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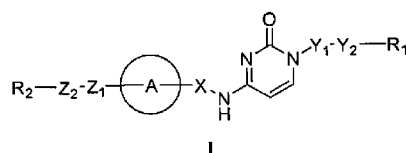
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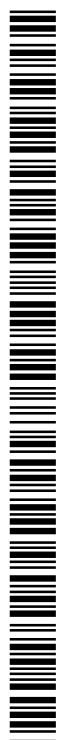
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(54) Title: ANTIMICROBIAL COMPOUNDS



(57) **Abstract:** Disclosed are compounds of formula I: or pharmaceutically acceptable salts thereof. Compounds of formula I are anti-microbials that inhibit, for instance, Mycobacterium tuberculosis (Mtb) H37Ra. Compounds of formula I also have anti-tubercular activity, exhibit limited cytotoxicity, and inhibit protein synthesis. Processes for making compounds of formula I are also disclosed, as well as methods of using compounds of formula I for the treatment of bacterial infections, particularly tuberculosis.



ANTIMICROBIAL COMPOUNDS

Background of the Invention

[0001] Tuberculosis (TB) remains one of the world's leading causes of death from a single infectious agent, second only to Human Immunodeficiency Virus (HIV). About one third of the world's population is infected with latent TB, with over 9 million active TB cases and 1.3 million TB-related deaths in 2012. Recent years have seen an increase in the number of deadly strains of TB. As of 2012, extensively drug resistant TB (XDR-TB) has been reported in over 91 countries, as well as totally drug resistant strains in Italy, Iran, and India.

[0002] TB is the most common illness among people with HIV. The World Health Organization estimated that 12 million people living with HIV are co-infected with TB. It is the leading cause of death among people with HIV infection with about 320,000 HIV-associated TB deaths reported in 2012.

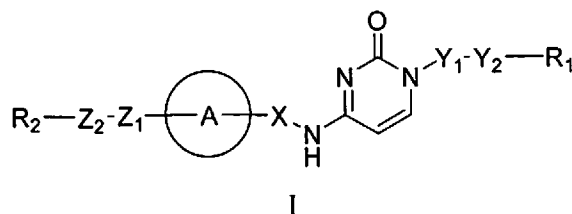
[0003] TB-HIV co-infection is aggravated by the activation of hepatic cytochromes (CYP2C9 and CYP3A4) by the current TB drugs (e.g. rifampin). There are several mechanisms by which these enzymes are upregulated. CYP2C9 and CYP3A4 are liver proteins that degrade drugs including the anti-retrovirals, especially HIV-protease inhibitors and NNRTIs used in treating HIV. Activation of these proteins renders the plasma levels of the anti-retrovirals subtherapeutic, which concomitantly accelerates the progression of TB due to increased weakening of the immune system. Further, an ineffective regimen of TB therapeutics leads to increased resistance in organisms.

[0004] Current treatment regimens are long (6-24 months), complicated (IV and oral dosing) and the side-effects significant enough to preclude treatment until the patient becomes symptomatic. The reasons for TB latency are not fully understood, but it has been hypothesized that its ability to dwell in the biofilm phenotype may be, at a minimum, partially responsible. Inhibiting Mtb biofilm development (with an unrelated chemotype) may therefore hold promise to treat latent TB.

[0005] Given this global health threat and the inadequacy of currently available treatments, it is imperative to identify new drug candidates which are 1) active against TB and XDR-TB, 2) non-cytotoxic; and 3) compatible with anti-retroviral therapeutics (ART) (i.e. non-cytochrome inducing).

Summary of the Invention

[0006] These and other needs are met by the present invention which provides in one aspect a compound of formula I:



or a pharmaceutically acceptable salt thereof, wherein:

X is absent or is selected from the group consisting of $-(C=O)-$ and $-SO_2-$;

A is phenylene optionally substituted with one or two halo;

Y_1 is selected from the group consisting of CH_2 or optionally substituted phenylene;

Y_2 is absent or is selected from the group consisting of optionally substituted C_1 - C_{10} alkylene, optionally substituted C_1 - C_{10} alkenylene, and optionally substituted C_1 - C_{10} alkynylene, wherein up to three carbons of the optionally substituted C_1 - C_{10} alkylene, optionally substituted C_1 - C_{10} alkenylene, and optionally substituted C_1 - C_{10} alkynylene, are independently replaced by optionally substituted phenylene, O, NH, N-(C_{1-6} alkyl) (C=O), or NH(C=O);

R_1 is selected from the group consisting of H, halo, $NR_1'R_1''$, and heterocycloalkyl optionally substituted with NH_2 or Me; wherein R_1' and R_1'' are each independently selected from H and Me;

Z_1 is absent or is selected from the group consisting of CH_2 , phenylene, $-CH_2O-$, $-CH_2NH-$, $-CH_2N(C_{1-6} \text{ alkyl})-$, $-CH_2(C=O)-$, $C=O$, and $-NH(C=O)-$;

Z_2 is absent or is selected from the group consisting of optionally substituted C_1 - C_{10} alkylene, and optionally substituted heterocycloalkylene; and

R_2 is selected from H, OH, NH_2 , $NH(C_{1-6} \text{ alkyl})$, $N(C_{1-6} \text{ alkyl})_2$, $NH(\text{cycloalkyl})$, $N(\text{cycloalkyl})_2$.

[0007] Compounds of formula I are structurally related to amicetin, a ribosomal antibiotic isolated from *Streptomyces vinaceusdrappus*. Amicetin is a known inhibitor of protein synthesis that is active against a number of acid-fast gram-positive bacteria including *Mycobacterium tuberculosis* (Mtb). Amicetin exhibits an IC_{50} of $0.24 \mu M$ ($0.15 \mu g/mL$) against Mtb H37Ra and an EC_{50} of $4.4 \mu M$ ($2.8 \mu g/mL$) against CEM/TART T-Cell leukemia lineage, respectively, corresponding to almost 20-fold selectivity index. Amicetin was also found to be a poor inducer of CYP2C9 and CYP3A4 (< 2 fold induction as measured by qPCR in the HepG2 cell line), making it potentially compatible with ART. However, due to its chemical complexity and instability it remains a poor drug candidate. Most notably the

cytosine-glycol linkage is labile and hydrolysis produces two fragments (amicetamine and cytidine) which are not active against MTb.

[0008] We surprisingly found that while compounds of formula I selectively inhibit Mtb H37Ra, they exhibit limited cytotoxicity against mammalian cells and low CYP induction.

[0009] In another aspect, the invention provides methods of using compounds of formula I for the treatment of bacterial infections.

[0010] In a further aspect, the invention provides processes for making compounds of formula I as depicted in the synthetic schemes.

Brief Description of the Drawings

[0011] FIG. 1 provides IC₅₀ curves for selected compounds of formula I compared to ampicillin.

[0012] FIG. 2 provides protein synthesis inhibition curves for selected compounds of formula I compared to ampicillin.

Detailed Description of the Invention

[0013] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety, including U.S. Pat. Publ. No. 2013/0090326. In case of conflict, the present specification, including these definitions, will control.

[0014] The terms “a,” “an,” and “the” as used herein not only include aspects with one member, but also include aspects with more than one member.

[0015] The term “about” as used herein means “approximately” and is used to modify a numerical value indicates a defined range around that value. If “X” were the value, “about X” would generally indicate a value from 0.95X to 1.05X. Any reference to “about X” specifically indicates at least the values X, 0.95X, 0.96X, 0.97X, 0.98X, 0.99X, 1.01X, 1.02X, 1.03X, 1.04X, and 1.05X. Thus, “about X” is intended to teach and provide written description support for a claim limitation of, e.g., “0.98X.” When the quantity “X” only includes whole-integer values (e.g., “X carbons”), “about X” indicates from (X-1) to (X+1).

In this case, “about X” as used herein specifically indicates at least the values X, X-1, and X+1.

[0016] When “about” is applied to the beginning of a numerical range, it applies to both ends of the range. Thus, “from about 5 to 20%” is equivalent to “from about 5% to about 20%.” When “about” is applied to the first value of a set of values, it applies to all values in that set. Thus, “about 7, 9, or 11%” is equivalent to “about 7%, about 9%, or about 11%.”

[0017] The term “acyl” as used herein includes an alkanoyl, aroyl, heterocycloyl, or heteroaroyl group as defined herein. Examples of acyl groups include, but are not limited to, acetyl, benzoyl, and nicotinoyl.

[0018] The term “alkanoyl” as used herein includes an alkyl-C(O)- group wherein the alkyl group is as defined herein. Examples of alkanoyl groups include, but are not limited to, acetyl and propanoyl.

[0019] The term “agent” as used herein includes a compound or mixture of compounds that, when added to a composition, tend to produce a particular effect on the composition’s properties. For example, a composition comprising a thickening agent is likely to be more viscous than an otherwise identical comparative composition that lacks the thickening agent.

[0020] The term “alkenyl” as used herein includes a straight or branched chain hydrocarbon containing at least one carbon-carbon double bond. The chain may contain an indicated number of carbon atoms. For example, “C₁-C₁₂ alkenyl” indicates that the group may have from 1 to 12 (inclusive) carbon atoms and at least one carbon-carbon double bond. When the indicated number of carbon atoms is 1, then the C_i alkenyl is double bonded to a carbon (*i.e.*, a carbon equivalent to an oxo group). In certain aspects, the chain includes 1 to 12, about 2 to 15, about 2 to 12, about 2 to 8, or about 2 to 6 carbon atoms. An alkenyl group can be preferably one stereoisomer (*i.e.*, *cis*- or, alternatively, *trans*-). Examples of an alkenyl group may include, but are not limited to, ethenyl (*i.e.*, vinyl), allyl, propenyl, butenyl, crotyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl, dodecenyl, cyclopentenyl, cyclohexenyl, 2-isopentenyl, allenyl, butadienyl, pentadienyl, 3-(1,4-pentadienyl), and hexadienyl.

[0021] An alkenyl group can be unsubstituted or optionally substituted. When optionally substituted, one or more hydrogen atoms of the alkenyl group (e.g., from 1 to 4, from 1 to 2, or 1) may be replaced with a moiety independently selected from the group consisting of fluoro, hydroxy, alkoxy, amino, alkylamino, acylamino, thio, and alkylthio, with the proviso that no hydrogen atom substituent on the carbon-carbon double bond is replaced by a

hydroxy, amino, or thio group. In some aspects, the alkenyl group is unsubstituted or not optionally substituted.

[0022] “Alkenylene” as used herein includes an alkenyl group that is substituted at two points. An example is but-2-enylene ($-\text{CH}_2\text{CH}=\text{CHCH}_2-$) and the like.

[0023] The term “alkyl” as used herein includes an aliphatic hydrocarbon chain that may be straight chain or branched. The chain may contain an indicated number of carbon atoms: For example, $\text{C}_1\text{-C}_{10}$ indicates that the group may have from 1 to 10 (inclusive) carbon atoms in it. If not otherwise indicated, an alkyl group contains from 1 to about 20 carbon atoms. In some aspects, alkyl groups have 1 to about 10 carbon atoms. In some aspects, alkyl groups (“lower alkyl”) have 1 to 8, 1 to 6, or 1 to 3 carbon atoms in the chain. Examples may include, but are not limited to, methyl, ethyl, propyl, isopropyl (iPr), 1-butyl, 2-butyl, isobutyl (iBu), *tert*-butyl, pentyl, 2-methylbutyl, 1,1-dimethylpropyl, hexyl, heptyl, octyl, nonyl, decyl, dodecyl, cyclopentyl, or cyclohexyl.

[0024] An alkyl group can be unsubstituted or optionally substituted. When optionally substituted, one or more hydrogen atoms of the alkyl group (e.g., from 1 to 4, from 1 to 2, or 1) may be replaced with a moiety independently selected from the group consisting of fluoro, hydroxy, haloalkyl, alkoxy, amino, alkylamino, acylamino, thio, and alkylthio. In some aspects, the alkyl group is unsubstituted or not optionally substituted.

[0025] “Alkylene” as used herein includes an alkyl group that is substituted at two points. An example is methylene ($-\text{CH}_2-$), propylene ($-\text{CH}_2\text{CH}_2\text{CH}_2-$), and the like.

[0026] An alkylene group can be unsubstituted or optionally substituted. When optionally substituted, one or more hydrogen atoms of the alkyl group (e.g., from 1 to 4, from 1 to 2, or 1) may be replaced with a moiety independently selected from the group consisting of fluoro, aryl, hydroxy, haloalkyl, haloalkoxy, alkyl, alkoxy, amino, alkylamino, acylamino, thio, and alkylthio. In some aspects, the alkylene group is unsubstituted or not optionally substituted.

[0027] The term “alkoxy” as used herein includes a straight or branched chain saturated or unsaturated hydrocarbon containing at least one oxygen atom in an ether group (e.g., $\text{EtO}-$). The chain may contain an indicated number of carbon atoms. For example, “ $\text{C}_1\text{-C}_{12}$ alkoxy” indicates that the group may have from 1 to 12 (inclusive) carbon atoms and at least one oxygen atom. Examples of a $\text{C}_1\text{-C}_{12}$ alkoxy group include, but are not limited to, methoxy, ethoxy, isopropoxy, butoxy, *n*-pentoxy, isopentoxy, neopentoxy, and hexoxy.

[0028] An alkoxy group can be unsubstituted or optionally substituted. When optionally substituted, one or more hydrogen atoms of the alkoxy group (e.g., from 1 to 4, from 1 to 2, or 1) may be replaced with a moiety independently selected from the group consisting of

fluoro, hydroxy, alkoxy, amino, alkylamino, acylamino, thio, and alkylthio, with the proviso that no hydrogen atom alpha to the ether oxygen is replaced by a hydroxy, amino, or thio group. In some aspects, the alkoxy group is unsubstituted or not optionally substituted.

[0029] The term “alkynyl” as used herein includes a straight, branched, or cyclic hydrocarbon containing at least one carbon–carbon triple bond. Examples may include, but are not limited to, ethynyl, propargyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl, or decynyl.

[0030] “Alkynylene” as used herein includes an alkynyl group that is substituted at two points. An example is 2-butynylene ($-\text{CH}_2\text{CCCH}_2-$) and the like.

[0031] An alkynyl group can be unsubstituted or optionally substituted. When optionally substituted, one or more hydrogen atoms of the alkynyl group (e.g., from 1 to 4, from 1 to 2, or 1) may be replaced with a moiety independently selected from the group consisting of fluoro, hydroxy, alkoxy, amino, alkylamino, acylamino, thio, and alkylthio, with the proviso that no sp-hybridized hydrogen atom substituent is replaced by a hydroxy, amino, or thio group. In some aspects, the alkynyl group is unsubstituted or not optionally substituted.

[0032] The term “aryl” as used herein includes cyclic aromatic carbon ring systems containing from 6 to 18 carbons. Examples of an aryl group include, but are not limited to, phenyl, naphthyl, anthracenyl, tetracenyl, biphenyl and phenanthrenyl.

[0033] “Arylene” as used herein includes an aryl group that is substituted at two points. An example is phenylene.

[0034] An aryl group can be unsubstituted or optionally substituted. When optionally substituted, one or more hydrogen atoms of the aryl group (e.g., from 1 to 5, from 1 to 2, or 1) may be replaced with a moiety independently selected from the group consisting of alkyl, cyano, acyl, halo, hydroxy, alkoxy, amino, alkylamino, acylamino, thio, and alkylthio. In some aspects, the alkoxy group is unsubstituted or not optionally substituted.

[0035] The term “arylalkyl” or “aralkyl” as used herein includes an alkyl group as defined herein where at least one hydrogen substituent has been replaced with an aryl group as defined herein. Examples include, but are not limited to, benzyl, 1-phenylethyl, 4-methylbenzyl, and 1,1,-dimethyl-1-phenylmethyl.

[0036] An arylalkyl or aralkyl group can be unsubstituted or optionally substituted as per its component groups. For example, but without limitation, the aryl group of an arylalkyl group can be substituted, such as in 4-methylbenzyl. In some aspects, the group is unsubstituted or not optionally substituted, especially if including a defined substituent, such as a hydroxyalkyl or alkylaminoalkoxy group.

[0037] The term “cycloalkyl” as used herein includes a cyclic hydrocarbon group that may contain an indicated number of carbon atoms: For example, C₃-C₁₂ indicates that the group may have from 3 to 12 (inclusive) carbon atoms in it. If not otherwise indicated, a cycloalkyl group includes about 3 to about 20 carbon atoms. In some aspects, cyclo alkyl groups have 3 to about 12 carbon atoms in the group. In some aspects, cycloalkyl groups have 3 to about 7 carbon atoms in the group. Examples may include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 4,4-dimethylcyclohexyl, and cycloheptyl.

[0038] A cycloalkyl group can be unsubstituted or optionally substituted. When optionally substituted, one or more hydrogen atoms of the cycloalkyl group (*e.g.*, from 1 to 4, from 1 to 2, or 1) may be replaced with a moiety independently selected from the group consisting of fluoro, hydroxy, alkoxy, amino, alkylamino, acylamino, thio, and alkylthio. In some aspects, a substituted cycloalkyl group can incorporate an *exo*- or *endocyclic* alkene (*e.g.*, cyclohex-2-en-1-yl). In some aspects, a cycloalkyl group is unsubstituted or not optionally substituted.

[0039] The terms “disorder,” “disease,” and “condition” are used herein interchangeably for a condition in a subject. A disorder is a disturbance or derangement that affects the normal function of the body of a subject. A disease is a pathological condition of an organ, a body part, or a system resulting from various causes, such as infection, genetic defect, or environmental stress that is characterized by an identifiable group of symptoms. A disorder or disease can refer to a biofilm-related disorder or disorder caused by a planktonic bacterial phenotype that is characterized by a disease-related growth of bacteria.

[0040] The term “effective amount” or “effective dose” as used herein includes an amount sufficient to achieve the desired result and accordingly will depend on the ingredient and its desired result. Nonetheless, once the desired effect is identified, determining the effective amount is within the skill of a person skilled in the art.

[0041] As used herein, “fluoroalkyl” includes an alkyl group wherein the alkyl group includes one or more fluoro- substituents. Examples include, but are not limited to, trifluoromethyl.

[0042] As used herein, “geminal” substitution includes two or more substituents that are directly attached to the same atom. An example is 3,3-dimethyl substitution on a cyclohexyl or spirocyclohexyl ring.

[0043] As used herein, “halo” or “halogen” includes fluoro, chloro, bromo, or iodo.

[0044] The term “heteroaryl” includes mono and bicyclic aromatic groups of about 4 to about 14 ring atoms (*e.g.*, 4 to 10 or 5 to 10 atoms) containing at least one heteroatom. Heteroatom as used in the term heteroaryl refers to oxygen, sulfur and nitrogen. A nitrogen

atom of a heteroaryl is optionally oxidized to the corresponding N-oxide. Examples include, but are not limited to, pyrazinyl, furanyl, thienyl, pyridyl, pyrimidinyl, isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl, imidazo[1,2-a]pyridine, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, and benzothiazolyl.

[0045] An heteroaryl group can be unsubstituted or optionally substituted. When optionally substituted, one or more hydrogen atoms of the heteroaryl group (e.g., from 1 to 5, from 1 to 2, or 1) may be replaced with a moiety independently selected from the group consisting of alkyl, cyano, acyl, halo, hydroxy, alkoxy, amino, alkylamino, acylamino, thio, and alkylthio. In some aspects, the heteroaryl group is unsubstituted or not optionally substituted.

[0046] The term “heteroaroyl” as used herein includes a heteroaryl-C(O)- group wherein heteroaryl is as defined herein. Heteroaroyl groups include, but are not limited to, thiophenoyl, nicotinoyl, pyrrol-2-ylcarbonyl, and pyridinoyl.

[0047] The term “heterocycloyl” as used herein includes a heterocyclyl-C(O)- group wherein heterocyclyl is as defined herein. Examples include, but are not limited to, N-methyl prolinoyl and tetrahydrofuranoyl.

[0048] As used herein, the term “heterocyclyl” or “heterocycloalkyl” (which may be used interchangeably) includes a non-aromatic saturated monocyclic or multicyclic ring system of about 3 to about 10 ring atoms (e.g., 5 to about 10 ring atoms, or 3 to about 6 ring atoms), in which one or more of the atoms in the ring system is an element or elements other than carbon, *e.g.*, nitrogen, oxygen or sulfur. A heterocyclyl group optionally comprises at least one sp²-hybridized atom (*e.g.*, a ring incorporating an carbonyl, endocyclic olefin, or exocyclic olefin). In some embodiments, a nitrogen or sulfur atom of the heterocyclyl is optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Examples of monocyclic heterocyclyl rings include, but are not limited to, piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,3-dioxolanyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, azetidyl, and tetrahydropyranyl.

[0049] “Heterocycloalkylene” as used herein includes an alkynyl group that is substituted at two points. A heterocycyl group can be unsubstituted or optionally substituted. When optionally substituted, one or more hydrogen atoms of the group (*e.g.*, from 1 to 4, from 1 to

2, or 1) may be replaced with a moiety independently selected from the group consisting of fluoro, hydroxy, alkoxy, amino, alkylamino, acylamino, thio, and alkylthio. In some aspects, a substituted heterocycyl group can incorporate an exo- or endocyclic alkene (e.g., cyclohex-2-en-1-yl). In some aspects, the heterocycyl group is unsubstituted or not optionally substituted.

[0050] As used herein, the term “hydrophilic moiety” or “hydrophilic group” includes a moiety or a functional group that has a strong affinity to water. Examples may include, but are not limited to, a charged moiety, such as a cationic moiety or an anionic moiety, or a polar uncharged moiety, such as an alkoxy group or an amine group.

[0051] As used herein, the term “hydroxyalkyl” includes an alkyl group where at least one hydrogen substituent has been replaced with an alcohol (-OH) group. In certain aspects, the hydroxyalkyl group has one alcohol group. In certain aspects, the hydroxyalkyl group has one or two alcohol groups, each on a different carbon atom. In certain aspects, the hydroxyalkyl group has 1, 2, 3, 4, 5, or 6 alcohol groups. Examples may include, but are not limited to, hydroxymethyl, 2-hydroxyethyl, and 1-hydroxyethyl.

[0052] When any two substituent groups or any two instances of the same substituent group are “independently selected” from a list of alternatives, the groups may be the same or different. For example, if R^a and R^b are independently selected from the group consisting of alkyl, fluoro, amino, and hydroxyalkyl, then a molecule with two R^a groups and two R^b groups could have all groups be an alkyl group (e.g., four different alkyl groups). Alternatively, the first R^a could be alkyl, the second R^a could be fluoro, the first R^b could be hydroxyalkyl, and the second R^b could be amino (or any other substituents taken from the group). Alternatively, both R^a and the first R^b could be fluoro, while the second R^b could be alkyl (*i.e.*, some pairs of substituent groups may be the same, while other pairs may be different).

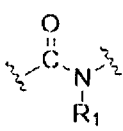
[0053] “Pharmaceutically acceptable acid addition salt” refers to those salts that retain the biological effectiveness of the free bases and that are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, as well as organic acids such as acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, orotic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

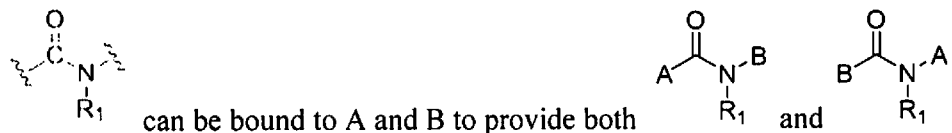
[0054] “Pharmaceutically acceptable base addition salts” include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Exemplary salts are the ammonium, potassium, sodium, calcium, and magnesium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins, and the like. Exemplary organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline, and caffeine. (See, for example, S. M. Berge, et al., “Pharmaceutical Salts,” J. Pharm. Sci., 1977;66:1-19 which is incorporated herein by reference.)

[0055] As used herein, “or” should in general be construed non-exclusively. For example, an embodiment of “a composition comprising A or B” would typically present an aspect with a composition comprising both A and B, and an embodiment of “a method to disperse or kill biofilms” could disperse, kill, or a combination of both. “Or” should, however, be construed to exclude those aspects presented that cannot be combined without contradiction (*e.g.*, a composition pH that is between 9 and 10 or between 7 and 8).

[0056] As used herein, “spirocycloalkyl” includes a cycloalkyl in which geminal substituents on a carbon atom are replaced to join in forming a 1,1-substituted ring. For example, but without limitation, for a $-C(R^1)(R^2)-$ group that was part of a longer carbon chain, if R^1 and R^2 joined to form a cyclopropyl ring incorporating the carbon to which R^1 and R^2 were bonded, this would be a spirocycloalkyl group (*i.e.*, spirocyclopropyl).

[0057] As used herein, “spiroheterocyclyl” includes a heterocycloalkyl in which geminal substituents on a carbon atom are replaced to join in forming a 1,1-substituted ring. For example, but without limitation, for a $-C(R^1)(R^2)-$ group that was part of a longer carbon chain, if R^1 and R^2 joined to form a pyrrolidine ring incorporating the carbon to which R^1 and R^2 were bonded, this would be a spiroheterocyclyl group.

[0058] It is to be understood that molecular fragments such as  and the like are bound to two other groups in either orientation. For example, unless otherwise indicated,



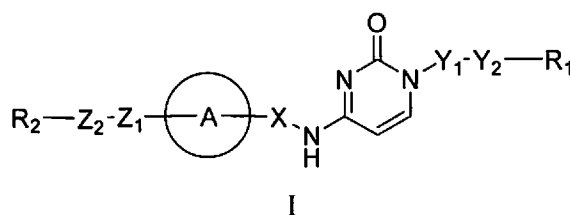
[0059] As used herein, the term “treat,” “treating,” or “treatment” includes administering or applying a composition (e.g., a composition described herein) in an amount, manner (e.g., schedule of administration), and mode (e.g., route of administration) that is effective to improve a disorder or a symptom thereof, or to prevent, to retard, or to slow the progression of a disorder or a symptom thereof. Such improvements can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of the extent of a disease, stabilizing (*i.e.*, not worsening) the state of disease, prevention of a disease’s transmission or spread, delaying or slowing of disease progression, amelioration or palliation of the disease state, diminishment of the reoccurrence of disease, and remission, whether partial or total and whether detectable or undetectable.

[0060] “Treating” and “treatment” as used herein also include prophylactic treatment. In certain embodiments, treatment methods comprise administering to a subject a therapeutically effective amount of a composition of the invention. The administering step may consist of a single administration or may comprise a series of administrations. The length of the treatment period depends on a variety of factors, such as the severity of the condition, the age of the patient, the concentration of active agent in the composition, the activity of the compositions used in the treatment, or a combination thereof. It will also be appreciated that the effective dosage of an agent used for the treatment or prophylaxis may increase or decrease over the course of a particular treatment or prophylaxis regime. Changes in dosage may result and become apparent by standard diagnostic assays known in the art. In some aspects, chronic administration may be required. For example, the compositions are administered to the subject in an amount, and for a duration, sufficient to treat the patient.

Embodiments

Compounds

[0061] In the first aspect, the invention provides a compound of formula I:



or a pharmaceutically acceptable salt thereof, wherein:

X is absent or is selected from the group consisting of $-(C=O)-$ and $-SO_2-$;

A is phenylene optionally substituted with one or two halo;

Y_1 is selected from the group consisting of CH_2 or optionally substituted phenylene;

Y_2 is absent or is selected from the group consisting of optionally substituted C_1-C_{10} alkylene, optionally substituted C_1-C_{10} alkenylene, and optionally substituted C_1-C_{10} alkynylene, wherein up to three carbons of the optionally substituted C_1-C_{10} alkylene, optionally substituted C_1-C_{10} alkenylene, and optionally substituted C_1-C_{10} alkynylene, are independently replaced by optionally substituted phenylene, O, NH, N-(C_{1-6} alkyl) (C=O), or NH(C=O);

R_1 is selected from the group consisting of H, halo, $NR_1'R_1''$, and heterocycloalkyl optionally substituted with NH_2 or Me; wherein R_1' and R_1'' are each independently selected from H and Me;

Z_1 is absent or is selected from the group consisting of CH_2 , phenylene, $-CH_2O-$, $-CH_2NH-$, $-CH_2N(C_{1-6} \text{ alkyl})-$, $-CH_2(C=O)-$, $C=O$, and $-NH(C=O)-$;

Z_2 is absent or is selected from the group consisting of optionally substituted C_1-C_{10} alkylene, and optionally substituted heterocycloalkylene; and

R_2 is selected from H, OH, NH_2 , $NH(C_{1-6} \text{ alkyl})$, $N(C_{1-6} \text{ alkyl})_2$, $NH(\text{cycloalkyl})$, $N(\text{cycloalkyl})_2$.

[0062] In one embodiment of a compound of formula I, X is absent.

[0063] In another embodiment of a compound of formula I, X is $-(C=O)-$ or $-SO_2-$.

[0064] In another embodiment of a compound of formula I, X is $-(C=O)-$.

[0065] In another embodiment of a compound of formula I, A is phenylene substituted with one or two halo.

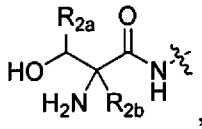
[0066] In one embodiment of a compound of formula I, Y_1 is CH_2 .

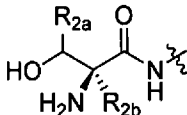
[0067] In another embodiment of a compound of formula I, Y_1 is optionally substituted aryl. In another embodiment, Y_1 is optionally substituted phenyl.

[0068] In one embodiment of a compound of formula I, Y_2 is absent.

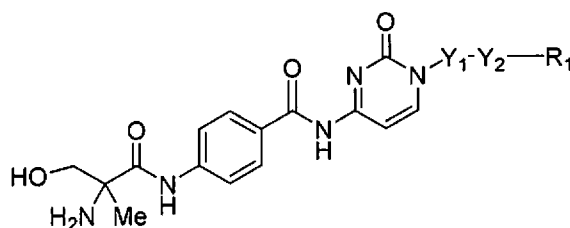
- [0069] In another embodiment of a compound of formula I, Y₂ is optionally substituted C₁-C₁₀ alkylene, wherein up to three carbon atoms are independently replaced by O, NH, N-(C₁₋₆ alkyl) optionally substituted phenylene, (C=O), or NH(C=O).
- [0070] In another embodiment of a compound of formula I, Y₂ is optionally substituted C₁-C₁₀ alkenylene, wherein up to three carbon atoms are independently replaced by O, NH, N-(C₁₋₆ alkyl), optionally substituted phenylene, (C=O), or NH(C=O).
- [0071] In another embodiment of a compound of formula I, Y₂ and optionally substituted C₁-C₁₀ alkynylene, wherein up to three carbon atoms are independently replaced by O, NH, N-(C₁₋₆ alkyl), optionally substituted phenylene, (C=O), or NH(C=O).
- [0072] In one embodiment of a compound of formula I, R₁ is H.
- [0073] In another embodiment of a compound of formula I, R₁ is halo.
- [0074] In another embodiment of a compound of formula I, R₁ is NR_{1'}R_{1''} wherein R_{1'} and R_{1''} are each independently selected from H and Me.
- [0075] In another embodiment of a compound of formula I, R₁ is heterocycloalkyl optionally substituted with NH₂ or Me.
- [0076] In one embodiment of a compound of formula I, Z₁ is absent.
- [0077] In another embodiment of a compound of formula I, Z₁ is CH₂.
- [0078] In another embodiment of a compound of formula I, Z₁ is -CH₂O-.
- [0079] In another embodiment of a compound of formula I, Z₁ is -CH₂NH-.
- [0080] In another embodiment of a compound of formula I, Z₁ is -CH₂N(C₁₋₆ alkyl)-.
- [0081] In another embodiment of a compound of formula I, Z₁ is -CH₂(C=O)-.
- [0082] In another embodiment of a compound of formula I, Z₁ is -NH(C=O)-.
- [0083] In another embodiment of a compound of formula I, Z₁ is (C=O).
- [0084] In one embodiment of a compound of formula I, Z₂ is absent.
- [0085] In another embodiment of a compound of formula I, Z₂ is optionally substituted C₁-C₁₀ alkylene.
- [0086] In another embodiment of a compound of formula I, Z₂ optionally substituted heterocycloalkyl.
- [0087] In one embodiment of a compound of formula I, R₂ is H.
- [0088] In another embodiment of a compound of formula I, R₂ is OH.
- [0089] In another embodiment of a compound of formula I, R₂ is NH₂.
- [0090] In another embodiment of a compound of formula I, R₂ is NH(C₁₋₆ alkyl).
- [0091] In another embodiment of a compound of formula I, R₂ is N(C₁₋₆ alkyl)₂.
- [0092] In another embodiment of a compound of formula I, R₂ is NH(cycloalkyl).

[0093] In another embodiment of a compound of formula I, R₂ is N(cycloalkyl)₂.

[0094] In one embodiment of a compound of formula I, R₂-Z₂-Z₁ is , wherein R_{2a} is selected from the group consisting of hydrogen and (C₁-C₆ alkyl) and R_{2b} is selected from the group consisting of hydrogen, (C₁-C₆ alkyl), (C₂-C₆ alkenyl), aryl, and arylalkyl.

[0095] In another embodiment R₂-Z₂-Z₁ is  wherein R_{2a} and R_{2b} are defined as previously.

[0096] In another embodiment, the compound of formula I is a compound of formula IA:



IA

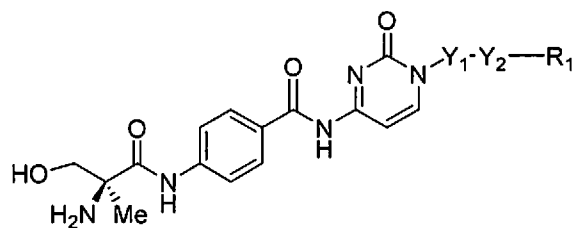
or a pharmaceutically acceptable salt thereof, wherein:

Y₁ is selected from the group consisting of CH₂ or optionally substituted phenylene;

Y₂ is absent or is selected from the group consisting of optionally substituted C₁-C₁₀ alkylene, optionally substituted C₁-C₁₀ alkenylene, and optionally substituted C₁-C₁₀ alkynylene, wherein up to three carbons of the optionally substituted C₁-C₁₀ alkylene, optionally substituted C₁-C₁₀ alkenylene, and optionally substituted C₁-C₁₀ alkynylene, are independently replaced by O, NH, N-(C₁₋₆ alkyl), optionally substituted phenylene, (C=O), or NH(C=O);

R₁ is selected from the group consisting of H, halo, NR_{1'}R_{1''}, and heterocycloalkyl optionally substituted with NH₂ or Me; wherein R_{1'} and R_{1''} are each independently selected from H and Me.

[0097] In a further embodiment, the compound of formula IA is a compound of formula IAi:



IAi

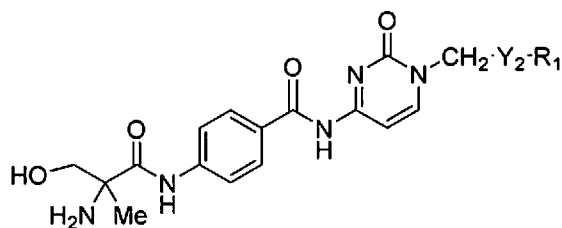
or a pharmaceutically acceptable salt thereof, wherein:

Y_1 is selected from the group consisting of CH_2 or optionally substituted phenylene;

Y_2 is absent or is selected from the group consisting of optionally substituted C_1 - C_{10} alkylene, optionally substituted C_1 - C_{10} alkenylene, and optionally substituted C_1 - C_{10} alkynylene, wherein up to three carbons of the optionally substituted C_1 - C_{10} alkylene, optionally substituted C_1 - C_{10} alkenylene, and optionally substituted C_1 - C_{10} alkynylene, are independently replaced by O, NH, N-(C_{1-6} alkyl) (C=O), or NH(C=O); and

R_1 is selected from the group consisting of H, halo, $NR_1'R_1''$, and heterocycloalkyl optionally substituted with NH_2 or Me; wherein R_1' and R_1'' are each independently selected from H and Me.

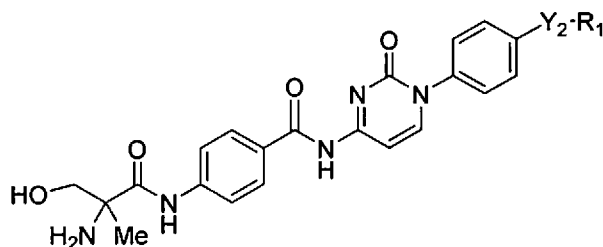
[0098] In a further embodiment, the compound of formula IAI and thus of formula IA and thus of formula I is a compound of formula IA-1:



IA-1

or a pharmaceutically acceptable salt thereof.

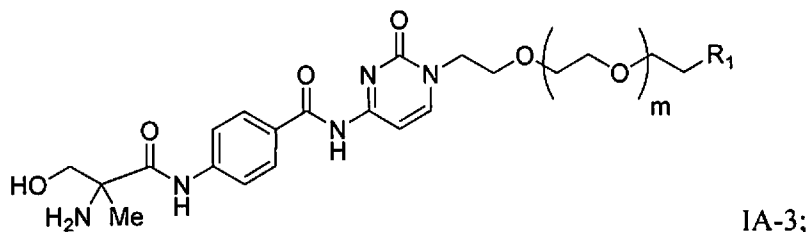
[0099] In a further embodiment, the compound of formula IAI and thus of formula IA and thus of formula I is a compound of formula IA-2:



IA-2

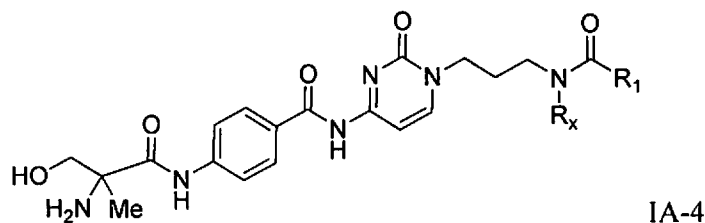
or a pharmaceutically acceptable salt thereof.

[00100] In a further embodiment, the compound of formula IA-I and thus of formula IA and thus of formula I is a compound of formula IA-3:



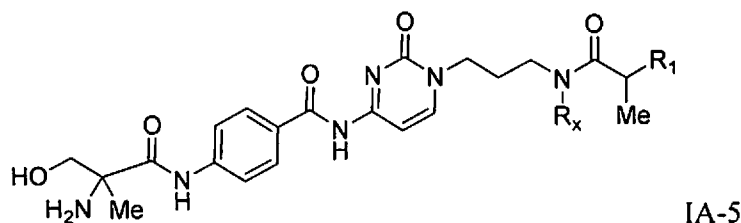
or a pharmaceutically acceptable salt thereof, wherein m is 0, 1, or 2; and R_1 is selected from the group consisting of $NR_1'R_1''$, and heterocycloalkyl optionally substituted with NH_2 or Me ; wherein R_1' and R_1'' are each independently selected from H and Me . In one embodiment of a compound of formula IA-3, R_1 is halo. In a further embodiment of a compound of formula IA-3, R_1 is chloro. In a further embodiment, R_1 is $N(Me)_2$.

[00101] In a further embodiment, the compound of formula IA-I and thus of formula IA and thus of formula I is a compound of formula IA-4:



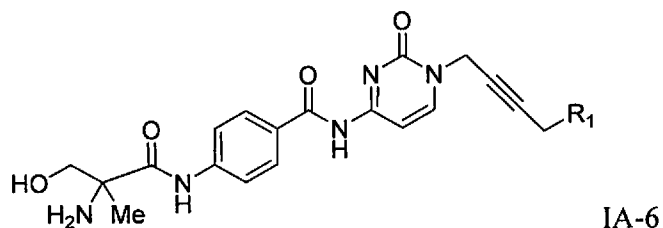
or a pharmaceutically acceptable salt thereof, wherein R_x is H or methyl; and R_1 is heterocycloalkyl.

[00102] In a further embodiment, the compound of formula IA-I and thus of formula IA and thus of formula I is a compound of formula IA-5:



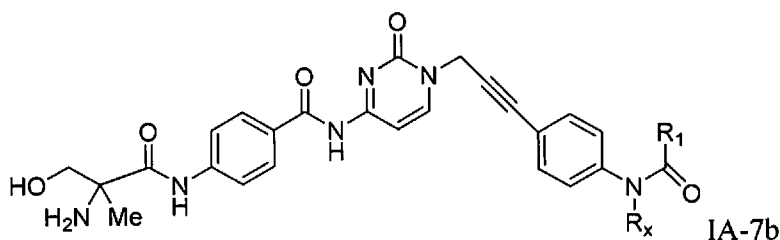
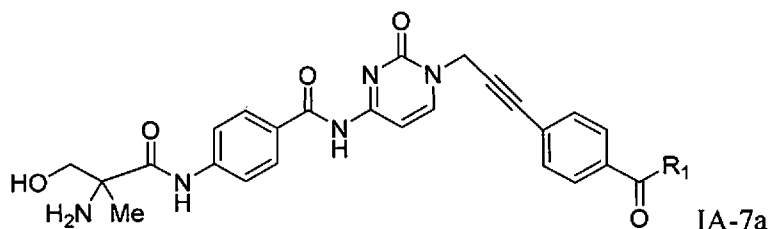
or a pharmaceutically acceptable salt thereof, wherein R_x is H or methyl; and R_1 is selected from the group consisting of H , halo, $NR_1'R_1''$, and heterocycloalkyl optionally substituted with NH_2 or Me ; wherein R_1' and R_1'' are each independently selected from H and Me . In a further embodiment of a compound of formula IA-4, R_1 is NH_2 .

[00103] In a further embodiment, the compound of formula IA-I and thus of formula IA and thus of formula I is a compound of formula IA-6:



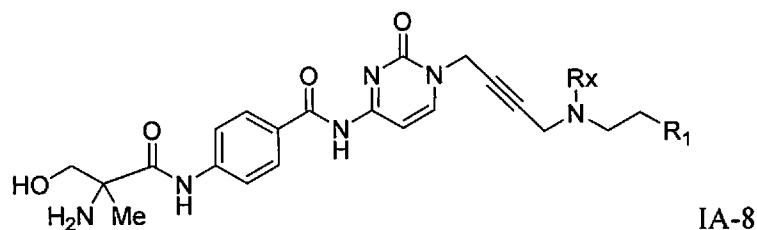
or a pharmaceutically acceptable salt thereof, wherein R_1 is selected from the group consisting of H, halo, $NR_1'R_1''$, and heterocycloalkyl optionally substituted with NH_2 or Me; wherein R_1' and R_1'' are each independently selected from H and Me. In a further embodiment, R_1 is heterocycloalkyl optionally substituted with NH_2 or Me.

[00104] In a further embodiment, the compound of formula IA-I and thus of formula IA and thus of formula I is a compound of formula IA-7a or IA-7b:



or a pharmaceutically acceptable salt thereof, wherein R_1 is heterocycloalkyl optionally substituted with NH_2 or Me.

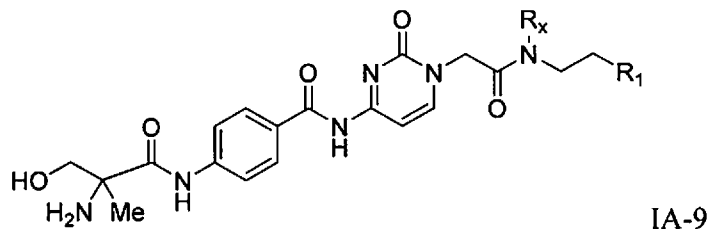
[00105] In a further embodiment, the compound of formula IA-I and thus of formula IA and thus of formula I is a compound of formula IA-8:



or a pharmaceutically acceptable salt thereof, wherein R_x is H or methyl and R_1 is selected from the group consisting of H, $NR_1'R_1''$, and heterocycloalkyl optionally substituted with

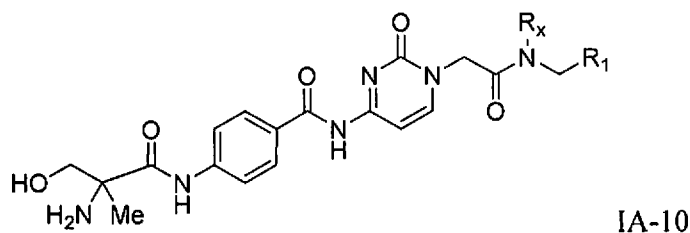
NH₂ or Me; wherein R_{1'} and R_{1''} are each independently selected from H and Me. In a further embodiment, R₁ is heterocycloalkyl optionally substituted with NH₂ or Me.

[00106] In a further embodiment, the compound of formula IA-I and thus of formula IA and thus of formula I is a compound of formula IA-9:



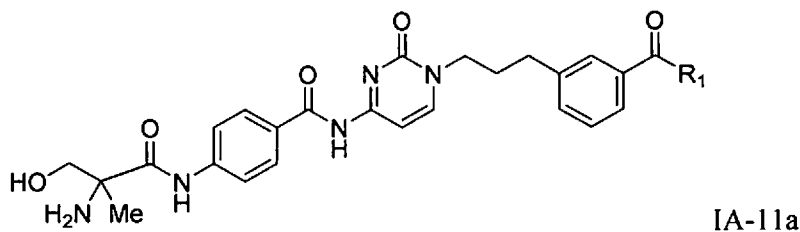
or a pharmaceutically acceptable salt thereof, wherein R_x is H or methyl and R₁ is selected from the group consisting of H, NR_{1'}R_{1''}, and heterocycloalkyl optionally substituted with NH₂ or Me; wherein R_{1'} and R_{1''} are each independently selected from H and Me. In a further embodiment, R₁ is heterocycloalkyl optionally substituted with NH₂ or Me.

