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(54) Titre : COMPOSES ANTIMICROBIENS ET PROCEDES
(54) Title: ANTIMICROBIAL COMPOUNDS AND METHODS

(57) Abrégé/Abstract:
The invention is directed to compounds that are active as antibacterial agents. The invention compounds are active against gram-positive and gram-negative bacteria and can be used to treat infections caused by gram-positive and gram-negative bacteria. Also disclosed are processes and intermediates for making the compounds.

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(54) Title: ANTIMICROBIAL COMPOUNDS AND METHODS

(57) Abstract: The invention is directed to compounds that are active as antibacterial agents. The invention compounds are active against gram-positive and gram-negative bacteria and can be used to treat infections caused by gram-positive and gram-negative bacteria. Also disclosed are processes and intermediates for making the compounds.

ANTIMICROBIAL COMPOUNDS AND METHODS

Cross-Reference to Related Applications

[0001] This application claims priority to U.S. Provisional Application Serial Number 62/793,216, the entire contents of which are incorporated by reference herein.

Field of the Invention

[0002] The present disclosure relates to compounds that are active as antibacterial agents. The present disclosure also relates to methods of treating bacterial infections with the present compounds.

Background of the Invention

[0003] Antibacterial resistance is a worldwide problem. Both gram-positive and gram-negative bacteria are increasingly becoming resistant to antibiotics.

[0004] Gram-positive bacteria such as methicillin resistant *Staphylococcus aureus* (MRSA) are resistant to most antibiotics that are related to penicillin. MRSA strains are commonly involved in infections acquired in health care facilities and can cause infections in greater communities.

[0005] Gram-negative bacteria are believed to be more resistant to antibiotics than Gram-positive bacteria, because of the impermeability of their cell walls. According to the National Institutes of Health (NIH), Gram-negative bacteria can cause many types of infections and are spread to humans in a variety of ways. Several species, including *Escherichia coli,* are common causes of foodborne disease. *Vibrio cholerae,* the bacteria responsible for cholera, is a waterborne pathogen. Gram-negative bacteria can also cause respiratory infections, such as certain types of pneumonia, and sexually transmitted diseases, including gonorrhea. *Yersinia pestis*, the Gram-negative bacterium responsible for plague, is transmitted to people through the bite of an infected insect or handling an infected animal. See www.niaid.nih.gov/research/gram-negative-bacteria (last visited January 7, 2020).

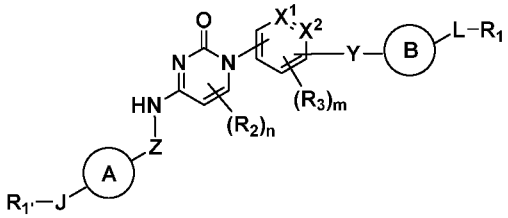
[0006] Certain types of Gram-negative bacteria have become increasingly resistant to available antibiotic drugs. Some strains are now resistant to many, most, or all available treatments resulting in increased illness and death from bacterial infections and contributing to escalating healthcare costs. Examples of Gram-negative bacteria that have demonstrated drug resistance include: *E. coli,* which causes the majority of urinary tract infections; *Acinetobacter baumanii*, which causes disease mainly in healthcare settings; *Pseudomonas aeruginosa*, which causes bloodstream infections and pneumonia in hospitalized patients and is a common cause of pneumonia in patients with cystic fibrosis; *Klebsiella pneumoniae*, which causes many types of healthcare-associated infections, including pneumonia, urinary

tract infections, and bloodstream infections; and *Neisseria gonorrhoeae*, which causes the sexually transmitted disease gonorrhea and is the second most commonly reported infectious disease in the United States.

[0007] As a result, new drugs to combat Gram-positive and Gram-negative bacterial infections are needed.

Summary of the Invention

[0008] These and other needs are met by the present invention which provides in one aspect a compound of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

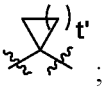
Z is (C=O), (C=S), (C=NR_z), (S=O), or SO_2; wherein R_z is H, C_1-C_6 alkyl, or CN;

ring A is a monocyclic heterocycloalkylene or bicyclic heterocycloalkylene, wherein the monocyclic heterocycloalkylene or bicyclic heterocycloalkylene are optionally substituted with up to three substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, halo, CN, C_1-C_6 haloalkyl, phenyl, OH, NH_2, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)$_2$, COOH, COO(C_1-C_6 alkyl), -$CONH_2$, and oxo;

J is absent or is C_1-C_6 alkylene, heterocycloalkylene, C_1-C_6 alkylene-heterocycloalkylene or C_1-C_6 alkylene-cycloalkylene, any of which may be optionally substituted with up to three substituents independently selected from the group consisting of halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, NH_2, CN, and OH; wherein at each occurrence of C_1-C_6 alkylene, up to two methylene units of the C_1-C_6 alkylene may independently and optionally be replaced with O, S, SO_2, C=O, or  ; wherein t is 1, 2, 3, or 4;

X^1 and X^2 are each independently C-H or N;

Y is a linear C_1-C_8 alkylene, C_2-C_8 alkenylene, or C_2-C_8 alkynylene, any of which are optionally substituted with OH, NH_2, CN, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, COO(C_1-C_6 alkyl), COOH, $CONH_2$, or C_1-C_6 alkoxy, and wherein up to two carbon atoms of the C_2-C_8 alkylene, C_2-C_8 alkenylene, or C_2-C_8 alkynylene may be independently replaced by O, NH,

N-(C_1-C_6 alkyl), N-(C_1-C_6 hydroxyalkyl), N-(C_1-C_6 haloalkyl), N-(C_{1-6} alkylene-cycloalkyl), N-(C_{3-8} cycloalkyl), NH(C=O), N-(C_{1-6} alkyl) (C=O), (C=O), or ; wherein t' is 1, 2, 3, or 4;

ring B is a monocyclic cycloalkylene or monocyclic heterocycloalkylene, either of which is optionally substituted with up to three substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CN, NH_2, C_1-C_6 haloalkyl, OH, COOH, COO(C_1-C_6 alkyl), $CONH_2$, and C_1-C_6 hydroxyalkyl;

L is absent, or is a C_1-C_6 alkylene, wherein up to two methylene units of the C_1-C_6 alkylene may independently be replaced with O, NH, (C=O), NH(C=O), N-(C_{1-6} alkyl)(C=O), (C=NH), NH(C=N), or N-(C_{1-6} alkyl);

R_1 is H, halo, C_1-C_6 haloalkyl, $NR_{x'}R_{y'}$, or monocyclic heterocycloalkyl optionally substituted with NH_2, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)$_2$, wherein $R_{x'}$ and $R_{y'}$ are each independently H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, or an amino protecting group, wherein the C_1-C_6 alkyl and C_3-C_8 cycloalkyl are optionally substituted with up to three substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CN, C_1-C_6 haloalkyl, phenyl, OH, NH_2, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)$_2$, -COO(C_1-C_6 alkyl), -$CONH_2$, and oxo; or R_1 is NH(C=O)-(C_1-C_6) alkyl, or NH-(C=NH)-NH_2, either of which may be optionally substituted with up to three substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CN, C_1-C_6 haloalkyl, phenyl, OH, NH_2, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)$_2$, COO(C_1-C_6 alkyl), $CONH_2$, and oxo;

$R_{1'}$ is H or NR_xR_y, wherein R_x and R_y are each independently H, C_1-C_6 alkyl, C_1-C_6 alkyl-SO_3, CO(C_1-C_6 alkyl), CO-(C_1-C_6 alkylene)-NH_2, or an amino protecting group;

R_2 and R_3 are each independently selected from the group consisting of C_1-C_6 alkyl, halo, CN, OH, NH_2, O(C_1-C_6 haloalkyl), NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)$_2$, -COO(C_1-C_6 alkyl), -$CONH_2$, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy; and

m and n are each independently 0, 1, 2, or 3.

[0009] In another aspect, the invention provides methods of using compounds of formula I or a pharmaceutically acceptable salt thereof for the treatment of bacterial infections.

[0010] In another aspect, the invention provides pharmaceutical compositions comprising a compound of formula I or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

[0011] In a further aspect, the invention provides processes for making compounds of formula I or a pharmaceutically acceptable salt thereof, as well as compound intermediates used in the processes, as depicted in the synthetic schemes.

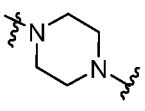
Detailed Description of the Invention

[0012] 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.

[0013] 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.

[0014] 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.

[0015] 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%."

[0016] As used herein, a wavy line drawn on a structure can be used to show the attachment point of the structure, such as , wherein "〰" indicates points of attachment.

[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 "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, C_1-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, docecyl, cyclopentyl, or cyclohexyl.

[0021] 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, alkoxy, amino, alkylamino, acylamino, thio, and alkylthio. In some aspects, the alkyl group is unsubstituted or not optionally substituted.

[0022] "Alkylene" as used herein includes an alkyl group that is substituted at two points. An example is methylene (-CH_2-), propylene (-$CH_2CH_2CH_2$-), and the like.

[0023] 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, "C_1-C_{12} 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-(l,4-pentadienyl), and hexadienyl.

[0024] 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.

[0025] "Alkenylene" as used herein includes an alkenyl group that is substituted at two points. An example is but-2-enylene (-CH_2CH=$CHCH_2$-) and the like.

[0026] 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.

[0027] 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.

[0028] "Alkynylene" as used herein includes an alkynyl group that is substituted at two points. An example is 2-butynylene (-CH_2CCCH_2-) and the like.

[0029] 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., EtO-). The chain may contain an indicated number of carbon atoms. For example, "C_1-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 C_1-C_{12} alkoxy group include, but are not limited to, methoxy, ethoxy, isopropoxy, butoxy, n-pentoxy, isopentoxy, neopentoxy, and hexoxy.

[0030] 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.

[0031] 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.

[0032] The term "cycloalkyl" as used herein includes non-aromatic saturated monocyclic or multicyclic ring system that may contain an indicated number of carbon atoms. For example, C_3-C_{12} 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. The term "cycloalkyl" also includes multicyclic rings such as a bicyclic cycloalkyl, or a tricyclic cycloalkyl which may be in a fused, bridged, or spiro orientation.

[0033] The term "cycloalkylene" as used herein includes a cycloalkyl group that is substituted at two points.

[0034] The terms "disorder" and "disease" 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.

[0035] 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.

[0036] 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.

[0037] 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.

[0038] As used herein, "halo" or "halogen" includes fluoro, chloro, bromo, and iodo.

[0039] As used herein, "heterocycloalkyl" includes a non-aromatic saturated ring of about 3 to about 12 ring atoms (e.g., 5 to about 10 ring atoms, 3 to about 8 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 heterocycloalkyl group optionally comprises at least one sp^2-hybridized atom (*e.g.*, a ring incorporating a carbonyl, endocyclic olefin, or exocyclic olefin). In some embodiments, a nitrogen or sulfur atom of the heterocycloalkyl is optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. The monocyclic heterocycle means a three-, four-, five-, six-, seven-, or eight-membered ring containing at least one heteroatom independently selected from the group consisting of O, N, and S. The three- or four-membered ring contains zero or one double bond, and one heteroatom selected from the group consisting of O, N, and S. The five-membered ring contains zero or one double bond and one, two or three heteroatoms selected from the group consisting of O, N and S. The six-membered ring contains zero, one or two double bonds and one, two, or three heteroatoms selected from the group consisting of O, N, and S. The seven- and eight-membered rings contains zero, one, two, or three double bonds and one, two, or three heteroatoms selected from the group consisting of O, N, and S. Representative examples of monocyclic heterocycloalkyl include, but are not limited to, azetidinyl, azepanyl, aziridinyl, diazepanyl, 1,3-dioxanyl, 1,3-dioxolanyl, 1,3-dithiolanyl, 1,3-dithianyl, imidazolinyl, imidazolidinyl, isothiazolinyl, isothiazolidinyl, isoxazolinyl, isoxazolidinyl, morpholinyl, oxadiazolinyl, oxadiazolidinyl, oxazolinyl, oxazolidinyl, piperazinyl, piperidinyl, pyranyl, pyrazolinyl, pyrazolidinyl, pyridazin-3(2H)-onyl, pyridin-2(1H)-onyl, pyrrolinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothienyl, thiadiazolinyl, thiadiazolidinyl, thiazolinyl, thiazolidinyl, thiomorpholinyl, 1,1-dioxidothiomorpholinyl (thiomorpholine sulfone), thiopyranyl, and trithianyl.

[0040] The term "heterocycloalkylene" as used herein includes a heterocycloalkyl group that is substituted at two points.

[0041] The term "heterocycloalkyl" also includes multicyclic rings such as a bicyclic heterocycle, or a tricyclic heterocycle which may be in a fused, bridged, or spiro orientation. The bicyclic heterocycle is a monocyclic heterocycle fused to a phenyl group, or a

monocyclic heterocycle fused to a monocyclic cycloalkyl, or a monocyclic heterocycle fused to a monocyclic cycloalkenyl, or a monocyclic heterocycle fused to a monocyclic heterocycle, or a bridged monocyclic heterocycle ring system in which two non-adjacent atoms of the ring are linked by an alkylene bridge of 1, 2, 3, or 4 carbon atoms, or an alkenylene bridge of two, three, or four carbon atoms. Representative examples of bicyclic heterocycles include, but are not limited to, 3-azabicyclo[3.1.0]hexane, 3-azabicyclo[4.1.0]heptane, 3-azabicyclo[3.2.0]heptane, (3aR,6aS)-hexahydro-1H-2λ_2-cyclopenta[c]pyrrole, (3aR,7aS)-octahydro-2λ_2-isoindole.

[0042] Tricyclic heterocycles are exemplified by a bicyclic heterocycle fused to a phenyl group, or a bicyclic heterocycle fused to a monocyclic cycloalkyl, or a bicyclic heterocycle fused to a monocyclic cycloalkenyl, or a bicyclic heterocycle fused to a monocyclic heterocycle, or a bicyclic heterocycle in which two non-adjacent atoms of the bicyclic ring are linked by an alkylene bridge of 1, 2, 3, or 4 carbon atoms, or an alkenylene bridge of two, three, or four carbon atoms.

[0043] A heterocycloalkyl 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 heterocycloalkyl group is unsubstituted or not optionally substituted.

[0044] The monocyclic, bicyclic, and tricyclic heterocycles are connected to the parent molecular moiety through any carbon atom or any nitrogen atom contained within the rings, and can be unsubstituted or substituted.

[0045] 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.

[0046] 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.

[0047] 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).

[0048] "Amino protecting group" is a protecting group that is suitable for preventing undesired reactions at an amino nitrogen. Representative amino-protecting groups include, but are not limited to, formyl; acyl groups, for example alkanoyl groups, such as acetyl and trifluoroacetyl; alkoxycarbonyl groups, such as tert-butoxycarbonyl (Boc); arylmethoxycarbonyl groups, such as benzyloxycarbonyl (Cbz) and 9-fluorenylmethoxycarbonyl (Fmoc); arylmethyl groups, such as benzyl (Bn), trityl (Tr), and 1,1-di-(4'-methoxyphenyl)methyl; and the like.

[0049] "Hydroxyl protecting group" is a protecting group that is suitable for preventing undesired reactions at a hydroxyl oxygen. Representative hydroxy-protecting groups include, but are not limited to, acyl groups, for example alkanoyl groups, such as acetyl; arylmethyl groups, such as benzyl (Bn), trityl (Tr), and 1,1-di-(4'-methoxyphenyl)methyl; silyl groups, such as trimethylsilyl (TMS) and tert-butyldimethylsilyl (TBDMS); and the like.

[0050] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge et al., describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66, 1-19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods

used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like.

[0051] "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.

[0052] "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.)

[0053] 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. "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).

[0054] As used herein, "spiro bicyclic cycloalkyl" 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 spiro bicyclic cycloalkyl group (i.e., spirocyclopropyl).

[0055] The term "spiro bicyclic cycloalkylene" as used herein includes a spiro bicyclic cycloalkyl group that is substituted at two points.

[0056] As used herein, "spiro bicyclic heterocycloalkyl" 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 spiro bicyclic heterocycloalkyl group.

[0057] The term "spiro bicyclic heterocycloalkylene" as used herein includes a spiro bicyclic heterocycloalkyl group that is substituted at two points.

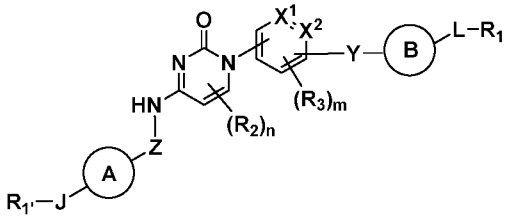
[0058] Some compounds disclosed herein are characterized by the presence of amino functional groups. One of ordinary skill would therefore understand that compounds can be isolated as salts wherein the amino functional group nitrogen is quarternized.

[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 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, 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.

Embodiments

Compounds

[0060] In a first aspect, the disclosure provides a compound of Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

Z is (C=O), (C=S), (C=NR_z), (S=O), or SO_2; wherein R_z is H, C_1-C_6 alkyl, or CN;

ring A is a monocyclic heterocycloalkylene or bicyclic heterocycloalkylene, wherein the monocyclic heterocycloalkylene or bicyclic heterocycloalkylene are optionally substituted with up to three substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, halo, CN, C_1-C_6 haloalkyl, phenyl, OH, NH_2, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)$_2$, COOH, COO(C_1-C_6 alkyl), -$CONH_2$, and oxo;

J is absent or is C_1-C_6 alkylene, heterocycloalkylene, C_1-C_6 alkylene-heterocycloalkylene or C_1-C_6 alkylene-cycloalkylene, any of which may be optionally substituted with up to three substituents independently selected from the group consisting of halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, NH_2, CN, and OH; wherein at each occurrence of C_1-C_6 alkylene, up to two methylene units of the C_1-C_6 alkylene may independently and optionally be replaced with O, S, SO_2, C=O, or  ; wherein t is 1, 2, 3, or 4;

X^1 and X^2 are each independently C-H or N;

Y is a linear C_1-C_8 alkylene, C_2-C_8 alkenylene, or C_2-C_8 alkynylene, any of which are optionally substituted with OH, NH_2, CN, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, COO(C_1-C_6 alkyl), COOH, $CONH_2$, or C_1-C_6 alkoxy, and wherein up to two carbon atoms of the C_2-C_8 alkylene, C_2-C_8 alkenylene, or C_2-C_8 alkynylene may be independently replaced by O, NH, N-(C_1-C_6 alkyl), N-(C_1-C_6 hydroxyalkyl), N-(C_1-C_6 haloalkyl), N-(C_{1-6} alkylene-cycloalkyl), N-(C_{3-8} cycloalkyl), NH(C=O), N-(C_{1-6} alkyl) (C=O), (C=O), or  ; wherein t' is 1, 2, 3, or 4;

ring B is a monocyclic cycloalkylene or monocyclic heterocycloalkylene, either of which is optionally substituted with up to three substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CN, NH_2, C_1-C_6 haloalkyl, OH, COOH, COO(C_1-C_6 alkyl), $CONH_2$, and C_1-C_6 hydroxyalkyl;

L is absent, or is a C_1-C_6 alkylene, wherein up to two methylene units of the C_1-C_6 alkylene may independently be replaced with O, NH, (C=O), NH(C=O), N-(C_{1-6} alkyl)(C=O), (C=NH), NH(C=N), or N-(C_{1-6} alkyl);

R_1 is H, halo, C_1-C_6 haloalkyl, $NR_{x'}R_{y'}$, or monocyclic heterocycloalkyl optionally substituted with NH_2, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)$_2$, wherein $R_{x'}$ and $R_{y'}$ are each independently H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, or an amino protecting group, wherein the C_1-C_6 alkyl and C_3-C_8 cycloalkyl are optionally substituted with up to three substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CN, C_1-C_6 haloalkyl, phenyl, OH, NH_2, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)$_2$, -COO(C_1-C_6 alkyl), -$CONH_2$, and oxo; or R_1 is NH(C=O)-(C_1-C_6) alkyl, or NH-(C=NH)-NH_2, either of which may be optionally substituted with up to three substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CN, C_1-C_6 haloalkyl, phenyl, OH, NH_2, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)$_2$, COO(C_1-C_6 alkyl), $CONH_2$, and oxo;

$R_{1'}$ is H or NR_xR_y, wherein R_x and R_y are each independently H, C_1-C_6 alkyl, C_1-C_6 alkyl-SO_3, CO(C_1-C_6 alkyl), CO-(C_1-C_6 alkylene)-NH_2, or an amino protecting group;

R_2 and R_3 are each independently selected from the group consisting of C_1-C_6 alkyl, halo, CN, OH, NH_2, O(C_1-C_6 haloalkyl), NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)$_2$, -COO(C_1-C_6 alkyl), -$CONH_2$, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy; and

m and n are each independently 0, 1, 2, or 3.

[0061] In one embodiment of a compound of formula I or a pharmaceutically acceptable salt thereof, Z is (C=S), ($C=NR_z$), S=O, or SO_2, wherein R_z is H, C_1-C_6 alkyl, or CN.

[0062] In another embodiment of a compound of formula I or a pharmaceutically acceptable salt thereof, Z is C=NH, C=N(C_1-C_6 alkyl), or C=N-CN.

[0063] In another embodiment of a compound of formula I or a pharmaceutically acceptable salt thereof, Z is -(C=O)-.

[0064] In another embodiment of a compound of formula I or a pharmaceutically acceptable salt thereof, ring A is a 4 to 8 membered monocyclic heterocycloalkylene or a 6 to 12 membered bicyclic heterocycloalkylene, wherein the monocyclic heterocycloalkylene and bicyclic heterocycloalkylene are optionally substituted with up to three substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, halo, C_1-C_6 haloalkyl, phenyl, OH, NH_2, COOH, COO(C_1-C_6 alkyl), and $CONH_2$.

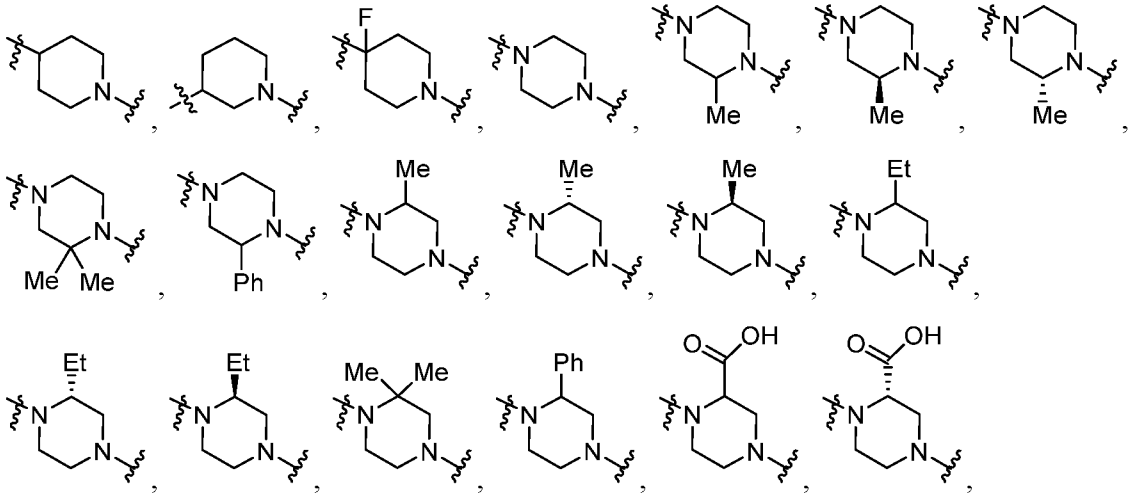
[0065] In another embodiment, ring A is a 4 to 7 membered monocyclic heterocycloalkylene optionally substituted with up to three substituents selected from the

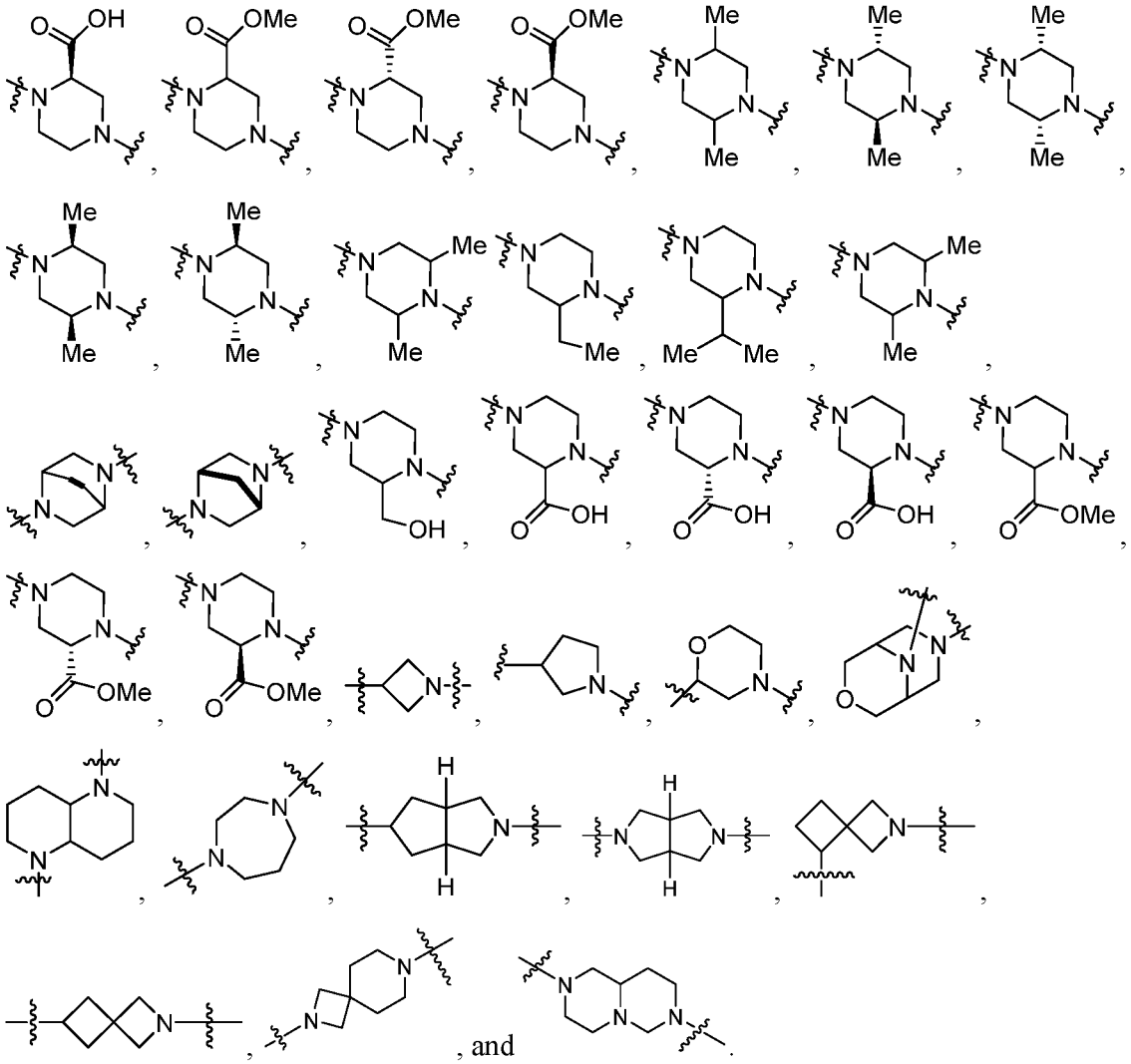
group consisting of halo, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, phenyl, COOH, and COO(C_1-C_6 alkyl). In another embodiment, ring A is a 4 to 7 membered monocyclic heterocycloalkylene optionally substituted with up to two substituents independently selected from the group consisting of halo, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, phenyl, COOH, and COO(C_1-C_6 alkyl), wherein the monocyclic heterocycloalkylene contains up to two heteroatoms selected from nitrogen and oxygen. In another embodiment, ring A contains two nitrogen atoms. In another embodiment, ring A is a 6 membered monocyclic heterocycloalkylene optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, phenyl, COOH, or COO(C_1-C_6 alkyl), wherein the monocyclic heterocycloalkylene contains two nitrogen atoms.

[0066] In another embodiment, ring A is a 6 to 12 membered bicyclic heterocycloalkylene optionally substituted with up to three substituents selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, halo, C_1-C_6 haloalkyl, phenyl, OH, NH_2, COOH, COO(C_1-C_6 alkyl), and -$CONH_2$. In another embodiment, ring A is a 6 to 11 membered bicyclic heterocycloalkylene optionally substituted with up to three substituents selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, halo, C_1-C_6 haloalkyl, phenyl, OH, NH_2, COOH, COO(C_1-C_6 alkyl), and -$CONH_2$, wherein the bicyclic heterocycloalkylene contains up to three heteroatoms selected from nitrogen and oxygen. In another embodiment, ring A is a 6 to 10 membered bicyclic heterocycloalkylene contains up to three heteroatoms selected from nitrogen and oxygen. In another embodiment, ring A is a 6 to 10 membered fused, spiro, or bridged bicyclic heterocycloalkylene containing up to three heteroatoms selected from nitrogen and oxygen.

[0067] In another embodiment of a compound of formula I or a pharmaceutically acceptable salt thereof, ring A is selected from any of the moieties provided in Table 1:

Table 1





[0068] In another embodiment of a compound of formula I or a pharmaceutically acceptable salt thereof, J is absent.

[0069] In another embodiment of a compound of formula I or a pharmaceutically acceptable salt thereof, J is C_1-C_6 alkylene, heterocycloalkylene, C_1-C_6 alkylene-heterocycloalkylene or C_1-C_6 alkylene-cycloalkylene, any of which may be optionally substituted with up to two substituents independently selected from halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, NH_2, CN, or OH; wherein at each occurrence of C_1-C_6 alkylene, one or two methylene units of the C_1-C_6 alkylene may independently and optionally be replaced with (C=O) or , wherein t is 1, 2, or 3.

[0070] In another embodiment, J is C_1-C_6 alkylene, C_1-C_6 alkylene-heterocycloalkylene or C_1-C_6 alkylene-cycloalkylene, wherein one methylene unit of the C_1-C_6 alkylene may be replaced with (C=O). In another embodiment, J is C_1-C_6 alkylene, wherein one methylene

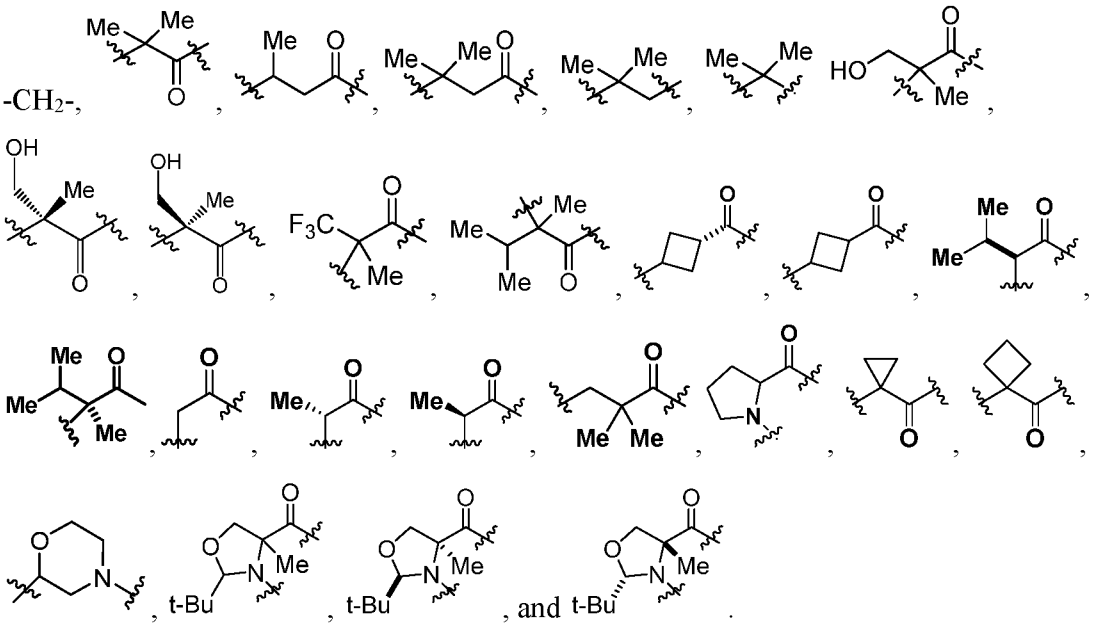
unit of the C_1-C_6 alkylene may be replaced with (C=O). In another embodiment, J is (C=O)-heterocycloalkylene, wherein the heterocycloalkylene is a 5 or 6 membered nitrogen containing heterocycloalkylene optionally substituted with up to two C_1-C_6 alkyl. In another embodiment, J is (C=O)-(C_3-C_6 cycloalkylene).

[0071] In another embodiment, J is C_1-C_6 alkylene optionally substituted with halo, C_1-C_6 haloalkyl, or OH, wherein one methylene unit of the C_1-C_6 alkylene may be replaced with (C=O). In another embodiment, J is C_1-C_6 alkylene, wherein one methylene unit of the C_1-C_6 alkylene may be replaced with (C=O), and another methylene unit of the C_1-C_6 alkylene may be replaced by , wherein t is 1, 2, 3, or 4. In another embodiment, t is 1 or 2.

[0072] In another embodiment, J is a C_1-C_6 alkylene optionally substituted with CF_3 or OH, wherein one methylene unit of the optionally substituted C_1-C_6 alkylene may be replaced with -(C=O)-.

[0073] In another embodiment of a compound of formula I or a pharmaceutically acceptable salt thereof, J is selected from any of the moieties provided in Table 2:

Table 2



[0074] In another embodiment of a compound of formula I or a pharmaceutically acceptable salt thereof, $R_{1'}$ is H or NR_xR_y, wherein R_x and R_y are each independently H, C_1-C_6 alkyl, C_1-C_6 alkyl-SO_3, CO(C_1-C_6 alkyl), or CO-(C_1-C_6 alkylene)-NH_2. In another embodiment, $R_{1'}$ is H, NH_2, NH(C_1-C_6 alkyl), NH(C_1-C_6 alkyl)$_2$, NH-CO(C_1-C_6 alkyl), or NH-CO-(C_1-C_6 alkylene)-NH_2. In another embodiment, $R_{1'}$ is H, NH_2, or NH(C_1-C_6 alkyl). In

another embodiment, $R_{1'}$ is H or NH_2. In another embodiment, $R_{1'}$ is H. In another embodiment, $R_{1'}$ is NH_2.

[0075] $R_{1'}$ is H or NR_xR_y, wherein R_x and R_y are each independently H, C_1-C_6 alkyl, C_1-C_6 alkyl-SO_3, CO(C_1-C_6 alkyl), CO-(C_1-C_6 alkylene)-NH_2, or an amino protecting group.

[0076] In another embodiment of a compound of formula I or a pharmaceutically acceptable salt thereof, Z is (C=O); ring A is a 4 to 7 membered monocyclic heterocycloalkylene optionally substituted with up to two substituents independently selected from the group consisting of halo, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, phenyl, COOH, and COO(C_1-C_6 alkyl), wherein the monocyclic heterocycloalkylene contains up to two heteroatoms selected from nitrogen or oxygen; J is C_1-C_6 alkylene, C_1-C_6 alkylene-heterocycloalkylene or C_1-C_6 alkylene-cycloalkylene, any of which may be optionally substituted with up to two substituents independently selected from halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, NH_2, CN, or OH; wherein at each occurrence of C_1-C_6 alkylene, one or two methylene units of the C_1-C_6 alkylene may independently and optionally be replaced with C=O or , wherein t is 1, 2, or 3; and $R_{1'}$ is H, NH_2, or NH(C_1-C_6 alkyl). In another embodiment, Z is (C=O); ring A is selected from any of the moieties provided in Table 1; J is selected from any of the moieties provided in Table 2; and $R_{1'}$ is H, NH_2, or NH(C_1-C_6 alkyl).

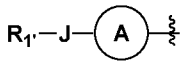
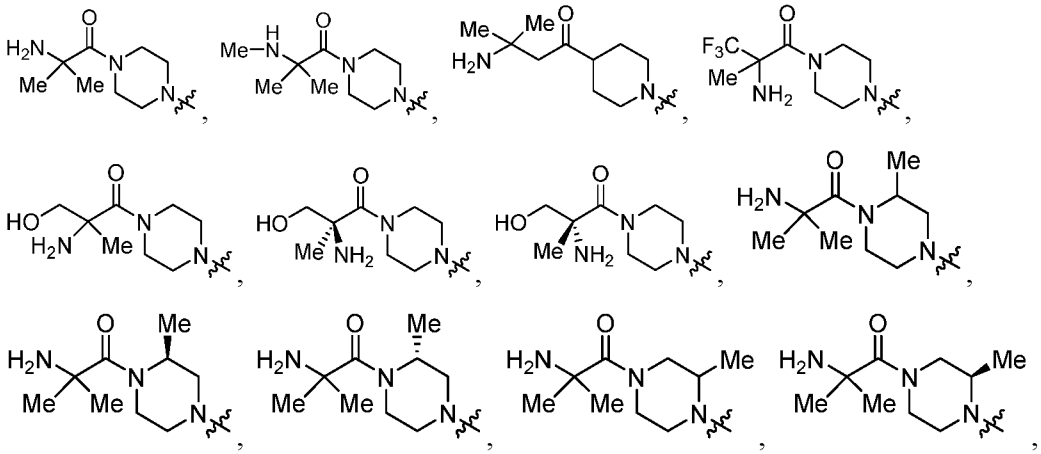
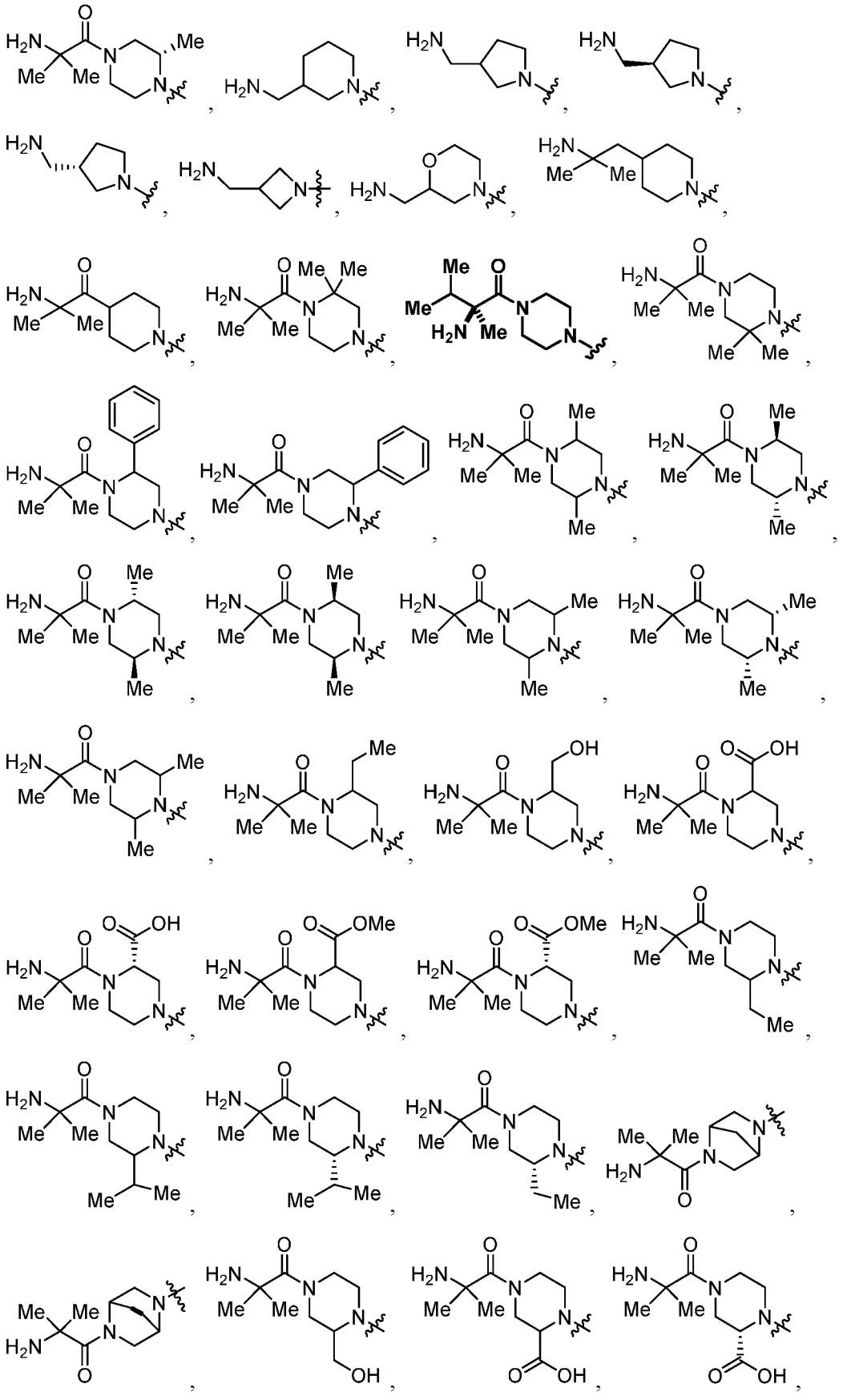
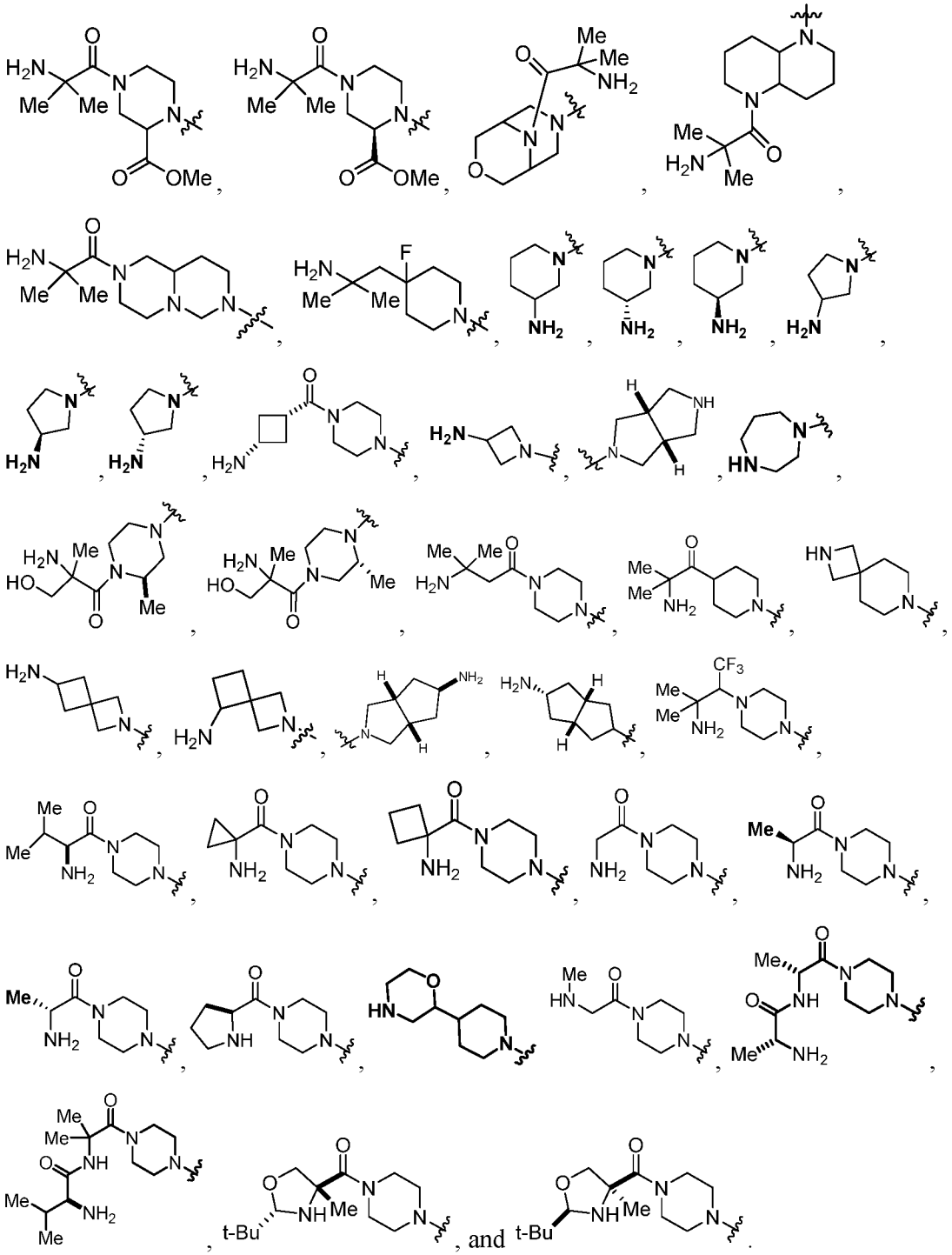
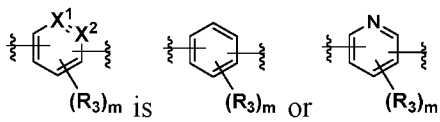
[0077] In another embodiment of a compound of formula I or a pharmaceutically acceptable salt thereof,  is selected from any of the moieties provided in Table 3:

Table 3

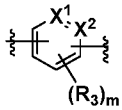
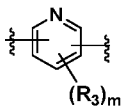


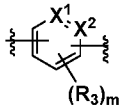
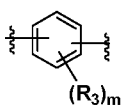


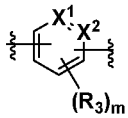
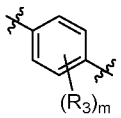
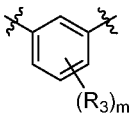


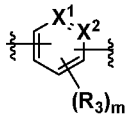
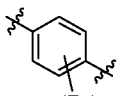
[0078] In another embodiment of a compound of formula I or a pharmaceutically acceptable salt thereof,  is or , wherein each R_3 is independently selected from C_1-C_6 alkyl, halo, CN, OH, NH_2, $NH(C_1$-C_6 alkyl), $O(C_1$-C_6

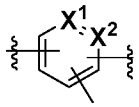
haloalkyl), N(C_1-C_6 alkyl)$_2$, COO(C_1-C_6 alkyl), $CONH_2$, C_1-C_6 haloalkyl, or C_1-C_6 alkoxy, wherein m is 0, 1, 2, or 3. In another embodiment, each R_3 is independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, O(C_1-C_6 haloalkyl), and C_1-C_6 haloalkyl, wherein m is 0, 1 or 2.

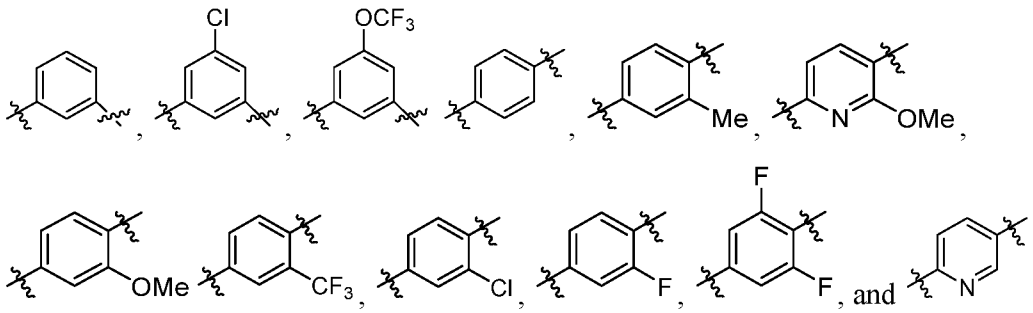
[0079] In another embodiment,  is .

[0080] In another embodiment,  is .

[0081] In another embodiment,  is  or , wherein each R_3 is independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, O(C_1-C_6 haloalkyl), and C_1-C_6 haloalkyl, wherein m is 0, 1 or 2.

[0082] In another embodiment,  is , wherein each R_3 is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, O(C_1-C_6 haloalkyl), and C_1-C_6 haloalkyl, wherein m is 0, 1, or 2.

[0083] In another embodiment,  is selected from the group consisting of



[0084] In one embodiment of a compound of formula I or a pharmaceutically acceptable salt thereof, Y is a linear C_1-C_8 alkylene optionally substituted with OH, NH_2, CN, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, COO(C_1-C_6 alkyl), COOH, $CONH_2$, or C_1-C_6 alkoxy, wherein up to two methylene units of the C_1-C_8 alkylene are optionally and independently replaced by O, NH, N-(C_1-C_6 alkyl), N-(C_1-C_6 hydroxyalkyl), N-(C_1-C_6 haloalkyl), N-(C_{1-6} alkylene-C_{3-8}

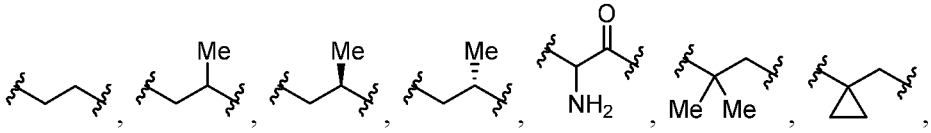
cycloalkyl), N-(C_{3-8} cycloalkyl), NH(C=O), N-(C_{1-6} alkyl) (C=O), (C=O), or , wherein t' is 1 or 2.

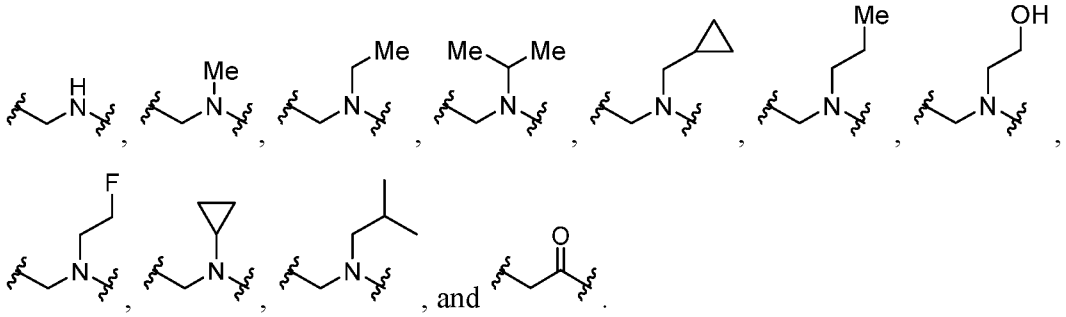
[0085] In another embodiment, Y is a linear C_1-C_6 alkylene optionally substituted with OH, NH_2, CN, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, COO(C_1-C_6 alkyl), COOH, $CONH_2$, or C_1-C_6 alkoxy, wherein up to two methylene units of the C_1-C_8 alkylene are optionally and independently replaced by O, NH, N-(C_1-C_6 alkyl), N-(C_1-C_6 hydroxyalkyl), N-(C_1-C_6 haloalkyl), N-(C_{1-6} alkylene-C_{3-8} cycloalkyl), N-(C_{3-8} cycloalkyl), NH(C=O), N-(C_{1-6} alkyl) (C=O), (C=O), or , wherein t' is 1 or 2.

[0086] In another embodiment, Y is a linear C_1-C_4 alkylene optionally substituted with OH, NH_2, CN, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, COO(C_1-C_6 alkyl), COOH, $CONH_2$, or C_1-C_6 alkoxy, wherein up to two methylene units of the C_1-C_8 alkylene are optionally and independently replaced by O, NH, N-(C_1-C_6 alkyl), N-(C_1-C_6 hydroxyalkyl), N-(C_1-C_6 haloalkyl), N-(C_{1-6} alkylene-C_3 cycloalkyl), N-(C_3 cycloalkyl), NH(C=O), N-(C_{1-6} alkyl) (C=O), (C=O), or , wherein t' is 1 or 2.

[0087] In another embodiment, Y is CR_iR_{ii}, wherein R_i and R_{ii} are each independently H, OH, NH_2, CN, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, COO(C_1-C_6 alkyl), COOH, $CONH_2$, or C_1-C_6 alkoxy. In another embodiment, R_i and R_{ii} are each independently H, C_1-C_6 alkyl, COO(C_1-C_6 alkyl), or COOH. In another embodiment, CR_iR_{ii} is CH_2, CH(C_1-C_6 alkyl), C(C_1-C_6 alkyl)$_2$, CHCOO(C_1-C_6 alkyl) and CHCOOH. In another embodiment, CR_iR_{ii} is CH_2, $CH(CH_3)$, CH(COOEt), or CH(COOH). In another embodiment, CR_iR_{ii} is CH_2.

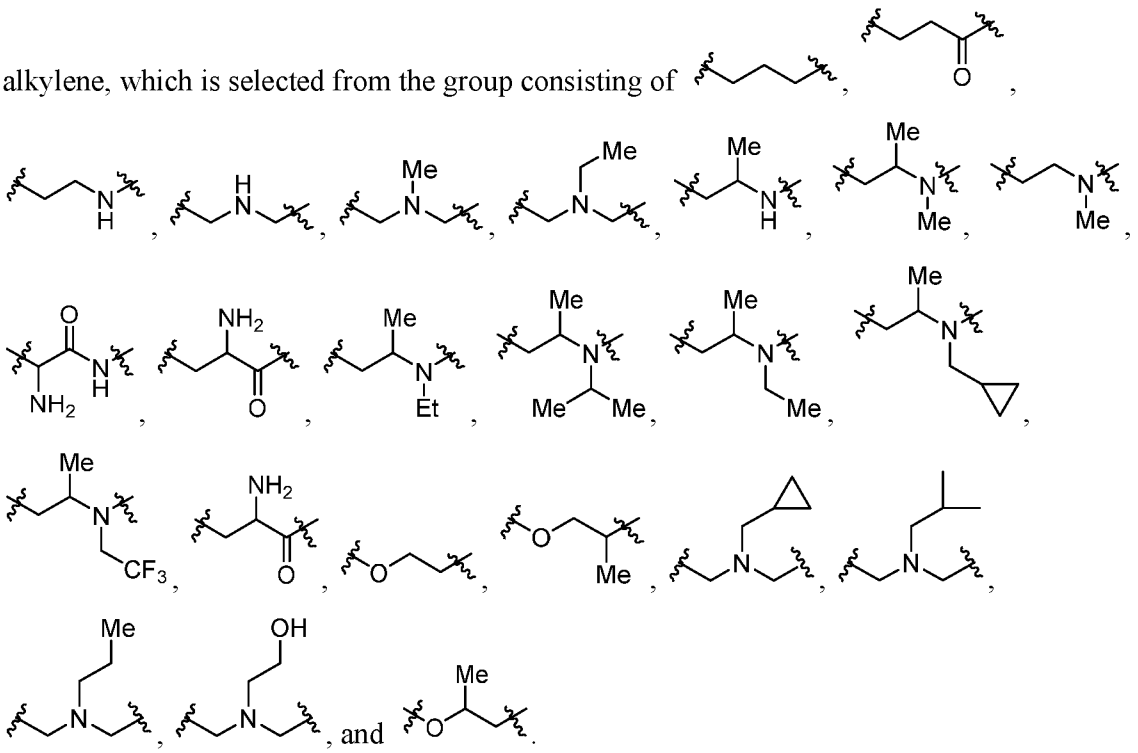
[0088] In another embodiment, Y is -C(R_iR_j)-C($R_{i'}R_{j'}$)-, wherein R_i, R_j, $R_{i'}$, $R_{j'}$ are each independently H or C_1-C_6 alkyl, wherein C(R_iR_j) and C($R_{i'}R_{j'}$) are each independently and optionally replaced with NH, N-(C_{1-6} alkyl), N-(C_1-C_6 hydroxyalkyl), N-(C_1-C_6 haloalkyl), N-(C_{1-6} alkylene-C_{3-8} cycloalkyl), N-(C_{3-8} cycloalkyl), , or (C=O), wherein t' is 1 or 2.

[0089] In another embodiment, Y is C-(R_iR_j)-C($R_{i'}R_{j'}$)-, which is selected from the group consisting of 



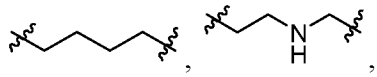
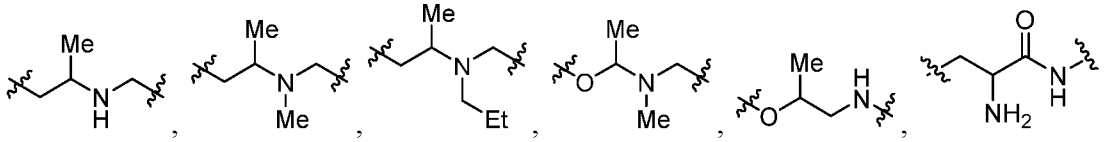
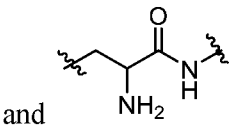
[0090] In another embodiment, Y is a linear C_3 alkylene, C_3 alkenylene, or C_3 alkynylene, any of which are optionally substituted with OH, NH_2, halo, C_1-C_6 alkyl, or C_1-C_6 alkoxy, and wherein one or two carbon atoms of the C_3 alkylene, C_3 alkenylene, or C_3 alkynylene is replaced by O, NH, N-(C_1-C_6 alkyl), N-(C_1-C_6 hydroxyalkyl), N-(C_1-C_6 haloalkyl), N-(C_{1-6} alkylene-C_{3-8} cycloalkyl), NH(C=O)-, N-(C_{1-6} alkyl)(C=O)-, or (C=O). In another embodiment, Y is a linear C_3 alkylene optionally substituted with NH_2 or C_1-C_6 alkyl, wherein up to two one methylene units of the linear C_3 alkylene are optionally and independently replaced by O, NH, N-(C_1-C_6 alkyl), N-(C_1-C_6 hydroxyalkyl), N-(C_1-C_6 haloalkyl), N-(C_{1-6} alkylene-C_{3-8} cycloalkyl), or (C=O).

[0091] In another embodiment, Y is the optionally substituted and replaced linear C_3 alkylene, which is selected from the group consisting of



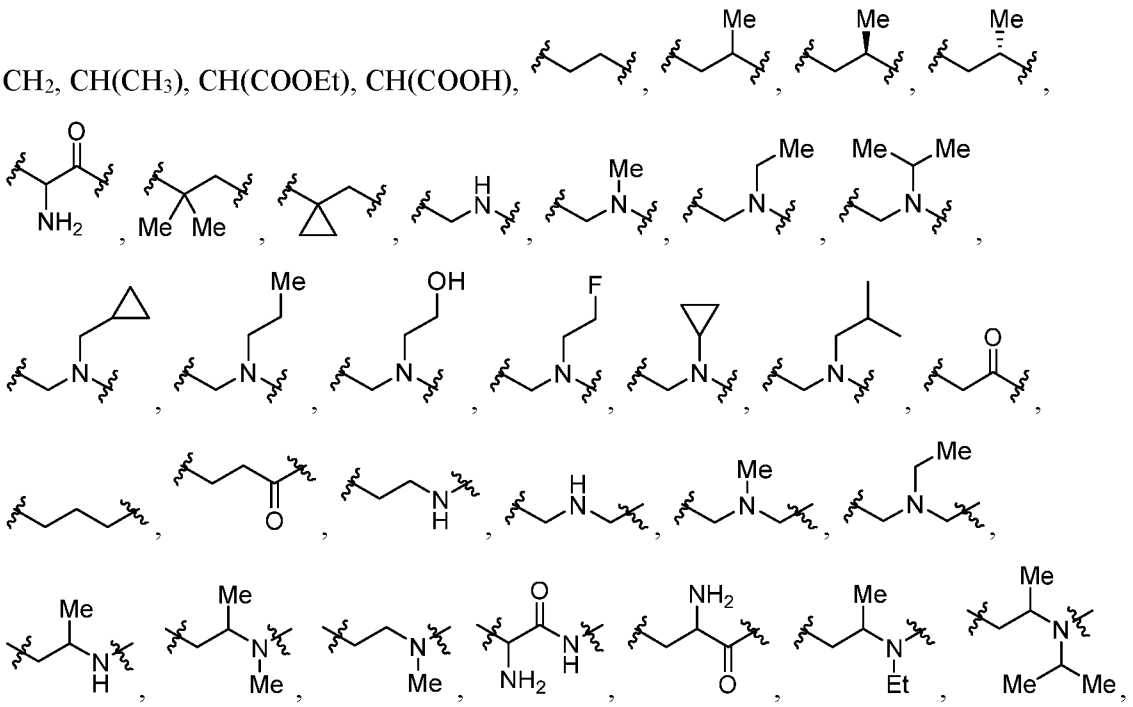
[0092] In another embodiment, Y is a linear C_4 alkylene, C_4 alkenylene, or C_4 alkynylene, any of which are optionally substituted with OH, NH_2, halo, C_1-C_6 alkyl, or C_1-C_6 alkoxy,

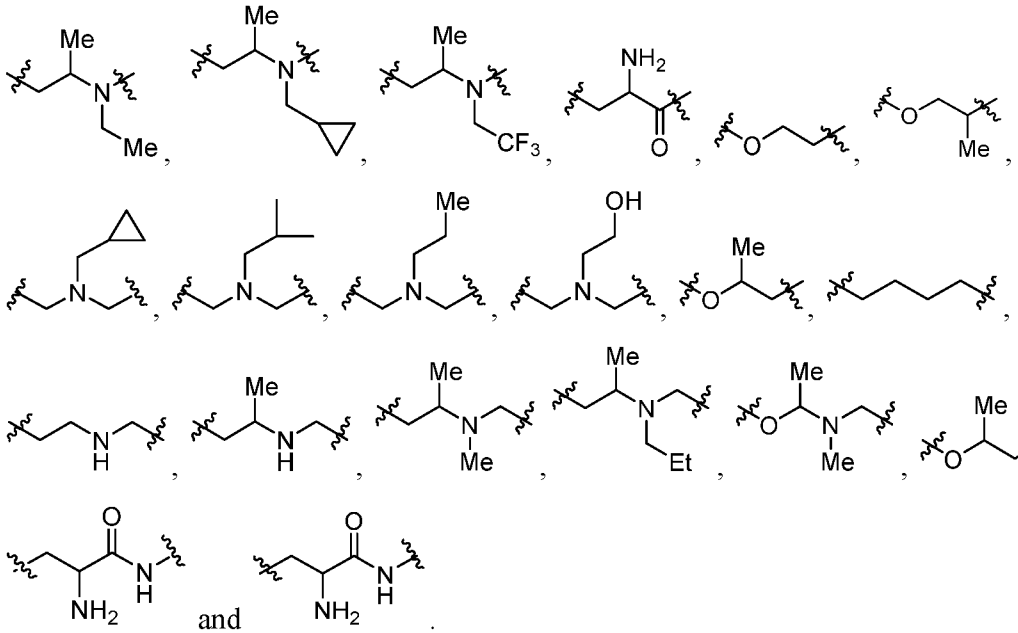
and wherein one or two carbon atoms of the C_4 alkylene, C_4 alkenylene, or C_4 alkynylene is replaced by O, NH, N-(C_1-C_6 alkyl), N-(C_1-C_6 hydroxyalkyl), N-(C_1-C_6 haloalkyl), N-(C_{1-6} alkylene-cycloalkyl), NH(C=O)-, N-(C_{1-6} alkyl)(C=O)-, or (C=O). In another embodiment, Y is a linear C_4 alkylene optionally substituted with NH_2 or C_1-C_6 alkyl, wherein up to two one methylene units of the linear C_3 alkylene are optionally and independently replaced by O, NH, N-(C_1-C_6 alkyl), or (C=O).

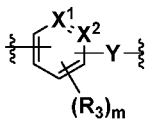
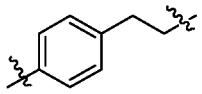
[0093] In another embodiment, Y is the optionally substituted and replaced linear C_4 alkylene, which is selected from the group consisting of , ,  and .

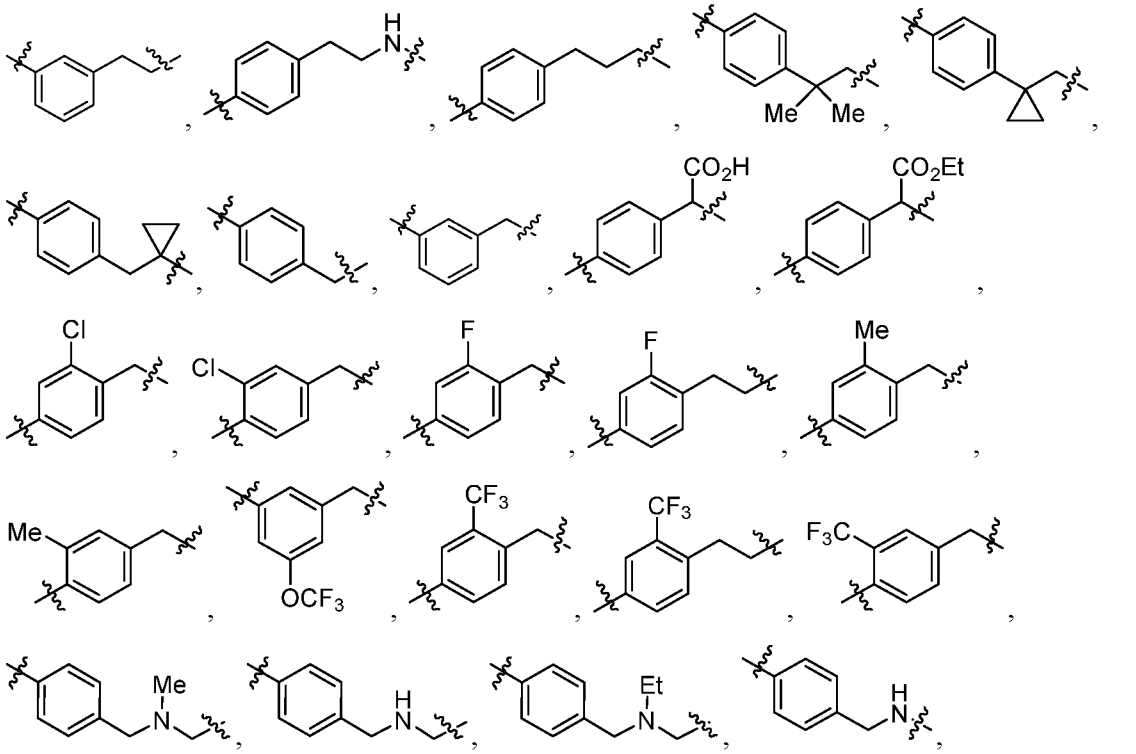
[0094] In another embodiment, Y is selected from any of the moieties provided in Table 4:

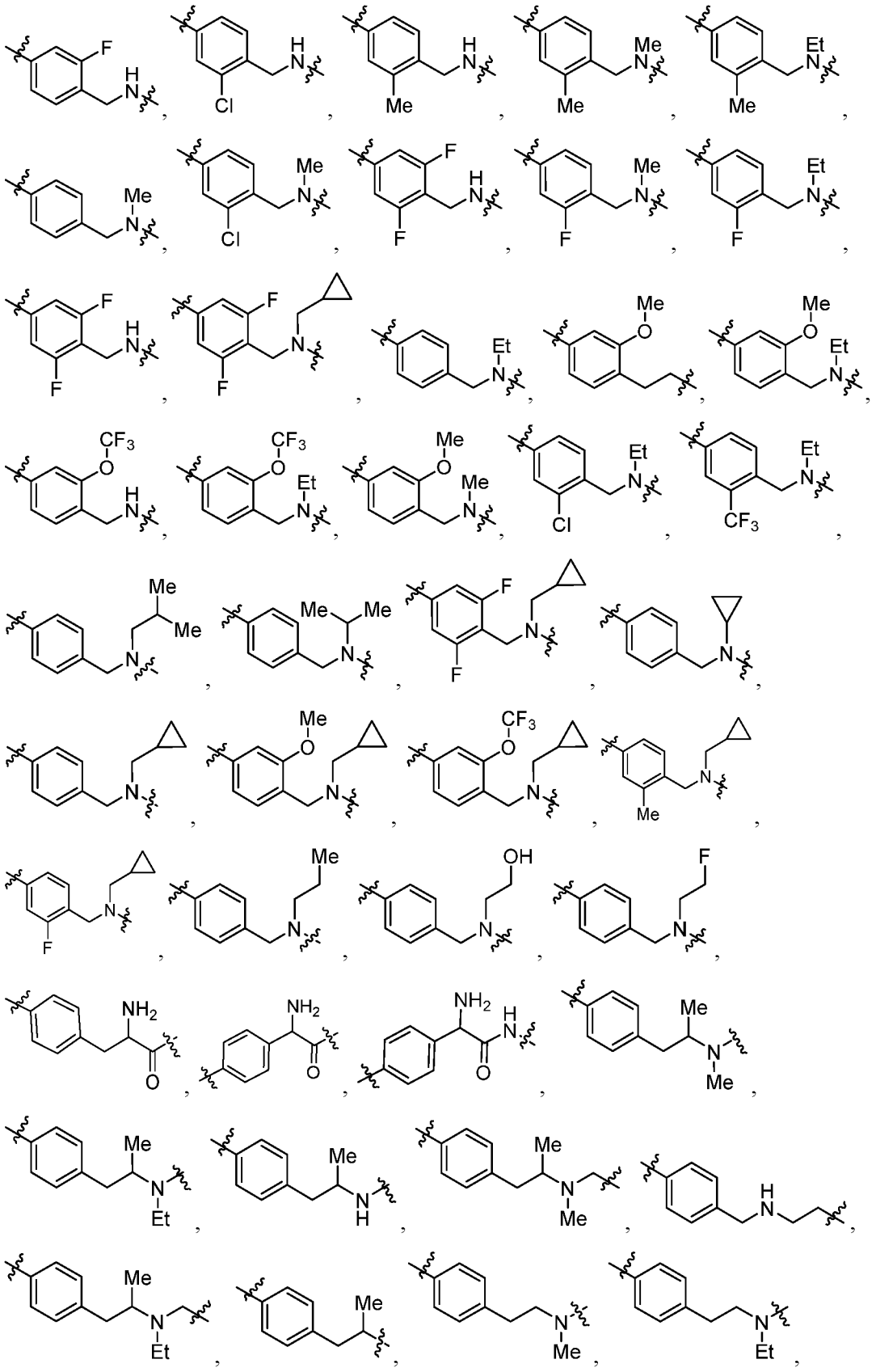
Table 4

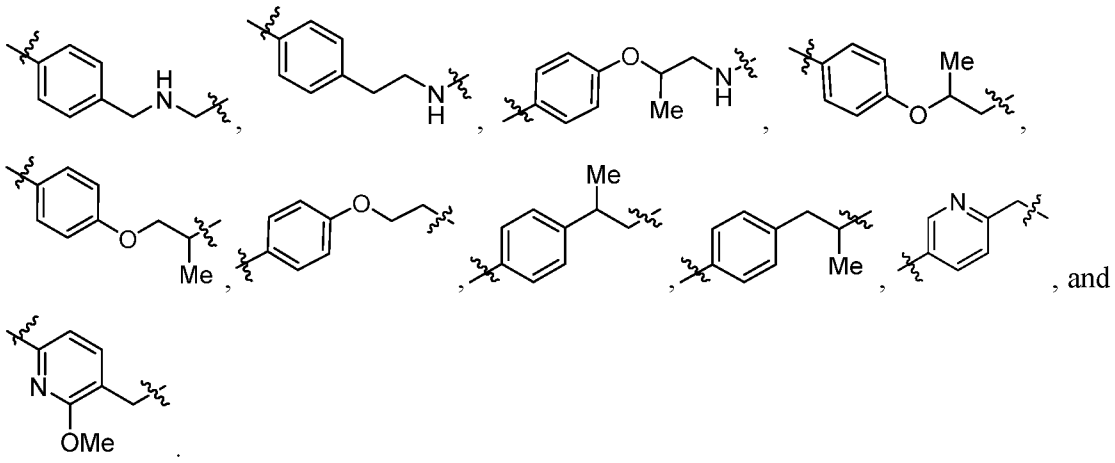
CH_2, $CH(CH_3)$, CH(COOEt), CH(COOH), 



[0095] In another embodiment of a compound of formula I or a pharmaceutically acceptable salt thereof,  is selected from the group consisting of ,







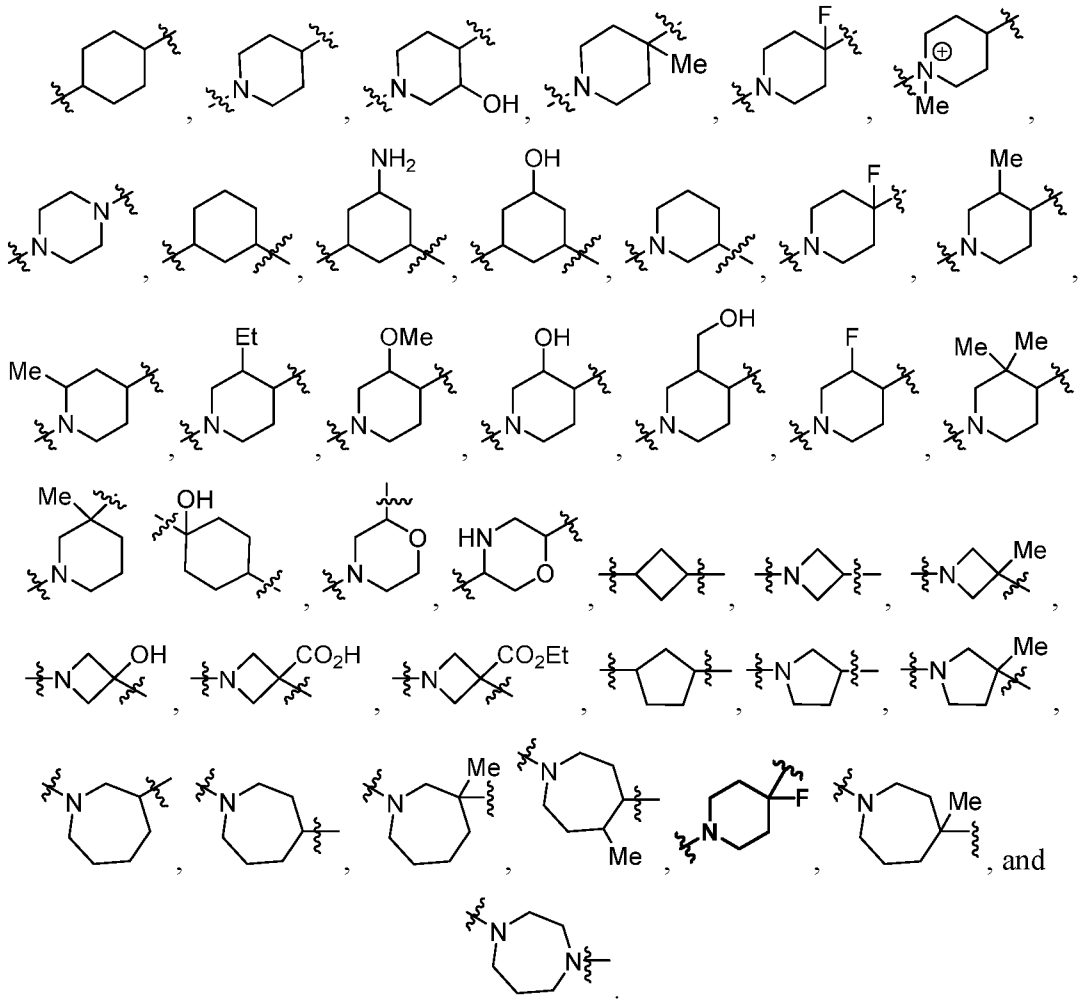
[0096] In another embodiment of a compound of formula I or a pharmaceutically acceptable salt thereof, ring B is a 4-7 membered monocyclic cycloalkylene or 4-7 membered monocyclic heterocycloalkylene, either of which is optionally substituted with up to three substituents selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, NH_2, C_1-C_6 haloalkyl, OH, COO(C_1-C_6 alkyl), COOH, and C_1-C_6 hydroxyalkyl.

[0097] In another embodiment, ring B is a 4-6 membered monocyclic cycloalkylene optionally substituted with up to two substituents selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, NH_2, C_1-C_6 haloalkyl, OH, COO(C_1-C_6 alkyl), COOH, and C_1-C_6 hydroxyalkyl. In another embodiment, ring B is a 4-6 membered monocyclic cycloalkylene.

[0098] In another embodiment, ring B is a 4-7 membered monocyclic heterocycloalkylene optionally substituted with up to two substituents selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, NH_2, C_1-C_6 haloalkyl, OH, COO(C_1-C_6 alkyl), COOH, and C_1-C_6 hydroxyalkyl, wherein the monocyclic heterocycloalkylene contains up to two heteroatoms selected from nitrogen and oxygen. In another embodiment, ring B is a 5 or 6 membered monocyclic heterocycloalkylene optionally substituted with up to two substituents selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, NH_2, C_1-C_6 haloalkyl, OH, COO(C_1-C_6 alkyl), COOH, and C_1-C_6 hydroxyalkyl, wherein the monocyclic heterocycloalkylene contains up to two heteroatoms selected from nitrogen and oxygen.

[0099] In another embodiment, ring B is selected from any of the moieties provided in Table 5:

Table 5

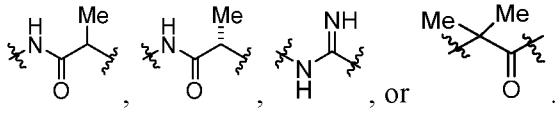


[00100] In another embodiment of a compound of formula I or a pharmaceutically acceptable salt thereof, L is absent.

[00101] In another embodiment of a compound of formula I or a pharmaceutically acceptable salt thereof, L is a linear or branched C_1-C_6 alkylene optionally substituted with C_1-C_6 alkoxy, halo, CN, OH, NH_2, $COO(C_1$-C_6 alkyl), or $CONH_2$, wherein up to two methylene units of the C_1-C_6 alkylene are optionally and independently replaced with O, NH, (C=O), NH(C=O), N-(C_{1-6} alkyl)(C=O), (C=NH), NH(C=N), or N-(C_{1-6} alkyl). In another embodiment, L is a linear or branched C_1-C_6 alkylene, wherein up to two methylene units of the C_1-C_6 alkylene are optionally and independently replaced with O, NH, (C=O), NH(C=O), N-(C_{1-6} alkyl)(C=O), (C=NH), NH(C=N), or N-(C_{1-6} alkyl).

[00102] In another embodiment, L is a linear or branched C_1-C_4 alkylene, wherein up to two methylene units of the C_1-C_4 alkylene are optionally and independently replaced with NH, (C=O), NH(C=O), (C=NH), NH(C=N), or N-(C_{1-6} alkyl). In another embodiment, L is a

linear or branched C_1-C_4 alkylene optionally substituted with OH or NH_2, wherein one methylene unit of the C_1-C_4 alkylene may be replaced with (C=O). In another embodiment, L is C_1-C_4 alkylene.

[00103] In another embodiment, L is absent or is CH_2, CH_2CH_2, $C(Me)_2$, CH(Me), CH(Et), (C=NH), , or .

[00104] In another embodiment, L is absent or is CH_2.

[00105] In another embodiment of a compound of formula I or a pharmaceutically acceptable salt thereof, R_1 is H, halo, C_1-C_6 haloalkyl, $NR_{x'}R_{y'}$, or monocyclic heterocycloalkyl optionally substituted with NH_2, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)$_2$, wherein $R_{x'}$ and $R_{y'}$ are each independently H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, or an amino protecting group. In another embodiment, R_1 is H, NH_2, NH(C_1-C_6 alkyl), NH(C_1-C_6 alkyl)$_2$, NH(C_3-C_6 cycloalkyl), CF_3, or 4 to 6 membered monocyclic heterocycloalkyl optionally substituted with NH_2. In another embodiment, R_1 is H or NH_2. In another embodiment, R_1 is H. In another embodiment, R_1 is NH_2.

[00106] In another embodiment, R_1 is NH(C=O)-(C_1-C_6) alkyl, or NH-(C=NH)-NH_2, either of which may be optionally substituted with up to three substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CN, C_1-C_6 haloalkyl, phenyl, OH, NH_2, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)$_2$, COO(C_1-C_6 alkyl), $CONH_2$, and oxo. In another embodiment, R_1 is NH(C=O)-(C_1-C_6) alkyl, or NH-(C=NH)-NH_2.

[00107] In another embodiment of a compound of formula I or a pharmaceutically acceptable salt thereof, Y is any one of the moieties provided in Table 4; ring B is any one of the moieties provided in Table 5; L is a linear or branched C_1-C_4 alkylene, wherein up to two methylene units of the C_1-C_4 alkylene are optionally and independently replaced with NH, (C=O), NH(C=O), (C=NH), NH(C=N), or N-($C_{1\text{-}6}$ alkyl); and R_1 is H, NH_2, or NH(C_1-C_6 alkyl). In another embodiment, Y is any one of the moieties provided in Table 4; ring B is any one of the moieties provided in Table 5; L is absent or is C_1-C_4 alkylene; and R_1 is H or NH_2.

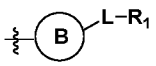
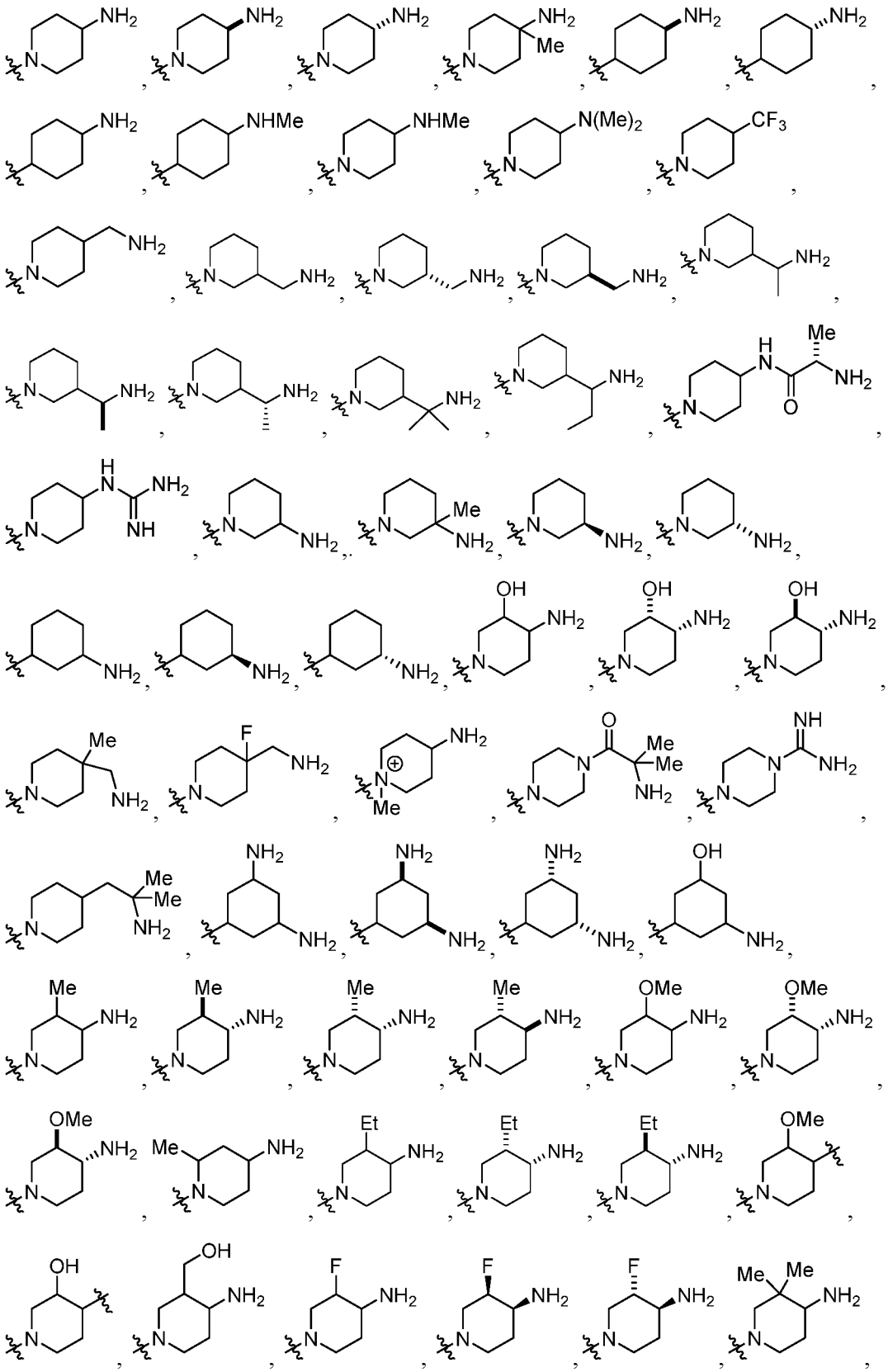
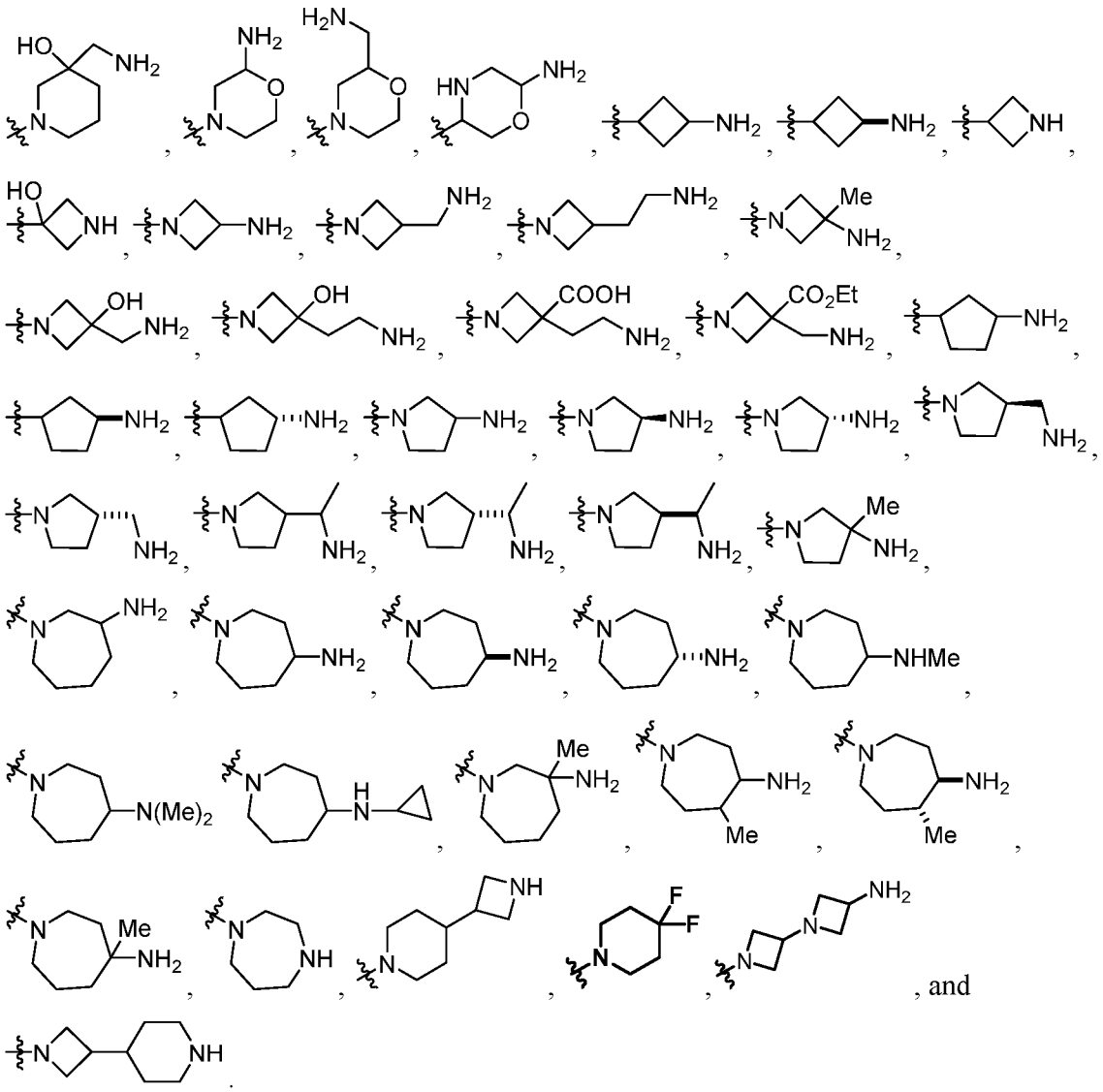
[00108] In another embodiment of a compound of formula I or a pharmaceutically acceptable salt thereof,  is selected from any of moieties provided in Table 6:

Table 6



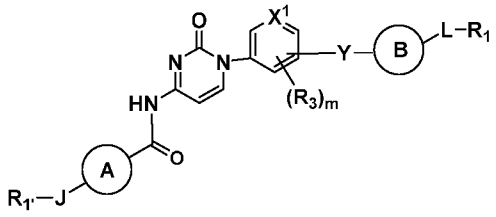


, and

[00109] In another embodiment of a compound of formula I or a pharmaceutically acceptable salt thereof, each R_2 and R_3 is independently selected from the group consisting of C_1-C_6 alkyl, halo, C_1-C_6 haloalkyl, O(C_1-C_6 haloalkyl), and C_1-C_6 alkoxy, and m and n are each independently 0, 1, or 2. In another embodiment, each R_3 is C_1-C_6 alkyl, halo, C_1-C_6 haloalkyl, O(C_1-C_6 haloalkyl), or C_1-C_6 alkoxy, m is 0, 1, or 2.

[00110] In another embodiment of a compound of formula I or a pharmaceutically acceptable salt thereof, n is 0, m is 0, 1 or 2, and each R_3 is independently selected from the group consisting CH_3, Cl, F, OCH_3, OCF_3, and CF_3.

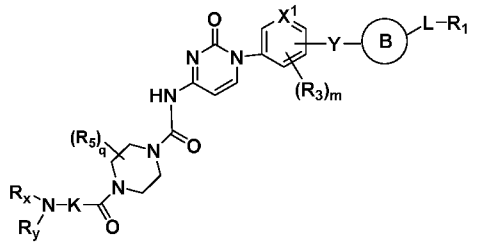
[00111] In another embodiment, the compound of formula I is a compound of formula I-1:



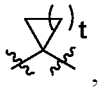
I-1

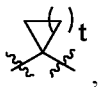
or a pharmaceutically acceptable salt thereof, wherein ring A, ring B, J, L, Y, R_1, $R_{1'}$, R_3, X^1, and m are the same as defined herein.

[00112] In another embodiment, the compound of formula I or I-1 is a compound of formula I-2:

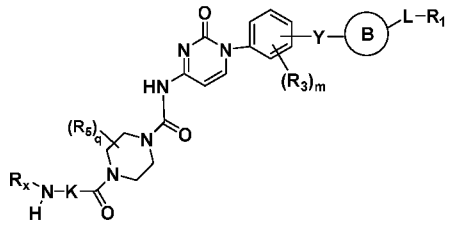


I-2

or a pharmaceutically acceptable salt thereof, wherein ring B, L, Y, R_1, R_3, R_x, R_y, X^1, and m are the same as defined herein; K is C_1-C_5 alkylene, 4 to 7 membered heterocycloalkylene, or 4 to 6 membered cycloalkylene, any of which may be optionally substituted with up to two substituents independently selected from halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, NH_2, CN, or OH, wherein one methylene unit of the C_1-C_5 alkylene is optionally replaced with , wherein t is 1, 2, 3, or 4; each R_5 is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, halo, CN, C_1-C_6 haloalkyl, phenyl, OH, NH_2, $NH(C_1$-C_6 alkyl), $N(C_1$-C_6 alkyl)$_2$, COOH, $COO(C_1$-C_6 alkyl), $CONH_2$, or oxo; R_x and R_y are each independently H, C_1-C_6 alkyl, C_1-C_6 alkyl-SO_3, $CO(C_1$-C_6 alkyl), CO-(C_1-C_6 alkylene)-NH_2; and q is 0, 1, 2, or 3.

[00113] In another embodiment of a compound of formula I-2 or a pharmaceutically acceptable salt thereof, K is C_1-C_5 alkylene optionally substituted with C_1-C_6 haloalkyl, NH_2, or OH, wherein one methylene unit of the C_1-C_5 alkylene is optionally replaced with , wherein t is 1 or 2; each R_5 is independently halo, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, phenyl, COOH, and $COO(C_1$-C_6 alkyl); and q is 0, 1, or 2.

[00114] In another embodiment, the compound of formula I, I-1, or I-2 is a compound of formula I-3:

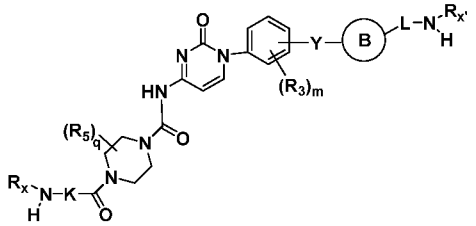


I-3

or a pharmaceutically acceptable salt thereof, wherein ring B, L, Y, K, R_1, R_3, R_5, R_x, q, and m are the same as defined herein.

[00115] In another embodiment of a compound of formula I-3 or a pharmaceutically acceptable salt thereof, K is C_1-C_4 alkylene optionally substituted with halo, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, or OH; each R_5 is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, C_1-C_6 haloalkyl, phenyl, OH, NH_2, COOH, or COO(C_1-C_6 alkyl); and q is 0, 1, or 2.

[00116] In another embodiment, the compound of formula I, I-1, I-2, or I-3 is a compound of formula I-4:

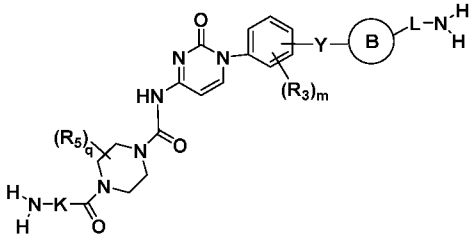


I-4

or a pharmaceutically acceptable salt thereof, wherein ring B, L, Y, K, R_x, $R_{x'}$, R_3, R_5, q, and m are the same as defined herein.

[00117] In another embodiment of a compound of formula I-4 or a pharmaceutically acceptable salt thereof, Y is a linear C_1-C_4 alkylene optionally substituted with C_1-C_6 alkyl, COOH, COO(C_1-C_6 alkyl), or NH_2, and wherein up to two methylene units of the C_1-C_4 alkylene are optionally and independently replaced by (C=O), O, NH, N-(C_1-C_6 alkyl), N-(C_1-C_6 hydroxyalkyl), N-(C_1-C_6 haloalkyl), N-(C_{1-6} alkylene-C_{3-6} cycloalkyl), N-(C_{3-8} cycloalkyl), or , wherein t' is 1 or 2; each R_3 is independently C_1-C_6 alkyl, halo, C_1-C_6 haloalkyl, O(C_1-C_6 haloalkyl), or C_1-C_6 alkoxy; m is 0, 1, or 2; and R_x and $R_{x'}$ are each independently H or C_1-C_6 alkyl.

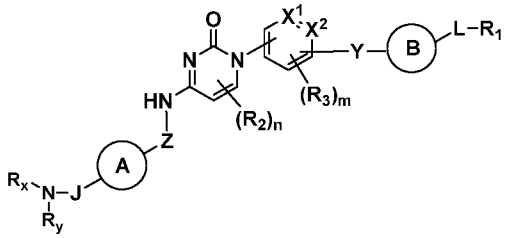
[00118] In another embodiment, the compound of formula I, I-1, I-2, I-3, or I-4 is a compound of formula I-5:



I-5

or a pharmaceutically acceptable salt thereof, wherein ring B, L, Y, K, R_3, R_5, q, and m are the same as defined herein.

[00119] In another aspect, the disclosure provides a compound of Formula II:



II

or a pharmaceutically acceptable salt thereof, wherein:

Z is -(C=O)-;

ring A is a monocyclic heterocycloalkylene or bicyclic heterocycloalkylene, wherein the monocyclic heterocycloalkylene or bicyclic heterocycloalkylene are optionally substituted with up to three substituents selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CN, C_1-C_6 haloalkyl, phenyl, OH, NH_2, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)$_2$, -COO(C_1-C_6 alkyl), -$COONH_2$, and oxo;

J is C_1-C_6 alkylene optionally substituted with halo, hydroxy, or alkoxy, wherein one or two carbons of the C_1-C_6 alkylene may optionally be replaced with O, S, SO_2, or C=O;

R_x and R_y are each independently H, C_1-C_6 alkyl, or a protecting group;

X^1 and X^2 are each independently C-H or N;

Y is a linear C_1-C_8 alkylene, C_2-C_8 alkenylene, or C_2-C_8 alkynylene, any of which are optionally substituted with OH, NH_2, halo, C_1-C_6 alkyl, or C_1-C_6 alkoxy, and wherein up to two carbon atoms of the C_2-C_8 alkylene, C_2-C_8 alkenylene, or C_2-C_8 alkynylene may be independently replaced by O, NH, N-(C_1-C_6 alkyl), N-(C_1-C_6 hydroxyalkyl), N-(C_1-C_6 haloalkyl), N-(C_{1-6} alkylene-cycloalkyl), NH(C=O), N-(C_{1-6} alkyl) (C=O), or (C=O);

ring B is a monocyclic cycloalkylene or moncyclic heterocycloalkylene which is optionally substituted with up to three substituents selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CN, C_1-C_6 haloalkyl, OH, -COO(C_1-C_6 alkyl), -$COONH_2$, and

C_1-C_6 hydroxyalkyl;

L is absent, or is a C_1-C_6 alkylene, wherein up to two carbon atoms of the C_1-C_6 alkylene may be replaced with O, NH, (C=O), NH(C=O), N-(C_{1-6} alkyl)(C=O), (C=NH), NH(C=N), or N-(C_{1-6} alkyl);

R_1 is H, halo, haloalkyl, $NR_{x'}R_{y'}$, wherein $R_{x'}$ and $R_{y'}$ are each independently H, C_1-C_6 alkyl which may be optionally substituted with up to three substituents selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CN, C_1-C_6 haloalkyl, phenyl, OH, NH_2, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)$_2$, -COO(C_1-C_6 alkyl), -$COONH_2$, and oxo, or a or a protecting group; NH(C=O)-(C_1-C_6) alkyl, or NH-(C=N)-NH_2; which may be optionally substituted with up to three substituents selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CN, C_1-C_6 haloalkyl, phenyl, OH, NH_2, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)$_2$, -COO(C_1-C_6 alkyl), -$COONH_2$, and oxo;

R_2 and R_3 are each independently selected from the group consisting of C_1-C_6 alkyl, halo, CN, OH, NH_2, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)$_2$, -COO(C_1-C_6 alkyl), -$COONH_2$, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy; and

m and n are each independently 0, 1, 2, or 3.

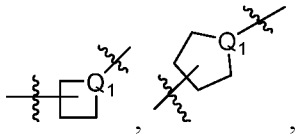
[00120] In another embodiment of a compound of formula I or II or a pharmaceutically acceptable salt thereof, Z is -(C=O)-.

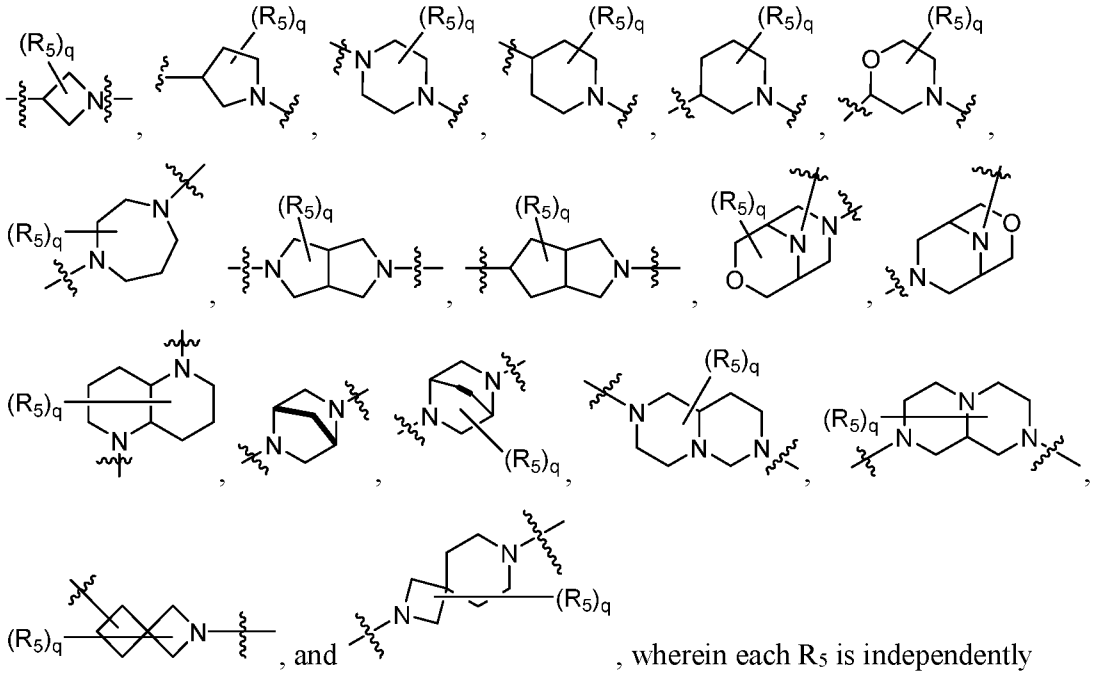
[00121] In another embodiment of a compound of formula I or II or a pharmaceutically acceptable salt thereof, ring A is a monocyclic heterocycloalkylene or bicyclic heterocycloalkyene, wherein the monocyclic heterocycloalkylene and bicyclic heterocycloalkylene are optionally substituted with up to three substituents selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CN, C_1-C_6 haloalkyl, phenyl, OH, NH_2, and oxo.

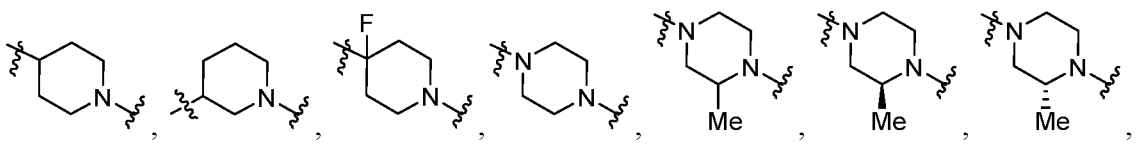
[00122] In another embodiment, ring A is a monocyclic heterocycloalkylene optionally substituted with up to three substituents selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CN, C_1-C_6 haloalkyl, phenyl, OH, NH_2, and oxo.

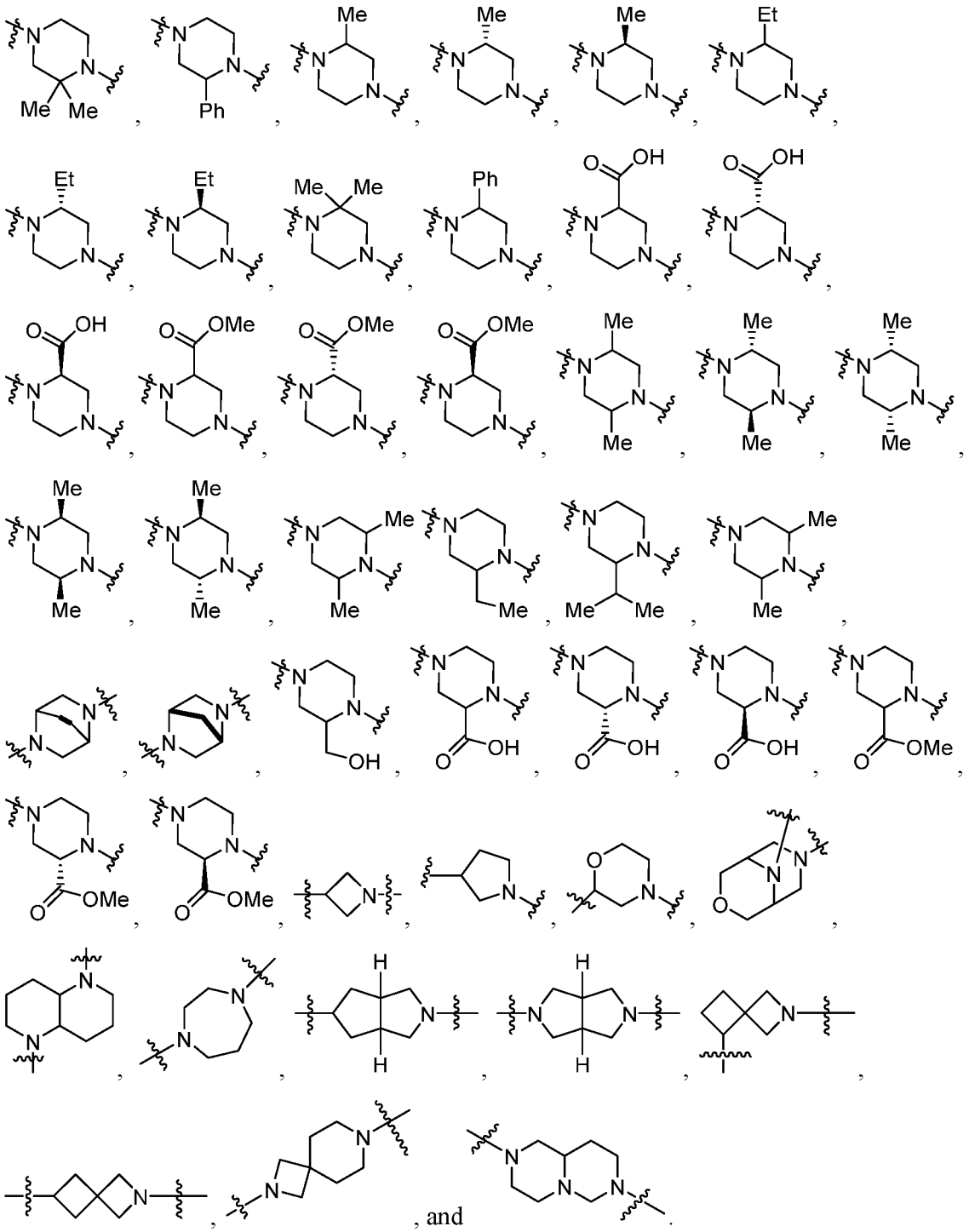
[00123] In another embodiment, ring A is a bicyclic heterocycloalkylene optionally substituted with up to three substituents selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CN, C_1-C_6 haloalkyl, phenyl, OH, NH_2, and oxo.

[00124] In another embodiment, ring A is a monocyclic heterocycloalkylene or bicyclic heterocycloalkyene, wherein the monocyclic heterocycloalkylene and bicyclic

heterocycloalkylene are selected from the group consisting of , wherein Q_1 is N, and Q_2 and Q_3 are each independently selected from the group consisting of C, N, S, or O, and wherein the monocyclic heterocycloalkylene and bicyclic heterocycloalkylene may be optionally substituted with up to three substituents selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CN, C_1-C_6 haloalkyl, phenyl, OH, NH_2, -CO_2H, -CO_2Me, -CO_2Et, and oxo.

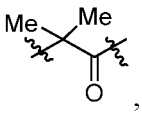
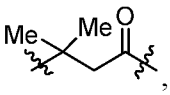
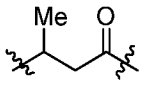
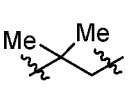
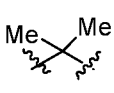
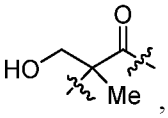
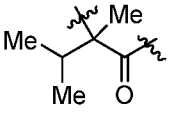
[00125] In another embodiment, ring A is selected from the group consisting of , wherein each R_5 is independently selected from the group consisting of H, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CN, C_1-C_6 haloalkyl, phenyl, OH, NH_2, and oxo, wherein q is 1, 2, or 3.

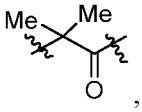
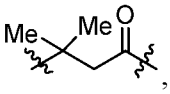
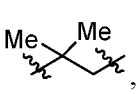
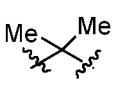
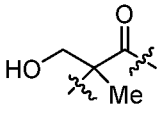
[00126] In another embodiment, ring A is selected from the group consisting of 

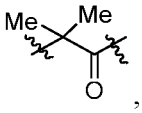
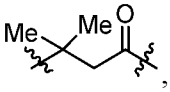
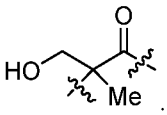


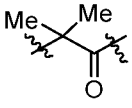
[00127] In another embodiment of a compound of formula I or II or a pharmaceutically acceptable salt thereof, one of the C_1-C_6 alkylene carbons of J is -(C=O)-.

[00128] In another embodiment, J is optionally substituted with -OH.

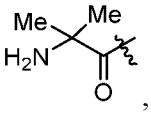
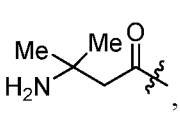
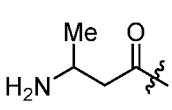
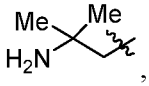
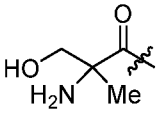
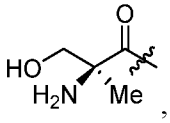
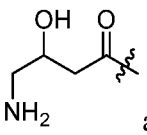
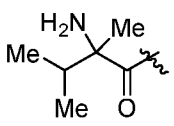
[00129] In another embodiment, J is selected from the group consisting of CH_2, , , , , , , and .

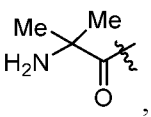
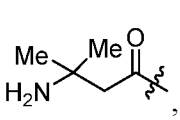
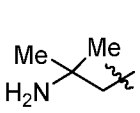
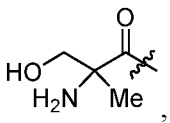
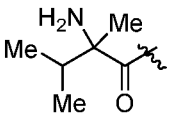
[00130] In another embodiment, J is selected from the group consisting of CH_2, , , , , and .

[00131] In another embodiment, J is selected from the group consisting of CH_2, , , and .

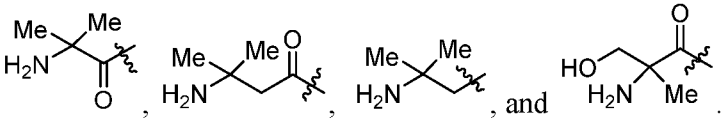
[00132] In another embodiment, J is .

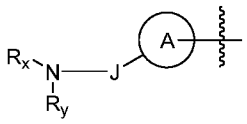
[00133] In another embodiment of a compound of formula I or II or a pharmaceutically acceptable salt thereof, NR_xR_y is selected from the group consisting of NH_2, NHMe, NHEt, NHPG, $N(Me)_2$, and $N(Et)_2$.

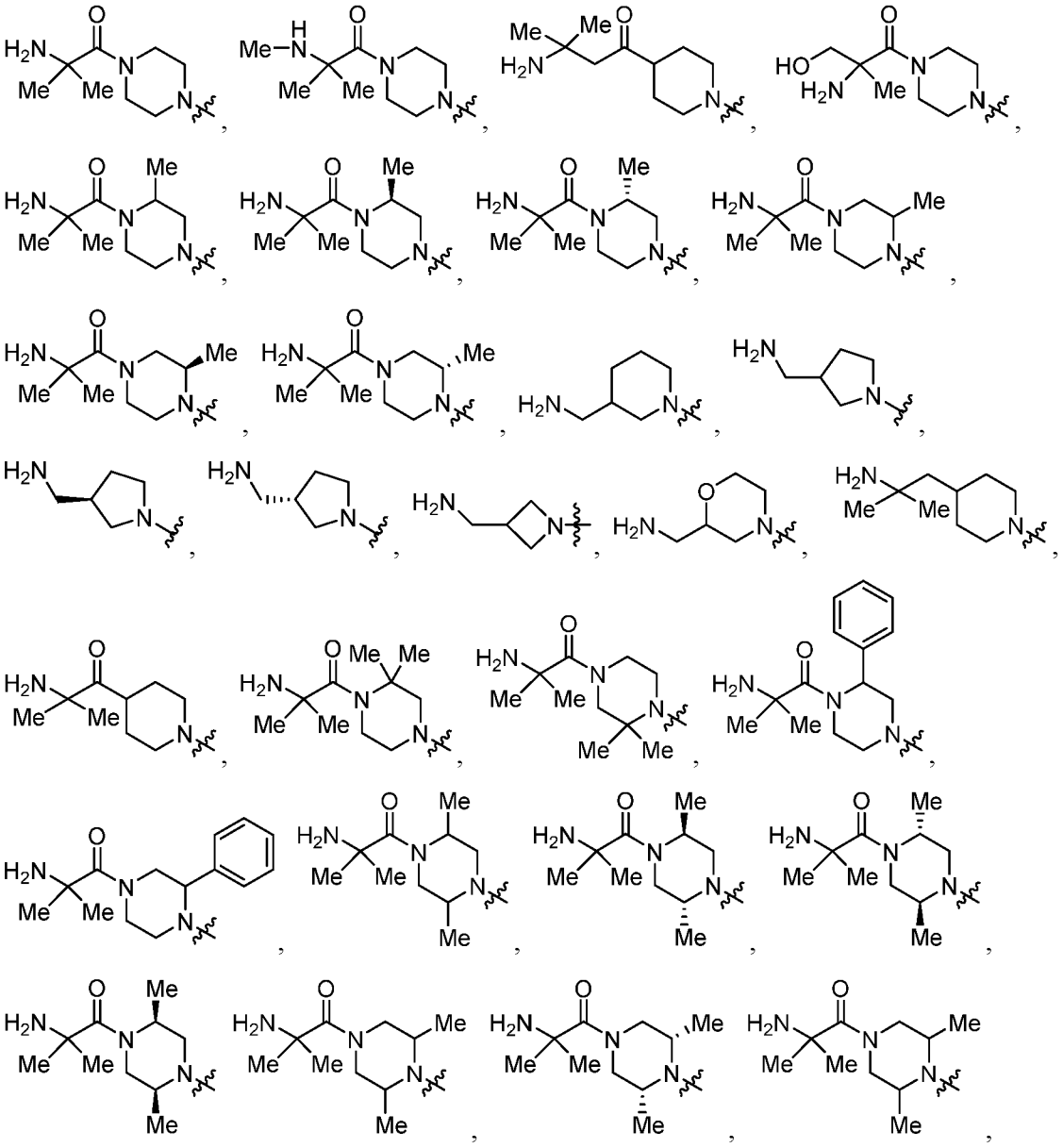
[00134] In another embodiment of a compound of formula I or II or a pharmaceutically acceptable salt thereof, $(R_x\ R_y)NJ$ is selected from the group consisting of H_2N-CH_2-, , , , , , , , and .

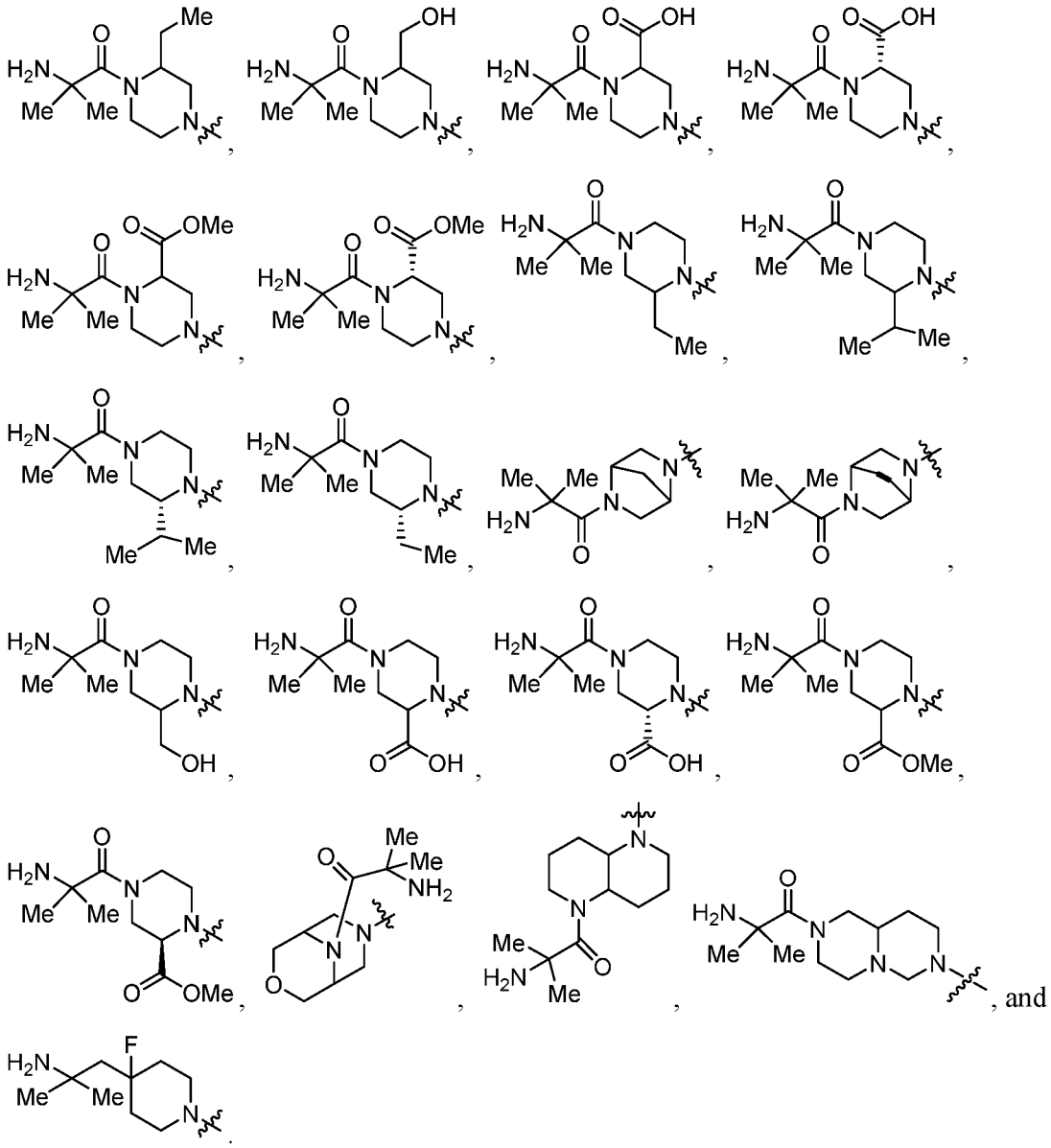
[00135] In another embodiment of a compound of formula I or II or a pharmaceutically acceptable salt thereof, $(R_x\ R_y)NJ$ is selected from the group consisting of H_2N-CH_2-, , , , , and .

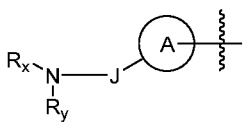
[00136] In another embodiment of a compound of formula I or II or a pharmaceutically acceptable salt thereof, $(R_x\ R_y)NJ$ is selected from the group consisting of $H_2N\text{-}CH_2\text{-}$,

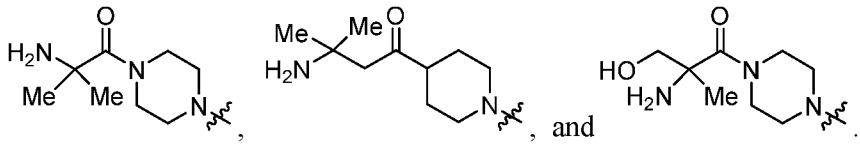


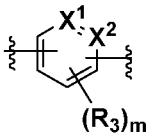
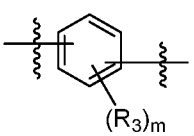
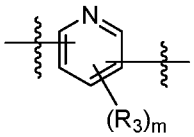
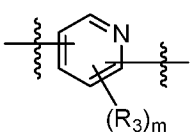
[00137] In another embodiment of a compound of formula I or II or a pharmaceutically acceptable salt thereof,  is selected from the group consisting of

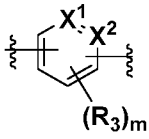
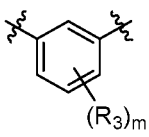


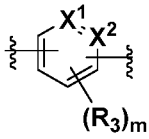
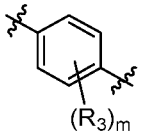


[00138] In another embodiment of a compound of formula I or II or a pharmaceutically acceptable salt thereof,  is selected from the group consisting of



[00139] In another embodiment of a compound of formula I or II or a pharmaceutically acceptable salt thereof,  is , , or , wherein each R_4 is independently selected from the group consisting of C_1-C_6 alkyl, halo, C_1-C_6 haloalkyl, wherein m is 0, 1, or 2.

[00140] In another embodiment,  is .

[00141] In another embodiment,  is , wherein each R_3 is independently selected from the group consisting of C_1-C_6 alkyl, halo, C_1-C_6 haloalkyl, wherein m is 0, 1, or 2.

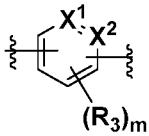
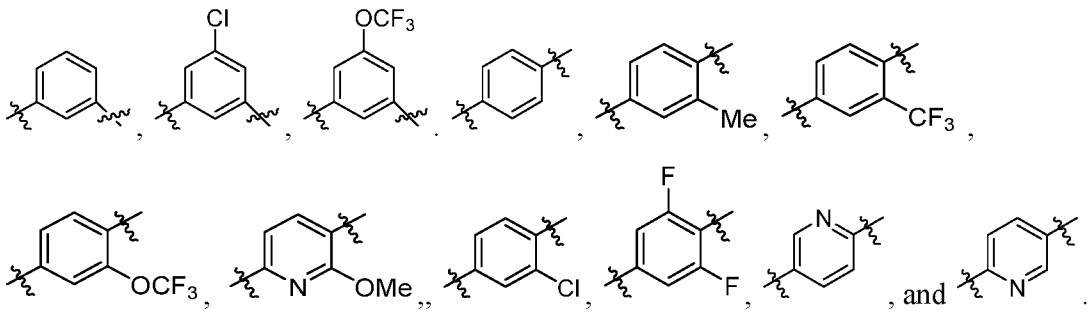
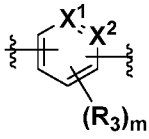
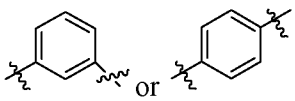
[00142] In another embodiment,  is selected from any of the moieties provided in Table 7:

Table 7



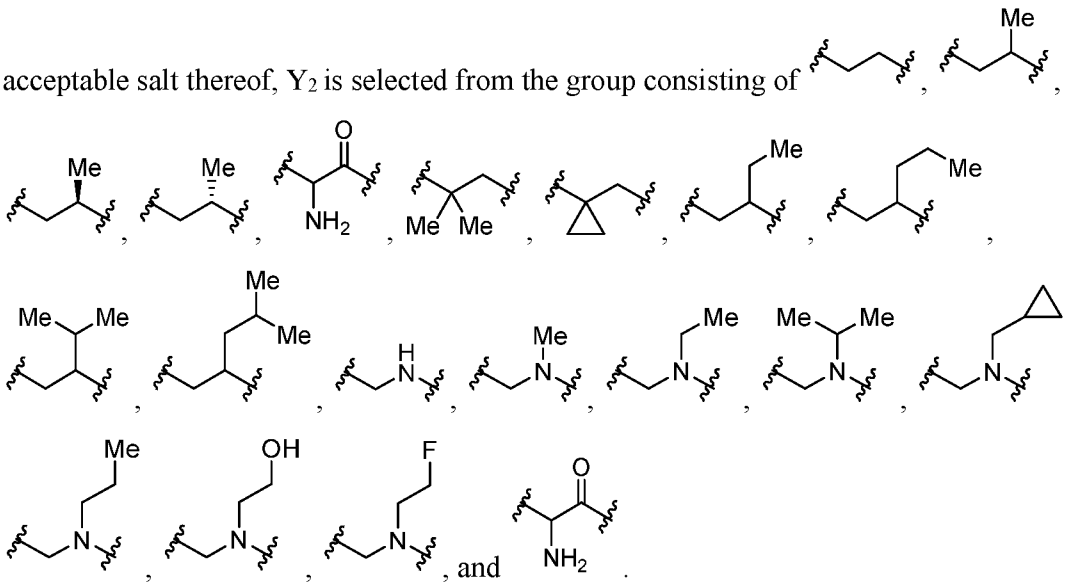
[00143] In another embodiment,  is .

[00144] In another embodiment of a compound of formula I or II or a pharmaceutically acceptable salt thereof, Y is Y_1 and Y_1 is -$C(R_iR_j)$-, wherein R_i, and $R_{i'}$ are each independently H or C_1-C_6 alkyl which may be optionally substituted with halo, or hydroxy, wherein $C(R_iR_j)$ or $C(R_{i'}R_{j'})$ may be replaced with NH, N-($C_{1\text{-}6}$ alkyl), or (C=O).

[00145] In another embodiment of a compound of formula I or II or a pharmaceutically acceptable salt thereof, Y is Y_1, and Y_1 is CR_iR_{ii}, which is selected from the group consisting of CH_2, $CH(C_1\text{-}C_6$ alkyl), $C(C_1\text{-}C_6$ alkyl)$_2$, CH-$COO(C_1\text{-}C_6$ alkyl) and CHCOOH.

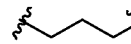
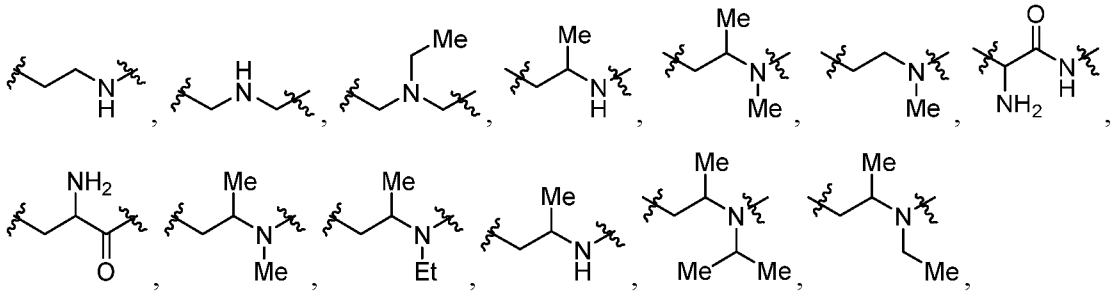
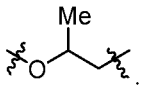
[00146] In another embodiment of a compound of formula I or II or a pharmaceutically acceptable salt thereof Y_1 is selected from the group consisting of CH_2, $CH(CH_3)$, CH(COOEt) and CH(COOH).

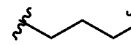
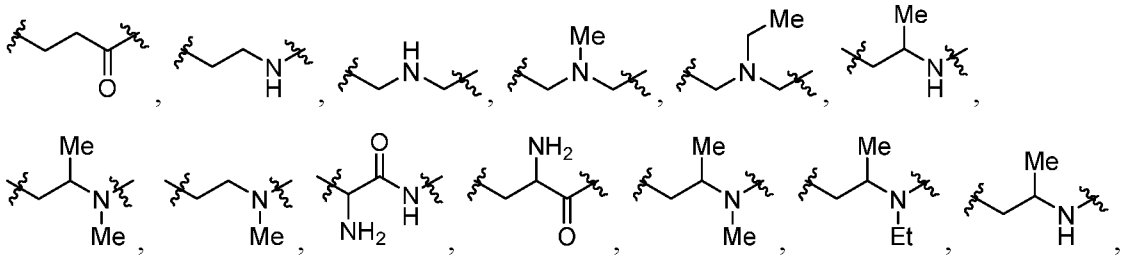
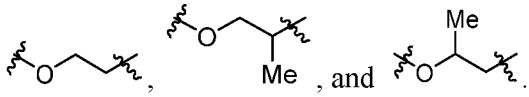
[00147] In another embodiment of a compound of formula I or II or a pharmaceutically acceptable salt thereof, Y is Y_2, and Y_2 is $-C(R_iR_j)-C(R_{i'}R_{j'})-$, wherein R_i, R_j, $R_{i'}$, $R_{j'}$ are each independently H or $C_1\text{-}C_6$ alkyl optionally substituted with OH or halo, and wherein $C(R_iR_j)$ or $C(R_{i'}R_{j'})$ may be replaced with NH, N-($C_{1\text{-}6}$ alkyl), or (C=O).

[00148] In another embodiment of a compound of formula I or II or a pharmaceutically acceptable salt thereof, Y_2 is selected from the group consisting of , and .

[00149] In another embodiment, Y is Y_3, and Y_3 is a linear C_3 alkylene, C_3 alkenylene, or C_3 alkynylene, any of which are optionally substituted with OH, NH_2, halo, $C_1\text{-}C_6$ alkyl, or $C_1\text{-}C_6$ alkoxy, and wherein one or two carbon atoms of the C_3 alkylene, C_3 alkenylene, or C_3 alkynylene is replaced by O, NH, N-($C_1\text{-}C_6$ alkyl), N-($C_1\text{-}C_6$ hydroxyalkyl), N-($C_1\text{-}C_6$ haloalkyl), N-($C_{1\text{-}6}$ alkylene-cycloalkyl), -NH(C=O)-, -N-($C_{1\text{-}6}$ alkyl)(C=O)-, -O(C=O)-, or -(C=O).

[00150] In another embodiment, Y_3 is C_3 alkylene, or C_3 alkenylene, either of which is optionally substituted with OH, NH_2, halo, $C_1\text{-}C_6$ alkyl, or $C_1\text{-}C_6$ alkoxy, and wherein one or two carbon atoms of the C_3 alkylene, C_3 alkenylene, is replaced by O, NH, N-($C_1\text{-}C_6$ alkyl), N-($C_1\text{-}C_6$ hydroxyalkyl), N-($C_1\text{-}C_6$ haloalkyl), N-($C_{1\text{-}6}$ alkylene-cycloalkyl), -NH(C=O)-, -N-($C_{1\text{-}6}$ alkyl)(C=O)-, -O(C=O)-, or -(C=O)-.

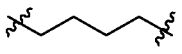
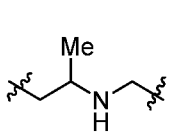
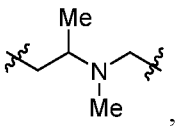
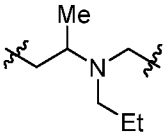
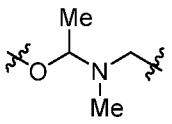
[00151] In another embodiment, Y_3 is selected from the group consisting of , , and .

[00152] In another embodiment, Y_3 is selected from the group consisting of , , , and .

[00153] In another embodiment, Y is Y_4, and Y_4 is a linear C_4 alkylene, C_4 alkenylene, or C_4 alkynylene, any of which are optionally substituted with OH, NH_2, halo, C_1-C_6 alkyl, or C_1-C_6 alkoxy, and wherein one or two carbon atoms of the C_4 alkylene, C_4 alkenylene, or C_4 alkynylene is replaced by O, NH, N-(C_1-C_6 alkyl), N-(C_1-C_6 hydroxyalkyl), N-(C_1-C_6 haloalkyl), N-(C_{1-6} alkylene-cycloalkyl), -NH(C=O)-, -N-(C_{1-6} alkyl)(C=O)-, -O(C=O)-, or -(C=O)-.

[00154] In another embodiment, Y_4 is C_4 alkylene, or C_4 alkenylene, either of which is optionally substituted with OH, NH_2, halo, C_1-C_6 alkyl, or C_1-C_6 alkoxy, and wherein one or

two carbon atoms of the C_3-C_8 alkylene, C_3-C_8 alkenylene is replaced by O, NH, N-(C_1-C_6 alkyl), N-(C_1-C_6 hydroxyalkyl), N-(C_1-C_6 haloalkyl), N-(C_{1-6} alkylene-cycloalkyl), -NH(C=O)-, -N-(C_{1-6} alkyl)(C=O)-, -O(C=O)-, or -(C=O)-.

[00155] In another embodiment, Y_4 is selected from the group consisting of , , , , and .

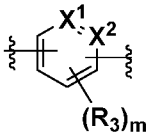
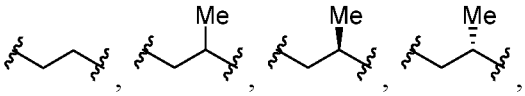
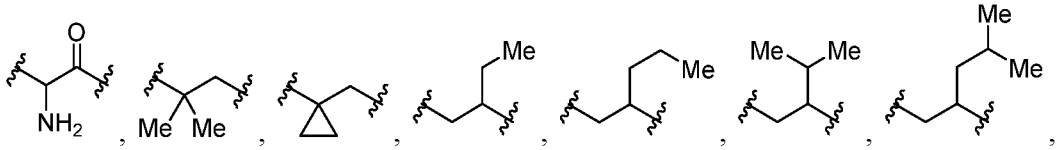
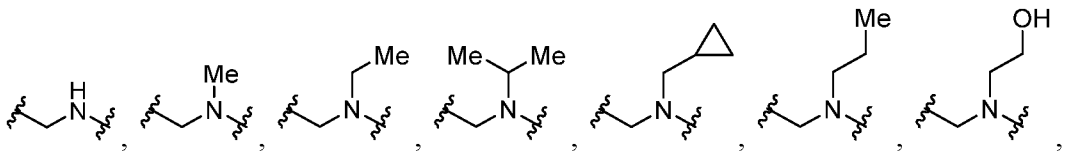
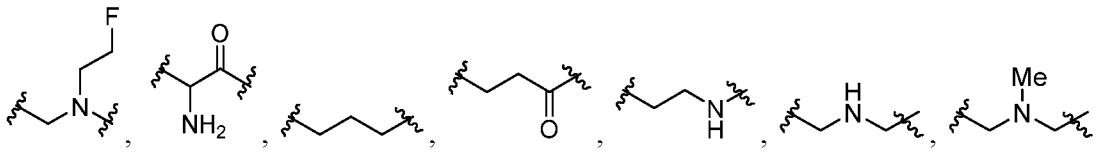
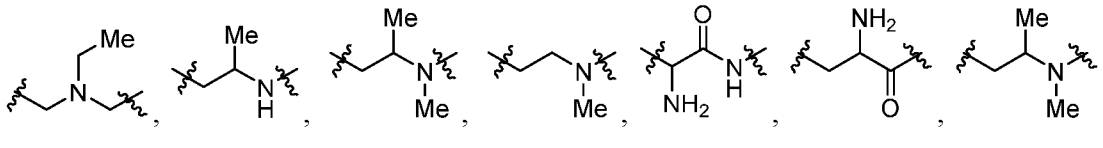
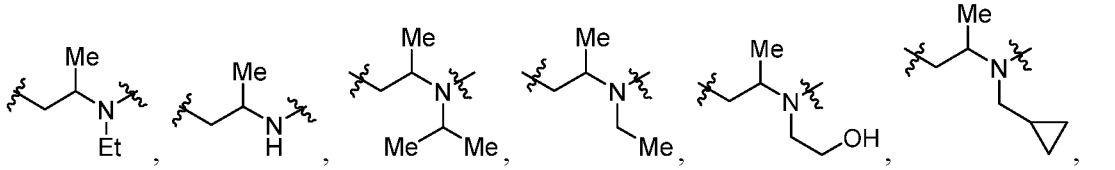
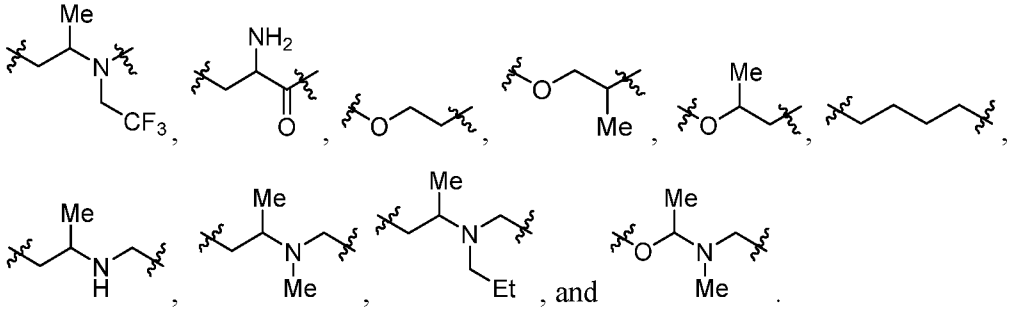
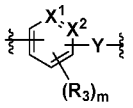
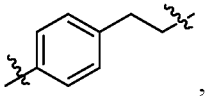
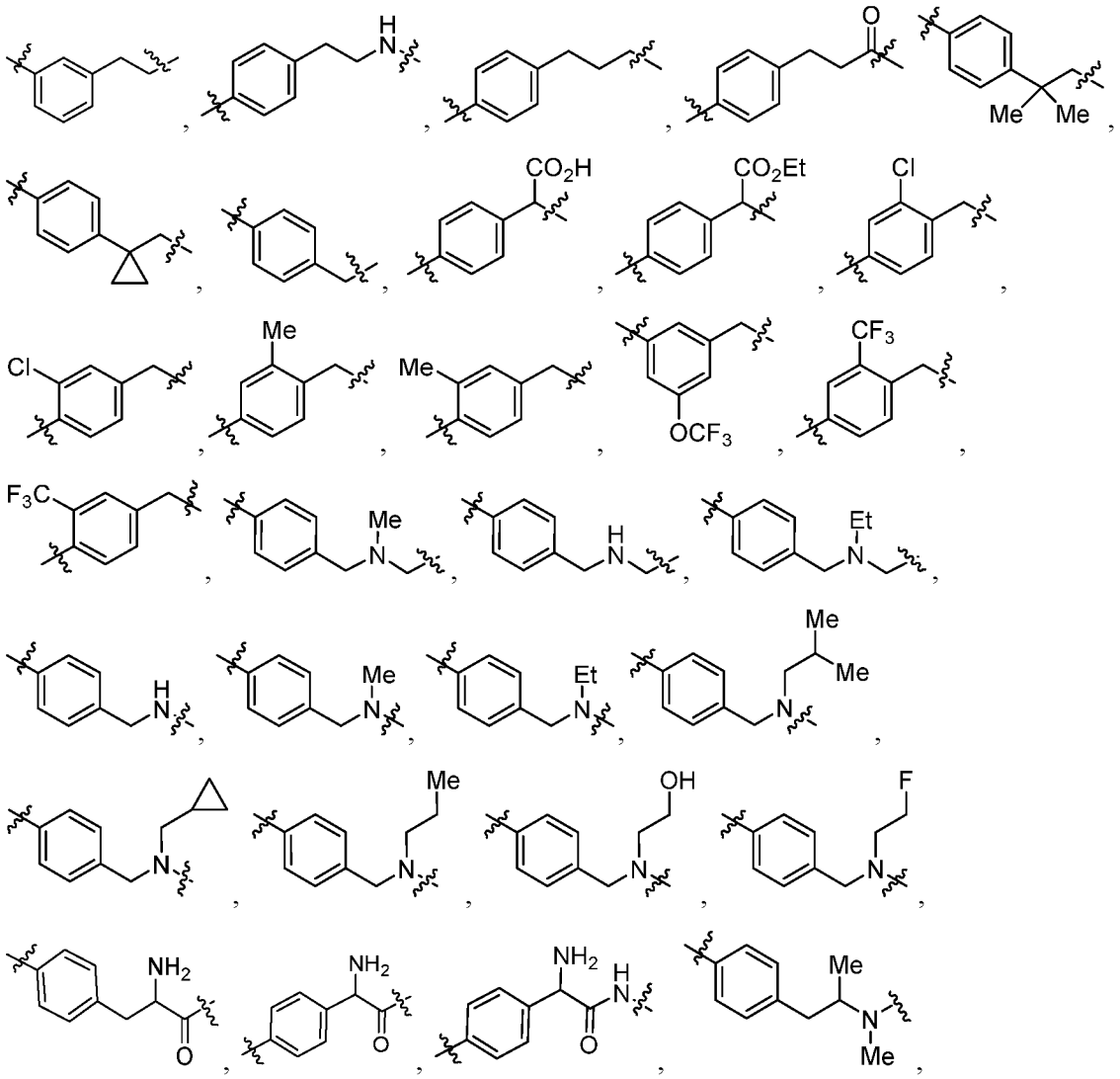
[00156] In another embodiment of a compound of formula I or II or a pharmaceutically acceptable salt thereof,  is selected from any of the moieties provided in Table 7; and Y is selected from any of the moieties provided in Table 8:

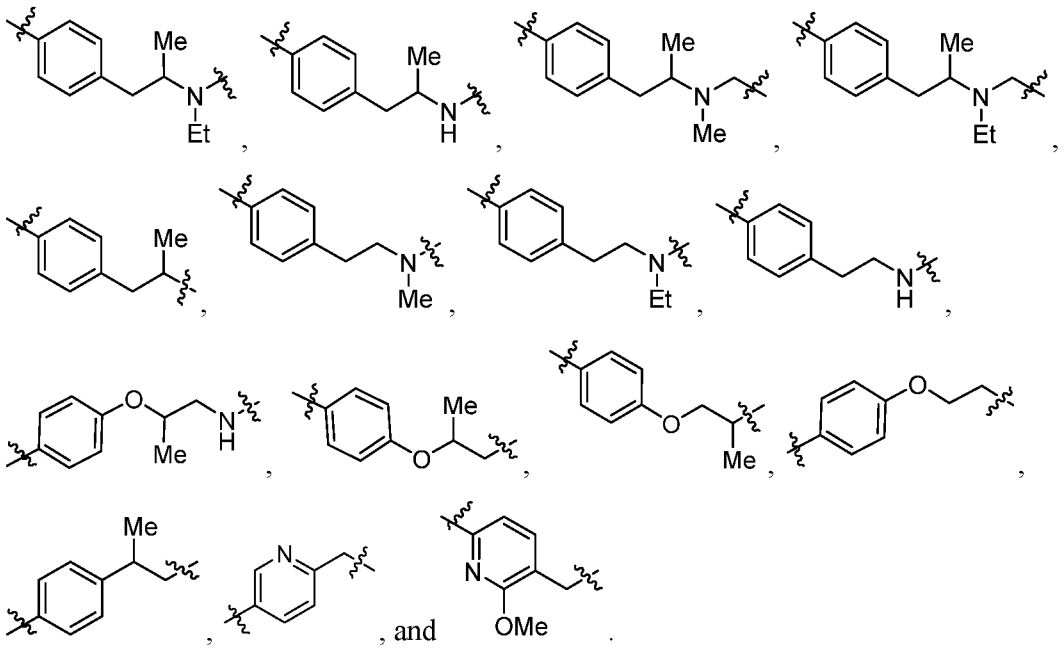
Table 8

CH_2, $CH(CH_3)$, CH(COOEt), CH(COOH), , , , , , 

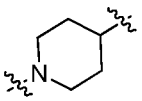


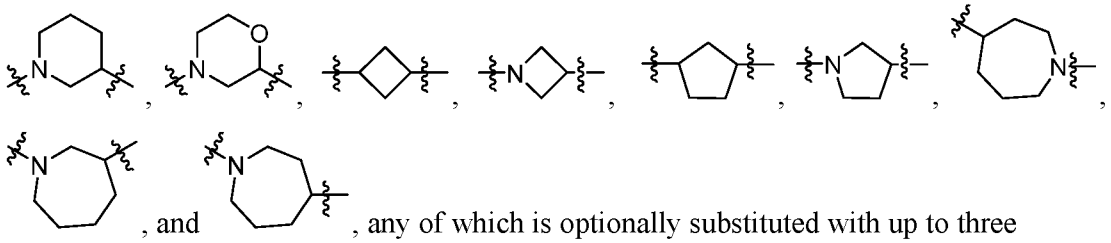
[00157] In another embodiment of a compound of formula I or II or a pharmaceutically acceptable salt thereof,  is selected from the group consisting of ,





[00158] In another embodiment of a compound of formula I or II or a pharmaceutically acceptable salt thereof, ring B is a 4-7 membered monocyclic cycloalkylene or 4-7 membered monocyclic heterocycloalkylene, either of which is optionally substituted with up to three substituents selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CN, C_1-C_6 haloalkyl, OH, -COO(C_1-C_6 alkyl), -$COONH_2$, and C_1-C_6 hydroxyalkyl.

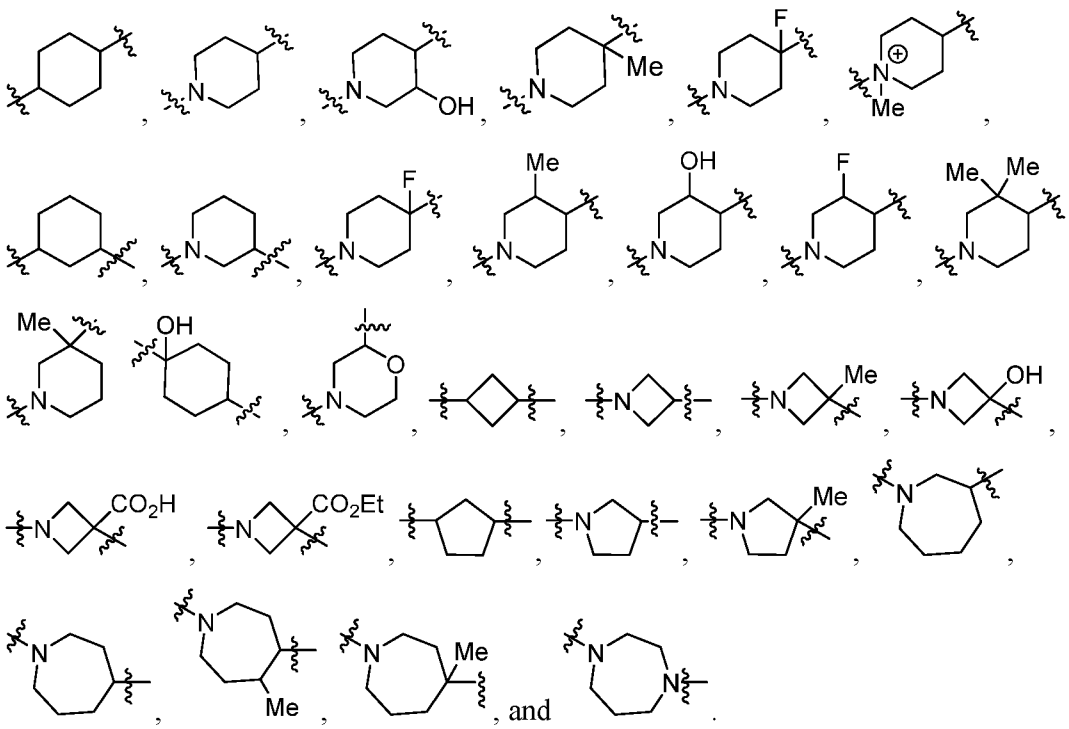
[00159] In another embodiment of a compound of formula I or II or a pharmaceutically acceptable salt thereof, ring B is selected from the group consisting of ,



, and , any of which is optionally substituted with up to three substituents selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CN, C_1-C_6 haloalkyl, OH, -COO(C_1-C_6 alkyl), -$COONH_2$, and C_1-C_6 hydroxyalkyl.

[00160] In another embodiment of a compound of formula I or II or a pharmaceutically acceptable salt thereof, ring B is selected from any of the moieties provided in Table 9:

Table9



[00161] In another embodiment of a compound of formula I or II or a pharmaceutically acceptable salt thereof, L is absent.

[00162] In another embodiment, L is a linear or branched C_1-C_6 alkylene, wherein up to two carbon atoms of the C_1-C_6 alkylene may be replaced with O, NH, (C=O), NH(C=O), N-(C_{1-6} alkyl)(C=O), (C=NH), NH(C=N), or N-(C_{1-6} alkyl)

[00163] In another embodiment, L is -CH_2-.

[00164] In another embodiment, L is –CH(Me)-.

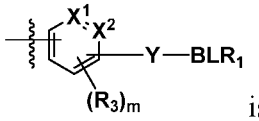
[00165] In another embodiment, L is –CH(Et)-.

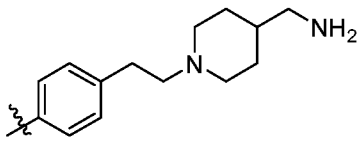
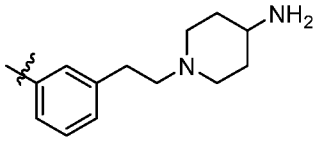
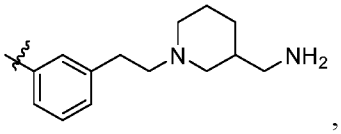
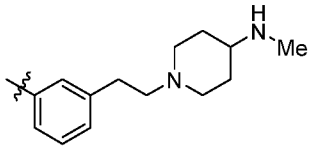
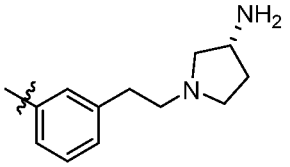
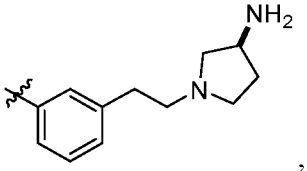
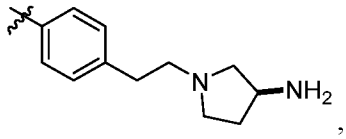
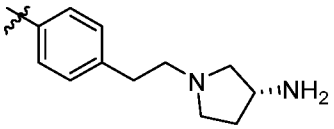
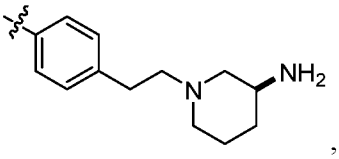
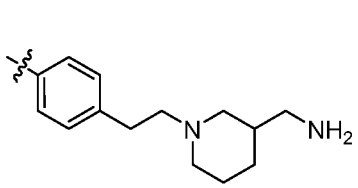
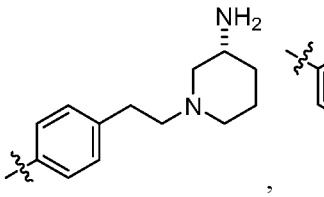
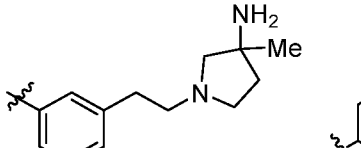
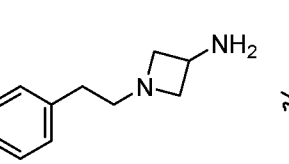
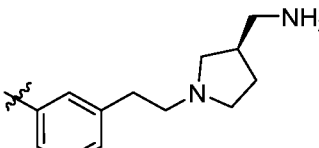
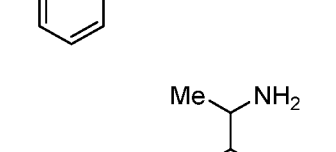
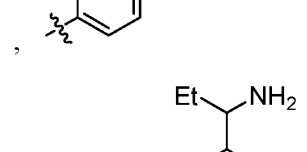
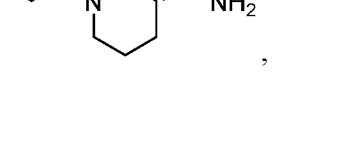
[00166] In another embodiment, L is C=O.

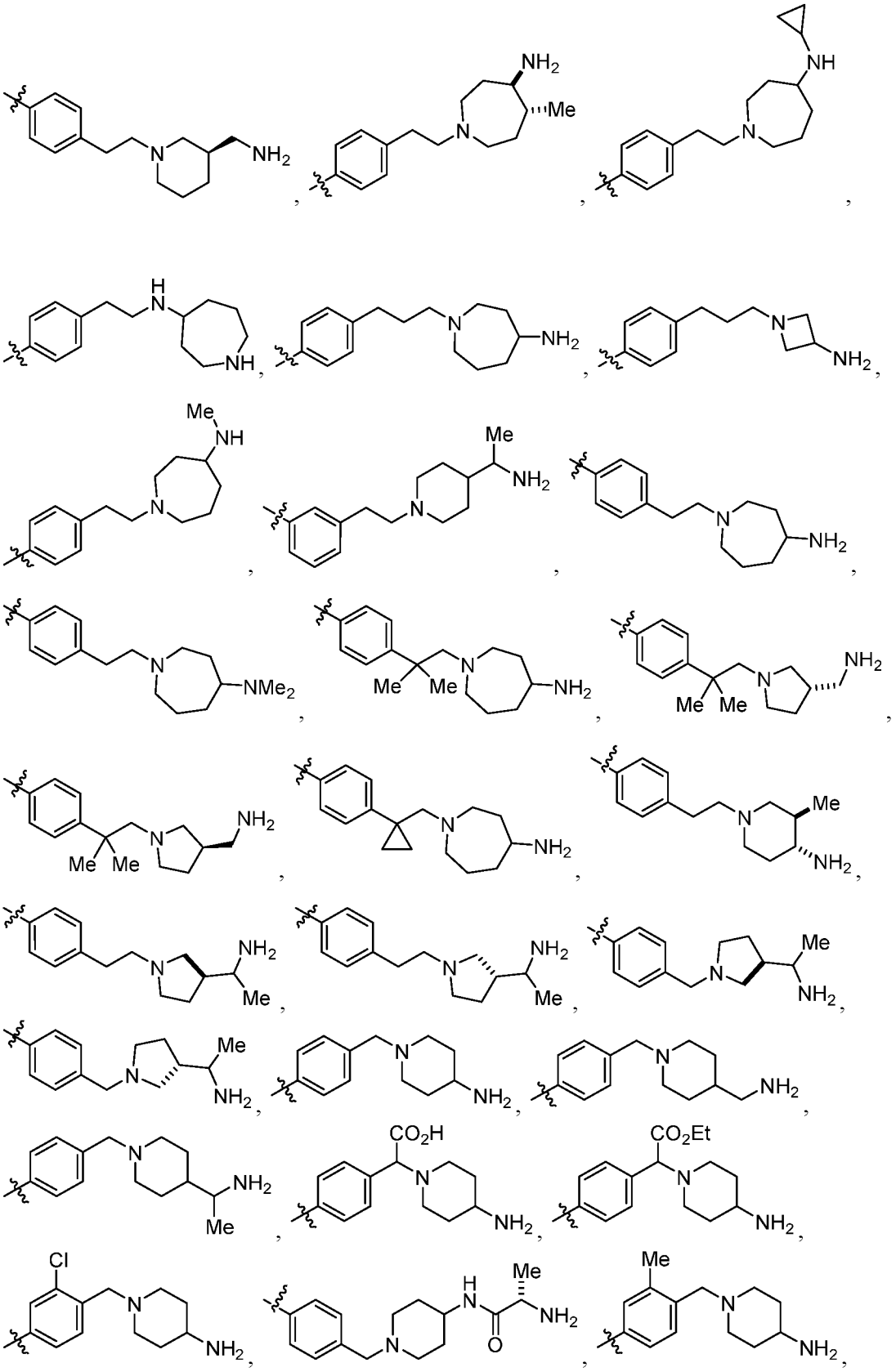
[00167] In another embodiment of a compound of formula I or II or a pharmaceutically acceptable salt thereof, R_1 is H, fluoro, NH_2, NH(C_1-C_6 alkyl) NH(C_3-C_6 cycloalkyl), or a protecting group.

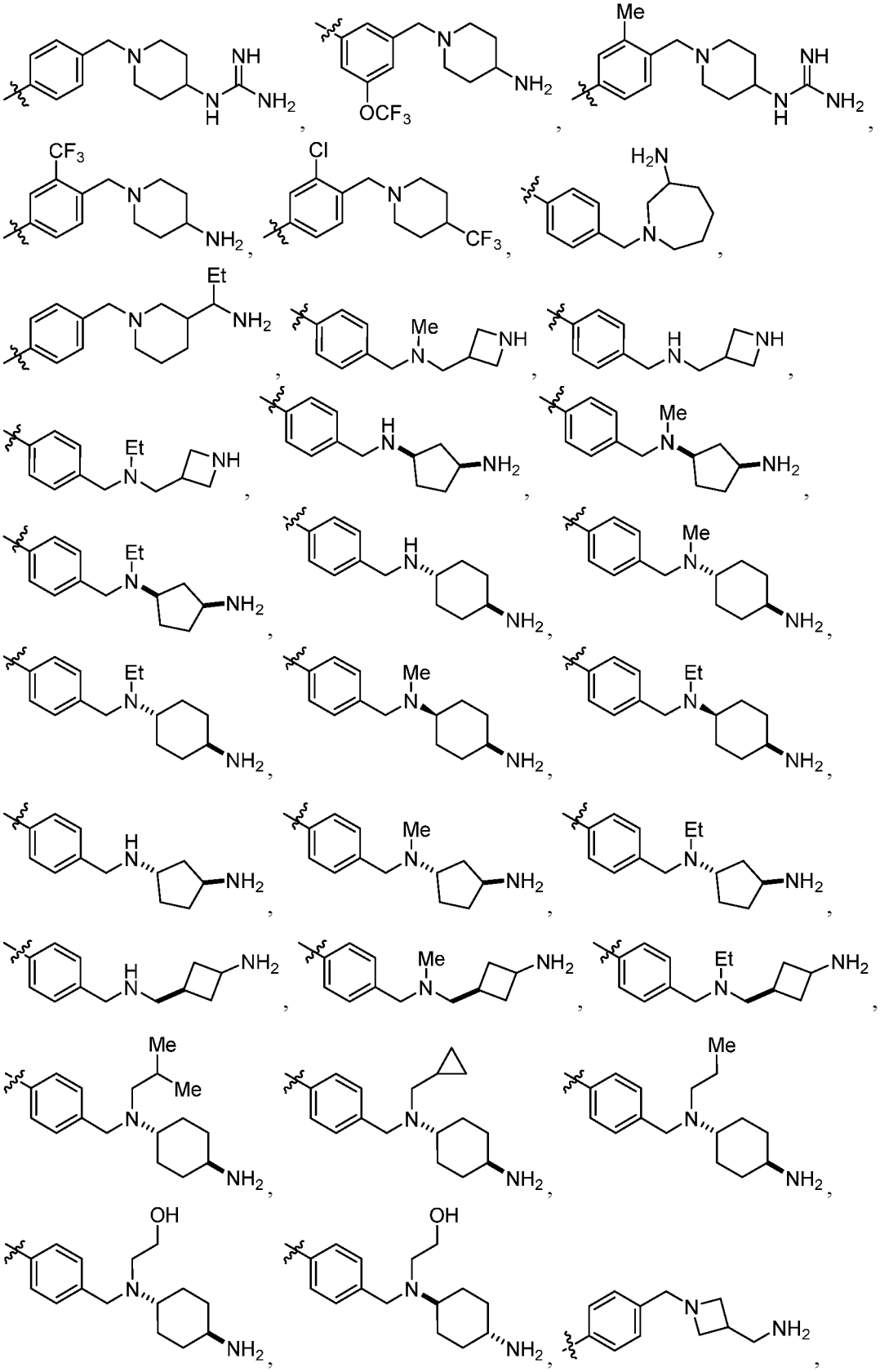
[00168] In another embodiment of a compound of formula I or II or a pharmaceutically acceptable salt thereof, R_1 is H, F, CF_3, H, NH_2, $NHCH_3$, NH-cyclopropyl, NH(C=O)-C_1-C_6 alkyl-NH_2, or NH(C=N)NH_2.

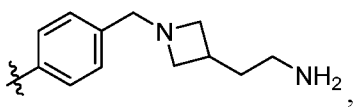
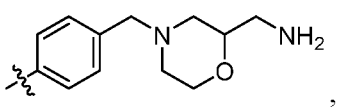
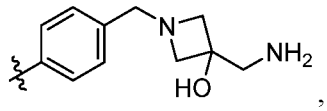
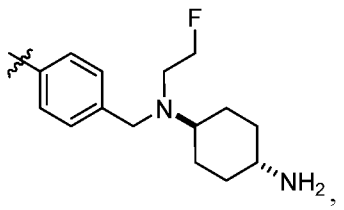
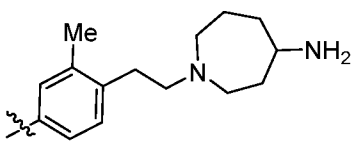
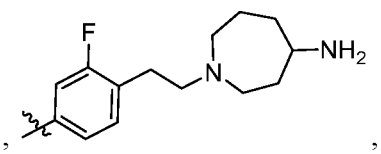
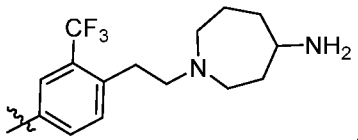
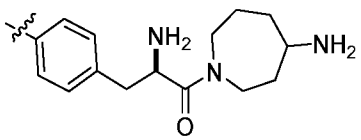
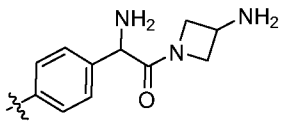
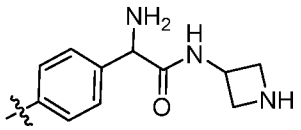
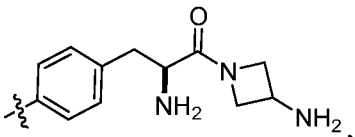
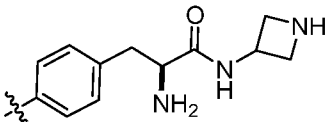
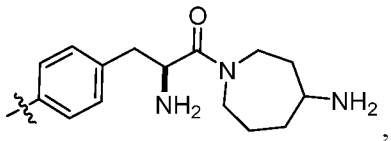
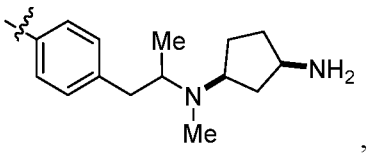
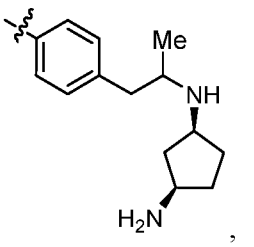
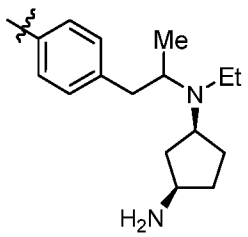
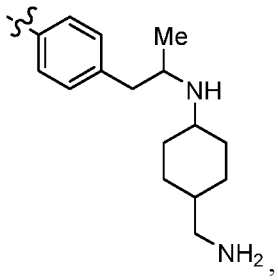
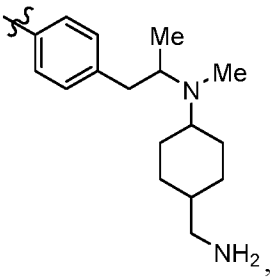
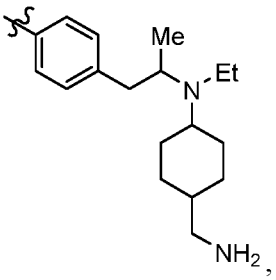
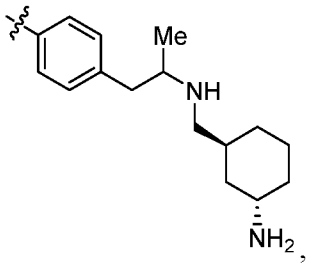
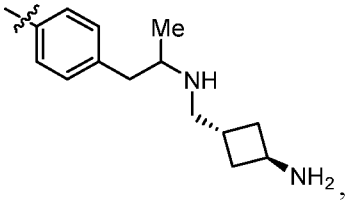
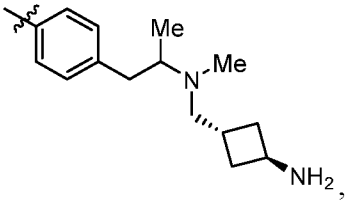
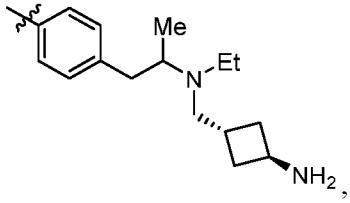
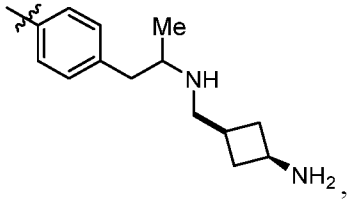
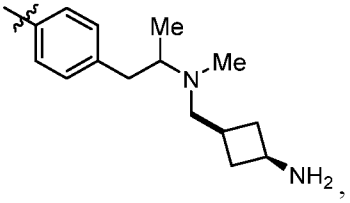
[00169] In another embodiment, R_1 is H or NH_2.

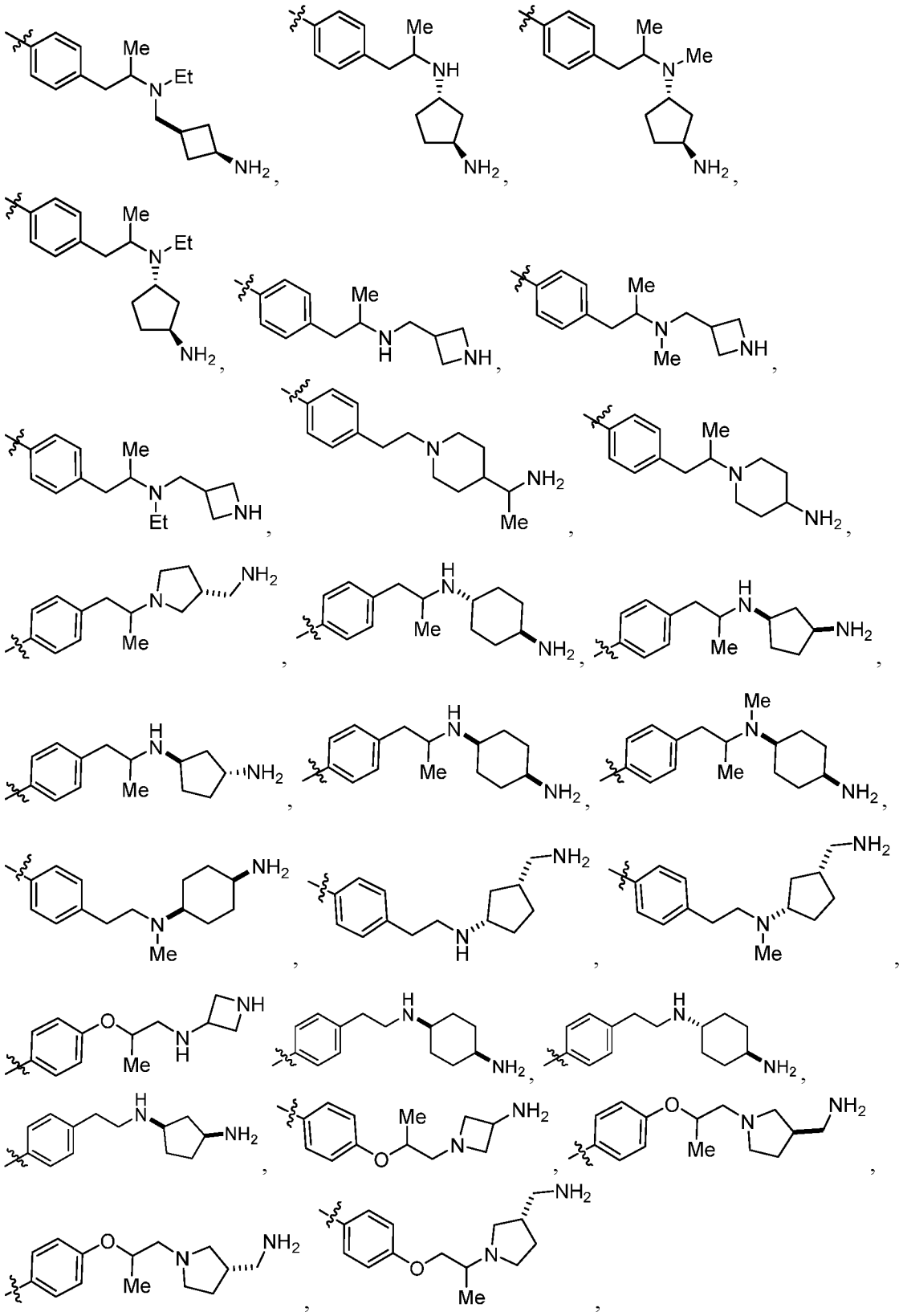
[00170] In another embodiment of a compound of formula I or II or a pharmaceutically acceptable salt thereof,  is selected from the group consisting of:

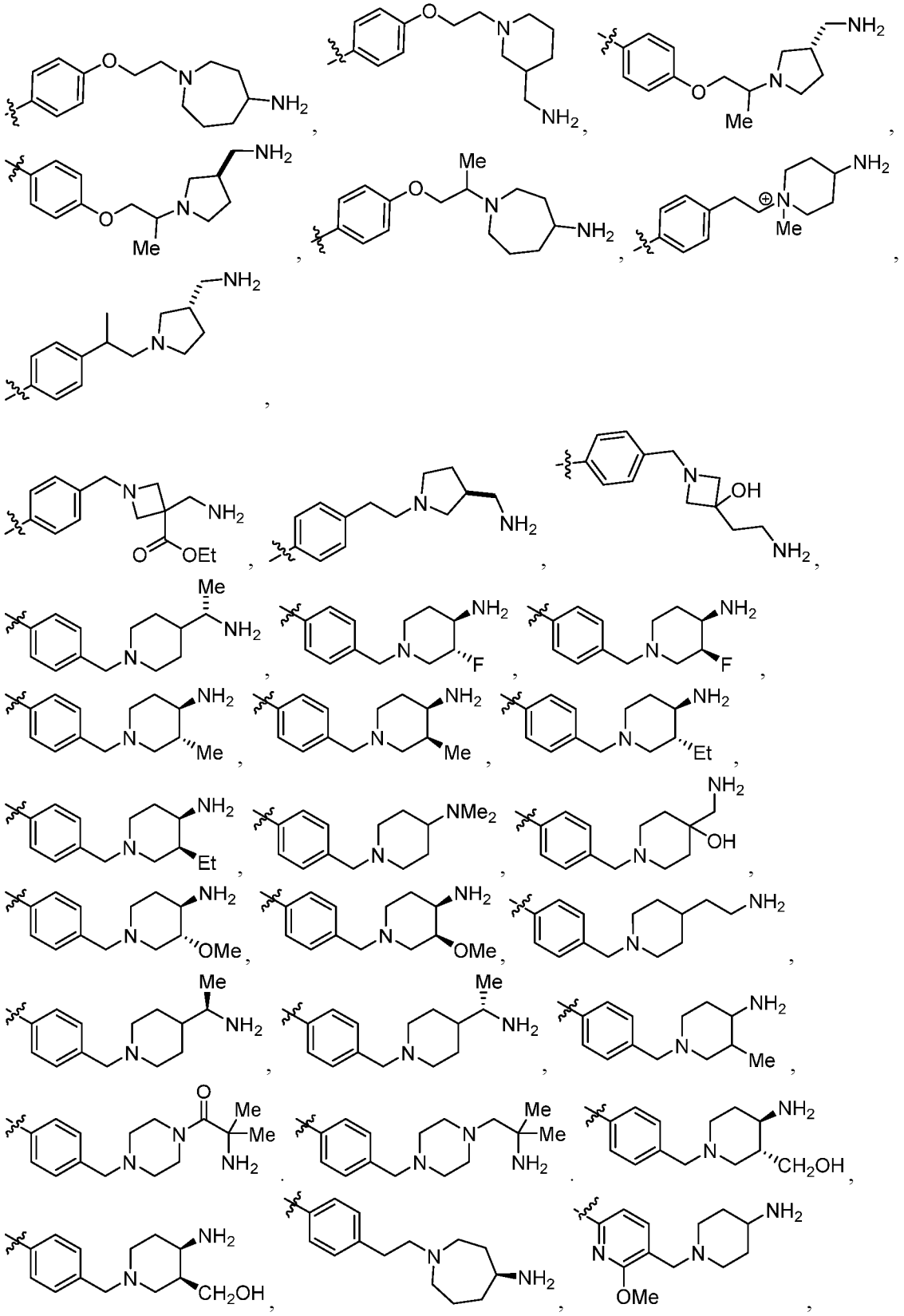
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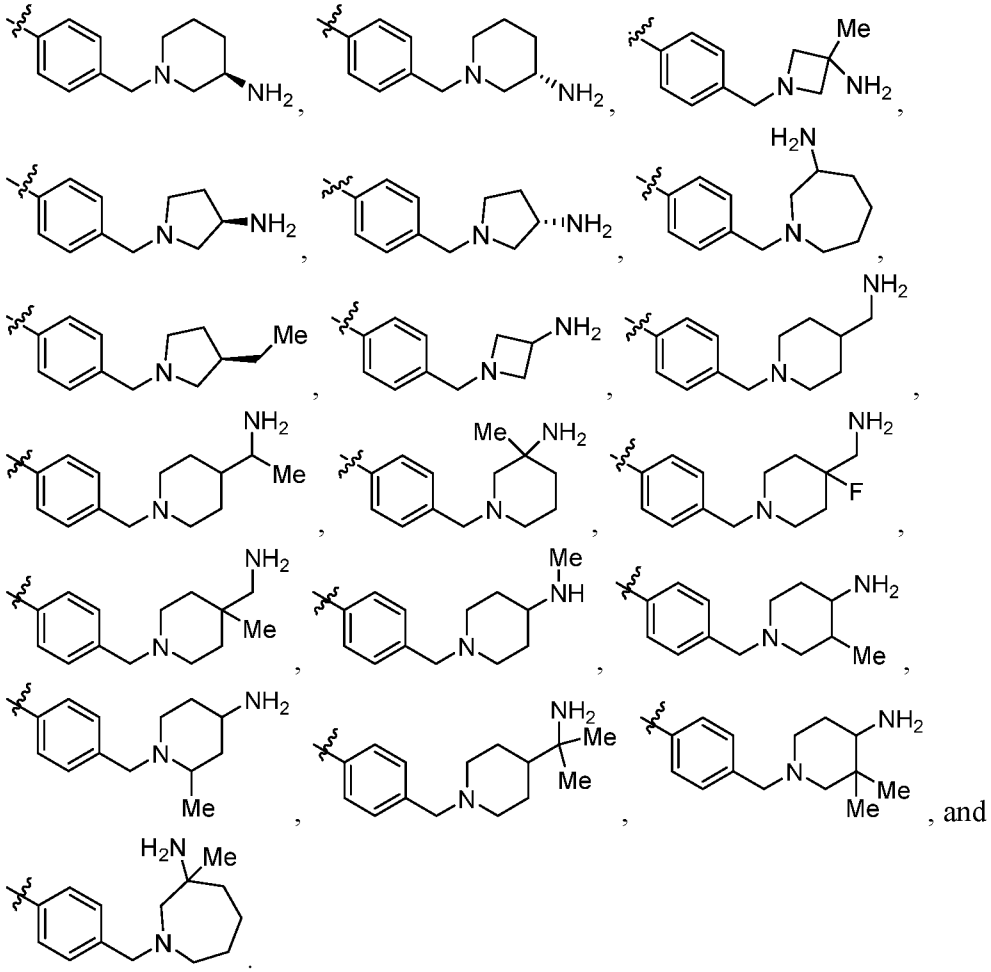






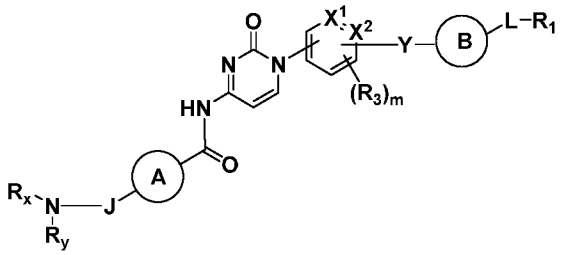




[00171] In another embodiment of a compound of formula I or II or a pharmaceutically acceptable salt thereof, R_2 and R_3 are each independently selected from the group consisting of C_1-C_6 alkyl, halo, C_1-C_6 haloalkyl, and C_1-C_6 alkoxy and m and n are each independently 0, 1, or 2.

[00172] In another embodiment, R_2 and R_3 are each independently selected from the group consisting of CH_3, Cl, F, OCH_3, CH_3, and CF_3, and m and n are each independently 0 or 1.

