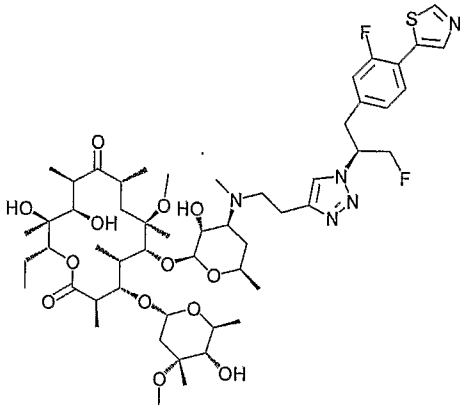
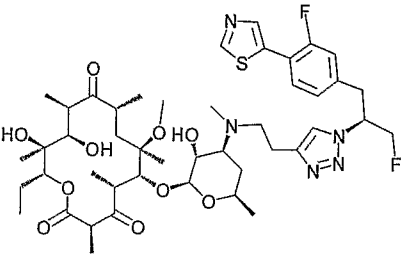
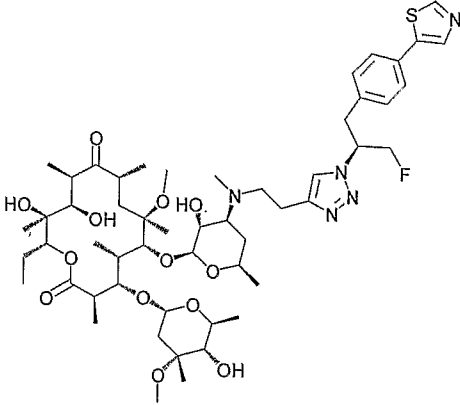
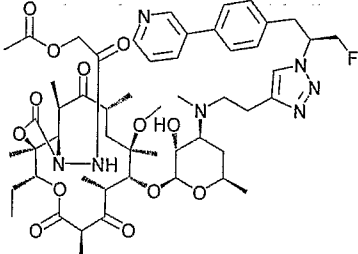
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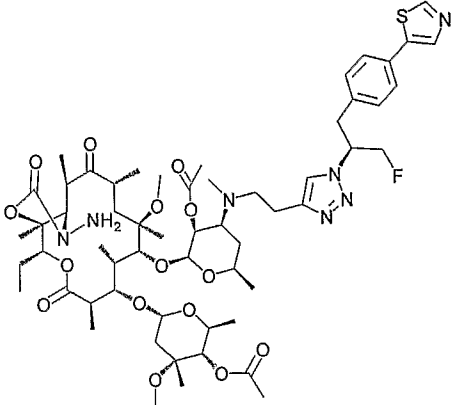
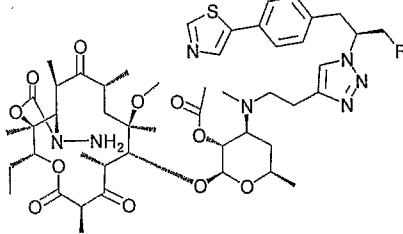
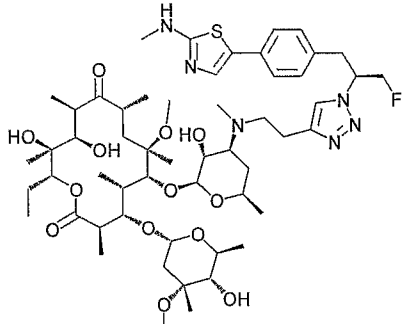
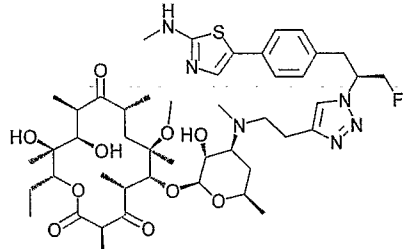
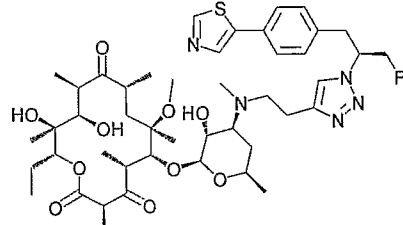
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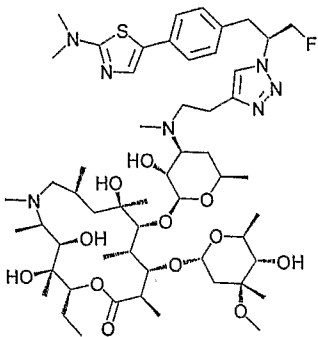
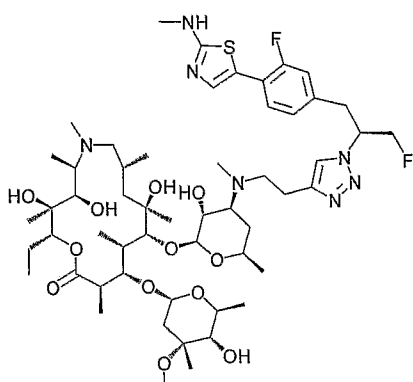
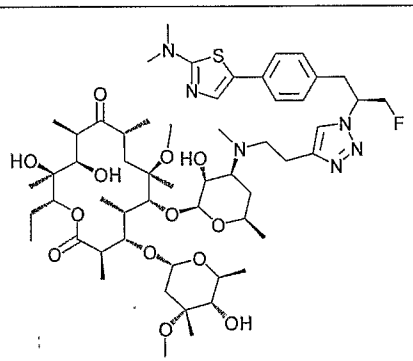
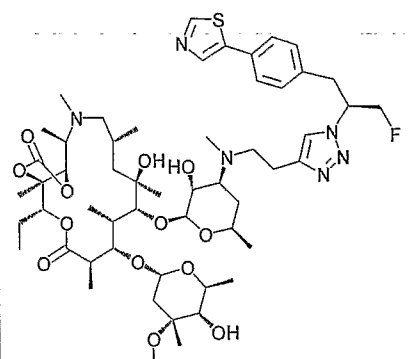
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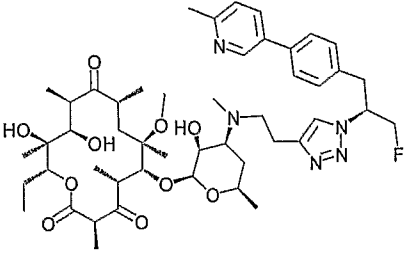
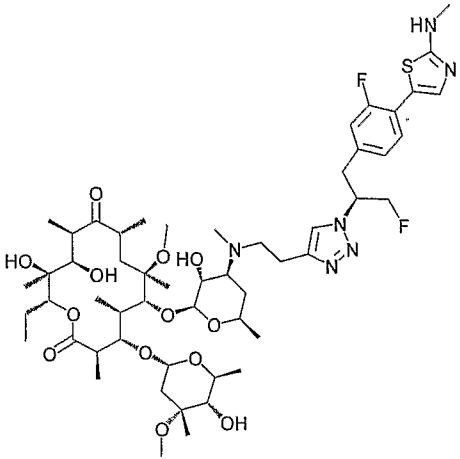
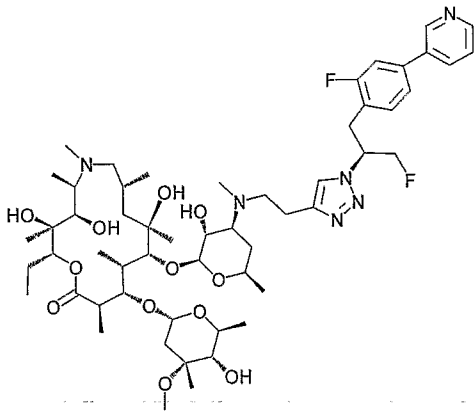
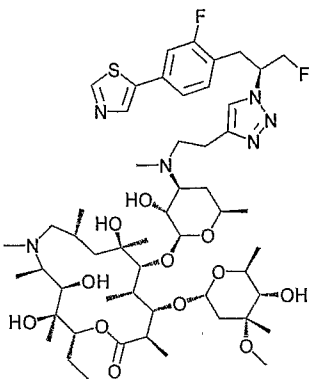
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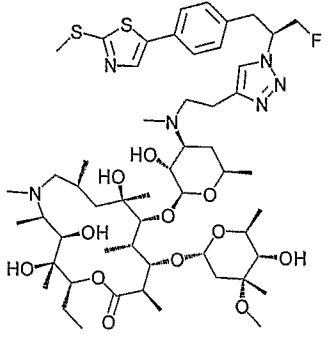
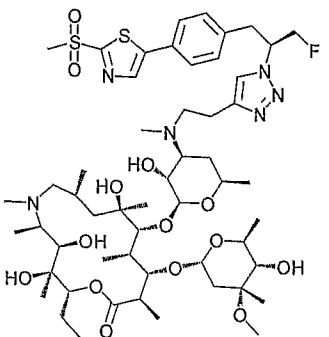
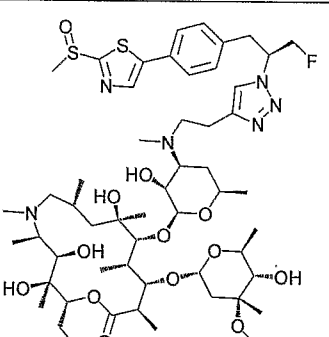
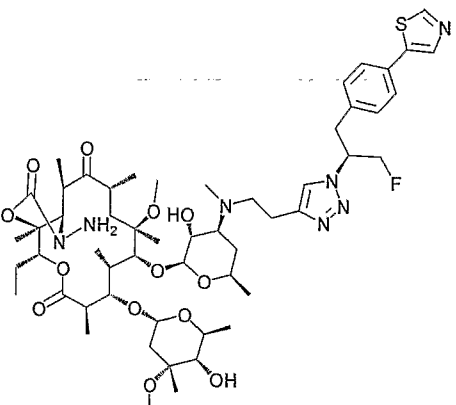
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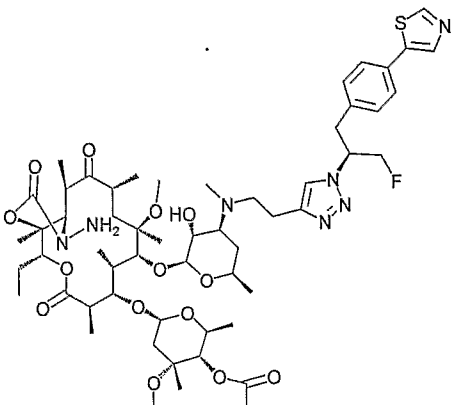
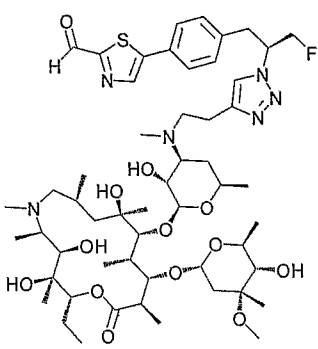
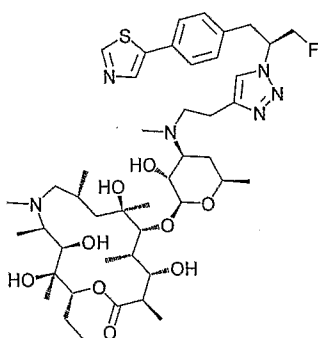
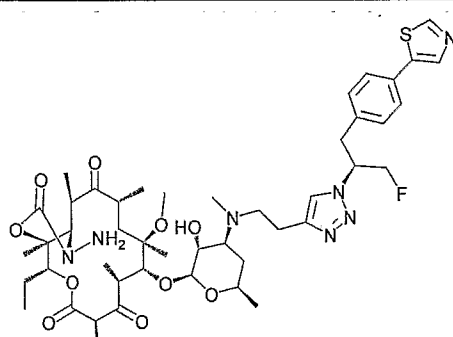
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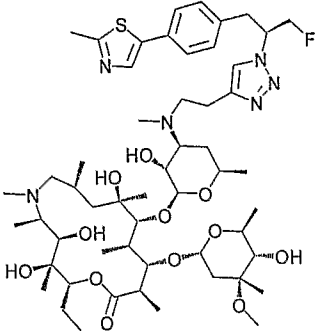
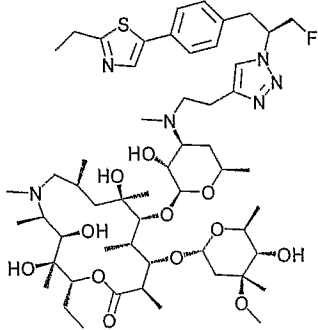
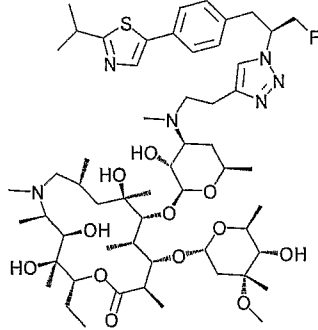
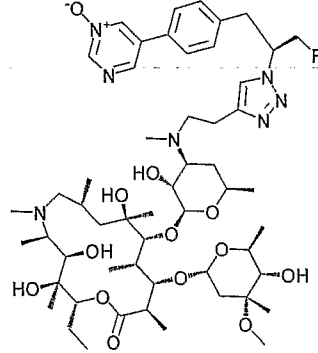
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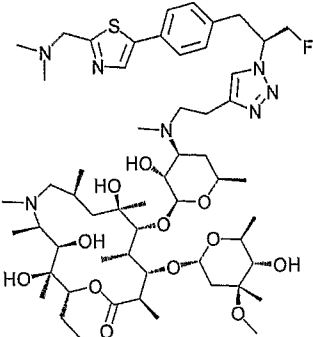
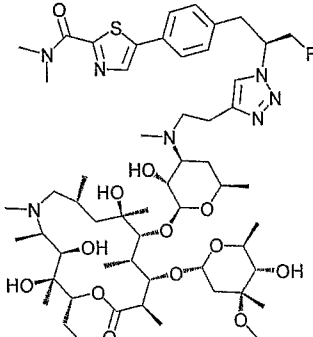
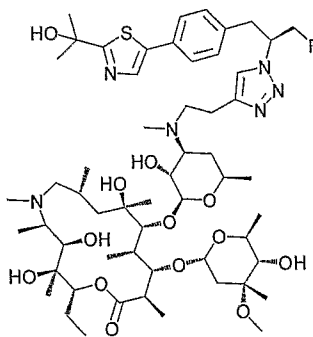
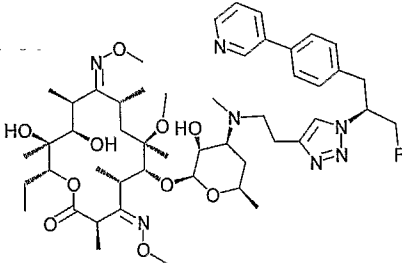
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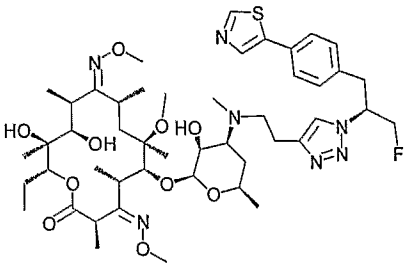
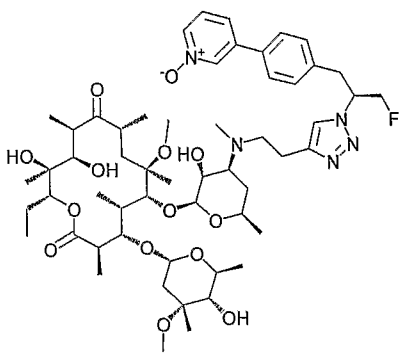
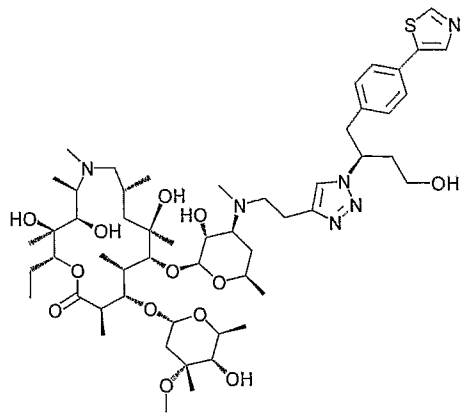
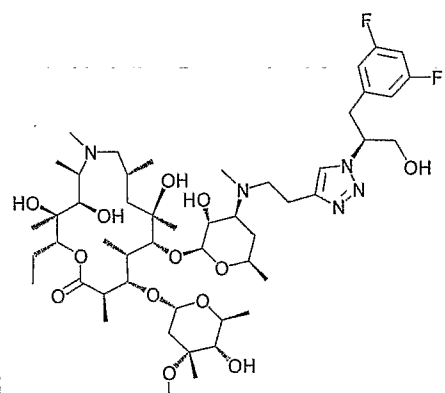
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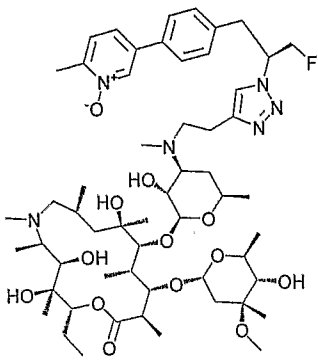
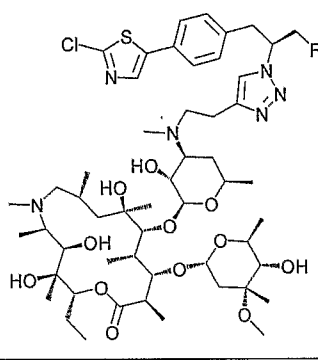
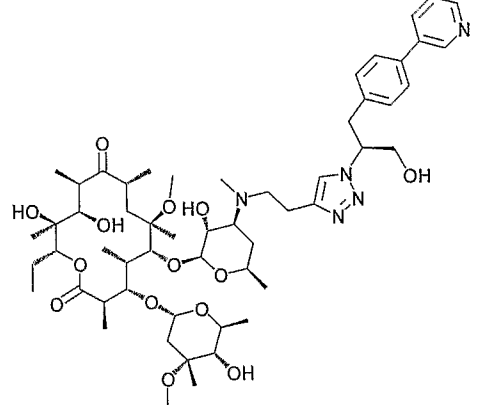
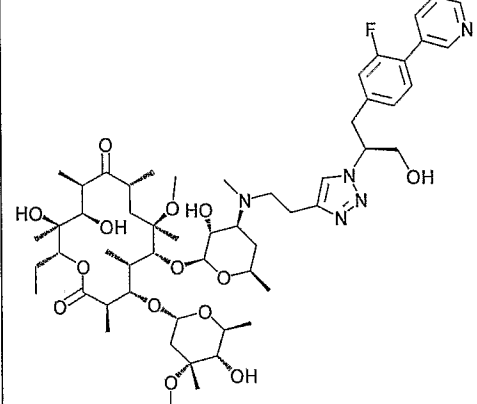
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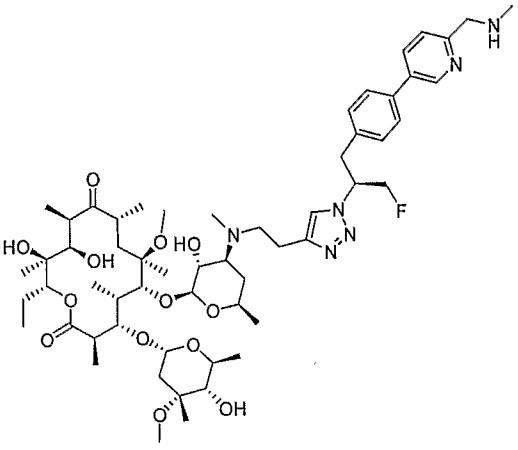
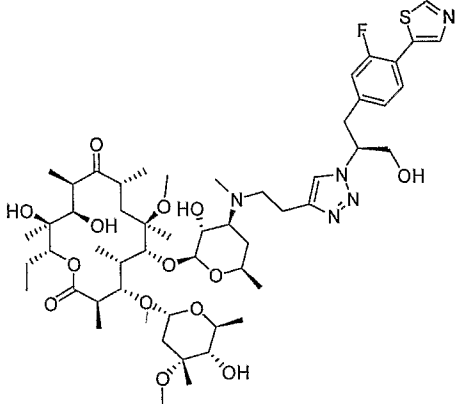
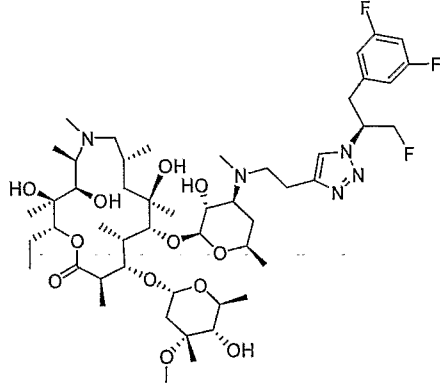
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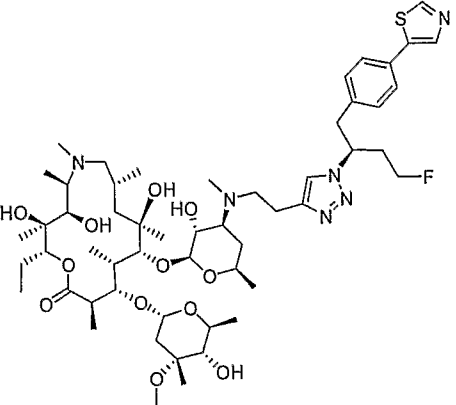
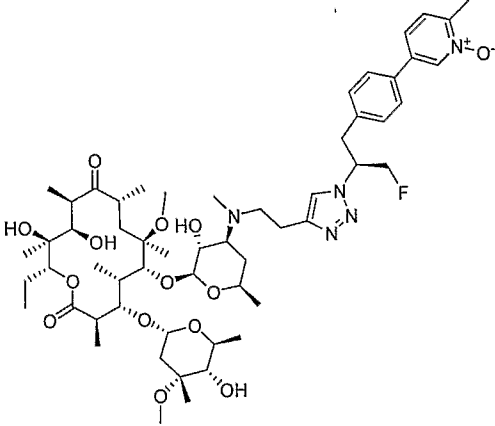
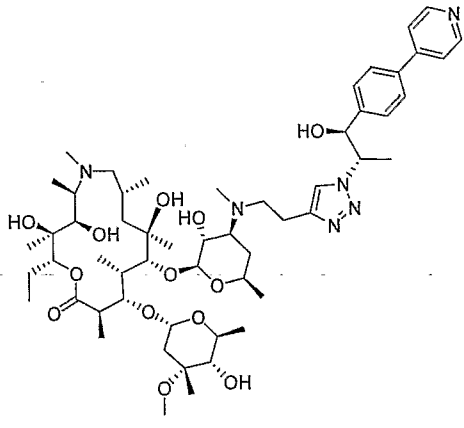
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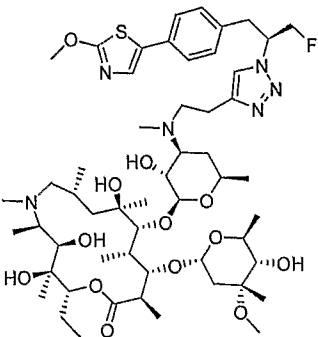
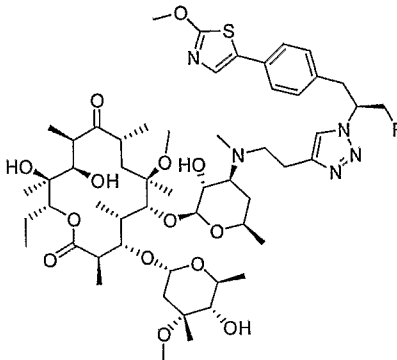
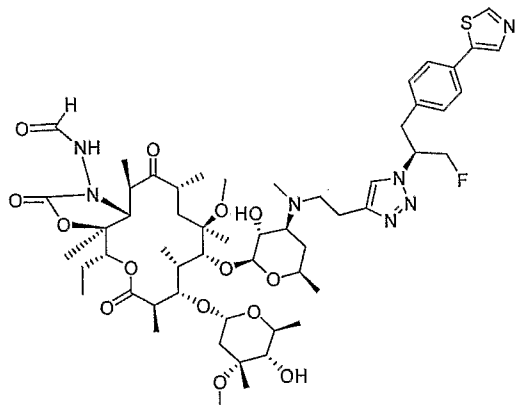
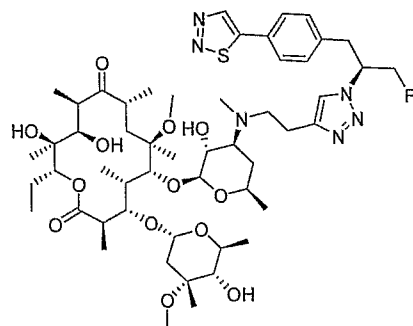
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1255		 Chemical structure of compound 1255: A complex molecule featuring a central core with multiple hydroxyl groups and a carbonyl group. The core is substituted with a side chain containing a triazole ring, a fluorine atom, and a phenyl ring with a pyridine substituent.
1256		 Chemical structure of compound 1256: A complex molecule featuring a central core with multiple hydroxyl groups and a carbonyl group. The core is substituted with a side chain containing a triazole ring, a hydroxyl group, and a phenyl ring with a thiazole substituent.
1257		 Chemical structure of compound 1257: A complex molecule featuring a central core with multiple hydroxyl groups and a carbonyl group. The core is substituted with a side chain containing a triazole ring, a fluorine atom, and a phenyl ring with a fluorine substituent.