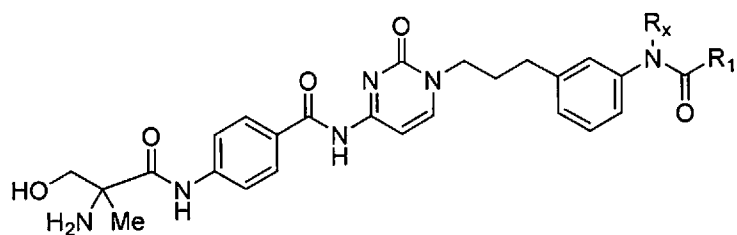
[00107] In a further embodiment, the compound of formula IA-I and thus of formula IA and thus of formula I is a compound of formula IA-10:



or a pharmaceutically acceptable salt thereof, wherein R_x is H or methyl and R₁ is selected from the group consisting of H, NR_{1'}R_{1''}, and heterocycloalkyl optionally substituted with NH₂ or Me; wherein R_{1'} and R_{1''} are each independently selected from H and Me. In a further embodiment, R₁ is heterocycloalkyl optionally substituted with NH₂ or Me.

[00108] In a further embodiment, the compound of formula IA-I and thus of formula IA and thus of formula I is a compound of formula IA-11a or IA-11b:

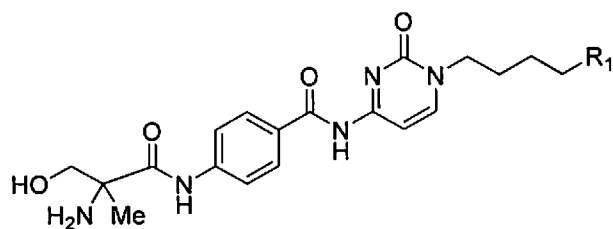




IA-11b

or a pharmaceutically acceptable salt thereof, wherein R_x is H or methyl and R_1 is selected from the group consisting of NR_1' , R_1'' , and heterocycloalkyl optionally substituted with NH_2 or Me; wherein R_1' and R_1'' are each independently selected from H and Me. In a further embodiment, R_1 is heterocycloalkyl optionally substituted with NH_2 or Me.

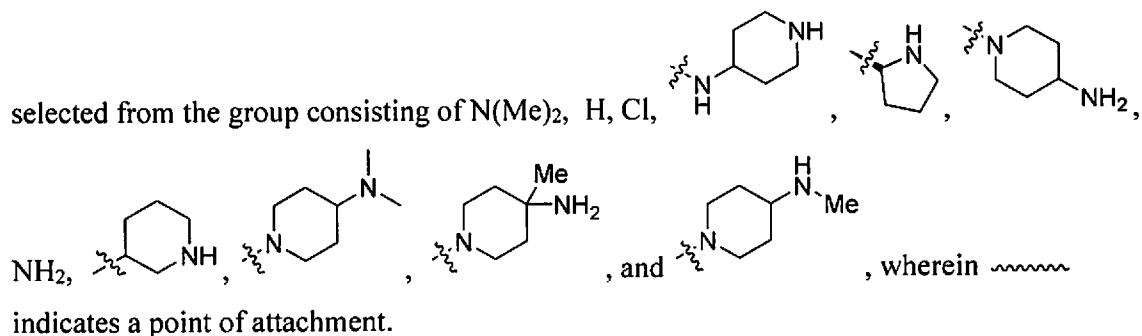
[00109] In a further embodiment, the compound of formula IA-I and thus of formula IA and thus of formula I is a compound of formula IA-12:



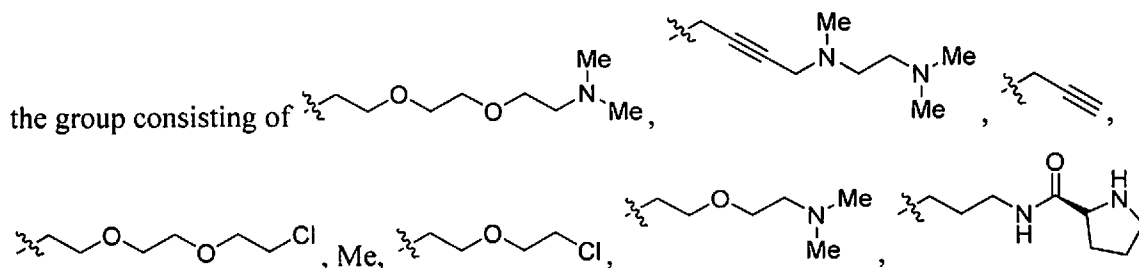
IA-12

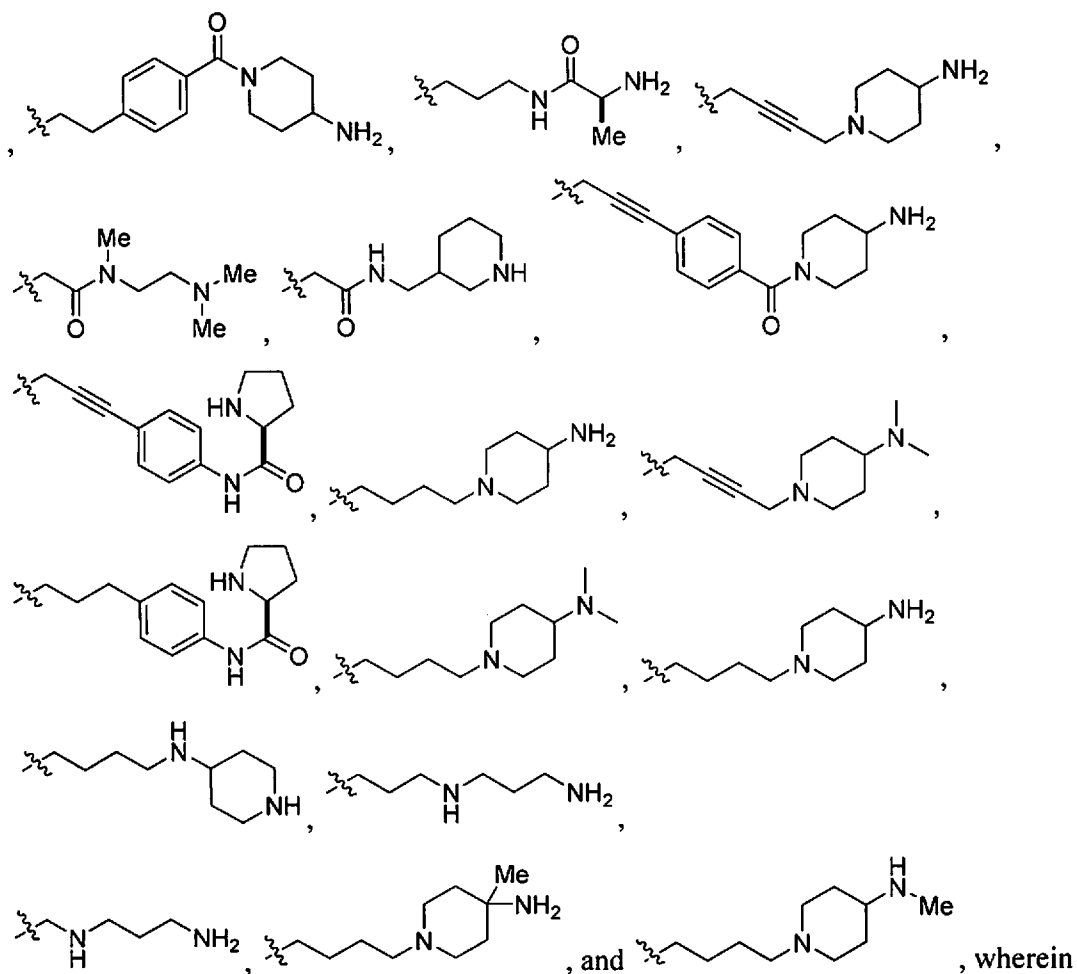
or a pharmaceutically acceptable salt thereof, wherein R_1 is selected from the group consisting of H, halo, NR_1' , R_1'' , and heterocycloalkyl optionally substituted with NH_2 or Me; wherein R_1' and R_1'' are each independently selected from H and Me. In a further embodiment, R_1 is heterocycloalkyl optionally substituted with NH_2 or Me.

[00110] In a further embodiment of a compound of formula IA and thus of formula I, R_1 is