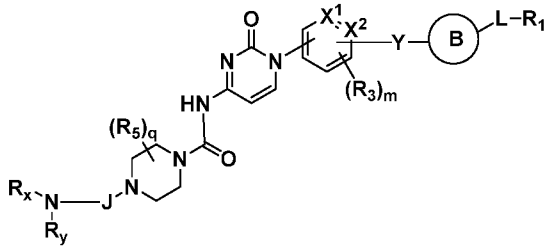
[00173] In another embodiment, the compound of formula I or II is a compound of formula IIA-1:



IIA-1

or a pharmaceutically acceptable salt thereof, wherein the variables are described herein.

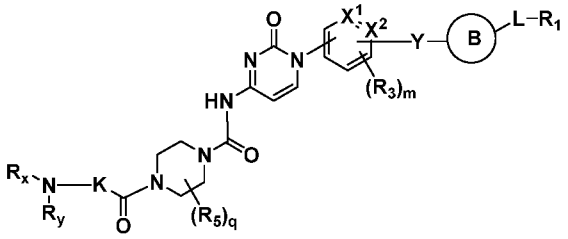
[00174] In another embodiment, the compound of formula I or II is a compound of formula IIA-2:



IIA-2

or a pharmaceutically acceptable salt thereof, wherein the variables are described herein; R_5 is selected from the group consisting of H, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CN, C_1-C_6 haloalkyl, phenyl, OH, NH_2, and oxo; and q is 0, 1, 2, or 3.

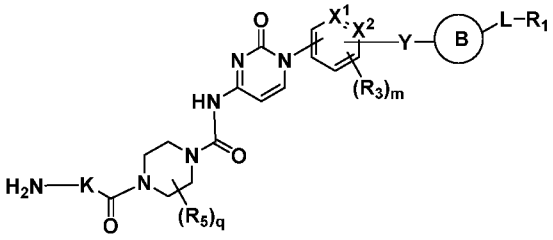
[00175] In another embodiment, the compound of formula I or II is a compound of formula IIA-3:



IIA-3

or a pharmaceutically acceptable salt thereof, wherein the variables are described herein. In another embodiment, K is C_1-C_4 alkylene optionally substituted with hydroxy or alkoxy.

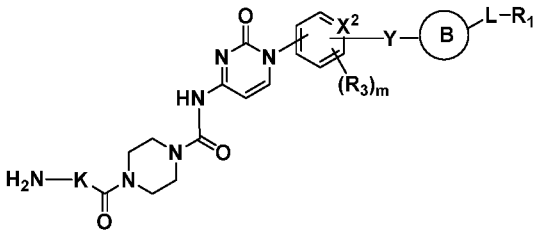
[00176] In another embodiment, the compound of formula I or II is a compound of formula IIA-4:



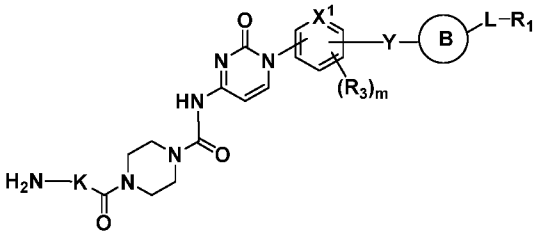
IIA-4

or a pharmaceutically acceptable salt thereof, wherein the variables are described herein.

[00177] In another embodiment, the compound of formula I or II is a compound of formula IIA-4a or IIA-4b:



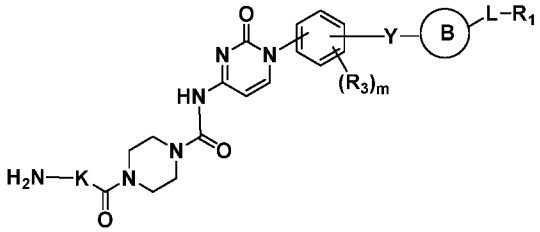
IIA-4a



IIA-4b

or a pharmaceutically acceptable salt thereof, wherein the variables are described herein.

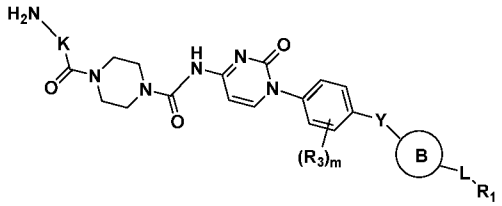
[00178] In another embodiment, the compound of formula I or II is a compound of formula IIA-5:



IIA-5

or a pharmaceutically acceptable salt thereof, wherein the variables are described herein. In another embodiment, R_3 is selected from the group consisting of C_1-C_6 alkyl, halo, C_1-C_6 haloalkyl, and C_1-C_6 alkoxy; m is 0, 1, or 2.

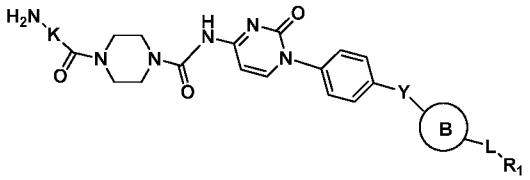
[00179] In another embodiment, the compound of formula I or II is a compound of formula IIA-6:



IIA-6

or a pharmaceutically acceptable salt thereof.

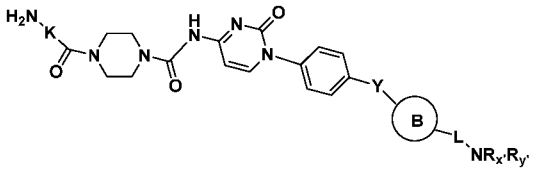
[00180] In another embodiment, the compound of formula I or II is a compound of formula IIA-7:



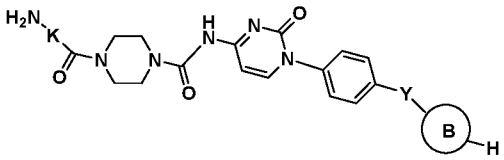
IIA-7

or a pharmaceutically acceptable salt thereof.

[00181] In another embodiment, the compound of formula I or II is a compound of formula IIA-8a of IIA-8b:



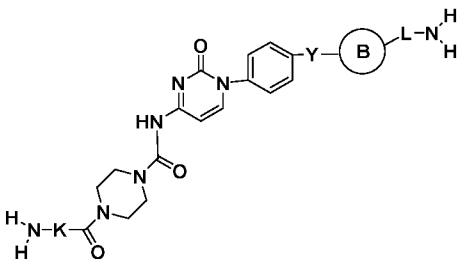
IIA-8



IIA-8b

or a pharmaceutically acceptable salt thereof.

[00182] In another embodiment, the compound of formula I or II is a compound of formula IIA-9:

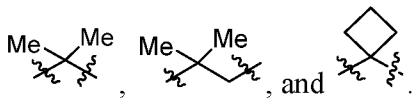


IIA-9

or a pharmaceutically acceptable salt thereof.

[00183] In embodiment of a compound of formula IIA-9 or a pharmaceutically acceptable salt thereof, ring B is selected from any of the moieties provided in Table 9.

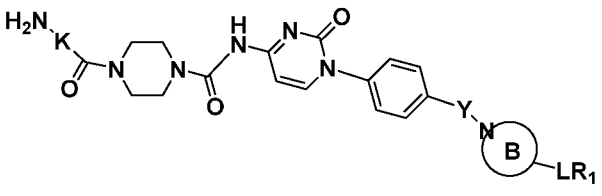
[00184] In another embodiment of a compound of formula IIA-3 through IIA-9 or a pharmaceutically acceptable salt thereof, K is selected from the group consisting of



, and .

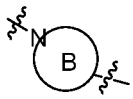
[00185] In another embodiment of compounds IIA-1 through IIA-9, Y is selected from any of the moieties provided in Table 8.

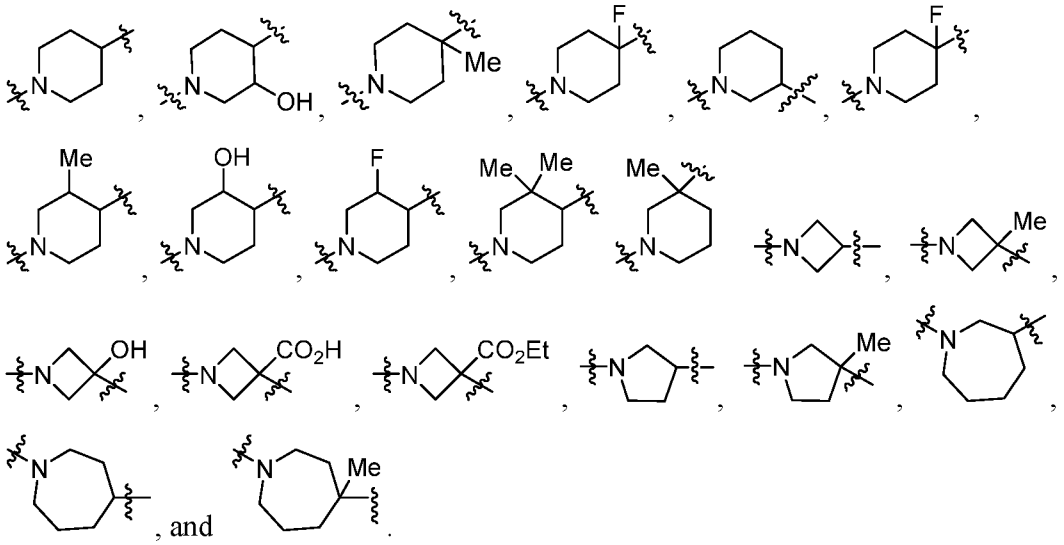
[00186] In another embodiment, the compound of formula I or II is a compound of formula IIA-10:



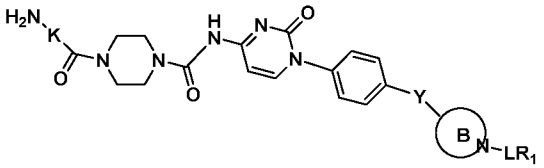
IIA-10

or a pharmaceutically acceptable salt thereof.

[00187] In another embodiment,  is selected from the group consisting of

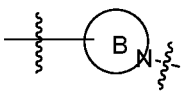


[00188] In another embodiment, the compound of formula I or II is a compound of formula IIA-11:

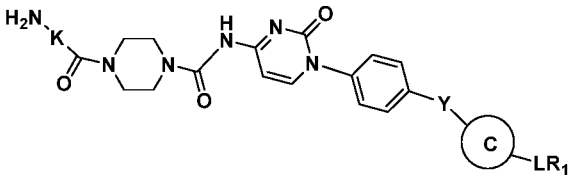


IIA-11

or a pharmaceutically acceptable salt thereof.

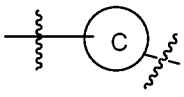
[00189] In another embodiment,  is 

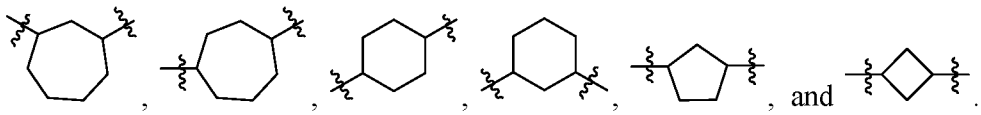
[00190] In another embodiment, the compound of formula I or II is a compound of formula IIA-12:



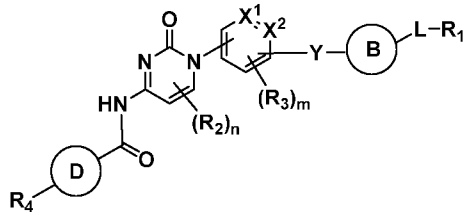
IIA-12

or a pharmaceutically acceptable salt thereof wherein ring C is an optionally substituted C_3-C_7 cycloalkylene.

[00191] In another embodiment,  is selected from the group consisting of



[00192] In another aspect, the disclosure provides a compound of formula III:



III

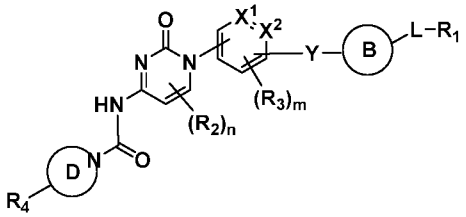
or a pharmaceutically acceptable salt thereof, wherein:

R_1, R_2, R_3, X^1, X^2, Y, ring B, L, m, and n are as defined herein;

ring D is a monocyclic heterocycloalkylene or bicyclic heterocycloalkylene, wherein the bicyclic heterocycloalkylene and bicyclic heterocycloalkylene are optionally substituted with up to three substituents selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CN, C_1-C_6 haloalkyl, phenyl, OH, NH_2, $NH(C_1$-C_6 alkyl), $N(C_1$-C_6 alkyl)$_2$, $-COO(C_1$-C_6 alkyl), $-COONH_2$, and oxo; and

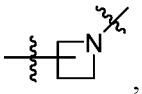
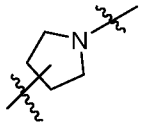
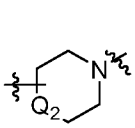
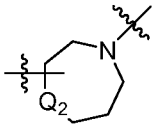
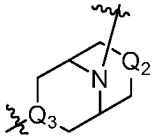
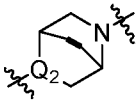
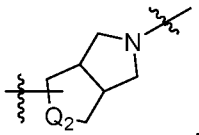
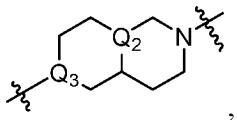
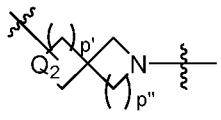
R_4 is H or $NR_{x''}R_{y''}$, wherein $R_{x''}$ and $R_{y''}$ are each independently H or C_1-C_6 alkyl.

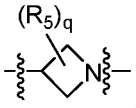
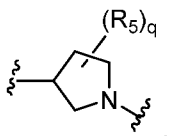
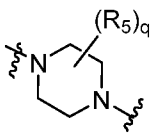
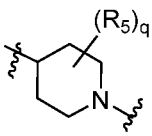
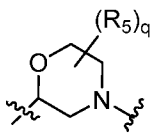
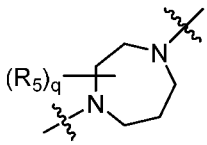
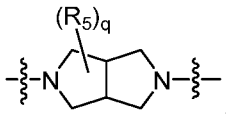
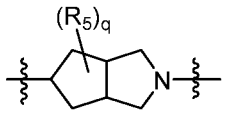
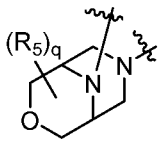
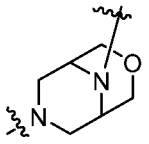
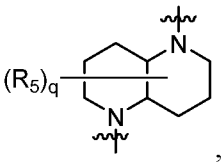
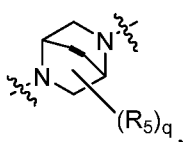
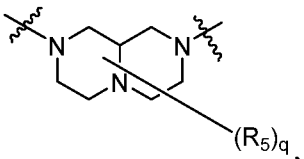
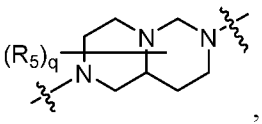
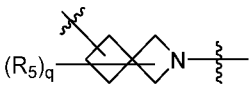
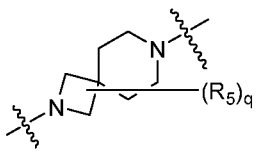
[00193] In one embodiment, the compound of formula III is a compound of formula IIIA:



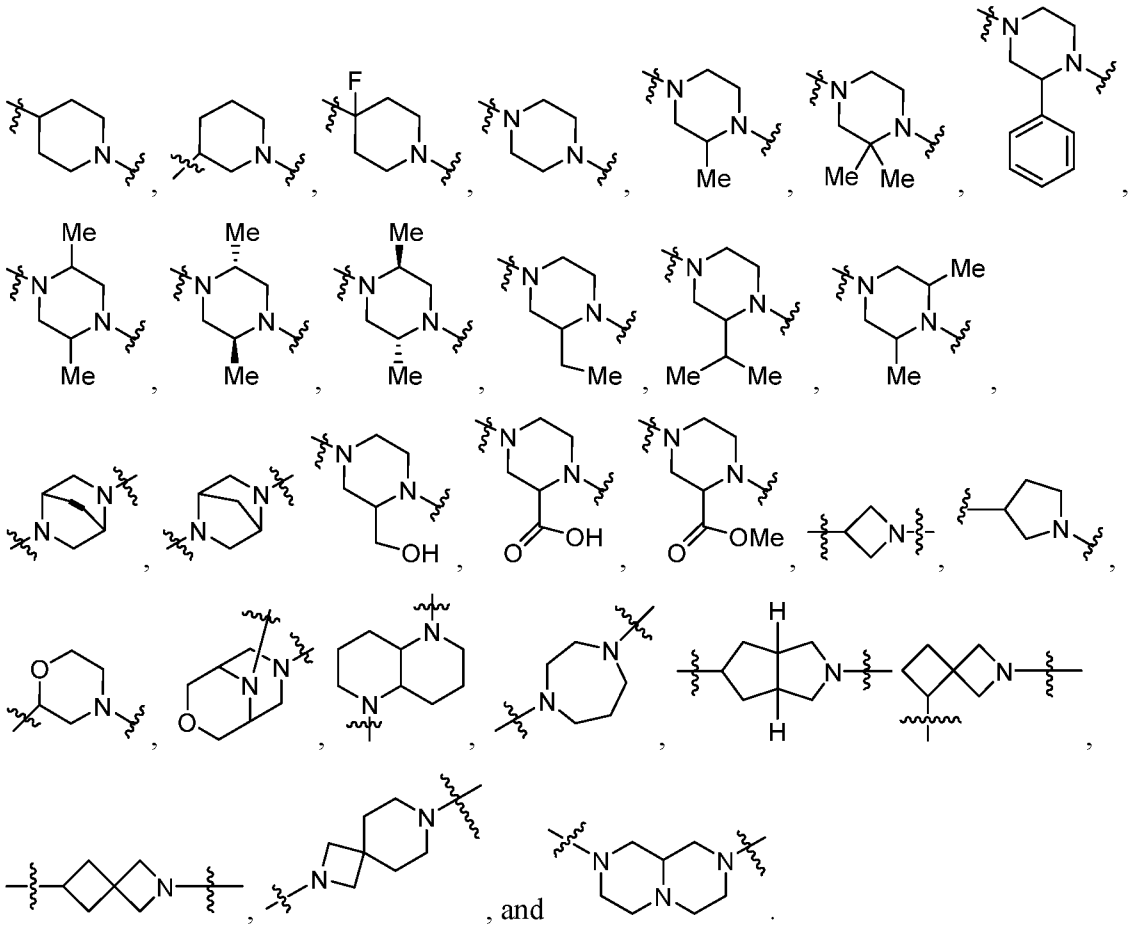
IIIA

or a pharmaceutically acceptable salt thereof.

[00194] In another embodiment, ring D is selected from the group consisting of , , , , , , , , and , wherein p' and p" are each independently 0, 1, 2, 3, 4, or 5; wherein Q_1 is N, and Q_2 and Q_3 are independently selected from the group consisting of C, N, S, or O, and wherein the monocyclic heterocycloalkylene and bicyclic heterocycloalkylene may be optionally substituted with up to three substituents selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CN, C_1-C_6 haloalkyl, phenyl, OH, NH_2, -CO_2H, -CO_2Me, -CO_2Et, and oxo.

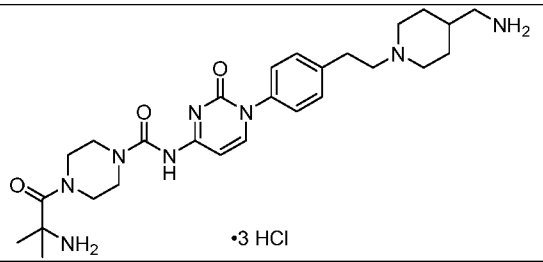
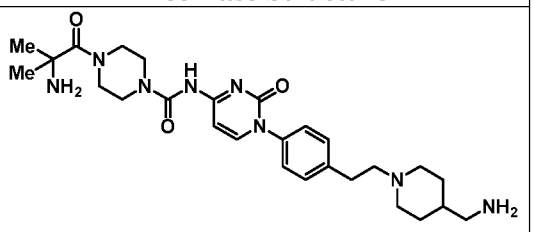
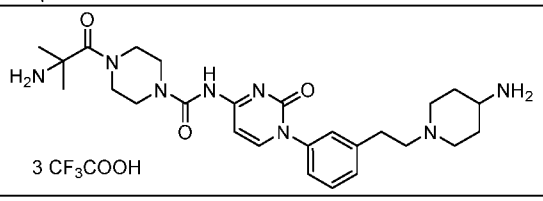
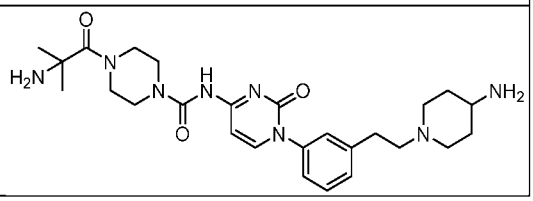
[00195] In another embodiment, ring D is selected from the group consisting of , , , , , , , , , , , , , , , and , wherein each R_5 is independently selected from the group consisting of H, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CN, C_1-C_6 haloalkyl, phenyl, OH, NH_2, and oxo, wherein q is 1, 2, or 3.

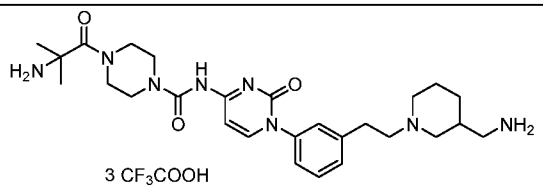
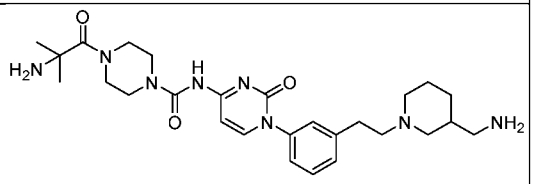
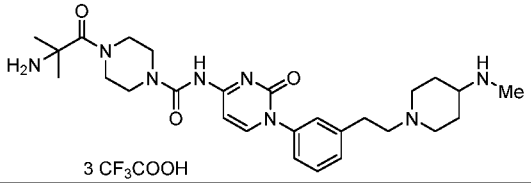
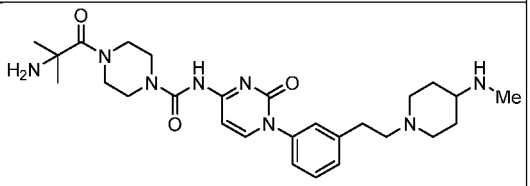
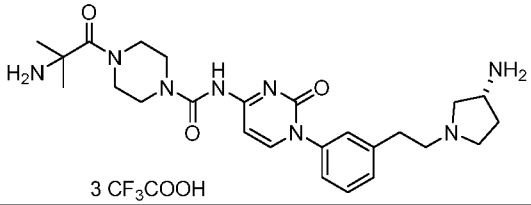
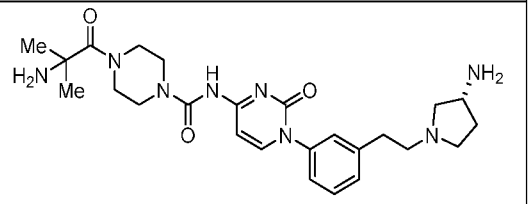
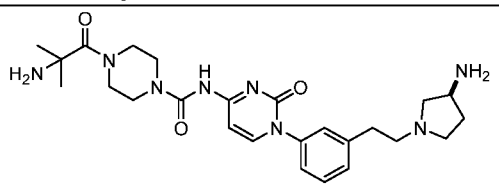
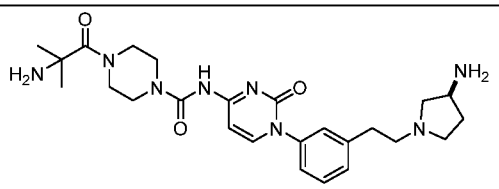
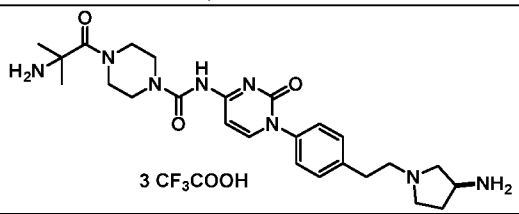
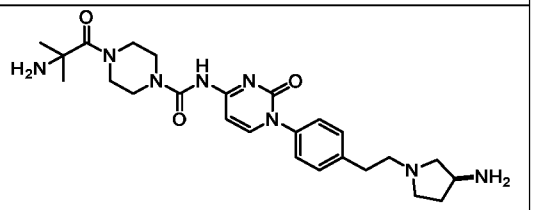
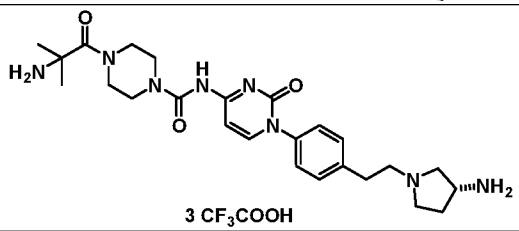
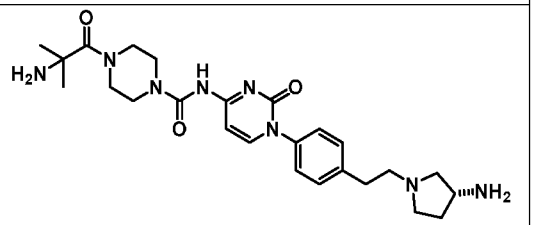
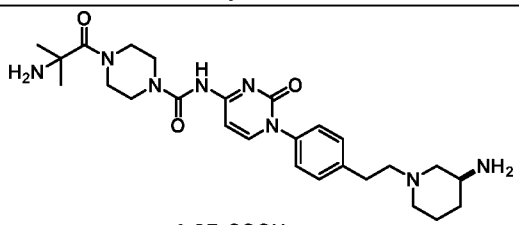
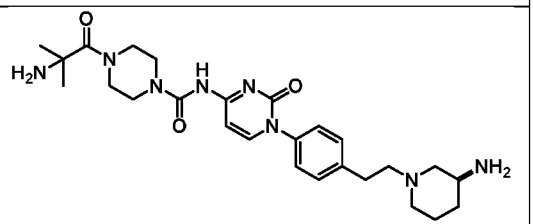
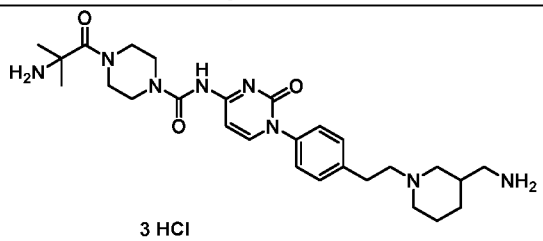
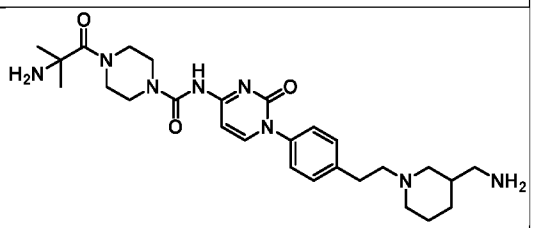
[00196] In another embodiment, ring D is selected from the group consisting of

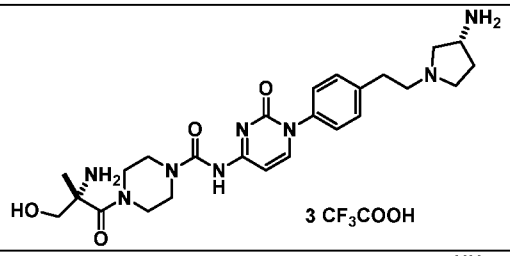
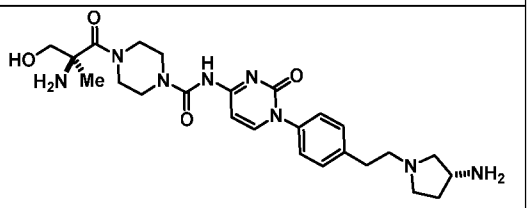
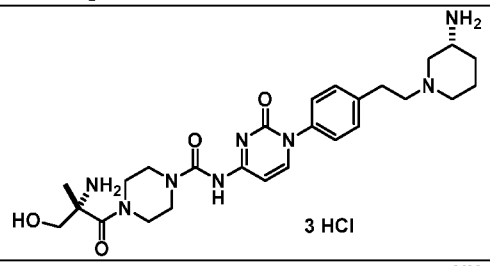
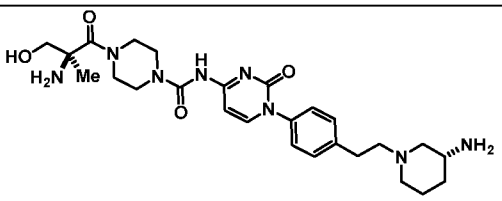
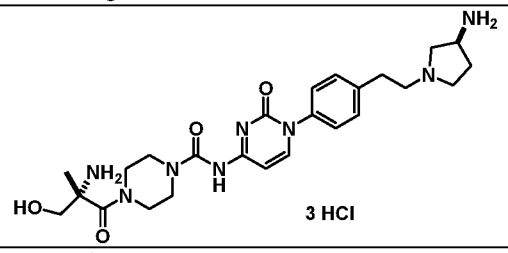
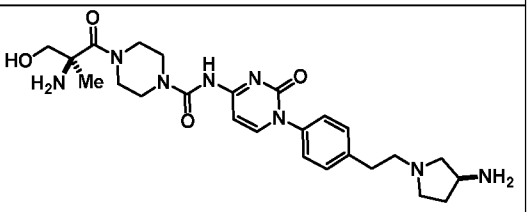
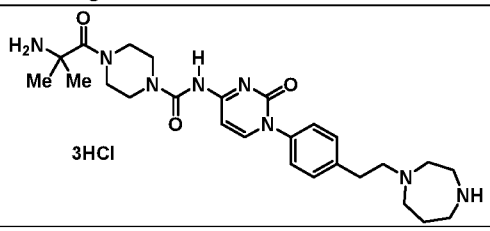
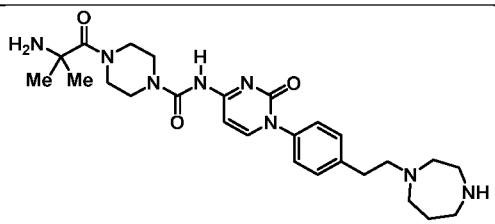
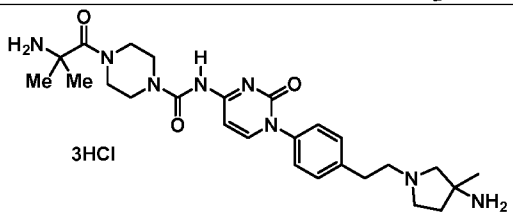
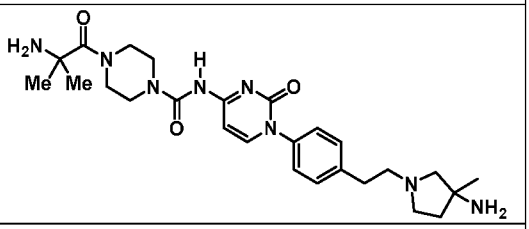
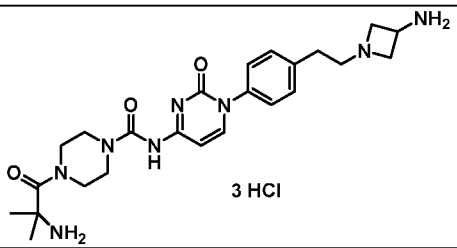
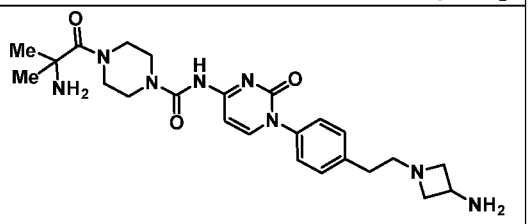
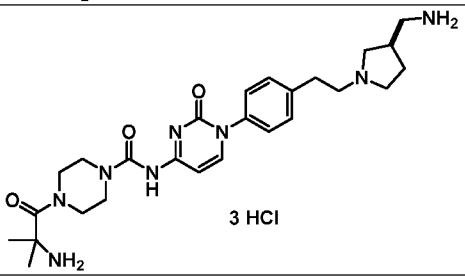
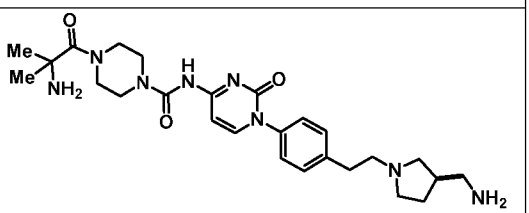


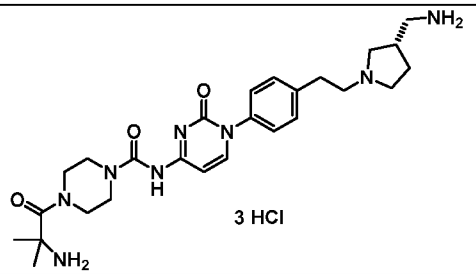
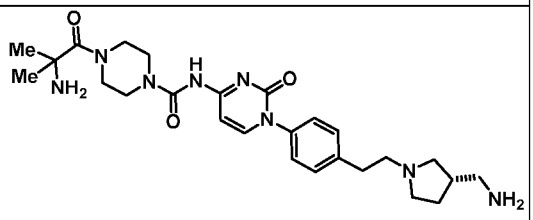
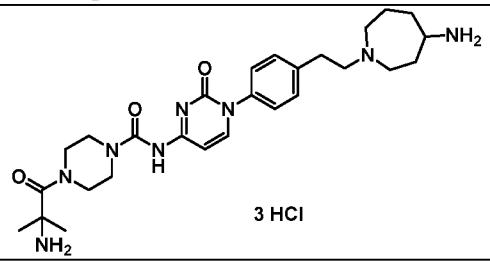
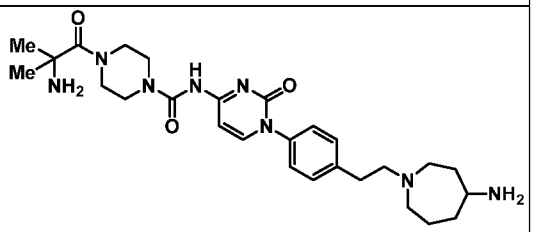
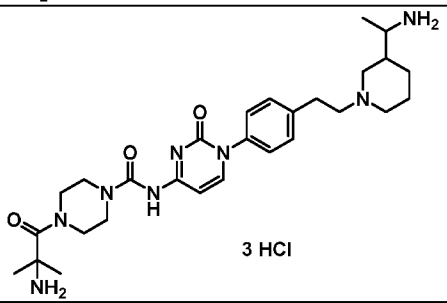
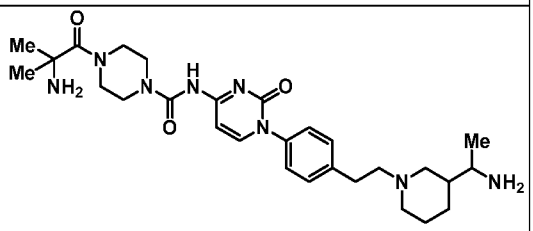
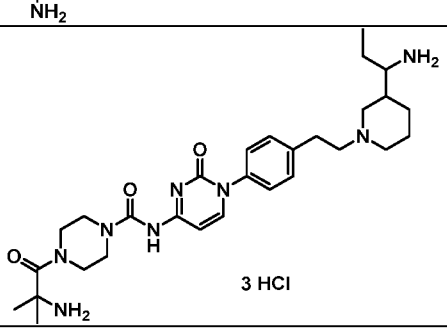
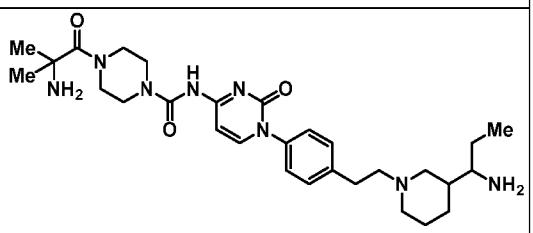
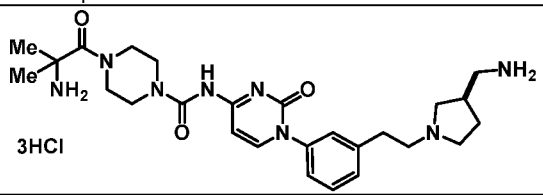
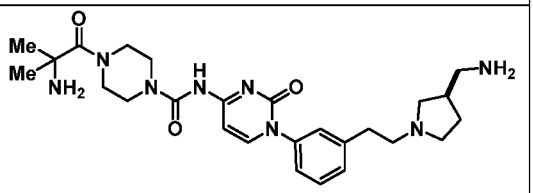
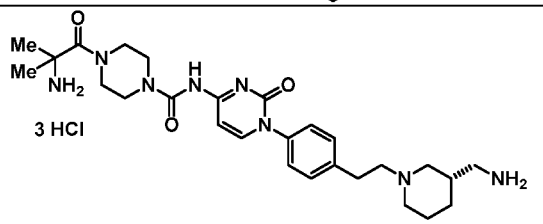
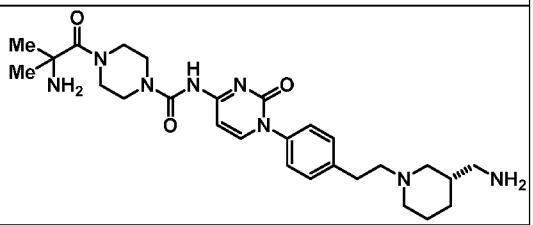
[00197] In another aspect, the disclosure provides a compound or a pharmaceutically acceptable salt thereof which is depicted in Table 10. In Table 10, free base and salt structures of the compounds of the invention are depicted.

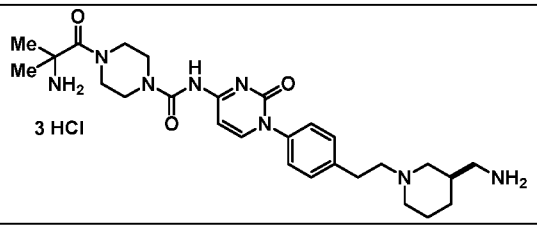
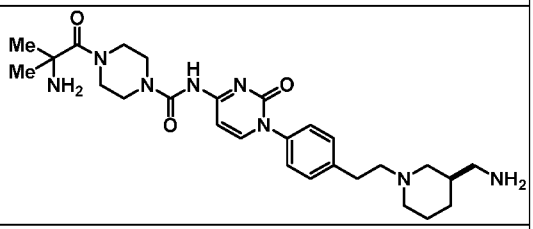
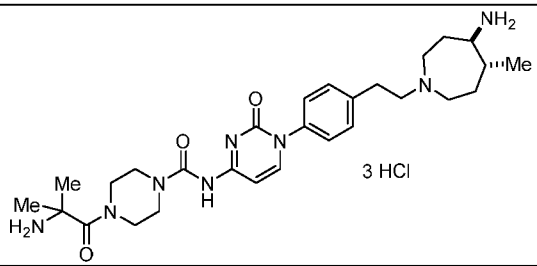
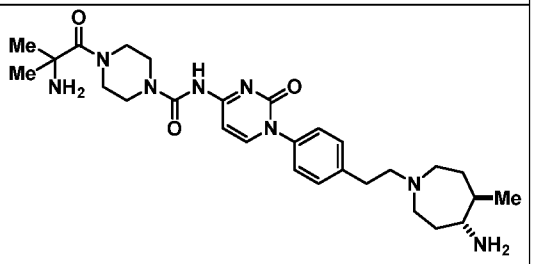
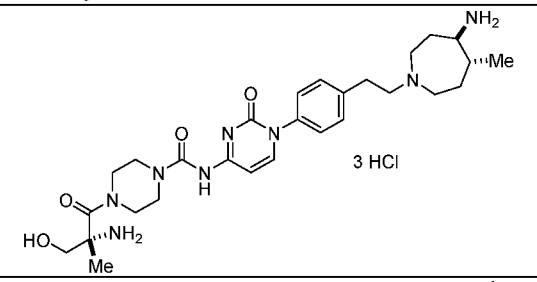
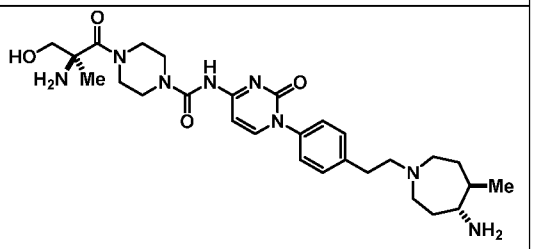
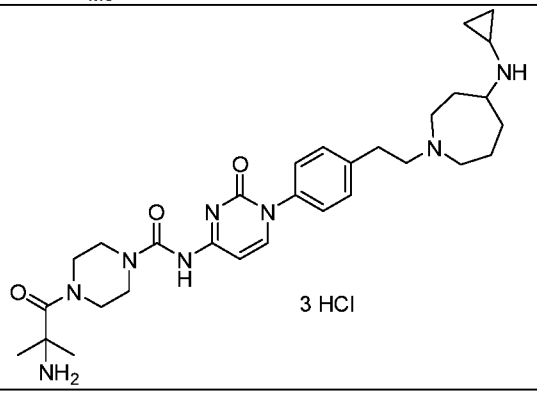
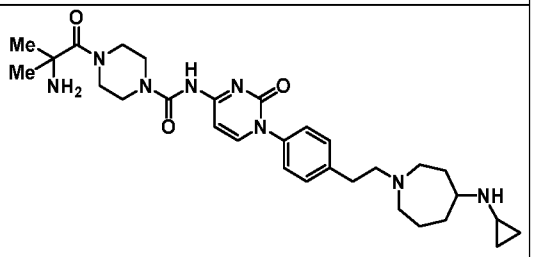
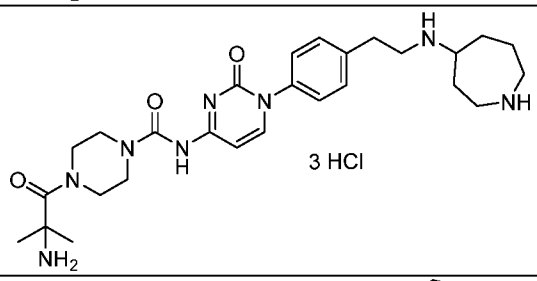
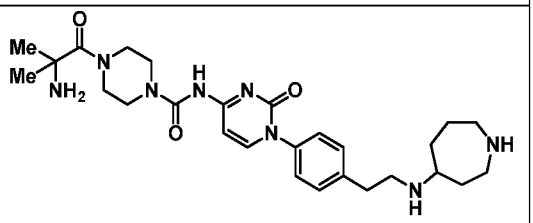
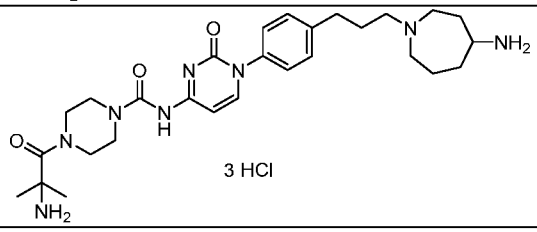
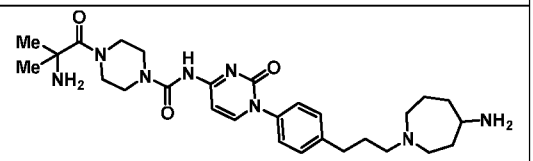
Table 10 Compounds of Formula I

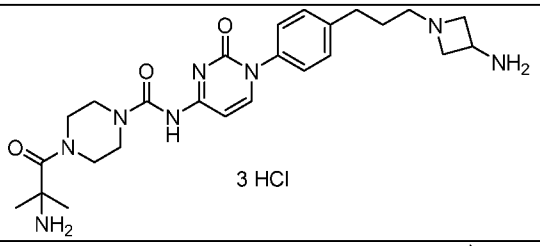
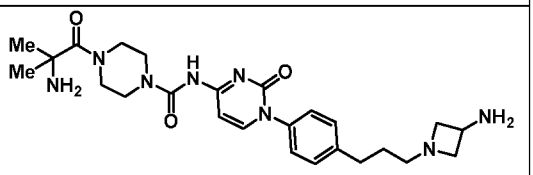
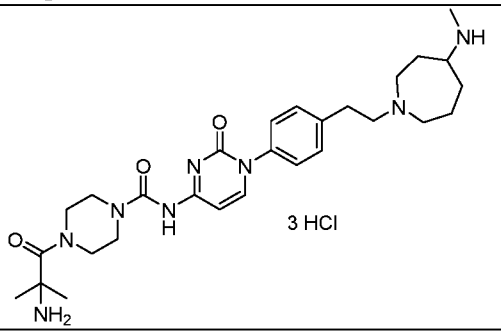
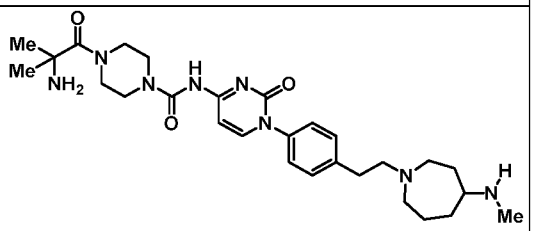
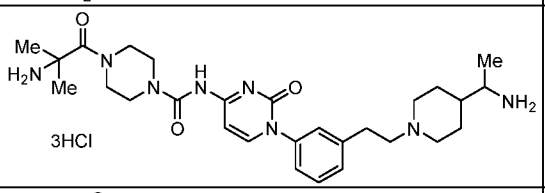
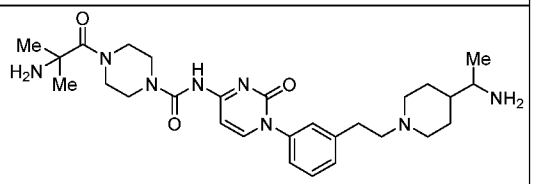
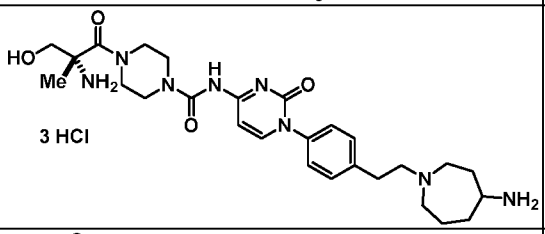
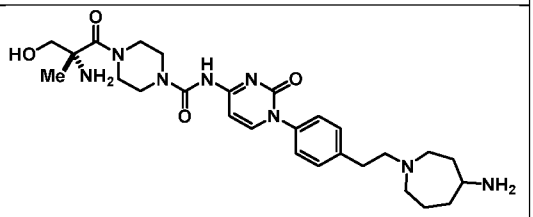
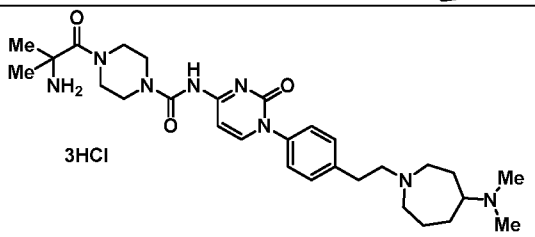
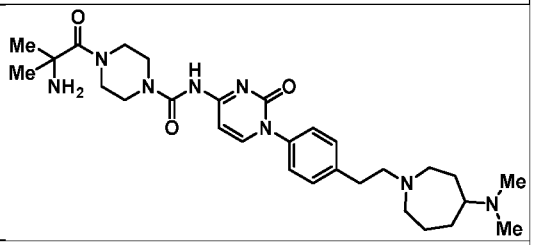
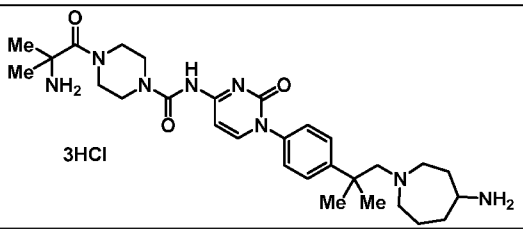
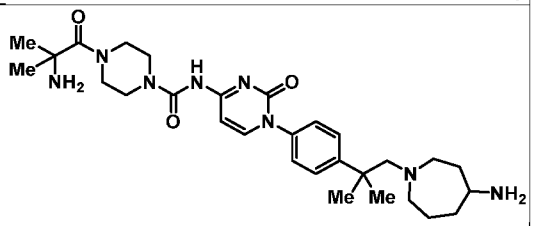
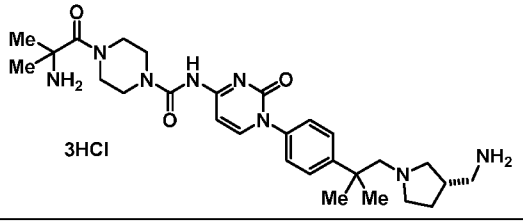
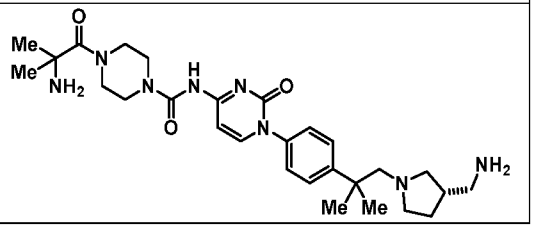
No.	Salt Structure	Free Base Structure
1		
2		

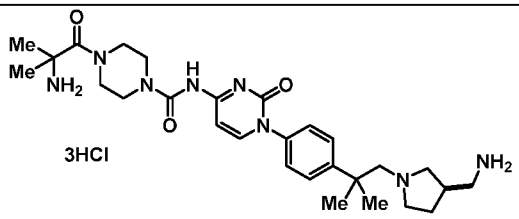
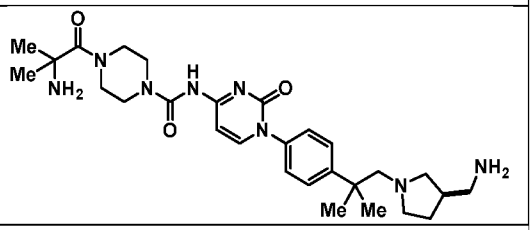
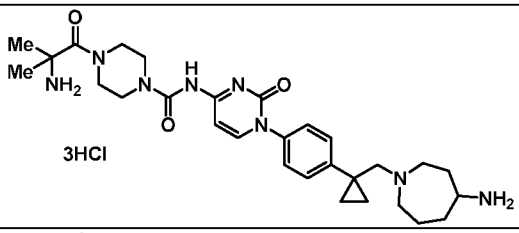
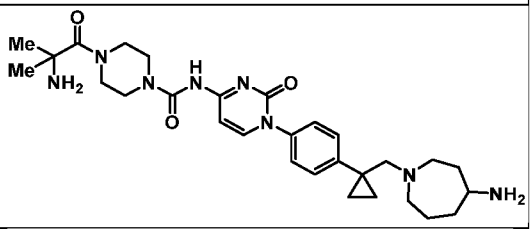
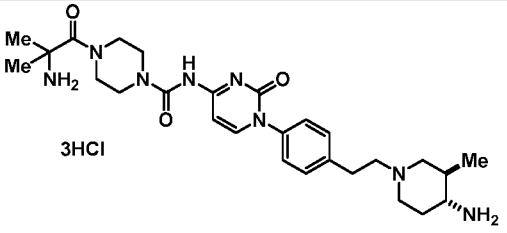
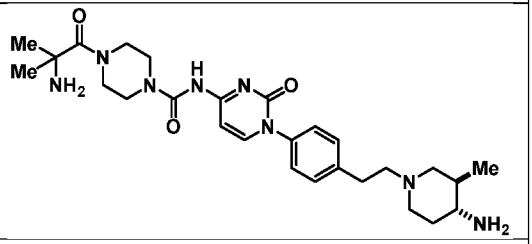
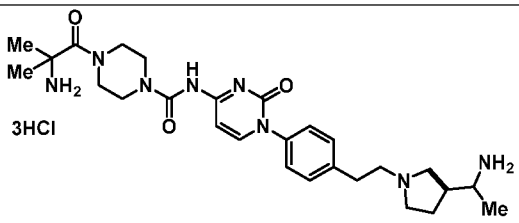
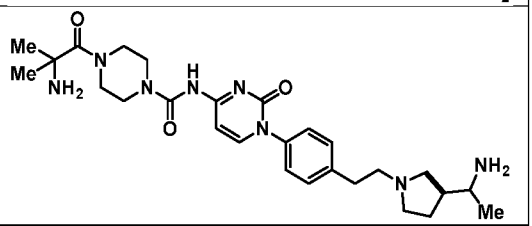
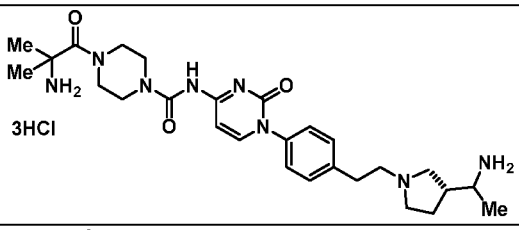
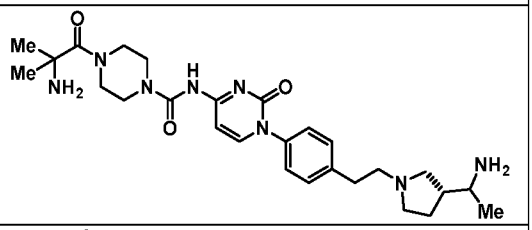
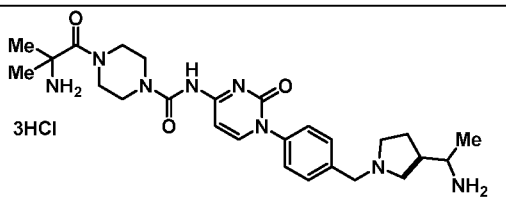
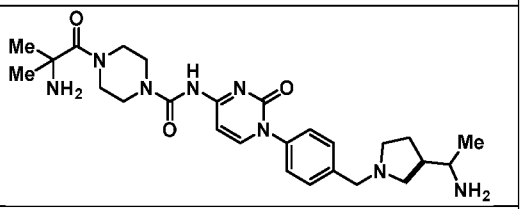
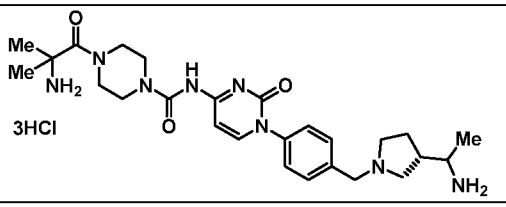
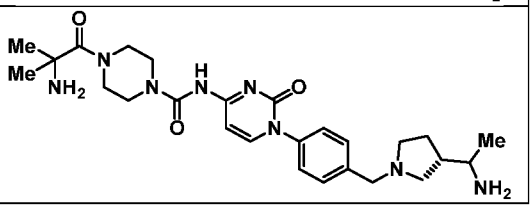
No.	Salt Structure	Free Base Structure
3	 3 CF_3COOH	
4	 3 CF_3COOH	
5	 3 CF_3COOH	
6	 3 CF_3COOH	
7	 3 CF_3COOH	
8	 3 CF_3COOH	
9	 3 CF_3COOH	
10	 3 HCl	

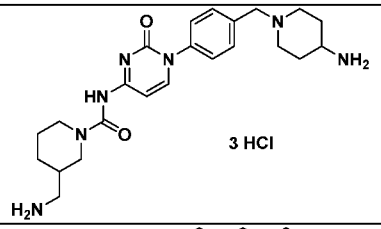
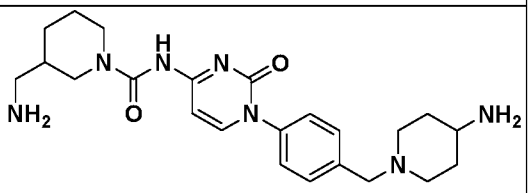
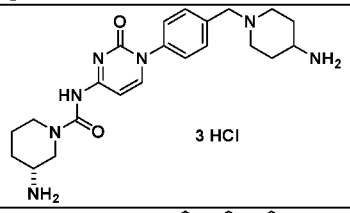
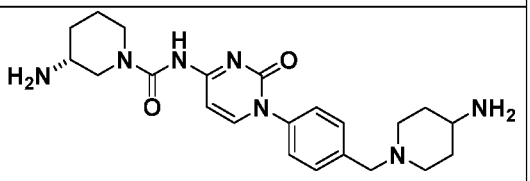
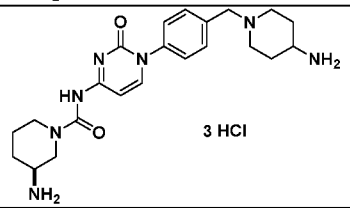
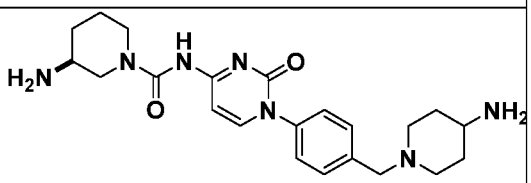
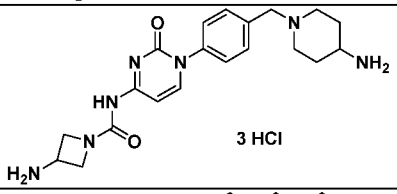
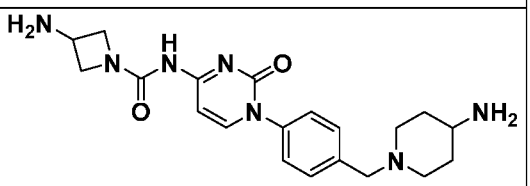
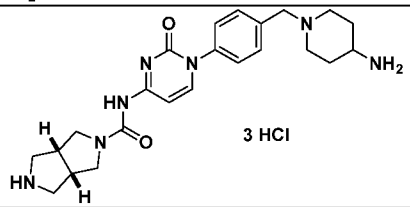
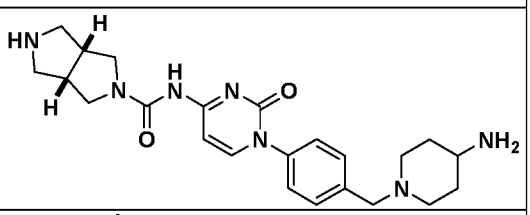
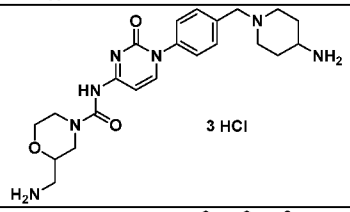
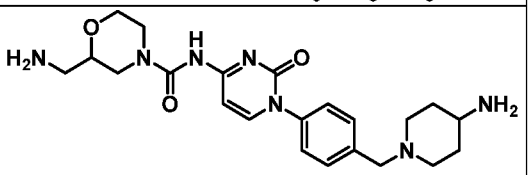
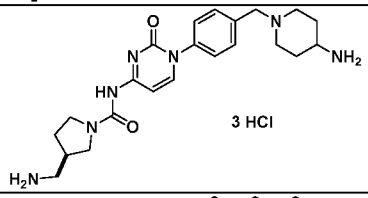
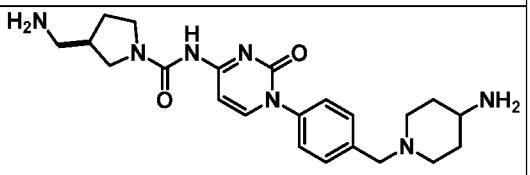
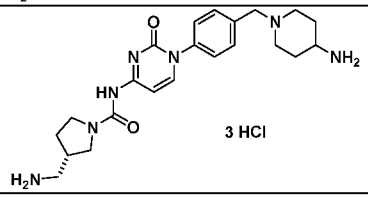
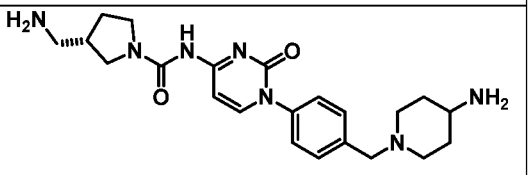
No.	Salt Structure	Free Base Structure
11	 3 CF_3COOH	
12	 3 HCl	
13	 3 HCl	
14	 3HCl	
15	 3HCl	
16	 3 HCl	
17	 3 HCl	

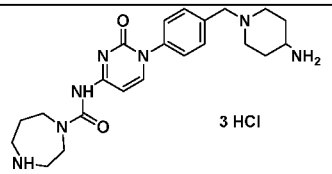
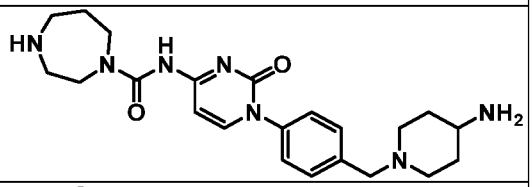
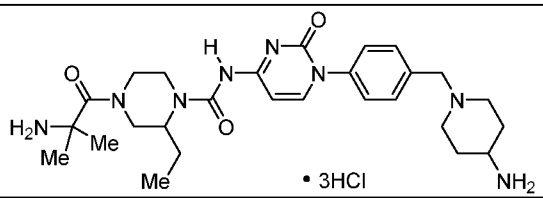
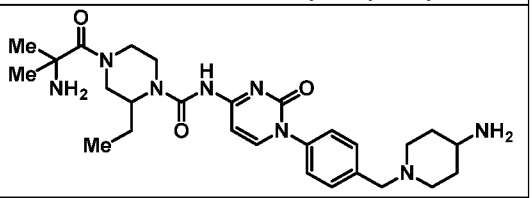
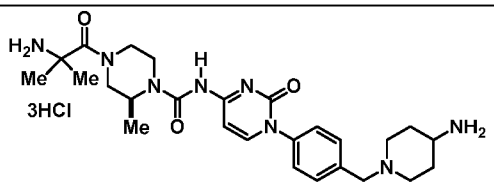
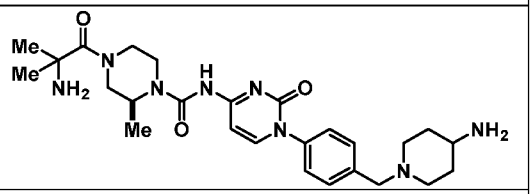
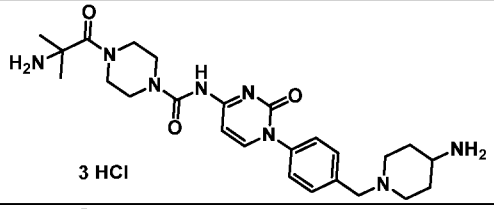
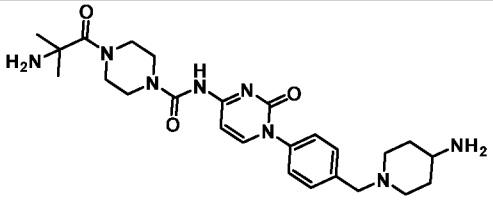
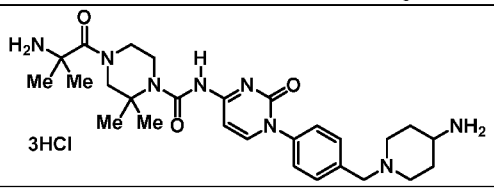
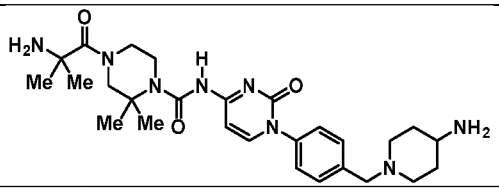
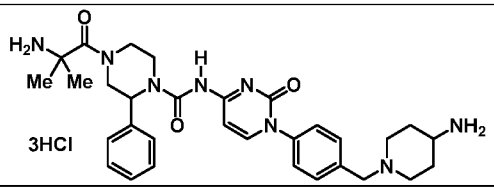
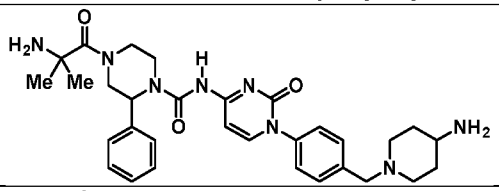
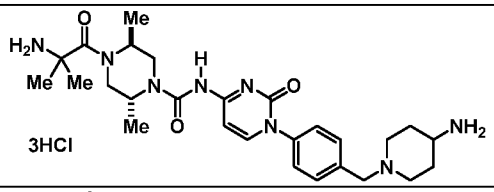
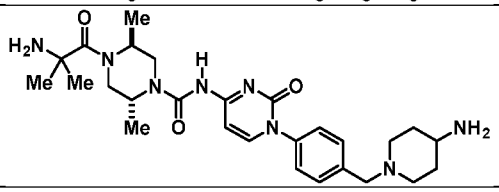
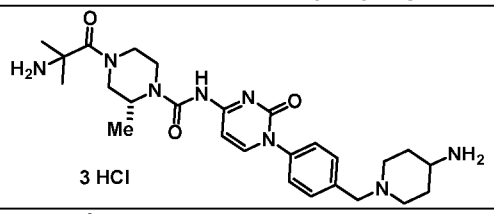
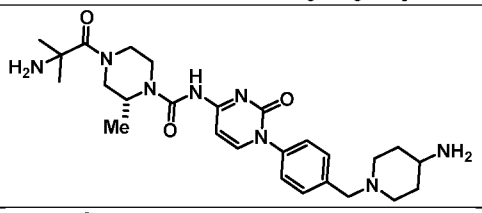
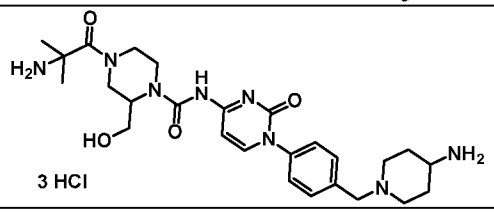
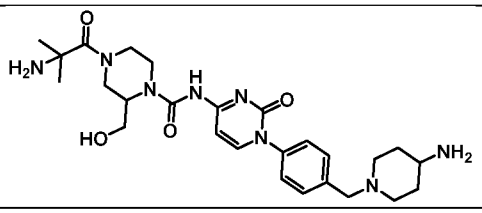
No.	Salt Structure	Free Base Structure
18	 3 HCl	
21	 3 HCl	
22	 3 HCl	
23	 3 HCl	
24	 3HCl	
25	 3 HCl	

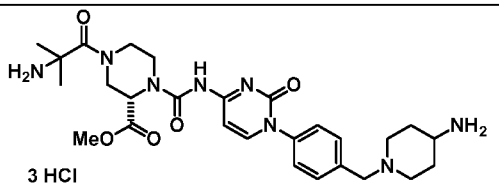
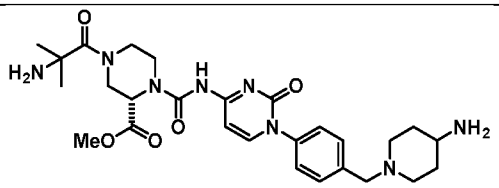
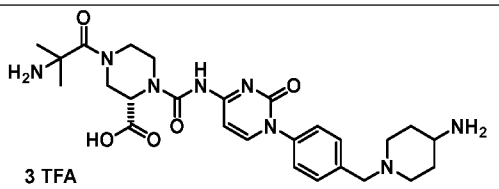
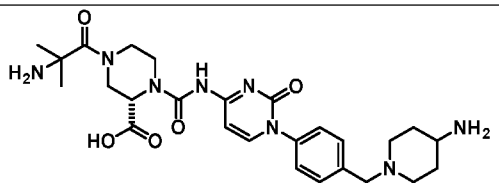
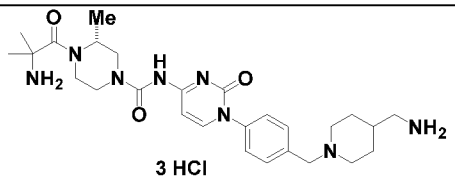
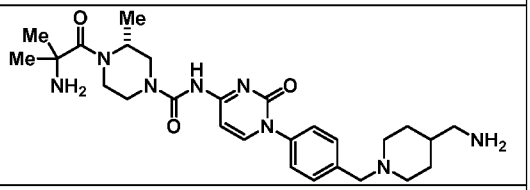
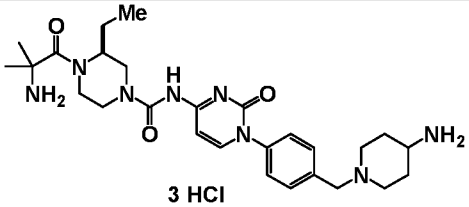
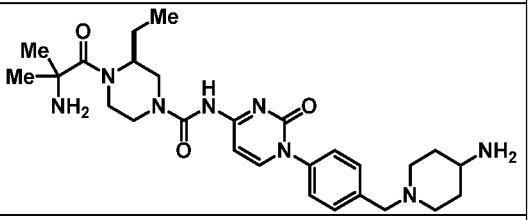
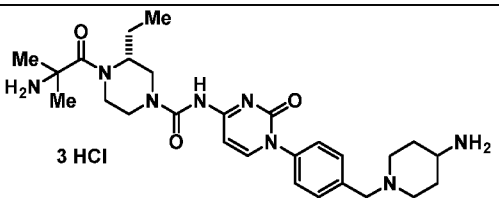
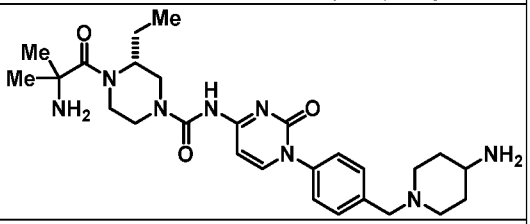
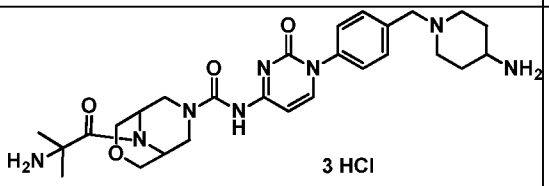
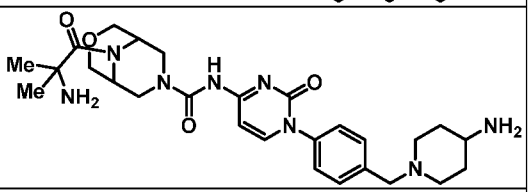
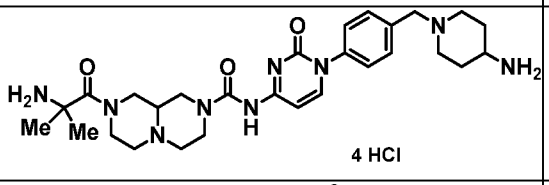
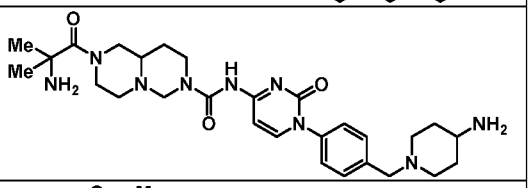
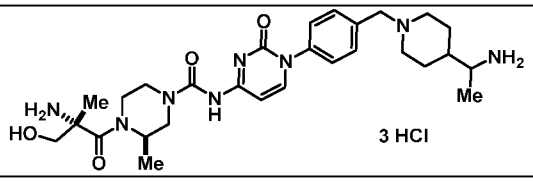
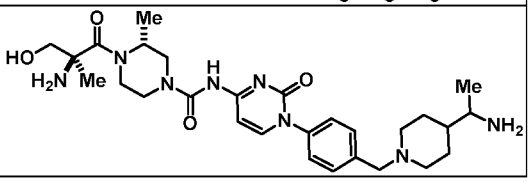
No.	Salt Structure	Free Base Structure
26		
27		
28		
29		
30		
31		

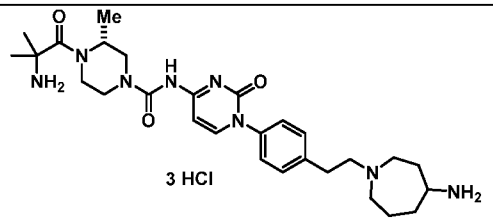
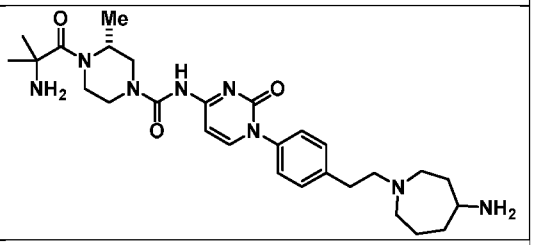
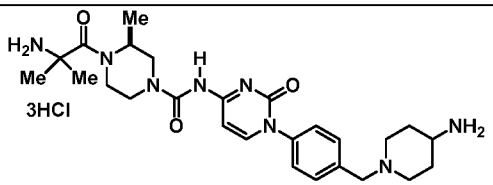
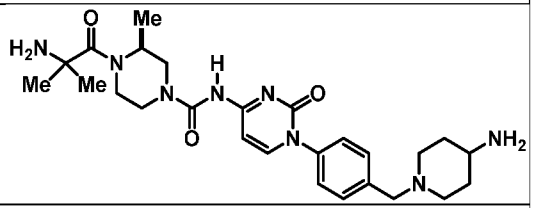
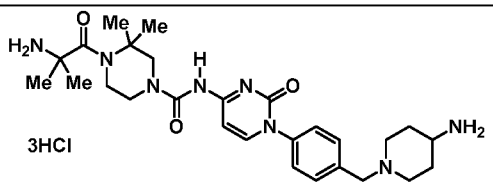
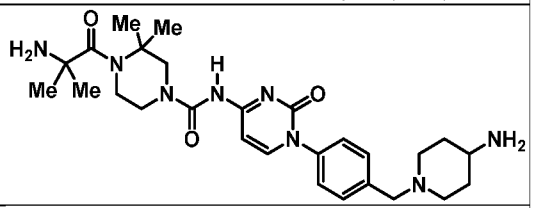
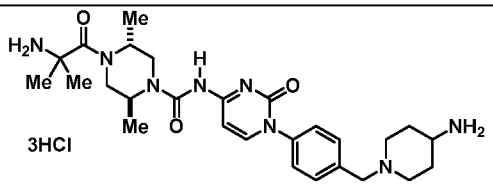
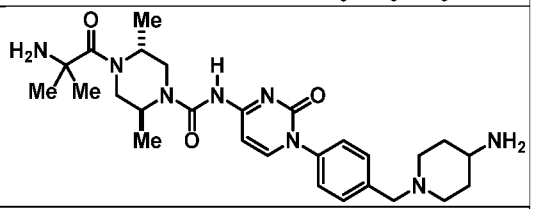
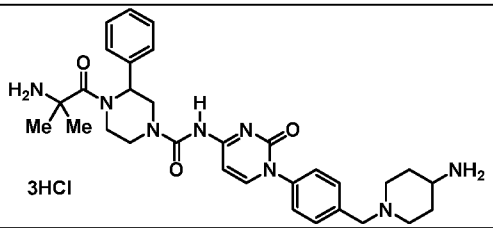
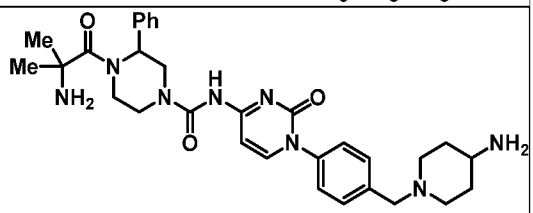
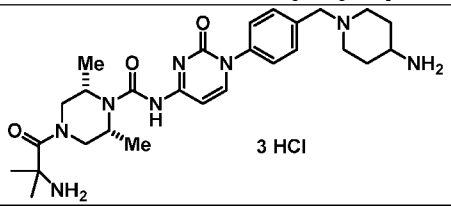
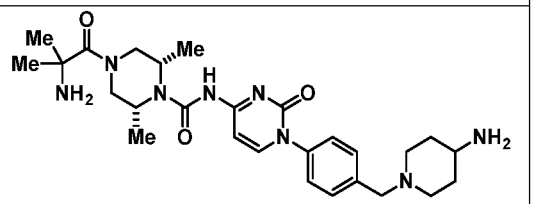
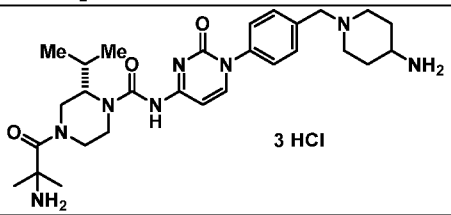
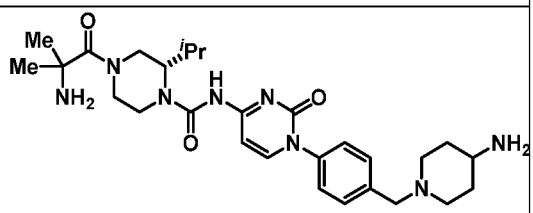
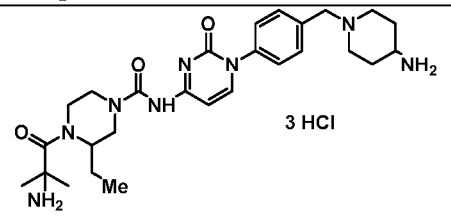
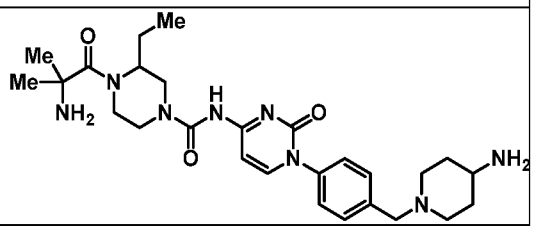
No.	Salt Structure	Free Base Structure
32	 3 HCl	
33	 3 HCl	
34	 3HCl	
35	 3 HCl	
36	 3HCl	
37	 3HCl	
38	 3HCl	

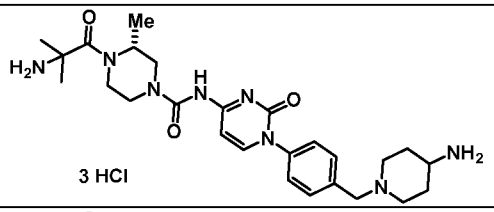
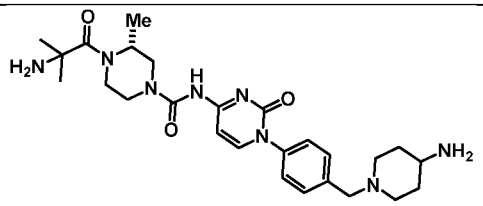
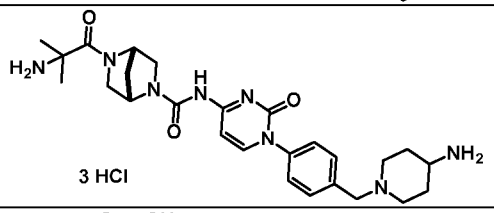
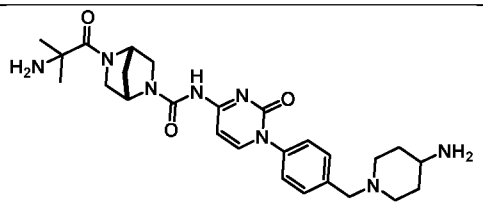
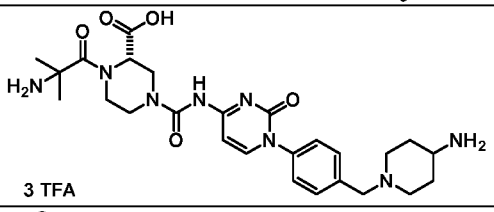
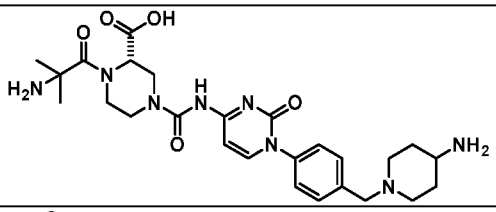
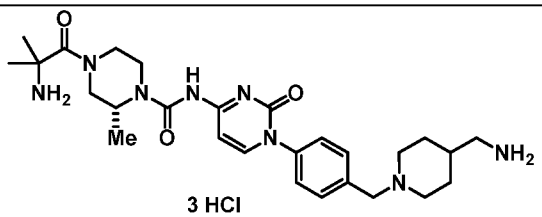
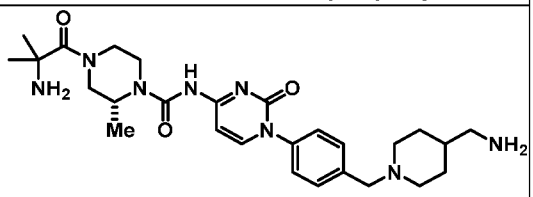
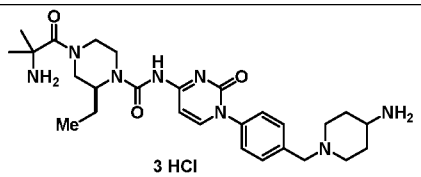
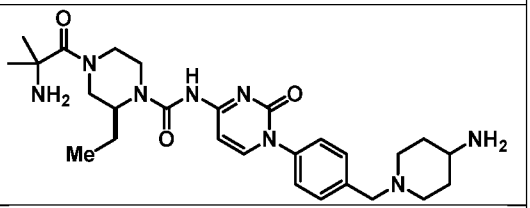
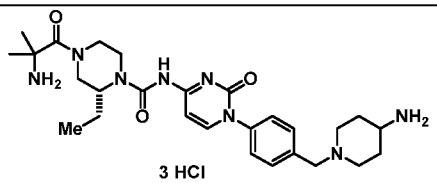
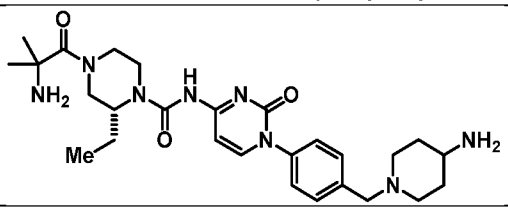
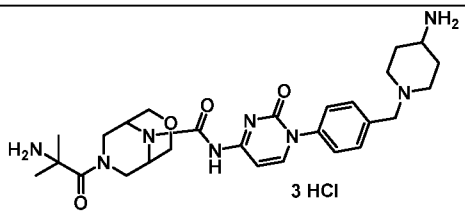
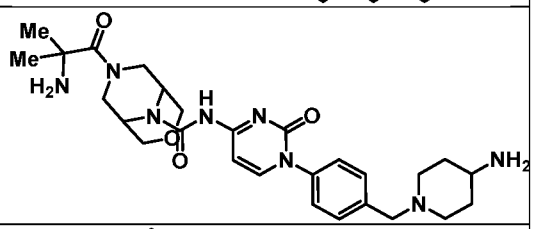
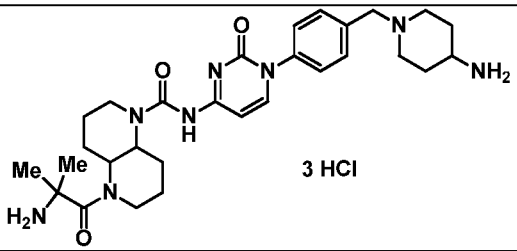
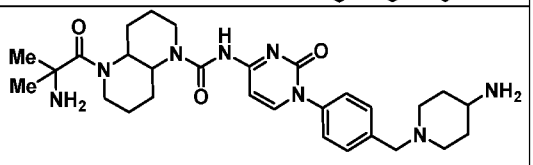
No.	Salt Structure	Free Base Structure
39		
40		
41		
42		
43		
44		
45		

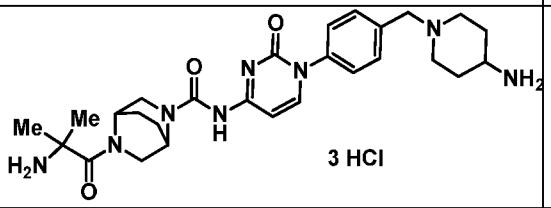
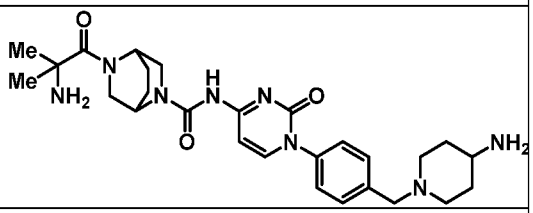
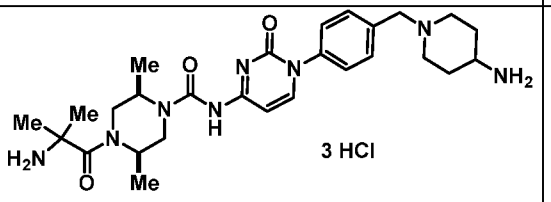
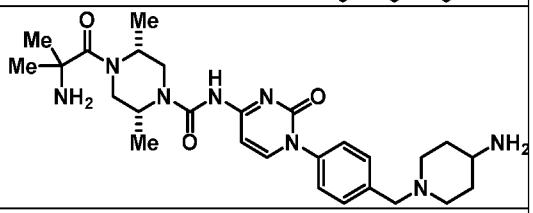
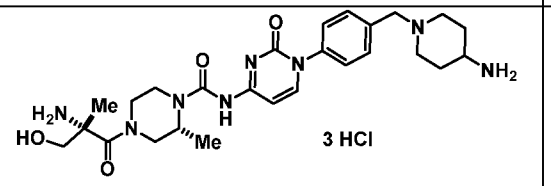
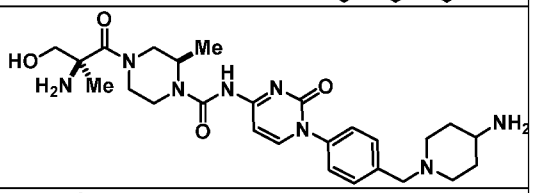
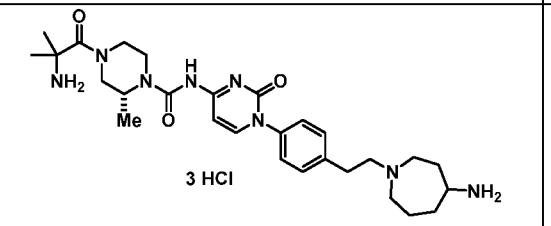
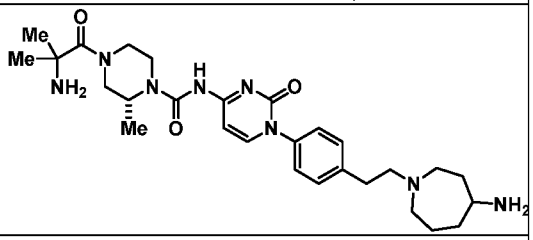
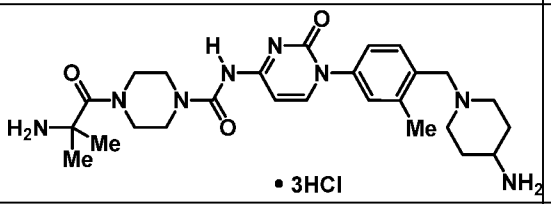
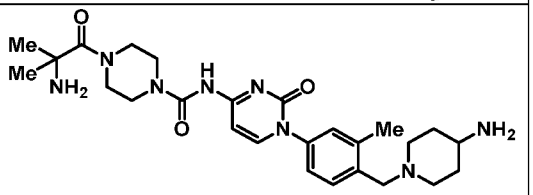
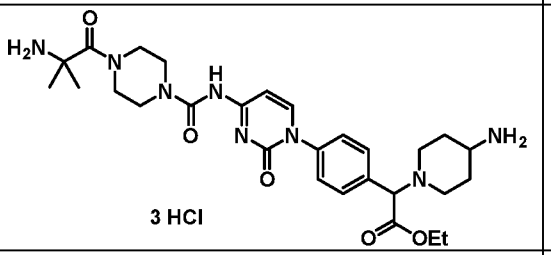
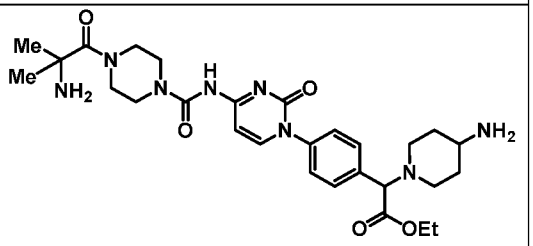
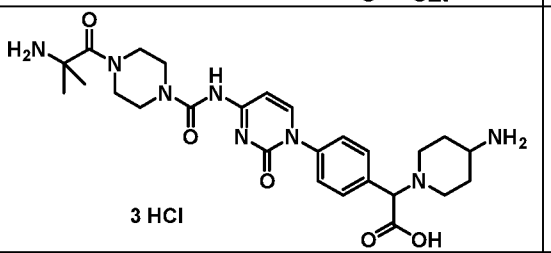
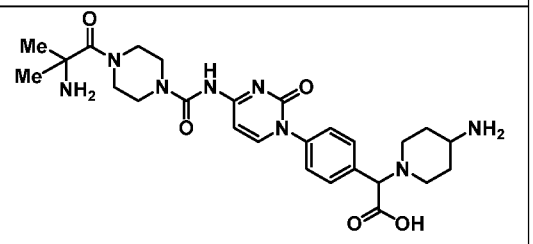
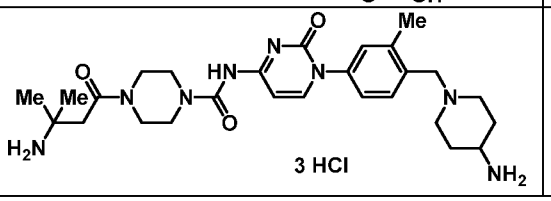
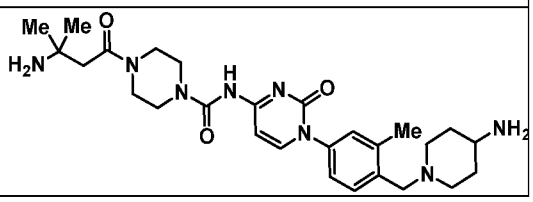
No.	Salt Structure	Free Base Structure
46		
47		
48		
49		
50		
51		
52		
53		

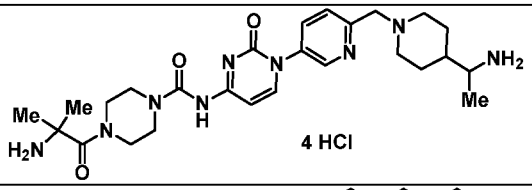
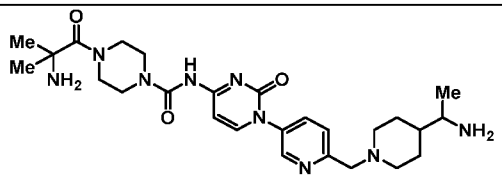
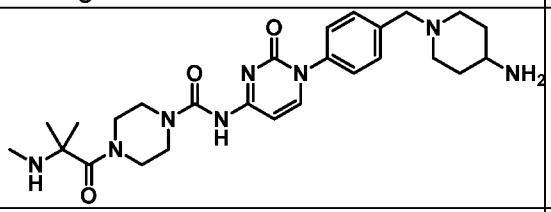
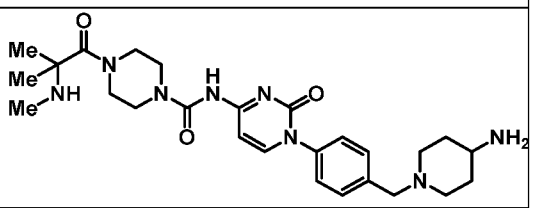
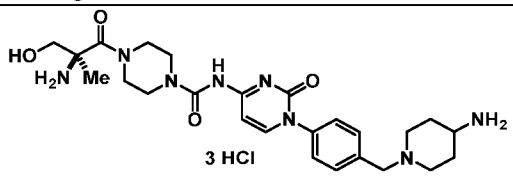
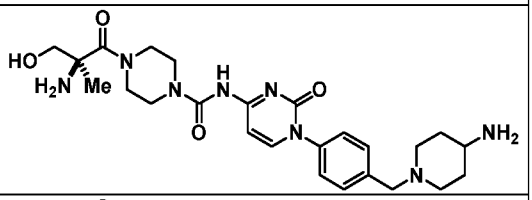
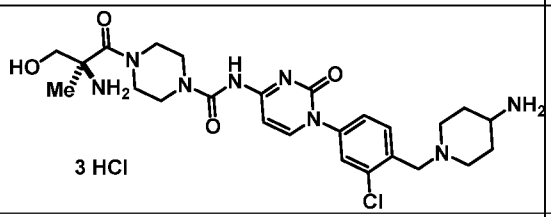
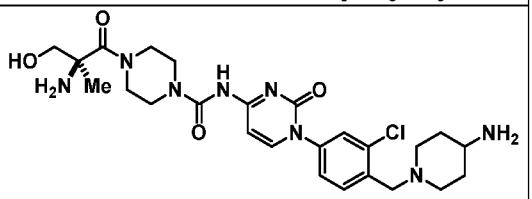
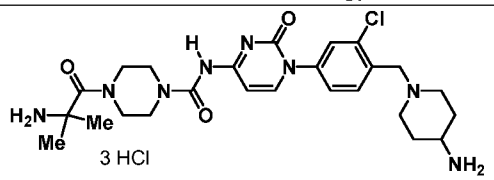
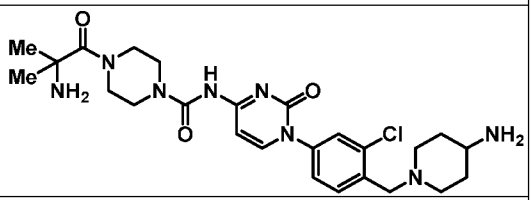
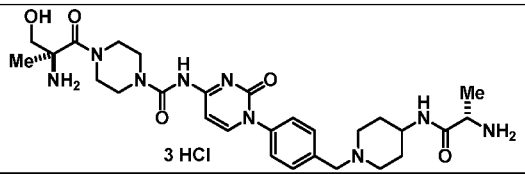
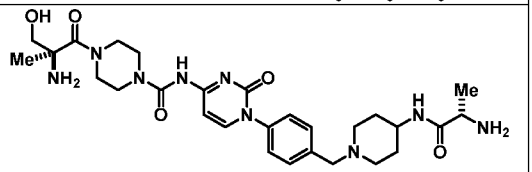
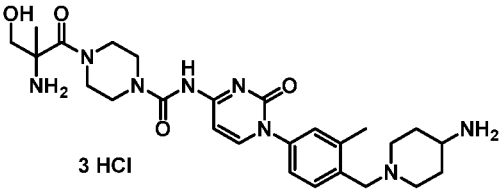
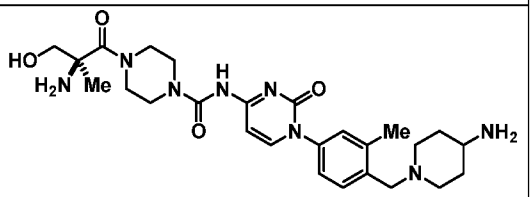
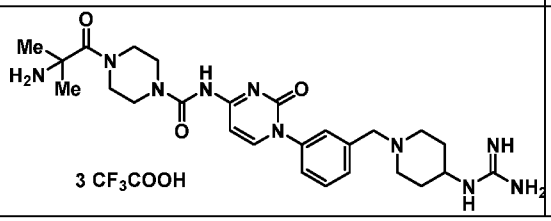
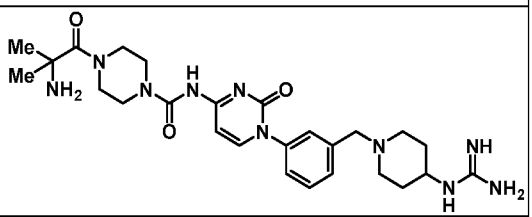
No.	Salt Structure	Free Base Structure
54	 3 HCl	
55	 • 3HCl	
56	 3HCl	
57	 3 HCl	
58	 3HCl	
59	 3HCl	
60	 3HCl	
61	 3 HCl	
62	 3 HCl	

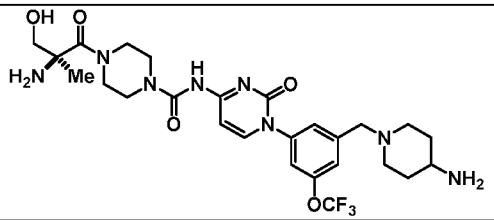
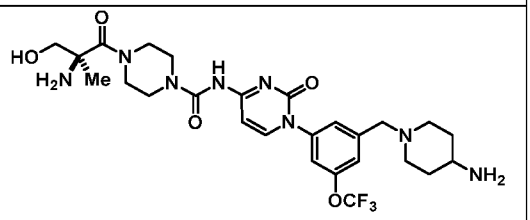
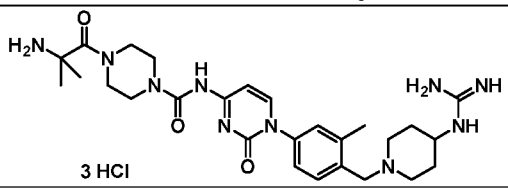
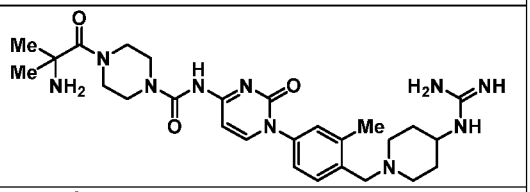
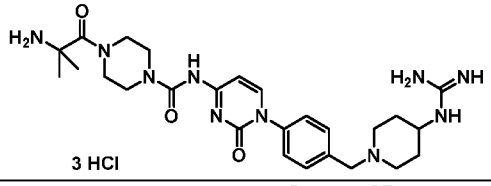
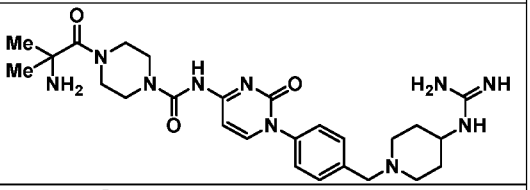
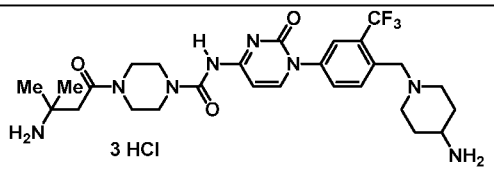
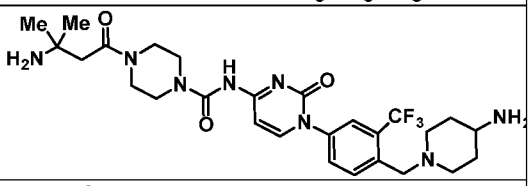
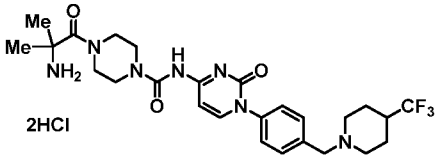
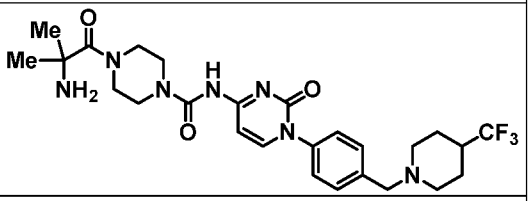
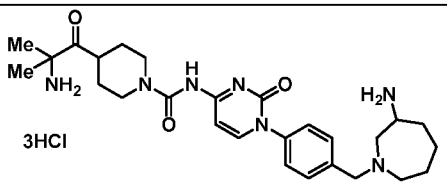
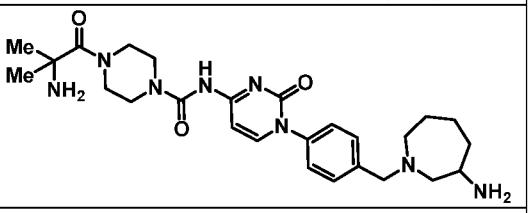
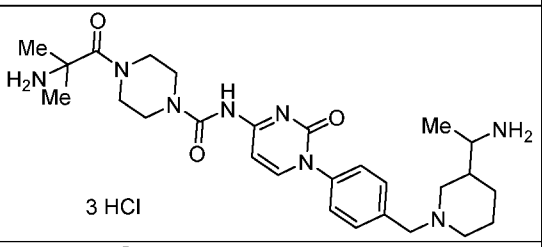
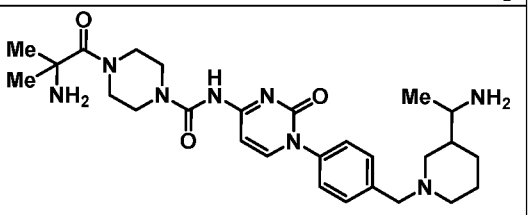
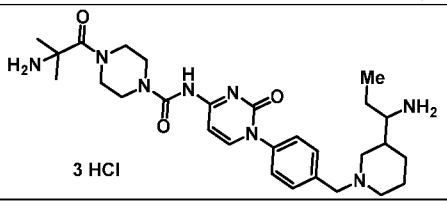
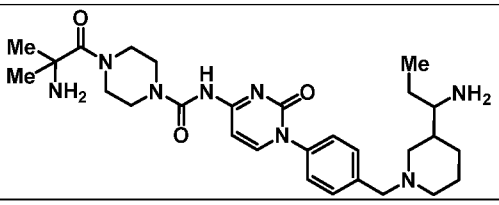
No.	Salt Structure	Free Base Structure
63	 3 HCl	
64	 3 TFA	
65	 3 HCl	
66	 3 HCl	
67	 3 HCl	
68	 3 HCl	
69	 4 HCl	
70	 3 HCl	

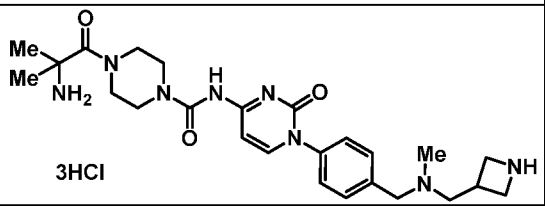
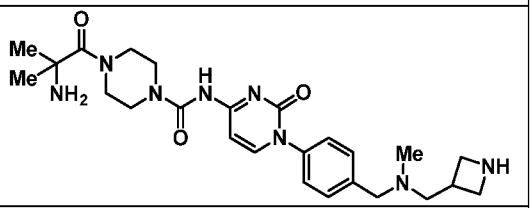
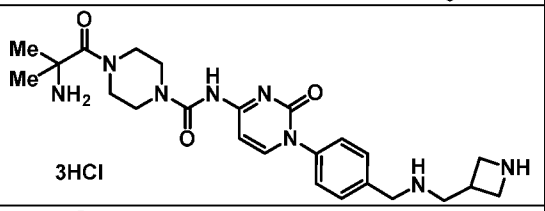
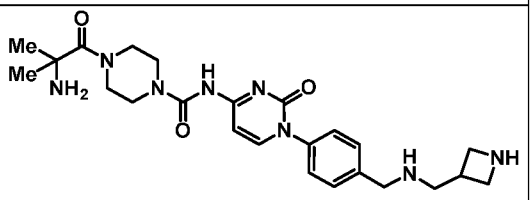
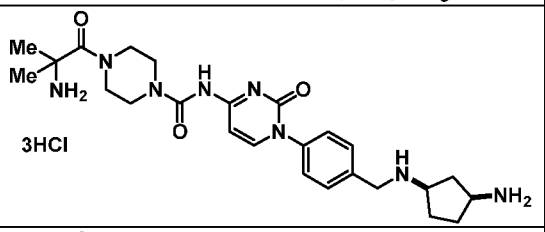
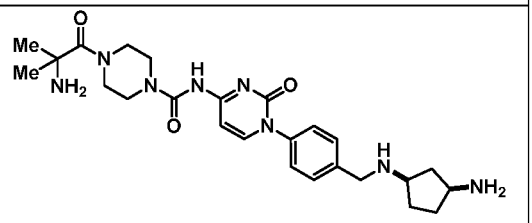
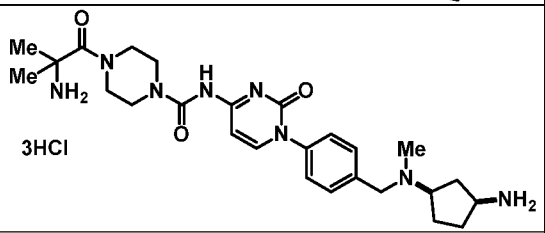
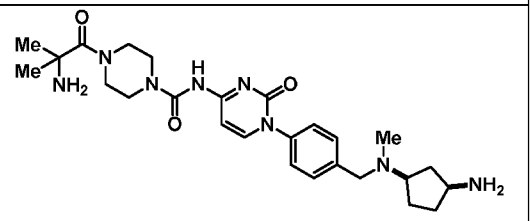
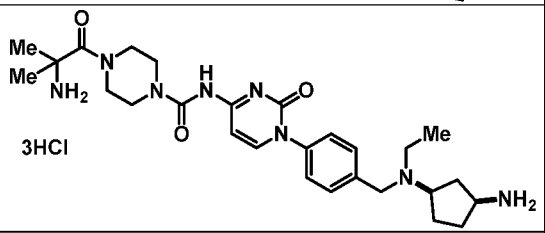
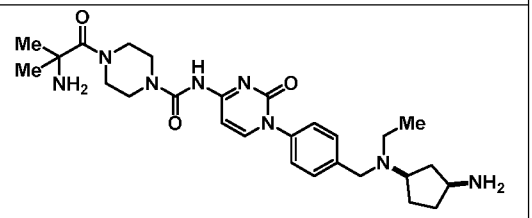
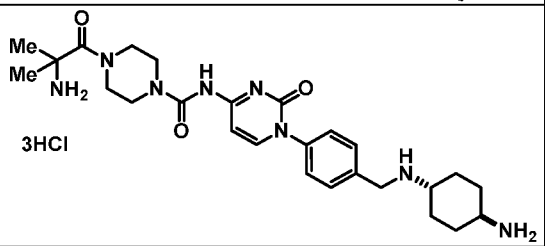
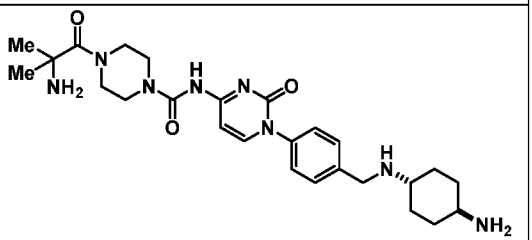
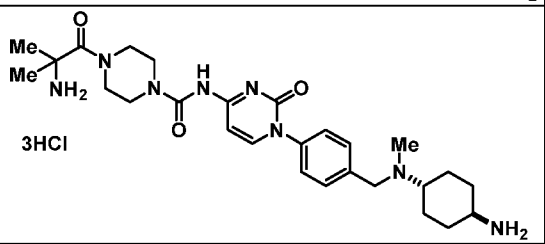
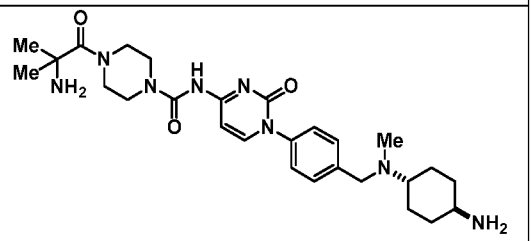
No.	Salt Structure	Free Base Structure
71		
72		
73		
74		
75		
76		
77		
78		

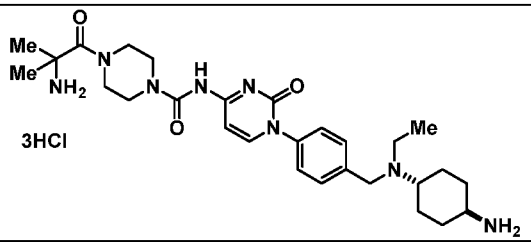
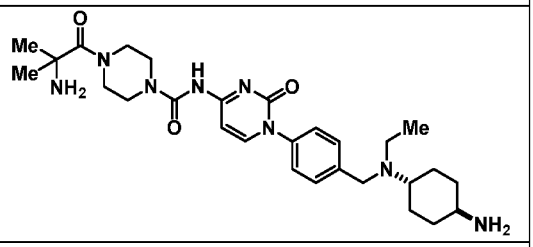
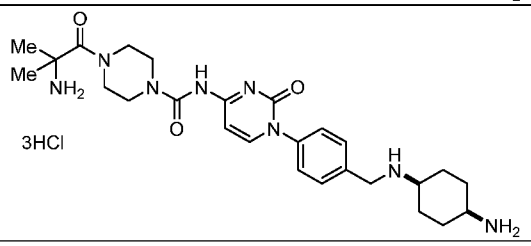
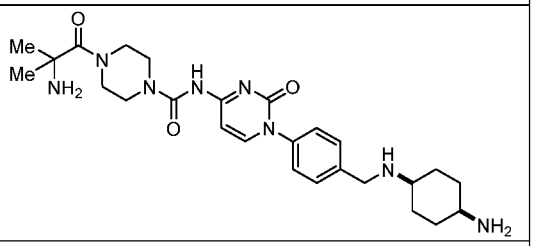
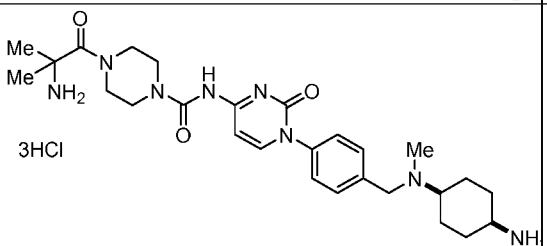
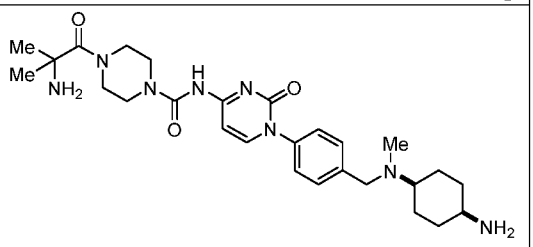
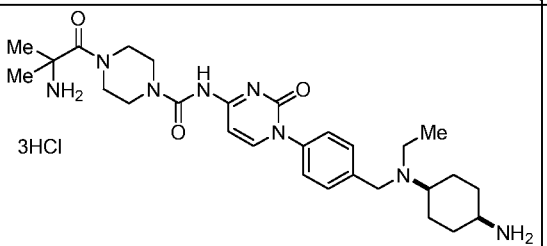
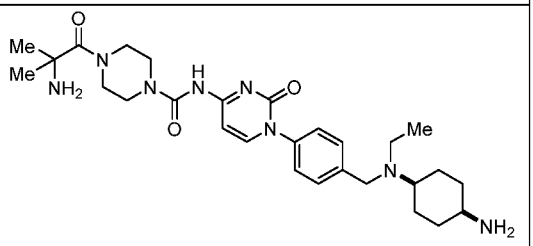
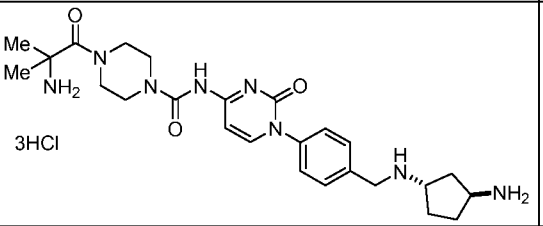
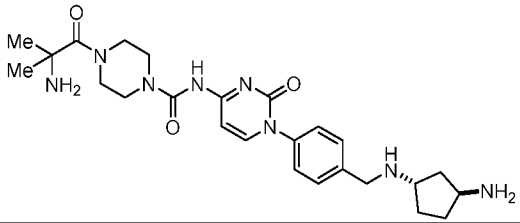
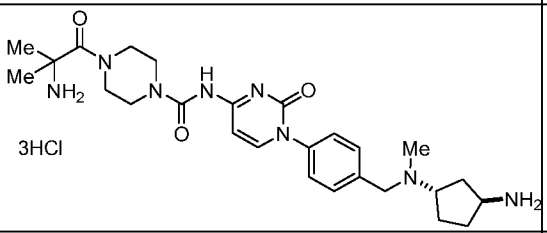
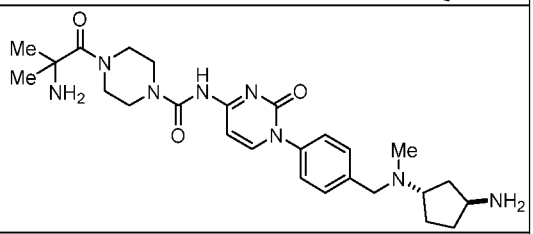
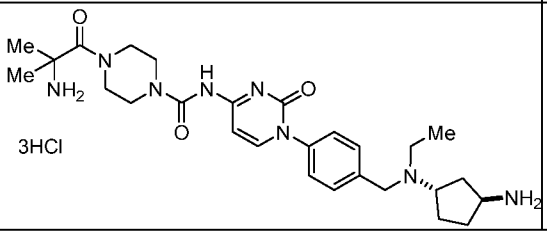
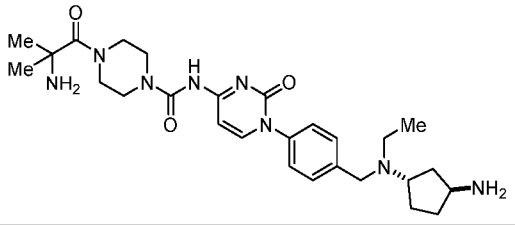
No.	Salt Structure	Free Base Structure
79	 3 HCl	
80	 3 HCl	
81	 3 TFA	
82	 3 HCl	
83	 3 HCl	
84	 3 HCl	
85	 3 HCl	
86	 3 HCl	

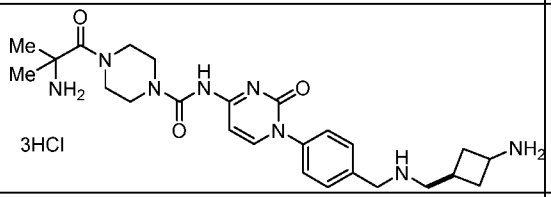
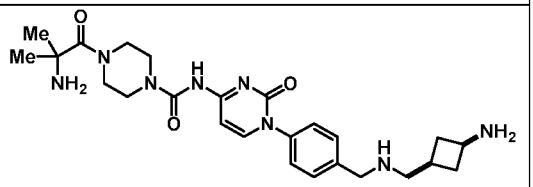
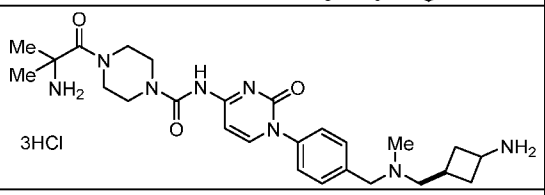
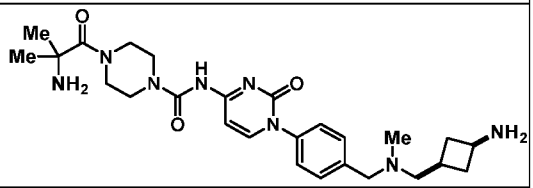
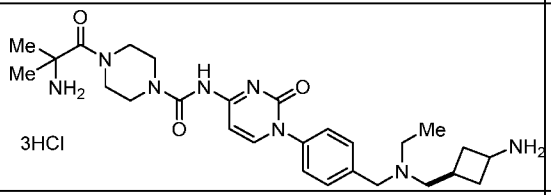
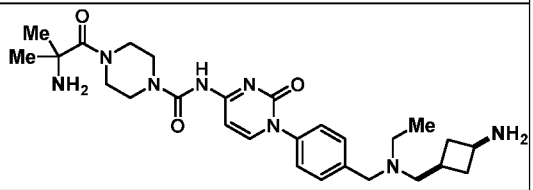
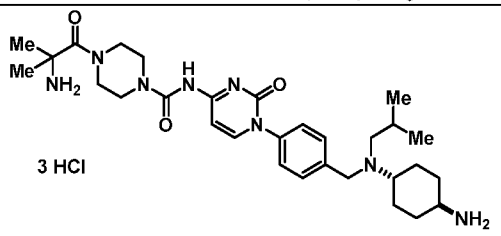
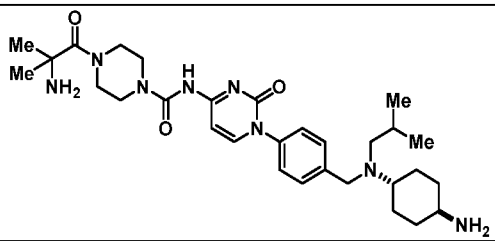
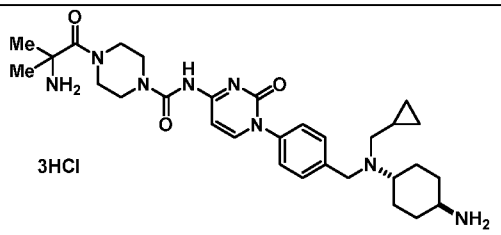
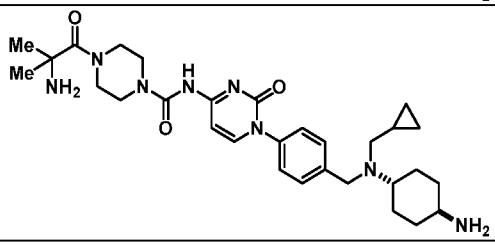
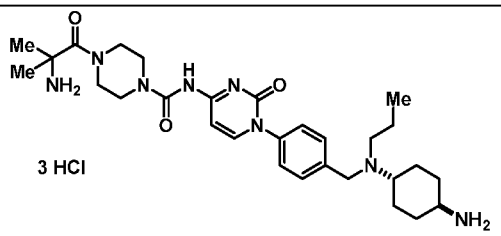
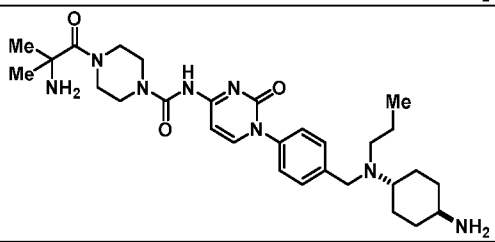
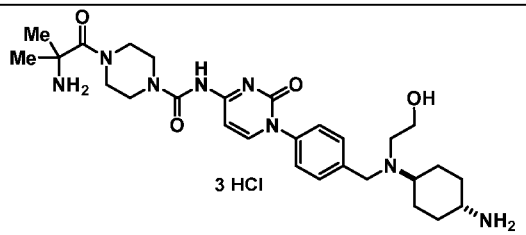
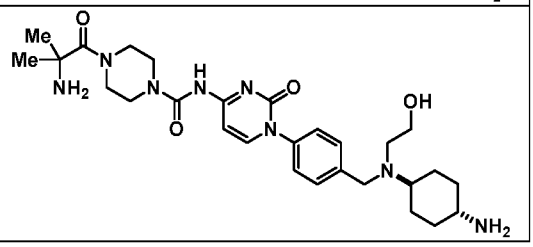
No.	Salt Structure	Free Base Structure
87	 3 HCl	
88	 3 HCl	
89	 3 HCl	
90	 3 HCl	
91	 • 3HCl	
92	 3 HCl	
93	 3 HCl	
94	 3 HCl	

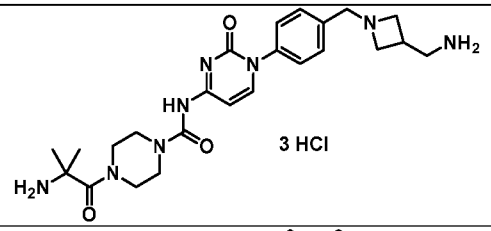
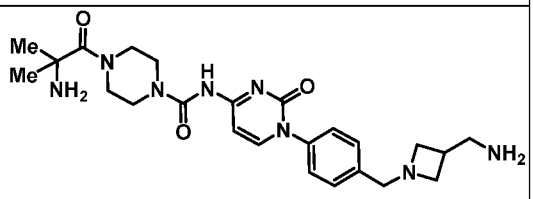
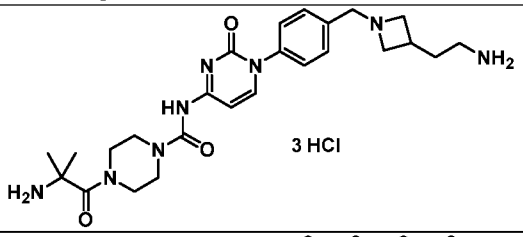
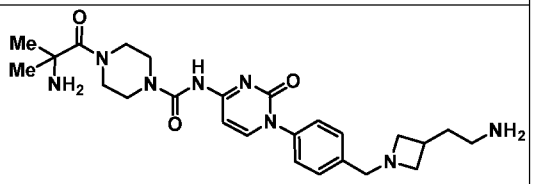
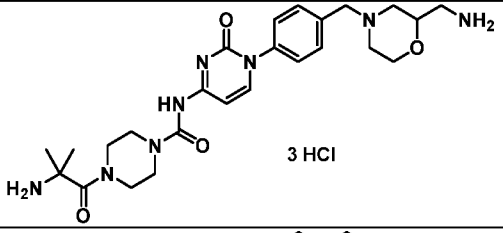
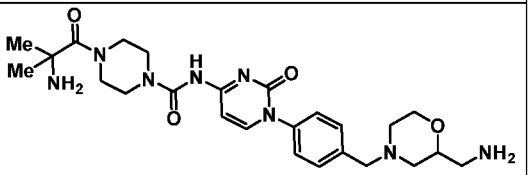
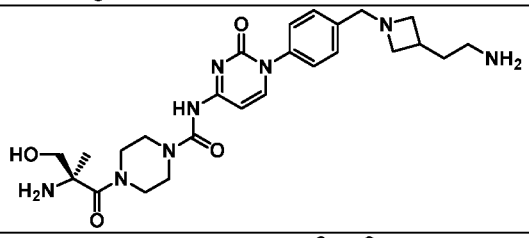
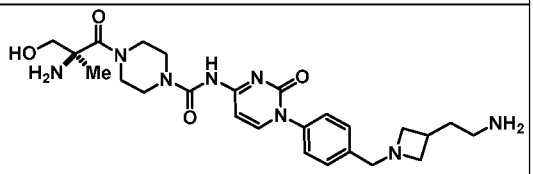
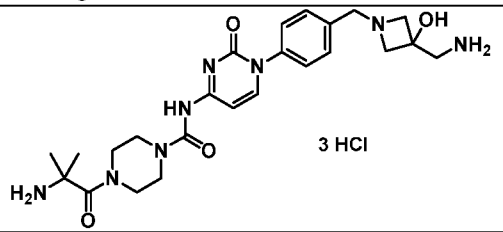
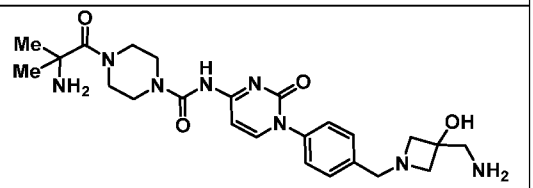
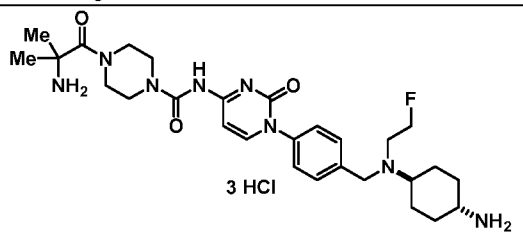
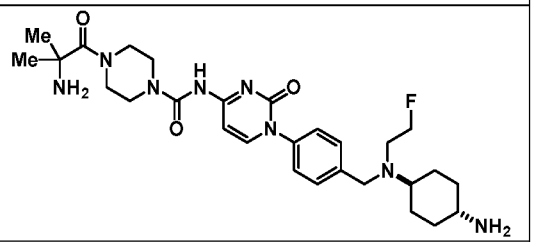
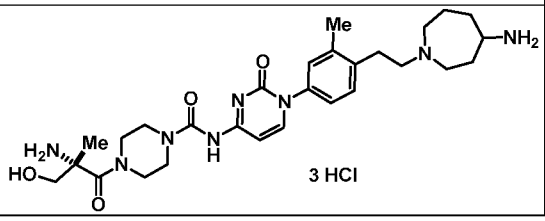
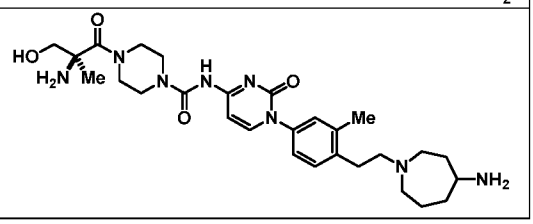
No.	Salt Structure	Free Base Structure
95	 4 HCl	
96		
97	 3 HCl	
98	 3 HCl	
99	 3 HCl	
100	 3 HCl	
101	 3 HCl	
102	 3 CF_3COOH	

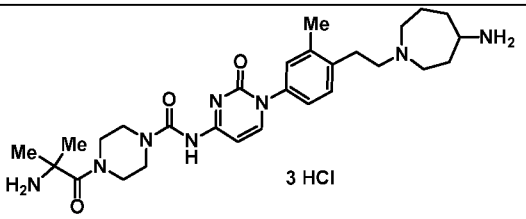
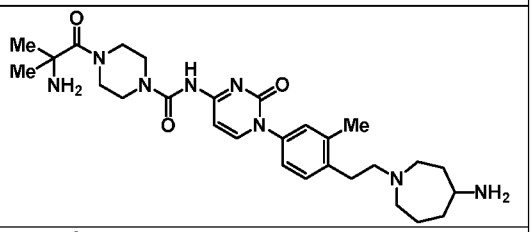
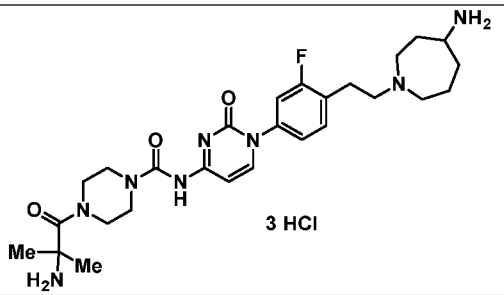
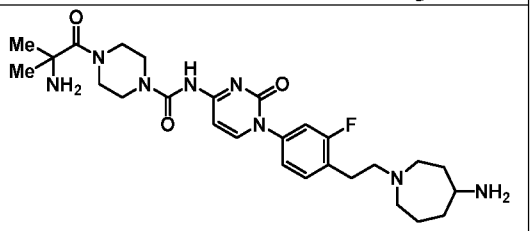
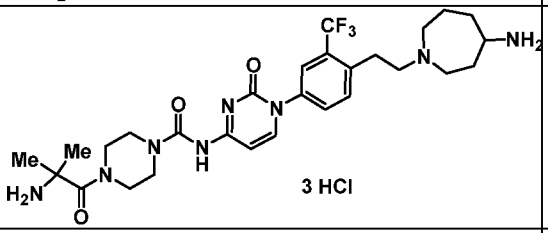
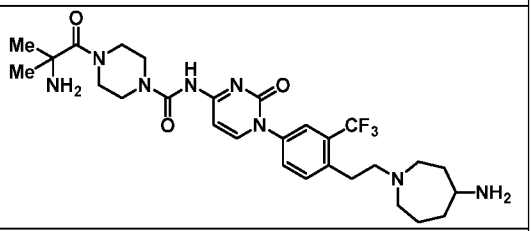
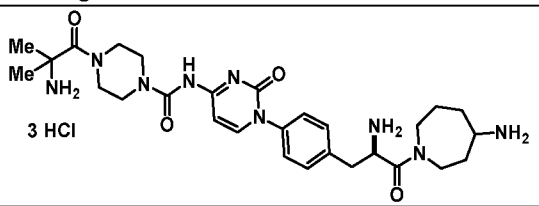
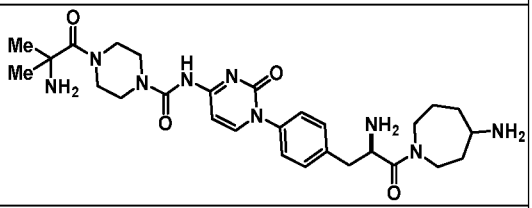
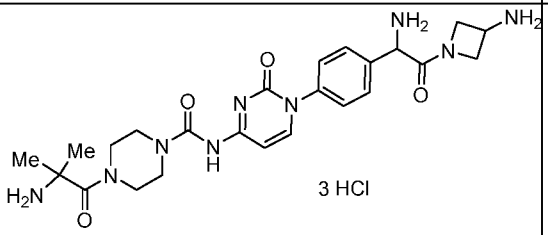
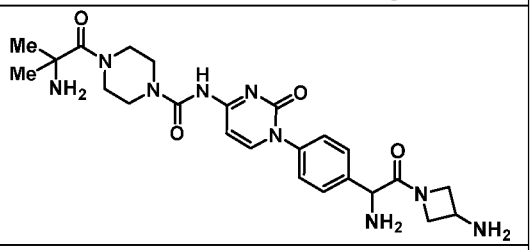
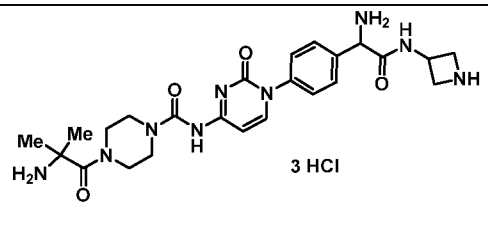
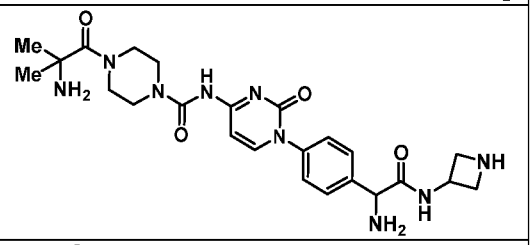
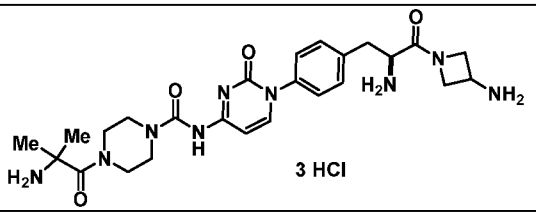
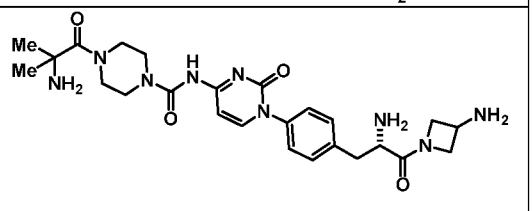
No.	Salt Structure	Free Base Structure
103		
104		
105		
106		
107		
108		
109		
110		

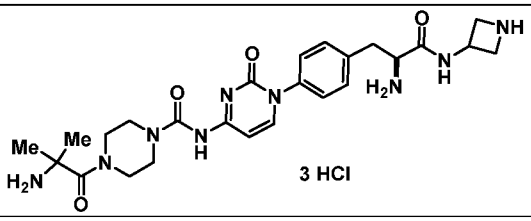
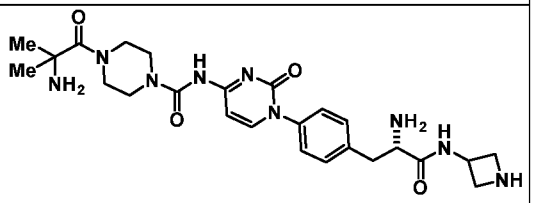
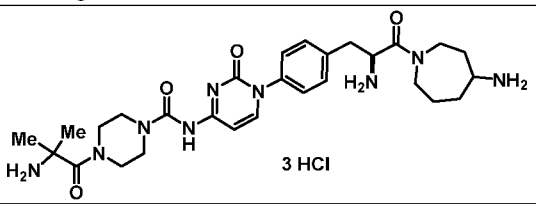
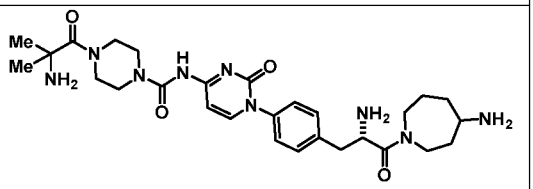
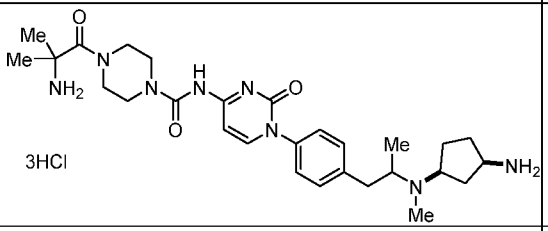
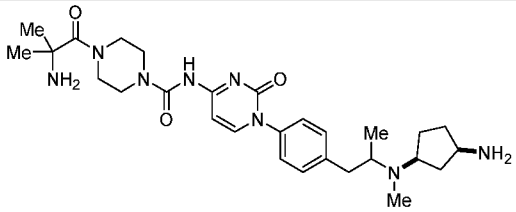
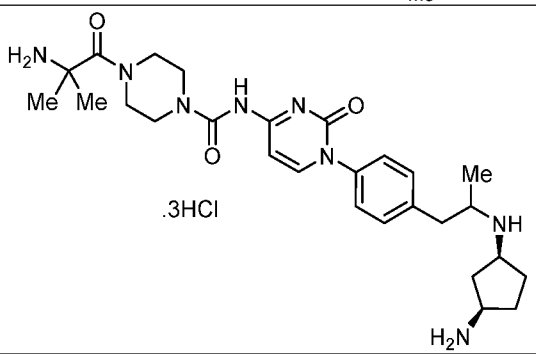
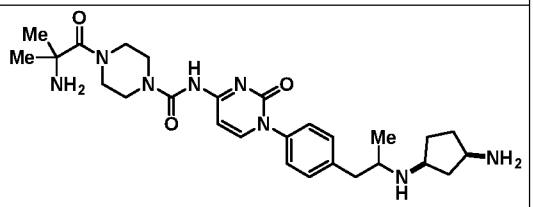
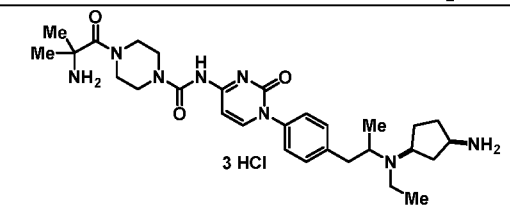
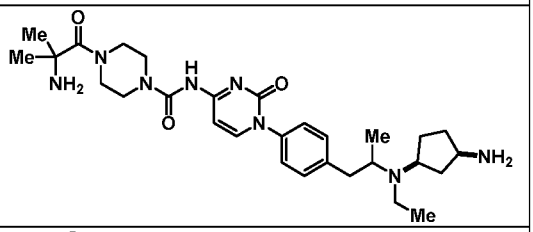
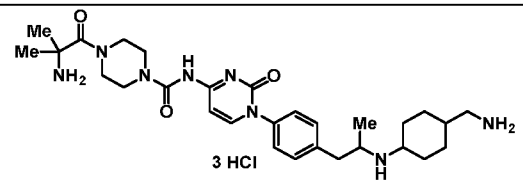
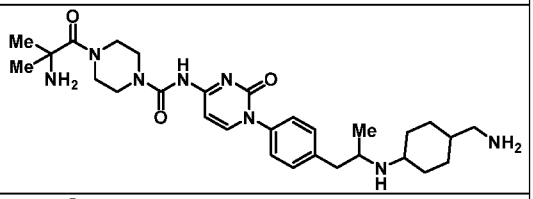
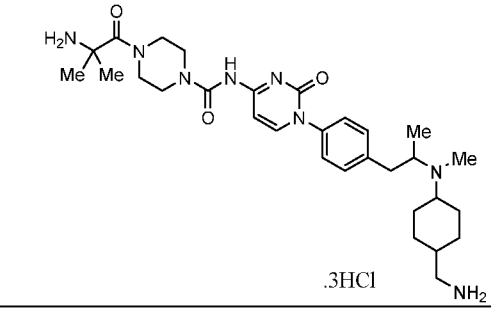
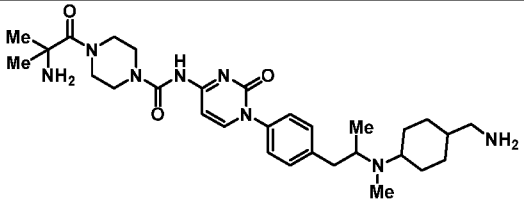
No.	Salt Structure	Free Base Structure
111		
112		
114		
115		
116		
117		
118		

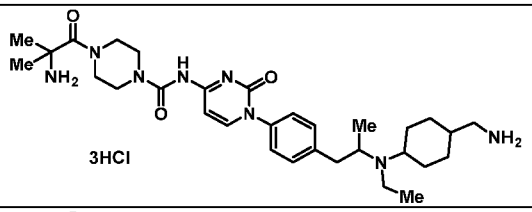
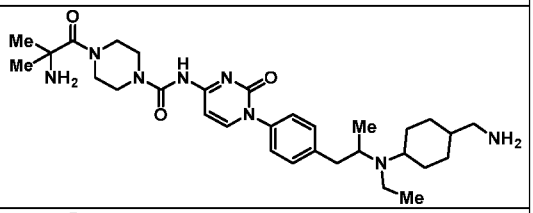
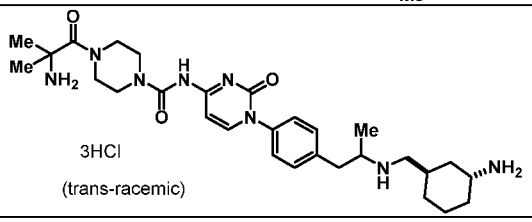
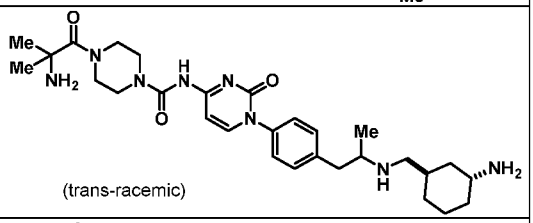
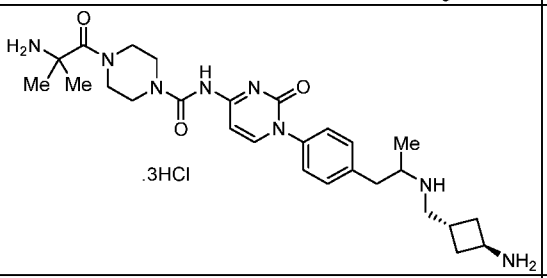
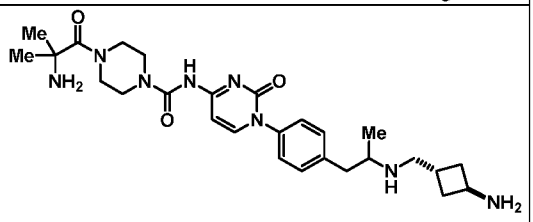
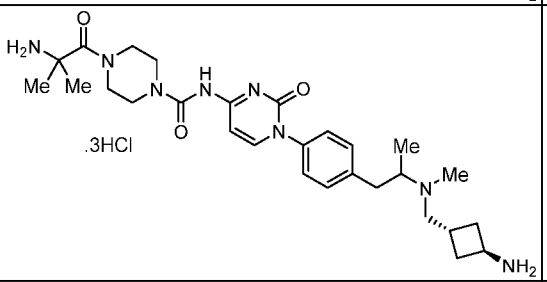
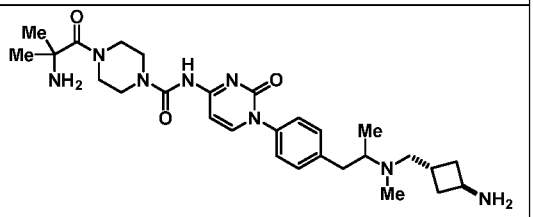
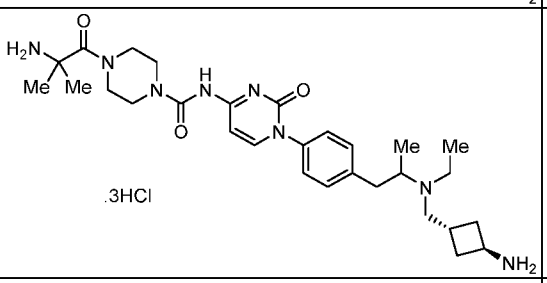
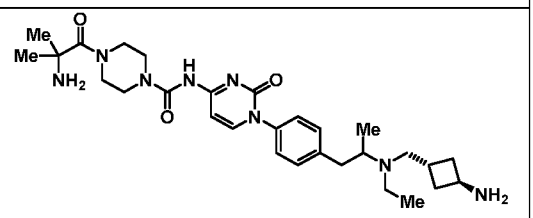
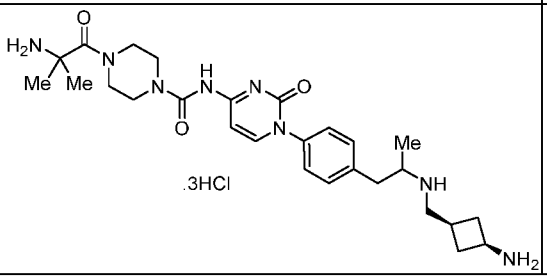
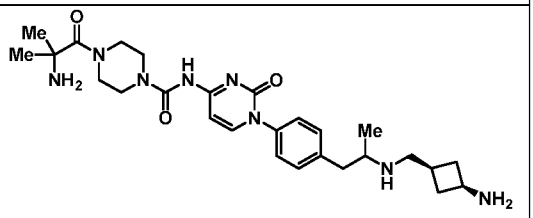
No.	Salt Structure	Free Base Structure
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120		
121		
122		
123		
124		
125		

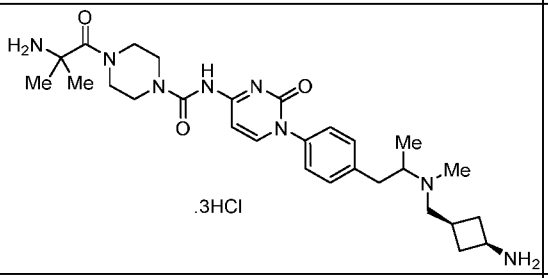
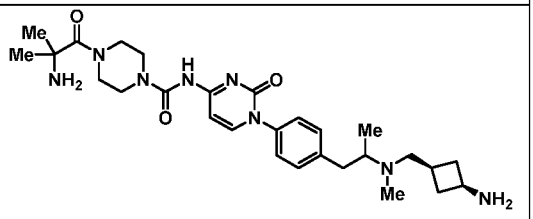
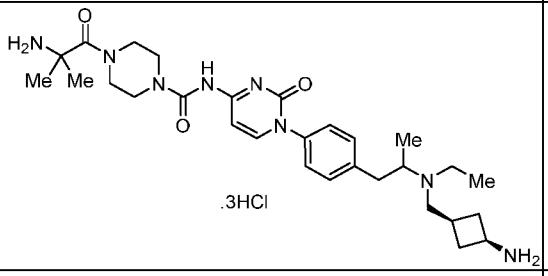
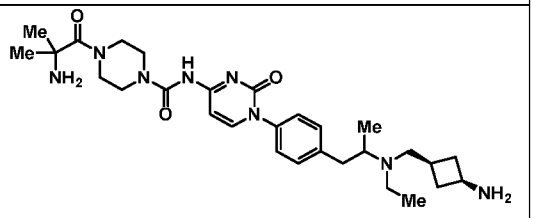
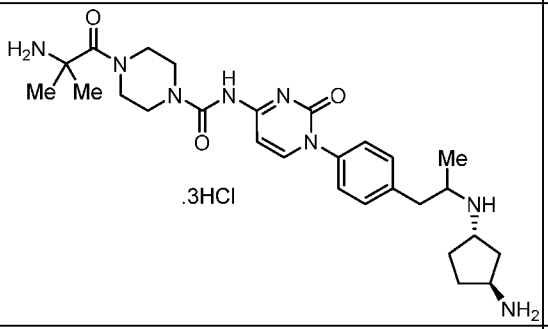
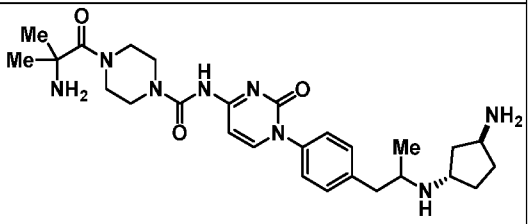
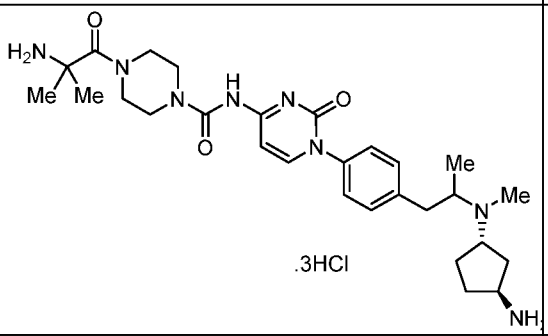
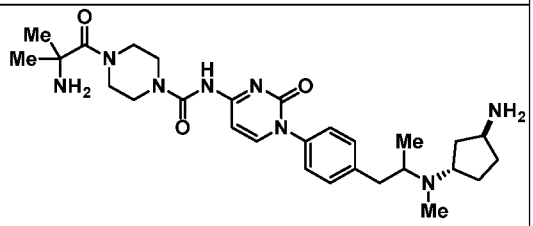
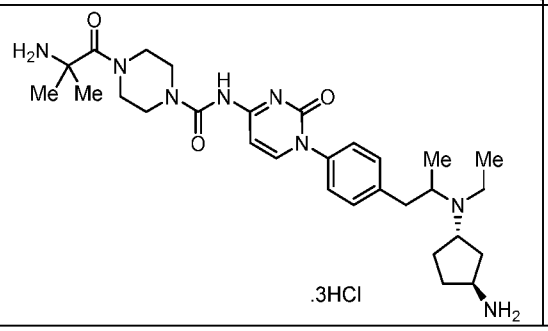
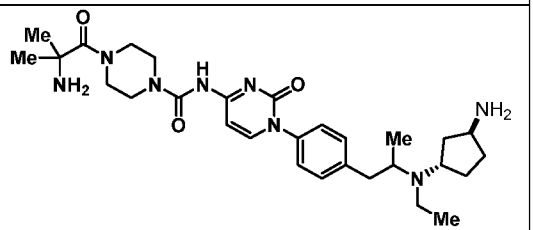
No.	Salt Structure	Free Base Structure
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127		
128		
129		
130		
131		
132		

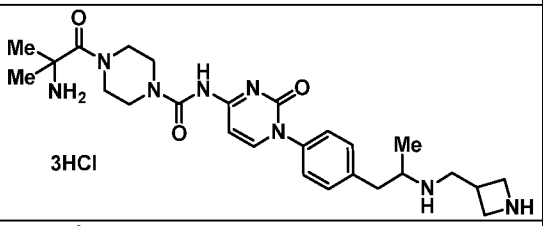
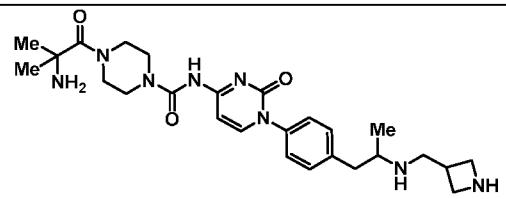
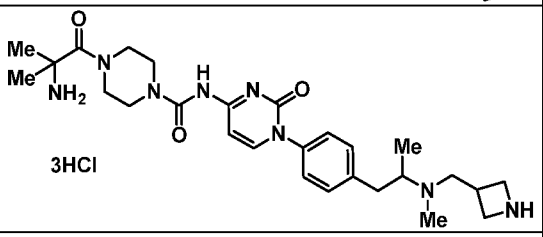
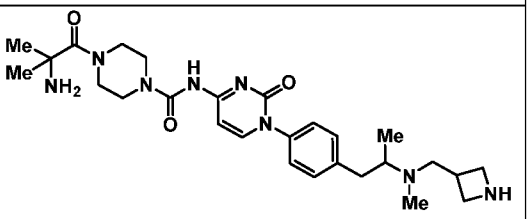
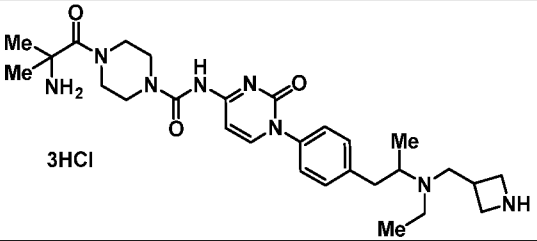
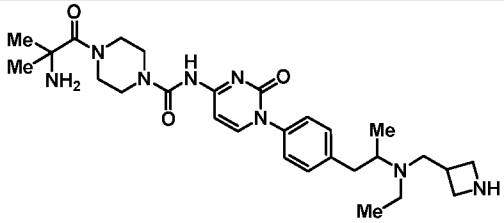
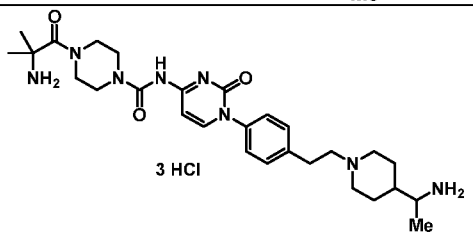
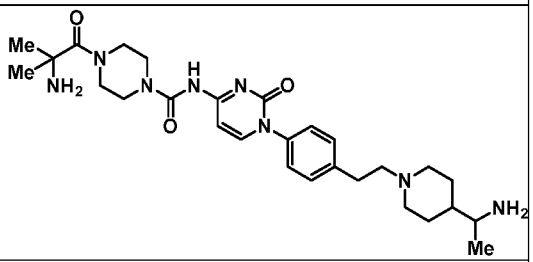
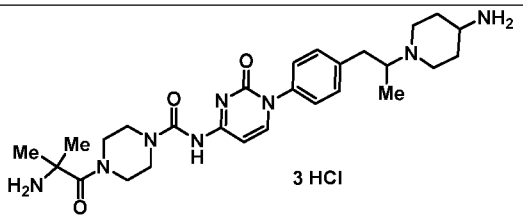
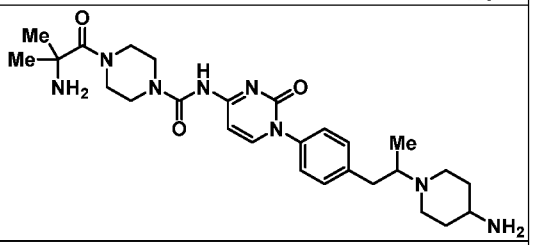
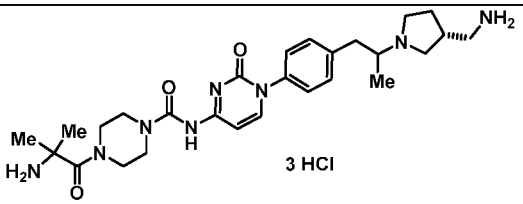
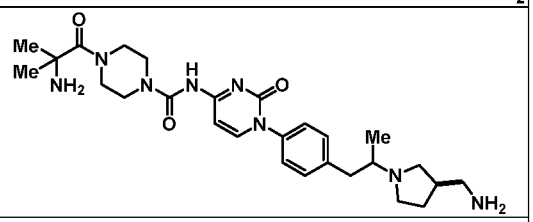
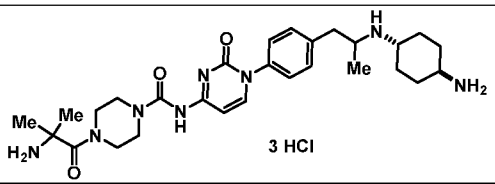
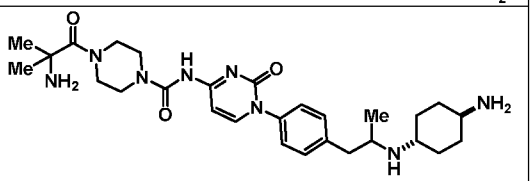
No.	Salt Structure	Free Base Structure
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134		
135		
136		
137		
138		
139		

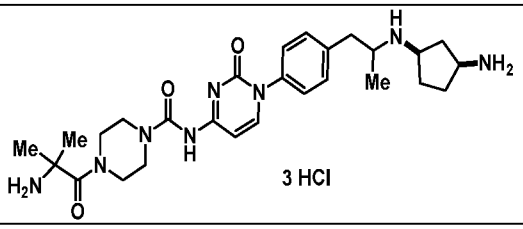
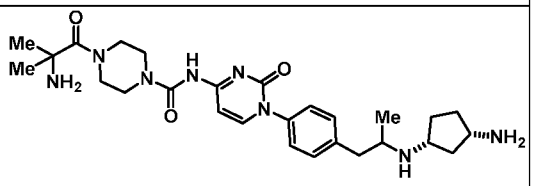
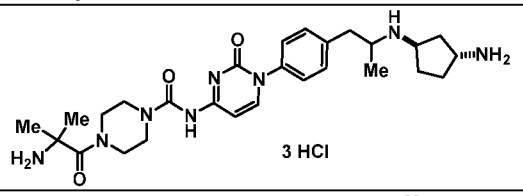
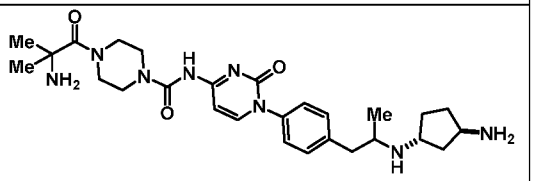
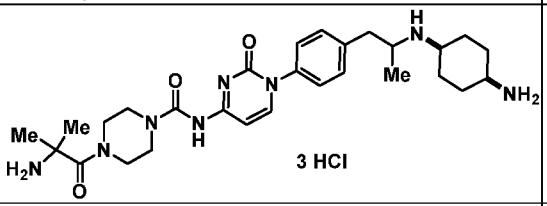
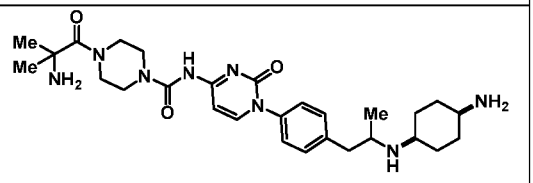
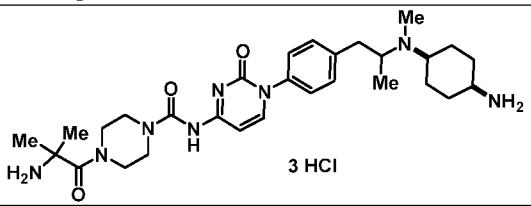
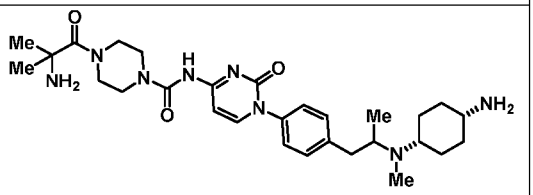
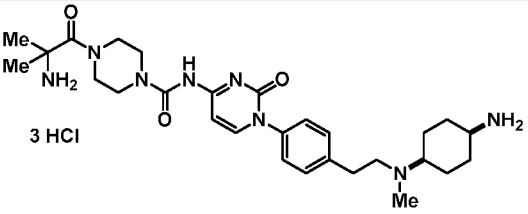
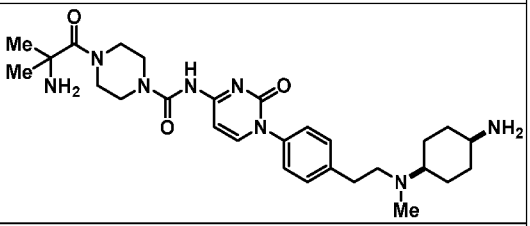
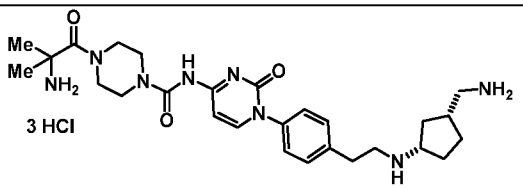
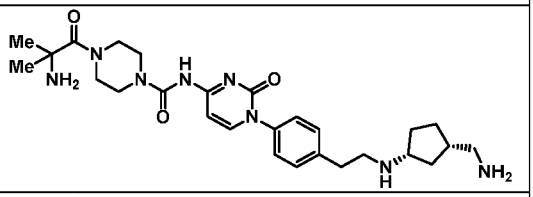
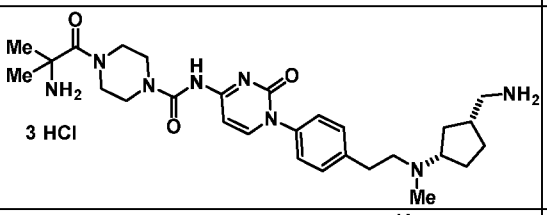
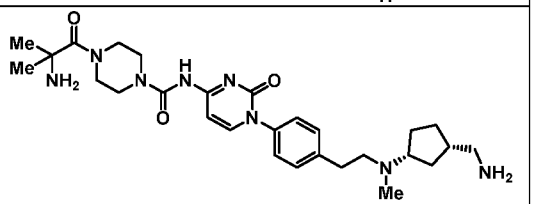
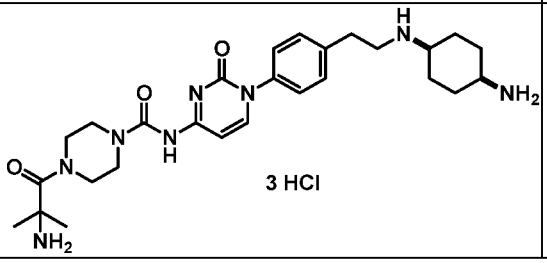
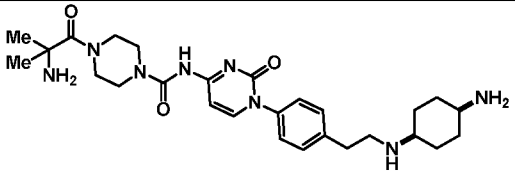
No.	Salt Structure	Free Base Structure
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141		
142		
143		
144		
145		
146		

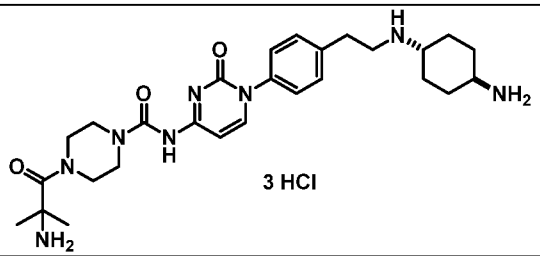
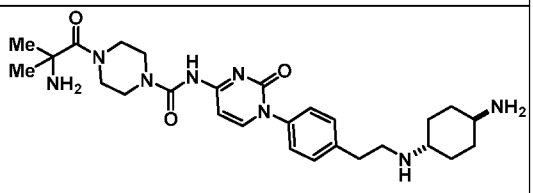
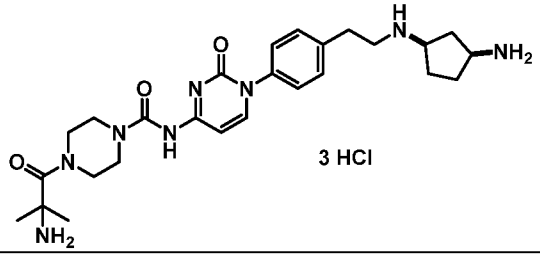
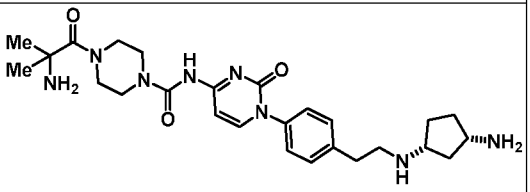
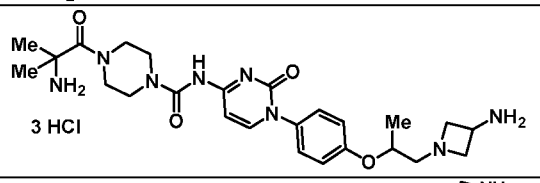
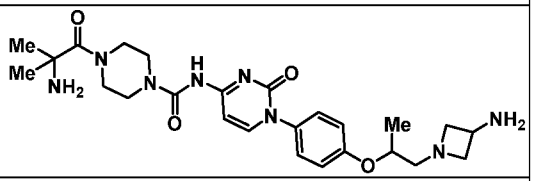
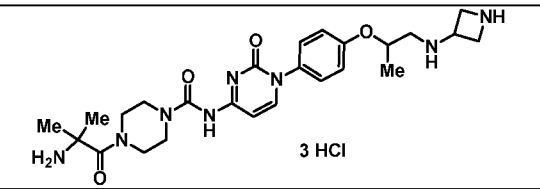
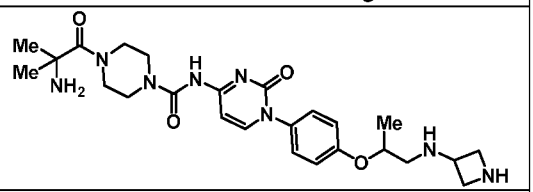
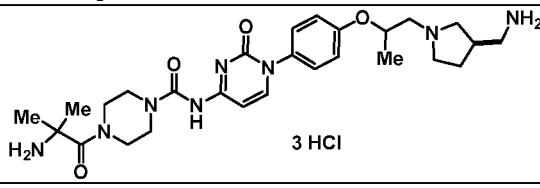
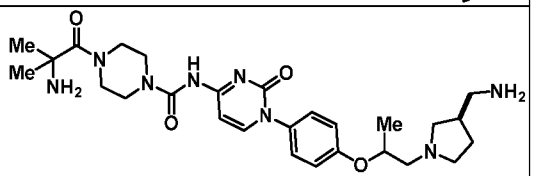
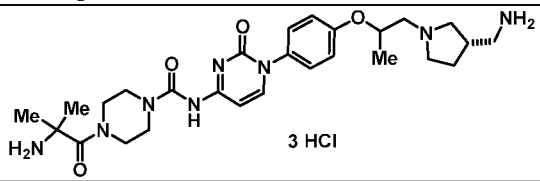
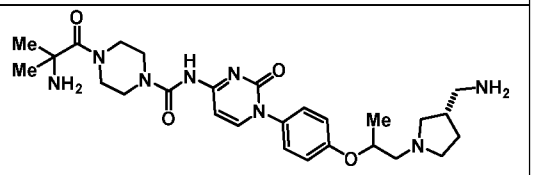
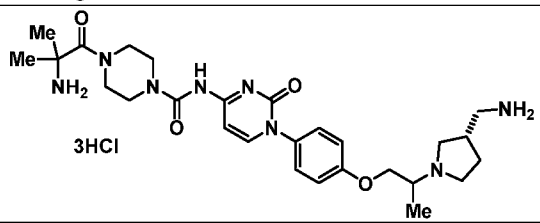
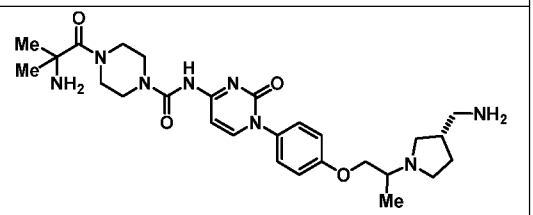
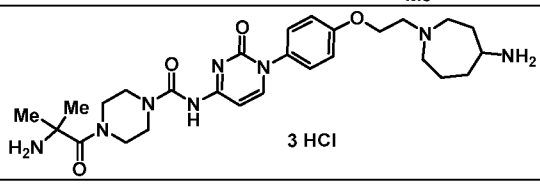
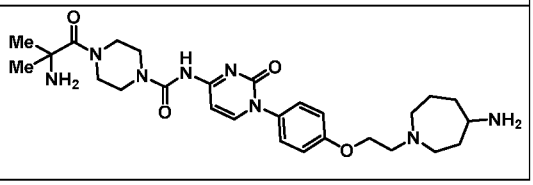
No.	Salt Structure	Free Base Structure
147	 3 HCl	
148	 3 HCl	
149	 3HCl	
150	 .3HCl	
151	 3 HCl	
152	 3 HCl	
153	 .3HCl	

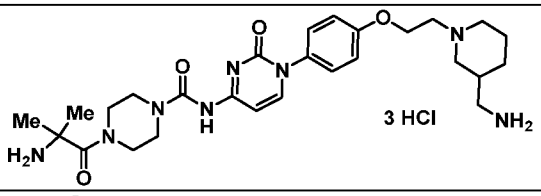
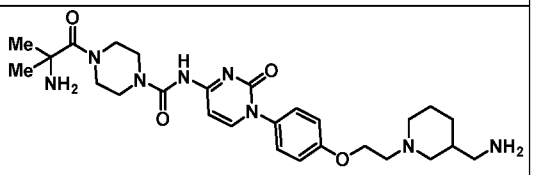
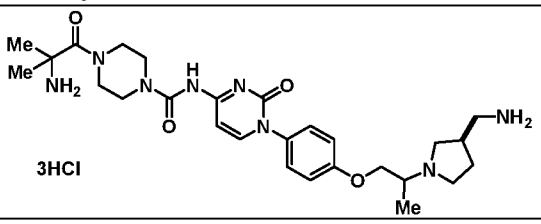
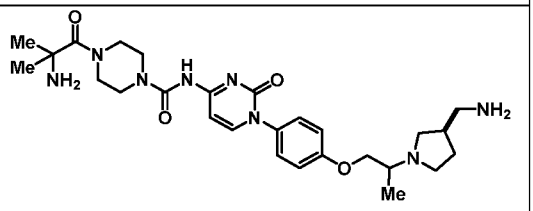
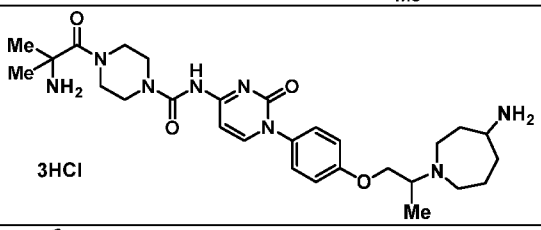
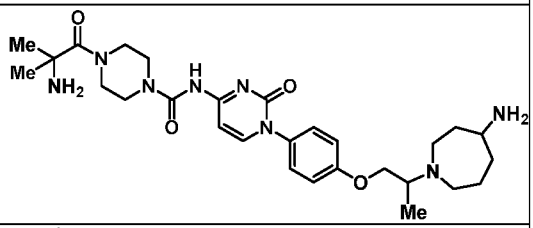
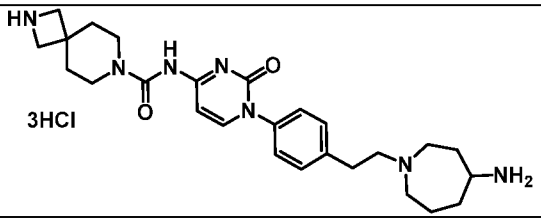
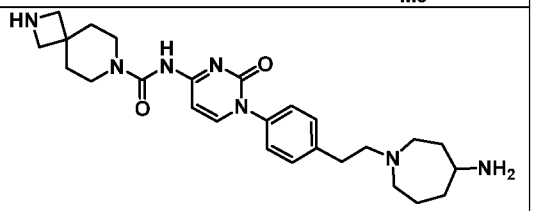
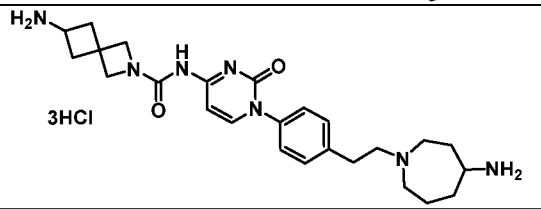
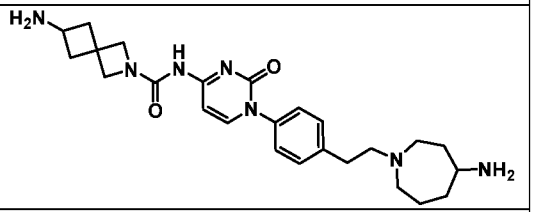
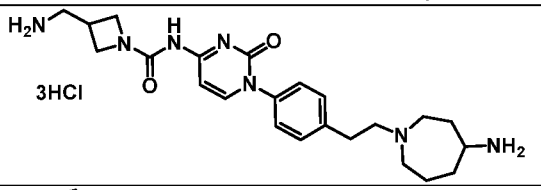
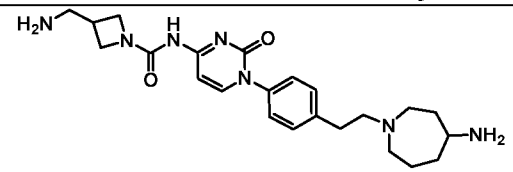
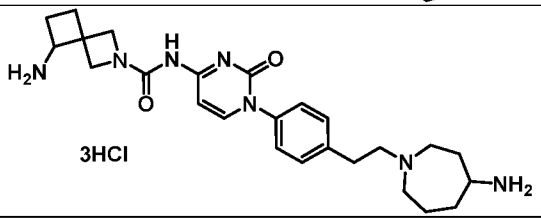
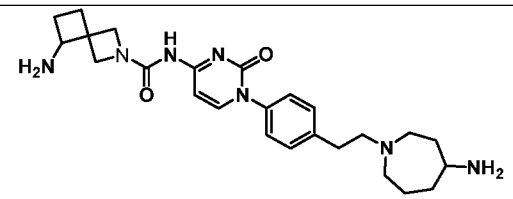
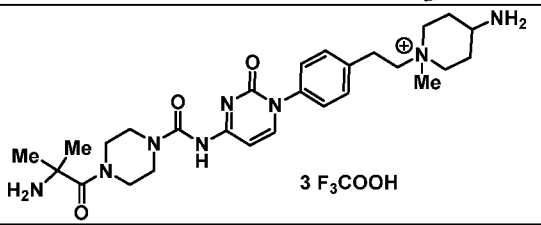
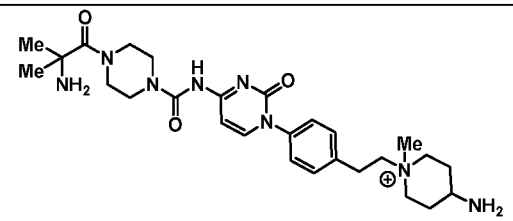
No.	Salt Structure	Free Base Structure
154	 3HCl	
155	 3HCl (trans-racemic)	 (trans-racemic)
156	 .3HCl	
157	 .3HCl	
158	 .3HCl	
159	 .3HCl	

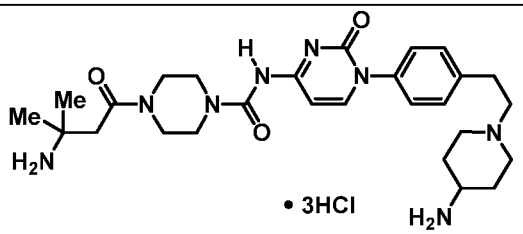
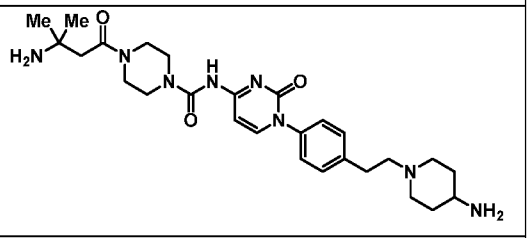
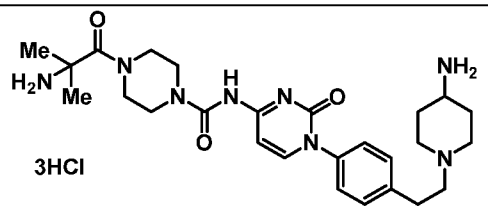
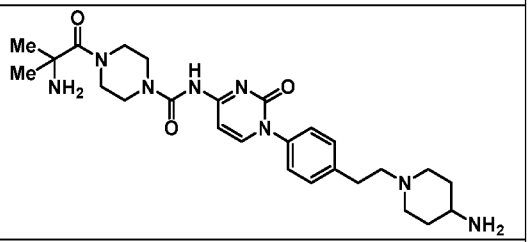
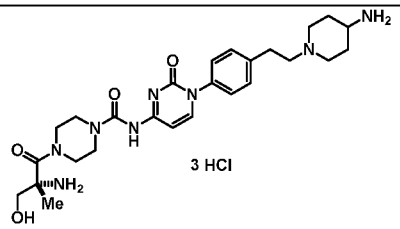
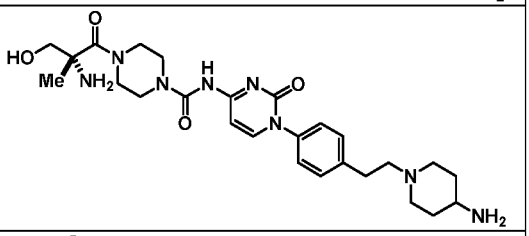
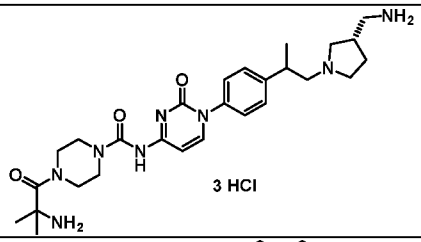
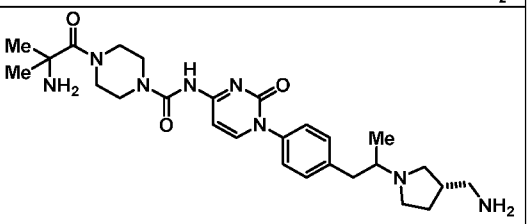
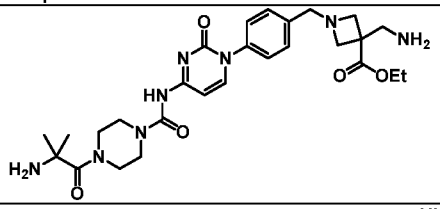
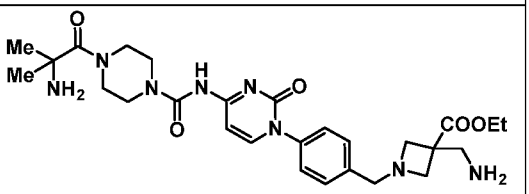
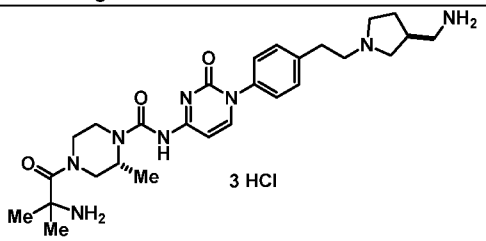
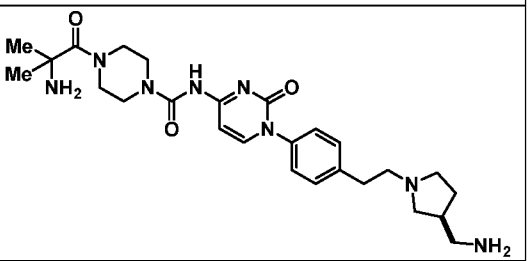
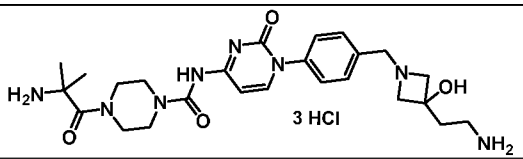
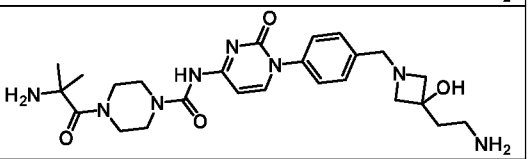
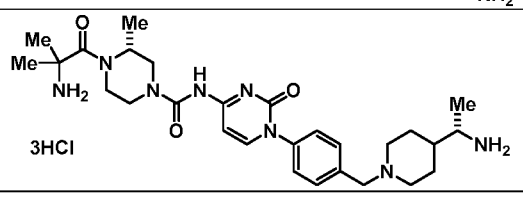
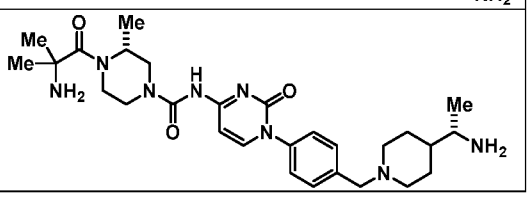
No.	Salt Structure	Free Base Structure
160		
161		
162		
163		
164		