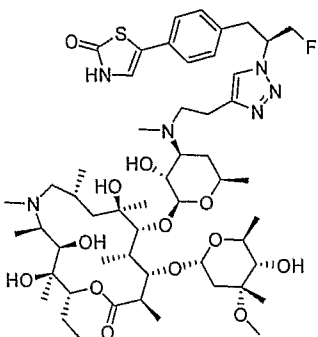
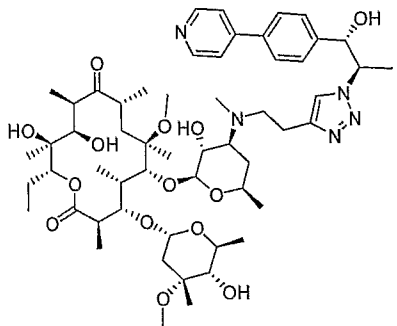
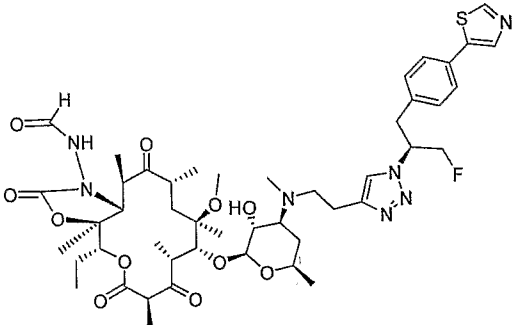
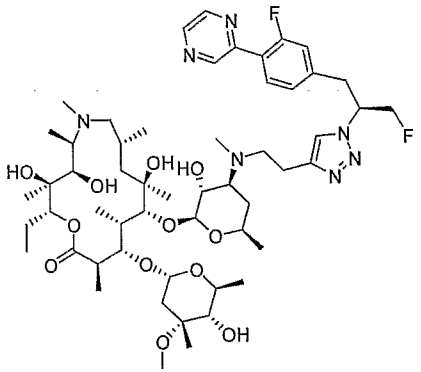
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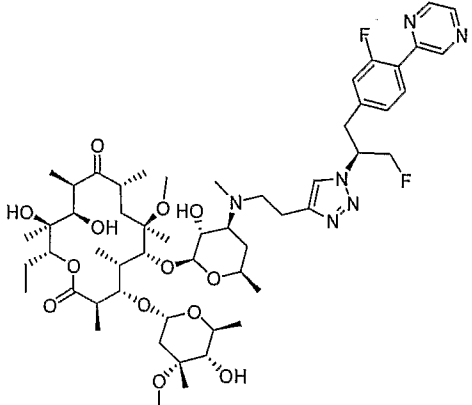
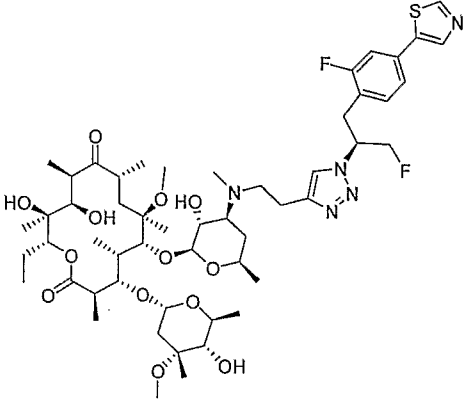
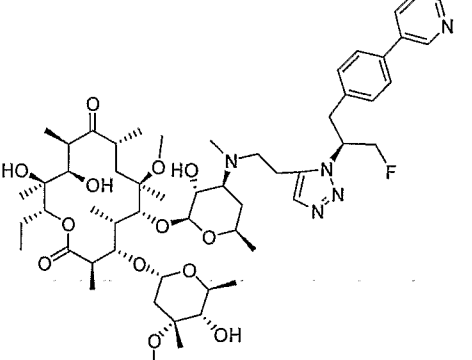
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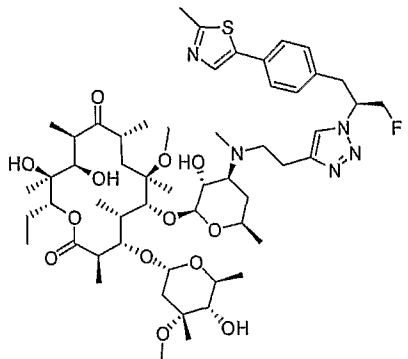
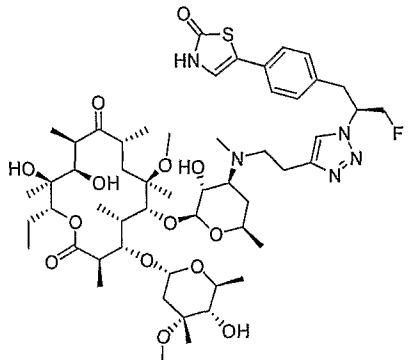
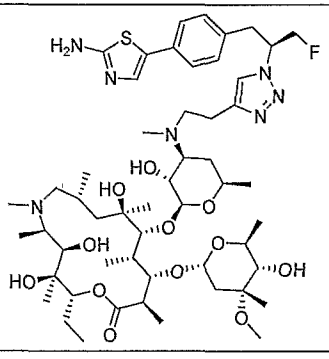
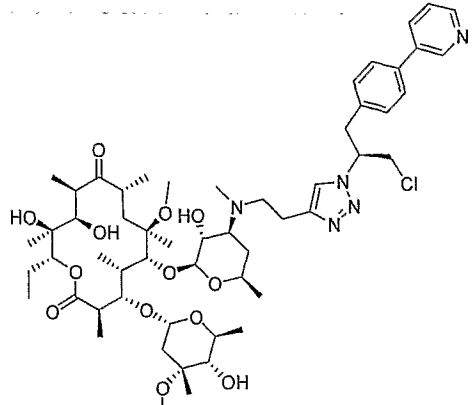
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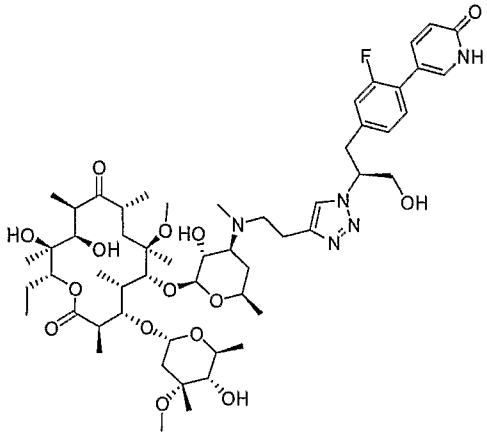
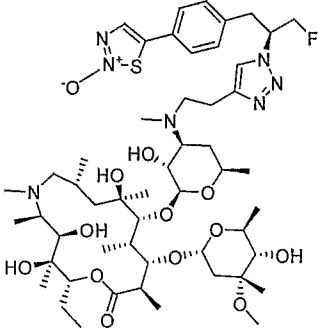
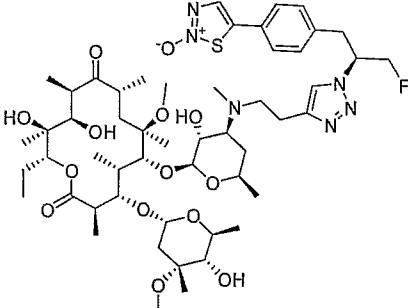
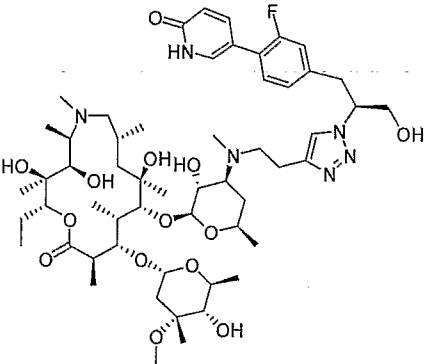
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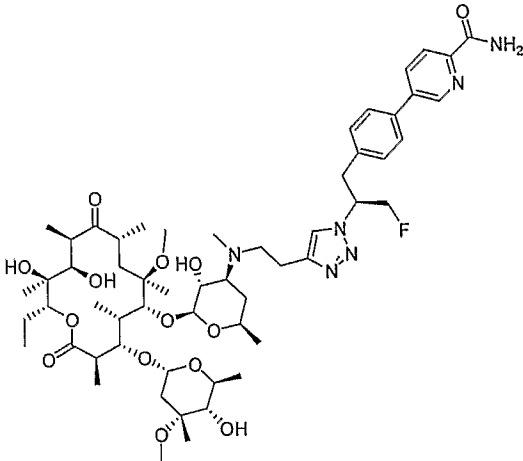
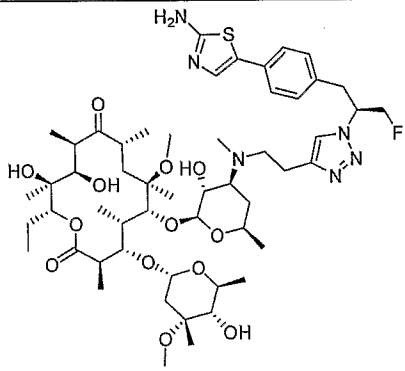
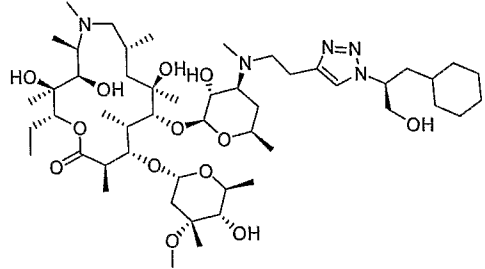
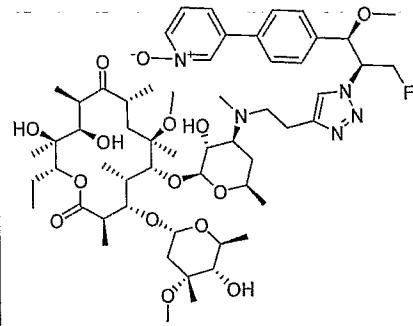
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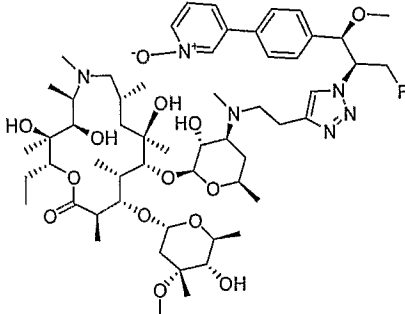
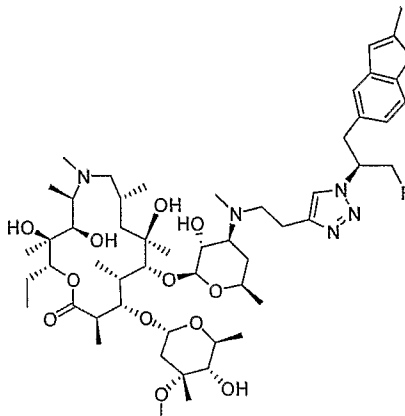
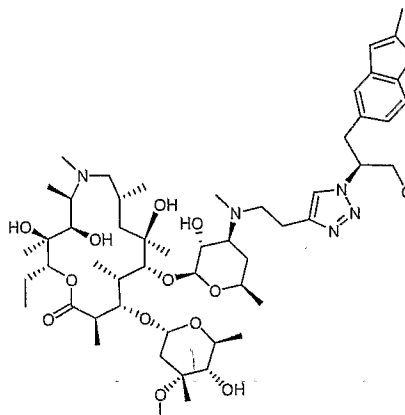
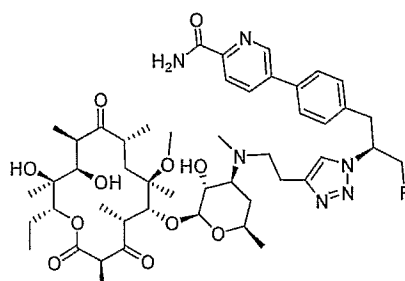
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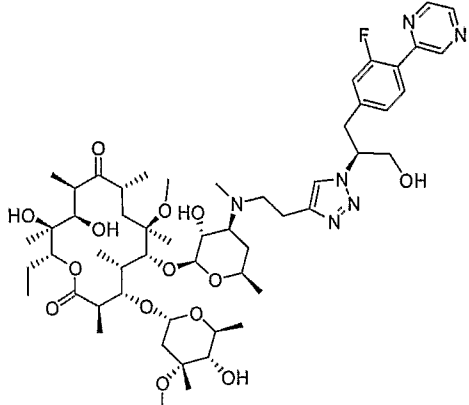
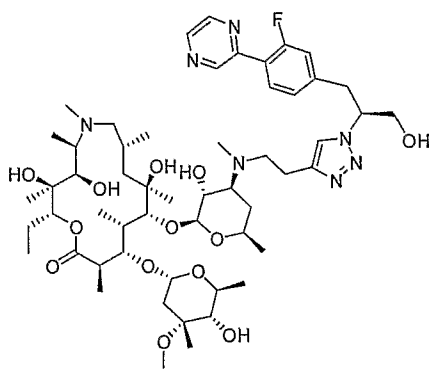
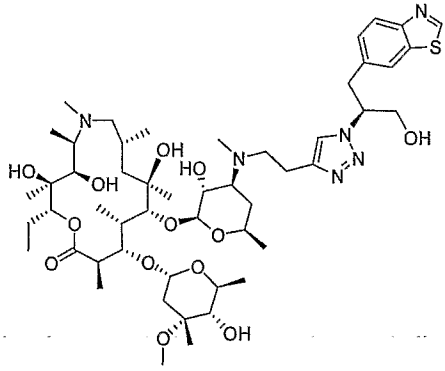
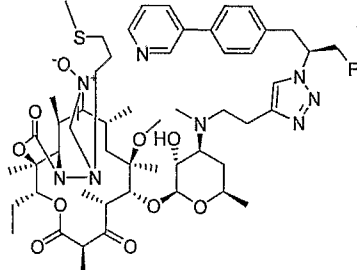
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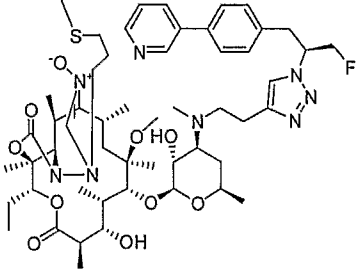
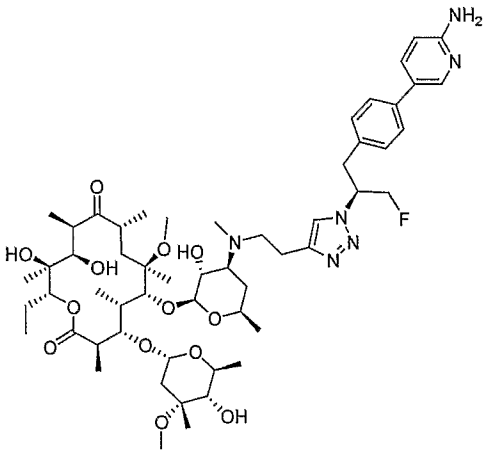
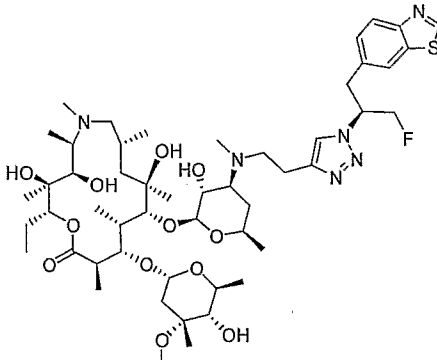
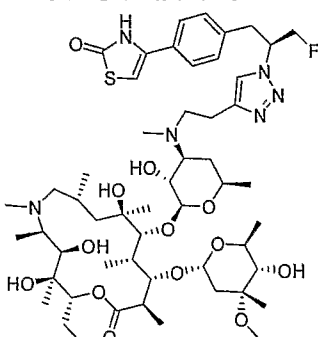
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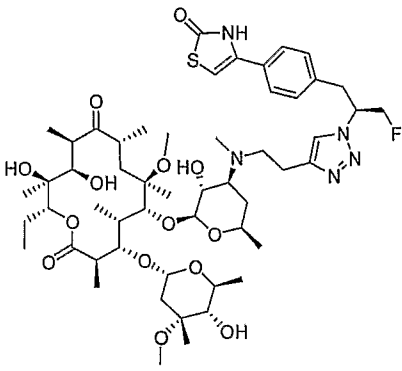
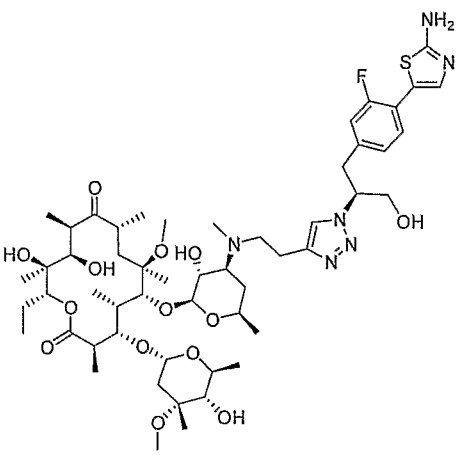
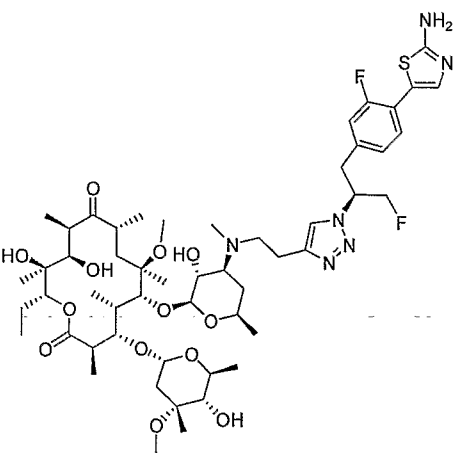
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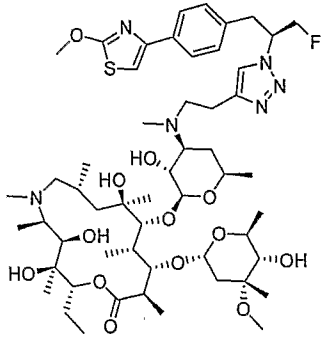
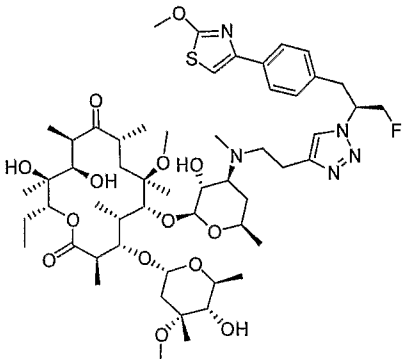
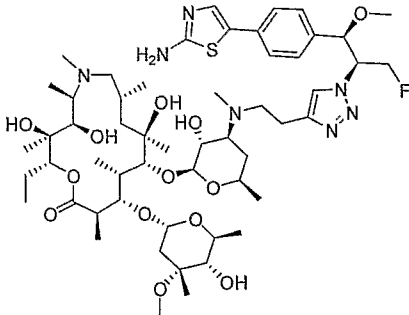
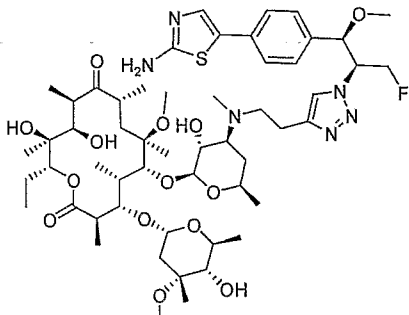
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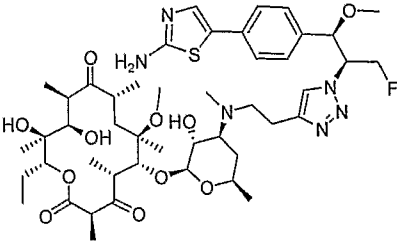
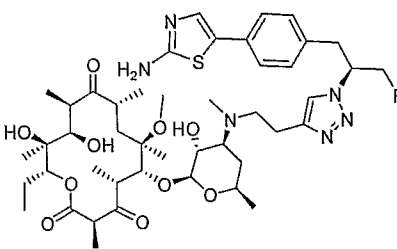
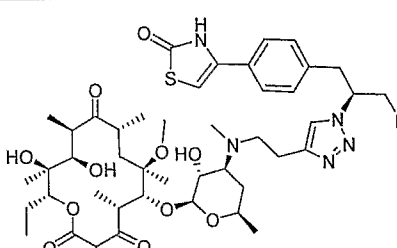
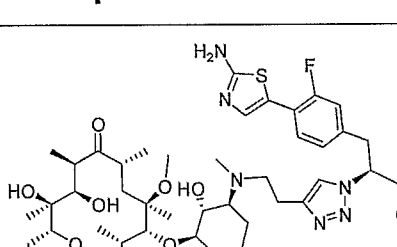
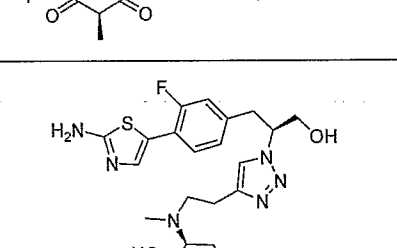
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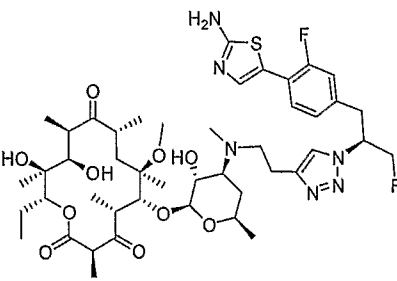
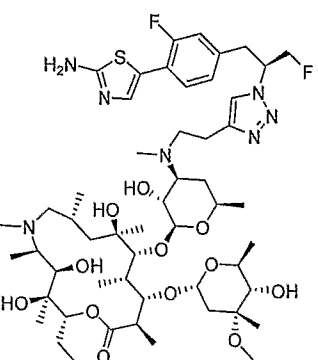
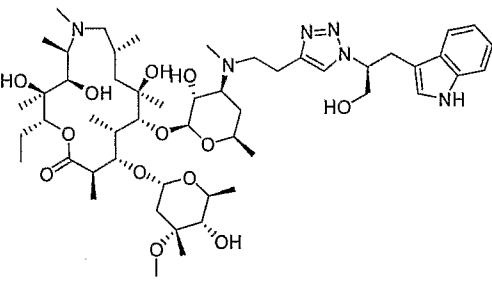
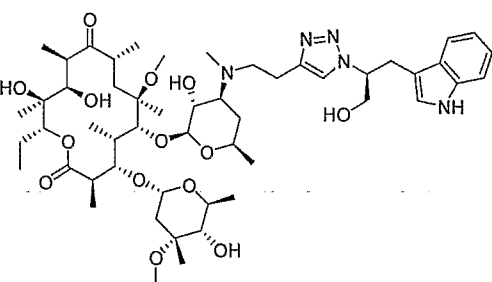
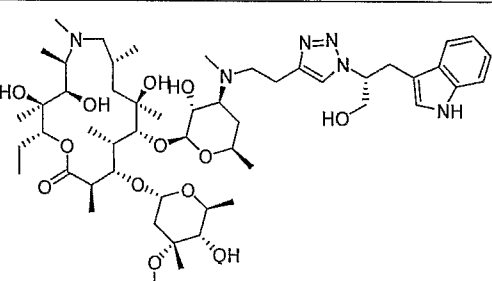
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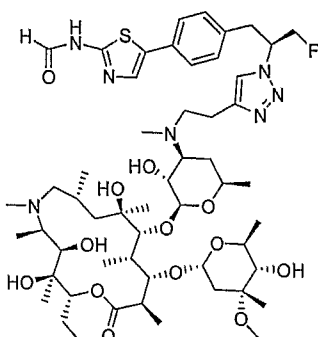
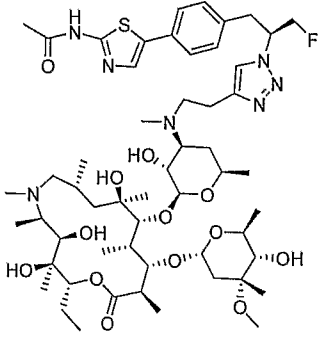
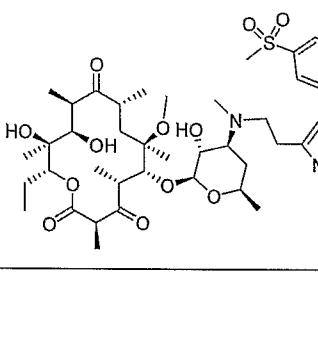
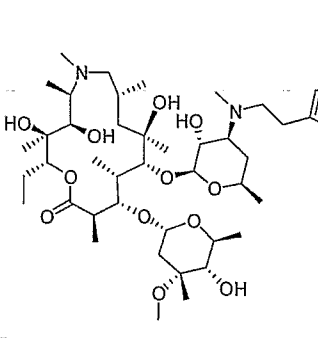
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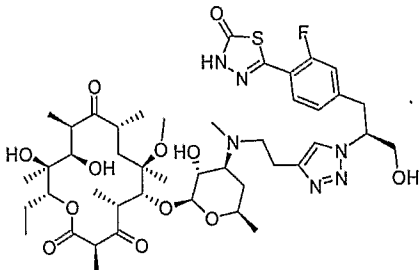
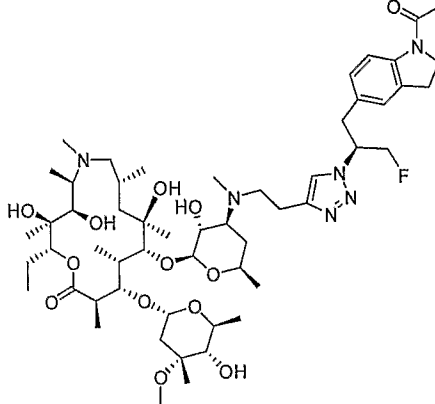
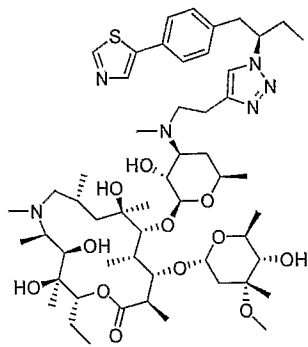
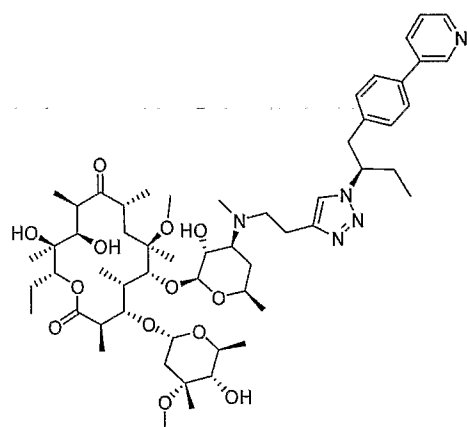
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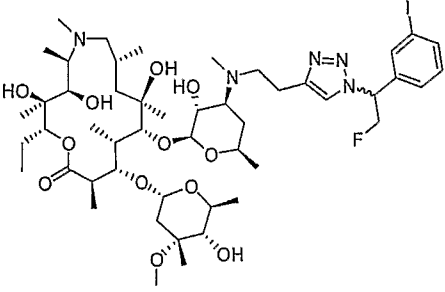
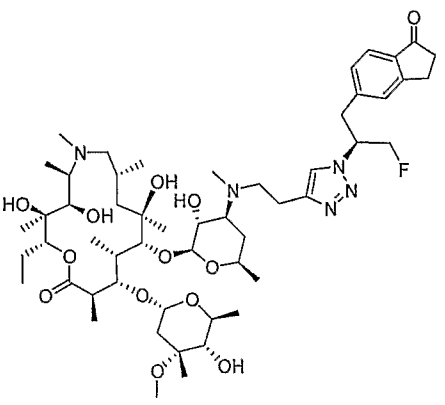
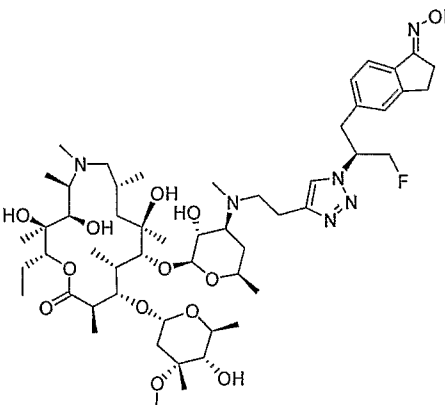
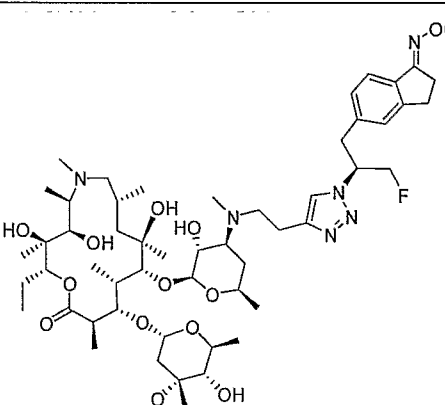
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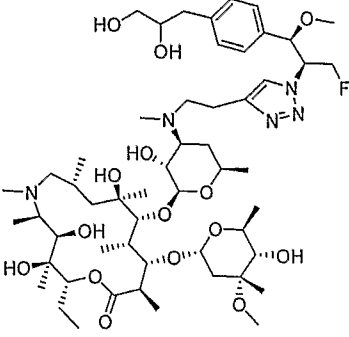
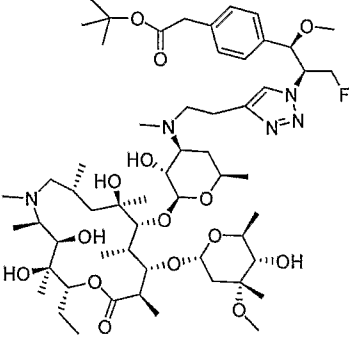
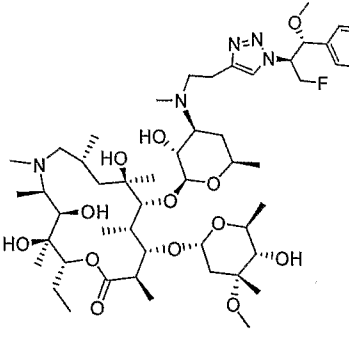
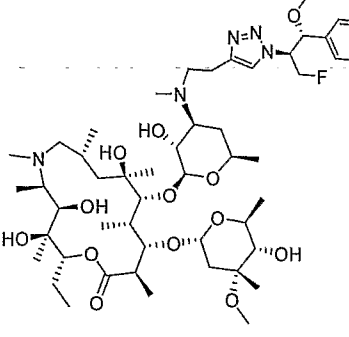
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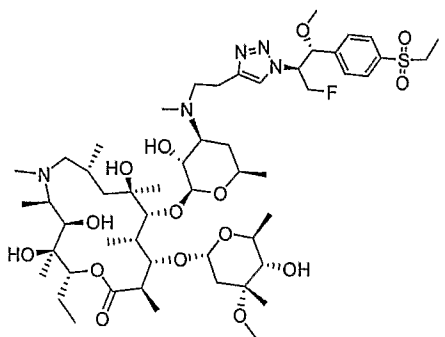
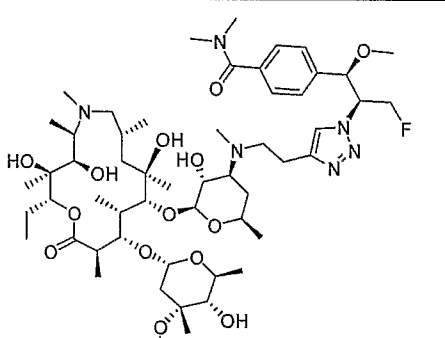
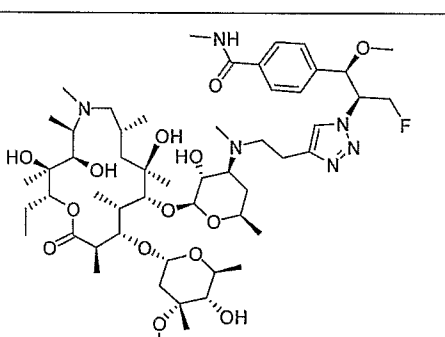
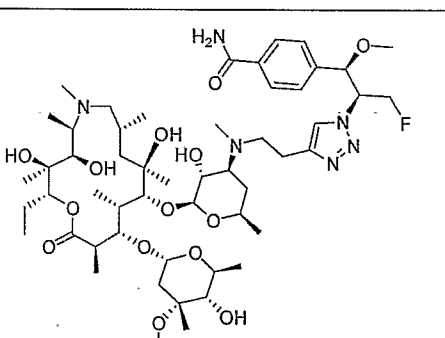
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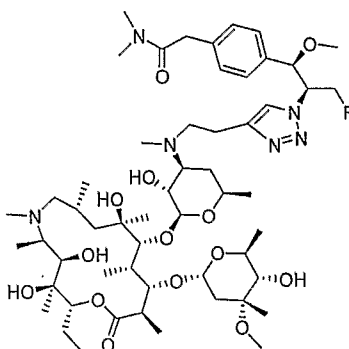
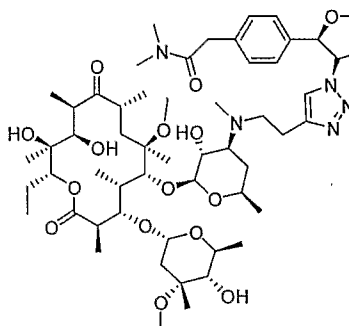
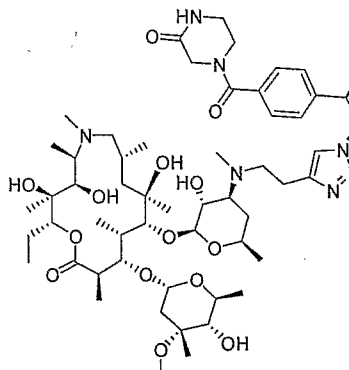
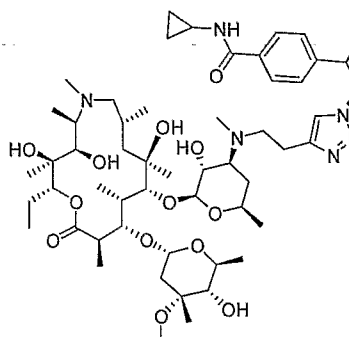
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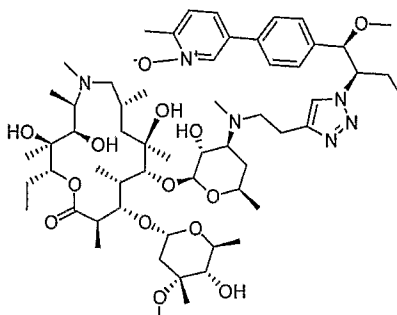
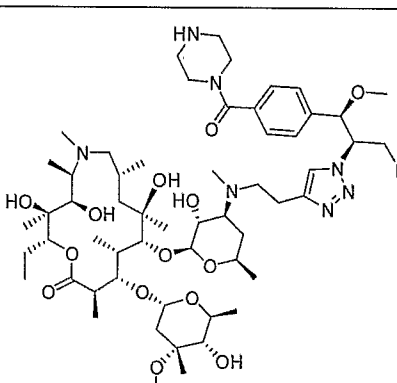
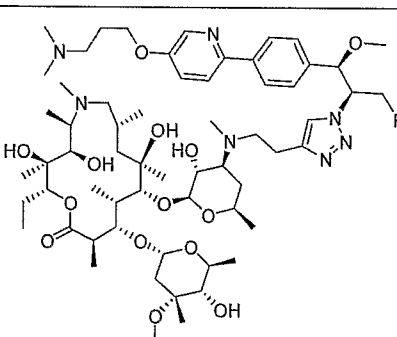
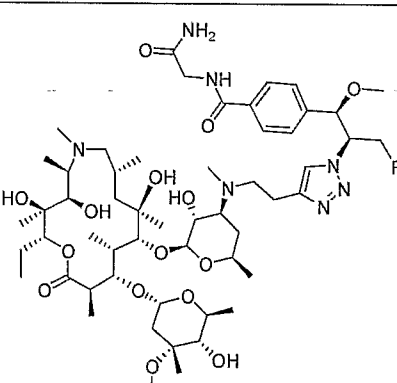
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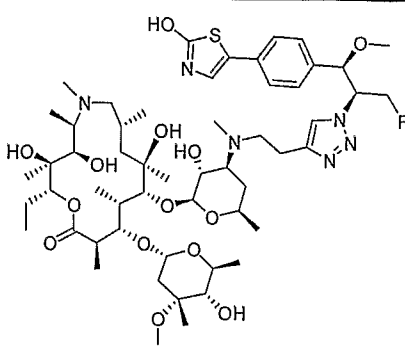
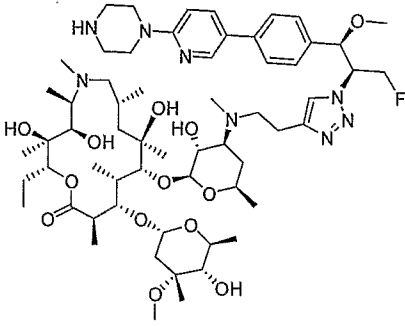
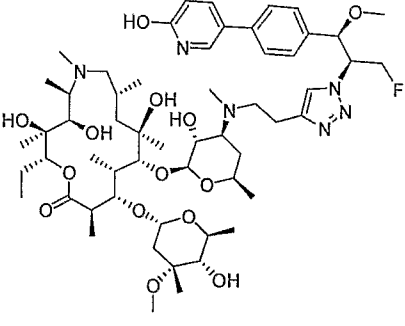
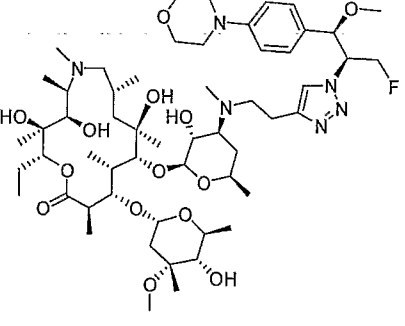
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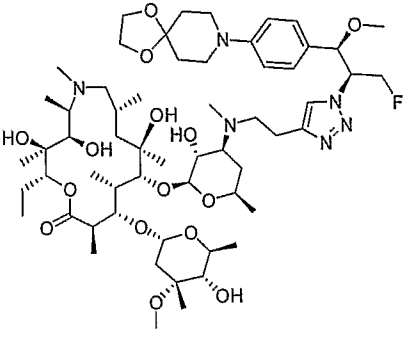
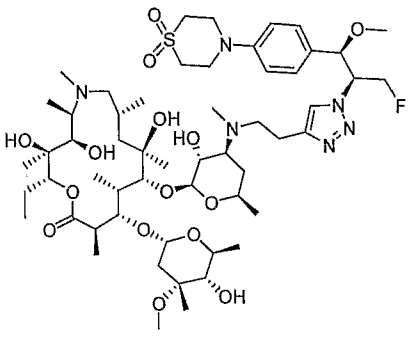
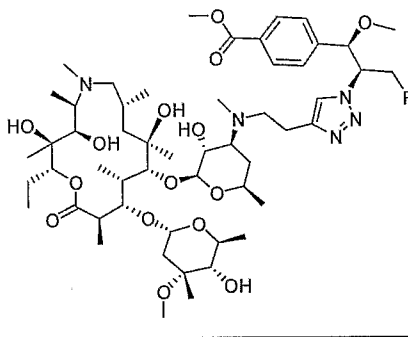
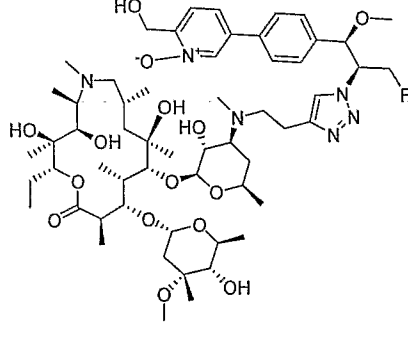
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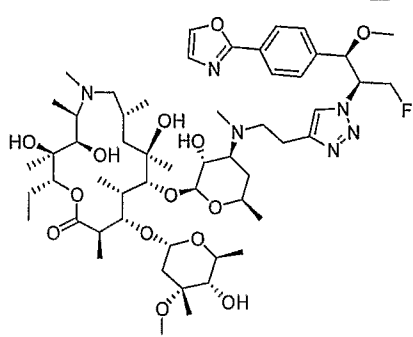
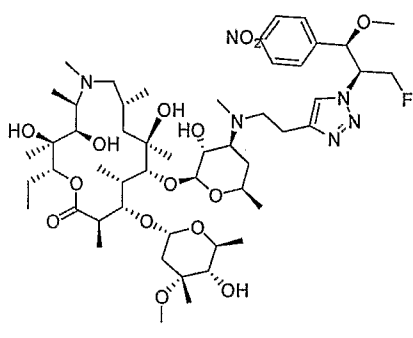
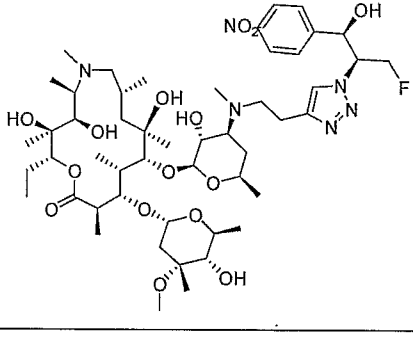
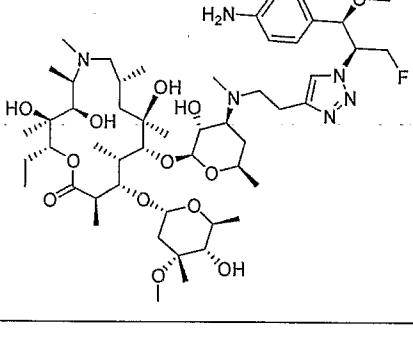
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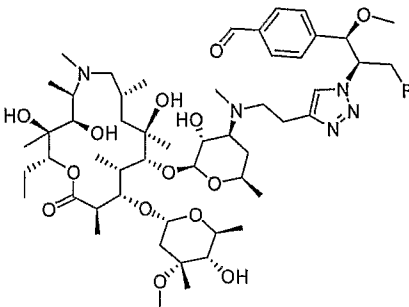
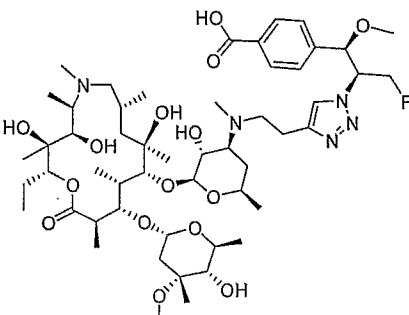
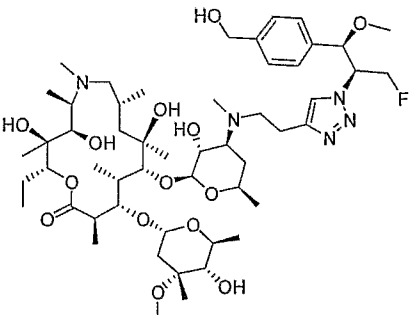
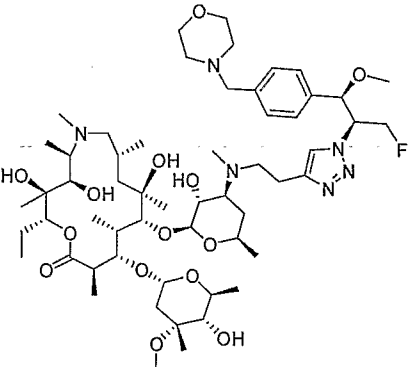
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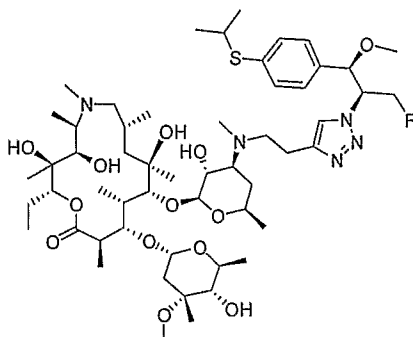
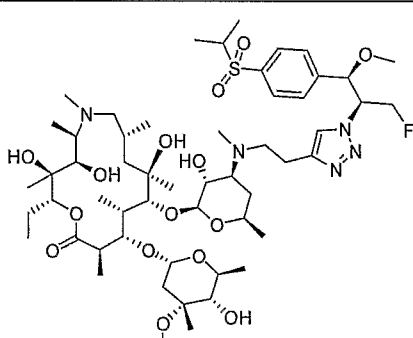
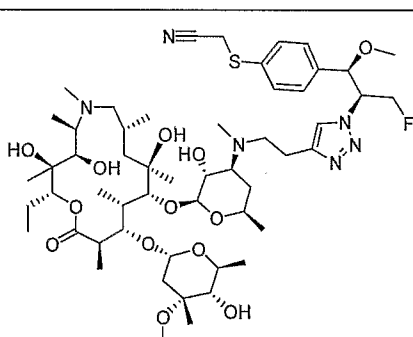
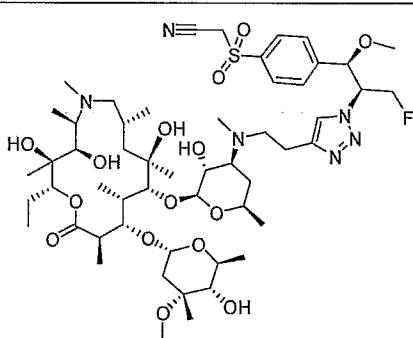
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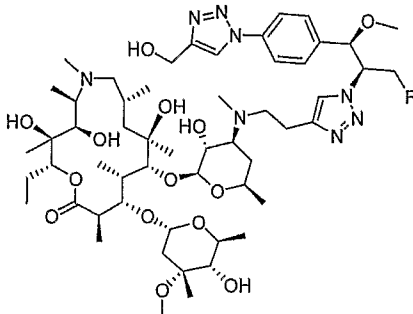
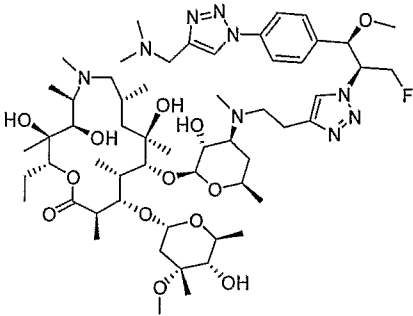
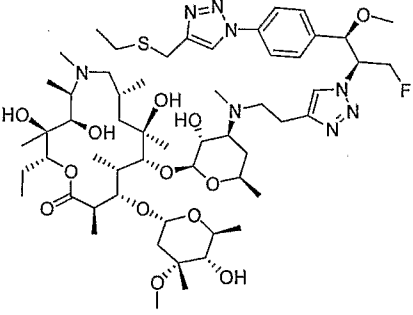
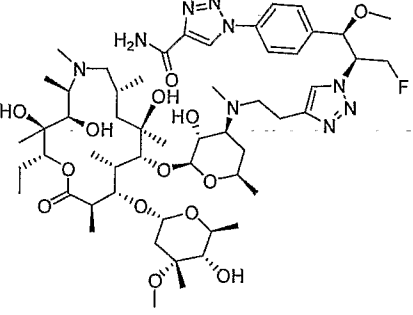
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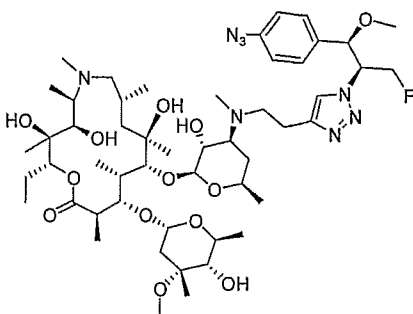
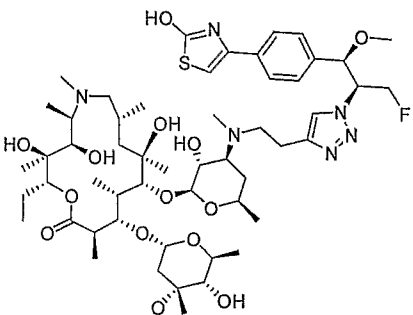
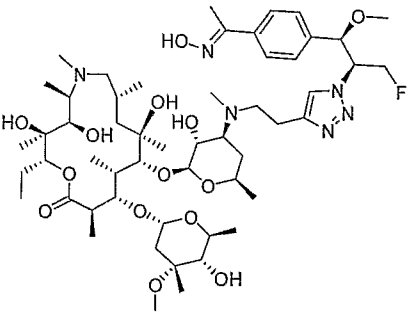
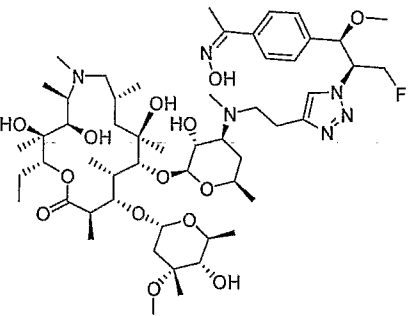
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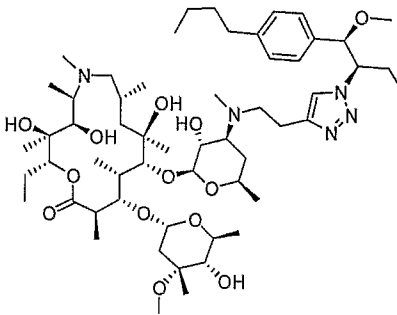
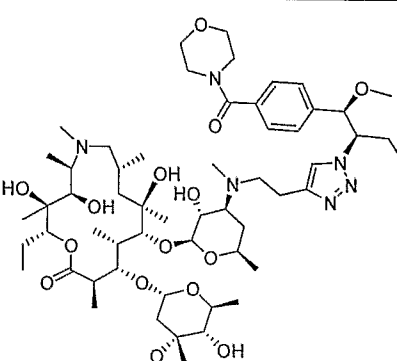
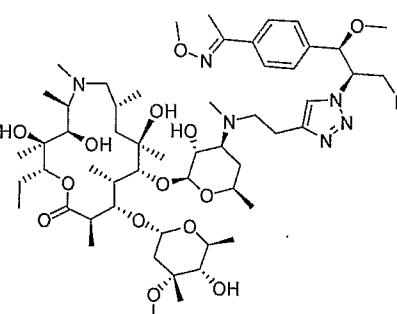
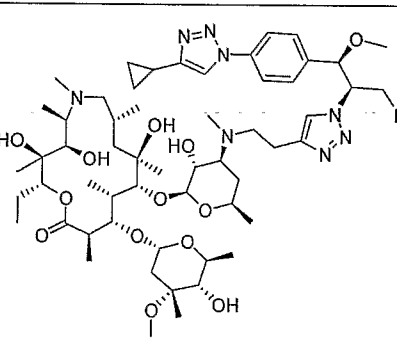
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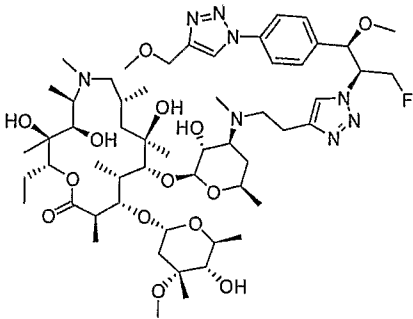
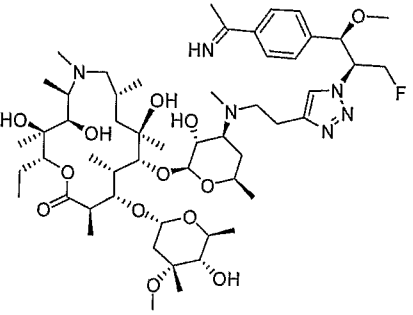
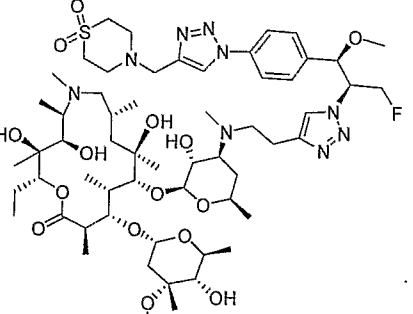
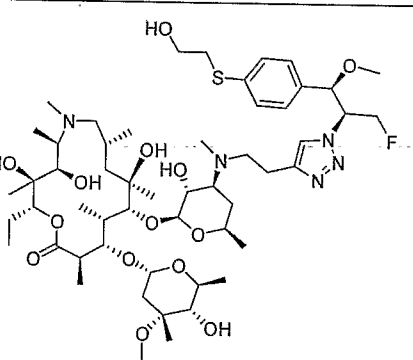
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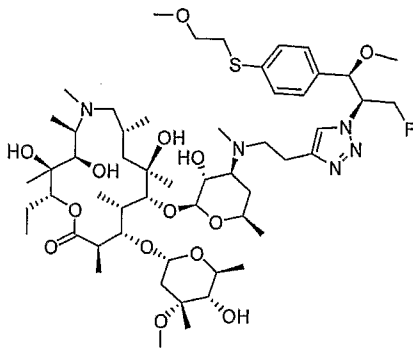
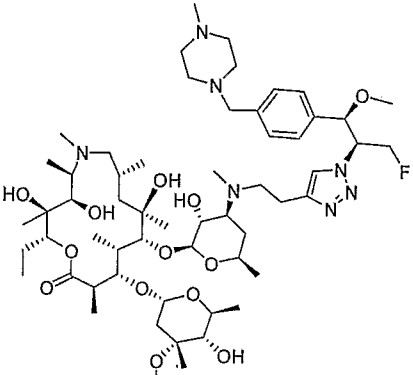
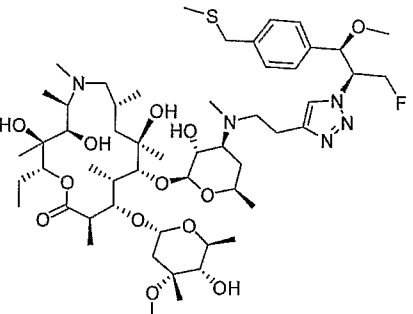
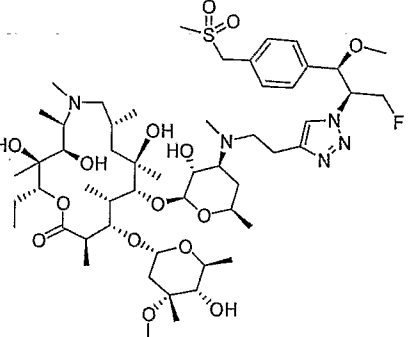
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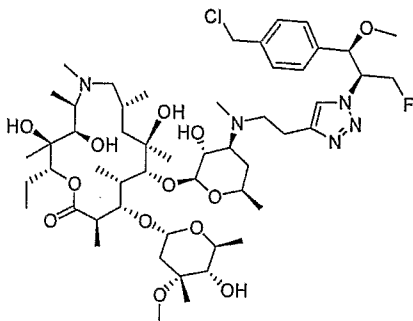
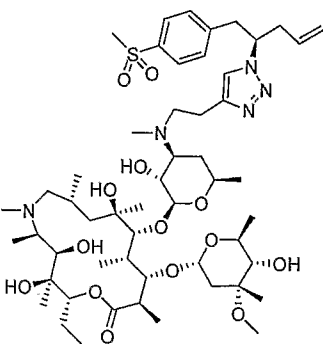
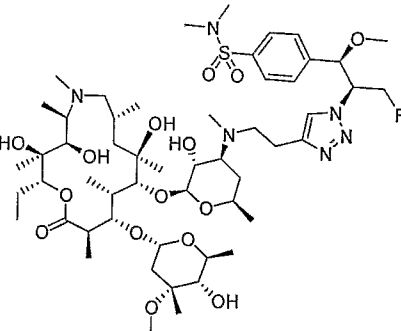
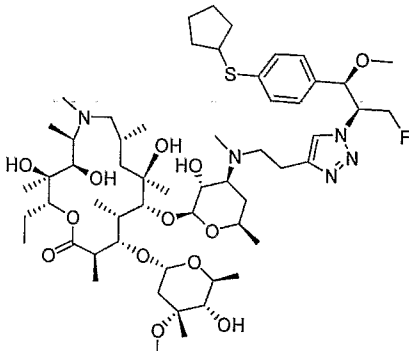
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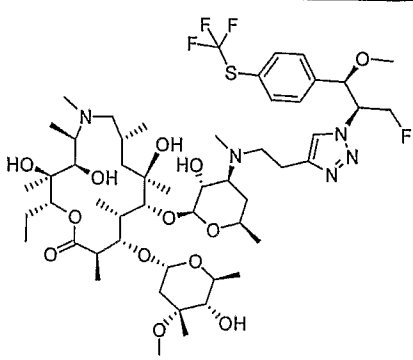
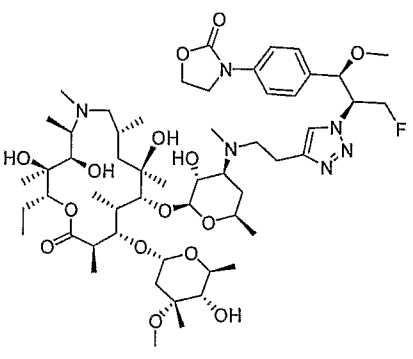
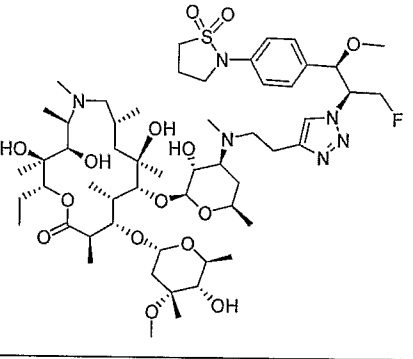
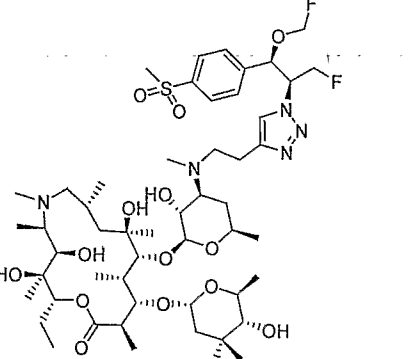
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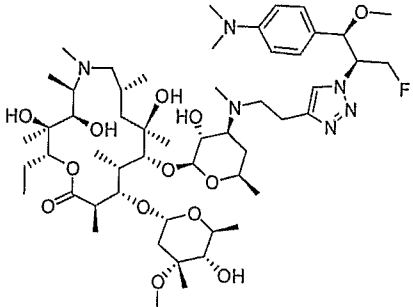
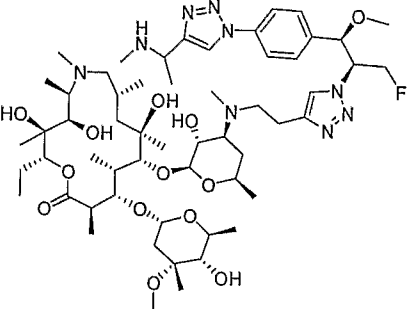
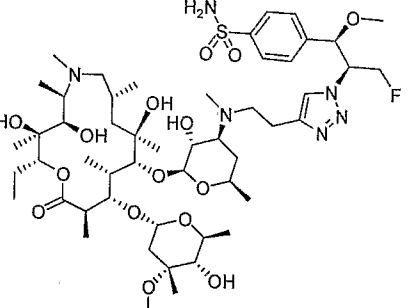
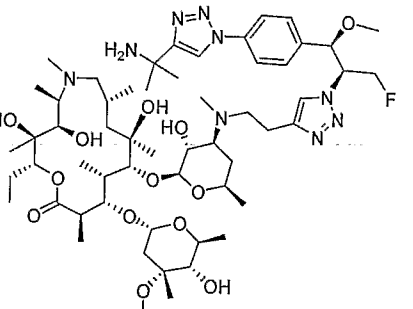
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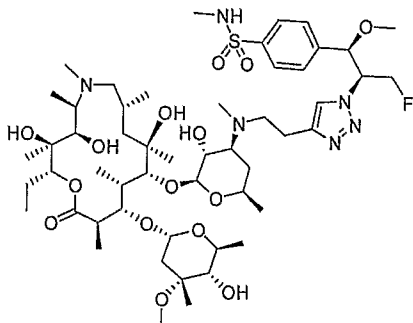
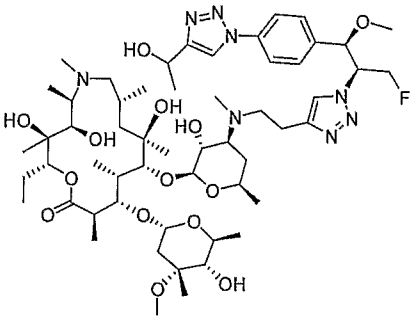
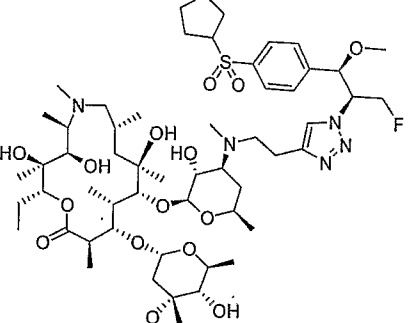
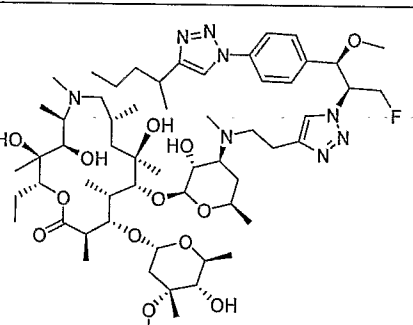
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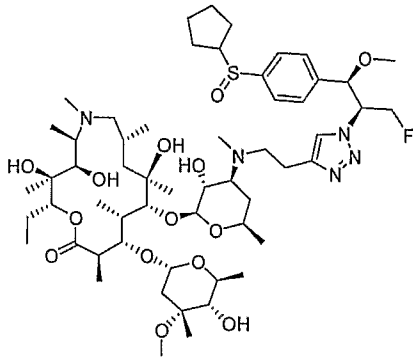
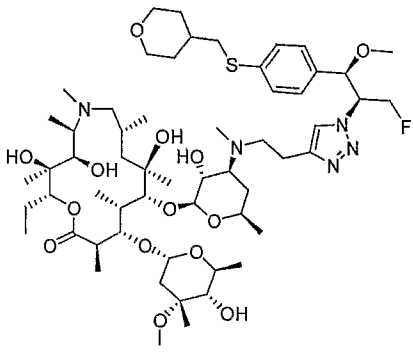
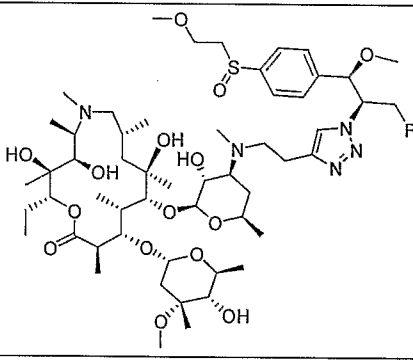
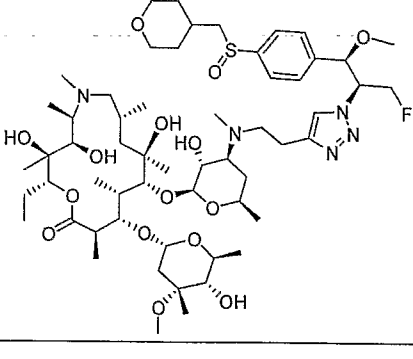
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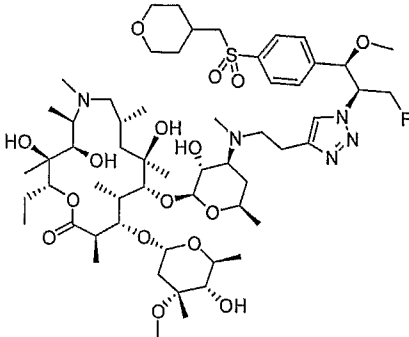
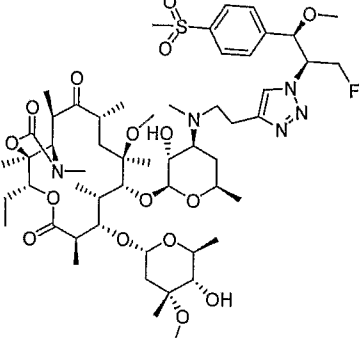
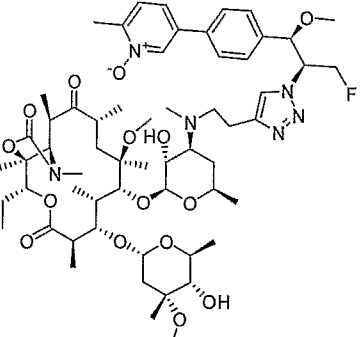
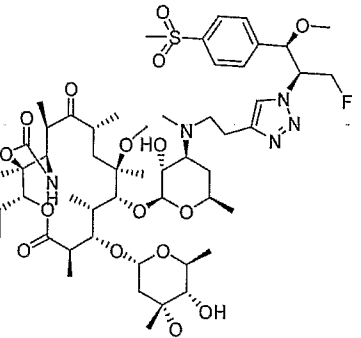
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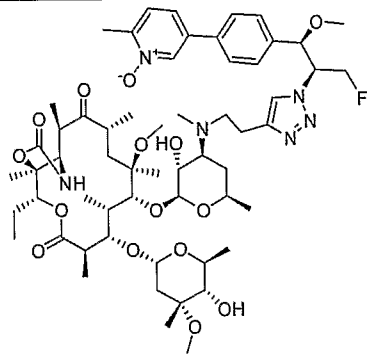
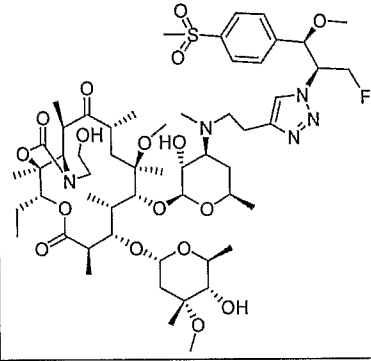
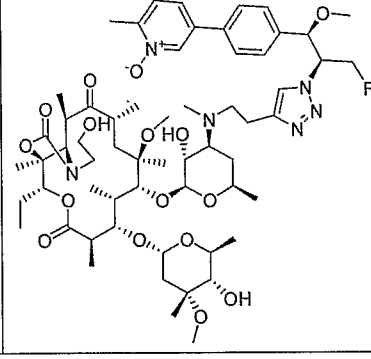
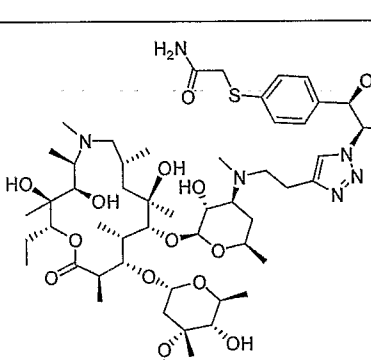
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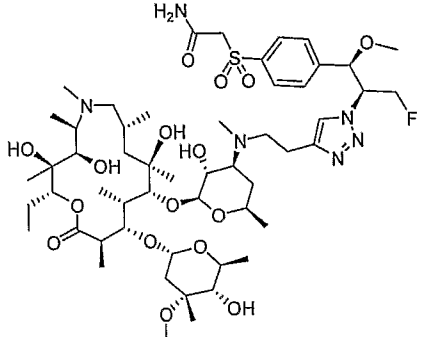
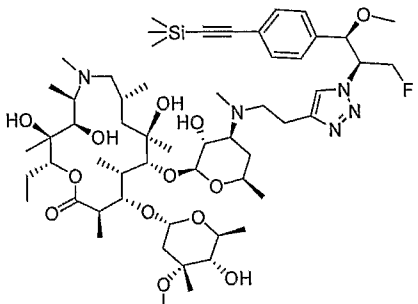
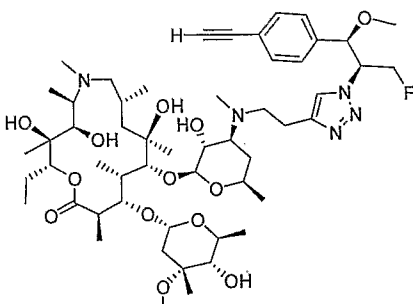
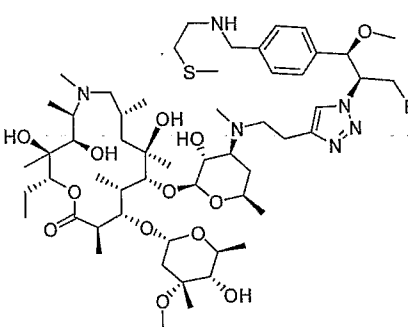
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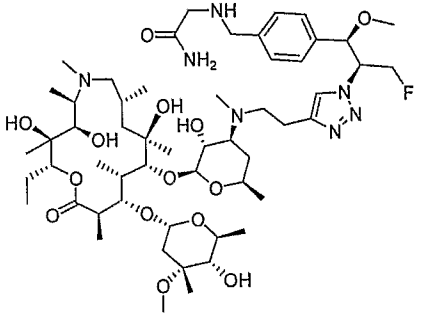
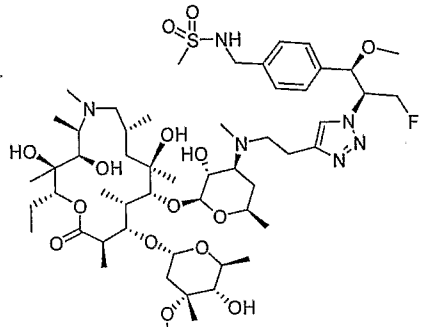
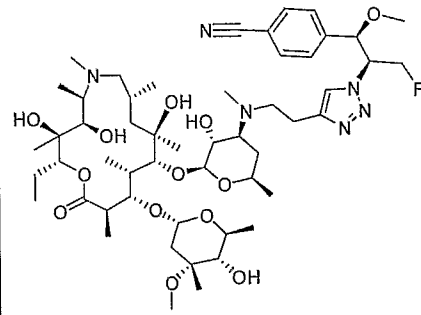
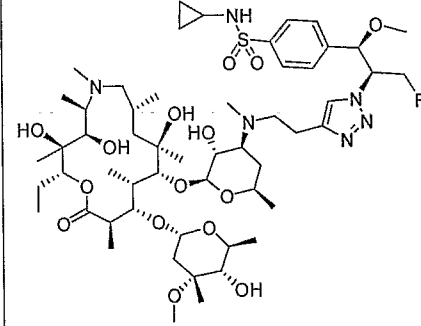
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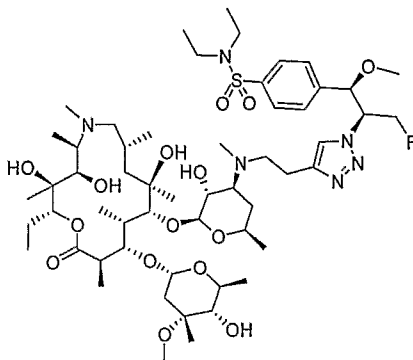
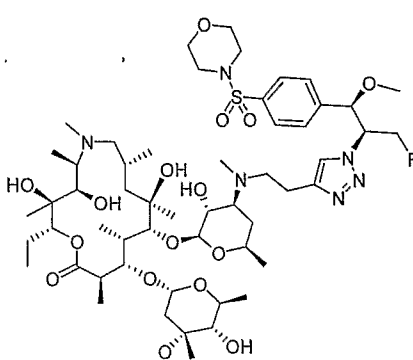
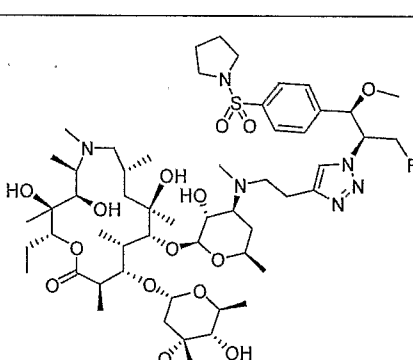
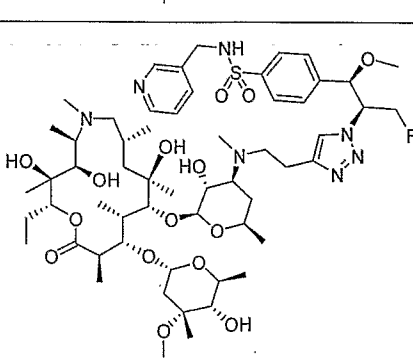
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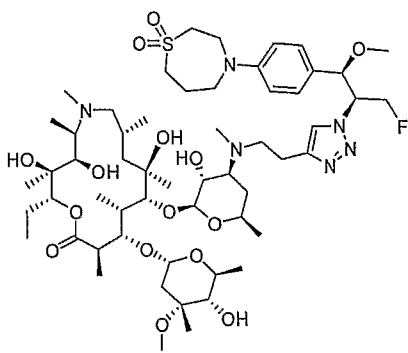
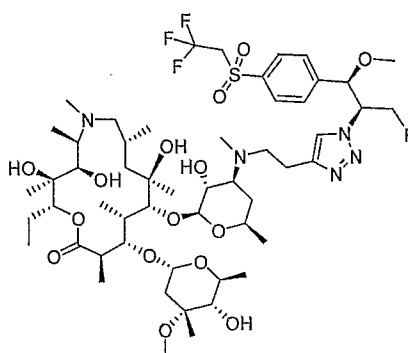
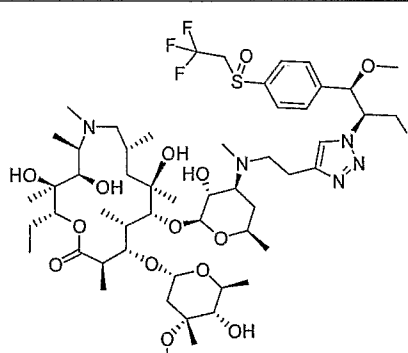
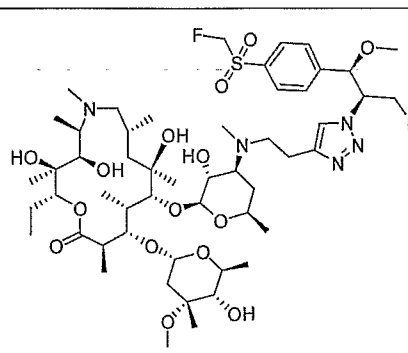
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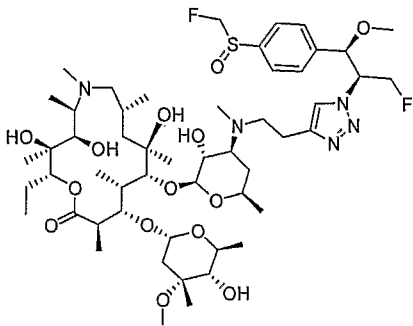
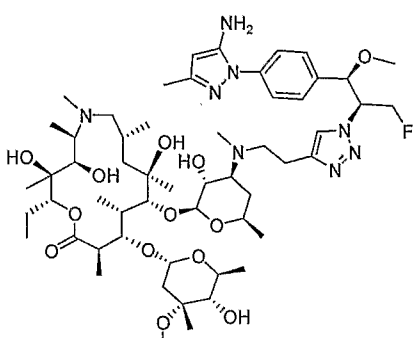
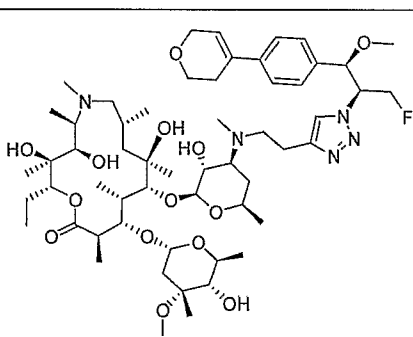
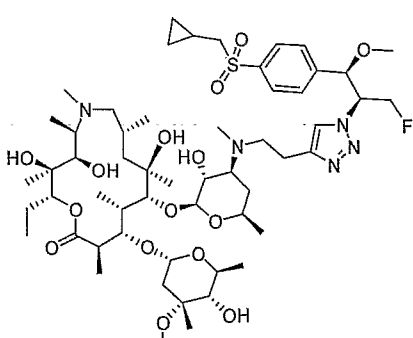
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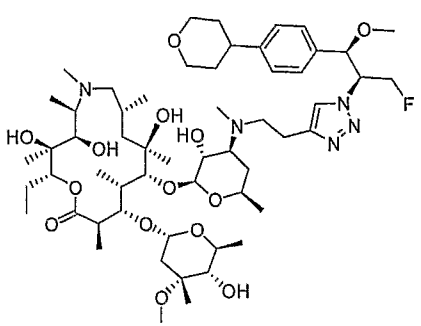
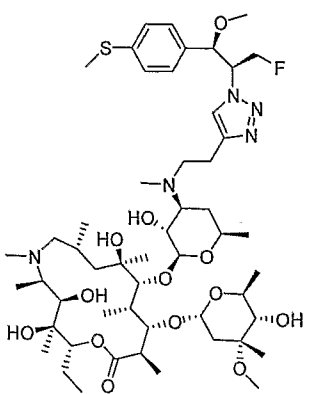
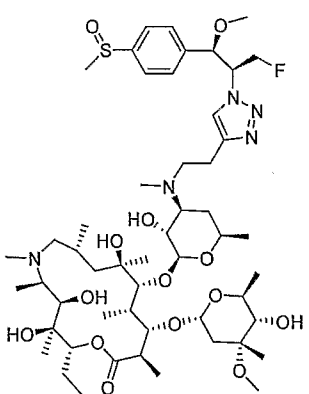
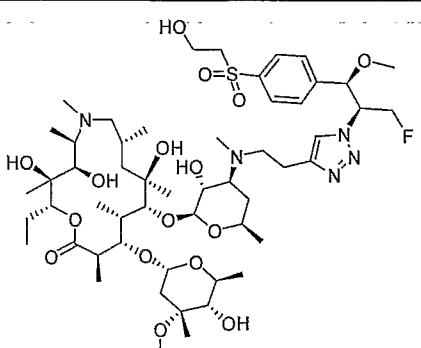
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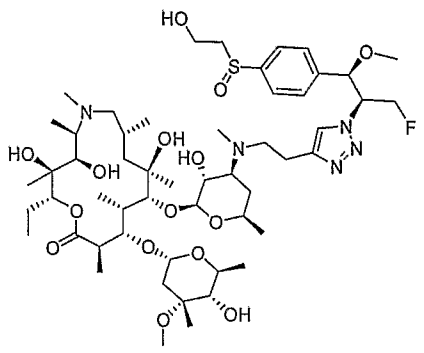
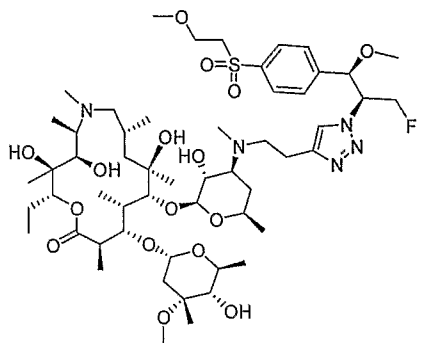
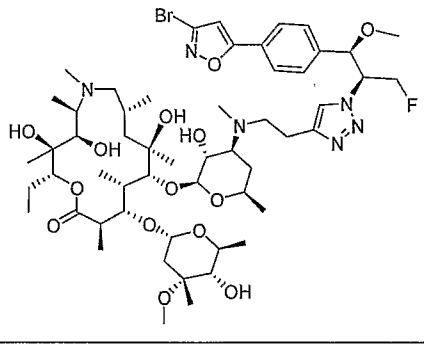
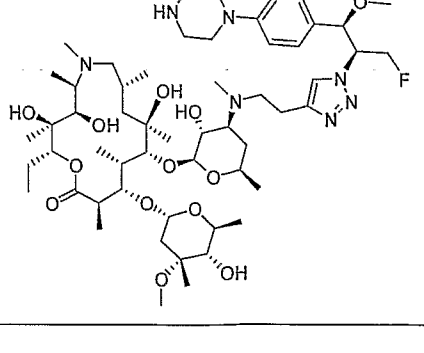
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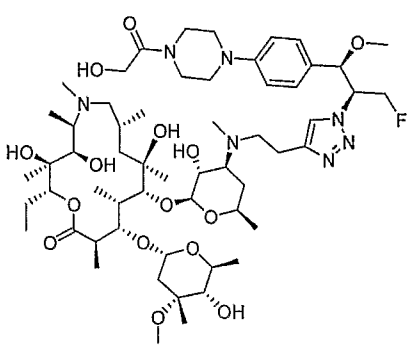
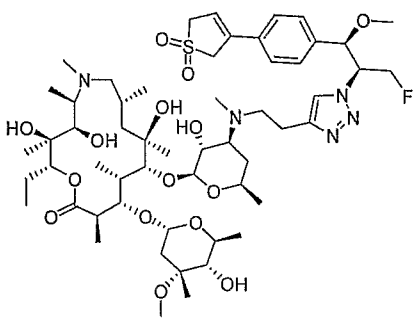
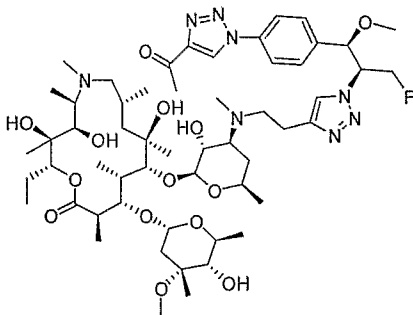
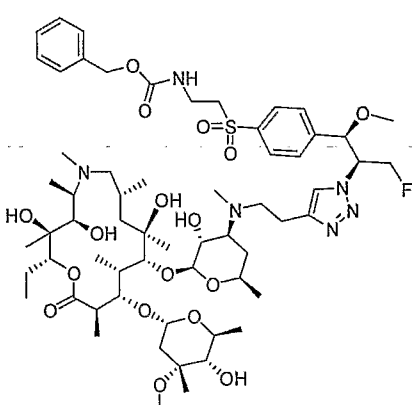
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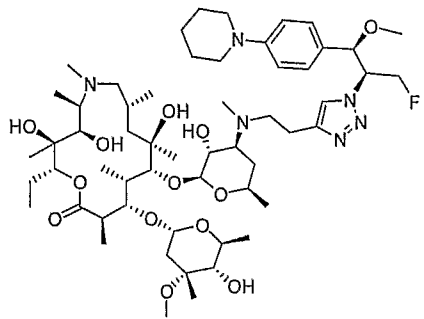
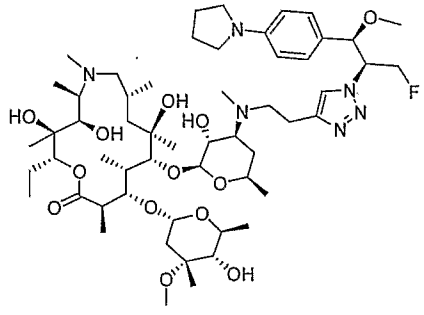
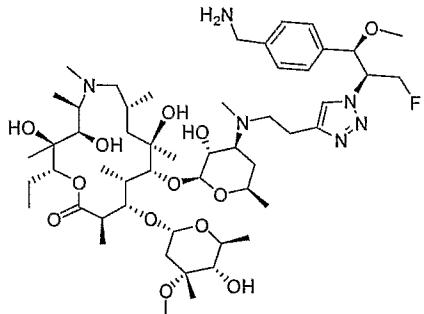
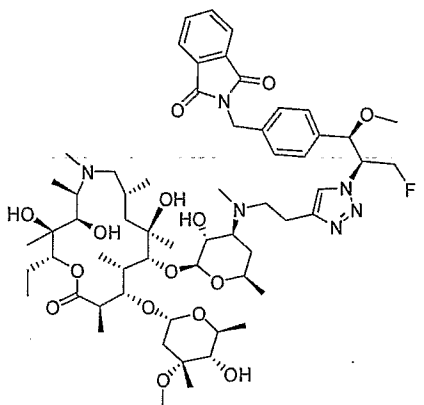
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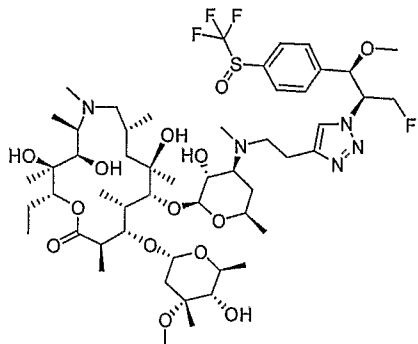
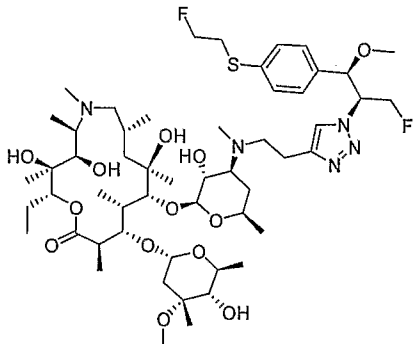
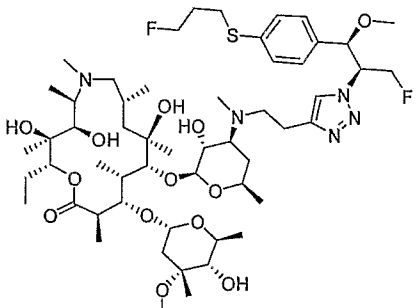
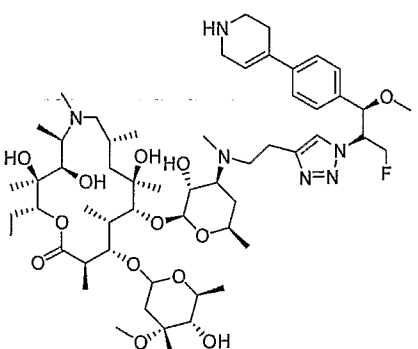
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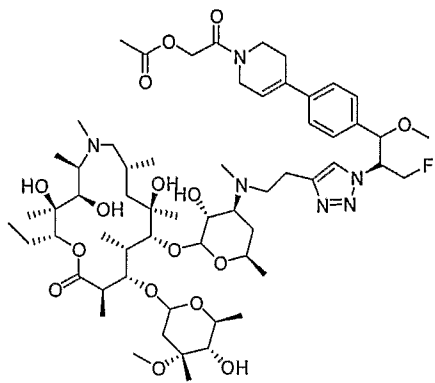
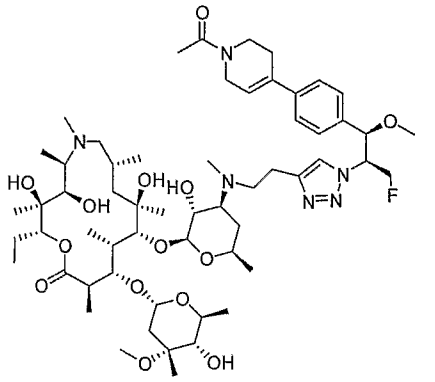
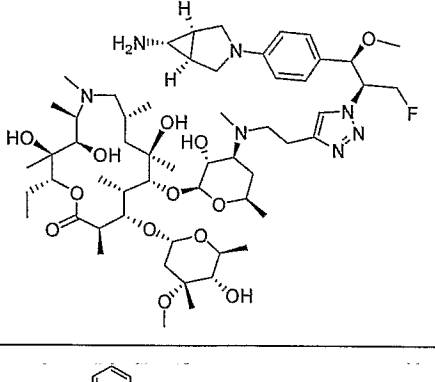
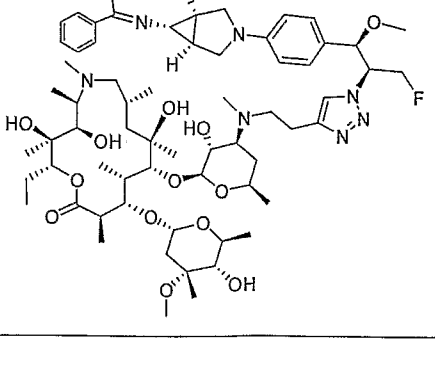
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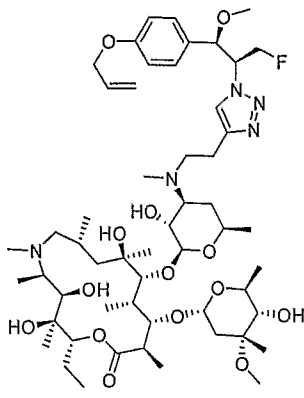
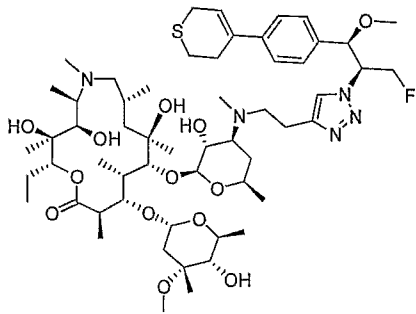
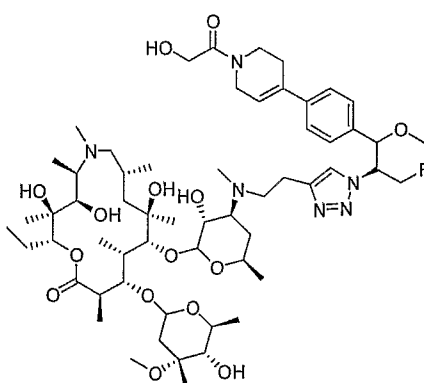
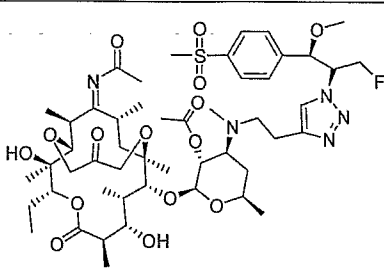
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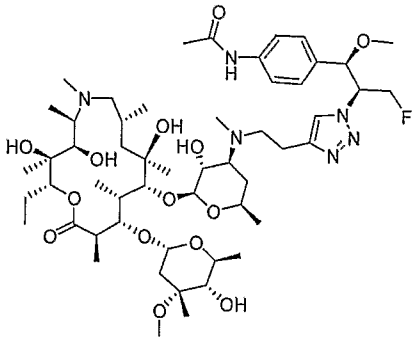
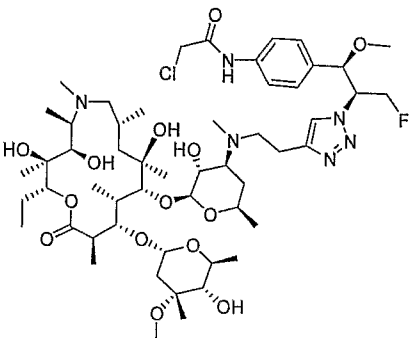
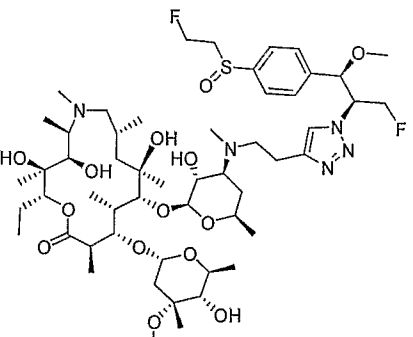
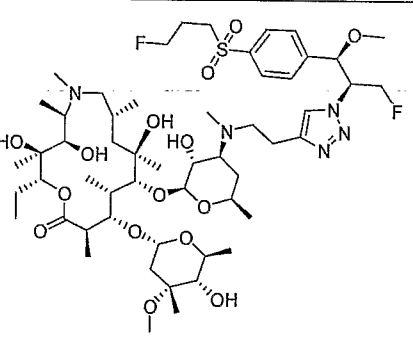
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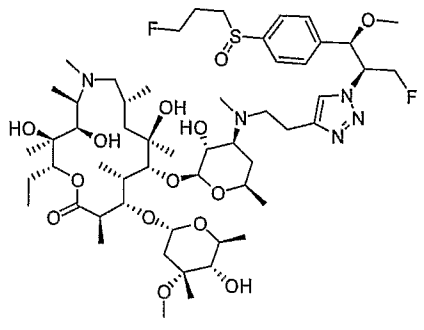
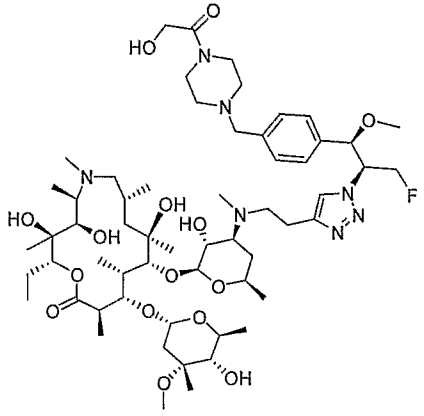
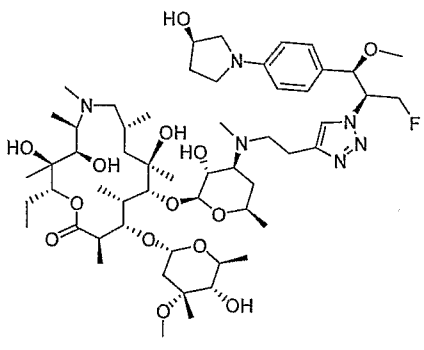
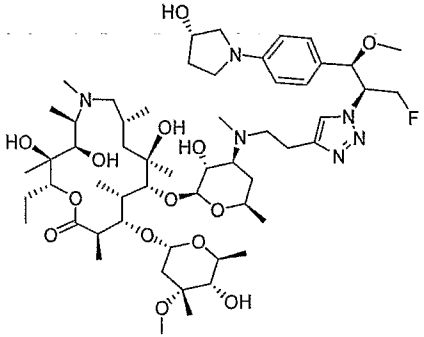
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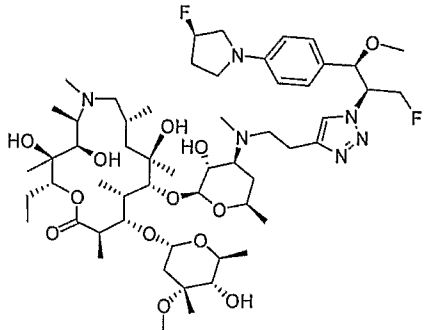
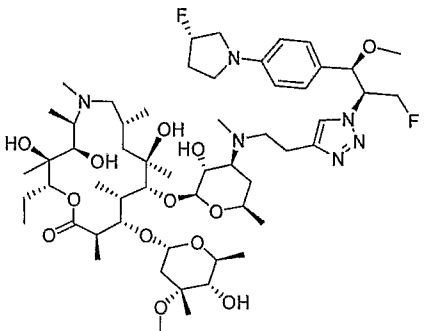
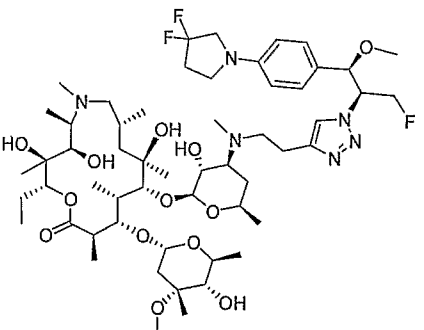
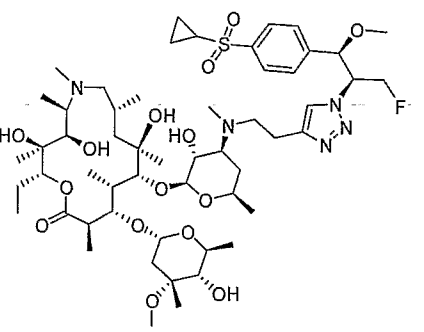
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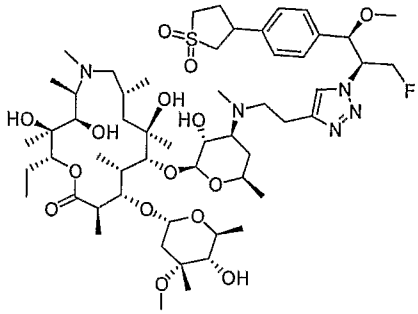
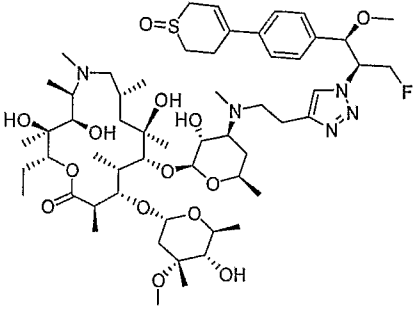
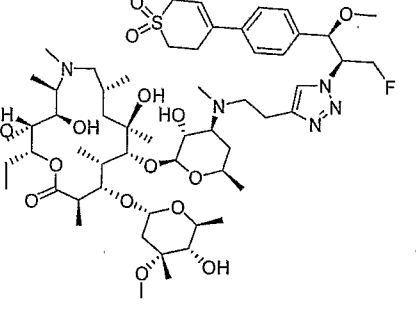
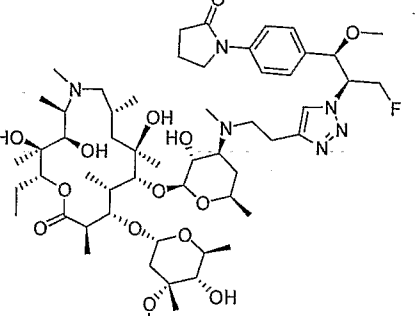
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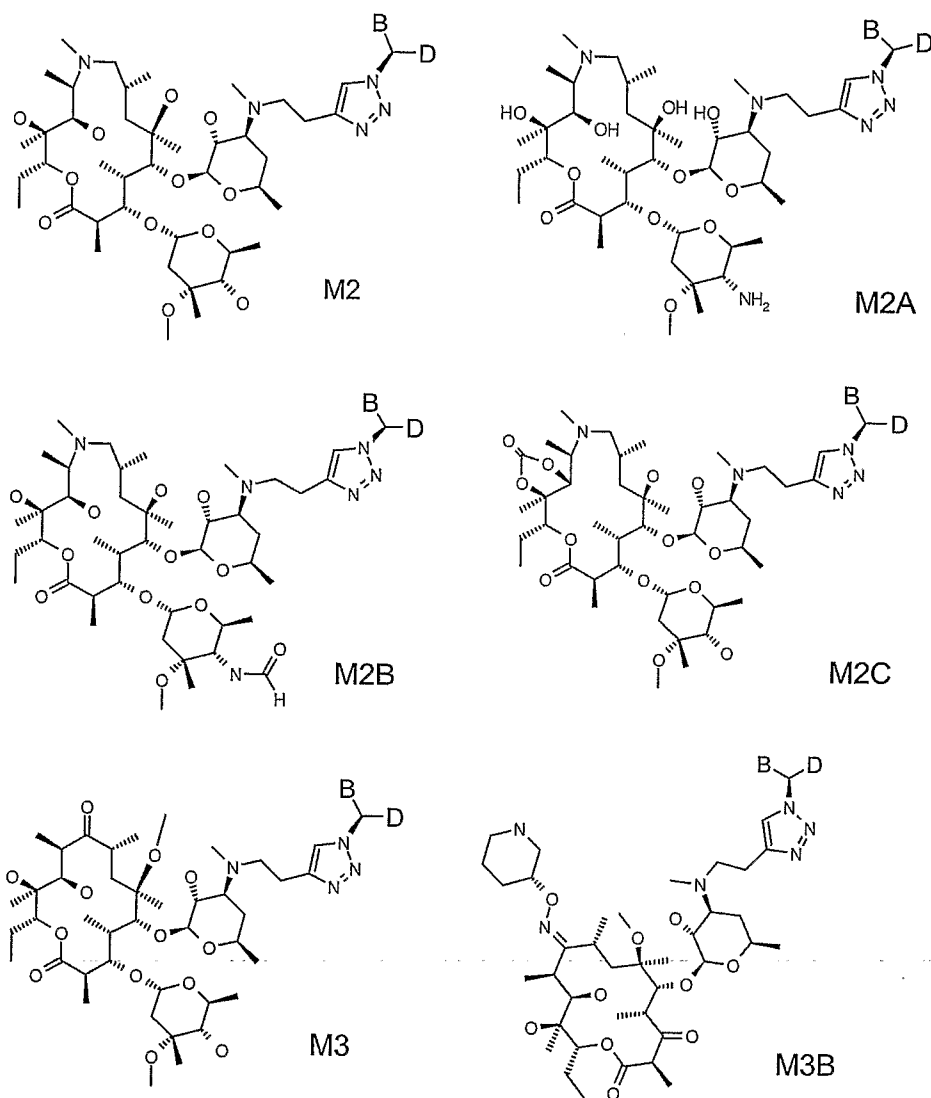
Example 1 - Synthesis of Compounds 101-311 and 812-814