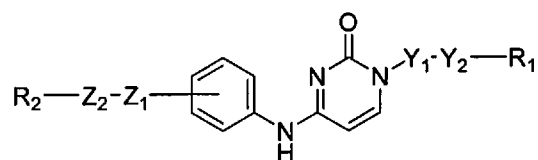
[00111] In a further embodiment of a compound of formula IA, Y_1 - Y_2 - R_1 is selected from





~~~~~ indicates a point of attachment.

**[00112]** In a further embodiment, the compound of formula I is a compound of formula IB:



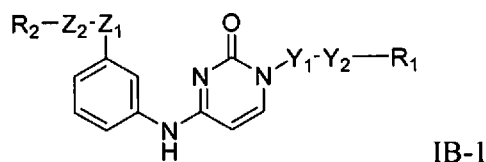
IB

or a pharmaceutically acceptable salt thereof. In a further embodiment, the phenylene ring

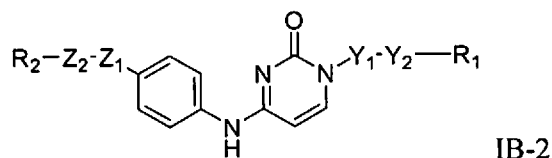


 in the compound of formula IB is optionally substituted with one or two halo selected from the group consisting of F and Cl.

**[00113]** In a further embodiment, the compound of formula IB and thus of formula I is a compound of formula IB-1 or IB-2:



IB-1

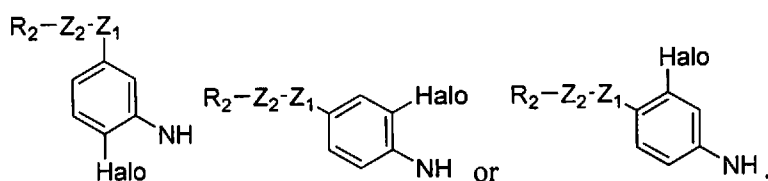


IB-2

or pharmaceutically acceptable salts thereof. In a further embodiment, the phenylene ring

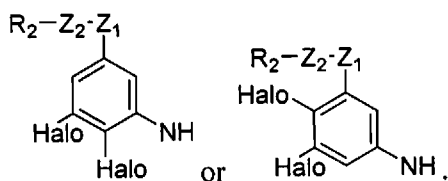


 in the compound of formula IB is optionally substituted with one or two halo selected from the group consisting of F and Cl. In one embodiment, when one halo group is present,



it is at an ortho position; i.e.,

In one embodiment, when two halo groups are present, they are at an ortho and meta



positions; i.e.,

or

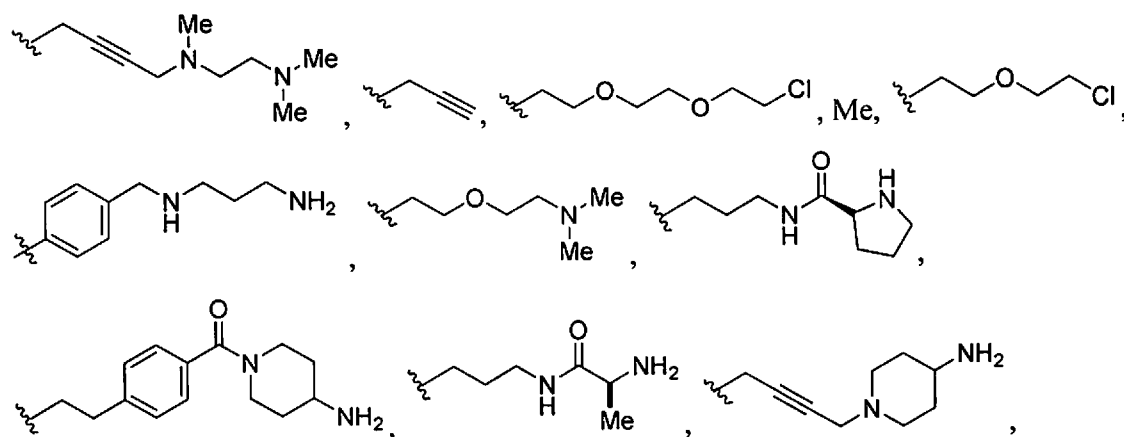
$$\text{Halo} \text{---} \text{CH}=\text{CH} \text{---} \text{NH}_2$$

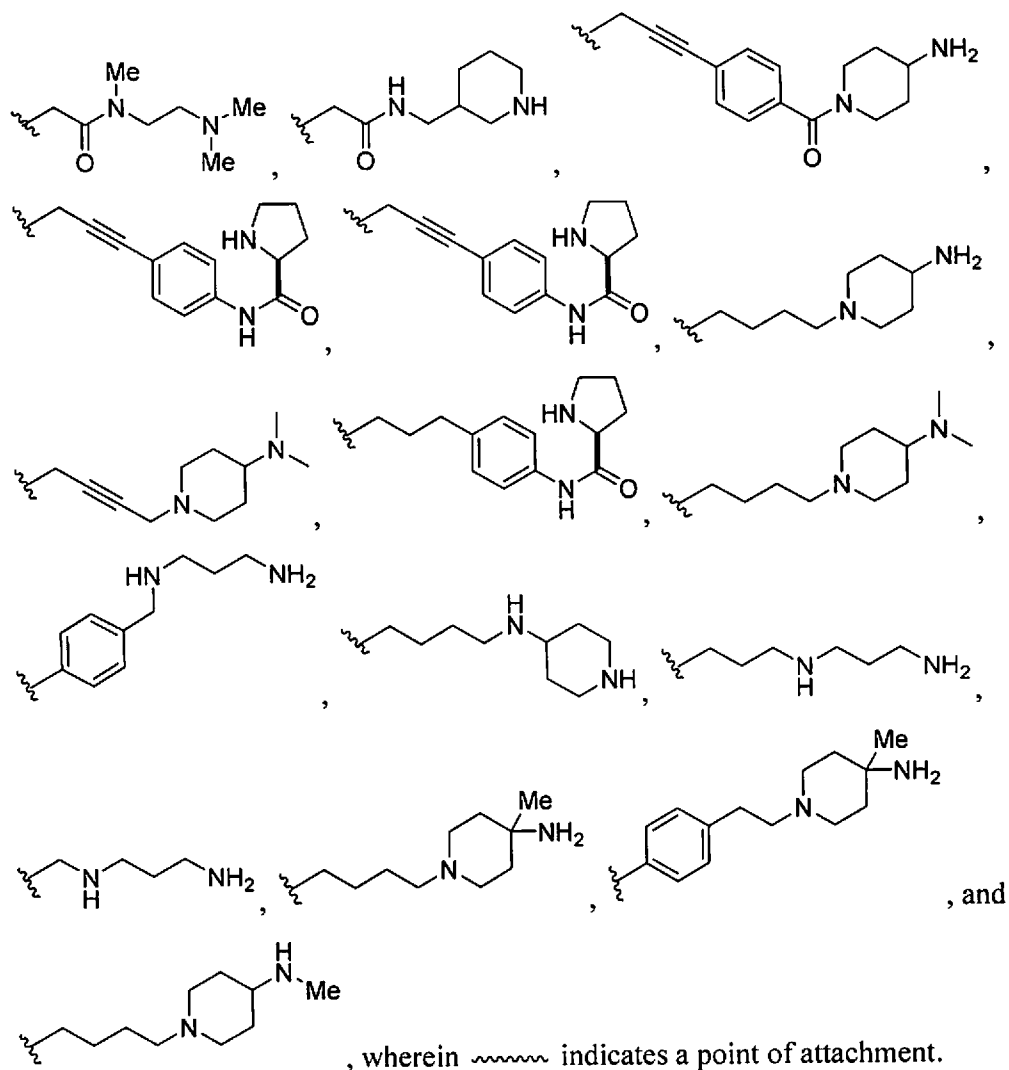
**[00114]** In another embodiment of a compound of a compound of formula IB and thus of IB-

1 and IB-2, R<sub>1</sub>-Y<sub>2</sub>-Y<sub>1</sub> is selected from the group consisting of:

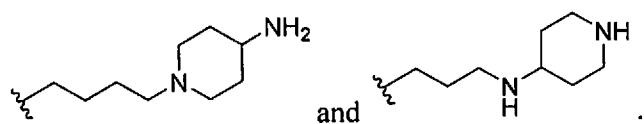


The structure shows a wavy line on the left, connected to a chain of three methylene groups, followed by an oxygen atom, another three methylene groups, a second oxygen atom, and a final three methylene groups terminating in a dimethylamino group (NMe<sub>2</sub>).

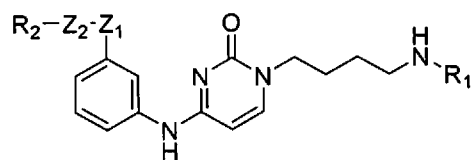




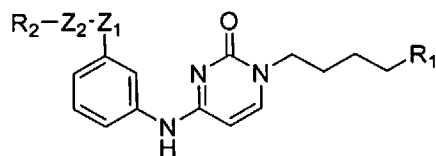
**[00115]** In a further embodiment, R<sub>1</sub>-Y<sub>2</sub>-Y<sub>1</sub> is selected from the group consisting of



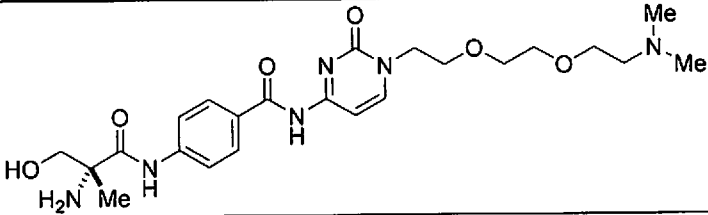
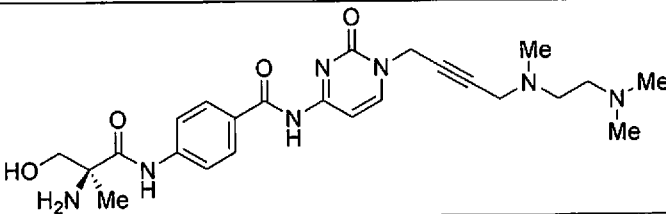
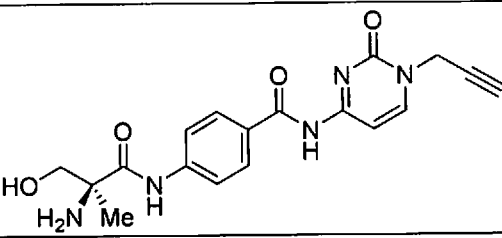
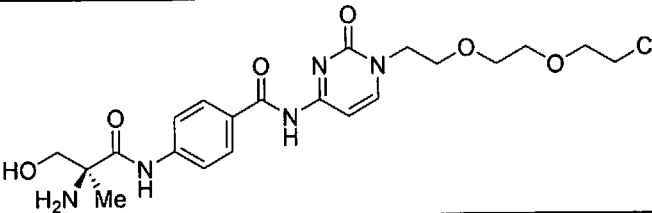
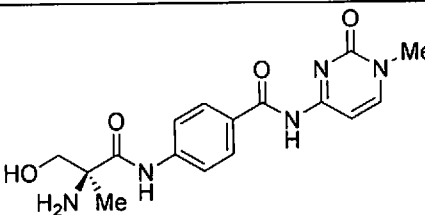
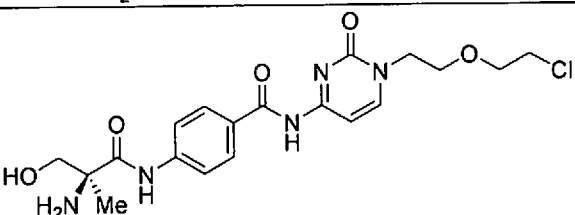
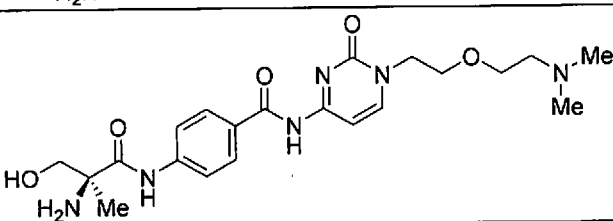
**[00116]** In a further embodiment of a compound of formula IB-1 and thus of IB is a compound of formula IB-1a or IB-1b:

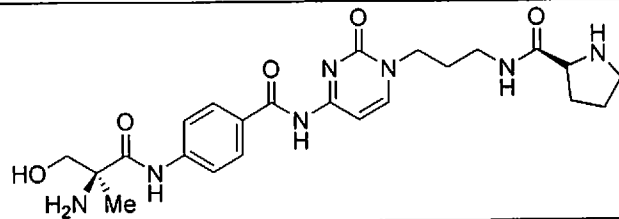
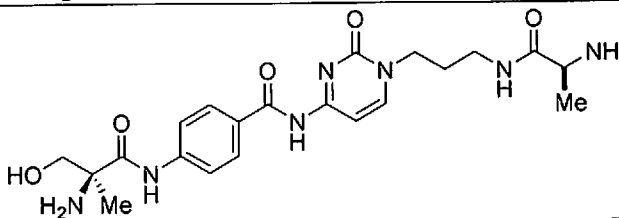
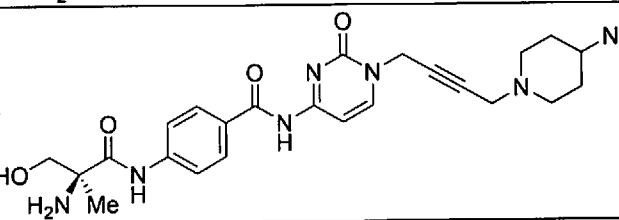
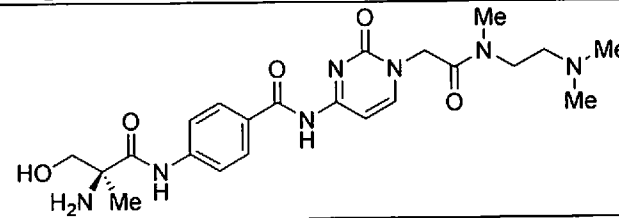
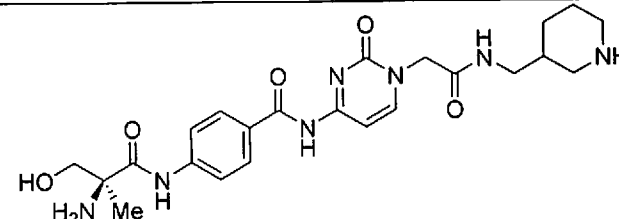
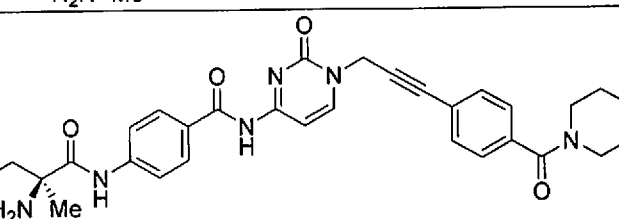
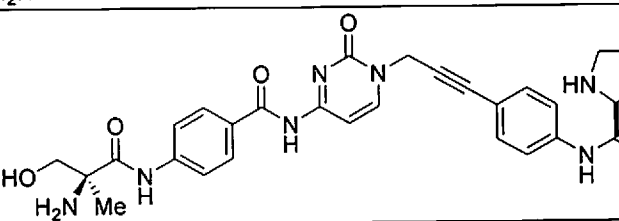


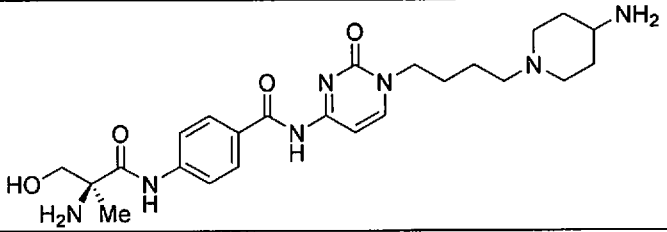
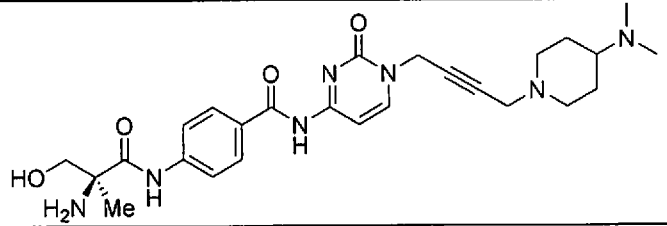
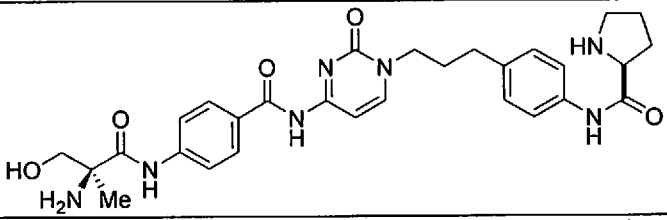
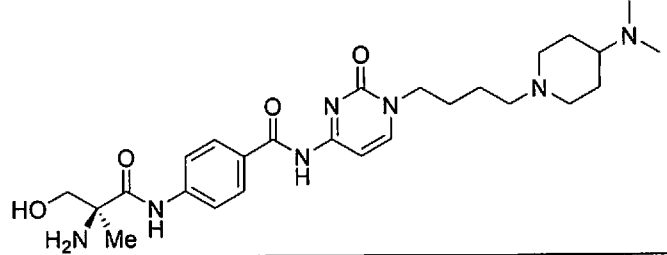
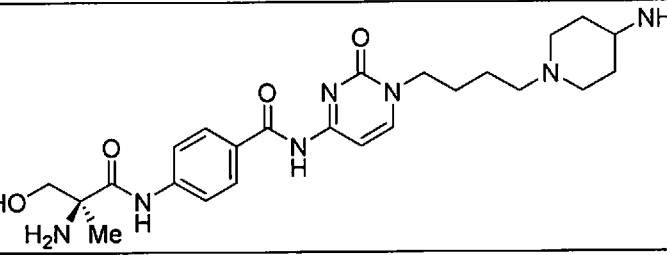
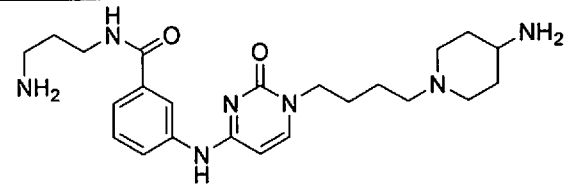
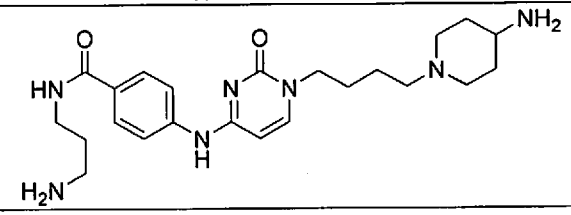
**IB-1a**

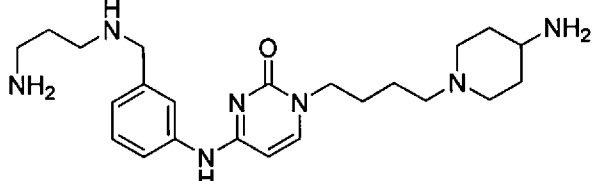
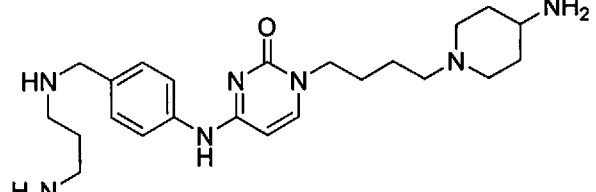
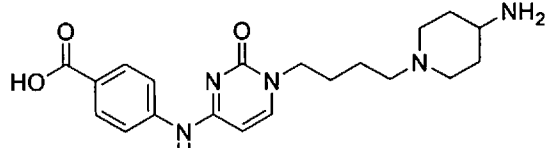
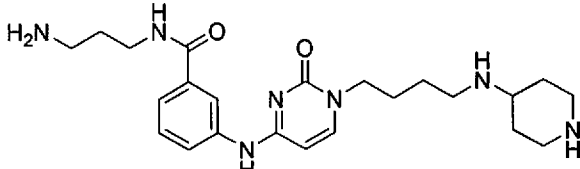
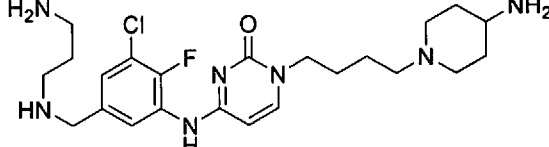
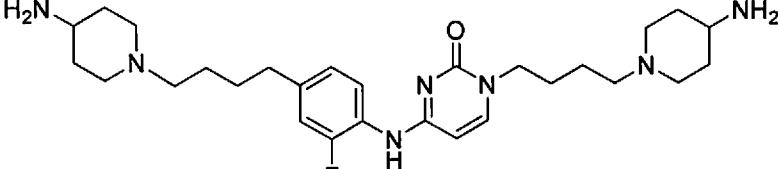
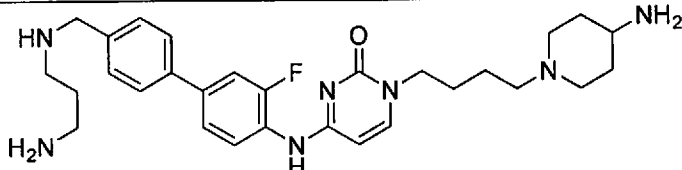
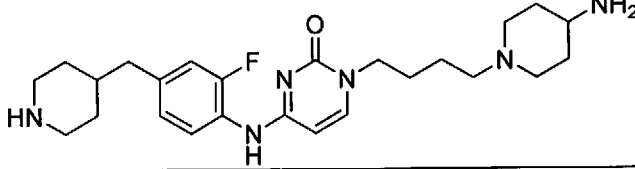
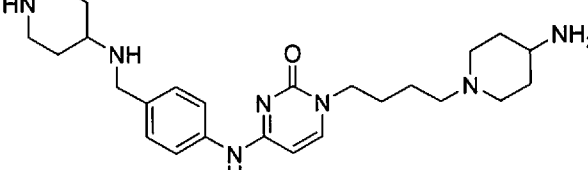


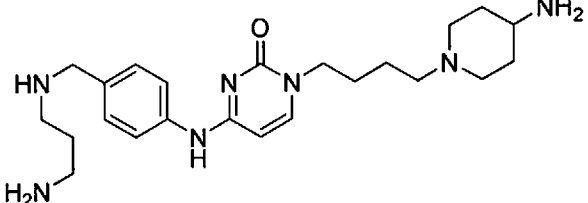
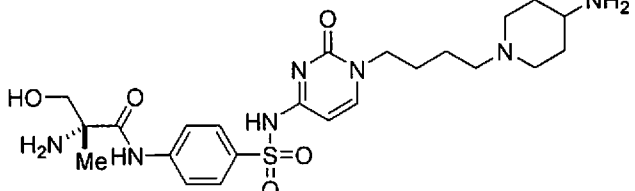
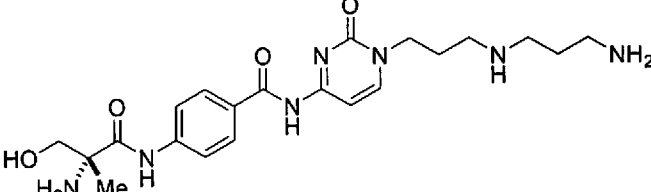
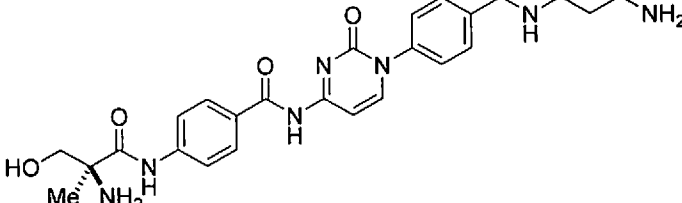
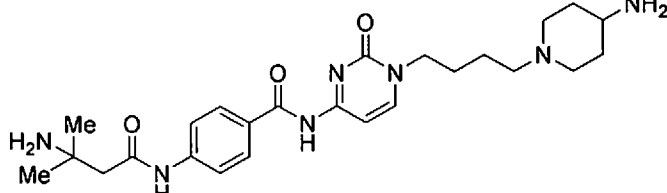
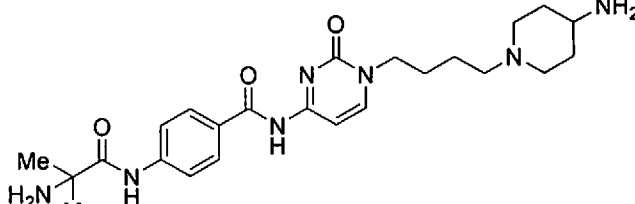
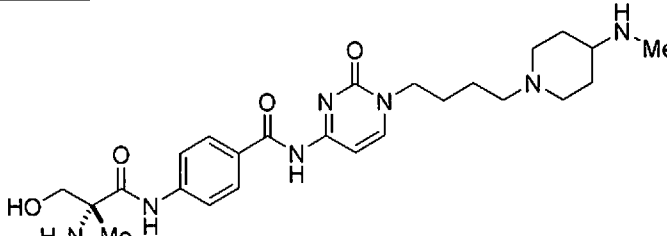


| No. | Compound                                                                             |
|-----|--------------------------------------------------------------------------------------|
| 2   |    |
| 3   |    |
| 4   |    |
| 5   |   |
| 6   |  |
| 7   |  |
| 8   |  |

| No. | Compound                                                                             |
|-----|--------------------------------------------------------------------------------------|
| 9   |    |
| 10  |    |
| 11  |    |
| 12  |   |
| 13  |  |
| 14  |  |
| 15  |  |

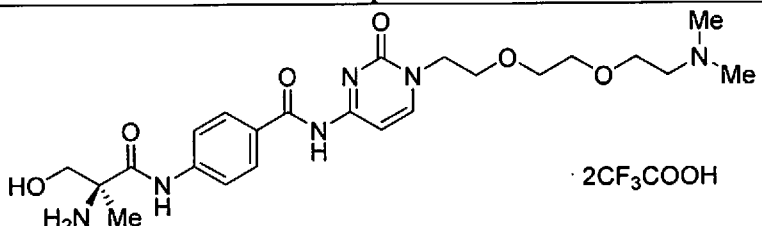
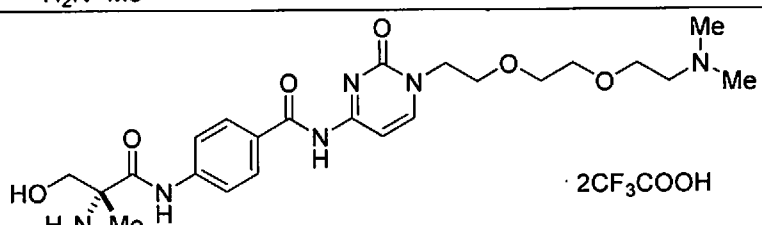
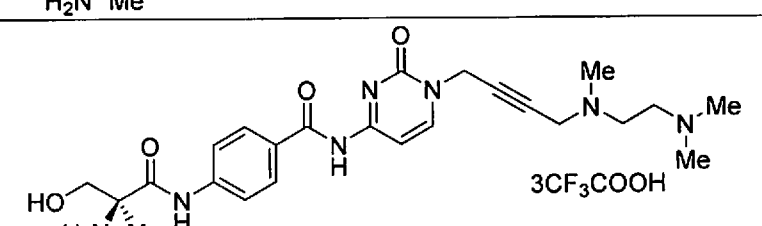
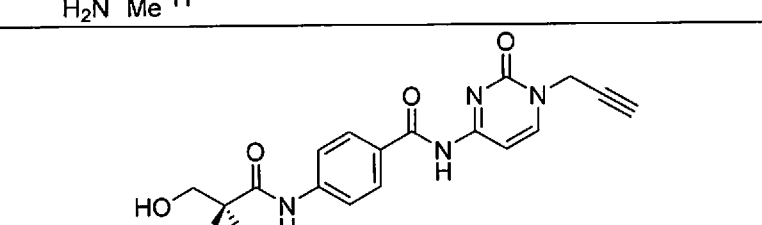
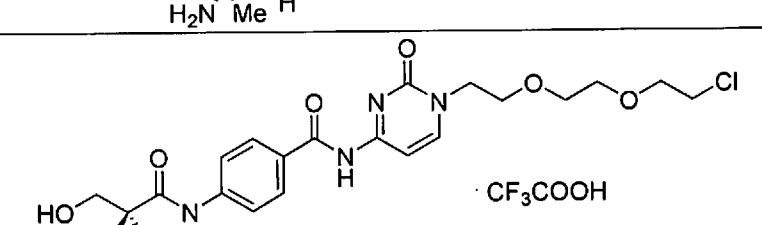
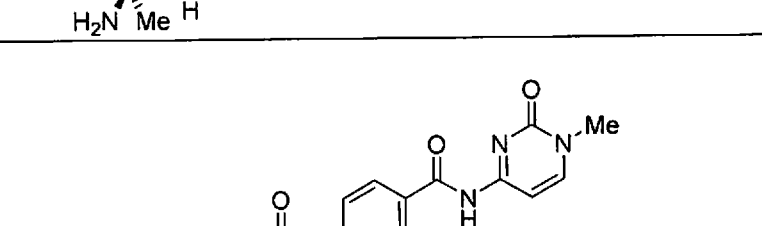
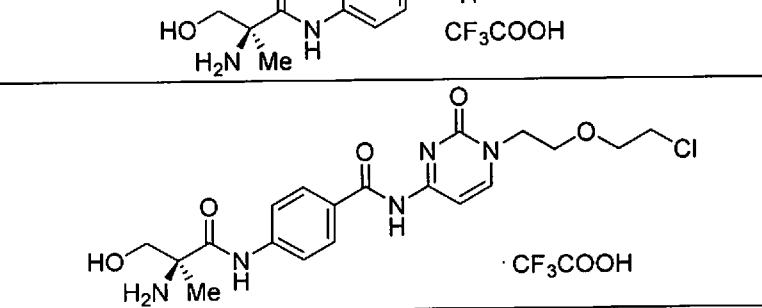
| No. | Compound                                                                             |
|-----|--------------------------------------------------------------------------------------|
| 16  |    |
| 17  |    |
| 18  |    |
| 19  |   |
| 20  |  |
| 21  |  |
| 22  |  |

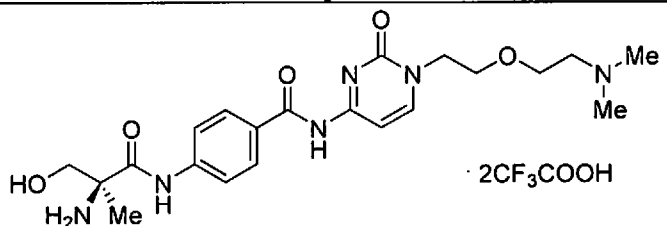
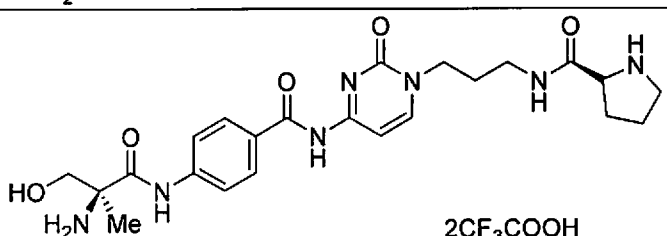
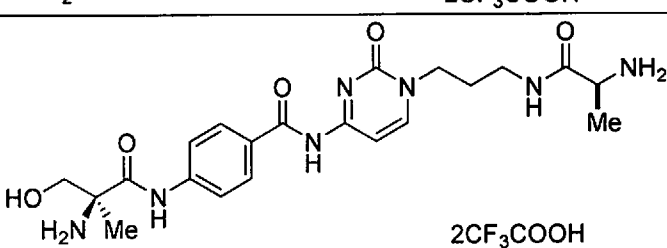
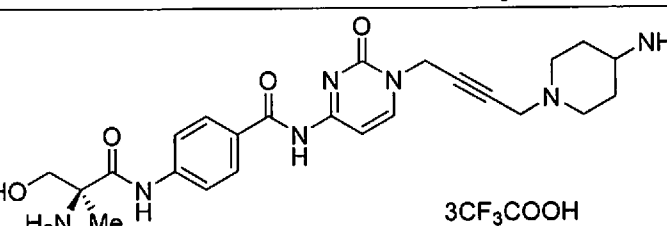
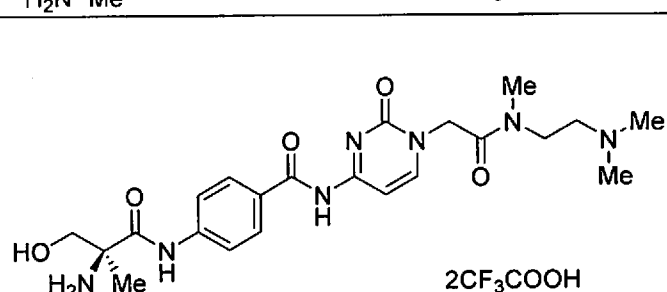
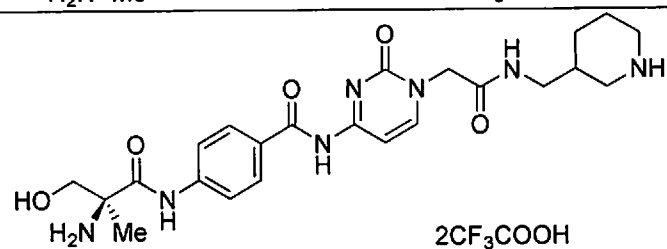
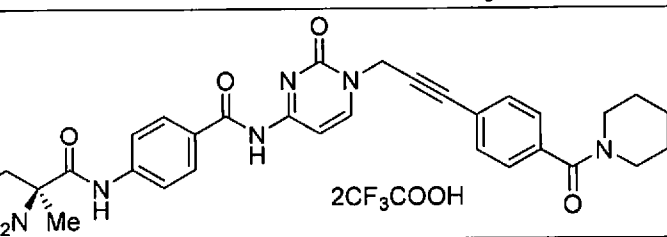
| No. | Compound                                                                             |
|-----|--------------------------------------------------------------------------------------|
| 23  |    |
| 24  |    |
| 25  |    |
| 26  |    |
| 27  |  |
| 28  |  |
| 29  |  |
| 30  |  |
| 31  |  |

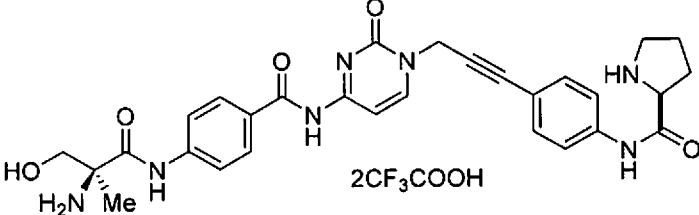
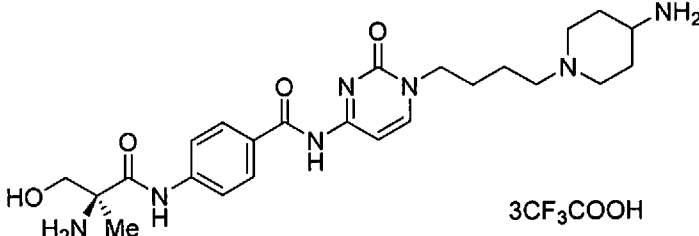
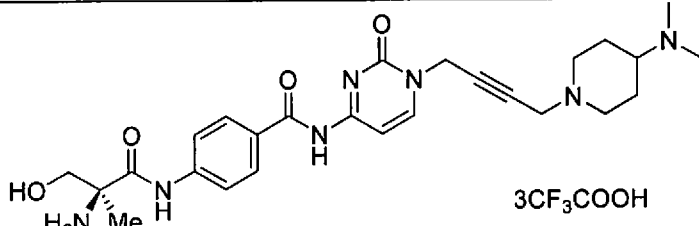
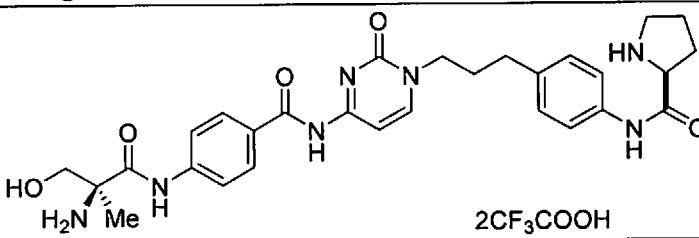
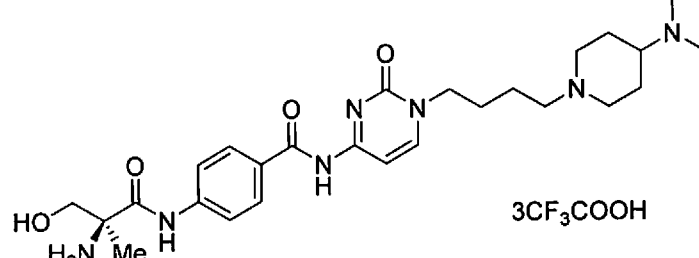
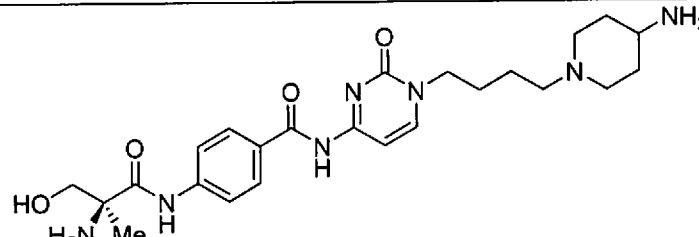
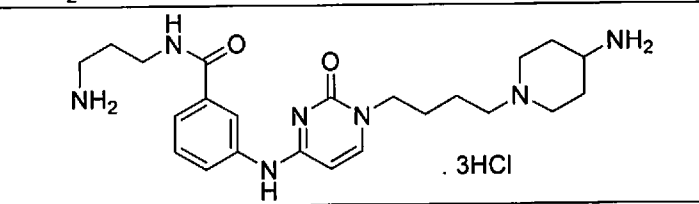
| No. | Compound                                                                             |
|-----|--------------------------------------------------------------------------------------|
| 32  |    |
| 33  |    |
| 34  |    |
| 35  |   |
| 36  |  |
| 37  |  |
| 38  |  |

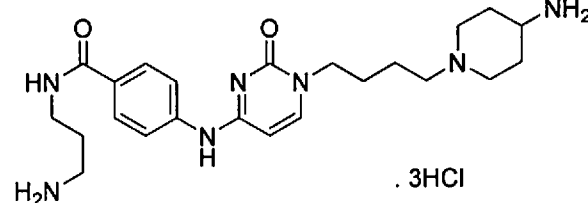
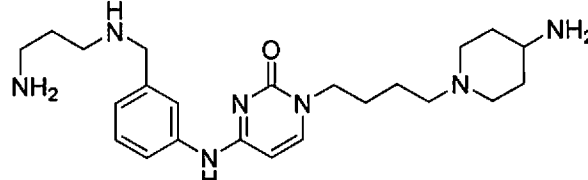
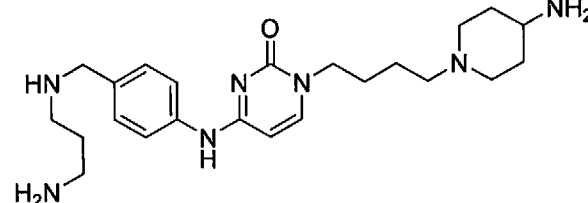
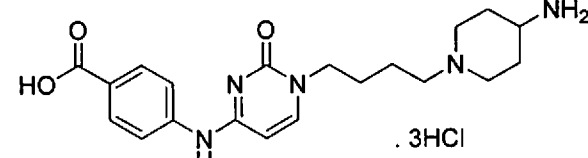
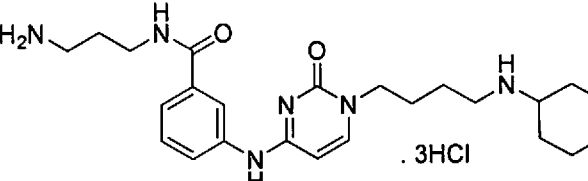
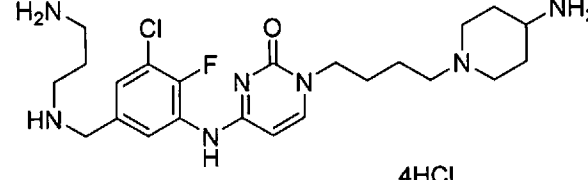
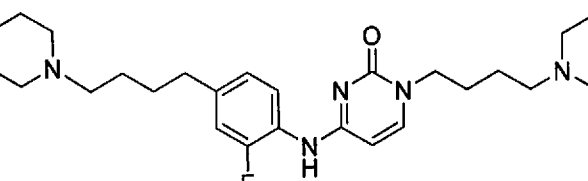
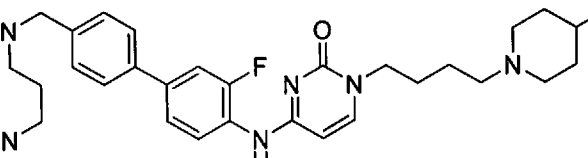
or a pharmaceutically acceptable salt thereof.

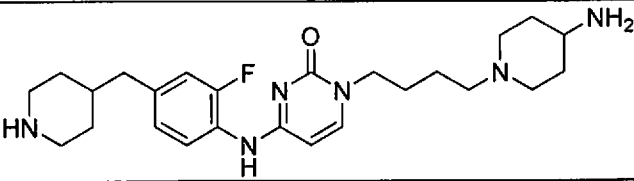
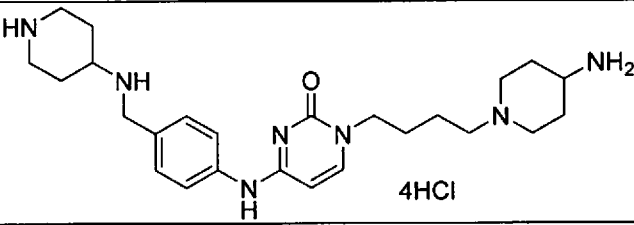
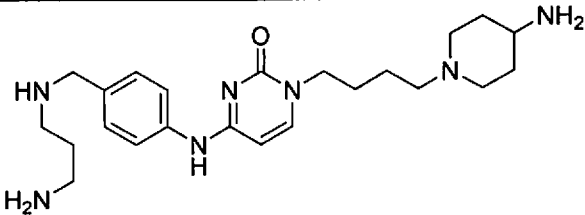
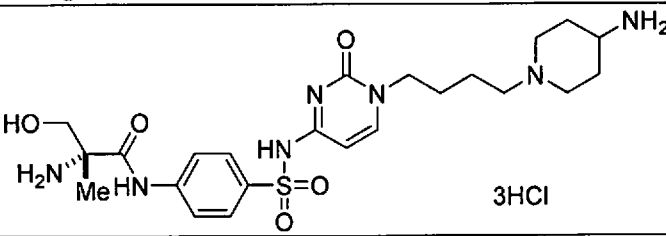
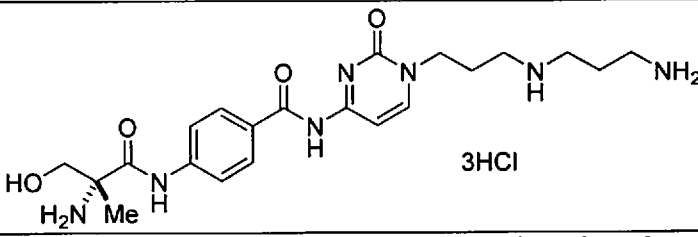
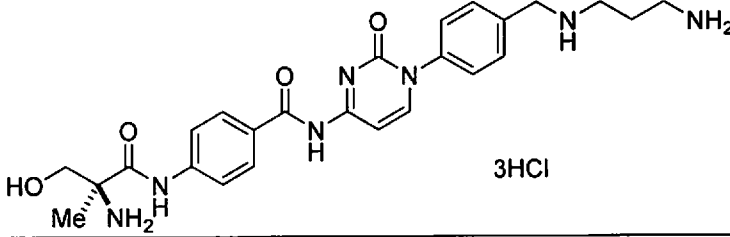
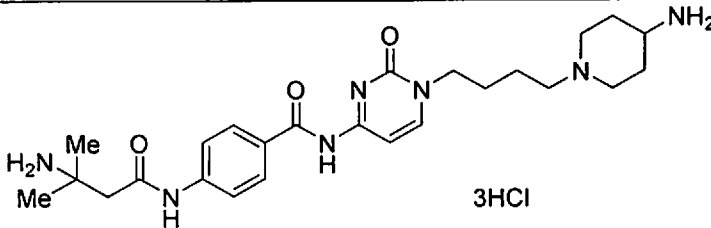
[00120] In another aspect, the invention provides a compound which is:

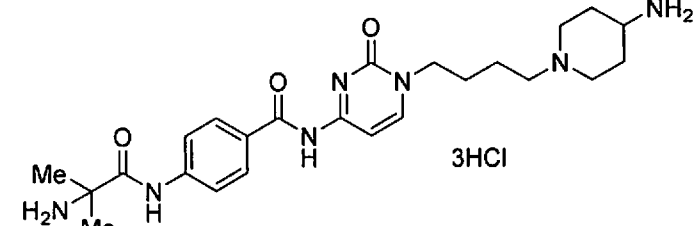
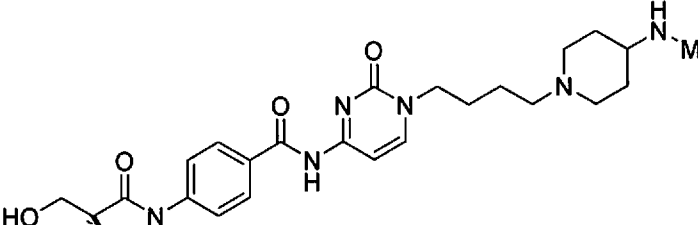
| No. | Compound                                                                             |
|-----|--------------------------------------------------------------------------------------|
| 1   |    |
| 2   |    |
| 3   |    |
| 4   |   |
| 5   |  |
| 6   |  |
| 7   |  |

| No. | Compound                                                                             |
|-----|--------------------------------------------------------------------------------------|
| 8   |    |
| 9   |    |
| 10  |    |
| 11  |   |
| 12  |  |
| 13  |  |
| 14  |  |

| No. | Compound                                                                             |
|-----|--------------------------------------------------------------------------------------|
| 15  |    |
| 16  |    |
| 17  |    |
| 18  |   |
| 19  |  |
| 20  |  |
| 21  |  |

| No. | Compound                                                                             |
|-----|--------------------------------------------------------------------------------------|
| 22  |    |
| 23  |    |
| 24  |    |
| 25  |   |
| 26  |  |
| 27  |  |
| 28  |  |
| 29  |  |

| No. | Compound                                                                                     |
|-----|----------------------------------------------------------------------------------------------|
| 30  |            |
| 31  | <br>4HCl   |
| 32  |            |
| 33  | <br>3HCl  |
| 34  | <br>3HCl |
| 35  | <br>3HCl |
| 36  | <br>3HCl |

| No. | Compound                                                                           |
|-----|------------------------------------------------------------------------------------|
| 37  |  |
| 38  |  |

### Pharmaceutical Compositions and Administration

[00121] The present invention provides pharmaceutical compositions comprising a compound of the present invention and a pharmaceutically acceptable excipient. In certain embodiments, the compound of the present invention is provided in an effective amount in the pharmaceutical composition. In certain embodiments, the effective amount is a therapeutically effective amount. In certain embodiments, the effective amount is a prophylactically effective amount.

[00122] Pharmaceutically acceptable excipients include any and all solvents, diluents, or other liquid vehicles, dispersions, suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. General considerations in formulation and/or manufacture of pharmaceutical compositions agents can be found, for example, in Remington's Pharmaceutical Sciences, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980), and Remington: The Science and Practice of Pharmacy, 21st Edition (Lippincott Williams & Wilkins, 2005).

[00123] Pharmaceutical compositions described herein can be prepared by any method known in the art of pharmacology. In general, such preparatory methods include the steps of bringing the compound of the present invention (the "active ingredient") into association with a carrier and/or one or more other accessory ingredients, and then, if necessary and/or desirable, shaping and/or packaging the product into a desired single- or multi-dose unit.

[00124] Pharmaceutical compositions can be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. As used herein, a "unit dose" is

discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage such as, for example, one-half or one-third of such a dosage.

[00125] Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition of the invention will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the composition is to be administered. By way of example, the composition may comprise between 0.1% and 100% (w/w) active ingredient.

[00126] Pharmaceutically acceptable excipients used in the manufacture of provided pharmaceutical compositions include inert diluents, dispersing and/or granulating agents, surface active agents and/or emulsifiers, disintegrating agents, binding agents, preservatives, buffering agents, lubricating agents, and/or oils. Excipients such as cocoa butter and suppository waxes, coloring agents, coating agents, sweetening, flavoring, and perfuming agents may also be present in the composition.

[00127] Exemplary diluents include calcium carbonate, sodium carbonate, calcium phosphate, dicalcium phosphate, calcium sulfate, calcium hydrogen phosphate, sodium phosphate lactose, sucrose, cellulose, microcrystalline cellulose, kaolin, mannitol, sorbitol, inositol, sodium chloride, dry starch, cornstarch, powdered sugar, and mixtures thereof.

[00128] Exemplary granulating and/or dispersing agents include potato starch, corn starch, tapioca starch, sodium starch glycolate, clays, alginic acid, guar gum, citrus pulp, agar, bentonite, cellulose and wood products, natural sponge, cation-exchange resins, calcium carbonate, silicates, sodium carbonate, cross-linked poly(vinyl-pyrrolidone) (crospovidone), sodium carboxymethyl starch (sodium starch glycolate), carboxymethyl cellulose, cross-linked sodium carboxymethyl cellulose (croscarmellose), methylcellulose, pregelatinized starch (starch 1500), microcrystalline starch, water insoluble starch, calcium carboxymethyl cellulose, magnesium aluminum silicate (Veegum), sodium lauryl sulfate, quaternary ammonium compounds, and mixtures thereof.

[00129] Exemplary surface active agents and/or emulsifiers include natural emulsifiers (e.g. acacia, agar, alginic acid, sodium alginate, tragacanth, chondrux, cholesterol, xanthan, pectin, gelatin, egg yolk, casein, wool fat, cholesterol, wax, and lecithin), colloidal clays (e.g. bentonite [aluminum silicate] and Veegum [magnesium aluminum silicate]), long chain amino acid derivatives, high molecular weight alcohols (e.g. stearyl alcohol, cetyl alcohol, oleyl alcohol, triacetin monostearate, ethylene glycol distearate, glyceryl monostearate, and

propylene glycol monostearate, polyvinyl alcohol), carbomers (e.g. carboxy polymethylene, polyacrylic acid, acrylic acid polymer, and carboxyvinyl polymer), carrageenan, cellulosic derivatives (e.g. carboxymethylcellulose sodium, powdered cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose), sorbitan fatty acid esters (e.g. polyoxyethylene sorbitan monolaurate [Tween 20], polyoxyethylene sorbitan [Tween 60], polyoxyethylene sorbitan monooleate [Tween 80], sorbitan monopalmitate [Span 40], sorbitan monostearate [Span 60], sorbitan tristearate [Span 65], glyceryl monooleate, sorbitan monooleate [Span 80]), polyoxyethylene esters (e.g. polyoxyethylene monostearate [Myrj 45], polyoxyethylene hydrogenated castor oil, polyethoxylated castor oil, polyoxymethylene stearate, and Solutol), sucrose fatty acid esters, polyethylene glycol fatty acid esters (e.g. Cremophor), polyoxyethylene ethers, (e.g. polyoxyethylene lauryl ether [Brij 30]), poly(vinyl-pyrrolidone), diethylene glycol monolaurate, triethanolamine oleate, sodium oleate, potassium oleate, ethyl oleate, oleic acid, ethyl laurate, sodium lauryl sulfate, Pluronic F 68, Poloxamer 188, cetrimonium bromide, cetylpyridinium chloride, benzalkonium chloride, docusate sodium, and/or mixtures thereof.

**[00130]** Exemplary binding agents include starch (e.g. cornstarch and starch paste), gelatin, sugars (e.g. sucrose, glucose, dextrose, dextrin, molasses, lactose, lactitol, mannitol, etc.), natural and synthetic gums (e.g. acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, cellulose acetate, poly(vinyl-pyrrolidone), magnesium aluminum silicate (Veegum), and larch arabogalactan), alginates, polyethylene oxide, polyethylene glycol, inorganic calcium salts, silicic acid, polymethacrylates, waxes, water, alcohol, and/or mixtures thereof.

**[00131]** Exemplary preservatives include antioxidants, chelating agents, antimicrobial preservatives, antifungal preservatives, alcohol preservatives, acidic preservatives, and other preservatives.

**[00132]** Exemplary antioxidants include alpha tocopherol, ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, monothioglycerol, potassium metabisulfite, propionic acid, propyl gallate, sodium ascorbate, sodium bisulfite, sodium metabisulfite, and sodium sulfite.

**[00133]** Exemplary chelating agents include ethylenediaminetetraacetic acid (EDTA) and salts and hydrates thereof (e.g., sodium edetate, disodium edetate, trisodium edetate, calcium disodium edetate, dipotassium edetate, and the like), citric acid and salts and hydrates thereof

(e.g., citric acid monohydrate), fumaric acid and salts and hydrates thereof, malic acid and salts and hydrates thereof, phosphoric acid and salts and hydrates thereof, and tartaric acid and salts and hydrates thereof. Exemplary antimicrobial preservatives include benzalkonium chloride, benzethonium chloride, benzyl alcohol, bronopol, cetrimide, cetylpyridinium chloride, chlorhexidine, chlorobutanol, chlorocresol, chloroxylenol, cresol, ethyl alcohol, glycerin, hexetidine, imidurea, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric nitrate, propylene glycol, and thimerosal.

[00134] Exemplary antifungal preservatives include butyl paraben, methyl paraben, ethyl paraben, propyl paraben, benzoic acid, hydroxybenzoic acid, potassium benzoate, potassium sorbate, sodium benzoate, sodium propionate, and sorbic acid.

[00135] Exemplary alcohol preservatives include ethanol, polyethylene glycol, phenol, phenolic compounds, bisphenol, chlorobutanol, hydroxybenzoate, and phenylethyl alcohol.

[00136] Exemplary acidic preservatives include vitamin A, vitamin C, vitamin E, beta-carotene, citric acid, acetic acid, dehydroacetic acid, ascorbic acid, sorbic acid, and phytic acid.

[00137] Other preservatives include tocopherol, tocopherol acetate, deteroxime mesylate, cetrimide, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), ethylenediamine, sodium lauryl sulfate (SLS), sodium lauryl ether sulfate (SLES), sodium bisulfite, sodium metabisulfite, potassium sulfite, potassium metabisulfite, Glydant Plus, Phenonip, methylparaben, Germall 115, Germaben II, Neolone, Kathon, and Euxyl. In certain embodiments, the preservative is an anti-oxidant. In other embodiments, the preservative is a chelating agent.

[00138] Exemplary buffering agents include citrate buffer solutions, acetate buffer solutions, phosphate buffer solutions, ammonium chloride, calcium carbonate, calcium chloride, calcium citrate, calcium gluconate, calcium gluceptate, calcium gluconate, D-gluconic acid, calcium glycerophosphate, calcium lactate, propanoic acid, calcium levulinate, pentanoic acid, dibasic calcium phosphate, phosphoric acid, tribasic calcium phosphate, calcium hydroxide phosphate, potassium acetate, potassium chloride, potassium gluconate, potassium mixtures, dibasic potassium phosphate, monobasic potassium phosphate, potassium phosphate mixtures, sodium acetate, sodium bicarbonate, sodium chloride, sodium citrate, sodium lactate, dibasic sodium phosphate, monobasic sodium phosphate, sodium phosphate mixtures, tromethamine, magnesium hydroxide, aluminum hydroxide, alginic acid, pyrogen-free water, isotonic saline, Ringer's solution, ethyl alcohol, and mixtures thereof.

**[00139]** Exemplary lubricating agents include magnesium stearate, calcium stearate, stearic acid, silica, talc, malt, glyceryl behenate, hydrogenated vegetable oils, polyethylene glycol, sodium benzoate, sodium acetate, sodium chloride, leucine, magnesium lauryl sulfate, sodium lauryl sulfate, and mixtures thereof.

**[00140]** Exemplary natural oils include almond, apricot kernel, avocado, babassu, bergamot, black current seed, borage, cade, camomile, canola, caraway, carnauba, castor, cinnamon, cocoa butter, coconut, cod liver, coffee, corn, cotton seed, emu, eucalyptus, evening primrose, fish, flaxseed, geraniol, gourd, grape seed, hazel nut, hyssop, isopropyl myristate, jojoba, kukui nut, lavandin, lavender, lemon, litsea cubeba, macademia nut, mallow, mango seed, meadowfoam seed, mink, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana, savoury, sea buckthorn, sesame, shea butter, silicone, soybean, sunflower, tea tree, thistle, tsubaki, vetiver, walnut, and wheat germ oils. Exemplary synthetic oils include, but are not limited to, butyl stearate, caprylic triglyceride, capric triglyceride, cyclomethicone, diethyl sebacate, dimethicone 360, isopropyl myristate, mineral oil, octyldodecanol, oleyl alcohol, silicone oil, and mixtures thereof.

**[00141]** Liquid dosage forms for oral and parenteral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredients, the liquid dosage forms may comprise inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (e.g., cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents. In certain embodiments for parenteral administration, the conjugates of the invention are mixed with solubilizing agents such as Cremophor, alcohols, oils, modified oils, glycols, polysorbates, cyclodextrins, polymers, and mixtures thereof.

**[00142]** Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation can be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and

solvents that can be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables. The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

**[00143]** A sterile injectable composition, e.g., a sterile injectable aqueous or oleaginous suspension, can be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as Tween 80) and suspending agents. The sterile injectable preparation can also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium (e.g., synthetic mono- or diglycerides). Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions can also contain a long-chain alcohol diluent or dispersant, or carboxymethyl cellulose or similar dispersing agents. Other commonly used surfactants such as Tweens or Spans or other similar emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms can also be used for the purposes of formulation.

**[00144]** In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This can be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

**[00145]** Compositions for rectal or vaginal administration are typically suppositories which can be prepared by mixing the conjugates of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which

are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active ingredient.

[00146] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active ingredient is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may comprise buffering agents.

[00147] Solid compositions of a similar type can be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally comprise opacifying agents and can be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. Solid compositions of a similar type can be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[00148] The active ingredient can be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active ingredient can be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills,

the dosage forms may comprise buffering agents. They may optionally comprise opacifying agents and can be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

**[00149]** Dosage forms for topical and/or transdermal administration of a compound of this invention may include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants and/or patches. Generally, the active ingredient is admixed under sterile conditions with a pharmaceutically acceptable carrier and/or any needed preservatives and/or buffers as can be required. Additionally, the present invention contemplates the use of transdermal patches, which often have the added advantage of providing controlled delivery of an active ingredient to the body. Such dosage forms can be prepared, for example, by dissolving and/or dispensing the active ingredient in the proper medium. Alternatively or additionally, the rate can be controlled by either providing a rate controlling membrane and/or by dispersing the active ingredient in a polymer matrix and/or gel.

**[00150]** Suitable devices for use in delivering intradermal pharmaceutical compositions described herein include short needle devices such as those described in U.S. Pat. Nos. 4,886,499; 5,190,521; 5,328,483; 5,527,288; 4,270,537; 5,015,235; 5,141,496; and 5,417,662. Intradermal compositions can be administered by devices which limit the effective penetration length of a needle into the skin, such as those described in PCT publication WO 99/34850 and functional equivalents thereof. Jet injection devices which deliver liquid vaccines to the dermis via a liquid jet injector and/or via a needle which pierces the stratum corneum and produces a jet which reaches the dermis are suitable. Jet injection devices are described, for example, in U.S. Pat. Nos. 5,480,381; 5,599,302; 5,334,144; 5,993,412; 5,649,912; 5,569,189; 5,704,911; 5,383,851; 5,893,397; 5,466,220; 5,339,163; 5,312,335; 5,503,627; 5,064,413; 5,520,639; 4,596,556; 4,790,824; 4,941,880; 4,940,460; and PCT publications WO 97/37705 and WO 97/13537. Ballistic powder/particle delivery devices which use compressed gas to accelerate vaccine in powder form through the outer layers of the skin to the dermis are suitable. Alternatively or additionally, conventional syringes can be used in the classical mantoux method of intradermal administration.

**[00151]** A pharmaceutical composition of the invention can be prepared, packaged, and/or sold in a formulation suitable for pulmonary administration via the buccal cavity. Such a formulation may comprise dry particles which comprise the active ingredient and which have a diameter in the range from about 0.5 to about 7 nanometers or from about 1 to about 6

nanometers. Such compositions are conveniently in the form of dry powders for administration using a device comprising a dry powder reservoir to which a stream of propellant can be directed to disperse the powder and/or using a self-propelling solvent/powder dispensing container such as a device comprising the active ingredient dissolved and/or suspended in a low-boiling propellant in a sealed container. Such powders comprise particles wherein at least 98% of the particles by weight have a diameter greater than 0.5 nanometers and at least 95% of the particles by number have a diameter less than 7 nanometers. Alternatively, at least 95% of the particles by weight have a diameter greater than 1 nanometer and at least 90% of the particles by number have a diameter less than 6 nanometers. Dry powder compositions may include a solid fine powder diluent such as sugar and are conveniently provided in a unit dose form.