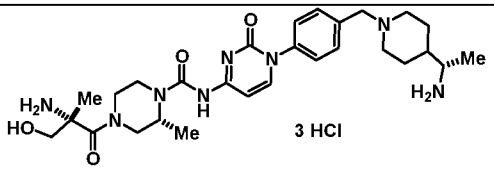
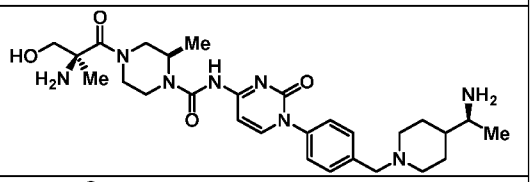
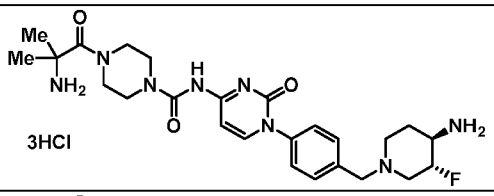
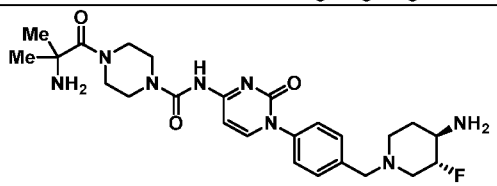
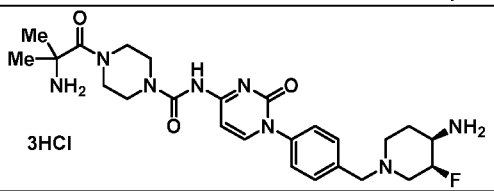
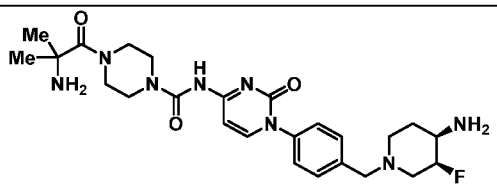
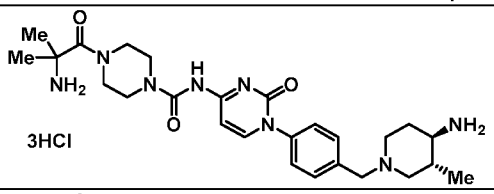
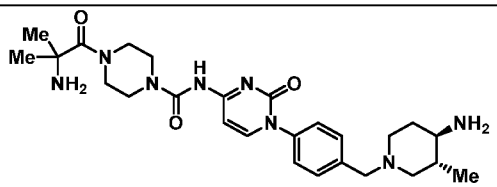
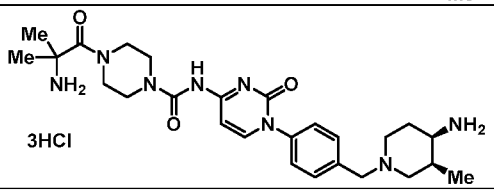
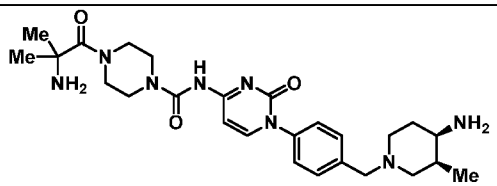
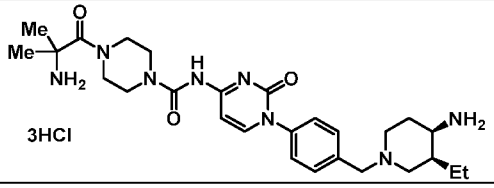
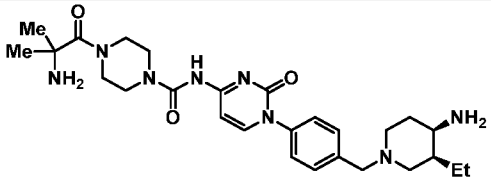
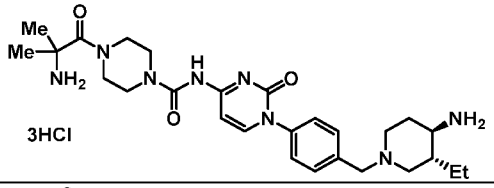
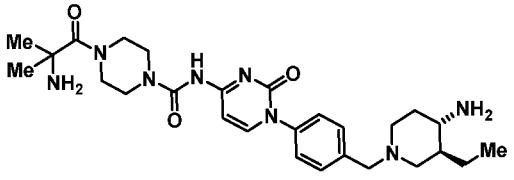
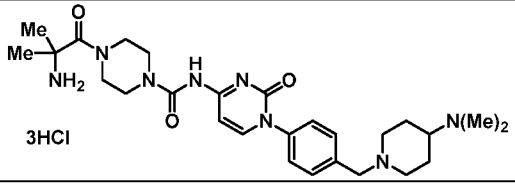
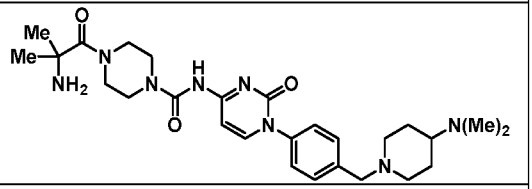
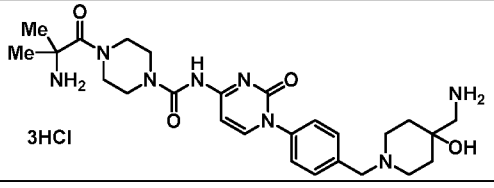
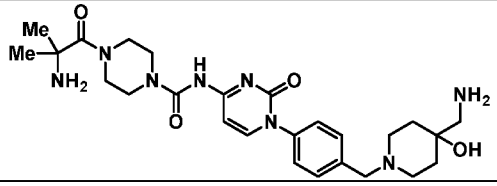
No.	Salt Structure	Free Base Structure
165	 3HCl	
166	 3HCl	
167	 3HCl	
168	 3 HCl	
169	 3 HCl	
170	 3 HCl	
171	 3 HCl	

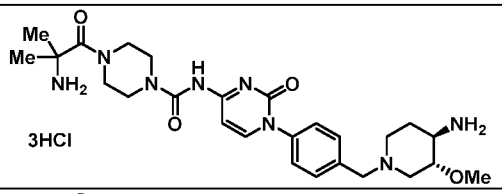
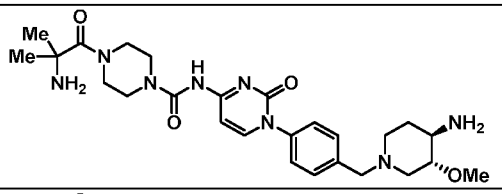
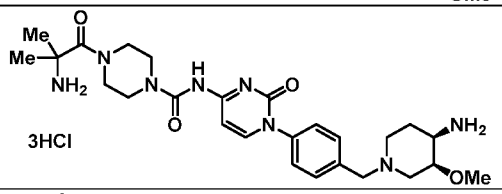
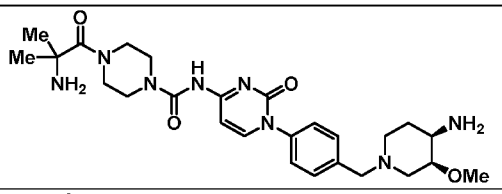
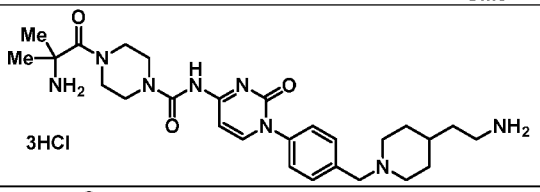
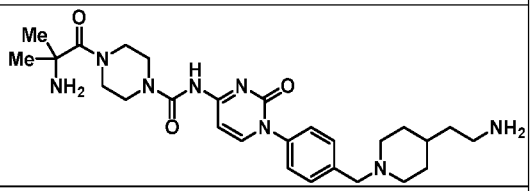
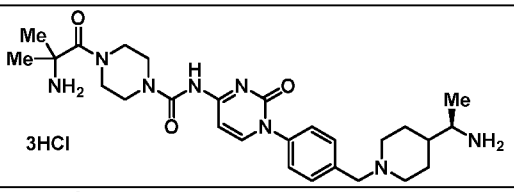
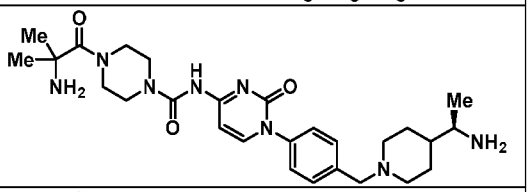
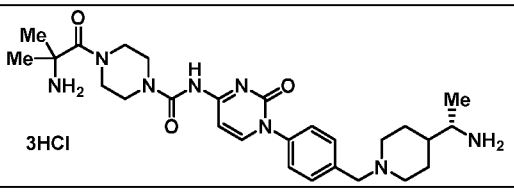
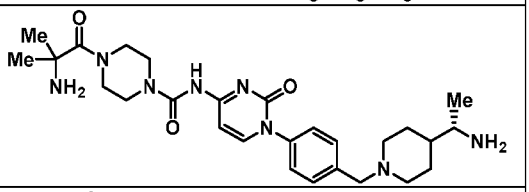
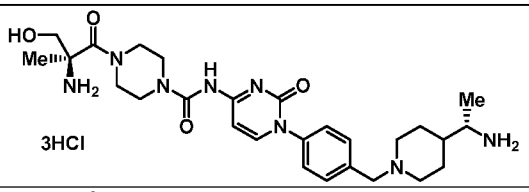
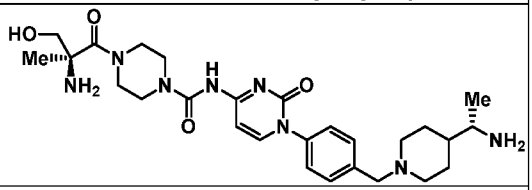
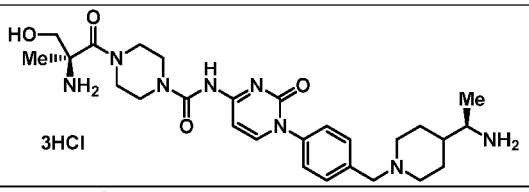
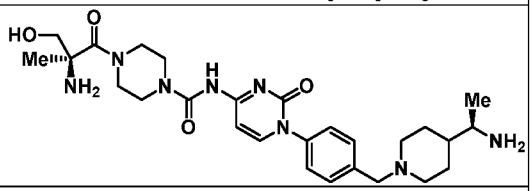
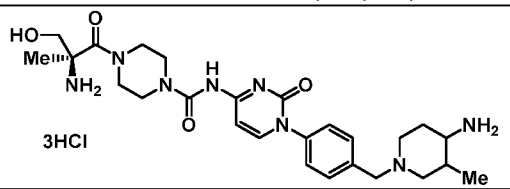
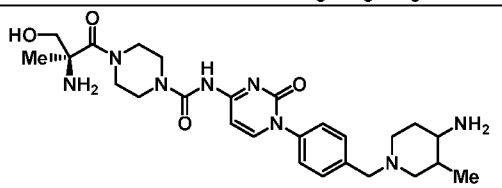
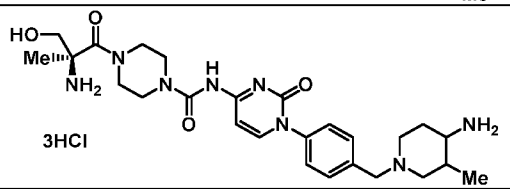
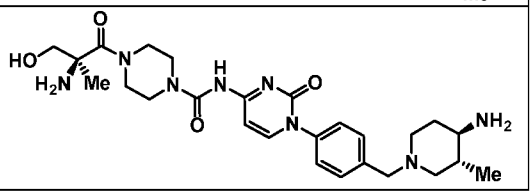
No.	Salt Structure	Free Base Structure
172	 3 HCl	
173	 3 HCl	
174	 3 HCl	
175	 3 HCl	
176	 3 HCl	
177	 3 HCl	
178	 3 HCl	
179	 3 HCl	

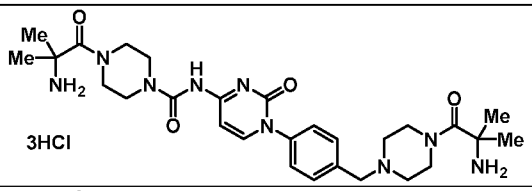
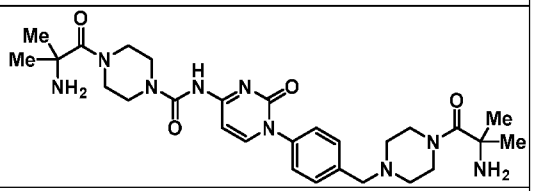
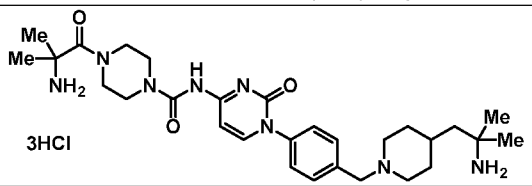
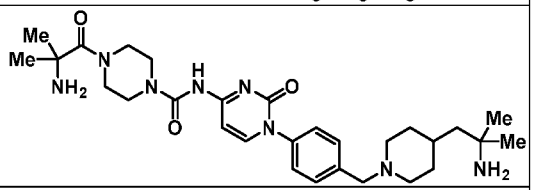
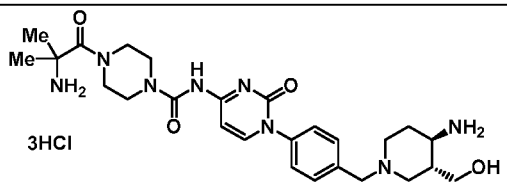
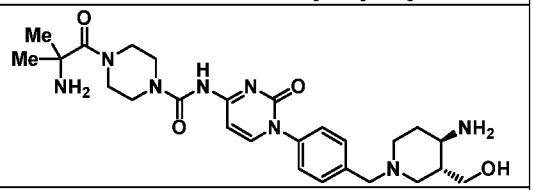
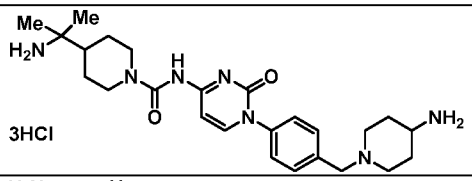
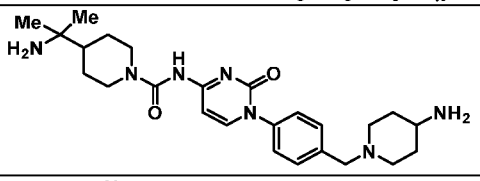
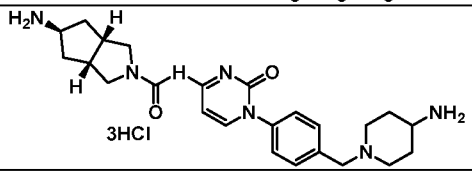
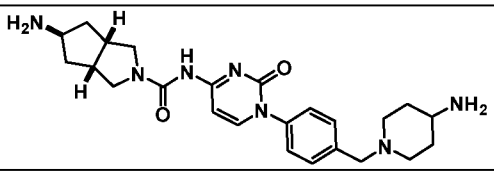
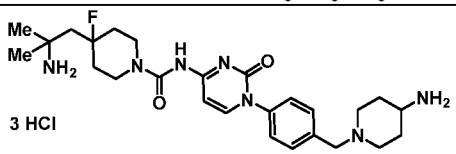
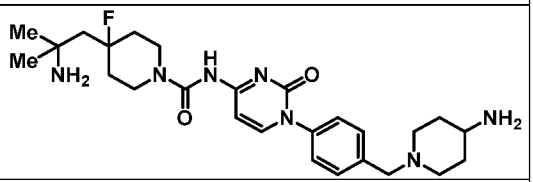
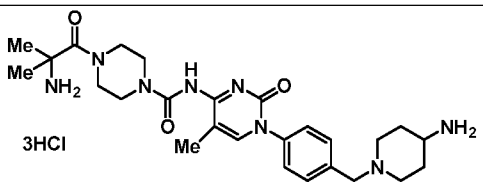
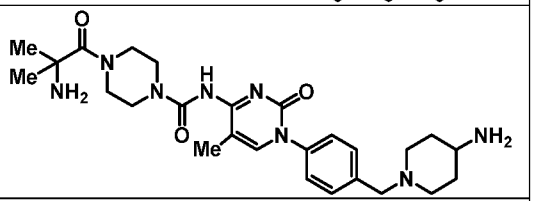
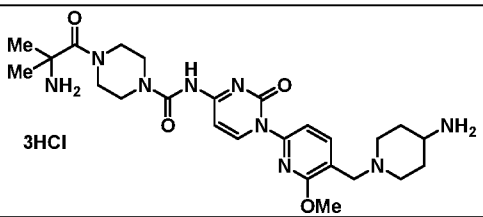
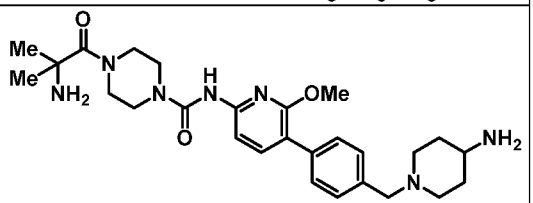
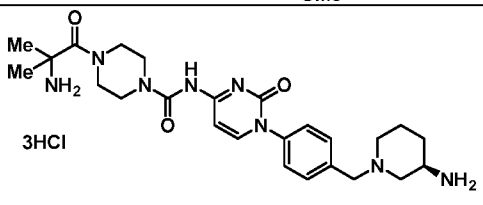
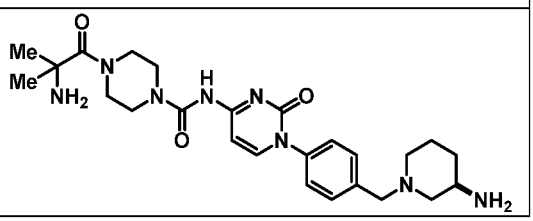
No.	Salt Structure	Free Base Structure
180		
181		
182		
183		
184		
185		
186		
187		

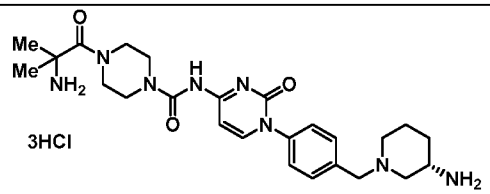
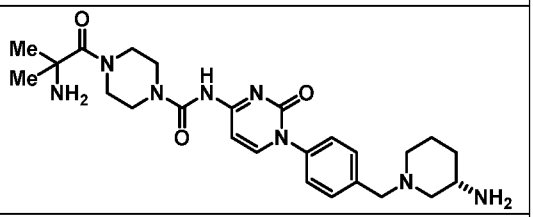
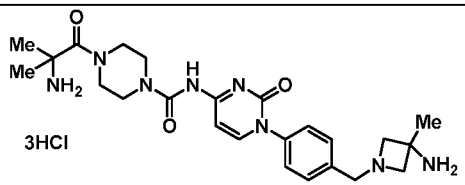
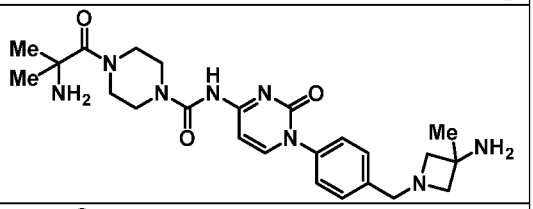
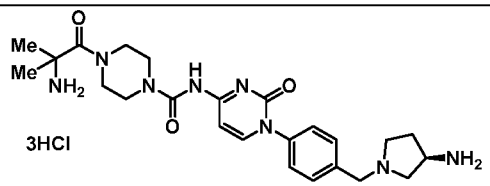
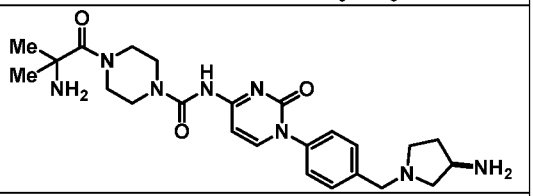
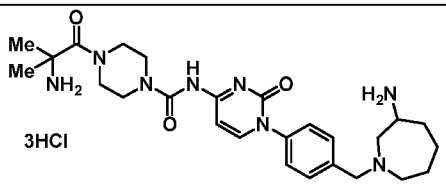
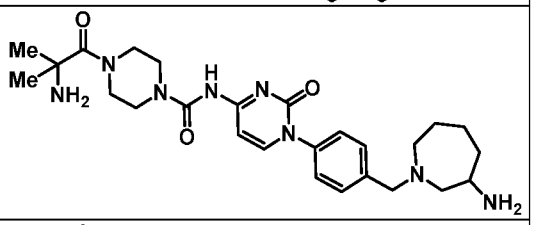
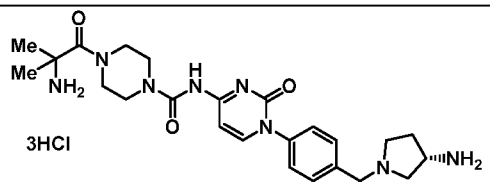
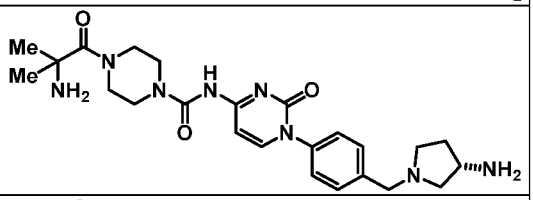
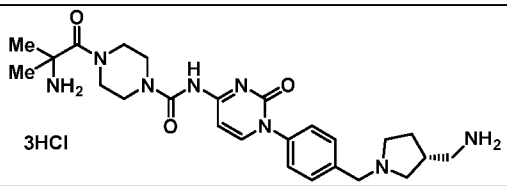
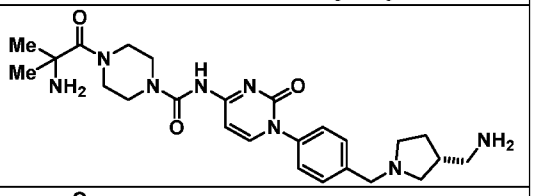
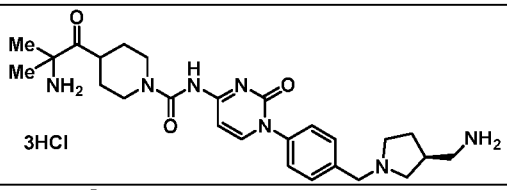
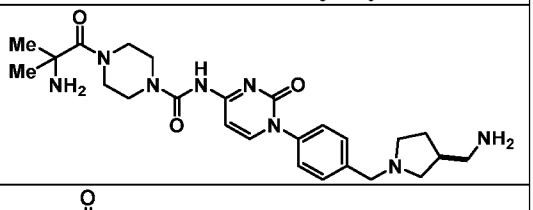
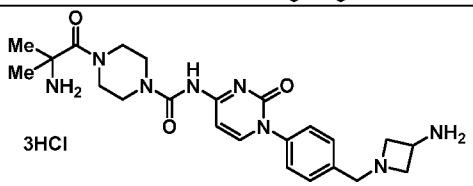
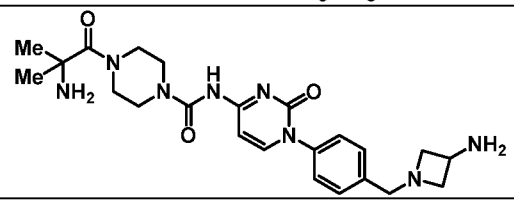
No.	Salt Structure	Free Base Structure
188		
190		
191		
192		
193		
194		
195		
196		

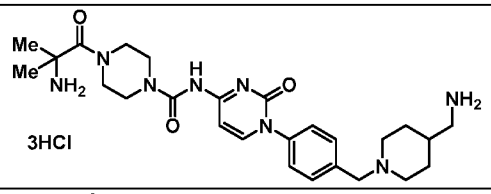
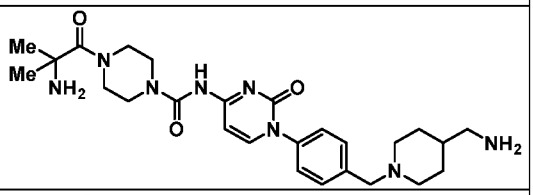
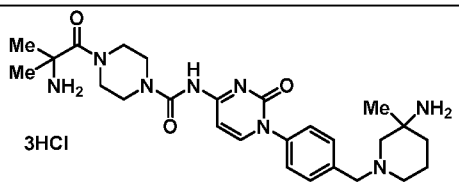
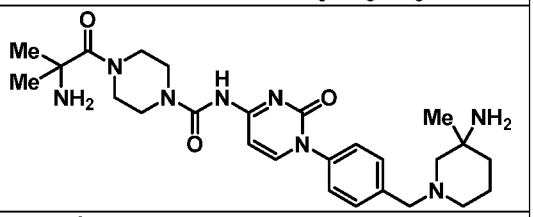
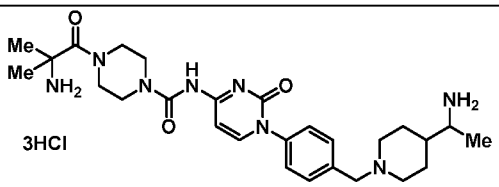
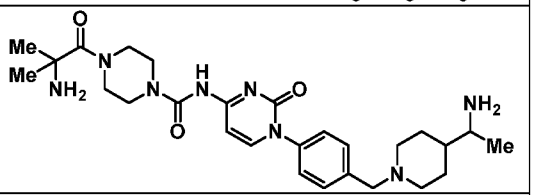
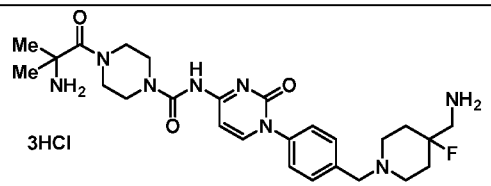
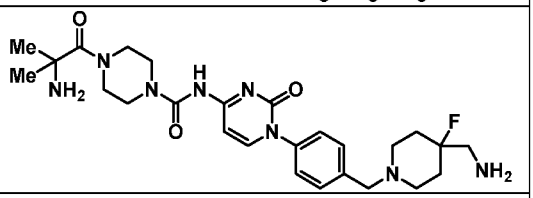
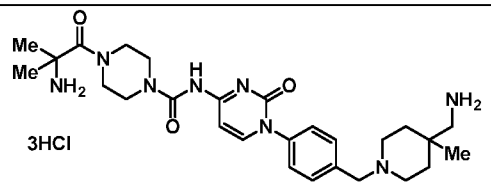
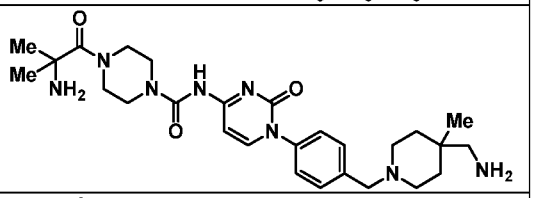
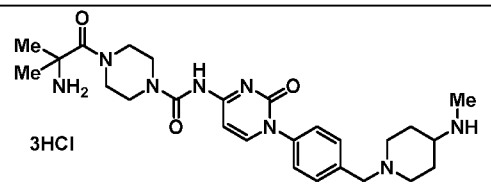
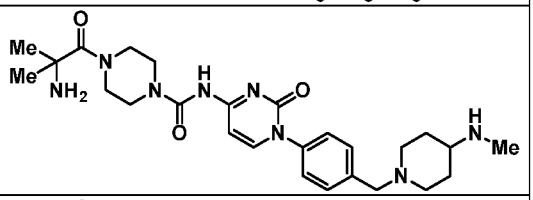
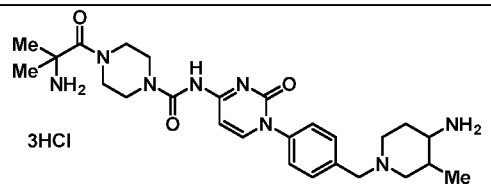
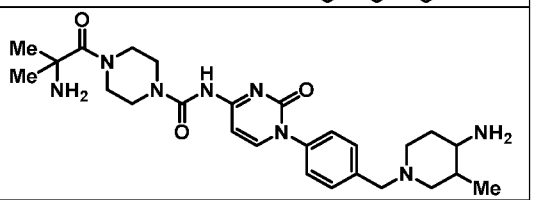
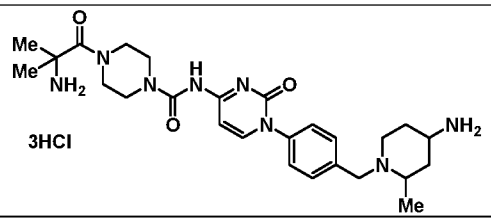
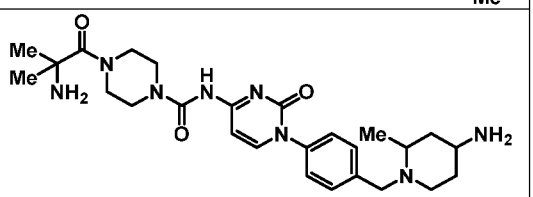
No.	Salt Structure	Free Base Structure
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198		
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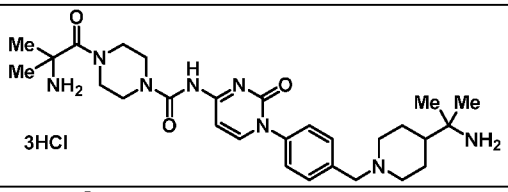
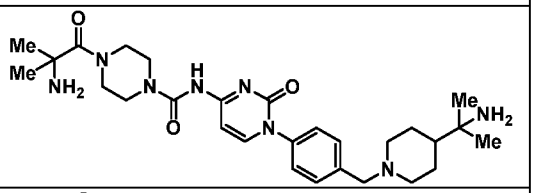
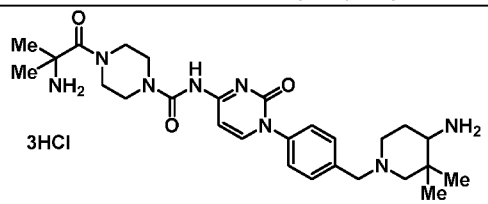
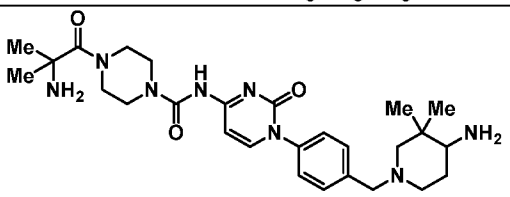
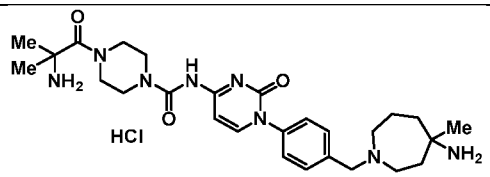
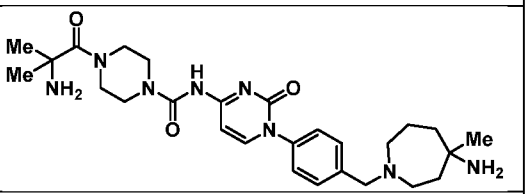
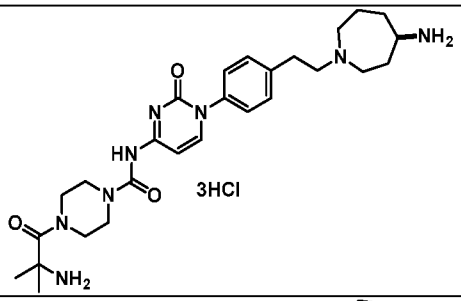
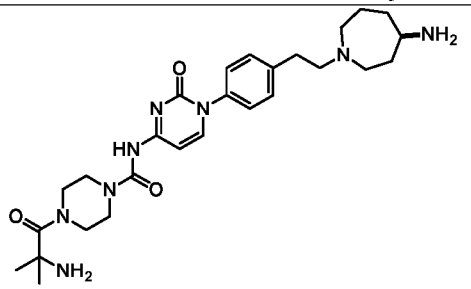
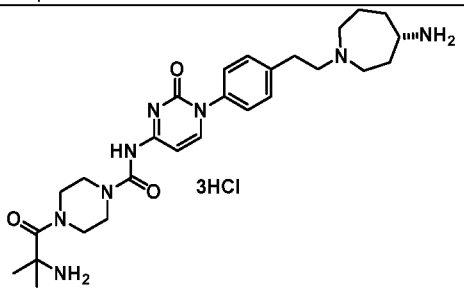
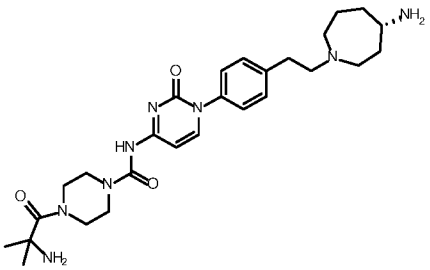
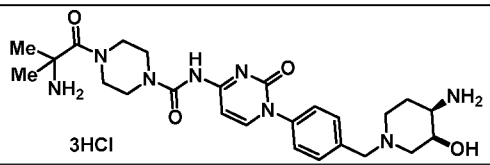
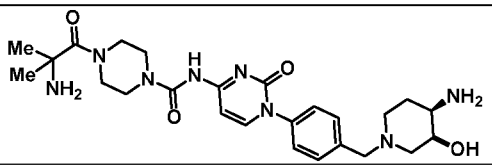
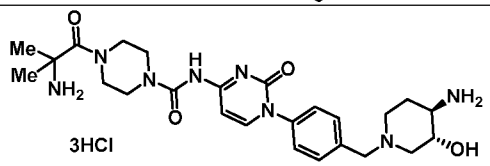
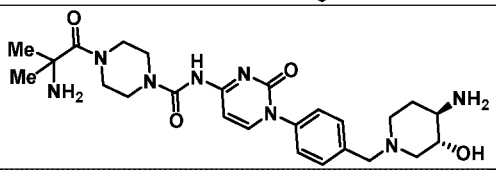
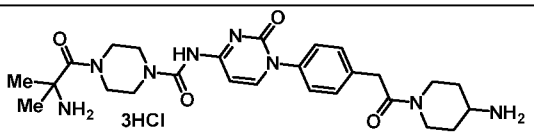
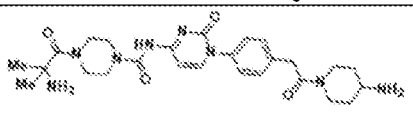
No.	Salt Structure	Free Base Structure
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No.	Salt Structure	Free Base Structure
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No.	Salt Structure	Free Base Structure
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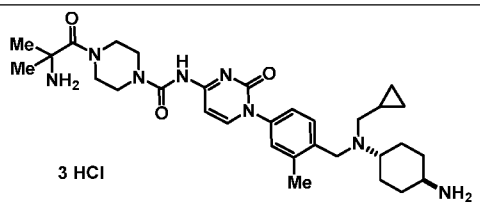
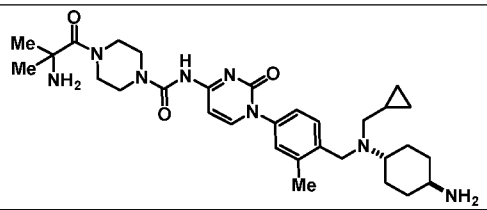
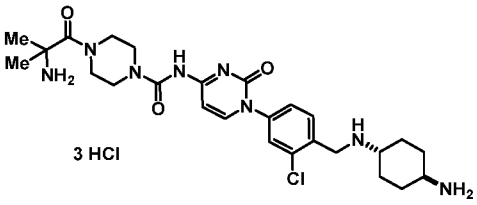
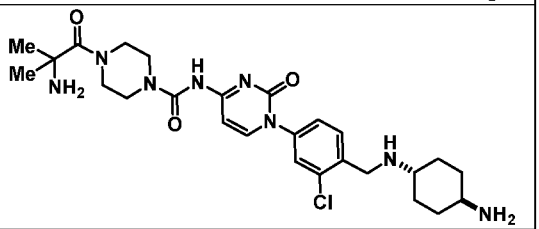
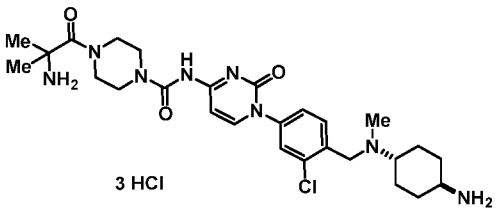
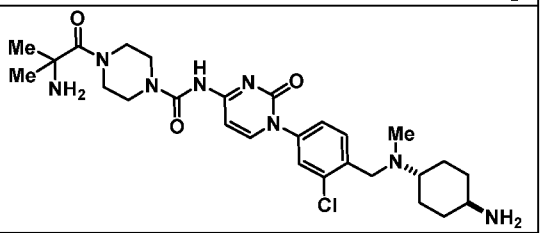
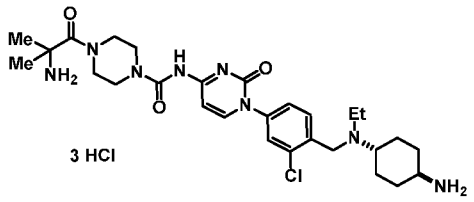
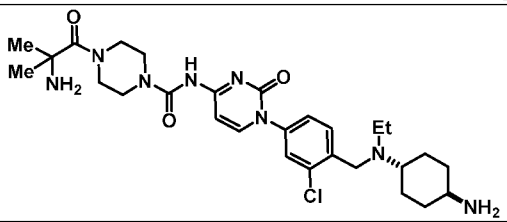
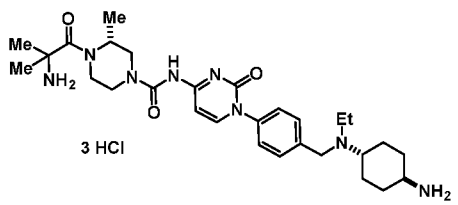
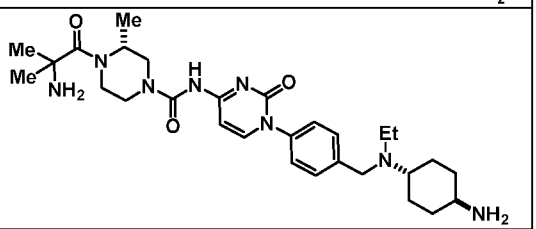
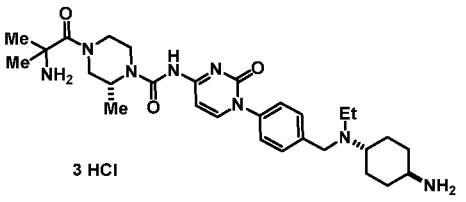
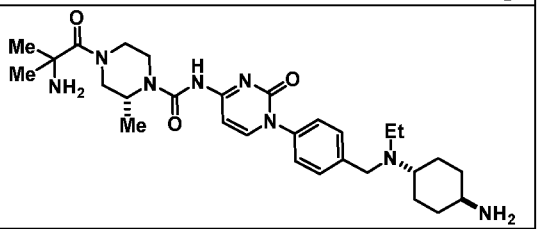
No.	Salt Structure	Free Base Structure
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238		
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244		

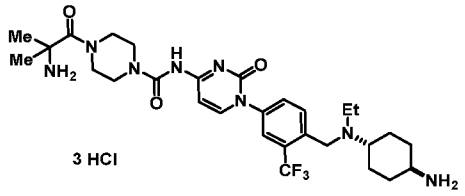
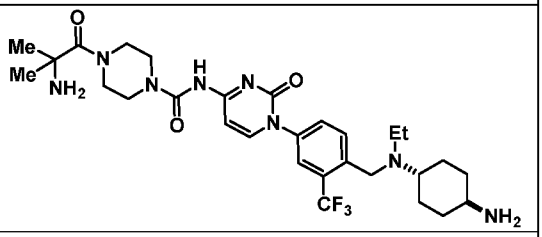
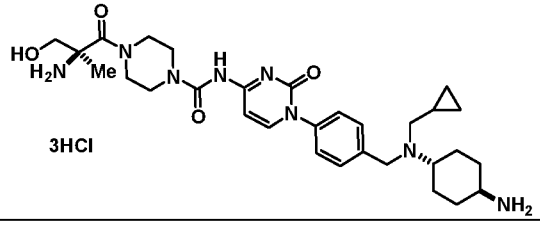
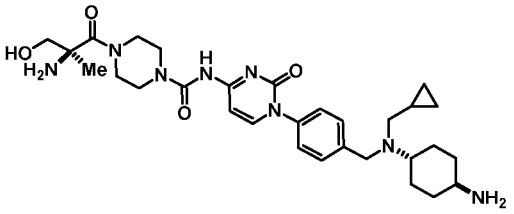
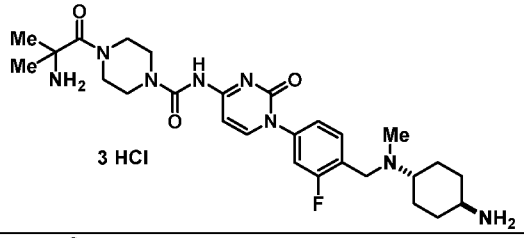
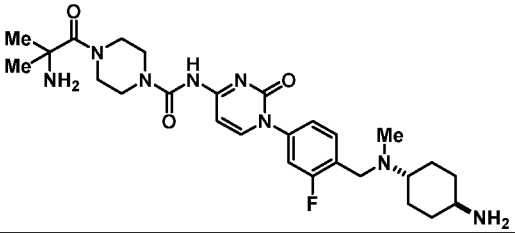
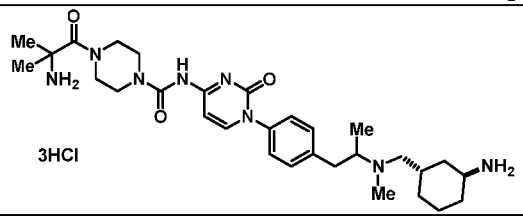
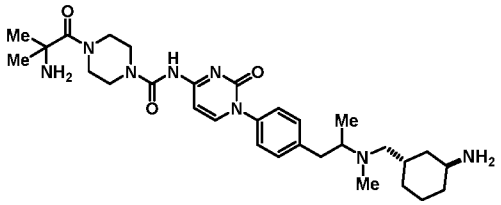
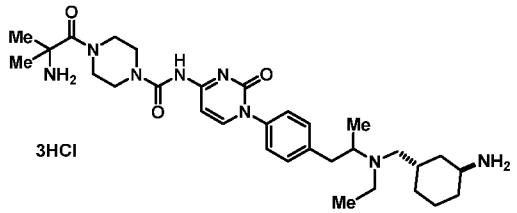
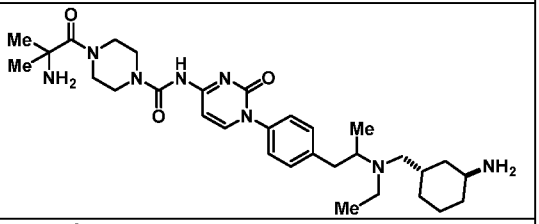
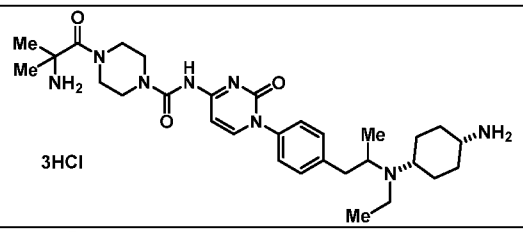
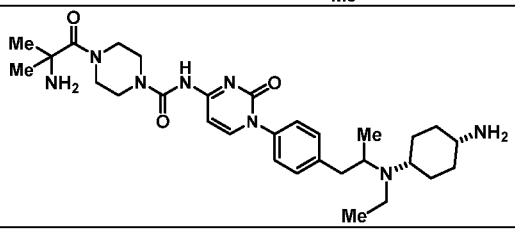
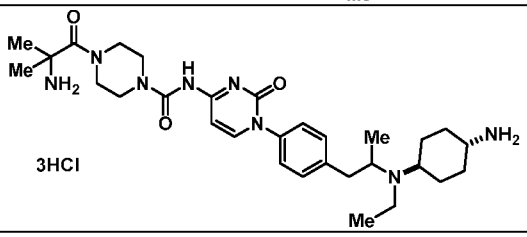
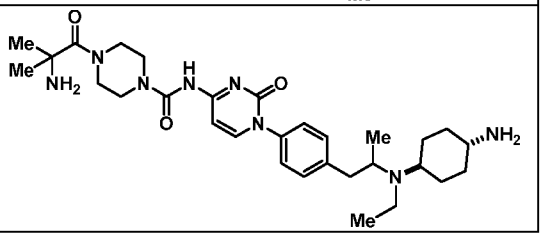
No.	Salt Structure	Free Base Structure
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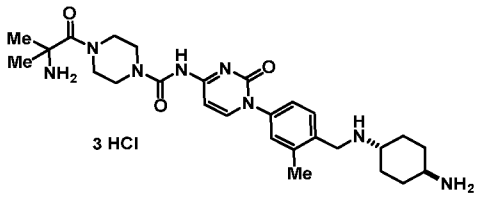
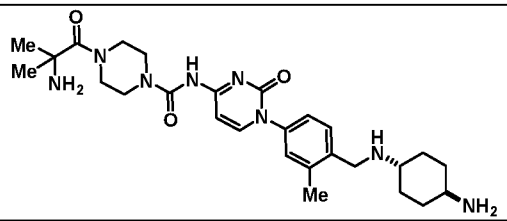
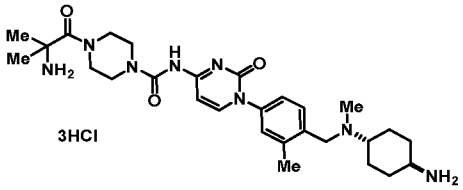
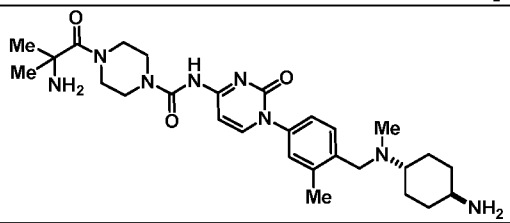
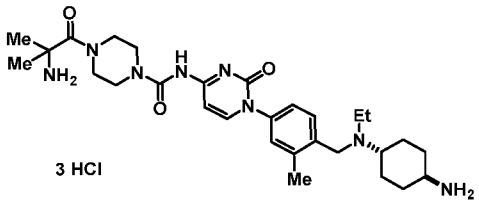
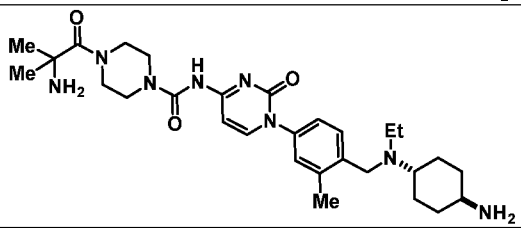
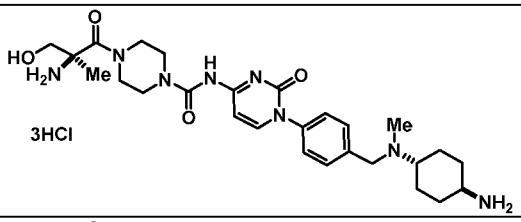
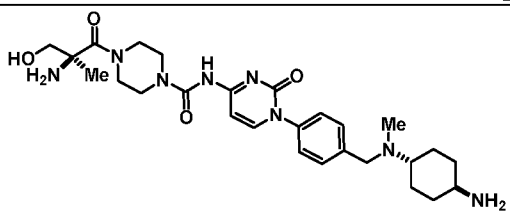
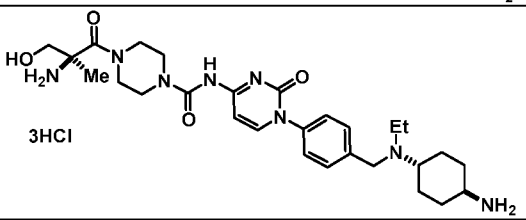
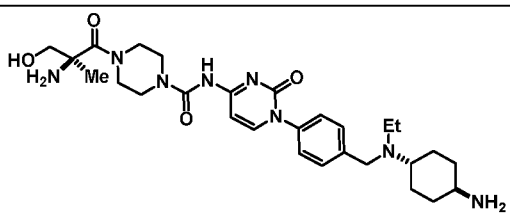
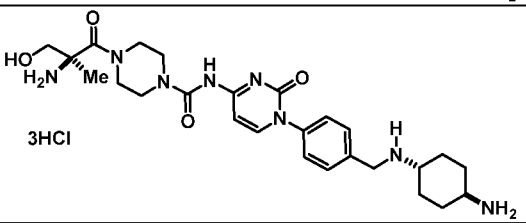
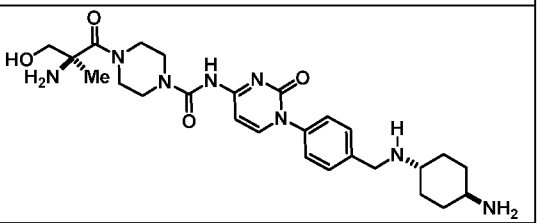
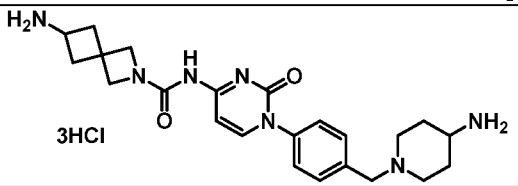
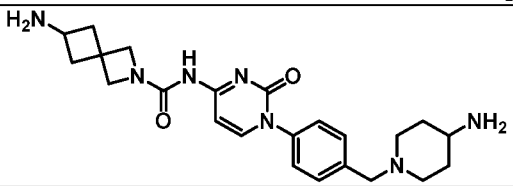
No.	Salt Structure	Free Base Structure
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268		
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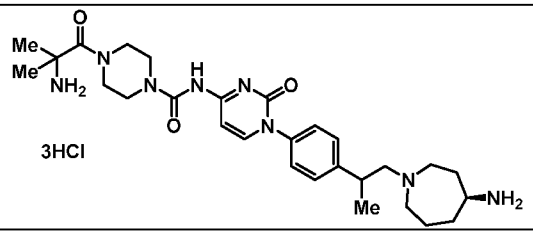
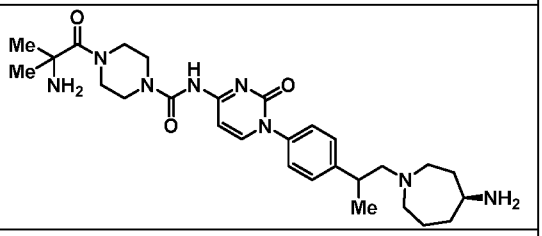
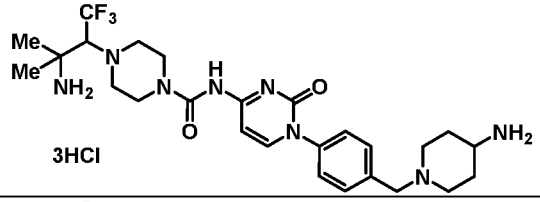
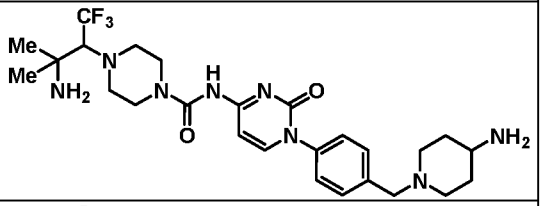
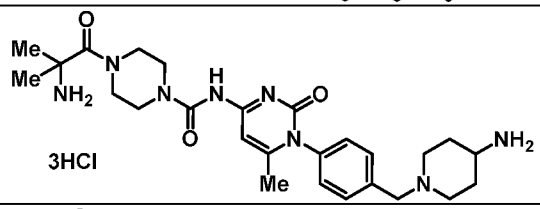
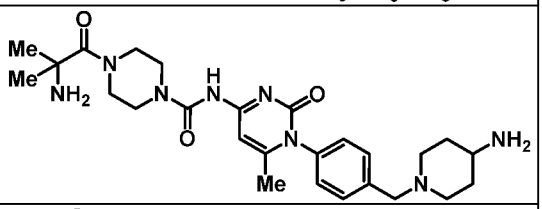
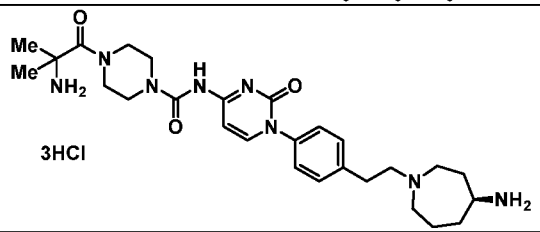
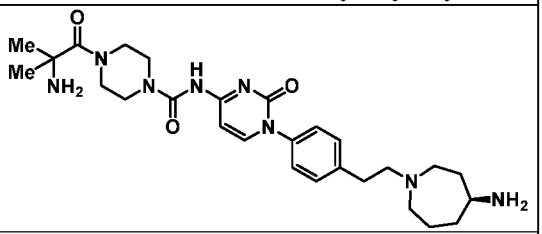
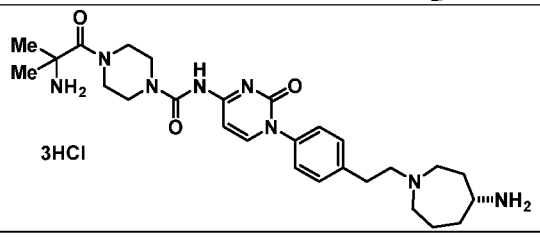
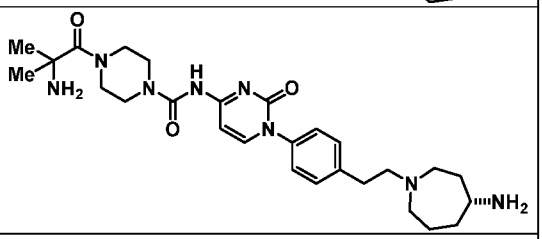
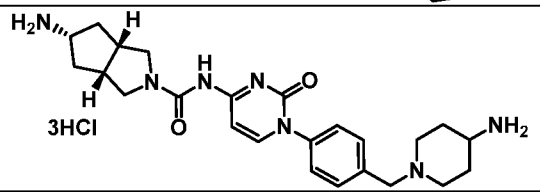
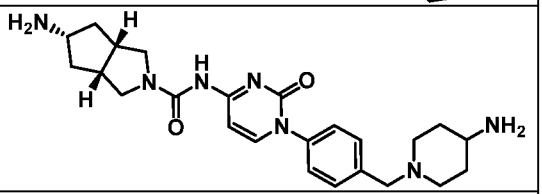
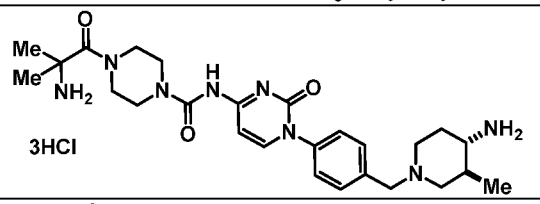
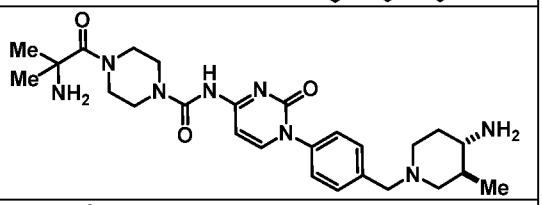
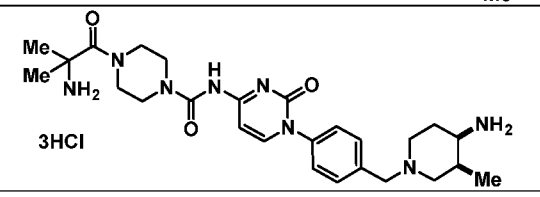
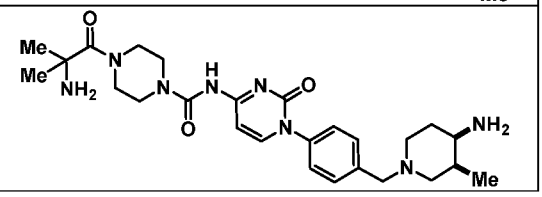
[00198] In another aspect, the disclosure provides a compound or a pharmaceutically acceptable salt thereof which is depicted in Table 11. In Table 11, free base and salt structures of the compounds of the invention are depicted

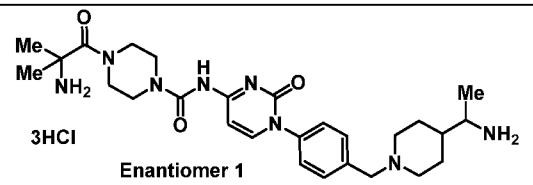
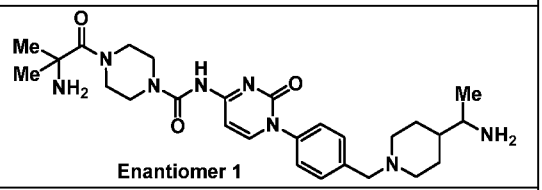
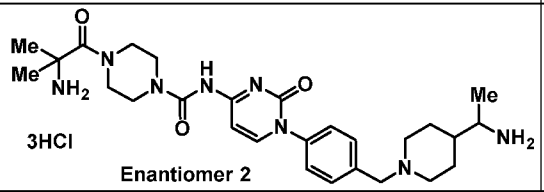
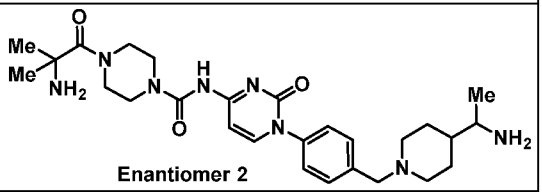
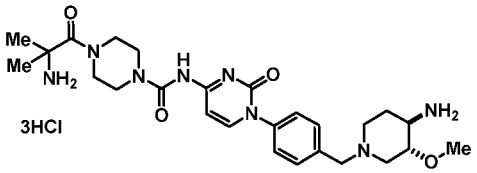
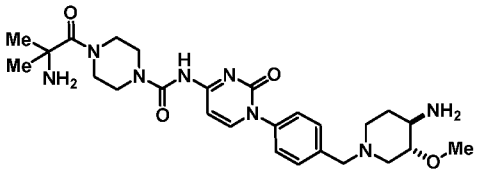
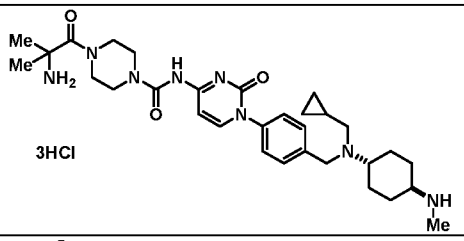
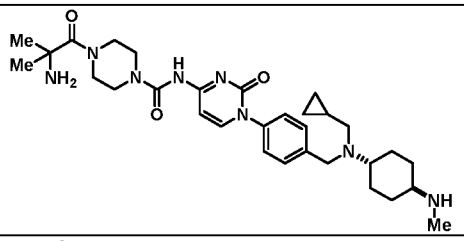
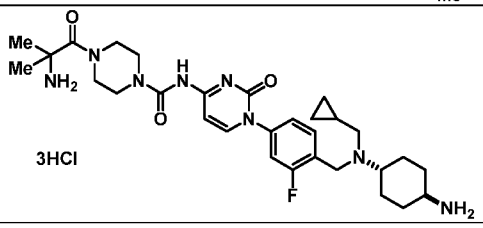
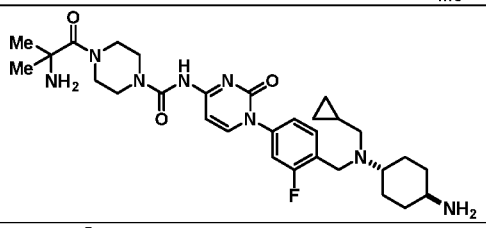
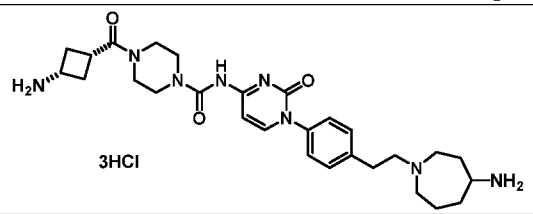
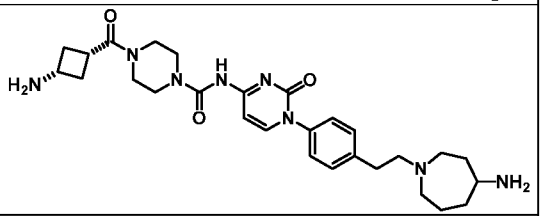
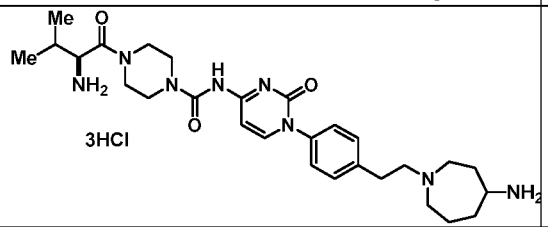
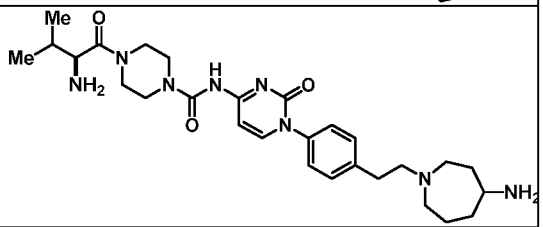
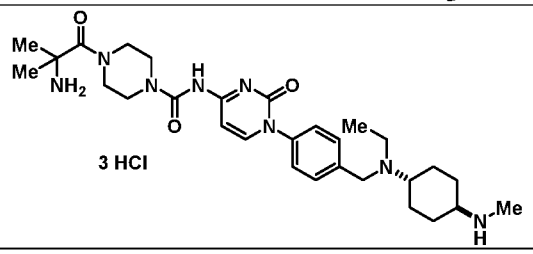
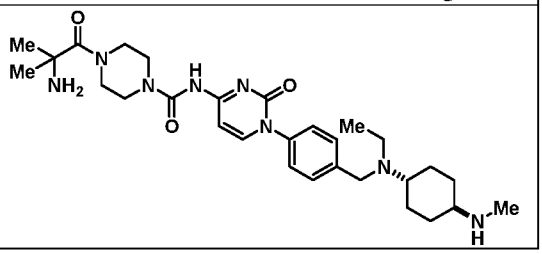
Table 11 Compounds of Formula I Continued

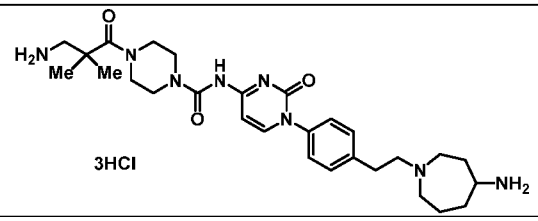
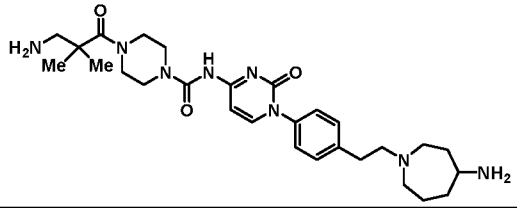
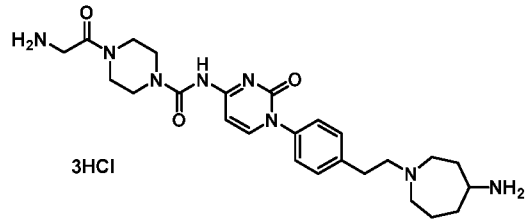
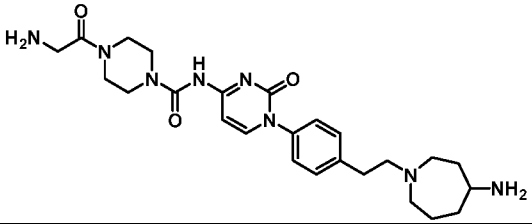
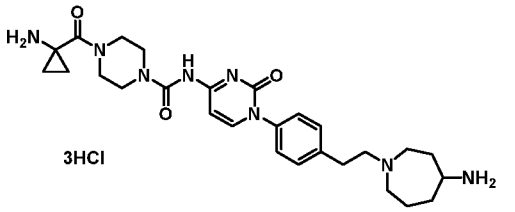
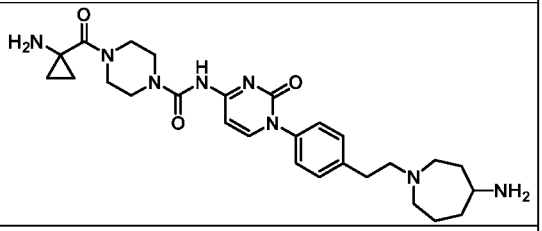
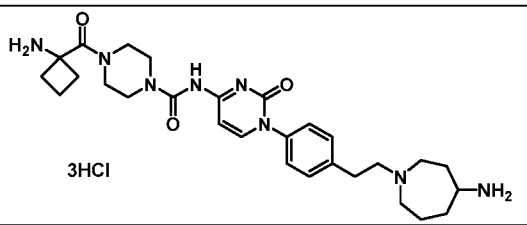
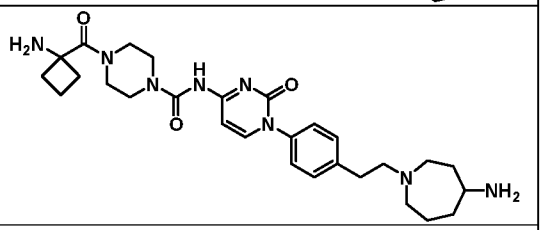
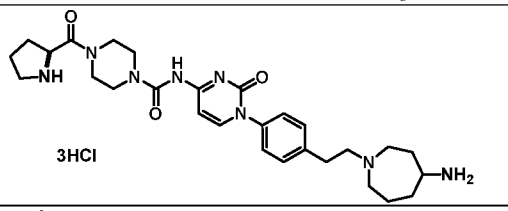
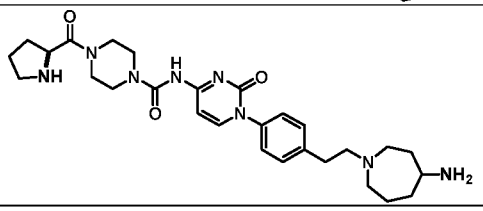
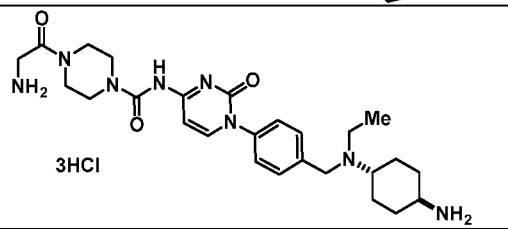
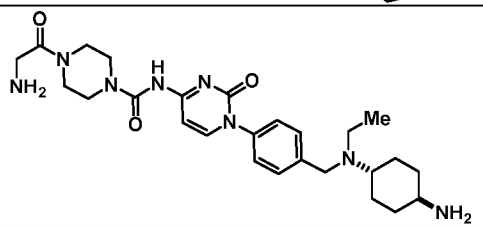
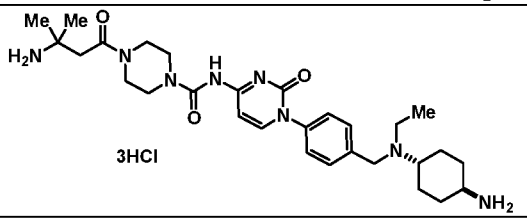
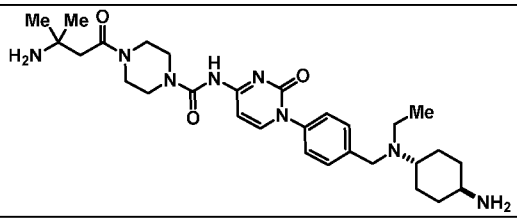
No.	Salt Structure	Free Base Structure
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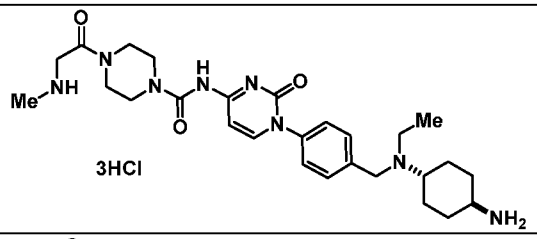
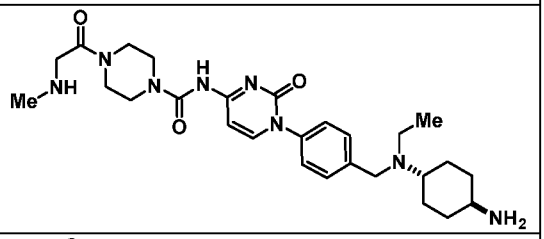
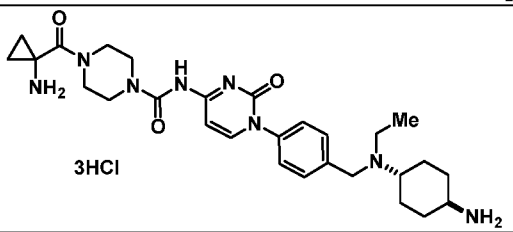
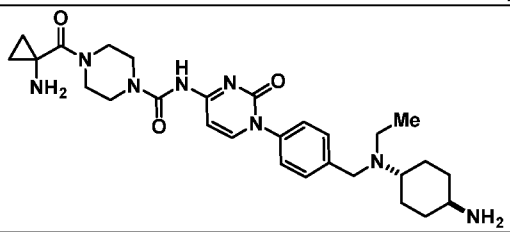
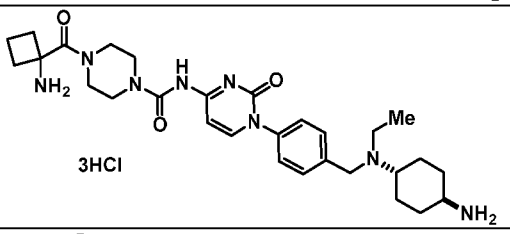
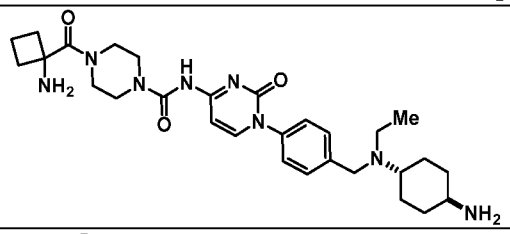
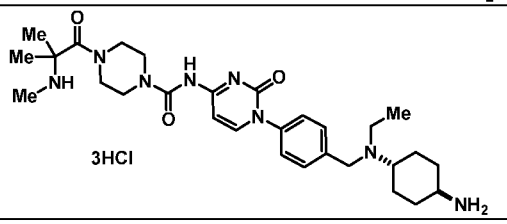
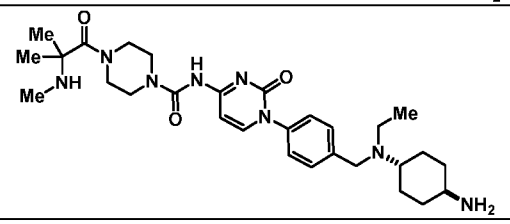
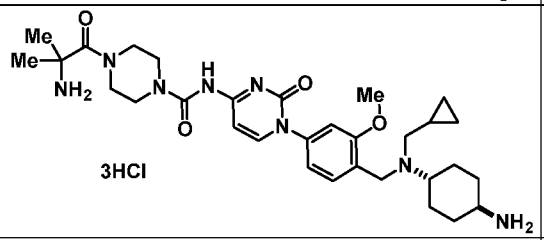
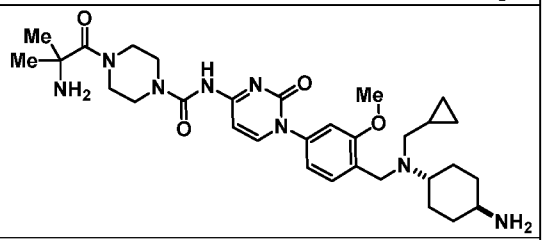
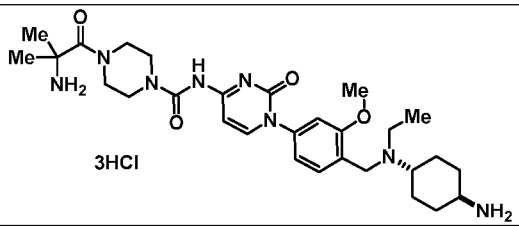
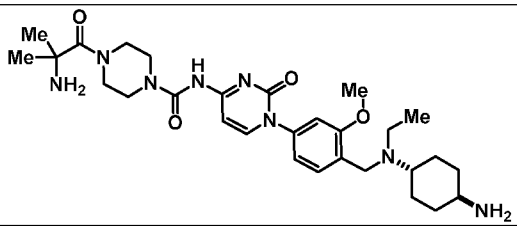
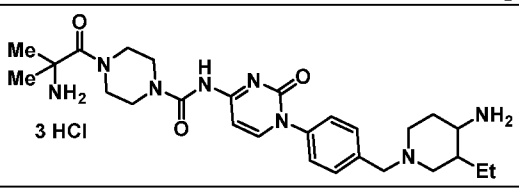
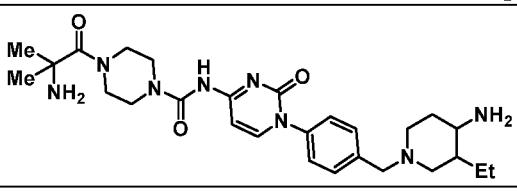
No.	Salt Structure	Free Base Structure
276	 3 HCl	
277	 3HCl	
278	 3 HCl	
279	 3HCl	
280	 3HCl	
281	 3HCl	
282	 3HCl	

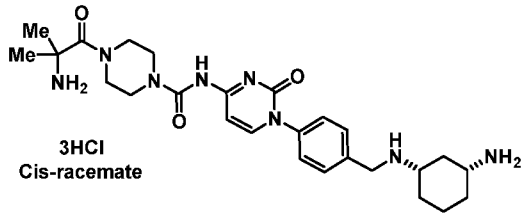
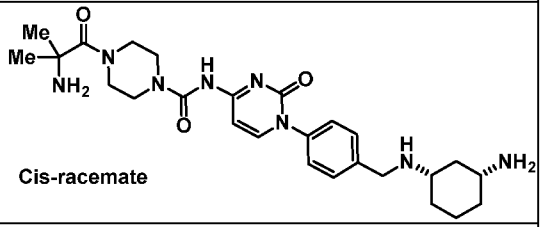
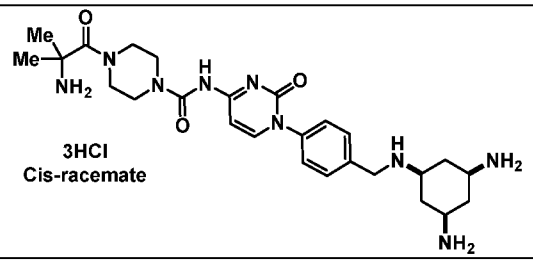
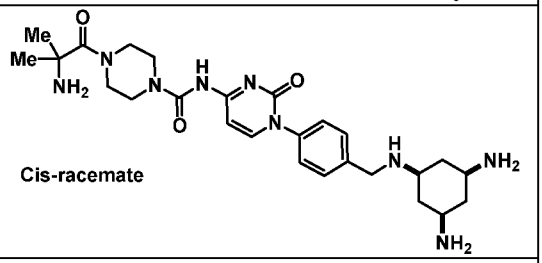
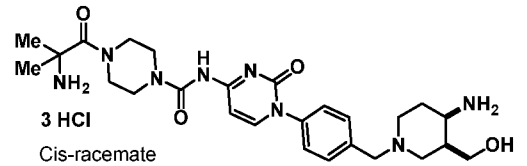
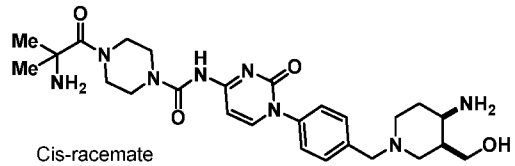
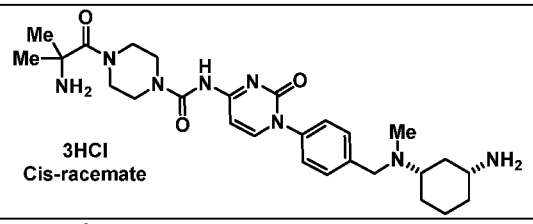
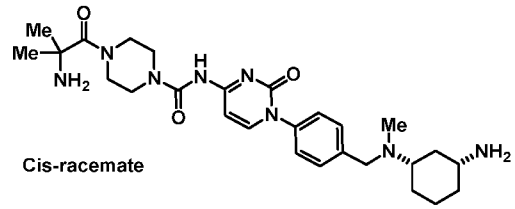
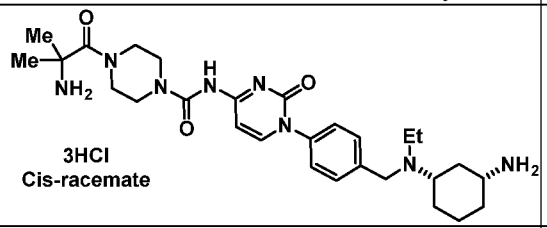
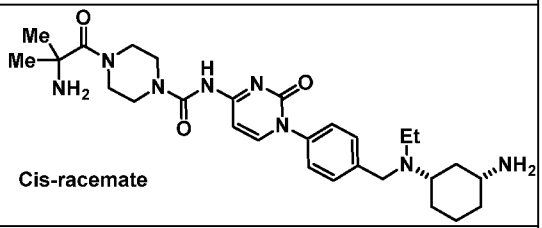
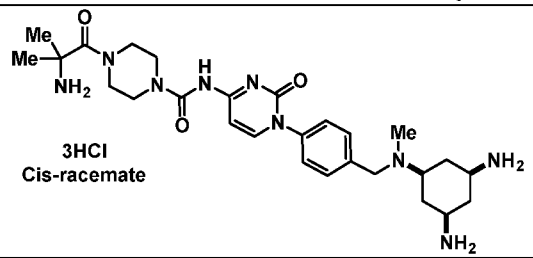
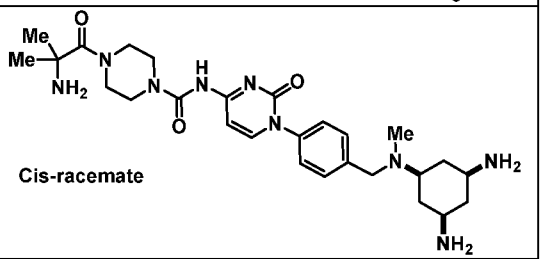
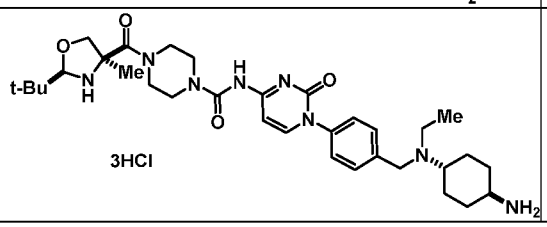
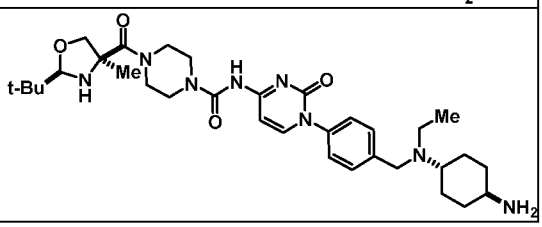
No.	Salt Structure	Free Base Structure
283	 3 HCl	
284	 3HCl	
285	 3 HCl	
286	 3HCl	
287	 3HCl	
288	 3HCl	
289	 3HCl	

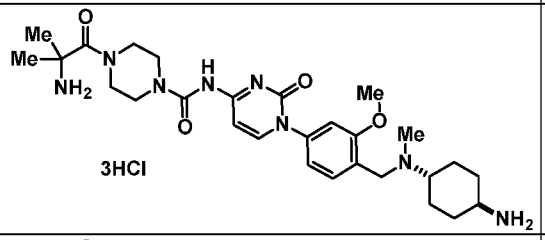
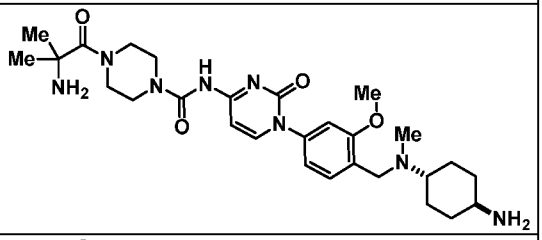
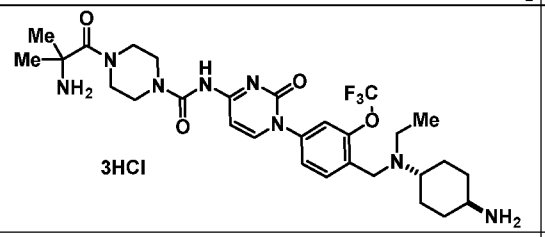
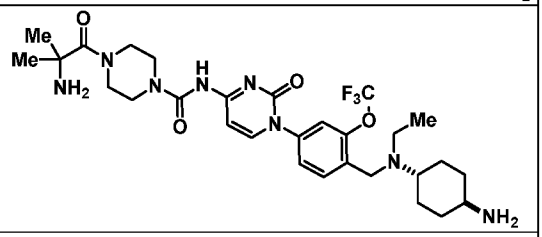
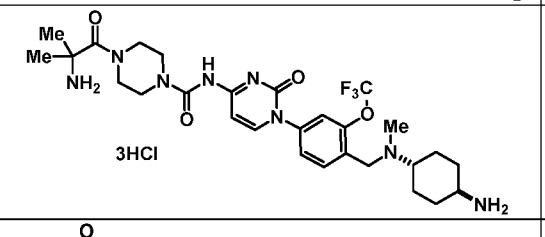
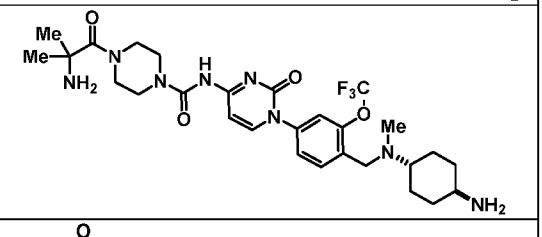
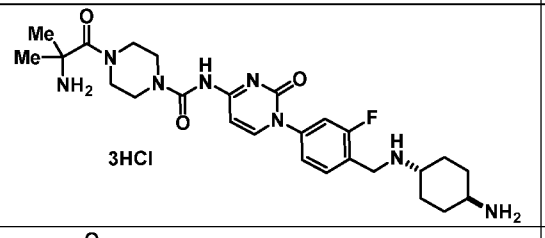
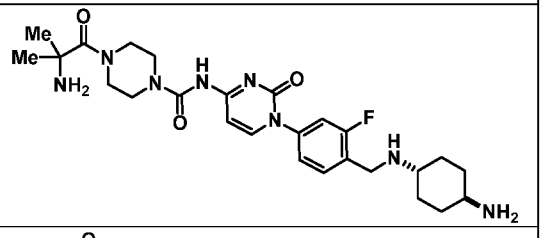
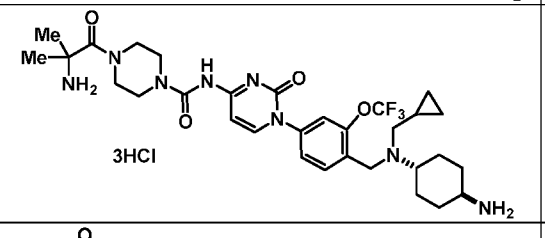
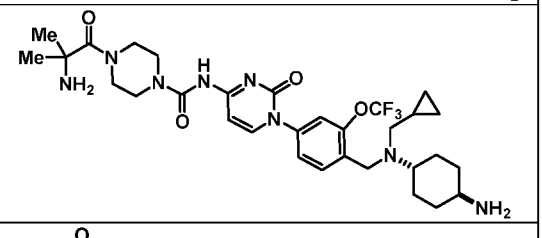
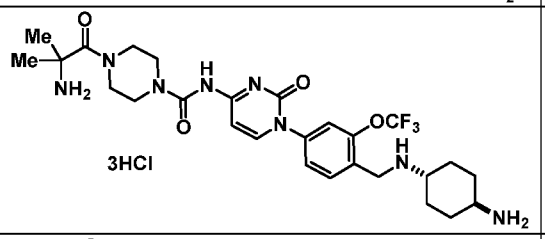
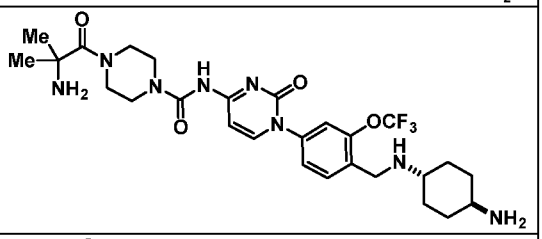
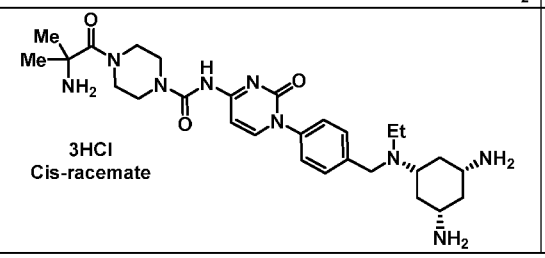
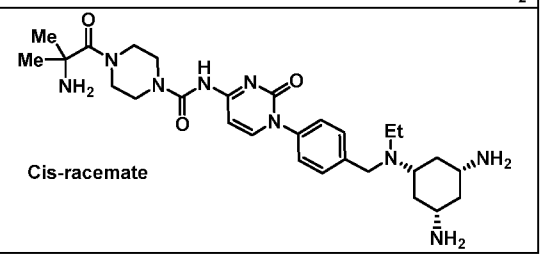
No.	Salt Structure	Free Base Structure
290		
291		
292		
293		
294		
295		
296		
297		

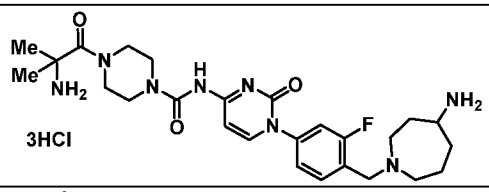
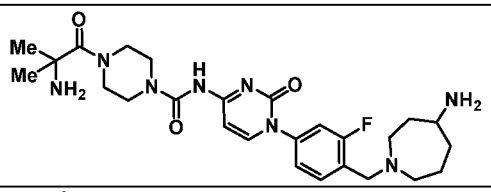
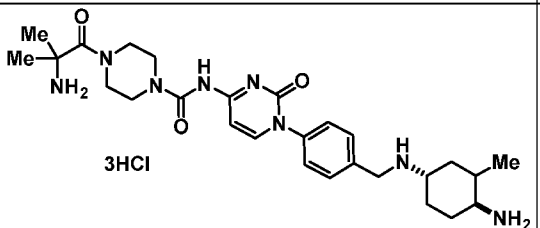
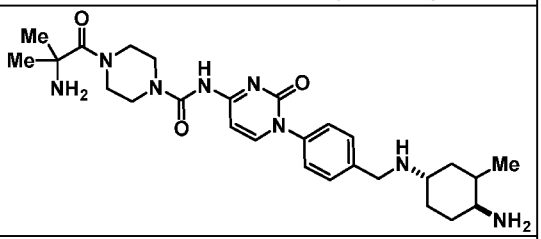
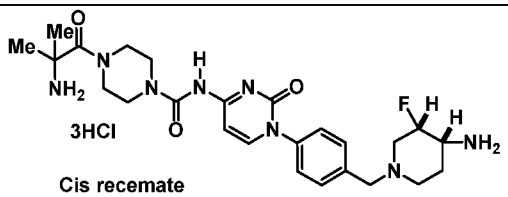
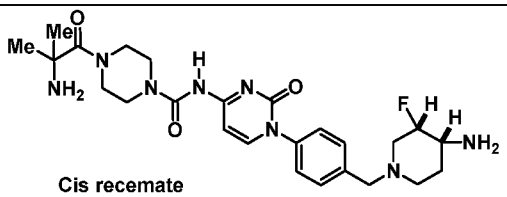
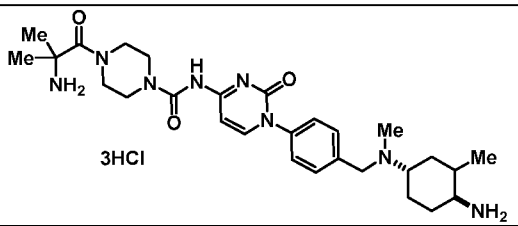
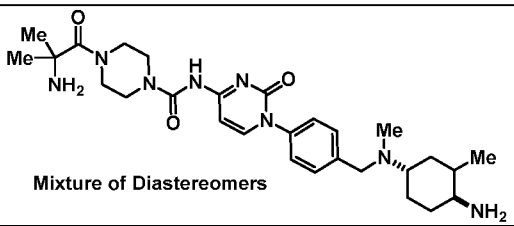
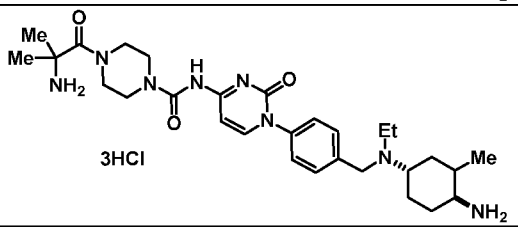
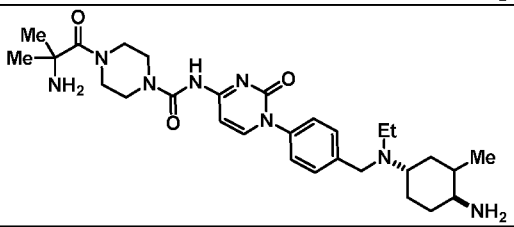
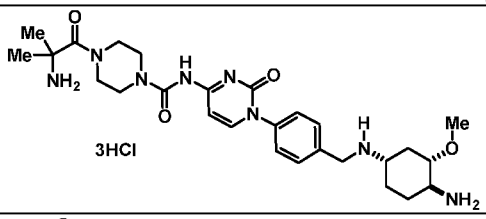
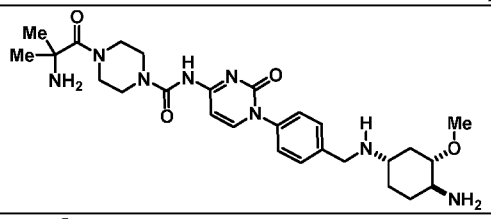
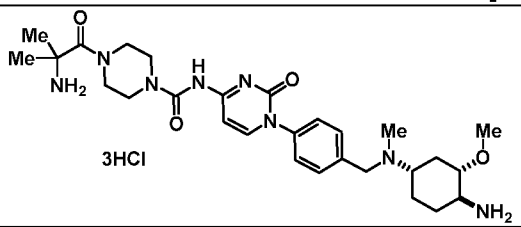
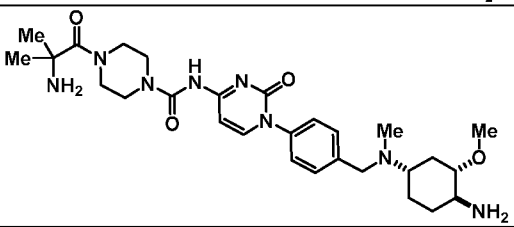
No.	Salt Structure	Free Base Structure
298	 3HCl Enantiomer 1	 Enantiomer 1
299	 3HCl Enantiomer 2	 Enantiomer 2
300	 3HCl	
301	 3HCl	
302	 3HCl	
303	 3HCl	
304	 3HCl	
305	 3 HCl	

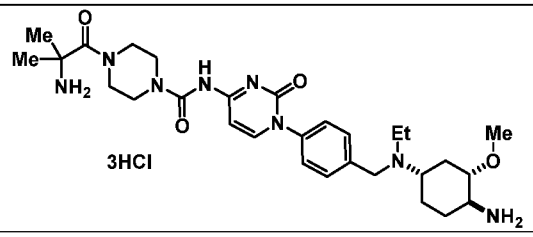
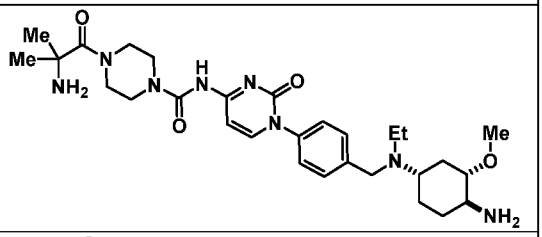
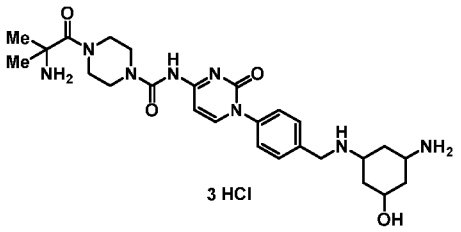
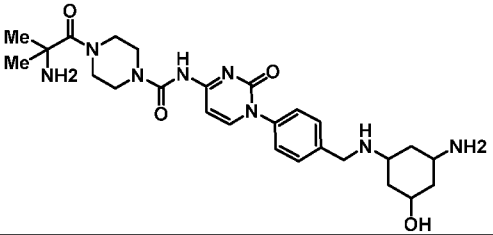
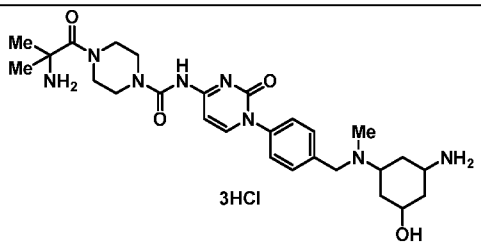
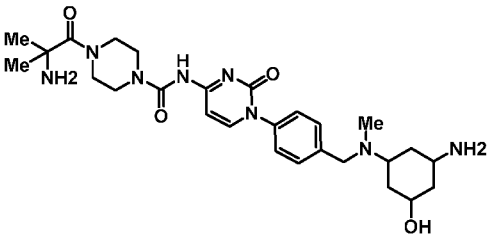
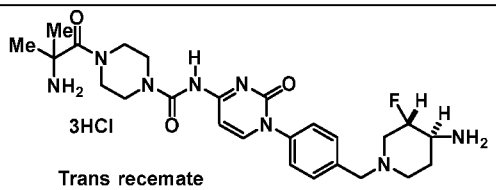
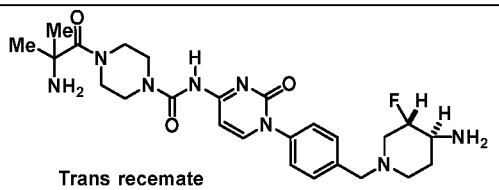
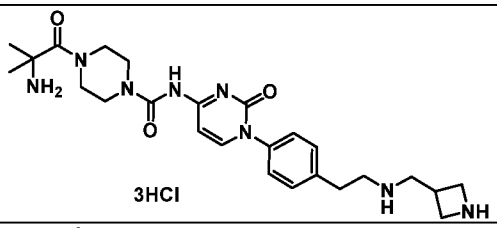
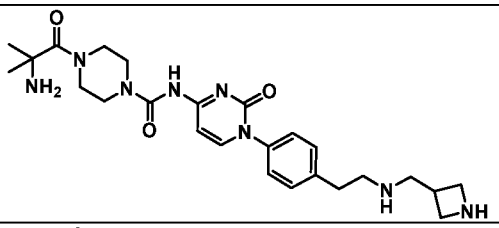
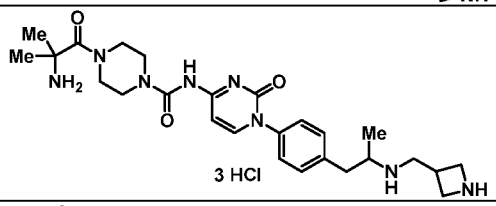
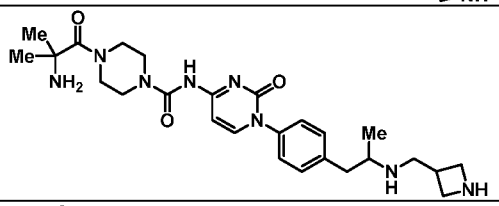
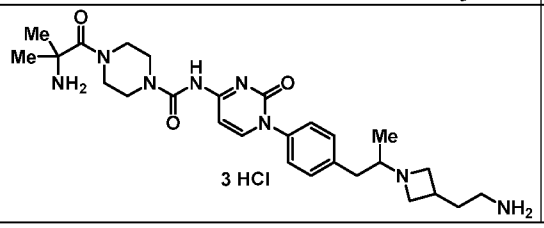
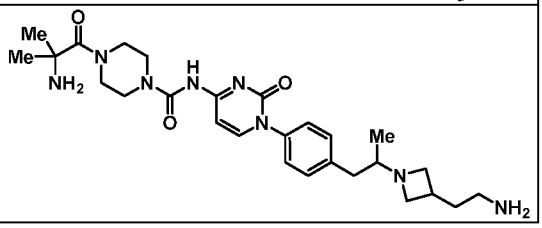
No.	Salt Structure	Free Base Structure
306		
307		
308		
309		
310		
311		
312		

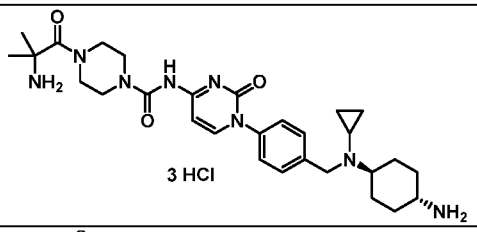
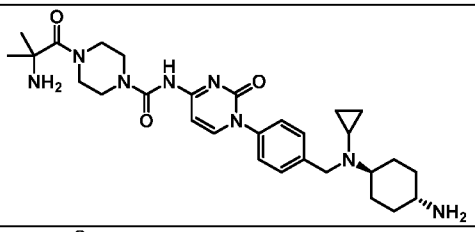
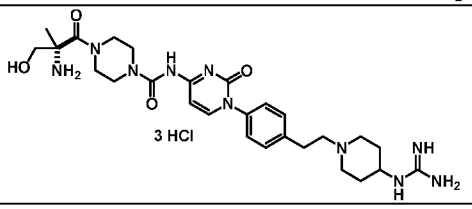
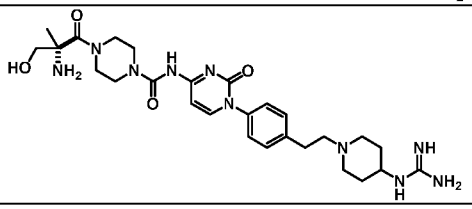
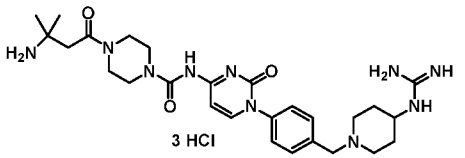
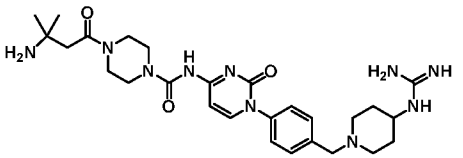
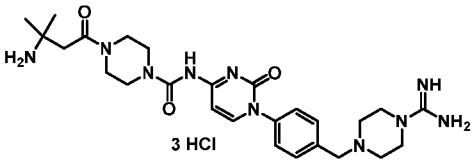
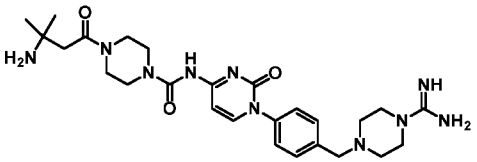
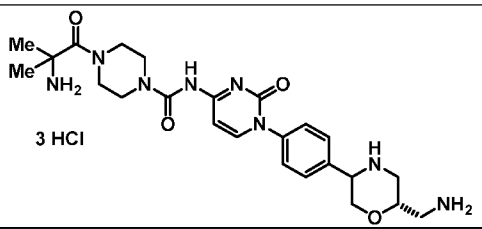
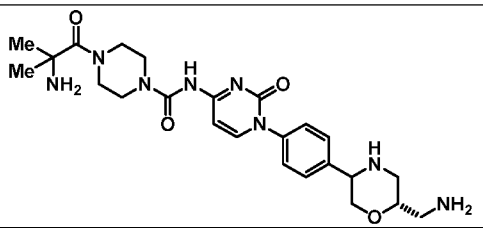
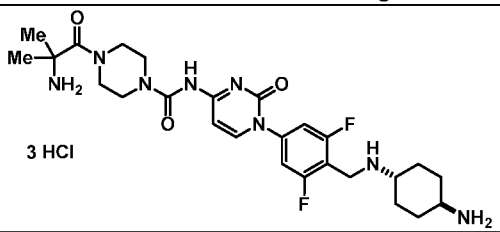
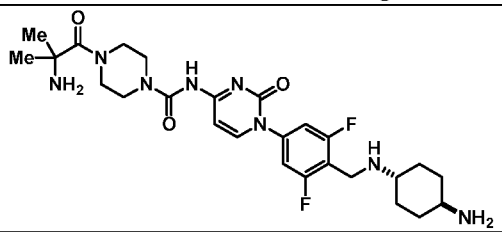
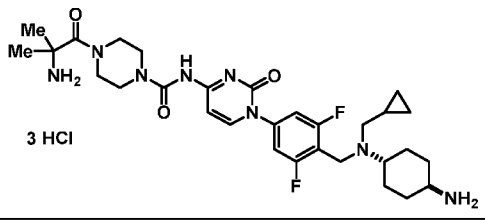
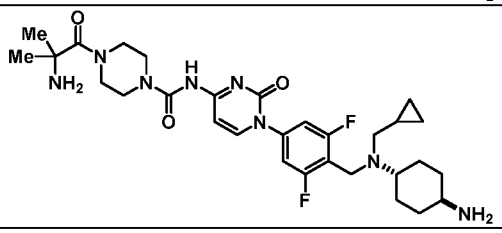
No.	Salt Structure	Free Base Structure
313	 3HCl	
314	 3HCl	
315	 3HCl	
316	 3HCl	
317	 3HCl	
318	 3HCl	
319	 3 HCl	

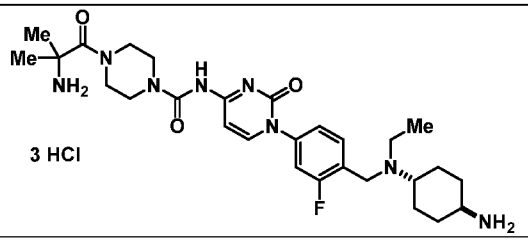
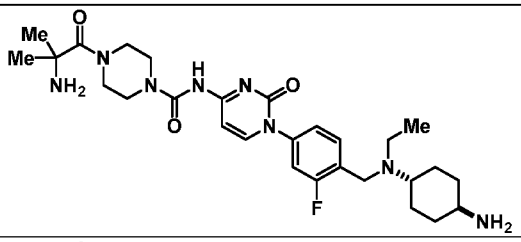
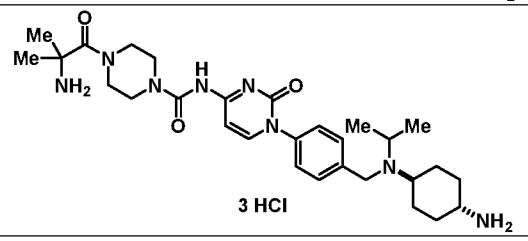
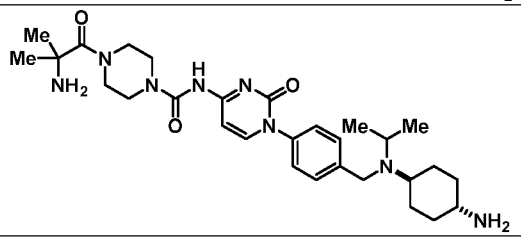
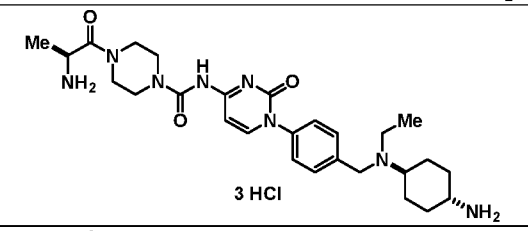
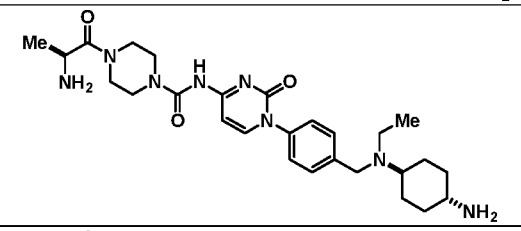
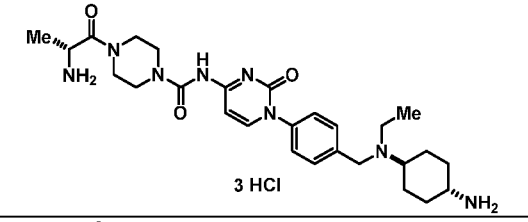
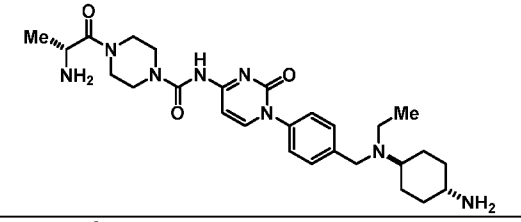
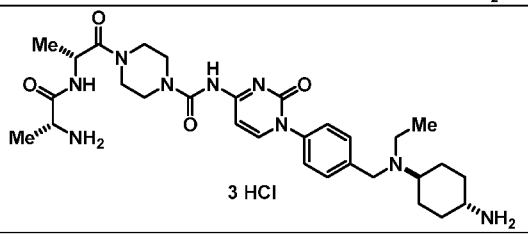
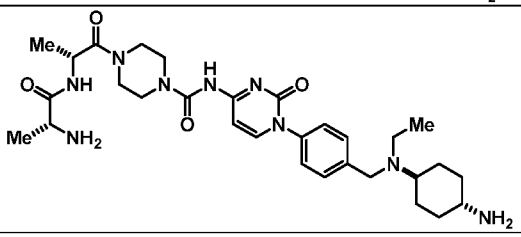
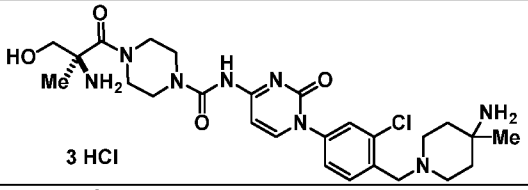
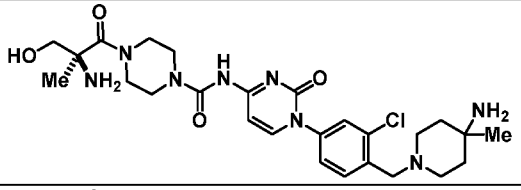
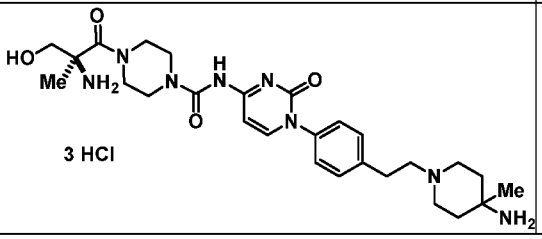
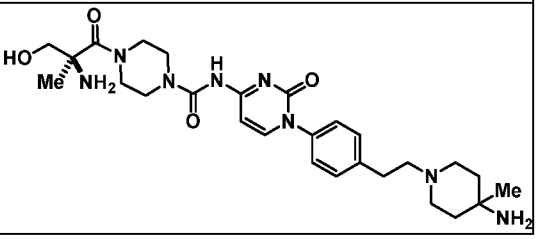
No.	Salt Structure	Free Base Structure
320	 3HCl Cis-racemate	 Cis-racemate
321	 3HCl Cis-racemate	 Cis-racemate
322	 3 HCl Cis-racemate	 Cis-racemate
323	 3HCl Cis-racemate	 Cis-racemate
324	 3HCl Cis-racemate	 Cis-racemate
325	 3HCl Cis-racemate	 Cis-racemate
326	 3HCl	

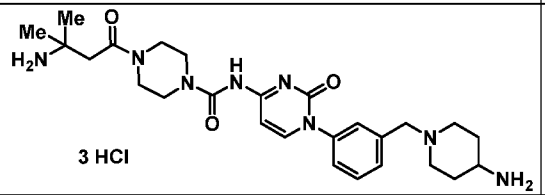
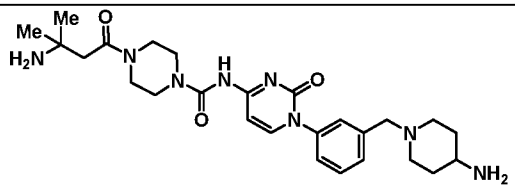
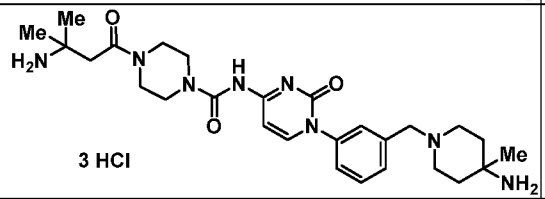
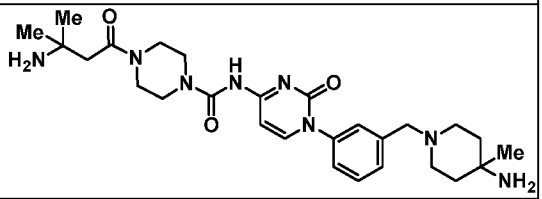
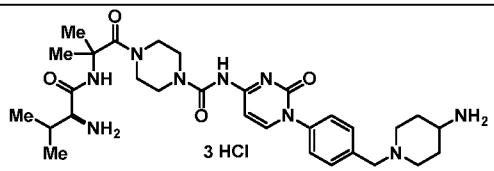
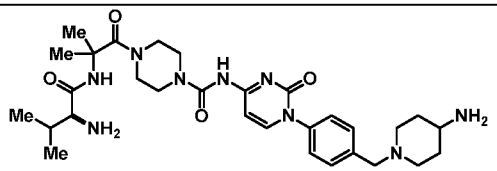
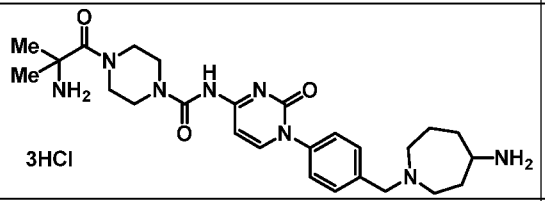
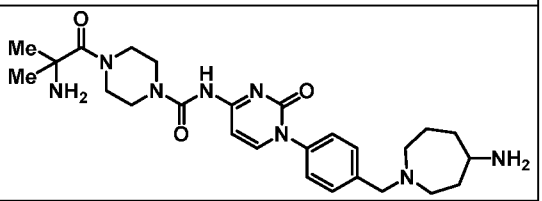
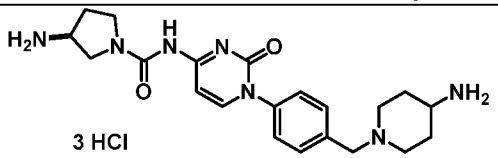
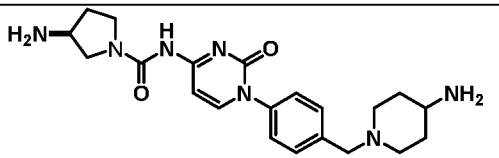
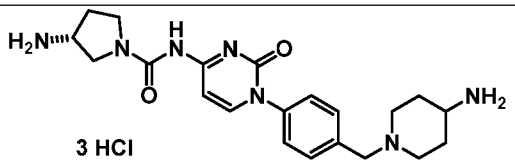
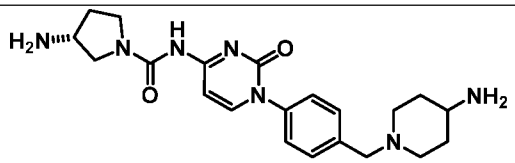
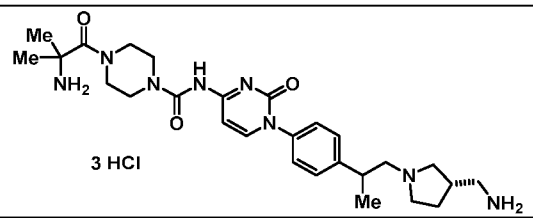
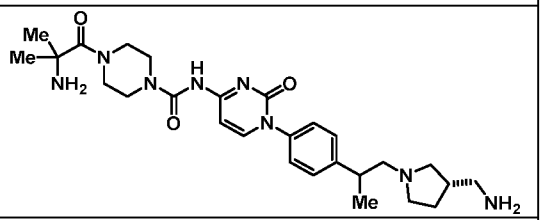
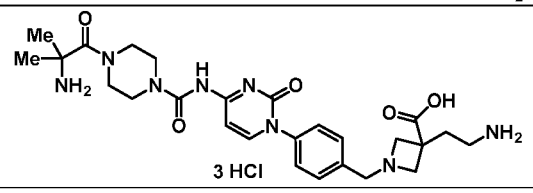
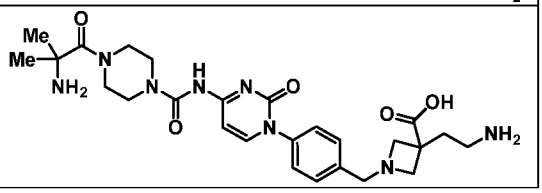
No.	Salt Structure	Free Base Structure
327	 3HCl	
328	 3HCl	
329	 3HCl	
330	 3HCl	
331	 3HCl	
332	 3HCl	
333	 3HCl Cis-racemate	 Cis-racemate

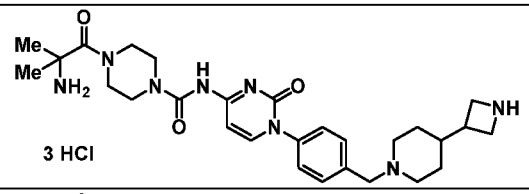
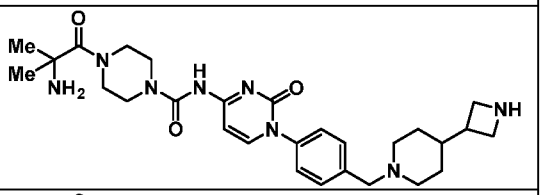
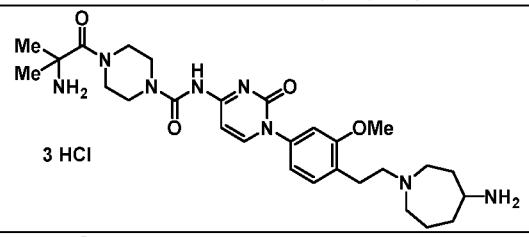
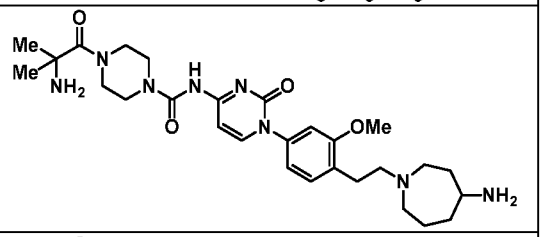
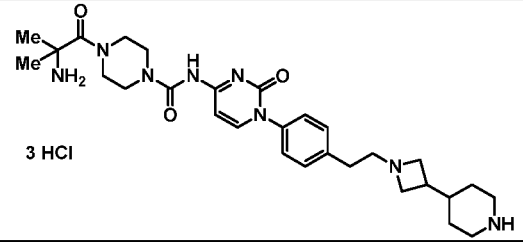
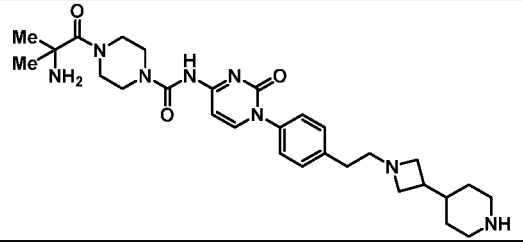
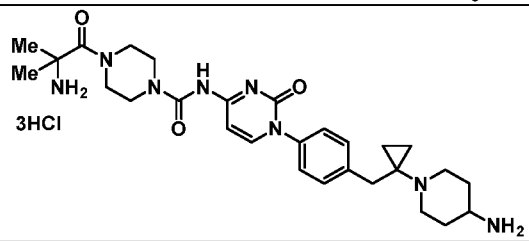
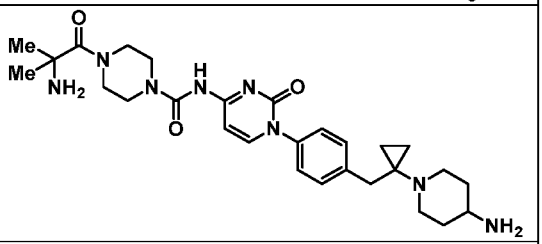
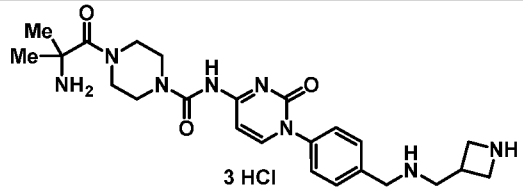
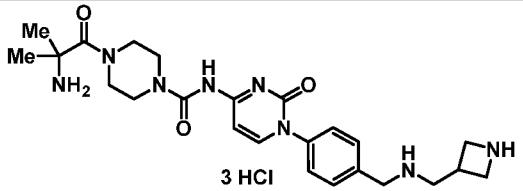
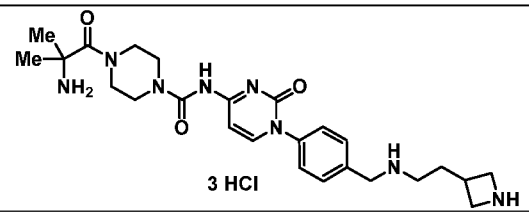
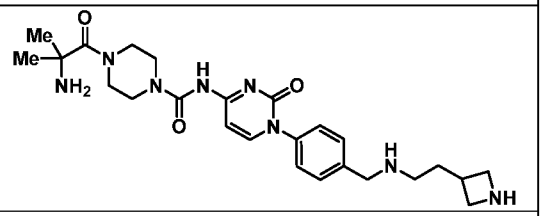
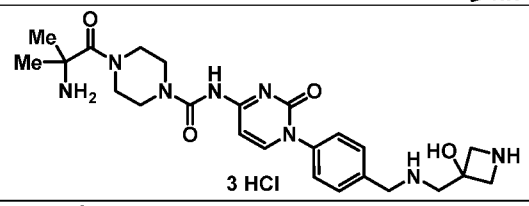
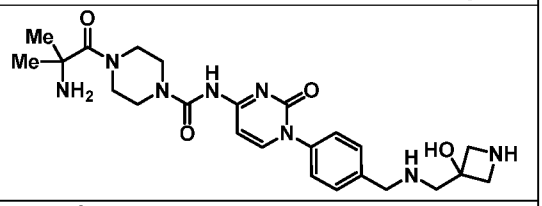
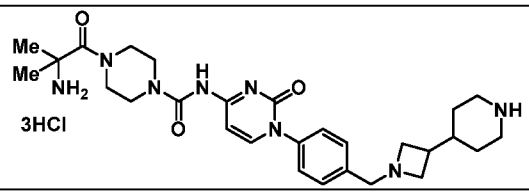
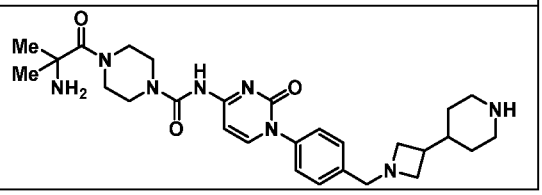
No.	Salt Structure	Free Base Structure
334	 3HCl	
335	 3HCl	
336	 3HCl Cis recemate	 Cis recemate
337	 3HCl	 Mixture of Diastereomers
338	 3HCl	
339	 3HCl	
340	 3HCl	

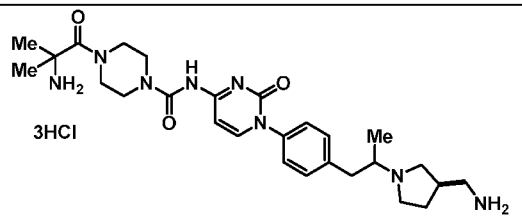
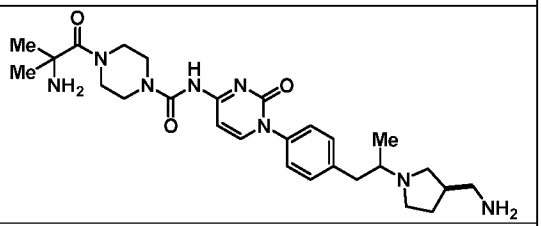
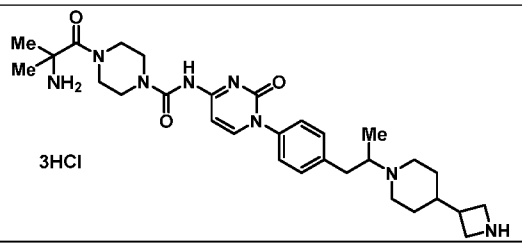
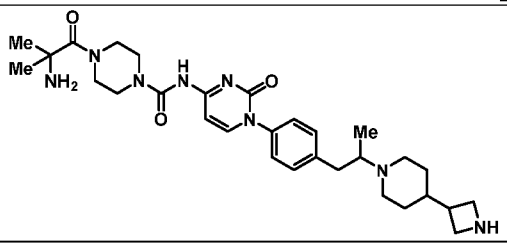
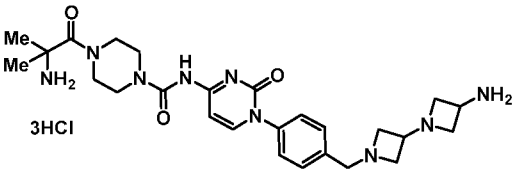
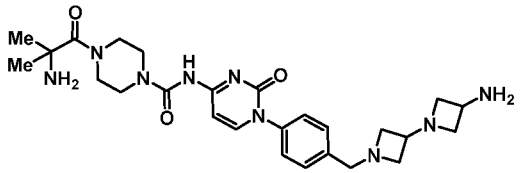
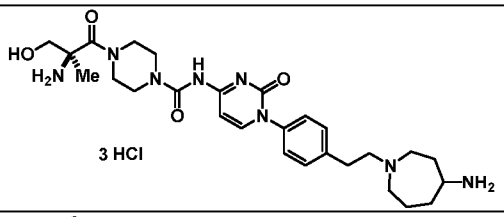
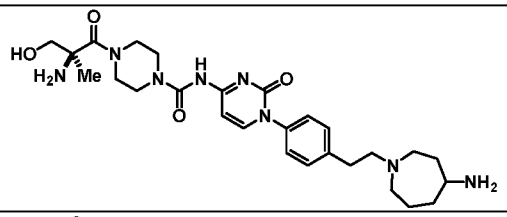
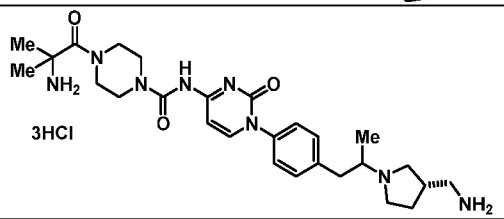
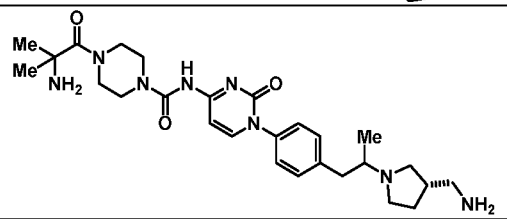
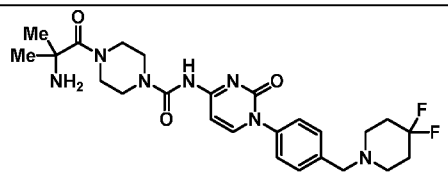
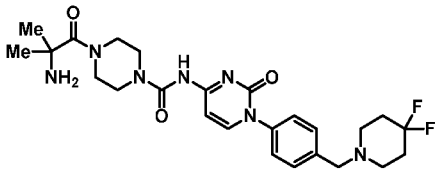
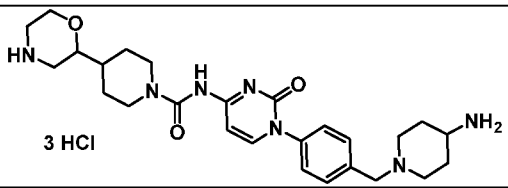
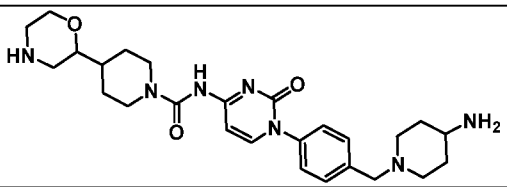
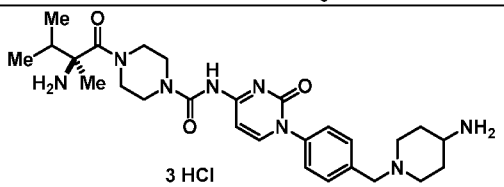
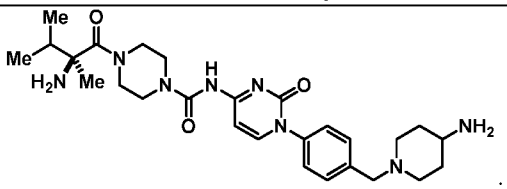
No.	Salt Structure	Free Base Structure
341	 3HCl	
342	 3 HCl	
343	 3HCl	
344	 3HCl Trans recemate	 Trans recemate
345	 3HCl	
346	 3 HCl	
347	 3 HCl	

No.	Salt Structure	Free Base Structure
348		
349		
350		
351		
352		
353		
354		

No.	Salt Structure	Free Base Structure
355		
356		
357		
358		
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360		
361		

No.	Salt Structure	Free Base Structure
362		
363		
364		
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367		
368		
369		

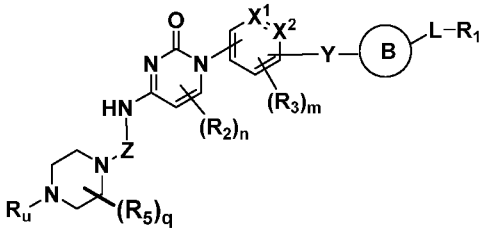
No.	Salt Structure	Free Base Structure
370		
371		
372		
373		
374		
375		
376		
377		

No.	Salt Structure	Free Base Structure
378	 3HCl	
379	 3HCl	
380	 3HCl	
381	 3 HCl	
382	 3HCl	
383	 2 HCl	
384	 3 HCl	
385	 3 HCl	

[00199] In another embodiment, the compound of formula I or a pharmaceutically acceptable salt thereof is selected from the compounds listed in any one of Table 10 and Table 11.

[00200] In another embodiment, the compound of formula II or III or a pharmaceutically acceptable salt thereof is selected from the compounds listed in Table 10.

[00201] In another aspect, the disclosure provides a compound of formula IV:

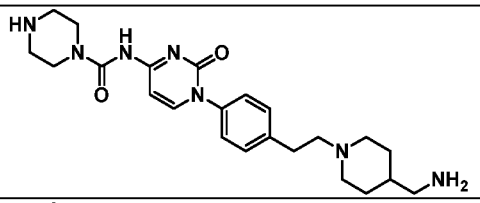
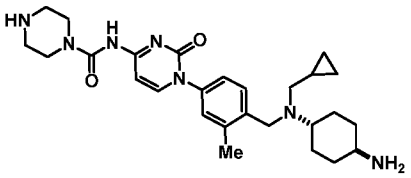
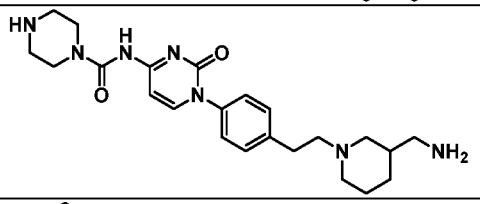
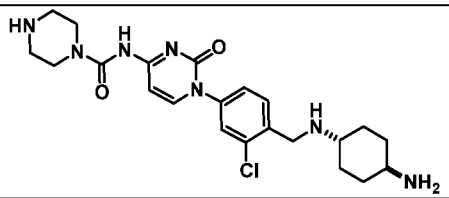
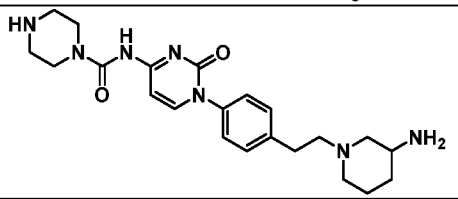
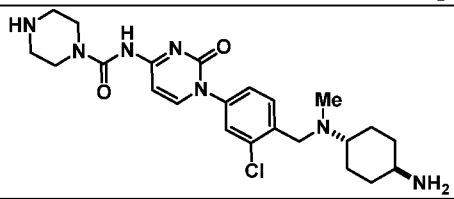
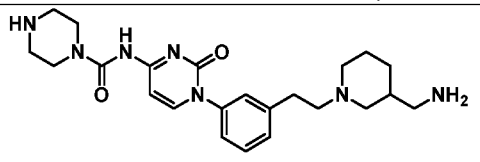
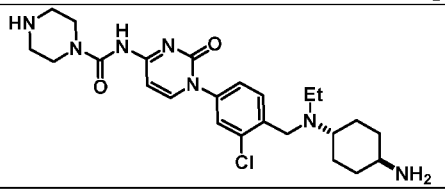


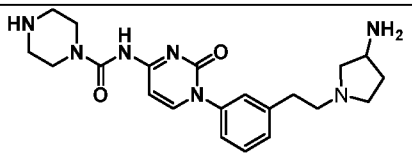
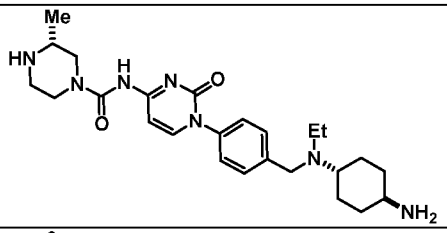
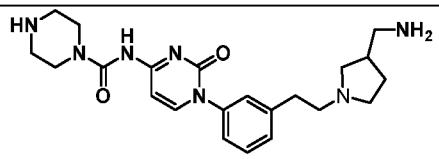
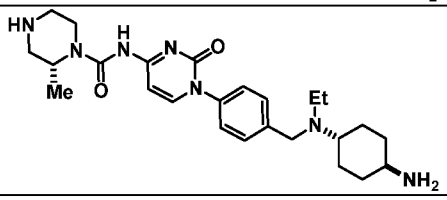
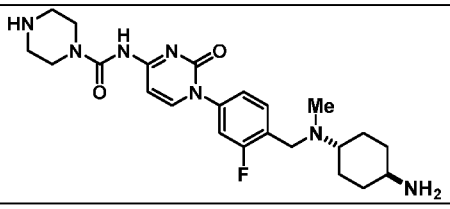
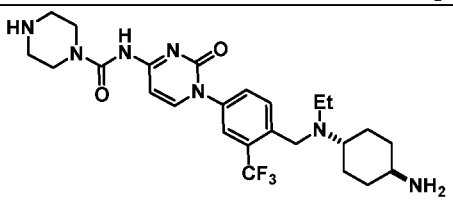
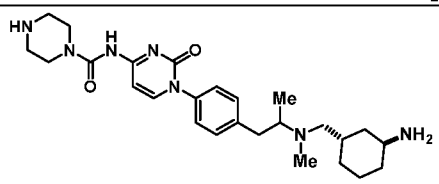
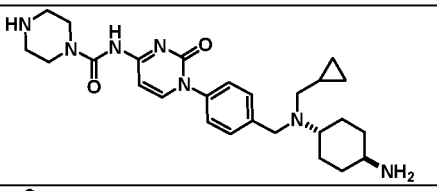
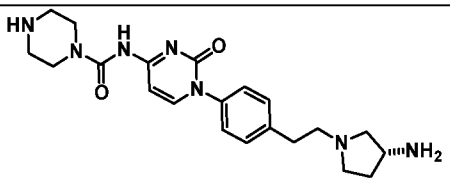
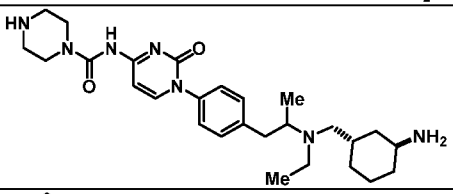
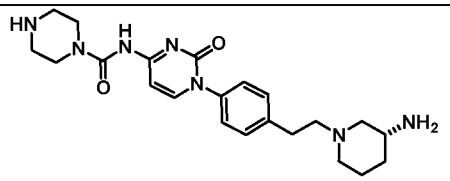
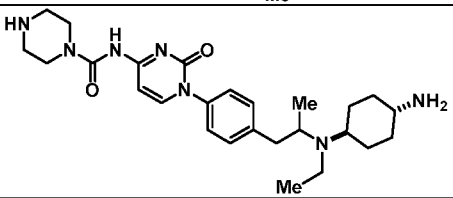
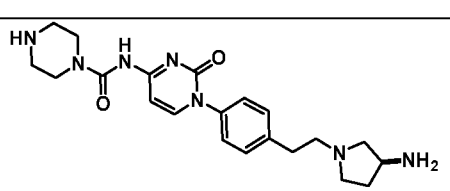
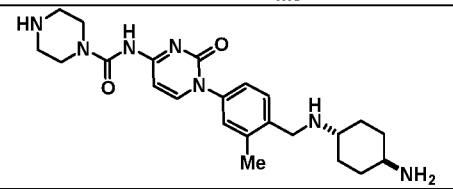
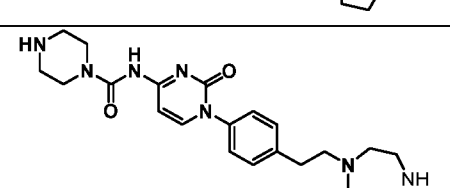
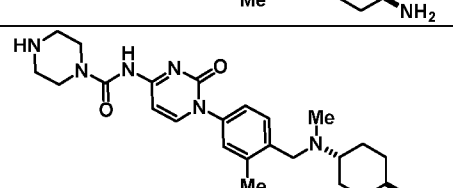
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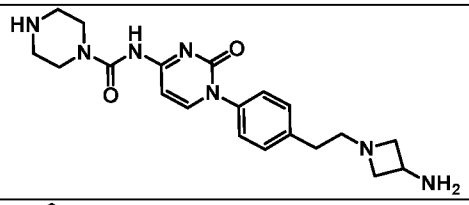
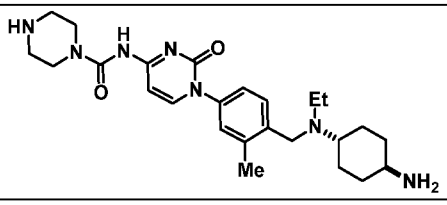
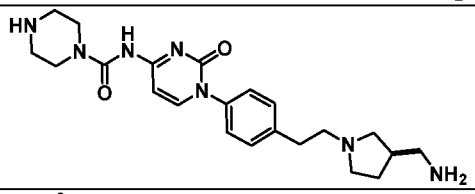
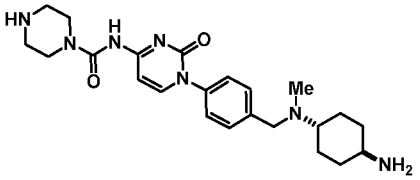
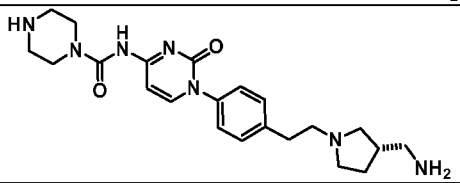
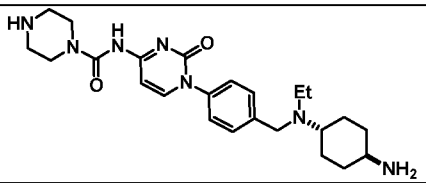
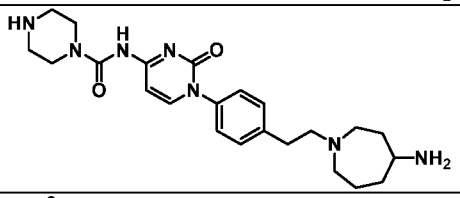
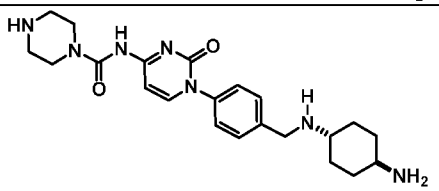
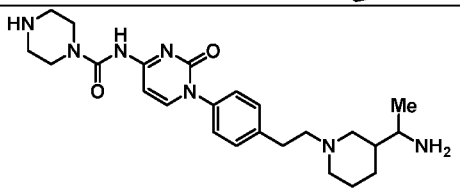
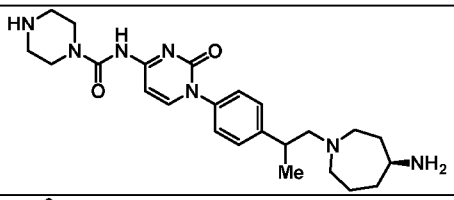
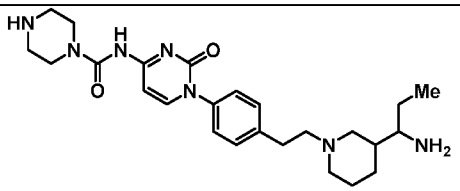
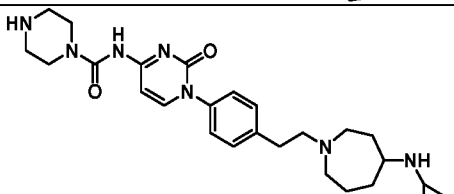
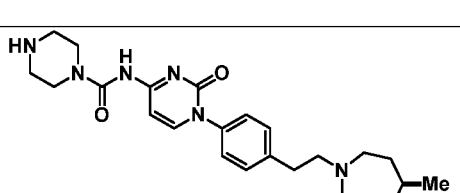
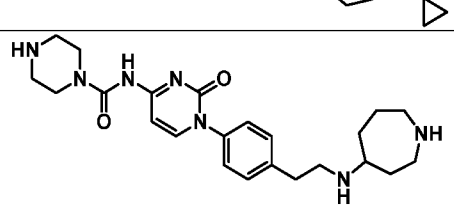
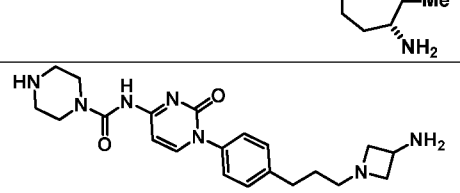
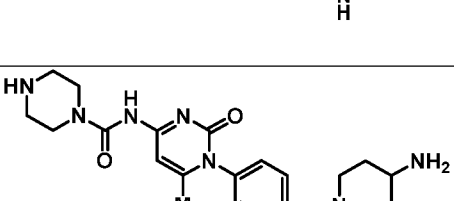
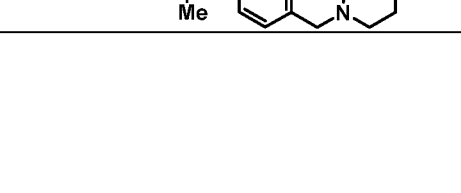
or a pharmaceutically acceptable salt thereof, wherein the variables have the definitions as defined herein and Ru is H or an amino protecting group.

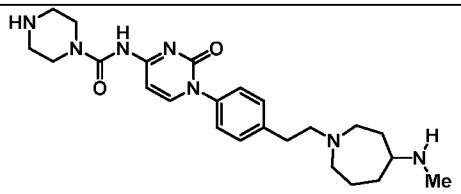
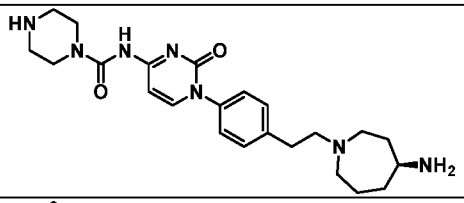
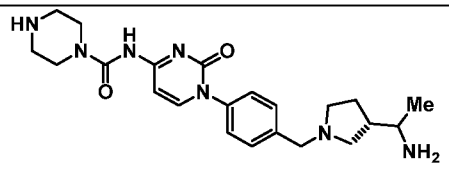
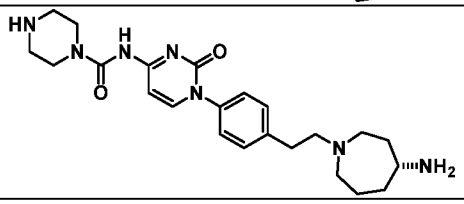
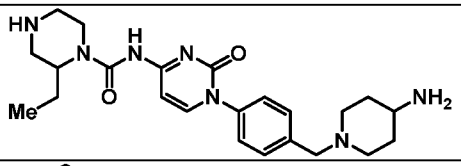
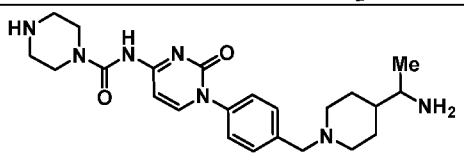
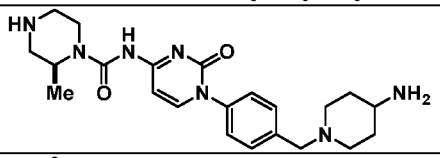
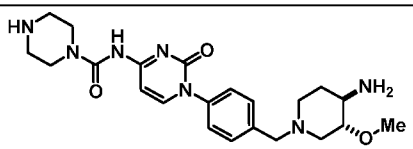
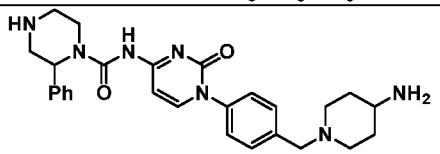
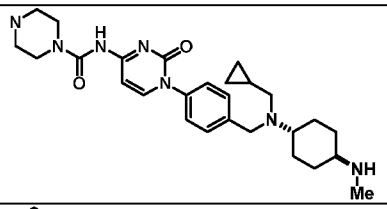
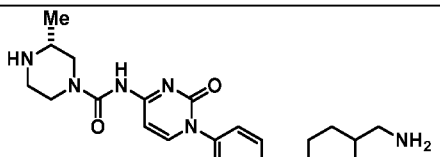
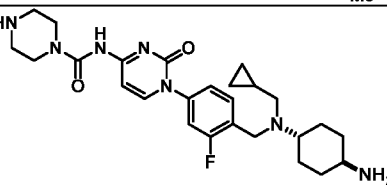
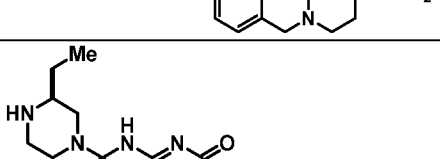
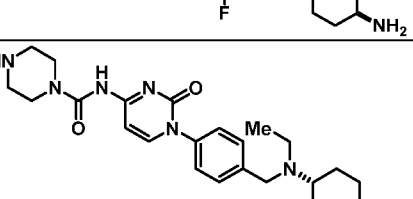
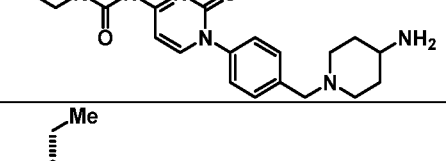
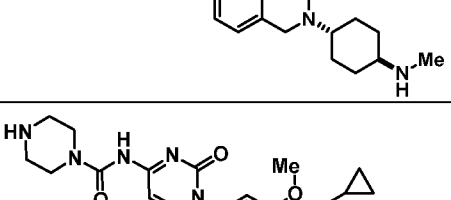
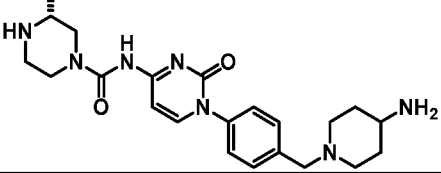
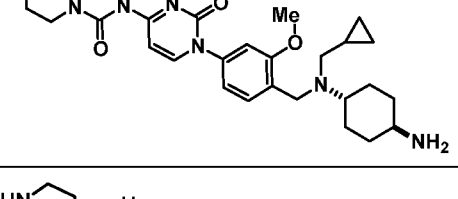
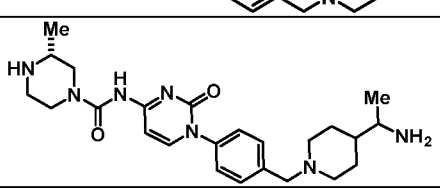
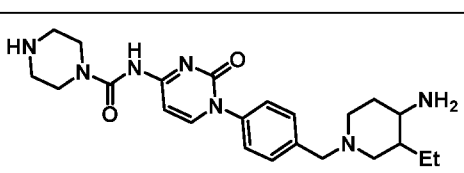
[00202] In another embodiment, the compound of formula IV is selected from the compounds as depicted in Table 12 below.

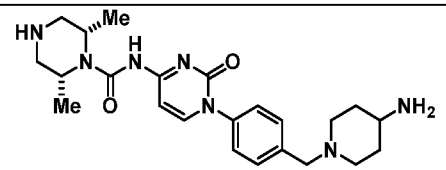
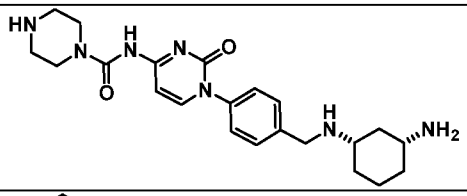
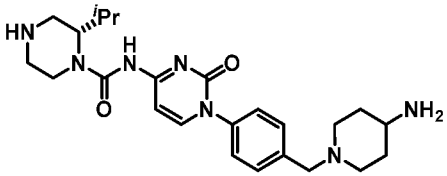
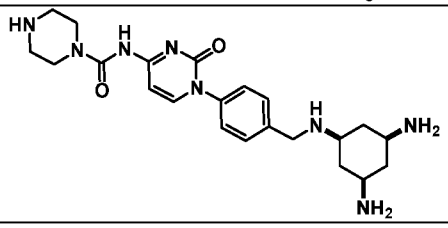
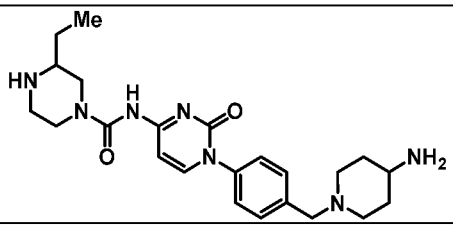
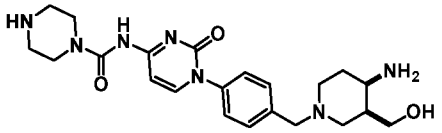
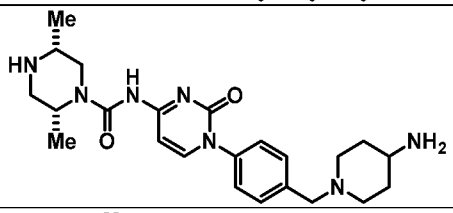
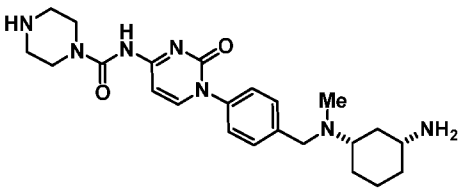
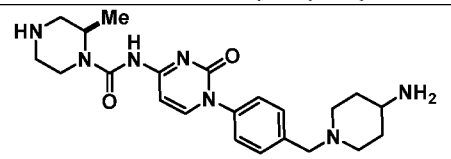
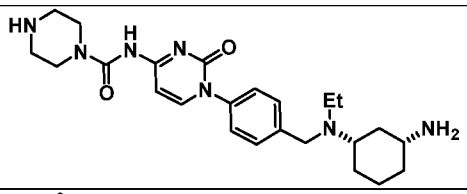
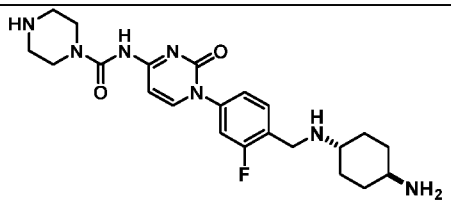
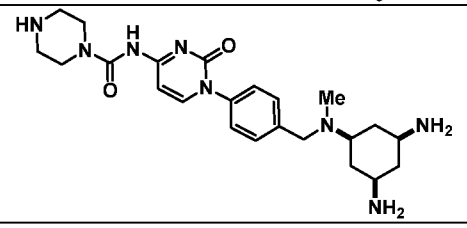
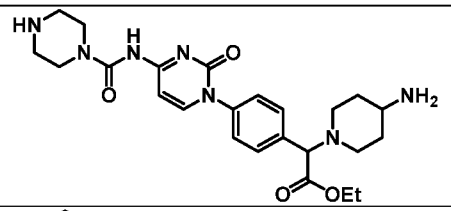
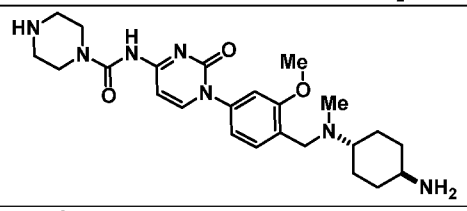
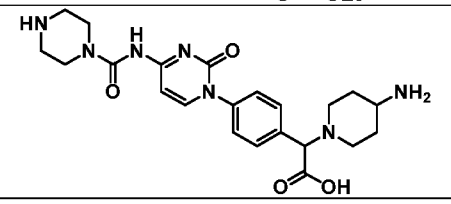
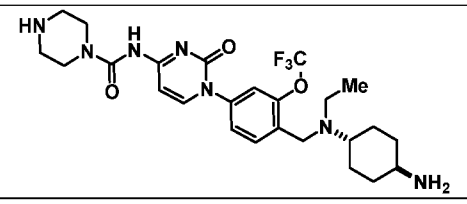
Table 12 Compounds of Formula IV

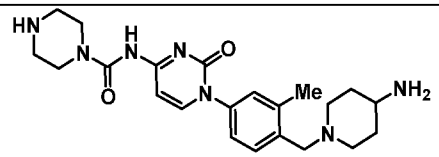
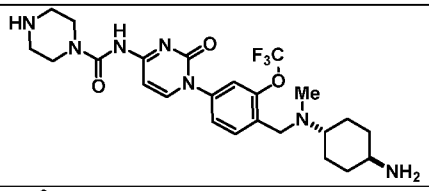
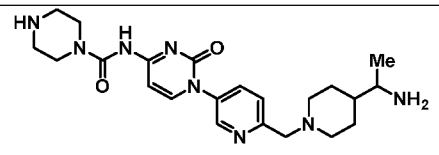
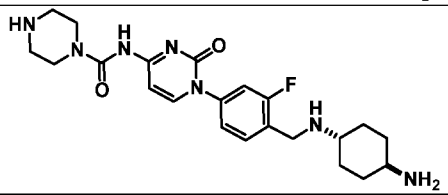
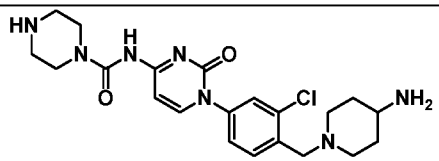
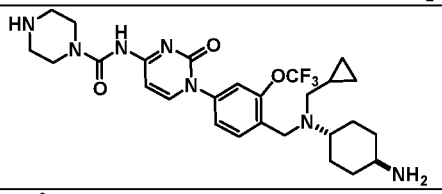
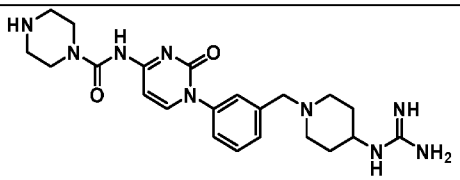
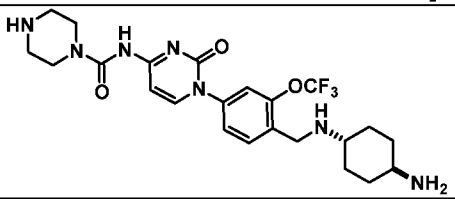
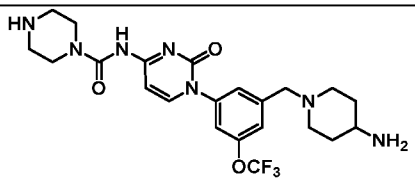
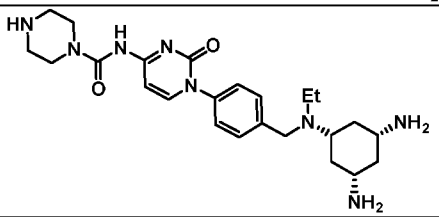
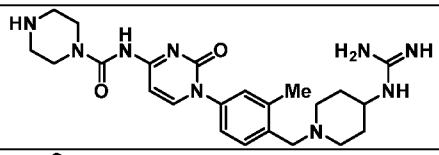
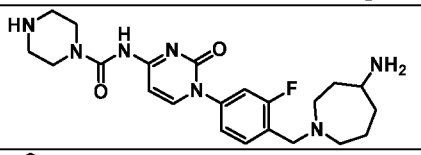
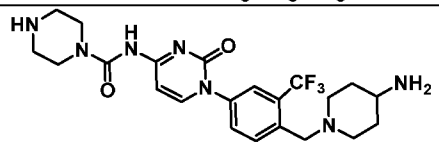
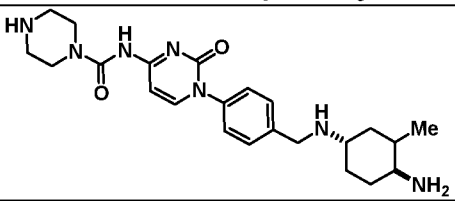
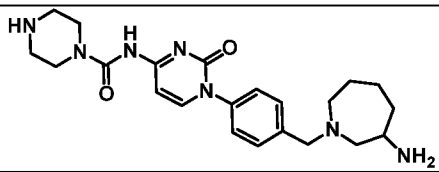
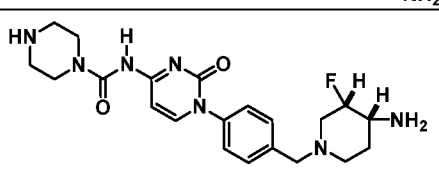
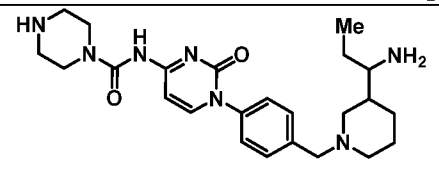
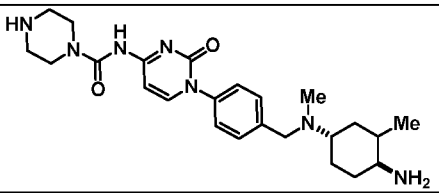
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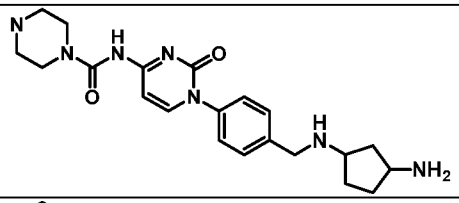
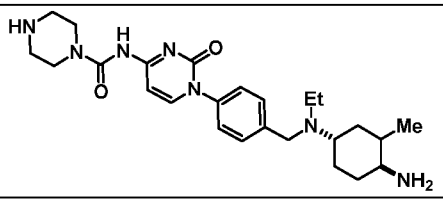
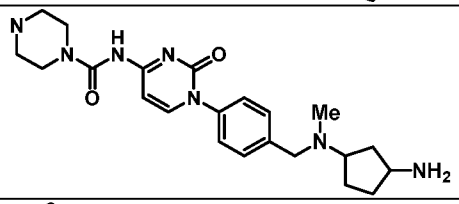
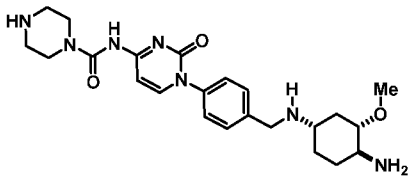
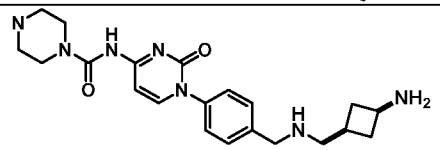
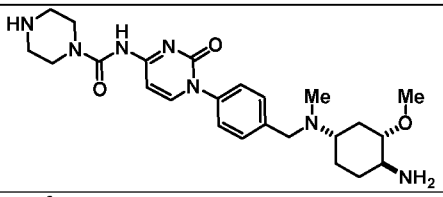
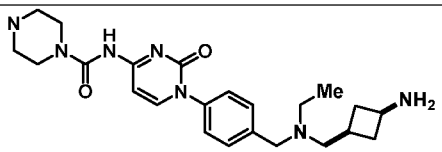
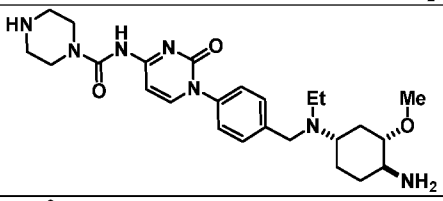
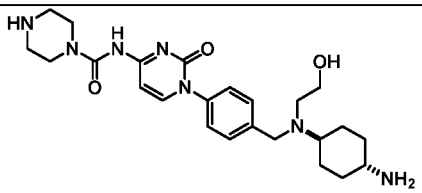
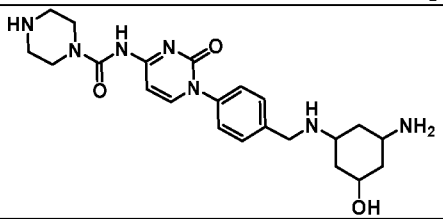
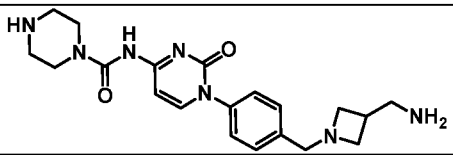
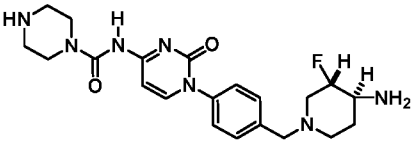
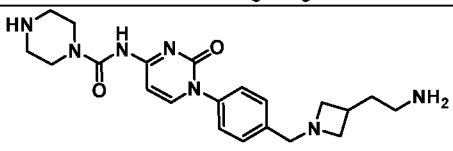
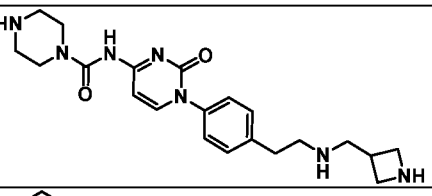
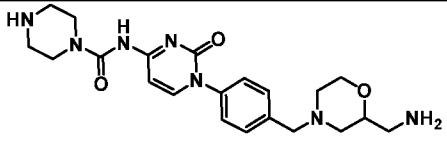
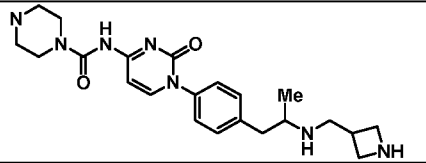
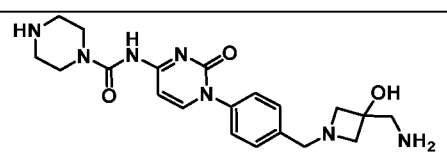
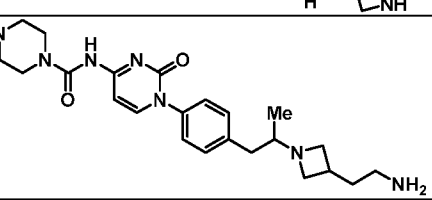
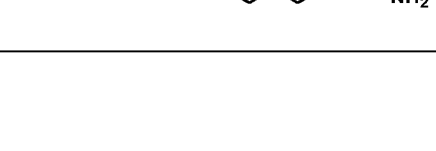
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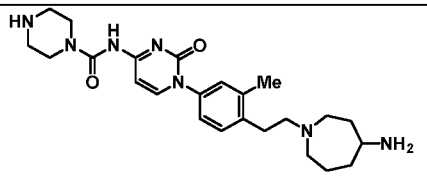
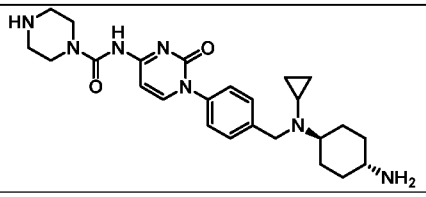
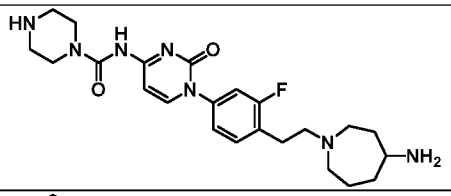
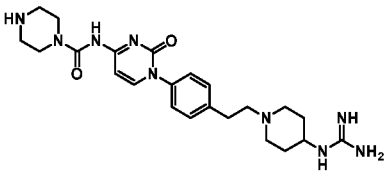
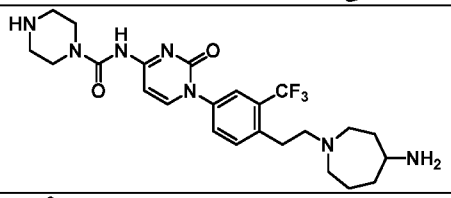
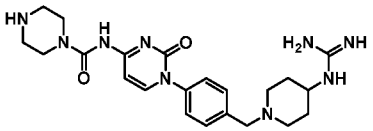
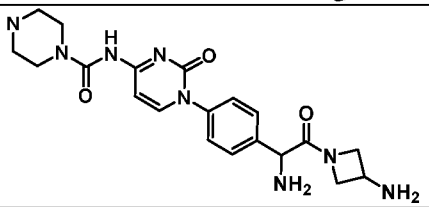
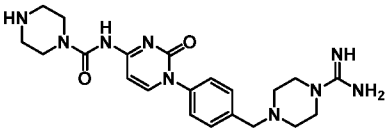
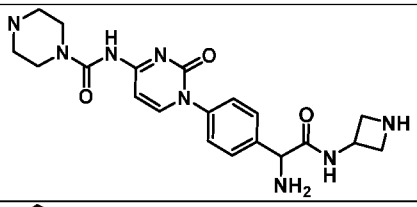
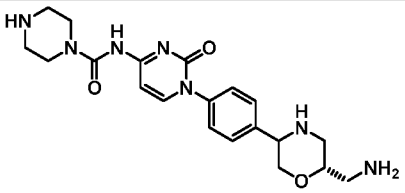
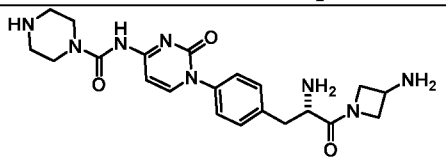
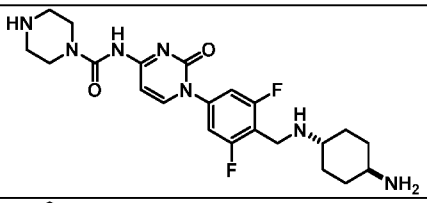
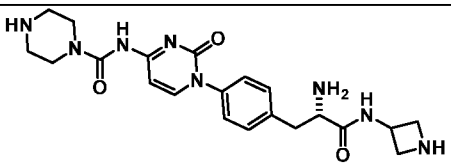
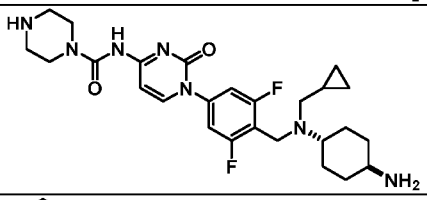
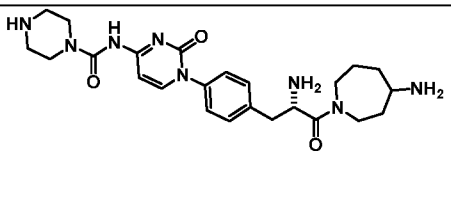
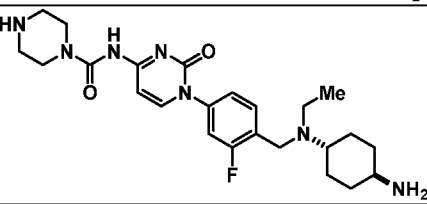
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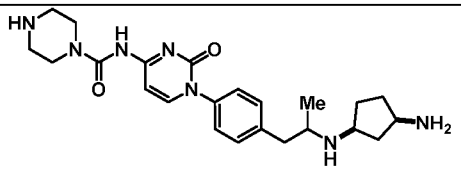
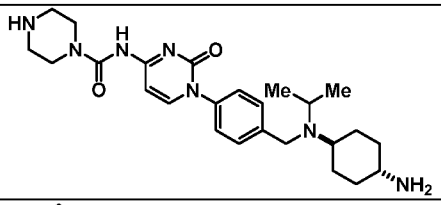
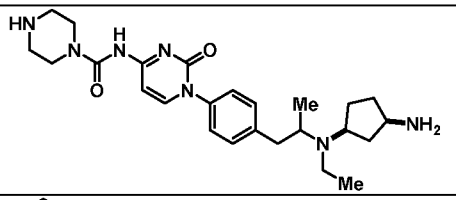
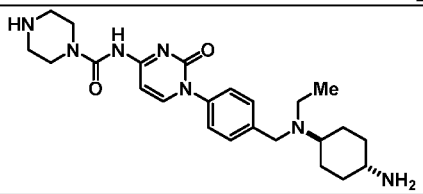
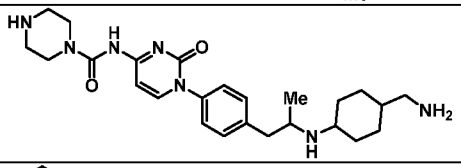
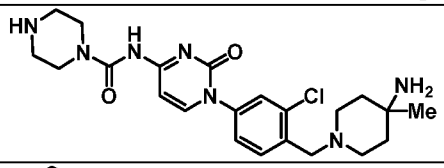
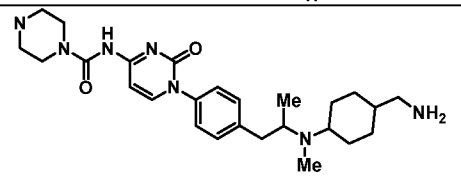
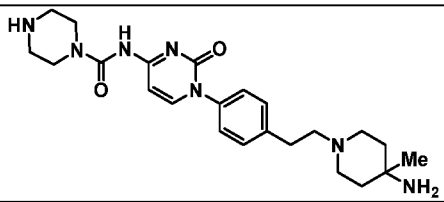
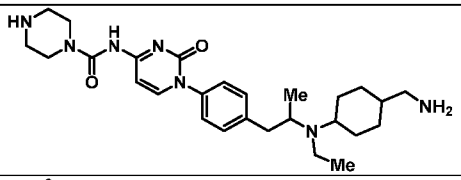
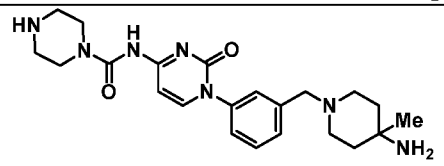
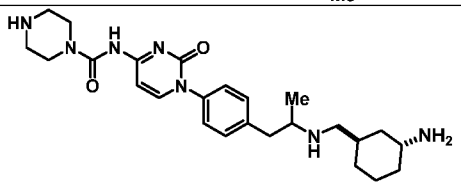
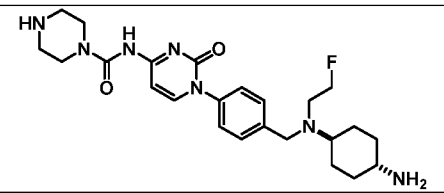
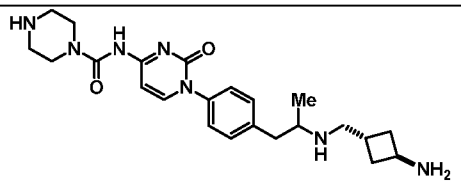
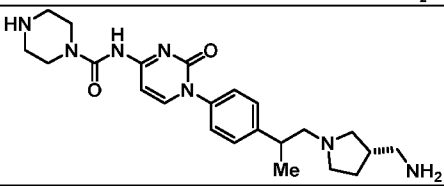
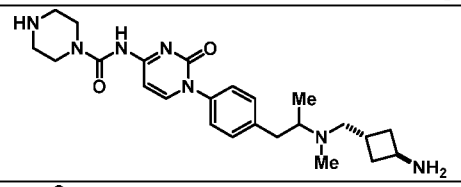
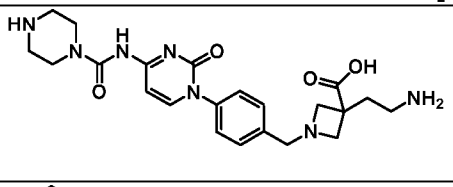
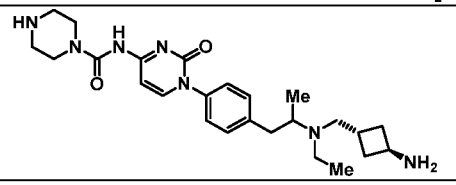
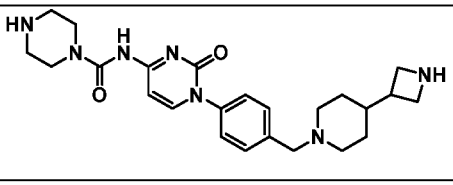
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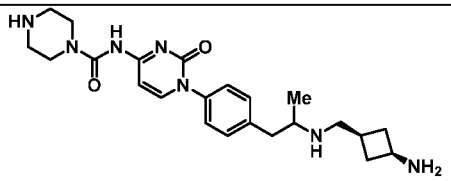
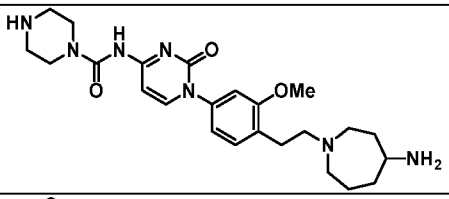
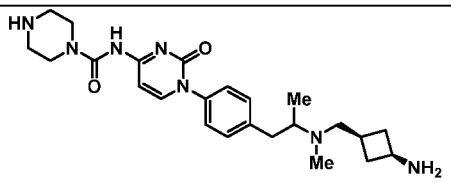
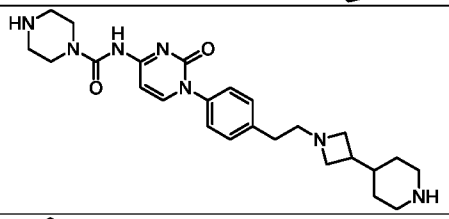
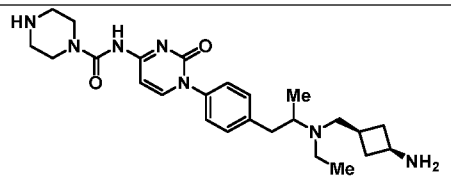
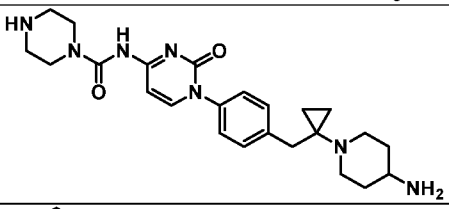
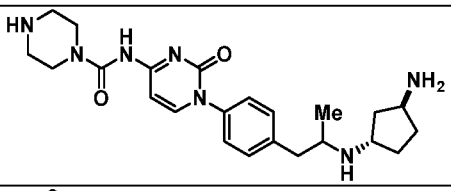
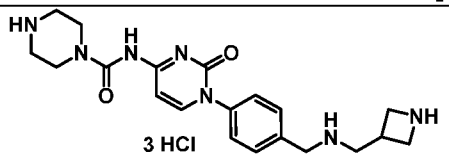
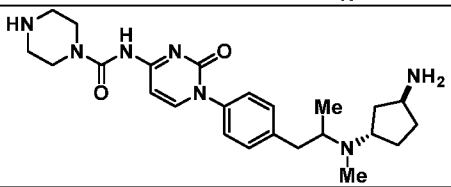
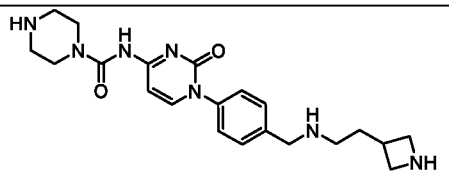
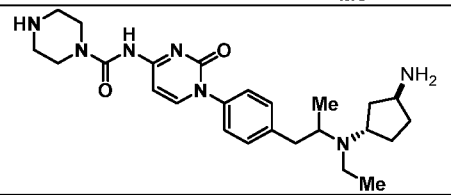
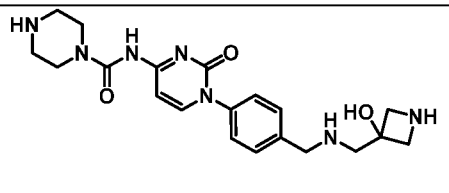
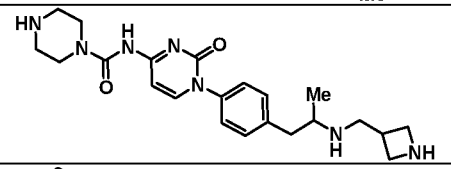
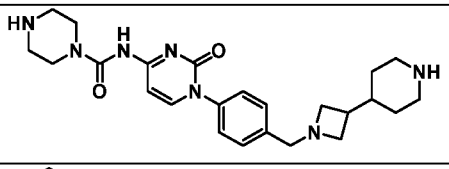
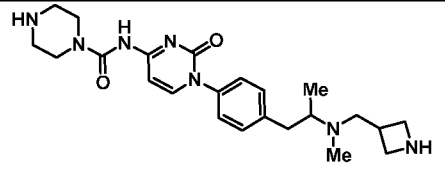
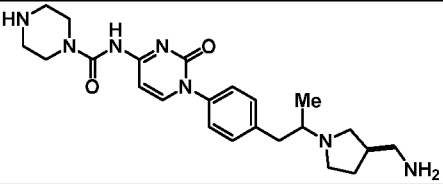
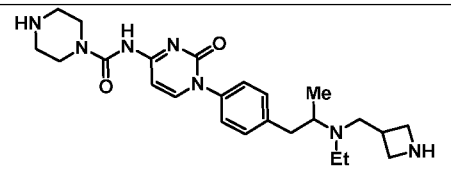
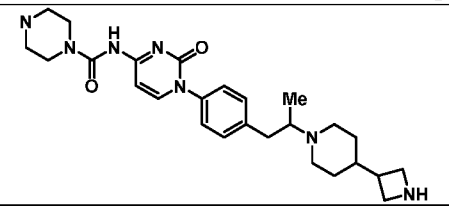
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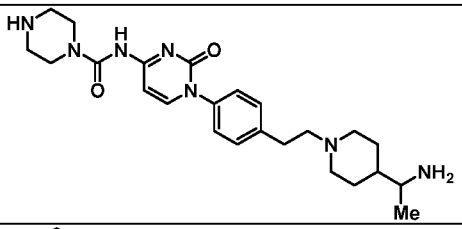
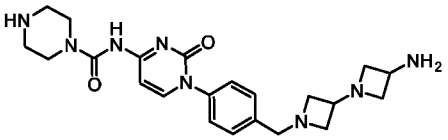
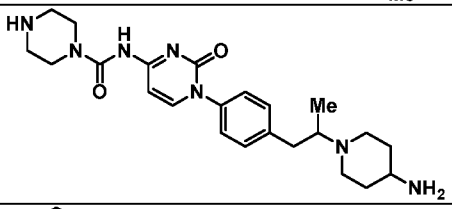
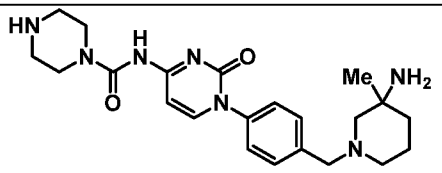
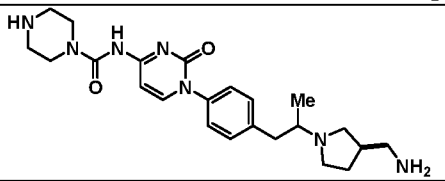
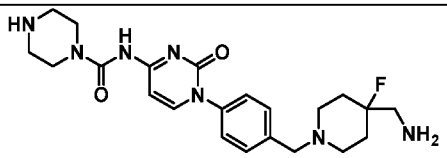
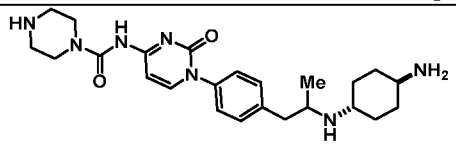
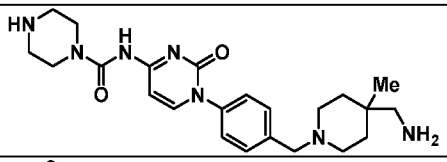
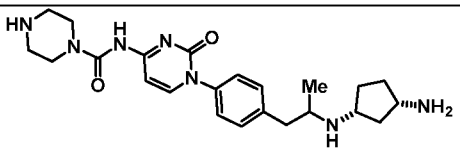
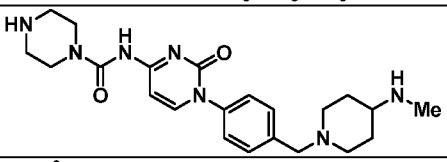
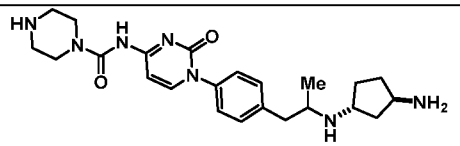
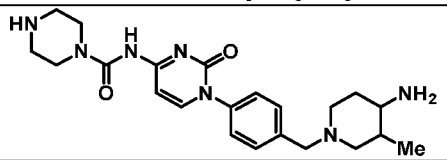
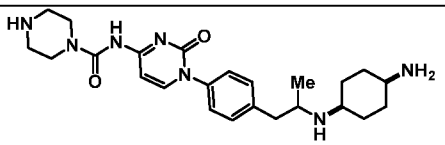
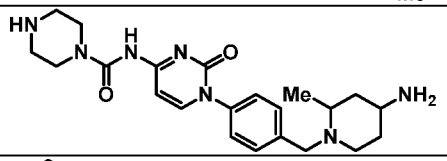
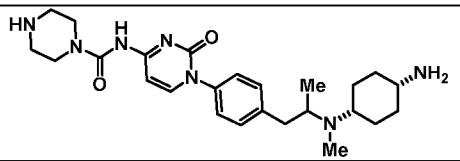
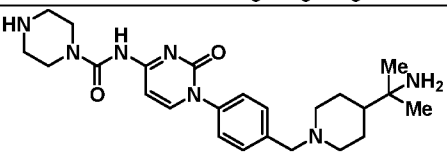
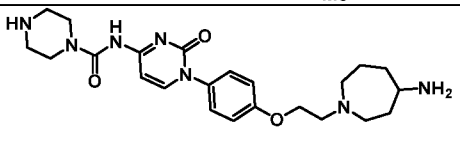
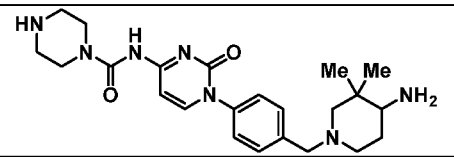
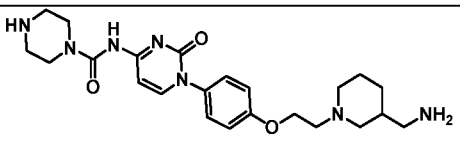
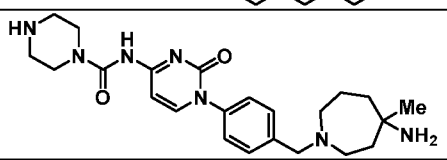
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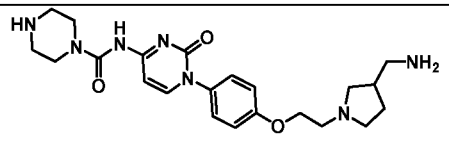
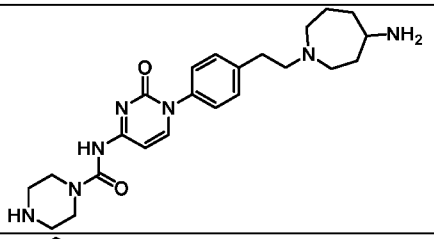
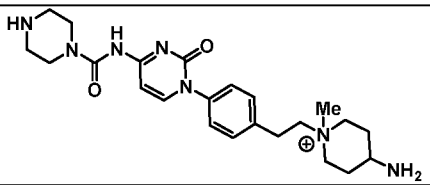
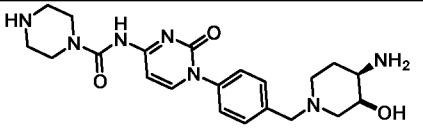
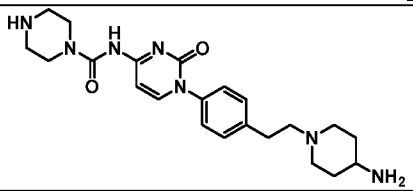
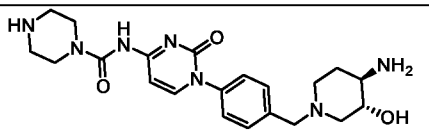
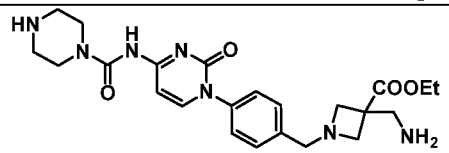
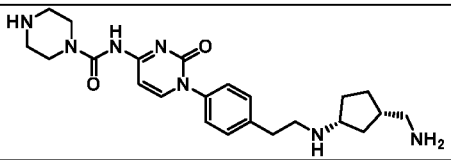
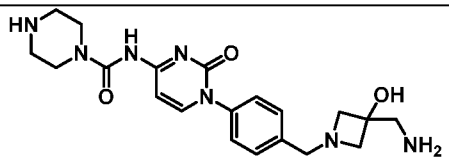
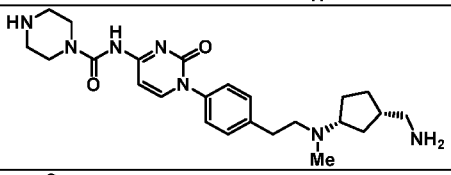
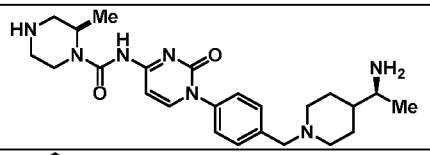
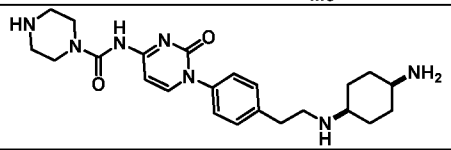
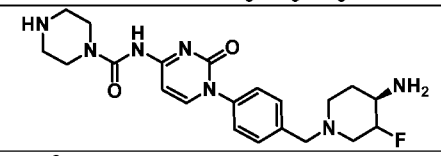
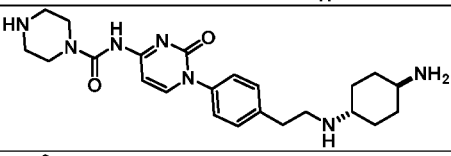
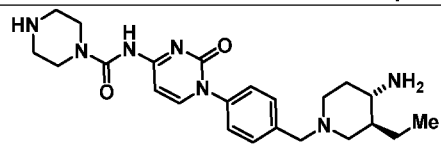
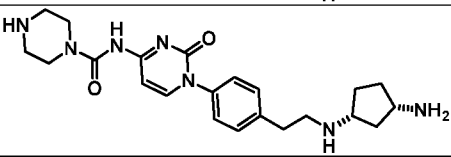
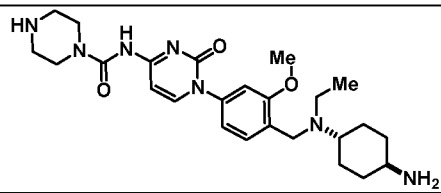
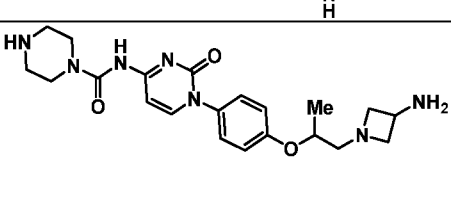
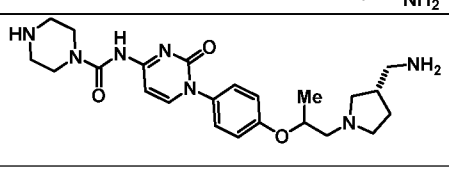
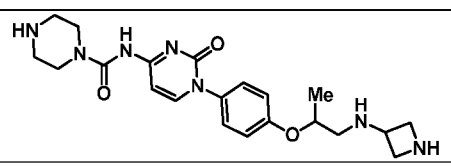
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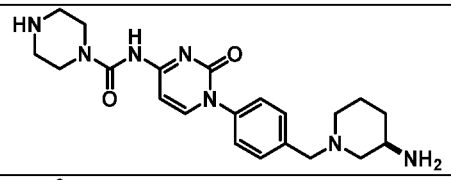
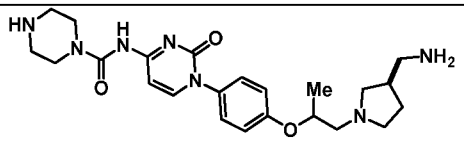
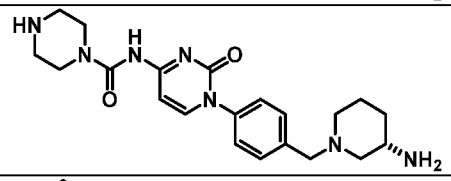
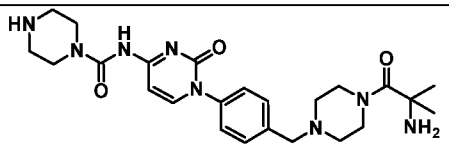
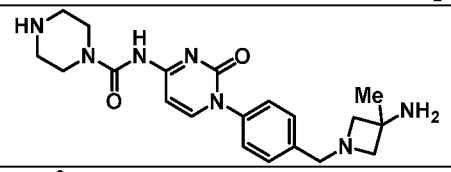
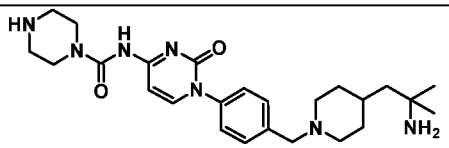
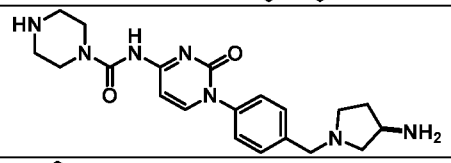
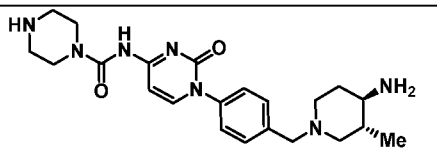
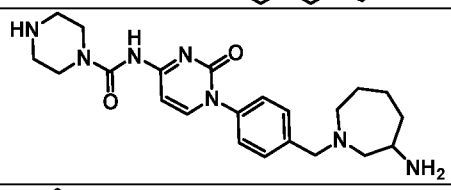
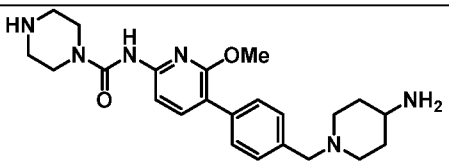
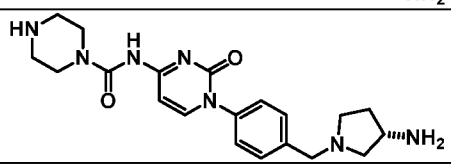
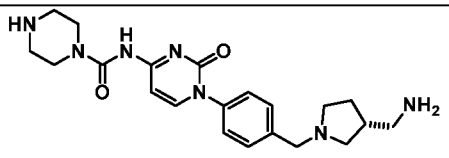
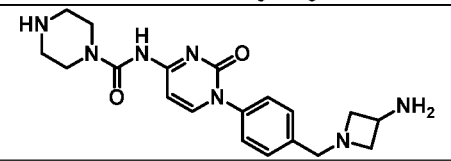
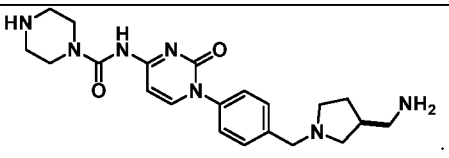
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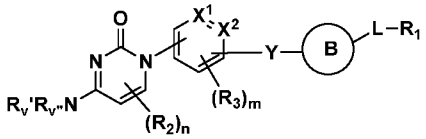
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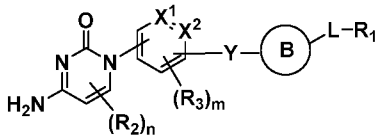
[00203] In another aspect, the disclosure provides a compound of formula V:



V

or a pharmaceutically acceptable salt thereof, wherein the variables have the definitions herein, and one of $R_{V'}$ and $R_{V''}$ is H and the other of $R_{V'}$ and $R_{V''}$ is H or an amino protecting group.