Schemes 100 and 101 below depict the synthesis of compounds **101-311** and **812-814**.
5 **814**. Demethylation of azithromycin **1** selectively produced 3'-*N*-desmethylazithromycin

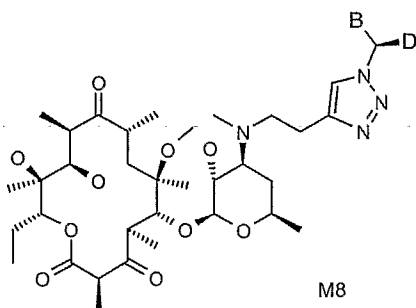
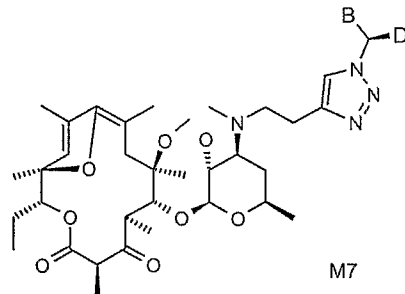
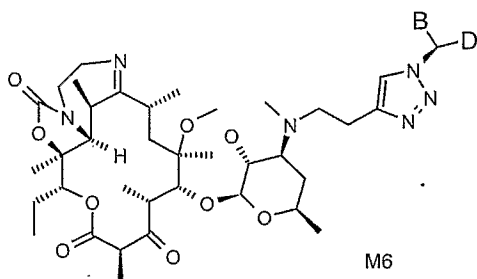
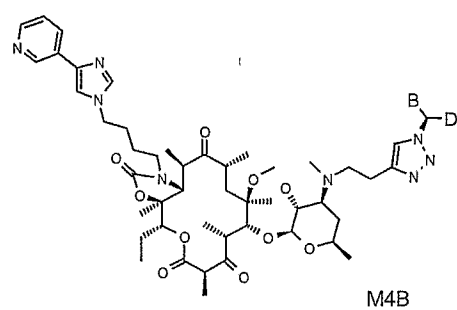
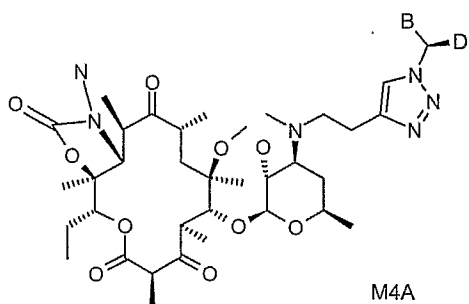
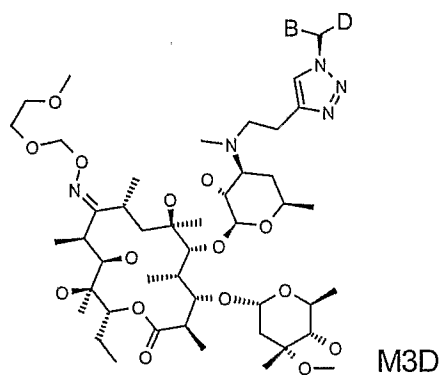
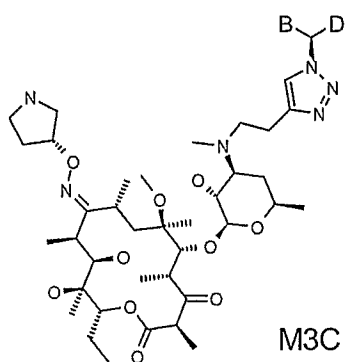
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2. Amine **2** was selectively alkylated with tosylate **11** to produce alkyne **3**, respectively. As shown in Scheme 101 alkyne **3** is reacted with corresponding azides in the presence of copper(I) iodide to selectively afford the triazoles **101-311** and **812-814**. The general structures for the macrolides in Tables 2 - 5 are shown below in Scheme 99.

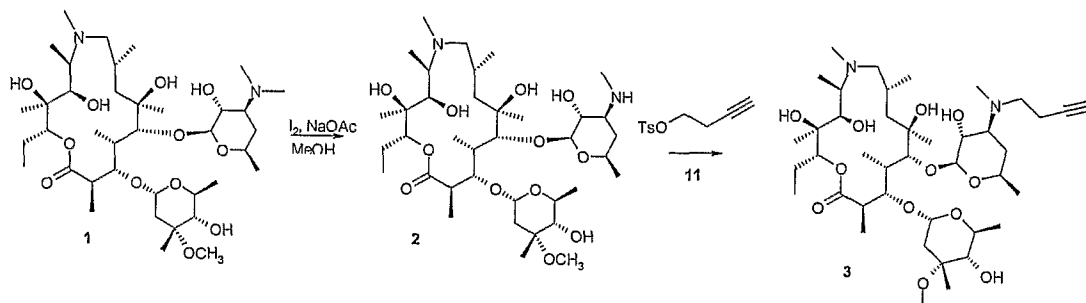
5 **Scheme 99: Macrolide structures for Tables 2 -5.**



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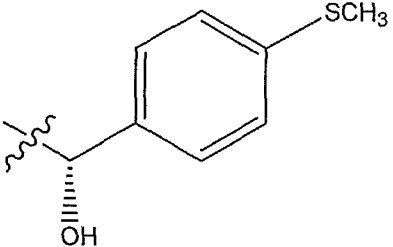
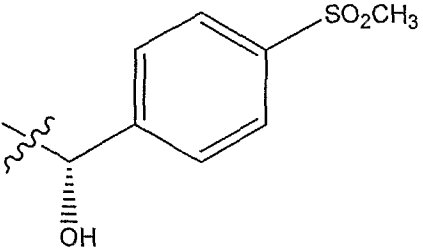
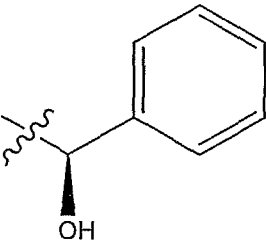
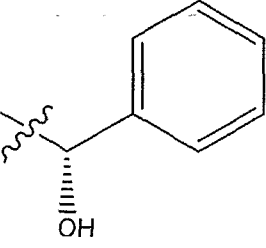
Scheme 100: Synthesis of alkyne 3.**Synthesis of 3'-N-desmethylazithromycin 2**

Azithromycin 1 (0.80 g, 1.02 mmol) and sodium acetate (NaOAc) (0.712 g, 8.06 mmol) were dissolved in 80% aqueous MeOH (25 mL). The solution was heated to 50°C followed by addition of iodine (I_2) (0.272 g, 1.07 mmol) in three batches within 3 minutes. The reaction was maintained at a pH between 8 and 9 by adding 1N sodium hydroxide (NaOH) (1 mL) at 10 min and 45 minute intervals. The solution turned colorless within 45 minutes, however, stirring was continued for 2 hours. TLC (CH_2Cl_2 /MeOH/ NH_4OH 10:1:0.05) after 2 hours showed a single major product (R_f = 0.66). The reaction was cooled to room temperature, poured into H_2O (75 mL) containing NH_4OH (1.5 mL) and extracted with $CHCl_3$ (3 x 30 mL). The combined organic layers were washed with H_2O (30 mL) containing NH_4OH (1.5 mL), dried over Na_2SO_4 and the solvent evaporated to give a white residue. The crude was purified on a silica gel column eluting with CH_2Cl_2 /MeOH/ NH_4OH 18:1:0.05 to 10:1:0.05 to provide amine 2 (0.41 g, 55%).

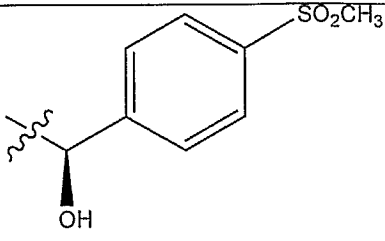
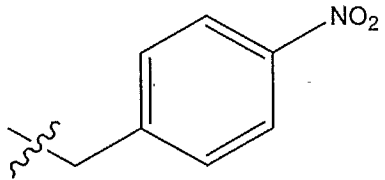
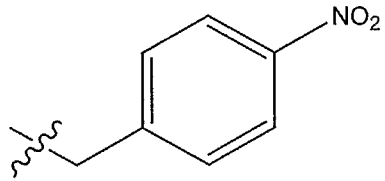
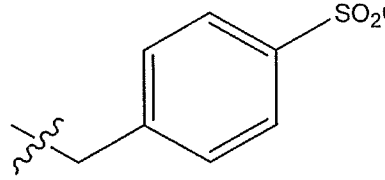
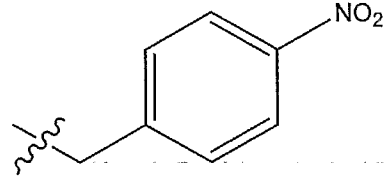
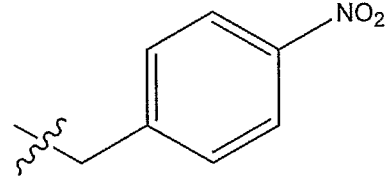
Synthesis of alkyne 3

A mixture of 3'-N-desmethylazithromycin 2 and tosylate 11 in Hunig's base was stirred. The reaction mixture was diluted to EtOAc and washed with $NaHCO_3$ (aq) and with brine. The organic layer was dried over K_2CO_3 and the solvent was evaporated to give product. The crude product was purified on silica gel column to give 3 as a white solid.

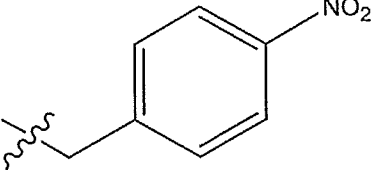
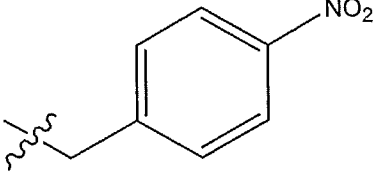
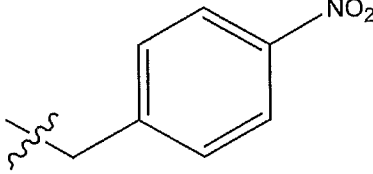
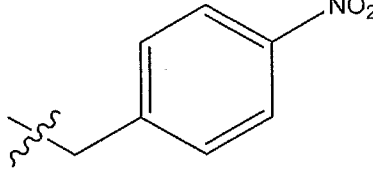
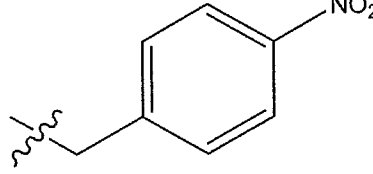
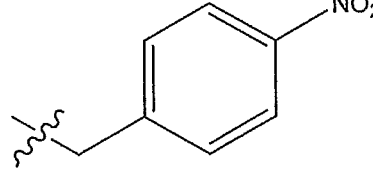
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Table 2					
Cmpd	B	Mac	D	Yield	LCMS
101		M2	CH ₂ OH	92%	514.1 (M+2H) ²⁺
102		M2	CH ₂ OH	38%	530.1 (M+2H) ²⁺
103		M2	CH ₃	39%	483.2 (M+2H) ²⁺
104		M2	CH ₃	37%	483.1 (M+2H) ²⁺
105		M2	CH ₂ F	35%	531.2 (M+2H) ²⁺

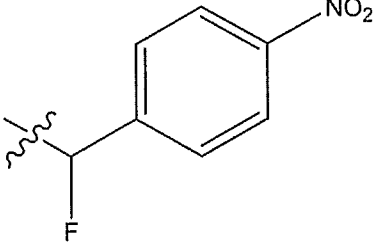
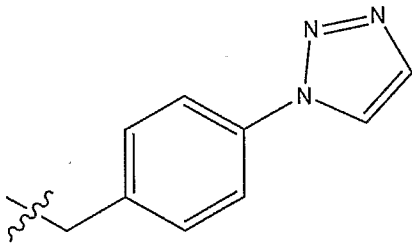
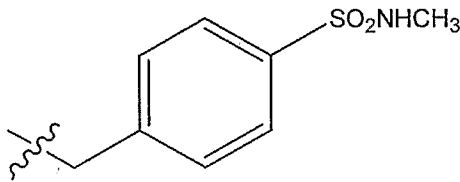
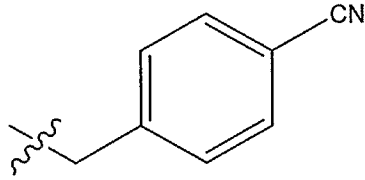
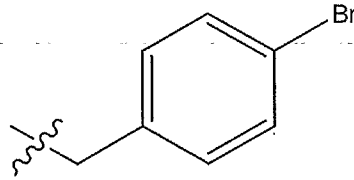
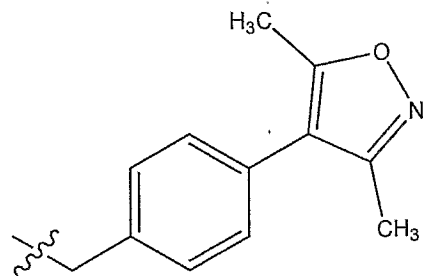
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106		M2	CH ₂ OH	83%	505.6 (M+2H) ²⁺ 1009.9 (M + H) ⁺ 1031.9 (M+Na) ⁺
107		M2	CH ₂ F	84%	506.6 (M+2H) ²⁺
108		M2	CH ₂ F	97%	1045 (M + H) ⁺
109		M2	CO ₂ H	67%	512.5 (M+2H) ²⁺
110		M2	CONH ₂	96%	512.1 (M+2H) ²⁺
111		M2	CO ₂ CH ₃	91%	519.5 (M+2H) ²⁺

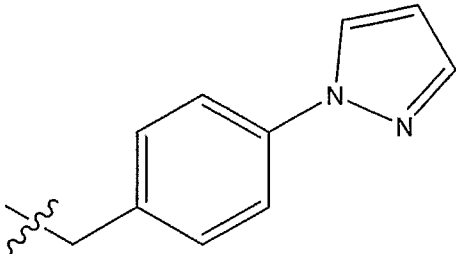
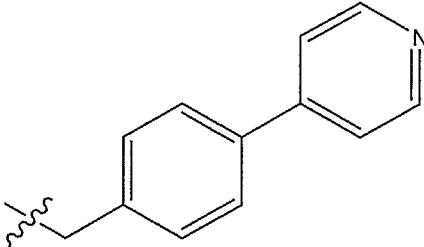
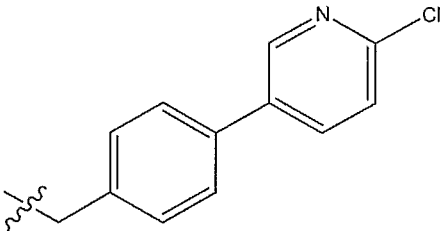
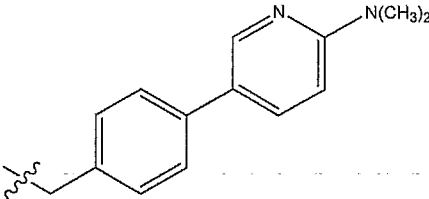
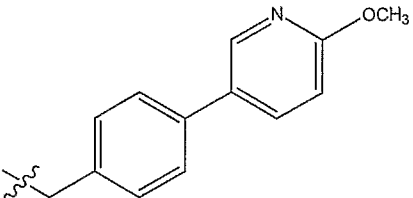
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112		M2	CH ₂ NH ₂	69%	505.0 (M+2H) ²⁺
113		M2	CH ₂ N ₃	97%	518.1 (M+2H) ²⁺
114		M2	CH ₂ N(C H ₃) ₂	73%	519.2 (M+2H) ²⁺
115		M2	CH ₂ -N- triazole	49%	531.1 (M+2H) ²⁺
116		M2	CH ₂ Cl	89%	514.6 (M+2H) ²⁺
117		M2	CH ₂ F	89%	1002.8 (M + H) ⁺

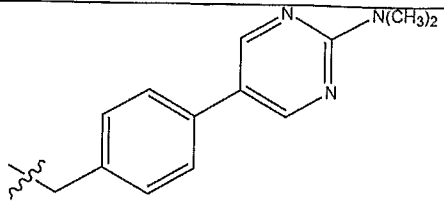
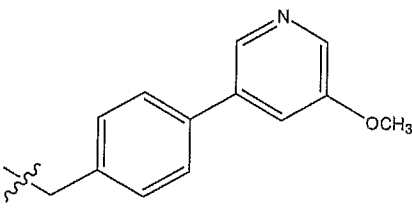
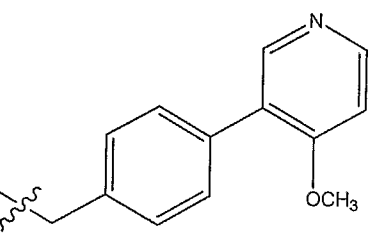
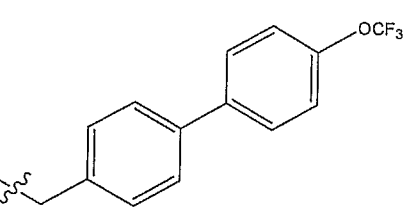
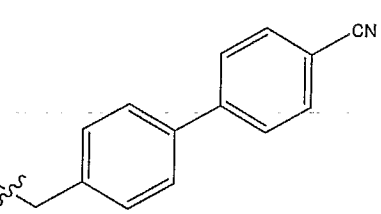
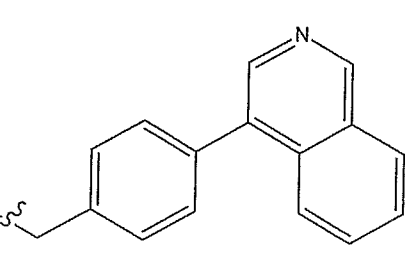
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118		M2	CH ₂ F	76%	530 (M+2H) ²⁺
119		M2	CH ₂ Cl	60%	1090.2 (M+H) ⁺
120		M2	CH ₂ F	81%	496.5 (M+2H) ²⁺
121		M2	CH ₂ F	81%	523.8 (M+2H) ²⁺
122		M2	CH ₂ F	94%	531.6 (M+2H) ²⁺

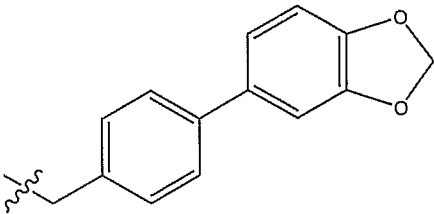
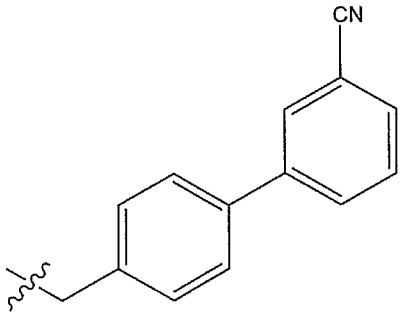
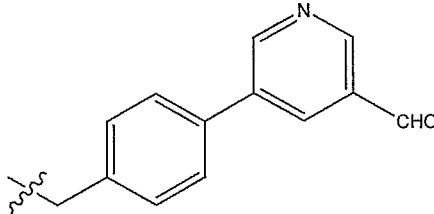
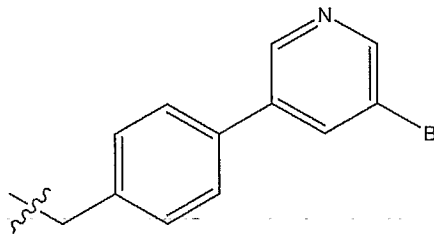
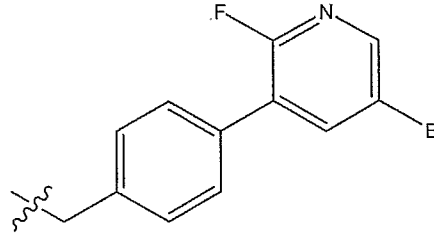
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123		M2	CH ₂ F	91%	517.1 (M+2H) ²⁺
124		M2	CH ₂ F	93%	522.5 (M+2H) ²⁺
125		M2	CH ₂ F	90%	539.5 (M+2H) ²⁺
126		M2	CH ₂ F	98%	544.1 (M+2H) ²⁺
127		M2	CH ₂ F	91%	537.6 (M+2H) ²⁺
128		M2	CH ₂ F	91%	544.5 (M+2H) ²⁺