**[00152]** Low boiling propellants generally include liquid propellants having a boiling point of below 65 °F at atmospheric pressure. Generally the propellant may constitute 50 to 99.9% (w/w) of the composition, and the active ingredient may constitute 0.1 to 20% (w/w) of the composition. The propellant may further comprise additional ingredients such as a liquid non-ionic and/or solid anionic surfactant and/or a solid diluent (which may have a particle size of the same order as particles comprising the active ingredient).

**[00153]** Pharmaceutical compositions of the invention formulated for pulmonary delivery may provide the active ingredient in the form of droplets of a solution and/or suspension. Such formulations can be prepared, packaged, and/or sold as aqueous and/or dilute alcoholic solutions and/or suspensions, optionally sterile, comprising the active ingredient, and may conveniently be administered using any nebulization and/or atomization device. Such formulations may further comprise one or more additional ingredients including, but not limited to, a flavoring agent such as saccharin sodium, a volatile oil, a buffering agent, a surface active agent, and/or a preservative such as methylhydroxybenzoate. The droplets provided by this route of administration may have an average diameter in the range from about 0.1 to about 200 nanometers.

**[00154]** Formulations described herein as being useful for pulmonary delivery are useful for intranasal delivery of a pharmaceutical composition of the invention. Another formulation suitable for intranasal administration is a coarse powder comprising the active ingredient and having an average particle from about 0.2 to 500 micrometers. Such a formulation is administered by rapid inhalation through the nasal passage from a container of the powder held close to the nares.

[00155] Formulations for nasal administration may, for example, comprise from about as little as 0.1% (w/w) and as much as 100% (w/w) of the active ingredient, and may comprise one or more of the additional ingredients described herein. A pharmaceutical composition of the invention can be prepared, packaged, and/or sold in a formulation for buccal administration. Such formulations may, for example, be in the form of tablets and/or lozenges made using conventional methods, and may contain, for example, 0.1 to 20% (w/w) active ingredient, the balance comprising an orally dissolvable and/or degradable composition and, optionally, one or more of the additional ingredients described herein. Alternately, formulations for buccal administration may comprise a powder and/or an aerosolized and/or atomized solution and/or suspension comprising the active ingredient. Such powdered, aerosolized, and/or aerosolized formulations, when dispersed, may have an average particle and/or droplet size in the range from about 0.1 to about 200 nanometers, and may further comprise one or more of the additional ingredients described herein.

[00156] Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to animals of all sorts. Modification of pharmaceutical compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and/or perform such modification with ordinary experimentation.

[00157] Compounds provided herein are typically formulated in dosage unit form for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of the compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular subject or organism will depend upon a variety of factors including the disease, disorder, or condition being treated and the severity of the disorder; the activity of the specific active ingredient employed; the specific composition employed; the age, body weight, general health, sex and diet of the subject; the time of administration, route of administration, and rate of excretion of the specific active ingredient employed; the duration of the treatment; drugs used in combination or coincidental with the specific active ingredient employed; and like factors well known in the medical arts.

[00158] To practice the method of this invention, the above-described compound or its pharmaceutical composition can be administered orally, parenterally, by inhalation spray,

topically, rectally, nasally, buccally, vaginally, rectally, or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional, and intracranial injection or infusion techniques. In general the most appropriate route of administration will depend upon a variety of factors including the nature of the agent (e.g., its stability in the environment of the gastrointestinal tract), and/or the condition of the subject (e.g., whether the subject is able to tolerate oral administration).

**[00159]** The exact amount of a compound required to achieve an effective amount will vary from subject to subject, depending, for example, on species, age, and general condition of a subject, severity of the side effects or disorder, identity of the particular compound(s), mode of administration, and the like. The desired dosage can be delivered three times a day, two times a day, once a day, every other day, every third day, every week, every two weeks, every three weeks, or every four weeks. In certain embodiments, the desired dosage can be delivered using multiple administrations (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations).

**[00160]** In certain embodiments, an effective amount of a compound for administration one or more times a day to a 70 kg adult human may comprise about 0.0001 mg to about 3000 mg, about 0.0001 mg to about 2000 mg, about 0.0001 mg to about 1000 mg, about 0.001 mg to about 1000 mg, about 0.01 mg to about 1000 mg, about 0.1 mg to about 1000 mg, about 1 mg to about 1000 mg, about 1 mg to about 100 mg, about 10 mg to about 1000 mg, or about 100 mg to about 1000 mg, of a compound per unit dosage form.

**[00161]** In certain embodiments, the compounds of the invention may be administered orally or parenterally at dosage levels sufficient to deliver from about 0.001 mg/kg to about 100 mg/kg, from about 0.01 mg/kg to about 50 mg/kg, preferably from about 0.1 mg/kg to about 40 mg/kg, preferably from about 0.5 mg/kg to about 30 mg/kg, from about 0.01 mg/kg to about 10 mg/kg, from about 0.1 mg/kg to about 10 mg/kg, and more preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

**[00162]** It will be appreciated that dose ranges as described herein provide guidance for the administration of provided pharmaceutical compositions to an adult. The amount to be administered to, for example, a child or an adolescent can be determined by a medical practitioner or person skilled in the art and can be lower or the same as that administered to an adult.

[00163] It will be also appreciated that a compound or composition, as described herein, can be administered in combination with one or more additional therapeutically active agents. The compounds or compositions can be administered in combination with additional therapeutically active agents that improve their bioavailability, reduce and/or modify their metabolism, inhibit their excretion, and/or modify their distribution within the body. It will also be appreciated that the therapy employed may achieve a desired effect for the same disorder, and/or it may achieve different effects.

[00164] The compound or composition can be administered concurrently with, prior to, or subsequent to, one or more additional therapeutically active agents. In general, each agent will be administered at a dose and/or on a time schedule determined for that agent. It will further be appreciated that the additional therapeutically active agent utilized in this combination can be administered together in a single composition or administered separately in different compositions. The particular combination to employ in a regimen will take into account compatibility of the inventive compound with the additional therapeutically active agent and/or the desired therapeutic effect to be achieved. In general, it is expected that additional therapeutically active agents utilized in combination be utilized at levels that do not exceed the levels at which they are utilized individually. In some embodiments, the levels utilized in combination will be lower than those utilized individually. Additional therapeutically active agents include antibiotic agents, e.g., antibiotics useful for treating tuberculosis. Exemplary antibiotics include, but are not limited to, isoniazid, rifampin, pyrazinamide, ethambutol, and streptomycin.

[00165] Also encompassed by the invention are kits (e.g., pharmaceutical packs). The kits provided may comprise an inventive pharmaceutical composition or compound and a container (e.g., a vial, ampule, bottle, syringe, and/or dispenser package, or other suitable container). In some embodiments, provided kits may optionally further include a second container comprising a pharmaceutical excipient for dilution or suspension of an inventive pharmaceutical composition or compound. In some embodiments, the inventive pharmaceutical composition or compound provided in the container and the second container are combined to form one unit dosage form.

### **Methods of Use and Treatment**

[00166] In another aspect, the invention provides a method of treating a bacterial infection in a patient in need of such treatment, comprising administering an effective amount of a compound of formula I or a composition comprising a compound of formula I. In certain

embodiments, the effective amount is a therapeutically effective amount. In certain other embodiments, the effective amount is a prophylactically effective amount.

[00167] In one embodiment, the bacterial infection is tuberculosis. In certain embodiments, the tuberculosis infection is a *Mycobacterium tuberculosis* infection. In certain embodiments, the tuberculosis infection is multi-drug-resistant tuberculosis (MDR-TB) infection, e.g., resistant to first-line TB drugs rifampicin and/or isoniazid. In certain embodiments, the tuberculosis infection is extensively-drug-resistant tuberculosis (XDR-TB) infection, e.g., also resistant to three or more of the six classes of second-line drugs (see, e.g., Centers for Disease Control and Prevention (CDC) (2006). "Emergence of *Mycobacterium tuberculosis* with extensive resistance to second-line drugs worldwide, 2000-2004". MMWR Morb Mortal Wkly Rep 55 (11): 301-5).

[00168] In some embodiments, the compounds of the invention can be active against a wide range of both Gram-positive and Gram-negative organisms. In these and other embodiments, the compounds of the invention can be used to treat infections and to inhibit microbial growth. Thus, the compounds of the invention can be used to treat humans and animals having a broad spectrum of bacterial infections such as impetigo, pneumonia, bronchitis, pharyngitis, endocarditis, urinary tract infections, diabetes foot ulcers, gastro-intestinal infections and bacteremia. These bacterial infections could be caused by any of the following bacteria--*Staphylococcus aureus*, coagulase negative staphylococci, methicillin-resistant *Staphylococcus aureus*, methicillin-resistant coagulase negative staphylococci, enterococci, beta-haemolytic streptococci, viridans group of streptococci, *Bacillus mycobacterial* infections due to multi-drug resistant *M. tuberculosis* and other atypical mycobacteria such as *M. intracellulare* and *M. avium*, as well as newly emerging Gram-negative pathogens such as *Chryseobacterium meningosepticum*, *Chryseobacterium indologense* and other Gram-negative pathogens such as *E. coli*, *Klebsiella*, *Proteus*, *Serratia*, *Citrobacter*, *Pseudomonas*, *Burkholderia*, *Brucella*, *Yersinia*, *Francisella*, *Coxiella*, *Chlamydia*, *Salmonella*, *Rickettsia*, *Shigella* and *Campylobacter*.

### Processes

[00169] In another aspect, the invention provides processes for preparing compounds of formula I. The process is depicted in the synthetic schemes in the following section.

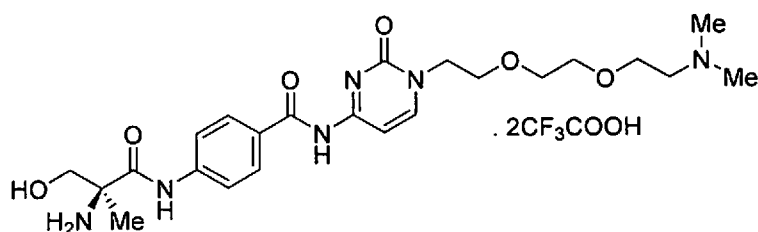
### Examples

[00170] The invention will now be demonstrated by the following non-limiting examples.

[00171] All reactions requiring anhydrous conditions were conducted in flame-dried glassware under a positive pressure of either nitrogen or argon. Commercially available reagents were used as received; otherwise, materials were purified according to *Purification of Laboratory Chemicals*. Dichloromethane ( $\text{CH}_2\text{Cl}_2$ ), *N,N'*-dimethylformamide (DMF), and tetrahydrofuran (THF) were degassed with nitrogen and passed through a solvent purification system (Innovative Technologies Pure Solv). Dry 1,4-dioxane was purchased from Acros Organics in a Acros Seal™ bottle. Triethylamine ( $\text{Et}_3\text{N}$ ) and *N,N*-diisopropylethylamine (DIPEA) were stored over 4 Å molecular sieves or distilled over 4 Å molecular sieves prior to usage. Microwave reactions were done in CEM Discover System Model 908005. Reactions were monitored by TLC and visualized by a dual short wave/long wave UV lamp and stained with ethanolic solutions of either  $\text{KMnO}_4$  or 12-phosphomolybdic acid. Flash chromatography was performed on Merck silica gel Kieselgel 60 (230-400 mesh) from EM Science with the indicated HPLC grade solvent. Reverse phase HPLC was conducted on a Gilson 322 using a Vydac C18 column eluting with  $\text{H}_2\text{O}$  (0.1% TFA) and 10%  $\text{H}_2\text{O}$ :90  $\text{CH}_3\text{CN}$  (0.1% TFA).

[00172] Melting points were determined using Mel-Temp® Capillary Melting Point Apparatus. Infrared spectra were obtained using Nicolet 380-FT IR spectrometer fitted with a Smart Orbit sample system. Optical rotations were obtained at ambient temperature on a Perkin Elmer Model 343 polarimeter (Na D line) using a microcell with a 1 decimeter path length. Mass spectra were determined on a Micromass Quattro II (ESI/APCI-TOF) for HRMS at the University of Utah Mass Spectrometry Facility or LCMS were collected on Thermo Scientific™ UltiMate™ 3000 UHPLC with electrochemical detector with a fluorescence detector monitored at either 214 or 254 nm.  $^1\text{H}$  NMR spectra were recorded at 500 MHz, 400 MHz, and 300 MHz, and  $^{13}\text{C}$  at 125 MHz. Proton resonances were reported relative to the deuterated solvent peak: 7.27 ppm for  $\text{CDCl}_3$ , 3.31 ppm (center line signal) for  $\text{CD}_3\text{OD}$ , 2.50 for  $\text{D}_6$ -DMSO and 4.79 for  $\text{D}_2\text{O}$  using the following format: chemical shift ( $\delta$ ) [multiplicity (s= singlet, br s= broad singlet, d= doublet, t= triplet, q= quartet, m= multiplet)]. Carbon resonances were reported as chemical shifts ( $\delta$ ) in parts per million, relative to the center line signal of the respective solvent peak: 77.23 ppm for  $\text{CDCl}_3$  and 49.15 ppm for  $\text{CD}_3\text{OD}$ . All the commercially available chemicals are purchased from Sigma-Aldrich, Acros, TCI America, Combi-Blocks, Alfa-Aesar, Ark Pharma, Strem Chemicals, Frontier Scientific, and AstaTech, Inc.

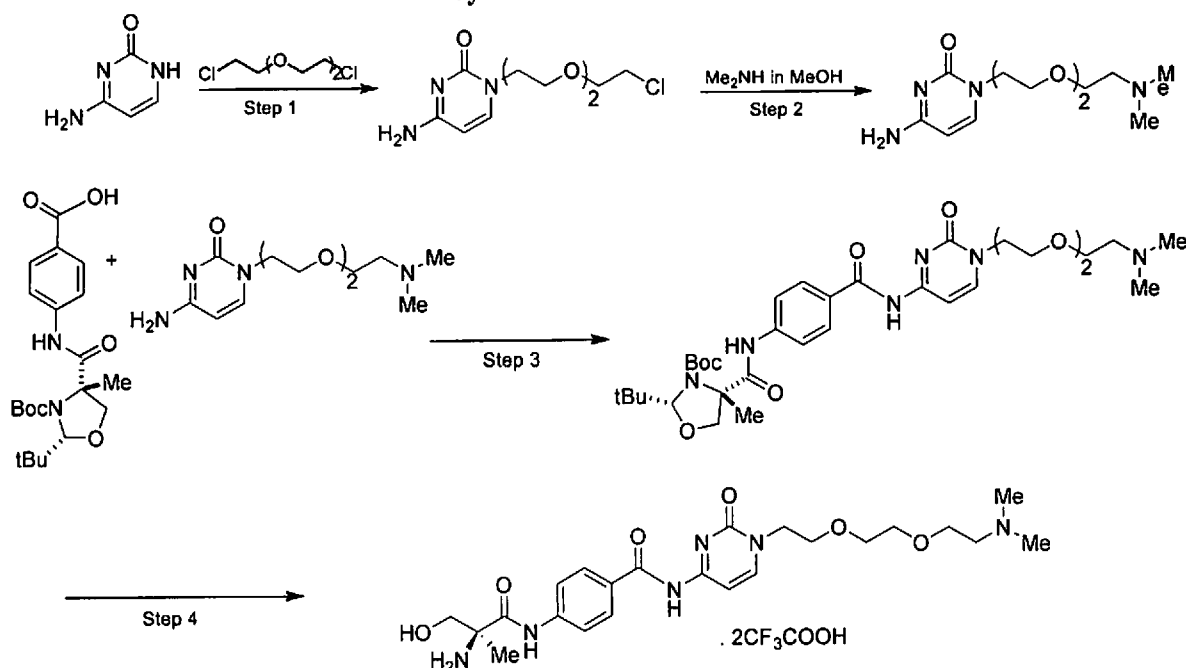
## Example 1



(*S*)-4-(2-Amino-3-hydroxy-2-methylpropanamido)-*N*-(1-(2-(2-(dimethylamino)ethoxy)ethoxy)ethyl)-2-oxo-1,2-dihydropyrimidin-4-yl)benzamide trifluoroacetate salt

[00173] Example 1 was prepared according to Synthetic Scheme 1.

## Synthetic Scheme 1



Reagents: Step 1)  $\text{Cs}_2\text{CO}_3$ , NaI (cat.),  $\text{CH}_3\text{CN}$ , reflux, 2h (2)  $\text{K}_2\text{CO}_3$ ,  $\text{CH}_3\text{CN}$ , 70 °C, 2h (3) EDC·Cl, HOBT,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , rt (4) 30% TFA in  $\text{CH}_2\text{Cl}_2$

**Step 1: 4-Amino-1-(2-(2-(2-chloroethoxy)ethoxy)ethyl)pyrimidin-2(1H)-one**

[00174] To a solution of cytosine (0.20 g, 1.80 mmol) in  $\text{CH}_3\text{CN}$  (12 mL),  $\text{Cs}_2\text{CO}_3$  (0.56 g, 1.80 mmol), bis(1,2-dichloroethoxy)ethane (0.34 g, 1.80 mmol), and a catalytic amount of NaI (0.03 g, 0.18 mmol) were combined under an atmosphere of nitrogen. The reaction mixture was heated to reflux for 2 h, and then was concentrated under reduced pressure. Purification of the residue on silica gel using flash chromatography (5%  $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 1%  $\text{Et}_3\text{N}$ ) afforded the desired product as a brown oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ );  $\delta$  ppm

7.44 (d, 1H), 5.71 (d, 1H), 3.98 (t, 2H), 3.76-3.70 (m, 4H), 3.64-3.61 (m, 6H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>); δ ppm 163.4, 153.9, 147.8, 95.1, 71.3, 70.4, 70.4, 68.4, 46.1, 43.1.

**Step 2: 4-Amino-1-(2-(2-(dimethylamino)ethoxy)ethyl)pyrimidin-2(1H)-one**

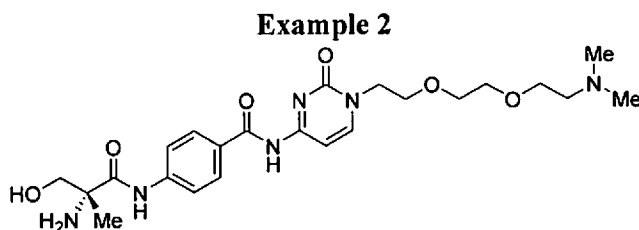
[00175] 4-Amino-1-(2-(2-(2-chloroethoxy)ethoxy)ethyl)pyrimidin-2(1H)-one (24 mg, 0.09 mmol), K<sub>2</sub>CO<sub>3</sub> (14 mg, 0.09 mmol) and dimethylamine in methanol (1 mL) in excess were combined under an atmosphere of nitrogen in an oven dried sealed tube. The reaction mixture was heated for 2 hrs at 70 °C and then was concentrated under reduced pressure. Purification on silica gel using flash chromatography (15% CH<sub>2</sub>Cl<sub>2</sub>/MeOH) afforded the desired product as a colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>); δ ppm 7.37 (d, 1H), 5.92 (d, 1H), 3.86 (t, 2H), 3.62 (t, 2H), 3.54 (t, 2H), 3.49 (br s, 6H), 2.70 (t, 2H), 2.39 (s, 6H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>); δ ppm 166.2, 157.1, 146.8, 94.7, 70.3, 70.2, 68.8, 67.8, 58.1, 49.5, 45.1. IR (neat) 3326, 3184, 2867, 1645, 1520, 1489, 1385 cm<sup>-1</sup>. HRMS (ESI) Calculated for C<sub>12</sub>H<sub>23</sub>N<sub>4</sub>O<sub>3</sub> m/z (M+H) 271.1770, Obs'd. 271.1770.

**Step 3: (2R,4S)-tert-Butyl-2-(tert-butyl)-4-((4-((1-(2-(2-(dimethylamino)ethoxy)ethyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)phenyl)carbamoyl)-4-methyloxazolidine-3-carboxylate**

[00176] To a solution of 4-((2R,4S)-3-(tert-butoxycarbonyl)-2-(tert-butyl)-4-methyloxazolidine-4-carboxamido)benzoic acid (20 mg, 0.04 mmol) in dichloromethane (2 mL), was added EDCI (11 mg, 0.05 mmol), HOBt (7 mg, 0.05 mmol), and NEt<sub>3</sub> (20 μL, 0.14 mmol). The resulting mixture was stirred at room temperature for 5 minutes and then 4-amino-1-(2-(2-(dimethylamino)ethoxy)ethyl)pyrimidin-2(1H)-one (12 mg, 0.04 mmol) was added. Stirring was continued for an additional 2 h. The reaction mixture was then quenched with saturated NaHCO<sub>3</sub> solution and diluted with 3 mL of dichloromethane. The organic layer was separated and washed with water (2x2 mL) followed by brine (1x2 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (5% MeOH/CHCl<sub>3</sub>, 1% Et<sub>3</sub>N) to afford the product as a yellow gummy mass. [α]<sub>D</sub><sup>20</sup> = -2.8 (c = 2, CHCl<sub>3</sub>). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>); δ ppm 7.90 (d, 2H), 7.82 (d, 1H), 7.69 (d, 2H), 7.40 (d, 1H), 5.21 (s, 1H), 4.82 (d, 1H), 4.11 (t, 2H), 3.84 -3.76 (m, 3H), 3.62 - 3.54 (s, 6H), 2.52 (t, 2H), 2.28 (s, 6H), 1.73 (s, 3H), 1.54 (s, 9H), 0.91 (s, 9H). IR (neat) 2961, 1733, 1683, 1653, 1635, 1598, 1521, 1481 cm<sup>-1</sup>. HRMS (ESI) Calculated for C<sub>33</sub>H<sub>51</sub>N<sub>6</sub>O<sub>8</sub> m/z (M+H) 659.3768, Obs'd (observed). 659.3771.

**Step 4: (S)-4-(2-Amino-3-hydroxy-2-methylpropanamido)-N-(1-(2-(2-(dimethylamino)ethoxy)ethoxy)ethyl)-2-oxo-1,2-dihydropyrimidin-4-yl)benzamide trifluoroacetate salt**

[00177] (2*R*,4*S*)-*tert*-Butyl-2-(*tert*-butyl)-4-(((4-((1-(2-(2-(dimethylamino)ethoxy)ethyl)-2-oxo-1,2-dihydropyrimidin-4-yl) carbamoyl)phenyl)carbamoyl)-4-methyloxazolidine-3-carboxylate (14 mg, 0.02 mmol) was dissolved in 30% TFA in dichloromethane (1 mL) and stirred at room temperature for 12 h. The reaction mixture was concentrated under reduced pressure, dissolved in water, and washed with ether (2x2 mL) to remove the organic impurities. The aqueous layer was basified with NaHCO<sub>3</sub> to pH 10 and was extracted with dichloromethane (2x4 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure, to leave a residue. The residue was stirred in 30% TFA in dichloromethane for 0.5h, the solvent was evaporated, and the remaining solid was triturated with diethyl ether. Filtration afforded the title compound (S)-4-(2-Amino-3-hydroxy-2-methylpropanamido)-N-(1-(2-(2-(2-(dimethylamino)ethoxy)ethoxy)ethyl)-2-oxo-1,2-dihydropyrimidin-4-yl)benzamide trifluoroacetate salt as a brick red-colored solid.  $[\alpha]^{20}_D = -2.8$  ( $c=2.00$ , CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O);  $\delta$  ppm 8.10 (d, 2H), 7.98 (d, 1H), 7.70 (d, 2H), 7.47 (d, 1H), 4.19 (d, 1H), 4.18-3.94 (m, 2H), 3.93 (d, 1H), 3.90 (t, 2H), 3.82 – 3.79 (m, 2H), 3.75 – 3.68 (m, 4H), 3.37-3.33 (m, 2H), 2.91 s, 6H), 1.73 (s, 3H) <sup>13</sup>C NMR (100 MHz, );  $\delta$  ppm.169.5, 168.7, 163.1, 157.8, 151.5, 140.9, 129.2, 121.8, 117.8, 114.9, 98.1, 69.7, 67.5, 63.9, 62.1, 56.7, 50.3, 46.6, 42.7, 22.4, IR (neat) 2924, 2854, 1699, 1669, 1652, 1635, 1558, 1506, 1488cm<sup>-1</sup>. HRMS (ESI) Calculated for C<sub>23</sub>H<sub>35</sub>N<sub>6</sub>O<sub>6</sub>  $m/z$  491.2618 (M<sup>+</sup>), Obs'd. 491.2628.

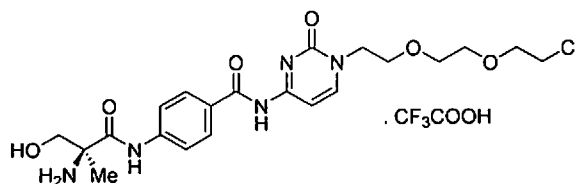


**(R)-4-(2-Amino-3-hydroxy-2-methylpropanamido)-N-(1-(2-(2-(2-(dimethylamino)ethoxy)ethoxy)ethyl)-2-oxo-1,2-dihydropyrimidin-4-yl)benzamide**

[00178] Example 2 was prepared in a similar fashion to Example 1 from (2*R*,4*R*)-*tert*-butyl-2-(*tert*-butyl)-4-(((4-(methoxycarbonyl)phenyl)carbamoyl)-4-methyloxazolidine-3-carboxylate and 4-amino-1-(2-(2-(2-(dimethylamino)ethoxy)ethyl)pyrimidin-2(1H)-one to afford the desired product as a yellow solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>);  $\delta$  7.86 ppm

(d, 2H), 7.77 (d, 1H), 7.56 (d, 2H), 7.42 (d, 1H), 4.14 (d, 1H), 4.05 (t, 2H), 3.74 (t, 2H), 3.57 – 3.54 (m, 2H), 3.52 – 3.48 (m, 4H), 3.45 (d, 1H), 2.46 (t, 2H), 2.23 (s, 6H), 1.31 (s, 3H).

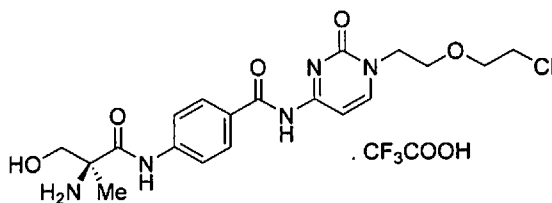
### Example 3



**(S)-4-(2-Amino-3-hydroxy-2-methylpropanamido)-N-(1-(2-(2-(2-chloroethoxy)ethoxy)ethyl)-2-oxo-1,2-dihydropyrimidin-4-yl)benzamide trifluoroacetate salt**

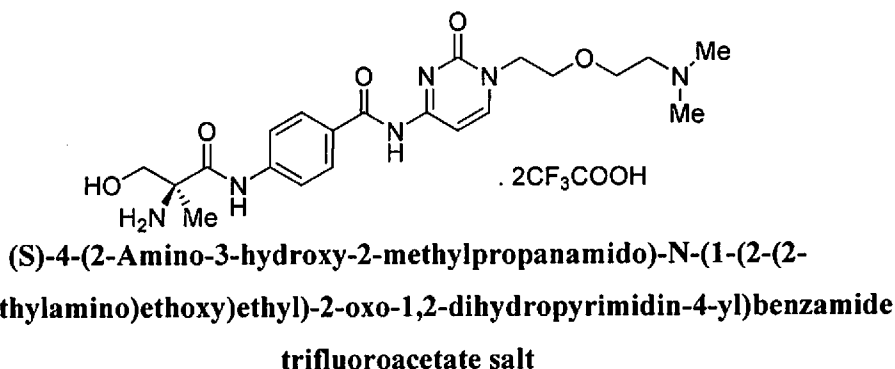
[00179] Example 3 was prepared in a similar fashion to Example 1 from (2*R*,4*R*)-*tert*-butyl-2-(*tert*-butyl)-4-((4-(methoxycarbonyl)phenyl)carbamoyl)-4-methyloxazolidine-3-carboxylate and 4-Amino-1-(2-(2-(chloro)ethoxy)ethyl)pyrimidin-2(1*H*)-one as a white solid. <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O); δ ppm 8.04 (d, 1H), 7.91 (d, 2H), 7.67 (d, 2H), 7.37 (d, 1H), 4.19 (d, 1H), 4.10 (br s, 2H), 3.97 (d, 1H), 3.84 (br s, 2H), 3.74 – 3.65 (m, 8H), 1.73 (s, 3H) <sup>13</sup>C NMR (100 MHz, ); δ ppm. 171.9, 170.6, 165.2, 159.5, 154.4, 143.6, 131.7, 131.4, 123.9, 100.3, 73.3, 72.2, 71.9, 69.8, 66.7, 64.7, 53.0, 45.8, 20.4.

### Example 4

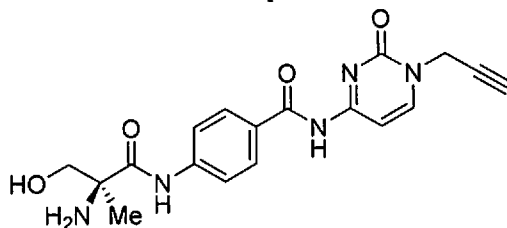


**(S)-4-(2-Amino-3-hydroxy-2-methylpropanamido)-N-(1-(2-(2-chloroethoxy)ethyl)-2-oxo-1,2-dihydropyrimidin-4-yl)benzamide trifluoroacetate salt**

[00180] Example 4 was prepared in a similar fashion to Example 1 from (2*R*,4*R*)-*tert*-butyl-2-(*tert*-butyl)-4-((4-(methoxycarbonyl)phenyl)carbamoyl)-4-methyloxazolidine-3-carboxylate and 4-amino-1-(2-(2-chloroethoxy)ethyl)pyrimidin-2(1*H*)-one to afford the desired product as a white solid <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O) δ ppm 8.04 (d, 1H), 7.91 (d, 2H), 7.66 (d, 2H), 7.44 (d, 1H), 4.18 (d, 1H), 4.12 (br s, 2H), 3.96 (d, 1H), 3.89 (br s, 2H), 3.80 (br s, 2H), 3.69 (br s, 2H), 1.72 (s, 3H).

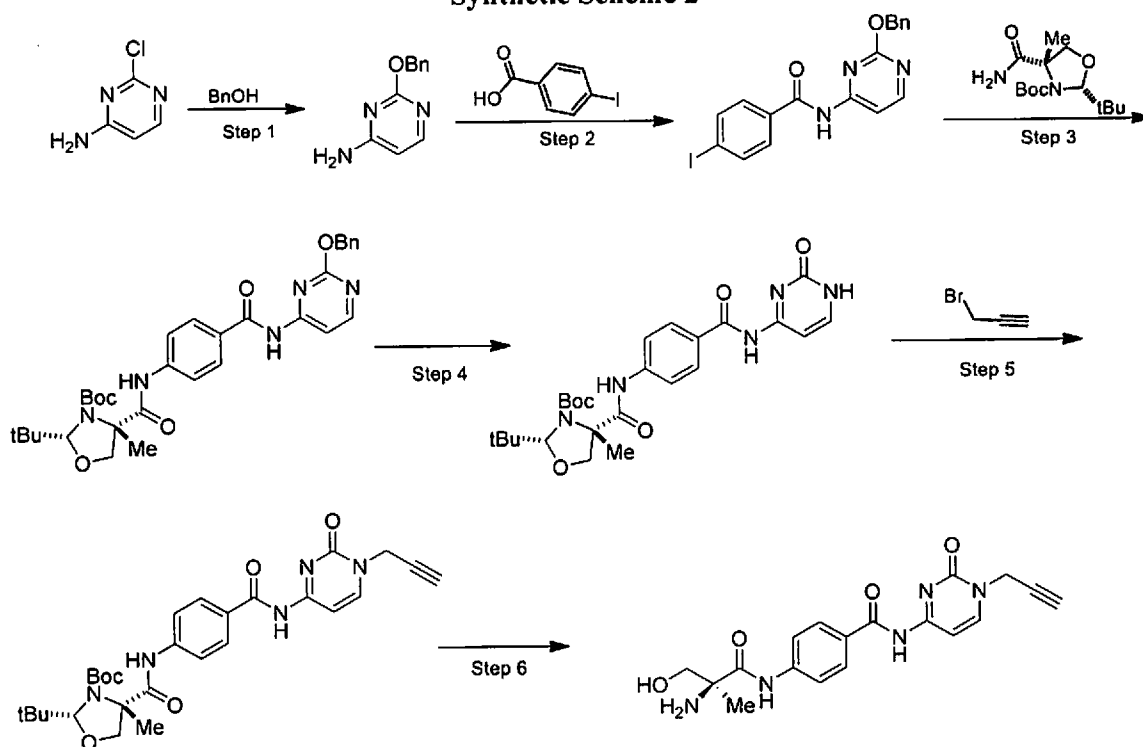
**Example 5**

[00181] Example 5 was prepared in a similar fashion to Example 1 from (2*R*,4*R*)-*tert*-butyl-2-(*tert*-butyl)-4-((4-(methoxycarbonyl)phenyl)carbamoyl)-4-methyloxazolidine-3-carboxylate and 4-amino-1-(2-(2-dimethylamino)ethyl)pyrimidin-2(1*H*)-one to afford the desired product as a white solid. <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O) δ ppm 8.17 (d, 1H), 8.02 (d, 2H), 7.74 (d, 2H), 7.54 (d, 1H), 4.19 (d, 1H), 4.16 (br s, 2H), 4.03 (d, 1H), 3.96 (br s, 2H), 3.88 (br s, 2H), 3.42 (br s, 2H), 2.94 (s, 6H), 1.76 (s, 3H).

**Example 6**

[00182] Example 6 was prepared according to Synthetic Scheme 2.

## Synthetic Scheme 2



Reagents: Step 1) NaH, THF, 0 °C to 50 °C, 16h (2) CO<sub>2</sub>Cl<sub>2</sub>, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to rt, 0.5h then, KHMDS in toluene, 0 °C to 50 °C (3) K<sub>2</sub>CO<sub>3</sub>, CuI (Cat.), *N,N'*-dimethylethylenediamine (Cat.), 1,4-dioxane, 110 °C, 24 h (4) 10% Pd/C, H<sub>2</sub>, MeOH, rt, 20min (5) Cs<sub>2</sub>CO<sub>3</sub>, CH<sub>3</sub>CN, 50 °C, 0.5h (6) 30% TFA in CH<sub>2</sub>Cl<sub>2</sub>, rt, 12h

**Step 1: 2-(Benzyloxy)pyrimidin-4-amine**

[00183] Benzyl alcohol (4.0 mL, 39.0 mmol) was added drop wise to a stirring mixture of NaH (0.36 g, 15.0 mmol) in dry THF (12 mL) at 0 °C, under nitrogen atmosphere. The mixture was stirred for another 30 minutes until it forms a clear solution followed by the addition of 4-Amino-2-chloropyrimidine (0.33 g, 2.55 mmol) at 0 °C and then heated at 80 °C for 12 h. The reaction mixture was concentrated under reduced pressure. The crude mixture was purified using column chromatography (60% EtOAc/Hexanes) to afford the desired product as a white solid. M.P. 76-78 °C (lit. 80-81 °C). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ ppm 7.82 (d, 1H), 7.36 (d, 2H), 7.25-7.21 (m, 3H), 5.95 (d, 1H), 5.89 (br s, 2H), 5.28 (s, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ ppm 165.0, 164.7, 156.5, 136.6, 128.1, 127.6, 127.5, 99.7, 68.1 ppm. IR (neat) 3465, 3324, 3034, 3034, 1635, 1559, 1455, 1352, 1292 cm<sup>-1</sup>. HRMS (ESI) Calculated for C<sub>11</sub>H<sub>12</sub>N<sub>3</sub>O *m/z* (M<sup>+</sup>) 202.0980, Obs'd 202.0977.

**Step 2: *N*-(2-(Benzyloxy)pyrimidin-4-yl)-4-iodobenzamide**

[00184] KHMDS, 0.5M solution in toluene (5.95 mL, 2.98 mmol), was added to a stirred solution of the 2-(benzyloxy)pyrimidin-4-amine (0.50 g, 2.48 mmol) in toluene (15 mL) at 0

°C under nitrogen atmosphere. The reaction was stirred for 30 min. In another flask, 4-iodobenzoic acid (1.85 g, 7.44 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) under an N<sub>2</sub>. The solution was cooled to 0 °C, oxalylchloride (0.65 mL, 5.16 mmol) was added dropwise followed by the addition of two drops of DMF. The reaction was allowed to stir for 30 min, until the solution becomes clear. The mixture was concentrated under reduced pressure; the acid chloride formed was dissolved in dichloromethane (10 mL) added into the deprotonated aminopyrimidine dropwise. The reaction was allowed to warm to rt and was stirred overnight. The reaction was quenched with saturated solution of NH<sub>4</sub>Cl (10 mL), extracted with EtOAc (3 x 10 mL). The combined fractions was washed with brine (10 mL) and dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification on silica gel using flash chromatography (10% EtOAc/hexanes) afforded the desired compound as a white solid. MP. 110 °C. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>); δ ppm 8.50 (d, 1H), 8.48 (br s, 1H), 7.96 (d, 1H), 7.88 (d, 2H), 7.60 (d, 2H), 7.47 (d, 2H), 7.38 (t, 2H), 7.34 (t, 1H), 5.43 (s, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>); δ ppm 165.4, 164.7, 160.9, 159.2, 138.5, 136.4, 132.8, 128.9, 128.6, 128.2, 128.0, 104.4, 100.6, 69.3. IR (neat); 3303, 3061, 1695, 1585, 1516, 1402, 1288 cm<sup>-1</sup>. HRMS (ESI) Calculated for C<sub>18</sub>H<sub>14</sub>N<sub>3</sub>O<sub>2</sub>NaI *m/z* (M+Na) 454.0028, Obs'd. 454.0030.