[00204] In another embodiment, the compound of formula V is a compound of formula VI:

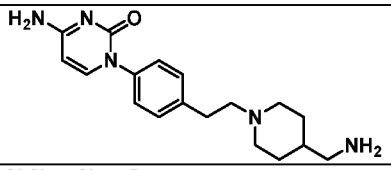
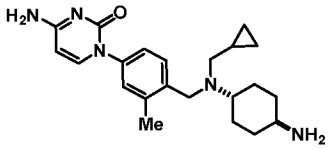
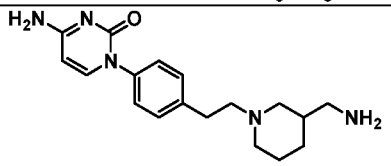
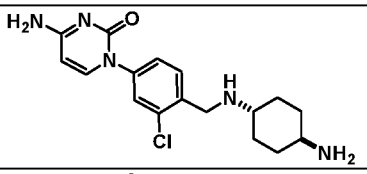
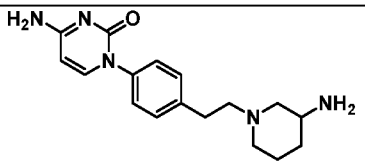
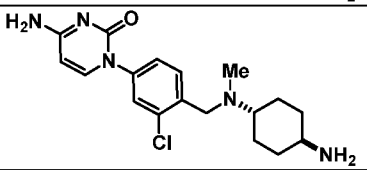
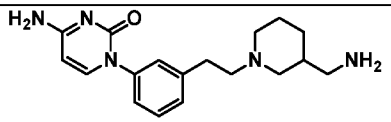
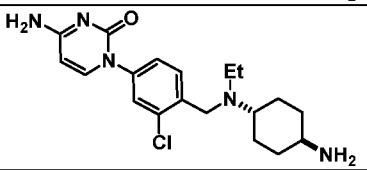
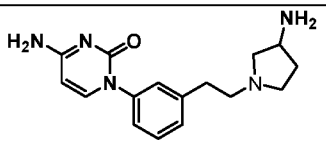
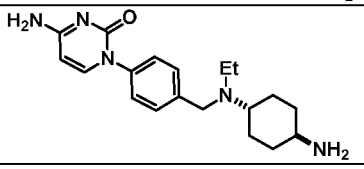
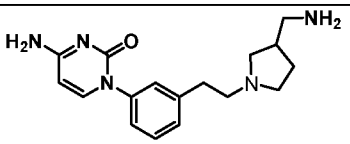
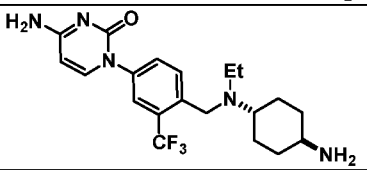
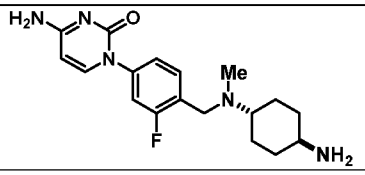
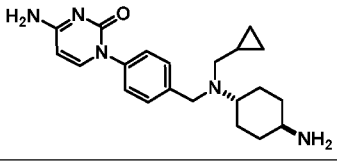


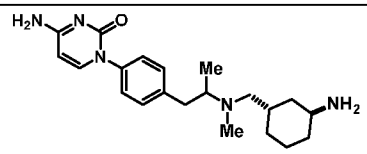
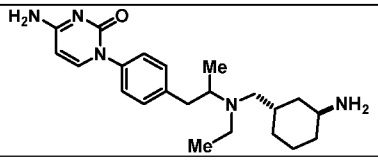
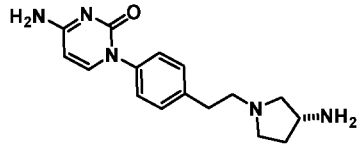
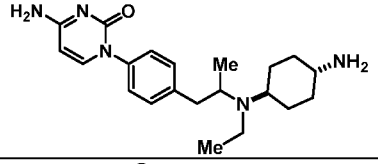
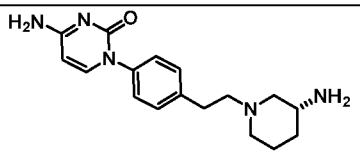
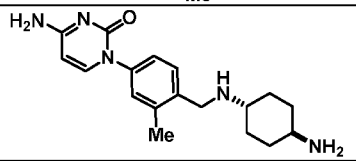
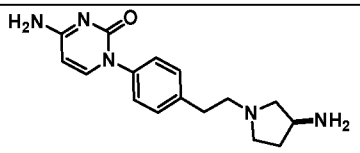
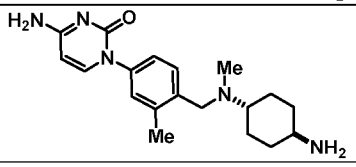
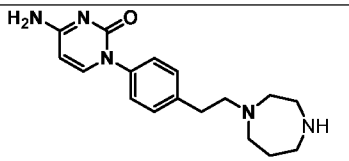
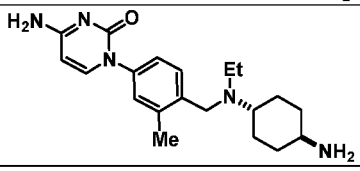
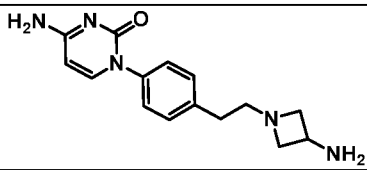
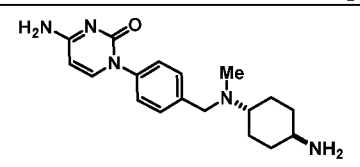
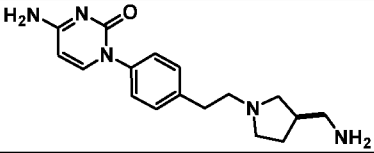
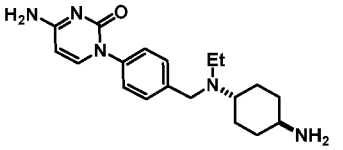
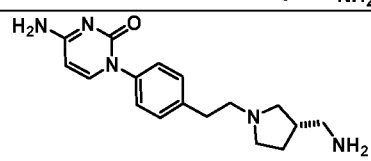
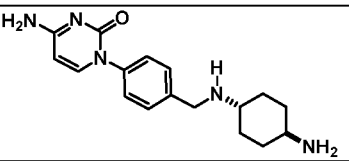
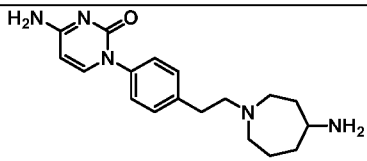
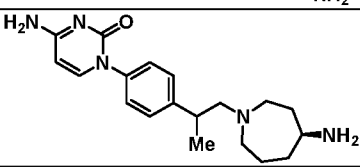
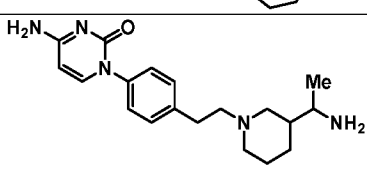
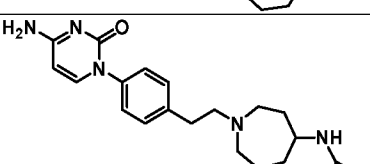
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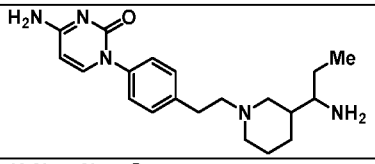
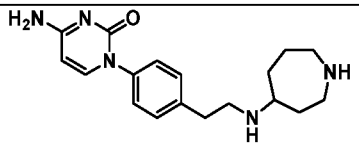
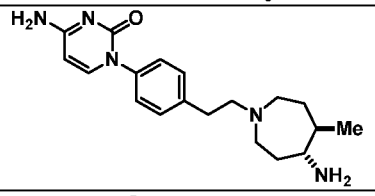
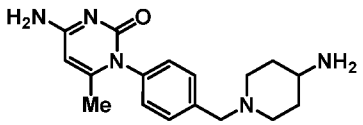
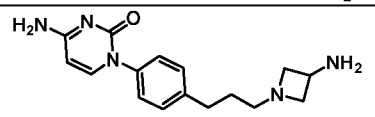
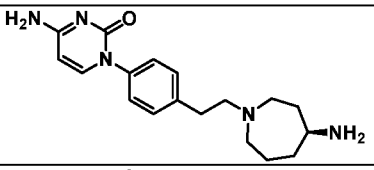
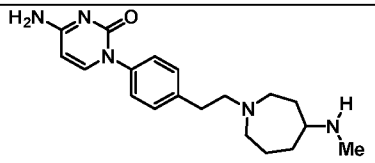
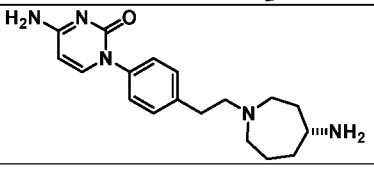
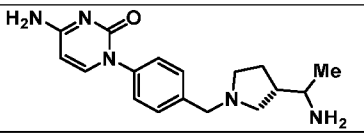
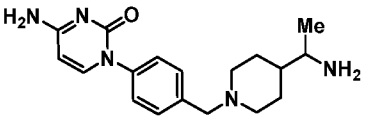
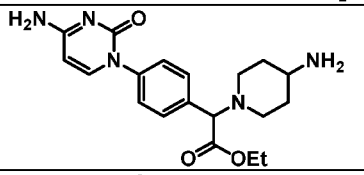
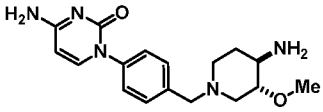
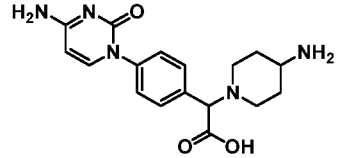
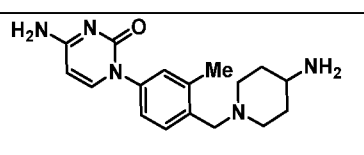
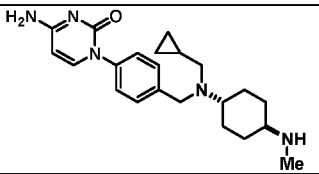
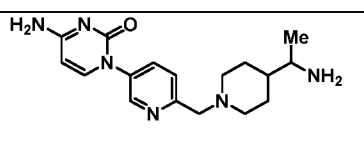
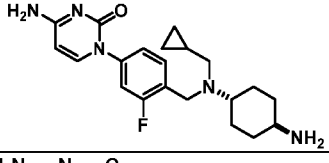
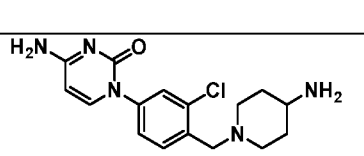
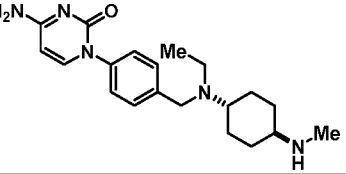
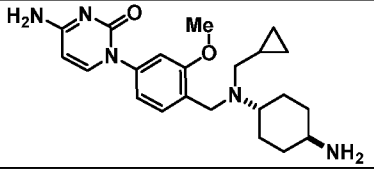
or a pharmaceutically acceptable salt thereof, wherein the variables have the definitions as disclosed herein.

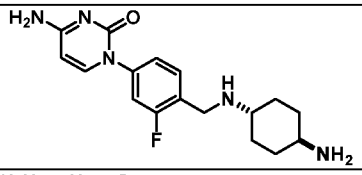
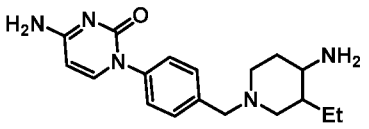
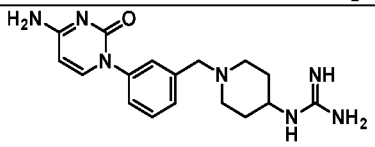
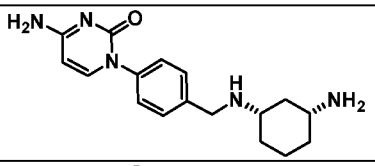
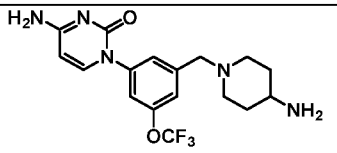
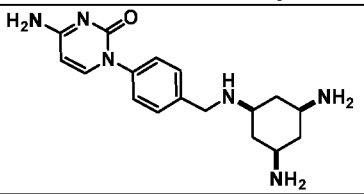
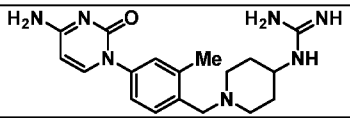
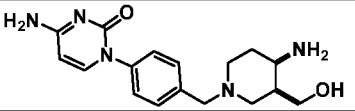
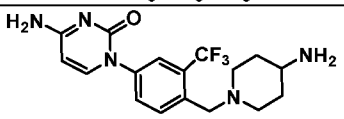
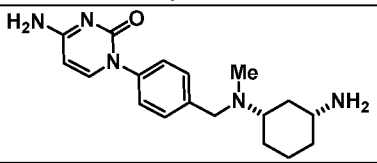
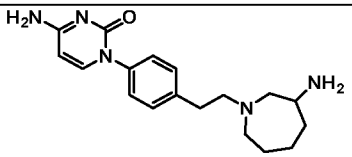
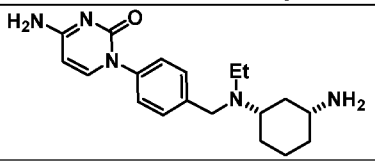
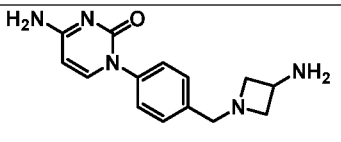
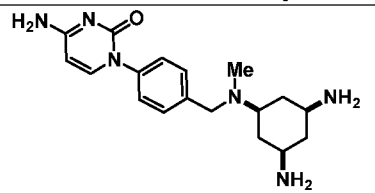
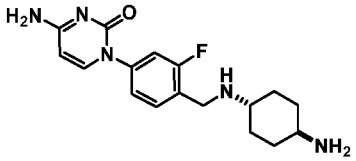
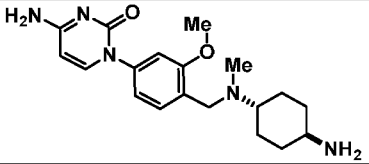
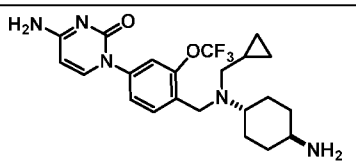
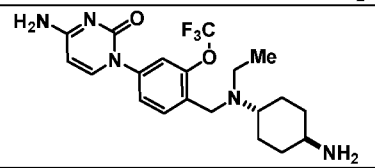
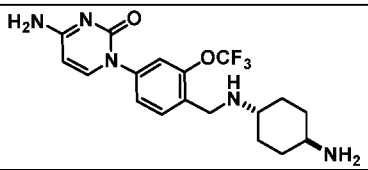
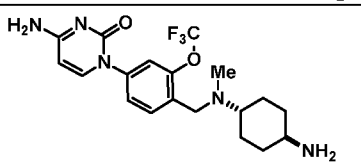
[00205] In another embodiment, the compound of formula V or VI is selected from the compounds as depicted in Table 13 below.

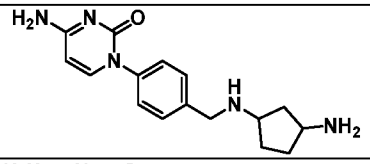
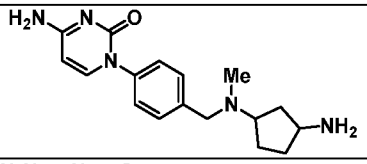
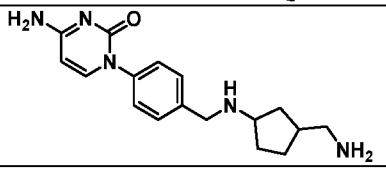
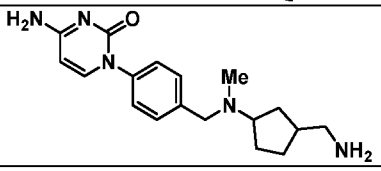
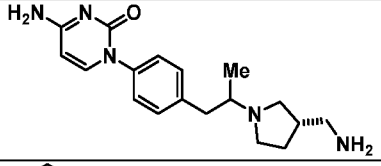
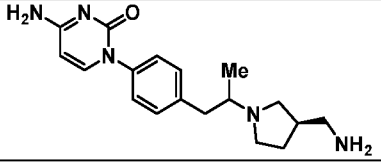
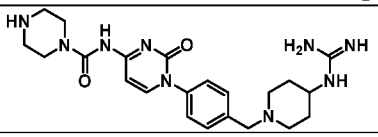
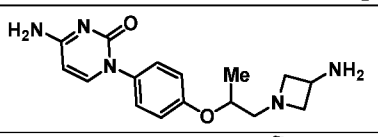
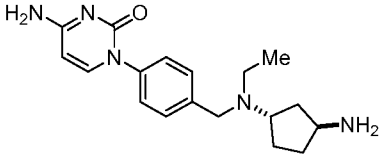
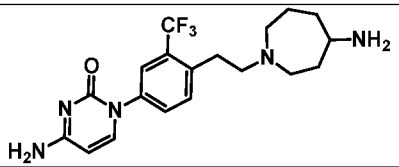
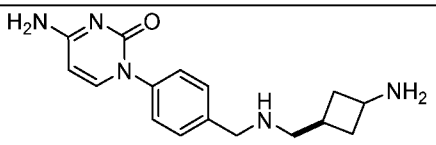
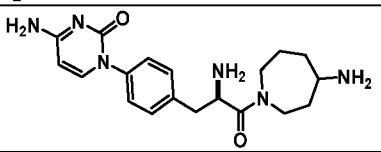
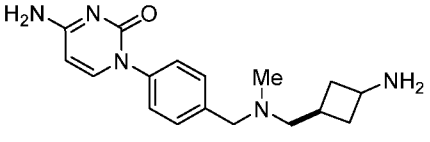
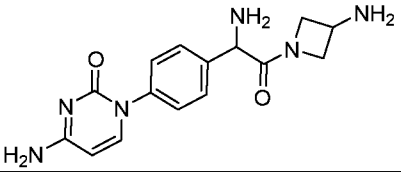
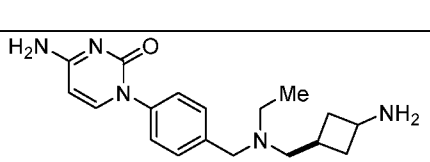
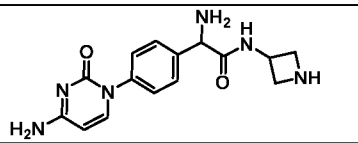
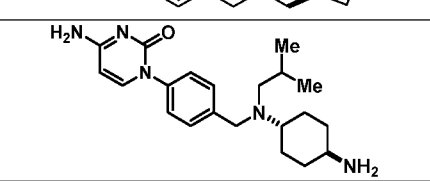
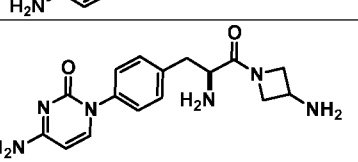
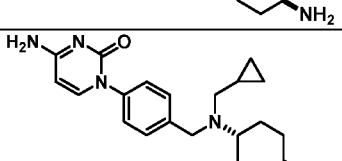
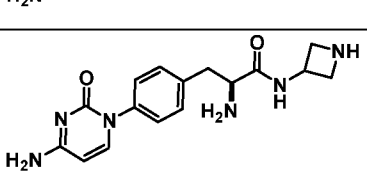
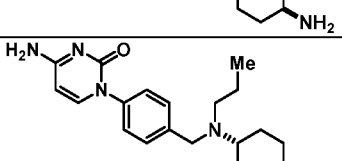
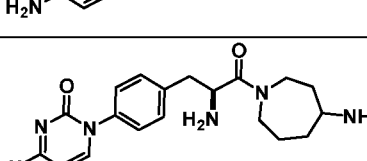
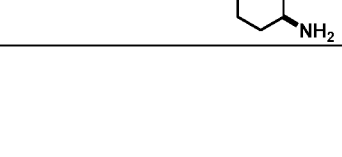
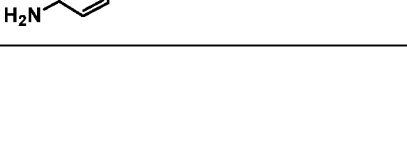
Table 13 Compounds of Formula VI

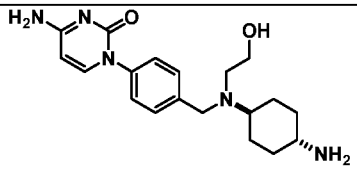
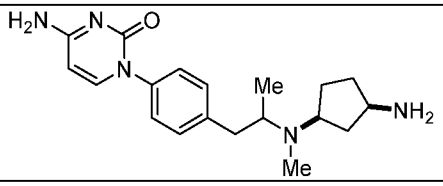
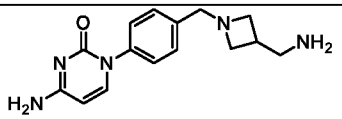
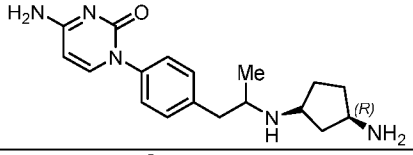
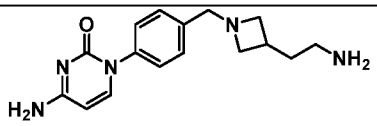
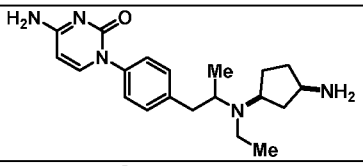
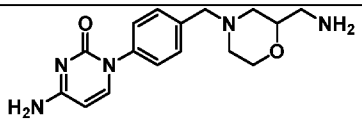
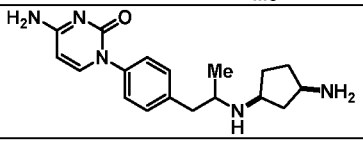
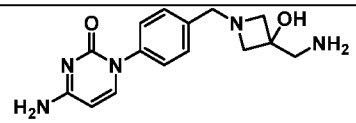
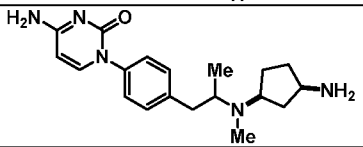
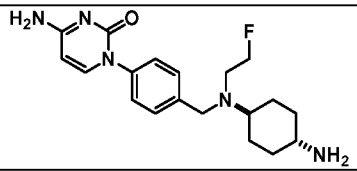
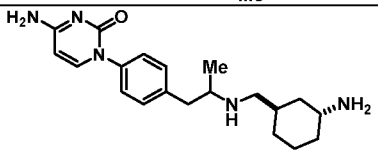
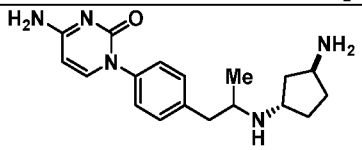
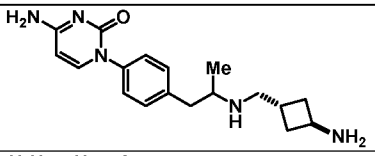
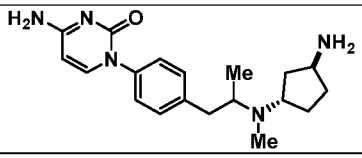
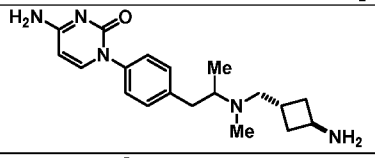
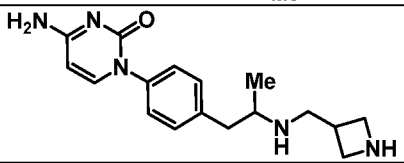
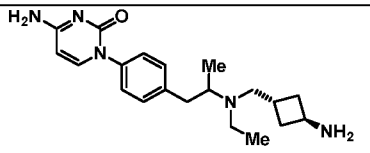
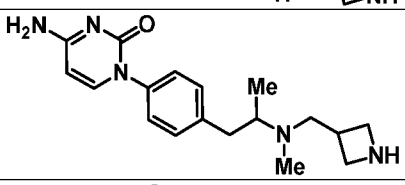
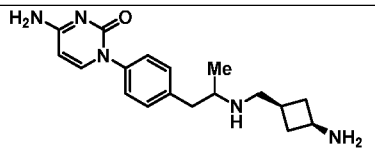
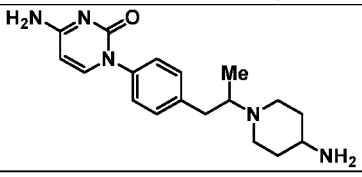
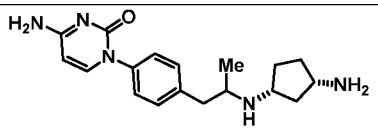
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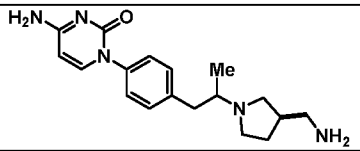
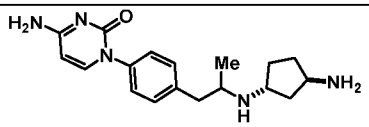
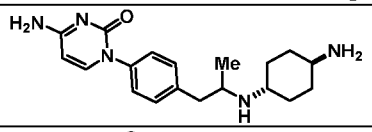
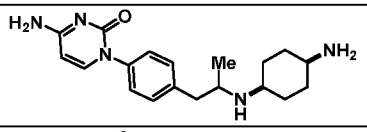
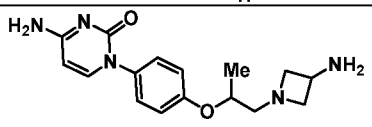
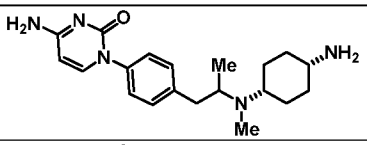
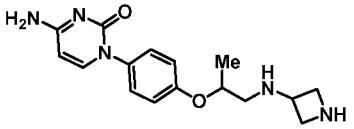
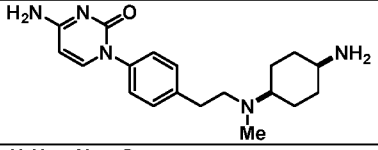
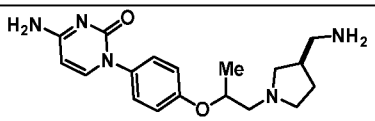
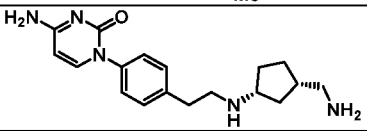
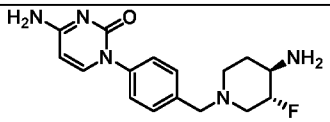
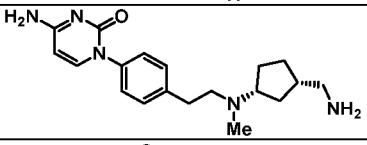
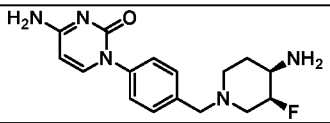
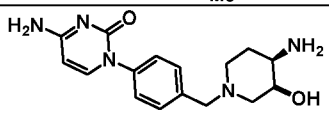
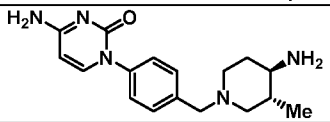
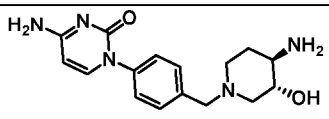
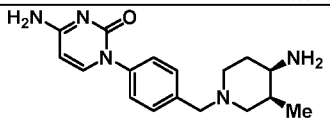
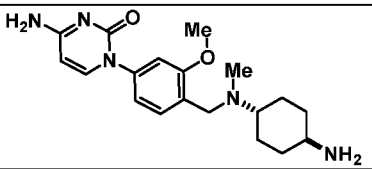
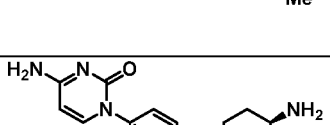
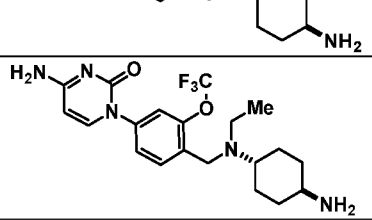
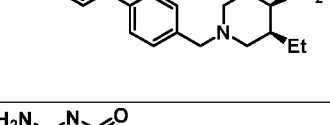
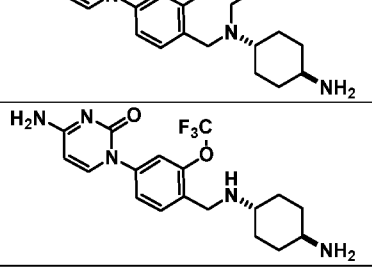
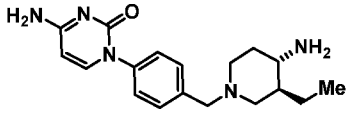
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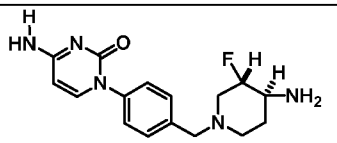
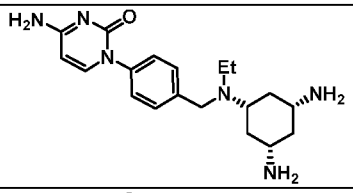
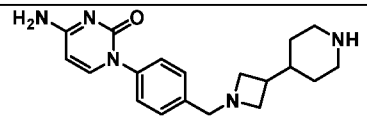
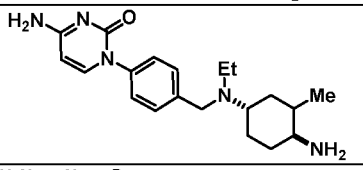
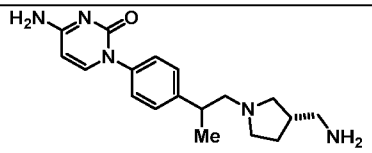
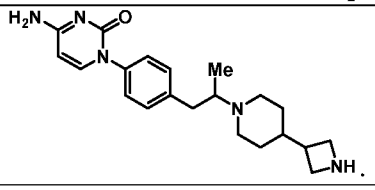
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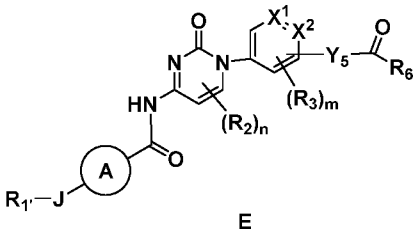
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[00206] In another aspect, the disclosure provides a compound of formula E:



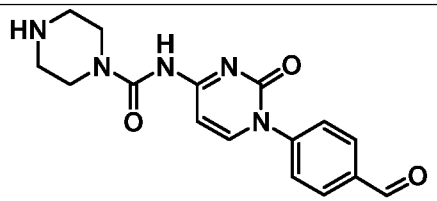
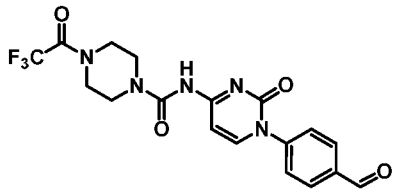
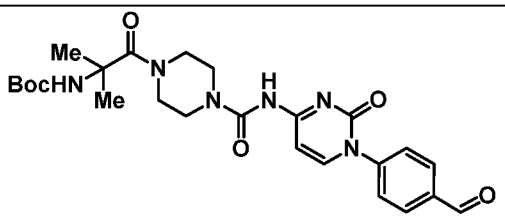
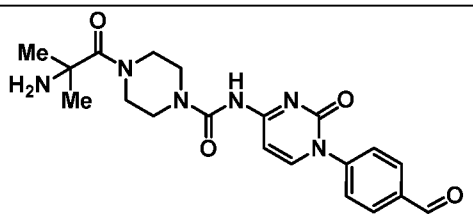
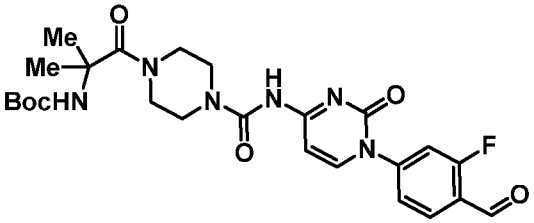
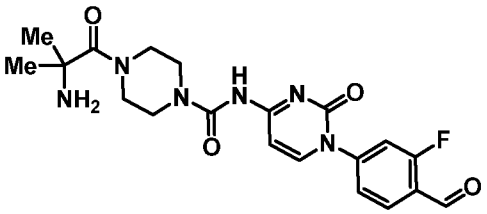
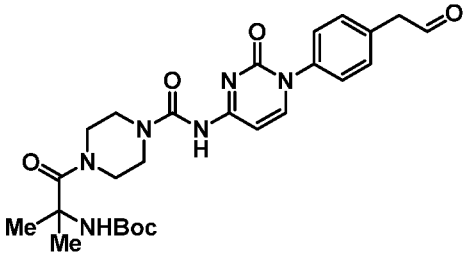
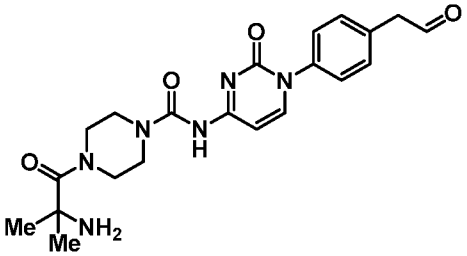
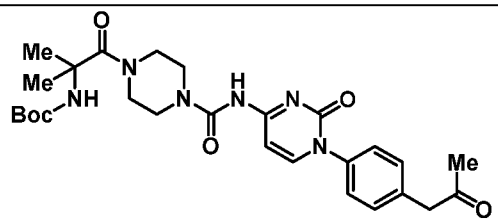
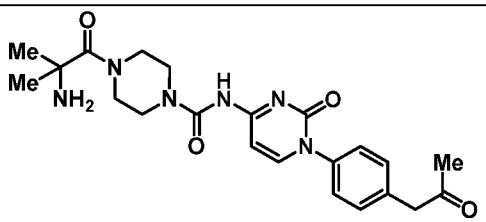
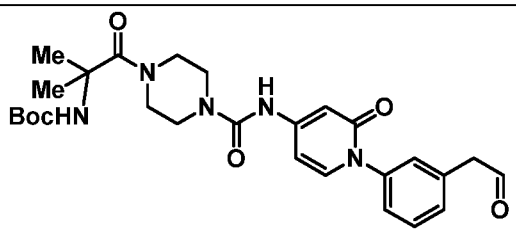
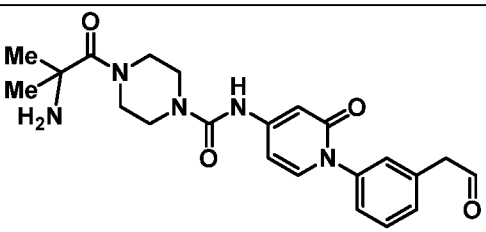
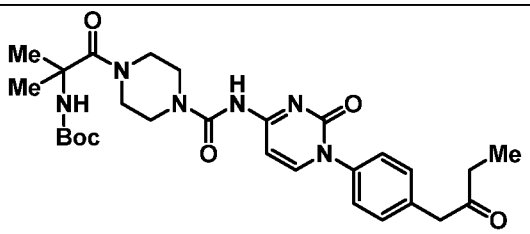
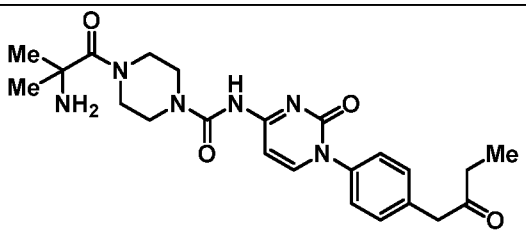
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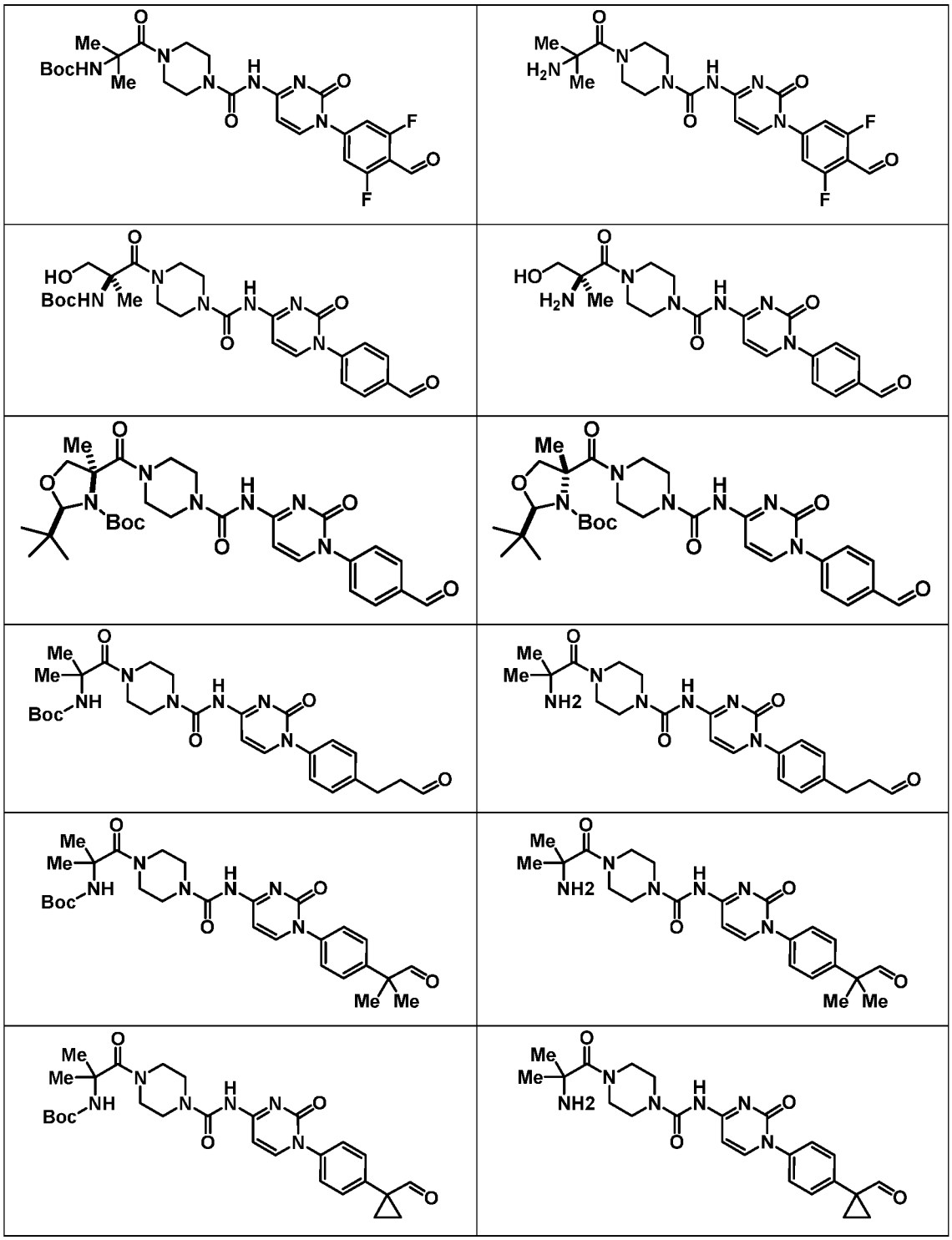
or a pharmaceutically acceptable salt thereof wherein ring A, ring B, J, X^1, X^2, $R_{1'}$, R_2, R_3, R_6, m, and n have the same definitions in the preceding paragraphs; Y_5 is a bond or is a linear C_1-C_7 alkylene, C_2-C_7 alkenylene, or C_2-C_7 alkynylene, any of which are optionally substituted with OH, NH_2, CN, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $COO(C_1$-C_6 alkyl), COOH, $CONH_2$, or C_1-C_6 alkoxy, wherein up to two carbon atoms of the C_2-C_7 alkylene, C_2-C_7 alkenylene, or C_2-C_7 alkynylene may be independently replaced by O, (C=O), or  wherein t' is 1, 2, 3, or 4; and R_6 is H or C_1-C_6 alkyl.

[00207] In another embodiment of the compound of formula E or a pharmaceutically acceptable salt, Y_5 is a bond or is a linear C_1-C_3 alkylene optionally substituted with OH, NH_2, halo, C_1-C_6 alkyl, or C_1-C_6 alkoxy.

[00208] In an embodiment, the compound of formula E or pharmaceutically acceptable salt thereof is selected from the compounds as depicted in Table 14 below.

Table 14 Compound of formula E



Pharmaceutical Compositions and Administration

[00209] 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.

[00210] 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).

[00211] 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.

[00212] 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.

[00213] 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.

[00214] 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.

[00215] 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.

[00216] 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.

[00217] 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.

[00218] 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.

[00219] Exemplary preservatives include antioxidants, chelating agents, antimicrobial preservatives, antifungal preservatives, alcohol preservatives, acidic preservatives, and other preservatives.

[00220] 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.

[00221] 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.

[00222] 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.

[00223] Exemplary alcohol preservatives include ethanol, polyethylene glycol, phenol, phenolic compounds, bisphenol, chlorobutanol, hydroxybenzoate, and phenylethyl alcohol.

[00224] 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.

[00225] Other preservatives include tocopherol, tocopherol acetate, deteroxime mesylate, cetrimide, butylated hydroxyanisol (BHA), butylated hydroxytoluened (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.

[00226] Exemplary buffering agents include citrate buffer solutions, acetate buffer solutions, phosphate buffer solutions, ammonium chloride, calcium carbonate, calcium chloride, calcium citrate, calcium glubionate, 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.

[00227] Exemplary lubricating agents include magnesium stearate, calcium stearate, stearic acid, silica, talc, malt, glyceryl behanate, hydrogenated vegetable oils, polyethylene glycol, sodium benzoate, sodium acetate, sodium chloride, leucine, magnesium lauryl sulfate, sodium lauryl sulfate, and mixtures thereof.

[00228] 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.

[00229] 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.

[00230] 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.

[00231] 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.

[00232] 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.

[00233] 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.

[00234] 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.

[00235] 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.

[00236] 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 a 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.

[00237] 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.

[00238] 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.

[00239] 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.

[00240] 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).

[00241] 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.

[00242] 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.

[00243] 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.

[00244] 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.

[00245] 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.

[00246] 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).

[00247] 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).

[00248] 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.

[00249] 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.

[00250] 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.

[00251] 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.

[00252] 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. In 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.

[00253] 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.

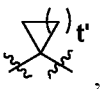
Uses and Methods of Treatment

[00254] 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 pharmaceutically acceptable salt thereof or a composition comprising a compound of formula I or a pharmaceutically acceptable salt thereof. In certain embodiments, the effective amount is a therapeutically effective amount. In certain other embodiments, the effective amount is a prophylactically effective amount.

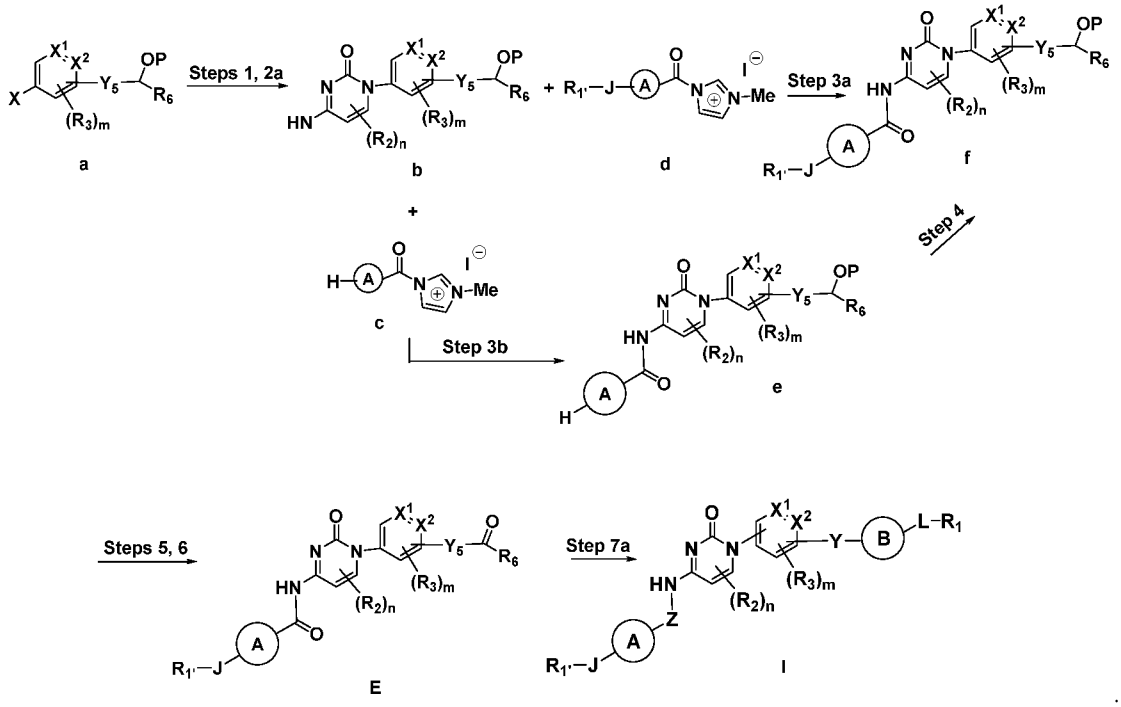
[00255] In some embodiments, the compounds of the invention can be active against a wide range of both Gram-positive and Gram-negative organisms. In these and other embodiments, the compounds of the invention can be used to treat infections and to inhibit microbial growth. Thus, the compounds of the 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.

[00256] 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).

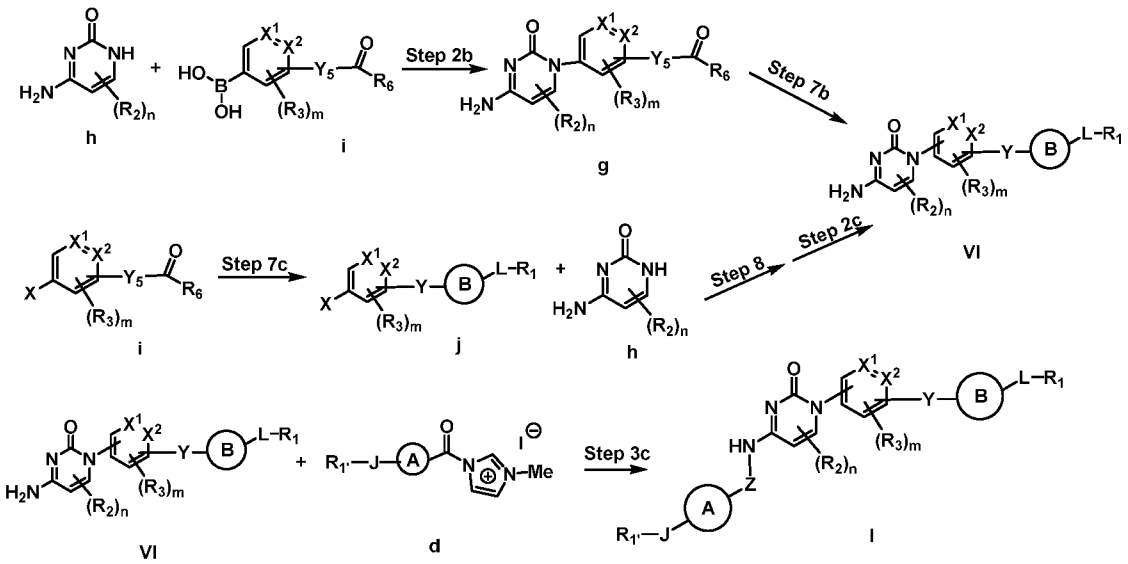
Processes

[00257] In some aspects, the compounds and intermediates of the present disclosure can be prepared according to General Synthetic Schemes G-1 and G-2 below. In the general schemes, variables such as ring A, ring B, J, L, X^1, X^2, Y, R_1, $R_{1'}$, R_2, R_3, R_6, m, and n have the same definitions in the preceding paragraphs; Y_5 is a bond or is a linear C_1-C_7 alkylene, C_2-C_7 alkenylene, or C_2-C_7 alkynylene, any of which are optionally substituted with OH, NH_2, CN, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, COO(C_1-C_6 alkyl), COOH, $CONH_2$, or C_1-C_6 alkoxy, and wherein up to two carbon atoms of the C_2-C_8 alkylene, C_2-C_8 alkenylene, or C_2-C_8 alkynylene may be independently replaced by O, (C=O), or , wherein t' is 1, 2, 3, or 4; R_6 is H or C_1-C_6 alkyl; X is halo; and P is a hydroxyl protecting group.

General Synthetic Scheme G-1



General Synthetic Scheme G-2



[00258] In step 1 of General Synthetic Scheme G-1, the protected alcohol (a) is reacted with a borate such as triisopropyl borate in the presence of a base such as butyl lithium to afford a boronate.

[00259] In steps 2a, 2b, and 2c of General Synthetic Schemes G-1 and G-2, the boronate or boric acid is cross-coupled with cytosine in the presence of a base such as a tertiary amine

and a copper reagent such as a copper (II) reagent to afford the compound of formula (b), (g), or (VI).

[00260] In steps 3a, 3b, and 3c of General Synthetic Schemes G-1 and G-2, the compound of formula (b) or (VI) and the iodide (c) or (d) undergo an amide coupling to yield the intermediate (e) or (f), or the compound of formula I. In a typical procedure, 1.1 to 2.0 molar equivalents of the compound of formula (b) or (VI) are combined with 1 molar equivalent of the iodide (c) or (d) in a suitable solvent, such as a polar aprotic solvent. Polar aprotic solvents include solvents such as dichloromethane, dimethylformamide, acetonitrile, and the like. The mixture in the polar aprotic solvent are then allowed to undergo reaction at a temperature of from about 0 °C to 100 °C for a sufficient time. Typically, the temperature is from about 25 °C to 95 °C or from about 50 °C to 95 °C and the reaction time is from about 1 to 24 hours and more typically 2 to 20 hours or from about 5 to 18 hours.

[00261] In step 4 of General Synthetic Scheme G-1, the compound of formula (e) may conduct a further coupling to afford the compound of formula (f).

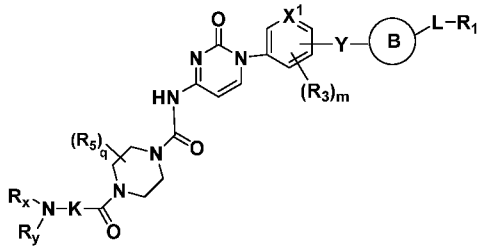
[00262] In steps 5 and 6 of General Synthetic Scheme G-1, the compound of formula (f) is deprotected to yield a free alcohol and then oxidized to a ketone, a compound of formula E.

[00263] In steps 7a, 7b and 7c of General Synthetic Scheme G-1 and G-2, the compound of formula E (or i, or g) is reacted with an amine under a reductive amination condition to afford the compound of formula I (or j, or VI). The reductive amination can be performed in the presence of a reducing agent and a suitable solvent. A suitable solvent includes protic solvents or aprotic solvents. Protic solvents include but is not limited to water and alcohols such as methanol, ethanol, propanol, and the like. Aprotic solvents include but is not limited to solvents such as dichloromethane, dimethylformamide, acetonitrile, and the like. The suitable solvent may also be a combination of two or three solvents. The reducing agent includes but is not limited to a borohydride reagent or a metal hydride reagent. Non-limiting examples are lithium borohydride, sodium borohydride, sodium cyanoborohydride and Sodium triacetoxyborohydride.

[00264] In step 8 of General Synthetic Scheme G-2, the compound of formula (j) is reacted with a boron agent such as bis(pinacolato)diboron (B_2pin_2) to form a pinacol boronic ester of compound (j) in the presence of a phosphine ligand such as [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium ($Pd(dppf)Cl_2$), a base, and a suitable solvent. The base includes but is not limited to sodium bicarbonate, sodium carbonate, potassium carbonate, sodium acetate, potassium acetate, and cesium carbonate. The suitable solvent can be an aprotic solvent such as dioxane, dichloromethane, dimethylformamide,

acetonitrile, and the like. In a typical procedure, 1.0 molar equivalents of a compound of formula (j) are combined with 1 to 2.0 molar equivalent of the boron agent together with the base, the phosphine ligand in a suitable solvent such as dioxane. The mixture is then allowed to undergo reaction at a temperature of from about 0 °C to 150 °C for a sufficient time. Typically, the temperature is from about 25 °C to 130 °C or from about 50 °C to 125 °C and the reaction time is from about 1 to 24 hours and more typically 2 to 24 hours or from about 10 to 24 hours.

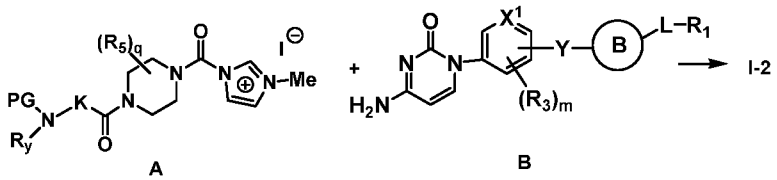
[00265] In one aspect, the disclosure provides a process for preparing a compound of formula I-2:



I-2

or a pharmaceutically acceptable salt thereof, the process comprising:

coupling a compound of formula A with a compound of formula B to provide a compound of formula I-2:



A B

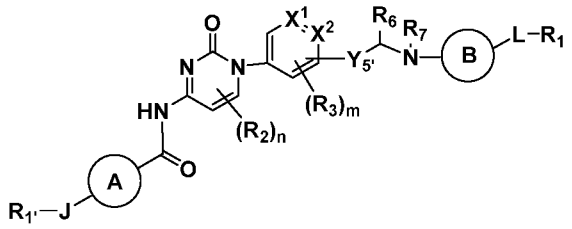
wherein ring B, K, L, Y, R_1, R_x, R_y, R_5, X^1, m, and q are as defined herein, and wherein PG is an amino protecting group.

[00266] Processes and conditions for performing the amide coupling of a compound of formula A to a compound of formula B are as in the general synthetic schemes Steps 3a, 3b, and 3c.

[00267] In one embodiment, the process further comprises the step of removing the amino protecting group PG.

[00268] In another embodiment, the compound of formula B is selected from the compounds as depicted in Table 13.

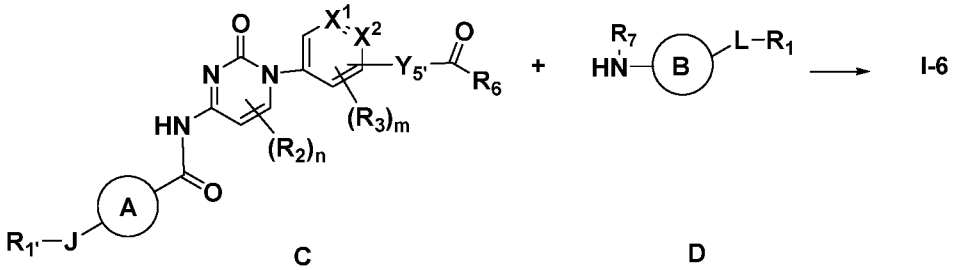
[00269] In another aspect, the disclosure provides a process for preparing a compound of formula I-6:



I-6

or a pharmaceutically acceptable salt thereof, the process comprising:

combining a compound of formula C with a compound of formula D under a reductive amination condition to provide a compound of formula I-6:



C D

wherein ring A, ring B, J, L, R_1, $R_{1'}$, R_2, R_3, X^1, X^2, m, and n are as defined herein;

$Y_{5'}$ is a bond or is a linear C_1-C_6 alkylene, C_2-C_6 alkenylene, or C_2-C_6 alkynylene, any of which are optionally substituted with OH, NH_2, CN, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, COO(C_1-C_6 alkyl), COOH, $CONH_2$, or C_1-C_6 alkoxy, and wherein up to two carbon atoms of the C_2-C_8 alkylene, C_2-C_8 alkenylene, or C_2-C_8 alkynylene may be independently replaced by O, (C=O), or  wherein t' is 1, 2, 3, or 4;

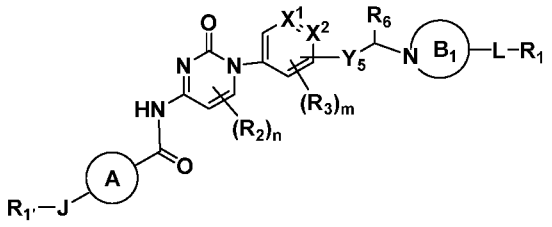
R_6 is H or C_1-C_6 alkyl; and

R_7 is H, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, or C_1-C_6 alkylene-C_3-C_8 cycloalkyl.

[00270] In another embodiment, $Y_{5'}$ is a bond or is a linear C_1-C_4 alkylene optionally substituted optionally substituted with OH, NH_2, halo, C_1-C_6 alkyl, or C_1-C_6 alkoxy.

[00271] In another embodiment, the compound of formula C is selected from the compounds as depicted in Table 14.

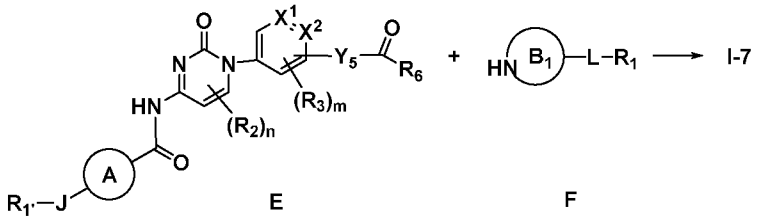
[00272] In another aspect, the disclosure provides processes for preparing a compound of formula I-7:



I-7

or a pharmaceutically acceptable salt thereof, the process comprising:

combining a compound of formula E with a compound of formula F under a reductive amination condition to provide a compound of formula I-7



wherein ring A, J, L, R_1, $R_{1'}$, R_2, R_3, X^1, X^2, m, and n are as defined herein;

ring B_1 is a nitrogen containing bicyclic heterocycloalkylene optionally substituted with up to three substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CN, C_1-C_6 haloalkyl, OH, COO(C_1-C_6 alkyl), $CONH_2$, and C_1-C_6 hydroxyalkyl;

Y_5 is a bond or is a linear C_1-C_7 alkylene, C_2-C_7 alkenylene, or C_2-C_7 alkynylene, any of which are optionally substituted with OH, NH_2, CN, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, COO(C_1-C_6 alkyl), COOH, $CONH_2$, or C_1-C_6 alkoxy, and wherein up to two carbon atoms of the C_2-C_8 alkylene, C_2-C_8 alkenylene, or C_2-C_8 alkynylene may be independently replaced by O, (C=O), or  wherein t' is 1, 2, 3, or 4; and

R_6 is H or C_1-C_6 alkyl.

[00273] In another embodiment, Y_5 is a bond or is a linear C_1-C_7 alkylene optionally substituted with OH, NH_2, halo, C_1-C_6 alkyl, or C_1-C_6 alkoxy.

[00274] The reductive amination between a compound of formula C and a compound of formula D or between a compound of formula E and a compound of formula F are as in general synthetic schemes Steps 7a and 7b. In a typical procedure, 1.1 to 2.0 molar equivalents of the compound of formula D (or F) are combined with 1 molar equivalent of a compound of formula C (or E) and 1.0 to 2.0 molar equivalents of the reducing agent in a suitable solvent. The mixture are then allowed to undergo reaction at a temperature of from

about 0 °C to 100 °C for a sufficient time. Typically, the temperature is from about 10 °C to 95 °C, or from about 10 °C to 50 °C, or at room temperature, and the reaction time is from about 1 to 24 hours and more typically 2 to 20 hours or from about 5 to 18 hours. Work-up and purification as needed provides the compound of formula I-6 or I-7.

[00275] In another embodiment, the compound of formula E is selected from the compounds listed in Table 14.

Compound Preparation

[00276] The preparation of starting materials that are commercially available, described in the literature, or readily obtainable by those skilled in the art is not described. It will be appreciated by the skilled person that where it is stated that compounds were prepared analogously to earlier examples or intermediates, the reaction time, number of equivalents of reagents, and temperature, can be modified for each specific reaction and that it may be necessary or desirable to employ different work-up or purification techniques. Where reactions are carried out using microwave irradiation, the microwave oven used was either a Biotage Initiator or in CEM Discover System Model 908005. The actual power supplied varies during the reaction in order to maintain a constant temperature.

General Methods

[00277] 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 (CH_2Cl_2), *N,N'*-dimethylformamide (DMF), toluene 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 an Acros Seal™ bottle. Triethylamine (Et_3N) *N,N*-diisopropylethylamine (DIPEA were distilled from CaH_2 immediately prior to use, 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/or stained with ethanolic solutions of either $KMnO_4$, 12-phosphomolybdic acid or other commonly used stains. Flash chromatography was performed on Merck silica gel Kieselgel 60 (230-400 mesh) from EM Science with the indicated HPLC grade solvent or an automated medium pressure column chromatography system (Teledyne ISCO CombiFlash RF75 or CombiFlash Rf+). Reverse phase HPLC was conducted on a Waters HPLC Semi Prep 150B system with Sunfire C18 Prep Column or Atlantis T3 Prep Column with isocratic or gradient conditions with H_2O

(0.1% TFA) and 10%H_2O:90 CH_3CN (0.1% TFA) as eluents

[00278] 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 determined by LCMS were collected on Thermo Scientific™ UltiMate™ 3000 UHPLC with electrochemical detector with a fluorescence detector monitored at either 214 or 254 nm, or a Waters Aquity UPLC H-Class Series with photodiode array detector and QDa mass detector. ^1H NMR spectra were recorded at 500 MHz, 400 MHz, and 300 MHz, and ^{13}C at 125 MHz. Proton resonances were reported relative to the deuterated solvent peak: 7.27 ppm for $CDCl_3$, 3.31 ppm (center line signal) for CD_3OD, 2.50 for D*6*-DMSO and 4.79 for D_2O using the following format: chemical shift (δ (ppm)) [multiplicity (s= singlet, br s= broad singlet, d= doublet, t= triplet, q= quartet, m= multiplet)]. Carbon resonances were reported as chemical shifts (δ) in parts per million, relative to the center line signal of the respective solvent peak: 77.23 ppm for $CDCl_3$ and 49.15 ppm for CD_3OD. Commercially available chemicals are purchased from vendors including Sigma-Aldrich, Acros, Enamine, TCI America, Combi-Blocks, Alfa-Aesar, Angene, Ark Pharma, PharmaBlock, Strem Chemicals, Frontier Scientific, and AstaTech, Inc.

Liquid Chromatography-Mass Spectrometry Methods

[00279] Liquid Chromatography-Mass Spectrometry Method A

[00280] Total ion current (TIC) and DAD UV chromatographic traces together with MS and UV spectra associated with the peaks were taken on a UPLC/MS Acquity™ system equipped with PDA detector and coupled to a Waters single quadrupole mass spectrometer operating in alternated positive and negative electrospray ionization mode. [LC/MS-ES (+/-): analyses performed using an Acquity UPLC™ CSH, C18 column (50 x 2.1mm, 1.7 µm particle size), column temperature 40 °C, mobile phase: A-water + 0.1% HCOOH/ B- CH_3CN + 0.1% HCOOH, flow rate: 1.0 mL/min, runtime=2.0 min, gradient: t=0 min 3%B, t=1.5 min 99.9% B, t=1.9 min 99.9% B, t=2.0 min 3% B, stop time 2.0 min. Positive ES 100-1000, Negative ES 100-1000, UV detection DAD 210-350 nm.

[00281] Liquid Chromatography-Mass Spectrometry Method B

[00282] Total ion current (TIC) and DAD UV chromatographic traces together with MS and UV spectra associated with the peaks were taken on a UPLC/MS Acquity™ system equipped with PDA detector and coupled to a Waters single quadrupole mass spectrometer operating in alternated positive and negative electrospray ionization mode. [LC/MS-ES (+/-): analyses

performed using an Acquity UPLC™ BEH, C18 column (50 x 2.1mm, 1.7 µm particle size), column temperature 40 °C, mobile phase: A- 0.1% v/v aqueous (aq) ammonia solution pH 10/ B- CH_3CN, flow rate: 1.0 mL/min, runtime=2.0 min, gradient: t=0 min 3%B, t=1.5 min 99.9% B, t =1.9 min 99.9% B, t=2.0 min 3% B, stop time 2.0 min. Positive ES 100-1000, Negative ES 100-1000, UV detection DAD 210-350 nm.

[00283] Liquid Chromatography-Mass Spectrometry Method C

LC/MS-ES (+/-): analyses performed using an AQUITY with PDA detector and QDA Performance, C18 column (50 x 2.1mm, 1.6 µm particle size), column temperature 35 °C, mobile phase: A- 0.1 % Formic acid in Milli Q water (pH= 2.70)/ B- 0.1%Formic acid in water : Acetonitrile (10:90), flow rate: 0.8-1.0 mL/min, runtime=4.0 min, gradient: t=0 min 3%B, t= 2.7 min 98% B, t=3.0 min 100% B, t=3.51 min 3% B, stop time 4.0 min.

[00284] Liquid Chromatography-Mass Spectrometry Method D

[00285] LC/MS-ES (+/-): analyses performed using AQUITY H-Class with PDA detector and QDA, C18 column (50 x 2.1mm, 1.6 µm particle size), column temperature 35 °C, mobile phase: A- 0.1 % Formic acid in Milli Q water (pH= 2.70)/ B- 0.1%Formic acid in water : Acetonitrile (10:90), flow rate: 0.8-1.0 mL/min, runtime = 4.0 min, gradient: t=0 min 3%B, t=2.7 min 98% B, t=3.0 min 100% B, t=3.51 min 3% B, stop time 4.0 min.

[00286] Liquid Chromatography-Mass Spectrometry Method E

[00287] LC/MS-ES (+/-): analyses performed using AQUITY H-Class with PDA detector and QDA, C18 column (50 x 2.1mm, 1.6 µm particle size), column temperature 35 °C, mobile phase: A 0.1 % Formic acid in water (pH= 2.70)/ B 0.1%Formic acid in water : Acetonitrile (10:90), runtime=9.0 min, gradient: t=0 min 1%B, t=2.5 min 50% B, t=4.5 min 97.5% B, t=6.5 min 1% B, stop time 9.0 min.

[00288] Liquid Chromatography-Mass Spectrometry Method F

[00289] LC/MS-ES (+/-): analyses performed using Agilent Infinity II G6125C LCMS, C18 column (50 x 4.6mm, 3.5 µm particle size), column temperature 35 °C, mobile phase: A 5mM Ammonium Bicarbonate in Milli-Qwater (pH = 7.35)/ B- Methanol, runtime =7.0 min, gradient: t=0 min 8%B, t= 3.0 min 70% B, t=3.7 min 95% B, t=4.2 min 100% B, t=5.21 min 8% B, stop time 7.0 min.

[00290] Liquid Chromatography-Mass Spectrometry Method G

[00291] LC/MS-ES (+/-): analyses performed using Waters Alliance 2690 and 996 PDA detector with Micromass ZQ, C18 column (150 x 4.6mm, 3.5 µm particle size), column temperature 35 °C, mobile phase: A- 5mM Ammonium Acetate + 0.1% FA in Water / B- Methanol, runtime = 17.0 min, gradient: t=0 min 10%B, t=7.0 min 90% B, t=9.0 min 100%

B, t=14.01 min 10% B, stop time 17.0 min.

[00292] Liquid Chromatography-Mass Spectrometry Method H

[00293] LC/MS-ES (+/-): analyses performed using AQUITY with PDA detector and QDA Performance, C18 column (50 x 2.1mm, 1.6 µm particle size), column temperature 35 °C, mobile phase: A- 0.1 % Formic acid inMilli Q water (pH= 2.70)/ B- 0.1%Formic acid in water : Acetonitrile (10:90), flow rate: 0.9 mL/min, runtime = 3.0 min, gradient: t=0 min 5%B, t=1.8 min 98% B, t=2.0 min 100% B, t=2.51 min 5% B, stop time 17.0 min.

Analytical Methods

[00294] ^{1}H Nuclear magnetic resonance (NMR) spectroscopy was carried out using one of the following instruments: a Bruker Avance 400 instrument equipped with probe DUAL 400 MHz S1, a Bruker Avance 400 instrument equipped with probe 6 S1 400 MHz 5mm ^{1}H-^{13}C ID, a Bruker Avance III 400 instrument with nanobay equipped with probe Broadband BBFO 5 mm direct, a 400 MHz Agilent Direct Drive instrument with ID AUTO-X PFG probe, all operating at 400 MHz, or an Agilent VNMRS500 Direct Drive instrument equipped with a 5 mm Triple Resonance $^{1}H\{^{13}C/^{15}N\}$ cryoprobe operating at 500 MHz . The spectra were acquired in the stated solvent at around room temperature unless otherwise stated. In all cases, NMR data were consistent with the proposed structures. Characteristic chemical shifts (δ (ppm)) are given in parts-per-million using conventional abbreviations for designation of major peaks: e.g. s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dt, doublet of triplets; br, broad.

[00295] Thin layer chromatography (TLC) refers to silica gel TLC using silica gel F254 (Merck) plates. Column chromatography was performed using an automatic column chromatography (Biotage SP1 or Isolera) system over Biotage silica gel cartridges (KP-Sil or KP-NH) or in the case of reverse phase chromatography over Biotage C18 cartridges (KP-C18).

[00296] Prep HPLC were performed on Shimadzu LC-20AP, Waters 2545 and Agilent 1260 infinity. Purity was determined on Waters Alliance e2695- PDA detector 2998 and Agilent 1260 Infinity-II. (Mobile phase: 0.05% HCl in Water/Methanol in gradient elution method).

Table 15 Abbreviations and Names of Reagents

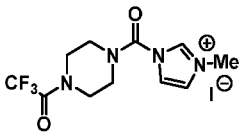
Abbreviations/Acronyms	Full Name/Description
AcOH	Acetic acid
aq.	Aqueous
CH_3CN	Acetonitrile
B_2pin_2	Bis(pinacolato)diboron
Boc_2O	Di-tert-butyl dicarbonate

Abbreviations/Acronyms	Full Name/Description
$BH_3 \cdot SMe_2$	Borane dimethyl sulfide complex
i-BuMgBr	Isobutyl magnesium bromide
n-BuLi	*n*-Butyllithium
$B(O\text{-}iPr)_3$.	Triisopropyl borate
CBzCl	Benzyl chloroformate
CDI	1,1'-Carbonyldiimidazole
DAST	Diethylaminosulfur trifluoride
DCE	1,2-Dichloethane
DCM	Dichloromethane
DIAD	Diisopropyl azodicarboxylate
DIPEA	*N,N*-Diisopropylethylamine
DMAP	*N,N*-dimethylaminopyridine
DMF	*N,N'*-dimethylformamide
DMP	Dess–Martin periodinane
DMSO	Dimethylsulfoxide
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
DPPA	Diphenylphosphoryl azide
Et_2O	Diethyl ether
Et_3N	Triethylamine
EtOAc	Ethyl acetate
EtOH	Ethanol
EtMgBr	Ethylmagnesium bromide
HATU	Hexafluorophosphate azabenzotriazole tetramethyl uronium
HPLC	High performance liquid chromatography
KHMDS	Potassium bis(trimethylsilyl)amide
LCMS	Liquid chromatography mass spectrometry
LDA	Lithium diisopropylamide
$Li(ALH)_4$	Lithium aluminum hydride
$LiAlH(Ot\text{-}Bu)_3$	Lithium tri-tert-butoxyaluminum hydride
LHMDS	Lithium bis(trimethylsilyl)amide
MeOH	Methanol
MeI	Methyl Iodide
min.	minutes
NMR	Nuclear magnetic resonance
rt	Room temperature
$NaBH_4$	Sodium borohydride
$NaBH(Oac)_3$	Sodium triacetoxyborohydride
NaOAc	Sodium acetate
$NaBH_3CN$	Sodium cyanoborohydride
PCC	Pyridinium chlorochromate
$Pd(dba)_2$	Bis(dibenzylideneacetone)palladium
$Pd(dppf)Cl_2$	[1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium
PPh_3	Triphenylphosphine
i-PrBr	2-Bromopropane
Sat.	Saturated

Abbreviations/Acronyms	Full Name/Description
TBAF	Tetrabutlyammonium fluoride
TBSCl/TBDMSCl	*t*-butyldimethylsilyl chloride
Ti(O-*i*Pr)$_4$	Titanium isopropoxide
TEA	Triethylamine
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TMEDA	*N,N,N',N'*-Tetramethylethylenediamine
TMSCN	Trimethylsilyl cyanide
TsOH	p-Toluenesulfonic acid

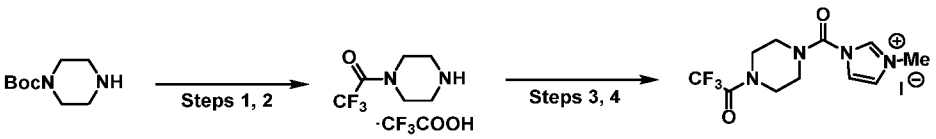
Intermediate Synthesis

Intermediate 1



3-Methyl-1-(4-(2,2,2-trifluoroacetylpiperazine-1-carbonyl)-1*H*-imidazol-3-ium iodide

Scheme I-1



Reagents: 1) TFAA, CH_2Cl_2, 0° C to rt, 16h 2) TFA, CH_2Cl_2, rt, 1.5h 3) CDI, CH_2Cl_2, 16h 4) MeI, CH_3CN, rt, 16h.

[00297] Step 1: *tert*-butyl 4-(2,2,2-trifluoroacetyl)piperazine-1-carboxylate. A solution of *tert*-butyl piperazine-1-carboxylate (20 g, 107 mmol) in dry CH_2Cl_2 (100 mL) was cooled to 0° C under a nitrogen atmosphere. Trifluoroacetic anhydride (15.0 ml, 107 mmol) was added dropwise over 10min. The reaction was allowed to warm to rt and stirred for 16h. The reaction mixture was diluted with CH_2Cl_2 (1 L), and quenched with saturated $NaHCO_3$ solution (1 L). The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the title compound (29.1 g, 96%) as a pale orange solid.

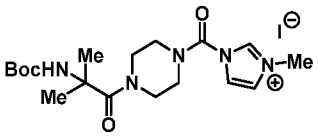
[00298] Step 2: 2,2,2-trifluoro-1-(piperazin-1-yl)ethan-1-one triflouroacetate salt. To a solution of trifluoroacetic acid in CH_2Cl_2 (50 mL, 1:1) was added *tert*-butyl 4-(2,2,2-trifluoroacetyl) piperazine-1-carboxylate (29.1 g, 103 mmol). The reaction was left to stir at rt for 1.5 h. The solvent and trifluoroacetic acid were removed under reduced pressure. The crude reaction mixture was triturated with diethyl ether to yield a solid precipitate. The solid

was filtered and washed with diethyl ether to yield the title compound (29.5 g, 97%) as a white solid.

[00299] Step 3: 1-(4-(1H-imidazole-1-carbonyl)piperazin-1-yl)-2,2,2-trifluoroethan-1-one. To a round bottom flask containing 2,2,2-trifluoro-1-(piperazin-1-yl)ethan-1-one trifluoroacetate salt (26.0 g, 88 mmol) was added 1,1'-carbonyldiimidazole (17.1 g, 105 mmol) and dry CH_2Cl_2 (100 mL) to yield a suspension. This suspension was stirred at rt for 16 h. The solvent was subsequently removed under reduced pressure and the crude reaction mixture was purified by flash chromatography to afford the title compound (18 g, 76%) as a white solid.

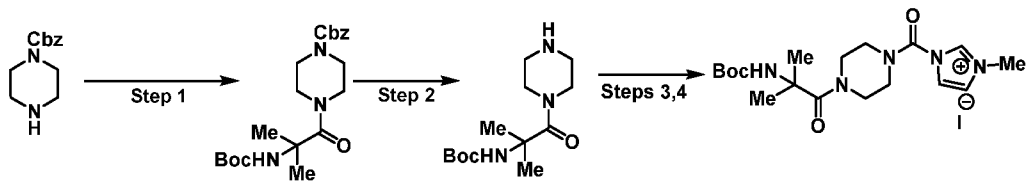
[00300] 3-methyl-1-(4-(2,2,2-trifluoroacetylpiperazine-1-carbonyl)-1*H*-imidazol-3-ium iodide. To a round bottom flask containing a solution of 1-(4-(1H-imidazole-1-carbonyl)piperazin-1-yl)-2,2,2-trifluoroethan-1-one (10.8 g, 39.1 mmol) in dry MeCN (80 mL) was added iodomethane (15.0 mL, 235 mmol). The reaction stirred for 24 h at rt. The solvent and excess iodomethane were removed under reduced pressure to yield the title compound (27.6 g, 98%) as a light yellow solid.

Intermediate 2



1-(4-(2-((*tert*-Butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carbonyl)-3-methyl-1H-imidazol-3-ium iodide

Scheme I-2



Reagents: 1) Boc-AIB, HATU, DIPEA, DMF, rt, 16h 2)10% Pd/C, MeOH, rt, 16h 3) CDI, DCM, rt, 16h 4) MeI, CH_3CN, rt, 16h.

[00301] Step 1: benzyl 4-(2-((*tert*-butoxycarbonyl) amino)-2-methylpropanoyl) piperazine-1-carboxylate. To a stirred solution of 2-((*tert*-butoxycarbonyl) amino)-2-methylpropanoic acid (35.5 g, 174.8 mmol) in DMF (350 mL) were added DIPEA (51.24 g, 397.2 mmol) and HATU (90.62 g, 238.3 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 45 min. Benzyl piperazine-1-carboxylate (35 g, 158.9 mmol) was added into the reaction mixture at 0 °C and stirred at rt for 16h. The resulting reaction mixture was poured

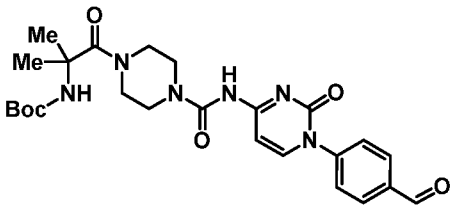
into H_2O (1.5L) and extracted with EtOAc (3x700 mL) and the combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude material was purified by flash chromatography (20-30% EtOAc:Hex) to afford the title compound (36.0 g, 55%) as an off-white solid LCMS [M+H] 406.

[00302] Step 2: *tert*-butyl (2-methyl-1-oxo-1(piperazn-1-yl) propan-2-yl)carbamate. To a stirred solution of benzyl 4-(2-((*tert*-butoxycarbonyl) amino)-2-methylpropanoyl) piperazine-1-carboxylate (35.0 g, 86.4 mmol) in MeOH (500 mL) was added 10% Pd/C (3.5 g). The reaction mixture was stirred under a hydrogen atmosphere at rt for 16h. The resulting reaction mixture was filtered through Celite® and washed with MeOH (1500 mL). The resulting filtrate was concentrated under reduced pressure and dried to afford the title compound (25.0 g, Quant.) as a viscous oil. LCMS [M+H] 272.

[00303] Step 3: *tert*-butyl (1-(4-1*H*-imidazole-1-carbonyl) piperazin-1-yl)-2-methyl-1-oxopropan-2-yl) carbamate. To a stirred solution of *tert*-butyl (2-methyl-1-oxo-1(piperazn-1-yl) propan-2-yl) carbamate (25.0 g, 92.2 mmol) in CH_2Cl_2 (300 mL) was added CDI (17.78 g, 109.7 mmol) at rt. The reaction mixture was stirred at rt for 16h. The reaction mixture was concentrated under reduced pressure. The resulting crude material was purified by column chromatography (4-5% MeOH in CH_2Cl_2) to afford the title compound (30.0 g, 89%) as an off-white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.04 (s, 1H), 7.48 (s, 1H), 7.36 (s, 1H), 7.03 (s, 1H), 3.65-3.52 (m, 4H), 3.51-3.40 (m, 4H), 1.38 (s, 6H), 1.30 (s, 9H). LCMS [M+H] 366.3.

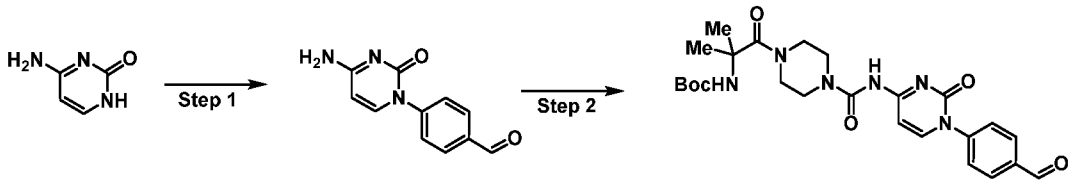
[00304] Step 4: 1-(4-(2-((*tert*-butoxycarbonyl) amino)-2-methylpropanoyl) piperazine-1-carbonyl)-3-methyl-1H-imidazol-3-ium iodide. To a stirred solution of *t*-butyl (1-(4-1*H*-imidazole-1-carbonyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate (20.0 g, 54.8 mmol) in CH_3CN (250 mL) was added MeI (46.66 g, 20.8 mL, 328.7 mmol) at 0 °C. The reaction mixture was stirred at rt for 16h. The reaction mixture was concentrated under reduced pressure to afford the title compound (30.0 g, quantitative) as a pale yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.57 9s, 1H), 8.05 (s, 1H), 7.87 (t, 1H), 7.40 (s, 1H), 3.93 (s, 3H), 3.78-3.65 (m, 4H), 3.59-3.45 (m, 4H), 1.40 (s, 6H), 1.32 (S, 9H). LCMS [M+H] 380.2 (-iodide).

Intermediate 3



***tert*-Butyl N-[1-(4-{[1-(4-formyl-phenyl)-2-oxo- 1,2-dihydropyrimidin-4-yl]carbamoyl}piperazin-1-yl)-2-methyl-1-oxopropan-2-yl]carbamate**

Scheme I-3

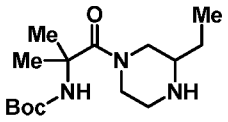


Reagents: 1) 4-formylphenylboronic acid, TMEDA, $Cu(OAc)_2 \cdot H_2O$, 2) 1-(4-(2-((*tert*-butoxycarbonyl) amino)-2-methylpropanoyl)piperazine-1-carbonyl)-3-methyl-1H-imidazol-3-ium iodide, CH_3CN, 78°C, 22h.

[00305] Step 1: 4-(4-amino-2-oxopyrimidin-1(2*H*)-yl)benzaldehyde. Copper (II) acetate monohydrate (18.0 g, 90.2 mmol) and TMEDA (16.2 mL, 108 mmol) were added to a mixture of cytosine (10.0 g, 90.1 mmol) and (4-formylphenyl)boronic acid (13.5 g, 90.2 mmol) in MeOH (400 mL) and H_2O (100 mL), and the mixture was stirred at rt open to the air for 6 days. It was concentrated to remove the MeOH, ice and water were added (ca. 1 L total), and the precipitate was collected by vacuum filtration to afford the title compound (8.84 g, 41.1 mmol) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.04 (s, 1H), 7.98 (d, 2H), 7.71 (d, 1H), 7.61 (d, 2H), 7.46 – 7.27 (m, 2H), 5.85 (d, 1H).

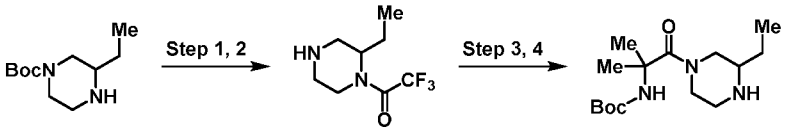
[00306] *tert*-butyl N-[1-(4-{[1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl]carbamoyl}piperazin-1-yl)-2-methyl-1-oxopropan-2-yl]carbamate. A mixture of 4-(4-amino-2-oxopyrimidin-1(2*H*)-yl)benzaldehyde (1.0 g, 4.67 mmol) and 1-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carbonyl)-3-methyl-1H-imidazol-3-ium iodide (3.57 g, 5.62 mmol) in CH_3CN (35 mL) was stirred at reflux for 22h. The reaction mixturewas cooled, diluted with EtOAc (250 mL), washed with sat. aq. $NaHCO_3$ (2 x 200 mL) and brine (200 mL), dried over Na_2SO_4, decanted, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc/MeOH) to afford the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.01 (br. s., 1H), 10.07 (s, 1H), 8.01 (d, 2H), 7.58 (d, 2H), 7.31 (d, 1H), 5.90 (d, 1H), 4.95-4.72 (m, 1H), 3.95-3.57 (m, 8H), 1.52 (s, 6H), 1.44 (s, 9H). LCMS [M+H] 513.1.

Intermediate 4



***tert*-Butyl (1-(3-ethylpiperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate**

Scheme I-4



Reagents: 1) TFAA, Et_3N, CH_2Cl_2, 0 °C, 16h 2) TFA, 1.5h 3) 2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoic acid, HATU, DIPEA, CH_2Cl_2, 16h 4) LiOH, THF:H_2O, 2h.

[00307] Step 1: *tert*-butyl 3-ethyl-4-(2,2,2-trifluoroacetyl)piperazine-1-carboxylate. A solution of *tert*-butyl 3-ethylpiperazine-1-carboxylate (500 mg, 2.4 mmol) in dry CH_2Cl_2 (15 mL) and NEt_3 (0.39 mL, 2.8 mmol) was cooled to 0° C. Trifluoroacetic anhydride (0.34 mL, 2.4 mmol) was added dropwise over 10 min. The reaction was warmed to rt and stirred for 16h. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and quenched with sat. $NaHCO_3$ (75 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford the title compound.

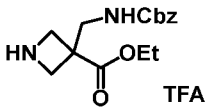
[00308] Step 2: 1-(2-ethylpiperazin-1-yl)-2,2,2-trifluoroethan-1-one triflouroacetate salt. *tert*-Butyl 3-ethyl-4-(2,2,2-trifluoroacetyl)piperazine-1-carboxylate (700 mg, 2.2 mmol) was dissolved in a 1:1 solution of trifluoroacetic acid and CH_2Cl_2 (20 mL). The reaction was stirred at rt for 1.5h. The reaction mixture was concentrated under reduced pressure. The crude reaction mixture was triturated with diethyl ether to yield a solid precipitate, which was collected by filtration and washed with diethyl ether to yield the title compound.

[00309] Step 3: *tert*-butyl (1-(3-ethyl-4-(2,2,2-trifluoroacetyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate. To a suspension of 2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoic acid (144 mg, 0.71 mmol) and HATU (270 mg, 0.71 mmol) in CH_2Cl_2, was added DIPEA (0.31 ml, 1.8 mmol). The suspension was stirred for 10 min. and 1-(2-ethylpiperazin-1-yl)-2,2,2-trifluoroethan-1-one trifluoroacetate salt (250 mg, 0.71 mmol) was added. The solution was stirred at rt for 16h. The reaction mixture was diluted with CH_2Cl_2 (75 mL) and washed with H_2O. The organic layer was concentrated under reduced pressure and purified by flash chromatography (EtOAc:Hex) to afford the title compound.

[00310] Step 4: *tert*-butyl (1-(3-ethylpiperazin-1-yl)-2-methyl-1-oxopropan-2-yl) carbamate. *tert*-Butyl (1-(3-ethyl-4-(2,2,2-trifluoroacetyl)piperazin-1-yl)-2-methyl-1-

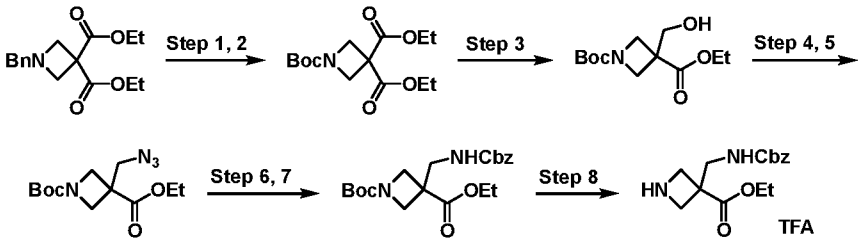
oxopropan-2-yl)carbamate (132 mg, 0.31 mmol) and $LiOH \cdot H_2O$ (139 mg, 3.1 mmol) were suspended in THF:H_2O (1:1) and stirred at rt for 2h. The solvent was removed under reduced pressure, diluted with H_2O (50mL), and extracted with $CHCl_3$ (3x50 mL). The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford the title compound.

Intermediate 5



ethyl 3-((((benzyloxy)carbonyl)amino)methyl)azetidine-3-carboxylate trifluoroacetate salt

Scheme I-5



Reagents: 1) H_2, $Pd(OH)_2/C$, 4.0 M HCl in dioxane, EtOH, rt, 6d 2) Boc_2O, sat. aq. $NaHCO_3$, dioxane, rt, 24h 3) $LiAlH(Ot\text{-}Bu)_3$, THF, 0 °C to rt, 24h 4) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 24h 5) NaN_3, DMF, 50 °C, 24h 6)H_2, Pd/C, EtOH, rt, 24h 7) CbzCl, sat. aq. $NaHCO_3$, dioxane, rt, 4d 8) TFA, CH_2Cl_2, rt, 1.5h.

[00311] Step 1: diethyl azetidine-3,3-dicarboxylate hydrochloride. A mixture of diethyl 1-benzylazetidine-3,3-dicarboxylate (prepared according to *Syn. Commun.* 2003, *33*, 3347) (830 mg, 2.85 mmol), 4.0 MHCl in dioxane (0.78 mL, 3.12 mmol), and 20 w/w% $Pd(OH)_2/C$ (173 mg) in EtOH (25 mL) was stirred under an atmosphere ofH_2 for 6 days. The reaction mixture filtered through a pad of Celite® and rinsed with MeOH. The filtrate was concentrated to afford the title compound.

[00312] Step 2: 1-(*tert*-butyl) 3,3-diethyl azetidine-1,3,3-tricarboxylate. A mixture of diethyl azetidine-3,3-dicarboxylate hydrochloride (756 mg, 2.85 mmol) and Boc_2O (0.82 mL, 4.00 mmol) in dioxane (12 mL) and sat. aq. $NaHCO_3$ was stirred at rt for 24 h. The reaction mixture was diluted with sat. aq. $NaHCO_3$ (100 mL) and extracted with EtOAc (2x75 mL). The extracts were washed with brine (75 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (Hexanes/EtOAc) to afford the title compound. ^1H NMR (500 MHz, $CDCl_3$) δ 4.22-4.31 (m, 8H), 1.44 (s, 9H), 1.28 (t, 6H).

[00313] Step 3: 1-(*tert*-butyl) 3-ethyl 3-(hydroxymethyl)azetidine-1,3-dicarboxylate. $LiAlH(Ot\text{-}Bu)_3$ in THF (1.0M, 4.4 mL) was added dropwise to a solution of 1-(*tert*-butyl) 3,3-diethyl azetidine-1,3,3-tricarboxylate (604 mg, 2.01 mmol) in dry THF (20 mL) at 0 °C under N_2. The mixture was warmed to rt and stirred for 24h. The reaction mixture was diluted with EtOAc (100 mL), washed with 1 M HCl (2x50 mL) and brine (50 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (Hexanes/EtOAc) to afford the title compound.

[00314] Step 4: 1-(*tert*-butyl) 3-ethyl 3-(((methylsulfonyl)oxy)methyl)azetidine-1,3-dicarboxylate. MsCl (0.16 mL, 2.07 mmol) was added dropwise to a solution of 1-(*tert*-butyl) 3-ethyl 3-(hydroxymethyl)azetidine-1,3-dicarboxylate (452 mg, 1.74 mmol) and Et_3N (0.34 mL, 2.44 mmol) in dry CH_2Cl_2 (12 mL) at 0 °C under N_2. The mixture was warmed to rt while stirring for 4 h. The reaction mixture was poured into 2M K_2CO_3 (50 mL) and extracted with CH_2Cl_2 (3×35 mL). The extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo to give the crude product which was carried on as-is.

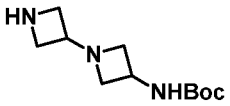
[00315] Step 5: 1-(*tert*-butyl) 3-ethyl 3-(aminomethyl)azetidine-1,3-dicarboxylate. A mixture of 1-(*tert*-butyl) 3-ethyl 3-(((methylsulfonyl)oxy)methyl)azetidine-1,3-dicarboxylate (604 mg, 1.743 mmol) and NaN_3 (351 mg, 5.40 mmol) in dry DMF (10 mL) was stirred at 50 °C under N_2 for 24 h. It was cooled, diluted with Et_2O (100 mL), washed with sat. aq. $NaHCO_3$ (75 mL) and brine (2×75 mL), dried over Na_2SO_4, filtered, and concentrated to dryness to afford the title compound.

[00316] Step 6: 1-(*tert*-butyl) 3-ethyl 3-(aminomethyl)azetidine-1,3-dicarboxylate. A mixture of 1-(*tert*-butyl) 3-ethyl 3-(azidomethyl)azetidine-1,3-dicarboxylate (453 mg, 1.593 mmol) and 10% Pd (52 mg) in EtOH (20 mL) was stirred under an atmosphere ofH_2 for 20 h. It was filtered through a pad of Celite®, rinsed with MeOH, and the filtrate was concentrated to dryness to afford the title compound.

[00317] Step 7: 1-(*tert*-butyl) 3-ethyl 3-((((benzyloxy)carbonyl)amino)methyl)azetidine-1,3-dicarboxylate. A mixture of 1-(*tert*-butyl) 3-ethyl 3-(aminomethyl)azetidine-1,3-dicarboxylate (414 mg, 1.593 mmol) and benzyl chloroformate (0.45 mL, 3.15 mmol) in dioxane (16 mL) and sat. aq. $NaHCO_3$ (16 mL) was stirred at rt under N_2 for 4 days. It was diluted with EtOAc (75 mL), washed with sat. aq. $NaHCO_3$ (2×50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (Hexanes/EtOAc) to afford the title compound. ^1H NMR (500 MHz, $CDCl_3$) δ 7.28 -7.44 (m, 5H), 5.15 -5.26 (m, 1H), 5.11 (br.s., 2H), 4.22 (q, 2H), 4.12 (d, 2H), 3.79 (m, 2H), 3.65 -3.75 (m, 2H), 1.44 (s, 9H), 1.29 (t, 3H).

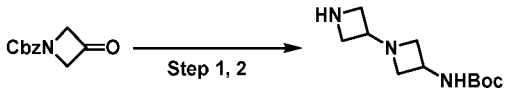
[00318] Step 8: ethyl 3-((((benzyloxy)carbonyl)amino)methyl)azetidine-3-carboxylate trifluoroacetate salt. A mixture of 1-(*tert*-butyl) 3-ethyl 3-((((benzyloxy)carbonyl)amino)methyl)azetidine-1,3-dicarboxylate (101.5 mg, 0.259 mmol) and TFA (1.0 mL) in dry CH_2Cl_2 (3 mL) was stirred at rt for 1.5 h and concentrated to dryness to afford the title compound.

Intermediate 6



***tert*-Butyl [1,3'-biazetidin]-3-ylcarbamate**

Scheme I-6

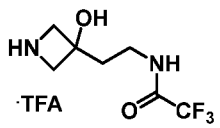


Reagents: 1) *tert*-butyl azetidin-3-ylcarbamate, $NaBH(OAc)_3$, AcOH, DCE, rt, 20h 2)H_2, Pd/C, EtOH, rt, 2h.

[00319] Step 1: benzyl 3-((*tert*-butoxycarbonyl)amino)-[1,3'-biazetidine]-1'-carboxylate. $NaBH(OAc)_3$ (1.67 g, 7.86 mmol) was added to a mixture of benzyl 3-oxoazetidine-1-carboxylate (522 mg, 2.54 mmol), *tert*-butyl azetidin-3-ylcarbamate (433 mg, 2.52 mmol), and acetic acid (0.10 mL) in dry DCE (25 mL). The mixture was stirred at rt under N_2 for 20 h. It was quenched with sat. aq. $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (2×100 mL). The extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (Hexanes/EtOAc/MeOH) to afford the title compound.

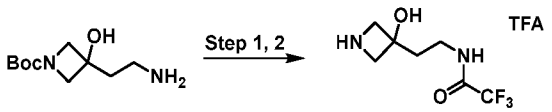
[00320] Step 2: *tert*-butyl [1,3'-biazetidin]-3-ylcarbamate. A mixture of benzyl 3-((*tert*-butoxycarbonyl)amino)-[1,3'-biazetidine]-1'-carboxylate (521 mg, 1.44 mmol) and 10% Pd (61 mg) in EtOH (20 mL) was stirred under an atmosphere ofH_2 for 2 h. The reaction mixture was filtered through a pad of Celite®, rinsed with MeOH, and the filtrate was concentrated to dryness to afford the title compound.

Intermediate 7



2,2,2-Trifluoro-N-(2-(3-hydroxyazetidin-3-yl)ethyl)acetamide trifluoroacetate salt

Scheme I-7

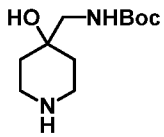


Reagents: 1) Trifluoroacetic anhydride, Et_3N, CH_2Cl_2, rt, 6h 2) TFA, CH_2Cl_2, rt, 1.5h.

[00321] Step 1: *tert*-butyl 3-(2-(2,2,2-trifluoroacetamido)ethyl)-3-(2,2,2-trifluoroacetoxy)azetidine-1-carboxylate. Trifluoroacetic anhydride (0.16 mL, 1.15 mL) was added dropwise to a solution of *tert*-butyl 3-(2-aminoethyl)-3-hydroxyazetidine-1-carboxylate (116 mg, 0.54 mmol) and Et_3N (0.22 mL, 1.58 mmol) in dry CH_2Cl_2 (5 mL), and the mixture was stirred at rt under N_2 for 6 h. The mixture was poured into sat. aq. $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (2×25 mL). The extracts were dried over Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography (Hexanes/EtOAc) to afford the title compound.

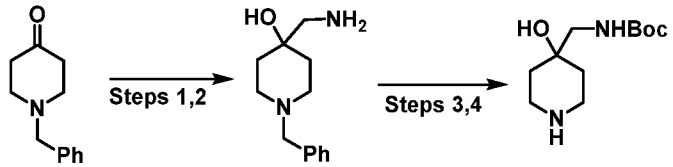
[00322] Step 2: 2,2,2-trifluoro-N-(2-(3-hydroxyazetidin-3-yl)ethyl)acetamide. A mixture of *tert*-butyl 3-(2-(2,2,2-trifluoroacetamido)ethyl)-3-(2,2,2-trifluoroacetoxy)azetidine-1-carboxylate (81.1 mg, 0.199 mmol) and TFA (0.5 mL) in dry CH_2Cl_2 (2.0 mL) was stirred at rt for 1.5h and concentrated to dryness to afford the title compound.

Intermediate 8



***tert*-Butyl ((4-hydroxypiperidin-4-yl)methyl)carbamate**

Scheme I-8



Reagents: 1) NaH, Me_3SOI, DMSO 2) NH_4OH, MeOH 3) Boc_2O, DCM 4) HCO_2NH_4, Pd/C, MeOH.

[00323] Step 1: 6-benzyl-1-oxa-6-azaspiro[2.5]octane. NaH (60% oil dispersion, 121 mg, 3.16 mmol) was added to a solution of trimethylsulfoxonium iodide (640 mg, 2.91 mmol) in DMSO (2.5 mL) at 0 °C. The mixture was warmed to 10 °C, stirred for 10 min. and warmed to rt. After 1h, a solution of *N*-benzylpiperidone (500 mg, 2.64 mmol) in DMSO (1.5 mL) was added via syringe. The mixture was stirred at rt for 1.5h, diluted with Et_2O and quenched with sat. aq NH_4Cl solution. The layers were separated and the organic portion was dried

over Na_2SO_4 and concentrated under reduced pressure to afford the crude epoxide (590 mg). LCMS [M+H] 204.2.

[00324] Step 2: 4-(aminomethyl)-1-benzylpiperidin-4-ol. An aqueous ammonia solution (28%, 7 mL) was added to a solution of 6-benzyl-1-oxa-6-azaspiro[2.5]octane (590 mg) in MeOH (3.5 mL) at 0 °C. The mixture was warmed to rt and stirred for 16 h. Volatiles were removed under reduced pressure. The residue was dissolved in DCM and the organic portion was washed with 1M aq. NaOH solution. The aqueous portion was extracted with DCM. The combined organic portions were dried and concentrated under reduced pressure to afford (497 mg) the crude aminol. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.23 (m, 5H), 3.55 (s, 2H), 2.74-2.58 (m, 4H), 2.48-2.30 (m, 2H), 1.64-1.50 (m, 4H).

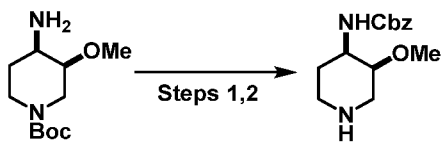
[00325] Step 3: *tert*-butyl ((1-benzyl-4-hydroxypiperidin-4-yl)methyl)carbamate. Di-*tert*-butyl dicarbonate (226 mg, 1.04 mmol) was added to a solution of 4-(aminomethyl)-1-benzylpiperidin-4-ol (230 mg) in DCM (3 mL) and the reaction was stirred at rt for 1 h. Volatiles were removed under reduced pressure. The crude product was purified by column chromatography (DCM/MeOH) to afford (235 mg) the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.23 (m, 5H), 3.55 (s, 2H), 3.22-3.10 (m, 2H), 2.70-2.56 (m, 2H), 2.49-2.33 (m, 2H), 1.74-1.54 (m, 4H), 1.46 (s, 9H). LCMS [M+H] 321.4.

[00326] Step 4 : *tert*-butyl ((4-hydroxypiperidin-4-yl)methyl)carbamate. Ammonium formate (276 mg, 4.78 mmol) and Pd/C (10% wt, 24 mg) were added to a solution of *tert*-butyl N-[(1-benzyl-4-hydroxypiperidin-4-yl)methyl]carbamate (235 mg, 0.73 mmol) in MeOH (4 mL) and the resulting mixture was refluxed for 1.5 h. Additional Pd/C was added and stirring at reflux was prolonged for 1 h. The cooled mixture was filtered through a pad of Celite® and the solution was concentrated under reduced pressure to afford the crude amine (163 mg), which was directly progressed to the next step. LCMS [M+H] 231.4.

Intermediate 9

cis-Benzyl N-[3-methoxypiperidin-4-yl]carbamate (racemate)

Scheme I-9



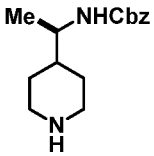
Reagents: 1) Benzyl chloroformate, DIPEA, DCM 2) 3M HCl in MeOH, MeOH.

[00327] Step 1: *tert*-butyl (*cis*)-4-(((benzyloxy)carbonyl)amino)-3-methoxypiperidine-1-carboxylate. Benzyl chloroformate (36 μL, 0.26 mmol) and DIPEA (76 μL, 0.43 mmol) were added to a solution of *cis*-4-(2-aminopropan-2-yl)-1-boc-piperidine (50 mg, 0.217

mmol) in DCM (4 mL) at 0 °C. The reaction was warmed to rt and stirred for 2 h. Benzyl chloroformate (36 μL, 0.26 mmol) and DIPEA (76 μL, 0.434 mmol) were added. The mixture was stirred for 1h, diluted with DCM and washed with sat. aq. $NaHCO_3$ solution and water. The organic portion was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (cyclohexane-EtOAc, 100:0 to 80:20) to afford the title compound (54 mg, 68%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.30 (m, 5H), 5.38-5.20 (m, 1H), 5.12 (s, 2H), 4.55-4.26 (m, 1H), 4.23-3.90 (m, 1H), 3.82-3.58 (m, 1H), 3.44-3.25 (m, 4H), 2.95-2.62 (m, 2H), 1.82-1.59 (m, 2H), 1.48 (s, 9H). LCMS [M+Na] 387.5.

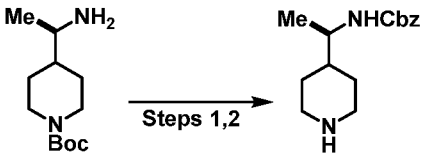
[00328] Step 2: benzyl ()-3-methoxypiperidin-4-yl)carbamate. A 3M solution of HCl in MeOH (246 μL, 0.740 mmol) was added to a solution of *cis-tert*-butyl 4-(2-{[(benzyloxy)carbonyl]amino} propan-2-yl)piperidine-1-carboxylate (54 mg, 0.148 mmol) in MeOH (3 mL). After 16 h, volatiles were removed under reduced pressure to afford (40 mg) the title compound. LCMS [M+H] 265.3.

Intermediate 10



Benzyl N-[(1R)-1-(piperidin-4-yl)ethyl]carbamate

Scheme I-10



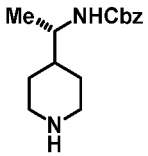
Reagents: 1) Benzyl chloroformate, K_2CO_3, THF 2) TFA, DCM.

[00329] Step 1: *tert*-butyl (R)-4-(1-(((benzyloxy)carbonyl)amino)ethyl)piperidine-1-carboxylate. Benzyl chloroformate (0.74 mL, 5.26 mmol) was added dropwise to a mixture of *tert*-butyl 4-[(1R)-1-aminoethyl]piperidine-1-carboxylate (1.0 g, 4.38 mmol) and K_2CO_3 (1.21 g, 8.76 mmol) in THF (20 mL). The mixture was stirred at rt for 16 h. Further benzyl chloroformate (0.5 mL) was added. After 5h, the reaction was diluted with water and extracted with EtOAc. The organic portion was concentrated under reduced pressure to afford (2.30 g) the title compound. LCMS [M+H] 363.4.

[00330] Step 2: benzyl (R)-(1-(piperidin-4-yl)ethyl)carbamate. TFA (3 mL) was added to a solution of *tert*-butyl 4-[(1R)-1-{[(benzyloxy)carbonyl]amino}ethyl]piperidine-1-

carboxylate (1 g, crude) in DCM (12 mL). The reaction was stirred at rt for 2 h. Volatiles were removed under reduced pressure and the crude residue was purified by column chromatography (MeOH, 1M NH_3 solution in MeOH) to afford (610 mg) the title compound. ^{1}H NMR (400 MHz, DMSO) δ 7.41-7.27 (m, 4H), 7.12-7.05 (m, 1H), 5.00-4.97 (m, 2H), 4.17-3.99 (m, 1H), 3.43-3.23 (m, 1H), 2.91 (br.d, 2H), 2.43-2.27 (m, 2H), 1.62-1.46 (m, 2H), 1.39-1.23 (m, 1H), 1.07-0.92 (m, 5H). LCMS [M+H] 263.3.

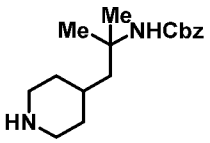
Intermediate 11



Benzyl N-[(1S)-1-(piperidin-4-yl)ethyl]carbamate.

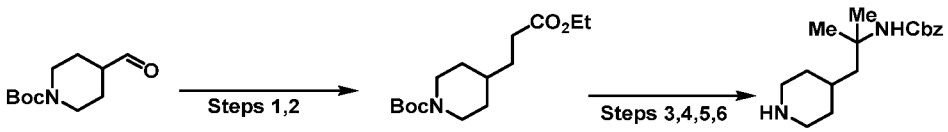
[00331] Prepared in a similar fashion as Scheme I-10 from *tert*-butyl 4-[(1S)-1-aminoethyl]piperidine-1-carboxylate. ^{1}H NMR (400 MHz, DMSO) δ 7.41-7.27 (m, 4H), 7.14-7.04 (m, 1H), 5.00 (s, 2H), 3.43-3.23 (m, 1H), 2.98-2.85 (m, 2H), 2.44-2.28 (m, 2H), 1.62-1.46 (m, 2H), 1.39-1.23 (m, 1H), 1.07-0.92 (m, 5H).

Intermediate 12



Benzyl N-[2-methyl-1-(piperidin-4-yl)propan-2-yl]carbamate

Scheme I-11



Reagents: 1) Triethyl phosphonoacetate, NaH, THF 2) H_2, Pd/C, EtOH 3) LDA, MeI, THF; LDA, MeI, THF 4) NaOH, EtOH-H_2O 5) DPPA, TEA, DCE, BnOH 6) TFA, DCM.

[00332] Step 1: *tert*-butyl (E)-4-(3-ethoxy-3-oxoprop-1-en-1-yl)piperidine-1-carboxylate. NaH (60% oil dispersion, 1.09 g, 28.5 mmol) was suspended in THF (20 mL) at 0 °C. A solution of triethyl phosphonoacetate (5.6 mL, 28.5 mmol) in THF (10 mL) was added dropwise over 15 min. The reaction was warmed to rt, stirred for 30 min and cooled to 0 °C. A solution of 1-Boc-piperidine-4-carboxaldehyde (5.00 g, 23.5 mmol) in THF (10 mL) was added dropwise over 15 min. The reaction was warmed to rt, stirred for 16 h, cooled to 0 °C and water added. The organic solvent was evaporated and the aqueous portion was

extracted three times with EtOAc. The combined organic portions were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford (6.79 g) the crude title compound. LCMS [M+H] 284.4.

[00333] Step 2: *tert*-butyl 4-(3-ethoxy-3-oxopropyl)piperidine-1-carboxylate. A mixture of *tert*-butyl 4-[3-ethoxy-3-oxoprop-1-en-1-yl]piperidine-1-carboxylate (6.79 g) and Pd/C (10% wt, 180 mg) in EtOH (60 mL) was stirred underH_2 atmosphere for 16 h. Further Pd/C (10% wt, 150 mg) was added and stirring underH_2 atmosphere was prolonged for 16 h. The reaction was filtered through a pad of Celite®. The solvent was removed under reduced pressure to afford the crude title compound (6.64 g). LCMS [M+H] 286.4.

[00334] Step 3: *tert*-butyl 4-(3-ethoxy-2-methyl-3-oxopropyl)piperidine-1-carboxylate. BuLi (1.6M solution in hexanes, (20 mL, 32 mmol) was added dropwise to a solution of diispropylamine (4.48 mL, 15 mmol) in THF (40 mL) at -60 °C. The mixture was warmed to -20 °C and stirred for 30 min., cooled to -60 °C and a solution of *tert*-butyl 4-(3-ethoxy-3-oxopropyl)piperidine-1-carboxylate (6.64 g) in THF (10 mL) was added dropwise. The mixture was stirred at -60 °C for 1 h. A solution of MeI (6.7 mL, 108 mmol) in THF (10 mL) was added dropwise. The reaction was warmed to rt, stirred for 16h, and quenched with sat. aq. NH_4Cl solution. The aqueous portion was extracted three times with EtOAc. The combined organic portions were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (cyclohexane-EtOAc) to afford (5.53 g, 85%) the title compound. LCMS [M+H] 300.4.

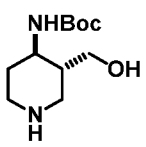
[00335] Step 4: *tert*-butyl 4-(3-ethoxy-2,2-dimethyl-3-oxopropyl)piperidine-1-carboxylate. BuLi (1.6M solution in hexanes, 17.3 mL, 27.8 mmol) was added dropwise to a solution of diisopropylamine (3.9 mL, 27.8 mmol) in THF (40 mL) at-60 °C. The mixture was warmed to -20 °C and stirred for 30 min. The reaction mixture was cooled to -60 °C, and a solution of *tert*-butyl 4-(3-ethoxy-2-methyl-3-oxopropyl)piperidine-1-carboxylate (5.53 g, 18.5 mmol) in THF (10 mL) was added dropwise. The mixture was stirred at -60 °C for 1h. A solution of MeI (5.76 mL, 92.5 mmol) in THF (10 mL) was added dropwise. The reaction was allowed to reach rt, stirred for 16 h, and quenched with sat. aq. NH_4Cl solution. The aqueous portion was extracted three times with EtOAc. The combined organic portions were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (cyclohexane-EtOAc, 100:0 to 70:30) to afford the title compound (4.76 g, 82%). ^1H NMR (400 MHz, $CDCl_3$) δ 4.13 (q, 2H), 4.08-3.94 (m, 2H),

2.76-2.59 (m, 2H), 1.62-1.41 (m, 14H), 1.27 (t, 3H), 1.20 (s, 6H), 1.18-1.05 (m, 2H). LCMS [M+H] 314.4.

[00336] Step 5: 3-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)-2,2-dimethylpropanoic acid. NaOH (2.0 g, 50 mmol) was added to a solution of *tert*-butyl 4-(3-ethoxy-2,2-dimethyl-3-oxopropyl)piperidine-1-carboxylate (4.76 g, 15.2 mmol) in 5:1 EtOH-H_2O (24 mL). The reaction was refluxed for 16h. The organic solvent was removed under reduced pressure. The aqueous portion was washed twice with Et_2O, acidified with 3M HCl and extacted with EtOAc (3x). The combined organic portions were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the title compound (2.72 g) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.04 (br s, 2H), 2.70 (t, 2H), 1.69-1.50 (m, 5H), 1.47 (s, 9H), 1.30-1.09 (m, 8H). LCMS [M+H] 286.4.

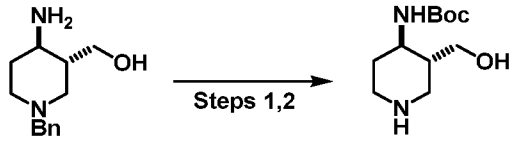
[00337] Step 6: benzyl (2-methyl-1-(piperidin-4-yl)propan-2-yl)carbamate. Et_3N (1.23 mL, 9.26 mmol) and DPPA (1.10 mL, 5.09 mmol) were sequentially added to a solution of 3-{1-[(*tert*-butoxy)carbonyl]piperidin-4-yl}-2,2-dimethylpropanoic acid (1.32 g, 4.63 mmol) in DCE (20 mL). The reaction was stirred at 80 °C for 3h. DPPA (0.50 mL, 2.31 mmol) was added and the reaction mixture heated for2 h. Benzyl alcohol (0.93 mL, 9.26 mmol) was added and mixture was stirred at 80°C for 1 h. Benzyl alcohol (3.2 mL, 31 mmol) was added and the solution was stirred at 80°C for 16h. Sat. aq. $NaHCO_3$ solution was added and extracted with DCM (3x). The combined organic portions were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (cyclohexane-EtOAc, 100:0 to 80:20) to afford a mixture of the title compound and benzyl alcohol (~30% wt, 3.1 g), which was progressed to the next step without any further purification. TFA (5 mL) was added to a solution of this mixture in DCM (15 mL) and the resulting solution was stirred at rt for 4 h. Volatiles were removed under reduced pressure. The crude product was purified by column chromatography (MeOH, 1M NH_3 in MeOH) to afford the title compound (490 mg, 36% over two steps) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.30 (m, 5H), 5.18-4.94 (m, 2H), 4.65 (br. s., 1H), 3.09-2.96 (m, 2H), 2.60 (td, 2H), 1.73-1.58 (m, 4H), 1.57-1.41 (m, 1H), 1.38-1.14 (m, 8H). LCMS [M+H] 291.3.

Intermediate 13



***trans-tert*-Butyl N-[3-(hydroxymethyl)piperidin-4-yl]carbamate (racemate)**

Scheme I-12

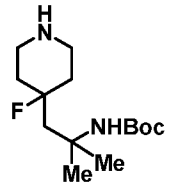


Reagents: 1) Boc_2O, DCM, MeOH; 2) H_2, Pd/C, MeOH.

[00338] Step 1: *tert*-butyl ((*trans*)-1-benzyl-3-(hydroxymethyl)piperidin-4-yl)carbamate. Di-*tert*-butyl dicarbonate (198 mg, 0.91 mmol) was added to a solution of *trans*-[4-amino-1-benzylpiperidin-3-yl]methanol (200 mg, 0.91 mmol) in a 3:1 MeOH-DCM solution (10 mL). The reaction was stirred at rt for 16 h and concentrated under reduced pressure. The crude product was purified by column chromatography (DCM-MeOH) to afford the title compound (59 mg, 20%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.22 (m, 5H), 4.52 (d, 1H), 3.79-3.62 (m, 2H), 3.59 (d, 1H), 3.52-3.43 (m, 2H), 3.01 (dd, 1H), 2.90 (d, 1H), 2.01 (td, 1H), 1.91-1.71 (m, 2H), 1.68-1.56 (m, 1H), 1.45 (s, 9H), 1.23-1.09 (m, 1H). LCMS [M+H] 321.4.

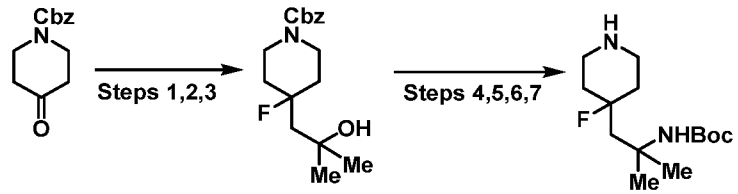
[00339] Step 2: *tert*-butyl ((*trans*)-3-(hydroxymethyl)piperidin-4-yl)carbamate. Pd/C (10% wt, 5 mg) was added to a solution of *trans-tert*-butyl N-[1-benzyl-3-(hydroxymethyl)piperidin-4-yl]carbamate (59 mg, 0.18 mmol) in EtOH (20 mL). The reaction was stirred underH_2 atmosphere for 16h and filtered through Celite®. Volatiles were removed under reduced pressure to afford the title compound (34.5 mg, 83%), which was directly progressed to the next step. LCMS [M+H] 231.3.

Intermediate 14



***tert*-butyl (1-(4-fluoropiperidin-4-yl)-2-methylpropan-2-yl)carbamate**

Scheme I-13



Reagents: 1) LDA, EtOAc, THF; 2) DAST, DCM; 3) MeMgBr, THF; 4) AcOH, H_2SO_4, chloroacetonitrile; 5) AcOH, thiourea, EtOH; 6) Boc_2O, DCM; 7) H_2, Pd/C, MeOH.

[00340] Step 1: benzyl 4-(2-ethoxy-2-oxoethyl)-4-hydroxypiperidine-1-carboxylate. Lithium diisopropylamide (1.8M in THF, 7 mL) was added to a solution of EtOAc (1.12 g, 12.7 mmol) in THF (20 mL) at -78 °C. After 30 min. a solution of benzyl 4-oxopiperidine-1-carboxylate (2.0 g, 8.5 mmol) in THF (15 mL) was added. The mixture was warmed to -40 °C and stirred for 5 h. The reaction was quenched with sat. aq. NH_4Cl solution (10 mL) and extracted twice with EtOAc. The combined organic portions were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (cyclohexane-EtOAc, 100:0 to 40:60) to afford the title compound (1.3 g, 47%). LCMS [M+H] 322.1.

[00341] Step 2: benzyl 4-(2-ethoxy-2-oxoethyl)-4-fluoropiperidine-1-carboxylate. DAST (602 mg, 3.74 mmol) was added to a solution of benzyl 4-(2-ethoxy-2-oxoethyl)-4-hydroxypiperidine-1-carboxylate (600 mg, 1.87 mmol) in DCM (20 mL). The reaction was stirred at rt for 16h and concentrated under reduced pressure. The crude product was purified by column chromatography (cyclohexane-EtOAc) to afford the title compound (305 mg, 50%). LCMS [M+H] 324.1.

[00342] Step 3: benzyl 4-fluoro-4-(2-hydroxy-2-methylpropyl)piperidine-1-carboxylate. Methyl magnesium bromide (3M in Et_2O, 0.78 mL) was added dropwise to a solution of benzyl 4-(2-ethoxy-2-oxoethyl)-4-fluoropiperidine-1-carboxylate (305 mg, 0.94 mmol) in THF (10 mL) at 0°C. The reaction was stirred at 0°C for 1h, warmed to 20°C and stirred for 1h and quenched with sat. aq. NH_4Cl solution. The aqueous portion was extracted twice with DCM. The combined organic portions were concentrated under reduced pressure to afford the title compound (260 mg).

[00343] Step 4: benzyl 4-(2-(2-chloroacetamido)-2-methylpropyl)-4-fluoropiperidine-1-carboxylate. AcOH (161 mg, 2.7 mmol) and H_2SO_4 (172 mg, 3.4 mmol) were added dropwise to a solution of benzyl 4-fluoro-4-(2-hydroxy-2-methylpropyl)piperidine-1-carboxylate (260 mg) in chloroacetonitrile (4 mL) at 0 °C. The reaction was stirred at rt for 24 h. An aqueous solution of Na_2CO_3 (10%, 10 mL) and THF (15 mL) were added and the mixture was stirred at rt for 20 min. Benzyl chloroformate (1 mL) was added and the mixture was stirred for 2h. The aqueous portion was extracted with DCM. The organic portion was concentrated under reduced pressure and purified by column chromatography (cyclohexane-EtOAc) to afford the title compound (125 mg). LCMS [M+H] 385.1.

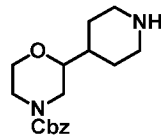
[00344] Step 5: benzyl 4-(2-amino-2-methylpropyl)-4-fluoropiperidine-1-carboxylate. ACOH (500 μL) and thiourea (50 mg, 0.65 mmol) were sequentially added to a solution of

benzyl 4-[2-(2-chloroacetamido)-2-methylpropyl]-4-fluoropiperidine-1-carboxylate (125 mg, 0.324 mmol) in EtOH (5 mL). The reaction was heated to 80 °C and stirred for 6 h. An aqueous solution of $NaHCO_3$ (5%, 10 mL) was added and the mixture was extracted with DCM. The organic portion was concentrated under reduced pressure to afford the title compound (78 mg, 78%). LCMS [M+H] 309.1.

[00345] Step 6: benzyl 4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropyl)-4-fluoropiperidine-1-carboxylate. Di-*tert*-butyl dicarbonate (110 mg, 0.50 mmol) was added to a solution of benzyl 4-(2-amino-2-methylpropyl)-4-fluoropiperidine-1-carboxylate (78 mg, 0.253 mmol) in DCM (5 mL). The reaction was stirred at rt for 16 h and quenched with sat. aq. NH_4Cl solution. After 1h, the aqueous phase was extracted with DCM. The organic portion was concentrated under reduced pressure to afford the crude title compound (99 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.30 (m, 5H), 5.15 (s, 2H), 4.66-4.53 (m, 1H), 4.08-3.86 (m, 2H), 3.24-3.02 (m, 2H), 2.25-1.91 (m, 4H), 1.77-1.54 (m, 2H), 1.44 (s, 9H), 1.37 (s, 6H).

[00346] Step 7: *tert*-butyl (1-(4-fluoropiperidin-4-yl)-2-methylpropan-2-yl)carbamate. Pd/C (10% wt, 5 mg) was added to a solution of benzyl 4-(2-{[(*tert*-butoxy)carbonyl]amino}-2-methylpropyl)-4-fluoropiperidine-1-carboxylate (99 mg) in MeOH (2 mL). The reaction was stirred underH_2 atmosphere for 5h, filtered and concentrated under reduced pressure to afford the crude title compound (65 mg). LCMS [M+H] 275.3.

Intermediate 15



Benzyl 2-(piperidin-4-yl)morpholine-4-carboxylate

Scheme I-14



Reagents: 1) 2-Bromoacetyl chloride, DIPEA, DCM; 2) KOtBu, dioxane; 3) $BH_3{\cdot}SMe_2$, THF; 4) benzyl chloroformate, TEA, DCM; 5) TFA, DCM.

[00347] Step 1: *tert*-butyl 4-(2-(2-bromoacetamido)-1-hydroxyethyl)piperidine-1-carboxylate. 2-Bromoacetyl chloride (401 mg, 2.55 mmol) was added to a solution of *tert*-butyl 4-(2-amino-1-hydroxyethyl)piperidine-1-carboxylate (566 mg, 2.32 mmol) and DIPEA (1.6 mL, 9.28 mmol) in DCM (15 mL) at 0 °C. The reaction was stirred for 8h. The mixture was diluted with DCM and washed with 5% aq. citric acid solution. The organic portion was

concentrated under reduced pressure to afford the crude title compound (744 mg). LCMS [M+H] 321.1.

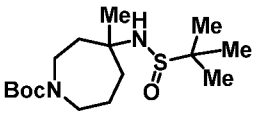
[00348] Step 2: *tert*-butyl 4-(5-oxomorpholin-2-yl)piperidine-1-carboxylate. Potassium *tert*-butoxide (1.04 g, 9.28 mmol) was added to a solution of *tert*-butyl 4-(2-(2-bromoacetamido)-1-hydroxyethyl)piperidine-1-carboxylate (744 mg) in dioxane (15 mL) and the resulting mixture was stirred at 50 °C for 1h. Water (20 mL) and sat. aq. NH_4Cl (15 mL) were added and the solution was extracted twice with DCM. The combined organic portions were concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc-MeOH, 100:0 to 75:25) to afford the title compound (230 mg, 35% over two steps). LCMS [M+H] 285.1.

[00349] Step 3: *tert*-butyl 4-(morpholin-2-yl)piperidine-1-carboxylate. Borane dimethyl sulfide complex (2M in Et_2O, 0.425 mL) was added to a solution of *tert*-butyl 4-(5-oxomorpholin-2-yl)piperidine-1-carboxylate (230 mg, 0.81 mmol) in THF (10 mL) at 0°C. The reaction was warmed to rt and stirred for 1h. The reaction was cooled to 0 °C and borane dimethyl sulfide complex (2M in Et_2O, 0.425 mL) was added. The mixture was warmed to rt and stirred for 2 h. Water (30 mL) was added and the aqueous portion was extracted with DCM. The organic portion was concentrated under reduced pressure to afford the crude title compound (95 mg), which was directly progressed to the next step. LCMS [M+H] 271.1.

[00350] Step 4: benzyl 2-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)morpholine-4-carboxylate. Benzyl chloroformate (0.055 mL, 0.39 mmol) was added to a solution of *tert*-butyl 4-(morpholin-2-yl)piperidine-1-carboxylate (95 mg) and TEA (0.058 mL, 0.42 mmol) in DCM (2 mL) at 0°C. The reaction was warmed to rt and stirred for 2h. The mixture was diluted with DCM and washed with 5% aq. citric acid. The organic portion was concentrated under reduced pressure. The crude product was purified by column chromatography (cyclohexane-EtOAc) to afford the title compound (117 mg, 36% over two steps). LCMS [M+H] 405.2.

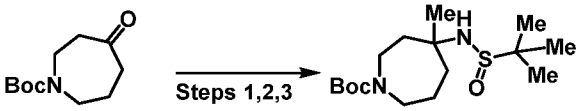
[00351] Step 5: benzyl 2-(piperidin-4-yl)morpholine-4-carboxylate. TFA (0.5 mL) was added to a solution of benzyl 2-{1-[(*tert*-butoxy)carbonyl]piperidin-4-yl}morpholine-4-carboxylate (117 mg, 0.290 mmol) in DCM (0.5 mL). The reaction was stirred at rt for h and concentrated under reduced pressure. The crude solid was washed with 1:1 Et_2O-EtOAc solution to afford the title compound as its trifluoroacetate salt (108 mg). LCMS [M+H] 305.1.

Intermediate 16



2-Methyl-N-(4-methylazepan-4-yl)propane-2-sulfinamide

Scheme I-15



Reagents: 1) 2-methyl-2-propanesulfinamide, $Ti(OEt)_4$, THF, 70°C; 2) MeLi, $AlMe_3$, THF, -78 °C to rt; 3) TFA, DCM.

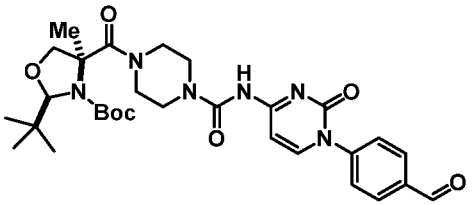
[00352] Step 1: *tert*-butyl (Z)-4-((*tert*-butylsulfinyl)imino)azepane-1-carboxylate. 2-Methyl-2-propanesulfinamide (125 mg, 1.03 mmol) and $Ti(OEt)_4$ (428 mg, 1.87 mmol) were added to a solution of *tert*-butyl 4-oxoazepane-1-carboxylate (400 mg, 1.87 mmol) in THF (4 mL) and the mixture was stirred at 70 °C in a sealed vial for 18h. The mixture was diluted with DCM. The organic portion was washed with water and filtered from the solid. Volatiles were removed under reduced pressure and the crude product was purified by column chromatography (cyclohexane-EtOAc, 100:0 to 40:60) to afford the title compound (425 mg, 72%) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 3.88-2.58 (m, 8H), 1.95-1.72 (m, 2H), 1.47 (s, 9H), 1.26 (s, 9H). LCMS [M+H] 317.3.

[00353] Step 2: *tert*-butyl 4-((*tert*-butylsulfinyl)amino)-4-methylazepane-1-carboxylate. Trimethylaluminum (690 μL, 1.39 mmol) was added to a solution of *tert*-butyl 4-[(2-methylpropane-2-sulfinyl)imino]azepane-1-carboxylate (200 mg, 0.632 mmol) in toluene (5 mL) at -78 °C. After 20 min. methyllithium (1.6M in Et_2O, 1.7 mL) was added. The reaction was warmed to rt and stirred for 16h. The reaction mixture was cooled to -15 °C and methyllithium (1.4 mL, 2.21 mmol) was added. The mixture was warmed to 0 °C and stirred for further 16h. Water was added. The aqueous portion was extracted twice with EtOAc. The combined organic portions were dried Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (cyclohexane-EtOAc) to afford the title compound (12.0 mg, 6%) as a pale yellow wax. LCMS [M+H] 333.4.

[00354] Step 3: 2-methyl-N-(4-methylazepan-4-yl)propane-2-sulfinamide. TFA (400 μL) was added to a solution of *tert*-butyl 4-methyl-4-[(2-methylpropane-2-sulfinyl)amino]azepane-1-carboxylate (12.0 mg, 0.036 mmol) in DCM (1.6 mL) and the resulting solution was stirred at rt for 1.5h. Volatiles were removed under reduced pressure to

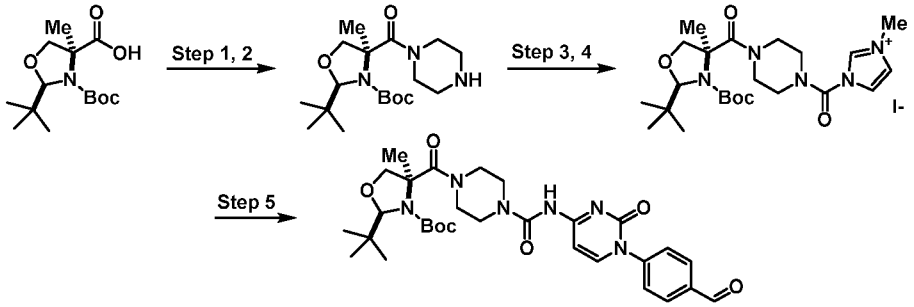
afford the crude 2-methyl-N-(4-methylazepan-4-yl)propane-2-sulfinamide as the trifluoroacetate salt. LCMS [M+H] 233.3.

Intermediate 17



***tert*-Butyl (2R,4S)-2-(*tert*-butyl)-4-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazine-1-carbonyl)-4-methyloxazolidine-3-carboxylate**

Scheme I-16



Reagents: 1) benzyl 1-piperazinecarboxylate, HATU, DIPEA, DMF, rt, 16h 2)10% Pd/C, MeOH, H_2, rt, 16h 3) CDI, DCM, rt, 16h 4) MeI, CH_3CN, rt, 16h 5) 4-(4-amino-2-oxopyrimidin-1(2H)-yl)benzaldehyde, CH_3CN, reflux, 16h.

[00355] Step 1: *tert*-butyl (2R,4S)-4-(4-((benzyloxy)carbonyl)piperazine-1-carbonyl)-2-(*tert*-butyl)-4-methyloxazolidine-3-carboxylate. To a stirred solution of (2R,4S)-3-(*tert*-butoxycarbonyl)-2-(*tert*-butyl)-4-methyloxazolidine-4-carboxylic acid (0.60 g, 2.11 mmol, Prepared in a similar fashion as *Org. Lett.* **2011**, 13, 5000) in DMF (10 mL) was added DIPEA (0.68 g, 5.28 mmol) and HATU (0.97 g, 2.53mmol). After 15 min. benzyl 1-piperazinecarboxylate (0.463 g, 2.11 mmol) was added, and the mixture was stirred at rt for 16h. The reaction mixture was poured into sat. aq. LiCl (30 mL) and stirred for 20 min. The precipitate was filtered and purified by flash chromatography (EtOAc:Hex) to afford the title compound (0.85 g, 82%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 5H), 5.22 (s, 1H), 5.17 (s, 2H), 4.95 (d, 1H), 3.83 (br s, 2H), 3.53 (br s, 3H) 3.31 (d, 1H), 1.61 (s, 3H), 1.51 (s, 9H), 0.89 (s, 12H).

[00356] Step 2: *tert*-Butyl (2R,4S)-2-(*tert*-butyl)-4-methyl-4-(piperazine-1-carbonyl)oxazolidine-3-carboxylate. To a stirred solution of *tert*-butyl (2R,4S)-4-(4-((benzyloxy)carbonyl)piperazine-1-carbonyl)-2-(*tert*-butyl)-4-methyloxazolidine-3-

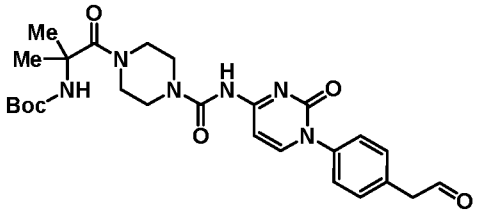
carboxylate (0.85 g, 1.73 mmol) in MeOH (20 mL) was added Pd/C 10% wt (0.1 g). The reaction mixture was stirred under hydrogen atmosphere at rt for 16h, filtered through Celite® and washed with MeOH (50 mL). The filtrate was concentrated under reduced pressure and dried to afford the title compound (0.58 g, 95%) as a viscous oil.

[00357] Step 3: *tert*-butyl (2R,4S)-4-(4-(1H-imidazole-1-carbonyl)piperazine-1-carbonyl)-2-(*tert*-butyl)-4-methyloxazolidine-3-carboxylate. To a stirred solution of *tert*-butyl (2R,4S)-2-(*tert*-butyl)-4-methyl-4-(piperazine-1-carbonyl)oxazolidine-3-carboxylate (0.58 g, 1.64 mmol) in CH_2Cl_2 (20 mL) was added CDI (0.53 g, 3.27 mmol). The reaction mixture was stirred at rt for 16h then concentrated under reduced pressure. The residue was purified by column chromatography to afford the title compound (0.66 g, 90%) as an off-white solid.

[00358] Step 4: 1-(4-((2R,4S)-3-(*tert*-butoxycarbonyl)-2-(*tert*-butyl)-4-methyloxazolidine-4-carbonyl)piperazine-1-carbonyl)-3-methyl-1H-imidazol-3-ium iodide. To a stirred solution of *tert*-butyl (2R,4S)-4-(4-(1H-imidazole-1-carbonyl)piperazine-1-carbonyl)-2-(*tert*-butyl)-4-methyloxazolidine-3-carboxylate (0.66 g, 1.47 mmol) in CH_3CN (15 mL) was added MeI (20.8 ml, 14.7 mmol). The reaction mixture was stirred at rt for 16h concentrated under reduced pressure to afford the title compound (0.88 g, quant.) as a pale yellow solid.

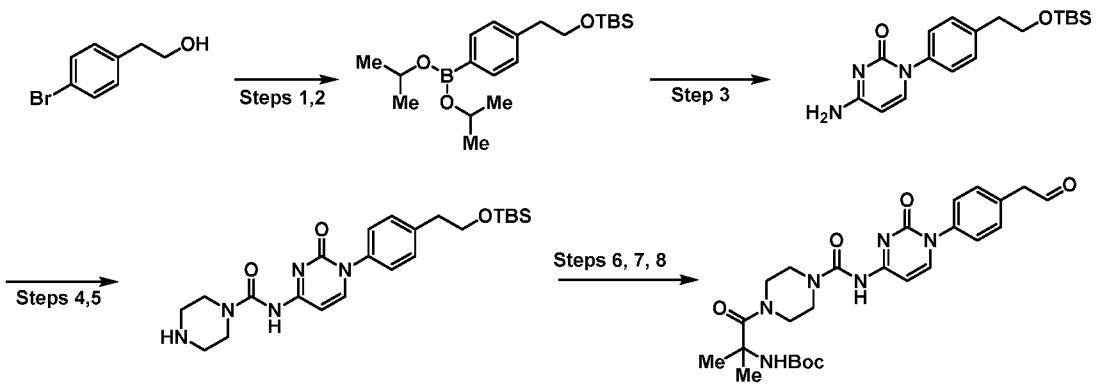
[00359] Step 5: *tert*-butyl (2R,4S)-2-(*tert*-butyl)-4-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazine-1-carbonyl)-4-methyloxazolidine-3-carboxylate. A mixture of 1-(4-((2R,4S)-3-(*tert*-butoxycarbonyl)-2-(*tert*-butyl)-4-methyloxazolidine-4-carbonyl)piperazine-1-carbonyl)-3-methyl-1H-imidazol-3-ium iodide (0.88 g, 1.50 mmol) and 4-(4-amino-2-oxopyrimidin-1(2H)-yl)benzaldehyde in CH_3CN was stirred at reflux for 16h. The solvent was evaporated and the residue was purified by flash chromatography to afford the title compound (0.54 g, 60%) as a pale yellow solid. LCMS [M+H] 597.2.

Intermediate 18



***tert*-Butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate**

Scheme I-17



Reagents: 1) TBSCl, imidazole, DMF, rt, 16h 2) BuLi, THF, -78 °C, (iPrO)$_3$B, 2NHCl 3) cytosine, TMEDA, Cu(OAc)$_2$·H$_2$O, 4:1 MeOH:H$_2$O, rt, 48h 4) 3-methyl-1-(4-(2,2,2-trifluoroacetyl)piperazine-1-carbonyl)-1H-imidazol-3-ium iodide, CH$_3$CN, 85°C, 16h 5) K$_2$CO$_3$, MeOH, rt, 3h 6) Boc-AIB-OH,HATU, DIPEA, DMF, rt, 8h 7) TBAF, THF 0 °C to rt, 16h 8) DMP, 1% CH$_2$Cl$_2$:H$_2$O, rt, 1h.

[00360] Step 1: (4-bromophenethoxy)(*tert*-butyl)dimethylsilane. To a stirring solution of 2-(4-bromophenyl)ethan-1-ol (7.0 mL, 49.7 mmol) in DMF (50 mL) was added imidazole (5.1g, 74.6 mmol) and *tert*-butyldimethylsilyl chloride (9.0 g, 60.0 mmol). The solution was stirred 16h. The reaction mixture was diluted with EtOAc (100 mL) and extracted with aqueous LiCl (3×50 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography (Hex:EtOAc) to afford the title compound.

[00361] Step 2: bisisopropyl (4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)phenyl)boronate. A stirred solution of (4-bromophenethoxy)(*tert*-butyl)dimethylsilane (9.0 g, 28.0 mmol) in THF (100 mL) was cooled to -78°C. 2.5 M BuLi in Hexanes (28.0 mL, 71.4 mmol) was added dropwise over 30 min. and the temperature maintained below -60 °C. After 25 min., triisopropyl borate (10.0 mL, 42.0 mmol) was added dropwise over 30 min. The reaction mixture was warmed to rt and stirred for 15 min. 2NHCl (50 mL) was added and the reaction was stirred for 30 min. The biphasic mixture was separated and the aq. layer extracted with CH_2Cl_2 (2×50 mL). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure afford the title compound.

[00362] Step 3: 4-amino-1-(4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)phenyl)pyrimidin-2(1*H*)-one. A suspension of cytosine (10.5g, 95.0 mmol) and diisopropyl (4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)phenyl)boronate (26.6g, 95.0 mmol), in MeOH:H$_2$O (4:1, 600 ml) was stirred at rt in open air for 30 min. TMEDA (17.0 ml, 114.0 mmol) and Cu(OAc)$_2$·H$_2$O (19.0 g, 95.0 mmol) were added and the reaction was stirred in open air for

48h at rt. The reaction mixture was concentrated under reduced pressure, and cold H_2O (100 mL) was added. The solid was filtered and washed with H_2O (5x50 mL), Et_2O (3x30 mL), and H_2O (2×30 mL) to afford the title compound. LCMS [M+H] 346.2.

[00363] Step 4: *N*-(1-(4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-4-(2,2,2-trifluoroacetyl)piperazine-1-carboxamide. To a stirred solution of 4-amino-1-(4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)phenyl)pyrimidin-2(1*H*)-one (2.41 g, 7.0 mmol) in CH_3CN (50 mL) was added 3-methyl-1-(4-(2,2,2-trifluoroacetyl)piperazine-1-carbonyl)-1*H*-imidazol-3-ium iodide (3.79 g, 8.4 mmol). The vessel was flushed with nitrogen and heated to 85 °C and refluxed for 16h. The reaction mixture was concentrated under reduced pressure, which was purified by column chromatography (CH_2Cl_2:MeOH:NH_4OH) to afford the title compound. LCMS [M+H] 554.3.

[00364] Step 5: *N*-(1-(4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide. *N*-(1-(4-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-4-(2,2,2-trifluoroacetyl)piperazine-1-carboxamide (4.50 g, 8.1 mmol) and K_2CO_3 (3.36 g, 24.3 mmol) were dissolved in MeOH (200 mL), and stirred at rt for 3h. The reaction mixture was concentrated under reduced pressure to give a solid residue and purified by column chromatography (CH_2Cl_2:MeOH:NH_4OH) to afford the title compound.

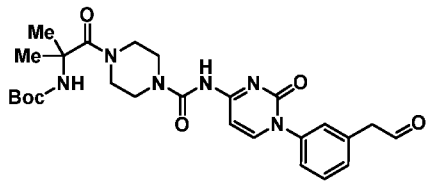
[00365] Step 6: *tert*-butyl (1-(4-((1-(4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate. To a solution of *N*-(1-(4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide (3.66 g, 8.1 mmol) in DMF (30 mL) was added 2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoic acid (1.63 g, 8.1 mmol) followed by DIPEA (3.36 mL, 24.2 mmol). The solution stirred for 5 min, and HATU (5.51 g, 14.5 mmol) was then added and the solution was stirred at rt for an additional 8h. The crude reaction mixture was dissolved in EtOAc (50 mL) and washed with aqueous LiCl (3×30 mL). The organic layer was dried over Na_2SO_4, concentrated under reduced pressure and purified by flash chromatography (CH_2Cl_2:MeOH:NH_4OH) to afford the desired compound. LCMS [M+H] 643.4.

[00366] Step 7: *tert*-butyl (1-(4-((1-(4-(2-hydroxyethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate. To a solution of *tert*-butyl (1-(4-((1-(4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate (1.0 g, 1.63 mmol) in THF (30 mL) at 0 °C was

added TBAF in THF (2M, 3.27 mL) over 20 min. The solution was warmed to rt and stirred for 16h. The crude reaction mixture was concentrated under reduced pressure to give an oily residue, which was purified by column chromatography (CH_2Cl_2:MeOH) to afford the desired compound. LCMS [M+H] 529.4.

[00367] Step 8: *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate. To a stirred solution of *tert*-butyl (1-(4-((1-(4-(2-hydroxyethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate (150.0 mg, 0.28 mmol) in CH_2Cl_2:H_2O (100:1, 10 mL) was added Dess-Martin periodinane (361.0 mg, 0.85 mmol). The solution was stirred for 1h. The crude reaction mixture was dissolved in additional CH_2Cl_2 (50 mL) and washed with aq. $NaHCO_3$/$Na_2S_2O_3$ (1 x 50 mL). The aq. layer was extracted with CH_2Cl_2 (1 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford the title compound which was used immediately.

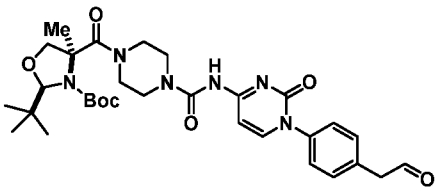
Intermediate 19



***tert*-Butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(3-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate**

[00368] Prepared in a similar fashion to Scheme I-17 from 2-(3-bromophenyl)ethan-1-ol.

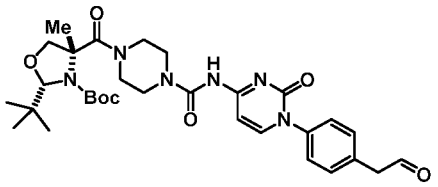
Intermediate 20



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

[00369] Prepared in a similar fashion to Scheme I-17 using 1-(4-((2R,4S)-3-(*tert*-butoxycarbonyl)-2-(*tert*-butyl)-4-methyloxazolidine-4-carbonyl)piperazine-1-carbonyl)-3-methyl-1H-imidazol-3-ium iodide.

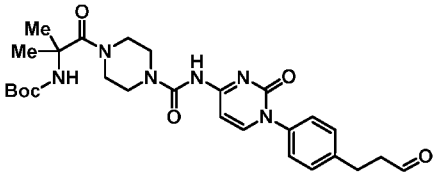
Intermediate 21



***tert*-butyl (2S,4R)-2-(*tert*-butyl)-4-methyl-4-(4-((2-oxo-1-(4-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazine-1-carbonyl)oxazolidine-3-carboxylate**

[00370] Prepared in a similar fashion to Scheme I-17 using 1-(4-((2S,4R)-3-(*tert*-butoxycarbonyl)-2-(*tert*-butyl)-4-methyloxazolidine-4-carbonyl)piperazine-1-carbonyl)-3-methyl-1H-imidazol-3-ium iodide.

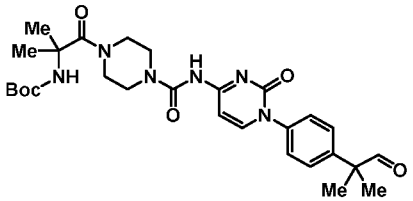
Intermediate 22



***tert*-Butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(3-oxopropyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate**

[00371] Prepared in a similar fashion to Scheme I-17 from 3-(4-bromophenyl)propan-1-ol.

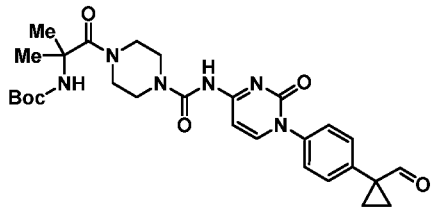
Intermediate 23



***tert*-Butyl (2-methyl-1-(4-((1-(4-(2-methyl-1-oxopropan-2-yl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-1-oxopropan-2-yl)carbamate**

[00372] Prepared in a similar fashion to Scheme I-17 from 2-(4-bromophenyl)-2-methylpropan-1-ol.

Intermediate 24

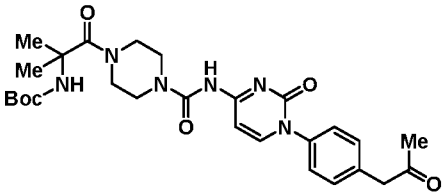


***tert*-Butyl (1-(4-((1-(4-(1-formylcyclopropyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-**

yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate

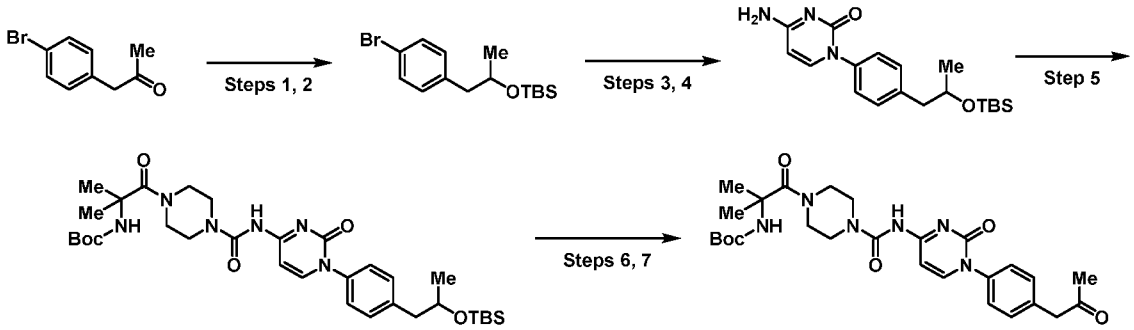
[00373] Prepared in a similar fashion to Scheme I-17 from (1-(4-bromophenyl)cyclopropyl)methanol.

Intermediate 25



***tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxopropyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate**

Scheme I-18



Reagents: 1) $NaBH_4$, MeOH, rt, 3 h 2) TBDMSCl, Imidazole, CH_2Cl_2, rt, 16h 3) n-BuLi, $B(OiPr)_3$, THF, -78 °C-rt, 3h 4) Cytosine, TMEDA, $Cu(OAc)_2H_2O$, MeOH:H_2O (4:1), O_2, rt, 16h 5) 1-(4-(2-((*t*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carbonyl)-3-methyl-1*H*-imidazol-3-ium iodide, MeCN, 90 °C, 16h 6) TBAF, THF, rt, 16h 7) DMP, CH_2Cl_2, rt, 3h.

[00374] Step 1: 1-(4-bromophenyl) propan-2-ol. To a stirred solution of 1-(4-bromophenyl) propan-2-one (30.0 g, 141 mmol) in MeOH (150 mL) was added $NaBH_4$ (13.3 g, 352 mmol) at 0 °C. The reaction mixture was stirred at rt for 3h. The reaction mixture was poured into H_2O (500 mL) and extracted with EtOAc (3x200 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the title compound (29.0 g, 95%) as a colorless oil. ^1H NMR (DMSO-d_6, 400 MHz) δ 7.43 (d, 2H), 7.15 (d, 2H), 4.58 (d, 1H), 3.82-3.73 (m, 1H), 2.64-2.48 (m, 2H), 1.01 (d, 3H).

[00375] Step 2: ((1-(4-bromophenyl) propan-2-yl)oxy)(*tert*-butyl)dimethylsilane. To a stirred solution of 1-(4-bromophenyl) propan-2-ol (29.0 g, 134.9 mmol) in CH_2Cl_2 (300 mL) were added imidazole (13.8 g, 202 mmol) and *t*-butyldimethylsilyl chloride (24.4 g, 161.8 mmol) at 0 °C. The reaction mixture was stirred at rt for 16h. The reaction mixture was poured intoH_2O (500 mL) and extracted with CH_2Cl_2 (3x700 mL). The combined organics

were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the title compound (40.0 g, 90%) as a yellow oil. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.43 (d, 2H), 7.13 (d, 2H), 3.98-3.90 (m, 1H), 2.68-2.64 (m, 1H), 2.56-2.48 (m, 1H), 1.09 (d, 3H), 0.76 (s, 9H), 0.10 (s, 3H), -0.27 (s, 3H).

[00376] Step 3: diisopropyl (4-(2-((*tert*-butyldimethylsilyl)oxy)propyl)phenyl)boronate. To a stirred solution of ((1-(4bromophenyl) propan-2-yl)oxy)(*t*-butyl) dimethylsilane (20.0 g, 60.8 mmol) in THF (300 mL) at -78 °C, was added n-BuLi in THF (1.6M, 94 mL). The reaction mixture was stirred -78°C for 30 min. Triisopropyl borate (21.2 mL, 91.2 mmol) was added at -78 °C. The reaction mixture was warmed to rt and stirred for 3h. The reaction mixture was poured into NH_4Cl solution (100 mL) and extracted with EtOAc (3x300 ml). The combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the title compound (20 g, 86%).

[00377] Step 4: 4-amino-1-(4-(2-((*tert*-butyldimethylsilyl)oxy)propyl)phenyl)pyrimidin-2(1*H*)-one. To a solution of diisopropyl (3-(2-((isopropyldimethylsilyl)oxy)ethyl)phenyl) boronate (20.0 g, 52.9 mmol) and cytosine (5.87 g, 52.9 mmol) in MeOH:H_2O (300 mL, 4:1) was stirred at rt in open air for 30 min. TMEDA (9.58 mL, 63.5 mmol) and $Cu(OAc)_2.H_2O$ (9.6 g , 52.9 mmol) were added and the reaction mixture stirred in open air at rt for 48h. The reaction mixture was concentrated under reduced pressure and cold H_2O (100 mL) was added into the mixture. The solid was filtered off and washed with H_2O (5x100 mL) and Et_2O (2x60 mL) under reduced pressure. The resulting solid was dried to afford the title compound (9.2 g, 48%) as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.52 (d, 1H), 7.25-7.22 (m, 6H), 5.80 (bs, 1H), 4.00-3.99 (m, 1H), 2.70-2.65 (m, 2H), 1.10 (d, 3H), 0.79 (s, 9H), -0.55 (s, 3H), -0.178(s, 3H). LCMS [M+H] 360.3.

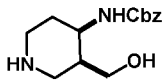
[00378] Step 5: *tert*-butyl (1-(4-((1-(4(2-hydroxypropyl)phenyl)-2-oxo-1,2-dihydropyrimidine-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate. To a stirred solution of 4-amino-1-(4-(2-((*t*-butyldimethylsilyl)oxy)propyl)phenyl) pyrimidin-2(1*H*)-one (3.0 g, 8.3 mmol) and 1-(4-(2-((*t*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carbonyl)-3-methyl-1*H*-imidazol-3-ium iodide (6.35 g, 12.5 mmol) in CH_3CN (45 mL) was heated at 90 °C for 16h. The reaction mixture was concentrated under reduced pressure and the crude material was purified by column chromatography (CH_3OH/CH_2Cl_2) to afford the title compound. LCMS [M+H] 357.2.

[00379] Step 6: *tert*-butyl (1-(4-((1-(4-(2-hydroxypropyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-

yl)carbamate. To a stirred solution of *t*-butyl(1-4-(-2-((*t*-butyldimethylsilyl)oxy)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate (3.1 g, 4.72 mmol) in THF (40 mL) was added TBAF (1.0 M in THF,18.9 mL) at 0 °C. The reaction mixture was stirred at rt for 16h. The reaction mixture was poured in to sat. aq. $NaHCO_3$ (25 mL) and extracted with 9:1 CH_2Cl_2:MeOH (3x100 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (5% MeOH in CH_2Cl_2) to afford the title compound as an off-white solid (2.4 g, 93%). LCMS [M+H] 543.2.

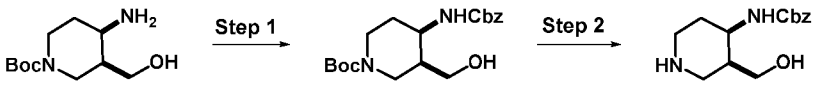
[00380] Step 7: *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxopropyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate. To a stirred solution of *t*-butyl (1-(4-((1-(4(2-hdroxypropyl)phenyl)-2-oxo-1,2-dihydropyrimidine-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate (0.5 g, 0.92 mmol) in CH_2Cl_2 (5 mL) was added DMP (0.78 g, 1.84 mmol) at 0 °C. The reaction mixture was stirred at rt for 3h, poured in to $NaHCO_3$ solution (20 mL) and extracted with CH_2Cl_2 (3x50 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated under reduced pressure at low temperature (30-35°C) to afford the title compound (0.7 g, quant.) as an off-white solid. LCMS [M+H] 541.0.

Intermediate 26



***cis*-Benzyl (3-(hydroxymethyl)piperidin-4-yl)carbamate**

Scheme I-19

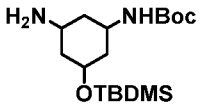


Reagents: Step 1) Cbz-Cl, $NaHCO_3$, dioxane:water, rt, 4h 2) 4MHCl in dioxane, rt, 4h.

[00381] Step 1*: cis-tert*-butyl 4-(((benzyloxy)carbonyl)amino)-3-(hydroxymethyl)piperidine-1-carboxylate. To a stirred solution of *cis-tert*-butyl-4-amino-3-(hydroxymethyl)piperidine-1-carboxylate (0.2 g, 0.86 mmol) in 1:1 dioxane: water (4 mL) were added $NaHCO_3$ (0.59 g, 7 mmol) and CBZ-Cl (0.25mL, 1.73 mmol) at 0°C. The reaction mixture was stirred at rt for 4 h. The reaction mixture was poured into water (20 mL) and extracted with EtOAc (3x10 mL). The combined organic phase was dried over Na_2SO_4, filtered and concentrated purified by column chromatography (EtOAc/Hexane) to afford the title compound (0.3 g, 80%) as off white solid. LCMS [M-Boc+H] 265.0.

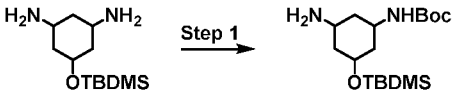
[00382] Step 2: *cis*-benzyl (3-(hydroxymethyl)piperidin-4-yl)carbamate. To a stirred a solution of *cis-tert*-butyl 4-(((benzyloxy)carbonyl)amino)-3-(hydroxymethyl)piperidine-1-carboxylate (0.3 g, 0.8 mmol) in dioxane (6 mL) were added 4M HCl in dioxane (3 mL) at 0°C. The reaction mixture was stirred at rt for 4h. The reaction mixture was concentrated under reduced pressure to afford the title compound (0.2 g, quant.) as yellow oil. LCMS [M+H] 265.6.

Intermediate 27



***tert*-Butyl (3-amino-5-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)carbamate**

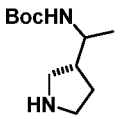
Scheme I-20



Reagents: Boc_2O, TEA, MeOH, rt, 16 h.

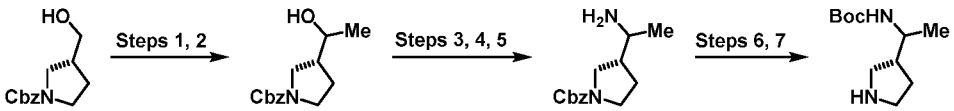
[00383] *tert*-butyl (3-amino-5-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)carbamate. To a stirred solution of 5-((*tert*-butyldimethylsilyl)oxy)cyclohexane-1,3-diamine (0.5 g, 2.1 mmol), prepared according to *New J. Chem.*, **2005**, *29*, 1152, was added TEA (0.6 ml, 4.1 mmol) and Boc_2O (0.9 g, 4.1 mmol) at rt. The reaction mixture was stirred at rt for 16h. The reaction mixture was poured into water (50 mL) and extracted with DCM (3x50 mL). The combined organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the title compound (0.7 g, quantitative) as brown colored oil. LCMS [M+H] 345.4.

Intermediate 28



***tert*-Butyl (1-(R-pyrrolidin-3-yl)ethyl)carbamate**

Scheme I-21



Reagents: 1) PCC, Celite®, CH_2Cl_2 2) MeMgCl, THF, -78 °C 3) MsCl, NEt_3, CH_2Cl_2, 0°C 4) NaN_3, DMF, 80°C 5) PPh_3, THF, H_2O, 45°C 6) Boc_2O, NEt_3, THF 7) H_2 $Pd(OH)_2/C$, MeOH.

[00384] Step 1: benzyl (R)-3-formylpyrrolidine-1-carboxylate. To a solution of benzyl (R)-3-(hydroxymethyl)pyrrolidine-1-carboxylate (1.4 g, 6.0 mmol), in CH_2Cl_2 (50 mL) was added PCC (1.95g, 9.0 mmol) in Celite® (500 mg). The reaction was stirred for 16 h. The solvent was removed and the crude solution was purified by column chromatography (Hex:EtOAc) to afford the title compound.

[00385] Step 2: benzyl (3R)-3-(1-hydroxyethyl)pyrrolidine-1-carboxylate. A solution of (R)-3-formylpyrrolidine-1-carboxylate (590 mg, 2.5 mmol) in THF (15 mL) was cooled to -78°C. To the mixture was added 3M MeMgCl (1.69 mL, 5.08 mmol) over 30 min. The solution was warmed to rt and stirred for 16h. The organic layer was washed with aq. citric acid (1x15 mL) and the organic layer was dried over Na_2SO_4, concentrated under reduced pressure to afford the title compound.

[00386] Step 3: benzyl (3R)-3-(1-((methylsulfonyl)oxy)ethyl)pyrrolidine-1-carboxylate. A solution of benzyl (3R)-3-(1-hydroxyethyl)pyrrolidine-1-carboxylate (330 mg, 1.3 mmol) in NEt_3 (0.6 mL, 4.2 mmol) and CH_2Cl_2 (10 mL) was cooled to 0°C and MsCl (0.18 mL, 2.4 mmol) was added dropwise over 5 min. The solution was stirred for 4h and washed with $NaHCO_3$ (1x20 mL). The aqueous layer was extracted with CH_2Cl_2 (1x20 mL). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure to afford the title compound.

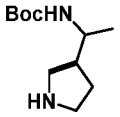
[00387] Step 4: benzyl (3R)-3-(1-azidoethyl)pyrrolidine-1-carboxylate. To a solution of benzyl (3R)-3-(1-((methylsulfonyl)oxy)ethyl)pyrrolidine-1-carboxylate (1.3 mmol) in DMF (12 mL) was added NaN_3 (430 mg, 6.6 mmol). The solution was warmed to 80 °C and stirred for 16h. The solution was dissolved in EtOAc (50 mL) and washed with sat. LiCl (4x20 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure and purified by column chromatography (Hex:EtOAc) to afford the title compound.

[00388] Step 5: benzyl (3R)-3-(1-aminoethyl)pyrrolidine-1-carboxylate. To a solution of benzyl (3R)-3-(1-azidoethyl)pyrrolidine-1-carboxylate (235 mg, 0.85 mmol) in 12:1 THF:H_2O (8 mL) was added PPh_3 (448 mg, 1.70 mmol). The solution was warmed to 45 °C and stirred for 16h. The solution was concentrated under reduced pressure and purified by column chromatography (Hex:EtOAc EtOAc:MeOH:NH_4OH) to afford the title compound.