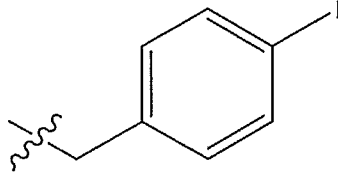
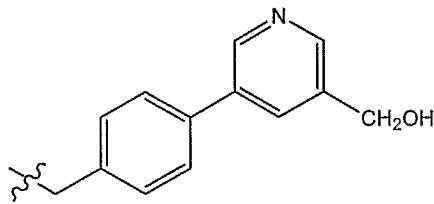
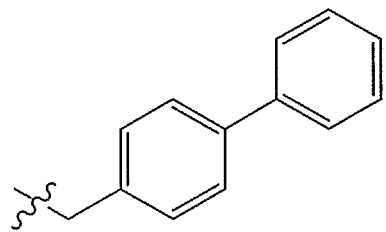
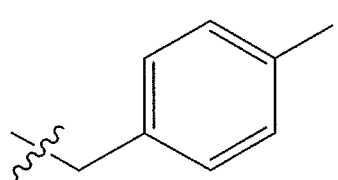
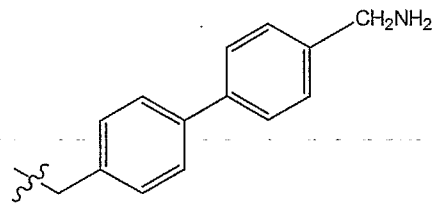
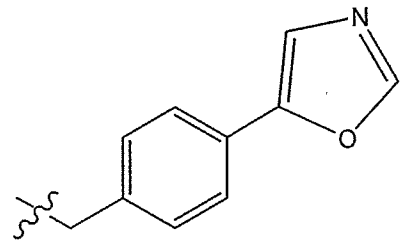
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129		M2	CH ₂ F	60%	537.6 (M+2H) ²⁺
130		M2	CH ₂ F	79%	537.6 (M+2H) ²⁺
131		M2	CH ₂ F	92%	564.0 (M+2H) ²⁺
132		M2	CH ₂ F	95%	534.5 (M+2H) ²⁺
133		M2	CH ₂ F	83%	547.8 (M+2H) ²⁺

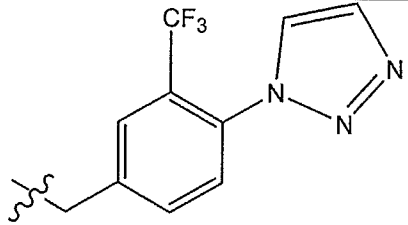
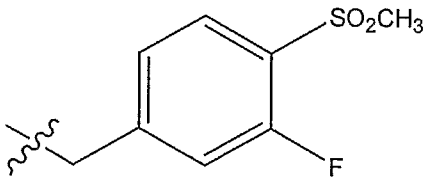
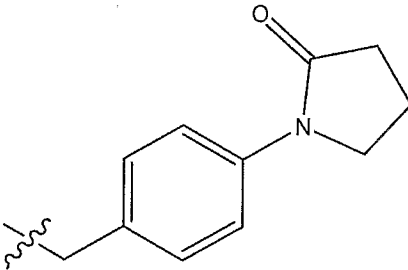
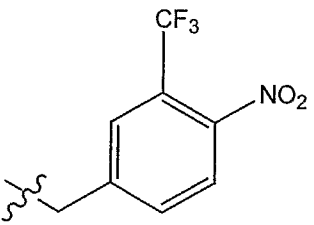
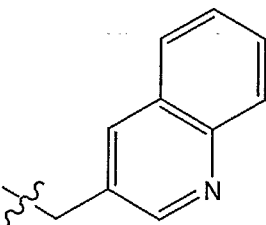
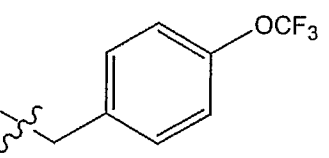
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134		M2	CH ₂ F	71%	544.2 (M+2H) ²⁺
135		M2	CH ₂ F	84%	534.8 (M+2H) ²⁺
136		M2	CH ₂ F	76%	536.6 (M+2H) ²⁺
137		M2	CH ₂ F	70%	562.5 (M+2H) ²⁺
138		M2	CH ₂ F	76%	570.9 (M+2H) ²⁺
139		M2	CH ₂ F	72%	547.1 (M+2H) ²⁺

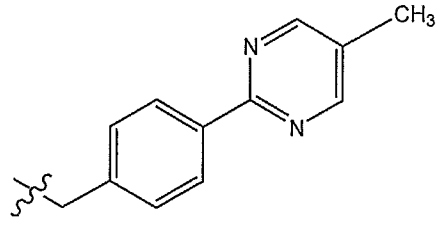
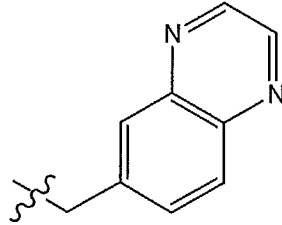
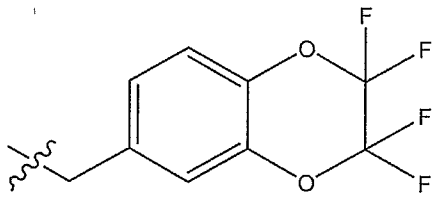
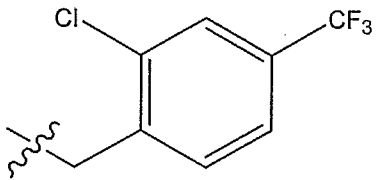
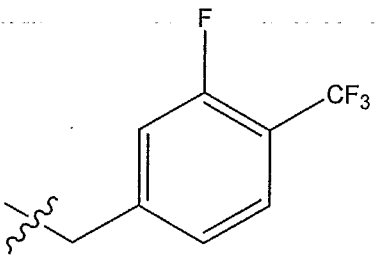
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140		M2	CH ₂ F	81%	537.8 (M+2H) ²⁺
141		M2	CH ₂ F	83%	522.0 (M+2H) ²⁺
142		M2	CH ₂ F	72%	1023.0 (M+H) ⁺
143		M2	CH ₂ F	51%	536.8 (M+2H) ²⁺
144		M2	CH ₂ F	82%	1034.3 (M+H) ⁺
145		M2	CH ₂ F	72%	551.6 (M+2H) ²⁺

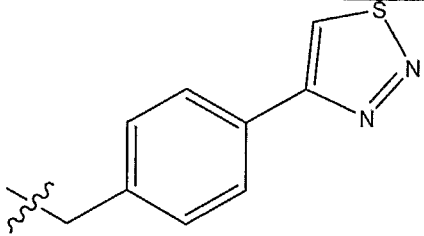
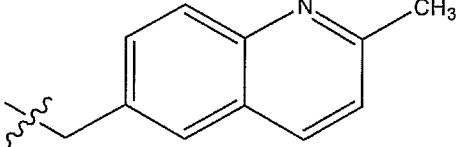
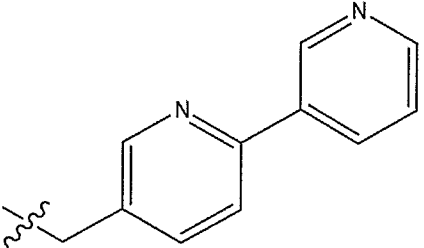
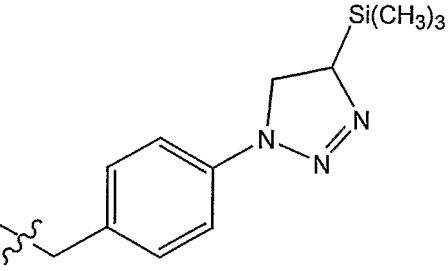
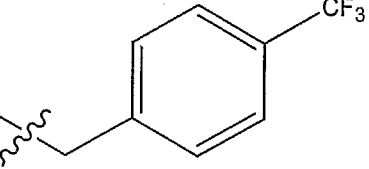
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146		M2	CH ₂ F	50%	532.1 (M+2H) ²⁺
147		M2	CH ₂ F	61%	1049.9 (M+H) ⁺
148		M2	CH ₂ F	64%	1079.9 (M+H) ⁺
149		M2	CH ₂ F	58%	1017.9 (M+H) ⁺
150		M2	CH ₂ F	56%	1051.0 (M+H) ⁺

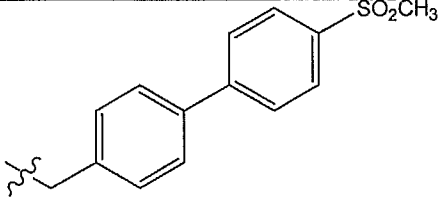
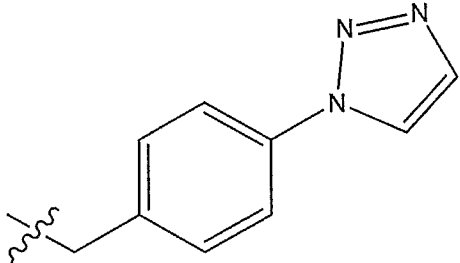
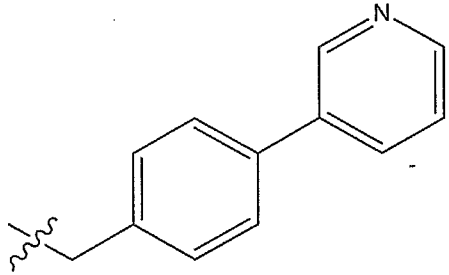
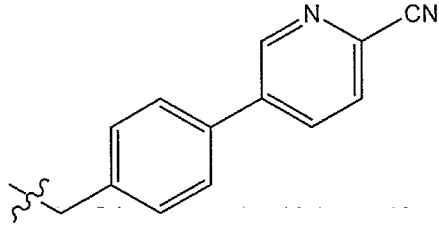
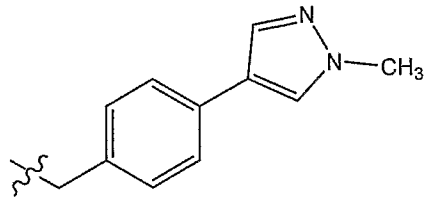
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151		M2	CH ₂ F	35%	530.2 (M+2H) ²⁺
152		M2	CH ₂ F	31%	510.2 (M+2H) ²⁺
153		M2	CH ₂ F	46%	549.1 (M+2H) ²⁺
154		M2	CH ₂ F	67%	534.8 (M+2H) ²⁺
155		M2	CH ₂ F	71%	527.0 (M+2H) ²⁺
156		M2	CH ₂ F	38%	526.1 (M+2H) ²⁺

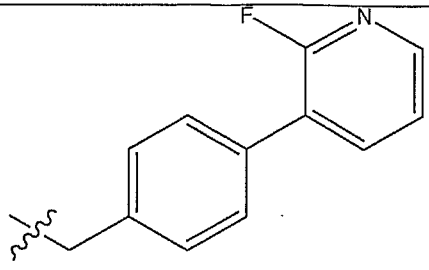
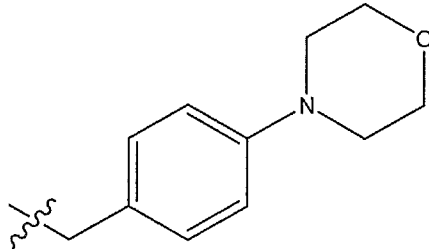
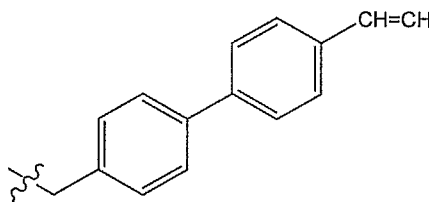
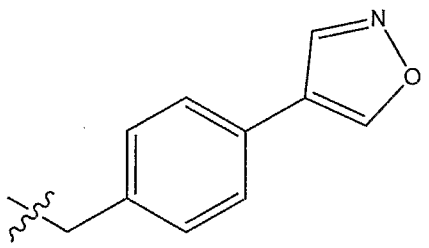
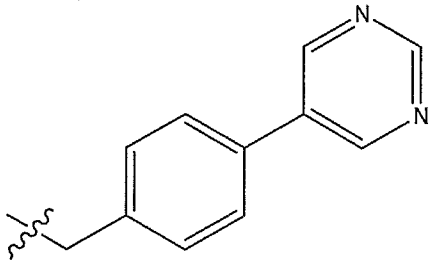
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157		M2	CH ₂ F	26%	516.5 (M + H) ²⁺
158		M2	CH ₂ F	58%	523.2 (M+H) ²⁺
159		M2	CH ₂ F	23%	553.6 (M+2H) ²⁺ 1105.8 (M+H) ⁺
160		M2	CH ₂ F	90%	518 (M+2H) ²⁺
161		M2	CH ₂ F	76%	561.1 (M+2H) ²⁺

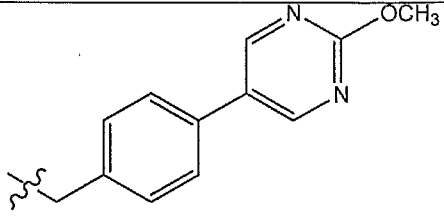
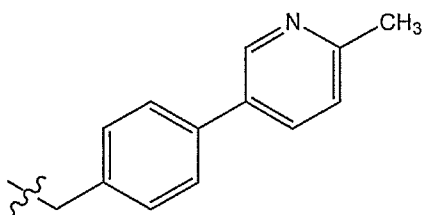
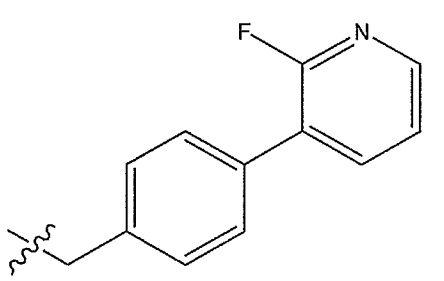
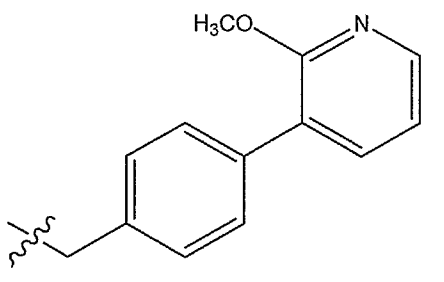
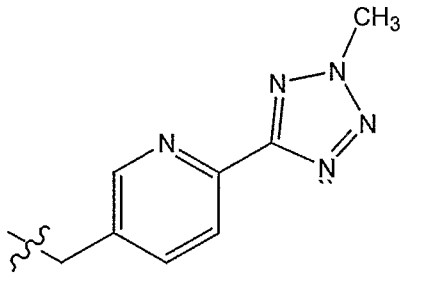
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162		M2	CH ₂ F	25%	1032.8 (M+H) ⁺
163		M2	CH ₂ F	92%	522.4 (M+2H) ²⁺
164		M2	CH ₂ F	68%	535.1 (M+2H) ²⁺
165		M2	CH ₂ F	94%	524.1 (M+2H) ²⁺
166		M2	CH ₂ F	94%	531.1 (M+2H) ²⁺

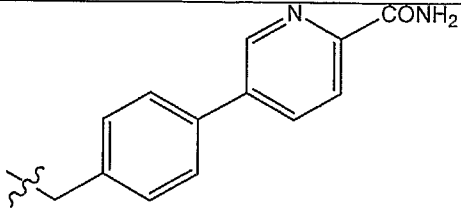
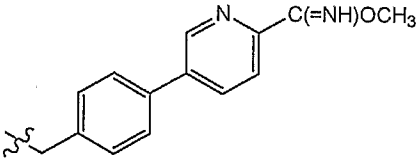
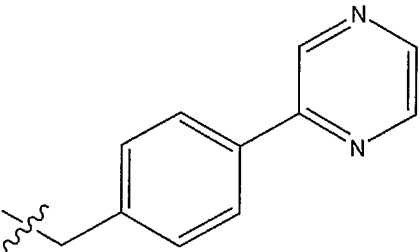
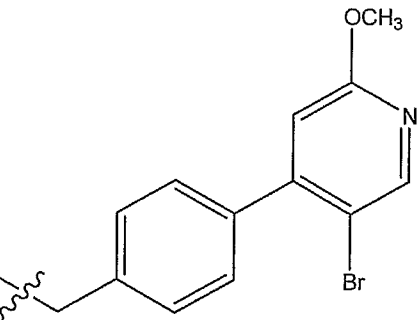
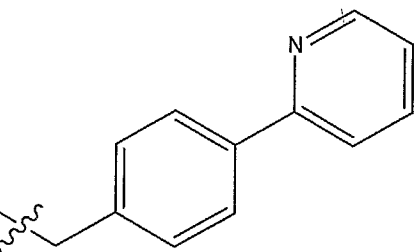
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167		M2	CH ₂ F	95%	526.5 (M+2H) ²⁺
168		M2	CH ₂ F	95%	535.1 (M+2H) ²⁺
169		M2	CH ₂ F	96%	517.5 (M+2H) ²⁺
170		M2	CH ₂ F	90%	523.1 (M+2H) ²⁺
171		M2	CH ₂ F	77%	538.1 (M+2H) ²⁺

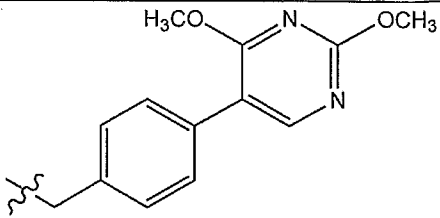
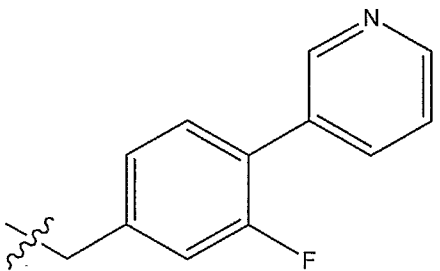
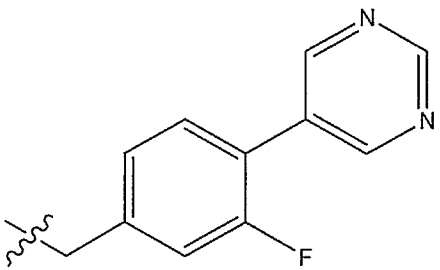
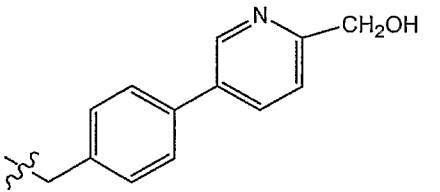
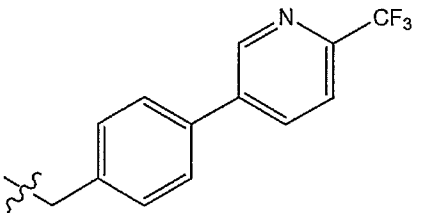
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172		M2	CH ₂ F	87%	529.6 (M+2H) ²⁺
173		M2	CH ₂ F	85%	531.3 (M+2H) ²⁺
174		M2	CH ₂ F	91%	537.5 (M+2H) ²⁺
175		M2	CH ₂ F	92%	563.2 (M+2H) ²⁺
176		M2	CH ₂ F	69%	544.3 (M+2H) ²⁺

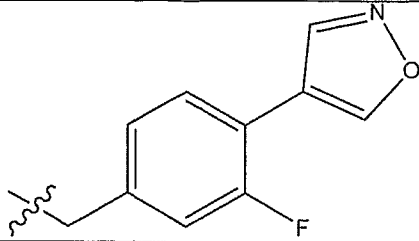
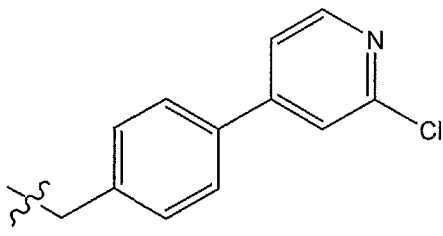
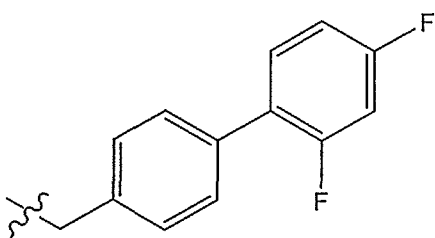
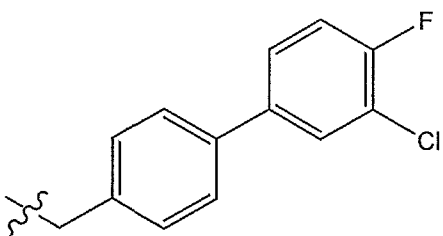
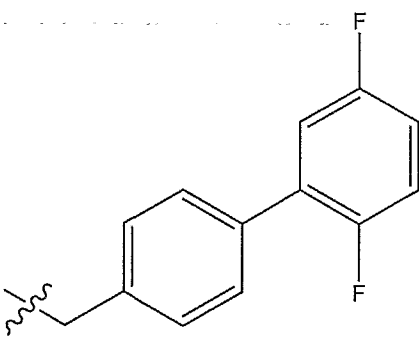
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177		M2	CH ₂ F	50%	551.9 (M+2H) ²⁺
178		M2	CH ₂ F	63%	523.2 (M+2H) ²⁺
179		M2	CH ₂ F	91%	577.4 (M+2H) ²⁺
180		M2	CH ₂ F	58%	522.4 (M+2H) ²⁺
181		M2	CH ₂ F	90%	553.1 (M+2H) ²⁺ +

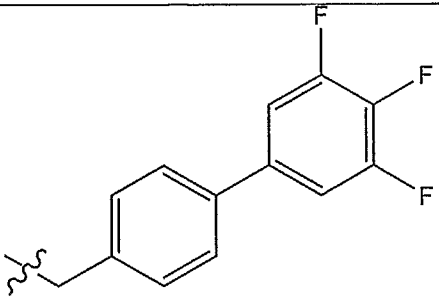
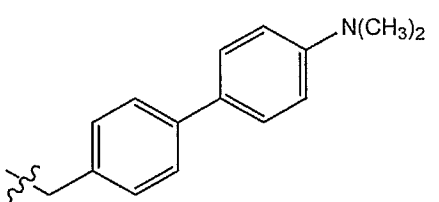
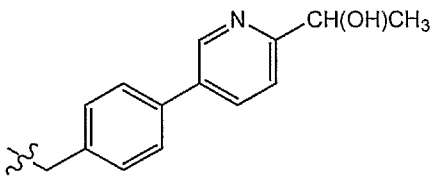
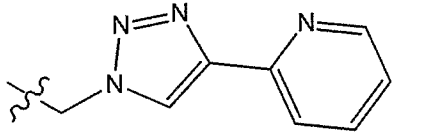
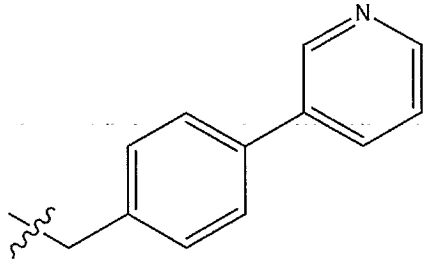
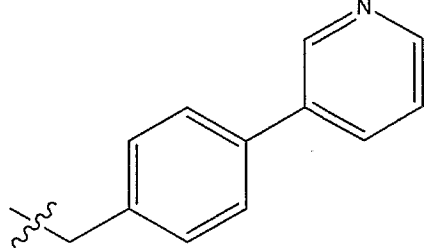
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182		M2	CH ₂ F	81%	531.8 (M+2H) ²⁺
183		M2	CH ₂ F	70%	532.2 (M+2H) ²⁺
184		M2	CH ₂ F	75%	537.8 (M+2H) ²⁺
185		M2	CH ₂ F	72%	557.0 (M+2H) ²⁺
186		M2	CH ₂ F	86%	526.6 (M+2H) ²⁺

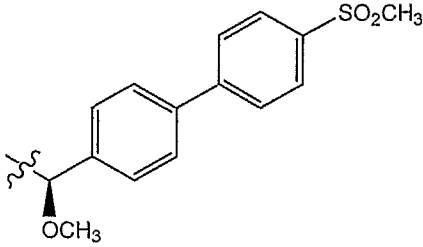
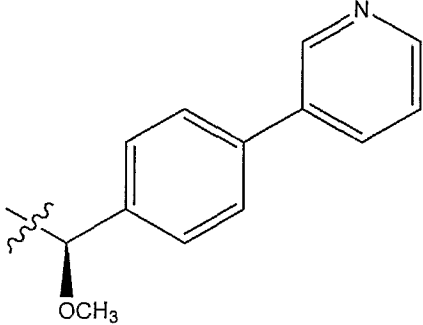
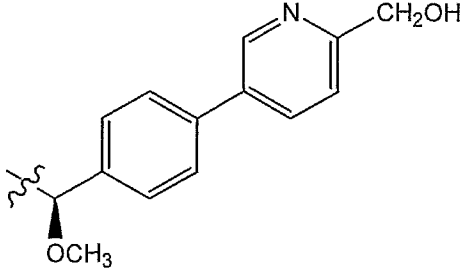
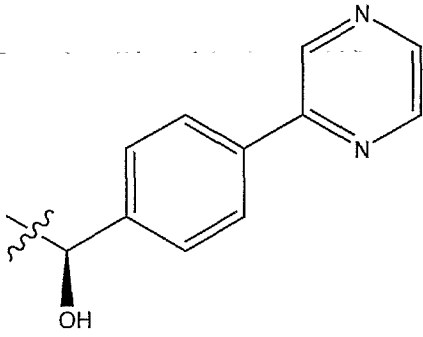
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187		M2	CH ₂ F	86%	539.5 (M+2H) ²⁺
188		M2	CH ₂ F	42%	540.1 (M+2H) ²⁺
189		M2	CH ₂ F	67%	548.1 (M+2H) ²⁺
190		M2	CH ₂ F	78%	540.1 (M+2H) ²⁺
191		M2	CH ₂ F	88%	549.1 (M+2H) ²⁺

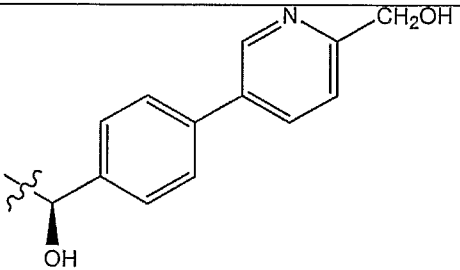
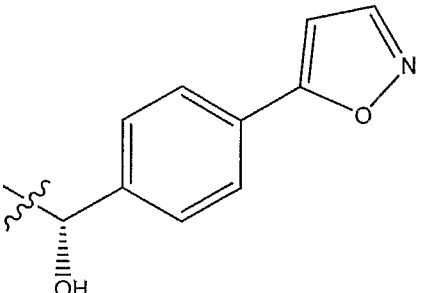
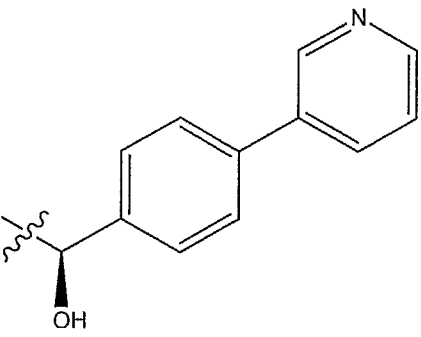
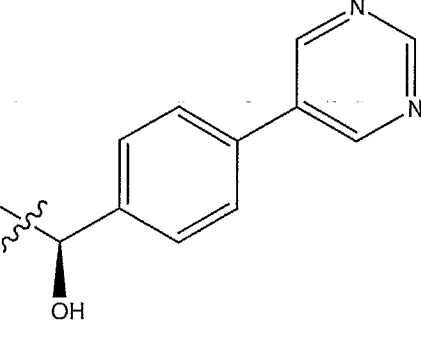
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192		M2	CH ₂ F	32%	544.1 (M+2H) ²⁺
193		M2	CH ₂ F	34%	544.8 (M+2H) ²⁺
194		M2	CH ₂ F	63%	1051 (M+Na) ⁺
195		M2	CH ₂ F	94%	522.0 (M+2H) ²⁺
196		M2	CH ₂ F	46%	530.0 (M+2H) ²⁺

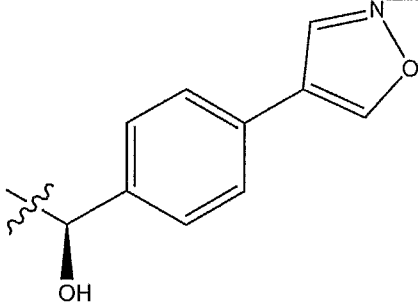
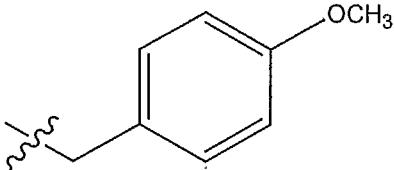
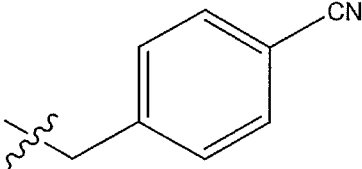
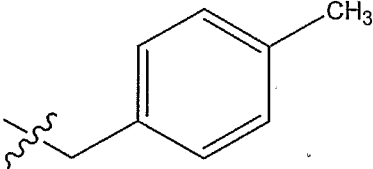
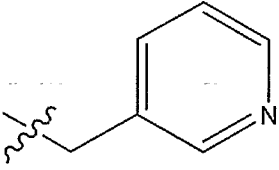
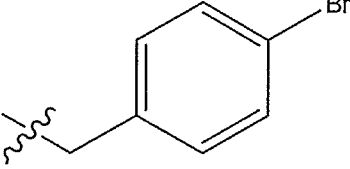
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197		M2	CH ₂ F	56%	538.1 (M+2H) ²⁺
198		M2	CH ₂ F	60%	537.6 (M+2H) ²⁺
199		M2	CH ₂ F	65%	552.8 (M+2H) ²⁺
200		M2	CH ₂ F	79%	531.1 (M+2H) ²⁺
201		M2	CH ₂ F	76%	545.6 (M+2H) ²⁺

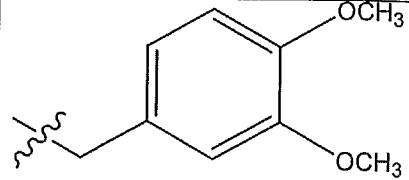
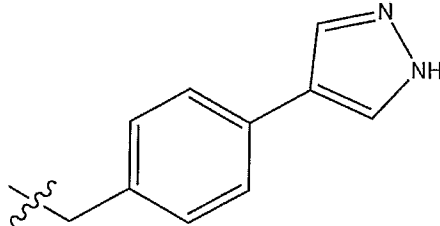
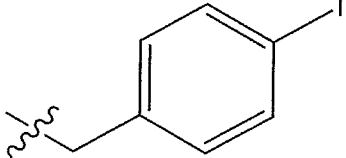
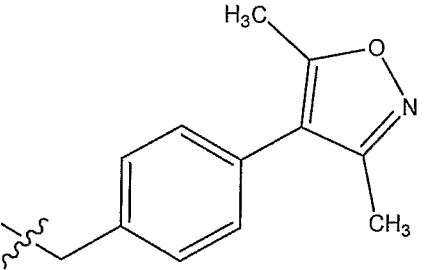
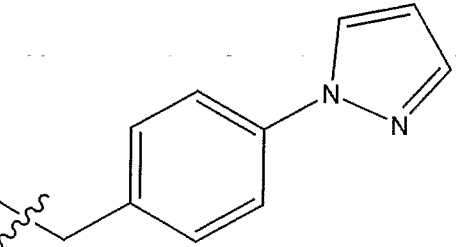
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202		M2	CH ₂ F	44%	525.6 (M+2H) ²⁺
203		M2	CH ₂ F	81%	530.6 (M+2H) ²⁺
204		M2	CH ₂ F	83%	531.2 (M+2H) ²⁺
205		M2	CH ₂ F	85%	525.7 (M+2H) ²⁺

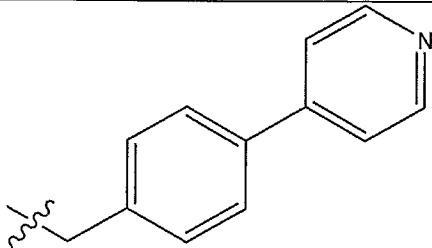
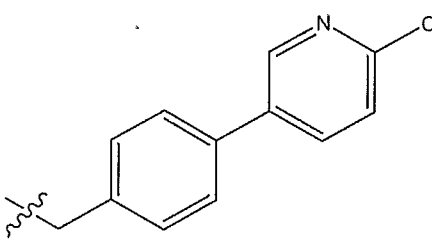
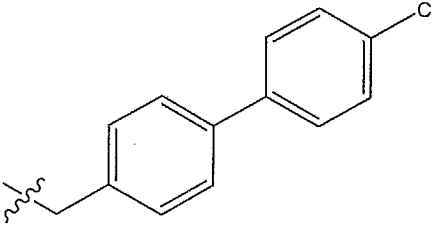
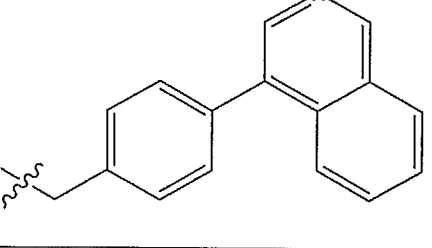
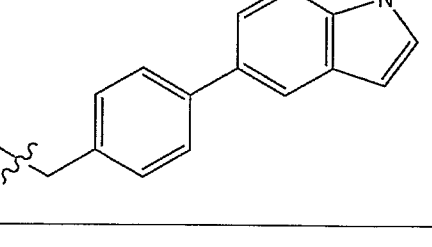
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206		M2	CH ₂ OH	74%	498.0 (M+2H) ²⁺
207		M2	CH ₂ OH	87%	495.5 (M+2H) ²⁺
208		M2	CH ₂ OH	89%	490.1 (M+2H) ²⁺
209		M2	CH ₂ OH	72%	483.6 (M+2H) ²⁺
210		M2	CH ₂ OH	74%	522.8 (M+2H) ²⁺
211		M2	CH ₂ OH	92%	513.1 (M+2H) ²⁺

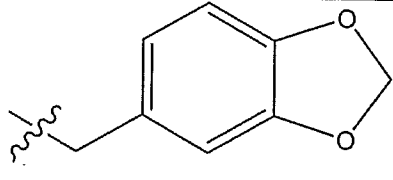
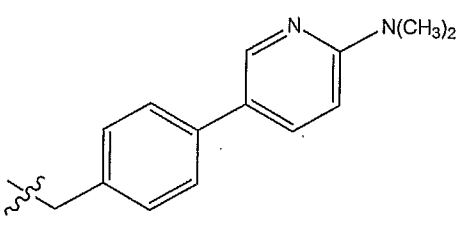
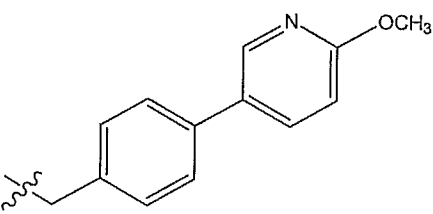
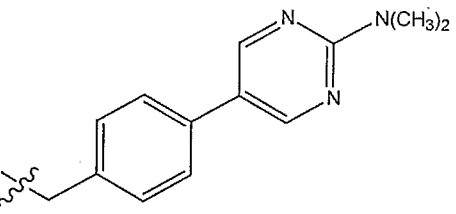
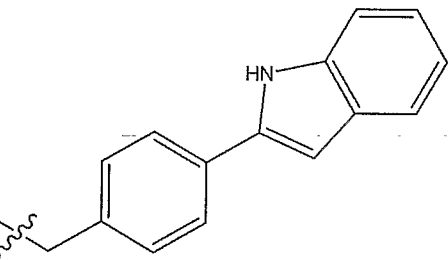
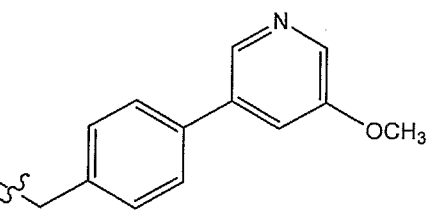
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212		M2	CH ₂ OH	76%	516.1 (M+2H) ²⁺
213		M2	CH ₂ OH	76%	546.0 (M+2H) ²⁺
214		M2	CH ₂ OH	85%	530.6 (M+2H) ²⁺
215		M2	CH ₂ OH	71%	516.1 (M+2H) ²⁺
216		M2	CH ₂ OH	65%	521.6 (M+2H) ²⁺

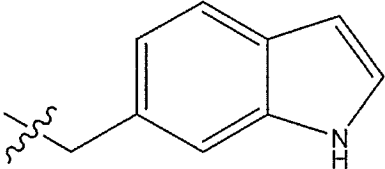
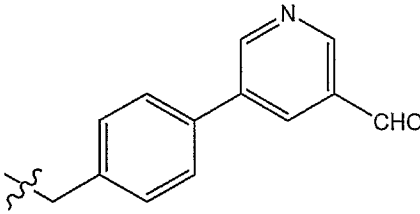
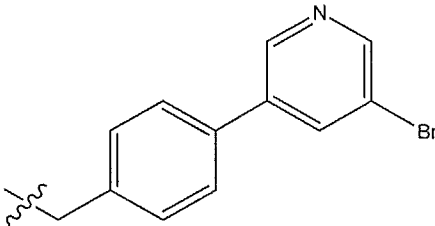
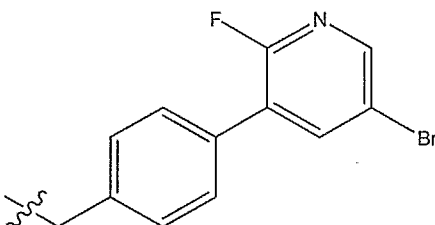
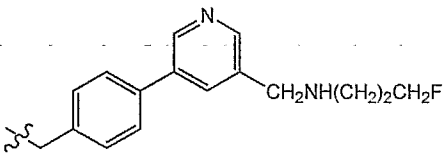
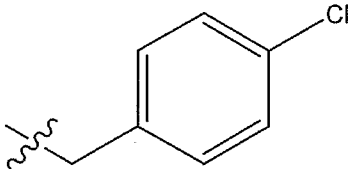
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217		M2	CH ₂ OH	82%	538.8 (M+2H) ²⁺
218		M2	CH ₂ OH	87%	533.5 (M+2H) ²⁺
219		M2	CH ₂ OH	88%	546.6 (M+2H) ²⁺
220		M2	CH ₂ OH	83%	540.5 (M+2H) ²⁺
221		M2	CH ₂ OH	90%	543.2 (M+2H) ²⁺

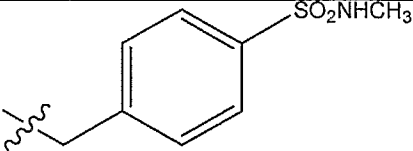
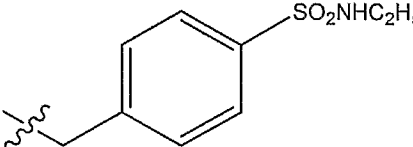
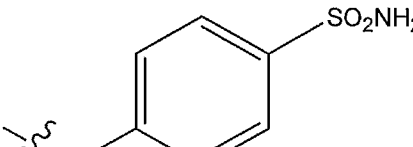
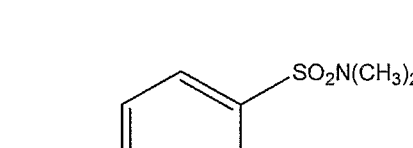
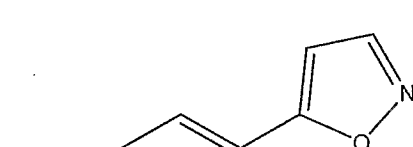
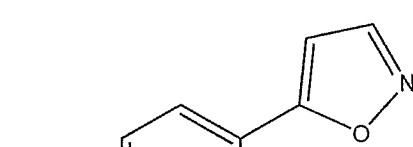
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222		M2	CH ₂ OH	90%	543.1 (M+2H) ²⁺
223		M2	CH ₂ OH	96%	536.3 (M+2H) ²⁺
224		M2	CH ₂ OH	77%	543.6 (M+2H) ²⁺
225		M2	CH ₂ OH	95%	540.6 (M+2H) ²⁺
226		M2	CH ₂ OH	86%	536.6 (M+2H) ²⁺

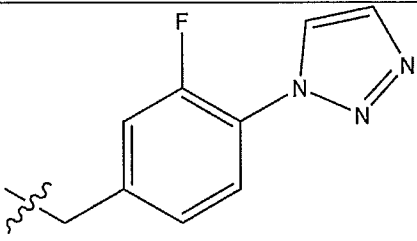
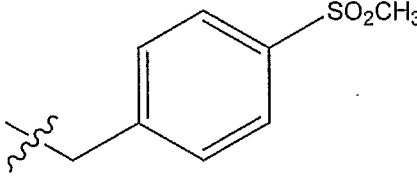
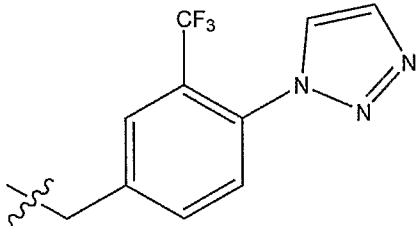
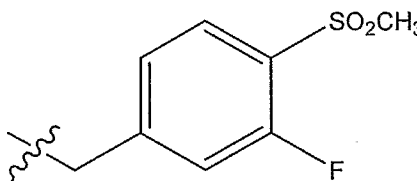
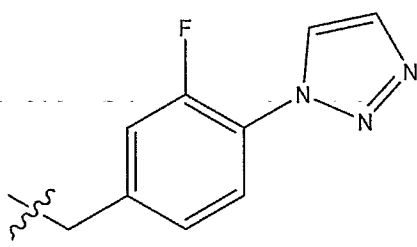
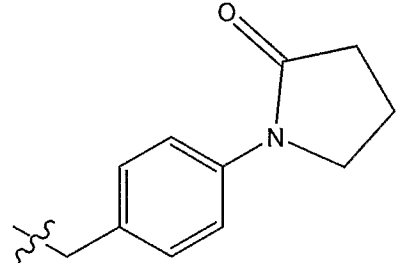
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227		M2	CH ₂ OH	60%	540.7 (M+2H) ²⁺
228		M2	CH ₂ OH	76%	535.8 (M+2H) ²⁺
229		M2	CH ₂ OH	82%	561.3 (M+2H) ²⁺
230		M2	CH ₂ OH	90%	570.5 (M+2H) ²⁺
231		M2	CH ₂ OH	75%	566.3 (M+2H) ²⁺
232		M2	CH ₂ OH	69%	500.6 (M+2H) ²⁺
233		M2	CH ₂ OH	75%	1057.8 (M+H) ⁺

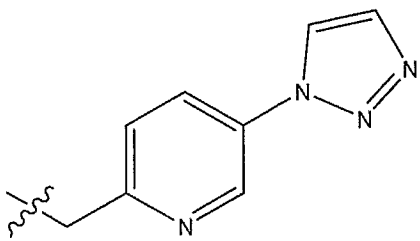
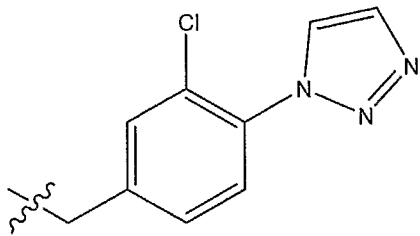
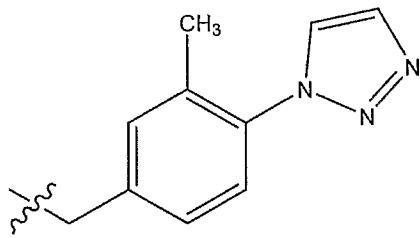
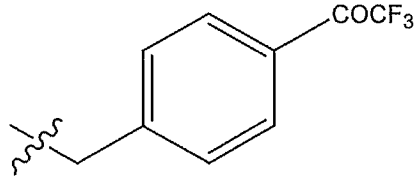
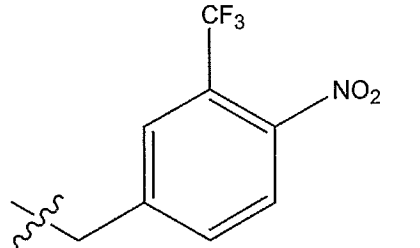
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234		M2	CH ₂ OH	85%	1071.8 (M+H) ⁺
235		M2	CH ₂ OH	38%	1044.7 (M+H) ⁺
236		M2	CH ₂ OH	46%	1071.9 (M+H) ⁺
237		M2	CH ₂ OH	31%	1053.9 (M+Na) ⁺
238		M2	CH ₂ OH	42%	1053.9 (M+Na) ⁺
239		M2	CH ₂ OH	42%	1049.0 (M+H) ⁺

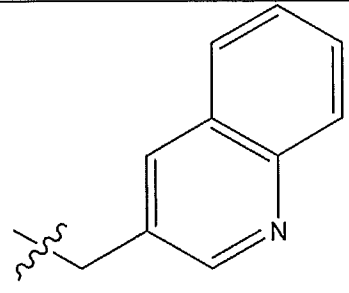
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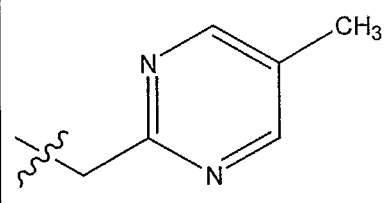
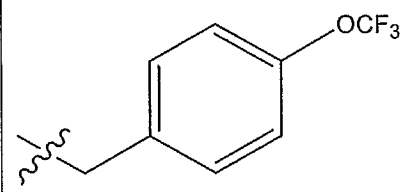
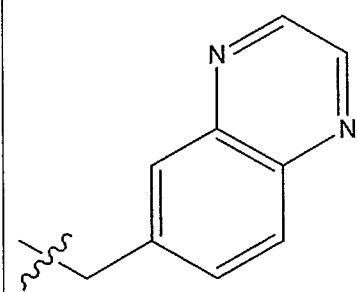
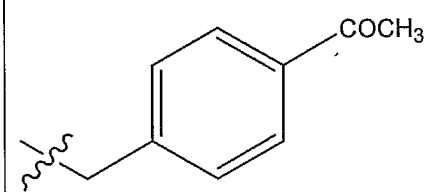
					
240		M2	CH ₂ OH	55%	522.1 (M+2H) ²⁺
241		M2	CH ₂ OH	27%	550.6 (M+2H) ²⁺
242		M2	CH ₂ OH	37%	531.1 (M+2H) ²⁺
243		M2	CH ₂ OH	31%	555.4 (M+2H) ²⁺
244		M2	CH ₂ OH	56%	524.6 (M+2H) ²⁺

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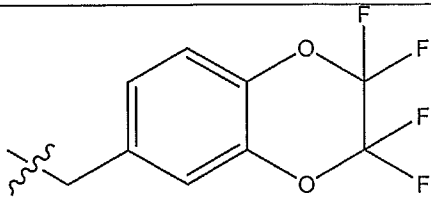
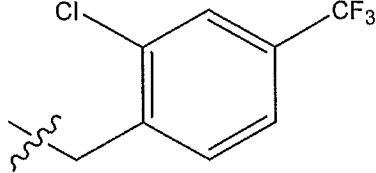
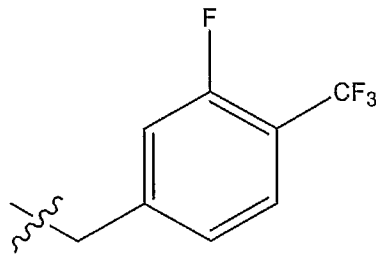
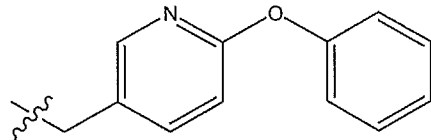
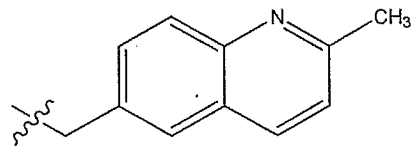
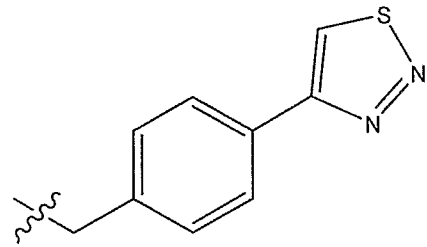
245		M2	CH ₂ OH	19%	517 (M+2)/2
246		M2	CH ₂ OH	33%	533.8 (M+2H) ²⁺
247		M2	CH ₂ OH	35%	523.4 (M+2H) ²⁺
248		M2	CH ₂ OH	31%	539.9 (M+2H) ²⁺
249		M2	CH ₂ OH	55%	539.6 (M+2H) ²⁺
250		M2	CH ₂ OH	56%	508.5 (M+2H) ²⁺