**Step 3: (2*R*,4*S*)-tert-Butyl 4-((4-((2-(benzyloxy)pyrimidin-4-yl)carbamoyl)phenyl)carbamoyl)-2-(tert-butyl)-4-methyloxazolidine-3-carboxylate:**

[00185] An oven dried sealed tube was charged with recrystallized CuI (0.01 g, 0.05 mmol), anhydrous K<sub>2</sub>CO<sub>3</sub> (1.44 g, 1.04 mmol), and *N*-(2-(benzyloxy)pyrimidin-4-yl)-4-iodobenzamide (0.23 g, 0.52 mmol). The flask was then fitted with a rubber septum. A solution of (2*R*,4*S*)-tert-Butyl 2-(tert-butyl)-4-carbamoyl-4-methyloxazolidine-3-carboxylate (0.29 g, 0.52 mmol) in dioxane (7 mL) was added to the reaction flask via syringe under a nitrogen atmosphere. Additional dioxane (1.5 mL) was used to wash the walls of the sealed tube. *N*,*N*'-dimethylethane-1,2-diamine (20 µL, 0.05 mmol) was then added into the reaction mixture via a syringe. The reaction mixture was degased and flushed with nitrogen. The rubber septum was replaced with the screw cap. The reaction was stirred and heated at 110 °C for 24 h. The reaction mixture was then diluted with EtOAc (10 mL), filtered through a pad of celite and concentrated under reduced pressure. Purification on silica gel using flash chromatography (50% EtOAc/hexanes) afforded the desired compound as a white solid. M.P. 152 – 154 °C. [α]<sub>D</sub><sup>20</sup> = -53 (*c* = 0.20, CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>); δ ppm 8.48 (t, 2H), 7.98 (d, 1H), 7.89 (d, 2H), 7.70 (d, 2H), 7.48 (d, 1H), 7.39-7.27 (m, 3 H), 5.45 (s, 2H), 5.22 (s, 1H), 4.82 (d, 1H), 3.82 (d, 1H), 1.74 (s, 3H), 1.55 (s, 9H), 0.93 (s, 9H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ );  $\delta$  ppm 171.7, 165.0, 164.5, 160.5, 159.2, 155.9, 142.5, 136.3, 128.5, 128.4, 128.2, 127.9, 127.8, 119.4, 104.2, 97.9, 82.9, 76.0, 69.0, 68.0, 38.1, 28.1, 26.1, 22.0. IR (neat); 2967, 2210, 1976, 1691, 1591, 1493, 1460, 1365  $\text{cm}^{-1}$ . HRMS (ESI) Calculated for  $\text{C}_{32}\text{H}_{39}\text{N}_5\text{O}_6\text{Na}$   $m/z$  (M+Na) 612.2798, Obs'd. 612.2809.

**Step 4: (2R,4S)-tert-Butyl-2-(tert-butyl)-4-methyl-4-((4-((2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)phenyl)carbamoyl)oxazolidine-3-carboxylate:**

[00186] To a mixture of (2R,4S)-tert-butyl 4-((4-((2-(benzyloxy)pyrimidin-4-yl)carbamoyl)phenyl)carbamoyl)-2-(tert-butyl)-4-methyloxazolidine-3-carboxylate (0.2 g, 0.34 mmol) and 10% Pd/C (0.02 g, 10% wt) was carefully added methanol (10 mL). The reaction mixture was degassed, purged with hydrogen gas (3 times), and stirred for 20 min. The reaction mixture was filtered through a pad of celite and the filtrate was concentrated under reduced pressure to afford the desired product as a white solid. M.P. 206-208 °C.  $[\alpha]_D^{20} = -10$  ( $c=0.12$ , MeOH).  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-d}_6$ );  $\delta$  ppm 8.03 (d, 2H), 7.85 (d, 1H), 7.69 (d, 2H), 7.17 (brs, 1H), 5.07 (s, 1H), 4.41 (d, 1H), 4.40 (brs, 1H), 3.85 (d, 1H), 1.64 (s, 3H), 1.46 (s, 9H), 0.90 (s, 9H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ );  $\delta$  ppm 170.6, 163.7, 154.4, 147.0, 141.9, 129.5, 128.6, 128.4, 119.3, 96.8, 95.5, 81.3, 79.1, 75.8, 67.6, 38.0, 27.7, 25.9, 21.1. IR (neat) 2972, 1691, 1594, 1493, 1459  $\text{cm}^{-1}$ . HRMS (ESI) Calculated for  $\text{C}_{25}\text{H}_{33}\text{N}_5\text{O}_6\text{Na}$   $m/z$  (M+Na) 522.2329, Obs'd. 522.2333.

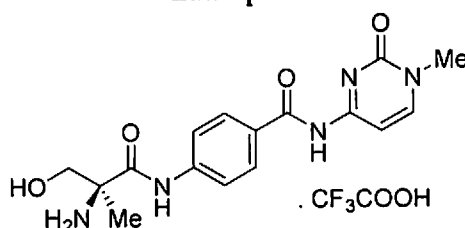
**Step 5: (2R,4S)-tert-Butyl-2-(tert-butyl)-4-methyl-4-((4-((2-oxo-1-(prop-2-yn-1-yl)-1,2-dihydropyrimidin-4-yl)carbamoyl)phenyl)carbamoyl)oxazolidine-3-carboxylate:**

[00187] To a solution of (2R,4S)-tert-butyl-2-(tert-butyl)-4-methyl-4-((4-((2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)phenyl)carbamoyl)oxazolidine-3-carboxylate (0.04 g, 0.08 mmol) in  $\text{CH}_3\text{CN}$  (2 mL),  $\text{Cs}_2\text{CO}_3$  (33 mg, 0.10 mmol) and propargyl bromide (12 mg, 0.10 mmol) was added under an atmosphere of nitrogen. The reaction mixture was stirred for 0.4 h at 50 °C, and concentrated under reduced pressure. Purification on silica gel using flash chromatography (1.5%  $\text{CH}_2\text{Cl}_2/\text{MeOH}$ ) afforded the desired product as a colorless oil.  $[\alpha]_D^{20} = -87$  ( $c=1.00$ ,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ );  $\delta$  ppm 8.01 (d, 1H), 7.90 (d, 2H), 7.69 (d, 2H), 7.55 (bs, 1H), 5.20 (s, 1H), 4.79 (d, 1H), 4.72 (d, 2H), 3.79 (d, 1H), 2.59 (t, 1H), 1.71 (s, 3H), 1.53 (s, 9H), 0.90 (s, 9H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ );  $\delta$  ppm 171.7, 162.5, 155.8, 146.6, 142.8, 128.9, 119.3, 97.9, 97.06, 82.9, 76.0, 75.7, 68.0, 44.6, 38.8, 38.1, 28.1, 26.1, 22.0. IR (neat) 3259.88, 2974.64, 1663.00, 1625.25, 1596.70, 1481.56, 1359.16  $\text{cm}^{-1}$ . HRMS (ESI) Calculated for  $\text{C}_{28}\text{H}_{35}\text{N}_5\text{O}_6\text{Na}$   $m/z$  (M+Na) 560.2485, Obs'd. 560.2490.

**Step 6: (S)-4-(2-Amino-3-hydroxy-2-methylpropanamido)-N-(2-oxo-1-(prop-2-yn-1-yl)-1,2-dihydropyrimidin-4-yl)benzamide:**

[00188] (2*R*,4*S*)-*tert*-Butyl-2-(*tert*-butyl)-4-methyl-4-((4-((2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl) phenyl)carbamoyl)oxazolidine-3-carboxylate (53.8 mg, 0.10 mmol) was dissolved in 30% TFA in dichloromethane (1.5 mL) and stirred at rt for 6h. The reaction mixture was concentrated under reduced pressure dissolved in water and washed with ether (2 X 2 mL). The aqueous layer was basified with NaHCO<sub>3</sub> to pH 10 and the compound was extracted with dichloromethane (2 X 4 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to afford desired product as a yellow solid. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ ppm 8.21 (d, 1H), 7.97 (d, 2H), 7.81 (d, 2H), 7.61 (d, 1H), 4.75 (d, 2H), 3.96 (d, 1H), 3.46 (d, 1H), 3.02 (t, 1H), 1.34 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ ppm 170.3, 168.2, 164.9, 149.8, 143.6, 130.2, 121.4, 98.9, 79.4, 77.4, 76.8, 65.5, 63.6, 49.8, 40.1, 18.8.

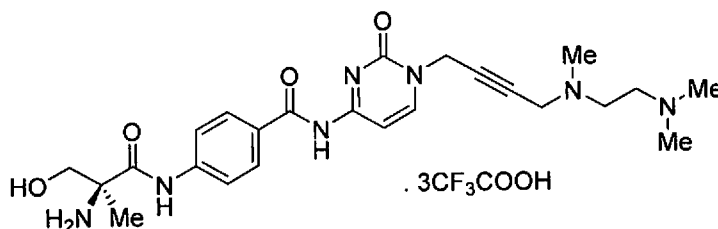
### Example 7



### (*S*)-4-(2-Amino-3-hydroxy-2-methylpropanamido)-*N*-(1-methyl-2-oxo-1,2-dihydropyrimidin-4-yl)benzamide trifluoroacetate salt

[00189] Example 7 was prepared in a similar fashion to Example 1 from (2*R*,4*S*)-*tert*-butyl-2-(*tert*-butyl)-4-methyl-4-((4-((2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl) phenyl)carbamoyl)oxazolidine-3-carboxylate and methyl iodide to afford the desired product as a white solid. <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O) δ ppm 8.03 (d, 1H), 7.90 (d, 2H), 7.65 (d, 2H), 7.30 (d, 1H), 4.17 (d, 1H), 3.94 (d, 2H), 3.50 (s, 3H), 1.71 (s, 3H). <sup>13</sup>C NMR (100 MHz, D<sub>2</sub>O) δ ppm 172.1, 171.0, 165.2, 154.9, 145.6, 143.8, 132.0, 124.2, 100.6, 95.0, 68.8, 66.9, 41.2, 20.6.

### Example 8

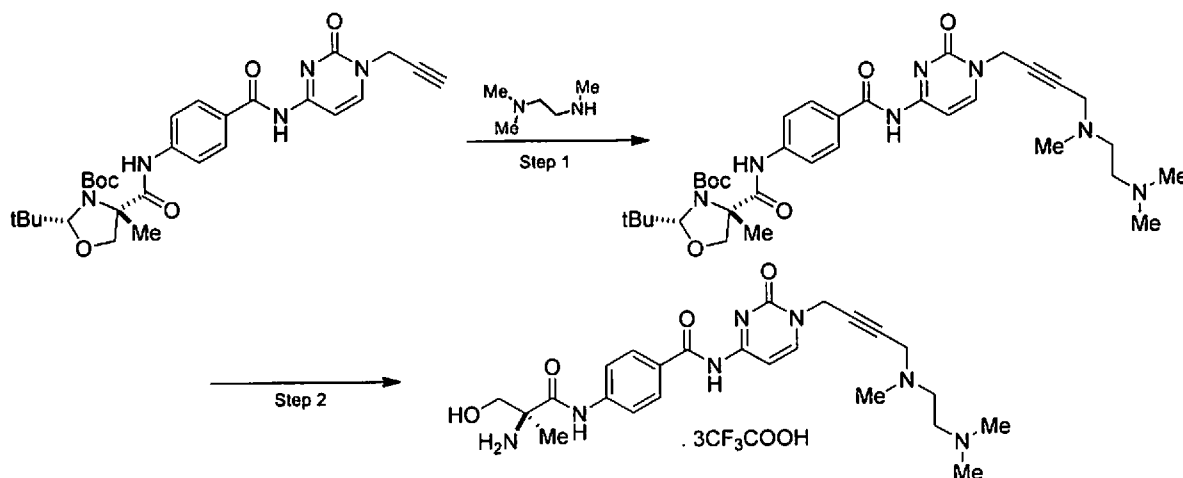


### (*S*)-4-(2-Amino-3-hydroxy-2-methylpropanamido)-*N*-(1-(4-((2-(dimethylamino)ethyl)(methylamino)but-2-yn-1-yl)-2-oxo-1,2-dihydropyrimidin-4-

## yl)benzamide trifluoroacetate salt

[00190] Example 8 was prepared according to Synthetic Scheme 3.

## Synthetic Scheme 3



Reagents: Step 1)  $\text{Cu}(\text{OAc})_2$ ,  $(\text{HCHO})_n$ , 1,4-dioxane, 80 °C, MW, 200W, 20Min (2) 30% TFA in  $\text{CH}_2\text{Cl}_2$ , rt, 12h

**Step 1: (2R,4S)-tert-Butyl 2-((tert-butyl)-4-((4-((1-(4-((2-(dimethylamino)ethyl)(methyl)amino)but-2-yn-1-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)phenyl)carbamoyl)-4-methyloxazolidine-3-carboxylate:**

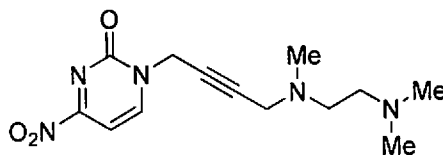
[00191] An oven dried pressure flask was charged with  $\text{Cu}(\text{OAc})_2$  (1 mg g, 3  $\mu\text{mol}$ ), paraformaldehyde (4 mg, 0.11 mmol), *N,N,N'*-trimethylethylenediamine (4 mg, 0.04 mmol), and 1,4-Dioxane (1.5 mL). The reaction mixture was degassed and purged with nitrogen (3 times). The flask was then fitted with a pressure tube cap. The reaction was stirred and heated in a focused CEM microwave reactor (80 °C, 200 W) for 5 minutes. To this mixture was (2R,4S)-tert-butyl 2-((tert-butyl)-4-methyl-4-((4-((2-oxo-1-(prop-2-yn-1-yl)-1,2-dihydropyrimidin-4-yl)carbamoyl)phenyl)carbamoyl)oxazolidine-3-carboxylate (20 mg, 0.04 mmol). The reaction mixture was stirred and heated in a focused CEM microwave reactor at microwave conditions (80 °C 200 W) for 12 minutes. The reaction mixture was then diluted with EtOAc (1 mL) and filtered through a pad of celite and concentrated under reduced pressure. Purification on silica gel using flash chromatography (20% MeOH/ $\text{CHCl}_3$ , 1%  $\text{Et}_3\text{N}$ ) afforded the desired product as a yellow gummy mass.  $[\alpha]_D^{20} = -35.2$  ( $c=1$ ,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ );  $\delta$  ppm 8.03 (d, 1H), 7.88 (d, 2H), 7.65 (d, 2H), 7.51 (d, 1H), 5.17 (s, 1H), 4.77 (d, 1H), 4.73 (s, 2H), 3.77 (d, 1H), 3.43 (s, 2H), 2.51 (t, 2H), 2.32 (t, 2H), 2.29 (s, 3 H), 2.21 (s, 6H), 1.69 (s, 3H), 1.50 (s, 9H), 0.87 (s, 9H) ppm.  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ );  $\delta$  ppm 171.8, 166.1, 162.5, 156.0, 155.2, 146.9, 142.9, 129.1, 128.2,

128.0, 119.4, 98.0, 97.0, 84.3, 83.1, 76.1, 68.1, 57.5, 57.4, 53.6, 46.3, 45.8, 45.7, 45.6, 45.5, 42.3, 39.4, 38.2, 29.7, 28.2, 26.2, 22.1 ppm. IR (neat) 2973, 1662, 1624, 1596, 1540, 1481, 1358, 1301  $\text{cm}^{-1}$ . HRMS (ESI) Calculated for  $\text{C}_{34}\text{H}_{50}\text{N}_7\text{O}_6$   $m/z$  (M+H) 652.3823, Obs'd. 652.3831.

**Step 2: (S)-4-(2-Amino-3-hydroxy-2-methylpropanamido)-N-(1-(4-((2-(dimethylamino)ethyl)(methyl)amino)but-2-yn-1-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)benzamide trifluoroacetate salt:**

**[00192]** (2*R*,4*S*)-*tert*-Butyl 2-(*tert*-butyl)-4-((4-((1-(4-((2-(dimethylamino)ethyl)(methyl)amino)but-2-yn-1-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)phenyl)carbamoyl)-4-methyloxazolidine-3-carboxylate (15 mg, 23  $\mu\text{mol}$ ) was dissolved in 30% TFA in dichloromethane (1 mL) and stirred at room temperature for 12 h. The reaction mixture was concentrated under reduced pressure, dissolved in water, and washed with diethyl ether (2 X 2 mL). The aqueous layer was basified with  $\text{NaHCO}_3$  to pH 10 and the compound was extracted with dichloromethane (2 X 4 mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure. The residue was stirred in 30% TFA in dichloromethane for 0.5h, and then the solvent was evaporated and triturated with diethyl ether. Filtration afforded the title compound (S)-4-(2-amino-3-hydroxy-2-methylpropanamido)-N-(1-(4-((2-(dimethylamino)ethyl)(methyl)amino)but-2-yn-1-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)benzamide trifluoroacetate salt as an orange colored solid. M.P. 108-110  $^{\circ}\text{C}$ ,  $[\alpha]_D^{20} = -2.8$  ( $c=2.00$ ,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ );  $\delta$  ppm 8.06 (d, 1H), 7.91 (d, 2H), 7.71 (d, 2H), 7.58 (d, 1H), 4.75 (s, 1H), 4.17 (d, 1H), 3.48 – 3.44 (m, 3H), 2.56 (t, 2H), 2.42 (t, 2H), 2.33 (s, 3 H), 2.26 (s, 6H), 1.35 (s, 3H) ppm.  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 175.7, 162.6, 155.5, 146.8, 142.1, 129.1, 127.8, 119.2, 97.2, 84.3, 69.2, 64.2, 59.8, 57.2, 53.6, 46.2, 45.8, 42.2, 39.5, 29.7, 23.7. IR (neat) 2920, 2850, 1733, 1683, 1674, 1653, 1457  $\text{cm}^{-1}$ . HRMS (ESI) Calculated for  $\text{C}_{24}\text{H}_{34}\text{N}_7\text{O}_4\text{Na}$   $m/z$  484.2672 (M+H), Obs'd. 484.2676.

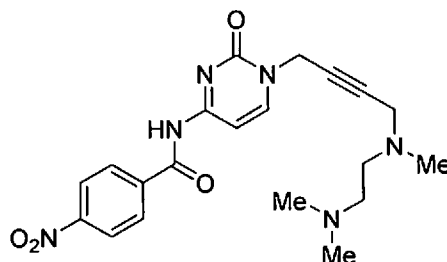
**Example 9**



**4-Amino-1-(4-((2-(dimethylamino)ethyl)(methyl)amino)but-2-yn-1-yl)pyrimidin-2(1H)-one**

[00193] Example 9 was prepared in a similar fashion to Example 5 from 4-amino-1-(prop-2-yn-1-yl)pyrimidin-2(1H)-one, paraformaldehyde and N1,N1,N2-trimethylethane-1,2-diamine to afford the desired product as a brick red solid. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ ppm 7.48 (d, 1H), 5.92 (d, 1H), 4.54 (br s, 2H), 3.34 (br s, 2H), 2.47 (t, 2H), 2.34 (t, 2H), 2.24 (s, 3H), 2.19 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ ppm 166.4, 156.4, 143.3, 95.6, 82.3, 78.4, 57.2, 53.4, 46.3, 45.7, 42.2, 38.4.

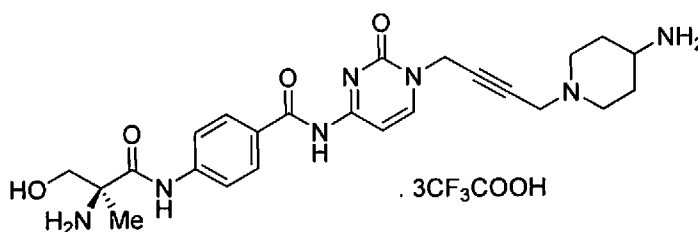
#### Example 10



**N-(1-(4-((2-(Dimethylamino)ethyl)(methyl)amino)but-2-yn-1-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)-4-nitrobenzamide**

[00194] Example 10 was prepared in a similar fashion to Example 5 from 4-nitro-N-(2-oxo-1,2-dihydropyrimidin-4-yl)benzamide, paraformaldehyde and N1,N1,N2-trimethylethane-1,2-diamine to afford the desired product as a brick red solid. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ ppm 8.26 (d, 2H), 8.24 (d, 1H), 8.17 (d, 2H), 8.01 (d, 1H), 4.68 (br s, 2H), 3.41 (br s, 2H), 2.49 (t, 2H), 2.35 (t, 2H), 2.27 (s, 3H), 2.22 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ ppm 167.8, 162.6, 153.9, 150.3, 146.9, 139.4, 130.8, 123.9, 98.5, 84.5, 76.7, 57.3, 53.6, 46.3, 45.8, 42.3, 39.4.

#### Example 11

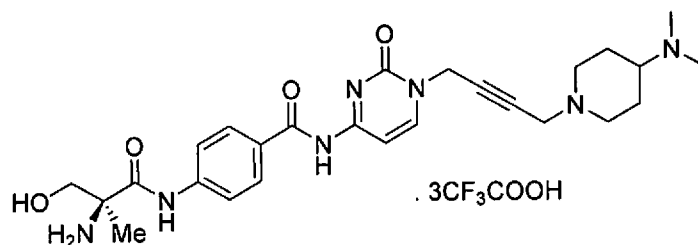


**(S)-4-(2-Amino-3-hydroxy-2-methylpropanamido)-N-(1-(4-(4-aminopiperidin-1-yl)but-2-yn-1-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)benzamide trifluoroacetate salt**

[00195] Example 11 was prepared in a similar fashion to Example 5 from (2*R*,4*S*)-*tert*-butyl-2-(*tert*-butyl)-4-methyl-4-(((4-((2-oxo-1,2-dihydropyrimidin-4-yl) carbamoyl) phenyl)carbamoyl) oxazolidine-3-carboxylate, paraformaldehyde and *tert*-butyl piperidin-4-ylcarbamate to afford the desired product as a yellow solid. <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O) δ ppm

8.34 (d, 1H), 8.00 (d, 2H), 7.72 (d, 2H), 7.33 (d, 1H), 4.90 (s, 2H), 4.19 (d, 1H), 4.17 (s, 2H), 3.95 (d, 1H), 3.82 (d, 2H), 3.64-3.55 (m, 1H), 3.28 (t, 2H), 2.42 (d, 2H), 1.99 (q, 2H), 1.72 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{D}_2\text{O}$ )  $\delta$  ppm 172.0, 169.6, 166.2, 159.8, 152.5, 143.5, 131.8, 131.0, 124.3, 120.3, 101.3, 86.3, 76.4, 66.7, 64.7, 52.7, 47.6, 43.0, 29.5, 25.0, 20.4

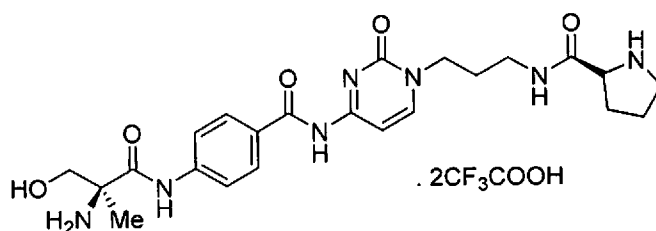
### Example 12



**(S)-4-(2-amino-3-hydroxy-2-methylpropanamido)-N-(1-(4-(4-(dimethylamino)piperidin-1-yl)but-2-yn-1-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)benzamide trifluoroacetate salt**

[00196] Example 12 was prepared in a similar fashion to Example 5 from (2*R*,4*S*)-*tert*-butyl-2-(*tert*-butyl)-4-methyl-4-((4-((2-oxo-1,2-dihydropyrimidin-4-yl) carbamoyl)phenyl)carbamoyl) oxazolidine-3-carboxylate, paraformaldehyde and 4-dimethylamino-piperidine to afford the desired product as a yellow solid.  $^1\text{H}$  NMR (500 MHz,  $\text{D}_2\text{O}$ )  $\delta$  ppm 8.33 (d, 1H), 8.00(d, 2H), 7.72 (d, 2H), 7.37 (d, 1H), 4.91 (s, 2H), 4.19 (d, 1H), 4.18 (s, 2H), 3.97 (d, 1H), 3.89 (d, 2H), 3.63-3.54 (m, 1H), 3.28 (t, 2H), 2.96 (s, 6H), 2.49 (d, 2H), 2.09 (q, 2H), 1.74 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{D}_2\text{O}$ )  $\delta$  ppm 169.4, 168.8, 163.0, 162.7, 150.5, 141.0, 129.3, 121.7, 121.6, 83.6, 64.0, 62.0, 59.5, 50.1, 45.7, 40.5, 39.8, 26.1, 23.8, 22.4, 17.7

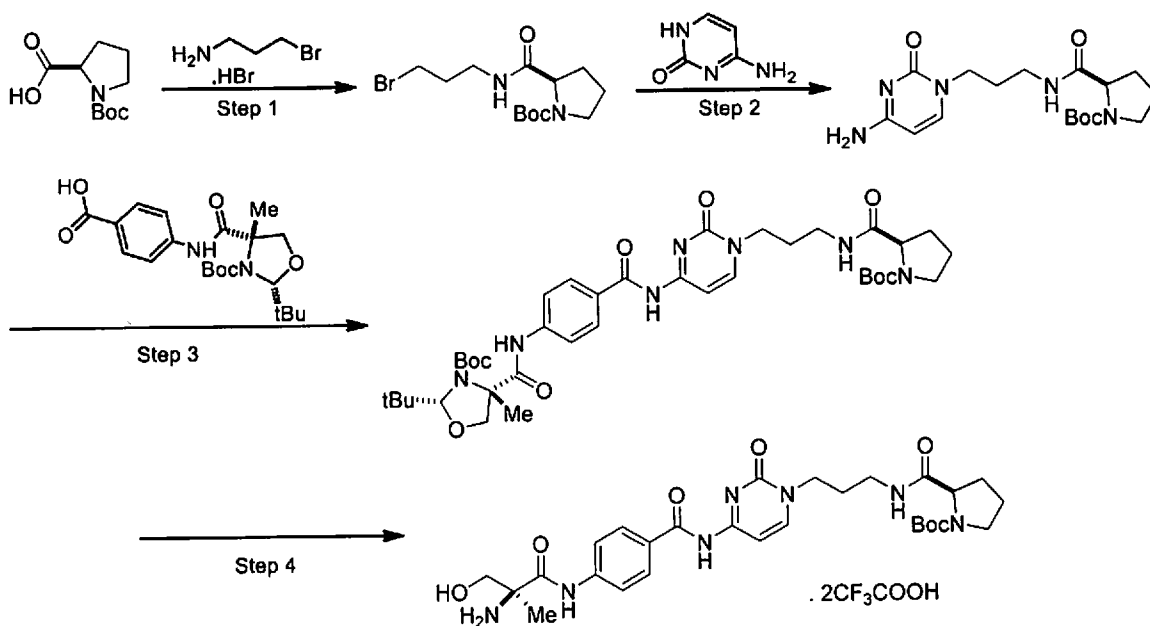
### Example 13



**(R)-N-(3-(4-(4-((S)-2-amino-3-hydroxy-2-methylpropanamido) benz-amido)-2-oxopyrimidin-1(2H)-yl)propyl)pyrrolidine-2-carboxamide trifluoroacetate salt**

[00197] Example 13 was prepared as provided in Synthetic Scheme 4.

## Synthetic Scheme 4



Reagents: Step 1) Ethylchloroformate, *N*-Methylmorpholine, THF:DMF (5:1), -20 °C to rt, 12 h (2) CH<sub>3</sub>CN, Cs<sub>2</sub>CO<sub>3</sub>, reflux, 2h (3) EDC·Cl, HOBT, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, rt, 24h (4) 30% TFA in CH<sub>2</sub>Cl<sub>2</sub>, rt, 12h.

**Step 1: *tert*-Butyl (*R*)-2-((3-bromopropyl)carbamoyl)pyrrolidine-1-carboxylate:**

[00198] Under a nitrogen atmosphere was added ethylchloroformate (0.29 mL, 3.11 mmol) was added to a cold (-20 °C) solution of *N*-Boc L-proline (0.64g, 3.00 mmol) and *N*-Methylmorpholine (0.32 mL, 4.50 mmol) in dry THF (5 mL). After 5 minutes, 3-bromopropylamine hydrobromide dissolved in THF : DMF (1:4 v/v) was added to the above mixture followed by the addition of *N*-methylmorpholine (0.53 mL, 7.8 mmol). After stirring the mixture at -20 °C for 10 minutes, it was warmed to room temperature and stirred for 4 hours. The reaction mixture was diluted with ethyl acetate (25 mL) washed with water followed by brine. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. Purification on silica gel using flash chromatography (30% EtOAc : Hexanes) afforded the desired product as a white solid.

**Step 2: *tert*-butyl (*S*)-2-((3-(4-amino-2-oxopyrimidin-1(2*H*)-yl)propyl)carbamoyl)pyrrolidine-1-carboxylate:**

[00199] To a stirred solution of cytosine (0.22 g, 2.00 mmol) in CH<sub>3</sub>CN (12 mL), Cs<sub>2</sub>CO<sub>3</sub> (0.65 g, 2.00 mmol) and *tert*-butyl (*S*)-2-((3-bromopropyl)carbamoyl)pyrrolidine-1-carboxylate (0.67 g, 2.00 mmol) was added under an atmosphere of nitrogen. The reaction mixture was heated to reflux for 2 h and then was concentrated under reduced pressure.

Purification on silica gel using flash chromatography (10% CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 1% NH<sub>4</sub>OH) afforded the desired product as a white colored solid.

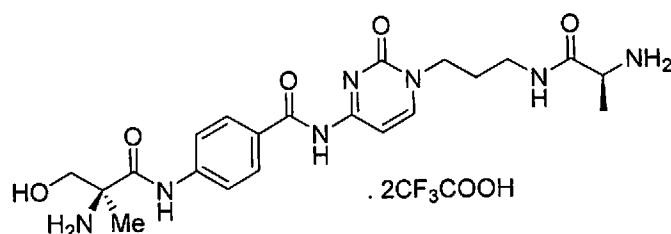
**Step 3: *tert*-Butyl (2*R*,4*S*)-4-((4-((1-(3-((*S*)-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxamido)propyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)phenyl)carbamoyl)-2-(*tert*-butyl)-4-methyloxazolidine-3-carboxylate:**

[00200] To a solution of 4-((2*R*,4*S*)-3-(*tert*-butoxycarbonyl)-2-(*tert*-butyl)-4-methyloxazolidine-4-carboxamido)benzoic acid (102 mg, 0.25 mmol) in dichloromethane (12 mL) was added EDC·Cl (110 mg, 0.5 mmol), HOBt (70 mg, 0.50 mmol), NEt<sub>3</sub> (137 μL, 1.00 mmol) and stirred at rt for 5 min. *Tert*-butyl (*S*)-2-((3-(4-amino-2-oxopyrimidin-1(2*H*)-yl)propyl)carbamoyl)pyrrolidine-1-carboxylate (116 mg, 0.25 mmol) was added to this mixture and stirred for 2 h. The reaction mixture was quenched with saturated NaHCO<sub>3</sub> (3 mL) solution and diluted with 3 mL of dichloromethane. The organic layer was separated and washed with water (2 X 2 mL) followed by a brine wash (1 X 2 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at reduced pressure. The crude product was purified by flash chromatography (5% MeOH/CHCl<sub>3</sub>) to afford desired compound as a white solid.

**Step 4: (*S*)-*N*-(3-(4-(4-((*S*)-2-Amino-3-hydroxy-2-methylpropanamido)benzamido)-2-oxo pyrimidin-1(2*H*)-yl)propyl)pyrrolidine-2-carboxamide trifluoroacetate salt:**

[00201] *tert*-Butyl (2*R*,4*S*)-4-((4-((1-(3-((*S*)-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxamido)propyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)phenyl)carbamoyl)-2-(*tert*-butyl)-4-methyloxazolidine-3-carboxylate (76.0 mg, 0.10 mmol) was dissolved in 30% TFA in dichloromethane (4 mL) and stirred at room temperature for 12 h. The reaction mixture was concentrated under reduced pressure, dissolved in water washed with ether (2 X 2 mL) to remove the organic impurities. The aqueous layer was basified with NaHCO<sub>3</sub> to pH 10 and the compound was extracted with dichloromethane (2 X 4 mL) dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was stirred in 30% TFA in dichloromethane for 0.5h. The solvent was evaporated and triturated with diethyl ether followed by filtration afforded the title compound (*S*)-*N*-(3-(4-(4-((*S*)-2-amino-3-hydroxy-2-methylpropanamido)benzamido)-2-oxo pyrimidin-1(2*H*)-yl)propyl)pyrrolidine-2-carboxamide trifluoroacetate salt (42.0 mg, 53%). <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O) δ 8.12 (d, 1H), 7.98 (d, 2H), 7.70 (d, 2H), 7.46 (d, 1H), 4.38 (t, 1H), 4.18 (d, 1H), 4.01 (t, 2H), 3.95 (d, 2H), 3.50-3.32 (m, 4H), 2.50-2.43 (m, 1H), 2.12-2.02 (m, 5H), 1.72 (s, 3H). <sup>13</sup>C NMR (100 MHz, D<sub>2</sub>O) δ 169.4, 162.9, 157.7, 150.9, 140.8, 129.2, 121.9, 117.8, 110.0, 98.5, 64.1, 62.1, 59.8, 48.5, 46.4, 36.7, 29.6, 27.4, 23.7, 17.8.

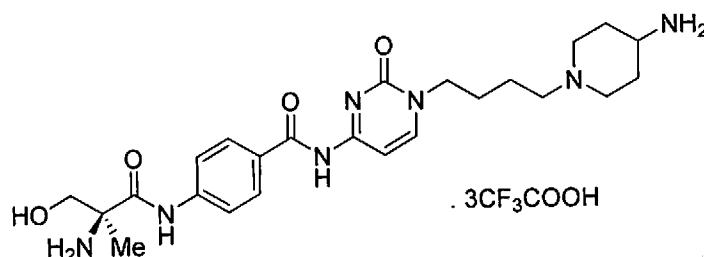
## Example 14



**4-((S)-2-amino-3-hydroxy-2-methylpropanamido)-N-(1-(3-((S)-2-aminopropanamido)propyl)-2-oxo-1,2-dihydropyrimidin-4-yl)benzamide trifluoroacetate salt**

[00202] Example 14 was prepared in a similar fashion to Example 13 from (2*R*,4*S*)-*tert*-butyl-2-(*tert*-butyl)-4-methyl-4-((4-((2-oxo-1,2-dihydropyrimidin-4-yl) carbamoyl) phenyl)carbamoyl) oxazolidine-3-carboxylate, and 4-((2*R*,4*S*)-3-(*tert*-butoxycarbonyl)-2-(*tert*-butyl)-4-methyloxazolidine-4-carboxamido)benzoic acid to afford the desired product as a brown solid. <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O) δ ppm 8.17 (d, 1H), 8.01 (d, 1H), 7.72 (d, 1H), 7.47 (d, 1H), 4.20 (d, 1H), 4.03 (br s, 2H), 3.98 (d, 1H), 3.37 (br s, 2H), 2.76 (br s, 1H), 2.06 (br s, 2H), 1.74 (s, 3H), 1.57 (d, 3H).

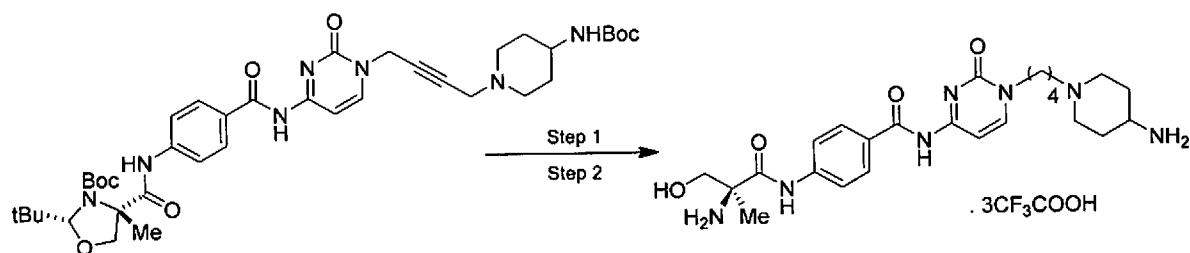
## Example 15



**(S)-4-(2-amino-3-hydroxy-2-methylpropanamido)-N-(1-(4-(4-aminopiperidin-1-yl)butyl)-2-oxo-1,2-dihydropyrimidin-4-yl)benzamide trifluoroacetate salt**

[00203] Example 15 was prepared as provided in Synthetic Scheme 5.

## Synthetic Scheme 5



Reagents: Step 1) 10% Pd/C, H<sub>2</sub>, rt, MeOH, 6h (2) 30% CF<sub>3</sub>COOH in CH<sub>2</sub>Cl<sub>2</sub>, rt, 6h

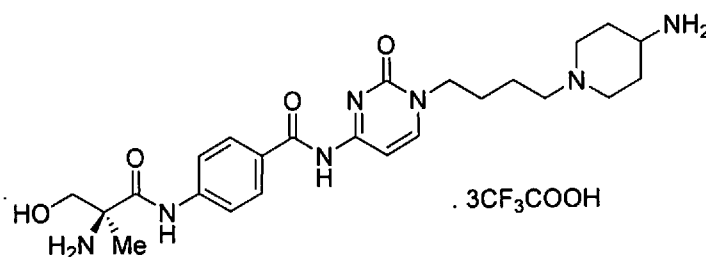
**Step 1: (tert-Butyl (2R,4S)-4-((4-((1-(4-(4-((tert-butoxycarbonyl)amino)piperidin-1-yl)butyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)phenyl)carbamoyl)-2-(tert-butyl)-4-methyloxazolidine-3-carboxylate:**

[00204] 10% Pd/C (13 mg) was added to a solution of *tert*-butyl (2R,4S)-4-((4-((1-(4-(4-((tert-butoxycarbonyl)amino)piperidin-1-yl)but-2-yn-1-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl) phenyl)carbamoyl)-2-(*tert*-butyl)-4-methyloxazolidine-3-carboxylate (68 mg, 92.0  $\mu$ mol) in ethyl acetate (4 mL) and continued to stir for 6 hours under hydrogen atmosphere (1 atm). The reaction mixture was filtered through celite and the solvent was evaporated under reduced pressure. The residue was used in the next step without further purification.

**Step 2: (S)-4-(2-amino-3-hydroxy-2-methylpropanamido)-N-(1-(4-(4-aminopiperidin-1-yl)butyl)-2-oxo-1,2-dihydropyrimidin-4-yl)benzamide hydrochloride salt:**

[00205] *tert*-Butyl (2R,4S)-4-((4-((1-(4-(4-((tert-butoxycarbonyl)amino)piperidin-1-yl)butyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)phenyl) carbamoyl)-2-(*tert*-butyl)-4-methyloxazolidine-3-carboxylate (68 mg, 0.10 mmol) was dissolved in methanolic HCl (4 mL) and stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure and the residue was triturated with diethyl ether followed by filtration afforded the desired compound (30.0 mg, 42%).  $^1\text{H}$  NMR (500 MHz,  $\text{D}_2\text{O}$ )  $\delta$  8.34 (d, 1H), 8.04 (d, 2H), 7.75 (d, 2H), 7.18 (d, 1H), 4.20 (d, 1H), 4.09 (t, 2H), 3.98 (d, 1H), 3.77 (d, 2H), 3.62-3.57 (m, 2H), 3.26 (t, 2H), 3.16 (t, 2H), 2.02-1.95 (m, 2H), 1.93-1.85 (m, 5H), 1.74 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{D}_2\text{O}$ )  $\delta$  163.5, 162.6, 157.7, 157.2, 156.9, 143.9, 135.1, 123.3, 122.6, 115.9, 115.7, 77.5, 68.5, 58.2, 56.2, 44.1, 39.7, 39.3, 34.5, 21.2.

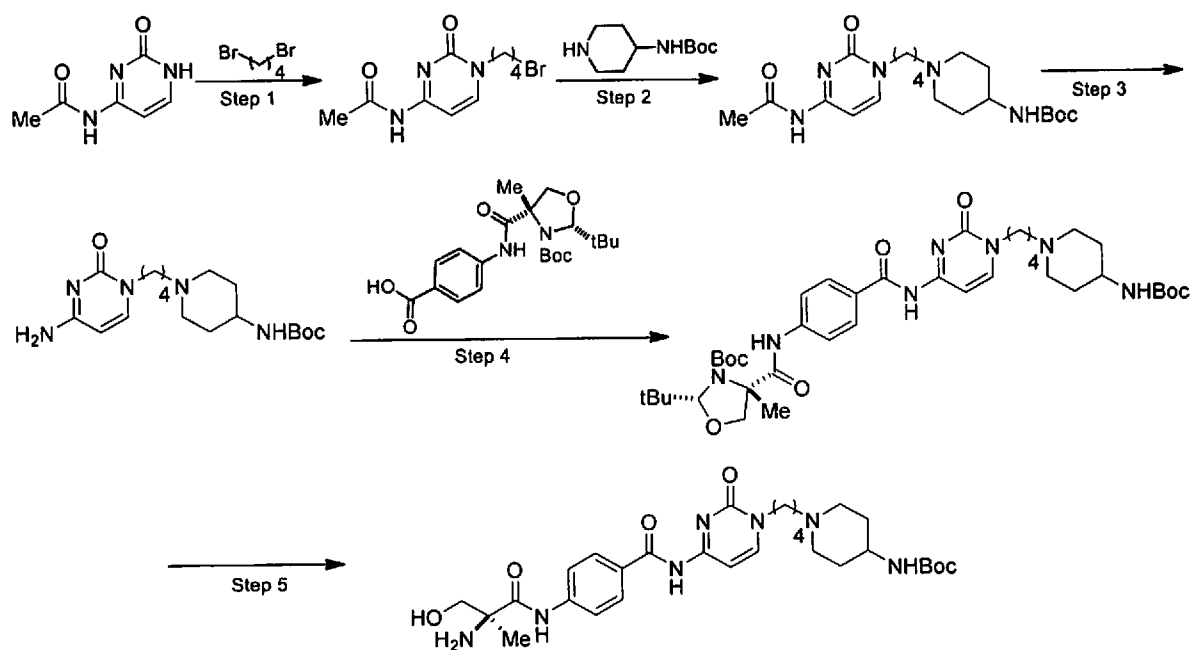
**Example 15a**



**(S)-4-(2-Amino-3-hydroxy-2-methylpropanamido)-N-(1-(4-(4-aminopiperidin-1-yl)butyl)-2-oxo-1,2-dihydropyrimidin-4-yl)benzamide**

[00206] An alternate synthetic procedure for the preparation of Example 15 free amine is provided in Synthetic Scheme 6.

## Synthetic Scheme 6



Reagents: Step 1)  $\text{Cs}_2\text{CO}_3$ ,  $\text{CH}_3\text{CN}$ , reflux, 2h (2)  $\text{K}_2\text{CO}_3$ ,  $\text{CH}_3\text{CN}$ , 70 °C, 2h (3)  $\text{NH}_4\text{OH}$ ,  $\text{MeOH}$ , 12h (4) HATU, DIPEA, DMF, rt, 16h (2) Methanolic HCl, rt, 0.5h

**Step 1: *N*-(1-(4-Bromobutyl)-2-oxo-1,2-dihydropyrimidin-4-yl)acetamide:**

[00207] To a pre-heated (at 50 °C, 15 minutes) suspension of *N*-(2-oxo-1,2-dihydropyrimidin-4-yl)acetamide (0.30g, 2.0 mmol) and  $\text{Cs}_2\text{CO}_3$  (0.79g, 2.4 mmol) in dry  $\text{CH}_3\text{CN}$  (20 mL), 1,4-dibromobutane (518 mg, 2.4 mmol) was added under an atmosphere of nitrogen. After, the reaction mixture was stirred for 0.5h at 50 °C, filtered and the filtrate was concentrated under reduced pressure. Purification on silica gel using flash chromatography afforded the desired product as a pale yellow colored solid.

**Step 2: *tert*-Butyl (1-(4-(4-acetamido-2-oxopyrimidin-1(2H)-yl)butyl)piperidin-4-yl)carbamate:**

[00208] To a stirring suspension of *N*-(1-(4-bromobutyl)-2-oxo-1,2-dihydropyrimidin-4-yl)acetamide (220 mg, 0.77 mmol), and potassium carbonate (211 mg, 1.53 mmol) in acetonitrile (12 mL), 4-Boc amino piperidine (150 mg, 0.75 mmol) dissolved on DMF (1 mL) was added. The reaction mixture was allowed to stir under heating conditions (70 °C) for 2h, then filtered and concentrated under reduced pressure. The compound was used in the next step without further purification.

**Step 3: *tert*-Butyl (1-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)butyl)piperidin-4-yl)carbamate:**

[00209] *Tert*-butyl (1-(4-(4-acetamido-2-oxopyrimidin-1(2H)-yl)butyl)piperidin-4-

yl)carbamate (220 mg, 0.54 mmol) was dissolved in MeOH (10 mL) followed by the addition of ammoniumhydroxide (2 mL). The reaction mixture was allowed to stir at rt for 16h, then the solvent was evaporated. Flash column chromatography afforded the desired compound as a white solid.

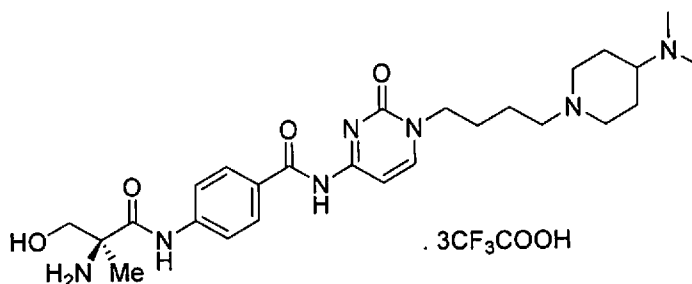
**Step 4: (tert-Butyl (2R,4S)-4-((4-((1-(4-(4-((tert-butoxycarbonyl)amino)piperidin-1-yl)butyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)phenyl)carbamoyl)-2-(tert-butyl)-4-methyloxazolidine-3-carboxylate:**

[00210] To a solution of 4-((2R,4S)-3-(tert-butoxycarbonyl)-2-(tert-butyl)-4-methyloxazolidine-4-carboxamido)benzoic acid (250 mg, 0.61 mmol) in HATU (280 mg, 0.73 mmol), DIPEA (0.12 mL, 0.73 mmol) in DMF (3 mL), tert-butyl (1-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)butyl)piperidin-4-yl)carbamate (224 mg, 0.61 mmol) dissolved in DMF (1 mL) is added. The reaction mixture was allowed to stir for 16 h and quenched with saturated LiCl solution and diluted with 5 mL of distilled water. The solid crashed out was filtered and dried under vacuum to afford the desired compound (300 mg, 65%) as a white solid.

**Step 5: (S)-4-(2-Amino-3-hydroxy-2-methylpropanamido)-N-(1-(4-(4-aminopiperidin-1-yl)butyl)-2-oxo-1,2-dihydropyrimidin-4-yl)benzamide:**

[00211] (tert-Butyl (2R,4S)-4-((4-((1-(4-(4-((tert-butoxycarbonyl)amino)piperidin-1-yl)butyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl) phenyl)carbamoyl)-2-(tert-butyl)-4-methyloxazolidine-3-carboxylate (150 mg, 0.20 mmol) is dissolved in methanolic HCl (10 mL) and allowed stir for 0.5h. The solvent was evaporated and the mixture was neutralized with triethylamine and purified by MPLC to afford the title compound as a yellow solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ ppm 8.07 (d, 1H), 7.97 (d, 2H), 7.82 (d, 2H), 7.32 (d, 1H), 3.97 (br s, 2h), 3.94 (d, 1H), 3.43 (d, 1H), 2.93 (d, 2H), 2.69-2.64 (m, 1H), 2.40 (t, 2H), 2.05 (t, 2H), 1.86-1.75 (m, 4H), 1.60-1.53 (m, 2H), 1.47-1.38 (m, 2H), 1.31 (s, 3H). <sup>13</sup>C NMR (100 MHz, D<sub>2</sub>O) δ ppm 177.5, 168.3, 164.8, 158.8, 151.1, 143.9, 130.3, 129.6, 120.4, 98.5, 79.5, 69.7, 60.6, 58.9, 53.4, 51.6, 49.5, 34.9, 28.0, 24.6, 23.3.