[00389] Step 6: benzyl (3R)-3-(1-((*tert*-butoxycarbonyl)amino)ethyl)pyrrolidine-1-carboxylate. To a solution of benzyl (3R)-3-(1-aminoethyl)pyrrolidine-1-carboxylate (200 mg, 0.80 mmol) in THF (20 mL) was added Boc_2O (349 mg, 1.60 mmol) and NEt_3 (0.33 mL, 2.4 mmol). The solution was stirred for 16h. The solution was concentrated under reduced pressure and purified by column chromatography (Hex:EtOAc) to afford the title compound.

[00390] Step 7: *tert*-butyl (1-((R)-pyrrolidin-3-yl)ethyl)carbamate. To a N_2 sparged solution of benzyl (3R)-3-(1-((*tert*-butoxycarbonyl)amino)ethyl)pyrrolidine-1-carboxylate (140 mg, 0.40 mmol) in MeOH (10 mL) was added $Pd(OH)_2$ 10% wt (14mg). The reaction was stirred for 16h under H_2 atmosphere. The reaction mixture was filtered through a pad of Celite® and washed with MeOH (5x20 mL). The combined organics were concentrated under reduced pressure to afford the title compound.

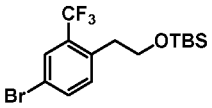
Intermediate 29



***tert*-Butyl (1-((S)-pyrrolidin-3-yl)ethyl)carbamate**

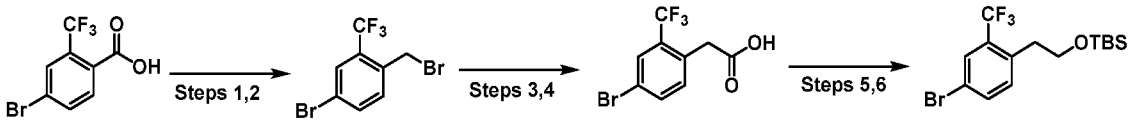
[00391] Prepared in a similar fashion as Scheme I-21 from benzyl (S)-3-(hydroxymethyl)pyrrolidine-1-carboxylate.

Intermediate 30



(4-Bromo-2-(trifluoromethyl)phenethoxy)(*tert*-butyl)dimethylsilane

Scheme I-22



Reagents: 1) BH_3THF, THF 0 °C to rt, 4h 2) CBr_4, PPh_3 DMF, 0 °C to rt, 4h 3) KCN, EtOH:H_2O, 70 °C, 3h. 4) LiOH,H_2O, 100°C, 16h. 5) BH_3THF, THF 0 °C to rt, 4h 5) TBSCl, NEt_3, CH_2Cl_2, rt, 16h.

[00392] Step 1: (4-bromo-2-(trifluoromethyl)phenyl)methanol. To a solution of 4-bromo-2-(trifluoromethyl)benzoic acid (2.65 g, 10.0 mmol) in THF (50 mL) stirred at 0°C was added 1M BH_3•THF in THF (20.0 mL) dropwise over 15 min The solution was warmed to rt for 4h. The reaction mixture was quenched with the addition of 2N HCl, and the biphasic mixture was separated. The aqueous layer was and extracted with EtOAc (2x50 mL), and the combined organics were dried over Na_2SO_4. The reaction mixture was purified by flash chromatography (Hexanes:EtOAc) to afford the desired compound.

[00393] Step 2: 4-bromo-1-(bromomethyl)-2-(trifluoromethyl)benzene. To a stirred solution of (4-bromo-2-(trifluoromethyl)phenyl)methanol (1.35 g, 5.12 mmol) in DMF (20 mL) at 0 °C was added triphenylphosphine (2.02 g, 7.70 mmol) and carbon tetrabromide (2.54 g, 7.70 mmol). The solution was warmed to rt and stirred for 3h. The reaction mixture

was diluted with EtOAc (100mL) and washed with sat. LiCl solution (3x100mL). The crude reaction mixture was purified by flash chromatography (Hexanes:EtOAc) to afford the desired compound.

[00394] Step 3: 2-(4-bromo-2-(trifluoromethyl)phenyl)acetonitrile. To a solution of 4-bromo-1-(bromomethyl)-2-(trifluoromethyl)benzene (1.84 g, 5.14 mmol) in EtOH:H_2O 3:1 was added KCN (366 mg, 5.61 mmol). The reaction was heated to 70 °C for 3h. The reaction mixture was cooled and diluted with EtOAc (100 mL) andH_2O (50 mL). The biphasic mixture was separated and the aqueous layer was and extracted with EtOAc (2x50 mL). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure. The reaction mixture was purified by flash chromatography (Hexanes:EtOAc) to afford the desired compound,

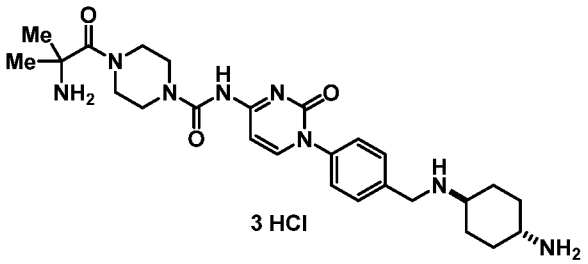
[00395] Step 4: 2-(4-bromo-2-(trifluoromethyl)phenyl)acetic acid. To a suspension of 2-(4-bromo-2-(trifluoromethyl)phenyl)acetonitrile (423 mg, 1.62 mmol) in H_2O (30 mL), was added LiOH (386 mg, 16.2 mmol). The reaction was heated to 100 °C and stirred for 16h. The reaction mixture was diluted with H_2O (50 mL) and washed with Et_2O (1x50 mL) and the organic layer was discarded. The aqueous layer was acidified with 2N HCl and was extracted with EtOAc, (3x50 mL). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure to afford the desired compound.

[00396] Step 5: 2-(4-bromo-2-(trifluoromethyl)phenyl)ethan-1-ol. To a solution of 2-(4-bromo-2-(trifluoromethyl)phenyl)acetic acid (333 mg, 1.18 mmol) in THF (25 mL) stirred at 0°C was added 1M BH_3•THF (2.36 mL) dropwise over 10 min. The solution was warmed and allowed to stir at rt for 4h. The reaction mixture was quenched with the addition of 2NHCl, and the biphasic mixture was separated. The aqueous layer was and extracted with EtOAc (2x50 mL), and the combined organics were dried over Na_2SO_4. The reaction mixture was purified by flash chromatography (Hexanes:EtOAc) to afford the desired compound.

[00397] Step 6: (4-bromo-2-(trifluoromethyl)phenethoxy)(*tert*-butyl)dimethylsilane the desired compound. To a solution of 2-(4-bromo-2-(trifluoromethyl)phenyl)ethan-1-ol (317 g, 46.5 mmol) in CH_2Cl_2 (150 mL) was added imidazole (4.79g, 70.5 mmol) and *tert*-butyldimethylsilyl chloride (10.6 g, 70.5 mmol). The solution was stirred for 16h at rt. The reaction mixture concentrated under reduced pressure and the solid was dissolved in EtOAc (250 mL) and washed with H_2O (250mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure and purified by flash chromatography (Hexanes:EtOAc) to afford the title compound.

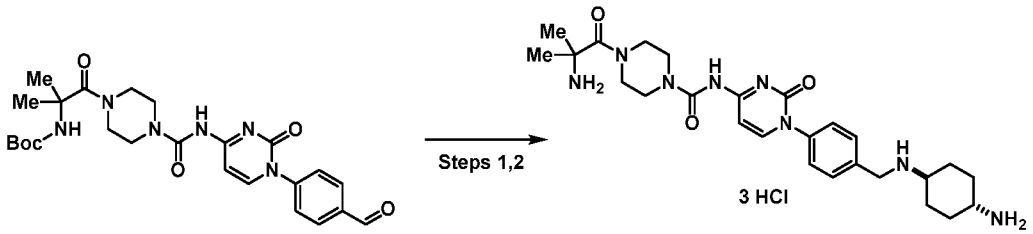
Compound Synthesis

Compound 117



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((*trans*-4-aminocyclohexyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

Scheme C-1



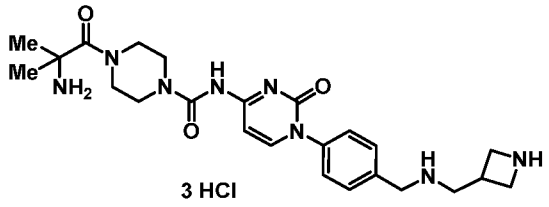
Reagents: 1) N-Boc-*trans*-1,4-cyclohexanediamine, $NaBH_3CN$, MeOH, rt, 3d 2) 2 MHCl in MeOH, rt, 17h.

[00398] Step 1: *tert*-butyl (*trans*-4-((4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine -1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)amino)cyclohexyl)carbamate. $NaBH_3CN$ (379 mg, 6.03 mmol) was added to a mixture of *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate (1.03 g, 2.01 mmol) and N-boc-*trans*-1,4-cyclohexanediamine (527 mg, 2.46 mmol) in dry MeOH (20 mL), and the mixture was stirred at rt for 3 days. It was directly dry-loaded onto silica and Celite®, and the residue was purified by flash chromatography (MeOH/EtOAc) to afford the title compound (804 mg, 1.13 mmol) as a white solid.

[00399] Step 2: 4-(2-amino-2-methylpropanoyl)-N-(1-(4-(((*trans*-4-aminocyclohexyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt. A mixture of *tert*-butyl (*trans*-4-((4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)amino)cyclohexyl)carbamate (369 mg, 0.519 mmol) and 2M HCl in MeOH

(12 mL, 24 mmol) was stirred at rt for 17h. The precipitate was collected by vacuum filtration to afford the title compound (270 mg, 0.435 mmol) as a white solid. ^{1}H NMR (500 MHz, D_2O) δ 7.82 (d, 1H), 7.51 (d, 2H), 7.39 (d, 2H), 6.70 (d, 1H), 4.22 (s, 2H), 3.51-3.76 (m, 8H), 3.06-3.21 (m, 2H), 2.15-2.24 (m, 2H), 2.02-2.10 (m, 2H), 1.58 (s, 6H), 1.33-1.52 (m, 4H). LCMS [M+H] 511.4.

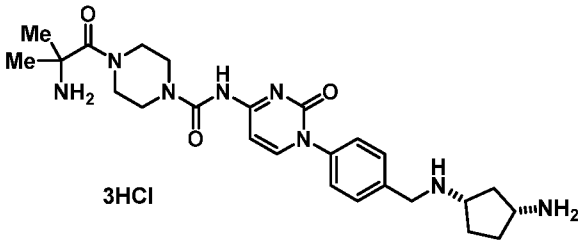
Compound 112



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((azetidin-3-ylmethyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00400] Prepared in a similar fashion to Scheme C-1 using *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl 3-(aminomethyl)azetidine-1-carboxylate. ^{1}H NMR (400 MHz, D_2O) δ 7.78 (d, 1H), 7.49 (d, 2H), 7.38 (d, 2H), 6.69 (d, 1H), 4.18 (s, 2H), 4.09 (t, 2H), 3.90 (t, 2H), 3.72-3.55 (m, 8H), 3.35-3.31 (m, 2H), 3.30-3.18 (m, 1H), 1.56 (s, 6H). LCMS [M+H] 483.

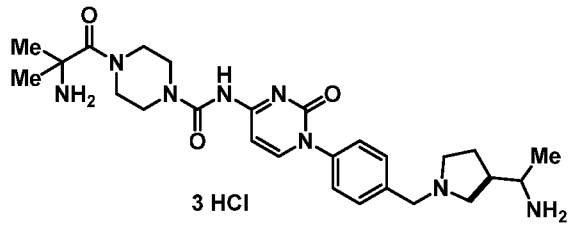
Compound 114



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((((1S,3R)-3-aminocyclopentyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00401] Prepared in a similar fashion to Scheme C-1 using *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl ((1R,3S)-3-aminocyclopentyl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.81 (d, 1H), 7.50 (d, 2H), 7.38 (d, 2H), 6.69 (d, 1H), 4.20 (s, 2H), 3.68-3.57 (m, 9H), 2.63-2.55 (m, 1H), 2.17-2.04 (m, 2H), 1.85-1.63 (m, 4H), 1.59 (s, 6H). LCMS [M+H] 497.3.

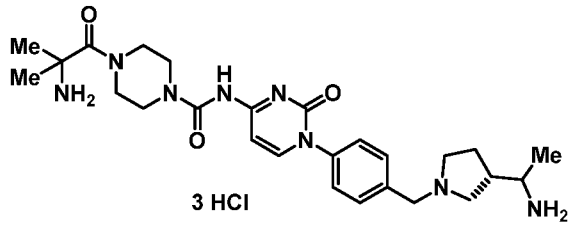
Compound 44



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((3R)-3-(1-aminoethyl)pyrrolidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00402] Prepared in a similar fashion to Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl (1-((R)-pyrrolidin-3-yl)ethyl)carbamate. ^{1}H NMR (500 MHz, D_2O) δ 8.07 (d, 1H), 7.70 (d, 2H), 7.58 (d, 2H), 6.82 (d, 1H), 4.52 (s, 2H), 3.85-3.64 (m, 8H), 3.64-3.35 (m, 3H), 3.24-3.03 (m, 1H), 2.99-2.70 (m, 1H), 2.67-2.51 (m, 1H), 2.48-2.21 (m, 1H), 2.18-2.01 (m, 1H), 1.72 (s, 6H), 1.35-1.28 (m, 3H) LCMS [M+H] 511.2.

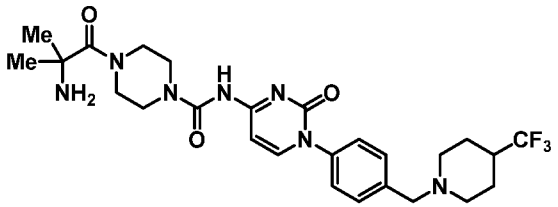
Compound 45



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((3S)-3-(1-aminoethyl)pyrrolidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00403] Prepared in a similar fashion to Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl (1-((S)-pyrrolidin-3-yl)ethyl)carbamate. ^{1}H NMR (500 MHz, D_2O) δ 8.01 (d, 1H), 7.69 (d, 2H), 7.57 (d, 2H), 6.84 (d, 1H), 4.52 (s, 2H), 3.83-3.63 (m, 8H), 3.60 (t, 1H), 3.53-3.36 (m, 2H), 3.22-3.10 (m, 1H), 2.91-2.79 (m, 1H), 2.68-2.52 (m, 1H), 2.48-2.19 (m, 1H), 2.15-2.02 (m, 1H), 1.73 (s, 6H), 1.38-1.28 (m, 3H). LCMS [M+H] 511.2.

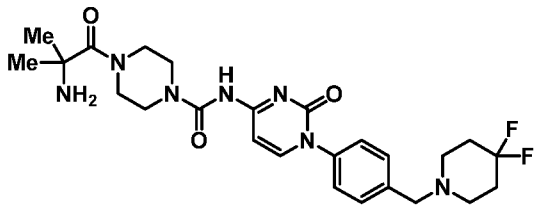
Compound 107



4-(2-Amino-2-methylpropanoyl)-*N*-(2-oxo-1-(4-((4-(trifluoromethyl)piperidin-1-yl)methyl)phenyl)-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00404] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1, 2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and 4-(trifluoromethyl)piperidine. ^{1}H NMR (500 MHz, D_2O) δ 7.99 (d, 1H), 7.69 (d, 2H), 7.58 (d, 2H), 6.85 (d, 1H), 4.44 (s, 2H), 3.83-3.75 (m, 4H), 3.74-3.70 (m, 4H), 3.68 (d, 2H), 3.13 (t, 2H), 2.66-2.60 (m, 1H), 2.22 (d, 2H), 1.88-1.78 (m, 2H), 1.74 (s, 6H). LCMS [M+H] 550.3.

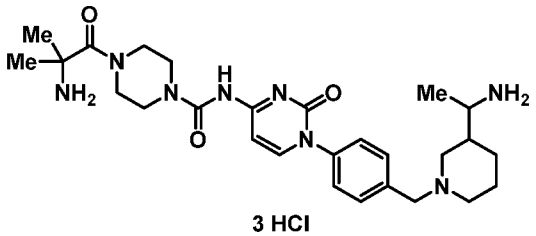
Compound 383



4-(2-Amino-2-methylpropanoyl)-*N*-(1-(4-((4,4-difluoropiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00405] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1, 2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and 4,4-difluoropiperidine. ^{1}H NMR (500 MHz, D_2O) δ 8.09 (d, 1H), 7.82 (d, 2H), 7.70 (d, 2H), 6.96 (d, 1H), 4.61 (s, 2H), 3.94-3.86 (m, 4H), 3.85-3.83 (m, 4H), 3.82-3.79 (m, 2H), 3.54-3.50 (m, 2H), 2.64-2.50 (m, 2H), 2.49-2.32 (m, 2H), 1.86 (s, 6H). LCMS [M+H] 417.3.

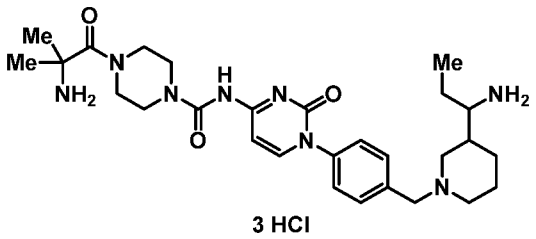
Compound 109



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((3-(1-aminoethyl)piperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00406] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1, 2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl (1-(piperidin-3-yl)ethyl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.98 (d, 1H), 7.71 (d, 2H), 7.59 (d, 2H), 6.87 (d, 1H), 4.48 (s, 2H), 3.79 (br. s, 2H), 3.74 (s, 6H), 3.60 (t, 2H), 3.35 (t, 1H), 3.11- 2.86 (m, 2H), 2.24–2.03 (m, 2H), 1.98 (t, 1H), 1.75 (s, 6H), 1.49–1.12 (m, 4H). LCMS [M+H] 525.3.

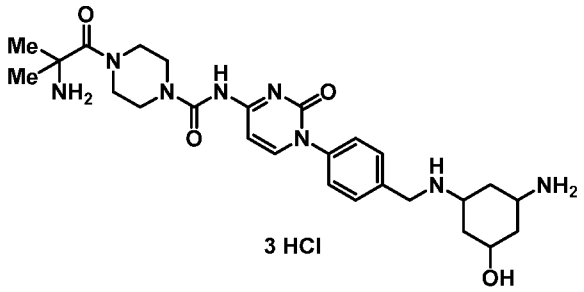
Compound 110



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((3-(1-aminopropyl)piperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00407] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1, 2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl (1-(piperidin-3-yl)propyl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 8.09 (d, 1H), 7.72 (d, 2H), 7.61 (d, 2H), 6.85 (d, 1H), 4.47 (s, 2H), 3.81 (br. s, 2H), 3.69 (br.s, 6H), 3.59 (d, 2H), 3.29–3.13 (m, 1H), 3.00 (t, 2H), 2.22 (t, 1H), 2.11 (d, 1H), 1.98 (d, 1H), 1.83–1.56 (m, 8H), 1.50–1.23 (m, 2H), 1.09–0.90 (m, 3H). LCMS [M+H] 539.2.

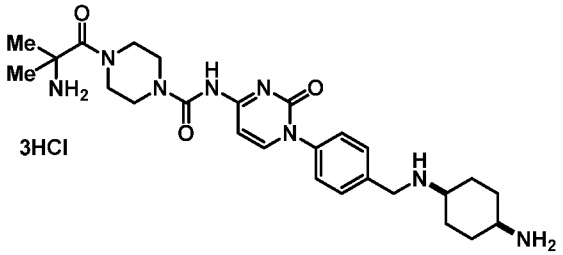
Compound 342



4-(2-amino-2-methylpropanoyl)-N-(1-(4-(((3-amino-5-hydroxycyclohexyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00408] Prepared in a similar fashion to Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1, 2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl (3-amino-5-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.89 (d, 1H), 7.55 (d, 2H), 7.41 (d, 2H), 6.70 (d, 1H), 4.27 (m, 3H), 3.79-3.76 (m, 2H), 3.63-3.50 (m, 8H), 2.34-2.23 (m, 2H), 2.00-1.72 (m, 4H), 1.58 (s, 6H). LCMS [M+H] 527.3.

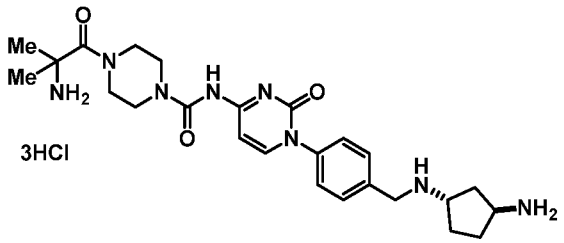
Compound 120



***cis*-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((4-aminocyclohexyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt**

[00409] Prepared in a similar fashion to Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1, 2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and 1-N-Boc-*cis*-1,4-cyclohexyldiamine. ^{1}H NMR (400 MHz, D_2O) δ 7.77 (d, 1H), 7.53 (d, 2H), 7.39 (d, 2H), 6.72 (d, 1H), 4.25 (s, 2H), 3.68-6.55 (m, 8H), 3.47-3.40 (m, 1H), 3.34-3.28 (m, 1H), 1.99-1.92 (m, 2H), 1.85-1.65 (m, 6H), 1.58 (s, 6H). LCMS [(M+2H)/2] 256.2.

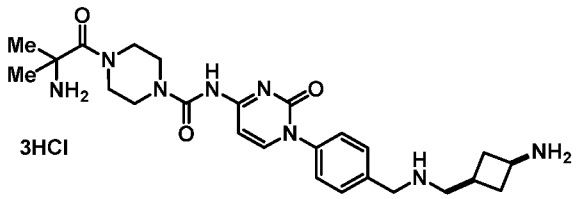
Compound 123



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((((1S,3S)-3-aminocyclopentyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00410] Prepared in a similar fashion to Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1, 2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl ((1S,3S)-3-aminocyclopentyl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.79 (d, 1H), 7.52 (d, 2H), 7.40 (d, 2H), 6.73 (d, 1H), 4.22 (s, 2H), 3.82-3.73 (m, 2H), 3.68-3.55 (m, 8H), 2.32-2.15 (m, 4H), 1.78-1.60 (m, 2H), 1.57 (s, 6H). LCMS [(M+2H/2] 249.0.

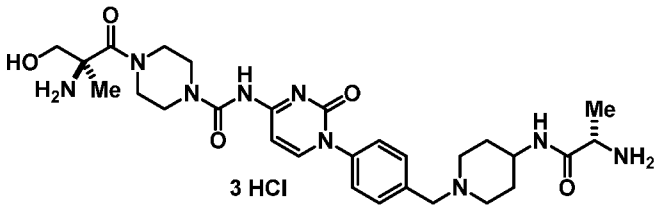
Compound 126



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((((*cis*-3-aminocyclobutyl)methyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00411] Prepared in a similar fashion to Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1, 2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl (*cis*-3-(aminomethyl)cyclobutyl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.81 (d, 1H), 7.49 (d, 2H), 7.38 (d, 2H), 6.70 (d, 1H), 4.15 (s, 2H), 3.68-3.57 (m, 8H), 3.10-3.05 (m, 2H), 2.49-2.35 (m, 4H), 1.88-1.79 (m, 2H), 1.57 (s, 6H). LCMS [(M+2H)/2] 249.1.

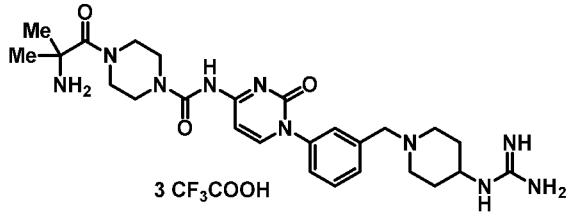
Compound 100



4-((*S*)-2-Amino-3-hydroxy-2-methylpropanoyl)-*N*-(1-(4-((4-((*S*)-2-aminopropanamido)piperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00412] Prepared in a similar fashion to Scheme C-1 from *tert*-butyl (2R,4S)-2-(*tert*-butyl)-4-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazine-1-carbonyl)-4-methyloxazolidine-3-carboxylate and *tert*-butyl (S)-(1-oxo-1-(piperidin-4-ylamino)propan-2-yl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 8.01 (d, 1H), 7.72 (d, 2H), 7.60 (d, 2H), 6.87 (d, 1H), 4.47 (d, 2H), 4.19 (d, 1H), 4.09–3.98 (m, 1H), 3.93 (d, 1H), 3.87-3.70 (m, 8H), 3.65 (d, 2H), 3.22 (t, 2H), 2.23 (d, 2H), 1.85–1.74 (m, 1H), 1.71 (s, 3H), 1.54 (d, 3H), 1.12 (d, 2H). LCMS [M+H] 584.4.

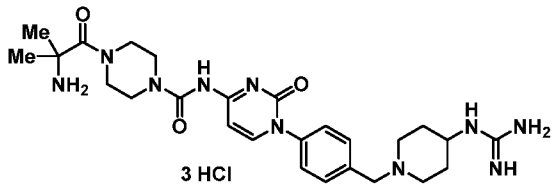
Compound 102



4-(2-Amino-2-methylpropanoyl)-*N*-(1-(3-((4-guanidinopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide trifluoroacetate salt

[00413] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(3-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and 1,2-bis(*tert*-butoxycarbonyl)-3-(piperidin-4-yl)guanidine. LCMS [M+H] 539.4.

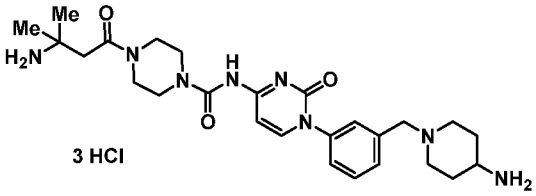
Compound 105



4-(2-Amino-2-methylpropanoyl)-*N*-(1-(4-((4-guanidinopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt.

[00414] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and 1,2-bis(*tert*-butoxycarbonyl)-3-(piperidin-4-yl)guanidine . ^{1}H NMR (500 MHz, CD_3OD) δ 7.75 (d, 1H), 7.71 (d, 2H), 7.57 (d, 2H), 6.65 (s, 1H), 4.43 (s, 2H), 3.76-3.65 (m, 9H), 3.60 (d, 2H), 3.16 (dd, 2H), 2.21 (d, 2H), 1.93-1.81 (m, 2H), 1.70 (s, 6H). LCMS [M+H] 539.4.

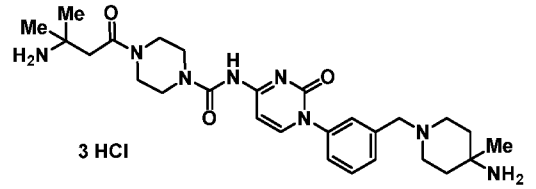
Compound 362



4-(3-Amino-3-methylbutanoyl)-N-(1-(3-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00415] Prepared in a similar fashion to Scheme C-1 from *tert*-butyl (4-(4-((1-(3-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-4-oxobutan-2-yl)carbamate and *tert*-butyl piperidin-4-ylcarbamate. ^{1}H NMR (400 MHz, CD_3OD) δ 8.47 (d, 1H), 7.88 (s, 1H), 7.79 (t, 1H), 7.71 (d, 2H), 6.86 (d, 1H), 4.48 (s, 2H), 3.86–3.69 (m, 8H), 3.64 (d, 2H), 3.53 (t, 1H), 3.26 (t, 2H), 2.84 (s, 2H), 2.29 (d, 2H), 2.11 (q, 2H), 1.45 (s, 6H). LCMS [M+H] 511.3.

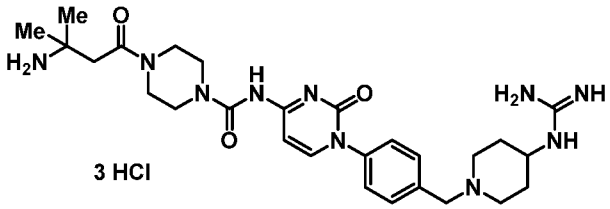
Compound 363



4-(3-Amino-3-methylbutanoyl)-N-(1-(3-((4-amino-4-methylpiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00416] Prepared in a similar fashion to Scheme C-1 from *tert*-butyl (4-(4-((1-(3-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-4-oxobutan-2-yl)carbamate and *tert*-butyl (4-methylpiperidin-4-yl)carbamate. ^{1}H NMR (400 MHz, CD_3OD) δ 8.53 (d, 1H), 7.91 (s, 1H), 7.82 (s, 1H), 7.71 (d, 2H), 6.89 (s, 1H), 4.55 (s, 2H), 3.89-3.63 (m, 8H), 3.54 (s, 2H), 3.47–3.33 (m, 2H), 2.86 (d, 2H), 2.28 (d, 2H), 2.18–2.00 (m, 2H), 1.59 (s, 3H), 1.46 (s, 6H). LCMS [M+H] 525.3.

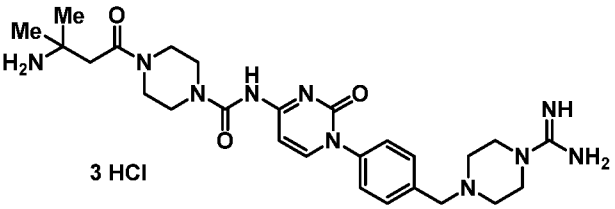
Compound 350



4-(3-Amino-3-methylbutanoyl)-N-(1-(4-((4-guanidinopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00417] Prepared in a similar fashion to Scheme C-1 from *tert*-butyl (4-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-4-oxobutan-2-yl)carbamate and 1,2-bis(*tert*-butoxycarbonyl)-3-(piperidin-4-yl)guanidine. ^{1}H NMR (400 MHz, CD_3OD) δ 8.42 (d,1H), 7.86 (d, 2H), 7.68 (d, 2H), 6.89 (d, 1H), 3.96 (s, 2H), 3.90-3.64 (m, 9H), 3.58 (d, 2H), 3.25 (d, 2H), 2.84 (s, 2H), 2.28–2.16 (m, 2H), 1.95 (d, 2H), 1.48–1.38 (m, 6H). LCMS [M+H] 553.3.

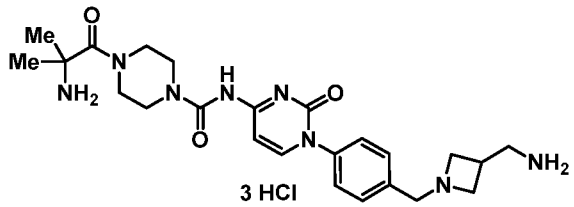
Compound 351



4-(3-Amino-3-methylbutanoyl)-N-(1-(4-((4-carbamimidoylpiperazin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00418] Prepared in a similar fashion to Scheme C-1 from *tert*-butyl (4-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-4-oxobutan-2-yl)carbamate and 1-[N,N'-bis(*tert*-butoxycarbonyl)amidino]piperazine. ^{1}H NMR (400 MHz, CD_3OD) δ 8.37 (d, 1H), 7.89 (d, 2H), 7.69 (d, 2H), 6.87 (d, 1H), 3.97 (s, 2H), 3.91–3.52 (m, 16H), 2.84 (s, 2H), 1.52–1.41 (m, 6H). LCMS [M+H] 539.3.

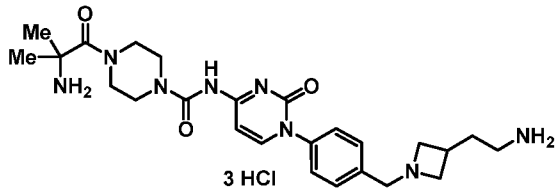
Compound 133



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((3-(aminomethyl)azetidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00419] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl (azetidin-3-ylmethyl)carbamate. ^{1}H NMR (500 MHz, CD_3OD) δ 8.35 (d, 1H), 7.77 (m, 2H), 7.60-7.68 (m, 2H), 6.82 (d, 1H), 4.56 (m, 2H), 4.34-4.42 (m, 1H), 4.16-4.29 (m, 2H), 4.06-4.14 (m, 1H), 3.78 (m, 8H), 3.38-3.43 (m, 1H), 3.32-3.36 (m, 1H), 3.18-3.28 (m, 1H), 1.71 (s, 6H). LCMS [M+H] 483.3.

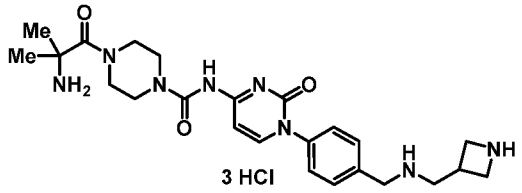
Compound 134



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((3-(2-aminoethyl)azetidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00420] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl (2-(azetidin-3-yl)ethyl)carbamate hydrochloride. ^{1}H NMR (500 MHz, CD_3OD) δ 8.33-8.44 (m, 1H), 7.77 (m, 2H), 7.59-7.70 (m, 2H), 6.80-6.90 (m, 1H), 4.52 (m, 2H), 4.28-4.36 (m, 1H), 4.18-4.27 (m, 1H), 4.05-4.15 (m, 1H), 3.93-4.02 (m, 1H), 3.78 (m, 8H), 2.95-3.08 (m, 1H), 2.84-2.95 (m, 2H), 2.10-2.18 (m, 1H), 2.03-2.10 (m, 1H), 1.71 (s, 6H). LCMS [M+H] 497.3.

Compound 374

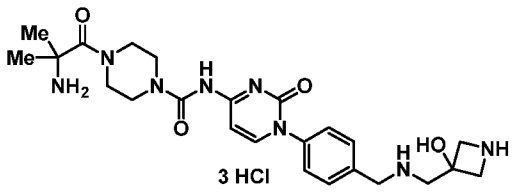


4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((azetidin-3-ylmethyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00421] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-

oxopropan-2-yl)carbamate and *tert*-butyl 3-(aminomethyl)azetidine-1-carboxylate. ^{1}H NMR (500 MHz, D_2O) δ 7.79 (d, 1H), 7.51 (d, 2H), 7.40 (d, 2H), 6.71 (d, 1H), 4.20 (s, 2H), 4.07-4.16 (m, 2H), 3.87-3.96 (m, 2H), 3.50-3.72 (m, 8H), 3.34 (d, 2H), 3.22-3.31 (m, 1H), 1.58 (s, 6H). LCMS [M+H] 483.4.

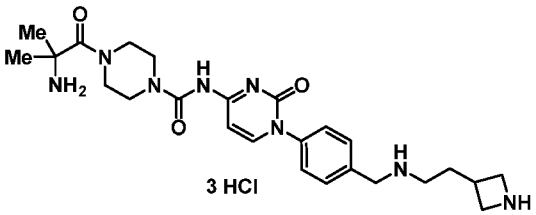
Compound 376



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((((3-hydroxyazetidin-3-yl)methyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00422] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl 3-(aminomethyl)-3-hydroxyazetidine-1-carboxylate. ^{1}H NMR (500 MHz, D_2O) δ 7.80 (d, 1H), 7.55 (d, 2H), 7.42 (d, 2H), 6.73 (d, 1H), 4.28 (s, 2H), 4.13 (d, 2H), 4.04 (d, 2H), 3.51-3.72 (m, 8H), 3.42 (s, 2H), 1.59 (s, 6H). LCMS [M+H] 499.4.

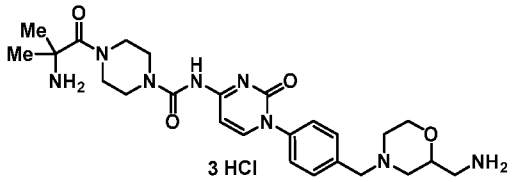
Compound 375



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((2-(azetidin-3-yl)ethyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00423] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl 3-(2-aminoethyl)azetidine-1-carboxylate. ^{1}H NMR (500 MHz, D_2O) δ 7.78 (d, 1H), 7.50 (d, 2H), 7.39 (d, 2H), 6.71 (d, 1H), 4.18 (s, 2H), 4.00 - 4.09 (m, 2H), 3.70 - 3.79 (m, 2H), 3.50 - 3.70 (m, 8H), 2.83 - 2.96 (m, 3H), 1.91 - 2.00 (m, 2H), 1.58 (s, 6H). LCMS [M+H] 497.3.

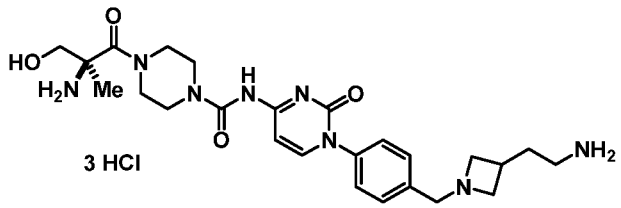
Compound 135



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((2-(aminomethyl)morpholino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00424] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl (morpholin-2-ylmethyl)carbamate. ^{1}H NMR (500 MHz, CD_3OD) δ 8.32-8.41 (m, 1H), 7.87 (d, 2H), 7.68 (d, 2H), 6.82-6.89 (m, 1H), 4.46-4.59 (m, 2H), 4.15-4.26 (m, 2H), 3.97-4.07 (m, 1H), 3.69-3.86 (m, 8H), 3.44-3.58 (m, 2H), 3.26-3.36 (m, 1H), 3.16-3.25 (m, 1H), 3.05-3.15 (m, 1H), 2.95-3.04 (m, 1H), 1.71 (s, 6H). LCMS [M+H] 513.3.

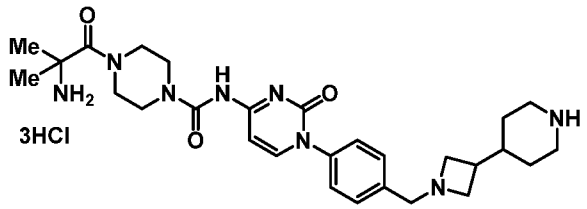
Compound 136



(S)-4-(2-Amino-3-hydroxy-2-methylpropanoyl)-N-(1-(4-((3-(2-aminoethyl)azetidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00425] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (2R,4S)-2-(*tert*-butyl)-4-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazine-1-carbonyl)-4-methyloxazolidine-3-carboxylate and *tert*-butyl (2-(azetidin-3-yl)ethyl)carbamate hydrochloride. ^{1}H NMR (500 MHz, D_2O) δ 7.44 (d, 1H), 7.33 (d, 2H), 7.22 (d, 2H), 6.28 (d, 1H), 3.45-3.76 (m, 11H), 3.41 (d, 1H), 3.28 (dd, 1H), 3.14-3.24 (m, 2H), 3.02-3.11 (m, 1H), 2.70 (dd, 1H), 2.48-2.54 (m, 1H), 2.29-2.40 (m, 1H), 1.98-2.08 (m, 1H), 1.43-1.54 (m, 1H), 1.22 (s, 3H). LCMS [M+H] 513.3.

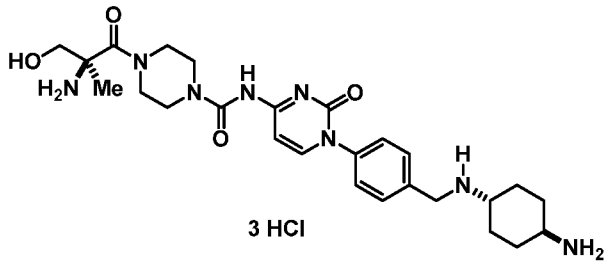
Compound 377



4-(2-Amino-2-methylpropanoyl)-N-(2-oxo-1-(4-((3-(piperidin-4-yl)azetidin-1-yl)methyl)phenyl)-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00426] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl 4-(azetidin-3-yl)piperidine-1-carboxylate. ^{1}H NMR (400 MHz, D_2O) δ 8.23 (d, 1H), 7.67 (d, 2H), 7.60 (d, 2H), 6.82 (d, 1H), 4.46 (s, 2H), 4.29-4.43 (m, 2H), 4.42-4.04 (m, 2H), 3.83-3.76 (m, 8H), 3.45 (d, 2H), 3.01 (t, 2H), 2.83-2.75 (m, 1H), 2.04-1.84 (m, 3H), 1.74 (s, 6H), 1.39-1.28 (m, 2H). LC-MS [M+H] 537.3.

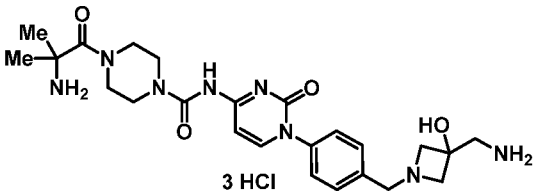
Compound 288



4-((*S*)-2-Amino-3-hydroxy-2-methylpropanoyl)-N-(1-(4-(((*trans*-4-aminocyclohexyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00427] Prepared in a similar fashion as Scheme C-1 using *tert*-butyl (2R,4S)-2-(*tert*-butyl)-4-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazine-1-carbonyl)-4-methyloxazolidine-3-carboxylate and *tert*-butyl (*trans*-4-aminocyclohexyl)carbamate. ^{1}H NMR (500 MHz, D_2O) δ 7.94 (d, 1H), 7.63 (d, 2H), 7.51 (d, 2H), 6.83 (d, 1H), 4.34 (s, 2H), 4.14 (d, 1H), 3.87 (d, 1H), 3.76–3.69 (m, 8H), 3.32–3.21 (m, 2H), 2.32 (d, 2H), 2.19 (d, 2H), 1.66 (s, 3H), 1.62–1.48 (m, 4H). LCMS [M+H] 527.3.

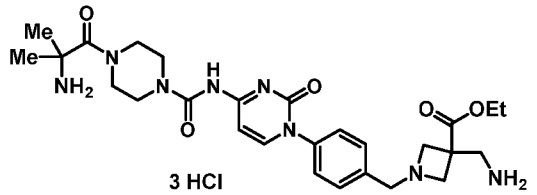
Compound 137



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((3-(aminomethyl)-3-hydroxyazetidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00428] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl ((3-hydroxyazetidin-3-yl)methyl)carbamate. ^{1}H NMR (500 MHz, D_2O) δ 7.78 (d, 1H), 7.47-7.56 (m, 2H), 7.42 (d, 2H), 6.71 (d, 1H), 4.36-4.51 (m, 2H), 4.24-4.33 (m, 2H), 4.01-4.20 (m, 2H), 3.51-3.72 (m, 8H), 3.29 (s, 2H), 1.59 (s, 6H). LCMS [M+H] 499.3.

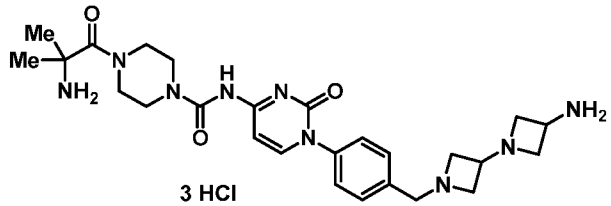
Compound 201



Ethyl 1-(4-(4-(4-(2-amino-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)-3-(aminomethyl)azetidine-3-carboxylate hydrochloride salt

[00429] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and ethyl 3-((((benzyloxy)carbonyl)amino)methyl)azetidine-3-carboxylate trifluoroacetate salt. ^{1}H NMR (500 MHz, CD_3OD) δ 7.69 (d, 1H), 7.45 (d, 2H), 7.38 (d, 2H), 6.52-6.72 (m, 1H), 4.21 (q, 2H), 3.61-3.88 (m, 12H), 3.50 (d, 2H), 3.11 (s, 2H), 1.42 (s, 6H), 1.29 (t, 3H). LCMS [M+H] 555.3.

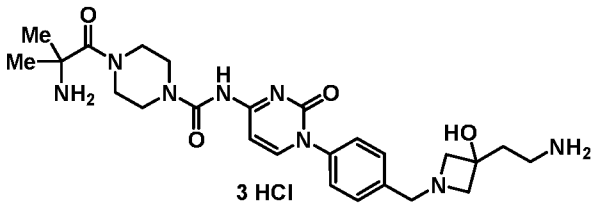
Compound 380



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((3-amino-[1,3'-biazetidin]-1'-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00430] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl [1,3'-biazetidin]-3-ylcarbamate. ^{1}H NMR (500 MHz, D_2O) δ 7.60 (d, 1H), 7.29 (d, 2H), 7.24 (d, 2H), 6.54 (d, 1H), 3.46-3.73 (m, 10H), 3.34-3.44 (m, 3H), 3.21-3.33 (m, 3H), 2.93 (t, 2H), 2.69-2.80 (m, 2H), 1.32 (s, 6H). LCMS [M+H] 524.2.

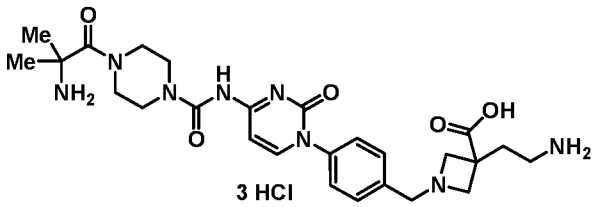
Compound 205



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((3-(2-aminoethyl)-3-hydroxyazetidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00431] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and 2,2,2-trifluoro-N-(2-(3-hydroxyazetidin-3-yl)ethyl)acetamide trifluoroacetate salt. ^{1}H NMR (500 MHz, D_2O) δ 7.81 (d, 1H), 7.46-7.54 (m, 2H), 7.41 (d, 2H), 6.70 (d, 1H), 4.33-4.46 (m, 2H), 4.13-4.21 (m, 2H), 3.95-4.10 (m, 2H), 3.48-3.74 (m, 8H), 2.90-3.03 (m, 2H), 2.04-2.14 (m, 2H), 1.58 (s, 6H). LCMS [M+H] 513.3.

Compound 369

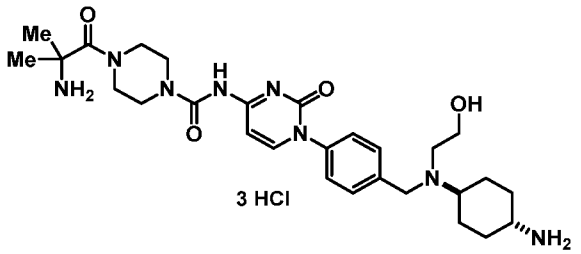


1-(4-(4-(4-(2-Amino-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)-3-(2-aminoethyl)azetidine-3-carboxylic acid hydrochloride salt

[00432] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl 3-(2-((*tert*-butoxycarbonyl)amino)ethyl)azetidine-3-

carboxylate. ^{1}H NMR (500 MHz, CD_3OD) δ 7.71-7.86 (m, 1H), 7.61-7.70 (m, 2H), 7.48-7.59 (m, 2H), 5.78-5.84 (m, 1H), 4.38-4.59 (m, 4H), 4.17-4.34 (m, 2H), 3.58-3.86 (m, 7H), 3.41-3.51 (m, 1H), 2.88-3.02 (m, 2H), 2.32-2.48 (m, 2H), 1.69 (s, 6H). LCMS [M+H] 541.4.

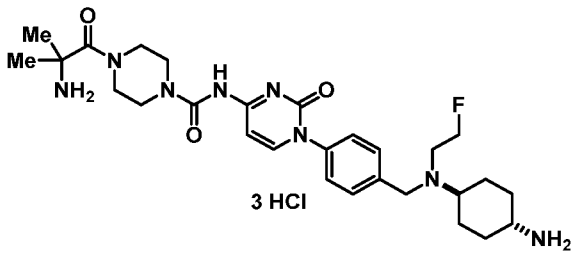
Compound 132



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((*trans*-4-aminocyclohexyl)(2-hydroxyethyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00433] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl (*trans*-4-((2-((*tert*-butyldimethylsilyl)oxy)ethyl)amino)cyclohexyl)carbamate. ^{1}H NMR (500 MHz, D_2O) δ 7.85 (d, 1H), 7.60 (d, 2H), 7.45 (d, 2H), 6.73 (d, 1H), 4.36-4.48 (m, 2H), 3.54-3.81 (m, 10H), 3.32-3.44 (m, 2H), 3.06-3.20 (m, 2H), 2.02-2.28 (m, 4H), 1.67-1.82 (m, 2H), 1.60 (s, 6H), 1.35-1.51 (m, 2H). LCMS [M+H] 555.3.

Compound 138

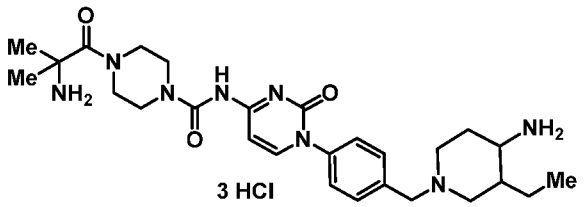


4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((*trans*-4-aminocyclohexyl)(2-fluoroethyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00434] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl (*trans*-4-((2-fluoroethyl)amino)cyclohexyl)carbamate. ^{1}H NMR (500 MHz, D_2O) δ 7.83-7.92 (m, 1H), 7.55-7.66 (m, 2H), 7.41-7.53 (m, 2H), 6.69-6.77 (m, 1H), 4.35-4.54 (m, 2H), 3.49-3.80 (m,

10H), 3.36-3.48 (m, 2H), 3.09-3.28 (m, 2H), 2.05-2.28 (m, 4H), 1.68-1.85 (m, 2H), 1.61 (s, 6H), 1.36-1.52 (m, 2H). LCMS [M+H] 557.2.

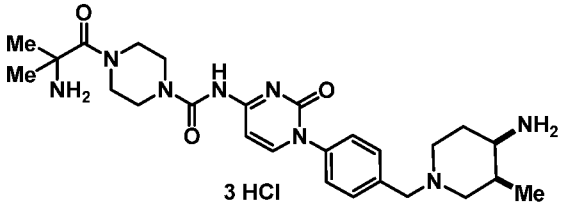
Compound 319



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((4-amino-3-ethylpiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00435] Prepared in a similar fashion to Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1, 2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl (3-ethylpiperidin-4-yl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.78 (d, 1H), 7.56 (d, 2H), 7.43 (d, 2H), 6.73 (d, 1H), 4.36-4.28 (m, 2H), 3.61-3.58 (m, 6H), 3.08-3.04 (m, 2H), 2.92-2.86 (m, 1H), 2.20-2.04 (m, 3H), 1.59 (s, 6H), 1.39 (m, 1H) 1.28 (s, 2H), 0.84-0.72 (m, 4H). LCMS [M+H] 525.4.

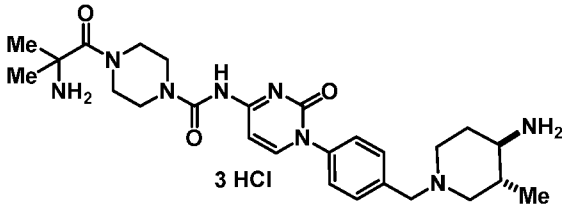
Compound 297



***cis*-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((4-amino-3-methylpiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt**

[00436] Prepared in a similar fashion to Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1, 2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *cis-tert*-butyl (3-methylpiperidin-4-yl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.78 (d, 1H), 7.52 (s, 2H), 7.41 (d, 2H), 6.69 (d, 1H), 4.33-4.22 (m, 2H), 3.61-3.48 (m, 11H), 3.31 (t, 2H), 3.20 (d, 1H), 3.02 (d, 1H), 2.85 (t, 1H), 2.44 (bs, 1H) 2.11 (s, 1H), 1.99 (s, 1H), 1.56 (s, 6H), 2.85 (t, 1H), 0.98 (d, 2H) 0.90 (d, 2H). LCMS [M+H] 511.3.

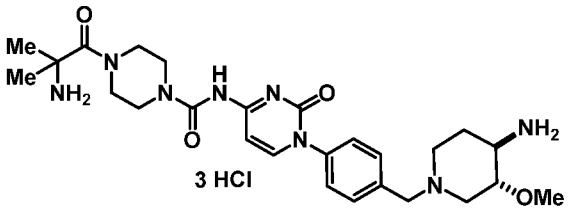
Compound 296



***trans*-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((4-amino-3-methylpiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt**

[00437] Prepared in a similar fashion to Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1, 2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *trans-tert*-butyl (3-methylpiperidin-4-yl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.8 (d, 1H), 7.55 (d, 2H), 7.44 (d, 2H), 6.73 (d, 1H), 4.35-4.26 (m, 2H), 3.64-3.59 (m, 8H), 3.5 (d, 1H), 3.40 (d, 1H), 3.24-2.98 (m, 3H), 2.81 (t, 1H), 2.22 (d, 1H) 2.04-1.98 (m, 2H), 1.86-1.65 (m, 2H) 1.55 (s, 6H), 0.96-0.88 (m, 3H). LCMS [M+H] 511.3.

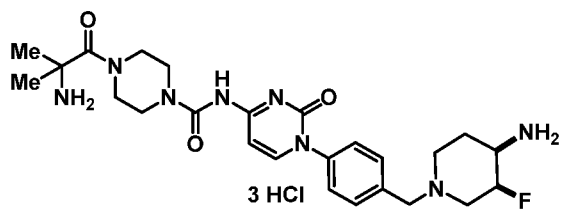
Compound 300



***trans*-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((4-amino-3-methoxypiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt**

[00438] Prepared in a similar fashion to Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1, 2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *trans*-4-(Boc-amino)-3-methoxypiperidine. ^{1}H NMR (400 MHz, D_2O) δ 7.76 (d, 1H), 7.55 (d, 2H), 7.42 (d, 2H), 6.72 (d, 1H), 4.35-4.26 (m, 2H), 3.85-3.70 (m, 1H), 3.65-3.49 (m, 10H), 3.42-3.29 (m, 4H), 3.07 (t, 1H), 2.88-2.81 (m, 1H), 2.25 (d, 1H) 1.91-1.75 (m, 1H), 1.57 (s, 6H). LCMS [M+H] 527.8.

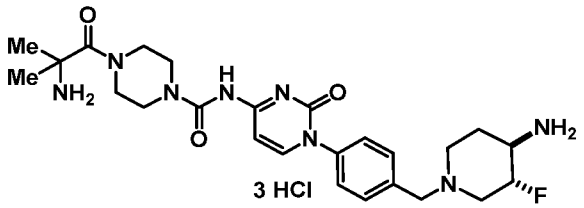
Compound 336



***cis*-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((4-amino-3-fluoropiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt**

[00439] Prepared in a similar fashion to Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1, 2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *cis*-4-(Boc-amino)-3-fluoropiperidine. ^{1}H NMR (400 MHz, D_2O) δ 7.78 (d, 1H), 7.54 (d, 2H), 7.42 (d, 2H), 6.71 (d, 1H), 5.22 (s, 1H), 5.11 (m, 1H), 4.36 (s, 2H), 3.84 (t, 1H), 3.71-3.56 (m, 8H), 3.49-3.30 (m, 2H), 3.18-3.12 (m, 1H) 2.14-2.05 (m, 2H), 1.57 (s, 6H). LCMS [M+H] 515.3.

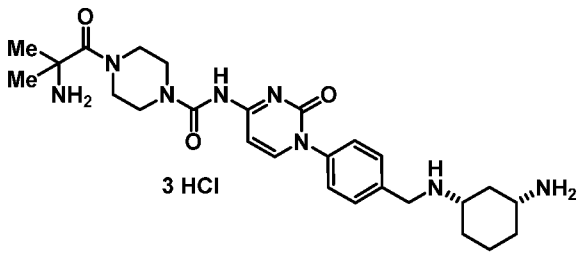
Compound 344



***trans*-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((4-amino-3-fluoropiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt**

[00440] Prepared in a similar fashion to Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1, 2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *trans*-4-(Boc-amino)-3-fluoropiperidine. ^{1}H NMR (400 MHz, D_2O) δ 7.86 (d, 1H), 7.59 (d, 2H), 7.47 (d, 2H), 6.73 (d, 1H), 4.82-4.81 (m, 1H), 4.49-4.38 (m, 2H), 3.82-3.79 (m, 1H), 3.65-3.53 (m, 10H), 3.24-3.15 (m, 2H), 2.39-3.35 (m, 1H), 1.96-1.86 (m, 1H) 1.60 (s, 6H). LCMS [(M+2H)/2] 258.3.

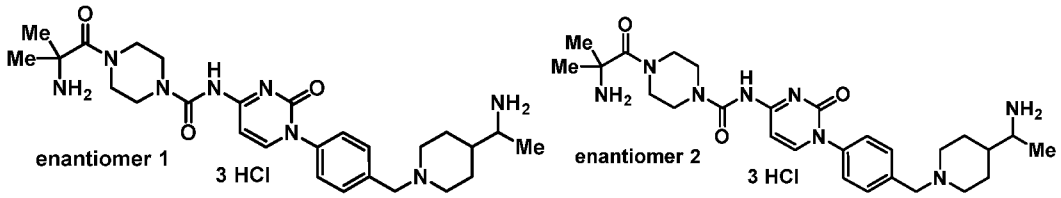
Compound 320



***cis*-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((3-aminocyclohexyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt**

[00441] Prepared in a similar fashion to Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1, 2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *cis-tert*-butyl (3-aminocyclohexyl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.83 (d, 1H), 7.52 (d, 2H), 7.40 (d, 2H), 6.72 (d, 1H), 5.75-5.55 (m, 1H), 4.25 (s, 2H), 3.75-3.59 (m, 8H), 3.33-3.19 (m, 2H), 2.51-2.40 (m, 1H), 2.13 (bs, 1H), 2.05-1.89 (m, 3H) 1.59 (s, 6H), 1.52-1.43 (m, 2H), 1.30-1.19 (m, 4H). LCMS [M+H] 511.3.

Compounds 298 and 299



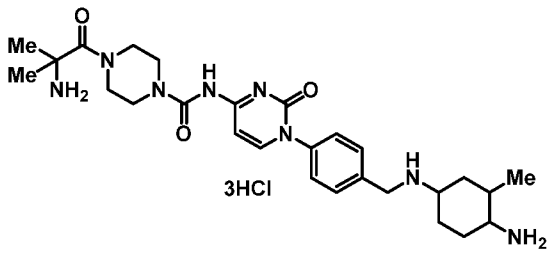
4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((4-(1-aminoethyl)piperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00442] Prepared in a similar fashion to Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1, 2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl (1-(piperidin-4-yl)ethyl)carbamate. Prior to Boc-deprotection the two enantiomers were separated by Chiral Prep-HPLC and used separately in the final step.

Isomer 1: ^{1}H NMR (400 MHz, D_2O) δ 7.76 (t, 1H), 7.52 (t, 2H), 7.42 (t, 2H), 6.71 (t, 1H), 4.25 (d, 2H), 3.61-3.56 (m, 9H), 3.5 (d, 4H), 3.16-3.14 (m, 1H), 2.91 (bs, 2H), 1.89 (bs, 2H), 1.81 (s, 1H) 1.28 (s, 2H), 1.55 (d, 5H) 1.43 (s, 2H), 1.15-1.08 (m, 4H). LCMS [M+H] 525.3.

Isomer 2: ^{1}H NMR (400 MHz, D_2O) δ 7.80 (d, 1H), 7.52 (s, 2H), 7.40 (d, 2H), 6.69 (d, 1H), 4.24 (s, 3H), 4.12-4.06 (m, 2H), 3.58-3.48 (m, 5H), 3.13 (bs, 2H), 2.92 (bs, 3H), 1.79-1.87 (m, 4H), 1.56 (s, 6H) 1.12 (s, 8H), 0.71 (s, 3H). LCMS [M+H] 525.5.

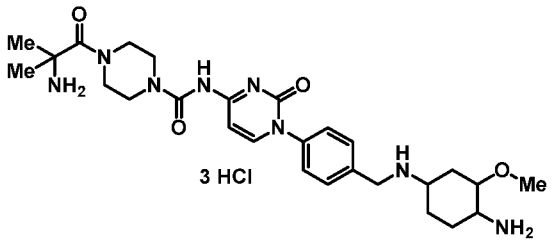
Compound 335



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((4-amino-3-methylcyclohexyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00443] Prepared in a similar fashion to Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl (4-amino-2-methylcyclohexyl)carbamate (prepared according to WO2012101062A1). ^{1}H NMR (400 MHz, D_2O) Mixture of diastereomers δ 7.83 (d, 1H), 7.55 (d, 2H), 7.44 (d, 2H), 6.76 (d, 1H), 4.29 (s, 2H), 3.67-3.56 (m, 8H), 3.28 (bs, 1H), 2.87 (bs, 1H), 2.26-2.14 (m, 2H), 2.12-2.10 (m, 2H), 1.70-1.76 (bs, 1H), 1.63 (s, 6H), 1.53-1.47 (m, 2H), 1.33 (d, 1H), 1.19 (d, 1H), 1.10 (d, 3H). LCMS [M+H] 525.3.

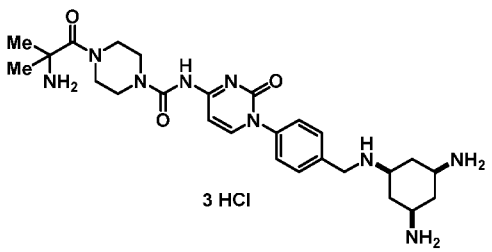
Compound 339



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((4-amino-3-methoxycyclohexyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00444] Prepared in a similar fashion to Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1, 2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl (4-amino-2-methoxycyclohexyl)carbamate (prepared according to WO2012101062A1). ^{1}H NMR (400 MHz, D_2O) Mixture of diastereomers δ 7.84 (d, 1H), 7.54 (d, 2H), 7.41 (d, 2H), 6.71 (d, 1H), 4.26 (s, 2H), 3.63-3.50 (m, 8H), 3.34 (br s, 2H), 3.29 (s, 3H), 2.27 (d, 1H), 2.10-1.95 (m, 3H), 1.79-1.76 (m, 1H), 1.58 (s, 6H), 1.51-1.46 (m, 2H). LCMS [M+H] 541.5.

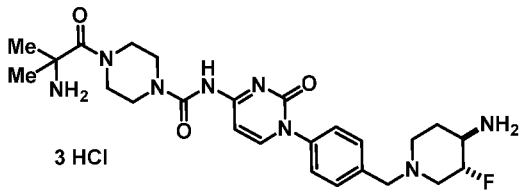
Compound 321



cis-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((3,5-diaminocyclohexyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00445] Prepared in a similar fashion to Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1, 2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *cis*-di-*tert*-butyl (5-aminocyclohexane-1,3-diyl)dicarbamate (prepared according to *J. Am. Chem. Soc.* 2004, *126*, 4543). ^{1}H NMR (400 MHz, D_2O) Mixture of rotamers δ 7.83 (d, 1H), 7.55 (d, 2H), 7.42 (d, 2H), 6.73 (d, 1H), 4.31 (s, 2H), 3.64-3.51 (m, 8H), 3.49-3.46 (m, 1H), 3.42-3.33 (m, 2H), 3.27 (m, 1H), 2.51 (d, 2H), 2.38 (d, 1H), 1.65-1.52 (m, 9H). LCMS [M+H] 526.6.

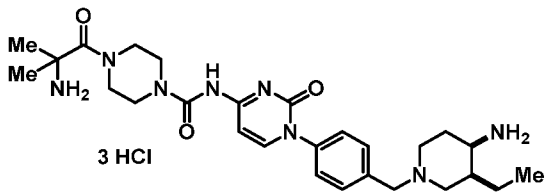
Compound 208



***trans*-4-(2-Amino-2-methylpropanoyl)-N-[1-(4-{[4-amino-3-fluoropiperidin-1-yl]methyl}phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl]piperazine-1-carboxamide hydrochloride salt**

[00446] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl ((*trans*)-3-fluoropiperidin-4-yl)carbamate to give the title compound as the hydrochloride salt (8.8 mg, 56%). ^{1}H NMR (400 MHz, D_2O) δ 7.86 (d, 1H), 7.66 (d, 2H), 7.53 (d, 2H), 6.82 (d, 1H), 5.06-4.82 (m, 1H), 4.53 (d, 1H), 4.47 (d, 1H), 3.94-3.82 (m, 1H), 3.81-3.57 (m, 10H), 3.39-3.16 (m, 2H), 2.55-2.33 (m, 1H), 2.06-1.89 (m, 1H), 1.68 (s, 6H). LCMS [M+H] 515.5.

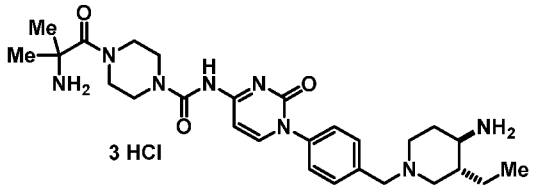
Compound 212



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((cis)-4-amino-3-ethylpiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00447] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl (3-ethylpiperidin-4-yl)carbamate. The two isomers were separated by semi-preparative HPLC on a Gemini 5 μm C18 110A AXIA (100x30 mm) column using a mobile phase of A: 10 mM ammonium bicarbonate aq. solution adjusted to pH 10 with ammonia/ B: CH_3CN, flow rate: 40 mL/min, runtime = 15.0 min., gradient: t=0 min. 10% B, t=10 min. 60% B, t = 10.5 min. 100% B, t=14.5 min. 100% B, t=15 min. 10% B. Structural assignments were performed on free bases. ^1H NMR (D_2O, 400 MHz) δ 7.90 (d, 1H), 7.66 (d, 2H), 7.53 (d, 2H), 6.81 (d, 1H), 4.51-4.30 (m, 2H), 3.81-3.43 (m, 11H), 3.26-2.90 (m, 2H), 2.38-2.00 (m, 3H), 1.68 (s, 6H), 1.54-1.30 (m, 2H), 1.00-0.72 (m, 3H). LCMS [M+H] 525.6.

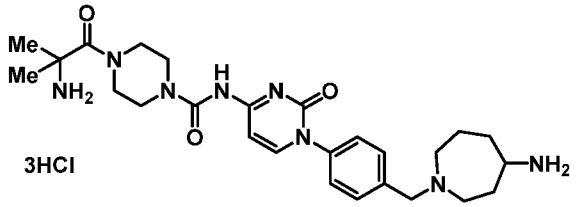
Compound 213



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((trans)-4-amino-3-ethylpiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00448] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl (3-ethylpiperidin-4-yl)carbamate. The two isomers were separated by semi-preparative HPLC on a Gemini 5 μm C18 110A AXIA (100x30 mm) column using a mobile phase of A: 10 mM ammonium bicarbonate aq. solution adjusted to pH 10 with ammonia B: CH_3CN, flow rate: 40 mL/min, runtime =15.0 min., gradient: t=0 min. 10% B, t=10 min. 60% B, t=10.5 min 100% B, t=14.5 min 100% B, t=15 min 10% B. Structural assignments were performed on free bases. ^1H NMR (D_2O, 400 MHz) δ 7.84 (d, 1H), 7.64 (d, 2H), 7.52 (d, 2H), 6.84-6.78 (m, 1H), 4.41 (d, 1H), 4.38 (d, 1H), 3.80-3.54 (m, 10H), 3.38-3.26 (m, 1H), 3.20-3.07 (m, 1H), 2.96 (t, 1H), 2.38-2.25 (m, 1H), 2.10-1.81 (m, 2H), 1.68 (s, 7H), 1.43-1.29 (m, 1H), 0.86 (t, 3H). LCMS [M+H] 525.6.

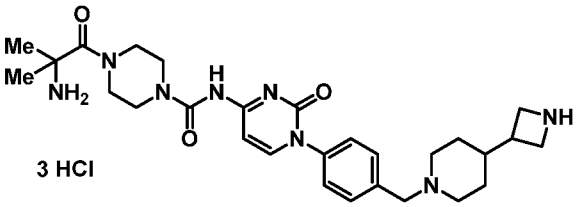
Compound 365



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((4-aminoazepan-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00449] Prepared in a similar fashion as Scheme C-1 from tert-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl azepan-4-ylcarbamate. LCMS [M+H] 511.3.

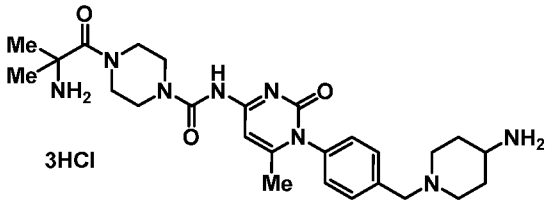
Compound 370



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((4-(azetidin-3-yl)piperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00450] Prepared in a similar fashion as Scheme C-1 from tert-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl 3-(piperidin-4-yl)azetidine-1-carboxylate. LCMS [M+H] 537.4.

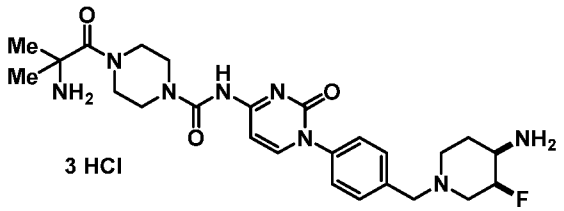
Compound 292



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-6-methyl-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00451] Prepared in a similar fashion as Scheme C-1. LCMS [M+H] 511.3.

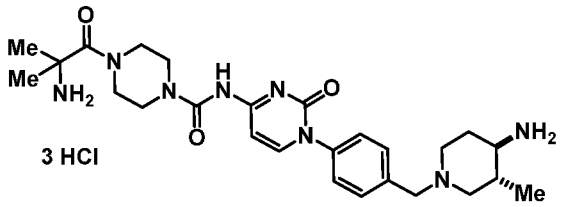
Compound 209



***cis*-4-(2-Amino-2-methylpropanoyl)-N-[1-(4-{[4-amino-3-fluoropiperidin-1-yl]methyl}phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl]piperazine-1-carboxamide hydrochloride salt**

[00452] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl ((*cis*)-3-fluoropiperidin-4-yl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.83 (d, 1H), 7.64 (d, 2H), 7.53 (d, 2H), 6.82 (d, 1H), 5.27 (d, 1H), 4.53-4.38 (m, 2H), 4.02-3.88 (m, 1H), 3.85-3.57 (m, 10H), 3.55-3.18 (m, 2H), 2.32-2.16 (m, 2H), 1.68 (s, 6H). LCMS [M+H] 515.5.

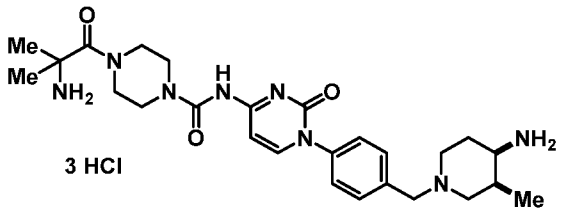
Compound 210



***trans*-4-(2-Amino-2-methylpropanoyl)-N-[1-(4-{[4-amino-3-methylpiperidin-1-yl]methyl}phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl]piperazine-1-carboxamide hydrochloride salt**

[00453] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl ((*trans*)-3-methylpiperidin-4-yl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.88 (d, 1H), 7.64 (d, 2H), 7.52 (d, 2H), 6.81 (d, 1H), 4.42 (d,1H), 4.37 (d, 1H), 3.81-3.58 (m, 9H), 3.57-3.44 (m, 1H), 3.27-3.07 (m, 2H), 2.90 (t, 1H), 2.36-2.25 (m, 1H), 2.14-2.01 (m, 1H), 1.98-1.82 (m, 1H), 1.68 (s, 6H), 1.04 (d, 3H). LCMS [M+H] 511.5.

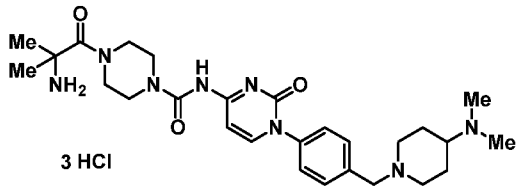
Compound 211



***cis*-4-(2-Amino-2-methylpropanoyl)-N-[1-(4-{[4-amino-3-methylpiperidin-1-yl]methyl}phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl]piperazine-1-carboxamide (racemate) hydrochloride salt**

[00454] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl ((*cis*)-3-methylpiperidin-4-yl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.85 (d, 1H), 7.64 (d, 2H), 7.52 (d, 2H), 6.82 (d,1H), 4.49-4.30 (m, 2H), 3.81-3.54 (m, 10H), 3.48-3.37 (m, 1H), 3.35-2.90 (m, 2H), 2.63-2.32 (m, 1H), 2.29-2.05 (m, 2H), 1.68 (s, 6H), 1.13-0.98 (m, 3H). LCMS [M+H] 511.5.

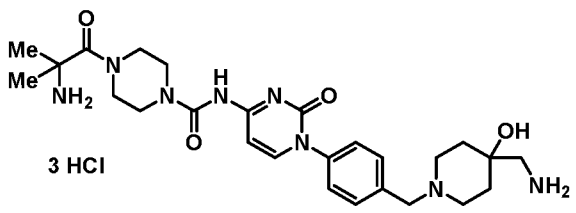
Compound 214



4-(2-Amino-2-methylpropanoyl)-N-[1-(4-{[4-(dimethylamino)piperidin-1-yl]methyl}phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl]piperazine-1-carboxamide hydrochloride salt

[00455] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and N,N-dimethylpiperidin-4-amine. ^{1}H NMR (400 MHz, D_2O) δ 7.89 (d, 1H), 7.65 (d, 2H), 7.53 (d, 2H), 6.81 (d, 1H), 4.41 (s, 2H), 3.81-3.50 (m, 11H), 3.17 (br. s., 2H), 2.86 (s, 6H), 2.36 (br s, 2H), 2.05-1.86 (m, 2H), 1.69 (s, 6H). LCMS [M+H] 525.3.

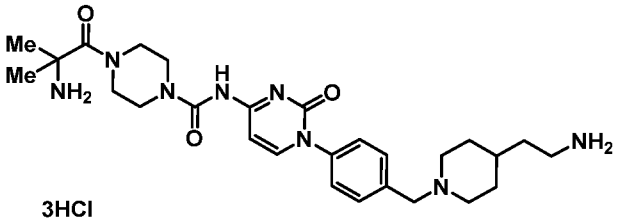
Compound 215



4-(2-Amino-2-methylpropanoyl)-N-[1-(4-{[4-(aminomethyl)-4-hydroxypiperidin-1-yl]methyl}phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl]piperazine-1-carboxamide hydrochloride salt

[00456] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl ((4-hydroxypiperidin-4-yl)methyl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.86 (d, 1H), 7.64 (d, 2H), 7.52 (d, 2H), 6.81 (d, 1H), 4.40 (s, 2H), 3.80-3.61 (m, 8H), 3.51-3.41 (m, 2H), 3.37-3.23 (m, 2H), 3.05 (s, 2H), 2.00-1.78 (m, 4H), 1.68 (s, 6H). LCMS [M+H] 527.4.

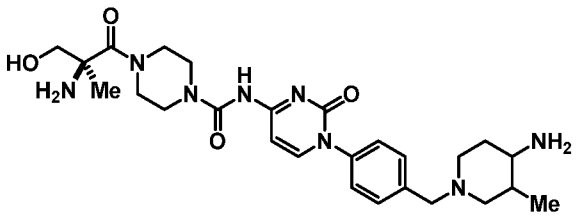
Compound 218



4-(2-Amino-2-methylpropanoyl)-N-[1-(4-{[4-(2-aminoethyl)piperidin-1-yl]methyl}phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl]piperazine-1-carboxamide hydrochloride salt

[00457] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl (2-(piperidin-4-yl)ethyl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.84 (d, 1H), 7.65-7.58 (m, 2H), 7.53-7.47 (m, 2H), 6.82 (d, 1H), 4.33 (s, 2H), 3.81-3.60 (m, 8H), 3.56-3.48 (m, 2H), 3.08-2.93 (m, 4H), 2.01-1.91 (m, 2H), 1.90-1.54 (m, 9H), 1.49-1.32 (m, 2H). LCMS [M+H] 525.4.

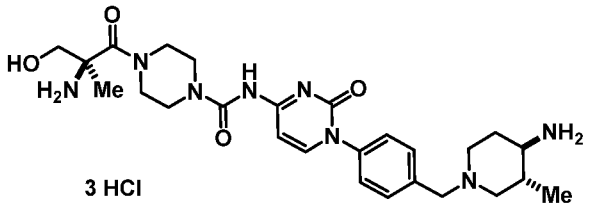
Compound 223



4-[(2S)-2-Amino-3-hydroxy-2-methylpropanoyl]-N-(1-{4-[(4-amino-3-methylpiperidin-1-yl)methyl]phenyl}-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00458] Prepared in a similar fahion as Scheme C-1 from *tert*-butyl (2R,4S)-2-(*tert*-butyl)-4-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazine-1-carbonyl)-4-methyloxazolidine-3-carboxylate and *tert*-butyl (3-methylpiperidin-4-yl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.80 (d, 1H), 7.56 (d, 2H), 7.44 (d, 2H), 6.73 (d, 1H), 4.39-4.21 (m, 2H), 4.02 (d, 1H), 3.77 (d, 1H), 3.73-2.81 (m, 13H), 2.56-2.24 (m, 1H), 2.22-1.92 (m, 2H), 1.55 (s, 3H), 1.09-0.87 (m, 3H). LCMS [M+H] 527.5.

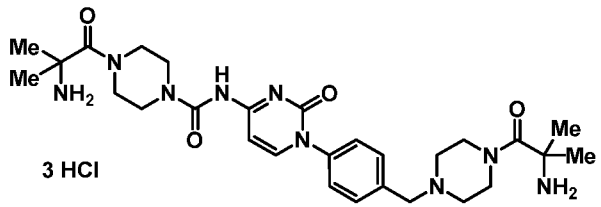
Compound 224



***trans*-4-[(2S)-2-Amino-3-hydroxy-2-methylpropanoyl]-N-(1-{4-[(4-amino-3-methylpiperidin-1-yl)methyl]phenyl}-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt**

[00459] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (2R,4S)-2-(*tert*-butyl)-4-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazine-1-carbonyl)-4-methyloxazolidine-3-carboxylate and *tert*-butyl ((*trans*)-3-methylpiperidin-4-yl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.86 (d, 1H), 7.63 (d, 2H), 7.51 (d, 2H), 6.81 (d, 1H), 4.46-4.30 (m, 2H), 4.18-3.81 (m, 2H), 3.80-3.58 (m, 8H), 3.69-3.57 (m, 1H), 3.57-3.38 (m, 1H), 3.24-3.03 (m, 2H), 2.89 (t, 1H), 2.30 (d, 1H), 2.09 (br. s., 1H), 1.90 (q, 1H), 1.63 (s, 3H), 1.16-0.83 (m, 3H). LCMS [M+H] 527.5.

Compound 225

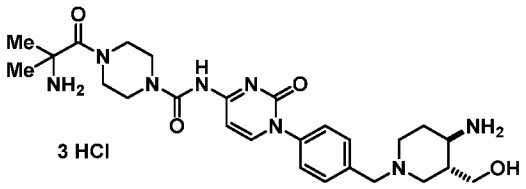


4-(2-Amino-2-methylpropanoyl)-N-[1-(4-{[4-(2-amino-2-methylpropanoyl)piperazin-1-yl]methyl}phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl]piperazine-1-carboxamide hydrochloride salt

[00460] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl (2-methyl-1-oxo-1-(piperazin-1-yl)propan-2-

yl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.84 (d, 1H), 7.64 (d, 2H), 7.53 (d, 2H), 6.82 (d, 1H), 4.43 (s, 2H), 3.85-3.26 (m, 16H), 1.68 (s, 6H), 1.66 (s, 6H). LCMS [M+H] 568.5.

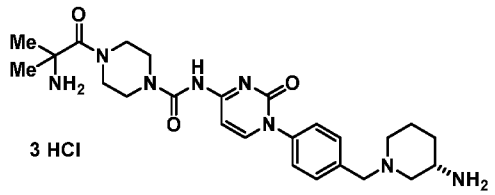
Compound 227



***trans*-4-(2-Amino-2-methylpropanoyl)-N-[1-(4-{[4-amino-3-(hydroxymethyl)piperidin-1-yl]methyl}phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl]piperazine-1-carboxamide (racemate) hydrochloride salt**

[00461] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl ((*trans*)-3-(hydroxymethyl)piperidin-4-yl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.97 (d, 1H), 7.71 (d, 2H), 7.59 (d, 2H), 6.85 (d, 1H), 4.53 (s, 2H), 3.90-3.58 (m, 13H), 3.29-3.08 (m, 2H), 2.09 (d, 2H), 1.80-1.53 (m, 7H). LCMS [M+H] 527.6.

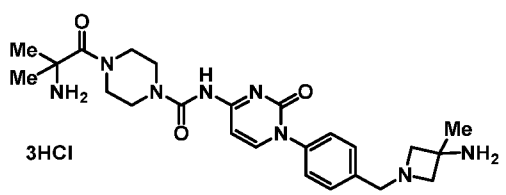
Compound 237



4-(2-Amino-2-methylpropanoyl)-N-[1-(4-{[(3S)-3-aminopiperidin-1-yl]methyl}phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl]piperazine-1-carboxamide hydrochloride salt

[00462] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and t*ert*-butyl (S)-piperidin-3-ylcarbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.84 (d, 1H), 7.64 (d, 2H), 7.53 (d, 2H), 6.82 (d, 1H), 4.47 (s, 2H), 3.77-3.62 (m, 9H), 3.62-3.49 (m, 2H), 3.20-2.92 (m, 2H), 2.25-2.15 (m, 1H), 2.13-2.04 (m, 1H), 1.87-1.72 (m, 1H), 1.71-1.56 (m, 7H). LCMS [M+H] 497.4.

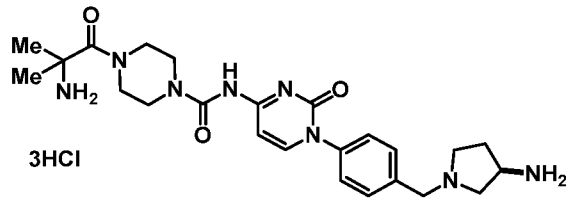
Compound 238



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((3-amino-3-methylazetidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00463] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl (3-methylazetidin-3-yl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.83 (d, 1H), 7.62-7.57 (m, 2H), 7.54-7.48 (m, 2H), 6.81 (d, 1H), 4.57-4.50 (m, 4H), 4.32-4.25 (m, 2H), 3.76-3.62 (m, 8H), 1.71 (s, 3H), 1.68 (s, 6H). LCMS [M+H] 483.4.

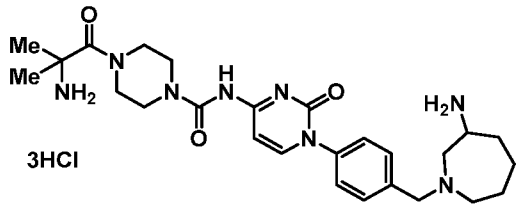
Compound 239



4-(2-Amino-2-methylpropanoyl)-N-[1-(4-{[(3R)-3-aminopyrrolidin-1-yl]methyl}phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl]piperazine-1-carboxamide hydrochloride salt

[00464] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl (R)-pyrrolidin-3-ylcarbamate.^{1}H NMR (400 MHz, D_2O) δ 7.85 (d, 1H), 7.65 (d, 2H), 7.52 (d, 2H), 6.81 (d, 1H), 4.53 (s, 2H), 4.27-4.12 (m, 1H), 4.00-3.40 (m, 12H), 2.69-2.52 (m, 1H), 2.30-2.12 (m, 1H), 1.67 (s, 6H). LCMS [M+H] 483.4.

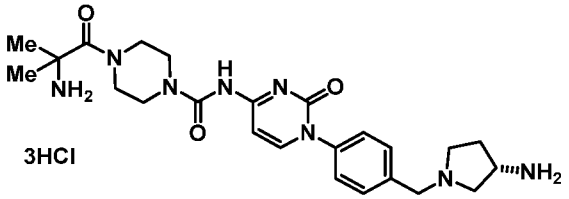
Compound 240



4-(2-Amino-2-methylpropanoyl)-N-(1-{4-[(3-aminoazepan-1-yl)methyl]phenyl}-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00465] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl azepan-3-ylcarbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.83 (d, 1H), 7.65 (d, 2H), 7.51 (d, 2H), 6.80 (d, 1H), 4.50 (d, 2H), 4.43 (d, 2H), 3.85-3.25 (m, 11H), 2.26-2.08 (m, 1H), 1.96-1.60 (m, 11H). LCMS [M+H] 511.4.

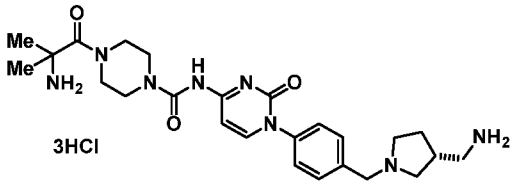
Compound 241



4-(2-Amino-2-methylpropanoyl)-N-[1-(4-{[(3S)-3-aminopyrrolidin-1-yl]methyl}phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl]piperazine-1-carboxamide hydrochloride salt

[00466] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl (S)-pyrrolidin-3-ylcarbamate. ^{1}H NMR (D_2O, 400 MHz) δ 7.85 (d, 1H), 7.65 (d, 2H), 7.53 (d, 2H), 6.82 (d, 1H), 4.53 (s, 2H), 4.29-4.13 (m, 1H), 3.99-3.82 (m, 1H), 3.44-3.82 (m, 11H), 2.71-2.51 (m, 1H), 2.30-2.10 (m, 1H), 1.68 (s, 6H). LCMS [M+H] 483.3.

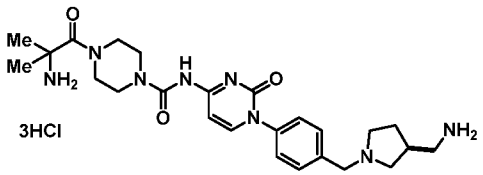
Compound 242



4-(2-Amino-2-methylpropanoyl)-N-[1-(4-{[(3R)-3-(aminomethyl)pyrrolidin-1-yl]methyl}phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl]piperazine-1-carboxamide hydrochloride salt

[00467] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl (S)-(pyrrolidin-3-ylmethyl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.85 (d, 1H), 7.64 (d, 2H), 7.51 (d, 2H), 6.86-6.79 (m, 1H), 4.51-4.43 (m, 2H), 3.84-2.21 (m, 14H), 2.05-1.63 (m, 9H). LCMS [M+H] 497.5.

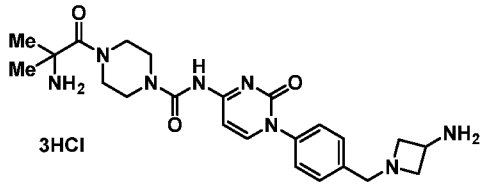
Compound 243



4-(2-Amino-2-methylpropanoyl)-N-[1-(4-{[(3S)-3-(aminomethyl)pyrrolidin-1-yl]methyl}phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl]piperazine-1-carboxamide hydrochloride salt

[00468] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl (R)-(pyrrolidin-3-ylmethyl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.88 (d, 1H), 7.66 (d, 2H), 7.53 (d, 2H), 6.83 (d, 1H), 4.56-4.42 (m, 2H), 3.92-1.64 (m, 23H). LCMS [M+H] 497.4.

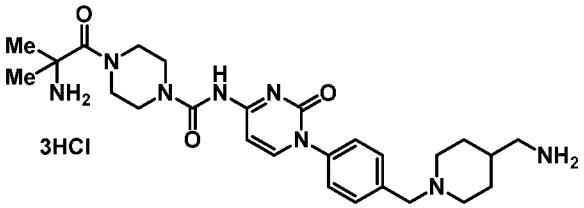
Compound 244



4-(2-Amino-2-methylpropanoyl)-N-(1-{4-[(3-aminoazetidin-1-yl)methyl]phenyl}-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00469] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl azetidin-3-ylcarbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.90 (d, 1H), 7.61 (d, 2H), 7.52 (d, 2H), 6.79 (d, 1H), 4.59-4.40 (m, 7H), 3.79-3.61 (m, 8H), 1.67 (s, 6H). LCMS [M+H] 469.3.

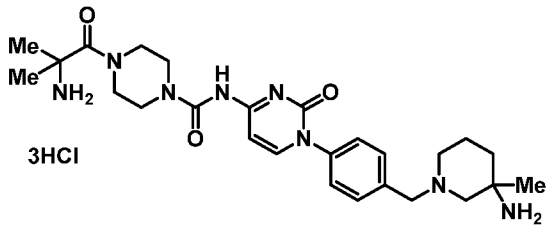
Compound 245



4-(2-Amino-2-methylpropanoyl)-N-[1-(4-{[4-(aminomethyl)piperidin-1-yl]methyl}phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl]piperazine-1-carboxamide hydrochloride salt

[00470] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl (piperidin-4-ylmethyl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.86 (d, 1H), 7.63 (d, 2H), 7.51 (d, 2H), 6.81 (d, 1H), 4.36 (s, 2H), 3.81-3.63 (m, 8H), 3.62-3.51 (m, 2H), 3.13-2.99 (m, 2H), 2.92 (d, 2H), 2.09-1.93 (m, 3H), 1.69 (s, 6H), 1.58-1.40 (m, 2H). LCMS [M+H] 511.3.

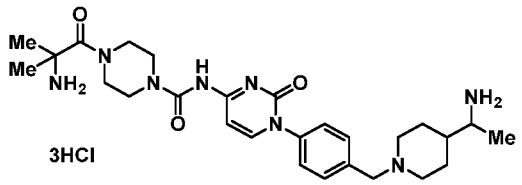
Compound 246



4-(2-Amino-2-methylpropanoyl)-N-(1-{4-[(3-amino-3-methylpiperidin-1-yl)methyl]phenyl}-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00471] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl (3-methylpiperidin-3-yl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.88 (d, 1H), 7.66 (d, 2H), 7.54 (d, 2H), 6.82 (d, 1H), 4.50 (d, 1H), 4.44 (d, 1H), 3.95-2.91 (m, 12H), 2.24-1.61 (m, 10H), 1.47 (br s, 3H). LCMS [M+H] 511.5.

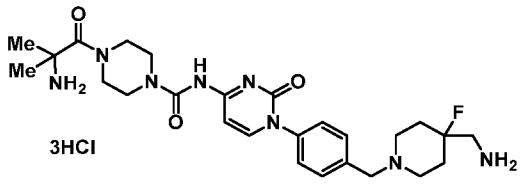
Compound 247



4-(2-Amino-2-methylpropanoyl)-N-[1-(4-{[4-(1-aminoethyl)piperidin-1-yl]methyl}phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl]piperazine-1-carboxamide hydrochloride salt

[00472] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl (1-(piperidin-4-yl)ethyl)carbamate. LCMS [M+H] 525.4.

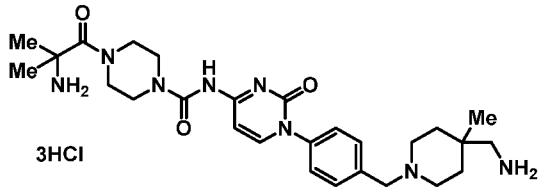
Compound 248



4-(2-Amino-2-methylpropanoyl)-N-[1-(4-{[4-(aminomethyl)-4-fluoropiperidin-1-yl]methyl}phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl]piperazine-1-carboxamide hydrochloride salt

[00473] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl ((4-fluoropiperidin-4-yl)methyl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.86 (d, 1H), 7.65 (d, 2H), 7.53 (d, 2H), 6.82 (d, 1H), 4.43 (s, 2H), 3.82-3.62 (m, 8H), 3.61-3.50 (m, 2H), 3.42-3.24 (m, 4H), 2.35-2.17 (m, 2H), 2.13-1.86 (m, 2H), 1.69 (s, 6H). LCMS [M+H] 529.5.

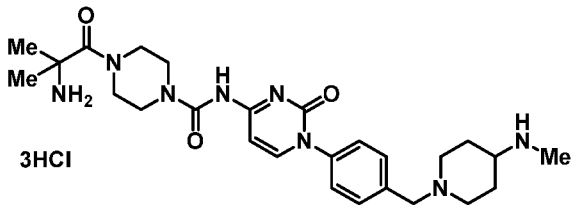
Compound 249



4-(2-Amino-2-methylpropanoyl)-N-[1-(4-{[4-(aminomethyl)-4-methylpiperidin-1-yl]methyl}phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl]piperazine-1-carboxamide hydrochloride salt

[00474] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl ((4-methylpiperidin-4-yl)methyl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.84 (d, 1H), 7.63 (d, 2H), 7.51 (d, 2H), 6.82 (d, 1H), 4.39 (s, 2H), 3.84-3.57 (m, 8H), 3.52-3.37 (m, 2H), 3.27-2.86 (m, 4H), 1.99-1.55 (m, 10H), 1.21-1.04 (m, 3H). LCMS [M+H] 525.4.

Compound 250

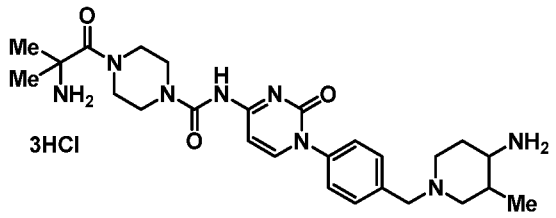


4-(2-amino-2-methylpropanoyl)-N-(1-(4-((4-(methylamino)piperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00475] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl methyl(piperidin-4-yl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.85 (d, 1H), 7.63 (d, 2H), 7.52 (d, 2H), 6.81 (d, 1H), 4.39 (s, 2H), 3.78-3.57

(m, 10H), 3.49-3.34 (m, 1H), 3.21-3.05 (m, 2H), 2.70 (s, 3H), 2.44-2.29 (m, 2H), 1.94-1.76 (m, 2H), 1.68 (s, 6H). LCMS [M+H] 511.7.

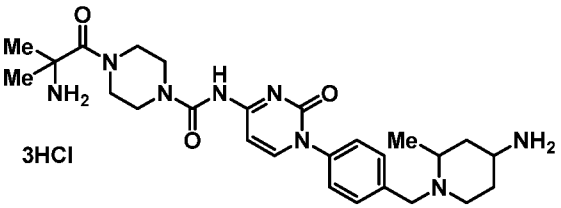
Compound 251



4-(2-amino-2-methylpropanoyl)-N-(1-(4-((4-amino-3-methylpiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00476] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl (3-methylpiperidin-4-yl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.86 (d, 1H), 7.64 (d, 2H), 7.52 (d, 2H), 6.81 (d, 1H), 4.50-4.29 (m, 2H), 3.87-2.82 (m, 13H), 2.66-1.81 (m, 3H), 1.68 (m, 6H), 1.22-0.94 (m, 3H). LCMS [M+H] 511.5.

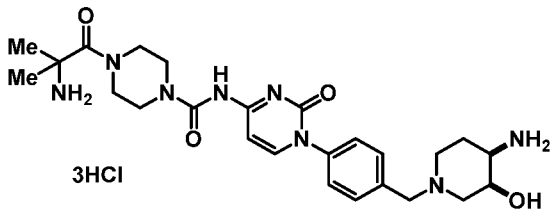
Compound 252



N-(1-(4-((4-amino-2-methylpiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-4-(2-amino-2-methylpropanoyl)piperazine-1-carboxamide hydrochloride salt

[00477] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl (2-methylpiperidin-4-yl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.85 (d, 1H), 7.59-7.70 (m, 2H), 7.52 (d, 2H), 6.82 (d, 1H), 4.91-4.07 (m, 2H), 4.02-2.95 (m, 12H), 2.44-1.66 (m, 10H), 1.63-1.45 (m, 3H). LCMS [M+H] 511.5.

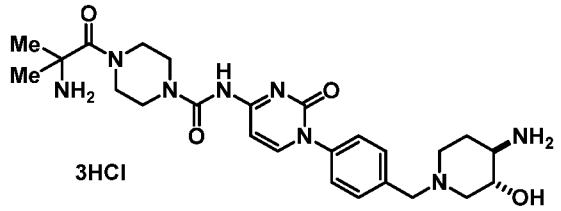
Compound 267



4-(2-amino-2-methylpropanoyl)-N-(1-(4-((*cis*-4-amino-3-hydroxypiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00478] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl ((*cis*)-3-hydroxypiperidin-4-yl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.83 (d, 1H), 7.63 (d, 2H), 7.52 (d, 2H), 6.82 (d, 1H), 4.45 (d, 1H), 4.37 (d, 1H), 4.29 (br. s., 1H), 3.83-3.44 (m, 11H), 3.34-3.07 (m, 2H), 2.32-2.16 (m, 1H), 2.15-2.06 (m, 1H), 1.68 (s, 6H). LCMS [M+H] 513.4.

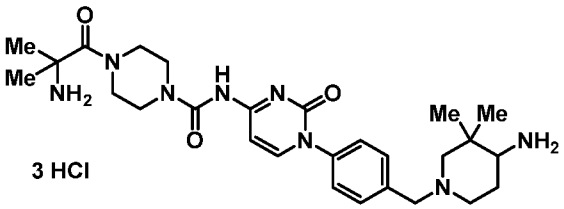
Compound 268



4-(2-amino-2-methylpropanoyl)-N-(1-(4-((*trans*-4-amino-3-hydroxypiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00479] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl (*trans*-3-hydroxypiperidin-4-yl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.85 (d, 1H), 7.65 (d, 2H), 7.53 (d, 2H), 6.82 (d, 1H), 4.45 (s, 2H), 4.01-3.89 (m, 1H), 3.82-3.56 (m, 10H), 3.41-3.28 (m, 1H), 3.25-3.13 (m, 1H), 3.01 (t, 1H), 2.43-2.30 (m, 1H), 2.00-1.83 (m, 1H), 1.69 (s, 6H). LCMS [M+H] 513.5.

Compound 254

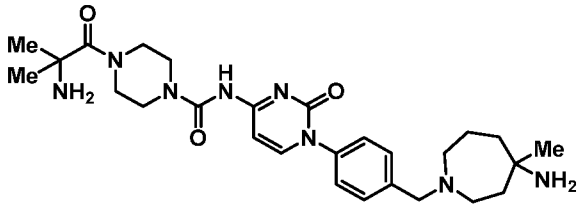


4-(2-Amino-2-methylpropanoyl)-N-(1-{4-[(4-amino-3,3-dimethylpiperidin-1-yl)methyl]phenyl}-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00480] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-

oxopropan-2-yl)carbamate and *tert*-butyl (3,3-dimethylpiperidin-4-yl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.85 (d, 1H), 7.64 (d, 2H), 7.52 (d, 2H), 6.82 (d, 1H), 4.45 (d, 1H), 4.34 (d, 1H), 383-3.57 (m, 9H), 3.35 (dd, 1H), 3.30-3.22 (m, 1H), 3.20-3.09 (m, 1H), 2.98 (d, 1H), 2.23-2.00 (m, 2H), 1.68 (s, 6H), 1.09 (s, 6H). LCMS [M+H] 525.5.

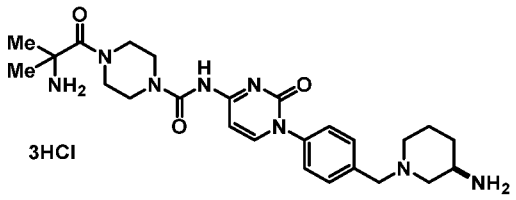
Compound 255



4-(2-Amino-2-methylpropanoyl)-N-(1-{4-[(4-amino-4-methylazepan-1-yl)methyl]phenyl}-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt.

[00481] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and 2-methyl-N-(4-methylazepan-4-yl)propane-2-sulfinamide. ^{1}H NMR (400 MHz, D_2O) δ 7.83 (d, 1H), 7.63 (d, 2H), 7.51 (d, 2H), 6.81 (d, 1H), 4.42 (s, 2H), 3.89-3.00 (m, 12H), 2.30-1.75 (m, 6H), 1.68 (s, 6H), 1.38 (br. s., 3H). LCMS [M+H] 525.5.

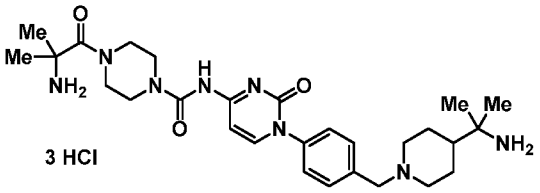
Compound 236



4-(2-Amino-2-methylpropanoyl)-N-[1-(4-{[(3R)-3-aminopiperidin-1-yl]methyl}phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl]piperazine-1-carboxamide hydrochloride salt

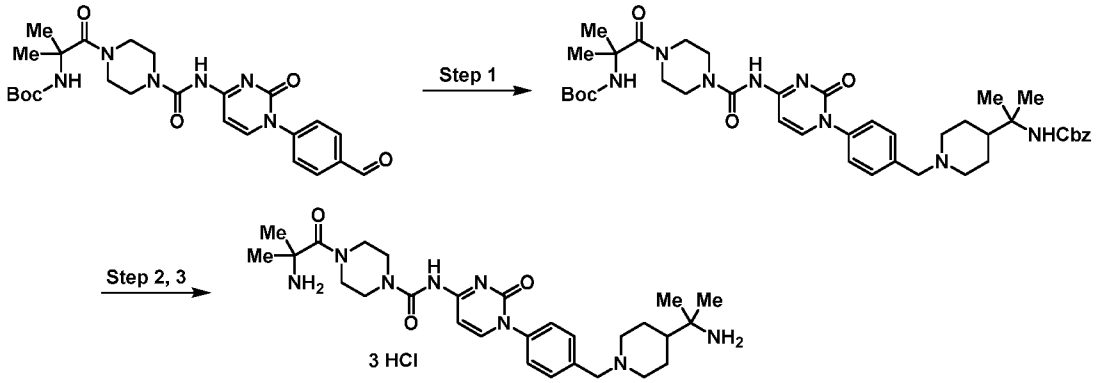
[00482] Prepared in a similar fashion as Scheme C-1 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl (R)-piperidin-3-ylcarbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.84 (d, 1H), 7.68-7.60 (m, 2H), 7.57-7.47 (m, 2H), 6.82 (d, 1H), 4.47 (s, 2H), 3.81-3.47 (m, 11H), 3.19-2.93 (m, 2H), 2.25-2.04 (m, 2H), 1.91-1.54 (m, 8H). LCMS [M+H] 497.4.

Compound 253



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((4-(2-aminopropan-2-yl)piperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

Scheme C-2



Reagents: 1) Benzyl N-[2-(piperidin-4-yl)propan-2-yl]carbamate, $NaBH(OAc)_3$, DCM 2) H_2, Pd/C, MeOH 3) 3M HCl in MeOH.

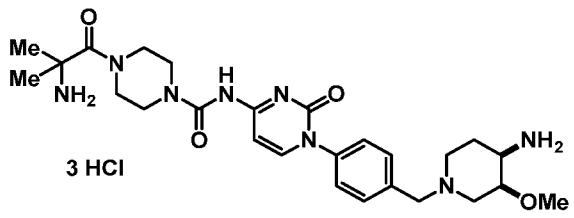
[00483] Step 1: Benzyl (2-(1-(4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)propan-2-yl)carbamate. Benzyl (2-(piperidin-4-yl)propan-2-yl)carbamate (11.5 mg, 0.054 mmol) was added to a suspension of *tert*-butyl N-[1-(4-{[1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl]carbamoyl}piperazin-1-yl)-2-methyl-1-oxopropan-2-yl]carbamate (40 mg, 0.078mmol) in DCM (3 mL). The reaction mixture was stirred at rt for 15 min and $NaBH(OAc)_3$ (195 mg, 0.090 mmol) was added. The reaction was stirred at rt for 7h. Additional $NaBH(OAc)_3$ (20 mg) was added and the reaction was stirred overnight. The reaction was diluted with DCM and washed with sat. aq. $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by reverse phase chromatography (H_2O : 0.1% aq. NH_4OH in CH_3CN, 20:80) and the recovered fractions purified by reverse phase chromatography (H_2O:CH_3CN, 20:80) to afford the title compound (12.0 mg, 33%). ^1H NMR (400 MHz, $CDCl_3$) δ 12.94 (br s, 1H), 7.44 (d, 2H), 7.40-7.22 (m, 8H), 5.84 (d, 1H), 5.06 (s, 2H), 4.94-

4.80 (m, 1H), 4.66 (s, 1H), 3.97-3.57 (m, 8H), 3.52 (s, 2H), 3.01-2.90 (m, 2H), 2.02-1.82 (m, 3H), 1.70-1.59 (m, 2H), 1.54 (s, 6H), 1.46 (s, 9H), 1.43-1.25 (m, 8H). LCMS [M+H] 773.7.

[00484] Step 2: *tert*-Butyl (1-(4-((1-(4-((4-(2-aminopropan-2-yl)piperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate. Pd/C Degussa type (10% wt, 3.0 mg) was added to a solution of benzyl (2-(1-(4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)propan-2-yl)carbamate (12.0 mg, 0.015 mmol) in EtOAc (4 mL). The mixture was stirred under H_2 atmosphere for 24h. The reaction was filtered and concentrated under reduced pressure. The crude product was purified (EtOAc-MeOH, 90:10) to afford the title compound (4.5 mg, 47%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, 2H), 7.33-7.24 (m, 3H), 5.84 (d, 1H), 4.86 (br. s., 1H), 3.98-3.58 (m, 8H), 3.54 (br.s., 2H), 3.03-2.94 (m, 2H), 2.04-1.90 (m, 2H), 1.79-1.13 (m, 20H), 1.08 (s, 6H). LCMS [M+H] 639.7.

[00485] Step 3: 4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((4-(2-aminopropan-2-yl)piperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt. A solution of *tert*-butyl (1-(4-((1-(4-((4-(2-aminopropan-2-yl)piperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate (4.5 mg, 0.007 mmol) in 3M HCl in MeOH (1.5 mL) was stirred at rt for 16h. The reaction mixture was concentrated under reduced pressure, dissolved in MeOH and precipitated with EtOAc. The solid was filtered washed with Et_2O and dried to afford the title compound (3.9 mg, 86%) as a colorless wax. ^{1}H NMR (400 MHz, D_2O) δ 7.83 (d, 1H), 7.62 (d, 2H), 7.50 (d, 2H), 6.81 (d, 1H), 4.35 (s, 2H), 3.84-3.53 (m, 10H), 3.11-2.97 (m, 2H), 2.04-1.94 (m, 2H), 1.93-1.82 (m, 1H), 1.72-1.50 (m, 8H), 1.27 (s, 6H). LCMS [M+H] 539.5.

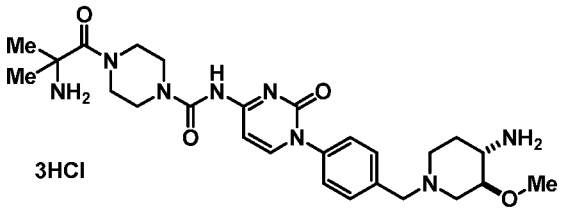
Compound 217



***cis*-4-(2-Amino-2-methylpropanoyl)-N-[1-(4-{[4-amino-3-methoxypiperidin-1-yl]methyl}phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl]piperazine-1-carboxamide (racemate) hydrochloride salt**

[00486] Prepared in a similar fashion as Scheme C-2 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and benzyl ((*cis*)-3-methoxypiperidin-4-yl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.62 (d, 2H), 7.56-7.48 (m, 3H), 7.46-7.41 (m, 1H), 4.42-4.22 (m, 2H), 3.99-2.80 (m, 17H), 2.21-2.03 (m, 2H), 1.68 (s, 3H), 1.66 (s, 3H). LCMS [M+H] 527.6.

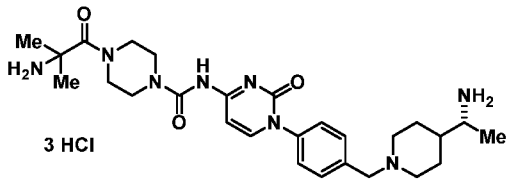
Compound 216



***trans*-4-(2-Amino-2-methylpropanoyl)-N-[1-(4-{[4-amino-3-methoxypiperidin-1-yl]methyl}phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl]piperazine-1-carboxamide (racemate) hydrochloride salt**

[00487] Prepared in a similar fashion as Scheme C-2 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and benzyl ((*trans*)-3-methoxypiperidin-4-yl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.86 (d, 1H), 7.65 (d, 2H), 7.53 (d, 2H), 6.81 (d, 1H), 4.46 (s, 2H), 3.94-3.82 (m, 1H), 3.80-3.55 (m, 10H), 3.48-3.32 (m, 4H), 3.11-3.25 (m, 1H), 3.07-2.91 (m, 1H), 2.44-2.28 (m, 1H), 2.02-1.85 (m, 1H), 1.67 (s, 6H). LCMS [M+H] 527.6.

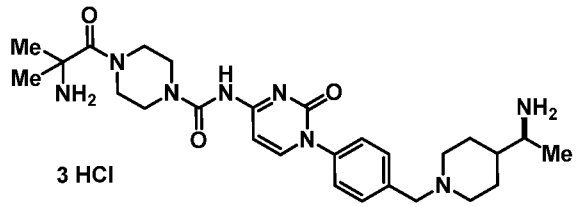
Compound 219



4-(2-Amino-2-methylpropanoyl)-N-{1-[4-({4-[(1R)-1-aminoethyl]piperidin-1-yl}methyl)phenyl]-2-oxo-1,2-dihydropyrimidin-4-yl}piperazine-1-carboxamide hydrochloride salt

[00488] Prepared in a similar fashion as Scheme C-2 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and benzyl (R)-(1-(piperidin-4-yl)ethyl)carbamate. ^{1}H NMR (600 MHz, D_2O) δ 8.06-8.02 (m, 1H), 7.73-7.67 (m, 2H), 7.61-7.56 (m, 2H), 6.84 (d, 1H), 4.42 (s, 2H), 3.88-3.68 (m, 8H), 3.65 (d, 2H), 3.35-3.28 (m, 1H), 3.14-3.06 (m, 2H), 2.10-1.91 (m, 3H), 1.74 (s, 6H), 1.66-1.55 (m, 2H), 1.40-1.28 (m, 3H). LCMS [M+H] 525.4.

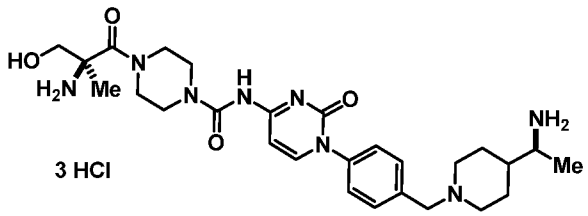
Compound 220



4-(2-Amino-2-methylpropanoyl)-N-{1-[4-({4-[(1S)-1-aminoethyl]piperidin-1-yl}methyl)phenyl]-2-oxo-1,2-dihydropyrimidin-4-yl}piperazine-1-carboxamide hydrochloride salt

[00489] Prepared in a similar fashion as Scheme C-2 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and benzyl (S)-(1-(piperidin-4-yl)ethyl)carbamate. ^{1}H NMR (600 MHz, D_2O) δ 7.91 (d, 1H), 7.68 (d, 2H), 7.56 (d, 2H), 6.86 (d, 1H), 4.55-4.38 (m, 2H), 3.85-3.68 (m, 8H), 3.65 (d, 2H), 3.31 (quin, 1H), 3.09 (t, 2H), 2.05 (t, 2H), 2.00-1.89 (m, 1H), 1.75-1.71 (m, 6H), 1.65-1.54 (m, 2H), 1.39-1.26 (m, 3H). LCMS [M+H] 525.4.

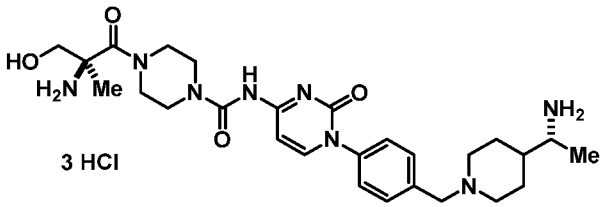
Compound 221



4-[(2S)-2-Amino-3-hydroxy-2-methylpropanoyl]-N-{1-[4-({4-[(1S)-1-aminoethyl]piperidin-1-yl}methyl)phenyl]-2-oxo-1,2-dihydropyrimidin-4-yl}piperazine-1-carboxamide hydrochloride salt

[00490] Prepared in a similar fashion as Scheme C-2 from *tert*-butyl (2R,4S)-2-(*tert*-butyl)-4-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazine-1-carbonyl)-4-methyloxazolidine-3-carboxylate and benzyl (S)-(1-(piperidin-4-yl)ethyl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.84 (d, 1H), 7.62 (d, 2H), 7.51 (d, 2H), 6.81 (d, 1H), 4.36 (s, 2H), 4.11 (d, 1H), 3.85 (d, 1H), 3.79-3.54 (m, 10H), 3.31-3.20 (m, 1H), 3.04 (t, 2H), 2.07-1.95 (m, 2H), 1.95-1.83 (m, 1H), 1.63 (s, 3H), 1.61-1.47 (m, 2H), 1.24 (d, 3H). LCMS [M+H] 541.3.

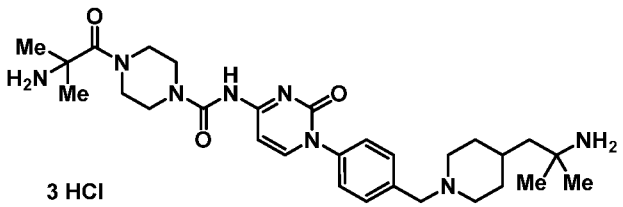
Compound 222



4-[(2S)-2-Amino-3-hydroxy-2-methylpropanoyl]-N-{1-[4-({4-[(1R)-1-aminoethyl]piperidin-1-yl}methyl)phenyl]-2-oxo-1,2-dihydropyrimidin-4-yl}piperazine-1-carboxamide hydrochloride salt

[00491] Prepared in a similar fashion as Scheme C-2 *tert*-butyl (2R,4S)-2-(*tert*-butyl)-4-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazine-1-carbonyl)-4-methyloxazolidine-3-carboxylate and benzyl (R)-(1-(piperidin-4-yl)ethyl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.85 (d, 1H), 7.62 (d, 2H), 7.51 (d, 2H), 6.81 (d, 1H), 4.35 (s, 2H), 4.10 (d, 1H), 3.85 (d, 1H), 3.79-3.53 (m, 10H), 3.30-3.22 (m, 1H), 3.04 (t, 2H), 2.06-1.82 (m, 3H), 1.63 (s, 3H), 1.61-1.45 (m, 2H), 1.24 (d, 3H). LCMS [M+H] 541.3.

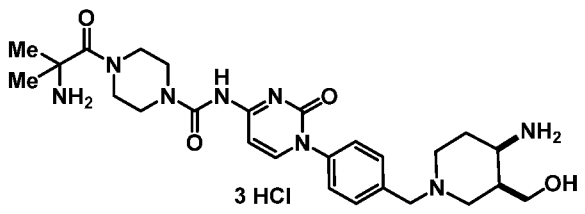
Compound 226



4-(2-Amino-2-methylpropanoyl)-N-[1-(4-{[4-(2-amino-2-methylpropyl)piperidin-1-yl]methyl}phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl]piperazine-1-carboxamide hydrochloride salt

[00492] Prepared in a similar fashion as Scheme C-2 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and benzyl (2-methyl-1-(piperidin-4-yl)propan-2-yl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.83 (d, 1H), 7.61 (d, 2H), 7.50 (d, 2H), 6.88-6.75 (m, 1H), 4.32 (s, 2H), 3.81-3.61 (m, 8H), 3.52-3.41 (m, 2H), 3.09-2.94 (m, 2H), 2.04-1.93 (m, 2H), 1.84-1.40 (m, 11H), 1.32 (s, 6H). LCMS [M+H] 553.6.

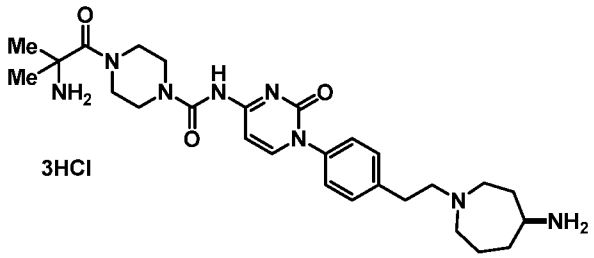
Compound 322



cis-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((4-amino-3-(hydroxymethyl)piperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00493] Prepared in a similar fashion to Scheme C-2 from *tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1, 2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and benzyl (*cis*-3-(hydroxymethyl)piperidin-4-yl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.88 (d, 1H), 7.62-7.59 (m, 2H), 7.48 (d, 2H), 6.75 (d, 1H), 4.41-4.39 (m, 2H), 4.27 (d, 1H), 3.84-3.81 (m, 2H), 3.78-3.74 (m, 4H), 3.67-3.55 (m, 6H), 3.44 (m, 1H), 1.59 (s, 6H), 3.24-3.17 (m, 2H), 2.17 (s, 2H), 1.63 (s, 6H). LCMS [M+H] 527.6.

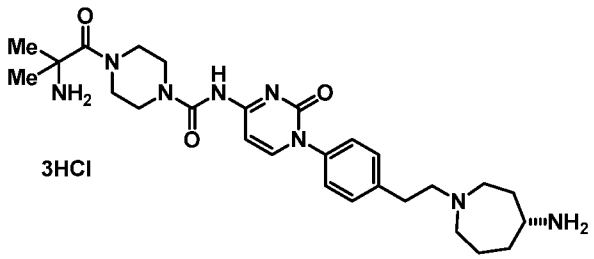
Compound 293



(S)-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(4-aminoazepan-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00494] Prepared in a similar fashion as Scheme C-2 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and benzyl (S)-azepan-4-ylcarbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.88 (d, 1H), 7.51-7.45 (m, 2H), 7.45-7.39 (m, 2H), 6.83 (d, 1H), 3.83-3.66 (m, 9H), 3.64-3.46 (m, 5H), 3.45-3.13 (m, 4H), 2.44-2.21 (m, 2H), 2.18-1.97 (m, 2H), 1.90-1.76 (m, 1H), 1.72 (s, 6H). LCMS [M+H] 525.4. e.e. >99% as determined on a Chiralpak AD-H (25x0.46 cm, 5 μm); mobile phase: n-hexane/EtOH:MeOH, 1:1 + 0.1% isopropylamine, 10/90% v/v; flow rate:1 mL/min; retention time: 27.1 min.

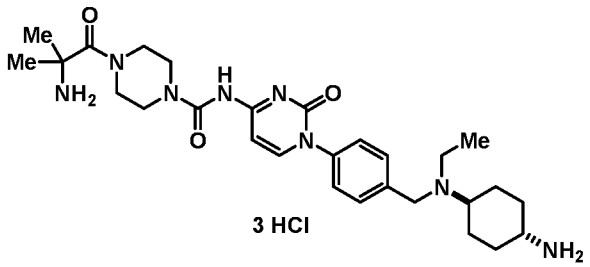
Compound 294



(R)-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(4-aminoazepan-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

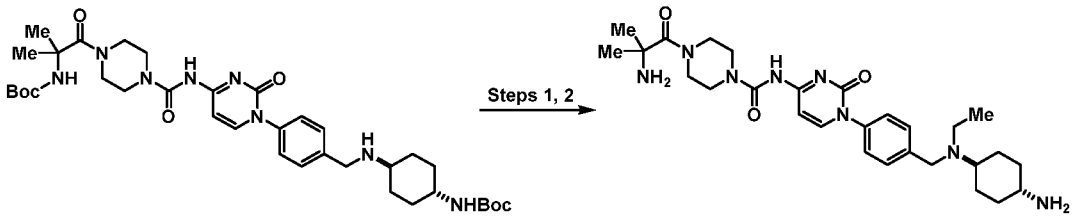
[00495] Prepared in a similar fashion as Scheme C-2 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and benzyl (R)-azepan-4-ylcarbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.88 (d, 1H), 7.51-7.45 (m, 2H), 7.45-7.39 (m, 2H), 6.83 (d, 1H), 3.83-3.66 (m, 9H), 3.64-3.46 (m, 5H), 3.45-3.13 (m, 4H), 2.44-2.21 (m, 2H), 2.18-1.97 (m, 2H), 1.90-1.76 (m, 1H), 1.72 (s, 6H). LCMS [M+H] 525.4. e.e.=100% as determined on a Chiralpak AD-H (25x0.46 cm, 5 μm); mobile phase: n-hexane/EtOH:MeOH, 1:1 + 0.1% isopropylamine, 10/90% v/v; flow rate:1 mL/min; retention time: 30.3 min.

Compound 119



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((*trans*-4-aminocyclohexyl)(ethyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

Scheme C-3



Reagents: 1) CH_3CHO, $NaBH_3CN$, MeOH, rt, 18h 2) 2 M HCl in MeOH, rt, 18h.

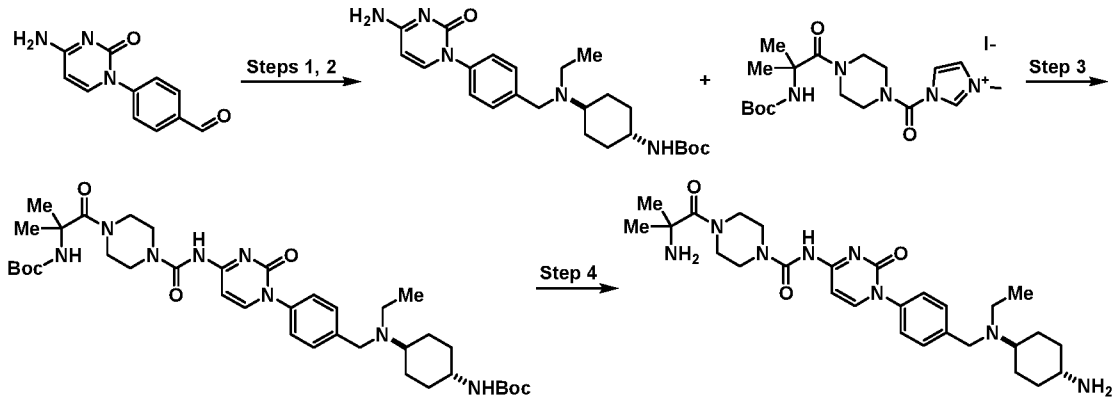
[00496] Step 1: *tert*-butyl (*trans*-4-((4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)(ethyl)amino)cyclohexyl)carbamate. $NaBH_3CN$ (96 mg, 1.53 mmol) was added to a mixture of *tert*-butyl (*trans*-4-((4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)amino)cyclohexyl)carbamate (488 mg, 0.69 mmol) and acetaldehyde (0.5 mL) in dry MeOH (8 mL), and the mixture was stirred at rt for 18h. The mixture was concentrated to about 2 mL, added to 2 M aq. K_2CO_3 (50 mL), and extracted with DCM (3x50 mL). The extracts were dried over Na_2SO_4, decanted, concentrated, and the residue was purified by

flash chromatography (MeOH/EtOAc/Hexanes) to afford the title compound as a white solid (365 mg, 0.494 mmol).

[00497] Step 2: 4-(2-amino-2-methylpropanoyl)-N-(1-(4-(((*trans*-4-aminocyclohexyl)(ethyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt. A mixture of *tert*-butyl (*trans*-4-((4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)(ethyl)amino)cyclohexyl)carbamate (365 mg, 0.49 mmol) and 2 MHCl in MeOH (20 mL, 40 mmol) was stirred at rt for 18h and concentrated. The residue was purified by flash chromatography (DCM/MeOH/NH_4OH). Product fractions were concentrated to dryness, converted to the HCl salt with 2 M HCl in MeOH, and concentrated to dryness to afford the title compound (264 mg, 0.407 mmol) as a white solid. ^1H NMR (500 MHz, D_2O) δ 7.97 (d, 1H), 7.63 (d, 2H), 7.52 (d, 2H), 6.78 (d, 1H), 4.50 (d, 1H), 4.32 (d, 1H), 3.59-3.82 (m, 8H), 3.35-3.45 (m, 1H), 3.14-3.33 (m, 3H), 2.11-2.27 (m, 4H), 1.71-1.89 (m, 2H), 1.67 (s, 6H), 1.43-1.57 (m, 2H), 1.25 (t, 3H). LCMS [M+H] 539.4.

[00498] Alternatively, 4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((*trans*-4-aminocyclohexyl)(ethyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt may be prepared according to Scheme C-4.

Scheme C-4



Reagents: Step 1) N-Boc-*trans*-1,4-cyclohexanediamine, $NaBH_4$, MeOH, rt, 22h 2) CH_3CHO, $NaBH_3CN$, MeOH, rt, 44h 3) CH_3CN, reflux, 18h 4) 2 M HCl in MeOH, rt, 18h.

[00499] Step 1: *tert*-butyl (*trans*-4-((4-(4-amino-2-oxopyrimidin-1(2H)-yl)benzyl)amino)cyclohexyl)carbamate. A mixture of 4-(4-amino-2-oxopyrimidin-1(2H)-yl)benzaldehyde (1.38 g, 6.38 mmol) and N-Boc-*trans*-1,4-cyclohexanediamine (1.51 g, 7.04 mmol) in dry MeOH (75 mL) was stirred at rt for 30 min. The mixture was concentrated to dryness and resuspended in dry MeOH (75 mL). $NaBH_4$ (750 mg, 19.8 mmol) was added portionwise, and the mixture was stirred at rt for 22 hours. It was concentrated to about 10

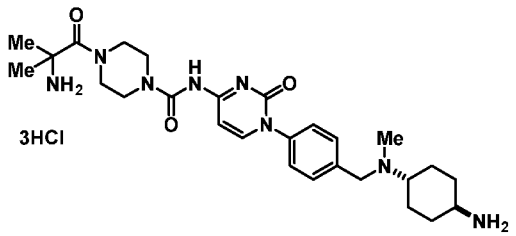
mL total volume and H_2O (100 mL) was added. The precipitate was collected by vacuum filtration to provide the title compound (1.21 g, 2.92 mmol) as a white solid.

[00500] Step 2: *tert*-butyl (*trans*-4-((4-(4-amino-2-oxopyrimidin-1(2H)-yl)benzyl)(ethyl)amino)cyclohexyl)carbamate. $NaBH_3CN$ (1.03 g, 16.4 mmol) was added to a mixture of *tert*-butyl (*trans*-4-((4-(4-amino-2-oxopyrimidin-1(2H)-yl)benzyl)amino)cyclohexyl)carbamate (3.23 g, 7.81 mmol) and acetaldehyde (1 mL) in dry MeOH (100 mL), and the mixture was stirred at rt for 44h. It was concentrated to 25 mL total volume, and 1 M NaOH (150 mL) was added. The precipitate was collected by vacuum filtration to afford the title compound (3.55 g) as a white solid.

[00501] Step 3: *tert*-butyl (*trans*-4-((4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)(ethyl)amino)cyclohexyl)carbamate. A mixture of *tert*-butyl (*trans*-4-((4-(4-amino-2-oxopyrimidin-1(2H)-yl)benzyl)(ethyl)amino)cyclohexyl)carbamate (674 mg, 1.53 mmol) and 1-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carbonyl)-3-methyl-1H-imidazol-3-ium iodide (1.01 g, 1.99 mmol) in dry CH_3CN (20 mL) was stirred at reflux for 18h. The reaction mixture was cooled and concentrated in vacuo, EtOAc (75 mL) added and the organic layer washed with sat. aq. $NaHCO_3$ (2x50 mL), brine (50 mL), dried over Na_2SO_4, decanted and concentrated. The residue was purified by flash chromatography (MeOH/EtOAc/Hexanes) to afford the title compound (726 mg) as a white solid.

[00502] Step 4: 4-(2-amino-2-methylpropanoyl)-N-(1-(4-(((*trans*-4-aminocyclohexyl)(ethyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt. A mixture of *tert*-butyl (*trans*-4-((4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)(ethyl)amino)cyclohexyl)carbamate (726 mg, 0.98 mmol) and 2 M HCl in MeOH (25 mL, 50 mmol) was stirred at rt for 18 h. The reaction mixture was concentrated and purified by flash chromatography (DCM/MeOH/NH_4OH) followed by reverse-phase HPLC (CH_3CN/H_2O/TFA). Product fractions were concentrated to dryness, converted to the HCl salt with 2M HCl in MeOH, and again concentrated to dryness to afford the title compound (437 mg) as a white solid. ^1H NMR (500 MHz, D_2O) δ 7.89 (d, 1H), 7.54 (d, 2H), 7.43 (d, 2H), 6.69 (d, 1H), 4.41 (d, 1H), 4.23 (d, 1H), 3.48-3.76 (m, 8H), 3.26-3.37 (m, 1H), 3.16-3.24 (m, 1H), 3.06-3.16 (m, 2H), 2.02-2.19 (m, 4H), 1.61-1.81 (m, 2H), 1.58 (s, 6H), 1.34-1.48 (m, 2H), 1.16 (t, 3H). LCMS [M+H] 539.4.

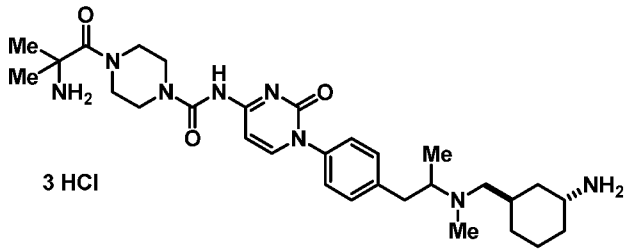
Compound 118



***trans*-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((4-aminocyclohexyl)(methyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt**

[00503] Prepared in a similar fashion as Scheme C-3 using *tert*-butyl (*trans*-4-((4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)amino)cyclohexyl)carbamate and formaldehyde. ^{1}H NMR (400 MHz, D_2O) mixture of rotamers, δ 7.80 (d, 1H), 7.53 (d, 2H), 7.42 (d, 2H), 6.71 (d, 1H), 4.45 (d, 1H), 4.16 (d, 1H), 3.57-3.70 (m, 8H), 3.33-3.27 (m, 1H), 3.15-3.09 (m, 1H), 2.63 (s, 3H), 2.18-2.07 (m, 4H), 1.74-1.69, (m, 2H), 1.58 (s, 6H), 1.46-1.37 (m, 2H). LCMS [M+H] 525.2.

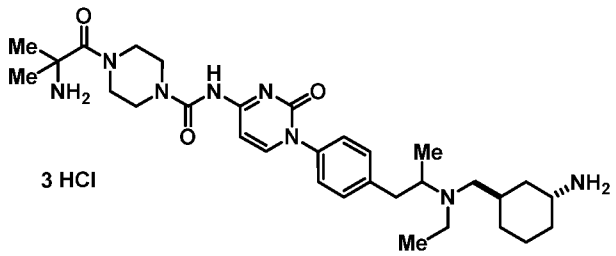
Compound 279



***trans*-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(((3-aminocyclohexyl)methyl)(methyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt**

[00504] Prepared in a similar fashion as Scheme C-3 from *tert*-butyl (1-(4-((1-(4-(2-((((*trans*)-3-((tert-butoxycarbonyl)amino)cyclohexyl)methyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and formaldehyde. ^{1}H NMR (400 MHz, D_2O) mixture of rotamers, δ 7.78 (d, 1H), 7.36-7.29 (m, 4H), 6.70 (d, 1H), 3.63-3.58 (m, 8H), 3.45-3.38 (m, 1H), 3.20-3.10 (m, 3H), 3.00-2.97 (m, 3H), 2.89-2.75 (m, 3H), 2.22-2.15 (m, 1H), 1.90-1.40 (m, 12H), 1.31-1.25 (m, 1H), 1.15 (t, 3H). LCMS [M+H] 567.3.

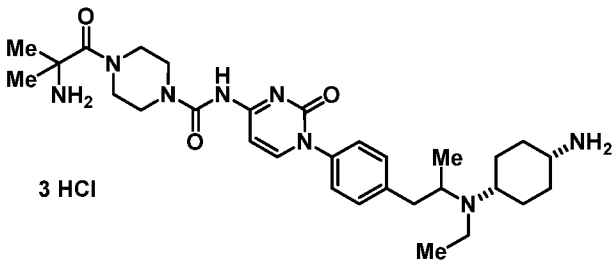
Compound 280



***trans*-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(((3-aminocyclohexyl)methyl)(ethyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt**

[00505] Prepared in a similar fashion as Scheme C-3 from *tert*-butyl (1-(4-((1-(4-(2-((((*trans*)-3-((tert-butoxycarbonyl)amino)cyclohexyl)methyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and acetaldehyde. ^{1}H NMR (400 MHz, D_2O) mixture of rotamers, δ 7.85 (d, 1H), 7.37-7.10 (m, 4H), 6.70 (d, 1H), 3.75-3.60 (m, 8H), 3.49-3.36 (m, 1H), 3.36-3.11 (m, 4H), 3.09-2.76 (m, 3H), 2.31-2.11 (m, 1H), 1.76-1.66 (m, 4H), 1.60 (s, 6H), 1.55-1.50 (m, 3H), 1.32-1.23 (m, 3H), 1.50 (t, 3H). LCMS [M+H] 581.3.

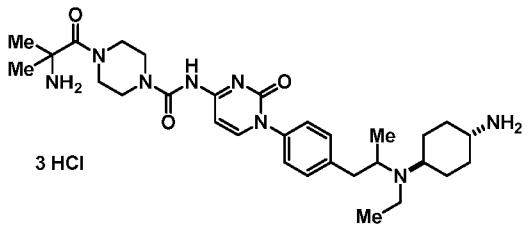
Compound 281



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(((cis)-4-aminocyclohexyl)(ethyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00506] Prepared in a similar fashion as Scheme C-3 from *tert*-butyl (*cis*-4-((1-(4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)phenyl)propan-2-yl)amino)cyclohexyl)carbamate and acetaldehyde. ^{1}H NMR (400 MHz, D_2O) Mixture of rotamers, δ 8.43 (d, 1H), 8.08-8.02 (m, 4H), 7.34 (d, 1H), 4.54 (m, 2H), 4.33-4.29 (m, 8H), 4.20-3.79 (m, 4H), 3.63-3.57 (m, 1H), 2.70-2.67 (m, 4H), 2.56-2.46 (m, 4H), 2.32 (s, 6H), 2.15-1.85 (m, 6H). LCMS [M+H] 567.3.

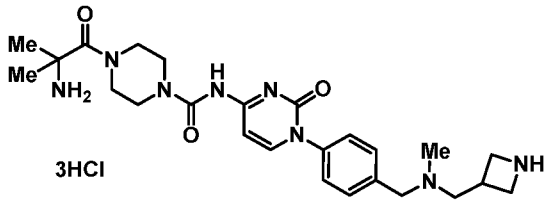
Compound 282



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(((*trans*)-4-aminocyclohexyl)(ethyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00507] Prepared in a similar fashion as Scheme C-3 from *tert*-butyl (*trans*-4-((1-(4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)phenyl)propan-2-yl)amino)cyclohexyl)carbamate and acetaldehyde. LCMS [M+H] 567.4.

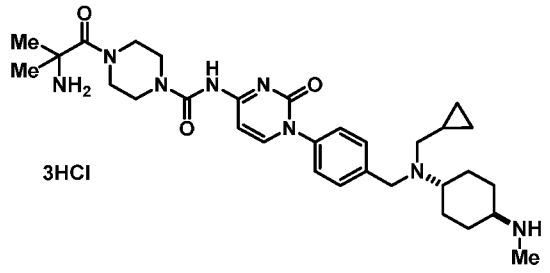
Compound 111



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((azetidin-3-ylmethyl)(methyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00508] Prepared in a similar fashion to Scheme C-3 from *tert*-butyl 3-(((4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)amino)methyl)azetidine-1-carboxylate and formaldehyde. ^{1}H NMR (400 MHz, D_2O) mixture of rotamers, δ 7.80 (d, 1H), 7.53 (d, 2H), 7.43 (d, 2H), 6.71 (d, 1H), 4.39-4.22 (m, 2H), 4.20-4.00 (m, 2H), 3.95-3.85 (m, 2H), 3.70-3.50 (m, 9H), 3.42-3.41 (m, 2H), 2.66 (s, 3H), 1.57 (s, 6H). LCMS [M+H] 497.1.

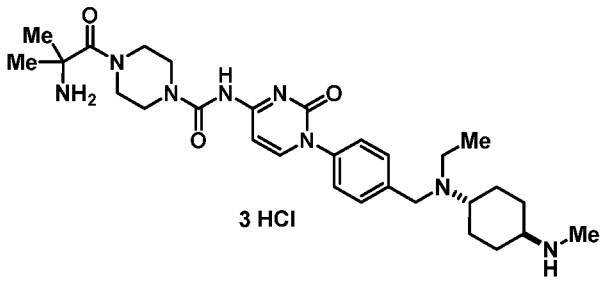
Compound 301



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((cyclopropylmethyl)(*trans*-4-(methylamino)cyclohexyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00509] Prepared in a similar fashion as a similar fashion to Scheme C-3 from *tert*-butyl (*trans*-4-((4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)amino)cyclohexyl)(methyl)carbamate and cyclopropanecarbaldehyde. ^{1}H NMR (500 MHz, D_2O) δ 7.98 (d, 1H), 7.73-7.67 (m, 2H), 7.57 (d, 2H), 6.85 (d, 1H), 4.53 (q, 2H), 3.87-3.63 (m, 8H), 3.58 (t, 1H), 3.31-3.02 (m, 3H), 2.75-2.71 (m, 3H), 2.37-1.76 (m, 6H), 1.72 (s, 6H), 1.61-1.48 (m, 2H), 0.72 (d, 1H), 0.36-0.22 (m, 4H).

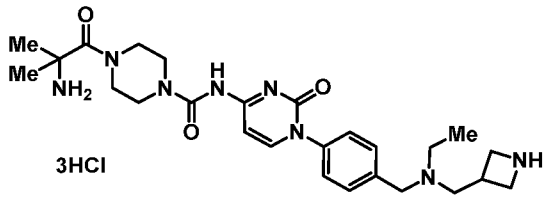
Compound 305



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((ethyl(*trans*-4-(methylamino)cyclohexyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00510] Prepared in a similar fashion as a similar fashion to Scheme C-3 from *tert*-butyl (*trans*-4-((4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)amino)cyclohexyl)(methyl)carbamate and acetaldehyde. ^{1}H NMR (500 MHz, D_2O) δ 8.14 (d, 1H), 7.78-7.72 (m, 2H), 7.65 (d, 2H), 6.89 (d, 1H), 4.79 (m under D_2O, 2H) 3.89-3.77 (m, 8H), 3.60-3.16 (m, 4H), 2.83-2.75 (m, 3H), 2.41-1.80 (m, 6H), 1.78 (s, 6H), 1.69-1.47 (m, 2H), 1.37 (t, 3H). LCMS [M+H] 553.4.

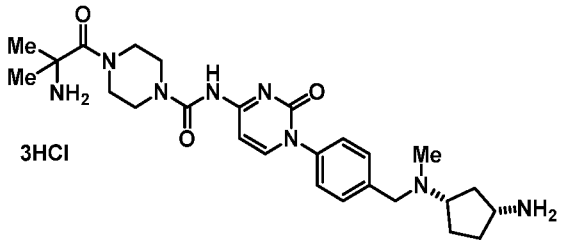
Compound 113



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((azetidin-3-ylmethyl)(ethyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00511] Prepared in a similar fashion as Scheme C-3 from *tert*-butyl 3-(((4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)amino)methyl)azetidine-1-carboxylate and acetaldehyde. ^{1}H NMR (400 MHz, D_2O) Mixture of rotamers, δ 7.74 (d, 1H), 7.52 (d, 2H), 7.42 (d, 2H), 6.72 (d, 1H), 4.35-4.20 (m, 2H), 4.19-4.08 (m, 2H), 3.91-3.81 (m, 2H), 3.65-3.55 (m, 8H), 3.45-3.35 (m, 3H), 3.11-3.05 (m, 2H), 1.57 (s, 6H), 1.21 (t, 3H). LCMS [M+H] 511.1.

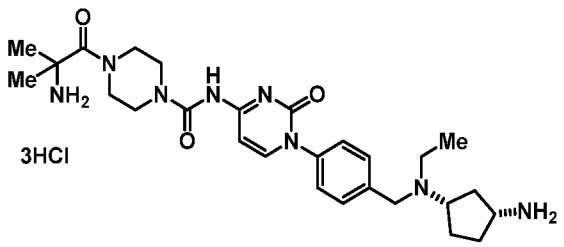
Compound 115



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((((1S,3R)-3-aminocyclopentyl)(methyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00512] Prepared in a similar fashion as Scheme C-3 from *tert*-butyl (1-(4-((1-(4-((((1S,3R)-3-((*tert*-butoxycarbonyl)amino)cyclopentyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and formalin. ^{1}H NMR (400Mz, D_2O) Mixture of rotamers, δ 7.90 (d, 1H), 7.58 (d, 2H), 7.47 (d, 2H), 6.72 (d, 1H), 4.55 (d, 1H), 4.16 (d, 1H), 3.80-3.78 (m, 1H), 3.76-3.51 (m, 8H), 2.68 (s, 3H), 2.62-2.59 (m, 1H), 2.29-2.27 (m, 1H), 2.16-2.11 (m, 1H), 2.10-2.01 (m, 4H), 1.61 (s, 6H). LCMS [M+H] 511.0.

Compound 116

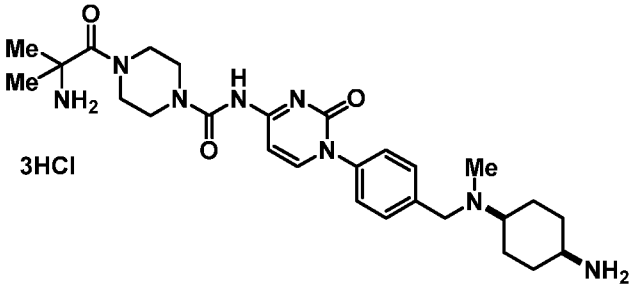


4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((((1S,3R)-3-aminocyclopentyl)(ethyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00513] Prepared in a similar fashion as Scheme C-3 from *tert*-butyl (1-(4-((1-(4-((((1S,3R)-3-((*tert*-butoxycarbonyl)amino)cyclopentyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and

acetaldehyde. ^{1}H NMR (400 MHz, D_2O) Mixture of rotamers, δ 7.74 (d, 1H), 7.54 (d, 2H), 7.42 (d, 2H), 6.73 (d, 1H), 4.45-4.2 (m, 2H), 3.92-3.81 (m, 1H), 3.68-3.52 (m, 8H), 3.19-3.06 (m, 3H), 2.60-2.57 (m, 1H), 2.25-1.7 (m, 5H), 1.58 (s, 6H), 1.31-1.18 (m, 3H). LCMS [M+H] 525.2.

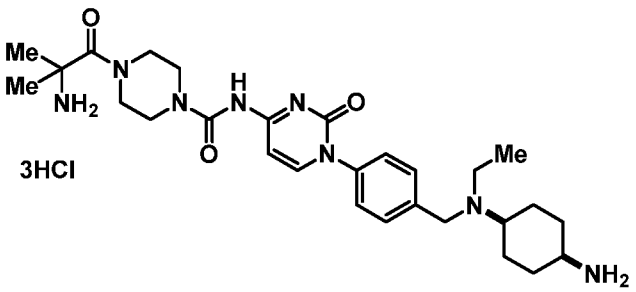
Compound 121



***cis*-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((4-aminocyclohexyl)(methyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt**

[00514] Prepared in a similar fashion as Scheme C-3 from *tert*-butyl (1-(4-((1-(4-(((*cis*-4-((*tert*-butoxycarbonyl)amino) cyclohexyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and formalin. ^{1}H NMR (400 MHz, D_2O) Mixture of rotamers, δ 7.76 (d, 1H), 7.53 (d, 2H), 7.41 (d, 2H), 6.71 (d, 1H), 4.44 (d, 1H), 4.21 (d, 1H), 3.68-3.515 (m, 8H), 3.51-3.49 (m, 1H), 3.41-3.32 (m, 1H), 2.65 (s, 3H), 2.15-1.93 (m, 4H), 1.82-1.72 (m, 4H), 1.57 (s, 6H). LCMS [(M+2H)/2] 263.3.

Compound 122

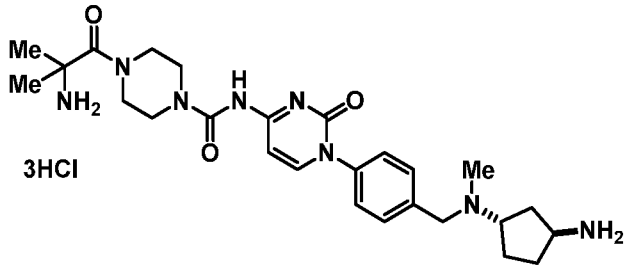


***cis*-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((4-aminocyclohexyl)(ethyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt**

[00515] Prepared in a similar fashion as Scheme C-3 from *tert*-butyl (1-(4-((1-(4-(((*cis*-4-((*tert*-butoxycarbonyl)amino)cyclohexyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and acetaldehyde. ^{1}H

NMR (400 MHz, D_2O) Mixture of rotamers, δ 7.78 (d, 1H), 7.53 (d, 2H), 7.41 (d, 2H), 6.70 (d, 1H), 4.42 (d, 1H), 3.68-3.45 (m, 10H), 3.49-3.41 (m, 1H), 3.39-3.30 (m, 1H), 3.28-3.05 (m, 1H), 2.10-1.90 (m, 4H), 1.88-1.72 (m, 4H), 1.57 (s, 6H), 1.16 (t, 3H). LCMS [(M+2H)/2] 270.3

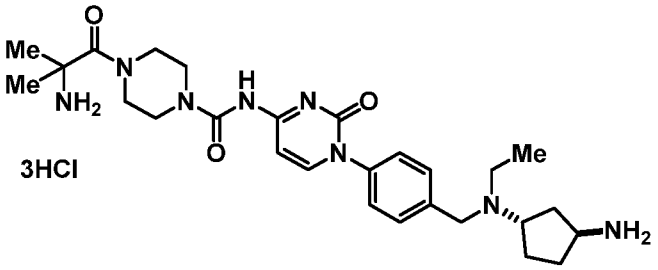
Compound 124



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((((1S,3S)-3-aminocyclopentyl)(methyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00516] Prepared in a similar fashion as Scheme C-3 from *tert*-butyl (1-(4-((1-(4-((((1S,3S)-3-((*tert*-butoxycarbonyl)amino)cyclopentyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and formalin. ^1H NMR (400 MHz, D_2O) mixture of rotamers, δ 7.84 (d, 1H), 7.59 (d, 2H), 7.48 (d, 2H), 6.76 (d, 1H), 4.55-4.50 (m, 1H), 4.22-4.15 (m, 1H), 3.95-3.80 (m, 2H), 3.65-3.55 (m, 8H), 2.69 (s, 3H), 2.45-2.20 (m, 4H), 1.95-1.64 (m, 2H), 1.63 (s, 6H). LCMS [M+H] 511.

Compound 125

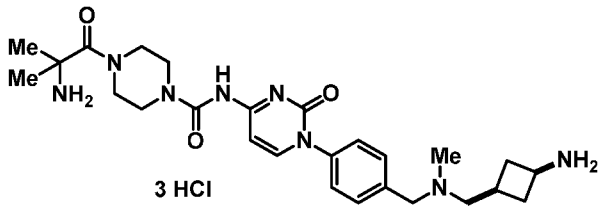


4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((((1S,3S)-3-aminocyclopentyl)(ethyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00517] Prepared in a similar fashion as Scheme C-3 from *tert*-butyl (1-(4-((1-(4-((((1S,3S)-3-((*tert*-butoxycarbonyl)amino)cyclopentyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and acetaldehyde. ^1H NMR (400 MHz, D_2O) mixture of rotamers, δ 7.80 (d, 1H), 7.56 (d, 2H), 7.44 (d, 2H), 6.72 (d, 1H), 4.45-4.38 (m, 1H), 4.35-4.25 (m, 1H), 4.00-3.94 (m, 1H), 3.85-

3.75 (m, 1H), 3.70-3.55 (m, 8H), 3.13-3.05 (m, 2H), 2.38-2.15 (m, 4H), 1.90-1.70 (m, 1H), 1.68-1.58 (m, 1H), 1.59 (s, 6H), 1.23-1.17 (m, 3H). LCMS [(M+2H)/2] 263.2.

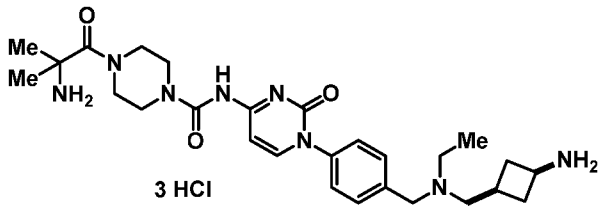
Compound 127



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((((*cis*)-3-aminocyclobutyl)methyl)(methyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00518] Prepared in a similar fashion as Scheme C-3 from *tert*-butyl (1-(4-((1-(4-(((((*cis*)-3-((*tert*-butoxycarbonyl)amino)cyclobutyl)methyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and formalin. ^{1}H NMR (400 MHz, D_2O) mixture of rotamers, δ 7.84 (d, 1H), 7.52 (d, 2H), 7.42 (d, 2H), 6.69 (d, 1H), 4.32 (d, 1H), 4.19 (d, 1H), 3.68-3.55 (m, 8H), 3.30-3.21 (m, 2H), 2.66 (s, 3H), 2.60-2.2.40 (m, 4H), 1.92-1.75 (m, 2H), 1.79 (s, 6H). LCMS [(M+2H)/2] 256.1.

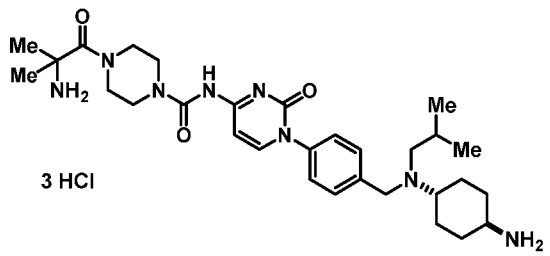
Compound 128



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((((*cis*)-3-aminocyclobutyl)methyl)(ethyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00519] Prepared in a similar fashion as Scheme C-3 from *tert*-butyl (1-(4-((1-(4-(((((*cis*)-3-((*tert*-butoxycarbonyl)amino)cyclobutyl)methyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and acetaldehyde. ^{1}H NMR (400 MHz, D_2O) mixture of rotamers, δ 7.81 (d,1H), 7.52 (d, 2H), 7.42 (d, 2H), 6.70 (d, 1H), 4.32-4.22 (m, 2H), 3.76-3.55 (m, 8H), 3.17 (t, 2H), 3.08 (q, 2H) 2.52-2.43 (m, 4H), 1.86-1.75 (m, 2H), 1.56 (s, 6H)), 1.27 (t, 3H). LCMS [(M+2H)/2] 263.2.

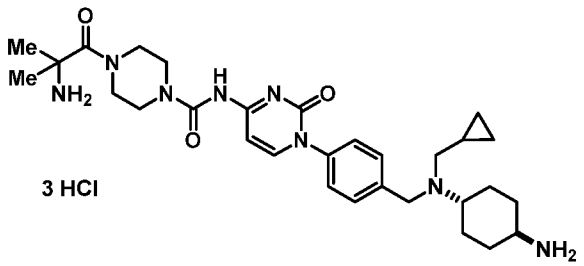
Compound 129



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((*trans*-4-aminocyclohexyl)(isobutyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00520] Prepared in a similar fashion as Scheme C-3 from *tert*-butyl (1-(4-((1-(4-(((*trans*-4-((*tert*-butoxycarbonyl)amino)cyclohexyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and isobutyraldehyde. ^{1}H NMR (500 MHz, D_2O) δ 7.95 (d, 1H), 7.74 (d, 2H), 7.59 (d, 2H), 6.87 (d, 1H), 4.57 (d, 1H), 4.45 (d, 1H), 3.86-3.71 (m, 8H), 3.46 (t, 1H), 3.29 (t, 1H), 3.22-3.15 (m, 1H), 3.05-2.99 (m, 1H), 2.41-2.16 (m, 4H), 1.94-1.83 (m, 3H), 1.75 (s, 6H), 1.65-1.49 (m, 2H), 0.98 (d, 3H), 0.86 (d, 3H). LCMS [M+H] 567.2.

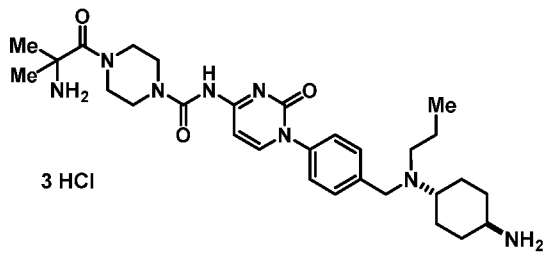
Compound 130



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((*trans*-4-aminocyclohexyl)(cyclopropylmethyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00521] Prepared in a similar fashion as Scheme C-3 from *tert*-butyl (1-(4-((1-(4-(((*trans*-4-((*tert*-butoxycarbonyl)amino)cyclohexyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and cyclopropanecarbaldehyde. ^{1}H NMR (500 MHz, D_2O) δ 8.01 (d, 1H), 7.72 (d, 2H), 7.59 (d, 2H), 6.87 (d, 1H), 4.54 (q, 2H), 3.85-3.70 (m, 8H), 3.60 (t, 1H), 3.32-3.22 (m, 2H), 3.11-3.04 (m, 1H), 2.36-2.17 (m, 4H), 1.96-1.79 (m, 2H), 1.74 (s, 6H), 1.64-1.50 (m, 2H), 1.08-1.02 (m, 1H), 0.74 (d, 2H), 0.39-0.26 (m, 2H). LCMS [M+H] 565.3.

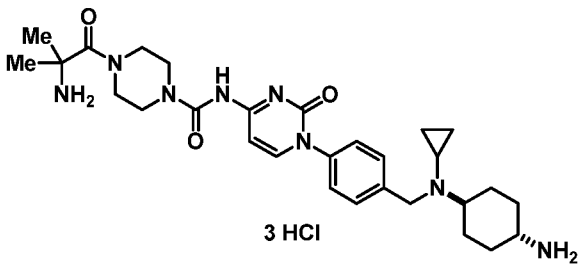
Compound 131



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((*trans*-4-aminocyclohexyl)(propyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00522] Prepared in a similar fashion as Scheme C-3 from *tert*-butyl (1-(4-((1-(4-(((*trans*-4-((*tert*-butoxycarbonyl)amino)cyclohexyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and propionaldehyde. ^{1}H NMR (500 MHz, D_2O) δ 8.00 (d, 1H), 7.71 (d, 2H), 7.60 (d, 2H), 6.87 (d, 1H), 4.58 (d, 1H), 4.40 (d, 1H), 3.85-3.69 (m, 8H), 3.47 (t, 1H), 3.33-3.19 (m, 2H), 3.18-3.07 (m, 1H), 2.37-2.21 (m, 4H), 1.97-1.81 (m, 2H), 1.75 (s, 6H), 1.71-1.50 (m, 4H), 0.92 (t, 3H). LCMS [M+H] 553.3.

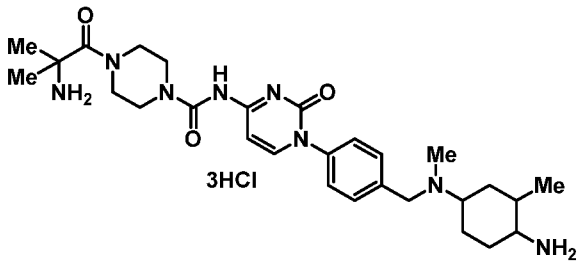
Compound 348



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((*trans* -4-aminocyclohexyl)(cyclopropyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00523] Prepared in a similar fashion as Scheme C-3 from *tert*-butyl (1-(4-((1-(4-(((*trans*-4-((*tert*-butoxycarbonyl)amino)cyclohexyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and (1-ethoxycyclopropoxy)trimethylsilane. 1H NMR (500 MHz, D2O) δ 7.99 (d, 1H), 7.72 (d, 2H), 7.56 (d, 2H), 6.86 (d, 1H), 4.63–4.46 (m, 2H), 3.89–3.60 (m, 8H), 3.56–3.41 (m, 1H), 3.38–3.22 (m, 1H), 3.01–2.86 (m, 1H), 2.46–2.32 (m, 2H), 2.31–2.19 (m, 2H), 2.00–1.89 (m, 2H), 1.74 (s, 6H), 1.63–1.47 (m, 2H), 1.09–0.80 (m, 4H). LCMS [M+H] 551.5.

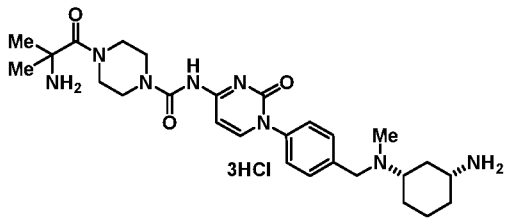
Compound 337



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((4-amino-3-methylcyclohexyl)(methyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00524] Prepared in a similar fashion to Scheme C-3 from *tert*-butyl (4-((4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)amino)-2-methylcyclohexyl)carbamate and formaldehyde. ^{1}H NMR (400 MHz, D_2O) Mixture of diastereomers δ 7.82 (d, 1H), 7.55 (d, 2H), 7.44 (d, 2H), 6.73 (d, 1H), 4.63 (d, 1H), 4.49-4.46 (m, 2H), 4.20-4.08 (m, 3H), 3.94 (d, 1H), 3.65-3.59 (m, 8H), 3.42-3.36 (m, 3H), 2.86-2.81 (m, 1H), 2.67-2.58 (m, 4H), 2.12-1.93 (m, 4H), 1.60 (s, 6H), 1.46 (m, 1H), 1.22-1.14 (m, 1H), 1.03-0.99 (m, 3H). LCMS [(M+2H)/2] 270.3.

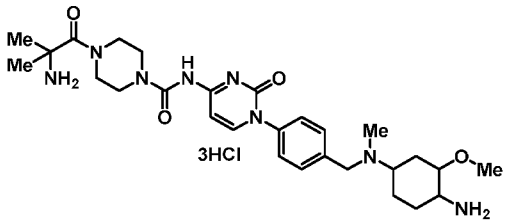
Compound 323



***cis*-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((3-aminocyclohexyl)(methyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt**

[00525] Prepared in a similar fashion to Scheme C-3 from *cis-tert*-butyl (3-((4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)amino)cyclohexyl)carbamate and formaldehyde. ^{1}H NMR (400 MHz, D_2O) δ 7.89 (d, 1H), 7.58 (d, 2H), 7.47 (d, 2H), 4.51 (d, 2H), 4.31-4.23 (m, 1H), 3.75-3.61 (m, 7H), 3.42-3.39 (m, 1H), 3.41-3.22 (m, 1H), 2.69 (s, 3H), 2.42-2.32 (m, 1H), 2.15-2.09 (m, 1H) 2.05-1.97 (m, 3H), 1.61 (s, 1H) 1.60-1.59 (m, 2H), 1.33-1.21 (m, 2H). LCMS [M+H] 525.5.

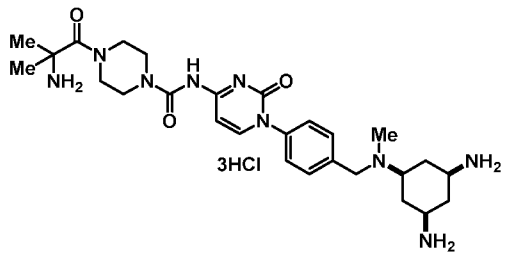
Compound 340



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((4-amino-3-methoxycyclohexyl)(methyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00526] Prepared in a similar fashion to Scheme C-3 from *tert*-butyl (4-((4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)amino)-2-methoxycyclohexyl)carbamate and formaldehyde. ^{1}H NMR (400 MHz, D_2O) mixture of diastereomers, δ 7.82 (d, 1H), 7.55 (d, 2H), 7.44 (d, 2H), 6.73 (d, 1H), 4.63 (d, 1H), 4.49-4.46 (m, 2H), 4.20-4.08 (m, 3H), 3.94 (d, 1H), 3.65-3.59 (m, 8H), 3.42-3.36 (m, 3H), 2.86-2.81 (m, 1H), 2.67-2.58 (m, 4H), 2.12-1.93 (m, 4H), 1.60 (s, 6H), 1.46 (m, 1H), 1.22-1.14 (m, 1H), 1.03-0.99 (m, 3H). LCMS [(M+2H)/2] 278.3.

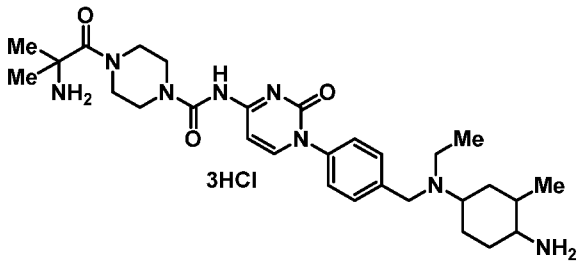
Compound 325



***cis*-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((3,5-diaminocyclohexyl)(methyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt**

[00527] Prepared in a similar fashion to Scheme C-3 from *cis-tert*-butyl (2-hydroxypropan-2-yl) (5-((4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)amino)cyclohexane-1,3-diyl)dicarbamate and formaldehyde. ^{1}H NMR (400 MHz, D_2O) Mixture of rotamers, δ 7.86 (d, 1H), 7.56 (d, 2H), 7.44 (d, 2H), 6.70 (d, 1H), 4.41 (bs, 2H), 3.57-3.62 (m, 10H), 3.38 (t, 3H), 3.24 (s, 1H), 2.70 (s, 3H), 2.44 (s, 2H), 2.35 (d, 1H), 1.82-1.73 (m, 2H) 1.62-1.52 (m, 6H). LCMS [M+H] 540.4.

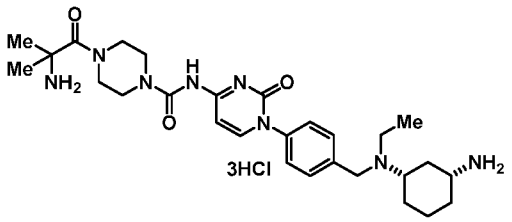
Compound 338



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((4-amino-3-methylcyclohexyl)(ethyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00528] Prepared in a similar fashion to Scheme C-3 from *tert*-butyl (4-((4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)amino)-2-methylcyclohexyl)carbamate and acetaldehyde. ^{1}H NMR (400 MHz, D_2O) Mixture of diastereomers, δ 7.82 (d, 1H), 7.53 (d, 2H), 7.42 (d, 2H), 6.70 (d, 1H) 4.41 (d, 2H), 4.29 (d, 2H), 3.62-3.58 (m, 8H), 3.50 (s, 2H), 3.40-3.37 (m, 2H), 3.20-3.12 (m, 3H), 2.81 (t, 1H), 2.10-2.00 (m, 3H), 1.58 (s, 6H), 1.48-1.41 (m, 1H), 1.22-1.11 (m, 3H), 0.92-0.87 (m, 3H). LCMS [(M+2H)/2] 277.3.

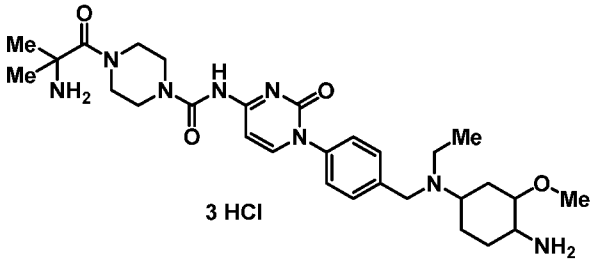
Compound 324



***cis*-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((3-aminocyclohexyl)(ethyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt**

[00529] Prepared in a similar fashion to Scheme C-3 from *cis-tert*-butyl (3-((4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)amino)cyclohexyl)carbamate and acetaldehyde. ^{1}H NMR (400 MHz, D_2O) δ 7.88-7.46 (d, 1H), 7.58 (d, 2H), 7.47 (d, 2H), 6.75 (d, 1H), 4.47 (d, 1H), 4.29 (d, 1H), 3.64 (d, 1H), 3.40 (d, 8H), 3.42-3.40 (m, 2H), 3.25-3.17 (m, 3H), 2.40-2.30 (m, 1H) 2.10-1.96 (m, 3H), 1.81-1.65 (m, 1H) 1.62 (s, 6H), 1.40-1.25 (m, 2H), 1.21 (t, 3H). LCMS [M+H] 539.5.

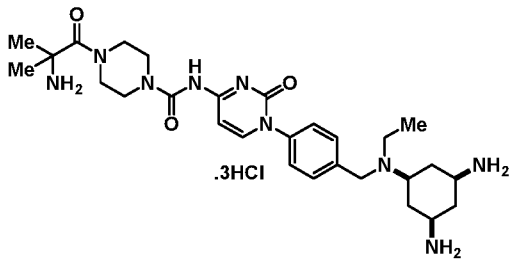
Compound 341



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((4-amino-3-methoxycyclohexyl)(ethyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00530] Prepared in a similar fashion to Scheme C-3 from *tert*-butyl (4-((4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)amino)-2-methoxycyclohexyl)carbamate and acetaldehyde. ^{1}H NMR (400 MHz, D_2O) Mixture of diastereomers, δ 8.01 (d, 1H), 7.60 (d, 2H), 7.48 (d, 2H), 6.71 (d, 1H), 4.53-4.48 (m, 1H), 4.31-4.26 (m, 1H), 3.66-3.61 (m, 4H), 3.51-3.49 (m, 8H), 3.30 (s, 3H), 3.17 (bs, 2H), 2.31-2.28 (m, 1H), 2.09 (d, 1H) 1.94-1.89 (m, 3H), 1.76 (bs, 1H), 1.60 (s, 6H), 1.21 (m, 3H). LCMS [M+H] 569.6.

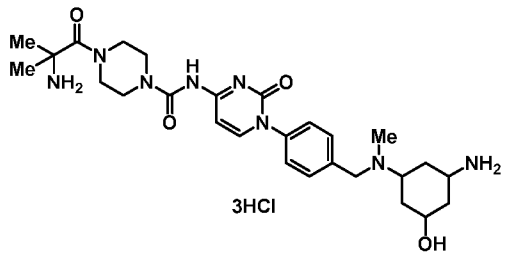
Compound 333



***cis*-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((3,5-diaminocyclohexyl)(ethyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt**

[00531] Prepared in a similar fashion to Scheme C-3 from *cis-tert*-butyl (2-hydroxypropan-2-yl) (5-((4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)amino)cyclohexane-1,3-diyl)dicarbamate and acetaldehyde. ^{1}H NMR (400 MHz, D_2O) Mixture of rotamers, δ 7.91(d, 1H), 7.55 (d, 2H), 7.45 (d, 2H), 6.70 (d, 1H), 4.42 (bs, 2H), 3.62-3.46 (m, 9H), 3.38-3.35 (m, 2H), 3.24 (bs, 2H), 2.42-2.33 (m, 4H), 1.82 (d, 2H), 1.57 (s, 6H), 1.19 (t, 3H). LCMS [M+H] 554.4.

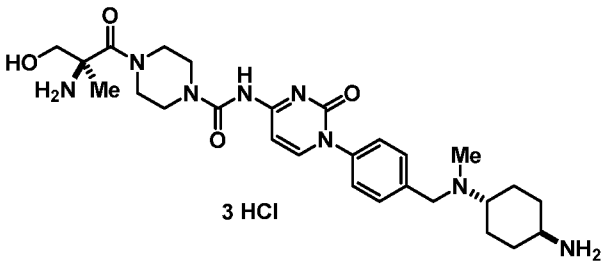
Compound 343



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((3-amino-5-hydroxycyclohexyl)(methyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00532] Prepared in a similar fashion to Scheme C-3 from *tert*-butyl (1-(4-((1-(4-(((3-((*tert*-butoxycarbonyl)amino)-5-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)(methyl)amino) methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and formaldehyde. ^{1}H NMR (400 MHz, D_2O) δ 7.77 (d, 1H), 7.58 (d, 2H), 7.44 (d, 1H), 7.30 (d, 1H), 6.73 (d, 1H), 4.33 (m, 3H), 4.25-4.23 (m, 2H), 3.98-3.96 (m, 3H), 3.86-3.59 (m, 7H), 3.52-3.36 (m, 3H), 3.27 (m, 2H), 2.71-2.64 (m, 4H), 2.61-2.58 (m, 2H), 2.02-1.90 (m, 3H), 1.78 (m, 3H), 1.59 (s, 6H), 1.29-1.25 (d, 6H), 1.21-1.19 (m, 1H). LCMS [(M+2H)/2] 271.2.

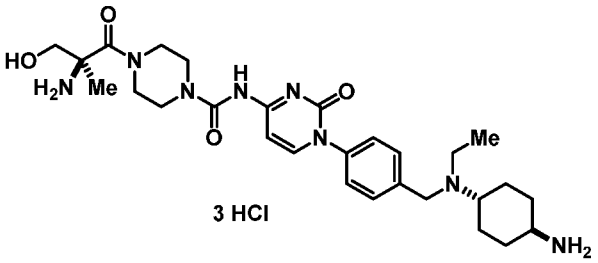
Compound 286



4-((*S*)-2-Amino-3-hydroxy-2-methylpropanoyl)-N-(1-(4-(((*trans*-4-aminocyclohexyl)(methyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00533] Prepared in a similar fashion as Scheme C-3 from *tert*-butyl (2R,4S)-4-(4-((1-(4-(((*trans*-4-((*tert*-butoxycarbonyl)amino)cyclohexyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazine-1-carbonyl)-2-(*tert*-butyl)-4-methyloxazolidine-3-carboxylate and formalin. ^{1}H NMR (500 MHz, D_2O) δ 7.97 (d, 1H), 7.65 (d, 2H), 7.54 (d, 2H), 6.81 (d, 1H), 4.56 (d, 1H), 4.28 (d, 1H), 4.12 (d, 1H), 3.86 (d, 1H), 3.76–3.68 (m, 8H), 3.41 (t, 1H), 3.23 (t, 1H), 2.74 (s, 3H), 2.29–2.18 (m, 4H), 1.83–1.76 (m, 2H), 1.64 (s, 3H), 1.53 (q, 2H). LCMS [M+H] 541.3.

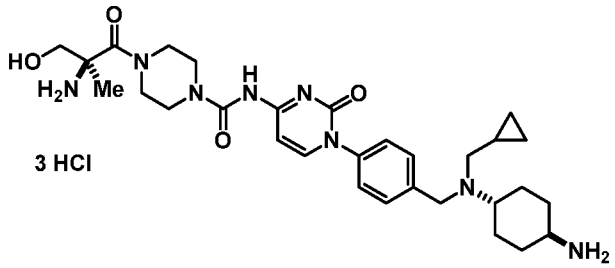
Compound 287



4-((*S*)-2-Amino-3-hydroxy-2-methylpropanoyl)-N-(1-(4-(((*trans*-4-aminocyclohexyl)(ethyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00534] Prepared in a similar fashion as scheme C-3 from *tert*-butyl (2R,4S)-4-(4-((1-(4-(((*trans*-4-((*tert*-butoxycarbonyl)amino)cyclohexyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazine-1-carbonyl)-2-(*tert*-butyl)-4-methyloxazolidine-3-carboxylate and acetaldehyde. ^{1}H NMR (500 MHz, D_2O) δ 8.00 (d, 1H), 7.65 (d, 2H), 7.54 (d, 2H), 6.81 (d, 1H), 4.52 (d, 1H), 4.33 (d, 1H), 4.11 (d, 1H), 3.86 (d, 1H), 3.76–3.68 (m, 8H), 3.41 (t, 1H), 3.31–3.20 (m, 3H), 2.24–2.18 (m, 4H), 1.86–1.76 (m, 2H), 1.64 (s, 3H), 1.51 (q, 2H), 1.27 (t, 3H). LCMS [M+H] 555.4.

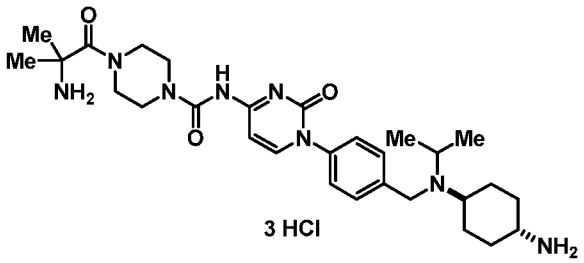
Compound 277



4-((S)-2-Amino-3-hydroxy-2-methylpropanoyl)-N-(1-(4-(((*trans*-4-aminocyclohexyl)(cyclopropylmethyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

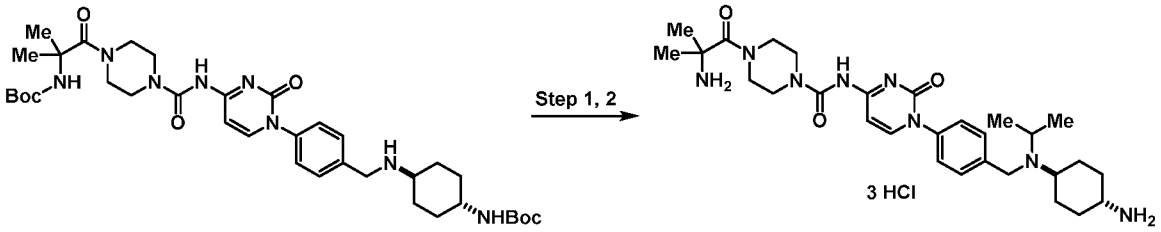
[00535] Prepared in a similar fashion as Scheme C-3 from *tert*-butyl (2R,4S)-4-(4-((1-(4-(((*trans*-4-((*tert*-butoxycarbonyl)amino)cyclohexyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazine-1-carbonyl)-2-(*tert*-butyl)-4-methyloxazolidine-3-carboxylate and cyclopropane carboxaldehyde. ^{1}H NMR (500 MHz, D_2O) δ 7.95 (d, 1H), 7.69 (d, 2H), 7.56 (d, 2H), 6.85 (d, 1H), 4.55 (d, 1H), 4.50 (d, 1H), 4.15 (d, 1H), 3.90 (d, 1H), 3.79–3.68 (m, 8H), 3.60–3.54 (m, 1H), 3.28–3.23 (m, 2H), 3.08–3.03 (m, 1H), 2.33–2.16 (m, 4H), 1.90–1.79 (m, 2H), 1.68 (s, 3H), 1.61–1.49 (m, 2H), 1.08–0.99 (m, 1H), 0.74–0.67 (m, 2H), 0.36–0.25 (m, 2H). LCMS [M+H] 581.4.

Compound 356



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((*trans*-4-aminocyclohexyl)(isopropyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

Scheme C-5



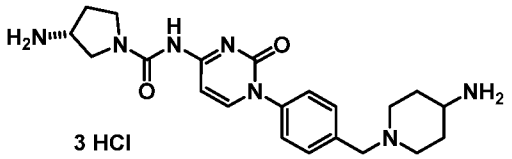
Reagents: 1) *i*-PrBr, K_2CO_3, DMF, 55 °C, 40h 2) HCl in MeOH, rt, 22h.

[00536] Step 1. *tert*-butyl (*trans*-4-((4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl) piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)yl)benzyl)(isopropyl)amino)cyclohexyl) carbamate. A mixture of *tert*-butyl (*trans*-4-((4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)amino)cyclohexyl)carbamate (71.1 mg, 0.10 mmol), K_2CO_3 (44.1 mg, 0.32 mmol), and 2-bromopropane (30 µL, 0.32 mmol) in DMF (0.5 mL) was stirred at 55 °C for 18h. Another portion of 2-bromopropane (30 µL, 0.32 mmol) was added and stirring continued at 55 °C for 22 h. The mixture was cooled, diluted with EtOAc (10 mL), washed with sat. aq. $NaHCO_3$ (2x10 mL) and brine (2x10 mL), dried over Na_2SO_4, decanted, and concentrated. The residue was purified by flash chromatography (Hexanes/EtOAc/MeOH) to provide the title compound (44.5 mg, 59%) as a white solid. LCMS [M+H] 753.9.