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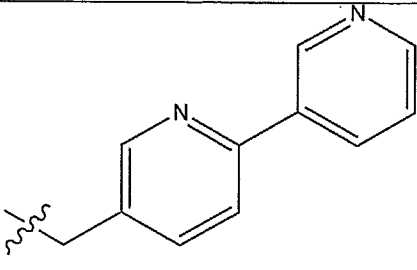
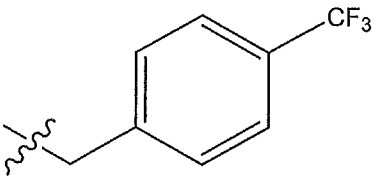
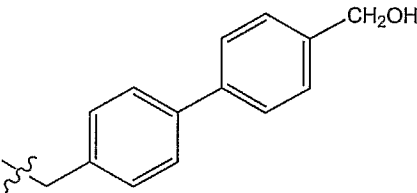
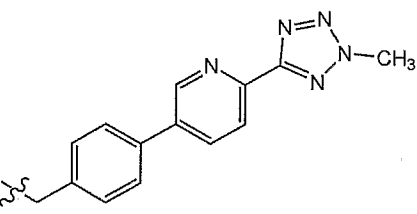
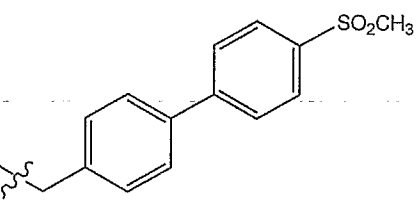
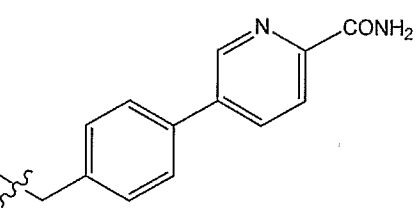
					

251		M2	CH ₂ OH	77%	1056.9 (M+H) ⁺
252		M2	CH ₂ OH	77%	525.2 (M+2H) ²⁺
253		M2	CH ₂ OH	80%	509.2 (M+2H) ²⁺
254		M2	CH ₂ OH	71%	504.2 (M+2H) ²⁺
255		M2	CH ₂ OH	64%	548.1 (M+2H) ²⁺

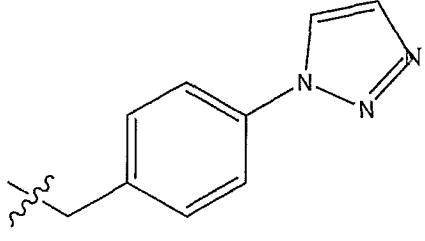
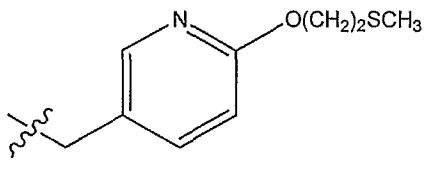
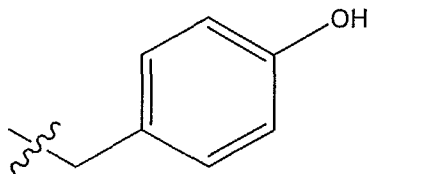
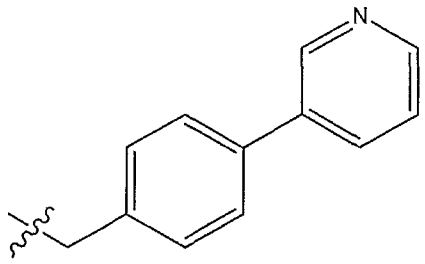
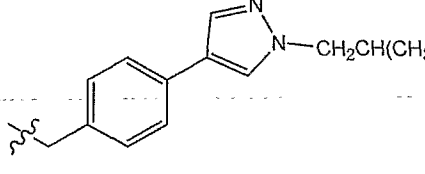
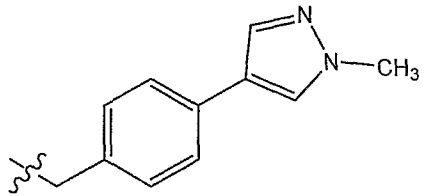
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256		M2	CH ₂ OH	75%	534.1 (M+2H) ²⁺
257		M2	CH ₂ OH	77%	526.1 (M+2H) ²⁺
258		M2	CH ₂ OH	71%	529.0 (M+2H) ²⁺
259		M2	CH ₂ OH	47%	515.7 (M+2H) ²⁺
260		M2	CH ₂ OH	69%	525.1 (M+H) ²⁺
261		M2	CH ₂ OH	98%	522.1 (M+2H) ²⁺

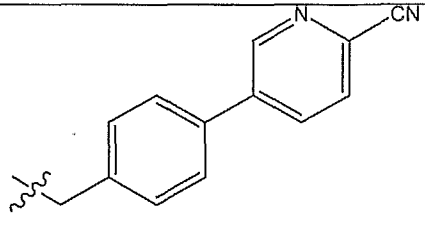
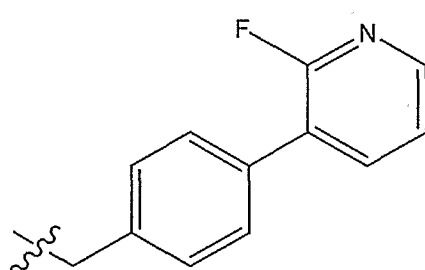
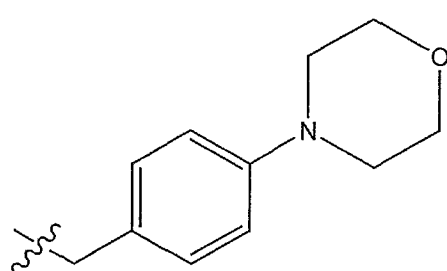
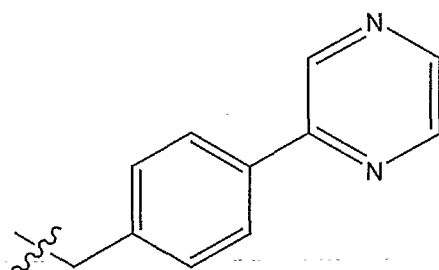
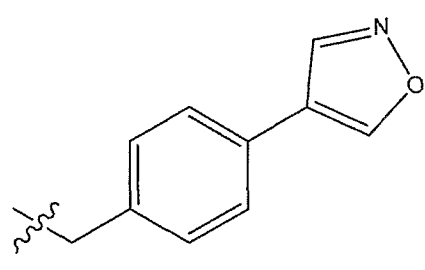
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262		M2	CH ₂ OH	84%	517 (M+2H) ²⁺
263		M2	CH ₂ OH	72%	536.1 (M+2H) ²⁺
264		M2	CH ₂ OH	76%	562.7 (M+2H) ²⁺
265		M2	CH ₂ OH	89%	560.1 (M+2H) ²⁺
266		M2	CH ₂ OH	78%	543.1 (M+2H) ²⁺
267		M2	CH ₂ OH	80%	516.6 (M+2H) ²⁺

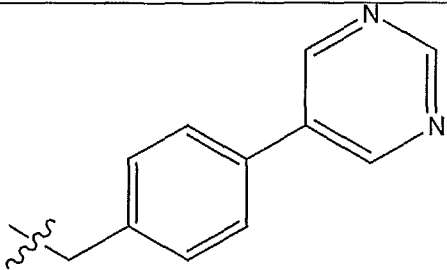
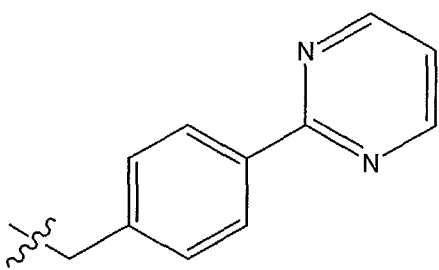
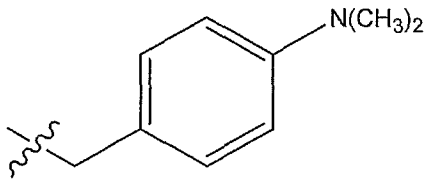
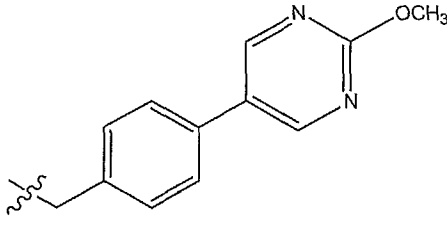
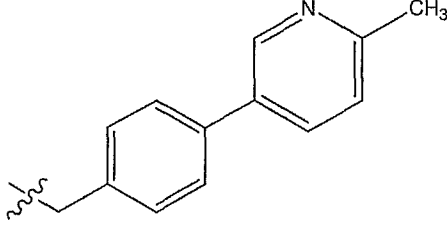
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268		M2	CH ₂ OH	92%	527.8 (M+2H) ²⁺
269		M2	CH ₂ OH	95%	491 (M+2H) ²⁺
270		M2	CH ₂ OH	79%	521.6 (M+2H) ²⁺
271		M2	CH ₂ OH	91%	544.1 (M+2H) ²⁺
272		M2	CH ₂ OH	95%	523.1 (M+2H) ²⁺
273		M2	CH ₂ OH	59%	534.1 (M+2H) ²⁺

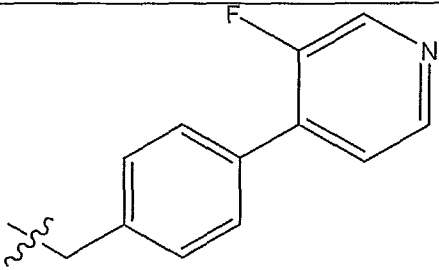
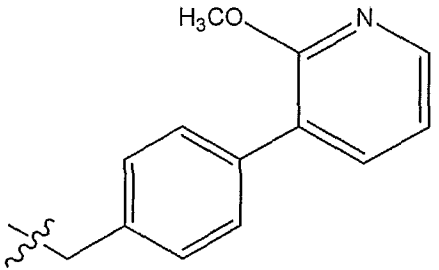
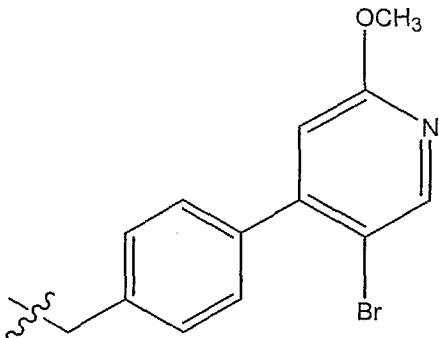
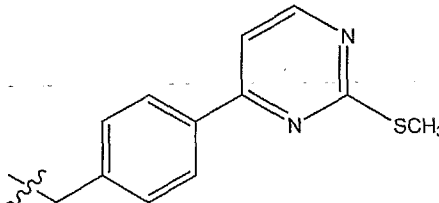
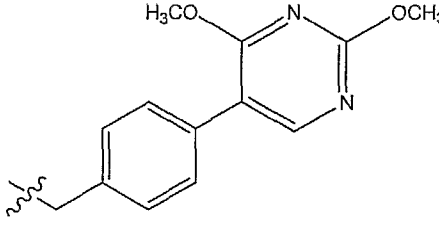
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274		M2	CH ₂ OH	89%	530.3 (M+2H) ²⁺
275		M2	CH ₂ OH	95%	525.6 (M+2H) ²⁺
276		M2	CH ₂ OH	82%	522.1 (M+2H) ²⁺
277		M2	CH ₂ OH	93%	516.6 (M+2H) ²⁺
278		M2	CH ₂ OH	93%	522 (M+2H) ²⁺

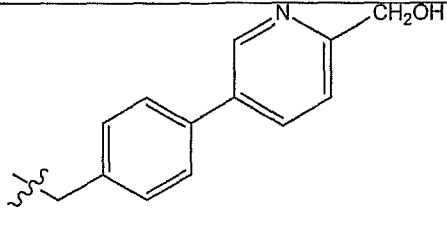
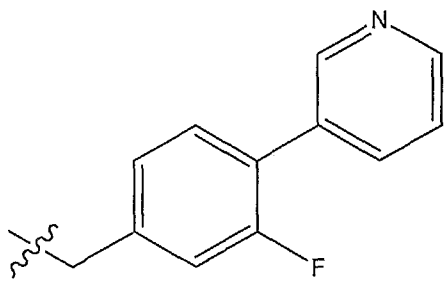
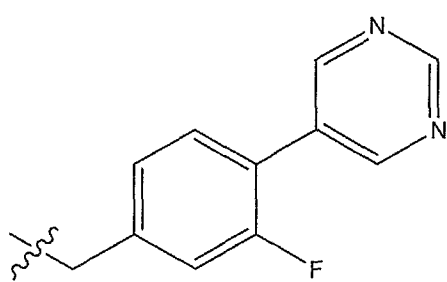
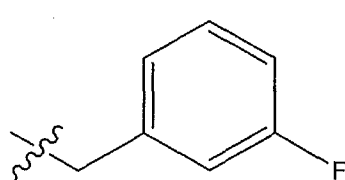
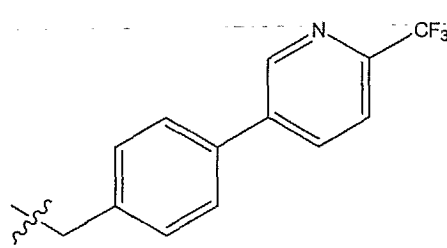
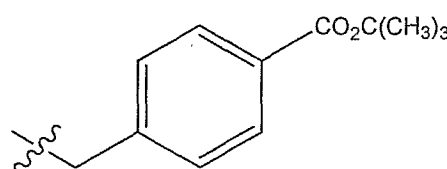
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279		M2	CH ₂ OH	54%	522 (M+2H) ²⁺
280		M2	CH ₂ OH	78%	504.5 (M+2H) ²⁺
281		M2	CH ₂ OH	90%	537.1 (M+2H) ²⁺
282		M2	CH ₂ OH	82%	528.4 (M+2H) ²⁺
283		M2	CH ₂ OH	74%	530.5 (M+2H) ²⁺ 060 (M+H) ⁺

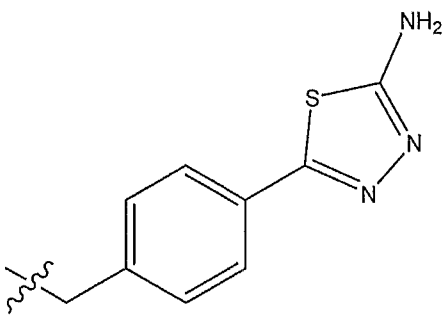
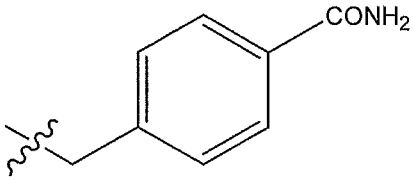
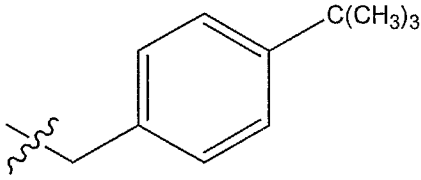
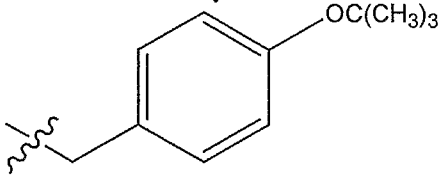
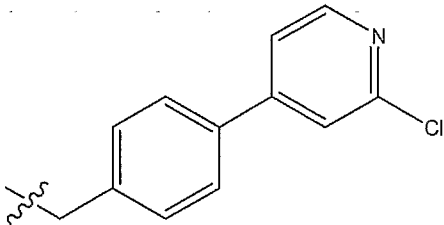
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284		M2	CH ₂ OH	89%	536.6 (M+2H) ²⁺
285		M2	CH ₂ OH	96%	576.5 (M+2H) ²⁺
286		M2	CH ₂ OH	89%	545.1 (M+2H) ²⁺
287		M2	CH ₂ OH	85%	552.2 (M+2H) ²⁺
288		M2	CH ₂ OH	84%	536.5

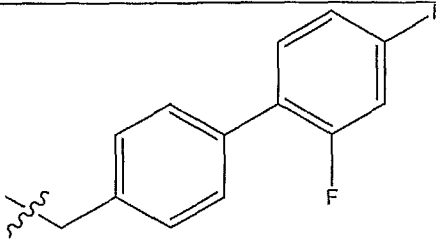
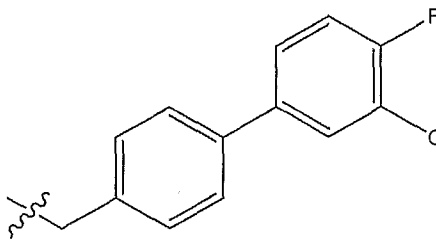
- 296 -

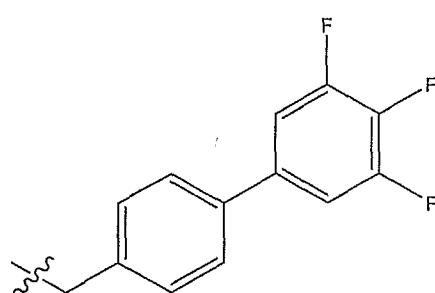
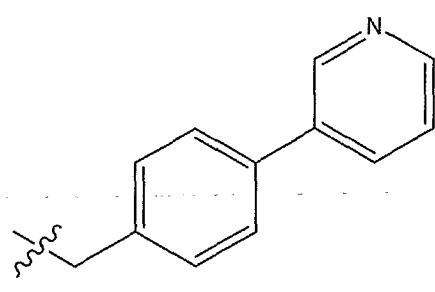
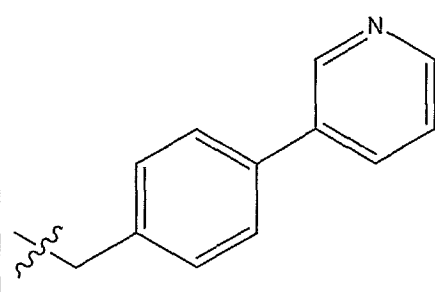
					$(M+2H)^{2+}$
289		M2	CH ₂ OH	94%	530.6 $(M+2H)^{2+}$
290		M2	CH ₂ OH	89%	531.2 $(M+2H)^{2+}$
291		M2	CH ₂ OH	89%	492.2 $(M+2H)^{2+}$
292		M2	CH ₂ OH	81%	555.8 $(M+2H)^{2+}$
293		M2	CH ₂ OH	73%	533.1 $(M+2H)^{2+}$

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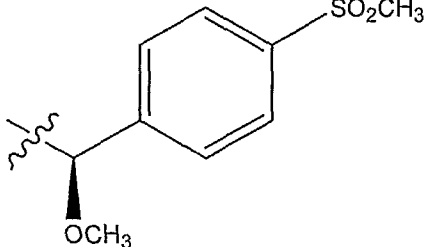
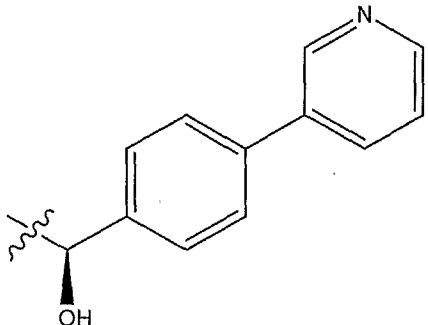
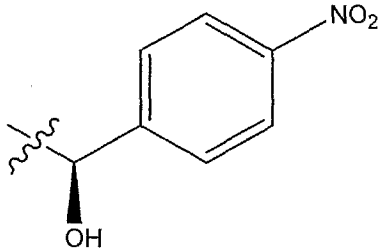
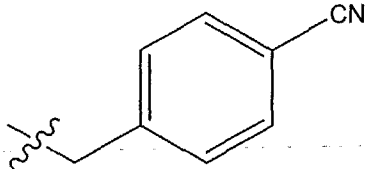
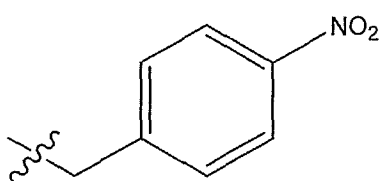
294		M2	CH ₂ OH	63%	532.6 (M+2H) ²⁺
295		M2	CH ₂ OH	40%	504.6 (M+2H) ²⁺
296		M2	CH ₂ OH	91%	511.2 (M+2H) ²⁺
297		M2	CH ₂ OH	77%	519.1 (M+2H) ²⁺
298		M2	CH ₂ OH	98%	538.5 (M+2H) ²⁺
299		M2	CH ₂ OH	49%	539.1 (M+2H) ²⁺

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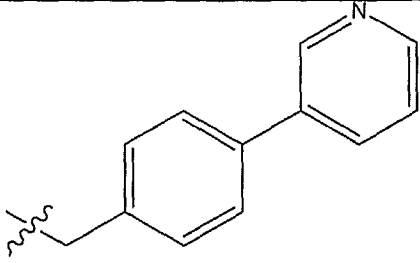
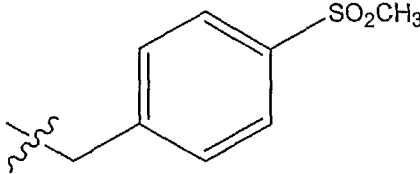
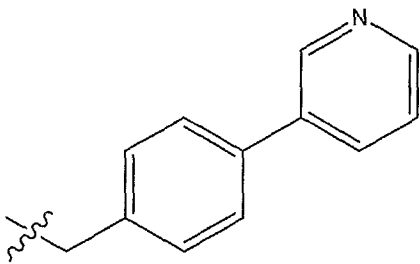
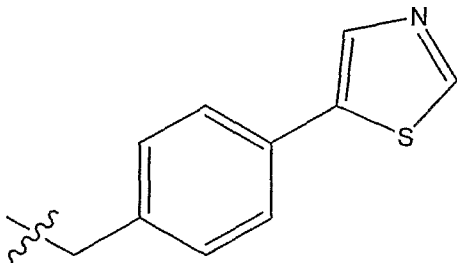
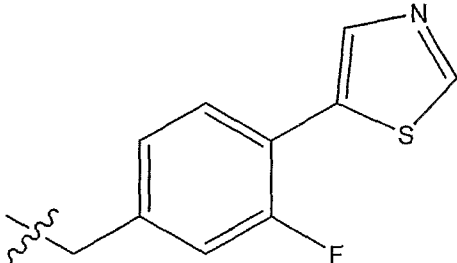
					
300		M2	CH ₂ OH	50%	547.2 (M+2H) ²⁺

301		M2	CH ₂ OH	84%	548.1 (M+2H) ²⁺
302		M2	CH ₂ OH	78%	522.0 (M+2H) ²⁺
303		M2	CH ₂ OH	38%	529.0 (M+2H) ²⁺

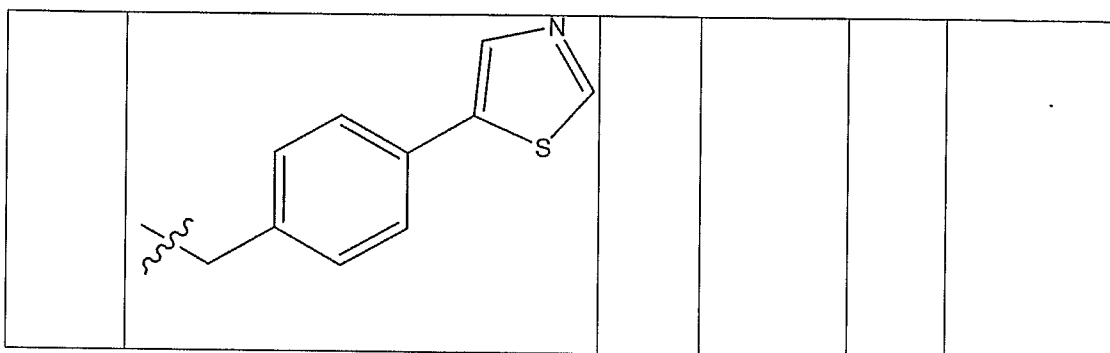
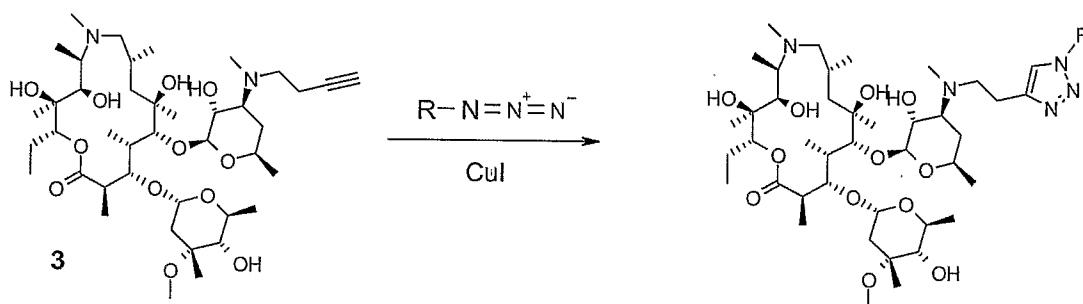
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304		M2	CH ₂ OH	52%	537.1 (M+2H) ²⁺
305		M2	CH ₂ OH	90%	529.6 (M+2H) ²⁺
306		M2	CH ₂ OH	42%	513.6 (M+2H) ²⁺
307		M2	CO ₂ CH ₃	46%	509.5 (M+2H) ²⁺
308		M2A	CH ₂ F	25%	506.1 (M+2H) ²⁺
309		M2A	CH ₂ F	61%	522.1 (M+2H) ²⁺

- 300 -

					
310		M2B	CH ₂ F	83%	536.4 (M+2H) ²⁺
311		M2C	CH ₂ F	80%	535.9 (M+2H) ²⁺
812		M2	CH ₂ F	87%	1050 (M + H) ⁺
813		M2	CH ₂ OH	95%	1066 (M + H) ⁺
814		M3	CH ₂ F	78%	1048 (M + H) ⁺

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**Scheme 101: Synthesis of compounds of Table 2**

Triazoles of Table 2 were produced from alkyne 3 using the corresponding azides using
 5 conditions closely analogous to those described in commonly-owned, previously-filed
 patent applications. The time required for each reaction to proceed to completion was
 variable and was dependent upon several factors including: the specific substrates; the
 amount of Cu(I) salt used; the presence or absence of Hunig's base; and the concentration
 of the reactants. Reactions were monitored for the disappearance of the starting materials
 10 by TLC and/or LCMS and were typically allowed to run for between about 2h to about
 72h. Reactions were stopped when analysis demonstrated that the starting alkyne substrate
 had been substantially consumed. The workup and purification protocols are typical of
 those used previously. Slight modifications to the described workup procedures may have
 been used (such modifications include the use of different aqueous wash solutions,
 15 different organic solvents for extraction, the use of other anhydrous salts for the drying of
 organic extracts, and the employment of different solvent mixtures for the
 chromatographic purification of the compounds). In all cases, the methods used for the
 workup of the reaction mixtures, the extraction of products, the drying of organic extracts,
 and for the isolation and purification of the title compounds were typical of procedures
 20 familiar to those trained in the art of organic synthesis. There were no specific or unusual
 protocols employed in the isolation and purification of the reaction products that were

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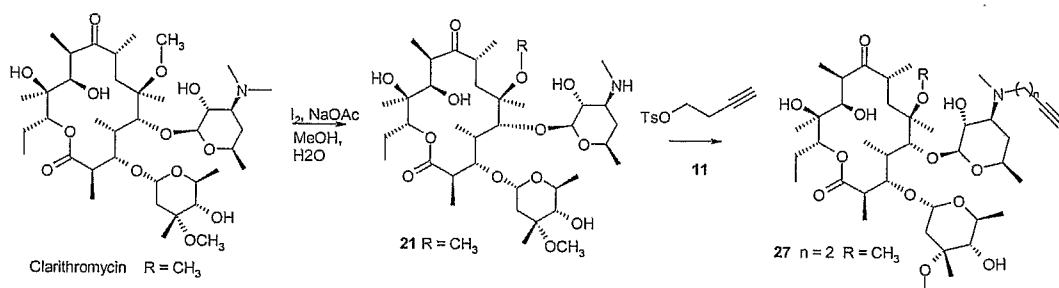
found to be critical in these processes. The isolated chemical yields for the synthesis of compounds **101-311**, **813** and **814** were variable and are indicated in the penultimate column of Table 2.

5 Example 2 - Synthesis of Compounds 401-406

Schemes 103 and 104 below depict the synthesis of compounds **401-406**.

Demethylation of clarithromycin yielded 3'-N-desmethyl-clarithromycin **21**. Amine **21** was selectively *N*-alkylated with tosylates **11** to produce alkyne **27**. As shown in Scheme 104 alkyne **27** is reacted with corresponding azides in the presence of copper (I) iodide to selectively afford the triazoles **401-406**.

Scheme 103: Synthesis of alkyne 27.



15 Synthesis of 3'-N-desmethyl-clarithromycin 21

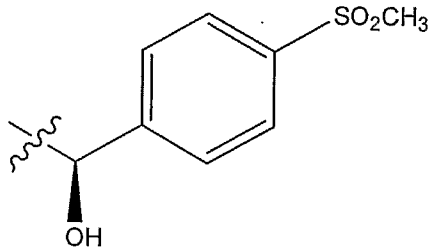
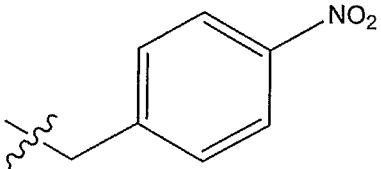
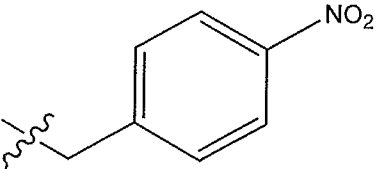
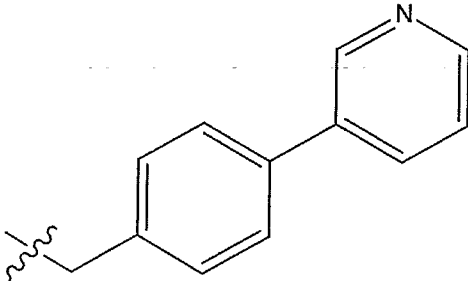
To a mixture of clarithromycin (1.00 g, 1.3 mmol) and NaOAc·3H₂O (0.885 g, 6.5 mmol) was added MeOH-H₂O (20 mL, 4:1), and the mixture heated to 55-60°C. Iodine (0.330 g, 1.3 mmol) was added portion-wise and the reaction stirred at 55-60°C for 3 h. The reaction mixture was poured into 50 mL CHCl₃ containing 1 mL ammonium hydroxide. It was extracted with CHCl₃ (4 x 50 mL), washed with water (70 mL) containing 5 mL ammonium hydroxide, dried (anhydrous Na₂SO₄), concentrated, and purified by flash chromatography (silica gel, CHCl₃:MeOH:NH₄OH 100:10:0.1) to afford **21**. Yield: 0.9g (92%).

Synthesis of alkyne 27

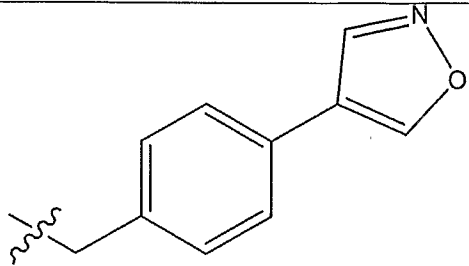
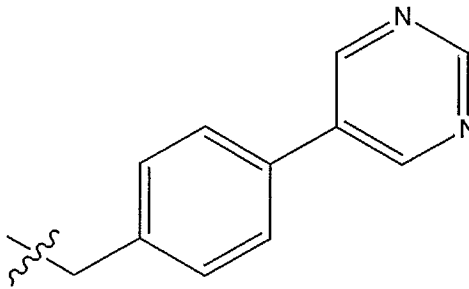
A mixture of 3'-N-desmethyl-clarithromycin **21** and tosylate **11** in anhydrous THF and Hunig's base was stirred. The reaction was poured into CH₂Cl₂, extracted with 2% aqueous NH₄OH and saturated brine. The organic layer was dried over Na₂SO₄ and the

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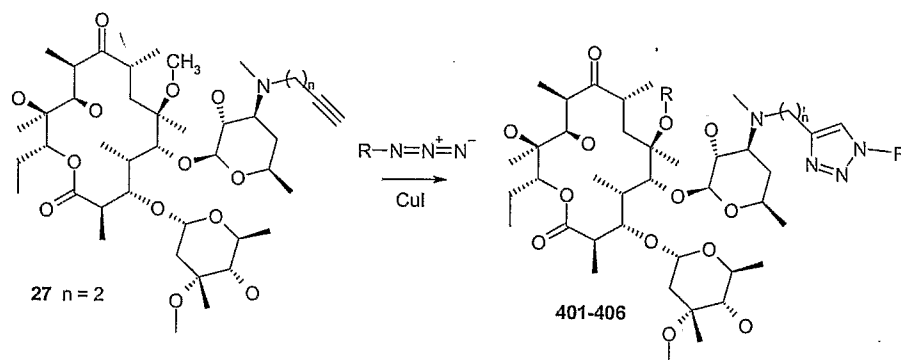
solvent was evaporated away. The crude material was purified on a silica gel column to give 27.

Table 3					
Cmpd	B	Mac	D	Yield	LCMS
401		M3	CH ₂ F	59%	1059.9 (M+H) ⁺ 1081.8 (M+Na) ⁺
402		M3	CH ₂ OH	79%	1008.9 (M+H) ⁺ 1030.9 (M+Na) ⁺
403		M3	CH ₂ F	85%	1010.8 (M+H) ⁺ 1032.8 (M+Na) ⁺
404		M3	CH ₂ F	81%	522.2 (M+2H) ²⁺
405		M3	CH ₂ F	91%	514.6 (M+2H) ²⁺

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406		M3	CH ₂ F	92%	1044.0 (M+2H) ²⁺

Scheme 104: Synthesis of compounds of Table 3



Triazoles **401-406** were produced from alkyne **27** using the corresponding azides under reaction conditions as exemplified above for compounds **101-3119** in Example 1. The use of conditions that do not include the step of degassing the reaction mixture, resulted in the formation of iodinated side-products and generally lower yields. Additionally, reduction of the amount of copper salt used in the reaction to 0.5 molar equivalents or less resulted in reduced formation of iodinated by-products.

The compounds in Table 3 were synthesized using conditions closely analogous to conditions described above. The time required for each reaction to proceed to completion was again variable and was dependent upon the several variables noted above including: the specific substrates, the amount of Copper (I) salt used, the presence or absence of

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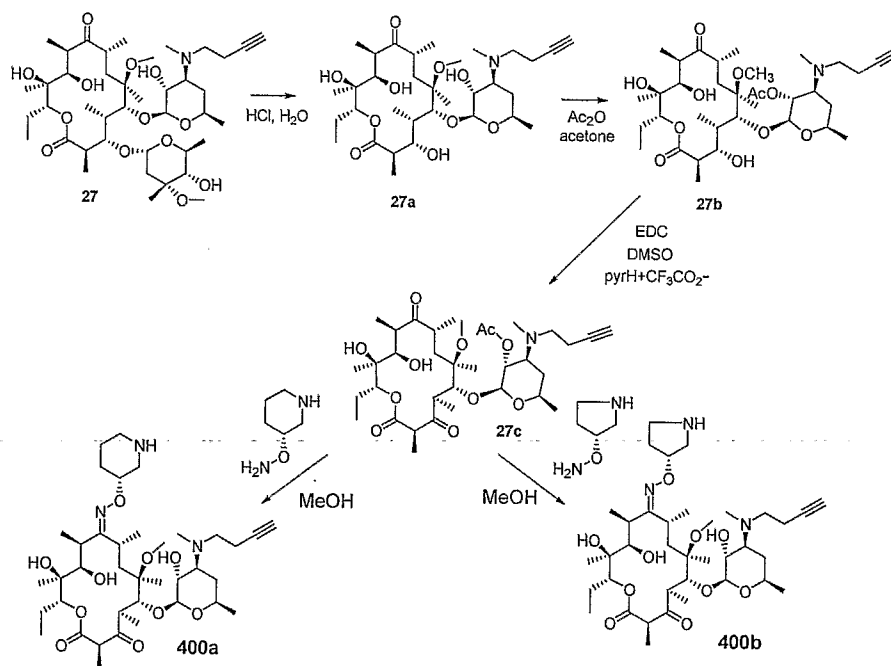
Hunig's base, and the concentration of the reactants. Reactions were monitored for the disappearance of the starting materials by TLC and/or LCMS and were typically allowed to run for between about 2h to about 72h with the majority being about 16h. Reactions were stopped when analysis demonstrated that the starting alkyne substrate had been

5 substantially consumed. The workup and purification protocols are typical of those used for all products in Table 3. Slight modifications to the described workup procedures may have been used as set forth above for the compounds of Table 2.

Example 3: Synthesis of compounds 501-507

10 The oximes **501-507** of Table 4 were synthesized from alkynes **400a** to **400i** by copper(I)-promoted cycloaddition with azides **14a-14gm** in a manner analogous to the procedures presented previously. Alkyne precursors **401a** – **401i** with substituted oxime functionality at the 9-position of the macrocyclic ring were prepared from alkynes **27**, **24**, and as shown below.

15 Scheme 107



Synthesis of alcohol 27a

To the alkyne **27** (0.700 g) was added 10 mL 0.9N HCl and the mixture was stirred for 4

20 h at room temperature. The reaction mixture was saturated with sodium chloride and was

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adjusted to pH 8 using aqueous NH_4OH solution. The solution was extracted with ethyl acetate (3 x 30 mL), dried (with Na_2SO_4), and concentrated under reduced pressure.

Purification of the crude reaction mixture by flash chromatography (silica gel, 60% ethyl acetate in hexane) afforded 0.200 g (35% yield) of the descladinose derivative **27**. Data for **27**: ^1H NMR (300 MHz, CDCl_3 , partial): δ 0.82 (t, 3H), 2.25 (s, 3H), 3.00 (s, 3H), 3.25 (dd, 1H), 3.55 (m, 2H), 3.70 (s, 1H), 3.85 (s, 1H), 3.95 (s, 1H), 4.40 (d, 1H), 5.15 (dd, 1H).

Synthesis of acetate **27b**

To a solution of **27a** (0.200 g, 0.32 mmol) in acetone (2 mL) was added acetic anhydride (0.050 mL, 0.5 mmol) and the mixture was stirred overnight at room temperature. The reaction was quenched with water and extracted with ethyl acetate (3 x 50 mL). The combined organic fractions were washed with saturated sodium bicarbonate (3 x 50 mL), dried (anhydrous Na_2SO_4), and concentrated under reduced pressure. The crude reaction mixture was purified by flash chromatography (silica gel, 50% ethyl acetate in hexane) to yield 0.100 g (50% yield) of acetate **27b**. Data for **27b**: ^1H NMR (300 MHz, CDCl_3 , partial): δ 0.84 (t, 3H), 2.00 (s, 3H), 2.20 (s, 3H), 2.90 (s, 3H), 3.00 (q, 1H), 3.25 (s, 1H), 3.47 (m, 2H), 3.70 (bs, 1H), 3.82 (bs, 1H), 3.97 (s, 1H), 4.60 (d, 1H), 4.77 (dd, 1H), 5.15 (dd, 1H).

Synthesis of ketolide **27c**

To a solution of acetate **27b** (0.090 g, 0.134 mmol), EDC•HCl (0.172 g, 0.90 mmol), and DMSO (0.171 mL, 2.41 mmol) in CH_2Cl_2 (1.5 mL) was added dropwise a solution of pyridinium trifluoroacetate (0.174 g, 0.90 mmol) in CH_2Cl_2 (1 mL) at 15°C . The reaction mixture was slowly warmed up to room temperature and stirred for 3 h. The reaction was quenched with water (2 mL), and allowed to stir for 30 min. The mixture was then poured into CHCl_3 (50 mL), and the organic layer was washed with water (2 x 50 mL), dried (over anhydrous Na_2SO_4), and concentrated under reduced pressure. The crude material was purified by flash chromatography (silica gel, 30% ethyl acetate in hexane) to yield 0.070 g (78%) of the ketolide **27c**. Data for **27c**: MS (ESI) m/e 668 ($\text{M}+\text{H}^+$); ^1H NMR (300 MHz, CDCl_3 , partial): δ 0.86 (t, 3H), 2.00 (s, 3H), 2.24 (s, 3H), 2.70 (s, 3H), 2.95-3.10 (m, 1H), 3.15-3.05 (m, 1H), 3.45-3.65 (m, 1H), 3.80 (q, 1H), 3.90 (s, 1H), 4.28 (d, 1H), 4.40 (d, 1H), 4.76 (dd, 1H), 5.10 (dd, 1H).

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Synthesis of oxime 400a

To a solution of **27c** (2.0 g, 2.9 mmol) in MeOH (10 mL) was added (R)-*N*-Piperidin-3-yl-hydroxylamine hydrobromide (1.26 g, 4.4 mmol). The reaction mixture was stirred at rt
 5 for 14h. The mixture was then poured into (50 mL) and water (50 mL) the pH was adjusted to 11 by addition of NH₄OH and the organic layer was separated and washed with brine (50 mL), dried (over anhydrous Na₂SO₄), and concentrated under reduced pressure. The crude material was purified by flash chromatography (silica gel, 12:1 CH₂Cl₂ and 2M methanolic ammonia) to yield 2g (78%) of the oxime **400a** as a 1:1 mixture of E/Z
 10 isomers. Data for **400a**: MS (ESI) *m/e* 724.7 (M+H)⁺.

Synthesis of oxime 400b

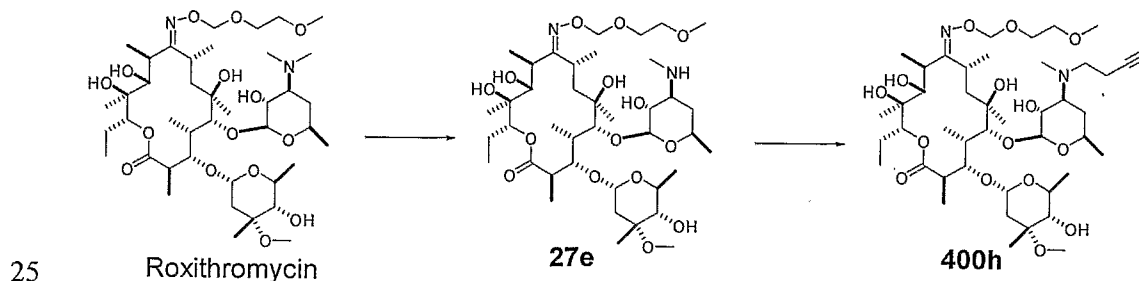
Oxime **400b** was synthesized from alkyne **27c** and (R)-*N*-Pyrrolidin-3-yl-hydroxylamine hydrobromide using the conditions described above for the synthesis of oxime **400a**. Data
 15 for **400b**: MS (ESI) *m/e* 710.6 (M+H)⁺.

Synthesis of oxime triazoles 426 and 431

These triazoles were synthesized from the alkyne **400a** and the azides indicated in Table 6 using the standard copper-promoted cycloaddition conditions as previously described.
 20

Synthesis of oxime triazoles 433

These triazoles were synthesized from the alkyne **400b** and the azides indicated in Table 6 using the standard copper-promoted cycloaddition conditions as previously described.

Scheme 112 Synthesis of intermediate 400h**Synthesis of compound 27e**

To a mixture of Roxithromycin (850mg, 0.914mmol, 90%) and NaOAc (828mg, 10.000mmol) in a mixture of MeOH (6.0mL) and water (1.5mL) at 48°C was added I₂ in

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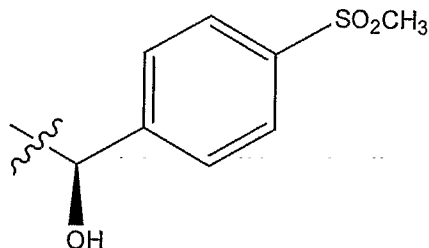
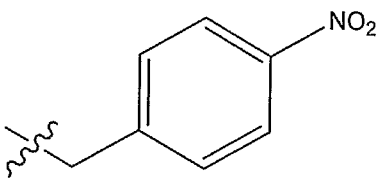
four portions (each portion: 63.5mg) over 30min, after each portion I_2 , followed by 1N NaOH (400 μ L). The reaction was continued for 30min. The solvent was removed and EtOAc (100mL) was added, followed by water (20mL). The organic phase was washed with brine (40mLX2), dried with Na₂SO₄. The residue was separated by FC (6/94/0.2 MeOH/CH₂Cl₂/NH₄OH), gave 600mg compound **27e** in 80% yield. LCMS (ESI) m/e 824 (M+H)⁺.

Synthesis of compound 400h

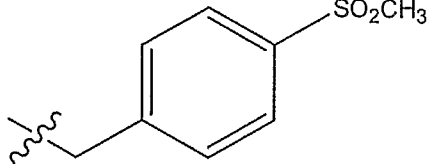
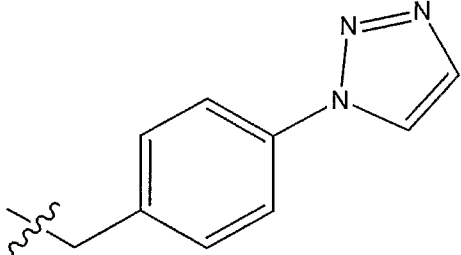
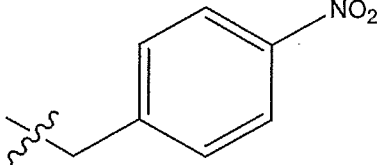
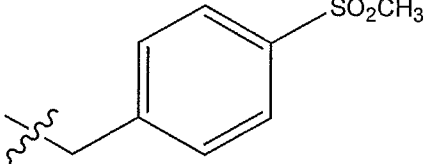
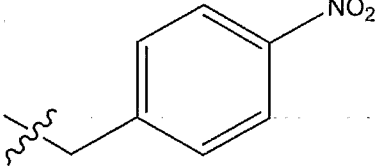
A mixture of compound **27e** (500mg, 0.608mmol) and toluene-4-sulfonic acid but-3-ynyl ester in a mixture solvents of THF (5.4mL) and Hunig's base (1.6mL) was refluxed for 48hr. The reaction mixture was concentrated, then, EtOAc (100mL) was added. The organic layer was washed with Sat. NaHCO₃ (20mL), and brine (50mL). Compound **400h** was isolated by FC (3/100/0.2 MeOH/CH₂Cl₂/NH₄OH), gave 316mg in 59% yield. LCMS (ESI) m/e 876 (M+H)⁺.

Synthesis of compound 447

This compound was synthesized from alkyne **400h** and azide **14bt** using the conditions described in Example 1.

Table 4					
Cmpd	B	Mac	D	Yield	LCMS
501		M3B	CH ₂ F	48%	459.0 (M+2H) ²⁺ 919.9 (M + H) ⁺
502		M3B	CH ₂ OH	66%	451.1 (M+2H) ²⁺ 902.7 (M + H) ⁺
503		M3B	CH ₂ F	43%	491.6 (M+2H) ²⁺

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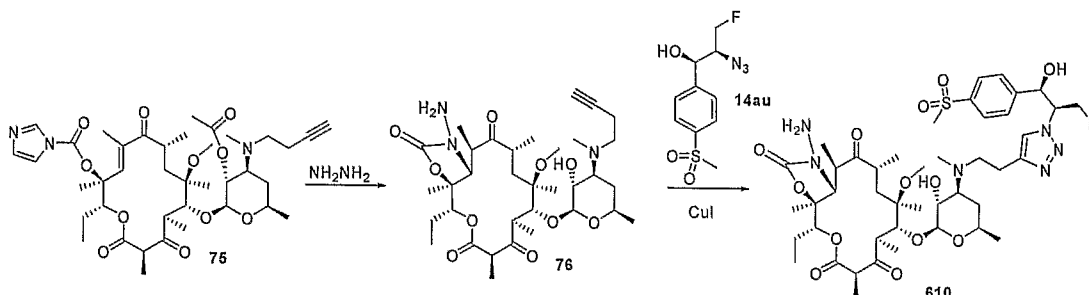
					
504		M3B	CH ₂ F	50%	485.9 (M+2H) ²⁺
505		M3C	CH ₂ OH	45%	444.9 (M+2H) ²⁺ 888.6 (M + H) ⁺
506		M3C	CH ₂ F	46%	584.5 (M+2H) ²⁺
507		M3D	CH ₂ F	86%	550 (M+2H) ²⁺ 1100 (M + H) ⁺

Example 4 synthesis of compounds 601-607

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Synthesis of compound 610

Scheme 155



A solution of acylimidazole **75** (0.74 g, 1.0 mmol) in acetonitrile (20 mL) and H₂O (3 mL) was treated with hydrazine monohydrate (0.50 mL, 10 mmol) and stirred at 50 °C for 1 h. The reaction mixture was evaporated to yellow foam and redissolved in methanol (50 mL) and heated to reflux for 20 h. Solvent was evaporated purification by flash chromatography (SiO₂, 50–100% ethyl acetate/hexanes) provide the alkyne carbazate **76** (0.50 g, 0.75 mmol) as a white powder.