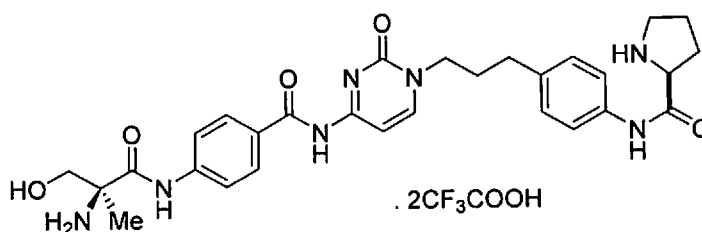
**Example 16**



**(S)-4-(2-Amino-3-hydroxy-2-methylpropanamido)-N-(1-(4-(4-(dimethylamino)piperidin-1-yl)butyl)-2-oxo-1,2-dihydropyrimidin-4-yl)benzamide trifluoroacetate salt**

[00212] Example 16 was prepared in a similar fashion to Scheme 6 from 4-amino-1-(4-(4-(dimethylamino)piperidin-1-yl)butyl)pyrimidin-2(1H)-one and 4-((2R,4S)-3-(tert-butoxycarbonyl)-2-(tert-butyl)-4-methyloxazolidine-4-carboxamido)benzoic acid to afford the desired product as a brown solid. <sup>1</sup>H NMR (500 MHz, D<sub>2</sub>O) δ ppm 8.02 (d, 1H), 7.83 (d, 2H), 7.58 (d, 2H), 7.32 (d, 1H), 4.11 (d, 1H), 3.91-3.86 (m, 3H), 3.74 (d, 2H), 3.57-3.51 (m, 1H), 3.24 (t, 2H), 2.98 (s, 6H), 2.37 (d, 2H), 2.01-1.93 (m, 2H), 1.83-1.75 (m, 5H), 1.64 (s, 3H). <sup>13</sup>C NMR (100 MHz, D<sub>2</sub>O) δ ppm 169.3, 162.9, 162.6, 151.0, 141.1, 129.2, 121.3, 62.0, 59.7, 56.0, 55.2, 50.5, 42.5, 39.8, 36.2, 34.8, 25.1, 24.9, 23.8, 20.6, 17.7.

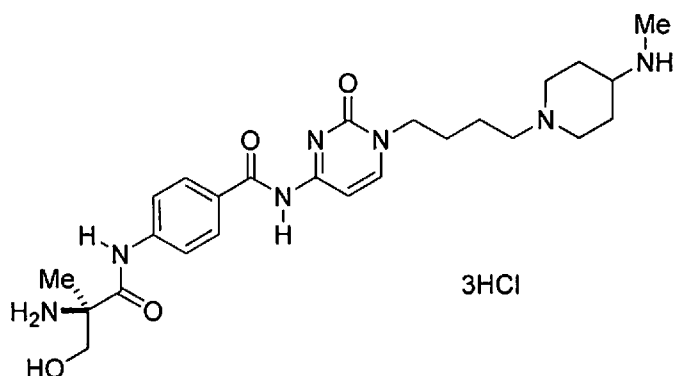
**Example 17**



**(S)-N-(4-(3-(4-(4-((S)-2-Amino-3-hydroxy-2-methylpropanamido)benzamido)-2-oxopyrimidin-1(2H)-yl)propyl)phenyl)pyrrolidine-2-carboxamidebenzamide trifluoroacetate salt**

[00213] Example 17 was prepared in a similar fashion to Scheme 6 from tert-butyl (S)-2-((4-(3-(4-amino-2-oxopyrimidin-1(2H)-yl)propyl)phenyl)carbamoyl)pyrrolidine-1-carboxylate and 4-((2R,4S)-3-(tert-butoxycarbonyl)-2-(tert-butyl)-4-methyloxazolidine-4-carboxamido)benzoic acid to afford the desired product as a brown solid. <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O) δ 7.96 (d, 2H), 7.91 (d, 1H), 7.71 (d, 2H), 7.31 (d, 2H), 7.20 (d, 2H), 7.11 (d, 1H), 4.35 (t, 1H), 4.18 (d, 1H), 4.00 (br s, 2H), 3.96 (d, 1H), 3.39-3.30 (m, 2H), 2.76 (t, 2H), 2.36-2.31 (m, 1H), 2.23-2.17 (m, 2H), 1.98-1.72 (m, 3H), 1.72 (s, 3H).

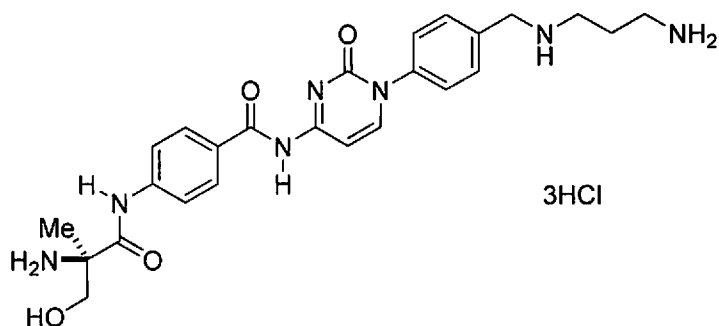
## Example 18



**(S)-4-(2-Amino-3-hydroxy-2-methylpropanamido)-N-(1-(4-(4-(methylamino)piperidin-1-yl)butyl)-2-oxo-1,2-dihydropyrimidin-4-yl)benzamide.**

[00214] Example 18 was prepared in a similar fashion to Scheme 6 from *tert*-butyl (1-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)butyl)piperidin-4-yl)(methyl)carbamate and 4-((2*R*,4*S*)-3-(*tert*-butoxycarbonyl)-2-(*tert*-butyl)-4-methyloxazolidine-4-carboxamido)benzoic acid. <sup>1</sup>H NMR (500 MHz, D<sub>2</sub>O) δ 8.21 (d, 1H), 7.93 (d, 2H), 7.66 (d, 2H), 7.20 (d, 1H), 4.14 (d, 1H), 3.99 (bs, 2H), 3.91 (d, 1H), 3.75 (bs, 2H), 3.48-3.43 (m, 1H), 3.20 (bs, 2H), 3.10 (t, 2H), 2.73 (s, 3H), 2.42 (d, 2H), 1.93-1.86 (m, 2H), 1.82 (bs, 4H), 1.68 (s, 3H). <sup>13</sup>C NMR (125 MHz, D<sub>2</sub>O) δ 170.1, 169.5, 162.1, 155.0, 153.1, 142.0, 130.2, 129.3, 122.4, 98.3, 64.8, 62.8, 56.9, 53.5, 51.3, 51.0, 30.7, 26.3, 25.8, 21.3, 18.5.

## Example 19

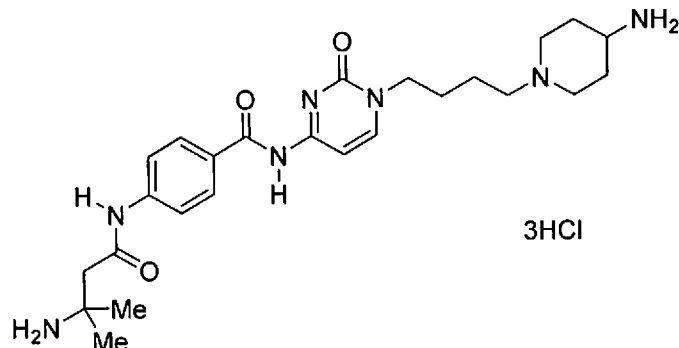


**(S)-4-(2-Amino-3-hydroxy-2-methylpropanamido)-N-(1-(4-(((3-aminopropyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)benzamide.**

[00215] Example 19 was prepared in a similar fashion to Scheme 6 from *tert*-butyl (4-(4-amino-2-oxopyrimidin-1(2H)-yl)benzyl)(3-((*tert*-butoxycarbonyl)amino)propyl)carbamate and 4-((2*R*,4*S*)-3-(*tert*-butoxycarbonyl)-2-(*tert*-butyl)-4-methyloxazolidine-4-carboxamido)benzoic acid. <sup>1</sup>H NMR (500 MHz, D<sub>2</sub>O) δ 8.14 (d, 1H), 7.95 (d, 2H), 7.66 (d, 4H), 7.53 (d, 2H), 7.46 (d, 1H), 4.35 (s, 2H), 4.14 (d, 1H), 3.91 (d, 1H), 3.22 (t, 2H), 3.09 (t,

2H), 2.16-2.08 (m, 2H), 1.67 (s, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{D}_2\text{O}$ )  $\delta$  170.1, 169.4, 164.0, 156.9, 151.7, 141.8, 140.5, 132.7, 132.0, 130.1, 129.6, 127.7, 122.3, 99.0, 64.8, 62.8, 51.2, 44.9, 37.2, 24.4, 18.5.

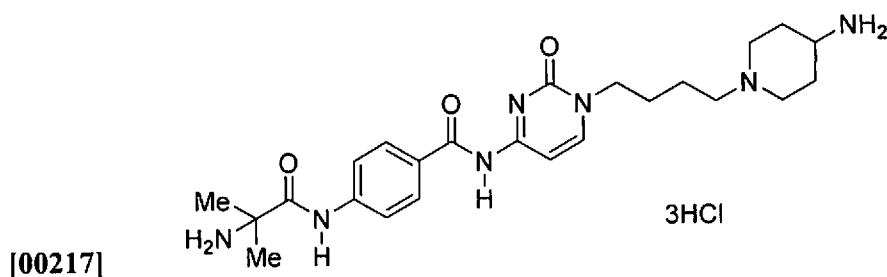
### Example 20



#### 4-(3-Amino-3-methylbutanamido)-N-(1-(4-(4-aminopiperidin-1-yl)butyl)-2-oxo-1,2-dihydropyrimidin-4-yl)benzamide hydrochloride salt

[00216] Example 20 was prepared in a similar fashion to Scheme 6 from tert-butyl (1-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)butyl)piperidin-4-yl)carbamate and 4-(3-((tert-butoxycarbonyl)amino)-3-methylbutanamido)benzoic acid.  $^1\text{H}$  NMR (500 MHz,  $\text{D}_2\text{O}$ )  $\delta$  8.28 (d, 1H), 7.91 (d, 2H), 7.64 (d, 2H), 7.09 (d, 1H), 4.01 (br s, 2H), 3.71 (br s, 2H), 3.59-3.56 (m, 1H), 3.20 (s, 2H), 3.11 (t, 2H), 2.79 (s, 2H), 2.34 (d, 2H), 1.98-1.91 (m, 2H), 1.83 (br s, 4H), 1.45 (s, 6H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{D}_2\text{O}$ )  $\delta$  171.4, 169.4, 161.3, 153.9, 153.0, 142.7, 130.4, 128.1, 121.2, 97.8, 56.9, 53.7, 51.4, 48.4, 46.1, 44.9, 27.8, 25.7, 21.4.

### Example 21

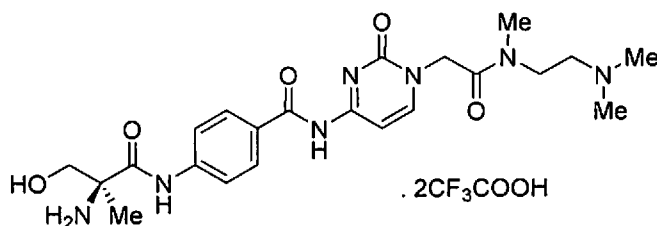


#### 4-(2-Amino-2-methylpropanamido)-N-(1-(4-(4-aminopiperidin-1-yl)butyl)-2-oxo-1,2-dihydropyrimidin-4-yl)benzamide hydrochloride salt

[00218] Example 21 was prepared in a similar fashion to Scheme 6 from tert-butyl (1-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)butyl)piperidin-4-yl)carbamate and 4-(2-((tert-butoxycarbonyl)amino)-2-methylpropanamido)benzoic acid.  $^1\text{H}$  NMR (500 MHz,  $\text{D}_2\text{O}$ )  $\delta$  8.30 (d, 1H), 7.95 (d, 2H), 7.66 (d, 2H), 7.09 (d, 1H), 4.01 (br s, 2H), 3.17 (br s, 2H), 3.58-3.54 (m, 1H), 3.21 (d, 2H), 3.11 (t, 2H), 2.33 (d, 2H), 1.99-1.87 (m, 2H), 1.83 (br s, 4H), 1.73

(s, 6H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{D}_2\text{O}$ )  $\delta$  171.2, 169.6, 161.2, 154.1, 152.8, 142.4, 130.3, 128.8, 122.4, 97.7, 58.4, 56.9, 51.4, 51.1, 46.1, 27.8, 25.7, 23.6, 21.3.

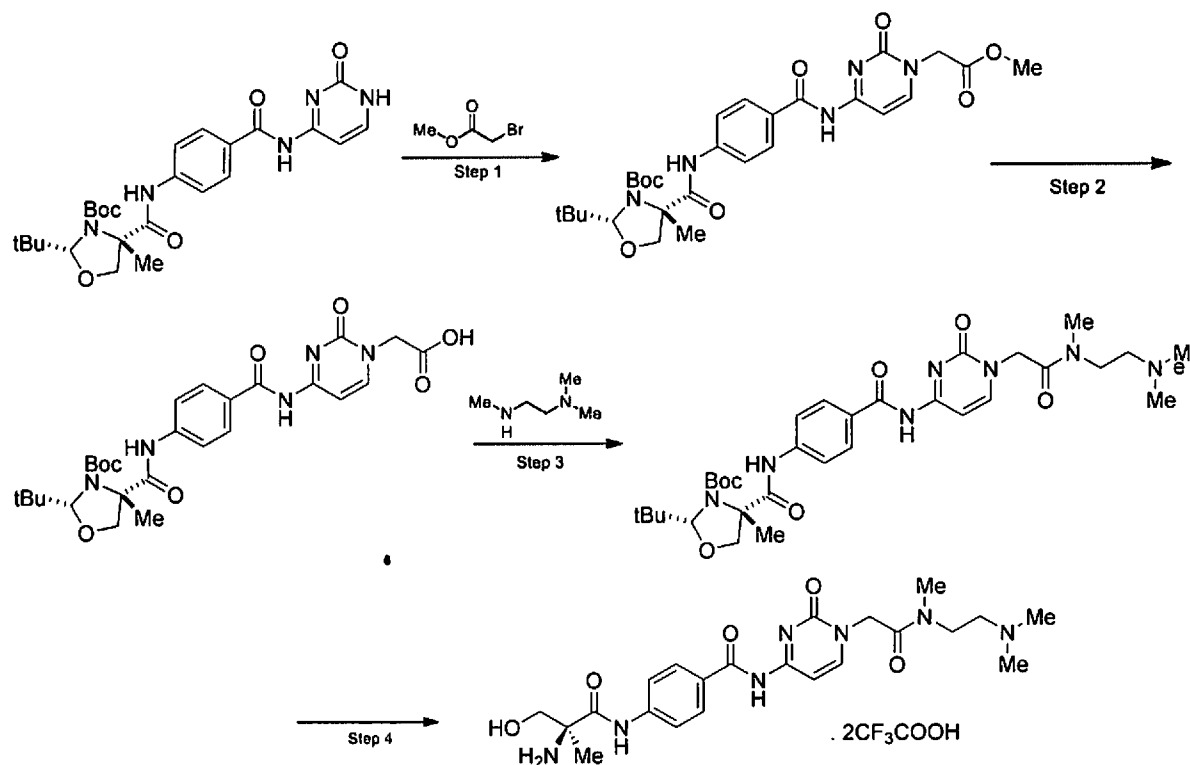
### Example 22



(*S*)-4-(2-Amino-3-hydroxy-2-methylpropanamido)-*N*-(1-(2-((dimethylamino)ethyl)(methyl)amino)-2-oxoethyl)-2-oxo-1,2-dihydropyrimidin-4-yl)benzamide trifluoroacetate salt

[00219] Example 22 was prepared as provided in Synthetic Scheme 7.

### Synthetic Scheme 7



Reagents: Step 1)  $\text{Cs}_2\text{CO}_3$ ,  $\text{CH}_3\text{CN}$ , 50 °C, 0.5h (2)  $\text{LiOH}$ ,  $\text{H}_2\text{O}:\text{THF}$  (1:1), 6h (3)  $\text{EDC}\cdot\text{Cl}$ ,  $\text{HOBT}$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , rt, 24h (4) 30% TFA in  $\text{CH}_2\text{Cl}_2$ , rt, 6h.

**Step 1: *tert*-Butyl (2*R*,4*S*)-2-(*tert*-butyl)-4-((4-((1-(2-methoxy-2-oxoethyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)phenyl)carbamoyl)-4-methyloxazolidine-3-carboxylate:**

[00220] To a pre-heated (at 50 °C, 15 minutes) solution of (2*R*,4*S*)-*tert*-butyl-2-(*tert*-butyl)-

4-methyl-4-((4-((2-oxo-1,2-dihydropyrimidin-4-yl) carbamoyl)phenyl)carbamoyl)oxazolidine-3-carboxylate (80.0 mg, 0.2 mmol) in CH<sub>3</sub>CN (4 mL), Cs<sub>2</sub>CO<sub>3</sub> (70.0 mg, 0.22 mmol), methyl 2-bromoacetate (32.0 mg, 0.20 mmol) was added under an atmosphere of nitrogen. The reaction mixture was stirred for 0.4h at 50 °C, filtered and the filtrate was concentrated under reduced pressure. Purification on silica gel using flash chromatography (1.5% CH<sub>2</sub>Cl<sub>2</sub>/MeOH) afforded the product as a colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 10.4 (br s, 1H), 8.82 (br s, 1H), 7.91 (d, 2H), 7.80 (d, 1H), 7.69 (d, 2H), 7.60 (d, 1H), 5.29 (s, 2H), 5.21 (s, 1H), 4.80 (d, 1H), 3.81 (d, 1H), 3.78 (s, 3H), 1.72 (s, 3H), 1.53 (s, 9H), 0.90 (s, 9H).

**Step 2: 2-(4-(4-((2*R*,4*S*)-3-(*tert*-butoxycarbonyl)-2-(*tert*-butyl)-4-methyloxazolidine-4-carboxamido)benzamido)-2-oxopyrimidin-1(2*H*)-yl)acetic acid:**

[00221] To a solution of *tert*-butyl (2*R*,4*S*)-2-(*tert*-butyl)-4-((4-((1-(2-methoxy-2-oxoethyl)-2-oxo-1,2-dihydropyrimidin-4-yl) carbamoyl)phenyl)carbamoyl)-4-methyloxazolidine-3-carboxylate (70.0 mg, 0.12 mmol) in THF (1 mL) was added a solution of LiOH (25.0 mg, 0.60 mmol) in H<sub>2</sub>O (1 mL). The mixture was stirred at room temperature for 4h, diluted with ethyl acetate and washed with brine. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. Used in the next step without further purification as a white solid.

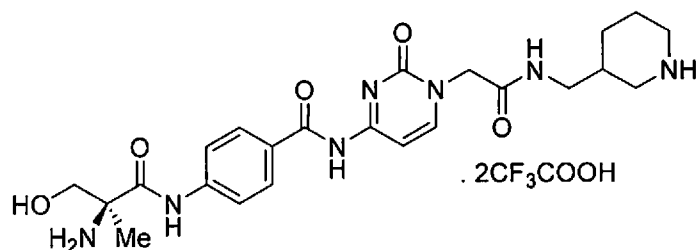
**Step 3: *tert*-Butyl (2*R*,4*S*)-2-(*tert*-butyl)-4-((4-((1-(2-((3-(dimethylamino)propyl)(methyl)amino)-2-oxoethyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)phenyl)carbamoyl)-4-methyloxazolidine-3-carboxylate:**

[00222] *N,N,N'*-Trimethylethylenediamine (1.80 mg, 18.0 μmol) was added to a solution of 2-(4-(4-((2*R*,4*S*)-3-(*tert*-butoxycarbonyl)-2-(*tert*-butyl)-4-methyloxazolidine-4-carboxamido)benzamido)-2-oxopyrimidin-1(2*H*)-yl)acetic acid (10.0 mg, 18.0 μmol), Et<sub>3</sub>N (8 μL, 54.0 μmol), EDCI (4.12 mg, 21.6 μmol), and HOBt (3.00 mg, 21.6 μmol) in dichloromethane (1 mL). The reaction mixture was allowed to stir for 2 h and quenched with saturated NaHCO<sub>3</sub> solution and diluted with 3 mL of dichloromethane. The organic layer was separated and washed with water (2 X 2 mL) followed by a brine wash (1 X 2 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by flash column chromatography (5% MeOH/CHCl<sub>3</sub>, 1% Et<sub>3</sub>N) afforded the desired compound as a yellow solid.

**Step 4: (S)-4-(2-Amino-3-hydroxy-2-methylpropanamido)-*N*-(1-(2-((2-(dimethylamino)ethyl) (methyl)amino)-2-oxoethyl)-2-oxo-1,2-dihydropyrimidin-4-yl)benzamide trifluoroacetate salt:**

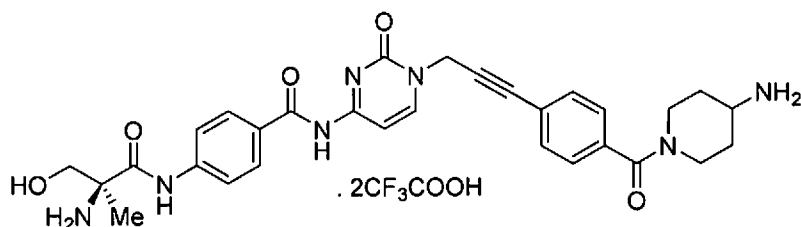
[00223] *tert*-Butyl (2*R*,4*S*)-2-(*tert*-butyl)-4-((4-((1-(2-((3-(dimethylamino)propyl)(methylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)phenyl)carbamoyl)-4-methyloxazolidine-3-carboxylate (5.0 mg, 7.80  $\mu$ mol) was dissolved in 30% TFA in dichloromethane (0.5 mL) and allowed to stir for 6h. The reaction mixture was concentrated under reduced pressure and the residue was triturated with diethyl ether followed by filtration afforded the title compound (*S*)-4-(2-amino-3-hydroxy-2-methylpropanamido)-*N*-(1-(2-((2-(dimethylamino)ethyl) (methylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyrimidin-4-yl)benzamide trifluoroacetate salt (4.0 mg, 80%) as a brown solid.  $^1\text{H}$  NMR (400 MHz,  $\text{D}_2\text{O}$ )  $\delta$  ppm 8.07-8.02 (m, 3H), 7.73 (d, 2H), 7.58 (d, 1H), 5.29 (s, 2H), 5.00 (s, 2H), 4.21 (d, 1H), 3.98 (d, 1H), 3.89 (t, 2H), 3.46 (t, 2H), 3.23 (s, 3H), 2.99 (s, 6H), 1.72 (s, 3H).

### Example 23



(*S*)-4-(2-Amino-3-hydroxy-2-methylpropanamido)-*N*-(2-oxo-1-(2-oxo-2-((piperidin-3-ylmethyl)amino)ethyl)-1,2-dihydropyrimidin-4-yl)benzamide trifluoroacetate salt  
 [00224] Example 23 was prepared in a similar fashion to Example 18 from 2-(4-(4-((2*R*,4*S*)-3-(*tert*-butoxycarbonyl)-2-(*tert*-butyl)-4-methyloxazolidine-4-carboxamido)benzamido)-2-oxopyrimidin-1(2H)-yl)acetic acid and *tert*-butyl 3-(aminomethyl)piperidine-1-carboxylate.  $^1\text{H}$  NMR (400 MHz,  $\text{D}_2\text{O}$ )  $\delta$  ppm 8.06 (d, 1H), 7.96 (d, 2H), 7.68 (d, 2H), 7.47 (d, 1H), 5.61 (s, 2H), 4.19 (d, 1H), 3.96 (d, 1H), 3.61-3.45 (m, 2H), 3.26-3.19 (m, 1H), 3.10-3.00 (m, 2H), 2.93-2.91 (m, 1H), 2.09-2.04 (m, 1H), 1.73 (s, 3H), 1.72-1.66 (m, 1H), 1.57-1.51 (m, 1H), 1.30 (t, 1H), 1.22-1.17 (m, 1H).

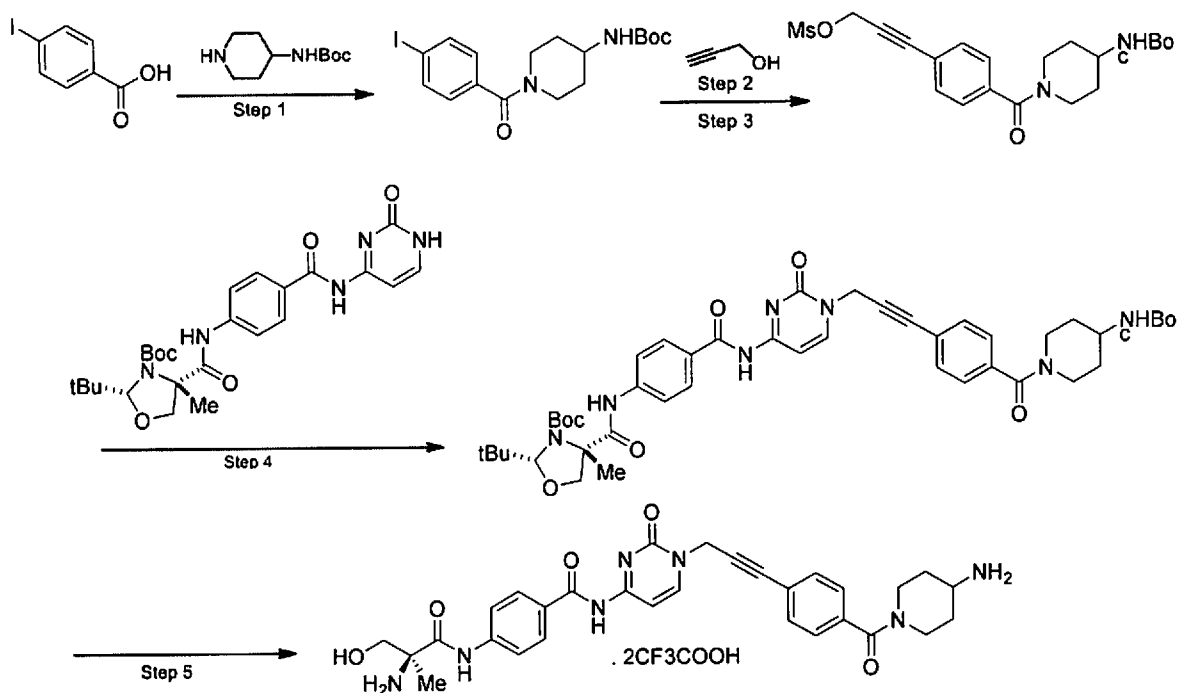
### Example 24



**(S)-4-(2-Amino-3-hydroxy-2-methylpropanamido)-N-(1-(3-(4-(4-aminopiperidine-1-carbonyl)phenyl)prop-2-yn-1-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)benzamide trifluoroacetate salt**

[00225] Example 24 was prepared as provided in Synthetic Scheme 8.

**Synthetic Scheme 8**



Reagents: Step 1)  $\text{CO}_2\text{Cl}_2$ , DMF (cat.),  $\text{CH}_2\text{Cl}_2$ , 0 °C to rt, 2h then  $\text{Et}_3\text{N}$  (2)  $\text{Pd}(\text{PPh})_2\text{Cl}_2$ ,  $\text{CuI}$ ,  $\text{Et}_3\text{N}$ , 70 °C, 3h (3)  $\text{MeSO}_2\text{Cl}$ ,  $\text{Et}_3\text{N}$ , 0 °C to rt, 2 h (4)  $\text{CH}_3\text{CN}$ ,  $\text{Cs}_2\text{CO}_3$ , 50 °C, 20Min (5) 30%  $\text{CF}_3\text{COOH}$  in  $\text{CH}_2\text{Cl}_2$ , rt, 6h

**Step 1: *tert*-Butyl (1-(4-iodobenzoyl)piperidin-4-yl)carbamate:**

[00226] To a cold solution of 4-Iodobenzoic acid (1g, 4.04 mmol) in dichloromethane (20 mL) oxalyl chloride (0.42 mL, 4.85 mmol) followed by the addition of catalytic amount of DMF. The reaction mixture was allowed to stir at room temperature (rt) for 2h, then the resultant acid chloride was added to a solution of 4-Bocamino piperidine (0.5g, 2.50mmol) in dichloromethane (10 mL) at 0 °C and allowed to stir at rt for 2h. The reaction mixture was diluted with dichloromethane and washed with water followed by brine. The organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. Purification by flash column chromatography (30% EtOAc:Hexanes) afforded the desired compound as a white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 7.73 (d, 2H), 7.10 (d, 2H), 4.53 (br s, 2H), 3.67 (br s, 2H), 3.05-2.95 (m, 3H), 1.95 (br s, 2H), 1.42 (s, 9H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 169.6, 155.2, 137.8, 135.5, 128.8, 96.0, 79.8, 77.6, 77.2, 76.9, 48.0, 33.3, 32.3, 28.6.

**Step 2: *tert*-Butyl (1-(4-(3-hydroxyprop-1-yn-1-yl)benzoyl)piperidin-4-yl)carbamate:**

[00227] An oven dried pressure tube was charged with *tert*-butyl (1-(4-iodobenzoyl)piperidin-4-yl)carbamate (760 mg, 1.77 mmol), propargyl alcohol (0.11 mL, 1.77 mmol), CuI (17.0 mg, 0.09 mmol) Pd(PPh<sub>3</sub>)<sub>4</sub>, followed by Et<sub>3</sub>N (15 mL). The reaction mixture was degassed and purged with nitrogen and allowed to stir under heating conditions for 3h. The solvent was evaporated under reduced pressure and purification using flash column chromatography afforded the desired product (510 mg, 82%) as yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO) δ ppm 7.48 (d, 2H), 7.34 (d, 2H), 6.87 (d, 1H), 5.35 (t, 1H), 4.31 (d, 2H), 4.29 (br s, 1H), 3.50 (br s, 2H), 3.10-2.86 (m, 2H), 1.77 (br s, 2H), 1.38 (s, 9H), 1.29 (br s, 2H).

**Step 3: 3-(4-(4-((*tert*-Butoxycarbonyl)amino)piperidine-1-carbonyl)phenyl)prop-2-yn-1-yl methanesulfonate:**

[00228] To a solution of *tert*-butyl (1-(4-(3-hydroxyprop-1-yn-1-yl)benzoyl)piperidin-4-yl)carbamate (72 mg, 0.20 mmol) in dichloromethane (2 mL) at 0 °C methanesulfonyl chloride was added followed by the addition of Et<sub>3</sub>N. The reaction was allowed to stir at rt for 2h. The reaction mixture was diluted with dichloromethane and washed with water followed by brine. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by flash column chromatography (10% EtOAc:Hexanes) afforded the desired compound (66 mg, 76%) as a yellow solid. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ ppm 7.49 (d, 2H), 7.36 (d, 2H), 5.08 (s, 2H), 4.50 (br s, 2H), 3.68 (br s, 2H), 3.15 (s, 3H), 3.14-2.80 (m, 3H), 2.00 (br s, 2H), 1.43 (s, 9H).

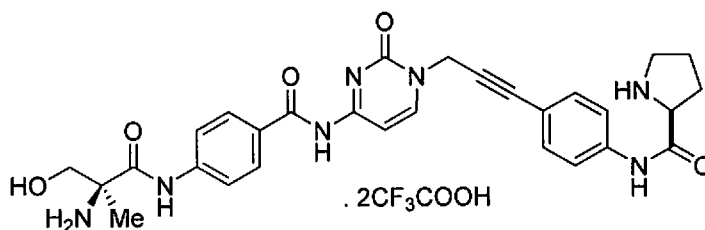
**Step 4: (2*R*,4*S*)-*tert*-Butyl 4-((4-((1-(3-(4-(4-((*tert*-butoxycarbonyl)amino)piperidine-1-carbonyl)phenyl)prop-2-yn-1-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)phenyl)carbamoyl)-2-(*tert*-butyl)-4-methyloxazolidine-3-carboxylate:**

[00229] To a pre heated solution of (2*R*,4*S*)-*tert*-butyl 2-(*tert*-butyl)-4-methyl-4-((4-((2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)phenyl)carbamoyl) oxazolidine-3-carboxylate (29 mg, 58.0 μmol), Cesium carbonate (19 mg, 58.0 μmol) in acetonitrile was added the solution of 3-(4-(4-((*tert*-butoxycarbonyl)amino)piperidine-1-carbonyl)phenyl)prop-2-yn-1-yl methanesulfonate in acetonitrile. The reaction mixture was stirred for 20min. The reaction mixture was filtered and the filtrate was evaporated followed by purification by flash column chromatography afforded the desired compound (38 mg, 66%) as a yellow solid. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ ppm 8.21 (d, 1H), 7.90 (d, 2H), 7.68 (d, 1H), 7.58 (d, 2H), 7.49 (d, 2H), 7.35 (d, 2H), 5.19 (s, 1H), 4.95 (s, 2H), 4.81 (d, 1H), 4.59 (br s, 2H), 3.80 (d, 1H), 3.67 (br s, 2H), 3.10-2.80 (m, 3H), 1.92 (br s, 2H), 1.71 (s, 3H), 1.52 (s, 9H), 1.44 (br s, 2H), 1.42 (br s, 9H), 0.89 (s, 9H).

**Step 5: (S)-4-(2-amino-3-hydroxy-2-methylpropanamido)-N-(1-(3-(4-(4-aminopiperidine-1-carbonyl)phenyl)prop-2-yn-1-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)benzamide trifluoroacetate salt:**

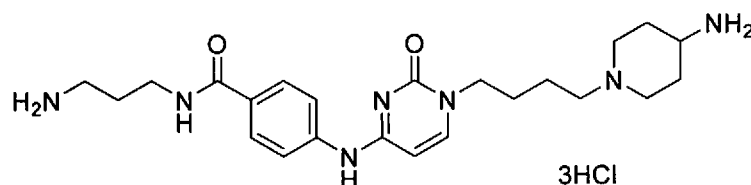
[00230] (2*R*,4*S*)-*tert*-Butyl 4-((4-((1-(3-(4-(4-((*tert*-butoxycarbonyl)amino)piperidine-1-carbonyl)phenyl) prop-2-yn-1-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)phenyl)carbamoyl)-2-(*tert*-butyl)-4-methyloxazolidine-3-carboxylate (30 mg, 32  $\mu$ mol) was dissolved in 30% TFA in dichloromethane (1 mL). The reaction mixture was stirred for 6h at rt. The reaction mixture was concentrated under reduced pressure and the residue was triturated with diethyl ether followed by filtration to afford the title compound (S)-4-(2-amino-3-hydroxy-2-methylpropanamido)-N-(1-(3-(4-(4-aminopiperidine-1-carbonyl)phenyl)prop-2-yn-1-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)benzamide trifluoroacetate salt (15 mg, 88%) as a yellow solid. <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O)  $\delta$ .ppm 8.24 (d, 1H), 7.91 (d, 2H), 7.66 (d, 2H), 7.57 (d, 2H), 7.43-7.38 9m, 3H), 4.91 (s, 2H), 4.17 (d, 1H), 3.95 (d, 1H), 3.78 (br s, 1H), 3.57-3.52 (m, 2H), 3.03-2.94 (m, 2H), 2.22-2.18 (m, 2H), 2.03-1.98 (m, 2H), 1.75 (s, 3H).

**Example 25**



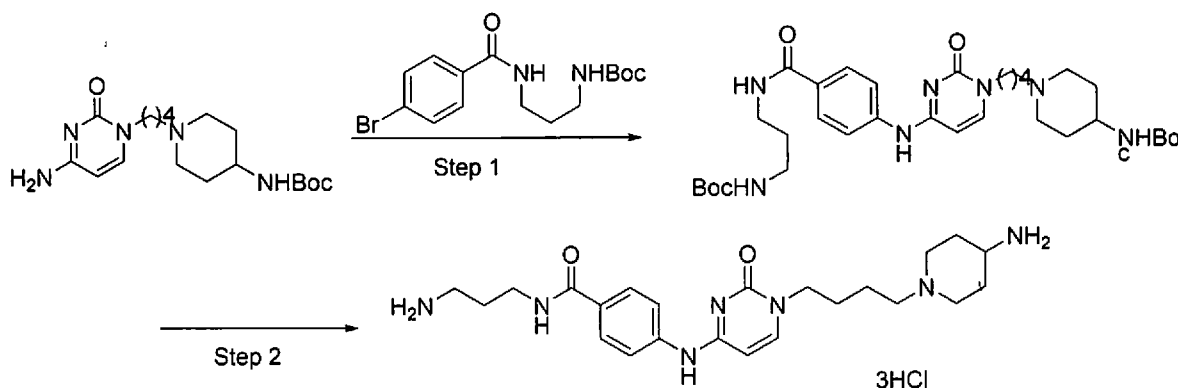
**(S)-N-(4-(3-(4-(4-((S)-2-amino-3-hydroxy-2-methylpropanamido)benzamido)-2-oxopyrimidin-1(2H)-yl)prop-1-yn-1-yl)phenyl)pyrrolidine-2-carboxamide trifluoroacetate salt**

[00231] Example 25 was prepared in a similar fashion to Example 20 from (2*R*,4*S*)-*tert*-butyl 2-(*tert*-butyl)-4-methyl-4-((4-((2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)phenyl)carbamoyl) oxazolidine-3-carboxylate and (S)-*tert*-butyl 2-((4-(3-((methylsulfonyl)oxy)prop-1-yn-1-yl)phenyl)carbamoyl)pyrrolidine-1-carboxylate to afford the desired product as a yellow solid. <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O)  $\delta$ .ppm 8.26 (d, 1H), 7.94 (d, 2H), 7.94 (d, 2H), 7.52-7.45 (m, 5H), 4.92 (s, 2H), 4.51(t, 1H), 4.18 (d, 1H), 3.95 (d, 1H), 3.51-3.44 (m, 2H), 2.54-2.49 (m, 1H), 2.16-2.10 (m, 3H), 1.71 (s, 3H).

**Example 26**

**4-((1-(4-(4-Aminopiperidin-1-yl)butyl)-2-oxo-1,2-dihydropyrimidin-4-yl)amino)-N-(3-aminopropyl)benzamide hydrochloride salt;**

[00232] Example 26 was prepared as provided in Synthetic Scheme 9.

**Synthetic Scheme 9**

Reagents; Step 1) Pd(dba)<sub>2</sub>, Xantphos, Cs<sub>2</sub>CO<sub>3</sub>, dry 1,4-dioxane, 110 °C, 16h (2) Methanolic HCl

**Step 1: *tert*-Butyl (1-(4-(4-((3-((*tert*-butoxycarbonyl)amino)propyl)carbamoyl)phenyl)amino)-2-oxopyrimidin-1(2H)-yl)butyl)piperidin-4-yl)carbamate:**

[00233] An oven dried pressure flask was charged with *tert*-butyl (3-(4-bromobenzamido)propyl) carbamate (1.0 equiv.), *tert*-butyl (1-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)butyl)piperidin-4-yl)carbamate (1.01 equiv.), cesium carbonate (2 equiv.), Pd(dba)<sub>2</sub> (0.1 equiv.), Xantphos (0.2 equiv.) and dry dioxane (12 mL). The reaction mixture was degassed and purged with nitrogen 3 times and stirred at 110 °C for 16h. After which the reaction mixture is diluted with CHCl<sub>3</sub> (25 mL) and filtered through a pad of celite and concentrated under reduced pressure. Purification on silica gel using flash chromatography afforded *tert*-butyl (1-(4-(4-((4-((3-((*tert*-butoxycarbonyl)amino)propyl)carbamoyl)phenyl)amino)-2-oxopyrimidin-1(2H)-yl)butyl) piperidin-4-yl)carbamate as a yellow solid.

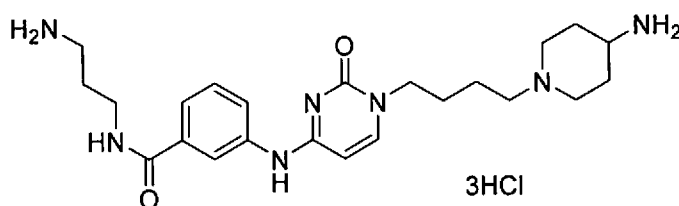
**Step 2: 4-((1-(4-(4-Aminopiperidin-1-yl)butyl)-2-oxo-1,2-dihydropyrimidin-4-yl)amino)-N-(3-aminopropyl)benzamide:**

[00234] *tert*-Butyl (1-(4-(4-((4-((3-((*tert*-butoxycarbonyl)amino)propyl)carbamoyl)phenyl)amino)-2-oxopyrimidin-1(2H)-yl)butyl) piperidin-4-yl)carbamate was dissolved in

methanolic HCl and stirred for 4h. The methanol was evaporated and the resultant solid was triturated with ether and dried under vacuum to yield the desired product as yellow solid.  $^1\text{H}$  NMR (500 MHz,  $\text{D}_2\text{O}$ )  $\delta$  8.00 (d, 1H), 7.95 (d, 2H), 7.60 (d, 2H), 6.35 (d, 1H), 3.99 (br s, 2H), 3.79 (d, 2H), 3.66-3.60 (m, 1H), 3.58 (t, 2H), 3.27 (br s, 2H), 3.21-3.14 (m, 4H), 2.41 (d, 2H), 2.10-1.97 (m, 4H), 1.87 (br s, 4H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{D}_2\text{O}$ )  $\delta$  171.9, 170.0, 158.3, 150.4, 137.0, 133.3, 129.0, 125.0, 94.9, 56.3, 50.8, 49.3, 45.4, 37.1, 36.7, 27.1, 26.7, 25.1, 20.7 ppm.

[00235] Following compounds were prepared in a similar fashion to Example 26.

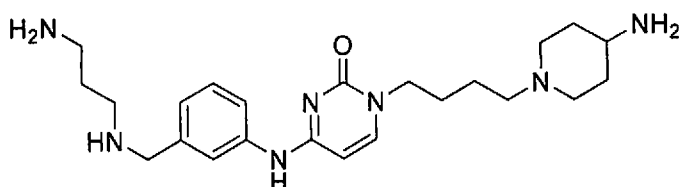
#### Example 27



**3-((1-(4-(4-Aminopiperidin-1-yl)butyl)-2-oxo-1,2-dihydropyrimidin-4-yl)amino)-N-(3-aminopropyl)benzamide hydrochloride salt**

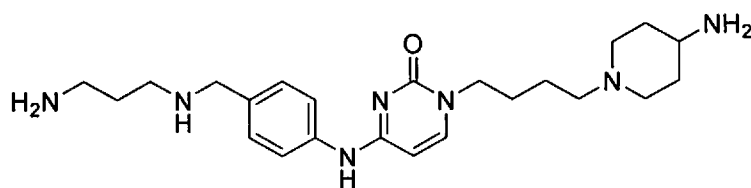
[00236] Example 27 was prepared in a similar fashion to Synthetic Scheme 9 from tert-butyl (3-(3-bromobenzamido)propyl)carbamate and tert-butyl (1-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)butyl)piperidin-4-yl)carbamate to afford the desired product.

#### Example 28



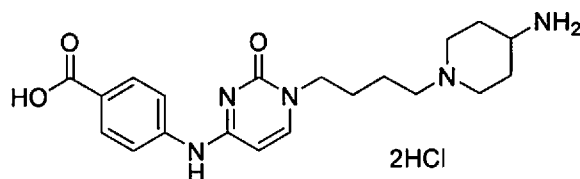
**1-(4-(4-Aminopiperidin-1-yl)butyl)-4-(((3-((3-aminopropyl)amino)methyl)phenyl)amino)pyrimidin-2(1H)-one**

[00237] Example 28 was prepared in a similar fashion to Synthetic Scheme 9 from tert-butyl (3-bromobenzyl)(3-((tert-butoxycarbonyl)amino)propyl)carbamate and tert-butyl (1-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)butyl)piperidin-4-yl)carbamate to afford the desired product.  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  7.89 (s, 1H), 7.69 (d, 1H), 7.29 (br s, 1H), 7.04 (br s, 1H), 6.08 (d, 1H), 3.84 (t, 2H), 3.79 (s, 2H), 3.00-2.87 (m, 4H), 2.78-2.65 (m, 3H), 2.39 (t, 2H), 2.05 (t, 2H), 1.85 (d, 2H), 1.81-1.69 (m, 4H), 1.60-1.50 (m, 2H), 1.49-1.40 (m, 2H) ppm.

**Example 29**

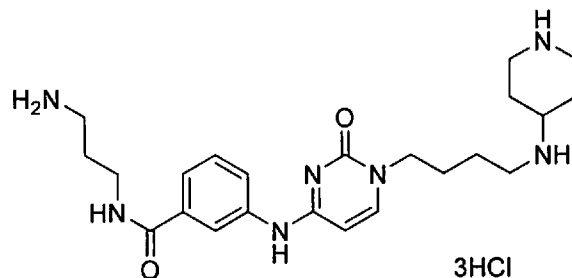
**1-(4-(4-Aminopiperidin-1-yl)butyl)-4-((4-((3-aminopropyl)amino)methyl)phenyl)amino)pyrimidin-2(1H)-one**

[00238] Example 29 was prepared in a similar fashion to Synthetic Scheme 9 from tert-butyl (4-bromobenzyl)(3-((tert-butoxycarbonyl)amino)propyl)carbamate and tert-butyl (1-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)butyl)piperidin-4-yl)carbamate to afford the desired product. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 7.73 (br s, 1H), 7.68 (d, 2H), 7.33 (d, 2H), 6.05 (s, 1H), 3.85 (t, 2H), 3.74 (s, 2H), 2.93 (m, 2H), 2.75 (t, 2H), 2.70-2.63 (m, 3H), 2.40 (t, 2H), 2.05 (t, 2H), 1.83 (d, 2H), 1.77-1.69 (m, 4H), 1.60-1.54 (m, 2H), 1.47-1.38 (m, 2H). <sup>13</sup>C NMR (125 MHz, CD<sub>3</sub>OD) δ 164.6, 159.2, 147.0, 139.5, 136.1, 130.2, 122.3, 97.5, 59.2, 54.1, 53.6, 51.1, 49.6, 47.6, 40.7, 35.3, 32.4, 28.3, 24.8 ppm.

**Example 30**

**4-((1-(4-(4-Aminopiperidin-1-yl)butyl)-2-oxo-1,2-dihydropyrimidin-4-yl)amino)benzoic acid hydrochloride salt**

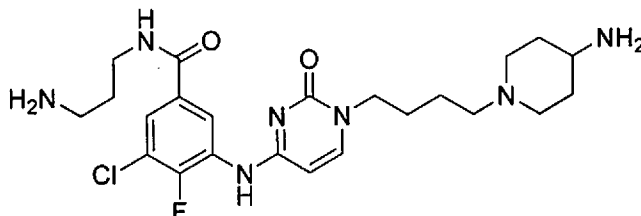
[00239] Example 30 was prepared in a similar fashion to Synthetic Scheme 9 from ethyl 4-bromobenzoate and tert-butyl (1-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)butyl)piperidin-4-yl)carbamate to afford the desired product.

**Example 31**

**N-(3-Aminopropyl)-3-((2-oxo-1-(4-(piperidin-4-ylamino)butyl)-1,2-dihydropyrimidin-4-yl)amino)benzamide hydrochloride salt**

[00240] Example 31 was prepared in a similar fashion to Synthetic Scheme 9 from tert-butyl (3-(3-bromobenzamido)propyl)carbamate and tert-butyl (1-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)butyl)piperidin-4-yl)carbamate to afford the desired product.

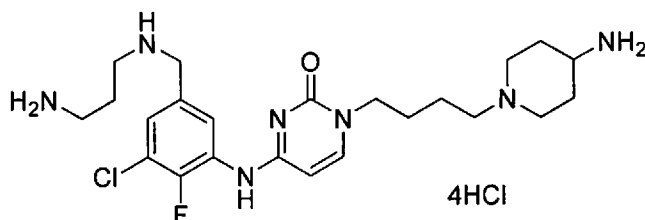
### Example 32



### 3-((1-(4-(4-Aminopiperidin-1-yl)butyl)-2-oxo-1,2-dihydropyrimidin-4-yl)amino)-N-(3-aminopropyl)-5-chloro-4-fluorobenzamide

[00241] Example 32 was prepared in a similar fashion to Synthetic Scheme 9 from tert-butyl (3-(3-chloro-4-fluoro-5-iodobenzamido)propyl)carbamate and tert-butyl (1-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)butyl)piperidin-4-yl)carbamate to afford the desired product. <sup>1</sup>H NMR (500 MHz, D<sub>2</sub>O) δ 8.45 (d, 1H), 7.63 (d, 1H), 7.51 (d, 1H), 6.08 (d, 1H), 3.69 (t, 2H), 3.29 (t, 2H), 2.76 (t, 2H), 2.71 (d, 2H), 2.66-2.59 (m, 1H), 2.17 (t, 2H), 1.88 (t, 4H), 1.71 (d, 2H), 1.55 (d, 2H), 1.38-1.30 (m, 4H). <sup>13</sup>C NMR (125 MHz, D<sub>2</sub>O) δ 167.8, 164.4, 159.0, 153.1 (d), 148.2, 131.8, 129.3 (d), 125.9, 122.9, 122.2 (d), 97.4, 58.8, 53.1, 51.5, 49.4, 39.0, 38.2, 33.6, 30.7, 28.1, 24.6 ppm. LC-MS [M+H] 494.2

### Example 33

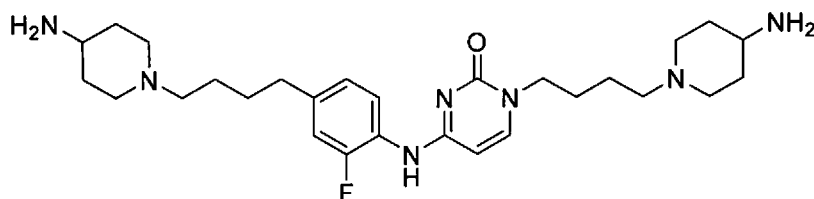


### 1-(4-(4-Aminopiperidin-1-yl)butyl)-4-((5-(((3-aminopropyl)amino)methyl)-3-chloro-2-fluorophenyl)amino)pyrimidin-2(1H)-one

[00242] Example 33 was prepared in a similar fashion to Synthetic Scheme 9 from tert-butyl (3-((tert-butoxycarbonyl)amino)propyl)(3-chloro-4-fluoro-5-iodobenzyl)carbamate and tert-butyl (1-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)butyl)piperidin-4-yl)carbamate to afford the desired product. <sup>1</sup>H NMR (500 MHz, D<sub>2</sub>O) δ 7.95 (d, 1H), 7.76 (br s, 1H), 7.65 (br s, 1H), 6.26 (br s, 1H), 4.29 (s, 2H), 3.91 (br s, 2H), 3.71 (d, 2H), 3.58-3.53 (m, 1H), 3.32-3.17 (m, 4H), 3.09 (t, 4H), 2.34 (d, 2H), 2.15-2.08 (m, 2H), 1.98-1.90 (m, 2H), 1.80 (br s, 4H). <sup>13</sup>C NMR (125 MHz, D<sub>2</sub>O) δ 160.0, 153.1, 149.7, 131.3, 128.0, 127.1, 124.1, 122.6, 122.4, 94.95,

56.2, 50.7, 50.0, 49.4, 46.6, 45.3, 44.2, 36.5, 27.05, 25.03, 23.65, 20.61 ppm. LC-MS [M+H]  
480.3

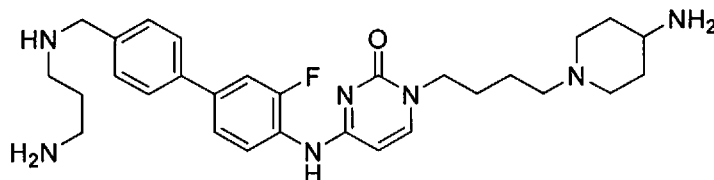
### Example 34



### 1-(4-(4-Aminopiperidin-1-yl)butyl)-4-((4-(4-(4-aminopiperidin-1-yl)butyl)-2-fluorophenyl)amino)pyrimidin-2(1H)-one

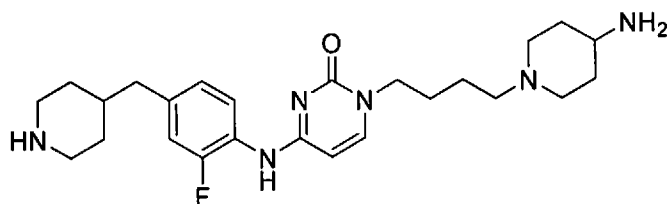
[00243] Example 34 was prepared in a similar fashion to Synthetic Scheme 9 from tert-butyl (1-(4-(4-bromo-3-fluorophenyl)butyl)piperidin-4-yl)carbamate and tert-butyl (1-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)butyl)piperidin-4-yl)carbamate to afford the desired product.<sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 7.91 (br s, 1H), 7.71 (d, 1H), 7.01 (t, 2H), 6.11 (br s, 1H), 3.83 (t, 2H), 2.95 (d, 4H), 2.82 (t, 2H), 2.64 (t, 2H), 2.40 (t, 4H), 2.06 (t, 4H), 1.89 (d, 4H), 1.75-1.68 (m, 4H), 1.66-1.58 (m, 4H), 1.57-1.44 (m, 4H). <sup>13</sup>C NMR (125 MHz, CD<sub>3</sub>OD) δ 165.0, 159.1, 156.5 (d, 1C), 147.5, 142.5, 131.4 (d, 1C), 126.9, 125.2, 124.8, 116.4, 96.9, 59.2, 58.8, 53.03, 49.4, 49.4, 36.0, 33.4, 30.3, 28.1, 27.1, 24.6 ppm.

### Example 35



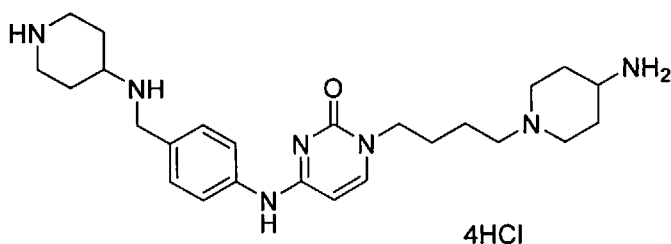