[00537] Step 2. 4-(2-amino-2-methylpropanoyl)-N-(1-(4-(((*trans*-4-aminocyclohexyl)(isopropyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt. A mixture of *tert*-butyl (*trans*-4-((4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)(isopropyl)amino)cyclohexyl)carbamate (44.5 mg, 0.059 mmol) and 2M HCl in MeOH (3 mL) was stirred at rt for 22h and concentrated. The residue

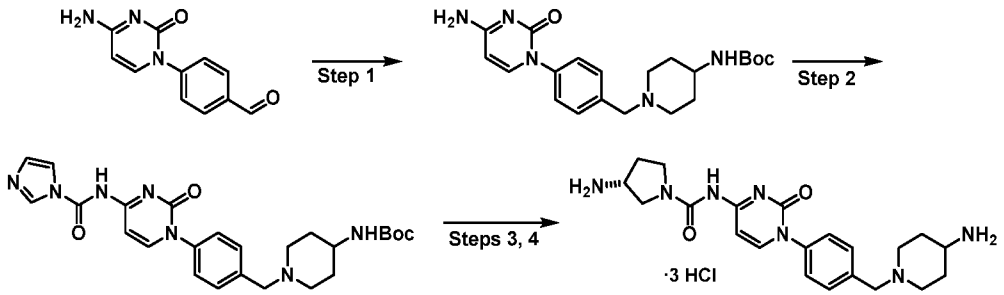
was purified by reverse phase HPLC (CH_3CN/H_20/TFA), and the product fractions were converted to the HCl salt with 2M HCl in MeOH to afford the title compound (22.3 mg, 57.0 %) as a white solid. ^1H NMR (500 MHz, D_2O) δ 7.67 (d, 2H), 7.53 (d, 2H), 7.40 (d, 1H), 6.07 (d, 1H), 5.39–5.26 (m, 1H), 4.40 (s, 2H), 3.91–3.59 (m, 8H), 3.43–3.23 (m, 2H), 2.47–2.33 (m, 2H), 2.32–2.19 (m, 2H), 1.77 (s, 6H), 1.71–1.55 (m, 4H), 1.52 (d, 6H). LCMS [(M+2H)/2] 277.3.

Compound 367



(*R*)-3-Amino-*N*-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)pyrrolidine-1-carboxamide hydrochloride salt

Scheme C-6



Reagents: 1) *tert*-butyl piperidin-4-ylcarbamate, DIPEA, $NaBH(OAc)_3$, DCE, CH_3CN, rt, 16h 2) CDI, CH_2Cl_2, rt, 16h 3) *tert*-butyl (*R*)-pyrrolidin-3-ylcarbamate, CH_3CN, rt, 20h 4) HCl, MeOH, rt, 4h.

[00538] Step 1: *tert*-butyl (1-(4-(4-amino-2-oxopyrimidin-1(2*H*)-yl)benzyl)piperidin-4-yl)carbamate. To a suspension of 4-(4-amino-2-oxopyrimidin-1(2*H*)-yl)benzaldehyde (1.00 g 4.6 mmol) and *tert*-butyl piperidin-4-ylcarbamate (1.39 g, 7.0 mmol) in 1:1 DCE:MeCN (25 mL) was added DIPEA (1.61 mL, 9.2 mmol) and $NaBH(OAc)_3$ (1.97 g, 9.3 mmol). The reaction was stirred at rt for 16h. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in $CHCl_3$ and washed with 10% NaOH. Purification by column chromatography ($MeOH:CHCl_3$) afforded the title compound.

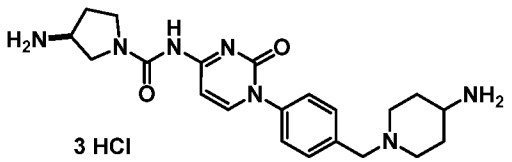
[00539] Step 2: *tert*-butyl (1-(4-(4-(1*H*-imidazole-1-carboxamido)-2-oxopyrimidin-1(2*H*)-yl)benzyl)piperidin-4-yl)carbamate. A suspension of *tert*-butyl (1-(4-(4-amino-2-oxopyrimidin-1(2*H*)-yl)benzyl)piperidin-4-yl)carbamate (350 mg , 0.82 mmol) and CDI (195 mg, 0.84 mmol) in CH_2Cl_2 was stirred at rt for 16h. The solvent was removed under reduced

pressure, and the residue was triturated with EtOAc. The solid was collected by filtration to give the title compound.

[00540] Step 3: *tert*-butyl (*R*)-(1-(4-(4-(3-((*tert*-butoxycarbonyl)amino)pyrrolidine-1-carboxamido)-2-oxopyrimidin-1(2*H*)-yl)benzyl)piperidin-4-yl)carbamate. A mixture of *tert*-butyl (1-(4-(4-(1*H*-imidazole-1-carboxamido)-2-oxopyrimidin-1(2*H*)-yl)benzyl)piperidin-4-yl)carbamate (60 mg, 0.12 mmol) and *tert*-butyl (*R*)-pyrrolidin-3-ylcarbamate (22.6 mg, 0.12 mmol) in MeCN (2 mL) was stirred at rt for 20h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (Hexanes:EtOAc:MeOH) to afford the title compound.

[00541] Step 4. (*R*)-3-amino-*N*-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)pyrrolidine-1-carboxamide hydrochloride salt. A mixture of *tert*-utyl (*R*)-(1-(4-(4-(3-((*tert*-butoxycarbonyl)amino)pyrrolidine-1-carboxamido)-2-oxopyrimidin-1(2*H*)-yl)benzyl)piperidin-4-yl)carbamate (63.1 mg, 0.10 mmol) and 2M HCl in MeOH (4.0 mL) was stirred at rt for 4h. The mixture was concentrated to dryness and dry MeOH added and removed under reduced pressure to give the title compound. ^{1}H NMR (500 MHz, D_2O) δ 7.87 (d, 1H), 7.56 (d, 2H), 7.45 (d, 2H), 7.00 (d, 1H), 4.32 (s, 2H), 3.92-4.03 (m, 1H), 3.72-3.88 (m, 1H), 3.50-3.70 (m, 5H), 3.37-3.49 (m, 1H), 3.02-3.14 (m, 2H), 2.29-2.44 (m, 1H), 2.17-2.26 (m, 2H), 2.03-2.16 (m, 1H), 1.73-1.87 (m, 2H). LCMS [M+H] 412.3.

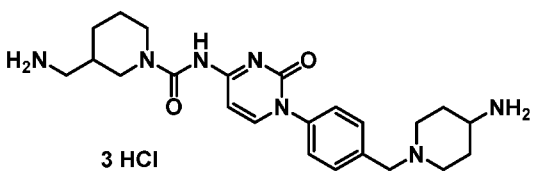
Compound 366



(*S*)-3-Amino-*N*-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)pyrrolidine-1-carboxamide hydrochloride salt

[00542] Prepared in a similar fashion to Scheme C-6 from *tert*-butyl (1-(4-(4-(1*H*-imidazole-1-carboxamido)-2-oxopyrimidin-1(2*H*)-yl)benzyl)piperidin-4-yl)carbamate and *tert*-butyl (*S*)-pyrrolidin-3-ylcarbamate. LCMS [M+H] 412.3.

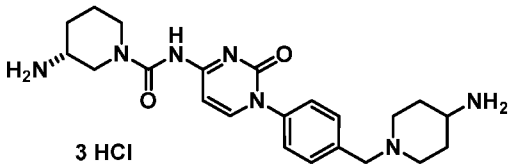
Compound 46



3-(Aminomethyl)-*N*-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperidine-1-carboxamide hydrochloride salt

[00543] Prepared in a similar fashion to Scheme C-6 from *tert*-butyl (1-(4-(4-(1*H*-imidazole-1-carboxamido)-2-oxopyrimidin-1(2*H*)-yl)benzyl)piperidin-4-yl)carbamate and *tert*-butyl (piperidin-3-ylmethyl)carbamate. ^{1}H NMR (500 MHz, D_2O) δ 7.81 (d, 1H), 7.56 (d, 2H), 7.44 (d, 2H), 6.71 (d, 1H), 4.31 (s, 2H), 3.93-4.01 (m, 1H), 3.78-3.89 (m, 1H), 3.52-3.61 (m, 2H), 3.39-3.49 (m, 1H), 3.07 (m, 3H), 2.88-2.95 (m, 1H), 2.79-2.87 (m, 2H), 2.16-2.27 (m, 2H), 1.67-1.94 (m, 5H), 1.40-1.53 (m, 1H), 1.21-1.33 (m, 1H). LCMS [M+H] 440.3.

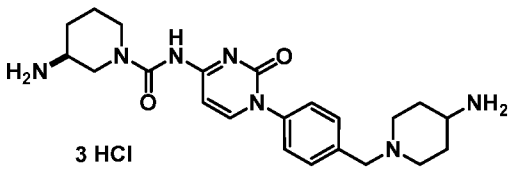
Compound 47



(*R*)-3-Amino-*N*-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperidine-1-carboxamide hydrochloride salt

[00544] Prepared in a similar fashion to Scheme C-6 from *tert*-butyl (1-(4-(4-(1*H*-imidazole-1-carboxamido)-2-oxopyrimidin-1(2*H*)-yl)benzyl)piperidin-4-yl)carbamate and *tert*-butyl (R)-piperidin-3-ylcarbamate. ^{1}H NMR (500 MHz, D_2O) δ 7.81 (d, 1H), 7.56 (d, 2H), 7.44 (d, 2H), 6.70 (d, 1H), 4.31 (s, 2H), 3.91-3.98 (m, 1H), 3.62-3.70 (m, 1H), 3.52-3.61 (m, 2H), 3.25-3.48 (m, 4H), 3.03-3.13 (m, 2H), 2.16-2.26 (m, 2H), 1.98-2.07 (m, 1H), 1.70-1.86 (m, 3H), 1.51-1.69 (m, 2H). LCMS [M+H] 426.2.

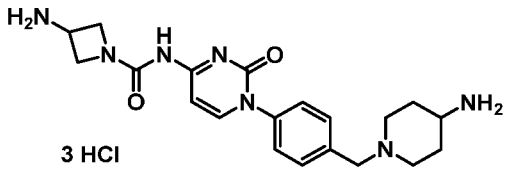
Compound 48



(*S*)-3-Amino-*N*-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperidine-1-carboxamide hydrochloride salt

[00545] Prepared in a similar fashion to Scheme C-6 from *tert*-butyl (1-(4-(4-(1*H*-imidazole-1-carboxamido)-2-oxopyrimidin-1(2*H*)-yl)benzyl)piperidin-4-yl)carbamate and *tert*-butyl (S)-piperidin-3-ylcarbamate. ^{1}H NMR (500 MHz, D_2O) δ 7.81 (d, 1H), 7.56 (d, 2H), 7.44 (d, 2H), 6.70 (d, 1H), 4.31 (br. s., 1H), 3.90-3.99 (m, 1H), 3.62-3.72 (m, 1H), 3.52-3.61 (m, 2H), 3.23-3.49 (m, 4H), 3.01-3.14 (m, 2H), 2.16-2.28 (m, 2H), 1.97-2.08 (m, 1H), 1.70-1.87 (m, 3H), 1.51-1.70 (m, 2H). LCMS [M+H] 426.1.

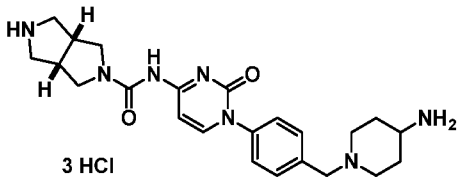
Compound 49



3-Amino-*N*-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)azetidine-1-carboxamide hydrochloride salt

[00546] Prepared in a similar fashion to Scheme C-6 from *tert*-butyl (1-(4-(4-(1*H*-imidazole-1-carboxamido)-2-oxopyrimidin-1(2*H*)-yl)benzyl)piperidin-4-yl)carbamate and *tert*-butyl azetidin-3-ylcarbamate. ^{1}H NMR (500 MHz, D_2O) δ 7.89 (d, 1H), 7.56 (d, 2H), 7.44 (d, 2H), 7.02 (d, 1H), 4.41-4.48 (m, 2H), 4.31 (s, 2H), 4.07-4.20 (m, 3H), 3.51-3.61 (m, 2H), 3.38-3.49 (m, 1H), 3.02-3.13 (m, 2H), 2.17-2.26 (m, 2H), 1.74-1.87 (m, 2H). LCMS [M+H] 398.2.

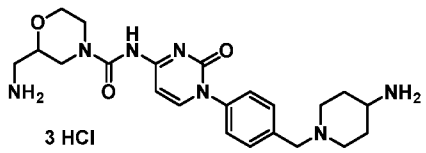
Compound 50



***cis*-*N*-(1-(4-((4-Aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxamide hydrochloride salt**

[00547] Prepared in a similar fashion to Scheme C-6 from *tert*-butyl (1-(4-(4-(1*H*-imidazole-1-carboxamido)-2-oxopyrimidin-1(2*H*)-yl)benzyl)piperidin-4-yl)carbamate and *tert*-butyl (*cis*)-hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate. ^{1}H NMR (500 MHz, D_2O) δ 7.91 (d, 1H), 7.57 (d, 2H), 7.45 (d, 2H), 6.94 (d, 1H), 4.32 (s, 2H), 3.67-3.79 (m, 2H), 3.39-3.62 (m, 7H), 3.13-3.21 (m, 4H), 3.03-3.12 (m, 2H), 2.17-2.27 (m, 2H), 1.73-1.88 (m, 2H). LCMS [M+H] 438.1.

Compound 51

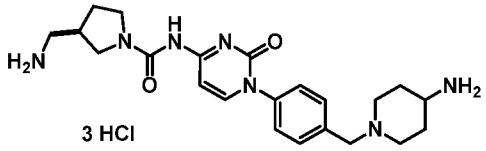


2-(Aminomethyl)-*N*-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)morpholine-4-carboxamide hydrochloride salt

[00548] Prepared in a similar fashion to Scheme C-6 from *tert*-butyl (1-(4-(4-(1*H*-imidazole-1-carboxamido)-2-oxopyrimidin-1(2*H*)-yl)benzyl)piperidin-4-yl)carbamate and *tert*-butyl (morpholin-2-ylmethyl)carbamate. ^{1}H NMR (500 MHz, D_2O) δ 7.72 (d, 1H), 7.50 (d, 2H),

7.38 (d, 2H), 6.66 (d, 1H), 4.25 (s, 2H), 3.95 (d, 1H), 3.79-3.91 (m, 2H), 3.62-3.72 (m, 1H), 3.44-3.58 (m, 3H), 3.31-3.43 (m, 1H), 2.97-3.13 (m, 4H), 2.88-2.96 (m, 1H), 2.74-2.86 (m, 1H), 2.09-2.21 (m, 2H), 1.67-1.82 (m, 2H). LCMS [M+H] 442.2.

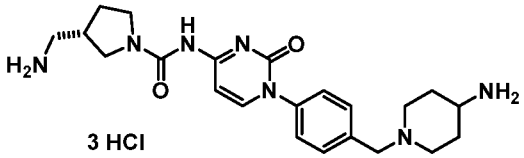
Compound 52



(*R*)-3-(Aminomethyl)-*N*-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)pyrrolidine-1-carboxamide hydrochloride salt

[00549] Prepared in a similar fashion to Scheme C-6 from *tert*-butyl (1-(4-(4-(1*H*-imidazole-1-carboxamido)-2-oxopyrimidin-1(2*H*)-yl)benzyl)piperidin-4-yl)carbamate and *tert*-butyl (S)-(pyrrolidin-3-ylmethyl)carbamate. ^{1}H NMR (500 MHz, D_2O) δ 7.94 (d, 1H), 7.59 (d, 2H), 7.47 (d, 2H), 6.98 (d, 1H), 4.34 (s, 2H), 3.34-3.83 (m, 7H), 2.95-3.21 (m, 4H), 2.47-2.68 (m, 1H), 2.05-2.31 (m, 3H), 1.62-1.91 (m, 3H). LCMS [M+H] 426.3.

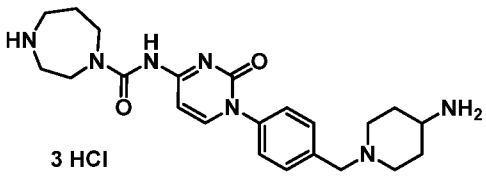
Compound 53



(*S*)-3-(Aminomethyl)-*N*-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)pyrrolidine-1-carboxamide hydrochloride salt

[00550] Prepared in a similar fashion to Scheme C-6 from *tert*-butyl (1-(4-(4-(1*H*-imidazole-1-carboxamido)-2-oxopyrimidin-1(2*H*)-yl)benzyl)piperidin-4-yl)carbamate and *tert*-butyl (R)-(pyrrolidin-3-ylmethyl)carbamate. ^{1}H NMR (500 MHz, D_2O) δ 7.92 (d, 1H), 7.59 (d, 2H), 7.47 (d, 2H), 7.00 (d, 1H), 4.33 (s, 2H), 3.36-3.83 (m, 7H), 2.96-3.21 (m, 4H), 2.47-2.68 (m, 1H), 2.06-2.30 (m, 3H), 1.62-1.90 (m, 3H). LCMS [M+H] 426.4.

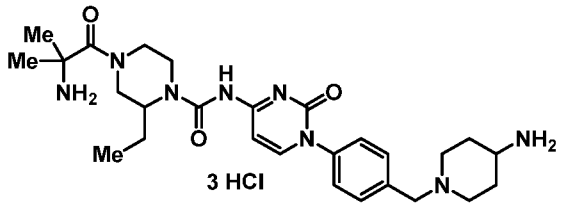
Compound 54



***N*-(1-(4-((4-Aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-1,4-diazepane-1-carboxamide hydrochloride salt**

[00551] Prepared in a similar fashion to Scheme C-6 from *tert*-butyl (1-(4-(4-(1*H*-imidazole-1-carboxamido)-2-oxopyrimidin-1(2*H*)-yl)benzyl)piperidin-4-yl)carbamate and *tert*-butyl 1,4-diazepane-1-carboxylate. ^{1}H NMR (500 MHz, D_2O) δ 7.86 (d, 1H), 7.59 (d, 2H), 7.47 (d, 2H), 6.72-6.85 (m, 1H), 4.33 (s, 2H), 3.74-3.88 (m, 2H), 3.65 (t, 2H), 3.58 (d, 2H), 3.41-3.51 (m, 1H), 3.32-3.39 (m, 2H), 3.26-3.32 (m, 2H), 3.04-3.15 (m, 2H), 2.19-2.29 (m, 2H), 2.03-2.14 (m, 2H), 1.75-1.89 (m, 2H). LCMS [M+H] 426.4.

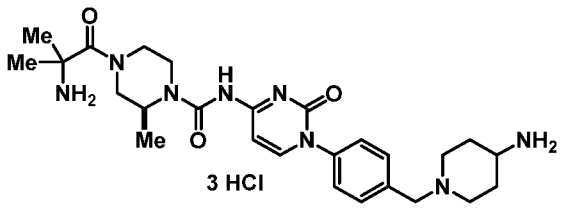
Compound 55



4-(2-Amino-2-methylpropanoyl)-*N*-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2-ethylpiperazine-1-carboxamide hydrochloride salt

[00552] Prepared in a similar fashion to Scheme C-6 from *tert*-butyl (1-(4-(4-(1*H*-imidazole-1-carboxamido)-2-oxopyrimidin-1(2*H*)-yl)benzyl)piperidin-4-yl)carbamate and *tert*-butyl (1-(3-ethylpiperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate. ^{1}H NMR (500 MHz, D_2O) δ 7.82 (d, 1H), 7.59 (d, 2H), 7.47 (d, 2H), 6.70 (d, 1H), 4.34 (s, 2H), 4.22-4.31 (m, 1H), 4.06-4.18 (m, 1H), 3.95-4.05 (m, 1H), 3.55-3.64 (m, 2H), 3.41-3.51 (m, 1H), 3.16-3.41 (m, 3H), 2.92-3.16 (m, 3H), 2.19-2.29 (m, 2H), 1.76-1.90 (m, 2H), 1.57-1.70 (m, 7H), 1.45-1.56 (m, 1H), 0.78 (t, 3H). LCMS [M+H] 525.3.

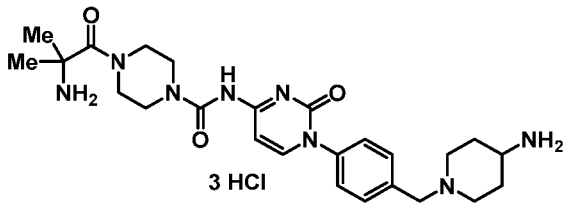
Compound 56



(*S*)-4-(2-Amino-2-methylpropanoyl)-*N*-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2-methylpiperazine-1-carboxamide hydrochloride salt

[00553] Prepared in a similar fashion as Scheme C-6 from *tert*-butyl (1-(4-(4-(1H-imidazole-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate and *tert*-butyl (S)-(2-methyl-1-(3-methylpiperazin-1-yl)-1-oxopropan-2-yl)carbamate. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.26 (s, 1H), 7.84 (d, 2H), 7.67 (d, 2H), 6.82 (s, 1H), 4.66 (s, 1H), 4.47 (s, 2H), 4.29 (d, 3H), 3.64 (d, 2H), 3.57-3.18 (m, 4H), 2.29 (d, 2H), 2.09 (t, 2H), 1.75 (s, 3H), 1.72 (s, 3H), 1.30 (s, 3H). LCMS [M+H] 511.3.

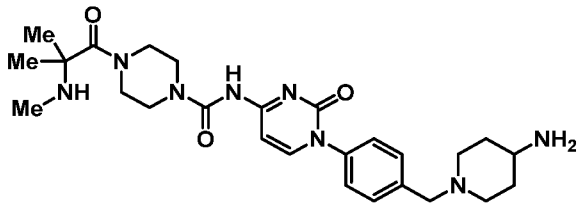
Compound 57



4-(2-Amino-2-methylpropanoyl)-*N*-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00554] Prepared in a similar fashion as Scheme C-6 from *tert*-butyl (1-(4-(4-(1H-imidazole-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate and *tert*-butyl (2-methyl-1-oxo-1-(piperazin-1-yl)propan-2-yl)carbamate. LCMS [M+H] 497.3.

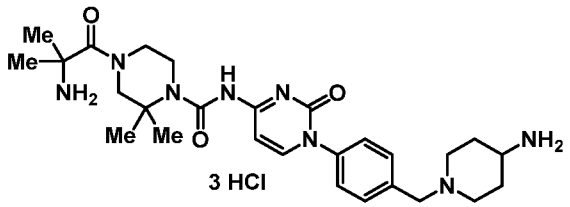
Compound 96



N-(1-(4-((4-Aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-4-(2-methyl-2-(methylamino)propanoyl)piperazine-1-carboxamide

[00555] Prepared in a similar fashion as Scheme C-6 from *tert*-butyl (1-(4-(4-(1H-imidazole-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate and benzyl methyl(2-methyl-1-oxo-1-(piperazin-1-yl)propan-2-yl)carbamate. ^{1}H NMR (500 MHz, CD_3OD) δ 7.71 (d, 1H), 7.52 (d, 2H), 7.41 (d, 2H), 6.37-6.76 (m, 1H), 3.64-3.78 (m, 10H), 3.10-3.20 (m, 1H), 2.99-3.09 (m, 2H), 2.67 (s, 3H), 2.22-2.32 (m, 2H), 1.98-2.05 (m, 2H), 1.65-1.76 (m, 8H). LCMS [M+H] 511.3.

Compound 58

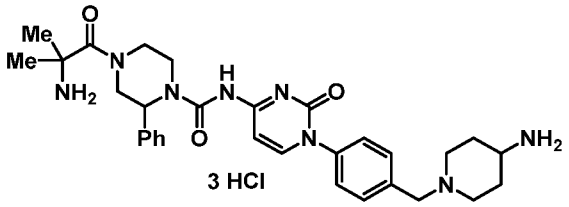


4-(2-Amino-2-methylpropanoyl)-*N*-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2,2-dimethylpiperazine-1-carboxamide hydrochloride salt

[00556] Prepared in a similar fashion as Scheme C-6 from *tert*-butyl (1-(4-(4-(1H-imidazole-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate and *tert*-butyl (1-(3,3-dimethylpiperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate. ^{1}H NMR

(400 MHz, D_2O) δ 8.06 (d, 1H), 7.72 (d, 2H), 7.60 (d, 2H), 6.76 (d, 1H), 4.46 (s, 2H), 4.05–3.63 (m, 8H), 3.63–3.50 (m, 1H), 3.22 (t, 2H), 2.35 (d, 2H), 2.03–1.88 (m, 2H), 1.75 (s, 6H), 1.56 (s, 6H). LCMS [M+H] 525.3.

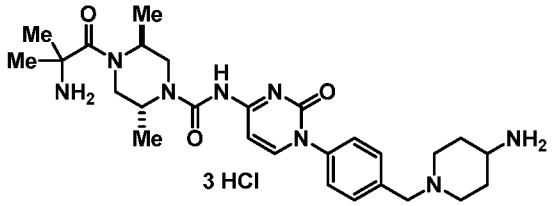
Compound 59



4-(2-Amino-2-methylpropanoyl)-*N*-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2-phenylpiperazine-1-carboxamide hydrochloride salt

[00557] Prepared in a similar fashion as Scheme C-6 from *tert*-butyl (1-(4-(4-(1H-imidazole-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate and *tert*-butyl (2-methyl-1-oxo-1-(3-phenylpiperazin-1-yl)propan-2-yl)carbamate. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.39 (d, 1H), 7.84 (d, 2H), 7.65 (d, 2H), 7.38 (d, 4H), 7.34–7.24 (m, 1H), 6.92 (d, 1H), 5.71 (s, 1H), 4.45 (s, 2H), 4.31 (d, 1H), 4.06 (d, 1H), 3.70–3.44 (m, 6H), 3.32 (s, 1H), 3.24 (d, 2H), 2.26 (d, 2H), 2.08 (d, 2H), 1.53 (d, 6H). LCMS [M+H] 573.2.

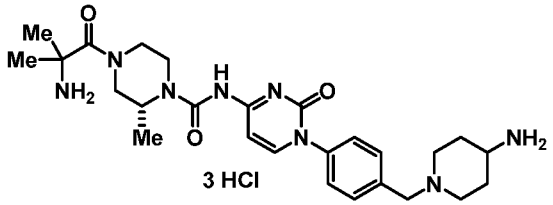
Compound 60



(2*R*,5*S*)-4-(2-Amino-2-methylpropanoyl)-*N*-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2,5-dimethylpiperazine-1-carboxamide hydrochloride salt

[00558] Prepared in a similar fashion as Scheme C-6 from *tert*-butyl (1-(4-(4-(1H-imidazole-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate and *tert*-butyl (1-((2S,5R)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 8.12 (d, 1H), 7.73 (d, 2H), 7.62 (d, 2H), 6.86 (d, 1H), 4.57 (s, 2H), 4.47 (s, 2H), 4.04 (d, 2H), 3.72 (d, 2H), 3.67–3.53 (m, 1H), 3.53-3.32 (m, 2H), 3.30–3.16 (m, 2H), 2.37 (d, 2H), 2.05–1.88 (m, 2H), 1.78 (s, 6H), 1.32 (d, 6H). LCMS [M+H] 525.3.

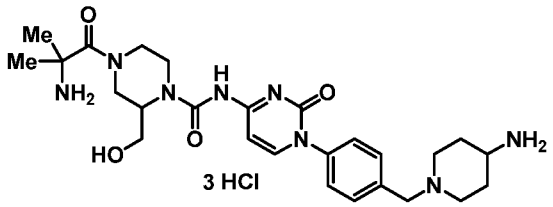
Compound 61



(*R*)-4-(2-Amino-2-methylpropanoyl)-*N*-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2-methylpiperazine-1-carboxamide hydrochloride salt

[00559] Prepared in a similar fashion as Scheme C-6 from *tert*-butyl (1-(4-(4-(1H-imidazole-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate and *tert*-butyl (R)-(2-methyl-1-(3-methylpiperazin-1-yl)-1-oxopropan-2-yl)carbamate. LCMS [M+H] 511.3.

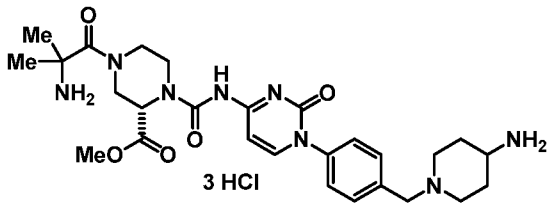
Compound 62



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2-(hydroxymethyl)piperazine-1-carboxamide hydrochloride salt

[00560] Prepared in a similar fashion as Scheme C-6 from *tert*-butyl (1-(4-(4-(1H-imidazole-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate and *tert*-butyl (1-(3-(((tert-butyldimethylsilyl)oxy)methyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate. LCMS [M+H] 527.2.

Compound 63

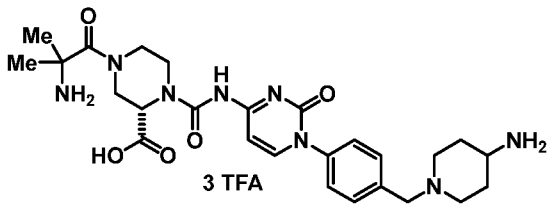


Methyl (S)-4-(2-amino-2-methylpropanoyl)-1-((1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazine-2-carboxylate hydrochloride salt

[00561] Prepared in a similar fashion as Scheme C-6 from *tert*-butyl (1-(4-(4-(1H-imidazole-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate and

methyl (S)-4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-2-carboxylate. LCMS [M+H] 555.4.

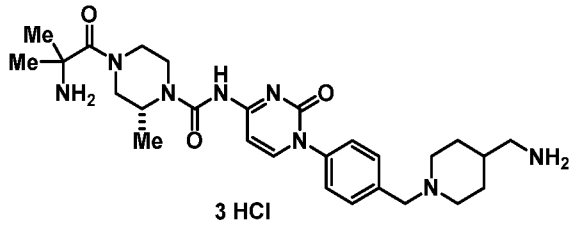
Compound 64



(S)-4-(2-Amino-2-methylpropanoyl)-1-((1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazine-2-carboxylic acid trifluroacetetate salt

[00562] Prepared in a similar fashion as Scheme C-6 from *tert*-butyl (1-(4-(4-(1H-imidazole-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate and methyl (S)-4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-2-carboxylate. ^{1}H NMR (400 MHz, CD_3OD) δ 7.73–7.56 (m, 3H), 7.59–7.31 (m, 2H), 6.47 (s, 1H) 4.37 (s, 2H), 4.21 (d, 1H), 3.58 (d, 2H), 3.50–3.20 (m, 7H), 3.14 (t, 2H), 2.24 (d, 2H), 1.96 (d,H), 1.68 (s,3H), 1.65 (s, 3H). LCMS [M+H] 541.2.

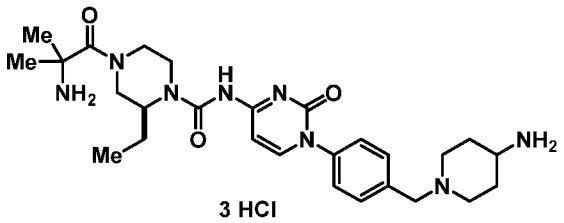
Compound 82



(R)-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((4-(aminomethyl)piperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2-methylpiperazine-1-carboxamide hydrochloride salt

[00563] Prepared as is scheme C-6 from *tert*-butyl ((1-(4-(4-(1H-imidazole-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)methyl)carbamate and (R)-*tert*-butyl (2-methyl-1-(3-methylpiperazin-1-yl)-1-oxopropan-2-yl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 8.01 (d, 1H), 7.71 (d, 2H), 7.59 (d, 2H), 6.85 (d, 1H), 4.55 (d, 1H), 4.43 (s, 2H), 4.23 (d, 1H), 4.10 (d, 1H), 3.64 (d, 2H), 3.56-3.25 (d, 2H), 3.12 (t, 2H), 2.99 (d, 2H), 2.10 (d, 3H), 1.77 (d, 6H), 1.62–1.45 (m, 2H), 1.29 (s, 5H). LCMS [M+H] 525.3.

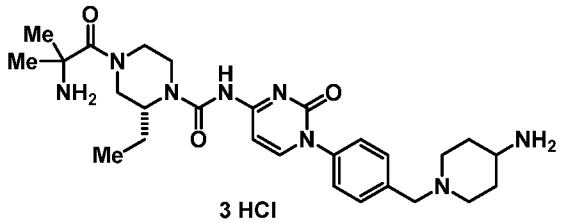
Compound 83



(S)-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2-ethylpiperazine-1-carboxamide hydrochloride salt

[00564] Prepared as is scheme C-6 from *tert*-butyl (1-(4-(4-(1H-imidazole-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate and (S)-*tert*-butyl (1-(3-ethylpiperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 8.15 (d, 1H), 7.73 (d, 2H), 7.62 (d, 2H), 6.81 (d, 1H), 4.46 (s, 2H), 4.43–4.35 (m, 2H), 4.23 (s, 1H), 4.12 (d, 1H), 3.75–3.66 (m, 2H), 3.65–3.51 (m, 2H), 3.46-3.32 (m, 2H), 3.23 (t, 2H), 2.35 (d, 2H), 2.04–1.89 (m, 2H), 1.75 (d, 6H), 1.70-1.55 (d, 2H), 0.90 (t, 3H). LCMS [M+H] 525.3.

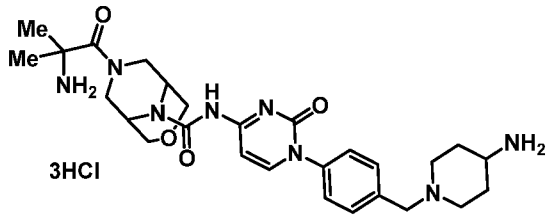
Compound 84



(R)-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2-ethylpiperazine-1-carboxamide hydrochloride salt

[00565] Prepared as is scheme C-6 from *tert*-butyl (1-(4-(4-(1H-imidazole-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate and (R)-*tert*-butyl (1-(3-ethylpiperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 8.00 (d, 1H), 7.71 (d, 2H), 7.60 (d, 2H), 6.82 (d, 1H), 4.44 (d, 2H), 4.43–4.33 (m, 2H), 4.23 (s, 1H), 4.12 (d, 1H), 3.79-3.65 (m, 3H), 3.65-3.53 (m, 1H), 3.36 (s, 2H), 3.22 (t, 2H), 2.36 (d, 2H), 2.03-1.87 (m, 2H), 1.76 (d, 6H), 1.70-1.56 (m, 2H), 0.90 (t, 3H). LCMS [M+H] 525.3.

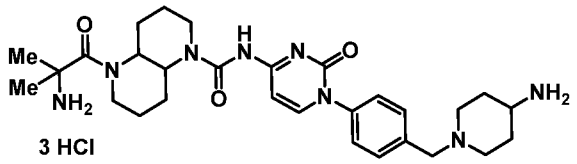
Compound 85



7-(2-Amino-2-methylpropanoyl)-N-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-3-oxa-7,9-diazabicyclo[3.3.1]nonane-9-carboxamide hydrochloride salt

[00566] Prepared as is scheme C-6 from *tert*-butyl (1-(4-(4-(1H-imidazole-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate and *tert*-butyl (1-(3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl)-2-methyl-1-oxopropan-2-yl)carbamate. LCMS [M+H] 539.2.

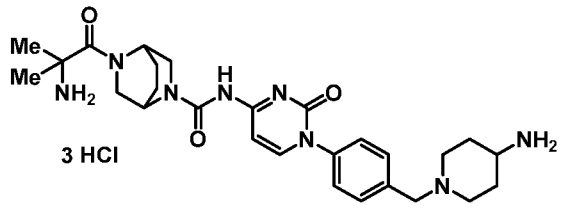
Compound 86



5-(2-Amino-2-methylpropanoyl)-N-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)octahydro-1,5-naphthyridine-1(2H)-carboxamide hydrochloride salt

[00567] Prepared as is scheme C-6 from *tert*-butyl (1-(4-(4-(1H-imidazole-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate and *tert*-butyl (2-methyl-1-(octahydro-1,5-naphthyridin-1(2H)-yl)-1-oxopropan-2-yl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 8.02 (d, 1H), 7.70 (d, 2H), 7.59 (d, 2H), 6.81 (d, 1H), 4.62 (s, 2H), 4.46 (s, 2H), 3.92 (s, 2H), 3.71 (d, 2H), 3.58 (t, 2H), 3.38–3.15 (m, 3H), 2.36 (d, 2H), 2.16 (br. s, 2H), 2.03–1.86 (m, 4H), 1.82–1.56 (m, 10H). LCMS [M+H] 551.2.

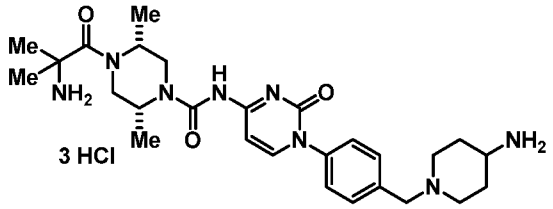
Compound 87



5-(2-Amino-2-methylpropanoyl)-N-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2,5-diazabicyclo[2.2.2]octane-2-carboxamide hydrochloride salt

[00568] Prepared as is scheme C-6 from *tert*-butyl (1-(4-(4-(1H-imidazole-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate and *tert*-butyl (1-(2,5-diazabicyclo[2.2.2]octan-2-yl)-2-methyl-1-oxopropan-2-yl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 8.13 (d, 1H), 7.72 (d, 2H), 7.61 (d, 2H), 7.07 (d, 1H), 4.61 (d, 2H), 4.47 (s, 2H), 4.18–3.76 (m, 2H), 3.71 (d, 2H), 3.67-3.43 (m, 3H), 3.23 (t, 2H), 2.36 (d, 2H), 2.15 (s, 2H), 2.06-1.84 (m, 4H), 1.74 (s, 6H). LCMS [M+H] 523.3.

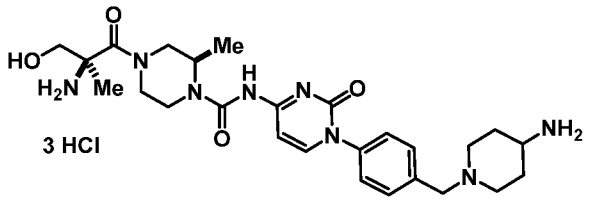
Compound 88



(2R,5R)-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2,5-dimethylpiperazine-1-carboxamide hydrochloride salt

[00569] Prepared as is scheme C-6 from *tert*-butyl (1-(4-(4-(1H-imidazole-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate and *tert*-butyl (1-((2R,5R)-2,5-dimethylpiperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.97 (d, 1H), 7.71 (d, 2H), 7.60 (d, 2H), 6.88 (d, 1H), 4.46 (s, 2H), 4.43–4.28 (m, 2H), 4.22 (d, 1H), 4.10 (d, 1H), 3.71 (d, 2H), 3.59 (s, 1H), 3.51–3.39 (m, 1H), 3.23 (t, 3H), 2.36 (d, 2H), 2.02–1.88 (m, 2H), 1.74 (d, 6H), 1.28 (d, 3H), 1.18 (d, 3H). LCMS [M+H] 525.3.

Compound 89

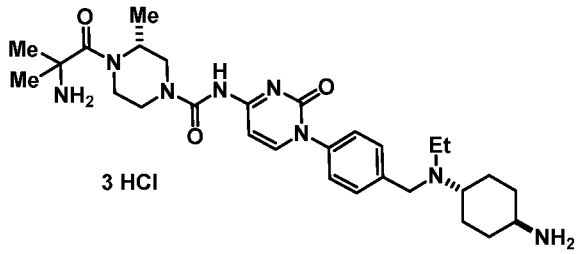


(R)-4-((S)-2-Amino-3-hydroxy-2-methylpropanoyl)-N-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2-methylpiperazine-1-carboxamide hydrochloride salt

[00570] Prepared as is scheme C-6 from *tert*-butyl (1-(4-(4-(1H-imidazole-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate and (2R,4S)-*tert*-butyl 2-(*tert*-butyl)-4-methyl-4-((R)-3-methylpiperazine-1-carbonyl)oxazolidine-3-carboxylate. ^{1}H NMR (400 MHz, D_2O) δ 7.98 (d, 1H), 7.71 (d, 2H), 7.60 (d, 2H), 6.85 (d, 1H), 4.57 (s, 1H), 4.46 (s, 2H), 4.23 (d, 1H), 4.18 (d, 1H), 4.10 (d, 1H), 3.93 (d, 1H), 3.71 (d, 3H), 3.63-3.53 (m, 1H),

3.53-3.33 (m, 3H), 3.22 (t, 2H), 2.36 (d, 2H), 1.99-1.87 (m, 2H), 1.73 (s, 3H), 1.29 (d, 3H). LCMS [M+H] 527.3.

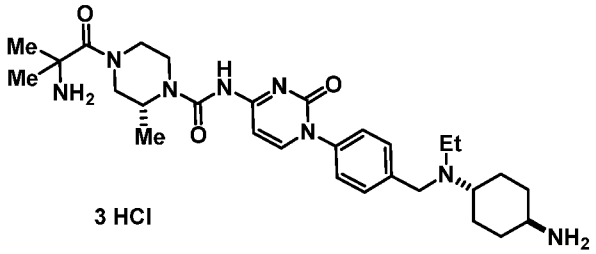
Compound 274



(R)-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((((*trans*)-4-aminocyclohexyl)(ethyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-3-methylpiperazine-1-carboxamide hydrochloride salt

[00571] Prepared in a similar fashion as Scheme C-6 from *tert*-butyl ((*trans*)-4-((4-(4-(1H-imidazole-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)(ethyl)amino)cyclohexyl)carbamate and *tert*-butyl (R)-(2-methyl-1-(2-methylpiperazin-1-yl)-1-oxopropan-2-yl)carbamate. ^{1}H NMR (400 MHz, D2O) δ 8.00 (d, 1H), 7.71 (d, 2H), 7.60 (d, 2H), 6.87 (d, 1H), 4.69 (s, 1H), 4.58 (d,1H), 4.39 (d, 1H), 4.19 (s, 1H), 4.00 (s, 2H), 3.69 (s, 1H), 3.53–3.41 (m, 1H), 3.40–3.18 (m, 5H), 2.41–2.19 (m, 4H), 1.99–1.80 (m, 2H), 1.74 (s, 6H), 1.58 (t, 2H), 1.33 (t, 3H), 1.26 (s, 3H). LCMS [M+H] 553.4.

Compound 275

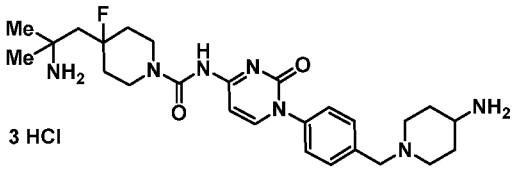


(R)-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((((*trans*)-4-aminocyclohexyl)(ethyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2-methylpiperazine-1-carboxamide hydrochloride salt

[00572] Prepared in a similar fashion as Scheme C-6 from *tert*-butyl ((*trans*)-4-((4-(4-(1H-imidazole-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)(ethyl)amino)cyclohexyl)carbamate and *tert*-butyl (R)-(2-methyl-1-(3-methylpiperazin-1-yl)-1-oxopropan-2-yl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.94 (d, 1H), 7.70 (d, 2H), 7.59 (d, 2H), 6.85 (d, 1H), 4.57 (d, 2H), 4.39 (d, 1H), 4.23 (d, 1H), 4.09 (d,

1H), 3.48 (s, 3H), 3.41–3.21 (m, 5H), 2.37–2.15 (m, 4H), 1.98–1.81 (m, 2H), 1.77 (s, 6H), 1.70–1.50 (m, 2H), 1.33 (t, 3H), 1.28 (s, 3H). LCMS [M+H] 553.4.

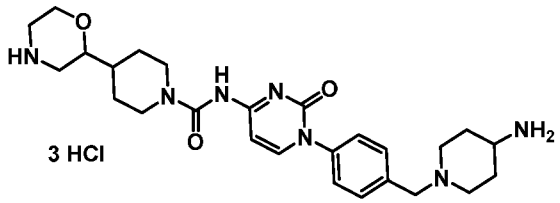
Compound 233



4-(2-Amino-2-methylpropyl)-N-(1-{4-[(4-aminopiperidin-1-yl)methyl]phenyl}-2-oxo-1,2-dihydropyrimidin-4-yl)-4-fluoropiperidine-1-carboxamide hydrochloride salt

[00573] Prepared in a similar fashion as Scheme C-6 from *tert*-butyl (1-(4-(4-(1H-imidazole-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate and *tert*-butyl (1-(4-fluoropiperidin-4-yl)-2-methylpropan-2-yl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.92-7.83 (m, 1H), 7.64 (d, 2H), 7.52 (d, 2H), 6.89-6.77 (m, 1H), 4.39 (s, 2H), 4.11-3.93 (m, 2H), 3.70-3.62 (m, 2H), 3.57-3.46 (m, 1H), 3.37-3.23 (m, 2H), 3.22-3.08 (m, 2H), 2.34-2.24 (m, 2H), 2.18-2.04 (m, 4H), 1.96-1.69 (m, 4H), 1.45 (s, 6H). LCMS [M+H] 500.4.

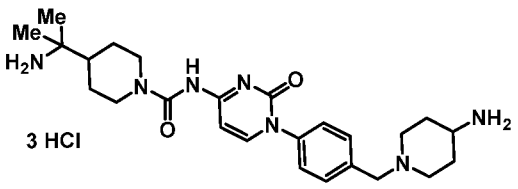
Compound 384



N-(1-{4-[(4-Aminopiperidin-1-yl)methyl]phenyl}-2-oxo-1,2-dihydropyrimidin-4-yl)-4-(morpholin-2-yl)piperidine-1-carboxamide hydrochloride salt

[00574] Prepared in a similar fashion as Scheme C-6 from *tert*-butyl (1-(4-(4-(1H-imidazole-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate and *tert*-butyl 2-(piperidin-4-yl)morpholine-4-carboxylate. ^{1}H NMR (400 MHz, D_2O) δ 7.86 (d, 1H), 7.63 (d, 2H), 7.51 (d, 2H), 6.80 (d, 1H), 4.38 (s, 2H), 4.21-4.02 (m, 3H), 3.84-3.79 (m, 1H), 3.71-3.58 (m, 3H), 3.57-3.45 (m, 1H), 3.38 (d, 1H), 3.28 (d, 1H), 3.20-3.07 (m, 3H), 3.06-2.84 (m, 3H), 2.35-2.18 (m, 2H), 1.98-1.75 (m, 4H), 1.74-1.63 (m, 1H), 1.44-1.24 (m, 2H). LCMS [M+H] 496.4.

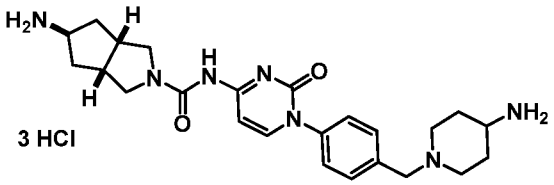
Compound 230



N-(1-{4-[(4-Aminopiperidin-1-yl)methyl]phenyl}-2-oxo-1,2-dihydropyrimidin-4-yl)-4-(2-aminopropan-2-yl)piperidine-1-carboxamide hydrochloride salt

[00575] Prepared in a similar fashion as Scheme C-6 from *tert*-butyl (1-(4-(4-(1H-imidazole-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate and *tert*-butyl (2-(piperidin-4-yl)propan-2-yl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.87 (d, 1H), 7.63 (d, 2H), 7.51 (d, 2H), 6.80 (d, 1H), 4.38 (s, 2H), 4.30-4.15 (m, 2H), 3.72-3.58 (m, 2H), 3.57-3.44 (m, 1H), 3.21-3.09 (m, 2H), 3.03-2.88 (m, 2H), 2.33-2.22 (m, 2H), 1.96-1.73 (m, 5H), 1.45-1.21 (m, 8H). LCMS [M+H] 468.5.

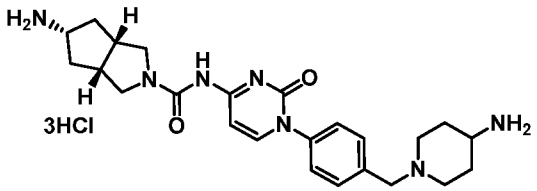
Compound 231



(3aR,5S,6aS)-5-Amino-N-(1-{4-[(4-aminopiperidin-1-yl)methyl]phenyl}-2-oxo-1,2-dihydropyrimidin-4-yl)-octahydrocyclopenta[c]pyrrole-2-carboxamide hydrochloride salt

[00576] Prepared in a similar fashion as Scheme C-6 from *tert*-butyl (1-(4-(4-(1H-imidazole-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate and *tert*-butyl ((3aR,5s,6aS)-octahydrocyclopenta[c]pyrrol-5-yl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.99 (d, 1H), 7.69 (d, 2H), 7.57 (d, 2H), 7.12 (d, 1H), 4.51-4.33 (m, 2H), 4.01-3.86 (m, 1H), 3.83-3.64 (m, 4H), 3.63-3.33 (m, 3H), 3.20 (t, 2H), 3.04 (br. s., 2H), 2.34 (d, 2H), 2.18-1.84 (m, 6H). LCMS [M+H] 452.4.

Compound 295

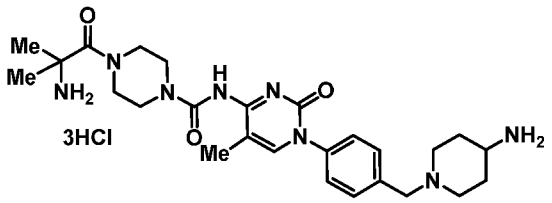


(3aR,5R,6aS)-5-Amino-N-(1-{4-[(4-aminopiperidin-1-yl)methyl]phenyl}-2-oxo-1,2-dihydropyrimidin-4-yl)-octahydrocyclopenta[c]pyrrole-2-carboxamide hydrochloride salt.

[00577] Prepared in a similar fashion as Scheme C-6 from *tert*-butyl (1-(4-(4-(1H-imidazole-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate and *tert*-butyl ((3aR,5r,6aS)-octahydrocyclopenta[c]pyrrol-5-yl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.92 (d, 1H), 7.64 (d, 2H), 7.52 (d, 2H), 7.09 (d, 1H), 4.39 (s, 2H), 3.81-3.41 (m, 8H),

3.23-3.09 (m, 2H), 2.91-2.75 (m, 2H), 2.50-2.36 (m, 2H), 2.34-2.24 (m, 2H), 1.94-1.78 (m, 2H), 1.57-1.44 (m, 2H). LCMS [M+H] 452.4.

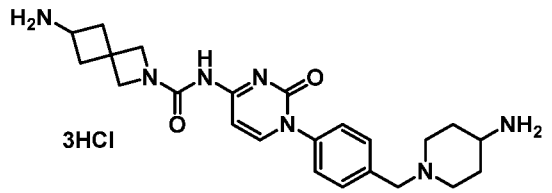
Compound 234



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-5-methyl-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00578] Prepared in a similar fashion as Scheme C-6 from *tert*-butyl (1-(4-(4-(1H-imidazole-1-carboxamido)-5-methyl-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate and *tert*-butyl (2-methyl-1-oxo-1-(piperazin-1-yl)propan-2-yl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.62 (d, 2H), 7.53-7.45 (m, 3H), 4.38 (br.s., 2H), 3.86-3.40 (m, 11H), 3.14 (br. t., 2H), 2.34-2.22 (m, 2H), 2.01-1.78 (m, 5H), 1.68 (s, 6H). LCMS [M+H] 511.5.

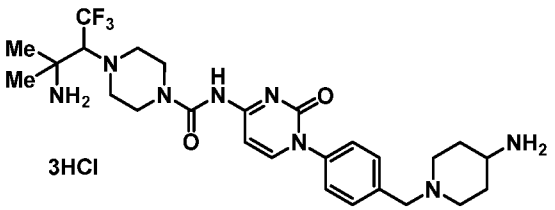
Compound 289



6-Amino-*N*-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2-azaspiro[3.3]heptane-2-carboxamide hydrochloride salt.

[00579] Prepared in a similar fashion as Scheme C-6 from *tert*-butyl (1-(4-(4-(1H-imidazole-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate and *tert*-butyl (2-azaspiro[3.3]heptan-6-yl)carbamate. LCMS [M+H] 438.3.

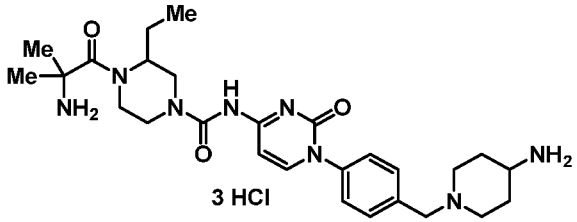
Compound 291



4-(3-Amino-1,1,1-trifluoro-3-methylbutan-2-yl)-N-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

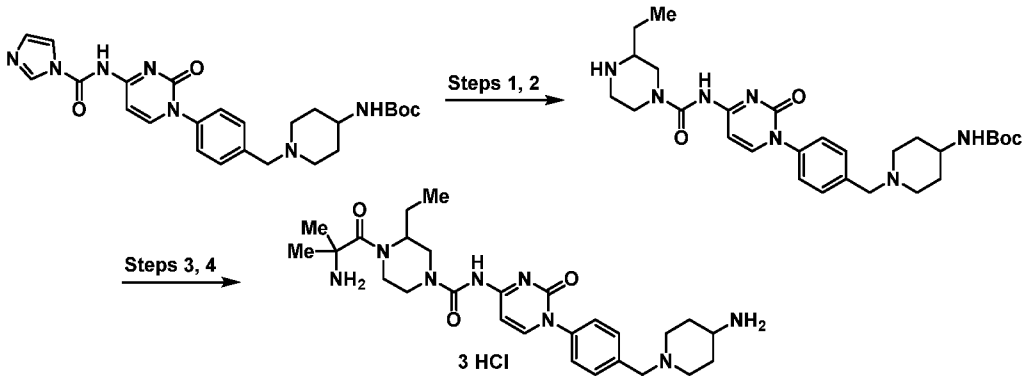
[00580] Prepared in a similar fashion as Scheme C-6 from *tert*-butyl (1-(4-(4-(1H-imidazole-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate and *tert*-butyl (4,4,4-trifluoro-2-methyl-3-(piperazin-1-yl)butan-2-yl)carbamate. LCMS [M+H] 551.4.

Compound 78



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-3-ethylpiperazine-1-carboxamide hydrochloride salt

Scheme C-7



Reagents: 1) 1-(2-ethylpiperazin-1-yl)-2,2,2-trifluoroethan-1-one trifluoroacetate, CH_3CN, 85 °C, 2h 2) $LiOH{\cdot}H_2O$, THF:H_2O, rt, 2h 3) 2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoic acid, HATU, DIPEA, DMF, 50 °C, 16h 4) HCl, MeOH, rt, 4h.

[00581] Step 1: *tert*-butyl (1-(4-(4-(3-ethyl-4-(2,2,2-trifluoroacetyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate. *tert*-Butyl (1-(4-(4-(1H-imidazole-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate (135 mg, 0.26 mmol) and 1-(2-ethylpiperazin-1-yl)-2,2,2-trifluoroethan-1-one triflouroacetate (91 mg, 0.26 mmol) were dissolved in CH_3CN and heated to reflux for 2h. The solvent was removed under reduced pressure. The crude reaction mixture was dissolved in EtOAc (25 mL) and washed with water (3x25 mL). Purification by column chromatography ($CHCl_3$:MeOH) afforded the title compound.

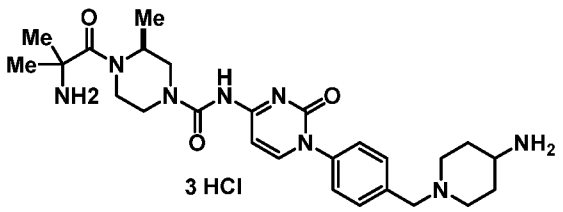
[00582] Step 2: *tert*-butyl (1-(4-(4-(3-ethylpiperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate. *tert*-Butyl (1-(4-(4-(3-ethyl-4-(2,2,2-trifluoroacetyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-

yl)carbamate (138 mg, 0.21 mmol.) and $LiOH{\cdot}H_2O$ (97 mg, 2.1 mmol) were suspended in THF:H_2O (1:1) and stirred at rt for 2h. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with H_2O (50mL) and the extracted with $CHCl_3$ (3x50mL). The organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield the title compound.

[00583] Step 3: *tert*-butyl (1-(4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)-3-ethylpiperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate. To a suspension of 2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoic acid (28 mg, 0.14 mmol) and HATU (52 mg, 0.14 mmol) in DMF, was added DIPEA (0.03 mL, 0.17 mmol). The suspension was stirred for 10 min, a solution of *tert*-butyl (1-(4-(4-(3-ethylpiperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate (75 mg, 0.14 mmol) in DMF was added dropwise. The mixture was stirred at 50 °C for 16h. Sat. aq. LiCl (10 mL) was added and the mixture was extracted with EtOAc (1x15 mL). The organic layer was concentrated under reduced pressure and purified by column chromatography ($CHCl_3$:MeOH) to afford the title compound.

[00584] Step 4: 4-(2-amino-2-methylpropanoyl)-N-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-3-ethylpiperazine-1-carboxamide hydrochloride salt. *tert*-Butyl (1-(4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)-3-ethylpiperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate (80 mg, 0.11 mmol) in HCl in MeOH (2N, 10 mL) was stirred at rt for 4h, concentrated under reduced pressure to afford the title compound as a white solid. ^1H NMR (400 MHz, CD_3OD) δ 8.35 (s, 1H), 7.85 (d, 2H), 7.67 (d, 2H), 6.90 (s, 1H), 4.47 (s, 2H), 4.35 (s, 2H), 3.63 (d, 2H), 3.52 (t, 2H), 3.28-3.11 (s, 5H), 2.29 (d, 3H), 2.11 (t, 2H), 1.74 (s, 3H), 1.58 (s, 3H), 1.29 (s, 2H), 0.95 (t, 3H). LCMS [M+H] 525.2.

Compound 72

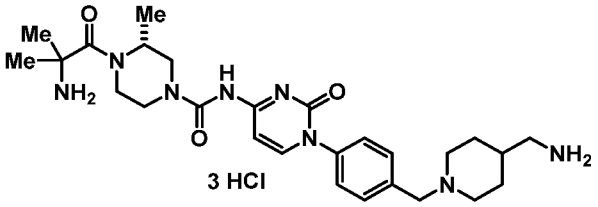


(S)-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-3-methylpiperazine-1-carboxamide hydrochloride salt

[00585] Prepared in a similar fashion as scheme C-7 from *tert*-butyl (1-(4-(4-(1H-imidazole-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate and 2-((*tert*-

butoxycarbonyl)amino)-2-methylpropanoic acid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.34 (s, 1H), 7.86 (d, 2H), 7.68 (d, 2H), 6.91 (s, 1H), 4.48 (s, 2H), 4.27 (d, 2H), 3.73–3.16 (m, 10H), 2.29 (d, 2H), 2.11 (t, 2H), 1.73 (s, 3H), 1.71 (s, 3H), 1.31 (d, 3H). LCMS [M+H] 511.3.

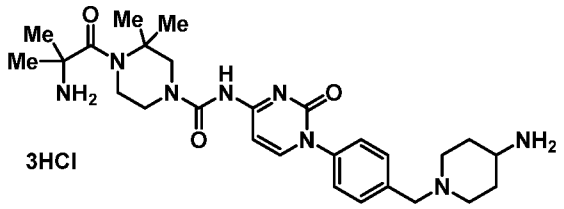
Compound 65



(R)-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((4-(aminomethyl)piperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-3-methylpiperazine-1-carboxamide hydrochloride salt

[00586] Prepared in a similar fashion as Scheme C-7 from (R)-*tert*-butyl ((1-(4-(4-(3-methylpiperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)methyl)carbamate and 2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoic acid. ^{1}H NMR (400 MHz, D_2O) δ 7.95 (d, 1H), 7.73 (d, 2H), 7.62 (d, 2H), 6.93 (d, 1H), 4.53 (s, 2H), 4.24 (s, 1H), 4.14–3.97 (m, 2H), 3.87–3.64 (m, 3H), 3.41 (s, 2H), 3.27 (d, 2H), 2.97 (s, 1H) 2.50 (s, 2H), 1.93–1.72 (m, 6H), 1.68 (s, 3H), 1.55 (s, 2H), 1.34 (d, 3H).

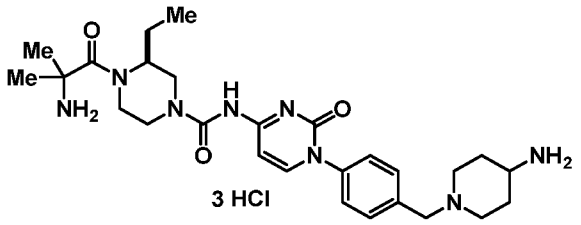
Compound 73



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-3,3-dimethylpiperazine-1-carboxamide hydrochloride salt

[00587] Prepared in a similar fashion as scheme C-7 from *tert*-butyl (1-(4-(4-(3,3-dimethylpiperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate and 2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoic acid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.94 (d, 1H), 7.81 (d, 2H), 7.63 (d, 2H), 6.64 (s, 1H), 4.47 (s, 2H), 3.97 (s, 2H), 3.77 (d, 2H), 3.66 (d, 2H), 3.52 (s, 2H), 3.25 (s, 2H), 2.30 (d, 2H), 2.11 (t, 2H), 1.71 (s, 2H), 1.49 (d, 6H), 1.31 (s, 6H). LCMS [M+H] 525.3.

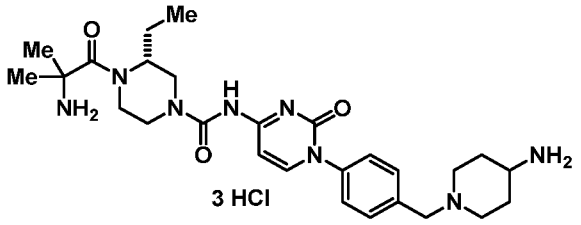
Compound 66



(S)-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-3-ethylpiperazine-1-carboxamide hydrochloride salt

[00588] Prepared in a similar fashion as Scheme C-7 from (S)-*tert*-butyl (1-(4-(4-(3-ethylpiperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate and 2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoic acid. ^{1}H NMR (400 MHz, D_2O) δ 7.93 (d, 1H), 7.71 (d, 2H), 7.59 (d, 2H), 6.84 (d, 1H), 4.46 (s, 2H), 4.19 (d, 2H), 4.00 (d, 1H), 3.77–3.63 (m, 2H), 3.58 (s, 2H),3.35-3.30 (m, 1H) 3.30-3.15 (m, 4H), 2.36 (d, 2H), 2.02-1.85 (m, 2H),), 1.60 (d, 6H), 1.37-1.23 (m, 2H) 0.86 (s, 3H). LCMS [M+H] 525.3.

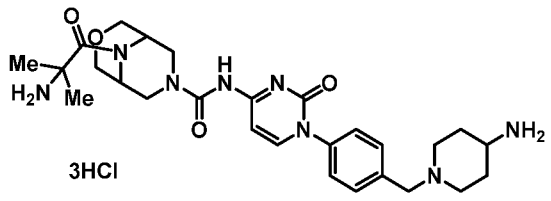
Compound 67



(R)-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-3-ethylpiperazine-1-carboxamide hydrochloride salt

[00589] Prepared in a similar fashion as Scheme C-7 from (R)-*tert*-butyl (1-(4-(4-(3-ethylpiperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate and 2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoic acid. ^{1}H NMR (400 MHz, D_2O) δ 7.98 (d, 1H), 7.71 (d, 2H), 7.60(d, 2H), 6.84 (d, 1H), 4.58 (s, 1H), 4.46 (s, 2H), 4.22 (d, 2H), 4.02 (d, 1H), 3.71 (d, 2H), 3.62-3.55 (m, 2H), 3.22 (t, 4H), 2.36 (d, 2H), 1.00-1.90 (m, 2H), 1.76 (d, 6H), 1.73–1.63 (m, 2H), 0.86 (s, 3H). LCMS [M+H] 525.2.

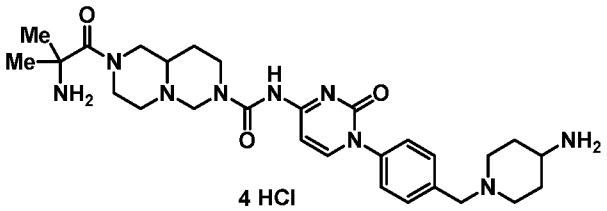
Compound 68



9-(2-Amino-2-methylpropanoyl)-N-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-3-oxa-7,9-diazabicyclo[3.3.1]nonane-7-carboxamide hydrochloride salt

[00590] Prepared in a similar fashion as Scheme C-7 from *tert*-butyl (1-(4-(4-(3-oxa-8,10-diazabicyclo[4.3.1]decane-8-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate and 2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoic acid. ^{1}H NMR (400 MHz, D_2O) δ 8.05 (d, 1H), 7.72 (d, 2H), 7.61 (d, 2H), 6.79 (d, 1H), 4.64-4.37 (m, 6H), 4.17 (d, 2H), 3.94 (s, 2H), 3.71 (d, 2H), 3.59 (t, 2H), 3.21 (t, 2H), 2.36 (d, 2H), 2.07–1.88 (m, 2H), 1.75 (s, 6H), 1.59 (d, 1H). LCMS [M+H] 539.2.

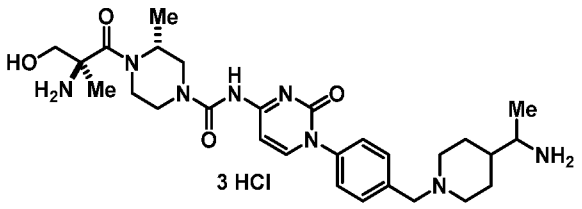
Compound 69



8-(2-Amino-2-methylpropanoyl)-N-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)hexahydro-1H-pyrazino[1,2-a]pyrazine-2(6H)-carboxamide hydrochloride salt

[00591] Prepared in a similar fashion as Scheme C-7 from *tert*-butyl (1-(4-(4-(octahydro-1H-pyrazino[1,2-a]pyrazine-2-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate and 2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoic acid. ^{1}H NMR (400 MHz, D_2O) δ 7.90 (d, 1H), 7.71 (d, 2H), 7.59 (d, 2H), 6.76 (d, 1H), 4.56 (s, 2H), 4.46 (s, 2H), 3.76-3.66 (m, 4H), 3.66 -3.45 (m, 2H), 3.22 (d, 4H), 2.36 (d, 2H), 2.02-1.86 (m, 2H), 1.75 (s, 6H), 1.35 (d, 4H), 1.29 (t, 2H). LCMS [M+H] 552.2.

Compound 70

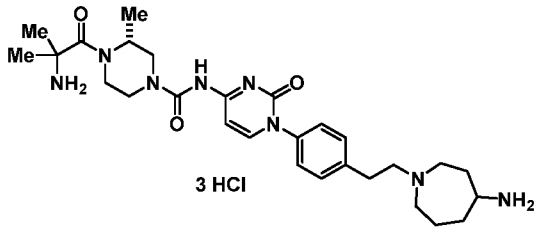


(3R)-4-((S)-2-Amino-3-hydroxy-2-methylpropanoyl)-N-(1-(4-((4-(1-aminoethyl)piperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-3-methylpiperazine-1-carboxamide hydrochloride salt

[00592] Prepared in a similar fashion as Scheme C-7 from tert-butyl (1-(1-(4-(4-((R)-3-methylpiperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-

yl)ethyl)carbamate and (2R,4S)-2-(tert-butyl)-4-methyloxazolidine-4-carboxylic acid. LCMS [M+H] 555.4.

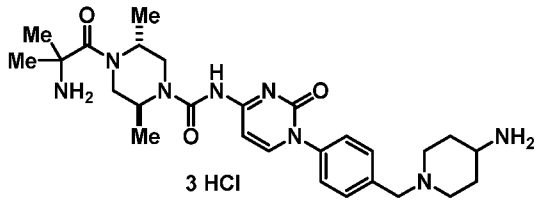
Compound 71



(3R)-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(4-aminoazepan-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-3-methylpiperazine-1-carboxamide hydrochloride salt

[00593] Prepared in a similar fashion as Scheme C-7 from *tert*-butyl (1-(4-(4-((R)-3-methylpiperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)phenethyl)azepan-4-yl)carbamate and 2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoic acid. ^{1}H NMR (400 MHz, D_2O) δ 7.78 (d, 1H), 7.36 (d, 2H), 7.29 (d, 2H), 6.70 (d, 1H), 4.01 (s, 1H), 3.87 (s, 1H), 3.58 (s, 2H), 3.49–3.32 (m, 5H), 3.33–2.95 (m, 7H), 2.18 (s, 2H), 2.04–1.79 (m, 2H), 1.59 (d, 7H), 1.41–0.95 (m, 4H). LCMS [M+H] 539.3.

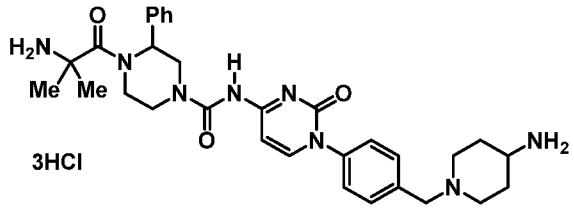
Compound 74



(2S,5R)-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2,5-dimethylpiperazine-1-carboxamide hydrochloride salt

[00594] Prepared in a similar fashion as scheme C-7 from *tert*-butyl (1-(4-(4-((2S,5R)-2,5-dimethylpiperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate and 2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoic acid. ^{1}H NMR (400 MHz, D_2O) δ 7.89 (d, 1H), 7.71 (d, 2H), 7.60 (d, 2H), 6.85 (d, 1H), 4.61 (s, 2H), 4.47 (s, 2H), 4.03 (d, 2H), 3.72 (d, 2H), 3.59 (t, 1H), 3.37 (s, 2H), 3.23 (s, 2H), 2.37 (d, 2H), 1.96 (d, 2H), 1.78 (s, 6H), 1.47–1.15 (m, 6H). LCMS [M+H] 525.3.

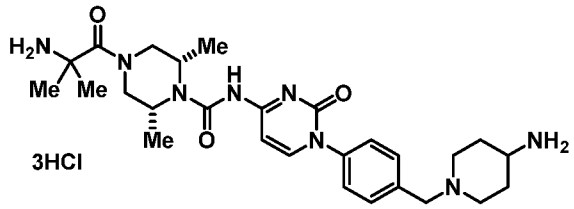
Compound 75



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-3-phenylpiperazine-1-carboxamide hydrochloride salt

[00595] Prepared in a similar fashion as scheme C-7 from *tert*-butyl (1-(4-(2-oxo-4-(3-phenylpiperazine-1-carboxamido)pyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate and 2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoic acid. LCMS [M+H] 573.2.

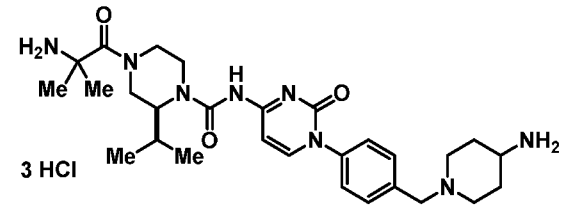
Compound 76



***cis*-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2,6-dimethylpiperazine-1-carboxamide hydrochloride salt**

[00596] Prepared in a similar fashion as scheme C-7 from *tert*-butyl (1-(4-(4-(*cis*-2,6-dimethylpiperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate and 2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoic acid. ^{1}H NMR (500 MHz, CD_3OD) δ 8.27-8.40 (m, 1H), 7.85 (d, 2H), 7.66 (d, 2H), 6.89-7.01 (m, 1H), 4.55-4.69 (m, 2H), 4.46 (s, 2H), 4.23-4.39 (m, 2H), 3.58-3.68 (m, 2H), 3.45-3.57 (m, 1H), 3.19-3.40 (m, 4H), 2.22-2.35 (m, 2H), 2.03-2.17 (m, 2H), 1.74 (s, 6H), 1.34-1.45 (m, 6H). LCMS [M+H] 525.3.

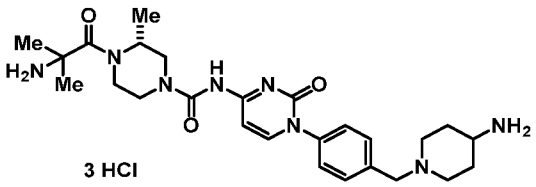
Compound 77



(S)-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2-isopropylpiperazine-1-carboxamide hydrochloride salt

[00597] Prepared in a similar fashion as scheme C-7 from *tert*-butyl (S)-(1-(4-(4-(2-isopropylpiperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate and 2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoic acid. ^{1}H NMR (500 MHz, CD_3OD) δ 8.39 (d, 1H), 7.85 (d, 2H), 7.67 (d, 2H), 6.85-7.08 (m, 1H), 4.47 (s, 2H), 4.25-4.37 (m, 1H), 4.14-4.24 (m, 2H), 3.58-3.68 (m, 2H), 3.37-3.57 (m, 3H), 3.19-3.28 (m, 2H), 2.94-3.17 (m, 2H), 2.28 (d, 2H), 2.04-2.17 (m, 2H), 1.90-2.04 (m, 1H), 1.75 (s, 3H), 1.69 (s, 3H), 1.05-1.17 (m, 3H), 0.92 (d, 3H). LCMS [M+H] 539.3.

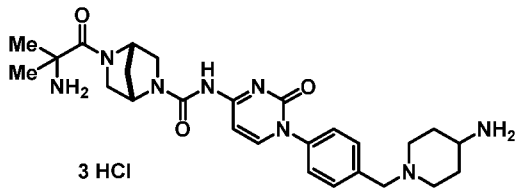
Compound 79



(R)-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-3-methylpiperazine-1-carboxamide hydrochloride salt

[00598] Prepared in a similar fashion as scheme C-7 from *tert*-butyl (R)-(1-(4-(4-(3-methylpiperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate and 2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoic acid. LCMS [M+H] 511.3.

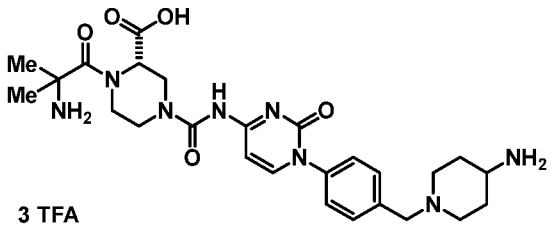
Compound 80



***cis*-5-(2-Amino-2-methylpropanoyl)-N-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxamide hydrochloride salt**

[00599] Prepared in a similar fashion as scheme C-7 from *tert*-butyl (1-(4-(4-(*cis*-2,5-diazabicyclo[2.2.1]heptane-2-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate and 2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoic acid. LCMS [M+H] 509.3.

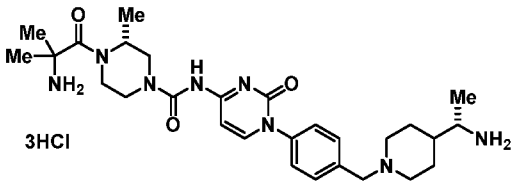
Compound 81



(S)-1-(2-Amino-2-methylpropanoyl)-4-((1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazine-2-carboxylic acid trifluoroacetate salt

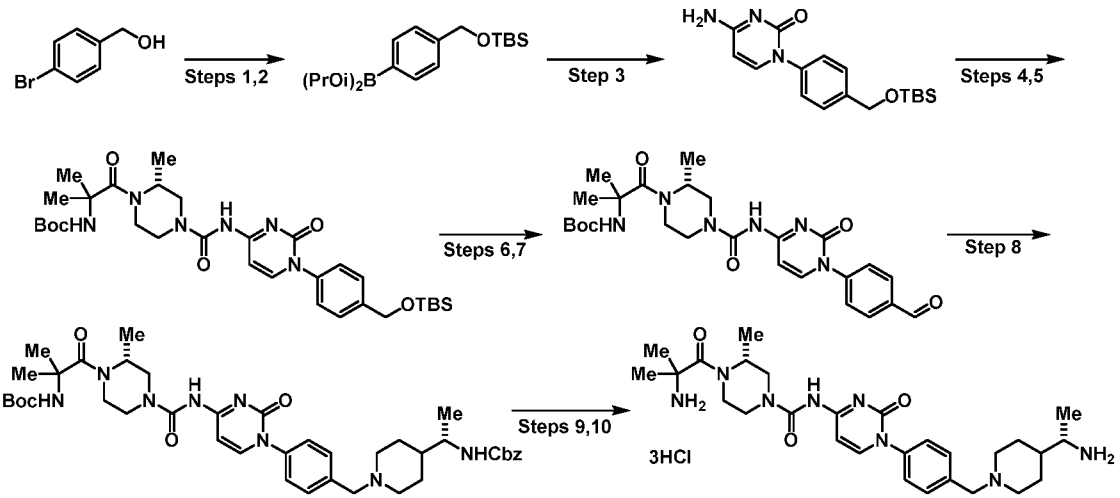
[00600] Prepared in a similar fashion as scheme C-7 from methyl (S)-4-((1-(4-((4-((*tert*-butoxycarbonyl)amino)piperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazine-2-carboxylate and 2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoic acid. LCMS [M+H] 456.3.

Compound 206



(R)-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((4-((S)-1-aminoethyl)piperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-3-methylpiperazine-1-carboxamide hydrochloride salt

Scheme C-8



Reagents: 1) TBSCl, imidazole, CH_2Cl_2, rt, 16h 2) BuLi, THF, -78 °C (iPrO)$_3$B 3) cytosine, TMEDA, $Cu(OAc)_2 \cdot H_2O$, 4:1 MeOH:H_2O rt, 48h 4) CDI, CH_2Cl_2, rt, 4h 5) *tert*-butyl (R)-(2-methyl-1-(2-

methylpiperazin-1-yl)-1-oxopropan-2-yl)carbamate, CH_3CN, 85 °C, 16h 6) TBAF, THF 0 °C to rt, 16h 7) Dess-Martin periodinane, 0.1% H_20:CH_2Cl_2 8) benzyl (S)-(1-(piperidin-4-yl)ethyl)carbamate, $Na(OAc)_3BH$, DIPEA, DCE, rt, 16h 9) Degussa type Pd/C, H_2, MeOH, rt 16h 10) HCl in MeOH, rt, 8h.

[00601] Step 1: ((4-bromobenzyl)oxy)(*tert*-butyl)dimethylsilane. To a solution of (4-bromophenyl)methanol (2.0 g, 10.6 mmol) in CH_2Cl_2 (50 mL) was added imidazole (1.4 g, 21.2 mmol) and *tert*-butyldimethylsilyl chloride (1.9 g, 12.6 mmol). The solution was stirred for 16 h. The reaction mixture was concentrated under reduced pressure and the solid dissolved in EtOAc (100 mL) and washed with H_2O (100mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure and purified by flash chromatography (Hexanes:EtOAc) to afford the title compound.

[00602] Step 2: diisopropyl (4-(((*tert*-butyldimethylsilyl)oxy)methyl)phenyl)boronate. A solution of ((4-bromobenzyl)oxy)(*tert*-butyl)dimethylsilane (2.0 g, 6.67 mmol) in THF (50 mL) was cooled to -78 °C. 2.5M BuLi in Hexanes (8.0 mL) was added dropwise over 30 min. and the temperature maintained below -60 °C. The reaction was stirred for 25 min.Triisopropyl borate (2.3 mL, 10.0 mmol) was added dropwise over 30 min. The reaction mixture was warmed to rt and stirred for 15 min. 2N HCl (50 mL) was added and the reaction was stirred for 30 min. The biphasic mixture was separated and the aq. layer extracted with CH_2Cl_2 (2×50 mL). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure to afford the title compound.

[00603] Step 3: 4-amino-1-(4-(((*tert*-butyldimethylsilyl)oxy)methyl)phenyl)pyrimidin-2(1H)-one. A suspension of cytosine (0.74 g, 6.67 mmol) and diisopropyl (4-(((*tert*-butyldimethylsilyl)oxy)methyl)phenyl)boronate (2.3 g, 6.67 mmol), in MeOH:H_2O (4:1, 60 ml) was stirred at rt in open air for 30 min. TMEDA (1.2 ml, 8.0 mmol) and $Cu(OAc)_2H_2O$ (1.33 g, 6.67 mmol) were added and the reaction was stirred in open air for 48 h at rt. The reaction mixture was concentrated under reduced pressure, and cold H_2O (100 mL) was added. The solid was filtered and washed with H_2O (2x15 mL) and Et_2O (3x10 mL) to afford the title compound.

[00604] Step 4: N-(1-(4-(((*tert*-butyldimethylsilyl)oxy)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-1H-imidazole-1-carboxamide. A suspension of 4-amino-1-(4-(((*tert*-butyldimethylsilyl)oxy)methyl)phenyl)pyrimidin-2(1H)-one (500 mg, 1.5 mmol) and 1,1'-carbonyldiimidazole (365 mg, 2.25 mmol) in dry CH_2Cl_2 was stirred for 16 h at rt. The solvent was removed under reduced pressure, and the solid was triturated with EtOAc to give the title compound which was used in the next step without further purification.

[00605] Step 5: (R)-*tert*-butyl (1-(4-((1-(4-(((*tert*-butyldimethylsilyl)oxy)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)-2-methylpiperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate. N-(1-(4-(((*tert*-butyldimethylsilyl)oxy)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-1H-imidazole-1-carboxamide (141 mg, 0.33 mmol) and (R)-*tert*-butyl (2-methyl-1-(2-methylpiperazin-1-yl)-1-oxopropan-2-yl)carbamate as prepared in Scheme 1 step 2, (95 mg, 0.33 mmol) were dissolved in CH_3CN and heated to reflux for 2h. The reaction mixture was concentrated under reduced pressure and the crude reaction mixture was dissolved in EtOAc (25 mL) and washed with water (3x25 mL). Purification by flash chromatography (MeOH/$CHCl_3$) yielded the title compound.

[00606] Step 6: (R)-*tert*-butyl (1-(4-((1-(4-(hydroxymethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)-3-methylpiperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate. To a solution of (R)-*tert*-butyl (1-(4-((1-(4-(((*tert*-butyldimethylsilyl)oxy)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)-2-methylpiperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate (90 mg, 0.14 mmol) in THF (10 mL) at 0 °C was added 2M TBAF in THF (0.28 mL) over 5 min. The solution was stirred for 16h. The crude reaction mixture was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography to afford the title compound.

[00607] Step 7: (R)-*tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)-2-methylpiperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate. To a stirred solution of (R)-*tert*-butyl (1-(4-((1-(4-(hydroxymethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)-3-methylpiperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate (150.0 mg, 0.24 mmol) in 0.1% H_2O:CH_2Cl_2 (10 mL) was added Dess-Martin periodinane (100 mg, 0.25 mmol). The solution was stirred for 1h. The crude reaction mixture was dissolved in additional CH_2Cl_2 (20 mL) and washed with aq. $NaHCO_3$/$Na_2S_2O_3$ (1×20 mL). The aq. layer was extracted with CH_2Cl_2 (1×10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give the title compound.

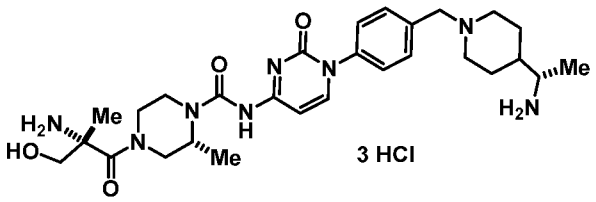
[00608] Step 8: *tert*-butyl (1-((R)-4-((1-(4-((4-((S)-1-(((benzyloxy)carbonyl)amino)ethyl)piperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)-2-methylpiperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate. To a stirred solution (R)-*tert*-butyl (1-(4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)-2-methylpiperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate (15 mg, 0.03 mmol) in DCE (10 mL) was added (S)-benzyl (1-(piperidin-4-yl)ethyl)carbamate (7.8 mg, 0.035 mmol) followed by $Na(OAc)_3BH$ (13 mg, 0.06 mmol) and

DIPEA (0.01 mL, 0.06 mmol). The reaction was stirred for 16h. The reaction mixture was treated with 1 N NaOH (10 mL) and extracted with CH_2Cl_2 (2×20 mL). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure to afford the title compound, which was used in the next reaction without further purification

[00609] Step 9: *tert*-butyl (1-((R)-4-((1-(4-((4-((S)-1-aminoethyl)piperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)-2-methylpiperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate. To a mixture of *tert*-butyl (1-((R)-4-((1-(4-((4-((S)-1-(((benzyloxy)carbonyl)amino)ethyl)piperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)-2-methylpiperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate (12 mg, 0.03 mmol) and Degussa type Pd/C (10% wt, 2.4 mg) at rt was added MeOH under N_2. The reaction mixture was flushed with H_2 and stirred for 16 h under H_2 atmosphere. The reaction mixture was filtered through Celite®. The organic layer was concentrated under reduced pressure to afford the title compound.

[00610] Step 10: (R)-4-(2-amino-2-methylpropanoyl)-N-(1-(4-((4-((S)-1-aminoethyl)piperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-3-methylpiperazine-1-carboxamide hydrochloride salt. *tert*-Butyl *tert*-butyl (1-((R)-4-((1-(4-((4-((S)-1-aminoethyl)piperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)-2-methylpiperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate was dissolved in a solution of HCl/MeOH (5 mL) and stirred for 8h. The solvent was evaporated and the crude solid was purified by RPHPLC (H_2O:CH_3CN:TFA) and concentrated under reduced pressure. Addition of HCl/MeOH (3x15 mL) and evaporation under reduced pressure afforded the title compound. ^{1}H NMR (400 MHz, D_2O) δ 7.84 (d, 1H), 7.63 (d, 2H), 7.51 (d, 2H), 7.39 (d, 1H), 4.36 (s, 2H), 4.09 (d, 1H), 3.93 (t, 2H), 3.64-3.55 (m, 4H), 3.26 (s, 2H), 3.05 (t, 2H), 2.57 (s, 1H), 2.03 (d, 4H), 1.90 (s, 1H), 1.67 (d, 6H), 1.56 (s, 2H), 1.23 (d, 4H). LCMS [M+H] 539.4.

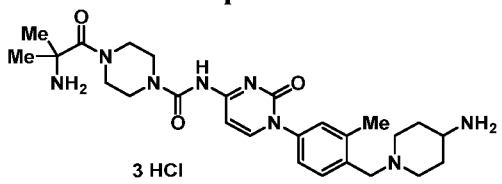
Compound 207



(R)-4-((S)-2-Amino-3-hydroxy-2-methylpropanoyl)-N-(1-(4-((4-((S)-1-aminoethyl)piperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2-methylpiperazine-1-carboxamide hydrochloride salt

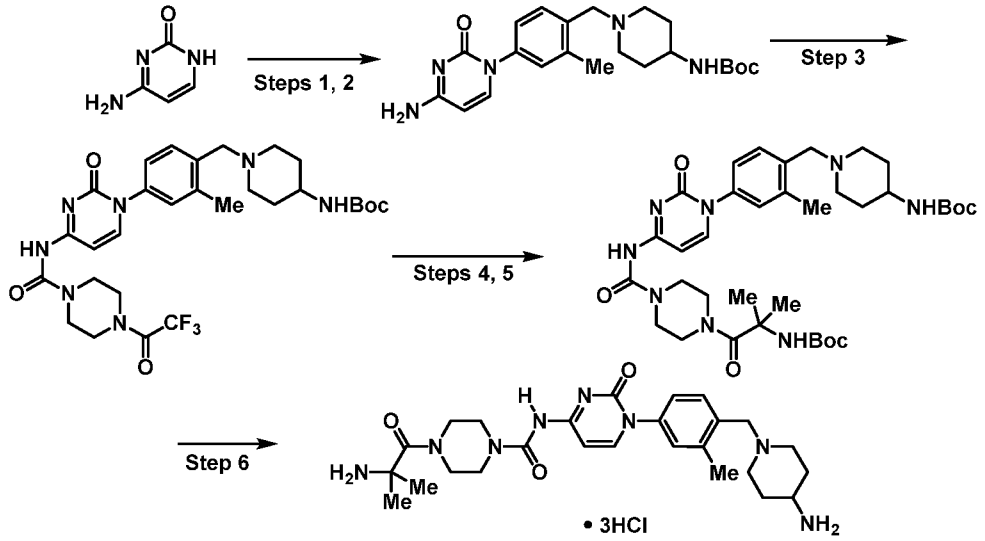
[00611] Prepared as is scheme C-8 from *tert*-butyl (2R,4S)-2-(*tert*-butyl)-4-((R)-4-((1-(4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)-3-methylpiperazine-1-carbonyl)-4-methyloxazolidine-3-carboxylate and (S)-benzyl (1-(piperidin-4-yl)ethyl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.83 (d, 1H), 7.63 (d , 2H), 7.51 (d, 2H), 6.80 (d, 1H), 4.50 (s, 2H), 4.36 (s, 2H), 4.18 (s, 1H), 4.13 (d, 1H), 4.02 (s, 1H), 3.86 (d, 1H), 3.60 (d, 2H), 3.40 (s, 2H), 3.29–3.21 (m, 1H), 3.05 (t, 2H), 2.03 (d, 2H), 2.01–1.96 (m, 1H), 1.89 (s, 1H), 1.67 (s, 3H), 1.55 (s, 2H), 1.26–1.17 (m, 6H). LCMS [M+H] 555.3.

Compound 91



4-(2-Amino-2-methylpropanoyl)-*N*-(1-(4-((4-aminopiperidin-1-yl)methyl)-3-methylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

Scheme C-9



Reagents: 1) (4-formyl-3-methylphenyl)boronic acid, TMEDA, $Cu(OAc)_2•H_2O$, MeOH:H_2O, rt, 16h 2) DIPEA, $Na(OAc)_3BH$, DCE:CH_3CN, rt, 16h 3) CH_3CN, 85 °C, 16h 4) K_2CO_3, MeOH, rt, 2h 5) 2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoic acid, HATU, DIPEA, CH_2Cl_2, rt, 16h 6) HCl, MeOH, rt, 4h.

[00612] Step 1: 4-(4-amino-2-oxopyrimidin-1(2H)-yl)-2-methylbenzaldehyde. A suspension of cytosine (2.60 g, 24 mmol) and (4-formyl-3-methylphenyl)boronic acid (3.53 g 24 mmol), in a mixture of solvents MeOH:H_2O (4:1, 25ml) was stirred at rt in open air. After 30 min., TMEDA (6.70 ml, 28 mmol) and $Cu(OAc)_2•H_2O$ (4.70 g, 24 mmol) were added.

The reaction was stirred at rt in open air for 16h. The MeOH was evaporated reduced pressure, and the remaining mixture was diluted with H_2O and stirred for 15 min at 0°C, allowing a solid to precipitate. The solid was filtered and washed with H_2O (1x 25 mL) and Et_2O (1x25 mL) to yield the title compound.

[00613] Step 2: *tert*-butyl (1-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)-2-methylbenzyl)piperidin-4-yl)carbamate. To stirring suspension of 4-(4-amino-2-oxopyrimidin-1(2H)-yl)-3-methylbenzaldehyde (1.00 g 4.6 mmol) and *tert*-butyl piperidin-4-ylcarbamate (1.39 g, 7.0 mmol) in DCE:CH_3CN (1:1, 25mL), were added *N,N*-diisopropylethylamine (1.61 mL, 9.2 mmol) and $Na(OAc)_3BH$ (1.97g, 9.3 mmol). The reaction was stirred for 16h at rt and the solvent was evaporated reduced pressure. The solid was dissolved in $CHCl_3$ and washed with 10% NaOH. Purification via flash chromatography (MeOH/$CHCl_3$) yielded the title compound.

[00614] Step 3: *tert*-butyl (1-(2-methyl-4-(2-oxo-4-(4-(2,2,2-trifluoroacetyl)piperazine-1-carboxamido)pyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate. A solution of 3-methyl-1-(4-(2,2,2-trifluoroacetyl)piperazine-1-carbonyl)-1H-imidazol-3-ium iodide (211 mg, 0.72 mmol) and *tert*-butyl (1-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)-3-methylbenzyl)piperidin-4-yl)carbamate (300 mg, 0.72 mmol), in dry CH_3CN (12 mL) was heated to 85 °C and refluxed for 8h. The solvent was removed under reduced pressure and the crude reaction mixture was partitioned between $CHCl_3$ (125 mL) and H_2O (125 mL). The organic layer was concentrated under reduced pressure and purified by flash chromatography (MeOH/$CHCl_3$) to afford the title compound.

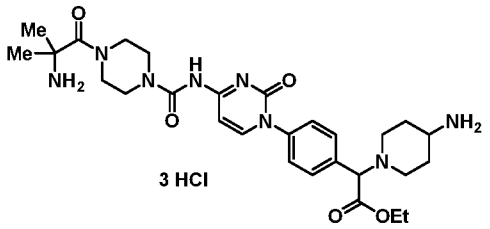
[00615] Step 4: *tert*-butyl (1-(3-methyl-4-(2-oxo-4-(piperazine-1-carboxamido)pyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate. *tert*-Butyl (1-(2-methyl-4-(2-oxo-4-(4-(2,2,2-trifluoroacetyl)piperazine-1-carboxamido)pyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate (125 mg, 0.2 mmol) and K_2CO_3 (83 mg, 0.6 mmol) were dissolved in MeOH, and stirred at rt for 2h and the solvent was removed under reduced pressure. The crude solid was dissolved in H_2O (25 mL) and the aqueous layer was extracted with $CHCl_3$ (3x25 mL). The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to yield title compound.

[00616] Step 5: *tert*-butyl (1-(4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-3-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)-2-methylbenzyl)piperidin-4-yl)carbamate. To a suspension of 2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoic acid (37 mg, 0.18 mmol) and HATU (68.4 mg, 0.18 mmol) in CH_2Cl_2 (10 mL), was added *N,N*-diisopropylethylamine (0.03mL, 0.22 mmol).

The suspension was stirred for 15 min. Solid *tert*-butyl (1-(3-methyl-4-(2-oxo-4-(piperazine-1-carboxamido)pyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate was added and the solution and was stirred at rt for 16h. The solution was diluted with CH_2Cl_2 (10 mL) and washed with H_2O (1x25 mL). The combined organics were concentrated and purified by flash chromatography ($MeOH/CHCl_3$) to yield the title compound.

[00617] Step 6: 4-(2-amino-2-methylpropanoyl)-N-(1-(4-((4-aminopiperidin-1-yl)methyl)-3-methylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt. The *tert*-butyl (1-(4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)-2-methylbenzyl)piperidin-4-yl)carbamate (95 mg, 0.14 mmol), was dissolved in 2M HCl/MeOH (10mL) at rt for 4h. The reaction mixture was concentrated under reduced pressure, and the solid was triturated with diethyl ether to afford the title compound. ^{1}H NMR (500 MHz, CD_3OD): δ 8.37 (s, 1H), 7.89 (d, 1H), 7.55 (s, 1H), 7.54 (d, 1H), 6.89 (s, 1H), 4.52 (s, 2H), 3.86-3.76 (m, 8H), 3.69 (d, 2H), 3.61-3.51 (m, 1H), 3.44-3.34 (m, 1H), 3.37 (s, 1H), 2.60 (s, 3H), 2.31 (d, 2H), 2.22-2.12 (m, 2H), 1.74 (s, 6H). LCMS [M+H] 511.3.

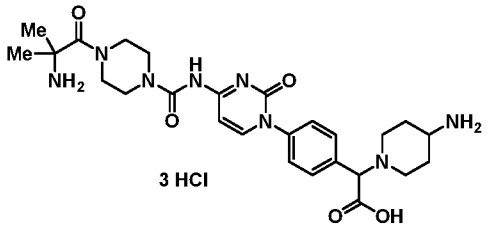
Compound 92



Ethyl 2-(4-(4-(4-(2-amino-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2*H*)-yl)phenyl)-2-(4-aminopiperidin-1-yl)acetate hydrochloride salt

[00618] Prepared in a similar fashion as scheme C-9 from ethyl 2-(4-((*tert*-butoxycarbonyl)amino)piperidin-1-yl)-2-(4-(2-oxo-4-(piperazine-1-carboxamido)pyrimidin-1(2H)-yl)phenyl)acetate and 2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoic acid. LCMS [M+H] 569.4.

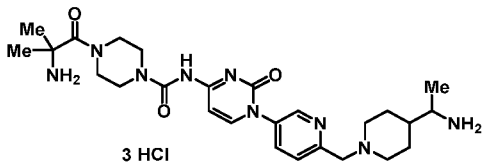
Compound 93



2-(4-(4-(4-(2-Amino-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2*H*)-yl)phenyl)-2-(4-aminopiperidin-1-yl)acetic acid hydrochloride salt.

[00619] Prepared in a similar fashion as scheme C-9 from ethyl 2-(4-((*tert*-butoxycarbonyl)amino)piperidin-1-yl)-2-(4-(2-oxo-4-(piperazine-1-carboxamido)pyrimidin-1(2H)-yl)phenyl)acetate and 2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoic acid. ^{1}H NMR (500 MHz, CD_3OD): δ 8.24 (s, 1H), 7.81 (d, 2H), 7.72 (d, 2H), 6.81 (s, 1H), 5.38 (s, 1H), 3.82-3.72 (m, 8H), 3.35 (s, 5H), 2.38-2.03 (m, 4H), 1.71 (s, 3H), 1.19 (s, 3H). LCMS [M+H] 541.3.

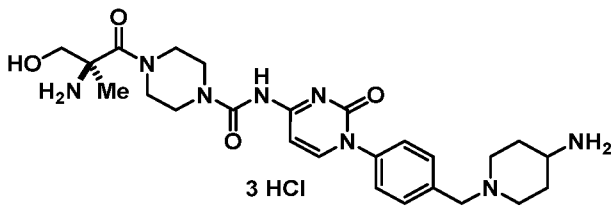
Compound 95



4-(2-Amino-2-methylpropanoyl)-N-(1-(6-((4-(1-aminoethyl)piperidin-1-yl)methyl)pyridin-3-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

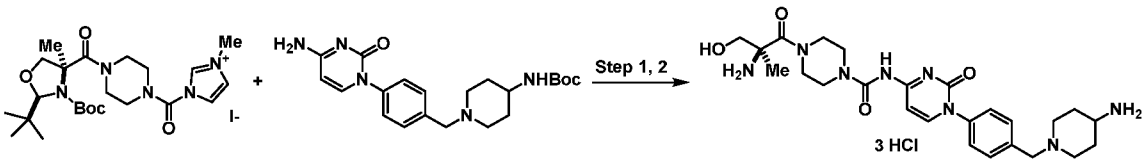
[00620] Prepared in a similar fashion as scheme C-9 from *tert*-butyl (1-(4-((1-(6-formylpyridin-3-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl (1-(piperidin-4-yl)ethyl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 8.73 (d, 1H), 8.07–8.01 (m, 1H), 7.98 (d, 1H), 7.72 (d, 1H), 6.84 (d, 1H), 4.53 (s, 2H), 3.83–3.61 (m, 10H), 3.47 (s, 1H), 3.30 (d, 2H), 3.25–3.10 (m, 2H), 2.02 (s, 2H), 1.95 (s, 1H), 1.70 (s, 6H), 1.32–1.28 (m, 3H). LCMS [M+H] 526.4.

Compound 97



(S)-4-(2-Amino-3-hydroxy-2-methylpropanoyl)-N-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

Scheme C-10

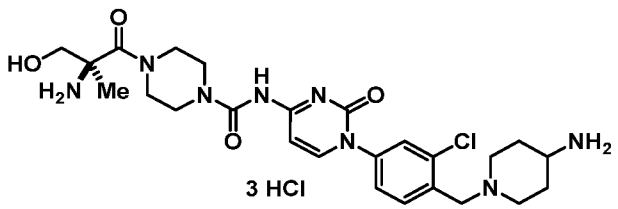


Reagents: 1) CH_3CN, 85° C, 8h 2) HCl, MeOH, rt, 4h.

[00621] Step 1: *tert*-butyl (2R,4S)-4-(4-((1-(4-((4-((*tert*-butoxycarbonyl)amino)piperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazine-1-carbonyl)-2-(*tert*-butyl)-4-methyloxazolidine-3-carboxylate. A mixture of 1-(4-((2R,4S)-3-(*tert*-butoxycarbonyl)-2-(*tert*-butyl)-4-methyloxazolidine-4-carbonyl)piperazine-1-carbonyl)-3-methyl-1H-imidazol-3-ium iodide (48 mg, 0.08 mmol) and *tert*-butyl (1-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate (34 mg, 0.08 mmol) in CH_3CN (12 mL) was stirred at reflux for 8h. The solvent was removed under reduced pressure and the residue was partitioned between $CHCl_3$ (50 mL) andH_2O (50 mL). The organic layer was concentrated under reduced pressure and purified by flash chromatography (MeOH/$CHCl_3$) to afford the title compound.

[00622] Step 2: (S)-4-(2-amino-3-hydroxy-2-methylpropanoyl)-N-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt. A mixture of *tert*-butyl (2R,4S)-4-(4-((1-(4-((4-((*tert*-butoxycarbonyl)amino)piperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazine-1-carbonyl)-2-(*tert*-butyl)-4-methyloxazolidine-3-carboxylate (28 mg, 0.04 mmol) and HCl in MeOH (1.5 M, 10 mL) was stirred at rt for 4h. The solvent was removed under reduced pressure, and the solid was triturated with diethyl ether to yield the title compound. ^{1}H NMR (400 MHz, CD_3OD) δ 8.38 (s, 1H), 7.85 (d, 2H), 7.68 (d, 2H), 6.87 (s, 1H), 4.47 (s, 2H), 4.11 (d, 1H), 3.94-3.69 (m, 9H), 3.63 (d, 2H), 3.52 (s, 1H), 3.28 (d, 2H), 2.29 (d, 2H), 2.17-2.03 (m, 2H), 2.17 (s, 3H). LCMS [M+H] 513.3.

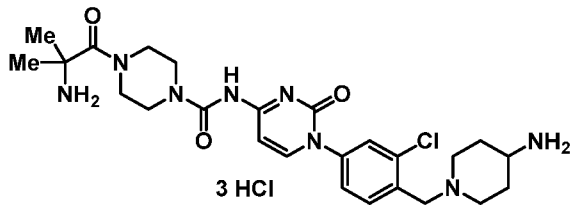
Compound 98



(S)-4-(2-Amino-3-hydroxy-2-methylpropanoyl)-N-(1-(4-((4-aminopiperidin-1-yl)methyl)-3-chlorophenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

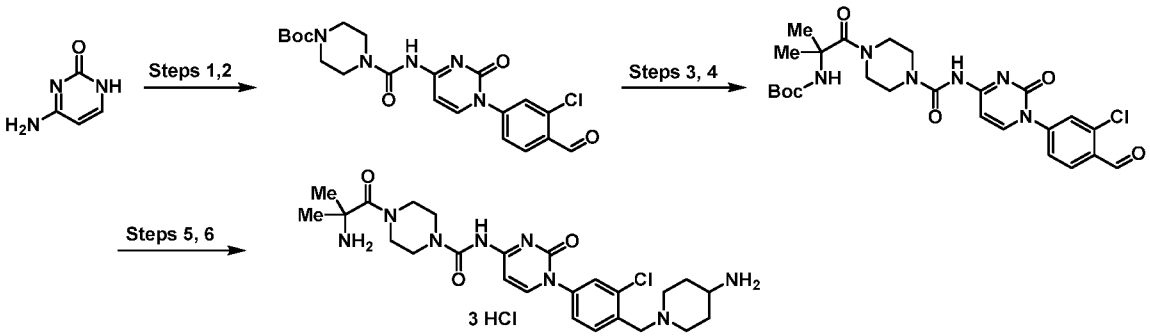
[00623] Prepared in a similar fashion as scheme C-10 from 1-(4-((2R,4S)-3-(*tert*-butoxycarbonyl)-2-(*tert*-butyl)-4-methyloxazolidine-4-carbonyl)piperazine-1-carbonyl)-3-methyl-1H-imidazol-3-ium iodide and *tert*-butyl (1-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)-2-chlorobenzyl)piperidin-4-yl)carbamate. ^{1}H NMR (500 MHz, D_2O) δ 7.67-7.83 (m, 1H), 7.50-7.58 (m, 2H), 7.28-7.37 (m, 1H), 6.62-6.87 (m, 1H), 4.04 (d, 1H), 3.83-3.97 (m, 2H), 3.78 (d, 1H), 3.67 (br. s., 4H), 3.61 (br. s., 4H), 3.20-3.30 (m, 1H), 3.07-3.20 (m, 2H), 2.39-2.63 (m, 2H), 1.94-2.06 (m, 2H), 1.59-1.72 (m, 2H), 1.57 (s, 3H). LCMS [M+H] 547.3.

Compound 99



4-(2-Amino-2-methylpropanoyl)-*N*-(1-(4-((4-aminopiperidin-1-yl)methyl)-3-chlorophenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

Scheme C-11



Reagents: 1) (3-chloro-4-formylphenyl)boronic acid, TMEDA, $Cu(OAc)_2•H_2O$, MeOH:H_2O, 16h, rt, 2) 1-(4-(*tert*-butoxycarbonyl)piperazine-1-carbonyl)-3-methyl-1H-imidazol-3-ium iodide, CH_3CN, 16h, rt 3) TFA, CH_2Cl_2, 1.5h 4) 2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoic acid, HATU, DIPEA, CH_2Cl_2, rt, 16h 5) *tert*-butyl piperidin-4-ylcarbamate, DIPEA, $Na(OAc)_3BH$, DCE:CH_3CN, rt, 16h 6) HCl, MeOH, rt, 4h.

[00624] Step 1: 4-(4-amino-2-oxopyrimidin-1(2H)-yl)-2-chlorobenzaldehyde. A suspension of cytosine and (3-chloro-4-formylphenyl)boronic acid, in a mixture of MeOH:H_2O (4:1, 25ml) was stirred at rt in an open atmosphere. After 30 min., TMEDA and $Cu(OAc)_2•H_2O$ were added. The reaction was stirred in an open atmosphere for 16h at rt. The MeOH was evaporated reduced pressure, and the remaining mixture was diluted with H_2O

(25ml) and left to stir at 0 °C for 15 minutes. The mixture was filtered and the title compound was collected as a white solid.

[00625] Step 2: *tert*-butyl 4-((1-(3-chloro-4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazine-1-carboxylate. 1-(4-(*tert*-butoxycarbonyl)piperazine-1-carbonyl)-3-methyl-1H-imidazol-3-ium iodide and 4-(4-amino-2-oxopyrimidin-1(2H)-yl)-2-chlorobenzaldehyde dissolved in dry CH_3CN (12 mL). The solution was heated to reflux for 16h under an atmosphere of nitrogen. After, the solvent was removed under reduced pressure and the crude reaction mixture was partitioned between $CHCl_3$ (50 mL) and water (50 mL). The organic layer was concentrated and purified via flash chromatography to afford the title compound (85%) as a white solid.

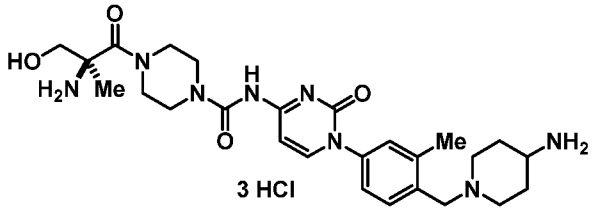
[00626] Step 3: N-(1-(3-chloro-4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide trifluoroacetate salt. *tert*-Butyl 4-((1-(3-chloro-4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazine-1-carboxylate was dissolved in a solution of 1:1 trifluoroacetic acid: CH_2Cl_2 (10 mL). The reaction was stirred for 1.5 h at rt. The solvent and trifluoroacetic acid were removed reduced pressure. The crude reaction mixture was triturated with diethyl ether to yield a solid precipitate. The precipitate was filtered and washed with diethyl ether to yield the title compound as a white solid.

[00627] Step 4: *tert*-butyl (1-(4-((1-(3-chloro-4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate. To a suspension of 2-((*tert*-butoxycarbonyl)amino)-24-methylpropanoic acid and HATU in dry CH_2Cl_2 was added DIPEA. The suspension was stirred for 10 min. Solid N-(1-(3-chloro-4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide trifluoroacetate salt was added and the solution was stirred at rt for 16h. The solution was diluted with CH_2Cl_2 (25mL) and washed with water. The organic layers were concentrated and purification via flash chromatography yielded the title compound as a white solid.

[00628] Step 5: *tert*-butyl (1-(4-((1-(4-((4-((*tert*-butoxycarbonyl)amino)piperidin-1-yl)methyl)-3-chlorophenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate. To suspension of *tert*-butyl (1-(4-((1-(3-chloro-4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl piperidin-4-ylcarbamate in 1:1 DCE:MeCN (25mL), DIPEA and $Na(OAc)_3BH$ were added. The reaction was left to stir for 16h at rt, after which the solvent was removed reduced pressure. The solid was dissolved in $CHCl_3$ and washed with 10% NaOH. Purification via flash chromatography yielded the title compound as a white solid.

[00629] Step 6: 4-(2-amino-2-methylpropanoyl)-N-(1-(4-((4-aminopiperidin-1-yl)methyl)-3-chlorophenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride. The *tert*-butyl (1-(4-((1-(4-((4-((*tert*-butoxycarbonyl)amino)piperidin-1-yl)methyl)-3-chlorophenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate was treated with 2M HCl in MeOH (10mL) and stirred at rt for 4h. The solvent and excess HCl were removed under reduced pressure and the solid was triturated with diethyl ether and dried under high vacuum to yield the title compound. ^{1}H NMR (400 MHz, CD_3OD) δ 8.29 (d, 1H), 8.06 (d, 1H), 7.86 (s, 1H), 7.65 (d, 1H), 6.85 (d, 1H), 4.64 (s, 2H), 3.79 (br. s, 9H), 3.72 (d, 2H), 3.41 (t, 2H), 2.30 (d, 2H), 2.13 (q, 2H), 1.72 (d 6H). LCMS [M+H] 531.3.

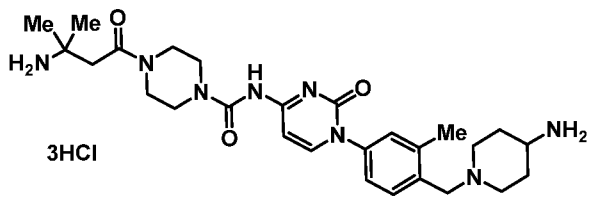
Compound 101



(S)-4-(2-Amino-3-hydroxy-2-methylpropanoyl)-N-(1-(4-((4-aminopiperidin-1-yl)methyl)-3-methylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00630] Prepared in a similar fashion as scheme C-11 from *tert*-butyl (2R,4S)-2-(*tert*-butyl)-4-(4-((1-(4-formyl-3-methylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazine-1-carbonyl)-4-methyloxazolidine-3-carboxylate and *tert*-butyl piperidin-4-ylcarbamate. ^{1}H NMR (500 MHz, CD_3OD): δ 7.79 (d, 1H), 7.81-7.74 (m, 1H), 7.42-7.34 (m, 3H), 4.23 (s, 2H), 4.10 (d, 1H), 3.84 (d, 1H), 3.78-3.67 (m, 8H), 3.65-3.28 (m, 1H), 2.54 (s, 3H), 2.28 (d, 2H), 2.19-2.06 (m, 2H). LCMS [M+H] 527.4.

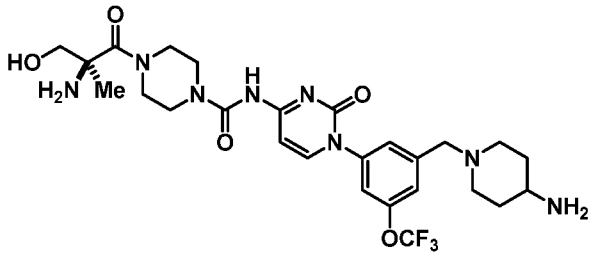
Compound 94



4-(3-Amino-3-methylbutanoyl)-N-(1-(4-((4-aminopiperidin-1-yl)methyl)-3-methylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00631] Prepared in a similar fashion to Scheme C-11 from *tert*-butyl (4-(4-((1-(4-formyl-3-methylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-4-oxobutan-2-yl)carbamate and *tert*-butyl piperidin-4-ylcarbamate. ^{1}H NMR (500 MHz, D_2O) δ 8.00 (d, 1H), 7.66 (d, 1H), 7.47 (s, 1H), 7.42 (d 1H), 6.87 (d, 1H), 4.50 (s, 2H), 3.76 (br s. 2H), 3.74 (br s, 8H), 3.65-3.56 (m, 1H), 3.32 (t, 2H), 2.88 (s, 2H), 2.51 (s, 3H), 2.36 (d, 2H), 2.03-1.94 (m, 2H), 1.46 (s, 6H). LCMS [M+H] 525.3.

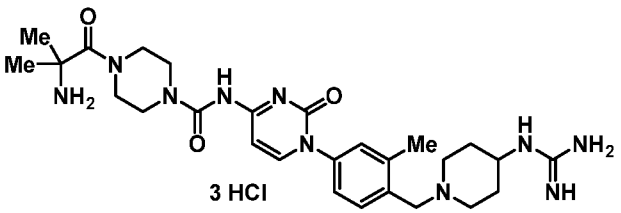
Compound 103



(*S*)-4-(2-Amino-3-hydroxy-2-methylpropanoyl)-*N*-(1-(3-((4-aminopiperidin-1-yl)methyl)-5-(trifluoromethoxy)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide

[00632] Prepared in a similar fashion as scheme C-11 from *tert*-butyl (2R,4S)-2-(*tert*-butyl)-4-(4-((1-(3-formyl-5-(trifluoromethoxy)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazine-1-carbonyl)-4-methyloxazolidine-3-carboxylate and *tert*-butyl piperidin-4-ylcarbamate. LCMS [M+H] 597.3.

Compound 104

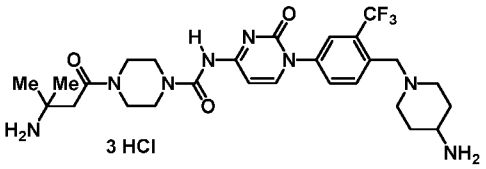


4-(2-Amino-2-methylpropanoyl)-*N*-(1-(4-((4-guanidinopiperidin-1-yl)methyl)-3-methylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00633] Prepared in a similar fashion as scheme C-11 from *tert*-butyl (1-(4-((1-(4-formyl-3-methylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and 1,2-bis(*tert*-butoxycarbonyl)-3-(piperidin-4-yl)guanidine. ^{1}H NMR (500 MHz, CD3OD) δ 8.40 (s, 1H), 7.83 (s, 1H), 7.71 (s, 1H), 7.50 (d, 2H), 6.87 (s, 1H), 4.49 (s, 1H), 3.83-3.71 (m, 10H), 3.64-3.55 (m, 3H), 3.3 (s, 8H), 2.56 (s, 3H), 2.56 (s,

3H), 2.26-2.13 (m, 3H), 2.03-1.91 (m, 3H), 1.69 (s, 6H), 1.55 (s, 6H), 1.26 (s, 2H). LCMS [M+H] 553.3.

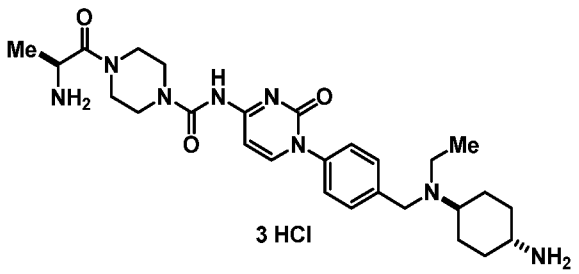
Compound 106



4-(3-Amino-3-methylbutanoyl)-*N*-(1-(4-((4-aminopiperidin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

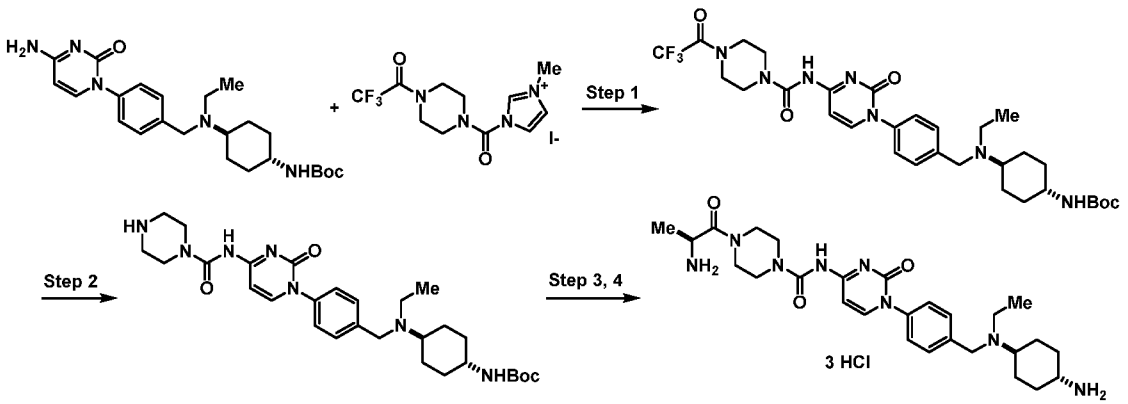
[00634] Prepared in a similar fashion as scheme C-11 from *tert*-butyl (4-(4-((1-(4-formyl-3-(trifluoromethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-4-oxobutan-2-yl)carbamate and *tert*-butyl piperidin-4-ylcarbamate. LCMS [M+H] 579.3.

Compound 357



4-(L-Alanyl)-N-(1-(4-(((*trans*-4-aminocyclohexyl)(ethyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

Scheme C-12



Reagents: 1) CH_3CN, reflux, 20h 2) K_2CO_3, MeOH, rt, 2d 3) Boc-L-Ala, HATU, DIPEA, DMF, rt, 17h 4) 2.0 M HCl in MeOH, rt, 18h.

[00635] Step 1. *tert*-butyl (*trans*-4-(ethyl(4-(2-oxo-4-(4-(2,2,2-trifluoroacetyl)piperazine-1-carboxamido)pyrimidin-1(2H)-yl)benzyl)amino)cyclohexyl)carbamate. A mixture of *tert*-butyl (*trans*-4-((4-(4-amino-2-oxopyrimidin-1(2H)-yl)benzyl)(ethyl)amino)cyclohexyl) carbamate (605 mg, 1.37 mmol) and 3-methyl-1-(4-(2,2,2-trifluoroacetyl)piperazine-1-carbonyl)-1H-imidazol-3-ium iodide (687 mg, 1.64 mmol) in CH_3CN (20 mL) was stirred at reflux for 20h. The reaction mixture was concentrated and EtOAc (75 mL) added, washed with sat. aq. $NaHCO_3$ (3x50 mL) and brine (1x50 mL), dried over Na_2SO_4, decanted and concentrated. The residue was purified by flash chromatography (Hexanes/EtOAc/MeOH) to afford the title compound (515 mg, 58%) as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 12.87 (br s, 1H), 7.46 (d, 2H), 7.34–7.18 (m, 3H), 5.88–5.75 (m, 1H), 4.35–4.31 (m, 1H), 4.02–3.88 (m, 2H), 3.77–3.66 (m, 4H), 3.65–3.56 (m, 4H), 3.44–3.24 (m, 1H), 2.59–2.44 (m, 3H), 2.10–1.98 (m, 2H), 1.83 (d, 2H), 1.50–1.32 (m, 11H), 1.14–1.02 (m, 2H), 0.98 (t, 3H).

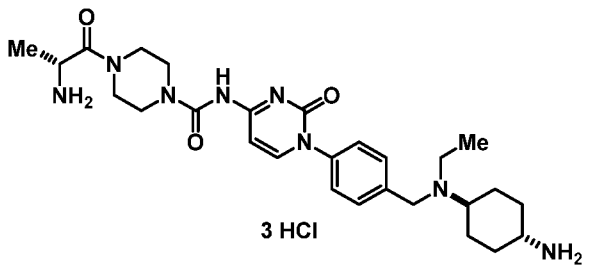
[00636] Step 2. *tert*-butyl (*trans*-4-(ethyl(4-(2-oxo-4-(piperazine-1-carboxamido)pyrimidin-1(2H)-yl)benzyl)amino)cyclohexyl)carbamate. A mixture of *tert*-butyl (*trans*-4-(ethyl(4-(2-oxo-4-(4-(2,2,2-trifluoroacetyl)piperazine-1-carboxamido)pyrimidin-1(2H)-yl)benzyl)amino)cyclohexyl)carbamate (515 mg, 0.79 mmol) and K_2CO_3 (349 mg, 2.53 mmol) in MeOH (10 mL) was stirred at rt for 2 d. The solvent was removed, sat. aq. $NaHCO_3$ (50 mL) was added and the aqueous layer was extracted with DCM (3x75 mL). The extracts were concentrated to dryness to give the title compound (456 mg, 93 %) as a white solid.

[00637] Step 3. *tert*-butyl (*trans*-4-((4-(4-(4-((*tert*-butoxycarbonyl)-L-alanyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)(ethyl)amino)cyclohexyl)carbamate. A mixture of *tert*-butyl (*trans*-4-(ethyl(4-(2-oxo-4-(piperazine-1-carboxamido)pyrimidin-1(2H)-yl)benzyl)amino)cyclohexyl)carbamate (75 mg, 0.13 mmol), (*tert*-butoxycarbonyl)-L-alanine (33 mg, 0.17 mmol),HATU (64.9 mg, 0.17 mmol), and DIPEA (0.07 mL, 0.4 mmol) in DMF (0.5 mL) was stirred at rt for 17h. The mixture was diluted with EtOAc (10 mL), washed with sat. aq. $NaHCO_3$ (2x8 mL) and brine (2x8 mL). The organic layer along with the remaining emulsion was concentrated, water (5 mL) was added, and the solid was collected by vacuum filtration to give the title compound (68.8 mg, 70.5 %) as a white solid.

[00638] Step 4. 4-(L-Alanyl)-N-(1-(4-(((*trans*-4-aminocyclohexyl)(ethyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt. A mixture of *tert*-butyl (*trans*-4-((4-(4-(4-((*tert*-butoxycarbonyl)-L-alanyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)(ethyl)amino)cyclohexyl)carbamate (69 mg, 0.10 mmol) and 2M HCl in MeOH (2

mL, 4 mmol) was stirred at rt for 18h, concentrated. The residue was purified by HPLC (CH_3CN/H_20/TFA) and by flash chromatography (DCM/MeOH/NH_4OH). The product fractions were converted to the HCl salt with 2M HCl in MeOH to afford the title compound (21.9 mg, 36.4 %) as a white solid. ^1H NMR (500 MHz, D_2O) δ 8.10–7.95 (m, 1H), 7.81–7.68 (m, 2H), 7.68–7.55 (m, 2H), 6.97–6.81 (m, 1H), 4.64–4.54 (m, 1H), 4.42 (d, 1H), 3.89–3.64 (m, 8H), 3.63–3.55 (m, 1H), 3.55–3.45 (m, 1H), 3.45–3.23 (m, 3H), 2.43–2.19 (m, 4H), 2.03–1.79 (m, 2H), 1.71–1.49 (m, 5H), 1.44–1.29 (m, 3H). LCMS [M+H] 525.4.

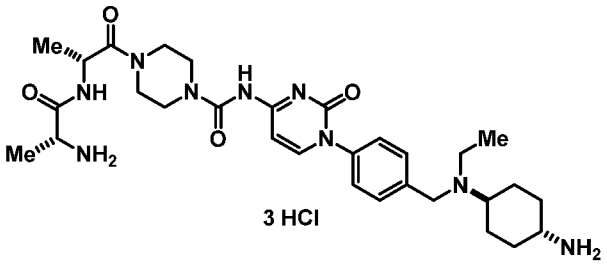
Compound 358



4-(D-Alanyl)-N-(1-(4-(((*trans*-4-aminocyclohexyl)(ethyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00639] Prepared in a similar fashion to Scheme C-12 from *tert*-butyl (*trans*-4-(ethyl(4-(2-oxo-4-(piperazine-1-carboxamido)pyrimidin-1(2H)-yl)benzyl)amino)cyclohexyl)carbamate and (*tert*-butoxycarbonyl)-L-alanine. ^1H NMR (500 MHz, D_2O) δ 8.07 (d, 1H), 7.74 (d, 2H), 7.63 (d, 2H), 6.89 (d, 1H), 4.65–4.55 (m, 2H), 4.42 (d, 1H), 3.86–3.69 (m, 8H), 3.56–3.46 (m, 1H), 3.44–3.25 (m, 3H), 2.39–2.22 (m, 4H), 2.00–1.81 (m, 2H), 1.69–1.51 (m, 5H), 1.36 (t, 3H). LCMS [M+H] 525.3.

Compound 359

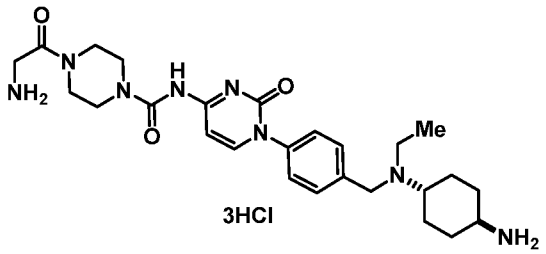


4-(D-Alanyl-D-alanyl)-N-(1-(4-(((*trans*-4-aminocyclohexyl)(ethyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamidehydrochloride salt

[00640] Prepared in a similar fashion to Scheme C-12 from *tert*-butyl (*trans*-4-(ethyl(4-(2-oxo-4-(piperazine-1-carboxamido)pyrimidin-1(2H)-yl)benzyl)amino)cyclohexyl)carbamate and (*tert*-butoxycarbonyl)-D-alanyl-D-alanine. ^1H NMR (500 MHz, D_2O) δ 8.06 (d, 1H), 7.74 (d, 2H), 7.63 (d, 2H), 6.90 (d, 1H), 4.95–4.87 (m, 1H), 4.61 (d, 1H), 4.43 (d, 1H), 4.16

(q, 1H), 3.92–3.66 (m, 8H), 3.56–3.45 (m, 1H), 3.44–3.25 (m, 3H), 2.40–2.21 (m, 4H), 2.01–1.81 (m, 2H), 1.69–1.53 (m, 5H), 1.43 (d, 3H), 1.36 (t, 3H). LCMS [M+H] 596.4.

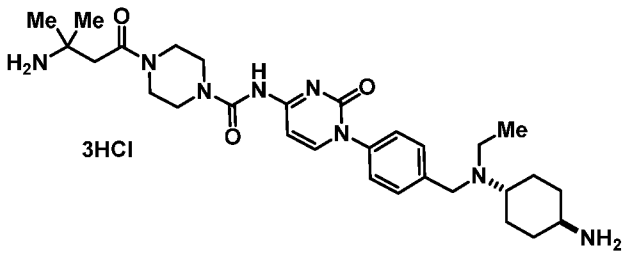
Compound 311



N-(1-(4-(((*trans*-4-Aminocyclohexyl)(ethyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-4-glycylpiperazine-1-carboxamide hydrochloride salt

[00641] Prepared in a similar fashion to Scheme C-12 from *tert*-butyl (*trans*-4-(ethyl(4-(2-oxo-4-(piperazine-1-carboxamido)pyrimidin-1(2H)-yl)benzyl)amino)cyclohexyl)carbamate and (*tert*-butoxycarbonyl)glycine. ^{1}H NMR (500 MHz, CD_3OD) δ 7.84 (d, 1H), 7.71 (d, 2H), 7.59 (d, 2H), 6.66 (d, 1H), 4.58 (s, 1H), 4.38 (s, 1H), 4.00 (s, 2H), 3.74–3.68 (m, 6H), 3.51 (t, 2H), 3.46–3.41 (m, 1H), 3.28–3.17 (m, 3H), 2.31–2.21 (m, 4H), 1.92–1.82 (m, 2H), 1.60–1.52 (m, 2H), 1.32 (t, 3H). LCMS [M+H] 511.3.

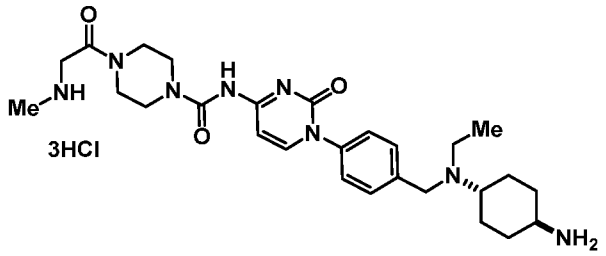
Compound 312



4-(3-Amino-3-methylbutanoyl)-N-(1-(4-(((*trans*-4-aminocyclohexyl)(ethyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00642] Prepared in a similar fashion to Scheme C-12 from *tert*-butyl (*trans*-4-(ethyl(4-(2-oxo-4-(piperazine-1-carboxamido)pyrimidin-1(2H)-yl)benzyl)amino)cyclohexyl)carbamate and 3-((*tert*-butoxycarbonyl)amino)-3-methylbutanoic acid. ^{1}H NMR (500 MHz, CD_3OD) δ 7.83 (d, 1H), 7.71 (d, 2H), 7.59 (d, 2H), 6.67 (d, 1H), 4.56 (s, 1H), 4.37 (s, 1H), 3.76–3.68 (m, 8H), 3.43 (t, 1H), 3.28–3.17 (m, 3H), 3.03 (s, 2H), 2.31–2.21 (m, 4H), 1.92–1.82 (m, 2H), 1.60–1.52 (m, 2H), 1.44 (s, 6H), 1.33 (t, 3H). LCMS [M+H] 553.4.

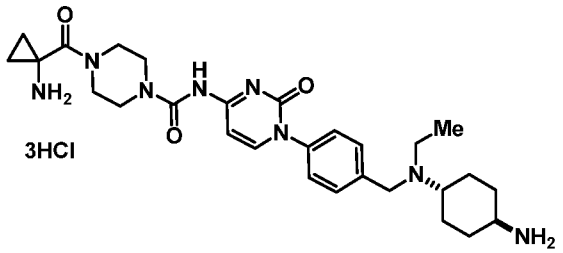
Compound 313



N-(1-(4-(((*trans*-4-Aminocyclohexyl)(ethyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-4-(methylglycyl)piperazine-1-carboxamide hydrochloride salt

[00643] Prepared in a similar fashion to Scheme C-12 from *tert*-butyl (*trans*-4-(ethyl(4-(2-oxo-4-(piperazine-1-carboxamido)pyrimidin-1(2H)-yl)benzyl)amino)cyclohexyl)carbamate and *N*-(*tert*-butoxycarbonyl)-N-methylglycine. ^{1}H NMR (500 MHz, CD_3OD) δ 7.83 (d, 1H), 7.71 (d, 2H), 7.59 (d, 2H), 6.66 (d, 1H), 4.56 (s, 1H), 4.37 (s, 1H), 4.13 (s, 2H), 3.74–3.68 (m, 6H), 3.50 (t, 2H), 3.46–3.41 (m, 1H), 3.28–3.17 (m, 3H), 2.76 (s, 3H), 2.31–2.21 (m, 4H), 1.92–1.82 (m, 2H), 1.61–1.52 (m, 2H), 1.33 (t, 3H). LCMS [M+H] 525.3.

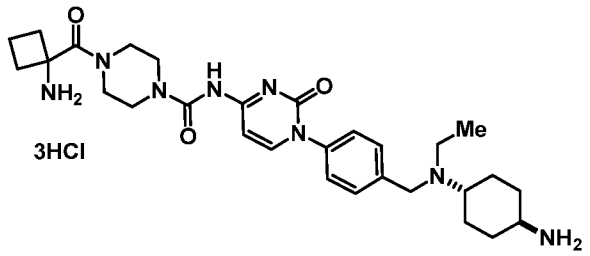
Compound 314



N-(1-(4-(((*trans*-4-Aminocyclohexyl)(ethyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-4-(1-aminocyclopropane-1-carbonyl)piperazine-1-carboxamide hydrochloride salt

[00644] Prepared in a similar fashion to Scheme C-12 from *tert*-butyl (*trans*-4-(ethyl(4-(2-oxo-4-(piperazine-1-carboxamido)pyrimidin-1(2H)-yl)benzyl)amino)cyclohexyl)carbamate and 1-((*tert*-butoxycarbonyl)amino)cyclopropane-1-carboxylic acid. ^{1}H NMR (500 MHz, CD_3OD) δ 7.74 (d, 1H), 7.70 (d, 2H), 7.59 (d, 2H), 6.54 (d, 1H), 4.56 (s, 1H), 4.37 (s, 1H), 3.92 (t, 4H), 3.43 (t, 1H), 3.40 (t, 8H), 3.28–3.17 (m, 3H), 2.31–2.21 (m, 4H), 1.92–1.82 (m, 2H), 1.60–1.52 (m, 2H), 1.34 (t, 3H).

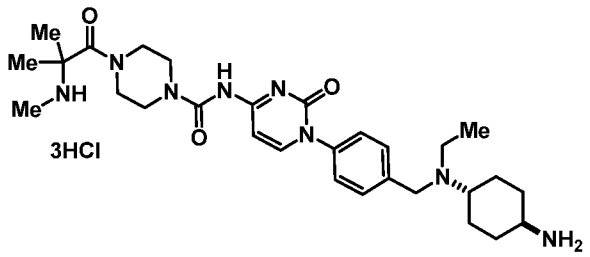
Compound 315



4-(1-Aminocyclobutane-1-carbonyl)-N-(1-(4-(((*trans*-4-aminocyclohexyl)(ethyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00645] Prepared in a similar fashion to Scheme C-12 from *tert*-butyl (*trans*-4-(ethyl(4-(2-oxo-4-(piperazine-1-carboxamido)pyrimidin-1(2H)-yl)benzyl)amino)cyclohexyl)carbamate and 1-((*tert*-butoxycarbonyl)amino)cyclobutane-1-carboxylic acid. ^{1}H NMR (500 MHz, CD_3OD) δ 7.84 (d, 1H), 7.71 (d, 2H), 7.59 (d, 2H), 6.66 (d, 1H), 4.56 (s, 1H), 4.37 (s, 1H), 3.75–3.61 (m, 8H), 3.44 (t, 1H), 3.28–3.17 (m, 3H), 2.92–2.85 (m, 2H), 2.45–2.37 (m, 2H), 2.36–2.32 (m, 1H), 2.31–2.21 (m, 4H), 2.12–2.05 (m, 1H), 1.92–1.82 (m, 2H), 1.60–1.52 (m, 2H), 1.34 (t, 3H). LCMS [M+H] 551.4.

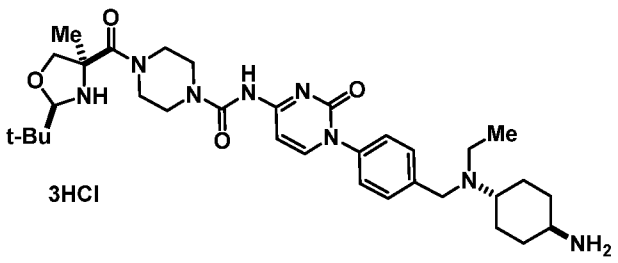
Compound 316



N-(1-(4-(((*trans*-4-Aminocyclohexyl)(ethyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-4-(2-methyl-2-(methylamino)propanoyl)piperazine-1-carboxamide hydrochloride salt

[00646] Prepared in a similar fashion to Scheme C-12 from *tert*-butyl (*trans*-4-(ethyl(4-(2-oxo-4-(piperazine-1-carboxamido)pyrimidin-1(2H)-yl)benzyl)amino)cyclohexyl)carbamate and 2-((*tert*-butoxycarbonyl)(methyl)amino)-2-methylpropanoic acid. ^{1}H NMR (500 MHz, CD_3OD) δ 7.77 (d, 1H), 7.70 (d, 2H), 7.59 (d, 2H), 6.65 (d, 1H), 4.56 (s, 1H), 4.37 (s, 1H), 3.71 (s, 8H), 3.43 (t, 1H), 3.35 (s, 3H), 3.28–3.17 (m, 3H), 2.31–2.21 (m, 4H), 1.92–1.82 (m, 2H), 1.70 (s, 6H), 1.61–1.52 (m, 2H), 1.33 (t, 3H).

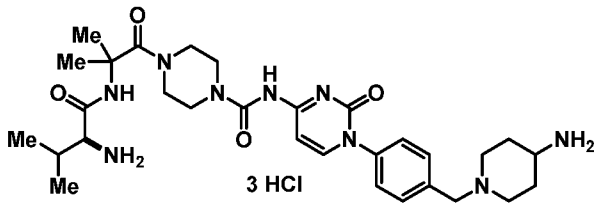
Compound 326



N-(1-(4-(((*trans*-4-Aminocyclohexyl)(ethyl)amino)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-4-((2R,4S)-2-(*tert*-butyl)-4-methyloxazolidine-4-carbonyl)piperazine-1-carboxamide hydrochloride salt

[00647] Prepared in a similar fashion to Scheme C-12 from *tert*-butyl (*trans*-4-(ethyl(4-(2-oxo-4-(piperazine-1-carboxamido)pyrimidin-1(2H)-yl)benzyl)amino)cyclohexyl)carbamate, and (2*R*,4*S*)-3-(*tert*-butoxycarbonyl)-2-(*tert*-butyl)-4-methyloxazolidine-4-carboxylic acid. ^{1}H NMR (500 MHz, CD_3OD) δ 7.71 (d, 1H), 7.50 (d, 2H), 7.35 (d, 2H), 6.62 (d, 1H), 4.50 (s, 1H), 4.23 (s, 1H), 4.05 (s, 1H), 3.89–3.63 (m, 8H), 3.56 (d, 1H), 3.52–3.38 (m, 1H), 3.27 (d, 1H), 2.70 (t, 1H), 2.62–2.54 (m, 3H), 1.99–1.84 (m, 4H), 1.49 (s, 3H), 1.48–1.38 (m, 2H), 1.24–1.15 (m, 2H), 1.02 (t, 3H), 0.95 (d, 9H). LCMS [M+H] 623.4.

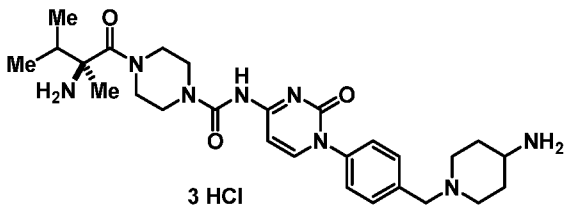
Compound 364



(S)-4-(2-(2-Amino-3-methylbutanamido)-2-methylpropanoyl)-N-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00648] Prepared in a similar fashion to Scheme C-12 from *tert*-butyl (1-(4-(2-oxo-4-(piperazine-1-carboxamido)pyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate and (S)-2-(2-((*tert*-butoxycarbonyl)amino)-3-methylbutanamido)-2-methylpropanoic acid. LCMS [M+H] 569.4.

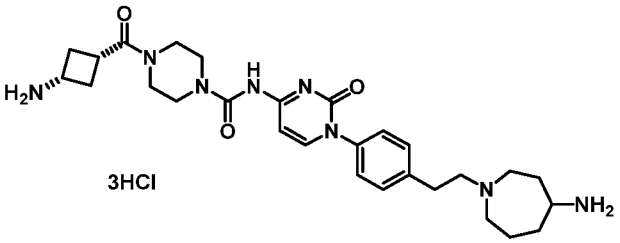
Compound 385



(S)-4-(2-Amino-2,3-dimethylbutanoyl)-N-(1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00649] Prepared in a similar fashion to Scheme C-12 from *tert*-butyl (1-(4-(2-oxo-4-(piperazine-1-carboxamido)pyrimidin-1(2H)-yl)benzyl)piperidin-4-yl)carbamate and (S)-2-((*tert*-butoxycarbonyl)amino)-2,3-dimethylbutanoic acid.

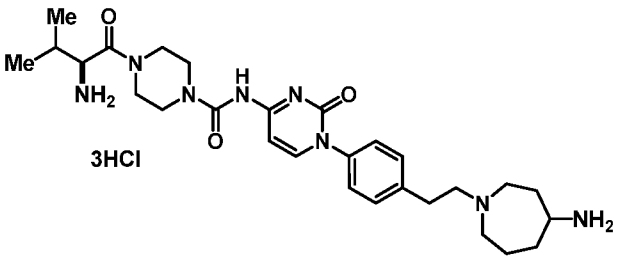
Compound 303



N-(1-(4-(2-(4-Aminoazepan-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-4-(*cis*-3-aminocyclobutane-1-carbonyl)piperazine-1-carboxamide hydrochloride salt

[00650] Prepared in a similar fashion to Scheme C-12 from *tert*-butyl (1-(4-(2-oxo-4-(piperazine-1-carboxamido)pyrimidin-1(2H)-yl)phenethyl)azepan-4-yl)carbamate and 1-(*tert*-butoxycarbonyl)azetidine-3-carboxylic acid. ^{1}H NMR (500 MHz, D_2O) δ 8.12 (d, 1H), 7.57 (d, 2H), 7.51 (d, 2H), 6.87 (d, 1H), 3.82-3.45 (m, 17H), 3.25 (t, 2H), 2.76-2.66 (m, 4H), 2.48-1.75 (m, 6H). LCMS [M+H] 537.4.

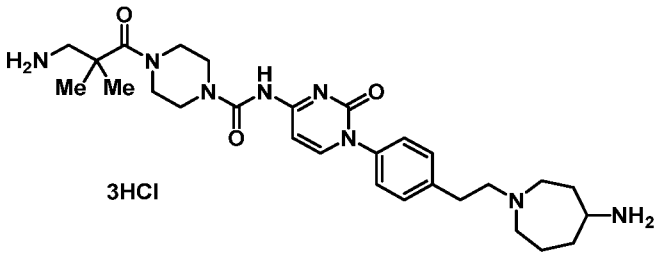
Compound 304



4-(L-Valyl)-N-(1-(4-(2-(4-minoazepan-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00651] Prepared in a similar fashion to Scheme C-12 from *tert*-butyl (1-(4-(2-oxo-4-(piperazine-1-carboxamido)pyrimidin-1(2H)-yl)phenethyl)azepan-4-yl)carbamate and (*tert*-butoxycarbonyl)-L-valine. ^{1}H NMR (500 MHz, D_2O) δ 8.10 (d, 1H), 7.56 (d, 2H), 7.51 (d, 2H), 6.86 (d, 1H), 3.86-3.51 (m, 16H), 3.25 (t, 2H), 2.48-2.24 (m, 3H), 2.23-2.00 (m, 2H), 1.98-1.73 (m, 2H), 1.15 (d, 3H), 1.06 (d, 3H). LCMS [M+H] 539.4.

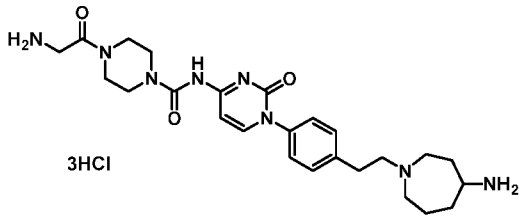
Compound 306



4-(3-Amino-2,2-dimethylpropanoyl)-N-(1-(4-(2-(4-aminoazepan-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00652] Prepared in a similar fashion to Scheme C-12 from *tert*-butyl (1-(4-(2-oxo-4-(piperazine-1-carboxamido)pyrimidin-1(2H)-yl)phenethyl)azepan-4-yl)carbamate and 3-((*tert*-butoxycarbonyl)amino)-2,2-dimethylpropanoic acid. ^{1}H NMR (500 MHz, D_2O) δ 8.04 (d, 1H), 7.50 (d, 2H), 7.44 (d, 2H), 6.81 (d, 1H), 3.88-3.62 (m, 8H), 3.64-3.34 (m, 6H), 3.27-3.16 (m, 3H), 3.10 (s, 2H), 2.42-1.97 (m, 4H), 1.90-1.60 (m, 2H), 1.43 (s, 6H). LCMS [M+H] 539.4.

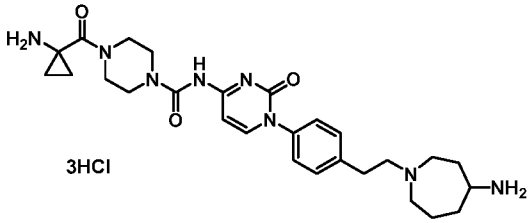
Compound 307



N-(1-(4-(2-(4-Aminoazepan-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-4-glycylpiperazine-1-carboxamide hydrochloride salt

[00653] Prepared in a similar fashion to Scheme C-12 from *tert*-butyl (1-(4-(2-oxo-4-(piperazine-1-carboxamido)pyrimidin-1(2H)-yl)phenethyl)azepan-4-yl)carbamate and (*tert*-butoxycarbonyl)glycine. ^{1}H NMR (500 MHz, D_2O) δ 8.15 (d, 1H), 7.53 (d, 2H), 7.47 (d, 2H), 6.80 (d, 1H), 4.10 (s, 2H), 3.78-3.49 (m, 15H), 3.20 (t, 2H), 2.43-1.61 (m, 6H). LCMS [M+H] 497.3.

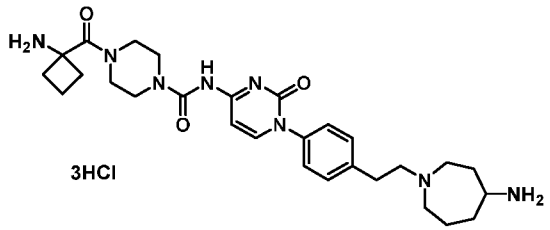
Compound 308



N-(1-(4-(2-(4-Aminoazepan-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-4-(1-aminocyclopropane-1-carbonyl)piperazine-1-carboxamide hydrochloride salt

[00654] Prepared in a similar fashion to Scheme C-12 from *tert*-butyl (1-(4-(2-oxo-4-(piperazine-1-carboxamido)pyrimidin-1(2H)-yl)phenethyl)azepan-4-yl)carbamate and 1-((*tert*-butoxycarbonyl)amino)cyclopropane-1-carboxylic acid. ^{1}H NMR (500 MHz, D_2O) δ 8.08 (d, 1H), 7.50 (d, 2H), 7.45 (d, 2H), 6.80 (d, 1H), 3.84-3.67 (m, 8H), 3.63-3.47 (m, 5H), 3.43-3.27 (m, 2H), 3.18 (t, 2H), 2.40-1.63 (m, 6H), 1.47-1.14 (m, 4H). LCMS [M+H] 523.4.

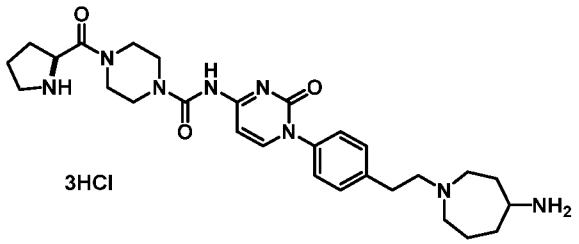
Compound 309



N-(1-(4-(2-(4-Aminoazepan-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-4-(1-aminocyclobutane-1-carbonyl)piperazine-1-carboxamide hydrochloride salt

[00655] Prepared in a similar fashion to Scheme C-12 from *tert*-butyl (1-(4-(2-oxo-4-(piperazine-1-carboxamido)pyrimidin-1(2H)-yl)phenethyl)azepan-4-yl)carbamate and 1-((*tert*-butoxycarbonyl)amino)cyclobutane-1-carboxylic acid. ^{1}H NMR (500 MHz, D_2O) δ 8.05 (d, 1H), 7.54 (d, 2H), 7.48 (d, 2H), 6.86 (d, 1H), 3.83-3.74 (m, 8H), 3.67-3.53 (m, 5H), 3.23 (t, 2H), 2.97-2.88 (m, 2H), 2.55-1.66 (m, 12H). LCMS [M+H] 537.4.

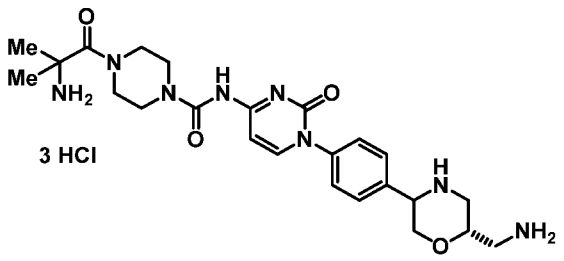
Compound 310



4-(L-Prolyl)-N-(1-(4-(2-(4-aminoazepan-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

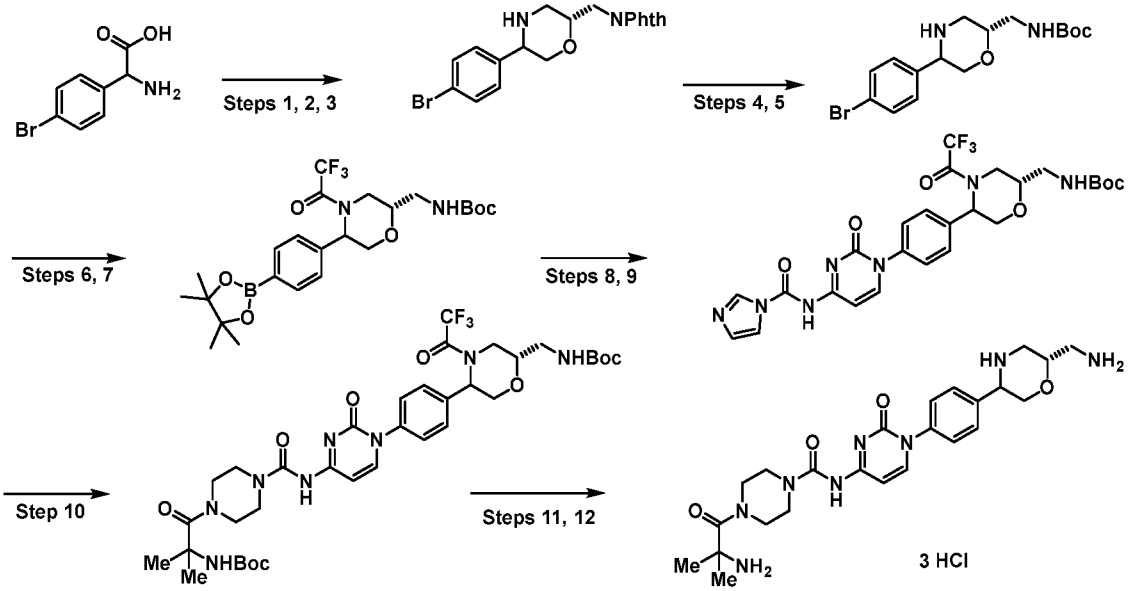
[00656] Prepared in a similar fashion to Scheme C-12 from *tert*-butyl (1-(4-(2-oxo-4-(piperazine-1-carboxamido)pyrimidin-1(2H)-yl)phenethyl)azepan-4-yl)carbamate and (*tert*-butoxycarbonyl)-L-proline. LCMS [M+H] 537.3.

Compound 352



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((6S)-6-(aminomethyl)morpholin-3-yl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

Scheme C-13



Reagents: 1) $NaBH_4$, I_2, THF, 65 °C, 16h 2) (S)-glycidyl phthalimide, EtOH, 65 °C, 24h 3) DIAD, PPh_3 0°C to rt, 4h 4) hydrazine monohydrate, EtOH, 70°C, 4h 5) Boc_2O, Et_3N, CH_2Cl_2, rt, 16h 6) TFAA, Et_3N, CH_2Cl_2, 0°C to rt, 16h 7) $(B(pin))_2$, $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, KOAc, dioxane, 100°C, 16h 8) cytosine, TMEDA, $Cu(OAc)_2 \cdot H_2O$, 4:1 MeOH:H_2O rt. 48h 9) 1,1'-carbonyldiimidazole, CH_2Cl_2, rt. 4h 10) *tert*-butyl (2-methyl-1-oxo-1-(piperazin-1-yl)propan-2-yl)carbamate CH_3CN, 85 °C, 3h 11) LiOH, 1:1 THF:H_2O rt, 16h 12) HCl in MeOH, rt, 4h.

[00657] Step 1: 2-amino-2-(4-bromophenyl)ethan-1-ol. To a suspension of 2-amino-2-(4-bromophenyl)acetic acid in THF (2.0 g, 8.6 mmol) at 0 °C, was added $NaBH_4$ (826 mg, 21.7 mmol). A solution of I_2 (2.2 g, 8 mmol) in THF was added dropwise over 10 min. and the reaction was heated to 65 °C for 16h. The reaction was cooled to rt and quenched with the addition of MeOH (5 mL). The reaction mixture was concentrated under reduced pressure and diluted with 10% NaOH (100 mL) and stirred for 2h. The aqueous phase was extracted with $CHCl_3$ (3x150 mL), and the combined organics were concentrated under reduced

pressure. The crude reaction mixture was purified by column chromatography (NH_4OH:MeOH:$CHCl_3$) to afford the title compound.

[00658] Step 2: 2-((2R)-3-((1-(4-bromophenyl)-2-hydroxyethyl)amino)-2-hydroxypropyl)isoindoline-1,3-dione. A solution of 2-amino-2-(4-bromophenyl)ethan-1-ol (214 mg, 1.0 mmol) and (S)-glycidyl phthalimide (203 mg, 1.0 mmol) in EtOH (20 mL) was heated to 80 °C for 24h. The reaction mixture was concentrated under reduced pressure and the crude solid was purified by column chromatography (Hexanes:EtOAc) to afford the title compound.

[00659] Step 3: 2-(((2R)-5-(4-bromophenyl)morpholin-2-yl)methyl)isoindoline-1,3-dione. To a stirred solution of 2-((2R)-3-((1-(4-bromophenyl)-2-hydroxyethyl)amino)-2-hydroxypropyl)isoindoline-1,3-dione (100 mg, 0.23 mmol) and triphenylphosphine (60 mg, 0.23 mmol) in THF (10 mL) at 0 °C, was added DIAD (0.048 mL, 0.23 mmol) dropwise over 5 min. The reaction mixture was warmed to rt and stirred for 4h. The reaction was concentrated under reduced pressure and purified by column chromatography (Hexanes:EtOAc) to afford the title compound.

[00660] Step 4: ((2S)-5-(4-bromophenyl)morpholin-2-yl)methanamine. To a solution of 2-(((2R)-5-(4-bromophenyl)morpholin-2-yl)methyl)isoindoline-1,3-dione (100 mg, 0.25 mmol) in EtOH (5mL) was added hydrazine monohydrate (0.025 mL, 0.50 mmol). The reaction mixture was heated to 70°C for 4h, concentrated and diluted with $CHCl_3$ (5 mL). The solid filtered and the filtrate concentrated under reduced pressure. The crude residue was dissolved in $CHCl_3$ (25 mL) and washed with H_2O (10 mL) and sat. aq. NaCl (15 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford the title compound.

[00661] Step 5: *tert*-butyl (((2R)-5-(4-bromophenyl)morpholin-2-yl)methyl)carbamate. To a suspension of ((2S)-5-(4-bromophenyl)morpholin-2-yl)methanamine (312 mg, 1.16 mmol) in CH_2Cl_2 (10 mL) was added Et_3N (0.65 mL, 4.6 mmol) and di-*tert*-butyl-dicarbonate (503 mg, 2.30 mmol) and was stirred at rt for 16h. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with H_2O (50 mL) and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (Hexanes:EtOAc) to afford the title compound.

[00662] Step 6: *tert*-butyl (((2S)-5-(4-bromophenyl)-4-(2,2,2-trifluoroacetyl)morpholin-2-yl)methyl)carbamate. To a solution of *tert*-butyl (((2R)-5-(4-bromophenyl)morpholin-2-yl)methyl)carbamate (180 mg, 0.49 mmol) in CH_2Cl_2 (10 mL) at 0 °C, was added Et_3N (0.10 mL, 0.73 mmol) and TFAA (0.082 mL, 0.085 mmol). The reaction was warmed to rt and

stirred for 16h. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with H_2O (1x50 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford the title compound.

[00663] Step 7: *tert*-butyl (((2S)-5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-4-(2,2,2-trifluoroacetyl)morpholin-2-yl)methyl)carbamate. A suspension of *tert*-butyl (((2S)-5-(4-bromophenyl)-4-(2,2,2-trifluoroacetyl)morpholin-2-yl)methyl)carbamate (210 mg, 0.49 mmol), bis-pinacolato diboron (150 mg, 0.58 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (10 mg, 0.014 mmol), and KOAc (143 mg, 1.46 mmol) in dioxane was degassed and heated to 100 °C for 16h. The crude reaction mixture was filtered through Celite® and the filtrate was concentrated under reduced pressure. Purification by column chromatography (Hexanes:EtOAc) afforded the title compound.

[00664] Step 8: *tert*-butyl (((2S)-5-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)phenyl)-4-(2,2,2-trifluoroacetyl)morpholin-2-yl)methyl)carbamate. A suspension of cytosine (37 mg, 0.33 mmol) and *tert*-butyl (((2S)-5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-4-(2,2,2-trifluoroacetyl)morpholin-2-yl)methyl)carbamate (110 mg, 0.33 mmol), in MeOH:H_2O (4:1, 100 mL) was stirred at rt in open air for 30 min. TMEDA (0.090 mL, 0.40 mmol) and $Cu(OAc)_2 \cdot H_2O$ (66 mg, 0.33 mmol) were added and the reaction was stirred in open air for 48h at rt. The reaction mixture was concentrated under reduced pressure and H_2O (10 mL) was added. The aqueous phase was extracted with $CHCl_3$ (3x15 mL), and the combined organics were concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography ($CHCl_3$:MeOH) to afford the title compound.

[00665] Step 9: *tert*-butyl (((2S)-5-(4-(4-(1H-imidazole-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)phenyl)-4-(2,2,2-trifluoroacetyl)morpholin-2-yl)methyl)carbamate. A suspension of *tert*-butyl (((2S)-5-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)phenyl)-4-(2,2,2-trifluoroacetyl)morpholin-2-yl)methyl)carbamate (45 mg , 0.09 mmol) and 1,1'-carbonyldiimidazole (24mg, 0.14 mmol) in CH_2Cl_2 (12 mL) was stirred for 16h at rt. The reaction mixture was concentrated under reduced pressure, and the residue was triturated with EtOAc. The solid was collected to afford the title compound.

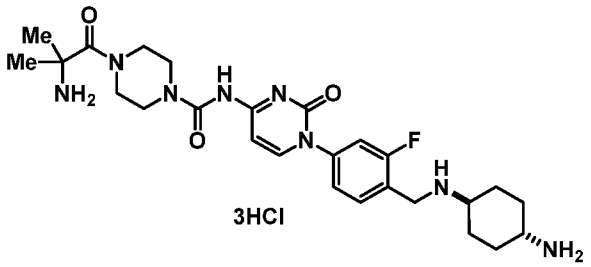
[00666] Step 10: *tert*-butyl (1-(4-((1-(4-((6S)-6-(((*tert*-butoxycarbonyl)amino)methyl)-4-(2,2,2-trifluoroacetyl)morpholin-3-yl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate. *tert*-butyl (((2S)-5-(4-(4-(1H-imidazole-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)phenyl)-4-(2,2,2-trifluoroacetyl)morpholin-2-yl)methyl)carbamate (53 mg, 0.09 mmol) and *tert*-butyl (2-methyl-1-oxo-1-(piperazin-1-yl)propan-2-yl)carbamate (24 mg, 0.09 mmol) were dissolved

in MeCN (5 mL) and heated to reflux for 2h. The reaction mixture was concentrated under reduced pressure and the crude reaction mixture was dissolved in EtOAc (25 mL) and washed with H_2O (3x20 mL). The reaction mixture was purified by column chromatography (Hexanes:EtOAc) to afford the title compound.

[00667] Step 11: *tert*-butyl (1-(4-((1-(4-((6R)-6-(((*tert*-butoxycarbonyl)amino)methyl)morpholin-3-yl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate. To a solution of *tert*-butyl (1-(4-((1-(4-((6S)-6-(((*tert*-butoxycarbonyl)amino)methyl)-4-(2,2,2-trifluoroacetyl)morpholin-3-yl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate (75 mg, 0.09 mmol) in 1:1 THF:H_2O (2 mL) was added LiOH (10 mg, 0.45 mmol). The reaction was stirred at rt for 16h, diluted with H_2O (5 mL) and acidified by the addition of 2N HCl. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (3x10 mL). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure to give the title compound.

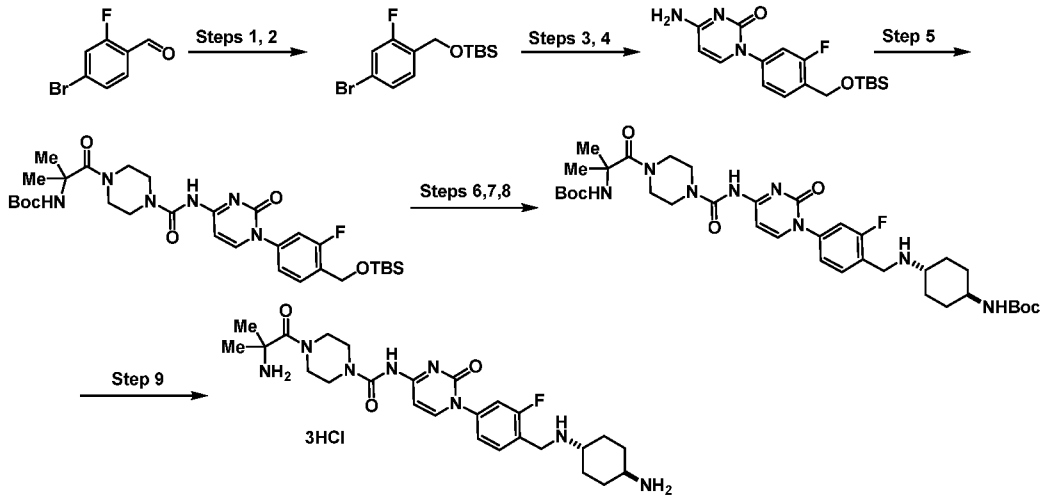
[00668] Step 12: 4-(2-amino-2-methylpropanoyl)-N-(1-(4-((6S)-6-(aminomethyl)morpholin-3-yl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide. *tert*-Butyl (1-(4-((1-(4-((6R)-6-(((*tert*-butoxycarbonyl)amino)methyl)morpholin-3-yl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate was dissolved in a solution of HCl/MeOH (5 mL) and stirred for 4h. The reaction mixture was concentrated under reduced pressure and the crude solid was purified by RPHPLC (H_2O:CH_3CN:TFA). Addition of 2N HCl in MeOH (5 mL) and evaporation under reduced pressure afforded the title compound. ^{1}H NMR (400 MHz, D_2O) δ 8.14 (d, 1H), 7.64 (d, 2H), 7.53 (d, 2H), 6.81 (d, 1H), 5.21 (d, 1H), 4.32 (s, 1H), 3.79 (s, 3H), 3.75 (s, 5H), 3.48 (s, 1H), 3.45–3.33 (m, 2H), 3.25 (d, 2H), 3.10–2.99 (m, 1H), 1.73 (s, 6H).

Compound 330



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((*trans*-4-aminocyclohexyl)amino)methyl)-3-fluorophenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

Scheme C-14



Reagents: 1) $NaBH_4$, MeOH, 2h 2) TBSCl, imidazole, DMF, 16h 3) BuLi, THF, -78 °C $(iPrO)_3B$, NaHCO3, 3h 4) cytosine, TMEDA, $Cu(OAc)_2 \cdot H_2O$, 4:1 MeOH:H_2O, 16-48h 5) 1-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carbonyl)-3-methyl-1H-imidazol-3-ium iodide, CH_3CN, 80 °C, 16h 6) TsOH, MeOH, 45 min 7) Dess-Martin periodinane, CH_2Cl_2, 1h 8) *tert*-butyl (*trans*-4-aminocyclohexyl)carbamate, $NaBH_4$, MeOH, 16h 9) HCl, MeOH, rt, 4h.

[00669] Step 1: (4-bromo-2-fluorophenyl)methanol. A solution of 4-bromo-2-fluorobenzaldehyde (10.2 g, 50 mmol) in MeOH (500 mL) was cooled to 0°C and $NaBH_4$ (5.70 g, 151 mmol) added over 10 min. The solution was stirred for 16h. The excess MeOH was removed and the crude mixture was partitioned between EtOAc (500 mL) and 1N NaOH (500 mL). The 1N NaOH was washed with an additional portion of EtOAc (300 mL). The combined organics were dried over Na_2SO_4 and concentrated to afford the title compound as a viscous oil to white solid which was in the next step without further purification.

[00670] Step 2: ((4-bromo-2-fluorobenzyl)oxy)(*tert*-butyl)dimethylsilane. To a crude solution of 4-bromo-2-fluorophenyl)methanol (10.1 g, 49.3 mmol) in DMF (250 mL) was added TBSCl (11.1 g, 73.9 mmol) followed by Imidizole (6.71 g, 98.5 mmol). The solution was stirred for 16h. The crude solution was partitioned between EtOAc (500 mL) and LiCl (500 mL). The LiCl was discarded and the organic layer was washed with additional LiCl (2x250 mL). The combined organics were dried over Na2SO4 and concentrated to afford a crude oil which was purified via colomn chromatagrohy (Hexanes:EtOAc) to afford the title compound as a clear oil.

[00671] Step 3: *tert*-butyl((2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)oxy)dimethylsilane. A stirred solution of ((4-bromo-2-fluorobenzyl)oxy)(*tert*-butyl)dimethylsilane (15.0 g, 47.0 mmol) in THF (350 mL) was cooled to -78 °C. 1 M BuLi inHexanes (47.0 mL, 117 mmol) was added dropwise over 30 min. and the temperature maintained below -60 °C. After 25 min triisopropyl borate (16.0 mL, 70.5 mmol) was added dropwise over 30 min. The reaction mixture was warmed to rt and stirred for 15 min. 150 mL of NaHCO3 aq. (freshly made) was added and the reaction was stirred for 30 min. The biphasic mixture was separated and the aq. layer washed with CH_2Cl_2 (2×250 mL). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure to afford the title compound.

[00672] Step 4: 4-amino-1-(4-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-fluorophenyl)pyrimidin-2(1H)-one. A suspension of cytosine (17.25 g, 47.0 mmol) and *tert*-butyl((2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)oxy)dimethylsilane (17.3 g, 47.1 mmol), in MeOH:H_2O (4:1, 500 ml) was stirred at rt in open air for 30 min. TMEDA (6.0 g, 51.8 mmol) and $Cu(OAc)_2H_2O$ (9.4 g, 47.1 mmol) were added and the reaction was stirred in open air for 48h at rt. The reaction mixture was concentrated under reduced pressure, and cold H_2O (100 mL) was added. The solid was filtered and washed with H_2O (5x50 mL), Et_2O (3x30 mL), and H_2O (2x30 mL) to afford the title compound.

[00673] Step 5: *tert*-butyl (1-(4-((1-(4-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-fluorophenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate. To a stirred solution 4-amino-1-(4-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-fluorophenyl)pyrimidin-2(1H)-one (1.93 g, 5.5 mmol) and 1-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carbonyl)-3-methyl-1H-imidazol-3-ium iodide (3.92 g, 7.7 mmol) in CH_3CN (75 mL) was heated at 80 °C for 16h. The reaction mixture was concentrated under reduced pressure and the crude material was purified by column chromatography (EtOAc:MeOH) to afford the title compound. LCMS [M+H] 647.4.

[00674] Step 6: *tert*-butyl (1-(4-((1-(3-fluoro-4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate. A solution of *tert*-butyl (1-(4-((1-(4-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-fluorophenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate (550 mg, 0.85 mmol) and TsOH (323 mg, 1.70 mmol) in MeOH (20 mL) were stirred for 1h. The excess MeOH was removed in vacuo. The crude mixture

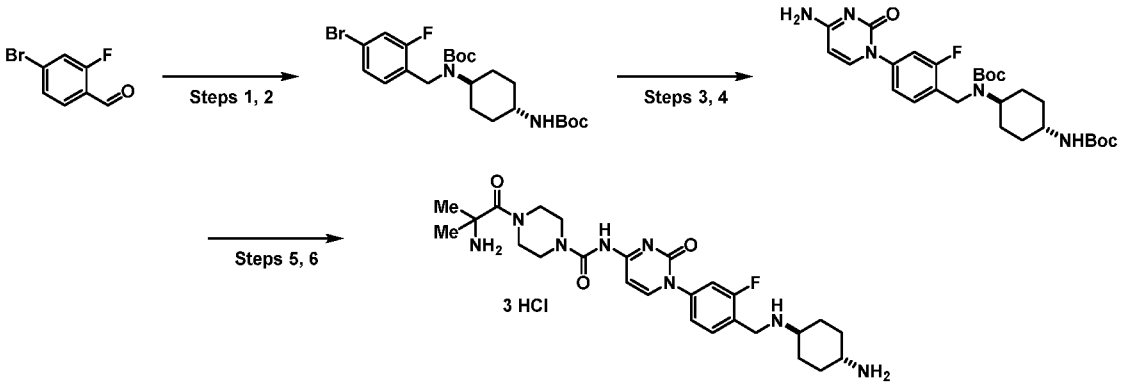
was partitioned between CH_2Cl_2 (75 mL) and $NaHCO_3$ (150 mL). The CH_2Cl_2 (75 mL) solution was taken and to this was added DMP (652 mg, 1.54 mmol) and stirred for 1h. The solution was partitioned between CH_2Cl_2 and $NaHCO_3$ and $Na_2S_2O_3$ (100 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford the title compound. LCMS [M+H] 531.2.

[00675] Step 7: *tert*-butyl (1-(4-((1-(4-(((*trans*-4-((*tert*-butoxycarbonyl)amino)cyclohexyl)amino)methyl)-3-fluorophenyl)-2-oxo-1,2,5,6-tetrahydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate. To a solution of *tert*-butyl (1-(4-((1-(3-fluoro-4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate (80 mg, 0.15 mmol) in MeOH (15 mL) was added *tert*-butyl (*trans*-4-aminocyclohexyl)carbamate (32 mg, 0.15 mmol). The solution was stirred for 16h and to this was added $NaBH_4$ (17 mg, 0.45 mmol) and the solution was stirred an additional 1h. The excess MeOH was removed and the crude mixture was partitioned between EtOAc (100 mL) and 1 N NaOH (100 mL) and the aqueous layer washed with additional EtOAc (2x100 mL). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified via column chromatography (EtOAc:MeOH) to afford the title compound. LCMS [M+H] 729.8

[00676] Step 8: 4-(2-amino-2-methylpropanoyl)-N-(1-(4-(((*trans*-4-aminocyclohexyl)amino)methyl)-3-fluorophenyl)-2-oxo-1,2,5,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt. To solid *tert*-butyl (1-(4-((1-(4-(((*trans*-4-((*tert*-butoxycarbonyl)amino)cyclohexyl)amino)methyl)-3-fluorophenyl)-2-oxo-1,2,5,6-tetrahydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate (0.15 mmol) was added HCl in MeOH (50 mL). The solution was stirred for 4h and the excess MeOH was removed in vacuo. The crude solid was purified by recrystallization from water and isopropanol by dissolution into water, heating to 80°C with stirring and adding antisolvent until cloudy and allowing to cool to rt or via RPHPLC and conversion to the hydrochloride salt with the addition of 2N HCl in MeOH (5 mL) and evaporation under reduced pressure. ^{1}H NMR (500 MHz, D_2O) δ 8.04 (d, 1H), 7.69 (t, 1H), 7.46-7.37 (m, 2H), 6.83 (d, 1H), 4.42 (s, 2H), 3.85-3.67 (m, 8H), 3.38-3.22 (m, 2H), 2.39-2.19 (m, 4H), 1.72 (s, 6H), 1.68-1.49 (m, 4H). LCMS [M+H] 529.3.

[00677] Alternatively, compound 330 may be prepared according to Scheme C-14a.

Scheme C-14a



Reagents: 1) *tert*-butyl (*trans*-4-aminocyclohexyl)carbamate, $NaBH_4$, MeOH, 0 °C to rt, 16h 2) Boc_2O, K_2CO_3, THF:H_2O, rt, 16h 3) $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, B_2pin_2, KOAc, dioxane, reflux, 16h 4) cytosine, $Cu(OAc)_2 \cdot H_2O$, TMEDA, MeOH:H_2O, rt, 4d 5) 1-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carbonyl)-3-methyl-1H-imidazol-3-ium iodide, CH_3CN, reflux, 2d 6) 2 M HCl/MeOH, rt, 18h.

[00678] Step 1: *tert*-butyl (*trans*-4-((4-bromo-2-fluorobenzyl)amino)cyclohexyl)carbamate. To a solution of 4-bromo-2-fluorobenzaldehyde (5.0 g, 25 mmol) in MeOH (30 mL) at 0 °C, was added *tert*-butyl (*trans*-4-aminocyclohexyl)carbamate (7.9 g, 37 mmol) followed by $NaBH_4$ (0.47 g, 12 mmol). The reaction was warmed to rt and stirred for 16h. The reaction mixture was concentrated under reduced pressure, diluted with CH_2Cl_2 (500 mL), and washed with 10% NaOH (1 x 500 mL) which was back extracted with CH_2Cl_2 (500 mL). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude title compound. LCMS [M+H] 401.2.

[00679] Step 2: *tert*-butyl (4-bromo-2-fluorobenzyl)(*trans*-4-((*tert*-butoxycarbonyl)amino)cyclohexyl)carbamate. To a solution of *tert*-butyl (*trans*-4-((4-bromo-2-fluorobenzyl)amino)cyclohexyl)carbamate (9.0 g, 22 mmol) in THF:H_2O (1:1, 30 mL) was added Boc_2O (7.3 g, 34 mmol) and K_2CO_3 (15 g, 110 mmol). The reaction was stirred at rt for 16h. The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organics were washed with sat. aq. NaCl (1 x 100 mL) and dried over Na_2SO_4. The crude was purified by flash chromatography (Hex:EtOAc) to afford the title compound (9.8 g, 20 mmol). ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 – 7.16 (m, 2H), 7.11 (br s, 1H), 4.32 (s, 3H), 4.06 (br. s, 1H), 3.31 (br. s, 1H), 2.00 (d, 2H), 1.70 (br. s, 2H), 1.42 (s, 9H), 1.36 (br. s, 11H), 1.19 (s, 2H).

[00680] Step 3: *tert*-butyl (*trans*-4-((*tert*-butoxycarbonyl)amino)cyclohexyl)(2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)carbamate. A flask containing *tert*-butyl (4-bromo-2-fluorobenzyl)(*trans*-4-((*tert*-butoxycarbonyl)amino)cyclohexyl)carbamate (9.8 g, 20 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (0.48 g, 0.59 mmol), potassium acetate (5.8 g, 59 mmol), and B_2pin_2 (5.5 g, 21 mmol) was evacuated and back-filled with N_2. Dioxane (6 mL) was added, the mixture was de-gassed with N_2, then heated to 105 °C for 16h. The reaction mixture was diluted with EtOAc (30 mL) and filtered through a pad of Celite ®. The filtrate was concentrated in vacuo and purified by flash chromatography (Hex:EtOAc) to afford the title compound (9.9 g 18 mmol), which was immediately carried-on to the next step. ^1H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, 1H), 7.41 (d, 1H), 7.22 (br. s, 1H), 4.35 (br s, 2H), 4.07 (br. s, 1H), 3.29 (br. s, 1H), 1.98 (d, 2H), 1.73 (br. s, 2H), 1.55 – 1.02 (m, 34H).