A solution of **76** (0.10 g, 0.15 mmol) in tetrahydrofuran (3.0 mL) was treated with azide **14au** (62 mg, 0.22 mmol), diisopropylethylamine (0.080 mL, 0.46 mmol), and copper (I) iodide (8.0 mg, 0.042 mmol) and stirred at 23 °C for 24 h. The reaction mixture was diluted with ammonium hydroxide (30 mL) and extracted with dichloromethane (3 × 30 mL), dried (Na₂SO₄), and evaporated. Preparative thin-layer chromatography (SiO₂, 10% methanol/dichloromethane, then ethyl acetate) provided **610** (98 mg, 0.10 mmol) as a white solid: LCMS (ESI) *m/e* 940 (M+H)⁺.

Synthesis of compound 612

Compound **612** was synthesized from alkyne **27d** and azide **14au** using the copper catalyzed cycloaddition conditions of Example 1.

Example 5 - Synthesis of Compounds 702-706

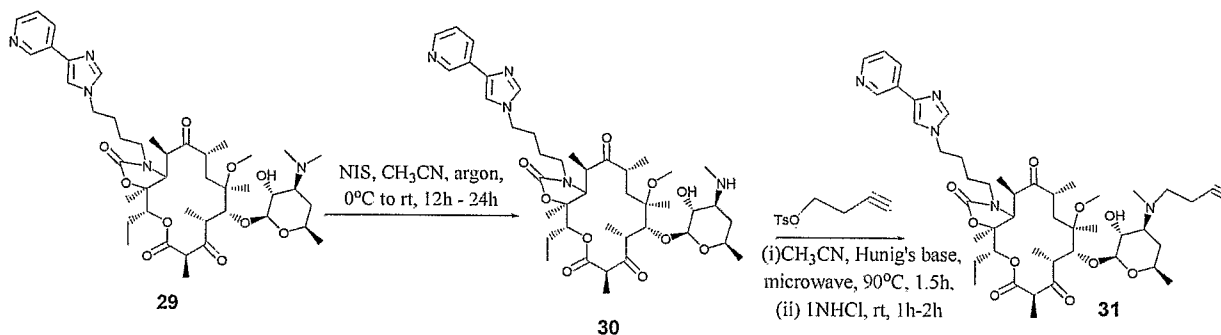
Compounds **702-706** shown in Table 6 were derived from telithromycin, as well as additional macrolides. Using methodology analogous to that described above for the compounds of Tables 2 and 3, telithromycin was selectively *N*-demethylated and then alkylated with tosylate **11** as described for azithromycin, erythromycin and clarithromycin above. The resulting alkyne was elaborated to the corresponding triazoles using the same copper catalyzed [3 + 2] cycloaddition reaction with azides discussed above.

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Synthesis of 3'-N-Desmethyl telithromycin 30:

To a solution of telithromycin **29** (3.0 g, 3.60 mmol) in anhydrous acetonitrile (70 mL) was added N-iodosuccinimide (NIS) (0.98 g, 4.32 mmol) in two portions within 30 min at 0°C under argon atmosphere. The mixture was allowed to warm to rt and stirred overnight.

5 CH_2Cl_2 (250 mL) and 5 % $\text{Na}_2\text{S}_2\text{O}_3$ (80 mL) were added and the two layers separated. The organic layer was extracted with 5 % $\text{Na}_2\text{S}_2\text{O}_3$ (1 X 80 mL), dilute NH_4Cl (1 X 80 mL) and dried over Na_2SO_4 . Solvent was evaporated and the crude was purified on silica gel eluting with 0 – 8 % methanolic ammonia (2N NH_3) in CH_2Cl_2 to give compound **30** as white solid (1.95 g, 68 %). MS (ESI) m/e ; $\text{M}+\text{H}^+$ 798.6.

10 **Scheme 105 Synthesis of alkyne 31.****Synthesis of 3'-N-(but-3-ynyl) telithromycin 31:**

Protocol A: A mixture of amine **30** (0.66 g, 0.83 mmol) and tosylate **11** (0.33 g, 1.49 mmol) in THF (15 mL) and Hunig's base (3 mL) was heated at 90°C for 5 days. The solvent was evaporated; the residue was dissolved in 1N HCl (50 mL) and kept stirring at room temperature for about 1h. CH_2Cl_2 (30 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 X 30 mL) and basified with NaOH (1N) to form a whitish-suspension. The suspension was extracted with CH_2Cl_2 (3 X 30 mL) and the organic layer was dried over Na_2SO_4 . Solvent was evaporated and the crude was purified on silica gel eluting with 0 – 6 % methanolic ammonia (2N NH_3) in CH_2Cl_2 to give compound **31** as white solid (0.12 g, 17 %). MS (ESI) m/e 850.8 ($\text{M}+\text{H}^+$).

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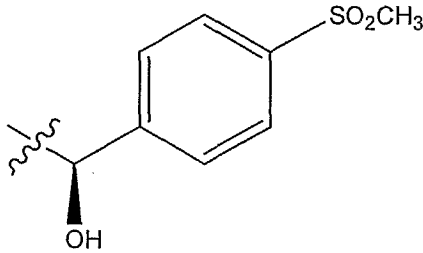
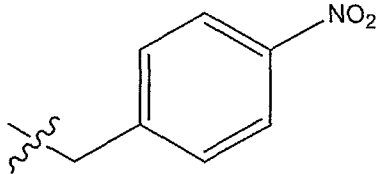
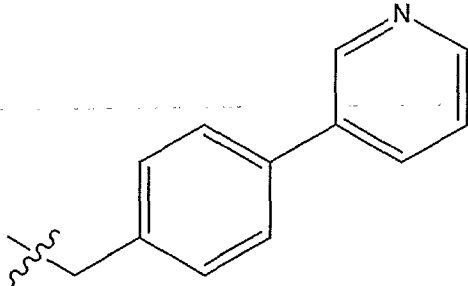
Synthesis of 3'-N-(but-3-ynyl) telithromycin 31:

Protocol B: A mixture of amine **30** (0.66 g, 0.83 mmol), and tosylate **11** (0.40 g, 1.84 mmol) in acetonitrile (10 mL) and Hunig's base (0.18 mL, 1.0 mmol) was microwave heated to 90°C within 10 min and maintained at 90°C for 1.5h. The reaction was vented within 15 min and solvent was evaporated. The residue was dissolved in 1N HCl (60 mL) and kept stirring at room temperature for about 2h. CH_2Cl_2 (30 mL) was added and the

25

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- two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 X 30 mL) and basified with 50 % KOH to form a whitish-suspension. The suspension was extracted with CH_2Cl_2 (3 X 30 mL) and the organic layer was dried over Na_2SO_4 . The solvent was evaporated and the crude was purified by preparative TLC (2000 micron plate) eluting with CH_2Cl_2 /methanolic ammonia (2N NH_3) 12:1 to give compound **31** as white solid (0.19 g, 27 %). MS (ESI) m/e 850.8 ($\text{M}+\text{H}$)⁺.

Table 5					
Cmpd	B	Mac	D	Yield	LCMS
601		M4A	CH_2F	20%	940 ($\text{M}+\text{H}$) ⁺
602		M4A	CH_2F	65%	890 ($\text{M}+\text{H}$) ⁺
603		M4A	CH_2F	42%	462.0 ($\text{M}+2\text{H}$) ²⁺
604		M4A	CH_2F	80%	457 ($\text{M}+2\text{H}$) ²⁺ , 912.7 ($\text{M}+\text{H}$) ⁺

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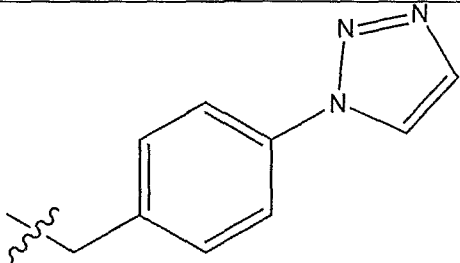
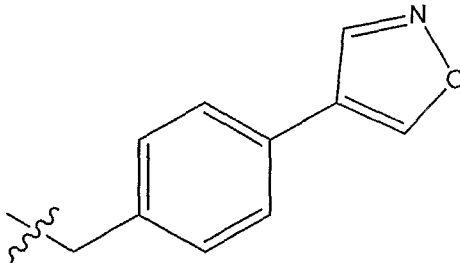
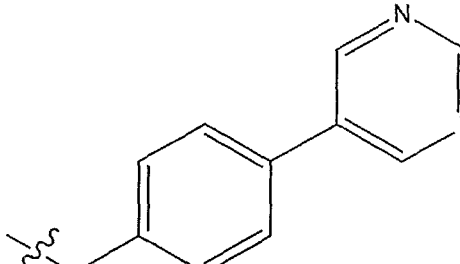
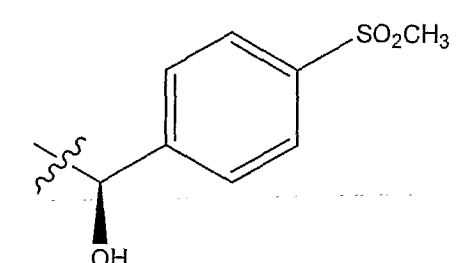
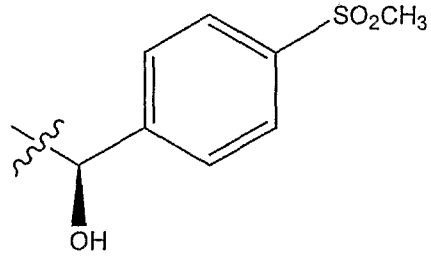
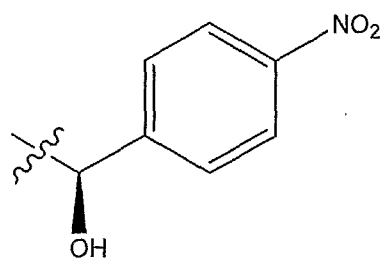
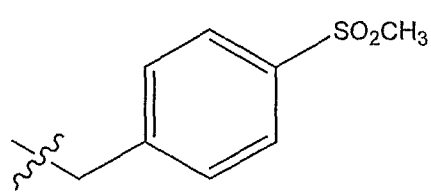
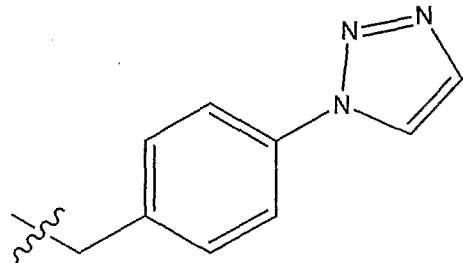
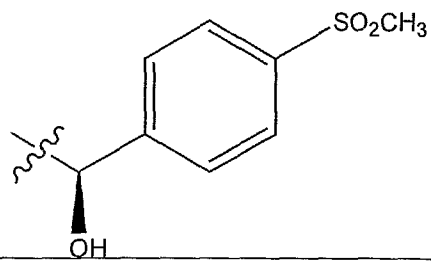
					
605		M4A	CH ₂ F	73%	457.0 (M+2H) ²⁺
606		M4A	CH ₂ F	74%	462.6 (M+2H) ²⁺
607		M8	CH ₂ F	31%	899 (M + H) ⁺

Table 6

Cmpd	B	Mac	D	Yield	LCMS

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702		M4B	CH ₂ F	66%	545.8 (M+2H) ²⁺
703		M4B	CH ₂ OH	38%	562.8 (M+2H) ²⁺
704		M6	CH ₂ F	80%	467.4 (M+2H) ²⁺
705		M6	CH ₂ OH	83%	461.0 (M+2H) ²⁺
706		M7	CH ₂ F	6%	864 (M+H) ⁺

Triazoles **702 -706** were produced from alkyne **31** using the corresponding azides under reaction conditions similar to those described above for the compounds of Tables 4 and 5. As above, the use of conditions which did not include the step of degassing the

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reaction mixture, resulted in the formation of iodinated side-products and generally lower yields. Additionally, reduction of the amount of copper salt used in the reaction to 0.5 molar equivalents or less resulted in reduced formation of iodinated by-products.

The procedure for the synthesis of the compounds in Table 6 is similar to that
5 described in Example 1, the time required for each reaction to proceed to completion was again variable and was dependent upon the several variables noted above including: the specific substrates, the amount of Copper (I) salt used, the presence or absence of Hunig's base, and the concentration of the reactants. Reactions were monitored for the
10 disappearance of the starting materials by TLC and/or LCMS and were typically allowed to run for between about 6h to about 24h and were stopped when analysis demonstrated that the starting alkyne substrate had been substantially consumed. The workup and purification protocols exemplified in conditions A-D in Example 1 are typical of those used for all products in Table 6. Slight modifications to the described workup procedures may have been used as described above in Example 1 for the synthesis of compounds of
15 Table 4.

Example 6 - Synthesis of azides 14

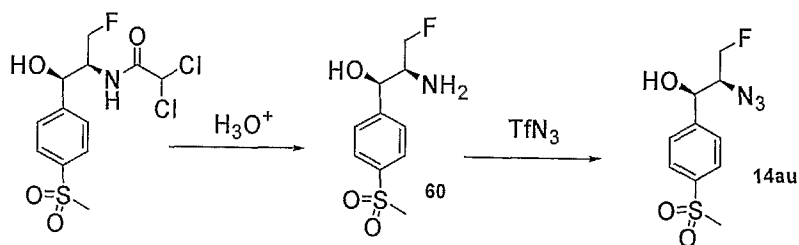
The azides **14** shown in Table 7 were used to synthesize numerous compounds of the invention. The azides were readily synthesized by methods known from the literature.
20 Exemplary azide syntheses are presented below. The remaining azides of Table 7 were synthesized in analogous fashion from appropriate commercial starting materials.

TABLE 7

Structure	Compound	Structure	Compound	Structure	Compound	Structure	Compound
	14s		14bt		14eo		14du
	14cv		14ev		14eq		14fx
	14cy		14gj		14er		14ed
	14fr		14au		14es		14ef
	14fu		14ah		14eu		14eg
	14ag		14ai		14bq		14eh
	14aj						

The majority of the azides in Table 7, and additional azides, were synthesized according to known procedures and the specific route used for each azide was determined by the available commercial starting materials. When possible, azides were produced from the corresponding substituted alkyl bromides by direct displacement with azide ion. When the required alkyl bromides were not readily available, the compounds were derived from substituted alkanols: to accomplish this, the alcohols were first activated as their sulfonyl ester derivatives and then substituted with azide ion. If neither the required bromides nor alkanols were commercially available, the azides were synthesized from the corresponding carboxylic acids by reduction with borohydride to the corresponding alcohols. The resulting alkanols were then treated as above to yield the azides. Finally, some azides of Table 7 were synthesized from the corresponding substituted alkyl amines by reaction with triflic azide. In a few cases, azides were synthesized by modification of other azides that had been synthesized according to the methodologies above.

Scheme 127. Synthesis of azide **14au**



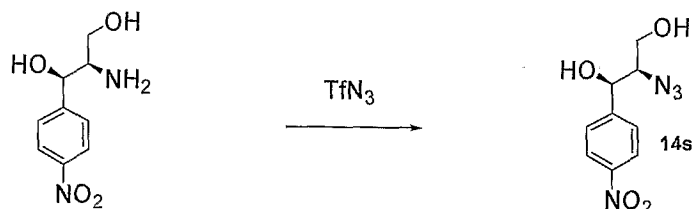
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Synthesis of 14au

A solution of florfenicol (0.090 g, 0.25 mmol) in acetic acid (3.0 mL) was treated with sulfuric acid (10%, 15 mL) and heated to 110 °C for 12 h. The reaction mixture was cooled to room temperature, treated with 10 M aqueous sodium hydroxide to adjust the pH to 14, extracted with dichloromethane (3 × 30 mL), dried (Na₂SO₄), and evaporated to provide florfenicol amine **60** (65 mg, 0.25 mmol) as a yellow oil.

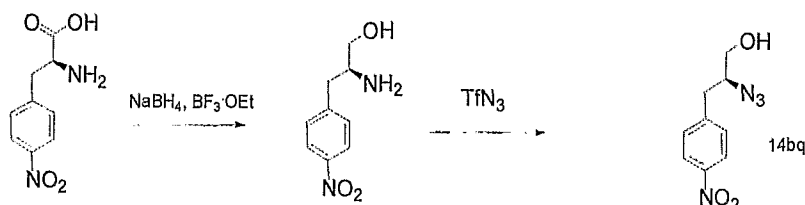
A solution of florfenicol amine **60** (0.90 g, 3.6 mmol) in H₂O (10 mL) and methanol (30 mL) was treated with triethylamine (1.5 mL, 10.8 mmol) and trifluoromethanesulfonyl azide (13.4 mmol dissolved in 20 mL of dichloromethane; solution prepared according to method described in *J. Am. Chem. Soc.* **2002**, *124*, 10773), and stirred at 0 °C 3 h and then warmed to 23 °C for 1 h. The reaction mixture was diluted with H₂O (30 mL), extracted with dichloromethane (30 mL) and evaporated. Flash chromatography (SiO₂, 50–100% ethyl acetate/hexanes) provided azide **14au** (0.65 g, 2.4 mmol) as a yellow solid.

15 Scheme 128. Synthesis of azide **14s**

**Synthesis of azide 14s**

A solution of D-(-)-threo-2-amino-1-(4-nitrophenyl)-1,3-propanediol (0.42 g, 2.0 mmol) in H₂O (5 mL) and methanol (17 mL) was treated with triethylamine (0.84 mL, 6.0 mmol) and trifluoromethanesulfonyl azide (3.0 mmol dissolved in 5 mL of dichloromethane; solution prepared according to method described in *J. Am. Chem. Soc.* **2002**, *124*, 10773), and stirred at 23 °C for 3 h. The reaction mixture was diluted with H₂O (30 mL), extracted with dichloromethane (30 mL) and evaporated. Flash chromatography (SiO₂, 50–100% ethyl acetate/hexanes) provided azide **14s** (0.28 g, 1.2 mmol) as a yellow solid.

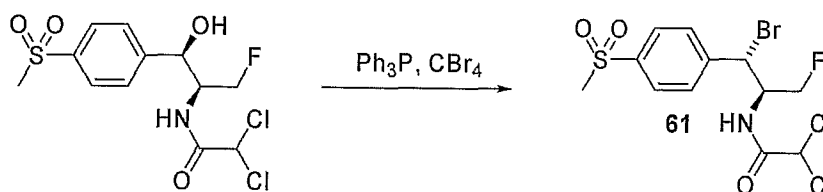
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Scheme 129. Synthesis of azide **14bq**Synthesis of azide **14bq**

To a stirred 0°C solution of 4-nitrophenylalanine (4.6g, 20 mmol) and NaBH₄ (3.2g, 84 mmol) in THF (50 mL) was added BF₃·OEt (14.8 mL, 106 mmol). The reaction was warmed to rt and stirred for 24h. The mixture was cooled to 0°C and quenched with methanol. The reaction mixture was filtered and the filtrate concentrated to give a solid residue. 10% of this residue was dissolved in water (5mL), methanol (20mL) and triethyl amine (0.9 mL). Triflic azide solution (3.5 mmol dissolved in 7 mL of dichloromethane; solution prepared according to method described in *J. Am. Chem. Soc.* **2002**, *124*, 10773) was added and the mixture was stirred at rt for 14h. The reaction mixture was diluted with dichloromethane (30mL) washed with saturated NaHCO₃, and with brine. The organic extract was dried, filtered and concentrated to give **14bq** as a white solid (150mg)

Synthesis of azide **14ed**

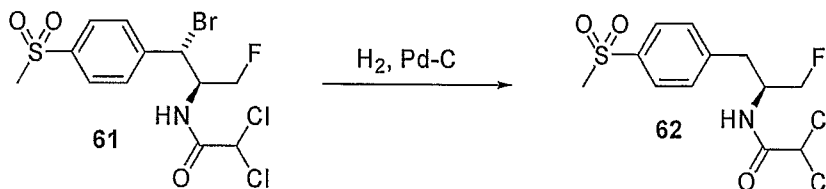
Scheme 130



A solution of florfenicol (0.494 g, 1.38 mmol) in acetonitrile (15.0 mL) was treated with carbontetrabromide (0.594 g, 1.66 mmol) and triphenylphosphine (0.434 g, 1.66 mmol), and stirred at 23 °C for 12 h. The reaction mixture evaporated to a yellow residue and purified by flash chromatography (SiO₂, 10% ethyl acetate/dichloromethane) to provide **61** (0.28 g, 0.67 mmol) as a white powder.

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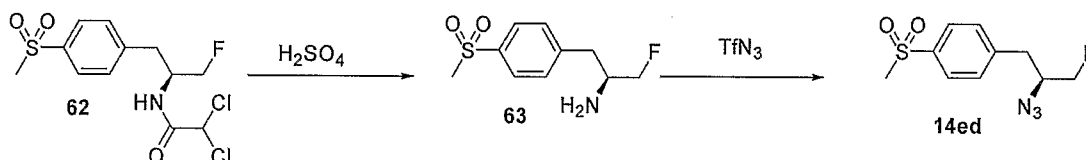
Scheme 131



A solution of **61** (0.20 g, 0.41 mmol) in methanol (5.0 mL) was treated with 10% palladium on charcoal (20 mg) and stirred at 23 °C for 2 h under a balloon of hydrogen.

- 5 The reaction mixture was filtered, evaporated and purified by preparative thin-layer chromatography (SiO₂, 10% ethyl acetate/dichloromethane) to afford **62** (90 mg, 0.26 mmol) as a white film.

Scheme 132



- 10 A solution of **62** (90 mg, 0.26 mmol) in acetic acid (3.0 mmol) was treated with 10% sulfuric acid (15 mL) and heated to 110 °C for 12 h. The reaction mixture was cooled to room temperature, treated with 10 M aqueous sodium hydroxide to adjust the pH to 14, extracted with dichloromethane (3 × 30 mL), dried (Na₂SO₄), and evaporated to provide crude **63** as a yellow oil. A solution of this crude amine (83 mg) in methanol (3.6 mL) and dichloromethane (3.0 mL) was cooled to 0 °C and treated with triethylamine (0.14 mL, 1 mmol) and triflic azide (1.2 mL of a 0.3 M solution in dichloromethane) and allowed to warm to 23 °C. After 2 h, the reaction mixture was evaporated and purified by preparative thin-layer chromatography (SiO₂, 10% ethyl acetate/dichloromethane) to afford the **63** (60 mg, 0.23 mmol) as a colorless oil.

20 Synthesis of azide **14ag**

Azide **14ag** was synthesized from 1S, 2S 2-Amino-1-(4-methylsulfonyl-phenyl)-propane-1,3-diol using the procedure described for the synthesis of azide **14bq**.

Synthesis of azide **14bn** from azide **14bk**

- 25 Azide **14bn** was prepared from **14bk** according to the procedure described for the synthesis of azide **14bp**.

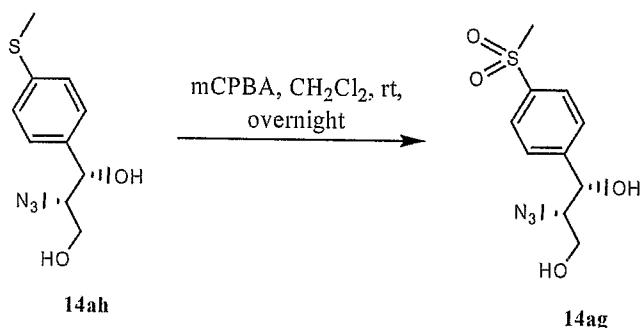
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Scheme 149

**Synthesis of azide 14bt from azide 14bq**

To a stirred -78°C solution of azide **14bt** (111 mg, 0.5 mmol) in CH_2Cl_2 was added (diethylamino)sulfur trifluoride (DAST) (0.1 mL, 0.82 mmol). The reaction was stirred at -78°C for 2h, then allowed to warm to rt and stirred for 14h. The reaction mixture was poured into water and extracted with CH_2Cl_2 . The organic extracts were dried, filtered, and concentrated to give **14bq** as a solid (36mg, 0.16 mmol).

Scheme 151

**Synthesis of azide 14ah from 14ag**

To a solution of azide **14ah** (0.27 g, 1.1 mmol) in CH_2Cl_2 (15 mL) was added mCPBA (1.10 g, 4.5 mmol) and the mixture was stirred at room temperature overnight. Solvent was evaporated and the crude was purified on silica gel eluting with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 20:1 to 15:1 to 12:1 to give azide **14ag** as colorless paste that solidified on standing (0.26 g, 87 %).

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 can 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.

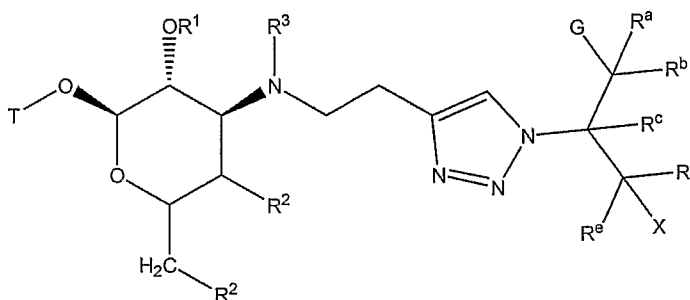
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Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

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What is claimed is:

1. A compound having the structure:



- or a pharmaceutically acceptable salt, ester, *N*-oxide, or prodrug thereof,
wherein
- T is a 14- or 15-membered macrolide connected via a macrocyclic ring carbon atom;
X is selected from (a) H, (b) halogen, (c) a C₁₋₆ alkyl group, (d) a C₂₋₆ alkenyl group, (e) a C₂₋₆ alkynyl group, (f) -OH, (g) -OR⁵, (h) -NR⁴R⁴, (i) -C(O)R⁵, (j) -C(O)OR⁵, (k) -C(O)-NR⁴R⁴, (l) -C(S)R⁵, (m) -C(S)OR⁵, (n) -C(O)SR⁵, (o) -C(S)-NR⁴R⁴, (p) -N₃, (q) -CN, (r) -CF₃, (s) -CF₂H, (t) -CFH₂, (u) -S(O)_pH, (v) -SR⁵, (w) -S(O)_pOH, (x) -S(O)_pOR⁵, (y) -S(O)_pNR⁴R⁴, (z) -S(O)_pC₁₋₆alkyl, (aa) -S(O)_paryl, (bb) a C₃₋₇ saturated, unsaturated, or aromatic carbocycle, and (cc) a 3-7 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur;
- R^a and R^b independently are selected from: (a) H, (b) a C₁₋₆ alkyl group, (c) a C₂₋₆ alkenyl group, (d) a C₂₋₆ alkynyl group, (e) -OH, (f) -OR⁵, (g) -NR⁴R⁴, (h) -C(O)R⁵, (i) -C(O)OR⁵, (j) -C(O)-NR⁴R⁴, (k) -C(S)R⁵, (l) -C(S)OR⁵, (m) -C(O)SR⁵, (n) -C(S)-NR⁴R⁴, or (m) halogen, (n) -SH, (o) -SR⁵;
- or alternatively R^a and R^b are taken together with the carbon to which they are attached to form (a) -C(O)-, (b) -C(S)-, (c) -C=NR⁴, (d) -C=NOR⁵, wherein (b) -(d) are further optionally substituted with one or more R⁵;
- R^c is selected from: (a) H, (b) a C₁₋₆ alkyl group, (c) a C₂₋₆ alkenyl group, (d) a C₂₋₆ alkynyl group, (e) -OH, (f) -OR⁵, (g) -NR⁴R⁴, (h) -C(O)R⁵, (i) -C(O)OR⁵, (j) -C(O)-NR⁴R⁴, (k) -C(S)R⁵, (l) -C(S)OR⁵, (m) -C(O)SR⁵, (n) -C(S)-NR⁴R⁴, or (m) halogen;
- R^d and R^e independently are selected from: (a) H, (b) a C₁₋₆ alkyl group, (c) a C₂₋₆ alkenyl group, (d) a C₂₋₆ alkynyl group, (e) -OH, (f) -OR⁵, (g) -NR⁴R⁴, (h) -C(O)R⁵, (i) -C(O)OR⁵, (j) -C(O)-NR⁴R⁴, (k) -C(S)R⁵, (l) -C(S)OR⁵, (m) -C(O)SR⁵, (n) -C(S)-NR⁴R⁴, or (m) halogen;

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25 C(O)OR⁵, (h) -C(O)-NR⁴R⁴, (i) -C(S)R⁵, (j) -C(S)OR⁵, (k) -C(O)SR⁵, (l) -C(S)-NR⁴R⁴, or
 26 (m) halogen, or

27 alternatively, R^c and R^d or R^c and R^e are taken together to form a carbon-carbon
 28 double bond between the carbon atoms to which they are attached;

29 alternatively R^d and X are taken together to form =CR⁵R⁵; or

30 alternatively R^d and R^e are taken together with the carbon to which they are attached
 31 to form (a) -C(O)-, (b) -C(S)-, (c) -C=NR⁴, or (d) -C=NOR⁵, (e) =CH₂, or (f) 3-10-
 32 membered carbocycle or heterocycle optionally substituted with one or more R⁵;

33 R¹ and R³ independently are selected from: (a) H, (b) a

34 C₁₋₆ alkyl group, (c) a C₂₋₆ alkenyl group, (d) a C₂₋₆ alkynyl group, (e) -C(O)R⁵,
 35 (f) -C(O)OR⁵, (g) -C(O)-NR⁴R⁴, (h) -C(S)R⁵, (i) -C(S)OR⁵, (j) -C(O)SR⁵, or (k) -C(S)-
 36 NR⁴R⁴;

37 alternatively R¹ and R³ are taken together with the oxygen to which R¹ is attached, the
 38 nitrogen to which R³ is attached and the two intervening carbons to form a 5 or 6 membered
 39 ring, said ring being optionally substituted with one or more R⁵

40 R² is hydrogen or -OR¹²;

41 G is selected from: (a) -B' and (b) -B'-Z-B'', wherein

42 i) each B' and B'' is independently selected from (aa) an aryl
 43 group, (bb) a heteroaryl group, (cc) a biaryl group, (dd) a fused
 44 bicyclic or tricyclic saturated, unsaturated or aromatic ring
 45 system optionally containing one or more heteroatoms selected
 46 from nitrogen, oxygen, and sulfur, (ee) a 3-10 membered
 47 saturated or unsaturated heterocycle containing one or more
 48 heteroatoms selected from nitrogen, oxygen, and sulfur, (ff) a
 49 3-10 membered saturated, or unsaturated carbocycle, wherein
 50 each (aa)-(ff) optionally is substituted with one or more R¹¹ or
 51 R^{11a} groups; and

52 ii) Z is selected from

53 (aa) a single bond, (bb) a C₁₋₆ alkyl group, (cc) a C₂₋₆ alkenyl group,
 54 (dd) a C₂₋₆ alkynyl group, (ee) -C(O)-, (ff) -C(O)O-, (gg) -C(O)NR⁴-
 55 , (hh) -C(=NR⁴)-, (ii) -C(=NR⁴)O-, (jj) -C(=NR⁴)NR⁴-, (kk) -S(O)_p-,
 56 (ll) -OC(O)-, (mm) -C(S)-, (nn) -C(S)NR⁴-, (oo) -C(NR⁴)S-, (pp) -
 57 C(O)S-, (qq) -O-, (rr) -NR⁴-, (ss) -NR⁴C(O)-, (tt) -OC(NR⁴)-, (uu)

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58 $-\text{NC}(\text{NR}^4)-$, (vv) $-\text{C}(\text{S})\text{O}-$, (ww) $-\text{SC}(\text{O})-$, (xx) $-\text{OC}(\text{S})-$ or (yy) $-\text{S}(\text{O})_{\text{p}}-$;
 59

60 R^4 , at each occurrence, independently is selected from:

61 (a) H, (b) a C_{1-6} alkyl group, (c) a C_{2-6} alkenyl group, (d) a C_{2-6} alkynyl group,
 62 (e) a C_{6-10} saturated, unsaturated, or aromatic carbocycle, (f) a 3-12 membered
 63 saturated, unsaturated, or aromatic heterocycle containing one or more
 64 heteroatoms selected from nitrogen, oxygen, and sulfur, (g) $-\text{C}(\text{O})-\text{C}_{1-6}$ alkyl,
 65 (h) $-\text{C}(\text{O})-\text{C}_{2-6}$ alkenyl, (i) $-\text{C}(\text{O})-\text{C}_{2-6}$ alkynyl, (j) $-\text{C}(\text{O})-\text{C}_{6-10}$ saturated,
 66 unsaturated, or aromatic carbocycle, (k) $-\text{C}(\text{O})-3-12$ membered saturated,
 67 unsaturated, or aromatic heterocycle containing one or more heteroatoms
 68 selected from nitrogen, oxygen, and sulfur, (l) $-\text{C}(\text{O})\text{O}-\text{C}_{1-6}$ alkyl, (m) $-\text{C}(\text{O})\text{O}-\text{C}_{2-6}$ alkenyl, (n) $-\text{C}(\text{O})\text{O}-\text{C}_{2-6}$ alkynyl,
 69 (o) $-\text{C}(\text{O})\text{O}-\text{C}_{6-10}$ saturated, unsaturated, or aromatic carbocycle, (p) $-\text{C}(\text{O})\text{O}-$
 70 3-12 membered saturated, unsaturated, or aromatic heterocycle containing one
 71 or more heteroatoms selected from nitrogen, oxygen, and sulfur, and (q) $-\text{C}(\text{O})\text{NR}^6\text{R}^6$,
 72
 73

74 wherein any of (b)–(p) optionally is substituted with one or more R^5
 75 groups,

76 alternatively, NR^4R^4 forms a 3-7 membered saturated, unsaturated or aromatic ring
 77 including the nitrogen atom to which the R^4 groups are bonded, wherein said ring is
 78 optionally substituted at a position other than the nitrogen atom to which the R^4 groups are
 79 bonded, with one or more moieties selected from O, $\text{S}(\text{O})_{\text{p}}$, N, and NR^8 ;

80 R^5 is selected from:

81 (a) R^7 , (b) a C_{1-8} alkyl group, (c) a C_{2-8} alkenyl group, (d) a C_{2-8} alkynyl group,
 82 (e) a C_{3-12} saturated, unsaturated, or aromatic carbocycle, and (f) a
 83 3-12 membered saturated, unsaturated, or aromatic heterocycle containing one
 84 or more heteroatoms selected from nitrogen, oxygen, and sulfur, or
 85 alternatively two R^5 groups, when present on the same carbon atom can be
 86 taken together with the carbon atom to which they are attached to form a spiro
 87 3-6 membered carbocyclic ring or heterocyclic ring containing one or more
 88 heteroatoms selected from nitrogen, oxygen, and sulfur;

89 wherein any of (b)–(f) immediately above optionally is substituted
 90 with one or more R^7 groups;

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91 R^6 , at each occurrence, independently is selected from:
 92 (a) H, (b) a C_{1-6} alkyl group, (c) a C_{2-6} alkenyl group, (d) a C_{2-6} alkynyl group,
 93 (e) a C_{3-10} saturated, unsaturated, or aromatic carbocycle, and (f) a 3-10
 94 membered saturated, unsaturated, or aromatic heterocycle containing one or
 95 more heteroatoms selected from nitrogen, oxygen, and sulfur,
 96 wherein any of (b)–(f) optionally is substituted with one or more
 97 moieties selected from:
 98 (aa) a carbonyl group, (bb) a formyl group, (cc) F, (dd) Cl, (ee)
 99 Br, (ff) I, (gg) CN, (hh) NO_2 , (ii) $-OR^8$,
 100 (jj) $-S(O)_pR^8$, (kk) $-C(O)R^8$, (ll) $-C(O)OR^8$,
 101 (mm) $-OC(O)R^8$, (nn) $-C(O)NR^8R^8$,
 102 (oo) $-OC(O)NR^8R^8$, (pp) $-C(=NR^8)R^8$,
 103 (qq) $-C(R^8)(R^8)OR^8$, (rr) $-C(R^8)_2OC(O)R^8$,
 104 (ss) $-C(R^8)(OR^8)(CH_2)_rNR^8R^8$, (tt) $-NR^8R^8$,
 105 (uu) $-NR^8OR^8$, (vv) $-NR^8C(O)R^8$,
 106 (ww) $-NR^8C(O)OR^8$, (xx) $-NR^8C(O)NR^8R^8$,
 107 (yy) $-NR^8S(O)_tR^8$, (zz) $-C(OR^8)(OR^8)R^8$,
 108 (ab) $-C(R^8)_2NR^8R^8$, (ac) $=NR^8$,
 109 (ad) $-C(S)NR^8R^8$, (ae) $-NR^8C(S)R^8$,
 110 (af) $-OC(S)NR^8R^8$, (ag) $-NR^8C(S)OR^8$,
 111 (ah) $-NR^8C(S)NR^8R^8$, (ai) $-SC(O)R^8$,
 112 (aj) a C_{1-8} alkyl group, (ak) a C_{2-8} alkenyl group, (al) a
 113 C_{2-8} alkynyl group, (am) a C_{1-8} alkoxy group, (an) a C_{1-8}
 114 alkylthio group, (ao) a C_{1-8} acyl group, (ap) $-CF_3$,
 115 (aq) $-SCF_3$, (ar) a C_{3-10} saturated, unsaturated, or aromatic
 116 carbocycle, and (as) a 3-10 membered saturated, unsaturated, or
 117 aromatic heterocycle containing one or more heteroatoms
 118 selected from nitrogen, oxygen, and sulfur,
 119 alternatively, NR^6R^6 forms a 3-10 membered saturated, unsaturated or aromatic ring
 120 including the nitrogen atom to which the R^6 groups are attached wherein said ring is
 121 optionally substituted at a position other than the nitrogen atom to which the R^6 groups are
 122 bonded, with one or more moieties selected from O, $S(O)_p$, N, and NR^8 ;
 123 alternatively, CR^6R^6 forms a carbonyl group;

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R^7 , at each occurrence, is selected from:

(a) H, (b) =O, (c) F, (d) Cl, (e) Br, (f) I, (g) $-CF_3$,
 (h) $-CN$, (i) $-N_3$ (j) $-NO_2$, (k) $-NR^6(CR^6R^6)_tR^9$, (l) $-OR^9$, (m) $-$
 $S(O)_pC(R^6R^6)_tR^9$, (n) $-C(O)(CR^6R^6)_tR^9$, (o) $-OC(O)(CR^6R^6)_tR^9$, (p) $-$
 $SC(O)(CR^6R^6)_tR^9$, (q) $-C(O)O(CR^6R^6)_tR^9$, (r) $-NR^6C(O)(CR^6R^6)_tR^9$, (s) $-$
 $C(O)NR^6(CR^6R^6)_tR^9$, (t) $-C(=NR^6)(CR^6R^6)_tR^9$, (u) $-C(=NNR^6R^6)(CR^6R^6)_tR^9$,
 (v) $-C(=NNR^6C(O)R^6)(CR^6R^6)_tR^9$, (w) $-C(=NOR^9)(CR^6R^6)_tR^9$, (x) $-$
 $NR^6C(O)O(CR^6R^6)_tR^9$, (y) $-OC(O)NR^6(CR^6R^6)_tR^9$, (z) $-$
 $NR^6C(O)NR^6(CR^6R^6)_tR^9$, (aa) $-NR^6S(O)_p(CR^6R^6)_tR^9$, (bb) $-$
 $S(O)_pNR^6(CR^6R^6)_tR^9$, (cc) $-NR^6S(O)_pNR^6(CR^6R^6)_tR^9$, (dd) $-NR^6R^6$, (ee) $-$
 $NR^6(CR^6R^6)$, (ff) $-OH$, (gg) $-NR^6R^6$, (hh) $-OCH_3$, (ii) $-S(O)_pR^6$, (jj) $-$
 $NC(O)R^6$, (kk) a C_{1-6} alkyl group, (ll) a C_{2-6} alkenyl group, (mm) a
 C_{2-6} alkynyl group, (nn) $-C_{3-10}$ saturated, unsaturated, or aromatic carbocycle,
 and (oo) 3-10 membered saturated, unsaturated, or aromatic heterocycle
 containing one or more heteroatoms selected from nitrogen, oxygen, and
 sulfur,

wherein any of (kk)–(oo) optionally is substituted with one or more R^9
 groups;

alternatively, two R^7 groups can form $-O(CH_2)_uO-$;

R^8 is selected from:

(a) R^5 , (b) H, (bc) a C_{1-6} alkyl group, (cd) a C_{2-6} alkenyl group, (de) a
 C_{2-6} alkynyl group, (ef) a C_{3-10} saturated, unsaturated, or aromatic carbocycle,
 (fg) a 3-10 membered saturated, unsaturated, or aromatic heterocycle
 containing one or more heteroatoms selected from nitrogen, oxygen, and
 sulfur, (gh) $-C(O)-C_{1-6}$ alkyl, (hi) $-C(O)-C_{1-6}$ alkenyl, (ij) $-C(O)-C_{1-6}$
 alkynyl, (jk) $-C(O)-C_{3-10}$ saturated, unsaturated, or aromatic carbocycle, and
 (kl) $-C(O)-3-10$ membered saturated, unsaturated, or aromatic heterocycle
 containing one or more heteroatoms selected from nitrogen, oxygen, and
 sulfur,

wherein any of (bc)–(k) optionally is substituted with one or more
 moieties selected from : (aa) H, (bb) F, (cc) Cl, (dd) Br, (ee) I, (ff) CN,

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(gg) NO₂, (hh) OH, (ii) NH₂, (jj) NH(C₁₋₆ alkyl), (kk) N(C₁₋₆ alkyl)₂,
 (ll) a C₁₋₆ alkoxy group, (mm) an aryl group, (nn) a substituted aryl
 group, (oo) a heteroaryl group, (pp) a substituted heteroaryl group, and
 qq) a C₁₋₆ alkyl group optionally substituted with one or more moieties
 selected from an aryl group, a substituted aryl group, a heteroaryl
 group, a substituted heteroaryl group, F, Cl, Br, I, CN, NO₂, CF₃, SCF₃,
 and OH;

R⁹, at each occurrence, independently is selected from:

(a) R¹⁰, (b) a C₁₋₆ alkyl group, (c) a C₂₋₆ alkenyl group, (d) a C₂₋₆ alkynyl
 group, (e) a C₃₋₁₀ saturated, unsaturated, or aromatic carbocycle, and (f) a 3-10
 membered saturated, unsaturated, or aromatic heterocycle containing one or
 more heteroatoms selected from nitrogen, oxygen, and sulfur,
 wherein any of (b)–(f) optionally is substituted with one or more R¹⁰
 groups;

R¹⁰, at each occurrence, independently is selected from:

(a) H, (b) =O, (c) F, (d) Cl, (e) Br, (f) I, (g) –CF₃, (h) –CN, (i) –NO₂, (j) –
 NR⁶R⁶, (k) –OR⁶, (l) –S(O)_pR⁶, (m) –C(O)R⁶, (n) –C(O)OR⁶, (o) –OC(O)R⁶,
 (p) NR⁶C(O)R⁶, (q) –C(O)NR⁶R⁶, (r) –C(=NR⁶)R⁶, (s) –NR⁶C(O)NR⁶R⁶, (t) –
 NR⁶S(O)_pR⁶, (u) –S(O)_pNR⁶R⁶, (v) –NR⁶S(O)_pNR⁶R⁶, (w) a C₁₋₆ alkyl group,
 (x) a C₂₋₆ alkenyl group, (y) a C₂₋₆ alkynyl group, (z) a C₃₋₁₀ saturated,
 unsaturated, or aromatic carbocycle, and (aa) a 3-10 membered saturated,
 unsaturated, or aromatic heterocycle containing one or more heteroatoms
 selected from nitrogen, oxygen, and sulfur,
 wherein any of (w)–(aa) optionally is substituted with one or more
 moieties selected from R⁶, F, Cl, Br, I, CN, NO₂, –OR⁶, –NH₂, –
 NH(C₁₋₆ alkyl), –N(C₁₋₆ alkyl)₂, a C₁₋₆ alkoxy group, a C₁₋₆ alkylthio
 group, and a C₁₋₆ acyl group;

R¹¹ and R^{11a} at each occurrence, independently is selected from:

(a) a carbonyl group, (b) a formyl group, (c) F, (d) Cl, (e) Br, (f) I, (g) CN, (h)
 NO₂, (i) OR⁸, (j) –S(O)_pR⁸, (k) –C(O)R⁸, (l) –C(O)OR⁸,
 (m) –OC(O)R⁸, (n) –C(O)NR⁸R⁸, (o) –OC(O)NR⁸R⁸,
 (p) –C(=NR⁸)R⁸, (q) –C(R⁸)(R⁸)OR⁸, (r) –C(R⁸)₂OC(O)R⁸,

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(s) $-C(R^8)(OR^8)(CH_2)_rNR^8R^8$, (t) $-NR^8R^8$, (u) $-NR^8OR^8$,
 (v) $-NR^8C(O)R^8$, (w) $-NR^8C(O)OR^8$, (x) $-NR^8C(O)NR^8R^8$, (y) $-NR^8S(O)_pR^8$,
 (z) $-C(OR^8)(OR^8)R^8$, (aa) $-C(R^8)_2NR^8R^8$, (bb) $=NR^8$, (cc) $-C(S)NR^8R^8$, (dd) $-$
 $NR^8C(S)R^8$, (ee) $-OC(S)NR^8R^8$, (ff) $-NR^8C(S)OR^8$, (gg) $-NR^8C(S)NR^8R^8$,
 (hh) $-SC(O)R^8$, (ii) $-N_3$, (jj) $-Si(R^{13})_3$, (kkii) a C_{1-8} alkyl group, (lljj) a
 C_{2-8} alkenyl group, (mmkk) a C_{2-8} alkynyl group, (nnll) a C_{1-8} alkoxy group,
 (oomm) a C_{1-8} alkylthio group, (ppnn) a C_{1-8} acyl group, (qqoo) a C_{3-10}
 saturated, unsaturated, or aromatic carbocycle, and (rrpp) a 3-10 membered
 saturated, unsaturated, or aromatic heterocycle containing one or more
 heteroatoms selected from nitrogen, oxygen, and sulfur, wherein (kkii)-
 (mmkk) optionally are substituted with one or more R^5 groups;

R^{12} is selected from:

(a) H, (b) a C_{1-6} alkyl group, (c) a C_{2-6} alkenyl group, (d) a C_{2-6} alkynyl group,
 (e) $-C(O)R^5$, (f) $-C(O)OR^5$, (g) $-C(O)-NR^4R^4$, (h) $-C(S)R^5$, (i) $-C(S)OR^5$, (j)
 $-C(O)SR^5$, (k) $-C(S)-NR^4R^4$, (l) a C_{3-10} saturated, unsaturated, or aromatic
 carbocycle, or (m) a 3-10 membered saturated, unsaturated, or aromatic
 heterocycle containing one or more heteroatoms selected from nitrogen,
 oxygen, and sulfur, (n) a $-(C_{1-6} \text{ alkyl})-C_{3-10}$ saturated, unsaturated, or
 aromatic carbocycle, or (o) a $-(C_{1-6} \text{ alkyl})$ -3-10 membered saturated,
 unsaturated, or aromatic heterocycle containing one or more heteroatoms
 selected from nitrogen, oxygen, and sulfur,

wherein (a)-(d) and (l)-(o) optionally are substituted with one or more

R^5 groups;

each R^{13} is independently selected from (a) $-C_{1-6}$ alkyl and (b) $-O-(C_{1-6} \text{ alkyl})$;

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

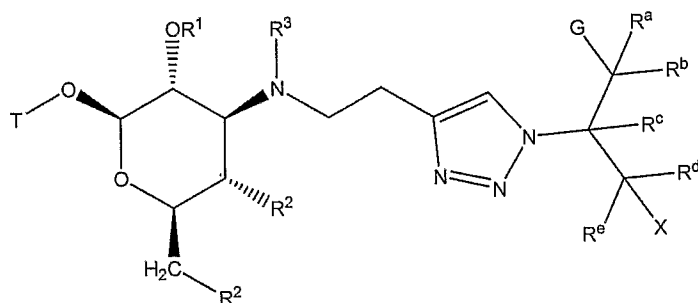
r at each occurrence is 0, 1, or 2;

t at each occurrence is 0, 1, or 2;

and u at each occurrence is 1, 2, 3, or 4.