### 1-(4-(4-Aminopiperidin-1-yl)butyl)-4-((4'-(((3-aminopropyl)amino)methyl)-3-fluoro-[1,1'-biphenyl]-4-yl)amino)pyrimidin-2(1H)-one

[00244] Example 35 was prepared in a similar fashion to Synthetic Scheme 9 from tert-butyl (((4'-bromo-3'-fluoro-[1,1'-biphenyl]-4-yl)methyl)(3-((tert-butoxycarbonyl)amino)propyl)carbamate and tert-butyl (1-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)butyl)piperidin-4-yl)carbamate to afford the desired product.<sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 8.19 (br s, 1H), 7.72 (d, 1H), 7.60 (d, 2H), 7.45-7.36 (m, 4H), 6.18 (d, 1H), 3.83 (t, 2H), 3.80 (s, 2H), 2.93 (d, 2H), 2.89 (t, 2H), 2.80 (p, 1H), 2.72 (t, 2H), 2.38 (t, 2H), 2.05 (t, 2H), 1.88 (d, 2H), 1.80 (p, 2H), 1.71 (p, 2H), 1.56-1.45 (m, 4H). <sup>13</sup>C NMR (125 MHz, CD<sub>3</sub>OD) δ 165.0, 159.3, 156.6 (d, *J*<sub>C-F</sub>=247.4 Hz), 147.8, 140.1, 139.6, 130.4, 128.0, 127.0, 126.7 (d, *J*<sub>C-F</sub>=11.4 Hz), 123.6, 114.7 (d, *J*<sub>C-F</sub>=19.9 Hz), 97.2, 59.0, 54.0, 53.2, 51.1, 49.7, 47.6, 40.3, 33.7, 29.7, 28.3, 24.8 ppm. LC-MS [M+H] 522.3.

**Example 36**

**1-(4-(4-Aminopiperidin-1-yl)butyl)-4-((2-fluoro-4-(piperidin-4-ylmethyl)phenyl)amino)pyrimidin-2(1H)-one**

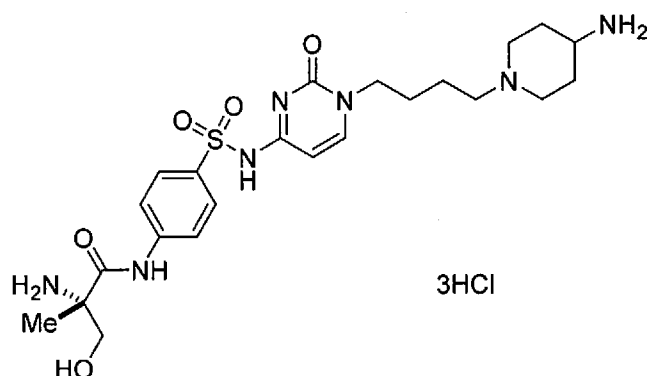
[00245] Example 36 was prepared in a similar fashion to Synthetic Scheme 9 tert-butyl 4-(4-bromo-3-fluorobenzyl)piperidine-1-carboxylate and tert-butyl (1-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)butyl)piperidin-4-yl)carbamate to afford the desired product. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 7.86 (br s, 1H), 7.74 (d, 1H), 7.03-6.97 (m, 2H), 6.15 (br s, 1H), 3.83 (t, 2H), 3.20 (d, 2H), 2.94 (d, 2H), 2.85-2.72 (m, 3H), 2.56 (d, 2H), 2.39 (t, 2H), 2.06 (t, 2H), 1.89 (d, 2H), 1.81-1.68 (m, 5H), 1.59-1.45 (m, 4H), 1.40-1.30 (m, 2H). <sup>13</sup>C NMR (125 MHz, CD<sub>3</sub>OD) δ 163.6, 157.7, 155.2 (d, 1C), 146.2, 138.6, 124.7 (d, 1C), 124.6, 115.9, 115.7, 95.6, 57.5, 51.7, 49.6, 48.1, 44.3, 41.6, 36.1, 32.2, 29.6, 26.8, 23.3 ppm.

**Example 37**

**1-(4-(4-aminopiperidin-1-yl)butyl)-4-(((4-((piperidin-4-ylamino)methyl)phenyl)amino)pyrimidin-2(1H)-one) 4HCl**

[00246] Example 37 was prepared in a similar fashion to Synthetic Scheme 9 from tert-butyl (((4'-bromo-[1,1'-biphenyl]-4-yl)methyl)(3-((tert-butoxycarbonyl)amino)propyl)carbamate and tert-butyl (1-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)butyl)piperidin-4-yl)carbamate to afford the desired product as a yellow solid. <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O) δ 7.83 (br s, 3H), 7.59 (br s, 2H), 6.14 (br s, 1H), 4.30 (s, 2H), 3.93 (t, 2H), 3.71 (t, 3H), 3.58-3.49 (m, 3H), 3.20-3.11 (m, 3H), 2.45 (d, 2H), 2.30-2.20 (m, 4H), 2.07 (t, 4H), 1.97-1.91 (m, 6H) ppm.

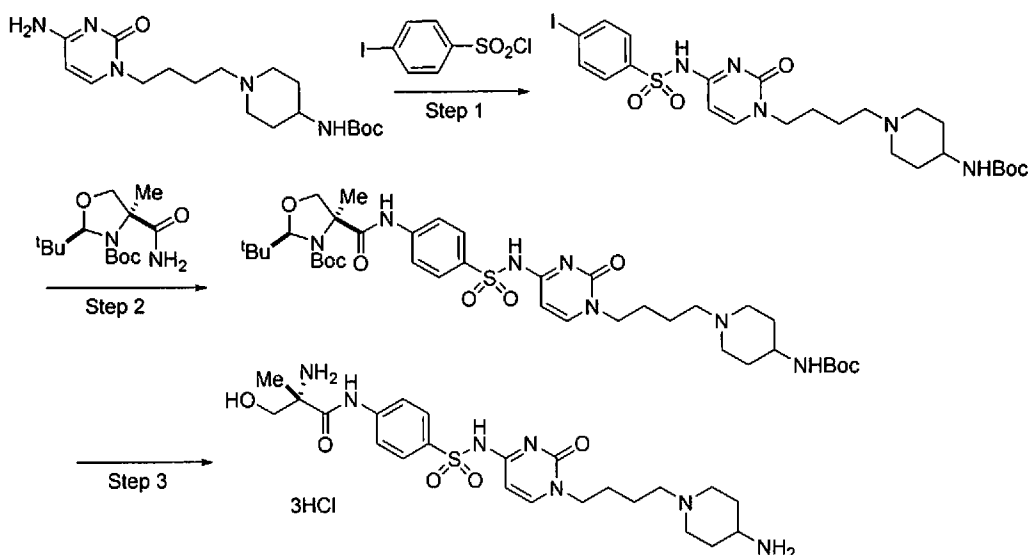
## Example 38



(S)-2-Amino-N-(4-(N-(1-(4-(4-aminopiperidin-1-yl)butyl)-2-oxo-1,2-dihydropyrimidin-4-yl)sulfamoyl)phenyl)-3-hydroxy-2-methylpropanamide hydrochloride salt

[00247] Example 38 was prepared as provided in Synthetic Scheme 10.

## Synthetic Scheme 10



Reagents: Step (1) DMAP, DMF, 70 °C, 2h (2) CuI, K<sub>3</sub>PO<sub>4</sub>, trans-N,N'-Dimethylcyclohexane-1,2-diamine, 1,4-dioxane, 110 °C, 16h (3) Methanolic HCl, 4h.

**Step 1. tert-Butyl (1-(4-(4-((4-iodophenyl)sulfonamido)-2-oxopyrimidin-1(2H)-yl)butyl)piperidin-4-yl)carbamate:**

An oven dried pressure flask was charged with *tert*-butyl (1-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)butyl)piperidin-4-yl)carbamate (1.0 equiv.), 4-iodobenzenesulfonyl chloride (1.02 equiv.), DMAP (1 equiv.), and DMF (1M). The reaction mixture was stirred at 70 °C for 2h. The reaction mixture was cooled to rt and poured in to ice water. The title compound crashed out and then was filtered and dried under vacuum to afford the desired product.

**[00248] Step 2. tert-Butyl (2R,4S)-4-((4-(N-(1-(4-(4-((tert-butoxycarbonyl)amino)piperidin-1-yl)butyl)-2-oxo-1,2-dihydropyrimidin-4-yl)sulfamoyl)phenyl)carbamoyl)-2-(tert-butyl)-4-methyloxazolidine-3-carboxylate:**

**[00249]** An oven dried pressure flask was charged with tert-butyl (1-(4-(4-((4-iodophenyl)sulfonamido)-2-oxopyrimidin-1(2H)-yl)butyl) piperidin-4-yl)carbamate (1.0 equiv.), tert-butyl (2R,4S)-2-(tert-butyl)-4-carbamoyl-4-methyloxazolidine-3-carboxylate (1.2 equiv.), CuI (0.1 equiv.), K<sub>3</sub>PO<sub>4</sub> (2.5 equiv.), *trans*-N,N'-Dimethylcyclohexane-1,2-diamine, and dry 1,4-dioxane (0.2 M). The reaction mixture was degassed and purged with nitrogen (2 times) and then sealed and stirred at 110 °C for 16h. The reaction mixture was cooled to rt and poured into ice water. The title compound crashed out was filtered and dried under vacuum to afford the desired product. **Step 3. (S)-2-Amino-N-(4-(N-(1-(4-(4-aminopiperidin-1-yl)butyl)-2-oxo-1,2-dihydropyrimidin-4-yl)sulfamoyl)phenyl)-3-hydroxy-2-methylpropanamide:**

*tert*-Butyl (2R,4S)-4-((4-(N-(1-(4-(4-((tert-butoxycarbonyl)amino)piperidin-1-yl)butyl)-2-oxo-1,2-dihydropyrimidin-4-yl)sulfamoyl)phenyl)carbamoyl)-2-(tert-butyl)-4-methyloxazolidine-3-carboxylate was dissolved in methanolic HCl and stirred for 4h at rt. The solvent was evaporated and the residue was triturated with diethyl ether to afford the desired product as yellow-colored solid. <sup>1</sup>H NMR (500 MHz, D<sub>2</sub>O) δ 7.92 (d, 2H), 7.74 (d, 1H), 7.69 (d, 2H), 6.46 (d, 1H), 4.14 (d, 1H), 3.91 (d, 1H), 3.84 (d, 2H), 3.69 (d, 2H), 3.55 (t, 1H), 3.16 (d, 2H), 3.09 (t, 2H), 2.33 (d, 2H), 1.93 (q, 2H), 1.74 (br s, 4H), 1.68 (s, 3H). <sup>13</sup>C NMR (125 MHz, D<sub>2</sub>O) δ 169.4, 161.0, 150.5, 148.8, 140.6, 136.5, 127.4, 122.2, 97.1, 64.1, 62.1, 56.1, 50.6, 48.6, 45.3, 27.0, 25.0, 20.5, 17.7 ppm.

### Biological Examples

#### Standard Microbiological Activity:

**[00250]** A certified BSL-2 laboratory was used for testing. Compounds were evaluated using the microdilution minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) assays defined by Clinical and Laboratory Standards Institute (CLSI) in the M26-A guideline against Mtb H37Ra, *M. smegmatus*, *M. bovis* BCG, MRSA, *E. coli*, and *P. aeruginosa*.

**[00251] *E. coli* S30:** Inhibition of bacterial protein synthesis was determined using the *E. coli* S30 Extract System for Circular DNA (Promega catalog #L-2010) and Luciferase Assay Reagent (Promega catalog #E1500) with slight modifications to a published protocol. Fyfe, C., Sutcliffe, J.A. and Grossman, T.H. (2012) "Development and characterization of a

*Pseudomonas aeruginosa* in vitro coupled transcription-translation assay system for evaluation of translation inhibitors” J. Microbiol. Methods 90(3), 256–261.

[00252] Compounds were serially diluted in 0.5 mL microcentrifuge tubes by mixing and transferring 50  $\mu$ L from the highest concentration to 50  $\mu$ L of water, mixing and transferring 50  $\mu$ L of this 2-fold dilution to 50  $\mu$ L of water. This mixing and transferring was repeated so that there are a total of 8 tubes with serial dilutions of compound at 10x the desired screening concentration that are ultimately diluted to 1x by the addition of S30 luciferase synthesis mixture. Serial dilutions of compounds were added (2  $\mu$ L) to wells in a black round bottom 96-well plate. Water (2  $\mu$ L) was used as a “no inhibitor” control in 4 wells/plate. No DNA control reaction mixture (20  $\mu$ L; see below) was used as a control in 4 wells/plate for background luminescence. S30 luciferase synthesis mixture (18  $\mu$ L; see below) was added to wells with compounds or water mixture and incubated at 37 °C for 1 hour. Reactions were stopped by transferring to 4 °C refrigerator for 5 minutes then 25  $\mu$ L of luciferase activity mix was added. Luminescence was measured using a BioTek Synergy HTX plate reader. % Inhibition was determined relative to no inhibitor controls.

S30 luciferase synthesis mixture:  
445  $\mu$ L S30 extract, circular  
712  $\mu$ L S30 Premix without amino acids  
4.45  $\mu$ L pBESTluc<sup>TM</sup> DNA (1  $\mu$ g/  $\mu$ L)  
78  $\mu$ L complete amino acid mixture  
267  $\mu$ L water

No DNA control:  
20  $\mu$ L S30 extract, circular  
32  $\mu$ L S30 Premix without amino acids  
7  $\mu$ L complete amino acid mixture  
21  $\mu$ L water

#### **Rabbit Reticulocyte lysate**

[00253] Inhibition of eukaryotic protein synthesis was determined using the Rabbit Reticulocyte Lysate System, Nuclease-Treated from Promega (catalog #L-4960) with slight modifications to the manufacturer’s protocol. Compounds were serially diluted in 0.5 mL microcentrifuge tubes by mixing and transferring 50  $\mu$ L from the highest concentration to 50  $\mu$ L of water, mixing and transferring 50  $\mu$ L of this 2-fold dilution to 50  $\mu$ L of water. This mixing and transferring was repeated so that there are a total of 8 tubes with serial dilutions of compound at 10x the desired screening concentration that are ultimately diluted to 1x by the addition of rabbit reticulocyte luciferase synthesis mixture. Serial dilutions of compounds were added (2.5  $\mu$ L) to wells in a black round bottom 96-well plate. Water (2.5  $\mu$ L) was used

as a “no inhibitor” control in 4 wells/plate. No RNA control reaction mixture (2  $\mu$ L; see below) was used as a control in 4 wells/plate for background luminescence. Rabbit reticulocyte luciferase synthesis mixture (22.5  $\mu$ L; see below) was added to wells with compounds or water mixture and incubated at 30 °C for 90 minutes. Luciferase assay reagent (25  $\mu$ L) was added with luminescence measured using a BioTek Synergy HTX plate reader.

% Inhibition was determined relative to no inhibitor controls.

Rabbit reticulocyte luciferase synthesis mixture:

1,000  $\mu$ L rabbit reticulocyte lysate  
5.7  $\mu$ L Luciferase Control RNA (1  $\mu$ g/  $\mu$ L)  
26  $\mu$ L complete amino acid mixture  
395  $\mu$ L water

No RNA Control

70  $\mu$ L rabbit reticulocyte lysate  
2  $\mu$ L complete amino acid mixture  
28  $\mu$ L water

#### **Minimum Inhibitory Concentration (MIC)**

[00254] MICs were determined using the Clinical Laboratory and Standards Institute (CLSI) Broth Microdilution Method with slight modification. Clinical and Laboratory Standards Institute (2012). "Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard, 9th ed. M07-A9. Clinical and Laboratory Standards Institute, Wayne, PA." Serial two-fold dilutions of compounds are prepared in sterile clear round-bottom 96-well plates.

[00255] To prepare microdilution trays, two-fold dilutions of antimicrobial agent are prepared by adding 200  $\mu$ L of the highest concentration, prepared in Cation-Adjusted Mueller-Hinton Broth (CAMHB), to be tested (64  $\mu$ g/mL, for example) in row A, mixing and transferring 100  $\mu$ L from row A to 100  $\mu$ L CAMHB in row B, then repeating the mixing and transferring through row H of the 96-well plate, discarding the excess 100  $\mu$ L remaining. This slight modification to the CLSI protocol enables evaluation of MICs for 3 compounds per plate in triplicate, albeit with only 8 compound dilutions (CLSI protocol enables 2 compounds in triplicate with 10 dilutions). Bacterial suspensions are added to a final concentration of  $5 \times 10^4$  CFU/well by adding 5  $\mu$ L of a 1:10 dilution of a 0.5 McFarland suspension ( $1 \times 10^8$  CFU/mL) for each bacterium evaluated. Bacterial suspensions were prepared using the growth method described by CLSI. Well-isolated colonies (3-5 from an agar plate) were selected using a sterile loop and used to inoculate a tube containing 4 mL of tryptic soy broth. The cultures are incubated at  $35 \pm 2^\circ\text{C}$  until it achieves or exceeds the

turbidity of the 0.5 McFarland standard, determined by measuring A<sub>600nm</sub> (usually two to six hours). When growth exceeds a 0.5 McFarland standard, the turbidity is adjusted with broth to be equivalent to a 0.5 McFarland standard.

[00256] Data for compounds is provided in Table 1. An IC<sub>50</sub> value that is 1 μM or greater is designated by a “+”. An IC<sub>50</sub> value that is 0.5 μM or greater and less than 1 μM is designated by a “++”. An IC<sub>50</sub> value that is less than 0.5 μM is designated by “+++”. An MIC value that is 32 μg/mL or greater and less than 128 μg/mL is designated by a “+”. An MIC value that is 8 μg/mL or greater and less than 32 μg/mL is designated by a “++”. An MIC value that is less than 8 μg/mL is designated by “+++”.

Biological Activity of Compounds of Formula I

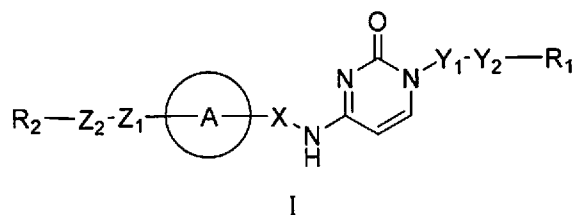
| Compound | MRSA<br>MIC<br>( $\mu\text{g/mL}$ ) | S.<br>aureus<br>MIC<br>( $\mu\text{g/mL}$ ) | E. coli<br>MIC<br>( $\mu\text{g/mL}$ ) | E. coli<br>D22<br>MIC<br>( $\mu\text{g/mL}$ ) | K.<br>pneumo<br>MIC<br>( $\mu\text{g/mL}$ ) | S30<br>IC50<br>( $\mu\text{M}$ ) | retic.<br>IC50<br>( $\mu\text{M}$ ) | Mtb<br>H37Rv<br>IC50<br>( $\mu\text{M}$ ) | M<br>smegmatis<br>MIC<br>( $\mu\text{g/mL}$ ) |
|----------|-------------------------------------|---------------------------------------------|----------------------------------------|-----------------------------------------------|---------------------------------------------|----------------------------------|-------------------------------------|-------------------------------------------|-----------------------------------------------|
| 1        | +                                   | -                                           | +                                      | -                                             | -                                           | -                                | -                                   | -                                         | -                                             |
| 2        | +                                   | -                                           | +                                      | -                                             | -                                           | -                                | -                                   | -                                         | -                                             |
| 3        | +                                   | -                                           | +                                      | -                                             | -                                           | -                                | -                                   | -                                         | -                                             |
| 4        | +                                   | -                                           | +                                      | -                                             | -                                           | -                                | -                                   | -                                         | -                                             |
| 5        | +                                   | -                                           | +                                      | -                                             | -                                           | -                                | -                                   | -                                         | -                                             |
| 6        | +                                   | -                                           | +                                      | -                                             | -                                           | -                                | -                                   | -                                         | +                                             |
| 7        | +                                   | -                                           | +                                      | -                                             | -                                           | -                                | -                                   | -                                         | -                                             |
| 8        | +                                   | -                                           | +                                      | -                                             | -                                           | -                                | -                                   | -                                         | -                                             |
| 9        | +                                   | -                                           | +                                      | -                                             | -                                           | -                                | -                                   | -                                         | -                                             |
| 10       | -                                   | -                                           | -                                      | -                                             | -                                           | -                                | -                                   | -                                         | -                                             |
| 11       | +                                   | -                                           | +                                      | -                                             | -                                           | +                                | +                                   | -                                         | +                                             |
| 12       | -                                   | -                                           | -                                      | -                                             | -                                           | -                                | -                                   | -                                         | -                                             |
| 13       | -                                   | -                                           | -                                      | -                                             | -                                           | -                                | -                                   | -                                         | -                                             |
| 14       | -                                   | -                                           | -                                      | -                                             | -                                           | -                                | -                                   | -                                         | -                                             |
| 15       | +                                   | -                                           | +                                      | -                                             | -                                           | -                                | -                                   | -                                         | -                                             |
| 16       | +                                   | -                                           | +                                      | -                                             | -                                           | -                                | -                                   | -                                         | +++                                           |
| 17       | -                                   | -                                           | -                                      | -                                             | -                                           | +                                | +                                   | -                                         | -                                             |
| 18       | -                                   | -                                           | -                                      | -                                             | -                                           | -                                | -                                   | -                                         | -                                             |
| 19       | -                                   | -                                           | -                                      | -                                             | -                                           | +                                | +                                   | -                                         | -                                             |
| 20       | -                                   | -                                           | -                                      | -                                             | +                                           | +++                              | +                                   | ++                                        | -                                             |
| 21       | +                                   | -                                           | +                                      | -                                             | -                                           | +                                | -                                   | -                                         | +                                             |
| 22       | +                                   | -                                           | +                                      | -                                             | -                                           | +                                | +                                   | +                                         | ++                                            |
| 23       | ++                                  | -                                           | ++                                     | -                                             | -                                           | +                                | +                                   | +                                         | ++                                            |
| 24       | +                                   | -                                           | +++                                    | -                                             | +++                                         | +++                              | ++                                  | +++                                       | +++                                           |
| 25       | +                                   | -                                           | +                                      | -                                             | -                                           | +                                | -                                   | +                                         | +                                             |
| 26       | +                                   | -                                           | +                                      | -                                             | -                                           | +                                | -                                   | -                                         | +                                             |

| Compound | MRSA<br>MIC<br>( $\mu\text{g/mL}$ ) | S.<br>aureus<br>MIC<br>( $\mu\text{g/mL}$ ) | E. coli<br>MIC<br>( $\mu\text{g/mL}$ ) | E. coli<br>D22<br>MIC<br>( $\mu\text{g/mL}$ ) | K.<br>pneumo<br>MIC<br>( $\mu\text{g/mL}$ ) | S30<br>IC50<br>( $\mu\text{M}$ ) | retic.<br>IC50<br>( $\mu\text{M}$ ) | Mtb<br>H37Rv<br>IC50<br>( $\mu\text{M}$ ) | M<br>smegmatis<br>MIC<br>( $\mu\text{g/mL}$ ) |
|----------|-------------------------------------|---------------------------------------------|----------------------------------------|-----------------------------------------------|---------------------------------------------|----------------------------------|-------------------------------------|-------------------------------------------|-----------------------------------------------|
| 27       | +                                   | -                                           | +                                      | -                                             | -                                           | +                                | -                                   | -                                         | +                                             |
| 28       | +                                   | -                                           | +                                      | -                                             | -                                           | +                                | -                                   | +                                         | ++                                            |
| 29       | +                                   | -                                           | +                                      | -                                             | -                                           | +                                | -                                   | +                                         | ++                                            |
| 30       | +                                   | -                                           | +                                      | -                                             | -                                           | +                                | -                                   | -                                         | +                                             |
| 31       | +                                   | -                                           | +                                      | -                                             | +                                           | +                                | -                                   | -                                         | +++                                           |