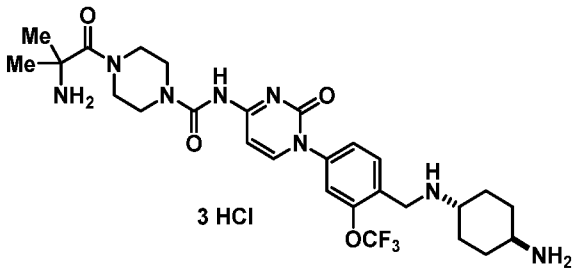
[00681] Step 4: *tert*-butyl (4-(4-amino-2-oxopyrimidin-1(2H)-yl)-2-fluorobenzyl)(*trans*-4-((*tert*-butoxycarbonyl)amino)cyclohexyl)carbamate. A mixture of *tert*-butyl (*trans*-4-((*tert*-butoxycarbonyl)amino)cyclohexyl)(2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)carbamate (9.9 g 18 mmol) and cytosine (2.0 g, 18 mmol) in MeOH (450 mL) and H_2O (150 mL) was stirred at rt for 30 min. $Cu(OAc)_2 \cdot H_2O$ (3.6 g, 18 mmol) and TMEDA (3.3 mL, 22 mmol) were added to the reaction and it was stirred open to the air at rt for 4 days. The reaction mixture was concentrated under reduced pressure to remove the MeOH, H_2O was added (ca. 650 mL), and the suspension was stirred vigorously for several hours and scraped with a spatula until the gummy residue had turned into a solid. The precipitate was collected by vacuum filtration to give the title compound in about 60% purity (6.56 g, 69 %) as an off-white solid. LCMS [M+H] 532.3.

[00682] Step 5: *tert*-butyl (4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)-2-fluorobenzyl)((*trans*)-4-((*tert*-butoxycarbonyl)amino)cyclohexyl)carbamate. A mixture of *tert*-butyl (4-(4-amino-2-oxopyrimidin-1(2H)-yl)-2-fluorobenzyl)((*trans*)-4-((*tert*-butoxycarbonyl)amino)cyclohexyl)carbamate (6.56 g, 12.3 mmol) and 1-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carbonyl)-3-methyl-1H-imidazol-3-ium iodide (8.20 g, 16.2 mmol) in CH_3CN (125 mL) was stirred at reflux for 2 days. The mixture was cooled, diluted with EtOAc (500 mL), washed with sat. aq. $NaHCO_3$ (2 x 350 mL) and brine (350 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (MeOH/EtOAc/Hexanes) to give the title compound (4.38 g, 42.8 %) as a light yellow solid. ^1H NMR (500 MHz, $CDCl_3$) δ 12.94 (s, 1H), 7.41–7.29 (m, 1H), 7.28–7.21 (m, 1H), 7.13–7.05 (m, 2H), 5.87–5.79 (m, 1H), 4.91–4.82 (m, 1H), 4.50–4.28 (m,

3H), 4.15–3.98 (m, 1H), 3.92–3.55 (m, 8H), 3.38–3.24 (m, 1H), 2.05–1.95 (m, 2H), 1.77–1.67 (m, 2H), 1.58–1.28 (m, 33H), 1.26–1.11 (m, 4H). LCMS [M+H] 829.6.

[00683] Step 6: 4-(2-amino-2-methylpropanoyl)-N-(1-(4-((((*trans*)-4-aminocyclohexyl)amino)methyl)-3-fluorophenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt. A mixture of *tert*-butyl (4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)-2-fluorobenzyl)((*trans*)-4-((*tert*-butoxycarbonyl)amino)cyclohexyl)carbamate (3.88 g, 4.68 mmol) and 2 M HCl in MeOH (100 mL, 200 mmol) was stirred at rt for 18h. The precipitate was collected by vacuum filtration, and the solid was washed with isopropanol then Et_2O. The solid was recrystallized from H_2O/isopropanol to give the title compound as a white solid. Analytical data was consistent with previous data.

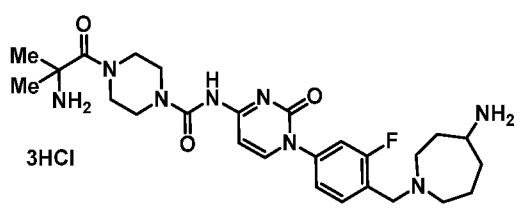
Compound 332



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((*trans*-4-aminocyclohexyl)amino)methyl)-3-(trifluoromethoxy)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00684] Prepared in a similar fashion to Scheme C-14 from *tert*-butyl (1-(4-((1-(4-formyl-3-(trifluoromethoxy)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and N-boc-*trans*-1,4-cyclohexanediamine. ^{1}H NMR (500 MHz, D_2O) δ 7.90 (d, 1H), 7.75 (d, 1H), 7.64 (s, 1H), 7.50 (d, 1H), 6.84 (d, 1H), 4.44 (s, 2H), 3.79-3.65 (m, 8H), 3.36-3.21 (m, 2H), 2.39-2.18 (m, 4H), 1.71 (s, 6H), 1.67-1.48 (m, 4H). LCMS [M+H] 595.2.

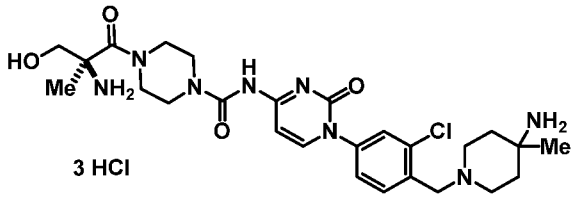
Compound 334



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((4-aminoazepan-1-yl)methyl)-3-fluorophenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00685] Prepared in a similar fashion to Scheme C-14 from *tert*-butyl (1-(4-((1-(3-fluoro-4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl azepan-4-ylcarbamate. ^{1}H NMR (500 MHz, D_2O) δ 8.18 (d, 1H), 7.76 (t, 1H), 7.49 (d, 1H), 7.44 (d, 1H), 6.80 (d, 1H), 4.54 (s, 2H), 3.82-3.69 (m, 8H), 3.64-3.44 (m, 4H), 3.41-3.19 (m, 1H), 2.42-1.96 (m, 5H), 1.84 (m, 1H), 1.71 (s, 6H). LCMS [M+H] 529.3.

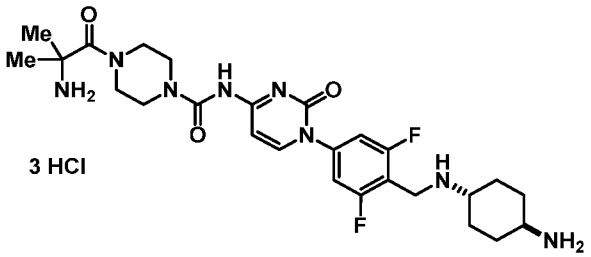
Compound 360



(S)-4-(2-Amino-3-hydroxy-2-methylpropanoyl)-N-(1-(4-((4-amino-4-methylpiperidin-1-yl)methyl)-3-chlorophenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00686] Prepared in a similar fashion to Scheme C-14 from *tert*-butyl (2R,4S)-2-(*tert*-butyl)-4-(4-((1-(3-chloro-4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazine-1-carbonyl)-4-methyloxazolidine-3-carboxylate and *tert*-butyl (4-methylpiperidin-4-yl)carbamate. LCMS [M+H] 561.2.

Compound 353

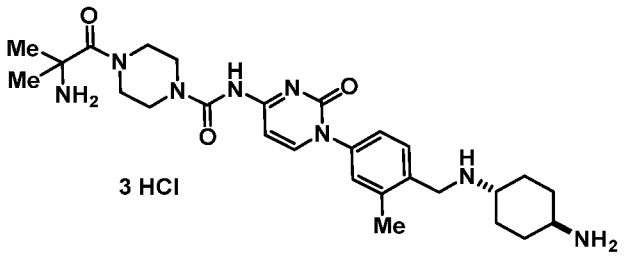


4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((*trans*-4-aminocyclohexyl)amino)methyl)-3,5-difluorophenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00687] Prepared in a similar fashion to Scheme C-14 from *tert*-butyl (1-(4-((1-(3,5-difluoro-4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and N-boc-*trans*-1,4-cyclohexanediamine. 1H NMR

7.86 (d, 1H), 7.31 (d, 2H), 6.85 (d, 1H), 4.46 (s, 2H), 3.86-3.66 (m, 8H), 3.41-3.23 (m, 2H), 2.41-2.20 (m, 4H), 1.72 (s, 6H), 1.68-1.49 (m, 4H). LCMS [M+H] 547.4.

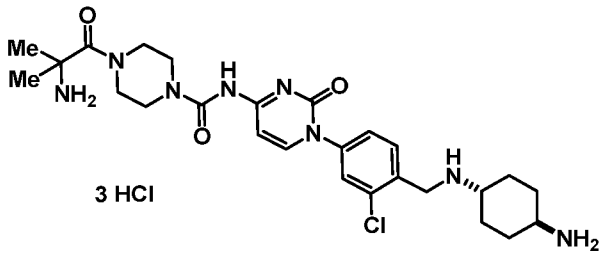
Compound 283



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((((*trans*)-4-aminocyclohexyl)amino)methyl)-3-methylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00688] Prepared in a similar fashion as scheme C-14 from *tert*-butyl (1-(4-((1-(4-formyl-3-methylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl ((*trans*)-4-aminocyclohexyl)carbamate. LCMS [M+H] 525.36.

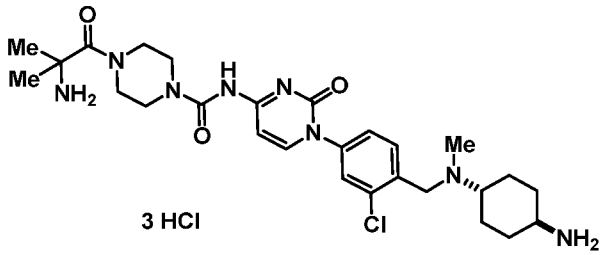
Compound 271



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((((*trans*)-4-aminocyclohexyl)amino)methyl)-3-chlorophenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00689] Prepared in a similar fashion as scheme C-14 from *tert*-butyl (1-(4-((1-(3-chloro-4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl ((*trans*)-4-aminocyclohexyl)carbamate. ^{1}H NMR (400 MHz, D2O) δ 8.00 (d, 1H), 7.75 (t, 2H), 7.57–7.52 (m, 1H), 6.86 (d, 1H), 4.53 (s, 2H), 3.79 (s, 3H), 3.74 (s, 5H), 3.48–3.38 (m, 1H), 3.36–3.24 (m, 1H), 2.41 (d, 2H), 2.25 (d, 2H), 1.74 (d, 6H), 1.71–1.52 (m, 4H). LCMS [M+H] 545.3.

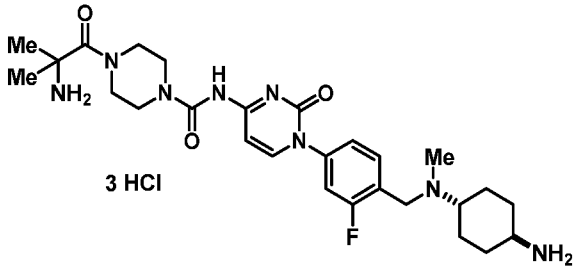
Compound 272



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((((*trans*)-4-aminocyclohexyl)(methyl)amino)methyl)-3-chlorophenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide

[00690] Prepared in a similar fashion as in Scheme C-14 from *tert*-butyl (1-(4-((1-(3-chloro-4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate. ^{1}H NMR (400 MHz, D2O) δ 8.06 (d, 1H), 7.82–7.77 (m, 2H), 7.61–7.55 (m, 1H), 6.85 (d, 1H), 4.83 (d, 1H), 4.37 (d, 1H), 3.78 (s, 3H), 3.75 (s, 5H), 3.63–3.48 (m, 2H), 3.34–3.26 (m, 1H), 2.85 (s, 3H), 2.42–2.23 (m, 4H), 2.03–1.78 (m, 2H), 1.74 (s, 6H), 1.70–1.55 (m , 2H). LCMS [M+H] 559.3.

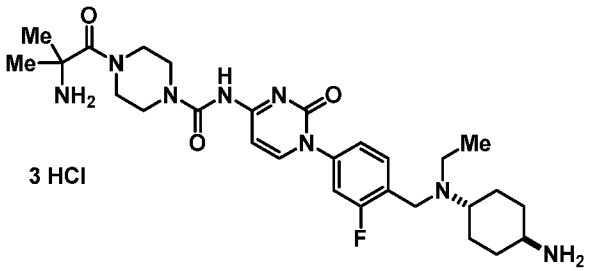
Compound 278



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((*trans*-4-aminocyclohexyl)(methyl)amino)methyl)-3-fluorophenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00691] Prepared in a similar fashion as in Scheme C-14 from *tert*-butyl (1-(4-((1-(3-fluoro-4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate. ^{1}H NMR (500 MHz, D_2O) δ 7.88 (d, 1H), 7.71 (t, 1H), 7.50–7.33 (m, 2H), 6.86 (d, 1H), 4.69 (d, 1H), 4.32 (d, 1H), 3.92–3.59 (m, 8H), 3.49 (t, 1H), 3.28 (t, 1H), 2.83 (s, 3H), 2.36-2.22 (m, 2H), 1.92-1.76 (m, 2H), 1.73 (s, 6H), 1.64-1.53 (m, 4H). LCMS [M+H] 543.3.

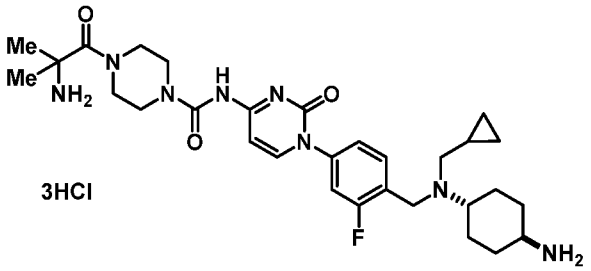
Compound 355



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((*trans*-4-aminocyclohexyl)(ethyl)amino)methyl)-3-fluorophenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00692] Prepared in a similar fashion as in Scheme C-14 from *tert*-butyl (1-(4-((1-(3-fluoro-4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.74 (d, 1H), 7.56 (dd, 1H), 7.30 (dd, 1H), 7.25 (dd, 1H), 6.70 (d, 1H), 4.49 (d, 1H), 4.21 (d, 1H), 3.61 (br s, 3H), 3.58–3.50 (m, 5H), 3.39–3.29 (m, 1H), 3.25–3.07 (m, 3H), 2.17–2.03 (m, 4H), 1.85–1.59 (m, 2H), 1.57 (s, 6H), 1.49–1.35 (m, 2H), 1.17 (t, 3H). LCMS [M+H] 557.3.

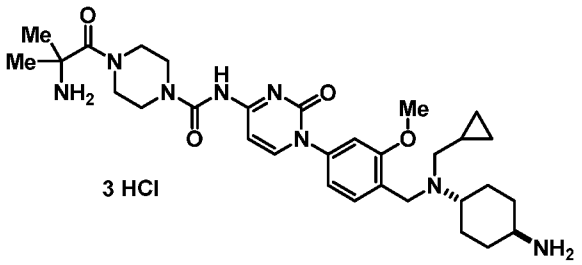
Compound 302



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((*trans*-4-aminocyclohexyl)(cyclopropylmethyl)amino)methyl)-3-fluorophenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00693] Prepared in a similar fashion as in Scheme C-14 from *tert*-butyl (1-(4-((1-(3-fluoro-4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and cyclopropanecarbaldehyde. LCMS [M+H] 583.3.

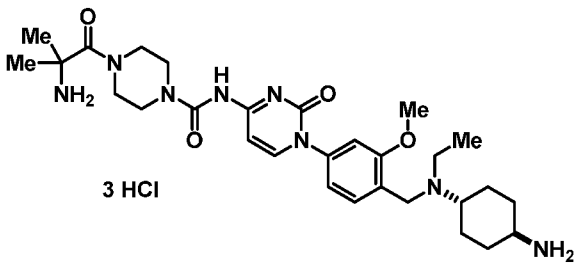
Compound 317



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((*trans*-4-aminocyclohexyl)(cyclopropylmethyl)amino)methyl)-3-methoxyphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00694] Prepared in a similar fashion as in Scheme C-14 from *tert*-butyl (1-(4-((1-(4-formyl-3-methoxyphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and cyclopropanecarbaldehyde. ^{1}H NMR (500 MHz, D_2O) δ 8.01 (d, 1H), 7.57 (d, 1H), 7.23 (s, 1H), 7.12 (d, 1H), 6.83 (d, 1H), 4.61-4.39 (m, 2H), 3.93 (s, 3H), 3.84-3.65 (m, 8H), 3.57 (t, 2H), 3.29-3.04 (m, 3H), 2.32-2.16 (m, 4H), 1.98-1.78 (m, 2H), 1.72 (s, 6H), 1.62-1.48 (m, 1H), 1.11-1.02 (m, 1H), 0.75-0.69 (m, 2H), 0.40-0.27 (m, 2H). LCMS [M+H] 595.4

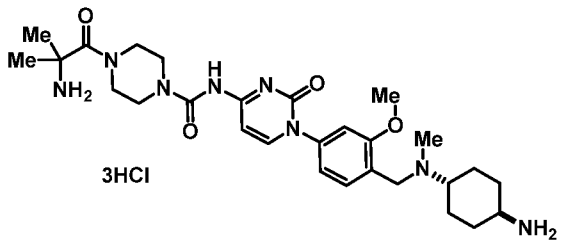
Compound 318



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((*trans*-4-aminocyclohexyl)(ethyl)amino)methyl)-3-methoxyphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00695] Prepared in a similar fashion as in Scheme C-14 from *tert*-butyl (1-(4-((1-(4-formyl-3-methoxyphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate. ^{1}H NMR (500 MHz, D_2O) δ 7.95 (d, 1H), 7.56 (d, 1H), 7.21 (s, 1H), 7.10 (d, 1H), 6.83 (d, 1H), 4.61-4.22 (m, 2H), 3.92 (s, 3H), 3.83-3.66 (m, 8H), 3.50-3.23 (m, 4H), 2.28-2.18 (m, 4H), 1.97-1.75 (m, 2H), 1.72 (s, 6H), 1.66-1.49 (m, 2H), 1.30 (t, 3H). LCMS [M+H] 569.4.

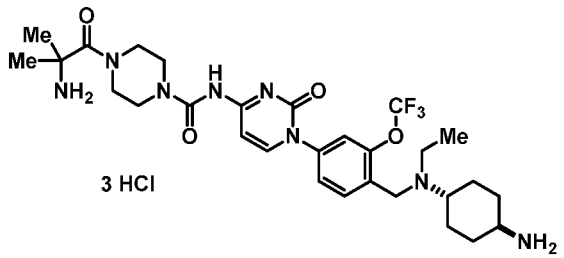
Compound 327



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((*trans*-4-aminocyclohexyl)(methyl)amino)methyl)-3-methoxyphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00696] Prepared in a similar fashion as Scheme C-14 from *tert*-butyl (1-(4-((1-(4-formyl-3-methoxyphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate. ^{1}H NMR (500 MHz, D_2O) δ 8.02 (d, 1H), 7.58 (d, 1H), 7.23 (s, 1H), 7.13 (d, 1H), 6.83 (d, 1H), 4.66 (d, 1H), 4.12 (d, 1H), 3.92 (s, 3H), 3.87-3.69 (m, 8H), 3.42 (t, 1H), 3.26 (t, 1H), 2.79 (s, 3H), 2.33-2.23 (m, 4H), 1.99-1.75 (m, 2H), 1.73 (s, 6H), 1.65-1.51 (m, 2H). LCMS [M+H] 555.4.

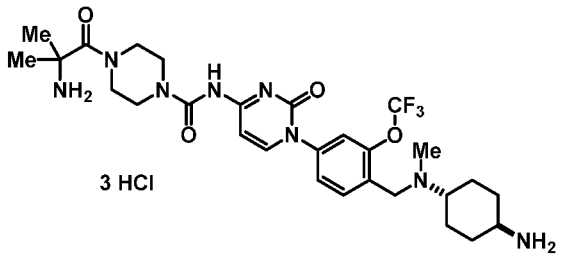
Compound 328



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((*trans*-4-aminocyclohexyl)(ethyl)amino)methyl)-3-(trifluoromethoxy)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00697] Prepared in a similar fashion as in Scheme C-14 from *tert*-butyl (1-(4-((1-(4-formyl-3-(trifluoromethoxy)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate. ^{1}H NMR (500 MHz, D_2O) δ 8.00 (d, 1H), 7.81 (d, 1H), 7.69 (s, 1H), 7.55 (d, 1H), 6.83 (d, 1H), 4.69 (d, 1H), 4.34 (d, 1H), 3.80-3.65 (m, 8H), 3.49 (t, 1H), 3.38-3.23 (m, 3H), 2.32-2.17 (m, 4H), 2.01-1.78 (m, 2H), 1.72 (s, 6H), 1.64-1.54 (m, 2H), 1.32 (t, 3H). LCMS [M+H] 623.4.

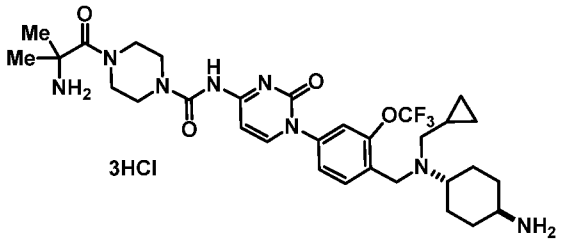
Compound 329



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((*trans*-4-aminocyclohexyl)(methyl)amino)methyl)-3-(trifluoromethoxy)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00698] Prepared in a similar fashion as in Scheme C-14 from *tert*-butyl (1-(4-((1-(4-formyl-3-(trifluoromethoxy)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate. ^{1}H NMR (500 MHz, D_2O) δ 8.05 (d, 1H), 7.82 (d, 1H), 7.69 (s, 1H), 7.56 (d, 1H), 6.83 (d, 1H), 4.78-4.71 (m, 1H), 4.27 (d, 1H), 3.82-3.68 (m, 8H), 3.48 (t, 1H), 3.28 (t, 1H), 2.82 (s, 3H), 2.36-2.20 (m, 4H), 1.97-1.76 (m, 2H), 1.72 (s, 6H), 1.64-1.51 (m, 2H). LCMS [M+H] 609.4.

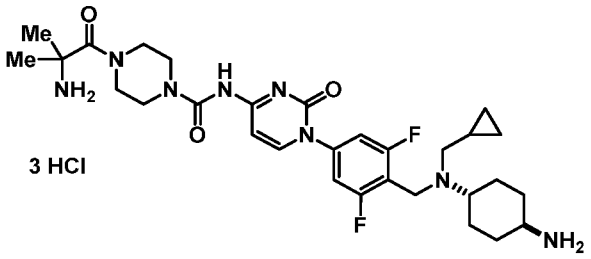
Compound 331



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((*trans*-4-aminocyclohexyl)(cyclopropylmethyl)amino)methyl)-3-(trifluoromethoxy)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00699] Prepared in a similar fashion as in Scheme C-14 from *tert*-butyl (1-(4-((1-(4-formyl-3-(trifluoromethoxy)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and cyclopropanecarbaldehyde. ^{1}H NMR (500 MHz, D_2O) δ 7.96 (d, 1H), 7.81 (d, 1H), 7.69 (s, 1H), 7.55 (d, 1H), 6.85 (d, 1H), 4.68 (d, 2H), 4.52 (d, 2H), 3.87-3.67 (m, 8H), 3.64 (t, 1H), 3.29-3.10 (m, 1H), 2.36-2.17 (m, 4H), 2.01-1.78 (m, 2H), 1.72 (s, 6H), 1.67-1.50 (m, 2H), 1.11-1.04 (m, 1H), 0.74 (d, 2H), 0.36 (d, 2H). LCMS [M+H] 649.4.

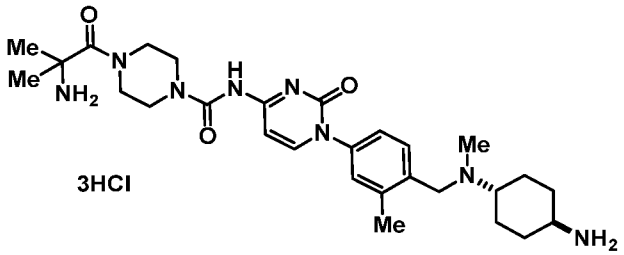
Compound 354



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(((*trans*-4-aminocyclohexyl)(cyclopropylmethyl)amino)methyl)-3,5-difluorophenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00700] Prepared in a similar fashion as in Scheme C-14 from *tert*-butyl (1-(4-((1-(3,5-difluoro-4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and cyclopropanecarbaldehyde. ^{1}H (400 MHz, D_2O) NMR δ 7.86 (d, 1H), 7.34 (d, 2H), 6.85 (d, 1H), 4.65-4.50 (m, 2H), 3.83-3.61 (m, 8H), 3.32-3.13 (m, 4H), 3.39-1.77 (m, 5H), 1.71 (s, 6H), 1.64-0.95 (m, 4) 0.80-0.35 (m, 4H). LCMS [M+H] 601.5.

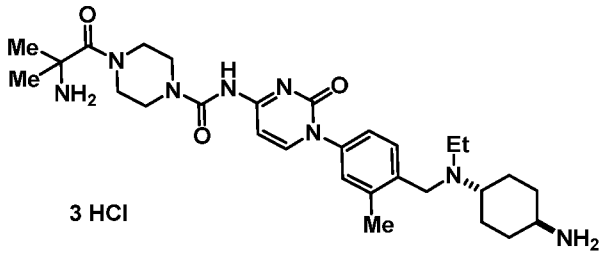
Compound 284



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((((*trans*)-4-aminocyclohexyl)(methyl)amino)methyl)-3-methylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00701] Prepared in a similar fashion as Scheme C-14 from *tert*-butyl (1-(4-((1-(4-formyl-3-methylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and formalin. ^{1}H NMR (400 MHz, D_2O) δ 8.08 (d, 1H), 7.63 (d, 1H), 7.47 (s, 1H), 7.45–7.40 (m, 1H), 6.84 (d, 1H), 4.68 (d, 1H), 4.28 (d, 1H), 3.79 (s, 3H), 3.76 (s, 5H), 3.59–3.50 (m, 1H), 3.35–3.26 (m, 1H), 2.81 (s, 3H), 2.49 (s, 3H), 2.39–2.24 (m, 4H), 2.02–1.79 (m, 2H), 1.74 (s, 6H), 1.70–1.56 (m, 2H). LCMS [M+H] 539.3.

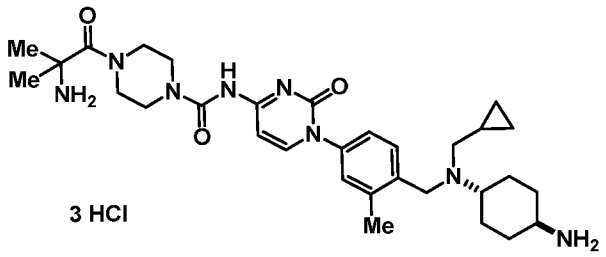
Compound 285



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((((*trans*)-4-aminocyclohexyl)(ethyl)amino)methyl)-3-methylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00702] Prepared in a similar fashion as in Scheme C-14 from *tert*-butyl (1-(4-((1-(4-formyl-3-methylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and acetaldehyde. ^{1}H NMR (400 MHz, D_2O) δ 8.01 (d, 1H), 7.62 (d, 1H), 7.46 (s, 1H), 7.44–7.39 (m, 1H), 6.85 (d, 1H), 4.62 (d, 1H), 4.33 (d, 1H), 3.79 (s, 3H), 3.75 (s, 5H), 3.60–3.50 (m, 1H), 3.43–3.26 (m, 3H), 2.48 (s, 3H), 2.36–2.23 (m, 4H), 2.12–1.96 (m, 1H), 1.96–1.80 (m, 1H), 1.75 (s, 6H), 1.71–1.56 (m, 2H), 1.33 (t, 3H). LCMS [M+H] 553.4.

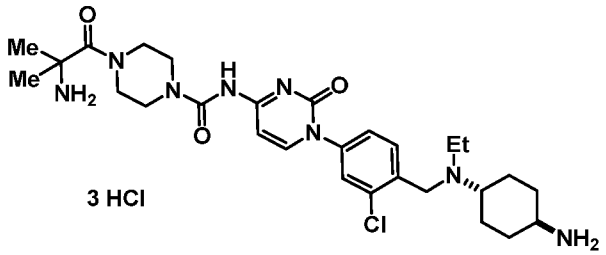
Compound 270



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((((*trans*)-4-aminocyclohexyl)(cyclopropylmethyl)amino)methyl)-3-methylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00703] Prepared in a similar fashion as in Scheme C-14 from *tert*-butyl (1-(4-((1-(4-formyl-3-methylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and cyclopropanecarbaldehyde. ^{1}H NMR (400 MHz, D_2O) δ 8.01 (d, 1H), 7.63 (d, 1H), 7.46 (s, 1H), 7.42 (d, 1H), 6.85 (d, 1H), 4.60 (d, 1H), 4.46 (d, 1H), 3.79 (s, 3H), 3.74 (d, 6H), 3.34–3.22 (m, 2H), 3.18–3.05 (m, 1H), 2.50 (s, 3H), 2.41–2.20 (m, 4H), 2.10–1.94 (m, 1H), 1.94–1.81 (m, 1H), 1.74 (d, 6H), 1.72–1.51 (m, 2H), 1.17–1.02 (m, 1H), 0.82–0.70 (m, 2H), 0.42–0.27 (m, 2H). LCMS [M+H] 579.6.

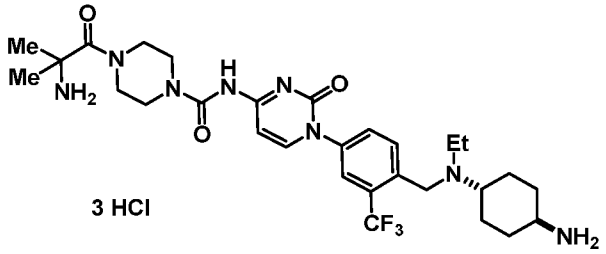
Compound 273



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((((*trans*)-4-aminocyclohexyl)(ethyl)amino)methyl)-3-chlorophenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00704] Prepared in a similar fashion as in Scheme C-14 from *tert*-butyl (1-(4-((1-(3-chloro-4-formylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and acetaldehyde. ^{1}H NMR (400 MHz, D_2O) δ 8.02 (d, 1H), 7.83–7.77 (m, 2H), 7.57 (dd, 1H), 6.86 (d, 1H), 4.76 (d, 1H), 4.46 (d, 1H), 3.79 (br. s, 3H), 3.74 (br. s, 5H), 3.62–3.50 (m, 1H), 3.43–3.25 (m, 3H), 2.39–2.25 (m, 4H), 2.10–1.95 (m, 1H), 1.95–1.81 (m, 1H), 1.75 (s, 6H), 1.69–1.56 (m, 2H), 1.35 (t, 3H). LCMS [M+H] 573.6.

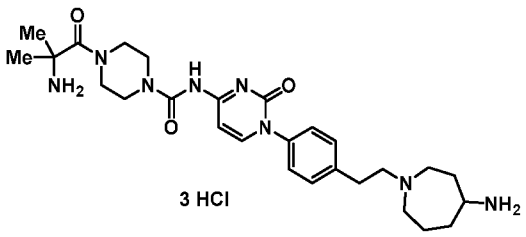
Compound 276



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((((*trans*)-4-aminocyclohexyl)(ethyl)amino)methyl)-3-(trifluoromethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

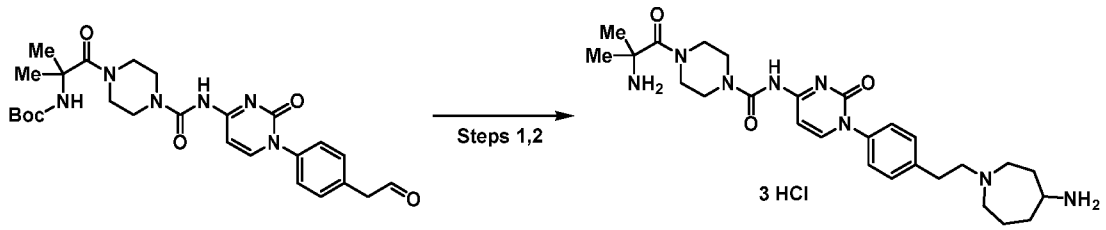
[00705] Prepared in a similar fashion as in Scheme C-14 from *tert*-butyl (1-(4-((1-(4-formyl-3-(trifluoromethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and acetaldehyde. ^{1}H NMR (400 MHz, D_2O) δ 8.05 (s, 1H), 7.96 (d, 1H), 7.94–7.82 (m, 2H), 6.89 (d, 1H), 4.83 (d, 1H), 4.51 (d, 1H), 3.79 (s, 3H), 3.74 (s, 5H), 3.64–3.55 (m, 1H), 3.44–3.22 (m, 3H), 2.30 (d, 4H), 2.05–1.82 (m, 2H), 1.75 (s, 6H), 1.72–1.54 (m, 2H), 1.33 (t, 3H). LCMS [M+H] 607.4.

Compound 21



4-(2-Amino-2-methylpropanoyl)-*N*-(1-(4-(2-(4-aminoazepan-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

Scheme C-15



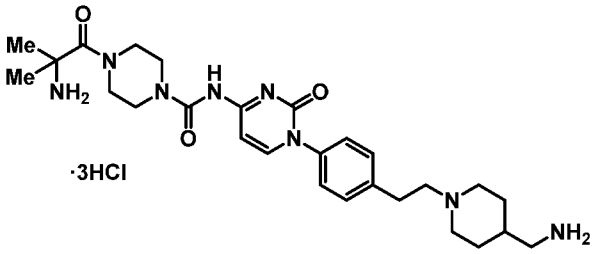
Reagents: 1) *tert*-butyl azepan-4-ylcarbamate, $NaCNBH_3$, MeOH, 16h 2) HCl, MeOH, rt, 4h.

[00706] Step 1: *tert*-butyl (1-(4-((1-(4-(2-(4-((*tert*-butoxycarbonyl)amino)azepan-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate. To a solution of *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate (50.0 mg, 0.10 mmol) in MeOH (10 mL) was added tert-butyl azepan-4-ylcarbamate (30.0 mg, 0.14 mmol) followed by $NaCNBH_3$ (25.0 mg, 0.4 mmol). The reaction was stirred at rt for 16h. The excess MeOH was removed and the crude solution was partitioned between EtOAc (50 mL) and 1N NaOH (50 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford the title compound.

[00707] Step 2: 4-(2-amino-2-methylpropanoyl)-*N*-(1-(4-(2-(4-aminoazepan-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt. Tert-butyl (1-(4-((1-(4-(2-(4-((tert-butoxycarbonyl)amino)azepan-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate was dissolved in a solution of HCl/MeOH (50 mL) and stirred for 4h. The solvent was evaporated and the crude solid was purified by RPHPLC (H_2O:CH_3CN:TFA) and concentrated under reduced pressure. Product fractions were converted to the HCl salt with the addition of HCl in MeOH and removal under reduced pressure to afford the title compound. ^1H NMR (500 MHz, D_2O) δ 8.05 (d, 1H), 7.55 (d, 2H),

7.49 (d, 2H), 6.86 (d, 1H), 3.85-3.74 (m, 8H), 3.65-3.54 (m, 5H), 3.23 (t, 2H), 3.03-3.00 (m, 1H), 2.44-2.31 (m, 2H), 2.19-2.02 (m, 3H), 1.77 (s, 6H), 1.37 (t, 2H). LCMS [M+H] 525.3.

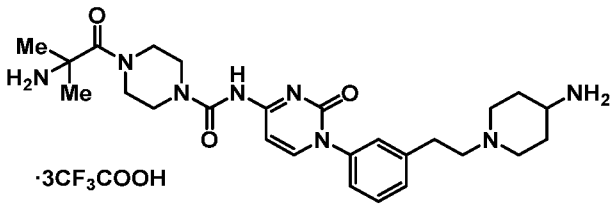
Compound 1



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(4-(aminomethyl)piperidin-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00708] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl (piperidin-4-ylmethyl)carbamate. LCMS [M+H] 525.3.

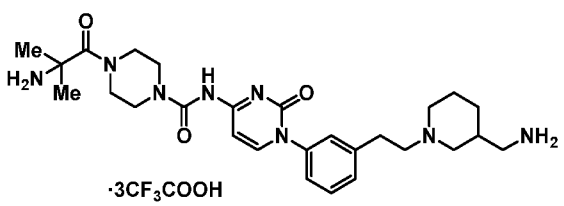
Compound 2



4-(2-Amino-2-methylpropanoyl)-*N*-(1-(3-(2-(4-aminopiperidin-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide tri-trifluroacetetate

[00709] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(3-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl piperidin-4-ylcarbamate. ^{1}H NMR (500 MHz, D_2O) δ 7.89 (d, 1H), 7.59 (t, 1H), 7.51-7.48 (m, 1H), 7.42 (s, 1H), 7.39 (d, 1H), 6.89 (d, 1H), 3.84-3.70 (m, 8H), 3.52-3.47 (m, 2H), 3.23-3.16 (m, 3H), 2.41-2.34 (m, 4H), 2.01-1.91 (m, 4H), 1.75 (s, 6H) LCMS [M+H] 511.3.

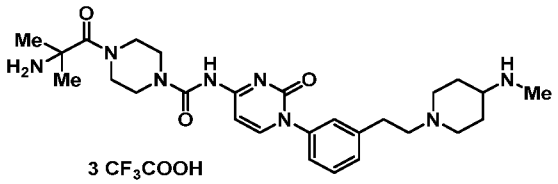
Compound 3



4-(2-Amino-2-methylpropanoyl)-*N*-(1-(3-(2-(3-(aminomethyl)piperidin-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide triflouroacetate salt

[00710] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(3-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl (piperidin-3-ylmethyl)carbamate. ^{1}H NMR (500 MHz, D_2O) δ 8.02 (d, 1H), 7.59 (t, 1H), 7.50 (d, 1H), 7.43 (s, 1H), 7.39 (d, 1H), 6.84 (d, 1H), 3.85-3.67 (m, 8H), 3.48 (t, 2H), 3.21 (t, 2H), 3.09-2.95 (m, 3H), 2.86 (t, 2H), 2.32-2.22. (m, 1H), 2.13-2.02 (m, 2H), 1.75 (s, 6H), 1.43-1.33 (m, 3H). LCMS [M+H] 525.4.

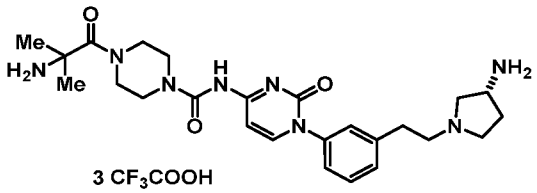
Compound 4



4-(2-Amino-2-methylpropanoyl)-*N*-(1-(3-(2-(4-(methylamino)piperidin-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide triflouroacetate salt.

[00711] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(3-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl methyl(piperidin-4-yl)carbamate. ^{1}H NMR (500 MHz, D_2O) δ 8.05 (d, 1H), 7.60 (t, 1H), 7.51 (d, 1H), 7.43 (s, 1H), 7.40 (d, 1H), 6.84 (d, 1H), 3.88-3.71 (m, 10H), 3.52-3.47 (m, 2H), 3.23-3.16 (m, 4H), 2.77 (s, 3H), 2.46 (d, 2H), 2.00-1.91 (m, 2H), 1.75 (s, 6H). LCMS [M+H] 525.4.

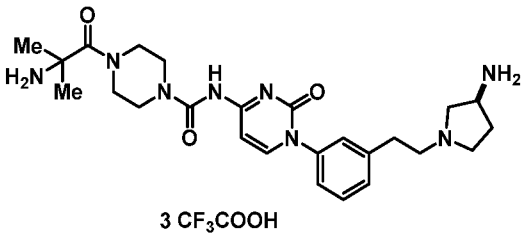
Compound 5



(*R*)-4-(2-Amino-2-methylpropanoyl)-*N*-(1-(3-(2-(3-aminopyrrolidin-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide triflouroacetate salt.

[00712] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(3-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl (R)-pyrrolidin-3-ylcarbamate. LCMS [M+H] 497.4.

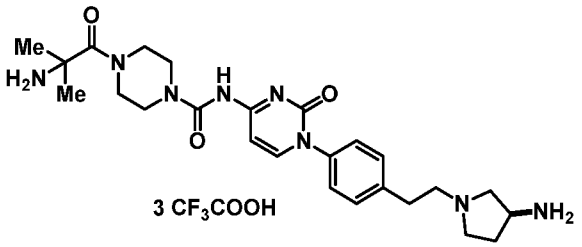
Compound 6



(*S*)-4-(2-Amino-2-methylpropanoyl)-*N*-(1-(3-(2-(3-aminopyrrolidin-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide triflouroacetate salt.

[00713] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(3-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl (S)-pyrrolidin-3-ylcarbamate. LCMS [M+H] 497.3.

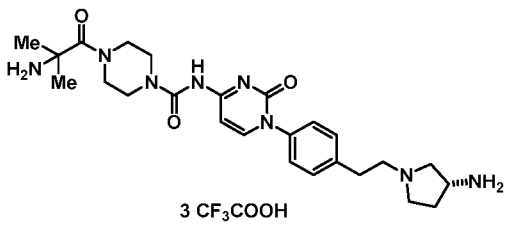
Compound 7



(*S*)-4-(2-Amino-2-methylpropanoyl)-*N*-(1-(4-(2-(3-aminopyrrolidin-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide triflouroacetate salt.

[00714] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl (S)-pyrrolidin-3-ylcarbamate ^{1}H NMR (500 MHz, D_2O) δ 8.09 (d, 1H), 7.54 (d, 2H), 7.48 (d, 2H), 6.82 (d, 1H), 4.38-4.10 (m, 2H), 3.83-3.64 (m, 11H), 3.59-3.31 (m, 2H), 3.22 (t, 2H), 2.83-2.08 (m, 2H), 1.75 (s, 6H). LCMS [M+H] 497.3.

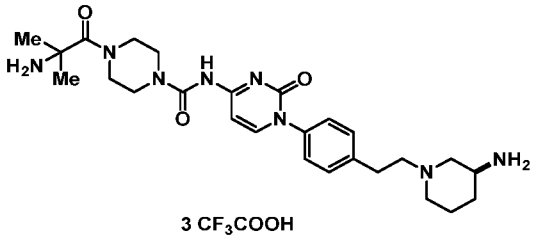
Compound 8



(*R*)-4-(2-Amino-2-methylpropanoyl)-*N*-(1-(4-(2-(3-aminopyrrolidin-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide triflouroacetate salt.

[00715] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl (R)-pyrrolidin-3-ylcarbamate ^{1}H NMR (500 MHz, D_2O) δ 8.09 (d, 1H), 7.54 (d, 2H), 7.48 (d, 2H), 6.82 (d, 1H), 4.38-4.10 (m, 2H), 3.83-3.64 (m, 11H), 3.59-3.31 (m, 2H), 3.22 (t, 2H), 2.83-2.08 (m, 2H), 1.75 (s, 6H). LCMS [M+H] 497.3.

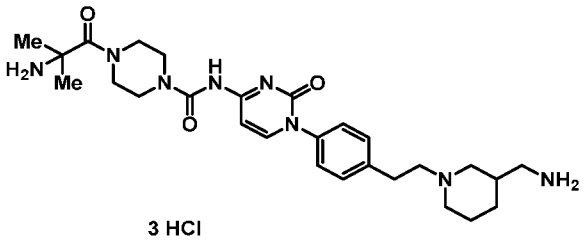
Compound 9



(*S*)-4-(2-Amino-2-methylpropanoyl)-*N*-(1-(4-(2-(3-aminopiperidin-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide triflouroacetate salt.

[00716] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl (S)-piperidin-3-ylcarbamate. ^{1}H NMR (500 MHz, D_2O) δ 8.19 (d, 1H), 7.52 (d, 2H), 7.46 (d, 2H), 6.78 (d, 1H), 3.91-3.61 (m, 12H), 3.55 (t, 2H), 3.22 (t, 2H), 3.17-3.00 (m, 2H), 2.29-2.13 (m, 2H), 1.95-1.78 (m, 1H), 1.72 (s, 6H). LCMS [M+H] 511.4.

Compound 10

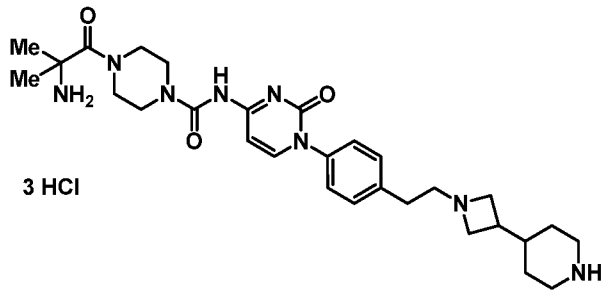


4-(2-Amino-2-methylpropanoyl)-*N*-(1-(4-(2-(3-(aminomethyl)piperidin-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt.

[00717] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl (piperidin-3-ylmethyl)carbamate. ^{1}H NMR (500 MHz, D_2O) δ 8.13 (d, 1H), 7.52 (d, 2H), 7.47 (d, 2H), 6.81 (d, 1H), 3.84-3.69 (m, 10H), 3.48

(t, 2H), 3.21 (t, 2H), 3.11-3.05 (m, 1H), 3.03-2.95 (m, 2H), 2.88 (t, 1H), 2.27 (bs, 1H), 2.14-2.02 (m, 2H), 1.88-1.78 (m, 1H), 1.74 (s, 6H), 1.39-1.29 (m, 1H).

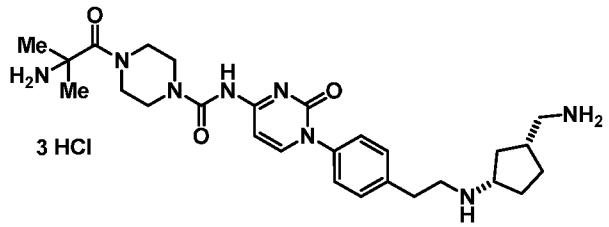
Compound 372



4-(2-Amino-2-methylpropanoyl)-N-(2-oxo-1-(4-(2-(3-(piperidin-4-yl)azetidin-1-yl)ethyl)phenyl)-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00718] Prepared in a similar fashion to Scheme C-15 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl 4-(azetidin-3-yl)piperidine-1-carboxylate. ^{1}H NMR (400 MHz, D_2O) δ 8.13 (d, 1H), 7.54–7.44 (m, 4H), 6.80 (d, 1H), 4.29 (t, 1H), 4.13 (d, 1H), 3.91 (t, 1H), 3.79 (s, 3H), 3.75 (s, 5H), 3.62 (t, 1H), 3.55 (t, 2H), 3.43 (d, 2H), 3.09–2.93 (m, 4H), 2.82–2.69 (m, 1H), 2.01–1.80 (m, 3H), 1.74 (s, 6H), 1.41–1.24 (m, 2H). LCMS [M+H] 551.3.

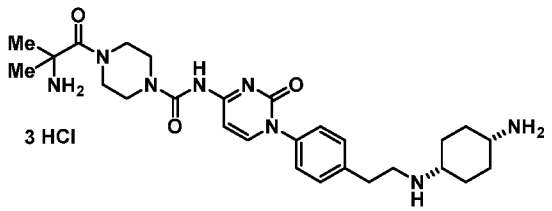
Compound 177



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(((1S,3R)-3-(aminomethyl)cyclopentyl)amino) ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00719] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate. ^{1}H NMR (500 MHz, D_2O) δ 8.00 (d, 1H), 7.57 (d, 2H), 7.51 (d, 2H), 6.91 (d, 1H), 3.88-3.75 (m, 8H), 3.46 (t, 2H), 3.22-3.08 (m, 5H), 2.55-2.45 (m, 1H), 2.40-2.32 (m, 1H), 2.30-2.22 (m, 1H), 2.11-2.01 (m, 1H), 1.92-1.85 (m, 1H), 1.81 (s, 6H), 1.66-1.52 (m, 1H), 1.49-1.37 (m, 1H). LCMS [M+H] 525.1.

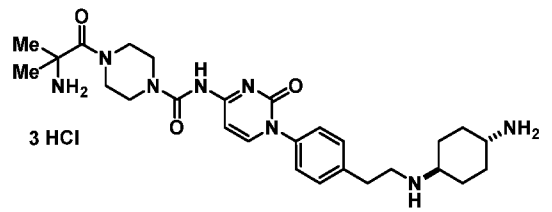
Compound 179



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-((*cis*-4-aminocyclohexyl)amino)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt.

[00720] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and boc-*cis*-1,4-cyclohexanediamine . ^{1}H NMR (500 MHz, D_2O) δ 8.08 (d, 1H), 7.50 (d, 2H), 7.44 (d, 2H), 6.80 (d, 1H), 3.86-3.67 (m, 8H), 3.55-3.49 (m, 1H), 3.43-3.35 (m, 3H), 3.12 (t, 2H), 2.07-1.98 (m, 2H), 1.98-1.85 (m, 4H), 1.84-1.74 (m, 2H), 1.72 (s, 6H). LCMS [M+H] 525.3.

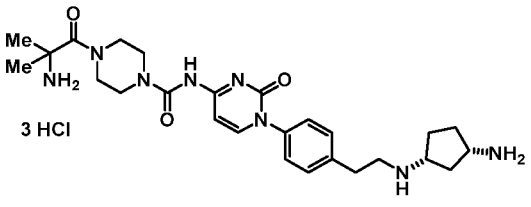
Compound 180



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-((*trans*-4-aminocyclohexyl)amino)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00721] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and boc-*trans*-1,4-cyclohexanediamine. ^{1}H NMR (500 MHz, D_2O) δ 7.98 (d, 1H), 7.49 (d, 2H), 7.43 (d, 2H), 6.82 (d, 1H), 3.81-3.68 (m, 8H), 3.39 (t, 2H), 3.27-3.18 (m, 2H), 3.10 (t, 2H), 2.21 (d, 4H), 1.72 (s, 6H), 1.59-1.47 (m, 4H). [M+H] 525.3.

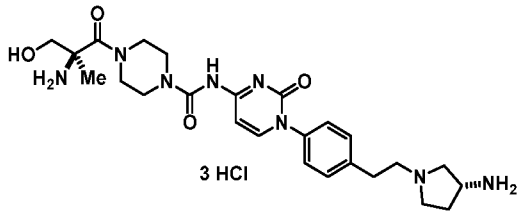
Compound 181



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(((1R,3S)-3-aminocyclopentyl)amino)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00722] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl ((1R,3S)-3-aminocyclopentyl)carbamate . ^{1}H NMR (500 MHz, D_2O) δ 7.98 (d, 1H), 7.50 (d, 2H), 7.44 (d, 2H), 6.82 (d, 1H), 3.84-3.65 (m, 10H), 3.40 (t, 2H), 3.13 (t, 2H), 2.69 (p, 1H), 2.22 (sept, 2H), 1.95-1.83 (m, 2H), 1.79-1.70 (m, 7H). [M+H] 511.4.

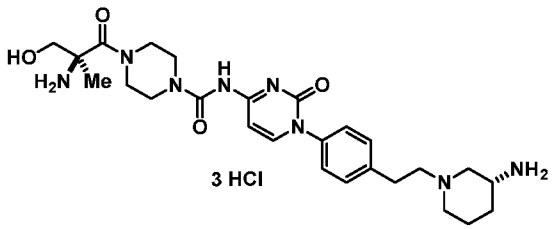
Compound 11



4-((S)-2-Amino-3-hydroxy-2-methylpropanoyl)-N-(1-(4-(2-((R)-3-aminopyrrolidin-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00723] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2R,4S)-2-(*tert*-butyl)-4-methyl-4-(4-((2-oxo-1-(4-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazine-1-carbonyl)oxazolidine-3-carboxylate and *tert*-butyl (R)-pyrrolidin-3-ylcarbamate. ^{1}H NMR (500 MHz, D_2O) δ 8.10 (d, 1H), 7.55 (d, 2H), 7.48 (d, 2H), 6.83 (d, 1H), 4.33-4.13 (m, 3H), 4.04-3.63 (m, 12H), 3.55.3.37 (m, 2H), 3.22 (t, 2H), 2.86-2.10 (m, 2H), 1.70 (s, 3H). LCMS [M+H] 513.4.

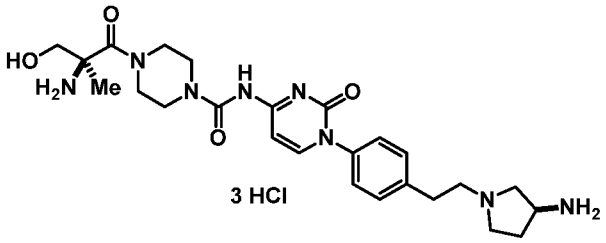
Compound 12



4-((*S*)-2-Amino-3-hydroxy-2-methylpropanoyl)-*N*-(1-(4-(2-((*R*)-3-aminopiperidin-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00724] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2R,4S)-2-(*tert*-butyl)-4-methyl-4-(4-((2-oxo-1-(4-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazine-1-carbonyl)oxazolidine-3-carboxylate and *tert*-butyl (R)-piperidin-3-ylcarbamate. ^{1}H NMR (500 MHz, D_2O) δ 8.11 (d, 1H), 7.53 (d, 2H), 7.48 (d, 2H), 6.82 (d, 1H), 4.17 (d, 1H), 3.91 (d, 2H), 3.85-3.64 (m, 10H), 3.58 (t, 2H), 3.24 (t, 2H), 3.19-3.04 (m, 2H), 2.31-2.16 (m, 2H), 1.96-1.82 (m, 1H), 1.77-1.67 (m, 4H). LCMS [M+H] 527.3.

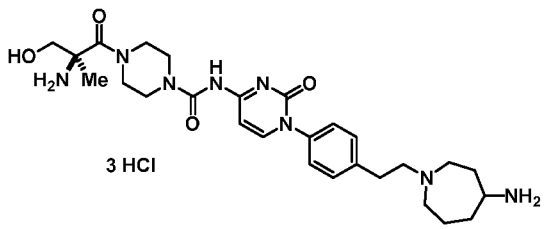
Compound 13



4-((*S*)-2-Amino-3-hydroxy-2-methylpropanoyl)-*N*-(1-(4-(2-((*S*)-3-aminopyrrolidin-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00725] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2R,4S)-2-(*tert*-butyl)-4-methyl-4-(4-((2-oxo-1-(4-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazine-1-carbonyl)oxazolidine-3-carboxylate and *tert*-butyl (S)-pyrrolidin-3-ylcarbamate. ^{1}H NMR (500 MHz, D_2O) δ 8.10 (d, 1H), 7.55 (d, 2H), 7.48 (d, 2H), 6.83 (d, 1H), 4.33-4.13 (m, 3H), 4.04-3.63 (m, 12H), 3.55.3.37 (m, 2H), 3.22 (t, 2H), 2.86-2.10 (m, 2H), 1.70 (s, 3H). LCMS [M+H] 513.4.

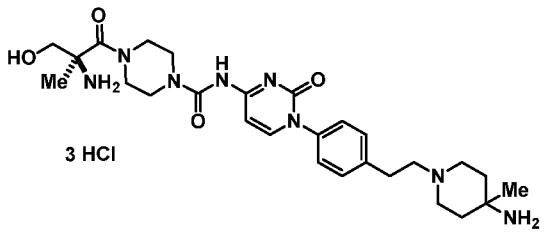
Compound 381



4-((S)-2-Amino-3-hydroxy-2-methylpropanoyl)-N-(1-(4-(2-(4-aminoazepan-1-yl)ethyl) phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00726] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2R,4S)-2-(*tert*-butyl)-4-methyl-4-(4-((2-oxo-1-(4-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazine-1-carbonyl)oxazolidine-3-carboxylate and *tert*-butyl azepan-4-ylcarbamate. LCMS [M+H] 541.4.

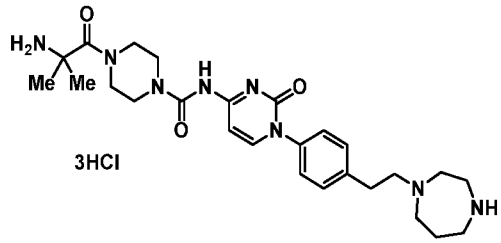
Compound 361



(S)-4-(2-Amino-3-hydroxy-2-methylpropanoyl)-N-(1-(4-(2-(4-amino-4-methylpiperidin-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00727] Prepared in a similar fashion to Scheme SC-15from *tert*-butyl (1-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)phenethyl)-4-methylpiperidin-4-yl)carbamate and 1-(4-((2R,4S)-3-(*tert*-butoxycarbonyl)-2-(*tert*-butyl)-4-methyloxazolidine-4-carbonyl)piperazine-1-carbonyl)-3-methyl-1H-imidazol-3-ium iodide. LCMS [M+H] 541.3.

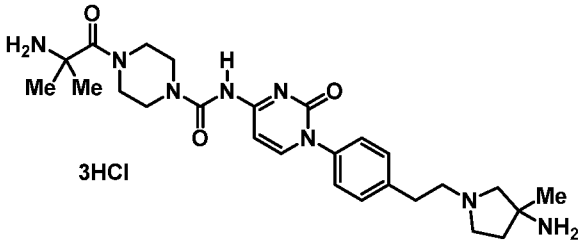
Compound 14



***N*-(1-(4-(2-(1,4-Diazepan-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-4-(2-amino-2-methylpropanoyl)piperazine-1-carboxamide hydrochloride salt**

[00728] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl 1,4-diazepane-1-carboxylate. ^{1}H NMR (500 MHz, D_2O) δ 8.21 (d, 1H), 7.53 (d, 2H), 7.48 (d, 2H), 6.79 (d, 1H), 3.87-3.67 (m, 14H), 3.61 (t, 2H), 3.51 (t, 2H), 3.23 (t, 2H), 2.33 (s, 2H), 1.73 (s, 6h). LCMS [M+H] 511.3.

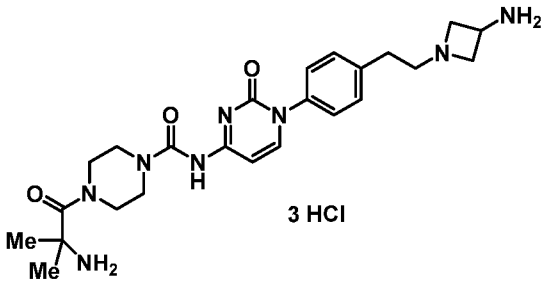
Compound 15



4-(2-Amino-2-methylpropanoyl)-*N*-(1-(4-(2-(3-amino-3-methylpyrrolidin-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00729] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl (3-methylpyrrolidin-3-yl)carbamate. ^{1}H NMR (500 MHz, D_2O) δ 8.09 (d, 1H), 7.54 (d, 2H), 7.48 (d, 2H), 6.82 (d, 1H), 3.80-3.72 (m, 10H), 3.68 (t, 2H), 3.63-3.42 (m, 2H), 3.21 (t, 2H), 2.44 (bs, 2H), 1.74 (s, 6H), 1.65 (s, 3H). LCMS [M+H] 511.4.

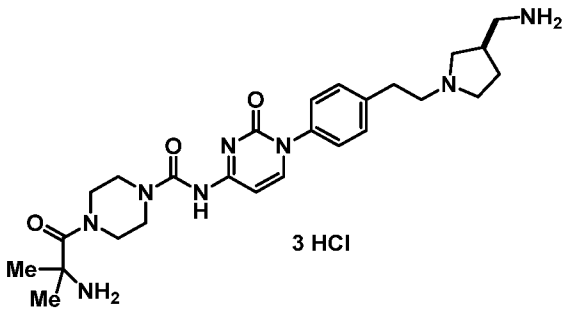
Compound 16



4-(2-Amino-2-methylpropanoyl)-*N*-(1-(4-(2-(3-aminoazetidin-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00730] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl azetidin-3-ylcarbamate. ^{1}H NMR (500 MHz, D_2O) δ 8.14 (d, 1H), 7.53 (d, 2H), 7.48 (d, 2H), 6.81 (d, 1H), 4.65-4.34 (m, 5H), 3.84-3.70 (m, 10H), 3.10 (t, 2H), 1.74 (s, 6H). LCMS [M+H] 483.4.

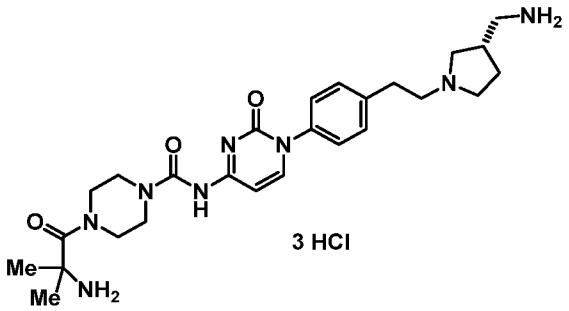
Compound 17



(*R*)-4-(2-Amino-2-methylpropanoyl)-*N*-(1-(4-(2-(3-(aminomethyl)pyrrolidin-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00731] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl (S)-(pyrrolidin-3-ylmethyl)carbamate. ^{1}H NMR (500 MHz, D_2O) δ 8.23 (d, 1H), 7.54 (d, 2H), 7.48 (d, 2H), 6.79 (d, 1H), 3.97-3.93 (m, 1H), 3.84-3.73 (m, 8H) 3.63-3.57 (m, 2H), 3.55-3.51 (m, 1H), 3.18 (t, 2h), 3.12-3.07 (m, 1H), 3.02-2.90 (m, 1H), 2.77-2.69 (m, 1H), 2.51-2.45 (m, 1H), 2.37-2.29 (m, 1H), 2.04-1.96 (m, 1H), 1.84-1.77 (m, 1H), 1.73 (s, 6H). LCMS [M+H] 511.5.

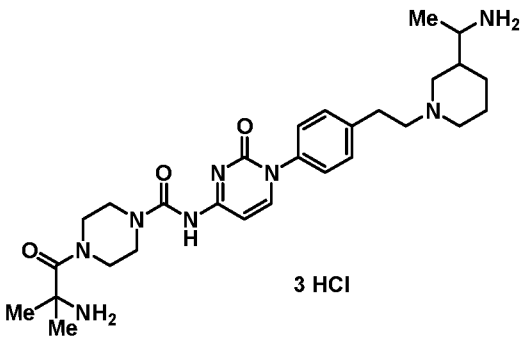
Compound 18



(*S*)-4-(2-Amino-2-methylpropanoyl)-*N*-(1-(4-(2-(3-(aminomethyl)pyrrolidin-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00732] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl (R)-(pyrrolidin-3-ylmethyl)carbamate. ^{1}H NMR (500 MHz, D_2O) δ 8.23 (d, 1H), 7.54 (d, 2H), 7.48 (d, 2H), 6.79 (d, 1H), 3.97-3.93 (m, 1H), 3.84-3.73 (m, 8H) 3.63-3.57 (m, 2H), 3.55-3.51 (m, 1H), 3.18 (t, 2h), 3.12-3.07 (m, 1H), 3.02-2.90 (m, 1H), 2.77-2.69 (m, 1H), 2.51-2.45 (m, 1H), 2.37-2.29 (m, 1H), 2.04-1.96 (m, 1H), 1.84-1.77 (m, 1H), 1.73 (s, 6H). LCMS [M+H] 511.4.

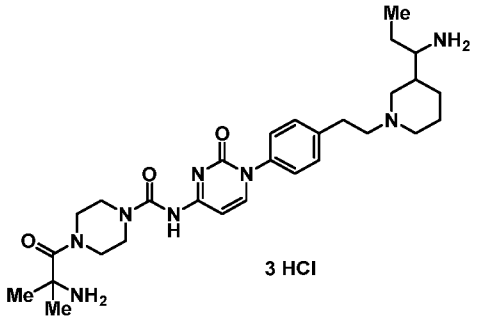
Compound 22



4-(2-Amino-2-methylpropanoyl)-*N*-(1-(4-(2-(3-(1-aminoethyl)piperidin-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00733] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl (1-(piperidin-3-yl)ethyl)carbamate. ^{1}H NMR (500 MHz, D_2O) δ 8.02 (d, 1H), 7.55 (d, 2H), 7.49 (d, 2H), 6.87 (d, 1H), 3.82-3.71 (m, 10H), 3.55-3.52 (m, 2H), 3.45-3.41 (m, 2H), 3.25 (t, 2H), 2.17 (d, 2H), 2.11-1.95 (m, 2H), 1.96-1.88 (m, 1H), 1.77 (s, 6H), 1.52-1.41 (m, 1H), 1.38 (d, 3H). LCMS [M+H] 539.4.

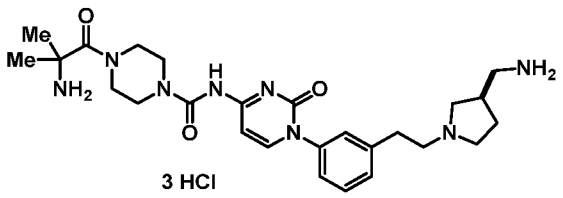
Compound 23



4-(2-Amino-2-methylpropanoyl)-*N*-(1-(4-(2-(3-(1-aminopropyl)piperidin-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00734] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl (1-(piperidin-3-yl)propyl)carbamate. ^{1}H NMR (500 MHz, D_2O) δ 8.06 (d, 1H), 7.55 (d, 2H), 7.49 (d, 2H), 6.86 (d, 1H), 3.82-3.66 (m, 10H), 3.55-3.52 (m, 2H), 3.27-3.25 (m, 3H), 3.06-2.98 (q, 2H), 2.38-2.22 (m, 1H), 2.19-2.12 (m, 1H), 2.06-1.99 (m, 1H), 1.90-1.81 (m, 2H), 1.77 (s, 6H), 1.74-1.67 (m, 1H), 1.56-1.37 (m, 1H), 1.04 (t, 3H). LCMS [M+H] 553.4.

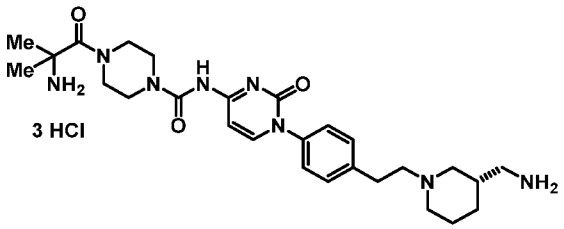
Compound 24



(R)-4-(2-Amino-2-methylpropanoyl)-N-(1-(3-(2-(3-(aminomethyl)pyrrolidin-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride

[00735] Prepared in a similar fashion as scheme C-15 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(3-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl (S)-(pyrrolidin-3-ylmethyl)carbamate. ^{1}H NMR (400 MHz, D_2O) mixture of rotamers δ 7.86 (d, 1H), 7.43 (t, 1H), 7.36 (d, 1H), 7.31-7.21 (m, 2H), 6.71 (d, 1H), 3.81-3.77 (m, 1H), 3.64-3.59 (m, 8H), 3.51-3.45 (m, 4H), 3.25-2.92 (m, 6H), 2.89-2.75 (m, 1H), 2.62-2.53 (m, 1H), 2.34-2.30 (m, 1H), 2.20-2.15 (m, 1H), 1.90-1.81 (m, 1H),1.59 (s, 6H). LCMS [(M+2H)/2] 256.1.

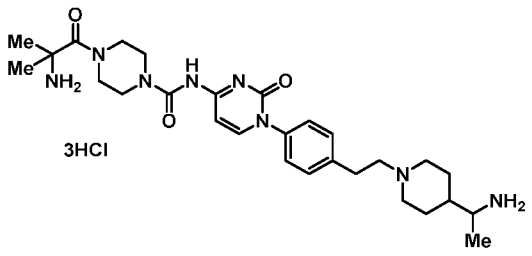
Compound 25



(S)-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(3-(aminomethyl)piperidin-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00736] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl (R)-(piperidin-3-ylmethyl)carbamate. ^{1}H NMR (500 MHz, D_2O) δ 7.97 (d, 1H), 7.51 (d, 2H), 7.45 (d, 2H), 6.84 (d, 1H), 3.86-3.67 (m, 10H), 3.48 (t, 2H), 3.21 (t, 2H), 3.11-2.95 (m, 3H), 2.87 (t, 1H), 2.34-2.20 (m, 1H), 2.15-2.01 (m, 2H), 1.89-1.77 (m, 1H), 1.74 (s, 6H), 1.41-1.30 (m, 1H). LCMS [M+H] 525.3.

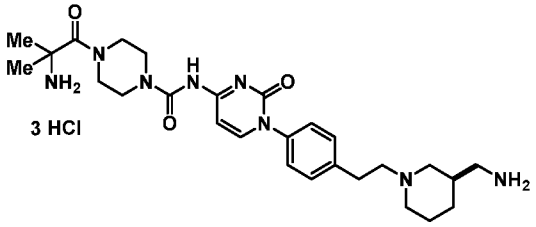
Compound 168



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(4-(1-aminoethyl)piperidin-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00737] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl (1-(piperidin-4-yl)ethyl)carbamate. LCMS [M+H] 539.2.

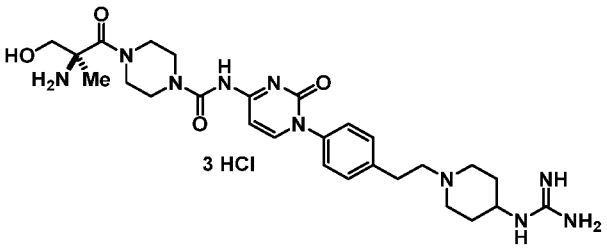
Compound 26



(R)-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(3-(aminomethyl)piperidin-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00738] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl (S)-(piperidin-3-ylmethyl)carbamate. ^{1}H NMR (500 MHz, D_2O) δ 7.97 (d, 1H), 7.51 (d, 2H), 7.45 (d, 2H), 6.84 (d, 1H), 3.86-3.67 (m, 10H), 3.48 (t, 2H), 3.21 (t, 2H), 3.11-2.95 (m, 3H), 2.87 (t, 1H), 2.34-2.20 (m, 1H), 2.15-2.01 (m, 2H), 1.89-1.77 (m, 1H), 1.74 (s, 6H), 1.41-1.30 (m, 1H). LCMS [M+H] 525.3.

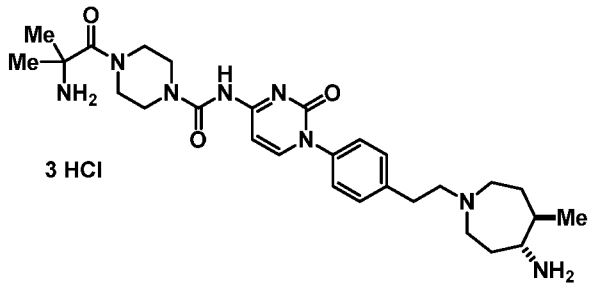
Compound 349



(S)-4-(2-Amino-3-hydroxy-2-methylpropanoyl)-N-(1-(4-(2-(4-guanidinopiperidin-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00739] Prepared in a similar fashion as Scheme C-15 from 4-((2S,4S)-2-(*tert*-butyl)-4-methyloxazolidine-4-carbonyl)-N-(2-oxo-1-(4-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide and 1,2-bis(*tert*-butoxycarbonyl)-3-(piperidin-4-yl)guanidine. LCMS [M+H] 553.4.

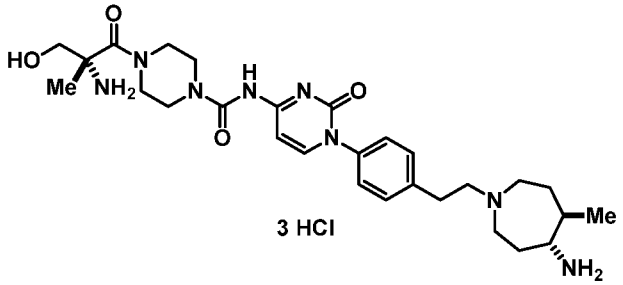
Compound 27



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(*trans*-4-amino-5-methylazepan-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00740] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *trans-tert*-butyl (5-methylazepan-4-yl)carbamate. ^{1}H NMR (500 MHz, D_2O) δ 7.86 (d, 1H), 7.46 (d, 2H), 7.40 (d, 2H), 6.81 (d, 1H), 3.80-3.65 (m, 8H), 3.58-3.43 (m, 5H), 3.26-3.11 (m, 4H), 2.30-2.21 (m, 2H), 2.08-1.85 (m, 3H), 1.70 (s, 6H), 1.15-1.09 (m, 3H). LCMS [M+H] 539.2.

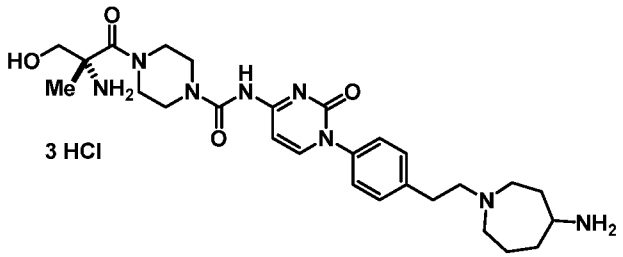
Compound 28



4-((R)-2-Amino-3-hydroxy-2-methylpropanoyl)-N-(1-(4-(2-(*trans*-4-amino-5-methylazepan-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00741] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2S,4R)-2-(*tert*-butyl)-4-methyl-4-(4-((2-oxo-1-(4-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazine-1-carbonyl)oxazolidine-3-carboxylate and and *trans-tert*-butyl (5-methylazepan-4-yl)carbamate. ^{1}H NMR (500 MHz, D_2O) δ 8.01 (d, 1H), 7.50 (d, 2H), 7.44 (d, 2H), 6.82 (d, 1H), 4.15 (d, 1H), 3.89 (d, 1H), 3.81-3.69 (m, 9H), 3.60-3.47 (m, 4H), 3.30-3.13 (m, 4H), 2.33-2.11 (m, 2H), 2.09-1.88 (m, 3H), 1.68 (s, 3H), 1.15 (t, 3H). LCMS [M+H] 555.4.

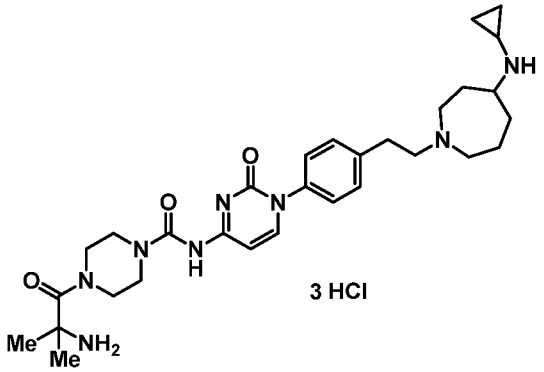
Compound 35



4-((R)-2-Amino-3-hydroxy-2-methylpropanoyl)-N-(1-(4-(2-(4-aminoazepan-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00742] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2S,4R)-2-(*tert*-butyl)-4-methyl-4-(4-((2-oxo-1-(4-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazine-1-carbonyl)oxazolidine-3-carboxylate and *tert*-butyl azepan-4-ylcarbamate. ^{1}H NMR (500 MHz, D_2O) δ 8.18 (d, 1H), 7.56 (d, 2H), 7.51 (d, 2H), 6.84 (d, 1H), 4.20 (d, 1H), 3.94 (d, 1H), 3.87-3.72 (m, 8H), 3.65-3.48 (m, 3H), 3.28-3.21 (m, 2H), 2.44-1.98 (m, 8H), 1.72 (s, 3H), 1.41-1.24 (m, 2H).

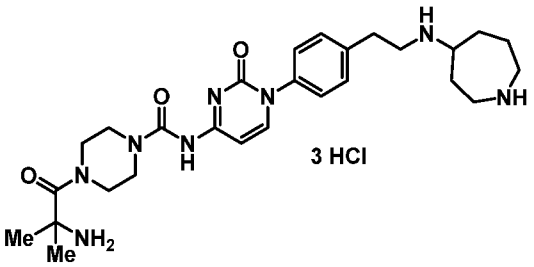
Compound 29



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(4-(cyclopropylamino)azepan-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00743] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl azepan-4-yl(cyclopropyl)carbamate. ^{1}H NMR (500 MHz, D_2O) δ 8.05 (d, 1H), 7.51 (d, 2H), 7.46 (d, 2H), 6.82 (d, 1H), 3.84-3.68 (m, 10H), 3.68-3.37 (m, 6H), 3.20 (t, 2H), 2.80-2.72 (m, 1H), 2.62-2.38 (m, 2H), 2.34-1.98 (m, 2H), 1.91-1.77 (m, 1H), 1.73 (s, 6H), 1.00-0.84 (m, 4H). LCMS [M+H] 565.4.

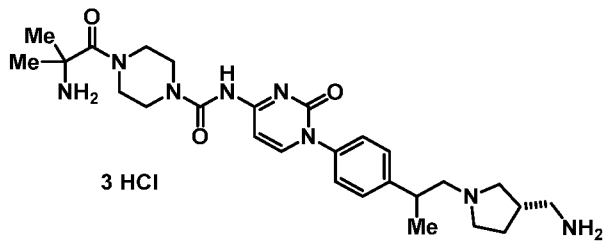
Compound 30



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(azepan-4-ylamino)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt.

[00744] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl) carbamate and *tert*-butyl 4-aminoazepane-1-carboxylate. ^{1}H NMR (500 MHz, D_2O) δ 7.94 (d, 1H), 7.51 (d, 2H), 7.44 (d, 2H), 6.85 (d, 1H), 3.85-3.69 (m, 8H), 3.58-3.48 (m, 2H), 3.47-3.38 (m, 2H), 3.30-3.18 (m, 2H), 3.14 (t, 2H), 2.49-2.32 (m, 2H), 2.16-2.00 (m, 2H), 1.93-1.75 (m, 2H), 1.74 (s, 6H). MS [M+H] 525.4.

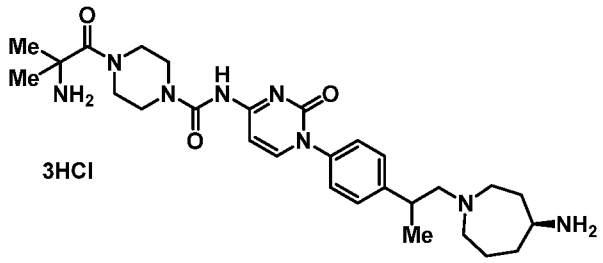
Compound 368



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(1-((S)-3-(aminomethyl)pyrrolidin-1-yl)propan-2-yl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide

[00745] Prepared in a similar fashion as in Scheme C-15 from 2-(4-bromophenyl)propan-1-ol and *tert*-butyl (R)-(pyrrolidin-3-ylmethyl)carbamate in Scheme 5. ^{1}H NMR (500 MHz, D_2O) δ 7.96 (d, 1H), 7.57 (d, 2H), 7.48 (d, 2H), 6.84 (d, 1H), 3.82-3.69 (m, 8H), 3.68-3.58 (m, 2H), 3.56-3.34 (m, 2H), 3.22-3.06 (m, 2H), 3.05-2.96 (m, 1H), 2.94-2.82 (m, 1H), 2.71-2.59 (m, 1H), 2.46-2.34 (m, 1H), 2.30-2.20 (m, 1H), 2.01-1.88 (m, 1H), 1.73 (s, 6H), 1.36 (d, 3H) LCMS [M+H] 525.3.

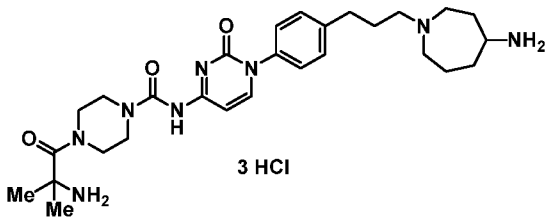
Compound 290



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(1-((S)-4-aminoazepan-1-yl)propan-2-yl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00746] Prepared in a similar fashion as in Scheme C-15 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(1-oxopropan-2-yl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl (S)-azepan-4-ylcarbamate. LCMS [M+H] 539.4.

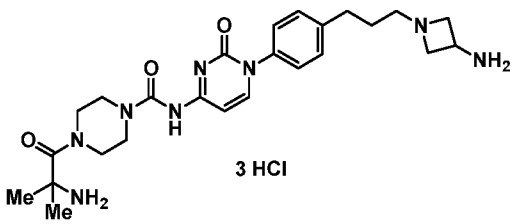
Compound 31



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(3-(4-aminoazepan-1-yl)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00747] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(3-oxopropyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl azepan-4-ylcarbamate. ^{1}H NMR (500 MHz, D_2O) δ 8.18 (d, 1H), 7.45 (d, 2H), 7.41 (d, 2H), 6.76 (d, 1H), 3.82-3.69 (m, 8H), 3.64-3.57 (m, 1H), 3.57-3.41 (m, 2H), 3.29-3.06 (m, 4H), 2.79 (t, 2H), 2.35-1.90 (m, 7H), 1.81-1.61 (m, 7H). LCMS [M+H] 539.4.

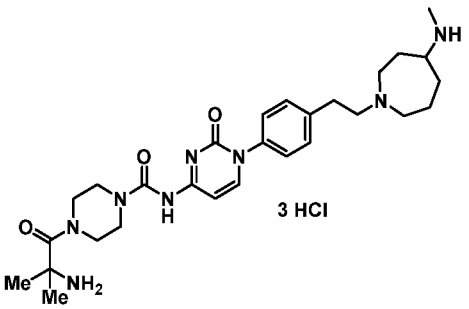
Compound 32



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(3-(3-aminoazetidin-1-yl)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00748] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(3-oxopropyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl azetidin-3-ylcarbamate. ^{1}H NMR (500 MHz, D_2O) δ 8.02 (d, 1H), 7.43 (d, 2H), 7.38 (d, 2H), 6.79 (d, 1H), 4.70-4.56 (m, 2H), 4.56-4.36 (m, 2H), 4.32-4.22 (m, 1H), 3.85-3.68 (m, 8H), 3.36 (t, 2H), 2.80 (t, 2H), 2.01-1.92 (m, 2H), 1.73 (s, 6H). LCMS [M+H] 497.4.

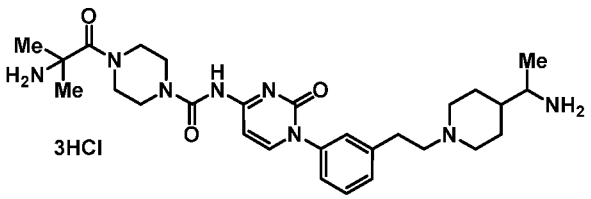
Compound 33



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(4-(methylamino)azepan-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00749] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl) carbamate and *tert*-butyl azepan-4-yl(methyl)carbamate. ^{1}H NMR (500 MHz, D_2O) δ 7.92 (d, 1H), 7.50 (d, 2H), 7.44 (d, 2H), 6.84 (d, 1H), 3.85-3.67 (m, 8H), 3.63-3.39 (m, 6H), 3.28-3.17 (m, 3H), 2.74 (s, 3H), 2.56-2.30 (m, 2H), 2.29-1.96 (m, 3H), 1.88-1.75 (m, 1H), 1.73 (s, 6H). LCMS [M+H] 539.3.

Compound 34

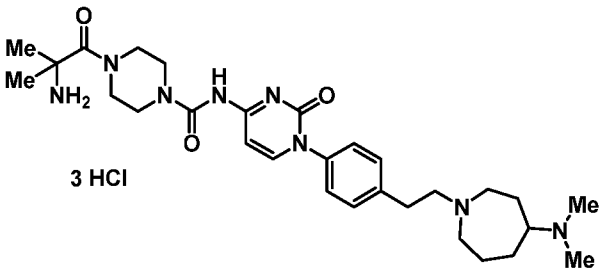


4-(2-Amino-2-methylpropanoyl)-N-(1-(3-(2-(4-(1-aminoethyl)piperidin-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride.

[00750] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(3-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl (1-(piperidin-4-yl)ethyl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.85 (d, 1H), 7.46 (t, 1H), 7.39-7.24 (m, 3H), 6.71 (d, 1H), 3.63-3.60 (m, 8H),

3.32 (t, 2H), 3.25-3.15 (m, 1H), 3.05 (t, 2H), 2.95 (t, 2H), 1.97-1.93 (m, 2H), 1.88-1.82 (m, 1H), 1.60 (s, 6H), 1.51-1.48 (m, 4H), 1.17 (d, 3H). LCMS [M+H] 539.2.

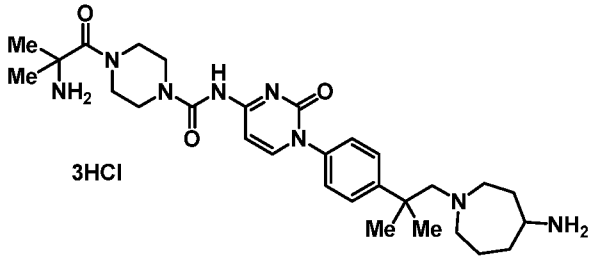
Compound 36



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(4-(dimethylamino)azepan-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00751] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and N,N-dimethylazepan-4-amine. ^{1}H NMR (500 MHz, D_2O) δ 7.87 (d, 1H), 7.50 (d, 2H), 7.44 (d, 2H), 6.86 (d, 1H), 3.82-3.69 (m, 8H), 3.68-3.51 (m, 4H), 3.24-3.18 (m, 2H), 2.86 (d, 1H), 2.44-2.29 (m, 4H), 2.09-1.84 (m, 4H), 1.74 (s, 6H), 1.35 (d, 6H) LCMS [M+H] 553.3.

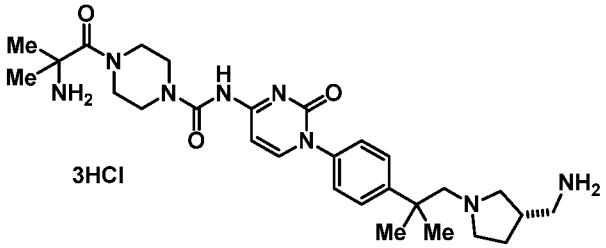
Compound 37



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(1-(4-aminoazepan-1-yl)-2-methylpropan-2-yl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00752] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2-methyl-1-(4-((1-(4-(2-methyl-1-oxopropan-2-yl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-1-oxopropan-2-yl)carbamate and *tert*-butyl azepan-4-ylcarbamate. ^{1}H NMR (500 MHz, D_2O) δ 7.91 (d, 1H), 7.69 (d, 2H), 7.48 (d, 2H), 6.83 (d, 1H), 3.79-3.67 (m, 8H), 3.65-3.37 (m, 4H), 3.29-2.97 (m, 5H), 2.26-2.10 (m, 2H), 2.01-1.78 (m, 2H), 1.71 (s, 6H), 1.50 (d, 6H). LCMS [M+H] 553.2.

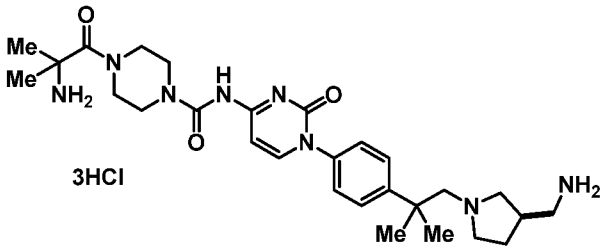
Compound 38



(S)-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(1-(3-(aminomethyl)pyrrolidin-1-yl)-2-methylpropan-2-yl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00753] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2-methyl-1-(4-((1-(4-(2-methyl-1-oxopropan-2-yl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-1-oxopropan-2-yl)carbamate and *tert*-butyl (R)-(pyrrolidin-3-ylmethyl)carbamate. ^{1}H NMR (500 MHz, D_2O) δ 7.89 (d, 1H), 7.71 (d, 2H), 7.51 (d, 2H), 6.88 (d, 1H), 3.84-3.69 (m, 8H), 3.61-3.42 (m, 2H), 3.34-3.16 (m, 2H), 3.14-3.00 (m, 1H), 2.85-2.54 (m, 2H), 2.40-2.02 (m, 1H), 1.94-1.80 (m, 1H), 1.75 (s, 6H), 1.54 (s, 6H), 1.35 (d, 2H). LCMS [M+H] 539.2.

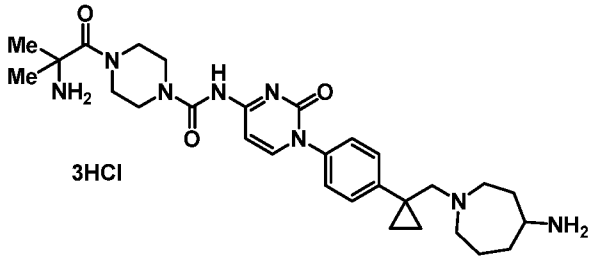
Compound 39



(R)-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(1-(3-(aminomethyl)pyrrolidin-1-yl)-2-methylpropan-2-yl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00754] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2-methyl-1-(4-((1-(4-(2-methyl-1-oxopropan-2-yl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-1-oxopropan-2-yl)carbamate and *tert*-butyl (S)-(pyrrolidin-3-ylmethyl)carbamate. ^{1}H NMR (500 MHz, D_2O) δ 7.89 (d, 1H), 7.71 (d, 2H), 7.51 (d, 2H), 6.88 (d, 1H), 3.84-3.69 (m, 8H), 3.61-3.42 (m, 2H), 3.34-3.16 (m, 2H), 3.14-3.00 (m, 1H), 2.85-2.54 (m, 2H), 2.40-2.02 (m, 1H), 1.94-1.80 (m, 1H), 1.75 (s, 6H), 1.54 (s, 6H), 1.35 (d, 2H). LCMS [M+H] 539.2.

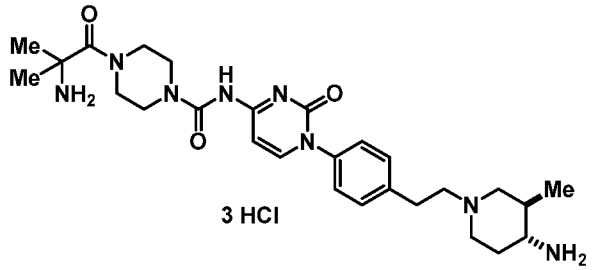
Compound 40



4 4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(1-((4-aminoazepan-1-yl)methyl)cyclopropyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00755] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (1-(4-((1-(4-(1-formylcyclopropyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl azepan-4-ylcarbamate. ^{1}H NMR (500 MHz, D_2O) δ 7.99 (d, 1H), 7.69 (d, 2H), 7.46 (d, 2H), 6.81 (d, 1H), 3.82-3.67 (m, 8H), 3.67-3.54 (m, 3H), 3.50-3.33 (m, 3H), 3.19-3.01 (m, 1H), 2.29-2.18 (m, 2H), 2.03-1.85 (m, 2H), 1.72 (s, 6H), 1.69-1.54 (m, 2H), 1.25-1.06 (m, 4H). LCMS [M+H] 551.2.

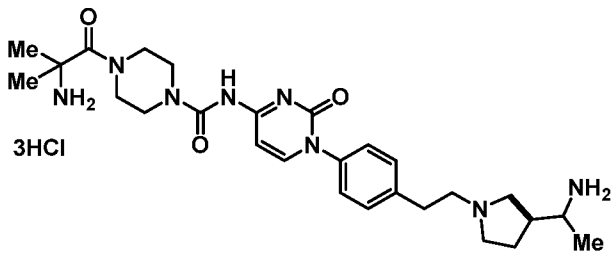
Compound 41



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(*trans*-4-amino-3-methylpiperidin-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00756] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl ((*trans*)-3-methylpiperidin-4-yl)carbamate. ^{1}H NMR (500 MHz, D_2O) δ 7.90 (d, 1H), 7.50 (d, 2H), 7.44 (d, 2H), 6.85 (d, 1H), 3.85-3.68 (m, 8H), 3.49 (t, 2H), 3.31-3.26 (m, 1H), 3.20 (t, 1H), 2.97 (t, 1H), 2.42-2.36 (m, 1H), 2.22-2.14 (m, 2H), 2.08 (s, 3H), 2.04-1.98 (m, 1H), 1.74 (s, 6H), 1.35 (d, 1H), 1.25 (t, 1H), 1.14 (d, 1H). LCMS [M+H] 525.4.

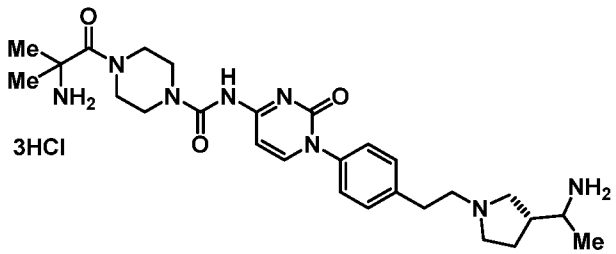
Compound 42



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-((3S)-3-(1-aminoethyl)pyrrolidin-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00757] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl (1-((S)-pyrrolidin-3-yl)ethyl)carbamate. ^{1}H NMR (500 MHz, D_2O) δ 7.93 (d, 1H), 7.50 (d, 2H), 7.43 (d, 2H), 6.83 (d, 1H), 3.82-3.68 (m, 8H), 3.63-3.56 (m, 2H), 3.54-3.42 (m, 1H), 3.17 (t, 2H), 3.10-3.00 (m, 2H), 2.87-2.78 (m, 1H), 2.66-2.54 (m, 1H), 2.42-2.22 (m, 1H), 2.09-2.01 (m, 1H), 1.86-1.79 (m, 1H), 1.72 (s, 6H), 1.38-1.31 (m, 3H) LCMS [M+H] 525.3.

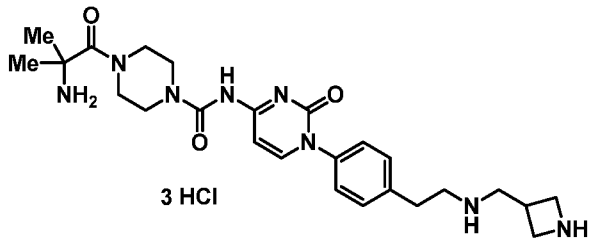
Compound 43



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-((3R)-3-(1-aminoethyl)pyrrolidin-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00758] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl (1-((R)-pyrrolidin-3-yl)ethyl)carbamate. ^{1}H NMR (500 MHz, D_2O) δ 7.93 (d, 1H), 7.50 (d, 2H), 7.43 (d, 2H), 6.83 (d, 1H), 3.82-3.68 (m, 8H), 3.63-3.56 (m, 2H), 3.54-3.42 (m, 1H), 3.17 (t, 2H), 3.10-3.00 (m, 2H), 2.87-2.78 (m, 1H), 2.66-2.54 (m, 1H), 2.42-2.22 (m, 1H), 2.09-2.01 (m, 1H), 1.86-1.79 (m, 1H), 1.72 (s, 6H), 1.38-1.31 (m, 3H) LCMS [M+H] 525.3.

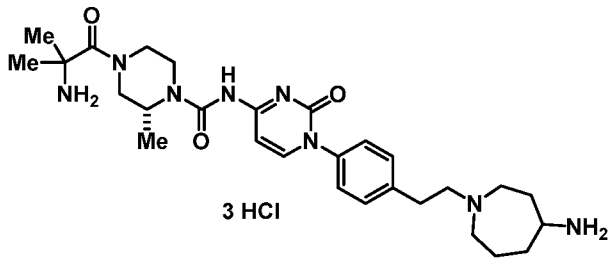
Compound 345



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-((azetidin-3-ylmethyl)amino)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00759] Prepared in a similar fashion as Scheme C-15 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl 3-(aminomethyl)azetidine-1-carboxylate. ^{1}H NMR (500 MHz, D_2O) δ 8.04 (d, 1H), 7.52 (d, 2H), 7.47 (d, 2H), 6.85 (d, 1H), 4.28 (t, 2H), 4.09 (t, 2H), 3.88-3.72 (m, 8H), 3.49-3.38 (m, 5H), 3.15 (t, 2H), 1.76 (s, 6H). LCMS [M+H] 497.27

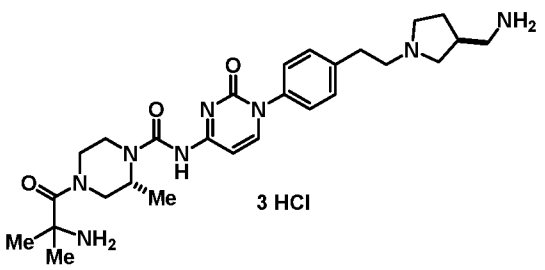
Compound 90



(2R)-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(4-aminoazepan-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2-methylpiperazine-1-carboxamide hydrochloride salt

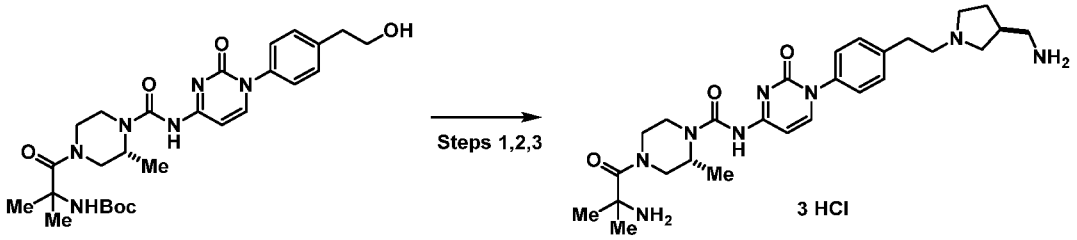
[00760] Prepared in a similar fashion as scheme C-15 from (R)-*tert*-butyl (2-methyl-1-(3-methyl-4-((2-oxo-1-(4-(2-oxoethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-1-oxopropan-2-yl)carbamate and *tert*-butyl azepan-4-ylcarbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.98 (d, 1H), 7.52 (d, 2H), 7.46 (d, 2H), 6.83 (d, 1H), 4.57 (s, 1H), 4.22 (d, 1H), 4.09 (d, 1H), 3.72 (s, 1H), 3.65–3.11 (m, 13H), 2.34 (s, 2H), 2.08 (d, 2H), 1.76 (d, 7H), 1.31 (d, 3H) LCMS [M+H] 539.3.

Compound 204



(R)-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-((S)-3-(aminomethyl)pyrrolidin-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2-methylpiperazine-1-carboxamide hydrochloride salt

Scheme C-16



Reagents: 1) TsCl, Et_3N, DMAP CH_2Cl_2, rt. 16h 2) K_2CO_3, (S)-*tert*-butyl (pyrrolidin-3-ylmethyl)carbamate, CH_3CN, 70 °C, 16h 3) HCl, CH_3OH, rt. 4h.

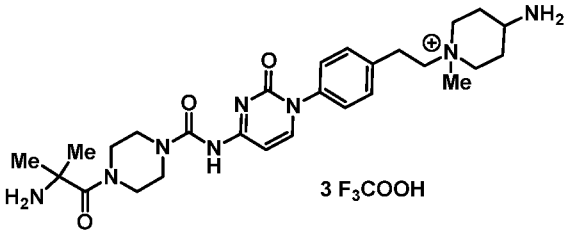
[00761] Step 1: (R)-4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)-2-methylpiperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)phenethyl 4-methylbenzenesulfonate. To a solution of (R)-*tert*-butyl (1-(4-((1-(4-(2-hydroxyethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)-3-methylpiperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate (52 mg, 0.10 mmol) and Et_3N (0.04 mL, 0.28 mmol) in CH_2Cl_2 at rt were added tosyl chloride (28.5 mg, 0.15 mmol) and DMAP (0.2 mg, 0.002 mmol). The reaction was stirred for 16h and concentrated under reduced pressure. The crude solid was dissolved in EtOAc (15 mL) and washed with saturated $NaHCO_3$ (1x15 mL) and H_2O (15 mL). The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure to afford the title compound.

[00762] Step 2: *tert*-butyl (((R)-1-(4-(4-((R)-4-(2-amino-2-methylpropanoyl)-2-methylpiperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)phenethyl)pyrrolidin-3-yl)methyl)carbamate. To a solution of (R)-4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)-2-methylpiperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)phenethyl 4-methylbenzenesulfonate (54 mg, 0.08mmol) in MeCN, was added (S)-*tert*-butyl (pyrrolidin-3-ylmethyl)carbamate (19 mg, 0.10 mmol) and K_2CO_3 (21 mg, 0.16 mmol). The reaction was heated to 70 °C for 16h, and the solvent was removed under reduced pressure. The crude solid was dissolved in $CHCl_3$, filtered and the filtrate was purified via flash chromatography ($CHCl_3$/MeOH) to afford the title compound.

[00763] Step 3: (R)-4-(2-amino-2-methylpropanoyl)-N-(1-(4-(2-((R)-3-(aminomethyl)pyrrolidin-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2-methylpiperazine-1-carboxamide hydrochloride salt. *tert*-Butyl (((R)-1-(4-(4-((R)-4-(2-amino-2-methylpropanoyl)-2-methylpiperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-

yl)phenethyl)pyrrolidin-3-yl)methyl)carbamate was treated with a solution of HCl/MeOH (10 mL) and stirred at rt for 4 h. The reaction mixture was concentrated under reduced pressure and the solid was triturated with Et_2O to afford the title compound. ^1H NMR (400 MHz, D_2O) δ 7.87 (d, 1H), 7.38 (d, 2H), 7.31 (d, 2H), 6.67 (d, 1H), 4.41 (s, 1H), 4.07 (d, 1H), 3.94 (d, 1H), 3.85–3.73 (m, 1H), 3.73–3.55 (m, 1H), 3.46 (d, 2H), 3.41–2.91 (m, 9H), 2.78 (m, 2H), 2.39–2.11 (m, 1H), 1.91-1.62 (m, 1H), 1.60 (s, 6H), 1.12 (s, 3H). LCMS [M+H] 525.3.

Compound 196



4-Amino-1-(4-(4-(4-(2-amino-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)phenethyl)-1-methylpiperidin-1-ium trifluoroacetate salt

Scheme C-17



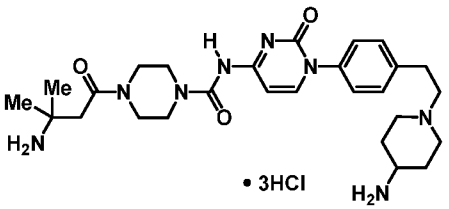
Reagents: 1) MeI, CH_3CN, rt, 4h 2) TFA, CH_2Cl_2, rt, 1.5h.

[00764] Step1: 4-((*tert*-butoxycarbonyl)amino)-1-(4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)phenethyl)-1-methylpiperidin-1-ium iodide. To a solution of *tert*-butyl (1-(4-((1-(4-(2-(4-((*tert*-butoxycarbonyl)amino)piperidin-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate (10 mg, 0.014 mmol) in CH_3CN (1 mL), was added MeI (4.4 µL, 0.070 mmol). The solution was stirred for 4 h at rt, forming a white precipitate. The solid was collected and triturated with EtOAc, to afford the title compound.

[00765] Step 2: 4-amino-1-(4-(4-(4-(2-amino-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)phenethyl)-1-methylpiperidin-1-ium trifluoroacetate salt. To a suspension of 4-((*tert*-butoxycarbonyl)amino)-1-(4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)phenethyl)-1-methylpiperidin-1-ium iodide (8 mg, 0.011 mmol) in DCM (0.5 mL) was added triflouroacetic acid (0.5 mL). The solution was stirred for 1.5h at rt, after which

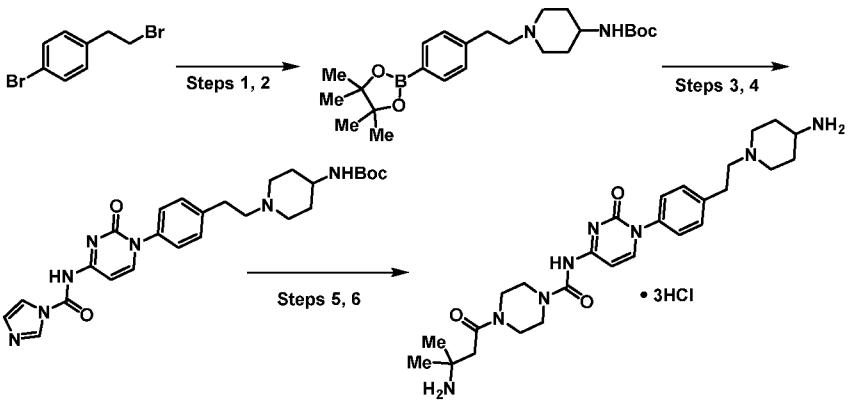
the reaction mixture was concentrated under reduced pressure. Purification with HPLC. ^{1}H NMR (400 MHz, D_2O) δ 8.10 (d, 1H), 7.49 (d, 2H), 7.44 (s, 2H), 6.77 (d, 1H), 3.88-3.64 (m, 10H), 3.63–3.42 (m, 3H), 3.32–3.12 (m, 5H), 2.38–2.08 (m, 4H), 2.06–1.88 (m, 2H), 1.70 (s, 6H). LCMS [M +H] 526.2.

Compound 197



4-(3-Amino-3-methylbutanoyl)-*N*-(1-(4-(2-(4-aminopiperidin-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

Scheme C-18



Reagents: Step 1) *tert*-butyl piperidin-4-ylcarbamate, K_2CO_3, CH_3CN, NaI, 70 °C, 4h 2) B_2pin_2 $Pd(dppf)_2Cl_2$, KOAc, 1,4-dioxane, 110°C 3) cytosine, TMEDA, $Cu(OAc)_2 \cdot H_2O$, MeOH:H_2O (4:1), rt, 24h 4) CDI, CH_2Cl_2, rt, 16h 5) *tert*-butyl (2-methyl-4-oxo-4-(piperazin-1-yl)butan-2-yl)carbamate, THF, reflux, 16h 6) MeOH, HCl, rt, 4h.

[00766] Step 1: *tert*-butyl (1-(4-bromophenethyl)piperidin-4-yl)carbamate. To a suspension of potassium carbonate (2.10 g, 15.2 mmol), sodium iodide (0.57 g, 3.8 mmol) and 4-(*N*-Boc-amino)piperidine (0.76 mg, 3.8 mmol) in dry CH_3CN (22 mL) at 70 °C under N_2 was added 1-bromo-4-(2-bromoethyl)benzene (1.0 g, 3.8 mmol) dropwise over 3 min. The reaction was stirred for 16h at 70°C, cooled and the solid was filtered. The filtrate was concentrated and purified by flash chromatography to afford the title compound.

[00767] Step 2: *tert*-butyl (1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenethyl)piperidin-4-yl)carbamate. An oven dried pressure flask was charged with *tert*-butyl (1-(4-bromophenethyl)piperidin-4-yl)carbamate (0.30 mg, 0.78 mmol), bis(pinacolato)diboron (0.24 g, 0.94 mmol), KOAc (0.22 g, 2.19 mmol), $Pd(dppf)_2Cl_2$ (0.13

mg, 0.02 mmol), and dry dioxane (10 mL). The reaction mixture was degassed and flushed with nitrogen (3x). The reaction was placed in a preheated oil bath at 110 °C and stirred for 16h. The mixture was cooled, concentrated under reduced pressure and $CHCl_3$ (10 mL) was added. The solution was washed with sat. aq. $NaHCO_3$ (30 mL) and the aqueous layer was extracted (2 x10 mL chloroform). The organic layers were combined, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography to afford the title compound.

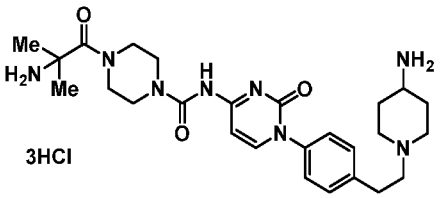
[00768] Step 3: *tert*-butyl (1-(4-(4-amino-2-oxopyrimidin-1(2*H*)-yl)phenethyl)piperidin-4-yl)carbamate. A mixture of cytosine (52.0 mg, 0.47 mmol) and *tert*-butyl (1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenethyl)piperidin-4-yl)carbamate (0.20 g, 0.47 mmol) were dissolved in a stirring solution of 4:1 MeOH:water (15 mL) open to air. After 30 minutes $Cu(OAc)_2 \cdot H_2O$ (93.0 mg, 0.47 mmol) and *N,N,N',N'*-tetramethylethylenediamine (64.0 mg, 0.55 mmol) were added and the solution was stirred for 12h. The methanol was evaporated under reduced pressure. Ice (20 g) was added and the mixture stirred for 30 min. The precipitate was collected by vacuum filtration to afford the title compound.

[00769] Step 4: *tert*-butyl (1-(4-(4-(1*H*-imidazole-1-carboxamido)-2-oxopyrimidin-1(2*H*)-yl)phenethyl)piperidin -4-yl)carbamate. An oven dried round bottom flask equipped with a stir bar, was charged with *tert*-butyl (1-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)phenethyl)piperidin-4-yl)carbamate (50 mg, 0.21 mmol) and CDI (33 mg, 0.21 mmol), and dry CH_2Cl_2 (10 mL) was added under nitrogen atmosphere. The reaction mixture was stirred for 16h at rt under N_2. The mixture was concentrated under reduced pressure to afford the title compound.

[00770] Step 5: *tert*-butyl (4-(4-((1-(4-(2-(4-((*tert*-butoxycarbonyl)amino)piperidin-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-4-oxobutan-2-yl)carbamate. To a stirring solution of *tert*-butyl (1-(4-(4-(1*H*-imidazole-1-carboxamido)-2-oxopyrimidin-1(2*H*)-yl)phenethyl)piperidin -4-yl)carbamate (0.21 mmol) in dry THF (6 mL), *tert*-butyl (2-methyl-4-oxo-4-(piperazin-1-yl)butan-2-yl)carbamate (51 mg, 0.18 mmol) dissolved in dry THF (2 mL) was added dropwise. The reaction mixture was stirred at reflux for 16h, after which the solvent was evaporated reduced pressure. The residue was dissolved in EtOAc and partitioned between EtOAc and water. The organic layer was washed with water (3x50 mL) and brine (15 mL), dried over Na_2SO_4, filtered and concentrated reduced pressure. Purification via flash chromatography afforded the title compound.

[00771] Step 6: 4-(3-amino-3-methylbutanoyl)-*N*-(1-(4-(2-(4-aminopiperidin-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt. *tert*-Butyl (4-(4-((1-(4-(2-(4-((*tert*-butoxycarbonyl)amino)piperidin-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-4-oxobutan-2-yl)carbamate (90 mg, 0.13 mmol) was dissolved in a solution of 2M methanolic HCl (10 mL). The reaction mixture was stirred for 4h and concentrated reduced pressure. The solid was triturated with diethyl ether and dried to afford the title compound. LCMS [M+H] 525.4.

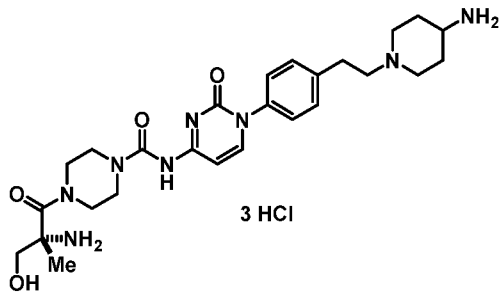
Compound 198



4-(2-Amino-2-methylpropanoyl)-*N*-(1-(4-(2-(4-aminopiperidin-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00772] Prepared in a similar fashion as Scheme C-18 from *tert*-butyl (1-(4-(4-(1H-imidazole-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)phenethyl)piperidin-4-yl)carbamate and *tert*-butyl (2-methyl-1-oxo-1-(piperazin-1-yl)propan-2-yl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 8.06–7.94 (m, 1H), 7.53 (d, 2H), 7.50–7.40 (m, 2H), 6.85 (d, 1H), 3.79 (d, 10H), 3.67–3.57 (m, 1H), 3.56–3.46 (m, 2H), 3.24 (d, 4H), 2.40 (d, 2H), 2.07-1.91 (m, 2H), 1.76 (d, 6H). LCMS [M+H] 511.5.

Compound 199

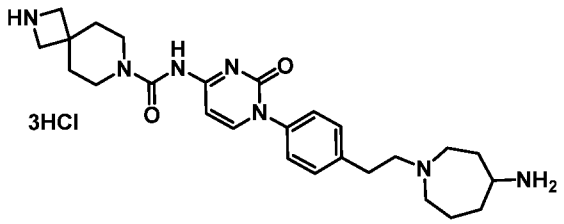


(R)-4-(2-Amino-3-hydroxy-2-methylpropanoyl)-N-(1-(4-(2-(4-aminopiperidin-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00773] Prepared in a similar fashion as Scheme C-18 from *tert*-butyl (1-(4-(4-(1H-imidazole-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)phenethyl)piperidin-4-yl)carbamate and

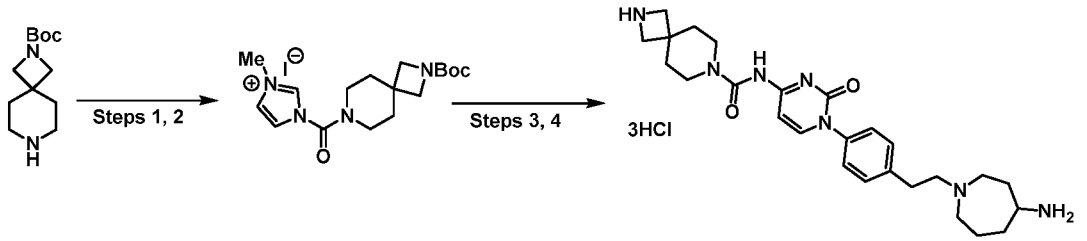
(2S,4R)-*tert*-butyl 2-(*tert*-butyl)-4-methyl-4-(piperazine-1-carbonyl)oxazolidine-3-carboxylate. ^{1}H NMR (400 MHz, D_2O) δ 8.12 (d, 1H), 7.53 (d, 2H), 7.47 (d, 2H), 6.82 (d, 1H), 4.17 (d, 1H), 3.92 (d, 1H), 3.85-3.70 (m, 10H) 3.66–3.54 (m, 1H), 3.54-3.46 (m, 2H), 3.26-3.15 (m, 4H), 2.39 (d, 2H), 2.06–1.91 (m, 2H), 1.70 (s, 3H). LCMS [M+H] 527.4.

Compound 192



N-(1-(4-(2-(4-Aminoazepan-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2,7-diazaspiro[3.5]nonane-7-carboxamide hydrochloride salt

Scheme C-19



Reagents: Step 1) CDI, CH_2Cl_2, rt, 2h 2) MeI, CH_3CN, rt, 16h 3) *tert*-butyl (1-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)phenethyl)azepan-4-yl)carbamate CH_3CN, 90 °C, 16h 4) 4M HCl in dioxane, rt, 4h.

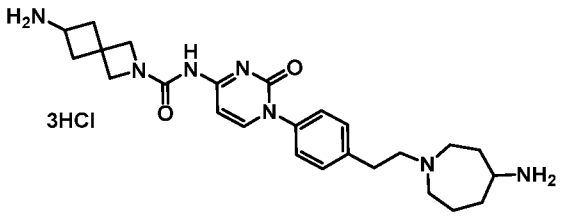
[00774] Step 1: *tert*-butyl 7-(1H-imidazole-1-carbonyl)-2,7-diazaspiro[3.5]nonane-2-carboxylate. To a stirred solution of *tert*-butyl 2,7-diazaspiro[3.5]nonane-2-carboxylate (0.2 g, 0.88 mmol) in CH_2Cl_2 (5 mL) was added CDI (0.172 g, 1.06 mmol), and the mixture was stirred at rt for 2h. It was poured into H_2O (50 mL) and extracted with CH_2Cl_2 (3×20 mL). The extracts were dried over Na_2SO_4, filtered and concentrated in vacuo to afford the title compound. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.98 (d, 1H), 7.42 (t, 1H), 7.02 (t, 1H), 3.65-3.55 (m, 4H), 3.45-3.35 (m, 4H), 1.75 (t, 4H), 1.37 (s, 9H). LCMS [M+H] 321.1.

[00775] Step 2: 1-(2-(*tert*-butoxycarbonyl)-2,7-diazaspiro[3.5]nonane-7-carbonyl)-3-methyl-1H-imidazol-3-ium iodide. To a stirred solution of *tert*-butyl 7-(1H-imidazole-1-carbonyl)-2,7-diazaspiro[3.5]nonane-2-carboxylate (0.28 g, 0.87 mmol) in CH_3CN (3 mL) was added MeI (0.74 g, 0.34 mL, 5.25 mmol). The mixture was stirred at rt for 16h concentrated in vacuo to afford the title compound. LCMS [M+H] 335.1.

[00776] Step 3: *tert*-butyl 7-((1-(4-(2-(4-((*tert*-butoxycarbonyl)amino)azepan-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)-2,7-diazaspiro[3.5]nonane-2-carboxylate. A mixture of *tert*-butyl (1-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)phenethyl)azepan-4-yl)carbamate (0.2 g, 0.46 mmol) and 1-(2-(*tert*-butoxycarbonyl)-2,7-diazaspiro[3.5]nonane-7-carbonyl)-3-methyl-1H-imidazol-3-ium iodide (0.26 g, 0.56 mmol) in CH_3CN (3 mL) was stirred at 90 °C for 16h. The mixture was concentrated in vacuo and the residue was purified by flash chromatography (CH_3OH/CH_2Cl_2) to afford the title compound. LCMS [M+H] 680.2.

[00777] Step 4: N-(1-(4-(2-(4-aminoazepan-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2,7-diazaspiro[3.5]nonane-7-carboxamide hydrochloride salt. A mixture of *tert*-butyl 7-((1-(4-(2-(4-((*tert*-butoxycarbonyl)amino)azepan-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)-2,7-diazaspiro[3.5]nonane-2-carboxylate (0.09 g, 0.13 mmol) and 4 M HCl in dioxane (5 mL, 20 mmol) in 1,4-dioxane (3 mL) was stirred at rt for 4h. It was concentrated in vacuo, triturated with diethyl ether (10 mL), and the residue was purified by prepHPLC to afford the title compound. ^1H NMR (400 MHz, D_2O) δ 7.74 (d, 1H), 7.34 (d, 2H), 7.27 (d, 2H), 6.67 (d, 1H), 3.83 (s, 4H), 3.59-3.55 (m, 1H), 3.43-3.37 (m, 7H), 3.05-3.07 (m, 2H), 2.18-2.07 (m, 2H), 1.97-1.87 (m, 3H), 1.98-1.89 (m, 2H), 1.82-1.79 (m, 4H), 1.70-1.55 (m, 2H). LCMS [M+H] 480.2.

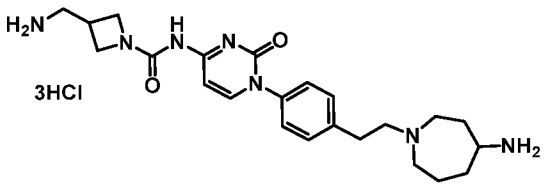
Compound 193



6-Amino-N-(1-(4-(2-(4-aminoazepan-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2-azaspiro[3.3]heptane-2-carboxamide hydrochloride salt

[00778] Prepared in a similar fashion as Scheme C-19 from *tert*-butyl (1-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)phenethyl)azepan-4-yl)carbamate and *tert*-butyl (2-azaspiro[3.3]heptan-6-yl)carbamate hydrochloride. LCMS [M+H] 466.2.

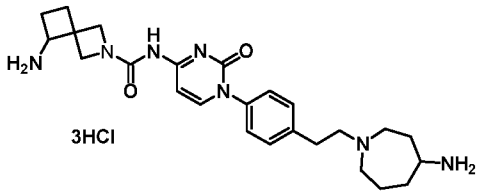
Compound 194



N-(1-(4-(2-(4-Aminoazepan-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-3-(aminomethyl)azetidine-1-carboxamide hydrochloride salt

[00779] Prepared in a similar fashion as Scheme C-19 from *tert*-butyl (1-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)phenethyl)azepan-4-yl)carbamate and *tert*-butyl (azetidin-3-ylmethyl)carbamate. LCMS [M+H] 440.4.

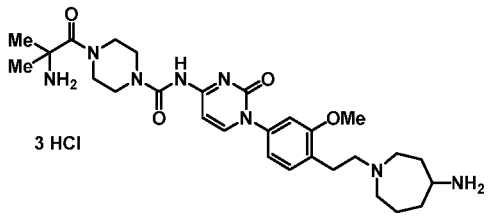
Compound 195



5-Amino-N-(1-(4-(2-(4-aminoazepan-1-yl)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2-azaspiro[3.3]heptane-2-carboxamide hydrochloride salt

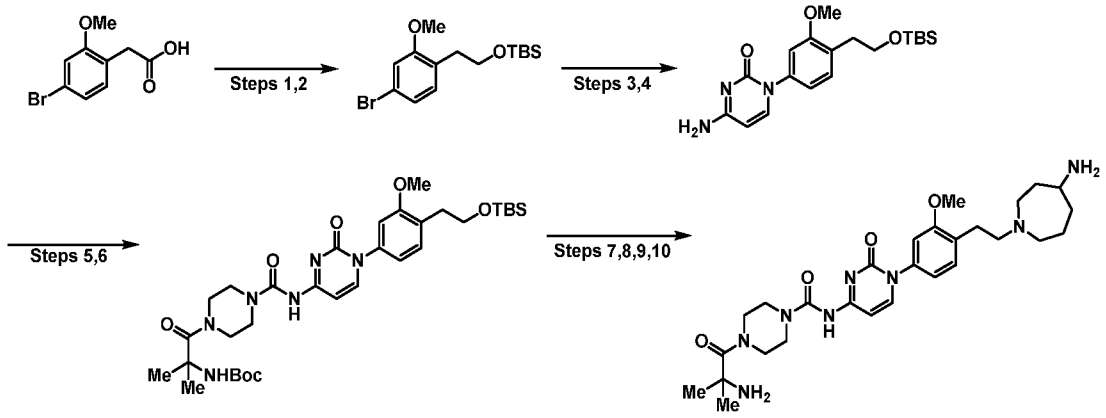
[00780] Prepared in a similar fashion as Scheme C-19 from *tert*-butyl (1-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)phenethyl)azepan-4-yl)carbamate and *tert*-butyl azepan-4-ylcarbamate and *tert*-butyl (2-azaspiro[3.3]heptan-5-yl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.84 (d, 1H), 7.34 (d, 2H), 7.27 (d, 2H), 6.99 (d, 1H), 4.05-3.96 (m, 4H), 3.79 (t, 1H), 3.58-3.55 (m, 2H), 3.41-3.37 (m, 4H), 3.28-3.11 (m, 2H), 3.05-3.01 (m, 2H), 2.18-2.04 (m, 4H), 1.95-1.83 (m, 3H), 1.70-1.55 (m, 2H). LCMS [M+H] 466.2.

Compound 371



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(4-aminoazepan-1-yl)ethyl)-3-methoxyphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

Scheme C-20



Reagents 1) BH_3THF, THF 0 °C 2) TBSCl, NEt_3, DMF 3) BuLi, THF, -78 °C $(iPrO)_3B$, 2N HCl 4) cytosine, TMEDA, $Cu(OAc)_2 \cdot H2O$, 4:1 MeOH:H_2O 5) CDI, CH_2Cl_2 6) *tert*-butyl (2-methyl-1-oxo-1-(piperazin-1-yl)propan-2-yl)carbamate , CH_3CN, 80°C 7) TBAF, THF 0°C to rt 8) DMP, 0.1% H_2O:CH_2Cl_2, 15 min 9) *tert*-butyl azepan-4-ylcarbamate, $NaH(OAc)_3$, DIPEA, DCE, 16h 10) HCl in MeOH, 4-8h.

[00781] Step 1: 2-(4-bromo-2-methoxyphenyl)ethan-1-ol. A solution of 2-(4-bromo-2-methoxyphenyl)acetic acid (2.00 g, 8.23 mmol) in THF (100 mL) was cooled to 0°C to this was added $BH_3 \cdot THF$ (16.46 ml, 16.46 mmol) drop wise over 30 min. The solution was stirred for 16h. The excess $BH_3 \cdot THF$ was quenched with MeOH (100 mL) and the solvent evaporated to afford the title compound.

[00782] Step 2: (4-bromo-2-methoxyphenethoxy)(*tert*-butyl)dimethylsilane. To a solution of 2-(4-bromo-2-methoxyphenyl)ethan-1-ol (8.23 mmol) in DMF (25 mL) was added NEt_3 (2.2 ml, 16.5 mmol) and TBSCl (1.48 g, 9.9 mmol). The reaction was stirred for 16h. The reaction mixture was partitioned between EtOAc (50 mL) and LiCl (50 mL). The organic layer was washed with LiCl (2x50 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give an oily residue, which was purified by column chromatography (Hexanes:EtOAc) to afford the title compound.

[00783] Step 3: diisopropyl (4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-methoxyphenyl)boronate. A stirred solution of (4-bromo-2-methoxyphenethoxy)(*tert*-butyl)dimethylsilane (1.2 g, 3.5 mmol) in THF (30 mL) was cooled to -78°C. 1M BuLi in Hexanes (3.5 mL, 8.8 mmol) was added dropwise over 30 min. and the temperature maintained below -60 °C. After 25 min triisopropyl borate (1.2 mL, 5.3 mmol) was added dropwise over 30 min. The reaction mixture was warmed to rt and stirred for 15 min. 2N HCl (20 mL) was added and the reaction was stirred for 30 min. The biphasic mixture was separated and the aq. layer washed with CH_2Cl_2 (2×50 mL). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure to afford the title compound.

[00784] Step 4: 4-amino-1-(4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-methoxyphenyl)pyrimidin-2(1H)-one. A suspension of cytosine (0.39 g, 3.5 mmol) and diisopropyl (4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-methoxyphenyl)boronate (3.5 mmol), in MeOH:H_2O (4:1, 40ml) was stirred at rt in open air for 30 min. TMEDA (0.67 ml, 3.7 mmol) and $Cu(OAc)_2 \cdot H_2O$ (0.69 g, 3.5 mmol) were added and the reaction was stirred in open air for 48h at rt. The reaction mixture was concentrated under reduced pressure, and cold H_2O (50 mL) was added. The solid was filtered and washed with H_2O (5x50 mL), Et_2O (3x30 mL) and H_2O (2×30 mL) to afford the title compound.

[00785] Step 5: N-(1-(4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-methoxyphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-1H-imidazole-1-carboxamide. A suspension of 4-amino-1-(4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-methoxyphenyl)pyrimidin-2(1H)-one (200 mg , 0.53 mmol) and 1,1'-carbonyldiimidazole (146 mg, 0.90 mmol) in CH_2Cl_2 (12 mL) was stirred at rt for 16h. The solvent was removed under reduced pressure to afford the title compound.

[00786] Step 6: *tert*-butyl (1-(4-((1-(4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-methoxyphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate. N-(1-(4-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-3-methoxyphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-1H-imidazole-1-carboxamide (0.81 mmol) and *tert*-butyl (2-methyl-1-oxo-1-(piperazin-1-yl)propan-2-yl)carbamate as prepared in scheme 1 (329 mg, 1.2 mmol) were dissolved in CH_3CN (30 mL) and heated to reflux for 2h. The reaction mixture was concentrated under reduced pressure and the solid was dissolved in EtOAc (25 mL) and washed with water (3x20 mL). The reaction mixture was purified by flash chromatography (Hexanes:EtOAc) to afford the title compound.

[00787] Step 7: *tert*-butyl (1-(4-((1-(4-(2-hydroxyethyl)-3-methoxyphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate. To a stirred solution of *tert*-butyl (1-(4-((1-(4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-methoxyphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate (300 mg, 0.45 mmol) in THF (30 mL) at 0 °C was added 2M TBAF in THF (1.0 mL) over of 20 min. The solution was stirred for 16h. The crude reaction mixture was concentrated under reduced pressure to give an oily residue, which was purified by column chromatography (CH_2Cl_2:MeOH) to afford the title compound.

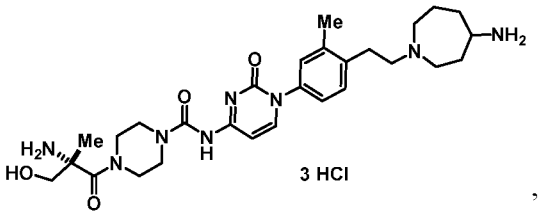
[00788] Step 8: *tert*-butyl (1-(4-((1-(3-methoxy-4-(2-oxoethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-

yl)carbamate. To a stirred solution of *tert*-butyl (1-(4-((1-(4-(2-hydroxyethyl)-3-methoxyphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate (45 mg, 0.08 mmol) in 0.1% H_2O:CH_2Cl_2 (20 mL) was added Dess-Martin periodinane (55 mg, 0.13 mmol). The solution was stirred for 15 min. The crude reaction mixture was dissolved in additional CH_2Cl_2 (50 mL) and washed with aq. $NaHCO_3$/$Na_2S_2O_3$ (1×50 mL). The aq. layer was extracted with CH_2Cl_2 (1×10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford the title compound.

[00789] Step 9: *tert*-butyl (1-(4-((1-(4-(2-(4-((*tert*-butoxycarbonyl)amino)azepan-1-yl)ethyl)-3-methoxyphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate. To a stirred solution *tert*-butyl (1-(4-((1-(3-methoxy-4-(2-oxoethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate (22 mg, 0.04 mmol) was added *tert*-butyl azepan-4-ylcarbamate (13 mg, 0.06 mmol) followed by $NaH(OAc)_3$ (17 mg, 0.08 mmol) and DIPEA (1 drop). The reaction was stirred for 16h. The reaction mixture was treated with 1N NaOH (10 mL) and extracted with CH_2Cl_2 (2×20 mL). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure to afford the title compound.

[00790] Step 10: 4-(2-amino-2-methylpropanoyl)-N-(1-(4-(2-(4-aminoazepan-1-yl)ethyl)-3-methoxyphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt. *tert*-Butyl (1-(4-((1-(4-(2-(4-((*tert*-butoxycarbonyl)amino)azepan-1-yl)ethyl)-3-methoxyphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate was dissolved in a solution of HCl/MeOH (50 mL) and stirred for 4h. The HCl/MeOH was evaporated and the crude solid was purified by RPHPLC (H_2O:CH_3CN:TFA) and concentrated under reduced pressure. Addition of HCl/MeOH (3x15 mL) and evaporation under reduced pressure afforded the title compound. ^{1}H NMR (500 MHz, D_2O) δ 8.01 (d, 1H), 7.41 (d, 1H), 7.12 (s, 1H), 7.03 (d, 1H), 6.82 (d, 1H), 3.88 (s, 3H), 3.84-3.70 (m, 8H), 3.62-3.53 (m, 3H), 3.48-3.38 (m, 3H), 3.32-3.20 (m, 1H), 3.14 (t, 2H), 2.41-2.20 (m, 3H), 2.22-1.98 (m, 2H), 1.89-1.75 (m, 1H), 1.73 (s, 6H). LCMS [M+H] 555.2.

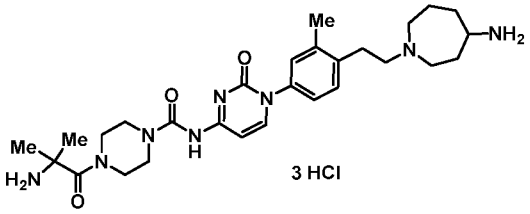
Compound 139



4-((S)-2-Amino-3-hydroxy-2-methylpropanoyl)-N-(1-(4-(2-(4-aminoazepan-1-yl)ethyl)-3-methylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00791] Prepared in a similar fashion as Scheme C-20 from 2-(4-bromo-2-methylphenyl)ethan-1-ol, 1-(4-((2R,4S)-3-(*tert*-butoxycarbonyl)-2-(*tert*-butyl)-4-methyloxazolidine-4-carbonyl)piperazine-1-carbonyl)-3-methyl-1H-imidazol-3-ium iodide, and *tert*-butyl azepan-4-ylcarbamate. ^{1}H NMR (400 MHz, D_2O) δ 8.00 (d, 1H), 7.38 (d, 1H), 7.30 (s, 1H), 7.25 (d, 1H), 6.78 (d, 1H), 4.13 (d, 1H), 3.87 (d, 1H), 3.76 (s, 2H), 3.71 (s, 7H), 3.58 (s, 2H), 3.39 (t, 3H), 3.32(s, 2H), 3.19–3.11 (m, 2H), 2.37 (s, 3H), 2.34–2.20 (m, 2H), 2.19–1.96 (m, 2H), 1.91–1.68 (m, 1H), 1.65 (s, 3H). LCMS [M+H] 555.3.

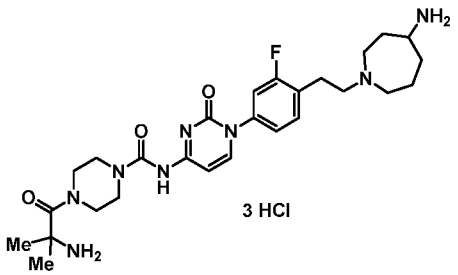
Compound 140



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(4-aminoazepan-1-yl)ethyl)-3-methylphenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00792] Prepared in a similar fashion as Scheme C-20 from *tert*-butyl (2-methyl-1-(4-((1-(3-methyl-4-(2-oxoethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-1-oxopropan-2-yl)carbamate and *tert*-butyl azepan-4-ylcarbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.98 (d, 1H), 7.38 (d, 1H), 7.30 (s, 1H), 7.25 (d, 1H), 6.78 (d, 1H), 3.75, (s, 2H), 3.71 (s, 8H), 3.58 (s, 2H), 3.41 (t, 2H), 3.31 (s, 2H), 3.15 (t, 2H), 2.37 (s, 3H), 2.36–2.19, (m, 2H), 2.18-1.98 (m, 2H), 1.90-1.73 (m, 1H), 1.70 (s, 6H). LCMS [M+H] 539.4.

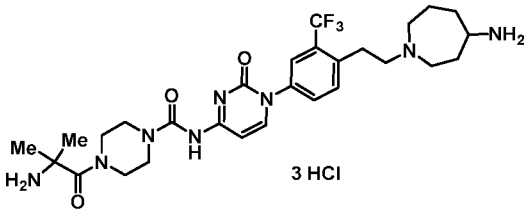
Compound 141



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(4-aminoazepan-1-yl)ethyl)-3-fluorophenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00793] Prepared in a similar fashion as Scheme C-20 from *tert*-butyl (1-(4-((1-(3-fluoro-4-(2-oxoethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and *tert*-butyl azepan-4-ylcarbamate. ^{1}H NMR (500 MHz, D_2O) δ 8.26-8.22 (m, 1H), 7.51 (t, 1H), 7.35-7.24 (m, 2H), 6.73 (d, 1H), 3.79-3.66 (m, 8H), 3.59-3.39 (m, 5H), 3.39-3.33 (m, 1H), 3.22-3.12 (m, 3H), 2.38-1.70 (m, 6H), 1.67 (s, 6H). LCMS [M+H] 543.3.

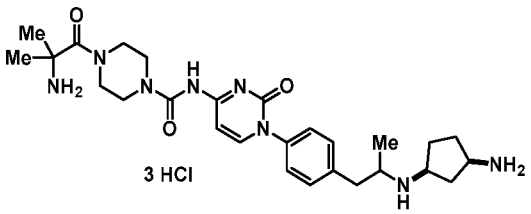
Compound 142



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(4-aminoazepan-1-yl)ethyl)-3-(trifluoromethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

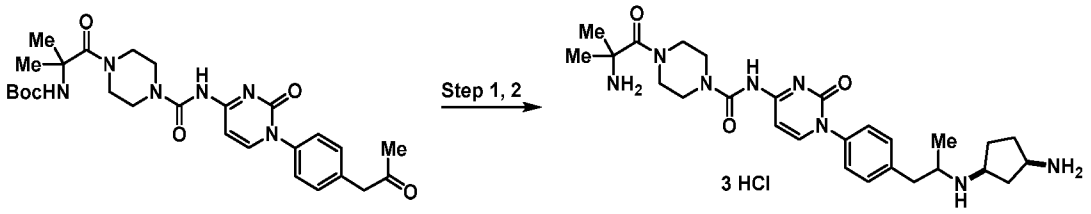
[00794] Prepared in a similar fashion as Scheme C-20 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxoethyl)-3-(trifluoromethyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl azepan-4-ylcarbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.90 (d, 1H), 7.85 (d, 1H), 7.72–7.60 (m, 2H), 6.82 (d, 1H), 3.74 (s, 4H), 3.69 (s, 6H), 3.63–3.52 (m, 4H), 3.51–3.41 (m, 2H), 3.36–3.26 (m, 2H), 2.41–2.20 (m, 2H), 2.18–1.92 (m, 2H), 1.91–1.72 (m, 1H), 1.70 (s, 6H). LCMS [M+H] 593.2.

Compound 150



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(((1S,3R)-3-aminocyclopentyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

Scheme C-21

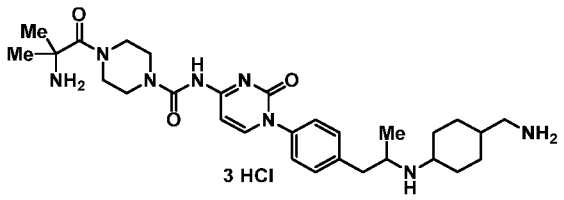


Reagents: 1) *tert*-butyl ((1R,3S)-3-aminocyclopentyl)carbamate, $NaBH_3CN$, 4 Å ms, MeOH, rt, 16h 2)HCl in dioxane, dioxane, rt, 4h.

[00795] Step 1: *tert*-butyl (1-(4-((1-(4-(2-(((1S,3R)-3-((*tert*-butoxycarbonyl)amino)cyclopentyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate. To a stirred solution of *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxopropyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate (0.45g, 0.74 mmol) and *tert*-butyl ((1R,3S)-3-aminocyclopentyl)carbamate (177 mg, 0.88 mmol) in methanol (10 mL) were added activated 4Å ms (3.0 g) and $NaBH_3CN$ (0.105 g, 1.66 mmol) at 0 °C under N_2 atmosphere. The reaction mixture was stirred at rt for 24 h. The resulting reaction mixture was concentrated under reduced pressure and purified by flash chromatography ($MeOH/CH_2Cl_2$) to afford the title compound (0.36 g, 60%) as a pale yellow solid. LCMS [M+H] 725.2.

[00796] Step 10: 4-(2-amino-2-methylpropanoyl)-N-(1-(4-(2-(((1S,3R)-3-aminocyclopentyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt. To a stirred solution of *tert*-butyl (1-(4-((1-(4-(2-(((1S,3R)-3-((*tert*-butoxycarbonyl)amino)cyclopentyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate (0.09 g, 0.12 mmol) in 1,4-dioxane (3 mL) was added 4 M HCl in dioxane (5 ml). The mixture was stirred at rt for 4h concentrated under reduced pressure and triturated with diethyl ether (10 mL). The resulting crude material was purified by semi-preparative HPLC to afford the title compound. ^1H NMR (400 MHz, D_2O) δ 7.89 (d, 1H), 7.31-7.25 (m, 4H), 6.62 (d, 1H), 3.76-3.72 (m, 1H), 3.58-3.49 (m, 10H), 3.12-3.07 (m, 1H), 2.75-2.70 (m, 1H), 2.53-2.50 (m, 1H), 2.09-2.01 (m, 2H), 1.76-1.72 (m, 2H), 1.64-1.58 (m, 1H), 1.53 (s, 6H), 1.09 (d, 3H). LCMS [M+H] 525.2.

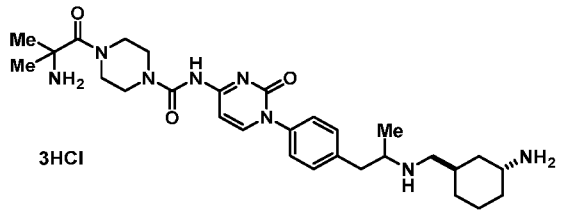
Compound 152



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-((4-(aminomethyl)cyclohexyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00797] Prepared in a similar fashion as Scheme C-21 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxopropyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl ((4-aminocyclohexyl)methyl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.72 (d, 1H), 7.34-7.27 (m, 4H), 6.71 (d, 1H), 3.62-3.51 (m, 8H), 3.38-3.34 (m, 1H), 3.22-3.10 (m, 2H), 3.95-2.85 (m, 2H), 2.76-2.22 (m, 2H), 2.10-2.00 (m, 1H), 1.95-1.75 (m, 3H), 1.59 (s, 6H), 1.55-1.45 (m, 1H), 1.35-1.25 (m, 1H), 1.22 (t, 3H), 1.05-0.90 (m, 2H). LCMS [M+H] 553.3.

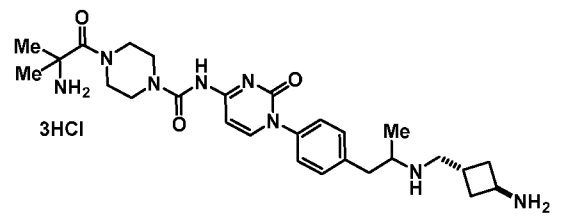
Compound 155



***trans*-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(((3-aminocyclohexyl)methyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt**

[00798] Prepared in a similar fashion as Scheme C-21from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxopropyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.77 (d, 1H), 7.33-7.27 (m, 4H), 6.68 (d, 1H), 3.70-3.40 (m, 8H), 3.40-3.30 (m, 2H), 31.7-3.10 (m, 1H), 2.80-2.65 (m, 2H), 2.10-2.01 (m, 1H), 1.75-1.41 (m, 13H), 1.26-1.19 (m, 2H), 1.12 (d, 3H). LCMS [M+H] 553.3.

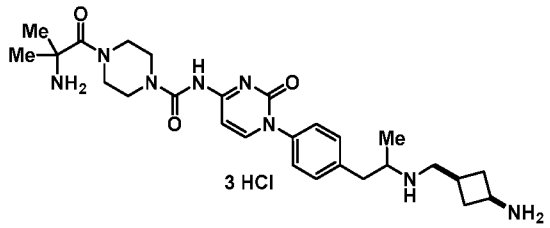
Compound 156



trans-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(((3-aminocyclobutyl)methyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt.

[00799] Prepared in a similar fashion as Scheme C-21 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxopropyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate. ^{1}H NMR (D_2O, 400 MHz) δ 7.83 (d, 1H), 7.83-7.29 (m, 4H), 6.75-6.70 (br s, 1H), 3.82-3.79 (m, 1H), 3.63-3.48 (m, 8H), 3.24-3.10 (m, 3H), 2.79-2.55 (m, 3H), 2.25-2.33 (m, 2H), 2.22-2.17 (m, 2H), 1.58 (s, 6H), 1.13 (d, 3H). LCMS[(M+2H)/2] 263.1.

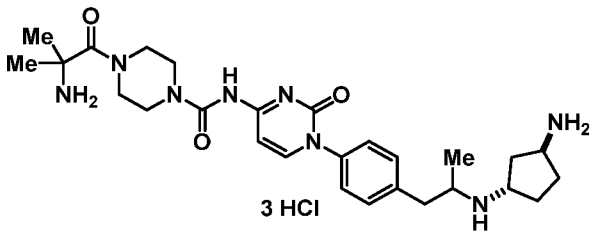
Compound 159



cis-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(((3-aminocyclobutyl)methyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00800] Prepared in a similar fashion as Scheme C-21 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxopropyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.80 (d, 1H), 7.36-7.30 (m, 4H), 6.72 (d, 1H), 3.68-3.48 (m, 10H), 3.15-3.11 (m, 3H), 2.89-2.72 (m, 1H), 2.50-2.39 (m, 3H), 1.87-1.84 (m, 2H), 1.59 (s, 6H), 1.14 (d, 3H). LCMS [(M+2H)/2] 263.1.

Compound 162

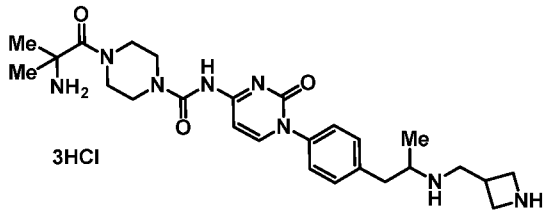


4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(((1S,3S)-3-aminocyclopentyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt.

[00801] Prepared in a similar fashion as Scheme C-21 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxopropyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl ((1S,3S)-3-aminocyclopentyl)carbamate. ^{1}H NMR

(D_2O, 400 MHz) δ 7.76 (d, 1H), 7.34-7.27 (m, 4H), 6.79 (d, 1H), 3.93-3.88 (m, 1H), 3.79-3.71 (m, 2H), 3.68-3.51 (m, 8H), 3.16-3.10 (m, 1H), 2.80-2.71 (m, 1H), 2.25-2.23 (m, 2H), 2.11 (t, 2H), 1.67-1.52 (m, 8H), 1.14-1.12 (m, 3H). LCMS [M+H] 525.4

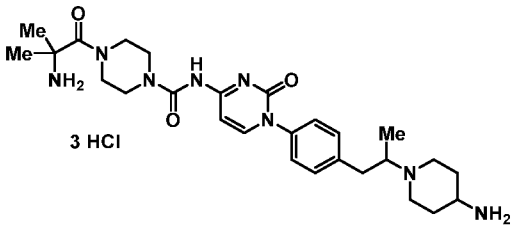
Compound 165



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-((azetidin-3-ylmethyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride.

[00802] Prepared in a similar fashion as Scheme C-21 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxopropyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl 3-(aminomethyl)azetidine-1-carboxylate. ^{1}H NMR (400 MHz, D_2O): δ 7.86 (d, 1H), 7.35-7.29 (m, 4H), 6.68 (d, 1H), 4.15-4.11 (m, 2H), 3.95-3.89 (m, 2H), 3.69-3.48 (m, 9H), 3.41-3.21 (m, 4H), 2.79-2.73 (m, 1H), 1.58 (s, 6H), 1.13 (d, 3H). LCMS [M+2H]/2 256.1.

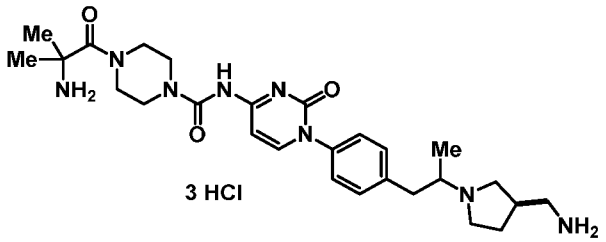
Compound 169



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(4-aminopiperidin-1-yl)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00803] Prepared in a similar fashion as Scheme C-21 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxopropyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and 4-Boc amino piperidine.. ^{1}H NMR (400 MHz, D_2O) δ 7.96 (d, 1H), 7.50 (d, 2H), 7.46 (d, 2H), 6.85 (d, 1H), 3.84-3.67(m, 11H), 3.67-3.55 (m, 1H), 3.44–3.31 (m, 3H), 3.04–2.91 (m, 1H), 2.44 (d, 2H), 2.15–1.97 (m, 2H), 1.75 (s, 6H), 1.39–1.15 (m, 3H). LCMS [M+H] 525.3.

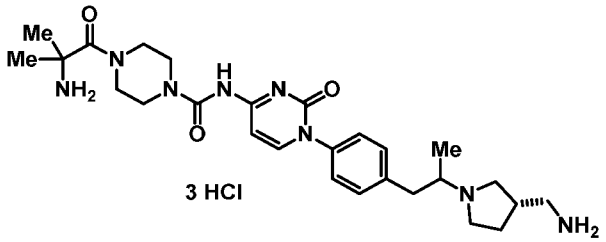
Compound 170



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-((R)-3-(aminomethyl)pyrrolidin-1-yl)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00804] Prepared in a similar fashion as Scheme C-21 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxopropyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl (S)-(pyrrolidin-3-ylmethyl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.95 (d, 1H), 7.44 (d, 2H), 7.40 (d, 2H), 6.78 (d, 1H), 3.97–3.55 (m, 9H), 3.51-3.39 (m, 1H), 3.38-3.25 (m, 2H), 3.27-2.96 (m, 3H), 2.93–2.64 (m, 3H), 2.49-2.26 (m, 1H), 1.99–1.71 (m, 1H), 1.68 (d, 6H), 1.24 (d, 3H). LCMS [M+H] 525.3.

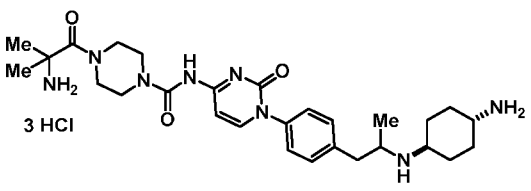
Compound 200



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-((S)-3-(aminomethyl)pyrrolidin-1-yl)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00805] Prepared in a similar fashion as Scheme C-21 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxopropyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl (R)-(pyrrolidin-3-ylmethyl)carbamate. ^{1}H NMR (500 MHz, D_2O) δ 7.96 (d, 1H), 7.57 (d, 2H), 7.48 (d, 2H), 6.84 (d, 1H), 3.82-3.69 (m, 9H), 3.58-3.43 (m, 1H), 3.43-3.30 (m, 2H), 3.30-3.00 (m, 3H), 2.99-2.68 (m, 3H), 2.71-2.59 (m, 1H), 2.50-2.29 (m, 1H), 2.05-1.76 (m, 1H), 1.73 (s, 6H), 1.30 (d, 3H). LCMS [M+H] 525.3.

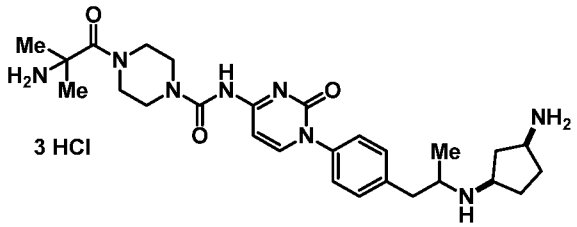
Compound 171



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-((*trans*-4-aminocyclohexyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00806] Prepared in a similar fashion as Scheme C-21 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxopropyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and N-Boc-*trans*-1,4-cyclohexanediaminet. ^{1}H NMR (400 MHz, D_2O) δ 7.89 (d, 1H), 7.48 (s, 2H), 7.45 (d, 2H), 6.86 (d, 1H), 3.78 (s, 4H), 3.74 (s, 5H), 3.39 (s, 1H), 3.26 (s, 2H), 2.91 (s, 1H), 2.31–2.16 (m, 4H), 1.75 (s, 6H), 1.65–1.50 (m, 4H), 1.29 (d, 3H). LCMS [M+H] 539.3.

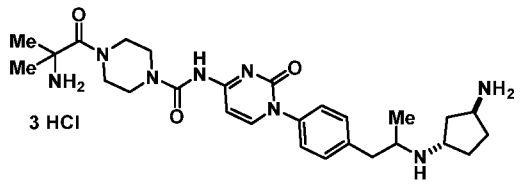
Compound 172



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(((1R,3S)-3-aminocyclopentyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00807] Prepared in a similar fashion as Scheme C-21 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxopropyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl ((1R,3S)-3-aminocyclopentyl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.95 (d, 1H), 7.49 (s, 2H), 7.46 (d, 2H), 6.85 (d, 1H), 3.94 (s, 1H), 3.79 (s, 4H), 3.74 (s, 6H), 3.34–3.23 (m, 1H), 3.04–2.88 (m, 1H), 2.80–2.66 (m, 1H), 2.34–2.17 (m, 2H), 1.99–1.76 (m, 3H), 1.75 (s, 6H), 1.30 (d, 3H). LCMS [M+H] 525.4.

Compound 173

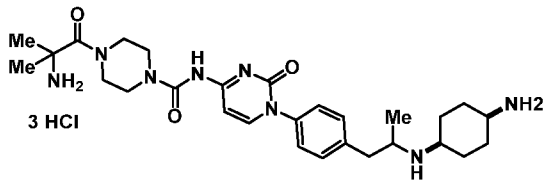


4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(((1S,3S)-3-aminocyclopentyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamidehydrochloride salt.

[00808] Prepared in a similar fashion as Scheme C-21 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxopropyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-

yl)propan-2-yl)carbamate and *tert*-butyl ((1R,3S)-3-aminocyclopentyl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 7.92 (d, 1H), 7.53–7.43 (m, 4H), 6.86 (d, 1H), 4.13–3.99 (m, 1H), 3.95–3.88 (m, 1H), 3.78 (s, 3H), 3.73 (s, 6H), 3.35–3.23 (m, 1H), 2.97–2.87 (m, 1H), 2.40 (s, 2H), 2.28 (t, 2H), 1.79 (s, 2H), 1.75 (s, 6H), 1.29 (d, 3H). LCMS [M+H] 525.3.

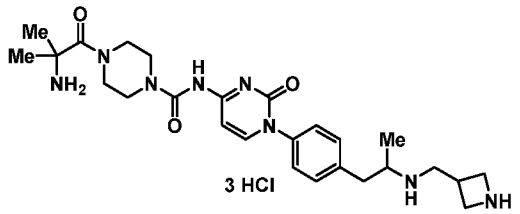
Compound 174



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-((*cis*-4-aminocyclohexyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt.

[00809] Prepared in a similar fashion as Scheme C-21 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxopropyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and N-Boc-*cis*-1,4-cyclohexanediamine. ^{1}H NMR (400 MHz, D_2O) δ 7.98 (d 1H), 7.51 (d, 2H), 7.46 (d, 2H), 6.85 (d, 1H), 3.80 (s, 4H), 3.75 (s, 5H), 3.63–3.50 (m, 2H), 3.35–3.29 (m, 1H), 2.91 (t, 1H), 2.08 (s, 2H), 1.97 (s, 4H), 1.86–1.75 (m, 2H), 1.75 (s, 6H), 1.29 (d, 3H). LCMS [M+H] 539.3.

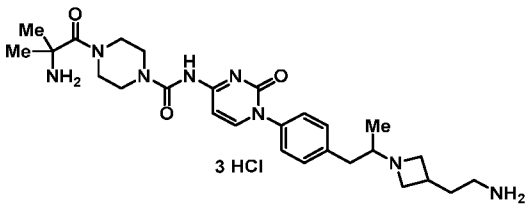
Compound 346



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-((azetidin-3-ylmethyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00810] Prepared in a similar fashion as Scheme C-21 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxopropyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl 3-(aminomethyl)azetidine-1-carboxylate. ^{1}H NMR (400 MHz, D_2O) δ 8.11 (d, 1H), 7.48 (s, 4H), 6.81 (d, 1H), 4.28 (s, 2H), 4.07 (s, 2H), 3.79 (s, 3H), 3.75 (s, 5H), 3.66 (s, 1H), 3.58–3.43 (m, 2H), 3.43–3.33 (m, 1H), 3.28 (d, 1H), 2.91 (t, 1H), 1.74 (d, 6H), 1.28 (d, 3H). LCMS [M+H] 511.2.

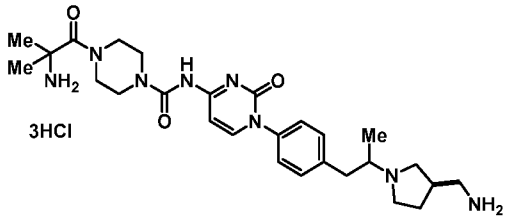
Compound 347



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(3-(2-aminoethyl)azetidin-1-yl)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00811] Prepared in a similar fashion as Scheme C-21 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxopropyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl (2-(azetidin-3-yl)ethyl)carbamate. ^{1}H NMR (400 MHz, D2O) δ 7.96 (d, 1H), 7.53–7.39 (m, 4H), 6.85 (d, 1H), 4.36–4.18 (m, 2H), 4.07–3.84 (m, 2H), 3.79 (br. s, 3H), 3.73 (br. s, 5H), 3.05–2.89 (m, 2H), 2.84 (s, 2H), 2.16–1.93 (m, 2H), 1.74 (d, 6H), 1.28 (t 2H) 1.21 (d, 3H). LCMS [M+H] 525.3.

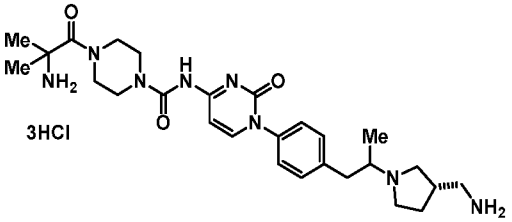
Compound 378



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-((R)-3-(aminomethyl)pyrrolidin-1-yl)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00812] Prepared in a similar fashion as Scheme C-21 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxopropyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl (S)-(pyrrolidin-3-ylmethyl)carbamate. LCMS [M+H] 525.4.

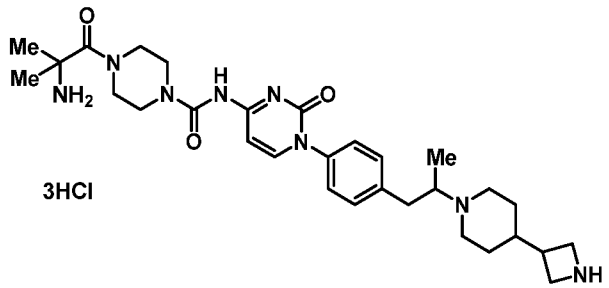
Compound 382



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-((R)-3-(aminomethyl)pyrrolidin-1-yl)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00813] Prepared in a similar fashion as Scheme C-21 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxopropyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl (R)-(pyrrolidin-3-ylmethyl)carbamate. LCMS [M+H] 525.3.

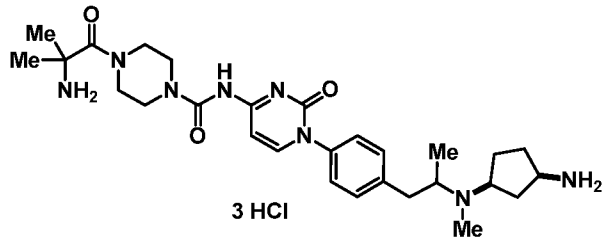
Compound 379



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(4-(azetidin-3-yl)piperidin-1-yl)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00814] Prepared in a similar fashion as Scheme C-21 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxopropyl)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl 3-(piperidin-4-yl)azetidine-1-carboxylate. LCMS [M+H] 565.4.

Compound 149



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(((1S,3R)-3-aminocyclopentyl)(methyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

Scheme C-22

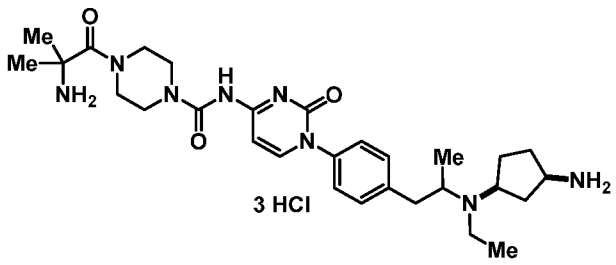


Reagents: 1) formaldehyde (37%), $NaCNBH_3$, 4 Å ms, MeOH, rt, 16h 2) HCl in dioxane, dioxane, rt, 3h.

[00815] Step 1: *tert*-butyl (1-(4-((1-(4-(2-(((1S,3R)-3-((*tert*-butoxycarbonyl)amino)cyclopentyl)(methyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate. To a stirred solution of *tert*-butyl (1-(4-((1-(4-(2-(((1S,3R)-3-((*tert*-butoxycarbonyl)amino)cyclopentyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate (0.110 g, 0.15 mmol) and formaldehyde (37% in water, 0.12 ml, 1.51 mmol) in MeOH (3.0 ml) at 0 °C were added activated 4Å molecular sieves (0.80 g) and $NaCNBH_3$ (0.019 g, 0.30 mmol), and the mixture was stirred at rt for 16 h. The resulting reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography (MeOH:CH_2Cl_2) to afford the title compound. LCMS [(M+2H-Boc)/2] 320.0.

[00816] Step 2: 4-(2-amino-2-methylpropanoyl)-N-(1-(4-(2-(((1S,3R)-3-aminocyclopentyl)(methyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt. To a stirred solution of *tert*-butyl (1-(4-((1-(4-(2-(((1S,3R)-3-((*tert*-butoxycarbonyl)amino)cyclopentyl)(methyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate (0.09 g, 0.12 mmol) in 1,4-dioxane (3 mL) was added 4 MHCl in dioxane (5 mL). The mixture was stirred at rt for 3h, concentrated under reduced pressure and triturated by diethyl ether (10 mL). The resulting crude material was purified by PrepHPLC to afford the title compound. ^1H NMR (400 MHz, D_2O, 80°C) mixture of rotamers, δ 7.40-8.39 (m, 1H), 8.05-8.01 (m, 4H), 7.33-7.30 (m, 1H), 4.50-4.27 (m, 12H), 4.05-4.01 (m, 1H), 3.83-3.81 (m, 1H), 3.53-3.46 (m, 4H), 3.30-3.23 (m, 2H), 2.87-2.79 (m, 3H), 2.61-2.49 (m, 4H), 2.31-2.29 (m, 6H), 1.87-1.84 (m, 3H). LCMS [M+H] 539.4.

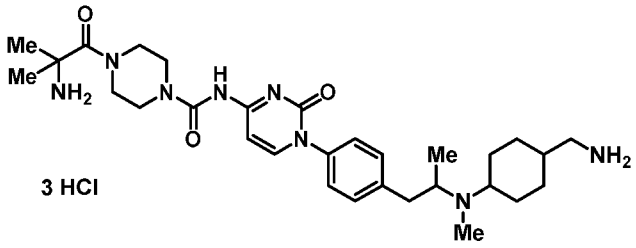
Compound 151



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(((1S,3R)-3-aminocyclopentyl)(ethyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00817] Prepared in a similar fashion as Scheme C-22 from *tert*-butyl (1-(4-((1-(4-(2-(((1S,3R)-3-((*tert*-butoxycarbonyl)amino)cyclopentyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and acetaldehyde. ^{1}H NMR (400 MHz, D_2O) mixture of rotamers, δ 7.77 (d, 1H), 7.33-7.27 (m, 4H), 6.69 (d, 1H), 3.97-3.50 (m, 12H), 3.46 -3.39 (m, 2H), 3.22-3.11 (m, 3H), 2.95-2.75 (m, 2H), 2.68-2.50 (m, 2H), 2.20-1.70 (m, 6H), 1.57 (s, 6H), 1.31-1.26 (m, 3H), 1.17-1.11 (m, 3H). LCMS [M+H] 553.1.

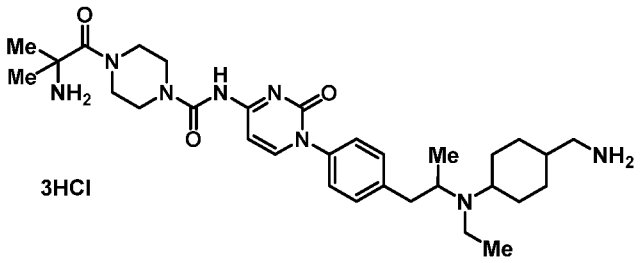
Compound 153



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-((4-(aminomethyl)cyclohexyl)(methyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00818] Prepared in a similar fashion as Scheme C-22 from *tert*-butyl (1-(4-((1-(4-(2-((4-(((*tert*-butoxycarbonyl)amino)methyl)cyclohexyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and formalin. ^{1}H NMR (400 MHz, D_2O + 1 drop TFA) mixture of rotamers, δ 8.03 (d, 1H), 7.40-7.30 (m, 3H), 7.08-7.23 (m, 1H), 6.64 (d, 1H), 3.81-3.50 (m, 9H), 3.34-3.08 (m,3H), 2.92-2.56 (m, 6H), 2.20-1.81 (m,5H), 1.58-1.41 (m, 9H) 1.26-1.00 (m, 5H). LCMS [M+H] 567.3.

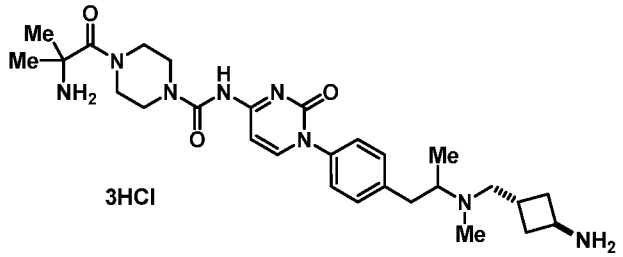
Compound 154



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-((4-(aminomethyl)cyclohexyl)(ethyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00819] Prepared in a similar fashion as Scheme C-22 from *tert*-butyl (1-(4-((1-(4-(2-((4-(((*tert*-butoxycarbonyl)amino)methyl)cyclohexyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and acetaldehyde. ^{1}H NMR (400 MHz, D_2O) mixture of rotamers, δ 7.74 (d, 1H), 7.34-7.27 (m, 4H), 6.70 (d, 2H), 3.85-3.75 (m, 2H), 3.65-3.51 (m, 7H), 3.40-3.10 (m, 5H), 2.95-2.72 (m, 4H), 2.15-1.61 (m, 6H), 1.60-1.41 (m, 8H), 1.27-1.24 (m, 3H), 1.18-1.04 (m, 5H). LCMS [M+H] 581.2.

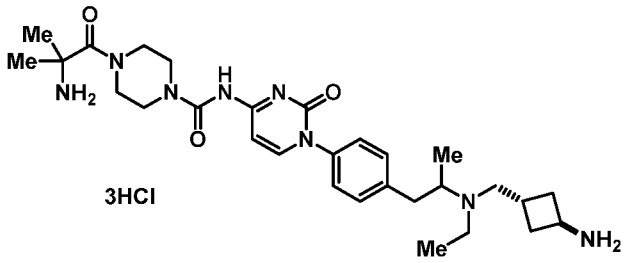
Compound 157



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(((*trans*-3-aminocyclobutyl)methyl)(methyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00820] Prepared in a similar fashion as Scheme C-22 from *tert*-butyl (1-(4-((1-(4-(2-(((*trans*-3-((*tert*-butoxycarbonyl)amino)cyclobutyl)methyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and formalin. ^{1}H NMR (D_2O, 400 MHz) mixture of rotamers, δ 7.77 (d, 1H), 7.35-7.28 (m, 4H), 6.70 (d, 1H), 3.85-3.75 (m, 1H), 3.65-3.55 (m, 8H), 3.45-3.34 (m, 2H), 3.23-3.10 (m, 2H), 2.84 (t, 2H), 2.71 (d, 3H), 2.32-2.20 (m, 4H), 1.58 (s, 6H), 1.12 (t, 3H). LCMS [(M+2H)/2] 270.2.

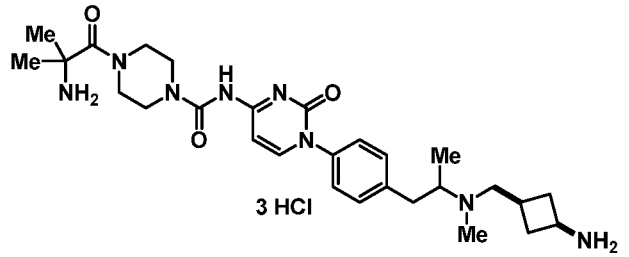
Compound 158



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(((*trans*-3-aminocyclobutyl)methyl)(ethyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00821] Prepared in a similar fashion as Scheme C-22 from *tert*-butyl (1-(4-((1-(4-(2-(((*trans*-3-((*tert*-butoxycarbonyl)amino)cyclobutyl)methyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and acetaldehyde. ^{1}H NMR (D_2O, 400 MHz) mixture of rotamers, δ 7.82 (d, 1H), 7.35-7.28 (m, 4H), 6.72 (br s, 1H), 3.78-87 (m, 1H), 3.76–3.52 (m, 9H), 3.48–3.10 (m, 7H), 2.88–2.79 (m, 2H), 2.32–2.20 (m, 4H), 1.55 (s, 6H), 1.25–1.17 (m, 3H), 1.14-1.09 (m, 3H). LCMS [(M+2H)/2] 277.2.

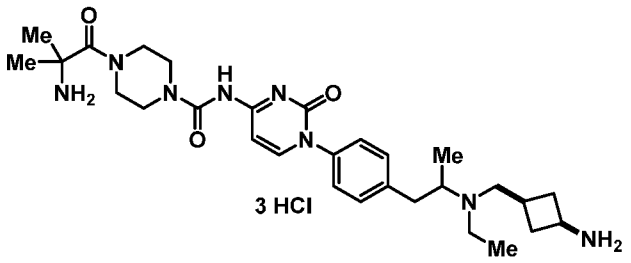
Compound 160



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(((*cis*-3-aminocyclobutyl)methyl)(methyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00822] Prepared in a similar fashion as Scheme C-22 from *tert*-butyl (1-(4-((1-(4-(2-(((*cis*-3-((*tert*-butoxycarbonyl)amino)cyclobutyl)methyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and formalin. ^{1}H NMR (400 MHz, D_2O, 80 °C) mixture of rotamers, δ 8.42 (d, 1H), 8.07-8.02 (m, 4H), 7.34 (d, 1H), 4.66-4.28 (m, 12H), 3.85-3.95 (m, 3H), 3.57-3.51 (m, 1H), 3.44 (s, 3H), 3.28-3.14 (m, 3H), 2.63-2.61 (m, 2H), 2.32 (s, 6H) 1.87 (d, 3H). LCMS [M+H] 539.2.

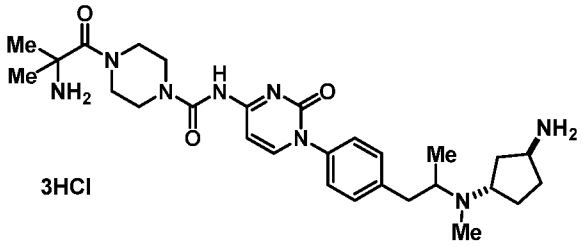
Compound 161



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(((*cis*-3-aminocyclobutyl)methyl)(ethyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00823] Prepared in a similar fashion as Scheme C-22 from *tert*-butyl (1-(4-((1-(4-(2-(((*cis*-3-((*tert*-butoxycarbonyl)amino)cyclobutyl)methyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and acetaldehyde. ^{1}H NMR (400 MHz, D_2O, 80 °C) mixture of rotamers , δ 8.38 (d, 1H), 8.12-7.95 (m, 4H), 7.31 (d, 1H), 4.40-4.27 (m, 11H), 3.95-3.75 (m, 4H), 3.58-3.48 (m, 1H), 3.23-3.16 (m, 3H), 2.65-2.55 (m, 2H), 2.30 (s, 6H), 1.92-1.99 (m, 3H), 1.84 (d, 3H). LCMS [M+H] 553.3.

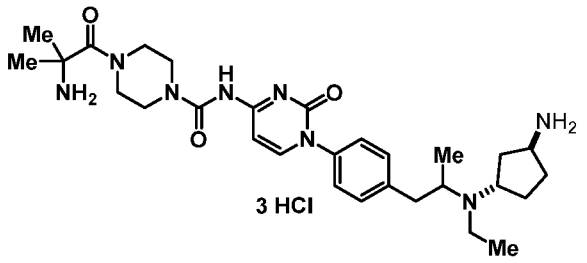
Compound 163



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(((1S,3S)-3-aminocyclopentyl)(methyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00824] Prepared in a similar fashion as Scheme C-22 from *tert*-butyl (1-(4-((1-(4-(2-(((1S,3S)-3-((*tert*-butoxycarbonyl)amino)cyclopentyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and formalin. LCMS [M+H] 539.6.

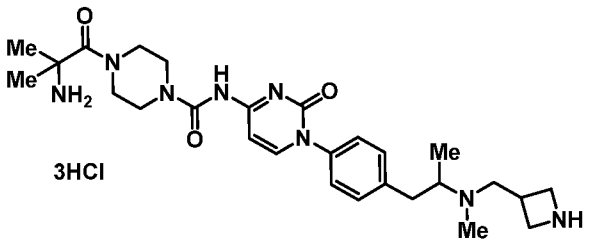
Compound 164



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(((1S,3S)-3-aminocyclopentyl)(ethyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00825] Prepared in a similar fashion as Scheme C-22 from *tert*-butyl (1-(4-((1-(4-(2-(((1S,3S)-3-((*tert*-butoxycarbonyl)amino)cyclopentyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and acetaldehyde. LCMS [(M+2H)/2] 277.2.

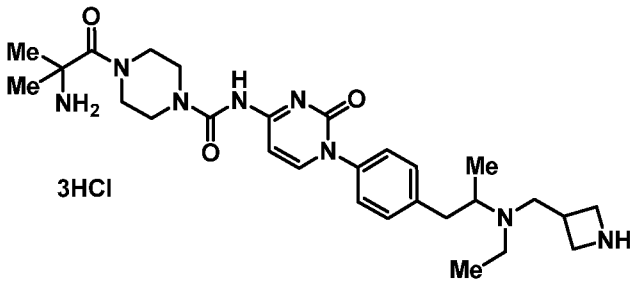
Compound 166



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-((azetidin-3-ylmethyl)(methyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00826] Prepared in a similar fashion as Scheme C-22 from *tert*-butyl 3-(((1-(4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)phenyl)propan-2-yl)amino)methyl)azetidine-1-carboxylate and formalin. ^{1}H NMR (400 MHz, D_2O) mixture of rotamers, δ 7.75 (d, 1H), 7.36-7.29 (m, 4H), 6.71 (d, 1H), 4.21-4.10 (m, 2H), 4.13-3.96 (m, 2H), 3.90-3.53 (m, 8H), 3.41-3.39 (m, 3H), 3.15-3.11 (m, 2H), 2.87-2.81 (m, 1H), 2.72 (s, 3H), 1.59 (s, 6H), 1.14 (d, 3H). LCMS [(M+2H)/2] 263.1.

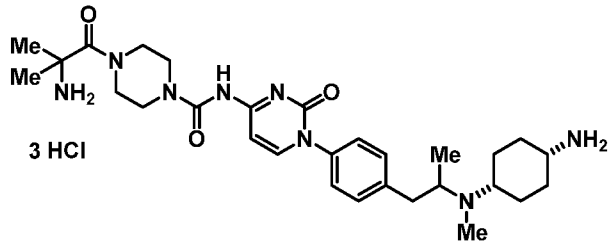
Compound 167



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-((azetidin-3-ylmethyl)(ethyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00827] Prepared in a similar fashion as Scheme C-22 from *tert*-butyl 3-(((1-(4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)phenyl)propan-2-yl)amino)methyl)azetidine-1-carboxylate and acetaldehyde. ^{1}H NMR (400 MHz, D_2O) mixture of rotamers, δ 7.75 (d, 1H), 7.36-7.29 (m, 4H), 6.71 (d, 1H), 4.17 (t, 2H), 3.40-3.90 (m, 2H), 3.80-3.55 (m, 9H), 3.49-3.33 (m, 4H), 3.20-3.11 (m, 4H), 2.95-2.70 (m, 2H), 1.59 (s, 6H), 1.30-1.18 (m, 3H), 1.15-1.11 (m, 3H). LCMS [(M+2H)/2] 269.9.

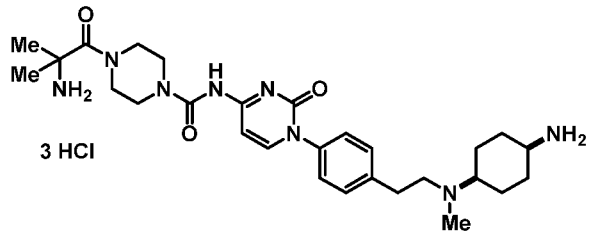
Compound 175



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-((*cis*-4-aminocyclohexyl)(methyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00828] Prepared in a similar fashion as Scheme C-22 from *tert*-butyl (1-(4-((1-(4-(2-((*cis*-4-((*tert*-butoxycarbonyl)amino)cyclohexyl)amino)propyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and formalin. ^{1}H NMR (400 MHz, D_2O) δ 7.97 (d, 1H), 7.55–7.42 (m, 4H), 6.84 (d, 1H), 4.05–3.95 (m, 1H), 3.78 (s, 3H), 3.74 (s, 5H), 3.65 (s, 2H), 3.54 (s, 1H), 3.41–3.26 (m, 1H), 3.11–3.02 (m, 1H), 2.92 (d, 3H), 2.23–1.78 (m, 7H), 1.74 (s, 6H), 1.37–1.24 (m, 3H). LCMS [M+H] 553.2.