1 2. A compound according to claim 1, having the structure:

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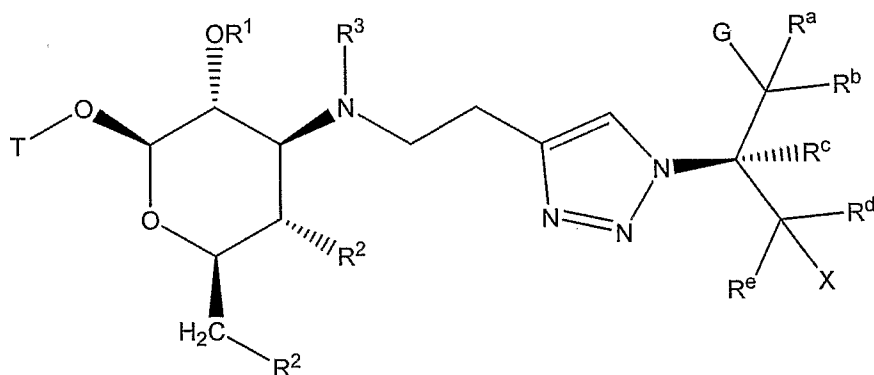


2

3 or a pharmaceutically acceptable salt, ester, *N*-oxide, or prodrug thereof, wherein G, T, X, R¹,
 4 R², R³, R^a, R^b, and R^c, are as described in claim 1.

5

1 3. A compound according to claim 2, having the structure:

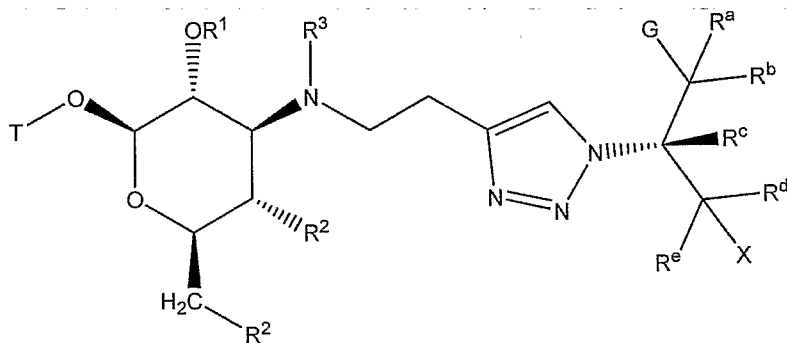


2

3 or a pharmaceutically acceptable salt, ester, *N*-oxide, or prodrug thereof wherein G, T, X, R¹,
 4 R², R³, R^a, R^b, and R^c, are as described in claim 1.

5

1 4. A compound according to claim 2, having the structure:



2

3 or a pharmaceutically acceptable salt, ester, *N*-oxide, or prodrug thereof wherein G, T, X, R¹,
 4 R², R³, R^a, R^b, and R^c, are as described in claim 1.

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5

1 5. A compound according to any one of claims 1-4 wherein X is selected from (a) H, (b)
2 Cl, (c) Br, (d) F, (e) -OH, (f) -CN, (g) -CF₃, (h) -CF₂H, (i) -CFH₂, (j) -O(C₁₋₆ alkyl), (k) -N₃,
3 (l) -COOH, (m) -COO(C₁₋₆alkyl), (n) -NH₂, (o) -NH(C₁₋₆alkyl), (p) -N(C₁₋₆alkyl)₂, (q) -
4 C(O)NH₂, (r) -C(O)NH(C₁₋₆alkyl), (s) -C(O)N(C₁₋₆alkyl)₂, (t) -NHC(O)H, (u) -NHC(O)(C₁₋₆
5 alkyl), (v) -N(C₁₋₆alkyl)C(O)H, (w) -N(C₁₋₆alkyl)C(O)N(C₁₋₆alkyl).

6

1 6. A compound according to any one of claims 1-5 wherein X is selected from F and OH.

2

1 7. A compound according to any one of claims 1-6 wherein X is F.

2

1 8. A compound according to any one of claims 1-6 wherein X is OH.

2

1 9. A compound according to any one of claims 1-8 wherein R^d and R^e are selected from
2 (a) Cl, (b) Br, (c) F, (d) H and (e) C₁₋₆alkyl.

3

1 10. A compound according to any one of claims 1-9 wherein R^d and R^e are H.

2

1 11. A compound according to any one of claims 1-10 wherein R^c is selected from (a) H,
2 (b) Cl, (c) Br, (d) F, (e) C₁₋₆alkyl, (f) -CF₃, (g) -CF₂H, and (h) -CFH₂.

3

1 12. A compound according to any one of claims 1-11 wherein R^c is H.

2

1 13. A compound according to any one of claims 1-12 wherein R^a and R^b are selected from
2 (a) H, (b) Cl, (b) Br, (d) F, (g) -OH, (h) -O(C₁₋₆ alkyl), (i) -N₃, (j) -COOH, (k) -COO(C₁₋₆
3 alkyl), (l) -CN, (m) -NH₂, (n) -NH(C₁₋₆alkyl), (o) -N(C₁₋₆alkyl)₂, (p) -C(O)NH₂, (q) -
4 C(O)NH(C₁₋₆alkyl), (r) -C(O)N(C₁₋₆alkyl)₂, (s) -NHC(O)H, (t) -NHC(O)(C₁₋₆alkyl), (u) -
5 N(C₁₋₆alkyl)C(O)H, (v) -N(C₁₋₆alkyl)C(O)N(C₁₋₆alkyl), or alternatively R^a and R^b are taken
6 together with the carbon to which they are attached to form (aa) -CO or (bb) -CS.

7

1 14. A compound according to any one of claims 1-13 wherein R^a and R^b are selected from
2 H, F, and OH.

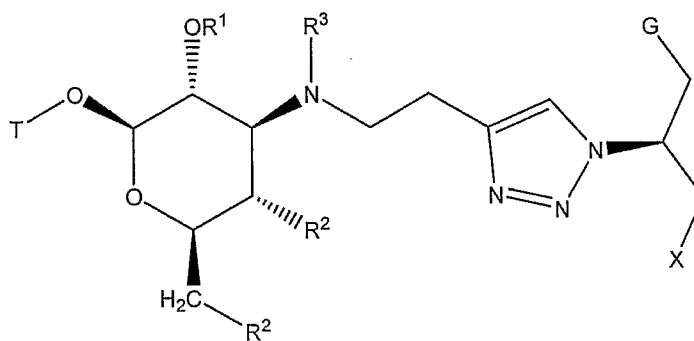
3

- 331 -

- 1 15. A compound according to any one of claims 1-14 wherein R^a is H and R^b is F.
2
- 1 16. A compound according to any one of claims 1-14 wherein R^a is H and R^b is -OH.
2
- 1 17. A compound according to any one of claims 1-14 wherein R^a and R^b are taken
2 together with the carbon to which they are attached to form -C=O.
3
- 1 18. A compound according to any one of claims 1-17 wherein R¹ is H.
2
- 1 19. A compound according to any one of claims 1-18 wherein R² is H.
2
- 1 20. A compound according to any one of claims 1-19 wherein R³ is C₁₋₆alkyl.
1
- 1 21. A compound according to any one of claims 1-20 wherein R³ is methyl.
2
- 1 22. A compound according to any one of claims 1-21, wherein G is B'.
2
- 1 23. A compound according to any one of claims 1-22, wherein B' is selected from: (a) an
2 aryl group, (b) a heteroaryl group, (c) a biaryl group, and (d) a fused bicyclic or tricyclic
3 unsaturated or aromatic ring system optionally containing one or more carbonyl groups and
4 one or more heteroatoms selected from nitrogen, oxygen, and sulfur, wherein each (a)-(d)
5 optionally is substituted with one or more R¹¹ groups.
6
- 1 24. A compound according to any one of claims 1-21, wherein G is -B'-Z-B".
2
- 1 25. A compound according to claim 24, wherein B' and B" are independently selected
2 from: (a) an aryl group, (b) a heteroaryl group, (c) a biaryl group, and (d) a fused bicyclic or
3 tricyclic unsaturated or aromatic ring system optionally containing one or more carbonyl
4 groups and one or more heteroatoms selected from nitrogen, oxygen, and sulfur, wherein
5 each (a)-(d) optionally is substituted with one or more R¹¹ groups, and Z is selected from
6 (aa) a single bond, (bb) -O-, (cc) -NR⁴-, (dd) -C(O)-, (ee) -C(S)-, (ff) -S(O)_p-, and (gg) a C₁₋₆
7 alkyl.
8

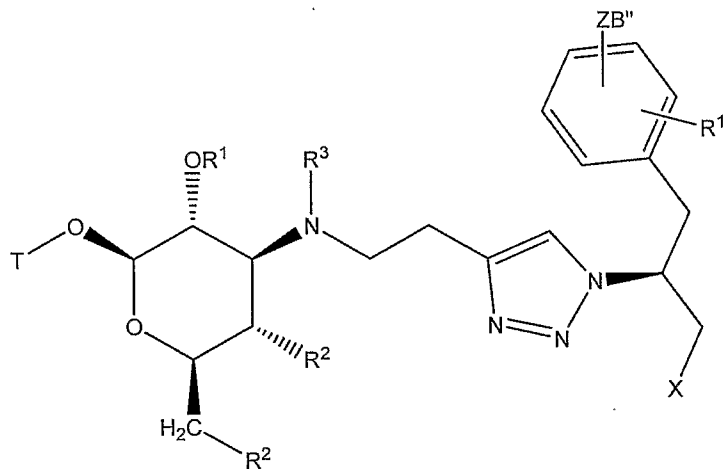
- 332 -

- 1 26. A compound according to claim 3, having the structure:



- 2
3 or a pharmaceutically acceptable salt, ester, *N*-oxide, or prodrug thereof wherein G, T, X, R¹,
4 R², and R³ are as described in claim 1.

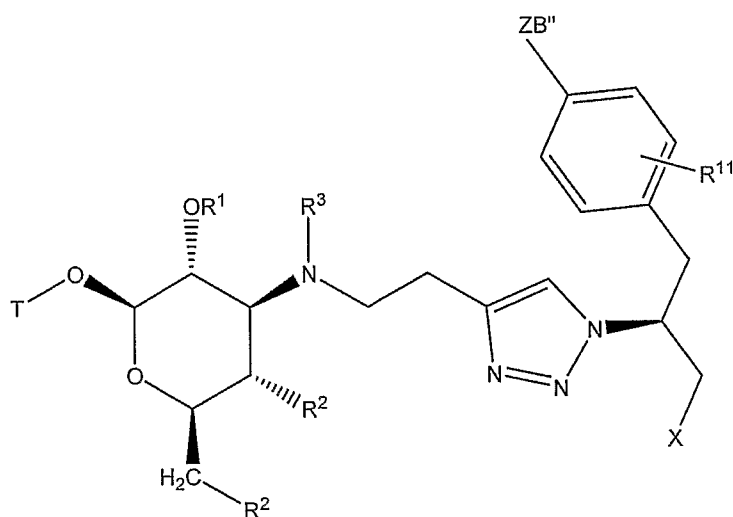
- 5
1 27. A compound according to claim 3, having the structure:



- 2
3 or a pharmaceutically acceptable salt, ester, *N*-oxide, or prodrug thereof wherein B'', T, X, Z,
4 R¹, R², R³, and R¹¹ are as described in claim 1.

- 5
1 28. A compound according to claim 3, having the structure:

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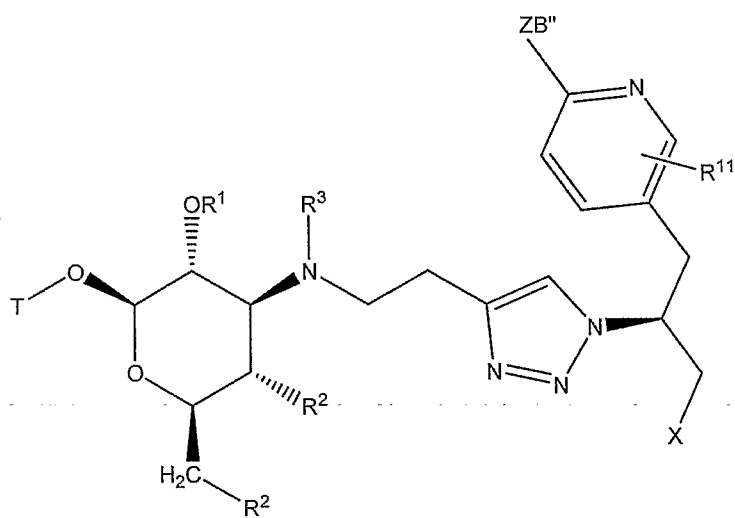


2

3 or a pharmaceutically acceptable salt, ester, *N*-oxide, or prodrug thereof wherein B'', T, X, Z,
 4 R¹, R², R³, and R¹¹ are as described in claim 1.

5

1 29. A compound according to claim 3, having the structure:



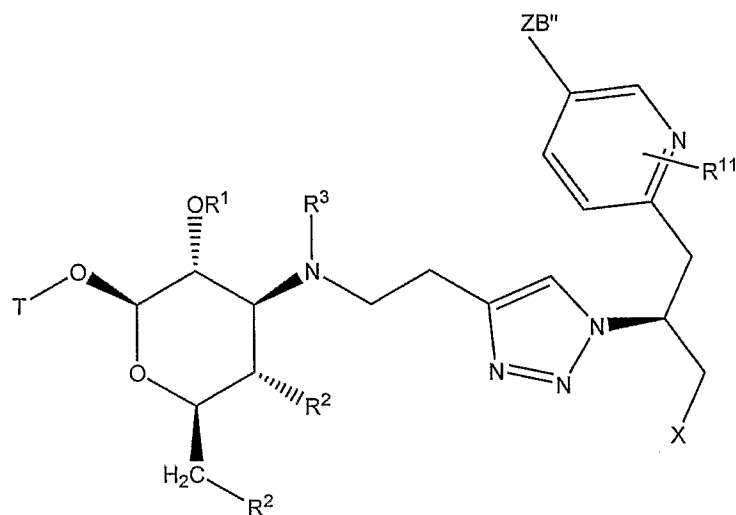
2

3 or a pharmaceutically acceptable salt, ester, *N*-oxide, or prodrug thereof wherein B'', T, X, Z,
 4 R¹, R², R³, and R¹¹ are as described in claim 1.

5

1 30. A compound according to claim 3, having the structure:

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or a pharmaceutically acceptable salt, ester, *N*-oxide, or prodrug thereof wherein B'', T, X, Z, R¹, R², R³, and R¹¹ are as described in claim 1.

31. A compound according to any of claims 1-30 wherein X is selected from F and OH.

32. A compound according to claim 31 wherein X is F.

33. A compound according to claim 31 wherein X is OH.

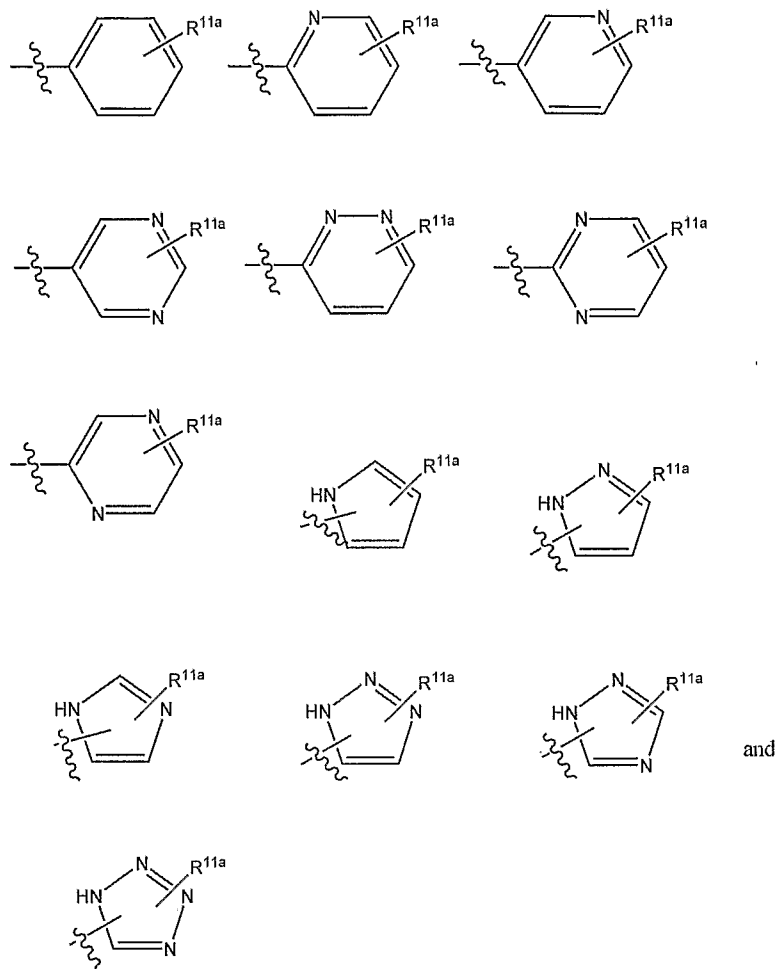
34. A compound according to any of claims 1-33 wherein R¹¹ is selected from H and F.

35. A compound according to any of claims 34 wherein R¹¹ is H.

36. A compound according to any of claims 34 wherein R¹¹ is F.

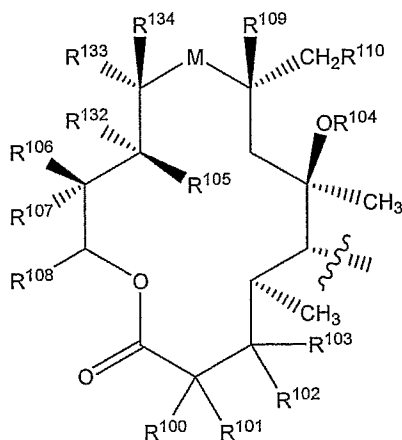
37. A compound according to any of claims 1-36 wherein -ZB'' is selected from:

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wherein R^{11a} is as described as in claim 1.

38. A compound according to any one of according to any one of claims 1-37, wherein T is:



or a pharmaceutically acceptable salt, ester, N-oxide, or prodrug thereof,

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wherein:

M is selected from:

- (a) $-C((O)-$, (b) $-CH(-OR^{114})-$, (c) $-NR^{114}-CH_2-$, (d) $-CH_2-NR^{114}-$, (e) $-CH(NR^{114}R^{114})-$, (f) $-C(=NNR^{114}R^{114})-$, (g) $-NR^{114}-C(O)-$, (h) $-C(O)NR^{114}-$, (i) $-C(=NR^{114})-$, (j) $-CR^{115}R^{115}-$, and (k) $-C(=NOR^{127})-$;

R^{100} is selected from (a) H, (b) F, (c) Cl, (d) Br, (e) $-SR^{114}$, and (f) C_{1-6} alkyl, wherein (f) optionally is substituted with one or more R^{115} groups;

R^{101} is selected from:

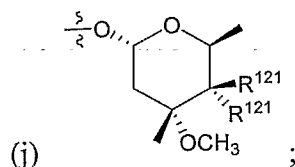
- (a) H, (b) Cl, (c) F, (d) Br, (e) I, (f) $-NR^{114}R^{114}$, (g) $-NR^{114}C(O)R^{114}$, (h) $-OR^{114}$, (i) $-OC(O)R^{114}$, (j) $-OC(O)OR^{114}$, (k) $-OC(O)NR^{114}R^{114}$, (l) $-O-C_{1-6}$ alkyl, (m) $-OC(O)-C_{1-6}$ alkyl, (n) $-OC(O)O-C_{1-6}$ alkyl, (o) $-OC(O)NR^{114}-C_{1-6}$ alkyl, (p) C_{1-6} alkyl, (q) C_{1-6} alkenyl, and (r) C_{1-6} alkynyl,

wherein any of (l) – (r) optionally is substituted with one or more R^{115} groups;

R^{102} is H, (b) F, (c) Cl, (d) Br, (e) $-SR^{114}$, (f) C_{1-6} alkyl, wherein (f) optionally is substituted with one or more R^{115} groups;

R^{103} is selected from:

- (a) H, (b) $-OR^{114}$, (c) $-O-C_{1-6}$ alkyl- R^{115} , (d) $-OC((O)R^{114}$, (e) $-OC(O)-C_{1-6}$ alkyl- R^{115} , (f) $-OC(O)OR^{114}$, (g) $-OC(O)O-C_{1-6}$ alkyl- R^{115} , (h) $-OC(O)NR^{114}R^{114}$, (i) $-OC(O)NR^{114}-C_{1-6}$ alkyl- R^{115} , and



alternatively, R^{102} and R^{103} taken together with the carbon to which they are attached form (a) a carbonyl group or (b) a 3-7 membered saturated, unsaturated or aromatic carbocyclic or heterocyclic ring which can optionally be substituted with one or more R^{114} groups;

alternatively, R^{101} and R^{103} taken together are a single bond between the respective carbons to which these two groups are attached thereby creating a double bond between the carbons to which R^{100} and R^{102} are attached;

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alternatively, R^{101} and R^{103} taken together with the carbons to which they are attached form a 3-membered saturated, unsaturated or aromatic carbocyclic or heterocyclic ring which can optionally be substituted with one or more R^{114} groups ;

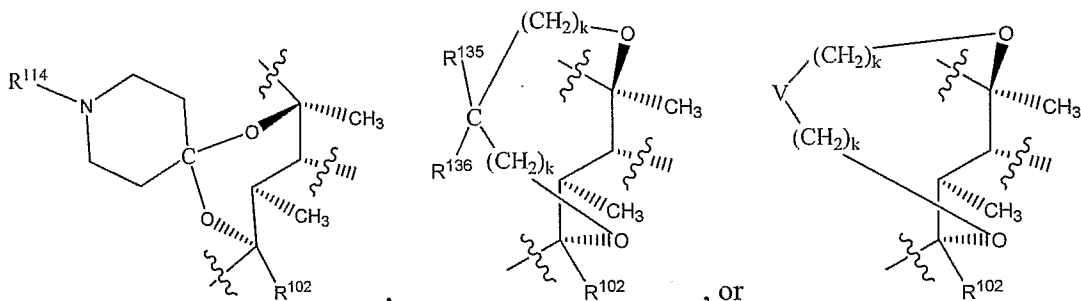
R^{104} is selected from:

(a) H, (b) R^{114} , (c) $-C(O)R^{114}$, (d) $-C(O)OR^{114}$, (e) $-C(O)NR^{114}R^{114}$, (f) $-C_{1-6}$ alkyl-K- R^{114} , (g) $-C_{2-6}$ alkenyl-K- R^{114} , and (h) $-C_{2-6}$ alkynyl-K- R^{114} ;

K is selected from:

(a) $-C(O)-$, (b) $-C(O)O-$, (c) $-C(O)NR^{114}-$, (d) $-C(=NR^{114})-$, (e) $-C(=NR^{114})O-$,
 (f) $-C(=NR^{114})NR^{114}-$, (g) $-OC(O)-$, (h) $-OC(O)O-$, (i) $-OC(O)NR^{114}-$,
 (j) $-NR^{114}C(O)-$, (k) $-NR^{114}C(O)O-$, (l) $-NR^{114}C(O)NR^{114}-$,
 (m) $-NR^{114}C(=NR^{114})NR^{114}-$, and (o) $-S(O)_p-$;

alternatively R^{103} and R^{104} , taken together with the atoms to which they are bonded, form:



wherein R^{135} and R^{136} are selected from (a) hydrogen, (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 containing one or more oxygen, nitrogen, or sulfur atoms, (g) F, (h) Br, (i) I, (j) OH, (k) $-N_3$, wherein (b) through (e) are optionally substituted with one or more R^{117} ; or alternatively, R^{135} and R^{136} are taken together to form $=O$, $=S$ and $=NR^{114}$, $=NOR^{114}$, $=NR^{114}$, and $=N-NR^{114}$, R^{114}],

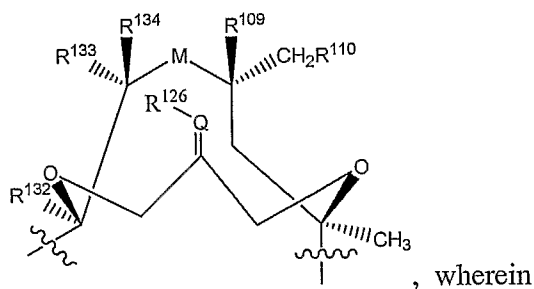
wherein V is selected from (a) $-(C_4\text{-alkyl})-$, (b) $-(C_4\text{-alkenyl})-$, (c) O, (d) S, and (e) NR^{114} , wherein (a) and (b) are optionally further substituted with one or more R^{117} ;

R^{105} is selected from:

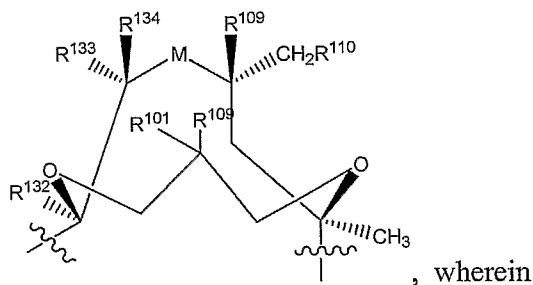
(a) R^{114} , (b) $-OR^{114}$, (c) $-NR^{114}R^{114}$, (d) $-O-C_{1-6}$ alkyl- R^{115} , (e) $-C(O)-R^{114}$,
 (f) $-C(O)-C_{1-6}$ alkyl- R^{115} , (g) $-OC(O)-R^{114}$, (h) $-OC(O)-C_{1-6}$ alkyl- R^{115} ,
 (i) $-OC(O)O-R^{114}$, (j) $-OC(O)O-C_{1-6}$ alkyl- R^{115} , (k) $-OC(O)NR^{114}R^{114}$,
 (l) $-OC(O)NR^{114}-C_{1-6}$ alkyl- R^{115} , (m) $-C(O)-C_{2-6}$ alkenyl- R^{115} , and
 (n) $-C(O)-C_{2-6}$ alkynyl- R^{115} ;

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alternatively, R^{104} and R^{105} , taken together with the atoms to which they are bonded,
form

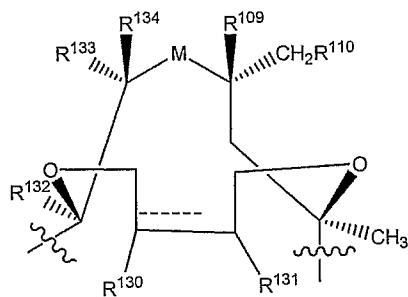


Q is CH or N, and R^{126} is $-OR^{114}$, $-NR^{114}$ or R^{114} ;
alternatively, R^{104} and R^{105} , taken together with the atoms to which they are bonded,
form:



- i) R^{101} is as defined above;
- ii) alternately, R^{101} and R^{109} can be taken together with the carbon to which they are attached to form a carbonyl group;
- iii) alternately, R^{101} and R^{109} can be taken together to form the group $-O(CR^{116}R^{116})_nO-$;

alternatively, R^{104} and R^{105} , taken together with the atoms to which they are bonded,
form:

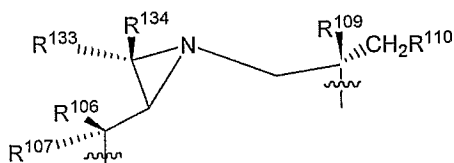


wherein in the preceding structure the dotted line indicates an optional double bond

- i) R^{130} is $-OH$, or R^{114} ,
- ii) R^{131} is $-OH$, or R^{114} ,

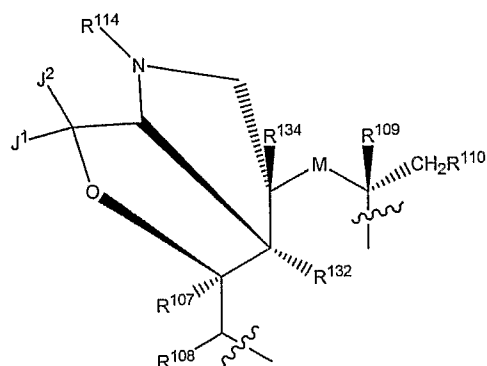
- 339 -

- 81 iii) alternately, R^{130} and R^{131} together with the carbons to which
 82 they are attached form a 3-7 membered saturated, unsaturated
 83 or aromatic carbocyclic or heterocyclic ring which can
 84 optionally be substituted with one or more R^{114} groups;
 85 iv) alternately, R^{130} and the carbon to which it is attached or R^{131}
 86 and the carbon to which it is attached are each
 87 independently $-C(=O)-$;
 88 alternately, R^{105} , R^{132} and M, taken together with the atoms to which they are
 89 attached, form:



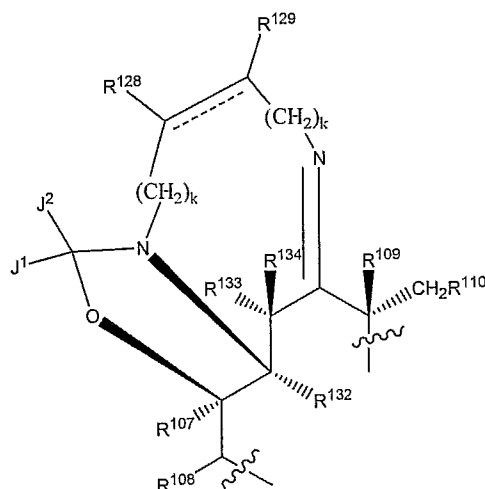
- 90
 91 R^{106} is selected from:
 92 (a) $-OR^{114}$, (b) $-C_{1-6}$ alkoxy- R^{115} , (c) $-C(O)R^{114}$, (d) $-OC(O)R^{114}$, (e) $-$
 93 $OC(O)OR^{114}$, (f) $-OC(O)NR^{114}R^{114}$, and (g) $-NR^{114}R^{114}$,
 94 alternately, R^{105} and R^{106} taken together with the atoms to which they are
 95 form a 5-membered ring by attachment to each other through a chemical moiety selected
 96 from:
 97 (a) $-OC(R^{115})_2O-$, (b) $-OC(O)O-$, (c) $-OC(O)NR^{114}-$, (d) $-NR^{114}C(O)O-$,
 98 (e) $-OC(O)NOR^{114}-$, (f) $-NOR^{114}-C(O)O-$, (g) $-OC(O)NNR^{114}R^{114}-$,
 99 (h) $-NNR^{114}R^{114}-C(O)O-$, (i) $-OC(O)C(R^{115})_2-$, (j) $-C(R^{115})_2C(O)O-$, (k) $-$
 100 $OC(S)O-$, (l) $-OC((S)NR^{114}-$, (m) $-NR^{114}C(S)O-$, (n) $-OC(S)NOR^{114}-$, (o) $-$
 101 $NOR^{114}-C(S)O-$, (p) $-OC(S)NNR^{114}R^{114}-$, (q) $-NNR^{114}R^{114}-C(S)O-$, (r) $-$
 102 $OC(S)C(R^{115})_2-$, and (s) $-C(R^{115})_2C(S)O-$;
 103 alternately, R^{105} , R^{106} , and R^{133} taken together with the atoms to which they are
 104 form:

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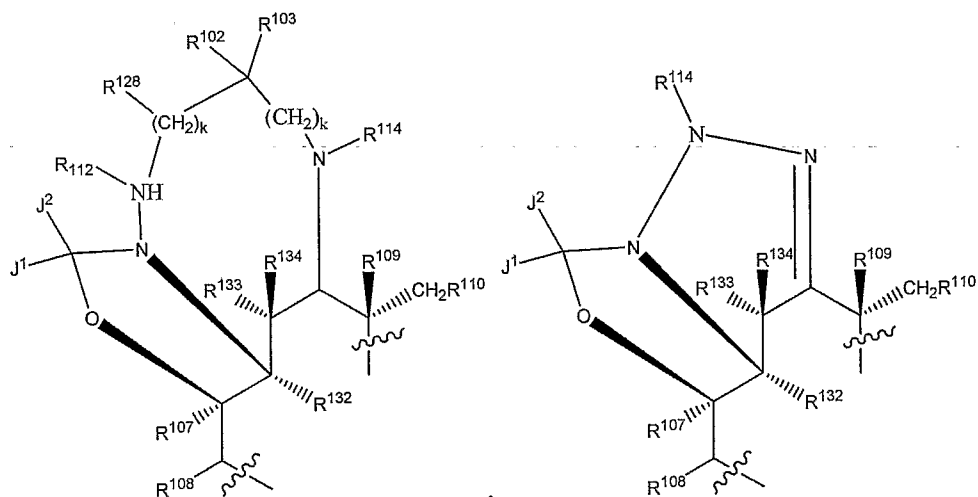
105

106 alternatively, M, R¹⁰⁵, and R¹⁰⁶ taken together with the atoms to which they are attached
 107 form:



108

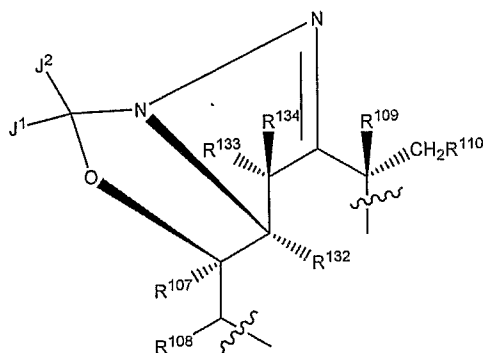
109 wherein in the preceding structure the dotted line indicates an optional double bond,



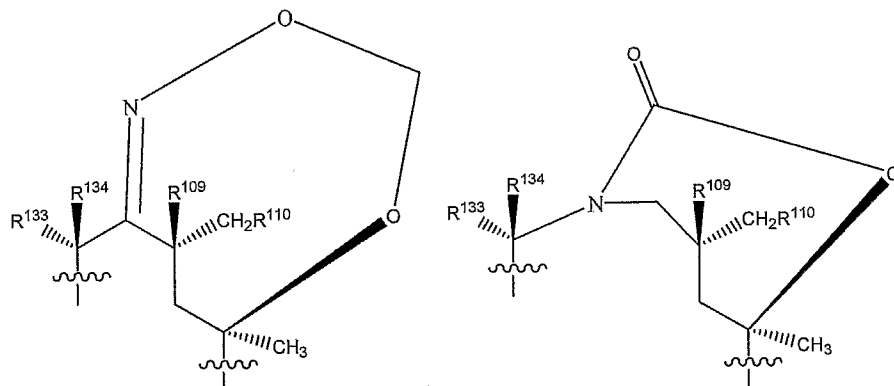
110

, or

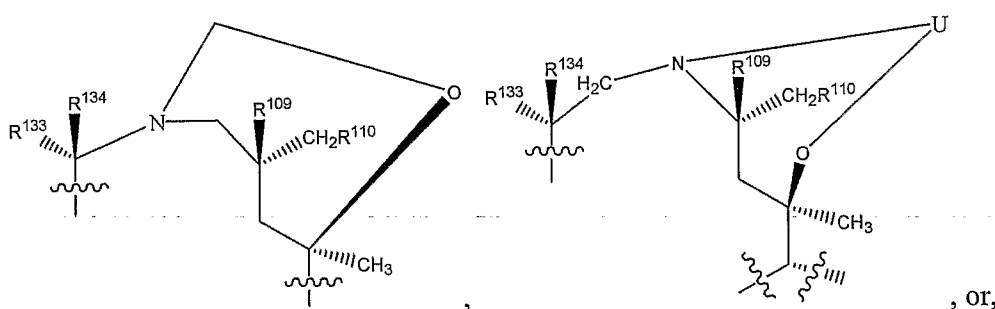
- 341 -



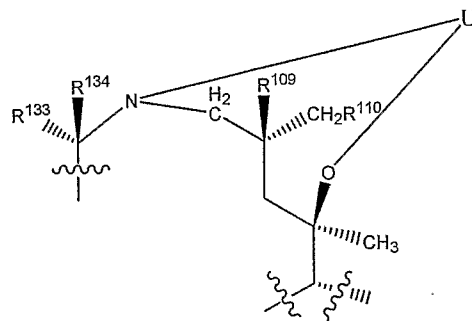
111

112 wherein J^1 and J^2 are selected from hydrogen, Cl, F, Br, I, OH, $-C_{1-6}$ alkyl, and $-O(C_{1-6}$ alkyl)113 or are taken together to form $=O$, $=S$ and $=NR^{114}$, $=NOR^{114}$, $=NR^{114}$, and $=N-$ 114 NR^{114} , R^{114} ,115 alternatively, M and R^{104} taken together with the atoms to which they are attached form:

116



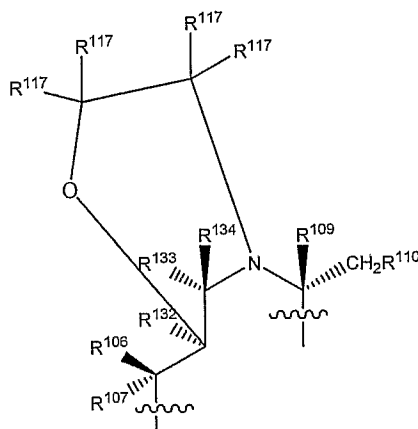
117



118

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119 wherein U is selected from (a) $-(C_4\text{-alkyl})-$ and (b) $-(C_4\text{-alkenyl})-$, wherein (a) and (b)
 120 are optionally further substituted with one or more R^{117} ;
 121 alternatively, M and R^{105} are taken together with the atoms to which they are attached
 122 to form:



123

124 R^{107} is selected from

125 (a) H, (b) $-C_{1-4}$ alkyl, (c) $-C_{2-4}$ alkenyl, which can be further substituted with
 126 C_{1-12} alkyl or one or more halogens, (d) $-C_{2-4}$ alkynyl, which can be further
 127 substituted with C_{1-12} alkyl or one or more halogens, (e) aryl or heteroaryl,
 128 which can be further substituted with C_{1-12} alkyl or one or more halogens, (f) $-$
 129 $C(O)H$, (g) $-COOH$, (h) $-CN$, (i) $-COOR^{114}$, (j) $-C(O)NR^{114}R^{114}$, (k) $-$
 130 $C(O)R^{114}$, and (l) $-C(O)SR^{114}$, wherein (b) is further substituted with one or
 131 more substituents selected from (aa) $-OR^{114}$, (bb) halogen, (cc) $-SR^{114}$, (dd)
 132 C_{1-12} alkyl, which can be further substituted with halogen, hydroxyl,
 133 C_{1-6} alkoxy, or amino, (ee) $-OR^{114}$, (ff) $-SR^{114}$, (gg) $-NR^{114}R^{114}$, (hh) $-CN$,
 134 (ii) $-NO_2$, (jj) $-NC(O)R^{114}$, (kk) $-COOR^{114}$, (ll) $-N_3$, (mm) $=N-O-R^{114}$, (nn)
 135 $=NR^{114}$, (oo) $=N-NR^{114}R^{114}$, (pp) $=N-NH-C(O)R^{114}$, and (qq) $=N-NH-$
 136 $C(O)NR^{114}R^{114}$;

137 alternatively R^{106} and R^{107} are taken together with the atom to which they are attached
 138 to form an epoxide, a carbonyl, an olefin, or a substituted olefin, or a C_3-C_7 carbocyclic,
 139 carbonate, or carbamate, wherein the nitrogen of said carbamate can be further substituted
 140 with a C_1-C_6 alkyl;

141 R^{108} is selected from:

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

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143 wherein any of (a)–(c) optionally is substituted with one or more R^{114}
 144 groups;

145 R^{111} is selected from H and $-C(O)R^{114}$;

146 R^{112} is selected from H, OH, and OR^{114} ;

147 R^{113} is selected from:

148 (a) H, (b) R^{114} , (c) $-C_{1-6}$ alkyl- $K-R^{114}$, (d) $-C_{2-6}$ alkenyl- $K-R^{114}$, and

149 (e) $-C_{2-6}$ alkynyl- $K-R^{114}$,

150 wherein any of (c)–(e) optionally is substituted with one or more R^{115}
 151 groups;

152 R^{114} , at each occurrence, independently is selected from:

153 (a) H, (b) C_{1-6} alkyl, (c) C_{2-6} alkenyl, (d) C_{2-6} alkynyl, (e) C_{6-10} saturated,
 154 unsaturated, or aromatic carbocycle, (f) 3-12 membered saturated, unsaturated,
 155 or aromatic heterocycle containing one or more heteroatoms selected from
 156 nitrogen, oxygen, and sulfur, (g) $-C(O)-C_{1-6}$ alkyl, (h) $-C(O)-C_{2-6}$ alkenyl,
 157 (i) $-C(O)-C_{2-6}$ alkynyl, (j) $-C(O)-C_{6-10}$ saturated, unsaturated, or aromatic
 158 carbocycle, (k) $-C(O)-3-12$ membered saturated, unsaturated, or aromatic
 159 heterocycle containing one or more heteroatoms selected from nitrogen,
 160 oxygen, and sulfur, (l) $-C(O)O-C_{1-6}$ alkyl, (m) $-C(O)O-C_{2-6}$ alkenyl, (n) –
 161 $C(O)O-C_{2-6}$ alkynyl, (o) $-C(O)O-C_{6-10}$ saturated, unsaturated, or aromatic
 162 carbocycle, (p) $-C(O)O-3-12$ membered saturated, unsaturated, or aromatic
 163 heterocycle containing one or more heteroatoms selected from nitrogen,
 164 oxygen, and sulfur, (q) $-C(O)NR^{116}R^{116}$, (r) $-NR^{116}CO-C_{2-6}$ alkyl, (s) –
 165 $NR^{116}CO-C_{6-10}$ saturated, unsaturated, or aromatic carbocycle, and (t) –
 166 $NR^{116}C(O)-3-12$ membered saturated, unsaturated, or aromatic heterocycle
 167 containing one or more heteroatoms selected from nitrogen, oxygen, and
 168 sulfur,

169 wherein any of (b)–(t) optionally is substituted with one or more R^{115}
 170 groups, wherein one or more non-terminal carbon moieties of any of
 171 (b)–(d) optionally is replaced with oxygen, $S(O)_p$, or $-NR^{116}$,

172 alternatively, $NR^{114}R^{114}$ forms a 3-7 membered saturated, unsaturated or aromatic ring
 173 including the nitrogen atom to which the R^{114} groups are bonded and optionally one or more
 174 moieties selected from O, $S(O)_p$, N, and NR^{118} ;

175 R^{115} is selected from:

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176 (a) R^{117} , (b) C_{1-8} alkyl, (c) C_{2-8} alkenyl, (d) C_{2-8} alkynyl, (e) C_{3-12} saturated,
 177 unsaturated, or aromatic carbocycle, (f) 3-12 membered saturated, unsaturated,
 178 or aromatic heterocycle containing one or more heteroatoms selected from
 179 nitrogen, oxygen, and sulfur,

180 wherein any of (b)–(f) optionally is substituted with one or more R^{117}
 181 groups;

182 R^{116} , at each occurrence, independently is selected from:

183 (a) H, (b) C_{1-6} alkyl, (c) C_{2-6} alkenyl, (d) C_{2-6} alkynyl, (e) C_{3-10} saturated,
 184 unsaturated, or aromatic carbocycle, and (f) 3-10 membered saturated,
 185 unsaturated, or aromatic heterocycle containing one or more heteroatoms
 186 selected from nitrogen, oxygen, and sulfur,

187 wherein one or more non-terminal carbon moieties of any of (b)–(d)
 188 optionally is replaced with oxygen, $S(O)_p$, or $-NR^{114}$, wherein any of
 189 (b)–(f) optionally is substituted with one or more moieties selected
 190 from:

191 (aa) carbonyl, (bb) formyl, (cc) F, (dd) Cl, (ee) Br, (ff) I, (gg)
 192 CN, (hh) N_3 , (ii) NO_2 , (jj) OR^{118} , (kk) $-S(O)_pR^{118}$, (ll) $-$
 193 $C(O)R^{118}$, (mm) $-C(O)OR^{118}$, (nn) $-OC(O)R^{118}$, (oo) $-$
 194 $C(O)NR^{118}R^{118}$, (pp) $-OC(O)NR^{118}R^{118}$, (qq) $-C(=NR^{118})R^{118}$,
 195 (rr) $-C(R^{118})(R^{118})OR^{118}$, (ss) $-C(R^{118})_2OC(O)R^{118}$, (tt) $-$
 196 $C(R^{118})(OR^{118})(CH_2)_rNR^{118}R^{118}$, (uu) $-NR^{118}R^{118}$; (vv) $-$
 197 $NR^{118}OR^{118}$, (ww) $-NR^{118}C(O)R^{118}$, (xx) $-NR^{118}C(O)OR^{118}$,
 198 (yy) $-NR^{118}C(O)NR^{118}R^{118}$, (zz) $-NR^{118}S(O)_pR^{118}$, (ab) $-$
 199 $C(OR^{118})(OR^{118})R^{118}$, (ac) $-C(R^{118})_2NR^{118}R^{118}$, (ad) $=NR^{118}$,
 200 (ae) $-C(S)NR^{118}R^{118}$, (af) $-NR^{118}C(S)R^{118}$, (ag) $-$
 201 $OC(S)NR^{118}R^{118}$, (ah) $-NR^{118}C(S)OR^{118}$, (ai) $-$
 202 $NR^{118}C(S)NR^{118}R^{118}$, (aj) $-SC(O)R^{118}$, (ak) C_{1-8} alkyl, (al)
 203 C_{2-8} alkenyl, (am) C_{2-8} alkynyl, (an) C_{1-8} alkoxy, (ao) C_{1-8}
 204 alkylthio, (ap) C_{1-8} acyl, (aq) saturated, unsaturated, or aromatic
 205 C_{3-10} carbocycle, and (ar) saturated, unsaturated, or aromatic
 206 3-10 membered heterocycle containing one or more
 207 heteroatoms selected from nitrogen, oxygen, and sulfur,

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alternatively, $\text{NR}^{116}\text{R}^{116}$ forms a 3-10 membered saturated, unsaturated or aromatic ring including the nitrogen atom to which the R^{116} groups are attached and optionally one or more moieties selected from O, $\text{S}(\text{O})_p$, N, and NR^{118} ;

alternatively, $\text{CR}^{116}\text{R}^{116}$ forms a carbonyl group;

R^{117} , at each occurrence, is selected from:

(a) H, (b) =O, (c) F, (d) Cl, (e) Br, (f) I, (g) $(\text{CR}^{116}\text{R}^{116})_r\text{CF}_3$, (h) $(\text{CR}^{116}\text{R}^{116})_r\text{CN}$, (i) $(\text{CR}^{116}\text{R}^{116})_r\text{NO}_2$, (j) $(\text{CR}^{116}\text{R}^{116})_r\text{NR}^{116}(\text{CR}^{116}\text{R}^{116})_t\text{R}^{119}$, (k) $(\text{CR}^{116}\text{R}^{116})_r\text{OR}^{119}$, (l) $(\text{CR}^{116}\text{R}^{116})_r\text{S}(\text{O})_p(\text{CR}^{116}\text{R}^{116})_t\text{R}^{119}$, (m) $(\text{CR}^{116}\text{R}^{116})_r\text{C}(\text{O})(\text{CR}^{116}\text{R}^{116})_t\text{R}^{119}$, (n) $(\text{CR}^{116}\text{R}^{116})_r\text{OC}(\text{O})(\text{CR}^{116}\text{R}^{116})_t\text{R}^{119}$, (o) $(\text{CR}^{116}\text{R}^{116})_r\text{SC}(\text{O})(\text{CR}^{116}\text{R}^{116})_t\text{R}^{119}$, (p) $(\text{CR}^{116}\text{R}^{116})_r\text{C}(\text{O})\text{O}(\text{CR}^{116}\text{R}^{116})_t\text{R}^{119}$, (q) $(\text{CR}^{116}\text{R}^{116})_r\text{NR}^{116}\text{C}(\text{O})(\text{CR}^{116}\text{R}^{116})_t\text{R}^{119}$, (r) $(\text{CR}^{116}\text{R}^{116})_r\text{C}(\text{O})\text{NR}^{116}(\text{CR}^{116}\text{R}^{116})_t\text{R}^{119}$, (s) $(\text{CR}^{116}\text{R}^{116})_r\text{C}(=\text{NR}^{116})(\text{CR}^{116}\text{R}^{116})_t\text{R}^{119}$, (t) $(\text{CR}^{116}\text{R}^{116})_r\text{C}(=\text{NNR}^{116}\text{R}^{116})(\text{CR}^{116}\text{R}^{116})_t\text{R}^{119}$, (u) $(\text{CR}^{116}\text{R}^{116})_r\text{C}(=\text{NNR}^{116}\text{C}(\text{O})\text{R}^{116})(\text{CR}^{116}\text{R}^{116})_t\text{R}^{119}$, (v) $(\text{CR}^{116}\text{R}^{116})_r\text{C}(=\text{NOR}^{119})(\text{CR}^{116}\text{R}^{116})_t\text{R}^{119}$, (w) $(\text{CR}^{116}\text{R}^{116})_r\text{NR}^{116}\text{C}(\text{O})\text{O}(\text{CR}^{116}\text{R}^{116})_t\text{R}^{119}$, (x) $(\text{CR}^{116}\text{R}^{116})_r\text{OC}(\text{O})\text{NR}^{116}(\text{CR}^{116}\text{R}^{116})_t\text{R}^{119}$, (y) $(\text{CR}^{116}\text{R}^{116})_r\text{NR}^{116}\text{C}(\text{O})\text{NR}^{116}(\text{CR}^{116}\text{R}^{116})_t\text{R}^{119}$, (z) $(\text{CR}^{116}\text{R}^{116})_r\text{NR}^{116}\text{S}(\text{O})_p(\text{CR}^{116}\text{R}^{116})_t\text{R}^{119}$, (aa) $(\text{CR}^{116}\text{R}^{116})_r\text{S}(\text{O})_p\text{NR}^{116}(\text{CR}^{116}\text{R}^{116})_t\text{R}^{119}$, (bb) $(\text{CR}^{116}\text{R}^{116})_r\text{NR}^{116}\text{S}(\text{O})_p\text{NR}^{116}(\text{CR}^{116}\text{R}^{116})_t\text{R}^{119}$, (cc) $(\text{CR}^{116}\text{R}^{116})_r\text{NR}^{116}\text{R}^{116}$, (dd) C_{1-6} alkyl, (ee) C_{2-6} alkenyl, (ff) C_{2-6} alkynyl, (gg) $(\text{CR}^{116}\text{R}^{116})_r\text{C}_{3-10}$ saturated, unsaturated, or aromatic carbocycle, and (hh) $(\text{CR}^{116}\text{R}^{116})_r\text{3-10}$ membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur,

wherein any of (dd)–(hh) optionally is substituted with one or more R^{119} groups;

alternatively, two R^{117} groups can form $-\text{O}(\text{CH}_2)_u\text{O}-$;