| 32       | +                                   | -                                           | ++                                     | -                                             | +++                                         | ++                               | ++                                  | -                                         | +++                                           |
| 33       | +                                   | -                                           | +                                      | -                                             | -                                           | +                                | +                                   | -                                         | +                                             |
| 34       | +                                   | -                                           | +                                      | -                                             | -                                           | +                                | +                                   | -                                         | ++                                            |
| 35       | +                                   | -                                           | +                                      | -                                             | -                                           | +++                              | +                                   | -                                         | +                                             |
| 36       | -                                   | +                                           | +                                      | +                                             | +                                           | +                                | +                                   | -                                         | -                                             |
| 37       | -                                   | ++                                          | +                                      | ++                                            | +                                           | +++                              | +                                   | -                                         | -                                             |
| 38       | -                                   | +                                           | +                                      | +                                             | +                                           | +                                | +                                   | -                                         | -                                             |

[00257] The foregoing disclosure has been described in some detail by way of illustration and example, for purposes of clarity and understanding. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications can be made while remaining within the spirit and scope of the invention. It will be obvious to one of skill in the art that changes and modifications can be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

## Claims

1. A compound of formula I:



or a pharmaceutically acceptable salt thereof, wherein:

X is absent or is selected from the group consisting of  $-(C=O)-$  and  $-SO_2-$ ;

A is phenylene optionally substituted with one or two halo;

Y<sub>1</sub> is selected from the group consisting of CH<sub>2</sub> or optionally substituted phenylene;

Y<sub>2</sub> is absent or is selected from the group consisting of optionally substituted C<sub>1</sub>-C<sub>10</sub> alkylene, optionally substituted C<sub>1</sub>-C<sub>10</sub> alkenylene, and optionally substituted C<sub>1</sub>-C<sub>10</sub> alkynylene, wherein up to three carbons of the optionally substituted C<sub>1</sub>-C<sub>10</sub> alkylene, optionally substituted C<sub>1</sub>-C<sub>10</sub> alkenylene, and optionally substituted C<sub>1</sub>-C<sub>10</sub> alkynylene, are independently replaced by optionally substituted phenylene, O, NH, N-(C<sub>1-6</sub> alkyl) (C=O), or NH(C=O);

R<sub>1</sub> is selected from the group consisting of H, halo, NR<sub>1'</sub>R<sub>1''</sub>, and heterocycloalkyl optionally substituted with NH<sub>2</sub> or Me; wherein R<sub>1'</sub> and R<sub>1''</sub> are each independently selected from H and Me;

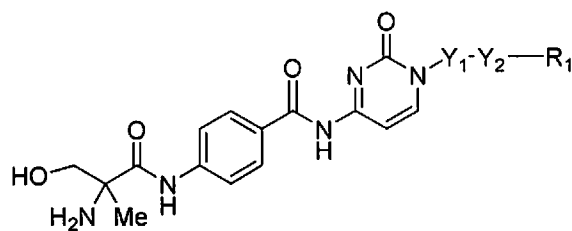
Z<sub>1</sub> is absent or is selected from the group consisting of CH<sub>2</sub>, phenylene,  $-CH_2O-$ ,  $-CH_2NH-$ ,  $-CH_2N(C_{1-6} \text{ alkyl})-$ ,  $-CH_2(C=O)-$ , C=O, and  $-NH(C=O)-$ ;

Z<sub>2</sub> is absent or is selected from the group consisting of optionally substituted C<sub>1</sub>-C<sub>10</sub> alkylene, and optionally substituted heterocycloalkylene; and

R<sub>2</sub> is selected from H, OH, NH<sub>2</sub>, NH(C<sub>1-6</sub> alkyl), N(C<sub>1-6</sub> alkyl)<sub>2</sub>, NH(cycloalkyl), N(cycloalkyl)<sub>2</sub>.

2. The compound of claim 1, wherein X is  $-(C=O)-$ .

3. The compound of claims 1-2, wherein the compound of formula I is a compound of formula IA:



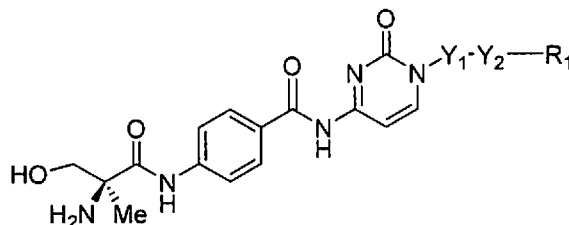
IA

or a pharmaceutically acceptable salt wherein:

$Y_1$  is selected from the group consisting of  $CH_2$  or optionally substituted phenylene;  
 $Y_2$  is absent or is selected from the group consisting of optionally substituted  $C_1$ - $C_{10}$  alkylene, optionally substituted  $C_1$ - $C_{10}$  alkenylene, and optionally substituted  $C_1$ - $C_{10}$  alkynylene, wherein up to three carbons of the optionally substituted  $C_1$ - $C_{10}$  alkylene, optionally substituted  $C_1$ - $C_{10}$  alkenylene, and optionally substituted  $C_1$ - $C_{10}$  alkynylene, are independently replaced by O, NH, N-( $C_{1-6}$  alkyl) (C=O), or NH(C=O);

$R_1$  is selected from the group consisting of H, halo,  $NR_1'R_1''$ , and heterocycloalkyl optionally substituted with  $NH_2$  or Me; wherein  $R_1'$  and  $R_1''$  are each independently selected from H and Me.

4. The compound of claims 1-3, wherein the compound of formula IA is a compound of formula IAi:



IAi

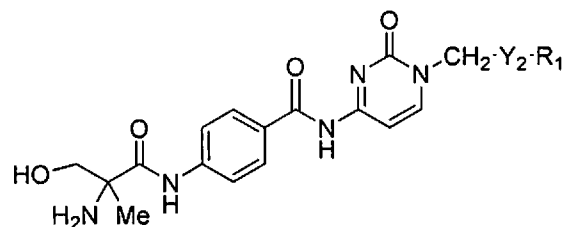
or a pharmaceutically acceptable salt thereof wherein:

$Y_1$  is selected from the group consisting of  $CH_2$  or optionally substituted phenylene;

$Y_2$  is absent or is selected from the group consisting of optionally substituted  $C_1$ - $C_{10}$  alkylene, optionally substituted  $C_1$ - $C_{10}$  alkenylene, and optionally substituted  $C_1$ - $C_{10}$  alkynylene, wherein up to three carbons of the optionally substituted  $C_1$ - $C_{10}$  alkylene, optionally substituted  $C_1$ - $C_{10}$  alkenylene, and optionally substituted  $C_1$ - $C_{10}$  alkynylene, are independently replaced by O, NH, N-( $C_{1-6}$  alkyl) (C=O), or NH(C=O); and

$R_1$  is selected from the group consisting of H, halo,  $NR_1'R_1''$ , and heterocycloalkyl optionally substituted with  $NH_2$  or Me; wherein  $R_1'$  and  $R_1''$  are each independently selected from H and Me.

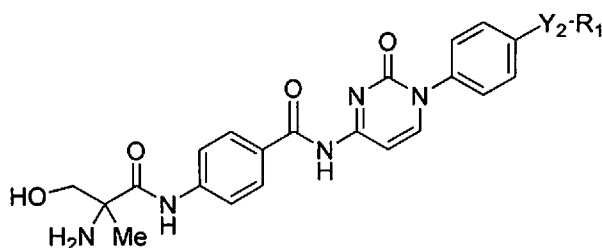
5. The compound of claims 1-4, which is a compound of formula IA-1:



IA-1

or a pharmaceutically acceptable salt thereof.

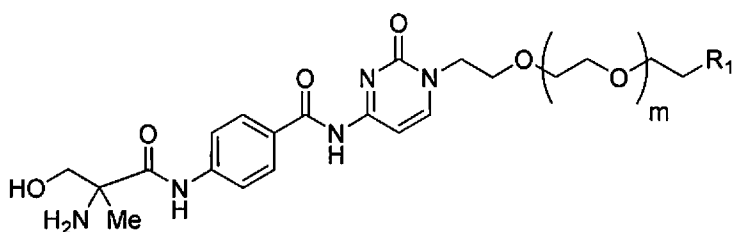
6. The compound of claims 1-4 which is a compound of formula IA-2:



IA-2

or a pharmaceutically acceptable salt thereof.

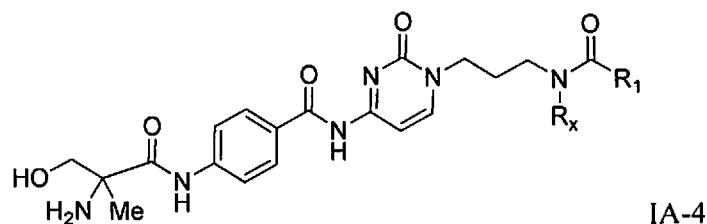
7. The compound of claims 1-4 which is a compound of formula IA-3:



IA-3;

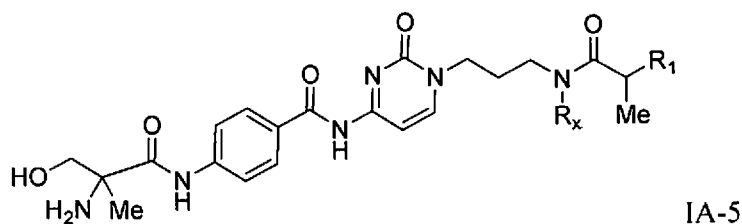
or a pharmaceutically acceptable salt thereof, wherein  $m$  is 0, 1, or 2; and  $R_1$  is selected from the group consisting of  $NR_1'R_1''$ , and heterocycloalkyl optionally substituted with  $NH_2$  or Me; wherein  $R_1'$  and  $R_1''$  are each independently selected from H and Me.

8. The compound of claims 1-4 which is a compound of formula IA-4:



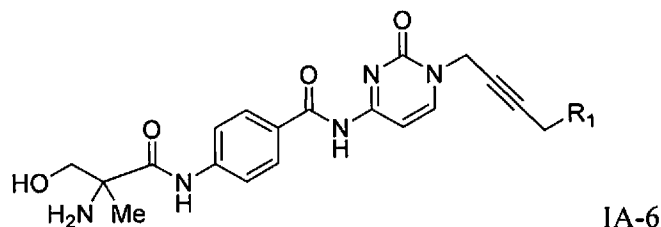
or a pharmaceutically acceptable salt thereof, wherein  $R_x$  is H or methyl; and  $R_1$  is heterocycloalkyl.

9. The compound of claims 1-4 which is a compound of formula IA-5:



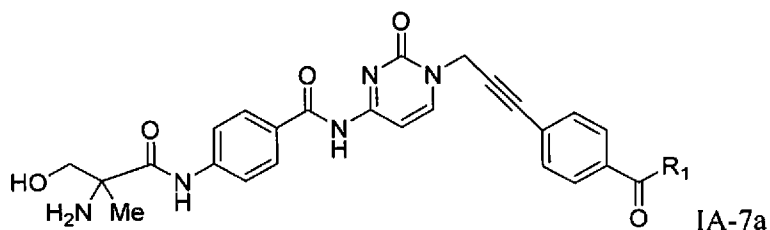
or a pharmaceutically acceptable salt thereof, wherein  $R_x$  is H or methyl; and  $R_1$  is selected from the group consisting of H, halo,  $NR_1'R_1''$ , and heterocycloalkyl optionally substituted with  $NH_2$  or Me; wherein  $R_1'$  and  $R_1''$  are each independently selected from H and Me.

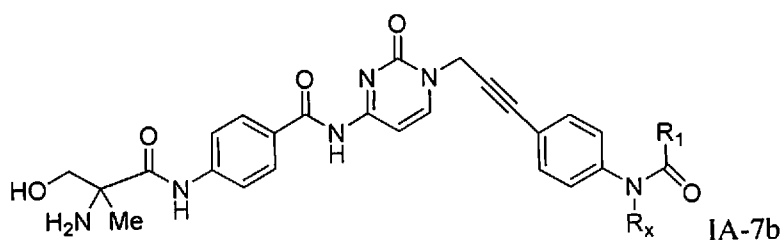
10. The compound of claims 1-4 which is a compound of formula IA-6:



or a pharmaceutically acceptable salt thereof, wherein  $R_1$  is selected from the group consisting of H, halo,  $NR_1'R_1''$ , and heterocycloalkyl optionally substituted with  $NH_2$  or Me; wherein  $R_1'$  and  $R_1''$  are each independently selected from H and Me.

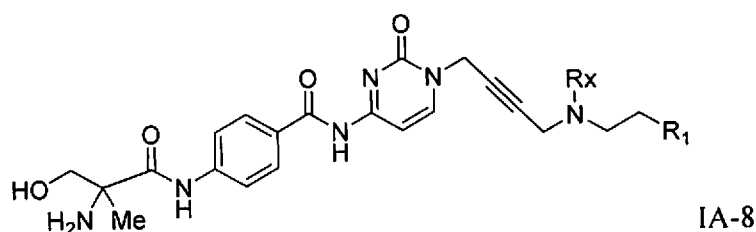
11. The compound of claims 1-4 which is a compound of formula IA-7a or IA-7b:





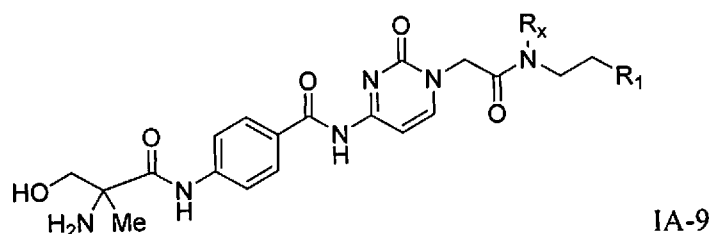
or a pharmaceutically acceptable salt thereof, wherein  $R_1$  is heterocycloalkyl optionally substituted with  $NH_2$  or Me.

12. The compound of claims 1-4 which is a compound of formula IA-8:



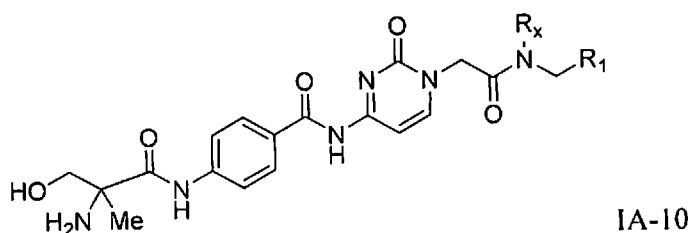
or a pharmaceutically acceptable salt thereof, wherein  $R_x$  is H or methyl and  $R_1$  is selected from the group consisting of H,  $NR_1'R_1''$ , and heterocycloalkyl optionally substituted with  $NH_2$  or Me; wherein  $R_1'$  and  $R_1''$  are each independently selected from H and Me.

13. The compound of claims 1-4 which is a compound of formula IA-9:



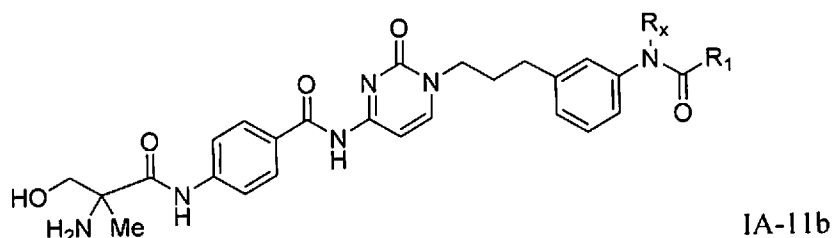
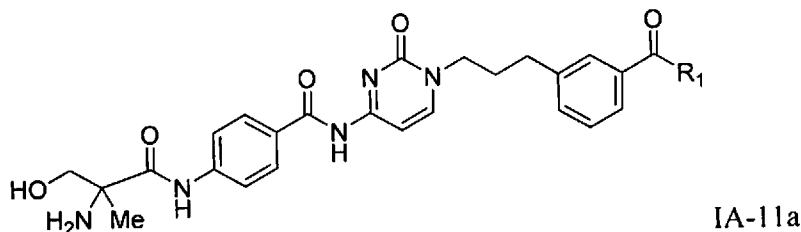
or a pharmaceutically acceptable salt thereof, wherein  $R_x$  is H or methyl and  $R_1$  is selected from the group consisting of H,  $NR_1'R_1''$ , and heterocycloalkyl optionally substituted with  $NH_2$  or Me; wherein  $R_1'$  and  $R_1''$  are each independently selected from H and Me.

14. The compound of claims 1-4 which is a compound of formula IA-10:



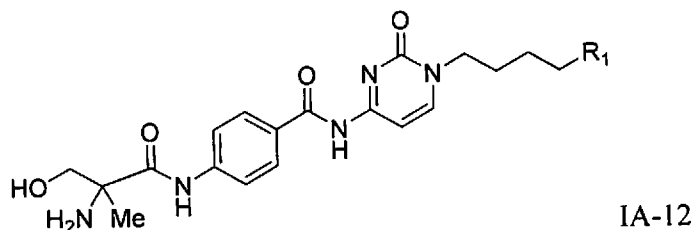
or a pharmaceutically acceptable salt thereof, wherein  $R_x$  is H or methyl and  $R_1$  is selected from the group consisting of H,  $NR_1'R_1''$ , and heterocycloalkyl optionally substituted with  $NH_2$  or Me; wherein  $R_1'$  and  $R_1''$  are each independently selected from H and Me.

15. The compound of claims 1-4 which is a compound of formula IA-11a or IA-11b:



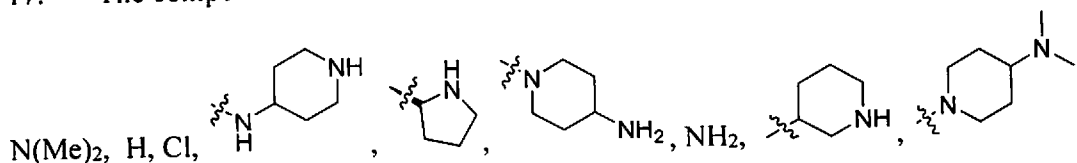
or a pharmaceutically acceptable salt thereof, wherein  $R_x$  is H or methyl and  $R_1$  is selected from the group consisting of  $NR_1'R_1''$ , and heterocycloalkyl optionally substituted with  $NH_2$  or Me; wherein  $R_1'$  and  $R_1''$  are each independently selected from H and Me.

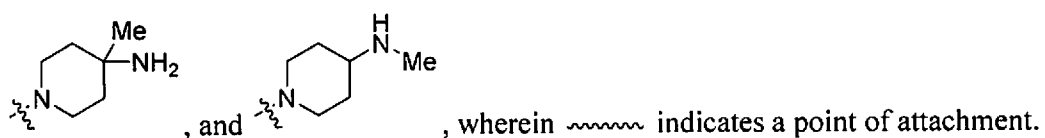
16. The compound of claims 1-4 which is a compound of formula IA-12:



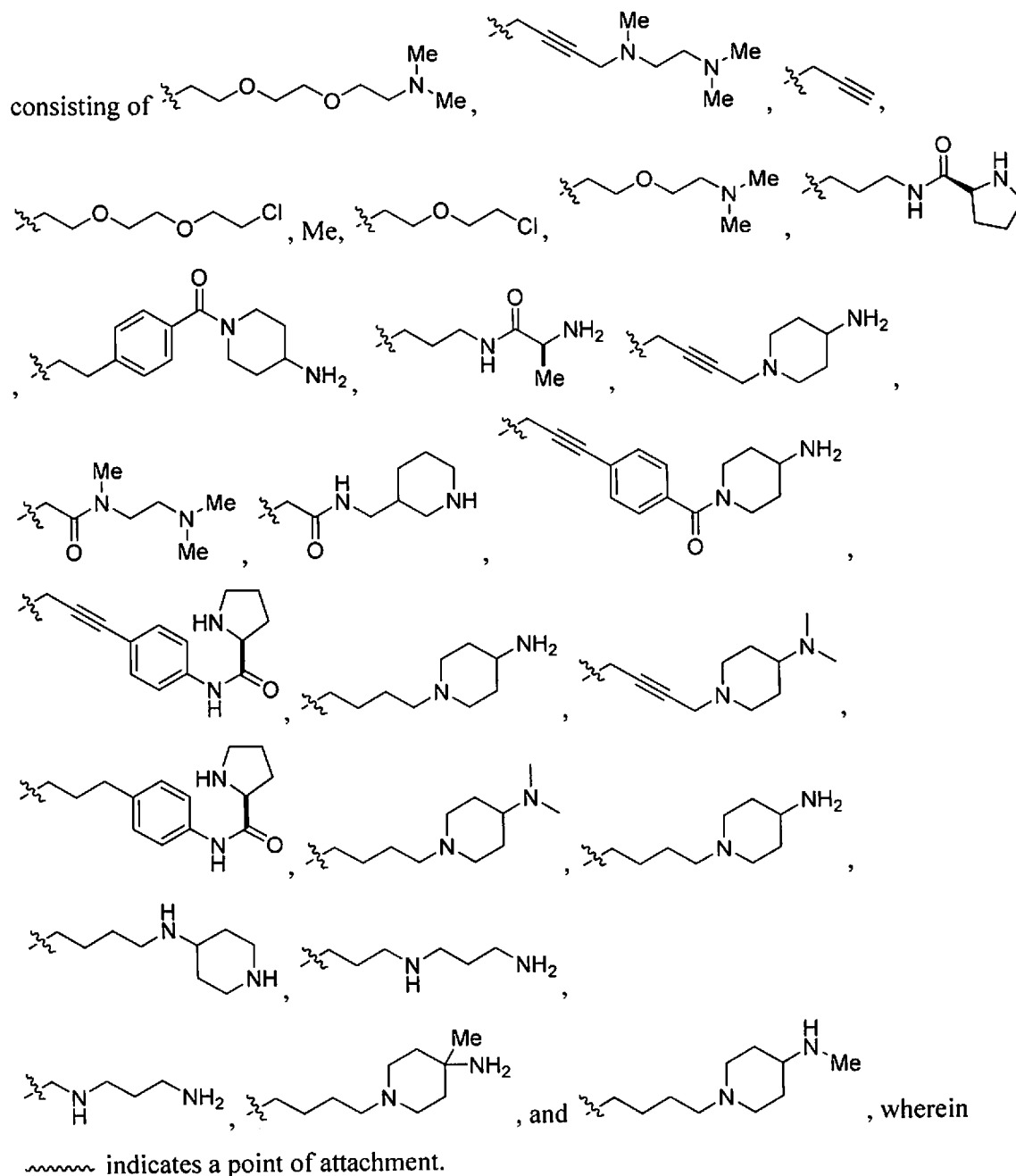
or a pharmaceutically acceptable salt thereof, wherein  $R_1$  is selected from the group consisting of H, halo,  $NR_1'R_1''$ , and heterocycloalkyl optionally substituted with  $NH_2$  or Me; wherein  $R_1'$  and  $R_1''$  are each independently selected from H and Me.

17. The compounds of claims 1-16 wherein  $R_1$  is selected from the group consisting of

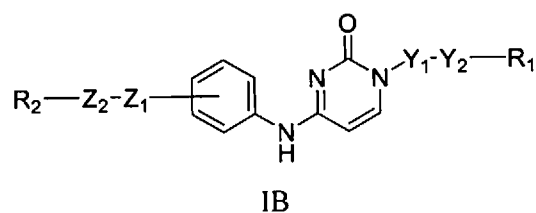




18. The compounds of claims 1-17, wherein  $Y_1$ - $Y_2$ - $R_1$  is selected from the group

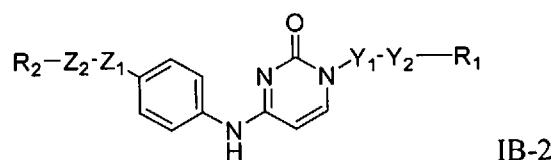
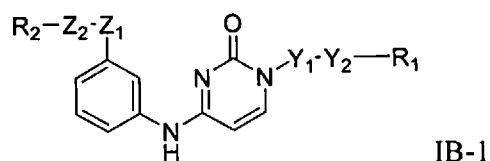


19. The compound of claim 1, which is a compound of formula IB:



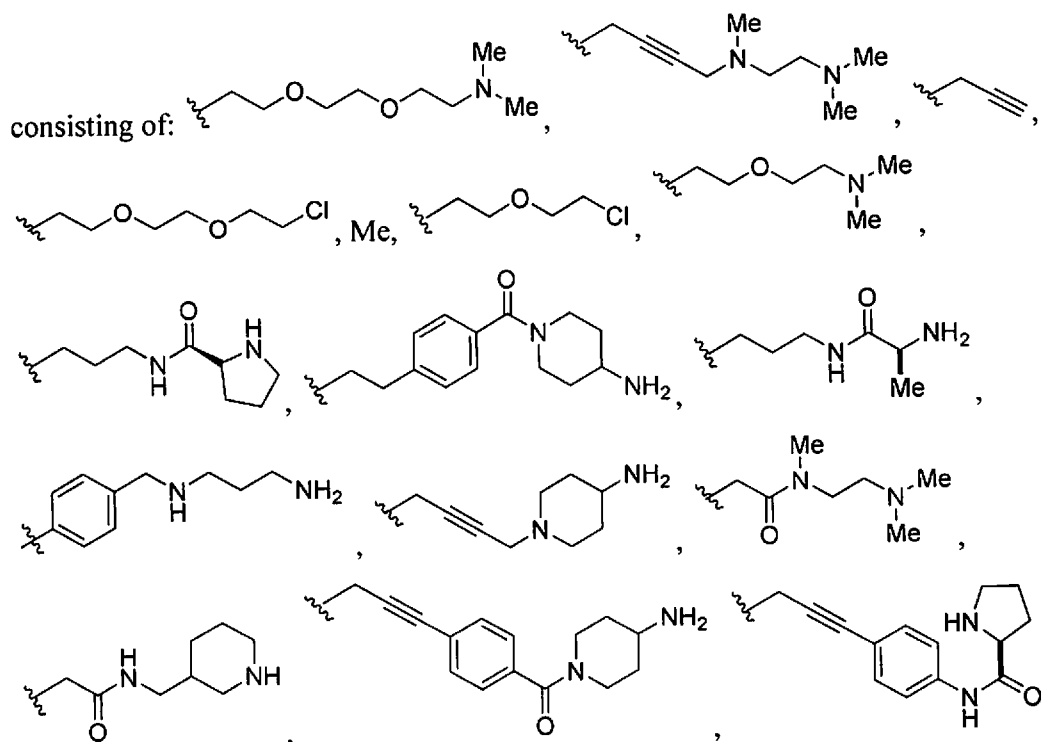
or a pharmaceutically acceptable salt thereof, wherein  is optionally substituted with one or two halo selected from the group consisting of F and Cl.

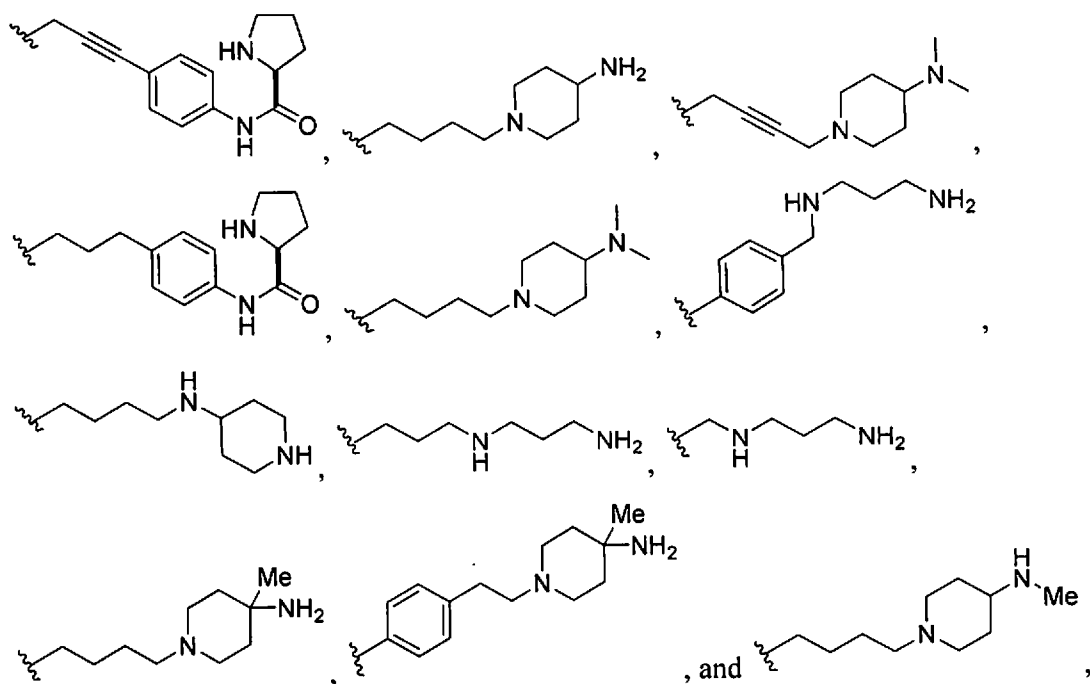
20. The compound of claim 19, which is a compound of formula IB-1 or IB-2:



or pharmaceutically acceptable salts thereof.

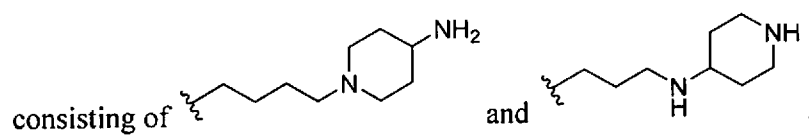
21. The compound of claims 19-20, wherein R<sub>1</sub>-Y<sub>2</sub>-Y<sub>1</sub> is selected from the group



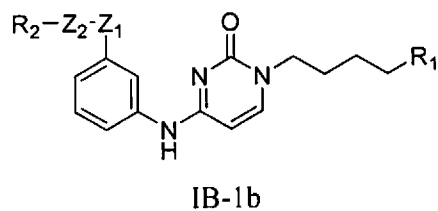
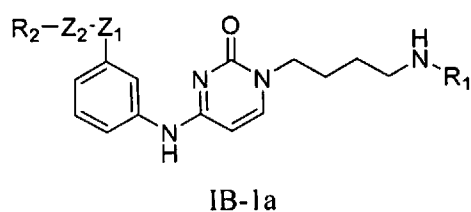


wherein indicates a point of attachment.

22. The compound of claims 21, wherein  $R_1$ - $Y_2$ - $Y_1$  is selected from the group

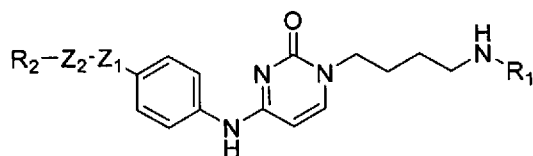


23. The compound of claims 19-20, which is a compound of formula IB-1a or IB-1b:

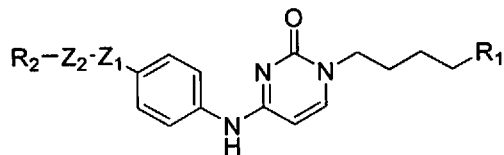


or a pharmaceutically acceptable salt thereof.

24. The compound of claims 19-20, which is a compound of formula IB-2a, or IB-2b:



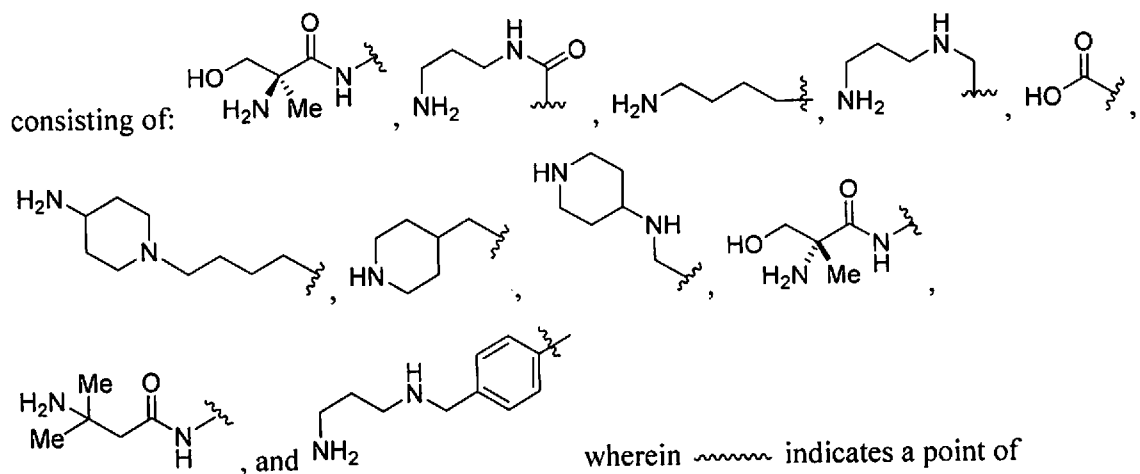
IB-2a



IB-2b

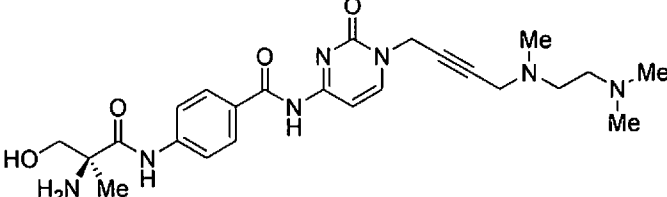
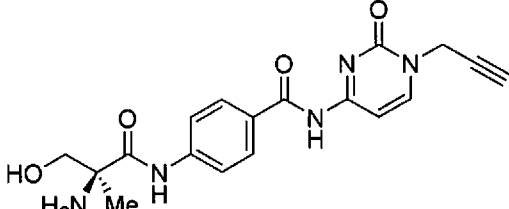
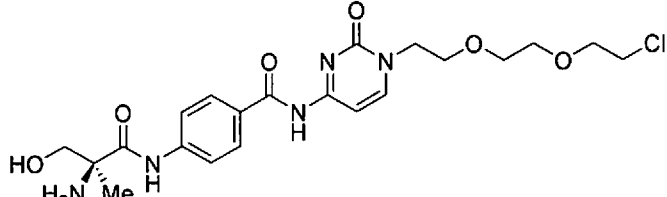
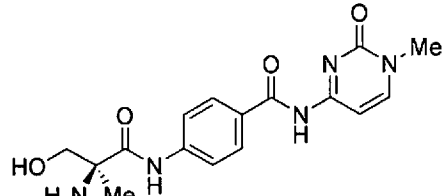
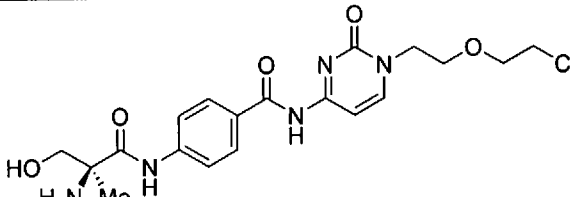
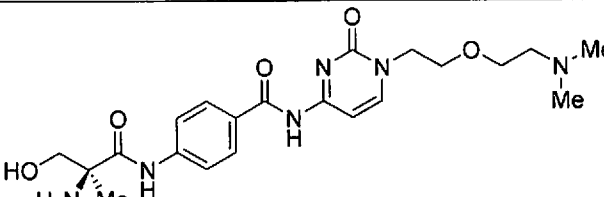
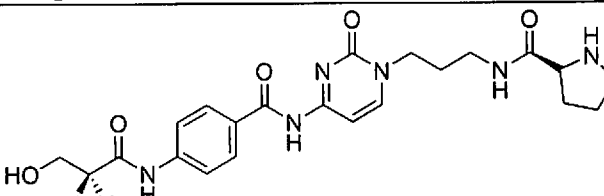
or a pharmaceutically acceptable salt thereof.

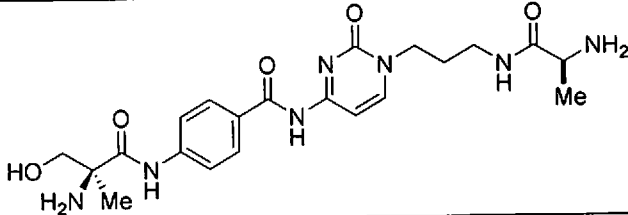
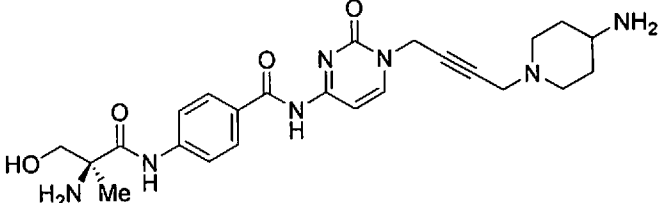
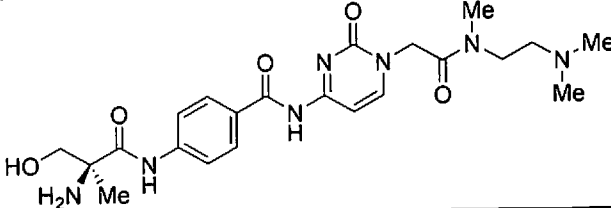
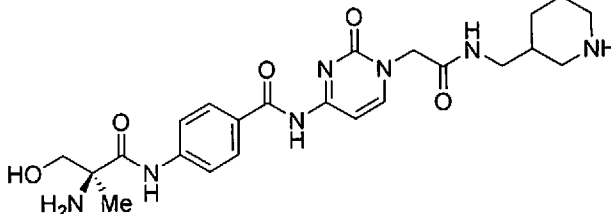
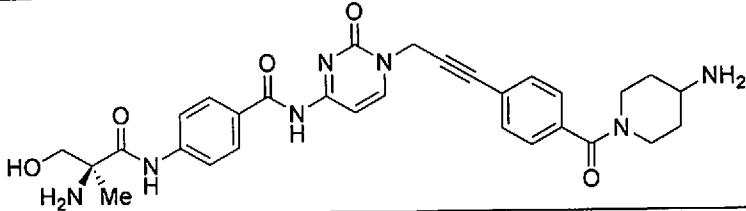
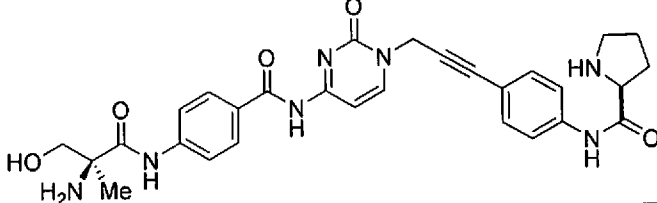
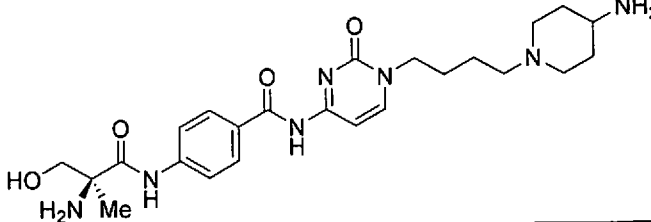
25. The compound of claims 19-24, wherein  $R_2-Z_2-Z_1$  is selected from the group

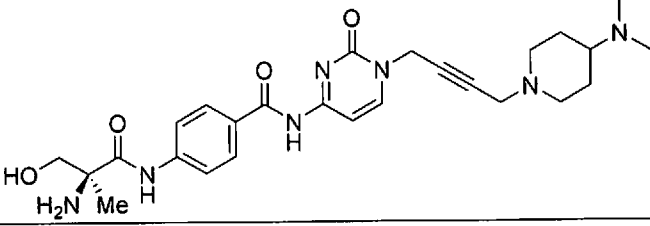
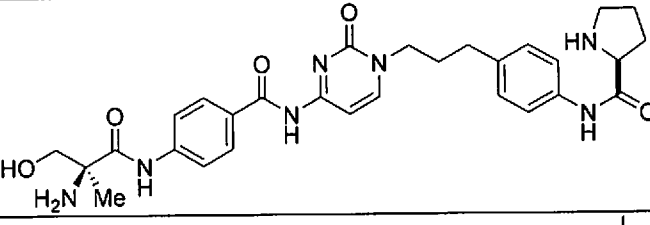
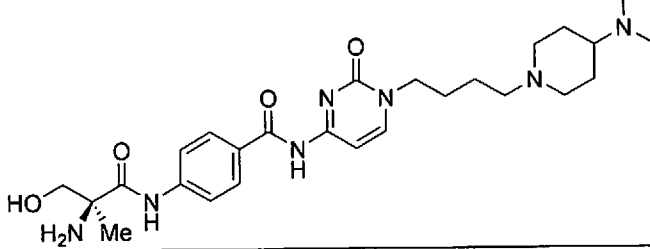
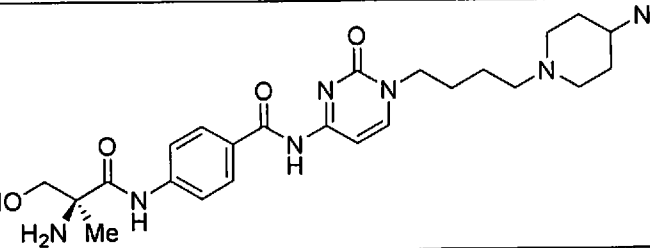
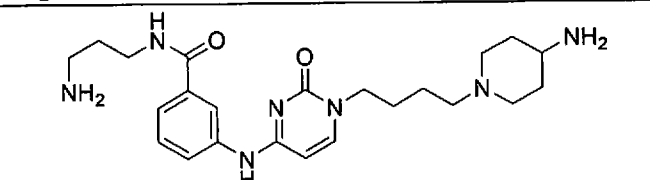
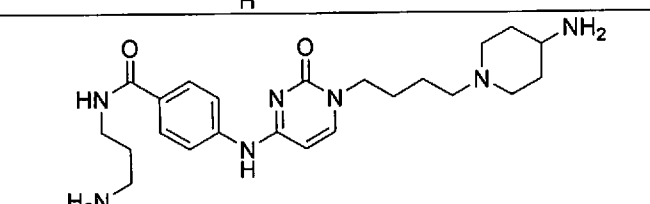
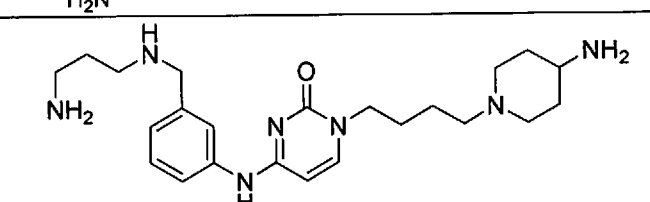


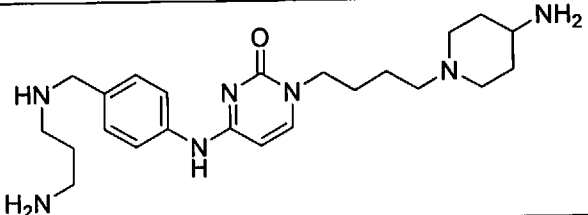
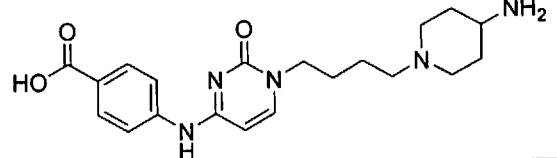
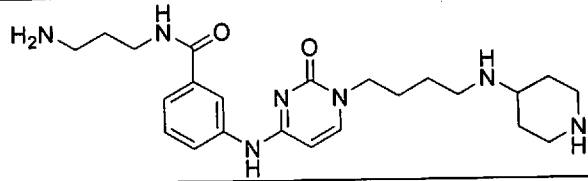
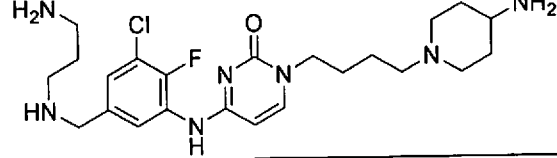
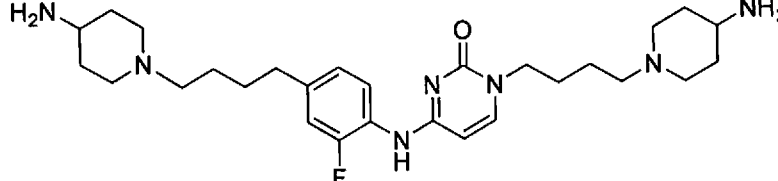
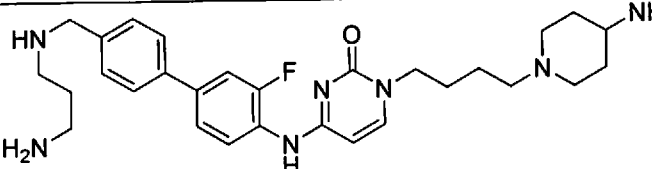
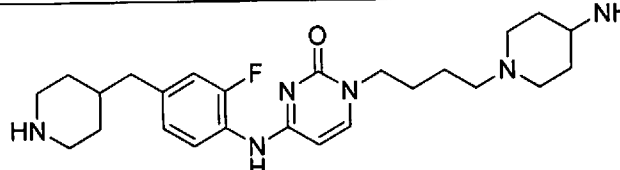
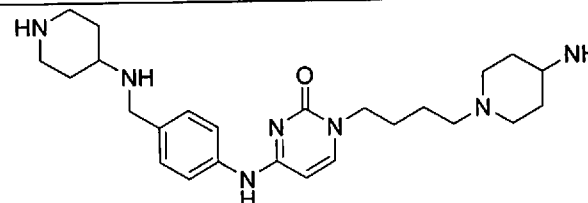
26. A compound which is:

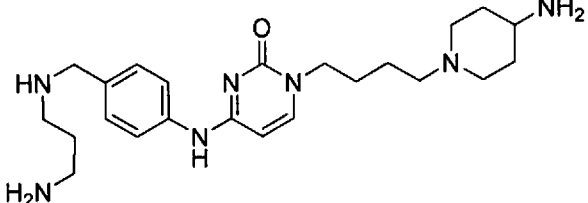
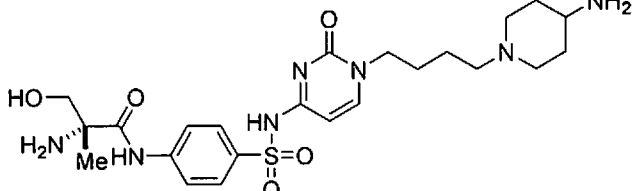
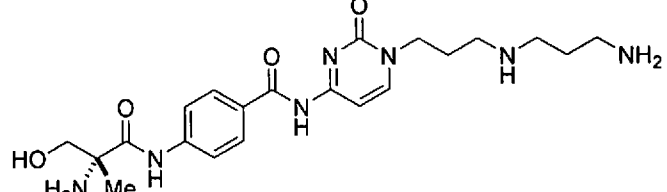
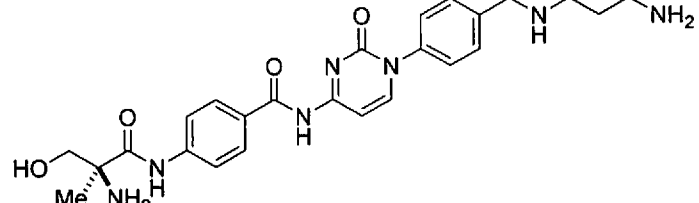
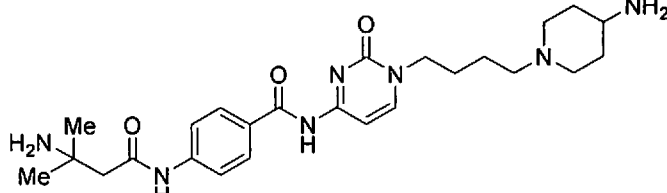
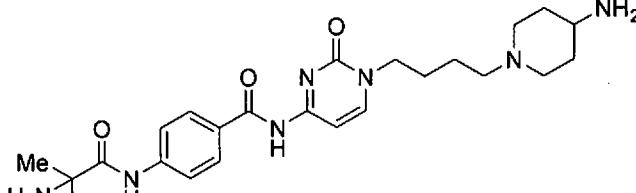
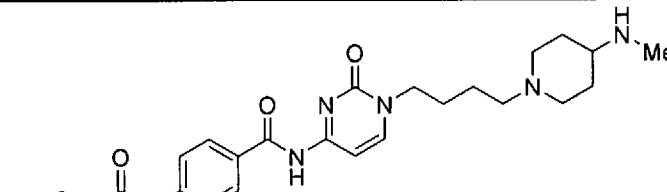
| No. | Compound |
|-----|----------|
| 1   |          |
| 2   |          |

| No. | Compound                                                                             |
|-----|--------------------------------------------------------------------------------------|
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| 4   |    |
| 5   |    |
| 6   |   |
| 7   |  |
| 8   |  |
| 9   |  |

| No. | Compound                                                                             |
|-----|--------------------------------------------------------------------------------------|
| 10  |    |
| 11  |    |
| 12  |    |
| 13  |   |
| 14  |  |
| 15  |  |
| 16  |  |

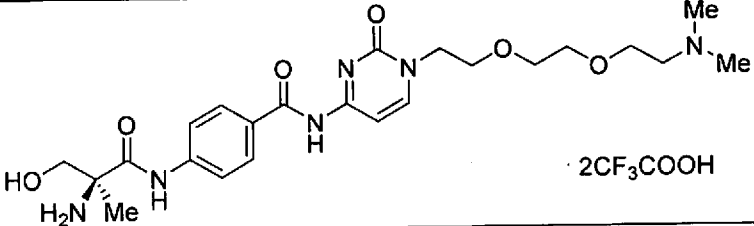
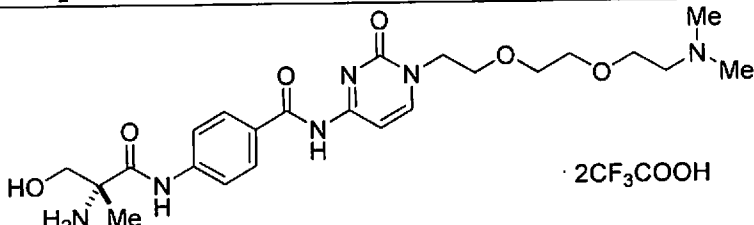
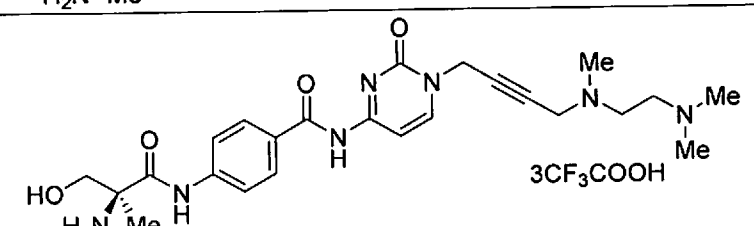
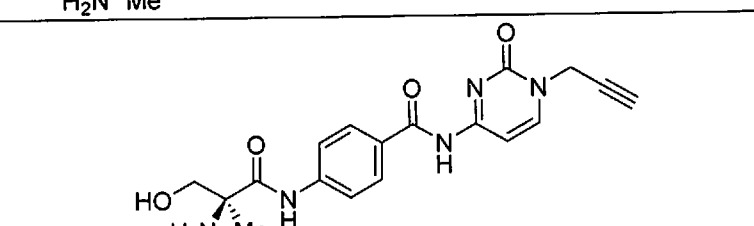
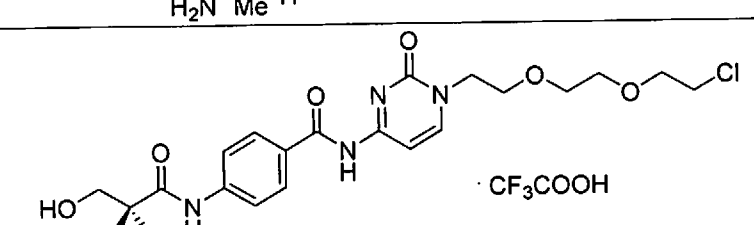
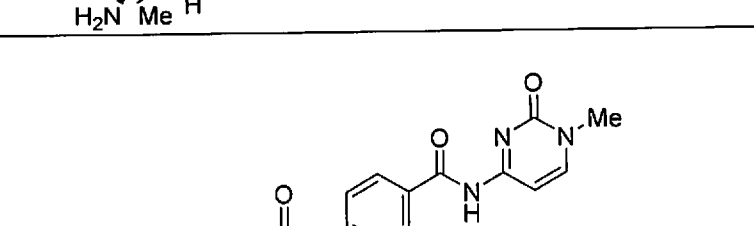
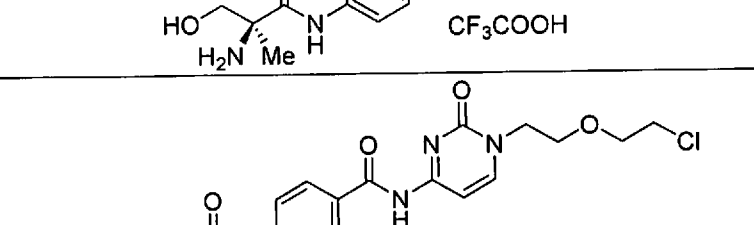
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|-----|--------------------------------------------------------------------------------------|
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| 19  |    |
| 20  |   |
| 21  |  |
| 22  |  |
| 23  |  |

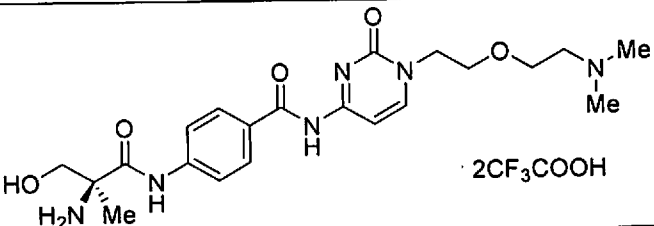
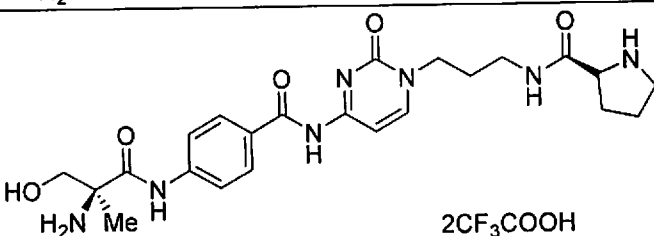
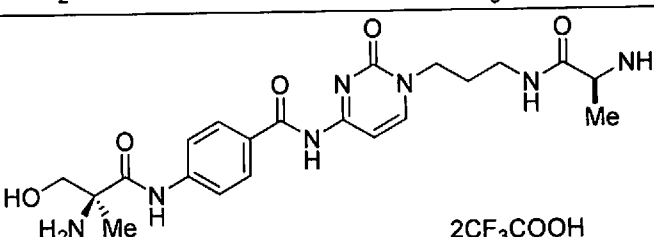
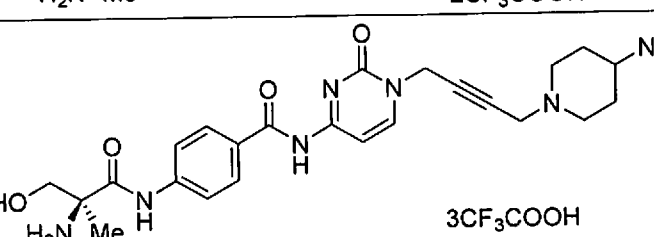
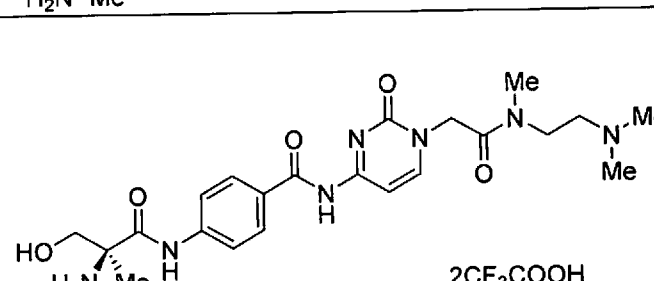
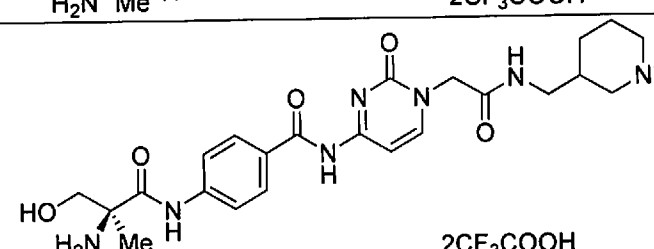
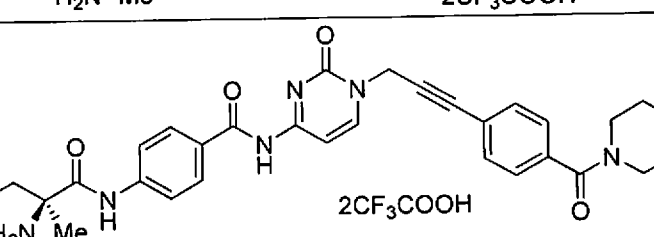
| No. | Compound                                                                             |
|-----|--------------------------------------------------------------------------------------|
| 24  |    |
| 25  |    |
| 26  |    |
| 27  |    |
| 28  |   |
| 29  |  |
| 30  |  |
| 31  |  |

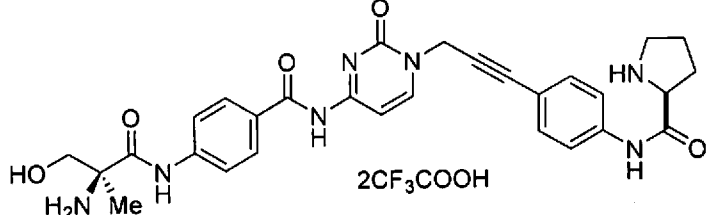
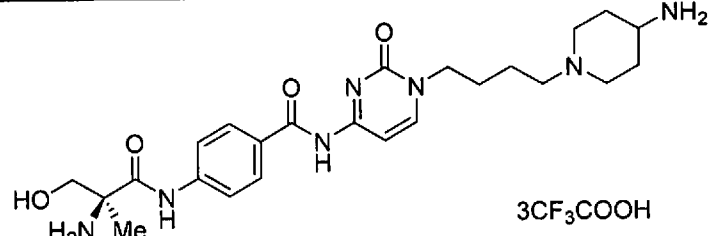
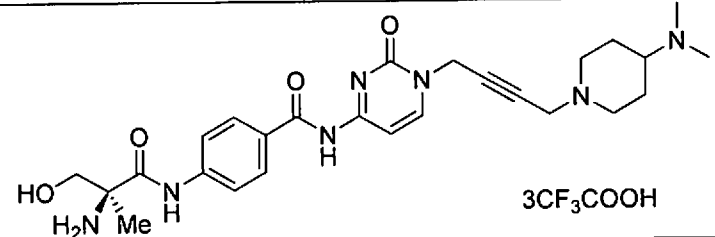
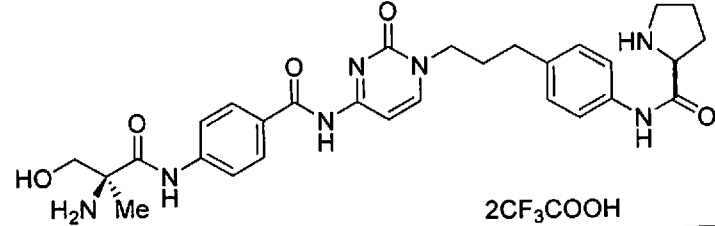
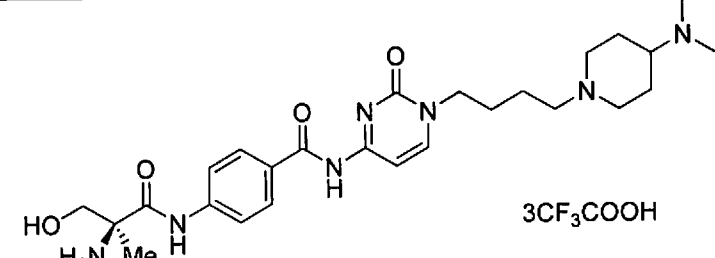
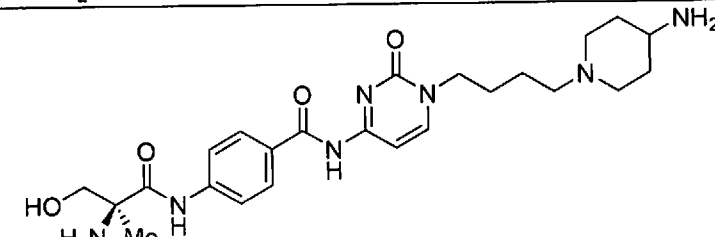
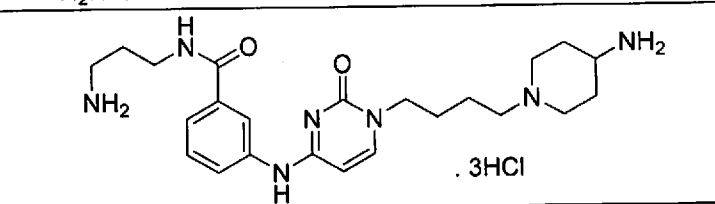
| No. | Compound                                                                             |
|-----|--------------------------------------------------------------------------------------|
| 32  |    |
| 33  |    |
| 34  |    |
| 35  |   |
| 36  |  |
| 37  |  |
| 38  |  |

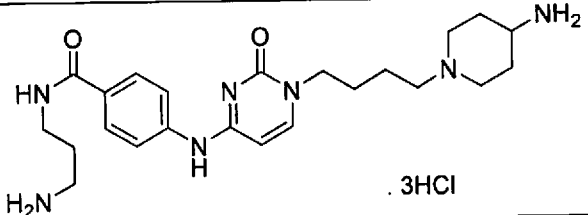
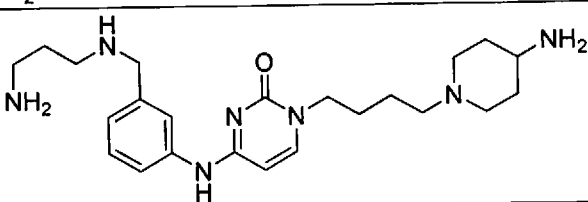
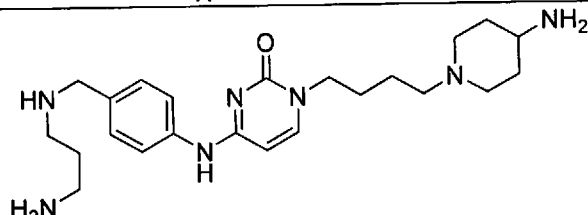
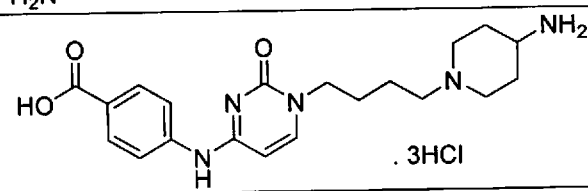
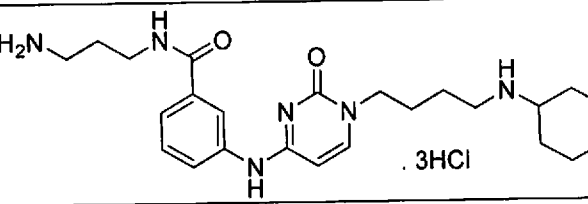
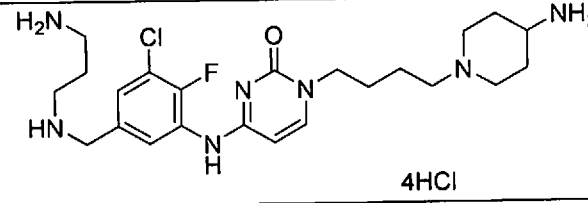
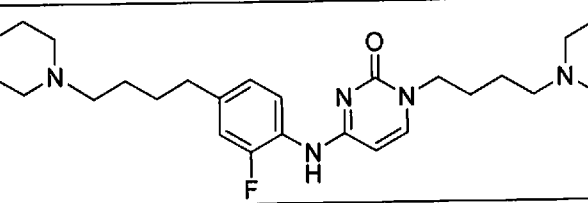
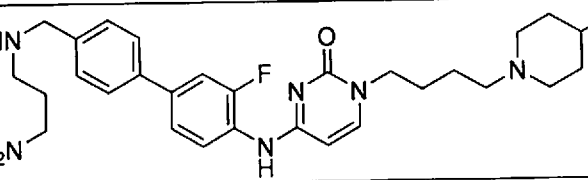
or a pharmaceutically acceptable salt thereof.

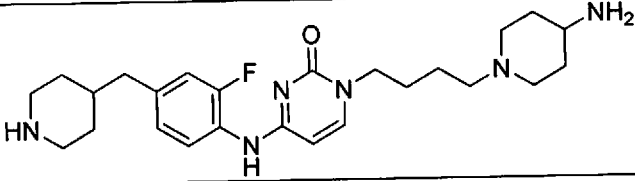
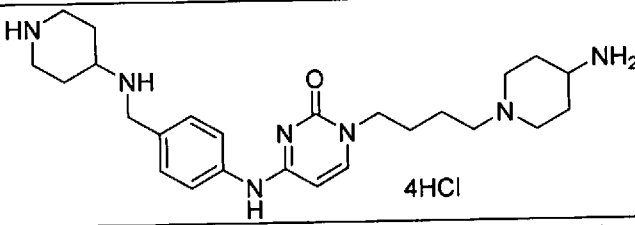
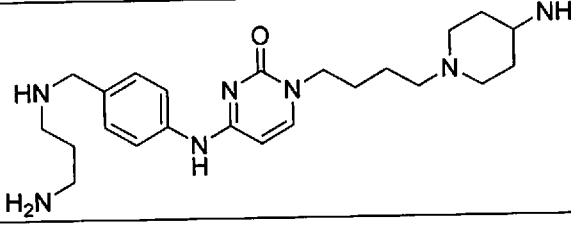
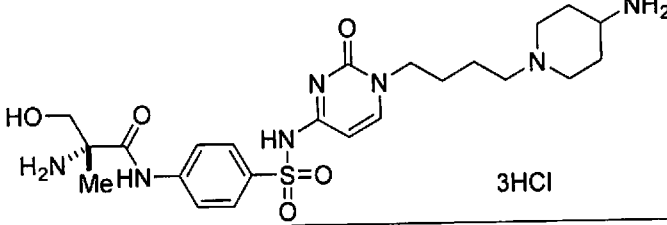
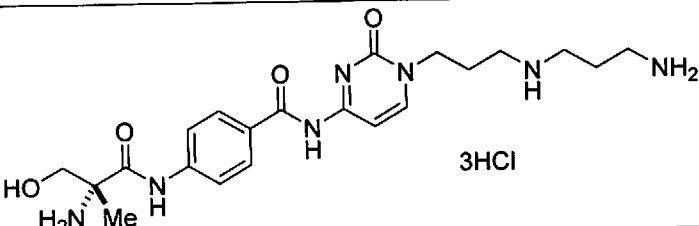
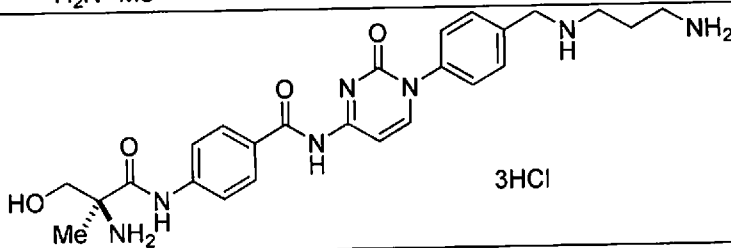
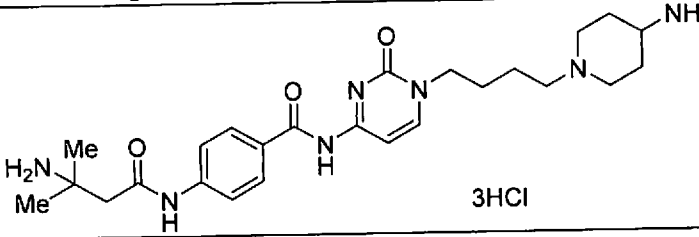
27. A compound which is:

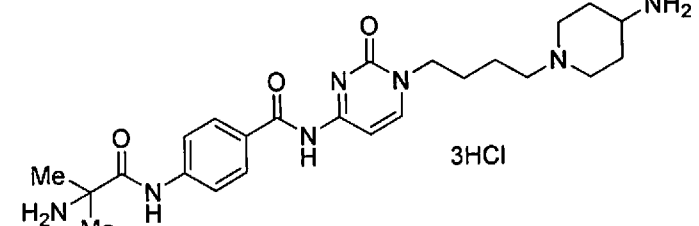
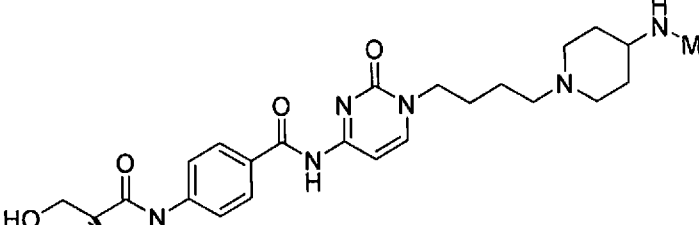
| No. | Compound                                                                             |
|-----|--------------------------------------------------------------------------------------|
| 1   |    |
| 2   |    |
| 3   |    |
| 4   |   |
| 5   |  |
| 6   |  |
| 7   |  |

| No. | Compound                                                                             |
|-----|--------------------------------------------------------------------------------------|
| 8   |    |
| 9   |    |
| 10  |    |
| 11  |   |
| 12  |  |
| 13  |  |
| 14  |  |

| No. | Compound                                                                                                        |
|-----|-----------------------------------------------------------------------------------------------------------------|
| 15  |  <p>2CF<sub>3</sub>COOH</p>   |
| 16  |  <p>3CF<sub>3</sub>COOH</p>   |
| 17  |  <p>3CF<sub>3</sub>COOH</p>   |
| 18  |  <p>2CF<sub>3</sub>COOH</p>  |
| 19  |  <p>3CF<sub>3</sub>COOH</p> |
| 20  |  <p>3CF<sub>3</sub>COOH</p> |
| 21  |  <p>. 3HCl</p>              |

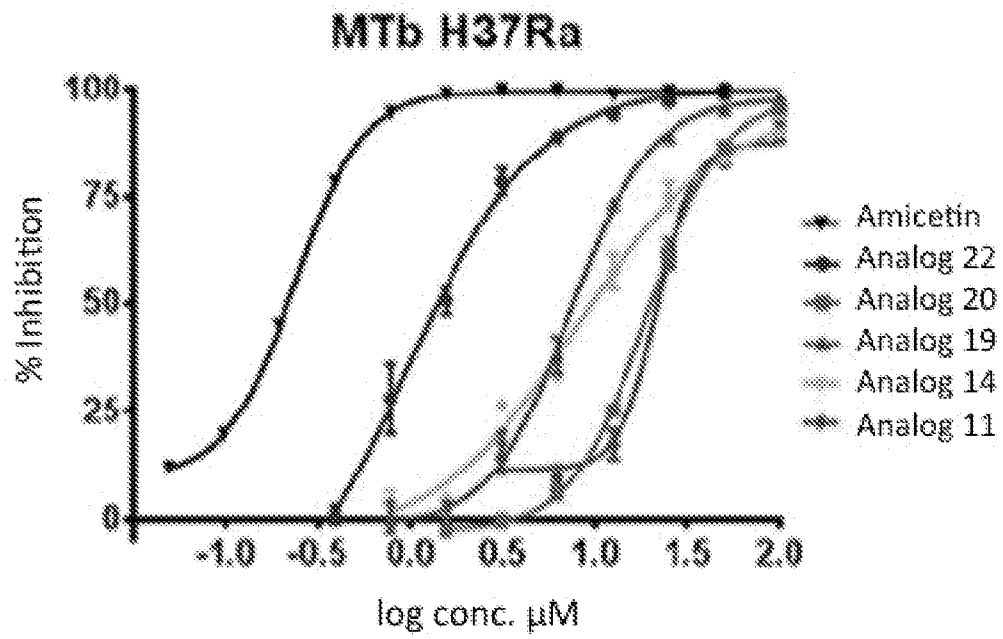
| No. | Compound                                                                             |
|-----|--------------------------------------------------------------------------------------|
| 22  |    |
| 23  |    |
| 24  |    |
| 25  |   |
| 26  |  |
| 27  |  |
| 28  |  |
| 29  |  |

| No. | Compound                                                                                     |
|-----|----------------------------------------------------------------------------------------------|
| 30  |            |
| 31  | <br>4HCl   |
| 32  |            |
| 33  | <br>3HCl  |
| 34  | <br>3HCl |
| 35  | <br>3HCl |
| 36  | <br>3HCl |

| No. | Compound                                                                                   |
|-----|--------------------------------------------------------------------------------------------|
| 37  | <br>3HCl |
| 38  | <br>3HCl |

28. A pharmaceutical composition comprising a compound of claims 1-27 and a pharmaceutically acceptable excipient.
29. A method of treating a bacterial infection in a patient in need of such treatment, comprising administering the composition of any one of claims 1-28 or the pharmaceutical composition of claim 28.
29. The method of claim 28, wherein the bacterial infection is tuberculosis.

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**FIG. 1**

2/2

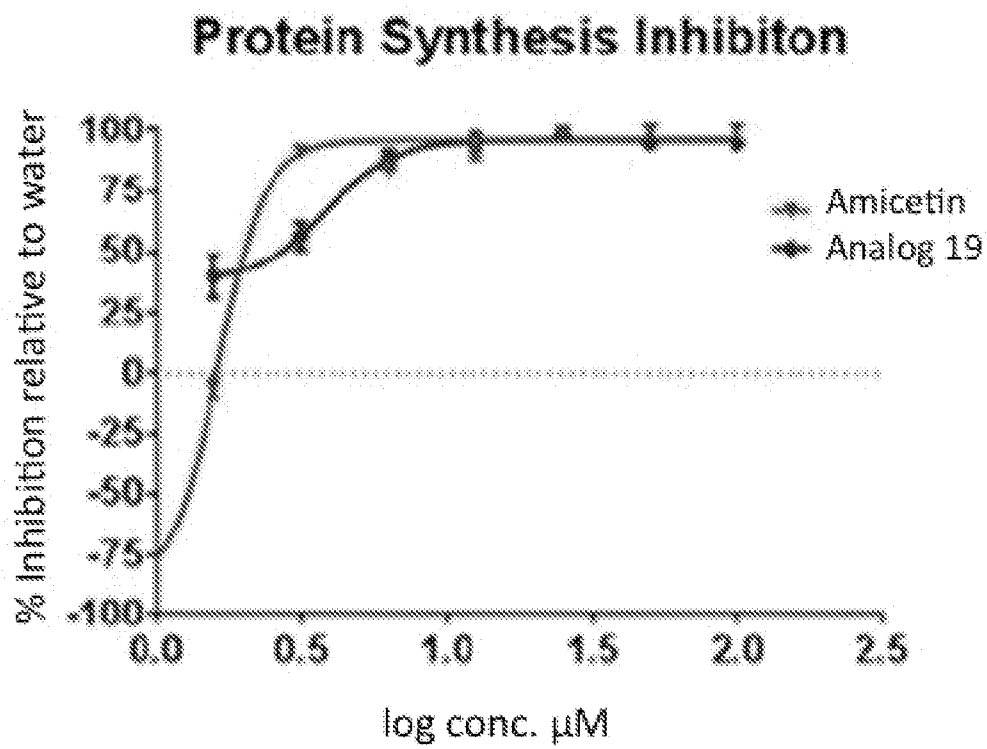


FIG. 2

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2017/041790

A. CLASSIFICATION OF SUBJECT MATTER  
INV. C07D239/10 C07D239/22 C07D239/36 C07D239/47 A61K31/505  
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                                                                           | Relevant to claim No. |
|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X         | <p>DOUB L ET AL: "N SULFANILYL-1-ALKYL CYTOSINES A NEW HIGHLY ACTIVE CLASS OF SOLUBLE SHORT ACTING SULFANILAMIDES", JOURNAL OF MEDICINAL CHEM, AMERICAN CHEMICAL SOCIETY, vol. 13, no. 2, 1970, pages 242-246, XP009080233, ISSN: 0022-2623, DOI: 10.1021/JM00296A018 page 242, right-hand column, "Sulfacytine (8c)"; page 243, Tables I to IV; page 244, Scheme I and compound 8</p> <p>-----<br/>-/--</p> | 1-25,<br>28-30        |



Further documents are listed in the continuation of Box C.



See patent family annex.

## \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

1 December 2017

Date of mailing of the international search report

15/12/2017

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040,  
Fax: (+31-70) 340-3016

Authorized officer

Sen, Alina

## INTERNATIONAL SEARCH REPORT

International application No

PCT/US2017/041790

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                                                                           | Relevant to claim No. |
|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X         | ELENA A. SHIROKOVA, NATALIA B. TARUSSOVA, ALEXANDER V. SHIPITSIN, DMITRY G. SEMIZAROV, ALEXANDER A. KRAYEVSKY: "Novel Acyclic Nucleotides and Nucleoside 5'-Triphosphates Imitating 2',3'-Dideoxy-2',3'-dideohydro nucleotides: Synthesis and Biological Properties", JOURNAL OF MEDICINAL CHEMISTRY, 1994, pages 3739-3748, XP002776297, DOI: 10.1021/jm00048a010<br>page 3745, compound 34a<br>-----       | 1-25,<br>28-30        |
| X         | CHENGYI LIANG AT AL.: "Synthesis of L-Dioxolane Nucleosides and Related Chemistry", JOURNAL OF ORGANIC CHEMISTRY, vol. 60, 1995, pages 1546-1553, XP002776298,<br>page 1547, Scheme 2, compound 14; pages 1551-1552, "Experimental" for compound 14<br>-----                                                                                                                                                 | 1-25                  |
| X         | MARIA L. PELLIZZARO ET AL.: "Conformer-Independent Ureidoimidazole Motifs - Tools to Probe Conformational and Tautomeric Effects on the Molecular Recognition of Triply Hydrogen-Bonded Heterodimers", CHEMISTRY - A EUROPEAN JOURNAL, vol. 17, no. 51, 23 November 2011 (2011-11-23), pages 14508-14517, XP002776299, DOI: 10.1002/chem.201102128<br>page 14509, Scheme 1, compound of structure 4<br>----- | 1-25                  |
| X         | A. M. KRITSYN, L. I. KOLOBUSHKINA, S. N. MIKHAILOV, V. L. FLORENT'EV: "Nonglycoside analogs of nucleotides I. 2,3-Dihydroxypropyl derivatives of nucleic bases", CHEMISTRY OF HETEROCYCLIC COMPOUNDS, vol. 11, no. 1, 1975, pages 108-113, XP002776300,<br>page 109, compound IIIb<br>-----                                                                                                                  | 1-25                  |
| Y         | US 2013/090326 A1 (DUFFY ERIN M [US] ET AL) 11 April 2013 (2013-04-11) [0011]; [0302], Table 1, e.g. compounds 176, 189, 190, 199, 208, 213; examples, e.g. Example 2 and Table 2; claims<br>-----<br>-/--                                                                                                                                                                                                   | 1-30                  |

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2017/041790

| C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT |                                                                                                                                                                                                                                                                                                                                                                                                        |                       |
|------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Category*                                            | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                                                                     | Relevant to claim No. |
| Y                                                    | <p>YING-YUE BU ET AL.: "Anti-Mycobacterial Nucleoside Antibiotics from a Marine-Derived Streptomyces sp. TPU1236A", MARINE DRUGS, vol. 12, 2014, pages 6102-6112, XP002776301, ISSN: 1660-3397, DOI: 10.3390/md12126102 abstract, "amicetin (9) showed the MIC of 8 microgram/mL; page 6103, Figure 2, compounds (7)-(9); page 6108, lines 1-10 and Table 3; page 6110, "Conclusions"</p> <p>-----</p> | 1-30                  |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2017/041790

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
|-------------------------------------------|---------------------|----------------------------|---------------------|
| US 2013090326                             | A1                  | 11-04-2013                 |                     |
|                                           |                     | AU 2010306650 A1           | 03-05-2012          |
|                                           |                     | AU 2016231568 A1           | 20-10-2016          |
|                                           |                     | CA 2777741 A1              | 21-04-2011          |
|                                           |                     | CN 102725274 A             | 10-10-2012          |
|                                           |                     | EA 201270567 A1            | 28-12-2012          |
|                                           |                     | EP 2488502 A2              | 22-08-2012          |
|                                           |                     | JP 2013508299 A            | 07-03-2013          |
|                                           |                     | MX 339000 B                | 09-05-2016          |
|                                           |                     | NZ 599290 A                | 31-10-2014          |
|                                           |                     | US 2013090326 A1           | 11-04-2013          |
|                                           |                     | US 2016031828 A1           | 04-02-2016          |
|                                           |                     | WO 2011047323 A2           | 21-04-2011          |
| -----                                     |                     |                            |                     |