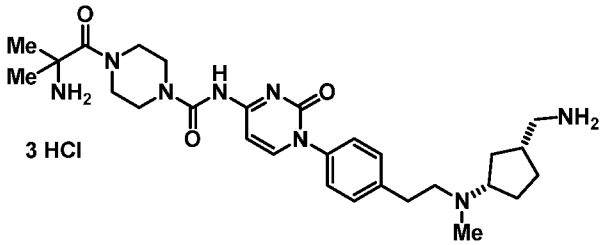
Compound 176



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-((*cis*-4-aminocyclohexyl)(methyl)amino)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00829] Prepared in a similar fashion as Scheme C-22 from *tert*-butyl (1-(4-((1-(4-(2-((*cis*-4-((*tert*-butoxycarbonyl)amino)cyclohexyl)amino)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and formalin. ^{1}H NMR (500 MHz, D_2O) δ 7.94 (d, 1H), 7.52 (d, 2H), 7.45 (d, 2H), 6.85 (d, 1H), 3.83-3.70 (m, 8H), 3.68-3.57 (m, 2H), 3.55-3.42 (m, 2H), 3.30-3.21 (m, 1H), 3.20-3.12 (m, 1H), 2.94 (s, 3H), 2.12-1.80 (m, 8H), 1.74 (s, 6H). LCMS [M+H] 539.4.

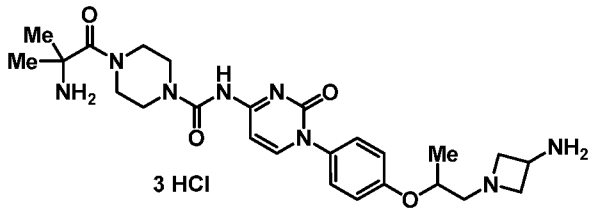
Compound 178



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(((1S,3R)-3-(aminomethyl)cyclopentyl)(methyl)amino)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

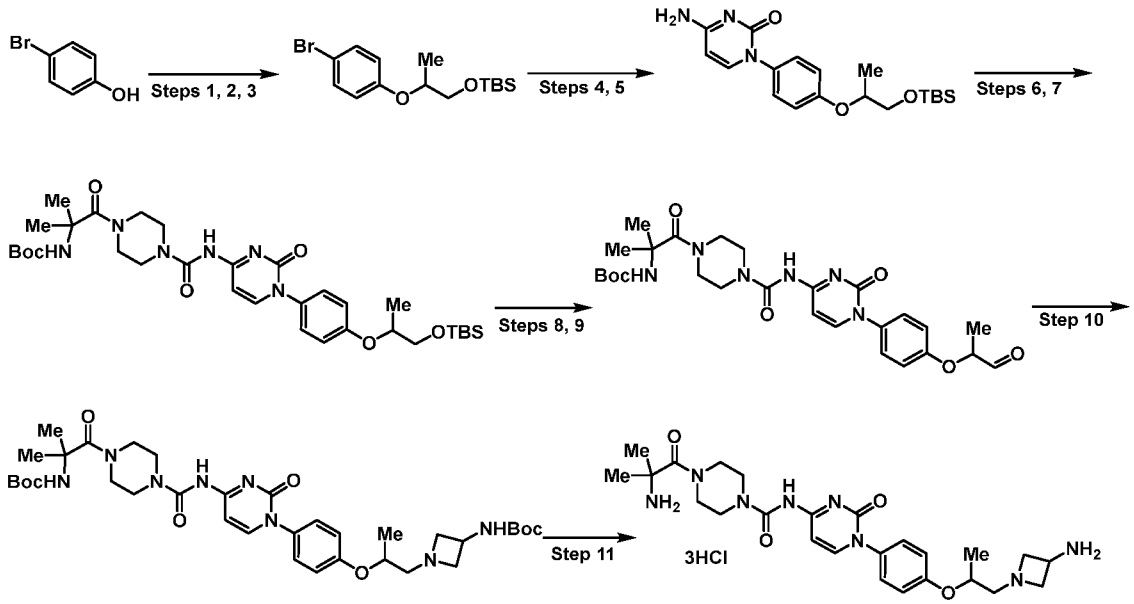
[00830] Prepared in a similar fashion as Scheme C-22 from *tert*-butyl (1-(4-((1-(4-(2-(((1S,3R)-3-(((*tert*-butoxycarbonyl)amino)methyl)cyclopentyl)amino)ethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate and formalin. ^{1}H NMR (500 MHz, D_2O) δ 8.13 (d, 1H), 7.52 (d, 2H), 7.45 (d, 2H), 6.79 (d, 1H), 3.87-3.68 (m, 8H), 3.61-3.50 (m, 1H), 3.42-3.35 (m, 1H), 3.32 (s, 3H), 3.30-3.21 (m, 1H), 3.15-2.99 (m, 2H), 2.94 (d, 2H), 2.45-2.15 (m, 3H), 2.03-1.82 (m, 2H), 1.72 (s, 6H), 1.56-1.44 (m, 1H), 0.91 (t, 1H). LCMS [M+H] 539.7.

Compound 182



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((1-(3-aminoazetidin-1-yl)propan-2-yl)oxy)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt.

Scheme C-23



Reagents: 1) methyl 2-hydroxypropanoate, DIAD, PPh_3, 0 °C to rt, 16h 2) $NaBH_4$, EtOH, 0 °C to rt, 16h 3) TBSCl, imidazole, CH_2Cl_2, rt, 16h 4) BuLi, THF, -78 °C, $(iPrO)_3B$ 5) cytosine, TMEDA, $Cu(OAc)_2 \cdot H_2O$, 4:1 MeOH:H_2O, rt, 48h 6) CDI, CH_2Cl_2, rt. 4h 7) *tert*-butyl (2-methyl-1-oxo-1-(piperazin-1-yl)propan-2-yl)carbamate, CH_3CN, 85 °C, 3h 8) TBAF, THF, 0 °C to rt, 16h 9) DMP, 0.1% CH_2Cl_2:H_2O, rt, 15 min. 10) *tert*-butyl azetidin-3-ylcarbamate, $NaBH_3CN$, MeOH, rt, 16h 11) HCl in MeOH, rt, 4h.

[00831] Step 1: methyl 2-(4-bromophenoxy)propanoate. To a stirred solution of 4-bromophenol (2.50 g, 14.4 mmol), methyl 2-hydroxypropanoate (1.50 g, 14.4 mmol), and triphenylphosphine (3.77 g 14.4 mmol) at 0 °C was added DIAD (2.9 mL, 1.4 mmol) dropwise over 15 min. The reaction was stirred at rt for 16h. The volatiles were removed under reduced pressure and the reaction mixture was purified by flash chromatography to afford the title compound.

[00832] Step 2: 2-(4-bromophenoxy)propan-1-ol. To a stirred solution of methyl 2-(4-bromophenoxy)propanoate (1.2 g, 4.6 mmol) in EtOH (40 mL) at 0 °C was added $NaBH_4$

(521 mg, 13.8 mmol). The solution was warmed to rt and stirred for 36h. The reaction mixture was concentrated under reduced pressure, dissolved in $CHCl_3$ (100 mL) and washed with 10% NaOH solution (100 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the title compound.

[00833] Step 3: (2-(4-bromophenoxy)propoxy)(*tert*-butyl)dimethylsilane. To a solution of 2-(4-bromophenoxy)propan-1-ol (1.07 g, 4.6 mmol) in CH_2Cl_2 (50 mL) was added imidazole (468 mg, 6.9 mmol) and *t*-butyldimethylsilyl chloride (1.03 g, 6.9 mmol). The solution was stirred at rt for 16h. The reaction mixture was concentrated under reduced pressure, EtOAc (100 mL) was added and washed with H_2O (100mL). The organic layer was dried over Na_2SO_4, concentrated under reduced pressure, and purified by flash chromatography (Hexanes:EtOAc) to afford the title compound.

[00834] Step 4: *tert*-butyldimethyl(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)propoxy)silane. A solution of (2-(4-bromophenoxy)propoxy)(*tert*-butyl)dimethylsilane (350 mg, 3.21 mmol) in THF (50 mL) was cooled to -78 °C and 2.5M BuLi in hexanes (3.80 mL) was added dropwise over 30 min. The temperature was maintained below -60°C. The reaction was stirred for 25 min. and triisopropyl borate (1.12 mL, 4.82 mmol) was added dropwise over 30 min. The reaction mixture was warmed to rt and stirred for 15 min. 2N HCl (50 mL) was added and the reaction was stirred for 30 min. The biphasic mixture was separated and the aq. layer extracted with CH_2Cl_2 (2×50 mL). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure to afford the title compound.

[00835] Step 5: 4-amino-1-(4-((1-((*t*-butyldimethylsilyl)oxy)propan-2-yl)oxy)phenyl)pyrimidin-2(1H)-one. A suspension of cytosine (355 mg, 3.2 mmol) and *tert*-butyldimethyl(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)propoxy)silane (992 mg, 3.2 mmol), in 4:1, MeOH:H_2O (100 mL) was stirred at rt in open air for 30 min. TMEDA (0.87 mL, 3.8 mmol) and $Cu(OAc)_2 \cdot H_2O$ (640 mg, 3,2 mmol) were added and the reaction was stirred in open air at rt for 48h. The reaction mixture was concentrated under reduced pressure and cold H_2O (100 mL) was added. The solid was filtered and washed with H_2O (2×20 mL) and Et_2O (3×20 mL) to afford the title compound.

[00836] Step 6: N-(1-(4-((1-((*t*-butyldimethylsilyl)oxy)propan-2-yl)oxy)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-1H-imidazole-1-carboxamide. A suspension of 4-amino-1-(4-((1-((*t*-butyldimethylsilyl)oxy)propan-2-yl)oxy)phenyl)pyrimidin-2(1H)-one (100 mg , 0.27 mmol) and 1,1'-carbonyldiimidazole (68 mg, 0.37 mmol) in CH_2Cl_2 (12 mL) was stirred at rt

for 16h. The solvent was removed under reduced pressure, and the solid was triturated with EtOAc. The solid was collected to afford the title compound.

[00837] Step 7: *t*-butyl (1-(4-((1-(4-((1-((*t*-butyldimethylsilyl)oxy)propan-2-yl)oxy)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate. N-(1-(4-((1-((*t*-butyldimethylsilyl)oxy)propan-2-yl)oxy)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-1H-imidazole-1-carboxamide (122 mg, 0.260 mmol) and *t*-butyl (2-methyl-1-oxo-1-(piperazin-1-yl)propan-2-yl)carbamate (72 mg, 0.26 mmol) were dissolved in CH_3CN (10 mL) and heated to reflux for 2h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in EtOAc (25 mL) and washed with water (3×20 mL). The reaction mixture was purified by flash chromatography (Hexanes:EtOAc) to afford the title compound.

[00838] Step 8: *t*-butyl (1-(4-((1-(4-((1-hydroxypropan-2-yl)oxy)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate. To a solution of *t*-butyl (1-(4-((1-(4-((1-((*t*-butyldimethylsilyl)oxy)propan-2-yl)oxy)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate (150 mg, 0.22 mmol) in THF (50 mL) at 0 °C was added 1M TBAF in THF (0.45 mL) dropwise over 5 min. The solution was warmed to rt and stirred for 16h. The crude reaction mixture was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography to afford the title compound.

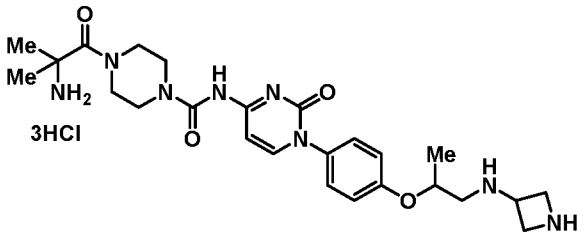
[00839] Step 9: *t*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-((1-oxopropan-2-yl)oxy)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate. To a stirred solution of *t*-butyl (1-(4-((1-(4-((1-hydroxypropan-2-yl)oxy)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate (40 mg, 0.07 mmol) in 0.1% H_2O:CH_2Cl_2 (10 mL) was added Dess-Martin periodinane (44 mg, 0.01 mmol). The solution was stirred for 1h. CH_2Cl_2 (15 mL) was added the reaction mixture washed with aq. $NaHCO_3$/$Na_2S_2O_3$ (15 mL). The aq. layer was extracted with CH_2Cl_2 (15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to the title compound.

[00840] Step 10: *tert*-butyl (1-(4-((1-(4-((1-(3-((*tert*-butoxycarbonyl)amino)azetidin-1-yl)propan-2-yl)oxy)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate. To a stirred solution of *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-((1-oxopropan-2-yl)oxy)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate (28 mg, 0.05 mmol) in MeOH, was added *tert*-butyl azetidin-3-ylcarbamate (13 mg, 0.075 mmol) and $NaBH_3CN$ (5.0 mg, 0.08

mmol). The reaction mixture was stirred for 16h at rt. The reaction mixture was concentrated under reduced pressure, $CHCl_3$ (15 mL) added and washed with 10% NaOH solution (15 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford the title compound.

[00841] Step 11: 4-(2-amino-2-methylpropanoyl)-N-(1-(4-((1-(3-aminoazetidin-1-yl)propan-2-yl)oxy)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt. A mixture of *tert*-butyl (1-(4-((1-(4-((1-(3-((*tert*-butoxycarbonyl)amino)azetidin-1-yl)propan-2-yl)oxy)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate (0.05 mmol) and a solution of HCl/MeOH (5 mL) was stirred at rt for 4h. The solvent was evaporated and the crude solid was purified by RPHPLC (H_2O:CH_3CN:TFA) and concentrated under reduced pressure. Addition of HCl/MeOH and evaporation under reduced pressure afforded the title compound. ^{1}H NMR (400 MHz, D_2O) δ 8.06 (d, 1H), 7.44 (d, 2H), 7.18 (d, 2H), 6.81 (d, 1H), 4.94–4.85 (m, 2H), 4.70 (s, 2H), 4.65–4.47 (m, 2H), 3.79 (s, 4H), 3.74 (s, 6H), 1.74 (s, 6H), 1.38 (d, 3H). LCMS [M+H] 513.3.

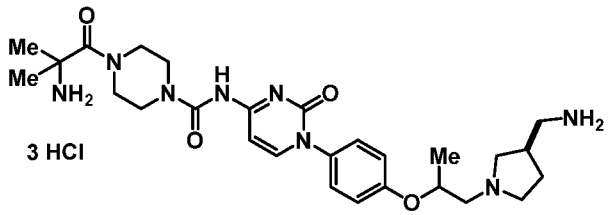
Compound 183



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((1-(azetidin-3-ylamino)propan-2-yl)oxy)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt.

[00842] Prepared in a similar fashion as Scheme C-23 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-((1-oxopropan-2-yl)oxy)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl-3-amino-azetidine-1-carboxylate. ^{1}H NMR (400 MHz, D_2O) δ 8.12 (d, 1H), 7.46 (d, 2H), 7.22 (d, 2H), 6.80 (d, 1H), 4.92 (s, 1H), 4.62–4.42 (m, 5H), 3.80 (br. s, 4H), 3.76 (br. s, 4H), 3.47–3.37 (m, 2H), 1.74 (s, 6H), 1.40 (d, 3H). LCMS [M+H] 513.3.

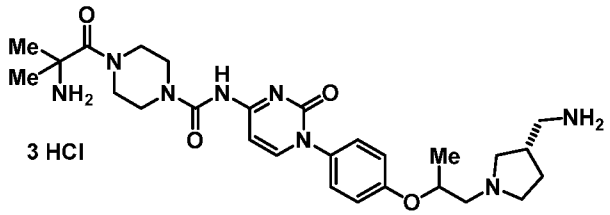
Compound 184



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((1-((R)-3-(aminomethyl)pyrrolidin-1-yl)propan-2-yl)oxy)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00843] Prepared in a similar fashion as Scheme C-23 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-((1-oxopropan-2-yl)oxy)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl (S)-(pyrrolidin-3-ylmethyl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 8.11 (d, 1H), 7.46 (d, 2H), 7.22 (d, 2H), 6.81 (d, 1H), 4.97 (s, 1H), 3.96–3.53 (m, 12H), 3.52–3.29 (m, 1H), 3.26–3.02 (m, 3H), 3.01–2.66 (m, 1H), 2.53–2.29 (m, 1H), 2.09–1.76 (m, 1H), 1.74 (s, 6H), 1.39 (d, 3H). LCMS [M+H] 541.2.

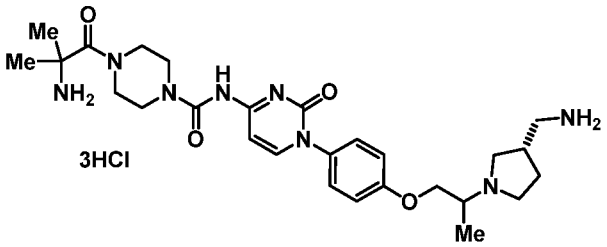
Compound 185



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((1-((S)-3-(aminomethyl)pyrrolidin-1-yl)propan-2-yl)oxy)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

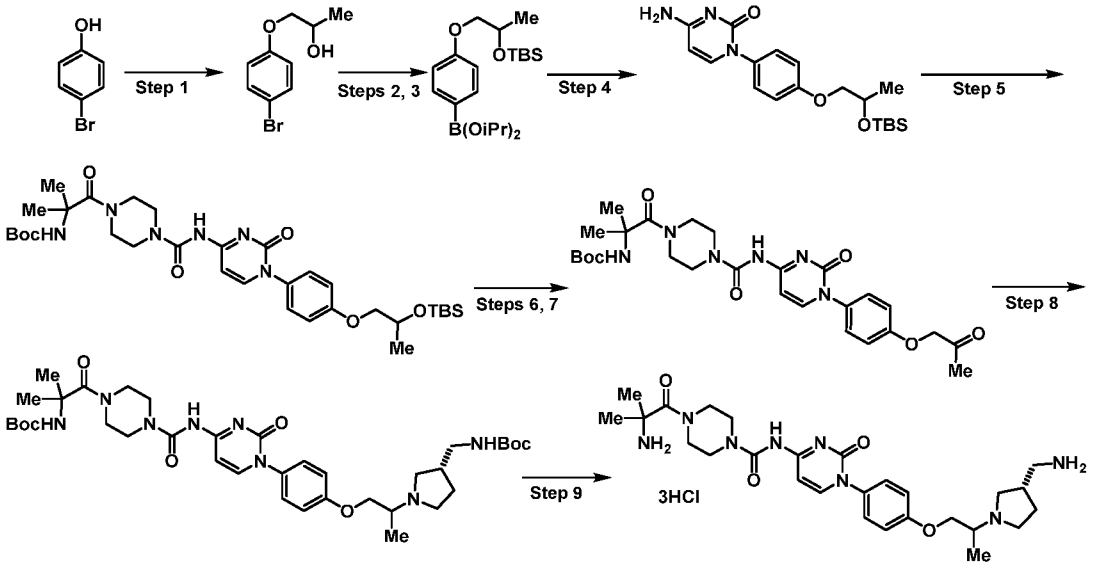
[00844] Prepared in a similar fashion as Scheme C-23 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-((1-oxopropan-2-yl)oxy)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl (R)-(pyrrolidin-3-ylmethyl)carbamate. ^{1}H NMR (400 MHz, D_2O) δ 8.11 (d, 1H), 7.46 (d, 2H), 7.22 (d, 2H), 6.81 (d1H), 4.98 (s, 1H), 4.05–3.50 (m, 12H), 3.50–3.33 (m, 1H), 3.26–3.03 (m, 3H), 3.02–2.71 (m, 1H), 2.55–2.26 (m, 1H), 2.10–1.78 (m, 1H), 1.74 (s, 6H), 1.39 (d, 3H). LCMS [M+H] 541.3.

Compound 186



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-((S)-3-(aminomethyl)pyrrolidin-1-yl)propoxy)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

Scheme C-24



Reagents: Step 1) Propylene glycol, K_2CO_3, diethyl carbonate, 110 °C, 8 days 2) TBSCl, imidazole, CH_2Cl_2, rt, 16h 3) nBuLi, B(O*i*Pr)$_3$, THF, -78°C to rt, 3h 4) Cytosine, TMEDA, $Cu(OAc)_2 \cdot H_2O$, CH_3OH:H_2O (4:1), rt, 16h 5) 1-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carbonyl)-3-methyl-1*H*-imidazol-3-ium iodide, CH_3CN, 90°C, 16h 6) TBAF, THF, rt, 16h 7) Dess-Martin periodinane, CH_2Cl_2, rt, 3h 8) *tert*-butyl (R)-(pyrrolidin-3-ylmethyl)carbamate, $NaBH_3CN$, 4 Å MS, CH_3OH, rt, 16h 9) 4.0 MHCl in dioxane, dioxane, rt, 3h.

[00845] Step 1: 1-(4-bromophenoxy)propan-2-ol. A mixture of 4-bromophenol (25 g, 145 mmol), propane-1,2-diol (32.9 g, 434 mmol), and K_2CO_3 (2.0 g, 14.5 mmol) in diethyl carbonate (25 mL, 202 mmol) was stirred at 110 °C for 8 days. The resulting reaction mixture was poured into 1N NaOH (200 mL) and extracted with EtOAc (3×200 mL). The extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.44-7.39 (m, 2H), 6.91-6.87 (m, 2H), 4.89 (d, 1H), 3.95-3.90 (m, 1H), 3.81-3.73 (m, 2H), 1.14 (d, 3H).

[00846] Step 2: ((1-(4-bromophenoxy)propan-2-yl)oxy)(*t*-butyl)dimethylsilane. To a stirred solution of 1-(4-bromophenoxy)propan-2-ol (18 g, 78 mmol) in CH_2Cl_2 (200 mL) at 0°C was added imidazole (7.94 g, 117 mmol) and *t*-butyldimethylsilyl chloride (14.1 g, 93 mmol). The reaction mixture was stirred at rt for 16h, poured into H_2O (200 mL) and extracted with CH_2Cl_2 (3×200 mL). The extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford the title compound. ^1H NMR (400 MHz, DMSO-d_6) δ 7.44-7.40 (m, 2H), 6.89-6.86 (m, 2H), 4.13-4.08 (m, 1H), 3.86-3.66 (m, 2H), 1.14 (d, 3H), 0.84 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H).

[00847] Step 3: diisopropyl (4-(2-((*t*-butyldimethylsilyl) oxy) propoxy) phenyl) boronate. To a stirred solution of ((1-(4-bromophenoxy)propan-2-yl)oxy)(*t*-butyl)dimethylsilane (5.0 g, 14.5 mmol) in THF (300 mL) at -78 °C under N_2 was added n-BuLi (1.6M in THF, 22.64 mL) dropwise. The reaction mixture was stirred for 30 min. Triisopropyl borate (5.04 mL, 21.7 mmol) was added dropwise. The reaction mixture was warmed to rt and stirred for 3 h. The reaction mixture was poured into sat. aq. NH_4Cl (400 mL) and extracted with EtOAc (3×1000 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford the title compound.

[00848] Step 4: 4-amino-1-(4-(2-((*t*-butyldimethylsilyl)oxy)propoxy)phenyl)pyrimidin-2(1H)-one. A mixture of diisopropyl (4-(2-((*t*-butyldimethylsilyl)oxy)propoxy) phenyl)boronate (6.5 g, 16.5 mmol) and cytosine (1.8 g, 16.5 mmol) in 4:1 CH_3OH:H_2O (50 mL) was stirred at rt open to air for 30 min. TMEDA (2.3 mL, 19.8 mmol) and $Cu(OAc)_2 \cdot H_2O$ (2.3 g, 16.5 mmol) were added and the mixture was stirred at rt open to air for 48h. It was concentrated in vacuo to remove the CH_3OH, and cold H_2O (100 mL) was added. The precipitate was collected by vacuum filtration, washed with H_2O (5×50 mL) and Et_2O (2×20 mL) and dried to yield the title compound. ^1H NMR (400 MHz, DMSO-d_6) δ 7.57 (d, 1H), 7.21 (d, 2H), 6.94 (d, 2H), 5.73 (d, 1H), 4.13-4.08 (m, 1H), 3.87-3.86 (m, 1H), 3.81-3.80 (m, 1H), 1.17 (d, 3H), 0.86 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H). LCMS [M+H] 376.1.

[00849] Step 5: *t*-butyl (1-(4-((1-(4-(2-((*t*-butyldimethylsilyl)oxy)propoxy)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate. A mixture of 4-amino-1-(4-(2-((*t*-butyldimethylsilyl)oxy)propoxy)phenyl) pyrimidin-2(1H)-one (0.5 g, 1.33 mmol) and 1-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carbonyl)-3-methyl-1*H*-imidazol-3-ium iodide (1.01 g, 2.0 mmol) in CH_3CN (15 mL) was stirred at 90°C for 16h. The reaction mixture was concentrated in vacuo and the residue was purified by flash chromatography (CH_3OH:CH_2Cl_2) to afford the title compound. LCMS [M+H] 673.1.

[00850] Step 6: *t*-butyl (1-(4-((1-(4-(2-hydroxypropoxy)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate. To a stirred solution of *t*-butyl (1-(4-((1-(4-(2-((*t*-butyldimethylsilyl)oxy) propoxy)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate (0.4 g, 0.59 mmol) in THF (10 mL) at 0 °C was added 1M TBAF in THF (2.4 mL). The reaction mixture was warmed to rt and stirred for 16h. The reaction mixture was poured into sat. aq. $NaHCO_3$ (10 mL) and extracted with 9:1 CH_2Cl_2:CH_3OH (3×50 mL). The extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo, and the residue purified by flash chromatography (CH_3OH:CH_2Cl_2) to afford the title compound. LCMS [M+H] 559.1.

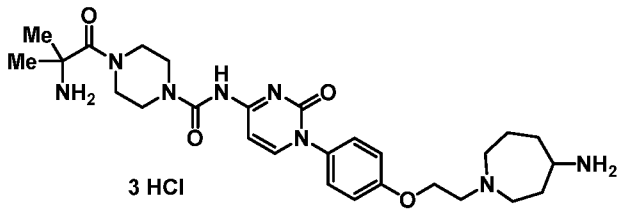
[00851] Step 7: *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxopropoxy)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate. To a stirred solution of *t*-butyl (1-(4-((1-(4-(2-hydroxypropoxy)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate (0.3 g, 0.53 mmol) in CH_2Cl_2 (5.0 mL) at 0 °C under N_2 was added Dess-Martin periodinane (1.36 g, 3.22 mmol). The reaction mixture was stirred at rt for 3h, poured into sat. aq. $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3×50 mL). The extracts were dried over Na_2SO_4, filtered and concentrated in vacuo at <35 °C to afford the title compound. LCMS [M+H] 557.1.

[00852] Step 8: *tert*-butyl (1-(4-((1-(4-(2-((S)-3-(((*tert*-butoxycarbonyl)amino)methyl)pyrrolidin-1-yl)propoxy)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate. To a stirred solution of *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxopropoxy)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate (0.28 g, 0.50 mmol) and *tert*-butyl (R)-(pyrrolidin-3-ylmethyl)carbamate (0.12 g, 0.60 mmol) in CH_3OH (10 mL) at 0 °C under N_2 was added activated 4 Å molecular sieves followed by $NaBH_3CN$ (0.67 g, 1.07 mmol). The mixture was stirred at rt for 16h concentrated in vacuo. The residue was purified by flash chromatography (CH_3OH:CH_2Cl_2) to afford the title compound.

[00853] Step 9: 44-(2-amino-2-methylpropanoyl)-N-(1-(4-(2-((S)-3-(aminomethyl)pyrrolidin-1-yl)propoxy)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt. To a stirred solution of *tert*-butyl (1-(4-((1-(4-(2-((S)-3-(((*tert*-butoxycarbonyl)amino)methyl)pyrrolidine-1-yl)propoxy)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate (0.2 g, 0.26 mmol) in dioxane (3 mL) was added 4M HCl in dioxane (5 mL).

The mixture was stirred at rt for 3h, concentrated in vacuo, and triturated with Et_2O (10 mL). The residue was purified by HPLC (CH_3CN/H_2O/TFA). Addition of HCl/MeOH (3x15 mL) and evaporation under reduced pressure afforded the title compound. ^1H NMR (400 MHz, D_2O) mixture of rotamers, mixture of diastereomers, δ 7.86 (d, 1H), 7.28 (d, 2H), 7.03(d, 2H), 6.67 (d, 1H), 4.33-4.30 (m, 1H), 4.15-4.10 (m, 1H), 3.80-3.50 (m, 11H), 3.45-3.20 (m, 2H), 3.12-2.93 (m, 3H), 2.83-2.55 (m, 2H), 2.40-2.15 (m, 2H), 1.91-1.60 (m, 2H), 1.59 (s, 6H), 1.40 (d, 3H). LCMS[(M+2H)/2] 271.1.

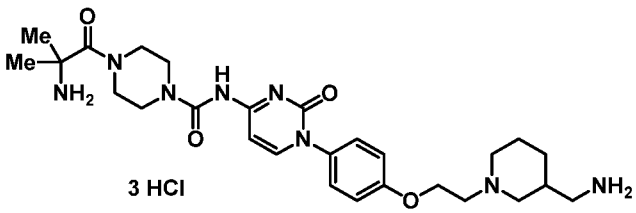
Compound 187



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(4-aminoazepan-1-yl)ethoxy)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00854] Prepared in a similar fashion as Scheme C-24 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxoethoxy)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl azepan-4-ylcarbamate. ^1H NMR (400 MHz, D_2O) δ 7.95 (d, 1H), 7.43 (d, 2H), 7.18 (d, 2H), 6.84 (d, 1H), 4.47 (s, 2H), 3.79 (s, 4H), 3.73 (s, 6H), 3.68–3.55 (m, 3H), 3.55–3.42 (m, 1H), 3.42–3.25 (m, 2H), 2.43–2.27 (m, 2H), 2.25–2.09 (m, 2H), 2.09–1.85 (m, 1H), 1.75 (s, 6H). LCMS [M+H] 541.4.

Compound 188

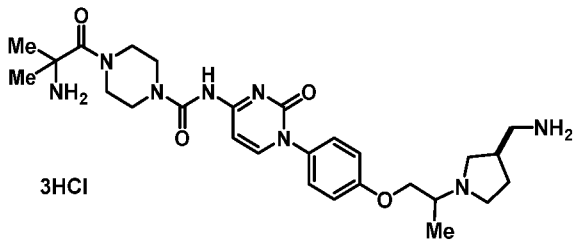


4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(3-(aminomethyl)piperidin-1-yl)ethoxy)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00855] Prepared in a similar fashion as Scheme C-24 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxoethoxy)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl (piperidin-3-ylmethyl)carbamate. ^1H NMR (400 MHz, D_2O) δ 7.96 (d, 1H), 7.43 (d, 2H), 7.18 (d, 2H), 6.84 (d, 1H), 4.51–4.46 (m, 2H), 3.78

(s, 4H), 3.74 (s, 6H), 3.71–3.65 (m, 2H), 3.12–3.02 (m, 2H), 3.02–2.89 (m, 2H), 2.33 (s, 1H), 2.18–2.01 (m, 2H), 1.96–1.83 (m, 1H), 1.75 (s, 6H), 1.43–1.30 (m, 1H). LCMS [M+H] 541.3.

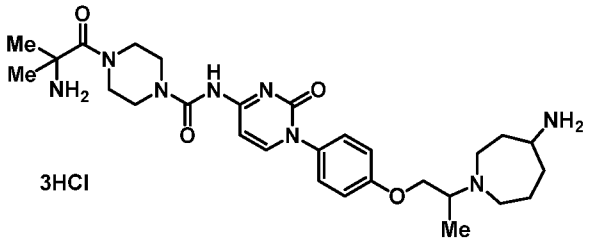
Compound 190



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-((R)-3-(aminomethyl)pyrrolidin-1-yl)propoxy)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00856] Prepared in a similar fashion as Scheme C-24 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxopropoxy)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl (S)-(pyrrolidin-3-ylmethyl)carbamate. ^{1}H NMR (400 MHz, D_2O) mixture of rotamers, mixture of diastereomers, δ 7.82 (d, 1H), 7.27 (d, 2H), 7.02 (d, 2H), 6.67 (d, 1H), 4.31-4.29 (m, 1H), 4.14-4.12 (m, 1H), 3.80-3.51 (m, 10H), 3.38-3.31 (m, 1H), 3.25-3.21 (m, 2H), 3.08-2.92 (m, 3H), 2.79-2.74 (m, 1H), 2.64-2.62 (m, 1H), 2.36-2.33 (m, 1H), 2.23-2.21 (m, 1H), 1.87-1.85 (m, 1H), 1.70-1.59 (m, 1H), 1.58(s, 6H), 1.39 (d, 3H). LCMS [(M+2H)/2] 271.2.

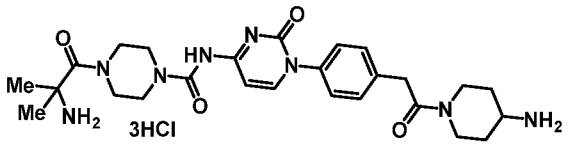
Compound 191



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(4-aminoazepan-1-yl)propoxy)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt.

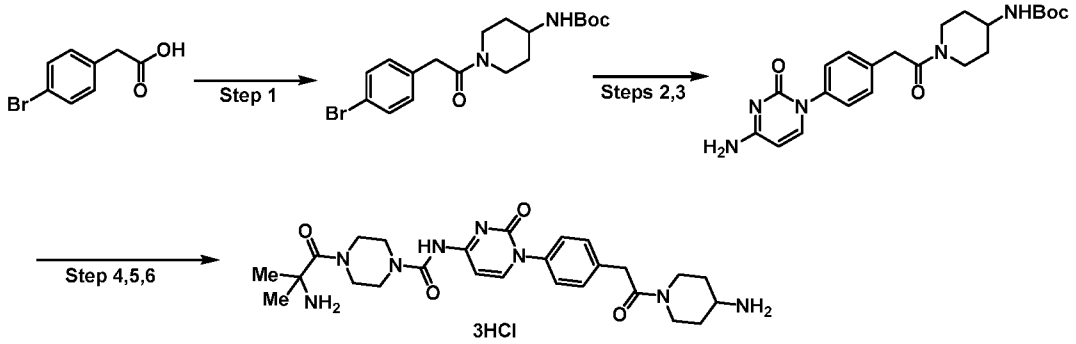
[00857] Prepared in a similar fashion as Scheme C-24 from *tert*-butyl (2-methyl-1-oxo-1-(4-((2-oxo-1-(4-(2-oxopropoxy)phenyl)-1,2-dihydropyrimidin-4-yl)carbamoyl)piperazin-1-yl)propan-2-yl)carbamate and *tert*-butyl azepan-4-ylcarbamate. ^{1}H NMR (400 MHz, D_2O) mixture of rotamers, mixture of diastereomers, δ 7.77 (d, 1H), 7.31 (d, 2H), 7.06 (d, 2H), 6.74 (d, 1H), 4.76-4.70 (m, 3H), 4.30-4.20 (m, 2H), 3.98-3.90 (m,1H), 3.67-3.61 (m, 8H), 3.51-3.45 (m, 3H), 2.40-2.10 (m, 3H), 1.63 (s, 6H), 1.45-1.35 (m, 3H). LCMS [M+H] 555.3.

Compound 269



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-(4-aminopiperidin-1-yl)-2-oxoethyl) phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

Scheme C-25



Reagents: 1) *tert*-butyl piperidin-4-ylcarbamate, HATU, DIPEA, DMF, rt, 6h 2) $B(Pin)_2$, KOAc, $Pd(dppf)Cl_2$, Dioxane, 110°C, 16h 3) cytosine, $Cu(OAc)_2.H_2O$, TMEDA, MeOH:H_2O (4:1), rt, 48h 4) CDI, CH_2Cl_2, rt, 16h 5) *tert*-butyl (2-methyl-1-oxo-1-(piperazin-1-yl)propan-2-yl)carbamate, CH_3CN, reflux, 16h 6) MeOH, AcCl, rt, 4h.

[00858] Step 1: *tert*-butyl (1-(2-(4-bromophenyl)acetyl)piperidin-4-yl)carbamate. To a stirred solution of 4-bromo phenylacetic acid (2.15 g, 10 mmol), 4-Boc amino piperidine (2.0 g, 10 mmol) and HATU (4.5 g, 12 mmol) in DMF was added DIPEA (2.61 mL, 15 mmol) and the reaction mixture stirred for 6h at rt. Saturated LiCl solution was added and the solid was filtered and vacuum dried to afford the title compound (3.5g, 90%) as gray solid.

[00859] Step 2: *tert*-butyl (1-(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetyl)piperidin-4-yl)carbamate. To a stirred suspension of *tert*-butyl (1-(2-(4-bromophenyl)acetyl)piperidin-4-yl)carbamate (0.39 g, 1 mmol) in a flame dried pressure flask was added bis(pinacolato) diboron (0.31g, 1.2 mmol), KOAc (0.30g, 3 mmol) and $Pd(dppf)Cl_2$ (25 mg, 0.03 mmol). The reaction mixture was degassed and purged with N_2 (g) (3x). The pressure flask was sealed and stirred at 110°C for 16h. The mixture was diluted with EtOAc and filtered through Celite®. The filtrate was concentrated and purified using flash column chromatography to afford the title compound ad a brown colored sticky solid.

[00860] Step 3: *tert*-butyl (1-(2-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)phenyl)acetyl)piperidin-4-yl)carbamate. A suspension of cytosine (0.093 g, 0.84 mmol) and *tert*-butyl (1-(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetyl)piperidin-4-yl)carbamate (0.38 g, 0.84 mmol), in a mixture of solvents 4:1 MeOH:H_2O (12ml) was

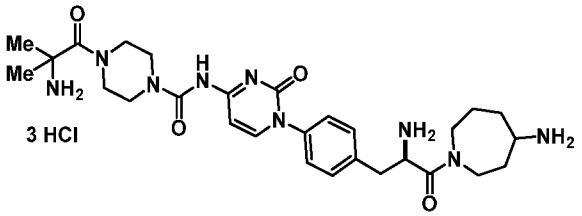
stirred at rt in open air. After 30 min. TMEDA (0.15 ml, 1.10 mmol) and $Cu(OAc)_2 \cdot H_2O$ (0.17 g, 0.84 mmol) were added. The reaction was stirred in open air for 48h at rt. The solvent was evaporated reduced pressure, and the residue was crystallized with EtOH to afford the title compound.

[00861] Step 4: *tert*-butyl (1-(2-(4-(4-(1H-imidazole-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)phenyl)acetyl)piperidin-4-yl)carbamate. To a suspension of *tert*-butyl (1-(2-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)phenyl)acetyl)piperidin-4-yl)carbamate (0.21 g, 0.5 mmol) in dichloromethane (12 mL) was added CDI (98 mg, 0.6 mmol) and the reaction mixture stirred for 16h at rt. The solvent was evaporated under reduced pressure and the solid was used in the next step without further purification.

[00862] Step 5: *tert*-butyl (1-(2-(4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)phenyl)acetyl)piperidin-4-yl)carbamate. *tert*-Butyl (1-(2-(4-(4-(1H-imidazole-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)phenyl)acetyl)piperidin-4-yl)carbamate (90 mg, 0.17 mmol) and *tert*-butyl (2-methyl-1-oxo-1-(piperazin-1-yl)propan-2-yl)carbamate (56 mg, 0.172 mmol) were suspended in acetonitrile and refluxed for 16h. The solvent was evaporated and the residue was diluted with EtOAc (15 mL) and the excess imidazole was removed by water wash (3x10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the title compound.

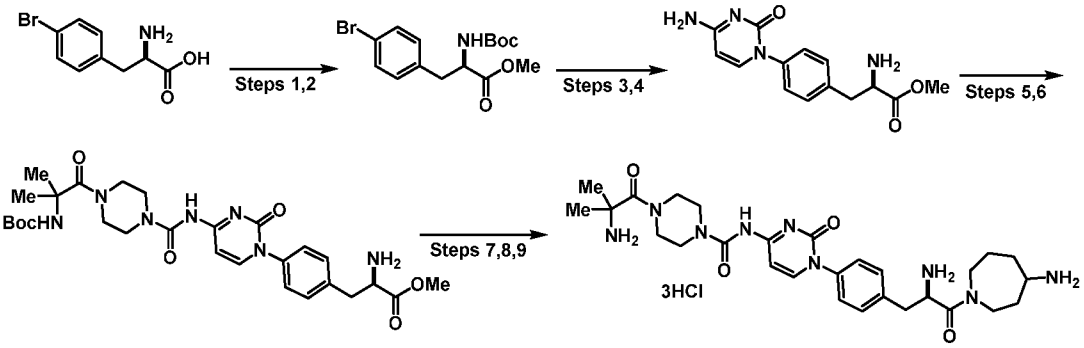
[00863] Step 6: 4-(2-amino-2-methylpropanoyl)-N-(1-(4-(2-(4-aminopiperidin-1-yl)-2-oxoethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt. *tert*-Butyl (1-(2-(4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)phenyl)acetyl)piperidin-4-yl)carbamate (56 mg, 0.08 mmol) was dissolved in methanolic HCl and stirred for 4h. The solvent was evaporated and the residue was purified by RPHPLC and converted to the hydrochloride salt with the addition of 2N HCl in MeOH (5 mL) and evaporation under reduced pressure. ^1H NMR (500 MHz, D_2O) δ 8.11 (d, 1H), 7.41 (br s, 4H), 6.77 (d, 1H), 4.50 (d, 1H), 4.11 (d, 1H), 3.93 (s, 2H), 3.83-3.73 (m, 8H), 3.45 (t, 1H), 3.21 (t, 1H), 2.80 (t, 1H), 2.12-1.98 (m, 2H), 1.73 (s, 6H), 1.57-1.49 (m, 2H). LCMS [M+H] 525.43

Compound 143



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((2R)-2-amino-3-(4-aminoazepan-1-yl)-3-oxopropyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

Scheme C-26



Reagents: 1) HCl, MeOH, rt, 16h 2) Boc_2O, Et_3N, CH_2Cl_2, rt, 16h 3) $Pd(dppf)_2$, KOAc, B_2Pin_2, dioxane, 100 °C, 16h 4) cytosine, $Cu(OAc)_2$, TMEDA, MeOH, H_2O rt, 48h 5) CDI, CH_2Cl_2, rt, 16h 6) *tert*-butyl (2-methyl-1-oxo-1-(piperazin-1-yl)propan-2-yl)carbamate, CH_3CN, 80°C, 2h 7) LiOH, THF, H_2O, 2h 8) *tert*-butyl azepan-4-ylcarbamate, HATU, DIPEA, DMF, rt, 3h 9) HCl, MeOH, rt, 4h.

[00864] Step 1: methyl (R)-2-amino-3-(4-bromophenyl)propanoate. (R)-2-Amino-3-(4-bromophenyl)propanoic acid (2.5 g, 10.2 mmol) was added to a solution of HCl in MeOH (100 mL) and the reaction was stirred for 16h. The reaction mixture was concentrated under reduced pressure to afford the title compound.

[00865] Step 2: methyl (R)-3-(4-bromophenyl)-2-((*tert*-butoxycarbonyl)amino)propanoate. To a solution of methyl (R)-2-amino-3-(4-bromophenyl)propanoate (1.10 g, 3.74 mmol) in CH_2Cl_2 (100 mL) was added NEt_3 (2.0 mL, 14.96 mmol) followed by Boc_2O (1.05 g, 4.86 mmol). The reaction mixture was stirred for 16h and concentrated under reduced pressure and purified via column chromatography (hexanes:EtOAc) to afford the title compound.

[00866] Step 3: methyl (R)-2-((*tert*-butoxycarbonyl)amino)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate. A mixture of (R)-3-(4-bromophenyl)-2-((*tert*-butoxycarbonyl)amino)propanoate (0.68 g, 1.9 mmol), bis(pinacolato)diboron (0.96 g, 3.8

mmol), $Pd(dppf)_2$ (0.07g, 5 mol%), and KOAc (0.46 g, 4.76 mmol) was evacuated and flushed with N_2 (3x). Dioxane (30 mL) was added and the mixture was subjected to 3 freeze pump thaw cycles. The mixture was placed under N_2 and heated to 100 °C for 16h, concentrated under reduced pressure and purified via column chromatography (hexanes:EtOAc) to afford the title compound.

[00867] Step 4: methyl (R)-3-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)phenyl)-2-((*tert*-butoxycarbonyl)amino)propanoate. A suspension of cytosine (0.14 g, 1.3 mmol) and methyl (R)-2-((*tert*-butoxycarbonyl)amino)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate (0.50 g, 1.3 mmol), in 4:1 MeOH:H_2O (60 ml) was stirred at rt in open air for 30 min. TMEDA (0.2 ml, 1.6 mmol) and $Cu(OAc)_2 \cdot H_2O$ (0.3 g, 1.3 mmol) were added and the reaction was stirred in open air for 48h at rt. The reaction mixture was concentrated under reduced pressure, and cold H_2O (50 mL) was added. The solid was filtered and washed with H_2O (5×50 mL), Et_2O (3×30 mL), and H_2O (2×30 mL) to afford the title compound.

[00868] Step 5: methyl (R)-3-(4-(4-(1H-imidazole-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)phenyl)-2-((*tert*-butoxycarbonyl)amino)propanoate. A suspension of methyl (R)-3-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)phenyl)-2-((*tert*-butoxycarbonyl)amino)propanoate (100 mg, 0.25 mmol) and 1,1'-carbonyldiimidazole (70 mg, 0.42 mmol) in CH_2Cl_2 (20 mL) was stirred at rt for 16h. The solvent was removed under reduced pressure to afford the title compound.

[00869] Step 6: methyl (R)-2-((*tert*-butoxycarbonyl)amino)-3-(4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)phenyl)propanoate. Methyl (R)-3-(4-(4-(1H-imidazole-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)phenyl)-2-((*tert*-butoxycarbonyl)amino)propanoate (0.25 mmol) and *tert*-butyl (2-methyl-1-oxo-1-(piperazin-1-yl)propan-2-yl)carbamate (115 mg, 0.42 mmol) were dissolved in CH_3CN (20 mL) and heated to reflux for 2h. The reaction mixture was concentrated under reduced pressure and the solid was dissolved in EtOAc (25 mL) and washed with water (3×20 mL). The reaction mixture was purified by flash chromatography (Hexanes:EtOAc) to afford the title compound.

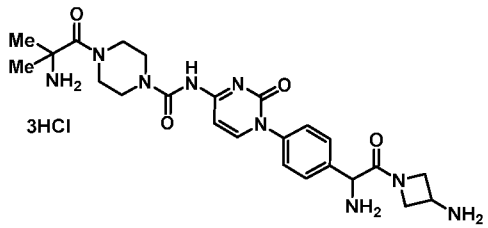
[00870] Step 7: (R)-2-((*tert*-butoxycarbonyl)amino)-3-(4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)phenyl)propanoic acid. To a solution of methyl (R)-2-((*tert*-butoxycarbonyl)amino)-3-(4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)phenyl)propanoate (50 mg, 0.07 mmol) in 1:1 THF:H_2O (10 ml) was added LiOH (10 mg, 0.44 mmol) and the

reaction was stirred for 2 h. The reaction mixture was acidified to pH 4 and extracted with EtOAc (3×20 mL) to afford the title compound.

[00871] Step 8: *tert*-butyl ((2R)-3-(4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)phenyl)-1-(4-((*tert*-butoxycarbonyl)amino)azepan-1-yl)-1-oxopropan-2-yl)carbamate. To a solution of (R)-2-((*tert*-butoxycarbonyl)amino)-3-(4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)phenyl)propanoic acid (22 mg, 0.03 mmol) in DMF (5 mL) was added *tert*-butyl azepan-4-ylcarbamate (8 mg, 0.04 mmol), DIPEA (1 drop), and HATU (18 mg, 0.05 mmol). The reaction mixture was stirred for 3h and partitioned between EtOAc (50 mL) and LiCl (50 mL). The organic layer was washed with LiCl (2×50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (CH_2Cl_2:MeOH) to afford the title compound.

[00872] Step 9: 4-(2-amino-2-methylpropanoyl)-N-(1-(4-((2R)-2-amino-3-(4-aminoazepan-1-yl)-3-oxopropyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt. A mixture of HCl in MeOH (100 ml) was added to *tert*-butyl ((2R)-3-(4-(4-(4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)phenyl)-1-(4-((*tert*-butoxycarbonyl)amino)azepan-1-yl)-1-oxopropan-2-yl)carbamate (8 mg, 0.01 mmol) and the reaction was stirred for 4h. The reaction mixture was concentrated under reduced pressure to afford the title compound. ^{1}H NMR (500 MHz, D_2O): δ 8.01 (d, 1H), 7.50-7.45 (m, 4H), 6.81 (d, 1H), 3.85-3.66 (m, 8H), 3.65-3.38 (m, 3HH), 3.34-3.02 (m, 5H), 2.27-1.83 (m, 6H), 1.72 (s, 6H). LCMS [M+H] 568.3.

Compound 144

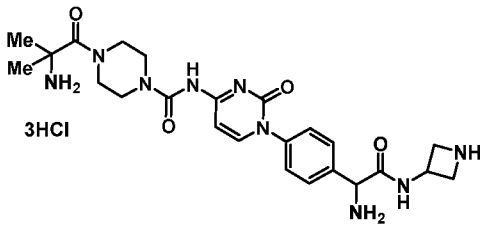


N-(1-(4-(1-Amino-2-(3-aminoazetidin-1-yl)-2-oxoethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-4-(2-amino-2-methylpropanoyl)piperazine-1-carboxamide hydrochloride salt

[00873] Prepared in a similar fashion as Scheme C-26 from 2-amino-2-(4-bromophenyl)acetic acid. ^{1}H NMR (400 MHz, D_2O) δ 7.92 (d, 1H), 7.69 (d, 2H), 7.65 (d,

2H), 6.89 (d, 1H), 5.34 (d, 1H), 4.56–4.36 (m, 1H), 4.33–4.20 (m, 2H), 4.15–4.01 (m, 2H), 3.79 (s, 2H), 3.74 (s, 6H), 1.75 (s, 6H). LCMS [M+H] 512.2.

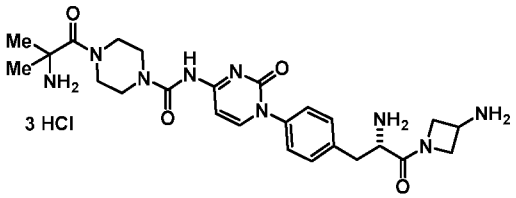
Compound 145



N-(1-(4-(1-Amino-2-(azetidin-3-ylamino)-2-oxoethyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-4-(2-amino-2-methylpropanoyl)piperazine-1-carboxamide hydrochloride salt

[00874] Prepared in a similar fashion as Scheme C-26 from 2-amino-2-(4-bromophenyl)acetic acid. ^{1}H NMR (400 MHz, D_2O) δ 7.95 (d, 1H), 7.70 (d, 2H), 7.61 (d, 2H), 6.88 (d, 1H), 5.28 (s, 1H), 4.43–4.30 (m, 3H), 4.17 (d, 2H), 3.79 (s, 4H), 3.73 (s, 4H), 1.75 (s, 6H). LCMS [M+H] 512.2.

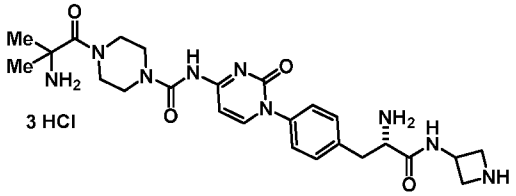
Compound 146



(S)-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-amino-3-(3-aminoazetidin-1-yl)-3-oxopropyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt.

[00875] Prepared in a similar fashion as Scheme C-26 from (S)-2-amino-3-(4-bromophenyl)propanoic acid. ^{1}H NMR (400 MHz, D_2O) δ 8.16 (d, 1H), 7.58–7.49 (m, 4H), 6.86–6.80 (m, 1H), 4.66 (t, 1H), 4.51–4.24 (m, 2H), 4.17–4.00 (m, 2H), 3.88–3.66 (m, 9H), 3.32–3.18 (m, 2H), 1.75 (s, 6H). LCMS [M+H] 526.4.

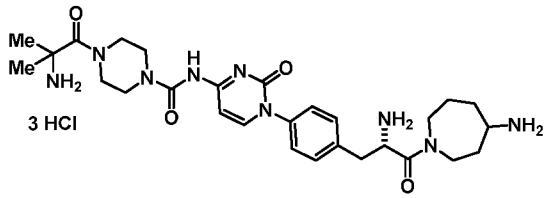
Compound 147



(S)-4-(2-Amino-2-methylpropanoyl)-N-(1-(4-(2-amino-3-(azetidin-3-ylamino)-3-oxopropyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

[00876] Prepared in a similar fashion as Scheme C-26 from (S)-2-amino-3-(4-bromophenyl)propanoic acid. ^{1}H NMR (400 MHz, D_2O) δ 8.08 (d, 1H), 7.50 (s, 4H), 6.83 (d, 1H), 4.74 (d, 1H), 4.38–4.24 (m, 3H), 4.17–4.09 (m, 1H), 3.98–3.90 (m, 1H), 3.80 (s, 3H), 3.75 (s, 5H), 3.38–3.24 (m, 2H), 1.75 (s, 6H). LCMS [M+H] 526.3.

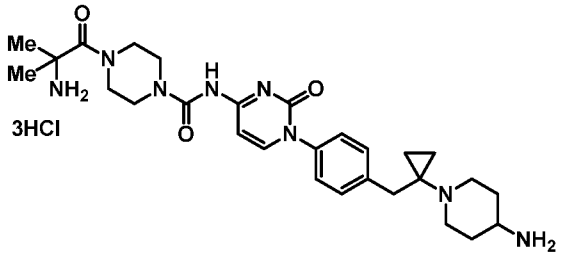
Compound 148



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((2S)-2-amino-3-(4-aminoazepan-1-yl)-3-oxopropyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride sal

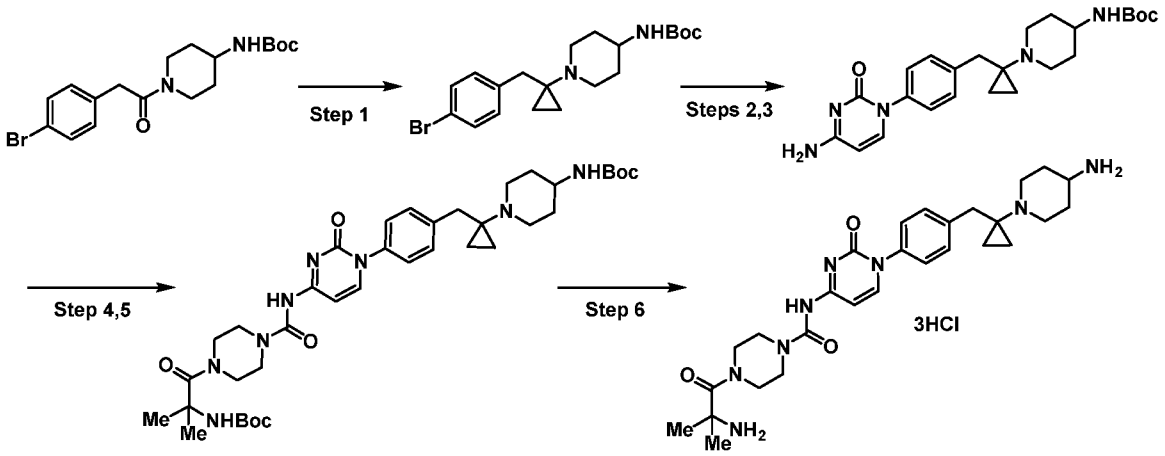
[00877] Prepared in a similar fashion as Scheme C-26 from (S)-2-amino-3-(4-bromophenyl)propanoic acid. ^{1}H NMR (400 MHz, D_2O) δ 8.02 (d, 1H), 7.49 (d, 4H), 6.83 (d, 1H), 3.93–3.41 (m, 12H), 3.39–3.05 (m, 4H), 2.30–2.11 (m, 1H), 2.11–1.87 (m, 2H), 1.75 (s, 6H), 1.70–1.22 (m, 3H). LCMS [M+H] 568.4.

Compound 373



4-(2-Amino-2-methylpropanoyl)-N-(1-(4-((1-(4-aminopiperidin-1-yl)cyclopropyl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt

Scheme C-27



Reagents: 1) Ti(^{i}OPr)$_4$, EtMgBr, THF, rt, 16h 2) B(Pin)$_2$, KOAc, Pd(dppf)Cl$_2$, Dioxane, 110°C, 16h 3) Cu(OAc)$_2$. H_2O, TMEDA, MeOH:H_2O (4:1), rt, 48h 4) CDI, CH_2Cl_2, 16h 5) CH_3CN, reflux, 16h 6) HCl MeOH, rt, 4h.

[00878] Step 1: To a stirred solution of *tert*-butyl (1-(2-(4-bromophenyl)acetyl)piperidin-4-yl)carbamate (0.5 g, 1.26 mmol) and Ti(iOPr)4 (0.76 mL, 2.52 mmol) was added ethyl magnesium bromide solution (3M in Et_2O, 2.1 mL, 6.30 mmol). The rection mixture was stirred for 16h at rt followed by the addition of a solution of Rochelle salt and dilution with ethyl acetate. The mixture was stirred for 96h. The organic layer was separated, dried over Na2SO4 , filtered and evaporated under reduced pressure to yield *tert*-butyl (1-(1-(4-bromobenzyl)cyclopropyl)piperidin-4-yl)carbamate as a yellow colored sticky solid which was used in next step without further purification.

[00879] Step 2: *tert*-butyl (1-(1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)cyclopropyl)piperidin-4-yl)carbamate. To a stirred suspension of *tert*-butyl (1-(1-(4-bromobenzyl)cyclopropyl)piperidin-4-yl)carbamate (0.21 g, 0.5 mmol), bis (pinacolato) diboron (0.15g, 0.6 mmol), and KOAc (0.15g, 1.5 mmol) in a flame dried pressure flask was added Pd(dppf)Cl_2 (13 mg, .02 mmol) and the reaction mixture was purged with nitrogen. The pressure flask was sealed and stirred at 110 °C for 16h. The mixture was diluted with ethyl acetate and filtered through celite. The filtrate was concentrated to give the title compound as a brown colored sticky solid.

[00880] Step 3. *tert*-butyl (1-(1-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)benzyl)cyclopropyl)piperidin-4-yl)carbamate. A suspension of cytosine (0.06 g, 0.5 mmol) and *tert*-butyl (1-(1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)cyclopropyl)piperidin-4-yl)carbamate (0.23 g, 0.5 mmol), in a mixture of 4:1 MeOH:H_2O (10ml) was stirred at rt in open air. After 30 min. TMEDA (0.09 ml, 0.6 mmol)

and $Cu(OAc)_2 \cdot H_2O$ (0.10 g, 0.5 mmol) were added. The reaction was stirred in open air for 48h at rt. The MeOH was evaporated reduced pressure, and the residue was crystallized with EtOH to yield the title compound.

[00881] Step 4. *tert*-butyl (1-(1-(4-(4-(1H-imidazole-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)cyclopropyl)piperidin-4-yl)carbamate. To a stirred suspension of *tert*-butyl (1-(1-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)benzyl)cyclopropyl)piperidin-4-yl)carbamate (0.05 g, 0.11 mmol) in dichloromethane (12 mL) was added CDI (24 mg, 0.14 mmol) and the mixture stirred for 16h at rt. The solvent was evaporated under reduced pressure and the resultant solid was used in the next step without further purification.

[00882] Step 5. *tert*-butyl (1-(1-(4-(4-(4-(2-((tert-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)cyclopropyl) piperidin-4-yl)carbamate. *tert*-Butyl (1-(1-(4-(4-(1H-imidazole-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)cyclopropyl)piperidin-4-yl)carbamate (60 mg, 0.11 mmol) and *tert*-butyl (2-methyl-1-oxo-1-(piperazin-1-yl)propan-2-yl)carbamate (37 mg, 0.14 mmol) were suspended in acetonitrile and refluxed for 16h. The solvent was evaporated and the residue was diluted with ethyl acetate (12 mL) and extracted (3x8 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the title compound.

[00883] Step 6. 4-(2-amino-2-methylpropanoyl)-N-(1-(4-((1-(4-aminopiperidin-1-yl)cyclopropyl)methyl)phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)piperazine-1-carboxamide hydrochloride salt. *tert*-Butyl (1-(1-(4-(4-(4-(2-((tert-butoxycarbonyl)amino)-2-methylpropanoyl)piperazine-1-carboxamido)-2-oxopyrimidin-1(2H)-yl)benzyl)cyclopropyl) piperidin-4-yl)carbamate (60 mg, 0.08 mmol) was dissolved in methanolic HCl and stirred for 4h. The solvent was evaporated and the residue was purified using HPLC. Collection and evaporation of the desired fraction, addition and removal of methanolic HCl yielded the title compound as a brown solid. ^1H NMR (500 MHz, D_2O) δ 7.95 (d, 1H), 7.44 (br s, 2H), 7.41 (br s, 2H), 6.78 (d, 1H), 3.80-3.63 (m, 9H), 3.68-3.43 (m, 4H), 3.32 (s, 2H), 2.32 (d, 2H), 1.99-1.84 (m, 2H), 1.69 (s, 6H), 1.13 (br s, 2H), 0.86 (br s, 2H). LCMS [M+H] 537.36.

Biological Examples

Standard Microbiological Activity:

[00884] A certified BSL-2 laboratory was used for testing. Compounds were evaluated using the broth 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 *S. aureus* (Sa), *E. coli* (Ec), *K. pneumoniae* (Kp), *A. baumannii* (Ab), *E. faecalis* (Ef) and *P. aeruginosa* (Pa).

[00885] E. coli S30 extract: 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.

[00886] Compounds were serial diluted in 0.5 mL microcentrifuge tubes by mixing and transferring 50 µL from the highest concentration to 50 µL of water, mixing and transferring 50 µL of this 2-fold dilution to 50 µL 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 µL) to wells in a black round bottom 96-well plate. Water (2 µL) was used as a "no inhibitor" control in 4 wells/plate. No DNA control reaction mixture (20 µL; see below) was used as a control in 4 wells/plate for background luminescence. S30 luciferase synthesis mixture (18 µL; 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 µL 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 µL S30 extract, circular
712 µL S30 Premix without amino acids
4.45 µL pBESTluc™ DNA (1 µg/ µL)
78 µL complete amino acid mixture
267 µL water

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

Rabbit Reticulocyte lysate

[00887] 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 serial diluted in 0.5 mL microcentrifuge tubes by mixing and transferring 50 µL from the highest concentration to 50 µL of water, mixing and transferring 50 µL of this 2-fold dilution to 50 µL 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 µL) to wells in a black round bottom 96-well plate. Water (2.5 µL) was used as a "no inhibitor" control in 4 wells/plate. No RNA control reaction mixture (2 µL; see below) was used as a control in 4 wells/plate for background luminescence. Rabbit reticulocyte luciferase synthesis mixture (22.5 µL; see below) was added to wells with compounds or water mixture and incubated at 30 °C for 90 minutes. Luciferase assay reagent (25 µL) 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 µL rabbit reticulocyte lysate
5.7 µL Luciferase Control RNA (1 µg/ µL)
26 µL complete amino acid mixture
395 µL water

No RNA Control
70 µL rabbit reticulocyte lysate
2 µL complete amino acid mixture
28 µL water

Minimum Inhibitory Concentration (MIC)

[00888] 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.

[00889] To prepare microdilution trays, two-fold dilutions of antimicrobial agent are prepared in growth medium: Cation-Adjusted Mueller-Hinton Broth (CAMHB), or CAMHB supplemented with sodium bicarbonate (6.25 or 25 mM final concentration prepared from a 1.0M stock solution) or CAMHB supplemented with heat inactivated human serum (Fisher Cat. # BP2657100) 0-50% by adding 200 µL of the highest concentration to be tested (64 µg/mL, for example) in row A, mixing and transferring 100 µL from row A to 100 µL growth

medium in row B, then repeating the mixing and transferring through row H of the 96-well plate, discarding the excess 100 µL 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 5×10^4 CFU/well by adding 5 µL of a 1:10 dilution of a 0.5 McFarland suspension (1×10^8 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 CAMHB. The cultures are incubated at 35 ± 2°C until it achieves or exceeds the turbidity of the 0.5 McFarland standard, determined by measuring A_{600nm} (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.

[00890] Data for compounds is provided in Table 16. An IC_{50} value (µM) that is 1 µM or greater (% inhibition is ≤ 50% @ 1 µM) is designated by a "+". An IC_{50} value that is 0.5 µM or greater and less than 1 µM (% inhibition is > 50% and ≤ 90% @ 1 µM) is designated by a "++". An IC_{50} value that is less than 0.5 µM (% inhibition is > 90% @ 1 µM) is designated by "+++". An MIC value (µg/mL) that is 32 µg/mL or greater is designated by a "+". An MIC value (µg/mL) that is 8 µg/mL or greater and less than 32 µg/mL is designated by a "++". An MIC value (µg/mL) that is less than 8 µg/mL is designated by "+++". "NA" means not available.

Table 16. Biological Activity of Compounds of Formula I or a pharmaceutically acceptable salt thereof

No.	Sa + bicarb MIC	E. coli + bicarb MIC	Kp (1705) + bicarb MIC	Kp (060) + bicarb MIC	Pa MIC + bicarb	Ab + bicarb MIC	Ef + bicarb MIC	S30 IC_{50} (µM/ % inhib.)	Rabbit reticulocyte IC_{50} (µM/% inhib.)
1	NA	NA	NA	NA	NA	NA	NA	++	+
2	NA	++	NA	+	+	NA	NA	+++	+
3	NA	NA	NA	NA	NA	NA	NA	+	NA
4	NA	NA	NA	NA	NA	NA	NA	+	NA
5	NA	NA	NA	NA	NA	NA	NA	+	+
6	NA	NA	NA	NA	NA	NA	NA	+	+
7	NA	NA	NA	NA	NA	NA	NA	+	NA
8	NA	NA	NA	NA	NA	NA	NA	NA	NA
9	NA	NA	NA	NA	NA	NA	NA	+	NA
10	NA	NA	NA	NA	NA	NA	NA	+++	+
11	NA	NA	NA	NA	NA	NA	NA	++	+

No.	Sa + bicarb MIC	E. coli + bicarb MIC	Kp (1705) + bicarb MIC	Kp (060) + bicarb MIC	Pa MIC + bicarb	Ab + bicarb MIC	Ef + bicarb MIC	S30 IC_{50} (μM/ % inhib.)	Rabbit reticulocyte IC_{50} (μM/% inhib.)
12	NA	+	+	NA	+	+	NA	++	+
13	NA	NA	NA	NA	NA	NA	NA	+	+
14	NA	NA	NA	NA	NA	NA	NA	NA	NA
15	NA	NA	NA	NA	NA	NA	NA	NA	NA
16	NA	NA	NA	NA	NA	NA	NA	+	+
17	NA	NA	NA	NA	NA	NA	NA	+++	+
18	NA	NA	NA	NA	NA	NA	NA	+++	+
21	+++	+++	+++	+++	++	+	+++	+++	+
22	+++	+++	++	NA	+	NA	NA	+++	+
23	++	+++	++	+++	+	+	+	+	+
24	++	++	+	+	+	+	+	+++	+
25	+++	+++	++	++	+	+	+	++	+
26	+++	+++	++	+++	+	+	++	+++	+
27	+++	+++	+++	+++	++	+	+++	+++	+
28	+++	+++	+++	+++	+	+	+++	+++	+
29	++	+++	+	++	+	+	+	+	+
30	+++	+++	++	++	+	+	+	+++	+
31	+++	+++	++	+++	+	+	++	+++	+
32	++	++	+	++	+	+	+	+	+
33	++	+++	+	+	+	+	+	++	+
34	+++	+++	++	++	+	+	+++	+++	+
35	+++	+++	++	++	++	+	+++	+	+
36	NA	NA	NA	NA	NA	NA	NA	+	+
37	NA	NA	NA	NA	NA	NA	NA	+	+
38	NA	NA	NA	NA	NA	NA	NA	+	+
39	NA	NA	NA	NA	NA	NA	NA	+	+
40	NA	NA	NA	NA	NA	NA	NA	+	+
41	NA	NA	NA	++	NA	+	++	+++	+
42	NA	+++	++	++	++	+	++	+++	+
43	NA	+++	+++	++	++	+	++	+++	+
44	NA	NA	NA	++	NA	+	+++	+++	+
45	NA	NA	NA	+++	NA	+	+++	+++	+
46	NA	NA	NA	NA	NA	NA	NA	+	+
47	NA	NA	NA	NA	NA	NA	NA	+	+
48	NA	NA	NA	NA	NA	NA	NA	+	+
49	NA	+	+	NA	+	+	NA	+	+
50	NA	NA	NA	NA	NA	NA	NA	+	+
51	NA	NA	NA	NA	NA	NA	NA	+	+
52	NA	NA	NA	NA	NA	NA	NA	+	+
53	NA	NA	NA	NA	NA	NA	NA	+	+
54	NA	NA	NA	NA	NA	NA	NA	+	+
55	NA	NA	NA	NA	NA	NA	NA	++	+

No.	Sa + bicarb MIC	E. coli + bicarb MIC	Kp (1705) + bicarb MIC	Kp (060) + bicarb MIC	Pa MIC + bicarb	Ab + bicarb MIC	Ef + bicarb MIC	S30 IC_{50} (µM/ % inhib.)	Rabbit reticulocyte IC_{50} (µM/% inhib.)
56	NA	+++	NA	+	+	NA	NA	+++	+
57	+++	+++	++	+++	+	+	++	+++	+
58	NA	++	+	NA	+	+	NA	+++	+
59	NA	+	+	NA	+	+	NA	+	+
60	NA	NA	NA	NA	NA	NA	NA	NA	+
61	+++	+++	+	++	+	+	++	+++	+
62	+	+++	+	+	+	+	+	+++	+
63	NA	NA	NA	NA	NA	NA	NA	++	+
64	NA	+	NA	+	+	NA	NA	+++	+
65	NA	+++	NA	+	+	NA	NA	+++	+
66	NA	NA	NA	NA	NA	NA	NA	+	+
67	NA	NA	NA	NA	NA	NA	NA	+	+
68	+	+++	+	NA	+	NA	NA	++	+
69	NA	NA	NA	NA	NA	NA	NA	+	+
70	+++	+++	+++	++	+	+	+++	+++	+
71	+++	+++	+++	+++	++	+++	+++	+++	+
72	NA	NA	NA	NA	NA	NA	NA	++	+
73	NA	NA	NA	NA	NA	NA	NA	NA	+
74	NA	+	+	NA	+	+	NA	NA	+
75	NA	NA	NA	NA	NA	NA	NA	NA	+
76	NA	NA	NA	NA	NA	NA	NA	NA	+
77	NA	NA	NA	NA	NA	NA	NA	+	+
78	NA	NA	NA	NA	NA	NA	NA	+	+
79	+++	+++	++	++	+	+	++	+++	+
80	NA	NA	NA	NA	NA	NA	NA	++	+
81	NA	NA	NA	NA	NA	NA	NA	+	+
82	+++	+++	++	++	+	++	+++	+++	+
83	NA	NA	NA	NA	NA	NA	NA	+	+
84	NA	NA	NA	NA	NA	NA	NA	+	+
85	+	+++	+	NA	+	NA	NA	+	+
86	NA	NA	NA	NA	NA	NA	NA	+	+
87	NA	NA	NA	NA	NA	NA	NA	+	+
88	NA	NA	NA	NA	NA	NA	NA	+	+
89	NA	NA	NA	+	NA	+	+	+++	+
90	+++	+++	+++	+++	+	+++	+++	+++	+
91	NA	+++	+++	++	+	+	+++	+++	+
92	NA	+	NA	NA	NA	NA	NA	+	NA
93	NA	+	NA	NA	NA	NA	NA	+	NA
94	NA	NA	NA	NA	NA	NA	NA	+	+
95	++	+++	++	++	+	+	+	+++	+
96	+++	+++	+	NA	+	NA	NA	+	+
97	NA	++	NA	NA	NA	NA	NA	+++	+

No.	Sa + bicarb MIC	E. coli + bicarb MIC	Kp (1705) + bicarb MIC	Kp (060) + bicarb MIC	Pa MIC + bicarb	Ab + bicarb MIC	Ef + bicarb MIC	S30 IC_{50} (µM/ % inhib.)	Rabbit reticulocyte IC_{50} (µM/% inhib.)
98	+++	+++	+	NA	+	NA	NA	+++	+
99	NA	+++	++	++	+	NA	NA	+++	+
100	NA	NA	NA	NA	NA	NA	NA	++	+
101	NA	NA	NA	NA	NA	NA	NA	++	+
102	NA	NA	NA	NA	NA	NA	NA	+	+
103	NA	+	NA	NA	NA	+	NA	+	+
104	NA	NA	+	NA	NA	NA	NA	+++	+
105	NA	NA	NA	NA	NA	NA	NA	+++	+++
106	NA	NA	NA	NA	NA	NA	NA	+	+
107	NA	NA	NA	NA	NA	NA	NA	+	+
108	NA	+	+	NA	NA	NA	NA	++	+
109	+++	+++	+++	NA	+	NA	NA	+++	+
110	+++	+++	++	+++	+	+	++	+++	+
111	++	++	+	+	+	+	+	++	+
112	++	++	+	+	+	+	+	+++	+
113	++	++	+	+	+	+	+	+++	+
114	+	+++	++	++	+	+	+	+++	+
115	+++	+++	+	+	+	+	++	+++	+
116	++	+++	++	++	+	+	++	+++	+
117	+++	+++	+++	+++	+	+	+++	+++	+
118	+++	+++	+++	+++	++	++	+++	+++	+
119	+++	+++	+++	+++	+++	+++	+++	+++	+
120	+++	+++	++	++	+	+	++	+++	+
121	+++	+++	+++	+++	+	+	+++	+++	+
122	+++	+++	+++	+++	+	+	+++	+++	+
123	+++	+++	++	+++	+	+	+	+++	+
124	+++	+++	+++	+++	+	+	+++	+++	+
125	+++	+++	+++	+++	+	+	+++	+++	+
126	++	+++	++	++	+	+	+	+++	+
127	+++	+++	+++	+++	+	+	+++	+++	+
128	+++	+++	++	+++	++	+	+++	+++	+
129	+++	+++	+++	+++	++	+++	+++	+++	+
130	+++	+++	+++	+++	++	++	+++	+++	+
131	+++	+++	+++	+++	++	+++	+++	+++	+
132	+++	+++	+	+	+	+	+	+++	+
133	NA	NA	NA	+	NA	+	+	+++	+
134	NA	+++	NA	++	+	+	++	+++	+
135	NA	NA	NA	NA	NA	NA	NA	+	+
136	++	++	++	+	+	+	++	+++	+
137	++	+++	++	+	+	+	+	+++	+
138	+++	+++	+	+	+	+	+	++	+
139	+++	+++	++	++	++	+	+++	+++	+

No.	Sa + bicarb MIC	E. coli + bicarb MIC	Kp (1705) + bicarb MIC	Kp (060) + bicarb MIC	Pa MIC + bicarb	Ab + bicarb MIC	Ef + bicarb MIC	S30 IC_{50} (µM/ % inhib.)	Rabbit reticulocyte IC_{50} (µM/% inhib.)
140	+++	+++	+++	+++	++	++	+++	+++	+
141	+++	+++	+++	++	++	+	+++	+++	+
142	+++	+++	++	+	++	++	+++	+++	+
143	+	+	+	+	+	+	+	+	+
144	+	+	+	+	+	+	+	+	+
145	+	+	+	+	+	+	+	++	+
146	+	+	+	+	+	+	+	+	+
147	+	+	+	+	+	+	+	+	+
148	+	+	+	+	+	+	+	+++	+
149	+++	+++	++	++	+	+	++	+++	+
150	+++	+++	+	+	+	+	+	++	+
151	+++	+++	++	+++	++	+	+++	+++	+
152	+++	+++	++	+++	+	+	+	+	+
153	+++	+++	++	++	+	+	+	+	+
154	+++	+++	+++	+++	+	+	+++	+++	+
155	++	+++	+	++	+	+	+	+	+
156	+++	+++	++	+++	+	+	++	+++	+
157	+++	+++	++	+++	+	+	+++	+++	+
158	+++	+++	+++	+++	++	+	+++	+++	+
159	+++	+++	++	+++	+	+	++	+++	+
160	+++	+++	+++	+++	+	+	+++	+++	+
161	+++	+++	+++	+++	+	++	+++	+++	+
162	+++	+++	++	++	+	+	++	+++	+
163	++	++	+	+	+	+	+	+	+
164	+++	+++	+++	+++	+	++	+++	+++	+
165	+	++	+	++	+	+	+	+	+
166	++	++	+	+	+	+	+	+	+
167	++	+++	+	+	+	+	++	+	+
168	NA	NA	NA	++	NA	+	++	+++	+
169	+++	+++	+++	+++	++	++	+++	+++	+
170	++	+++	+++	++	++	+	+	+++	+
171	++	+++	+	+	+	+	+	+	+
172	+++	+++	+	++	+	+	+++	+++	+
173	+++	+++	+	++	+	+	++	+++	+
174	+++	+++	++	++	+	++	+++	+++	+
175	+++	+++	+++	+++	++	+	+++	+++	+
176	+++	+++	++	++	+	+	+++	+++	+
177	+++	+++	++	++	+	+	+	+	+
178	++	+++	+	++	+	+	+	+	+
179	+++	+++	++	++	+	+	++	+++	+
180	++	+++	+	++	+	+	+	++	+
181	+++	+++	++	++	+	+	++	+++	+

No.	Sa + bicarb MIC	E. coli + bicarb MIC	Kp (1705) + bicarb MIC	Kp (060) + bicarb MIC	Pa MIC + bicarb	Ab + bicarb MIC	Ef + bicarb MIC	S30 IC_{50} (µM/ % inhib.)	Rabbit reticulocyte IC_{50} (µM/% inhib.)
182	+	++	+	+	+	+	+	+	+
183	+	+	+	+	+	+	+	+	+
184	+++	+++	+	++	+	+	++	+++	+
185	+++	+++	+	++	+	+	++	+++	+
186	+++	+++	++	++	+	+	++	+++	+
187	+++	+++	+++	+++	+	++	+++	+++	+
188	+++	+++	++	++	+	+	+++	+++	+
190	+++	+++	++	++	+	+	+++	+++	+
191	+++	+++	+	++	+	+	++	++	+
192	+++	+++	++	++	+	+	++	+	+
193	+++	+++	++	++	+	+	++	+++	+
194	+	+++	+	+	+	+	+	++	+
195	++	+	+	+	+	+	+	++	+
196	NA	NA	NA	NA	NA	NA	NA	+++	+
197	NA	NA	NA	NA	NA	NA	NA	+	NA
198	++	+++	++	+++	+	+	++	+++	+
199	++	+++	+	++	+	+	+	+++	+
200	++	++	++	++	++	+	++	+++	+
201	+	+	+	+	+	+	+	+	+
204	NA	NA	NA	NA	NA	NA	NA	++	+
205	++	+++	++	+	+	+	+	+++	+
206	NA	NA	NA	NA	NA	NA	NA	+	+
207	NA	NA	NA	NA	NA	NA	NA	+	+
208	NA	++	+	NA	NA	NA	NA	+	NA
209	+	+++	+	+	+	+	+	+	+
210	+++	+++	++	++	+	+	+++	+++	+
211	+++	+++	+	++	+	+	++	++	+
212	+++	+++	+	+	+	+	+++	++	+
213	+++	+++	++	++	+	+	+++	+++	+
214	NA	+++	+	NA	NA	NA	NA	+++	NA
215	NA	+++	+	NA	NA	NA	NA	+++	NA
216	NA	++	+	NA	NA	NA	NA	+	NA
217	NA	NA	NA	NA	NA	NA	NA	NA	NA
218	NA	+++	+++	NA	NA	NA	NA	+++	+
219	+++	+++	++	++	+	+	++	++	+
220	+++	+++	++	+++	+	++	++	+++	+
221	NA	+++	+++	NA	NA	NA	NA	+++	+
222	NA	+++	+++	NA	NA	NA	NA	+++	+
223	NA	+++	++	++	+	+	+++	++	+
224	NA	+++	+	NA	NA	NA	NA	+++	+
225	NA	NA	NA	NA	NA	NA	NA	+	+
226	NA	+++	+++	NA	NA	NA	NA	+++	+

No.	Sa + bicarb MIC	E. coli + bicarb MIC	Kp (1705) + bicarb MIC	Kp (060) + bicarb MIC	Pa MIC + bicarb	Ab + bicarb MIC	Ef + bicarb MIC	S30 IC_{50} (μM/ % inhib.)	Rabbit reticulocyte IC_{50} (μM/% inhib.)
227	+	++	+	+	+	+	+	+	+
230	NA	++	+	NA	NA	NA	NA	+	+
231	NA	NA	NA	NA	NA	NA	NA	+	+
233	+++	+++	+	+	+	+	+	+	+
234	NA	+	+	NA	NA	NA	NA	+	+
235	NA	+	+	NA	NA	NA	NA	+	+
236	NA	+++	+	NA	NA	NA	NA	+	+
237	NA	+++	+	NA	NA	NA	NA	++	+
238	NA	+++	++	NA	NA	NA	NA	+	+
239	NA	+++	++	NA	NA	NA	NA	+++	+
240	NA	+	+	NA	NA	NA	NA	++	+
241	NA	++	+	NA	NA	NA	NA	+++	+
242	+++	+++	+	+	+	+	++	+++	+
243	+++	+++	++	++	+	+	++	+++	+
244	NA	+++	+	NA	NA	NA	NA	+	+
245	+++	+++	+++	+++	+	+	+++	+++	+
246	NA	+++	+	NA	NA	NA	NA	+	+
247	+++	+++	+++	+++	+	+	+++	+++	+
248	NA	+++	+	NA	NA	NA	NA	+++	+
249	+++	+++	++	+++	+	+	++	+++	+
250	NA	+++	+	NA	NA	NA	NA	+++	+
251	+++	+++	++	++	+	+	+++	+++	+
252	NA	+++	++	NA	NA	NA	NA	+++	+
253	NA	+++	+	NA	NA	NA	NA	+++	+
254	+++	+++	++	++	+	+++	+++	++	+
255	NA	+++	++	NA	NA	NA	NA	+++	+
267	NA	+++	+	NA	NA	NA	NA	+++	+
268	++	++	+	+	+	+	+	+	+
269	+	++	+	++	+	+	+	+	+
270	+++	+++	+++	+++	++	+++	+++	+++	+
271	+++	+++	+++	+++	+	+	+++	+++	+
272	+++	+++	+++	+++	++	+++	+++	+++	+
273	+++	+++	+++	+++	++	+++	+++	+++	+
274	+++	+++	+++	+++	++	+++	+++	+++	+
275	+++	+++	+++	+++	++	+++	+++	+++	+
276	+++	+++	+	+	+	+	+++	++	+
277	+++	+++	+++	+++	+	+	+++	+++	+
278	+++	+++	+++	+++	++	++	+++	+++	+
279	+++	+++	++	++	+	+	++	+	+
280	+++	+++	++	+++	+	+	+++	++	+
281	+++	+++	++	+++	++	+	+++	+++	+
282	+++	+++	+	++	+	+	+	+	+

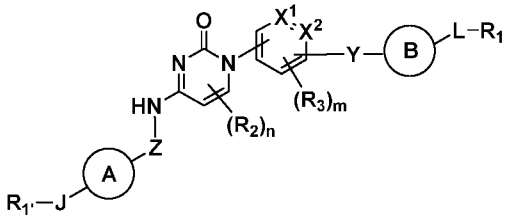
No.	Sa + bicarb MIC	E. coli + bicarb MIC	Kp (1705) + bicarb MIC	Kp (060) + bicarb MIC	Pa MIC + bicarb	Ab + bicarb MIC	Ef + bicarb MIC	S30 IC_{50} (µM/ % inhib.)	Rabbit reticulocyte IC_{50} (µM/% inhib.)
283	+++	+++	++	+++	+	+	+++	+++	+
284	+++	+++	+++	+++	++	+++	+++	+++	+
285	+++	+++	+++	+++	++	+++	+++	+++	+
286	+++	+++	+++	+++	+	+	+++	+++	+
287	+++	+++	+++	+++	++	+	+++	+++	+
288	+++	+++	+++	+++	+	+	+++	+++	+
289	+++	+++	+	++	+	+	+	++	+
290	+++	+++	++	+++	+	+++	+++	++	+
291	+++	++	+	+	+	++	++	+	+
292	+	+	+	+	+	+	+	+	+
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294	+++	+++	+++	+++	+	+	++	+++	+
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296	+++	+++	++	++	+	+	+++	+++	+
297	+++	+++	+	+	+	+	++	++	+
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300	++	+	+	+	+	+	+	+	+
301	+++	+++	+++	+++	+	++	+++	++	+
302	+++	+++	+++	+++	+	+++	+++	+++	+
303	+++	+++	+	+	+	+	+	+	+
304	+++	+++	++	++	+	+	+++	+++	+
305	+++	+++	+++	+++	+	+	+++	+++	+
306	+++	+++	+	+	+	+	+	+	+
307	+++	+++	++	+++	++	+	+	+++	+
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310	++	+++	+	+	+	+	+	++	+
311	+++	+++	+	++	+	+	++	+++	+
312	+++	+++	+	+	+	+	+	+	+
313	+++	+++	+	+	+	+	+	++	+
314	+	+++	+	+	+	+	+	+	+
315	++	++	+	+	+	+	+	+	+
316	+++	+++	+	++	+	+	++	+++	+
317	+++	+++	+	+	+	+	++	+++	+
318	+++	+++	+	+	+	+	+	+++	+
319	++	++	+	+	+	+	+	++	+
320	++	+++	+	+	+	+	+	+++	+
321	+	++	++	++	+	+	+	+++	+
322	+	++	+	+	+	+	+	++	+
323	++	+++	+	+	+	+	+	+++	+
324	++	+++	+	+	+	+	+	+++	+

No.	Sa + bicarb MIC	E. coli + bicarb MIC	Kp (1705) + bicarb MIC	Kp (060) + bicarb MIC	Pa MIC + bicarb	Ab + bicarb MIC	Ef + bicarb MIC	S30 IC_{50} (µM/ % inhib.)	Rabbit reticulocyte IC_{50} (µM/% inhib.)
325	+	++	+	+	+	+	+	+++	+
326	++	+++	+	+	+	+	+	+++	+
327	++	+++	+	++	+	+	+	+++	+
328	+++	+++	+	+	+	+	+++	+++	+
329	+++	+++	+	+	+	+	+++	+++	+
330	++	+++	+	++	+	+	+	+++	+
331	++	+++	+	+	+	+	++	+++	+
332	++	+++	+	+	+	+	++	+++	+
333	++	++	+	+	+	+	+	+++	+
334	++	+++	+	+	+	+	+	+++	+
335	+++	+++	++	++	+	+	+	+++	+
336	+	++	+	+	+	+	+	+	+
337	+++	+++	+	+	+	+	++	+++	+
338	+++	+++	+	++	+	+	++	+++	+
339	++	+++	+	+	+	+	+	+++	+
340	++	+++	+	+	+	+	+	++	+
341	++	++	+	+	+	+	+	++	+
342	+	++	+	+	+	+	+	+++	+
343	+	++	+	+	+	+	+	++	+
344	+	+	+	+	+	+	+	+	+
345	+	+	+	+	+	+	+	++	+
346	+	+	+	+	+	+	+	++	+
347	++	+++	+	+	+	+	+	++	+
348	++	+++	+	+	+	+	+	+++	+
349	++	+++	+	NA	NA	NA	NA	+++	++
350	NA	NA	NA	NA	NA	NA	NA	+	+
351	NA	NA	NA	NA	NA	NA	NA	+	+
352	+	++	+	+	+	+	+	+++	+
353	++	+++	+	+	+	+	+	+++	+
354	+++	+++	+	+	+	+	++	+++	+
355	+++	+++	+	+	+	+	+++	+++	+
356	+	+	+	+	+	+	+	+	+
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358	+++	+++	+	+	+	+	++	++	+
359	++	+	+	+	+	+	+	+	+
360	NA	NA	NA	NA	NA	NA	NA	+++	+
361	NA	NA	NA	NA	NA	NA	NA	+	+
362	NA	NA	NA	NA	NA	NA	NA	+	+
363	NA	NA	NA	NA	NA	NA	NA	+	+
364	NA	NA	NA	NA	NA	NA	NA	+++	+
365	+++	+++	++	+++	+	+	+++	+++	+
366	NA	NA	NA	NA	NA	NA	NA	+	**NA**

No.	Sa + bicarb MIC	E. coli + bicarb MIC	Kp (1705) + bicarb MIC	Kp (060) + bicarb MIC	Pa MIC + bicarb	Ab + bicarb MIC	Ef + bicarb MIC	S30 IC_{50} (µM/ % inhib.)	Rabbit reticulocyte IC_{50} (µM/% inhib.)
367	NA	NA	NA	NA	NA	NA	NA	+	+
368	NA	NA	NA	NA	NA	NA	NA	+	+
369	NA	NA	NA	NA	NA	NA	NA	+	+
370	+++	+++	++	++	+	+	+++	+++	+
371	++	+++	++	++	+	+	++	+++	+
372	+++	+++	++	+++	+	+	+	+	+
373	+++	+++	+	++	+	+	++	+	+
374	++	+++	+	++	+	+	++	+++	+
376	+++	+++	++	+++	+	+	+++	+++	+
376	+	++	+	+	+	+	+	+++	+
377	+++	+++	++	++	+	+	+	+++	+
378	+++	+++	++	++	+	+	++	+++	+
379	+++	+++	+	+	+	+	+	+	+
380	+++	+++	++	++	+	+	++	+++	+
381	NA	+++	NA	NA	NA	NA	NA	+++	+
382	+++	+++	+++	+++	++	+	+++	+++	+
383	NA	NA	NA	NA	NA	NA	NA	+	+

Claims

1. A compound of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

Z is (C=O), (C=S), (C=NR_z), (S=O), or SO_2; wherein R_z is H, C_1-C_6 alkyl, or CN;

ring A is a monocyclic heterocycloalkylene or bicyclic heterocycloalkylene, wherein the monocyclic heterocycloalkylene or bicyclic heterocycloalkylene are optionally substituted with up to three substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, halo, CN, C_1-C_6 haloalkyl, phenyl, OH, NH_2, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)$_2$, COOH, COO(C_1-C_6 alkyl), $CONH_2$, and oxo;

J is absent or is C_1-C_6 alkylene, heterocycloalkylene, C_1-C_6 alkylene-heterocycloalkylene or C_1-C_6 alkylene-cycloalkylene, any of which may be optionally substituted with up to three substituents independently selected from the group consisting of halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, NH_2, CN, and OH; wherein at each occurrence of C_1-C_6 alkylene, up to two methylene units of the C_1-C_6 alkylene may independently and optionally be replaced with O, S, SO_2, C=O, or ; wherein t is 1, 2, 3, or 4;

X^1 and X^2 are each independently C-H or N;

Y is a linear C_1-C_8 alkylene, C_2-C_8 alkenylene, or C_2-C_8 alkynylene, any of which are optionally substituted with OH, NH_2, CN, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, COO(C_1-C_6 alkyl), COOH, $CONH_2$, or C_1-C_6 alkoxy, and wherein up to two carbon atoms of the C_2-C_8 alkylene, C_2-C_8 alkenylene, or C_2-C_8 alkynylene may be independently replaced by O, NH, N-(C_1-C_6 alkyl), N-(C_1-C_6 hydroxyalkyl), N-(C_1-C_6 haloalkyl), N-(C_{1-6} alkylene-cycloalkyl), N-(C_{3-8} cycloalkyl), NH(C=O), N-(C_{1-6} alkyl) (C=O), (C=O), or ; wherein t' is 1, 2, 3, or 4;

ring B is a monocyclic cycloalkylene or monocyclic heterocycloalkylene, either of which is optionally substituted with up to three substituents independently selected from the

group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CN, NH_2, C_1-C_6 haloalkyl, OH, COOH, $COO(C_1$-C_6 alkyl), $CONH_2$, and C_1-C_6 hydroxyalkyl;

L is absent, or is a C_1-C_6 alkylene, wherein up to two methylene units of the C_1-C_6 alkylene may independently be replaced with O, NH, (C=O), NH(C=O), N-(C_{1-6} alkyl)(C=O), (C=NH), NH(C=N), or N-(C_{1-6} alkyl);

R_1 is H, halo, C_1-C_6 haloalkyl, $NR_{x'}R_{y'}$, or monocyclic heterocycloalkyl optionally substituted with NH_2, $NH(C_1$-C_6 alkyl), $N(C_1$-C_6 alkyl)$_2$, wherein $R_{x'}$ and $R_{y'}$ are each independently H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, or an amino protecting group, wherein the C_1-C_6 alkyl and C_3-C_8 cycloalkyl are optionally substituted with up to three substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CN, C_1-C_6 haloalkyl, phenyl, OH, NH_2, $NH(C_1$-C_6 alkyl), $N(C_1$-C_6 alkyl)$_2$, -$COO(C_1$-C_6 alkyl), -$CONH_2$, and oxo; or R_1 is NH(C=O)-(C_1-C_6) alkyl, or NH-(C=NH)-NH_2, either of which may be optionally substituted with up to three substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CN, C_1-C_6 haloalkyl, phenyl, OH, NH_2, $NH(C_1$-C_6 alkyl), $N(C_1$-C_6 alkyl)$_2$, $COO(C_1$-C_6 alkyl), $CONH_2$, and oxo;

$R_{1'}$ is H or NR_xR_y, wherein R_x and R_y are each independently H, C_1-C_6 alkyl, C_1-C_6 alkyl-SO_3, $CO(C_1$-C_6 alkyl), CO-(C_1-C_6 alkylene)-NH_2, or an amino protecting group;

R_2 and R_3 are each independently selected from the group consisting of C_1-C_6 alkyl, halo, CN, OH, NH_2, $O(C_1$-C_6 haloalkyl), $NH(C_1$-C_6 alkyl), $N(C_1$-C_6 alkyl)$_2$, -$COO(C_1$-C_6 alkyl), -$CONH_2$, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy; and

m and n are each independently 0, 1, 2, or 3.

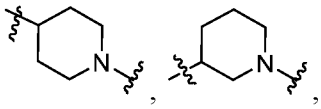
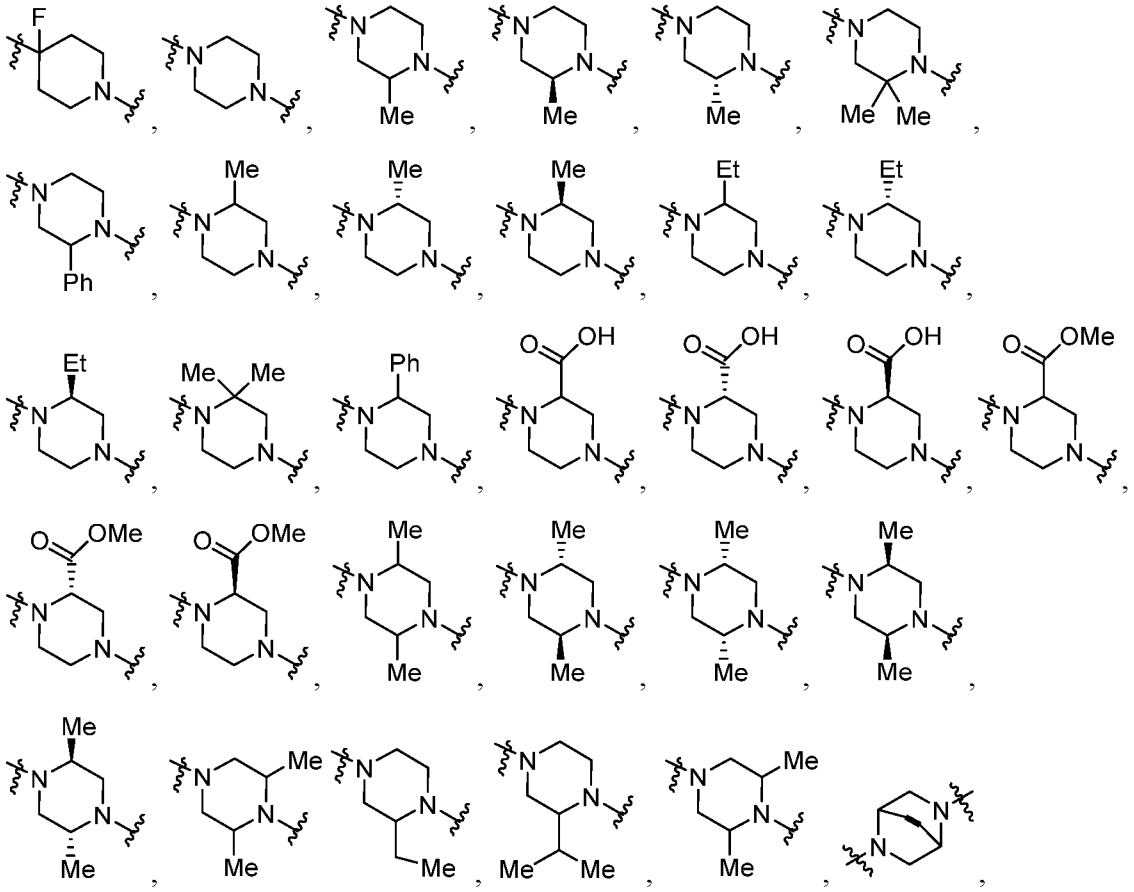
2. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein *Z* is -(C=O)-.

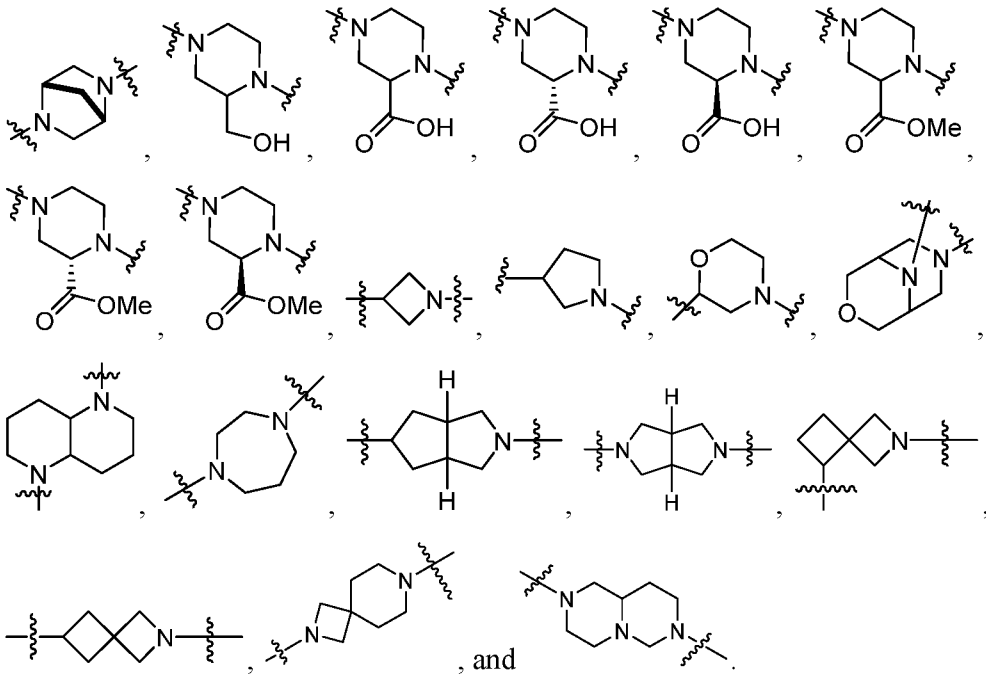
3. The compound of any one of claims 1-2 or a pharmaceutically acceptable salt thereof, wherein ring A is a 4 to 8 membered monocyclic heterocycloalkylene or 6 to 12 membered bicyclic heterocycloalkylene, wherein the monocyclic heterocycloalkylene and bicyclic heterocycloalkylene are optionally substituted with up to three substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, halo, C_1-C_6 haloalkyl, phenyl, OH, NH_2, COOH, $COO(C_1$-C_6 alkyl), and -$CONH_2$.

4. The compound of any one of claims 1-3 or a pharmaceutically acceptable salt thereof, wherein ring A is a 4 to 7 membered monocyclic heterocycloalkylene optionally substituted

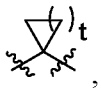
with up to two substituents independently selected from the group consisting of halo, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, phenyl, COOH, and COO(C_1-C_6 alkyl), wherein the monocyclic heterocycloalkylene contains up to two heteroatoms selected from nitrogen and oxygen.

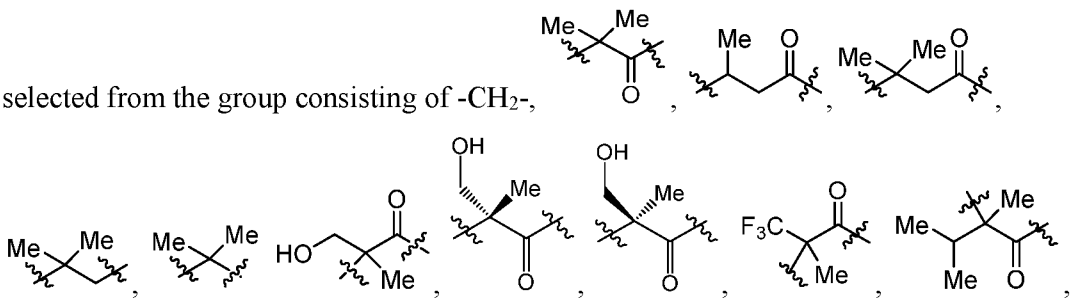
5. The compound of any one of claims 1-3 or a pharmaceutically acceptable salt thereof, wherein ring A is a 6 to 11 membered bicyclic heterocycloalkylene optionally substituted with up to three substituents selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, halo, C_1-C_6 haloalkyl, phenyl, OH, NH_2, COOH, COO(C_1-C_6 alkyl), and -$CONH_2$, wherein the bicyclic heterocycloalkylene contains up to three heteroatoms selected from nitrogen and oxygen.

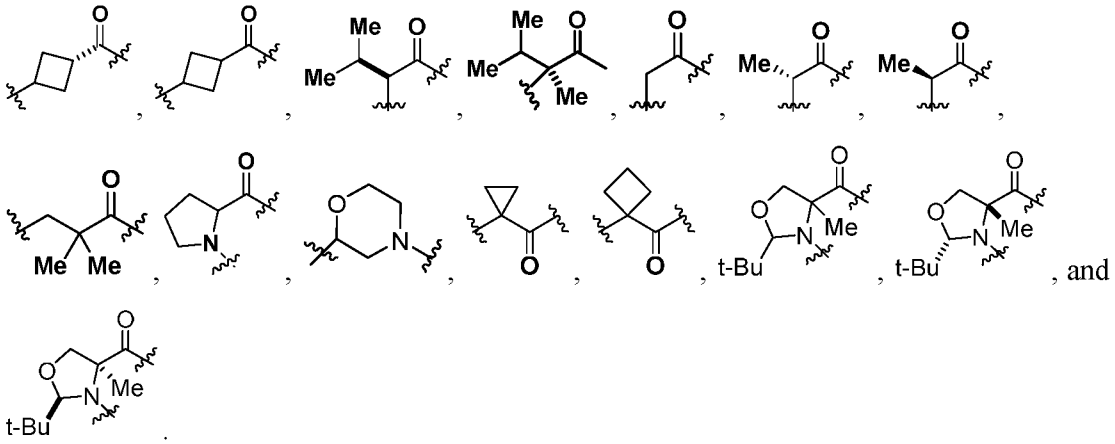
6. The compound of any one of claims 1-5 or a pharmaceutically acceptable salt thereof, wherein ring A is selected from the group consisting of , 



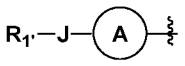
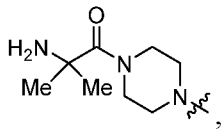
7. The compound of any one of claims 1-6 or a pharmaceutically acceptable salt thereof, wherein J is absent.

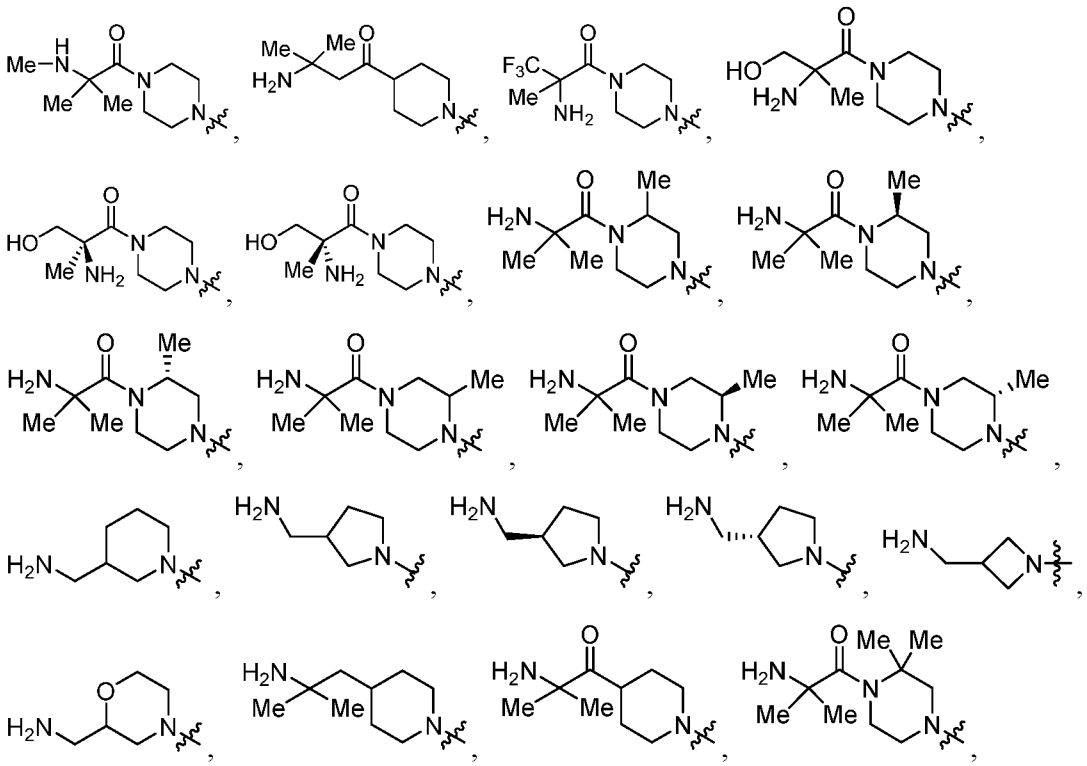
8. The compound of any one of claims 1-6 or a pharmaceutically acceptable salt thereof, wherein J is C_1-C_6 alkylene, heterocycloalkylene, C_1-C_6 alkylene-heterocycloalkylene or C_1-C_6 alkylene-cycloalkylene, any of which may be optionally substituted with up to two substituents independently selected from the group consisting of halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, NH_2, CN, and OH; wherein at each occurrence of C_1-C_6 alkylene, one or two methylene units of the C_1-C_6 alkylene may independently and optionally be replaced with C=O or , wherein t is 1, 2, or 3.

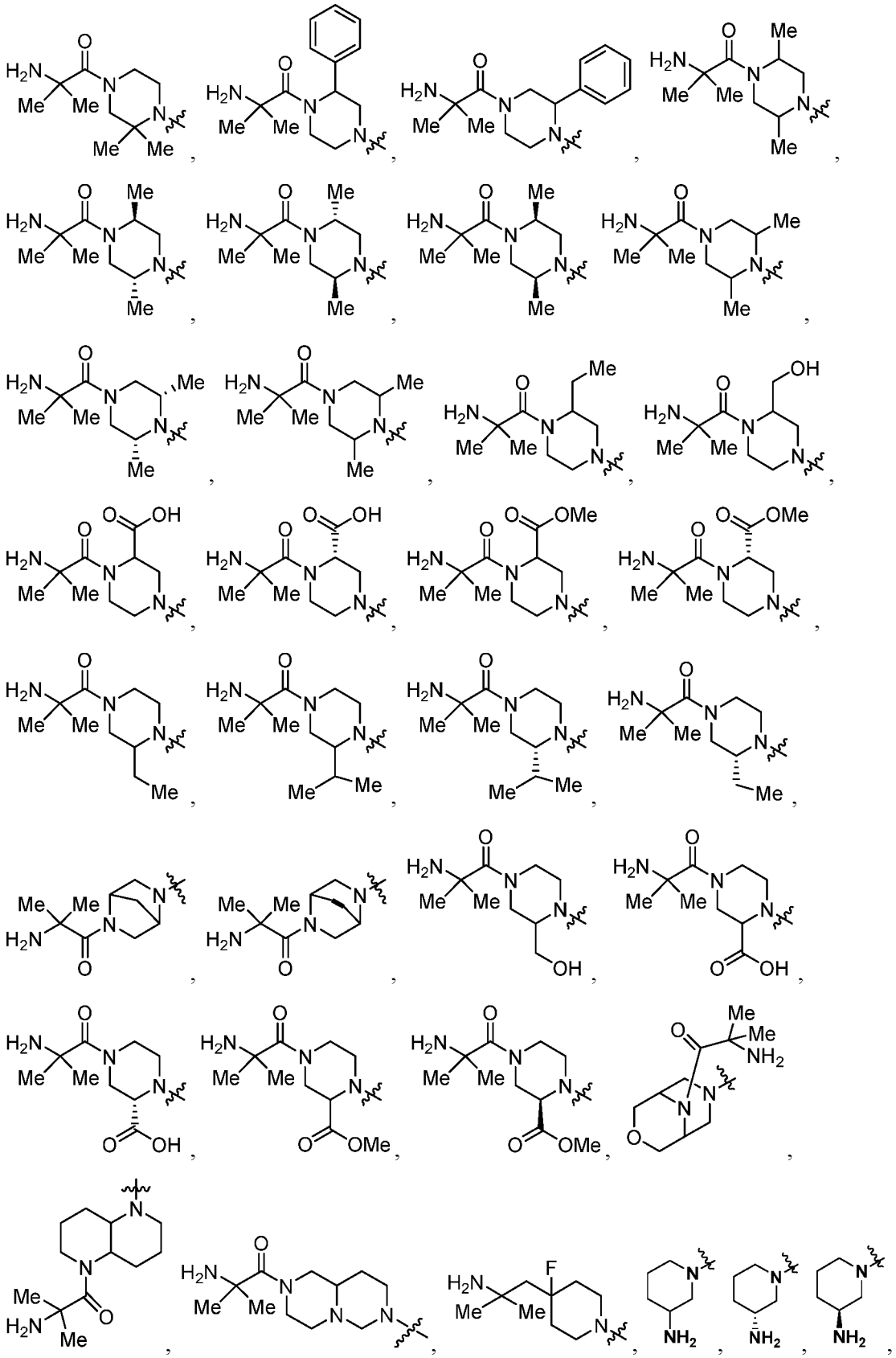
9. The compound of claim 8 or a pharmaceutically acceptable salt thereof, wherein J is selected from the group consisting of -CH_2-, 

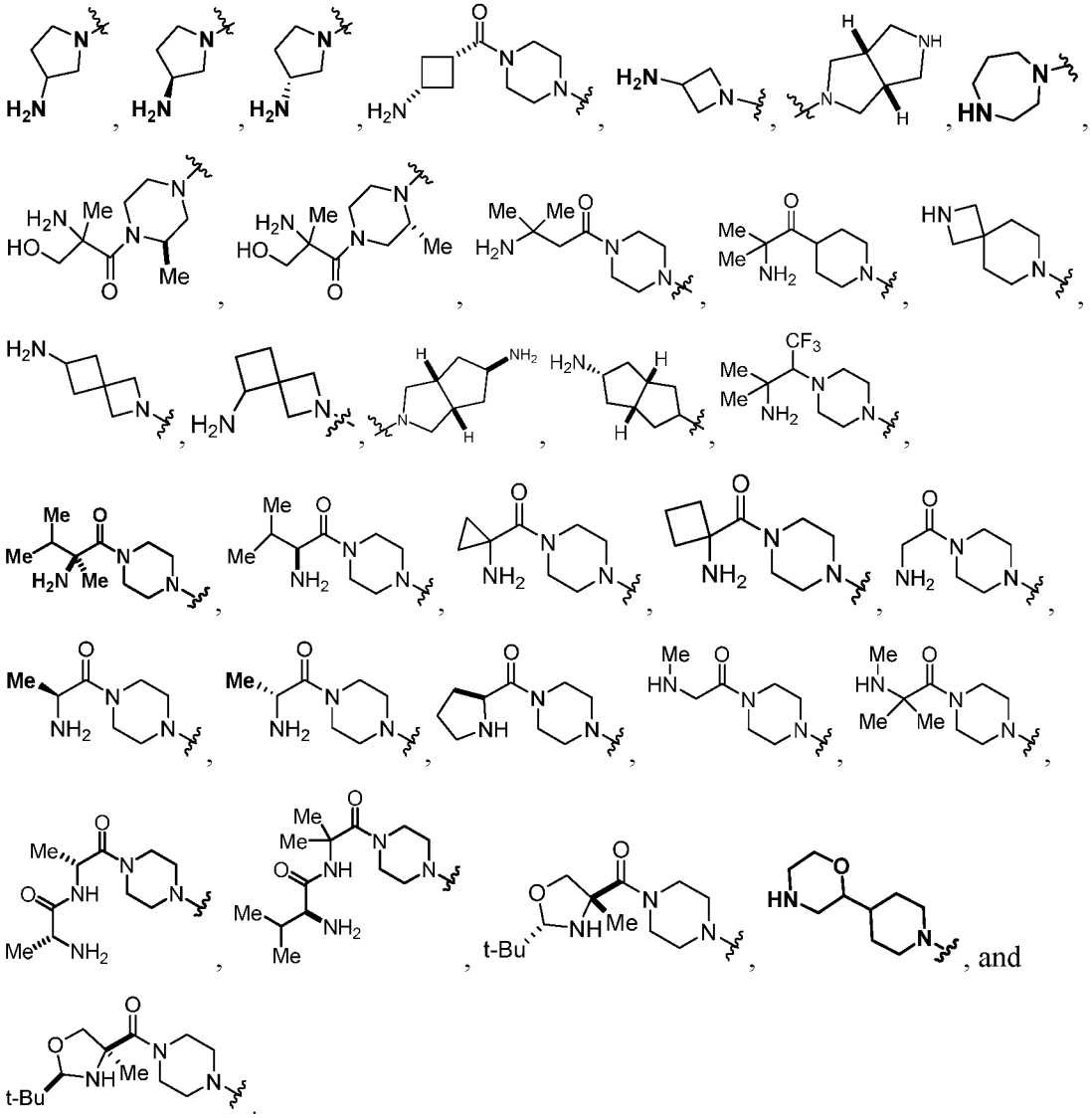


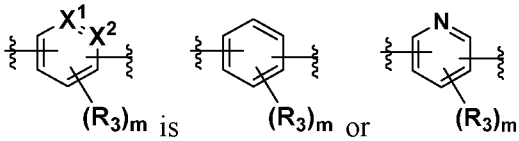
10. The compound of any one of claims 1-9 or a pharmaceutically acceptable salt thereof, wherein $R_{1'}$ is H, NH_2, $NH(C_1\text{-}C_6$ alkyl), or $NH(C_1\text{-}C_6$ alkyl$)_2$.

11. The compound of any one of claims 1-10 or a pharmaceutically acceptable salt thereof, wherein  is selected from the group consisting of ,

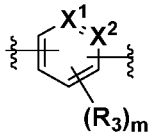
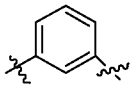
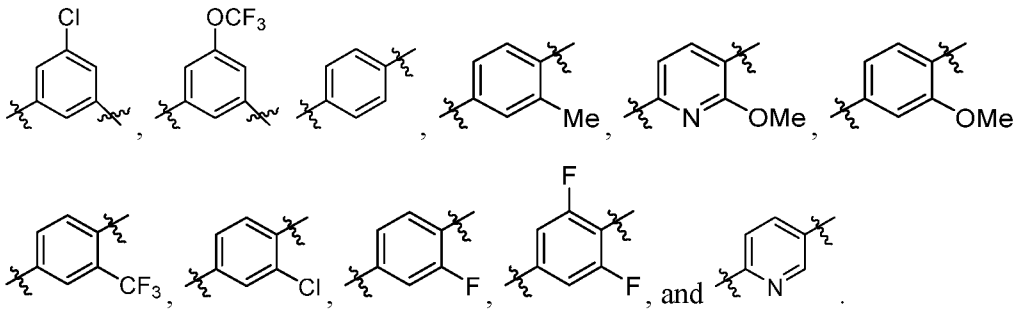




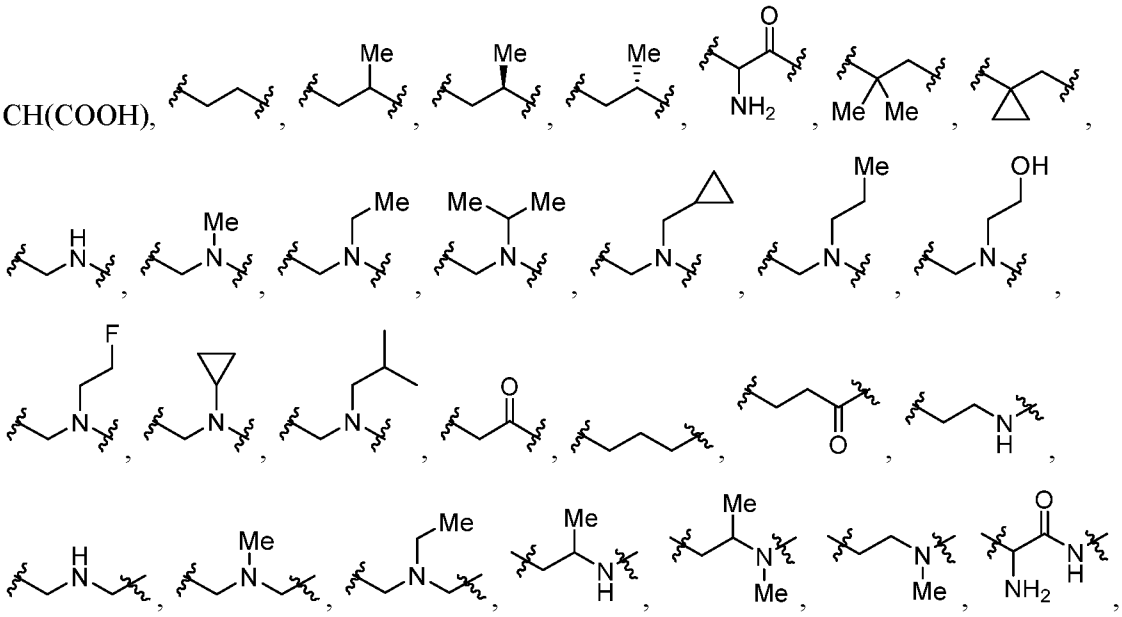


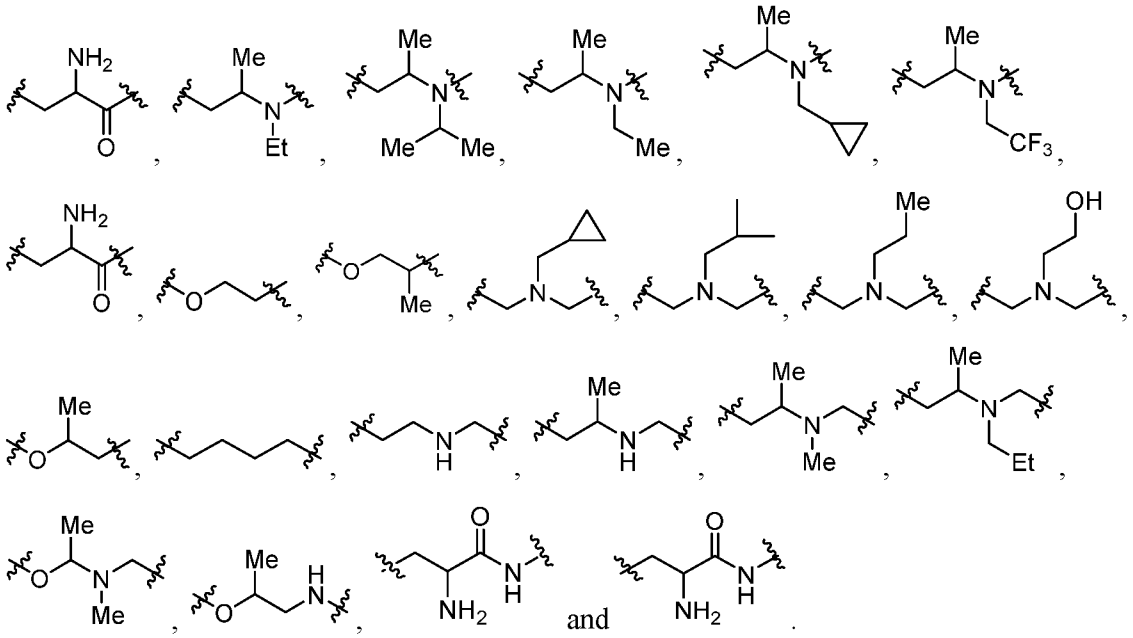
12. The compound of any one of claims 1-11 or a pharmaceutically acceptable salt thereof, wherein  is or , wherein each R_3 is independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, O(C_1-C_6 haloalkyl), and C_1-C_6 haloalkyl, wherein m is 0, 1 or 2.

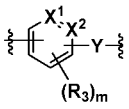
13. The compound of any one of claims 1-12 or a pharmaceutically acceptable salt

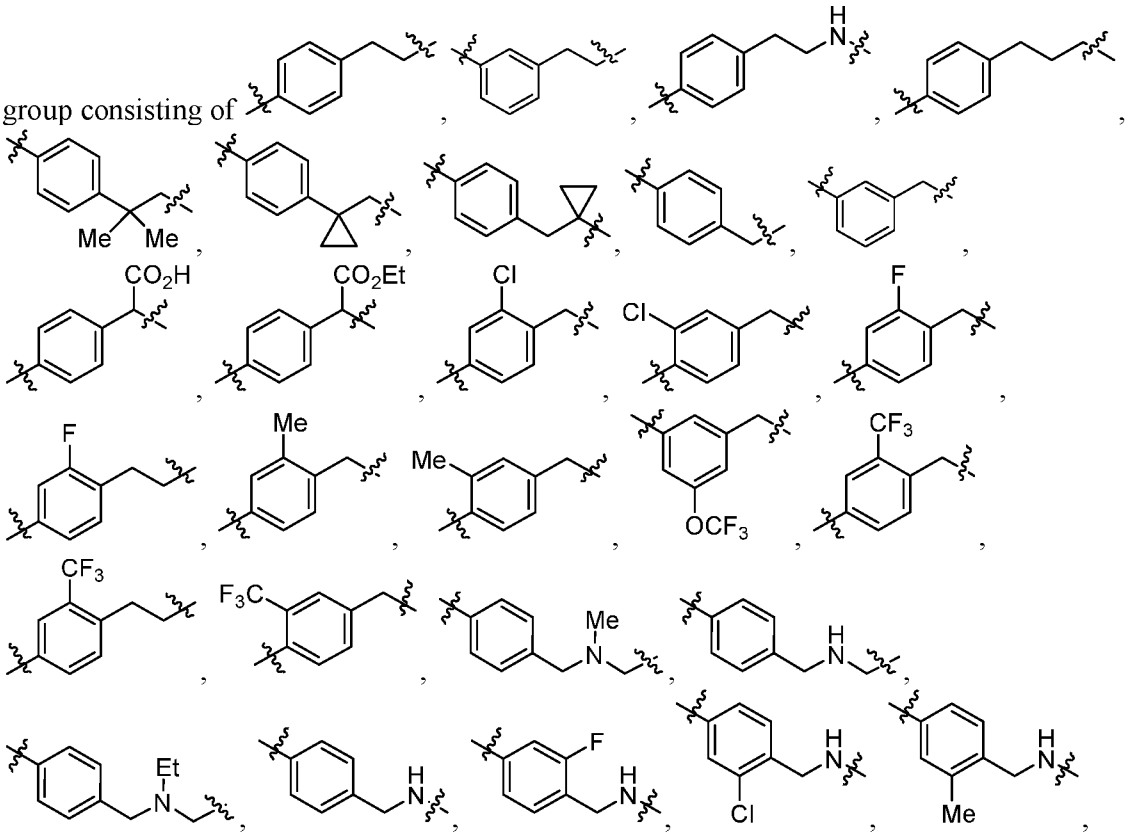
thereof, wherein  is selected from the group consisting of ,


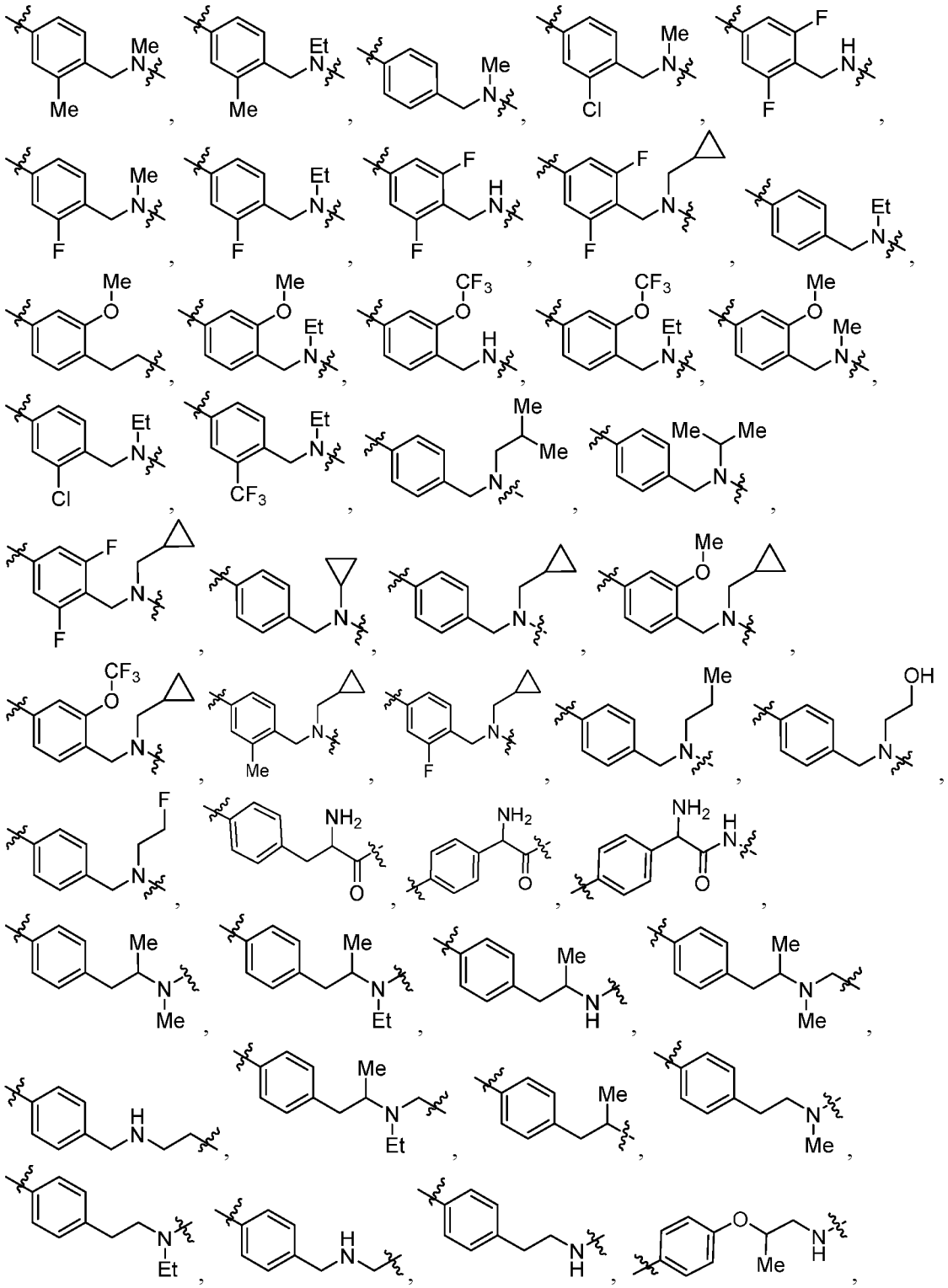
14. The compound of any one of claims 1-13 or a pharmaceutically acceptable salt thereof, wherein Y is a linear C_1-C_8 alkylene optionally substituted with OH, NH_2, CN, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, COO(C_1-C_6 alkyl), COOH, $CONH_2$, or C_1-C_6 alkoxy, and wherein up to two methylene units of the C_1-C_8 alkylene are optionally and independently replaced by O, NH, N-(C_1-C_6 alkyl), N-(C_1-C_6 hydroxyalkyl), N-(C_1-C_6 haloalkyl), N-(C_{1-6} alkylene-C_{3-8} cycloalkyl), N-(C_{3-8} cycloalkyl), NH(C=O), N-(C_{1-6} alkyl) (C=O), (C=O), or ; wherein t' is 1 or 2.

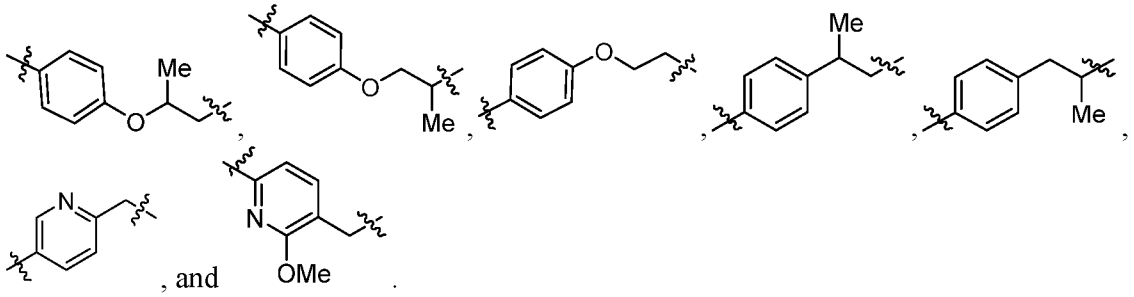
15. The compound of any one of claims 1-14 or a pharmaceutically acceptable salt thereof, wherein Y is selected from the group consisting of CH_2, $CH(CH_3)$, CH(COOEt), CH(COOH), 



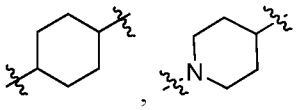
16. The compound of any one of claims 1-15 wherein  is selected from the group consisting of

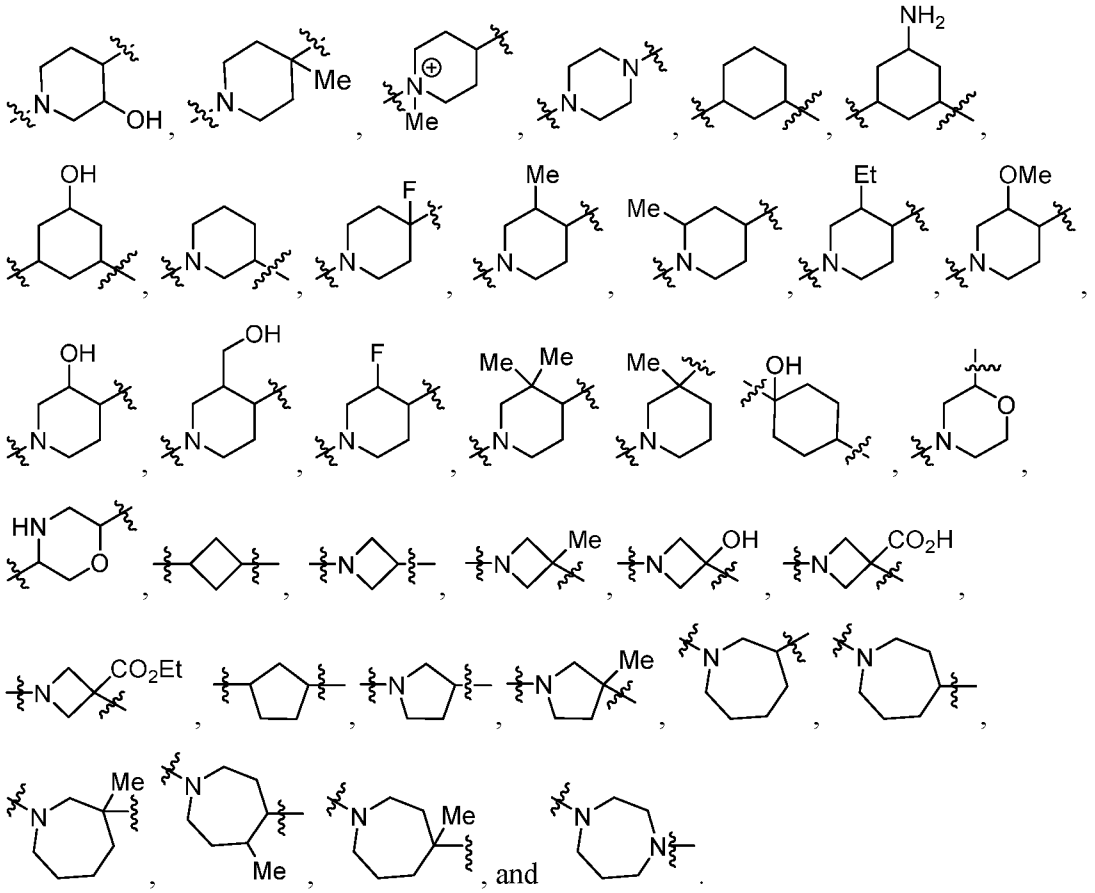






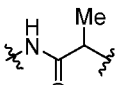
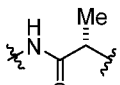
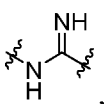
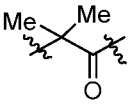
17. The compound of any one of claims 1-16 or a pharmaceutically acceptable salt thereof, wherein ring B is a 4-7 membered monocyclic cycloalkylene or 4-7 membered monocyclic heterocycloalkylene, either of which is optionally substituted with up to three substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, NH_2, C_1-C_6 haloalkyl, OH, COO(C_1-C_6 alkyl), COOH, and C_1-C_6 hydroxyalkyl.

18. The compound of any one of claims 1-17 or a pharmaceutically acceptable salt thereof, wherein ring B is selected from the group consisting of 

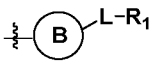
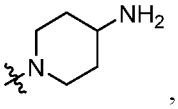
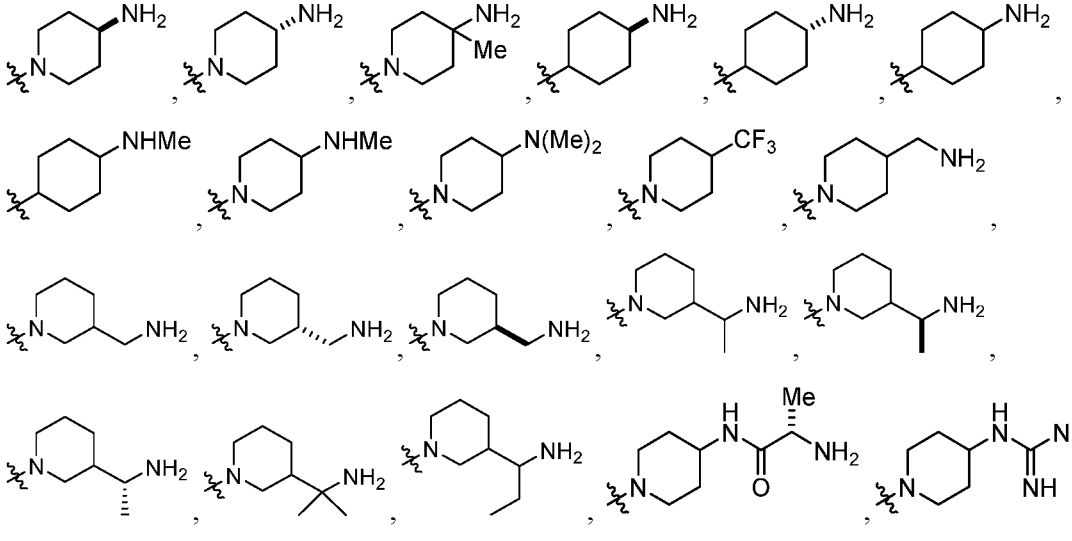


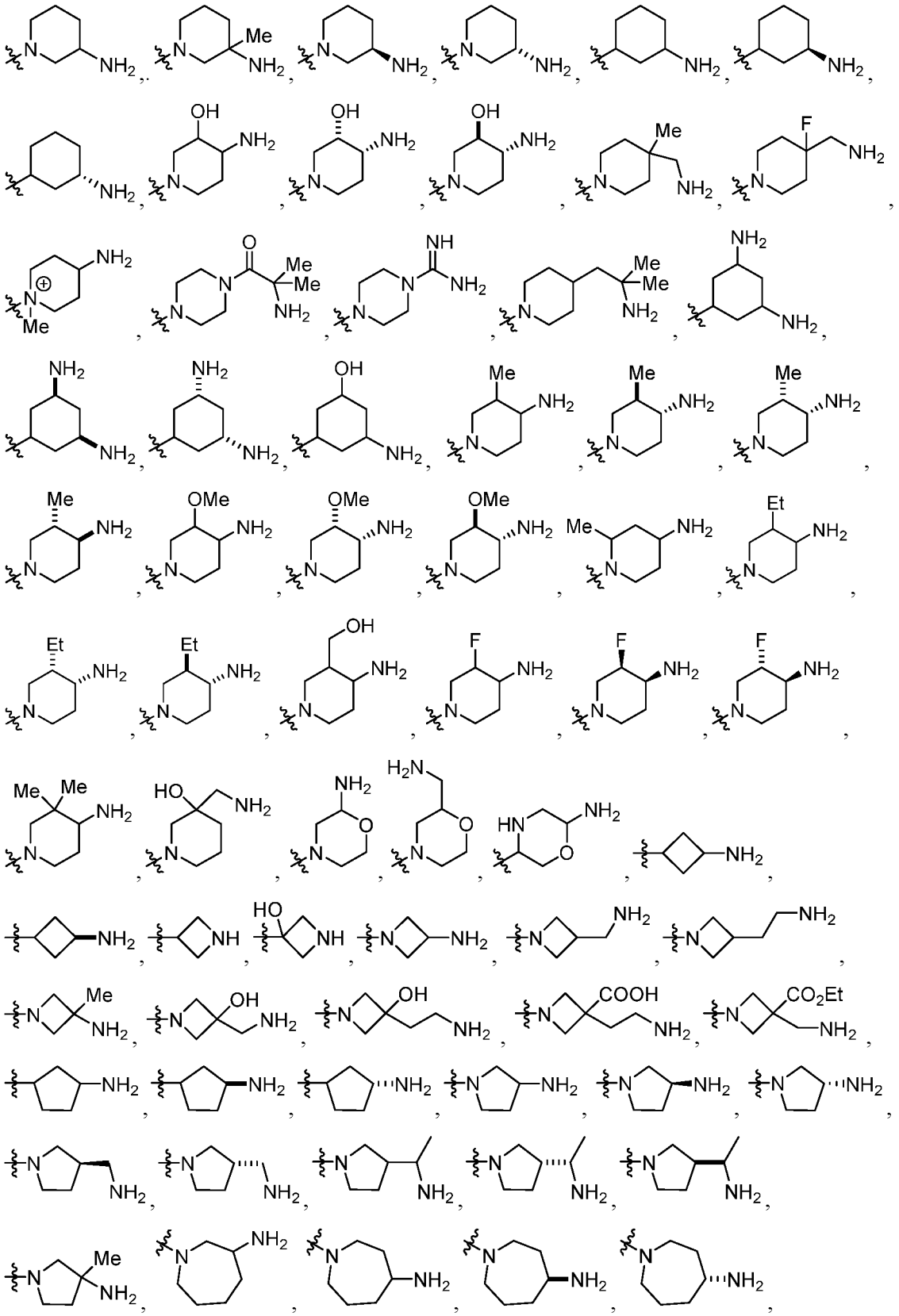
19. The compound of any one of claims 1-18 or a pharmaceutically acceptable salt thereof, wherein L is absent.

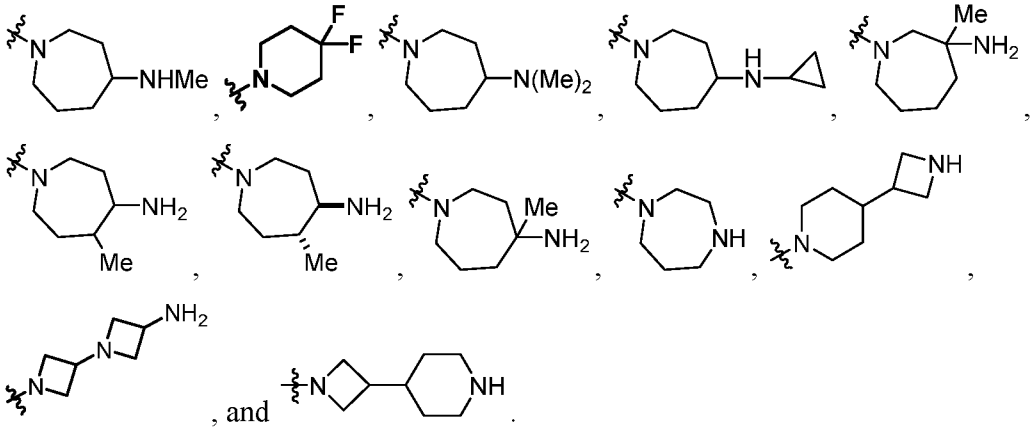
20. The compound of any one of claims 1-18 or a pharmaceutically acceptable salt thereof, wherein L is a linear or branched C_1-C_6 alkylene, wherein up to two methylene units of the C_1-C_6 alkylene are optionally and independently replaced with O, NH, (C=O), NH(C=O), N-(C_{1-6} alkyl)(C=O), (C=NH), NH(C=N), or N-(C_{1-6} alkyl).

21. The compound of any one of claims 1-20 or a pharmaceutically acceptable salt thereof, wherein L is absent or is selected from the group consisting of CH_2, CH_2CH_2, $C(Me)_2$, CH(Me), CH(Et), (C=NH), , , , and .

22. The compound of any one of claims 1-21 or a pharmaceutically acceptable salt thereof, wherein R_1 is selected from the group consisting of H, NH_2, NH(C_1-C_6 alkyl), NH(C_1-C_6 alkyl)$_2$, NH(C_3-C_6 cycloalkyl), CF_3, and a 4 to 6 membered monocyclic heterocycloalkyl optionally substituted with NH_2.

23. The compound of any one of claims 1-22 or a pharmaceutically acceptable salt thereof, wherein  is selected from the group consisting of , 

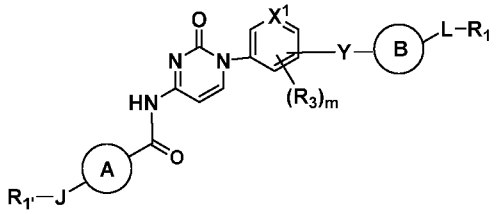




24. The compound of any one of claims 1-23 or a pharmaceutically acceptable salt thereof, wherein R_2 and R_3 are each independently selected from the group consisting of C_1-C_6 alkyl, halo, C_1-C_6 haloalkyl, O(C_1-C_6 haloalkyl), and C_1-C_6 alkoxy, and m and n are each independently 0, 1, or 2.

25. The compound of any one of claims 1-24 or a pharmaceutically acceptable salt thereof, wherein each R_3 is C_1-C_6 alkyl, halo, C_1-C_6 haloalkyl, O(C_1-C_6 haloalkyl), or C_1-C_6 alkoxy, m is 0, 1, or 2, and n is 0.

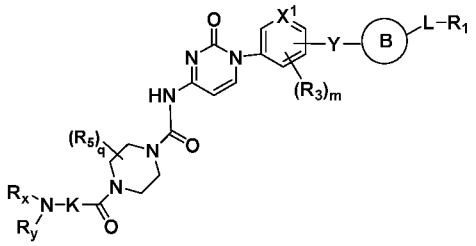
26. The compound of any one of claims 1-25 or a pharmaceutically acceptable salt thereof which is a compound of formula I-1:



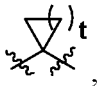
I-1

wherein X^1 is CH or N.

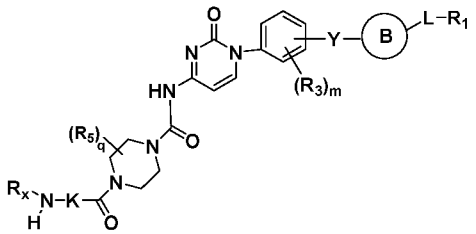
27. The compound of any one of claims 1-26 or a pharmaceutically acceptable salt thereof which is a compound of formula I-2:



I-2

wherein K is C_1-C_5 alkylene, 4 to 7 membered heterocycloalkylene, or 4 to 6 membered cycloalkylene, any of which may be optionally substituted with up to two substituents independently selected from halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, NH_2, CN, or OH, wherein one methylene unit of the C_1-C_5 alkylene is optionally replaced with , wherein t is 1, 2, 3, or 4; each R_5 is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, halo, CN, C_1-C_6 haloalkyl, phenyl, OH, NH_2, $NH(C_1$-C_6 alkyl), $N(C_1$-C_6 alkyl)$_2$, COOH, $COO(C_1$-C_6 alkyl), $CONH_2$, or oxo; R_x and R_y are each independently H, C_1-C_6 alkyl, C_1-C_6 alkyl-SO_3, $CO(C_1$-C_6 alkyl), CO-(C_1-C_6 alkylene)-NH_2; and q is 0, 1, 2, or 3.

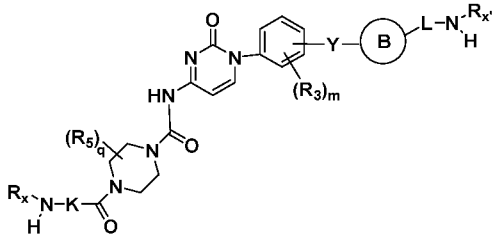
28. The compound of any one of claims 1-27 or a pharmaceutically acceptable salt thereof which is a compound of formula I-3:



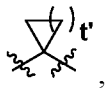
I-3

wherein K is C_1-C_4 alkylene optionally substituted with halo, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, or OH; each R_5 is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, C_1-C_6 haloalkyl, phenyl, OH, NH_2, COOH, or $COO(C_1$-C_6 alkyl); and q is 0, 1, or 2.

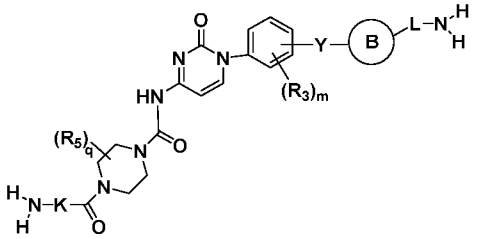
29. The compound of any one of claims 1-28 or a pharmaceutically acceptable salt thereof which is a compound of formula I-4:



I-4

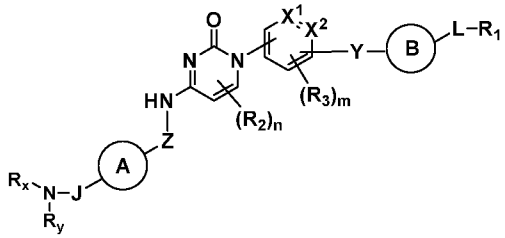
wherein Y is a linear C_1-C_4 alkylene optionally substituted with C_1-C_6 alkyl, COOH, COO(C_1-C_6 alkyl), or NH_2, and wherein up to two methylene units of the C_1-C_4 alkylene are optionally and independently replaced by (C=O), O, NH, N-(C_1-C_6 alkyl), N-(C_1-C_6 hydroxyalkyl), N-(C_1-C_6 haloalkyl), N-(C_{1-6} alkylene-C_{3-6} cycloalkyl), N-(C_{3-8} cycloalkyl), or , wherein t' is 1 or 2; each R_3 is independently C_1-C_6 alkyl, halo, C_1-C_6 haloalkyl, O(C_1-C_6 haloalkyl), or C_1-C_6 alkoxy; m is 0, 1, or 2; and R_x and $R_{x'}$ are each independently H or C_1-C_6 alkyl.

30. The compound of any one of claims 1-29 or a pharmaceutically acceptable salt thereof which is a compound of formula I-5:



I-5.

31. The compound of claim 1 or a pharmaceutically acceptable salt thereof which is a compound of formula II:



II

wherein:

Z is (C=O);

ring A is a monocyclic heterocycloalkylene or bicyclic heterocycloalkylene, wherein

the monocyclic heterocycloalkylene or bicyclic heterocycloalkylene are optionally substituted with up to three substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CN, C_1-C_6 haloalkyl, phenyl, OH, NH_2, $NH(C_1$-C_6 alkyl), $N(C_1$-C_6 alkyl)$_2$, $COO(C_1$-C_6 alkyl), -$CONH_2$, and oxo;

J is C_1-C_6 alkylene optionally substituted with halo, hydroxy, or alkoxy, wherein one or two methylene units of the C_1-C_6 alkylene may optionally be replaced with O, S, SO_2, or C=O;

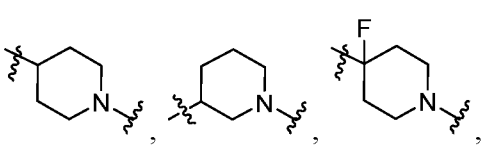
R_x and R_y are each independently H, C_1-C_6 alkyl, or an amino protecting group;

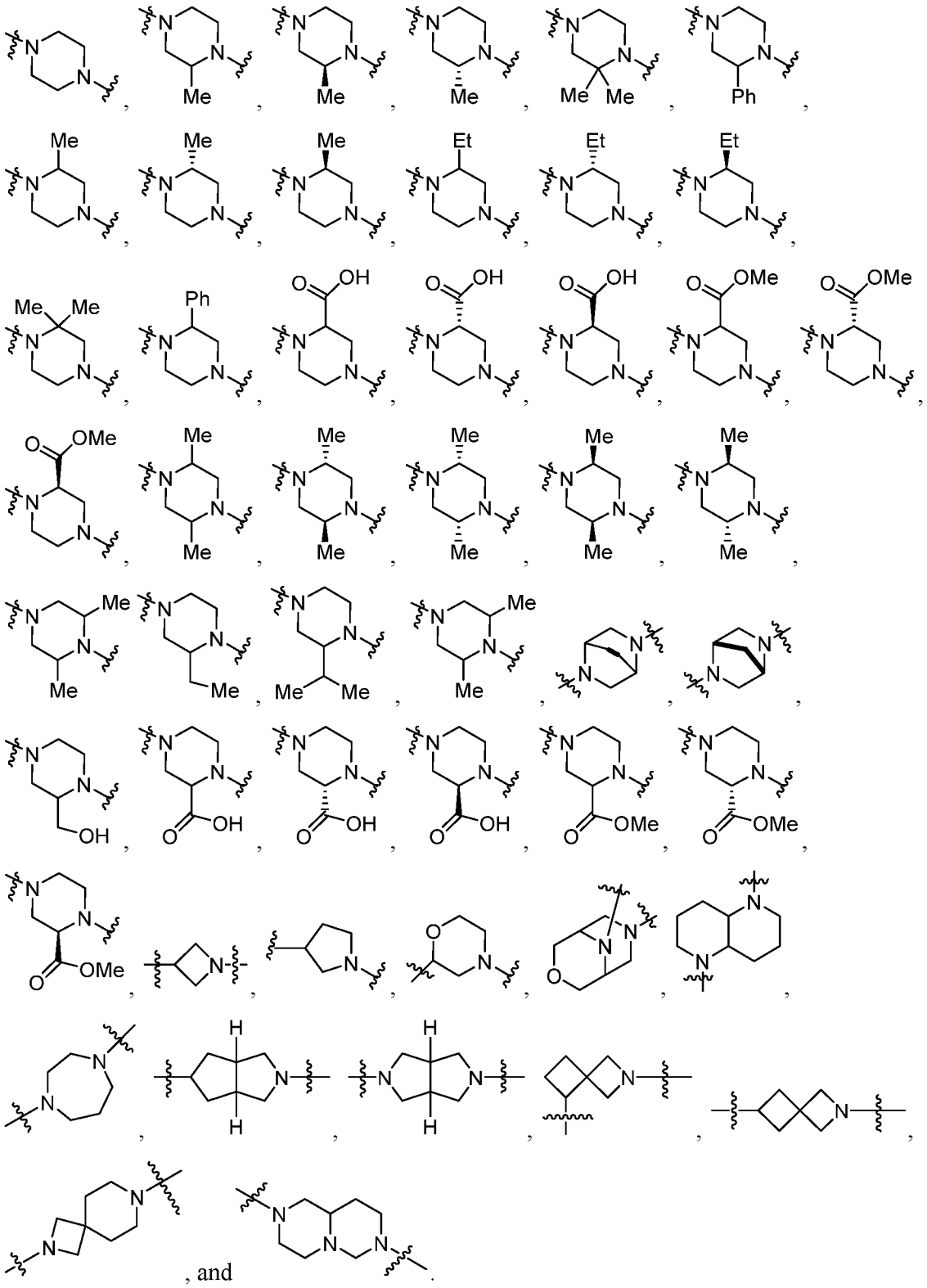
Y is a linear C_1-C_8 alkylene, C_2-C_8 alkenylene, or C_2-C_8 alkynylene, any of which are optionally substituted with OH, NH_2, halo, C_1-C_6 alkyl, or C_1-C_6 alkoxy, and wherein up to two carbon atoms of the C_2-C_8 alkylene, C_2-C_8 alkenylene, or C_2-C_8 alkynylene may be independently replaced by O, NH, N-(C_1-C_6 alkyl), N-(C_1-C_6 hydroxyalkyl), N-(C_1-C_6 haloalkyl), N-(C_{1-6} alkylene-cycloalkyl), NH(C=O), N-(C_{1-6} alkyl) (C=O), or (C=O);

ring B is a monocyclic cycloalkylene or moncyclic heterocycloalkylene which is optionally substituted with up to three substituents selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CN, C_1-C_6 haloalkyl, OH, -$COO(C_1$-C_6 alkyl), -$CONH_2$, and C_1-C_6 hydroxyalkyl;

R_1 is H, halo, C_1-C_6 haloalkyl, or $NR_{x'}R_{y'}$, wherein $R_{x'}$ and $R_{y'}$ are each independently H, C_1-C_6 alkyl which may be optionally substituted with up to three substituents selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CN, C_1-C_6 haloalkyl, phenyl, OH, NH_2, $NH(C_1$-C_6 alkyl), $N(C_1$-C_6 alkyl)$_2$, -$COO(C_1$-C_6 alkyl), -$COONH_2$, and oxo, or a or a protecting group; or R_1 is NH(C=O)-(C_1-C_6) alkyl, or NH-(C=NH)-NH_2, either of which may be optionally substituted with up to three substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CN, C_1-C_6 haloalkyl, phenyl, OH, NH_2, $NH(C_1$-C_6 alkyl), $N(C_1$-C_6 alkyl)$_2$, -$COO(C_1$-C_6 alkyl), -$CONH_2$, and oxo; and

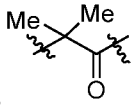
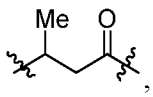
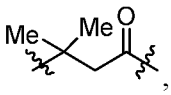
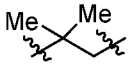
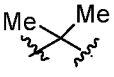
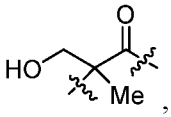
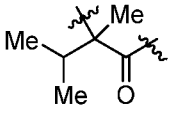
R_2 and R_3 are each independently selected from the group consisting of C_1-C_6 alkyl, halo, CN, OH, NH_2, $NH(C_1$-C_6 alkyl), $N(C_1$-C_6 alkyl)$_2$, -$COO(C_1$-C_6 alkyl), -$CONH_2$, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy.

32. The compound of claim 31 or a pharmaceutically acceptable salt thereof, wherein ring A is selected from the group consisting of ,

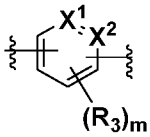
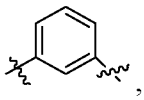
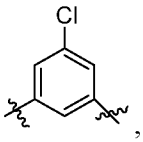
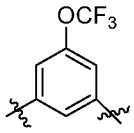
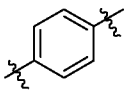
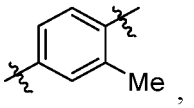
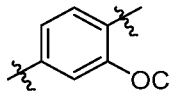
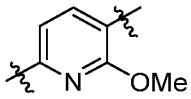
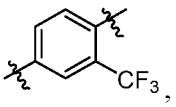
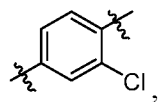
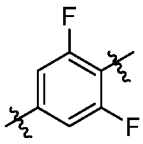
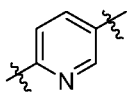


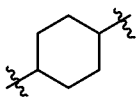
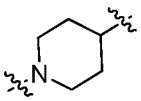
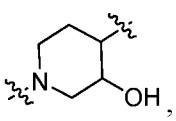
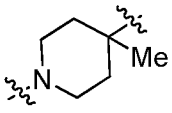
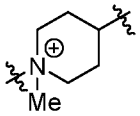
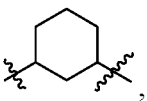
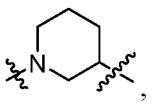
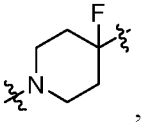
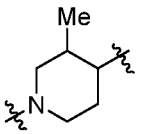
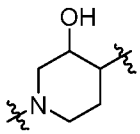
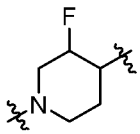
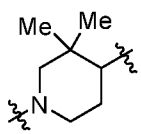
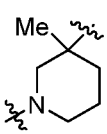
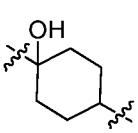
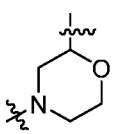
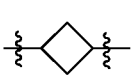
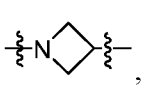
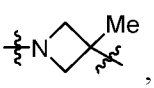
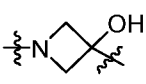
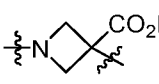
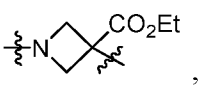
, and .

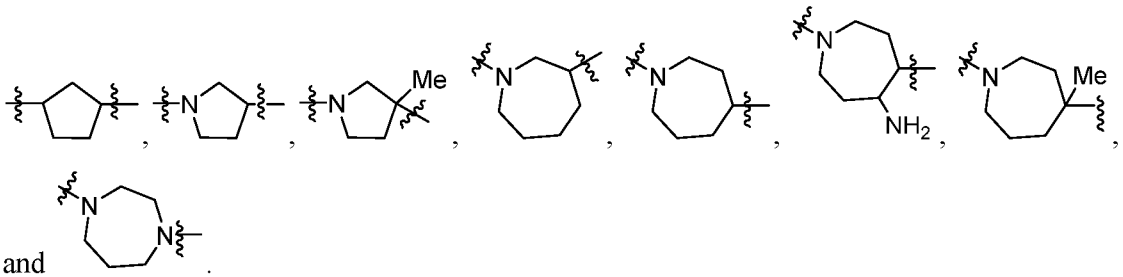
33. The compound of claim 31 or 32 or a pharmaceutically acceptable salt thereof,

wherein J is selected from the group consisting of -CH_2-, , , , , , , and .

34. The compound of any one of claims 31-33 or a pharmaceutically acceptable salt thereof, wherein NR_xR_y is NH_2, NHMe, NHEt, NHPG, $N(Me)_2$, or $N(Et)_2$, wherein PG is the amino protecting group.

35. The compound of any one of claims 31-34 or a pharmaceutically acceptable salt thereof, wherein  is selected from the group consisting of , , , , , , , , , , and .

36. The compound of any one of claims 31-35 or a pharmaceutically acceptable salt thereof, ring B is selected from the group consisting of , , , , , , , , , , , , , , , , , , , , .



and .

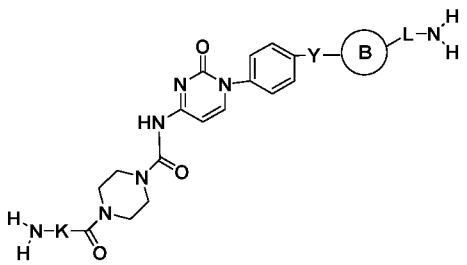
37. The compound of any one of claims 31-36 or a pharmaceutically acceptable salt thereof, wherein L is absent.

38. The compound of any one of claims 31-36 or a pharmaceutically acceptable salt thereof, wherein L is a linear or branched C_1-C_6 alkylene, wherein up to two carbon atoms of the C_1-C_6 alkylene may be replaced with O, NH, (C=O), NH(C=O), N-(C_{1-6} alkyl)(C=O), (C=NH), NH(C=N), or N-(C_{1-6} alkyl).

39. The compound of any one of claims 31-38 or a pharmaceutically acceptable salt thereof, wherein R_1 is H, fluoro, NH_2, NH(C_1-C_6 alkyl), or NH(C_3-C_6 cycloalkyl).

40. The compound of any one of claims 31-39 or a pharmaceutically acceptable salt thereof, wherein R_2 and R_3 are each independently selected from the group consisting of C_1-C_6 alkyl, halo, C_1-C_6 haloalkyl, and C_1-C_6 alkoxy and m and n are each independently 0, 1, or 2.

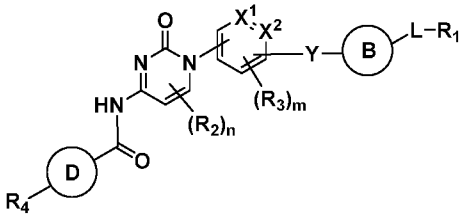
41. The compound of any one of claims 31-40 or a pharmaceutically acceptable salt thereof which is a compound of formula IIA-9:



IIA-9

wherein K is C_1-C_4 alkylene optionally substituted with hydroxy or alkoxy.

42. The compound of claim 1, or a pharmaceutically acceptable salt thereof, which is a compound of formula III:



III

wherein:

Y is a linear C_1-C_8 alkylene, C_2-C_8 alkenylene, or C_2-C_8 alkynylene, any of which are optionally substituted with OH, NH_2, halo, C_1-C_6 alkyl, or C_1-C_6 alkoxy, and wherein up to two carbon atoms of the C_2-C_8 alkylene, C_2-C_8 alkenylene, or C_2-C_8 alkynylene may be independently replaced by O, NH, N-(C_1-C_6 alkyl), N-(C_1-C_6 hydroxyalkyl), N-(C_1-C_6 haloalkyl), N-(C_{1-6} alkylene-cycloalkyl), NH(C=O), N-(C_{1-6} alkyl) (C=O), or (C=O);

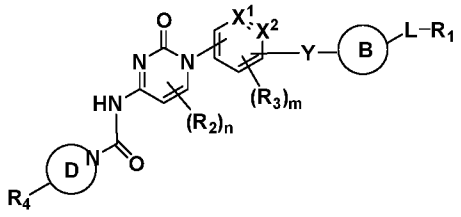
R_1 is H, halo, C_1-C_6 haloalkyl, or $NR_{x'}R_{y'}$, wherein $R_{x'}$ and $R_{y'}$ are each independently H, C_1-C_6 alkyl which may be optionally substituted with up to three substituents selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CN, C_1-C_6 haloalkyl, phenyl, OH, NH_2, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)$_2$, -COO(C_1-C_6 alkyl), -$CONH_2$, and oxo, or a or a protecting group; or R_1 is NH(C=O)-(C_1-C_6) alkyl, or NH-(C=NH)-NH_2, either of which may be optionally substituted with up to three substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CN, C_1-C_6 haloalkyl, phenyl, OH, NH_2, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)$_2$, -COO(C_1-C_6 alkyl), -$CONH_2$, and oxo;

ring D is a monocyclic heterocycloalkylene or bicyclic heterocycloalkylene, wherein the bicyclic heterocycloalkylene, and bicyclic heterocycloalkylene are optionally substituted with up to three substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CN, C_1-C_6 haloalkyl, phenyl, OH, NH_2, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)$_2$, COO(C_1-C_6 alkyl), $CONH_2$, and oxo; and

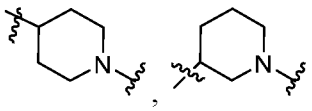
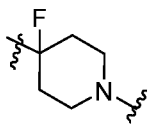
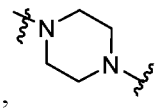
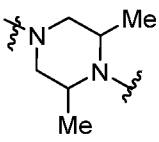
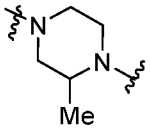
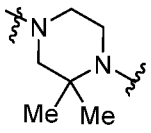
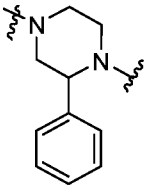
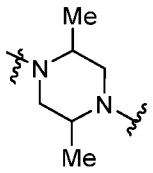
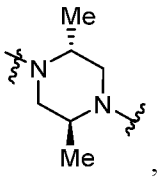
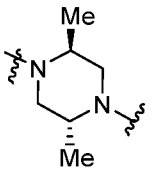
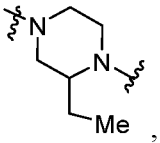
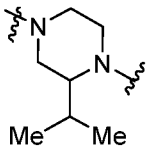
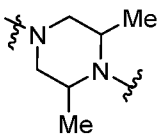
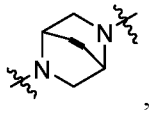
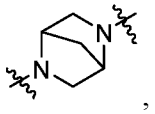
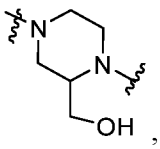
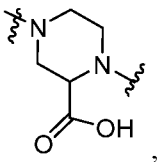
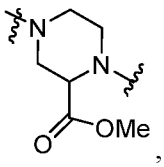
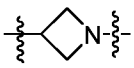
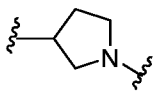
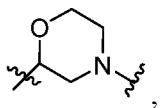
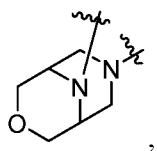
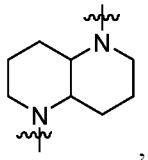
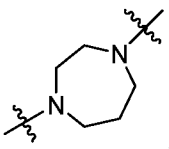
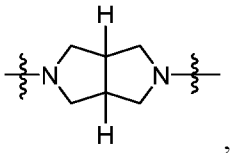
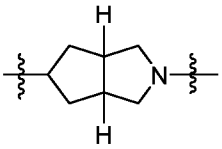
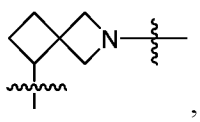
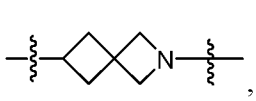
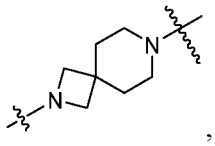
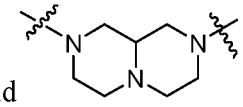
R_2 and R_3 are each independently selected from the group consisting of C_1-C_6 alkyl, halo, CN, OH, NH_2, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)$_2$, COO(C_1-C_6 alkyl), $CONH_2$, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R_4 is H or $NR_{x''}R_{y''}$, wherein $R_{x''}$ and $R_{y''}$ are each independently H or C_1-C_6 alkyl.

43. The compound of claim 42 or a pharmaceutically acceptable salt thereof, which is a compound of formula IIIA:



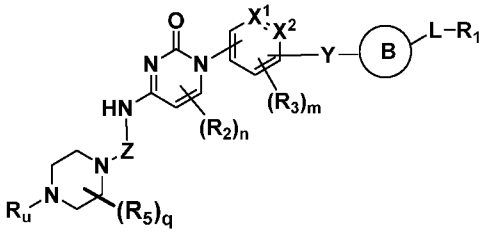
IIIA.

44. The compound of claim 42 or 43 or a pharmaceutically acceptable salt thereof, wherein ring D is selected from the group consisting of , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , and .

45. A compound or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the compounds listed in Table 10.

46. A compound or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the compounds listed in Table 11.

47. A compound of formula IV:

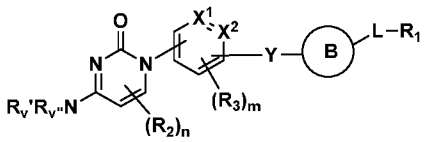


IV

or a pharmaceutically acceptable salt thereof, wherein the variables have the definitions as defined in any one of claims 1-44, and R_u is H or an amino protecting group.

48. A compound or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the compounds listed in Table 12.

49. A compound of formula V:

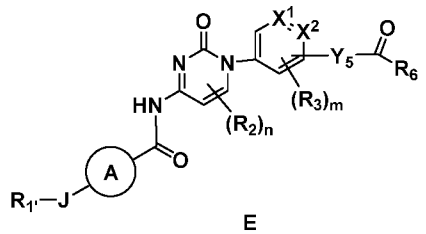


V

or a pharmaceutically acceptable salt thereof, wherein the variables have the definitions defined in any one of claims 1-44, and one of $R_{v'}$ and $R_{v''}$ is H and the other of $R_{v'}$ and $R_{v''}$ is H or an amino protecting group.

50. A compound or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the compounds listed in Table 13.

51. A compound of formula E:



E

or a pharmaceutically acceptable salt thereof wherein ring A, ring B, J, X^1, X^2, $R_{1'}$, R_2, R_3, R_6, m, and n have the same definitions in any one of claims 1-44; Y_5 is a bond or is a linear

C_1-C_7 alkylene, C_2-C_7 alkenylene, or C_2-C_7 alkynylene, any of which are optionally substituted with OH, NH_2, CN, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $COO(C_1$-C_6 alkyl), COOH, $CONH_2$, or C_1-C_6 alkoxy, wherein up to two carbon atoms of the C_2-C_7 alkylene, C_2-C_7 alkenylene, or C_2-C_7 alkynylene may be independently replaced by O, (C=O), or 
wherein t' is 1, 2, 3, or 4; and R_6 is H or C_1-C_6 alkyl.

52. A compound or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the compounds listed in Table 14.

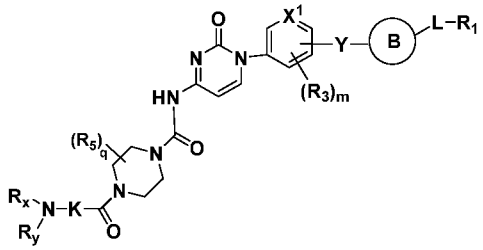
53. A pharmaceutical composition comprising a compound of any one of claims 1-46, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

54. A method of treating a bacterial infection in a patient in need of such treatment, comprising administering the compound of any one of claims 1-46, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 53.

55. The method of claim 54, wherein the bacterial infection is caused by a bacterium including gram positive and gram negative bacteria.

56. The method of claim 55, wherein the bacterium includes Francisella tularensis, Burkholderia mallei, Burkholderia pseudomallei, Bacillus anthracis, Yersinia pestis, Salmonella. Clostridium difficile, Citrobacter, Enterobacter, Burkholderia genus, cepacia, Mycobacterium, Proteus, Streptococcus, Serratia, Enterobacteriaceae, Escherichia, Klebsiella, Pseudomonas, and Acinitobacter.

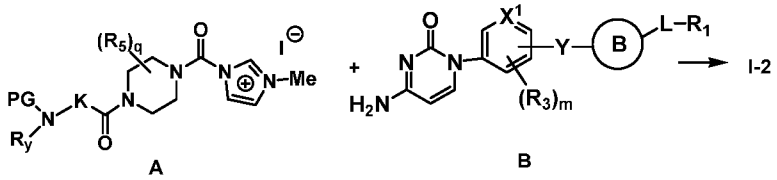
57. A process for preparing a compound of formula I-2:



I-2

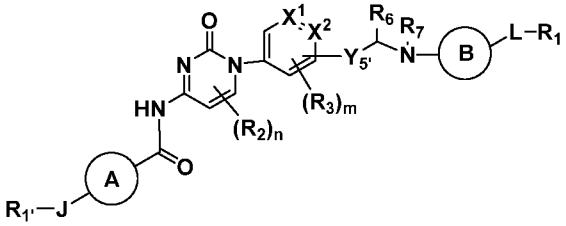
or a pharmaceutically acceptable salt thereof, the process comprising:

coupling a compound of formula A with a compound of formula B to provide a compound of formula I-2:



wherein ring B, K, L, Y, R_1, R_x, R_y, R_5, X^1, m, and q are as defined in any one of claims 1-44, and wherein PG is an amino protecting group.

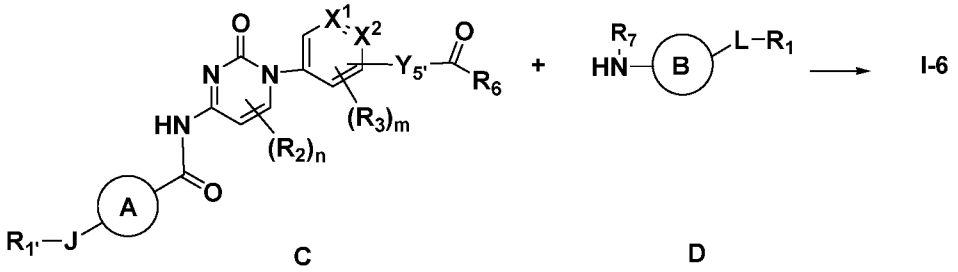
58. A process for preparing a compound of formula I-6:



I-6

or a pharmaceutically acceptable salt thereof, the process comprising:

combining a compound of formula C with a compound of formula D under a reductive amination condition to provide a compound of formula I-6:



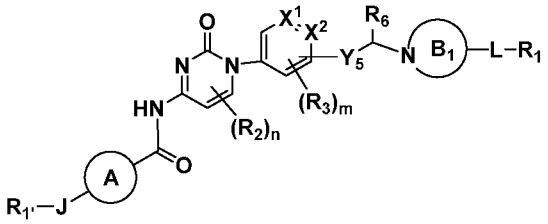
wherein ring A, ring B, J, L, R_1, $R_{1'}$, R_2, R_3, X^1, X^2, m, and n are as defined in any one of claims 1-44;

$Y_{5'}$ is a bond or is a linear C_1-C_6 alkylene, C_2-C_6 alkenylene, or C_2-C_6 alkynylene, any of which are optionally substituted with OH, NH_2, CN, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $COO(C_1$-C_6 alkyl), COOH, $CONH_2$, or C_1-C_6 alkoxy, and wherein up to two carbon atoms of the C_2-C_8 alkylene, C_2-C_8 alkenylene, or C_2-C_8 alkynylene may be optionally and independently replaced by O, (C=O), or  ; wherein t' is 1, 2, 3, or 4;;

R_6 is H or C_1-C_6 alkyl; and

R_7 is H, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, C_3-C_8 cycloalkyl, or C_1-C_6 alkylene-C_3-C_8 cycloalkyl.

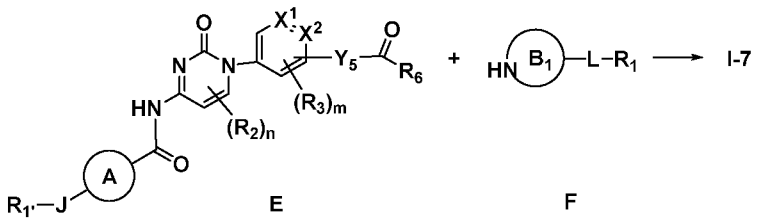
59. A process for preparing a compound of formula I-7:



I-7

or a pharmaceutically acceptable salt thereof, the process comprising:

combining a compound of formula E with a compound of formula F under a reductive amination condition to provide a compound of formula I-7



E F

wherein ring A, ring B, J, L, R_1, $R_{1'}$, R_2, R_3, X^1, X^2, m, and n are as defined in any one of claims 1-44;

ring B_1 is a nitrogen containing monocyclic heterocycloalkylene optionally substituted with up to three substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CN, C_1-C_6 haloalkyl, OH, COO(C_1-C_6 alkyl), $CONH_2$, and C_1-C_6 hydroxyalkyl;

Y_5 is a bond or is a linear C_1-C_7 alkylene, C_2-C_7 alkenylene, or C_2-C_7 alkynylene, any of which are optionally substituted with OH, NH_2, halo, C_1-C_6 alkyl, or C_1-C_6 alkoxy; and

R_6 is H or C_1-C_6 alkyl.