R^{118} is selected from:

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(a) H, (b) C₁₋₆ alkyl, (c) C₂₋₆ alkenyl, (d) C₂₋₆ alkynyl, (e) C₃₋₁₀ saturated, unsaturated, or aromatic carbocycle, (f) 3-10 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur, (g) -C(O)-C₁₋₆ alkyl, (h) -C(O)-C₁₋₆ alkenyl, (g) -C(O)-C₁₋₆ alkynyl, (i) -C(O)-C₃₋₁₀ saturated, unsaturated, or aromatic carbocycle, and (j) -C(O)-3-10 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur,

wherein any of (b)-(j) optionally is substituted with one or more moieties selected from : (aa) H, (bb) F, (cc) Cl, (dd) Br, (ee) I, (ff) CN, (gg) NO₂, (hh) OH, (ii) NH₂, (jj) NH(C₁₋₆ alkyl), (kk) N(C₁₋₆ alkyl)₂, (ll) C₁₋₆ alkoxy, (mm) aryl, (nn) substituted aryl, (oo) heteroaryl, (pp) substituted heteroaryl, and (qq) C₁₋₆ alkyl, optionally substituted with one or more moieties selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, F, Cl, Br, I, CN, NO₂, and OH;

R¹¹⁹, at each occurrence, independently is selected from:

(a) R¹²⁰, (b) C₁₋₆ alkyl, (c) C₂₋₆ alkenyl, (d) C₂₋₆ alkynyl, (e) C₃₋₁₀ saturated, unsaturated, or aromatic carbocycle, and (f) 3-10 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur,

wherein any of (b)-(f) optionally is substituted with one or more R¹¹⁹ groups;

R¹²⁰, at each occurrence, independently is selected from:

(a) H, (b) =O, (c) F, (d) Cl, (e) Br, (f) I, (g) (CR¹¹⁶R¹¹⁶)_rCF₃, (h) (CR¹¹⁶R¹¹⁶)_rCN, (i) (CR¹¹⁶R¹¹⁶)_rNO₂, (j) (CR¹¹⁶R¹¹⁶)_rNR¹¹⁶R¹¹⁶, (k) (CR¹¹⁶R¹¹⁶)_rOR¹¹⁴, (l) (CR¹¹⁶R¹¹⁶)_rS(O)_pR¹¹⁶, (m) (CR¹¹⁶R¹¹⁶)_rC(O)R¹¹⁶, (n) (CR¹¹⁶R¹¹⁶)_rC(O)OR¹¹⁶, (o) (CR¹¹⁶R¹¹⁶)_rOC(O)R¹¹⁶, (p) (CR¹¹⁶R¹¹⁶)_rNR¹¹⁶C(O)R¹¹⁶, (q) (CR¹¹⁶R¹¹⁶)_rC(O)NR¹¹⁶R¹¹⁶, (r) (CR¹¹⁶R¹¹⁶)_rC(=NR¹¹⁶)R¹¹⁶, (s) (CR¹¹⁶R¹¹⁶)_rNR¹¹⁶C(O)NR¹¹⁶R¹¹⁶, (t) (CR¹¹⁶R¹¹⁶)_rNR¹¹⁶S(O)_pR¹¹⁶, (u) (CR¹¹⁶R¹¹⁶)_rS(O)_pNR¹¹⁶R¹¹⁶, (v) (CR¹¹⁶R¹¹⁶)_rNR¹¹⁶S(O)_pNR¹¹⁶R¹¹⁶, (w) C₁₋₆ alkyl, (x) C₂₋₆ alkenyl, (y) C₂₋₆ alkynyl, (z) (CR¹¹⁶R¹¹⁶)_r-C₃₋₁₀ saturated, unsaturated, or aromatic

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271 carbocycle, and (aa) $(CR^{116}R^{116})_1$ -3-10 membered saturated, unsaturated, or
 272 aromatic heterocycle containing one or more heteroatoms selected from
 273 nitrogen, oxygen, and sulfur,

274 wherein any of (w)-(aa) optionally is substituted with one or more
 275 moieties selected from R^{116} , F, Cl, Br, I, CN, NO_2 , $-OR^{116}$, $-NH_2$, $-$
 276 $NH(C_{1-6} \text{ alkyl})$, $-N(C_{1-6} \text{ alkyl})_2$, C_{1-6} alkoxy, C_{1-6} alkylthio, and
 277 C_{1-6} acyl;

278 R^{121} , at each occurrence, independently is selected from:

279 (a) H, (b) $-OR^{118}$, (c) $-O-C_{1-6} \text{ alkyl}-OC(O)R^{118}$, (d) $-O-C_{1-6} \text{ alkyl}-$
 280 $OC(O)OR^{118}$, (e) $-O-C_{1-6} \text{ alkyl}-OC(O)NR^{118}R^{118}$, (f) $-O-C_{1-6} \text{ alkyl}-$
 281 $C(O)NR^{118}R^{118}$, (g) $-O-C_{1-6} \text{ alkyl}-NR^{118}C(O)R^{118}$, (h) $-O-C_{1-6} \text{ alkyl}-$
 282 $NR^{118}C(O)OR^{118}$, (i) $-O-C_{1-6} \text{ alkyl}-NR^{118}C(O)NR^{118}R^{118}$, (j) $-O-C_{1-6} \text{ alkyl}-$
 283 $NR^{118}C(=N(H)NR^{118}R^{118})$, (k) $-O-C_{1-6} \text{ alkyl}-S(O)_pR^{118}$, (l) $-O-C_{2-6} \text{ alkenyl}-$
 284 $OC(O)R^{118}$, (m) $-O-C_{2-6} \text{ alkenyl}-OC(O)OR^{118}$, (n) $-O-C_{2-6} \text{ alkenyl}-$
 285 $OC(O)NR^{118}R^{118}$, (o) $-O-C_{2-6} \text{ alkenyl}-C(O)NR^{118}R^{118}$, (p) $-O-C_{2-6} \text{ alkenyl}-$
 286 $NR^{118}C(O)R^{118}$, (q) $-O-C_{2-6} \text{ alkenyl}-NR^{118}C(O)OR^{118}$, (r) $-O-C_{2-6} \text{ alkenyl}-$
 287 $NR^{118}C(O)NR^{118}R^{118}$, (s) $-O-C_{2-6} \text{ alkenyl}-NR^{118}C(=N(H)NR^{118}R^{118})$, (t) $-O-$
 288 $C_{2-6} \text{ alkenyl}-S(O)_pR^{118}$,
 289 (u) $-O-C_{2-6} \text{ alkynyl}-OC(O)R^{118}$, (v) $-O-C_{2-6} \text{ alkynyl}-OC(O)OR^{118}$,
 290 (w) $-O-C_{2-6} \text{ alkynyl}-OC(O)NR^{118}R^{118}$, (x) $-O-C_{2-6} \text{ alkynyl}-C(O)NR^{118}R^{118}$,
 291 (y) $-O-C_{2-6} \text{ alkynyl}-NR^{118}C(O)R^{118}$, (z) $-O-C_{2-6} \text{ alkynyl}-NR^{118}C(O)OR^{118}$,
 292 (aa) $-O-C_{2-6} \text{ alkynyl}-NR^{118}C(O)NR^{118}R^{118}$,
 293 (bb) $-O-C_{2-6} \text{ alkynyl}-NR^{118}C(=N(H)NR^{118}R^{118})$, (cc) $-O-C_{2-6} \text{ alkynyl}-$
 294 $S(O)_pR^{118}$; and (dd) $-NR^{118}R^{118}$;

295 alternatively, two R^{121} groups taken together form $=O$, $=NOR^{118}$, or $=NNR^{118}R^{118}$;
 296 R^{122} is R^{115} ;

297 R^{123} is selected from:

298 (a) R^{116} , (b) F, (c) Cl, (d) Br, (e) I, (f) CN, (g) NO_2 , and (h) $-OR^{114}$;

299 alternatively, R^{122} and R^{123} taken together are $-O(CH_2)_uO-$;

300 R^{124} , at each occurrence, independently is selected from:

301 (a) H, (b) F, (c) Cl, (d) Br, (e) I, (f) CN, (g) $-OR^{114}$, (h) $-NO_2$, (i) $-NR^{114}R^{114}$,
 302 (j) $C_{1-6} \text{ alkyl}$, (k) $C_{1-6} \text{ acyl}$, and (l) $C_{1-6} \text{ alkoxy}$;

303 R^{125} is selected from:

- 348 -

304 (a) C₁₋₆ alkyl, (b) C₂₋₆ alkenyl, (c) C₂₋₆ alkynyl, (d) C₁₋₆ acyl, (e) C₁₋₆ alkoxy,
 305 (f) C₁₋₆ alkylthio, (g) saturated, unsaturated, or aromatic C₅₋₁₀ carbocycle,
 306 (h) saturated, unsaturated, or aromatic 5-10 membered heterocycle containing
 307 one or more heteroatoms selected from nitrogen, oxygen, and sulfur, (i) -O-
 308 C₁₋₆ alkyl-saturated, unsaturated, or aromatic 5-10 membered heterocycle
 309 containing one or more heteroatoms selected from nitrogen, oxygen, and
 310 sulfur, (j) -NR¹¹⁴-C₁₋₆ alkyl-saturated, unsaturated, or aromatic 5-10
 311 membered heterocycle containing one or more heteroatoms selected from
 312 nitrogen, oxygen, and sulfur, (k) saturated, unsaturated, or aromatic 10-
 313 membered bicyclic ring system optionally containing one or more heteroatoms
 314 selected from nitrogen, oxygen, and sulfur, (l) saturated, unsaturated, or
 315 aromatic 13-membered tricyclic ring system optionally containing one or more
 316 heteroatoms selected from nitrogen, oxygen, and sulfur, (m) -OR¹¹⁴,
 317 (n) -NR¹¹⁴R¹¹⁴, (o) -S(O)_pR¹¹⁴, and (p) -R¹²⁴,

318 wherein any of (a)-(l) optionally is substituted with one or more R¹¹⁵
 319 groups;

320 alternatively, R¹²⁵ and one R¹²⁴ group, taken together with the atoms to which they are
 321 bonded, form a 5-7 membered saturated or unsaturated carbocycle, optionally substituted
 322 with one or more R¹¹⁵ groups; or a 5-7 membered saturated or unsaturated heterocycle
 323 containing one or more atoms selected from nitrogen, oxygen, and sulfur, and optionally
 324 substituted with one or more R¹¹⁵ groups;

325 R¹²⁶ at each occurrence, independently is selected from:

326 (a) hydrogen, (b) an electron-withdrawing group, (c) aryl, (d) substituted aryl,
 327 (e) heteroaryl, (f) substituted heteroaryl, and (g) C₁₋₆ alkyl, optionally
 328 substituted with one or more R¹¹⁵ groups;

329 alternatively, any R¹²⁶ and any R¹²³, taken together with the atoms to which they are
 330 bonded, form a 5-7 membered saturated or unsaturated carbocycle, optionally substituted
 331 with one or more R¹¹⁵ groups; or a 5-7 membered saturated or unsaturated heterocycle
 332 containing one or more atoms selected from nitrogen, oxygen, and sulfur, and optionally
 333 substituted with one or more R¹¹⁵ groups;

334 R¹⁰⁹ is H or F;

335 R¹²⁷ is R¹¹⁴, a monosaccharide or disaccharide (including amino sugars and halo
 336 sugar(s), -(CH₂)_n-(O-CH₂CH₂)_m-O(CH₂)_pCH₃ or -(CH₂)_n-(O-CH₂CH₂)_m-OH

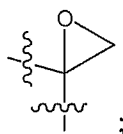
- 349 -

337 R^{128} is R^{114} ;

338 R^{129} is R^{114} ;

339 R^{110} is R^{114} ;

340 alternatively, R^{109} and R^{110} taken together with the carbons to which they are attached
341 form:



342

343 alternately, R^{128} and R^{129} together with the carbons to which they are attached form a
344 3-6 membered saturated, unsaturated or aromatic carbocyclic or heterocyclic ring
345 which can optionally be substituted with one or more R^{114} groups;

346 R^{132} , R^{133} , and R^{134} are each independently selected from (a) H, (b) F, (c) Cl, (d) Br,
347 (e) $-OR^{114}$, (f) $-SR^{114}$, (g) $-NR^{114}R^{114}$, and (h) C_{1-6} alkyl, wherein (h) optionally is
348 substituted with one or more R^{115} groups;

349 alternatively, R^{132} and R^{133} are taken together to form a carbon-carbon double;

350 alternatively, R^{133} and R^{134} are taken together to form $=O$, $=S$, $=NOR^{114}$, $=NR^{114}$, and
351 $=N-NR^{114}R^{114}$;

352 alternatively, R^{105} and R^{134} are taken together with the carbons to which they are
353 attached to form a 3-membered ring, said ring optionally containing an oxygen or
354 nitrogen atom, and said ring being optionally substituted with one or more R^{114}
355 groups;

356 alternatively when M is a carbon moiety, R^{134} and M are taken together to form a
357 carbon-carbon double bond;

358 k, at each occurrence is 0, 1, or 2;

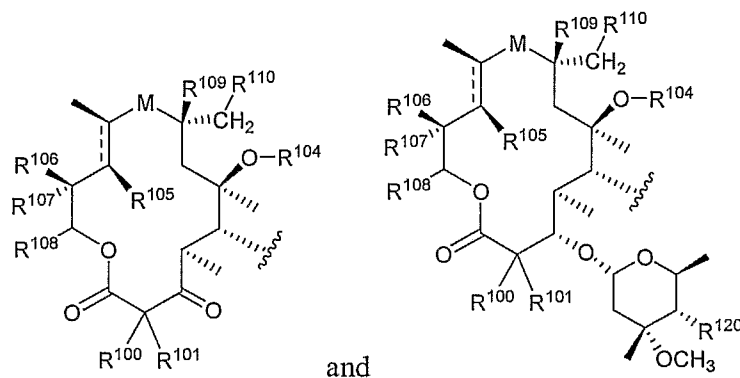
359 m, at each occurrence is 0, 1, 2, 3, 4, or 5;

360 n, at each occurrence is 1, 2, or 3.

361

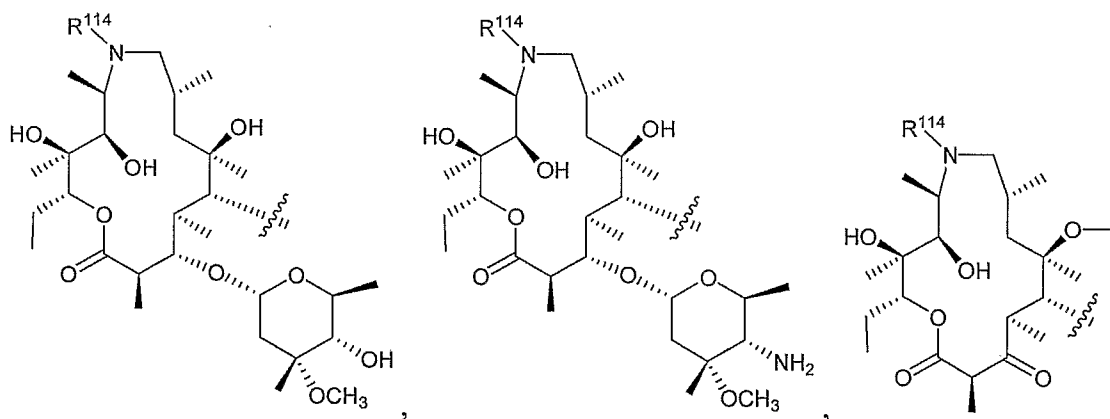
- 1 39. A compound according to any one of claims 1-38, wherein T is a macrolide selected
- 2 from:

- 350 -

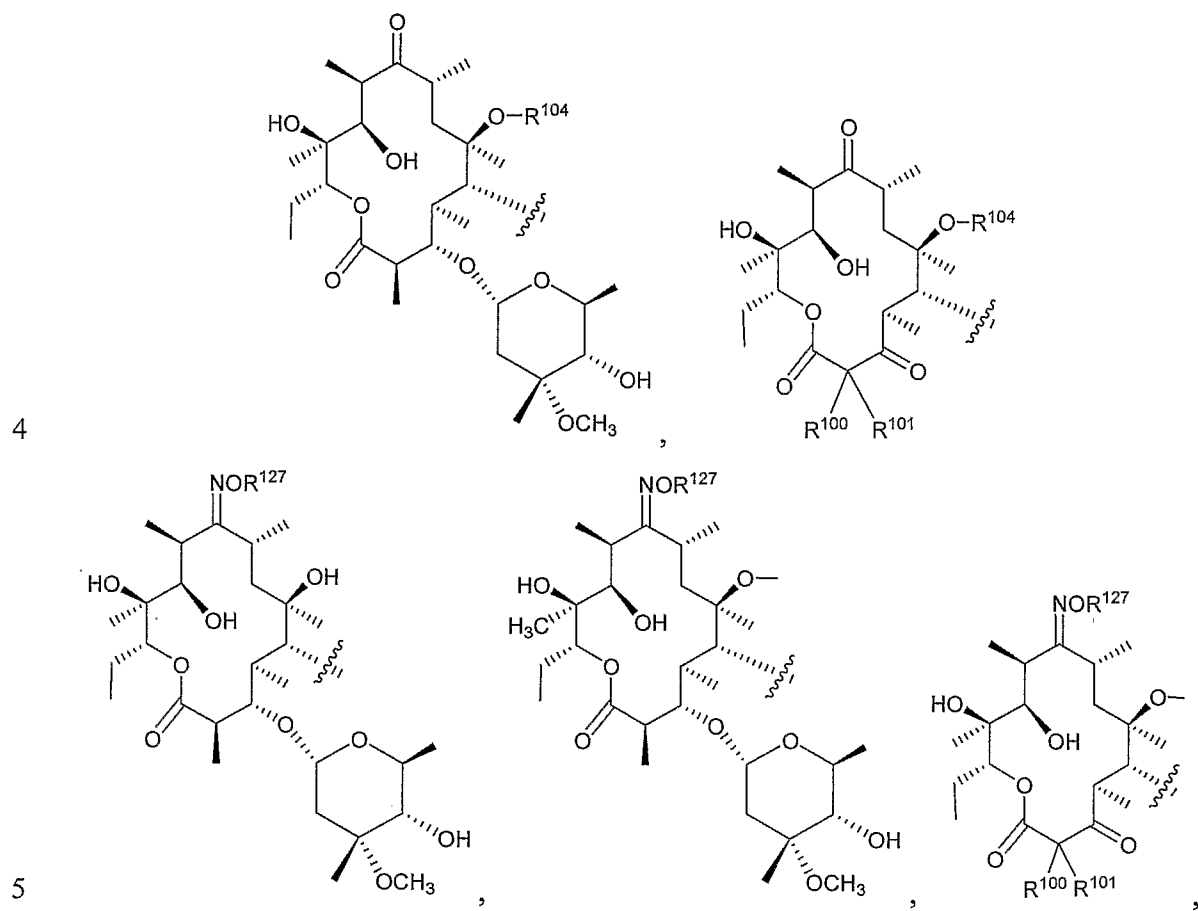


or an *N*-oxide, pharmaceutically acceptable salt, ester, or prodrug thereof, wherein M, R¹⁰⁰, R¹⁰¹, R¹⁰⁴, R¹⁰⁵, R¹⁰⁶, R¹⁰⁷, R¹⁰⁸, R¹⁰⁹, R¹¹⁰, and R¹²⁰ are as described in claim 38 and where the dotted lines indicate optional double bonds.

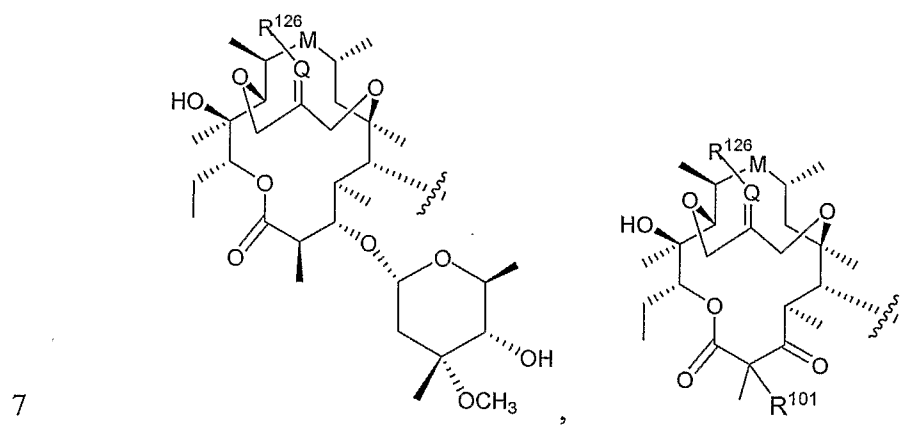
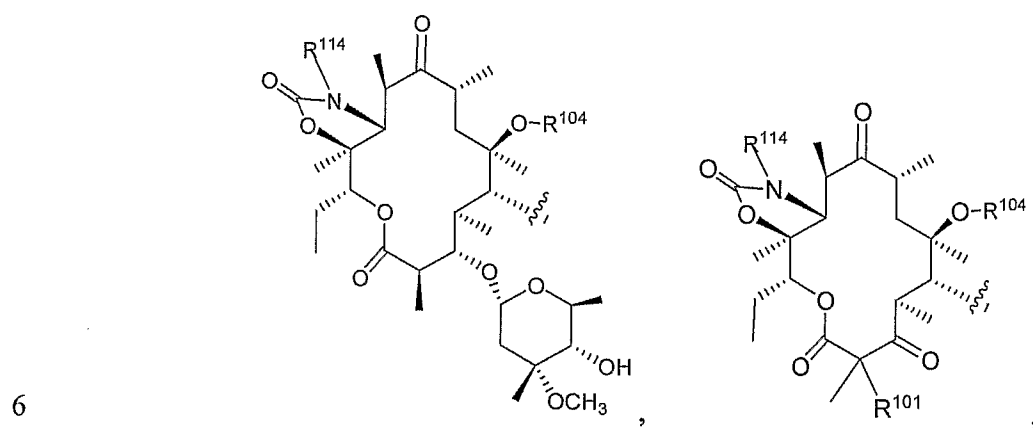
40. A compound according to any one of claims 1-39, wherein T is a macrolide selected from:



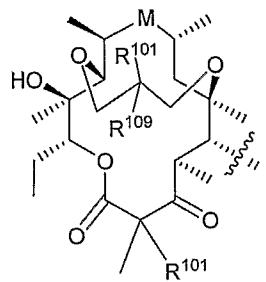
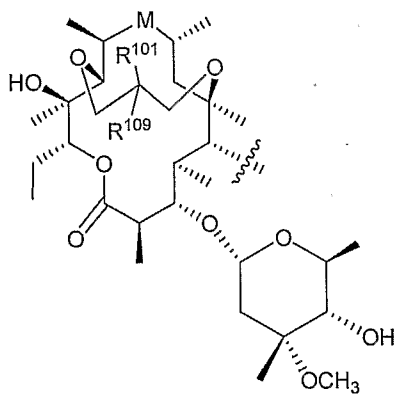
- 351 -



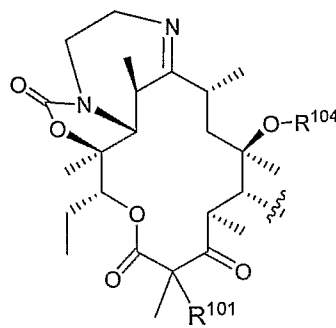
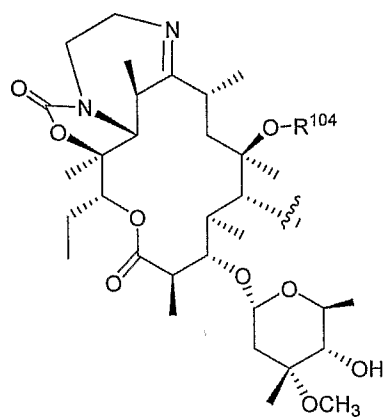
- 352 -



- 353 -



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9

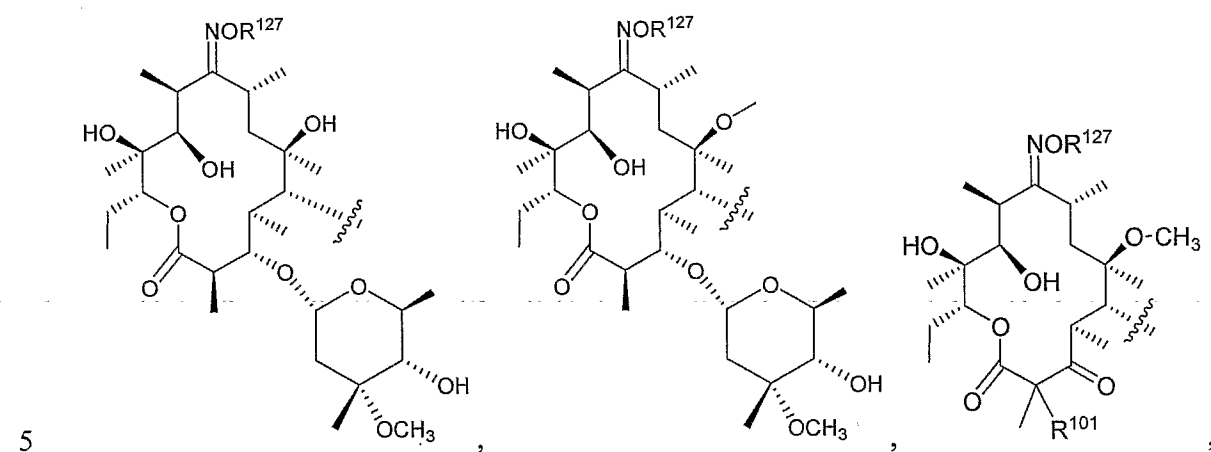
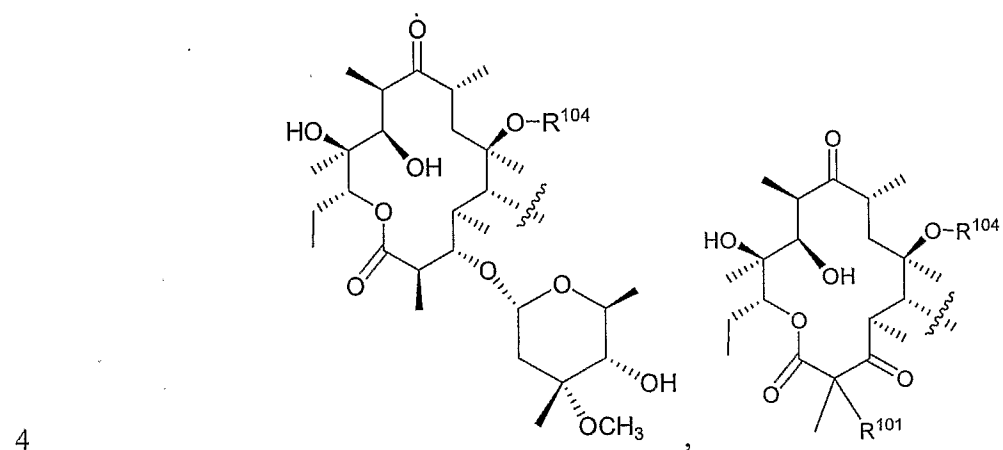
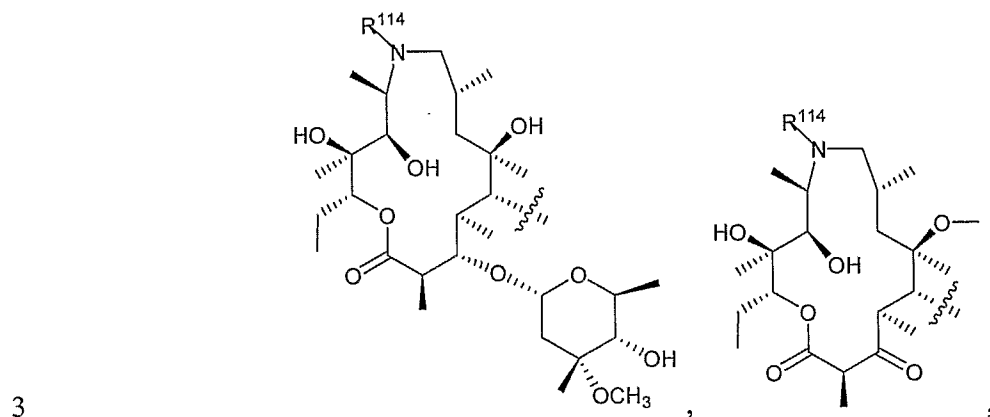
10 or an *N*-oxide, pharmaceutically acceptable salt, ester, or prodrug thereof,

11 wherein M, R¹⁰⁰, R¹⁰¹, R¹⁰², R¹⁰⁴, R¹⁰⁹, R¹¹⁴, R¹²⁶ and R¹²⁷ are as described in claim 38.

12

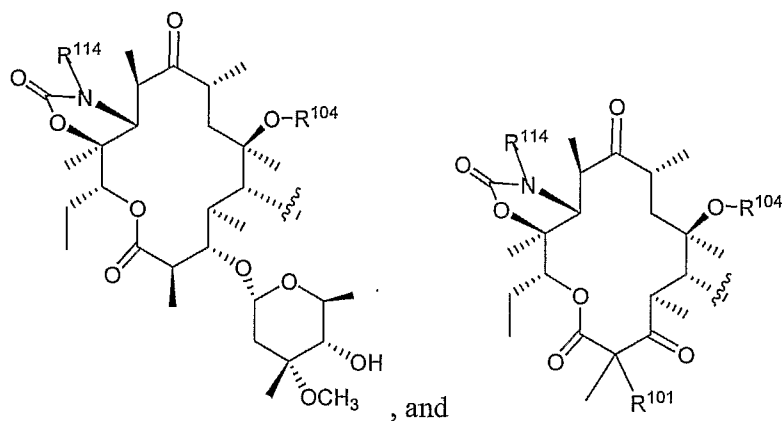
1 41. A compound according to any one of claims 1-40, wherein T is a macrolide selected
2 from:

- 354 -



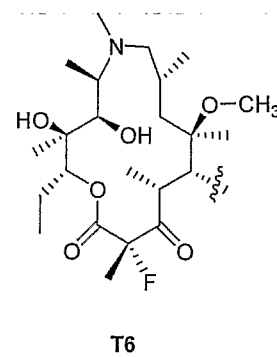
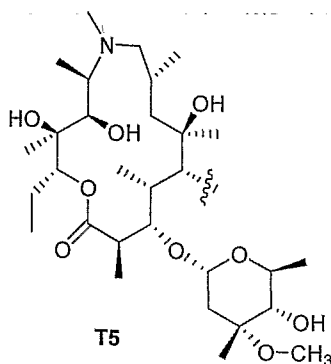
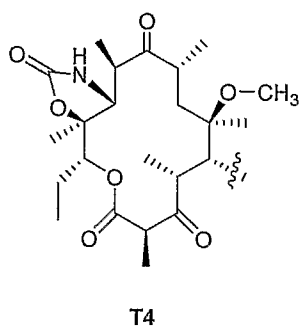
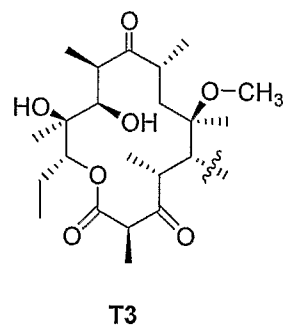
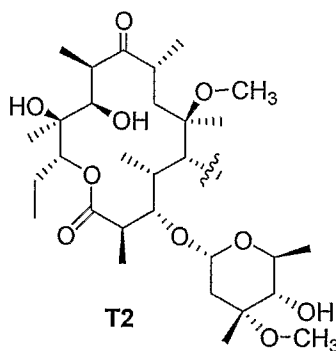
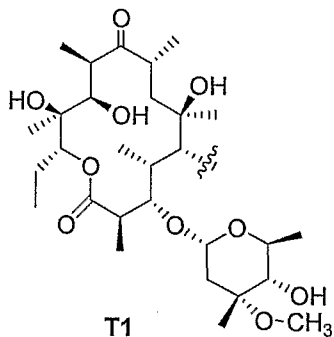
6

- 355 -

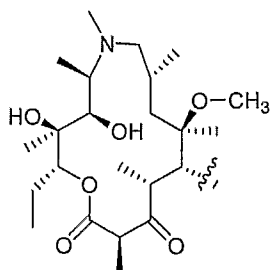


or an *N*-oxide, pharmaceutically acceptable salt, ester, or prodrug thereof,
 wherein M, R¹, R², R¹⁰⁴, R¹¹⁴, R¹⁰⁹ and R¹²⁷ are as described in claim 38.

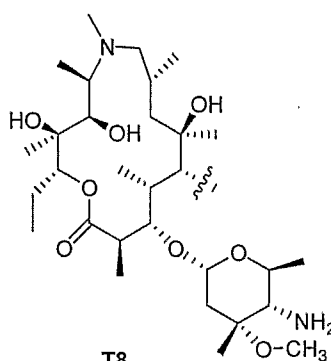
42. A compound according to any one of claims 1-41, wherein T is a macrolide selected from T1 through T33:



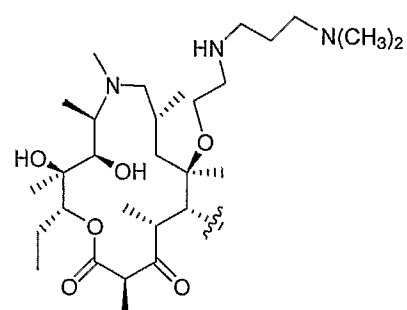
- 356 -



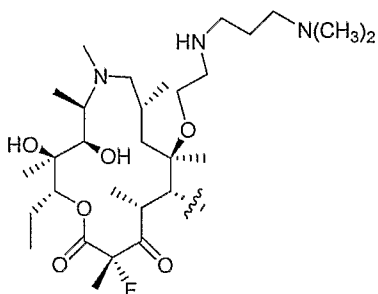
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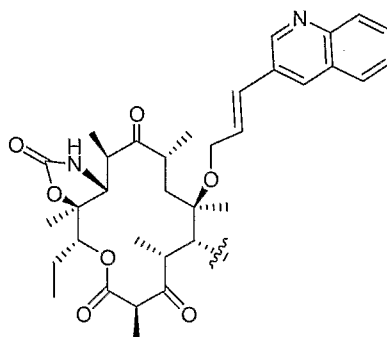
T8



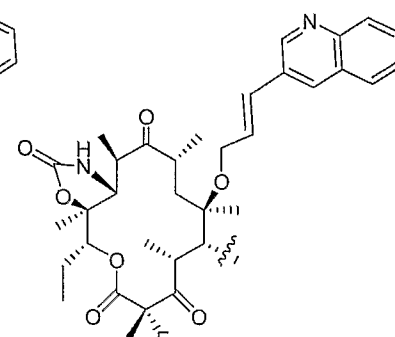
T9



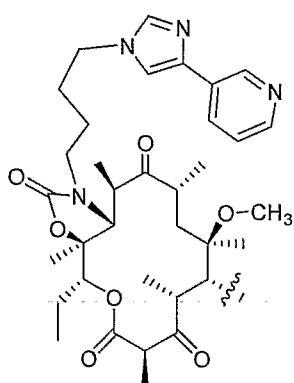
T10



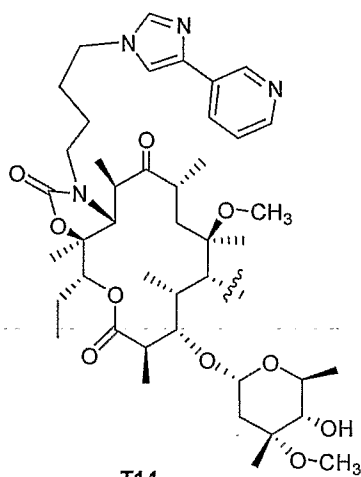
T11



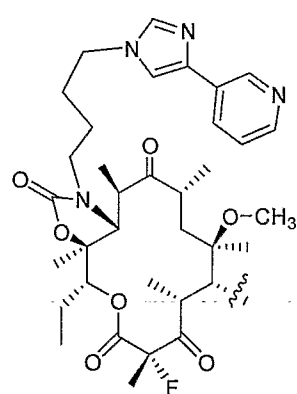
T12



T13

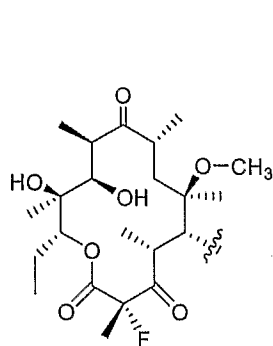


T14

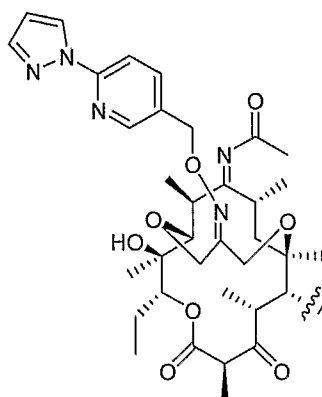


T15

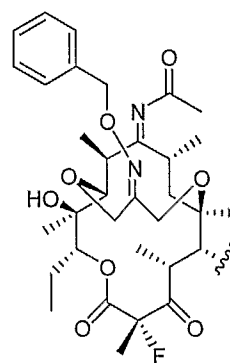
- 357 -



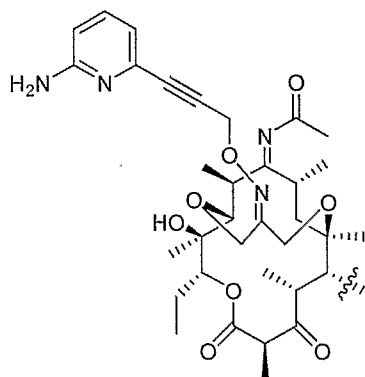
T16



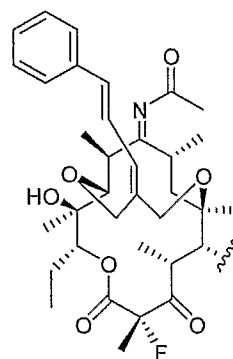
T17



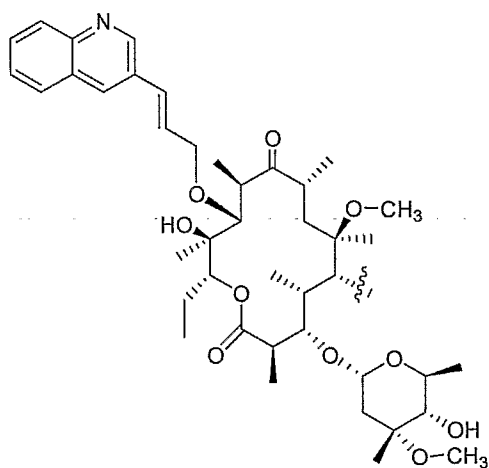
T18



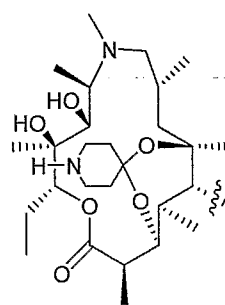
T19



T20



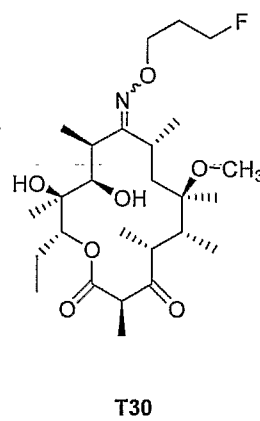
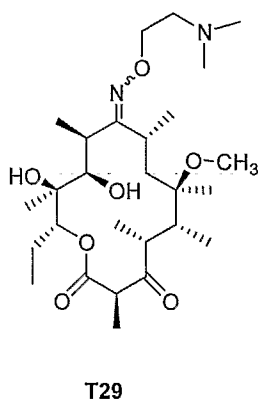
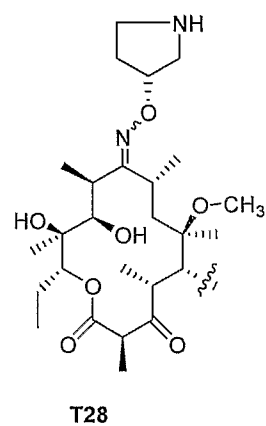
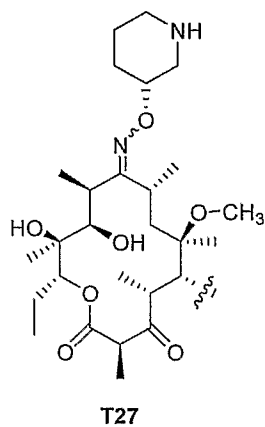
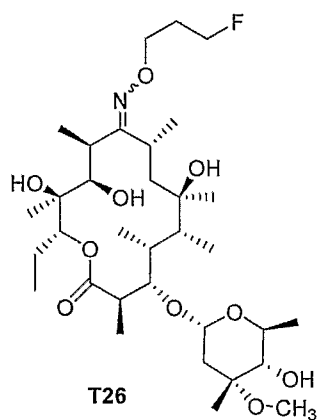
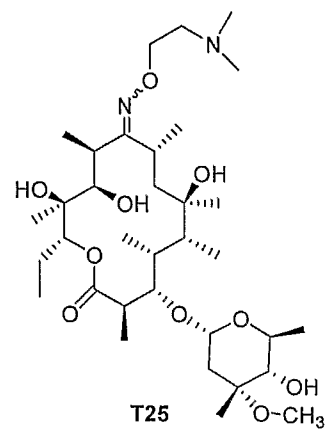
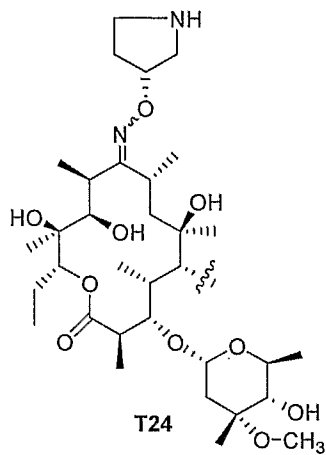
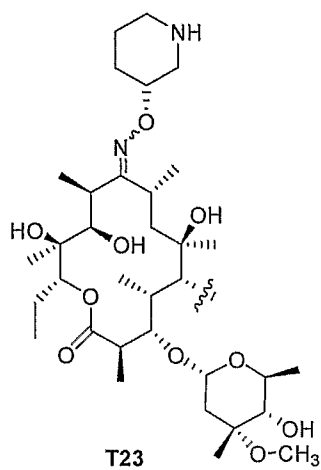
T21



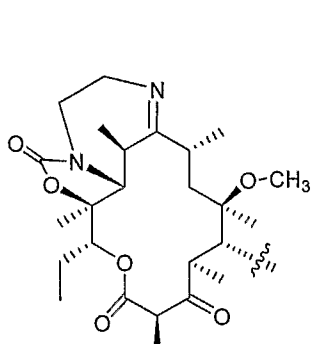
T22

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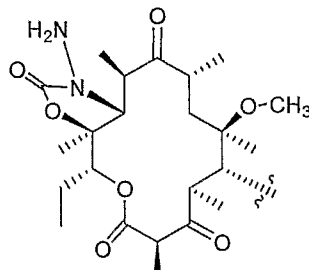
- 358 -



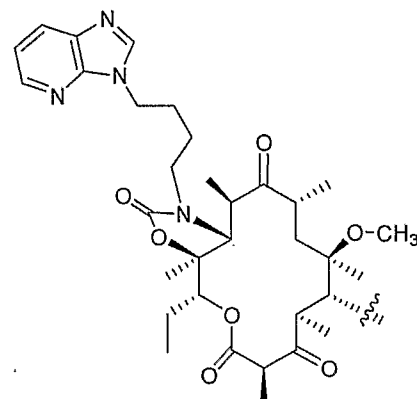
- 359 -



T31



T32



T33

29

30

1 43. A compound having the structure corresponding to any one of the structures listed in
 2 Table 1 or 1A, or a pharmaceutically acceptable salt, ester, *N*-oxide, or prodrug
 3 thereof.

4

1 44. A pharmaceutical composition comprising a compound according to any one of
 2 claims 1-43, or a pharmaceutically acceptable salt, ester, *N*-oxide, or prodrug thereof, and a
 3 pharmaceutically acceptable carrier.

4

1 45. A method for treating or preventing a disease state in a mammal comprising
 2 administering to a mammal in need thereof an effective amount of a compound according to
 3 any one of claims 1-43, or a pharmaceutically acceptable salt, ester, *N*-oxide, or prodrug
 4 thereof.

5

1 46. A method of treating a microbial infection in a mammal comprising administering to
 2 the mammal an effective amount of a compound according to any one of claims 1-43, or a
 3 pharmaceutically acceptable salt, ester, *N*-oxide, or prodrug thereof.

4

5 47. A method according to claim 46 wherein said microbial infection is an uncomplicated
 6 skin or soft tissue infection (uSSTI).

7

1 48. A method according to claim 46 wherein said microbial infection is a community
 2 acquired or community associated infection.

3

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1 49. A method according to claim 48 wherein said microbial infection is an uncomplicated
2 skin or soft tissue infection (uSSTI).
3

1 50. A method of treating a fungal infection in a mammal comprising administering to the
2 mammal an effective amount of a compound according to any one of claims 1-43, or a
3 pharmaceutically acceptable salt, ester, *N*-oxide, or prodrug thereof.
4

1 51. A method of treating a parasitic disease in a mammal comprising administering to the
2 mammal an effective amount of a compound according to any one of claims 1-43, or a
3 pharmaceutically acceptable salt, ester, *N*-oxide, or prodrug thereof.
4

1 52. A method of treating a proliferative disease in a mammal comprising administering to
2 the mammal an effective amount of a compound according to any one of claims 1-43, or a
3 pharmaceutically acceptable salt, ester, *N*-oxide, or prodrug thereof.
4

1 53. A method of treating a viral infection in a mammal comprising administering to the
2 mammal an effective amount of a compound according to any one of claims 1-43, or a
3 pharmaceutically acceptable salt, ester, *N*-oxide, or prodrug thereof.
4

1 54. A method of treating an inflammatory disease in a mammal comprising administering
2 to the mammal an effective amount of a compound according to any one of claims 1-43, or a
3 pharmaceutically acceptable salt, ester, *N*-oxide, or prodrug thereof.
4

1 55. A method of treating a gastrointestinal motility disorder in a mammal comprising
2 administering to the mammal an effective amount of a compound according to any one of
3 claims 1-43, or a pharmaceutically acceptable salt, ester, *N*-oxide, or prodrug thereof.
4

1 56. A method of treating or preventing a disease state in a mammal caused or mediated by
2 a nonsense or missense mutation comprising administering to a mammal in need thereof an
3 effective amount of a compound according to any one of claims 1-43, or a pharmaceutically
4 acceptable salt, ester, *N*-oxide, or prodrug thereof, to suppress expression of the nonsense or
5 missense mutation.
6

-361-

1 57. The method according to any one of claims 45-56 wherein the compound, or a
2 pharmaceutically acceptable salt, ester, *N*-oxide, or prodrug thereof, is administered orally,
3 parentally, or topically.

4

1 58. A method of synthesizing a compound according to any of claims 1-43, or a
2 pharmaceutically acceptable salt, ester, *N*-oxide, or prodrug thereof.

3

1 59. A medical device containing a compound according to any one of claims 1-43, or a
2 pharmaceutically acceptable salt, ester, *N*-oxide, or prodrug thereof.

3

60. The medical device according to claim 59, wherein the device is a stent.

5